

# Familial Hypercholesterolemia

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## Overview

## Practice Essentials

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol (LDLc).[1, 2, 3]

Xanthomas are noted commonly on the Achilles tendons and metacarpal phalangeal extensor tendons of the hands of patients with untreated FH. See the image below.



Metacarpophalangeal joint tendon xanthomas in a 45-year-old man with heterozygous familial hypercholesterolemia.

## Signs and symptoms

Homozygous FH

Signs and symptoms of homozygous FH in children include the following:

- Symptoms consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or aortic stenosis
- Articular symptoms such as tendonitis or arthralgias
- Unusual skin lesions, such as cutaneous xanthomas at birth or by early childhood (eg, planar xanthomas, tuberous xanthomas; later, tendon xanthomas)
- Corneal arcus may be present and is sometimes circumferential
- Murmur of aortic stenosis may be present

Most patients with homozygous FH do not survive adulthood beyond age 30 years unless treated with unusual methods, such as liver transplantation, LDL apheresis, or ileal bypass surgery to dramatically lower their LDLc levels.

Heterozygous FH

Children with heterozygous FH do not have symptoms related to coronary heart disease (CHD), and most do not develop tendon xanthomas or corneal arcus. However, one parent will have severe hypercholesterolemia and will also probably have either a personal or family history for premature coronary artery disease (CAD).

Signs and symptoms of heterozygous FH in adults include the following:

- Long-standing history of severe hypercholesterolemia dating back to childhood
- If no previous acute coronary event, symptoms consistent with ischemic heart disease, especially in the presence of other cardiovascular risk factors (especially smoking)
- Past or present symptoms of recurrent Achilles tendonitis or arthritic complaints
- If heterozygous FH is left untreated, tendon xanthomas (Achilles tendons, metacarpophalangeal [MCP] extensor tendons) will occur by the third decade of life in more than 60% of patients
- Xanthelasmas

See Clinical Presentation for more details.

## Diagnosis

The diagnosis of both homozygous and heterozygous FH is based primarily on the finding of severe LDLc elevations in the absence of secondary causes of hypercholesterolemia.

A probable diagnosis of heterozygous FH can be made if the LDLc level is greater than 330 mg/dL or if tendon xanthomas are present in a patient with an LDLc level above the 95th percentile. Definitive diagnosis can be made only with gene or receptor analysis. However, a substantial increase in serum triglyceride levels should raise the possibility of another lipid disorder.

## Testing

Findings on lipid analysis in patients with FH include the following:

- Homozygous FH: Severely elevated cholesterol levels (total cholesterol and LDLc levels >600 mg/dL); triglyceride levels within the reference range
- Heterozygous FH: Elevated LDLc levels commonly greater than 250 mg/dL; in patients younger than 20 years, an LDLc level higher than 200 mg/dL is highly suggestive of heterozygous FH or, possibly, familial ligand defective apoB-100; in adults, LDLc levels higher than 290-300 mg/dL suggest heterozygous FH

LDL receptor analysis can be used to identify the specific LDL receptor defect, and LDL receptor or apoB-100 studies can help distinguish heterozygous FH from the similar syndrome of familial defective apoB-100.

In August 2013, the European Atherosclerosis Society (EAS) published a consensus statement for screening and treatment of heterozygous FH.[4, 5] The recommendations for screening for heterozygous FH include patients with[4, 5] :

- A family member presenting with diagnosed FH;
- Plasma cholesterol in an adult  $\geq 8$ mmol/L ( $\geq 310$  mg/dL);
- Plasma cholesterol in a child  $\geq 6$ mmol/L ( $\geq 230$  mg/dL);
- Premature CHD;
- Tendon xanthomas; or
- Sudden premature cardiac death.

See Workup for more detail.

## Management

The goal of FH treatment is to reduce the risk of CHD or risk of a CHD-equivalent condition (eg, carotid artery disease, diabetes, peripheral arterial disease).[6, 7, 8]

Risk categories for developing CHD are as follows:

- High risk: CHD or CHD risk equivalent (10-year risk >20%)
- Moderately high risk: More than 2 risk factors (10-year risk 10-20%)
- Moderate risk: More than 2 risk factors (10-year risk 10%)
- Lower risk: 0-1 risk factor

## Homozygous FH

The following are used in the management of homozygous FH:

- Lifestyle changes: Recommended for cardiovascular benefits[9, 10]
- High doses of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) combined with bile acid sequestrants, ezetimibe, and niacin[11]
- Anti-protein convertase subtilisin/kexin type 9 (anti-PCSK9) monoclonal antibodies (specifically, evolocumab and alirocumab) can be used as an adjunct to diet and maximally tolerated statin therapy,[12] or
- Evinacumab, or
- Lomitapide in severe cases (with or without LDL apheresis)
- LDL apheresis for selective removal of lipoproteins that contain apo-B (when the LDL receptors are absent or nonfunctional)
- Estrogen replacement therapy in postmenopausal women

The following are procedures used in the treatment of homozygous FH:

- Portacaval anastomosis
- Liver transplantation (rarely)

Investigative therapies for homozygous and heterozygous FH include probucol, which causes regression of cutaneous and tendon xanthomas in patients with both homozygous and heterozygous FH but no long-term benefits for reduced coronary atherosclerosis, and gene therapy.

#### Heterozygous FH

The following are used in the management of heterozygous FH:

- Lifestyle modification, including diet (limited saturated fats, trans fats, and cholesterol); weight management; aerobic/toning exercises
- HMG-CoA reductase inhibitors (statins) (eg, simvastatin, atorvastatin, or rosuvastatin), and one or more other LDL lowering medications, or
- Adenosine triphosphate-citrate lyase (ACL) inhibitor (eg, bempedoic acid) added to maximally tolerated statin therapy, or
- Bile acid sequestrants, or
- Ezetimibe, or
- Niacin
- Estrogen replacement therapy in postmenopausal women

Consider LDL apheresis for the following patients:

- Those with documented CHD whose LDLc level cannot be lowered below 200 mg/dL by conventional therapy
- Those without CHD but who have an LDLc level greater than 300 mg/dL

The 2013 EAS consensus statement for treatment of heterozygous FH includes the following recommendations[4, 5] :

- An LDL target of < 3.5 mmol/L (< 135 mg/dL) for children with FH (age 8–10);
- An LDL target of < 2.5 mmol/L (< 100 mg/dL) for adults with FH; and
- An LDL target of < 1.8 mmol/L (< 70 mg/dL) for adults with known CHD or diabetes.

See Treatment and Medication for more details.

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## Background

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol (LDLc).[1, 2, 3] Although moderate hypercholesterolemia is a common finding in

industrialized countries, heterozygous FH occurs in approximately 1 in 200-250 persons in the general population, about two-fold higher than previously thought.[13]

Because FH is associated with a high risk for premature coronary artery disease (CAD), health professionals should be alert to the signs found during a physical examination and to the laboratory values suggestive of FH.[14] Early detection and aggressive management to lower the LDLc level helps prevent or slows the progression of coronary atherosclerosis. Moreover, if the first-degree relatives of a patient with FH are screened, other gene carriers can be identified and treated. [15]

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## Pathophysiology

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FH is a disorder of absent or grossly malfunctioning low-density lipoprotein (LDL) receptors. The LDL receptor gene is located on the short arm of chromosome 19, and the protein is composed of 860 amino acids. It is the primary determinant of hepatic LDL uptake, which normally processes approximately 70% of circulating LDL. Two ligands on LDL bind to the receptor, apolipoprotein B-100 (apoB-100) and apoE. The LDL receptor also binds another ligand, apoE, and is, therefore, more accurately termed the B,E receptor. ApoE is found on most lipoproteins other than LDL, including very low-density lipoprotein (VLDL) and chylomicrons and their remnants, intermediate-density lipoprotein (IDL), and a subclass of high-density lipoprotein (HDL). The LDL receptor binds apoE with higher affinity than apoB-100, and some mutations in the receptor may spare uptake of LDL by allowing binding to apoE.[16, 17, 18]

Goldstein and Brown discovered the LDL receptor and determined that FH was caused by an autosomal dominant mutation. [19, 20] Since then, more than 1700 mutations have been identified, with 79% of of them probably expressed as a hypercholesterolemic phenotype. Defects in the genes encoding apoB and proprotein convertase subtilisin/kexin type 9 (PCSK9) are responsible for approximately 5% and less than 1% of FH cases, respectively.[13] LDL receptor function varies from nonexistent up to about 25% of normal receptor activity.[21]

Five classes of mutations have been defined as follows:

- Class 1 includes null alleles that result in complete absence of the LDL receptor.
- Class 2 includes defective transport alleles, which disrupt normal folding of the receptor and cause either failure in transport to the cell surface or successful transport of truncated, mutated receptors.
  - Class 2a mutations completely block the transport of the receptor from the endoplasmic reticulum to the Golgi apparatus.
  - Class 2b mutations result in a partial blockade of transport of the receptor from the endoplasmic reticulum to the Golgi apparatus.
- Class 3 includes defective binding alleles that affect binding of LDL and, in some cases, binding of VLDL as well.
- Class 4 includes defective internalization alleles that affect the concentration of normal receptors in clathrin-coated pits for internalization by the hepatocyte.
- Class 5 includes defective recycling alleles that prevent dissociation of the receptor and the ligand and thereby interrupt recycling of the receptor.

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## Frequency

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### United States

The prevalence of heterozygous FH has been thought to be approximately 1 case per 500 persons, although it has been more recently estimated at 1 case per 299 persons.[22] The prevalence of homozygous FH is 1 case per 1 million persons.

