Chinese expert consensus on blood lipid management in patients with diabetes (2024 edition)

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ABSTRACT

Diabetes is a significant independent risk factor for atherosclerotic cardiovascular disease (ASCVD), with dyslipidemia playing a critical role in the initiation and progression of ASCVD in diabetic patients. In China, the current prevalence of dyslipidemia in diabetes is high, but the control rate remains low. Therefore, to enhance lipid management in patients with diabetes, the Endocrinology and Metabolism Physician Branch of the Chinese Medical Doctor Association, in collaboration with the Experts' Committee of the National Society of Cardiometabolic Medicine, has convened experts to develop a consensus on the management of dyslipidemia in patients with type 1 or type 2 diabetes. The development of this consensus is informed by existing practices in lipid management among Chinese diabetic patients, incorporating contemporary evidence-based findings and guidelines from national and international sources. The consensus encompasses lipid profile characteristics, the current epidemiological status of dyslipidemia, ASCVD risk stratification, and lipid management procedures in diabetic patients. For the first time, both low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol have been recommended as primary targets for lipid intervention in diabetic patients. The consensus also includes a summary and recommendations for lipid management strategies in special diabetic populations, including children and adolescents, individuals aged 75 years and older, patients with chronic kidney disease, metabolic-associated fatty liver disease, and those who are pregnant. This comprehensive consensus aims to improve cardiovascular outcomes in diabetic patients by contributing to the dissemination of key clinical advancements and guiding clinical practice.

Key words: diabetes mellitus, type 1, type 2, dyslipidemia, atherosclerotic cardiovascular disease

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The prevalence of diabetes in China is on a continuous upward trend. From 2011 to 2021, the number of diabetic patients in China increased from 90 million to 140 million.[1] Diabetes poses a tremendous threat and is a significant independent risk factor for atherosclerotic cardiovascular disease (ASCVD), a common complication and the primary cause of death in diabetic patients. The prevalence of dyslipidemia is significantly higher in diabetic patients, especially those with type 2 diabetes mellitus (T2DM) than in nondiabetic populations.[2] Dyslipidemia is the primary risk factor for the occurrence, development, and progression of ASCVD.

For diabetic patients, the primary goal of dyslipidemia prevention is to reduce the risk of ASCVD. However, there is currently a lack of guidelines or consensus specific to dyslipidemia related to atherosclerotic risk in all diabetic populations (type 1 diabetes mellitus [T1DM] and T2DM patients, patients aged ≥ 40 years, and patients aged < 40 years). In recent years, a large number

of epidemiological and clinical intervention research results have been published, and related clinical research evidence continues to advance and accumulate. To better regulate the management of blood lipids in diabetic patients in China, the Endocrinology and Metabolism Branch of the Chinese Medical Doctor Association and the Cardiovascular Metabolism Committee of the National Cardiovascular Disease Expert Committee have brought together experts in the relevant fields to summarize domestic and international research progress and expert experience, and have formulated the Chinese Expert Consensus on Blood Lipid Management in Patients with Diabetes (2024 Edition). The evidence has been classified into Levels A, B, and C: Level A evidence is based on multiple randomized controlled trials or meta-analyses; Level B evidence is based on single randomized controlled trials or multiple nonrandomized controlled trials; and Level C evidence is based on expert consensus opinions, as well as small-scale research, retrospective research, and registry research results.

LIPID SPECTRUM CHARACTERISTICS AND CARDIOVASCULAR HARMS IN DIABETIC PATIENTS

Lipid spectrum characteristics of T2DM patients

Characteristics of dyslipidemia

The lipid spectrum of T2DM patients is mainly characterized by mixed dyslipidemia, including (1) fasting and postprandial hypertriglyceridemia and decreased levels of high-density lipoprotein cholesterol (HDL-C), (2) normal or slightly elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), and (3) changes in low-density lipoprotein (LDL) particle subtypes, with an increase in small dense low-density lipoprotein (sdLDL) particles.[3-5]

Main causes of dyslipidemia

The main cause of dyslipidemia in T2DM patients is the presence of insulin resistance and relative insulin deficiency, which increase levels of free fatty acids in the body. This process results in an increase in the substrates available for the liver to synthesize very LDL (VLDL) and a decrease in the activity of insulin-dependent lipoprotein lipase (LPL), reducing the clearance of VLDL. These chances ultimately lead to increased levels of triglycerides (TG) and TG-rich lipoproteins (TRL). Poor blood glucose control in diabetic patients tends to further elevate TG levels. Hypertriglyceridemia stimulates the activity of the cholesterol ester transfer protein, which significantly increases the exchange of TG and cholesteryl esters between TRL and LDL and high-density lipoprotein (HDL), leading to an increase in TG content and a decrease in cholesteryl esters in LDL and HDL particles. Subsequently, when the TG in LDL and HDL is hydrolyzed by LPL and hepatic esterase, the process not only promotes sdLDL generation but also accelerates HDL metabolism, thereby decreasing HDL-C levels.[6,7]

Lipid spectrum characteristics of T1DM patients

T1DM patients with poor blood glucose control

The dyslipidemia of T1DM patients is usually similar to that of T2DM patients, and is characterized by mixed dyslipidemia, which mainly involves fasting and postprandial hypertriglyceridemia, accompanied by decreased HDL-C levels and increased sdLDL levels.[8] T1DM often starts with diabetic ketoacidosis (DKA). During DKA, due to severe insulin deficiency, the condition can manifest as a significant increase in TG levels, accompanied by a decrease in HDL-C and LDL-C levels. These lipid abnormalities can be quickly restored with sufficient insulin treatment.

T1DM patients with good blood glucose control

Due to the long-term use of exogenous insulin, which leads to peripheral hyperinsulinemia, the resulting condition can cause an increase in LPL activity, normal or reduced TG levels, and normal or elevated HDL-C levels. Hyperinsulinemia may upregulate LDL receptors, thereby promoting the clearance of LDL, and LDL-C levels may decrease.[9] However, some studies have shown that even if T1DM patients have good blood glucose control, their sdLDL levels are still higher than those of the normal population.[8]

Dyslipidemia in diabetic patients and ASCVD risk

LDL-C Levels

Among the cardiovascular risks brought about by dyslipidemia in diabetic patients, LDL-C is recognized as the primary risk factor. In 2008, the United Kingdom prospective diabetes study (UKPDS) on T2DM patients showed that for every 1.0 mmol/L increase in LDL-C levels, the risk of coronary artery events increased by 57%.[10] In 2016, the diabetes control and complications trial (DCCT) study on T1DM patients also suggested that after correcting for risk factors, such as age and glycated hemoglobin (HbA1c), for every 0.56 mmol/L increase in LDL-C levels, the risk of major adverse cardiovascular events (MACE) in T1DM patients increased by 7%.[11] In addition to higher LDL-C levels, diabetic patients also demonstrate elevated sdLDL levels. Because sdLDL circulates in the blood for a long time, it is likely to enter and stay underneath the arterial intima, and is ultimately phagocytosed by macrophages to form foam cells. Therefore, sdLDL has a stronger atherogenic effect than LDL.

