



## Society Position Statement

# Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at [www.ccs.ca](http://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 judgement 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.

**ABSTRACT**

Familial hypercholesterolemia (FH) is the most common monogenic disorder causing premature atherosclerotic cardiovascular disease. It affects 1 in 250 individuals worldwide, and of the approximately 145,000 Canadians estimated to have FH, most are undiagnosed. Herein, we provide an update of the 2014 Canadian Cardiovascular Society position statement on FH addressing the need for case identification, prompt recognition, and treatment with statins and ezetimibe, and cascade family screening. We provide a new Canadian definition for FH and tools for clinicians to make a diagnosis. The risk of atherosclerotic cardiovascular disease in patients with “definite” FH is 10- to 20-fold that of a normolipidemic individual and initiating treatment in youth or young adulthood can normalize life expectancy. Target levels for low-density lipoprotein cholesterol are proposed and are aligned with the Canadian Cardiovascular Society guidelines on dyslipidemia. Recommendation for the use of inhibitors of proprotein convertase kexin/subtilisin type 9 are made in patients who cannot achieve therapeutic low-density lipoprotein cholesterol targets on maximally tolerated statins and ezetimibe. The writing committee used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology in the preparation of the present document, which offers guidance for practical evaluation and management of patients with FH. This position statement also aims to raise awareness of FH nationally, and to mobilize patient support, promote knowledge translation, and availability of treatment and health care resources for this under-recognized, but important medical condition.

Heterozygous familial hypercholesterolemia (FH) is the most common monogenic disorder encountered in clinical practice and affects 1 in 250 individuals.<sup>1</sup> It is transmitted as an autosomal codominant disorder and causes elevated low-density lipoprotein cholesterol (LDL-C) levels across the lifespan. Affected patients are at markedly increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Prompt recognition and initiation of therapy with statins in youth or young adulthood has been shown to markedly decrease the risk of ASCVD and to normalize life expectancy.<sup>2</sup> Nonetheless, many patients with FH remain unrecognized and undertreated in countries that have not enacted a national registry, as has been done in the Netherlands, Norway, the United Kingdom, and Spain.<sup>2</sup> There is a considerable challenge to raise awareness among health care professionals and patients and an opportunity to identify patients with FH in a cost-effective way through cascade screening of first-degree relatives, and to treat affected individuals. Herein, we provide an update to the 2014 Canadian Cardiovascular Society (CCS) position statement on FH,<sup>3</sup> with the following additions:

- A Web site ([www.FHCanada.net](http://www.FHCanada.net)), which provides information and resources for patients and health care professionals;
- Better estimates of the prevalence of FH in Canada and the world<sup>1</sup>;

**RÉSUMÉ**

L'hypercholestérolémie familiale (HF) est la maladie monogénique la plus courante à l'origine d'une pathologie cardiovasculaire athéroscléreuse précoce. Elle touche 1 personne sur 250 dans le monde et, chez la plupart des quelque 145 000 Canadiens atteints selon les estimations, demeure non diagnostiquée. Dans cet article, nous présentons une mise à jour de l'énoncé de position de la Société canadienne de cardiologie de 2014 sur la HF soulignant la nécessité du diagnostic rapide, du traitement par des statines et de l'ézétimibe et du dépistage familial en cascade. Nous proposons une nouvelle définition canadienne de la HF et des outils diagnostiques à l'intention des cliniciens. Le risque de maladie cardiovasculaire athéroscléreuse chez les patients ayant reçu un diagnostic de HF est de 10 à 20 fois supérieur à celui d'une personne normolipidémique, et l'instauration d'un traitement chez les jeunes ou les jeunes adultes peut normaliser leur espérance de vie. Des valeurs cibles du taux de cholestérol à lipoprotéines de basse densité conformes aux lignes directrices sur la dyslipidémie de la Société canadienne de cardiologie sont proposées. L'administration d'inhibiteurs de la proprotéine convertase kexine/subtilisine de type 9 est recommandée chez les patients qui ne parviennent pas à atteindre les cibles thérapeutiques en matière de cholestérol à lipoprotéines de basse densité aux doses maximales tolérées de statine et d'ézétimibe. Le comité de rédaction a utilisé la méthodologie GRADE (*Grading of Recommendations, Assessment, Development, and Evaluation*) pour élaborer le présent document, qui contient des recommandations pratiques pour l'évaluation et la prise en charge des patients atteints de HF. Cet énoncé de position a également pour objectifs de promouvoir la sensibilisation à la HF à l'échelle nationale, l'offre de mesures de soutien aux patients, l'application des connaissances et la disponibilité des ressources en matière de traitement et de soins de santé pour cette affection dont l'importance a été longtemps négligée.

- A new, simplified definition of FH specific to the Canadian context<sup>4</sup>;
- A validated tool to calculate the baseline LDL-C during treatment with statins or ezetimibe<sup>5</sup>;
- Diagnostic tools (<http://www.circl.ubc.ca/cardiorisk-calculator.html>) for health care professionals to make a precise diagnosis of FH;
- Initial data from the FH Canada registry<sup>6</sup>; and
- Genetic testing for FH in a Clinical Laboratory Improvement Amendments-certified laboratory.