### International

The prevalence of heterozygous FH in Europe approximates that of the United States, but certain regions, such as Iceland and Finland, or populations have a higher incidence. The prevalence of heterozygous FH among French Canadians is 1 case per 270 persons and is 1 case per 170 persons in Christian Lebanese. Due to the founder effect and relatively isolated populations, 3 distinct populations within South Africa have an extremely high prevalence of FH: 1 case per 67 in Ashkenazi Jews and 1 case per 100 persons in both Afrikaners and South African Indians.

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## Mortality/Morbidity

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### Homozygous FH

Severe and widespread atherosclerosis affects all major arterial beds, including the carotid, coronary, femoral, and iliac.

Children are at risk for early coronary events, and sudden death or acute myocardial infarction may occur in patients as young as 1-2 years. Without heroic interventions to lower blood cholesterol levels, survival beyond young adulthood is unlikely.

Valve abnormalities are common, particularly aortic stenosis.

Accumulation of cholesterol in nonvascular tissue is of less clinical significance. Corneal arcus and planar, tendon, and tuberous xanthomas are present early in childhood and sometimes at birth. Recognition of the cutaneous manifestations of FH permits early diagnosis and treatment to prevent the otherwise severe and inevitable cardiovascular complications.[23, 24]

### Heterozygous FH

Premature CAD is the most serious and preventable manifestation. Untreated men are likely to develop symptoms by the fourth decade of life. The onset of symptoms in women lags behind men by approximately 10-15 years. No accurate estimates of mortality rates are available.

Cholesterol deposition in nonvascular tissue is common, although heterozygous children do not usually have physical manifestations; adults do not invariably develop them. Corneal arcus is the most frequent finding, particularly in patients older than 30 years, but this finding is also common in older patients and African Americans without hypercholesterolemia. Similarly, xanthelasma (palpebral xanthomas) can occur in older individuals with normal cholesterol levels. Neither xanthelasma nor corneal arcus is of clinical significance, except possibly cosmetically.

Xanthomas, most commonly of the Achilles tendon and extensor tendons of the hands, are rare in children and common in untreated adults. Tendon xanthomas may occur with other conditions such as familial defective apoB-100 and type III hyperlipoproteinemia. These deposits can cause Achilles tendonitis and articular symptoms, particularly of the hands, wrists, knees, and ankles.[25]

### Race

Certain populations with Finnish, Lebanese, Ashkenazi Jewish, Afrikaner, or French Canadian origins have a higher prevalence of FH.

### Sex

The gene for FH is on chromosome 19; therefore, the inheritance pattern is the same for males and females.

In heterozygous FH, the consequences of severe hypercholesterolemia manifest earlier in men than in women because of the sex protection that benefits women until the postmenopausal years. Although a woman with no other major risk factors for CAD may not develop symptomatic CAD during her lifetime, men are rarely so fortunate.

Homozygous girls and boys have the same risk for a very early cardiovascular event.

### Age

The consequences of a defective LDL receptor and subsequent elevations of LDLc are present at birth, but age is relevant because the longer patients live with extremely elevated LDLc levels, the higher their risk of CAD.

Early diagnosis and treatment to lower LDL levels and treat other coronary risk factors slows the progression of coronary atherosclerosis.

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## Presentation

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### History

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#### Children with homozygous FH

These patients may have symptoms consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or aortic stenosis. Such symptoms may be confused with conditions that are more benign unless the diagnosis of

homozygous FH is considered.

Patients may have articular symptoms such as tendonitis or arthralgias.

Patients have a history of unusual skin lesions.

Because they are obligate heterozygous hypercholesteroleemics, both parents must have severe elevations in LDLc; although they are often too young to have developed symptomatic CAD. Because each must have a parent with heterozygous FH, a history of significant hypercholesterolemia and premature CHD can be traced to the patient's second degree relatives.

### **Children with heterozygous FH**

Children with heterozygous FH do not have symptoms related to CHD.

One parent will have severe hypercholesterolemia and will probably have either a personal or family history for early CAD.

Statistically, because the gene for FH is dominant, 50% of the patient's siblings will also have heterozygous FH.

### **Adults with homozygous FH**

Most patients do not survive beyond age 30 years unless treated with unusual methods, such as liver transplantation, LDL apheresis, or ileal bypass surgery to dramatically lower their LDLc levels.

Their family history should be positive for severe hypercholesterolemia and premature CAD in both parental family lines.

### **Adults with heterozygous FH**

These patients have a long-standing history of severe hypercholesterolemia dating back to childhood.

If an acute coronary event has not already occurred, symptoms consistent with ischemic heart disease are not uncommon, especially if other cardiovascular risk factors (especially smoking) are present.

Past or present symptoms of recurrent Achilles tendonitis or arthritic complaints may be present.

Premature CAD and severe hypercholesterolemia are present in one or more first-degree relatives.

If carefully questioned, patients with either homozygous or heterozygous FH may describe first-degree relatives who had visible tendon xanthomas on their hands.

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### **Physical**

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The presence of tendon xanthomas is usually stated to be pathognomonic for FH, but that is not the case. As described in Causes, patients with familial ligand defective apoB-100 may have tendon xanthomas and elevated LDLc levels. 27-hydroxylase deficiency (cerebrotendinous xanthomatosis) causes tendon xanthomas due to the accumulation of both cholesterol and cholestanol. However, this rare disease causes other abnormalities (eg, dementia, ataxia, cataracts) with reference range cholesterol levels and, therefore, cannot be confused with FH. Sitosterolemia (phytosterolemia), a rare autosomal recessive disease, is characterized by hyperabsorption of plant sterols. Tendon xanthomas are present at an early stage although cholesterol levels are within the reference range or only mildly elevated. Uncommonly, patients with dysbetalipoproteinemia have tendon xanthomas.

### **Homozygous FH**

These patients may have cutaneous xanthomas at birth or by early childhood.

Several types of xanthomas are usually obvious in the first decade of life, and they include (1) planar xanthomas (on hands, elbows, buttocks, or knees), which are diagnostic for the homozygous state and are distinct from other cutaneous xanthomas because of their yellow-to-orange coloration; (2) tuberous xanthomas (on hands, elbows, or knees); and (3) tendon xanthomas (especially on extensor tendons of hands or Achilles tendon) will occur somewhat later.

Children may have corneal arcus, which is sometimes circumferential. While occasionally present in older adults with normal cholesterol levels, corneal arcus is highly unusual in children, and this finding should prompt a workup for homozygous FH.

The murmur of aortic stenosis may be heard.

### **Heterozygous FH**

Most children with heterozygous FH do not develop tendon xanthomas or corneal arcus. By the third decade of life, more than 60% of patients with untreated FH develop tendon xanthomas as in the image below.



Metacarpophalangeal joint tendon xanthomas in a 45-year-old man with heterozygous familial hypercholesterolemia.

Xanthomas are noted commonly on the Achilles tendons and metacarpal phalangeal extensor tendons of the hands.

The figures in many textbooks suggest that tendon xanthomas in heterozygous patients are readily apparent upon gross inspection. Unfortunately, this often is not the case. Careful palpation rather than simple inspection may be necessary for detection of Achilles tendon xanthomas. A diffusely thickened tendon or one with discreet irregularities is suggestive of a xanthoma.

Tendon xanthomas of the metacarpophalangeal joints may be seen by careful inspection and palpation. Slowly flexing and extending the digits and watching for nodules that move with the motion of the tendon make these xanthomas more noticeable and distinguish them from cutaneous or subcutaneous nodules.

Xanthelasma may occur in older patients with normal cholesterol levels and this finding is, therefore, not specific for FH.

The presence of tendon xanthomas is often stated to be pathognomonic for FH but that is not the case.

As described below, patients with familial ligand defective apoB-100 may have tendon xanthomas and equivalent laboratory values.

27-hydroxylase deficiency (cerebrotendinous xanthomatosis) causes tendon xanthomas due to the accumulation of both cholesterol and cholestanol. But this rare disease causes other abnormalities (dementia, ataxia, cataracts) with normal cholesterol levels and, therefore, cannot be confused with FH.

Sitosterolemia (phytosterolemia), a rare autosomal recessive disease, is characterized by hyperabsorption of plant sterols. [24, 26] Tendon xanthomas may be present though cholesterol levels are normal or only mildly elevated.

Uncommonly, patients with dysbetalipoproteinemia have tendon xanthomas.

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## Causes

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A major change in the number or functional status of LDL receptors directly affects serum cholesterol levels. If the liver does not take up LDL particles, serum LDLc levels increase. Also, when LDL is not internalized by hepatocytes, hepatic synthesis of cholesterol is not suppressed. This leads to further cholesterol production despite high levels of circulating cholesterol. Therefore, circulating cholesterol levels are increased dramatically. The total and LDLc levels of infants and children with homozygous FH are higher than 600 mg/dL. In patients with heterozygous FH, half the LDL receptors are normal and half are rendered ineffective by the mutation. These patients' total cholesterol and LDLc levels are twice as high as the population average. LDLc levels of 200-400 mg/dL are common.

High levels of LDLc increase cholesterol uptake in nonhepatic cells that is independent of LDL receptors. These scavenger pathways allow cholesterol uptake by monocytes and macrophages, leading to foam cell formation, plaque deposition in the endothelium of coronary arteries, and premature CAD. Cholesterol also accumulates in other areas, particularly the skin, causing xanthelasma and a variety of xanthomas. Early corneal arcus is frequent, and, in patients with the homozygous condition, valvular abnormalities, most frequently aortic stenosis, are common secondary to the deposition of cholesterol.

Several conditions other than FH cause severely elevated LDL levels, and each is caused by a single gene abnormality.

## Familial ligand defective apoB-100

Familial ligand defective apoB-100 (FLDB), also called familial defective apoB-100, is responsible for a syndrome almost indistinguishable from heterozygous FH. Instead of an abnormal or absent LDL receptor, this syndrome is caused by an abnormality at the binding site of apoB-100, which impedes its role as a ligand for the receptor. ApoB-100 is a single polypeptide chain composed of 4536 amino acids. The gene resides on the short arm of chromosome 2 and the first described mutation was a substitution of glycine for arginine at the codon for amino acid 3500. Different mutations at the same and different codons have since been described.

