

The Agenda for Familial Hypercholesterolemia A Scientific Statement From the American Heart Association

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Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health

Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disease present in all racial and ethnic groups and has long been recognized as a cause of premature atherosclerotic coronary heart disease.¹⁻³ Heterozygous FH has the highest prevalence of genetic defects that cause significant premature mortality (\approx 1:200 to 1:500 or higher in founder populations). The genetic basis of the disorder, impaired functioning of the low-density lipoprotein (LDL) receptor, was first recognized by Goldstein and Brown⁴ in their Nobel Prize-winning work. Studies of LDL receptor function have identified additional mechanisms for the pathogenesis of FH (defects in apolipoprotein [apo] B impairing binding with the LDL receptor and gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 [PCSK9] that enhance LDL receptor degradation). FH leads to elevated LDL concentrations, with levels in heterozygous FH generally in untreated adults >190 mg/dL LDL cholesterol (LDL-C) and in untreated children or adolescents >160 mg/dL LDL-C. Long-term exposure to elevated plasma concentrations of LDL-C begins in utero, leading in heterozygotes to premature ischemic heart disease in mid adulthood and in homozygotes to ischemic heart disease in childhood or early adulthood. In those who meet clinical definitions of FH based on LDL-C levels and family history, genetic testing identifies mutations in most children and a large percentage of adults.^{5,6}

Complementing these cell biology discoveries has been drug discovery that has linked enhancement of LDL receptor function to LDL-C lowering and successful prevention of ischemic heart disease, first with statins and now with newer drugs that affect LDL receptor function in other ways, including those that impair PCSK9 regulation of LDL receptor recycling.⁷ The natural history of FH, the natural history of genetic disorders that lead to lifelong low LDL-C, and the dramatic improvement in life expectancy created by effective cholesterol lowering provide the biological underpinning of the cholesterol hypothesis with regard to atherosclerotic vascular disease.⁸⁻¹¹

Despite these scientific advances, FH remains underdiagnosed and undertreated worldwide.¹ Most patients receive treatment in primary care settings without recognition of the genetic implications of the disease. Guidelines and consensus statements have been published to improve FH awareness and care.^{1-3,12,13} Improved identification of heterozygous and homozygous individuals at a young age has emerged as a priority given that lifelong exposure to elevated LDL-C levels is the cause of ischemic heart disease and that effective treatment to lower LDL-C levels and to prevent or delay future ischemic heart disease exists. FH has been recognized as a tier 1 genetic disorder by the Centers for Disease Control Office of Public Health Genomics in the United States, meaning that

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sufficient evidence for health benefit exists to implement case finding via family history–based screening, cascade screening, or other strategies. Importantly, FH advocacy groups, often led by affected individuals with the support of interested scientists and clinicians, have organized to increase FH awareness and to lobby for an improved focus on FH care needs in individual countries.

Nevertheless, significant challenges to optimizing FH care exist. These include controversy over the value of universal or cascade cholesterol screening for identifying those with FH, lack of prevention research specific to FH distinct from lipid research in the larger community, and lack of integrated case management protocols across the continuum of care for the family with multiple affected members. The Familial Hypercholesterolemia Foundation and the National Lipid Association have proposed the creation of specific *International Classification of Diseases, 10th Revision*, codes for heterozygous FH, homozygous FH, and family history of FH. Having specific diagnostic coding will allow FH patients insurance rights similar to those of individuals with other inherited diseases.

The purpose of this scientific statement is to provide an agenda for further progress, building on the platform provided by recent guidelines and reviews of progress with regard to diagnosis and treatment. Patient perspectives are critical to optimizing care because patients have to live with fears concerning premature heart disease, implications of genetic diagnosis, and lifelong pharmacological care for a condition that has no symptoms before a coronary event. Genetic diagnosis and genotype/phenotype correlations have created questions related to diagnosis, particularly with regard to the meaning of heterozygosity and homozygosity, inheritance risk, genetic interactions, and genetic modifiers and defining disease severity.¹⁴ Important aspects of natural history need to be better understood, including rates of disease progression in both heterozygous and homozygous FH, the role of subclinical atherosclerosis screening in clinical decision making, and the role of computed tomographic (CT) coronary imaging for risk stratification in middle age. Identification of all patients with FH is critical, but the optimal screening strategy has not been determined, and the complementary roles of genetic testing, family history, and LDL-C need to be further defined, particularly for children. Strategies for the initiation of treatment and for treatment goals have been developed, but evidence gaps remain. Internationally, different healthcare systems with different resources create a need for local models of care (MoCs) for FH recognition and treatment.

Patient Perspectives

Although FH is a common genetic disorder that substantially shortens life expectancy, public awareness is low, and less is known about patient perceptions compared with other inherited disorders, including conditions such as breast cancer and colon cancer. Each patient confronted with the diagnosis of FH will have a unique perspective on all medical aspects considered in this report, including medical morbidity, diagnostic and genetic testing, and lifetime treatment, informed by his or her personal or family's past experiences. Certain broad themes affect patient engagement, including family stress and emotional vulnerability. Inadequate assessment of family history and experience

may lead to poor communication between providers and families. Consideration should be given to the effects of preventive treatment in the youngest individuals, fear of coronary artery disease (CAD) in older individuals, burden of long-term care, and concerns for the next generation in parents and grandparents. Clear explanations are required of diagnostic tests, including plasma lipids, use of genetic testing, and cascade screening (systematic evaluation of first-degree relatives for FH and further if needed). Although the diagnostic process in FH can create concerns about cost, insurance implications, loss of privacy, and possible discrimination, cascade screening has not led to psychological or social harm to adults or children.^{15–17}

Perception of risk may affect patient behavior. Patients may underestimate their cardiovascular disease risk and inappropriately have little confidence in lifestyle measures. Family history of disease may be more impactful to patients than their genetic mutation status. Risk perception is personal and dynamic and may be changed by a CAD event in the family, a change in or an onset of symptoms, or a major life event such as becoming a parent. Patients feel safer while taking medication and guilty when noncompliant.^{18,19} Parents are critical in promoting treatment adherence, but gaps often exist between children's and parents' perspectives of the disease. These perceptions affect adherence to both lifestyle interventions and medications.^{20,21}

Studies assessing the quality of life (QOL) of treatment modality in FH patients are small with the exception of 1 Dutch study. All studies were conducted outside the United States and used different methods to assess QOL.^{22–27} In general, pediatric and adult FH patients receiving dietary and pharmacotherapy have a QOL comparable to that of healthy reference populations.^{22,24} Patients appeared to feel safer when taking their medications, but women appear to be more worried about the effects that the medications may have on their or their children's bodies.^{22–24} In general, ≈80% of patients self-report that medication and dietary adherence and clinical benefits outweigh other concerns. Nonetheless, slightly <10% would rather not comply with treatment recommendations; the remainder are intermittently compliant. Unfortunately, most recent intervention trials do not assess QOL during treatment.

Patients undergoing lipoprotein apheresis (LA) appear to have a lower QOL compared with patients receiving dietary therapy and pharmacotherapy only, but concurrent cardiovascular disease may be contributory to this perception.^{25,26} Relief of angina improves QOL, but frequent testing and other monitoring requirements with apheresis reduce QOL.

Clinicians' provision of longitudinal and patient-specific education about treatments helps ensure that patients understand the benefits and risk, minimize adverse events, reduce anxiety, enhance adherence, maximize benefits, and improve QOL. Clinicians need to recognize variation in risk perception because it can affect the patient's vulnerability, health-seeking behavior, and motivation for medical treatment. Genetic counselors may be extremely helpful in the counseling process. Discussion of side effects should be frank and accurate and include side effects not associated with statins. Most important, clinicians must recognize differences between their perceptions of risk and their patients' perceptions of risk. Table 1 provides a list of issues to address in counseling, and Table 2 provides a list of international resources for FH education.

Table 1. Issues to Address With Families Affected by FH

Individual and family experiences, including CVD events, response to treatment
Genetics and implications of genetic diagnosis
Risk perception, including fear of future events
Medication side effects, including short-term, midterm, and lifetime treatment needs
Medication adherence
Assessment and treatment of other cardiovascular risk factors
Pregnancy
Costs and insurance
Lifestyle behaviors, self-efficacy around lifestyle change

CVD indicates cardiovascular disease; and FH, familial hypercholesterolemia.

Pathogenesis and Genetics

FH was described for the first time >125 years ago. Initially, it was classified as a dermatological disorder given its visual characteristics such as xanthomas and xanthelasmas.²⁸ Later, FH was linked to a high incidence of premature atherosclerosis, resulting in coronary, cerebral, or peripheral arterial disease.²⁹ Family studies by Wilkinson et al³⁰ laid the hereditary basis for FH, after which Khachadurian³¹ demonstrated the autosomal-dominant mode of inheritance. Increased LDL-C was recognized as the hallmark of the disease.^{32,33} This observation led to the discovery of a receptor for LDL particles.³⁴ It was later proven that the underlying molecular cause of FH consisted of mutations in the gene that coded for the LDL receptor protein. Mutations in this gene result in failure to produce LDL receptor protein or in a reduction in LDL receptor activity, with increased levels of LDL-C in plasma as a consequence.³⁵

Table 2. Resources for FH Education for Patients and Families

Global genes (globalgenes.org)
International FH Foundation (www.fh-foundation.org)
Australia
Australian Heart Foundation (www.heartfoundation.org.au)
FH Australasian Network (www.athero.org.au)
Brazil
Hipercol Brasil (www.hipercolesterolemia.com.br)
Spain
Fundación Hipercolesterolemia Familiar (www.cholesterolfamiliar.org)
United Kingdom
Heart UK—The Cholesterol Charity (www.heartuk.org.uk)
British Heart Foundation (www.bhf.org.uk)
United States
The FH Foundation (www.thefhfoundation.org)
The Foundation of the National Lipid Association (www.learnyourlipids.com)
National Human Genome Research Institute, National Institutes of Health (www.genome.gov/25520184)
National Institutes of Health, clinical trials (clinicalstudies.info.nih.gov)
National Organization for Rare Disorders (www.rarediseases.org)
Preventive Cardiovascular Nurses Association (www.pcvna.net/patients/familial-hypercholesterolemia)

FH indicates familial hypercholesterolemia.

LDL accounts for 75% of the cholesterol transport in the body, and the majority of LDL, ≈70%, is cleared from the plasma by LDL receptors located on the cellular membranes of liver cells. The LDL receptor is responsible for the binding and subsequent cellular uptake of apolipoprotein B (apoB)- and apoE-containing lipoproteins. The LDL receptor locus is located on chromosome 19p13.1-13.3 and comprises 18 coding regions (exons) and 17 intervening noncoding regions (introns; Figure 1).³⁶ The LDL receptor gene is a housekeeping gene that is translated into LDL receptors in most tissues. The transcription is regulated by a negative feedback mechanism controlled by the cellular content of cholesterol that involves steroid regulatory element-binding protein. Prevention of LDL receptor recycling to the cell surface and subsequent degradation are regulated by PCSK9, a peptide that directs the receptor to lysosomal degradation within the hepatocyte.

