Key Points Interpretation of the Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024): Post-print

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Abstract

Familial hypercholesterolemia (FH) is a severe inherited metabolic disorder, among which homozygous FH (HoFH) is rare and particularly severe. Early screening, diagnosis, and treatment can substantially improve patient prognosis; however, the recognition and management of HoFH remain severely inadequate both domestically and internationally. In recent years, multiple guidelines and expert consensuses for FH have been issued internationally, yet expert consensuses specifically targeting HoFH are relatively scarce. Recently, multidisciplinary experts including the Laboratory Medicine Branch of the Chinese Medical Association jointly published the "Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024)," which clarifies the early screening and diagnostic procedures for HoFH and updates and optimizes treatment strategies. This article provides a detailed interpretation of the five key points of this consensus, integrated with our team's work on HoFH family screening: (1) introducing artificial intelligence to multidimensionally optimize HoFH early screening strategies; (2) refining HoFH clinical diagnostic criteria and emphasizing the importance of collaborative genetic diagnosis; (3) underscoring the significance of prenatal diagnosis and newborn screening; (4) focusing on the differential diagnosis between sitosterolemia and HoFH; and (5) updating and optimizing HoFH treatment strategies with stratified low-density lipoprotein cholesterol treatment targets. Furthermore, based on our screening practice, we propose a clinical practice-driven approach focusing on long-term HoFH management, aiming to provide a reference for early screening and clinical management of HoFH in China.

Full Text

Key Points Interpretation of the Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024)

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Abstract

Familial hypercholesterolemia (FH) is a severe inherited metabolic disorder. Early diagnosis and treatment can greatly improve patient prognosis, yet the recognition and management of homozygous familial hypercholesterolemia (HoFH) remain severely inadequate globally. In recent years, numerous international guidelines and expert consensus documents on FH have been issued, but there are relatively few expert consensuses specifically addressing HoFH. Recently, the Chinese Society of Laboratory Medicine and a multidisciplinary expert panel developed and published the *Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024)*, which clarifies the early identification and diagnosis process for HoFH and updates and optimizes therapeutic protocols.

This article provides a detailed interpretation of the five key points of this consensus based on our team's HoFH family screening practice, including: (1) introducing artificial intelligence for multidimensional optimization of HoFH early screening strategies; (2) refining clinical diagnostic criteria for HoFH and emphasizing the importance of gene diagnosis collaboration; (3) highlighting the significance of prenatal diagnosis and newborn screening; (4) focusing on the differential diagnosis between phytosterolemia and HoFH; and (5) updating and optimizing HoFH treatment strategies with stratified low-density lipoprotein cholesterol treatment target values. Additionally, combining HoFH screening practices, this article proposes driving clinical practice and focusing on long-term HoFH management, aiming to provide references for early screening and clinical management of HoFH in China.

Keywords: Homozygous familial hypercholesterolemia; Early screening; Diagnosis; Management; Expert consensus; Interpretation

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Familial hypercholesterolemia (FH) is a severe autosomal dominant inherited disease characterized by markedly elevated serum low-density lipoprotein cholesterol (LDL-C) levels, xanthomas on the skin and/or tendons, and extremely high risk of premature atherosclerotic cardiovascular disease (ASCVD). FH is primarily divided into homozygous FH (HoFH) and heterozygous FH (HeFH). HoFH is rare yet life-threatening, with an incidence of 1/300,000 to 1/160,000. Patients experience premature severe ASCVD with extremely high-risk status and rapid progression, often developing clinical symptoms during childhood. Without treatment, the typical life expectancy is less than 30 years.

In recent years, to improve public awareness of HoFH and enable earlier diagnosis and better treatment of FH patients, international research on HoFH management has increased, with numerous FH management guidelines published. In 2014, the European Atherosclerosis Society expert panel formulated an expert consensus on HoFH diagnosis and management, sounding the clarion call for HoFH diagnosis and treatment. However, FH research in China started relatively late, and there is currently no unified diagnostic standard. Given China's large population and complex genetic background, the number of potential HoFH patients is approximately 8,000, but the diagnosis rate is low and treatment is severely inadequate, lacking comprehensive guidance for HoFH diagnosis and management. Recently, the Affiliated Suzhou Hospital of Nanjing Medical University (Suzhou Municipal Hospital), during the implementation of the national "14th Five-Year Plan" key research and development project, collaborated with the Chinese Society of Laboratory Medicine and multidisciplinary experts to develop and publish the *Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024)* (hereinafter referred to as the "Consensus"). The Consensus provides multidimensional discussion and analysis on early screening, diagnostic criteria, and management strategies for HoFH, aiming to enhance clinicians' attention and improve the diagnosis and treatment system for HoFH to improve patient prognosis.

