Familial hypercholesterolemia

Review of diagnosis, screening, and treatment

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Abstract

Objective To summarize the pathophysiology, epidemiology, screening, diagnosis, and treatment of familial hypercholesterolemia (FH).

Quality of evidence A PubMed search was conducted (inception to July 2014) for articles on pathophysiology, screening, diagnosis, and management of FH, supplemented with hand searches of bibliographies of guidelines and reviews. A supporting level of evidence for each recommendation was categorized as level I (randomized controlled trial or systematic review of randomized controlled trials), level II (observational study), or level III (expert opinion). The best available evidence is mostly level II or III.

Main message Familial hypercholesterolemia affects 1 in 500 Canadians. Risk of a coronary event is high in these patients and is underestimated by risk calculators (eg, Framingham). Clinicians should screen patients according to guidelines and suspect FH in any patient with a premature cardiovascular event, physical stigmata of hypercholesterolemia, or an elevated plasma lipid level. Physicians should diagnose FH using either the Simon Broome or Dutch Lipid Network criteria. Management of heterozygous FH includes reducing low-density lipoprotein levels by 50% or more from baseline with high-dose statins and other lipid-lowering agents. Clinicians should refer any patient with homozygous FH to a specialized centre.

Conclusion Familial hypercholesterolemia represents an important cause of premature cardiovascular disease in Canadians. Early identification and aggressive treatment of individuals with FH reduces cardiovascular morbidity and mortality.

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that produces elevations in low-density lipoprotein (LDL) cholesterol.[1] High levels of circulating LDL lead to the rapid development of atherosclerosis early in life, which results in the premature development of atherosclerotic cardiovascular disease (ASCVD). In practice, clinicians underrecognize FH and frequently only make the diagnosis once patients present with an ASCVD event at a young age.[1,2] Patients with FH require aggressive treatment, often with multiple pharmacologic agents, to reduce their levels of circulating LDL cholesterol in order to curtail ASCVD risk. In this review, we aim to summarize the pathophysiology, epidemiology, screening, diagnosis, and treatment of FH.

Quality of evidence

We conducted a PubMed search (inception to July 2014), supplemented with hand searches of bibliographies of clinical practice guidelines, position papers, and reviews. Recommendations from Canadian authorities, when available, were prioritized. Recommendations were rated from levels I to III: level I evidence included 1 or more properly conducted randomized controlled

EDITOR'S KEY POINTS

- Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that produces elevations in low-density lipoprotein (LDL) cholesterol. It is an underrecognized and undertreated cause of cardiovascular disease.
- The primary goal for the treatment of FH is to reduce mortality and atherosclerotic cardiovascular disease events, which is achieved by reducing plasma LDL levels. Although there is no evidence to support any specific LDL target in this population, guidelines generally recommend a reduction of 50% or more from baseline. Dietary modifications are important to lower LDL levels; however, additional interventions are required to achieve target lipid levels.
- Patients with FH require aggressive treatment, often with multiple pharmacologic agents, as well as atherosclerotic cardiovascular disease risk factor management (eg, tobacco use, hypertension).

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trials (RCTs) or systematic reviews of RCTs with or without meta-analysis; level II evidence included 1 or more controlled observational studies (cohort, case-control, or other relevant epidemiologic studies); and level III evidence included all opinion-based statements with no empiric supporting evidence.

Main message

Pathophysiology and epidemiology. Genetic mutations cause FH.[3] Defects in the genes that code for the LDL receptor, apolipoprotein B, or proprotein convertase subtilisin-kexin type 9 (PCSK9) ultimately lead to impaired clearance of LDL cholesterol from the plasma. Low-density lipoprotein receptors, found primarily on hepatocyte cell membranes, are responsible for uptake of LDL particles and thus removal of cholesterol from plasma. Apolipoprotein B is the LDL-bound protein that binds to the LDL receptor. Finally, PCSK9 is responsible for the degradation of LDL receptors; thus, genetic defects leading to elevated PCSK9 levels will result in decreased LDL receptors on hepatocytes, and thus hyperlipidemia. A single copy of the defective gene (heterozygous) leads to moderate accumulation of plasma LDL, whereas 2 copies of the same defective gene (homozygous) or 2 coexisting mutations (compound heterozygous) lead to extensive accumulation due to minimal or no LDL cholesterol clearance. Clinically, patients with heterozygous FH (HeFH) typically have an LDL plasma concentration of 5 to 13 mmol/L, whereas patients with homozygous FH (HoFH) have an LDL level well above 13 mmol/L.[4]

