Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 81 (2018) 853–859

www.jcma-online.com

Review Article

Comparison of the 2017 Taiwan lipid guidelines and the Western lipid guidelines for high risk patients

Yi-Heng Li [a,*], Hung-I Yeh [b,c], Jiann-Shing Jeng [d], Min-Ji Charng [e,f]

[a] *Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC*
[b] *Departments of Internal Medicine and Medical Research, Mackay Memorial Hospital, Taipei, Taiwan, ROC*
[c] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan, ROC*
[d] *Stroke Center and Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan, ROC*
[e] *Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[f] *Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*

Received March 22, 2018; accepted May 6, 2018

Abstract

Dyslipidemia is a major contributor in initiation, development and progression of atherosclerotic cardiovascular disease (ASCVD). Most lipid guidelines are from Europe and America and centered on the reduction of atherogenic lipids levels through lifestyle intervention and pharmacotherapy. Recently, the 2017 Taiwan lipid guidelines for high risk patients was published to facilitate the control of dyslipidemia in patients that are highly susceptible to ASCVD, including patients with preexisting ASCVD, diabetes, chronic kidney disease and familial hypercholesterolemia. Most recommendations outlined in the 2017 Taiwan lipid guidelines for high risk patients are in concordance with those of Western guidelines. However, based on evidence from the studies originating from Asia and local expert opinions, there are some recommendations different from the other guidelines. The purpose of the current review is to compare the similarities and differences between the perspectives of the 2017 Taiwan lipid guidelines for high risk patients and other Western guidelines in individuals at high risk of ASCVD. The definitions of high risk groups and treatment goals defined to achieve ASCVD risk reduction are specifically compared.

Keywords: Dyslipidemia; Guideline; Statin; Taiwan

1. Introduction

Cardiovascular disease (CVD) was responsible for approximately 17.64 million deaths in 2016, equating to 44.6% of all global non-communicable disease deaths and more than twice that caused by cancer.[1] Atherosclerotic CVD (ASCVD), such as coronary artery disease (CAD), ischemic stroke, carotid stenosis and peripheral arterial disease (PAD), accounts for the greatest proportion of CVD-related death. One of the most important events in initiating and propagating of ASCVD is the accumulation of low-density lipoprotein cholesterol (LDL-C) within the arterial wall and development of atherosclerotic plaques. In recent years, multiple lines of evidence from epidemiological, genetic and randomized clinical studies unequivocally indicate that increased circulating level of LDL-C plays a critical role in the progression of atherosclerotic plaques and the risk of ASCVD.[2] Therefore, LDL-C becomes the major target of lipid treatment. A number of major medical societies worldwide, primarily from America and Europe, have released and continuously updated lipid management guidelines to assist healthcare professionals for the management of dyslipidemia in different populations at risk of developing ASCVD. In Asia, following these Western

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Yi-Heng Li, Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, 138, Sheng Li Road, Tainan 704, Taiwan, ROC.
E-mail address: heng@mail.ncku.edu.tw (Y.-H. Li).

https://doi.org/10.1016/j.jcma.2018.05.003

guidelines did not come without caveats. From inception, the European and American lipid guidelines were to provide recommendations to benefit individuals residing in their respective regions as opposed to being used globally. The incidence and prevalence of ASCVD are also different between Asian and Western countries. Guidelines that fit the Asian conditions based on clinical studies and treatment experiences from this region become necessary.

Recently, the Taiwan Society of Lipids and Atherosclerosis published the 2017 Taiwan Lipid Guidelines (TLG) for High Risk Patients in a move to enhance the control of dyslipidemia in this country.[3] The necessity for TLG was prompted due to the rising mortality rate of ASCVD and increasing prevalence of dyslipidemia. The CVD-related death in Taiwan increased from 121.5 in 2007 to 163.3 deaths per 100,000 people in 2017.[4] A comparison between the 1993 to 1996 and 2005 to 2008 national nutrition and health surveys in Taiwan indicated the prevalence of hypercholesterolemia, defined as total cholesterol ≥240 mg/dL, and hypertriglyceridemia, defined as triglyceride ≥200 mg/dL, in men rose to 13% and 21% from 10% and 13%, respectively.[5] Moreover, it was revealed in a hospital-based survey in 2015 that 46% patients with ASCVD still had LDL-C > 100 mg/dL.[6] Only 60% and 38% of patients in Taiwan who have acute coronary syndrome (ACS) or acute ischemic stroke, respectively, were prescribed a lipid-lowering drug at discharge.[7,8] Collectively, the evidence so far pointed toward a need for a local lipid guideline to support clinicians to make proper decisions in the management of ASCVD.

