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ORIGINAL RESEARCH

CARDIOMETABOLIC

Homozygous Familial Hypercholesterolemia in Canada

An Observational Study

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ABSTRACT

BACKGROUND Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease characterized by very high levels of low-density lipoprotein cholesterol (LDL-C). Untreated patients present with extensive xanthomas and premature atherosclerosis. Lipid-lowering therapy is highly efficacious and has dramatically increased life expectancy of patients with HoFH.

OBJECTIVES The aim of the study was to obtain a comprehensive registry of HoFH in Canada, known to have several founder effect regions, and describe the clinical characteristics and cardiovascular outcomes of this population over time.

METHODS Clinical and genetic data on patients with HoFH were collected via a standardized questionnaire sent to academic sites participating in the Familial Hypercholesterolemia Canada network.

RESULTS A total of 48 patients with HoFH were enrolled. The median age at diagnosis was 12 years (interquartile range [IQR]: 5-24) and untreated LDL-C levels were 15.0 mmol/L (IQR: 10.5-18.6 mmol/L; 580 mg/dL IQR: 404-717 mg/dL). At last follow-up visit, median age was 40 years (IQR: 26-54 years). Treated LDL-C levels were 6.75 mmol/L (IQR: 4.73-9.51 mmol/L; 261 mg/dL IQR: 183-368 mg/dL) with 95.5% of patients on statins, 88.6% on ezetimibe, 34.1% on proprotein convertase subtilisin/kexin type 9 inhibitors, 27.3% on lomitapide, 13.6% on evinacumab, and 56.8% were treated with low-density lipoprotein apheresis or plasmapheresis. Deaths were reported in 7 (14.5%) and major adverse cardiovascular events were observed in 14.6% of patients with the average onset at 30 years (IQR: 20-36 years). Aortic stenosis was reported in one-half the patients (47.9%) and 10 (20.8%) underwent aortic valve replacement.

CONCLUSIONS This HoFH patient registry in Canada will provide important new health-related knowledge about the phenotypic manifestations and determinants of cardiovascular risk in this population, allowing for closer examination of quality of life and burden to the health care system. (JACC Adv 2023;2:100309) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

APOB = apolipoprotein B

ASCVD = atherosclerotic cardiovascular disease

CABG = coronary artery bypass grafting

FH = familial hypercholesterolemia

HeFH = heterozygous familial hypercholesterolemia

HoFH = homozygous Familial Hypercholesterolemia

IQR = interquartile range

LDL = low-density lipoprotein

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

LLT = lipid-lowering therapy

MACE = major adverse cardiovascular event

PCI = percutaneous coronary intervention

PCSK9 = proprotein convertase subtilisin/kexin type 9

Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal semi-dominant disorder resulting from bi-allelic pathogenic variants of the low-density lipoprotein receptor gene (*LDLR*) gene involved in the receptor-mediated endocytosis of low-density lipoprotein (LDL) particles. HoFH has a genetic probability of 1 in approximately 386,000, and the rare diseases inventory Orphanet estimates its worldwide prevalence at 1 in 1,000,000 individuals.[1] In Canada, this would predict an estimated 38 to 100 cases, based on the current population of 38,000,000. The province of Quebec has a higher burden of HoFH due to at least 2 founder effects.[2] The demographics of genetic disorders like HoFH have changed considerably in the past few decades, as immigration constitutes a major determinant of population growth and source of new pathogenic variants.

The disease is characterized by markedly high circulating levels of low-density lipoprotein cholesterol (LDL-C), and patients often present in childhood with cutaneous and tendinous xanthomas, xanthelasmas, and premature atherosclerosis.[3] The diagnosis of HoFH is based on an untreated elevated LDL-C > 13 mmol/L (>500 mg/dL; the 95th percentile for Canadians <20 years being 3.5 mmol/L or 135 mg/dL), the presence of xanthomas, and both parents being affected with heterozygous familial hypercholesterolemia (HeFH).[4] Since the identification of genes involved in familial hypercholesterolemia (FH), namely *LDLR*, apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes, the definition has been extended to include severe hypercholesterolemia and bi-allelic pathogenic variants.

Standard lipid-lowering therapies such as statins, ezetimibe, and PCSK9 inhibitors have proven to be highly efficacious in patients with HeFH and can reduce the risk of atherosclerotic cardiovascular disease (ASCVD) toward background population rates.[5,6] Owing to a lifelong exposure to elevated LDL-C, patients with HoFH are predisposed to a significant increase in risk of ASCVD that can clinically manifest before 20 years of age if left untreated.[7,8] Prior to the introduction of pharmacological treatments such as lomitapide and evinacumab, and extracorporeal LDL filtration techniques, event-free survival beyond the third decade of life was uncommon.[9] Clinical outcomes in patients with HoFH, especially ASCVD events such as myocardial infarctions (MIs) and stroke, are difficult to capture, in part due to the rarity of the disorder and the lack of registry infrastructure focusing on the disease. The Canadian HoFH Registry was created to understand the burden of disease of HoFH, current treatments, outcomes, and cost to society, as well as to provide scientific evidence for advocacy for greater access to specialized therapies. Our aim in the present study was to describe the clinical characteristics and outcomes of a well-defined Canadian HoFH population over time.

Box 1: Criteria for diagnosis of homozygous familial hypercholesterolemia used in the registry. Modified from Cuchel et al.[4]

- Genetic confirmation of 2 pathogenic variants at the low-density lipoprotein receptor gene, apolipoprotein B, or proprotein convertase subtilisin/kexin type 9 gene loci.

OR

- An untreated low-density lipoprotein cholesterol (LDL-C) >13 mmol/L (>500 mg/dL) or treated LDL-C ≥8 mmol/L (>300 mg/dL)[a] together with either:
  - Cutaneous or tendon xanthomas before age 10 years, or
  - Untreated elevated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents.

[a]These LDL-C levels are only approximations, and lower levels do not exclude homozygous familial hypercholesterolemia, especially in children or in treated patients.

