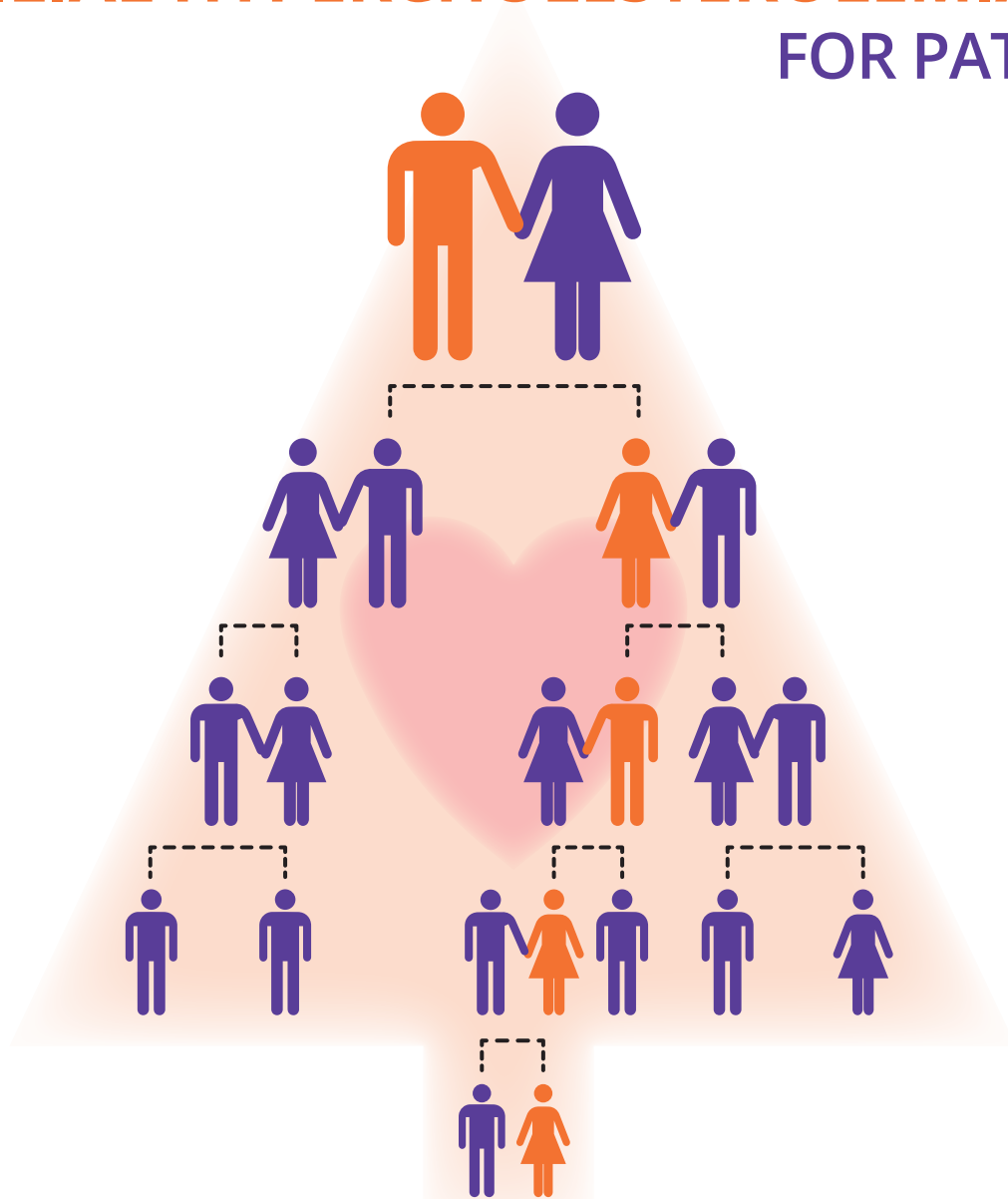


A GUIDE TO FAMILIAL HYPERCHOLESTEROLEMIA (FH) FOR PATIENTS



Heterozygous familial hypercholesterolemia - example of a family tree

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PART 1: WHAT IS FAMILIAL HYPERCHOLESTEROLEMIA (FH)?

