2016 Chinese guidelines for the management of dyslipidemia in adults

Joint committee for guideline revision
National Expert Committee on Cardiovascular Diseases, National Center for Cardiovascular Diseases
Chinese Society of Cardiology, Chinese Medical Association
Chinese Diabetes Society, Chinese Medical Association
Chinese Society of Endocrinology, Chinese Medical Association
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Keywords: Adults; Chinese guidelines; Dyslipidemia

Abbreviations
ACS: acute coronary syndrome
ALT: alanine aminotransferase
Apo: apolipoprotein
ASCVD: atherosclerotic cardiovascular disease
AST: aspartate aminotransferase
BMI: body mass index
CKD: chronic kidney disease
CM: chylomicron
ESDR: end-stage renal disease
FH: familial hypercholesterolemia
GFR: glomerular filtration rate
HDL-C: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A
HoFH: homozygous familial hypercholesterolemia
IDL: intermediate-density lipoprotein
LDL-C: low-density lipoprotein cholesterol
LP: lipoprotein
Lp (a): lipoprotein(a)
LPL: lipoprotein lipase
Ox-LDL: oxidized low-density lipoprotein
PCI: percutaneous coronary intervention
PCSK: proprotein convertase subtilisin/kexin
PPARα: peroxisome proliferator activated receptor α
sLDL: small and low density lipoprotein
TC: total cholesterol
TG: triglyceride
TIA: transient ischemic attack
TLC: therapeutic lifestyle changes
VLDL-C: very-low-density lipoprotein cholesterol

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1 Introduction

Over the last 30 years, the blood lipid level in the Chinese population has gradually increased, and the incidence of dyslipidemia has significantly increased. A nationwide survey in 2012 showed that the average serum total cholesterol (TC) value in adults was 4.50 mmol/L and that the prevalence of hypercholesterolemia was 4.9%; the average value of triglyceride (TG) was 1.38 mmol/L, and the prevalence of hypertriglyceridemia was 13.1%; the average value of high-density lipoprotein cholesterol (HDL-C) was 1.19 mmol/L, and the prevalence of HDL-C hypolipidemia was 33.9%.[1] The overall prevalence of dyslipidemia among Chinese adults reached 40.4%, which has substantially increased since 2002. The increase of serum cholesterol level in the population will increase by approximately 9.2 million cases of cardiovascular events in China between 2010 and 2030.[2] The prevalence of hypercholesterolemia among Chinese children and adolescents is also significantly increasing,[3] suggesting that the development of dyslipidemia and the relevant disease burdens in Chinese adults will continue to increase.

Dyslipidemia characterized by the increase of low-density lipoprotein cholesterol (LDL-C) or TC is an important risk factor for atherosclerotic cardiovascular diseases. The reduction of LDL-C levels can significantly decrease the development and mortality risks of atherosclerotic cardiovascular diseases.[4] Other types of dyslipidemia (e.g., increases of TG or decreases of HDL-C) are also correlated with the increase of developing atherosclerotic cardiovascular diseases.[5–7]

The effective control of dyslipidemia has important significance for the management of atherosclerotic cardiovascular diseases in China. Encouraging people to adopt a healthy lifestyle is the basic strategy for managing dyslipidemia and atherosclerotic cardiovascular diseases. The focus of dyslipidemia management is to increase the awareness, treatment, and control rates of dyslipidemia. Although the awareness and treatment rates of Chinese adult dyslipidemia patients have increased over recent years,[8] they remain at low levels. Therefore, the management work of dyslipidemia urgently needs to be strengthened.

In 2007, a joint committee of multidisciplinary experts together formulated the “Chinese Guidelines for the Management of Dyslipidemia in Adults” (referred to as “Guidelines” hereafter). Based on the full adoption of epidemiological and clinical study results from the Chinese population and combined with international study results and guideline recommendations, the “Guidelines” proposed recommendations that were more appropriate for the management of dyslipidemia in the Chinese population. These recommendations had important guiding functions for the management of dyslipidemia in China.[9]

Since 2007, more clinical study results have further validated the effectiveness and safety of cholesterol-lowering treatments on the primary and secondary prevention of atherosclerotic cardiovascular diseases. Many international academic institutions successively updated or formulated new management guidelines for dyslipidemia. During this period, studies in the clinical blood lipid field in China made...
significant progress. Prospective cohort studies on the Chinese population obtained new 20-year follow-up data. Based on the 10-year overall risk assessment program recommended by the 2007 Guidelines, the lifetime risk assessment program was proposed.\(^\text{[10]}\)

In November 2013, supported by the Department of Diseases Control of the National Health and Family Planning Commission of the People’s Republic of China (NHFPC), the National Expert Committee on Cardiovascular Diseases of the National Center for Cardiovascular Diseases, the Chinese Society of Cardiology of Chinese Medical Association, the Chinese Diabetes Society of the Chinese Medical Association, the Chinese Society of Endocrinology of the Chinese Medical Association, and the Chinese Society of Laboratory Medicine of the Chinese Medical Association formed a joint committee to revise the blood lipid guidelines. These committee members extensively collected core issues to be addressed by the new guidelines. After discussion, 17 core issues across 4 aspects (the overall principle of guideline revisions, the overall cardiovascular risk assessment, the goals of lipid-lowering treatment, and lipid-lowering treatments for special populations) were eventually confirmed. The guideline-revision working group targeted these core issues to formulate specific literature retrieval and evaluation strategies as well as comprehensively evaluate and screen the relevant literature. The literature retrieval databases included the Chinese Biomedicine Literature Database (CBM), Wanfang Data Knowledge Service Platform, China National Knowledge Infrastructure (CKNI), the American Biomedical Literature Database (PubMed), and the Dutch Excerpta Medica database (EMBASE). In addition, new data from long-term cohort studies in China were used to conduct targeted analyses. The recommendations and suggestions proposed by the revised guidelines were developed after repeated discussion among multidisciplinary experts based on a systemic assessment. When the expert opinions disagreed, the consensus of the majority of experts was accepted based on a full consideration of the different opinions.

The guideline revision referenced the standard procedures developed by the World Health Organization (WHO) and the Chinese Medical Association’s clinical guidelines.\(^\text{[11]}\) During the process of guideline revision, the National Center for Cardiovascular Diseases raised funds to avoid conflicts of interest with vendors.

The definitions of the recommendation classifications in the “Guidelines” reference the definitions in the relevant European and American blood lipid guidelines.\(^\text{[12,13]}\) The specific descriptions are shown below:

Class I: Manipulations or treatments that have been confirmed/unanimously recognized as beneficial, useful, and effective are recommended.

Class II: Manipulations or treatments that still have contradictions or different opinions according to useful/effective evidence.

Class IIa: Relevant evidence/opinions tend to be useful/effective. The application of these manipulations or treatments is reasonable.

Class IIb: Relevant evidence/opinions cannot be fully confirmed as useful/effective. Its application can be considered.

Class III: It has been confirmed/consistently recognized as useless/ineffective and manipulations or treatments might be harmful in some cases. Its application is not recommended.

The definitions of the level of evidence in the “Guidelines” are described below:

Evidence level A: Evidence based on many randomized clinical trials or meta-analyses.

Evidence level B: Evidence based on single randomized clinical trials or many non-randomized controlled studies.

Evidence level C: Only expert consensus opinion or based on the results of small-scale studies, retrospective studies, or registry studies.

## 2 Blood lipids and lipoproteins

### Highlights:

Blood lipids are the collective term for cholesterol, TG, and lipoids (e.g., phospholipids) in the serum. Blood lipids that have a close clinical association are primarily cholesterol and TG. Cholesterol in the human body primarily exists in the forms of free cholesterol and cholesteryl ester. TG is formed by the fatty acid esterification of the three hydroxyl groups in the glycerol molecule. Blood lipids are insoluble in water, and they can be dissolved in water after binding to special proteins, lipoproteins (Apo), to form lipoproteins that are transferred to tissues to be metabolized. Lipoproteins are classified as CM, VLDL, IDL, LDL, HDL, and Lp (a).

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Table 1. The characteristics and functions of lipoproteins.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Hydration density, g/mL</th>
<th>Particle diameter, nm</th>
<th>Main component</th>
<th>Major apolipoproteins</th>
<th>Sources</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td>&lt; 0.950</td>
<td>80–500</td>
<td>TG</td>
<td>B&lt;sub&gt;48&lt;/sub&gt;, A1, A2</td>
<td>Synthesis in small intestine</td>
<td>Transfers TG and cholesterol in food from small intestine to other tissues</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.950–1.006</td>
<td>30–80</td>
<td>TG</td>
<td>B&lt;sub&gt;100&lt;/sub&gt;, E, Cs</td>
<td>Synthesis in liver</td>
<td>Transfers endogenous TG to the peripheral tissues to release free fatty acids after lipase hydrolysis</td>
</tr>
<tr>
<td>IDL</td>
<td>1.006–1.019</td>
<td>27–30</td>
<td>TG, cholesterol</td>
<td>B&lt;sub&gt;120&lt;/sub&gt;, E</td>
<td>Formed after lipase hydrolysis of TG in VLDL</td>
<td>Belongs to the LDL-C precursor; some are metabolized in liver</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.019–1.063</td>
<td>20–27</td>
<td>Cholesterol</td>
<td>B&lt;sub&gt;30&lt;/sub&gt;</td>
<td>Formed after lipase hydrolysis of TG in VLDL and IDL</td>
<td>The major carrier of cholesterol, taken-up (mediated by LDL-C receptors) and used by the peripheral tissues. Directly associated with ASCVD</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.063–1.210</td>
<td>8–10</td>
<td>Phospholipid, cholesterol</td>
<td>A1, A2, Cs</td>
<td>Primarily synthesized by liver and small intestine</td>
<td>Promotes the removal of cholesterol from the peripheral tissues. Transfers cholesterol to liver or other tissues for re-distribution. LDL-C is negatively correlated with ASCVD</td>
</tr>
<tr>
<td>Lp (a)</td>
<td>1.055–1.085</td>
<td>26</td>
<td>Cholesterol</td>
<td>B&lt;sub&gt;125&lt;/sub&gt;, (a)</td>
<td>Complex formed by lipoprotein (a) and LDL-C through disulfide bonds in liver</td>
<td>Might be associated with ASCVD</td>
</tr>
</tbody>
</table>

ASCVD: atherosclerotic cardiovascular disease; CM: chylomicron; HDL-C: high-density lipoprotein cholesterol; IDL: intermediate-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; Lp (a): lipoprotein(a); TG: triglyceride; VLDL: very-low-density lipoprotein cholesterol.

Lipoproteins are classified as chylomicrons (CM), very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL-C, and HDL-C. One type of lipoprotein is known as lipoprotein (a) (Lp[a]). The physical properties, main components, sources, and functions of lipoproteins are listed in Table 1.[14,15]

2.1 CM

CM is the largest lipoprotein particle in the blood. The major component is TG, which accounts for approximately 90% of CM. The density is low. Blood collected after healthy individuals fast for 12 h shows that no CM exists in serum. After a meal or under certain pathological conditions when the blood contains a large amount of CM, the appearance of the blood shows a white turbidity. When the serum tube is stored at 4°C overnight, CM will float to the upper layer of the serum to aggregate, and the shape is like butter. This simple method is used to examine the presence of CM.

2.2 VLDL

VLDL is synthesized by the liver. Its TG content accounts for approximately 55% of its mass. VLDL and CM are collectively termed as “TG-rich lipoproteins”. In serum without the presence of CM, the TG concentration can reflect the amount of VLDL. Because the VLDL molecule is smaller than CM, the serum after fasting for 12 h is clear and transparent. When the TG level in fasting serum is > 3.4 mmol/L (300 mg/dL), the serum will exhibit emulsion luster until it becomes turbid.

