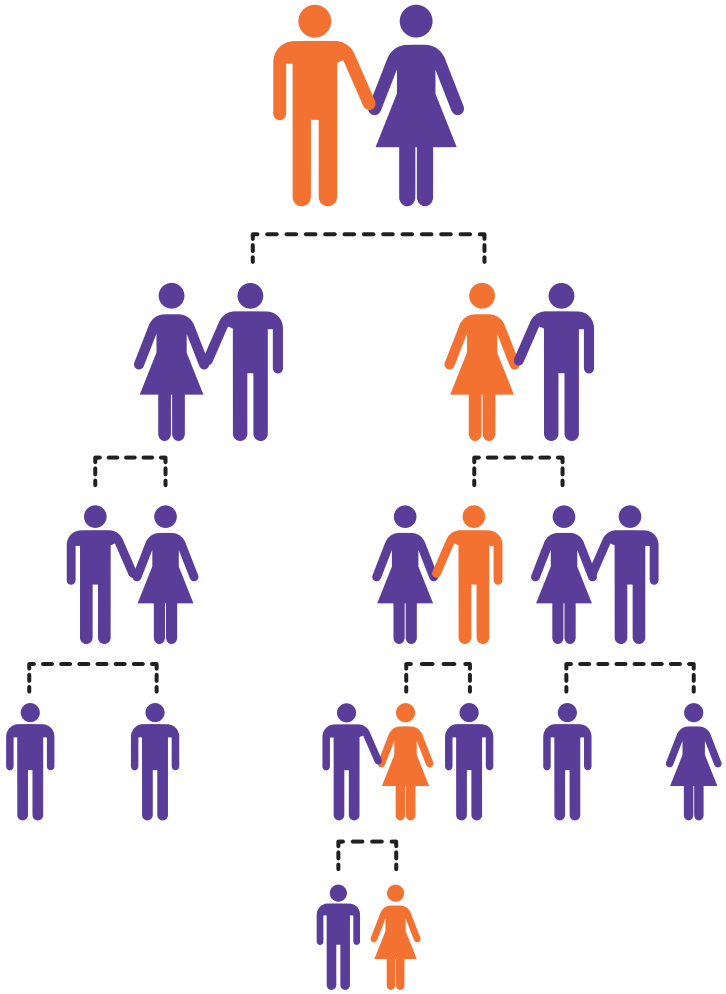
A GUIDE TO
FAMILIAL HYPERCHOLESTEROLEMIA (FH)
FOR HEALTHCARE PROFESSIONALS



Heterozygous familial hypercholesterolemia - example of a family tree

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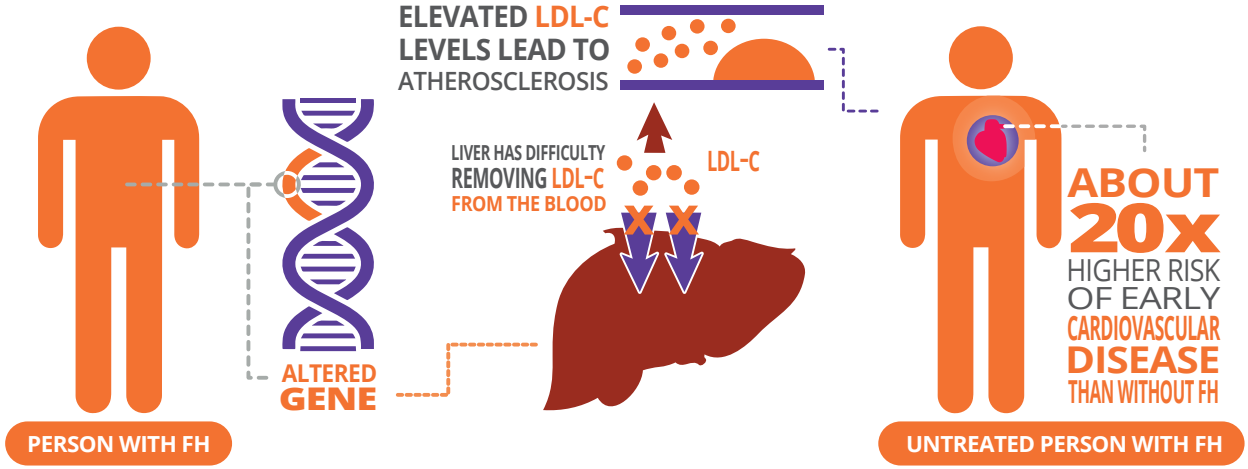
PART 1:
WHAT IS FAMILIAL HYPERCHOLESTEROLEMIA?

