

# FAMILIAL HYPERCHOLESTEROLEMIA

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#### Updated November 28, 2023

#### ABSTRACT

Familial hypercholesterolemia (FH) is a prevalent, autosomal co-dominant disorder of lipid metabolism that results in elevated low-density lipoprotein cholesterol (LDL-C) levels and premature atherosclerosis. Screening for identifying and heterozygous FH in childhood is critical, given its high prevalence and asymptomatic presentation. Furthermore, treatment of FH in childhood is effective at lowering LDL-C levels and has the potential to atherosclerotic cardiovascular reduce disease (ASCVD) events in adulthood. Selective screening based on family history had previously been recommended to identify children and adolescents with FH or other lipid disorders. However, studies indicated that many individuals with heterozygous FH were missed with this approach, and therefore in 2011 the National Heart, Lung, and Blood Institute Expert Panel recommended universal screening of children and adolescents between ages 9 and 11 years and again at ages 17 to 21 years, in addition to selective screening, in order to identify pediatric individuals with heterozygous FH. This approach was affirmed in the 2018 American College of Cardiology and the American Heart Association (ACC/AHA) Cholesterol Guidelines, along with endorsing cascade screening as another reasonable approach to identifying children with FH. Once FH is diagnosed, prompt treatment with lifestyle modification should be initiated. When lifestyle interventions are not sufficient, pharmacotherapy using statins has been shown to be effective at lowering LDL-C, generally safe in short and mediumterm studies, and may be beneficial at reducing ASCVD events. Other medications can be useful at lowering LDL-C in conjunction with statin therapy, although generally statins are sufficient in young patients. Homozygous FH is a rare disorder manifesting as extremely high LDL-C and ASCVD in childhood. requiring aggressive multimodal management. Overall, studies are needed to determine the optimal timing and intensity of statin therapy, and to better understand long-term safety and ASCVD outcomes in adulthood for lipid-lowering pharmacotherapy initiated in pediatric patients with heterozygous FH.

#### INTRODUCTION

Familial hypercholesterolemia (FH), as classically described, is the most common single gene disorder of lipoprotein metabolism and causes severely elevated low-density lipoprotein cholesterol (LDL-C) levels. The prevalence of FH is 1 in 200 to 1 in 300 individuals of different ethnicities (1,2), and it is strongly associated with premature coronary artery disease (CAD) (3). Data from observational studies suggest that untreated FH is associated with ~90-fold increase in mortality due to atherosclerotic cardiovascular disease (ASCVD) in young adults (4). Since early treatment may significantly reduce CAD-related morbidity and mortality in individuals with

heterozygous FH (5), early identification and intervention during childhood may greatly improve outcomes in adulthood.

## EPIDEMIOLOGY

The prevalence of FH varies substantially, depending upon the criteria used to define the disorder and the ancestry of the population. Previously, the prevalence had been described as 1 in 500 individuals based on early work by Drs. Brown and Goldstein (6,7). More recent analysis of white European populations, which tend to be less ethnically and racially diverse than the US, show higher prevalence rates (8,9). An analysis using a modified version of the Dutch Lipid Clinic (DLC) criteria applied to participants in the 1999 to 2012 National Health and Education National Surveys (NHANES), a nationally representative survey of the US population, suggest FH affects 1 in 250 US adults (1). The prevalence of FH in US children and adolescents is not as well characterized, although presumably it is similar. Some estimate that as few as 10% of individuals with FH have been identified in the US.

