The Effect of Decreasing Statin's Dosage on LDL-C Levels After Target Levels Achieved

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Abstract-

Objective: Evidences from clinical trials had demonstrated that statins reduce the risk of cardio-cerebral vascular events. But lipid lowering therapy (LLT) was suboptimal in stroke patients and clinically, observation of reducing the dosage of statins is common when target low density lipoprotein cholesterol (LDL-C) level achieved. We aim to explore the changes in lipid profile after reducing statin's dosage when target LDL-C level achieved.

Methods: One hundred and three consecutive stroke patients follow up at out-patient clinic (44 women, 59 men) were recruited. Twenty two patients had their statin's dosage decreased to half while eighty one patients had their initial statin's dosage maintained after target LDL-C (< 100mg/dL) level achieved. Lipid profile before and after LLT adjustment were compared.

Results: The follow-up LDL-C level was significant higher while the percentage of patients with LDL-C level < 100 mg/dL was significant lower in patients with statin's dosage decreased. For all patients, regardless the adjustment of LLT, the percentage of patients with LDL-C level < 100 mg/dL was significant lower in follow- up lipid profile comparing with the baseline, but only the follow-up total cholesterol and LDL-C level were significant higher in the patients group with reduced statin's dosage. No significant change was found in follow-up high density-lipoprotein cholesterol and triglyceride level in either group.

Conclusion: More patients had LDL-C level > 100 mg/dL after dosage of statins decreased. We suggested that only for absolute contraindication or adverse effects of statins should we adjust LLT, it is better to maintain the dosage of statins after target level achieved. The impact of lipid profile changed after LLT adjustment on clinical outcomes needs further studied.

Key Words: lipid lowering therapy, statins, low density lipoprotein cholesterol, cardio-cerebral vascular event

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INTRODUCTION

Cerebrovascular disease is the third leading cause of death in Taiwan. It remains one of the major healthcare problems and is among the principal causes of long-term disability worldwide. About 20% of stroke survivors require institutional care three months after the event and 15-30% being permanently disabled[1]. The medical costs spent on cerebrovascular disease are huge and bring up the importance of stroke prevention. In Taiwan, with a population of 23 million, approximately 80 000 new or recurrent strokes a year, spent a total of US $375 million in medical costs for stroke in 2007.

Prevention of stroke is focused on reducing modifiable risk factors. Among them, plasma lipids and lipoproteins is a prominent risk factor for cardiovascular disease while the association between cholesterol and stroke remains inconsistent and controversial[2,3]. Despite this fact, large clinical trials and meta-analyses had clearly shown that reduction of cholesterol levels via statins safely reduces the risk of stroke[4-6]. Accordingly, lipid-lowering therapy (LLT) with either non-pharmacological or pharmacological interventions, in particular with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) treatment has emerged as guideline therapy for stroke prevention in hypercholesterolemic patients with atherosclerosis and also in normocholesterolemic individuals. American Heart Association/ American Stroke Association recommended statin therapy with intensive lipid-lowering effects to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic stroke (TIA) who have evidence of atherosclerosis, and who are without known coronary heart disease (CHD) with target low-density lipoprotein cholesterol (LDL-C) level <100 mg/dL. For patients with atherosclerotic ischemic stroke or TIA and without known CHD, it is reasonable to target a reduction of at least 50% in LDL-C or a target LDL-C level of < 70 mg/dL to obtain maximum benefit[7].

In Taiwan, all medical expenditure is conditionally reimbursed by the Bureau of National Health Insurance (NHI). Due to the limited medical resources, guidelines and rules existed in managing all kind of medical situations. For stroke patients with dyslipidemia, NHI recommended LLT including used of statins life long but it also suggested when target total cholesterol (TC) or LDL-C levels achieved, treating physicians may consider to reduce the statins' dosage. In clinical practice, for reasons which are poorly understood, but postulated to relate to medical costs, we have observed that dosage of statins was always reduced when target TC or LDL-C level achieved even without medication contraindication or serious adverse drug effects. Many efforts had been done to adjust LLT in order to achieve the desired LDL-C level, data regarding the influence of lipid profile changed after statins' dosage decreased is sparse.

