Postprint of "Similarities and Differences in the Diagnosis and Treatment of Familial Hypercholesterolemia in China and Abroad"

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Abstract

Familial hypercholesterolemia (FH) is a common hereditary metabolic disease, primarily characterized by abnormally elevated low-density lipoprotein cholesterol (LDL-C), and may manifest clinically with corneal arcus, xanthomas, and other signs. Persistently high levels of LDL-C increase the risk of atherosclerotic cardiovascular disease (ASCVD). Patients with FH have a higher risk of premature ASCVD, and the condition is more severe in homozygous FH. The global prevalence of FH has attracted increasing attention, yet gaps remain in its diagnosis and treatment. In the context of the publication of the "2023 Chinese Guideline for Lipid Management," this article mainly compares the differences between domestic and international recommendations on FH screening and diagnosis, in order to emphasize the importance of lipid screening and to advocate for early identification of FH patients. At the same time, genetic testing is also recommended; it should not be limited to a small number of genes, but should include other related genes or even whole-genome testing. In addition, this article compares the differences among various guidelines regarding target LDL-C levels for the management of FH, as well as new elements in ASCVD risk stratification based on different LDL-C thresholds. It also compares differences in dietary recommendations, lifestyle modification, and pharmacologic control, pointing out that there is a consensus domestically and internationally that statins are the main lipid-lowering drugs and that combination therapy is particularly important. However, for patients whose LDL-C remains above target despite maximal statin doses, the international lipid care guidelines have been updated to some extent. Furthermore, for patients with homozygous FH (HoFH), high-intensity statin therapy combined with other agents is the preferred option; early treatment is even more crucial. Appropriately earlier initiation of lipoprotein apheresis and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors helps reduce the incidence and mortality of ASCVD.

Full Text

Familial Hypercholesterolemia: Diagnostic Differences between Domestic and Foreign Guidelines

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Abstract

Familial hypercholesterolemia (FH) is a common genetic metabolic disease characterized by abnormally elevated low-density lipoprotein cholesterol (LDL-C), which may manifest as corneal arcus, xanthomas, and other symptoms. Long-term high levels of LDL-C increase the risk of atherosclerotic cardiovascular disease (ASCVD). FH patients have a higher risk of early-onset ASCVD, with homozygous FH being more severe. The global prevalence of FH has gradually gained attention, but diagnosis and treatment remain inadequate. Leveraging the release of the *2023 Chinese Lipid Management Guidelines*, this article primarily compares domestic and foreign screening and diagnostic approaches to emphasize the importance of lipid screening and recommend early identification of FH patients. Additionally, genetic testing is recommended, including not only a few key genes but also other related genes or whole-genome detection. Furthermore, this article compares different guidelines regarding LDL-C control management levels and new elements of ASCVD risk factors stratified by LDL-C levels. It highlights differences in dietary recommendations, lifestyle advice, and medication control between domestic and foreign guidelines, pointing out that statins are universally recognized as the primary cholesterol-lowering agents, with combination therapy being particularly crucial. However, for patients who fail to achieve LDL-C control after maximally tolerated therapy, international lipid management guidelines have been updated. For homozygous FH (HoFH) patients, high-intensity statin combination therapy with other medications is the preferred approach, and early treatment is critical; timely consideration of lipoprotein apheresis and PCSK9 inhibitors can help reduce the incidence and mortality of ASCVD.

Keywords: Hypercholesterolemia; Molecular basis; Diagnosis; Diagnostic and treatment plan; Guideline; Differences

