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Risk factor control and medical therapy of coronary artery disease in Taiwan – Review and Recommendations – Part I: Blood lipid management for patients with coronary artery disease

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Abstract: Cardiovascular disease (CVD) is the leading cause of death in the world and the second important cause of death in Taiwan. Atherosclerosis CVD (ASCVD) especially coronary artery disease (CAD) is the major cause of CVD [1]. Clinically, the presentation of CAD can be divided into acute unstable disease, so-called acute coronary syndrome (ACS) and chronic stable disease. Up to now, the main risk factors for CAD are known as hyperlipidemia, hypertension, hyperglycemia, smoking and family history. The control of the above risk factors and lifestyle modifications can improve the prognosis of CAD patients [1,2]. Here, we described the blood lipid control, blood pressure control, blood glucose control, and lifestyle modifications for CAD in Taiwan. The followings are the part I for blood lipid control.

1. Therapeutic goals for patients with acute coronary syndrome (ACS)

Cardiovascular disease (CVD) is the leading cause of death in the world, atherosclerosis CVD (ASCVD) is the major cause of CVD [1]. It is well known that elevated serum cholesterol especially low-density lipoprotein cholesterol (LDL-C) is one of the most important risk factors of ASCVD [2]. Lipid-lowering drugs significantly reduce plasma lipids and improve the clinical outcomes of ASCVD. However, the global rate to achieve the therapeutic goal of LDL-C is still disappointing. In the recent T-SPARCLE registry study in Taiwan, there are only 54% of the ASCVD patients with a serum LDL-C level <100 mg / dL [3]. Recently, the "Guidelines for blood lipid in Taiwan high risk patients" was published to promote the effective treatment of dyslipidemia by the health care professionals and to reduce the risk of ASCVD in high-risk patients in Taiwan [4]. This guide is written according to the evidence-based medicine for advanced versus usual serum LDL-C control in patients of acute coronary

syndrome (ACS) with the data primary from the MIRACL study [5], PROVE IT-TIMI 22 study [6], and IMPROVE-IT study [7]. While the significant reduction on future primary adverse CV events by advanced lipid control compared with that by usual lipid control, the average achieved serum LDL-C level in patients with advanced lipid control was 72 mg/dL in MIRACL study, 62 mg/dL in PROVE IT-TIMI 22 study, and 53 mg/dL in IMPROVE IT study individually. Given that there have been no randomized clinical trials to explore the specific therapeutic goals of serum LDL-C level, it seems feasible to suggest that in ACS patients, serum LDL-C should be treated if it is >70 mg/dL.

2. Therapeutic goals for patients with stable coronary heart disease (CAD)

For patients with stable coronary heart disease (CAD), the "***2017 guideline of blood lipid control for high risk patients in Taiwan***" suggests that the therapeutic goal of serum LDL-C should be <70 mg/dL [4]. However, there were arguments for this issue in serial expert meetings for this guideline in Taiwan. According to the recently published data from the Taiwan secondary prevention observation T-SPARCLE registry study, for patients with stable ASCVD (including CAD, cerebrovascular disease or peripheral arterial disease), future CV events were significantly reduced with achieved serum LDL-C level <100 mg/dL compared with that ≥100 mg/dL. However, there were no differences in the incidence of future CV events between patients with an achieved serum LDL-C level <70 mg/dL and those with an achieved serum LDL-C level ≥70 mg/dL [8,9]. While there are no randomized clinical trials specific for the appropriate therapeutic target of serum LDL-C [10–14], the current recommendations of serum LDL-C level <70 mg/dL for stable CAD patients in the "***2017 guideline of blood lipid control for high risk patients in Taiwan***" are simply a consensus of most of the attendants in the expert meeting.

In particular, there are no sufficient evidence to support the therapeutic goals of serum LDL-C level <70 mg/dL in ASCVD patients without comorbidities. While the data of the recent FOURIER study may be controversial [15], the clinical benefits with the LDL-C <70 mg/dL in previous clinical trials for stable ASCVD patients mainly come from the reduction on surrogate or alternative endpoints rather than on the major cardiovascular events (MACE) including death, acute myocardial infarction, and stroke [16–19]. In the recent REAL-CAD study for stable CAD patients [20], the average achieved serum LDL-C level was 73.7 mg/dL (rather than< 70 mg/dL) in patients with high-dose treatment for 6 months compared with 89.4 mg/dL in patients with low-dose treatment. During the follow-up for 3.9 years, the incidence of CV death, non-fatal myocardial infarction, non-fatal ischemic stroke or unstable angina pectoris requiring emergent hospitalization was reduced by 19% in high-dose compared with that in low-dose group. Thus, the findings of REAL-CAD study may not support the therapeutic goal of serum LDL-C level <70 mg/dL for stable CAD patients without comorbidity. On the other hand, in the recently published ODYSSEY trial [21], only the CAD patients with a baseline serum LDL-C level >100 mg/dL could get clinical benefits from the advanced reduction of serum LDL-C with a PCSK9 inhibitor. Another recent meta-analysis by Navarese et al also indicated that the clinical benefits of lipid lowering for future CV events could be attended only in patients with baseline LDL-C >100mg/dL [22]. Taken together, there are no sufficient evidence to suggest the clinical benefit with an achieved serum LDL-C level <70mg/dL in stable ASCVD patients especially those without comorbidities. Accordingly, it may be feasible to recommend lipid lowering treatment for stable CAD patients with comorbidities if their serum LDL-C >70 mg/dL (**IB**). However, for stable CAD patients without comorbidities, lipid lowering treatment should be given only if their serum LDL-C level >100 mg/dL (**IA**).

