

Preventing Early Cardiovascular Death in Patients With Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting in severe elevation of total and low-density lipoprotein cholesterol levels. There are more than 600,000 individuals in the United States with FH. Individuals with FH tend to experience premature cardiovascular disease and often die from sudden cardiac death at a young age. Statins alone or in combination with other lipid-lowering medications are effective in managing FH and preventing cardiovascular events. For patients who do not respond to or are intolerant of pharmacotherapy, low-density lipoprotein apheresis is available as a nonpharmacologic treatment option. Despite the prevalence of FH, it is undiagnosed and untreated in the majority of patients. Screening, combined with appropriate drug therapy, can save lives. The authors review the screening, diagnosis, and management of FH.

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The role of hypercholesterolemia in the pathogenesis of atherosclerosis and cardiovascular disease is well known. Although cardiovascular disease is still the leading cause of death in the United States,¹ the annual number of deaths from this disease decreased markedly over the last few decades of the 20th century, in large part because of the aggressive management of dyslipidemia and other risk factors.²⁻⁵ It is likely that most physicians are aware of the benefits of lipid-lowering medications and the evidence-based guidelines for their use. However, many may not be as well informed about the diagnosis and management of genetic dyslipidemias, many of which cause premature cardiovascular disease in individuals who otherwise would not be thought of as high risk.

Familial hypercholesterolemia (FH) is a common inherited lipid disorder that greatly increases the risk for cardiovascular disease. It is usually autosomal dominant and caused by defective function of the hepatic low-density lipoprotein (LDL) receptor, which results in extreme elevation of serum total and LDL cholesterol levels. Worldwide, an estimated 10 million people have FH, of whom approximately 200,000 die prematurely each year.⁶ There are more than 600,000 individuals with FH in the United States.^{7,8} Despite the high prevalence of FH, approximately 80% to 85% of individuals with this disorder remain undiagnosed.^{7,9,10} It is estimated that 84% of these individuals are not receiving any lipid-lowering therapy. Without aggressive lipid management, people with FH are at increased risk for cardiovascular disease. Often, individuals are not screened or diagnosed until after they experience a premature cardiovascular event.^{6,7,10,11}

KEY POINTS

Familial hypercholesterolemia is the most common monogenetic disorder in Europe and the United States. The incidence of heterozygous familial hypercholesterolemia is 1:500 in the general population. For individuals with the disorder who are left untreated, the risk of premature cardiovascular disease is increased by 100-fold. Without treatment, approximately 50% will survive to age 60 years.

All family members of patients with familial hypercholesterolemia should be screened. Children of patients with familial hypercholesterolemia should be screened with fasting lipid profile or nonfasting non-high-density lipoprotein cholesterol beginning at age 2 or 3 years. Universal screening of all children is recommended at age 9 to 11 years, regardless of family history.

Statins are considered first-line therapy for patients with familial hypercholesterolemia. Additional lipid-lowering medications can be used in combination with statins to achieve therapeutic goals. Low-density lipoprotein apheresis is a treatment option for patients who do not respond to or are intolerant of maximal drug therapy.

Although statins are typically effective in the prevention of cardiovascular events in individuals with FH, some patients do not respond to or are intolerant of statins. For these individuals, LDL apheresis is now available as an alternative to pharmacotherapy.

The purpose of the present review is to update physicians on the current guidelines for the screening, diagnosis, and management of FH.

Pathophysiologic Processes, Genetics, and Prevalence

In individuals with normal lipid metabolism, the LDL receptor binds to apolipoprotein B on the LDL particle and removes LDL cholesterol from the peripheral circulation.¹² In individuals with FH, however, the function of

the LDL receptor is often absent or impaired. Individuals with FH have elevated total and LDL cholesterol levels from birth. The LDL particles remain in the plasma longer and are more readily oxidized. These modified LDL particles are taken up peripherally by macrophages and form foam cells. Cholesterol deposits eventually develop on the eyelids (xanthelasma), in the extensor tendons (xanthoma), in the peripheral margins of the cornea (corneal arcus), and in the arteries.¹²