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Familial hypercholesterolemia (FH) is a common genetic metabolic disease in

which patients often present with elevated low-density lipoprotein cholesterol (LDL-C) in the blood [1], with severe cases developing lipid deposits in various locations (corneal arcus, xanthomas, aortic calcification, etc.) [2]. LDL-C levels in FH are typically 2-4 times higher than in normal individuals [3], and prolonged exposure to high LDL-C levels poses a serious threat to patients' physical and mental health and healthcare burden, whether through earlier onset or increased severity of premature coronary artery disease (CAD). With the release of the 2023 Chinese Lipid Management Guidelines [4], current awareness of FH prevalence has increased to 1/250-1/200, presenting a serious challenge for clinical identification and early management. In clinical practice, how to screen for FH and improve diagnostic rates remains a critical issue. The earliest domestic research on FH began with case reports in 1971, with subsequent focus on epidemiological investigations. HU et al. [14] first documented 252 FH cases in Hong Kong, followed by JIANG et al. [15] who systematically analyzed LDL receptor (LDLR) variants in Chinese FH patients, after which CAO et al. [16] proposed a simplified screening method for FH in China. For a long time, FH did not receive sufficient attention, with screening only conducted in a few European countries. A 2017 meta-analysis showed that heterozygous familial hypercholesterolemia (HeFH) patients accounted for approximately 1:500 in the population [17]. In recent years, SABINA et al. [18] re-analyzed 104 global studies encompassing 11 million patients, raising awareness of HeFH prevalence to 1:313, with regional variations of 1:137 in Denmark [19] and 1:353 in Australia [20]. Large-scale domestic studies remain limited, with estimates of 1:286-1:357 in 2021 [21] and 1:250-1:300 in 2023 [4]. These trends suggest increasing attention to FH, yet routine understanding of its detection, diagnosis, and treatment has not been established. This article reviews current knowledge of FH and compares 2023 domestic and international guidelines to improve clinical awareness regarding early identification, intervention (diet, lifestyle, medication control), and reducing CAD occurrence and progression.

1.1 Definition and Epidemiological Characteristics of FH

FH is a common autosomal dominant genetic metabolic disease, with the most prominent blood indicator being abnormal elevation of LDL-C [1], clinically manifested as lipid deposits in various locations such as corneal arcus, xanthomas, and aortic calcification (Table 1) [2]. Based on inheritance patterns, FH can be mainly classified into four types: homozygous, heterozygous, compound heterozygous, and double heterozygous [4]. Regardless of type, the resulting LDL-C elevation is the clinical focus. According to the 2019 European Society of Cardiology (ESC) report [5], long-term high levels of LDL-C deposited under the vascular intima increase patients' risk of ASCVD, leading to acute myocardial infarction (AMI) and stroke. SHI et al. [6] extracted clinical data from over 13,000 AMI patients from the Chinese Acute Myocardial Infarction Registry (CAMI), finding FH patients accounted for 4.2% and were younger in age. KOU et al. [7] studied 531 acute coronary syndrome (ACS) patients, with FH patients comprising 4.2%, and after 12 months of follow-up, the probability

of major cardiovascular and cerebrovascular events (MACCE) in FH patients was 7 times that of the normal group.

HeFH patients have LDL-C levels 2-4 times higher than normal individuals [3], with higher risk of premature CAD. HoFH exceeds HeFH in both blood LDL-C elevation and the timing and severity of clinical manifestations, with ASCVD often occurring before age 20 and survival typically less than 30 years [8]. Therefore, inadequate diagnosis and treatment of FH will increase ASCVD risk in the population.

1.2 Genetic Loci

Genetic studies of hypercholesterolemia began with CARL MÜLLER et al. [22] in 1938, followed by KHACHADURIAN [23] who studied the genetics and phenotype of FH in Lebanese families, and GOLDSTEIN et al. [24] who identified LDLR in 1974 and isolated the LDLR gene in 1985. INNERARITY proposed and isolated APOB in 1984 [25]. Additionally, ABIFADEL et al. [26] discovered pathogenic FH variants in PCSK9 in 2003. LDLR, apolipoprotein B gene (APOB), and proprotein convertase subtilisin/kexin type 9 gene (PCSK9) are the three major genes involved in autosomal dominant inheritance in FH. In 2001, LDLRAP1 gene variants were identified in ARH subjects [27].

