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# Familial Hypercholesterolemia

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## Abstract

Familial hypercholesterolemia is a common, inherited disorder of cholesterol metabolism that leads to early cardiovascular morbidity and mortality. It is underdiagnosed and undertreated. Statins, ezetimibe, bile acid sequestrants, niacin, lomitapide, mipomersen and LDL apheresis are treatments that can lower LDL cholesterol levels. Early treatment can lead to substantial reduction of cardiovascular events and death in patients with FH. It is important to increase awareness of this disorder in physicians and patients in order to reduce the burden of this disorder.

### Keywords

familial hypercholesterolemia; statins; ezetimibe; bile acid sequestrants; LDL apheresis; lomitapide; mipomersen

## Introduction

Familial hypercholesterolemia (FH) is an inherited condition resulting in high levels of low-density lipoprotein cholesterol (LDL-C) and increased risk of premature cardiovascular disease in men and women. FH causes lifetime exposure to high LDL-C levels. It is not rare, but it is underdiagnosed. Although therapies for FH are available, it is commonly undertreated. Early diagnosis and treatment mitigate the excess risk of premature atherosclerotic cardiovascular disease that occurs with FH. (1,2,3)

### Pathophysiology

The pathophysiology of FH is due to decreased function of LDL receptors. (Box 1)

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## Genetics of FH

FH is an autosomal dominant disorder with a gene dosage effect. Patients who are homozygotes (or compound heterozygotes) have much higher LDL-C levels and earlier coronary artery disease onset than heterozygous patients. (1,2,3,4) The underlying defect in FH was initially thought to be due to increased synthesis of cholesterol, but we now know that the fractional catabolic rate of LDL is decreased in heterozygous FH individuals compared to normal subjects (5). The LDL receptor pathway was characterized by Brown and Goldstein and revealed receptor-mediated endocytosis (6).

The most common form of FH is a monogenic, autosomal dominant disorder, which causes defects in the gene that encodes the LDL receptor (LDLR)(1,2,3).

Over 900 mutations of this gene have been identified (1), most pathogenic, leading to the LDL receptor having decreased capacity to clear LDL from the circulation.

There are also defects in the LDL receptor binding region of apolipoprotein B (APOB) (1) and rare gain of function proprotein convertase subtilisin/kexin type 9 (PCSK9) gene mutations (7).

A rare autosomal recessive form of FH caused by loss-of-function mutations in the LDL receptor adaptor protein 1 (LDLRAP1), which encodes a protein required for clathrin-mediated internalization of the LDL receptor, has also been described (3). (Table 1)

## Prevalence of FH

Historically, the prevalence of heterozygous FH was 1 in 500 persons. Recent genetic studies suggest a prevalence of 1 in 200 to 250 (8,9). In populations such as French Canadians, Ashkenazi Jews, Lebanese, and several South African populations, the prevalence may be as high as 1 in 100 (10). Based on a prevalence of 1 in 500, there are an estimated 620,000 FH patients in the United States (11), but this number may be as high as 1,500,000 based on a prevalence of 1 in 250. The historical prevalence estimate of homozygous (or compound heterozygous) patients is 1 in 1 million, and this would also change based on current studies. Recent data from the Netherlands suggest that the prevalence could be as low as 1 in 160,000 and is likely to be about 1 in 250,000.(9) Most patients with homozygous FH have extreme hypercholesterolemia with rapidly accelerated atherosclerosis when left untreated.(3,10) Though single gene disorders play a crucial role in the etiology of FH, linkage studies suggest that some cases are caused by the presence of multiple single nucleotide polymorphisms.(12) Heterozygotes arise when a mutation is inherited from one parent only; whereas homozygotes develop when the same mutated gene is inherited from both parents. Compound heterozygotes are due to inheritance of a different mutation from each parent. Untreated heterozygotes have LDL-C in the range of 155 to 500 mg/dl whereas untreated homozygotes (or compound heterozygotes) typically have LDL-C greater than 500 mg/dl. Recent data suggest wide variation in LDL-C levels (1, 2, 3 10).

