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Lipid Lowering Therapy for Acute Coronary Syndrome and Coronary Artery Disease: Highlights of the 2017 Taiwan Lipid Guidelines for High Risk Patients

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Intensive lipid lowering therapy is important in patients with acute coronary syndrome (ACS) and stable coronary artery disease (CAD). The 2017 Taiwan Lipid Guidelines for High Risk Patients was recently published. The guideline suggests that low-density lipoprotein cholesterol (LDL-C) should be the primary target, and that the treatment goal of LDL-C is < 70 mg/dL for patients with ACS or stable CAD. A lower target of < 55 mg/dL is appropriate for patients with ACS and diabetes mellitus. Non-high-density lipoprotein cholesterol (non-HDL-C) < 100 mg/dL can be considered as the secondary target after achieving the LDL-C goal for patients with a triglyceride level > 200 mg/dL. Statins are usually the first-line therapy. Moderate or high intensity statins are preferred, and up-titration to the highest recommended and tolerable dose to reach the target is necessary. Combination therapy with statins and other lipid-lowering drugs can also be considered. We hope the clinical outcomes of patients with ACS or CAD can be improved in Taiwan through the implementation of the guideline recommendations.

Key Words: Coronary artery disease • Guideline • Statin

INTRODUCTION

Cardiovascular disease (CVD) is the second leading cause of death in Taiwan,[1] in which a large portion of the patients have acute coronary syndrome (ACS) and stable coronary artery disease (CAD). It has been well established that elevated circulating cholesterol, especially low-density lipoprotein cholesterol (LDL-C), is one of the most important risk factors for atherosclerotic CVD, including CAD and ACS.[2] Reducing LDL-C with lipid lowering drugs can significantly improve the clinical outcomes of CAD or ACS.[2] However, LDL-C is treated inadequately in Taiwan. In the first Taiwan ACS Registry conducted from October 2008 to January 2010, only 60% of ACS patients received statins at discharge and during 1 year of follow-up.[3] In addition, in the Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Registry conducted from January 2010 to February 2011, only 54% of the patients with CAD or cerebrovascular disease achieved an LDL-C level < 100 mg/dL.[4] Moreover, in the Dyslipidemia International Study II conducted from 2012 to 2013, 79% of ACS patients in Taiwan received lipid-lowering therapy at 4 months of follow-up, and this prescription rate was lower than neighboring Asian countries.[5,6] The Taiwan Lipid Guidelines for High Risk Patients was recently published.[7] The purposes of the guideline

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are to assist the healthcare professionals in Taiwan to treat dyslipidemia effectively, decrease inertia and reduce atherosclerotic CVD in high risk patients.[8] The aims of this article were to highlight the recommendations proposed in the guideline for patients with ACS and CAD, and briefly overview the scientific basis of these recommendations. Very recently published clinical trials and studies not included in the guideline were also reviewed.

ACUTE CORONARY SYNDROME

ACS is defined as acute ST segment elevation myocardial infarction (MI), non-ST segment elevation MI and unstable angina. ACS usually results from acute rupture or erosion of coronary atherosclerotic plaque and thrombotic occlusion of coronary lumen. There are seven recommendations for ACS in the guideline:

1. **Statins or statins plus ezetimibe should be used for all ACS patients if there is no contraindication.**
2. **The LDL-C target should be < 70 mg/dL in ACS patients.**

In the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis that included 170,000 individuals from 26 randomized trials, continued LDL-C reduction with intensive statin therapy resulted in a decrease in the incidence of cardiovascular events, and no treatment threshold of cholesterol was found.[9] In the Korean Acute MI Registry, 1,054 patients with acute MI who had baseline LDL-C levels < 70 mg/dL were included, and statin therapy was shown to significantly improve the clinical outcomes in these patients.[10] Taken together, these findings suggest that LDL-C lowering therapy should be given to all ACS patients if there are no contraindications.

In the guideline, the results from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial,[11] the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial,[12] and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial[13] were used as the rationale for the basis of the recommendations for ACS. All of the trials demonstrated the benefits of statin or statin plus ezetimibe therapy for ACS patients in reducing cardiac events. In Asia, the ESTABLISH study[14] and the Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study[15] from Japan also showed the benefits of statin or statin plus ezetimibe therapy in regressing coronary plaque in ACS. The average LDL-C levels achieved in the intensive LDL-C lowering group were 72 mg/dL in the MIRACL study, 62 mg/dL in the PROVE IT-TIMI 22 study, 53 mg/dL in the IMPROVE IT study, 70 mg/dL in the ESTABLISH study, and 63 mg/dL in the PRECISE-IVUS study. Although no specific randomized clinical trials have addressed the treatment target of LDL-C in ACS, it was defined as < 70 mg/dL for ACS in the guideline based on these study results.