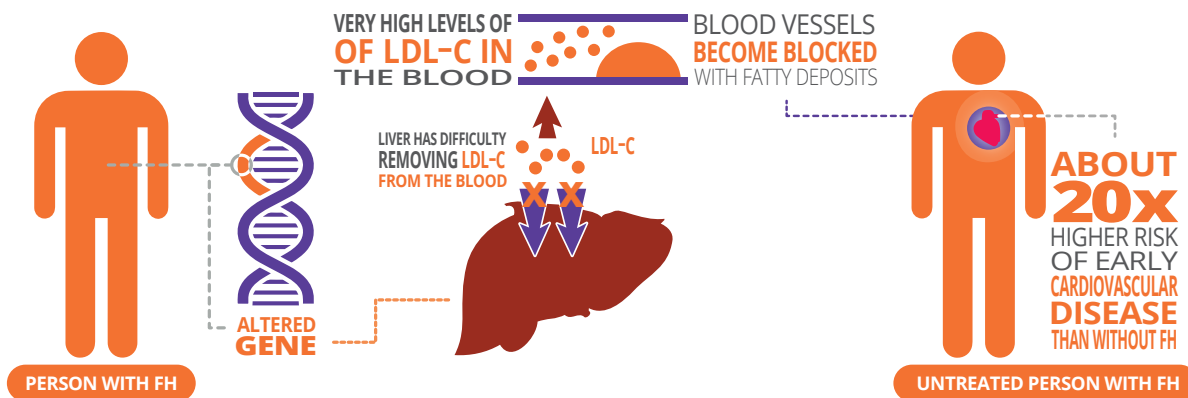
F = FAMILIAL = PASSED ON THROUGH FAMILIES (INHERITED)

H = HYPERCHOLESTEROLEMIA = HIGH LEVELS OF 'BAD' CHOLESTEROL IN THE BLOOD
CHOLESTEROL = A FATTY SUBSTANCE

FH is an inherited condition, which results in very **high levels of cholesterol in the blood**. An altered gene in FH decreases the liver's ability to remove cholesterol properly. Very high levels of low-density lipoprotein cholesterol (**LDL-C**), sometimes called '**bad**' cholesterol, can **block blood vessels** and **increase the risk of cardiovascular disease** at an early age (for example, before age 55 years in men and before age 60 years in women).

Many people worldwide without FH have high cholesterol (common hypercholesterolemia) in middle age, but people with FH have **very high cholesterol from birth**.

What is FH?^{1,2}



FH is the most common genetic disorder causing premature CVD^{1,2}

- In Canada, between **1 in every 500 people** has heterozygous FH (see page 6 for more details on the different types of FH)¹
- Between **14 and 34 million** individuals worldwide are estimated to have FH¹

FH RUNS IN FAMILIES. IT CAUSES VERY HIGH BLOOD LDL-C LEVELS AND AN INCREASED RISK OF CARDIOVASCULAR DISEASE EARLY IN LIFE

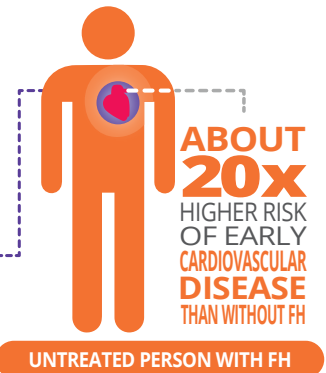
FH AND CARDIOVASCULAR DISEASE

Cardiovascular disease refers to diseases of the heart and blood vessels caused by atherosclerosis, such as **heart attacks and stroke**. In atherosclerosis, fat (including cholesterol) builds up in blood vessels, causing them to become narrow, which reduces or blocks the flow of blood. Reduced blood flow to the heart can cause angina or a heart attack. Reduced blood flow to the brain can cause a stroke.

VERY HIGH LEVELS OF
OF LDL-C IN
THE BLOOD



BLOOD VESSELS
BECOME BLOCKED
WITH FATTY DEPOSITS



Due to very high cholesterol levels, people with FH who are untreated have about a **20-fold higher risk of developing cardiovascular disease** compared with people without FH at an early age.²

FH is **treatable**. The risk of cardiovascular disease in FH can be reduced with changes to **lifestyle, diet and with medication**.