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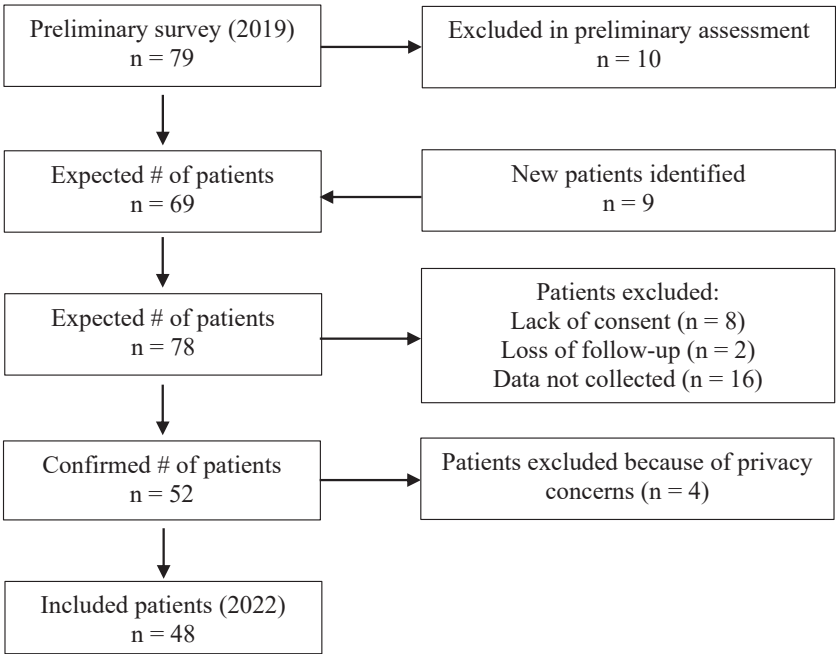
FIGURE 1 Search Strategy of the Canadian HoFH Registry



The homozygous familial hypercholesterolemia registry used an observational study design and was conducted within the framework of the National FH Canada Registry.[11,14] A total of 78 patients with homozygous familial hypercholesterolemia was expected. Patients were excluded based on preliminary assessments of their diagnosis. The inclusion of additional patients not captured in the original survey is also shown. Data were collected on 48 patients. HoFH = homozygous familial hypercholesterolemia.

TABLE 1 Demographic, Clinical, and Lipid Characteristics in Patients With Homozygous Familial Hypercholesterolemia (N = 48)

Sex	
Male	21 (43.8)
Female	27 (56.2)
At time of diagnosis	
Age, y	12 (5.0-24.0)
Xanthomas	39 (81.3)
Corneal arcus	12 (25.0)
Untreated lipids	
TC (mmol/L)	17.1 (12.3-21.0)
TC (mg/dL)	659 (474-812)
LDL-C (mmol/L)	15.0 (10.5-18.6)
LDL-C (mg/dL)	580 (404-717)
HDL-C (mmol/L)	0.90 (0.70-1.20)
HDL-C (mg/dL)	35 (27-46)
TG (mmol/L)	1.38 (0.98-2.51)
TG (mg/dL)	122 (87-222)
Lp(a) (mg/dL)[a]	2.94 (0.85-7.03)

Continued in the next column

TABLE 1 Continued

At last follow-up visit	
Age, y	40 (25.5-53.8)
Body mass index, kg/m^2	25.5 (22.4-31.0)
Diabetes	3 (6.3)
Hypertension	12 (25.0)
Current smoker	6 (12.5)
Previous smoker	12 (25.0)
Deceased	7 (14.6)
Double or compound heterozygote	18 (37.5)
Most recent lipids	
TC (mmol/L)	8.48 (5.98-11.23)
TC (mg/dL)	328 (231-434)
LDL-C (mmol/L)	6.75 (4.73-9.51)
LDL-C (mg/dL)	261 (183-368)
Lowest lipid levels achieved	
TC (mmol/L)	4.81 (3.52-6.76)
TC (mg/dL)	186 (136-261)
LDL-C (mmol/L)	3.40 (2.30-5.41)
LDL-C (mg/dL)	131 (89-209)

Values are n (%) or median (IQR). [a]Data available in n = 14.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); TC = total cholesterol; TG = triglycerides.

CENTRAL ILLUSTRATION **Main Findings From the Canadian HoFH Registry**

The Canadian Homozygous Familial Hypercholesterolemia Registry

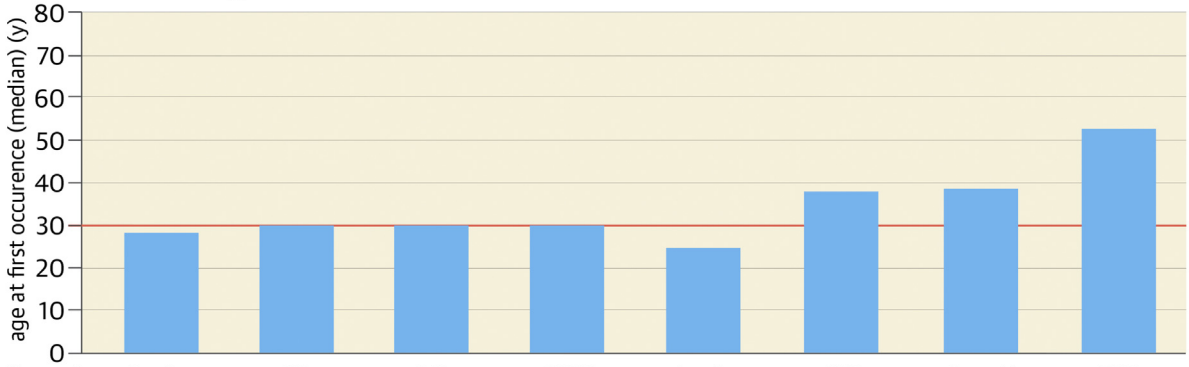
Diagnosis

- n=48
- 43.8% male
- Median age (IQR): 12 (5-24) years
- 81.3% with xanthomas
- Untreated LDL-C: 15.0 (10.5-18.6) mmol/L
  580 (404-717) mg/dL

Last Follow-up Visit

- n=7 deceased (14.6%)
- Median age (IQR): 40 (25.5-53.8) years
- Treated LDL-C: 6.75 (4.73-9.51) mmol/L
  261 (183-368) mg/dL
- 81.8% of patients on 3 or more lipid lowering therapies; including 56.8% on LDL filtration

Age at First Occurence of Adverse Cardiovascular Events



cardiovascular event	Angina pectoris	MI	PCI	CABG	Aortic stenosis	AVR	Carotid stenosis	PAD
N. of patients (%)	12 (25.0%)	7 (14.6%)	10 (20.8%)	21 (43.8%)	23 (47.9%)	10 (20.8%)	14 (29.2%)	4 (25.0%)
Median age (y)	28.0	30.0	30.0	30.0	24.5	37.5	38.5	52.5
Minimum age (y)	12	16	16	8	8	15	17	26
Maximum age (y)	37	53	37	50	79	64	60	60

