Familial hypercholesterolemia (FH) is a genetic condition that causes high low-density lipoprotein (LDL) cholesterol (sometimes referred to as bad cholesterol) from birth. FH means high cholesterol that runs in a family. FH is caused by specific DNA changes that are passed on from parents to their children. It is not caused by lifestyle factors such as a high-fat diet or lack of exercise. There are 2 main types of FH, homozygous and heterozygous, that have different symptoms, risks, and treatments. In this Cardiology Patient Page, we focus on heterozygous FH, which we will call FH. FH affects 1 in 200 to 300 people. FH is usually inherited from 1 parent in an autosomal dominant pattern. This means a parent with FH has a 50% chance of passing it on to each child, regardless of sex. This also means all first-degree relatives (parents, siblings, and children) of a person with FH have a 50% chance to have FH, and a 50% chance to not have FH.

Healthcare providers and the general public lack awareness about FH. Therefore, it is underdiagnosed and undertreated. A person with FH who is not treated is 20 times more likely to develop coronary artery disease than a person without FH. Coronary artery disease can lead to heart attacks and other major cardiovascular diseases, including stroke and sudden cardiac death. However, early diagnosis with universal lipid screening, cascade screening in families, and appropriate treatment with statins and other medications can reduce this risk.

How Is FH Diagnosed?
Most people with FH will not have any symptoms until complications of untreated high cholesterol arise years later. Rarely, patients may have visible signs of extremely high cholesterol, such as a corneal arcus or tendon xanthomas. A corneal arcus is a yellowish ring along the edge of the colored part of one or both eyes. Tendon xanthomas are cholesterol deposits on tendons that can be felt as bumps on the surface of the backs of the heels and fingers. However, these physical signs are often not seen in FH.

FH is usually diagnosed based on cholesterol levels, premature coronary artery disease, and family history, but there is no standard used by all physicians. LDL-cholesterol (LDL-C) levels are measured with a blood test. Physicians should begin to think about FH if adults (≥20 years) have LDL-C levels ≥190 mg/dL, or children (<20 years) have LDL-C levels ≥160 mg/dL. The higher the LDL-C value, the more likely it is that a person has FH.

Healthcare providers should obtain a family history to check if any relatives of the patient also have high cholesterol or a history of early heart disease (men <55 years of age and women <65 years of age). Family history is an important clue for FH, but having no relatives with heart disease does not mean a patient does not have FH. For example, the patient may be the first person in the family to have a cholesterol test or develop heart disease. Other relatives may also be affected but not yet diagnosed. Also, some relatives may have FH and be able to pass this on to their children without having high cholesterol or heart disease themselves because of protective genetic changes.

Although medical history, family history, and cholesterol levels are important information for diagnosing FH, a healthcare provider may also recommend a genetic test. A genetic test

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The information contained in this Circulation Cardiology Patient Page is not a substitute for medical advice, and the American Heart Association recommends consultation with your doctor or healthcare professional.

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involves taking a small sample of blood and sending it to a laboratory. Genetic testing can help confirm FH. A significant percentage of patients with high LDL-C and positive family history will have negative FH genetic testing. If these patients meet diagnostic criteria, they need to be treated as FH patients and their relatives should have cholesterol testing.

Why Is FH So Important to Recognize?

FH patients have high levels of LDL-C in the blood at birth. This causes cholesterol plaque buildup in the walls of arteries. This is called atherosclerosis and can begin during childhood. Plaque buildup in the arteries of the heart is called coronary artery disease (CAD) and can cause heart attacks. If FH patients are not treated, men have a 50% risk of CAD by 50 years of age, and women have a 30% risk by 60 years of age. CAD can lead to heart attack and early death. It is important to know, however, that FH is manageable!

