

CCS Guidelines and Position Statements

Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia

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ABSTRACT

Familial hypercholesterolemia (FH) is the most common genetic disorder causing premature cardiovascular disease and death. Heterozygous FH conservatively affects approximately 1:500 Canadians, and the more serious homozygous form affects approximately 1:1,000,000 Canadians, although these numbers might be underestimated. Of approximately 83,500 Canadians estimated to have FH, most are undiagnosed, which represents a simultaneous public health deficit and opportunity, because early treatment of heterozygous FH can normalize life expectancy. Diagnostic algorithms for FH

Familial hypercholesterolemia (FH) is an autosomal codominant genetic disorder characterized by very high plasma levels of low-density lipoprotein (LDL) cholesterol (LDL-C), increased cardiovascular risk—by up to 20-fold—and early onset

RÉSUMÉ

L'hypercholestérolémie familiale (HF) qui est la maladie génétique la plus fréquente entraîne de manière précoce la maladie cardiovasculaire et la mort. Bien que ces chiffres puissent être sous-estimés, la forme hétérozygote de l'HF touche environ 1 Canadien sur 500, alors que la forme homozygote, qui s'avère être la forme la plus sérieuse, touche environ 1 Canadien sur 1 000 000. On estime que parmi les quelque 83 500 Canadiens souffrant d'HF la plupart ne sont pas diagnostiqués, ce qui représente simultanément un déficit et une opportunité pour la santé publique, puisque le traitement précoce de

cardiovascular disease.¹⁻³ FH is the most common monogenic disorder leading to premature coronary heart disease and cardiac death. FH is often unrecognized until the inaugural cardiovascular event. Early diagnosis and treatment of FH can normalize

Received for publication September 13, 2014. Accepted September 22, 2014.

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The disclosure information of the authors and reviewers is available from the CCS website: www.ccs.ca. This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to

formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

incorporate increased plasma low-density lipoprotein cholesterol, pathognomonic clinical features, and family history of early cardiovascular disease and hyperlipidemia. DNA-based detection of causative mutations in FH-related genes can help with diagnosis. Maximizing diagnosis and treatment of FH in Canada will involve a multipronged approach, including: (1) increasing awareness of FH among health care providers and patients; (2) creating a national registry for FH individuals; (3) setting standards for screening, including cascade screening in affected families; (4) ensuring availability of standard-of-care therapies, in particular optimization of plasma low-density lipoprotein cholesterol levels and timely access to future validated therapies; (5) promoting patient-based support and advocacy groups; and (6) forming alliances with international colleagues, resources, and initiatives that focus on FH. This document aims to raise awareness of FH nationally, and to mobilize knowledge translation, patient support, and availability of treatment and health care resources for this underrecognized, but important medical condition.

life expectancy. If left untreated, men with FH develop cardiovascular disease in the third to fourth decade of life and women 10 years later on average. The prevalence of heterozygous FH (HeFH) had been conservatively estimated at 1:500, based on a survey of familial lipoprotein disorders in myocardial infarction survivors.⁴ Recent molecular studies indicate that 3.4% of patients with early myocardial infarction have FH mutations.⁵ Increased rates of FH are observed in populations in which founder effects are present.¹ The prevalence of HeFH in French-Canadians is estimated at approximately 1:270.⁶ Thus, assuming that the prevalence of HeFH in the rest of Canada is 1:500, and that populations of Quebec and the rest of Canada are 8 and 27 million, respectively, the number of FH subjects in Canada is approximately 83,500, although this likely underestimates the true number, because recent population surveys using direct molecular screening in Europeans diagnosed approximately 1:250 individuals with HeFH.^{1,3,7} Unfortunately, most FH patients are unrecognized, because of factors including inconsistent screening practices and general unawareness regarding diagnosis. National programs that include a patient registry and targeted cascade screening for FH have proven to be cost-effective and to improve outcomes in several European countries. The aim of this Position Statement is to raise awareness and stimulate discussion toward development of national guidelines for the diagnosis and treatment of FH in Canada.

Choice of Outcomes and Appraisal of the Evidence

The most relevant outcomes in the diagnosis and care of patients with FH are: (1) biochemical, specifically attaining optimal LDL-C levels; (2) clinical, primarily reducing cardiovascular events; and (3) societal, including processes of care. Another potential outcome is sequential imaging of atherosclerosis burden as a surrogate marker for the treatment effectiveness (see the section on Secondary Testing and Imaging in FH). No randomized cardiovascular end point trials

la forme hétérozygote de l'HF peut normaliser l'espérance de vie. Les algorithmes diagnostiques de l'HF incorporent l'augmentation de la concentration plasmatique du cholestérol à lipoprotéines de basse densité, les signes cliniques pathognomoniques et les antécédents familiaux de maladie cardiovasculaire précoce et d'hyperlipidémie. L'analyse de l'ADN pour la détection des mutations causales dans les gènes liés à l'HF peut faciliter le diagnostic. La maximisation du diagnostic et du traitement de l'HF au Canada impliquera une approche à volets multiples, y compris : 1) accroître la sensibilisation des prestataires de soins de santé et des patients à l'HF; 2) créer un registre national d'individus souffrant de l'HF; 3) fixer des normes de dépistage, y compris le dépistage en cascade auprès des familles touchées; 4) assurer la disponibilité des traitements correspondant aux normes de soins, en particulier l'optimisation des concentrations plasmatiques de cholestérol à lipoprotéines de basse densité et l'accès en temps opportun aux traitements validés futurs; 5) promouvoir les groupes de soutien et de défense des droits des patients; 6) conclure des alliances internationales avec les collègues, les ressources et les initiatives qui se concentrent sur l'HF. Ce document a pour objectif d'accroître la sensibilisation de l'HF sur le plan national et de mobiliser les connaissances, le soutien au patient et la disponibilité des traitements et des ressources en soins de santé concernant cette maladie méconnue, mais importante.

exist to prove that lowering of LDL-C should be the primary treatment target in FH patients, however overwhelming evidence from the general population indicates that reducing LDL-C is effective.⁸ Moreover, the totality of evidence reviewed strongly suggests that early diagnosis and institution of multidimensional risk factor modification in FH patients, including lifestyle modification and appropriate use of pharmacotherapy is cost-effective and life-saving.

Processes of Care As an Outcome

Underestimation of FH prevalence and insufficient awareness of favourable cost-benefit of interventions, make the implementation of processes of care at the societal level a key outcome. Such primary processes include: (1) prompt recognition of patients at high risk of having FH (eg, adults with LDL-C > 5.0 mmol/L); (2) implementation of strict lifestyle changes in patients with probable or definite FH, including smoking cessation, prudent diet, weight management, avoidance of sedentary lifestyle, and control of other cardiovascular risk factors; (3) referral of probable and definite cases of FH for specialist care; (4) cascade screening of probands and relatives to identify additional cases; (5) construction of a national FH registry to collect data on FH incidence and prevalence and to disseminate educational material to health care providers, patients, and the general public; and (6) education of primary care physicians, and specialists in internal medicine, pediatrics, cardiology, endocrinology, and obstetrics and gynecology on the basics of diagnosis and treatment of FH.

RECOMMENDATION

1. We suggest implementation of standard processes of care for the identification and treatment of subjects with FH (Conditional Recommendation, Moderate-Quality Evidence).