The naturally occurring mutations of the LDL receptor can be divided into 6 classes affecting different aspects of LDL receptor function^{37–39} (Table 3 and Figure 2), and to date, >1200 different mutations of all type have been described.^{40–42} The functional defects in the LDL receptor are complex, and a mutation can belong to >1 class.³⁷ In practice, it is simpler to classify mutations into 2 groups: LDL receptor-deficient mutations (ie, null alleles that do not produce LDL receptor protein) and LDL receptor-defective mutations (ie, gene variants that affect function such as the interaction with the ligand-binding domain of LDL).

Mutations in other genes impairing LDL receptor function are also known to cause inherited hypercholesterolemia, with clinical features indistinguishable from FH.^{43,44} Structural rearrangements in the domain of apoB that interacts with the LDL receptor, caused by mutations principally in exons 26 and 29 of the *APOB* gene, interfere with binding of the LDL particle to the LDL receptor and result in elevated LDL-C, although levels may be slightly lower than for LDL receptor defects.^{45,46} This disorder has also been referred to as familial defective apoB.

A specific mutation in the gene coding for PCSK9 was shown to be involved in the pathogenesis of autosomal-dominant hypercholesterolemia.⁴⁷ These gain-of-function mutations enhance the affinity of the PCSK9 protein to bind to the LDL receptor, interfere with the dissociation of the LDL receptor/LDL complex in the endosomes, prevent recycling of the receptor, increase degradation of the LDL receptor, and hence reduce the number of LDL receptors on the surface of the liver cell.⁴⁸ The *APOE* gene may be a fourth locus containing FH-causing mutations.^{49,50} Autosomal-recessive hypercholesterolemia, caused by loss-of-function mutations in LDL receptor adaptor protein 1, located on chromosome 1p36-35, causes a very small percentage of cases. LDL receptor adaptor protein 1 mutations lead to the production of a small, nonfunctional LDL receptor adaptor protein 1 protein or prevent cells from making this protein, thereby preventing LDL receptors from removing LDL from the circulation effectively. Although the receptors can still bind normally to LDL, the lack of LDL receptor adaptor protein 1 prevents the LDL receptor/LDL complex to be transported into the cell.⁵¹ Because the gene is recessive, parents may not have elevated cholesterol. The phenotype is often less severe than homozygous FH caused by LDL receptor defects. A second autosomal-recessive genetic cause, lysosomal acid lipase deficiency, has recently been identified.⁵²

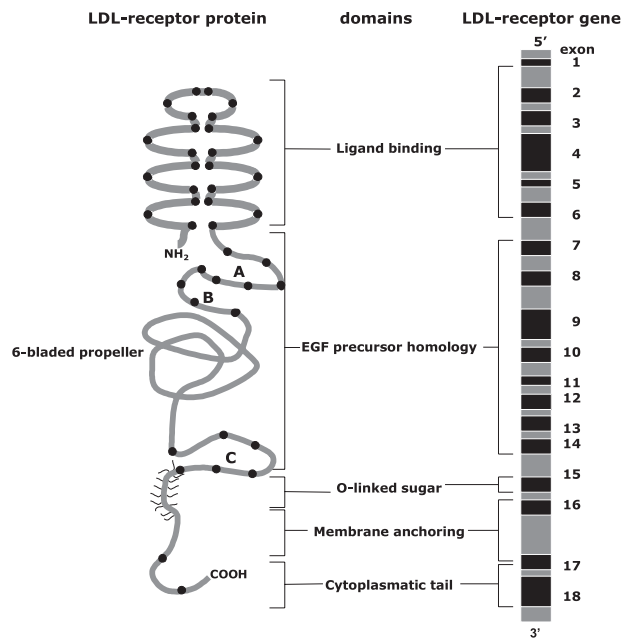


Figure 1. The different domains in the low-density lipoprotein (LDL) receptor protein are encoded by specific regions in the LDL receptor gene. EGF indicates endothelial growth factor.

Numerous studies have investigated the relationship between specific mutations or mutation classes and the clinical expression of the disease.^{40,53–59} The major effect of the

type of LDL receptor mutation relates to the contribution of the defect to the LDL-C level.⁵⁹ Additional genetic variants that affect LDL-C level to a small degree explain variation in LDL-C levels independently of the major FH-causing gene.^{5,44} Gene mutations that cause FH can rarely occur in combination with genes that lower LDL-C in the same individual, causing lower-than-expected LDL-C levels.⁶⁰ Triglyceride and high-density lipoprotein cholesterol levels are usually unaffected by FH-causing gene mutations but may be altered by obesity and insulin resistance.⁶¹

In the future, genetic testing provides the hope for the most accurate diagnostic classification. Although LDL-C levels drive risk, interactions among the many cholesterol-raising and -lowering genes will have implications for the individual and his or her offspring because any given person has only 1 set of these diverse alleles that determine variation in cholesterol for himself or herself and risk of disease transmission to the next generation.

Natural History of Heterozygous FH and the Role of Subclinical Atherosclerosis Imaging

Youth

In childhood and adolescence, the only clinical recognition is provided by the presence of an extremely elevated LDL-C level, often >190 mg/dL. However, LDL-C levels as low as 140 mg/dL have been found in genetically confirmed cases.^{3,13}

Table 3. Classes of LDL Receptor Mutations

Class 1: synthesis of receptor or precursor protein is absent	The so-called null allele is a prevalent class of mutations and is generally associated with very high LDL-C levels. The molecular basis of this type of mutation shows a wide variety: point mutations introducing a stop codon, mutations in the promoter region completely blocking transcription, mutations giving rise to incorrect excision of mRNA, and finally, large deletions preventing the assembly of a normal receptor.
Class 2: absent or impaired formation of receptor protein	This class comprises mutations in which the normal routing through the cell is not complete or is only very slowly completed. Usually, there is a complete blockade of transport, and LDL receptors are unable to leave the ER. The Golgi apparatus is not reached, and the increase of 40 000 Da in molecular weight does not take place. Truncated proteins, as a result of a premature stop codon, and misfolded proteins, as a result of mutations in cysteine-rich regions leading to free or unpaired cysteine residues, are retained in the ER. However, quality control by the ER is not perfect, given the observation that sometimes misfolded proteins leave the ER but are processed more slowly. Such mutations give rise to class 2B mutations, in contrast to class 2A mutations that cause complete retaining in the ER.
Class 3: normal synthesis of receptor protein, abnormal LDL binding	Receptors characterized by this class of alleles show the normal rate of synthesis, exhibit normal conversion into receptor protein, and are transported to the cell surface, but binding to LDL is impaired. It is obvious that mutations in the binding domain underlie this class of receptors.
Class 4: clustering in coated pits, internalization of the receptor complex does not take place	The receptors in this class lack the property to cluster in coated pits (class 4A). This phenomenon, which makes interaction of receptors with the fuzzy coat impossible, is caused by mutations in the carboxyterminal part of the receptor protein. These mutated receptors are synthesized normally, folding and transport are normal, but clustering in coated pits is impossible, and sometimes the receptors are secreted even after they have reached the cell surface (class 4B).
Class 5: receptors are not recycled and are rapidly degraded	All mutations in this class are localized in the EGF-precursor homologous domain of the LDL receptor protein. This domain seems to be involved in the acid-dependent dissociation of the receptor-ligand complex in endosomes, after which the receptor can be recycled. When the entire EGF-precursor homologous domain is deleted by site-directed mutagenesis or when such a deletion occurs naturally in a homozygous FH patient, the receptor is trapped in the endosomes, and rapid degradation subsequently is observed.
Class 6: receptors fail to be targeted to the basolateral membrane	The class of mutations was recently discovered and is caused by alterations in the cytoplasmic tail of the protein. Such receptors do not reach the liver cell membrane and are probably rapidly degraded. ³⁸

EGF indicates endothelial growth factor; ER, endoplasmic reticulum; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; and LDL-C, low-density lipoprotein cholesterol.

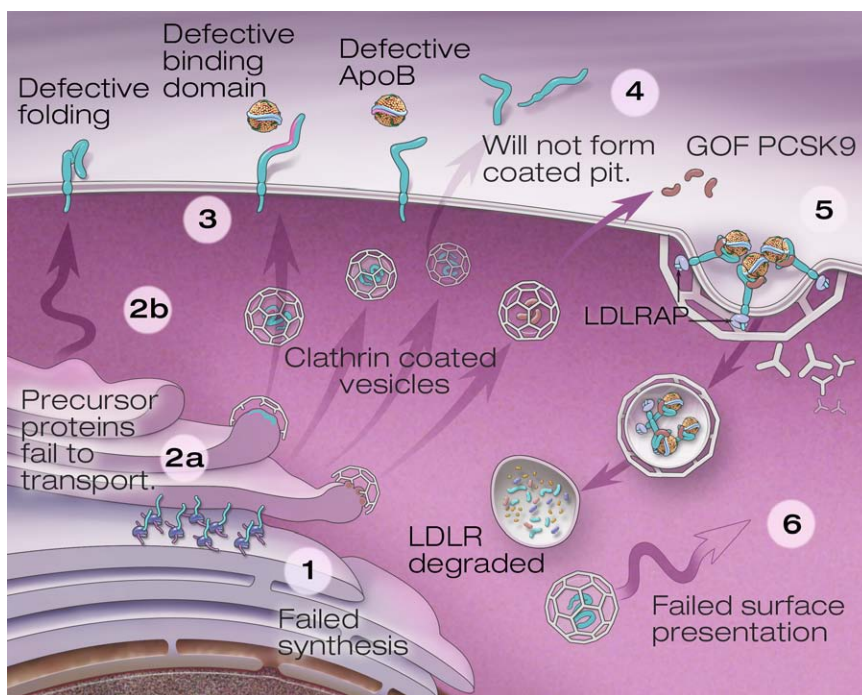


Figure 2. The known mechanisms causing familial hypercholesterolemia linked to low-density lipoprotein (LDL) receptor (LDLR) function. Numbers 1 through 6 correspond to the mechanisms of LDLR dysfunction discussed in the text and Table 3. Familial defective apolipoprotein B (apoB) impairs the ability of the apoB to bind with the LDLR. LDLR adaptor protein (LDLRAP) impairs the ability of the LDLR to interact with LDL particles to extract cholesterol. Proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function (GOF) mutations inhibit LDLR function and increase the degradation of LDLRs.