Approximately 1 in 500 Canadians has HeFH. Prevalence of FH varies based on ethnic background, with higher rates among Québécois French Canadians (1 in 270), Lebanese (1 in 85), Afrikaners (1 in 72), and Ashkenazi Jews (1 in 67).[5] Homozygous FH, the more severe form, affects approximately 1 out of every 1 million individuals.[5]

Complications and prognosis. Without early and aggressive treatment, FH manifests as premature ASCVD events, often affecting the coronary arteries. Patients with untreated HeFH tend to experience a first coronary event 20 or more years earlier than the general population (mean age 42 vs 64).[6] Consequently, their cumulative risk of a coronary event by age 50 is up to 44% in men and 20% in women.[6,7] This cardiovascular risk is far greater than that predicted by cardiovascular risk calculators (eg, Framingham risk score), and therefore these calculators should not be used in patients with FH.[8] Untreated HoFH is associated with an even worse prognosis, with many patients experiencing coronary events in childhood or adolescence.[9,10]

Lipid screening. **Table 1** provides a summary of the recommendations on screening for FH. The Canadian Cardiovascular Society (CCS) dyslipidemia guidelines and FH position statement recommend universal screening of plasma lipids in all men 40 years of age or older and all women 50 years of age or older or after menopause.[1,8] Furthermore, they recommend screening individuals with conditions that increase their risk of cardiovascular disease (eg, those who have hypertension, diabetes mellitus, chronic kidney disease, or who are current smokers) regardless of age.

For pediatric screening, guidelines released by the National Heart Lung and Blood Institute recommend routine universal screening of plasma lipids at 11 years of age, or as early as 12 months in children with a first-degree family history of ASCVD or FH.[11] As atherosclerosis begins early in life for individuals with FH (especially in HoFH), childhood screening is intended to facilitate early identification and treatment. Despite the theoretical benefits of the National Heart Lung and Blood Institute screening program, there are complex logistical challenges in implementation, as well as limited data for the optimal time to initiate treatment, which have stimulated controversy.[12]

Once a proband (or index case) of FH has been identified, the CCS position statement on FH recommends further "cascade screening."[1] This involves the screening of first-degree relatives of individuals with confirmed FH to identify undiagnosed cases. If a relative is found to have FH, their relatives should also be screened, and so forth. This strategy is based on the autosomal dominant inheritance pattern of FH. Individuals who are first-, second-, and third-degree relatives of an individual with HeFH will have a 50%, 25%, and 12.5% likelihood, respectively, of also having FH. On average, cascade screening identifies 8 new cases of FH for every proband.[13] A number of countries have initiated different variations of cascade screening, which have demonstrated favourable cost-effectiveness.[14] Patients can be enrolled into the Canadian FH registry through referral to a participating clinician or centre. Information can be obtained from the FH Canada website (**www.fhcanada.net/fh-canada-registry**).

Diagnosis. In practice, clinicians frequently miss FH. Of the estimated 83 500 individuals with FH in Canada, only approximately 5% have received an appropriate diagnosis.[1,2] Clinicians should suspect FH in any patient with a premature cardiovascular event, physical stigmata of hypercholesterolemia (ie, arcus senilis, xanthoma, or tendinous xanthoma) or a plasma LDL level of 5 mmol/L or higher.[15]

Once hypercholesterolemia is identified, physicians should rule out secondary causes, such as medical conditions (eg, hypothyroidism, diabetes mellitus, nephrotic syndrome, obstructive liver disease), drugs (eg, corticosteroids, diuretics), excess alcohol consumption, very poor diet, and a sedentary lifestyle (**Table 1**).

