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REVIEW ARTICLE

2017 Taiwan lipid guidelines for high risk patients☆

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In Taiwan, the prevalence of hyperlipidemia increased due to lifestyle and dietary habit changes. Low density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (non-HDL-C) are all significant predicting factors of coronary artery disease in Taiwan. We recognized that lipid control is especially important in patients with existed atherosclerotic cardiovascular diseases (ASCVD), including coronary artery disease (CAD), ischemic stroke and peripheral arterial disease (PAD). Because the risk of ASCVD is high in patients with diabetes mellitus (DM), chronic kidney disease (CKD) and familial hypercholesterolemia (FH), lipid control is also necessary in these patients. Lifestyle modification is the first step to control lipid. Weight reduction, regular physical exercise and limitation of alcohol intake all reduce triglyceride (TG) levels. Lipid-lowering drugs include HMG-CoA reductase inhibitors (statins), cholesterol absorption inhibitors (ezetimibe), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, nicotinic acids (niacin), fibric acids derivatives (fibrates), and long-chain omega-3 fatty acids. Statin is usually the first line therapy. Combination therapy with statin and other lipid-lowering agents may be considered in some clinical settings. For patients with acute coronary syndrome (ACS) and stable CAD, LDL-C $<$ 70 mg/dL is the major target. A lower target of LDL-C $<$55 mg/dL can be considered in ACS patients with DM. After treating LDL-C to target, non-HDL-C can be considered as a secondary target for patients with TG $\geq$ 200 mg/dL. The suggested non-HDL-C target is $<$ 100 mg/dL in ACS and CAD patients. For patients with ischemic stroke or transient ischemic attack presumed to be of atherosclerotic origin, statin therapy is beneficial and LDL-C $<$ 100 mg/dL is the suggested target. For patients with symptomatic carotid stenosis or intracranial arterial stenosis, in addition to antiplatelets and blood pressure control, LDL-C should be lowered to $<$ 100 mg/dL. Statin is necessary for DM patients with CV disease and the LDL-C target is $<$ 70 mg/dL. For diabetic patients who are $\geq$ 40 years of age, or who are $<$ 40 years of age but have additional CV risk factors, the LDL-C target should be $<$ 100 mg/dL. After achieving LDL-C target, combination of other lipid-lowering agents with statin is reasonable to attain TG $<$ 150 mg/dL and HDL-C $>$40 in men and $>$50 mg/dL in women in DM. LDL-C increased CV risk in patients with CKD. In adults with glomerular filtration rate (GFR) $<$ 60 mL/min/1.73m^2 without chronic dialysis (CKD stage 3–5), statin therapy should be initiated if LDL-C $\geq$ 100 mg/dL. Ezetimibe can be added to statin to consolidate the CV protection in CKD patients. Mutations in LDL receptor, apolipoprotein B and PCSK9 genes are the common causes of FH. Diagnosis of FH usually depends on family history, clinical history of premature CAD, physical findings of xanthoma or corneal arcus and high levels of LDL-C. In addition to conventional lipid lowering therapies, adjunctive treatment with mipomersen, lomitapide, or PCSK9 inhibitors become necessary to further reduce LDL-C in patients with FH. Overall, these recommendations are to help the health care professionals in Taiwan to treat hyperlipidemia with current scientific evidences. We hope the prescription rate of lipid lowering drugs and control rate of hyperlipidemia in high risk patients could be increased by implementation of the clinical guidelines. The major purpose is to improve clinical outcomes of these high risk patients through the control of hyperlipidemia.

Introduction

Purpose of the guideline

Cardiovascular (CV) and cerebrovascular diseases are the second and third leading causes of death in Taiwan. Atherosclerotic CV diseases (ASCVD), including coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease (PAD), contribute to the major portion of CV diseases and continue to be a major public health issue in Taiwan. For example, the overall incidence of acute myocardial infarction (MI) in Taiwan increased progressively from 1999 to 2008.[1] A recent study using the Taiwan National Health Insurance Research Database showed that the incidence of ST segment elevation MI decreased after 2004, but non-ST segment elevation MI continued to increase up to 2011.[2] Data from the Taiwan Ministry of Health and Welfare showed that CV disease causes one death every 27 minutes in Taiwan in 2014. Hyperlipidemia is one of the major CV risk factors. In a 2007 survey in Taiwan, patients with hypertension, hyperglycemia, or hyperlipidemia have 1.9-, 1.5-, and 1.8-fold higher risks of CV disease than those without these risk factors. In the second Nutrition and Health Survey in Taiwan from 2005 to 2008, the prevalence of hypercholesterolemia defined as total cholesterol (TC) $\geq$ 240 mg/dL was 13%, and hypertriglyceridemia defined as triglyceride (TG) $\geq$ 200 mg/dL was 21% in men.[3] Because increased circulating low-density lipoprotein cholesterol (LDL-C) is highly atherogenic and a strong independent predictor of CV events, LDL-C control becomes especially important in high-risk patients, including patients with existing ASCVD, diabetes mellitus (DM), and

chronic kidney disease (CKD). Lower high-density lipoprotein cholesterol (HDL-C) is also associated with CV events, but under statin treatment, all pharmacological intervention trials of HDL-C raising therapies failed to show the benefit up to now. Patients with familial hypercholesterolemia (FH) due to mutations in LDL-C metabolism related genes also carry a high risk of ASCVD. FH patients have very high levels of circulating LDL-C and often suffer from premature atherosclerosis and death. Despite being a critical and modifiable risk factor of atherosclerosis, the control rate of hyperlipidemia in Taiwan is not adequate. In a recent survey of 3486 patients with stable CAD and cerebrovascular disease, only 54% of the patients had LDL-C $<$ 100 mg/dL.[4] The prescription rate of lipid-lowering drugs is also not high in high-risk patients. Lipid-lowering drugs were used in only 60% patients with acute coronary syndrome (ACS) and in 38% of patients with ischemic stroke at discharge in Taiwan.[5,6]

The major purpose of this guideline is to make recommendations to the healthcare professionals dealing with the management of hyperlipidemia in Taiwan based on current lines of evidence; and through the implementation of this guideline, we hope that the control rate of hyperlipidemia can be increased in high-risk patients and improve the clinical outcomes of these patients. Most of the recommendations in this guideline are made according to the results of international large-scale clinical trials, but some results from small-scale clinical trials and observational studies in Asia and Taiwan are also taken into consideration to make these suggestions. All recommendations in this guideline provide common principles in evaluating and treating hyperlipidemia. Because clinical conditions vary among high-risk patients, the management of hyperlipidemia in each patient still depends on their physicians' decisions and should be individualized.

How was the guideline developed?

In 2003, the Taiwan Society of Lipids and Atherosclerosis published the first Chinese version of the "Guideline for Prevention and Management of Dyslipidemia" and the updated second version was published in 2009. In an effort to respond to the evolving data from new lipid studies in these years, the executive board of the Taiwan Society of Lipids and Atherosclerosis decided to revise this guideline and published it in a journal with science citation index so that more healthcare workers could access and read it. The executive board of Taiwan Society of Lipids and Atherosclerosis assigned a chairperson and the members of the writing committee. Each member of the writing committee was responsible for a specific topic regarding lipid control based on their expertise. Advisory board meetings were held in June 2015 to determine the major contents of this guideline and the board decided to focus on the lipid control in high-risk patient groups, including patients with ACS, CAD, PAD, ischemic stroke, DM, CKD, and FH. In 2016, symposiums were held throughout the country to discuss about the detailed suggestions in this guideline. Opinion leaders from the Taiwan Society of Cardiology, Taiwan Society of Cardiovascular Intervention, Taiwan Stroke Society, Taiwan Diabetes Association, and Taiwan Nephrology Association were invited to join the symposia and give valuable comments regarding the guideline. The recommendations of this guideline are not only based on lines of evidence from literature reviews but also included expert opinions from these major societies. The full manuscript of the guideline was formed through a period of 6 months. The initial draft of this guideline was sent for review and modified by all these major societies in Taiwan, and the final document was endorsed by these societies.

The guideline recommendations were generated after reviewing international randomized clinical trials that are relevant to the above-mentioned high-risk patient groups. In addition, *post hoc* analyses of these international clinical trials and clinical trials performed in Asia were included. Other data from retrospective studies, cohort studies, and registry studies were also taken into consideration. The evidence-based classification system, including class of recommendation (COR) and level of evidence (LOE) developed by the American College of Cardiology/American Heart Association (ACC/AHA) was used in this guideline. The COR is used to denote whether a given treatment is useful or harmful. Class I recommendations indicate the treatment is useful, indicated, and should be used. Class III recommendations refer to the treatment that is harmful, contraindicated, and should not be done. Class II recommendations fall in between classes I and III. Class IIa indicates that the lines of evidence favor the treatment effect, whereas class IIb indicates that the treatment effect is less well established (Table 1). The LOE is used to denote the evidence intensity supporting the recommendations. LOE A indicates that results from multiple randomized trials support the recommendations. LOE B indicates that only a few randomized trials or observation studies support the recommendations. LOE C indicates that only expert opinions suggest the recommendations (Table 2).

Epidemiology

Background

ASCVD, including CAD, stroke, and PAD, have been a great burden in public health among Taiwanese citizens, and hyperlipidemia plays an important role for the risk of atherosclerosis.[7,8] In addition, hypertriglyceridemia and low HDL-C level have been associated with metabolic syndrome and Type 2 DM. Moreover, previous population-based studies showed a significant increase in hypercholesterolemia prevalence for the general population in Taiwan.[9] The prevalence of low HDL-C and hypertriglyceridemia, which are strongly related to lifestyle factors, also increased in these years owing to the progressive economic development in Taiwan.[3] Although the mean cholesterol levels were stable during 1980 and 2008 globally, the mean cholesterol levels for both sexes increased among the Asian Pacific countries because of changes in economic status and dietary habits.[8] In addition, the international Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group compared the profiles between 1980 and 2008 and found a significant association between TC and national income and Western diet. These factors have a great influence on the lipid profile change in Asian countries.[7]

Table 1 Class of recommendation.

Class of recommendation	Definition	Strength
Class I	Evidence or general agreement that a given treatment is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence or a divergence of opinion about the usefulness/efficacy of a treatment.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness or efficacy is less well established by evidence or opinion.	May be considered
Class III	Evidence or general agreement that the given treatment is not useful or effective and in some cases may be harmful.	Is not recommended

Table 2 Level of evidence.

Level of evidence A	Data derived from multiple randomized clinical trials
Level of evidence B	Data derived from a single randomized clinical trial, meta-analyses, or large nonrandomized studies
Level of evidence C	Subgroup analyses, *post hoc* analyses, retrospective studies, cohort studies, registries, small studies, or expert opinion

Therefore, evaluating the trend of hyperlipidemia change in Taiwan has become an important issue for health policy makers. Understanding the epidemiological pattern of hyperlipidemia and its role for CV disease in Taiwan will be a key factor in the control and management of disease burden of atherosclerosis.

Hyperlipidemia in Taiwan

According to the national survey of adult population in Taiwan during 2012, the age-adjusted prevalence of hyperlipidemia, defined as TC $\geq$ 240 mg/dL or TG $\geq$ 200 mg/dL or on lipid-lowering medications, was 9.7%. However, because of the varying definitions, study populations, and study periods, the prevalence rates of hyperlipidemia among Taiwanese people varied modestly (Table 3). In 1995, Pan and Chiang[9]

Table 3 Prevalence of hyperlipidemia in Taiwan based on various populations.

Author, year	Study period	Study design and participants	Definition	Men (%)	Women (%)
Pan and Chiang, 1995[9]	1991–1993	Ju-Dung, n = 77,789, age $\geq$35 y	Total cholesterol $\geq$ 240 mg/dL	9–13	7–18
	1991–1993	Pu-Tzu, n = 45,018, age $\geq$35 y	Total cholesterol $\geq$ 240 mg/dL	7–18	5–17
	1990	National survey, age 35–64 y	Triglycerides $\geq$ 200 mg/dL	12.0	7.0
Chang et al, 2002[10]	2002	National survey, n = 5643, age $\geq$45 y	Total cholesterol $\geq$ 240 mg/dL or on medication	12.6	24.4
			Triglycerides $\geq$ 200 mg/dL or on medication	12.3	11.9
			LDL-C $\geq$160 mg/dL	14.8	17.2
			HDL-C $<$ 35 mg/dL	14.4	9.5
Chien et al, 2005[11]	1990–1991	Chin-Shan, n = 3605, age $\geq$35 y	Total cholesterol $\geq$ 240 mg/dL	14.1	19.8
			Triglycerides $\geq$ 200 mg/dL	14.4	12.0
			HDL-C $<$ 40 mg/dL	36.5	27.0
			LDL-C $\geq$ 160 mg/dL	24.7	31.5
Pan et al, 2011[3]	1993–1996	National survey, age $\geq$19 y	Total cholesterol $\geq$ 240 mg/dL	10.2	11.2
	2005–2008		Total cholesterol $\geq$ 240 mg/dL	12.5	10.0
	1993–1996		Triglycerides $\geq$ 200 mg/dL	13.4	6.1
	2005–2008		Triglycerides $\geq$ 200 mg/dL	20.8	7.9

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

summarized the age- and sex-specific hyperlipidemia patterns in the local communities (1991—1993) and national representative data (1990), and showed that the prevalence rates of hypercholesterolemia were 7—18% for men and 5—18% for women, and for hypertriglyceridemia they were 12% for men and 7% for women in local communities. In addition, based on more than 5000 representative participants from the National and Health Survey in Taiwan, Chang et al[10] reported that the prevalence rates of hypercholesterolemia were 12.6% for men and 24.4% for women. Furthermore, Pan et al[3] compared the data from two national nutritional surveys from 1993 to 2008. They found significant lifestyle and dietary habit changes in Taiwan. Increased intake of animal fats and calories with sedentary behavioral pattern, especially in the younger population were observed in Taiwan. These changes were accompanied with a significantly increased prevalence rate of hypertriglyceridemia among men (from 13.4% to 20.8%, $p = 0.034$), but not in women. However, a local community-based study on adults aged 35 years and older with a median follow-up time of 9 years since 1990 showed a higher prevalence of hypercholesterolemia among women compared with men.[11] The rates of hyperlipidemia increased progressively with age, especially among postmenopausal women.[9] The prevalence of other lipid profiles, including apolipoprotein (Apo) A1 and B, non-HDL-C, and lipoprotein (a), need to be further investigated in the Taiwanese population.

Various lipid markers, including Apo B, non-HDL-C, and LDL-C, were reported to predict the risk of CAD. The relative importance of lipid markers among Taiwanese was also studied. Chien et al[12] conducted a community-based prospective cohort study involving 3568 participants and found that 122 individuals developed CAD during a median follow-up of 13.6 years. The adjusted relative risk (RR) of CAD in the highest quintile compared with the lowest quintile was 2.74 [95% confidence interval (CI), 1.45—5.19] for Apo B, 1.98 (95% CI, 1.00—3.92) for non-HDL-C, and 1.86 (95% CI, 1.00—3.49) for LDL-C (all p for trend < 0.05) (Fig. 1). The data provided strong evidence that Apo B, non-HDL-C, and LDL-C concentrations are all important predictors of CAD in Taiwan. Further analysis showed that Apo B had the highest receiver operator characteristic curve area and the highest likelihood ratio in predicting CAD. Because of economic progress and lifestyle changes, the prevalence of hyperlipidemia, including elevated TC and TG, increased significantly in Taiwan. These epidemiological data carried important clinical implications. First, health education through programs in individual and general population levels needs to be enforced to promote healthy lifestyle, especially for healthy diets and increased physical activity. Second, a screening strategy should be implemented to identify individuals with hyperlipidemia, and adequate risk assessment and management should be provided. The control of hyperlipidemia in primary and secondary prevention will reduce the disease burden of atherosclerosis in Taiwan.

