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2022 focused update of the 2017 Taiwan lipid guidelines for high risk patients: Coronary artery disease, peripheral artery disease and ischemic stroke☆,☆☆

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The previously published 2017 Taiwan Lipid Guidelines for High Risk Patients becomes the standard guidance of dyslipidemia management for patients with atherosclerotic cardiovascular disease (ASCVD) in Taiwan. New clinical trials of lipid lowering therapy were published successively after 2017. The study results changed the treatment concept of ASCVD. Therefore, an update focusing on the lipid treatment strategy for patients with ASCVD becomes necessary. In this focused update of the 2017 guideline, the treatment targets of low-density lipoprotein cholesterol (LDL-C) for patients with ASCVD were modified. The algorithm of LDL-C lowering therapy was revised. The recommendations in this focused update were made mainly based on the scientific evidence from recently published clinical trials and endorsed by the major medical societies in Taiwan.

Contents

Introduction

In 2017, the Taiwan Society of Lipids and Atherosclerosis, in association with the Taiwan Society of Cardiology, Taiwan Society of Cardiovascular Intervention, Taiwan Stroke Society, Taiwan Diabetes Association, Taiwanese Association of Diabetes Educators and Taiwan Society of Nephrology, published the 2017 Taiwan Lipid Guidelines for High Risk Patients.[1] The optimal lipid target and treatment strategy were recommended for patients with coronary artery disease (CAD), acute coronary syndrome (ACS), peripheral artery disease (PAD), ischemic stroke, diabetes mellitus, chronic kidney disease, and familial hypercholesterolemia.[1] After publication of the 2017 guideline, new scientific evidence regarding lipid lowering therapy in patients with atherosclerotic cardiovascular disease (ASCVD) was reported successively. In particular, there were important clinical trials published about proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for ACS/CAD and intensive lipid lowering with statins among patients with ischemic stroke or transient ischemic attack (TIA) of atherosclerotic origin.[2–4] The study results changed the treatment concept in these high risk patients. Therefore, an update focusing on the lipid treatment strategy for these patients becomes necessary. The recommendations in this focused update were made based on the scientific evidence from recently published clinical trials but modified by the expert opinions and considerations of the real-world situation in Taiwan. The draft of this guideline update was developed by the Taiwan Society of Lipids and Atherosclerosis and sent to the Taiwan Society of Cardiology, Taiwan Society of Cardiovascular Intervention and Taiwan Stroke Society for review. The final document was endorsed by these societies. As usual, the guideline update adopted the same evidence-based classification system as the 2017 guideline, including 3 classes of recommendation (COR) and 3 levels of evidence (LOE).[1]

ACS/CAD

New statin data in Asia

In the 2017 Taiwan Lipid Guidelines for High Risk Patients, the recommended target of low-density lipoprotein cholesterol (LDL-C) for patients with CAD/ACS is 70 mg/dL. The benefit of lowering down LDL-C to around 70 mg/dL for Asian CAD patients was recently proved in the REAL-CAD study, a large-scale randomized clinical trial performed in Japan.[5] The study included stable CAD patients with (1) history of ACS, including acute myocardial infarction (MI) or unstable angina >3 months, or (2) previous coronary revascularization, including percutaneous coronary intervention or coronary artery bypass graft >3 months, or (3) angiographically documented coronary artery stenosis of at least 75% diameter stenosis. These patients were randomized to high dose (4 mg/day) or low dose (1 mg/day) pitavastatin therapy. The primary outcome was a composite end point of cardiovascular death, nonfatal MI, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization. The cumulative 4-year incidence of the primary outcome events was significantly lower in patients treated with intensive statin therapy to achieve an LDL-C level around 73 mg/dL compared to those with less intensive statin therapy with an LDL-C level around 90 mg/dL.[5] This trial was the first one performed in Asia and demonstrated that aggressive LDL-C lowering with high dose statin is not only beneficial but also well tolerated in Asian population.

