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Chapter

Prevalence of Dyslipidemia and Goal Attainment with Lipid-Lowering Therapy: Insights from Thai Multicenter Study and Overview of the Major Guidelines

Songkwan Silaruks, Charn Sriratanasathavorn, Petch Rawdaree, Rapeephon Kunjara-Na-Ayudhaya, Bandit Thinkhamrop and Piyamitr Sritara

Abstract

Background Since the release in Thailand in 2001 of the Third Guidelines by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults or the Adult Treatment Panel (ATP III), there have been no nationwide studies on the proportion of dyslipidaemic patients who have achieved the low-density lipoprotein cholesterol (LDL-C) goals. The authors therefore aimed to estimate the percentage achievement of LDL-C goals based on the modified NCEP ATP III guidelines in intermediate- to high-risk patients. Methods The authors conducted a hospital-based, cross-sectional, epidemiological survey. Patients (1240) were selected consecutively from 50 hospitals across Thailand. Patients were included if they had been treated with statins for at least 3 months. Results Two-thirds were female, and the mean age was 61.7+69.5 years. The median duration of statin treatment was 21 months. Half (633/1240) of the patients achieved the LDL-C goal levels as defined by the NCEP guidelines (51.1%, 95% CI 48.3% to 53.8%). The very high-risk group had the lowest percentage achievement (11.6%; 95% CI 1.6% to 21.6%), compared with 54.2% (95% CI 50.9% to 57.4%) for the high-risk group and 47.0% (95% CI 41.1% to 52.8%) for the moderate-risk group. More males achieved the LDL-C goals than females (55.6% vs. 48.9%; P = 0.029). Conclusions Overall, 51.1% of the patients with cardiovascular risk, on statins treatment, achieved the NCEP ATP III LDL-C goal levels.

Keywords: dyslipidemia, goal attainment, Thailand

1. Introduction

Dyslipidemia is a major risk factor for the development of atherosclerotic disease. Therefore, lifestyle interventions and pharmacological approaches to decrease

cholesterol are widely used in cardiovascular disease prevention. The introduction and widespread use of 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) for individuals at risk of atherosclerotic disease has been an important advance in cardiovascular care [1].

Since 1993, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP) has periodically updated the treatment guidelines which identify LDL-C as a cause of CHD and the primary aim for diagnosis and treatment of hypercholesterolaemia [1–3].

In 2001, the recommendations were released in the Third ATP Report (NCEP ATP III) [3] which reaffirmed the risk of CHD from increased LDL-C, the benefit of LDL-C-lowering therapy and maintaining intensive treatment of patients with CHD. The report also added a call for more intensive LDL-C-lowering therapy as the primary aim for patients with a CHD risk equivalent.

There can be no doubt that better control of dyslipidemia, even in subjects whose low-density lipoprotein cholesterol level is not particularly high, has reduced overall event rates. On a background of lifestyle interventions, statins are routinely used to decrease risk along with aspirin and interventions to control hypertension and diabetes. The efficacy of statins in atherosclerotic conditions, particularly in the treatment and prevention of CHD, has been well established [4]. Large-scale, randomized, prospective trials involving patients with CHD have shown that statins reduce the clinical consequences of atherosclerosis, including cardiovascular-related deaths, non-fatal MI and stroke, hospitalization for acute coronary syndrome and heart failure, as well as the need for coronary revascularization [5–7].

2. Clinical practice

Although the guidelines have been widely available, achieving the lower LDL-C goals in practice has been suboptimal. In a US study, only 38% of 4888 patients under primary care in five regions achieved the LDL-C target levels [8]. The respective success rates were 68% and 37% in the low- and high-risk groups. Only 18% of the patients with established CHD with the highest risk of future CHD events achieved the lower LDL-C targets. Another study, based on the records of 461 patients in rural areas, covering all risk levels from four practices, found that only 54% of dyslipidaemic patients achieved the NCEP ATP III goals [9]. In 1998, a survey in Thailand assessing the achievement of LDL-C goals in high-risk patients indicated an unsatisfactorily low percentage of 39.2% [10]. The most recent nationwide survey was conducted between December 2002 and June 2003 [11]. The study involved 1921 patients from 48 hospitals across Thailand. Percentage achievements of LDL-C targets in the CHD and CHD equivalents, high-, and low-risk group were 34.6, 56.4 and 76.8%, respectively [11]. In 2004, several changes were made to the guideline, released as the Modified NCEP ATP III in that year [12]. There has, however, been no recent nationwide study in Thailand investigating the proportion of dyslipidemia patients who have achieved the updated LDL-C goals.