Values and Preferences. Stakeholders in health care management should support regional centres of expertise in the detection of FH, cascade screening, and molecular diagnosis.

Diagnosis of FH

Early diagnosis of FH enables early initiation of preventive measures to reduce cardiovascular disease risk.⁹ In Canada, most HeFH patients are diagnosed using clinical and biochemical features,¹⁰ including: (1) very high LDL-C (typically > 5.0 mmol/L); (2) typical physical findings (stigmata) such as tendon xanthomata, xanthelasma, and arcus corneae (Fig. 1); (3) personal history of early cardiovascular disease; and (4) family history of early cardiovascular disease or of marked hyperlipidemia, often requiring treatment.

Secondary or nongenetic causes of increased LDL-C^{1,10} must first be ruled out (Table 1). The most commonly used diagnostic algorithms for HeFH are the United Kingdom Simon Broome Registry¹¹ and the Dutch Lipid Clinic Network criteria¹² (Table 2). The less widely used US MedPed criteria focuses on LDL-C levels, without regard to clinical features.¹³ The Simon Broome Registry and Dutch Lipid Clinic Network criteria incorporate weighted combinations of the aforementioned factors,^{11,12} and produce scores that lead to classification of either “definite” or “probable” FH, with a third category of “possible FH” in the Dutch Lipid Clinic Network system. Detection of a pathogenic DNA mutation in an FH-related gene essentially leads to a diagnosis of “definite FH”.^{11,12} Head-to-head comparisons suggest that the Simon Broome Registry and Dutch Lipid Clinic Network criteria perform comparably well in diagnosing HeFH.¹⁴ DNA sequence analysis of FH-associated genes can help in specific instances (see Supplemental material sub-section “DNA testing for FH” and Fig. 2). There are several reasons to consider development of Canadian-specific diagnostic criteria for FH (see Supplemental material sub-section “Need for new Canadian-specific diagnostic criteria for HeFH”, and Fig. 3).

RECOMMENDATION

2. We suggest that the diagnosis of FH should rely on the Simon Broome Registry or Dutch Lipid Clinic Network criteria (Conditional Recommendation, Moderate-Quality Evidence).

Values and Preferences. Because there is no “gold standard” to diagnose FH, further clarification of specific criteria to facilitate diagnosis is required—especially to increase diagnostic sensitivity in the primary care setting.

Screening for FH in Adults

Early detection of affected individuals is the cornerstone of cardiovascular disease prevention. Furthermore, FH is among the few genetic disorders that meets all conditions for large-scale screening programs.¹⁵ Universal screening for dyslipidemia is already recommended for Canadian men 40 years of age and older, for women 50 years of age and older, or those who are postmenopausal, and for subjects at risk of cardiovascular disease; some cases of FH will be found this way.¹⁶

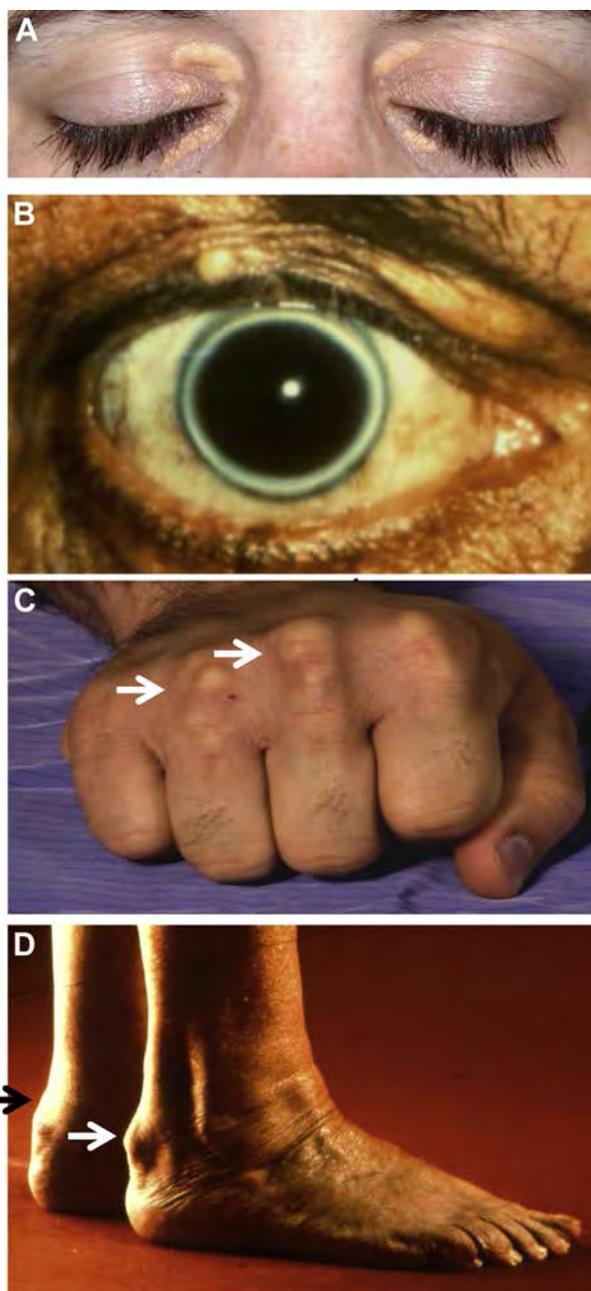


Figure 1. Physical findings (stigmata) in FH. (A) Bilateral xanthelasma on eyelids. (B) Bilateral arcus corneae, which are pathognomonic when detected by the fifth decade of life, but are nonspecific to FH by the eighth decade of life. (C) Arrows indicate xanthoma with the extensor tendon of the hand. (D) Arrows indicate xanthomas within the Achilles tendons. FH, familial hypercholesterolemia.

To maximize identification of previously undiagnosed adult FH subjects, 2 complementary strategies are proposed: (1) targeted screening to identify FH index cases (proband) among hypercholesterolemic adults with at least 1 feature such as personal or family history of clinical stigmata, personal or familial history of premature cardiovascular disease, or family history of significant hypercholesterolemia; and (2) cascade screening—or systematic family tracing—of first-, second-, and eventually third-degree relatives of probands to detect

Table 1. Secondary causes of severe increased low-density lipoprotein cholesterol

<ul style="list-style-type: none"> • Obstructive liver disease • Hypothyroidism • Nephrotic syndrome • Anorexia

affected members; each of whom then serves as an index case.¹¹ Identification of index cases requires a fasting lipid profile performed while the subject is free of intercurrent illnesses. Although cascade screening is largely based on LDL-C levels, screened subjects with “possible” or “probable” FH can be considered for genetic testing to confirm the diagnosis (see [Supplemental material](#) sub-section “DNA testing for FH”).

Cascade screening, starting with LDL-C measurement, after ascertaining an index patient, can effectively identify related affected individuals who can be treated. Because HeFH shows autosomal dominant transmission, 50%, 25%,

and 12.5% of first-, second-, and third-degree relatives screened, respectively, will be affected.¹¹ We suggest that: (1) Canadian primary care providers should be sensitized to the diagnosis of FH and offered tools to effectively identify index cases; (2) national, provincial, and local protocols should be developed for screening of adults and children with FH; (3) community laboratories could alert providers about abnormal LDL-C (eg, ≥ 5.0 mmol/L); (4) opportunistic screening should be performed systematically around the time of a cardiovascular disease event; (5) Canadian-specific cascade screening should be maximally cost-effective, systematic, and centrally coordinated; (6) national, provincial, and local registries of FH subjects can support cascade screening; (7) genetic testing should be performed only in specialized, accredited laboratories; (8) counselling before and after testing should be available; and (9) local ethics boards should review the sensitive issue of contacting relatives in the course of cascade screening.