2. Purpose of the review

The 2017 TLG was developed with the intention to provide guidance on the treatment of patients at high risk of developing ASCVD events rather than a comprehensive compendium for the primary prevention of ASCVD in healthy subjects with only dyslipidemia. The patient populations at high risk defined by the 2017 TLG are those with preexisting ASCVD, diabetes mellitus (DM), chronic kidney disease (CKD) and familial hypercholesterolemia (FH). Many recommendations in the 2017 TLG are consistent with those suggested in the lipid guidelines from Western countries. The 2017 TLG regards LDL-C elevation plays the most significant role in atherosclerosis and statin should be used as a first-line therapy to reduce LDL-C and ASCVD risk. However, some divergences are also noted. The purpose of this review aims to highlight the major similarities and differences between the perspectives of the 2017 TLG and the other 4 lipid guidelines from America and Europe: (1) the 2017 American Association of Clinical Endocrinologists (AACE) guidelines for management of dyslipidemia and prevention of cardiovascular disease,[9] (2) the 2016 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias,[10] (3) the 2015 National Lipid Association (NLA) recommendations for patient-centered management of dyslipidemia[11] and (4) the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.[12]

3. Scientific evidence

A wide range of clinical evidence was examined to sculpt the recommendations in the 2017 TLG. This wide evidence encompassing approach was similarly employed in building the recommendations in 2017 AACE, 2016 ESC/EAS and 2015 NLA guidelines. In addition to randomized clinical trials (RCTs) and meta-analysis of such studies, retrospective studies, observational studies, and consecutive case studies also represent the sources of evidence in the guidelines to formulate lipid management recommendations. In contrast, a more conservative approach in evidence selection was adopted in the 2013 ACC/AHA guideline and only results from RCTs were surveyed to formulate the recommendations within the guideline. This approach exhibits limitations to statin only therapy because the vast majority of RCTs with positive results are from the investigations of using statins for lipid control. Additional evidence of non-statin therapy, including ezetimibe and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, in secondary prevention of ASCVD emerged from RCTs in recent years. To overcome the limitations, an ACC expert consensus decision pathway on the role of non-statin therapies was published in 2016 to add the treatment role of ezetimibe and PCSK9 inhibitors.[13] With the inclusion of multiple types of evidence by the 2017 TLG and the other three guidelines, recommendations were generated with a greater scope. Some recommendations can be generated only from the results of non-RCTs, registry studies or expert opinions. This approach provides suggestions more applicable to clinical reality because RCTs could not provide evidence covering all patient types. However, these recommendations may not carry the equivalent level of scientific evidence as those recommendations derived from RCTs.

4. High risk patients

4.1. ASCVD

It is generally agreed by all guidelines mentioned in this review that individuals with preexisting or history of ASCVD carry the highest risk of developing cardiovascular events. ASCVD is classified as high risk, very high risk or extreme risk in these guidelines. However, there are variations between the definitions of ASCVD among the guidelines. In common, the 2017 TLG along with the other guidelines classify CAD/ACS, ischemic stroke/transient ischemic attack (TIA), carotid stenosis and PAD as ASCVD. The 2017 TLG additionally points out that intracranial arterial stenosis that occurs more often in Asians carries high risk.[14,15] It suggests that patients with intracranial arterial stenosis >50% with or without symptoms should receive aggressive blood pressure and lipid control. In the 2016 ESC/EAS and 2015 NLA guidelines, aortic aneurysm is also recognized as ASCVD. The 2017

AACE guideline is less clear as to what conditions constitute as ASCVD though indicates patients with ACS, CAD, carotid disease and PAD are at high ASCVD risk.