Although the LDL receptors are normal in both number and function, LDL is taken up inefficiently, leading to elevated LDLc levels that can be indistinguishable from those associated with heterozygous FH. These patients can present with cutaneous manifestations and an increased risk of premature CAD similar to patients with heterozygous FH. Because LDL receptors function normally with respect to the apoE ligand, uptake of very low-density lipoprotein, very low-density lipoprotein remnants, and intermediate-density lipoprotein is normal. The consequence may be that patients with defective apoB-100 may have a clinically more benign course than patients with heterozygous FH. The finding that patients homozygous for familial defective apoB-100 are clinically similar to those with the heterozygous condition supports this supposition.

## Autosomal recessive hypercholesterolemia

Another recently identified molecular defect that also causes severely elevated LDL levels is autosomal recessive hypercholesterolemia. These patients have LDLc levels that are higher than 400 mg/dL; however, heterozygous individuals have normal levels.

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## DDx

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## Differential Diagnoses

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- Dysbetalipoproteinemia (type III hyperlipidemia)
- Familial ligand defective apoB-100, familial defective apoB-100
- Homozygous autosomal recessive hypercholesterolemia
- Sitosterolemia (Phytosterolemia)

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Workup

## Workup

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## Laboratory Studies

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The diagnosis of both homozygous and heterozygous FH is based primarily on the finding of severe LDLc elevations in the absence of secondary causes of hypercholesterolemia with triglyceride levels that are within the reference range or mildly elevated and HDL cholesterol (HDLc) levels that are within the reference range or slightly low. A probable diagnosis of heterozygous FH can be made if the LDLc level is greater than 330 mg/dL or if tendon xanthomas are present in a patient with an LDLc level above the 95th percentile. Definitive diagnosis can be made only with gene or receptor analysis.

A substantial increase in serum triglyceride levels should raise the possibility of another lipid disorder.

## Lipid analysis

Cholesterol levels are severely elevated in children and adults with homozygous FH, with total cholesterol and LDLc levels greater than 600 mg/dL and triglyceride levels within the reference range.

In patients with heterozygous FH, LDLc levels are commonly higher than 250 mg/dL and usually increase with age. An LDLc level higher than 200 mg/dL in a patient younger than 20 years is highly suggestive of heterozygous FH or, possibly, familial ligand defective apoB-100 (see Pathophysiology). In adults, LDLc levels higher than 290-300 mg/dL suggest heterozygous FH.

Lipoprotein (a) may be measured because patients with both heterozygous FH and high levels of lipoprotein (a) (>30 mg/dL) have a worse prognosis than those with normal levels of lipoprotein (a). However, all patients with FH are at very high risk for CAD and because no data are available to suggest that lipoprotein (a) should be specifically targeted for treatment.

## Tests to rule out secondary hypercholesterolemia

Other laboratory testing may be suggestive by findings discerned thorough history and physical examination.

In the absence of symptoms or signs suggestive of a particular disorder, a limited workup should be performed to rule out secondary hypercholesterolemia.

Basic tests to rule out diabetes, hypothyroidism, hepatic disease, and renal disease are usually sufficient.

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## Imaging Studies

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Patients with homozygous FH should receive Doppler echocardiographic evaluation of the heart and aorta annually and, if available, computed-tomography coronary angiography every 5 years or more frequently if clinically indicated, taking into account the radiation exposure and severity of subclinical disease.

Children with homozygous FH should be referred to a pediatric cardiologist for consideration of vascular imaging studies (Pet scan, determination of carotid intima medial thickness, coronary catheterization) that can direct treatment for hypercholesterolemia.

Radiographic imaging of the Achilles tendon helps accurately measure Achilles tendon xanthomas, but the findings do not change lipid management.

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## Other Tests

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Lipoprotein electrophoresis is expensive and is unnecessary for the diagnosis of FH. Moreover, in the absence of preparative ultracentrifugation, it has no place in the workup of any lipid disorder. If fasting lipid analysis reveals elevated triglyceride levels and the diagnosis of FH is in doubt, beta quantification (ultracentrifugation and electrophoresis) may be performed at a major lipid center or one of the few commercial sites in the United States and other countries that performs this procedure.

LDL receptor analysis can be used to identify the specific LDL receptor defect. However, this analysis can only be performed at certain research laboratories and is expensive; and the results have no impact on management. LDL receptor or apoB-100 studies can help distinguish heterozygous FH from the similar syndrome of familial defective apoB-100, but this finding would not alter treatment.

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## Procedures

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The presence of an unusually high LDLc level should make identifying a cutaneous lesion straightforward. Possible entities include xanthelasmas or xanthomas.

If identification of a cutaneous lesion is unclear and the diagnosis of heterozygous FH is uncertain, a biopsy can be performed. Both xanthelasmas and the xanthomas of FH contain accumulations of cholesterol. By contrast, eruptive xanthomas in patients with severe hypertriglyceridemia (levels >1000 mg/dL) contain triglycerides (fat).

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## Treatment

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### Medical Care

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The National Cholesterol Education Program (NCEP) ATPIII defined LDLc goals and cutpoints for therapeutic intervention based on risk for CHD (see Table 2 and Table 3).[6, 7]

The guidelines were updated in 2004 to reflect the findings of several interventional trials demonstrating that coronary event rate was reduced after lowering the LDLc well below 100 mg/dL.[8]

The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) have also released guidelines for the management of dyslipidemias, available at the ESC site.[27]

In addition, the American College of Cardiology/American Heart Association (ACC/AHA) released updated blood cholesterol guidelines, in 2018; however, they do not address a specific approach to and management of FH.[28] .

## Risk Categories

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### CHD or CHD risk equivalent

See the list below:

- Clinical CHD
- Symptomatic carotid artery disease or carotid stenosis greater than 70%
- Peripheral artery disease
- Abdominal aortic aneurysm
- Diabetes
- Global 10-year risk of major CHD event (ie, fatal or nonfatal myocardial infarction) greater than 20%

### Determination of risk

Treatment of elevated LDLc levels is based upon the risk for a coronary heart disease (CHD) event (see Table 1). The 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) defined target LDLc levels and levels based on risk for CHD.[6] The 2004 update added optional lower LDLc goals to reflect the findings of several interventional trials demonstrating that more aggressive LDLc lowering further reduced coronary event rate.[8]

In patients without atherosclerotic disease, the risk for developing CHD is defined by the number of major risk factors for CHD and by the following:

- Hypertension (blood pressure  $\geq 140/90$  mm Hg or treatment for hypertension)
- Cigarette smoking (any within the past mo)
- HDLc level below 40 mg/dL
- Male sex and age 45 years or older
- Female sex and age 55 years or older
- Family history of premature CHD: Clinical CHD or sudden death in first-degree male relative younger than 55 years or first-degree female relative younger than 65 years

An HDLc level of 60 mg/dL or greater is a negative risk factor for CHD and its presence removes one risk factor from the total.

Percent risk for developing CHD or having a major CHD event (ie, fatal or nonfatal myocardial infarction) is determined by calculating the Framingham risk score, which is available through the US National Heart, Lung, and Blood Institute (see Risk Assessment Tool for Estimating 10-Year Risk of Developing Hard CHD).

- LDLc goal less than 100 mg/dL
- Therapeutic lifestyle changes (TLC) instituted at LDL 100 mg/dL or more
- Medical therapy initiated at LDL 100 mg/dL or more (new 2004 cut off point)

Optional LDLc goal less than 70 mg/dL, especially for very high risk patients include the following:

- Patients with CHD and multiple other major risk factors for CHD, especially diabetes
- Severe, poorly controlled risk factors, especially continued cigarette smoking
- Multiple risk factors of the metabolic syndrome
- Patients admitted with an acute coronary syndrome

### Moderately high risk, more than 2 risk factors

See the list below:

- See Table 2
- Global risk 10-20% - LDLc goal less than 130 mg/dL, optional LDLc goal less than 100 mg/dL
- Consider medical therapy for LDL 100-129

### Moderate risk, 2 risk factors or more

See the list below:

- Global risk less than 10% - LDLc goal less than 130 mg/dL

### Low risk

See the list below:

- None to 1 major risk factor for CHD
- LDLc goal less than 160 mg/dL
- Low-risk patients have fewer than 2 risk factors and a 10-year risk for a major CHD event that is almost always less than 10%. The goal LDLc is less than 160 mg/dL.
- Moderate risk patients have 2 or more factors and a 10-year risk for CHD of less than 10%. The goal LDLc is less than 130 mg/dL.
- Moderately high risk patients have 2 or more risk factors and a 10-year risk of 10-20%. The goal LDLc is less than 130 mg/dL and the update suggested an optional goal LDLc of less than 100 mg/dL.

The highest category of risk includes CHD and CHD risk equivalents include the following:

- Clinical CHD
- Symptomatic carotid artery disease (transient ischemic attack or stroke of carotid origin)
- Peripheral artery disease
- Abdominal aortic aneurysm
- Diabetes
- 10-year risk less than 20%

The LDLc goal for high-risk patients is less than 100 mg/dL and the 10-year risk is greater than 20%. In addition to lifestyle changes, institution of medication is recommended if LDLc level is greater than 100 mg/dL. Patients at high or very high risk have an optional LDLc goal of less than 70 mg/dL.

Patients with cardiovascular disease who are at very high risk have an optional LDLc goal of less than 70 mg/dL.