Familial hypercholesterolemia (FH) is a common genetic condition characterised by **very high elevations in plasma levels of low-density lipoprotein cholesterol (LDL-C)** and increased risk of premature coronary heart disease (CHD) (Figure 1).[1] The risk of premature CHD may be about 20-fold higher in untreated people with FH compared with individuals without FH.[2]

Figure 1. FH is caused by a mutation in one of a number of genes involved in LDL metabolism, resulting in markedly elevated LDL-C levels, early atherosclerosis and increased risk of premature CHD[1,2]

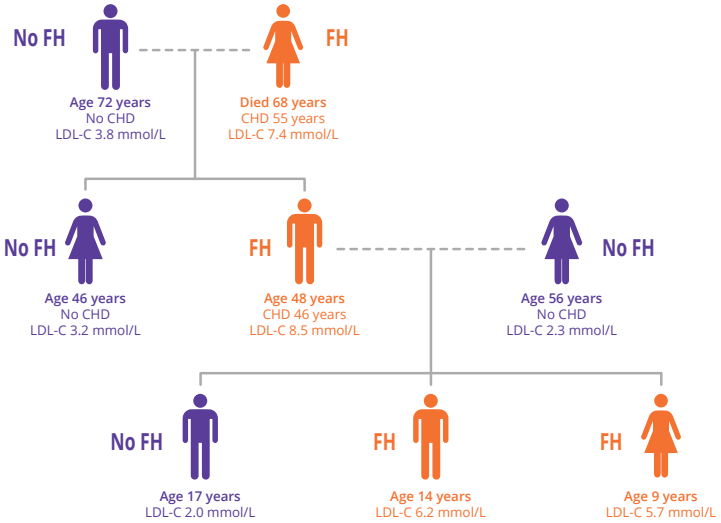


Heterozygous FH

The most common form of FH is heterozygous FH (HeFH), in which patients inherit one abnormal gene (Figure 2).[3] HeFH occurs at a prevalence of approximately **1 in 200** to **1 in 500** people; an estimated **14 to 34 million** individuals worldwide, respectively, are thought to have HeFH.[1] In Canada, it is conservatively estimated that **1 in 500** Canadians is affected by HeFH and that the prevalence in French-Canadians is approximately **1 in 270**.[2] The prevalence of HeFH may be as high as 1 in 50 to 1 in 100 people, for example, in Christian Lebanese Dutch Afrikaner and Ashkenazi Jews where there are relatively isolated populations (founder effect).[3]

Typically, untreated people with HeFH may experience a CHD event, e.g. myocardial infarction (MI) or angina pectoris, before they are aged 55 years for men and before 60 years for women.[1]

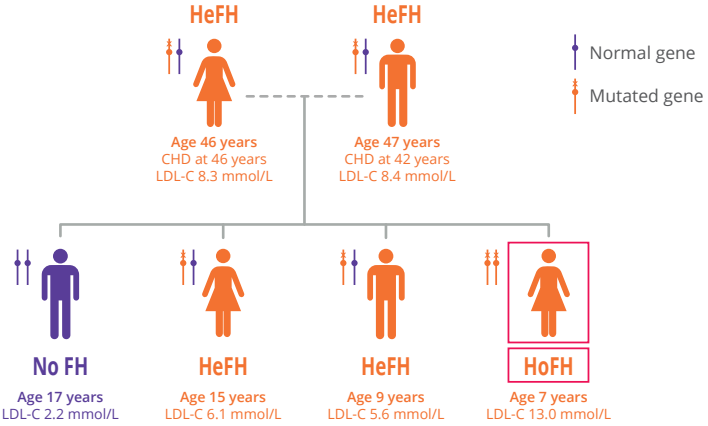
Figure 2. A typical HeFH family tree



Homozygous FH

Homozygous FH (HoFH) results from the **same mutation in both alleles** of the same gene and globally occurs in approximately **1 in 160,000 to 1 in 1,000,000 individuals** (Figure 3).[2,4] Due to extreme hypercholesterolemia and rapidly accelerated atherosclerosis, untreated HoFH patients rarely survive beyond 30 years of age.[4]

Figure 3. A typical HoFH family tree

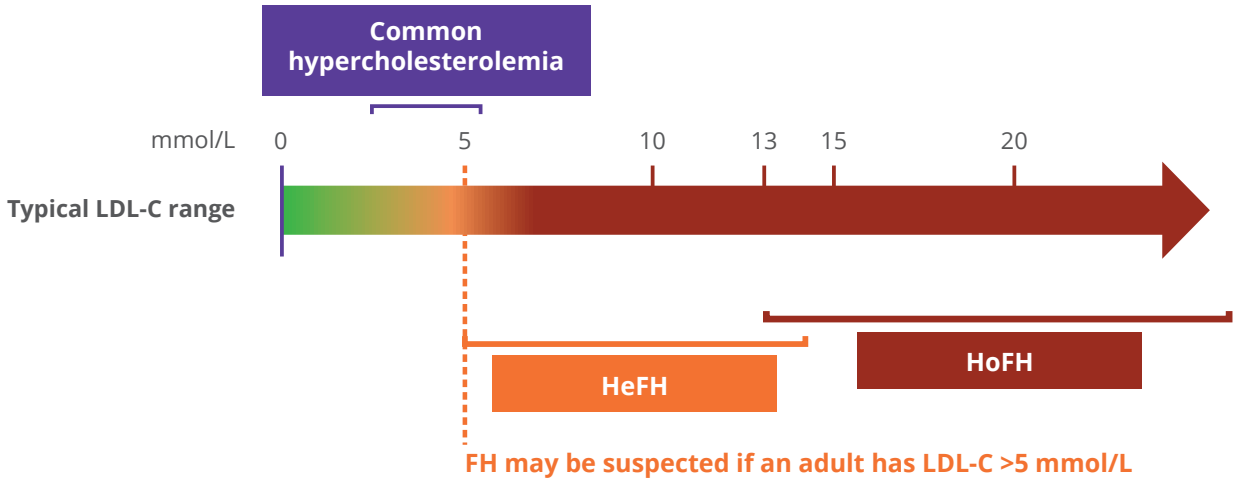


PART 2:
ATHEROSCLEROTIC BURDEN AND CARDIOVASCULAR RISK IN FH

Many people have high LDL-C levels in middle age (common hypercholesterolemia), but patients with **FH have LDL-C levels ~2-fold higher** (typically >5 mmol/L) **from birth** (Figure 4).[1] However, the phenotype of FH can vary and not all cases of FH have high levels of LDL-C at diagnosis.[1]

