Lipid-Lowering Treatment in Hypercholesterolemic Patients: the CEPHEUS Thailand Survey

Apichard Sukonthasarn MD*, Mayuree Homsanit MD, MPH, PhD Epidemiology**,
Bundit Prommete MD***, Chunhakasem Chotinaiwattarakul MD**,
Chumpol Piamsomboon MD****, Khanchit Likittanasombat MD*****

** Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
*** Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
**** Her Majesty Cardiac Center, Faculty of Medicine, Mahidol University Bangkok, Thailand*
*****Phramongkutklao Hospital, Bangkok, Thailand*
****** Department of Medicine, Ramathibodi Hospital, Bangkok, Thailand*

Background: *Atherosclerotic cardiovascular disease (ASCVD) has become the leading cause of death and disability in Thailand. Low-density lipoprotein cholesterol is the major risk factor of this condition that can be intervened by means of lifestyle modification and pharmacologic treatment. Adequacy of hypercholesterolemia treatment with lipid lowering drugs in Thailand needed to be more clarified. The present study was conducted to determine low-density cholesterol goal attainment in Thai population at risk for developing ASCVD*

Material and Method: *Twenty-seven physicians with their 909 hypercholesterolemic patients whose age of ≥ 18 years, actively under pharmacologic treatment for at least three months with no dose adjustment for a minimum of six weeks from seven centers across Thailand were enrolled. Plasma glucose, total cholesterol, LDL cholesterol, HDL-cholesterol, and triglyceride levels were measured after overnight fast. Demographic and other relevant data including information on lipid lowering drug used were retrieved. Patients' awareness, knowledge on their management, compliance, and satisfaction were evaluated by questionnaire survey as well as physicians' use of guidelines, choice of management and goal setting, and their attitudes towards lipid management. Cardiovascular risk level and LDL goal were assessed by the updated 2004 NCEP-ATP III guidelines.*

Results: *All patients had LDL goal of < 130 mg/dl with 86.1% needed LDL goal of < 100 mg/dL. Overall, 52.7% of the patients reached their LDL goal. The most prescribed treatment was statin monotherapy (82.7%). LDL goal attainment was inversely associated with LDL goal set by NCEP-ATP III according to the patients' risk profile, with only 16.7% of those who were in the very high risk group with LDL goal of < 70 mg/dL achieved their goal whereas 60.6% and 84.7% of those with high (LDL goal < 100 mg/dl) and moderately high-risk (LDL goal < 130 mg/dl) achieved their goal, respectively ($p < 0.001$). Other factors associated with less favorable LDL goal attainment were coronary heart disease, carotid artery disease, diabetes, 10-year risk of > 20%, and metabolic syndrome ($p < 0.05$ for all). Type of lipid lowering drug was not significantly associated with LDL goal attainment.*

Conclusion: *LDL goal attainment was not achieved in a high proportion of Thai patients especially in those who had high to very high risk for developing cardiovascular disease. Despite availability of well-established treatment guideline and efficacious lipid lowering drugs, many patients still miss the opportunity to effectively control their lipid profile.*

Keywords: *Lipid lowering treatment, LDL goal*

J Med Assoc Thai 2011; 94 (12): 1424-34
Full text. e-Journal: *http://www.jmat.mat.or.th*

Atherosclerotic cardiovascular disease (ASCVD) has become the leading cause of morbidity and mortality worldwide. According to the nation statistics, cardiovascular disease claimed more than 34,000 lives of Thai people in the year 2009, or more than 90 lives each day[1,2]. Prevention of the disease can be achieved by means of lifestyle changes and treatment of modifiable risk factors. Among the modifiable factors, hypercholesterolemia is the major atherosclerotic cardiovascular risk. In order to reduce its morbidity and mortality, dyslipidemic individuals at risk for cardiovascular events need their

Correspondence to:
Homsanit M, Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2419-7284
E-mail: mhomsanit@gmail.com

LDL-cholesterol (LDL-C) to be reduced to the target levels[3]. Many studies have shown the beneficial effect of LDL-C reduction in both primary and secondary prevention for cardiovascular disease[4,5]. Thus, the target LDL-C levels for patients with various categories of risk are determined by many authorities to set the management guidelines for dyslipidemia. The Adult Treatment Panel III guidelines of the National Cholesterol Educational Program (NCEP-ATP III) on cholesterol management[6] with updated 2004 version[7] recommends the LDL-C goals at 160 mg/dl for those with 0-1 risk factor, 130 mg/dl for those with $\geq$ 2 risk factors with 10-year risk < 10%, 130 mg/dl or optional 100 mg/dl for those with $\geq$ 2 risk factors with 10-year risk 10-20% and 100 mg/dl for those with coronary heart disease (CHD) or CHD equivalents with optional 70 mg/dL for those at very high risk (established CHD plus major risk factor especially diabetes, severe and poorly controlled risk factor especially continued smoking, multiple risk factors of metabolic syndrome, or acute coronary syndrome).

Management of hypercholesterolemia includes therapeutic lifestyle change and utilizing of lipid lowering drugs. The beneficial effects of pharmacologic therapy to reduce cardiovascular events have been demonstrated. However, there is still problem achieving LDL-C goal in many individuals. The Lipid Treatment Assessment Project II in Thailand (LTAP-II Thailand) studied the LDL-C goal achievement for patients whose LDL-C goals were less than 160, 130, and 100 mg/dL. The result of this study showed that the overall LDL-C-goal achievement success rate was 46.5% according to the NCEP ATP III recommendation with lower LDL-C achievement rate in higher risk patients (34.6%, 56.4% and 76.8% in those whose LDL-C goal of < 100, < 130 and < 160 mg/dl, respectively), consistent with the result from other studies[8]. However, since the very high-risk patients might need their LDL-C to be less than 70 mg/dL according to the revised NCEP-ATP III recommendation[7], the information on adequacy of dyslipidemia management with lipid lowering agents is therefore still needed to be investigated. The present study -the Centralized Pan-Asian Survey on the Under Treatment of Hypercholesterolemia (CEPHEUS)-Thailand was aimed to evaluate Thai patients at risk for developing ASCVD in achievement of target LDL-C regarding the updated NCEP ATP III recommendation, and to evaluate the factors that associated with LDL-C goal attainment.

