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2022 Taiwan lipid guidelines for primary prevention

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Elevated circulating low-density lipoprotein cholesterol (LDL-C) is a major risk factor of atherosclerotic cardiovascular disease (ASCVD). Early control of LDL-C to prevent ASCVD later in life is important. The Taiwan Society of Lipids and Atherosclerosis in association with the other seven societies developed this new lipid guideline focusing on subjects without clinically significant ASCVD. In this guideline for primary prevention, the recommended LDL-C target is based on risk stratification. A healthy lifestyle with recommendations for foods, dietary supplements and alcohol drinking are described. The pharmacological therapies for LDL-C reduction are recommended. The aim of this guideline is to decrease the risk of ASCVD through adequate control of dyslipidemia in Taiwan.

Contents

Introduction

Cardiovascular (CV) disease, including atherosclerotic cardiovascular disease (ASCVD), is one of the major leading causes of death in Taiwan.[1] Multiple evidences from laboratory, epidemiological, and genetic studies indicate that increased circulating low-density lipoprotein cholesterol (LDL-C) causes accelerated deposition of cholesterol in the arterial wall leading to vascular inflammation and atherosclerosis.[2,3] The causal link of LDL-C and ASCVD was further proved in many clinical trials showing that intensive reduction of LDL-C is an effective therapy to attenuate the progression of coronary atherosclerosis and improve CV outcomes.[4–7] Recent study demonstrated that, in individuals without established coronary atherosclerosis, early initiation of statin therapy to decrease LDL-C could obtain a similar CV risk as those with untreated low LDL-C levels.[8] It is clear that maintaining an adequate LDL-C level earlier in life is an effective intervention for prevention of ASCVD. However, the control rate of LDL-C is disappointing in Taiwan. Even in patients with ASCVD, only 54% of them could achieve an LDL-C level $<$100 mg/dL.[9] The Taiwan Society of Lipids and Atherosclerosis, in association with seven other major societies in Taiwan, published the Taiwan Lipid Guidelines for High Risk Patients in 2017.[10] The optimal lipid target and treatment strategy were recommended for high risk patients, including those with coronary artery disease (CAD), acute coronary syndrome (ACS), ischemic stroke, peripheral artery disease (PAD), diabetes mellitus (DM), chronic kidney disease (CKD), and familial hypercholesterolemia (FH). The 2017 Taiwan Lipid Guidelines for High Risk Patients received critical acclaim in Taiwan and became the standard guidance for dyslipidemia treatment in high risk patients.

The management of dyslipidemia for subjects without the above-mentioned high risk features was not mentioned in the 2017 guidelines. In the Nutrition and Health Surveys in Taiwan performed from 2005 to 2008, hypercholesterolemia defined as a cholesterol level $\geq$240 mg/dL was found in 12.5% in men and 10% in women.[11] The Taiwan Society of Lipids and Atherosclerosis decided to move forward to primary prevention and developed a new lipid guideline targeting the subjects without clinically significant ASCVD, but may carry other various vascular risk factors. Advisory board meetings were held by the Taiwan Society of Lipids and Atherosclerosis from November 2020 to March 2021. Experts and opinion leaders from the Taiwan Association of Family Medicine, Taiwan Society of Cardiology, Taiwan Stroke Society, Taiwan Diabetes Association, Taiwan Association of Diabetes Educators, Taiwan Society of Nephrology and Taiwan Association of Lipid Educators attended the advisory board meetings and gave important suggestions. Scientific evidence is the major consideration of the guideline. However, we recognized that there may be insufficient data in Taiwan to support the recommendations in every aspect of dyslipidemia management for primary prevention. Many recommendations were consensus from the expert opinions after discussion. Similar to the 2017 Taiwan Lipid Guidelines for High Risk Patients, this guideline uses class of recommendation (COR) and level of evidence (LOE) to describe the intensities of the recommendations and their related scientific evidence.[10] The COR includes 3 levels, including class I (the recommendations are useful, indicated, and necessary), class IIa (the recommendations maybe useful and indicated, but their intensity of evidence are less than class I), class IIb (the recommendations could be considered but their effects are less well established) and class III (the recommendations refer to the treatment that is harmful, contraindicated, and should not be done). The LOE also has 3 levels, including LOE A (the recommendations are supported by multiple randomized clinical trials), LOE B (the recommendations are from limited randomized trials or observational studies only), LOE C (the recommendations are from experts' consensus).

Definition of primary prevention

Since this is a primary prevention guideline, the definitions of clinically significant ASCVD should be described first. It has been demonstrated that atherosclerosis originates in childhood as early as 2 years of age. A series of pathology studies, from autopsies of soldiers killed in the Korean and Vietnam Wars to the more recent Pathobiological Determinants of Atherosclerosis in Youth[12] and Bogalusa Heart studies,[13] demonstrated that coronary fatty streaks develop early in life and advanced fibrous plaques are present in a proportion of adolescents. During the past decades, convincing evidence has emerged that CV risk factors, such as cigarette smoking, dyslipidemia, hypertension, insulin resistance, obesity, and DM, accelerate the atherosclerotic process throughout the life span.[14] The major purpose of "primary prevention" refers to prevention of clinically significant ASCVD by removing or modifying risk factors. The clinically significant ASCVD include: (1) CAD, such as angina with positive stress test and/or major coronary artery diameter stenosis $>$50% by imaging studies; (2) ACS, such as myocardial infarction and unstable angina; (3) cerebrovascular disease, such as transient ischemic attack, ischemic stroke, and carotid artery stenosis $>$50% by imaging studies; (4) PAD with major extremity artery diameter stenosis $>$50% by imaging studies; and (5) aortic atherosclerotic disease, such as abdominal aortic aneurysm by imaging studies. Treatment of dyslipidemia for clinically significant ASCVD should be referred to the recommendations in the 2017 Taiwan Lipid Guidelines for High Risk Patients and its focused update. This primary prevention guideline addresses the general principles of lipid control in subjects without clinically significant ASCVD. Risk stratification is the first step to determine the lipid lowering strategy in primary prevention.