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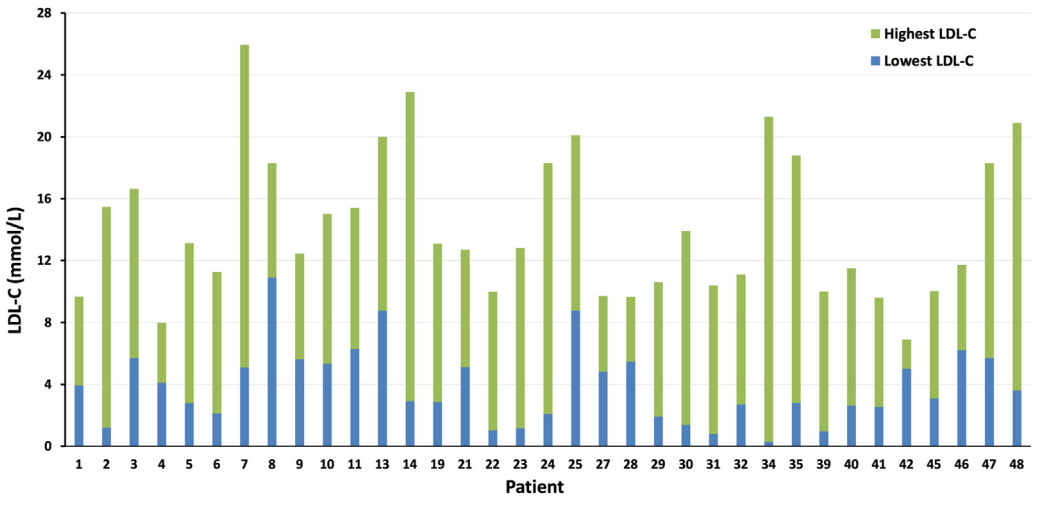
Summary of results from the Canadian registry on homozygous familial hypercholesterolemia patients, conducted within the framework of the National FH Canada Registry[11,14] **(top)**. The histogram shows the age (median) at first occurrence of various adverse cardiovascular events. Data are presented as n (%) or median (IQR). AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

METHODS

DATA COLLECTION. The HoFH registry used an observational study design, and was conducted within the framework of the national FH Canada registry (www.FHCanada.net), which includes 19 academic centers and over 200 clinicians and health care providers across Canada, as well as numerous peripheral sites, in a 'hub and spoke' model.[10,11] The Canadian FH registry scientific protocol was reviewed and accepted by the Research Ethics Board of the McGill University Health Center (protocol no. 13-292 BMD).[11] Patients were eligible for inclusion in the Canadian HoFH registry if they had received a clinical or genetic diagnosis of HoFH by the treating physician. The data collection was started in 2008 and medical charts were retrospectively examined. The date were selected based on the start of this registry[12] and to provide at least 10 years of follow-up on average. Where genetic data were available, patients were considered HoFH if they presented bi-allelic *LDLR*, *APOB*, or *PCSK9* variants (Box 1). Pathogenicity of the genetic variants was assessed using the revised American College of Medical Genetics and

FIGURE 2 Histogram of Highest Observed LDL-C vs Lowest LDL-C Level Achieved for Individual Patients With Available Data



The figure compares the highest low-density lipoprotein cholesterol level to the lowest low-density lipoprotein cholesterol lever ever achieved in each individual patient with available data, and shows that with aggressive multimodal treatment, patients with homozygous familial hypercholesterolemia can reach very low levels of low-density lipoprotein cholesterol. Levels of low-density lipoprotein cholesterol are in mmol/L; please multiply by 38.67 for mg/dL. *Patient 4 underwent a liver transplantation and the highest low-density lipoprotein cholesterol on record was 7.97 mmol/L at age 31 years. **The highest low-density lipoprotein cholesterol recorded for patient 42 was 8.40 mmol/L at 2 years and 8.67 mmol/L at 7 years. LDL-C = low-density lipoprotein cholesterol.

Genomics guidelines.[13] Only patients who were alive and being followed-up in 2008 or after were included in the study in order to accumulate temporal data on patients.[12] All details on the method of data collection, variables collected, and definitions are described in an accompanying paper.[14] Major adverse cardiovascular event (MACE) was defined as a 3-point composite of cardiovascular death, non-fatal MI, and stroke. MACE plus was defined as a composite of cardiovascular death, non-fatal MI, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), angina pectoris, non-fatal ischemic stroke, carotid stenting, carotid endarterectomy, and peripheral artery disease.

STATISTICAL ANALYSIS. Participant demographic, clinical and lipid characteristics, lipid-lowering therapies, and cardiovascular events are presented using standard descriptive statistics, including median (IQR), and frequency with percentage. SPSS Statistics 24 (IBM SPSS) was used for all analyses.

RESULTS

Since 2008, 48 patients across 5 Canadian provinces: Quebec, Ontario, British Columbia, Alberta, and Nova Scotia in whom individual data were available were identified (Figure 1). Patient demographic and clinical characteristics are described in Table 1 and summarized in the Central Illustration. Of the 48 patients, 21 were male (43.8%) and 27 were female (56.2%). The median age of diagnosis was 12 years (IQR: 5.0-24.0 years) and 81.3% showed signs of physical stigmata such as xanthomas at the time of diagnosis. The median age at last follow-up visit was 40 years (IQR: 25.5-53.8 years); the registry included 8 patients aged <18 years old. The prevalence of additional cardiovascular risk factors in this cohort was: diabetes (6.3%); hypertension (25.0%); and previous or current smoking (37.5%). The median untreated LDL-C levels were 15.0 mmol/L (IQR: 10.5-18.6 mmol/L; 580 mg/dL, IQR: 404-717 mg/dL), and most recent LDL-C levels were 6.75 mmol/L (IQR: 4.73-9.51 mmol/L; 261 mg/dL, IQR: 183-368 mg/dL). The lowest LDL-C levels achieved were 3.40 mmol/L (IQR: 2.30-5.41 mmol/L; 131 mg/dL, IQR: 89-209 mg/dL). A comparison of highest LDL-C and the lowest achieved in each patient with available data is illustrated in Figure 2. Median untreated lipoprotein(a) levels were 2.94 mg/dL (IQR: 0.85-7.03 mg/dL).

