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Familial hypercholesterolemia in Canada: Initial results from the FH Canada national registry

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ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is under-diagnosed and under-treated in most of the world, including Canada. National registries play a key role in identifying patients with FH, understanding gaps in care, and advancing the science of FH to better treat these patients.
Methods: FH Canada has established a national registry across 19 academic sites acting as "hubs" in Canada to increase awareness and access to standard-of-care therapies.
Results: To-date, more than 3000 patients with FH have been entered into a secure, web-based database. Early outcomes of this initiative include a greater understanding of treatment gaps for patients with FH in Canada, the development of a new, simplified Canadian definition of FH, and tools to aid in the diagnosis of FH, including imputation of baseline levels of LDL cholesterol.
Conclusions: As the national registry expands in size and scope, further learning will emerge with ultimate benefit for the diagnosis and treatment of FH in Canada.

1. Introduction

Familial hypercholesterolemia (FH) is among the most common genetic disorders in humans and causes significant morbidity and mortality. FH is an autosomal co-dominant disease caused, most frequently, by mutations in the *LDLR*, *APOB* or *PCSK9* genes. Left untreated, 50% of men with FH develop clinical atherosclerotic cardiovascular disease (ASCVD) by age 60 [1]. Treatment with lipid-lowering therapy, especially statins, is highly efficacious in patients with FH and can reduce the risk of ASCVD to background population rates [2].

However, FH is under-recognized and under-treated worldwide [3]. In many countries of the world, more than 85% of cases are thought to be undiagnosed, even after presentation with ASCVD

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[4]. National registries of FH play a key role in increasing the detection of patients with FH, understanding gaps in care, and improving management and outcomes [5]. Here we discuss recent progress in the development of a National FH Registry in Canada, and early outcomes of this work.

2. Materials and methods

2.1. Canadian FH registry

Canada is a geographically large and ethnically diverse country. In some regions of Canada, for example the province of Quebec, founder populations exist with a very high prevalence of FH [6], [7]. Indeed, in some areas of Quebec, such as Kamouraska, the prevalence of heterozygous FH is as high as 1 in 80 individuals [8]. This is also thought to be the epicenter of the del15 kB *LDLR* deletion found in >65% of French Canadians with FH [6]. The population displays higher ethnic diversity in other regions of Canada. Accordingly, most Canadian patients with molecularly-confirmed FH have unique mutations [9].

The first FH registry in Canada was established in the province of British Columbia (BC) in 2013 [10]. Since that time, the FH Canada National registry has expanded to include 19 academic centres across Canada, as well as numerous peripheral sites, in a 'hub and spoke' model (Fig. 1). The registry uses a centralized, secure web-based database to allow data entry from the individual sites. The primary inclusion criteria for entry to the Registry is a diagnosis of heterozygous FH (HeFH) according to either the Dutch Lipid Clinic Network Criteria (DLCNC) ('possible', 'probable' or 'definite') or the Canadian definition ('probable' or 'definite', described below), or physician diagnosis of homozygous FH (HoFH). As of December 2017, data from 3122 participants have been entered into the database, and this number is expected to grow rapidly as additional sites upload data from patients. The FH Canada registry is approved by the institutional review board at all participating sites, and the study is registered at www.ClinicalTrials.gov (NCT02009345).

3. Results

The baseline characteristics of patients entered into the national database to date are shown in Table 1. The mean age of patients with HeFH is 43 years, the LDL-C at time of first visit was 6.06 mmol/L, and 16.6% had coronary artery disease. At the baseline visit, 40% of these individuals were not receiving lipid-lowering therapy, speaking to the opportunity to improve screening and care in this population made possible by their identification and diagnosis. Fourteen patients with HoFH have been entered into the Registry with a mean LDL-C of 11.2 mmol/L at the time of first visit.

