REVIEW

CME CREDIT

**CHRISTOPHER SIBLEY, MD**
Department of Cardiology, Johns Hopkins University, Baltimore, MD

**NEIL J. STONE, MD***
Professor of Clinical Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

# Familial hypercholesterolemia: A challenge of diagnosis and therapy

## ABSTRACT

People with familial hypercholesterolemia (FH) have dramatically high levels of low-density lipoprotein cholesterol (LDL-C), which can lead to accelerated atherosclerosis and, if untreated, early cardiovascular death. Although the heterozygous form of FH is often unrecognized, detecting it early can enable risk reduction before premature coronary heart disease occurs.

## KEY POINTS

Atherosclerotic vascular disease occurs at much younger ages in FH than in other dyslipidemias, and the incidence is likely related to the duration and severity of the hypercholesterolemia.

FH causes characteristic tendon xanthomas, especially in the Achilles tendons, that can be missed unless specifically sought. In young white patients, arcus corneae may be a clue to heterozygous FH.

Relatives of patients with FH should have their cholesterol checked.

For patients with heterozygous FH, statin therapy markedly reduces LDL-C and is the mainstay of a multidrug treatment regimen. Patients with homozygous FH are at high risk of premature aortic valvular stenosis and coronary atherosclerosis and need intensive multidrug therapy at an early age. LDL apheresis can be added to a multidrug regimen if such therapy fails to control cholesterol levels.

MANY PEOPLE have high cholesterol, but a distinct minority have extremely high levels due to genetic defects in lipoprotein metabolism.

These patients need our special attention because they are at high risk of atherosclerotic cardiovascular disease at a young age.[1] Moreover, their relatives (including their children) also need our attention because many of them share the same genetic defects.

Unfortunately, appreciation of the challenges in the treatment of those with disorders of lipoprotein metabolism lags significantly behind our knowledge of the evaluation and treatment of mild or moderate hypercholesterolemia.

This article focuses on familial hypercholesterolemia (FH), an autosomal-codominant monogenic disorder of low-density lipoprotein cholesterol (LDL-C) metabolism. There are other familial forms of high cholesterol, but FH has characteristic clinical features that clinicians should be able to recognize.[2,3]

## FH IS DUE TO MUTATIONS IN THE LDL RECEPTOR GENE

FH is primarily due to mutations in the LDL receptor gene on the short arm of chromosome 19.[4] These mutations can reduce the absolute number of LDL-C receptors or prevent LDL-C from binding to these receptors. The result is a greatly diminished ability to remove LDL-C from the blood.

The homozygous form of FH is rare, with a prevalence of about 1 in 1 million. Patients

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**TABLE 1**

## LDL-C cut points for diagnosis of heterozygous FH: Degree of relationship to an affected relative

| AGE (YEARS) | LDL-C CUT POINT (MG/DL) | | | |
|---|---|---|---|---|
| | FIRST-DEGREE RELATIVE | SECOND-DEGREE RELATIVE | THIRD-DEGREE RELATIVE | GENERAL POPULATION |
| < 20 | 155 | 165 | 170 | 200 |
| 20–29 | 170 | 180 | 185 | 220 |
| 30–39 | 190 | 200 | 210 | 240 |
| ≥ 40 | 205 | 215 | 225 | 260 |

WILLIAMS RR, HUNT SC, SCHUMACHER MC, ET AL. DIAGNOSING HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA USING NEW PRACTICAL CRITERIA VALIDATED BY MOLECULAR GENETICS. AM J CARDIOL 1993; 72:171–176.

are considered to have homozygous FH if they have two mutant copies of the gene, regardless of whether both alleles carry the same mutation or different mutations (ie, in "double heterozygotes"). In either case, the clinical presentation is characteristic and dramatic: skin and tendon xanthomas, total cholesterol levels between 500 and 1,000 mg/dL, and the onset in childhood of symptomatic coronary disease as well as aortic valve and proximal root disease.[4]

**Without treatment, 50% of men with heterozygous FH develop coronary disease by age 60**

In contrast, the heterozygous form of FH is relatively common, with an estimated prevalence of 1 in 500 in the United States and United Kingdom. The frequency is much higher among Chinese Canadians, French Canadians, Finns, Dutch, Icelanders, Lebanese Christians, Lithuanian Jews, and South African Afrikaners. This "founder effect" occurs in communities founded by a small number of immigrants, some of whom carried specific mutations.[5]

Total cholesterol levels in heterozygous FH average 325 to 450 mg/dL. The clinical presentation is not as dramatic or as pronounced as in homozygous FH, but many patients remain at markedly elevated risk for coronary heart disease and death in the fourth or fifth decade of life if untreated.