Lifestyle modification

Lifestyle change on TC and LDL-C

The roles of lifestyle modification and dietary supplements have been widely studied to influence lipid levels and

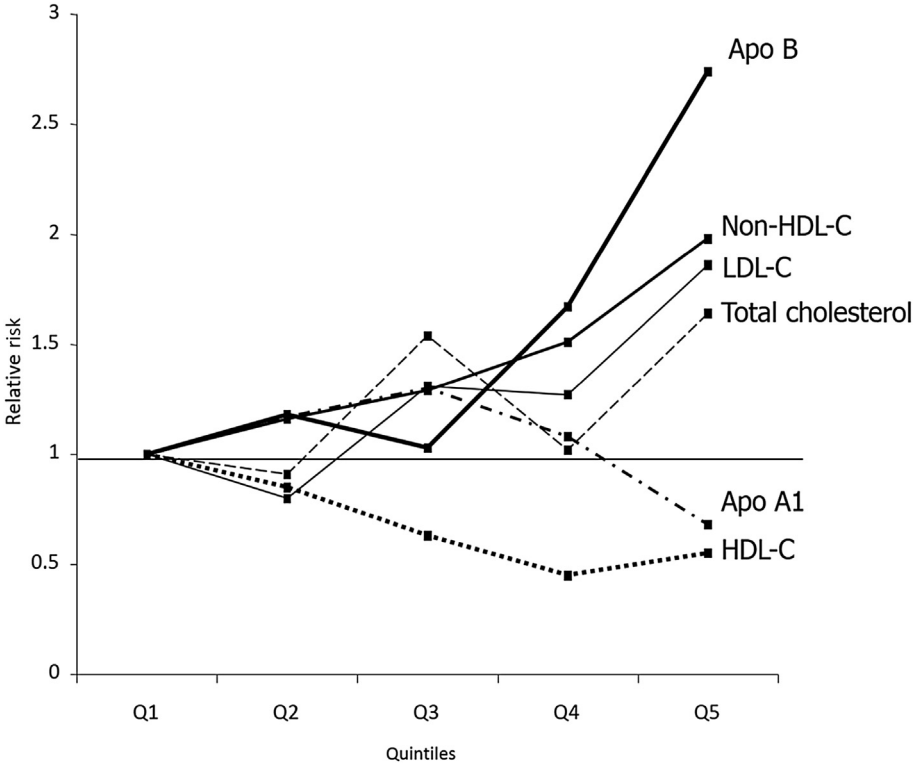

Figure 1 Adjusted relative risks of various lipid profiles for the risk of coronary heart disease events in the community-based cohort study in Taiwan. Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

prevent CV disease. The drops in TC and LDL-C of 19 and 7.7 mg/dL, respectively, were observed for every 10 kg of body weight loss.[13] Meta-analysis found that exercise did not significantly reduce TC and LDL-C.[14,15] Egg intake has been shown to promote the formation of large LDL-C, which is less atherogenic and does not alter the LDL-C/HDL-C ratio.[16] Meta-analysis suggests that egg consumption is not associated with the risk of CV disease and mortality in the general population. However, egg consumption may be associated with an increased incidence of Type 2 DM among the general population and CV morbidity among diabetic patients.[17] Lifestyle intervention including reduction of trans or saturated fat and diet enriched with phytosterol (plant sterol) or fiber can lower TC and LDL-C.[18–20] Dietary cholesterol is not necessary for our body needs. The relationship between dietary cholesterol and blood cholesterol level is still questionable.[21] A common healthy diet pattern including consuming <10% calories from saturated fats and <10% calories from added sugar is strongly suggested.[21]

Lifestyle change on TG and HDL-C

Diet or exercise could produce comparable and favorable changes in TG and HDL-C.[22] Regular exercise can reduce TG by 17.7 mg/dL more than those without exercise.[14] There was a clear beneficial effect on TG and HDL-C concentrations in the high-amount and high-intensity exercise.[23] Typical interventions shown to be effective include aerobic physical activity at least 12 weeks in duration, three to four sessions per week, lasting on average 40 min/session, and involving moderate- to vigorous-intensity physical activity.[24] Weight reduction improves insulin sensitivity and decreases TG levels. The drop in TG of 13.3 mg/dL is observed for every 10 kg of weight loss. Stabilized weight reduction has a beneficial influence on HDL-C levels, and a 3.5 mg/dL increase for every 10 kg body weight reduction was found.[13] TG increased by 0.19 mg/dL per gram of alcohol consumed in a day and 5.69 mg/dL per 30 g consumed in a day. The average individual consuming 30 g of alcohol a day would expect an increase in HDL-C of 3.99 mg/dL.[25] It is generally agreed that alcohol intake should be limited to <30 g/d in men and <20 g/d in women. HDL-C elevation can be observed after smoking cessation, but attention should be also paid to prevent weight gain associated with smoking cessation.[26,27] Lifestyle intervention including reduced intake of dietary carbohydrate, monosaccharides, and disaccharides can lower TG. Increase in HDL-C is observed with the reduction of dietary trans fat and carbohydrate.[28–30] The overall healthy lifestyle recommendations are provided in the 2015 Taiwan Hypertension Guideline (Table 4).[24]

Recommendation

- Adequate weight reduction to reduce TG and increase HDL-C is suggested. (COR I, LOE A)
- Regular physical exercise to reduce TG and increase HDL-C is suggested. (COR I, LOE A)
- Reduction of excess alcohol intake to reduce TG is suggested. (COR I, LOE A)
- Avoid trans fat intake to reduce LDL-C and increase HDL-C is suggested. (COR I, LOE A)

Table 4 Healthy lifestyle recommendations.

Lifestyle change	Recommendation
Sodium restriction	2.0–4.0 gm/d
Alcohol limitation	Men: <30 gm/d ethanol Women: <20 gm/d ethanol
Body weight reduction	BMI: 22.5–25.0
Cigarette smoking cessation	Complete abstinence
Diet adaptation	DASH diet: rich in fruits and vegetables (8–10 servings/d), rich in low-fat dairy products (2–3 servings/d), and reduced in saturated fat and cholesterol
Exercise adoption	Aerobic, at least 40 min/d, and at least 3–4 d/wk

BMI = body mass index; DASH = Dietary Approaches to Stop Hypertension.
Note. From "2015 guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension," by C.E. Chiang, T.D. Wang, K.C. Ueng, T.H. Lin, H.I. Yeh, C.Y. Chen CY et al, 2015, *J Chin Med Assoc*, *78*, p. 1–47. Copyright 2017, *Journal of the Chinese Medical Association*. Adapted with permission.

Other dietary supplements

In addition to lifestyle change, some dietary supplements may be considered for individuals with hyperlipidemia in whom the total CV risk assessment does not justify the use of lipid-lowering drugs. The dietary supplements considered to be beneficial for people to improve lipid profile include: (1) Fish oil. Fish oil supplementation produces a clinically significant dose-dependent reduction of fasting TG but not TC, LDL-C, or HDL-C in hyperlipidemic patients.[31] Reduction of TG is correlated with both eicosapentenoic acid (EPA) and docosahexenoic acid (DHA) intake dose and initial TG level. A more detailed description of fish oil is given in Section "Omega-3 fatty acids/fish oil". (2) Dark chocolate. The influence of dark chocolate on lipid levels is mainly attributable to flavonoids, which could inhibit cholesterol absorption. Meta-analysis showed that intake of dark chocolate for 2–12 weeks significantly reduced TC and LDL-C (−6.23 and −5.90 mg/dL), respectively.[32] (3) Red yeast rice. Red yeast rice is a traditional Chinese food. During the rice fermentation process, monacolins possessing 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity are produced as metabolites. In a meta-analysis of studies using red yeast rice from 1200 mg/d to 4800 mg/d, containing 4.8–24 mg monacolin K, red yeast rice could reduce LDL-C from 19 to 61 mg/dL with a pooled estimate of 39 mg/dL compared to placebo.[33] There was no significant difference in the efficacy of LDL-C reduction between monacolin K (10 mg) daily and pravastatin (40 mg), simvastatin (10 mg), or lovastatin (20 mg) daily.[33] The safety outcomes of red yeast rice have not been extensively studied. (4) Soybean. Isoflavones in soy protein cause arterial vasodilation and lower serum

cholesterol. However, soy protein only slightly decreased LDL-C and had no effect on HDL-C and TG.[34]

Pharmacological therapy

Currently available lipid-lowering drugs include HMG-CoA reductase inhibitors (statins), cholesterol absorption inhibitors (ezetimibe), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, nicotinic acids (niacin), fibric acids derivatives (fibrates), and long-chain omega-3 fatty acids (Table 5). Prior to initiating therapy, adults with abnormal lipid profiles should be assessed for secondary causes, familial disorders, and other underlying conditions that may influence lipid levels.

Statins

Statins decrease the production of TC and reduce LDL-C by as much as 20% to 60%. Statins reduce CV morbidity and mortality across a range of LDL-C levels. Intensive treatment using statins at doses that effectively reduce LDL-C $\geq$ 50% slows down the progression or even promotes the regression of coronary atherosclerosis.[35,36] In clinical trials, initiation of moderate-intensity (lowering LDL-C by approximately 30% to <50%) or high-intensity statin therapy (lowering LDL-C $\geq$ 50%) is a critical factor in reducing CV events (Table 6).[37] Moreover, statin therapy reduces ASCVD across a spectrum of baseline LDL-C levels > 70 mg/dL.[38] The reduction of cardiac risk is consistent for primary and secondary prevention and also in various patient subgroups. Currently available statins in Taiwan include lovastatin, pravastatin, simvastatin, fluvastatin, pitavastatin, atorvastatin, and rosuvastatin. Conventional dosing regimens and the range of expected changes in the lipid profile are listed in Table 5. The reduction of LDL-C by statin is dose-dependent; each doubling dose of statin causes a drop of about 6% in LDL-C levels. Statins can lower TG ranging from 7% to 30%. HDL-C generally rises by 5—15%,

Table 5 Summary of lipid-lowering drugs.

Drug class	Agents and daily doses	Lipid/lipoprotein effects	Side effects	Other considerations
Statins	Lovastatin (20—80 mg) Pravastatin (20—40 mg) Simvastatin (20—40 mg) Fluvastatin (20—80 mg) Atorvastatin (10—80 mg) Rosuvastatin (5—40 mg) Pitavastatin (1—4 mg)	LDL ↓ 20—60% HDL ↑ 5—15% TG ↓ 7—30% Non-HDL↓ 15—50%	Myalgia Myositis Increased serum transaminases	Rare rhabdomyolysis Cognitive decline New-onset diabetes
Cholesterol absorption inhibitor	Ezetimibe 10 mg	LDL ↓ 15—22% HDL ↑ 1—2% TG ↓ 5—10% Non-HDL↓ 14—19%	Headache Muscle pain	Effective in combination with statin
PCSK9 inhibitors	Evolocumab (140 mg, s.c., Q2W) Alirocumab (75 mg, s.c., Q2W)	LDL ↓ 50—70% HDL ↑ 4—7% TG ↓ 6—19% Non-HDL ↓ 20—50%	Injection site reaction (5%)	Not increased serum transaminases Require subcutaneous injection
Nicotinic acid	IR nicotinic acid (1.5—3 g) ER nicotinic acid (1—2g) SR nicotinic acid (1—2 g)	LDL ↓ 15—18% HDL ↑ ~25% TG ↓ 20—40% Non-HDL ↓ 8—23%	Flushing Hyperglycemia Hyperuricemia GI distress Hepatotoxicity Excess infection	Glucose intolerance ER niacin more tolerable than IR
Fibric acids	Gemfibrozil, 600 mg bid Bezafibrate, 200 mg bid/tid Fenofibrate, 200 mg qd Fenofibric acid, 135 mg qd	LDL ↓ 10-15% HDL ↑10-20% TG ↓ 20-50% Non-HDL↓ 5-19%	Dyspepsia Increased serum transaminases Gallstones Myopathy	May ↑ creatinine + homocysteine Do not combine gemfibrozil + statin
Omega-3 fatty acids	Omega-3 fatty acids 2—4 g	LDL ↓6%—↑25% HDL ↓5%—↑7% TG ↓ 20—45% Non-HDL↓ 5—14%	Fishy smell Skin eruption	Combination with statin improve postprandial TG level

ER = extended-release; HDL-C = high-density lipoprotein cholesterol; IR = immediate-release; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SR = sustained-release; s.c. = subcutaneous; TG = triglyceride.

Table 6 Intensity of statin therapy.

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

LDL-C = low-density lipoprotein cholesterol.
[a] The maximal dose approved for rosuvastain in Taiwan is 20 mg once daily. The 40 mg dose of rosuvastatin is reserved only for those patients who have familial hypercholesterolemia (FH).

but greater increases could occur in persons with low HDL-C and elevated TG.

Statin monotherapy is generally well tolerated, with a low frequency of adverse events. The most common statin side effect is muscle-related symptoms. Incidence of myalgia without serum creatine kinase (CK) elevation ranges from <5% in randomized clinical trials to >18% in reported real-world data. The clinical presentation of myalgia can be subtle or nonspecific that causes difficulty in deciding whether myalgia is statin-induced or caused by other musculoskeletal conditions. Less often, myositis (elevated CK > 10 times the upper limit of normal) or rhabdomyolysis (CK > 10,000 IU/L or accompanied by significant elevation in creatinine level) develops. In randomized controlled trials, the incidence of statin myopathy is ~1.5—5.0%. Myopathy is most likely to occur in persons with multiple comorbidities, who are taking multiple medications, or in elderly persons, those with smaller body size, people of Asian ethnicity, etc. Certain concomitant medications may increase the risk of statin myopathy, and these include fibrates, particularly gemfibrozil; niacin; cyclosporine; azole antifungals; macrolide antibiotics; HIV protease inhibitors; verapamil and diltiazem; amiodarone and grapefruit juice. Routine measurement of CK levels in asymptomatic patients prior to or during statin treatment is not necessary. There is no need to discontinue statin therapy in asymptomatic patients whose CK levels are elevated <10 times the upper limit of normal. However, when patients become symptomatic or their urine darkens, the drug should be stopped promptly. The frequency of fatal rhabdomyolysis has been estimated to be as low as 0.15 deaths per million prescriptions. Elevated hepatic transaminases generally occur in 0.5—2.0% of cases and are dose-dependent. Serious liver injury with statins is rare and unpredictable in individual patient, and routine periodic monitoring of liver enzymes is not required unless symptoms develop. Other adverse effects of statins such as cognitive decline, confusion, hyperglycemia, increased risk of cancer, and sleep disturbance have been reported. But the CV benefits of statins outweigh these unproven small increased risks.