1.2.1 LDLR LDLR mutations are the mutation type in the vast majority of FH patients (60%-80%) [28]. Over the years, up to 4,900 LDLR-related variants have been detected [29], classified as pathogenic, likely pathogenic, and variants of unknown significance [30]. BOURBON et al. [31] analyzed and reported over 1,800 mutation types in 2017, noting that only 15% of mutation types could be definitively identified as pathogenic, with mutation locations mainly in exons 4, 9, 5, 11, and 7. MESHKOV et al. [32] conducted a systematic review of FH in Russian regions, finding 91 region-specific variants accounting for 59% of all variants. JIANG et al. [15] completed a systematic analysis of LDLR variants in Chinese FH in 2015, noting that related pathogenic mutations in exons 4, 9, 13, and 14 were the most common mutation sites, with 60% being missense mutations. The three primary mutations were C308Y (c.986G>A, p.Cys329Tyr), H562Y (c.1747C>T, His583Tyr), and A606T (c.1879G>A, p.Ala627Thr), with significant differences between southern and northern China. These studies indicate that Chinese LDLR variants are similar to European countries, while numerous variants of uncertain pathogenicity pose difficulties for genetic diagnosis.

1.2.3 APOB APOB is the most abundant apolipoprotein component in the body, carrying triglycerides (TG) and free fatty acids (FFA) to form very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL, while also binding to LDLR (mainly through special sites within its $ $3 structure) [33]. APOB is a special secretory protein whose quantity is regulated primarily through co-translational degradation (post-translational attachment

to the endoplasmic reticulum surface exposes most nascent polypeptides in the cell for hepatic degradation). A series of APOB variants have been identified as important in FH. AHMED [34] discovered homozygous variants in Saudi families' APOB, expanding the mutation spectrum. ALVES [35] identified functional APOB mutations, including p.Arg1164Thr and p.Gln4494del, which significantly reduce LDL internalization [36]. MESHKOV [32] reported 14 APOB variants in a Russian FH cohort, with 36.1% being novel. A series of studies have explored the prevalence of APOB variants in Chinese FH. MAHDIEH [36] found in 2020 that the p.Arg3527Trp variant is common in Chinese heterozygous patients, while XIANG [37] discovered two APOB mutations in FH patients in central-southern China in 2017.

1.2.4 PCSK9 PCSK9 is a secretory protein that binds to LDLR and promotes LDLR endocytosis and degradation in phagolysosomes. PCSK9 expression is primarily regulated at the transcriptional level by sterol regulatory element-binding protein (SREBP)-2, a membrane-bound transcription factor that regulates multiple genes involved in cellular cholesterol homeostasis, including the LDL receptor. Although PCSK9' s main function is degrading LDL receptors, emerging research suggests the protein may play additional roles in cholesterol metabolism through apolipoprotein (APO) B. NOGUCHI [38] found that the E32K variant significantly affects LDL-C levels by increasing circulating PCSK9 function and concentration. HUIJGEN [39] identified several novel PCSK9 variants in 2020, including the G516V variant found to be pathogenic. KAYA [40] reported in 2017 higher frequencies of two PCSK9 gain-of-function mutations, R496W and D374Y, in a Turkish FH cohort. TARANTO [41] further confirmed the pathogenicity of two PCSK9 variants, p.(Ser636Arg) and p.(Arg357Cys), through in vitro characterization. These studies collectively highlight PCSK9 variants' role in FH and the need for further research to understand their impact.

1.2.5 Other Rare Genes In addition to the three most common mutation genes in FH, a few other genes have been discovered whose mutations are related to FH: (1) LDLRAP1 causing autosomal recessive hypercholesterolemia (ARH) (mainly functioning to link the LDL-LDLR complex and deliver it to lysosomes), with only about 100 cases reported globally [42]. (2) Some studies discovered cholesterol regulatory element-binding protein-2 (SREBP2) (mainly regulating PCSK9 protein quantity changes to affect lipid metabolism), signal transduction adaptor protein-1 (STAP1), and epoxide hydrolase 2 (EPHX2) mutations in South Indian patients [42]. (3) APOA5 (this protein mainly reduces plasma triglyceride levels by stimulating lipoprotein lipase activity and is related to obesity and metabolic syndrome [43]) - its mutations were previously considered related to diabetes or causing abnormal chylomicron elevation, but they were first discovered in South Indian FH patients [42]. (4) Cholesterol ester transfer protein (CETP) gene was first reported in familial hyperalphalipoproteinemia, with its main function causing cholesterol esters to transfer from HDL to VLDL and LDL particles. When CETP functions, overall cholesterol esters and HDL