In an older but instructive report of the "natural history" of heterozygous FH,[6] 116 affected US families were referred to the National Institutes of Health in the late 1960s and early 1970s (before statins were available). The index cases were omitted from the analyses. The risk of coronary heart disease by age 60 was 1 in 2 for male heterozygous patients and 1 in 6 for their female counterparts—strikingly higher than in their otherwise similar but unaffected relatives.

## DIAGNOSIS IS CLINICAL

Although markedly elevated LDL-C is the key to the diagnosis of FH, this laboratory value alone is not sufficient.

A clinical diagnosis of heterozygous FH is best made with the finding of elevated LDL-C in the context of:

- A family history of elevated cholesterol in childhood
- A family or individual history of premature coronary disease
- Physical findings of tendon xanthomas.

As the prevalence of heterozygous FH is markedly higher in first-degree relatives of patients with the disorder than in the general population—1 in 2 vs 1 in 500—it follows that the screening criteria should vary according to the degree of relationship to a patient with known FH.[7] Having a known case of FH in the family clearly raises the pretest probability of having FH and lowers the LDL-C cut point necessary to confirm the diagnosis. **TABLE 1** summarizes the LDL-C diagnostic criteria for heterozygous FH from the MEDPED (Make Early Diagnosis—Prevent Early Death) study[8] according to age and degree of relationship to a patient with known FH.

DNA tests can confirm the diagnosis. However, their use is limited in the United

States owing to the large number of mutations in the LDL receptor gene in this country (in contrast to neighboring Quebec, for example, where only a few mutations are found).

### Children of patients with FH should be screened for it

Cholesterol levels in FH are elevated from early childhood. In patients believed to be at risk for FH because they have a parent with very high cholesterol levels, screening for the disease can begin as early as age 2 to 3 years.

A large case series in children in the Netherlands suggested that an LDL-C cut point of 135 mg/dL had only a 5% false-negative rate in predicting an LDL receptor mutation.[9] Moreover, children whose parents had heterozygous FH or who had first-degree relatives with premature coronary heart disease had higher levels of LDL-C, lower levels of high-density lipoprotein cholesterol (HDL-C), and higher levels of lipoprotein(a). Conversely, parents of children with the above characteristics had shorter event-free survival than parents of children with less abnormal values.

Although the LDL receptor mutation is the primary determinant of the LDL-C level, environmental influences may, in some cases, affect the severity of the phenotypic expression. A study from the Netherlands[10] noted that the risk of death can vary significantly even within the same kindred. This suggests, in some cases, that a strong contribution of environmental factors can help explain the rates of coronary heart disease.

Therefore, detecting FH in a child should give us the opportunity to monitor and treat his or her cholesterol levels, to persuade him or her to avoid high-risk behaviors such as becoming obese and smoking cigarettes, and to encourage other relatives to have their cholesterol checked.

### Xanthomas develop early in life

Clinical signs of FH also begin to develop early in life.

Tendon xanthomas, which result from deposition of excess LDL-C, are present in more than 70% of patients with FH by age 40 to 50. In homozygous FH, striking skin and tendon xanthomas are seen by age 10, while in heterozygous FH they can appear in young adulthood.

## Xanthomas in familial hypercholesterolemia

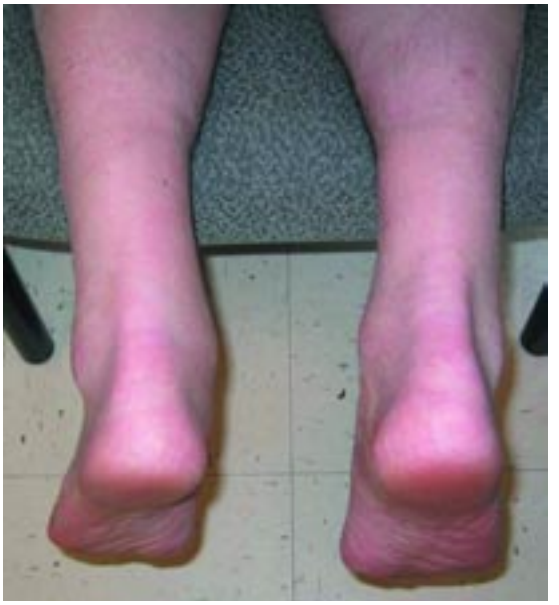

**FIGURE 1.** Xanthomas of the Achilles tendons. Note the position used for examination.

Surprisingly, xanthomas are often missed on routine physical examination. If a patient has elevated cholesterol, have him or her kneel on the seat of a chair facing towards its back so that you can inspect and palpate the Achilles tendons and elicit ankle reflexes (**FIGURE 1**). In addition, since tendon xanthomas can occur in more than one location, it is important to look for them in other extensor tendons as well (eg, over the metacarpals).

