Determinants for Achieving the LDL-C Target of Lipid Control for Secondary Prevention of Cardiovascular Events in Taiwan

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Abstract

Background

Epidemiological and clinical studies have clearly established the link between low-density lipoprotein cholesterol (LDL-C) and atherosclerosis-related cardiovascular consequences. Although it has been a common practice for physicians to prescribe lipid-lowering therapy for patients with dyslipidemia, the achievement rate is still not satisfied in Taiwan. Therefore, the determinants for achieving the LDL-C target needed to be clarified for better healthcare of the patients with dyslipidemia.

Method

This registry-type prospective observational study enrolled the patients with cardiovascular diseases (coronary artery disease (CAD) and cerebrovascular disease (CVD)) from 18 medical centers across Taiwan, and clinically followed them for five years. At every clinical
visit, vital signs, clinical endpoints, adverse events, concurrent medications and laboratory specimens were obtained as thoroughly as possible. The lipid profile (total cholesterol, high-density lipoprotein cholesterol, LDL-C, triglyceride), liver enzymes, and creatinine phosphokinase were evaluated at baseline, and every year thereafter. The cross sectional observational data was analyzed for this report.

**Result**

Among the 3,486 registered patients, 54% had their LDL-C < 100 mg/dL. By univariate analysis, the patients achieving the LDL-C target were associated with older age, more male sex, taller height, lower blood pressure, more under lipid-lowering therapy, more smoking cessation, more history of CAD, DM, physical activity, but less history of CVD. The multivariate analysis showed statin therapy was the most significant independent determinant for achieving the treatment target, followed by age, history of CAD, diabetes, blood pressure, and sex. However, most patients were on regimens of very-low to low equipotent doses of statins.

**Conclusion**

Although the lipid treatment guideline adherence is improving in recent years, only 54% of the patients with cardiovascular diseases have achieved their LDL-C target in Taiwan, and the most significant determinant for this was statin therapy.

**Introduction**

Cardiovascular disease, including coronary artery disease (CAD) and cerebrovascular disease (CVD), is common in the general population, especially in adults past the age of 60 years. In 2012, cardiovascular disease was estimated to result in 17.3 million deaths worldwide on an annual basis [1]. Atherosclerosis is responsible for almost all cases of cardiovascular diseases, especially CAD. A variety of factors are associated with an increased risk for atherosclerosis, including age, family history, current cigarette smoking, hypertension, diabetes and dyslipidemia.

Twenty-five year follow-up data from the Seven Countries study show that serum total cholesterol (TC) levels are linearly related to CAD mortality across cultures [2]. The link between high cholesterol levels and increased incidence of cardiovascular disease has also been shown in the prospective part of the Multiple Risk Intervention study [3]. In epidemiological studies, measurements of serum cholesterol have been routinely used. Besides, high LDL-cholesterol (LDL-C) level is a particularly important risk factor for atherosclerosis [4,5], and has been associated with an increased incidence of CAD in a large number of studies [6]. Therefore, LDL-C has long been identified by NCEP as the primary target of cholesterol-lowering therapy. In 2004 updated NCEP ATP III and 2006 updated ACC/AHA guidelines, LDL-C should be < 100 mg/dL for all patients with CAD or CAD risk equivalents, but in addition, it is reasonable to lower LDL-C to < 70 mg/dL in such patients with very high risk [7,8].

Although it has been a common practice for physicians to prescribe lipid-lowering therapy for patients with dyslipidemia, the achievement rate is still not satisfied in the real world [9,10]. In the REALITY-Asia study, only 38% of high risk patients attained ATP III targets for LDL-C (<100mg/dL) in Asians [11]. Although there is a well-established national medical insurance
system in Taiwan, the LDL-C goal attainment percentage is still low in those high-risk patients. Therefore, the determinants for achieving the LDL-C target needed to be clarified for better healthcare of the CVD patients.

Method

2.1 Study population

This study was conducted from a multi-center observational registry, the Taiwanese Secondary Prevention for patients with AtherosCLerotic disease (T-SPARCLE) Registry, from 14 teaching hospitals in Taiwan [12,13]. This registry attempts to recruit and follow-up a large population of patients with cardiovascular diseases who have been receiving secondary prevention therapies so as to define the current status of these therapies and their effects on morbidity and mortality in Taiwan.