Genetic confirmation was available in 87.5% of patients, and revealed that 27.1% of patients were compound heterozygotes, primarily for 2 distinct *LDLR* gene variants. One individual with digenic biallelic variants, ie, one each in *LDLR* and *APOB*

TABLE 2 Genetic Pathogenic Variants Identified

Type of FH	Gene	N
Homozygous	*LDLR* gene c.259T>G, p.Trp87Gly	9
Compound heterozygous	*LDLR* gene French-Canadian 1 deletion *LDLR* gene c.259T>G, p.Trp87Gly	6
Homozygous	*LDLR* gene French-Canadian 1 deletion	4
Homozygous	*LDLR* gene c.1775G>A, p.Gly592Glu	2
Homozygous	*LDLR* gene c.2043C>A, p.Cys681Ter	2
Homozygous	*LDLR* gene c.1291G>A, p.Ala431Thr	1
Homozygous	*LDLR* gene c.1061 (−1) G>C, p.?	1
Homozygous	*LDLR* gene c.906C>G, p.Cys302Trp	3
Homozygous	*LDLR* gene c.2054C>T, p.Pro685Leu	1
Homozygous	*LDLR* gene c.1060+2 T>G, p.?	1
Double heterozygous	*LDLR* gene French Canadian 1 deletion *APOB* gene c.10486A>G, p.Thr3496Ala	1
Compound heterozygous	*LDLR* gene c.691T>C, p.Cys231Arg *LDLR* gene c.2015delT, p.Leu672Argfs*37	1
Compound heterozygous	*LDLR* gene c.2215C>T, p.Gln739* Unknown deletion in *LDLR* gene	1
Compound heterozygous	*LDLR* gene c.1186G>A, p.Gly396Ser *LDLR* gene c.16_17insTTCCT, p.Trp6Phefs*202	1
Compound heterozygous	*LDLR* gene genomic change: GRCh37:chr19:11208974_11218285del *LDLR* gene genomic change: GRCh37:chr19:11240163_11244533del	1
Compound heterozygous	*LDLR* gene French Canadian 1 deletion *LDLR* gene c.2000G>A, p.Cys667Tyr	1
Compound heterozygous	*LDLR* gene c.2043C>A, p.Cys681Ter *LDLR* gene c.761A>C, p.Gln254Pro	1
Simple heterozygous	*LDLR* gene c.259T>G, p.(Trp87Gly) Other variant still unknown	3
Compound heterozygous	*LDLR* gene c.1230G>C or T, p.Arg410Ser *LDLR* gene c.1775G>A, p.Gly592Glu	1
Simple heterozygous	*LDLR* gene French Canadian 1 deletion Other variant still unknown	1
No genetic confirmation	-	6

APOB = apolipoprotein B; FH = familial hypercholesterolemia; LDLR = low-density lipoprotein receptor.

genes, was also observed. Four patients from this cohort were family members of an index-patient: 2 sisters were carrying the p.Cys302Trp *LDLR* gene variant, 2 sisters were carrying the p.Gly592Glu *LDLR* gene variant, and a pair of sisters and a pair of brothers were both carrying the p.Trp87Gly *LDLR* French-Canadian variant. More information on genetic variants in this cohort are presented in **Table 2**.

Lipid-lowering therapy (LLT) data at the most recent follow-up visit were available on 44 patients and described in **Table 3**. Of the 44 patients, 42 (95.5%) were on statin therapy; among those, 35 (79.5% of the total) were on high intensity statins, defined as atorvastatin 40 mg or more or rosuvastatin 20 mg or more per day. Ezetimibe was used by 88.6% of patients. More specialized LLT such as PCSK9 inhibitors were used by 34.1% of patients, whereas lomitapide and evinacumab were used less frequently by 27.3% and 13.6% of patients, respectively. Over one-half of patients (56.8%) were undergoing LDL apheresis or plasmapheresis.

Cardiovascular disease data in the population are presented in **Table 4** and summarized in the **Central Illustration**. The median age at which the first MACE occurred was 30 years (IQR: 20.0-35.5 years), with 7 patients (14.6%) having suffered cardiovascular death, non-fatal MI, and/or stroke. The number of patients who qualified as having a MACE plus, which additionally included PCI, CABG, angina pectoris, carotid stenting, carotid endarterectomy, and peripheral artery disease, was 23 (47.9%). There were 7 deaths, 2 of which were known to be due to cardiovascular causes, although the immediate cause of death was not available on all patients.

Of the 48 patients, 7 (14.6%) experienced 1 or more MIs; 12 (25.0%) experienced angina pectoris; 21 (43.8%) underwent 1 or more CABG procedures; and 10 (20.8%) underwent 1 or more PCI procedures. The median age at the first event or onset was 30 years for MI (IQR: 20.0-35.5 years); 28 years for angina pectoris (IQR: 19.3-34.5 years); 30 years for CABG (IQR: 21.0-40.0 years); and 30 years for PCI (IQR: 28.0-36.8 years).

Mild or severe aortic stenosis was reported in 23 patients (47.9%) and 10 (20.8%) had undergone an aortic valve replacement. The median age patients underwent their first aortic valve replacement was 38 years (IQR: 23.8-52.5 years).

Survival age of these patients, including age of death when appropriate, is illustrated in **Figure 3**. Time to first and subsequent MACE and MACE plus for individual patients is also shown in **Figures 4A to 4F**. Patients in the latter figures are separated according to the molecular basis of HoFH, as described.

DISCUSSION

This study reports the clinical characteristics and outcomes on the largest cohort of Canadian patients with HoFH to date. Assuming a prevalence of HoFH between 1 in 386,000 and 1 in 1 million, and a population of 38 million, approximately 38 to 100 cases are expected in Canada. As such, our study population is expected to reflect a substantial proportion, if not a majority of all patients with HoFH in Canada. However, our screening process highlights a continued need for increased identification and genetic testing for HoFH in Canada, as well as a larger registry infrastructure to capture these patients.

Our findings show that patients with HoFH in Canada present with significantly higher LDL-C levels and severe manifestations of cardiovascular disease much earlier in life than in non-FH

TABLE 3 Lipid-Lowering Therapy at Last Follow-up Visit (N = 44)[a]

Any statin	42 (95.5)
High-intensity statin	35 (79.5)
Ezetimibe	39 (88.6)
PCSK9 inhibitors	15 (34.1)
Lomitapide	12 (27.3)
Evinacumab	6 (13.6)
LDL apheresis or plasmapheresis	25 (56.8)
On 1 LLT	2 (4.5)
On 2 LLT	5 (11.4)
On 3 LLT	13 (29.5)
On 4 LLT	19 (43.2)
On 5 LLT	4 (9.1)

Values are n (%). LLT can include LDL apheresis or plasmapheresis. Detailed LLT description at last follow-up visit was not available in 4 patients; proportion in each LLT category is calculated on a total group of patients with available data (n = 44). [a]At last follow-up visit, 1 patient was pregnant and not taking any LLT.

LDL = low-density lipoproteins; LLT = Lipid-lowering treatment; PCSK9 = proprotein convertase subtilisin/kexin type 9.