**Tendon xanthomas are present in > 70% of patients with FH by age 50**

The combination of tendon xanthomas and a total cholesterol level greater than 300 mg/dL is usually a good indicator of FH, although other conditions should be considered. For example, this combination can also be seen in familial type III hyperlipoproteinemia, but other distinguishing features of familial type III are markedly elevated triglyceride values (which are often equivalent to the cholesterol values), planar xanthomas in the palmar creases, and tuberous xanthomas over the elbows.

Tendon xanthomas can also be seen in a rare autosomal-recessive condition called homozygous sitosterolemia.[11] This condition

## Corneal arcus in familial hypercholesterolemia

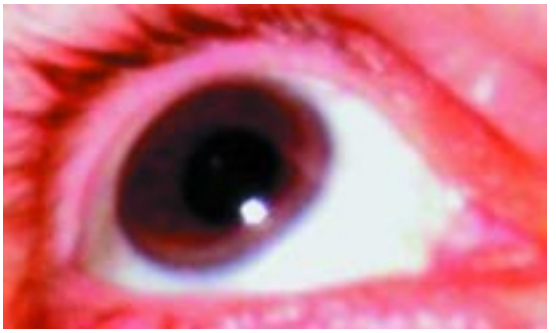

**FIGURE 2.** Corneal arcus in a white patient with hypercholesterolemia.

clinically resembles homozygous FH but, unlike FH, it responds dramatically to diet.

### Corneal arcus is a sign of FH in younger white patients

A corneal arcus is a white or gray opaque ring in the corneal margin resulting from cholesterol deposits. Although a circumferential corneal arcus is a common and nonspecific finding in older patients, in younger white patients an inferior pole arcus (FIGURE 2) can be a sign of FH. If you notice one in a young white patient, look for Achilles tendon thickening and measure his or her LDL-C, but remember that it is not a clue to FH in nonwhites and especially in older adults.

**Detecting FH in a child gives us the opportunity to intervene**

## CORONARY DISEASE BEGINS EARLY

People with FH begin to develop obstructive and progressive atherosclerotic disease and impaired endothelial function at a young age.[12] Homozygous FH can result in symptomatic angina in childhood and adolescence.[13] Patients with heterozygous FH can develop clinically evident coronary heart disease in their 30s or 40s, especially if they have other risk factors such as cigarette smoking and a strong family history of premature coronary heart disease.[6,9,14]

In one large case series,[9] higher LDL-C values, low HDL-C levels, and elevated lipoprotein(a) levels in the offspring predicted coronary heart disease in the parents. Indeed, elevated levels of lipoprotein(a) and homocysteine have been thought to be markers of an adverse prognosis in some[15,16] but not all analyses.[17]

On coronary angiography, two striking features of heterozygous FH are that obstructive lesions tend to be proximal rather than distal[18] and that, in those with low HDL-C, coronary ectasia is common.[19] The aortic valve may be thickened, and in homozygous cases a characteristic form of supravalvular aortic stenosis is present.[13]

## SELECTED ISSUES IN CLINICAL MANAGEMENT

### Start lifestyle interventions in childhood

FH can be diagnosed in childhood, and it should be looked for in families with premature coronary heart disease. Children should be tested before age 10, but there is little advantage to screening before age 2.

Before age 2, dietary cholesterol restriction is not recommended because it could negatively affect neural growth and development. After age 2, the diet should be low in cholesterol, saturated fat, and trans-fatty acids, with plenty of fruits, vegetables, and fiber and sufficient calories and nutrients to support normal growth. Parents may wish to consult a dietitian experienced in lipid management.

In addition, children with FH should be encouraged to establish a pattern of regular exercise to help avoid obesity and should be strongly discouraged from starting to smoke.