4.2. DM

All five guidelines consider diabetic patients are at high risk of ASCVD, but slight variations appear in these guidelines. In the 2017 TLG, all diabetic patients with age ≥40 years or <40 years with other ASCVD risk factors are considered as high risk and should have their lipid levels controlled to target. The 2013 ACC/AHA guideline also takes age into consideration. It indicates that only DM patients aged 40–75 years with LDL-C 70–189 mg/dL are considered to get benefit from statin therapy. The other guidelines do not use age as the determining factor in risk stratification for DM. In the 2015 NLA guideline, DM patients with >1 major ASCVD risk factor or evidence of end-organ damage are at very high risk and DM patients with 0–1 major ASCVD risk factor are at high risk. In the 2016 ESC/EAS guideline, DM patients with target organ damage (such as proteinuria) or with a major risk factor such as smoking, hypertension or dyslipidemia are classified as very high risk. All other DM patients are classified as high risk. The suggestions in the 2017 AACE guideline are similar to the 2016 ESC/EAS guideline that all DM patients are at high risk and DM patients have 1 or more risk factors are at very high risk.

4.3. CKD

CKD is usually defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline by using change of glomerular filtration rate (GFR): GFR 45–59 mL/min/1.73 m^2 is stage 3a, 30–44 mL/min/1.73 m^2 is stage 3b, 15–29 mL/min/1.73 m^2 is stage 4 and <15 mL/min/1.73 m^2 is stage 5.[16] The 2017 TLG indicates all CKD patients with GFR < 60 mL/min/1.73 m^2 (stage 3–5) are at high risk and suggests to start lipid lowering therapy if their LDL-C > 100 mg/dL except in patients with chronic dialysis. On the contrary, the 2013 ACC/AHA guideline does not consider CKD a major comorbidity that increases ASCVD risk. The 2015 NLA guideline recognizes CKD stage 3b or 4 as high risk. In the 2016 ESC guideline, severe CKD (stage 4 and 5, GFR < 30 mL/min/1.73 m^2) is classified as very high risk and moderate CKD (stage 3a and b, GFR 30–59 mL/min/1.73 m^2) is at high risk. In the 2017 AACE guideline, all CKD at stage 3 or 4 is considered as high risk and, if patients with CKD at stage 3 or 4 are associated with 1 or more risk factors, they are at very high risk.

4.4. Severe hypercholesterolemia or FH

The 2017 TLG indicates all FH patients, including hetero- and homozygous FH, are at high risk to develop ASCVD and suggests early control with medications even in children and adolescents. FH should be diagnosed by the Taiwan FH Diagnostic Criteria in the guideline.[3] Early pharmacological intervention for pediatric FH ≥ 10 years is suggested in Japan.[17] In Europe, statin is also recommended to start for children with FH aged 8–10 years.[18] The 2013 ACC/AHA guideline considers adults >21 years of age with baseline LDL-C > 190 mg/dL not due to secondary modifiable causes, such as hypothyroidism, are at high risk of developing ASCVD events and need statin treatment. Management of hypercholesterolemia in children and adolescents is not covered in the 2013 ACC/AHA guideline. In the 2015 NLA guideline, LDL-C > 190 mg/dL is considered a severe hypercholesterolemia phenotype, which includes FH. The guideline classifies these patients as high risk and suggests lifestyle intervention and pharmacotherapy. The 2016 ESC guideline considers patients with markedly elevated single risk factors, particularly total cholesterol >310 mg/dL (e.g. in FH), as high risk. In the 2017 AACE guideline, heterozygous FH patients are classified as very high risk.

4.5. Risk calculator

The 2017 TLG was designed specifically to provide recommendations for management of dyslipidemia in high risk patients for ASCVD. Healthy subjects without these high risk conditions were not included; therefore the risk assessment tool was omitted from its list of recommendations. For subjects without previously mentioned high risk conditions, other lipid guidelines recommend the use of ASCVD risk assessment tools to stratify patients into ASCVD risk categories. For example, the 2016 ESC/EAS guideline proposes the Systemic Coronary Risk Estimation (SCORE) calculator and 2013 ACC/AHA recommends the Pooled Cohort Equations for risk estimations. In the 2015 NLA guideline, high risk threshold is defined as >10% using Adult Treatment Panel III Framingham Risk Score, >15% using the 2013 Pooled Cohort Equations, or >45% using the Framingham long-term cardiovascular disease risk calculation. In the 2017 AACE guideline, Framingham risk scoring is applied to determine 10-year risk; > 20% is considered as very high risk and 10–20% as high risk. Despite the usefulness of such tools, it should be noticed that the overall ASCVD risk of individuals with diseases commonly associated with dyslipidemia, such as DM, CKD or FH, may be underestimated by these risk score calculators. Clinicians should also be reminded that over or under estimation of ASCVD risk can occur if the calculators are applied on populations outside the validation group.[19,20]