The gene encoding the LDL receptor is located on chromosome 19p13. To date, more than 1000 mutations have been identified.¹³ Inheritance of FH is usually autosomal dominant, which means that 50% of first-degree relatives of people with FH are at risk of having the disorder. Individuals with heterozygous FH inherit 1 normal and 1 abnormal gene. The cholesterol-level elevation in heterozygous FH, therefore, is not as severe as that in individuals with homozygous FH who have inherited 2 abnormal genes. Less often, abnormal apolipoprotein B 100 and mutations in the genes for autosomal recessive hypercholesterolemia and proprotein convertase subtilisin/kexin type 9, or PCSK9, cause phenotypes clinically indistinguishable from classic monogenetic FH caused by LDL receptor gene mutations.¹¹

Individuals with severe FH often experience premature cardiovascular events, including myocardial infarction, aortic sclerosis, peripheral vascular disease, and sudden death. Some individuals experience their initial, sometimes fatal, cardiovascular events as early as their 20s. If FH is left untreated, the risk of cardiovascular disease in young adults aged 20 to 39 years is increased by 100-fold.¹⁴ In those individuals with heterozygous FH who are not treated, approximately 50% of men and 30% of women experience cardiovascular events by age 60.¹⁵ Without treatment, an estimated 50% of individuals with FH will survive to age 60 years and 20% will survive to age 70 years.¹⁶

There is a misconception that FH is rare.¹⁷ Rather, FH is the most common monogenetic disorder in Europe and the United States.⁹ Although homozygous FH is indeed

rare, occurring in approximately 1 in 1 million individuals, heterozygous FH is much more common, occurring in approximately 1 in 500 individuals.^{7,9-11} Heterozygous FH is more common than other disorders that clinicians are more familiar with including cystic fibrosis,¹⁸ polycystic kidney disease,¹⁹ and Down syndrome.²⁰ In children and adolescents, the prevalence of heterozygous FH is similar to, if not slightly greater than, type 1 diabetes mellitus.^{8,21} It is estimated that about 1 in 8 patients who present with cardiovascular disease before age 65 years have FH.¹⁶

Diagnosis

Patients with FH tend to be young and thin and do not typically have any of the usual other risk factors expected in someone at high risk for cardiovascular disease (eg, cigarette smoking, uncontrolled hypertension, diabetes mellitus). Tendon xanthomas are a classic pathognomonic physical examination finding, detected in approximately 20% to 40% of those with FH (*Figure*).^{22,23} Other physical examination findings such as xanthelasma and premature corneal arcus are common but not specific for FH. The sine qua non of FH is severe elevation of total and LDL cholesterol levels. Adults with heterozygous FH have total cholesterol levels that are approximately twice as high as normal levels, typically ranging from 350 to 550 mg/dL. Adults with homozygous FH may have total cholesterol levels from 650 to more than 1000 mg/dL.^{7,9} Serum triglycerides may be mildly to moderately elevated in some patients. However, triglycerides are usually not markedly elevated unless the patient also has an unrelated lipid disorder.^{7,9} When severe hypertriglyceridemia is present, other lipid disorders, such as familial combined hyperlipidemia or secondary mixed dyslipidemia, must be ruled out.

Three sets of criteria have been devised to diagnose FH. The Simon Broome criteria (*Table 1*) uses family history, clinical findings, and genetic testing.¹⁴ A “definite diagnosis” is made if there are elevated cholesterol levels and tendon xanthoma or mutation identified on

genetic testing, and a “probable diagnosis” is made if there are elevated cholesterol levels and family history of a total cholesterol level of more than 290 mg/dL or premature cardiovascular disease.¹⁴

The Dutch Lipid Clinic Network criteria²⁴ are similar to the Simon Broome criteria. Points are awarded on the basis of family history of hypercholesterolemia, premature cardiovascular disease, clinical findings such as tendon xanthoma and corneal arcus, elevated LDL cholesterol levels, and genetic mutation. The total number of points determines whether the diagnosis is definite, probable, or possible.²⁴