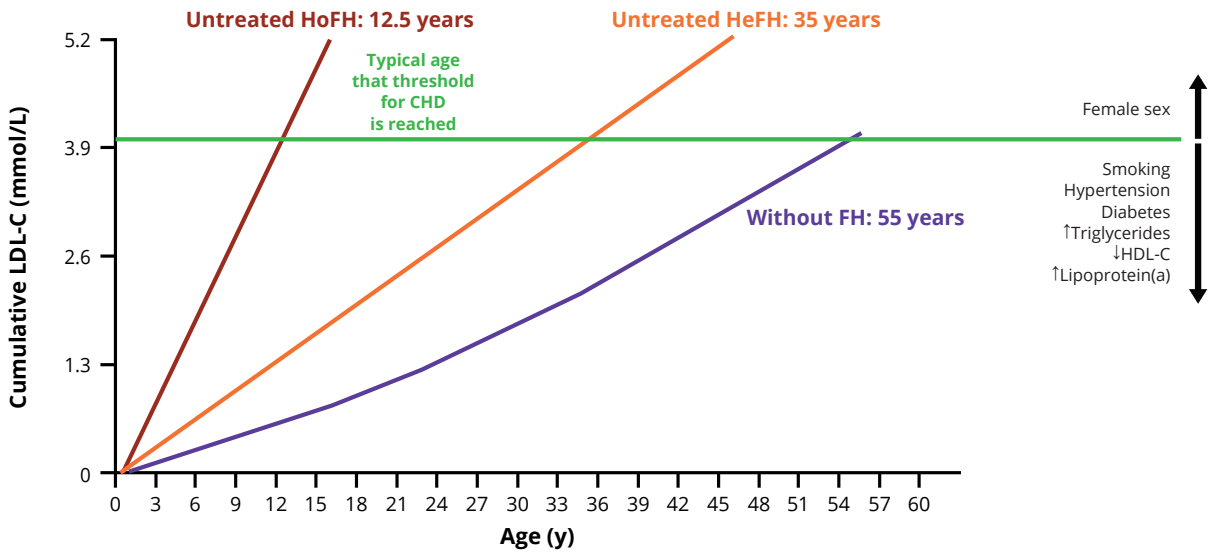
Untreated HoFH is characterized by extreme hypercholesterolemia, with LDL-C levels >13 mmol/L (Figure 4).[4]

Figure 4. Typical LDL-C levels in patients with common hypercholesterolemia, HeFH and HoFH[1]



The lifelong accumulation of LDL-C in FH translates into accelerated atherosclerosis and increased risk of early cardiovascular events – **risk for CHD is approximately 20-fold higher in untreated people with FH** compared with unaffected individuals.[2] It has been estimated that the cumulative LDL-C burden of ~4.1 mmol/L sufficient for CHD to develop at 55 years in people without FH, may occur at 35 years in untreated HeFH and at 12.5 years in HoFH (Figure 5).[1]

Figure 5. An LDL-C burden sufficient to develop CHD is observed at around 12.5 years of age in HoFH and around 35 years in HeFH, compared with 55 years in people without FH (all untreated)[1]



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Not only is LDL-C elevated in FH, but there may also be an increase in the levels of other atherogenic apolipoprotein (apo)-B-containing particles. Lipoprotein(a) **[Lp(a)]** may be particularly **high in HeFH and HoFH**.[1,6] Of note, elevated Lp(a) levels are independently associated with increased CHD in FH.[6] Because **Lp(a) significantly enhances the risk of premature CHD** in those already at very high risk due to FH, there is a **particular need for aggressive LDL-C lowering in people with FH** and high levels of Lp(a).[1]