quantities decrease while VLDL and LDL quantities increase [44]. GUAY et al. [42] recruited 98 untreated FH patients and demonstrated the relationship between CETP and FH through methylation analysis, similarly discovered again in South India. (5) ABCG5/8 mutations (mainly secreting cholesterol into bile) cause sitosterolemia, APOE mutations cause dysbetalipoproteinemia, and LIPA mutations cause cholesterol esterase deficiency - they all cause clinical signs similar to FH, but genetic testing often overlooks their existence. Summarized gene mutations are shown in Table 2 [45].

The wide variety of genetic phenotypes poses serious challenges for our genetic screening, making more economical routine screening an essential and important means for broad FH screening.

2 Diagnostic Methods for FH

2.1 Screening The 2023 Chinese Lipid Management Guidelines [4] emphasize universal lipid screening in the population, specifying that adults under 40 should have lipid testing every 2-5 years, while those $ $40 years should be tested annually. Testing indicators should include TC, LDL-C, HDL, and TG, with increased frequency for patients with ASCVD risk based on individual circumstances. The guidelines particularly emphasize adding Lp(a) testing to lipid panels. They advocate including lipid testing in routine primary and secondary school physical examinations and implementing cascade screening for first- and second-degree relatives of FH probands to improve detection rates. Individuals with ASCVD history, multiple ASCVD risk factors, family history of premature ASCVD (men before 55, women before 65), or clinical symptoms of lipid deposition (tendon xanthomas, skin xanthomas) should be priority targets for lipid testing.

The 2023 International Atherosclerosis Society Guidelines on Implementation of Best Practice in FH Care [43] (hereinafter referred to as the 2023 International Care Guidelines) do not directly specify lipid testing frequency but instead emphasize the collaborative role of community, pediatric, obstetric, and gynecologic physicians in general examinations. Local communities should coordinate with expert centers to establish comprehensive detection and reporting mechanisms linked to clinical quality grades. The guidelines stress that non-cardiovascular physicians should cooperate: dermatologists should conduct lipid testing before starting isotretinoin, rheumatology and orthopedic physicians should recognize whether tendon xanthomas and tenosynovitis patients have dyslipidemia, and ophthalmologists should detect premature corneal arcus, chloasma, and facial xanthomas early. They also emphasize that clinical systems should provide special alerts for abnormal lipid test results, reminding physicians to provide further interpretation and referral to improve FH detection rates.

Since 2019, CAO et al. [16] recruited 12,921 patients and proposed the Simplified Chinese Criteria for Familial Hypercholesterolemia (SSCFH) (Figure 1 [Figure

1: see original paper]). Experiments demonstrated that SSCFH has the same diagnostic efficacy as the Dutch Lipid Clinic Network (DLCN) [46] (Table 3) or Simon Broome diagnostic criteria [47] (Table 4) previously encouraged by the European Society of Cardiology/American National Lipid Association (ESA/ECS). Therefore, the 2023 Chinese Lipid Management Guidelines adopt SSCFH as a screening standard or recommend using the 2018 Chinese Expert Consensus FH Screening Criteria [4] (Table 5). Similar to DLCN and Simon Broome diagnostic criteria, both the Chinese Expert Consensus and SSCFH consider premature corneal arcus and tendon xanthomas, with cascade screening being an important diagnostic tool. However, the 2018 Expert Consensus [48] did not emphasize the role of genetic testing. The National Lipid Association (NLA) Expert Consensus [49] (Table 6) more finely stratifies diagnostic LDL-C cutoff values by age, while the MEPED diagnostic criteria [50] (Table 7) provide TC cutoff values for patients' relatives in addition to age stratification. Compared with DLCN, Simon Broome, and AHA simplified criteria [51] (Table 8), SSCFH lowers the adult FH LDL-C standard to 4.8 mmol/L (185.5 mg/dL). Meanwhile, Chinese guidelines do not provide clinical standards for HoFH TC or LDL-C levels, while the 2022 Chinese Expert Consensus on Diagnosis and Treatment of Dyslipidemia in Children [52] provides diagnostic criteria of LDL-C $\geq$ 12.93 mmol/L (500 mg/dL). In contrast, Simon Broome diagnostic criteria and the ESA Updated Expert Consensus (Table 9) [53] consider HoFH LDL-C levels should be above 10 mmol/L (400 mg/dL). Other differences are shown in Table 10 .