This article interprets the Consensus based on HoFH screening practice, aiming to provide references for early screening and clinical management of HoFH in China. Through analysis of the Consensus, five key points were identified: (1) pioneering the integration of artificial intelligence (AI) with traditional screening methods and registry networks to comprehensively optimize HoFH early screening strategies; (2) refining HoFH clinical diagnostic criteria and clarifying the importance of combining clinical and genetic diagnosis in HoFH management; (3) emphasizing the importance of prenatal diagnosis and newborn screening, focusing on screening in special populations; (4) highlighting the role of phytosterolemia in differential diagnosis of HoFH; and (5) updating and optimizing treatment strategies, strengthening the long-term management system

for HoFH, and highlighting clinical practice.

The Five Key Points of the Consensus

The Consensus provides comprehensive summary from disease characteristics and diagnostic challenges to treatment strategies and follow-up monitoring of HoFH, proposing 13 recommendations to provide effective diagnostic and therapeutic guidance for Chinese HoFH patients, facilitating implementation of early screening and management and promoting improvement in HoFH diagnosis and treatment levels. This article analyzes the Consensus to identify five key points: (1) introducing AI to multidimensionally optimize HoFH early screening strategies; (2) refining HoFH clinical diagnostic standards and strengthening the importance of genetic diagnosis collaboration; (3) deepening the importance of prenatal diagnosis and newborn screening; (4) focusing on differential diagnosis between phytosterolemia and HoFH; and (5) updating and optimizing HoFH treatment strategies with stratified LDL-C treatment target values.

1.1 Introducing AI to Multidimensionally Optimize HoFH Early Screening Strategies

Significantly elevated plasma LDL-C levels lead to characteristic ASCVD in HoFH. The main features are accelerated atherosclerosis, commonly with cholesterol and calcium deposition, fibrosis, and inflammation of the aortic root and valves, leading to aortic valve stenosis, which often occurs in early childhood and teenage years, accompanied by xanthomas in skin and tendon areas and cognitive function issues. However, the diagnosis rate and lipid-lowering treatment acceptance are very low in clinical practice. The important cause of death is coronary cardiovascular disease, but early intervention can extend patient lifespan by 10-30 years. Therefore, the Consensus emphasizes that early screening and diagnosis are important measures to reduce ASCVD risk and improve clinical prognosis in HoFH patients.

As the critical initial step in disease control, early screening determines whether patients can be diagnosed timely, receive early intervention, effectively delay atherosclerosis progression, reduce cardiovascular mortality risk, and extend life expectancy. The Consensus points out that childhood is an important period for early detection of HoFH patients, recommending that children with serum LDL-C $\geq$ 6.0 mmol/L or total cholesterol (TC) $\geq$ 10.0 mmol/L, premature ASCVD, multiple skin and/or tendon xanthomas, FH family history, or early-onset ASCVD family history should be targeted for screening, with lipid testing performed before age 2. Screening includes medical history, physical examination, lipid testing, and cardiovascular examination, focusing on carotid intima-media thickness and aortic valve structure. Emphasizing early screening in children with HoFH can maximize reduction of adverse cardiovascular effects from hypercholesterolemia, seize optimal intervention timing, more effectively regulate lipid metabolism, and delay the occurrence and progression of atherosclerosis.

Meanwhile, the Consensus pioneers the proposal of AI innovative technology to assist in constructing HoFH early screening systems. AI innovation brings numerous breakthroughs to healthcare, such as disease diagnosis models and intelligent imaging technologies that assist diagnosis and treatment. Building clinical decision support systems (CDSS) and using machine learning to create AI models for HoFH screening can complement traditional screening methods. Verified through practical application, these AI models have extremely high sensitivity, can accurately capture potential cases, and significantly reduce missed diagnoses. In screening efficiency, traditional methods require manual review of numerous medical records, which is time-consuming and labor-intensive, while AI models can instantly process massive amounts of medical data, increasing screening speed several-fold and greatly shortening diagnosis cycles. Currently, there are international CDSS achievements for FH, and domestic CDSS applications for rare diseases also exist. Additionally, the Consensus recommends integrating Laboratory Information Management Systems (LIS) and Hospital Information Management Systems (HIS) into a unified test alert value management platform, adding HIS alerts with LDL-C $\geq$ 6.0 mmol/L or TC $\geq$ 10.0 mmol/L as warning thresholds to facilitate timely identification of suspected HoFH patients by physicians. Studies show that elevated LDL-C levels are the second major risk factor for ASCVD, but the LDL-C 达标率 (target achievement rate) is only 42.9% in high-risk ASCVD populations, and 93.4% of extremely high-risk patients have LDL-C $>$ 1.4 mmol/L at admission. Even among patients already using lipid-lowering medications, 88.6% fail to reach target values. Therefore, setting LDL-C warning thresholds is like building a health defense line, enabling precise identification in early disease stages, optimizing medical resource allocation, and improving patient prognosis. Furthermore, China has initially established registration networks for related rare diseases, and combining AI technology with HoFH early screening can enable information sharing across multi-level medical institutions, ensuring relatively centralized diagnosis and treatment for HoFH patients and two-way referrals.