Very high risk is defined as the presence of the following:

- Multiple other major risk factors for CHD, especially diabetes
- Severe, poorly controlled risk factors, especially continued cigarette smoking
- Multiple risk factors for the metabolic syndrome (especially triglycerides >200 mg/dL, non-HDLc >130 mg/dL, and HDLc < 40 mg/dL)
- Patients with acute coronary syndromes

Table 1. LDLc Target levels and levels Indicating Therapeutic Lifestyle Changes (TLC) and Drug Therapy ([Open Table in a new window](#))

Risk Category	LDLc Target level, mg/dL	LDLc level Indicating TLC, mg/dL	LDLc level for Considering Drug Therapy, mg/dL*

High risk: CHD or CHD risk equivalent (10-y risk >20%)	< 100  Optional goal < 70	>100	>100
Moderately high risk: More than 2 risk factors (10-y risk 10-20%)	130  Optional goal < 100	>130	>130  (100-129 may consider drug options)
Moderate risk: More than 2 risk factors (10-y risk 10%)	< 130	>130	>160
Lower risk: 0-1 risk factor	< 160	>160	>190  (160-189 LDL-lowering drug optional)

\*The 2004 update recommended that when statin therapy is initiated in patients at high or moderately high risk, a dose and strength should be chosen that achieves at least a 30-40% LDLc reduction (see Table 3).



## Treatment Recommendations for Homozygous FH

EAS guidelines for the screening and treatment of homozygous FH are summarized as follows:[27, 29]

- Treatment of homozygous FH involves a combination of lifestyle changes, statin therapy (first approach), and lipoprotein apheresis for severe cases, if available, and should be started as early as possible.
- LDL apheresis should begin as early as age 5 years and no later than age 8 years.
- For homozygous FH patients, the LDL cholesterol targets are < 100 mg/dL for adults, < 70 mg/dL for adults with clinical cardiovascular disease (CVD), and < 135 mg/dL for children.
- Other novel agents for LDL cholesterol lowering (eg, lomitapide with or without apheresis) can be considered as adjunctive treatments for patients who do not achieve the recommended LDL cholesterol targets and remain at high cardiovascular risk.

General treatment recommendations are discussed in more depth below.

Because of improved diet normally results in upregulation of LDL receptors, the impact of diet changes on LDLc levels in homozygous patients is negligible (there are no receptors to upregulate), but lifestyle changes have other cardiovascular benefits and should be strongly encouraged.[9, 10]

Because of the severity of CHD and lack of response, homozygous FH patients require heroic intervention.

Occasionally, the LDL receptors retain some degree of function and diet control and high doses of HMG-CoA reductase inhibitors combined with bile acid sequestrants, ezetimibe, and niacin can be effective.[11] Estrogen replacement therapy in

postmenopausal women is also effective, but this therapy is not recommended because of its adverse effects in older women. However, in some women the benefits may outweigh risks.

When the LDL receptors are absent or nonfunctional, one of the following is necessary:

LDL apheresis for homozygous FH involves selective removal of lipoproteins that contain apo-B by heparin precipitation, dextran sulfate cellulose columns, or immunoabsorption columns. All methods reduce LDLc levels more than 50% and also lower lipoprotein (a), VLDL, and triglyceride levels. HDL is spared. The procedure takes 3 or more hours and is performed at 1- to 2-week intervals. Few adverse events are experienced, most of which are noncritical episodes of hypotension. LDL apheresis is an extremely expensive procedure and is not readily available.[30, 31]

A study by Drouin-Chartier et al indicated that in patients with homozygous FH, the level of serum triglycerides prior to the initiation of LDL apheresis is inversely proportional to the effectiveness of dextran sulfate adsorption in the reduction of LDLc. Dividing pre-apheresis triglyceride concentrations into quartiles, the investigators found that LDL apheresis with dextran sulfate adsorption was 3.9% less effective in acutely reducing LDLc concentrations for patients in the highest quartile (over 2.09 mmol/L) than for those in the lowest quartile (0.93 mmol/L or below). The study also found that for LDL apheresis using heparin-induced extracorporeal LDL precipitation, pre-apheresis serum triglyceride levels did not significantly affect LDLc removal.[32]

## Portacaval anastomosis

Compared to liver transplantation (see Surgical Care), this procedure is less hazardous and requires no immunosuppression.

Although cholesterol levels are not reduced as dramatically when compared with transplantation or apheresis, the clinical benefits appear comparable.

LDLc reductions 50% have been reported; regression of coronary lesions, aortic lesions, and xanthomas have been documented.

The exact mechanism by which LDLc is lowered is unclear.

## Other treatments for homozygous FH

### Evolocumab

Evolocumab (Repatha) was approved in August 2015. It is indicated as an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous FH who require additional lowering of LDLc in adults and adolescents aged 13-17 years. It is also indicated for heterozygous FH in adults.

Approval of evolocumab was based on the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER) study. During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDLc levels.[33, 34] Additionally, the rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; P=0.003) in a prespecified exploratory analysis.[33] Results of the ongoing FOURIER trial is looking at cardiovascular outcomes and will include more than 27,000 patients with clinically evident cardiovascular disease and is expected to be completed in late 2017.[35]

An interim subset analysis of the Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders (TAUSSIG) also indicated that evolocumab is effective in reducing LDLc in homozygous FH, even without apheresis. Patients in the study underwent treatment with evolocumab 420 mg subcutaneously either monthly or, if also undergoing apheresis, every 2 weeks, with an option, for patients not on apheresis, to increase dosing to every 2 weeks following 12 weeks of treatment. Among the results obtained, the investigators found that after 12 weeks, the mean LDLc level had been reduced by 20.6% and the mean HDLc level had been increased by 7.6%. Patients not on apheresis who increased dosing to every 2 weeks experienced an additional mean LDLc reduction of 8.3%.[36]

### Alirocumab

Alirocumab (Praluent) gained FDA approval in April 2021 for adjunctive use with other LDLc-lowering therapies in the treatment of homozygous FH. Approval was based on the ODYSSEY HoFH trial, which found alirocumab to be associated with significant LDLc reductions in patients with the disease.[37]

### Lomitapide

Lomitapide (Juxtapid) is a first-in-class microsomal triglyceride transfer protein (MTP) inhibitor. It was approved by the US Food and Drug Administration (FDA) in December 2012 as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDLc, triglycerides, apoB, and non-HDLc in patients with homozygous familial hypercholesterolemia. Because lomitapide increases risk of hepatotoxicity, it is only available through a restricted access program. Approval was based on a small trial of 29 patients exposed to lomitapide, with 23 patients exposed to the drug for 1 year, 15 patients exposed for 2 years, and 5 patients exposed for 3 years. At baseline, the mean LDLc in the homozygous FH patients was 336 mg/dL, and this was reduced 50% after 26 weeks of treatment (P < 0.0001).[38]

A literature review by Liu et al reported that in patients with homozygous FH, lomitapide reduces LDLc, total cholesterol, apoB, and triglyceride levels, even without other lipid-lowering treatments, but also decreases HDLc and apoA-1 values.[39]

### Evinacumab

Evinacumab (Evkeeza) is a recombinant human monoclonal antibody that binds to and inhibits angiopoietin-like 3 (ANGPTL3). Lipoprotein lipase and endothelial lipase are inhibited by ANGPTL3, resulting in reduced lipid metabolism. Inhibition of ANGPTL3 by evinacumab allows increased lipid metabolism, leading to decreased LDLc, HDLc, and triglycerides (TG).

The FDA approved evinacumab in February 2021 as an adjunct to other LDLc-lowering therapies for HoFH in adults and adolescents aged 12 years or older. Approval was based on the phase 3 ELIPSE trial (n = 65). The study found that patients undergoing stable lipid-lowering treatment in whom an intravenous (IV) infusion of evinacumab was administered every 4 weeks achieved, by week 24, a 47.1% relative reduction in their LDLc level, compared with a 1.9% increase seen in patients treated with a placebo.[40]

### Probucol

Probucol, a medication with only mild LDL-lowering effects and an undesirable HDL-lowering impact, has been shown to cause regression of cutaneous and tendon xanthomas in patients with both homozygous and heterozygous FH. An animal model has demonstrated reduced coronary atherosclerosis. No long-term benefits have been documented for patients with FH.

### Gene therapy

Gene therapy is still at the investigational stage. Initially, expectations were high that genetic manipulation would be a less hazardous method for providing functional LDL receptors compared with liver transplantation; however, advances have been slow.

## e**medicine**

## Treatment for Heterozygous FH

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In patients with heterozygous FH, lifestyle modification should always be instituted but is unlikely to result in acceptable LDLc levels; therefore, cholesterol-lowering medication (usually more than one) is necessary.[10]

The 2013 European Atherosclerosis Society (EAS) consensus statement for screening and treatment of heterozygous FH includes the following treatment recommendations[4, 5] :

- An LDL target of < 3.5 mmol/L (< 135 mg/dL) for children with FH (age 8–10);
- An LDL target of < 2.5 mmol/L (< 100 mg/dL) for adults with FH; and
- An LDL target of < 1.8 mmol/L (< 70 mg/dL) for adults with known CHD or diabetes.

Lifestyle modifications include a diet that severely limits saturated fats, trans fats, and cholesterol (see Table 2).[9]

Desirable weight should be attained. Significant weight loss should improve all lipid parameters (LDLc, HDLc, triglycerides).

Aerobic and toning exercises improve blood lipid levels if performed for longer than 30 minutes, 4 or more days per week.

While these efforts often have only a modest impact on LDLc levels, rigorous dietary intervention works synergistically with lipid-lowering medications, especially diet.[9]

With 50% functional LDL receptors, heterozygous FH patients have an excellent response to the usual cholesterol-lowering drugs, but treatment still remains difficult.