TABLE 4 Cardiovascular Events in Patients With Homozygous Familial Hypercholesterolemia (N = 48)

Cardiovascular death	2 (4.17)
Unknown or non-cardiovascular death	5 (10.4)
Myocardial infarction (MI)	7 (14.6)
Age at first MI, y	30 (20.0-35.5)
Angina pectoris (AP)	12 (25.0)
Age at AP onset, y	28 (19.3-34.5)
Coronary artery bypass grafting (CABG) (1 or more)	21 (43.8)
Age at first CABG, y	30 (21.0-40.0)
Percutaneous coronary intervention (PCI) (1 or more)	10 (20.8)
Age at first PCI, y	30 (28.0-36.8)
Aortic stenosis (AS)	23 (47.9)
Aortic valve replacement (AVR)	10 (20.8)
Age at first AVR, y	38 (23.8-52.5)
MACE[a]	7 (14.6)
Age at first MACE, y	30 (20.0-35.5)
MACE plus[b]	23 (47.9)
Age at first MACE plus, y	23 (18.8-34.5)

Values are n (%) or median (IQR). [a]MACE is a 3-point composite of cardiovascular death, non-fatal myocardial infarction, and stroke. [b]MACE plus is a composite of cardiovascular death, non-fatal myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting, angina pectoris, non-fatal ischemic stroke, carotid stenting, carotid endarterectomy, and peripheral artery disease.

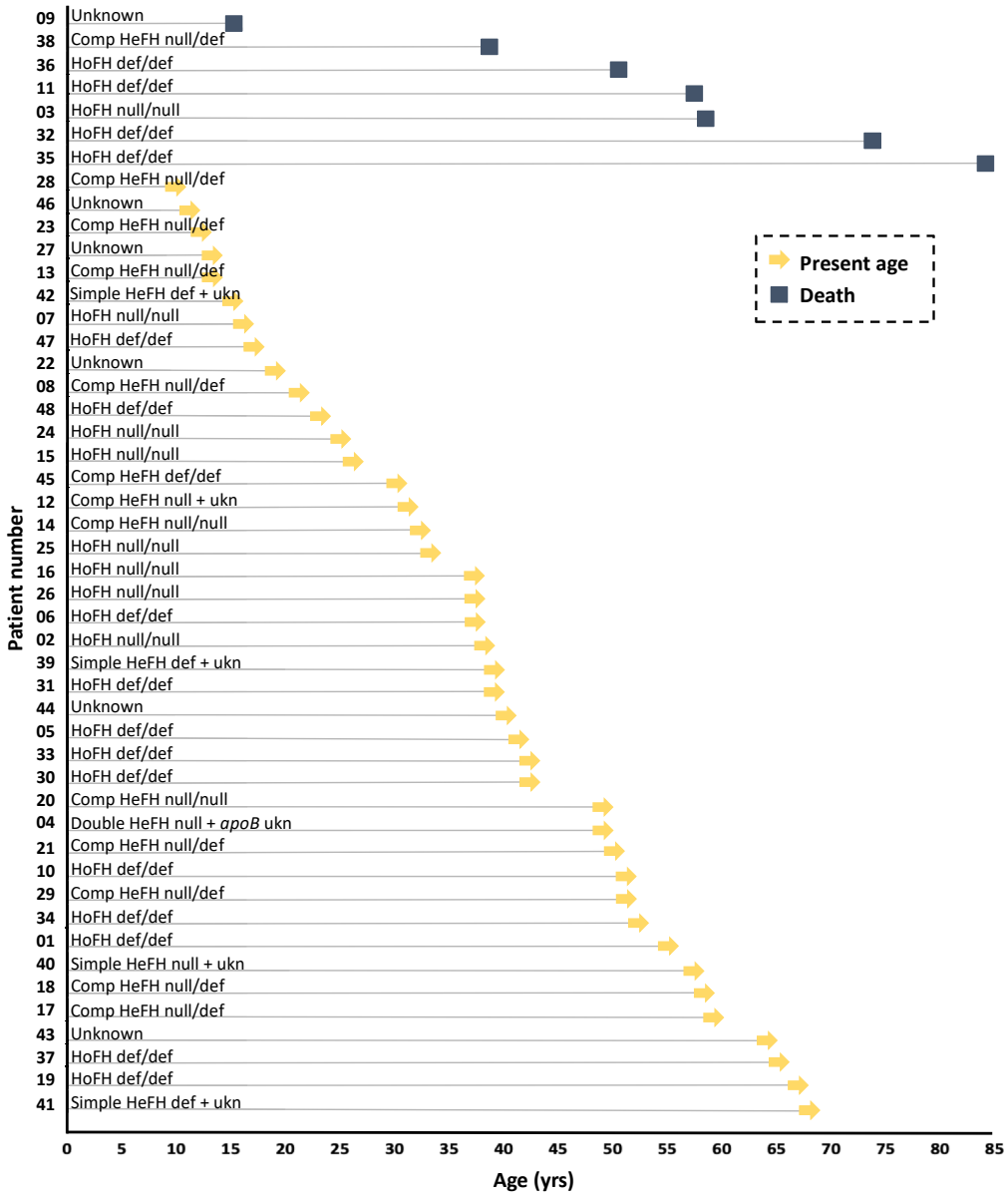
MACE = major adverse cardiovascular event.

populations, even with early diagnosis and access to standard and novel treatments. Despite widespread use of combined LLT in these patients, the median of most recent LDL-C levels was 6.75 mmol/L (261 mg/dL), and the median lowest LDL-C achieved was 3.40 mmol/L (131 mg/dL), both of which remain well above the guideline recommendations of 2.5 mmol/L in primary prevention for HeFH, and highlight the challenges of controlling lipid levels in this patient population.[15] However, several patients exhibited untreated LDL-C values below 10.0 mmol/L (387 mg/dL), and could reach treated LDL-C levels as low as 1.00 mmol/L (39 mg/dL). These exemplify how milder cases, such as certain defective HoFH mutations, can manifest quite differently and mimic heterozygous cases. Our group has previously published the detailed clinical course of 2 of the patients with HoFH included in the present registry.[16,17] Despite a rigorous follow-up and access to several therapeutic options, a lifelong burden of elevated LDL-C in these patients still contributes to severe complications of HoFH such as accelerated atherosclerosis and frequent intervention (**Figures 4A to 4F**). These observations underscore a need for earlier identification and more effective therapies.