Recommendation

- Statins are the first-line therapy, and moderate- or high-intensity statins are preferred, unless not tolerated, for high-risk patients. (COR I, LOE A)
- Based on individual risk, up titration to the highest recommended statin dose or highest tolerable dose to reach the target level is necessary. (COR IIa, LOE A)

Ezetimibe

Ezetimibe decreases cholesterol absorption in the intestine by binding directly to NPC1L1 protein in intestinal mucosa. The average reduction of LDL-C by ezetimibe (10 mg) monotherapy is 15—22%, and there is an additional reduction of LDL-C levels by 15—23% when used in combination with statins. Its effects on TG and HDL-C levels are negligible. The efficacy of ezetimibe in combination with simvastatin has been addressed in clinical trials. The Study of Heart and Renal Protection (SHARP) trial[39] evaluated simvastatin (20 mg) and ezetimibe (10 mg) versus placebo in 9270 CKD patients. Treatment with simvastatin and ezetimibe produced a 17% reduction in major atherosclerotic events compared to placebo ($p = 0.0021$). In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study,[40] 18,144 patients with ACS < 10 days were randomly assigned to either simvastatin (40 mg) plus ezetimibe (10 mg) or to simvastatin (40 mg) plus placebo. With a median follow-up of 6 years, simvastatin/ezetimibe was found to reduce the primary outcome of CV mortality, major CV event, or nonfatal stroke ($p = 0.016$). The data suggest incremental LDL-C reduction beyond statins, providing further clinical benefit. Ezetimibe can be coadministered with any dose of any statin. It has relatively few side effects when used alone. In several 1-year safety studies, ezetimibe in combination with statins demonstrated no significant difference in adverse event rate compared with either statin or ezetimibe monotherapy. Ezetimibe is contraindicated in pregnant or lactating women.

Recommendation

- Ezetimibe alone can be considered an alternative to statins in patients who have statin contraindications or intolerance. (COR IIa, LOE C)
- Ezetimibe can be used in combination with statins when the therapeutic target is not achieved at maximal tolerated statin dose. (COR IIa, LOE B)
- For patients with ACS, routine use of the moderate intensity statin combined with ezetimibe may be an alternative. (COR IIa, LOE B)

Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor

PCSK9 inhibitor (anti-PCSK9 monoclonal antibody) is a new class of drug that can decrease LDL receptor (LDLR) destruction and increase their recycling to the liver surface. The U.S. Food and Drug Administration (FDA) has approved

evolocumab and alirocumab to be used in patients with FH or CV disease who require additional LDL-C lowering in addition to diet and maximally tolerated statins. The European Medicines Agency has approved alirocumab and evolocumab for patients who fail to achieve acceptable lipid control despite optimal statin therapy, patients with homozygous FH (HoFH), and statin-intolerant patients. PCSK9 inhibitors, administered via injection every 2—4 weeks, have reduced LDL-C by as much as 50—70% across different patient populations with or without background statin therapy. Recently, significant reductions in CV event rates were reported from the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER),[41] and the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) studies.[42] Pooled analysis of phase II and III studies demonstrated similar incidence of serious adverse events in patients treated with PCSK9 inhibitors versus control.[43] Approximately 5% of injection site reaction was reported in the active treatment arms of evolocumab or alirocumab. Currently, PCSK9 inhibitors are being evaluated in the large clinical outcome trials (FOURIE and ODYSSEY) and the results will determine the future of these lipid-lowering therapies by establishing their clinical efficacy in terms of CV event reduction, safety, and the consequences of prolonged exposure to very low levels of LDL-C.

Recommendation

PCSK9 inhibitors should be considered in highly selected patients with

- FH (COR I, LOE A)
- Statin resistance (patients with CV disease not at LDL-C goal despite maximally tolerated statin ± ezetimibe) (COR IIa, LOE B)
- Statin intolerance (COR IIa, LOE B)

Nicotinic acid (niacin)

Nicotinic acid appears to increase HDL-C partially by reducing HDL-C catabolism and mainly by increasing Apo A1 synthesis in the liver. Niacin exerts broad-spectrum lipid-modulating action, raising HDL-C in a dose-dependent manner by 25% and reducing both LDL-C (by 15—18%) and TG (by 20—40%) at the 2 g/d dose. Niacin has demonstrated benefit in earlier studies in conjunction with statins and other drugs, as observed in the Cholesterol Lowering Atherosclerosis Study (CLAS)[44] and the HDL-Atherosclerosis Treatment Study (HATS).[45] However, two recently published studies [Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)[46] and Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)[47]] suggested that even though niacin produced favorable lipid changes, it did not produce further reduction of heart attack, stroke, or death in patients already under statin treatment. Although the HPS2-THRIVE study demonstrated that niacin with the anti-flushing agent laropiprant could not reduce the primary composite events in patients with optimal lipid parameters under statin therapy (baseline non-HDL-C of 84 mg/dL and LDL-C of 63 mg/dL), subgroup analysis suggested that patients with LDL-C greater than 76 mg/dL at baseline may benefit from niacin therapy. In the subgroup analysis of the AIM-HIGH study, a significant ($p = 0.03$) reduction of primary events was found in patients with TG $\geq$ 200 mg/dL and HDL-C $<$ 32 mg/dL with niacin treatment.[46] In a recent meta-analysis including 9959 participants derived predominantly from secondary prevention trials, allocation to niacin treatment yielded a 25% ($p = 0.02$) risk reduction of the CV end points.[48]

Niacin is available in immediate-release, sustained-release, and extended-release formulations. The most frequent side effect of niacin is cutaneous flushing, which can be reduced by using extended-release formulation, by taking niacin with food, or by taking aspirin (325 mg) 30 minutes prior to niacin dosing. The other side effects of niacin include hyperuricemia, liver toxicity, and glucose intolerance. Baseline hepatic transaminase, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained prior to the initiation of niacin. These should be followed up again during uptitration to a maintenance dose and every 6 months thereafter. Niacin should not be used if hepatic transaminase elevation is higher than 2—3 times of the upper limit of normal. To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to start niacin from low dose and titrate to a higher dose over a period of weeks as tolerated.

Recommendation

- Niacin may be considered an option in high-risk patients with low HDL-C and elevated LDL-C despite statin therapy. (COR IIa, LOE C)
- Niacin is indicated to reduce elevated TC, LDL-C, and TG levels, and to increase HDL-C in patients with mixed dyslipidemia. (COR IIa, LOE C)
- Niacin is considered as adjunctive therapy for treatment of patients with severe hypertriglyceridemia (TG $\geq$ 500 mg/dL) who present a risk of pancreatitis. (COR IIa, LOE B)
- Niacin in combination with statins may be appropriate options for patients with hypertriglyceridemia and associated low HDL-C. (COR IIa, LOE C)

Fibrate

Fibrates (gemfibrozil, bezafibrate, fenofibrate, and fenofibric acid) are agonists of peroxisome proliferator-activated receptor (PPAR) α, a nuclear receptor involved in the regulation of lipid metabolism. Fibrates reduce TG levels by approximately 20—50% and also raise HDL-C levels by about 10—20%. Fibrates have variable effects on LDL-C such that in patients with hypertriglyceridemia they may rather increase plasma LDL-C levels by 10—15%. The clinical benefits of fibrates in monotherapy are primarily demonstrated by four randomized clinical trials: the Helsinki Heart Study (HHS),[49] the Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT),[50] the Bezafibrate Infarction Prevention study (BIP),[51] and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD).[52] The data from these trials have shown a consistent decrease in nonfatal MI.

However, the effects on other clinical outcomes remained equivocal, and the overall efficacy of fibrates on CV outcomes is much less robust than that of statins. The FIELD trial demonstrated a significant effect in a subgroup of patients with TG levels $\geq$ 200 mg/dL and HDL-C $\leq$40 mg/dL. However, combination therapy with fenofibrate and simvastatin failed to reduce the risk of fatal CV events, nonfatal MI, or nonfatal stroke according to results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[53] Likewise, subgroup analyses in the ACCORD trial demonstrated that fibrate therapy could reduce CV events in those with TG $\geq$ 204 mg/dL and HDL-C $\leq$ 34 mg/dL. Therefore, there is a consistent finding in the fibrate trials for reduction of CV events in patients with high TG and low HDL-C whether or not they are treated with statins.

Fibrates are generally well tolerated, and the most common side effect is dyspepsia. Fibrates have been associated with muscle toxicity causing muscle pain or weakness, especially when used in patients with renal insufficiency or when used in combination with statins. Fenofibrate and fenofibric acid are less likely to interact with statins than gemfibrozil and are safer in patients who must take both medications. Fibrates promote cholesterol secretion into the bile and are associated with an increased risk of gallstones. Thus, fibrates are generally contraindicated in patients with gallstones and severe liver disease. Fibrates can raise creatinine levels and should be used with caution in CKD patients. Fibrates can potentiate the effect of warfarin and certain oral hypoglycemic agents, and therefore anticoagulation status and plasma glucose levels should be monitored in patients taking these agents.

Recommendation

- Fibrate alone could be used as a first-line agent for treatment of severe hypertriglyceridemia (TG $\geq$ 500 mg/dL) to prevent pancreatitis. (COR I, LOE B)
- In patients with a TG level $<$ 500 mg/dL, the role of fibrates is primarily in combination with statins in selected patients with mixed dyslipidemia. (COR IIa, LOE C)
- Statin—gemfibrozil combination therapy is not recommended. (COR III, LOE B)
- Fibrates are not recommended for dyslipidemia with exclusively elevated LDL-C. (COR IIb, LOE C)

Omega-3 fatty acids/fish oil/n-3 fatty acids/n-3 polyunsaturated fatty acids

N-3 polyunsaturated fatty acids (*n*-3 PUFAs; EPA and DHA) are components of fish oil and have been used to lower TG by 20—35% and even up to 45% in individuals with very high TG ($\geq$500 mg/dL) at doses of 2—4 g/d. Omega-3 fatty acid preparations containing EPA and DHA may increase LDL-C from 17% to 25% in patients with very high TG, although little or no increase is typically observed in patients with mixed dyslipidemia. The Japan EPA Lipid Intervention (JELIS) study, conducted in 18,645 Japanese patients with hypercholesterolemia, found that statin plus highly purified EPA ethyl ester (1800 mg/d) was associated with a 19% reduction in major coronary events.[54] The JELIS subgroup analysis reported that the reduction in CV risk with EPA ethyl esters (1.8 g/d) was larger in the subset of patients with TG $\geq$ 150 mg/dL and HDL-C $<$ 40 mg/dL than in the overall study participants. The FDA approved omega-3-carboxylic acids as an adjunct to diet to reduce TG in adults with severe hypertriglyceridemia (TG $\geq$ 500 mg/dL). The FDA approval was based on data from the Epanova for Lowering Very high Triglycerides (EVOLVE) trial, which examined its efficacy in lowering TG and other key lipid parameters in patients with very high TG level.[55] However, its effect on the risk of pancreatitis or CV mortality and morbidity has not been determined. The daily dose is 2 g or 4 g, making it the first prescription omega-3 fatty acid to have a dosing option. Recently, a randomized clinical trial using omega-3 fatty acid was performed in Taiwanese patients with hypertriglyceridemia.[56] Patients with TG levels from 200 to 1000 mg/dL received a concentrated preparation of omega-3 EPA plus DHA in a dose of 2 g/d, 4 g/d or placebo, for eight weeks. The TG levels were reduced 32.1% (4 g/d), and 29.7% (2 g/d) in omega-3 fatty acid group compared with 5.4% in placebo group ($p < 0.001$). Two outcomes trials are currently underway to assess the effect of omega-3 products on CV outcomes in patients with hypertriglyceridemia despite statin therapy. In general, omega-3 fatty acids are well tolerated and appear to be safe. However, the antithrombotic effects may increase the risk of bleeding, especially when given in addition to combination therapy with aspirin and other antiplatelet drugs.

Recommendation

- Omega-3 fatty acid is indicated for the treatment of very high TG ($\geq$500 mg/dL). (COR IIa, LOE B)
- EPA and DHA are recommended for patients with coronary heart disease and hypertriglyceridemia. (COR IIa, LOE B)

Cholesteryl ester transfer protein (CEPT) inhibitor

CETP inhibitors block the transfer of cholesteryl ester from HDL-C to LDL-C and VLDL (very low density lipoprotein)-C. CETP inhibitors lower LDL-C ($\sim$45%) and increase HDL-C (up to $\sim$179%). When combined with statins, CETP inhibitors yielded an additional decrease of LDL-C up to 50%. Four CETP inhibitors have reached late-stage clinical development over the past several years: anacetrapib, dalcetrapib, evacetrapib, and torcetrapib. Three CETP inhibitors—torcetrapib,[57] dalcetrapib,[58] and evacetrapib—have all failed in outcome trials. Available data suggest that CETP inhibitors might interfere with normal human HDL-C metabolism, yielding HDL-C that is less efficient in excretion of cholesterol. At the moment, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid modification (REVEAL) study is the only remaining phase 3 trial of a CETP inhibitor still underway. In this trial, more than 30,600 patients have been randomized to anacetrapib (100 mg daily) or placebo, and the final follow-up is expected to be completed in early 2017.

Combination therapy

Statins are the most widely prescribed lipid-lowering agents and are often used as monotherapy. A large portion of

patients could not reach their treatment goals on statin monotherapy or are troubled by statin side effects, prompting interest in combination therapy as a way to enhance the likelihood of achieving target lipid levels without having to increase statin dose and reduce side effects. Statins can be combined with ezetimibe, fibrate, niacin, or omega-3 fatty acid. However, except for ezetimibe, results of recent outcome trials of combining statin with fibrate or niacin failed to show additional reductions in CV events compared with statin monotherapy. The adverse effects of two or more drugs may be additive; clinical judgment is needed to balance the risks and benefits of combination therapy.

Recommendation

Combination therapy with statin and other lipid-modifying agents may be considered in the following settings:

- High-risk patients intolerant of or unresponsive to high-intensity statin monotherapy; lower intensity statin combined with nonstatin medications may be an alternative. (COR IIa, LOE B)
- When the cholesterol level is markedly increased (such as in FH) and statin monotherapy does not achieve the therapeutic goal. (COR IIa, LOE B).
- When mixed dyslipidemia is present. (COR IIa, LOE C).
- Niacin or fibrates in combination with statins may be appropriate options for high-risk patients with hypertriglyceridemia and low HDL-C. (COR IIa, LOE C)
- If maximum tolerated statin does not reach the non-HDL-C goal, add-on therapy with fibrate, omega-3, or niacin could be considered. (COR IIa, LOE C)

Follow-up and monitoring

Regular lipid monitoring may promote patient adherence to drug regimens and has a positive impact on their clinical outcomes. Response to therapy can be assessed at 6—8 weeks from initiation or dose increases for statins, but response to fibrates may take longer. In long-term follow-up, the standard practice for monitoring a complete lipid profile (TC, TG, LDL-C, and HDL-C) is 6—12 months. However, the specific interval should depend on patient adherence and individual clinical situation.

