LOW-DENSITY LIPOPROTEIN CHOLESTEROL GOAL ATTAINMENT AMONG MALAYSIAN DYSLIPIDEMIC PATIENTS

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Abstract. The aim of the present study was to evaluate Malaysian dyslipidemic patient treatment practices and outcomes. Factors contributing to success in reaching treatment goal were determined. A retrospective review of the records of dyslipidemic patients who attended the Universiti Sains Malaysia Hospital in 2007 was conducted. All the patients were receiving standard recommended doses of statins. Records were analysed for 890 patients. Patients were divided into three categories: 384 patients (43.1%) had coronary heart disease or coronary heart disease risk equivalents, 216 patients (24.3%) had moderate risk for coronary heart disease and 290 patients (32.6%) had low risk. Statins were the most commonly prescribed drug group (92%), of which atorvastatin was the most commonly prescribed drug (50.6%). The overall success rate for reaching goal was 64.2%. The percentages of patients achieving low-density lipoprotein cholesterol targets in the coronary heart disease and coronary heart disease risk equivalents, moderate, and low-risk groups were 50.5, 66.7, and 80.3%, respectively ($p<0.001$). Multiple logistic regression showed achievement of therapeutic goal declined with increasing risk group. The baseline low-density lipoprotein cholesterol value was inversely related to therapeutic goal attainment. An inadequate proportion of dyslipidemic patients achieved the National Cholesterol Education Program therapeutic goals for low-density lipoprotein cholesterol, especially those in the coronary heart disease and coronary heart disease risk equivalent group. The achievement of this goal was dependent on baseline low-density lipoprotein cholesterol levels.

Keywords: dyslipidemic patient, LDL-C, ATP III, goal attainment, Malaysia

INTRODUCTION

The relationship between low-density lipoprotein cholesterol (LDL-C) levels and coronary heart disease (CHD) risk is continuous over a broad range of LDL-C levels. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (1993) has therefore adopted a classification of LDL-C levels that ranges from optimal (<100 mg/dl, 2.6 mmol/l) to very high (≥190 mg/dl, 4.9 mmol/l) (Grundy *et al*, 2004). The ATP III

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has continued to identify elevated LDL-C as the primary target for cholesterol-lowering therapy. As a result, the primary goals of therapy and the cut-off points for initiating treatment are stated in terms of LDL-C levels. In addition to exercise and diet modification, statins (3 hydroxy-3-methylglutaryl coenzyme A inhibitors) are recommended as a means of reducing LDL-C level (Grundy *et al*, 2004). They have been widely used to lower elevated plasma lipids and reduce vascular risk (Baigent *et al*, 2005), as well as reducing mortality and morbidity in patients with CHD (Suzuki *et al*, 2008).

The use of statins at standard and intensive doses has been shown to be effective and well tolerated in Asian patients with CHD. When the statin dose was increased to obtain optimal efficacy, a high proportion of patients achieved the ATP III LDL-C target of 2.6 mmol/l (Chung *et al*, 2001).

The ATP III has identified smoking, hypertension, diabetes mellitus (DM) and a family history of premature CHD as important factors that modify the effects of treatment of LDL-C and contribute to the pathogenesis of CHD (Grundy *et al*, 2004).

Based on these risk determinants, ATP III recognizes three risk categories that modify the goals and modalities of LDL-C-lowering therapy. These are CHD and CHD risk equivalents, those with multiple (>2) risk factors, and those with ≤1 risk factor, for which the LDL-C goals are <2.6, <3.4 and <4.1 mmol/l, respectively (Grundy *et al*, 2004).

The aims of this study were to highlight the NCEP ATP III risk groups among Malaysian dyslipidemic patients, to assess the attainment of LDL-C goals according to the ATP III risk category, and to identify the factors affecting attainment.

MATERIALS AND METHODS

Before conduction the present study ethical approval was obtained from the Universiti Sains Malaysia's Research and Ethics Committee.