5. Treatment concept

There are two main prevailing views in regard to the management of LDL-C in high risk individuals: “target-driven” and “statin intensity-driven”. The 2017 TLG along with the 2017 AACE, 2016 ESC/EAS and 2015 NLA guidelines recommend the “target-driven” methodology which involves the up-titration or combination of cholesterol-lowering drugs until specific lipid targets are achieved according to the ASCVD risk. In contrast to most guidelines, the 2013 ACC/AHA guideline recommends the prescription of fixed statin

dosages (statin intensities) that have been used in multiple RCTs to provide for different risk categories. According to the 2013 ACC/AHA guideline, low-intensity stains lower LDL-C by <30%, moderate-intensity statins lower LDL-C by 30–50% and high-intensity statins lower LDL-C by ≥50%. The 2013 ACC/AHA expert panel nominated this methodology because they found ASCVD risk reduction was observed only in the RCTs with statin versus placebo or with high- versus low or moderate-intensity statin therapy. There was little clinical evidence from RCTs supporting the benefit of ASCVD risk reduction difference from different prespecified LDL-C targets. LDL-C levels monitoring is still recommended by the guideline, though it is used solely to evaluate patient compliance.

In guidelines adopted "target-driven", all consider the primary target is LDL-C except that the 2015 NLA guideline takes a unique position and recommends non-high density lipoprotein cholesterol (non-HDL-C) as the primary target. There are several reasons mentioned in the 2015 NLA guideline. The first is that it considers the superiority of non–HDL-C over LDL-C as a predictor of ASCVD events.[21,22] Furthermore, the measurement of non-HDL-C levels includes the assessment of triglycerides. Using non-HDL-C as the primary target for intervention simplifies the treatment in patients with high triglycerides. Finally, non-HDL-C is preferred because it is calculated as the difference between 2 stable parameters, total cholesterol and HDL-C, and avoids the artifact derived from LDL-C measurement or calculation. Given the historically used target in most lipid guidelines, the 2015 NLA guideline also provides LDL-C as the treatment target.

There are benefits of both approaches. Implementing the statin intensity approach to clinical practice simplifies the lipid management protocols and is completely supported by multiple large-scale RCTs. On the other hand, target approach facilitates effective communication between patients and clinicians and enhances long-term adherence to the lipid lowering therapy. Although the 2017 TLG adopts target approach, it still emphasizes the importance of statin intensity during treatment. The 2017 TLG recommends that moderate- or high-intensity statins are preferred, unless not tolerated, for high risk patients and up-titration to the highest recommended statin dose or highest tolerable dose to reach the target level is necessary. In the 2016 ESC/EAS guideline, in addition to reaching the absolute LDL-C target, an optional choice is to obtain a reduction of at least 50% LDL-C reduction in high or very high risk patients.

6. LDL-C target

The 2017 TLG has several suggestions about the LDL-C target different from the other guidelines (Table 1). First, the LDL-C target for patients with CAD/ACS is <70 mg/dL in all guidelines including the 2015 NLA guideline which takes non-HDL-C as the primary target. In addition, the 2017 TLG suggests LDL-C can be lowered down to <55 mg/dL in patients with ACS and DM based on the diabetic subgroup analysis of Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study.[23] This trial included 18,144 patients who had an ACS within the previous 10 days and were randomized to simvastatin or simvastatin plus ezetimibe. In the IMPROVE-IT trial, 27% of the study participants were diabetic patients. Diabetics receiving intensive LDL-C lowering treatment had more relative risk reduction for the primary composite endpoint than non-diabetics (14% vs. 2%, p for interaction = 0.023) after 6-year follow up. The achieved median LDL-C level was 53 mg/dL in the intensive treatment group.[23] However, because the evidence to support the benefit of LDL-C < 55 mg/dL in ACS and DM only came from a subgroup analysis and there are no randomized trials in Taiwan or Asia to evaluate the outcome of such low LDL-C target in those patients, the 2017 TLG only recommended a lower target can be considered and left the decision to physicians. The 2017 AACE guideline has similar opinion and suggests the LDL-C target to be <55 mg/dL in 3 extreme risk groups in patients with ASCVD: (1) progressive ASCVD, such as unstable angina, in individuals already achieving an LDL-C < 70 mg/dL; (2) ASCVD in individuals with DM, stage 3 or 4 CKD, or heterozygous FH and (3) premature ASCVD occurred <55 years in male and <65 years in female.[9] Lowering LDL-C across a broad range of baseline concentrations conferred similar cardiovascular risk reduction.[24] Further meta-analysis of eight RCTs of statin demonstrated that patients achieving an LDL-C < 50 mg/dL had a statistically significantly lower risk of major cardiovascular events when compared to patients achieving an LDL-C level between 75 and 100 mg/dL.[25] Therefore, a lower LDL-C target was also suggested for the highest risk patients in the 2017 AACE guideline. In recent years, a strict LDL-C control is also suggested in other Asian countries. In the 2017 guideline from the Japan Atherosclerosis Society, the LDL-C target is <70 mg/dL for patients with ACS/CAD with DM, peripheral arterial disease or CKD.[26] The 2015 Korean Guidelines for the Management of Dyslipidemia also suggests LDL-C < 70 mg/dL for patients with CAD.[27]