## PATHOPHYSIOLOGY AND GENETICS

FH was initially defined by Brown and Goldstein as a disorder or defect in the LDL receptor (LDL-R) (3). More recently, the description of FH has been expanded and used to describe any defects in LDL-C processing and/or signaling that may lead to a phenotype characteristic of FH (10). FH may be more common and complicated than previously thought, with many different genetic variants leading to

pathogenesis. Overall, nine genes are causative for autosomal forms of FH, and up to 50 polymorphic loci contribute to polygenic susceptibility to elevated LDLcholesterol levels (11). Some etiologies for the FH phenotype include defects in apoB100 lipoprotein, the major atherogenic lipoprotein component of LDL-C, as well as gain of function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9), which promotes the degradation of the LDLR, resulting in reduced LDL-C clearance (7). Gene mutations in LDL-R, the apolipoprotein B gene, or in PCSK9 occur in approximately 93, 5, and 2 percent of individuals with a phenotype consistent with FH, respectively (12). The associated impairment in function of these receptors or proteins results in overall reduced clearance of LDL particles from the circulation and elevation in plasma LDL-C. There is also increased uptake of modified LDL by macrophage scavenger receptors, resulting in lipid accumulation in macrophages and foam cell formation, a precursor to atherosclerotic plaque development (13). Thus, the typical lipid profile of FH is characterized by elevated LDL-C (as high as 300 mg/dL) with subsequently increased total cholesterol (TC) levels; in general, triglycerides are normal, and high-density lipoprotein (HDL-C) can be low or normal. FH has an autosomal dominant inheritance pattern which results in hypercholesterolemia and early ASCVD events.

There are various genetic mutations that can cause FH, which can either be monogenic or polygenic in nature. See Table 1 below for a list of genes that are associated with FH.

Table 1. Genes Associated with FH
Monogenic
Autosomal Dominant
LDLR
APOB
PCSK9
APOE*
Autosomal Recessive
LDLRAP1
LIPA (Lysosomal acid lipase deficiency**)
ABCG5 and ABCG8 (Sitosterolemia**)
Polygenic
Genetic variants associated with FH which together can impact LDL-C levels

\*Specific mutations or candidate regions associated with FH

\*\*Refer to specific Endotext sections on lysosomal acid lipase deficiency and sitosterolemia for more information

In general, homozygotes for mutations in the LDL-R gene are more adversely affected than heterozygotes, reflecting a "gene dosing effect" of inheritance. Unless there is consanguinity in a family in which heterozygous FH is present, homozygous FH is less prevalent and may affect as many as 1 in 160,000individuals 300,000 (14). Additionally, the homozygous FH phenotype can be seen in compound heterozygotes which can occur in offspring of unrelated parents due to a different disease-causing mutation on each allele. The severity of the FH phenotype does not necessarily depend upon the presence of true homozygosity or compound heterozygosity inheritance; rather it is determined by the degree of disturbance in LDL metabolism. For additional information on the genetics as well as pathophysiology, refer to "Familial Hypercholesterolemia: Genes and Bevond" bv Warden et al., www.endotext.org (15).

#### **FH PHENOTYPE**

#### **Clinical Symptoms**

#### HOMOZYGOUS FH

Due to the excessively high plasma LDL-C levels in homozygous FH, cholesterol deposits are common in the tendons (xanthomas) and eyelids (xanthelasmas), and generally appear by one year of age. Tendon xanthomata are most common in the Achilles tendons and dorsum of the hands but can occur at other sites. Tuberous xanthomata typically occur over extensor surfaces such as the knee and elbow. Planar xanthomas may occur on the palms of the hands and soles of the feet and are often painful. Xanthelasmas are cholesterol-filled, soft, yellow plaques that usually appear on the medial aspects of the eyelids. Corneal arcus is a white or grey ring around the cornea (16).

## HETEROZYGOUS FH

In addition to increased serum cholesterol and risk for premature coronary artery disease (see below), patients with heterozygous FH may have tendon xanthomas and corneal arcus that appear after the age of 20 years (16).

## LDL-C Levels

In clinical practice, there is not a universal LDL-C threshold that determines a diagnosis of FH. Generally, the level of LDL-C that warrants further evaluation depends upon the age of the patient and whether additional family members have known hypercholesterolemia and/or early ASCVD. As suggested by recent guidelines (7,17), children and adolescents with a negative or unknown family history

and LDL-C level persistently ≥190 mg/dL (4.9 mmol/L) suggests FH; in patients with a positive family history of hypercholesterolemia or early ASCVD, an LDL-C

level of  $\geq$ 160 mg/dL(4.1 mmol/L) is consistent with FH (see Table 2).