Table 2. Criteria for FH*

A. Simon Broome Registry		
Criteria		
1.	A plasma measurement of either: Total cholesterol > 7.5 mmol/L (adult patient) or > 6.7 mmol/L (child aged < 16 years) Low-density lipoprotein cholesterol > 4.9 mmol/L (adult patient) or > 4.0 mmol/L (child aged < 16 years)	
2.	Tendon xanthomas in the patient or any of the patient's first- or second-degree relatives	
3.	DNA-based evidence in the patient of mutation in <i>LDLR</i> or other FH-related gene	
4.	Family history of myocardial infarction before the age of: 50 Years, in any first- or second-degree relative 60 Years, in any first-degree relative	
5.	Family history of plasma total cholesterol > 7.5 mmol/L in any first- or second-degree relative	
B. Dutch Lipid Clinic Network		
Points	Criteria	Diagnosis
1	First-degree relative with premature cardiovascular disease or LDL-C > 95 th percentile, or personal history of premature peripheral or cerebrovascular disease, or LDL-C between 4.01 and 4.89 mmol/L (155 and 189 mg/dL)	Definite FH (≥ 8 points)
2	First-degree relative with tendinous xanthoma or corneal arcus, or First-degree relative child (< 18 years) with LDL-C > 95 th percentile, or personal history of coronary artery disease	Probable FH (6-7 points)
3	LDL-C between 4.91 and 6.44 mmol/L (190 and 249 mg/dL)	
4	Presence of corneal arcus in patient younger than 45 years of age	
5	LDL-C between 6.46 and 8.51 mmol/L (250 and 329 mg/dL)	Possible FH (3-5 points)
6	Presence of a tendon xanthoma	
8	LDL-C > 8.53 mmol/L (330 mg/dL), or functional mutation in the <i>LDLR</i> gene	

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; *LDLR*, gene encoding the LDL receptor.

* Criteria required for diagnosis of: definite HeFH, A + B or C; and probable HeFH, A + D or A + E.

RECOMMENDATION

3. We recommend strategic use of targeted and cascade screening for timely recognition and treatment of new adult cases of FH (Strong Recommendation, Low-Quality Evidence).

Values and Preferences. Cascade screening, starting with LDL-C measurement, can be considered after the identification of an index patient. DNA testing should be reserved for cases of diagnostic uncertainty, for example, when accurate family history is unavailable, when lipid levels are borderline, when screened family members have “possible” or “probable” FH, and in cases in which management will be altered by the results of such testing.

Screening for FH in Children

Except for individuals with rare homozygous FH (HoFH), children with FH have no physical findings or overt cardiovascular disease; hence, detection can only be accomplished using lipid screening. However, there remain important evidence gaps regarding the benefits, harms, and costs of childhood lipid screening.¹⁷⁻¹⁹ Also, appropriate management is limited by lack of resources and time within a busy clinical practice.²⁰ There will likely never be direct evidence that lipid screening in childhood reduces cardiovascular disease risk in adulthood, despite a compelling chain of observational evidence. Atherosclerosis does not progress uniformly across the lifespan, and is likely preventable and reversible during childhood. Optimizing risk factors during adolescence was associated with reduced odds of cardiometabolic risk factors and early atherosclerosis on carotid ultrasound 21 years later.²¹ Trials of statin therapy in children and adolescents with FH have shown normalized endothelial function,²² and regression of carotid intima-media thickness,²³ which is effective when initiated at younger ages.²⁴

The case for screening children to detect FH and initiate treatment is reasonably strong.^{25,26} As with adults, screening for FH in children can be accomplished using universal, targeted, or

cascade screening. Universal screening potentially allows for complete case ascertainment. Although cascade screening appears cost-effective, there are many uncertainties in the modelling. Because there are even more uncertainties in modelling its cost-effectiveness, we cannot recommend universal screening in children. Advice for pediatric screening for FH from other bodies is discussed in the [Supplemental material](#) section “ADDITIONAL POINTS ON SCREENING”.

RECOMMENDATION

4. We suggest targeted screening in children and adolescents with such cardiovascular risk factors as a positive family history of dyslipidemia or cardiovascular disease, obesity, smoking, hypertension, or type 2 diabetes (Conditional Recommendation, Low-Quality Evidence).

Values and Preferences. Screening the plasma lipid profile in children with a positive family history, and with poor lifestyle or cardiovascular risk factors might help motivate the adoption of preventive strategies.

Management of FH in Adults

Overall goals of treatment

Although no randomized trials exist to prove that lowering LDL-C is the primary treatment target in FH patients, overwhelming evidence from the general population shows the effectiveness of reducing LDL-C: a 1 mmol/L reduction reduces major cardiovascular disease events by approximately 20% after 5 years.⁸ Nonetheless, coronary heart disease risk is increased by up to 20-fold in untreated FH patients,¹ and cardiovascular disease events are dramatically reduced in observational studies of statin-treated FH patients.^{9,11} Extrapolating from the general population in the context of the high cardiovascular disease risk level in adult FH heterozygotes, it is reasonable to recommend > 50% reduction from baseline LDL-C as a minimal target for primary prevention.¹⁶ If cardiovascular disease is present, the LDL-C target to be strived for is < 2.0 mmol/L, although patients with severe HeFH or HoFH will likely not reach this target without more aggressive and complex therapy.

RECOMMENDATION

5. Conventional cardiovascular risk calculators that assess short-term risk are inaccurate in FH patients. We recommend considering all adults with FH as being at “high risk” as a result of lifelong exposure of arteries to high LDL-C (Strong Recommendation, Moderate-Quality Evidence).

Values and Preferences. Because FH patients are often young, with few other risk factors, risk calculators such as Framingham, Systematic Coronary Risk Evaluation (SCORE), and others will underestimate their lifetime

cardiovascular risk, and should not be used for risk assessment.

6. For primary prevention in adult FH patients, beginning at 18 years of age, we recommend a > 50% reduction of LDL-C from baseline. For secondary prevention, we recommend striving toward a target LDL-C < 2.0 mmol/L (Strong Recommendation, Low-Quality Evidence).

Values and Preferences. LDL-C is a strong surrogate for end points such as cardiovascular death, myocardial infarction, and the need for arterial revascularization.

Lifestyle factors

In addition to increased LDL-C levels, FH patients are also vulnerable to other risk factors. Thus, FH patients and families would benefit from lifestyle management education, including advice regarding diet, exercise, weight control, blood pressure control, diabetes control, and smoking cessation.^{27,28} Advice to children and young adults to refrain from starting smoking is especially important. Structured smoking cessation programs should be offered to smokers with FH.

RECOMMENDATION

7. We suggest that a healthy lifestyle including smoking cessation, prudent diet, caloric intake to maintain ideal body weight, daily exercise, and stress reduction be recommended for FH patients (Conditional Recommendation, Low-Quality Evidence).