Material and Method

The CEPHEUS Pan-Asian study (Clinical Trials.gov Identifier: NCT00687492) was a prospective, multinational, cross-sectional survey of subjects on lipid-lowering pharmacological treatment. This multicentre survey was conducted at 405 sites in Korea, Taiwan, Thailand, Indonesia, Philippines, Malaysia, Vietnam and Hong Kong SAR, China, with a target enrollment of approximately 8,000 patients. The survey in Thailand was conducted at seven sites with a target enrollment 930 of patients. The study protocol was reviewed and approved by the Investigational Review Board and the Ethics Committee governing each participating centre, with consent from the main board of the CEPHEUS, before the commencement of patient enrolment. The study was performed in accordance with the principles of good clinical research practice, and conformed to ethical guidelines of the 1975 Declaration of Helsinki. All participating patients provided written informed consent before being enrolled in the study.

Study population

Study subjects were patients who fulfilled the following criteria: (i) aged 18 years or above, (ii) had two or more cardiovascular risk factors as defined by the updated 2004 NCEP ATP III guidelines and (iii) had at the time of enrolment been on lipid-lowering drugs for at least three months, with no dose change for at least six weeks. Patients were excluded if they were found to have participated in any interventional clinical study during the preceding 90-day period, were unable or unwilling to provide informed consent, or were personally involved in the conduct of this study.

Objectives

The primary objective of the present study was to determine the proportion of patients on lipid-lowering pharmacological treatment attaining LDL-C goals, as defined by the updated 2004 NCEP ATP III guidelines[7]. Secondary objectives included: (i) determining the proportion of patients in primary or secondary prevention and with metabolic syndrome (NCEP ATP III definition) who attained LDL-C goals; (ii) identifying the determinants of undertreatment of hypercholesterolaemia and (iii) investigating patient and physician characteristics associated with the allocation of treatment approaches. For all purposes, definitions and criteria set by the updated 2004 NCEP ATP III guidelines were applied[7].

Survey instruments and procedure

The survey instrument consisted of a questionnaire each for the attending physician and the patient and a case record form (CRF) for the physician to record the patient's demographics, results of physical examination, cardiovascular medical history, known cardiovascular risk factors (including CHD or CHD risk equivalents and metabolic syndrome), past lipid profile (if any), current lipid-lowering therapy and reason for the treatment. The physician questionnaire comprised 23 questions designed to collect information on the physician's awareness and use of practice guidelines, therapeutic LDL-C goals adopted, their management of hypercholesterolaemia and related communications with patients, as well as personal attitudes pertaining to hypercholesterolaemia and its management. The patient questionnaire comprised 17 questions designed to find out the patient's perception of hypercholesterolaemia and its management, their compliance with lipid-lowering treatment, and personal satisfaction with the treatment.

On commencement of the present study, each physician investigator first completed the physician questionnaire. Consenting patients were then consecutively enrolled and assessed. Each participating patient completed the patient questionnaire before undergoing the assessment. On assessment, each patient's data were entered into the individual CRF. An overnight fasting blood sample was taken for determination of blood glucose and lipid (total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides) concentrations. The biochemical analysis was performed at the local laboratory in individual hospitals. The cardiovascular risk profile of each patient was determined based on criteria set by the updated 2004 NCEP ATP III guidelines[7].

Endpoints

The primary endpoint was the LDL-C goal attainment rate, defined as the proportion of patients on lipid-lowering treatment achieving their respective therapeutic LDL-C goals. The secondary endpoint was the LDL-C goal attainment rate in primary and secondary prevention patients and patients with metabolic syndrome. Additional endpoints included the percentage of patients in different CHD risk groups achieving LDL-C goals, attainment of LDL-C goals according to individual CHD risk factors, LDL-C goal attainment according to lipid-lowering drug type, determinants of lipid-lowering drug prescription and goal attainment and follow-up treatment of patients not achieving LDL-C targets.

Statistical analysis

Sample size was determined to ensure that the proportion of subjects reporting on the primary endpoint should be estimated with sufficient precision, overall and on a by-country basis, to represent the heterogeneity of the population. Accordingly, the authors determined that a sample size of 850 patients was sufficient to ensure that the proportion of subjects reporting on the primary endpoint could be estimated with the width of 95% confidence intervals (CIs) between $\pm$ 2.4 and $\pm$ 3.4%. The analyses were performed on 847 consenting patients from the seven study sites who completed the present study and whose attending physicians completed and returned the physician's questionnaire. Descriptive statistics, including frequency distributions, medians, means and standard deviations, were used to describe demographics data, anthropometric measurements, and concentrations of total cholesterol, LDL-C, HDL-C and triglycerides. In the analysis of the primary outcome variable (*i.e.* dichotomized results 'yes/no' in individual patients with regard to achievement of the LDL-C goals defined by the 2004 updated NCEP ATP III guidelines[7], the percentage of patients achieving the LDL-C goals, together with the 95% CI was presented. Exploratory analysis was done to determine factors affecting achievement of LDL-C goals in individual patients. Factors to be identified were grouped into two categories, patient determinants and physician determinants. For patients, these included the 17 questions on metabolic syndrome and individual components, risk category, type of therapy, previous lipid profile, duration since drug initiation and reason for prescribing current lipid-lowering drugs. For physicians, these included the 23 on age, gender, years of practice and specialization. Patient factors were screened in a univariate analysis by means of logistic model analysis, and physician factors were screened in a univariate analysis by means of generalized linear mixed model (GLMM) analysis with a random effect of physician using the NLMIXED procedure of the SAS system. In these univariate analyses, the response variable was the achievement of LDL-C goals. The factors that proved to be significant ($p < 0.01$) in the univariate analysis were then further evaluated in a multivariate analysis by means of GLMM approach for their possible association with the outcome (attainment of the set LDL-C goal). Factors were chosen

