CURRENT STATUS OF LIPID CONTROL FOR SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS IN TAIWAN

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Abstract
Atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral arterial disease (PAD), is the second leading cause of death in Taiwan. Dyslipidemia has long been recognized as the most important risk factor in the development of atherosclerosis in humans. The T-SPARCLE (Taiwanese Secondary Prevention for patients with AtherRosCLErotic disease) Registry was initiated in 2009 to register and monitor a large population of patients with ASCVD to define the current status of lipid-lowering therapy in Taiwan. It has observed that, although the lipid treatment guideline adherence has been improving in recent years, only 54% of the patients with ASCVD in Taiwan achieved their LDL-C target, and the most significant determinant was statin therapy. However, most patients receiving lipid-lowering therapy belonged to the regimens of very-low or low equipotent doses of statins. We therefore emphasize the importance of guideline adherence, especially the use of statin therapy, not only to the physicians but also to the patients.

Introduction
Atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), cerebrovascular disease (CVD)
and peripheral arterial disease (PAD), is the second leading cause of death in Taiwan. The incidence of acute MI in Taiwan has ever been increasing during the past few decades.\textsuperscript{1} A variety of factors, associated with an increasing risk of atherosclerosis, is known to be age, family history, cigarette-smoking, hypertension, diabetes, and dyslipidemia.

Dyslipidemia has long been recognized as the major risk factor in the development of atherosclerosis in humans. In Taiwan, the frequency for hypercholesterolemia or hypertriglyceridemia to occur has increased over the past 20 years;\textsuperscript{2-4} furthermore, low-serum high-density lipoprotein cholesterol (HDL-C) has potential to become an isolated and independent coronary risk factor as far as a recognizable portion of Taiwanese population is concerned.\textsuperscript{5} To reduce the risk of ASCVD, most clinicians admit that to reduce low-density lipoprotein cholesterol (LDL-C) levels is of prominent importance.\textsuperscript{6,7} Many large trials and meta-analyses have also concurred that statin therapy significantly reduces LDL-C levels and, subsequently, the incidence of cardiovascular events;\textsuperscript{8-11} hence, the current lipid management guidelines recommend statins as the first-choice medication for reducing LDL-C levels.\textsuperscript{12-15}

In spite of their therapeutic efficacy however, statins cannot eliminate the risk posed by ASCVD entirely; the residual cardiovascular risk stems, partially at least, from low HDL-C and elevated triglyceride (TG) levels – a condition termed as “atherogenic dyslipidemia”.\textsuperscript{16-18} There exist clinical and epidemiologic data illustrating the need to expand the scope of therapies to reduce the residual cardiovascular risk associated with low HDL-C levels and elevated TG levels, even when LDL-C levels are managed successfully.\textsuperscript{9-22} From the limited data published in the past few years and based on the National Cholesterol Education Program Adult Treatment Panel III (ATP III), the LDL-C goal attainment was unsatisfactory, irrespective of Taiwanese patients receiving primary or secondary prevention therapy.\textsuperscript{23-29} It is crucial to understand why physicians did not prescribe enough lipid-lowering drugs, and what kind of patients failed to attain the lipid goals. Registry data can help tracing the real-world proportion of patients on lipid-lowering therapy, who achieve the LDL-C goals: the T-SPARCLE (Taiwanese Secondary Prevention for patients with AtherosCLerotic disease) Registry was initiated in 2009 to register and monitor a large population of patients with ASCVD to define the current status of lipid-lowering therapy in Taiwan.

**Design of the T-SPARCLE Registry**

The design of the T-SPARCLE Registry has already been published:\textsuperscript{30} to sum up, the T-SPARCLE Registry sought to document clinical practices and medical care available to patients with ASCVD, in special regard to lipid management. The T-SPARCLE Registry included 14 participating sites in Taiwan, and the investigators included cardiologists, diabetologists, neurologists, and nephrologists. Patients aged 18 and above with established ASCVD were enrolled. ASCVD included the presence of significant coronary artery occlusion >50% in diameter, history of MI, angina with ischemic response to stress test, cerebral infarction, intracerebral hemorrhage not
due to trauma or other diseases, transient ischemic attack with an ultrasound confirming atheromatous changes with >70% blockage in the carotid artery, and symptoms of limb ischemia confirmed by ankle-brachial index, Doppler ultrasound, or angiography.