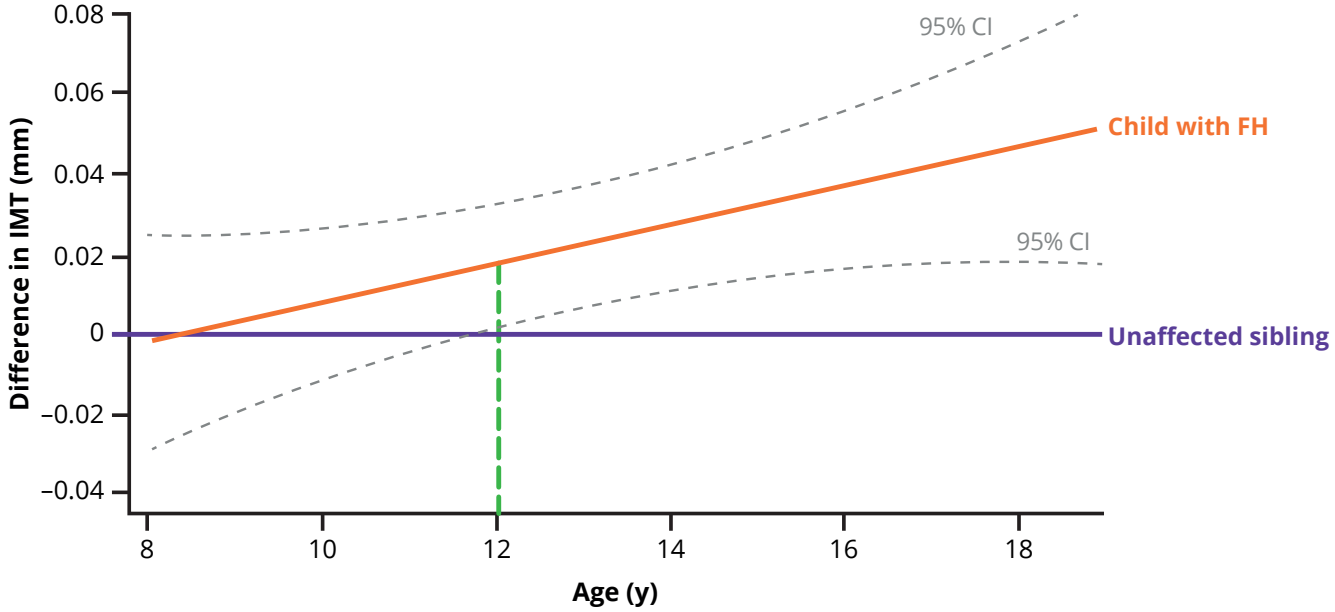
The elevations in atherogenic lipoproteins observed in FH lead to increased CHD due to cholesterol retention in the arterial wall and foam cell formation within the intima of arteries.[1] These early lesions typically progress to occlusive atherosclerosis with angina pectoris and/or plaque rupture with MI. Accelerated atherosclerosis has been demonstrated in the intima of carotid arteries of patients with FH using carotid intima media thickness (IMT) as a surrogate marker.[5*] It was found that a threshold IMT value ~0.8 mm was reached, on average, at age 80 years in untreated non-FH patients, whereas FH subjects reached this value around 40 years.[5]

* Atherosclerosis progression from childhood into seniority in controls and in FH subjects was estimated using cross-sectional standardized IMT measurements in 6 unaffected (n=118) and affected age groups (n=315). Carotid and femoral IMT was measured in all subjects and combined to a per-subject average.

Children with FH have been shown to have significantly higher carotid IMT values than their unaffected siblings by aged 12 years, with at least 5 times more rapid increase in carotid IMT during childhood than unaffected siblings (Figure 6).[9*]

Figure 6. Children with FH have more rapid increase in carotid IMT during childhood than unaffected siblings[6]

Difference in mean carotid IMT and 95% CI between children with FH and unaffected siblings (n=281) plotted against age, taking account of family relations



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* Analysis of carotid wall intima-media thickness (measured with B-mode ultrasound) in 201 children with heterozygous FH and 80 unaffected siblings (both age ranges 8-18 years).

PART 3:
GENETICS OF FH

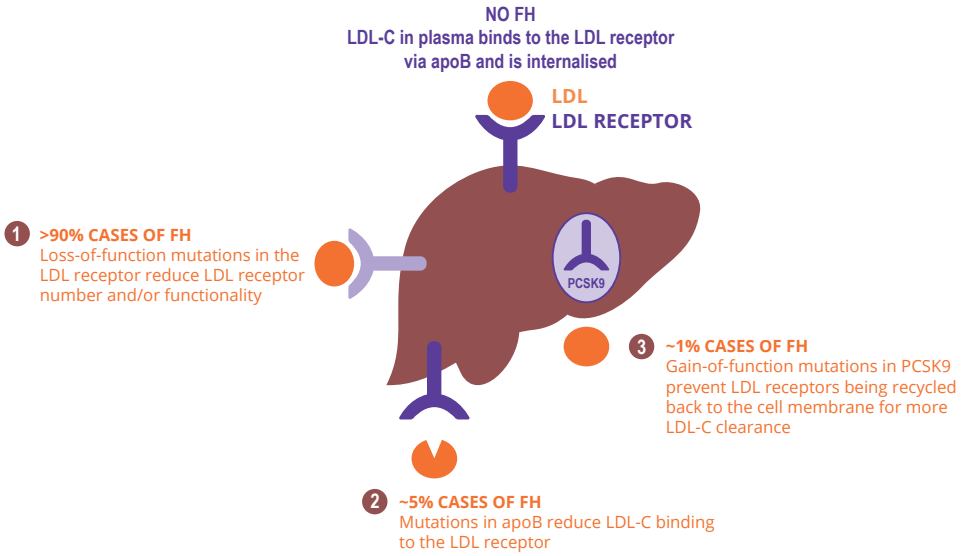
FH is most commonly attributable to mutations resulting in functional reductions in the capacity of LDL receptors to clear LDL from the circulation.[1,3]

Normally, apoB on LDL binds to LDL receptors on the liver cell membrane, the LDL and the LDL receptor are internalized into liver cells by endocytosis and the LDL particle is broken down. LDL receptors are then recycled back to the liver cell surface for more LDL removal. Patients with FH may express little or no LDL receptor activity.

