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Original Article

Registry of Lipid Control and the Use of Lipid-lowering Drugs for Secondary Prevention of Cardiovascular Events in Patients with Established Atherosclerotic Disease in Taiwan: Rationality and Methods☆

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SUMMARY

Background: Dyslipidemia is an important but modifiable risk factor of cardiovascular disease (CVD). However, no nationwide registry has been designed so far to document the inter-relationship between long-term clinical outcomes and the lipid control, and the use of lipid-lowering agents for secondary prevention of cardiovascular events in patients with established CVD in a large representative sample of public and private hospitals in Taiwan.

Methods: In this registry-type prospective observational study, we sought to record information with regard to the secondary prevention of patients with stable symptomatic atherosclerotic disease, classified by the presence of one of the following conditions: evidence of coronary artery disease, cerebrovascular disease, or peripheral vascular disease, focusing on lipid management, and long-term outcomes. The data on customary Taiwanese clinical practice applied to outpatients will be collected from 14 centers across Taiwan, including public and private hospitals, and will be clinically followed for 5 years after their inclusion.

Results: The analysis of this multicenter registry will demonstrate the treatment patterns, goal attainment, factors influencing treatment, and the clinical outcomes among patients suffering from CVD in Taiwan.

Conclusions: The registry may increase our understanding of the prevalence and consequences of atherothrombosis on a nationwide basis. In addition to academic interests, the results may have impact on future clinical practice pattern and national policy on lipid management in Taiwan.

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1. Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of disability and mortality in both gender, not just in Taiwan but throughout the world[1–4]. The rapid growth of CVD and CHD represents one of the most relevant public health issues today[4,5].

Dyslipidemia has long been recognized as the most important risk factor in the development of atherosclerosis in humans. In Taiwan, the rates of occurrence for hypercholesterolemia and hypertriglyceridemia have increased over the past 20 years[6–8]. Moreover, low serum high-density lipoprotein–cholesterol (HDL-C) was determined to be an isolated and independent coronary risk factor among a recognizable portion of Taiwanese population[9].

To reduce the risk of CVD, most clinicians recognize the importance of reducing low-density lipoprotein–cholesterol (LDL-C) levels[10,11]. Furthermore, many large trials and meta-analyses have consistently demonstrated that statin therapy significantly reduces LDL-C levels and subsequently the incidence of cardiovascular events[10–15]. In fact, the current lipid management guidelines also recommend statins as the first-choice medication for reducing LDL-C levels[16–19]. However, despite their therapeutic efficacy, statins have not entirely eliminated the risk posed by CVD.

☆ All contributing authors declare no conflict of interest.

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The residual cardiovascular risk stems, at least partially, from low HDL-C and elevated triglyceride (TG) levels, a condition termed as "atherogenic dyslipidemia"[20–22]. Clinical and epidemiologic data illustrate 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[23–26].

However, from the limited data published in the past few years, based on the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in Taiwanese patients, irrespective of receiving primary or secondary prevention therapy, the LDL-C goal attainment was still unsatisfactory[27–33]. Most importantly, the outcome study results produced insufficient data with regard to lipid control in Taiwanese population. It is thus necessary to organize rational and balanced guidelines for the management of hyperlipidemia in Taiwan, based on our local epidemiological, clinical, and basic research data. This is because almost all of the large-scale clinical trials on lipid management to date were conducted using Caucasian populations, and no extensive end-point research and lipid-lowering therapy in Asians have been published.

Therefore, this study attempts to register and follow-up a large population of patients receiving secondary prevention therapy for CVD so as to define the current status of lipid-lowering therapy in Taiwan, and the effects of lipid-lowering therapy on CVD morbidity and mortality.

2. Materials and methods

The Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Registry represents a documentation project about the current clinical practice of caring for patients with established CVD, focusing on lipid management in medical centers across all regions in Taiwan, including public and private hospitals, academic medical centers, and regional hospitals.

2.1. Design

The cross-sectional observational registry is intended to document the clinical practice of managing patients with stable symptomatic atherosclerotic disease in Taiwan. The medications prescribed will be at the discretion of the primary treating physicians; in addition, the patient or the physician will be free to withdraw from the registry at any time, for any reason. There will be also a longitudinal follow-up of these patients for 5 years.