Non-HDL-C Levels

Clinical epidemiological studies have shown that high TG levels are closely related to atherosclerosis in diabetic patients, making it one of the main factors in residual cardiovascular risk.[11-13] Increased TG levels in diabetic patients reflect an increase in TRL particles and non-HDL-C levels, and non-HDL-C indicates cholesterol in all atherogenic lipoprotein particles. Previous studies have shown that non-HDL-C levels can better predict ASCVD risk than LDL-C levels.[14] A meta-analysis suggested that non-HDL-C levels are associated with cardiovascular disease risk in male and female T2DM patients with hazard ratio values of 1.98 (95% confidence Interval [CI]: 1.70-2.30) and 1.63 (95% CI: 1.35-1.96), respectively.[15]

EPIDEMIOLOGY OF LIPID ABNORMALITIES RELATED TO ASCVD IN DIABETIC PATIENTS

T2DM patients

The prevalence of lipid abnormalities in Chinese T2DM patients is higher than in the general population, while rates of awareness, treatment, and control of lipid abnormalities are low. Patients often do not receive adequate treatment due to a lack of noticeable symptoms. In the China cardiovascular and metabolic research network-3B (CCMR-3B) study assessing cardiovascular risk factors in Chinese T2DM patients, a survey of lipid abnormalities in 25,817 outpatient T2DM patients from 104 hospitals nationwide showed that 42% of T2DM patients had lipid abnormalities, of which only 55% received lipid-lowering treatment. The proportion of patients who met all four lipid criteria (TC < 4.5 mmol/L, TG < 1.5 mmol/L, LDL-C < 2.6 mmol/L, and HDL-C > 1.04 mmol/L) was only 12%, with TC, TG, HDL-C, and LDL-C control rates of 36.1%, 46.6%, 71.9%, and 42.9%, respectively.[16] Another cross-sectional study of 4,807 T2DM patients aged 40-75 years from endocrinology clinics in 20 tertiary hospitals in major cities nationwide showed that the proportion of lipid abnormalities was as high as 67.1%; among T2DM patients with lipid abnormalities, the rates of awareness and treatment were 68.7% and 55.9%, respectively, and the rates of achieving LDL-C (< 2.6 mmol/L) and non-HDL-C (< 3.37 mmol/L) targets were 39.4% and 35.9%, respectively.[17]

The results of several national multicenter studies conducted in China are generally unoptimistic about the prevalence and control of lipid abnormalities in T2DM patients (Supplementary Table 1). These patients should pay special attention to the overall management of blood lipids and intervene in lipid abnormalities early to prevent ASCVD.

In addition to the overall high prevalence of lipid abnormalities among T2DM patients in China, there are also regional differences that may be related to different levels of economic development, natural conditions, and lifestyle habits in various parts of the country. In the Northwest, the prevalence of lipid abnormalities in T2DM patients is higher than in other regions, likely due to relatively poor economic levels and accessibility of care in this region, which inhibit patients' health awareness, as well as factors such as high carbohydrate and high-fat diets.[18]

T1DM patients

Cardiovascular disease is one of the main causes of death in T1DM patients. A meta-analysis of 26 studies showed that compared with the nondiabetic population, the rates of death from coronary heart disease in male and female T1DM patients are 5.62 and 11.32 times higher than the standard, respectively.[19] Although ASCVD risk in T1DM patients is increasing, relatively few large-scale studies have been conducted on the prevalence, awareness, and treatment rates of lipid abnormalities in this population. A cross-sectional survey of 18,976 newly diagnosed diabetic patients in 24 of China's provincial administrative regions included 1158 adult T1DM patients. The results showed that 29.0% of newly diagnosed adult T1DM patients had TG > 1.7 mmol/L, 50.3% had LDL-C > 2.6 mmol/L, and 39.6% had abnormal HDL-C (men < 1.0 mmol/L; women < 1.3 mmol/L, Supplementary Table 1).[20]

ASCVD RISK STRATIFICATION AND TREATMENT GOALS IN DIABETIC PATIENTS

Cardiovascular risk assessment in diabetic patients

Since diabetes is an important independent risk factor of ASCVD, and lipid abnormalities have the greatest impact on ASCVD risk in diabetic patients, their lipid management target values are set more strictly than in nondiabetic populations. To emphasize lipid control in diabetic patients and assess ASCVD risk, it is recommended to divide diabetic patients into extremely high-risk, very high-risk, and high-risk groups (Table 1) according to the length of their disease course, whether they have ASCVD, and the condition of damage to the major target organ.

Lipid intervention targets and target values in diabetic patients

Lipid intervention targets

The lipid intervention targets and target values for diabetic patients are shown in Table 2.

Table 1: ASCVD risk stratification in diabetic patients[21]

Risk stratification	Evaluation indicators
Extremely high-risk	Concurrent ASCVD
Very high-risk	Without ASCVD, but with any of the following conditions: (1) ≥ 40 years old; (2) < 40 years old and with a long course of DM (T2DM course ≥ 10 years, T1DM course ≥20 years); (3) < 40 years old and with ≥ 3 risk factors*; (4) < 40 years old and with target organ damage△
High-risk	< 40 years old and absence of characteristics in the extremely high-risk and very high-risk group

ASCVD: atherosclerotic cardiovascular disease; T2DM: type 2 diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; CKD: chronic kidney disease. ASCVD refers to a clear diagnosis of coronary atherosclerotic cardiovascular disease, including past or current diagnosis of acute coronary syndrome (myocardial infarction or unstable angina), stable angina, or coronary artery revascularization (percutaneous coronary intervention, stent implantation, or coronary artery bypass grafting); a clear diagnosis of stroke and transient ischemic attack; and a clear diagnosis of peripheral arterial disease. *Risk factors include: (1) smoking; (2) hypertension; (3) obesity (body mass index ≥ 28 kg/m^2); (4) family history of early onset coronary heart disease (male < 55 years old; female < 65 years old); (5) non-HDL-C ≥ 4.9 mmol/L; (6) lipoprotein (a) ≥ 300 mg/L;[22,23] (7) high-sensitivity C-reactive protein ≥ 2.0 mg/L.[24,25] The risk factor levels stated here all reflect values before intervention. △Target organ damage includes CKD Stages 3b and above (estimated glomerular filtration rate < 45 mL/min/1.73 m^2), proteinuria (urinary albumin/creatinine ratio > 300 mg/g), an ankle-brachial index of < 0.9, and left ventricular systolic/diastolic dysfunction.

LDL-C

Most lipid-lowering intervention studies use LDL-C as an indicator to observe the relationship between lipid-lowering effects and decreased ASCVD risk. A meta-analysis by the Cholesterol Treatment Trialists' Collaboration showed that for each 1.0 mmol/L decrease in LDL-C, the risks of MACE, cardiovascular death, and ischemic stroke in diabetic patients decreased by 21%, 13%, and 21%, respectively, regardless of baseline LDL-C levels.[29]

Several clinical studies have shown that T2DM patients aged 40-75 can benefit from taking statin drugs. In primary prevention studies, compared with placebos, moderate-intensity statins can significantly reduce the risk of ASCVD or all-cause death by lowering LDL-C to less than 2.6 mmol/L.[30,31] T2DM patients with multiple ASCVD risk factors or target organ damage are considered to have ASCVD. It is recommended that LDL-C be reduced by more than 50% from baseline for these diabetic patients, and the LDL-C target value should be set at less than 1.8 mmol/L.[32-34] In secondary prevention studies, stratified analysis of several intensified lipid-lowering studies that used statin drugs in combination with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors showed that reducing LDL-C to below 1.4 mmol/L can further reduce ASCVD risk among T2DM patients and that ASCVD patients with T2DM can benefit significantly from intensified lipid-lowering treatment.[26-28]

Lipid-lowering interventions for T1DM patients are currently understudied. In the heart protection study (HPS), the benefits of statin treatment in T1DM patients over 40 years old were found to be similar to those in T2DM patients,[30] so it is recommended that the lipid-lowering targets and target values for T1DM patients be the same as those for T2DM patients.