Recommendation

- Clinically significant ASCVD needs immediate and intensive reduction of LDL-C. (COR I, LOE A)
- For primary prevention in subjects without clinically significant ASCVD, risk stratification is necessary to determine the lipid lowering strategy. (COR I, LOE B)

Risk calculator

For primary prevention, population study-derived ASCVD risk estimate calculators, such as the Framingham risk score, are commonly used to decide whether a subject should receive lipid-lowering therapy or not. In recent years, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed the pooled cohort equation.[15,16] The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) used SCORE (Systematic COronary Risk Evaluation) for ASCVD risk assessment.[17,18] The UK National Institute for Health and Care Excellence (NICE) guidelines used the QRISK2 as the ASCVD risk assessment tool.[19] Although several population-specific risk assessment tools exist, none of the currently available models are derived from or prospectively validated in East Asians. The AHA/ACC pooled cohort equation for estimating the 10-year risk of ASCVD event is applicable to black and non-Hispanic white men and women 40 through 79 years of age.[15] This risk predictor may overestimate the ASCVD risk in the Chinese population.[20] The Framingham risk score also overestimated the ASCVD risk for ethnic Chinese.[21] In Taiwan, a point-based prediction model to predict the 10-year risk of CAD was developed from the Chin-Shan Community Cardiovascular Cohort study in 1990s.[22] However, the definite cut-off point to define high risk was not indicated. Some examinations, such as ankle-brachial index, pulse wave velocity, carotid ultrasound, and coronary calcium score, have been used in ASCVD risk assessment. The accessibility of these examinations is a major problem in local clinics. Concerns of cost and radiation exposure for examination of coronary calcium score are also important considerations. Basically, this guideline does not encourage to routinely screen the presence of subclinical atherosclerosis in asymptomatic subjects. At current stage, using the numbers of risk factors is a more convenient way for risk stratification in Taiwan.

Risk category

High risk (DM, CKD and LDL-C ≥ 190 mg/dL)

This primary prevention guideline decides to keep a conventional target approach and the LDL-C treatment targets are tailored according to the presence of CV risk factors. Since ASCVD is a major problem contributing to significant mortality in populations with DM and CKD, these 2 groups of patients are considered at high risk. The diagnosis of DM and management strategy of diabetic dyslipidemia was described in the 2017 Taiwan Lipid Guidelines for High Risk Patients.[10] For CKD, albuminuria is an important biomarker which is used to detect and define CKD. Albuminuria refers to increased urinary excretion of albumin. The urine albumin-to-creatinine ratio (UACR) in an untimed urine specimen has replaced 24-h urine albumin excretion as the preferred method for measuring albuminuria.[23–26] Albuminuria is defined as a UACR $\geq$30 mg/g and can be further categorized into microalbuminuria (UACR 30–300 mg/g) and macroalbuminuria (UACR $>$ 300 mg/g). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines defined CKD as kidney damage (UACR $\geq$ 30 mg/g) or a glomerular filtration rate (GFR) $<$ 60 mL/min/1.73 m^2 for at least three months.[27,28] The GFR is usually estimated from the serum creatinine level according to equations of the Modification of Diet in Renal Disease (MDRD)[29] or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[30] Immediate lipid lowering therapy is recommended for DM and non-dialysis CKD.

Severe hypercholesterolemia, defined as having an LDL-C $\geq$190 mg/dL, carries a high risk of ASCVD and premature CV events. These individuals have a 5 to 6-fold higher risk of CAD and develop CAD 10–20 years earlier in men and 20–30 years earlier in women than general population.[31] Early initiation of lipid-lowering therapy can significantly reduce morbidity and mortality in these subjects.[32] LDL-C $\geq$190 mg/dL significantly increases the likelihood for the presence of FH. Approximately 7% of the subjects with LDL-C $\geq$190 mg/dL may fulfill the diagnostic criteria of FH.[33] Genetic testing should be considered for this group of subjects for diagnosis of FH. Previous study demonstrated that, compared with a reference group with LDL-C $<$130 mg/dL without detected FH genetic mutation, subjects with LDL-C $\geq$190 mg/dL without detected FH mutation had a 6-fold higher risk for CAD, whereas those with both LDL-C $\geq$190 mg/dL and an FH mutation demonstrated a 22-fold increased risk.[34] Because LDL-C $\geq$190 mg/dL is a very unique and high risk group with a distinct long-term clinical outcome, it is classified as high risk. Just like DM and CKD, immediate lipid lowering therapy with intensive LDL-C control is recommended because the CV risk is so high in these patients.

Subjects without high risk

In subjects without DM, CKD, and LDL-C $\geq$190 mg/dL, other risk factors of ASCVD should be evaluated. These include: (1) hypertension, (2) age greater than 45 years in men or greater than 55 years in women or menopausal women, (3) family history of premature CAD (less than 55 years in men or less than 65 years in women), (4) high-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL in men or less than 50 mg/dL in women and (5) smoking.[35] Because central obesity, prediabetes and triglyceride (TG) are also considered to be ASCVD risk factors in some studies, metabolic syndrome that include all these items is regarded as the sixth independent risk factor in this guideline. Metabolic syndrome is defined according to the modified National Cholesterol Education Program Adult Treatment Panel III for Asians.[36,37] Patients who meet three or more of the following criteria are considered to have metabolic syndrome: (1) waist circumference greater than 90 cm in men or greater than 80 cm in women, (2) blood pressure of 130/85 mmHg or higher or use of antihypertensive medication, (3) fasting glucose level of 100 mg/dL or higher or use of antidiabetic drug, (4) fasting TG level of 150 mg/dL or higher or use of lipid-lowering agent for increased TG, and (5) HDL-C less than 40 mg/dL in men or less than 50 mg/dL in women (Table 1).