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## Patient evaluation

### Screening strategies

Although the atherosclerotic manifestations of FH usually occur in adulthood, the clinical effects of the disease can start in the first decade of life in homozygous patients (3). Unfortunately, FH is often diagnosed late and after the occurrence of a major coronary event. A combination of screening methods to identify at risk individuals is needed (11,13,14) to prevent premature atherosclerosis.

There are a number of barriers to the diagnosis and treatment of FH. Many individuals and family members with FH who have CAD have other common CAD risk factors; thus genetic hypercholesterolemia is not suspected and ultimately not diagnosed. Primary care physicians manage most patients with hypercholesterolemia, and there is often a lack of awareness of FH among physicians and the general public with only very severe cases being referred to specialists. (2, 13)

Cascade screening, in which health care providers actively screen for disease among the first and second degree relatives of patients diagnosed with FH (13), can increase detection rates but risks missing affected individuals. Several national and international guidelines recommend universal screening for elevated serum cholesterol by age 20 and cascade testing of first-degree relatives of all individuals with FH.(2,11,13,15,16) For children, cholesterol screening should be done at age 9 to 11 and considered beginning at age 2 in those with a family history of premature cardiovascular disease or elevated cholesterol. (11, 17, 18)

### Diagnosis

Diagnosis of FH is based lipid levels, family history, physical findings (if present), and, if available, genetic analysis. (Box 2). Physical examination findings of tendon xanthomas, arcus corneae (under age 45) and tuberous xanthomas or xanthelasma (under age 25) when present at an early age should also prompt suspicion for FH. However, physical findings are not present in all patients with FH. (1)

There are three well-defined clinical diagnostic tools that are used to diagnose FH:

- The US Make Early Diagnoses Prevent Early Deaths Program Diagnostic Criteria (MEDPED) (19),
  - Uses total and LDL cholesterol measurements and family history
- The Dutch Lipid Clinic Network Diagnostic Criteria (20)
  - Point system using LDL cholesterol levels, physical examination finings and family and personal history of coronary artery disease; presence of genetic mutations
- The Simon Broome Register Diagnostic Criteria (15)
  - LDL cholesterol levels, family history, tendon xanthomas, presence of genetic mutations

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The Dutch Lipid Clinic criteria are generally not useful in children. These sets of criteria are typically used to diagnose heterozygous FH.

The diagnosis of homozygous (or compound heterozygous) FH (HoFH) has been defined in a number of ways (3,10), with one possible definition shown in Box 3. However, recent data on the heterogeneity and prevalence of genetically defined HoFH suggest that older criteria may not always apply. (9)

### Genetic testing

Clinical criteria may not identify all patients with FH, and genetic testing is part of screening strategies in a number of countries, with the costs covered by national health services. (2, 3, 13, 15, 16). In the United States, it is done infrequently, partly due to cost and lack of insurance coverage. Genetic testing in certain populations has changed understanding of the frequency of both heterozygous and homozygous FH. However, a mutation is not always found in patients with clinical FH, and lack of a mutation should not change treatment. (1)

### Prognosis

Patients with heterozygous FH are generally asymptomatic in childhood and early adulthood. About 5% of heart attacks under the age 60 and as many as 20% under age 45 are due to FH (1,2).

Homozygous or compound heterozygous FH has a severe and variable clinical presentation usually within the first decade of life. Most of these individuals have extreme hypercholesterolemia with rapidly accelerated atherosclerosis when left untreated. The variation depends of the amount of LDL receptor activity (3,10). Coronary artery disease is the most common cause of premature death in these patients, but other cardiovascular disease including aortic and supravalvular aortic stenosis and aortic root disease is also common (3,10).

**Risk assessment tools** do not adequately predict 10-year CHD risk in FH patients, and the Framingham Risk Score is not recommended in FH patients (4). Risk calculators underestimate risk in patients with FH because of the significant effect of exposure to high cholesterol levels from birth.