To approach the recommended LDLc goals, a high dose of one of the 3 strongest HMG-CoA reductase inhibitors (statins), simvastatin, atorvastatin, or rosuvastatin, and one or more other LDL lowering medications, bile acid sequestrants, ezetimibe, or niacin, is recommended.[11] To decrease the risk of myopathy, one step below the maximum dose of the statin should be considered. For additional resources, please visit Landmark Statin Trials.

Because doubling the dose of any statin lowers the LDLc only 6-7%, adding a second, third, or even fourth agent is more effective.[41]

A pooled analysis of 5 statin trials revealed that intensive-dose therapy was associated with a greater risk of diabetes when compared with moderate dosing.[42]

In February 2020, the FDA approved bempedoic acid (Nexletol), the first adenosine triphosphate-citrate lyase (ACL) inhibitor. Reducing hepatic synthesis of LDLc, the enzyme ACL is upstream of HMG-CoA reductase in the cholesterol

biosynthesis pathway.

Bempedoic acid is indicated for adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease when additional LDLc reduction is needed, serving as an adjunct to diet and maximally tolerated statin therapy.

Approval of bempedoic acid was based on the phase-3 trials CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Harmony and CLEAR Wisdom. The addition of bempedoic acid to maximally tolerated statin therapy resulted in an average placebo-corrected LDLc reduction of 18%.<sup>[43, 44]</sup>

Bempedoic acid was also approved in combination with ezetimibe (Nexlizet). A mean 38% reduction in LDLc (in comparison with placebo) was seen when the combination was added to maximally tolerated statins.<sup>[45]</sup>

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, alirocumab (Praluent), was approved by the FDA in July 2015. It is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDLc.

Alirocumab was approved before the completion of its CV-outcomes trial. The primary outcome measures for ODYSSEY-Outcomes,<sup>[46]</sup> which is scheduled to finish by December 2017, include possible first occurrence of CHD death, any nonfatal MI, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalization. Secondary measures included time to first occurrence of any CHD event, major CHD event, any CV event, and all-cause mortality.

Alirocumab's approval was based on data from the pivotal Phase 3 ODYSSEY program, which showed consistent, positive results for alirocumab compared to placebo and included current standard of care therapy (statins). The ODYSSEY LONG TERM trial evaluated alirocumab 150 mg SC every 2 weeks. Alirocumab reduced LDL cholesterol by 58% compared with placebo at week 24 when added to current standard of care, including maximally tolerated statins.<sup>[47]</sup> In ODYSSEY COMBO I, Praluent 75 mg every 2 weeks as an adjunct to statins reduced LDL cholesterol by an additional 45% compared with placebo at week 12.<sup>[48]</sup> At week 24 in the same trial, alirocumab reduced LDL cholesterol by an additional 44% compared with placebo. In this study, if additional LDL cholesterol lowering was required based on prespecified criteria at week 8, alirocumab was up-titrated to 150 mg at week 12 for the remainder of the trial. Eighty-three percent of patients remained on their initial 75 mg dose.

Evolocumab (Repatha) is the second PCSK9 inhibitor approved in the United States in 2015. It is approved for adults as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic CVD who require additional lowering of LDLc. It is also approved for adults and adolescents with homozygous familial hypercholesterolemia (HoFH).

Approval of evolocumab was based on the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER) study. During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels.<sup>[33, 34]</sup> Additionally, the rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; P=0.003) in a prespecified exploratory analysis.<sup>[33]</sup> Results of the ongoing FOURIER trial is looking at cardiovascular outcomes and will include more than 27,000 patients with clinically evident cardiovascular disease and is expected to be completed in late 2017.<sup>[35]</sup>

In pediatric heterozygous FH, a study suggests rosuvastatin slows atherosclerotic progression. In a randomized study (CHARON trial) of 196 children and adolescents (age range, 6-17 y) with heterozygous FH and 65 unaffected sibling controls, treatment with rosuvastatin in affected patients for two years slowed the progression of subclinical atherosclerosis.<sup>[49, 50, 51]</sup> At baseline, the mean carotid intima-media thickness (IMT) was significantly higher among those with heterozygous FH (0.398 mm) compared with their healthy siblings (0.376 mm); following 2 years of treatment with rosuvastatin, there was no difference in the mean carotid IMT between the groups, and 38% of those receiving rosuvastatin met the target LDLc of less than 110 mg/dL.<sup>[49]</sup> Over 85% of patients in the treatment group reported adverse events that the investigators considered as mild (eg, headaches, nasopharyngitis, influenzalike symptoms). All patients remained within the normal height and weight range for their age.<sup>[49]</sup>

Fibrates have no place in treatment of patients with FH unless triglyceride levels are elevated.

Estrogen replacement therapy in postmenopausal women also helps lower LDLc levels, but this therapy is not recommended because of its adverse effects in older women, although the benefits may sometimes outweigh risks.

Patients with documented CHD whose LDLc level cannot be lowered below 200 mg/dL by conventional therapy are candidates for LDL apheresis. Patients without CHD but with an LDLc level of higher than 300 mg/dL also qualify for this intervention. However, health insurance coverage is not automatic, and decisions are made on a case-by-case basis because of the costs, which approach \$3000 for each treatment, every 2 weeks, for the patient's lifetime.

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## Surgical Care

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## Liver transplantation for homozygous FH

Liver transplantation is rarely performed because of the considerable risks associated with the surgery itself and long-term immunosuppression. But a new liver provides functional LDL receptors and causes dramatic decreases in LDLc levels.

If not normalized, LDLc levels then can be treated with the usual LDL-lowering medications.

## Portacaval anastomosis for homozygous FH

This may be indicated.

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## Consultations

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### Homozygous FH

Because the risk of sudden death or nonfatal myocardial infarction is so high, early or highly specialized treatment is necessary.

As soon as a child is diagnosed with homozygous FH, a referral should be made to a medical center specializing in severe lipid disorders.

Referral to center providing LDL apheresis

### Heterozygous FH

Refer to qualified nutritionist to provide guidance in reducing intake of saturated and trans fats and cholesterol and assist in weight reduction if indicated.

If patients do not reach recommended treatment goals under the care of their primary care physicians, they should be referred to an endocrinologist or lipid specialist and to a qualified nutritionist.

If patients are considered candidates for LDL apheresis and are willing to undertake this arduous procedure, referral should be made to a medical facility offering this procedure.

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## Diet

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Predicting the degree of improvement in an individual's lipids levels with dietary change is difficult because many variables affect the response, including the makeup of the baseline diet, the degree of patient compliance, and the individual's LDL responsiveness to the diet, which is genetically determined. A decrease of at least 15% can be expected in heterozygous patients who are willing to make significant dietary changes.

The 2001 NCEP ATPIII guidelines emphasize a multifaceted approach to the prevention of CHD.[6] Designated therapeutic lifestyle changes (TLC), its features include increased physical activity, weight reduction, and diet modification. The same diet is recommended for all patients with lipid abnormalities.

The NCEP recommendations for the dietary management of hypercholesterolemia are not highly restrictive, but a more stringent regimen may have a greater impact on lipid levels (see Table 2).

Restricting total fat is less important than reducing the intake of saturated fat, trans fat, and cholesterol. Moreover, diets very low in total fat are high in carbohydrates, which may increase triglyceride levels and lower HDLc levels. Substituting monounsaturated fats (eg, olive and canola oils, avocados, nuts) for carbohydrates does not increase LDLc levels and, in the absence of weight gain, may increase HDLc levels and lower triglyceride levels in patients who have maintained a diet very low in fat.

Diets should be rich in whole grains, whole fruit, and legumes and other vegetables. These foods are high in soluble fiber, which has a small (approximately 5%) cholesterol-lowering effect; they are also high in antioxidants and flavonoids, which may be cardioprotective.

Table 2. Recommended Dietary Intake ([Open Table in a new window](#))

Food Category	Typical US Diet	NCEP Diet	Diet for FH

Cholesterol, mg/d	500	< 200	100
Total fat, % energy (calories)	40	25-35	20
Saturated fat, % energy (calories)	14	< 7	< 6
Carbohydrate, % energy (calories)	45	50-60	65
Protein, % energy (calories)	Approximately 15	15	N/A

Other features of the NCEP diet are as follows:

- Fiber (soluble fiber): Intake should be 20-30 g/d.
- Carbohydrates: Intake should be 50-60% of total energy (caloric) intake. Carbohydrates should be derived predominantly from foods rich in complex carbohydrates, including grains, especially whole grains, fruits, and vegetables.
- Plant sterols and stanols: Intake should be 2 g/d.[26] These are present in commercial margarines (eg, Benacol, Take Control).
- Total energy (caloric) intake: Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain. Daily energy expenditure should include at least moderate physical activity, contributing approximately 200 Kcal/d (eg, a brisk walk of 2 miles or more).
- Trans- fatty acids (trans fats): Intake should be avoided. Products made with hydrogenated fats contain variable amounts of trans fats. Similar to saturated fats, trans fats increase LDLc levels. However, unlike saturated fats, trans fats decrease HDLc levels. Hydrogenated fats and trans fats are found in many margarines, cakes, cookies, crackers, and frosting.

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### Activity

Exercise has many cardiovascular benefits and can improve blood lipid levels. Although a greater proportion of time should be spent doing aerobic exercise because of its greater impact on lowering blood pressure and decreasing insulin resistance, resistance training also has benefits.

Patients with CAD or symptoms suggestive of ischemic heart disease should undergo a symptom-limited exercise stress test before undertaking a new program of vigorous exercise.