Based on the above-mentioned risk factor evaluation, the subjects with primary prevention can be classified into the following risk categories. High risk indicates subjects

Table 1 Metabolic syndrome.[a]

Criteria	Definition
Central obesity	Waist circumference: men $\geq$ 90 cm/women $\geq$ 80 cm
Increased blood pressure	Systolic pressure $\geq$ 130 mmHg and/or diastolic pressure $\geq$ 85 mmHg or use of antihypertensive medication
Low HDL-C	Men $<$ 40 mg/dL/women $<$ 50 mg/dL
Increased fasting glucose	$\geq$100 mg/dL or use of antidiabetic drug
Increased triglyceride	$\geq$150 mg/dL or use of lipid-lowering agent for increased triglyceride

HDL-C, high density lipoprotein cholesterol.
[a] Metabolic syndrome is diagnosed when $\geq$3 criteria are present.

Table 2 Risk categories for primary prevention.

Risk category	Risk factor	Treatment suggestion
Minimal risk	0 risk factor	Lifestyle modification first for 3 months before consideration of drug treatment
Low risk	1 risk factor	
Moderate risk	$\geq$2 risk factors	
High risk	LDL-C $\geq$ 190 mg/dL or diabetes mellitus or non-dialysis chronic kidney disease[a]	Start lipid lowering therapy with lifestyle modification

[a] Chronic kidney disease is defined as kidney damage (UACR $>$ 30 mg/g) or glomerular filtration rate $<$60 mL/min/1.73 m^2 for at least 3 months, and not on dialysis therapy. UACR, urine albumin-to-creatinine ratio.

with DM, CKD or LDL-C $\geq$190 mg/dL. In those without DM, CKD or LDL-C $\geq$190 mg/dL, moderate risk indicates subjects with 2 or more risk factors, low risk indicates with 1 risk factor and minimal risk indicates no risk factor. Subjects with high risk need immediate lipid lowering therapy to reach the recommended LDL-C target. Lifestyle modification first is recommended for 3 months before considering lipid lowering therapy in the subjects without high risk. The overall risk categories for primary prevention are summarized in Table 2.

Recommendation

- For primary prevention, subjects with DM, non-dialysis CKD, or LDL-C $\geq$190 mg/dL are at high risk of ASCVD and immediate lipid lowering therapy is necessary. (COR I, LOE A)
- In subjects without DM, CKD, or LDL-C $\geq$190 mg/dL, the risk of ASCVD should be classified as minimal, low, or moderate according to the risk factors. (COR I, LOE C)

LDL-C target

High risk (DM, CKD, LDL-C ≥ 190 mg/dL)

For subjects with DM, non-dialysis CKD, or LDL-C ≥190 mg/dL, this guideline suggests the LDL-C level for initiation of therapy and treatment target is 100 mg/dL. Because the ASCVD risk is high, lipid lowering therapy should be started immediately with lifestyle modification. There has been no randomized, placebo-controlled trial of statin therapy performed only in subjects with LDL-C $\geq$190 mg/dL. The WOSCOPS trial was a randomized placebo-controlled trial of pravastatin (40 mg/day) for subjects with hypercholesterolemia (mean LDL-C level of 192 $\pm$ 17 mg/dL) and without history of vascular disease.[38] The use of pravastatin significantly reduced the incidence of MI and CV mortality. The post hoc analyses among the 2560 subjects in the WOSCOPS trial with baseline LDL-C $\geq$190 mg/dL showed that statin therapy significantly reduced the risk of major adverse cardiovascular events (MACE) in the initial trial phase and over 20 years of follow-up.[32] Because of the high risk for ASCVD, the treatment target of LDL-C is $<$100 mg/dL in subjects with LDL-C $\geq$190 mg/dL. Since the baseline LDL-C level is high, moderate-to high-intensity statins combined with ezetimibe is recommended for subjects with LDL-C $\geq$190 mg/dL.

Recommendation

- In subjects with DM, non-dialysis CKD, LDL-C $\geq$190 mg/dL, immediate lipid lowering therapy should be started and the LDL-C target is $<$100 mg/dL. (COR I, LOE B)
- In subjects with LDL-C $\geq$190 mg/dL, moderate-to high-intensity statins combined with ezetimibe is recommended. (COR I, LOE B)

Moderate risk (≥2 risk factors)

The LDL-C level for initiation of therapy and treatment target in subjects with $\geq$2 risk factors is 115 mg/dL based on the experts' consensus. This recommended LDL-C level is close to the 2019 ESC lipid guidelines suggesting the LDL-C target $<$116 mg/dL in the low risk individuals.[18] The recommended LDL-C target of 115 mg/dL is lower than that in the Japanese and Korean lipid guidelines where the LDL-C target is $<$140 mg/dL for moderate risk in Japan and $<$130 mg/dL for those with 2 or more major risk factors in Korea.[39,40] Moderate-intensity statins are considered first if LDL-C remains higher than the target after 3 months of lifestyle adjustment.