The results of the ODYSSEY OUTCOMES trial were presented at the 2018 Scientific Session of the American College of Cardiology.[16] In patients who had a recent ACS event and could not achieve LDL-C < 70 mg/dL after receiving high intensity statin therapy, alirocumab or a placebo was added. Alirocumab was titrated to keep the LDL-C level between 25 and 50 mg/dL. The results showed that the use of alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, significantly reduced ischemic events (MI, stroke and unstable angina requiring hospitalization) and all-cause mortality compared with the placebo. The study results proved the efficacy and safety of alirocumab and reconfirmed the concept of "lower is better" for LDL-C in ACS. In the ODYSSEY OUTCOMES trial, the patients with a baseline LDL-C level ≥ 100 mg/dL had the greatest benefit compared with other lower baseline LDL-C groups, although the p value for interaction was statistically nonsignificant.[16] A recent meta-analysis demonstrated that more intensive LDL-C lowering therapy was associated with a reduction in risk in patients with higher baseline LDL-C levels, but not in those with baseline LDL-C level < 100 mg/dL.[17] It is likely that there is a progressive reduction in the benefit of LDL-C lowering as baseline LDL-C declines. PCSK9 inhibitors are expensive. It is still under discussion about how to best use the drugs with regards to being cost-effective. It is also unknown whether the study will change guidelines worldwide at current stage.

3. **In ACS patients with diabetes, a lower target of LDL-C < 55 mg/dL can be considered.**

The IMPROVE-IT study included 18,144 ACS patients and randomized them into simvastatin or simvastatin plus ezetimibe groups.[13] In this trial, 4,933 (27%) of the study participants had diabetes mellitus (DM). Intensive lipid lowering therapy with simvastatin plus ezetimibe achi-

eved a lower median level of LDL-C (DM group: 49 vs. 67 mg/dL; non DM group: 55 vs. 71 mg/dL). After 7 years of follow up, the reduction in the primary endpoint event was more significant in the DM group than in the non-DM group with simvastatin plus ezetimibe therapy (DM vs. non-DM: 5.5% vs. 0.7% absolute difference of risk reduction; p for interaction = 0.02).[18] The largest risk reductions in diabetic patients were for MI (24%) and ischemic stroke (39%). Since ACS patients with diabetes have worse clinical outcomes compared to those without diabetes,[19] therefore, for this very high risk group of patients with ACS and DM, a lower LDL-C target < 55 mg/dL is recommended.

4. **Statin or statin/ezetimibe therapy should be started within the first few days of hospitalization for ACS and prior to PCI for ACS.**

Regarding the timing of initiating lipid lowering therapy in ACS, two observational studies found no significant difference in outcomes between ACS patients who received early vs. late statin therapy after ACS during admission.[20,21] Percutaneous coronary intervention (PCI) is a common treatment modality for ACS. A meta-analysis demonstrated that starting statin therapy before PCI reduced the risk of 30-day cardiovascular events.[22] Therefore, the guideline suggests that lipid lowering therapy should be started as soon as possible during the hospitalization for ACS, and that it is best started prior to PCI for ACS.

5. **Increased triglyceride (TG) may be a risk factor for recurrent cardiovascular events after ACS.**
6. **Non-high density lipoprotein cholesterol (non-HDL-C) < 100 mg/dL can be the secondary target in patients with TG ≥ 200 mg/dL.**
7. **TG-lowering therapy is necessary in patients with TG ≥ 500 mg/dL to prevent pancreatitis.**