Values and Preferences. Randomized trials of lifestyle modification in FH subjects are unlikely to be performed. However, nonlipid cardiovascular disease risk factors amplify the already high risk in FH patients and should be managed.

Pharmaceutical therapies

Statins are the drug class of choice for HeFH, although clinical end point evidence for specific levels of absolute or relative reductions in plasma LDL-C is lacking. Following from the Canadian Cardiovascular Society guideline recommendations for adults with dyslipidemia, a reasonable therapeutic goal for primary prevention in adults with HeFH is to achieve a > 50% reduction in LDL-C levels,¹⁶ a goal that in many cases is achievable with high-dose statins alone. When LDL-C still requires reduction, addition of adjunctive agents is recommended on an individualized basis. In HeFH patients with established atherosclerotic cardiovascular disease, the Canadian Cardiovascular Society guideline recommended a goal of LDL-C < 2.0 mmol/L should be at the top-of-mind, but might not be feasible with currently available drugs.¹

RECOMMENDATION

8. We recommend that statins should be first-line therapy in FH patients, with the aim of lowering LDL-C by > 50%. In patients with atherosclerosis, maximally tolerated doses of statins with or without ezetimibe or bile acid sequestrants (cholestyramine, colestipol, or colesvelam) might further decrease LDL-C (Strong Recommendation, Low-Quality Evidence).

Values and Preferences. Statins have modified the natural course of FH. When treated early in life, event-free survival is essentially normalized in HeFH patients.

Statin intolerance or adverse effects in FH

Although statins are safe and easy to use, compliance can be an issue in up to 10% of patients because of side effects. Statin-related adverse effects have been extensively reviewed: muscle-related symptoms and early diabetes onset in diabetes-prone individuals are most consistent, and evidence of effects on liver function and cognitive function is much weaker.^{29,30} A large meta-analysis found no difference between statins and placebo with respect to side effect-related discontinuations, myalgia, or the incidence of cancer, and there were differences among individual statins regarding creatine kinase and liver function abnormalities.³¹ Additionally, statins appear to be associated with a small risk of new-onset type 2 diabetes.³⁰

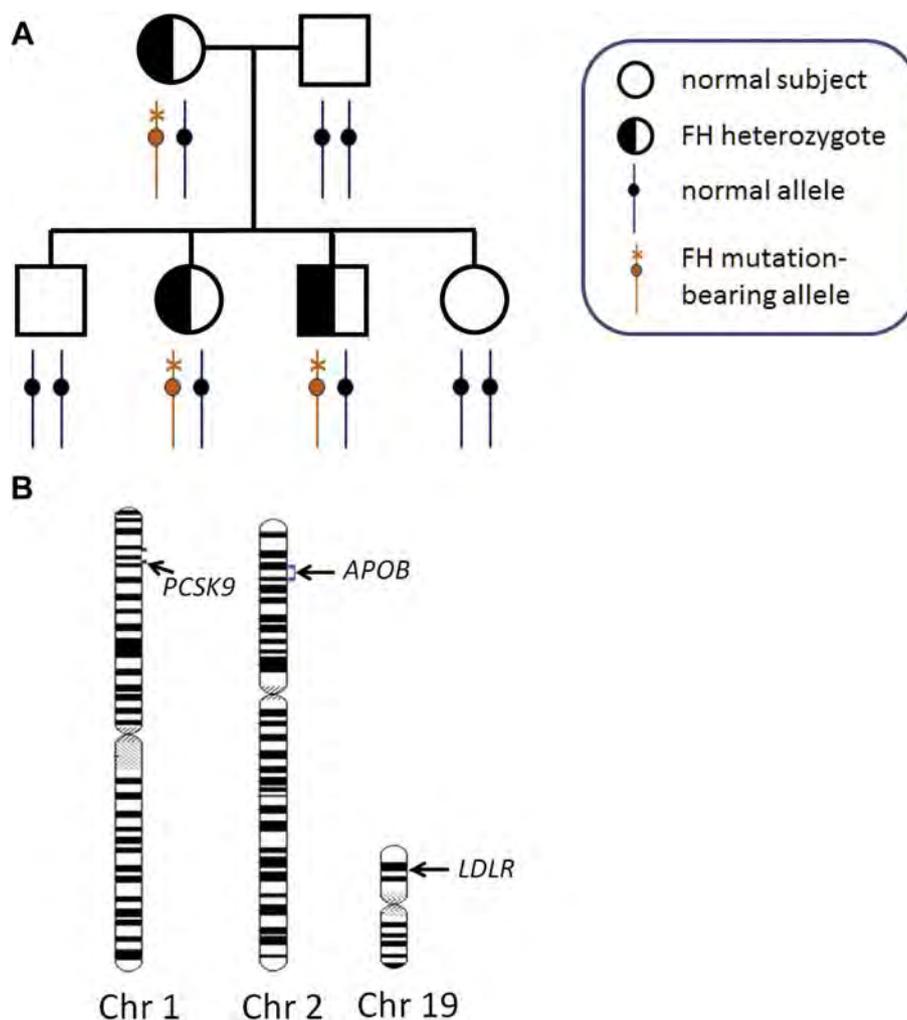


Figure 2. Genetics of FH. **(A)** Familial inheritance of heterozygous FH (HeFH). Squares and circles represent male and female individuals, respectively. Up to 1:250 matings in Canada involve an HeFH subject and a normolipidemic individual. Clinical and biochemical features of affected individuals are discussed in “Diagnosis of FH”, [Tables 2](#), and [Figure 1](#). Genotypic inheritance of FH-causing mutations and their cosegregation with the HeFH phenotype are shown below each pedigree symbol. Fifty percent of children of such a mating will have HeFH, which is usually fully expressed early in life. Because 50%, 25%, and 12.5% of first-, second-, and third-degree relatives of an affected individual will also have HeFH, systematic biochemical cascade screening of family members is considered by many to be a cost-effective approach to finding new cases. **(B)** Main genes causing FH. Chromosomal location of the main genes causing dominant HeFH and their chromosomal location: *LDLR* encoding the LDL receptor (approximately 95% of all causative mutations), *APOB* encoding apolipoprotein B (approximately 3% of all mutations), *PCSK9* encoding proprotein convertase subtilisin kexin 9 (approximately 1% of all mutations), and some very rare genes are not shown. *APOB*, gene encoding apolipoprotein B; Chr, chromosome; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; *LDLR*, gene encoding LDL receptor; *PCSK9*, gene encoding pro-protein convertase subtilisin/kexin type 9.