Recommendation

- In subjects with ≥2 risk factors and LDL-C ≥115 mg/dL, non-pharmacological therapy should be initiated and the LDL-C target is <115 mg/dL. (COR IIa, LOE C)
- If the treatment target is not met after 3 months of non-pharmacological therapy, moderate-intensity statin therapy should be considered (COR IIa, LOE C)

Minimal to low risk (< 2 risk factors)

Individuals with no or only one risk factor are classified as the minimal to low risk category. The optimal way to manage subjects at minimal to low risk but with elevated LDL-C is still controversial. International guidelines using risk calculator for 10-year risk estimation are prone to ignore younger patients with low risk because it is unlikely to see ASCVD-related adverse outcomes in the forthcoming decade, but increased LDL-C is still associated with an increased risk of ASCVD later in life.[41] Multiple evidences have proved that the risk of ASCVD is strongly correlated with the cumulative exposure to LDL-C in one's lifetime.[42,43] Therefore, it is necessary to act early in life to control LDL-C and prevent ASCVD later in life. Emerging evidence indicates that even among individuals with low risk at primary prevention, the benefit of lipid lowering therapy can be significant, especially when the baseline LDL-C is ≥135 mg/dL.[44]

For subjects without any risk factor, this guideline suggests that the LDL-C level for initiation of therapy and treatment target is 160 mg/dL based on the experts' consensus. For subjects with only 1 risk factor, the LDL-C level for initiation of therapy and treatment target is 130 mg/dL. There is no doubt that nonpharmacologic therapy with lifestyle modification is preferred and should be emphasized in this group. In the Japanese guidelines, the LDL-C target is <140 mg/dL in moderate risk and <160 mg/dL in low risk category.[39] In Korean guidelines, the LDL-C target is <160 mg/dL in those with one or fewer major risk factors.[40] Moderate-intensity statins are considered first if LDL-C remains higher than the target after 3 months of lifestyle adjustment. Further examinations, such as coronary calcium score, could be considered in redefining ASCVD risk and changing the intensity of statin treatment in this category. The decision of further examinations or long-term statin therapy in subjects at minimal to low risk category should be made after shared decision making with explanation and understanding of the benefit and risk of the examinations and treatment. The overall treatment algorithm of LDL-C for primary prevention is summarized in Fig. 1.

Recommendation

- In subjects with 1 risk factor and LDL-C ≥130 mg/dL, non-pharmacological therapy should be initiated and the LDL-C target is <130 mg/dL. (COR IIa, LOE C)
- In subjects without risk factor and LDL-C ≥160 mg/dL, non-pharmacological therapy should be initiated and the LDL-C target is <160 mg/dL. (COR IIa, LOE C)
- In subjects with 0 to 1 risk factor, if the LDL-C target is not achieved after 3 months of non-pharmacological therapy, moderate-intensity statins could be considered after shared decision making. (COR IIa, LOE C)

Non-pharmacological therapy

Diet

Several observational and randomized clinical studies have demonstrated association between a lower risk of ASCVD and healthy dietary patterns, such as Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension) diet, healthy Taiwanese eating approach (TEA), and Taiwanese vegetarian diet.[45–48] Taiwanese dietary pattern studies also identified fried foods, sweets and sweetened beverages, high fat and sugar-containing pastry, fatty and organ meats as risky foods for cardiometabolic diseases.[47,49] Based on these studies, a cardioprotective dietary pattern includes: rich plant-based foods including whole grains, vegetables, fresh fruits, nuts and seeds, tea, and unsaturated fatty acid-rich non-tropical plant oils (e.g., soybean oil, sunflower oil, olive oil); sources of omega-3 fatty acids (e.g., fish, nuts, legumes); good protein foods (low degree processed soy product, fish, egg, and lean animal protein); low in trans-fats, fried foods, fatty meat, processed meats or fish products (e.g., sausage, bacon, ham and hot dogs), and added/refined sugars.[50–54]

Meta-analysis indicated that low-carbohydrate diets may help weight loss and improve HDL-C and TG levels.[55] However, the potential consequence of elevated LDL-C and total cholesterol (TC) is a major concern. In the past decades, the modest association between eggs consumption and the development of ASCVD has been established but remains controversial. Eggs are not only low in saturated fatty acid but also rich in protein and various micronutrients, which have been shown to promote the formation of large LDL-C, which is less atherogenic.[56,57] Since there may still be a moderate dose—response relationship, the appropriate amount of egg consumption should be individualized based on individual's LDL-C target and nutrition status. Besides, the effect of dairy consumption is also controversial due to previous observation relating the saturated fatty acid content to increase LDL-C levels.[58] Recent meta-analyses revealed either positive or neutral effects on CV outcomes from consumption of dairy products, while a Taiwanese prospective study showed protective association.[47] Dairy, including fermented and preferably no-fat or low-fat products, may be consumed moderately as part of a healthy diet.[59]

Dietary supplements

Some dietary supplements are considered to be beneficial for health. Fish oil, or marine omega-3 fatty acid