The best way to prevent complications of FH is to recognize and treat FH early. Recommendations to check the cholesterol levels of everyone in a specific population, called universal screening, help to identify FH patients at young ages. Primary care physicians should use a blood test to screen all adults for high cholesterol. Similarly, according to the American Academy of Pediatrics, all children between ages 9 and 11 should be checked for high cholesterol. Children as young as 2 years old should be screened if there is a strong family history of high cholesterol or heart disease.

Because the relatives of FH patients are also at high risk, a process called cascade screening can help identify more individuals with FH. This means that all the first-degree relatives of a person with FH should be tested for high cholesterol. If a relative is diagnosed with FH, his or her first-degree relatives should then be tested, and so on. You may find it difficult to talk to your family about FH. There are tools created by genetic counselors and others, such as a Dear Family Member Letter, that can help you share information with your family and discuss testing for FH.

Can FH Be Treated?

Yes! As soon as FH is diagnosed, treatment should begin to lower LDL-C. The first goal is to reduce the LDL-C by at least 50%. For example, if your LDL-C level is 220 mg/dL, therapy should reduce it to at least less than 110 mg/dL. Early treatment and cholesterol lowering can drastically lower risk of CAD and heart attack. Cholesterol levels should be measured at least once per year to monitor the effects of therapies.

The main treatments are medications called statins. Statins make the body produce less cholesterol. Patients with FH typically require high doses of powerful statins in combination with other cholesterol-lowering drugs for the rest of their lives. Other medications that may be used include niacin, cholesterol absorption inhibitors (such as ezetimibe), and bile acid–binding resins (such as colesevelam). Newer therapies continue to arise, such as proprotein convertase subtilisin kexin 9 inhibitors, which were recently approved for use in FH patients.

Some studies have determined that it is safe to use statins in children, but this is still being researched. Current guidelines recommend considering statin treatment in children ≥8 years. Children with FH should be evaluated by a lipid specialist.

Medications do not always work to reach a goal cholesterol level in FH patients. Some patients need a procedure called LDL apheresis, which uses a machine to take blood out of the body, filter LDL out of the blood, and return the blood to the body.

Healthy lifestyle choices can help FH patients, in combination with medical therapies. Eating a low-fat diet and exercising regularly to maintain a healthy weight can help prevent atherosclerosis. Smoking or using tobacco products must be avoided, because tobacco greatly increases risk of CAD. Other risk factors for cardiovascular disease, like high blood pressure and diabetes mellitus, should be treated. Often, low-dose aspirin is taken daily to lower risk of stroke.

We have highlighted Key Points and Patient and Healthcare Provider Resources in Boxes 1 and 2, respectively.

Disclosures

A. Sturm has served on the Scientific Advisory Board for Ambry Genetics and as a consultant for Ambry Genetics, Invitae, Recombine, and The FH Foundation.

Additional Resources


Box 1. Key Points

- Familial hypercholesterolemia (FH) is a common cause of high cholesterol and early heart disease, including heart attacks.
- Parents, brothers, sisters, and children of individuals with FH have a 50% chance to also have FH.
- FH is different than other types of high cholesterol and needs to be treated differently.
- FH is manageable! Patients with FH need to take their medications, NEVER SMOKE, eat a healthy diet, and exercise.
- Children with FH should be evaluated by a lipid specialist.
- Genetic counselors can teach patients and families about FH and how it is passed down through a family. They can also explain genetic testing and discuss how to talk to family members about FH.
- There are many useful online tools and websites for patients with FH, including a patient-centered advocacy group, The FH Foundation.

Box 2. Patient and Healthcare Provider Resources

The FH Foundation – www.thefhfoundation.org
Get information about diagnosis and management and how to be involved in the FH community to raise awareness. Use the Find an FH Specialist Tool. Find Dear Family Member Letters here.

Foundation of the National Lipid Association (FNLA) – www.learnyourlipids.com
Find general information about high-cholesterol management, including classes and forums about high-cholesterol treatment, nutrition, and other special considerations.

CASCADE FH Registry – https://thefhfoundation.org/fh-research/registry/
Join a secure patient database used by researchers looking for better ways to diagnose and treat FH.