Adult patients (>18 year-old) who had stable cardiovascular diseases, including CAD and CVD, were recruited. Patients with CAD was defined as those who had significant coronary artery stenosis (>50%), or had a history of myocardial infarction, or who had angina showing ischemic electrocardiographic changes or positive response to stress tests. Patients with CVD were defined as those with cerebral infarction, intra-cerebral hemorrhage, transient ischemic attack attributed to cervical or intracranial large artery stenosis (>50%). Patients with neurocognitive or psychiatric condition, life expectancy of less than 6 months, and hemodynamically significant valvular or congenital heart disease are excluded.

2.2. Ethic statement

The study was approved by the Joint Institutional Review Board, Taiwan, R.O.C. for each participating hospital. The JIRB number was 09-S-015. Written informed consents were obtained from all patients.

2.3 Targets measurement

Eligible patients who fulfilled the enrolment criteria would be followed up every year for a total of 5 years. At every clinic visit, vital signs, clinical endpoints, adverse events, concurrent medications and laboratory specimens were obtained as thoroughly as possible. The lipid profiles (TC, HDL-C, LDL-C, and TG), liver enzymes, and creatinine phosphokinase were evaluated at baseline, and every year thereafter. The concurrent medications and their dosage were recorded in detail, especially the lipid-lowering drugs (e.g., statin, fibrate, ezetimibe, bile acid sequestrants, nicotinic acid).

The Taiwanese guideline recommended lipid target was applied for evaluation of the achievement. The optimal LDL-C level was <100mg/dL.

2.4 Statistical analysis

Categorical variables are presented as percentage and continuous or discrete variables as mean ± standard deviation. The χ² test was used to compare proportions; student’s t test or analysis of variance was applied to compare difference in continuous variables between groups. A logistic regression analysis was adapted to evaluate the odds ratio and 95% confidence intervals (CI) of the recommended lipid target. Statistical analyses were performed using the SPSS software package version 17.0 (SPSS Inc., Chicago, IL).
Result

From January, 2010 to February, 2011, 4561 patients were enrolled and 3486 patients (men, 68.4%; female, 31.6%; mean age, 65.8 ± 12 years) included in this analysis. Of these, 2163 (62.1%) had CAD; 921 (26.4%) had family history of premature CAD; 604 (17.3%) had previous stroke or TIA history. The demographics and clinical characteristics of the patients are shown in Table 1. Only 54% of the patients achieved the optimal LDL-C level (<100mg/dL); 69.1% achieved the HDL-C goal (>40mg/dL); 31.1% achieved optimal TG level (<150mg/dL).

Among these patients, 2434 (69.8%) had medical treatment for dyslipidemia. About 89.8% of the treated patients were on monotherapy with statin or other lipid-lowering medication. The details of lipid-lowering treatment are shown in Table 2. Most patients were on regimens of very low (<1 dose/day, 23%) to low (1–1.9 dose/day, 38%) equipotency doses of statins [14]. The statin potency comparison is listed in Table 3.

Table 1. Patients’ demographics and clinical characteristic.

