



Canadian Journal of Cardiology xx (2012) xxx

Viewpoint

Regional and National Familial Hypercholesterolemia Registries: Present International Application, Importance, and Needs for Canada

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Cardiovascular disease (CVD) is the leading cause of death in the Western world. Atherosclerosis is the most common pathological vascular change underlying CVD with hypercholesterolemia constituting a major risk factor. Heterozygous familial hypercholesterolemia (FH) is a common autosomal dominant disease with a prevalence of 1:500 in the general population.¹ Thus, approximately 13 million people worldwide and 68,000 in Canada are carriers of an FH gene. FH is caused by loss-of-function mutations in the low-density lipoprotein (LDL) receptor or apolipoprotein B-100 gene, or gain-of-function mutations in proprotein convertase subtilisin/kexin type 9, resulting in very high blood cholesterol levels and premature CVD.²⁻⁴ It is clinically characterized by arcus cornealis and tendon xanthomas,⁴⁻⁷ more common among people of French Canadian, Christian Lebanese, and Afrikaner descent. If undiagnosed and untreated, the cumulative risk of coronary artery disease by age 60 is more than 60% among men and 30% among women.⁸⁻¹⁰ In contrast to many other genetic diseases, treatment in the form of lifestyle management and lipid-lowering medications is highly effective in preventing not only CVD¹¹ but also total morbidity and mortality. Not infrequently, FH is diagnosed only after a major cardiovascular event; therefore implementation of nationwide screening is warranted to allow early diagnosis and treatment.

Despite an international effort to improve the identification and management of FH patients,^{12,13} only a few countries (The Netherlands, Spain, and Wales) have large-scale programs to systematically determine the FH status of relatives of FH patients.¹⁴⁻²³ Although FH is more common than type 1 diabetes mellitus,²⁴ both lay people and health professionals lack awareness of FH, its diagnostic features, and consequences. Framingham-based cardiovascular risk assessment should not be used in individuals with extreme hypercholesterolemia, but health professionals may still reassure FH patients

that they are at a low global cardiovascular risk. To our knowledge, only a minority of FH patients are currently diagnosed and treated adequately. The World Health Organization has estimated that FH is properly diagnosed in only approximately 15% of affected Canadians.¹³ Compounding the issue, only 10% of cardiologists and general practitioners screen their patients for FH.^{13,25} Estimates from the World Health Organization and other countries suggest that less than 25% of FH

Table 1. Dutch Lipid Clinic Network criteria for a diagnosis of FH

	Score
Family history	
First-degree relative with known premature coronary and vascular disease (men < 55 years, women < 60 years), or	1
First-degree relative with known LDL-C higher than the 95th percentile for age or sex	
First-degree relative with tendinous xanthomata and/or arcus cornealis, or	
Children aged younger than 18 years with LDL-C higher than the 95th percentile for age and sex	
Clinical history	
Patient with premature coronary artery disease (ages as above)	2
Patient with premature cerebral or peripheral vascular disease (as above)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age of 45 years	4
LDL-C (mmol/L)	
LDL-C \geq 8.5	8
LDL-C 6.5-8.4	5
LDL-C 5.0-6.4	3
LDL-C 4.0-4.9	1
DNA analysis: functional mutation in the <i>LDLR</i> , <i>APOB</i> , or <i>PCSK9</i> gene	8
Stratification	Total Score
Definite FH	\geq 8
Probable FH	6-7
Possible FH	3-5
Unlikely FH	< 3

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

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Received for publication April 3, 2012. Accepted April 30, 2012.