**Diagnosis of FH**

It is estimated that only approximately 10% of patients with FH in Canada have been diagnosed.<sup>2</sup> The most commonly used diagnostic criteria for FH include the Dutch Lipid Clinic Network Criteria (DLCNC), the Simon Broome Registry criteria, and the Make Early Diagnosis Prevent Early Death criteria.<sup>3</sup> In the United States, many physicians report using a “clinical diagnosis” of FH on the basis of clinical judgement alone or in combination with the formal diagnostic criteria.<sup>7</sup> In a large population in Denmark, the DLCNC (“probable” or “definite” diagnosis) offered the best predictive value for identifying an FH-causing DNA variant compared with the Simon Broome Registry or Make Early Diagnosis Prevent Early Death criteria.<sup>8</sup>

Limitations of the existing diagnostic criteria for FH include their complexity and heavy weighting toward the classic physical stigmata of FH (premature corneal arcus, tendon xanthomas, and xanthelasmas), which are infrequently observed in contemporary populations. The current algorithms are difficult to use in clinical practice and will miss some patients at high risk for ASCVD. It is often difficult to obtain the family history and the baseline LDL-C levels. The Familial Hypercholesterolemia Canada network ([www.FHCanada.net](http://www.FHCanada.net)) has proposed a new set of simplified, Canadian diagnostic criteria for FH (Fig. 1) on the basis of the 95th percentile LDL-C cut points determined for a large Canadian population (n = 3.3 million subjects), the presence of a DNA diagnosis, cutaneous manifestations, and family history.<sup>4</sup> The new Canadian definition shows excellent agreement with the DLCNC or Simon Broome Registry criteria.<sup>4</sup> Additional validation of these criteria against the “gold standard” genetic diagnosis of FH will provide further insight into their performance. These new, simplified criteria for FH are anticipated to enable health care providers in Canada and other jurisdictions to recognize FH more easily, and thus improve earlier treatment and better outcomes for these patients.

#### RECOMMENDATION

1. We recommend that FH be defined using the DLCNC, Simon Broome Registry, or FH Canada definition (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** There is no “gold standard” for the diagnosis of FH. Currently available definitions rely on a scoring system to increase diagnostic confidence.

#### Screening for FH

Universal screening of lipid levels is recommended for Canadian men 40 years of age and older and women 50 years of age or older, or earlier if other ASCVD risk factors are present.<sup>9</sup> There remains controversy as to whether screening in childhood (ie, around age 10 years) for FH should be implemented. This approach would be expected to identify some cases of FH. The initial screening should include a fasting or nonfasting lipid profile and the LDL-C calculated with the Friedewald formula. When the patient is taking statins with or without ezetimibe, the baseline LDL-C (ie, before treatment) can be reliably imputed<sup>5</sup> and this value should then be used in the FH diagnostic criteria. Cascade screening for FH<sup>10</sup> (lipid screening of first-degree relatives of individuals with FH and consideration of genetic testing) is recommended and has been shown to be effective in the Netherlands for the identification and treatment of new cases.<sup>11</sup> Opportunistic genetic screening of young individuals who present with an acute coronary syndrome has also been shown to be effective in diagnosing FH.<sup>12</sup> Genetic screening of FH can aid in the identification of individuals with FH who might not have been previously diagnosed.<sup>13</sup> Genetic testing can be requested by the treating physician to confirm the diagnosis in “probable” and

“definite” FH. The yield of genetic screening all patients with an LDL-C > 5 mmol/L—without further diagnostic criteria for FH—is in the range of 2%-3%.<sup>13,14</sup> Child and parent screening using cholesterol levels and presence of FH-causing DNA variants has also been proposed as a method to screen for the condition.<sup>15</sup> Where available, genetic counselling should be provided. Affected children should be referred to a pediatric specialist.

#### RECOMMENDATION

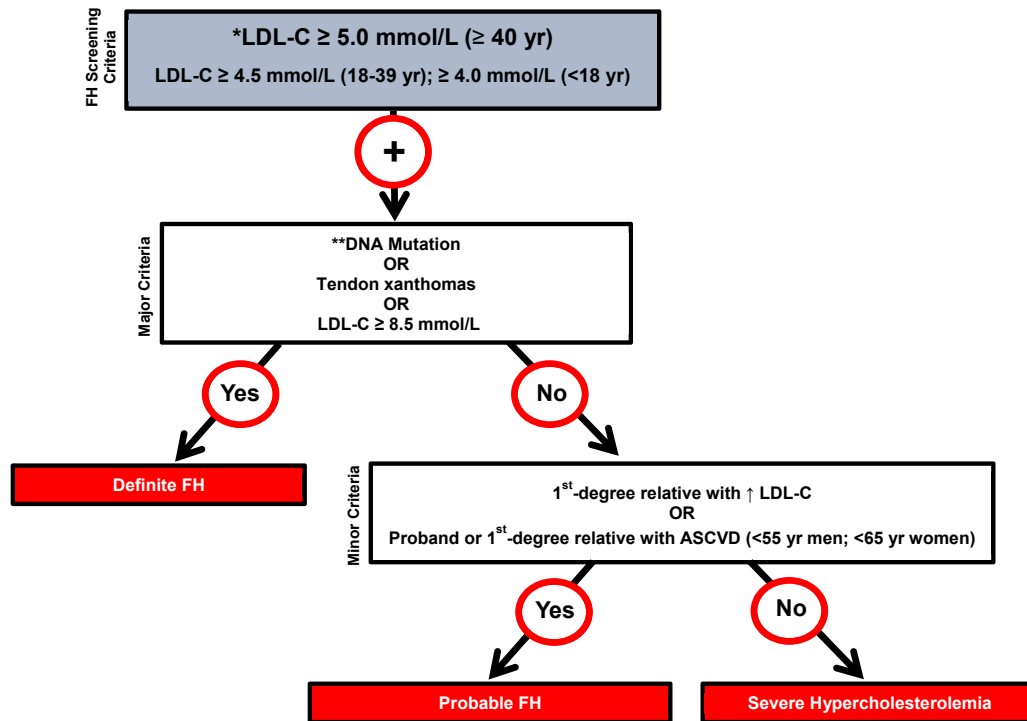
2. We recommend that cascade screening (lipid profile) protocols be implemented at the local, provincial, and national level in Canada and offered to first-degree relatives of patients with FH (Strong Recommendation, Moderate-Quality Evidence).