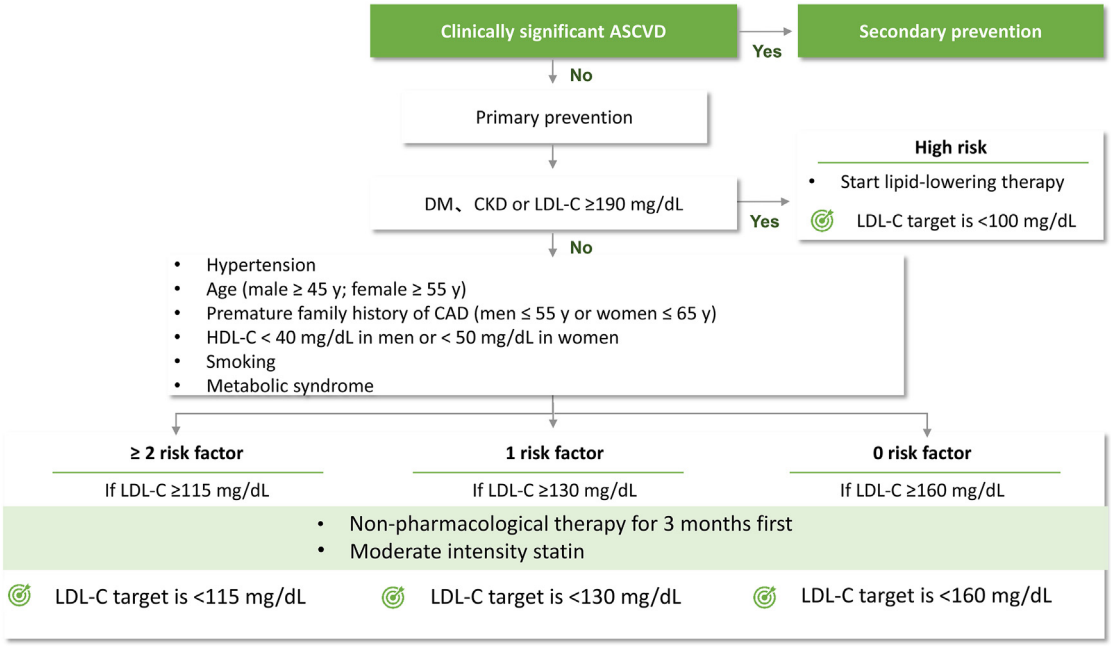

Figure 1 Treatment algorithm of LDL-C for primary prevention. ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease (non-dialysis); DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

supplementation, yields a dose-dependent reduction in TG from the effect of eicosapentenoic acid (EPA) and docosahexenoic acid (DHA), but no overt changes in TC, LDL-C or HDL-C.[60,61] Red yeast rice (RYR) extract has been applied as a cholesterol-lowering nutraceutical. During the rice fermentation, the main bioactive compound, monacolin K, is a weak reversible inhibitor of 3-hydroxy-3- methylglutaryl-coenzyme A (HMG-CoA) reductase. In a meta-analysis study, using RYR from 1200 mg/day to 4800 mg/day, LDL-C was lowered with 18.4 mg/dL compared to placebo.[62] However, the quality of RYR products in the market varied and RYR may possess a potential risk of pharmacological interactions and its safety outcomes have not been extensively studied yet. The flavonoids in cocoa products inhibit cholesterol absorption. A meta-analysis showed that consumption of dark chocolate for 2–12 weeks significantly reduced TC and LDL-C (6.2 and 5.9 mg/dL), respectively.[63] Nonetheless, it is a concern that dark chocolate products contained varied amount of saturated fats and added sugar. Vitamin D may affect circulating cholesterol levels by modulating the transcription activity of vitamin D receptor and insulin-induced gene-2 activity which inhibits HMG-CoA reductase expression.[64,65] Clinical study indicated that vitamin D supplementation has benefits on reducing TC, LDL-C, and TG but no influence on HDL-C level.[64] A meta-analysis of 14 randomized controlled trials showed that consumption of green tea or its extracts resulted in a moderate reduction in TC and LDL-C concentrations, but no change in HDL-C.[66] However, a longitudinal cohort study with 6-year follow-up showed that frequent tea consumption, including black tea and green tea, was associated with a slower age-related decrease in HDL-C concentrations.[67]

Exercise

Existing evidence on LDL-C response to exercises is controversial. It seems that exercise does not significantly reduce TC and LDL-C levels.[68] There was an apparent effect on reduction of TG and increase of HDL-C concentrations with the high-amount and high-intensity exercise.[69] Regular exercise can reduce TG by 17.7 mg/dL than those without exercise.[70] A large-scale observational study showed that regular jogging contributed to an increase of HDL-C and reduction of TG and TG/HDL-C ratio.[71] Other aerobic exercises such as swimming, dancing (including international standard dancing), and cycling were also associated with an elevated level of HDL-C.[71] Although the changes in lipid profiles by resistance exercise are inconsistent, it should still be encouraged due to several health benefits, including improving physical functioning and possibly lowering blood pressure. All adults are encouraged to engage in at least 150 min per week of accumulated moderate-intensity aerobic physical activity, or 75 min per week of vigorous-intensity aerobic physical activity to lower ASCVD risk.[54] Even exercise with a shorter duration of 5 or 10 min with 1- to 2-min interruption is as beneficial as the longer ones.[72]

Alcohol

Alcohol intake is associated with an increase in HDL-C, but the relation between alcohol consumption and ASCVD is controversial.[73,74] Although some studies suggest that low levels of alcohol consumption is associated with a decreased CV risk and diabetes,[75–77] many other studies have challenged this view.[78–81] More recently, in a

combined analysis of individual-participant data from 3 large-scale databases in 19 high-income countries (the Emerging Risk Factors Collaboration, EPIC-CVD, and the UK Biobank), alcohol consumption was linearly associated with an increased risk of stroke, CAD, heart failure, fatal hypertensive disease, and fatal aortic aneurysm, with hazard ratios per 100 g/week alcohol consumption of 1.14, 1.06, 1.09, 1.24, and 1.15, respectively.[82] A Mendelian randomization meta-analysis found that alcohol dehydrogenase 1B (ADH1B) variant allele carriers who had higher abstention, lower alcohol consumption, and lower prevalence of binge drinking had a significantly decreased risk of CAD (odds ratio [OR] 0.90, 95% confidence interval [CI] 0.84–0.96) and ischemic stroke (OR 0.83, 95% CI 0.72–0.95).[78] The potential detrimental effect of alcohol drinking could be more pronounced in about 40–50% of Taiwanese who carry the aldehyde dehydrogenase-2 (ALDH2) dysfunctional allele (ALDH2*2 variant).[83] The ALDH2*2 dysfunctional allele delays acetaldehyde metabolism following alcohol consumption and leads to "Asian alcohol flushing syndrome" or "alcohol intolerance syndrome".[84,85] Actually, alcohol use has been related to many acute and chronic diseases and is recognized as a leading risk factor for the burden of some of these diseases.[86,87]