The Make Early Diagnosis to Prevent Early Death (MEDPED) criteria bases diagnosis of FH on age, threshold cholesterol levels, and family history (*Table 2*).²⁵ For example, a child younger than 20 years with an LDL cholesterol level of more than 155 mg/dL and a first-degree relative with FH has a 98% chance of receiving an FH diagnosis.²⁵ Others, however, have determined that levels of LDL cholesterol even lower than the MEDPED criteria threshold levels may predict those who have inherited FH. In the children who have 1 parent with heterozygous FH, an LDL cholesterol level of 135 mg/dL or greater identified 98% of those who had inherited the disorder.²⁶



Figure. Image of tendon xanthoma, a pathognomonic physical examination finding in patients with familial hypercholesterolemia.

Table 1.
Simon Broome Criteria¹⁴ for the Diagnosis of Familial Hypercholesterolemia

	Child ^a	Adult ^b
Criteria		
Definite Familial Hypercholesterolemia Criteria		
Cholesterol, mg/dL		
Total	>260	>290
LDL	>155	>190
Additional Findings	Tendon xanthomas in the patient or in any first- or second-degree relative(s) ^c	DNA evidence of mutation in LDL receptor, familial defective apolipoprotein B-100, or PCSK9
Criteria		
Probable Familial Hypercholesterolemia Criteria		
Cholesterol, mg/dL		
Total	>260	>290
LDL	>155	>190
Additional Findings	Family history of myocardial infarction in relatives <50 y in any second-degree relative ^c or <60 y, in any first-degree relative ^c	Family history of plasma total cholesterol >290 mg/dL in any first- or second-degree relative ^c or >260 mg/dL in child or sibling aged <16 y

^a Age, <16 y.

^b Age, ≥16 y.

^c First-degree relative: parent, offspring, or sibling; second-degree relative: grandparent, grandchild, nephew, niece, or half-sibling.

Abbreviations: DNA, deoxyribonucleic acid; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

Genetic testing is included in the Simon Broome and the Dutch Lipid Clinic Network but not the MEDPED criteria. Deoxyribonucleic acid, or DNA, analysis may detect 90% of currently identified LDL receptor mutations.¹³ Genetic testing can be useful in distinguishing between FH and other types of inherited dyslipidemia, such as familial combined hyperlipidemia.¹³ Genetic testing may also be helpful in family counseling. Although genetic testing can be useful for diagnosing FH and initiating appropriate therapy earlier, it should be noted that not every mutation has been identified and negative genetic testing should therefore

not be used to rule out the diagnosis.⁷

However, because serum lipid testing is readily available, family history is straightforward and easy to obtain, and genetic testing is costly and often not covered by insurers, we favor the use of the MEDPED criteria as the initial tool to diagnose FH in the majority of patients at risk. Genetic testing may then be used to confirm the diagnosis in patients in whom the diagnosis is unclear.

Irrespective of which diagnostic criteria are used, it is advised that children of those with heterozygous FH be screened beginning at age 2 or 3 years.^{7,9,11} In addition, The National Lipid Association recommends universal

screening of all children with fasting lipid profiles or nonfasting non-HDL cholesterol beginning at age 9 to 11 years, regardless of family history.⁷

Treatment

Adults

Early treatment of FH patients can lower cardiovascular event rates to levels similar to that of the general population.^{7,27} Treatment of this patient population can be challenging, however. As previously mentioned, drug therapy—in addition to diet and lifestyle modification—is usually necessary for the management of FH. For FH patients aged 20 years or older, it is advised that drug treatment be initiated to achieve an LDL cholesterol level reduction of 50% or more.⁷ The LDL cholesterol target levels for people with FH should be determined according to each individual’s estimated risk. For example, those individuals with evidence of coronary heart disease or risk equivalents should be treated more aggressively, with a target LDL cholesterol level of 100 mg/dL or less.⁷ Those individuals without risk factors should have therapy intensified if LDL cholesterol levels are 160 mg/dL or more or if the initial 50% reduction in LDL cholesterol level is not achieved.⁷ Most individuals require high-dose combination LDL cholesterol-lowering therapy. Even with intensive pharmacotherapy, some individuals will not achieve recommended target levels for LDL cholesterol. Moreover, others may be unable to tolerate medications because of adverse effects.