The subjects for this study were drawn from a computer-generated list of 2,500 dyslipidemic patients (inpatients and outpatients) obtained from the Record Unit, Hospital of Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. The dyslipidemic patients included were those with prescribed lipid lowering therapy (LLT), statin or otherwise, from January 2007 (index date). Those on a standard statin dose were included in the study (atorvastatin 20 mg, pravastatin 20 mg, simvastatin 20 mg, rosuvastatin 10 mg, lovastatin 20 mg). Those receiving LLT before the index date or those on maximal doses of statin were excluded, resulting in a sample of newly treated patients with a standard statin dose for the year 2007. Nine hundred eighty files of dyslipidemic subjects who attended the HUSM during 2007 were reviewed.

The lipid profile before starting LLT was regarded as the baseline, and the most recent profile prior to December 2007 was used as the post-treatment result. Recorded variables included age, sex, concomitant LLT, smoking status, presence of related clinical problems, such as hypertension, family history of premature CHD (age of onset in first-degree relatives of <55 years for men and <65 years for women) (Scheuner *et al*, 2006), DM, CHD and stroke.

Patients were classified into one of the three NCEP ATP III categories: the first category included the highest risk patients with CHD and CHD risk equivalents, including other clinical forms of athero-

Table 1
Lipid profile study of subjects' pre and post treatment.

Lipid profile (mmol/l)	Baseline mean (SD)	Post treatment mean (SD)	Mean change (SD)	95% CI for the difference	% Change mean (SD)	*p*-value[a]
TC	6.4 (1.3)	5.2 (1.2)	-1.2 (1.5)	1.10, 1.30	-19.6 (7.2)	<0.001
LDL-C	4.1 (1.2)	2.9 (1.2)	-1.1 (1.5)	1.10, 1.30	-29.1 (4.5)	<0.001
HDL-C	1.37 (0.48)	1.4 (0.51)	0.1 (0.6)	-0.07, 0.005	9.1 (36.9)	0.086

[a]Paired *t*-test

sclerotic disease and DM. The second category included patients with ≥2 other risk factors recognised by the NCEP ATP III. These patients were defined as the moderate-risk group. Patients with ≤1 risk factor were defined as the low-risk group. A high-density lipoprotein cholesterol (HDL-C) ≥1.55 mmol/l was regarded as a "negative" risk factor; it subtracted 1 point factor from the total score (Grundy *et al*, 2004). LDL-C was classified according to risk factor categories into: <2.6, <3.4 and <4.1 mmol/l, respectively.

All numerical data are presented as mean ± standard deviation (SD). Significant differences in mean lipid profile parameters between baseline and post-treatment measurements were calculated using paired Student's *t*-tests. The chi-square test was used to compare the goal attainment rates between different groups. Multivariate analysis with logistic regression was performed to estimate the chance of attainment of the therapeutic goal, with the low-risk group regarded as the reference group. Potential covariates were included in the multivariate analysis if they showed a significant association with therapeutic success ($p<0.05$) in the univariate model. Percent change in LDL-C after treatment (effectiveness) was calculated as the difference between the post-treatment and baseline values divided by the baseline value. Statistical tests were two-tailed and performed at a significance level of 0.05 using SPSS 12.0.1.

Table 2
Percent attainment of LDL-C goal by risk category.

Parameters (*n*)	LDL-C attainment (%)	*p*-value[a]
CHD risk status		
1) 0-1 risk factor (290)	80.3	<0.001
2) ≥2 risk factors (216)	66.7	
3) CHD or CHD risk equivalent (384)	50.5	

[a]Chi-square test was used

RESULTS

Table 1 shows the total cholesterol (TC) and LDL-C levels were significantly reduced by LLT, compared with baseline levels, with no significant increases in HDL-C levels.

Prescription statin monotherapy was used in the majority of cases (92%). The most frequently used statin was atorvastatin (50.6%); lovastatin was the least used statin (3.5%).

By risk group, 384 patients (43.1%) had CAD and CAD risk equivalents, while

Table 3
Multiple logistic regression models for predictors of LDL.