3. ndividual lipid managements for different subgroups of patients with atherosclerotic cardiovascular disease

In the 2016 consensus of American College of Cardiology [23], the committee defined several subgroups of ASCVD patients including the patients without other comorbidities, the patients with comorbidities, and the patients with a baseline serum LDL-C level >190 mg/dL. The comorbidities include T2DM, recent CV events within 3 months, development of CV events even on statins, primary hypercholesterolemia with serum LDL-C >190 mg/dL, poor control of >2 other major ASCVD risk factors (including hypertension, smoking, and family history of ASCVD), elevated serum Lipoproteins (a) level, or chronic kidney disease (CKD). According to serial scientific evidence, the consensus suggests a serum LDL-C level <70 mg/dL for ASCVD patients with comorbidities, and a serum LDL-C level <100 mg/dL for ASCVD patients without comorbidities. Although the age of patient cohorts is usually <75 years in large randomized control trials (RCT) with statins, the current available evidence does support the continuous use of statins to reduce serum LDL-C in elderly patients aged >75 years if they are already on and tolerate to statins. On the other hand, given that serum LDL-C level is often normal and serum HDL-C level is usually low in patients with T2DM, both serum LDL-C level and non-HDL-C level are indicated for the high-risk patients in the 2016 consensus of American College of Cardiology.

The unpublished data from the recent T-PPARCLE T-SPARCLE registry studies for primary and secondary prevention in Taiwan show that in T2DM patients with either < or > 75 years of age, serum non-HDL-C level >130 mg/dL rather than HDL-C level could be the most significant residual risk factor for future MACE. However, in patients without T2DM, no lipid parameters other than LDL-C could predict future MACE regardless to patients' age. Accordingly, in stable ASCVD patients with comorbidities, it seems feasible to start lipid lowering treatment while serum LDL-C is >70mg/dL or serum non-HDL-C >100 mg/dL (**IB**). It may be also feasible to start lipid lowering treatment while serum LDL-C level is >100 mg/dL or serum non-HDL-C >130 mg/dL in stable ASCVD patients without comorbidities (**IA**).

4. Comprehensive lipid managements for patients with atherosclerotic cardiovascular disease (ASCVD)

It is well known that the risk of CAD is 2-4 times higher in patients with T2DM than in those patients without T2DM [24,25]. In T2DM patients, the residual risk of CVD is still high even with lifestyle modifications and statin tretment [26]. According to the pos-hoc analyses on the data from MIRACL study, PROVE IT-TIMI 22 study and dal-OUTCOME study, elevated serum triglyceride (TG) level could be one of the residual risk factors for future CV events in patients already on statins [27–29]. However, there are limited data for the prevention of future CV events by reducing serum TG level and/or by increasing serum HDL-C level [24]. In patients already on statin treatment, the add-on of niacin, and cholesteryl ester transfer protein (CETP) inhibitors did not improve clinical outcomes even though they may significantly reduce serum TG and increase serum HDL-C levels. It does not further reduce the risk of recurrence of vascular events. However, in a recent randomized trial named REVEAL, CETP inhibitor anacetrapib, compared with placebo could reduce future MACE in ASCVD patients who have been treated with statins [30]. There were 9% reduction on future MACE with anacetrapib treatment for 4.1 years, which seem related to the reduction on serum non-HDL rather than to serum LDL-C. While serum LDL-C has been considered as the major therapeutic target for lipid control in the past decades [31–33], it may not present all different types of atherogenic lipid granules. The data from T-SPARCLE observational study were recently analyzed for the residual risk of recurrent CV events in ASCVD patients in Taiwan [8,9]. The results show that while serum LDL-C level was <100 mg/dL by statin treatment, serum non-HDL-C, heart failure, advanced kidney disease and the absence of -adrenergic receptor blockers could be related to future MACE in ASCVD patients with T2DM. On the other hand, heart failure, advanced kidney disease and history of myocardial