#### Genetics

FH is caused most commonly by DNA variants in the *LDLR*, *APOB*, or *PCSK9* genes. A pathogenic variant in 1 of these genes can be identified in 30%-80% of individuals with clinical FH.<sup>16,17</sup> Most of these pathogenic variants are in the *LDLR* gene, whereas 1%-5% and up to 3% are found in *APOB* and *PCSK9* genes, respectively. Some cases of FH result from the combined effects of several allelic variations in these and other genes that influence LDL-C levels. This polygenic form of clinical FH can be ascertained using a “polygenic risk score.”<sup>18</sup> The reasons that a pathogenic variant is not identified in some individuals with clinical FH include: a genetic variant of uncertain significance in 1 of these genes (ie, with insufficient evidence to classify it as disease-causing); a polygenic cause of FH<sup>16</sup>; the presence of variants not detected by current sequencing or genotyping technologies (eg, complex rearrangements or noncoding variants); the presence of a disease-causing variant in rare genes (*STAP1*, *LDLRAP1*, *APOE*, *LIPA*); or a causative variant in an (as of yet) unidentified gene.

Genetic testing can aid in the diagnosis of FH,<sup>13</sup> and can greatly facilitate cascade screening of family members.<sup>10</sup> Data from SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) in Spain have shown that a positive genetic test result for FH is associated with increased use of lipid-lowering therapy and improved control of lipid levels.<sup>19</sup>

Genetic testing might also help to identify a subgroup of patients with clinical FH who are at particularly elevated risk for cardiovascular events, making early diagnosis and treatment imperative for improved prognosis. Adult subjects with an LDL-C > 5 mmol/L (corresponding approximately to a non-high-density lipoprotein cholesterol (HDL-C) > 6.5 mmol/L) with no FH-causing variant have a 6-fold increased risk for ASCVD relative to normolipidemic individuals; whereas in individuals with LDL-C > 5 mmol/L and an FH-causing variant, a 22-fold excess risk was observed.<sup>14</sup> Similarly, in a cohort of Japanese patients with LDL-C > 4.7 mmol/L, the presence of clinical signs of FH (xanthomas or family history) increased the risk of ASCVD by 4.6-fold, whereas the presence of clinical signs and a pathogenic variant increased risk by 11.6-fold.<sup>20</sup> In a study of a single-payer health



**Figure 1.** Canadian definition for the clinical diagnosis of familial hypercholesterolemia (FH). ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. \* Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [biliary cirrhosis], and medication especially antiretroviral agents). \*\* Causal DNA mutation refers to the presence of a known FH-causing variant in the *LDLR*, *APOB*, or *PCSK9* gene on the basis of presence of the variant in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar>), the Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>), or Western Database of Lipid Variants (<https://www.ncbi.nlm.nih.gov/pubmed/23623477>) databases, in the proband or a first-degree relative. Reproduced from Ruel et al.<sup>4</sup> with permission from Elsevier.

insurance provider in the United States, > 50,000 participants underwent DNA sequencing for the *LDLR*, *APOB*, and *PCSK9* genes. Carriers of a pathogenic *LDLR* variant had a 10-fold higher risk of premature ASCVD, compared with the general population.<sup>13</sup> These findings imply that knowledge of a patient's genotype can improve risk assessment for ASCVD in patients with FH. Nonetheless, it is important to emphasize that individuals with hypercholesterolemia without an FH-causing variant are also at significantly and sufficiently elevated risk of ASCVD to warrant therapy,<sup>9</sup> and the inability to detect an FH-causing variant, or inability to access genetic testing, should not be used as a basis to withhold treatment in such individuals.

Genetic testing for FH is recommended by the US Centers for Disease Control Office of Public Health Genomics,<sup>21</sup> the International Atherosclerosis Society,<sup>22</sup> and by the United Kingdom National Institutes for Clinical Excellence (NICE).<sup>23</sup> An international expert panel convened by the Familial Hypercholesterolemia Foundation has also recommended that genetic testing for FH should be offered to individuals strongly clinically suspected to have FH, and that cascade genetic screening be offered to first-degree relatives of affected probands.<sup>24</sup> *LDLR*, *APOB* and *PCSK9* are also considered medically actionable genes for which the diagnostic information leads to changes in treatment, as stated by the American College of Medical Genetics and Genomics.<sup>25</sup> Despite these recommendations, genetic testing for FH is currently not routinely available as part of clinical care in

Canada, outside of Quebec. Thus, genetic testing for FH cannot be mandated as a prerequisite to provide patient access to appropriate therapy.

## RECOMMENDATION

- We recommend that genetic testing be offered, when available, to complement a diagnosis of FH and enable cascade screening (Strong Recommendation, High-Quality Evidence).

The decision to request genetic screening should be made by the treating physician after discussion with the patient. A downloadable form is available at [www.FHCanada.net](http://www.FHCanada.net).

**Values and preferences.** Patient preferences and confidentiality must be considered. Genetic testing is currently not available in most provinces.