| Variable                  | N     | Mean  | STD   |
|---------------------------|-------|-------|-------|
| Age, yrs                  | 3486  | 65.79 | 11.96 |
| Male, %                   | 2386  | 68.45 |       |
| Waist, cm                 | 3110  | 93.53 | 11.08 |
| Hip, cm                   | 3034  | 100.60| 8.74  |
| W/H ratio                 | 3038  | 0.93  | 0.11  |
| Height, cm                | 3329  | 162.69| 8.31  |
| Weight, kg                | 3357  | 69.73 | 12.51 |
| BMI, kg/m²                | 3303  | 26.25 | 4.08  |
| Hypertension              | 2611  | 74    |       |
| SBP, mmHg                 | 3264  | 132.60| 17.36 |
| DBP, mmHg                 | 3240  | 76.14 | 11.10 |
| Pulse rate, beats/min     | 2607  | 74.80 | 12.80 |
| Current Smoker            | 487   | 14    |       |
| Physical Activity <3times/w, % | 1905 | 54.6% |       |
| TC, mg/dL                 | 3486  | 174.79| 40.88 |
| HDL-C, mg/dL              | 3486  | 45.69 | 14.11 |
| Low HDL <40mg/dL, %       | 1075  | 30.8% |       |
| LDL-C, mg/dL              | 3486  | 101.47| 34.48 |
| High LDL-C >100mg/dL, %   | 1604  | 46%   |       |
| TG, mg/dL                 | 3486  | 139.95| 90.04 |
| High TG >200mg/dL, %      | 2401  | 68.9% |       |
| Creatinine, mg/dL         | 3057  | 1.13  | 0.74  |
| AC Sugar, mg/dL           | 3080  | 118.36| 40.98 |
| HBA1C, %                  | 1750  | 7.29% | 4.68  |
| AST, mg/dL                | 1917  | 28.99 | 17.94 |
| ALT, mg/dL                | 2695  | 29.00 | 20.27 |
| CK, mg/dL                 | 1451  | 132.14| 303.98|

STD, standard deviation; W/H ratio, weight and height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase.

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By univariate analysis, the patients achieving the LDL-C target were associated with older age, more male sex, taller height, lower blood pressure, lower baseline cholesterol levels, more smoking cessation, more history of CAD, DM, physical activity, but less history of stroke or TIA (Table 4).

The multivariate analysis showed statin therapy was the most significant independent determinant for achieving the treatment target (odd ratio 1.53, p-value \(<0.0001\)), followed by age, history of CAD, DM, controlled blood pressure, and sex. (Table 5)

**Discussion**

It is well known that adequate control of dyslipidemia is important in both primary and secondary prevention of cardiovascular diseases. It has been a common practice for physicians to prescribe lipid-lowering therapy for patients with dyslipidemia and the use of lipid-lowering agents has increased in the recent years. However, there is still a large treatment gap between guideline recommendation and the real-world lipid target achievement although there has been a well-established national medical insurance system in Taiwan.

In 2009, Kornelia, K., et al. [15] compared the results of EUROASPIRE I, II and III surveys [16–18], which conducted in European countries and enrolled patients who had CAD and underwent coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, or had acute myocardial infarction history. The proportion of patients with raised blood
Table 4. Difference of clinical characteristics between the patients achieving and not achieving LDL-C target.

| Variable                   | LDL-C < 100 mg/dL | LDL-C ≥ 100 mg/dL |
|----------------------------|-------------------|-------------------|
|                            | N     | Mean  | Std   | N     | Mean  | Std   | p-value |
| Age, yrs                   | 1882  | 65.93 | 11.65 | 1604  | 65.63 | 12.31 | 0.4728  |
| Men, %                     | 1330  | 70.67%| 10.48%| 1056  | 65.84%| 11.06%| 0.0022  |
| Waist, cm                  | 1676  | 93.6  | 11.12 | 1434  | 93.44 | 11.03 | 0.6885  |
| Hip, cm                    | 1644  | 100.62| 8.36  | 1390  | 100.57| 9.16  | 0.8793  |
| W/H ratio                  | 1637  | 0.93  | 0.11  | 1401  | 0.93  | 0.12  | 0.7862  |
| Height, cm                 | 1784  | 163.03| 8.24  | 1545  | 162.29| 8.37  | 0.0106  |
| Weight, kg                 | 1801  | 69.61 | 12.3  | 1556  | 69.86 | 12.75 | 0.571   |
| BMI, kg/m²                 | 1784  | 26.35 | 4.27  | 1519  | 26.14 | 3.85  | 0.1272  |
| SBP, mmHg                  | 1752  | 131.68| 17.43 | 1512  | 133.66| 17.23 | 0.0012  |
| DBP, mmHg                  | 1740  | 75.12 | 11.03 | 1500  | 77.33 | 11.06 | 0.0001  |
| Pulse rate, beats/min      | 1338  | 74.5  | 12.76 | 1289  | 75.13 | 12.85 | 0.2116  |
| TC, mg/dL                  | 1882  | 149.85| 25.62 | 1604  | 204.05| 35.7  | 0.0001  |
| HDL-C, mg/dL               | 1882  | 45.07 | 14.67 | 1604  | 46.43 | 13.38 | 0.0042  |
| LDL-C, mg/dL               | 1882  | 77.04 | 15.45 | 1604  | 130.13| 27.99 | <0.0001 |
| TG, mg/dL                  | 1882  | 133.89| 99.51 | 1604  | 147.05| 77.44 | <0.0001 |
| Creatinine, mg/dL          | 1681  | 1.15  | 0.8   | 1376  | 1.11  | 0.66  | 0.1252  |
| AC sugar, mg/dL            | 1708  | 118.24| 41.27 | 1372  | 118.51| 40.63 | 0.8576  |
| HBA1C, %                   | 1014  | 7.43  | 5.95  | 736   | 7.11  | 1.82  | 0.1012  |
| AST, mg/dL                 | 1096  | 25.85 | 16.91 | 821   | 29.17 | 19.24 | 0.7057  |
| ALT, mg/dL                 | 1514  | 28.51 | 19.82 | 1181  | 29.69 | 20.82 | 0.1513  |
| CK, mg/dL                  | 883   | 126.79| 252.66| 568   | 140.47| 370   | 0.4397  |