Table 2. Acceptable, Borderline, and High Lipid Levels for Children and Adolescents				
Lipid	Low (mg/dl)	Acceptable (mg/dl	Borderline-High	High (mg/dl)
			(mg/dl)	
ТС		<170	170-199	>200
LDL-C		<110	110-129	>130
Non-HDL-C		<120	120-144	>145
Triglycerides				
0-9 years		<75	75-99	>100
10-19 years		<90	90-129	>130
HDL-C	< 40	>45		

Adapted from the NCEP expert panel on cholesterol levels in children (14)

#### Cardiovascular Disease

Cardiovascular risk in FH patients is determined by both the LDL-C concentration and by other traditional risk factors. Homozygotes have early-onset atherosclerosis, including myocardial infarction, in the first decade of life (reported as early as age two years), and are at increased risk for CAD-related mortality in the first and second decades (16). Additionally, patients with homozygous FH can develop cholesterol and calcium deposits that can lead to aortic stenosis and occasionally to mitral regurgitation.

Heterozygotes are also at increased risk for earlyonset CAD between the ages of 30-60 years (18). Children with heterozygous FH have thicker carotid intima-media thickness (cIMT), an anatomic measure of arterial thickness associated with atherosclerosis, compared to unaffected siblings and healthy controls (19,20). One study showed those treated with statin medications (HMG-CoA reductase inhibitors) at younger ages had less carotid atherosclerosis compared to the placebo group. Results from longterm studies of statins in children with FH are just emerging, and indicate that statin treatment during childhood may slow progression of cIMT and reduce the risk of CVD in adulthood (21).

# SCREENING

Given the high prevalence of FH and the improved outcomes with early treatment, pediatric lipid screening has become very important for the detection of FH. However, the approach to lipid screening in childhood and adolescences has varied over the past decades and is somewhat controversial, with the US Preventative Services Task Force (USPSTF) recently concluding that that the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents (22). Selective screening of young individuals with а family history of hypercholesterolemia and/or early CV events or patients at risk for atherosclerosis for other medical conditions has been recommended for several decades (23-25). However, screening individuals based only on family history may miss 30-50% of children with elevated LDL (24-26). Thus, the 2011 Expert Panel, supported by the more recent 2018 ACC/AHA Cholesterol Guidelines (27), recommended universal lipid screening, which involves screening in childhood at two time points, once between ages 9 and 11 years, and then again between ages 17 and 21 years (28). Universal screening is recommended in those not already selectively screened based on family history or personal risk factors (Table 3).

Selective screening for FH involves obtaining a fasting or non-fasting lipid panel in individuals ages 2 to 21 years with:

- 1. Family history of early atherosclerosis or high cholesterol.
- 2. Relatives of individuals with identified FH.

Lipid testing should also be performed in the presence of risk factors or medical diagnoses that increase risk for CVD (including hypertension, current cigarette smoking, body mass index  $\ge 85^{\text{th}}$  percentile, diabetes mellitus type I and II, chronic kidney disease/endstage renal disease, chronic inflammatory diseases, human immunodeficiency virus infection, and nephrotic syndrome) (28).

Universal screening involves obtaining either a fasting lipid profile or a non-fasting non-HDL, (calculated by subtracting HDL from TC) in childhood at two time points:

- 1. Between ages 9-11 years.
- 2. Between ages 17-21 years.