Dietary and Lifestyle Modification

Although most patients with FH will need to be treated with medication, dietary and lifestyle modification still plays an essential role. Patients with FH who have additional risk factors such as obesity, tobacco use, uncontrolled diabetes mellitus, or uncontrolled hypertension are at even higher risk for cardiovascular disease than they would be otherwise. These patients should be counselled to avoid tobacco, maintain a healthy body weight,

Table 2. MEDPED Criteria²⁵ for the Diagnosis of Familial Hypercholesterolemia

Age, y	Threshold Levels of LDL Cholesterol, mg/dL			
	First-Degree Relative ^a	Second-Degree Relative ^b	Third-Degree Relative ^c	General Population
<20	155	165	170	200
20-29	170	180	185	220
30-39	190	200	210	240
≥40	205	215	225	260

^a First-degree relative: parent, offspring, or sibling.

^b Second-degree relative: aunt, uncle, grandparent, niece, nephew.

^c Third-degree relative: first cousin or sibling of grandparent.

Abbreviations: LDL, low-density lipoprotein; MEDPED, Make Early Diagnosis to Prevent Early Death.

participate in routine physical activity, and make wise dietary choices. Intake of cholesterol and saturated fat should be minimized. Saturated fat decreases hepatic LDL receptor expression and increases serum cholesterol levels. Replacing saturated fat in the diet with unsaturated fat may lower both total and LDL cholesterol levels.⁹ Patients should be counselled to limit their total fat intake to approximately 25% to 35% of their total energy intake, their saturated fatty acids to 7% or less of their total energy intake, and their dietary cholesterol to less than 200 mg/d.⁶ Patients should also be encouraged to consume soluble fiber (10-20 g/d) and plant stanols and sterol esters (2 g/d).⁷ Regular intake of soluble fiber and plant sterols and stanols may lower cholesterol levels by as much as 10%.⁹

Statins

Statins inhibit HMG-CoA reductase in the liver, an essential enzyme in the metabolic pathway of cholesterol formation. Subsequent compensation for the reduced hepatic cholesterol results in upregulation of the hepatic LDL receptor and lowering of serum LDL cholesterol levels. Those individuals with heterozygous FH have 50% normal LDL receptors.¹² In heterozygous FH,

statins upregulate these normally functioning hepatic LDL receptors, lowering both total and LDL cholesterol levels. Because individuals with homozygous FH do not have functional LDL receptors, they often respond less well to statins and other medications than those with heterozygous FH.²⁸

Statins are considered the first-line agents in managing FH because they have the best data regarding primary and secondary cardiovascular prevention.^{9,11,16} In a study of 3382 patients with heterozygous FH, Neil et al¹⁵ observed a 48% reduction in coronary heart disease mortality in patients without established coronary heart disease who were treated with statins, compared with rates before statins became available. For patients with heterozygous FH who had established coronary heart disease, an approximate 25% reduction in coronary heart disease mortality was observed.¹⁵ There was a greater reduction in coronary heart disease mortality in women than in men.¹⁵

Additional Drug Therapy

Many patients do not achieve recommended LDL cholesterol targets with statin monotherapy alone. In these patients, additional LDL-lowering agents are necessary.^{9,11} Drugs that decrease gastrointestinal absorption of cholesterol, including bile acid sequestrants and ezetimibe, are especially effective when combined with statin therapy. Bile acid sequestrants lower LDL cholesterol levels an additional 10% to 30% beyond statin therapy

Worldwide, an estimated 10 million people have FH, of whom approximately 200,000 die prematurely each year.

alone.⁹ The use of bile acid sequestrants, however, is often limited by gastrointestinal and other side effects. Colesevelam is a newer bile acid sequestrant that may be more effective and better tolerated than traditional bile acid sequestrants.⁹ Bile acid sequestrants can affect absorption of fat soluble vitamins and certain medications as well as potentiate hypertriglyceridemia. Ezetimibe

inhibits intestinal absorption of cholesterol by a mechanism different from that of bile acid sequestrants. Ezetimibe is better tolerated than bile acid sequestrant and has fewer side effects. Ezetimibe may lower LDL cholesterol levels by 18% when used alone.²⁹ However, when ezetimibe is combined with a high-potency statin, LDL cholesterol levels can be lowered by 60% or more.^{9,11}