Recommendation

- Complete lipid profile (TC, TG, LDL-C, and HDL-C) should be monitored during the lipid lowering drug therapy. (COR IIa, LOE C)

Acute coronary syndrome (ACS)

ACS is a catastrophic complication of coronary atherosclerosis. It usually results from acute plaque rupture with coronary thrombus formation causing lumen obstruction and myocardial ischemia or infarction. Diagnosis of ACS depends on clinical presentation, electrocardiographic and biomarker change, and ranges from ST segment elevation MI to non-ST segment elevation MI or unstable angina.

Benefits of LDL lowering in ACS

LDL-C is the most important target of lipid intervention in ACS patients. Randomized clinical trials demonstrate clinical benefits of LDL-C lowering therapy with statin for ACS patients. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, ACS patients were randomly assigned to treatment with atorvastatin (80 mg/d) or placebo between 24 and 96 hours after admission and followed up for 16 weeks.[59] A lower risk of primary end point, including death, nonfatal MI, cardiac arrest, or recurrent myocardial ischemia, was achieved in the statin group (RR = 0.84; 95% CI, 0.70—1.00). In the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis In the Myocardial Infarction 22 (PROVE IT—TIMI 22) study, patients with ACS onset within the previous 10 days were randomized to pravastatin (40 mg) or atorvastatin (80 mg) daily.[60] After an average follow-up of 24 months, there was a 16% risk reduction ($p = 0.005$) of the primary end point including a significant reduction of revascularization and recurrent unstable angina and nonsignificant reduction of all-cause death (28%, $p = 0.07$) in patients treated with atorvastatin (80 mg) than those treated with pravastatin (40 mg). In the A to Z trial, although the primary end point was not significantly achieved, a favorable trend to major CV event reduction was observed with early initiation of simvastatin for ACS patients.[61] In the IMPROVE-IT trial, patients hospitalized within 10 days of ACS attack were included and randomized into simvastatin plus ezetimibe or simvastatin plus placebo.[40] The simvastatin/ezetimibe group had a lower risk of composite primary end point including CV death, MI, or stroke [hazard ratio (HR) = 0.936; 95% CI, 0.89—0.99]. In Japan, the ESTABLISH study randomized patients with ACS onset within 48 hours into statin therapy (atorvastatin, 20 mg/d) immediately after percutaneous coronary intervention (PCI) or standard care without lipid-lowering therapy. Statin therapy not only reduced coronary plaque volume observed from intravascular ultrasound (IVUS) but also predicted a lower risk of major adverse cardiac and cerebrovascular events (HR = 0.46; 95% CI, 0.23—0.86) during follow-up.[62,63] These data indicate that LDL-C lowering therapy with statin or statin plus ezetimibe is necessary to improve the clinical outcomes for ACS patients.

Treatment target of LDL-C in ACS

Observational studies found better clinical outcomes in ACS patients who received statin treatment even with a low baseline LDL-C. In the Global Registry of Acute Coronary Events (GRACE) registry, ACS patients with baseline LDL-C < 100 mg/dL prior to statin treatment have a lower risk of composite end point of MI, stroke, and death (adjusted odds ratio (OR) = 0.64; 95% CI, 0.47—0.88) compared with non-statin users at 6 months follow-up.[64] In the Korean Acute MI Registry, acute MI patients with baseline LDL-C < 70 mg/dL who received statin therapy had a reduced risk of the composite primary end point of death, recurrent MI, target vessel revascularization, and coronary artery bypass grafting (adjusted HR = 0.56; 95% CI, 0.34—0.89) at 1 year follow-up compared with nonstatin users.[65] In the Cholesterol Treatment Trialists' (CTT) Collaboration meta-

analysis involving 170,000 individuals in 26 randomized trials, further LDL-C reduction with more intensive statin results in further decrease of coronary events, revascularization, and ischemic stroke. No threshold of cholesterol level was found. The benefit of more intensive statin therapy was observed in patients with LDL-C $<$ 77 mg/dL.[66] Considering most of clinical and basic scientific data, statin therapy is suggested to be used in all patients with ACS if there is no contraindication of the drug.

There are no specific randomized clinical trials to address the treatment target of LDL-C in patients with ACS. In the MIRACL study, the achieved mean LDL-C was 72 mg/dL in the statin group and 132 in the control group.[59] In the PROVE IT—TIMI 22 study, the median levels of LDL-C achieved were 95 mg/dL in the pravastatin group and 62 mg/dL in the atorvastatin group.[60] In the IMPROVE-IT study, the achieved median LDL-C was 70 mg/dL in the simvastatin monotherapy group and 53 mg/dL in the simvastatin/ezetimibe group.[40] The benefits of simvastatin/ezetimibe were more evident in diabetic patients. In the ESTABLISH study in Japan, the median LDL-C achieved in the statin therapy group and control group were 69 mg/dL and 120 mg/dL, respectively.[62] In the China Intensive Lipid Lowering with Statins in Acute Coronary Syndrome study, ACS patients were randomized to receive atorvastatin (10 mg/d) (or equivalent dose of other statins) or atorvastatin (20—40 mg/d) (or equivalent dose of other statins).[67] At 3 months, the mean achieved LDL-C was 81 mg/dL and 78 mg/dL, respectively. No significant difference of the primary end point was observed at 2 years follow-up. In the Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study performed in Japan, the combination of atorvastatin and ezetimibe resulted in lower levels of LDL-C (63.2 $\pm$ 16.3 mg/dL vs. 73.3 $\pm$ 20.3 mg/dL) and greater coronary plaque regression than atorvastatin monotherapy.[68] The statin-induced coronary plaque regression was even more prominent in ACS patients than patients with stable angina. There is a close association between the achieved LDL-C and coronary plaque regression, and the plaques start to regress when LDL-C is lowered down to $<$70 mg/dL.[36,69] Previous meta-analysis study suggested a relation between IVUS-derived measures of coronary plaque burden and adverse CV events.[70] After considering all these data, controlling LDL-C to a target of $<$70 mg/dL is reasonable for all ACS patients. From the data in the IMPROVE-IT study, a lower target of LDL-C $<$ 55 mg/dL can be considered in ACS patients with DM.

Timing of therapy in ACS

In the MIRACL study, statin was started between 24 hours and 96 hours after hospital admission for ACS.[59] In the PROVE IT—TIMI 22 and IMPROVE-IT studies, statin or statin/ezetimibe was started in ACS onset within 10 days.[40,60] In the ESTABLISH study, statin was used within 48 hours after MI onset.[62] Li et al[71] divided ACS patients into early statin group (statin initiation $\leq$2 days after admission; mean initiation date, 1.72 $\pm$ 0.45 days) and late statin group ($>$2 days after admission and prior to discharge) and compared their clinical outcomes. There was no significant difference in the primary composite end point, including CV death, recurrent MI, angina requiring rehospitalization, revascularization procedures, and stroke, between the two groups at 4 months and 12 months follow-up. In another study, ACS patients were stratified according to statin initiation $<$24 hours and $>$24 hours after ACS presentation. No significant differences were observed in the clinical outcomes including death, MI, stroke, rehospitalization, and urgent revascularization between the two groups.[72] However, for patients with ACS undergoing PCI, a meta-analysis demonstrated that statin initiation before PCI reduced the risk of 30-day CV events compared with a post-PCI administration.[73] Statin given prior to PCI in ACS could be useful. Fig. 2 shows the LDL-C treatment algorithm for ACS patients.

Recommendation

- Statin or statin/ezetimibe should be used for all ACS patients if there is no contraindication. (COR I, LOE A)
- The LDL-C target should be $<$70 mg/dL in ACS patients. (COR I, LOE B)
- In ACS patients with diabetes, a lower target of LDL-C $<$ 55 mg/dL can be considered. (COR IIa, LOE B)
- Statin or statin/ezetimibe therapy should be started within the first few days of hospitalization for ACS and prior to PCI for ACS. (COR IIa, LOE B)

TG and HDL-C

The role of TG as a CV risk factor is still controversial. Several studies found that increased TG is a risk factor of recurrent cardiac events in ACS patients already under statin treatment. In the *post hoc* analysis of PROVE IT—TIMI 22 trial, on-treatment TG $<$ 150 mg/dL was associated with a lower risk of composite end point of death, MI, or recurrent ACS after adjusting for LDL-C, HDL-C, and other clinical variables.[74] Similar findings were also found in the MIRACL study. The primary end point events increased across tertiles of baseline TG, and the HR was 1.50 between the highest ($>$195 mg/dL) and the lowest ($\leq$135 mg/dL) tertile of TG in the atorvastatin group of the MIRACL study.[75] In the dal-OUTCOMES trial, patients were randomized to CETP inhibitor dalcetrapib or placebo at 4—12 weeks after ACS on the background of statin therapy.[58] The risk of primary end point also increased with the baseline TG, and the HR was 1.61 between the highest ($>$175 mg/dL) and the lowest ($\leq$80 mg/dL) quintile of TG.[75] Increased TG is usually associated with decreased concentrations of HDL-C.[76] Low HDL-C level has long been known as a cardiac risk factor. However, under statin control of LDL-C, all clinical trials with add-on therapy of fibrate,[53] niacin,[46,47] or CETP inhibitor[57,58] that decreased TG and increased HDL-C could not further reduce cardiac risk compared with placebo. Non-HDL-C (TC minus HDL-C) includes all potentially atherogenic lipoprotein particles, such as VLDL, intermediate density lipoprotein (IDL), LDL, and lipoprotein (a). Non-HDL-C is also a CV risk factor[12,77] and can be considered as a secondary treatment target for patients with TG $\geq$ 200 mg/dL. The suggested non-HDL-C target is $<$100 mg/dL in ACS patients.

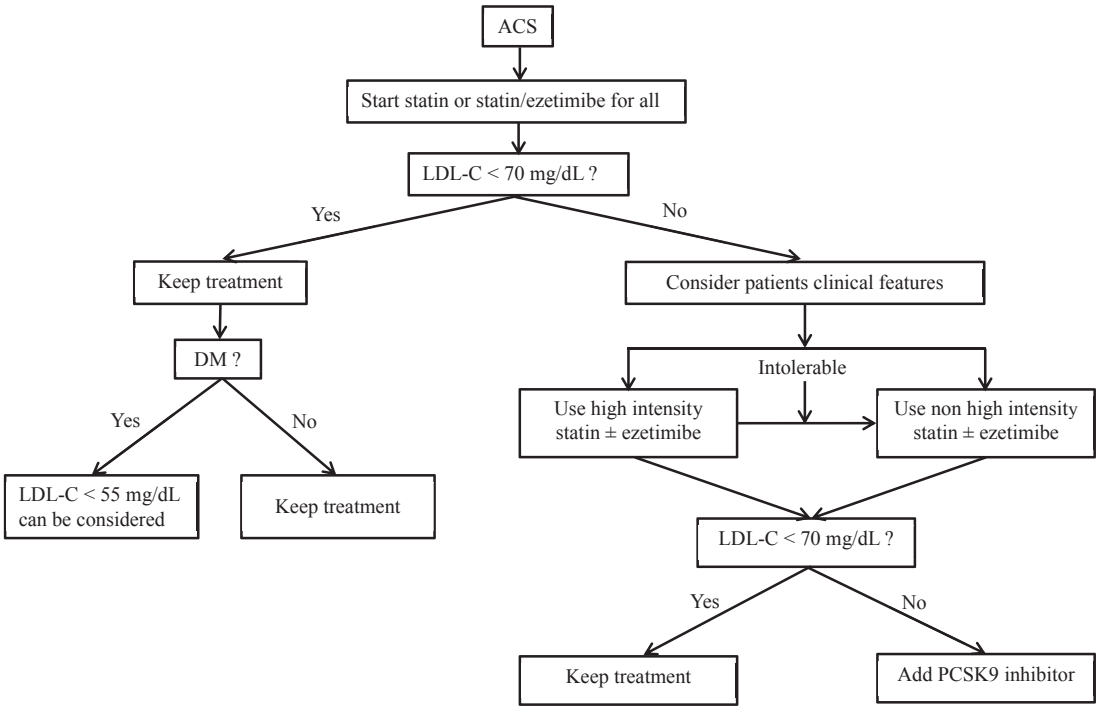

Figure 2 LDL-C treatment algorithm for ACS patients. ACS = acute coronary syndrome; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin 9.

Recommendation

- Increased TG may be a risk factor of recurrent CV events after ACS. (COR IIa, LOE B)
- Non-HDL-C $<$ 100 mg/dL can be the secondary target in patients with TG $\geq$ 200 mg/dL. (COR IIa, LOE B)
- TG-lowering therapy is necessary in patients with TG $\geq$ 500 mg/dL to prevent pancreatitis. (COR I, LOE B)

Stable coronary artery disease (CAD)

Patients with stable CAD have a high risk of myocardial ischemia, coronary revascularization, and ACS. Clinical diagnosis of CAD usually depends on a history of ACS or coronary revascularization, ischemic symptoms with positive stress tests, and the presence of significant coronary luminal narrowing by imaging studies.

Benefits of LDL lowering in stable CAD

LDL-C is the primary target in patients with stable CAD. Randomized clinical trials have clearly demonstrated the benefits of statin therapy for patients with CAD. In the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, CAD patients who had a history of MI or hospitalization for unstable angina were randomly assigned to treatment with pravastatin (40 mg/d) or placebo.[78] The primary study end point was mortality from CAD. A lower risk of primary end point was found with statin as compared to placebo (RR = 24%; 95% CI, 0.12—0.35). In the Cholesterol and Recurrent Events (CARE) study, 4159 patients with CAD, defined as having a history of MI, were randomized to take pravastatin (40 mg) or placebo.[79] There was a 24% RR reduction (95% CI, 0.09—0.36) in the occurrence of the primary end point including fatal coronary event or nonfatal MI. In the Scandinavian Simvastatin Survival Study (4S), 4444 patients with stable CAD, defined as having angina pectoris or previous MI (onset time >6 months), were randomly assigned to receive simvastatin (20—40 mg) or placebo.[80] Over 5.4 years of follow-up, there was a significant reduction of the primary end point, total mortality (RR = 0.70; 95% CI, 0.58—0.85). In the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study (HPS), 20,536 high-risk individuals were randomly allocated to receive 40 mg simvastatin or placebo for 5-year follow-up.[81] In this study, 13,386 participants had prior MI or CAD and statin treatment provided a significant reduction of first major vascular event (HR = 0.75; 95% CI, 0.67—0.84). In the Treating to New Targets (TNT) study, 10,001 stable CAD patients were randomized to atorvastatin (10 mg/d or 80 mg/d) and followed up for a median of 4.9 years.[82] The primary end point was the occurrence of a first major CV event, defined as death from CAD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke. Mean LDL-C levels were reduced to 77 mg/dL during treatment with high dose statin and resulted in a significant reduction in the risk of primary end point (HR = 0.78; 95% CI, 0.69—0.89).