Survival in patients from this Canadian registry is comparable with past studies on patients with HoFH. In 2011, Raal et al[17] reported a survival probability of 50% by age 40 in patients with HoFH on LLT. This is a marked improvement from the pre-statin era, as the efficacy of statins has doubled the survival age for HoFH.[5] With the development of new standard treatments for HoFH such as PCSK9 inhibitors, lomitapide, and evinacumab, our data suggest that survival in these patients is as good as or better than Raal's predicted survival.[17] LDL apheresis, a non-invasive procedure that removes LDL from the blood, is considered the standard of care for adults and children with HoFH and significantly lowers LDL-C, but access is not yet universal and is severely limited in Canada.[18-21] Only approximately one-half of the patients in this study were treated with LDL apheresis or plasmapheresis. Similarly, access to evinacumab, through a compassionate drug use program, is still challenging in Canada and varies across provinces. As for lomitapide, we have shown previously that although its use significantly reduced LDL-C in a subgroup of Canadian patients with HoFH, its adherence was limited by gastrointestinal side effects and elevated liver enzymes.[22] Improvements in the treatment of HoFH have been made in the past (PCSK9 inhibitors, lomitapide), but there is still a need for interventions to facilitate greater access to these treatments.

The present data also show an overrepresentation of CABG and aortic valve replacement in this cohort, with 43.8% having undergone at least 1 CABG at a mean age of 30 years, and 20.8% having undergone aortic valve replacement at a median age

FIGURE 3 Survival Age of HoFH Registry Patients



The figure illustrates the actual age of the individual patients **(yellow arrow)**, including age of death **(dark blue square)** when appropriate. Individual patient genotype is shown on each line. APOB = apolipoprotein B; Comp = compound; def = defective; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; Ukn = unknown.

of 38 years. Compared to global studies on HoFH outcomes, our data suggest that aortic stenosis is especially prevalent in the Canadian HoFH cohort, having been observed in 47.9% of patients, and the median age of Canadian patients receiving an aortic valve replacement is also later in life.[23] Historically, supravalvular aortic stenosis was the most commonly observed form of aortic calcification in patients with HoFH.[24] The introduction of multimodal lipid-lowering therapies has caused a shift in pathology and has made valvular aortic stenosis the dominant manifestation of the disease.[25-27] Further echocardiographic assessment in these patients is warranted.