and added to the model one by one at each step until no factors with a p-value < 0.01 remained. For the final models, the estimated odds ratio (OR) with associated 95% CI and p-value for each effect were provided. In this analysis, the adjustment of the multiplicity of statistical testing was not made because this analysis was exploratory. The association between follow-up plan when patients were not at treatment goal and the potential predictor variables (patient determinants) for the primary endpoint was evaluated. For categorical variables, cross-tables were produced. For continuous variables, descriptive statistics were calculated for each category of the follow-up plan.

Results

Twenty-seven physicians from seven study centers in Thailand enrolled 909 hypercholesterolemic patients, in which 847 (93.2%) of them can be statistically evaluated for the study end points.

Demographics characteristics of patients

Demographics and patients characteristics are shown in Table 1. Among 847 patients who were studied, 439 (51.8%) were female. Their mean age was 63.5 $\pm$ 10.8 years. Their body mass index (BMI) was most categorized as obesity with the BMI of $\geq$ 25 km/m^2 (58.4%). Their mean waist circumference was 94.18 $\pm$ 10.87 cm. Seventy patients (8.3%) were smokers. Regarding the cardiovascular risk factors that are shown in Table 2, 799 (94.3%) have hypertension which is the most prevalent risk factors for this group of subjects. Other risk factors found were low HDL-C (< 40 mg/dL in both men and women; 21.6%), family history of premature coronary heart disease (15.2%), and older age (men $\geq$ 45, women $\geq$ 55 years; 90%). The "negative" risk factor, HDL-C level of > 60 mg/dl, was found in 7.2% of the patients. For the high risk category which included CHD or CHD risk equivalents, the most prevalent factor is diabetes (58.9%) followed by CHD (29.3%), multiple risk factors with 10-year risk for CHD > 20% (8.3%), carotid artery disease (5.8%), peripheral arterial disease (1.1%) and abdominal aortic aneurysm (0.5%). Seventy-four percent of patients presented with fulfilling criteria of metabolic syndrome, in which blood pressure criteria is the most prevalent metabolic syndrome component (83.1%). Other metabolic syndrome component included abdominal obesity in 80.2%, hypertriglyceridemia in 48.6%, low HDL-C (< 40 mg/dl in men, < 50 mg/dl in women) in 46.3% and hyperglycemia in 71.5% of the patients. Overall, the proportion of patients with fulfilling criteria of very high-risk category whose LDL-C goal < 70 mg/dl was 31.1% (Fig. 1).

Patients' attitude to hypercholesterolemia

During the patients' visits, about third-quarter of them informed that they were told about cholesterol level and target LDL-C (74.3% and 79.8%, respectively).

Table 1. Anthropometric measurement data of study participants

Characteristics	Number of responses	Mean (SD)
Age (years)	847	63.50 (10.8)
Weight (kg)	847	66.99 (13.13)
Height (cm)	847	159.80 (8.7)
BMI (kg/m^2)	847	26.17 (4.50)
Waist circumference (cm)	846	94.18 (10.87)
SBP (mmHg)	846	135.20 (17.5)
DBP (mmHg)	847	78.00 (11.1)

Data are means $\pm$ SD
BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 2. Clinical characteristics of study participants

Characteristics	Number of responses	Prevalence (%)
Presence of CHD risk factors		
Cigarette smoking	847	8.3
Hypertension	847	94.3
Low HDL-cholesterol	844	21.6
Family history of premature CHD	847	15.2
Age (men $\geq$ 45 years; women $\geq$ 55 years)	847	90.0
Negative CHD risk factors		
High HDL-cholesterol	843	7.2
Presence of CHD or CHD risk equivalents		
Coronary heart disease	845	29.3
Peripheral arterial disease	846	1.1
Carotid artery disease	846	5.8
Abdominal aortic aneurysm	845	0.5
Diabetes	845	58.9
Multiple risk factors with 10-yr risk for CHD > 20%	836	8.3
Presence of metabolic syndrome	846	74.0
Fulfilling the criteria for very high-risk category	847	31.6

When they were first diagnosed with high cholesterol, nearly all of them (99.5%) were advised to change their lifestyle or prescribed lipid lowering drugs. After starting drugs therapy, 44.3% of the patients experienced increased dosage or switching to other drugs. On compliance, 40.8% of the patients agreed that they sometimes forgot to take their drugs with most of them (60.9%, n = 229) reported that they only forgot less than once a month, 15.2% (n = 57) forgot once every two weeks, 13.6% (n = 51) forgot once a week, and 10.4% forgot more than once a week. It is noted that the majority of them were satisfied with the level of information available to them about their lipid levels and nearly all of them satisfied about the way their cholesterol were treated.