Second, the 2017 TLG suggests the LDL-C target <100 mg/dL in ischemic stroke/TIA despite all other guidelines take 70 mg/dL as the target in this group of patients. In Taiwan, one of the major concerns for intensive LDL-C lowering in ischemic stroke is the risk of intracerebral hemorrhage. An epidemiological study showed that intracerebral hemorrhage accounted for a higher proportion of acute stroke in Chinese than Caucasian.[28] In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial for the secondary prevention of stroke, an increased risk of hemorrhagic stroke with high dose atorvastatin was observed.[29] Although several later studies found no association of statin use with risk of intracerebral hemorrhage,[30–32] the TLG decided to make a conservative suggestion about this controversial issue. Another consideration is that small vessel disease is a major etiology of ischemic stroke in Taiwan and occurs more often than large artery atherosclerosis.[8] Small vessel disease, including hypertensive angiopathy and cerebral amyloid angiopathy, is also an important

Table 1
LDL-C target for high risk patient groups according to different lipid guidelines.

Patient Population	2017 TLG	2017 AACE	2016 ESC/EAS	2015 NLA
Acute coronary syndrome/Coronary artery disease	● <70 mg/dL ● <55 mg/dL in ACS plus DM	● <70 mg/dL ● <55 mg/dL in (1) progressive ASCVD in individuals already achieving LDL-C < 70 mg/dL (2) ASCVD in individuals with DM, stage 3 or 4 CKD, or heterozygous FH (3) premature ASCVD occurred < 55 years in male and <65 years in female	● <70 mg/dL or >50% reduction if baseline LDL-C level is 70−135 mg/dL	● <70 mg/dL
Ischemic stroke/Transient ischemic attack/Carotid stenosis	● <100 mg/dL	● <70 mg/dL	● <70 mg/dL or >50% reduction if baseline LDL-C level is 70−135 mg/dL	● <70 mg/dL
Diabetes mellitus	● No ASCVD: <100 mg/dL ● Established ASCVD: <70 mg/dL or ≥30−40% reduction of LDL-C if target cannot be reached ● ACS: <55 mg/dL	● No other risk factors: <100 mg/dL ● >1 risk factor: <70 mg/dL ● Established ASCVD: <55 mg/dL	● No target organ damage and risk factor: <100 mg/dL ● Target organ damage or ≥1 major risk factor: <70 mg/dL	● 0−1 major risk factor and no evidence of end-organ damage: <100 mg/dL ● ≧2 other major risk factors or end-organ damage: <70 mg/dL
Chronic kidney disease	● CKD 3−5 except chronic dialysis: Start treatment if LDL-C > 100 mg/dL	● CKD 3/4 with no risk factors: <100 mg/dL ● CKD 3/4 with ≥1 risk factor: <70 mg/dL ● CKD 3/4 with ASCVD: <55 mg/dL	● CKD 3: <100 mg/dL ● CKD 4/5: <70 mg/dL	● CKD 3b/4: <100 mg/dL
Familial hypercholesterolemia	● No ASCVD: Adults < 100 mg/dL Children < 135 mg/dL ● Established ASCVD: <70 mg/dL	● No ASCVD: <70 mg/dL ● Established ASCVD:<55 mg/dL	● No ASCVD:<100 mg/dL ● Established ASCVD:<70 mg/dL	● LDL ≥ 190 mg/dL:<100 mg/dL

AACE = American Association of Clinical Endocrinologists; ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolemia; LDL-C = low density lipoprotein cholesterol; NLA = National Lipid Association.