These three recommendations are about TG and high density lipoprotein cholesterol (HDL-C). Increased TG levels were shown in the post hoc analysis of the MIRACL study, the PROVE IT-TIMI 22 study and the dal-OUTCOMES study to be a risk factor for recurrent cardiac events in ACS patients already under statin treatment.[23-25] However, in patients under statin treatment, add-on therapy with fibrate, niacin, and most cholesteryl ester transfer protein (CETP) inhibitors, all of which decrease TG and/or increase HDL-C levels, could not further reduce the risk of cardiac events. In the Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial, the CETP inhibitor anacetrapib or a placebo was used in patients with atherosclerotic vascular disease already under intensive statin therapy.[26] Although anacetrapib showed a better outcome in this trial, the benefit was mild with only a 9% reduction in relative risk during a median follow-up period of 4.1 years. It is also difficult to determine whether the benefit was from LDL-C reduction, TG reduction, or HDL-C elevation (anacetrapib vs. placebo, absolute difference -26, -10, 43 mg/dL, respectively), or a combined effect. Therefore, the results of this trial did not have any influence on the current guideline with regards to LDL-C as the primary target. Non-HDL-C includes all potentially atherogenic lipoprotein particles and is also a risk factor for CAD in Taiwan.[27] The guideline suggests that non-HDL-C can be considered as a secondary target in patients with TG levels ≥ 200 mg/dL, and that the non-HDL-C goal should be < 100 mg/dL in ACS patients.

STABLE CORONARY ARTERY DISEASE

The risk of myocardial ischemia, coronary revascularization, and ACS is high in patients with stable CAD. Control of LDL-C is also important in this patient group. There are three recommendations for stable CAD in the guideline:

1. **The LDL-C target should be < 70 mg/dL in stable CAD patients.**

The benefits of intensive statin therapy for patients with CAD has been clearly demonstrated in many randomized clinical outcome trials.[28-32] In Japan, the recently published Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study reconfirmed the concept of "lower is better" for LDL-C control in Asian populations.[33] The REAL-CAD trial included 13,054 patients with stable CAD and randomized them to receive 1 mg vs. 4 mg pitavastatin per day. The baseline LDL-C level after a run-in period of pitavastatin 1 mg/day before randomization was 88 mg/dL. At 6 months, the LDL-C level was 73.7 in the high-dose group and 89.4 mg/dL in the low-dose group. After a median of 3.9 years follow-up, there was a statistically significant 19% lower risk of the primary composite endpoint of cardiovascu-

lar death, nonfatal MI, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization in the high-dose group compared to the low-dose group. The results were independent of the baseline LDL-C level. All-cause mortality, MI and coronary revascularization were also significantly reduced. The results of the REAL-CAD study in Asian patients were similar to previous studies from Western countries.[28-32] Several observational studies have recently been published in Taiwan. In patients with stable symptomatic atherosclerotic diseases, including CAD, cerebrovascular disease, or peripheral arterial disease under statin treatment, the risk of recurrent cardiac events was lower in patients with a LDL-C level < 100 mg/dL compared with those with a LDL-C level ≥ 100 mg/dL.[34] There was no further analysis of the benefit of a lower LDL-C level in this study. In another study including patients with a recent history of MI, high intensity statin treatment was associated with a lower risk of all-cause mortality compared with moderate or low intensity statin treatment.[35] However, the LDL-C levels were not known in this analysis.

Statins not only improve clinical outcomes but also cause coronary atheroma regression. In addition to the PRECISE-IVUS study from Japan,[15] several other Asian studies, including the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS) trial from Japan[36] and the Atorvastatin versus Rosuvastatin Therapy with Equivalent Potency on Mild Coronary Atherosclerotic Plaques (ARTMAP) trial from Korea,[37] also showed the beneficial effect of statin therapy on coronary atherosclerotic plaque regression. No randomized clinical trials have been specifically designed to assess a specific treatment target of LDL-C in patients with stable CAD. However, across different randomized outcome trials in CAD, the level of LDL-C has been lowered to 73 to 97 mg/ dL. In addition, for coronary atheroma regression studies, the level of LDL-C with intensive treatment has been lowered to 53 to 82 mg/dL. A meta-analysis of 20 clinical trials including 5,910 CAD patients found that LDL-C should be reduced to a target < 78 mg/ dL to regress coronary atherosclerotic plaque.[38] Considering both outcome trials and plaque regression studies, the guideline recommends LDL-C < 70 mg/dL as a reasonable target in patients with stable CAD. Since there have been no target-driven randomized clinical trials to specifically assess the optimal treatment target of LDL-C in patients with stable CAD, the suggested target of 70 mg/dL is based on a consensus between the cardiologists who attended the expert meetings when formulating the guideline.

Recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial was published.[39] This trial included 27,564 patients with stable atherosclerotic CVD, including 80% with previous MI. The patients who could not achieve LDL-C < 70 mg/dL after statin therapy (69% with high intensity statin) were randomized to receive evolocumab or a placebo. Evolocumab, another PCSK9 inhibitor, markedly reduced LDL-C to a median of 30 mg/dL and was effective in reducing adverse cardiovascular events, including MI, stroke, and coronary revascularization. Subgroup analysis showed that Asian and North American patients had even better effects regarding the composite outcome of cardiovascular death, MI, or stroke. The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial randomized 968 CAD patients to receive evolocumab or placebo and underwent serial intravascular ultrasound determinations of coronary atheroma volume.[40] The LDL-C level was lower in the evolocumab group (36.6 vs. 93.0 mg/dL), and there was a significant reduction in atheroma volume (-0.95%) in the evolocumab but not the placebo group (+0.05%).[40] Despite the proven efficacy and safety of PCSK9 inhibitors in CAD, the financial barrier is still a major problem that prevents their widespread use.

2. **The benefits of statin therapy for CAD included patients with a history of ACS (> 6 months), history of coronary revascularization, presence of ischemic symptoms with positive stress tests, or suspected ischemic heart disease by electrocardiography or echocardiography, or transcatheter angiographic diagnosis of significant coronary stenosis (≥ 50% luminal narrowing).**
3. **Statins could be considered in patients who have non-obstructed coronary atherosclerosis (< 50% luminal narrowing).**

The definition of stable CAD varies in different clinical studies. It is usually defined as patients with a history of unstable angina requiring hospitalization or MI (onset > 1, 3 or 6 months), history of angina pectoris, coronary artery bypass grafting, or PCI. However, additional defi-

nitions have also been used in other clinical trials. Although there are diverse criteria for the diagnosis of stable CAD, the guideline used the five most commonly used criteria in clinical trials to define the benefits of statins in CAD. In light of the benefits of statins on coronary plaque volume and stability, statin therapy is also recommended in patients with non-obstructed coronary atherosclerosis (< 50% luminal narrowing). However, the strength of scientific evidence of this recommendation is weaker than the other recommendation due to lack of large scale clinical trials in this patient group. The recommendations for TG and HDL-C interventions in CAD patients are the same as those for ACS patients.

PHARMACOLOGICAL STRATEGY

The guideline recommends statins as the first-line therapy for LDL-C lowering. Non-statin therapies including cholesterol absorption inhibitors (ezetimibe) and PCSK9 inhibitors can be considered as add-on therapy to statins for intensive LDL-C lowering. There are two recommendations for statin therapy:

1. **Statins are the first-line therapy, and moderate or high intensity statins are preferred, unless not tolerated, for high risk patients.**
2. **Based on individual risk, up-titration to the highest recommended statin dose or the highest tolerable dose to reach the target level is necessary.**

Table 1 shows the intensity of currently available statins in Taiwan. Prescribing low-dose statins is very common in Taiwan, even in patients with CAD or ACS. In the T-SPARCLE study, 23% of atherosclerotic CVD patients were treated with < 5 mg and 38% were treated with 5-10 mg atorvastatin equivalent daily dose.[4] Another study showed that the average atorvastatin equivalent daily dose was only about 18 mg in Taiwanese ACS patients.[5] Therefore, the guideline emphasizes the importance of statin intensity and recommends moderate to high intensity statins for patients with ACS or CAD, except for those who cannot tolerate the therapy. It is also important to titrate the statin dose according to the LDL-C levels after treatment. It is recommended that statins should be up-titrated to the highest recommended or tolerated dose to reach the target LDL-C level.

For ezetimibe, there are three recommendations:

1. **Ezetimibe alone can be considered as an alternative to statins in patients who have statin contraindications or intolerance.**
2. **Ezetimibe can be used in combination with statins when the therapeutic target is not achieved at a maximum tolerated statin dose.**
3. **For patients with ACS, the routine use of moderate intensity statins combined with ezetimibe may be an alternative.**