## Treatment

The lifetime risk of CHD and premature onset CHD is very high in individuals with FH. Early treatment is beneficial and long term drug therapy can substantially reduce or eliminate the added lifetime risk of CHD from having FH and can lower the CHD event rate in heterozygous FH patients to levels similar to those of the general population (2, 21, 22). The 2013 ACC/AHA cholesterol treatment guideline recommends potent statin use in adult patients with LDL-C levels ≥ 190 mg/dL. (23) The National Lipid Association recommends that both children and adults with LDL cholesterol ≥190mg/dL (or non HDL cholesterol ≥ 220mg/dl) after life style changes be started on drug therapy. (17, 24)

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**Lifestyle and non-cholesterol risk factor modification** is an important part of treatment. (13, 24) Box 4

Homozygous patients require treatment as soon as the diagnosis is made and need lifestyle, medication and additional modalities. Treatment of homozygous FH patients can delay major cardiovascular events and early death. (3, 25)

## Pharmacologic therapy

Statins should be the initial drug for all adults with FH and in children with heterozygous FH starting at 8 to 10 years of age (4, 13, 15, 16, 17, 24). Patients with homozygous FH should be treated as soon as the diagnosis is made (3, 10, 13). The Food and Drug Administration has approved lovastatin, atorvastatin, simvastatin and rosuvastatin children above 10 years of age and pravastatin in those over 8 years (26). Statins increase the expression of LDL receptors by reducing HMG-CoA reductase, the rate-limiting step in cholesterol synthesis. Moderate to high potency statins should be used as first line treatment (atorvastatin, rosuvastatin, simvastatin, pitavastatin). See Table 2. Low potency statins are usually inadequate for FH patients (13, 24). Adult FH patients should have a treatment goal of ≥ 50% LDL-C reduction from baseline. Statin therapy is effective in heterozygous FH patients and may also benefit homozygous patients who have some LDL receptor activity. (3,10) (Table 2)

Long-term safety of statins in the pediatric population is still unknown, but the current benefits of therapy outweigh the risk of untreated pediatric populations. (17, 26, 27, 28) Children and adolescents being treated with statins should have regular follow up with close monitoring of creatinine kinase, aspartate amino transferase (AST) and alanine amino transferase levels (ALT). Baseline levels, then repeat testing should be done at 1-3 months after drug initiation and then yearly. If CK levels reach five times and AST or ALT three times the upper limit of normal, a 3-month drug-free holiday should be initiated with reintroduction of the same drug at a lower dose or a different statin if levels return to baseline (29).

Patients with FH who have a higher risk of CHD require more intensive drug therapy. (4, 13) High-risk patients include those with:

- Clinically evident CHD or other atherosclerotic cardiovascular disease
- Diabetes
- Family history of very early CHD (<45years in men and <55 years in women)
- Current smoking
- Two or more CHD risk factors
- High lipoprotein (a) (≥ 50mg/dL).
- In these patients, the LDL goal is <100 mg/Dl and non-HDL goal is <130 mg/dL.

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## Combination Therapy

Many patients with FH will require more than one medication to obtain optimal LDL-C lowering. Patients may require multiple medications depending on their baseline LDL-C levels and their responsiveness to therapy. Drugs that can be added to statins for LDL-C reduction include ezetimibe, bile-acid sequestrants, and niacin. (Table 3)

The addition of ezetimibe to a statin is the preferred approach in the treatment of patients with FH. (2, 3, 13, 16) Some patients may require three or more medications to lower LDL-C adequately.

Fibrates are most useful for triglyceride lowering but may have some LDL-C lowering effect. Ezetimibe, niacin, and bile acid sequestrants are also treatment options for drug intensification or for those intolerant of a statin. This should also be considered in FH patients who are not at very high risk when LDL-C does not decrease by 50% with statin monotherapy. It is important to note that doubling the dose of statin only achieves an additional LDL reduction by 6 -7% (30). Therefore, if additional reduction is needed, other medications should be added. Other options for those intolerant of statins include every other day statin therapy or lowering the dose while adding other treatment medications.

Drug interactions with statins are primarily due to cytochrome P450 metabolism, drug transporters and glucuronidation; thus caution should be used with medications metabolized by cytochrome P450 isoenzyme CYP 3A4. (31)

Ezetimibe is localized at the brush border of the small intestine and inhibits the absorption of cholesterol. It reduces LDL-C by about 15 to 20% when used alone and provides 20% percent additional reduction in combination with a statin (32).