3. Clinical practice in Thailand

In our study [13], we conducted a hospital-based, cross-sectional, epidemiological survey and retrospective chart review, in both secondary and tertiary care across Thailand. Our study aimed to estimate the percentage of LDL-C goals achievement

based on the NCEP ATP III guidelines in intermediate- to high-risk patients receiving statins for at least 3 months in clinical practice in Thailand. The data collection was conducted at the selected hospitals between March and July 2008. The primary outcome of this study was the percentage of dyslipidaemic patients on lipid-lowering therapy who had achieved their respective LDL-C target levels as defined by the NCEP ATP III guidelines.

3.1 Number of patients and participating hospitals

There are 95 secondary- and tertiary-care hospitals across Thailand, 50 (52.6%) of which were selected for the study. The number of selected hospitals in each region was proportional to the total number of eligible hospitals in each region (i.e., the North, the Northeast, the South and Central). A total of 1730 patients attending OPD clinics were screened by interviews, and 167 (9.6%) were excluded: 161 not currently treated with statin, five not consented and one not within 20–80 years of age. After the chart review was conducted, a further 323 (20.7%) cases were excluded: 216 treated <3 months before lipid profile became available, 32 lipid profile not available and 75 having not received the same statin before lipid profile became available.

The duration of statin treatment prior to the date of the most recent lipid profile ranged between 3 and 191 months (median 21 months), which represented the period of statin treatment at the time of assessing the treatment outcome.

The high-risk group accounted for the largest number of patients, followed by moderate- and high-risk patient types. The mean age was 61.7 ± 9.5 years, and approximately two-thirds were female. The mean age of each risk group was similar. Overall, the majority of males at risk (94%) were 45 years of age or higher. A similar percentage was seen in each risk group. For females at risk, about three-quarters were aged 55 years or older. Most common cardiovascular risks were diabetes mellitus (66.1%) and hypertension (57.6%).

3.2 Percentage achievement of LDL-C goals for all patients

Among the 1240 patients, 633 achieved the lower LDL-C goals as defined by the NCEP ATP III guidelines (51.1%; 95% CI 48.3% to 53.8%) (**Table 1**). The very high-risk group had the lowest achievement level at about one tenth. The achievement rate varies among regions where the highest achievement rate was 57.4% in the central area, and the lowest achievement rate was 42.6% in the eastern part of the country. On average, the very high-risk patients were about half, 49.7%, to reach the LDL-C target goal.

Patient groups*	Total	Achieved goals	Percentage	95% CI	Mean percentage† to target LDL-C
Very high risk	43	5	11.6	1.6 to 21.6	49.7
High risk	914	495	54.2	50.9 to 57.4	31.8
Moderate risk	283	133	47.0	41.1 to 52.8	9.9
Overall	1240	633	51.1	48.3 to 53.8	27.5

**Very high risk (LDL-C < 70 mg/dl); high risk (LDL-C < 100 mg/dl); moderate risk (LDL-C < 130 mg/dl).*
†Calculated based on the percentage difference between LDL-C level and the target goal among patients who did not achieve the LDL-C target.

Table 1.
Percentage and 95% CIs of low-density lipoprotein cholesterol (LDL-C) achievement goals by patient group.

Males had a statistically higher percentage achievement of the lower LDL-C goals than females (p = 0.024) (**Table 1**). The duration of statin treatment and the statin use, either alone or combined with other regimens, had a similar percentage achievement of lower LDL-C goals.