## ASCVD Risk and FH

### ASCVD risk stratification in patients with FH: Genetics

As described previously, individuals with FH-causing variants in the *LDLR*, *APOB*, or *PCSK9* genes are at a 5- to 22-fold increased risk of ASCVD compared with normolipidemic

individuals, because of lifelong exposure to elevated LDL-C.<sup>13,14</sup> This risk is further increased by conventional cardiovascular risk factors.

### ASCVD risk stratification in patients with FH: Clinical variables

Studies from large FH cohorts have identified independent clinical predictors of ASCVD risk. These include LDL-C, HDL-C, age, sex, diabetes, lipoprotein(a), body mass index, smoking, and hypertension.<sup>26</sup> Existing risk calculators developed in the general (non-FH) population, such as the Framingham Risk Score, the Pooled Cohort Equation, or the European SCORE were developed to predict the ASCVD risk in non-FH populations and are not designed to assess the risk in FH subjects.<sup>3,27</sup> Consequently, these scores and algorithms underestimate the risk of ASCVD in patients with FH, which results from lifelong extreme elevation in LDL-C level. These scores should thus not be used in FH. Attempts have been made to improve risk stratification in FH. The Montreal-FH-SCORE was specifically created to stratify cardiovascular risk in adults with FH.<sup>27</sup> This score was developed in a cohort of 670 Canadian adults with FH carrying a pathogenic variant in the *LDLR* gene. Age, HDL-C, male sex, hypertension, and smoking were independent predictors of ASCVD risk, and were combined to create the Montreal-FH-SCORE. The SAFEHEART registry also provides a similar risk estimation tool for patients with FH, on the basis of the Spanish experience.<sup>19</sup> A large study of 14,000 individuals with FH showed that patients with FH with diabetes are at an especially higher risk of ASCVD.<sup>28</sup>

### ASCVD risk stratification in patients with FH: Imaging

Detection of subclinical atherosclerosis might be warranted in a patient suspected of having FH.<sup>9</sup> Additionally, among individuals who meet “probable FH” criteria using the Canadian, the Simon Broome Registry, or the DLCNC algorithms, detection of premature atheroma using carotid ultrasound or coronary artery calcium scoring might promote more intensive treatment. It must be emphasized, however, that because of the effectiveness of long-term statin therapy, serial imaging using, for example, sonography of the carotid arteries during follow-up of statin-treated patients with FH, is of limited value.<sup>29</sup> Individuals with FH develop aortic calcifications in a gene-dosage and age-dependent manner. Assessment of the aortic valve and root using echocardiography is warranted in patients with severe FH to examine aortic valve calcification and stenosis. Stress testing, including stress imaging studies, might be warranted to rule out silent ischemia in patients who engage in rigorous exercise.

#### RECOMMENDATION

4. We recommend that current risk calculators (Framingham Risk Score, Pooled Cohort Equation, European SCORE) should not be used to determine cardiovascular risk in patients with FH (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** Because patients with FH are often young, with few other risk factors, the current risk

calculators will underestimate their lifetime cardiovascular risk assessment.

5. We suggest that if available, genetic testing should be used to stratify the ASCVD risk in patients with FH (Weak Recommendation, Moderate-Quality Evidence).

**Values and preferences.** An FH-causing genetic variant increases ASCVD risk, beyond that associated with an elevated LDL-C level. Patients should be informed of the high lifetime risk of ASCVD associated with FH.

6. We suggest that conventional risk factors such as age, sex, HDL-C, hypertension, smoking, lipoprotein(a), and diabetes be ascertained in patients with FH (Weak Recommendation, Moderate-Quality Evidence).

**Values and preferences.** If adult patients with FH require further stratification of their ASCVD risk, we suggest using the Montreal-FH-SCORE. Patients must be involved in healthy choices and preventive measures.

## Management of FH in Adults

### Overall goals of treatment

Although several prospective studies have shown that lifetime exposure to high levels of atherogenic apolipoprotein (apo) B-containing lipoproteins dramatically increases ASCVD risk in patients with FH, no randomized trials exist to support that reducing LDL-C should be the primary target in patients with FH, nor is there evidence for a specific LDL-C goal. Extrapolating from the general population, the therapeutic goal for patients with FH without ASCVD is a 50% reduction from baseline (untreated LDL-C) and LDL-C < 3.5 mmol/L.<sup>23</sup> Some suggest that a reasonable therapeutic goal for primary prevention in adults with FH is to reach a goal of LDL-C < 2.5 mmol/L.<sup>2</sup> In patients with FH with established ASCVD, the CCS guideline currently recommends a goal of LDL-C < 2.0 mmol/L or non-HDL-C < 2.6 mmol/L.<sup>9</sup> Accordingly, as discussed in the *Pharmacologic Therapies* section below, LDL-C goals will require individualization.

### Lifestyle factors

Increasing evidence suggests that lifestyle-related risk factors such as smoking, a low-quality diet, physical inactivity, suboptimal fitness levels, abdominal obesity, insulin resistance, and type 2 diabetes are associated with accelerated atherosclerosis and long-term cardiovascular risk in patients with FH. Thus, patients with FH and their families would benefit from lifestyle management education, including advice regarding diet, exercise, and correction of sedentary behaviours, weight control, blood pressure control, diabetes control, and smoking cessation. However, conclusive data regarding the effectiveness of dietary interventions in FH are unavailable.<sup>3,9</sup>

**RECOMMENDATION**

7. We suggest that patients with FH adopt a healthy lifestyle as recommended by the CCS guidelines on the diagnosis and treatment of dyslipidemias<sup>9</sup> (Weak Recommendation, Low-Quality Evidence).