Based on the growing evidence for the detrimental effect of alcohol, the Taiwan Health Promotion Administration suggests individuals without a habit of drinking alcohol should avoid starting drinking for any reason.[88] A limited alcohol consumption of <100 g/week (14 g/day or 1 drink/day) for men and <50 g/week (7 g/day or 0.5 drink/day) for women is recommended (one standard drink = 14 g pure alcohol). Alcohol abstention is strongly advised for those who carry the ALDH2*2 dysfunctional allele. If alcohol consumption is unavoidable in people carrying the ALDH2*2 dysfunctional allele, more limited alcohol consumption of <64 g/week (9 g/day or 4 drinks/week) for men and <28 g/week (4 g/day or 2 drinks/week) for women is recommended.[89] Binge drinking, defined as ≥5 drinks for men and ≥4 drinks for women within 2 h, should be strictly avoided.[88]

Recommendation

- People who do not have a habit of alcohol consumption should avoid starting drinking for any reason. (COR I, LOE C).
- Alcohol consumption should be limited to <100 g/week (14 g/day or 1 drink/day) in men and <50 g/week (7 g/day or 0.5 drink/day) in women without the ALDH2*2 dysfunctional allele. (COR I, LOE A).
- Alcohol consumption should be limited to <64 g/week (9 g/day or 4 drinks/week) in men and <28 g/week (4 g/day or 2 drinks/week) in women with the ALDH2*2 dysfunctional allele. (COR IIa, LOE B).
- Binge drinking, defined as ≥5 drinks for men and ≥4 drinks for women within 2 h, should be strictly avoided. (COR I, LOE C) (One standard drink = 14 g pure alcohol)

Cigarette smoking

Smoking is a lethal addictive disorder and more than 8 million people die from smoking every year.[90] In Taiwan, the prevalence of smoking among adult people has been declining from 21.9% (male 38.6%, female, 4.8%) in 2008 down to 13.1% (male 23.1%, female 2.9%) in 2019.[91] However, smoking still caused a huge loss of life in Taiwan and about 24,000 people die from smoking every year.[91] Smoking cessation saves life and reduces healthcare burden and the benefits are seen even in old smokers (≥60 years).[92] Continued medical education with group training of doctors and counsellors regarding knowledge and skill to help people quitting smoking followed by smoking cessation service contest among hospitals has been proved effective to promote smoking cessation for high CV risk smokers in Taiwan.[93]

Electronic cigarettes (EC) have been emerging as a popular way to facilitate tobacco cessation in recent years. However, large-scale meta-analysis about whether EC is superior to non-EC methods for tobacco cessation showed conflicting results.[94,95] In addition, growing evidence has raised critical concerns regarding the adverse effects of EC use, such as EC or vaping product-associated lung injury (EVALI) and increased blood pressure and arterial stiffness associated with EC use.[96–98] Collectively, there is still no solid evidence supporting that EC is a safer alternative for tobacco cessation, neither is there sufficient evidence to claim its long-term CV safety.

Recommendation

- Cessation of cigarette smoking is recommended to reduce overall CV risk. (COR I, LOE A)

Healthy lifestyle

All adults should consume a healthy diet which includes balanced macronutrients and emphasizes the intake of plant-based foods, lean animal protein with restriction of the amount of trans fat, processed red meat, and refined carbohydrate. Ideal body weight should be maintained. Regular exercise should be encouraged with emphasis on the total accumulated amount. Reduction in alcohol consumption and smoking cessation should be advocated. On the other hand, potential barriers to lifestyle modification, such as access to healthy diet or exercise options, should be recognized. Adherence to these suggestions may be enhanced through the process of shared decision making between clinicians and patients. The overall recommendations for lifestyle modification and the influences on lipid profile are shown in Table 3.

Recommendation

- Diet rich in plant-based foods, sources of omega-3 fatty acids (e.g., fish, nuts, legumes), lean animal

protein, which can maintain healthy body weight is suggested. (COR I, LOE B)
- Minimize the intake of trans and saturated fat, processed meat, and refined carbohydrate. (COR IIa, LOE B)
- Regular physical exercise is recommended. (COR I, LOE A)
- Reduction of alcohol intake and cessation of smoking are suggested. (COR I, LOE B)

Table 3 Recommendations of lifestyle modification and the influences on lipid profile.