infarction were the major residual risk factors for future CV events in ASCVD patients without T2DM. Accordingly, serum non-HDL-C rather than LDL-C is the most important predictor for future MACE in ASCVD patients with T2DM. The clinical characteristics of diabetic dyslipidemia are mainly associated with increased serum TG level, reduced serum HDL-C level, and increased serum small dense LDL-C particles [34,35]. Serum non-HDL-C may represent all the artherogenetic lipids including LDL-C, very low density lipoprotein (VLDL), medium Density Lipoprotein (IDL), and lipoprotein[a]. clinically, it could be also used for the alternative marker for apolipoprotein B (Apo B) [36]. While getting more and more attention, serum non-HDL-C rather than LDL-C has been identified as a good indicator for future CV events in recent years. Besides, in recent clinical trials, serum non-HDL-C was further suggested as a therapeutic target especially for high-risk patients [37–40]. In a recent meta-analysis with 233,455 patients, non-HDL-C but not LDL-C could be the most powerful predictor for CV events [41]. Therefore, the expert consensus of National Lipid Association of the United States (NLA) suggest the clinical impacts of serum non-HDL-C rather than LDL-C, on future ASCVD Risk, which is particularly important while the predicted risk may be inconsistent between non-HDL-C and LDL-C [42].

5. Blood lipid control in the patients with type 2 diabetes mellitus

The current evidence also supports stringent control of blood lipid profiles in T2DM patients rather than in non-DM patients [4,34]. The results of T-SPARCLE registry study showed the significant impacts of blood lipid profile on future CV events in T2DM patients even after the use of statins and statin intensity are statistically adjusted. However, no such impacts could be noted in non-diabetic patients [9]. In fact, the recent IMPROVE-IT trial did support the significant impacts of lipid abnormalities on clinical outcomes mainly in T2DM patients [7]. Pre-specified subgroup analysis showed that ezetimibe added to simvastatin treatment can further reduce serum LDL-C levels and also clinical CV events only in diabetic patients. Based on these evidence, 2016 and 2017 ACC expert consensus recommend that in ASCVD patients with T2DM, other non-statin drugs may be added to achieve LDL-C <70 mg/dL or non-HDL-C <100 mg/dL if they could not be achieved by statin treatment alone [23,43]. In summary, given the unique pathophysiology and blood lipid spectrum changes, more active and tight blood lipid control are quired for T2DM patients.

6. Blood lipid control in patients with chronic renal disease

In addition to the characteristics of lipids, the results of T-SPARCLE study also show that advanced kidney disease is critical to future MACE especially in T2DM patients. Some randomized controlled trials and observational studies have shown that the presence of kidney disease increases the risk of CVD and mortality in diabetic patients [44,45]. Previous studies also showed that chronic renal failure may increase the risk of atherosclerosis by altering the lipoprotein spectrum [46]. The results of T-SPARCLE study also showed the increased serum TG level and reduced LDL-C level in patients with chronic kidney disease (CKD). However, in patients undergoing statin therapy, none of the lipid parameters such as serum LDL-C, TG and HDL-C could be related to the risk of future MACE. Interestingly, among them, serum non-HDL-C could be critical to risk prediction in non-CKD patients, and was also marginally related to future MACE in CKD patients [47].

7. Recommendations

1. For patients with acute coronary syndrome (ACS), lipid lowering treatment should be given if their serum low density lipoprotein cholesterol (LDL-C) level >70mg / dL (**Class I, LOE: A**). For ACS patients with type 2 diabetes mellitus (T2DM) patients, lipid lowering treatment should be given if their serum LDL-C level >55mg/dL (**Class II, LOE: A**).
2. For coronary artery disease (CAD) patients with comorbidities including T2DM, recent cardiovascular (CV) events within 3 months, development of CV events even on statins, primary hypercholesterolemia with serum LDL-C> 190 mg/dL, poor control of > 2 other major CAD

risk factors (including hypertension, smoking, and family history of CAD), elevated serum Lipoproteins (a) level, or chronic kidney disease (CKD), lipid lowering treatment should be given if their serum LDL-C >70 mg/dL or serum non- high density lipoprotein cholesterol (HDL-C) level >100 mg/dL (**Class I, LOE: B**). For CAD patients without comorbidities, lipid lowering treatment should be given if their serum LDL-C level >100 mg/dL or serum non-HDL-C level >130 mg/dL (**Class I, LOE: A**).

3. For non-CAD patients with T2DM or primary hypercholesterolemia patients with serum LDL-C >190 mg/dL, drug therapy should be started if serum LDL-C >100 mg/dL or non-HDL-C >130 mg/dL after proper lifestyle modifications for 3-6 months (**Class I, LOE: A**).
4. For non-CAD patients with > 2 other major ASCVD risk factors (including hypertension, smoking, and family history of CAD), elevated serum Lipoproteins (a) level, or CKD, drug therapy should be started if serum LDL-C > 130 mg / dL or non-HDL-C > 160 mg / dL after proper lifestyle modifications for 3-6 months (**Class I, LOE: A**).
5. For non-CAD patients with 1 other major CAD risk factor (including hypertension, smoking, and family history of CAD), drug therapy should be started if serum LDL-C > 160 mg / dL or non-HDL-C > 190 mg / dL after proper lifestyle modifications for 3-6 months (**Class I, LOE: A**).

Conflicts of Interest:
The authors declare no conflict of interest.

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