**Values and preferences.** Non-lipid cardiovascular disease risk factors amplify the already high risk in patients with FH and should be managed.

**Pharmacologic therapies**

Randomized controlled trials on the reduction in cardiovascular events with the use of lipid-lowering agents for FH do not exist. Historical cohort data from the Netherlands FH registry shows that statin-treated patients with FH had cardiovascular outcomes similar to an age- and sex-matched population without FH.<sup>30</sup> In addition, several prospective cohort studies have shown that initiation of statin therapy in patients with FH is associated with a reduction in carotid intima-media thickness in adults and children.<sup>29,31</sup> Thus, despite the limited evidentiary basis, statins are the drug class of choice for FH, on the basis of landmark trials in the non-FH population that have shown that statins are the best treatment available for lowering LDL-C in patients with increased ASCVD risk. A recent analysis from the Dutch screening program for FH revealed that treatment with moderate- or high-intensity statins conferred a 44% relative risk reduction in ASCVD and mortality, compared with patients who did not use statins.<sup>30</sup>

The addition of adjunctive agents is recommended on an individualized basis to reach the desired LDL-C levels. In patients with FH in whom the target LDL-C level cannot be achieved with statin monotherapy, or when high doses of statins are not tolerated because of adverse effects, the combination of a lower dose of statins with ezetimibe can be an alternative. The combination of a statin with a bile acid sequestrant can also be used to achieve LDL-C target levels in patients with FH. Bile acid sequestrants can have adverse gastrointestinal effects, increase triglyceride levels, and reduce the intestinal absorption of many drugs, limiting their clinical use.

Inhibitors of proprotein convertase kexin/subtilisin type 9 (PCSK9) have emerged as a promising target for lowering LDL-C levels to reduce the risk of ASCVD in patients with FH. Health Canada has approved 2 PCSK9 monoclonal antibodies administered subcutaneously (alirocumab 75 or 150 mg every 2 weeks or 300 mg every month and evolocumab 140 mg every 2 weeks or 420 mg every month) for reducing LDL-C levels in patients with FH who have not achieved target LDL-C levels despite maximally tolerated doses of statins. In studies of patients with FH (n = 735), alicumab decreased LDL-C by approximately 50%-60% from baseline and was well tolerated, with a safety profile similar to that of placebo.<sup>32</sup> Similarly, evolocumab decreased LDL-C by a mean of 53.6% compared with standard of care in 440 patients with FH from 2 clinical trials.<sup>33</sup> Similar effectiveness has been observed with real-world use of PCSK9 inhibitors in Canadian patients with FH.<sup>34</sup>

Two large cardiovascular outcome trials in patients with established ASCVD showed that PCSK9 inhibitors reduced cardiovascular risk and were safe and well tolerated. The **Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)** trial examined 27,564 patients randomized to placebo (standard of care) or evolocumab 140 mg subcutaneously every 2 weeks. On a background of statin therapy (99% of patients), evolocumab lowered LDL-C levels to a median of 0.78 mmol/L and reduced the risk of cardiovascular events (15% relative risk reduction in the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization).<sup>35</sup> The **Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes)** trial tested the hypothesis that alicumab, 75 or 150 mg subcutaneously every 2 weeks, would reduce cardiovascular events in patients with an acute coronary syndrome 1-12 months before randomization. The trial randomized 18,924 patients to standard of care alone or standard of care and alicumab, on the background of statin use. There was a 15% reduction in the primary end point of coronary heart disease death, nonfatal myocardial infarction, stroke, or unstable angina requiring hospitalization.<sup>36</sup> Both drugs were well tolerated with an adverse event profile similar to that of placebo. Subgroup analyses of patients with FH from these outcome trials are pending. A third group of trials, the **Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE)** program, used the drug bococizumab, the development of which has been terminated because of an attenuation of its LDL-C-lowering effect because of frequent development of antidrug antibodies. Notwithstanding this limitation, a subgroup analysis in 1578 patients with FH in SPIRE showed that these patients had a similar benefit from bococizumab compared with placebo, with a 17% relative risk reduction in major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), with no statistical difference in benefit between patients with or without FH.<sup>37</sup>

On the basis of these results, monoclonal antibodies inhibitors of PCSK9 should be considered in patients with FH who have not achieved their therapeutic goals, after use of maximally tolerated statin therapy with ezetimibe.

**RECOMMENDATION**

- 8.1. Because the diagnosis of FH using validated clinical criteria and/or genotyping may occur at any age and imparts a high, lifelong risk of ASCVD, we recommend a personalized treatment plan, taking into account, at a minimum, age, additional cardiovascular risk factors, psychosocial and socioeconomic factors, and personal as well as family preferences, that should be developed as a shared-decision process (Strong Recommendation, Low-Quality Evidence).
- 8.2. We recommend that for patients with FH requiring medications, a personalized treatment plan should include statins as the primary therapy and secondary

agents as required, including ezetimibe and PCSK9 inhibitors according to the CCS guidelines on the diagnosis and treatment of dyslipidemias<sup>9</sup> (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** Because the primary target of therapy is LDL-C (with non-HDL-C or apolipoprotein B as alternate targets), the goal of therapy should conform to national dyslipidemia guidelines for children and for adults who require primary or secondary prevention. We recognize that guidelines preceding this one have diverse consensus goals such as an LDL-C target of < 2.5 mmol/L (European Society of Atherosclerosis, and in the United States, the National Lipid Association, the US FH Foundation, and the American Heart Association) for adult patients with FH because they are considered to be at high, lifetime cardiovascular risk. The NICE (United Kingdom) recommends an LDL-C target of < 3.5 mmol/L in adult patients with FH. In the absence of randomized controlled trial data of relevance to FH in the current therapeutic era, the general principle should be to attain the lowest level of LDL-C agreed upon between the patient and practitioner with the understanding that randomized controlled trial data from primary and secondary prevention trials suggest that low levels of LDL-C < 1.5 mmol/L are safe and associated with lower residual ASCVD risk.