## eMedicine

### Guidelines

#### Guidelines Summary

A 2017 consensus statement on pediatric familial hypercholesterolemia from a joint working group of the Japan Pediatric Society and the Japan Atherosclerosis Society included the following key points[52] :

- A family history of FH and the presence of premature CAD are important diagnostic factors in FH

- Because plasma LDLc levels fluctuate in children, multiple measurements of this value should be taken
- Following diagnosis of FH, the patient's family should be screened for the disease
- Regular examination for CAD is recommended in those pediatric patients with heterozygous FH who have Achilles tendon thickening or carotid artery atherosclerosis
- Pediatric patients with homozygous FH should undergo regular, systemic exams, performed by specialists, for atherosclerotic CVD
- Fat should account for 20-25% of the energy obtained from food, and carbohydrates should account for 50-60%; less than 7% of energy should be obtained from saturated fatty acids, and less than 200 mg of cholesterol should be consumed per day
- In pediatric patients with heterozygous FH, an LDLc level of 180 mg/dL or above from age 10 should prompt the initiation of drug therapy
- Statin therapy, initiated at a low dose, is the first choice for drug treatment in pediatric heterozygous FH; liver function tests should be carried out after one month and then, once a stable medication dose has been achieved, about once every 3-4 months; patients should undergo continuous monitoring for adverse effects and for abnormalities in growth and secondary sexual characteristics
- At initial diagnosis of pediatric homozygous FH, treatment with lifestyle interventions and maximally tolerated statin therapy should be instituted; children with homozygous FH frequently need treatment with a combination of lipid-lowering drugs, including ezetimibe
- Weekly or biweekly lipoprotein apheresis should be initiated in homozygous FH patients if target LDLc levels cannot be reached with statin therapy



## Medication

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### Medication Summary

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HMG-CoA reductase inhibitors (statins) are the medications of choice for the treatment of LDLc elevations in patients with heterozygous FH because they have the greatest efficacy and are easily tolerated and because multiple randomized, placebo-controlled trials have shown that lowering LDLc levels with statins reduces coronary morbidity and mortality and, in some cases, total mortality. The strongest statins, rosuvastatin and atorvastatin, at their maximum approved doses, can be expected to reduce LDLc levels 50-60%. [11, 53, 54, 55, 56]

The ATPIII update advises that the starting dose of a statin be sufficient to lower the LDLc 30-40% (see Table 3). [8]

Even the maximum doses of the strongest statins are usually inadequate for patients with FH, and the addition of one or more nonstatin cholesterol-lowering medications is necessary. ACL inhibitors [43, 44] and PCSK9 inhibitors [33, 34, 46, 47] are now available in the United States to add to maximally tolerated statins for patients with HeFH.

Bile acid sequestrants (eg, cholestyramine, colestipol, colesevelam) can be added with no risk of drug interaction, with the exception of absorption of the statin (and many other medications) if taken at the same time. Bile acid sequestrants modestly decrease LDLc levels with a small increase in HDLc and triglyceride levels. Other medications should be taken 1 hour before or 4 hours after a bile acid sequestrant. Colesevelam, which is a polymer, has less gastrointestinal side effects than the older resins and is effective at a lower dose (maximum 7 tabs/d).

Nicotinic acid (niacin) not only lowers LDLc levels but also has significant HDL-raising and triglyceride-lowering effects. There are few data to support the belief that niacin increases the risk of myopathy if combined with a statin.

Fibric acid derivatives include gemfibrozil (Lopid) and fenofibrate (Tricor). Outside of the United States, bezafibrate is also available. The fibrates lower triglyceride levels and raise HDLc levels, but they do not reliably lower LDLc levels. They increase the risk of statin-induced myositis more so than niacin. Therefore, this class of drugs is not usually useful in patients with FH.

Ezetimibe reduces LDLc levels approximately 18%, with small HDLc-raising and triglyceride-lowering effects. Because the mechanism by which it inhibits cholesterol absorption is quite specific, it does not interfere with the absorption of other drugs and does not cause the constipation associated with bile acid sequestrants. This medication has a major role in LDLc-lowering when a statin alone is not sufficient and can be administered as a single tablet when combined with simvastatin (Vytorin).

These statin combinations are particularly appropriate for patients with FH, most of whom will require 2 or more drugs to reach their LDLc goals. In addition, significantly greater than expected decreases in the LDLc level are frequently observed.

An extended follow-up of the Heart Protection Study examined the long-term efficacy and safety of LDLc-lowering with simvastatin treatment. In-trial cardiovascular benefits began after the first year and increased with each subsequent year of statin therapy and persisted 6 years beyond the end of the study. No difference in nonvascular morbidity or mortality was observed either during 5 years of statin therapy or in 6-year follow-up. The investigators recommend prompt initiation and long-term statin treatment in patients who are at increased risk for vascular events. [57]

Table 3. Statin and Statin Combination Approved Doses, Expected LDLc Decrease, and Dose Required for 30-40% LDLc Reduction ([Open Table in a new window](#))

Statin	FDA-Approved Dose	Expected LDLc Decrease	Dose Required for 30-40% LDLc Reduction
Atorvastatin	10-80 mg daily	35-60%	10 mg
Fluvastatin	20-40 mg at bedtime	20-30%	40 mg qd/bid
	40 mg bid	35%	40 mg bid
Extended-release fluvastatin (Lescol XL)	80 mg at bedtime	35-38%	80 mg at bedtime
Lovastatin	20-80 mg at supper	25-48%	40 mg at dinner
Extended-release lovastatin (Altoprev)	20-60 mg at bedtime	25-45%	60 mg at bedtime
Pravastatin	40-80 mg at bedtime	30-40%	40 mg at bedtime
Rosuvastatin	10-40 mg daily	40-60%	5 mg daily
Simvastatin	20-80 mg daily at bedtime	35-50%	20 mg at bedtime
Simvastatin + ezetimibe (Vytorin)	10/20 mg 10/40 mg 10/80 mg at bedtime	50-60%	10/20 mg at bedtime

## HMG-CoA reductase inhibitors (statins)

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### Class Summary

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Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. Reduction in hepatocyte cholesterol causes up-regulation of LDL (B,E) receptors, which, in turn, reduces plasma LDL levels. Statins are used adjunctively with diet and exercise to treat hypercholesterolemia and are the most potent LDL-lowering medications. All statins have modest triglyceride-lowering and HDL-raising effects. Randomized, double-blind, placebo-controlled trials demonstrate regression of coronary atherosclerosis but, even more importantly, reduction in rates of total mortality, coronary events, and stroke.

- Because hepatic cholesterol synthesis is greatest at night, most of the statins should be taken at bedtime. Lovastatin is better absorbed with food and is most effective taken with supper. Rosuvastatin and atorvastatin are the strongest statins because they have long half-lives.

- Atorvastatin, simvastatin, and lovastatin are metabolized by the P450 cytochrome 3A4, which is inhibited by many other drugs and may thereby increase the risk of myopathy. Rosuvastatin, fluvastatin, and pravastatin are metabolized by other pathways.

- The weaker statins (pravastatin, fluvastatin, lovastatin) do not lower LDLc levels as much and, therefore, are not the statins of choice for patients with FH. However, myopathy is dose and strength-related and thus these statins may not be as likely to cause severe myopathy.

- The Report of the National Lipid Association's Statin Safety Task Force published in the American Journal of Cardiology (Volume 97, Issue 8, Supplement 1, pages S1-S98, 17 April 2006)[58] provides the results of a rigorous, unbiased assessment of statin safety. It includes specific reports on the muscle, liver, renal, and neurologic effects of statins; as well as addressing drug interactions and other safety issues.

Atorvastatin and rosuvastatin are long-acting statins and do not require evening dosing. Simvastatin is the third strongest statin and should be administered at bedtime. The three weaker statins (pravastatin, fluvastatin, lovastatin) are not the statins of choice for patients with FH. Rosuvastatin, unlike atorvastatin and simvastatin is not metabolized by the cytochrome 3A4; and, therefore, may have fewer drug interactions.

### Atorvastatin (Lipitor)

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Second strongest LDL-lowering statin approved to date. Long half-life. Clinical trial has shown reduction in CHD events.

As an adjunct to diet, approved indications are to reduce total cholesterol, LDLc, triglycerides, and apoB; increase HDLc in patients with primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb); decrease triglycerides in patients with type IV; and treat patients with type III dysbetalipoproteinemia.

It is approved for treatment of adults with homozygous FH as an adjunct to other LDL-lowering measures (eg, LDL apheresis) or if other treatments are not available.

It is approved for children and adolescents aged  $\geq 10$  y if after an adequate trial of diet, LDLc remains  $\geq 190$  mg/dL, or if LDLc remains  $\geq 160$  mg/dL and there is a positive family history of premature CVD or the patient has  $>2$  other CVD risk factors.

### Simvastatin (Zocor)

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Third strongest LDL-lowering drug approved to date. Several randomized clinical trials in patients with and without CHD have shown clinically significant reductions in CHD morbidity and mortality rates and, in some cases, total mortality rates.

In addition to its multiple effects in improving lipid profiles (decrease in total cholesterol, LDLc, triglycerides, and apoB and increase in HDLc), has been approved in adults for homozygous FH and heterozygous FH, for reducing risk of total mortality by reducing CHD death, reducing risk of nonfatal MI and stroke, reducing need for coronary and noncoronary revascularization procedures, and for adolescents with heterozygous FH.

### Rosuvastatin (Crestor)

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Rosuvastatin has the strongest lipid-lowering potential of all the statins currently available. It is indicated for adults with primary hyperlipidemia and mixed dyslipidemia, homozygous FH, primary dysbetalipoproteinemia, and hypertriglyceridemia. In children and adolescents, it is indicated for homozygous FH and heterozygous FH.

### Pitavastatin (Livalo)

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HMG-CoA reductase inhibitor (statin) indicated for primary or mixed hyperlipidemia in adults. In clinical trials, 2 mg/d reduced total cholesterol and LDLc similar to atorvastatin 10 mg/d and simvastatin 20 mg/d. It is also indicated for the

reduction of elevated total cholesterol, LDLc, and apoB, in children aged 8 years or older with heterozygous FH.