Demographics and practice characteristics of physicians

Among 27 physicians, 19 (70.4%) of them were males. The mean age was 42.8 $\pm$ 6.2 years and they had been practicing for an average duration of 16.4 $\pm$ 6.3 years (range 7-30 years). These study physicians consisted of 12 (44.4%) Cardiologists, six (22.2%) Endocrinologists and nine (33.3%) other physicians. All physicians used LDL-C to set individual treatment target. Other lipid profile used to set the treatment target included total cholesterol in 51.9%, HDL-C in 66.7%, and triglyceride in 66.7% of the study physicians. Responses from 26 physicians reported that all of them used NCEP ATP III guidelines, with three (11.5%) using the National guidelines, three (11.5%) using local healthcare authority guidelines or recommendations, two (7.7%) using Joint European guidelines (SCORE), and two (7.7%) individual practice guidelines.

Lipid-lowering therapy

Therapeutic LDL-C cholesterol level according to 2004 updated NCEP ATP III guideline is shown in Fig. 1. Overall, the prevalence of patients whose LDL-C goal level was set at 70, 100 and 130 mg/dl were 31.1%, 45.0% and 23.9% respectively. None of them was set LDL-C goal at 160 mg/dl. In 842 corresponding patients on lipid-lowering therapy, objective for primary prevention was applied in 511 (60.7%) patients and 331 (39.3%) patients for secondary prevention. Regarding current lipid-lowering drug treatment, 728 (86.2%) patients were on a single drug (monotherapy). Of 728 patients, 699 (82.7%) were on statins. The most prescribing drug among those received statin monotherapy was simvastatin (51.0%), of which 77.6% the dosage prescribed was $\leq$ 20 mg/day. Other statins used were atorvastatin (25.4%) of which 54.6% the dosage used was $\leq$ 10 mg/day and rosuvastatin (16.8%) of which 86.9% the dosage used was $\leq$ 10 mg/day (Fig. 2). Others using monotherapy were on fibrate (2.8%) and other monotherapy (0.6%). Only 117 (13.8%) patients were on multiple lipid lowering drugs. Nearly all combination treatment was statins plus another lipid lowering drug with 53.0% received statins plus fibrate and 36.8% received statins plus ezetimibe. Overall, the majority of subjects received statin (96.4%) and the mean duration since drugs initiation was 4.3 $\pm$ 3.3 years.

Lipid-lowering drugs outcomes

The lipid values prior to lipid-lowering drugs initiation included total cholesterol, LDL-C, HDL-C

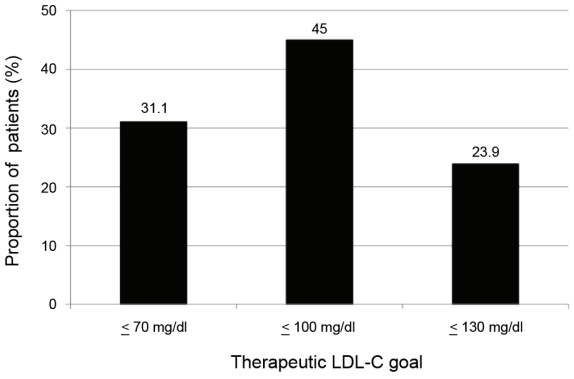

Fig. 1 Proportion of study patients with different therapeutic LDL-C goal

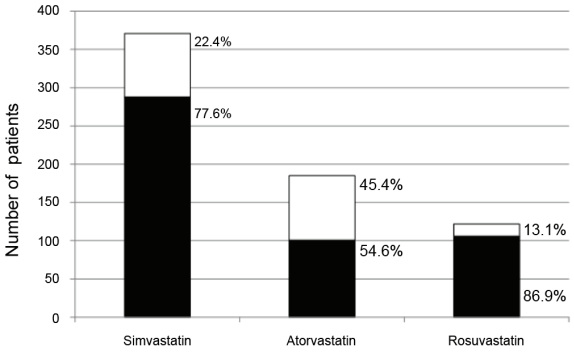

Fig. 2 Number of patients treated with statin monotherapy; ■ simvastatin $\leq$ 20, atovastatin $\leq$ 10, or rosuvastatin $\leq$ 10 mg/day; □ simvastatin > 20, atorvastatin > 10, or rosuvastatin > 10 mg/day

and triglyceride were 239.6 ± 53.8 mg/dl (n = 520), 154.7 ± 43.0 mg/dl (n = 436), 46.6 ± 12.5 mg/dl (n = 459) and 194.6 ± 126.0 mg/dl (n = 506), respectively. After patients had been on treatment with lipid lowering drugs, the mean levels of total cholesterol, LDL-C and triglyceride decreased significantly ($p < 0.001$ for all) while that of HDL-C increased slightly with no statistically significant difference from the pre-treatment level ($p = 0.226$, Fig. 3). The post-treatment lipid levels were 165.6 ± 35.6 (n = 842), 98.6 ± 29.5 (n = 847), 47.6 ± 12.9 (n = 838) and 144.0 ± 76.0 (n = 832) for total cholesterol, LDL-C, HDL-C and triglyceride, respectively (Table 3, Fig. 3). When analysis performed according to LDL-C target, the average pre- and post-treatment total cholesterol, LDL-C and triglyceride levels were similar in those with different LDL-C goals ($p > 0.05$ by ANOVA) but HDL-C level significantly improved in those at lower risk (Table 3). Of note, the mean LDL-C in high-risk group of which the LDL-C goal was < 70 mg/dl were 148.7 ± 47.6 and 96.3 ± 32.2 mg/dl for pre- and post-treatment values, respectively.