3.1. Identifying gaps in care

Although the FH registry initiative is in its early days in Canada, important findings are already emerging. For example, an analysis has been reported of patients in the provincial BC FH Registry up to December, 2015, including 339 patients with definite or probable FH, based on DLCNC, and representing more than 3700 patient-years of follow-up [11]. From the time of baseline entry into the registry to last follow-up, the use of lipid-lowering therapy increased significantly. However, at the time of last follow-up, despite aggressive treatment with statins and ezetimibe, recommended lipid targets were achieved in only a minority of patients. A 50% reduction in LDL cholesterol was achieved in only 35.8% of patients, and a LDL cholesterol $\leq$2 in only 8.3% of patients [11]. Importantly, patients in the registry were observed to have a 10-year rate of cardiovascular events of >15%, despite aggressive treatment. These data reinforce the challenges of appropriately controlling lipid levels in patients with FH and speak to the need to improve the care of these patients. An updated re-analysis of data from the BC registry showed that, following the introduction of inhibitors of PCSK9 [12–14], lipid levels improved in patients in the BC registry. Among patients in whom a PCSK9 inhibitor was used, >85% met guideline-recommended lipid targets, compared to ~50% of patients in whom a PCSK9 inhibitor was not used [15].

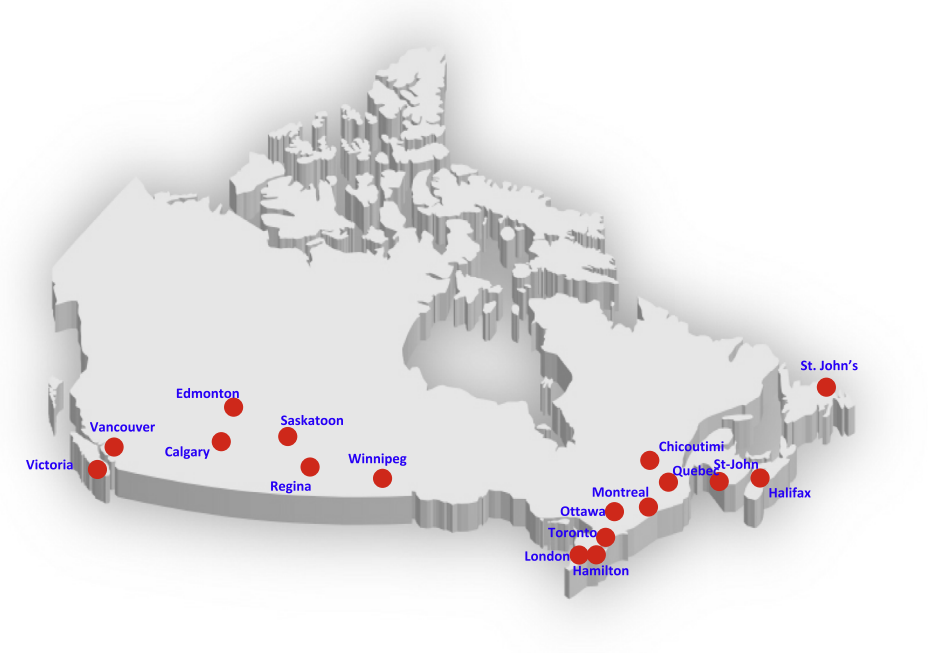

Fig. 1. Sites of FH Canada Registry.
The FH Canada network includes 19 active academic sites (of which 17 are shown), as well as 7 peripheral sites. Data from all sites are entered into a common, secure electronic database.

Table 1
Baseline characteristics of patients in the Canadian FH Registry.

Characteristic	HeFH	HoFH
N	3108	14
Age, years (mean ± SD) (n = 3022)	43 ± 17	38 ± 15
DLCNC[a] score (mean ± SD) (n = 3108)	5.7 ± 5.2	15.2 ± 5.2
Male sex (%) (n = 3097)	52.5%	57.1%
BMI[b], kg/m^2 (mean ± SD) (n = 2912)	26.0 ± 5.0	26.1 ± 4.0
Coronary artery disease (%) (n = 1857)	16.6%	57.1%
Systemic hypertension (%) (n = 2480)	21.1%	28.6%
Type 2 diabetes (%) (n = 1758)	5.6%	0%
Current smoker (%) (n = 2360)	17.0%	12.5%
Total cholesterol, mmol/L (mean ± SD) (n = 3043)	8.09 ± 1.83	13.0 ± 5.13
LDL-C, mmol/L (mean ± SD) (n = 2992)	6.06 ± 1.74	11.2 ± 5.35
HDL-C, mmol/L (mean ± SD) (n = 3037)	1.21 ± 0.37	1.03 ± 0.27
Triglycerides, mmol/L (median [interquartile range]) (n = 3035)	1.60 [1.03–2.30]	1.03 [0.85–2.6]
Apolipoprotein B, g/L (mean ± SD) (n = 1419)	1.48 ± 0.37	2.55 ± 0.83
Lipoprotein(a), mg/L (median [interquartile range]) (n = 994)	263 [81.0–678.0]	326 [97.7–1220.0]
Lipid-lowering therapy[c] (%) (n = 2293)	59.1%	78.6%
Any statin (%) (n = 2293)	51.4%	71.4%
High intensity statin (%) (n = 2293)	9.9%	57.1%