## Pravastatin (Pravachol)

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Pravastatin is indicated for heterozygous FH in children and adolescents aged  $\geq 8$  y if after an adequate trial of diet, LDLc remains  $\geq 190$  mg/dL, or if LDLc remains  $\geq 160$  mg/dL and there is a positive family history of premature CVD or the patient has  $>2$  other CVD risk factors.

## Lovastatin (Altoprev, Mevacor)

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Lovastatin is indicated for heterozygous FH in adults and in children and adolescents aged  $\geq 10$  y if after an adequate trial of diet, LDLc remains  $\geq 190$  mg/dL, or if LDLc remains  $\geq 160$  mg/dL and there is a positive family history of premature CVD or the patient has  $>2$  other CVD risk factors.

## Fluvastatin (Lescol, Lescol XL)

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Fluvastatin is indicated for heterozygous FH in adults and in children and adolescents aged  $\geq 10$  y if after an adequate trial of diet, LDLc remains  $\geq 190$  mg/dL, or if LDLc remains  $\geq 160$  mg/dL and there is a positive family history of premature CVD or the patient has  $>2$  other CVD risk factors.

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## Vitamins

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### Class Summary

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Niacin at doses of at least 1-1.5 g/d lowers LDLc levels 10-25%. HDLc levels can increase substantially, 30% or more, particularly at higher doses. Triglyceride levels decrease approximately 50%. Niacin, whether OTC or by prescription, costs less than any other lipid-lowering medication. For reasons not clearly understood, changing brands during treatment is more likely to cause hepatotoxicity, more so with time-release niacin than with regular niacin, particularly at a dose of 3 g/d or more. Nicotinamide, while acceptable treatment for vitamin B-3 deficiency, does not affect lipid levels, nor do most of the "no flush" niacin preparations, including inositol hexaniacinate.

On April 15, 2016, the FDA announced that it was withdrawing approval for the new drug applications (NDAs) for the use of niacin ER with statins. The action stemmed from the results of several large cardiovascular outcome trials, including AIM-HIGH, ACCORD, and HPS2-THRIVE, with the FDA determining that "scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-cholesterol levels in statin-treated patients results in a reduction in the risk of cardiovascular events."<sup>[59]</sup>

### Immediate-release niacin/vitamin B-3 (nicotinic acid, Niacor, Nicolar)

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Less hepatotoxic than SR niacin but not as well tolerated by patients because of prostaglandin-mediated flushing, itching, or rash. IR niacin started at low doses and gradually increased over several wk allows some patients to accommodate to these adverse effects.

Higher doses (4-6 g/d) can be used more safely than those of SR niacin.

Niacor and Nicolar are prescription formulations of IR niacin that, while more expensive than OTC brands, may decrease likelihood of patient switching brands. Changing formulation of niacin while on high doses may increase risk of hepatotoxicity.

### SR niacin (Slo-Niacin, Niaspan)

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More hepatotoxic than IR niacin; therefore, strongly advise against switching formulations or brands during treatment. Both OTC and prescription SR niacin is available. OTC brands cost less, but if using this option, only recommend reliable manufacturers.

Slo-Niacin is an OTC formulation available in 250-, 500-, and 750-mg tabs. Sundown also manufactures OTC SR niacin. Prescription SR niacin, Niaspan, is available in 375-, 500-, and 1000-mg tabs.

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## Bile acid sequestrants (resins)

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### Class Summary

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Anion-exchange compounds that work by preventing reabsorption of bile in the intestine. Modestly lower LDLc and increase HDLc levels but can raise triglyceride levels. When used with a statin, the LDLc-lowering effects are additive. Not absorbed systemically and, therefore, are safer than most medications. Powder should never be taken in dry form. Combine with water, other noncarbonated fluid, or soft food (eg, applesauce, soup). Probably more effective at mealtime. Colestipol is formulated both as a powder and a tablet; however, 1 tablet contains only 1 g of colestipol. Given that the maximum dose of colestipol powder is 30 g, taking an even 10 tablets (which most patients will object to) will have only minimal LDL-lowering impact.

Because resins can decrease absorption of many other medications, those medications should be taken 1 h before or 4 h after the resin. Major adverse effect is constipation, and patient compliance is often an issue.

WelChol is a polymer (not a resin) and is the newest bile acid sequestrant to enter the market. It is formulated as a tablet, and the maximum number is 7 tab/d, which may improve compliance. Reportedly causes fewer adverse GI effects and fewer drug interactions. Added to a statin, further LDLc reductions of as much as 20% can be expected.

### Cholestyramine (Questran)

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Orange-flavored and sweetened with either sucrose (Questran) or aspartame (Questran Light). Must be mixed with fluids or soft, high-moisture foods.

Forms a nonabsorbable complex with bile acids in the intestine, which, in turn, inhibits enterohepatic reuptake of intestinal bile salts.

Safer than most medications.

### Colestipol (Colestid)

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Formulated as dry, flavorless powder and as a tab. Otherwise, similar to cholestyramine. Because contains no flavoring or sweeteners, can be mixed with a wider variety of liquid foods (eg, soup, tomato juice).

### Colesevelam (WelChol)

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Better tolerated than older agents (eg, cholestyramine, colestipol), and drug interactions are less of a problem. Can lower LDLc 15-18% as monotherapy. Useful in patients who cannot tolerate statins, who have contraindications for statin therapy, or who request nonsystemic therapy. Can also be used in combination with a statin for additive LDLc lowering. Has no effect on serum triglycerides or beneficial effects on HDLc. Available in a 643-mg tab.

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## Lipid-Lowering Agents, Other

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### Class Summary

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A variety of agents are emerging on the market as adjuncts to existing drugs and other therapies.

### Lomitapide (Juxtapid)

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Lomitapide directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing apo B-containing lipoproteins assembly in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL; inhibition of VLDL synthesis leads to reduced LDLc plasma levels. This agent is indicated as an adjunct to a low-fat diet and other lipid lowering treatments, including LDL apheresis where available, to reduce LDLc, triglycerides, apo B, and non-HDLc in patients with homozygous familial hypercholesterolemia.

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## Lipid-Lowering Agents, 2-Azetidinones

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### Ezetimibe (Zetia)

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First in a new class of cholesterol-lowering agents. Inhibits cholesterol intestinal absorption. Approved as monotherapy or in combination with HMG-CoA reductase inhibitors.

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## PCSK9 Inhibitors

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### Class Summary

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease LDLR degradation by PCSK9, and thereby improve LDLc clearance and lower plasma LDLc.

### Alirocumab (Praluent)

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Alirocumab is a monoclonal antibody that binds to PCSK9. LDLc is cleared from the circulation preferentially through the LDL receptor (LDLR) pathway. PCSK9 is a serine protease that destroys LDLR in the liver, resulting in decreased LDLc clearance and increased plasma LDLc. PCSK9 inhibitors decrease LDLR degradation by PCSK9.

Indicated as an adjunct to diet, alirocumab is administered either alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), being employed for the reduction of LDLc in primary hyperlipidemia, including heterozygous FH. It is also FDA approved as an adjunctive treatment for homozygous FH.

Another indication for alirocumab is for the prevention of CV events, with the drug having been found to lower the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established CV disease.

### Evolocumab (Repatha)

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Evolocumab is a monoclonal antibody that inhibits the serine protease PCSK9. PCSK9 destroys the LDL receptor in the liver; therefore, decreasing LDLc clearance. It is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic CVD, who require additional lowering of LDLc. Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) for the treatment of adults and adolescents aged 13-17 y with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDLc.

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## Lipid-Lowering Agents, ACL Inhibitors

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### Class Summary

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Adenosine triphosphate-citrate lyase (ACL) inhibitors lower LDLc by inhibiting cholesterol synthesis in the liver. In the cholesterol biosynthesis pathway, the enzyme ACL is upstream of HMG-CoA reductase.

### Bempedoic acid (Nexletol)

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Indicated for adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease when additional LDLc reduction is needed, serving as an adjunct to diet and maximally tolerated statin therapy.

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## ANGPTL Inhibitors

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## Class Summary

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Lipoprotein lipase and endothelial lipase are inhibited by ANGPTL3, resulting in reduced lipid metabolism. Inhibition of ANGPTL3 by evinacumab allows increased lipid metabolism, leading to decreased LDLc, HDLc, and triglycerides.

### Evinacumab (Evkeeza)

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Recombinant human monoclonal antibody that binds to and inhibits angiotensin-like 3 (ANGPTL3). Indicated as an adjunct to other LDLc lowering therapies for HoFH in adults and adolescents aged 12 years and older.

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## Combination Products

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### Class Summary

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Clinicians may consider these products to provide additive effects in LDLc reduction and improve adherence to medication regimens.

### Simvastatin/ezetimibe (Vytorin)

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Contains the HMG-CoA inhibitor simvastatin, which reduces cholesterol synthesis, and the 2-azetidione ezetimibe, which inhibits cholesterol intestinal absorption. It is indicated for the reduction of elevated total cholesterol, LDLc, apoB, triglycerides, and non-HDLc, and for the increase of HDLc, in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia. Additionally, serving as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or a replacement if such treatments are unavailable, it is indicated for the reduction of elevated total cholesterol and LDLc in patients with homozygous familial hypercholesterolemia.

### Bempedoic acid/ezetimibe (Nexlizet)

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Contains the ACL inhibitor bempedoic acid, which inhibits hepatic cholesterol synthesis, and the 2-azetidione ezetimibe, which inhibits cholesterol intestinal absorption. Indicated for adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease when additional LDLc reduction is needed, serving as an adjunct to diet and maximally tolerated statin therapy.

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## Follow-up

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### Deterrence/Prevention

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Identifying relatives who are carriers of the FH gene allows medical intervention to prevent patients from developing CAD.