Recommendations	Potential health benefits			
Diet adaptation • Adequate intake[a] of vegetables, fruits, nuts, whole grains, no fat or low-fat dairies, and good quality protein foods[b] at individualized healthy caloric intake level[c] • Moderate intake of eggs • Limited intake of trans fats[d] and fried food, organ meat or high fat red meat, processed meat or fish products, refined carbohydrates (including various forms of sweets and sweetened beverages) • Increase serving numbers of vegetables, plant proteins, and whole grains to replace their counterparts given additional CVD risk factors	Positive effect on overall metabolic profiles and cardiovascular health, and provide sufficient levels of micronutrients to ensure total wellbeing.			
Dietary supplements[e]	TC	HDL-C	LDL-C	TG
Fish oil		▲		▼
Vitamin D	▼		▼	▼
Tea	▼		▼	
Smoking cessation		▲		
Moderation in alcohol consumption		▲		
Exercise		▲		▼

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
[a] According to Taiwan Food guide at multiple level of caloric intakes.
[b] Priority order: legumes and low level processed soy products, earth-friendly fish and sea foods, eggs, and poultry in that order.
[c] Individualized healthy caloric intake may be estimated from age, sex, height, and physical activity level.
[d] Taiwan Government has mandated no detection of trans-fat in processed foods.
[e] See section Dietary supplements for more suggestions on red yeast rice (RYR) and dark chocolate.

Pharmacological therapy

LDL-C lowering therapies with HMG CoA reductase inhibitors (statins), cholesterol absorption inhibitors (ezetimibe), and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have demonstrated efficacy in secondary prevention of ASCVD. Statins, the cornerstone of therapy, are also found to be efficacious in primary prevention. Ezetimibe and PCSK9 inhibitors are effective in improving clinical outcomes as add-on drugs to statin therapy in secondary prevention, but these drugs have not been well investigated in patients for primary prevention.

Statins for primary prevention

Statins are the first-line therapy and the benefit of statins for primary prevention of ASCVD is well established. In a systematic review and meta-analysis of 19 randomized clinical trials (n = 71,344) that evaluated the effect of statins versus placebo or no statin in adults at increased CV risk but without prior ASCVD, statins significantly reduced risk of all-cause mortality, CV mortality, stroke, MI, and composite CV outcomes.[99] In JUPITOR trial, the largest statin intervention trial for primary prevention, 17,802 apparently healthy persons with LDL-C <130 mg/dL but with elevated high-sensitivity C-reactive protein levels (≥2.0 mg/L) were randomly assigned to rosuvastatin 20 mg daily or placebo.[100] After a median follow-up of 1.9 years, statin therapy significantly reduced the incidence of major CV events, CV mortality and all-cause mortality.[100] In HOPE-3 trial, 12,705 participants without ASCVD but at intermediate risk were randomly assigned to rosuvastatin 10 mg daily or placebo. The LDL-C levels at baseline were 127 mg/dL in both groups.[101] After a period of 5.6 years, treatment with statin resulted in a significantly lower risk of CV events than placebo.[101] In MEGA study, the only large statin trial in Asian population for primary prevention, 7832 Japanese patients without history of CAD or stroke were randomly assigned to the diet only group or diet plus pravastatin 10–20 mg/day group.[102] After a mean follow-up of 5.3 years, treatment with statin significantly reduced the risk of CAD events in Japanese patients.[102]

The intensity of statin is divided into 3 categories: high-intensity statin (the dose reduces LDL-C by greater than or equal to 50%), moderate-intensity statin (the dose reduces LDL-C by 30%–49%), and low-intensity statin (the dose reduces LDL-C by <30%).[10] Based on the scientific evidence and baseline LDL-C levels in Taiwan, it is reasonable to initiate moderate-intensity statin first for primary prevention and titrate to high-intensity statin if the treatment goal is not reached. The safety of statins has been extensively evaluated. Although myopathy and abnormal liver function are encountered occasionally, statin therapy is well tolerated and safe for most patients.[103] Statin-associated muscle symptoms are the most common reported side effects, however, the risk of severe statin-induced muscle injury, including rhabdomyolysis, is very low.[104] Please refer to the 2019 Taiwan Society of Lipids and Atherosclerosis Expert Consensus Statement on Statin Intolerance for the diagnosis and management of statin-related muscle and hepatic side effects.[105] Statin therapy

is also associated with a slightly increased risk of new-onset diabetes. In a meta-analysis including 13 statin trials with 91,140 participants, statin therapy was associated with a 9% increased risk for incident diabetes.[106] The meta-regression analysis also indicated that the risk of new-onset diabetes with statins was higher in older subjects and associated with the statin's potency.[106]

Recommendation

- For primary prevention, statins are the first-line therapy. It is reasonable to initiate moderate-intensity statin first and titrate to high-intensity statin if the treatment goal is not reached. (COR I, LOE A).

Ezetimibe for primary prevention

Ezetimibe is a cholesterol absorption inhibitor that blocks dietary and biliary cholesterol absorption at the brush border of the intestine. The efficacy of ezetimibe in combination with statin for prevention of ASCVD has been well demonstrated in patients with CKD or ACS in large-scale studies.[107,108] The EWTOPIA 75 trial is a study to investigate the efficacy of ezetimibe monotherapy in primary prevention.[109] This multicenter, prospective, randomized clinical trial was conducted in Japan and examined the preventive efficacy of ezetimibe for patients aged $\geq$75 years with LDL-C $\geq$140 mg/dL but without history of CAD. In this elegant study, ezetimibe significantly reduced the incidence of the primary composite outcome, including sudden cardiac death, MI, coronary revascularization, or stroke, after a median follow-up of 4.1 years. This study proved the benefit of ezetimibe monotherapy in preventing CV events in individuals aged $\geq$75 years with elevated LDL-C for primary prevention.[109]

Recommendation

- Ezetimibe may be used in combination with statin in patients with primary prevention who could not reach the LDL-C target with statin alone. (COR IIb, LOE B).
- Ezetimibe may be used as monotherapy in patients with primary prevention who cannot tolerate statins. (COR IIb, LOE B).