Bile acid sequestrants inhibit the enterohepatic reuptake and increase fecal loss of bile salts. They decrease LDL-C by preventing the reabsorption of bile acids in the terminal ileum. Because they are not absorbed systemically, they are considered safer to use then other cholesterol-lowering medications (33). Like ezetimibe, the effect on LDL-C reduction can be additive with statins and even ezetimibe (34) The need for suspensions or large numbers of pills, gastrointestinal side effects, and multiple drug-drug interactions limits patient adherence and use. Colesevelam, as compared to other bile acid sequestrants, has fewer gastrointestinal side effects and drug-drug interactions. Colesevelam is also approved for treatment of diabetes and may help patients achieve both glycemic and lipid goals (35). Colesevelam is the recommended bile acid sequestrant for FH patients (24).

Niacin, a water-soluble B vitamin, lowers LDL-C and raises HDL. It comes in crystalline and extended release forms. Due to concerns for liver toxicity, most non-prescription sustained release forms are not recommended (24). The maximum dose of 2 g daily of niacin when added to statin is effective in lowering LDL-C (24). Fibrates lower triglycerides and raise HDL-C. Due to the increased risk of fibrate-induced myositis (particularly with gemfibrozil) with statins, they need to be used with caution.(31)

Women with FH who are of child bearing age should be advised to use contraception while on therapy and to stop any statin (category X), niacin (category C) or ezetimibe (category C)

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therapy at least 4 weeks prior to stopping contraception (24). Those who become pregnant on therapy or are breastfeeding should be advised to discontinue therapy immediately. Colesevelam is in category B and can used when clinically indicated (24). For pregnant women with homozygous FH, or heterozygous FH and atherosclerotic disease, LDL apheresis should be considered (13, 24).

**LDL apheresis** is an important treatment modality for homozygous FH patients and for heterozygous patients who have not met treatment goals despite optimal tolerated medical therapy. (24, 36) (Box 5) It is an extracorporeal treatment that uses various methods to remove LDL from the circulation. LDL apheresis is currently FDA approved and has been shown in clinical trials to prevent and slow the progression of CHD. (13,37,38).

Apheresis is generally done every 1 to 2 weeks with each session taking about 3 hours and removing greater than 60% of Apo-B containing lipoproteins (38). The LDL reduction with LDL apheresis is temporary and associated with a rebound elevation in lipid levels after the procedure. The efficacy of LDL apheresis can be enhanced by the addition of statin therapy. LDL apheresis treatment in homozygous FH patients has improved their life expectancy to over 50 years (38). Cost and limited availability decrease widespread use of LDL apheresis.

### Homozygous FH: Treatment considerations

Treatment starts at the time of diagnosis and involves age-appropriate diet, statin, ezetimibe, and often apheresis (3, 13). The FDA has approved two novel treatments for homozygous FH individuals above 18 years of age: lomitapide and mipomersen (39). Table 4. Lomitapide also has European approval. Lomitapide is a microsomal triglyceride transfer (MTP) protein inhibitor available as a capsule and used as an adjunct to other cholesterol lowering medications, lifestyle changes and LDL apheresis if needed. The function of MTP, which resides in the lumen of endoplasmic reticulum of enterocytes and hepatocytes, is to assist in the transfer of triglycerides to apolipoprotein B to form very-low-density lipoprotein particles (40). Lomitapide enabled some homozygous FH patients to discontinue or decrease the frequency of apheresis in some in a clinical trial.(41) Due to concerns about hepatotoxicity, prescription of lomitapide requires an FDA approved Risk Evaluation and Mitigation Strategy (REMS) program.

Mipomersen is delivered by subcutaneous injection with weekly dosing. It is an anti-sense oligonucleotide that causes a reduction in LDL by binding to messenger RNA and inhibits apolipoprotein B-100 synthesis (42). LDL, apo B and lipoprotein (a) concentrations are reduced. (43, 44). Reported side effects include injection site reactions, flu-like symptoms, increased ALT and steatosis. (42, 43, 44) Thus this medication also requires frequent monitoring of liver function tests and prescription approval via REMS.