PEOPLE WITH FH HAVE VERY HIGH LDL-C LEVELS AND INCREASED RISK OF EARLY CARDIOVASCULAR DISEASE BUT IT CAN BE REDUCED BY A HEALTHYLIFESTYLE, DIET AND WITH MEDICATIONS

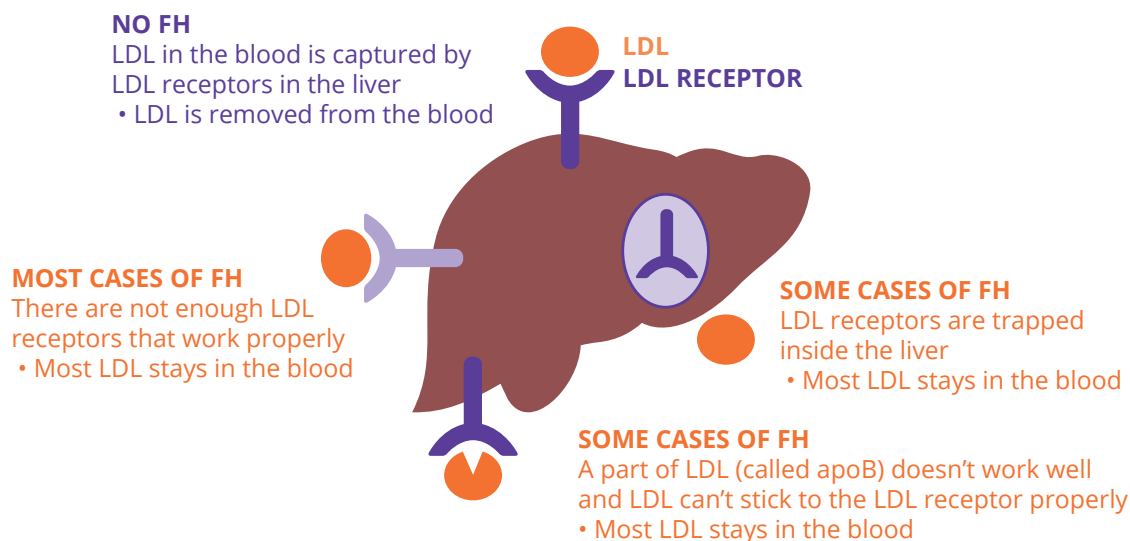
FH AND CHOLESTEROL

Cholesterol is needed to build cells, make hormones and bile acids. Cholesterol is transported around the body by two main types of lipoproteins:

- Cholesterol carried by **low-density lipoprotein (LDL)** is often described as **'bad' cholesterol** as this type may be deposited in blood vessels, builds up and can cause blockages. It is better to have only a small amount of LDL in the blood
- Cholesterol carried by **high-density lipoprotein (HDL)** is often described as **'good' cholesterol** as it helps to remove excess cholesterol from the body. It is OK to have a lot of HDL in your blood

LDL levels are normally controlled by **LDL receptors** in the liver. LDL receptors are like gates that let LDL leave the blood to be broken down in the liver when levels get too high.

In most people with **FH**, **LDL receptors do not work properly** and LDL levels become very high. This can lead to narrowed arteries, blocked arteries and cardiovascular disease.



FH IS CAUSED BY AN ALTERED GENE INVOLVED IN LDL REMOVAL. TOO MUCH LDL IN YOUR BLOOD CAN CAUSE NARROWED OR BLOCKED ARTERIES AND CARDIOVASCULAR DISEASE

HOW IS FH INHERITED?

FH may be passed from parent to child. Two types of FH exist: **heterozygous FH (HeFH)** and **homozygous FH (HoFH)**.