The number in parenthesis for each row indicates the number of HeFH participants for whom the data field was captured.
HeFH = heterozygous familial hypercholesterolemia. HoFH = homozygous familial hypercholesterolemia. Lipid levels were at the time of entry to registry.
[a] Dutch Lipid Clinic Network Criteria.
[b] Body mass index.
[c] Use of lipid lowering therapy is at time of entry into the Registry.

3.2. Prevalence of FH

FH was traditionally thought to affect 1 in 500 individuals. However, in recent years, genetic analyses of large cohorts of patients have suggested that FH-causing mutations can be identified in ~1 in 250 individuals [16], [17]. However, the prevalence reported in individual studies varies widely, and understanding the true prevalence of FH is a priority to design effective programs to identify and treat these patients.

Investigators from FH Canada recently reported a systemic review and meta-analysis of the prevalence of FH in many regions of the world [18]. This study included data from >2,400,000 unique individuals represented in 19 studies. The pooled prevalence of FH, based on either clinical or genetic diagnosis, was 0.4%, corresponding to 1 in 250 individuals. Prevalence was found to vary regionally, with lower prevalence in Europe and Asia, and higher prevalence in South Africa.

This first systematic meta-analysis provides important evidence that the true global prevalence of FH is 1 in 250 individuals, making it substantially more common than previously thought, and highlighting the importance of efforts to improve the diagnosis of these individuals. Based on these data, it is estimated that there are ~145,000 patients with FH in Canada.

3.3. Canadian definition of FH

Accurate and straightforward diagnosis of FH is essential to addressing the challenge of its worldwide under-diagnosis [3], and particularly to supporting the diagnosis of FH by non-lipid specialists. Yet, there is no globally accepted and easy to use set of diagnostic criteria for FH. At least 3 separate diagnostic criteria exist, the DLCNC [19,20], the Simon-Broome Registry criteria [21], and the Make Early Diagnosis Prevent Early Death (MEDPED) criteria [22]. Each of these has strengths and limitations. One limitation common to all is that they tend to be complex, multi-item criteria, which ultimately limits their dissemination and uptake by health professionals outside of specialty lipid clinics, and particularly in the primary care setting. Additionally, many of these criteria provide heavy weighting to the classic physical stigmata of FH, such as corneal arcus and tendon xanthomas, which, while helpful when observed, are found in only a minority of patients and therefore lack sensitivity.

To address these barriers, FH Canada has proposed a new set of simplified, Canadian diagnostic criteria for FH (Fig. 2) [23]. Importantly, these criteria are based on LDL-C cut-points determined for a very large population of Canadians to determine the 95th percentile LDL-C level in the population. When compared to DLCNC or Simon-Broome Registry criteria, the new Canadian definition displayed excellent agreement [42]. Additional formal analysis of the performance of the proposed Canadian definition relative to existing diagnostic criteria will be needed to define the accuracy of this approach. Validation of these criteria against 'gold standard' genetic diagnosis of FH will provide further insight into their performance. These new, simplified criteria for FH are anticipated to enable healthcare providers in Canada, and other jurisdictions, to recognize FH more easily, thus improving earlier treatment and better outcomes for these patients.