cause of intracerebral hemorrhage[33] and benefit less from aggressive lipid control. Consequently, most neurologists in Taiwan take a relatively conservative way of treating LDL-C in patients with ischemic stroke/TIA. Third, instead of recommending LDL-C treatment target, the 2017 TLG suggests a treatment threshold of LDL-C > 100 mg/dL in CKD patients. Overall, clear evidence is lacking about the optimal target in this group of patients. The Study of Heart and Renal Protection (SHARP) trial included 9270 CKD patients and randomly assigned them to receive simvastatin plus ezetimibe or placebo.[34] The study showed that CKD patients received lipid-lowering therapy obtained a 17% proportional reduction in major atherosclerotic events after a follow-up of 4.9 years. The benefit disappeared in patients with baseline LDL-C < 97 mg/dL (risk ratio 0.94, 95% confidence interval 0.78−1.15).[34] In addition, the analysis of the Alberta Kidney Disease Network Database showed the association between LDL-C and the risk of myocardial infarction was weaker in CKD patients with LDL-C < 100 mg/dL.[35] Therefore, the 2017 TLG recommends to start LDL-C lowering treatment in adults with GFR < 60 mL/min/1.73 m^2 without chronic dialysis if the baseline LDL-C > 100 mg/dL and no treatment target is suggested. However, LDL-C target is suggested in other guidelines for CKD. In the 2017 AACE guideline, stage 3 or 4 CKD with 1 or more risk factors, the LDL-C target is <70 mg/dL and <100 mg/dL if there is no other risk factor. The 2016 ESC/EAS guideline suggests LDL-C < 70 mg/dL in severe CKD (stage 4 and 5) and <100 mg/dL in moderate CKD (stage 3). The 2015 NLA guideline suggests LDL-C < 100 mg/dL in CKD stage 3b or 4.

7. Pharmacological strategy

Statin is universally recommended as the first line therapy in all lipid guidelines to reduce LDL-C levels in high risk individuals. As previously discussed, the 2013 ACC/AHA guideline adopts a "statin intensity-driven" approach and exclusively recommends the use of moderate-to high-intensity statin monotherapy to reduce ASCVD risk. In contrast, a "target-driven" methodology is recommended by the other guidelines. In the 2017 TLG, 2016 EAS/ESC and 2015 NLA guidelines, moderate- or high-intensity statins are suggested for high risk patients and up-titration to the highest recommended or tolerable dose is necessary. If the highest tolerated statin dose does not reach the target, combination treatment with ezetimibe or PCSK9 inhibitors for LDL-C lowering is suggested. The 2013 ACC/AHA guideline made an amendment in 2016 to change its "statin only" policy.[13] In the 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies,[36] patients with ASCVD should be treated first with maximally tolerated statin intensity. If LDL-C cannot be lowered down to <70 mg/dL after confirming statin adherence and intensifying lifestyle modification, ezetimibe or PCSK9 inhibitors can be added to reach the target and reduce ASCVD risk.

In conclusion, there are similarities and divergences between the perspectives of the 2017 TLG and the lipid guidelines from the Western countries. For high risk patients, the 2017 TLG along with most guidelines consider LDL-C as the major target and suggest controlling LDL-C levels to lower ASCVD risk. However, the 2017 TLG and the other guidelines have different definitions about high risk patients and ASCVD. The recommended LDL-C targets in the different categories of high risk patients are also different. This is a reflection of the 2017 TLG that more considerations were given to lipid management in the Asian/Taiwanese population.

Acknowledgments

This study was supported and sponsored by the Sanofi Taiwan Co. Ltd. The authors thank Chia-Jen Chi, MSc, Medical Lead for Cardiovascular Thrombosis Diseases of Sanofi Taiwan for her administrative support.