9. In patients with FH and ASCVD, we suggest that targets should follow the recommendations of the CCS guidelines on the diagnosis and treatment of dyslipidemias<sup>9</sup> (LDL-C < 2.0 mmol/L and non-HDL-C < 2.6 mmol/L) (Weak Recommendation, Moderate-Quality Evidence).
10. We recommend that statins be used as the primary line of therapy (Strong Recommendation, High-Quality Evidence).

**Cost.** The yearly cost of generic statins is approximately CAD \$300.

11. We suggest that ezetimibe be used as second-line agent to achieve unmet LDL-C goals (Weak Recommendation, Low-Quality Evidence).
12. We recommend that monoclonal antibody inhibitors of PCSK9 be considered in adult FH individuals without ASCVD if they have not achieved a 50% reduction in LDL-C from baseline level and reached an LDL-C level of at least < 3.5 mmol/L or lower (as determined by the shared decision process between physician and patient) on maximally tolerated statin therapy with or without ezetimibe, as per recommendation 8 (Strong Recommendation, High-Quality of Evidence).

**Values and preferences.** In a patient with FH, the decision to treat an asymptomatic condition (severe hypercholesterolemia) must balance the patient's perceived overall risk with actual risk of ASCVD.

**Cost.** Alirocumab and evolocumab are costly medications and must be used judiciously in a cost-constrained medical system.

## Lipoprotein apheresis

Extracorporeal removal of apolipoprotein B-containing lipoproteins—lipoprotein apheresis—is currently recommended in adults with homozygous FH (HoFH) and in children (> 15 kg in weight for LDL-C apheresis<sup>38</sup>) with refractory LDL-C > 5.0 mmol/L during maximally tolerated medical therapy. Plasmapheresis or plasma exchange, a nonselective extracorporeal method, is an alternative, but less preferred treatment in jurisdictions where LDL-C apheresis is not available. Patients with HoFH are at extremely high risk of ASCVD and should be referred to a lipid specialist centre for cholesterol-lowering therapy (see the HoFH section). Although clinical evidence has suggested that long-term lipoprotein apheresis can contribute to atherosclerotic plaque regression and stabilization, no hard efficacy data from a double-blind, randomized trial has ever shown its clinical benefit. A recent study underscores the importance of screening for the *LDLR* mutation in HoFH and the relevance of adapting lipoprotein apheresis therapy to the severity of the disease and the benefits associated with more frequent lipoprotein apheresis treatments.<sup>39</sup>

## Specific groups

**Pregnancy in FH.** Statins are the most commonly used class of drug to treat adolescents and women with FH of childbearing potential. Because of the potential teratogenicity risk, it is recommended to interrupt statin and ezetimibe therapy at least 1 month before stopping contraception. A recent meta-analysis of controlled observational studies has failed to corroborate this risk.<sup>40</sup> In addition, a cohort study of 886,996 completed pregnancies linked to live-born infants that included 1152 women who had used a statin during the first trimester did not find a significant teratogenic effect.<sup>41</sup> Although these new safety data are reassuring, suspension of statin treatment prior to pregnancy in women with FH is still advisable. For pregnant women with FH, bile acid sequestrants can be safely prescribed and in those with ASCVD (or those with HoFH) therapeutic apheresis can be considered.

## RECOMMENDATION

13. We recommend that statins should not be used during pregnancy (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** Women should be advised to stop statins at least 1 month before stopping contraceptives or before attempting conception, or immediately at the time of diagnosis of pregnancy.

Studies in primates showed that evolocumab crosses the placental barrier but reproduction studies have not shown an effect on embryo-fetal or early postnatal development. No studies have been conducted with PCSK9 inhibitors in pregnant women and there are no data on fetal harm when administered to pregnant women with FH. Therefore, PCSK9 inhibitors should also be discontinued before conception.

**Type 2 diabetes mellitus in patients with FH.** Statins increase the risk for new-onset diabetes mellitus in high cardiovascular risk patients, although the risk is modest and outweighed markedly by the reduction in cardiovascular events by taking a statin. Interestingly, patients with FH with mutations in the *LDLR* gene show a lower prevalence of type 2 diabetes mellitus than unaffected relatives and lower than observed in the general population despite exposure to long-term high-dose statin therapy.<sup>42</sup> Although the mechanism for lowered risk of diabetes is uncertain, it might relate to reduced LDLR-mediated uptake of cholesterol in pancreatic  $\beta$  cells. Patients with FH who also have type 2 diabetes represent an extraordinarily high-risk group for ASCVD and should be managed aggressively.