Detecting positive pathogenic genes is an important way to diagnose FH [54], but we cannot exclude FH diagnosis when pathogenic mutations are negative. With deepening understanding of FH-related genes in recent years, guidelines indicate that FH genetic testing should not be limited to LDLR, APOB, PCSK9, and LDLRAP1 but should also include lysosomal acid lipase, signal transduction adaptor protein 1 (STAP1), APOE, ABCG5/8, and other genetic tests, or even whole-genome testing, consistent with ESA' s updated recommendations for HoFH. However, for polygenic FH causing LDL elevation, there is currently no clear polygenic risk score standard [55] (using a weighted sum of LDL-C alleles involved in determining lipid concentrations as a potential tool to distinguish polygenic dyslipidemia), which may be a future direction for definitive FH diagnosis.

3.1.1 ASCVD Grading: Compared with the general population, FH patients have accelerated ASCVD progression due to elevated LDL-C levels from birth. Different FH gene defects also lead to different LDL-C levels, ultimately causing higher LDL-C levels in HoFH with more severe ASCVD onset and timing than HeFH. However, ASCVD progression is not affected by specific FH gene mutations but also includes patients' daily behaviors, clinical treatment, and other genetic factors. ASCVD grading is the core strategy for dyslipidemia prevention and treatment, and overall ASCVD risk assessment is the foundation for treatment decisions. The 2023 Chinese Lipid Guidelines list major ASCVD risk factors including high LDL-C ($4.9mmol/L), TC($ **7.2 mmol/L), diabetes, and chronic renal insufficiency (CKD stages 3-4). However, these risk factors mainly target general dyslipidemia patients and are insufficient for FH patients due to their higher LDL-C levels.**

The 2023 Greek Lipid Management Guidelines [56], based on the 2022 ESA Lipoprotein(a) Management Guidelines [57], emphasize the importance of Lp(a) levels for ASCVD risk. The 2024 Polish Lipoprotein(a) Expert Consensus also notes that every 20-50 mg/dL (50-125 mmol/L) increase in blood lipoprotein(a) increases ASCVD risk by 30% [58]. The Greek 2023 Lipid Management Guidelines [56] consider Lp(a) levels >180 mmol/L as a major ASCVD risk factor, with harm equivalent to having FH. The International FH Management Roadmap similarly considers lipoprotein(a) as another risk factor to consider, while also proposing that gender differences in FH patients affect risk assessment. Although traditional thinking holds that ASCVD incidence is higher in men than women, women have lower frequency of LDL-C-lowering medication use (discontinuing statins due to pregnancy, breastfeeding, etc.) and lower control targets than men, while women' s increased cancer risk leads to the need to reassess ASCVD risk in female FH patients. Meanwhile, general lipid management lacks consideration for tendon xanthomas (though rare) and arterial intima-media thickness. These comprehensive factors lead to the conclusion that Framingham risk scores, SCORE-2, and other tools are not used in FH patients, with recommendations to use the SAFEHEART risk equation and FH risk score to assess ASCVD risk in FH patients [59].