3.4. Imputation of baseline LDL

The diagnosis of FH begins with the detection of a very high level of LDL-C in a patient, and all diagnostic criteria for FH incorporate knowledge of a patient's baseline, untreated LDL-C level. Yet, by the time a patient comes to the attention of a specialist physician, lipid-lowering therapy has very frequently already been commenced, and the baseline LDL-C may be unknown. This issue is amplified in jurisdictions where fragmented or non-existent electronic health records preclude the easy determination of a patient's pre-treatment LDL-C level. This creates a two-fold challenge for the diagnosis of FH. Firstly, without clear documentation of a very high baseline LDL-C level, the possibility of FH may not be considered by health care providers. Secondly, even if FH is considered, the diagnosis is hampered without knowledge of a patient's baseline LDL-C, leading to difficulties in applying diagnostic criteria and thus receiving approval from payors for access to specific therapies.

To overcome these barriers in the diagnosis of FH, FH Canada has recently published the results of a validation study for imputation of baseline LDL-C in patients with FH [24]. This study made use of data from a prior meta-analysis of statin-treated patients to determine a correction factor for each available statin and dose, as

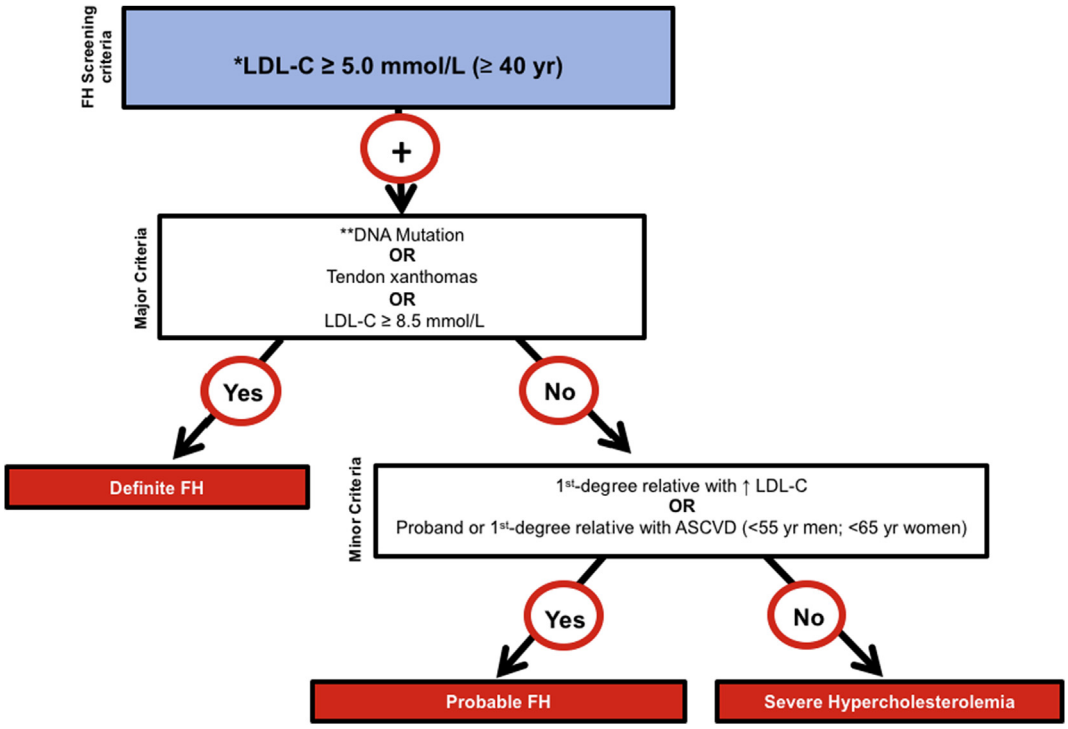

Fig. 2. Proposed Canadian definition of familial hypercholesterolemia.
A diagnosis of FH should be considered in a patient with a baseline LDL-C ≥ 5 mmol/L (or LDL-C ≥ 4.0 mmol/L for age < 18 years; LDL-C ≥ 4.5 mmol/L for age ≥ 18 yr and <40 years). The presence of 1 or more major criteria in such an individual establishes a diagnosis of Definite FH. In individuals without major criteria, the presence of 1 or more minor criteria establishes a diagnosis of 'Probable FH'. Individuals without major or minor criteria are defined as having 'Severe Hypercholesterolemia'. * = secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease (biliary cirrhosis), medication especially antiretroviral agents). ** = causal DNA mutation refers to the presence of a known FH-causing variant in the *LDLR*, *APOB* or *PCSK9* gene based on presence of the variant in ClinVar [38], HGMD [39] or WDLV [40] databases, in the proband or a first-degree relative.