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See page xxx for disclosure information.

subjects are diagnosed.^{13,14} Not much has happened in Canada in the 6 years since the Yuan et al. review of this subject.²⁶

One practical approach to identifying people at risk of FH is cascade screening. The Make Early Diagnoses to Prevent Early Deaths (MEDPED) program has proven that the most cost-effective method of identifying and treating people with FH is to screen the relatives of diagnosed FH patients.¹⁴ This process involves screening the first-, second-, and third-degree relatives of the index patient. There is a 50% probability of FH in first-degree, 25% in second-degree, and 12.5% in third-degree relatives.^{22,26-28} Cascade screening has been highly effective in identifying affected relatives and has led to decreased CVD and overall total morbidity and mortality.²⁹⁻³¹

The European Experience

Cascade screening has been implemented in The Netherlands, Wales, and Spain and is being developed regionally in other countries including Brazil, Australia, and Czech Republic.²⁴ The best example of an efficiently-functioning FH registry is in The Netherlands,²⁴ where cascade screening has been established since 1994, identifying up to 8 new FH cases per family. The Dutch Lipid Clinic Network criteria is used to identify the index cases (Table 1),³² and correctly identify 80%-85% of FH patients based on genetic testing. This approach has been very effective; to date over 25,000 FH patients have been identified. By diagnosing and treating 3 new FH patients, 1 myocardial infarction can be prevented. The average cost calculated for