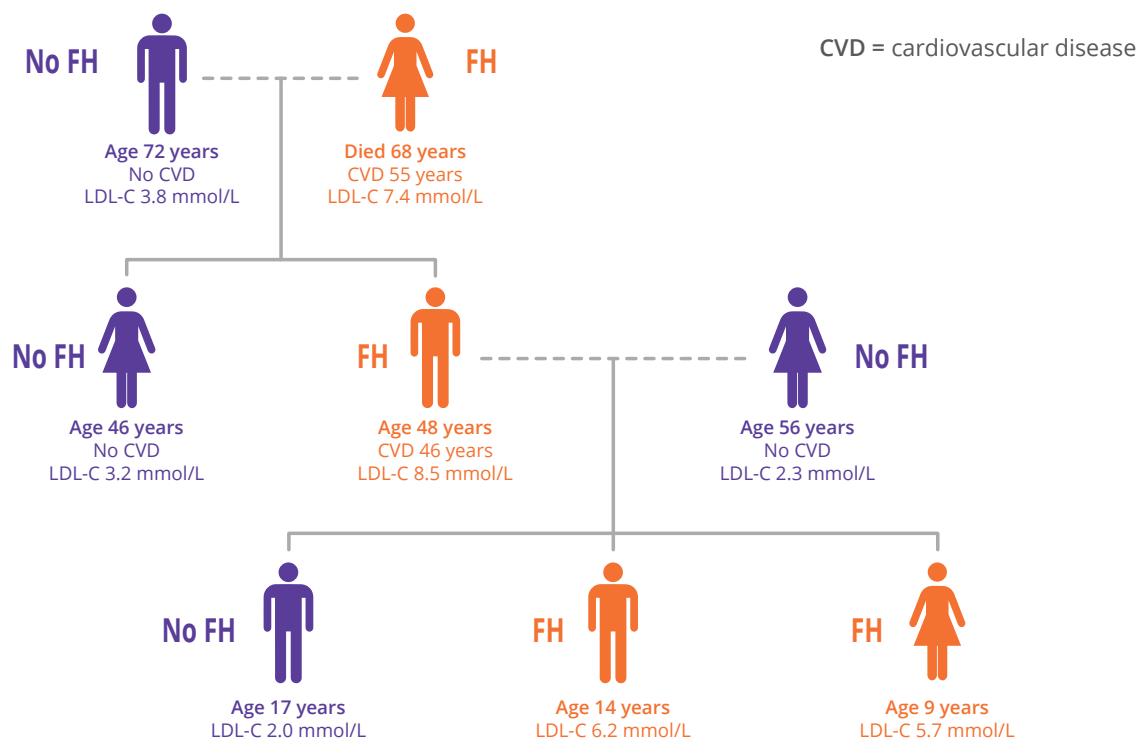
HeFH

Most people with FH have inherited an altered gene from one parent and a normal gene from the other parent. This is termed heterozygous FH (HeFH).

Not all family members are affected. Close relatives of someone with FH, for example, parents, brothers, sisters, children, have a **50:50 chance** of also having FH.

In people with HeFH, the average age for developing cardiovascular disease is 42 to 46 years for men and 51 to 52 years for women.⁵