FIGURE 4 Time to First and Subsequent MACE and MACE Plus Events

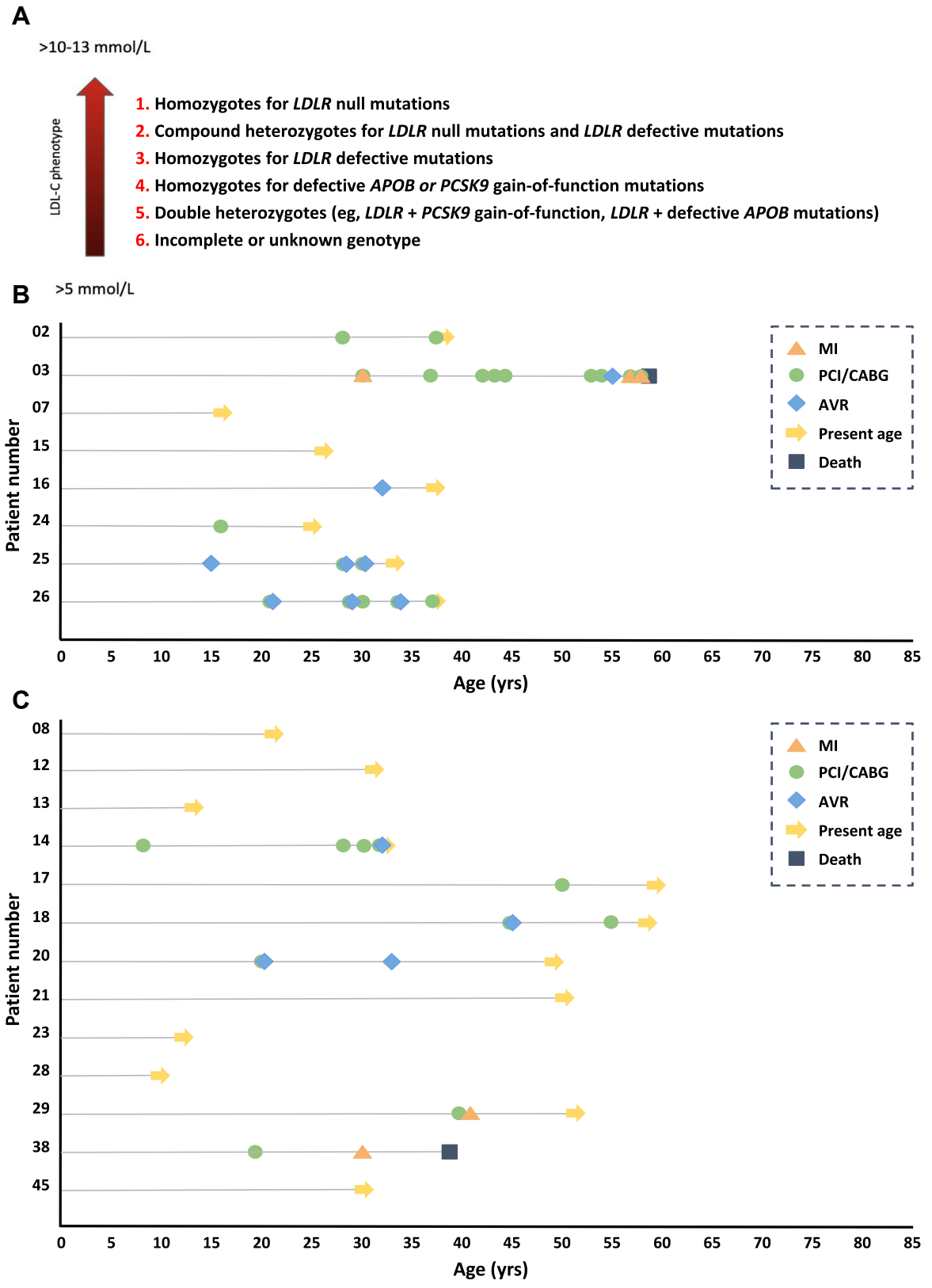


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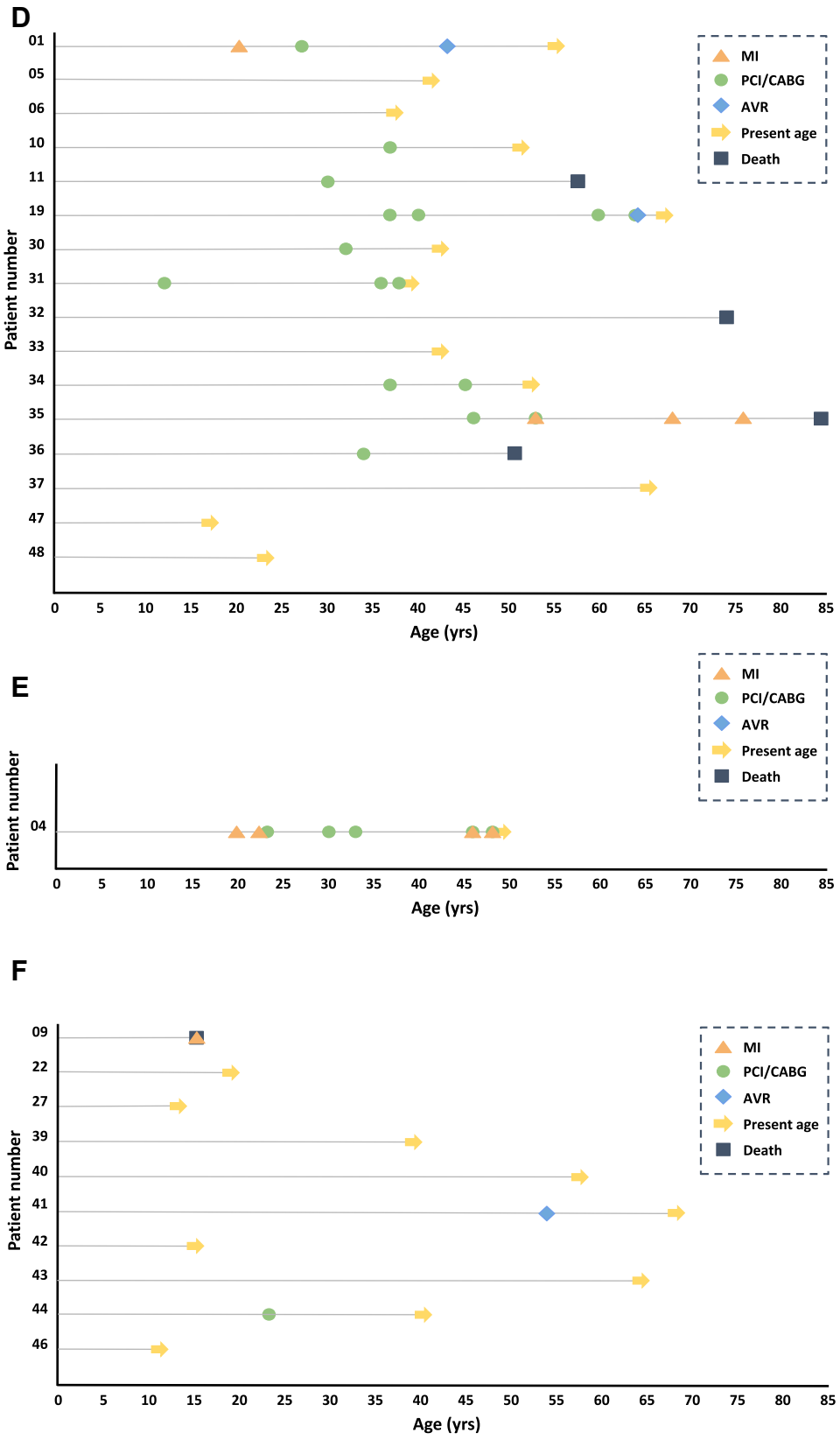
FIGURE 4 Continued



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STUDY LIMITATIONS. The limitations of this study merit discussion. Patients enrolled in this registry were managed through a network of academic medical centers and specialist clinics and may not capture less severe HoFH cases managed outside of academic centers by general physicians, or cases which are not seen in clinical practice. In fact, cascade screening of family members (direct or reverse) is mainly performed in specialized lipid clinics. At least 4 additional patients from pediatric centers were not included because of privacy concerns. Many provinces remain underrepresented in this registry as well, a reflection of the differing provincial regulations and provincial differences in levels of access to specialists and treatments. Quebec, a province with historic founder effects for FH, was largely overrepresented in the registry, likely due to its larger infrastructure for FH cascade screening and specialized treatment. Outcomes in Quebec thus may influence overall outcomes when performing an analysis on all Canadian patients. These limitations point to a need for more information on and more advocacy for the disorder, to better understand the burden of HoFH in all parts of Canada. The study design also has limitations: as it is an observational study and included only patients alive in 2008 or later, survival bias of patients with less severe phenotypes is possible. Retrospective data collection also reduced granularity of the data and introduced missing values, as data were collected by different institutions. Other potential treatment options for HoFH or their impact in the analysis such as portacaval shunt surgery or liver transplantation due to their infrequency in the cohort were not considered, which may have an effect on LDL-C and outcomes.[28,29] The long-term impact of very recent therapies, such as evinacumab, which shows promise in HoFH patients, remains to be examined in depth.[30]

CONCLUSIONS

This study highlights the contemporary outcomes of patients with HoFH in Canada. Although survival and treatment for these patients have improved markedly in the last few decades, HoFH is still an underdiagnosed and severe disease. A need persists for more strategies for timely diagnosis and more education on the disease, such as cascade screening at an early age, and more focus on pediatric diagnosis and treatment of HoFH in the form of better access to LDL apheresis and specialized care. Further characterization of phenotypic risks such as aortic stenosis, or social aspects of the disease such as quality of life and burden of disease will be generated by this registry and used to guide decisions for orphan drug treatment and LDL apheresis access in Canada. A major outcome of the establishment of the Canadian HoFH registry is its role as a platform that facilitates collaborative research across Canada and internationally, that will more comprehensively examine the effects of novel therapies and their roles in modifying the clinical course.

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FIGURE 4 Continued

A myocardial infarction event is indicated by a yellow triangle, a percutaneous coronary intervention or coronary artery bypass grafting event is indicated by a **green circle**, an aortic valve replacement is indicated as a **blue diamond**, present age of individual patients is indicated by a **yellow arrow** and death is shown as a **dark blue square**. **(A)** Homozygous familial hypercholesterolemia mutation severity according to low-density lipoprotein cholesterol phenotype. Adapted from Santos et al 2016.[31] Patients in the latter figures are separated according to the molecular basis of homozygous familial hypercholesterolemia, as described: **(B)** clinical course of patients homozygous for low-density lipoprotein receptor null mutations (Category 1, A); **(C)** clinical course of patients compound heterozygous for low-density lipoprotein receptor null mutations and low-density lipoprotein receptor defective mutations (Category 2, A); **(D)** clinical course of patients homozygous for low-density lipoprotein receptor defective mutations (Category 3, A); **(E)** clinical course of double heterozygous patients (Category 5, A); **(F)** clinical course of patients with an incomplete or unknown genotype (Category 6, A). APOB = apolipoprotein B; AVR = Aortic valve replacement; CABG = coronary artery bypass grafting; LDLR = low-density lipoprotein receptor; MI = myocardial infarction; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: HoFH still carries a very high morbidity and mortality, and early initiation of novel therapies may be lifesaving.