## Surgical therapy

For patients who do not achieve lipid goal reduction by the above modalities, other potential treatment options include partial ileal bypass and liver transplantation. Liver transplantation produces a significant lowering of LDL-C by providing normal LDL receptors. Liver transplantation is now used primarily in children with homozygous FH when apheresis is not

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an option or with concurrent heart transplantation. (13, 45) Its use, however, is limited due to risk of transplant surgery and the limited number of donor livers (13, 24, 29). Partial ileal bypass is rarely used and works by interrupting enterohepatic bile acid circulation (13, 24).

## Treatment Resistance/Complications

### Side effects of medications (See Tables 2 and 3)

### Statins and muscle problems

Statin side effects, particularly muscle complaints, are the limiting factors in their optimal usage. Muscle symptoms are the most common cause of statin discontinuation. They are typically dose dependent and can vary with the statin used. Statin induced myopathy appears to be positively associated with the dose and potency of the statin (23,46). Symptoms tend to occur more often with increasing age and number of medications, and decreasing renal function and body size. Management of statin related myopathy can be difficult. (23,46) See Box 6

### Statins and liver issues

Although liver toxicity from statins is often a concern for patients and physicians, it is not common, and serious hepatotoxicity is extremely rare. Hepatic aminotransferase elevation is usually mild and does not require discontinuation of the statin. It may be dose dependent. Only about 1% of patients have aminotransferase increases to greater than 3 times the upper limit of normal, and the elevation often decreases even if patients continue on the statin. A common cause is hepatic steatosis, which responds to weight loss. Statins can be used cautiously in the presence of liver disease as long as it is not decompensated (47). In particular, nonalcoholic fatty liver disease is not a contraindication. Hepatic transaminases should be obtained at baseline and during treatment if there is a clinical indication for their measurement. (23) Routine monitoring of hepatic transaminases was removed from product labeling by the U.S. Food and Drug Administration in 2012. If aminotransferases remain greater than 3 times the upper limit of normal, consider changing to a different statin and identify other contributing conditions or drugs. (48) Irreversible liver damage resulting from statins is extremely rare, with a liver failure rate of 1 case per 1 million person-years of use. (49)

Clinical trials and meta-analyses have shown a small increase in the risk of diabetes with statin use. In most cases of FH, the benefits of statin treatment far outweigh this risk. (23)

## Drugs in development

Drugs in development have the potential for additive effects with statins or other lipid-lowering medications to achieve further reduction of LDL-C.

The most promising new therapeutic approach for FH involves monoclonal antibodies to PCSK9. PCSK9 increases LDL cholesterol by binding to the epidermal growth factor-like repeat A (EGF-A) domain of the LDL receptor. This causes LDL-receptor degradation, thus reducing the amount of LDL cleared from the plasma (7). Gain of function mutations of PCSK9 result in elevation of LDL whereas loss of function mutations lead to life-long low

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LDL levels and are associated with decreased risk of cardiovascular disease.(50) Given by subcutaneous injection once every 2 to 4 weeks, monoclonal antibodies that inhibit the binding of PCSK9 to LDL receptors have produced 40 to 70% reductions of LDL-C in a variety of clinical situations, including FH. (51, 52, 53, 54, 55, 56) Cardiovascular outcomes trials with several of these antibodies are in progress.

## Summary

FH is a serious and treatable condition with a significantly increased risk of cardiovascular disease. Its onset is in early childhood with resultant premature death if not treated adequately. FH is underdiagnosed and undertreated, and more effort needs to be made to effectively screen and diagnose these patients because early treatment is necessary to decrease morbidity and mortality to the same level as in the general population. Lifestyle and diet changes are necessary but generally insufficient, and patients should be started on moderate and high potency statin therapy as initial treatment. Combination therapy is required in many patients. LDL apheresis should be considered in heterozygous and homozygous FH patients who have insufficient response to medical therapy. Recent medications for treatment of homozygous FH patients have been approved with other new treatment options currently undergoing clinical trials.