New PCSK9 inhibitor data

The benefit of an even lower LDL-C level <70 mg/dL was evaluated in clinical trials using PCSK9 inhibitor which is a novel and powerful class of LDL-C lowering therapy. PCSK9 inhibitor monotherapy provides 60% LDL-C reduction and PCSK9 inhibitor plus high-intensity statin decrease LDL-C up to 75%.[6] Currently available PCSK9 inhibitors in Taiwan are evolocumab and alirocumab. The benefits of even lower LDL-C values to reduce the risk of major adverse cardiovascular events (MACE) in CAD/ACS were demonstrated in the outcome trials of PCSK9 inhibitors, the FOURIER and ODYSSEY OUTCOMES studies.[2,3] In stable ASCVD with a prior history of MI, nonhemorrhagic stroke, or symptomatic PAD in the FOURIER study, evolocumab plus statin reduced the LDL-C level to a median of 30 mg/dL (interquartile range 19—46 mg/dL) and obtained a 15% significant risk reduction of MACE compared with those given statin therapy only with an LDL-C level of 92 mg/dL.[2] In patients with recent ACS in previous 1—12 months in the ODYSSEY OUTCOMES study, alirocumab plus statin was associated with a 15% significant risk reduction of MACE compared with statin only group.[3] The mean achieved LDL-C level was 40 and 53 mg/dL at 4 weeks and 48 weeks follow-up in the alirocumab plus statin group compared to 93 and 101 mg/dL in the statin only group. Despite their clinical efficacy, due to the high drug price, the cost-effectiveness of PCSK9 inhibitors becomes a major problem and limits the use of these drugs in Taiwan.[7]

Focusing the use of PCSK9 inhibitors to achieve a lower LDL-C target in CAD/ACS with higher risk is likely to provide maximal clinical benefit and improve the cost-effectiveness. In the FOURIER study with stable ASCVD patients, subgroup analyses were performed in (1) patients with prior MI and (2) patients with symptomatic lower extremity PAD.[8—10] It turns out that patients with a recent MI < 1 year, ≥ 2 prior MIs, presence of multivessel CAD (≥40% stenosis in ≥2 large vessels), and concomitant symptomatic PAD were at higher risk of MACE and obtained greater risk reduction from a lower LDL-C level achieved with evolocumab than those without these conditions.[8—10] For diabetic subgroup analysis in the FOURIER study, the risk reduction of MACE from PCSK9 inhibitor was almost similar between those with and without diabetes.[11] In the ODYSSEY OUTCOMES study with recent ACS patients, subgroup analyses were performed in (1) patients with polyvascular disease (CAD plus PAD or carotid stenosis) and (2) patients with diabetes.[12,13] The studies found these patients were at higher risk of MACE and intensive LDL-C lowering with alirocumab caused a larger risk reduction.[12,13] Just like a lower LDL-C target for ACS and diabetes recommended in the 2017 guideline, these studies indicate that more intensive LDL-C lowering therapy to achieve an even lower LDL-C target in these very high risk groups of CAD/ACS could obtain more clinical benefits. Actually, the similar concept was also raised in the 2018 American Heart Association/American College of Cardiology Cholesterol Guideline.[14] In this 2018 American guideline, patients with a history of multiple major ASCVD events, including recent ACS (within the past 12 months), history of MI, history of ischemic stroke and symptomatic PAD, are considered at very high risk and more intensive LDL-C reduction is recommended.[14]

Recommendation

- The LDL-C target is < 70 mg/dL in patients with CAD/ACS (COR I, LOE B).
- In addition to ACS plus diabetes, CAD/ACS at very high risk, including those with recent MI (<12 months), ≥2 prior MIs, multivessel CAD, or concomitant PAD (including extremity or carotid artery), a lower target of LDL-C < 55 mg/dL can be considered (COR IIa, LOE B).