1.2 Refining HoFH Clinical Diagnostic Criteria and Strengthening Genetic Diagnosis Collaboration

Currently, there are various international HoFH diagnostic standards with different detection rates across populations. However, China lacks unified diagnostic standards, so standardized criteria should be developed to improve disease detection rates. The core task of HoFH diagnosis is to further refine clinical diagnostic standards while emphasizing the importance of collaborative genetic diagnosis.

This Consensus considers serum LDL-C as the key indicator for clinical diagnosis of HoFH, recommending stricter LDL-C thresholds for clinical diagnosis. After excluding other diseases, suspected HoFH is diagnosed when fasting untreated serum LDL-C $\geq$ 10.0 mmol/L or treated serum LDL-C $\geq$ 8.0 mmol/L. The European HoFH Expert Consensus also states that LDL-C levels in families are

key to distinguishing HoFH from HeFH, with HoFH patients having average LDL-C levels 4 times higher than unaffected individuals, while HeFH patients have levels 2 times higher. However, research suggests that LDL-C thresholds should not be the sole diagnostic criterion. In the general population, there may be significant overlap in LDL-C levels between HeFH and HoFH patients, with genetically confirmed HoFH patients potentially having untreated LDL-C levels below 13 mmol/L. Therefore, HoFH diagnosis should also incorporate comprehensive evaluation of clinical manifestations, with skin and/or tendon xanthomas, premature ASCVD, and family history being important diagnostic evidence for HoFH, which can further clarify diagnosis.

HoFH is a monogenic dominant inherited disease with four main pathogenic genes: low-density lipoprotein receptor (LDLR), apolipoprotein B100 (ApoB100), proprotein convertase subtilisin/kexin type 9 (PCSK9), and low-density lipoprotein receptor adaptor protein 1 (LDLRAP1). Therefore, detection of gene mutations affecting LDLR function is considered the "gold standard" for FH diagnosis. Using gene mutation detection methods such as whole exome sequencing (WES) and targeted region sequencing technology to identify pathogenic gene mutation sites, and based on mutation characteristics and their impact on gene-encoded protein function, can assist in determining precise diagnosis of HoFH and provide scientific basis for patient treatment intervention. Additionally, if genetic diagnosis is negative, FH should not be excluded. If clinical phenotype strongly suggests FH, this situation may be due to undetected genetic variations, and clinical diagnosis should take priority over genetic diagnosis, with treatment initiated according to HoFH first.

Furthermore, other inherited lipid metabolism disorders such as phytosterolemia, cerebrotendinous xanthomatosis, and Alagille syndrome should be considered, as these diseases can also cause elevated LDL-C levels and present clinical features such as skin and/or tendon xanthomas. Therefore, differential diagnosis with HoFH should be prioritized.

1.3 Deepening the Importance of Prenatal Diagnosis and Newborn Screening

For HoFH, an autosomal dominant inherited disease, prenatal diagnosis is considered the most effective clinical intervention to prevent affected births. Its widespread application can not only identify potential patients early in pregnancy but also provide necessary decision-making support for families to develop corresponding management and intervention strategies according to individual circumstances, promoting healthy reproduction. Therefore, the Consensus recommends that pregnant women with HoFH family history or couples where both partners are HeFH carriers should receive genetic counseling and prenatal diagnosis in early pregnancy. This Consensus presents the management process for pregnant and perinatal periods in HoFH patients [Figure 1: see original paper]. With rapid development of assisted reproduction and genetic diagnosis technologies, third-generation IVF technology is one of the most re-

markable developments in human assisted reproductive technology in nearly 30 years, enabling genetic diagnosis before pregnancy, thereby achieving selective implantation of disease-free embryos, providing possibility for obtaining healthy offspring, and effectively blocking vertical transmission of HoFH.

