Introduction

Hyperlipidemia is a healthcare problem in Thai population and one of the important risk factors in coronary heart disease, ischemic heart disease, acute myocardial infarction, peripheral arterial disease, and cerebrovascular disease. Stroke is a major cause of mortality and morbidity in Thailand. The data from the cause of death in 1990 revealed that stroke was a major cause of death in female and a third of death in male Thai people. Moreover, this rate also increases every year in Thailand. Stroke is also a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and 15% to 30% being permanently disabled. Prevalence of stroke in Thailand is 690 : 100,000 population , approximately almost 500,000 stroke patients per 72 millions of Thai people.

Large epidemiology studies in ischemic stroke have shown a modest association of elevated total cholesterol or low-density lipoprotein cholesterol (LDL-C) with the increased risk of ischemic stroke and the relationship between low LDL-C and the greater risk of intracerebral hemorrhage. The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been approved by regulatory agencies for prevention of ischemic stroke in patients with coronary heart disease (CHD). Statins therapy with intensive lipid-lowering effects is recommended for patients with atherosclerotic ischemic stroke or transient ischemic attack (TIA) and without known CHD to reduce the risk of stroke and cardiovascular events. For those patients with atherosclerotic ischemic stroke or TIA and history of
CHD, it is recommended that clinicians follow the current 2011 the American Heart Association/American Stroke Association (AHA/ASA) guidelines for lipid management, which emphasize utilization of National Cholesterol Education Panel III guidelines (NCEP III).6

Prasat Neurological Institute (PNI), an excellence center for the advancement in stroke research and treatment in Thailand, has been providing care for a total of 22,000 out-patients and 1,000 in-patients with cerebrovascular diseases annually, based on data from 2008 to 2010. Multidisciplinary team and also clinical pharmacist have been working in the stroke unit since 2010. According to the concept of aggressive reduction in cholesterol level, we undertook retrospective charts review to determine the goal achievement of LDL-C levels in patients with ischemic stroke and hyperlipidemia and prevalence of adverse drug reactions including myalgia and rhabdomyolysis in these patients.

Methods

A cross-sectional descriptive design was employed in this study. The study was conducted at the inpatient department (IPD) of the Stroke Unit at Prasat Neurological Institute, Bangkok, Thailand, during March to November 2011. This institution is under the Department of Medical Services, Ministry of Public Health, Thailand.

Sample in this study was ischemic stroke patients with hyperlipidemia admitted in the Stroke Unit, Prasat Neurological Institute during March to November 2011. The inclusion criteria were as follows: patients who received statin drug before or during admission and their baseline LDL-C level were recorded before hospital discharge. The exclusion criteria included patients with diagnosis of cardioembolic stroke or loss of contact after hospital discharge. Patients were classified into 4 groups according to their diabetes mellitus (DM) diagnosis and statin use before admission; patients with no DM and no statin use before admission (group A), patients with no DM and with statin use before admission (group B), patients with DM and no statin use before admission (group C), and patients with DM and statin use before admission (group D). Their LDL goal achievements based on the follow-up measures were set according to their DM status: < 100 mg/dL for those with no DM (groups A and B) and < 70 mg/dL for those with DM (groups C and D).

This study was approved by the Institutional Review Board and Independent Ethics Committee of the Prasat Neurological Institute (approval number: 2.205/2554; approval date: December 3, 2010).

Data Analysis

Descriptive statistics including frequency, percentage, range, mean, and standard deviation were used to describe demographic data, laboratory data at admission and follow up, mean LDL-C and goal achievement of LDL-C level. Paired t-test was used to compare means of laboratory data and LDL-C at admission with those at follow-up visit.