PAD

LDL-C target

PAD is a clinical manifestation of systemic atherosclerosis. Insufficient blood supply due to atherosclerotic narrowing of lower extremity arteries leads to clinical symptoms of PAD, including claudication, ischemic ulcer and acute or critical limb ischemia.[15,16] PAD patients have higher risk of MI, ischemic stroke and cardiovascular mortality.[17,18] In fact, the risk of cardiovascular events is even higher in patients with PAD than CAD.[19] Because atherosclerosis accounts for the majority of pathogenesis and its high cardiovascular risk, it is reasonable to treat LDL-C more aggressively for PAD patients. A randomized controlled trial, the Heart Protection Study, investigating the efficacy

of LDL-C lowering by simvastatin revealed a 22% decrease of vascular events in 5-year follow-up in PAD patients taking simvastatin 40 mg daily compared to those taking placebo.[20] A meta-analysis reported that LDL-C lowering by statin in PAD was associated with lower all-cause mortality, lower nonfatal stroke as well as a trend of lower risk of MI.[21] LDL-C reduction with lipid-lowering therapy also alleviated clinical symptoms, improved exercise endurance, and slowed down the progression of atherosclerotic plaques in patients with PAD.[22–24] In the *post hoc* analysis of Scandinavian Simvastatin Survival Study, patients receiving simvastatin had a 38% decrease of intermittent claudication than those receiving placebo in a median follow-up of 5.4 years.[25] West et al. reported that reduction of LDL-C by simvastatin with or without ezetimibe hold the progression of atherosclerotic plaques in superficial femoral artery in PAD patients.[24] Based on the scientific evidence, most of the recent guidelines classify PAD as high risk or very high risk and recommend to achieve a LDL-C level <70 or 55 mg/dL.[6,14,26,27] A Korean retrospective cohort study assessed the influence of LDL-C on clinical outcomes in PAD patients receiving endovascular treatment.[28] They found patients with LDL-C < 70 mg/dL had lower risk of MACE which was a composite of all-cause mortality, nonfatal MI and stroke than those with LDL-C ≥ 70 mg/dL in a median follow-up of 4.8 months. The result implied that achieving a goal of LDL-C < 70 mg/dL is also important in Asian PAD patients. In most guidelines and clinical studies, the definitions of symptomatic PAD include (1) history of peripheral artery revascularization, (2) history of amputation for ischemic limb due to atherosclerotic disease, (3) clinical symptoms of PAD with > 50% stenosis of peripheral arteries confirmed by imaging studies. Intensive LDL-C control is beneficial in these well-defined symptomatic PAD patients.

New PCSK9 inhibitor data

In the FOURIER trial using evolocumab for ASCVD, there were 3642 subjects (13.2% of total participants) had PAD at enrollment, including those with a history of prior peripheral revascularization, a history of amputation for vascular cause, and/or had an ankle brachial index <0.85 with symptoms of claudication.[10] At 48 weeks, the median LDL-C level among the PAD group was 31 mg/dL (interquartile range, 19—49 mg/dL) with evolocumab plus statin therapy. The outcome analysis of PAD patients in the FOURIER trial showed that add-on evolocumab to statin significantly reduced the incidence of primary endpoint which was a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina or coronary revascularization by 21% (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66—0.94) in a follow-up of 2.5 years.[10] Moreover, PAD patients with evolocumab plus statin had significantly lower risk of major adverse limb events which was a composite of acute limb ischemia, major amputation or urgent revascularization (HR 0.58, 95% CI 0.38—0.88). The results of the analysis provided evidence supporting the clinical benefit of aggressive LDL-C reduction in patients with PAD.

Recommendation

- The LDL-C target is < 70 mg/dL in patients with symptomatic PAD including (1) history of peripheral artery revascularization, (2) history of amputation for ischemic limb due to atherosclerotic disease and (3) clinical symptoms of PAD with > 50% stenosis of peripheral arteries confirmed by imaging studies (COR I, LOE B).
- In symptomatic PAD with CAD or carotid stenosis, a lower target of LDL-C < 55 mg/dL may be considered (COR IIa, LOE B).