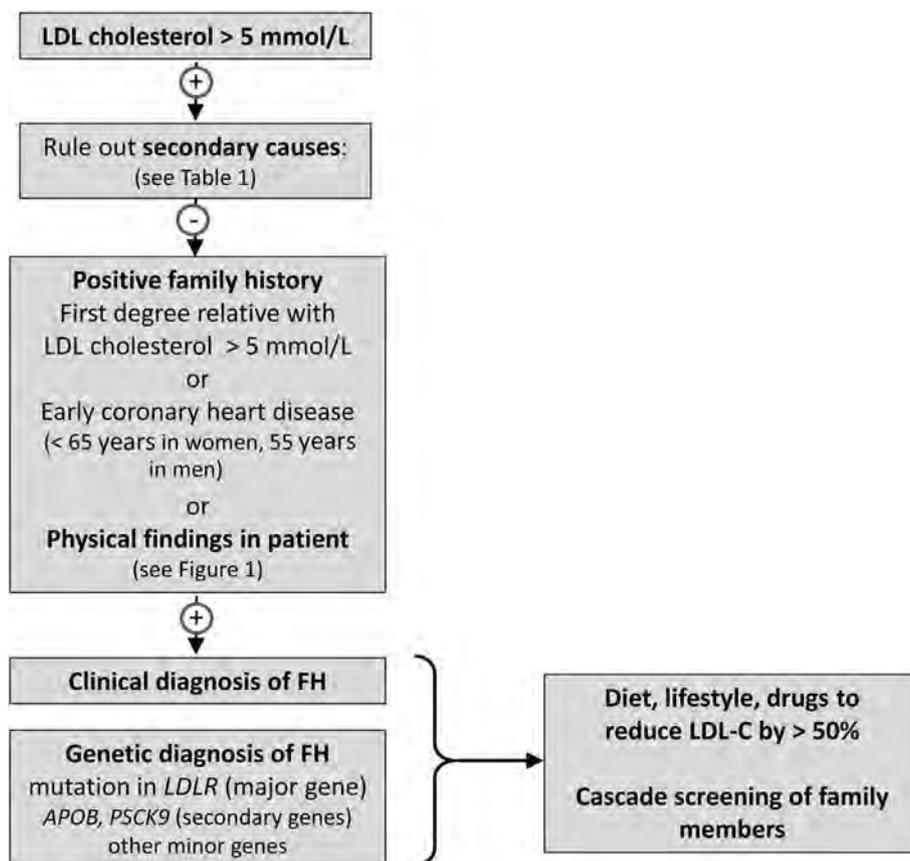


Figure 3. Diagnostic and treatment flow when familial hypercholesterolemia (FH) is suspected. *APOB*, gene encoding apolipoprotein B; C, cholesterol; LDL, low-density lipoprotein; *LDLR*, gene encoding LDL receptor; *PCSK9*, gene encoding pro-protein convertase subtilisin/kexin type 9.

The latter effects were seen with the higher-potency doses and were related to presence of metabolic risk factors for new-onset diabetes, such as obesity, impaired fasting glucose, hypertriglyceridemia, and hypertension.³² Moreover, the cardiovascular risk reduction benefit of statins far outweighs the risk of new-onset diabetes.

Concerns are often amplified when long-term therapy is considered for young and prepubertal patients with FH. Safety evidence specific to FH patients is not plentiful, but several meta-analyses show statins are generally very well tolerated without significant effects on growth or maturation.³³⁻³⁵ Although further evidence would be desirable, the current evidence base suggests that statins can be safely used in the FH population as in the general population, but with care in special circumstances, including treatment of children younger than 8 years of age, and avoidance of use in women intending to conceive or who are pregnant or breastfeeding.³⁶

Emerging therapies

Because of the importance of LDL-C as a cardiovascular disease risk factor, and because FH is the ultimate human model of extreme increased LDL-C level that increases cardiovascular disease risk, new classes of drugs to decrease LDL-C level have been or are being evaluated in FH. Discussed in detail in the [Supplemental material](#) section “EMERGING THERAPIES IN FH”, these include: (1) oral microsomal triglyceride transfer protein inhibitors, of which lomitapide

was recently approved in Canada for the restricted indication of treatment of HoFH³⁷; (2) subcutaneously administered apolipoprotein B antisense strategies, of which mipomersen was recently approved in the United States but not Canada³⁸; (3) orally administered cholesterol ester transfer protein inhibitors³⁹; and (4) subcutaneously administered proprotein convertase subtilisin/kexin type 9 inhibitors.⁴⁰

Management of FH in Children

Because atherosclerosis in FH starts early in life,^{41,42} untreated children with FH will develop endothelial dysfunction, premature plaques, and early coronary heart disease.⁴³⁻⁴⁶ Levels of LDL-C in FH children, even at birth, were increased 2- to 3-fold above the normal range. Counselling on lifestyle modification remains the essential starting point in the care of children and adolescents with FH.

RECOMMENDATION

9. We suggest that all children with a presumptive diagnosis of FH first undergo at least 12 months of lifestyle changes, including diet, exercise, and a tobacco-free environment (Conditional Recommendation, Low-Quality Evidence).

Values and Preferences. Lifestyle remains the cornerstone of cardiovascular disease prevention in children and adolescents with HeFH.

Pharmaceutical therapies

Clinical studies support the efficacy of statin therapy during childhood.³⁵ A meta-analysis of clinical trials of statins in children showed an average LDL-C reduction of 30% (95% confidence interval, -36% to -24%), with no increased risk of adverse events, including no increase of hepatic transaminase, a statistically significant change in height (0.33 cm; 95% confidence interval, 0.03-0.63 cm) favouring the treatment group, but no effect on pubertal development.³⁵ Similar data were reported for a longer follow-up period.²⁴ In children with HeFH, ezetimibe monotherapy was well tolerated and significantly reduced LDL-C.⁴⁷ Lipoprotein apheresis should be pursued in children with HoFH, managed at a lipid specialist centre.⁴⁸ Initiation of statin therapy, after ≥ 12 months of lifestyle changes as discussed herein, is now recommended at ages 8-10, when FH is believed to be "definite."^{1,49} The LDL-C target in children is < 3.5 mmol/L, but the presence of additional risk factors or high-risk conditions might decrease this target to < 2.5 mmol/L or could prompt initiation of statin therapy at an age younger than 10 years.

RECOMMENDATION

10. If drug treatment is believed to be necessary, assessed on an individual basis, statins are first-line therapy, with ezetimibe and bile acid binding resins considered as next-line therapies. Niacin is no longer recommended (Conditional Recommendation, Low-Quality Evidence).

Values and Preferences. A healthy lifestyle is the therapeutic cornerstone for all children with HeFH, and initiation of statins on an individualized basis as first-line pharmacological agents depends on additional variables, such as a high burden of cardiovascular disease risk factors and the absolute degree of the increase in LDL-C level.

Secondary Testing and Imaging in FH

Because the lifetime cardiovascular disease risk ranges from exceptionally high in HoFH to high in HeFH patients, there is no risk refinement or reclassification based on imaging, because all patients warrant therapy. Several specific situations might, however, warrant imaging. Methods to assess symptomatic FH patients should be relevant to the nature of the symptoms (eg, carotid duplex scanning for assessment of transient ischemic attacks or exercise testing for evaluation of chest pain, etc). Assessment of the aortic valve and root using echocardiography is warranted in patients with HoFH and perhaps also in those with severe HeFH and concomitant increased level of Lipoprotein(a) [Lp(a)], which is associated with aortic valve disease.⁵⁰⁻⁵³ Detection of premature atherosclerosis might be warranted in a patient suspected of having FH and without family history of cardiovascular disease.⁵⁴ Additionally, among individuals who meet "possible FH" criteria using the Simon Broome Registry or Dutch Lipid Clinic Network algorithms, detection of increased atheroma using carotid ultrasound or coronary artery calcium scoring could increase the chance of finding a discrete monogenic cause.⁵⁵ Stress testing, including stress imaging studies, might be warranted to rule out silent ischemia in patients who

engage in rigorous exercise.⁵⁶ Finally, suspicion of hepatic steatosis as a cause of increased levels of transaminases might require hepatic ultrasound evaluation.^{29,30} Vascular imaging is not recommended to monitor vascular effects of lipid-lowering therapy even though diverse imaging methods have been used in mechanistic, surrogate end point trials. The presence of severe vascular disease in an asymptomatic patient might prompt more aggressive intervention.