2.3 LDL-C

LDL-C is converted from VLDL and IDL (of which TG forms LDL-C after lipase hydrolysis). The LDL-C particle contains approximately 50% cholesterol, and it is the lipoprotein in blood with the highest cholesterol content; therefore, it is called a “cholesterol-rich” lipoprotein. In simple hypercholesterolemia, the increase of the cholesterol concentration parallels the serum LDL-C level. More than 95% of the Apo in LDL-C is Apo B<sub>100</sub>. Based on particle size and different density levels, LDL-C can be divided into different sub-components. LDL-C transfers cholesterol to the peripheral tissues. Most LDL-C is catabolized by hepatocytes and extrahepatic LDL-C receptors.

2.4 HDL-C

HDL-C is primarily synthesized by the liver and small intestine. HDL-C is the smallest particle lipoprotein. Lipid and protein portions almost account for half of the mass. The Apo in HDL-C is primarily Apo A1. HDL-C represents a group of heterogeneous lipoprotein because the quantity and quality of lipids, Apo, enzymes, and lipid transfer proteins in HDL-C particles are different. Using different separation methods, HDL-C can be divided into different sub-components. These HDL-C sub-components have different shapes, densities, particle sizes, electric charges, and anti-atherosclerotic characteristics. HDL-C transfers cholesterol from the peripheral tissues (including atherosclerotic plaques) to
the liver for recycling or excretion in the form of cholic acid. This process is called “reverse cholesterol transport”.

### 2.5 Lp (a)

Lp (a) represents a group of special lipoprotein discovered using immunization methods. The lipid components of Lp (a) are similar to those of LDL-C. In addition to one molecule of Apo B_{100}, however, its Apo fraction also contains one molecule of Apo (a). Little is known about the exact mechanisms of Lp (a) synthesis and catabolism.

### 2.6 Non-HDL-C

Non-HDL-C refers to the sum of cholesterol in other lipoproteins except for HDL-C. The calculation formula is non-HDL-C = TC – HDL-C. As a secondary target of lipid-lowering treatment during the management of atherosclerotic cardiovascular disease (ASCVD) and the high-risk population, non-HDL-C is applicable for individuals with LDL-C levels that are not high or have already reached the treatment goal when the TG level is 2.3–5.6 mmol/L (200–500 mg/dL). International blood lipid guidelines recommend using non-HDL-C as the marker for the primary and secondary prevention of ASCVD.[16]

### 3 Blood lipid examination

| Highlights: The basic items in clinical blood lipid examination are TC, TG, LDL-C, and HDL-C. The clinical application values of other blood lipid items (e.g., Apo A1, Apo B, and Lp (a)) have also received increasing attention. |

The basic items in clinical blood lipid examination are TC, TG, LDL-C, and HDL-C. The clinical application values of other blood lipid items (e.g., Apo A1, Apo B, and Lp (a)) have also received increasing attention.[17]

#### 3.1 TC

TC refers to the total amount of cholesterol in the various lipids in the blood. The major factors affecting the TC level include the following:

1. Age and gender. TC levels usually increase with age; however, it no longer increases or decreases after 70 years old. The level of TC in young and middle-aged women is lower than that in men. The TC level in women after menopause is higher than that in age-matched men.

2. Eating habits. Long-term high cholesterol and high-saturated fatty acid intake can increase TC.

3. Genetic factors. Mutations in lipoprotein metabolism-related enzymes or receptor genes are the major causes of significant increases in TC.

The risk assessment and prediction values of TC on ASCVD are not as accurate as those of LDL-C. The calculation of non-HDL-C and VLDL-C should detect TC.

#### 3.2 TG

TG level is affected by the effects of genetic and environmental factors and is associated with race, age, gender, and living habits (e.g., diet and exercise). Unlike TC, TG shows large variations within and between individuals. The TG level in the same individual is influenced by factors such as diet and different time points. Therefore, when the same individual receives multiple detections, the TG values might have significant differences. The serum TG levels in the population show an obvious positive skew.

Mild-to-moderate increases in TG usually reflect increases in VLDL and its remnant particles (VLDL with smaller particles). These remnant lipoproteins might directly cause atherosclerosis because the particles become smaller. However, most studies suggest that the increase of TG causes atherosclerosis through the influence of the structures of LDL-C or HDL-C. Survey data indicate that people with mild-to-moderate increases in serum TG levels are at increased risk for the development of coronary heart disease.[18] Severely increased TG is usually accompanied by acute pancreatitis.

#### 3.3 LDL-C

Cholesterol accounts for approximately 50% of LDL-C. Therefore, the LDL-C concentration basically reflects the total amount of LDL-C in the blood. The factors that affect TC can also affect the LDL-C level. The increase of LDL-C is a major risk factor for the initiation and progression of atherosclerosis.[12,16] LDL-C enters into the vascular wall through the vascular endothelia. LDL-C retained in the subcutaneous layer is modified into oxidized-LDL (Ox-LDL). After being phagocytized by macrophages, Ox-LDL forms a foam cell; the latter continues to increase and fuse to become the lipid core of atherosclerotic plaques. Although the pathology of atherosclerosis exhibits chronic inflammatory reaction features, LDL-C might be the basic element for the initiation and maintenance of this chronic inflammatory reaction. Under general conditions, LDL-C parallels TC; however, the TC level is also influenced by the HDL-C level. Therefore, it is better to use LDL-C as the assessment indicator for the risk of ASCVD.

#### 3.4 HDL-C

HDL-C can transport cholesterol in peripheral tissues such as the vascular wall to the liver for catabolism (i.e.,...
reverse cholesterol transport). HDL-C can reduce cholesterol deposition in the vascular wall to as an anti-atherosclerosis function. Because the cholesterol content in HDL-C is stable, its current cholesterol content is primarily measured to indirectly understand HDL-C levels in the blood.

Genetic factors also significantly influence the level of HDL-C. With the significant reduction of serum TC, people with severe malnutrition have decreased HDL-C. The HDL-C levels of obese people are also lower. Smoking can reduce HDL-C. Diseases such as diabetes, hepatitis, and cirrhosis can be accompanied by low HDL-C; however, exercise and a small amount of alcohol increase HDL-C. Much epidemiological data indicate that serum HDL-C levels are negatively correlated with the incidence of ASCVD.[19]

3.5 Apo A1

The Apo A1 levels in the normal population are primarily within the range of 1.2–1.6 g/L. The levels in women are slightly higher than those in men. The protein component of HDL-C particles (i.e., apolipoprotein) accounts for approximately 50% of its mass. In proteins, Apo A1 accounts for approximately 65%–75%, whereas little Apo A1 is present in other lipoproteins. Therefore, serum Apo A1 reflects the HDL-C level. It is positively correlated with HDL-C levels and has a similar clinical significance.

3.6 Apo B

The Apo B levels in the healthy population are primarily within the range of 0.8–1.1 g/L. Under normal conditions, LDL-C, IDL, VLDL, and Lp (a) particles have one molecule of Apo B. Because LDL-C particles account for the majority of these molecules, approximately 90% Apo B is distributed in LDL-C. There are two types of Apo B: Apo B48 and Apo B100. The former is primarily present in CM, whereas the latter is primarily present in LDL-C. Except for special instances, the Apo B routinely measured in clinics usually refers to Apo B100.

Serum Apo B primarily reflects the LDL-C level and is positively correlated with the serum LDL-C level. These two types have a similar clinical significance. In a few cases, Apo B hyperlipidemia and normal LDL-C concentrations can occur, suggesting the presence of increased small and dense LDL (sLDL) in the blood. During hypertriglyceridemia (high VLDL), sLDL (LDL pattern B) increases. However, compared with large and light LDL (LDL pattern A), sLDL particles have a high Apo B content and less cholesterol; therefore, this condition when LDL-C is not high but serum Apo B increases is called “Apo B hyperlipidemia”. This situation reflects the increase of LDL pattern B. Therefore, the measurement of ApoB and LDL-C together can help clinical diagnoses.

3.7 Lp (a)

Serum Lp (a) concentration is primarily associated with genetics. Gender, age, body weight, and most cholesterol-lowering drugs do not often affect this concentration. The Lp (a) level in the healthy population shows an obvious skew. Although the level in individuals can reach above 1,000 mg/L, the level in 80% healthy individuals is less than 200 mg/L. Usually, 300 mg/L is used as the cutoff point. People with levels higher than this cutoff are at a significantly increased risk for coronary heart disease, suggesting that Lp (a) causes atherosclerosis. However, clinical evidence is lacking.[20] Furthermore, an increase of Lp (a) can also be observed during various acute phase responses, nephrotic syndrome, diabetic nephropathy, pregnancy, and the administration of growth hormone. After all types of stress increase are excluded, Lp (a) is considered as an independent risk factor for ASCVD.

The expression unit of the values of all blood lipid measurement items is mmol/L according to the national standard of China. Some other countries use mg/dL. The conversion coefficients are: TC, HDL-C, LDL-C: 1 mg/dL = 0.0259 mmol/L; and TG: 1 mg/dL = 0.0113 mmol/L.

4 Appropriate levels and abnormal cutoff points

The major hazard of dyslipidemia is the increase of the risk for developing ASCVD. The “Guidelines” recommend the appropriate levels and abnormal cutoff points for the blood lipid components in the Chinese population (Table 2) based on the results of many long-term observational studies concerning the risk of developing ASCVD in Chinese populations with different blood lipid levels, including the independent influence of different blood lipid levels with regard to the cumulative risk for developing ASCVD in the study populations in 10 and 20 years. In addition, the recommendations and the references for the appropriate levels of blood lipid components in the many blood-lipid-related guidelines worldwide are referenced.[12,16,21,22] Importantly, these appropriate levels and abnormal cutoff points of blood lipids are primarily applicable for the target population regarding the primary prevention of ASCVD.

Highlights: The appropriate levels and abnormal cutoff points of blood lipids are primarily applicable for the target population regarding the primary prevention of ASCVD.
Table 2. The appropriate levels and abnormal stratified standards of blood lipids for the primary prevention population of ASCVD in China [mmol/L (mg/dL)].

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Non-HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal level</td>
<td>&lt; 2.6 (100)</td>
<td>&lt; 3.4 (130)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate level</td>
<td>&lt; 5.2 (200)</td>
<td>&lt; 3.4 (130)</td>
<td>&lt; 4.1 (160)</td>
<td>&lt; 1.7 (150)</td>
<td></td>
</tr>
<tr>
<td>Marginal increase</td>
<td>≥ 5.2 (200) and &lt; 6.2 (240)</td>
<td>≥ 3.4 (130) and &lt; 4.1 (160)</td>
<td>≥ 4.1 (160) and &lt; 4.9 (190)</td>
<td>≥ 1.7 (150) and &lt; 2.3 (200)</td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>≥ 6.2 (240)</td>
<td>≥ 4.1 (160)</td>
<td>≥ 4.9 (190)</td>
<td>≥ 2.3 (200)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤ 1.0 (40)</td>
</tr>
</tbody>
</table>

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

5 Classification of dyslipidemia

**Highlights:** The classification of dyslipidemia is complicated. The simplest methods include etiological classification and clinical classification, and the latter is the most practical.