Ischemic stroke/TIA

Statins in acute stroke

According to the data from Taiwan Stroke Registry with 30,599 stroke admissions between 2006 and 2008, the majority of stroke events (>70%) were ischemic in Taiwan. Among patients with ischemic stroke or TIA, hypertension (79.2%) and dyslipidemia (49.4%) were the two most prevalent risk factors.[29] Several large-scale clinical studies investigated the effect of statin treatment in stroke patients during admission. One study analyzed medical records from 12,689 patients admitted with ischemic stroke from a large integrated healthcare delivery system in California between January 2000 and December 2007.[30] Statin used before and during hospitalization was associated with a better survival rate. On the contrary, patients who underwent statin withdrawal in the hospital had a greater risk of death. The benefit was greater for higher statin dose and earlier initiation during stroke admission. Similarly, the beneficial effects of early initiation of statin therapy during hospitalization in patients with acute ischemic stroke were also shown in the Taiwan Stroke Registry and GWTG-Stroke Registry.[31,32] Moreover, one randomized clinical trial recruiting 215 patients admitted within 24 h of ischemic stroke and 89 patients having statins before stroke were further assigned either to statin withdrawal for the first 3 days after admission (n = 46) or to immediately resumed atorvastatin 20 mg/day (n = 43). The results showed that patients with statin withdrawal had a higher frequency of poor functional outcome at 3 months, greater final infarct volume and higher risk of early neurological deterioration at acute stage.[33] The concept of early initiation of statin during hospitalization and do not withdrawal pre-stroke statin after admission was further supported by results of meta-analysis.[34] The meta-analysis study also showed that in patients treated with thrombolytic agents, pre-stroke statin was associated with good functional outcome, despite an increased risk of symptomatic hemorrhagic transformation.

Recommendation

- In patients with acute ischemic stroke or TIA and LDL-C ≥ 100 mg/dL, it is indicated to prescribe statins (COR I, LOE A).

- It is reasonable to continue statins after admission for acute ischemic stroke or TIA in patients who have already received statins before the stroke (COR IIa, LOE B).

LDL-C target

A meta-analysis of 24 randomized controlled trials suggests that statin use is associated with a reduced stroke risk in people without a prior stroke. Every 10% decrease of LDL-C is associated with 7.5% stroke risk reduction and every 1 mmol/L (39 mg/dL) LDL-C reduction can decrease the risk of stroke by 15%–21%.[35,36] In the SPARCL trial, 4731 patients with a history of non-cardioembolic stroke or TIA within 6 months were randomly assigned to receive either atorvastatin 80 mg/day or placebo. The study found that patients received atorvastatin had a lower recurrent stroke during 4.9 years follow up (HR 0.84, 95% CI 0.71–0.99). The average LDL-C levels were 73 mg/dL and 129 mg/dL in atorvastatin and placebo groups, respectively.[37] The recently published Treat Stroke to Target (TST) trial randomly assigned 2860 patients with a history of ischemic stroke within 3 months or TIA within 15 days to two LDL-C treatment goals, $<$ 70 mg/dL vs. 90–110 mg/dL.[4] To be enrolled in the trial, patients had to have documented atherosclerotic diseases, including stenosis of an extracranial or intracranial cerebral artery, atherosclerotic plaques of the aortic arch measuring at least 4 mm in thickness, or a known history of CAD. During 3.5 years of follow-up, patients in the LDL-C $<$ 70 mg/dL group had a lower risk of major cardiovascular events (HR 0.78, 95% CI 0.61–0.98) compared to those in the 90–110 mg/dL group. The average achieved LDL-C levels were 65 mg/dL and 96 mg/dL in the 2 groups, respectively.[4] There was no significantly increased risk of hemorrhagic stroke or new-onset diabetes. For patients assigned to the intensive LDL-C lowering group, 24% received high-intensity statin, 76% received moderate-intensity statin, and 41% received statin/ezetimibe combination therapy. The TST trial contains subjects from France and South Korea. The overall primary endpoint is positive and there is no significant treatment-by-country interaction. However, the neutral outcomes in the subgroup analysis of Korean cohort still raise the concern that the results of TST trial may not be generalizable to Korean or Asian patients. Nevertheless, among the 2860 study participants in TST trial, there were 2148 (75.1%) from France and only 712 (24.9%) from South Korea. The median follow-up time was also much longer in France (5.3 years versus 2.0 years). These factors potentially caused a lack of power to detect a significant effect in Korean cohort. A recent prospective cohort study from Hong Kong with 904 Chinese ischemic stroke patients showed that patients with a mean post-event LDL-C $<$ 70 mg/dL were associated with a lower risk of major cardiovascular events compared to those with LDL-C $>$ 70 mg/dL after a mean follow up of 6.5 years.[38] A mean LDL-C $<$ 70 mg/dL was also associated with a lower risk of intracerebral hemorrhage in patients with significant large artery diseases.[38]