Newborn screening plays a crucial role in HoFH diagnosis and treatment. Population-based screening for HoFH in newborns can not only effectively reduce long-term impact of the disease on infant health but also provide necessary support and counseling services for families, thereby significantly improving quality of life for affected children. The Consensus recommends incorporating FH into newborn screening programs, using tandem mass spectrometry to detect TC, LDL-C, and ApoB in dried blood spots, to achieve early detection, early diagnosis, and early treatment of FH in children.

1.4 Focusing on Differential Diagnosis Between Phytosterolemia and HoFH

Phytosterolemia is a relatively rare lipid metabolism disorder with pathogenesis different from HoFH but may have similar clinical manifestations, posing certain challenges to clinical diagnosis. Therefore, differential diagnosis between the two is particularly important, with the overall process shown in [Figure 2: see original paper]. Phytosterolemia patients typically present with mild to moderate hypercholesterolemia, particularly with significantly elevated plant sterol concentrations. These patients usually consume large amounts of plant sterols in their diet, but due to abnormalities in their synthesis and metabolism mechanisms, plant sterols accumulate. Their clinical manifestations overlap with HoFH to some extent but also have differences. Although tendon xanthomas may also appear, their frequency and severity may be relatively lower. Some patients may develop arthritis symptoms, which are relatively uncommon in FH patients. Meanwhile, phytosterolemia patients may also have hematological abnormalities such as hemolytic anemia and thrombocytopenia, which are generally not seen in FH patients. These unique clinical manifestations help preliminary differentiation in clinical diagnosis.

Additionally, biochemical testing is an important tool to distinguish phytosterolemia from HoFH. Using advanced detection techniques such as Gas Chromatography-Mass Spectrometry (GC-MS) or High-Performance Liquid Chromatography (HPLC), serum plant sterol content can be accurately measured. Plant sterol levels in phytosterolemia patients are significantly elevated, such as sitosterol and campesterol, while LDL-C levels are relatively low. Conversely, HoFH patients exhibit extremely high LDL-C levels and normal or slightly elevated plant sterol levels. This difference in biochemical characteristics provides strong basis for differential diagnosis of the two diseases and helps physicians make more accurate diagnoses. Meanwhile, genetics plays a key role in differential diagnosis. Phytosterolemia is mostly caused by mutations in ABCG5 or ABCG8 genes, which regulate plant sterol absorption and excretion, while HoFH is mainly related to LDLR gene defects that directly

affect LDL-C clearance efficiency. Genetic testing can further confirm diagnosis and is also important for screening and evaluating family members.

1.5 Updating and Optimizing HoFH Treatment Strategies with Stratified LDL-C Treatment Target Values

All HoFH patients should receive multidisciplinary comprehensive long-term management with the primary treatment goal of reducing LDL-C levels, including lipid-lowering therapy and lifestyle modifications to reduce overall cardiovascular disease risk. The Consensus provides a comprehensive diagnosis and treatment plan for HoFH multidisciplinary treatment models, combining imaging, genetics, and clinical characteristics.

In lifestyle modification, dietary intervention is considered a fundamental strategy. According to the European Atherosclerosis Society (EAS) consensus group and National Heart, Lung, and Blood Institute (NHLBI) guidelines, recommended daily intake of total fat should be less than 30% of total calories, saturated fat less than 7%, and cholesterol intake controlled to <200 mg. This Consensus recommends a low-cholesterol diet with reduced saturated fatty acid intake, while encouraging smoking cessation, limiting alcohol consumption, and moderate physical exercise after cardiovascular risk assessment. Additionally, lipid-lowering therapy should begin as early as possible, with diverse treatment modalities including medication, surgery, and gene therapy. Statins remain the first choice and foundation for intensive lipid-lowering therapy. Adding cholesterol absorption inhibitor ezetimibe can further reduce LDL-C levels by 10%-15%. Combination with other novel lipid-lowering drugs can further reduce LDL-C and is expected to play an important role in HoFH treatment.