Aims:

In this study, we aim to explore the influence of reducing statin's dosage on LDL-C level after target level achieved.

METHODS

Study design

This was a single-centre, retrospective observational study. The study hospital was a medical centre and a main referral hospital serving an area with 3 million inhabitants.

Institutional review board approval was obtained from the Chang Gung Memorial Hospital Ethical Committee.

Subjects

Between July 2010 and June 2011, one hundred and three consecutive stroke patients with dyslipidemia and under LLT follow up at out-patient clinic (44 women, 59 men) were recruited. All data was registered from electronic medical records after reviewed. Eighty one patients had their statin's dosage maintained and twenty two patients had their statin's dosage decreased to half after target LDL-C level achieved (<100 mg/dL). We registered the basic characteristics of the patients including age, gender, common vascular risk factors, type of LLT and stroke type. Liver function, muscular side

Table 1. Demographic data of 103 participants

characteristics	Statin with initial dosage maintain n=81	Statin with half the initial dosage n=22	p value
age	68+/-10	66+/-11	0.248
sex (M:F)	45:36	14:8	0.628
ischemic stroke	67(83%)	14(64%)	0.076
Intracerebral hemorrhage	3(3.7%)	0(0%)	1
Hypertension	58(72%)	12(55%)	0.196
Diabetes Mellitus	33(41%)	5(23%)	0.142
Ishemic heart disease	13(16%)	4(18%)	0.756
atrial fibrillation	1(1.2%)	2(9%)	0.115
TC (mg/dL)	149+/-18	143+/-22	0.167
LDL-C (mg/dL)	76+/-15	70+/-22	0.111
HDL-C (mg/dL)	49+/-14	51+/-12	0.603
Triglyceride (mg/dL)	120+/-49	114+/-46	0.571
LDL-C < 100mg/dL	77(95%)	20(91%)	0.606
Follow-up			
TC (mg/dL)	151+/-23	188+/-36	<0.0001
LDL-C (mg/dL)	78+/-20	110+/-34	<0.0001
HDL-C (mg/dL)	49+/-13	50+/-10	0.631
Triglyceride (mg/dL)	129+/-88	144+/-61	0.473
LDL-C < 100mg/dL	67(84%)	9(41%)	<0.0001

TC: total cholesterol LDL-C: low density lipoprotein cholesterol HDL-C: high density lipoprotein cholesterol

effects or any discomfort related to the LLT documented in the records were reviewed to found out the reasons for adjusting LLT. We also looked for any vascular events documented during the studied period.

The last lipid profile before recruited and the follow-up lipid profile at least 3 months later after enrolled were registered for comparison. All patients were followed up for at least 6 months.

Recommendation of LLT by the Bureau of National Health Insurance

The Bureau of NHI defined dyslipidemia as having either TC serum levels >200 mg/dL or LDL-C levels >130 mg/dL or high-density lipoprotein cholesterol (HDL-C) levels <40 mg/dL combined with triglycerides (TG) levels >200 mg/dL.

For those who have either stroke, diabetes mellitus or ischemic heart disease and fulfill the above definition of dyslipidemia, in adjunct to life style modification, LLT is recommended for life long and the desired target level of LDL-C is <100 mg/dL. The treating physician might consider (not mandatory) to decrease dosage of LLT if the desired target level achieved. LLT will not be reimbursed if the above rules are not followed.

Statistical analysis

Data were given as frequencies and percentages. Additional descriptive statistics were provided for demographic, clinical, and follow-up variables. Mean and standard deviation were reported, as appropriate, for continuous variables. Frequencies and percentages were reported for categorical variables. To test for group differences, the chi-squared test was used for discrete variables to compare associations between categorical variables, and the independent-sample Student's t-test for variables measured on a continuous scale. A p-value of