Clinical evidence for the cardiovascular benefits of lipid-lowering treatment for T2DM and T1DM patients under 40 years of age is also scarce. Considering that, despite the low 10-year cardiovascular risk for diabetic patients under 40 years old, the lifetime risk is high, the LDL-C of diabetic patients under 40 years old should also be maintained at a lower level. At this time, the course of diabetes, other cardiovascular risk factors, and the condition of damage to the target organ should be considered comprehensively. Statin treatment should be initiated in a timely manner after a thorough discussion of treatment risks and benefits.[35,36]

Non-HDL-C

Using only LDL-C as a lipid-lowering target for diabetic patients may lead to underestimating ASCVD risk, and non-HDL-C is also a primary lipid-lowering target that diabetic patients must manage. Non-HDL-C is the cholesterol in plasma TC minus the cholesterol in HDL, which represents the cholesterol in all atherogenic lipoprotein particles. Whether or not statin therapy is administered, non-HDL-C reflects ASCVD risk better than LDL-C.[14,37,38] A meta-analysis found that the correlation between the reduction of both non-HDL-C and lowered ASCVD risk was stronger than that between the reduction of LDL-C and lowered ASCVD risk.[39] Currently, the Friedewald formula is widely used to calculate LDL-C levels; however, when plasma TG > 4.5 mmol/L or LDL-C < 1.8 mmol/L, this method faces certain challenges.[40,41] Since lipid abnormalities in diabetic patients are characterized by hypertriglyceridemia, using LDL-C as the primary target has certain limitations. Calculating non-HDL-C is simple, and the results are stable and minimally affected by plasma TG levels. Therefore, along with LDL-C, non-HDL-C is suitable for use as a primary lipid-lowering target for diabetic patients.

Apolipoprotein B (ApoB)

Regardless of particle size, all atherogenic lipoprotein particles contained one molecule of ApoB. Theoretically, ApoB detection more accurately reflects the number

of atherogenic lipoprotein particles. Diabetic patients are prone to hypertriglyceridemia, a condition in which ApoB content is high but LDL-C levels not reach the high threshold. Therefore, simultaneous measurement of ApoB and LDL-C levels is a useful method for assessing ASCVD risk in diabetic patients.[14,39] Recent studies on more intense lipid-lowering methods suggest that after controlling for the effects of LDL-C and non-HDL-C, reducing ApoB can independently predict a decrease in ASCVD risk.[42] ApoB testing is currently expensive and not widely used in clinical contexts; thus, it should be considered a secondary target for ASCVD risk interventions in diabetic patients.

Potential Lipid-Modifying Targets

Abnormalities in TG, lipoprotein (a) (Lp [a]), and HDL-C are all associated with an increased ASCVD risk. However, there is currently a lack of strong evidence to support drug intervention based on these lipid indicators as a means of reducing ASCVD risk. Therefore, they may be potential lipid-modifying targets for ASCVD risk management in diabetic patients and require clinical attention.

TG

Hypertriglyceridemia is common in diabetic patients. Most plasma TG is located in the TRL, and diabetic patients show an increase in remnant cholesterol and non-HDL-C levels. For this reason, a mild to moderate increase in TG levels increases the risk of ASCVD. Increased TG levels and increased remnant cholesterol in TRL are risk factors for myocardial infarction.[43] Lifestyle interventions and optimized hypoglycemic drugs can reduce the TG levels and ASCVD risk of diabetic patients,[44-47] but controversy remains over whether lipid-lowering drugs targeting TG (*e.g.*, fibrates, niacin, and prescription fish oil preparations) can reduce the risk of MACE in high-risk ASCVD diabetic patients.[48-53] Therefore, TG is currently recommended solely as a potential indicator of ASCVD risk in diabetic patients.

Lp (a)

In T2DM patients, elevated Lp (a) levels are independent risk factors for coronary heart disease and ischemic stroke.[32,54-56] For diabetic patients with stable angina, elevated Lp (a) levels significantly increase the risk of MACE.[57] It is recommended that adults have their Lp (a) levels checked at least once in their lifetime.[32,54-56] Based on research data obtained from Chinese populations,[57-62] it is suggested that Lp (a) > 300 mg/L be used as a cutoff value for increased ASCVD risk.[63]

HDL-C

One of the characteristics of lipids in diabetic patients is a reduction in HDL-C levels. Although low HDL-C levels are independent risk factors for ASCVD, the predictive effect of HDL-C on coronary heart disease is influenced by HDL function, and HDL function predicts ASCVD risk better than HDL-C levels. Moreover, genetic evidence has not yet proven a relationship between HDL-C levels and ASCVD risk, and treatment to raise HDL-C levels via medication has not resulted in cardiovascular event risk reduction. Therefore, HDL-C has not been included in lipid intervention targets for ASCVD risk management and is used only as a management indicator.[32,64]

LIPID-LOWERING TREATMENT STRATEGIES FOR DIABETIC PATIENTS

The lipid-lowering standardization strategy for diabetic patients also includes lifestyle interventions and drug treatment. Specific recommendations are shown in Table 3.

Lifestyle intervention

For T1DM and T2DM patients, lifestyle intervention is the foundation of lipid management. In addition to lowering lipid levels, lifestyle changes also benefit blood pressure, blood sugar, and overall cardiovascular health. Healthy, well-regulated lifestyle interventions are discussed below.

Healthy Balanced Diet

Limiting one's intake of total fat, cholesterol, trans fatty acids, and saturated fatty acids is an important measure for preventing hyperlipidemia and ASCVD.[36,73,86] Dietary fat intake should not exceed 20%-30% of total daily calories, and saturated fatty acid intake should not exceed 10% of total daily calories. Diabetic patients with high cholesterol should minimize their intake of saturated fatty acids to less than 7% of total daily calories, avoid cholesterol-rich food (*e.g.*, animal offal), and limit their daily cholesterol intake to less than 300 mg. Trans fatty acids (*e.g.*, hydrogenated vegetable oils) should account for less than 1% of total daily calories (i.e., not exceeding 2 g/day. The intake of unsaturated fatty acids (*e.g.*, vegetable oils), especially foods rich in ω-3 polyunsaturated fatty acids, should be increased.[87]

Adopting the mediterranean diet,[88] the dietary approaches to stop hypertension diet, or other dietary patterns that increase the consumption of vegetables, fruits, coarse fiber foods, and fish rich in ω-3 fatty acids is recommended. Dietary fiber intake should be no less than 25-30 g/day or 14 g/1000 kcal, and it is recommended to consume 35 g/day. The proportion of carbohydrates and proteins should be the same as for ordinary diabetic patients. In addition to limiting fatty acid intake, patients with high TG levels should pay particular attention to reducing the intake of refined carbohydrates and increasing the intake of fiber-rich, low-sugar foods (*e.g.*, whole grains).

Table 2: Recommended targets and target values of lipid intervention in diabetic patients

Recommendations	Recommendation level
LDL-C and non-HDL-C are both primary lipid-lowering targets for ASCVD risk control	Level A
For extremely high-risk patients, the LDL-C goal is < 1.4 mmol/L, and it should be reduced by > 50% from baseline[26-28]	Level A
For very high-risk patients, the LDL-C goal is < 1.8 mmol/L, and it should be reduced by > 50% from baseline[29]	Level A
For high-risk patients, the LDL-C goal is < 2.6 mmol/L	Level A
The non-HDL-C target value is the corresponding LDL-C target value + 0.8 mmol/L	Level B
ApoB can be used as a secondary target for ASCVD risk control in diabetic patients. For extremely high-risk, very high-risk, and high-risk patients, the ApoB target values are less than 0.7, 0.8, and 0.9 g/L respectively	Level C

LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease; ApoB: apolipoprotein B.