2.2. Eligibility and inclusion criteria

This study will be a multicenter registry facilitated by at least 50 cardiologists, diabetologists, neurologists, or nephrologists. Potentially eligible patients will be invited for a screening visit, where nonprobability sampling will be applied, including consecutive patients who meet eligibility criteria.

A total of 5000 male and female patients with stable symptomatic atherosclerotic disease under 18 years of age will be enrolled from the 14 participating sites. The definition of coronary atherosclerosis will be the presence of significant coronary artery occlusion >50% in diameter, which is identified by a cardiac catheterization examination, having a history of myocardial infarction (MI) as evidenced by electrocardiography or hospitalization, or angina with ischemic changes or positive response to stress test. Patients with cerebral vascular disease, defined as cerebral infarction, intracerebral hemorrhage (excluding intracerebral hemorrhage associated with trauma or other diseases), and transient ischemic attack whose ultrasound confirms atheromatous change with >70% blockage in the carotid artery, will be included. Peripheral atherosclerosis with symptoms of ischemia and confirmed by ankle-brachial index, Doppler ultrasound, or angiography will also be included.

2.3. Exclusion criteria

The main exclusion criteria will be refusal to provide necessary informed consent, neurocognitive or psychiatric condition which prevents in obtaining 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 condition or situation which, in the opinion of the investigator, was deemed to be unsuitable for this registration. Patients will not be allowed to participate if they have experienced an acute stroke, acute MI, acute coronary syndrome, or coronary revascularization procedure within the last 3 months, or have been scheduled to undergo coronary bypass graft surgery or valvular surgery before study enrollment.

2.4. Study protocol

All potential patients will be screened for eligibility based on their screening visit. Those who fulfill the inclusion criteria at the screening visit will be invited to join the registry study.

Regular patient follow-up will take place at the 6^{th}, 12^{th}, and 18^{th} month, and every year thereafter for a total of 5 years through clinical visits, follow-up phone calls, or record review from the National Health Insurance Bureau (NHIB) of Taiwan.

At every clinical visit, vital signs, clinical end points, adverse events, concurrent medication information, and laboratory specimens will be obtained as thoroughly as possible; however, when phone calls or records from NHIB are involved, only clinical end points will be recorded. The lipid profile (total cholesterol, HDL-C, TG), liver enzymes, and creatine phosphokinase levels will be evaluated at baseline, and every year thereafter. While addressing the lipid control and other medical needs of the study patients, the investigators will follow the recommendations from the NHIB regarding lipid-lowering guidelines. If the primary treating physician intends to treat the patient's lipid profile to the target, he/she can add, remove, or adjust the lipid-lowering drugs according to his/her clinical judgment.

The registry will also record concomitant secondary prevention interventions with proven benefits, including aspirin, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, smoking cessation, physical activity, and healthy nutritional guidelines.

2.5. Outcomes

The primary objective of this trial is to register the time of first occurrence of a major cardiovascular event, defined as cardiovascular death, hospitalization for nonfatal MI or stroke, or cardiac arrest with resuscitation in patients receiving secondary prevention therapy over a period of 5 years.

There will be two prespecified composite secondary outcomes: (1) any CHD event (coronary death or hospitalization for nonfatal MI, any coronary revascularization procedure, or hospitalization for unstable angina); (2) any cardiovascular events (any major cardiovascular events plus hospitalization for any revascularization procedure, unstable angina, congestive heart failure, nonfatal stroke, or peripheral arterial disease, defined as a new clinical diagnosis or hospitalization for such disease). In addition, individual components of the composite end points will be prespecified as secondary outcomes, and thus will be all-cause mortality.

The tertiary objective of this trial is to evaluate the lipid profile change, myopathy, or liver enzyme change after the lipid-lowering therapy. In addition, we will measure the proportion of patients receiving secondary prevention interventions recommended by treatment guidelines, and evaluate the impacts of different secondary prevention interventions and their adherence on late outcomes.

2.6. Sample calculation

In order to detect a proportion of 25% for the occurrence of the primary outcome in 5 years, considering a sampling error of 2%, an alpha of 5%, and a statistical power of 80%, at least 3300 patients must be included. Our sample size will manifestly be sufficient to meet the primary objectives of the study.