Dyslipidemia usually refers to increases in cholesterol, TG, or both levels in serum. This condition is generally called hyperlipidemia. In fact, dyslipidemia also extensively refers to various blood lipid abnormalities, including HDL-C hypolipidemia. The classification is complicated. The simplest classifications include the etiological classification and clinical classification, and the latter is the most practical.\textsuperscript{[16,23,24]}

5.1 Etiological classification of dyslipidemia

5.1.1 Secondary hyperlipidemia

Secondary hyperlipidemia refers to dyslipidemia caused by other diseases. The diseases that can induce dyslipidemia primarily include obesity, diabetes, nephrotic syndrome, hypothyroidism, renal failure, liver disease, systemic lupus erythematosus, glycogen storage disease, myeloma, lipatrophy, acute porphyria, and polycystic ovary syndrome. In addition, some drugs such as diuretics, non-cardiac selective β-blockers, and glucocorticoids can also induce secondary dyslipidemia.

5.1.2 Primary hyperlipidemia

In addition to the association between unhealthy lifestyles (e.g., high energy, high fat, and high sugar diet; excessive drinking; and others) and dyslipidemia, most cases of primary hyperlipidemia are caused by mutations on a single gene or multiple genes. Because hyperlipidemia caused by gene mutations has a family aggregation feature and an obvious genetic tendency (especially in people with a single gene mutation), this condition is usually called familial hyperlipidemia in the clinic.

For example, loss-of-function mutations on the gene encoding the LDL-C receptor, mutations on the gene encoding the Apo B that interacts with the LDL-C receptor, gain-of-function mutations on the gene encoding proprotein convertases subtilisin/kexin type 9 (PCSK9) that degrades the LDL-C receptor, and mutations on the gene encoding the LDL-C receptor modulator that modulates the LDL-C receptor to the surface of the plasma cell membrane can cause familial hypercholesterolemia (FH). In more than 80% of patients, FH is caused by a single gene mutation; however, hypercholesterolemia is associated with multiple gene mutations. Loss-of-function mutations on the LDL-C receptor gene are the major cause of FH. The incidence of homozygous familial hypercholesterolemia (HoFH) is approximately 1/300,000–1/160,000, whereas the incidence of heterozygous familial hypercholesterolemia (HeFH) is approximately 1/500–1/200.

Familial hypertriglyceridemia is caused by a single gene mutation. This condition is usually caused by a gene mutation to the lipoprotein lipases that are involved in TG metabolism, on the Apo C2 gene, or on the Apo A5 gene. It presents as severe hypertriglyceridemia (TG >10 mmol/L), and the incidence rate is 1/1000,000. Mild and moderate hypertriglyceridemia are usually associated with multiple gene mutations.\textsuperscript{[25,26]}

5.2 Clinical classification of dyslipidemia

In practice, dyslipidemia can be stratified based on a simple clinical classification (Table 3).

Table 3. Clinical classification of dyslipidemia.

<table>
<thead>
<tr>
<th>Type</th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>Equal to WHO phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>Increase</td>
<td></td>
<td></td>
<td>IIA</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Increase</td>
<td></td>
<td></td>
<td>IV, I</td>
</tr>
<tr>
<td>Mixed hyperlipidemia</td>
<td>Increase</td>
<td>Increase</td>
<td></td>
<td>IIb, III, IV, V</td>
</tr>
<tr>
<td>HDL-C hypolipidemia</td>
<td>Decrease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; WHO: world health organization.
6 Dyslipidemia screening

**Highlights**: Regular blood lipid examinations are an important measure for managing blood lipid levels and cardiovascular disease.

The early detection of individuals with dyslipidemia and the monitoring of their blood lipid level changes are important for the effective implementation of management measures for ASCVD. All MAST institutions in China have the ability to determine blood lipid levels. The detection and monitoring work for patients with dyslipidemia is primarily implemented through routine blood lipid examination in the populations who visit medical institutions. These populations include those who already have ASCVD as well as those who have not developed ASCVD. Health examinations are also an important route to detect dyslipidemia. For the early detection of dyslipidemia, adults between 20–40 years old should receive at least one blood lipid measurement (including TC, LDL-C, HDL-C, and TG) every 5 years. Men older than 40 years of age and postmenopausal women should receive blood lipid measurements every year. Patients with ASCVD and high-risk populations should receive one blood lipid measurement every 3–6 months. Patients who are admitted into hospitals because of ASCVD should receive blood lipid measurements at admission or within 24 h of admission.

The key participants for blood lipid examination are (1) people with a history of ASCVD; (2) populations with multiple ASCVD risk factors (e.g., hypertension, diabetes, obesity, and smoking); (3) people with a family history of early-onset cardiovascular diseases (i.e., immediate male family members younger than 55 years old or immediate female family members younger than 65 years old who develop ischemic cardiovascular disease) or patients with familial hyperlipidemia; and (4) people with skin or tendon xanthomas and Achilles tendon thickening.

Many factors influence blood lipid detection results. Implementing blood lipid detection should work according to the requirements of the clinical recommendations for determining blood lipids (Appendix 1).

7 Overall cardiovascular risk assessment

**Highlights**: Using different intensities of intervention measures based on the risk of developing ASCVD is the core strategy for the management of dyslipidemia. Overall cardiovascular risk assessment is the basis of dyslipidemia treatment decisions. Overall cardiovascular risk assessment should be performed according to recommended procedures. For people younger than 55 years old, a lifetime risk for cardiovascular disease should be considered.

LDL-C or TC levels are independent predictors of the risk of developing ASCVD in individuals and populations.[27–29] However, the risk levels of developing ASCVD in individuals are determined not only by the level of cholesterol but also by the number and levels of comorbid risk factors of ASCVD.[30–31] Individuals with the same LDL-C level might have significantly different overall risks regarding the development of ASCVD because of the different numbers and levels of other risk factors. More importantly, the overall ASCVD risk is not simply an addition of the cholesterol level and the independent functions of other risk factors; rather, it is the result of the complicated interaction between the cholesterol level and many combined risk factors. Therefore, the same cholesterol level can cause greater harm because of the presence of other risk factors. The comprehensive assessment of the overall risk of ASCVD is a necessary prerequisite for the management of dyslipidemia. The assessment of the overall risk of ASCVD can not only help to confirm the decision of lipid-lowering treatment for patients dyslipidemia but also help clinical physicians make personalized comprehensive treatment decisions targeting multiple risk factors, thereby reducing the overall risk of ASCVD in patients to the greatest degree. Currently, the core content of the dyslipidemia management guidelines released by China and other countries include the assessment methods and risk stratification standards for the overall risk of developing ASCVD.[8,12,13,16,22,32–35] The 2007 blood lipid guidelines proposed using the risk of development of “ischemic cardiovascular disease” (i.e., coronary heart disease and ischemic stroke) to reflect the comprehensive pathogenic risk of the major risk factors of dyslipidemia and other cardiovascular diseases. For people at moderate risk of developing ASCVD in 10 years who are < 55 years old, this edition of the “Guidelines” add recommendations for the assessment of the lifetime risk of ASCVD for the early recognition of individuals with a high lifetime risk of ASCVD to perform active interventions.[10]

During risk assessment, people who have been diagnosed with ASCVD are directly listed as a high-risk population. People who meet one of the following conditions are directly listed as a high-risk population: (1) LDL-C ≥ 4.9 mmol/L (190 mg/dL); (2) 1.8 mmol/L (70 mg/dL) ≤ LDL-C < 4.9 mmol/L (190 mg/dL), and diabetes patients older than 40 years of age. The very high-risk and high-risk populations who meet the above conditions do not need to receive an ASCVD risk stratification based on their number of risk factors.

When considering whether a lipid-lowering treatment is required, individuals who do not meet the above three conditions should receive an assessment of the overall risk of
developing ASCVD over the following 10 years according to the procedures shown in Figure 1. The risk assessment revised in the “Guidelines” has 21 combinations according to the level of LDL-C or TC, the presence of hypertension, and the number of other ASCVD risk factors. In addition, according to the average 10-year incidence risk of ASCVD across different combinations, these levels are defined as low-risk, medium-risk, and high-risk: < 5%, 5%–9%, and ≥ 10%, respectively. This revision continues the risk-stratification program published in the 2007 Blood Lipid Guidelines to use hypertension as an important parameter in risk stratification (Figure 1). This version of the “Guidelines” provides a more quantitative color figure of the risk stratification of ASCVD development as the reference for risk stratification (Appendix 2).

Because studies in China and other countries have already discovered the effect of the risk factor levels on the lifetime risk of people younger than 55 years old,[10,31,36,37] this revision of the “Guidelines” recommends assessing the lifetime risk of ASCVD in people who have medium 10-year incidence risk for ASCVD to identify middle-aged and young individuals who have high lifetime risks for developing ASCVD in 10 years to perform early interventions on certain risk factors including blood lipids. If people with medium 10-year incidence risk of ASCVD have any two or more of the following risk factors, then their lifetime risk of ASCVD is high: (1) systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg; (2) non-HDL-C ≥ 5.2 mmol/L (200 mg/dL); (3) HDL-C < 1.0 mmol/L (40 mg/dL); (4) body mass index (BMI) ≥ 28 kg/m²; and (5) smoking.

Figure 1. The risk assessment flow chart of ASCVD. *Including smoking, low HDL-C, and men ≥ 45 years of age or women ≥ 55 years of age. The risk assessment and treatment of patients with chronic kidney disease refer to the treatment of dyslipidemia in special populations. ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CM: chylomicron; HDL-C: high-density lipoprotein cholesterol; IDL: intermediate-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; VLDL: very-low-density lipoprotein cholesterol.
8 Principles of dyslipidemia treatment

**Highlights:** Very high-risk, LDL-C < 1.8 mmol/L; high-risk, LDL-C < 2.6 mmol/L; medium-risk and low-risk, LDL-C < 3.4 mmol/L.

People who cannot achieve the target value because the baseline value of LDL-C is higher should reduce LDL-C values by at least 50%. Very-high-risk people who have LDL-C baseline values within the target still should reduce LDL-C levels by approximately 30%.

For clinical lipid-lowering goal attainment, statin lipid-lowering drugs are preferred. At the beginning of treatment, medium-intensity statins should be applied. Doses should be properly adjusted according to individual lipid-lowering efficacy and tolerance conditions. If the cholesterol level cannot reach the goal, then other lipid-lowering drugs can be used in combination.

Dyslipidemia treatment seeks to manage ASCVD and reduce the incidence risk of clinical cardiovascular events, such as myocardial infarction, and ischemic stroke, and coronary heart disease mortality. Because of the differences in genetic background and living environments, the risk levels of the development of ASCVD among individuals significantly differ. Lipid-lowering treatment can benefit patients with ASCVD and high-risk populations. Whether the lipid-lowering drug treatment should be initiated should be based on the risk levels of ASCVD in individuals in the clinic (Class I recommendation, Level A evidence).

8.1 Lipid-lowering treatment targets

Dyslipidemia, especially an increase in LDL-C, is the key factor that causes the initiation and progression of ASCVD. Many clinical studies have repeatedly confirmed that regardless of the drugs or measures adopted, as long as the serum LDL-C level can be reduced, atherosclerotic lesions can be stably delayed or regressed, and the incidence, morbidity, and mortality of ASCVD can be significantly reduced. All of the guidelines for the management of dyslipidemia in China and other countries emphasize that LDL-C plays a core role in developing ASCVD, and they advocate reducing serum LDL-C levels to manage ASCVD risk.\[9,12,35,38\]

Therefore, the use of LDL-C as the preferred intervention target is recommended (Class I recommendation, Level A evidence).

Non-HDL-C can be used as the secondary intervention target (Class IIa recommendation, Level B evidence). Given that patients with hypertriglyceridemia have increased remnant lipoproteins in their bodies that might cause atherosclerosis, non-HDL-C is used as the secondary intervention target.