The final number of subjects included in the analysis was 1240. Initially, the calculated sample size was 1260, of which 20 (1.8%) patients had a statin treatment of <3 months. These were identified after enrolment and excluded from the analysis. This elimination did not, however, affect the study findings, that is, the percentage achievement of LDL-C goals was 52.5% when they were included, compared with 51.1% when they were excluded.

We, thus, included only patients who had been treated for at least 3 months with no maximum limit of treatment duration. The results in **Table 2** indeed suggest that the duration of statin treatment had no effect on the percentage achievement of LDL-C goals, which was about 51% for every interval of 12 months (p = 0.975).

Selected factors	**No**	**Percentage achievement**	**p Value**
Gender			0.029
Male	417	55.4	
Female	823	48.9	
Male by age (years) at risk			0.750
≥45	394	55.6	
<45	23	52.2	
Female by age (years) at risk			0.057
≥55 of age	623	50.7	
<55	200	43.0	
Duration (months) of statin treatment			0.997
3–6	136	50.7	
7–12	245	51.0	
13–24	349	50.4	
25–36	235	51.9	
≥37	275	51.3	
Statins received			0.842
Statins only	1156	51.1	
Statins with other lipid-lowering drugs	84	50.0	
Field of expertise of attending physicians			0.360
Internal medicine	1227	51.2	
Non-internal medicine	13	38.5	
Field of expertise of attending physicians who were in internal medicine			0.598
General	1029	51.2	
Cardiologist	128	53.9	
Endocrinologist, nephrologists or neurologist	67	46.3	

Table 2.
Percentage low-density lipoprotein cholesterol achievement goals by selected factors.

However, there are numerous factors which may confound the goal achievement, including statin dose, potency of statin, culture, socio-economic status, healthcare policy, concomitant medications, etc. Also, the selection bias from selected study sites, which were from diabetes and hypertension clinics even we tried to do the study in various parts of the country. This leads to a higher proportion of high-risk group than general populations.

Our study was based on the availability of lipid profiles of patients measured on request, as per real-life clinical practice; however, there were no significant differences between the percentage achievement of LDL-C goals among patients whose lipid profile was assessed before or after the median of 5.5 months prior to the survey date. This result might indicate that LDL-C levels were underutilized to adjust the treatment.

In our study, the percentage of lowered LDL-C according to goal levels, as defined by NCEP ATP III guidelines, among the high-cardiovascular-risk group, was 51.1% compared with 39.2% in a 1997–1998 study [10] and 34.6% in the 2002–2003 study [14]. The higher percentage found in our study could be due to various reasons: (1) we included only patients who used statins and not any other lipid-lowering agent alone; (2) there has been an increasing focus on the benefits of intensive cholesterol reduction; (3) new and more efficacious statins have been developed; (4) 95% of the patients in our study were attended by specialists who might be more likely to adhere to the guidelines; and (5) two-thirds of the patients in our study were females, who might have had a greater rate of compliance to the treatment or might have had a greater response to therapy than males, although there are few data to support this. As with other studies, our study found that the lowest percentage of achieving the recommended LDL-C target was in the very high-risk group [10, 14].

A number of aspects of our study can be considered strengths. First, the case selection was unbiased, as it was carried out consecutively and independent of the attending physicians. Second, we covered a large number (52.6%) of secondary- and tertiary-care hospitals across the country. Third, almost all of the studied patients (99.0%) were attended by an internal medicine, specialist, particularly the very high-risk and high-risk patients. Finally, our study represented real-life, clinical settings in Thailand, so the percentage achievement of LDL-C goals may represent clinical practice.

In summary, our study demonstrated that 51.1% of patients with cardiovascular risk on statin treatment achieved the LDL-C goal levels defined by the NCEP ATP III guidelines. We suggest that patients with a high CHD risk should be targeted for more aggressive lipid-lowering management. National campaigns to increase the awareness among both physicians and patients of the importance of achieving the LDL-C goals are needed to optimize the prevention of cardiovascular events and to further reduce the burden of cardiovascular diseases. Further investigation is needed to understand the reasons for patients not achieving lower LDL-C levels.