Many people with FH **(>90%)** have a **loss of function mutation in the LDL receptor gene** and there are not sufficient functional LDL receptors (Figure 7).[1,4] More than 1700 mutations in the LDL receptor gene are documented.[7]

Some cases of FH **(~5%)** are associated with a mutation **in the apoB gene** (Figure 7).[1,4] Without functional apoB, LDL does not bind to the LDL receptor effectively. A small proportion of FH cases **(~1%)** are associated with a **gain-of-function mutation in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene; PCSK9 prevents** recycling of LDL receptors back to the cell membrane for more LDL clearance (Figure 7).[1,4]

Figure 7.
Common mutations in FH: 1) reduced LDL receptor number or functionality, 2) reduced binding of LDL to the LDL receptor, 3) reduced LDL receptor recycling to the cell membrane[1]



THERE ARE FIVE MAJOR MECHANISMS OF FH:[1,3]

1. LDL receptors are not synthesized at all
2. LDL receptors do not properly bind LDL on the cell surface because of a defect in apoB or in the LDL receptor
3. LDL receptors are not recycled back to the cell surface due to a mutation in proprotein convertase subtilisin/kexin type 9 (PCSK9)
4. LDL receptors are not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface
5. LDL receptors bound to LDL do not properly undergo endocytosis due to reduced expression of LDL receptor accessory protein 1 (LDLRAP1)

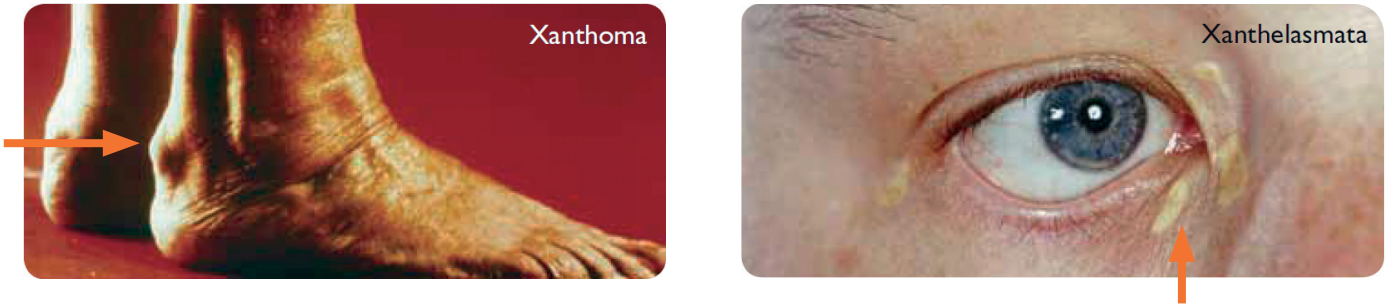
PART 4:
DIAGNOSIS OF FH

To reduce the burden of LDL-C, atherosclerosis and CHD, there is a need to identify and treat patients with FH as early as possible.[2]

Clinical signs of FH

The presence of certain physical signs, resulting from cholesterol deposition in peripheral tissues, should prompt the clinician to suspect FH, particularly if found in younger patients (Figure 8).[2, 3] Tendon xanthomas may appear in some patients (less than half) with FH, particularly in the Achilles tendon and less commonly in finger extensor tendons.[3] Xanthelasmata are lipid depositions around the eyes and are indicative of FH if observed in people aged 20–25 years.[3] If present in individuals younger than 45 years, lipid deposition in the cornea (corneal arcus) may also suggest FH.

Figure 8. Clinical signs found in some patients with FH



Of note, many people with FH do not present with these clinical signs and their absence does not rule out FH.

Diagnosis criteria

Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria. Three major diagnostic criteria exist: Simon Broome Register Diagnostic Criteria for FH, Make Early Diagnosis Prevent Early Death (MEDPED) Program Diagnostic Criteria for FH and Dutch Lipid Clinic Network Diagnostic Criteria for FH. These criteria primarily include a combination of very high cholesterol levels (either LDL-C or total cholesterol [TC]), presence of clinical signs e.g. tendon xanthomas, a family history of premature CHD and detected genetic defects.[2]

Simon Broome Register Group Definition of FH[2]

A DEFINITE DIAGNOSIS OF FH REQUIRES

1. A plasma measurement of either:

   Total cholesterol level above 7.5 mmol/L in adults or a total cholesterol level above 6.7 mmol/L or children under 16

OR

   LDL-C levels above 4.9 mmol/L in adults (>4.0 mmol/L in children under 16)

2. Tendon xanthomas in patient or first- or second-degree relatives
3. DNA-based evidence of mutation in *LDLR* or other FH-related gene
4. Family history of myocardial infarction before age 50 in a second-degree relative or before age 60 in a first-degree relative
5. Family history of plasma total cholesterol >7.5 mmol/L in any first- or second-degree relative

Adapted from Genest J et al. Can J Cardiol. 2014;30:1471-81.