8.2 Setting up lipid-lowering target values

Clinical physicians are familiar with establishing target values of lipid-lowering treatments and have experience applying such measures. However, certain newly published dyslipidemia diagnoses and treatment guidelines in other countries do not recommend establishing lipid-lowering target values,\[12,35\] because no evidence from randomized controlled studies support the specific target values of blood lipid treatment, and it is not known what type of blood lipid target values engender the largest degree of reduction of the risks of ASCVD. However, if lipid-lowering target values are eliminated, then the compliance of patients who take lipid-lowering drugs will be severely affected. Regarding the benefits of lipid-lowering treatment, a long-term adherence to treatment is important. Only when lipid-lowering target values are established can physicians more accurately evaluate the effectiveness of treatment methods, effectively communicate with patients, and increase the compliance of patients regarding lipid-lowering drugs. Furthermore, no evidence or reasons exists to eliminate lipid-lowering target values in China.\[38,39\] Therefore, target values should be established in a lipid-lowering treatment (Class I recommendation, Level C evidence).

8.3 Lipid-lowering goal attainment values

The basic target value of cholesterol to be achieved in lipid-lowering treatment should be confirmed according to the different risk levels of ASCVD. The recommendation for the reduction of LDL-C to a certain cutoff point (i.e., target value) is primarily based on risk-benefit analysis; when the risk for developing a cardiovascular event in the future is high, the benefit is larger. Although LDL-C might be reduced to a lower level, more clinical cardiovascular benefits exist, and the drug-related adverse reactions will also significantly increase. In addition, health economics are also important factors that affect making treatment decisions and should be considered.

Patients who are diagnosed with ASCVD [including acute coronary syndrome (ACS)], stable coronary heart disease, post revascularization, ischemic cardiomyopathy, ischemic stroke, transient ischemic attack (TIA), and peripheral atherosclerosis in the clinic all belong to the very high-risk population.\[13,35\] In the non-ASCVD population, risk assessment is performed according to cholesterol level, its severity, and the number of risk factors. These patients are divided into high-risk, medium-risk, and low-risk groups. The target value for reducing LDL-C is determined based on the risk of developing ASCVD among individuals. The LDL-C and non-HDL-C target values that must be achieved by populations with different risks show large differences (Table 4, Class I recommendation, Level B evidence).

All clinical study results of enhanced statin therapy show
that several increased doses of statins can reduce the risk of developing ASCVD events; however, the absolute values of these benefits are small, and the all-cause mortality is not decreased.\[40\] Studies of statins combined with ezetimibe treatment have also obtained similar results.\[41\] Reduction of LDL-C from 1.8 mmol/L to 1.4 mmol/L can further reduce the absolute risk of cardiovascular events by 2% and the relative risk by 6.4%; however, the risks of cardiovascular mortality and all-cause mortality are not reduced. These results suggest that although a clinical benefit exists after LDL-C is reduced, the absolute benefits are already decreased.

If the baseline value of LDL-C is high, then LDL-C is difficult to reduce to the basic target value after treatment with the existing standard lipid-lowering treatment for 3 months. Thus, the alternative goal of at least 50% reduction of LDL-C should be considered (Class Ia recommendation, Level B evidence). In the clinic, the LDL-C baseline values of certain very-high-risk patients are already within the basic target values. At this time, LDL-C can be reduced by approximately 30% from the baseline value (Class I recommendation, Level A evidence).

The target value of non-HDL-C is higher than that of LDL-C by 0.8 mmol/L (30 mg/dL). The target values of non-HDL-C treatment in populations at different risks are shown in Table 4 (Class I recommendation, Level B evidence).

### 8.4 Lipid-lowering goal attainment strategy

Over the last 20 years, the results of many large-scale clinical trials consistently show that statins can significantly reduce the risk of cardiovascular events (including myocardial infarction, coronary heart disease mortality, ischemic stroke, and others) with regard to the primary and secondary prevention of ASCVD. Statins have already become the most important drugs in the management of this group of diseases. Therefore, to lower lipids, statins should be a first-line treatment chosen in clinical practice (Class I recommendation, Level A evidence).

However, how to reasonably and effectively use statins remains controversial. Recent guidelines in other countries recommend using high-intensity (equivalent to the maximum allowable dose) statins at the beginning of clinical practice. However, the increased benefits and safety of the maximum allowable dose of statins in the Chinese population have not been confirmed.\[42\] The HPS2-THRIVE study indicates that the Chinese population can achieve lower LDL-C levels than their European counterparts when the exact same statin drug and dose are used.\[43\] The DYSISCHINA study showed that an increase of statin doses does not increase the goal attainment rate of LDL-C.\[44\] The CHILLAS study did not show that Chinese patients with ACS obtain more benefits from high-intensity statins.\[45\] In the Chinese population, safety must be considered during the use of high-intensity statins. More studies have indicated that high-intensity statin therapy is accompanied by high risks of myopathy and increases in the liver enzymes that are more prominent in the Chinese population. The HPS2-THRIVE study indicated that the incidence of adverse liver reactions was significantly higher in Chinese patients than in European patients during treatment with medium-intensity statins. The rate of increase in liver enzymes (> 3 times of the upper limit of the normal value) was more than 10 times higher than that among European patients, and the risk of myopathy was also 10 times higher. Currently, no safety data exist regarding high-intensity statin therapy in the Chinese population.

One feature of the efficacy of lipid-lowering statin drugs is that the initial dose of every statin has excellent lipid-lowering efficacy. When the dose is doubled, LDL-C is further reduced by 6% (the statin efficacy “rule of six”). When the statin dose is doubled, the drug cost proportionally increases, whereas the increase of the efficacy for LDL-C reduction is relative small. Therefore, the use of medium-intensity statins is recommended for initial treatment. The dose is properly adjusted according to individual lipid-lowering efficacy and tolerance conditions. If the cholesterol level does not reach the target, then other lipid-lowering drugs (e.g., ezetimibe) can be used in combination to obtain safe and effective lipid-lowering effects (Class I recommendation, Level B evidence).

### 8.5 Other dyslipidemia interventions

In addition to active cholesterol interventions, whether other dyslipidemia conditions also require treatment lacks the evidence of relevant clinical trial benefits. The appropriate level of serum TG is < 1.7 mmol/L (150 mg/dL). When serum TG is ≥ 1.7 mmol/L (150 mg/dL), non-drug intervention measurement is first applied including therapeutic diet, reduction of body weight, and abstinence from alcohol. If the TG level only shows a mild-to-moderate increase [i.e., 2.3–5.6 mmol/L (200–500 mg/dL)] to manage the risk of...
ASCVD, then although the reduction of the LDL-C level is the major goal, non-HDL-C should also reach the target value. If non-HDL-C cannot reach the target value even after statin therapy, then fibrates and high purity fish oil preparations should be used additionally with statins. For patients with severe hypertriglyceridemia and fasting TG levels of \( \geq 5.7 \text{ mmol/L} \) (500 mg/dL), drugs that reduce TG and VLDL-C should be considered first (e.g., fibrates, high purity fish oil preparations, or niacin).

For people with HDL-C < 1.0 mmol/L (40 mg/dL), diet should be controlled and lifestyle should be improved. Currently, not enough evidence exists for drug interventions.

8.6  Lifestyle interventions

Diet and lifestyle typically and significantly influence dyslipidemia. Dietary treatment and lifestyle improvements are the basic measures of dyslipidemia treatment. Whether a drug lipid-lowering therapy is performed, diet control and lifestyle improvement must be assured (Class I recommendation, Level A evidence). Excellent lifestyle habits include adhering to a heart-healthy diet and regular exercise, avoiding tobacco, and maintaining an ideal body weight. Lifestyle intervention is the therapeutic measure with the best cost-benefit and risk-benefit ratios.

For low- and medium-risk patients, if LDL-C fails to reach the goal after 6 months of lifestyle intervention, then a low/medium intensity statin therapy is initiated. For high- and very-high-risk patients, a medium-intensity statin drug treatment is initiated immediately combined with a lifestyle intervention.

8.7  Treatment process monitoring

Patients with dietary and non-drug treatment should test their blood lipid levels again in the first 3–6 months. If blood lipid control reaches the recommended target, then the non-drug treatment should continue and re-examinations should be performed every 6 months to 1 year. People who have attained long-term goals should receive a re-examination once every year. People who take lipid-lowering drugs require closer blood-lipid monitoring. People who take lipid-lowering drugs for the first time should receive re-examinations for blood lipids, transaminases, and creatine kinase within 6 weeks of drug administration. If their blood lipids reach the target value and no adverse drug reaction exists, then re-examination should be gradually changed to once every 6–12 months. If blood lipid levels do not reach the goal and no adverse drug reaction occurs, then monitoring should be performed once every 3 months. If blood lipids do not reach the target value even after 3–6 months of treatment, the dose and type of lipid-lowering drugs should be adjusted, or the treatment should be combined with lipid-lowering drugs with different action mechanisms. After each adjustment of the type or dose of lipid-lowering drugs, re-examination should be performed within 6 weeks of treatment. Therapeutic lifestyle change (TLC) and lipid-lowering drug treatment must be continued over the long term to obtain excellent clinical benefits.

9  Therapeutic lifestyle changes

Dyslipidemia is closely associated with diet and lifestyle. Dietary therapy and lifestyle improvement are the basic measures of dyslipidemia treatment.\(^{[46]}\) Whether the lipid-lowering drug treatment is chosen, control of diet and improvement of lifestyle should be maintained (Table 5). Daily essential nutrition and total energy requirements should be met when the total amount of saturated fatty acid and trans-fat uptake exceeds the upper limit; these compounds should be replaced with unsaturated fatty acids. The recommended daily cholesterol intake is < 300 mg; lipid intake should not be > 20%–30% total energy, especially for high-risk people for ASCVD and other similar conditions. Saturated fatty acid intake should be < 10% total energy for the general population. For patients with hypercholesterolemia, the amount of saturated fatty acid intake should be < 7% total energy, and the amount of trans-fat intake should be < 1% total energy. Patients with hypertriglyceridemia should reduce their total amount of daily fat intake as low as possible, and their daily consumption of

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<table>
<thead>
<tr>
<th>Element</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Limiting dietary ingredients that can increase LDL-C</td>
<td>Dietary cholesterol &lt; 300 mg/dL</td>
</tr>
<tr>
<td>Saturated fatty acid</td>
<td>&lt; 7% of total energy</td>
</tr>
<tr>
<td>Dietary cholesterol</td>
<td>&lt; 300 mg/dL</td>
</tr>
<tr>
<td>Increasing dietary ingredients to reduce LDL-C</td>
<td>Plant sterols 2–3 g/dL</td>
</tr>
<tr>
<td>Water soluble dietary fiber</td>
<td>10–25 g/dL</td>
</tr>
<tr>
<td>Total energy</td>
<td>Adjusting to the level that can maintain ideal body weight or reduce body weight</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Maintaining medium-intensity exercise and consuming at least 200 kcal</td>
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LDL-C: low-density lipoprotein cholesterol.
cooking oil should be <30 g. Regarding lipid intake, food that is rich in omega-3 polyunsaturated fatty acids should be selected first (e.g., deep-sea fish, fish oil, and vegetable oil).

The recommended daily carbohydrate intake accounts for 50%–65% of total energy. Carbohydrates rich in dietary fibers and low in glycemic index should be chosen to replace saturated fatty acids. Daily diets should include 25–40 g of dietary fiber (7–13 g of water-soluble dietary fiber). The carbohydrate intake should be primarily cereals, tubers, and whole grains. The intake of added sugar should not be over 10% total energy (this percentage is lower for people with obesity or hypertriglyceridemia). Food additives such as plant sterols/alkanols (2–3 g/dL) and soluble/viscous dietary fibers (10–25 g/dL) can help with blood lipid control; however, their safety requires long-term monitoring.