### Starting lipid-lowering therapy at a young age

Some young people with FH should start drug therapy. Although everyone with FH has an increased lifetime risk of coronary heart disease, factors that favor starting treatment at an early age or with a multidrug regimen or both include male sex, a family history of premature coronary heart disease, markedly elevated LDL-C, low HDL-C, cigarette smoking, and elevated lipoprotein(a).[9]

In four randomized, placebo-controlled studies in this age group,[20–23] atorvastatin, lovastatin, pravastatin, and simvastatin lowered LDL-C levels without adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue, although the numbers may not have been large enough to see a small

difference if one had been present. Importantly, statin treatment has beneficial effects on measures of subclinical atherosclerosis. In children with FH, after 2 years of pravastatin treatment, regression was seen in serial carotid studies of intima-medial thickness, whereas a trend towards progression was seen in controls.[21]

**In adolescent boys or young men** with FH, LDL-C-lowering drug therapy should be strongly considered. In past decades, bile acid sequestrants were used, but compliance was limited by the multiple doses per day that were required, the large volume of powder or number of pills needed, and by frequent gastrointestinal complaints due to the high dosages used. Statins have made it much easer to lower LDL-C by 40% or more.

HDL-C levels are lower in boys after puberty. Indeed, low HDL-C is often seen in adolescent boys with heterozygous FH.[24] In view of their increased coronary risk, it is important to emphasize nondrug measures to raise HDL-C such as avoiding cigarette smoking, obesity, sedentary lifestyle, and excess simple carbohydrates in this group.

**Adolescent girls and women in their 20s** with FH can be offered statins, but the decision is more complex than with their male counterparts. If they have no family history of premature coronary heart disease, do not smoke, and do not have markedly elevated LDL-C or low HDL-C, their risk of premature coronary disease appears lower.

Women of childbearing age with heterozygous FH should consider the issue of pregnancy before they begin statin therapy.[25] Statins may be teratogenic, and although the risk they pose to the fetus is currently difficult to quantify, they are best avoided.[18] Therefore, a woman in this age group should talk to her gynecologist about birth control before starting statin therapy. However, statins are not mutagenic, and women can take them as long as they stop taking them before trying to conceive.

## Statins are the mainstay of treatment for FH

3-Hydroxy-3 methylglutaryl (HMG) CoA reductase is the critical enzyme for the rate-limiting step of cholesterol synthesis. Statins are competitive inhibitors of HMG CoA reductase and hence reduce hepatic cholesterol synthesis. This results in enhanced LDL receptor activity in the liver, which, in turn, increases LDL catabolism while it decreases LDL-C production.[1] Statins have supplanted the less effective and less tolerable bile acid sequestrants that were the mainstay of therapy for young patients in the past.

The recent National Cholesterol Education Program, Adult Treatment Panel III update (ATP III) recommended using a statin dose that lowers LDL-C at least 30% for patients at high risk.[26] Adults with heterozygous FH need to lower their LDL-C by at least 40% to 50% to reach ATP III goals. Thus, high-dose statin therapy is often an important component, although not necessarily the only component, of drug regimens for heterozygous FH.

Remarkably, statins can be effective in homozygous FH. Both atorvastatin and simvastatin have been shown to lower LDL-C in patients with homozygous FH who have no functional LDL receptors by decreasing hepatic production and secretion of lipoproteins.[27,28]

## Other components of a multidrug regimen

**Nonabsorbable bile acid sequestrants** such as cholestyramine, colestipol, and colesevelam have merit as safe nonsystemic options and are important second drugs to augment the LDL-C lowering of statins. In addition, combined with niacin, they may be an important option for women of childbearing age who are afraid of becoming pregnant while taking a statin.

**Statins may be teratogenic, but the risk to the fetus is hard to quantify**

The tolerability of bile acid sequestrants is limited by their gastrointestinal side effects, the inconvenience of taking multiple pills or powder, and the need to take them at least twice a day. A practical tip is to take the bile acid sequestrant with psyllium to improve its LDL-C-lowering ability.[29] This can also mitigate the constipating effect of the sequestrant.

Physicians should carefully check for possible drug interactions. Cholestyramine and colestipol have significant interactions with commonly used drugs such as thyroxine, digoxin, and warfarin. The newest sequestrant, colesevelam, a nonabsorbable polymer, has the advantage of interfering less with other medications.[30]

**Niacin** is the best drug for raising HDL-C and is a useful component of multidrug regimens in adults with heterozygous FH. It comes in three forms: unmodified (short-acting), intermediate-release, and sustained-release. If cost is an issue, unmodified nicotinic acid can be titrated to effective dosages.