Autopsy studies suggest that the elevation of LDL-C associated with FH would confer a dramatic increase in atherosclerosis compared with normal LDL-C levels.^{62,63} Vascular imaging studies confirm the presence of subclinical atherosclerosis in affected individuals. By ≈ 8 to 10 years of age, the carotid intima-media thickness of affected siblings is greater than that of unaffected siblings, and aortic lesions can be seen by magnetic resonance imaging.^{64,65} About 25% of adolescents have detectable coronary artery calcium (CAC).⁶⁶

Adulthood

With aging, physical manifestations of sustained elevations of LDL-C may become apparent, including tendon xanthomas and corneal arcus. However, the primary cardiovascular manifestation of FH in adulthood is angina or premature myocardial infarction, which can occur as early as the third decade of life. In the prestatin era, the median age of onset for the first myocardial infarction was ≈ 50 years in men and 60 years in women.^{1,67}

Despite this high risk compared with unaffected individuals, the clinical course of atherosclerotic cardiovascular disease in FH subjects is variable, with the presence of higher LDL-C levels and additional risk factors increasing risk.^{2,7} The relative risk of mortality in FH compared with normolipidemic counterparts is much greater at younger ages than at older ages. Data from the Simon Broome registry in the prestatin era showed a standardized relative mortality rate of 125 (95% confidence interval, 15–451) and 48 (95% confidence interval, 18–105) for women and men, respectively, in the 20- to 29-year-old age group compared with paired normolipidemic subjects.⁶⁸ In contrast, the relative risk in the same time period for people 60 to 75 years of age was only 2.6 (95%

confidence interval, 1.3–4.5) for women and 1.1 (95% confidence interval, 0.5–2.3) for men. Similar results have been found in Dutch cohorts followed up longitudinally.^{11,69}

Traditional cardiovascular risk factors and lipoprotein(a) levels adversely affect the natural history of FH and CAD rates.^{61,70–74} Levels of lipoprotein(a) are inherited as a codominant trait. Lipoprotein(a) is established as a cardiovascular risk factor in the FH and non-FH population when levels exceed 50 mg/dL (75 nmol/L) with isoform-independent assays.^{74,75} Although most FH subjects will develop coronary events and early death, some will develop coronary events very late or will not develop heart disease. Protective genetic factors against CAD are incompletely understood. However, it is clear that patients without coexistent, noncholesterol risk factors who follow a healthy lifestyle bear a lower risk of CAD.^{60,61,71}

Subclinical Atherosclerosis and Detection of Myocardial Ischemia

Identification of silent myocardial ischemia indicates an elevated risk for the occurrence of CAD events. At present, there is no consensus on whether asymptomatic adult heterozygous FH subjects should be submitted systematically to myocardial stress evaluation to detect silent ischemia. Studies that include a small number of subjects performed in the prestatin era using either cardiac scintigraphy or exercise stress test showed the presence of silent ischemia in $\approx 20\%$ of asymptomatic heterozygous FH men and male teenagers (mean age, 16 years).^{76,77} In these studies, the presence of ischemia was not associated with LDL-C levels, smoking, or age. A positive exercise stress test was also found in 20% of 194 heterozygous FH men and women without previous manifestation of cardiovascular

disease.⁷⁸ However, in a larger group of 653 asymptomatic heterozygous FH patients (42% male subjects with an average age of 42 years, 70% using lipid-lowering therapy), a positive stress test was found in 9% of the subjects.⁷⁹ Exercise stress tests could also provide prognostic information in asymptomatic heterozygous FH patients. After a 6-year follow-up, when subjects with silent ischemia were excluded, lower exercise capacity, heart rate recovery at 1 minute, and peak pulse pressure were independently associated with the onset of CAD.⁷⁹ Considering the accelerated development of CAD in those with heterozygous FH, it seems reasonable to perform stress testing and to evaluate exercise capacity periodically in asymptomatic heterozygous FH patients, particularly those with late diagnosis, with lipid-lowering treatment started in adulthood, with a family history of early cardiac events, and with an interest in competitive sports.

Subclinical Atherosclerosis Imaging

Subclinical atherosclerosis imaging has demonstrated an asymptomatic atherosclerosis burden in FH populations. Cross-sectional case-control studies have found an increased prevalence and greater severity of subclinical coronary and carotid atherosclerosis in heterozygous FH compared with normolipidemic individuals.^{66,80–84} Differences can be identified beginning at 8 years of age.^{65,66,79,82} Cross-sectional studies have found not only higher CAC scores but also a greater prevalence of noncalcified and obstructive plaques with the use of cardiac CT angiography (CTA).^{80,84} Cardiac CTA allows the detection not only of calcified but also of noncalcified and mixed plaques if they are of sufficient size. CTA can also quantify vessel lumen disease. The presence of plaques on CTA was associated with older age, male sex, and higher cholesterol levels. In 1 study, the presence of coronary lumen obstruction was highly associated with higher CAC scores, and a CAC score of 0 Agatston units excluded obstructive CAD; conversely, 69% of patients with a CAC score >400 Agatston units exhibited obstructive CAD.^{80,84} Positron emission tomography has documented the presence of arterial wall inflammation in patients with severe FH requiring LA. This inflammation is relieved by the apheresis treatment.⁸⁵

A significant limitation of currently validated clinical algorithms for cardiovascular risk stratification, including the Framingham risk score, is that they underestimate risk related to lifelong exposure to elevated LDL-C levels.⁸⁶ Patients with FH should be considered high risk; additional risk factors will contribute to further reduced life expectancy. CAC score has been shown to reclassify the risk of cardiovascular disease in intermediate-risk non-FH patients⁸⁷ and in patients with type 2 diabetes mellitus.⁸⁸ An observational study suggests that imaging may improve clinical differentiation between patients with heterozygous FH and those with polygenic or secondary hypercholesterolemia.⁸⁹ Despite the evidence that subclinical atherosclerosis is more frequent and more intense in individuals with heterozygous FH than in matched normolipidemic subjects, there is to date no FH-specific evidence that the detection of advanced subclinical disease will improve reclassification of cardiovascular risk.^{80–83} Childhood may be particularly important because risk may be underestimated in this age group. In asymptomatic non-FH subjects, CTA helps in

identifying subjects at a higher risk for cardiovascular disease events when significant atherosclerosis may be present despite optimal treatment.⁹⁰ However, it does not add reclassification power over clinical evaluation and CAC quantification.

Population-based research on subclinical atherosclerosis imaging and testing for silent myocardial ischemia may not be generalizable to the FH population. Patients with FH are exposed to elevated LDL-C levels from birth, accelerating the development of atherosclerosis.

In FH, the expression of ischemic heart disease remains variable, ranging from severe premature disease in up to 10% of affected individuals by 40 years of age but absence of cardiovascular disease until late in life in a similar small percentage. Thus, there is a need for studies of risk stratification specific to heterozygous FH that include atherosclerosis imaging and stress evaluation. Current clinical studies are effective in documenting the extent of atherosclerosis in FH patients and in clinical practice. The identification of an FH patient with more advanced disease than expected may lead to lifesaving therapy. However, current research does not answer the question of how to successfully incorporate subclinical atherosclerosis imaging into regular clinical care. Imaging techniques such as CT for CAC quantification, CTA, and carotid intima-media thickness could be studied with regard to early atherosclerotic disease recognition, risk stratification for intensity of intervention, and tracking of the effects of treatment on disease. Moreover, it is necessary to determine whether imaging or stress testing incorporated into treatment algorithms improves outcomes. Both clinical trials and multicenter registries could be used for this purpose.^{80,84,91}

Natural History of Homozygous FH and Subclinical Atherosclerosis Imaging

Homozygous FH is characterized by a ≥ 4 -fold increase in plasma LDL-C concentrations detectable at birth.^{92–94} These high plasma LDL-C levels lead to deposits of cholesterol in tendons, cutaneous tissues, and vasculature, including the coronary arteries, aortic root and valve, carotid arteries, and renal arteries.⁹⁵ Severe and widespread atherosclerosis occurs in all major arterial beds from a young age.^{92,94} Untreated patients with homozygous FH who are LDL receptor negative (<2% residual of normal LDL receptor activity) rarely survive beyond the second decade. LDL receptor-defective patients (2%–25% residual activity) have a slightly better prognosis but, with few exceptions, develop clinically significant coronary and aortic valve disease by 30 years of age.⁹⁶

Most clinical features in homozygous FH appear in the first to second decade of life.⁹⁷ The clinical diagnosis of homozygous FH is typically based on the presence of cutaneous xanthomas (Figure 3) before 10 years of age and an untreated LDL-C >500 mg/dL (13 mmol/L).⁹⁴ Interdigital xanthomas, particularly between the thumb and index finger, are pathognomonic (Figure 4). The severity of atherosclerosis tends to be proportional to the extent and duration of elevated LDL-C.⁹⁸ In homozygous FH, children as young as 4 years of age have suffered sudden death resulting from acute myocardial infarction.^{99,100} Although severe coronary atherosclerosis is the major cause of death, supravalvular and aortic valve stenosis is also life-threatening; young adults with homozygous FH with often require



Figure 3. The clinical diagnosis of homozygous familial hypercholesterolemia is typically based on the presence of cutaneous xanthomas before 10 years of age and an untreated low-density lipoprotein cholesterol >500 mg/dL (13 mmol/L).

aortic valve replacement.^{101,102} Cholesterol-lowering treatment has been associated with improved outcomes (Figure 5).⁹

CTA detects the presence of CAD in both asymptomatic and symptomatic homozygous FH.^{103,104} CTA can be used to detect aortic plaques affecting the coronary ostia and the coronary tree. Because extensive CAC may not be present in plaques in young subjects, CTA is preferable to simple non-contrast CT to detect CAC.¹⁰⁴ CTA can exclude the presence of severe coronary luminal obstructions.¹⁰⁵ Finally, CTA can be used to evaluate the supra-aortic valve region that is usually compromised in homozygous FH.

As a result of hemodynamic stress over damaged valvular and supra-valvular regions, aortic disease may progress even when LDL-C levels have been reduced.¹⁰⁶ Transthoracic and transesophageal echocardiography can be used to quantify the severity of aortic valve and supra-aortic disease.¹⁰⁷ Magnetic resonance imaging can also be used as an alternative to CTA to study the aorta and to plan possible surgical interventions.¹⁰⁸ Finally, B-mode ultrasound can be used to detect carotid plaques and stenosis.¹⁰⁹



Figure 4. Interdigital xanthomas, particularly between the thumb and index finger, are pathognomonic for homozygous familial hypercholesterolemia.