Results

A total number of 197 patients admitted to the Stroke Unit during March to November 2011 were enrolled in this study. Demographic data are presented in Table 1. There were slightly more male patients than female counterparts in most groups except in group D (patients with DM and statin use before admission). Their mean ages were comparable (60.54 to 63.32 years). The majority in each group never smoked and never drank of which the highest proportions of both habits were found in group D (78.95% and 84.21%, respectively). The highest proportions of present smoking (44.12%) and present drinking and 38.24%) were found in group A (no DM and no statin use before admission).
Table 1 Demographic data of 197 patients with ischemic stroke and hyperlipidemia.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Group</th>
<th>A (N = 68)</th>
<th>B (N = 59)</th>
<th>C (N = 32)</th>
<th>D (N = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (69.11%)</td>
<td>33 (55.93%)</td>
<td>17 (53.13%)</td>
<td>14 (36.84%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (30.89%)</td>
<td>26 (44.07%)</td>
<td>15 (46.87%)</td>
<td>24 (63.16%)</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td></td>
<td>60.54</td>
<td>63.32</td>
<td>62.59</td>
<td>62.85</td>
</tr>
<tr>
<td>Standard deviation</td>
<td></td>
<td>13.29</td>
<td>12.86</td>
<td>10.94</td>
<td>9.66</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>16 - 85</td>
<td>36 - 83</td>
<td>44 - 85</td>
<td>43 - 78</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoking</td>
<td>35 (51.47%)</td>
<td>39 (66.11%)</td>
<td>14 (43.75%)</td>
<td>30 (78.95%)</td>
<td></td>
</tr>
<tr>
<td>Past smoking</td>
<td>3 (4.41%)</td>
<td>1 (1.69%)</td>
<td>5 (15.63%)</td>
<td>1 (2.63%)</td>
<td></td>
</tr>
<tr>
<td>Present smoking</td>
<td>30 (44.21%)</td>
<td>18 (30.51%)</td>
<td>13 (40.62%)</td>
<td>7 (18.42%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.00%)</td>
<td>1 (1.69%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol drinking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never drinking</td>
<td>39 (57.35%)</td>
<td>36 (61.02%)</td>
<td>18 (56.25%)</td>
<td>32 (84.21%)</td>
<td></td>
</tr>
<tr>
<td>Past drinking</td>
<td>3 (4.41%)</td>
<td>4 (6.78%)</td>
<td>3 (9.38%)</td>
<td>1 (2.63%)</td>
<td></td>
</tr>
<tr>
<td>Present drinking</td>
<td>26 (38.24%)</td>
<td>18 (30.51%)</td>
<td>11 (34.37%)</td>
<td>5 (13.16%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.00%)</td>
<td>1 (1.69%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Groups of patients: group A = patients with no diabetes mellitus (DM) and no statin use admission; group B = patients with no DM and with statin use admission; group C = patients with DM and no statin use admission; group D = patients with DM and statin use admission.

Laboratory data at admission and follow-up are presented in Table 2. Total cholesterol levels decreased significantly from admission both in groups A (from 206.24 to 147.61 mg/dL) and C (from 214.47 to 172.23 mg/dL) of which patients did not take any statin before admission (P < 0.001 for both groups). As expected, total cholesterol levels at admission in groups B (170.20 mg/dL) and D (172.23 mg/dL) where lower than those in groups A and C of which patients had not been any statins before admission.

HDL levels increased significantly in all groups where the mean HDL levels at follow-up of more than 45 mg/dL were found in all groups. Triglyceride levels decreased slightly from admission with no statistical significance.

Triglyceride levels decreased in all groups with no statistical significance. Patients in groups with statin use (groups B and D) had triglyceride levels at admission lower than their counterparts as expected.

ALT levels increased from admission among patients who did not use statin before admission (from 22.52 to 27.73 IU/L in group A and from 27.08 to 30.32 IU/L in group C), while those in patients who had been using statins decreased slightly (from 25.26 to 24.86 IU/L in group B and from 28.47 to 24.26 IU/L in group D). Changes in all 4 groups, however, did not reach any statistical significance. In constrast to ALT, AST levels decreased in all 4 groups with a statistical significance found in group D (from 31.59 to 23.37 IU/L, P = 0.014).

Creatine kinase levels were obtained in a very small number of patients in all 4 groups. Even with an increased level at follow-up in each of the 4 groups, creatine kinase levels cannot be test for statistical significance.

Fast blood sugar levels were found decreasing in all groups with no statistical significance. For HbA1c levels, a decrease in groups C and D (diabetes patients in both groups) was found with no statistical significance; while such changes with a very small magnitude were also found in patients with no diabetes (groups A and B) and could not be tested for statistical significance because a small number of patients were tested. As expected, patients with no diabetes (groups A and B) had fasting blood sugar and HbA1c levels lower than those of their counterparts.

In terms of LDL (Table 2), LDL levels at admission in patients with statin use (106.05 mg/dL in group B and 131.37 mg/dL in group D) where higher than those in patients without any statin use (140.93 mg/dL in group A and 141.38 mg/dL in group C). Decreases in LDL levels at follow-up were found with statistical significance in all groups (P < 0.001, = 0.01, < 0.001 and = 0.01, in groups A, B, C and D respectively). Largest decreases were found in groups A (from 140.93 to 85.18 mg/dL) and C (from 141.38 to 100.43 mg/dL) of which the patients had not used any statins before admission.