Homozygous FH: Identification and Treatment

Depending on the population and definition used, the prevalence of HoFH ranges from 1 in 250,000 to 1 in 1,000,000 individuals globally, and is increased in founder populations, such as French-Canadians.⁶ Diagnostic criteria are typically based on family history, which include HeFH in both parents, presence of cutaneous and tendinous manifestations at ages younger than 10 years, severe increased level of LDL-C (ie, untreated LDL-C $> 12-13$ mmol/L) and molecular diagnosis.^{6,57} HoFH patients are at extremely high risk of cardiovascular disease and should be evaluated at younger than 2 years of age for optimal prevention.^{57,68} HoFH patients should be referred to a lipid specialist centre for cholesterol-lowering therapies, including extracorporeal LDL removal, which has demonstrated beneficial effects on aortic and coronary atherosclerosis in HoFH⁵⁹⁻⁶³ and possibly for trials with new therapies (see [Supplemental material](#) section "EMERGING THERAPIES IN FH"). Apheresis is recommended in adults with HoFH with refractory LDL-C > 8.5 mmol/L and in children (> 15 kg in weight or older than 7 years of age) with refractory LDL-C > 5.0 mmol/L on maximally tolerated medical therapy.⁵⁹⁻⁶⁴ Lipid-lowering therapy is associated with delayed cardiovascular disease events and prolonged survival, and low-fat diet and optimization of other risk factors have less effect on the disease course.^{57,58} Calcific valvular and supravalvular aortic stenoses are almost universal and frequently require aortic valve replacement.⁶⁵ Patients with HoFH who require intensive LDL-C-lowering therapy with apheresis are generally monitored every 1-2 years to determine progression of carotid atherosclerosis (carotid ultrasound), progression of aortic valve/root disease (echocardiography), and progression of coronary atherosclerosis (stress exercise tests).^{57,63} Additional details on aetiology, diagnosis, and treatment of HoFH can be found in the [Supplemental material](#) section "ADDITIONAL POINTS RELATED TO HOMOZYGOUS FH."

RECOMMENDATION

11. HoFH patients older than 7 years of age and > 15 kg in weight should be referred to a specialized centre and considered for extracorporeal plasma exchange or LDL apheresis and emerging therapies (Conditional Recommendation, Low-Quality Evidence).

Values and Preferences. Clinical observation has shown that with apheresis, life expectancy of HoFH patients has more than doubled in the past 3 decades; this must be made available in specialized centres across Canada.

Pregnancy and Contraception in FH

Because of teratogenicity, women with FH who are planning pregnancy must interrupt statin therapy at least 1 month before stopping contraception, and remain without therapy until breastfeeding is completed. Adolescent and adult women with HeFH of childbearing potential should receive counseling on contraception and pregnancy. For couples planning a pregnancy in which one member has FH, the partner's lipid profile should be screened before conception to exclude coincident FH and the possibility of a child with HoFH; when both parents have HeFH, prenatal counselling might be sought. Barrier methods, intrauterine devices, tubal ligation, or partner vasectomy are preferred because in theory these have no effect on blood lipid levels and cardiovascular disease risk. However, oral contraceptives are the usual default method, for various reasons including convenience. No study has examined cardiovascular disease risk in women with FH who use oral contraceptives. If pregnancy occurs during statin therapy, it must be stopped immediately and an obstetrician consulted for early fetal evaluation, although the risk of fetal complications is low.⁶⁶ Cholestyramine, colestipol, or colesvelam can be safely prescribed during pregnancy and breastfeeding, but these reduce LDL-C by approximately 15% at most and have tolerability issues. For HoFH subjects and FH subjects with cardiovascular disease, LDL apheresis can decrease LDL-C and prevent complications.⁶⁷ For these women, shared care and cardiovascular assessment are strongly advised.

RECOMMENDATION

12. We recommend that women with FH who are considering pregnancy stop lipid-lowering therapy, with the exception of bile acid-binding resins, at least 4 weeks before conception and until cessation of breastfeeding (Strong Recommendation, Moderate-Quality Evidence).

Values and Preferences. Statin therapy during pregnancy is contraindicated.

Utility of an FH Registry

FH registries have been established in several European countries, of which the Dutch registry is the most successful. Using a cascade screening approach, 1500-2000 new FH cases are diagnosed yearly in the Netherlands; about half of that nation's expected FH cases have been enrolled in the FH registry. On average, 8 new cases are detected per family, and treatment starts at a mean age of 37 years. The 98% participation rate reflects a positive attitude toward the screening program.⁶⁸ Results were impressive with early initiation of treatment, with virtually complete avoidance of excess coronary heart disease morbidity and mortality. Furthermore, morbidity and mortality from other diseases (particularly cancer) also significantly decreased, attributed to the lifestyle counselling.⁶⁹

The United Kingdom National Institutes for Health and Clinical Excellence (NICE) registry also uses cascade screening

with genetic testing and LDL-C measurement to identify affected relatives of FH index cases. This approach: (1) reduced the average age at which the patients are diagnosed and treated; (2) increased the proportion of patients with FH who are receiving statin therapy, and who significantly decreased their lipid levels; (3) markedly reduced morbidity and mortality from coronary heart disease when statin treatment was initiated; (4) resulted in improved lipid levels in children with FH; and (5) yielded cost-effective interventions, with important economic benefits for society.⁷⁰

RECOMMENDATION

13. We recommend that a FH registry be implemented in Canada to improve health outcomes in patients with FH (Strong Recommendation, Moderate-Quality Evidence).

Values and Preferences. FH registries in several European countries have shown improvements in health services utilization and cardiovascular outcomes. A similar effort should be supported in Canada.

Acknowledgements

David Bewick, MD, Sabyasachi Bose, MD, Francois Bussieres, Claude Gagne, MD, Sophie Guerin, Pamela Katz, MD, Anne-Marie Laberge, MD, PhD, Lawrence A. Leiter, MD, Katherine Morrison, MD, Teik Chye Ooi, MD, Glen Pearson, Pharm D, and Tom Ransom, MD, participated in this work as members of the Secondary Panel.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <http://dx.doi.org/10.1016/j.cjca.2014.09.028>.

Canadian Cardiovascular Society
Position Statement on Familial Hypercholesterolemia:
Supplemental Material

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SUPPLEMENTAL MATERIAL

ADDITIONAL POINTS RELATED TO DIAGNOSIS OF FH

Need for new Canadian-specific diagnostic criteria for HeFH

Should new diagnostic criteria for HeFH be developed for Canada? Arguments supporting this view include: 1) adopting simpler, more streamlined validated criteria might improve the efficiency of diagnosing HeFH among primary care physicians, whose potential to identify the large numbers of undiagnosed patients in Canada is greatest; 2) since physical stigmata and premature CVD are tending to become less apparent clinically, due to earlier diagnosis and treatment, diagnostic algorithms should be updated to reflect the decreasing relevance of these findings; and 3) details regarding a patient's family history may not always be available or precise. Any new diagnostic criteria for FH would need to be validated against a gold standard diagnosis - which does not yet exist - and also against existing Simon Broome Registry (SBR) or Dutch Lipid Clinic Network (DLCN) criteria. Proposing new diagnostic criteria for FH is not our purpose here, but a more comprehensive national application of available diagnostic methods and assembling a registry are likely to provide insights into how to best refine these methods.