2.7. Statistical analysis

Quantitative variables will be expressed as mean and standard deviation in the presence of normal or median distribution, and interquartile range in the presence of asymmetric distribution. Qualitative variables will be presented in both absolute frequencies (number of patients) and relative frequencies (percentage).

The primary, secondary, and tertiary outcomes will be described by an overall percentage, taking all centers into consideration, and the percentage prescribed in each center. These will also be expressed by means of proportions and their confidence intervals of 95%. Where there is great variability in prescription, a weighted average variance at each center will be generated.

For regression models, we will report the odds ratio (logistic regression) or hazard ratio (for the regression of Cox proportional hazards), the corresponding standard error, the confidence intervals of 95%, and p values.

Additionally, we will report the p values up to three decimals; however, places with p values below 0.001 are reported as $p < 0.001$. In all the tests, we will use the two-tailed alpha significance level $= 0.05$.

2.8. Quality control and data management

For study data quality control, the following strategies will be used: initial classroom training, electronic case report form, central check of data, and tutoring.

2.9. Ethical considerations

The study will be approved by the institutional review board of each participating site, and written informed consent will be obtained from all patients. The clinical trial will be conducted in accordance with the principles of the current revision of the Declaration of Helsinki and the latest version of the Guidelines for Good Clinical Practice (ICH-GCP), and the study will be performed according to those local and regulatory legal requirements enforceable in Taiwan.

2.10. Data collection

Patient inclusion was initiated on December 9, 2009 at 14 participating centers and by February 9, 2011, 3486 patients had been included. The 1st year follow-up of the patients should be completed by the end of the 2nd quarter of 2012.

3. Discussion

Individuals presenting with any atherosclerotic disease for the first time are at risk of subsequent vascular events; for example, MI and stroke, two major manifestations of atherothrombosis, which are characterized by increasing incidence rates and require special attention in the future because of their increased association with morbidity, and the high socioeconomic burden they can cause[3,5,27,33–35]. Consequently, there is a need to develop strategies to prevent either the primary development of these clinical diseases, or to offer therapeutic interventions that can effectively lower long-term event rates in these vulnerable populations.

Lowering of LDL-C with statins has, in the last decade, become a part of the standard treatment for patients with hyperlipidemia[10,11]. Secondary and primary prevention trials have demonstrated that lipid lowering with a statin drug can dramatically and cost effectively reduce CHD morbidity and mortality with no increase in noncardiovascular mortality[10–15,36–40]. In 2001, while the newly released ATP III maintained a focus on intensive treatment of patients with CHD, its major new feature underscored the need for primary prevention in persons with multiple risk factors[16]. Afterwards, The Heart Protection Study, the largest lipid-lowering study to date including a wide range of high-risk patients covering both primary and secondary prevention, demonstrated striking lipid-lowering benefits by administering simvastatin compared with placebo[41]. The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm study that assessed the benefits of lowering cholesterol levels in the primary prevention of CHD had also clearly demonstrated a large reduction in major cardiovascular events by administering a dose atorvastatin within a short treatment period[42].

More recently, the Treating to New Targets study comparing high and low doses of atorvastatin in stable nonacute patients with CHD documented a significant improvement in prognosis with respect to CVD[43]. Hence, in 2004, the updated ATP III introduced a new target of $<$70 mg/dL (1.8 mmol/L) for patients with established CVD and at a very-high risk category[17]. Since then, the Incremental Decrease in End Points Through Aggressive Lipid Lowering study with intensive lowering of LDL-C with atorvastatin using the highest recommended dose had yielded an incremental benefit compared with the moderate, most widely used dose of simvastatin[44]. The latest Cholesterol Treatment Trialists' Collaboration Study, a prospective meta-analysis, further confirmed the efficacy and safety of more intensive lowering of LDL-C[15]. To sum up, statins are the first-choice medication for reducing LDL-C levels, and clinical trials have demonstrated beyond any doubt that lowering LDL-C levels with statins considerably diminishes the risk of CVD in a wide range of patients. It is not surprising, therefore, that the new 2011 European Guidelines for the Management of Dyslipidemia recommend the use of statin monotherapy up to the highest recommended dose, or highest tolerable dose to reach the target level. Currently, it is the only Class I Level A evidence-based pharmacological treatment for hypercholesterolemia[19].