PCSK9 inhibitors for primary prevention

PCSK9 binds to LDL receptor (LDL-R) on the surface of hepatocytes leading to degradation of the receptors and decreasing the reuse of LDL-R. Antibodies to PCSK9 interfere its binding with the LDL-R resulting in higher hepatic LDL-R expression and lower plasma LDL-C levels.[110] PCSK9 inhibitors, such as evolocumab or alirocumab, could be used in patients with FH or ASCVD who require additional LDL-C lowering in addition to maximally tolerated statins. One meta-analysis demonstrated the efficacy of PCSK9 inhibitors in those who might not be eligible for other lipid-lowering drugs or who cannot meet their lipid goals on the traditional therapies.[111] Most of the available studies of PCSK9 inhibitors preferentially enrolled patients with either established ASCVD, FH or at high risk. The evidence of PCSK9 inhibitors in those with low to moderate risk settings is minimal.

Recommendation

- PCSK9 inhibitors can be considered for primary prevention in patients at high risk who cannot achieve LDL-C target with high-intensity or maximal tolerated statins and ezetimibe. (COR IIa, LOE B)

Other lipid target and residual risk

Non-HDL-C and apoB

In addition to LDL-C, the levels of several other lipids or lipoproteins also may be used to predict the risk of ASCVD. Non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein-B (apoB) and TG have attracted attention recently. Non-HDL-C is calculated as TC minus HDL-C. The major components of apolipoproteins in HDL particles are apolipoprotein A, C, E and without apoB. Therefore, the calculation of non-HDL-C estimates the summation of all circulatory apoB-containing lipoproteins. Cholesterol-rich and triglyceride-rich apoB-containing lipoproteins have diameter less than 70 nm and can easily flux across the vascular endothelium. The trapped apoB-lipoproteins within the arterial wall trigger cellular responses that accelerate further lipid/lipoprotein retention and progression of atheromatous plaque.[112] However, some studies found there was discordance between the levels of non-HDL-C and apoB suggesting apoB as a more accurate risk marker.[113,114] Although there are well correlations between LDL-C, non-HDL-C, and apoB in most people, LDL-C measurement may be underestimated in those with elevated TG, DM, and obesity, thus underestimating the risk of ASCVD.[18,115] Non-HDL-C also provides residual risk estimation in Taiwanese populations who have been already on statin therapy.[116,117] Since the data of non-HDL-C is much easier to obtain than apoB in most hospitals or clinics in Taiwan, the level of non-HDL-C is recommended as a secondary target after LDL-C.[10] The target of non-HDL-C is 30 mg/dL above the recommended LDL-C target. For example, if the LDL-C target is 100 mg/dL, the secondary target of non-HDL-C is 130 mg/dL. Given the essential implications of apoB in atherosclerosis, direct measurement of the circulating concentration of apoB to assess the risk also can be considered if the measurement is available in the laboratory. In the 2019 European lipid guideline, ApoB is

recommended to be <65, 80, and 100 mg/dL for very-high, high-, and moderate-risk people, respectively.[18] Since apoB cannot be measured in most hospitals or clinics and rarely used in clinical practice in Taiwan, no specific target for apoB is recommended in this guideline.

Recommendation

- Non-HDL-C and apoB can be used to predict the risk of ASCVD, especially for people with high TG (>150 mg/dL), DM, obesity, or metabolic syndrome. (COR IIa, LOE B)
- Non-HDL-C is used as the secondary target and the target of non-HDL-C is 30 mg/dL above the recommended LDL-C target. (COR IIa, LOE B)

Triglyceride

Although very low-density lipoprotein (VLDL) and chylomicrons are both TG-rich particles, VLDL particles constitute the majority of circulating TG because of the ultrashort half-life of chylomicron. Additionally, VLDL particles, which are mostly smaller than 70 nm in diameter and contain apoB, can potentially be retained in the arterial wall and initiate atherosclerotic processes. Despite the atherogenic potential of VLDL particles, the association between TG and ASCVD remains inconclusive. The major problem is the insignificant predicting power of TG after adjusting the other lipoproteins.[118] The same results were also observed in the Mendelian genetic studies.[119] Interpretation of the data about TG should also be cautious because there exists significant correlations of TG with HDL-C, LDL-C, or lipoprotein(a).[120] However, it is still believed that elevated serum TG levels appear to be associated with a residual risk of ASCVD, despite the use of statin therapy. A secondary analysis from the PREDIMED study demonstrated that the VLDL particles and their remnant particles were associated with CV outcomes among patients without prior ASCVD.[121]

Unlike the great success of LDL-lowering agents in preventing ASCVD, almost all TG-lowering agents failed to improve CV outcome under statin therapy in the clinical trials. The REDUCE-IT trial evaluated the efficacy of purified high dose EPA. Study participants were patients with established ASCVD or diabetes with one additional risk factor and already received statin therapy with a fasting TG level of 135–499 mg/dL and LDL-C level of 41–100 mg/dL. The patients were randomized to 2 g of icosapent ethyl twice daily or placebo. After a median of 4.9 years follow-up, the icosapent ethyl group had 25% lower risk of CV events compared with the placebo group.[122] Of note, the average LDL-C level did not change over the study period, indicating the benefit of isolated TG-driven effect. Icosapent ethyl also demonstrated significant effect on regression of coronary plaque volume detected by computed tomography compared with placebo in the EVAPORATE trial.[123]

Recommendation

- High dose EPA (icosapent ethyl) therapy can be considered for patients with ASCVD or with diabetes and ≥ 1 risk factor who are already on maximally tolerated statin therapy with high TG level (>150 mg/dL). (COR IIa, LOE B)

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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