9.1 Controlling body weight

Obesity is an important risk factor for dyslipidemia. Overweight or obese people with dyslipidemia should take less energy than the body energy consumed to gradually reduce body weight to the ideal status. Reducing the total energy from daily food (by 300–500 kcal daily), improving dietary structure, and increasing physical activity can reduce more than 10% body weight in overweight and obese people. The maintenance of a healthy body weight (BMI: 20.0–23.9 kg/m²) is conducive to blood lipid control.

9.2 Physical activity

Medium-intensity metabolic exercise is recommended for 5–7 days every week, 30 min each time. Patients with ASCVD should first perform an exercise load test; after the safety of this exercise has been fully evaluated, physical activity is then performed.

9.3 Quit smoking

Patients should completely quit smoking and effectively avoid the inhalation of secondhand smoke to prevent ASCVD and to increase HDL-C levels. Smoking cessation treatments, smoking cessation hotline consultation, and medicines can be used to help quit smoking.

9.4 Limit drinking

A moderate amount of drinking (20–30 g of alcohol daily for men and 10–20 g of alcohol daily for women) can increase HDL-C levels. Even a small amount of drinking can further increase TG levels in patients with hypertriglyceridemia. No exact evidence exists regarding the influence of drinking on cardiovascular events. Restricted drinking is advocated.

10 Lipid-lowering drug treatments

**Highlights:** Whether the lipid-lowering drug treatment should be initiated should be based on the risk levels of ASCVD in individuals in the clinic.

The reduction of LDL-C levels should be used as the preferred intervention target in the management of ASCVD risks. Non-HDL-C can be used as the secondary intervention target.

Lipid-lowering treatment should establish very high-risk, LDL-C < 1.8 mmol/L; high-risk, LDL-C < 2.6 mmol/L; medium-risk and low-risk, LDL-C < 3.4 mmol/L.

People who cannot achieve the target value because the baseline value of LDL-C is higher should reduce LDL-C values by at least 50%. Very-high-risk people who have LDL-C baseline values within the target still should reduce LDL-C levels by approximately 30%.

For clinical lipid-lowering goal attainment, statin lipid-lowering drugs are preferred. At the beginning of treatment, medium-intensity statins should be applied. Doses should be properly adjusted according to individual lipid-lowering efficacy and tolerance conditions. If the cholesterol level cannot reach the goal, then other lipid-lowering drugs can be used in combination.

The blood lipid metabolic pathway in the human body is complicated. Many enzymes, receptors, and transport proteins are involved. Many types of lipid-lowering drugs can be chosen in clinical practice. Generally, these drugs can be divided into two large groups: (1) drugs that primarily reduce cholesterol; and (2) drugs that primarily reduce TG. Some lipid-lowering drugs can reduce both cholesterol and TG. Severe hyperlipidemia usually requires the combined application of many lipid-lowering drugs to obtain excellent efficacy.

10.1 Drugs that primarily reduce cholesterol

The major action mechanisms of this group of drugs inhibit cholesterol synthesis in hepatocytes, accelerate LDL-C catabolism, or reduce cholesterol absorption in the intestinal tract. This group of drugs includes statins, cholesterol absorption inhibitors, probucol, bile acid sequestrants, and other lipid-lowering drugs (e.g., Zhibitai and policosanol).

10.1.1 Statins

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, can inhibit the rate-limiting enzyme of cholesterol synthesis (HMG-CoA reductase) to reduce cholesterol synthesis and further up-regulate the LDL-C receptor on the cell surface and accelerate serum LDL-C catabolism. In addition, statins can also inhibit VLDL synthesis. Therefore, statins can significantly reduce serum TC, LDL-C, and Apo B levels as well as reduce serum TG levels and mildly increase HDL-C levels.

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The advent of statins was a milestone in the history of human ASCVD management. The 4S clinical trial first confirmed that statins reduce coronary heart disease mortality and overall patient mortality.\(^{[47]}\) The subsequent CARE,\(^{[48]}\) LIPID,\(^{[49]}\) and LIPSI\(^{[50]}\) studies also confirmed the important functions of this group of drugs with regard to the secondary prevention of coronary heart disease. The HPS study indicated that statin therapy benefits the high-risk population when their baseline cholesterol is not high,\(^{[51]}\) The clinical trials regarding enhanced statin therapy primarily included PROVE-IT,\(^{[52]}\) A to Z,\(^{[53]}\) TNT,\(^{[54]}\) MIRACL,\(^{[55]}\) and IDEAL.\(^{[56]}\) Compared with the routine dose of statins, enhanced statin therapy for patients with coronary heart disease further reduces the likelihood of cardiovascular events;\(^{[52,54]}\) however, the reduction level is not high,\(^{[53,56]}\) and total mortality is not reduced.\(^{[57]}\) The ASTEROID study confirmed that statin therapy reverses coronary atherosclerosis.\(^{[58]}\) The WOSCOPS,\(^{[59]}\) AFCAPS/TexCAPS,\(^{[60]}\) CARDS,\(^{[61]}\) JUPITER,\(^{[62]}\) and HPS\(^{[51]}\) studies expanded the application of statins from patients with ASCVD to primary prevention and more extensive populations. Currently, the function of statins with regard to the primary prevention of cardiovascular disease among high-risk populations has been affirmed. However, the application effect in people at low risk of cardiovascular disease awaits further study. Many studies have targeted special populations for investigation. The SPARCL,\(^{[63]}\) PROSPER,\(^{[64]}\) CARDS,\(^{[61]}\) ALLHAT-LLT,\(^{[65]}\) and ASCOT-LLA\(^{[66]}\) studies individually showed that statins have clinical benefits in the elderly as well as patients with stroke, diabetes, or hypertension. Furthermore, evidence from Chinese clinical studies does not support the cardiovascular benefits of short-term enhanced statin therapy before percutaneous coronary intervention (PCI) among patients with ACS. Moreover, the newest guidelines in other countries do not recommend short-term enhanced statin intervention strategies during the perioperative period of PCI.

Statin are applicable for patients with hypercholesterolemia, mixed hyperlipidemia, or ASCVD. Currently, lovastatin, simvastatin, pravastatin, fluvasatin, atorvastatin, rosuvastatin, and pitavastatin are used in clinical practice in China. The cholesterol reduction levels have large differences depending on the different types and doses of statins. However, when any statin does is doubled, the continued reduction of LDL-C is only 6% (i.e., the so-called “rule of six of statin efficacy”). Statins can reduce TG levels by 7%—30% and increase HDL-C levels by 5%—15%.

Statins can be administered once per day at any time. However, the administration of LDL-C at night might be associated with higher levels of LDL-C reduction. After the expected efficacy of statin administration is obtained, the long-term administration should be continued. If patients can tolerate this treatment, then drug withdrawal should be avoided. Previous studies have suggested that statin withdrawal might increase the development of cardiovascular events.\(^{[67]}\) If adverse reactions occur after statin administration, then this treatment should be replaced with another type of statin, the dose should be reduced, and drug administration should be performed every other day;\(^{[68]}\) otherwise, other non-statin lipid lowering drugs should be used.

The analytic results of the Cholesterol Treatment Trials’ (CTT) collaboration indicate that when LDL-C is reduced by 1 mmol/L after statin therapy in populations with different cardiovascular risk stratifications, the relative risk of major cardiovascular events is reduced by 20%, and all-cause mortality is reduced by 10%, whereas the mortality caused by non-cardiovascular reasons does not increase.\(^{[57,69]}\) Current studies have repeatedly confirmed that the level of clinical reduction benefits of ASCVD by statins is linearly and positively correlated with the level of LDL-C reduction. The clinical benefits produced by statin therapy originate from the effect of LDL-C reduction. The levels of LDL-C reduction via different types and doses of statins are shown in Table 6.\(^{[35]}\)

Although Xuezhikang capsules are classified as a lipid-lowering Chinese medicine, their lipid-lowering mechanism is similar to that of statins. These capsules are refined via the biological fermentation of a special monosaccharide added to rice using the modern GMP standard manufacturing process. The main ingredients of these capsules include 13 types of natural statin compounds, including lovastatin without a crystal structure and its homologs. The commonly used dose is 0.6 g twice per day. The China Coronary Secondary Prevention Study (CCSPS) and other clinical studies confirmed that Xuezhikang capsules reduce cholesterol and significantly reduce the overall mortality of patients with coronary heart disease, the incidence of cardiovascular events, and number of side effects.\(^{[70–73]}\)

Table 6. The cholesterol reduction intensity of stains.

<table>
<thead>
<tr>
<th>High intensity (daily dose can reduce LDL-C by ≥ 50%)</th>
<th>Medium intensity (daily dose can reduce LDL-C by 25%–50%)</th>
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<tbody>
<tr>
<td>Atorvastatin 40–80 mg*</td>
<td>Atorvastatin 10–20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 mg</td>
<td>Rosuvastatin 5–10 mg</td>
</tr>
<tr>
<td>Fluvastatin 80 mg</td>
<td>Fluvastatin 40 mg</td>
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<tr>
<td>Lovastatin 40 mg</td>
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<tr>
<td>Pravastatin 40 mg</td>
<td>Xuezhikang 1.2 g</td>
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<tr>
<td>Simvastatin 20–40 mg</td>
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<tr>
<td>Xuezhikang 1.2 g</td>
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*Studies of atorvastatin (80 mg) among the Chinese population are limited; please use with caution. LDL-C: low-density lipoprotein cholesterol.
Most people show excellent tolerance to statins. Adverse reactions are primarily observed in patients who receive large doses of statin therapy. The most common manifestations are discussed below.

1. Abnormal liver function.[74,75] The main presentation of this condition is the increase of transaminases. The incidence is approximately 0.5%–3%, and it shows dose dependence. Patients with an increase of serum alanine aminotransferase (A), aspartate aminotransferase (AST) higher than three times the upper limit of normal values, and the combined increase of total bilirubin should reduce or discontinue drug use. Patients with an increase of transaminases within three times of the upper limit of normal values can be observed based on the original doses or reduced doses. Some patients can restore normal transaminases after this treatment. The application contraindications of statins are decompensated cirrhosis and acute liver failure.

2. Statin-related adverse muscle reactions include myalgia, myositis, and rhabdomyolysis.[76,77] When patients have muscle discomfort, weakness, or both and continuous creatine kinase detection shows progressive increases, statins doses should be reduced or the drugs should be discontinued.

3. The long-term administration of statins might increase the risk of new-onset diabetes.[78] The incidence is approximately 10%–12%, and it is classified as a statin effect. The overall benefits of statins on cardiovascular diseases are more significant than the risk of new-onset diabetes. Patients with diabetes or those at high risk for diabetes who have statin therapy indications should adhere to the administration of this group of drugs.

4. Statin therapy can cause cognitive dysfunction.[79] However, this dysfunction is transient, and its incidence is not high. The results of a meta-analysis showed that statins do not have adverse effects on renal function.[80] The adverse reactions of statins also include headache, insomnia, and depression as well as digestive tract symptoms such as indigestion, diarrhea, abdominal pain, and nausea.

10.1.2 Cholesterol absorption inhibitors

Ezetimibe can effectively inhibit cholesterol absorption in the intestinal tract. The IMPROVE-IT study indicated that the administration of ezetimibe based on simvastatin further reduces the likelihood of cardiovascular events in patients with ACS.[41] The SHARP study showed that a combined treatment with ezetimibe and simvastatin improves cardiovascular disease prognosis in patients with CKD.[81] The recommended dose of ezetimibe is 10 mg/day. This drug shows excellent safety and tolerance, and the adverse reactions are mild and mostly transient. The major presentations are headache and digestive tract symptoms. When combined with statins, ezetimibe can produce adverse reactions such as transaminase increases and myalgia. Ezetimibe is prohibited during pregnancy and lactation.