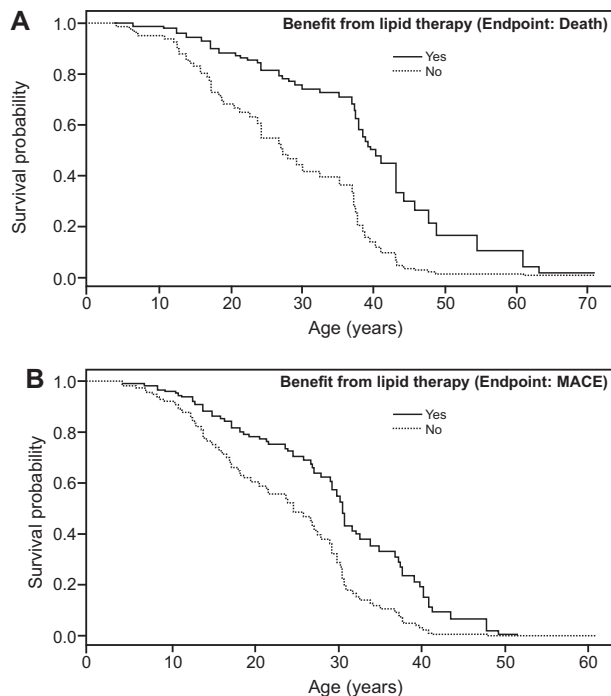


Figure 5. Cholesterol-lowering treatment has been associated with improved outcomes. Cox proportional hazards model with time-varying benefit from statin therapy comparing treated and untreated person-years for (A) survival and (B) first major adverse cardiovascular event (MACE) in patients with homozygous familial hypercholesterolemia, with year of birth fixed as mean year of birth. Reproduced from Raal et al.⁹ Copyright © 2011, American Heart Association, Inc.

In homozygous FH, the risk for CAD is high, and disease progression is rapid. Clinicians should assume that atherosclerosis is present at the time of diagnosis, and a baseline assessment of coronary atherosclerosis should be obtained. Noninvasive imaging should be used to monitor for both atherosclerotic (CTA, carotid intima-media thickness assessment, exercise stress testing) and aortic valve disease (echocardiography) progression and to guide intensification of therapy.

Diagnosis

Progress in FH has been hampered by the lack of a specific *International Classification of Diseases* code to flag FH patients once they have been identified. Current *International Classification of Diseases, Ninth Revision*, codes for pure hypercholesterolemia are widely applied to non-FH patients, leading to misclassification. This hampers the ability to identify and track FH patients, as well as the delivery of specific therapeutic recommendations, including the initiation of high-dose statin and triggering family-based cascade screening. A proposal to create formal diagnosis codes for FH is currently pending approval. This would create formal diagnoses for heterozygous FH, homozygous FH, and family history of FH. The existence of these codes would improve clinical recognition of FH, allow the use of electronic medical record and other database surveillance for FH outcomes, and improve access to care and resources for those diagnosed.

Historically, a number of established clinical criteria for diagnosing FH index cases by phenotype in adults have been

developed. They are driven by the goal of defining those with severe monogenic inherited hypercholesterolemia as having FH and have been updated to integrate genetic testing into algorithms. No international consensus exists on which set of criteria is superior. The Dutch Lipid Clinic Network Criteria use a scoring system combining plasma level of LDL-C, clinical signs, family history of CAD, and DNA markers, with a score >5 making the diagnosis highly probable.¹¹⁰ The Simon Broome system is comparable to the Dutch Lipid Clinic Network Criteria in predicting potential FH mutations but has simpler clinical and LDL-C criteria based on UK population cutoffs for index cases, which may not be appropriate elsewhere in the world.^{68,111} The Make Early Diagnosis to Prevent Early Deaths System relies on centiles of plasma total cholesterol and LDL-C. Ideally, these cholesterol measurements are known in other family members.¹¹² The Japanese criteria, which are comparable to the Simon Broome system, allow radiographic/ultrasonographic diagnosis of Achilles (calcaneal) tendon lipid accumulation xanthomata to aid in the diagnosis of index cases.¹² The plasma LDL-C levels to diagnose FH are lower in Asian countries than in the West.^{12,113} The use of diagnostic tools that rely on the presence of physical signs of FH limits the efficacy of these algorithms because they are more specific than sensitive; that is, they have a low false-positive but a high false-negative rate and hence are better at confirming FH than identifying those who might be screened to maximize identification. The Simon Broome criteria and Dutch Lipid Clinic Network Criteria are for diagnosing FH index cases and, because of ascertainment bias, should not be used strictly to detect new cases of FH during cascade or family screening. Plasma LDL-C thresholds, validated against FH-causing mutations, have been reported for this purpose.¹¹¹

Genetic strategies for diagnosis of FH are more cost-effective than LDL-C–based screening in countries where healthcare systems are more centrally organized.^{114,115} Yields from genetic testing of 70% to 80% are achievable only in adult patients with tendon xanthomata and are lower in adult patients without these clinical signs.⁶ Methods of increasing the yield in patients without tendon xanthomata include the use of imaging to identify patients with lifelong consequences of increased cholesterol burden, for example, increased carotid intima-media thickness or the presence of CAC at young ages.^{80,84,89} These can raise yields of genetic testing to 50% to 60%, but these strategies have not been systematically assessed in large population studies. In healthcare systems that are less cohesive such as the US system, genetic testing is controversial for individuals in confirming diagnosis, and implementing cascade screening will be more difficult.¹¹⁶ In most countries, genetic testing remains relatively expensive and has limited availability. A reduction in costs and improved efficiency of genetic testing is likely to increase its broader application in screening families for FH.¹¹⁷

In children, clinical diagnosis in the absence of genetic testing has generally relied on the presence of a positive family history of elevated LDL-C (or premature CAD if lipid levels were not known) and LDL-C levels >4 mmol/L. In childhood, LDL-C levels alone provide better discrimination than in adulthood.¹¹⁷ Age- and sex-adjusted and country-specific plasma levels of LDL-C should be used to test children for FH.^{3,111,118}

Before the diagnosis of FH is confirmed, secondary causes of severe hypercholesterolemia should be excluded. These

include hypothyroidism, nephrotic syndrome, obstructive liver disease, and diets with extremely elevated saturated fat/cholesterol content.

Limitations of Current Diagnostic Schema

In the FH diagnostic algorithms described above, FH, recognized as an autosomal-dominant trait, was classified according to mendelian terminology. Levels of LDL-C thought to reflect heterozygosity and homozygosity are used for discrimination purposes. Clinical use of genetic diagnosis, subsequent cascade screening, the recognition of a wider range of genetic variants affecting LDL-C levels (both higher and lower), and the recognition of overlap in LDL-C levels in documented heterozygotes and those with >1 abnormal gene (homozygous or compound heterozygous FH) have suggested that the mendelian classification system is overly simplistic.^{14,92,119} Further limitations in this classification scheme exist. Natural history is driven more by LDL-C level and long-term exposure than by a specific gene defect. A significant percentage of individuals who meet a clinical definition of FH will have negative genetic testing or polygenic elevations of LDL-C.^{5,49} Most important, diagnostic classification might have adverse implications for treatment eligibility because some newer drugs have received approval only for homozygous FH, but some heterozygotes may have equally high risk based on LDL-C levels.

For the above reasons, we believe a simpler clinical classification of FH (Table 4) is needed. Although diagnostic precision is an important goal, better recognition and treatment of FH are limited by cumbersome criteria difficult to implement in clinical practice. For simplicity and concordance with proposed *International Classification of Diseases, 10th Revision*, coding, we favor the retention of the terms heterozygous and homozygous FH. After exclusion of secondary causes, a diagnosis of FH can be made in the absence of genetic testing. Heterozygous FH is diagnosed in the presence of a positive family history of elevated cholesterol or premature CAD and LDL-C ≥ 160 mg/dL (4 mmol/L) in a child or ≥ 190 mg/dL (5 mmol/L) in an adult confirmed on 2 occasions. Severity of FH should be based on LDL-C level, with a threshold of >400 mg/dL (10 mmol/L) considered homozygous. Clinical manifestations of rapid disease progression such as xanthomas at a young age or aortic stenosis indicate very severe and particularly aggressive disease. We recommend that individuals classified as homozygous by clinical criteria, regardless of genetic diagnosis, be eligible for the use of LDL-C–lowering agents currently approved for homozygotes only, especially if they do not demonstrate a satisfactory response to multiple conventional therapies or have CAD.^{2,3,114,120–123}

When genetic testing is performed, classification can be revised on the basis of the results. Genetic testing provides more precise diagnostic information and facilitates cascade screening. Disease in an individual can be diagnosed as heterozygous FH with the presence of an FH gene mutation and LDL-C <160 mg/dL (4 mmol/L; usually identified in the setting of cascade screening) or can be as severe as homozygous FH if LDL-C is >400 mg/dL (10 mmol/L), usually in the setting of a receptor-null mutation or a high number of associated genetic risk variants that each raise cholesterol a small amount. Homozygous FH includes true homozygotes with 2 identical LDL-C–raising gene mutations, those with 2 different FH gene mutations, and

Table 4. FH Diagnostic Categories

<i>ICD-10</i> Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C \geq 160 mg/dL (4 mmol/L) for children and \geq 190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C-raising gene defect (LDL receptor, apoB, or PCSK9)	Presence of 1 abnormal LDL-C-raising (LDL receptor, apoB or PCSK9) gene defect Diagnosed as heterozygous FH if LDL-C-raising defect positive and LDL-C <160 mg/dL (4 mmol/L) Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes Presence of both abnormal LDL-C-raising (LDL receptor, apoB or PCSK9) gene defect(s) and LDL-C-lowering gene variant(s) with LDL-C <160 mg/dL (4 mmol/L)
Homozygous FH	LDL-C \geq 400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C-raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 y of age, homozygous FH highly likely	Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C-raising (LDL receptor, apoB or PCSK9) gene defects; includes the rare autosomal-recessive type Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

apoB indicates apolipoprotein B; FH, familial hypercholesterolemia; *ICD-10*, *International Classification of Diseases, 10th Revision*; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.

those heterozygotes described above. This criterion is necessary because of the now-recognized overlap in LDL-C levels in confirmed heterozygotes and homozygotes and the influence of additional cholesterol-raising and -lowering gene variants in any person.^{5,14,92} Individuals with multiple minor cholesterol-raising genes are not considered to have FH, but an individual with an LDL-C-raising gene variant and counteracting gene variants that lower cholesterol has FH because of the 50% risk to the offspring of inheriting FH.

We recognize that this diagnostic schema is functional and requires further study, including studies of concordance with genetic testing. A major limitation of this schema is that individuals with multiple gene variants that raise LDL-C incrementally will be misclassified as FH.⁵ The LDL-C thresholds chosen in this document reflect values typical in European and US white populations at this time. As more is learned about both LDL-C distributions in other societies and genotype/phenotype interactions, the absolute LDL-C thresholds may be adjusted.

