Familial Hypercholesterolemia: Overview of Genetics, Diagnosis, and Management

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Familial hypercholesterolemia (FH) is the most common inherited metabolic disease caused by mutations of the genes involved in low-density lipoprotein cholesterol (LDL-C) metabolism.[1] FH affects approximately 30 million individuals globally and is characterized by lifelong elevation of LDL-C leading to early onset atherosclerosis and increased risk of atherosclerotic cardiovascular disease (ASCVD) events, most notably coronary artery disease.[1] FH is inherited in an autosomal dominant pattern. A single allelic mutation is called "heterozygous" FH (HeFH), and its prevalence is estimated to be 1 in 250 of cases.[1] Patients with "homozygous" FH (HoFH) have 2 mutated alleles and a prevalence of 1:160,000 to 1:250,000.[2] Despite the high prevalence of HeFH, it is estimated that fewer than 1% of cases are diagnosed in most countries.[3]

During normal lipid regulation, LDL-C particles in the blood stream bind to LDL receptors on the surface of hepatocytes via their ligand apolipoprotein B-100 molecule. The complex is internalized, and the LDL-C is degraded while the LDL receptor is recycled numerous times to the cell surface to repeat the process. Proprotein convertase subtilisin/kexin type 9 (PCSK9) decreases recycling and increases degradation of the LDL receptors. A defect in any component of these pathways can potentially impair the function or quantity of LDL receptors on hepatocyte surfaces, resulting in reduced clearance of LDL-C particles and accumulation of LDL-C particles in the circulation. The clinical outcome being enhanced atherosclerosis leading to premature cardiovascular disease (CVD).[4,5]

Diagnosis

In general, FH can be diagnosed clinically, with genetic testing, or a combination of both. Several diagnostic systems (ie, the US Make Early Diagnosis to Prevent Early Death criteria, UK Simon Broome criteria, and Dutch Lipid Network criteria) have been developed to aid clinicians in diagnosis.[6] A clinical diagnosis of FH can be made on the basis of a constellation of physical findings, family history of severe hypercholesterolemia and/or premature CVD events (men aged <55 years, women aged <65 years), personal history of early onset ASCVD, and the baseline concentration of circulating LDL-C (≥190 mg/dL in adults, ≥160 mg/dL in children, adolescents, and young adults).[6] Physical examination findings, though not present in the majority of cases, can include the presence of extensor tendon xanthomas (typically Achilles, subpatellar, and/or hand extensor tendons), corneal arcus, and xanthelasmas (cholesterol deposits in the eye lids or skin).[6]

Although genetic testing is not required for an FH diagnosis, FH genotyping provides further aid in confirming a definitive diagnosis of HeFH or HoFH. Current estimates indicate that 70% to 95% of cases of FH result from pathogenic variants in the *LDLR*, *APOB*, and *PCSK9* genes, with variants in the *LDLR* gene accounting for 60% to 80% of cases.[2,7] The prevalence of HeFH is 7.2%, or 23-fold, higher among persons with LDL-C levels of 190 mg/dL or higher.[1] Individuals with an LDL-C level of 190 mg/dL or higher and have a pathogenic FH mutation have a 21- to 22-fold higher CVD risk than the general population, indicating a possible benefit for genetic diagnosis for additional risk stratification and intensification of therapies based on results.[1] Diagnosing FH in a child or parent provides the opportunity for "cascade" screening, which relies on identifying a patient with FH (proband) and active cholesterol testing, genetic testing, or both for all potentially affected relatives—a cycle that is repeated ("cascaded") for each relative diagnosed with FH, thereby expanding the number of potential cases detected.[8]

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Table. Recommendations for Treating FH and/or Severe Primary Hypercholesterolemia[9,10]

2019 ESC/EAS RECOMMENDATIONS	CLASS[9]	LEVEL[9]
For primary prevention for individuals with FH at very high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL should be considered.	IIa	C
For FH patients with ASCVD who are at very high risk, treatment to achieve a ≥50% reduction from baseline and an LDL-C <55 mg/dL is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C
Treatment with a PCSK9 inhibitor is recommended in individuals with very high-risk FH if the treatment goal is not achieved on maximally tolerated statin plus ezetimibe.	I	C
2018 AHA/ACC RECOMMENDATIONS	**COR[10]**	**LOE[10]**
For patients aged 20-75 years with an LDL-C level of ≥190 mg/dL, maximally tolerated statin therapy is recommended.	I	B-R
For patients aged 20-75 years with an LDL-C level of ≥ 190 mg/dL who achieve < 50% reduction in LDL-C while receiving a maximally tolerated statin therapy and/or have an LDL-C level of ≥ 100 mg/dL, ezetimibe therapy is reasonable.	IIa	B-R
For patients aged 20-75 years with a baseline LDL-C level of ≥190 mg/dL, who achieve <50% reduction in LDL-C and have a fasting triglyceride level of ≤300 mg/dL, while taking a maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.	IIb	B-R
For patients aged 30-75 years with heterozygous FH and an LDL-C level of ≥100 mg/dL while taking a maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.	IIb	B-R
For patients aged 40-75 years with a baseline LDL-C level of ≥220 mg/dL and achieve an on-treatment LDL-C level of ≥130 mg/ dL while receiving a maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.	IIb	C-LD

Abbreviations: ASCVD; atherosclerotic cardiovascular disease; COR, class of evidence; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; PCSK9, Proprotein convertase subtilisin/kexin type 9.