**HoFH.** HoFH, although rare (1 in 250,000 to 1 in 1,000,000 individuals), results in severe LDL-C elevations and manifest ASCVD in the first 2 decades of life.<sup>38</sup> Cutaneous and tendon xanthomata are present from a very young age and, together with family history of heterozygous FH in both parents, and an untreated LDL-C > 13 mmol/L, can lead to the diagnosis. Genetic testing of patients and their family members might reveal concordant or discordant (compound heterozygote) FH-causing mutations. Patients with 2 null mutations have higher LDL-C levels, and are more resistant to treatment and develop earlier ASCVD.<sup>38</sup> Cardiovascular disease in patients with HoFH is characterized by aggressive atherosclerosis of the aortic root, primarily affecting the aortic valve and supra-aortic region, although other vascular beds might be affected. Patients should be urgently referred to specialized care at the time of diagnosis and have a complete cardiovascular evaluation, because fatal coronary artery occlusions have been reported before 2 years of age. Lifestyle management and initiation of high-potency statin and ezetimibe with titration should be started as soon as the diagnosis is made. Nearly all patients with HoFH will require extracorporeal LDL-C removal, particularly if the LDL-C, with treatment, remains > 5 mmol/L or if ASCVD is present. Either plasmapheresis or preferably LDL-C apheresis should be started as soon as technically feasible, usually before 5 and at least by 8 years of age. Newer therapies, such as lomitapide, mipomersen, and PCSK9 inhibitors, have been advocated as adjunctive treatments. Frequent surveillance with cardiovascular imaging and stress testing is necessary to detect and monitor progression of atherosclerosis.

#### RECOMMENDATION

14. We recommend that patients with HoFH be referred to a specialized lipid clinic and undergo complete evaluation for genetic analysis, presence of ASCVD, and aggressive lipid-lowering therapies, including consideration for extracorporeal LDL-C removal, lomitapide, and PCSK9 inhibitors (Strong Recommendation, Moderate-Quality Evidence).

#### Pediatric aspects

As a genetic condition, FH causes a lifetime of elevated LDL-C, evident even in umbilical cord blood of affected individuals. This lifetime exposure is associated with high risk of accelerated atherosclerosis, and increased markers of early atherosclerosis are evident in affected youth. The atherosclerosis process is not uniform across the lifespan and is more readily reversible in its earliest stages. This has led some experts to advocate for a strategy aimed at reducing atherosclerosis early in the course of the disease with the goal of preventing ASCVD events. However, although the case is becoming more solid for FH, accrual of evidence to support such a strategy has many important and perhaps unsolvable challenges.<sup>15</sup>

**Screening and diagnosis.** Screening strategies targeted toward the children of parents with dyslipidemia or a positive family history of premature ASCVD are no more likely to identify children with elevated LDL-C than random screening,<sup>43</sup> although it is unclear if this is true for FH. Cascade screening depends on the effective identification of index cases and the willingness of family members to be screened; both have been problematic.<sup>10</sup> Parents have been more likely to desire that their children be tested than test themselves. These factors have led some organizations to recommend universal screening of children at specific ages.<sup>21</sup> Children with elevated LDL-C are more likely to have FH than adults with similar levels. Thus, universal lipid screening of children, with additional genetic testing when indicated, might result in a higher yield of confirmed cases. In addition, the identification of children with FH affords the opportunity for reverse cascade screening (ie, screening of the parents, who are usually of an age at which they have little contact with the health care system). A recent study by Wald et al. showed the effectiveness of incorporating such a universal screening strategy for infants in the setting of visits for routine vaccinations and health maintenance.<sup>15</sup> Nonetheless, lipid screening remains controversial depending on what level of evidence one views as sufficient. The diagnosis of FH in children, on the basis of criteria defined for adults, remains problematic unless a genetic mutation is confirmed, because physical findings are usually absent, and the family history is less contributory. In a study of 1034 Dutch children from families with FH, an LDL-C > 3.5 mmol/L predicted the presence of genetically confirmed FH with a 98% post-test probability.<sup>11</sup> Thus, lower LDL-C cut points for diagnosis of FH are needed for children.

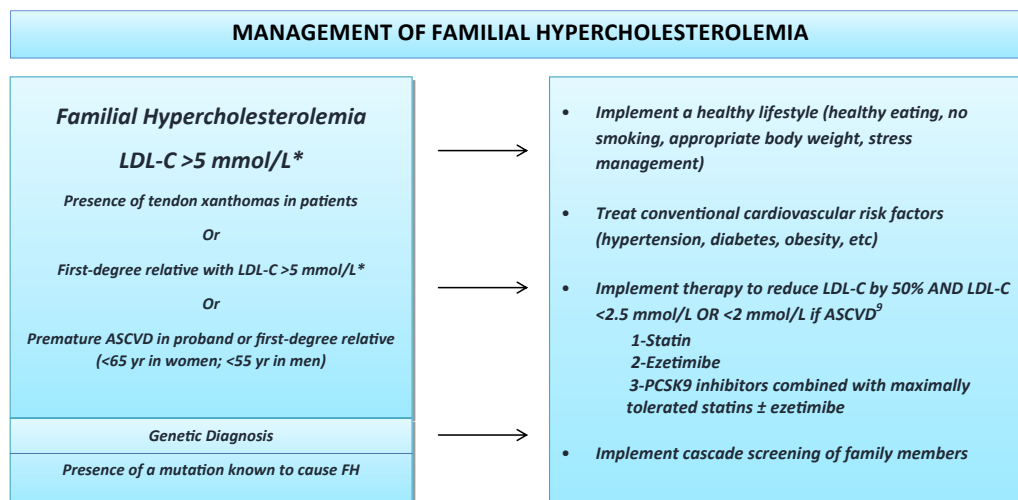
#### RECOMMENDATION

15. We suggest that universal cholesterol level screening be considered for detection of FH in children with reverse cascade screening of parents when warranted (Weak Recommendation, Moderate-Quality Evidence).

**Values and preferences.** Patient confidentiality must be protected. Potential psychosocial implications of "labelling" children with the diagnosis are unclear.