10.1.3 Probucol

Probucol influences lipoprotein metabolism through an incorporation into the core of LDL-C particles; thus, LDL-C is easily cleared through the non-receptor pathway. The commonly used dose of probucol is 0.5 g twice per day. This drug is primarily applicable for patients with hyperlipidemia, especially those with HoFH or xanthoma. Probucol relieves skin xanthomas.[82,83] Its common adverse reactions are gastrointestinal in nature. Probucol can also induce dizziness, headache, insomnia, and skin rash. Rare but severe adverse reactions include QT interval prolongation. Probucol is prohibited for patients with ventricular arrhythmia, QT interval prolongation, or hypokalemia.

10.1.4 Bile acid sequestrants

Bile acid sequestrants are basic anion exchange resins. They can block the reabsorption of cholesterol in the bile acid in the intestinal tract.[84] The clinical dosage of cholestyramine is 5 g three times per day, 5 g of colestipol three times per day, and 1.875 g of colesevelam twice per day. When combined with statins, these drugs can significantly increase lipid-lowering efficacy. The most common adverse reactions include gastrointestinal discomfort and constipation; furthermore, they can influence the absorption of certain drugs. The absolute contraindications of this group of drugs are abnormal dysbetalipoproteinemia and serum TG > 4.5 mmol/L (400 mg/day).

10.1.5 Other lipid-lowering drugs

Zhibitai is a compound preparation of monascus and traditional Chinese medicine (i.e., hawthorn, alisma, and atrac-tylodes). The most commonly used dose is 0.24–0.48 g twice per day. This compound has mild-to-moderate cholesterol-reducing functions.[85,86] This drug has few adverse reactions.

Policosanol is a mixture containing 8 types of advanced aliphatic alcohol purified from sugarcane wax. The most commonly used dose is 10–20 mg/day. Its lipid-lowering effect is slow, and rare but adverse reactions are known.[87,88]

10.2 Major TG-lowering drugs

Three major TG-lowering drugs exist: fibrates, niacin, and high-purity fish oil preparations.

10.2.1 Fibrates

Fibrates reduce serum TG levels and increase HDL-C
levels through the activation of peroxisome proliferator activated receptor-α (PPARα) and lipoprotein lipase (LPL).\[^{89-93}\]

The most commonly used fibrates include fenofibrate tablets 0.1 g three times per day, micronized fenofibrate 0.2 g once per day, gemfibrozil 0.6 g twice per day, and bezafibrate 0.2 g three times per day. The most common adverse reactions are similar to those of statins, including liver, muscle, and kidney toxicities. The incidence rates of increased serum creatine kinase and ALT levels are both < 1%. Meta-analyses of clinical trial results have shown that fibrates can reduce the risk of cardiovascular events in people with high TG combined with low HDL-C by approximately 10%. These drugs primarily reduce nonfatal myocardial infarction and coronary revascularization, but they do not significantly affect cardiovascular mortality, fatal myocardial infarction, or stroke.\[^{90-92}\]

10.2.2 Niacin

Niacin, also known as vitamin B3, is an essential vitamin in the human body. Niacin can decrease TC, LDL-C, and TG as well as increase HDL-C in large doses. Its lipid-lowering function is associated with the inhibition of hormone-sensitive lipase activities in adipose tissue, the reduction of free fatty acid entry into the liver, and the decrease of VLDL secretion. Niacin has two formulation types: general and sustained-releasing. The sustained-releasing formulation is more commonly used. The most commonly used dose of sustained-releasing tablets is 1–2 g once per day. Starting with a small dose (0.375–0.5 g/day) before going to bed is recommended. After four weeks, the dose gradually increases to the commonly used maximum dose. The most common adverse reaction is facial flushing. Other reactions include liver damage, hyperuricemia, hyperglycemia, acanthosis, and gastrointestinal discomfort. Niacin is prohibited for patients with chronic active liver disease, active peptic ulcer, or severe gout. The results of a meta-analysis of early clinical trials showed that whether used alone or as a combined application with other lipid-lowering drugs, niacin improves cardiovascular prognosis, reduces the risk of cardiovascular events by 30%, and reduce the risk of coronary events by 25%.\[^{94}\] Because clinical studies concerning the combination of niacin based on statins suggest that no cardiovascular protective function exists compared with using statins alone,\[^{95,96}\] niacin is being phased out of the lipid-lowering drug market in many European and American countries.

10.2.3 High-purity fish preparations

The main ingredient of fish oil is n-3 fatty acid (i.e., ω-3 fatty acids). The common dose is 0.5–1.0 g three times per day. Fish oil is primarily used to treat hypertriglycerideremia.\[^{97-99}\] Adverse reactions such as digestive tract symptoms are rare, and their incidence is approximately 2%–3%. A few patients have mild increases of transaminases or creatine kinase; a bleeding tendency is sometimes observed. An early clinical study showed that high-purity fish oil preparations reduce the risk of cardiovascular events,\[^{100}\] however, subsequent clinical trials did not confirm this result.\[^{101,102}\]

10.3 New types of lipid-lowering drugs

Three new types of lipid-lowering drugs have recently been approved for clinical applications in other countries.

10.3.1 Microsomal triglyceride transfer protein inhibitors

Lomitapide (brand name, Juxtapid) was approved for the market by the US Food and Drug Administration (FDA) in 2012. It is primarily used to treat HoFH. Lomitapide can reduce LDL-C by approximately 40%. This drug has higher adverse reaction rates, and the major presentations are an increase of transaminases or fatty liver.\[^{103,104}\]

10.3.2 Apolipoprotein B\(_{100}\) synthesis inhibitors

Mipomersen is a second-generation anti-sense oligonucleotide. In 2013, the FDA approved it for use alone or combined with other lipid-lowering drugs to treat HoFH. The action mechanism is an anti-sense oligonucleotide that targets the transcription of Apo B messenger ribonucleic acid (mRNA) to reduce VLDL synthesis and secretion and LDL-C levels. This drug can reduce LDL-C levels by 25%. The most common adverse reaction is an injection site reaction including local rash, swelling, itching, and pain. Most adverse reactions are mild to moderate.\[^{105}\]

10.3.3 PCSK9 inhibitor

PCSK9 is a secretory serine protease synthesized by the liver that can bind to the LDL-C receptor to cause its degradation, thereby reducing the clearance of serum LDL-C via the LDL-C receptor. Through the inhibition of PCSK9, LDL-C receptor degradation can be blocked to promote LDL-C clearance. Among PCSL09 inhibitors, the development PCSK9 monoclonal antibodies is the most rapid, and additional studies exist on alirocumab, evolocumab, and bococizumab. These study results show that whether used alone or combined with statins, PCSK9 inhibitors significantly reduce serum LDL-C levels and improve other blood lipid indicators including HDL-C and Lp (a). The European Medicines Agency and the US FDA have already approved two injection-type PCSK9 inhibitors (evolocumab and alirocumab) for the market. Preliminary clinical study results indicate that PCSK9 inhibitors can reduce LDL-C and cardiovascular events by 40%–70%.\[^{106,107}\] Currently, no re-
ports regarding severe or life-threatening adverse effects have been published.\textsuperscript{[108]} This drug is still in the clinical trial stage in China.

10.4 Combined application of lipid-lowering drugs

The combined application of lipid-lowering drugs represents a trend of intervention measures for dyslipidemia. The advantage of a combined application is to increase the goal attainment rate of blood lipids and simultaneously reduce the incidence of adverse reactions. Statin functions have been recognized; few adverse reactions are known that can reduce overall mortality. The combined lipid-lowering programs are primarily composed of statins and other types of lipid-lowering drugs with different action mechanisms. Different programs exist for the application of drug combinations targeting the different action mechanisms of lipid-lowering drugs.

10.4.1 Combined application of statins and ezetimibe

Two types of drugs can individually influence cholesterol synthesis and absorption to produce excellent synergistic effects. Combined treatment can reduce serum LDL-C based on statin therapy by approximately 18\%, but it does not increase the adverse reactions of statins.\textsuperscript{[109–111]} Many clinical trials have observed that ezetimibe combined with different types of statins shows excellent lipid-lowering effects.\textsuperscript{[110,112,113]} The IMPROVE-IT and SHARP studies independently showed that the administration of combined statins and ezetimibe in people with high-risk ASCVD and patients with CKD reduces the risk of cardiovascular events.\textsuperscript{[41,81]} People whose cholesterol levels do not reach the target after a medium-intensity statin therapy or who show intolerance should consider medium-to-low intensity statins combined with ezetimibe therapy (Class I recommendation (Level B evidence).

10.4.2 Combined application of statins and fibrates

The combination of these two drugs effectively reduces LDL-C and TG levels, increases HDL-C levels, and reduces sLDL-C. Fibrates include fenofibrate, gemfibrozil, and bezafibrate; of these compounds, fenofibrate has been the most studied and is associated with the most sufficient evidence.\textsuperscript{[114]} Previous studies have suggested that the combined application of statins and fenofibrate increases cardiovascular benefits among patients with high TG combined with low HDL-C.\textsuperscript{[115]} Fenofibrate is applicable for patients with severe hypertriglyceridemia with or without mixed hyperlipidemia of low HDL-C levels, especially for those with accompanied dyslipidemia, diabetes, and metabolic syndrome and high-risk cardiovascular patients who show poor control of their TG or HDL-C levels after statin therapy. Because the metabolic pathways of statins and fibrates are similar, they both have the possibility of damaging the liver function and risk myositis and myopathy. The chances of an adverse reaction during combined application can increase. Therefore, the safety of the combined application of statins and fibrates should be highly focused. Gemfibrozil combined with statins show relatively higher risks of myopathy. In the beginning of a combined application, small doses should be used via the administration of fibrates in the morning and the administration of statins at night to avoid significant increases in the blood drug concentration. In addition, muscle enzymes and liver enzymes should be monitored closely. If adverse reactions occur, then the dose of statins can be gradually increased.

10.4.3 Combined application of statins and PCSK9 inhibitors

Although PCSK9 inhibitors are still not on the Chinese market, the combined application of statins and PCSK9 inhibitors has already become a method for treating patients with severe dyslipidemia, especially those with FH, in Europe and America. This treatment can cause greater reductions in LDL-C levels and increase goal attainment rates compared with other single drug treatments. Patients with FH, especially those with HoFH, treated with the largest dose of lipid-lowering drugs (e.g., statins+ezetimibe) and lifestyle modification as well as patients with ASCVD and LDL-C levels $> 2.6$ mmol/L can also use PCSK9 inhibitors, constituting the combined application of three lipid-lowering drugs with different action mechanisms.

10.4.4 Combined application of statins and n-3 fatty acids

The combined application of statins and fish oil preparation n-3 fatty acids can be used to treat mixed hyperlipidemia without increasing adverse reactions. Because taking larger doses of n-3 polysaturated fatty acids has a bleeding risk and increases calorie intake in obese patients with diabetes, long-term application is not appropriate. Whether this combination can reduce cardiovascular events is currently under investigation.

11 Other measures for dyslipidemia treatment

11.1 Lipoprotein-plasma exchange

Highlights: Lipoprotein-plasma exchange, liver transplantation, partial ileal bypass surgery, and portacaval shunt are used as adjuvant treatment measures for patients with FH. The effect of lipoprotein-plasma exchange has been recognized.
Lipoprotein-plasma exchange is an important adjuvant treatment measure for patients with FH, especially for those with HoFH. This treatment can reduce LDL-C levels by 55%–70%. Long-term treatment can cause a reduction of skin xanthomas. The best treatment frequency is once each week. Currently, however, treatments are typically performed once every two weeks. Lipoprotein-plasma exchange can be persistently performed during pregnancy. This treatment measure is expensive, time-consuming, and risks infection. Adverse reactions include hypotension, abdominal pain, nausea, hypocalcemia, iron-deficiency anemia, and allergic reaction. However, with the development of science, technology, and materials, the incidence of relevant adverse reactions has already decreased.