The European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines for treating FH in adults recommend lifestyle modifications and the use of pharmacotherapy to achieve 50% or more reduction in LDL-C from baseline and an LDL-C level less than 70 mg/dL among patients with high risk for CVD events (**Table**).[9] An LDL-C level of less than 100 mg/dL may be considered for patients with moderate risk for CVD events, and an LDL-C level of less than 116 mg/dL should be achieved for patients with low risk.[9] For secondary prevention of ASCVD, the European guidelines recommend achieving an LDL-C goal of less than 55 mg/dL, whereas the 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend achieving an LDL-C goal of less than 70 mg/dL.[9,10] To achieve this goal, lipid-lowering therapeutics are of tantamount importance because of the need for significant LDL-C reduction unlikely achievable with nonpharmacologic treatment alone. However, standard therapeutic lifestyle changes and risk-reducing behaviors (eg, dietary modification, smoking cessation, increased exercise, blood pressure control) are still of vital importance for a CVD risk reduction plan.

Statin therapy remains the cornerstone of therapy for most patients with FH. Current guidelines for adults recommend maximum-tolerated statin therapy with high-intensity statins (eg, atorvastatin, 40-80 mg daily; rosuvastatin, 20-40 mg daily).[9,10] Although statins remain the cornerstone of treatment, FH is undertreated, with more than 80% of patients with statin-treated FH failing to attain LDL-C treatment targets, presumably related to adherence, tolerability, and genetic differences in statin responsiveness.[11] This necessitates the use of additional nonstatin lipid-lowering therapies. Ezetimibe, a cholesterol absorption inhibitor, is the guideline-preferred initial add-on agent of choice.[9,10] With an anticipated additional 13% to 20% LDL-C reduction, a statin plus ezetimibe may achieve the patient's LDL-C goal, but additional agents may still be needed.[10] In general, the third agent of choice would be an injectable PCSK9 inhibitor (eg, alirocumab, 75 mg or 150 mg every 2 weeks; evolocumab, 140 mg every 2 weeks).[10] These fully human monoclonal antibodies can further reduce LDL-C by 43% to 64% and will be sufficient to meet sustainable LDL-C goals in most patients.[10] In certain circumstances, other additional available oral agents such as bempedoic acid, 180 mg daily (anticipated 15%-25% LDL-C reduction) and bile acid sequestrants such as colesevlam, colestipol, or

cholestyramine (anticipated 10%-20% LDL-C reduction) could be considered.[9] Additional nonstatin therapies such as fibrates, niacin, or omega-3 fatty acid formulations are of little benefit for LDL-C reduction in FH patients.

Because baseline LDL-C is generally 400 mg/dL or higher among patients with HoFH, more advanced therapies are often needed to achieve LDL-C goals. Often, because of limited or lack of function of the LDL receptor, patients with HoFH may have reduced or no response to standard therapies that work by increasing LDL receptor expression, such as statins, bempedoic acid, and PCSK9 inhibitors. Fortunately, additional therapies are available. Lomitapide (5-60 mg daily), an inhibitor of the microsomal triglyceride transfer protein in the liver, can reduce LDL-C up to 50%.[12] Evinacumab (15 mg/kg/dose intravenous once every 4 weeks), a novel angiopoietin-like 3 inhibitor, can reduce LDL-C by 50% in patients with HoFH, even in those with complete dysfunction of their LDL receptors.12 Lipoprotein apheresis is an invasive procedure required biweekly to achieve and sustain an LDL-C reduction of 57% to 75% in patients with HoFH and 58% to 63% for patients with HeFH.[13] Several new investigational agents are on the horizon as well.

Conclusions

Despite our current advances in education, genetic diagnostics, and expanded treatment modalities, FH remains significantly underdiagnosed and undertreated. Patients with FH have a lifelong burden of elevated levels of LDL-C and significantly increased risk for early and recurrent ASCVD events that warrant enhanced recognition and diagnostic strategies along with aggressive LDL-C lowering therapy. With careful integration of patient support and education, a strong patient-provider team-based care approach with lifestyle coaching, and use of statin and nonstatin medications, achieving the goals of LDL-C reduction and improved outcomes are possible.

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