Variables	B (SE)	Adjusted OR (95% CI)	*p*-value
A) Baseline LDL-C	-0.48 (0.07)	0.62 (0.53, 0.71)	<0.001
B) Risk groups			
1) Low risk			
2) Moderate risk	-0.82 (0.22)	0.43 (0.28, 0.67)	<0.001
3) CHD or CHD risk equivalents	-1.64 (0.19)	0.15 (0.13, 0.28)	<0.001

216 (24.3%) had multiple risk factors, and 290 (32.6%) had ≤1 risk factor.

The LDL-C target was attained in 64.2% of all dyslipidemic patients. The low-risk group had the highest attainment rate (80.3%), followed by the moderate-risk group (66.7%), while the lowest attainment rate was found in the CHD and CHD equivalent group (50.5%) (Table 2). The difference between the risk groups in LDL-C goal attainment rates was significant (p<0.001).

For multiple logistic regression analysis, the low-risk group was regarded as the reference group, based on its relatively high attainment rate. The likelihood of achieving the therapeutic goal declined with increasing risk group. The baseline LDL-C value was also inversely related to therapeutic goal attainment in the entire study group (Table 3).

DISCUSSION

Most published studies on the use of LLT for hyperlipidemia have focused on western populations; few data are available for Asian patients (Chung *et al*, 2001). Many internationally accepted guidelines for cholesterol management are based on data from either the United States [Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, 1993] or Europe (Wood *et al*, 1998). Asian patients are generally treated with lower doses of statins, and the concept of increasing the dose to achieve maximum efficacy is not well established (Chung *et al*, 2001). As a consequence, Asian patients treated with LLT may not achieve sufficiently large reductions in LDL-C to achieve the NCEP target of 2.6 mmol/l (Chung *et al*, 2001). The current study investigated the factors that affect LDL-C attainment in dyslipidemic subjects. The study involved patients who were mostly prescribed statins (92%).

Statin treatment has been shown to reduce cardiovascular mortality, particularly when used at higher doses (Chung *et al*, 2001). Overall, standard statin therapy produced a 29% reduction in LDL-C levels, which is lower than that seen in a previous clinical trial (Sasaki *et al*, 2008). This finding is not unexpected, as clinical trials usually demonstrate a greater reduction than those shown in review studies, where the inclusion criteria are limited. This study was not designed to investigate the effect of diet and other lifestyle activities, that must also be taken into consideration, to affect the reduction; non-compliance may also have contributed to the lower LDL-C reduction (Bullano *et al*, 2006).

The increase in HDL was lower than that demonstrated in an earlier study (Ostad *et al*, 2009); this poor increase (9%) may be due to other factors, such as exercise and different genetic backgrounds (Sviridov and Nestel, 2007). The use of statins was common among our study group, similar to Asian patients with atherothrombosis (Bhatt *et al*, 2006).

With regard to the current study, lovastatin was not readily available as a standard drug on our formulary in 2007; many of the prescriptions for lovastatin came from peripheral healthcare facilities outside HUSM. This may explain the relatively low use of this drug in this study. Atorvastatin has been on the HUSM formulary for many years and is thus the initial drug of choice for LLT.

Attainment of the LDL-C goal was affected by the presence of CHD and its risk factors. In the moderate- and low-risk groups, 66.7% and 80.3%, respectively, attained their goals, while only 50% of those in the high-risk group achieved their therapeutic targets. These percentages are slightly higher than those found in a study in Thailand using the same LDL-C attainment goals (Nitiyanant *et al*, 2008). Failure to attain the therapeutic goals can be explained by the irregular treatment received by patients as noted in a study by Parris *et al* (2005). Increased saturated fat consumption and decreased physical activity are associated with adverse changes in the lipid profile (McKenney *et al*, 2005) although this was not explored by this study, as mentioned above. Use of highly potent statins, such as rosuvaststin, was low (4.2%) which may explain the poor reduction rate.