Screening

Current cardiovascular risk guidelines identify individuals with severely elevated LDL-C, but many are not diagnosed with FH.^{1,120,123–125} A systematic strategy for detecting index cases (ie, the first individuals diagnosed in families) of FH is essential.^{2,3,114,125} These index cases trigger family/cascade screening, the most efficient method of identifying additional cases given the autosomal-dominant inheritance of FH. Universal screening before 20 years of age and ideally at \approx 6 to 12 years of age when LDL-C levels improve discrimination for FH is feasible.¹²⁶ However, no data exist on the implementation of universal pediatric screening or a reverse cascade screening strategy in which adult family members are identified from pediatric index cases, although a trial of its effectiveness is in progress. Ideally, universal and cascade screening methods for FH should be closely integrated. Universal screening has the potential to detect more

people in the community, and cascade screening with an adequate supply of probands has a greater yield and is more cost-effective.^{114,126} The success of screening methods is dependent on recognizing several barriers, including population awareness of FH and family, physician, and societal concerns about the value of screening for FH.¹²⁷ Novel approaches to pediatric screening such as school-based screening may be more effective.¹²⁸

Potential index cases of FH should be sought among patients with atherosclerotic disease who are <60 years of age. The greatest yield will be from screening younger adult patients with cardiovascular disease.^{68,129} FH screening should also be offered to all patients with tendon xanthomata and premature arcus cornealis.^{2,12,114,125} Clinical laboratory reporting thresholds can be used to alert primary/secondary care physicians about FH on the basis of a highly raised plasma LDL-C in the FH range.^{130,131} These approaches can include computer-based searches for potential cases.¹³² When feasible, all patients with suspected FH should be referred to a specialist with expertise in FH for confirmation of the diagnosis.^{2,114,125}

Drawing of a pedigree (family tree) can be valuable in planning cascade screening in families. Cascade screening should start with first-degree relatives and then be extended to second- and third-degree relatives.^{114,121,133} Relatives may be approached, with appropriate consent, by the index case, the clinical service, or both.^{114,133,134} Dual risk notification may be the best option.^{114,121,133} All communications must be lucid and must emphasize the health gains of diagnosis and treatment. Consenting family members should be offered a standard plasma lipid profile and a genetic test if the family mutation is known and DNA testing is available.^{114,119,133,135} All should be made aware of and understand the implications of genetic testing for certain types of insurance coverage and political discrimination.^{10,133} A decision to risk notify without the consent of the index case should be made carefully, with attention to the privacy legislation in different countries and localities.^{133,136} Systematic

cascade screening for FH is best coordinated centrally by a dedicated service that operates closely with primary care and ideally with a patient organization.^{114,133,137} Cascade screening should be developed for country-specific and local needs.¹³³

Genetic Counseling

Genetic counseling for FH can help patients and their families complete their pedigree and understand the inheritance of FH and the personal and familial implications of the diagnosis.¹³⁸ Genetic counselors can facilitate genetic testing and interpret genetic test results. Counseling on the utility of genetic testing includes confirming the diagnosis of FH for the proband, cascade screening for the mutation in relatives with clinical features of FH, and screening of at-risk relatives not yet identified. Untreated FH is a lethal condition, and if the family is at very high risk (eg, a strong history of premature CAD), procedures for contacting relatives of index cases may be justifiable, but country-specific guidelines for genetic testing and training of those providing counseling should be followed.^{133,136}

Genetic testing for FH should include pretest and posttest genetic counseling sessions to ensure that the patient understands the financial costs, insurance implications, benefits, limitations, and implications of the testing. The sensitivity of genetic testing for FH is imperfect; a portion of patients have a clinical diagnosis of FH without a detectable mutation and therefore no identifiable genetic cause. Thus, particular emphasis should be placed on educating patients about the implications of a negative test, which does not imply that they do not have FH or that their hypercholesterolemia has a nongenetic origin. Genetic testing results may include mutations that are not or have not yet been associated with elevated LDL-C. Many patients interpret their negative FH genetic test result as meaning their hypercholesterolemia is not genetic.¹³⁹ Furthermore, patients may be frustrated by the lack of information received in the event of a negative test and want to discuss the implications of their result with a health professional, thus emphasizing the importance of posttest counseling in both mutation-positive and mutation-negative patients. Several psychological issues, including grief, guilt, survivor guilt, anger, and hurt, that alter family relationships may be encountered during testing for an inherited condition, and all these may need to be addressed.¹⁴⁰

Nondisclosure of genetic results can present an ethical dilemma when probands do not wish a personal diagnosis (including genetic) to be disclosed to relatives but *ipso facto* are placing relatives at high risk of developing preventable disease. This conflict between respect for confidentiality and preventing harm to relatives must be addressed through counseling. Counseling can help reframe the consequences, address shame, explore possible involvement of other relatives, offer practical assistance with mediation, and keep lines of communication open. Relatives should be directly notified of their risk without consent of the index case only if there is specific legislative provision for breach of confidentiality in the relevant jurisdiction.^{3,127}

FH has not been associated with birth defects or other adverse outcomes of pregnancy. Intrauterine exposure to elevated levels of LDL-C is associated with early vascular changes for the newborn, but the long-term implications of these findings are unknown.^{141–144}

Treatment

Heterozygous FH

FH treatment is based on LDL-C levels, not genetic abnormality or other clinical features. A limitation of current FH treatment strategies for heterozygotes is the lack of true long-term outcome studies with events as end points. Adult treatment is based on clinical trials of patients without FH, and pediatric clinical trials have a maximum duration of 2 years.¹⁴⁵ Long-term follow-up of adolescents started on statins suggests excellent safety and much lower event rates than for their affected parents.¹⁴⁷ Comparisons of event rates in the prestatin and poststatin eras demonstrate lower event rates in FH patients in the statin era.^{10,11} However, long-term questions about the side effects of treatment and treatment targets to guide therapy still need to be answered.

Current consensus guidelines, both specific for FH and for the general population, provide aggressive pharmacological treatment of affected individuals beginning at 8 to 10 years of age. Only younger children with extreme elevation of LDL-C or other major risk factors suggesting a high likelihood of very premature cardiovascular disease would be treated.^{1–3,120,122–124,145} Currently, pravastatin is approved for use at 8 years of age, and other statins are approved for use beginning at 10 years of age. Early treatment is critical because atherosclerosis begins early in life. However, there are no data to inform pediatric treatment goals, whether to target an LDL-C level of <100 or 130 mg/dL or to aim to achieve a 50% reduction in LDL-C from baseline.^{14,145} Before treatment is started, baseline levels of hepatic transaminases and creatine kinase should be obtained. Patients should be alerted to stop medication if unexplained muscle pain occurs; female patients should be counseled about the fact that statins are contraindicated during pregnancy. Response to treatment, including assessment of liver enzymes, should be assessed 1 to 3 months after the start of therapy and periodically thereafter according to published guidelines.³ Dietary treatment with a low-saturated-fat, low-cholesterol, calorie-appropriate, and nutrient-dense diet augments pharmacological treatment but will be insufficient by itself to achieve LDL-C targets.¹²³

For adult heterozygotes, Figure 6 shows the recommended drug formulary approach to treatment with an initial goal of reducing LDL-C by at least 50%, usually with a statin. This can be followed by achieving an LDL-C of <100 mg/dL (2.5 mmol/L [absence of CAD or other major risk factors]) or 70 mg/dL (<1.8 mmol/L [presence of CAD or other major risk factors]).³ Recommended targets are difficult to achieve with currently available treatments in the majority of FH patients. The maximal LDL-C reduction that can be tolerated with therapy is a pragmatic target, particularly for higher-risk patients. Therapeutic targets for apoB and non-high-density lipoprotein cholesterol have not been defined in FH. Ezetimibe or colesvelam is preferred as an additional LDL-C-lowering agent over niacin.

Figure 6 provides an overall schema for a drug formulary for FH. Table 5 provides a listing of available drugs for FH treatment, including pediatric and adult dose information. Table 6 describes the monitoring and drug interactions for lipid-lowering drugs.

In patients with severe statin-induced side effects or total intolerance to statins, several treatment strategies exist.^{127,148}

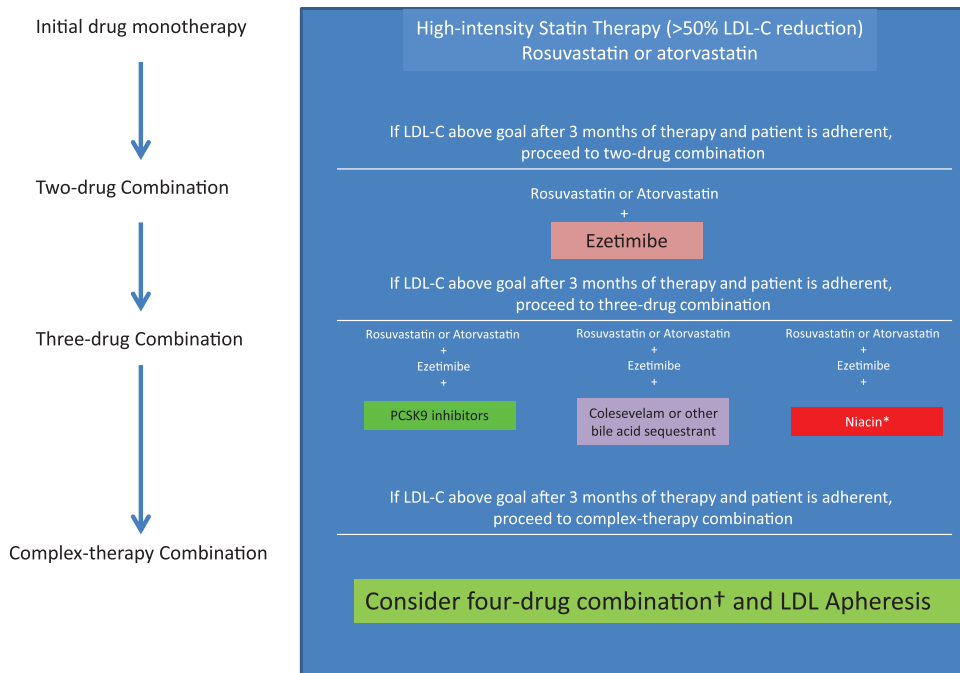


Figure 6. Preferred pharmacotherapy formulary. The decision to use a third-line agent must take into account multiple factors, including disease severity, patient preference, cost, and outcomes data if available. Future research on PCSK9 inhibitors and other new agents will also inform the choice of a third agent, particularly in the context of statin intolerance. HoFH indicates homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9. *Prescription niacin preferred. †Consider lomitapide or mipomersen in HoFH subjects.

When the statin-induced side effects are disabling but a statin response is present, treatment with a lower dose of a statin given daily or on alternate days may be sufficient, together with other lipid-lowering medications, to reduce LDL-C to reasonably acceptable levels and to limit the disabling side effects. A combination of ezetimibe, niacin, and bile acid sequestrants may also reduce LDL-C satisfactorily in patients with moderate elevations of LDL-C. Alternatively, LDL apheresis or new forms of therapy, including microsomal transfer protein inhibitors and apoB antisense oligonucleotides. PCSK9 inhibitors alirocumab and evolocumab have now been approved by the FDA for this purpose, based on LDL lowering and short-term studies suggesting a decrease in composite cardiovascular end points.^{149,150} Definitive hard outcomes data are not yet available.