Regarding LDL-goal achievement based on follow-up measures (Table 3), patients in group A and B (no diabetes) were expected to have an LDL level of less than 100 mg/dL while those in groups C and D were to have less than 70 mg/dL. It was found that 82.22% and 68.89% of patients in groups A and B, respectively, and 21.74% and 37.04% of patients in groups C and D, respectively, achieved their respective LDL goals.
Table 2: Laboratory measures at admission and follow-up in 4 groups of patients.

<table>
<thead>
<tr>
<th>Laboratory measures</th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>Group C</th>
<th></th>
<th>Group D</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>at admission</td>
<td>at follow-up</td>
<td>p-value</td>
<td>at admission</td>
<td>at follow-up</td>
<td>p-value</td>
<td>at admission</td>
<td>at follow-up</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>206.24 (26.44)</td>
<td>147.61 (28.26)</td>
<td>&lt; 0.001</td>
<td>170.20 (44.48)</td>
<td>159.91 (28.27)</td>
<td>0.604</td>
<td>214.47 (52.31)</td>
<td>172.23 (32.63)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>140.93 (34.98)</td>
<td>85.18 (22.75)</td>
<td>&lt; 0.001</td>
<td>106.05 (36.91)</td>
<td>87.71 (25.54)</td>
<td>0.01</td>
<td>141.38 (39.04)</td>
<td>100.43 (43.03)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>43.29 (14.18)</td>
<td>48.06 (14.31)</td>
<td>0.023</td>
<td>39.14 (12.90)</td>
<td>46.94 (12.58)</td>
<td>0.002</td>
<td>37.09 (11.72)</td>
<td>45.07 (13.11)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>133.63 (72.09)</td>
<td>104.23 (37.22)</td>
<td>0.194</td>
<td>117.61 (71.03)</td>
<td>120.24 (69.20)</td>
<td>0.985</td>
<td>172.38 (84.78)</td>
<td>149.60 (76.22)</td>
</tr>
<tr>
<td>ALT (IUL)</td>
<td>22.52 (18.89)</td>
<td>27.73 (18.88)</td>
<td>0.366</td>
<td>25.26 (17.01)</td>
<td>24.86 (15.18)</td>
<td>0.747</td>
<td>27.08 (14.49)</td>
<td>30.32 (24.30)</td>
</tr>
<tr>
<td>AST (IUL)</td>
<td>27.45 (12.23)</td>
<td>26 (8.30)</td>
<td>0.110</td>
<td>30.56 (17.01)</td>
<td>28.03 (4.95)</td>
<td>0.804</td>
<td>25.92 (5.18)</td>
<td>25.37 (8.76)</td>
</tr>
<tr>
<td>Creatinine kinase (IU/L)</td>
<td>88.33 (8.96)</td>
<td>117 (68.68)</td>
<td>-</td>
<td>80.25 (45.04)</td>
<td>134.27 (64.12)</td>
<td>0.295</td>
<td>85.00 (5.18)</td>
<td>99.50 (45.74)</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>97.90 (15.36)</td>
<td>101.26 (15.14)</td>
<td>0.268</td>
<td>102.33 (25.85)</td>
<td>101.21 (25.18)</td>
<td>0.139</td>
<td>160.38 (86.69)</td>
<td>152.48 (56.92)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.28 (1.63)</td>
<td>6.4 (0.96)</td>
<td>-</td>
<td>5.98 (0.68)</td>
<td>5.7 (0.28)</td>
<td>-</td>
<td>9.15 (2.51)</td>
<td>8.85 (3.33)</td>
</tr>
</tbody>
</table>

* P value comparing measures at admission with the one at follow-up, with a significance level of 0.05.

**Discussion**

There was no myalgia or rhabdomyolysis reported in this study (Table 4). Simvastatin was the most prescribed lipid lowering drug in patients with ischemic stroke and hyperlipidemia (176 cases, 89.34%), followed by atorvastatin (14 cases, 7.11%) (Table 4). Mean doses of simvastatin in each group were comparable, 20.49; 18.60; 20.0; and 21.71 mg in group A, B, C and D, respectively.