Table 2. Lipid profile after statin dosage adjusted

	baseline	follow-up	p value
Statin with initial dosage maintain (n=81)			
TC (mg/dL)	149+/-18	151+/-23	0.604
LDL-C (mg/dL)	76+/-15	78+/-20	0.551
HDL-C (mg/dL)	49+/-14	49+/-13	0.799
Triglyceride (mg/dL)	120+/-49	129+/-88	0.435
LDL-C < 100 mg/dL	77(95%)	67(84%)	0.022
Statin with half the initial dosage (n=22)			
TC (mg/dL)	143+/-22	188+/-36	<0.0001
LDL-C (mg/dL)	70+/-22	110+/-34	<0.0001
HDL-C (mg/dL)	51+/-12	50+/-10	0.751
Triglyceride (mg/dL)	114+/-46	144+/-61	0.082
LDL-C < 100 mg/dL	20(91%)	9(41%)	0.001

TC: total cholesterol LDL-C: low density lipoprotein cholesterol HDL-C: high density lipoprotein cholesterol

less than 0.05 was considered statistically significant. SPSS 13.0 software was used for statistical analysis.

RESULTS

The baseline characteristics of all subjects are outlined in Table 1. Eighty one patients had their initial statin dosage maintained (group A) while twenty two patients had their statin dosage reduced to half (group B). Within group A, 33 (41%) patients were prescribed with atorvastatin 40mg, 14 (17%) with rosuvastatin 10mg, 3 (4%) patients with simvastatin 40mg and 31 (38%) with fluvastatin XL 80mg respectively. Within group B, 10 (45%) patients were prescribed with atorvastatin 40mg, 8 (36%) with rosuvastatin 10mg, 3 (14%) patients with simvastatin 40mg and 1 (5%) with fluvastatin XL 80mg respectively.

Comparing the baseline demographic data of these two groups, no significant difference was found. But the follow-up TC and LDL-C level were significant higher while the percentage of patient with LDL-C level < 100 mg/dL was significant lower in group B. For all patients, regardless the adjustment of statin's dosage, the percentage of patients with LDL-C level < 100 mg/dL was significant lower in follow-up lipid profile comparing with the baseline, but only the follow-up TC and LDL-C level were significant higher in group B. No significant change was found in follow-up HDL-C and TG level in either group. (Table 2)

The reason for decreasing the dosage of statins was based on the recommendation of NHI. No obvious absolute medication contraindication or serious drug adverse effects documented in medical records and no recurrent vascular events documented in the medical records in either group in follow up.

DISCUSSION

Our observations reveal that after target LDL-C levels achieved in dyslipidemic stroke patients who were under LLT, reducing the dosage of statins significantly increased follow-up LDL-C and TC levels, and also significant less percentage of patients with LDL-C levels < 100 mg/dL. Interestingly, we found that even the dosage of statins remained no change after target level achieved, the percentage of patients with follow-up LDL-C level < 100 mg/dL was significantly less too although no significant change in total LDL-C and TC levels.

Many studies focusing on statins and stroke prevention have been published in recent years. A systematic analysis including the data of more than 90,000 patients found a significant 21% relative risk reduction (RRR) of

stroke incidence and most prevalent in patients at high vascular risk. Most recently, meta-regression analysis evaluating the data of more than 165,000 individuals enrolled in statin trials showed that each 1 mmol/l (39 mg/dl) reduction in LDL-C equates to a 21% RRR in stroke incidence[4,5,8].

The first statin study to investigate the effect of statin on secondary stroke prevention, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial had demonstrated that in patients with recent TIA or stroke, but without a history of CHD or atrial fibrillation[6], treatment with 80 mg/day atorvastatin reduced the incidence of fatal and nonfatal stroke with 16% RRR. Furthermore, secondary endpoints, including TIA and major cardiovascular events, were significantly reduced in the statin group. The SPARCL trial led to a change in guidelines. First, after TIA or first stroke, statin therapy should be initiated in patients with or without CHD. Second, stroke and TIA qualify as CHD risk equivalent. Third, patients at high vascular risk should receive statin therapy[7].

Although guidelines suggested intensive LLT in stroke patients but lipid management in clinical practice was suboptimal, with only one third to one half of patients achieving recommended cholesterol levels on LLT[9-12]. This was true in Taiwan.