| Questionnaire               | N     | %     | N     | %     | p-value |
|----------------------------|-------|-------|-------|-------|---------|
| Smoking-Never              | 1216  | 64.61 | 1045  | 65.15 | 0.1375  |
| -Current                   | 248   | 37.24 | 239   | 42.75 | —       |
| -Cessation                 | 418   | 62.76 | 320   | 57.25 | —       |
| Family history of MI/Sudden Death/CVD | 510   | 32.44 | 411   | 31.14 | 0.4526  |
| Family history of diabetes | 410   | 26.45 | 354   | 26.84 | 0.8153  |
| History of hypertension    | 1399  | 76.74 | 1212  | 78.19 | 0.3149  |
| History of Heart failure   | 168   | 9.8   | 124   | 8.8   | 0.3454  |
| History of MI or CAD       | 1274  | 74.27 | 887   | 63.18 | <0.0001 |
| History of DM, IFG, or IGT | 796   | 45.12 | 595   | 40.73 | 0.012   |
| History of ischemic stroke | 197   | 11.43 | 214   | 15.19 | 0.002   |
| History of non-ischemic stroke | 40   | 2.36  | 40    | 2.88  | 0.3711  |
| History of TIA             | 46    | 2.72  | 67    | 4.82  | 0.002   |
| Alcohol consumption        | 243   | 12.96 | 211   | 13.17 | 0.8539  |
| Physical activity habits   | 890   | 47.29 | 691   | 43.11 | 0.0134  |

W/H ratio, weight and height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; MI, myocardial infarction; CVD, cerebrovascular disease; CAD, coronary artery disease; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; TIA, transient ischemic attack.

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cholesterol concentration (>4.5mmol/L, 174mg/dL, set by the 2003 Joint European Societies’ guidelines) was lowest in the EUROASPIRE III, and highest in the EUROASPIRE I. That means the lipid target achievement rate has improved over time. Therapeutic control in those taking lipid-lowering drugs has also improved. However, the lipid target achievement rate in EUROASPIRE III was only 53.8%, which is still not satisfied.

In the United States, Jones, P.H., R. Nair, and K.M. Thakker [19] reported a cross-sectional, retrospective study of 3 data sources among 2003–2010, which showed, 67% to 77% achieved LDL-C <100 mg/dL in high-risk patients treated with statin monotherapy for >90 days. In contrast in Asia, the REALITY-Asia study published in 2008 [11], which enrolled 2622 patients from 6 Asian countries, showed only 38% of those with CAD/diabetes attained the ATP III targets for LDL-C (<100 mg/dL). The target achievement rate was lower than those of the Western countries. Among these Asian countries, goal achievement rate in Taiwan was the lowest (16%) in the CAD/diabetes group. In the present study, the target achievement rate was 54%, which is much higher than the result of REALITY-Asia, and is similar to the result of EUROASPIRE III. That means the physicians in Taiwan have paid more attention on the lipid control for the cardiovascular diseases secondary prevention in recent years.