Statins not only improve clinical outcome but also attenuate atheroma progression or enhance atheroma regression. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, a total of 654 CAD patients were randomized into two groups, administered either atorvastatin (80 mg/day) or pravastatin (40 mg/d).[35] After 18 months of treatment, progression of atherosclerotic plaque was halted in atorvastatin versus pravastatin group (percent

change in plaque volume, −0.4% vs. 2.7%). The mean LDL-C levels were reduced from 150.2 mg/dL to 79 mg/dL in the atorvastatin group. In the A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial, rosuvastatin (40 mg/d) was used for 24 months in 507 CAD patients.[36] The mean change in percent atheroma volume for the entire vessel was −0.98% ($p < 0.001$ vs. baseline). The mean baseline LDL-C of 130.4 mg/dL was decreased to 60.8 mg/dL in this study. Statins not only induce coronary plaque regression but also modify its composition and stabilize coronary plaque.[83] In Japan, the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS) study included 214 CAD patients who were assigned to receive rosuvastatin (5—20 mg daily) for 76 weeks.[84] Rosuvastatin treatment exerted significant regression of coronary atheroma (percent change of plaque volume by $-5.1 \pm 14.1\%$, $p < 0.0001$). The baseline mean LDL-C of 140.2 mg/dL declined to 82.9 mg/dL after statin treatment. Statin therapy also plays an important role in plaque composition and stability in patients with stable CAD. In Korea, the Atorvastatin versus Rosuvastatin Therapy with Equivalent Potency on Mild Coronary Atherosclerotic Plaques (ARTMAP) trial randomized 350 patients to atorvastatin (20 mg/d) versus rosuvastatin (10 mg/d).[85] At 6-month follow-up, the change in percent atheroma volume was not different between the two groups (-0.3 ± 4.2 vs. -1.1 ± 3.5, $p = 0.157$). The achieved LDL-C levels were 56 ± 18 mg/dL versus 53 ± 18 mg/dL, respectively. In a meta-analysis of 20 trials including 5910 patients with CAD, intensive lowering LDL-C (rosuvastatin mean 33 mg daily and atorvastatin mean 60 mg daily) for >17 months duration could lead to the regression of coronary atherosclerotic plaque. The LDL-C should be reduced at least by >40% or to a target level <78 mg/dL for atheroma regression.[86]

Treatment target of LDL-C in CAD

No randomized clinical trials were designed to examine a specific treatment target of LDL-C in patients with stable CAD. In the CARE study, the mean level of LDL-C was lowered to 97 mg/dL in the pravastatin group.[79] In the MRC/BHF HPS, the mean LDL-C was reduced to 88.9 mg/dL in the statin group and 127.7 mg/dL in the placebo group.[81] In the TNT study, the mean LDL-C was 77 mg/dL during treatment with high-dose statin and 101 mg/dL during treatment with low-dose statin.[82] In the CTT Collaboration meta-analysis, LDL-C reduction with more intensive statin results in further decrease of coronary events, revascularization, and ischemic stroke in patients with stable CAD or acute MI. No threshold of cholesterol level was found. The benefit of more intensive statin therapy was consistent regardless of the baseline LDL-C levels, even observed in patients with baseline LDL-C < 77 mg/dL (HR = 0.71; 95% CI, 0.52—0.98).[66] In the *post hoc* analysis of TNT study, there was a highly significant reduction in the rate of major CV events with descending achieved levels of on-treatment LDL-C ($p < 0.0001$ for trend across LDL-C).[87] Considering most of the data from randomized clinical trials and IVUS studies, statin therapy to treat LDL-C to a target of <70 mg/dL is reasonable for all stable CAD patients.

Who can benefit from statin therapy?

The definitions of stable CAD were diverse in the clinical trials. The mega outcome trials usually included patients with history of unstable angina hospitalization or MI (onset > 1 month, 3 months, or 6 months), medical history of angina pectoris, or coronary artery bypass grafting or angioplasty. In view of the diverse eligibility of participants with clinical diagnosis of CAD in these clinical trials, it is reasonable to recommend statin therapy in stable CAD patients based on medical history of CAD, including: (1) history of MI or unstable angina (>6 months); (2) history of coronary revascularization; (3) presence of ischemic symptoms with positive stress tests; (4) suspected ischemic heart disease by electrocardiography or echocardiography; (5) transcatheter angiographic diagnosis of significant coronary stenosis (≥50% luminal narrowing). To avoid overdiagnosis, asymptomatic patients with coronary stenosis <75% but ≥50% luminal narrowing diagnosed by coronary computed tomography angiography, further stress test is advised. For severe coronary lesions (≥75% luminal narrowing in major epicardial arteries or ≥50% luminal narrowing in the left main trunk), statin therapy is recommended. Statins could be considered in patients who have nonobstructed coronary atherosclerosis (<50% luminal narrowing) in view of the robust evidence supporting statin effect on coronary plaque volume and stability.

Recommendation

- The LDL-C target should be <70 mg/dL in stable CAD patients. (COR I, LOE B)
- Statin-benefit CAD included patients with history of ACS (>6 months), history of coronary revascularization, presence of ischemic symptoms with positive stress tests, or suspected ischemic heart disease by electrocardiography or echocardiography, or transcatheter angiographic diagnosis of significant coronary stenosis (≥50% luminal narrowing). (COR I, LOE B)
- Statin could be considered in patients who have nonobstructed coronary atherosclerosis (<50% luminal narrowing). (COR IIb, LOE C)

TG and HDL-C

The role of TG or HDL-C as a CV risk factor is still controversial. The *post hoc* analysis of the 4S study showed that lower baseline TG levels are associated with less major CV events (per 1 mmol/L reduction in TG: RR = −17.6%; 95% CI, −28.5 to −5.1) in the placebo arm.[88] For statin-treated CAD patients, some studies revealed that low HDL-C is a risk factor of major CV events, whereas higher TG has weak or no predicted value. For example, in the *post hoc* analysis of the statin arm in the 4S study, a significant RR by 0.8% was observed for each 1% increase in HDL-C, whereas there was no clear relationship with TG.[88] In the *post hoc* analysis of the TNT trial, the relationship between HDL-C and major CV events showed borderline significance ($p = 0.05$). In patients with LDL-C < 70 mg/dL, those in the highest quintile of HDL-C were at less risk for major CV events than those in the lowest quintile ($p = 0.03$).[89] Results from clinical trials with

TG-lowering/HDL-C-raising drugs in stable CAD patients were inconsistent, with a neutral effect of benzafibrate in the BIP study[51] and a positive effect of gemfibrozil in the HIT study.[50] Recent clinical trials all failed to show benefit of add-on TG-lowering/HDL-C-raising drugs on top of statin. Taken together, the prognostic role of HDL-C and TG in CAD patients with or without treatment with statin is controversial. The recommendations for TG or HDL-C intervention in CAD patients are the same as those in ACS patients.

Peripheral arterial disease

PAD is a manifestation of systemic atherosclerosis and is associated with an increased CV risk. PAD patients often have other comorbidities, and physicians should be alert of the coexisting CAD.[90,91] Weak or absent pulse is usually found during physical examination. The first-line diagnostic tool is ankle-brachial index (ABI). PAD is suspected when ABI is $\leq$0.90. ABI values of 0.91–0.99 are considered "borderline," and values >1.40 indicate noncompressible arteries. PAD is graded as mild to moderate if the ABI is between 0.41 and 0.90, and an ABI <0.40 is suggestive of severe PAD. Doppler ultrasound examination can be arranged to look at the site and extent of atherosclerosis. For further PAD diagnosis, computerized tomography, magnetic resonance angiography, or invasive angiography are widely used imaging techniques.

The data of PAD patients in the HPS trial showed that treatment with simvastatin (40 mg daily) reduced the rate of major vascular events by nearly 25% and also reduced the rate of peripheral vascular events by 16%, mainly because of reduction of noncoronary revascularizations, including amputations.[92] Simvastatin treatment reduced the rate of first major vascular events in patients with PAD without preexisting CAD, and the risk reduction was independent of the severity of preexisting PAD. The 4S trial demonstrated a 38% risk reduction of new or worsening intermittent claudication in the simvastatin group versus the placebo group, over a follow-up period of 5.4 years.[93] The other two studies showed that simvastatin treatment could improve total walking distance and pain-free walking distances in PAD patients.[94,95] Atorvastatin could also improve the symptomatology of patients with PAD. Atorvastatin (10 mg/d or 80 mg/d) was compared with the placebo group, and the pain-free walking distance improved by 63% in the 80 mg atorvastatin treatment group.[96] A meta-analysis including 17 lipid-lowering trials found 26% risk reduction of CV events in PAD patients treated with statins.[97] Although a number of lipid-lowering drugs were assessed, the most consistent benefits were shown by statins. Lipid-lowering therapy also improved PAD symptoms by increasing walking distance and alleviating claudication.

The data of nonstatin lipid-lowering drugs in PAD patients are rare. A study evaluated the effect of benzafibrate on CV events in patients with PAD. Benzafibrate reduced TG by 23.3% and LDL-C by 8.1%; it also increased HDL-C by 8%. However, benzafibrate treatment did not exert any benefit in the incidence of CAD and stroke.[98] The other study evaluated the evolution of atherosclerotic plaques in the superficial femoral artery by using magnetic resonance imaging in PAD patients treated with statin or statin plus ezetimibe. Statin therapy, with or without ezetimibe, could stop the progression of atherosclerosis, but adding ezetimibe to patients previously treated only with statin led to a progression of peripheral atherosclerosis, despite a 22% decrease in LDL-C.[99] Taken together, the benefit of nonstatin lipid-lowering drug in PAD patients is controversial. Overall, the treatment targets for patients with ACS, stable CAD, or PAD are summarized in Table 7.

Recommendation

- ABI measurement is recommended to identify PAD in patients with multiple risk factors. (COR IIa, LOE C)
- The LDL-C target in PAD should be <100 mg/dL and optimally <70 mg/dL if there is coexisting CAD. (COR IIa, LOE C)

Ischemic stroke and transient ischemic attack

TC/LDL-C and stroke risk

Observational studies have shown that higher TC and LDL-C are associated with increased risk of ischemic stroke.[100,101] In the Asia Pacific Cohort Studies Collaboration from 25 countries including 352,033 participants, every 1 mmol/L increase in TC had a 25% increase in ischemic stroke, a 45% increase in fatal or nonfatal MI, and a 20% decrease in fatal intracranial hemorrhage (ICH).[100] In a meta-analysis of 61 prospective observational studies, TC was positively associated with ischemic heart disease mortality in both middle and old age, but was only weakly associated with ischemic and total stroke mortality in middle age (40–59 years).[102] Ischemic stroke is a heterogeneous disease, and the association of lipids with ischemic stroke may vary by its subtypes.[103] The studies in Japan showed that elevated levels of TC or LDL-C were associated with increased risk for atherothrombotic infarction, but not for cardioembolism and lacunar infarction.[104,105] On the

Table 7 LDL-C targets in ACS, CAD, and PAD.

Disease category	LDL-C target
Primary target	
ACS	LDL-C < 70 mg/dL
ACS + DM	LDL-C < 55 mg/dL can be considered
Stable CAD	LDL < 70 mg/dL
PAD	LDL < 100 mg/dL
PAD + CAD	LDL < 70 mg/dL
Secondary target	
ACS, stable CAD, PAD with TG >200 mg/dL	Non-HDL-C < 100 mg/dL

ACS = acute coronary syndrome; CAD = coronary artery disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral arterial disease; TG = triglyceride.

contrary, lower TC and LDL-C were associated with increased risk of ICH.[106,107] A meta-analysis of 23 prospective studies including 1,430,141 participants showed that there is an inverse relationship between TC and ICH (OR = 0.85 per 1 mmol/L increment; 95% CI, 0.80—0.91), and less significant relationship between LDL-C and ICH (OR = 0.90; 95% CI, 0.77—1.05).[108]

Statins in stroke prevention

In a meta-analysis of 24 randomized trials, statin treatment has primary stroke risk reduction of 0.81 (95% CI, 0.75—0.87), and by metaregression analysis, every 1 mmol/L LDL-C reduction can decrease the risk of stroke by 21.1% and a 10% LDL-C reduction can decrease the risk of stroke by 7.5%.[109] Another meta-analysis including 27 trials showed that statin therapy has 15% risk reduction of stroke per 1 mmol/L LDL-C reduction.[38] An observation study in Taiwan also showed statin reduced risk of recurrent ischemic stroke in diabetic patients.[110] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was the only trial dedicated to evaluate statin in secondary stroke prevention. This trial randomized 4731 patients with recent stroke or transient ischemic attack (TIA), baseline LDL-C 100—190 mg/dL, and no known CAD history to receive atorvastatin (80 mg/d) versus placebo.[111] Over a median follow-up of 4.9 years, atorvastatin was associated with 2.2% absolute risk reduction of recurrent stroke (HR = 0.84; 95% CI, 0.71—0.99) and 3.5% absolute risk reduction of major CV events (HR = 0.80; 95% CI, 0.69—0.92). The benefit of statin on stroke risk reduction was similar across age, sex, and stroke subtypes.[112] The SPARCL trial found a higher incidence of ICH in the statin arm (2.3% vs. 1.4%; HR = 1.66; 95% CI, 1.08—2.55). The risk of ICH linked to statin was associated with hemorrhagic stroke as the entry event and old individuals.[113] A meta-analysis of 31 randomized trials showed statin did not increase ICH, and the occurrence of ICH was not related to LDL-C level.[114] One analysis from Taiwan's National Health Insurance database also showed that there was no association between cumulative statin use and ICH occurrence in individuals without stroke history.[115]

Recommendation

- For patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, intensive statin therapy is recommended. The goal of LDL-C < 100 mg/dL is suggested. (COR I, LOE A)
- For patients with stroke or TIA presumed to be of non-atherosclerotic origin, the benefit of intensive statin therapy is uncertain. (COR IIb, LOE C)

Statins in acute stroke

Beyond lipid-lowering effect, statins have pleiotropic anti-inflammatory activities and neuroprotective effects.[116] Early statin therapy after acute stroke may have beneficial effects of less stroke recurrence and better functional outcome. In contrast, statin discontinuation after stroke may be associated with increased risk of early neurological deterioration and poor outcome. A meta-analysis found that statin therapy at stroke onset was associated with better functional outcome and lower mortality at 90 days.[117] Another meta-analysis showed that prestroke statin use was associated with milder initial stroke severity, good functional outcome, and lower mortality; and statin withdrawal after acute stroke was associated with worse functional outcome.[118] In intravenous thrombolysis for acute ischemic stroke, a meta-analysis showed prior statin use was not associated with favorable outcome (OR = 0.99; 95% CI, 0.88—1.12), but was associated with an increased risk of symptomatic ICH (OR = 1.55; 95% CI, 1.23—1.95).[119]

From the Get With The Guidelines-Stroke Registry, ischemic stroke patients without prestroke statin use but discharged on statin therapy had lower risk of CV events, lower mortality and readmission, and no increased risk of hemorrhagic stroke in a 2-year follow-up.[120] Of 16,704 patients with acute ischemic stroke or TIA from the Taiwan Stroke Registry, lipid-lowering therapy during hospitalization was associated with a lower risk of recurrent stroke, ischemic heart disease, and death at 6 months after the stroke (HR = 0.78; 95% CI, 0.61—0.98).[121] However, only 38.7% of patients from Taiwan Stroke Registry with dyslipidemia received lipid-lowering drugs at discharge.[6] Data from the Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Registry also demonstrated that the use of lipid-lowering drugs and a target of LDL-C < 100 mg/dL for patients with cerebrovascular disease were still suboptimal in Taiwan.[122] A meta-analysis of 16 studies showed that pre-ICH statin use did not increase mortality, and had a better 3-month functional outcome as compared to no pre-ICH statin use.[123] One study from Taiwan National Health Insurance Research Database showed that ICH patients who had taken statins during hospitalization or within 3 months after discharge were associated with lower all-cause mortality and without increased recurrent ICH.[124]