well as ezetimibe [25]. These correction factors were then applied to a population of 951 patients with FH in whom both the pre-treatment and on-treatment LDL-C were known. The results showed a strong, consistent correlation between actual and imputed baseline LDL-C across a range of statins and doses (overall Pearson $r = 0.76$, $p < 0.001$) [24]. The actual versus imputed LDL-C did not differ significantly at a Bonferroni-corrected p value of $p < 0.002$ for any of the statins or doses tested. There was a statistically significantly though numerically small difference between the actual and imputed LDL-C for ezetimibe. These results suggest that imputation of baseline LDL-C is a highly accurate means to determine the baseline LDL-C in patients with FH on stable statin therapy, which should aid in the diagnosis of FH in such patients. Imputation of baseline-LDL is already used in some diagnostic criteria for FH, such as the Wales FH Scoring Criteria [26]. A notable limitation of the imputation method is that it is dependent on being able to accurately determine a patient's adherence to prescribed therapy.

3.5. Smartphone and web-based application for FH

Imputation of baseline LDL-C, as well as diagnosis of FH using the proposed Canadian definition, DLCNC and Simon-Broome Registry criteria, have been incorporated into a smart phone application. This freely available tool, which is available as both a smartphone and desktop application (http://www.circl.ubc.ca/), can also be used to generate a patient report based on the entered values for a patient, which can be added to a patient's medical record.

3.6. Stratifying cardiovascular risk in FH

While the FH population as a whole is at significantly increased cardiovascular risk relative to the general population, there exists remarkable diversity in ASCVD risk within the FH population. A major challenge is how do identify those patients with FH at highest risk who may benefit from the most intensive therapy. Part of the heterogeneity in risk may be attributable to non-LDL-C traditional risk factors [27]. However, well-established risk calculators such as the Framingham risk score are not applicable to FH subjects, which makes accurate risk stratification challenging. A risk score specifically developed for FH was reported in 2017 in a cohort of 670 adult French Canadian FH individuals carrying a mutation in the *LDLR* gene [28]. This study identified age, HDL-C, male sex, hypertension, and smoking as independent predictors of ASCVD risk in FH. This resulted in the creation of the Montreal-FH-SCORE, that showed a good predictive capacity for ASCVD (AUC of 0.840 (0.808–0.872), $p < 0.0001$). Patients with a high Montreal-FH-SCORE score had a 10-fold higher cardiovascular risk than patients with a low score (OR 10.3, 95% CI 6.7–15.7, $p < 0.0001$). Lp(a) was a significant predictor of ASCVD risk in FH in a multivariate model but did not significantly increase the C-statistic when added to the Montreal-FH-Score [28]. The Montreal-FH-SCORE has been further validated in another French Canadian cohort of FH patients [29]. Additional validation of this score in the FH Canada national registry is currently underway, and should provide a useful tool to risk stratify within the FH population.

4. Discussion

Having established the fundamental infrastructure, including multiple study sites, harmonized ethics, and a common electronic study database, the next stages of the FH Canada Registry will be to continue adding new patients to the database, to develop a larger and more accurate assessment of FH patients in Canada, and to increase the detection of FH in Canada. This resource will also facilitate cascade screening of families of identified index cases, which has been established as one of the most efficient methods to improve the detection of FH and lower morbidity and mortality [30]. Because of the provincial nature of healthcare delivery in Canada, cascade screening protocols need to be developed in Canada at the local, provincial and national level. Additional analysis of the FH Canada Registry data will include a focus on longitudinal changes in lipid levels and use of lipid-lowering therapy, as has been reported in the BC Registry [11].