4. Clinical implications in real world practice

Despite the >50% decrease in age-adjusted cardiovascular mortality over the past several decades, atherosclerotic disease is still the leading cause of morbidity and mortality. Moreover, cardiovascular disease accounts for more than half of all non-communicable diseases and has become the leading cause of death worldwide, a fact affirmed by the World Health Organization [15]. Large cohort studies dating back to the Framingham Heart Study have identified cholesterol as a modifiable risk factor, which can be treated with lifestyle and pharmacological interventions

[16]. Total cholesterol levels have decreased in high-income countries over the past 2 decades by 8–10% on average. Some countries with the highest levels were able to decrease levels more than this with targeted societal interventions, leading directly to dramatic decreases in event rates. As part of the United Nations declaration on non-communicable diseases, with a goal of reducing premature death by 25%, their target is a 20% relative reduction in high total cholesterol by 2025. To be truly effective, the treatment of dyslipidemia needs to be incorporated into a comprehensive plan of global risk reduction for patients at risk. This will involve lifestyle modification, policy change, and pharmacotherapy.

5. Similarities and differences in dyslipidemia guidelines

New dyslipidemia guidelines were released by the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) in 2011 [17], the CCS in 2012 [18], the International Atherosclerosis Society [19], and the American College of Cardiology (ACC)/American Heart Association (AHA), both in 2013 [20]. All are similar in many respects, yet have some key differences that are worthy of discussion. The 2012 CCS guidelines recommended risk stratification using the total cardiovascular disease **F**ramingham **R**isk **S**core (FRS) [21], advocated the use of low-density lipoprotein cholesterol (LDL-C) thresholds for the initiation of treatment in low- and intermediate-risk subjects and expanded the phenotype of high-risk subjects to include subjects with atherosclerosis, most patients with diabetes, high-risk hypertension (per **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial [ASCOT] inclusion criteria) [22] and predialysis chronic kidney disease (CKD). LDL-C continues to be used as the atherogenic metric, but now non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (apo B) could be measured as alternatives, especially under circumstances when LDL-C calculations are known to be erroneous. When treatment is initiated, LDL-C (<2.0 mmol/L or 50% reduction) continues to be the primary target of therapy. The CCS guidelines have been harmonized with other relevant Canadian guidelines as part of the Canadian Cardiovascular Harmonization National Guidelines Endeavor (C-CHANGE) initiative [23] (**Table 3**).

The ESC/EAS guidelines was a comprehensive document that encouraged the use of the **S**ystematic **Co**ronary **R**isk **E**valuation (SCORE) total cardiovascular mortality [24].

Calibrated for high- or low-risk countries in Europe. Of note, the SCORE risk assessment is also based on the Framingham risk equation. LDL-C thresholds were suggested with non-HDL-C or apo B as alternatives. The European guidelines also recognized CKD as very high-risk equivalent. Target levels of LDL-C were recommended but unlike the CCS guidelines, the goals were different between those at very high risk (<1.8 mmol/L) compared with those at high risk (<2.5 mmol/L) or intermediate risk (<3.0 mmol/L).

The International Atherosclerosis Society panel decided to recommend lifetime cardiovascular risk based on 4 different tools depending on ethnicity. They favored non-HDL-C as the primary atherogenic metric for risk determination, with LDL-C as a secondary measure. Optimal levels were defined based on criteria from Adult Treatment Panel-III (ATP-III), but did not recommend treatment targets. The intensity of statin therapy should be adjusted according to overall lifetime risk and practitioner practice.