COMPETENCY IN MEDICAL KNOWLEDGE: HoFH is an orphan disease. Early identification and aggressive treatment have been shown to decrease early morbidity and mortality and to increase event-free survival.

COMPETENCY IN PRACTICE-BASED LEARNING AND IMPROVEMENT: Physicians need to be aware of the genetic basis of HoFH and to refer patients to specialized clinics.

COMPETENCY IN SYSTEMS-BASED PRACTICE: National registries have shown that they can unite caregivers to provide earlier diagnosis and care.

TRANSLATIONAL OUTLOOK 1: Survival of patients with HoFH has double in the past 3 decades. Novel therapies including modulation of PCSK9 inhibition, lomitapide, ANGPTL3, and extracorporeal LDL filtration techniques can markedly improve survival.

TRANSLATIONAL OUTLOOK 2: Reverse cascade screening can help identify patients with HeFH, initiate therapy and change outcomes.

REFERENCES

1. Consortium O. *Orphanet report series: prevalence, incidence or reported number of published cases listed in alphabetical order of disease*. 2022. Accessed September 7, 2022. https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

2. Moorjani S, Roy M, Gagne C, et al. Homozygous familial hypercholesterolemia among French Canadians in Quebec Province. *Arteriosclerosis*. 1989;9(2):211-216.

3. Alves AC, Alonso R, Diaz-Diaz JL, et al. Phenotypical, clinical, and molecular aspects of adults and children with homozygous familial hypercholesterolemia in iberoamerica. *Arterioscler Thromb Vasc Biol*. 2020;40(10):2508-2515.

4. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35(32):2146-2157.

5. Belanger AM, Akioyamen L, Alothman L, Genest J. Evidence for improved survival with treatment of homozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2020;31(4):176-181.

6. Thompson GR, Seed M, Naoumova RP, et al. Improved cardiovascular outcomes following temporal advances in lipid-lowering therapy in a genetically-characterised cohort of familial hypercholesterolaemia homozygotes. *Atherosclerosis*. 2015;243(1):328-333.

7. Allen JM, Thompson GR, Myant NB, Steiner R, Oakley CM. Cadiovascular complications of homozygous familial hypercholesterolaemia. *Br Heart J*. 1980;44(4):361-368.

8. Al-Shaikh AM, Abdullah MH, Barclay A, Cullen-Dean G, McCrindle BW. Impact of the characteristics of patients and their clinical management on outcomes in children with homozygous familial hypercholesterolemia. *Cardiol Young*. 2002;12(2):105-112.

9. Kolansky DM, Cuchel M, Clark BJ, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. *Am J Cardiol*. 2008;102(11):1438-1443.

10. Brunham LR, Ruel I, Aljenedil S, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia: update 2018. *Can J Cardiol*. 2018;34(12):1553-1563.

11. Brunham LR, Ruel I, Khoury E, et al. Familial hypercholesterolemia in Canada: initial results from the FH Canada National Registry. *Atherosclerosis*. 2018;277:419-424.

12. Awan Z, Alrasadi K, Francis GA, et al. Vascular calcifications in homozygote familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2008;28(4):777-785.

13. Chora JR, Medeiros AM, Alves AC, Bourbon M. Analysis of publicly available LDLR, APOB, and PCSK9 variants associated with familial hypercholesterolemia: application of ACMG guidelines and implications for familial hypercholesterolemia diagnosis. *Genet Med*. 2018;20(6):591-598.

14. Brown L, Ruel I, Baass A et al Design, rationale and preliminary results of the Canadian homozygous familial hypercholesterolemia - HoFH registry (2008 - 2022 update). *Can J Health Tech*. Published online February 10, 2023. https://doi.org/10.51731/cjht.2023.572

15. Thompson GR, Blom DJ, Marais AD, Seed M, Pilcher GJ, Raal FJ. Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. *Eur Heart J*. 2018;39(14):1162-1168.

16. Banerjee A, Alothman L, Couture P, et al. The lifelong burden of homozygous familial hypercholesterolemia. *Can J Cardiol*. 2019;35(10):1419.e1-1419.e4.

17. Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation*. 2011;124(20):2202-2207.

18. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483-492.

19. Palcoux JB, Atassi-Dumont M, Lefevre P, et al. Low-density lipoprotein apheresis in children with familial hypercholesterolemia: follow-up to 21 years. *Ther Apher Dial*. 2008;12(3):195-201.

20. Keller C. LDL-apheresis in homozygous LDL-receptor-defective familial hypercholesterolemia: the Munich experience. *Atheroscler Suppl*. 2009;10(5):21-26.

21. Filler G, Lee M, Hegele RA. Barriers to the implementation of lipoprotein apheresis in Canada. *Can J Cardiol*. 2017;33(3):409-411.

22. Aljenedil S, Alothman L, Belanger AM, et al. Lomitapide for treatment of homozygous familial hypercholesterolemia: the Quebec experience. *Atherosclerosis*. 2020;310:54-63.

23. Tromp TR, Hartgers ML, Hovingh GK, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *Lancet*. 2022;399(10326):719-728.

24. Ribeiro P, Shapiro LM, Gonzalez A, Thompson GR, Oakley CM. Cross sectional echocardiographic assessment of the aortic root and coronary ostial stenosis in familial hypercholesterolaemia. *Br Heart J*. 1983;50(5):432-437.

25. Fahed AC, Shibbani K, Andary RR, et al. Premature valvular heart disease in homozygous familial hypercholesterolemia. *Cholesterol*. 2017;2017:3685265.

26. Rallidis L, Naoumova RP, Thompson GR, Nihoyannopoulos P. Extent and severity of atherosclerotic involvement of the aortic valve and root in familial hypercholesterolaemia. *Heart*. 1998;80(6):583-590.

27. Belanger AM, Akioyamen LE, Ruel I, Hales L, Genest J. Aortic stenosis in homozygous familial hypercholesterolaemia: a paradigm shift over a century. *Eur Heart J*. 2022;43(34):3227-3239.

28. Starzl TE, Chase HP, Ahrens EH Jr, et al. Portacaval shunt in patients with familial hypercholesterolemia. *Ann Surg*. 1983;198(3):273-283.

29. Martinez M, Brodlie S, Griesemer A, et al. Effects of liver transplantation on lipids and cardiovascular disease in children with homozygous familial hypercholesterolemia. *Am J Cardiol*. 2016;118(4):504-510.

30. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720.

31. Santos RD, Gidding SS, Hegele RA, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol*. 2016;4(10):850-861.

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