According to the recommendation for lipid management from National Cholesterol Education Panel or NCEP III (Class I recommendations), the target goal of cholesterol lowering for those patients with CHD or symptomatic atherosclerotic disease is LDL-C level < 100 mg/dL; while the LDL-C level < 70 mg/dL is recommended for a very high...
and then increased to 83% at 3 months after hospitalization

individuals with LDL-C < 100 mg/dL at admission was 46%

at a university teaching hospital, it was found that percent of

patients patient without DM and no statin use before

accomplishment of < 100 mg/dL were 82.22% among

the LDL-C achieved rate according to LDL-C goal

accomplishment and mean LDL-C at admission were lower

than patients with no diabetes and no statin use. Previous

study has shown that among patients in whom treatment

with secondary preventive drugs was prescribed at
discharge, the proportion on persistent medication during the

first 4 months after discharge varied from 95.5% for

antihypertensive drugs, 91.7% for statin drugs to 89.1% for

warfarin. 11 Although this study did not record the history

of statin use before admission, a relatively low success rate may be

12.1% in those not taking statin and 37.04% in those taking

statin before admission. A relatively low success rate may be

attributed to nonadherence after stroke was a major clinical problem in

our study may be due to an initiation of statin treatment for

patients with ischemic stroke and TIA during their hospitalization. These patients might also have had a high rate of

adherence to statin therapy after hospital discharge. Such

adherence could probably associate with a substantial improvement in the proportions of patients achieving target

national guideline LDL-C goals 3 months after hospitalization.

In patient without DM and had used statin (group B),
both of the control rate of LDL-C according to LDL-C goal
accomplishment and mean LDL-C at admission were lower
than patients with no diabetes and no statin use. Previous
study has shown that among patients in whom treatment
with secondary preventive drugs was prescribed at
discharge, the proportion on persistent medication during the

first 4 months after discharge varied from 95.5% for

antihypertensive drugs, 91.7% for statin drugs to 89.1% for

warfarin. 11 Although this study did not record the history

of statin use before admission, a relatively low success rate may be

attributed to nonadherence after stroke was a major clinical problem in

available evidence.11

In the study of Thailand Diabetes Registry Project
entitled “Current Status of Dyslipidemia in Thai Diabetic
Patients”12, the achievement rate of the LDL-C target (< 70
mg/dL) in diabetic patients with history of cardiovascular
disease was only 11.1%. Half of the patients (55%) were
taking lipid–lowering medication; however, another one-third
(30%) did not take any lipid-lowering medication even though
they should. 12 According to American Diabetes Association
recommendation, the LDL-C level < 70 mg/dL in type 2 DM
with overt cardiovascular disease, about 28% of patients met
target in Reality–Asia study.13 Among 7,427 coronary artery
disease (CAD) patients, 43% achieved an LDL-C goal (< 70
mg/dL), and 37% of those taking statin monotherapy14. In
our study, diabetic patients with history of ischemic stroke or
TIA who taking statin drugs attained the target LDL-C for
21.74% in those not taking statin and 37.04% in those taking
statin before admission. A relatively low success rate may be

Table 3 LDL-C goal achievements

<table>
<thead>
<tr>
<th>Group</th>
<th>LDL-C &lt; 100 mg/dL</th>
<th>LDL-C ≥ 100 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (%)</td>
<td>Mean LDL-C (SD)</td>
</tr>
<tr>
<td>A (N = 45)</td>
<td>37 (82.22%)</td>
<td>77.76 (4.38)</td>
</tr>
<tr>
<td>B (N = 45)</td>
<td>31 (68.89%)</td>
<td>75.00 (7.02)</td>
</tr>
</tbody>
</table>

Note: Groups of patients: group A = patients with no diabetes mellitus (DM) and no statin use before admission; group B = patients with no DM and with statin use before admission; group C = patients with DM and no statin use before admission; group D = patients with DM and statin use before admission. 
Abbreviation: LDL-C = low density lipoprotein cholesterol.

Table 4 Type of statins and adverse drug reactions classified by study groups.

<table>
<thead>
<tr>
<th>Adverse drug reactions</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (N = 68)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
</tr>
<tr>
<td>Rhadomyolysis</td>
<td>0</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>61 (90.7%)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>6 (8.80%)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>1 (1.50%)</td>
</tr>
<tr>
<td>Statin plus fibrate</td>
<td>0 (0.00%)</td>
</tr>
</tbody>
</table>

Note: Groups of patients: group A = patients with no diabetes mellitus (DM) and no statin use before admission; group B = patients with no DM and with statin use before admission; group C = patients with DM and no statin use before admission; group D = patients with DM and statin use before admission.