Dutch Lipid Clinic Network Diagnostic Criteria for FH[1]

Family history	Points
First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD) OR	1
First-degree relative with known LDL-C >95th percentile by age and gender for country	1
First-degree relative with tendon xanthoma and/or corneal arcus OR	2
Child(ren) <18 years with LDL-C >95th percentile by age and gender for country	2
Clinical history	
Subject has premature (<55 years, men; <60 years, women) CHD	2
Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthoma	6
Corneal arcus in a person <45 years	4
Biochemical results (LDL-C)	
>8.5 mmol/L	8
6.5–8.4 mmol/L	5
5.0–6.4 mmol/L	3
4.0–4.9 mmol/L	1
Molecular genetic testing (DNA analysis)	
Causative mutation shown in the *LDLR, APOB* or *PCSK9* genes	8

Definite FH: >8 points	Probably FH: 6-8 points	Possible FH: 3-5 points	Unlikely FH: 0-2 points

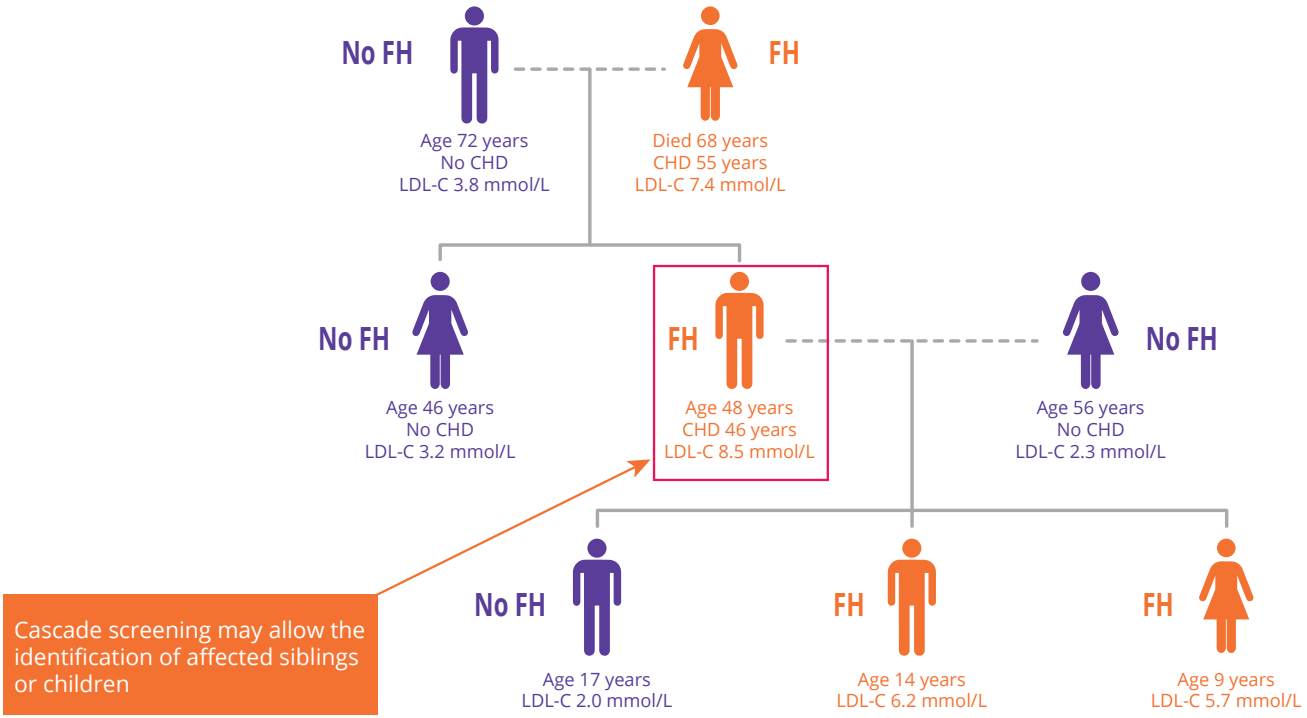
Only one score per group, the highest applicable, can be chosen. For example, when CHD and tendon xanthoma as well as dyslipidaemia are present in a family, the highest score for family history is 2. However, if persons with elevated LDL-C levels as well as premature CHD are present in a family, but no xanthoma or children with elevated LDL-C levels or a causative mutation are found, then the highest score for family history remains 1.

Genetic screening may be useful in those where diagnosis is uncertain and to identify a causal mutation in those strongly suspected of having FH.[1,3] Importantly, a negative genetic test does not exclude FH – a mutation may not be found in some patients with clinically definite FH, often due to genetic heterogeneity.[3], People with high LDL-C remain at high risk and should receive LDL-C lowering treatment according to best-practice guidelines regardless of the results of genetic testing.[3]

Cascade screening

Once a definitive diagnosis has been made using FH criteria, cascade screening is recommended, which involves screening the family members of known index cases to identify at-risk relatives (Figure 9).[1,3] Initial family members to be tested are biological first-degree relatives, namely parents, siblings and children. Cascade screening can be performed by lipid profiles alone, but genetic testing is recommended if the causative mutation is known.