The SPARCL trial showed that patients treated with atorvastatin 80 mg/day were associated with an increased risk of hemorrhagic stroke (HR 1.68, 95% CI 1.09–2.59) compared with the placebo. However, post hoc analysis of the SPARCL trial showed that the increased risk of hemorrhagic stroke was associated with increased blood pressure (systolic blood pressure $>$160 mmHg or diastolic blood pressure $>$100 mmHg) and hemorrhagic stroke at baseline, but not the LDL-C levels.[39] A meta-analysis including 31 randomized controlled trials showed that statin use was not associated with an increased risk of intracranial hemorrhage (HR 1.08, 95% CI 0.88–1.32).[40] A nationwide study conducted in Denmark suggested that stain use compared with no statin use was not associated with an increased risk of recurrent intracerebral hemorrhage in patients with intracerebral hemorrhage at baseline and was associated with a lower risk of intracerebral hemorrhage in patients with ischemic stroke at baseline.[41]

Recommendation

- In patients with ischemic stroke or TIA and cerebral or carotid atherosclerotic stenosis or known CAD, it is reasonable to control LDL-C target $<$ 70 mg/dL to reduce the risk of major cardiovascular events (COR IIa, LOE B).

LDL-C lowering agents other than statins

A meta-analysis of 6 randomized clinical trials suggested that ezetimibe added to statins compared to statins monotherapy was associated with a lower risk of nonfatal stroke (risk ratio [RR] 0.83, 95% CI 0.71–0.97).[42] The TST trial showed that 41% of patients assigned to the intensive LDL-C lowering group with LDL-C $<$ 70 mg/dL received ezetimibe combination therapy; whereas only 7% of patients received ezetimibe in the group with LDL-C between 90 and 110 mg/dL.[4] The IMPROVE-IT trial also showed that combined ezetimibe with simvastatin compared with simvastatin alone reduced the risk of stroke of any etiology (HR 0.60, 95% CI 0.38–0.95) and ischemic stroke (HR, 0.52, 95% CI, 0.31–0.86) among patients with ACS and a prior history of stroke.[43] In the IMPROVE-IT trial, the risk of hemorrhagic stroke was not increased in patients with LDL-C $<$ 30 mg/dL compared to those with LDL-C $\geq$ 70 mg/dL.[44] PCSK9 inhibitors also demonstrated their efficacy in preventing stroke. In the FOURIER trial using evolocumab for stable ASCVD patients, evolocumab plus statin significantly reduced all stroke (HR 0.79, 95% CI, 0.66–0.95) and ischemic stroke (HR 0.75, 95% CI 0.62–0.92) compared with statin monotherapy.[45] There was no significant difference in hemorrhagic stroke (HR 1.16, 95% CI 0.68–1.98). The effect was consistent across among the groups with and without prior ischemic stroke.[45] In the ODYSSEY OUTCOMES trial using alirocumab for patients with recent ACS, alirocumab reduced the risk of any stroke (HR 0.72, 95% CI 0.57–0.91) and ischemic stroke (HR, 0.73, 95% CI, 0.57–0.93).[46] There was no increased risk of hemorrhagic stroke (HR 0.83, 95% CI 0.42–1.65). Similarly, the effect of alirocumab on stroke was similar between patients with and without a history of previous stroke.[46] A meta-analysis of 39 randomized controlled trials showed that combination therapy of PCSK9 inhibitors (alirocumab or evolocumab) with statins were associated with a reduced risk of ischemic stroke (RR 0.78, 95% CI 0.67–0.89).[47]