Moderate exercise

At least 150 min of moderate-intensity exercise should be conducted weekly according to individualized exercise prescriptions. Those advised to lose weight should increase their current weekly exercise intensity and duration. However, exercise is not suitable when fasting blood glucose is higher than 16.7 mmol/L, in cases of recurrent hypoglycemia or large fluctuations in blood glucose, acute complications such as DKA, concurrent acute infections, proliferative retinopathy, severe kidney disease, and severe cardiovascular and cerebrovascular diseases (*e.g.*, unstable angina, severe arrhythmia, or transient ischemic attack). It is recommended to gradually resume exercise once the condition stabilizes.[73]

Maintain ideal weight

It is recommended to control total calorie intake and increase exercise to maintain a body mass index of < 24 kg/m^2. For those who are overweight or obese, the recommended initial weight loss goal is a 5%-10% reduction in body weight in 3-6 months. Those who are underweight should restore and maintain their ideal weight over the long term through a reasonable nutritional plan.[73]

Controlling other risk factors

It is recommended that smokers quit smoking (including e-cigarettes). Those without a habit of drinking are advised not to start drinking, and those with a habit of drinking should limit alcohol intake (men < 25 g/day; women < 15 g/day). Alcohol consumption plays a significant role in increasing TG, and those with high TG should strictly limit alcohol intake.

In summary, regardless of the type of lipid abnormality, maintaining a healthy, balanced diet is recommended as a lifestyle intervention. For patients who need to better control TC and LDL-C, regular exercise and weight control are suggested on the basis of a healthy diet. It is recommended that patients who need to increase HDL-C should quit smoking and those who need to lower TG should limit alcohol consumption, exercise regularly, and manage their weight.[68]

Cholesterol-lowering drug treatment strategy

Although healthy lifestyle interventions are the foundation of lipid-lowering treatment for all adult diabetic patients, it is often difficult to reach lipid-lowering targets through lifestyle interventions alone. Therefore, it is recommended that drug treatment be initiated alongside lifestyle interventions to achieve lipid-lowering targets as early as possible, thereby reducing the risk of ASCVD events.

The cholesterol-lowering treatment strategy and process for diabetic patients are shown in Figure 1. Cholesterol-lowering drugs can be divided into three major categories according to their mechanisms: statins, cholesterol absorption inhibitors, and PCSK9 inhibitors. Other cholesterol-lowering drugs used in clinical practice include Xuezhikang, bile acid sequestrants, probucol, Zhibitai, and policosanol. This consensus focuses on the three cholesterol-lowering drugs most commonly used in clinical practice (Table 4).

Statins

Statins are the most common drugs used in cholesterol-lowering treatments. By inhibiting the rate-limiting enzyme of cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase, statins reduce cholesterol synthesis, thereby upregulating LDL receptors on the surface of liver cells and encouraging liver cells to take up and clear LDL particles in the blood, thereby significantly lowering serum TC, LDL-C, and ApoB levels. Numerous studies have confirmed that statins can significantly reduce ASCVD events in diabetic patients (Supplementary Table 2), and the clinical benefits are linearly correlated with the extent of LDL-C reduction. However, when statin doses are doubled, the reduction in LDL-C increases by just 6%, while potential adverse reactions, including liver function

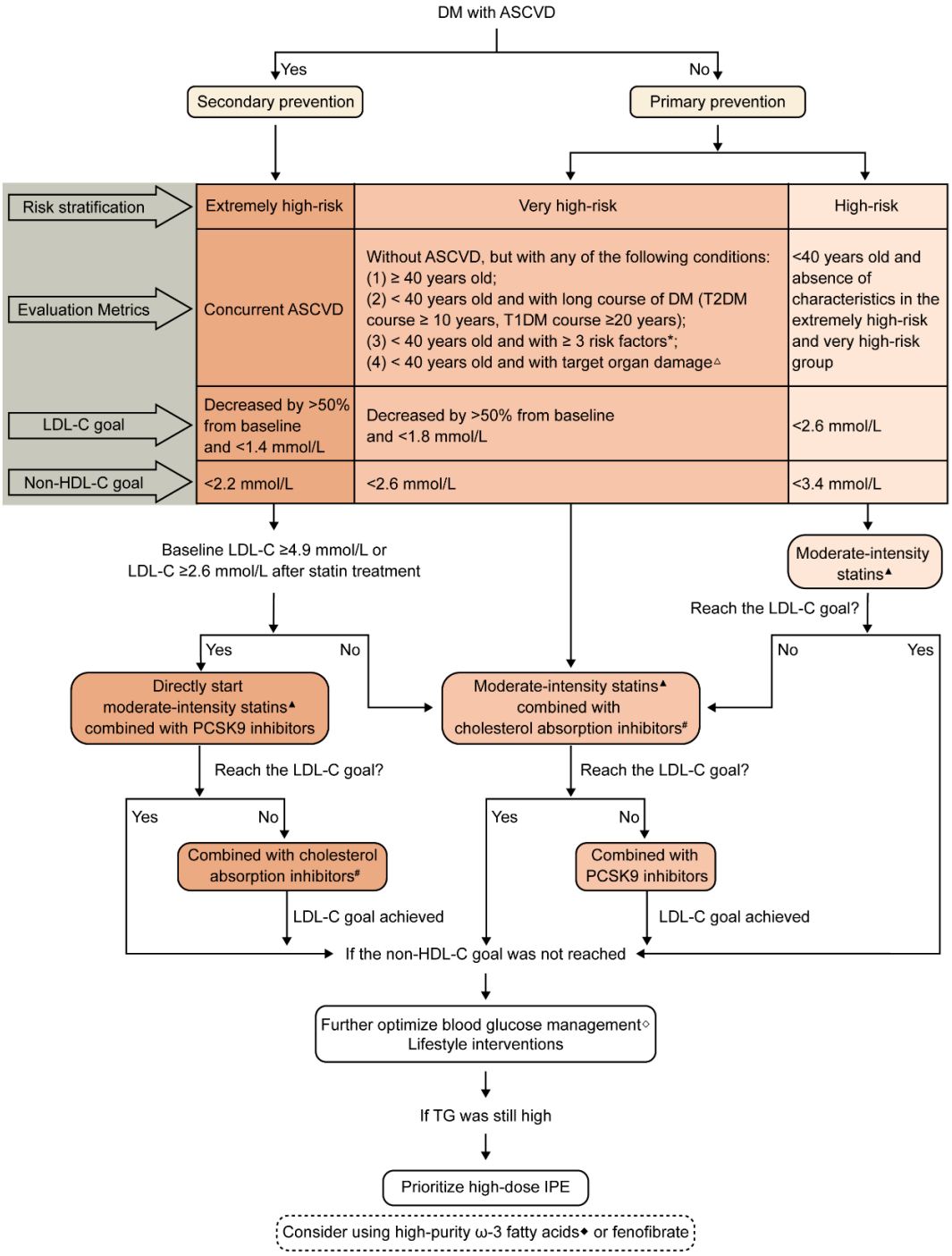

Figure 1: Cholesterol-lowering strategies and procedures for diabetic patients. ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; PCSK9: proprotein convertase subtilisin/kexin type 9; TG: triglyceride; IPE: icosapent ethyl; SGLT2i, sodium-glucose cotransporter-2 inhibitors. *Risk factors include: (1) smoking; (2) hypertension; (3) obesity (body mass index ≥ 28 kg/m^2); (4) family history of early onset coronary heart disease (male < 55 years old; female < 65 years old); (5) non-HDL-C ≥ 4.9 mmol/L; (6) lipoprotein (a) ≥ 300.0 mg/L;[22,23] (7) high-sensitivity C-reactive protein ≥ 2.0 mg/L.[24,25] The risk factor levels stated here all reflect values before intervention. △Target organ damage includes CKD Stages 3b and above (estimated glomerular filtration rate < 45 mL/min/1.73 m^2), proteinuria (urinary albumin/creatinine ratio > 300 mg/g), an ankle-brachial index of < 0.9, and left ventricular systolic/diastolic dysfunction. ▲Moderate-intensity statins refer to a daily dose that can reduce LDL cholesterol by 25%-50%. #Moderate-intensity statins combined with cholesterol absorption inhibitors may choose statin/ezetimibe single-pill combination. ◇Optimize blood glucose management includes enhancing diet control, exercise, and weight loss and/or initiating glucose-lowering drugs that improve the lipid spectrum or cardiac prognosis, such as metformin, SGLT2i, and glucagon-like peptide-1 receptor agonists. ◆ω-3 fatty acids refer to fish oil preparations containing eicosapentaenoic acid and docosahexaenoic acid.