DNA testing for FH

Molecular testing for HeFH is rarely performed in Canada, due to lack of availability, non-standardization of methods and expense. There are no clinical accreditation standards for molecular diagnosis of HeFH. In Quebec, health care providers can request DNA analysis for the most common known mutations found in FH patients of French descent;¹ however, this method does not test for hundreds of other mutations in other ethnic groups residing in Canada.²

While identifying a disease-causing mutation might seem to provide a definitive diagnosis, several factors confound a simple genotype-phenotype relationship in HeFH. False-positive tests are relatively uncommon, but can result when DNA sequence analysis identifies a rare but incidental and non-pathogenic mutation in a gene that normally causes HeFH. More commonly, false-negative results can occur in some HeFH patients who actually have a causative mutation because: 1) different types of mutations in the main FH gene – *LDLR* – require > 2 different laboratory detection methods, which are not available in most laboratories;² 2) causative mutations for HeFH can lie within several secondary genes, including *APOB* and *PCSK9*, and can be missed without further specialized detection methods that are usually unavailable; 3) concurrent but undetectable mutations in other genes can reduce LDL-C levels in an individual who carries a disease-causing HeFH mutation;³ and 4) ~20% of patients have “probable” or “definite” FH not because of mutation in a single gene, but rather the simultaneous presence of several

common single nucleotide polymorphisms (SNPs) that individually have small effects, but which combine to raise LDL-C levels into the HeFH range.⁴ Yet another specialized method is needed to detect this possibility. Additionally, at least 20% of HeFH patients may not have a mutation on DNA testing,⁵ demonstrating the shortcomings of this method as the “gold standard”, and outlining a potential opportunity and rationale to improve upon these limitations.

More than 95% of FH patients with identified mutations have one of >1700 different pathogenic *LDLR* mutations² with *APOB* mutations that affect binding to the LDL receptor explaining most of the remaining 5% of cases in whom mutations have been identified. Some exceedingly rare families have mutations in genes that include *PCSK9*, *APOE* and *STAP1* in autosomal dominant FH, and *LDLRAP1* and *LIPA* in autosomal recessive FH. A sequential approach for genetic testing may help minimize costs, at least in French-Canadians where, due to a founder effect, only a few *LDLR* gene mutations explain >80% of cases. However, for patients of other ethnic backgrounds, screening of all FH genes is now possible using dedicated next-generation resequencing methods.⁶ Results from genetic testing should clearly report whether the mutation is pathogenic, non-pathogenic or of uncertain significance. As mentioned, even comprehensive validated genetic analyses will not show any mutation in up to 20% of definite or probable FH patients; high LDL-C in these individuals is often due to a complex polygenic mechanism.⁴ The yield of DNA testing is greater in subjects with a definite clinical phenotype, and especially if LDL-C is >8.0 mmol/L. Despite these challenges, genetic testing might still be worth the effort, since knowing the causal mutation enables much less expensive targeted DNA testing to be undertaken as part of cascade screening. However, no prospective evidence shows that outcomes can be modified by knowing the precise disease-causing mutation in an FH patient, and potential ethical concerns involved in pursuing cascade testing need to be fully assessed.

Some relatives (perhaps 5%) who carry a pathogenic mutation may have normal LDL-C levels, either because of coexisting unmeasured cholesterol lowering genes or the impact of a prudent lifestyle. Such individuals can transmit FH susceptibility to offspring, despite the fact that they appear unaffected based on LDL-C alone. In contrast, for mutation-negative patients with the FH phenotype, cascade testing should be based on LDL-C and clinical criteria only. Important questions surrounding the issues of identification of index cases and cascade screening of family members in Canada include “who should perform these activities?” and “under what conditions?”.

ADDITIONAL POINTS ON SCREENING

Most pediatric guidelines over the past two decades have recommended targeted lipid screening beginning at age 2 years. The recent Expert Panel guidelines commissioned by the National Heart, Lung and Blood Institute and endorsed by the American Academy of Pediatrics likewise recommended targeted

screening in high-risk children.⁷ However, the DLCN registry showed that LDL-C levels accurately predicted genetically-confirmed FH in children, especially for LDL-C between 3.0 and 4.0 mmol/L. Further, in children an LDL-C level >3.5 mmol/L predicted FH with a 98% post-test probability.⁸ A systematic review of 9 studies of cascade screening showed cascade screening costs to range from 4 to 38 thousand dollars per life year gained.⁹ The cost-effectiveness was sensitive to the underlying prevalence of FH, the validity of the screening test, and the price and efficacy of lipid-lowering therapy. We thus recommend that if a child or adolescent is identified has LDL-C ≥ 3.35 mmol/L, screening of parents and siblings with a fasting lipid profile may be considered.

ADDITIONAL POINTS ON SECONDARY TESTING

Physicians counseling patients at intermediate CVD risk and intermediate levels of LDL-C - hence without FH - may base decisions to implement lipid lowering therapy on the results of imaging such as carotid ultrasound detection of plaques or increased intima-medial thickness (IMT) or coronary artery calcium scoring.¹⁰ Detection of premature atherosclerosis may be warranted in a patient suspected of having FH and without family history of CVD.¹¹ Additionally, some evidence suggests that among individuals who meet “possible FH” criteria by the SBR or DLCN algorithms, detection of increased atheroma by carotid ultrasound or coronary artery calcium scoring increases the chance of finding a discrete monogenic cause.⁹

ADDITIONAL POINTS RELATED TO HOMOZYGOUS FH

HoFH results most often from mutations in both copies of the *LDLR* gene.¹² In Canada, patients may be true homozygotes or compound heterozygotes, defined as having different mutations on each *LDLR* allele.¹³ The *LDLR* gene mutation class (negative versus defective) may affect LDL-C levels as well as clinical expression and CVD outcomes.^{13, 14} Patients who are LDLR negative have higher LDL-C levels and a worse prognosis than those who are LDLR defective.¹² Untreated receptor-negative HoFH patients rarely survive beyond the second decade whereas receptor-defective patients survive longer, often in spite of significant atherosclerosis by the age of 30 years.¹² HoFH patients, particularly those who are LDLR negative (function <2 % of normal), generally respond to statins to a lesser degree compared with HeFH individuals.¹⁵ Low statin dosages are started at initial diagnosis and the goal is >50 % reduction in LDL-C levels. As patients age (>7 years old), an appropriate goal is >75 % in reduction of LDL-C, particularly if apheresis is available.^{5, 12, 16}

Most HoFH patients require extra-corporeal LDL removal and considering its demonstrated beneficial effects on aortic and coronary atherosclerosis.^{5, 12, 16} Several apheresis methods are selective for atherogenic apo B-containing particles, and all lower LDL-C and Lp(a) levels by 50-70% following a

single treatment.^{5, 16} Weekly or bi-weekly extra-corporeal LDL removal may also be considered for some statin intolerant or refractory HeFH patients.^{5, 16} Finally, plasma exchange may be used, but is not selective for LDL-C and is less well tolerated.