Currently, novel lipid-lowering therapies in China have achieved phased progress. Taking PCSK9 inhibitors as an example, mature products such as evolocumab and alirocumab are already available in the Chinese market, mainly for FH, atherosclerotic cardiovascular disease and other indications. Some drugs have been included in the medical insurance catalog with relatively affordable prices. Notably, domestically developed drugs such as ongericimab demonstrate significant lipid-lowering efficacy, achieving over 50% reduction in LDL-C and Lp(a) dual targets, providing precise treatment options for patients intolerant to statins or with high lipid-lowering needs (such as high-intensity lipid-lowering populations and patients with diabetes combined with dyslipidemia), gradually highlighting value in primary prevention and secondary intervention of cardiovascular diseases. However, clinical popularization of novel therapies still faces multiple challenges: first, significant price barriers, with PCSK9 inhibitors not covered by medical insurance being expensive and difficult for patients to afford long-term, limiting widespread application; second, technical bottlenecks, with long-term safety data for PCSK9 inhibitors still requiring validation from large-scale cohorts, and gene therapy still facing challenges in targeted delivery efficiency, gene expression regulation, and immunogenicity; third, incomplete clinical application systems, with some

physicians having insufficient understanding of novel targets such as Lp(a), and lack of standardized guidance for treatment plan development. Future improvements require continued upgrading through medical insurance policy support and technological iteration.

Based on LDL-C treatment target values for HoFH, this Consensus proposes corresponding target values for different age groups stratified by ASCVD status or high-risk factors. For adult HoFH patients, LDL-C should be controlled below 1.4 mmol/L (with ASCVD) and 2.6 mmol/L (without ASCVD). Appropriate lipid levels vary significantly among ASCVD risk strata. In populations without risk factors, "normal" LDL-C levels may actually be significantly elevated for patients at extremely high or very high ASCVD risk. This phenomenon suggests that clinical practice should conduct more precise evaluation and management of lipid indicators according to individual risk status. Therefore, the Consensus recommends managing LDL-C from childhood as the primary target of lipid intervention, with treatment target values determined according to risk stratification. This strategy will help effectively reduce future cardiovascular disease risk at early stages.

For female HoFH patients, ASCVD risk during pregnancy is high. Studies show that healthy pregnant women have physiologically elevated LDL-C levels by 40%-50%, with triglycerides (TG) showing an upward trend at approximately 14 weeks of gestation. However, for HoFH patients, this risk increase is more pronounced, suggesting clinical management needs special attention to lipid changes and corresponding risk assessment during pregnancy. The *Chinese Guidelines for Lipid Management (2023)* clearly specifies lipid management points for special populations such as FH and pregnant women. Given the particularity of these populations in lipid metabolism status and response to drug therapy, the Consensus recommends implementing more individualized lipid management strategies for effective intervention. For HoFH patients, comprehensive management by multidisciplinary teams before pregnancy, during pregnancy, and postpartum is recommended, focusing on lipid screening. Currently, lipid-lowering drugs available for clinical use during pregnancy are relatively limited, and lipoprotein apheresis (LA) every 1-2 weeks may be considered to help optimize lipid levels.

2. Driving Clinical Practice and Focusing on Long-Term HoFH Management

Healthcare providers at primary levels in China and HoFH patients generally have insufficient awareness of ASCVD risk. Moreover, given China's large population and heavy genetic burden, the number of potential FH patients is substantial, with many patients experiencing serious consequences due to delayed appropriate treatment. Therefore, strengthening FH prevention is particularly important, focusing on enhanced publicity and education of FH-related scientific knowledge through media communication, community activities, and health lectures to improve public awareness and attention to HoFH.

Meanwhile, the *"Healthy China 2030" Planning Outline* explicitly proposes to "implement comprehensive chronic disease prevention and control strategies and strengthen construction of national comprehensive chronic disease prevention and control demonstration areas." In response, multiple hospitals in China have established specialized clinics for "dyslipidemia" and built a tiered diagnosis and treatment management registration platform for HoFH. Suzhou Municipal Hospital has established a specialized HoFH expert clinic, providing a series of precise diagnostic services for homozygous patient families, including free genetic testing and intestinal flora analysis, aiming to reduce patient economic burden. The hospital also provides genetic counseling to guide patients and their families in disease management and family planning, supporting early diagnosis and comprehensive management of HoFH patients from multiple aspects to promote improvement in their overall health.