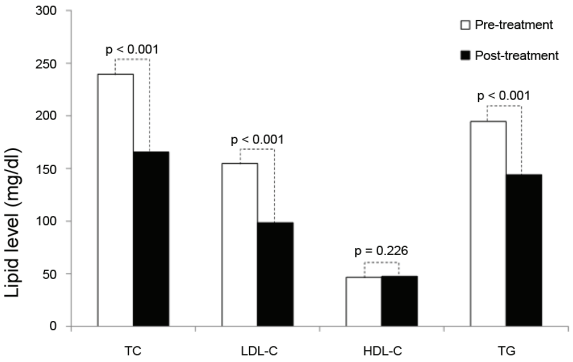

Fig. 3 Pre- and post-treatment lipid levels for the total patients studied

The predictors for achievement of LDL-C goals according to 2004 updated NCEP ATP III guideline was shown in Table 4. Overall, 52.7% of patients reached their LDL-C goal. Concerning each LDL-C goal, 84.7%, 60.6%, and 16.7% of patients achieved LDL-C target at 130, 100, and 70 mg/dl,

Table 3. Comparison of pre- and post-treatment lipid profiles

Lipid	n+	Pre-treatment level mean (SD)	Post-treatment level mean (SD)	Difference mean (SD)	p-value
Total study population*					
Total cholesterol	518	239.7 (53.8)	168.2 (37.0)	-71.5 (54.2)	<0.0001
LDL-C	436	154.7 (43.0)	100.1 (30.8)	-54.6 (44.6)	<0.0001
HDL-C	455	46.6 (12.5)	48.1 (13.2)	1.4 (13.3)	0.0226
TG	506	194.6 (126.0)	146.6 (75.7)	-47.9 (116.0)	<0.0001
Total cholesterol**					0.6140
LDL-C goal < 70	151	230.6 (55.1)	162.5 (36.1)	-68.1 (53.6)	
LDL-C goal < 100	225	238.9 (49.3)	165.1 (36.5)	-73.7 (52.0)	
LDL-C goal < 130	141	250.2 (57.5)	179.1 (36.8)	-71.1 (58.0)	
LDL-C**					0.6750
LDL-C goal < 70	130	148.7 (47.6)	96.3 (32.2)	-52.4 (49.5)	
LDL-C goal < 100	194	154.5 (37.7)	98.0 (31.0)	-56.5 (40.6)	
LDL-C goal < 130	111	161.4 (44.9)	108.2 (27.4)	-53.2 (45.2)	
HDL-C**					0.0018
LDL-C goal < 70	136	45.6 (11.9)	45.4 (11.9)	-0.3 (12.1)	
LDL-C goal < 100	203	47.3 (12.9)	47.8 (13.6)	0.5 (13.1)	
LDL-C goal < 130	115	46.3 (12.1)	51.5 (13.4)	5.2 (14.3)	
TG**					0.4221
LDL-C goal < 70	148	188.5 (106.8)	149.1 (78.7)	-39.4 (98.8)	
LDL-C goal < 100	223	200.5 (111.9)	145.4 (73.7)	-55.1 (109.6)	
LDL-C goal < 130	134	191.8 (163.2)	146.7 (76.2)	-45.2 (141.6)	

* Comparison of pre-treatment and current levels of lipid profiles by paired t-test

** Comparison of pre-treatment and current lipid profiles among three risk groups by analysis of variance (ANOVA)

+ Number of responses

Table 4. Predictors of achievement of LDL-C goals

Characteristics	n+	Odds ratio	95% CI	p-value
Age (compared to < 40 years)	847			0.099
40-54		0.36	0.11-1.19	
55-69		0.51	0.16-1.64	
≥ 70		0.40	0.12-1.31	
Female sex	847	1.54	1.18-2.03	0.002
BMI (compared to < 25 kg/m^2)	847			0.487
25 to < 30		0.92	0.68-1.23	
≥ 30		0.79	0.53-1.17	
CHD risk factor				
Cigarette Smoking	847	0.57	0.35-0.94	0.028
Hypertension	847	1.02	0.57-1.84	0.935
Low HDL-cholesterol	844	0.80	0.58-1.11	0.183
Family history of premature CHD	847	1.12	0.77-1.63	0.557
Age (Men ≥ 45 years; Women ≥ 55 years)	847	0.94	0.60-1.47	0.776
Negative risk factor: high HDL-cholesterol	843	1.65	0.96-2.83	0.07
CHD or CHD risk equivalent				
Coronary Heart Disease	845	0.14	0.10-0.20	<0.01
Peripheral Arterial Disease	846	0.45	0.11-1.80	0.257
Carotid Artery Disease	846	0.38	0.20-0.70	0.002
Abdominal aortic aneurysm	845	0.30	0.03-2.88	0.296
Diabetes	845	0.59	0.45-0.78	<0.001
Multiple risk factors with 10-yr risk for CHD > 20%	836	0.55	0.33-0.90	0.018
Metabolic syndrome	846	0.51	0.37-0.69	<0.001
Secondary prevention	842	0.30	0.22-0.40	<0.001
Lipid lowering treatment: non-statin versus statin	845	0.68	0.33-1.41	0.301
LDL-Cholesterol before treatment	436	0.99	0.99-1.00	0.003

+ number of responses

respectively. Increasing age was not associated with LDL-C goal attainment while women were more likely to achieve LDL-C goal compared to men. Regarding CHD risk factors, cigarette smoking was a significant negative predictor of LDL-C goal achievement. Only 40% of patients who smoked achieved LDL-C target, compared to 53.8% of those who did not (p = 0.028). Patients whose aim of treatment was secondary prevention were less likely to achieve their treatment goal compared to those who needed primary prevention (p < 0.001). Other factors associated with less favorable LDL-C goal achievement were coronary heart disease, carotid artery disease, diabetes, 10-year risk of > 20%, metabolic syndrome and higher pre-treatment LDL-C (p < 0.05 for all). The choices of lipid lowering drug used, whether considered as specific agents or as classes, or comparing monotherapy versus combination therapy, were not significantly associated with LDL-C goal attainment. In particular, choices of statins used which included rosuvastatin, atorvastatin, fluvastatin, pravastatin, and simvastatin, were not associated with LDL-C goal attainment (p = 0.906), as well as the dosage of each lipid lowering drug used (p = 0.458). Regarding patient's and physician's attitude and practice towards dyslipidemia treatment, for example, patient's forgetfulness in taking their medication and the treatment guideline of which physicians used, were not significantly associated with LDL-C goal attainment (data not shown).