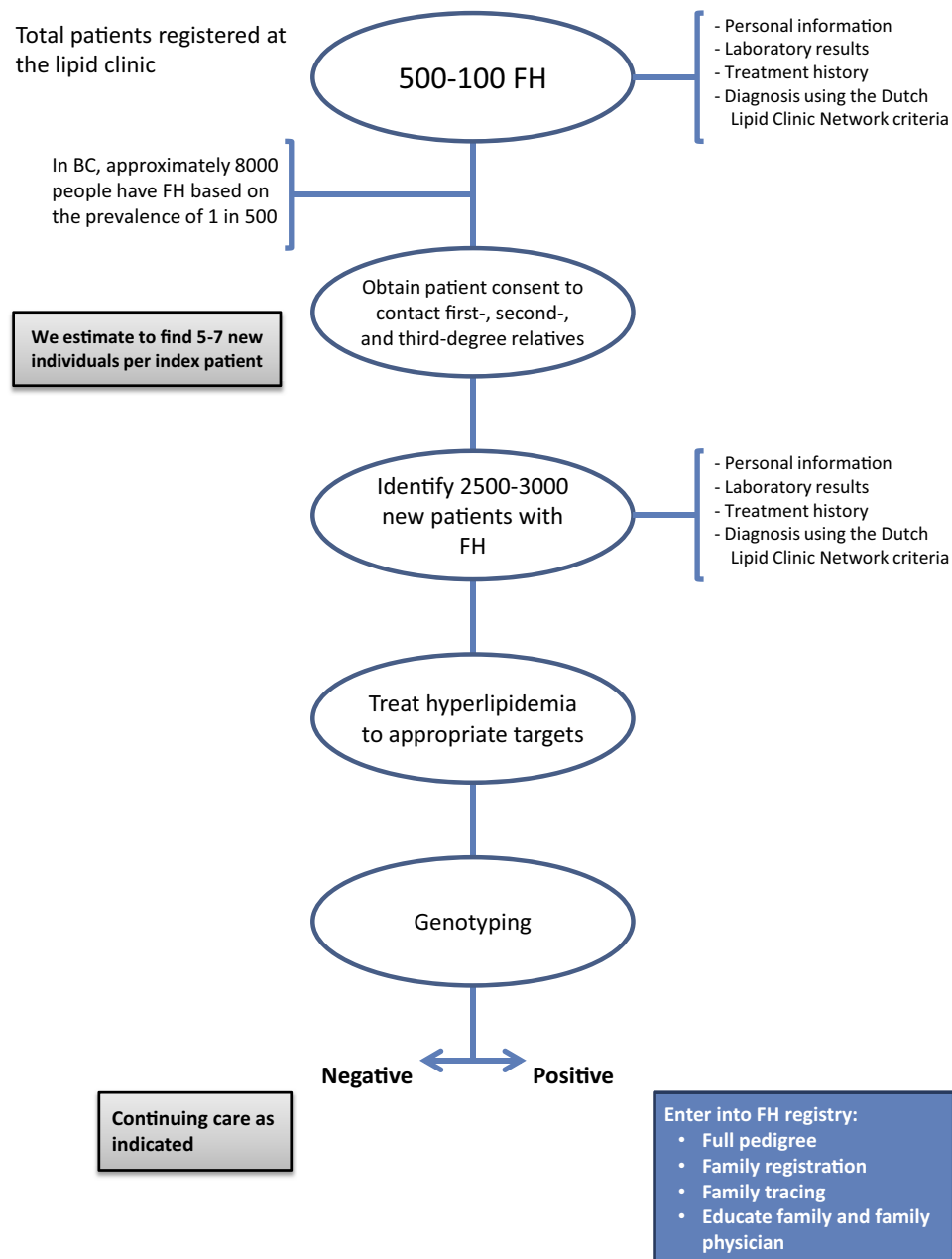


Figure 1. Schematic representation of the required integration of clinical services to provide a familial hypercholesterolemia (FH) patient pathway for the family cascade screening program in British Columbia (BC).

1 quality-adjusted life years is CAD\$21,000.³³ A follow-up study showed 93% adherence to lipid-lowering medications after 1 year and 80% after 2 years, and the participation rate of 98% reflects the acceptance of this program in affected families. The mean age of patients starting treatment is 37 years; thus, intervention is timely. Many patients already taking lipid-lowering medications were undertreated and reached treatment goals only after being identified in the program. In addition to the dramatic decrease in coronary artery disease in the Dutch FH population, there was also a significant decrease in overall morbidity and mortality due to emphasis on healthy lifestyle.³⁴

What Can We Expect in the Future in Canada?

There are currently no programs for screening patients for FH, although a number of Canadian lipid clinics have registries of index patients/families. In the majority of clinics, diagnosis is based on the Dutch criteria (Table 1). This type of screening also identifies more severe cases of familial combined hyperlipidemia, which could also be beneficial in the management of these individuals. Figure 1 summarizes a proposed pathway for cascade screening in British Columbia that could be used in other provinces. In implementing an FH registry in British Columbia, we will first identify index patients attending lipid clinics. We expect to identify approximately 500-1000 index cases using the Dutch Lipid Clinic Network criteria³² and approximately 5-7 FH individuals per each index patient. Finally, we are going to genotype all patients who have been identified. While the genotyping is necessary to confirm the diagnosis, even without it the fact that patients with severe hypercholesterolemia will be identified and treated is of benefit. If the result is positive, the patients will be informed and the family will be included in the registry.

Challenges

First, the ethical issues of contacting relatives of the index patients: although there are valid ethical questions about contacting relatives, experience in The Netherlands and elsewhere shows that 98% of index patients and their relatives were very positive about the screening and cooperated in these studies. It has been agreed that the best approach is for the investigators to contact both the index patients and their relatives.^{22,35}

Second, it may be more difficult in Canada than in The Netherlands to contact family members because of much lower population density. However, more than 80% of Canadians live in urban areas, so this should not be a major concern.

Third, there are concerns about increasing insurance premiums in newly-diagnosed patients. This has not happened in countries that presently have FH registries.^{36,37} Insurance companies appreciate the advantages of early diagnosis and effective treatment of participants.

Fourth, age at which to start treatment: though identification of FH results in a more effective treatment, some controversies exist about the age at which drug treatment should begin. The consensus is that family history is the best guide to treatment initiation timing.

Finally, in The Netherlands, Wales, and other jurisdictions, the FH registries were funded by the government. Because of the economic advantages of early diagnosis and treatment, we suggest that the best approach in Canada would be to establish a national advisory committee and lobby the federal government for funding of a standardized

clinical program for FH. Another advantage of a national program is the ability to register family members living in different parts of the country.

Conclusion

FH is associated with premature cardiovascular mortality and morbidity that is preventable by early diagnosis and treatment. Based on experience in other countries, establishing an FH registry will benefit individuals with FH and is highly cost-effective. In addition, appropriate training and education for health care professionals will ensure that delivery of services will continue to improve. So, why not in Canada?

Disclosures

The authors have no conflicts of interest to disclose.

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