Table 3. Screening for Hypercholesterolemia					
Approach	Age in Years	Population			
Selective	2-21	Family history of early atherosclerosis or high cholesterol Presence of risk factors or medical conditions that increased early CVD risk*			
Universal	9-11 and 17-21	All			

\*Selective screening is indicated in individuals with hypertension, current cigarette smoking, body mass index ≥ 85<sup>th</sup>percentile, diabetes mellitus type I and II, chronic kidney disease/end-stage renal disease, chronic inflammatory diseases, human immunodeficiency virus infection, and nephrotic syndrome

## DIAGNOSIS

The diagnosis of FH can be made clinically and through genetic testing; genotype needs to be interpreted in the context of phenotype. For heterozygous FH, the clinical diagnosis is made based on the presence of high levels of total and LDL cholesterol in combination with one or more of following (17):

- 1. Family history of hypercholesterolemia (especially in children) or known FH.
- 2. History of premature CAD in the patient or in family members.
- Physical examination findings of abnormal deposition of cholesterol in extravascular tissues (e.g., tendon xanthoma), although these rarely occur in childhood.

There are several clinical scoring systems used to diagnose FH, and these vary based on the weight given for each diagnostic criteria (11). In general,

clinical diagnosis of homozygous FH can be made in individuals with the following criteria (14):

- 1. Untreated LDL-C >500mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (>8 mmol/L), <u>AND</u>
- 2. Cutaneous or tendon xanthoma before age 10 years, <u>OR</u>
- 3. Elevated LDL-C levels consistent with heterozygous FH in both parents.

There are various disease states or other factors that can increase LDL-C levels and should be considered when diagnosing FH. Some of these include the following:

- Obesity
- Hypothyroidism
- Diabetes mellitus
- Nephrotic syndrome
- Chronic renal failure
- Cholestasis
- Biliary atresia

- Hepatitis
- Biliary cirrhosis
- HIV infection/AIDS
- Various drugs/medications
- Alcohol
- Pregnancy
- Very low carbohydrate ketogenic diets

# **Genetic Testing**

Identifiable gene defects in LDLR, APOB, or PCSK9 have been identified in 60 to 80% of individuals with a heterozygote FH phenotype. Genetic testing has not routinely been performed in the clinical setting due to concerns about cost to the patient and because it was not likely to alter management, given that treatment decisions were usually based on LDL-C levels. However, FH genetic testing has recently been recommended to become the standard of care for patients with definite or probable FH, and the rationale for such testing includes the following: 1) facilitation of definitive diagnosis of FH lowers the concern for other secondary causes of high LDL-C; 2) pathogenic variants correlate with higher cardiovascular risk, which indicates the potential need for more aggressive lipid lowering; 3) increase in initiation of and adherence to therapy; and 4) cascade testing of at-risk relatives (29). Overall, the clinical significance of normal or moderately elevated LDL-C levels in the setting of a genetic defect in the LDLR or other possibly pathogenic defects is unknown.

# TREATMENT

The guidelines for initiating treatment in patients with the FH phenotype are based on age, severity of LDL-C elevation, as well as family and medical histories. Lifestyle therapy is recommended for all children and adolescents with LDL-C levels  $\geq$  130 mg/dL. If lifestyle intervention is insufficient, medications can be considered in children beginning at age 10 years, or as early as age 8 in high-risk patients and in the presence of a very high-risk family history. For healthy children and adolescents ages 10-21 years, lifestyle therapy should be provided to those with an LDL-C  $\geq$  130 mg/dL, and medication should be initiated if LDL-C remains  $\geq$  190 mg/dL despite 6 or more months of lifestyle modification. If there is a family history of early atherosclerotic disease, then medication should be started in individuals with LDL-C levels  $\geq$  160 mg/dL who do not respond sufficiently to lifestyle modification. If an individual has a high-risk medical condition, as noted above, medication can be considered for those with a persistently elevated LDL- $C \ge 130 \text{ mg/dL}$ . In general, the goal of treatment is to maintain an LDL-C level  $\leq$  130 mg/dL or  $\geq$  50% reduction in LDL concentration; lower ranges may be considered in high-risk patients. Medications should be initiated in all patients with homozygous FH at the time of diagnosis, regardless of age, and additional treatments should also be considered.