Since 2020, Suzhou Municipal Hospital has actively participated in HoFH screening-related projects. In 2020, the hospital participated in China's FH Ten Thousand Screening Action Plan, and in 2021, as a sub-project of the national "14th Five-Year Plan" key research and development program, collaborated with multiple institutions to conduct screening for FH in China. To further promote HoFH screening, Suzhou Municipal Hospital established a National FH Screening Collaborative Group, with multiple hospitals joining subsequently to integrate medical resources and gradually expand the screening collaboration network. Starting September 2023, the hospital has successively carried out FH free clinic activities in 15 cities including Guangzhou Conghua, Xi'an, Shandong, Nanchang, Bengbu, Hangzhou, and Chongqing, providing local patients with personalized lipid screening and health consultation services, popularizing HoFH-related knowledge, and guiding patients to emphasize disease screening and management. Simultaneously, the hospital has strengthened cooperation with local medical institutions to improve regional HoFH screening and diagnosis and treatment levels. These initiatives aim to build an efficient and convenient dyslipidemia screening and treatment system, forming a large-scale, multi-regional dyslipidemia FH patient cohort across the country. Through early screening and diagnosis of patients with hereditary dyslipidemia such as HoFH, establishing FH diagnostic standards suitable for Chinese populations, hospitals can provide patients with precise diagnosis and treatment services. In the 2024 implementation of the national health commission science and technology innovation 2030 project for four major chronic diseases, our team participated in developing new lipid intervention strategies for ASCVD extremely high-risk populations (FH).

This article provides detailed interpretation of the five key points of the Consensus: (1) introducing AI to multidimensionally optimize HoFH early screening strategies; (2) refining HoFH clinical diagnostic criteria and strengthening the importance of genetic diagnosis collaboration; (3) deepening the importance of prenatal diagnosis and newborn screening; (4) focusing on differential diagnosis between phytosterolemia and HoFH; and (5) updating and optimizing treatment strategies with stratified LDL-C treatment target values. Combin-

ing HoFH screening practices, this article proposes driving clinical practice and focusing on long-term HoFH management.

Through systematic interpretation of the *Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024)*, this article fills the gap in in-depth analysis of the latest consensus in China, providing clear and actionable practice guidelines for clinicians. Emphasizing multidimensional screening, precise diagnosis, and stratified treatment not only helps improve early detection rates and standardized management levels of HoFH in China, but also has important significance for reducing cardiovascular event risk and delaying disease progression in patients, providing important theoretical and practical support for promoting construction of rare disease prevention and treatment systems in China and improving long-term survival quality of HoFH patients. Currently, diagnosis and management of HoFH patients in China are still in the initial stage, with relatively scarce research and numerous challenges in prevention and treatment. Therefore, we call on clinicians to pay more attention to this disease, refer to this Consensus, and combine it with China's actual conditions to establish a comprehensive HoFH management network, continuously optimize the diagnosis and treatment system, to improve patient prognosis.

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References

[1] CUCHEL M, BRUCKERT E, GINSBERG H N, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society[J]. Eur Heart J, 2014, 35(32): 2146-2157. DOI:10.1093/eurheartj/ehu274.

[2] WU C, LI S, ZHANG H W, et al. Clinical screening and characteristics of familial hypercholesterolemia in patients with premature myocardial infarction[J]. Chinese Journal of Molecular Cardiology, 2018, 18(6): 2655-2658. DOI:10.16563/j.cnki.1671-6272.2018.12.003.

[3] WEN W H, KUANG Z M, WANG L Y. Current status of familial hyperc-

holesterolemia management in China from guidelines[J]. Chinese General Practice, 2019, 22(5): 495-500. DOI:10.12114/j.issn.1007-9572.2018.00.430.

[4] CHENG S T. Study on the distribution pattern of common pathogenic mutations and establishment of genetic screening methods in familial hypercholesterolemia population in 16 provinces of China[D]. Shenyang: China Medical University, 2019. DOI:10.27652/d.cnki.gzyku.2019.000098.

[5] Chinese Society of Laboratory Medicine, Chinese Society of Lipids and Lipoproteins of Chinese Biochemistry and Molecular Biology Society, Cardiovascular Health Professional Committee of China Primary Health Care Foundation, et al. Chinese Expert Consensus on Early Screening and Management of Homozygous Familial Hypercholesterolemia (2024)[J]. Chinese Journal of Laboratory Medicine, 2024, 47(10): [page numbers].

[6] SHEN T Z, HU L J, JIANG L. Progress in diagnosis and treatment of familial hypercholesterolemia in children and adolescents[J]. Chinese Journal of Cardiovascular Medicine, 2023, 28(2): 184-188.

[7] MABUCHI H, KOIZUMI J, SHIMIZU M, et al. Development of coronary heart disease in familial hypercholesterolemia[J]. Circulation, 1989, 79(2): 225-232. DOI:10.1161/01.cir.79.2.225.