Recommendation

- For patients with acute ischemic stroke or TIA, early initiation of statin therapy is recommended. (COR IIa, LOE B)
- For patients with acute ischemic stroke treated with thrombolysis, statin therapy prior to or after thrombolysis is safe and may be beneficial. (COR IIb, LOE B)
- For patients with acute ischemic stroke, hemorrhagic stroke or TIA, discontinuation of prestroke statin therapy is not recommended. (COR III, LOE C)

Other lipid-lowering drugs for stroke prevention

In a metaregression analysis of 64 randomized trials, an association was found between baseline TG levels and stroke risk (RR = 1.05 per 10 mg/dL increase; 95% CI, 1.03—1.07).[125] However, fibrates had no effect on decreasing stroke risk in another meta-analysis.[126] Niacin, fibrates, and CETP inhibitors can raise the HDL-C level. A meta-analysis showed there was no significant effect on stroke outcomes for niacin (OR = 0.96; 95% CI, 0.75—1.22), fibrates (OR = 1.01; 95% CI, 0.90—1.13), or CETP inhibitors (OR = 1.14; 95% CI, 0.90—1.45).[127]

Carotid stenosis

Statins can stabilize carotid plaque, decrease plaque inflammation, and reduce carotid atherosclerotic progression. Over the past two decades, the annual stroke rate due to asymptomatic carotid stenosis has decreased significantly from 2% to 4% to <1%, which was largely attributed to improvement in medical management, including increased statin use.[128] A meta-analysis including 21 trials with 6317 individuals showed that statin therapy was associated with regression of common carotid artery intima-media thickness (pooled weighted mean difference between statin vs. placebo −0.029 mm; 95% CI, −0.045 to −0.013) by ultrasonography.[129] For asymptomatic carotid stenosis, other ASCVD is common and long-term mortality is high. In a review of 17 studies including 11,391 asymptomatic carotid artery stenosis patients, the 5-year all-cause mortality was 23.6%.[130] Treatment with statins improved long-term survival in patients with carotid stenosis.[131] In a subgroup analysis of patients with carotid stenosis from the SPARCL trial, high dose statin treatment was associated with a 33% risk reduction of stroke (HR = 0.67; 95% CI, 0.47−0.94).[132]

Recommendation

- For patients with symptomatic carotid stenosis, aggressive medical therapies with antiplatelet, blood pressure and lipid control, and other risk factor modifications are recommended. The goal of LDL-C < 100 mg/dL is suggested. (Class I, LOE A)
- For patients with asymptomatic carotid stenosis and clinical evidence of other ASCVD, aggressive medical therapies with antiplatelet, blood pressure and lipid control, and other risk factor modifications are recommended. The goal of LDL-C < 100 mg/dL is suggested. (Class IIa, LOE B)
- For patients with asymptomatic carotid stenosis and without clinical evidence of other ASCVD, lipid control could be considered. (COR IIb, LOE C)

Intracranial arterial stenosis

Intracranial arterial stenosis (ICAS) is an important cause of ischemic stroke, especially in Asian populations.[133,134] Patients with symptomatic ICAS have high risk of recurrent stroke. In the Warfarin−Aspirin Symptomatic Intracranial Disease (WASID) trial, 569 patients who had stroke or TIA attributed to ICAS 50−99% were randomized to receive warfarin (international normalized ratio 2−3) versus aspirin (1300 mg/d). After a mean follow-up of 1.8 years, 22.1% in the aspirin group and 21.8% in the warfarin group developed stroke or died (vascular death) ($p = 0.83$).[135] The WASID study highlighted the importance of risk factor control in prevention of recurrent stroke in patients with ICAS. Patients with LDL-C ≥ 100 mg/dL had higher risk of recurrent stroke compared with those with LDL-C < 100 mg/dL (HR = 1.72, $p = 0.03$), and patients with systolic blood pressure (SBP) ≥ 140 mmHg also had higher risk of recurrent stroke compared with patients with mean SBP < 140 mmHg (HR = 1.63, $p = 0.01$).[136] In a randomized trial conducted in Hong Kong to evaluate the effects of simvastatin (20 mg/d) on the progression of middle cerebral artery stenosis in 114 stroke-free individuals over 2 years, the results showed there was no apparent effect on the evolution of asymptomatic middle cerebral artery stenosis.[137] Another study in Taiwan showed atorvastatin (40 mg/d) resulted in regression in more than half of symptomatic ICAS patients, but there was no control group for comparison.[138] In the Trials of Cilostazol in Symptomatic intracranial arterial stenosis-2 (TOSS-2) study including 409 patients, lipid levels or statin use did not predict progression or regression of ICAS.[139]

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial compared stenting plus aggressive medical management versus aggressive medical management only in patients with TIA or stroke within 30 days attributed to ICAS 70−99%.[140] Aggressive medical therapy consisted of aspirin (325 mg/d), clopidogrel (75 mg/d) for 90 days after enrollment and intensive risk factors management that targeted SBP < 140 mmHg (<130 mmHg in patients with DM), LDL-C < 70 mg/dL, non-HDL-C < 100 mg/dL, and hemoglobin $A1_C$ < 7% in DM with a lifestyle modification program. This trial was stopped prematurely after 451 patients had been randomized because the 1-month stroke or mortality in the stenting group was significantly higher than that in the medical group (14.7% vs. 5.8%, $p = 0.002$). The event rate in the medical arm of SAMMPRIS was much better than that projected based on WASID trial, which may be explained by the differences in the intensity of medical management, including dual antiplatelet therapy for the first 3 months, aggressive blood pressure and LDL-C control, and a lifestyle program. After extending the follow-up time to 32.4 months, the SAMMPRIS cohort still demonstrated persistence of the early benefit of medical management over stenting.[141] A *post hoc* analysis of factors associated with recurrent ischemic stroke in the medical arm included old infarct in the territory, stroke as the qualifying event, and no statin use at enrollment (HR = 2.4; 95% CI, 1.1−5.2).[142]

Recommendation

- For patients with stroke or TIA attributable to ICAS 50−99%, intensive lipid and blood pressure control is recommended. The goal of LDL-C < 100 mg/dL is suggested (COR I, LOE B).
- For patients who have asymptomatic ICAS (>50%) and clinical evidence of other ASCVD, aggressive medical therapy, including antiplatelets, blood pressure, and lipid control, is recommended. The goal of LDL-C < 100 mg/dL is recommended (Class IIb, LOE C).
- For patients with asymptomatic ICAS (>50%) and without clinical evidence of other ASCVD, lipid control could be considered (Class IIb, LOE C).

Diabetes mellitus (DM)

Diagnosis

DM refers to a group of metabolic disorders characterized by the presence of hyperglycemia that results from insulin deficiency, insulin resistance, or both. Chronic hyperglycemia

is associated with both microvascular and macrovascular complications. The current diagnostic criteria of DM[143] (Table 8) are based on the glucose level at which substantial microvascular complications, especially retinopathy, occur.[144–146] Those with abnormal glucose homeostasis but not yet fulfilling the diagnostic criteria of DM are termed prediabetes, including impaired fasting glucose and impaired glucose tolerance (IGT) (Table 8).[143] Individuals with prediabetes are at high risk of developing diabetes and its complications.

Diabetic patients are frequently associated with dyslipidemia and ASCVD. Diabetic dyslipidemia is featured with increased serum TG, increased VLDL, decreased HDL-C, and increased small dense LDL-C. The risk of CV disease appears early in the course of dysglycemia and correlates with plasma glucose level.[147,148] However, because current diagnostic criteria are based on microvascular end points, macrovascular insults often present well before glucose level elevates to diabetic range.[149] Because plasma glucose concentration distributes over a continuum, it would not be surprising that both prediabetic and diabetic patients are at increased risk of CV disease.[147,148] Aggressive management for lipid disorder and other risk factors has been proven to reduce macrovascular complications in these patients. Comprehensive assessment and treatment of dyslipidemia in diabetic patients are recommended, and it may be prudent to apply the same principles to prediabetic patients as well. Intensive lifestyle intervention is simple and cost-effective and should always be incorporated into dyslipidemia treatment plans.

Table 8 Diagnostic criteria for diabetes mellitus and prediabetes.

Diabetes Mellitus	FPG $\geq$ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.[a] OR 2-h PG $\geq$ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a] OR A1C $\geq$ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.[a] OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L).
Prediabetes	FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG) OR 2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT) OR A1C 5.7 − 6.4% (39 − 46 mmol/mol)

DCCT = Diabetes Control and Complications Trial; FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NGSP = National Glycohemoglobin Standardization Program; OGTT, oral glucose tolerance test; PG = plasma glucose.

[a] In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Recommendation

- For DM and prediabetes patients, complete lipid profile (TC, TG, LDL-C and HDL-C) should be measured. (COR I, LOE A)

Lifestyle intervention for diabetic dyslipidemia

Lifestyle intervention is essential in the management of hyperglycemia and dyslipidemia in diabetes. It includes participating in an intensive diet counseling program, increasing moderate-intensity physical activity, and targeting a loss of 7% of body weight in obese individuals.[150] Intensive diet programs should focus on reducing saturated fat, cholesterol, and trans fat intake and increasing omega-3 fatty acids, plant sterols, and dietary fiber.[151–153] For diabetic patients, restricting saturated fat intake to <7% of total daily energy intake is recommended. Sugar control can also reduce plasma lipid levels in patients with very high TG and poor glycemic control. Medical nutrition therapy should be individualized according to each patient's age, pharmacological treatment, lipid levels, and medical conditions. Physical activity also plays a crucial role to help diabetic patients improve their lipid profile and maintain weight loss.[154] Moderate to high levels of aerobic physical activity are associated with substantial reductions in CV morbidity and mortality.[155] Moderate-intensity physical activity (such as brisk walk) for a minimum of 150 min/wk is recommended. However, those previously sedentary individuals with limited exercise tolerance may have to build up their amount of exercise gradually. Starting with as little as 5–10 minutes per day may be more practical. In summary, intensive lifestyle intervention is simple, safe, and cost-effective and should always be incorporated into hyperlipidemia treatment plan for diabetic patients.

Pharmacologic intervention for diabetic dyslipidemia

Statin is the most widely used lipid-lowering agent and often the first choice for treatment of diabetic dyslipidemia because the primary target is to lower LDL-C. A meta-analysis of 14 randomized trials of statin therapy in 18,686 diabetic patients demonstrated that there was a 9% reduction in all-cause mortality and 21% reduction in major vascular events per mmol/L reduction in LDL-C. MI, coronary revascularization, and stroke were also significantly reduced.[156] Several studies have investigated the efficacy and safety of statins among patients with dysglycemia in Taiwan. In prediabetic patients, the risk of new-onset diabetes and the reduction of CV events and death after statin therapy were parallel (HR = 1.20; 95%

CI, 1.08–1.32 and HR = 0.7; 95% CI, 0.61–0.80, respectively). Therapeutic advantages outweighed diabetic consequences in patients with earlier and more persistent treatments.[157] The Pitavastatin and Atorvastatin double-blind randomized comparative study among high-risk patients, including those with Type 2 DM in Taiwan (PAPAGO-T Study) has shown that both pitavastatin (2 mg/d) and atorvastatin (10 mg/d) were well tolerated and improved the lipid profiles to a comparable degree in high-risk Taiwanese patients with hypercholesterolemia, which included the diabetic population. Hemoglobin A1c levels were significantly higher in the atorvastatin group but not in the pitavastatin group.[158] Lai et al[159] found that neither atorvastatin nor rosuvastatin was associated with a significant change of renal function in Type 2 DM patients. Moreover, compared with high potency statin alone, simvastatin/ezetimibe therapy was associated with lower risk of major adverse cardiac events in Type 2 DM patients.[160] In addition to LDL-C, Wang and Chang[161] showed that non-HDL-C was a reliable predictor for early vascular inflammation or atherosclerosis among Taiwanese patients with Type 2 DM who did not use anti-inflammatory agents. Tseng et al[162] found that TG level was independently associated with CAD in Taiwanese adults with Type 2 DM, but other lipid parameters (e.g., TC and LDL-C) were not. A meta-analysis study focusing on the Asia Pacific region (including Taiwan) also supported serum TG or lipid ratios as a better predictor for CHD than LDL-C.[163] These lines of evidence suggest that in Taiwan's diabetic population, the role of TG or non-HDL-C in CV risk appears to be as important as LDL-C.

Suggestions for treatment of diabetic dyslipidemia in Taiwan

According to the 2016 guidelines of the American Diabetes Association, nearly everyone with diabetes aged >40 years would be considered to initiate moderate- or high-intensity statin therapy. The measurement of on-treatment LDL-C is to be used only as an assessment of drug compliance and efficacy rather than as a target for treatment. After reviewing current lines of evidence and considering the local practicing behavior of most physicians, the target approach for diabetic dyslipidemia treatment is suggested in Taiwan. For DM patients with CV disease, the need for statin therapy is reinforced. For patients with DM who are ≥40 years of age, or who are <40 years of age but have additional CV risk factors, statin therapy is necessary. The LDL-C target for diabetic patients who do not have overt CV disease should be <100 mg/dL (primary prevention). For those with DM and concomitant CV disease, the LDL-C goal of < 70 mg/dL is considered (secondary prevention). If the above LDL-C targets are not reached on maximal tolerated statin therapy, a reduction of at least 30–40% in LDL-C levels is an alternative therapeutic target. Because TG and non-HDL-C also predict future CV events in Taiwanese studies,[161–163] targets for TG and HDL-C in diabetic patients are set as secondary target. The combination of other lipid-lowering agents with statin is reasonable to attain TG < 150 mg/dL and HDL-C > 40 mg/dL in men and >50 mg/dL in women after the LDL-C target has been achieved. The recommendations are summarized in Table 9.

Recommendation

- The LDL-C target for diabetic patients who do not have overt CV disease is <100 mg/dL. (COR I, LOE A)
- The LDL-C target for diabetic patients with overt CV disease is <70 mg/dL. (COR I, LOE B)
- If the above LDL-C targets are not reached on maximal tolerated statin therapy, a reduction of at least 30–40% in LDL-C levels is an alternative target. (COR IIa, LOE B)
- TG < 150 mg/dL and HDL-C > 40 mg/dL in men and >50 mg/dL in women should be the secondary target after the LDL-C target has been achieved. (COR IIa, LOE B)

Chronic kidney disease (CKD)

Definition and staging

CKD is prevalent in Taiwan and associated with an increased risk of CV morbidity and mortality.[164,165] According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline, glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for more than 3 months is the most commonly used diagnostic indicator of CKD. Early stage CKD (stage 1 or 2)

Table 9 Lipid recommendations for diabetic patients.