Statin therapy, moreover, has the greatest efficacy in the presence of inflammation; several studies have already shown that statins reduce the inflammatory biomarker high-sensitivity C-reactive protein largely independent of LDL-C[45–49]. These findings are consistent with the pathophysiological understanding that atherothrombosis is a disorder of both hyperlipidemia and inflammation, and that statins have anti-inflammatory and lipid-lowering properties.

Other lipid-lowering drugs (e.g., fibrates) may also reduce the number of cardiovascular events in high-risk patients[20–26]. Fibrates

are used quite often in daily practice for treating diabetic dyslipidemia, because of their beneficial effects in reducing high TG and increasing the low HDL-C levels, the characteristic lipid abnormalities commonly seen in patients with diabetes or metabolic syndrome[23–26]. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial study, after a median follow-up of 5.1 years, administration of gemfibrozil, compared with placebo, resulted in a significant relative reduction (about 22%) of the primary event (nonfatal MI or death from coronary causes) in 2531 men with CHD whose HDL cholesterol levels were ≤40 mg/dL (1.0 mmol/L), and LDL cholesterol levels were ≤140 mg/dL (3.6 mmol/L)[23]. In the Fenofibrate Intervention and Event Lowering in Diabetes study, the use of fenofibrate did not significantly reduce the risk of the primary outcome of coronary events (CHD death or nonfatal MI) in 9795 participants with type 2 diabetes mellitus. However, it significantly reduced total cardiovascular events, mainly due to fewer nonfatal MI and revascularizations[24].

During the last decade, practice guidelines have become an important component of secondary prevention and the management of CVD[16–19]. The current guidelines emphasize that appropriate use of risk-reducing pharmacotherapies proffers a major opportunity for reducing events, during both outpatient visits and discharge after hospitalization for acute ischemic events[16–19]. However, the LDL-C goal attainment based on the ATP III goals in Taiwanese patients was still unsatisfactory, irrespective of any primary or secondary prevention methods that were used[27–33]. Although these results indicate that lipid-lowering therapy has been applied much more successfully in recent years than it was a decade ago, there is still substantial room for improvement, particularly in very high-risk patients with established CVD. Moreover, an extensive study regarding clinical outcomes in relation to lipid control in Taiwan is yet to be conducted. Those conclusions regarding the clinical benefits of lipid-lowering therapy are to date primarily drawn from large-scale clinical trials conducted almost exclusively in Caucasian populations. The T-SPARCLE Registry thus provides an opportunity to evaluate whether application of treatment guidelines is effective in reducing ischemic events because the database contains data on long-term risk-reduction interventions. We hypothesize that different ischemic event rates may be observed in those patients in whom guidelines are frequently adhered to, as compared with patients who fail to follow these guidelines diligently. We expect that the results of this study may have a major impact on future clinical practice patterns and national policy on lipid management in Taiwan.

Furthermore, given the current concept of cardiovascular prevention, it is more important to classify patients in terms of the cardiovascular risk presented by their diseases, as opposed to just classifying them as having diabetes mellitus, hypertension, or dyslipidemia[16–19]. Risk factors may have different effects on the various manifestations of atherothrombosis. For example, despite the fact that stroke and MI are both manifestations of atherosclerosis, high blood pressure is a more relevant risk for stroke; whereas elevated cholesterol has more relevance to risk for CHD events[2,9,50]. Therefore, prevention based on the concept of cardiovascular risk means guiding prevention efforts not in terms of risks attributable to the increase of isolated factors (such as blood pressure or cholesterol), but in terms of the sum of all risks due to multiple factors, estimated by the overall absolute risk in each individual[16–19]. In view of this circumstance, the T-SPARCLE Registry will provide an opportunity to gather important information about the possible contribution of different risk factors on the later development of vascular events, and gauge both the ischemic event rates and the use of risk-reduction therapies in a large Taiwanese population.