Table 3. Recommendations for lipid-lowering strategies for diabetic patients

Recommendations	Recommendation level
All diabetic patients should engage in lifestyle interventions as a basic lipid-lowering treatment[65-68]	Level A
Moderate-intensity statins should be used for initial pharmaceutical lipid-lowering treatment in diabetic patients[30,69-78]	Level A
When the use of moderate-intensity statins does not reach the LDL-C goal in diabetic patients, cholesterol absorption inhibitors should be added to the treatment[79,80]	Level A
When the combined use of moderate-intensity statins and cholesterol absorption inhibitors does not reach the LDL-C goal in diabetic patients, PCSK9 inhibitors should be added to the treatment[81,82]	Level A
To achieve > 50% LDL-C reduction in extremely high-risk and very high-risk patients, directly initiating treatment with moderate-intensity statins combined with cholesterol absorption inhibitors may be considered	Level C
For extremely high-risk diabetic patients with high baseline LDL-C levels*, where it is expected that reaching the LDL-C goal using moderate-intensity statins combined cholesterol absorption inhibitors will be difficult, directly initiating moderate-intensity statins combined with PCSK9 inhibitors may be considered[81,82]	Level B
For patients who cannot tolerate statins, the use of cholesterol absorption inhibitors, as well as PCSK9 inhibitors should be considered[28,83-85]	Level C
If the non-HDL-C goal is not achieved after the LDL-C goal is reached and TG levels are elevated, further reinforcement of lifestyle management (*e.g.*, diet, exercise, weight loss) and optimizing glucose-lowering and TG-lowering strategies should be considered△	Level A

LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; SGLT2i, sodium-glucose cotransporter-2 inhibitors. *High baseline LDL-C levels: LDL-C ≥ 2.6 mmol/L for those taking statins and LDL-C ≥ 4.9 mmol/L for those not taking statins. △To optimize glucose-lowering and TG-lowering strategies, prioritize the use of glucose-lowering drugs that can improve the lipid spectrum or cardiac prognosis (*e.g.*, metformin, SGLT2i, and glucagon-like peptide-1 receptor agonists), and use TG-lowering drugs when necessary.

damage, myopathy, and newly diagnosed diabetes, increase.

Chinese populations tolerate high-dose statins less well than Western populations. Therefore, in addition to concerns about safety, efficacy, and treatment costs, poor tolerance contraindicates the use of high-intensity statins, and moderate-intensity statins are instead recommended for use as part of an initial lipid-lowering plan.[30,69-78] The cholesterol-lowering potential of different types and doses of statins varies. Moderate intensity refers to a daily dose of statin capable of reducing LDL-C by 25%–50% (Table 4). Currently, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin are used in clinical practice in China. The lipid-lowering mechanism of Xuezhikang, a lipid-lowering medicine with a Chinese patent, is similar to that of statins. The China coronary secondary prevention study (CCSPS) subgroup analysis of diabetes confirmed that Xuezhikang capsules lowers LDL-C levels effectively, improve the lipid spectrum, significantly reduce the incidence of cardiovascular events in diabetic patients and the mortality rate of coronary heart disease, and have fewer side effects.[89] If LDL-C does not reach the target within 4-6 weeks of treatment with moderate-intensity statins, combination therapy with cholesterol absorption inhibitors, as well as PCSK9 inhibitors should be considered.[26-28,79-82]

Cholesterol absorption inhibitors

Cholesterol absorption inhibitors include ezetimibe and hybutimibe, which work mainly by acting selectively on Niemann-Pick C1-like protein 1 on the brush border of the small intestinal mucosa and inhibiting the intestinal absorption of dietary and biliary cholesterol. Studies have confirmed that when ezetimibe is used in combination with different types of statins, LDL-C can be further reduced by about 18%-20%, thus making the total LDL-C reduction greater than 50% without increasing the risk of adverse reactions to statins.[79,80,90] Subgroup analysis of the improved reduction of outcomes: vytorin efficacy international trial (IMPROVE-IT) study showed that a combination of statins and ezetimibe may enhance benefits for patients with acute coronary syndrome complicated by diabetes by reducing the risk of myocardial infarction, ischemic stroke, and major endpoint events by 24%, 29%, and 15%, respectively.[26,79]

Additionally, subgroup analyses of other clinical studies suggest that combining ezetimibe with statins can reduce adverse cardiovascular events in diabetic patients. A study based on an East Asian population showed that in ASCVD patients, the single-pill combination of rosuvastatin and ezetimibe (10 mg and 10 mg) had a higher LDL-C target achievement rate and better tolerance than high-intensity statin monotherapy. In terms of achieving further reductions in the risk of cardiovascular and cerebrovascular events, the single-pill combination of rosuvastatin and ezetimibe is not inferior to high-intensity statin monotherapy,[80] and the subgroup analysis conducted in this study showed that

Table 4: Types, usage, and adverse effects of commonly used cholesterol-lowering drugs in clinical practice*

Types		Medication dosage	Impact on blood sugar	Adverse effects
Moderate-intensity statins△	Atorvastatin	10-20 mg, once/day	Risk of new-onset diabetes or elevated glycosylated hemoglobin, especially for high-intensity and lipophilic statins	Abnormal liver function, myopathy, gastrointestinal symptoms, headaches, *etc*.
	Rosuvastatin	5-10 mg, once/day		
	Fluvastatin	40-80 mg, once/day		
	Lovastatin	40 mg, once/day		
	Simvastatin	20-40 mg, once/day		
	Pravastatin	40 mg, once/day		
	Pitavastatin	1-4 mg, once/day		
	Xuezhikang▲	0.6 g, twice/day	Neutral effects	Rare, similar to the abovementioned statins
Cholesterol absorption inhibitors	Ezetimibe	10 mg, once/day	Neutral effects	Headache, gastrointestinal symptoms, insomnia, rash, *etc*.
	Hybutimibe	10-20 mg, once/day	Neutral effects	
PCSK9 inhibitors	Evolocumab	140 mg, once/2 weeks or 420 mg, once/month	Neutral effects	Injection site reactions, hypersensitivity reactions, and flu-like symptoms, *etc*.
	Alirocumab	75-150 mg, once/2 weeks	Neutral effects	
	Inclisiran	284 mg, once/6 months	Neutral effects	
Others	Zhibitai	0.24-0.48 g, twice/day	Neutral effects	Rare
	Policosanol	10-20 mg, once/day	Neutral effects	Rare
	Probucol	0.5 g, twice/day	Neutral effects	Prolonged QT interval, headache, gastrointestinal symptoms, insomnia, rash, *etc*.