References

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global burden of disease study 2016. *Lancet* 2017;**390**:1151−210.
2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J* 2017;**38**:2459−72.
3. Li YH, Ueng KC, Jeng JS, Charng MJ, Lin TH, Chien KL, et al. Writing group of 2017 Taiwan lipid guidelines for high risk patients. 2017 Taiwan lipid guidelines for high risk patients. *J Formos Med Assoc* 2017;**116**:217−48.
4. Ministry of Health and Welfare. https://dep.mohw.gov.tw/DOS/lp-3960-113.html.
5. Pan WH, Wu HJ, Yeh CJ, Chuang SY, Chang HY, Yeh NH, et al. Diet and health trends in Taiwan: comparison of two nutrition and health surveys from 1993-1996 and 2005-2008. *Asia Pac J Clin Nutr* 2011;**20**:238−50.
6. Ho LT, Yin WH, Chuang SY, Tseng WK, Wu YW, Hsieh IC, et al. Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Registry Investigators. Determinants for achieving the LDL-C target of lipid control for secondary prevention of cardiovascular events in Taiwan. *PLoS One* 2015;**10**. e0116513.
7. Shyu KG, Wu CJ, Mar GY, Hou CGY, Li AH, Wen MS, et al. Clinical characteristics, management and in-hospital outcomes of patients with acute coronary syndrome - observations from the Taiwan ACS full spectrum registry. *Acta Cardiol Sin* 2011;**27**:135−44.
8. Hsieh FI, Lien LM, Chen ST, Bai CH, Sun MC, Tseng HP, et al. Taiwan Stroke Registry Investigators. Get with the guidelines-stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry: get with the guidelines- Taiwan. *Circulation* 2010;**122**:1116−23.
9. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American association of clinical enodcrinologists and Amercian college of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017;**23**(Suppl. 2):1−87.
10. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. Authors/Task force members; additional contributor. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999−3058.
11. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1−full report. *J Clin Lipidol* 2015;**9**:129−69.
12. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. American college of cardiology/American heart

association task force on practice guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of cardiology/American Heart association task force on practice guidelines. *J Am Coll Cardiol* 2014;**63**:2889−934.
13. Writing Committee, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly Jr DD, DePalma SM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American college of cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol* 2016;**68**:92−125.
14. Jeng JS, Tang SC, Liu HM. Epidemiology, diagnosis and management of intracranial atherosclerotic disease. *Expert Rev Cardiovasc Ther* 2010;**8**:1423−32.
15. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet* 2014;**383**:984−98.
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1−150.
17. Harada-Shiba M, Ohta T, Ohtake A, Ogura M, Dobashi K, Nohara A, et al. Guidance for pediatric familial hypercholesterolemia 2017. *J Atheroscler Thromb* 2018;**25**:539−53.
18. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;**36**:2425−37.
19. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;**162**:266−75.
20. DeFilippis AP, Young R, McEvoy JW, Michos ED, Sandfort V, Kronmal RA, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multiethnic cohort. *Eur Heart J* 2017;**38**:598−608.
21. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 2001;**161**:1413−9.
22. Farwell WR, Sesso HD, Buring JE, Gaziano JM. Non-high-density lipoprotein cholesterol versus low-density lipoprotein cholesterol as a risk factor for a first nonfatal myocardial infarction. *Am J Cardiol* 2005;**96**:1129−34.
23. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387−97.
24. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670−81.
25. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014;**64**:485−94.
26. http://www.j-athero.org/publications/index.html.
27. Committee for the Korean Guidelines for the Management of Dyslipidemia. 2015 Korean guidelines for the management of dyslipidemia: executive summary (English Translation). *Korean Circ J* 2016;**46**:275−306.
28. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. *Neurology* 2013;**81**:264−72.
29. Amarenco P, Bogousslavsky J, Callahan III A, Goldstein LB, Hennerici M, Rudolph AE, et al. Stroke prevention by aggressive reduction in cholesterol levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;**355**:549−59.
30. Chang CH, Lin CH, Caffrey JL, Lee YC, Liu YC, Lin JW, et al. Risk of intracranial hemorrhage from statin use in Asians: a nationwide cohort study. *Circulation* 2015;**131**:2070−8.
31. Chen PS, Cheng CL, Chang YC, Kao Yang YH, Yeh PS, Li YH. Early statin therapy in patients with acute intracerebral hemorrhage without prior statin use. *Eur J Neurol* 2015;**22**:773−80.
32. Gaist D, Goldstein LB, Cea Soriano L, García Rodríguez LA. Statins and the risk of intracerebral hemorrhage in patients with previous ischemic stroke or transient ischemic attack. *Stroke* 2017;**48**:3245−51.
33. Lovelock CE, Molyneux AJ, Rothwell PM. Oxford Vascular Study. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurol* 2007;**6**:487−93.
34. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. SHARP Investigators.The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181−92.
35. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, et al. Alberta kidney disease Network. Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol* 2013;**24**:979−86.
36. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly Jr DD, DePalma SM, et al. 2017 Focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol* 2017;**70**:1785−822.