Recommended Target	Individuals who should be targeted for lipid modification	Risk assessment algorithm
LDL-C: - Without CVD: < 100 mg/dL - With CVD: < 70 mg/dL or 30–40% reduction TG < 150 mg/dL HDL-C: Men: > 40 mg/dL Women > 50 mg/dL	1. All diabetic patients aged ≥40 y 2. Diabetic patients aged <40 y who have overt ASCVD or ASCVD risk factors	ASCVD risk factors include: - High blood pressure - Smoking - Overweight and obesity - Family history of premature ASCVD

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.

refers to GFR $\geq$ 60 mL/min/1.73 m^2 and simultaneous identification of other markers of kidney damage that have been present for more than 3 months (Table 10). End-stage renal disease generally indicates CKD with GFR $<$ 15 mL/min/1.73 m^2 and requires regular hemodialysis, peritoneal dialysis, or kidney transplantation. Both equations of Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) can be adopted to estimate GFR in Taiwan.[166] In the population of GFR $\geq$ 60 mL/min/1.73 m^2, the CKD-EPI equation was reported with higher accuracy than the MDRD equation.[167]

CKD and dyslipidemia

Increased plasma levels of TG and decreased levels of HDL-C are frequently observed in the early stage of CKD,[168] and similar results were also found in T-SPARCLE registry in Taiwan.[169] This phenomenon can be explained by redistribution of cholesterol from HDL to VLDL and IDL as well as defective removal of TG from LDL and HDL particles. Other forms of Apos—Apo A-I, Apo A-II, and Apo C-III—also play an important role in CKD-associated dyslipidemia. Nephrotic dyslipidemia, which is characterized by elevation of plasma TC and LDL-C, also superimposes to CKD-related lipid disorders when proteinuria become prominent.[170,171]

Dyslipidemia is a risk factor to predict renal dysfunction in the general population. Elevated TC, non-HDL-C, a high ratio of TC/HDL-C, and low HDL-C are all significantly associated with an increased risk of developing renal dysfunction in large cohort studies.[172–175] Glomerulosclerosis due to macrophage infiltration and foam cell formation was proposed as the mechanism.[176] However, in the CKD population, dyslipidemia showed inconsistent results to predict renal outcome. In the MDRD study, lower HDL-C independently predicted a faster decline in GFR,[177] but from a large cohort study, none of TC, TG, VLDL-C, LDL-C, HDL-C, Apo A-I, Apo B, and lipoprotein (a) were independently associated with progression of kidney disease.[178] For CV outcome, higher LDL-C predicts increased risk of future CV events in the CKD population; however, this association attenuated at lower baseline GFR.[179] Other forms of dyslipidemia are not demonstrated to be a risk factor in large cohort studies of CKD.[180,181]

Table 10 CKD definition and stage.

CKD stage	GFR (mL/min/1.73 m^2)
Stage 1[a]	90
Stage 2[a]	60–89
Stage 3a	45–59
Stage 3b	30–44
Stage 4	15–29
Stage 5	<15

CKD = chronic kidney disease; GFR = glomerular filtration rate.

[a] CKD (stage 1 or 2) is referred to GFR $\geq$ 60 mL/min/1.73 m^2 and simultaneous identification of below findings: albuminuria ($\geq$30 mg/24 h), urine sediment abnormalities, electrolyte, and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities, history of kidney transplantation.

Recommendation

- Dyslipidemia is a risk factor of developing CKD in the general population. (COR I, LOE A)
- Use of dyslipidemia to predict progression of renal function in CKD population is uncertain. (COR IIa, LOE B)
- Higher LDL-C predicts increased CV risk in CKD population, but this association attenuates at lower baseline GFR. (COR I, LOE B)

Screen, follow-up, and lifestyle modification

Routine evaluation of lipid profile in adults with newly identified CKD is reasonable and supported by other guidelines.[182–184] Complete lipid profiles, including TC, TG, HDL-C, LDL-C, are all recommended to be checked. Non-HDL-C, Apo-B, and lipoprotein (a) are considered alternative risk markers, but are not recommended to be measured routinely.[185] Follow-up of lipid values is not necessary in most CKD patients. Repeat measurements of lipid values are warranted in patients who have poor adherence to statin treatment, who have changed in renal replacement method, or who potentially develop newly secondary dyslipidemia.[182,184] Individuals with established CV disease need follow-up of lipid values to achieve the ideal therapeutic target. Lifestyle changes, including exercise, weight reduction, and dietary modification, to improve the lipid profile may provide CV protective effects in the general population, but such effects are not proven in CKD patients. However, in patients with high TG levels, therapeutic life changes are still considered first-line management because of prevalent secondary risks: overweight, sedentary life, or cigarette smoking.[186,187]

Recommendation

- In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), complete lipid profile (TC, TG, LDL-C, HDL-C), evaluation is recommended. (COR I, LOE C)
- The benefits with lifestyle changes in CKD patients are uncertain (COR IIb, LOE B), except for those with elevated TG. (COR IIa, LOE C)

Treatment target in CKD

The treatment threshold of LDL-C is 100 mg/dL in CKD stage 3–5 population. This recommendation is mainly based on the SHARP and TNT studies.[39,188] If diabetes, MI, or stroke is identified, the threshold of LDL-C should be modified according to these comorbidities. Ten year risk of CAD in kidney recipients, estimated from ALERT study is approximately 21.5%.[189] Dyslipidemia is frequently observed in kidney transplant recipients. The Assessment of Lescol in Renal Transplantation (ALERT) study showed a significant benefit of the combined secondary end point of cardiac death or nonfatal MI in the fluvastatin treatment group (RR = 0.65; 95% CI, 0.48–0.88).[189] Statin therapy seems reasonable in all kidney transplant recipients who have decreased GFR and higher LDL-C.[184] Drug–drug interactions should be carefully observed in renal

transplantation recipients, especially those metabolized by cytochrome P450 system. There have been no large-scale, randomized clinical trials to investigate the best therapeutic target of LDL-C in CKD patients. In the 2007 Kidney Disease Outcomes Quality Initiative (KDOQI), the LDL-C target in patients with diabetes and CKD stages 1–4 is <100 mg/dL, and <70 mg/dL is a therapeutic option.[190] In the 2016 European Society of Cardiology (ESC) guidelines, moderate CKD (GFR 30–59 mL/min/1.73 m^2) carries high risk and the LDL-C < 100 mg/dL is the suggested target. Severe CKD (GFR < 30 mL/min/1.73 m^2) should be regarded as very high risk, and LDL-C < 70 mg/dL is the suggested target.[185] The 2013 KDIGO guideline and the 2013 ACC/AHA guidelines did not recommend the target level of LDL-C.[183,184] In the SHARP study with 9270 CKD patients, the average LDL-C reduction was about 30% by simvastatin and ezetimibe in CKD patients without dialysis.[39] In the Collaborative Atorvastatin Diabetes Study (CARDS) and Prospective Pravastatin Pooling (PPP) study, LDL-C reduction showed CV benefits by statin in diabetic patients with CKD.[191,192] The LDL-C reduction was about 40% in the CARDS study. Currently, no definite LDL-C target is suggested for CKD patients without dialysis in Taiwan. Epidemiological studies, meta-analyses and cohort studies all reported a better prognosis in nondialysis CKD patients with cholesterol-lowering medications.[39,188,193] Therefore, based on the body of evidence, moderate-intensity statins are suggested in CKD patients without dialysis if LDL-C ≥ 100 mg/dL. For dialysis patients, randomized controlled trials indicated that statin or statin/ezetimibe initiated during chronic dialysis provided no benefits in CV events reduction.[39,194,195] However, a meta-analysis including 31 randomized clinical trials still showed minor but significant effect of statin therapy on CV outcome in dialysis patients.[196] We suggest that, when nondialysis CKD patients are already under LDL-C lowering treatment and progress to dialysis-dependent, the medications could be continued without interruption. The treatment algorithm for CKD is shown in Fig. 3.

Considering statin side effects, statins metabolized by liver, such as fluvastatin, atorvastatin, pitavastatin, and ezetimibe, are safe choices in CKD patients. Low dose statin is suggested in stage 5 CKD patients (GFR < 15 mL/min/1.73 m^2). In the SHARP study, there were no differences between the simvastatin/ezetimibe and placebo groups regarding the incidences of muscle pain, increasing CK, hepatitis, gallstone, and pancreatitis.[39] In a rosuvastatin-based study, including 2776 patients with dialysis, there was no difference in the incidence of rhabdomyolysis between the rosuvastatin and placebo groups (0.2% vs. 0.1%, $p = 0.66$).[195]

Recommendation

- In adults with GFR < 60 mL/min/1.73 m^2 without chronic dialysis (CKD stages 3–5), stain therapy should be initiated if LDL-C ≥ 100 mg/dL. (COR I, LOE B)
- Moderate-intensity statin is recommended in CKD patients without dialysis. (COR IIa, LOE B)
- Statin therapy initiated in adults with dialysis-dependent CKD has not been proven to provide additional benefits. (COR III, LOE A)
- Ezetimibe can be added to statin to consolidate CV protection in CKD patients. (COR IIa, LOE B)
- In renal transplantation recipients with GFR < 60 mL/min/1.73 m^2, statin should be initiated if LDL-C ≥ 100 mg/dL. (COR IIa, LOE B)
- If carefully used, statins do not increase the incidences of rhabdomyolysis and abnormal liver function in CKD patients with or without dialysis. (COR IIa, LOE B)

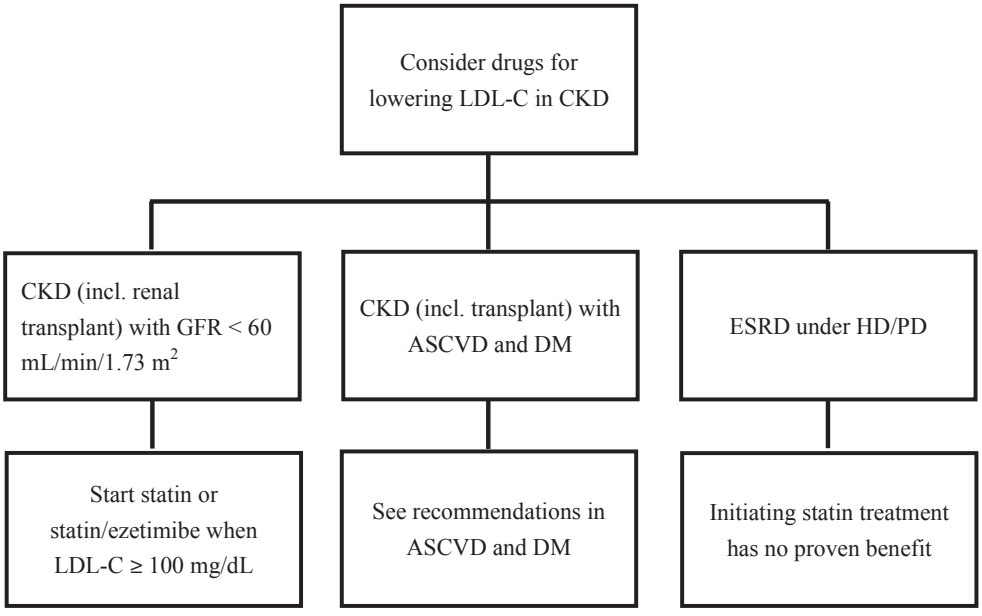

Figure 3 Algorithm for consideration of starting LDL-C lowering treatment in CKD. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HD = hemodialysis; LDL-C = low-density lipoprotein cholesterol; PD = peritoneal dialysis.

Familial hypercholesterolemia (FH)

Introduction

FH is an inherited disorder of lipoprotein metabolism, transmitted as autosomal codominant inheritance and characterized by elevated levels of LDL-C, presence of tendon xanthoma, and marked predisposition to premature CAD.[197,198] FH is known to be caused by mutations in three different genes, most commonly in the gene coding for LDLR, but mutations in Apo B gene, encoding the ligand of LDLR, cause a phenotypically identical condition. Mutations in a third gene, *PCSK9*, have more recently been reported to be involved in around 1% of FH cases. Patients can be heterozygous FH (HeFH) with one mutated allele. Individuals with HoFH may have two identical mutations (simple homozygous), two different mutations on the same gene (compound heterozygous), two different mutations on two different genes (double heterozygous), or two mutations in the autosomal recessive LDLR adaptor protein-1 (*LDLRAP1*) gene. Because the reduction of LDLR in HoFH is more pronounced than that seen in HeFH, cholesterol level is usually higher in HoFH than in HeFH.

The physical signs and symptoms of FH are characterized by accelerated atherosclerosis and the deposition of cholesterol. The physical signs of HoFH are generally more severe and occur earlier than in patients with HeFH. Atherosclerotic manifestations include vascular endothelial damage that produces premature CAD, PAD, and valvular disease (e.g., aortic stenosis). Deposition of cholesterol results in the development of cutaneous or tendonous xanthoma and corneal arcus. Xanthomas typically occur around the eyelids and extensor sides of tendons of the feet, hands, and elbows. The severe lipid abnormalities associated with HoFH result in accelerated CV disease, an increased risk of cardiac events, and early death. It is estimated that CV risk is increased by up to 20-fold in untreated patients and still elevated approximately 10-fold in patients receiving statins.[199–201] CV disease of FH patients occurs at an early age—typically prior to 20 years of age and as early as preteen years.[199,202] Young patients often have severe and widespread atherosclerosis in all major arterial beds, and there have been reports of acute MI and sudden death in patients as young as 4 years of age.[202] The CV risk is related to cumulative LDL-C exposure and is also related to the presence of other genetic or environmental risk factors. The effect of each risk factor is amplified in the setting of dramatically elevated cholesterol levels.

Epidemiology

The prevalence of HoFH is historically estimated to be approximately 1 in 1 million, but this data may underestimate the true prevalence rate of FH.[201] More recent studies based on surveys of unselected general populations found a prevalence of HeFH of 1 in ~200 in the general population and a prevalence of 6/1 million population in HoFH by extrapolation.[203] Accordingly, FH is the most common hereditary metabolic disorder worldwide. The prevalence of FH in Taiwan appears to be comparable to that in Western countries. Based on this estimation, there are about 100,000 or more FH patients in Taiwan. Founder mutations that reduce genetic variation can influence the prevalence in certain racial groups or geographic locations, resulting in increased prevalence in certain groups (e.g., French Canadian, South African Afrikaners).[204,205] A recent report showed that the detection rates of FH vary widely in different countries, and in general FH is vastly underdiagnosed in most countries including Taiwan.[201] Identification and early treatment of affected individuals is clearly desirable.