Nursing case management that is FH specific may improve outcomes. Integration of nursing into comprehensive care of patients with CAD helped improve outcomes in large, international outcomes trials, first the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and then the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA; in progress). Components of care that can be improved include family understanding, medication adherence, control of other cardiovascular risk factors, engagement in risk notification and cascade screening, and overall satisfaction with medical care.¹⁵¹

Before a female patient becomes pregnant or immediately after pregnancy is discovered, statin treatment should be discontinued. Bile acid sequestrant or apheresis may be used if treatment is required during pregnancy or lactation.² It is important to recognize the limitations of current evidence evaluation paradigms with regard to FH treatment.^{2,3,122,124,152} The evidence grade

for LDL-C-lowering treatment of adults is high but is based on clinical trials conducted in the non-FH general population and observational data in FH patients.¹²⁴ Pediatric trials conducted in FH-specific populations provide lower-level evidence because of major evidence gaps such as a lack of cardiovascular disease end points and long-term (>2 years) safety outcomes in those treated from a young age.¹⁴⁵ These evidence paradigms require clinical trial evidence of benefit (generally a reduction in cardiovascular events or mortality) versus harm from side effects and unintended consequences. There are ethical limitations in the conduct of pharmacological clinical trials in participants with a genetic disorder such as FH. Risk may be underestimated for adult FH patients compared with those without FH because FH patients have a lifetime exposure to elevated LDL-C levels. Disease may be more advanced at the time the need for treatment is recognized. For children, studies that rely on clinical outcomes require decades. Not only will trials of sufficient length be impossible to conduct, but also changes in treatment modalities will render ongoing trials obsolete. If treatment is started at a young age when atherosclerosis is just developing, LDL-C goals may not need to be as low as for adults with advanced disease. All the above considerations suggest the need to include subclinical atherosclerosis measurements in study designs. Registries currently underway or being developed in many countries may add important clinical information.¹⁵³

However, it would be imprudent to use the absence of CAC on CT imaging to limit statin therapy in FH patients. Significant atherosclerosis can be present in the absence of CAC.²

All patients with FH require treatment of associated cardiovascular risk factors, including obesity, hypertension, diabetes mellitus, and tobacco use.³ Regular physical activity and improvements in physical fitness should be

Table 5. Dosages of Lipid-Lowering Drugs

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Cholestyramine, adult	4 g every day or bid before main meal	4–8 g bid before main meals	8 g bid before main meals	May prescribe 24 g/d, but few patients can tolerate.
Cholestyramine, pediatric	...	2–4 g bid before main meals	8 g/d before main meals	...
Colestipol, adult	5 g powder or 2 g tablets every day before main meal	5 g powder or 4 g tablets bid before heaviest meals	10 g powder or 8 g tablets bid before heaviest meals	May prescribe 30 g of powder or 16 g of tablets per day, but few patients can tolerate.
Colestipol, pediatric	Not currently available	Same	Same	...
Colesevelam, adult	6×625 mg tablets or 3.75 g packet every day, or 3×625 mg tablets or 1.875 g packet bid	Same	Same	Less bulk is associated with less gastrointestinal intolerance.
Colesevelam, pediatric	3.75 g packet every day or 1.875 g packet bid (10–17 y for HeFH)	Same	Same	...
Ezetimibe, adult	10 mg every day	Same	Same	Can be administered with or without food. No dose adjustment needed in renal or mild hepatic insufficiency.
Ezetimibe, pediatric	10 mg every day (10–17 y for HeFH)	Same	Same	...
Niaspan, adult	500 mg QHS	1000–2000 mg QHS	2000 mg QHS	Increase dose by 500 mg daily every 4 wk as tolerated.
Niaspan, pediatric	Not currently available	Same	Same	...
Atorvastatin, adult	10–20 mg every day	10–40 mg every day	80 mg every day	Administer any time of day. Dose adjustment in patients with renal dysfunction is not necessary.
Atorvastatin, pediatric	10 mg every day (10–17 y for HeFH) 10–20 mg every day (>6 y for HoFH)	10–20 mg every day 10–80 mg every day	20 mg every day 80 mg every day	...
Fluvastatin, adult	20 mg QHS	20–80 mg divided every day bid	40 mg bid 80 mg XL every day	Dose adjustments for mild to moderate renal impairment are not necessary.
Fluvastatin, pediatric	20 mg QHS 80 mg XL every day (10–16 y for HeFH)	20–80 mg divided every day bid Same	40 mg bid 80 mg XL every day	...
Lovastatin, adult	20 mg with dinner	20–40 mg with dinner	40 mg bid	Administration with food increases bioavailability. Twice-daily dosing provides greater LDL-C-lowering efficacy than every-day dosing. In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dose increases >20 mg/d should be carefully considered and, if deemed necessary, implemented cautiously.
Lovastatin, pediatric	20 mg with dinner (10–17 y for HeFH)	10–40 mg with dinner	40 mg daily	...
Pitavastatin, adult	1–2 mg every day	1–2 mg every day	4 mg every day	Administer any time of the day with or without food. Moderate renal impairment (glomerular filtration rate, 30–60 mL·min ⁻¹ ·1.73 m ⁻²) and end-stage renal disease on hemodialysis: starting dose of 1 mg once daily and maximum dose of 2 mg.
Pitavastatin, pediatric	Not currently available	Same	Same	...
Pravastatin, adult	10–40 mg every day	10–40 mg every day	80 mg every day	Administer with food to reduce dyspepsia. In patients with a significant history of renal or hepatic dysfunction, a starting dose of 10 mg is recommended.
Pravastatin, pediatric	20 mg every day (8–13 y for HeFH) 40 mg every day (14–18 y for HeFH)	Same Same	Same Same	...

(Continued)

Table 5. Continued

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Rosuvastatin, adult	10–20 mg every day	10–20 mg every day	40 mg every day	Administer any time of the day. Consider 5-mg starting dose in Asians. In patients with creatinine clearance <30 mL/min who are not on hemodialysis, start with 5 mg with a maximum dose of 10 mg.
Rosuvastatin, pediatric	5–10 mg every day (10–17 y for HeFH)	5–20 mg every day	20 mg every day	...
Simvastatin, adult	20–40 mg QPM	20–40 mg QPM	40 mg QPM	Administer with food to reduce dyspepsia. Simvastatin 80 mg should be used only in patients who have been taking this dose for ≥12 mo without evidence of muscle injury (myopathy). In patients with severe renal impairment, start with 5 mg QPM.
Simvastatin, pediatric	10 mg QPM (10–17 y for HeFH) 40 mg QPM (>13 y for HoFH)	10–40 mg QPM Same	40 mg QPM Same	...
Ezetimibe and simvastatin, adult	10/10–10/20 mg QPM	10/10–10/40 mg QPM	10/40 mg QPM	Same as simvastatin, adult
Ezetimibe and simvastatin, pediatric	10/10 mg QPM (10–17 y HeFH)	10/10–10/40 mg QPM	10/40 mg QPM	...
Ezetimibe and atorvastatin, adult	10/10 mg every day	10/10–10/80 mg every day	10/80 mg every day	Same as atorvastatin, adult
Ezetimibe and atorvastatin, pediatric	Not currently available	Same	Same	...
Niaspan and lovastatin, adult	500/20 mg at bedtime	500/20–2000/40 mg at bedtime	2000/40 mg at bedtime	Same as lovastatin, adult
Niaspan and lovastatin, pediatric	Not currently available	Same	Same	...
Niaspan and simvastatin, adult	500/20 mg at bedtime	500/20–2000/40 mg at bedtime	2000/40 mg at bedtime	Same as simvastatin, adult
Niaspan and simvastatin, pediatric	Not currently available	Same	Same	...
Lomitapide, adult*	5 mg every day	10–40 mg every day	60 mg every day	Initiate a low-fat diet supplying <20% of energy from fat, and titrate dose based on acceptable safety/tolerability. The maintenance dose of lomitapide should be individualized, taking into account patient characteristics such as goal of therapy and response to treatment, to a maximum of 60 mg every day.
Lomitapide, pediatric*	Not currently available	Same	Same	...
Mipomersen, adult*	200 mg SC once weekly	Same	Same	Injection into the abdomen, thigh region, or outer areas of the upper arm should be given on the same day every week, but if a dose is missed, the injection should be given at least 3 d from the next weekly dose. Should be avoided in moderate or severe hepatic impairment or active liver disease, including unexplained persistent elevations of serum transaminases.
Mipomersen, pediatric*	Not currently available	Same	Same	...

(Continued)

Table 5. Continued

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Alirocumab, adult	75 mg SC every 2 wk	Same	150 mg SC every 2 wk	A single injection into the abdomen, thigh region, or outer areas of the upper arm should be given on the same day every 2 wk, but if a dose is missed, the injection should be given within 7 d from the missed dose and then resume the original schedule. If the missed dose is not administered within 7 d, wait until the next dose on the original schedule. Measure LDL-C levels within 4-8 wk of initiating or titrating to assess response and adjust dose, if needed.
Alirocumab, pediatric	Not currently available	Same	Same	...
Evolocumab, adult	140 mg every 2 wk OR 420 mg once monthly	Same	Same	The injection into the abdomen, thigh region, or outer areas of the upper arm should be given on the same day every 2 wk or once monthly. If every 2 wk or once monthly dose is missed, administer as soon as possible if there are >7 d until the next scheduled dose, or omit the missed dose and administer the next dose according to the original schedule. To administer the 420 mg dose, give 3 injections consecutively within 30 min. Dose for HoFH is 420 mg once monthly.
Evolocumab, pediatric	Not currently available	Same	Same	...

Multiple formulations are available and doses do vary.

bid indicates twice daily; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; QHS, every bedtime; QPM, every evening; and SC, subcutaneous.

*For HoFH only.

encouraged. Saturated fat, *trans* unsaturated fat, and cholesterol intake should be limited, and a regular intake of fruits and vegetables, whole grains, tree nuts, low-fat and nonfat dairy products, beans, fish, and lean meats should be encouraged.^{2,3,123} Alcohol intake should be moderated and psychological stress addressed. Dietary supplementation with plant sterols or stanols may be used to incrementally lower plasma LDL-C.

Homozygous FH

Pharmacotherapy

Lipid-lowering therapy, usually statins, should be instituted at diagnosis and as early as possible.⁹² Statins reduce LDL-C levels modestly in homozygous FH, even in those who are receptor negative.¹⁵⁴⁻¹⁵⁷ Statins probably lower LDL-C by inhibiting hepatic cholesterol synthesis, thereby limiting cholesterol availability for the formation and secretion of apoB-containing lipoproteins in receptor-negative homozygous FH patients and increasing residual LDL receptor activity in receptor-defective patients.¹⁵⁸ The requirement for functioning LDL receptors means that statins, even at high dose, deliver only modest reductions in LDL-C of 10% to 25% in the majority of homozygous FH patients.¹⁵⁸ Despite reducing LDL-C only modestly, statin therapy has been shown to reduce cardiovascular and all-cause mortality.⁹ The addition of the cholesterol absorption inhibitor ezetimibe to statin therapy has been shown to reduce LDL-C by an additional 10% to 15%.¹⁵⁹ Other cholesterol-lowering medications such as bile acid sequestrants, niacin, fibrates, and probucol have

also been used, but their LDL-C-reducing effects in homozygous FH are modest at best.