11.2 Liver transplantation and other surgical treatments

Liver transplantation can significantly improve LDL-C levels. Although simple liver transplantation or liver transplantation combined with heart transplantation is a successful treatment strategy, many problems exist including many post-transplantation complications, high mortality rates, a lack of donors, and the lifetime administration of immunosuppressive agents. Therefore, this treatment is rarely performed in clinical practice. Although partial ileal bypass and portacaval shunt are not recommended, they should be considered when more effective treatment is lacking for patients with severe HoFH.

12 Management of dyslipidemia in special populations

12.1 Diabetes

The major presentations of diabetes combined with dyslipidemia are increased TG, decreased HDL-C, and increased or normal LDL-C. Lipid-lowering treatment can significantly reduce the risk of developing cardiovascular events in patients with diabetes. The target level of LDL-C should be confirmed based on the severity of cardiovascular risks. Patients with diabetes aged 40 years or older should control their serum LDL-C levels below 2.6 mmol/L (100 mg/dL) and maintain their target values of HDL-C above 1.0 mmol/L (40 mg/dL). The principle of dyslipidemia treatment in patients with diabetes follows the ASCVD risk assessment flow chart (Figure 1) for intervention management. According to the features of dyslipidemia, the preferred choice is statin therapy. If patients have combined high TG levels or do not have combined low HDL-C levels, a combination application of statins and fibrates can be used.

12.2 Hypertension

For patients with hypertension and dyslipidemia, lipid-lowering treatments should be applied to determine lipid-lowering target values according to different risk levels (Figure 1). Lipid-lowering treatments enable most patients with hypertension to obtain adequate benefits. The results are often more prominent with regard to the reduction of coronary heart disease events. Therefore, the hypertension guidelines recommend that patients with hypertension and medium risk should initiate statin therapy. The newly released HOPE-3 study results suggest that statin therapy significantly reduces cardiovascular events for people at medium risk. For the subgroup population with systolic pressure >143.5 mmHg, the combined application of statins and antihypertensive drugs reduces cardiovascular risks more significantly.

12.3 Metabolic syndrome

Metabolic syndrome is a group of clinical conditions that combine the development of obesity, high blood glucose (sugar regulation impairment or diabetes), hypertension, and dyslipidemia (hypertriglyceridemia, HDL-C hypolipidemia, or both). One feature is the combination of interrelated risk factors in the body metabolism of the same individual. These factors directly promote ASCVD development and increase the risk of developing type 2 diabetes. Some evidence indicates that patients with metabolic syndrome are most likely to develop cardiovascular disease. Compared with people without metabolic syndrome, their risks for developing cardiovascular disease and type 2 diabetes are significantly increased.

The current cutoff points for determining the hyperglycemia, hypertension, and dyslipidemia aspects of metabolic syndrome were reached via a worldwide consensus. However, the core indicator of metabolic syndrome, obesity (especially central obesity), has different diagnostic criteria. The diagnostic criteria of metabolic syndrome formulated based on study evidence taken from the Chinese population should include three or more of the following items: (1) Central obesity/abdominal obesity: a waist circumference for men of ≥ 90 cm and that for women of ≥ 85 cm; (2) Hyperglycemia: fasting blood glucose ≥ 6.10 mmol/L (110 mg/dL) or 2-h blood glucose after glycemic load ≥ 7.80 mmol/L (140 mg/dL) or patients with confirmed diabetes who have received treatment; (3) Hypertension: blood pressure ≥ 130/85 mmHg or patients with hypertension who have received treatment; (4) Fasting TG ≥ 1.7 mmol/L (150 mg/dL); and (5) Fasting HDL-C < 1.0 mmol/L (40 mg/dL).

The major goal of metabolic syndrome management is to prevent ASCVD and type 2 diabetes. Patients who already
have ASCVD should seek to prevent cardiovascular events. Active and sustained lifestyle interventions are important measures to achieve these treatment goals. In principle, lifestyle treatments should be initiated first. If these goals cannot be achieved, then corresponding drug treatments should be adopted to target each component. The treatment goals for dyslipidemia in metabolic syndrome are LDL-C < 2.6 mmol/L (100 mg/dL), TG < 1.7 mmol/L (150 mg/dL), and HDL-C ≥ 1.0 mmol/L (40 mg/dL).

12.4 CKD

CKD is usually accompanied by dyslipidemia and can promote the development of ASCVD. No clinical study has investigated the LDL-C treatment goal of patients with CKD. Under the premise of tolerance, patients with CKD are advised to receive statin therapy. The treatment goals for patients with mild-to-moderate CKD are LDL-C < 2.6 mmol/L and non-HDL-C < 3.4 mmol/L; those for patients with severe CKD and CKD combined with hypertension or patients with diabetes are LDL-C < 1.8 mmol/L and non-HDL-C < 2.6 mmol/L. Medium-intensity statin therapy is recommended. When necessary, cholesterol absorption inhibitors are combined. For patients with end-stage renal disease (ESRD) and those receiving hemodialysis, the risks and benefits of cholesterol-lowering treatments should be assessed carefully. Drug selection and the setting of the LDL-C goal should be personalized.

Patients with CKD represent a population at high risk for statin-induced myopathy, especially when renal function has shown a progressive decline or the glomerular filtration rate (GFR) is < 30 mL/min per 1.73 m². In addition, the risk of disease development is closely associated with the statin dosage; therefore, the administration of large doses should be avoided. When LDL-C cannot reach the target level after treatment with medium-intensity statins, combination therapy with ezetimibe is recommended. Fibrate drugs can increase creatinine levels; when combined with statins among patients with moderate-to-severe CKD, the risk of myopathy might be increased.

12.5 FH

FH is an autosomal dominant hereditary cholesterol metabolism disorder. The pathogenic mechanism of FH is the functional genetic mutations on the LDL-C receptor, and a small number of cases are caused by functional mutations on Apo B or PCSK9. The newly discovered mutations on the LDL-C receptor modulator gene also explain the development of FH. The prominent clinical manifestations are the significant increase of serum LDL-C levels and early-onset coronary heart disease (myocardial infarction or angina pectoris). According to dominant genetic characteristics, the clinical phenotypes of FH are divided into the homozygous type (HoFH) and the heterozygous type (HeFH). Cholesterol level screening shows that the serum TC level of HeFH is usually > 8.5 mmol/L (328 mg/dl), and the serum TC level of HoFH is usually > 13.5 mmol/L (521 mg/dl). Left untreated, HeFH patients usually develop cardiovascular disease after 40 years (men) or 50 years (women) of age. HoFH patients typically develop severe cardiovascular disease during childhood, and the mortality rate from cardiovascular diseases in early adulthood is 100 times higher than that among non-FH patients.

The ultimate goal of FH treatment is to reduce the risk of ASCVD and decrease the development of fatal and disabling cardiovascular diseases. One focus of treatment is that all patients with FH (including HoFH and HeFH patients) should make enhanced therapeutic lifestyle changes to their diets (i.e., reduce lipid and cholesterol intake and consume a comprehensive balanced diet), exercise, and behavioral habits (i.e., quit smoking and reduce body weight). In addition, the management of other risk factors (e.g., hypertension and diabetes) should be emphasized. Next, patients with FH should adhere to long-term statin therapy beginning in adolescence to significantly reduce the risk of ASCVD. The target level of lipid-lowering treatment is the same as that for people at high cardiovascular risk. LDL-C is reduced by 25% in people with low LDL-C receptors after receiving statin therapy but only by 15% in people without LDL-C receptors. In fact, patients with FH usually require combined treatment with two or more types of lipid-lowering drugs. Patients at very high cardiovascular risk whose cholesterol levels still do not reach target levels after a combined lipid-lowering treatment, especially those with disease in progress, should consider receiving lipoprotein-plasma exchange as an adjuvant therapy.

12.6 Stroke

Whether other evidence of combined treatments for atherosclerosis exists, the use of long-term statin treatment for patients with non-cardiogenic ischemic stroke or TIA is recommended to reduce the risk of stroke and cardiovascular events (Class I recommendation, Level A evidence). If the baseline LDL-C level of patients is ≥ 2.6 mmol/L (100 mg/dL), then evidence of the treatment effect of statins is clear; if the baseline level of LDL-C is < 2.6 mmol/L (100 mg/dL), then clinical evidence is lacking. For patients with ischemic stroke resulting from intracranial large atherosclerotic stenosis (stenosis rate: 70%–99%) or patients with TIA, the recommended target value is LDL-C < 1.8 mmol/L (70 mg/dL; Class I recommendation, Level B evidence).
long-term administration of statin therapy is safe in general. For patients with non-cardiogenic ischemic stroke and a history of cerebral hemorrhage or patients with TIA, statins can be reasonably used after weighing the risks and benefits.

12.7 Elderly people

Elderly people ≥ 80 years old usually have many types of chronic diseases and take various types of drugs. Attention should be paid to the interaction among drugs and their adverse reactions. Most elderly patients have different degrees of liver and kidney dysfunction; therefore, the selection of doses of lipid-lowering drugs should be individualized. The initial dose should not be too high, and the doses of lipid-lowering drugs should be adjusted based on treatment effects; in addition, liver and kidney function and creatine kinase should be closely monitored. Because no randomized controlled studies regarding the target goals of statin therapy have been conducted among elderly patients, there are no special recommendations concerning these patients. Current studies indicate that elderly patients with hypercholesterolemia combined with cardiovascular disease or diabetes benefit from lipid-lowering therapy.

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Appendix

Appendix 1. Recommendations for the clinical determination of blood lipids.

Blood lipid measurement is an important component of the management of dyslipidemia. The accuracy of the detection results is the basic requirement for the effective management of dyslipidemia. Many factors influence the accuracy of blood lipid measurement results, including test participants and specimen conditions, measurement methods, instruments and reagents, and measurement manipulation. According to the current and relevant recommendations of the Chinese Society of Laboratory Medicine of the Chinese Medical Association, the relevant industrial and national standards in China, actual blood lipid measurement conditions in China, and the combined opinions of the Joint Committee of the Revision of the Chinese Guidelines for the Management of Dyslipidemia in Adults, the recommendations concerning the measurement of blood lipid items [including serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteins (Apo) A1, Apo B, and lipoprotein (a)] should promote the further standardization of blood lipid measurement in China and ensure the effective management of dyslipidemia.

1 Participant preparation and specimen collection

Many pre-analysis factors influence blood lipid levels including biological factors such as between-individual factors, including gender, age, and race; behavioral factors, such as diet, obesity, smoking, stress, alcohol drinking, coffee drinking, and exercise; clinical factors, such as secondary disease (i.e., endocrine or metabolic diseases, kidney diseases, hepatobiliary disease, and others) and drug induction (i.e., antihypertensive drugs, immunosuppressive agents, and estrogen); and specimen collection and processing factors, such as fasting status, blood concentration, anticoagulants, preservatives, capillary and venous blood, and specimen storage. The following measures to reduce the influence of controllable pre-analysis factors on blood lipid measurement results are recommended:

(1) Participants should be in a stable metabolic state before specimen collection and maintain general eating habits and a stable body weight for at least 2 weeks;
(2) Participants should not perform strenuous physical activity within 24 h of specimen collection;
(3) Participants should fast for approximately 12 h before specimen collection;
(4) Venous blood should be used as a specimen for blood lipid measurement. Participants should sit and rest for at least 5 min before blood drawing. Except under special conditions, participants should sit for blood drawing;
(5) A tourniquet should not be more than 1 min during venous puncture;
(6) Blood specimens should remain sealed, and shaking should be avoided;
(7) Serum samples should be used for blood lipid analyses. Blood specimens are centrifuged within 1–2 h to separate the serum (tubes containing anti-coagulants can be centrifuged within a briefer time period); and
(8) Serum samples should be analyzed in time to avoid storage. If the sample must be stored, then they should remain sealed. They can be stored at 4°C for up to 3 day; samples should be stored below 70°C for long-term storage.