An example of a HeFH family tree

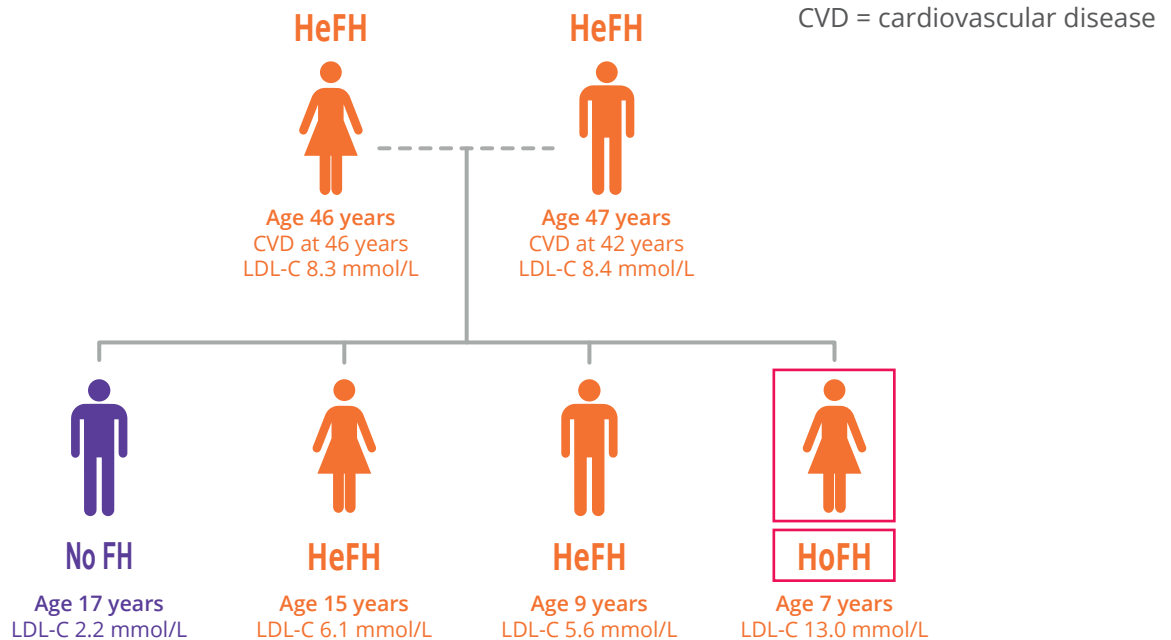


HoFH

In very rare cases (an estimated **1 in 160,000 to 1 in 1,000,000** people), a severe form of FH results from inheriting altered genes from both parents.^{2,4} This is termed **homozygous FH (HoFH)**.

People with HoFH may develop cardiovascular disease **before the age of 20 years** if not treated.⁴

An example of a HoFH family tree



NOT ALL FAMILY MEMBERS WILL BE AFFECTED BY FH, BUT IT IS IMPORTANT TO FIND OUT WHICH ONES ARE SO THEY CAN RECEIVE EARLY TREATMENT

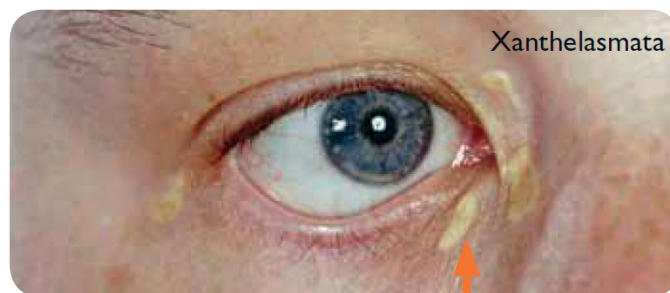
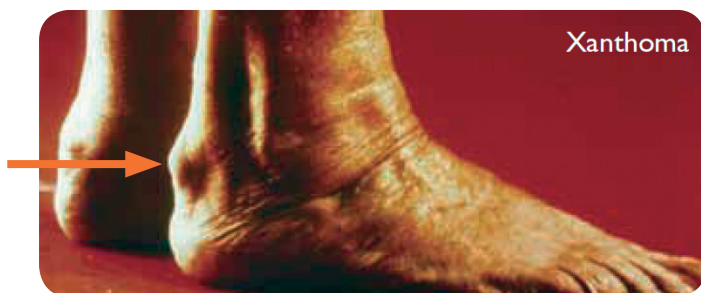
PART 2: DIAGNOSING FH

How is FH diagnosed?

FH is generally diagnosed based on a combination of:

- High cholesterol levels at an early age
- A family history of heart disease
- Certain visible signs in some people with FH (but not all)

Visible signs of FH include **swollen tendons on the back of the heel (xanthoma)** and **yellow deposits in the skin around the eyes (xanthelasmata)**.² **A white deposit of cholesterol in the shape of an arc** may also be seen around the coloured part of the eye (**corneal arcus**). However, most people with FH do not show these signs.



Many people have high LDL-C levels in middle age, called 'common hypercholesterolemia', and FH may be mistaken for this. However, the chances of early cardiovascular disease are much higher in FH than in people with common hypercholesterolemia.

Many cases of FH are not diagnosed.¹ People are often not aware that they have FH until they or a family member has a heart attack or stroke.

<1% OF
FH IS
DIAGNOSED¹

**AT LEAST 99% OF FH IS NOT DIAGNOSED
IN CANADA¹**

If your doctor thinks you have FH, they may ask for a blood lipid test to check levels of different types of cholesterol, including LDL-C and HDL-C, and other fats in the blood, such as triglycerides.

Genetic testing may also be used to see if you have an altered gene and to confirm the diagnosis.

Your doctor will want to know if other family members have cardiovascular disease and if they have high LDL-C levels. Other family members, including children, may have genetic testing to see if they have the altered gene.

Early diagnosis is important. Treatment is more effective when started early and before fatty deposits build up in blood vessels.

THERE ARE BENEFITS TO FINDING FH EARLY:

- **LDL-C levels may be lowered with diet modification, lifestyle changes and medication**
- **Early treatment can help reduce the chances of cardiovascular disease**
- **Close family members can be screened for FH and treatment can be started if needed**

PART 3: TREATING FH

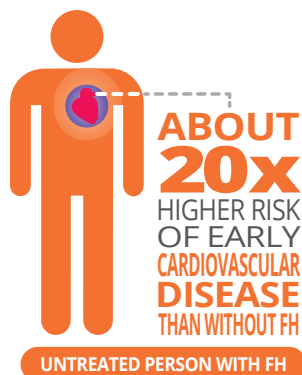
Can FH be treated?