3.1.2 Diet and Lifestyle: Control of diet and lifestyle is the first step in treating FH and forms the cornerstone of FH therapy. The 2019 ESA/ECS Guidelines [5] propose that dietary control should follow a Mediterranean diet pattern. ESA advocates reducing LDL-C and TC by avoiding excessive saturated fatty acids in the diet while increasing dietary fiber intake, consuming functional foods rich in plant sterols, recommending red yeast rice nutritional supplements, increasing daily exercise, and limiting body weight. U.S. national and international health authorities and organizations state that diet should shift from "unhealthy diet" to "healthy diet" [60], specifically recommending low-fat dairy products instead of high-fat dairy products; lean meat and lean meat products instead of fatty meats; eating fish 2-3 times per week to limit saturated fatty acids, trans fatty acids, and cholesterol intake; increasing monounsaturated fatty acids and ω-6 polyunsaturated fatty acids; using edible oils, liquid margarine, and soft margarine instead of hard margarine and butter. The Greek 2023 Lipid Management Guidelines [56] note that saturated fatty acids in food have the greatest impact on LDL-C levels, recommending plant oils, fish, and nuts as fat sources, but total fat content should be 20%-35% of total calories, ω-6 polyunsaturated fatty acids should account for 5%-10% of total energy, ω-3 polyunsaturated fatty acid intake should be 0.6%-2.0%, and trans fatty acid intake should be limited to less than 1% of total energy. However, due to large differences between domestic diet and Mediterranean diet structure, domestic guidelines recommend a Chinese heart-healthy dietary pattern while controlling daily cholesterol intake to <300 mg, with more dietary patterns needing experimental data support.

3.1.3 Drug Control and Other Methods: On the basis of healthy diet and lifestyle, combined application of lipid-lowering drugs is indispensable, with statins [3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) inhibitors] being the foundation for effectively reducing ASCVD risk [61]. However, compared with the 2023 FH Care Guidelines [62], Greek 2024 Lipid Management Guidelines, or 2019 ESC/ECS Lipid Management Guidelines that recommend maximally tolerated statin therapy for FH patients (i.e., atorvastatin 40-80 mg or rosuvastatin 20-40 mg), the 2023 Chinese Lipid Management Guidelines recommend starting statin therapy at moderate or conventional doses (Table 11) due to considerations of statin intolerance in domestic populations, while recommending natural statins contained in Xuezhikang (red yeast rice, also recommended by Greek guidelines for lipid management diet) for patients intolerant to conventional statins. Similar to the 2023 Chinese Lipid Management Guidelines, statin combination with ezetimibe or bempedoic acid combination preparations is recommended as the second-step treatment for patients with poor LDL-C control, followed by PCSK9 inhibitors [including conventional evolocumab or alirocumab, while small interfering RNA (inclisiran) is recommended for routine use by the 2023 FH Care Guidelines]. For patients with poor LDL-C control, the 2023 FH Care Guidelines suggest adding plant sterols or bile acid sequestrants (such as cholestyramine) to continue intensive lipid-lowering therapy, while the 2022 Chinese FH Expert Consensus 倾向于倾向于 plasma exchange to reduce LDL-C levels.

For more severe HoFH patients, the 2023 ESA Updated Expert Consensus [53] proposes starting with high-intensity statin combined with ezetimibe dual ther-

apy rather than monotherapy as in HeFH, then gradually adding PCSK9 inhibitors and bile acid sequestrants. The updated management guidelines do not limit patient age for PCSK9 inhibitor use (Chinese guidelines limit PCSK9 to $ $12 years), allowing direct use in non-biallelic LDLR null mutation patients within 8 weeks; if patients show additional LDLR level reduction $ $15% after 8 weeks, PCSK9 can be continued routinely. Lipoprotein apheresis (LA) is recommended as the basic treatment for HoFH. ESA recommends starting HoFH children from age 2 (rather than China' s recommended age 5), up to age 8, combined with non-LDLR-dependent lipid-lowering lomitapide (microsomal triglyceride transfer protein oral inhibitor) and evinacumab (ANGPTL3 monoclonal antibody), which have been FDA-approved and recommended by ESA. Finally, for non-biallelic LDLR null mutation patients or HoFH patients with persistently poor LDL-C control after LA and other lipid-lowering treatments, liver transplantation is recommended as the last resort. Contrary to ESA and Chinese recommendations, Greek guidelines do not recommend liver transplantation for patients without ASCVD, mainly due to a series of adverse events (surgical complications, mortality, infection, transplant rejection) and scarce donor considerations.