Mipomersen, an antisense inhibitor of apoB synthesis, can reduce LDL-C by an additional 25% in homozygous FH patients when given subcutaneously in combination with maximum tolerated doses of lipid-lowering therapy, but even the addition of mipomersen does not achieve the recommended LDL-C target in the vast majority of homozygous FH patients.¹⁶⁰ Lomitapide, an oral inhibitor of microsomal transfer protein, can also reduce LDL-C levels by up to by 50% in homozygous FH patients.¹⁶¹ However, given its mechanism of action, gastrointestinal side effects and elevation in liver enzymes are common. Extended use of both agents shows stable changes in liver fat content, but whether longer-term use is associated with cirrhosis and insulin resistance remains to be shown.^{162,163} There are no published data on the use of either agent in childhood. Mipomersen has not been approved by the European Medicines Agency because of safety concerns related to possible increased risk of cardiac events and a high proportion of volunteers stopping the medication as a result of injection site reactions and nonspecific complaints.¹⁶⁴ The relative benefits and risks of lomitapide and mipomersen were reviewed recently.¹⁶⁵ Both manufacturers of lomitapide and mipomersen were required by the FDA to submit a Risk Evaluation and Mitigation Strategy to ensure that the benefits outweigh the risks. The goals of both the lomitapide and mipomersen Risk Evaluation and Mitigation Strategy programs are to educate prescribers about the risk of hepatotoxicity and the need to monitor patients during treatment and to

Table 6. Monitoring Parameters, Adverse Effects, and Drug Interactions With Lipid-Lowering Drugs

Drug	Adverse Effects	Drug Interactions	Monitoring Parameters
Resin	Indigestion, bloating, nausea, constipation, abdominal pain, flatulence, although may be less with colesevelam	GI binding and reduced absorption of anionic drugs (warfarin, β -blockers, digitoxin, thyroxine, thiazide diuretics); administer drugs 12 h before or 4 h after resin	Lipid profile every 4–8 wk until stable dose; then every 6–12 mo long term. Check TG level after stable dose achieved, then as needed.
Niacin	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash, worsening of peptic ulcer, elevation in serum glucose and uric acid, hepatitis, and elevation in hepatic transaminase levels	Hypotension with BP-lowering drugs such as α -blockers possible; diabetics taking insulin or oral agents may require dose adjustment because of an increase in serum glucose levels	Lipid profile after 1000–1500 mg/d, after stable dose achieved, then every 6–12 mo long term. LFT at baseline and every 6–8 wk during dose titration, then as needed for symptoms. Uric acid and glucose at baseline and again after stable dose reached (or symptoms produced), more frequently in diabetic patients.
Statins	Headache, dyspepsia, myositis (myalgia, CPK >10 times normal), elevation in hepatic transaminase levels; statins should be discontinued promptly if patient becomes pregnant; an increased risk of new-onset diabetes mellitus has been associated with statin therapy, but the absolute risk is low	Increased myositis risk with concurrent use of drugs that inhibit or compete for CYP450 3A4 system (eg, cyclosporine, erythromycin, calcium blockers, fibrates, nefazodone, niacin, ketoconazole); risk greater with lovastatin and simvastatin; caution with concurrent fibrate or niacin use; lovastatin increases the PT with concurrent warfarin	Lipid profile 4–8 wk after dose change, then every 6–12 mo long term. LFT at baseline, in 3 mo, and periodically thereafter. CPK at baseline and if the patient has symptoms of myalgia.
Cholesterol absorption inhibitors	Upper respiratory tract infection, diarrhea, arthralgia, sinusitis, and pain in extremity	Using ezetimibe and cyclosporine concomitantly increases exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ezetimibe and cyclosporine. Cholestyramine combined with ezetimibe decreases the mean AUC of total ezetimibe by \approx 55%. Dose ezetimibe \geq 2 h before or \geq 4 h after administration of a bile acid sequestrant.	
Microsomal transfer protein inhibitors	Most common adverse reactions (incidence \geq 28%) are diarrhea, nausea, vomiting, dyspepsia, and abdominal pain; lomitapide increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases; because of the risk of hepatotoxicity, lomitapide is available only through a limited program under the REMS	Lomitapide is metabolized extensively by the CYP450 3A4 system; concomitant use of strong CYP3A4 inhibitors (eg, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) with lomitapide is contraindicated; lomitapide approximately doubles the exposure of simvastatin, so the recommended dose of simvastatin should be reduced by 50% when lomitapide is initiated and simvastatin dose should be limited to 20 mg daily (40 mg daily for patients who have previously tolerated simvastatin 80 mg daily for at least 1 y without evidence of muscle toxicity)	Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin. Obtain a negative pregnancy test in female patients of reproductive potential. Transaminases should be measured before any increase in dose, and dose adjustments are required for patients who develop transaminase values \geq 3 times the upper limit of normal.
apoB antisense	The most commonly reported adverse reactions (incidence \geq 10% and greater than placebo) are injection site reactions, flu-like symptoms, nausea, headache, and elevations in serum transaminases, specifically ALT; increases in hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases; because of the risk of hepatotoxicity, mipomersen is available only through a limited program under the REMS	Mipomersen is not a substrate for the CYP450 metabolism; no clinically relevant pharmacokinetic interactions have been reported between mipomersen and warfarin or between mipomersen and simvastatin or ezetimibe; coadministration of mipomersen with warfarin also did not result in a pharmacodynamic interaction as determined by INR, aPTT, and PT	Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin. Maximal reduction of LDL-C may be seen with mipomersen therapy after \approx 6 mo (based on the time to steady state seen in clinical studies). Assess the patient's LDL-C level after 6 mo to determine whether the LDL-C reduction achieved with mipomersen is sufficiently robust to warrant the potential risk of liver toxicity.
PCSK9 inhibitors	Most common (incidence \geq 2% of alirocumab and greater than placebo) are nasopharyngitis, injection site reactions, and influenza. Most common (incidence \geq 3% of evolocumab and greater than placebo) are nasopharyngitis, upper respiratory tract infections, and influenza.	Both alirocumab and evolocumab are eliminated by target (PCSK9) mediated elimination and a non-saturable proteolytic pathway. Therapeutic monoclonal antibodies are not substrates or inhibitors of the cytochrome P450 enzymes and transporter proteins such as P-gp and OATP.	Lipid profile 4–8 wk after initiation or dose change in dose

ALT indicates alanine aminotransferase; apoB, apolipoprotein B; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC, area under concentration curve; BP, blood pressure; CPK, creatinine phosphokinase; GI, gastrointestinal; INR, International Normalized Ratio; LDL-C, low-density lipoprotein cholesterol; LFT, liver function tests; OATP, organic anion transporting polypeptide; PCSK9, proprotein convertase subtilisin/kexin type 9; P-gp, P-glycoprotein; PT, protime; REMS, Risk Evaluation and Mitigation Strategy; TC, total cholesterol; and TG, triglyceride.

restrict access to patients with a clinical or laboratory diagnosis consistent with homozygous FH. Both manufacturers ensure that healthcare providers who prescribe their drugs are specially certified and must enroll in the Risk Evaluation and Mitigation Strategy program for whichever drug they are prescribing. Lomitapide and mipomersen can be dispensed only by certified pharmacies.¹⁶⁶ Monoclonal antibodies directed against PCSK9 have been shown to reduce LDL-C by an additional 50% to 60% on top of high-dose statin with or without ezetimibe in heterozygous FH.¹⁶⁷ Although the action of PCSK9 inhibitors depends on the presence of functional LDL receptors, this therapy has recently been shown to be partially effective in homozygous FH, at least in those subjects who are receptor defective.^{12,13,92,168–170}

Lipoprotein Apheresis

LA, an extracorporeal treatment that removes apoB-containing lipoproteins from the circulation, appears to improve cardiovascular outcomes and should be considered by 5 years of age or earlier in exceptional circumstances.^{12,171–174} Untreated homozygotes typically have plasma LDL-C >400 mg/dL (13 mmol/L) and should be treated with maximally tolerated pharmacotherapy before LA is considered.^{12,92,133,171,175} LDL-C selection criteria for LA include a reduction in LDL-C of <50% by other treatments and residual severe elevation of LDL-C, >300 mg/dL or >200 mg/dL with prevalent cardiovascular disease. Contraindications to apheresis include hemorrhagic diatheses and hypersensitivity to heparin. Good results have been reported in very young children (body weight as low as 13.5 kg).^{12,171,174} Women with severe FH may be treated successfully during pregnancy.^{12,175}

Plasmapheresis is an alternative to apheresis.¹⁷⁶ An extended international network of treatment centers and a registry of patients on LA are needed to better understand the risks, benefits, and practical issues related to LA in homozygous FH.^{12,171,174}

The frequency of LA should be adjusted to achieve a time-average plasma LDL-C concentration between therapies of 250 and 100 mg/dL (6.5 and <2.5 mmol/L). A mean reduction of 65% in LDL-C relative to no treatment is a simple target. This will require an acute reduction of ≥70% in LDL-C and weekly or fortnightly treatments. Statins should be continued to delay postexchange rebound in LDL. Angiotensin-converting enzyme inhibitors are contraindicated with the use of the dextran sulfate LDL absorption because of bradykinin reactions. Side effects (nausea, hypotension, vasovagal episodes, hypocalcaemia, anemia, sepsis) occur but are rarely serious. The role of newer medications in conjunction with LA is under investigation.^{133,171–173}

Liver Transplantation

Liver transplantation has been described as a treatment for both children and young adults with homozygous FH in the form of case series. LDL-C levels rapidly approach normal and xanthoma diminish in size or disappear by 2 years.^{177,178} Most transplantations have been performed in individuals who either are symptomatic from CAD or demonstrate significant coronary lesions despite maximal medical therapy and apheresis. Reported results are generally good in the short and medium term, as late as 9 years after liver transplantation, although progression of cardiovascular disease has been reported in 1 patient. In patients with advanced cardiac disease, combined heart/liver transplantation has been performed.^{179–181}

Table 7. Research Needs in FH

MoC	Population Science: Diagnostic Criteria, Screening, and Registries	Basic Science	Life Course	Clinical Research	Patient-Centric Research
Evaluation of country-specific FH care delivery	Use registries to understand natural history and impact of treatments	Identification of genes beyond <i>LDLR</i> , <i>APOB</i> , and <i>PCSK9</i>	Better define the natural history of atherosclerosis to direct timing and intensity of intervention to lower LDL-C	Clinical trials of new pharmacological agents and nutraceuticals	Assessment of patient and family perceptions of different aspects of care, including family contacts related to cascade screening
Role of allied health personnel (pharmacist, nurse, genetic counselor)	Determine FH prevalence in nonwhite and Hispanic populations	Understand the interactions of main gene effects with modifier genes	Close guideline gaps from pediatric to adult care; separate FH from population-based lipid treatment guidelines	Incorporate subclinical atherosclerosis imaging into trials as risk stratifiers	Patient and family awareness of FH
Better understand patient and family perspective on living with FH, including concerns about the disease, medication, and genetic testing	Compare diagnostic criteria schema for efficiency in diverse populations, including age-specific LDL-C levels	Create an FH biobank with a long-term goal of linkage of registry to biobank	Better define risk/benefit of lifelong FH care, including assessment of treatment goals and long-term side effects of treatment	Understand the natural history of apheresis and liver transplantation treatments for HoFH	Gaps in care (screening, diagnosis, drug adherence, and intolerance)
	Cost-effectiveness studies that include universal and/or cascade screening methods; also include children in risk/benefit assessment		Better understand the impact of pregnancy on the natural history of FH	Identify and study biomarkers that may improve identification of early atherosclerosis, risk prediction, and drug responsiveness	Decision aids (ie, tools to help children, young adults, and adults think through screening and treatment decisions)

FH indicates familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and MoC, models of care.