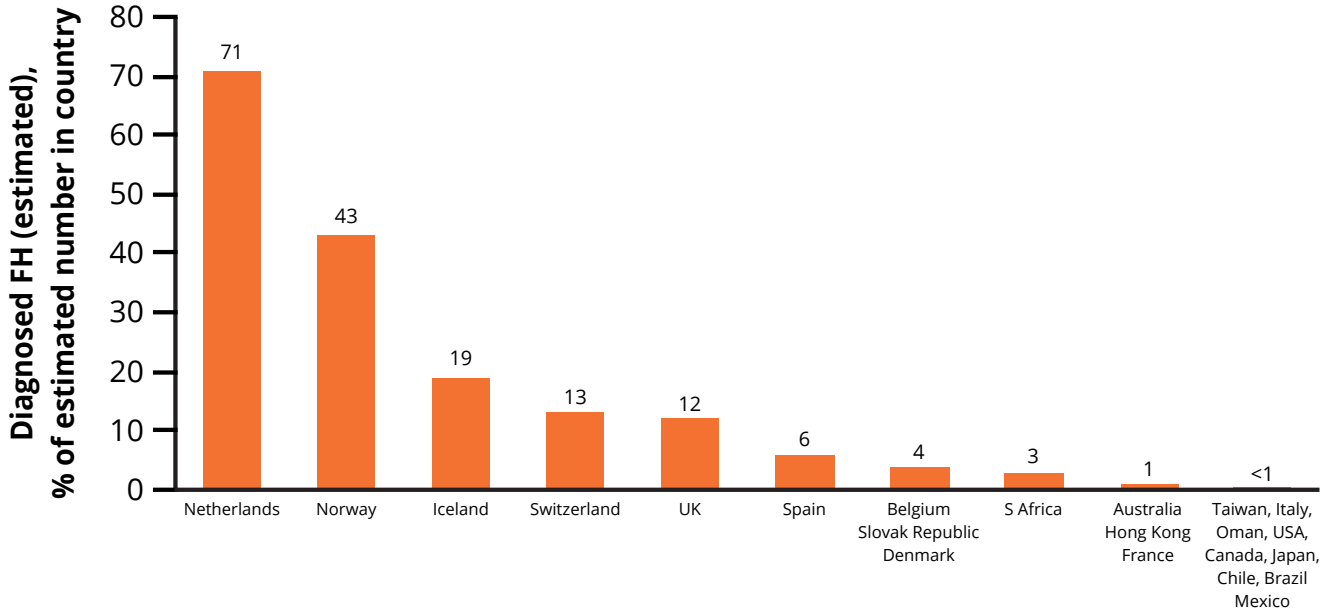
Figure 9. Cascade screening of index FH cases to identify at-risk family members



FH is not diagnosed in many people with the condition

Identifying new cases among those at highest risk for FH enables **early diagnosis and treatment**.[2] However, the majority of FH cases are either undiagnosed or diagnosed only after the primary coronary event.[2] Based on FH prevalence of 1 in 500 individuals, estimates of diagnosis rates range from 71% in the Netherlands and 43% in Norway, to ≤1% in other countries in Europe and in North America, South America and Asia (Figure 10).[1] Estimates for diagnosis rates would be even lower if calculated based on a prevalence of FH of 1 in 200 individuals.

Figure 10. Estimated diagnosis rates for FH in different countries based on an FH prevalence of 1 in 500 of the general population[1]



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Many cases of FH may be overlooked in the large number of individuals with CHD due to common risk factors[1] and FH may be misdiagnosed as common hypercholesterolemia. However, the risk of early CHD is much higher in FH than in common hypercholesterolemia and **early, aggressive LDL-C lowering is needed to help reduce the prolonged atherogenic lipoprotein burden on the blood vessels**.

PART 5:
TREATMENT OF FH

Treatment recommendations in FH

All patients with FH and their families should be counselled regarding lifestyle modifications, including smoking cessation, dietary changes and increased physical activity.[2] In addition, **cholesterol-lowering drugs should be initiated** immediately at diagnosis in all adults with FH and should be strongly considered in children **starting at age 8 to 10 years of age**.[1,2]