Table 1. Summary of recommendations

RECOMMENDATIONS	LEVEL OF EVIDENCE
Screening and diagnosis of FH	
Who should be screened?	
• In adults, screen plasma lipid levels in all men aged ≥ 40 y and all women aged ≥ 50 y or after menopause	III
• In pediatric patients, consider routine universal screening of plasma lipid levels at age 11 y or as early as 12 mo in children with a first-degree family history of ASCVD or FH	III
• Once an FH proband has been identified, perform cascade screening on their relatives	II
When should FH be suspected?	
• Any patient with premature ASCVD, physical stigmata of hypercholesterolemia, or a plasma LDL level of ≥ 5 mmol/L should be suspected of having FH	II
How should the diagnosis of FH be confirmed?	
• In patients with hypercholesterolemia, rule out secondary causes such as medical conditions (eg, hypothyroidism, diabetes mellitus, nephrotic syndrome, obstructive liver disease), drugs (eg, corticosteroids, diuretics), excess alcohol consumption, very poor diet, and sedentary lifestyle	III
• Diagnose FH using the Simon Broome Register or the Dutch Lipid Network criteria	II
Management	
Management of FH	
• Do not use cardiovascular risk calculators (eg, Framingham risk score) in patients with FH, as these do not reflect the true risk of ASCVD	II
• Consider enrolling patients with FH in the Canadian FH Registry* by referring them to a participating clinician or centre	III
• Aggressively manage traditional ASCVD risk factors, such as cessation of tobacco use and treatment of hypertension and diabetes	II
Management of HeFH	
• Reduce LDL level by ≥ 50% from baseline	III
• Use high-dose statin as first-line therapy	II
• In patients who fail to achieve a ≥ 50% reduction in LDL levels with maximally tolerated statin therapy, add other LDL-lowering agents, such as ezetimibe, bile-acid sequestrants (eg, cholestyramine, colesevelam), fibrates, or niacin	II
Management of HoFH	
• Refer patients with HoFH to a specialized centre	III

ASCVD—atherosclerotic cardiovascular disease, FH—familial hypercholesterolemia, HeFH—heterozygous familial hypercholesterolemia, HoFH—homozygous familial hypercholesterolemia, LDL—low-density lipoprotein.
*For more information, visit the FH Canada website at **www.fhcanada.net/fh-canada-registry**.

The CCS position statement on FH recommends making the diagnosis of FH using 1 of 2 score-based diagnostic criteria: the Simon Broome Register or the Dutch Lipid Network criteria (**Table 2**).[1,16] Both sets of diagnostic criteria perform reasonably well with no clear criterion standard.[17] The diagnosis of FH does not require genetic testing, as approximately 1 in 5 patients with a clinical diagnosis of HeFH have negative test results for all currently known genetic mutations.

Treatment. Despite the high ASCVD risk associated with FH, as many as 50% of patients with a proper diagnosis fail to receive adequately aggressive treatment, possibly owing to an underappreciation of the magnitude of the risk.[18,19] The primary goal for the treatment of FH is to reduce mortality and ASCVD events, which is achieved by reducing plasma LDL levels.[1,20,21]

Although there is no evidence to support any specific LDL target in this population, guidelines generally recommend a reduction of 50% or more from baseline,[1,20,21] similar to recommendations for the general population.[8] Dietary modifications are important to lower LDL levels; however, it is not possible for most FH patients to achieve their lipid level targets without additional interventions.[22] Management of traditional ASCVD risk factors, such as cessation of tobacco use and treatment of hypertension and diabetes, are crucial in FH patients owing to their high baseline ASCVD risk.[23]

In terms of the pharmacotherapeutic management of HeFH, high-dose statins are first-line therapy. In an RCT of patients with HeFH, treatment with 80 mg of atorvastatin daily reduced LDL levels by an average of 50% from baseline,[24] similar to results obtained in the population without FH.[25] Beyond LDL reduction, evidence supporting a reduction in clinically relevant outcomes with statin therapy (or any lipid-lowering therapy) in HeFH is primarily observational. One cohort study demonstrated that a moderate dose of statin therapy (eg, 40 mg of

