Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia

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 are intended 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.

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
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. Recent molecular studies indicate that 3.4% of patients with early myocardial infarction have FH mutations. Increased rates of FH are observed in populations in which founder effects are present. The prevalence of HeFH in French-Canadians is estimated at approximately 1:270. 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. 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 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. 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).
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-C1,10 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

To maximize identification of previously undiagnosed adult FH subjects, 2 complementary strategies are proposed: (1) targeted screening to identify FH index cases (probands) 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

- Obstructive liver disease
- Hypothyroidism
- Nephrotic syndrome
- Anorexia

affected members; each of whom then serves as an index case. 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. 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*  

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<thead>
<tr>
<th>Points</th>
<th>Criteria</th>
<th>Diagnosis</th>
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<tr>
<td>1</td>
<td>First-degree relative with premature cardiovascular disease or LDL-C &gt; 5th 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)</td>
<td>Definite FH (≥ 8 points)</td>
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<tr>
<td>2</td>
<td>First-degree relative with tendonous xanthoma or corneal arcus, or First-degree relative child (&lt; 18 years) with LDL-C &gt; 5th percentile, or personal history of coronary artery disease</td>
<td>Probable FH (6-7 points)</td>
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<tr>
<td>3</td>
<td>LDL-C between 4.91 and 6.44 mmol/L (190 and 249 mg/dL)</td>
<td>Possible FH (3-5 points)</td>
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<tr>
<td>4</td>
<td>Presence of corneal arcus in patient younger than 45 years of age</td>
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<td>5</td>
<td>LDL-C between 6.46 and 8.51 mmol/L (250 and 329 mg/dL)</td>
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<tr>
<td>6</td>
<td>Presence of a tendon xanthoma</td>
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<tr>
<td>7</td>
<td>LDL-C &gt; 8.53 mmol/L (330 mg/dL), or functional mutation in the LDLR gene</td>
<td></td>
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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. Also, appropriate management is limited by lack of resources and time within a busy clinical practice. 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. Trials of statin therapy in children and adolescents with FH have shown normalized endothelial function, and regression of carotid intima-media thickness, which is effective when initiated at younger ages.

The case for screening children to detect FH and initiate treatment is reasonably strong. 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. Nonetheless, coronary heart disease risk is increased by up to 20-fold in untreated FH patients, and cardiovascular disease events are dramatically reduced in observational studies of statin-treated FH patients. 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.

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. 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, 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.
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

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 colesevelam) 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.

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.
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. Moreover, the cardiovascular risk reduction benefit of statins far outweigh 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. Although further evidence would be desirable, the current evidence base suggests that statins can be as 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.

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

Management of FH in Children

Because atherosclerosis in FH starts early in life, untreated children with FH will develop endothelial dysfunction, premature plaques, and early coronary heart disease. 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. 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. Similar data were reported for a longer follow-up period. In children with HeFH, ezetimibe monotherapy was well tolerated and significantly reduced LDL-C. Lipoprotein apheresis should be pursued in children with HoFH, managed at a lipid specialist centre. 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." 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. Detection of premature atherosclerosis might be warranted in a patient suspected of having FH and without family history of cardiovascular disease. 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. Stress testing, including stress imaging studies, might be warranted to rule out silent ischemia in patients who engage in rigorous exercise. Finally, suspicion of hepatic steatosis as a cause of increased levels of transaminases might require hepatic ultrasound evaluation. Vascular imaging is not recommended to monitor vascular effects of lipid-lowering therapy even though diverse imaging methods have been used in mechanistic, surrogate endpoint 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. 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. HoFH patients are at extremely high risk of cardiovascular disease and should be evaluated at younger than 2 years of age for optimal prevention. 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 HoFH 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. 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. Calcific valvular and supraavalvular aortic stenoses are almost universal and frequently require aortic valve replacement. 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). 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 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.69 For these women, shared care and cardiovascular assessment are strongly advised.

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.

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.69

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.

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References


Supplementary Material

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