PCSK9: proprotein convertase subtilisin/kexin type 9; LDL: low-density lipoprotein. *Refer to the chinese lipid management guidelines (2023).[68] △Moderate-intensity statins refer to a daily dose that can reduce LDL cholesterol by 25%-50%. ▲The main component of Xuezhikang is a natural compound of 13 statins.

the efficacy and safety of this combined lipid-lowering treatment are retained in diabetic patients.[91] A single-pill combination of statin/ezetimibe may improve patient compliance. Therefore, to achieve an LDL-C reduction of > 50% in extremely high-risk and very high-risk patients, treatment that combines moderate-intensity statins and cholesterol absorption inhibitors should be initiated. Primary evidence for the use of cholesterol absorption inhibitors in cholesterol-lowering treatment in diabetic patients is shown in Supplementary Table 3.

PCSK9 inhibitors

PCSK9 inhibitors lower LDL-C levels primarily by inhibiting LDL receptor degradation, thereby increasing the clearance of serum LDL. Currently approved PCSK9 inhibitors include two fully human monoclonal antibodies, alirocumab and evolocumab, which bind competitively to PCSK9 in circulation, and inclisiran, a small interfering RNA targeting PCSK9. Research results show that PCSK9 inhibitors (including evolocumab, alirocumab, and inclisiran) can significantly reduce the average LDL-C level of diabetic patients within a range of 50%-70%.[92] At the same time, PCSK9 inhibitors also significantly improve other lipid components, reducing TG levels by 10%-30%, ApoB levels by 35%-41%, and Lp (a) levels by 20%-30%.[93-95] The results of the BANTING[96] and BERSON studies[97,98] further confirm that PCSK9 monoclonal antibodies can help high-risk and very high-risk ASCVD T2DM patients quickly achieve lipid control, with good safety and tolerability, without affecting blood glucose levels.

Several large-scale clinical studies, including the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) study,[81] the ODYSSEY OUTCOMES diabetes subgroup analysis,[27] and the ODYSSEY DM-INSULIN subgroup analysis,[99] confirm that PCSK9 inhibitors can significantly reduce the risk of cardiovascular events in diabetic patients and are positively correlated with LDL-C reduction.[93,100] Therefore, for diabetic patients with ASCVD and high baseline LDL-C levels (LDL-C ≥ 4.9 mmol/L for patients not using statins and LDL-C ≥ 2.6 mmol/L for patients using statins), or when it is expected that combining statins and cholesterol absorption inhibitors will be difficult to achieve, the combination of PCSK9 inhibitors may be considered.[81,82] The main evidence for the use of PCSK9 inhibitors in cholesterol-lowering treatment in diabetic patients is shown in Supplementary Table 4.

For patients who cannot tolerate statins, typically indicated by clinical adverse reactions or abnormal laboratory test indicators related to statins following their administration,

Table 5. Recommendations for TG management strategies for diabetic patients

Recommendations	Recommendation level
Correct other secondary causes of hypertriglyceridemia (including hypothyroidism, nephrotic syndrome, chronic liver disease, and drugs that raise TG levels)	Level A
Enhance lifestyle management (*e.g.*, diet, exercise, avoiding alcohol, and weight loss)	Level A
Optimize glucose-lowering strategies (prioritizing the use of glucose-lowering drugs that improve the lipid spectrum or cardiac prognosis, such as metformin, SGLT2i, and GLP-1 RA)	Level B
Based on treatment with moderate-intensity statins, if TG levels are still 2.3-5.6 mmol/L, it is recommended to combine treatment with a large dose of IPE (2 g, twice/day) to reduce ASCVD risk[51,105]	Level B
Based on treatment with moderate-intensity statins, if TG levels are still 2.3-5.6 mmol/L, a combined treatment with high-purity ω-3 fatty acids* or with fenofibrate may be considered to reduce ASCVD risk[48,49]	Level C
When TG is > 5.6 mmol/L, fibrates, high-purity ω-3 fatty acids*, or niacin drugs can be used to reduce the risk of pancreatitis[106]	Level C

TG: triglyceride; SGLT2i: sodium-glucose cotransporter-2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; ASCVD: atherosclerotic cardiovascular disease; IPE. icosapent ethyl. *ω-3 fatty acids refer to fish oil preparations containing eicosapentaenoic acid and docosahexaenoic acid.

Table 6. Dose adjustment plan for statin drugs at different stages of CKD

eGFR (mL/min/1.73 m^2)	Atorvastatin	Simvastatin	Fluvastatin	Rosuvastatin	Pitavastatin	Pravastatin
≥ 60	No reduction needed	No reduction needed	No reduction needed	No reduction needed	No reduction needed	No reduction needed
30-59	No reduction needed	No reduction needed	No reduction needed	No reduction needed	Restricted use	Restricted use
15-29	No reduction needed	Reduce the dosage	Restricted use	Restricted use	Restricted use	Restricted use
< 15	Restricted use	Restricted use	Restricted use	Restricted use	Restricted use	Restricted use

CKD: chronic kidney disease; eGFR: estimated glomeruar filtration rate.

cholesterol absorption inhibitors and PCSK9 inhibitors should also be considered.[28,83-85] In addition to these two types of non-statin drugs, a new lipid-lowering drug, bempedoic acid,[101,102] can reduce LDL-C levels by up to 30% by inhibiting adenosine triphosphate-citrate lyase and hepatic cholesterol synthesis.[103,104] The CLEAR-Outcomes study confirmed that bempedoic acid can reduce the risk of MACE with overall good safety and tolerability without leading to related myopathy, abnormal blood glucose, or other adverse reactions.[102] Bempedoic acid may also be an option for future statin-intolerant patients. Zhibitai, policosanol, and other well-tolerated cholesterol-lowering drugs may also be used as alternative drugs when statins are not tolerated.

After using the abovementioned cholesterol-lowering drugs to achieve the LDL-C target in diabetic patients, it is important to clarify whether non-HDL-C targets have been reached. Non-HDL-C contains LDL-C and remnant cholesterol, and an increase in remnant cholesterol levels in diabetic patients is closely related to increased TG levels; thus, the primary method of reducing remnant cholesterol levels is to reduce TG levels. The most recommended measures for reducing TG levels in diabetic patients include strict lifestyle intervention, optimized blood glucose management, and the use of TG-lowering drugs when necessary.

TG-lowering treatment strategy

The TG management strategy for diabetic patients is shown in Table 5.

When diabetic patients have hypertriglyceridemia, it is necessary to evaluate other secondary causes of hypertriglyceridemia, including hypothyroidism, nephrotic syndrome, chronic liver disease, and drugs that raise TG levels. Correcting the above secondary causes should be undertaken alongside strict lifestyle management. Studies show that improving diet and exercise, weight loss, and other lifestyle changes not only help control blood sugar but also lower TG levels and may reduce LDL-C and non-HDL-C levels by as much as 5%-15%.[65,107] Metabolic surgery, an invasive weight management strategy, can significantly reduce TG and non-HDL-C levels, as well as the risk of ASCVD.[108,109]

If diabetic patients' blood sugar, which can also affect TG and non-HDL-C control, does not reach the target levels even with strict lifestyle management, further optimization

of the glucose-lowering strategy should be considered to reduce TG levels, thereby helping non-HDL-C to reach the goal.[110-112] The optimized glucose-lowering strategy recommends prioritizing the use of glucose-lowering drugs that can improve the lipid spectrum or cardiac prognosis,[113] such as metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i). These three types of hypoglycemic drugs, each with specific characteristics, can all improve the lipid spectrum and can be used clinically according to the specific situation of each patient. Metformin and GLP-1 RA have obvious advantages in cases where weight loss is indicated and can reduce the TC, TG, and LDL-C levels of diabetic patients.[114,115] SGLT2i promotes the breakdown and oxidation of fatty acids, reduces fat synthesis and TG levels, increases HDL-C levels,[110,111,116] and also functions to prevent heart failure.