Table 2. Diagnostic criteria of FH

DIAGNOSTIC CRITERIA	DESCRIPTION	DIAGNOSIS
Simon Broome Register	• DNA mutation consistent with FH *(category A)* • Lipid panel *(category B)*: in adults, a TC level of > 7.5 mmol/L or LDL level of > 4.9 mmol/L; in pediatric patients, TC level of > 6.7 mmol/L or LDL level of > 4.0 mmol/L • Tendinous xanthoma in the patient or any first- or second-degree relative *(category C)* • Family history of myocardial infarction *(category D)*: age < 60 y in first-degree relative; age < 50 y in second-degree relative • Family history of a TC level of > 7.5 mmol/L in a first- or second-degree relative *(category E)*	Definite FH: • Category A • Category B + category C Probable FH: • Category B + category D or E
Dutch Lipid Network	History and physical characteristics: • Personal history of CAD, or first-degree relative < 18 y with LDL values > 95th percentile or with tendinous xanthoma or arcus senilis *(2 points)* • Personal history of premature cerebral or peripheral vascular disease or first-degree adult relative with premature CAD or LDL values > 95th percentile *(1 point)* • Tendinous xanthoma *(6 points)* • Arcus senilis at age < 45 y *(4 points)* LDL levels: • > 8.5 mmol/L *(8 points)* • 6.51-8.5 mmol/L *(5 points)* • 4.9-6.5 mmol/L *(1 point)* Genetic testing: • LDL-R gene functional mutation *(8 points)*	Definite FH: • ≥ 8 points Probable FH: • 6-7 points Possible FH: • 3-5 points

CAD—coronary artery disease, FH—familial hypercholesterolemia, LDL—low-density lipoprotein, LDL-R—low-density lipoprotein receptor, TC—total cholesterol.
Data from Varghese.[16]

atorvastatin daily) reduced the 10-year risk of coronary heart disease from 60% to 10% (adjusted hazard ratio 0.18, 95% CI 0.13 to 0.25).[19] Furthermore, patients with HeFH taking statin therapy had an ASCVD risk that was only slightly higher than an age-matched sample of the general population (6.7 vs 4.1 events per 1000 patient-years). Other studies show similar improvements in prognosis with statin treatment.[26,27]

In patients who fail to achieve a 50% or greater reduction in LDL levels with maximally tolerated statin therapy, the CCS position statement on FH recommends adding other LDL-lowering agents.[1] Ezetimibe lowers LDL levels by an additional 15% to 20% and generally has few adverse effects when combined with statin therapy.[28,29] The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial (known as the *ENHANCE* trial), which enrolled patients with HeFH, had insufficient power to detect changes in clinically relevant outcomes.[28] The largest ezetimibe RCT, IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), evaluated the use of ezetimibe in addition to 40 mg of simvastatin daily in 18 144 postacute coronary syndrome patients with LDL levels of 1.3 to 3.2 mmol/L.[29] In this secondary prevention population without FH, the addition of ezetimibe to statin therapy reduced the absolute risk of cardiovascular events—primarily nonfatal myocardial infarction or stroke—by 2% over the course of 7 years, with no increased risk of adverse events. The strong pathologic role of LDL levels in the development of ASCVD in FH would predict similar relative benefit in this population.

Additional options include bile-acid sequestrants (eg, cholestyramine, colesevelam), fibrates, or niacin.[20] Bile-acid sequestrants and niacin are often poorly tolerated owing to gastrointestinal adverse effects and skin flushing, respectively. Clinicians must use caution when combining a fibrate or niacin with statin therapy owing to the increased risk of myopathies.[30,31] Finally, PCSK9 inhibitors such as evolocumab might provide additional options to further lower LDL levels in the future, pending Health Canada approval. **Table 3**[32-38] summarizes the new lipid-lowering agents for the treatment of HoFH.

Limited data exist for the treatment of HeFH in children. Randomized controlled trials of lipid-lowering agents in pediatric patients have thus far demonstrated an LDL reduction consistent with that seen in adults but, owing to limited enrollment and follow-up, have not demonstrated an effect on clinical outcomes.[39-41] In general, the management of pediatric patients with HeFH is similar to treatment of adults.