3.2.1 HeFH 3.2.1.1 Adults: Chinese guidelines adopt the 2021 Australian Lipid Management Consensus method [63] to divide HeFH lipid control targets into three categories based on whether adult patients have developed ASCVD: (1) With clinical ASCVD, control <1.4 mmol/L (<55 mg/dL); (2) With subclinical ASCVD, control <1.8 mmol/L (<70 mg/dL); (3) Without ASCVD, <2.6 mmol/L (<100 mg/dL).

The 2023 International Familial Hypercholesterolemia Care Recommendations: For patients with other ASCVD risk factors, after approximately 50% LDL-C reduction, the following treatment targets should be considered based on ASCVD risk level: (1) With clinical ASCVD, LDL-C <1.4 mmol/L (<55 mg/dL); (2) With imaging evidence of isolated ASCVD or other major ASCVD risk factors, LDL-C <1.8 mmol/L (<70 mg/dL); (3) Without ASCVD or other major ASCVD risk factors, LDL-C <2.5 mmol/L (<100 mg/dL); for patients with recurrent ASCVD events within 2 years receiving maximally tolerated statin therapy, LDL-C reduction to <1.0 mmol/L (<40 mg/dL) may be considered.

The 2019 ESC/European Atherosclerosis Society (EAS) and Greek Lipid Management Guidelines propose: (1) In HeFH patients with established ASCVD, LDL-C target <1.4 mmol/L (<55 mg/dL), with mandatory consideration of $ $50% reduction from baseline; (2) In HeFH patients with type 2 diabetes (T2DM) or stage 4-5 chronic kidney disease (CKD), LDL-C target <1.4 mmol/L (<55 mg/dL), with consideration of $ $50% reduction from baseline; (3) In HeFH patients without these comorbidities, LDL-C target <1.8 mmol/L (<70 mg/dL).

Chinese guidelines have relatively 宽松 control levels for HeFH patients without ASCVD risk, only controlling to 2.6 mmol/L, while European regions be-

lieve even patients without other ASCVD risk factors need stricter control to <1.8 mmol/L, though they note that strict LDL-C control levels are not easily achievable, which may be why China adopts the Australian Lipid Management Consensus. Meanwhile, compared with FH Care Recommendations, Chinese guidelines pay insufficient attention to ASCVD recurrence within 2 years in HeFH patients, requiring substantial experimentation for specific analysis of LDL-C target control levels.

3.2.1.2 Children and Adolescents: Chinese guidelines propose LDL-C control targets for adolescent HeFH patients: (1) Without ASCVD, <3.5 mmol/L or $ $50% reduction from baseline; (2) With subclinical ASCVD, <2.6 mmol/L and $ $50% reduction from baseline; (3) With clinical ASCVD, <1.8 mmol/L and $ $50% reduction from baseline. Suspected HeFH children should be diagnosed early (no later than age 10); those confirmed should start statin therapy after lifestyle intervention if LDL-C $ $4.7 mmol/L on two occasions ($8 years old); if still $ $4.0 mmol/L after statin therapy, cholesterol absorption inhibitors may be combined ($10 years old).

The 2023 Lipid Care Guidelines [62] state: (1) For patients without other ASCVD risk factors [e.g., diabetes, hypertension, elevated lipoprotein(a) concentration, or parents with ASCVD history in their second or third decade], consider setting LDL-C target <3.5 mmol/L (<135 mg/dL) or reducing by about 50%; (2) Non-fasting blood samples can be used to monitor LDL-C levels in patients receiving stable therapy; (3) For patients with other ASCVD risk factors, consider setting LDL-C target <2.5 mmol/L (<100 mg/dL), and medication may be considered before age 8 in cases of two documented LDL-C >4.9 mmol/L (>190 mg/dL).