Other lipid-lowering medications are usually not considered first-line treatment for patients who have primarily elevation of total and LDL cholesterol levels, including most people with FH. Nevertheless, medications such as prescription extended-release niacin and fibrates can be useful for those patients who have not responded to statins and other LDL cholesterol-lowering agents, particularly in those patients with mixed dyslipidemia superimposed on FH.^{9,11} Before statins became available, niacin combined with a bile acid sequestrant was shown to lower LDL cholesterol levels by 45%.³⁰

Children

Children who have FH are at increased lifetime risk for cardiovascular disease. Atherosclerosis in individuals with FH begins in childhood and adolescence. Current guidelines advise dietary and lifestyle modification in children with FH beginning at age 2 years.³¹⁻³³ Like adult patients with FH, however, many children with FH do not reach desired targets with diet and lifestyle modification alone.

The use of pharmacotherapy in children with dyslipidemia who have not responded to dietary and lifestyle modification has until recently been somewhat more controversial.³⁴ The American Heart Association suggests the initiation of pharmacotherapy at age 10 years in boys and after the onset of puberty in girls with high-risk lipid abnormalities.^{31,32} The American Academy of Pediatrics recommends drug therapy in children aged 8 years or older who have not responded to diet and behavioral modification and who have an LDL cholesterol level of 190 mg/dL or higher without risk factors or who have an LDL cholesterol level of 160 mg/dL or higher with a

family history of premature cardiovascular disease or with multiple risk factors.³³ The National Lipid Association recommends initiation of lipid-lowering therapy in pediatric FH patients beginning at age 8 years, with the treatment goal being 50% or greater reduction in LDL cholesterol levels or an LDL cholesterol level of less than 130 mg/dL.⁷ However, more aggressive LDL cholesterol target levels may be appropriate for those with multiple risk factors, a family history of premature cardiovascular disease, or both.^{7,31,32}

Bile acid sequestrants have traditionally been the lipid-lowering agents recommended for the management of pediatric dyslipidemia. As with adult patients, however, the use of bile acid sequestrants in pediatric patients has been limited by gastrointestinal and other side effects. More recently, statins have become accepted for use in children and adolescents.^{7,31-33,35} Although long-term studies regarding cardiovascular outcomes and mortality are still lacking, short-term data have demonstrated statins to be effective in lowering LDL cholesterol levels and improving markers of cardiovascular risk, as well as tolerable and safe.³⁶⁻³⁸ According to Zapalla and Gidding,³² no study has shown negative effects on growth, hormones, or sexual development. There are now more data for the use of statins in children than for bile acid sequestrants.^{31-33,35} Other agents such as ezetimibe, extended-release niacin, and fibrates have not been as well studied in children as statins and bile acid sequestrants.

Pharmacotherapy is not generally recommended for children younger than 8 years unless severe hypercholesterolemia is present (LDL cholesterol >500 mg/dL).³³ In those rare children who have homozygous FH, initial cardiovascular events can occur when they are in their 20s or earlier. These children need to be treated more aggressively and at earlier ages than children with heterozygous FH or secondary dyslipidemia.⁷ Children with FH, as well as adults who do not respond to or who are intolerant of medications, may benefit from referral to a specialty center with experts in the management of severe lipid disorders.^{7,10,11}

Alternatives to Pharmacotherapy

Because FH is usually caused by defective LDL receptors, therapeutic options that lower LDL cholesterol levels through upregulation of the hepatic LDL receptor (ie, statins and bile acid sequestrants) are often less than fully effective. Several nonpharmacologic therapies for

An estimated 1 in 8 patients who present with cardiovascular disease before age 65 years have FH.

patients with FH have been investigated.^{28,39} Most of these, including partial ileal bypass and portacaval shunt procedures, were poorly tolerated, with serious adverse effects.²⁸ Liver transplantation provides an individual with new functional hepatic LDL receptors. However, because of limitations in finding a donor, risks associated with chronic immunosuppression, and possible rejection, liver transplantation is reserved for the most severe cases of homozygous FH.⁷ Other procedures such as plasmapheresis are nonselective and remove not only LDL cholesterol but also coagulation factors, immunoglobulins, and HDL cholesterol.³⁹⁻⁴¹ Gene therapy holds promise for potential future cure, but it is not yet available.