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**Box 1**

### Pathophysiology of FH

- Decreased LDL receptor function due to a genetic defect, typically one of the following classes: (1)
  - LDL receptor is not synthesized
  - LDL receptor is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface
  - LDL receptor does not properly bind LDL on the cell surface
  - LDL receptor does not properly cluster in clathrin-coated pits for receptor endocytosis
  - LDL receptor is not recycled back to the cell surface
- Therefore, LDL receptor-mediated endocytosis is decreased
- Leading to markedly elevated LDL levels
- Premature development of atherosclerotic plaque

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**Box 2**

### Clinical approach to diagnosis of FH

Consider FH in the following:

- Presence of premature atherosclerotic cardiovascular disease
- Fasting LDL-C levels >190 mg/dL in adults after exclusion of secondary causes of elevated LDL-C (hypothyroidism, nephrotic syndrome)
- Fasting untreated LDL-C levels that have an 80% probability of FH in the general population:
  - ≥250mg/dL in adults ≥ 30 years
  - ≥ 220mg/dL in adults aged 20 to 29
  - ≥ 190mg/dL in patients under age 20
- Presence of full corneal arcus under age 40
- Presence of tendon xanthomas
- Family history of premature atherosclerotic cardiovascular disease
- Family history of high cholesterol levels

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**Box 3**

**Diagnosis of Homozygous FH (3, 10)**

Genetic analysis showing mutations in two alleles at gene locus for *LDLR, APOB, PCKS9, LDLRAP1*

**OR**

Presence of untreated LDL >500 mg/dL or treated LDL > 300 mg/dL plus:

- Presence of cutaneous or tendon xanthomas before the age of 10 years
- or
- Both parents with evidence of heterozygous FH (except for the rare LDLRAP1 mutations)

Note that the range of untreated LDL-C levels in homozygous FH can be lower, especially in children.

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**Box 4**

- Dietary modification contributes to improvement in lipid profiles
  - A heart healthy diet including vegetables, fruit, non-fat dairy, beans, tree nuts, fish and lean meats should be encouraged
  - Restrict intake of saturated fat to less than 7% of calories
  - Avoid trans fats
  - If alcohol is used, amount should be moderate
  - Addition of plant stanols (2 g/day) and insoluble fiber (10–20 g/day) can provide some LDL-C lowering
  - Dietitian counseling is beneficial
- Physical activity
- Avoidance of weight gain
- Avoidance and cessation of smoking is mandatory
  - Discourage exposure to passive smoking
- Treat diabetes and hypertension
- Consider low-dose aspirin

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**Box 5**

**LDL apheresis recommendations (National Lipid Association and ACC/AHA cholesterol guideline) (24, 36)**

LDL apheresis is recommended for the following patients:

- LDL goal reduction has not been achieved despite diet and maximum drug therapy (after 6 months)
- Adequate drug therapy is not tolerated or contraindicated
- Functional homozygous FH patients with LDL cholesterol ≥ 300mg/DL (or non-HDL cholesterol ≥ 330 mg/dL)
- Functional heterozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL ≥ 330 mg/dL) and 0 -1 risk factors
- Functional heterozygous FH patients with LDL cholesterol ≥ 200 mg/dL (or non – HDL cholesterol ≥ 230 mg/dL) and with risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL
- Functional heterozygotes with LDL cholesterol ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL) and very high-risk characteristics (established CHD, other cardiovascular disease or diabetes.

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**Box 6**

**Approach to statin-related muscle problems (23,46)**

- Discontinue statin in patients who develop muscle symptoms until they can be evaluated. For severe symptoms, evaluate for rhabdomyolysis.
- For mild to moderate symptoms, evaluate for conditions increasing the risk of muscle symptoms, including renal or hepatic impairment, hypothyroidism, vitamin D deficiency, rheumatologic disorders, and primary muscle disorders
- Statin induced myalgias are likely to resolve within two months of discontinuing the drug.
- If symptoms resolve, the same or lower dose of the statin can be reintroduced.
- If symptoms recur, use a low dose of a different statin and increase as tolerated.
- If the cause of symptoms is determined to be unrelated, restart the original statin.

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**Keypoints**

- Familial hypercholesterolemia is a common genetic disorder leading to high cholesterol levels from birth and increased risk of atherosclerotic cardiovascular disease.
- Heterozygous FH occurs in approximately 1 in 250 people in many populations.
- Homozygous FH can lead to CAD in childhood and adolescence.
- Early treatment can decrease the risk of premature ASCVD in FH patients.