3.1. Study limitations

Although this is a large registry of atherothrombotic disease involving many regions in Taiwan, there are several noteworthy limitations to our study. The enrollment of patients should be consecutive, but because of the logistics involved on a nationwide basis, it is not possible to ensure that this occurs with enrollment logs, particularly in busy clinical practices. Nevertheless, the enrollment at each site occurred at a rapid pace, suggesting that only limited biases were introduced by not insuring absolute consecutive patient enrollment. Moreover, the site selection should be undertaken to reflect on the different patient management practices followed for treating atherothrombotic diseases across Taiwan. However, it was neither possible to randomize sites truly or hospitals for this endeavor, nor was it possible for a community-wide data collection. Because most of the patients with established CVD are treated by hospital-based specialists, we did not include general practitioners at local clinics in the registry. However, we have indeed made every effort to include public and private hospitals, academic medical centers as well as regional hospitals, to ensure that a representative population and sites were included in the T-SPARCLE Registry.

4. Conclusions

The T-SPARCLE Registry represents a significant opportunity to increase our understanding of the prevalence and consequences of atherothrombosis on a nationwide basis in Taiwan. These data are likely to offer an important opportunity to raise the awareness of this disease among a wide range of physicians and other medical professionals. It is also expected that the T-SPARCLE Registry may demonstrate the need for improvement in current clinical management standards, and will offer a cross-sectional database that can serve as a baseline while we work to improve the administration of methods to prevent and treat atherosclerotic disease in Taiwan.

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Appendix

1.1. Organization

1.1.1. Main investigators: Wei-Hsian Yin, Chau-Chung Wu, and Jaw-Wen Chen

1.1.2. Steering committee: Wei-Hsian Yin, Chau-Chung Wu, Jaw-Wen Chen, Yi-Heng Li, Hung-I Yeh, Ching-Chang Fang, Kuo-Yang Wang, Tsung-Hsien Lin, Wei-Kung Tseng, Ai-Hsien Li, Kwo-Chang Ueng, I-Chang Hsieh, Chiun-Hsiung Wang, Lien-Chi Huang, Wen-Harn Pan

1.1.3. Coordination of the Institute for Teaching and Research: Shao-Yuan Chuang, Yu-Hui Huang, Chin-Feng Cheng

1.1.4. Intellectual property: The Taiwan Society of Lipids and Atherosclerosis

1.1.5. Coordination and supervision: The Taiwan Society of Lipids and Atherosclerosis and Taiwan Consortium of Lipid and Atherosclerosis

1.1.6. Research centers: National Cheng Kung University Hospital, Tainan (Y.H.L.); Taipei Veterans General Hospital, Taipei (J.-W.C.); Cheng-Hsin General Hospital, Taipei (W.-H.Y.); National Taiwan University Hospital, Taipei (C.-C.W.); Mackay Memorial Hospital, Taipei (H.-I.Y.); Tainan Municipal

Hospital, Tainan (C.-C.F.); Taichung Veterans General Hospital, Taichung (K.-Y.W.); Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung (T.-H.L.); E-Da Hospital, Kaohsiung (W.-K.T.); Far Eastern Memorial Hospital, Taipei (A.-H.L.); Chung Shan Medical University, Taichung (K.-C.U.); Linkou Chang Gung Memorial Hospital, Taipei (I.-C.H.); Taipei City Hospital Renai Branch, Taipei (C.-H.W.); and Taipei City Hospital Heping Fuyou Branch, Taipei (L.-C.H.); National Health Research Institutes, Taiwan (W.-H.P.)

1.2. Publishing policy

All presentations of the study and/or publication of findings will be based on clear evidence verified and validated in order to ensure accurate results. Details concerning the responsibility and sequence of these presentations and/or publications will be in accordance with the Taiwan Society of Lipids and Atherosclerosis.

The authorship of publication of the main conclusions of this study will be decided by the contributions from the study centers in general. All participants in the registry (investigators and committee members included) should make an advance delegation of authority to the Taiwan Society of Lipids and Atherosclerosis. Any presentation or publication by any participant in the study should acknowledge the above facts, and should obtain the approval of the Taiwan Society of Lipids and Atherosclerosis.

1.3. Financing

This Registry is supported and owned by the Taiwan Society of Lipids and Atherosclerosis using funds dedicated to this purpose for its implementation.

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