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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].

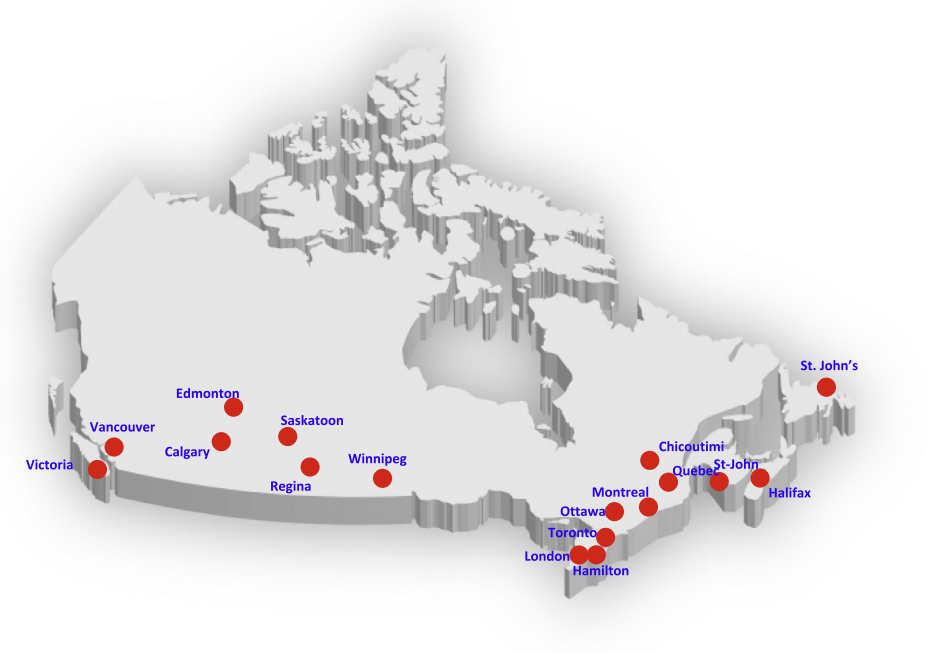

Fig. 1. Sites of FH Canada Registry.
The FH Canada network includes 19 active academic sites (of which 17 are shown), as well as 7 peripheral sites. Data from all sites are entered into a common, secure electronic database.