Our previous study showed that in-hospital LLT was initiated in 74% of dyslipidemic patients which was considered adequate as compared to other studies. However, 6 months after discharge from the hospital, as many as 55% of the patients who were previously on LLT, especially older patients left untreated. For those who received regular LLT, the target LDL-C cholesterol level (<100 mg/dL) was achieved in only 30% of patients[13]. A more recent large study, Surveillance of Stroke Care in the Taiwan Stroke Registry (TSR) had demonstrated that only 38% of patients with dyslipidemia were prescribed lipid-lowering drugs at discharge, in comparison to the corresponding Get With The Guideline-Stroke figure of greater than 73%[14,15]. The definition of LLT in TSR can explain the 36% discrepancy between the above two studies on the percentage of patients on LLT. In TSR, LLT was defined as lipid-lowering drug prescription for patients with ischemic stroke or TIA with low-density lipoprotein >100 mg/dL or patients taking lipid lowering agents on admission. But according to the NHI guideline in Taiwan, the LLT can be reimbursed only when the LDL-C level is greater than 130 mg/dL. Patients with LDL-C level between 101 and 129 mg/dL will not be given LLT unless patients agree to pay the medical cost. This treatment gap has considerable clinical and economic implications in terms of reduced effectiveness for preventing cardiovascular events and deaths, and increased costs to healthcare plans and payers[16].

There is much space to be improved in lipid management. To get the target LDL-C level, several multinational clinical trials have demonstrated that switching to a more efficacious statin improved lipid goal achievement[17,18]. A formulary conversion program within the military indicated that further LDL-C reduction can be achieved by shifting to more effective statins, such as rosuvastatin[19].

As adherence to evidence-based treatment following hospital discharge has been shown to be low, new practice guidelines are needed to optimize prevention of vascular events[20]. In this context, LDL-C might become an important biomarker.

While effort was given on how to improve adherence and to reach target LDL-C level, no studies explored the problem of LLT adjustment when target LDL-C level achieved as suggested by the NHI guideline in Taiwan. The target LDL-C level was set to be < 100mg/dL or even < 70mg/dL (high vascular risk patients) in the international guideline. According to the NHI guideline in Taiwan, reducing the dosage of LLT or keep LLT in the lowest maintenance dosage is suggested when target LDL-C level (< 100mg/dL) achieved. This suggestion of LLT adjustment by NHI after target LDL-C level achieved is unique. To be reimbursed or spend as little medical cost, get with the NHI guideline in Taiwan in managing dyslipidemia is common among clinical practice. In this study, we had shown that after LLT adjustment when desired target LDL-C level reached, the level of LDL-C or percentage of patients with > 100mg/dL will increase.

Studies had shown that discontinuation of statin

therapy following acute cerebrovascular or cardiovascular events may impede vascular function and increase morbidity and mortality[21]. Therefore, abrupt discontinuation of statin treatment in patients suffering ischemic stroke should be avoided. But the impact of the change in LDL-C level on clinical vascular outcomes after LLT adjustment was poorly understood. Although no recurrent vascular events found in this study after dosage of statin adjusted, we believe that negative impact existed if more patients were included and more long follow-up period.

There were limitations in this study. The results were from the small numbers of study subjects and it did not apply to whole dyslipidemic stroke population. More important, we failed to demonstrate the impact on clinical outcomes from the adjustment of statins therapy.

CONCLUSION

More patients had undesired follow-up LDL-C levels after the dosage of statins decreased. Regardless the adjustment of LLT or not, the percentage of patients with LDL-C < 100 mg/dL declined. We suggest that only for absolute contraindication or adverse effects of statins should we reduce or hold the treatment, it is better to maintain the dosage of statins after target LDL-C level achieved. The impact of returning to undesired LDL-C levels on clinical outcomes such as more vascular events needs further studied.

Our observations raises the need for NHI in Taiwan to review the lipid lowering guidelines for changing reimbursement policies and at least in parallel to the existed international guidelines such as The Adult Treatment Panel (ATP) III, updated in 2004[22]. We also suggested the guidelines should be revised regularly base on clinical evidences in the coming future in order to provide better medical care to the public.

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