# Lifestyle Treatment

The mainstay of treatment for pediatric lipid disorders is lifestyle modification. A low saturated fat diet, without trans-fat, and high in fruits and vegetables, is the recommended diet for lowering LDL-C. This dietary approach has been shown to be both safe and beneficial in the general pediatric population (28,30,31). Additionally, nutritional and physical activity interventions have been shown to lower LDL-C and improve CVD risk factors in children with obesity in meta-analyses (32). Despite this, in adults with FH, lifestyle modifications have been shown to only lower LDL-C modestly (33). Furthermore, the effect of physical activity on LDL-C levels has not been well studied in children with FH.

# Pharmacotherapy

# STATINS

The majority of patients with FH are treated with medications, and statins are the recommended first line pharmacotherapy. In a Cochrane meta-analysis of pediatric patients with FH, statins were shown to lower LDL-C by 32% (34). Furthermore, more intensive statin therapy in high doses has been shown to lower LDL-C even more significantly, by up to 50% (35,36).

Follow-up data from a statin trial in pediatric Dutch patients suggest efficacy and safety, as well as decreased atherosclerosis compared to the subjects' parents (37). Most recently, the use of statins in children with FH have shown reduced CVD risk in adulthood for these patients compared to their untreated parents with FH, after a 20 year follow-up (21). Although this study was not a controlled or placebo study, it suggests that long-term statin use in childhood may prevent ASCVD compared to not treating.

Several different formulations of statin therapy are available and approved by the US Food and Drug Administration (FDA) for use in children. Treatment is initiated at a low dose (generally 5-20mg depending on the statin potency), which is given once a day, often at night. If needed, the dose is increased to meet the goals of therapy. Side effects with statins are rare, but include myopathy, new-onset type 2 diabetes mellitus (reported in adult primary prevention statin trials), and hepatic enzyme elevation. In pediatric clinical trials, rates of side effects with statin therapy were low and adherence to statin therapy was generally good (38). Side effects of statins are more likely at higher doses patients taking other medications. and in particularly cyclosporine, azole antifungal agents, and other medications and foods (such as grapefruit) that impact the cytochrome P450 system. Adolescent females should be counseled about the possibility of drug teratogenicity and appropriate contraceptive methods while receiving statin therapy. Additionally, providers should be aware that oral contraceptive pills can increase lipid levels.

The NHLBI guidelines recommend the following baseline laboratory evaluation when initiating statin therapy (28):

- Fasting lipid profile.
- Serum creatine kinase (CK).
- Hepatic enzymes (i.e., serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST]).

Screening for type 2 diabetes is also reasonable prior to starting statins. Fasting lipid profiles are repeated at four weeks after the initiation of statin therapy to titrate dose and are repeated every six months in patients on stable therapy. Liver function tests, CK, and hemoglobin A1C should be obtained if signs of adverse effects arise, and may be obtained at regular intervals, for example after dose changes based on best clinical judgement. Ongoing monitoring of growth, other measures of general and cardiovascular health, and review for the presence of additional ASCVD risk factors, such as smoking exposure, should also occur at each visit.

## BILE ACID BINDING RESINS

Although bile acid binding resins or bile acid sequestrants have been shown to lower LDL-C by ~10-20% in pediatric trials (39,40), they are often difficult to tolerate given their unpalatability and associated adverse effects (such as bloating and constipation) (41). For these reasons, bile acid binding resins are used relatively infrequently. However, they may be useful in combination with a statin for patients who fail to meet target LDL-C levels (42). The sequestrants are not absorbed systemically, remain in the intestines, and are excreted along with bile containing cholesterol. Therefore, they are considered to be very safe. They can be used in patients who prefer to avoid statins, although they may not lower LDL-C sufficiently to achieve goal levels.