According to the results of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) and the Japan EPA lipid intervention study (JELIS) studies, if lifestyle changes and glucose-lowering strategy optimization do not sufficiently reduce TG levels to < 2.3 mmol/L, adding a large dose of icosapent ethyl (IPE) to the lipid-lowering treatment plan is recommended to reduce the risk of ASCVD.[51,105] Since fenofibrate only shows cardiovascular benefits in a subgroup analysis of the action control cardiovascular risk diabetes (ACCORD) study,[49] and high-purity ω-3 fatty acids (containing EPA and docosahexaenoic acid [DHA]) only shows a trend to reduce ASCVD risk in a meta-analysis,[48] fenofibrate and high-purity ω-3 fatty acids are indicated as second-choice drugs, after IPE, for managing ASCVD risks.

Epidemiological research suggests that when TG levels are significantly increased (> 5.6 mmol/L), the risk of pancreatitis increases.[106] A combination treatment plan of fibrates, large doses of high-purity ω-3 fatty acids, or niacin drugs can be used[106] to reduce TG levels as much as possible while reducing the risk of pancreatitis.

In recent years, new TG-lowering drugs have emerged, including angiopoietin-like protein 3 inhibitors (*e.g.*, Evinacumab, a fully human monoclonal antibody) and apolipoprotein C3 inhibitors (*e.g.*, Volanesorsen, an antisense oligonucleotide). Clinical research suggests that both the above drugs can reduce TG levels significantly while also reducing non-HDL-C and ApoB levels,[117,118] which is promising for improving overall cardiovascular health.

Treatment strategy for reducing Lp (a)

New drugs for reducing Lp (a) mainly include an antisense oligonucleotide of apo-Lp (a) (Pelacarsen) and small interfering RNAs of apo-Lp (a) (Olpasiran and SLN360). Although Phase I studies show that both can significantly reduce Lp (a) levels, large-scale international multicenter clinical studies with cardiovascular benefit endpoints are still ongoing. Therefore, no drugs for the treatment of Lp (a) are currently used in clinical contexts. For patients with elevated Lp (a) levels, further reducing cholesterol levels remains the primary focus. Of the cholesterol-lowering drugs discussed above, PCSK9 inhibitors can reduce the Lp (a) levels of diabetic patients by about 20%-30%, significantly reduce the occurrence of MACE and are available for clinical use.[119] Although niacin drugs and ApoB100 inhibitor mipomersen can also reduce Lp (a) levels by 20%-30%, both drugs lack evidence of cardiovascular benefits, and mipomersen was no longer recommended for use after being withdrawn from the market in 2019.[120-122]

The impact of lipid-lowering drugs on blood sugar and treatment strategies

Currently, the mechanism by which lipid-lowering drugs affect blood sugar is not fully understood. On one hand, it may be related to the impact of lipid-lowering drugs on the secretion of insulin by pancreatic β cells; on the other hand, it may be related to the impact of lipid-lowering drugs on insulin sensitivity and the subsequent impact on glucose metabolism in tissues and organs other than the pancreas (*e.g.*, fat and muscle).[123] At present, the results of large-scale clinical studies and meta-analyses suggest that statins and niacin are unfavorable for blood sugar control and increase the risk of new-onset diabetes.[72,123-126] Conversely, cholesterol absorption inhibitors, PCSK9 inhibitors, probucol, bempedoic acid, fibrates, and high-purity ω-3 fatty acids have a neutral effect on blood sugar regulation. Some research also suggests that these drugs can improve glucose metabolism and, to some extent, alleviate insulin resistance and fatty liver.[26,80,123] Although bile acid sequestrants can improve both sugar and lipid metabolism, because of their weak lipid-lowering effect[27,28,127] and significant gastrointestinal side effects, their clinical use in China is rare. Clinical research on new drugs that lower Lp (a) is ongoing, and the impact of their long-term use on blood sugar is not yet clear.

Given that the cardiovascular protective effect of statins is far greater than its unfavorable effects on blood sugar control (an average increase in HbA1c of 0.3% or less) and the risk of new-onset diabetes, it is not recommended that diabetic patients stop taking statins due to poor blood sugar control. The unfavorable effects of statins on blood sugar control and the risk of new-onset diabetes are dose-related, and different types of statins have different effects on blood sugar. For example, atorvastatin, rosuvastatin, simvastatin, and fluvastatin have similar adverse effects on blood sugar

regulation in normal populations and T2DM patients, while pitavastatin and pravastatin have a more neutral effect on blood sugar regulation.[72,124,125,128] Therefore, to control blood lipids in diabetic patients clinically, in addition to monitoring blood sugar or HbA1c before and during the use of statins, it is recommended to introduce cost-effective, medium-intensity statins and those that have a more neutral effect on blood sugar to reduce the associated metabolic abnormalities. If blood lipid control does not reach the desired goals, consider combining cholesterol absorption inhibitors or PCSK9 inhibitors. It is not recommended to increase the dose of statins.[27,28,80]

Research shows that statins cause metabolic abnormalities and insulin resistance in the body by reducing Clostridium-rich microbiota in the intestines and inhibiting the conversion of chenodeoxycholic acid to ursodeoxycholic acid, which leads to a decrease in intestinal GLP-1 secretion.[26,80,123,129] The combination of ursodeoxycholic acid and statins can reverse the glucose tolerance abnormalities caused by statins without changing their lipid-lowering efficacy, suggesting that combining statins and ursodeoxycholic acid may show promise as a future lipid-lowering treatment strategy.[26,80,123,129] At the same time, for diabetic patients, attention should be paid to reducing weight, maintaining a reasonable diet, and optimizing the hypoglycemic treatment plan. Niacin can cause abnormal glucose metabolism or worsen glucose tolerance, has no cardiovascular benefits for diabetic patients, and is generally not recommended for use in this population. If it is to be used, blood sugar levels should be monitored regularly.[68,123]

Monitoring during lipid-lowering treatment

For first-time users of lipid-lowering drugs, blood lipids, liver enzymes, creatine kinase, and other indicators should be checked 4-6 weeks after medication. If the blood lipid indicators reach the goals and there are no adverse drug reactions, gradually increase the recheck frequency to every 3-6 months. If the blood lipids do not reach the goals after 4-6 weeks of treatment, the dose or type of lipid-lowering drugs should be adjusted promptly, or lipid-lowering drugs with different mechanisms of action should be used in combination. Whenever the type or dose of lipid-lowering drugs is adjusted, the indicators should be rechecked 4-6 weeks after treatment. Given that long-term use of statins may cause abnormal glucose metabolism, blood sugar and HbA1c monitoring should be increased.[130]

LIPID-LOWERING TREATMENT IN SPECIAL POPULATIONS WITH DIABETES

Children and adolescents

It is recommended to test and evaluate blood lipids after blood sugar is controlled or after three months of hypoglycemic drug treatment in > 10 year-old children and adolescents diagnosed with diabetes. The ideal blood lipid levels for children and adolescent diabetic patients are LDL-C < 2.6 mmol/L, HDL-C > 0.9 mmol/L, TG < 1.7 mmol/L, and non-HDL-C < 3.4 mmol/L.[131] Interventions should be carried out for those with persistent lipid abnormalities to maintain blood lipids within the ideal range. Intervention measures include introducing a low-fat and high-fiber diet, regular exercise, maintaining an ideal weight, maintaining adequate sleep, and optimizing blood sugar control. For those with familial hypercholesterolemia, lipid-lowering treatment with statins, ezetimibe, bile acid sequestrants, or PCSK9 inhibitors may be considered, but evidence for the long-term safety of these drugs in children and adolescents is limited.