The main exclusion criteria were refusal to provide a necessary informed consent, neuro-cognitive or psychiatric condition preventing the attainment of reliable clinical data (as judged by investigators), life expectancy of <6 months (e.g., malignant metastatic neoplasm), hemodynamically significant valvular or congenital heart disease, treatment with immunosuppressive agents, or any other conditions which, in the opinion of the investigator, was deemed to be unsuitable for due registration. Patients were refused to participate if they had experienced an acute stroke, acute MI, acute coronary syndrome, or coronary revascularization procedure within the previous 3 months, or had been scheduled to undergo coronary bypass graft surgery or valve surgery prior to the study enrollment.

**Current status of lipid control in Taiwan**
From January 2010 to December 2016, 6921 patients were enrolled and 3486 patients (men, 68.4%; female, 31.6%; mean age, 65.8 ± 12 years) were analyzed in 2014. 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. Only 54% of the patients achieved the optimal LDL-C level (<100mg/dL); 69.1% the HDL-C goal (>40mg/dL); 31.1% 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. Most patients were on regimens of very low (<1 dose/day, 23%) to low (1–1.9 dose/day, 38%) equipotency doses of statins (1 dose = 10 mg simvastatin).31,32

**Determinants for achieving the LDL-C target**
According to the univariate analysis, the patients achieving the LDL-C target were older and taller men with lower blood pressure and cholesterol levels at enrollment, who smoked less, were more keen on physical exercises, and tended to have a history of CAD, DM, but not of stroke or TIA. The multivariate analysis showed that statin therapy was the most significant independent determinant for achieving the treatment target, and it was followed by age, history of CAD, DM, controlled blood pressure, and gender.31

**Less CVD patients to achieve LDL-C target**
Of these patients, 15.2% had CVD only, 77.4% had CAD only, and 7.4% had both CVD and CAD. Compared with patients with CAD only, those with CVD were older and often of feminine gender with diabetes mellitus, who had higher frequency of hypertension, and less inclined to physical activity. The serum levels of total cholesterol, HDL-C, and LDL-C were significantly higher in patients with CVD alone than in those with CAD alone or co-existing CVD. Compared with patients
with CAD only, those with CVD only or CVD and CAD co-existing were less likely to achieve the guideline-recommended lipid target according to the multivariate logistic regression analysis.

**Gender Difference in Statin Intervention on Blood Lipid Control**

Although LDL-C reduction by statin therapy exhibited benefits in decreasing cardiovascular events, subgroup analysis on the other hand, displayed no consistently positive outcomes in women compared with men in secondary prevention trials. In addition, women were found to receive a relatively less aggressive approach to cardiovascular risk factors and, mostly, to a less intense cholesterol management than men did. Therefore, the cardiovascular risk management in women now gets more attention though the gender gap between guidelines and clinical practice have remained elusive in Taiwan. In the T-SPARCLE Registry study, the percentages of statin use in men and women were 68.5% and 65.4% respectively. Multiple logistic regression model showed that men were more likely to achieve the target goal than women in TC, HDL-C, LDL-C and TG. Among men, those taking statin were more likely to achieve TC, HDL-C, LDL-C, and TG goals, but no compatible trends were found in women.

**Impact of Chronic Kidney Disease (CKD) on Lipid Management**

Patients with CKD belong to a very high risk cardiovascular disease population and should be treated aggressively. In T-SPARCLE Registry study, patients with CKD compared with those without, had more co-morbidities (hypertension, glucose intolerance, stroke and heart failure) and lower HDL but higher triglyceride levels. There was similar equivalent statin potency between CKD and non-CKD groups. The goal attainment, furthermore, was lower in HDL and TG in the CKD group as compared with non-CKD subjects. Although presenting with more comorbidities, the CKD population had a suboptimal lipid goal attainment rate as compared with the non-CKD population.

**Conclusions**

The percentage of patients achieving the treatment target in T-SPARCLE Registry study was not as low as reported from REALITY-Asia study. It is also encouraging to see that elderly patients and patients with diabetes had higher rates of achieving the LDL-C target, and which suggests that physicians in Taiwan put more effort into lipid control in these high-risk patients. Although the lipid treatment guideline adherence has been improving, only 54% of the patients with ASCVD in Taiwan achieved their LDL-C target, and its most significant determinant was statin therapy. However, most patients having lipid-lowering therapy were on regimens of very-low to low equipotent doses of statins. Consequently, we here emphasize the importance of guideline.
adherence, especially when the use of statin therapy is concerned, not only to physicians but also to patients\textsuperscript{31}.

**References**