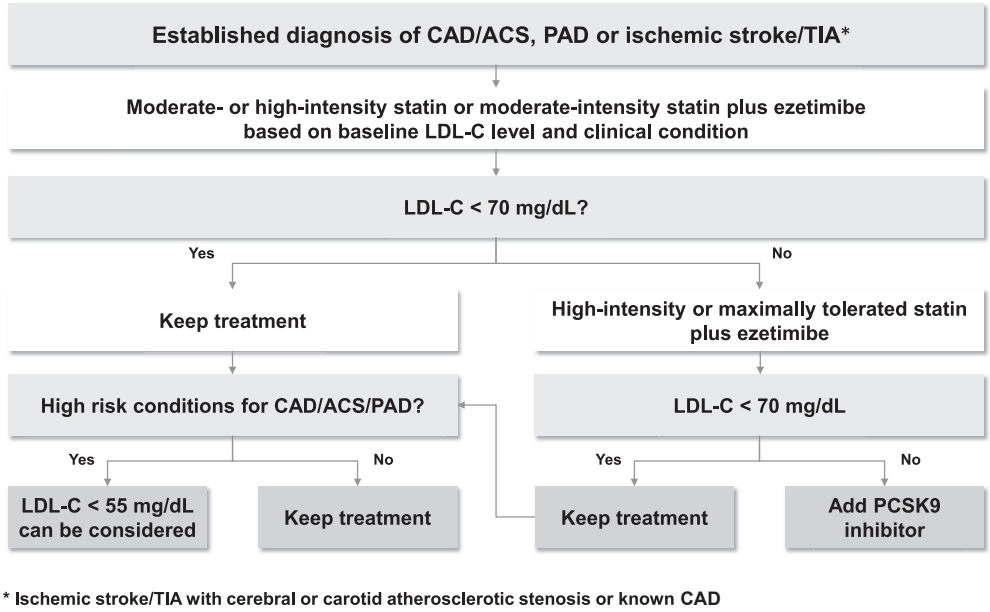

Figure 1 The recommended algorithm of LDL-C lowering therapy for patients with CAD/ACS, PAD and ischemic stroke/TIA in Taiwan. High risk conditions of CAD/ACS indicate ACS plus diabetes, recent MI, $\geq$ 2 prior MIs, multivessel CAD, or concomitant PAD. High risk condition of PAD indicate PAD with CAD or carotid stenosis. ACS, acute coronary syndrome; CAD, coronary artery disease, LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; TIA, transient ischemic attack.

Recommendation

- In patients with ischemic stroke or TIA and cerebral or carotid atherosclerotic stenosis or known CAD, it is reasonable to combine statin with ezetimibe to achieve LDL-C $<$ 70 mg/dL (COR IIa, LOE B).

Table 1 Recommended LDL-C targets in atherosclerotic cardiovascular diseases.

Disease categories	Recommended LDL-C target
CAD/ACS	$<$70 mg/dL
CAD/ACS with • ACS and diabetes or • Recent MI ($<$12 months) or • $\geq$2 prior MIs or • Multivessel CAD or • Concomitant PAD	$<$55 mg/dL can be considered
PAD	$<$70 mg/dL
• PAD with CAD or carotid stenosis	$<$55 mg/dL can be considered
Ischemic stroke or TIA with cerebral or carotid atherosclerotic stenosis or known CAD	$<$70 mg/dL

ACS, acute coronary syndrome; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

- In patients with ischemic stroke or TIA and cerebral or carotid atherosclerotic stenosis or known CAD, adding a PCSK9 inhibitor is reasonable if LDL-C $>$ 70 mg/dL under combined maximally tolerated statins plus ezetimibe (LOR IIa, LOE B).

Overall, Table 1 summarizes the recommended LDL-C targets in ASCVD. Fig. 1 shows the recommended algorithm of LDL-C lowering therapy for CAD/ACS, PAD and ischemic stroke/TIA patients in Taiwan.

Declaration of competing interest

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