In addition to treating hypercholesterolemia, cardiovascular risk factors should be identified and treated aggressively. Advise patients to begin aerobic exercise and, if indicated, a weight-loss program.

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## Complications

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The adverse effects of medications used to treat hypercholesterolemia can pose major, though uncommon, complications.

Statin therapy carries a negligible risk of liver toxicity.

Myositis progressing to rhabdomyolysis is a rare but life-threatening complication of statin therapy.

Statins in combination with a variety of medications (particularly cyclosporine, as well as gemfibrozil, verapamil, amiodarone, etc) increase the risk of myositis (see Medication).

Niacin may cause gout, peptic ulcer disease, increased insulin resistance, and severe hepatotoxicity. Fulminant hepatic failure has been reported with time-release niacin therapy.

## Prognosis

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Prognosis depends heavily on the extent to which LDLc levels can be reduced.

Patients with homozygous FH have an extremely limited life expectancy without major medical intervention.

Treatment of other modifiable risk factors such as smoking, hypertension, and diabetes further decreases the risk of CAD.

Because long-term prospective studies on subjects with FH are not available, precise predictions regarding improved outcomes are difficult.

## Patient Education

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Adult patients with FH must understand their high risk for premature CAD. Emphasizing the importance of complying with dietary and drug management of their hypercholesterolemia must be emphasized.

Other modifiable risk factors should be identified, and their additive impact on the risk of a cardiovascular event should be explained. Offer assistance with stopping smoking. Explain the importance of exercise and appropriate weight reduction in terms of the lipid and cardiovascular effects and the prevention or improvement in diabetes and hypertension.

For excellent patient education resources, visit eMedicineHealth's Cholesterol Center. Also, see eMedicineHealth's patient education articles High Cholesterol, Cholesterol Charts, Lifestyle Cholesterol Management, Cholesterol-Lowering Medications, and Statins for Cholesterol.

## Questions & Answers

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### Overview

[What is familial hypercholesterolemia \(FH\)?](#)

[What are the signs and symptoms of homozygous familial hypercholesterolemia \(FH\)?](#)

[What are the signs and symptoms of heterozygous familial hypercholesterolemia \(FH\) in children?](#)

[What are the signs and symptoms of heterozygous familial hypercholesterolemia \(FH\) in adults?](#)

[How is familial hypercholesterolemia \(FH\) diagnosed?](#)

[Which findings on lipid analysis are characteristic of familial hypercholesterolemia \(FH\)?](#)

[What are the European Atherosclerosis Society \(EAS\) guidelines for heterozygous familial hypercholesterolemia \(FH\) screening?](#)

[What are the CHD risk categories for patients with familial hypercholesterolemia \(FH\)?](#)

[How is homozygous familial hypercholesterolemia \(FH\) treated?](#)

[How is heterozygous familial hypercholesterolemia \(FH\) treated?](#)

[What are the European Atherosclerosis Society \(EAS\) recommendations for treatment of heterozygous familial hypercholesterolemia \(FH\)?](#)

[What is familial hypercholesterolemia \(FH\)?](#)

[What is the pathophysiology of familial hypercholesterolemia \(FH\)?](#)

[What are the classes of genetic mutations in familial hypercholesterolemia \(FH\)?](#)

[What is the prevalence of familial hypercholesterolemia \(FH\) in the US?](#)

[What is the global prevalence of familial hypercholesterolemia \(FH\) internationally?](#)

[What is the mortality and morbidity associated with homozygous familial hypercholesterolemia \(FH\)?](#)

What is the mortality and morbidity associated with heterozygous familial hypercholesterolemia (FH)?

What are the racial predilections in the prevalence of familial hypercholesterolemia (FH)?

What are the sexual predilections of familial hypercholesterolemia (FH)?

What are the risks of undiagnosed familial hypercholesterolemia (FH)?

### **Presentation**

What are the signs and symptoms of homozygous familial hypercholesterolemia (FH)?

What are the signs and symptoms of heterozygous familial hypercholesterolemia (FH)?

Which clinical history findings are characteristic of homozygous familial hypercholesterolemia (FH) in adults?

Which clinical history findings are characteristic of heterozygous familial hypercholesterolemia (FH) in adults?

Which physical findings are characteristic of familial hypercholesterolemia (FH)?

Which physical findings are characteristic of homozygous familial hypercholesterolemia (FH)?

Which physical findings are characteristic of heterozygous familial hypercholesterolemia (FH)?

What causes familial hypercholesterolemia (FH)?

What is the role of familial ligand defective apoB-100 in the etiology of familial hypercholesterolemia (FH)?

What is the role of autosomal recessive hypercholesterolemia in the etiology of familial hypercholesterolemia (FH)?

### **DDX**

What are the differential diagnoses for Familial Hypercholesterolemia?

### **Workup**

How is familial hypercholesterolemia (FH) diagnosed?

What is the role of lipid analysis in the diagnosis of familial hypercholesterolemia (FH)?

Which tests are performed to rule out secondary hypercholesterolemia in patients with familial hypercholesterolemia (FH)?

What is the role of imaging studies in the workup of familial hypercholesterolemia (FH)?

What is the role of lipoprotein electrophoresis in the diagnosis of familial hypercholesterolemia (FH)?

What is the role of LDL receptor analysis in the diagnosis of familial hypercholesterolemia (FH)?

What is the role of biopsy in the diagnosis of familial hypercholesterolemia (FH)?

### **Treatment**

What guidelines exist for the medical care of patients with familial hypercholesterolemia (FH)?

What are risk categories for coronary heart disease (CHD) in familial hypercholesterolemia (FH)?

What is the role of CHD risk in determining the treatment of familial hypercholesterolemia (FH)?

What are risk factors for coronary heart disease (CHD) in familial hypercholesterolemia (FH)?

How is the risk for developing CHD determined in patients with familial hypercholesterolemia (FH)?

Which patients have an optional low-density lipoprotein cholesterol (LDLc) goal of less than 70 mg/dL for the treatment of familial hypercholesterolemia (FH)?

How is familial hypercholesterolemia (FH) treated in patients with a moderately high risk of CHD?

How is familial hypercholesterolemia (FH) treated in patients with a moderate risk of CHD?

Which patients with familial hypercholesterolemia (FH) are at low risk for CHD?

What is the highest category of CHD risk in patients with familial hypercholesterolemia (FH)?

Which patients with familial hypercholesterolemia (FH) are at a very high risk for CHD?

What are the EAS treatment guidelines for homozygous familial hypercholesterolemia (FH)?

How is homozygous familial hypercholesterolemia (FH) treated?

How is homozygous familial hypercholesterolemia (FH) treated when the low-density lipoprotein (LDL) receptors are absent or nonfunctional?

What is the role of portacaval anastomosis in the treatment of homozygous familial hypercholesterolemia (FH)?

What are the roles of evolocumab and alirocumab in the treatment of homozygous familial hypercholesterolemia (FH)?

What is the role of lomitapide in the treatment of homozygous familial hypercholesterolemia (FH)?

What is the role of evinacumab in the treatment of homozygous familial hypercholesterolemia (FH)?

What is the role of probucol in the treatment of homozygous familial hypercholesterolemia (FH)?

What is the role of gene therapy to the treatment of homozygous familial hypercholesterolemia (FH)?

What is the role of lifestyle modifications in the treatment of heterozygous familial hypercholesterolemia (FH)?

What are the EAS treatment guidelines for heterozygous familial hypercholesterolemia (FH)?

How is heterozygous familial hypercholesterolemia (FH) treated?

What is the role of alirocumab in the treatment of heterozygous familial hypercholesterolemia (FH)?

What is the role of evolocumab (Repatha) in the treatment of heterozygous familial hypercholesterolemia (FH)?

What is the role of rosuvastatin in the treatment of pediatric heterozygous familial hypercholesterolemia (FH)?

What is the role of fibrates in the treatment of heterozygous familial hypercholesterolemia (FH)?

What is the role of estrogen replacement in the treatment of heterozygous familial hypercholesterolemia (FH)?

What is the role of LDL apheresis in the treatment of heterozygous familial hypercholesterolemia (FH)?

What is the role of liver transplantation in the treatment of homozygous familial hypercholesterolemia (FH)?

What is the role of portacaval anastomosis in the treatment of homozygous familial hypercholesterolemia (FH)?

Which specialist consultations are beneficial for patients with homozygous familial hypercholesterolemia (FH)?

Which specialist consultations are beneficial for patients with heterozygous familial hypercholesterolemia (FH)?

Which dietary modifications are used in the treatment of familial hypercholesterolemia (FH)?

Which activity modifications are used in the treatment of familial hypercholesterolemia (FH)?

## **Guidelines**

What are the Japan Pediatric Society and the Japan Atherosclerosis Society guidelines for the diagnosis and management of pediatric familial hypercholesterolemia (FH)?

## **Medications**

Which medications are used in the treatment of familial hypercholesterolemia (FH)?

What are the FDA approved statin doses for the treatment of familial hypercholesterolemia (FH)?

Which medications in the drug class Lipid-Lowering Agents, 2-Azetidinones are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class Lipid-Lowering Agents, Other are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class Bile acid sequestrants (resins) are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class Vitamins are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class HMG-CoA reductase inhibitors (statins) are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class ANGPTL Inhibitors are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class Lipid-Lowering Agents, ACL Inhibitors are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class PCSK9 Inhibitors are used in the treatment of Familial Hypercholesterolemia?

Which medications in the drug class Combination Products are used in the treatment of Familial Hypercholesterolemia?

### Follow-up

How is familial hypercholesterolemia (FH) prevented?

What are complications of familial hypercholesterolemia (FH)?

What is the prognosis of familial hypercholesterolemia (FH)?

What is included in patient education about familial hypercholesterolemia (FH)?

## eMedicine

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