Genetic testing for FH in Canada is not widely available at present outside of Quebec. Genetic testing for FH is recommended by the US Centre for Disease Control Office of Public Health Genomics [31], and by the United Kingdom National Institute for Health and Care Excellence [32]. The primary benefit of genetic diagnosis of FH is to facilitate cascade screening [33], and is particularly useful when the relatives of a proband have LDL-C levels near the diagnostic threshold. In addition, recent studies have suggested that presence of a pathogenic FH-causing mutation significantly increases cardiovascular risk, even compared to patients with comparable levels of LDL-C without such a mutation [17,34]. This suggests that knowledge of an individual's genotype provides clinically relevant information beyond that available by LDL-C level alone. Recent advances in the use of target next-generation sequencing for inherited lipid disorders have significantly reduced the cost of genetic testing for FH and related conditions [9,35–37]. The availability of large databases of known pathogenic FH-causing variants, including ClinVar [38], Human Gene Mutation Database [39] and the Western Database of Lipid Variants [40], further enhances the ability to determine pathogenicity of identified variants. Efforts are underway to develop clinically-approved assays for genetic testing of FH in several Canadian provinces. At the same time it is important to recognize that genetic testing is not required to diagnose FH, and even without an FH-causing mutation, patients with high LDL-C are at elevated risk and require treatment [34].

For patients with HoFH, lipoprotein apheresis is recommended [27], but is availability in Canada is limited, with most provinces offering plasmapheresis instead. Efforts are underway to improve access to lipoprotein apheresis for appropriate patients in Canada [41].

4.1. Conclusions

FH is the most common genetic disorder in humans and causes significant morbidity and mortality. National registries play an important role in improving care and increasing our understanding of this condition. The FH Canada Registry has established a national infrastructure for a Canada-wide registry of FH. Early outcomes have included a greater understanding of gaps in care for patients with FH in Canada, greater knowledge of the prevalence of the condition, a simplified set of diagnostic criteria for the Canadian population, and tools to aid in the diagnosis of FH. As the national registry further increases in size and scope, there will be more opportunities to develop knowledge to improve the diagnosis and care of patients with FH in Canada.

Conflict of interest

Jean Bergeron has received honoraria from Amgen and Sanofi for activities unrelated to the current manuscript. Liam R. Brunham sits on the advisory boards of Sanofi, Amgen, Akcea and has collaborated with Cerenis and The Medicines Company on clinical trials. Patrick Couture has received funding in the last 5 years from the Canadian Institutes for Health Research, Agriculture and Agri-Food Canada (Growing Forward program supported by the Dairy Farmers of Canada (DFC), Canola Council of Canada, Flax Council of Canada, Dow Agrosciences, Dairy Research Institute, Dairy Australia, Danone Institute, Merck, Pfizer, Atrium Innovations and the Kaneka Corporation. Gordon A. Francis has received honoraria from Amgen, Akcea and Sanofi, and has collaborated with Akcea and The Medicine's Company on clinical trials. Daniel Gaudet has received research grant support from FHCanada, Aegerion (Novelion Therapeutics), Amgen, Akcea Therapeutics a subsidiary of IONIS Pharmaceuticals, AstraZeneca, Chiesi, DalCor Pharma, Esperion, GlaxoSmithKline, Gemphire, IONIS, Pfizer, Regeneron and Sanofi, and served as a consultant for Amgen, Aegerion, Akcea, Chiesi, IONIS, Regeneron, Sanofi and UniQure. Robert A. Hegele has received honoraria for membership on advisory boards and speakers' bureaus for Aegerion, Akcea/Ionis, Amgen, Boston Heart Diagnostics, Gemphire, Pfizer, Regeneron, Sanofi and Valeant and has collaborated with Aegerion, Akcea/Ionis, Amgen, Pfizer and Sanofi on clinical trials. G. B. John Mancini has received honoraria from Sanofi, Amgen, Novartis, Janssen, Novonordisk Boehringer-Ingelheim, Merck. AstraZeneca, and Bayer and grants from Sanofi, Amgen, Janssen, B-I. Jacques Genest has received support from Sanofi, Amgen, Pfizer, Aegerion and Valeant for FH Canada. He has received honoraria from Novartis, Sanofi, Amgen and Merck, and has collaborated with Sanofi, Amgen, Novartis and Eli Lilly on clinical trials. No other competing interests are declared.

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