Table 3. Summary of new lipid-lowering agents for the treatment of HoFH

	CHARACTERISTICS							
LIPID-LOWERING AGENT	AVAILABILITY IN CANADA	MECHANISM	DOSING REGIMEN	MEAN LDL REDUCTION FROM BASELINE	CLINICAL OUTCOME EVIDENCE	CONTRAINDICATIONS	ADVERSE EFFECTS	POTENTIAL DRUG INTERACTIONS
Lomitapide*	Yes (approved February 4, 2014)	An MTP inhibitor that prevents assembly of VLDL thereby reducing LDL levels	5-60 mg orally once daily	38%-50%	None	Pregnancy; chronic bowel disease (eg, IBD, malabsorption); moderate or severe hepatic impairment; use of a moderate or strong CYP 3A4 inhibitor; coadministration with simvastatin ≥ 40 mg/d	Gastrointestinal intolerance, liver enzyme elevations, hepatic steatosis	• Inhibits CYP 3A4 (eg, interacts with atorvastatin, lovastatin, simvastatin, warfarin) • Inhibits P-glycoprotein (eg, interacts with colchicine, dabigatran, digoxin) • CYP 3A4 substrate
Mipomersen†	No	An antisense oligonucleotide targeted against Apo B mRNA, which prevents synthesis of Apo B thereby decreasing LDL levels	200 mg SC once weekly	25%	None	Moderate or severe hepatic impairment	Injection-site reaction, flulike symptoms, liver enzyme elevations, hepatic steatosis	None known
PCSK9 inhibitors (alirocumab, bococizumab, evolocumab)‡	No	A PCSK9 inhibitor that prevents the breakdown of LDL receptors thereby enhancing LDL elimination	• 75-150 mg of alirocumab SC every 2 wk • 150 mg of bococizumab SC every 2 wk • 140 mg of evolocumab SC every 2 wk or 420 mg SC every 4 wk	48%-65% for HeFH; 23% for HoFH	None	None known	Injection-site reaction; musculoskeletal symptoms	None known

Apo B—apolipoprotein B, CYP 3A4—cytochrome P450 enzyme subtype 3A4, HeFH—heterozygous familial hypercholesterolemia, HoFH—homozygous familial hypercholesterolemia, IBD—inflammatory bowel disease, LDL—low-density lipoprotein, mRNA—messenger ribonucleic acid, MTP—microsomal triglyceride transfer protein, PCSK9—proprotein convertase subtilisin-kexin type 9, SC—subcutaneously, VLDL—very low-density lipoprotein.
*Data for lomitapide characteristics from Rader and Kastelein,[32] Aegerion Pharmaceuticals,[33] and Cuchel et al.[34]
†Data for mipomersen characteristics from Rader and Kastelein,[32] Genzyme,[35] Raal et al,[36] and Akdim et al.[37]
‡Data for characteristics of PCSK9 inhibitors from Navarese et al.[38]

The management of HoFH requires specialist care with aggressive pharmacologic lipid-lowering treatment, as well as lipoprotein apheresis in select patients.[1] Lipoprotein apheresis is an expensive procedure that involves extracorporeal filtering of lipoproteins from blood, generally performed over a few hours on a weekly or twice-monthly basis. As with HeFH, statins and ezetimibe are first- and second-line therapy, with bile-acid sequestrants, fibrates, and niacin used less frequently. Two new agents, lomitapide and mipomersen (**Table 3**),[32-38] show promise in the treatment of HoFH. In 2014, Health Canada approved lomitapide for use in HoFH, whereas mipomersen is not yet commercially available in Canada. There might also be a future role for PCSK9 inhibitors in the treatment of HoFH patients.

Conclusion

Familial hypercholesterolemia is an underrecognized and undertreated cause of cardiovascular disease. Clinicians should screen patients for FH and diagnose it according to CCS recommendations. Core management of HeFH relies on aggressive pharmacologic lipid lowering and ASCVD risk factor management. Clinicians should refer all patients with HoFH to a specialized centre for aggressive lipid lowering. New and upcoming pharmacologic agents offer additional options for lipid lowering.

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Contributors
All authors contributed to the literature review, analysis, and interpretation, and to preparing the manuscript for submission.

Competing interests
None declared

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