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## Table 1
### Types of mutations causing familial hypercholesterolemia

| Mutation | Gene | Mechanism | Numbers of mutations (% of FH cases) |
|---|---|---|---|
| LDL receptor | *LDLR* | LDL receptor is absent or has decreased capacity to clear LDL from circulation | >900 (85-90%) |
| ApoB (also known as familial defective apoB) | *ApoB* | Impaired LDL receptor binding— mutation at binding site on LDL particle | Mutations around the 3500 residues--most common is Arg3500Gln (5-10%) |
| PCSK9 gain of function | *PCSK9* | Increased PCSK9 level leads to increased degradation of LDL receptors | Rare |
| LDL receptor adaptor protein | *LDLRAP1* | Protein needed for clathrin-mediated internalization of LDL receptor | Rare; autosomal recessive hypercholesterolemia |

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## Table 2
### Lipid lowering medications for use in FH: Statins

| Statin | Dose range (mg) | Mean reduction LDL-C (%) | Pharmacologic and safety issues |
|---|---|---|---|
| Rosuvastatin | 5 to 40 | 46 to 55 | Dose reduction in renal insufficiency, Asian, and elderly patients |
| Atorvastatin | 10 to 80 | 37 to 51 | Minimal renal excretion CYP3A4 substrate |
| Simvastatin | 5 to 80* | 26 to 47 | CYP3A4 substrate Dose reduction in severe renal insufficiency |
| Lovastatin | 10 to 80 | 21 to 40 | CYP3A4 substrate |
| Pravastatin | 10 to 80 | 20 to 36 | Dose reduction in severe renal insufficiency |
| Fluvastatin | 20 to 80 | 22 to 35 | Minimal renal excretion |
| Pitavastatin | 1 to 4 | 32 to 43 | Dose reduction in severe renal insufficiency |

*Simvastatin 80 mg dosage should only be used in patients previously taking this dose for > 1 year and no other contraindications.

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## Table 3

### LDL lowering drugs for FH: non-statins

| Medication | Dose range | Mean reduction LDL-C (%) | Pharmacologic and safety issues |
|---|---|---|---|
| Ezetimibe | 10 mg daily | 15 to 20 | Diarrhea, abdominal pain, myalgias |
| Bile acid sequestrants | | | Should be given with meal(s). Side effects: constipation, abdominal pain, bloating, nausea, flatulence. Interference with absorption of other medications: warfarin, digoxin, thyroid hormone, thiazide diuretics, amiodarone, glipizide, statins. (less with colesevelam) |
| Colesevelam | 3.75 to 4.375 g/day | 15 to 18 | |
| Colestipol | 4 to 15 g bid | 12 to 30 | |
| Cholestyramine | 4 to 12 g bid | 7 to 30 | |
| Niacin | 500 to 2000 mg daily | 5 to 20 | Side effects: flushing, pruritus, nausea, bloating, elevation of liver transaminases, hyperuricemia, and hyperglycemia. |
| Fenofibrate (multiplepreparations) | 30 to 200 mg daily | 0 to 20 | Reduced dosage in renal insufficiency Side effects: abdominal pain, gastrointestinal, elevation of liver enzymes, myalgias, risk of rhabdomyolysis, increased creatinine |

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**Table 4**

**Pharmacologic agents approved for homozygous FH**

| Treatment | Dosage | Mean reduction LDL-C (%) | Drug interactions | Safety issues | Side effects |
|---|---|---|---|---|---|
| Mipomersen | 200 mg subcutaneously once per week | 24 to 28 | None | Increased hepatic transaminases. Increased hepatic fat | Injection site reactions, pyrexia, malaise, fatigue, headache, nausea |
| Lomitapide | 5 to 60 mg orally per day | 38 to 50 | Cytochrome p450 3A4 (atorvastatin) | Increased hepatic enzymes. Increased hepatic fat. Cytochrome p450 3A4 interactions | Diarrhea, gastrointestinal side effects. Requires low fat diet and supplemental fat soluble vitamins |

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