The 2019 ESC/EAS and Greek 2023 Lipid Management Guidelines jointly recognize that FH children should receive appropriate dietary education and statin therapy from ages 8-10. The treatment target should be LDL-C <3.5 mmol/L (<135 mg/dL) after age 10. The ESA Updated Expert Consensus [53] proposes that children should control LDL-C <3 mmol/L (<115 mg/dL) while using imaging to assist in assessing ASCVD progression. Adults without major ASCVD risk factors should control LDL-C <1.8 mmol/L (<70 mg/dL); if with major ASCVD risk factors, control LDL-C <1.4 mmol/L (<55 mg/dL).

Domestic and international guidelines pay more attention to early identification and treatment in children and adolescent HeFH patients, emphasizing baseline lipid differences between children and adults. Regarding different LDL-C control target levels for children and adults, China is relatively conservative about early medication use in children, while international care guidelines propose that statins and other medications can be used before age 8 in children and adolescents with multiple high LDL-C levels to achieve early control and reduce future ASCVD risk.

3.2.2 Regarding HoFH, the 2022 Chinese Pediatric Consensus [64] states: (1) Recommend drug intervention to achieve LDL-C <3.49 mmol/L (135 mg/dL); (2) For children $ $14 years old with diabetes or family history of premature coronary atherosclerotic heart disease, recommend gradually adjusting statin dosage to maximum tolerated dose or combining ezetimibe with LDL-C <2.48 mmol/L (96 mg/dL) as treatment target. The latest lipid management guidelines have not explicitly provided lipid control levels for HoFH patients, so the 2022 Pediatric Lipid Management Expert Consensus is selected for comparison. The Pediatric Dyslipidemia Management Expert Consensus has relatively 宽松 LDL-C target levels compared to the ESA Updated Guidelines or 2023 Lipid Care Guidelines.

In summary, FH is a common autosomal dominant genetic disease causing significantly elevated LDL-C levels from birth and leading to premature CAD. The common mutation genes are LDLR, APOB, PCSK9, and LDLRAP1, but other rare mutation genes are continuously being discovered, posing serious challenges for genetic testing. Early diagnosis provides an opportunity to start drug therapy in childhood, greatly reducing cardiovascular disease risk in adulthood. Although many guidelines propose screening recommendations for FH, China' s current screening and diagnosis of FH remain inadequate. Multiple clinical diagnostic guidelines easily cause confusion, and simplified screening methods tailored to Chinese residents' lipid levels are more suitable for primary care practice. However, primary care still has insufficient awareness of FH, lacks good primary care statistical tools [56], and lacks cooperation between physicians from other specialties, so FH is usually diagnosed after cardiac events in adulthood. FH treatment targets depend on patients' ASCVD risk levels, and high-risk Lp(a) levels need further attention. Due to dietary differences between China and other countries, research on dietary patterns unique to Chinese residents should be prioritized. Domestic and international consensus recognizes that FH can be treated with currently available lipid-lowering therapies such as statins, ezetimibe, PCSK9 inhibitors, and lipoprotein apheresis in more severe cases. However, due to differences in drug tolerance among populations, changes in drug dosage are needed, and drug combinations need to be more familiar to achieve target control levels. Similarly, for more severe homozygous forms, appropriately earlier lipoprotein apheresis should be performed to start aggressive LDL-C reduction therapy as early as possible to minimize ASCVD morbidity and mortality. European regions adopt more aggressive control targets for FH, but whether this is suitable for patients' daily lipid management still requires long-term experimental verification. Meanwhile, there is insufficient attention to pure homozygous patients, and new management guidelines for HoFH should be proposed. Only with increased awareness of FH among healthcare professionals and patients can prevention of premature ASCVD events and reduction of mortality be truly accomplished.

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