The multivariate analysis in this study showed statin therapy was the most significant independent determinant for achieving the treatment target. However, most of the patients had low and very low equipotent doses of statins. From 2003 to 2005, we conducted an unpublished retrospective study to survey the physicians’ behaviour on statin usage. About 66% physicians would not modify their prescription even when the treatment target was not achieved at the starting dose of the drugs, especially among the physicians working in the local area hospitals. The most common (32%) rationale for this decision was they thought the TC or LDL-C level

Table 5. Determinants for achieving LDL-C target by multivariate analysis.

|                      | β     | Odds ratio | 95% confidence interval | p-value |
|----------------------|-------|------------|-------------------------|---------|
| **Age**              |       |            |                         |         |
| <65 years            | 1.00  |            |                         |         |
| 65–74 years          | 0.278 | 1.321      | 1.10–1.59               | 0.0033  |
| >75 years            | 0.399 | 1.49       | 1.22–1.83               | 0.0001  |
| **Sex: Male vs Female** | 0.246 | 1.279      | 1.06–1.55               | 0.0111  |
| **BMI**              |       |            |                         |         |
| <24                  | 1.00  |            |                         |         |
| 24–26.9              | -0.118| 0.889      | 0.73–1.08               | 0.2428  |
| > = 27               | -0.160| 0.852      | 0.70–1.04               | 0.1085  |
| **Hypertension**     |       |            |                         |         |
| SBP ≥ 140 or DBP ≥ 90| -0.221| 0.802      | 0.68–0.95               | 0.0086  |
| SBP <140 and DBP <90 | 1.00  |            |                         |         |
| **Smoking: Cessation vs Current** | -0.025| 0.975      | 0.81–1.17               | 0.7846  |
| **History of MI or CAD: Yes vs No** | 0.309| 1.362      | 1.13–1.64               | 0.0011  |
| **History of DM, IFG, or IGT: Yes vs No** | 0.247| 1.279      | 1.09–1.50               | 0.0023  |
| **History of CVD: Yes vs No** | -0.213| 0.808      | 0.65–1.01               | 0.0581  |
| **Physical activity: Yes vs No** | 0.070| 1.073      | 0.92–1.26               | 0.3854  |
| **Statin: Yes vs No** | 0.425| 1.53       | 1.29–1.81               | <0.0001 |
| **Fibrate: Yes vs No** | 0.173| 1.188      | 0.85–1.66               | 0.3149  |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; CAD, coronary artery disease; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CVD, cerebrovascular disease.

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has been acceptable although the targets were not achieved. It means that these physicians did not implant the treatment guidelines to their clinical practice and were not eager to have their patients to achieve the treatment target, or they didn’t catch up the latest guideline. About 17% physicians didn’t modify the prescription because they concerned the possible side effects induced by statin dosage adjustment might affect the drug compliance of the patients. From the patient’s aspect, 25% of patients without attaining their lipid goal preferred not increase their drug potency or dosage because of concerning the possible side effects of the more potent/higher dosage therapy. Therefore, to improve the achievement rate in Taiwan, we should educate not only the physicians, but also patients about the latest lipid guideline and the importance of guideline adherence, especially to those in the local area hospital.

In the present study, age is another significant determinant for achieving the treatment target. The result is consistent with the report of Jones, P.H., R. Nair, and K.M. Thakker [19]. In the last decade, several studies have confirmed the efficacy, safety and tolerability of HMG-CoA reductase inhibitors (statins) [20–22], and showed that elderly patients with high cardiovascular risk derive the highest benefits from statin treatment. However, statins are under-utilized in elderly patients according to the retrospective study reported by Ko, D.T., M. Mamdani, and D.A. Alter [23]. In contrast, Taiwanese physicians have done more to the lipid control in elderly patients, who have achieved the lipid target more easily than younger patients and may get higher benefit from it.