FH is **treatable**. Studies have shown that reducing high levels of LDL-C can lower the risk of cardiovascular disease.² However, it is important to start lowering levels of LDL-C as **early** as possible before fatty deposits build up and begin to block blood vessels.

It is also essential that people with FH continue treatment to make sure that LDL-C levels are kept as low as possible.

How is FH treated?

There are different ways to reduce LDL-C levels and help reduce the risk of cardiovascular disease. While healthy lifestyle changes and diet are important, most FH patients will need medication.



CARDIOVASCULAR DISEASE IN FH PATIENTS CAN BE REDUCED BY THE ASSOCIATION OF:

- **LIFESTYLE CHANGES**
 - NO SMOKING, REGULAR EXERCISE
- **DIET CHANGES**
 - EAT LESS SATURATED FAT
 - EAT MORE FIBRE, FRUITS AND VEGETABLES
- **MEDICATION**

Lifestyle changes

People with FH should change their lifestyle to protect their hearts. Important changes include **stopping smoking and exercising regularly**.

- Smoking itself causes additional damage to blood vessels, reduces levels of good cholesterol (HDL-C) and increases the risk of cardiovascular disease
- Regular exercise has beneficial effects on body fats (lipids) by reducing bad LDL-C and increasing good HDL-C
- Exercise can also improve other risk factors for cardiovascular disease, such as high blood pressure
- Exercise can reduce the risk of obesity and type 2 diabetes, which can themselves lead to cardiovascular disease

PEOPLE WITH FH SHOULD REDUCE RISK FACTORS FOR CARDIOVASCULAR DISEASE:

- Do not smoke
- Exercise regularly
- Avoid high blood pressure, for example, by eating less salt
- Avoid being overweight
- Eat a healthy diet



Diet changes

A low intake of cholesterol is recommended for people with high LDL-C levels in their blood, such as people with FH. Saturated fats, found in meat products, fatty dairy products, and fast food, can increase levels of LDL-C. Saturated fats should be replaced with unsaturated fats from plants and fish.

Fibre may also have a beneficial effect on cholesterol levels. People with FH should eat foods that are high in fibre, such as whole-wheat products, beans, peas, fruits and vegetables.



IMPORTANT GUIDELINES FOR A HEART-FRIENDLY DIET:

- Eat less fat, particularly less saturated fat (e.g. in red meat and butter)
- Replace saturated fats with unsaturated fat (e.g. vegetable oils)
- Limit food and drinks high in sugar or alcohol
- Eat more foods containing fibre, vegetables and fruit every day

Medication

A healthy diet and lifestyle changes can lower LDL-C, but people with FH will also need medication to lower LDL-C levels in the blood and therefore reduce the chance that blood vessels will become blocked.

If you have been diagnosed with FH, your doctor will discuss the medicines that are best for you. Several types of medicines are prescribed, which can be given alone or in combination. The types of drugs used to lower LDL-C to treat FH include statins. You might also receive other cholesterol-lowering medication, such as a bile-acid resin or a cholesterol uptake inhibitor.

- **Statins:** help reduce how much LDL-C is made in the body
- **Bile-acid resins:** help make the liver take more LDL-C out of the blood and increase removal in feces
- **Cholesterol uptake inhibitors:** help block the uptake of cholesterol from the gut so more is excreted in faeces

For patients with severe FH, including homozygous FH (HoFH), LDL-C levels may remain very high. Mechanical filtering of the blood to remove LDL-C may be required in a dialysis-like cleansing process called apheresis.

Cholesterol measurements: Know your level and your target

Sometimes cholesterol is measured as total cholesterol (LDL-C plus HDL-C and other lipids) or separately as LDL-C and as HDL-C. Doctors give cholesterol measurements in units called 'mmol/L'.

FH is often suspected if LDL-C is more than 4.9 mmol/L in adults or more than 4.0 mmol/L in children.

Your doctor will likely discuss with you a cholesterol target based on your current cholesterol levels and whether you have existing cardiovascular disease (e.g. if you have had a heart attack in the past). This target represents how low your doctor would like your cholesterol levels to go with a healthy lifestyle, diet and medication.