Discussion

The present study collected information on 847 Thai hypercholesterolemic patients with a primary objective to assess their achievement on LDL-C goal based on NCEP ATP III guideline. It is interesting that nearly half of the patients did not attain target LDL-C despite receiving lipid lowering drugs for many years. This result is worrisome because it shows that about half of the patients at risk for atherosclerotic cardiovascular disease were not adequately treated to

reduce their risk. In particular, those having high risk inversely achieved LDL-C goal. For instance, only 16.7% of very high risk patients whose LDL-C goal of less than 70 mg/dl succeeded to have LDL-C on target, compared to 84.7% in those whose LDL-C goal was less than 130 mg/dl. Furthermore, patients who had very high risk factors, CHD and CHD equivalent (carotid artery disease, diabetes, 10-year risk of > 20%) had significantly less favorable chance of attaining LDL-C goal. This could be implied that the more risk they had for cardiovascular disease, the less chance they would succeed in hypercholesterolemia control. The present result is consistent with other LDL-C goal achievement studies. A multicenter study from the United States (The Lipid Treatment Assessment Project; L-TAP) found that only 38% of patients achieved NCEP recommended LDL-C target levels[9]. In addition, a result from their second project (L-TAP2) in nine countries, which included two countries from Asia (Korea and Taiwan), showed that the proportion of patients achieving LDL-C goals according to relevant national guidelines ranged from 47% to 84% across the study countries, with 83.5% and 65.9% LDL-C goal attainment rate for Korea and Taiwan, respectively[10]. The LDL-C goal attainment rate was higher in LTAP2 than in LTAP and in the present study, however, those who were at higher risk had a consistently lower attainment rate compared to those at lower risk in all studies. In Europe, a study in 12 countries from the third European Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE III) showed that only 30.6% of patients on lipid lowering medication had reached their total cholesterol goals[11]. In Asia, the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study in six countries included China, Korea, Malaysia, Singapore, Taiwan and Thailand showed that 48% of the patients achieved ATP III targets for LDL-C, with only 38% of those with CHD or diabetes achieved the goal compared to 62% and 81% goal achievement in those with moderate and low risks, respectively[12]. The present study recruited patients who recently received statin monotherapy. This differs from the study that included patients who have been treated for a mean duration of 4.3 ± 3.3 years with various types of drug therapy. Furthermore, the present study found a higher proportion (52.7%) achieving their LDL-C goal. Compared to another study, LTAP-II Thailand[8], the present study subjects were older (58.6 and 63.5 years, respectively) and included the very high risk subjects whose LDL-C goal of less than 70 mg/dl which, consistent with other studies, were less likely to achieve LDL-C goal. This might explain in part the lower prevalence of LDL-C goal attainment found in our study. In addition, this is the first study in Thailand that evaluates very high-risk patients' LDL-C goal attainment, which should be lower than 70 mg/dl. The lower attainment rate in the higher risk group might be from lower LDL-C level set in each risk category, i.e. 70 mg/dl for the very high-risk compared to 130 mg/dl for the moderate risk. Considering the effect of lipid lowering drug, the initial starting dose is generally able to reduce LDL-C by 40% to 60% from the baseline level and if the target is not achieved, the 2-fold increase in dosage usually results in about 6% to 7% additional reduction[13]. Therefore, the very low target is more difficult to achieve. Moreover, the pre-treatment LDL-C levels in the present study patients were similar among the different risk groups, *i.e.* 148.7 ± 47.6, 154.5 ± 37.7 and 161.4 ± 44.9 mg/dl for those whose LDL-C goal < 70, < 100 and < 130 mg/dl, respectively ($p > 0.5$). In addition, the reduction after treatment were achieved in similar magnitude resulting in post treatment LDL-C levels of > 90 mg/dl for all groups which was not sufficient for those at very high-risk. This finding underscores the need for more aggressive treatment especially in the very high risk patients. The present study also found that those who smoked were less likely to achieve LDL-C goal. Besides low HDL-C, cigarette smoking was found to be associated with high LDL-C and might have a dose-response relationship[14,15]. Smoking may interfere with lipid metabolism by promoting central adiposity and insulin resistance. Moreover, smoking stimulates sympathetic nervous system which promotes the release of free fatty acid, however, lipoprotein lipase activity is not stimulated due to insulin resistance caused by smoking thus the circulating level of triglyceride is increased. This causes excess very low-density lipoprotein cholesterol (VLDL-C) production, which consequently provides precursor for LDL-C formation[16] and might explain the lower chance in achieving the LDL-C goal for the present subjects who smoked.