[8] CACERES B A, STREED C G Jr. Cardiovascular health concerns in sexual and gender minority populations[J]. Nat Rev Cardiol, 2021, 18(4): 227-228. DOI:10.1038/s41569-021-00518-3.

[9] JETTY V, GLUECK C J, LEE K, et al. Eligibility for alirocumab or evolocumab treatment in 1090 hypercholesterolemic patients referred to a regional cholesterol treatment center with LDL cholesterol $\geq$ 70 mg/dL despite maximal-tolerated LDL-cholesterol-lowering therapy[J]. Vasc Health Risk Manag, 2017, 13: 247-253. DOI:10.2147/VHRM.S133690.

[10] LUO R F, WANG J H, HU L J, et al. Applications of machine learning in familial hypercholesterolemia[J]. Front Cardiovasc Med, 2023, 10: 1237258. DOI:10.3389/fcvm.2023.1237258.

[11] PERSSON LINDELL O, KARLSSON L O, NILSSON S, et al. Clinical decision support for familial hypercholesterolemia (CDS-FH): Rationale and design of a cluster randomized trial in primary care[J]. Am Heart J, 2022, 247: 132-148. DOI:10.1016/j.ahj.2022.02.005.

[12] World Association of Chinese Laboratory and Pathology Physicians. Expert consensus on the model of diagnostic reporting for dyslipidemia diseases[J]. Chinese Medical Journal, 2018, 98(22): 1739-1742. DOI:10.3760/cma.j.issn.0376-2491.2018.22.004.

[13] MA X W, GONG L, WAN Z, et al. Analysis and reflection on the current status of rare disease clinical research in China[J]. West China Medical Journal, 2025, 40(1): 2-6.

[14] CHEN F X. Analysis and reflection on the use of lipid-lowering drugs in hospitals[J]. China Medical Guide, 2024, 22(32): 117-119. DOI:10.15912/j.issn.1671-8194.2024.32.034.

[15] ZENG Y H, LIU J, LIU J, et al. Impact of defining criteria for extremely high-risk ASCVD patients on lipid-lowering therapy needs in hospitalized ACS patients[J]. Chinese Journal of Cardiology, 2020, 48(12): 1039-1046. DOI:10.3760/cma.j.cn112148-20200324-00212.

[16] LANGSTED A, NORdestGAARD B G. Lipoprotein(a): is it more, less or equal to LDL as a causal factor for cardiovascular disease and mortality?[J]. Curr Opin Lipidol, 2020, 31(3): 125-131. DOI:10.1097/MOL.0000000000000681.

[17] SO J, ASZTALOS B F, HORVATH K, et al. Ethyl EPA and ethyl DHA cause similar and differential changes in plasma lipid concentrations and lipid metabolism in subjects with low-grade chronic inflammation[J]. J Clin Lipidol, 2022, 16(6): 887-894. DOI:10.1016/j.jacl.2022.10.002.

[18] HORTON A E, MARTIN A C, SRINIVASAN S, et al. Integrated guidance to enhance the care of children and adolescents with familial hypercholesterolemia: practical advice for the community clinician[J]. J Paediatr Child Health, 2022, 58(8): 1297-1312. DOI:10.1111/jpc.16096.

[19] HUANG H F, XU C M, WANG L L. Current status of blocking rare genetic diseases through preimplantation genetic testing in China[J]. Chinese Journal of Practical Gynecology and Obstetrics, 2020, 36(1): 10-15. DOI:10.19538/j.fk2020010102.

[20] ZHANG J, LI Y H. Treatment progress of homozygous familial hypercholesterolemia in children[J]. Chinese Journal of Practical Pediatrics, 2024, 39(11): 825-830. DOI:10.19538/j.ek2024110605.

[21] SUN Y F, WANG X, CAI W J, et al. ABCG5 gene mutation causing phytosterolemia: 1 case[J]. Journal of Clinical Pediatrics, 2020, 38(1): 65-68. DOI:10.3969/j.issn.1000-3606.2020.01.016.

[22] CAO K, LUO X J, LIU J, et al. Clinical phenotype, laboratory examination, genetic diagnosis and literature review of 3 children with phytosterolemia[J]. Journal of Clinical Laboratory Science, 2019, 37(6): 461-466. DOI:10.13602/j.cnki.jcls.2019.06.15.