The ACC/AHA guidelines were the latest to be released and created the most controversy [20]. A major novel aspect of these guidelines was the recommendation to calculate risk using the newly developed Pooled Cohort Equation. This approach

Guidelines	Year	Major features	Limitations
European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) in 2011 [17]	2011	Comprehensive document that encouraged the use of the Systematic Coronary Risk Evaluation (SCORE) total cardiovascular mortality 10 calibrated for high- or low-risk countries in Europe. Also recognized CKD as very high-risk equivalent	Target levels of LDL-C were recommended but unlike the CCS guidelines, the goals were different between those at very high risk (<1.8 mmol/L) compared with those at high risk (<2.5 mmol/L) or intermediate risk (<3.0 mmol/L)
Canadian Cardiovascular Society Guidelines (CCS) 2012 [18]	2012	Risk stratification using the total cardiovascular disease Framingham Risk Score (FRS), use of LDL-C thresholds for the initiation of treatment in low- and intermediate-risk subjects and expanded the phenotype of high-risk subjects to include subjects with atherosclerosis, most patients with diabetes, high-risk hypertension	LDL-C continues to be used as the atherogenic metric, but non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (apo B) could be measured as alternatives, especially under circumstances when LDL-C calculations are known to be erroneous
International Atherosclerosis Society [19]	2013	Recommend lifetime cardiovascular risk based on 4 different tools depending on ethnicity. They favored non-HDL-C as the primary atherogenic metric for risk determination, with LDL-C as a secondary measure. Optimal levels were defined based on criteria from Adult Treatment Panel-III (ATP-III)	Not recommend treatment targets. The intensity of statin therapy should be adjusted according to overall lifetime risk and practitioner practice.
American College of Cardiology (ACC)/ American Heart Association (AHA) [20]	2013	Recommendation to calculate risk using the newly developed Pooled Cohort Equation. No recommendation for treating to any specific target. "Fire and forget" approach	Created the most controversy. Novel aspect was the recommendation to calculate risk using the newly developed Pooled Cohort Equation. The new risk engine tended to overestimate events.

Table 3.
Similarities and differences in dyslipidemia guidelines.

represents a departure from the use of the FRS, used for decades. Of the 4 groups targeted for statin-based therapy, 3 were the same as the CCS guidelines. These include subjects with: (1) clinical evidence of atherosclerosis; (2) most subjects with diabetes; and (3) individuals with LDL-C ≥5.0 mmol/L. The fourth group includes subjects with a 10-year risk of total atherosclerotic events calculated using the Pooled Cohort Equation of ≥7.5% [25, 26]. There was no specific recommendation for CKD and other populations such as genetic dyslipidemia or high-risk hypertension. An additional novel aspect of these guidelines was the lack of specific targets of therapy. Although these guidelines recommend the use of high- or moderate-intensity statin regimens based on level of risk and anticipate a 50% LDL-C decrease with high-intensity statin therapy, there is no recommendation for treating to any specific target. Therefore, lipid measurements after initiation of statin therapy are recommended, primarily to ensure adherence.

6. The elimination of atherogenic lipoprotein targets

The new ACC/AHA guidelines were distinctly different from most previous recommendations in that they have discarded specific LDL-C (or alternative) targets when subjects are initiated with therapy. The rationale for this change was that no previous randomized trial specifically addressed whether a particular level produced

greater event reduction. Second, by eliminating targets it was believed that primary care treatment would be more straightforward and easier to implement. Third, having targets potentially promotes combination therapy, for which there is currently no good evidence from randomized trials. This is supported by data from meta-analysis of trials of fibrate therapy, **A**therothrombosis **I**ntervention in **M**etabolic Syndrome with Low **H**DL/High triglycerides and **I**mpact on **G**lobal **H**ealth Outcomes (AIM-HIGH) and **H**eart **P**rotection **S**tudy **2**: **T**reatment of **H**DL to **R**educe the **I**ncidence of **V**ascular **E**vents (HPS2-THRIVE) [27–29].When using combination therapy one must be aware that the addition of either fibrates or niacin to statin therapy may increase the risk of myositis. The increased risk of myositis is greatest when gemfibrozil is used in combination with statins. Fenofibrate has a much more modest risk and the FDA approved the use of fenofibrate in combination with moderate doses of statins. The increased risk with niacin appears to be modest. In the AIM-HIGH trial the risk of myositis was not increased in patients on the combination of Niaspan and statin, whereas in the HPS2-Thrive trial myopathy was increased in the group treated with the combination of niacin and statin. The absolute risks of combination therapy are relatively modest if patients are carefully selected; in many patients at high risk for cardiovascular disease combination therapy may be appropriate. As with many decisions in medicine one needs to balance the benefits of therapy with the risks of therapy and determine for the individual patient the best approach. In deciding to use combination therapy a key focus is the non-HDL-C level. When the LDL is at goal but the non-HDL-C is still markedly above goal it may be appropriate to resort to combination therapy in patients at high risk.