Although niacin therapy can raise HDL-C levels and lower triglycerides effectively at doses of 1.0 to 1.5 g/day, higher doses are needed to lower LDL-C substantially, and for this one needs unmodified niacin. Unlike other lipid-lowering drugs, niacin lowers lipoprotein(a).[31]

Niacin causes prostaglandin-mediated flushing and itching, which can be severe in some patients. Taking aspirin 325 mg about 1 hour before taking niacin can alleviate this side effect, which abates over time with continued use. Many patients prefer an extended-release form that has the advantages of once-daily dosing (at bedtime with food) and causing less flushing than immediate-release niacin and a lower rate of liver toxicity than sustained-release niacin preparations.[31]

**Ezetimibe,** a new cholesterol absorption inhibitor, lowers LDL-C when added to drug regimens for heterozygous and homozygous FH patients, without evidence of toxicity in short-term studies.[32] Ezetimibe interferes with net absorption of sterols and so is useful in those with sitosterolemia.[2]

**Stanol and sterol esters lower LDL-C by an additional 10% to 15% when added to a statin**

## Can diet lower LDL-C in FH?

Although dietary measures such as restricting saturated fat and cholesterol are important in any LDL-C-lowering regimen, they will not by themselves lower LDL-C to goal levels in patients with FH.

The ATP III report suggested including high viscous fiber, plant stanol, and sterol esters in the diet to greatly improve dietary lowering of LDL-C.[33] Sources of high viscous fiber such as oatmeal, oatbran, beans, and whole grain products should be stressed, as well as the use of psyllium.

Plant stanol and sterol ester supplementation interferes with micellar cholesterol absorption and lowers LDL-C by an additional 10% to 15% when added to a statin. There is evidence that plant stanol esters may be preferred, as they decrease both LDL-C and serum plant sterols at 2 months.[34] To avoid problems with decreased carotenoid absorption, the diet should be rich in fruits and vegetables.

Concerns have been raised about using these products, owing to the potential harm of increased sterol levels. Preliminary data in mice suggest no association between plasma levels of plant sterols and atherosclerosis.[35] On the other hand, if a young patient with premature atherosclerosis and xanthomas has only mildly or moderately elevated cholesterol levels and no obvious cause of the atherosclerosis and xanthomas, one should consider checking plant sterol levels to see if the rare sitosterolemia is present.[36]

## What is the evidence for using multiple drugs to lower LDL-C in FH?

Kane et al[37] performed serial angiography in 72 adults with heterozygous FH who were undergoing aggressive therapy to lower LDL-C. Their LDL-C levels decreased from 284 mg/dL at baseline to 173 mg/dL—a 39% reduction, which was statistically significant. Controls showed an increase in mean percent area of stenosis, while the treatment group showed a decrease ($P = .039$ by two-tailed $t$ test for the difference between groups). Lesions regressed in the treatment group in men and women. The change in percent area of stenosis correlated with LDL-C levels during the trial.

This impressive change suggests that those who do not reach their primary LDL-C goals should try for a secondary goal of 40% or more reduction in LDL-C.[38]

## What is the role of LDL apheresis?

LDL-C can be temporarily lowered by apheresis, a mechanical process that requires extracorporeal circulation of the patient's blood through filters that selectively adsorb LDL in a setup similar to that for hemodialysis.

Apheresis is an option for patients with severe, refractory FH,[38,39] especially if their current therapy poorly controls LDL-C and their risk of cardiovascular events is high. The decision to start LDL apheresis is not easy because of the cost and practical considerations involved. Problems with insurance, venous access, and patient compliance with

the biweekly apheresis sessions are important issues that must be considered in each patient before proceeding.

Although several different systems are available, the differences between them are not as crucial as deciding whether the patient would benefit from this therapy. Studies have shown that regular LDL apheresis, when added to medical therapy, markedly lowers LDL-C and also lowers lipoprotein(a). Since the only data showing LDL apheresis to be useful comes from clinical experience and nonsignificant trends in clinical trials,[38] the decision to start LDL apheresis should be made carefully, with every attempt given to maximize drug therapy options, and guided by regular and detailed cardiovascular assessments.

A recent review stressed that in cases of severe homozygous FH, starting intensive therapy with medication and LDL apheresis in childhood should not be delayed if one is to avoid potentially fatal coronary and aortic valvular disease.[40]

We recently reported the case of a boy who presented with severe hypercholesterolemia, xanthomas, angina, and an aortic murmur at age 13.[13] Found to have two different receptor defects, he required coronary bypass surgery and aortic valve and root replacement several years later. The prompt initiation of multidrug therapy to lower LDL-C, with plasma exchange at first and then regular LDL apheresis, undoubtedly contributed to his remarkable survival today, more than 30 years after presenting with coronary disease in childhood.

Although anecdotal, these rare cases highlight not only the great management challenges faced by clinicians, but also the potential benefit when markedly elevated LDL-C is successfully reduced.

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***ADDRESS:*** *Neil Stone, MD, Feinberg School of Medicine, Northwestern University, 211 E. Chicago Avenue, Suite 1050, Chicago, IL 60611; e-mail n-stone@northwestern.edu.*