**Cost.** Screening should be supported by provincial health agencies.





**Figure 2.** Diagnostic and treatment flow when familial hypercholesterolemia (FH) is suspected. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. \* LDL-C  $\geq$  4.0 mmol/L for age younger than 18 years; LDL-C  $\geq$  4.5 mmol/L for age 18 years and older and younger than 40 years.

**Management.** Although optimizing lifestyle behaviours is paramount, it does not cause sufficient reductions in LDL-C in children with FH, and its effect is mainly in preventing or managing other cardiovascular risk factors. Statin therapy is recommended, and algorithms to guide decision-making have been defined.<sup>21</sup> The age at statin initiation requires clinical judgement in conjunction with the family’s wishes. The usual age at initiation is 8-10 years, and the LDL-C threshold is informed by the presence of other risk factors or risk conditions. There have been pediatric trials in patients with FH with all of the available statins, and they have shown safety and efficacy similar to that in adults.<sup>44</sup> Although data regarding lifetime safety are likely to remain unavailable, it is reassuring that no safety concerns have been identified in longer-term pediatric studies. In recent pediatric trials that have incorporated vascular measures as outcomes, slowing or regression of carotid intima media thickness was seen, despite failure to reach optimal LDL-C targets in all.<sup>31</sup> If the goal is to reduce atherosclerosis with the aim of preventing adult ASCVD (for which a lifelong trial is not feasible or ethical, particularly for FH), then effective treatment starting in youth seems reasonable.

### Cascade Screening, FH Registry, Knowledge Translation

#### Cascade screening

Despite the very high risk of premature ASCVD with prolonged exposure to elevated LDL-C, and the proven benefits of treatment in improving clinical outcomes, it is estimated that fewer than 5% of individuals with FH are identified worldwide.<sup>2</sup> In Canada, regional discrepancies in FH diagnosis might be related to the prevalence and awareness of the disease.<sup>6</sup> Unfortunately, because of the asymptomatic nature of severe hypercholesterolemia, the clinical presentation is often an acute coronary syndrome. Potential models to identify cases include universal cholesterol screening at a particular age, such as at the time of immunization as mentioned previously, opportunistic screening in primary care, screening of people admitted to hospital with premature myocardial infarction, or cascade screening of family members of affected patients. Among the potential options, cascade screening of family members of affected individuals is considered the most cost-effective and practical strategy<sup>10</sup> and has been implemented in many countries globally as the basis for developing FH registries. With 50% of first-degree relatives being affected, this strategy of screening yields high results for case identification in the adult population.

#### FH registries

FH registries of individuals identified by cascade screening have been established in several European countries, of which the Dutch registry is the most successful.<sup>2</sup> The United Kingdom NICE registry also uses cascade screening with genetic testing and LDL-C measurement to identify affected relatives of FH index cases.<sup>23</sup> This approach: (1) reduced the average age at which the patients are diagnosed and treated; (2) increased the proportion of patients with FH receiving statin therapy, and significantly decreasing their lipid levels; (3) reduced morbidity and mortality from ASCVD when statin treatment was initiated; (4) improved lipid levels in

#### RECOMMENDATION

16. We suggest that statin therapy be considered usually between 8 and 10 years of age if LDL-C remains  $\geq$  4.9 mmol/L, or  $\geq$  4.1 mmol/L with a family history of premature ASCVD or other cardiovascular risk factors or risk conditions (Weak Recommendation, Moderate-Quality Evidence).

**Values and preferences.** The age at which statin treatment is started in children with FH should incorporate the preferences of the patient and family.

**Cost.** Low to moderate doses of all statins are generic.

children with FH; and (5) yielded cost-effective interventions. Additional benefits of FH registries include the ability to monitor effectiveness of therapy over time, to provide jurisdictional prevalence data, and to create a database for clinical trials and research.

The first FH registry in Canada was initiated in British Columbia in 2012, and has recently been expanded to become a pan-Canadian FH registry.<sup>6</sup> The registry is Web-based, password-secured, and allows data entry from member sites without the requirement for specific software. The intended outcomes include an increased diagnosis of FH, data on jurisdictional prevalence of FH, and availability of a clinical trial database.

### RECOMMENDATION

17. We recommend that a national registry for FH be implemented to raise awareness among patients and health care professionals and to provide advocacy to ensure access to effective therapies (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** Patient confidentiality must be protected.

**Cost.** Maintaining an FH registry should be supported as an assured provincial health service.

### Knowledge translation

The existence of cascade screening programs and FH registries will help with the identification of susceptible individuals and their family members at an early age and will serve to increase awareness of the prevalence of the condition, the high risk of premature ASCVD, and the importance of treatment starting from a young age in patients with FH. The persistent perception among the public and physicians that very elevated LDL-C is most often on the basis of poor diet, excess weight, or other secondary factors as opposed to genetic predisposition needs to be overcome, as part of an overall effort to identify and treat patients with FH more frequently and effectively.

### Conclusions

Herein, we provide an update of the 2014 Canadian Cardiovascular Society position statement on FH, which should be updated in accordance with an evolving evidence base (Fig. 2). The provision of optimal care to patients with FH presents many challenges to the patient, their family or caregivers, the physician, other health care providers, and the health care system as a whole. It represents the unique opportunity to make an accurate diagnosis using a simplified definition for FH,<sup>4</sup> and to provide early treatment, thus modifying the natural course of a disease that was once devastating for patients and their family.

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All members of the primary panel participated in the writing process and have reviewed and agree with the content of the article; all members of the secondary panel read and reviewed the manuscript and agree with the content of the article.

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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](http://www.onlinecjc.ca) and at <https://doi.org/10.1016/j.cjca.2018.09.005>.