[23] XU L Y, YANG Y, WANG L Y. Research progress on the relationship between phytosterolemia and premature coronary heart disease[J]. Chinese Journal of Evidence-Based Cardiovascular Medicine, 2019, 11(6): 754-756. DOI:10.3969/j.issn.1674-4055.2019.06.30.

[24] CHEN H H, CHEN P, GUO W, et al. Phytosterolemia diagnosed with stomatocytosis and macrothrombocytopenia: 1 case and literature review[J]. Laboratory Medicine and Clinic, 2021, 18(12): 1815-1817.

[25] ZHU L H, LONG X M, HUANG Y Q, et al. Phytosterolemia complicated

with common bile duct stones causing acute pancreatitis: 1 case[J]. Jiangsu Medical Journal, 2021, 47(1): 105-107. DOI:10.19460/j.cnki.0253-3685.2021.01.026.

[26] BARKAS F, BATHRELLOU E, NOMIKOS T, et al. Plant sterols and plant stanols in cholesterol management and cardiovascular prevention[J]. Nutrients, 2023, 15(13): 2845. DOI:10.3390/nu15132845.

[27] VAN DEN BOSCH S E, CORPELEIJN W E, HUTTEN B A, et al. How genetic variants in children with familial hypercholesterolemia not only guide detection, but also treatment[J]. Genes (Basel), 2023, 14(3): 669. DOI:10.3390/genes14030669.

[28] ARNETT D K, BLUMENTHAL R S, ALBERT M A, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines[J]. J Am Coll Cardiol, 2019, 74(10): 1376-1414. DOI:10.1016/j.jacc.2019.03.009.

[29] Expression of concern: effect of adding ticagrelor to standard aspirin on saphenous vein graft patency in patients undergoing coronary artery bypass grafting (POPular CABG): a randomized double-blind, placebo-controlled trial[J]. Circulation, 2021, 143(9): e755. DOI:10.1161/CIR.0000000000000962.

[30] JIANG M H, YI S W, ZHANG C H, et al. Research progress of novel lipid-lowering drugs regulating lipoprotein(a)[J]. Chinese Journal of Molecular Cardiology, 2024, 24(6): 6516-6520. DOI:10.16563/j.cnki.1671-6272.2024.12.013.

[31] GRECO A, FINOCCHIARO S, SPAGNOLO M, et al. Lipoprotein(a) as a pharmacological target: premises, promises, and prospects[J]. Circulation, 2025, 151(6): 400-415. DOI:10.1161/CIRCULATIONAHA.124.069210.

[32] MA G W, LIU S C, WANG H L, et al. Current status of PCSK9 inhibitors, novel lipid-lowering drugs, in atherosclerotic cardiovascular disease[J]. Journal of Pharmaceutical Research, 2024, 43(5): 487-494. DOI:10.13506/j.cnki.jpr.2024.05.013.

[33] SUN L Y, WANG W S, WANG X R, et al. Systematic review of economic evaluation of PCSK9 inhibitors for hypercholesterolemia[J]. Chinese Journal of New Drugs, 2025, 34(7): 778-784. DOI:10.20251/j.cnki.1003-3734.2025.07.014.

[34] CHEN Y, GUO F J, RUAN Y H, et al. Research progress on adverse reactions of PCSK9 inhibitors[J]. Journal of Clinical Cardiology, 2021, 37(8): 775-779. DOI:10.13201/j.issn.1001-1439.2021.08.021.

[35] BUCK J, GROSSEN P, CULLIS P R, et al. Lipid-based DNA therapeutics: hallmarks of non-viral gene delivery[J]. ACS Nano, 2019, 13(4): 3754-3782. DOI:10.1021/acsnano.8b07858.

[36] Joint Expert Committee on Revision of Chinese Guidelines for Lipid Management. Chinese guidelines for lipid management (2023)[J]. Chinese Circulation Journal, 2023, 38(3): 237-271.

[37] FERENCE B A, GINSBERG H N, GRAHAM I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel[J]. Eur Heart J, 2017, 38(32): 2459-2472. DOI:10.1093/eurheartj/ehx144.

[38] LIU W, LU Z L, HUANG J Y, et al. Expert recommendations on homogenized management models for diagnosis and treatment of rare diseases in children[J]. Chinese Journal of Contemporary Pediatrics, 2023, 25(7): 663-671.

[39] ZHANG L, LI J P. Establishment and promotion of a tiered diagnosis and treatment system for dyslipidemia management based on tiered medical care[J]. Chinese General Practice, 2024, 27(36): 4493-4497.

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Note: Figure translations are in progress. See original paper for figures.