Liver transplantation is now rarely considered.¹⁷ Portacaval shunting and partial ileal bypass surgeries have resulted only in modest LDL-C-lowering and are not known to be effective over the long term.¹⁸ There may be a future role for gene therapy in severe FH, but for now long term improvement has not been achieved.¹⁹⁻²¹

When apheresis is not available, or LDL-C goals are not reached on statin therapy, HoFH patients usually require additional lipid-lowering medications. Ezetimibe in combination with statins may be advantageous in HoFH patient.²² Several newer therapies may prove beneficial for treatment of HoFH. For instance, HoFH patients on maximally tolerated pharmacological therapy showed 25% and 31% reductions in LDL-C and Lp(a) levels with mipomersen, although the responses were highly variable.²³ Phase 3 results for lomitapide in HoFH patients showed a 51% LDL-C reduction but no change in Lp(a) levels.²⁴ Other potential therapies include PCSK9 inhibitors, which may achieve a 65% mean reduction of LDL-C in combination with atorvastatin in some receptor-defective patients, while receptor-negative patients respond poorly.²⁵

SPECIAL CASES: FH, CONTRACEPTIVES AND PREGNANCY

While FH is genetically transmitted, any affected woman considering pregnancy should not be discouraged due to fear of transmitting the disease to offspring, since offspring affected with HeFH are essentially asymptomatic until adulthood and can be effectively managed for CVD prevention starting early in life, with an expectation for a normal lifespan.

EMERGING THERAPIES IN FH

Microsomal triglyceride transfer protein (MTP) inhibitors

MTP is required for the hepatic assembly of very low density lipoproteins (VLDL), the precursor of LDL. Inhibition of MTP reduces secretion of all apoB-containing lipoproteins.²⁴ Because of significant potential hepatic fat accumulation, MTP inhibitors are presently approved in Canada only for confirmed HoFH. It has not been established whether MTP inhibitors reduce cardiovascular events. Lomitapide (Aegerion) reduces LDL-C by ~50% and has been approved by Health Canada for patients with HoFH.

ApoB antisense oligonucleotides

ApoB antisense oligonucleotides consist of short segments of DNA that bind to the mRNA of apoB, causing destruction of the heterodimer complex before the mRNA is translated into protein. This

treatment lowers LDL-C by up to 50% in patients with HeFH.²⁶ The apoB antisense oligonucleotide mipomersen (Genzyme) has been approved by the FDA for HoFH patients. There are no data on whether these agents prevent CVD. Hepatic fat accumulation and injection site reactions are important side effects. To date, this compound is not available in Canada.

Cholesteryl ester transfer protein (CETP) inhibitors

Patients with a natural deficiency of CETP have increased HDL-C levels. Small molecules that inhibit CETP increase HDL-C by up to 138%, lower LDL-C by 25-40% and lower Lp(a) by ~25-30%. Early trials with torcetrapib and dalcetrapib showed increased risk and no cardioprotective effect, respectively, in spite of significant increases in HDL-C.^{15, 27} Anacetrapib and evacetrapib are currently under evaluation in large phase III trials for their effect on CVD outcomes.²⁸ Their use in FH subjects remains under investigation, but may prove to be useful in combination with statins.

Pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

PCSK9 binds to the LDL receptor and directs it towards intracellular degradation, instead of recycling to the cell surface where it can continue to bind LDL and clear it from plasma. Because of the nature of the protein-protein interaction between PCSK9 and the LDL receptor, inhibiting this interaction is presently not amenable to a small molecule oral agent and instead requires a large volume of antibody solution administered parenterally. Fully humanized monoclonal antibodies are presently in advanced phase III trials in FH and high-risk cardiovascular subjects. These compounds, including evolocumab, alirocumab, EFJE and bococizumab^{29, 30} reduce LDL-C by 50-70% in patients with FH and other types of hypercholesterolemia, either as monotherapy or in combination with statins.

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SUPPORT GROUPS AND WEB-BASED RESOURCES

<i>FH Web Resources:</i>
US FH Foundation; http://thefhfoundation.org
Learning About Familial Hypercholesterolemia; http://www.genome.gov/25520184
The National Lipid Association; https://www.lipid.org
Learn your lipids (for patients); http://www.learnyourlipids.com
Site de Genzyme (Sanofi); http://www.fhjourneys.com
University of Utah School of medicine; http://www.medped.org/MEDPED-What-is-FH.html
Familial hypercholesterolemia [nlm.nih.gov] From Medline Plus
What is Cholesterol? [nhlbi.nih.gov] From the National Heart, Lung and Blood Institute's Health Topics.
Familial hypercholesterolemia [umm.edu] From the University of Maryland Medical Center.
Inherited Cholesterol Disorders - Familial Hypercholesterolemia [medped.org] From the University of Utah, Make Early Diagnosis to Prevent Early Deaths (MEDPED), a non-profit, worldwide preventive medicine project.
American Heart Association - Cholesterol [heart.org] Information from the American Heart Association on cholesterol.
Familial Hypercholesterolemia [rarediseases.org] From the National Organization for Rare Disorders.
Hypercholesterolemia, Autosomal Dominant [omim.org] From Online Mendelian Inheritance in Man (OMIM).
Hypercholesterolemia, Familial [emedicine.medscape.com] Article from eMedicine.
Familial Hypercholesterolemia [history.nih.gov] From Diagnosing and Treating Genetic Diseases.
Familial hypercholesterolemia [rarediseases.info.nih.gov] Information from the Genetics and Rare Diseases Information Center.
Finding Reliable Health Information Online. A listing of information and links for finding comprehensive genetics health information online.

Lipid Databases:

[Cyberlipid Center](#)

[LIPID Bank - Japan](#)

[LIIDAT](#)

[Lipid Library - Scottish Crop Research Institute](#)

[LIPID MAPS \(LIPID Metabolites And Pathways Strategy\) - USA](#)

[Oxylipin Profiling Database](#)

[SOFA - Seed oil fatty acids Database](#)

[SPHINGOMAP - Pathway Map for Sphingolipid Biosynthesis](#)

Organizations and initiatives related to lipidomics:

[AOCS - American Oil Chemist's Society](#)

[ASBMB Lipid Corner](#)

[ELife - The European Lipidomics Initiative; Shaping the life sciences](#)

[Euro Fed Lipid - European Federation for the Science and Technology of Lipids](#)

[GERLI - Research Group on Lipidomics \(Groupe d'Etude et de Recherche en Lipidomique\)](#)

[German Society for Fat Science - DGF \(Deutsche Gesellschaft für Fettwissenschaft\)](#)

[ICBL - International Conference on the Bioscience of Lipids](#)

[ILPS - The International Lecithin Phospholipid Society](#)

[ISF - International Society for Fat Research](#)

[ISSFAL - International Society for the Study of Fatty Acids and Lipids](#)

[LIPIDFORUM - Nordic Forum for Lipid Research and Technology](#)

[Lipidomics Research Center Graz](#)

[Lipids Online - Educational Resources in Atherosclerosis](#)

[Sphingolipid Club](#)