Other factors that might affect the attainment rate, for example, choices of lipid lowering drugs and the dosage used, were not significantly associated with LDL-C goal attainment in our study. This could be explained from variation in the patients' baseline lipid levels and responses to the treatment and thus the physicians had to justify the option of treatment accordingly. Another explanation is that the present

study used the cross-sectional design, the different effect of various lipid lowering agents on lipid profile would be better demonstrated by other study design such as cohort or randomized-control study. Although all physicians reported that they followed treatment guidelines especially the NCEP-ATP III recommendation in treating their patients, however, only about half of the patients were able to attain their LDL-C goal. The present study found that most of the patients were treated with low to moderate dose of statins, *i.e.* 86.9% of those on simvastatin had been treated with the dosage of $\leq$ 10 mg/day. Moreover, 55.6% of the patients had been on the same lipid drug since the start of treatment without any change in dosage or switching to other drug. Therefore, more aggressive treatment on dyslipidemia such as increment in dosage or switching to more potent drug is needed for optimization of LDL-C level then the risk for cardiovascular risk would be more appropriately reduced. The patients' factors such as attitude on lipid lowering treatment and compliance were also not associated with attainment rate. However, this part of the present study was performed by interview and therefore recall or reporting bias might occur. About 60% of the subjects accepted that they forgot to take their medication once a month or less and this result could be underreported. Moreover, substantial number of patients accepted that they sometimes forgot taking their medication with 10% of them forgot more than once a week. The most common prescribed statin in this study was simvastatin, of which plasma half-life is only 2 to 3 hours[17]. Therefore, frequency of missing doses may affect the plasma level of simvastatin and resulted in inadequate lowering of LDL-C.

The present study found that the negative predictors for achieving LDL-C goal are cigarette smoking, coronary heart disease, carotid artery disease, diabetes, 10-year risk for cardiovascular disease of > 20% and having metabolic syndrome. These results are comparable to the finding from the Centralized Pan-European survey on the under-treatment of hypercholesterolemia (CEPHEUS) study[18], which identified normal body mass index, not smoking, not having metabolic syndrome as positive predictors. The CEPHEUS study also found that being on statin therapy, good treatment compliance and high awareness of one's own LDL-C levels were associated with higher chance for LDL-C goal attainment which were different from finding in Thai subjects. Regarding statin therapy, 96.4% of Thai patients received this class of lipid lowering agent, therefore, comparison of statin with non-statin treatment may not be possible. On compliance and awareness of LDL-C levels, the present patients as a whole might underreport non-adherence or might not be informed enough about the significance of this problem.

Conclusion

The CEPHEUS-Thailand study demonstrated the current dyslipidemia treatment situation in Thailand of which substantial proportion of patients, especially those who were at very high risk, were not able to achieve their therapeutic LDL-C goal. The authors suggest more aggressive treatment for dyslipidemic Thai patients in order to reduce the risk for development of future cardiovascular disease. The option for treatment may be either prompt dosage adjustment of current lipid lowering drug used or consideration of more potent lipid lowering agent if response to initial pharmacologic treatment is not adequate. In addition, stress on patient's drug compliance and advice for patients to quit smoking should not be neglected because these factors may affect patients' lipid profiles and alter overall cardiovascular risk.

Potential conflicts of interest

None.

References

1. Health Information Unit, Bureau of Health Policy and Strategy, Ministry of Public Health of Thailand. Public health statistics [Internet]. 2007-2009 [cited 2011 Mar 16]. Available from: http://bps.ops.moph. go.th/Healthinformation/
2. Health Information Unit, Bureau of Health Policy and Strategy, Ministry of Public Health of Thailand. Public health statistics [Internet]. 2005-2009 [cited 2011 Mar 16]. Available from: http://bps.ops.moph. go.th/Statistic/2.3.4-52.pdf
3. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 1994; 308: 367-72.
4. Rosenson RS. Statins: can the new generation make an impression? Expert Opin Emerg Drugs 2004; 9: 269-79.
5. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425-35.
6. Executive summary of the third report of the

National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.
7. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-39.
8. Nitiyanant W, Sritara P, Deerochanawong C, Ngarmukos P, Koanantakul B. Lipid treatment assessment project II in Thailand (LTAP-II Thailand). J Med Assoc Thai 2008; 91: 836-45.
9. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000; 160: 459-67.
10. Waters DD, Brotons C, Chiang CW, Ferrieres J, Foody J, Jukema JW, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. Circulation 2009; 120: 28-34.
11. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Reiner Z, et al. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. Eur J Cardiovasc Prev Rehabil 2010; 17: 530-40.
12. Kim HS, Wu Y, Lin SJ, Deerochanawong C, Zambahari R, Zhao L, et al. Current status of cholesterol goal attainment after statin therapy among patients with hypercholesterolemia in Asian countries and region: the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study. Curr Med Res Opin 2008; 24: 1951-63.
13. Stein EA, Black DM. Lipoprotein changes with statins. Curr Atheroscler Rep 2002; 4: 14-8.
14. Mammas IN, Bertsias GK, Linardakis M, Tzanakis NE, Labadarios DN, Kafatos AG. Cigarette smoking, alcohol consumption, and serum lipid profile among medical students in Greece. Eur J Public Health 2003; 13: 278-82.
15. Meenakshisundaram R, Rajendiran C, Thirumalai-kolundusubramanian P. Lipid and lipoprotein profiles among middle aged male smokers: a study from southern India. Tob Induc Dis 2010; 8: 11.
16. Campbell SC, Moffatt RJ, Stamford BA. Smoking and smoking cessation—the relationship between cardiovascular disease and lipoprotein metabolism: a review. Atherosclerosis 2008; 201: 225-35.
17. Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation 2004; 109: III50-III57.
18. Park JE, Chiang CE, Munawar M, Pham GK, Sukonthasarn A, Aquino AR, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS Pan-Asian survey. Eur J Cardiovasc Prev Rehabil 2011 Mar 7. doi: 10.1177/1741826710397100

การสำรวจการรักษาโคเลสเตอรอลในเลือดสูงไม่ได้ผลตามเป้าหมาย

อภิชาต สุคนธสรรพ์, มยุรี หอมสนิท, บัณฑิต พรหมเมศร์, ชุณหเกษม โชตินัยวัตรกุล, ชุมพล เปี่ยมสมบูรณ์, ครรชิต ลิขิตธนสมบัติ