In a previous study of patients
with ischemic stroke or TIA admitted in the stroke service of a university teaching hospital, it was found that percent of

individuals with LDL-C < 100 mg/dL at admission was 46%

and then increased to 83% at 3 months after hospitalization

but data of lipid lowering drug history was not disclosed.8 L-
risk person with multiple risk factors.7 This present study
classified 197 patients admitted at a stroke unit according to
statin drug use history and the underlying disease of
diabetes mellitus. After hospital discharge from stroke unit,
the LDL-C achieved rate according to LDL-C goal
accomplishment of < 100 mg/dL were 82.22% among
patients patient without DM and no statin use before
admission, and 68.89% among those without DM and with
statin use before admission. In a previous study of patients
with ischemic stroke or TIA admitted in the stroke service of a university teaching hospital, it was found that percent of

individuals with LDL-C < 100 mg/dL at admission was 46%

and then increased to 83% at 3 months after hospitalization

but data of lipid lowering drug history was not disclosed.8 L-
due to the use of statin with low potency (simvastatin) in the majority of our patients (176 cases, 89.34%); while in previous study, only 37% received statin with low potency.

Recent studies suggest that a more aggressive target for lipid lowering may have added benefits, LDL-C change showed that patients with > 50% LDL-C reduction had a 31% reduction in stroke risk (hazard ratio, 0.69, 95% CI, 0.55 to 0.87, \( P = 0.0016 \)), a 33% reduction in ischemic stroke (\( P = 0.0018 \)), no statistically significant increase in hemorrhagic stroke (\( P = 0.8864 \)), and a 37% reduction in major coronary events (\( P = 0.0323 \)). In addition, every 1-mmole (39 mg/dL) decrease in LDL-C was associated with a 17% reduction in fatal and nonfatal stroke. In our study, a more potent statin could have lead to a larger decrease in LDL and consequently a higher rate of LDL-goal achievement. Unfortunately, health care system of Thailand has the limitation of drug access, especially in patient with the universal coverage policy where high potency statins were not allowed in the majority of patients in this study. With the approval of atrovastatin in a dose of 40 mg in the essential drug list of Thailand in 2012, a higher rate of LDL-C goal achievement could be seen in the future. However, not only the use of high potency drug, other measures including education should be considered influential for achieving treatment goal.

In terms of adverse drug reaction, myalgia and rhabdomyolysis were not found in this study. Nevertheless, the means of ALT were not more than 3 times of upper normal limit at admission and follow-up. The changes in AST and ALT levels were not clinically or statistically significant. In clinical practice, when an increase in ALT levels was observed, physicians discontinue or reduce statin dosage. Another reason for lack of reported adverse effects was the possible incomplete information in the medical charts. In a previous study, myalgia and rhabdomyolysis were detected in 3.2% and 0.5% of patients, respectively. A high occurrence of rhabdomyolysis was due to the concurrent use of high dosage of gemfibrozil (1,200 mg). Nevertheless, the estimation of rhabdomyolysis from randomized control trial of statin is similar to the corresponding estimate from the cohort studies of 3.4 per 100,000 person-year. The study of the effectiveness of additional reductions in cholesterol and homocysteine found that myopathy rate of was 0.9% associating with a high dose of simvastatin (80 mg/day) and 0.05% with a low dose (20 mg/day). Likewise, rhabdomyolysis rate in high dose of simvastatin (80 mg/day) was 0.12% and not found in low dose (20 mg/day). In this study, the combination of simvastatin 20 mg and gemfibrozil 600 mg per day was prescribed in 2 cases, but adverse drug reaction was not found.

The absence of adverse drug reactions, myalgia or rhabdomyolysis, were seen due to the low dosage of statin drugs of which simvastatin and atrovastatin doses were not more than 40 mg per day and rosuvastatin was not more than 10 mg per day. Since data of adverse drug reactions were reviewed from medical chart, the estimate of adverse events may be underestimated.

This study has few limitations. Since we did not exclude some patients who reached the goal of LDL-C level at admission, LDL-C goal achievement could be overestimated. Secondly, retrospective medical chart review in this study could lead to an underestimate of adverse drug reactions of statins. Findings from this study could help inform for multidisciplinary healthcare providers the success rate of LDL-goal achievement. A more aggressive hyperlipidemia therapy and an intensive patient education program should be encouraged.

Conclusion

This study determined the goal achievement of LDL-C in patients with ischemic stroke and hyperlipidemia at Prasat Neurological Institute. LDL-C goal accomplishment rates (LDL-C < 100 mg/dL) among patients with no diabetes were 82.22% and 68.89% for those without and with statin use before admission respectively. For patients with diabetes, LDL-C goal accomplishment rates (LDL < 70 mg/dL) of 21.74% and 37.04% were found in patients without and with statin use before admission respectively. Myalgia or rhabdomyolysis was not found in this study.

References

3. Ebrahim S, Sung J, Song Y-M, Ferrer RL, Lawlor DA, Smith GD. Serum cholesterol, haemorrhagic stroke, ischemic stroke, and