Table 8. FH: Take-Home Messages

FH is a highly prevalent genetic disorder causing premature atherosclerotic coronary artery heart disease. FH is underdiagnosed and undertreated worldwide.

Because of its long asymptomatic prodrome and its potentially devastating consequences and genetic origin, FH presents unique challenges for patients, families, and healthcare providers. A multidisciplinary medical team that includes physicians, nurses, genetic counselors, pharmacists, and dietitians is necessary for care.

A genetic cause related to LDL receptor function can be identified in most people with FH.

An *ICD-10* diagnostic code is needed for FH to distinguish those with severe genetic dyslipidemia from those with dyslipidemia secondary to diet or genetic causes related to a large burden of smaller effect size genes.

We propose a diagnostic schema that allows FH diagnosis based solely on clinical criteria or combined clinical and genetic information (Table 4).

The severity of FH is related to the degree and duration of exposure to plasma LDL-C levels. In heterozygous FH, elevated LDL-C is the most important clinical characteristic. Adults may develop physical stigmata if untreated. In homozygous FH, LDL-C is often >400 mg/dL. Physical stigmata and medical morbidity (including aortic valve disease) may be present in childhood.

Subclinical atherosclerosis imaging and exercise stress testing demonstrate accelerated atherosclerosis in FH patients. There is insufficient research on the best way to incorporate these measures into clinical practice for FH patients.

Cascade screening after identification of index cases should be performed to identify all affected family members. Universal screening is another potential strategy for case identification, particularly in childhood when discrimination of those with and without FH based on the combination of LDL-C levels and family history alone is most effective.

FH treatment should follow recently published FH-specific international and national guidelines and be consistent with evidence-based guidelines for the general population. A formulary for FH treatment is presented in Tables 5 and 6.^{1-3,12,13}

Newer medications for treating FH offer hope for the future; creative research design to determine the best way to integrate these medication with statin treatment is needed.

FH-specific outcomes research that includes assessments of safety, treatment goals, and role of subclinical atherosclerosis imaging in predicting outcomes is urgently needed. Registries will assist in achieving this goal.

Country-specific models of care for FH are required to increase FH awareness and recognition; these function best when centrally administered rather than relying on decentralized frameworks.

FH indicates familial hypercholesterolemia; *ICD-10*, *International Classification of Diseases, 10th Revision*; LDL, low-density lipoprotein; and LDL-C, low-density lipoprotein cholesterol.

Health Economics of Detection and Treatment of FH

Health economic modeling shows considerable savings from treating FH in identified patients. For patients in whom the causative mutation is known, cascade testing of their relatives with DNA analysis is very cost-effective because ≈50% of them inherit the mutation.¹⁸²⁻¹⁸⁵ International studies collectively show that the cost per life-year gained for DNA-based cascade testing and intensive statin therapy averages \$5000 to \$6800, which compares favorably with other widely accepted screening strategies such as mammography for breast cancer. A recent report on the health, social, and economic advantages of treating FH estimated that high-intensity statin therapy would lead to 10% fewer CAD deaths per 1000 FH patients treated (between 30 and 85 years of age) compared with no treatment.¹²¹ This would equate to roughly \$8 million in costs

averted from cardiovascular events avoided if 1000 relatives of index cases were identified and treated optimally over a 55-year period. Scaled up to a whole-population level, the cost savings on health care for many countries would be immense.

A systematic review also confirmed the cost-effectiveness of cascade screening but cautioned that different methodologies and assumptions had been used, that most studies were derived from European communities, and that evaluations were restricted to adults.^{2,127} Beyond cascade screening, some experts recommend universal screening, particularly of the young, but the cost-effectiveness of this approach is questionable.^{152,182} A cost-effective analysis of screening methods for FH in children has not been reported.¹⁸⁶ Moreover, in communities that cannot afford DNA testing, it remains to be seen whether screening with a plasma lipid profile alone is cost-effective. Preliminary data from the United Kingdom suggest that this is likely to be the case.¹⁸⁷ Finally, more country-specific health economic evaluations, including estimates of societal benefits, that also focus on children and the young are required to drive policy change and government funding for early detection and management programs for FH.¹⁸⁸

Structure of FH MoCs

MoCs for FH are more than guidelines; they encompass overarching systems, underpinned by theoretical, experimental, and evidence-based standards, for provision of the highest-quality healthcare services to a defined population.^{133,189} They are designed to correct current suboptimal care delivery for specific conditions.^{1,190} The development and implementation of initiatives and strategies to improve the care of FH require a close collaboration among healthcare systems, patient support groups, and related nongovernment organizations and health networks.¹⁹¹ These care pathways should be responsive to local needs and to patient flow among all health providers, including primary care providers.¹⁹² MoCs have been developed in countries such as the Netherlands, Spain, the United Kingdom, Australia, and Brazil with varying degrees of implementation; the United States lags far behind these countries.

“Top-down” MoCs for FH function best and should be coordinated by state or region. Services should be managed by personnel accredited in cardiovascular disease prevention.¹⁹² Primary care providers have an important role in detecting index cases, but cascade screening should be coordinated within a framework that integrates specialty and primary care.¹⁹³ Education and training of primary care providers in lipid management are important for improving and maintaining the total quality of care.¹⁹⁴ A structured review should be offered at least annually to all patients.^{114,195} A telehealth program can be used for remote care. Children are best cared for in a specialist pediatric clinic or a combined adult-pediatric clinic, which may be useful for families.^{122,123,196} Nurses have a role in coordinating screening and in clinical care, case management, patient education, and working with family support groups.¹⁹⁷ Dietetic services are highly desirable. Genetic counselors and health and adolescent psychologists have a role in family support and in counseling on genetic screening.¹⁴⁰ Pharmacists should use FH-specific formularies and may have a role in case detection and medication support.¹⁹⁸ FH services should have access to routine and advanced lipid analyses. DNA testing should be

carried out only by laboratories that can screen for mutations in all the major genes of interest.¹¹⁴ Adequate patient assessment may require access to cardiology and imaging facilities.¹⁹⁹

Information technology support systems are essential for the effective provision of services. An international database with information on recognized FH-causing mutations is available.⁴¹ A comprehensive clinical registry helps improve the quality of care and helps coordinate cascade screening at all levels in a family. Such registries are now being established around the world.^{200–202} A patient support group can provide a useful network for mutual support and education.¹⁹⁵

MoCs for FH need to be effectively translated and transferred into clinical care within the framework of a chronic care model similar to that defined by the World Health Organization and in a positive policy environment.²⁰³ Implementing and ensuring the uptake of MoC recommendations are challenges recognized by recent reports from several countries and emphasize the importance of a top-down approach.^{204,205} Implementation and sustainability are the real challenge. They require close collaboration between all stakeholders, including politicians, to translate the evidence into government healthcare policy. Financial support may derive from government or alternative private-public revenue sources. Because policy making draws on the values and priorities of the population, it is essential to raise community awareness about the benefits of early detection and treatment of FH.²⁰⁶ MoCs need to be subjected to regular auditing and economic evaluation to allow growth of the service models into a standard of excellence for the care of all patients with FH.¹³³

Summary, Evidence Gaps, and New Research Directions

FH is a genetic condition caused by pathogenic mutations in genes involved in LDL-C metabolism with the hallmarks of severely elevated LDL-C and personal (or family) history of premature atherosclerotic cardiovascular disease, particularly CAD. More specifically, FH is characterized by an autosomal dominant inheritance pattern, with “large-effect” mutations in

LDLR, *APOB*, and *PCSK9* explaining a high percentage of cases. FH has high penetrance, and in the absence of protective genetic alleles, there is severe elevation in LDL-C starting in utero. LDL-C levels >160 mg/dL (4 mmol/L) in children suggest the presence of FH; untreated adults with FH have LDL-C levels >190 mg/dL (5 mmol/L). At levels >400 mg/dL (10 mmol/L), patients may have either null or near-null LDL receptor mutations in 1 FH gene or have causal mutations in 2 distinct genes. In the absence of effective treatment, this lifetime burden of high LDL-C leads to markedly increased risk of premature CAD. Because of the high risk from FH, the identification of FH (or severely elevated LDL-C) in 1 family member necessitates attempts at cascade screening all other potentially affected family members.

Throughout the text, both evidence and evidence gaps with regard to FH have been identified. Table 7 summarizes these gaps and suggests a research agenda for the future. Table 8 summarizes the take-home messages from this review. The agenda should begin with the patient, identifying the best ways to create understanding of what it means to have FH for both the patient and the family. At the societal level, FH care should be organized within the context of healthcare financing to guarantee lifelong care in a cost-effective manner. There are significant gaps in knowledge with regard to FH prevalence for individuals of African, East Asian, and South Asian descent. Registries and epidemiological studies are needed to better define the scope of FH care needs in specific populations and the best ways to identify all those with the disease. Basic science, including genetic studies, is needed to improve diagnostic classification. A better understanding of the life course of FH is required to better estimate the risks and benefits of existing treatments. These insights should be linked to clinical trials that evaluate not only response to treatment but also the roles of subclinical atherosclerosis and biomarkers as tools for diagnostic precision and prognosis.

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*Modest.

†Significant.

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The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association

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on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health

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Correction

In the article by Gidding et al, “The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association,” which published ahead of print October 28, 2015, and appeared in the December 1, 2015, issue of the journal (*Circulation*. 2015;132:2167–2192. doi: 10.1161/CIR.000000000000297), a correction was needed.

On page 2175, Table 4, the third column, the second sentence read, “Diagnosed as heterozygous FH if gene-raising defect positive....” It has been changed to read, “Diagnosed as heterozygous FH if LDL-C-raising defect positive....”

This correction has been made to the print version and to the current online version of the article, which is available at <http://circ.ahajournals.org/content/132/22/2167.full>.