People aged ≥ 75 years

Diabetes has become one of the most common diseases among elderly populations, and the prevalence of diabetes in elderly populations in China has reached 30%.[132] Patients aged ≥ 75 years are rarely included in clinical trials; thus, evidence on whether diabetic patients aged ≥ 75 years can benefit from LDL-C lowering treatment is inadequate. A recent meta-analysis of 29 clinical studies on both primary and secondary prevention showed that patients aged ≥ 75 years may also benefit from LDL-C lowering treatment and that the reduction in the risk of cardiovascular and cerebrovascular events brought about by statin treatment and non-statin drugs (*e.g.*, ezetimibe and PCSK9 inhibitors) were not significantly different from each other. In terms of safety, lipid-lowering treatment did not increase the risk of tumors, hemorrhagic stroke, cognitive impairment, and new-onset diabetes in patients aged ≥ 75 years.[133]

Diabetic patients aged ≥ 75 years are considered to be at very high-risk for ASCVD, and vigorous lipid-lowering treatment is recommended for this population. Few randomized controlled trials have established targets for statin lipid-lowering treatment in elderly patients; therefore, this consensus does not make clear recommendations for LDL-C target values in this population. However, randomized control studies of non-statin drugs (*e.g.*, ezetimibe or PCSK9 inhibitors) have included patients aged ≥ 75 years as participants.[28,134] Taking into consideration concurrent liver and kidney diseases, combined medication, and expected lifespans for very high-risk patients aged ≥ 75 years, it is advisable to consider medium-intensity statins in combination with non-statin drugs as a means of intensifying lipid-lowering treatment. During treatment with medication, the monitoring of liver and kidney function, muscle damage, and other adverse reactions should be enhanced.

Patients with chronic kidney disease (CKD)

Approximately 30% of T1DM patients and 40% of T2DM patients have CKD.[135] The risk of cardiovascular death significantly increases in diabetic patients with CKD, who are directly classified as being at very high-risk for ASCVD. Reducing ASCVD risk with statin treatment is affected by renal function. For patients with mild to moderate renal dysfunction but who are not on dialysis, statin treatment can significantly reduce the risk of all-cause mortality.[136] Additionally, these patients may experience cardiovascular benefits with a combination of cholesterol absorption inhibitors or PCSK9 inhibitors based on statin treatment.[137-139] Statin treatment has not been shown to significantly reduce the risk of cardiovascular disease in hemodialysis patients.[139-141]

CKD patients are at high risk for statin-related myopathy, especially when renal function is progressively declining or the estimated glomerular filtration rate is < 30 mL/min/1.73 m^2, and the risk significantly increases in relation to the dose of statin drugs. Therefore, high doses of statin drugs should be avoided. The dose adjustment plan for statin drugs at different stages of CKD is shown in Table 6. Cholesterol absorption inhibitors and PCSK9 inhibitors are safe for patients with impaired renal function and do not require dose adjustments.

Patients with metabolic-associated fatty liver disease (MAFLD)

MAFLD refers to patients with evidence of fatty liver based on pathology or imaging and who have one of the three following conditions: T2DM, metabolic dysfunction, and overweight/obese. Diabetes and MAFLD are risk factors for each other, and the prevalence of MAFLD in T2DM patients can be as high as 55.5%.[142] MAFLD patients with T2DM have a higher risk of liver damage progressing to cirrhosis and liver cancer.[143,144] MAFLD is an independent risk factor for ASCVD,[145] and diabetics with MAFLD have a higher ASCVD risk than those without MAFLD.[146-149]

At present, there is no evidence to suggest that lipid control for T2DM patients with MAFLD should be stricter. During the use of lipid-lowering drugs, blood lipids and liver function should be monitored closely. Statins can cause elevated liver enzymes at an incidence rate of about 1%, which usually occurs within 12 weeks of starting medication or increasing the dose; such elevation is dose-dependent and rarely causes liver failure. In MAFLD patients with normal liver function, medium-intensity statins can be used. If serum alanine transaminase (ALT) or aspartate transaminase (AST) elevation does not exceed three times the normal upper limit and the total bilirubin level is normal, observation can be carried out on the basis of the original dose or reduced dose of statin use. If ALT or AST elevation exceeds three times the normal upper limit, statins should be discontinued. Patients with mild liver impairment (i.e., a Child-Pugh score of 5-6) can use cholesterol absorption inhibitors or PCSK9 inhibitors as alternatives. Decompensated cirrhosis and acute liver failure are contraindications for the use of statins,[68,150] and the use of other types of lipid-lowering drugs in these patients is not supported by evidence.

Patients with pregnancy

Pregnancy can cause a physiological increase in blood cholesterol levels, with LDL-C levels increasing by 50%, and abnormal elevation of cholesterol levels during pregnancy increases the risk of preterm birth and fetal atherosclerosis.[151] With choices of lipid-lowering drugs highly limited during pregnancy, lipid management should focus on screening, lifestyle changes (*e.g.*, dietary management, appropriate exercise, and eliminating smoking and alcohol consumption), and keeping blood sugar within an appropriate range.[152]

Based on animal experiments and case reports of fetal malformations caused by statins, it is generally not recommended to use statins during pregnancy. However, two recent randomized controlled studies and cohort studies related to pravastatin found no increased risk of birth defects from statins.[153,154] Meta-analysis results also suggest that statins do not increase the risk of birth defects, but that they are associated with an increased risk of spontaneous abortion.[155,156] Based on this evidence, the United States Food and Drug Administration requested the removal of the "Pregnancy X Class" label for statins in 2021. During pregnancy, for diabetic women who have previously had coronary events or have familial hypercholesterolemia, blood lipoprotein isolation technology to reduce LDL-C is relatively safe and effective, and statins may be chosen with caution after multidisciplinary consultation and a full assessment of the pros and cons.[68]

Diabetic patients with pregnancy have increased liver TG synthesis due to increased nutrient intake and estrogen secretion, which leads to abnormal TG elevation. Especially in late pregnancy, decreased LPL activity increases the risk of developing severe hypertriglyceridemia and acute pancreatitis. Pharmaceutical options for lowering TG during pregnancy are limited, and there is insufficient evidence regarding the safe use of fibrate drugs during pregnancy.

For pregnant patients with diabetes and hypertriglyceridemia, lifestyle improvement and dietary management are the primary recommendations. For patients still with severe hypertriglyceridemia (TG > 5.6 mmol/L) on the basis of blood sugar control, ω-3 fatty acids can effectively

and relatively safely lower TG levels. Besides, insulin and heparin can lower TG levels by activating LPL, which is relatively safe for pregnant patients.[157] If a patient with pancreatitis still has a serum TG level of > 11.3 mmol/L or a decrease of less than 50% after 24-48 h of drug treatment, lipoprotein apheresis treatment may be considered.[158]

CONCLUSION AND PROSPECTS

China has the highest number of diabetic patients in the world; thus, the effective management of lipid abnormalities and the reduction of cardiovascular event risks in diabetic patients have profound implications for implementing the Healthy China strategy. Performing ASCVD risk stratification for diabetic patients, determining lipid target values, and developing lipid-lowering treatment plans for different risk stratifications are key to lipid management in diabetic patients.

Several problems related to the lipid management of diabetic patients remain, including how to decide lipid-lowering treatment targets and goals, more randomized controlled studies needed for the novel lipid-lowering drugs, and how to make lipid-lowering treatment plans for special populations (*e.g.*, T1DM patients, elderly patients, children, and adolescents). In the future, larger-scale multicenter clinical studies that include T1DM and T2DM patients are recommended to provide more high-quality evidence for lipid management in diabetic patients.

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