**YOUR DOCTOR MIGHT TREAT YOU WITH MEDICATION TO HELP
LOWER YOUR LDL-C LEVELS.**

**CONTINUATION OF A HEALTHY LIFESTYLE, A HEART-FRIENDLY DIET AND
MEDICATIONS MAY HELP REDUCE YOUR RISK OF HEART ATTACK AND STROKE.**

PART 4: FH AND YOUR CHILD

If you have FH, there is a **50:50 chance that your children will have FH** as you may have passed on the altered gene.

If you or someone in your family has FH, your children and their cousins may be checked for FH by measuring their cholesterol levels and by genetic testing.

Confirming a diagnosis of FH early in childhood is important – lowering levels of LDL-C as early as possible will reduce the chances of your child developing cardiovascular disease when they are adults.

If FH is not treated, cardiovascular disease may develop in people with FH as young as in their 30s. Children with FH treated effectively from the age of 10 years may develop cardiovascular disease at a similar age as people who do not have FH.¹

**DIAGNOSING FH IN CHILDHOOD IS
IMPORTANT AS EARLY LIFESTYLE/
DIET CHANGES AND MEDICATION CAN
HELP REDUCE THE IMPACT OF FH AND
CARDIOVASCULAR DISEASE IN LATER LIFE**



WHAT HAVE YOU LEARNED FROM THIS BOOKLET?

You have learned that FH is a condition that runs in families and is caused by an altered gene for the removal of LDL-C (bad cholesterol) by the liver.

People with FH have very high LDL-C levels in the blood, which may lead to narrowed or blocked blood vessels and cardiovascular disease at an early age.

It is possible to find out if family members are affected by FH by measuring their LDL-C levels in their blood and finding out whether they have an altered gene.

Most importantly, you have learned how you and your family members that may have FH can reduce the risk of cardiovascular disease by adopting a healthy lifestyle, a heart-friendly diet and by taking medication.

This booklet may also serve as a starting point to help you discuss your disease with your doctor.

WHAT SHOULD I DO IF I AM WORRIED ABOUT FH?

Speak to your doctor and other health care professionals about your condition and treatments. Contact local patient associations to learn more about FH.

LEARN MORE!

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4. Cuchel M et al. Eur Heart J. 2014;35:2146-57
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GLOSSARY

APOB: LDL-C has a specific protein attached to it named apolipoprotein B or apoB. ApoB acts as a bridge between the LDL-C and the liver cells that carry the LDL receptor

ATHEROSCLEROSIS: The build-up of fatty deposits in the artery walls

CHOLESTEROL: Cholesterol is a fatty substance. It is stored in the body and is found in all foods derived from animals

FAMILIAL HYPERCHOLESTEROLEMIA (FH): An inherited condition that results in very high levels of cholesterol in the blood, which can lead to cardiovascular disease at an early age

GENE: A section of DNA that codes for a certain protein. A gene is passed from parent to child

HEART ATTACK: A heart attack occurs when the flow of blood to the heart is blocked, most often by a build-up of fat (cholesterol), which forms a plaque in the arteries that feed the heart. The interrupted blood flow can damage or destroy part of the heart muscle

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL (HDL-C): Also referred to as 'good cholesterol'. It is OK to have a lot of this in your blood

INHERITED: Passed from parent to child

LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL (LDL-C): Otherwise referred to as 'bad cholesterol'. It is better to have only a small amount of LDL-C in the blood

LDL RECEPTOR: LDL receptors on the liver bind to LDL so it can be removed from the blood. Most people who have inherited FH have too few LDL receptors that work properly. This means that LDL remains in the blood and may block blood vessels

LIPIDS: Fats

LIPOPROTEINS: Lipoproteins are small packages made up of cholesterol, triglycerides and protein and are a means by which fats can be transported in the blood. There are various kinds of lipoprotein including LDL and HDL

STROKE: A stroke occurs when the flow of blood to the brain is interrupted or severely reduced, depriving brain tissue of oxygen and nutrients

TRIGLYCERIDES: Another word for fats. The fats in food and blood are triglycerides. It is good to have low levels of triglycerides in the blood

NOTES

NOTES



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Sanofi and Regeneron are committed to providing resources
to better understand cholesterol management