Although this interpretation is literally correct, it fails to recognize several issues in the history of statin trials: the initial trials were as much studies of the lipid hypothesis as they were trials of statins. Thus, the first trials were in patients with the highest risk and highest cholesterol levels but at a time when only moderately potent statins were available, hence the use of the highest dose feasible. Because success was shown, and as more potent statins became available, ethical considerations mandated that research subjects had to have lower and lower risk and lower and lower cholesterol levels, again promoting use of the highest available dose. The latter was also influenced by a need to ensure simplicity in large trials and, to some extent, by marketing designed to promote drug potency differences. There are also 5 trials of higher vs. lower potency statins, which show consistent improvement in outcomes with the higher potency statin. The lowest risk cohort studied to date in the **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study reaped comparable benefit using the most potent statin currently available. Remarkably, no lower limit of achieved LDL-C beyond which benefit is accrued has yet been shown. The CCS dyslipidemia guideline primary panel reviewed these issues in early 2014 and recommended that until further evidence was available, we would continue to support the use of targets. Although it is certainly true that randomized trials have generally used a single statin dose approach, as opposed to a target LDL-C level, the epidemiology suggesting that lower levels of achieved LDL-C result in less events is rather compelling. Also, regression studies with intravascular ultrasound demonstrate a linear relationship between LDL-C and the amount of regression [30]. The crossing point for regression tends to occur at an LDL-C of around 2 mmol/L or a 50% reduction. A very recent meta-analysis used individual patient data from 8 statin trials [31]. Using a fixed dose of statin, there was a very large inter-individual variation in LDL-C reduction with statins. In addition, more than 40% of subjects did not achieve targets of <1.8 mmol/L with a fixed statin dose. Those who achieved very low levels of LDL-C had a lower event rate than those who achieved modest levels. The same trend was seen for non-HDL-C and apo B.

We will be able to test the "lower is better" hypothesis at very low levels of LDL-C when the results of ongoing trials using nonstatins (e.g., inhibitors of cholesterol absorption, proprotein convertase subtisilin/kexin type 9 (PCSK9) and cholesterol ester transfer protein (CETP) are well established and widely applicable to practitioners.

The ACC/AHA guidelines would appear at first blush to support a "fire and forget" approach. The text and algorithms do, however, suggest that measuring LDL-C after statin initiation is reasonable to help assess compliance and to ensure achievement of an expected percentage of decrease of LDL-C. Compliance and adherence are important issues with statin therapy [32] and beyond the scope of this review, but are certainly another practical reason that the CCS guidelines panel continues to recommend targets. Additionally, the text and algorithms of the ACC/AHA guidelines promote LDL-C measurement to ensure achievement of the expected response to moderate- and high-intensity statin dose choices and, when not achieved or in the face of statin intolerance, support dose escalation or addition of secondary, non-statin drugs.

The new ACC/AHA guidelines have generated considerable debate and confusion in the medical literature about the specifics of risk assessment and treatment of dyslipidemia in cardiovascular disease prevention. It is healthy to accept that there are different approaches to screening and management, because of the lack of decisive evidence in certain domains. The discussion should be used to highlight the need to address outstanding questions in the future. However, in the interim, our patients can be very well managed with existing guidelines that are updated on an ongoing basis when new knowledge is generated. A guidelines-based approach to screening, treatment, and compliance should continue to be the standard for all of our at-risk patients.

In conclusion, the National Guideline campaigns to increase the awareness among both physicians and patients of the importance of achieving the LDL-C goals are needed to optimize the prevention of cardiovascular events and to further reduce the burden of cardiovascular diseases.

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