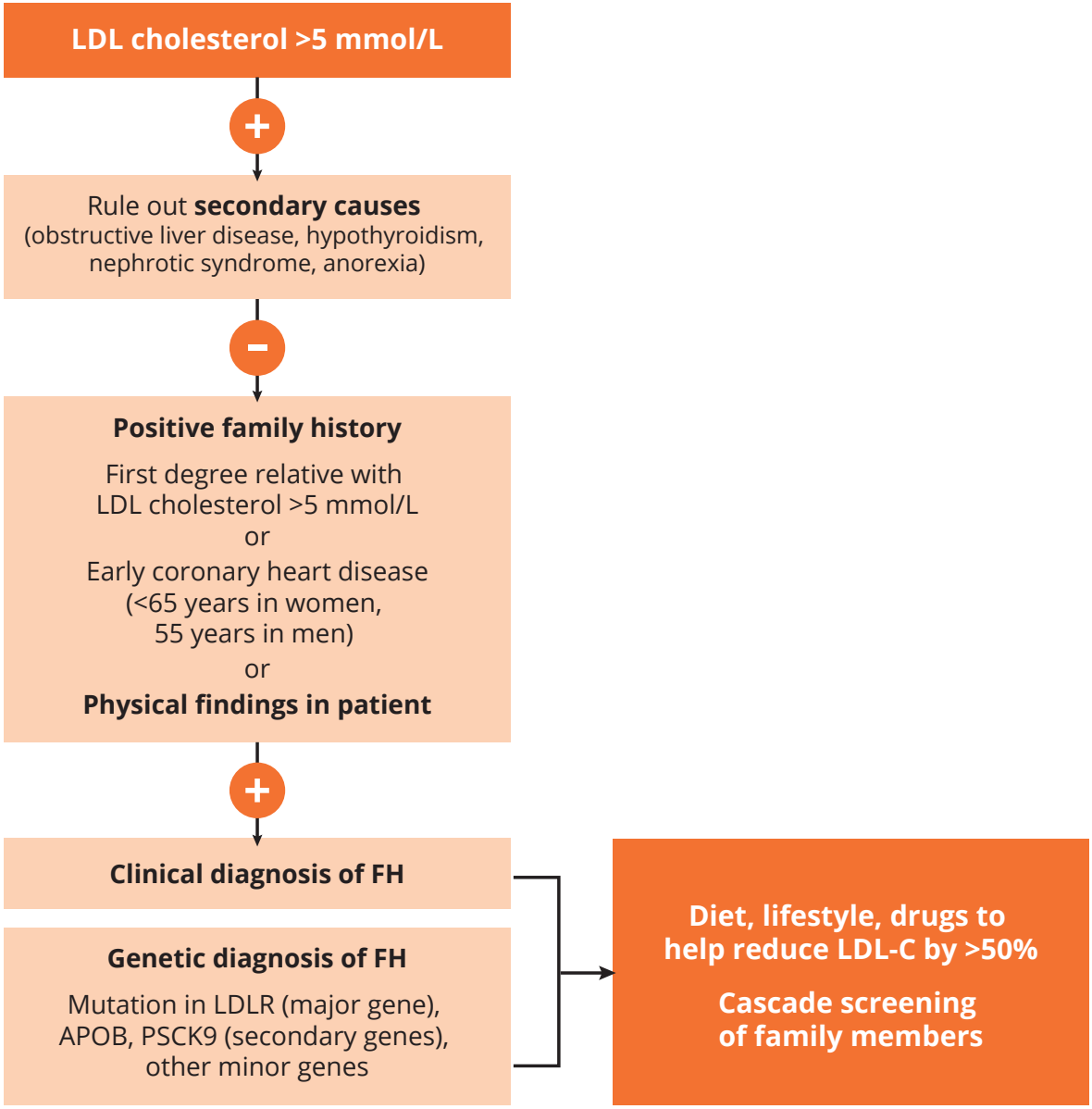
Statins are recommended as the initial treatment for FH.[1,2] Statins are the initial choice of treatment because of the large body of evidence that statin-mediated LDL-C lowering results in reductions in cardiovascular events.[1]

Statins have modified the natural course of FH. When treated early in life, event-free survival is essentially normalized in HeFH patients.[2] Lipid-lowering therapy is associated with delayed cardiovascular disease events and prolonged survival in HoFH patients.[2]

A reasonable therapeutic goal for primary prevention in adults with HeFH is to achieve a > 50% reduction in LDL-C levels, a goal that in many cases is achievable with high-dose statins alone. When LDL-C still requires reduction, addition of adjunctive agents is recommended on an individualized basis. In HeFH patients with established atherosclerotic cardiovascular disease, the Canadian Cardiovascular Society guideline recommended a goal of LDL-C < 2.0 mmol/L should be at the top-of-mind, but might not be feasible with currently available drugs.[2]

In accordance with guidelines from the Canadian Cardiovascular Society, statins should be first-line therapy in FH patients, with the aim of lowering LDL-C by > 50%. In patients with atherosclerosis, maximally tolerated doses of statins with or without ezetimibe or bile acid sequestrants (cholestyramine, colestipol, or colesevelam) might further decrease LDL-C.[2]

Figure 12 . Diagnostic and treatment flow when FH is suspected as recommended by the Canadian Cardiovascular Society[2]



Treatment recommendations suggested by the Canadian Cardiovascular Society in patients with HoFH[2]

HoFH patients older than 7 years of age and > 15 kg in weight should be referred to a specialized centre and considered for extracorporeal plasma exchange or LDL apheresis and emerging therapies

- Apheresis is recommended in adults with HoFH with refractory LDL-C > 8.5 mmol/L and in children (> 15 kg in weight or older than 7 years of age) with refractory LDL-C > 5.0 mmol/L on maximally tolerated medical therapy
- Clinical observation has shown that with apheresis, life expectancy of HoFH patients has more than doubled in the past 3 decades; this must be made available in specialized centres across Canada

SUMMARY

FH is common genetic disorder, affecting between **1 in 200 and 1 in 500** of the global population. When left untreated, elevated LDL-C levels in FH lead to substantial atherosclerosis in childhood and considerably increased risk of premature CHD. Validated diagnostic criteria exist including **LDL-C levels, clinical signs, family history and genetic testing**; however, many patients are not diagnosed with FH at all or until after a coronary event. Early diagnosis is important to ensure timely initiation of guideline-recommended treatment strategies to help reduce the prolonged burden of high LDL-C levels and subsequent CHD risk in FH. Initial treatment involves a statin in combination with other LDL-C lowering agents where needed to achieve LDL-C targets.

Clinicians should be aware of the key role they play in facilitating early diagnosis and ensuring the long-term effective treatment of this very high-risk condition.

References

1. Nordestgaard B et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478-90a.

2. Genest J et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol. 2014;30:1471-81.

3. Hopkins PN et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S9-17.

4. Cuchel M 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;35:2146-2157.

5. de Groot E et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. Circulation.2004;109(23 Suppl 1):III33-8.

6. Wiegman A et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. Lancet. 2004;363:369-70.

7. Strøm TB et al. Mutation G805R in the transmembrane domain of the LDL receptor gene causes familial hypercholesterolemia by inducing ectodomain cleavage of the LDL receptor in the endoplasmic reticulum. FEBS Open Bio. 2014;4:321-7.

NOTES

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