Male gender is also a determinant for target achievement. This result is in accordance with previous reports [24,25]. Singh, M., et al. conducted a retrospective study [25] to analyse the gender difference of LDL-C target achievement in secondary prevention after acute myocardial infarction over a 5-year period (2003–2007). No gender difference of lipid-lowering therapy was observed. However, females had a higher LDL than did males both in 2003 and 2007. In recent decades, more and more female patients suffer from coronary artery disease. The prognosis of female patients after acute coronary syndrome has been shown to be inferior to that of male patients [26,27]. Therefore, intensive lipid treatment should be emphasized for females to attain the lipid treatment target.

This study revealed that the target-achieved rate of lipids was significantly lower in the patients with CVD. Some previous studies have also shown similar findings [28–30]. In the World Health Organization study on Prevention of Recurrence of myocardial Infarction and Stroke (WHO-PREMISE) conducted in several developing countries, the prescription rate of statins was lower in the patients with stroke than in those with CAD [28]. In the Vascular Protection and Guideline-Oriented Approach to Lipid-Lowering registries in Canada, the LDL-C target achievement and statin use were around 10% lower in the patients with CVD than in those with CAD [29]. The CVD-CAD discrepancy in secondary prevention therapy of cardiovascular diseases can be explained in several ways. First, there are disparities of risk perception between CVD and CAD. Both patients and physicians regarded CAD as higher risk than CVD, and the risk-scoring was even lower in patients than in physicians [30]. Therefore, the risk factors management and target attainment may be dissimilar. Knowledge of risk factors for stroke and warning signs of stroke are often suboptimal [31]; only 30% of patients could recognize transient ischemic attack and minor stroke immediately after stroke in a population-based study of behaviour [32]. Second, stroke comprises heterogeneous etiologies, and the approach to management may be differential depending on the etiology. Statin for example, is recommended for use in the patients with atherosclerotic ischemic stroke or transient ischemic attack [31], but it is arguable whether statins should be routinely used in every CVD patient, including non-atherosclerotic diseases as dissection of small artery lacune [33].

Diabetic patients with existing cardiovascular diseases are considered to be in very high risk for further cardiovascular events. Previous studies have shown that patients with diabetes were
more likely to have untreated or insufficiently treated dyslipidemia [34–36]. However, due to the increasing use of lipid-lowering agents, lipid goal attainment percentage in diabetic patients increased year by year in the U.S [37]. In our present study, the patient with diabetes, impaired fasting glucose, or impaired glucose tolerance is an independent determinant for target achievement, similar with patients with CAD. It means that the physicians in Taiwan have realized the importance of lipid control in high risk diabetic patients and done more effort on it.

This study has several limitations. First, this study’s patients were recruited mainly from the departments of cardiology and neurology of the teaching hospitals, unlike the case in some studies where the patient source was mainly from the general practitioners. Although the results from the present study may have the problem of generalizability of our results, in Taiwan there was little restriction of patients’ access to teaching hospitals, and most patients often continued their outpatient clinics follow-up at the same hospitals where they were hospitalized for the major diseases. Second, it is likely that patients with severe stroke with ambulation difficulty may have restricted their presentation to an outpatient clinic and hence enrolment into this study. It is possible that an overestimation of medication use in CVD patients occurred in this study. The disparity of medication between CAD and CVD patients may be even bigger than shown here. Third, we had no detailed information about patients’ compliance and duration of secondary prevention therapies, contraindication or reasons for discontinuing some medications, and lifestyle modifications. However, the clinical information about each participant was obtained from direct medical records and interviewing, and would be followed-up periodically. The validity of these data is high.

**Conclusion**

Although the lipid treatment guideline adherence is improving in recent years, only 54% of the patients with cardiovascular diseases have achieved their LDL-C target in Taiwan, and the most significant determinant for this was statin therapy. However, most patients under lipid-lowering therapy were on regimens of very-low to low equipotent doses of statins. We should emphasize the importance of guideline adherence, especially the use of statin therapy, not only to physicians but also to patients.

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**Author Contributions**

Conceived and designed the experiments: LTH WHY HIY CCW JWC. Performed the experiments: LTH WHY WKT YWW ICH THL YHL YHL KYW KCU CCF HIY CCW JWC. Analyzed the data: SYC WHP CCW. Wrote the paper: LTH CCW.

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