# CHOLESTEROL ABSORPTION INHIBITORS (EZETIMIBE)

Ezetimibe is a lipid-lowering mediation that inhibits absorption of cholesterol and plant sterols in the intestines. This agent can be useful in pediatric patients with FH who are not able to reach LDL-C treatment goals on high-intensity statin therapy. Ezetimibe further lowers serum LDL-C and in adults has been shown to improve cardiovascular outcomes without altering the side effect profile (43–45). Specifically in the pediatric population, ezetimibe has been shown to be safe and effective at lowering LDL- C by up to almost 30%, even when used as monotherapy (44,46,47)

## PCSK9 INHIBITORS

PCSK9 inhibitors (evolocumab and alirocumab) are human monoclonal antibodies that bind to PCSK9 and promote plasma LDL cholesterol clearance. In Europe, evolocumab is approved in adolescents (≥12 years old) with homozygous FH. In the US, alirocumab is approved only for use in adult patients, and evolocumab is approved for use in adults with heterozygous FH and in homozygous FH, ages 13 and older, who have not responded to other LDL-C lowering therapies. Overall, PCSK9 inhibitors appear to have a good safety and side effect profile in adults (48). These medications have been shown to be very effective, reducing LDL-C by more than 15% in patients with homozygous FH and by 35% in patients FH with heterozygous (49–51). The main disadvantage of PCSK9 inhibitors is that they require injection for administration; cost is also a concern.

Inclisiran is another medical therapy that targets PCSK9 synthesis through a different mechanism. It is a small interfering RNA molecule that triggers the breakdown of messenger RNA coding for the PCSK9 protein. This medication has been recently approved for clinical use and has been shown to be safe and effective in adult patients with heterozygous FH (49). Clinical trials of inclisiran are currently underway in adolescent patients with heterozygous and homozygous FH (50).

# EMERGING MEDICAL THERAPIES

There are several promising therapies that aim to reduce LDL-C through different approaches. These include Bempedoic Acid, Lomitapide, and Evinacumab. Bempedoic acid blocks the cholesterol biosynthetic pathway upstream of HMG-CoA reductase through inhibition of adenosine triphosphate citrate lyase. This therapeutic agent has been shown effective to be in treating statin-resistant hypercholesterolemia and in reducing ASCVD in

adults (51,52). Bempedoic acid is currently being studied in children with heterozygous FH.

Microsomal triglyceride transfer protein (MTP) plays an essential role in the formation of apoB-containing lipoproteins and has been shown to be inhibited by Lomitapide (53). This drug can reduce LDL-C by approximately 58% and has been approved for use in adults with homozygous FH. So far, Lomitapide has been observed to be safe and effective in pediatric patients with homozygous FH (54).

Evinacumab is a human monoclonal antibody that targets angiopoietin-like 3 (ANGPTL3), which results in the reduction of LDL-C levels via an LDL-receptor independent mechanism (55-57). This drug has been shown to significantly reduce LDL-C in patients with homozygous FH who show little to no LDL-receptor activity and who have had poor response to other treatments (58). Additionally, patients with heterozygous FH have also shown improvements in LDL-C by 50% reduction (59). Evinacumab was approved in early 2021 by the FDA for the treatment of homozygous FH patients starting at age 12 years (60).

# Lipoprotein Apheresis

Although statin therapy has been shown to be effective in reducing LDL and prolonging life expectancy in patients with homozygous FH (61), medical treatment alone may not be adequate to achieve recommended treatment goals. Therefore, it is suggested that lipoprotein apheresis (LA) be initiated in patients with homozygous FH as young as 2 years. The efficacy is dependent upon the type of apheresis but can reduce LDL-C by as much as 45 to 80%. Studies in pediatric patients are limited, but there is some evidence suggesting that LA therapy is safe and effective in children with homozygous FH (62).

## SUMMARY

FH is an autosomal dominant disorder of LDL metabolism that affects 1 in 200 to 300

individuals. Screening involving lipid measurements, family and medical history, and physical examination is needed to identify affected individuals; cascade screening can be helpful. Lifestyle modification is the first-line therapy for hyperlipidemia in pediatric patients but is usually not sufficient to achieve goal LDL levels. Available evidence suggests that

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treatment with lipid-lowering pharmacotherapy, such as statins, is effective and generally safe in the short and medium-term. However, further studies are needed to determine the long-term safety and efficacy in preventing ASCVD of lipid lowering medication in pediatric patients with FH.

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