ภูมิหลัง: *โรคหัวใจและหลอดเลือดที่เกิดจากภาวะหลอดเลือดแดงแข็งเป็นสาเหตุที่สำคัญของการเสียชีวิตและความพิการของประชากรในประเทศไทย ปัจจัยเสี่ยงที่สำคัญของภาวะนี้คือ LDL-cholesterol (LDL) ซึ่งสามารถให้การรักษาได้โดยการปรับพฤติกรรมการบริโภคอาหารและการออกกำลังกายรวมถึงการใช้ยาลดไขมัน ผลของการรักษาด้วยยาเพื่อลดระดับไขมันในเลือดให้ได้ตามเป้าหมายจำเป็นต้องได้รับการศึกษาเพิ่มเติม การศึกษานี้จึงดำเนินขึ้นเพื่อศึกษาผลของการรักษาด้วยยาลดไขมันให้ได้ตามเป้าหมายในประชากรไทยที่มีความเสี่ยงต่อการเกิดโรคหัวใจและหลอดเลือด*

วัสดุและวิธีการ: *แพทย์ 27 ราย และผู้ป่วย hypercholesterolemia ซึ่งได้รับการรักษาจากแพทย์ 27 รายนี้จำนวน 909 ราย ที่มีอายุตั้งแต่ 18 ปีขึ้นไป และได้รับยาลดไขมันเป็นเวลาอย่างน้อย 3 เดือน โดยไม่มีการปรับขนาดยาเป็นเวลาอย่างน้อย 6 สัปดาห์ จากสถานพยาบาล 7 แห่ง ในประเทศไทยได้เข้าร่วมการศึกษา ผู้ป่วยได้รับการตรวจระดับ plasma glucose, total cholesterol, LDL, HDL และ triglyceride ภายหลังงดอาหารข้ามคืน และได้รับการสัมภาษณ์ข้อมูลพื้นฐานและข้อมูลอื่น ๆ ที่เกี่ยวข้องรวมถึงประวัติการใช้ยาลดไขมัน ความตระหนัก และความรู้ของผู้ป่วยต่อการรักษา การปฏิบัติตามคำแนะนำ และความพึงพอใจของผู้ป่วยได้รับการประเมินโดยแบบสอบถาม เช่นเดียวกับการใช้แนวทางการรักษาของแพทย์ทางเลือกในการรักษา การตั้งเป้าหมายในการลดไขมัน และทัศนคติของแพทย์ต่อการรักษาภาวะไขมันในเลือดสูง ความเสี่ยงต่อการเกิดโรคหัวใจและหลอดเลือด และระดับ LDL เป้าหมายได้รับการประเมินโดยแนวทางการรักษาภาวะไขมันในเลือดผิดปกติโดย updated 2004 NCEP-ATP III guidelines*

ผลการศึกษา: *ผู้ป่วยทั้งหมดในการศึกษานี้มีระดับ LDL เป้าหมายต่ำกว่า 130 mg/dl โดยที่ร้อยละ 86.1 ต้องการ LDL เป้าหมายต่ำกว่า 100 mg/dl เมื่อพิจารณาผู้ป่วยทั้งหมดพบว่าผู้ป่วยร้อยละ 52.7 สามารถมีระดับ LDL ต่ำกว่าเป้าหมาย ยาลดไขมันที่ใช้มากที่สุดได้แก่การใช้ statin ชนิดเดียว (ร้อยละ 82.7) ผลการรักษาที่ได้ LDL ตามเป้าหมายมีความสัมพันธ์ผกผันกับระดับ LDL เป้าหมายที่กำหนดโดย NCEP-ATP III ตามปัจจัยเสี่ยงของผู้ป่วย โดยเพียงร้อยละ 16.7 ของผู้ที่มีความเสี่ยงสูงซึ่ง LDL ควรต่ำกว่า 70 mg/dl มีระดับ LDL ไม่เกินเกณฑ์ดังกล่าว ร้อยละ 60.6 และร้อยละ 84.7 ของผู้ที่ LDL ควรต่ำกว่า 100 และ 130 mg/dl มีระดับ LDL ไม่เกินเกณฑ์ดังกล่าว ตามลำดับ ($p < 0.001$) ปัจจัยอื่น ๆ ที่สัมพันธ์กับผลการรักษาที่ไม่ได้ระดับ LDL ตามเป้าหมายได้แก่ coronary heart disease, carotid artery disease, เบาหวาน, ความเสี่ยงต่อโรคหัวใจและหลอดเลือดใน 10 ปีข้างหน้า มากกว่าร้อยละ 20, และกลุ่มอาการเมตะบอลิก ($p < 0.05$ สำหรับทุกปัจจัย) ชนิดของยาลดไขมันที่ใช้ไม่สัมพันธ์กับผลการรักษาที่ได้ระดับ LDL ตามเป้าหมาย*

สรุป: *ผู้ป่วยไทยจำนวนมากยังไม่สามารถได้รับการรักษาจนได้ระดับ LDL ตามเป้าหมาย โดยเฉพาะอย่างยิ่งในกลุ่มผู้ที่มีความเสี่ยงสูงต่อการเกิดโรคหัวใจและหลอดเลือด ถึงแม้จะมีแนวทางในการรักษาและมียาลดไขมันที่ประสิทธิภาพสูงผู้ป่วยจำนวนมากก็ยังพลาดโอกาสที่จะได้รับการควบคุมปัจจัยเสี่ยงอย่างมีประสิทธิภาพ การปรับการรักษาอย่างเหมาะสมทั้งทางด้านแพทย์ และผู้ป่วยจึงมีความจำเป็นเพื่อที่จะให้ได้คุณภาพของการรักษาที่ดีขึ้น*