As noted in the ATP III guidelines, more aggressive therapy is needed for high-risk patients. Therefore, with a more intense treatment regimen, a higher achievement rate should be possible (Bhatt *et al*, 2006). The dyslipidemic patients in the present study were taking standard LLT. However, the LDL-C therapeutic goal attainment was noted to be lower than that found in other studies in France (Laforest *et al*, 2008) and Asia (Chung *et al*, 2001), using the same standard statin doses. Our results show that patients in intermediate- and high-risk categories were less likely to reach their therapeutic goals than low-risk patients, which is in agreement with the results of another review (Laforest *et al*, 2008).

Reluctance of the managing physician to titrate the dose up in this group of patients may have been responsible for the relatively low attainment of the therapeutic goal. Particular attention has been paid to the use of high statin doses to achieve therapeutic targets and reduce cardiovascular risk (LaRosa *et al*, 2005). Trials have shown that the higher the statin dose, the greater the risk reduction. A lower statin dose might be inadequate to lower the LDL-C level to the therapeutic goal. Many run the risk of eventually progressing to a higher risk category (Laforest *et al*, 2008). This study compared the outcomes of LDL-C using routine medication doses.

In the present study multiple logistic regression models showed the intermediate and high risk categories were less likely to acquire therapeutic attainment compared to the low risk group, which is in harmony with other studies (Laforest *et al*, 2008). The achievement rate is dependent on the baseline LDL-C after adjustment for other factors as recorded by others (Athyros *et al*, 2004).

In summary, an unacceptably low proportion of dyslipidemic patients attained NCEP ATP III LDL-C therapeutic

goals with the use of the standard statin dose. Attainment of the therapeutic goal depended on basal LDL-C levels.

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REFERENCES

Athyros VG, Mikhailidis DP, Papageorgiou AA, *et al.* Relationship between LDL-C and non-HDL-C levels and clinical outcome in the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study. *Curr Med Res Opin* 2004; 20: 1385-92.

Baigent C, Keech A, Kearney PM, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; 366: 1267-78.

Bhatt DL, Steg PG, Ohman EM, *et al.* International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295: 180-9.

Bullano MF, Wertz DA, Yang GW, *et al.* Effect of rosuvastatin compared with other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. *Pharmacotherapy* 2006; 26: 469-78.

Chung N, Cho SY, Choi DH, *et al.* STATT: a titrate-to-goal study of simvastatin in Asian patients with coronary heart disease. Simvastatin Treats Asians to Target. *Clin Ther* 2001; 23: 858-70.

Grundy SM, Cleeman JI, Merz CN, *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110: 227-39.

Laforest L, Moulin P, Souchet T, *et al.* Correlates of LDL-cholesterol goal attainment in patients under lipid lowering therapy. *Atherosclerosis* 2008; 199: 368-77.

LaRosa JC, Grundy SM, Waters DD, *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425-35.

McKenney JM, Davidson MH, Saponaro J, Thompson PD, Bays HE. Use of a treatment algorithm to achieve NCEP ATP III goals with atorvastatin. *J Cardiovasc Pharmacol* 2005; 46: 594-9.

NCEP. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection E, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; 269: 3015-23.

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.

Ostad MA, Eggeling S, Tschentscher P, *et al.* Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. *Atherosclerosis* 2009; 205: 227-32.

Parris ES, Lawrence DB, Mohn LA, Long LB. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care* 2005; 28: 595-9.

Sasaki J, Ikeda Y, Kuribayashi T, *et al.* A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-den-

sity lipoprotein cholesterol and glucose intolerance. *Clin Ther* 2008; 30: 1089-101.

Scheuner MT, Whitworth WC, McGruder H, Yoon PW, Khoury MJ. Expanding the definition of a positive family history for early-onset coronary heart disease. *Genet Med* 2006; 8: 491-501.

Suzuki T, Nozawa T, Sobajima M, *et al*. Atorvastatin-induced changes in plasma coenzyme q10 and brain natriuretic peptide in patients with coronary artery disease. *Int Heart J* 2008; 49: 423-33.

Sviridov D, Nestel PJ. Genetic factors affecting HDL levels, structure, metabolism and function. *Curr Opin Lipidol* 2007; 18: 157-63.

Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis* 1998; 140: 199-270.