2 Selection of detection methods

The principles of all blood lipid measurement methods differ. The analytic performance, openness, and analyses cost are also different. Routine blood lipid measurement should select appropriate measurements based on relevant conditions.

2.1 Serum TC detection

The measurements of serum TC include chemical, chromatography, and enzymatic methods. Enzymatic methods are the simplest; they are easy to automate and show excellent analytic performance. Therefore, they are currently the most commonly used methods for routine TC measurements. Other methods are currently only used under certain conditions (e.g., specific chemical methods and chromatography are used as reference methods). Enzymatic methods are recommended for routine TC measurements.

2.2 Serum TG detection

Methods for serum TG measurement include chemical, chromatography, and enzymatic methods. Currently, enzymatic methods are the most commonly used routine TG measurements. Currently, most TG enzymatic methods measure total glycerol. Some enzymatic methods deduct free glycerol. Enzymatic methods are recommended for routine serum TG measurement. Generally, the total glycerol measurement
can be used. When necessary, measurement methods that eliminate the influence of free glycerol should be considered.

2.3 Serum HDL-C detection

Many methods for HDL-C measurement exist, and these methods can roughly be divided into ultracentrifugation, electrophoresis, chromatography, precipitation, and homogeneous methods. Previous routine HDL-C measurements primarily used precipitation methods. The precipitation methods that pass strict certification can achieve a high analytic specificity. However, their major shortcomings are that specimens should undergo processing methods such as precipitation and centrifugation in advance. High TG levels easily affect the results. The current major methods for routine HDL-C measurement are homogenous methods including clearance, polyethylene glycol (PEG)-modified enzyme, selective inhibition, and immune separation methods. The greatest advantages of homogeneous methods are ease of use, no sample processing is required, and they show excellent analytic performance. However, some methods might have a specificity issue. Homogeneous methods are recommended for routine serum HDL-C measurement.

2.4 Serum LDL-C detection

The measurement methods for serum LDL-C include ultracentrifugation, electrophoresis, chromatography, formula calculation, precipitation, and homogeneous methods. The major methods are formula calculation, precipitation, and homogeneous methods. Formula calculation methods were once the most commonly used LDL-C measurement worldwide. They remain extensively used in certain countries. The most used formula is the Friedewald formula, where LDL-C = TC − HDL-C − TG/5 (mg/dL) or LDL-C = TC − HDL-C − TG/2.2 (mmol/L). The greatest advantages of this method are that no detection is required and the formula is easy to calculate. When TG is < 2.8 mmol/L (250 mg/dL), a certain level of reliability is present. The limitations are that it cannot be used when TG > 4.5 mmol/L (TG > 400 mg/dL); alternatively, the measurement quality of three indicators (TC, TG and HDL-C) affect the LDL-C results in some specimens of abnormal lipoproteinemia. Some countries formerly used precipitation methods for LDL-C measurement. However, due to their limited specificity and complicated manipulation, their application is not extensive. Homogeneous methods are currently the major methods for LDL-C measurement in China; these methods include clearance, calixarene, solubilization reaction, and protecting reagent methods. This group of methods is easy to use and can be applied to analyze high TG samples. However, some methods might have specificity issues. Homogeneous methods are recommended for routine LDL-C measurement.

2.5 Serum Apo A1, Apo B, and Lp (a) detection

The measurement of serum Apo A1, Apo B, and Lp (a) is based on immunochemistry principles. Early measurements primarily used immunoelectrophoresis and radiomuno- and enzyme-linked immunosorbent assays. These methods are associated with complicated manipulations, and their analysis performance is limited; therefore, they are currently rarely used. The current immunoturbidimetric assay primarily used includes transmission turbidimetry and nephelometry. These methods are easy to use and show excellent performance. Some Lp (a) measurements might have obvious specificity issues. Immunoturbidimetric assay is recommended for routine measurements of serum Apo A1, Apo B, and Lp (a).

3 Selection of analysis systems

The specific instrument, reagents, standard materials, and working parameters required for the operation of the above methods are known as “analysis systems”. Currently, routine blood lipid measurements generally use commercial instruments, reagents, and calibration materials. Many brands exist; therefore, many analysis systems are available to perform the same method. Different analysis systems usually show different analysis performances. Therefore, the selection of a reliable analysis system is the key to ensure the quality of blood lipid analyses.

3.1 Types of analysis systems

The automation level of analytic instruments can be divided into fully automatic (automatic biochemical analyzers), semi-automatic (semi-automatic analyzers), and manual (spectrophotometer) analysis systems. In addition to analytic instruments, reagents, and calibration materials, semi-automatic and manual analysis systems also include equipment and apparatuses for liquid transfer and incubation. Currently, most clinical laboratories in China use fully automatic analysis systems. Certain small laboratories might use semi-automatic analysis systems. Automation degree negatively predicts the number of influencing factors. Fully automatic analysis systems are recommended for routine blood lipid measurements. When appropriate, semi-automatic analysis systems can be used.

Based on the sources of instruments, reagents, and calibration materials, analysis systems can be divided into 3 types: (1) closed system (i.e., the instruments, reagents, and calibration materials are from the same vendor; they are
used in matches; and the working parameters are built-in); (2) open system (i.e., the reagents and calibration materials are from the same vendor and used in matches; the instruments are selected elsewhere; and the reagent vendors usually provide the parameters); and (3) combination system (i.e., the instruments, reagents, and calibration materials are from different vendors or institutions and assembled by laboratories; and the laboratories established the working parameters). Currently, all three types of analysis systems are extensively used in China. Laboratories can choose their analysis system based on their specific conditions.

3.2 Quality and technique indicators of analysis systems

The selected analysis systems should conform to the following quality and technique indicators.

3.2.1 Precision, correctness, and accuracy

Precision refers to the degree of consistency among results obtained from the repeated analysis of the same sample across multiple independent analyses. This variable reflects the random error of the analysis system, and it is expressed as the variation coefficient. The variation coefficients of serum measurements of TC, TG, HDL-C, LDL-C, Apo A1, Apo B, and Lp (a) should be lower than 3%, 5%, 4%, 4%, 3%, 3%, and 4%, respectively.

Correctness refers to the difference between the mean of the results obtained from repeated analyses of the same sample across multiple independent detection analyses and the target value. This variable reflects the system error of the analysis system, and it is expressed as a deviation (B). The target value usually refers to the definite value of the reference (standard) material or the value measured using reference methods. The measured deviations of serum TC, TG, HDL-C, LDL-C, Apo A1, Apo B, and Lp (a) should be within the ranges of ±3%, ±5%, ±4%, ±5%, ±5%, ±5%, ±10%, respectively.

Accuracy refers to the maximum difference between the obtained results from the analysis of many representative samples within a single time period across multiple independent detection analyses and the target value, which is expressed using total error. The target value generally refers to the measurement value using reference methods or other reliable methods. Assuming that the analysis system shows excellent specificity, accuracy is determined via precision and correctness (expressed using the formula total error = absolute value of deviation + 1.96 × variation coefficient). The total errors of serum TC, TG, HDL-C, and LDL-C should be lower than 9%, 15%, 13%, and 12%, respectively.

Precision, correctness, and (especially) accuracy are the main quality indicators of the analysis system. Currently, the precision of most blood lipid analysis systems in China are excellent. Some analysis systems might have correctness and accuracy issues.

3.2.2 Specificity

Specificity is an important factor affecting accuracy. The analysis system should have the ability that it only functions with regard to target blood lipid indicators and is not influenced by other serum components. Currently, the TC and TG analysis systems in China show excellent specificity. Some lipoprotein and Apo analysis systems might have specificity issues.

3.2.3 Calibration

Calibration is the decisive factor of accuracy. The analysis of the value of the calibration materials in the system should be able to track clinical specimen measurement results to the existing reference system.

3.2.4 Detection range

The detection range of the analysis system should cover the following blood lipid ranges: TC, 2–10 mmol/L; TG, 0.3–10 mmol/L; HDL-C, 0.3–2.5 mmol/L; LDL-C, 0.5–7 mmol/L; ApoA1 0.5–2.0 g/L; ApoB 0.5–2.0 g/L and Lp (a), 5–800 mg/L.

3.3 Validation of analysis system performance

Any newly selected analysis system should receive a performance validation before being used with regard to a clinical sample to ensure that its performance can meet the aforementioned quality technical indicators. The specific validation methods should reference relevant industrial standards or literature.

3.4 Blood lipid analysis

A blood lipid analysis for clinical specimens is performed using a validated analysis system. Analysis manipulation is performed according to the procedures regulated in the instructions of the analysis system or reagents.

4 Quality control and assurance

Clinical laboratories should regulate the working conditions and procedures of all major links in blood lipid measurement. Blood lipid measurement should be performed according to regulations.

In Chinese medical institutions, specimen collection and detection analysis research usually occurs in different departments. Different departments should communicate closely to ensure the effective implementation of relevant working
procedures to try to minimize the effect of pre-analysis factors on blood lipid measurement.

Clinical laboratories should select blood lipid measurement methods and analysis systems (primarily the brands of reagents and calibration materials) with reliable performance according to experience, industrial communications, and the scientific literature. They should try to keep the same type of analysis system, which should not be changed arbitrarily or frequently.

Clinical laboratories should perform internal quality control. Quality control samples should be appropriate for blood lipid analysis, homogeneous, and stable. The concentrations should approximate the main medical decision levels and have at least two levels. The same type of quality control samples should be used for as long as possible and should not be changed frequently. The analysis of quality control samples should be performed at least once for each batch of detection analyses.

Clinical laboratories should regularly participate in nationally or regionally recognized quality assessment plans across laboratories.

5 Result report and explanation

Clinical laboratories should report TC, TG, HDL-C, and LDL-C measurement results using the Chinese legal unit of measurement (mmol/L). When necessary, results using the traditional unit (mg/dL) can be reported.

Blood lipid examination reports should indicate the major medical decision levels regulated by the Chinese Guidelines for the Management of Dyslipidemia.

The explanation of blood lipid detection results should consider analytic variations and the influence of biological variations among individuals. If blood lipid results approximate the medical decision level, then a decision should be made based on multiple blood lipid measurement results.


<table>
<thead>
<tr>
<th>Pressure level</th>
<th>Male</th>
<th>Non-smoking</th>
<th>Smoking</th>
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<tr>
<td>Normal HDL-C</td>
<td>Low HDL-C</td>
<td>Normal HDL-C</td>
<td>Low HDL-C</td>
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<tr>
<td>Level III</td>
<td>Level II</td>
<td>Level I</td>
<td>Normal</td>
</tr>
<tr>
<td>≥ 20%</td>
<td>10%–15%</td>
<td>5%-9%</td>
<td>&lt;5%</td>
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</table>

<table>
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<tr>
<th>Age group (years)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TC (mmol/L)</td>
<td>LDL-C (mmol/L)</td>
</tr>
<tr>
<td>4.1–6.2</td>
<td>2.6–3.4</td>
</tr>
<tr>
<td>&gt; 7.2</td>
<td>&gt; 4.9</td>
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<tr>
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</table>

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