Genetics

It is known that mutations in three genes cause FH. These include mutations in the LDLR gene (*LDLR*, MIM # 606945), which lead to lack or defect of functional hepatic receptors for uptake of circulating LDL-C; mutations in the Apo B gene (*APOB*, MIM # 107730), which is the ligand for interaction with the LDLR; and mutations in the PCSK9 gene (*PCSK9*, MIM # 607786), which is involved in the degradation of LDLR protein.[197,198] Mutations in the LDLRAP-1 (*LDLRAP1*, MIM # 605747), which cause autosomal recessive hypercholesterolemia, are extremely rare. Autosomal recessive hypercholesterolemia is a loss-of-function mutation of LDLRAP-1, which inhibits the internalization of LDL ligand—receptor complex in hepatic cells, consequently leading to LDL-C degradation failure, and thus induces LDL-C elevation. So far, more than 1700 mutation sites have been identified worldwide (http://www.ucl.ac.uk/fh), of which 136 mutations have been reported in Han Chinese.[198] There are no special hot spot mutations in Chinese individuals. This pattern of diverse spectrum of disease-causing mutations of *LDLR* is commonly seen in most multicultural populations. Of the 136 different *LDLR* mutations identified, there are 134 point mutations and nine large rearrangements include insertion or deletion of *LDLR*. Five mutations were reported more frequently—APOB-R3500W (c. 10579C > T, 9.6%), LDLR-C308Y (c.986G > A, 8.3%), LDLR-H562Y (c.1747C > T, 6.5%), LDLR-A606T (c.1879G > A, 4.9%), and LDLR-D69N (c. 268G > A, 4.7%)—which together accounted for 34% of mutations found in the Han Chinese population.[198] Only one proband with *PSCK9* mutation, PCSK9-R306S (c.918C > T), has been reported in Han Chinese in China, but not in Taiwan.[206] HoFH can be simple homozygous (mutations in both alleles of the same gene) or, more commonly, compound heterozygous (different mutations in each allele of the same gene) or double heterozygous (mutations in 2 different genes affecting LDLR function).[201,203] The severity of HoFH depends on residual LDLR activity. Patients with HoFH are classified as either receptor-negative (i.e., < 2% residual activity) or receptor-defective (i.e., 2—25% residual activity).[203] As the clinical phenotype of FH is highly variable in terms of severity, diagnosing FH on the basis of clinical criteria alone are not very reliable and may overlook substantial proportion of FH. Genetic testing to identify functional mutations can provide unequivocal diagnosis.

Diagnosis

Clinically, patients with severe hypercholesterolemia, tendon xanthoma, and/or premature CV disease and family

history of hypercholesterolemia should be suspected of having FH. Taiwan FH diagnostic criteria, a modification of Dutch Lipid Clinic Network criteria and established by the Taiwan Society of Lipids and Atherosclerosis, is recommended for the diagnosis of FH in Taiwan (Table 11). The criteria take into account four areas to make the clinical diagnosis of FH, including family history, clinical history of premature CAD, physical examination of xanthoma or corneal arcus, and level of LDL-C. The diagnosis of FH is definite when the total scores exceed 8 points, probable for scores of 6—8 points, and possible for scores of 3—5 points. Patients who further meet the following three clinical symptoms, or positive for HoFH in genetic tests, can be diagnosed as having HoFH: (1) skin/tendon xanthoma, corneal arcus; (2) untreated LDL-C > 330 mg/dL and/or TC > 500 mg/dL; and (3) parents who have hypercholesterolemia (untreated TC > 250 mg/dL) or premature CAD. Genetic testing can confirm the diagnosis of FH and is helpful for familial cascade screening (i.e., identifying family members at risk), although it is not widely available and not routinely used in clinical practice. Such cascade screening is important because most patients identified via screening were not aware of the diagnosis and were therefore not receiving therapy.[207] The goal of familial cascade screening is to reduce morbidity and mortality for CV diseases by identifying FH patients in earlier age and also starting effective treatment earlier. All patients with FH should be assessed for other CV risk factors, as well as the presence of symptomatic or subclinical atherosclerosis.

Table 11 Taiwan FH diagnostic criteria.

Parameter	Points
Familial history	
First-degree relative with early vascular/coronary disease (male <45 y, female <55 y) OR Adult first-degree relative with LDL-C > 160 mg/dL	1
First-degree relative with xanthoma and/or corneal arcus OR First-degree relative <18 y with LDL-C > 130 mg/dL	2
Clinical history	
Patient with early coronary artery disease (male <45 y, female <55 y)	2
Patient with early cerebral or peripheral arterial disease (male <45 y, female <55 y)	1
Physical examination	
Xanthoma	6
Corneal arcus (<45 y)	4
Level of LDL-C (mg/dL)	
≥330	8
250—329	5
190—249	3
155—189	1
Genetic testing	
Presence of functional mutation of *LDL-R*, *ApoB-100*, or *PCSK9* gene	8
(Diagnostic of FH)	
Definite FH	>8 points
Probable FH	6—8 points
Possible FH	3—5 points

FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

Recommendation

- Patients with severe hypercholesterolemia, tendon xanthoma, and/or premature CAD should be screened for FH. (COR I, LOE C)
- Familial cascade screening should be performed for patients with FH. (COR I, LOE C)

Treatment

The primary target of treatment in FH patients is the reduction of LDL-C via a combination of lifestyle change, pharmacotherapy, or apheresis.[203,208] Because lipid-lowering therapy is associated with a delayed onset of CV disease and prolonged survival, early and aggressive therapy should be initiated as soon as possible.[200,203] Because of very high baseline LDL-C levels, achievement of target LDL-C is extremely difficult. As an initial goal, therapy should aim for >50% reduction of plasma LDL-C levels. In addition, in the absence of CAD or other major risk factors, an LDL-C treatment goal of <100 mg/dL is recommended, whereas a goal of <70 mg/dL is suggested for patients with CAD or diabetes. Statins effectively lower cholesterol around 50% in patients with HeFH and are the first line of pharmacotherapy. However, in patients with HoFH, lacking fully functioning LDLR, statins are not generally effective and reduce LDL-C only modestly (~20%). The addition of ezetimibe, an inhibitor of cholesterol absorption, to statins may further reduce LDL-C levels by 10—15%, while also reducing the incidence of CV events. Combining statins with other drugs, such as bile acid resins or niacin, may also lower LDL-C levels, but the use of these combinations may be limited by adverse events.

The inability of standard lipid-lowering therapies to produce the necessary effect is further exacerbated by the fact that these agents work by increasing expression of LDLRs. Thus, lipoprotein apheresis should be considered in all patients with HoFH and should be initiated early. Lipoprotein apheresis selectively removes LDL-C without affecting immunoglobulins or other proteins with reductions in LDL-C of approximately 60%.[209] However, a rapid rebound in LDL-C is seen with levels returning to baseline within 2—4 weeks. Although there are no randomized trials evaluating the effect of apheresis on clinical outcomes, there is clinical evidence that apheresis can contribute to regression and/or stabilization of atherosclerotic plaque.[203] Limitations to the use of apheresis include lack of availability in some locations, high cost, long procedure duration, and the need to maintain vascular access. It is recommended that patients on apheresis undergo routine monitoring to assess carotid atherosclerosis, progression of aortic valve/root disease, and progression of coronary atherosclerosis.[199]

Recommendation

- LDL-C targets in both HeFH and HoFH are <100 mg/dL in adults or <135 mg/dL in children. (COR I, LOE C)
- LDL-C < 70 mg/dL is recommended for both HeFH and HoFH patients with ASCVD. (COR I, LOE C)

New pharmacological therapies

Despite the availability and use of conventional pharmacotherapy, only a small proportion of patients with HoFH achieve the recommended LDL-C targets, underscoring the need for novel treatment options that decrease atherogenic LDL-C. Recently, three novel agents have become available as adjunctive treatment of FH—mipomersen, lomitapide, and PCSK9 inhibitor (evolocumab and alirocumab)—each with a unique mechanism of action. Two of these agents (mipomersen and lomitapide) target VLDL production, whereas the PCSK9 inhibitor causes increased catabolism of LDL-C via increased LDLR recycling.[203] Properties of these agents are summarized in Table 12. These agents produce additive LDL-C lowering when combined with other lipid-lowering therapies such as statins, ezetimibe, and apheresis, and represent promising approaches to the treatment of FH for those patients who cannot achieve LDL-C targets with conventional therapy.[203]

Mipomersen: Apo B is the primary protein of VLDL and LDL, and is essential for the production and catabolism of VLDL and LDL. Mipomersen is an antisense oligonucleotide against the mRNA of ApoB-100, the primary ligand for the LDLR.[210] The drug reduces Apo B mRNA translation, and thereby the synthesis of Apo B, resulting in a reduction of VLDL secretion. Mipomersen is indicated as an adjunct to lipid-lowering medications and diet to reduce TC, LDL-C, and Apo B in patients with HoFH. The phase III trial of mipomersen in patients with HoFH included 51 patients with clinical diagnosis or genetically confirmed HoFH.[211] The mean baseline LDL-C was 402 mg/dL. Patients who received maximally tolerated doses of lipid-lowering drug were randomized to receive mipomersen (200 mg) subcutaneously ($n = 34$) or placebo ($n = 17$) once weekly for 26 weeks. At 26 weeks, mipomersen-treated patients achieved significantly greater reductions in TC (−21.2%), LDL-C (−24.7%), and Apo B (−26.8%). In addition, mipomersen was also associated with substantial reductions in lipoprotein (a) (−31.1%) and a significant increase in HDL-C (+15.1%). Notably, there was substantial variability in the reduction of LDL-C concentrations among HoFH patients receiving mipomersen with values ranging from +2% to −82%. Common adverse events with mipomersen included flulike reactions, injection site reactions, and elevations in alanine aminotransaminase levels. Mipomersen was also associated with an increase in hepatic fat in 9.6% of patients compared with 0.02% of placebo-treated patients. Mipomersen carries a black box warning for the risk of hepatotoxicity, and the drug is only available in the United States via a Risk Evaluation and Mitigation Strategy program.[212]

Lomitapide: The microsomal triglyceride transfer protein (MTP) is an intracellular lipid-transfer protein located in the lumen of the endoplasmic reticulum. MTP is a major mediator of the assembly and secretion of Apo B-containing lipoproteins such as VLDL from the liver, and chylomicrons from the intestine.[213,214] The rare genetic condition, abetalipoproteinemia, is characterized by loss-of-function mutations in the gene encoding MTP (i.e., *MTTP*) and is associated with marked hypocholesterolemia and an absence of Apo B-containing lipoproteins in the plasma.[215] Lack of functional MTP in abetalipoproteinemia results in the inability to load Apo B with lipoproteins and the targeted proteasomal degradation of Apo B. This leads to a loss of intestinal secretion of chylomicrons and liver secretion of VLDL and a consequent lack of LDL-C in the plasma. Thus, inhibition of MTP is a potentially powerful therapeutic target to reduce the production of Apo B-containing lipoproteins, particularly VLDL, the precursor of LDL.[213] Lomitapide is a small molecule that inhibits MTP. By binding directly to MTP, lomitapide inhibits the synthesis of TG-rich chylomicrons in the intestine and VLDL in the liver, with a resulting reduction in plasma LDL-C.[216] Lomitapide is approved in Taiwan, United States, and Europe as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis, to reduce TC, LDL-C, and Apo B in patients with HoFH. The pivotal phase III open-label trial included 29 patients with HoFH.[217] Patients with HoFH was initiated at 5 mg/d and titrated at 4-week intervals up to a maximum of 60 mg/d. At the end of 26 weeks, patients achieved statistically significant reductions in TC (−46%; $p < 0.0001$) and LDL-C (−50%; $p < 0.0001$). Furthermore, eight patients achieved LDL-C < 100 mg/dL. Significant reductions from baseline were also seen for VLDL (−45%), non-HDL-C (−50%), TG (−45%), and

Table 12 Novel therapies for familial hypercholesterolemia.

Agent	Mechanism	Indication	Dosage and administration
Mipomersen	Oligonucleotide inhibitor of apolipoprotein B-100 synthesis	Adjunctive therapy in HoFH	HoFH: 200 mg s.c. once weekly
Lomitapide	Microsomal triglyceride transfer protein inhibitor	Adjunctive therapy in HoFH	HoFH: initiate at 5 mg/d, titrating to maximum of 60 mg/d
Evolocumab	PCSK9 inhibitor	Adjunctive therapy in HeFH and HoFH	HeFH: 140 mg s.c. every 2 wk or 420 mg s.c. once monthly HoFH: 420 mg s.c. once monthly
Alirocumab	PCSK9 inhibitor	Adjunctive therapy in HeFH	HeFH: 75—150 mg s.c. every 2 wk

PCSK9 = proprotein convertase subtilisin/kexin type 9; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; s.c. = subcutaneous.

Apo B (−49%). These reductions were maintained throughout the 52-week safety phase with reductions in TC (−35%) and LDL-C (−38%), respectively, despite changes in concomitant lipid-lowering therapy. The Lomitapide Observational Worldwide Evaluation Registry (LOWER) is a registry open to lomitapide-treated patients that is designed to evaluate the long-term safety and efficacy of lomitapide in clinical practice for at least 10 years.[218] Titration of lomitapide occurred slower than in the pivotal phase III trial, with a mean dose of 10 mg reached only after 12 months. The mean reduction in LDL-C at Month 4 was 42%, with 38% of patients achieving a reduction of at least 50% at 6 months.[218,219] Oral lomitapide was generally well tolerated in patients with HoFH. The most common adverse events were gastrointestinal in nature, manifested as diarrhea, nausea, dyspepsia, and vomiting, accumulation of liver fat and elevation of liver transaminases. In the LOWER registry, elevated transaminase levels ≥3-fold of the upper limit of normal were observed in 19% of patients.[219] The accumulation of fat appears to be reversible after discontinuation of lomitapide.[216] Whether this fat accumulation is a risk factor for the development of steatohepatitis and cirrhosis is currently unknown.

PCSK9 inhibitors: PCSK9 is a key regulator of LDLR function. PCSK9 binds and targets LDLR for degradation in lysosomes and prevents normal recycling of LDLR back to the cell surface, thereby increasing LDL-C plasma concentrations. Inhibition of PCSK9, by preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface, can get rid of LDL-C from circulation. Two PCSK9 inhibitors, both monoclonal antibodies, are now available for treatment of patients with FH. Evolocumab for treatment of both HeFH and HoFH, and alirocumab for HeFH only, were approved in 2015 by the U.S. FDA in combination with other lipid-lowering therapies. The phase III randomized, double-blind, placebo-controlled trial included 49 patients with HoFH on stable lipid-lowering therapy. Patients were randomized in a 2:1 ratio to receive evolocumab (420 mg) or placebo every 4 weeks.[220] The mean decrease in LDL-C was 23.1% for those receiving evolocumab compared with a 7.9% increase for the placebo group. Interestingly, one patient with LDLR-negative mutations in both alleles and one with autosomal recessive hypercholesterolemia did not respond to evolocumab.[220] The most common adverse events among those receiving evolocumab were upper respiratory tract infection, influenza, gastroenteritis, and nasopharyngitis, which were similar between treatment and placebo groups.[220] There were no adverse event-related treatment discontinuations.

FH and pregnancy

FH patients should be instructed to stop therapy with lipid-lowering agents other than bile acid resins at least 3 months prior to trying to become pregnant and during the lactation period after delivery. Those women who become pregnant should be counseled on intensive lifestyle modifications. LDL apheresis may be used in pregnant HoFH patients with LDL-C ≥ 300 mg/dL and LDL-C ≥ 190 mg/dL in the presence of CAD. Lomitapide is not recommended in HoFH patients during pregnancy because of concerns about fetal harm. There are no available safety data for the use of mipomersen in pregnancy.

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