More recently, LDL apheresis has become available for the management of severe elevation of LDL cholesterol levels in patients who fail to respond, or who are intolerant of, maximal lipid-lowering therapy.^{39,40} Previously available in Europe and Japan for decades, LDL apheresis was approved by the US Food and Drug Administration (FDA) for the management of severe refractory FH in 1996.^{39,40} In patients for whom it is indicated, LDL apheresis is covered by Medicare and most private insurers.⁴² During LDL apheresis, plasma is separated from whole blood and the LDL is removed by means of dextran sulfate adsorption (LIPO-SORBER) or heparin-mediated extracorporeal precipitation (H.E.L.P.), both of which are currently approved for use in the United States.^{39-41,43}

Peripheral intravenous access for LDL apheresis is usually obtained through the antecubital veins. Some patients, however, may require access through an arteriovenous fistula or a synthetic graft. An LDL apheresis procedure is usually performed in the outpatient clinic setting. Most patients undergo 2- to 3-hour treatment sessions every 2 weeks. In patients with severe or homozygous FH, treatments may be increased to occur every week if less frequent treatments do not lower LDL cholesterol levels to the treatment goal.⁴⁰

Early treatment can lower cardiovascular event rates in FH patients to levels similar to those of the general population.

Low-density lipoprotein apheresis acutely lowers LDL cholesterol levels by 60% to 83%.^{40,41} Because apheresis is a treatment and not a cure, levels of LDL cholesterol slowly return to baseline and the procedure must be repeated. This treatment not only lowers levels of LDL cholesterol, lipoprotein (a), and very-LDL cholesterol, but it also reduces symptoms of angina, delays onset of electrocardiographic ST segment depression during exercise, improves blood viscosity, increases myocardial blood flow, and reduces inflammatory markers.^{39,41,43-46} Combined with drug therapy, LDL apheresis has been shown to reduce progression of atherosclerosis and regress plaque.^{39,40,45-47} An observational study of 130 patients with heterozygous FH and angiography-confirmed coronary artery disease revealed that those treated with long-term LDL apheresis had a 72% lower rate of cardiovascular events than those treated with medications alone (10% vs 36%, $P=.0088$).⁴⁸ Long-term survival has been reported in patients with severe FH who have been treated with LDL apheresis.⁴⁹

In most patients, LDL apheresis is well tolerated, without adverse effects. Hypotension and vasovagal reaction have been reported in up to 3% of patients who receive this treatment.^{39,41} These symptoms are transient

and self-limited. Serious events such as allergic reaction or shock are extremely rare and have been reported in less than 0.3% of treatments.⁴¹

Limitations of LDL apheresis include expense, lack of availability in many communities, and the requirement of repeated treatments indefinitely. Because of these limitations, pharmacotherapy combined with dietary and lifestyle modification is the initial treatment of choice. Low-density lipoprotein apheresis is reserved for those who do not respond to or who do not tolerate standard therapy.^{39,40} New lipid-lowering agents including PCSK9 inhibitors are currently under investigation. In the future, additional treatment options may become available.

Comment

There is a great need for the education of physicians as well as patients and their families about FH. In our experience, patients with FH often believe that they have no choice but to inevitably have recurrent cardiovascular events, receive repeat interventions, and die prematurely as so many of their family members have. Many people with FH do not know anyone outside of their immediate families with the diagnosis. In spring 2011, the Foundation of the National Lipid Association initiated an awareness campaign aimed at educating the public about FH.⁵⁰

Conclusion

Physicians are strongly encouraged to be diligent in screening and taking thorough family histories for those patients who may be at risk for FH. By diagnosing FH early and managing this disorder aggressively, physicians can prevent cardiovascular events and save lives.

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