Ezetimibe acts by decreasing cholesterol absorption in the intestine through the inhibition of NPC1L1 in intestinal mucosa. Monotherapy with ezetimibe 10 mg/day reduces LDL-C by 15% to 22%. Ezetimibe can be combined with any statin, and combination therapy is an effective way to reduce LDL-C. The benefits of combination therapy were shown in the Study of Heart and Renal Protection (SHARP) study[41] and the IMPROVE-IT study.[13] The IMPROVE-IT study was designed specifically for ACS patients. Statin plus ezetimibe was shown to cause a greater LDL-C reduction and lower cardiovascular risk after 7 years of follow up.[13] Therefore, the guideline suggests moderate intensity statins plus ezetimibe as an alternative for ACS patients. Overall, the pharmacological strategy recommended in the guideline is to choose adequate intensity statins depending on the patients' clinical characteristics and baseline LDL-C levels. Titration up to high intensity statins is then advised if LDL-C is still > 70 mg/dL with initial moderate intensity statins. Because LDL-C levels drop by only about 6% for each doubling dose of statin, early ezetimibe combination therapy should be considered in patients who cannot tolerate high intensity statins or with very high LDL-C levels (Figure 1).

Table 1. Intensity of statins

High intensity statins daily dosage ↓ LDL-C ≥ 50%	Moderate intensity statins daily dosage ↓ LDL-C 30% to < 50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40* mg	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2-4 mg
	Pravastatin 40-80 mg
	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg

* The maximal dose approved for rosuvastatin in Taiwan is 20 mg once daily.
LDL-C, low-density lipoprotein cholesterol.
Adapted from reference 7.

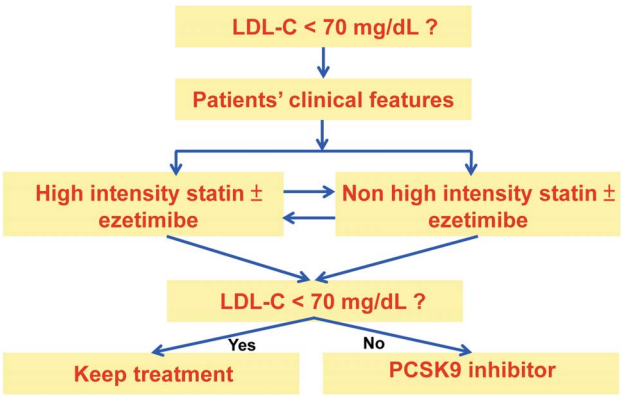

Figure 1. *Pharmacological strategy of LDL-C lowering therapy for ACS/CAD. The guideline suggests using moderate to high intensity statins initially depending on patients' clinical characteristics and baseline LDL-C levels. Titrate up to high intensity statins if the target is not achieved with initial moderate intensity statins. Early statin and ezetimibe combination therapy also can be considered. PCSK9 inhibitor is the last resort. ACS, acute coronary syndrome; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9. Adapted and modified from reference 7.*

For PCSK9 inhibitors, the recommendation is:

PCSK9 inhibitors should be considered in highly selected patients with

1. **Familial hypercholesterolemia.**
2. **Statin resistance (patients with CVD who cannot achieve the LDL-C goal despite maximally tolerating statins ± ezetimibe).**
3. **Statin intolerance.**

PCSK9 inhibitors are a new class of drug that reduce circulating LDL-C levels by increasing recycling of LDL receptors to the hepatic surface for uptake of LDL-C into the liver. PCSK9 inhibitors administered every 2 to 4 weeks have been shown to reduce LDL-C by as much as 50% to 70% across different patient populations with or without background statin therapy. PCSK9 inhibitors have been shown in clinical trials to reduce LDL-C effectively in patients with familial hypercholesterolemia.[42-45]

Recently, the FOURIER and ODYSSEY OUTCOMES trials demonstrated the clinical efficacy and safety of PCSK9 inhibitors in patients with atherosclerotic CVD who cannot achieve the LDL-C target after high or moderate intensity statin therapy.[16,39] The efficacy of PCSK9 inhibitors have also been proven in patients with statin intolerance.[46,47] Currently, the guideline suggests PCSK9 inhibitors as the last resort and only to be used in highly selected patients who have familial hypercholesterolemia with very high LDL-C levels and who are statin resistant or statin intolerant.

CONCLUSIONS

Overall, the 2017 Taiwan Lipid Guidelines for High Risk Patients provide seven recommendations for ACS, three recommendations for CAD and six recommendations for LDL-C lowering pharmacotherapy. The most important thing is to achieve the recommended LDL-C target. The initial pharmacological strategy is to use moderate to high intensity statins. Ezetimibe or PCSK9 inhibitors should be considered if statins fail or the patients cannot tolerate statins.

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