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My Approach to the Patient With Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH), a relatively common Mendelian genetic disorder, is associated with a dramatically increased lifetime risk of premature atherosclerotic cardiovascular disease due to elevated plasma low-density lipoprotein cholesterol (LDL-C) levels. The diagnosis of FH is based on clinical presentation or genetic testing. Early identification of patients with FH is of great public health importance because preventive strategies can lower the absolute lifetime cardiovascular risk and screening can detect affected relatives. However, low awareness, detection, and control of FH pose hurdles in the prevention of FH-related cardiovascular events. Of the estimated 0.65 million to 1 million patients with FH in the United States, less than 10% carry a diagnosis of FH. Based on registry data, a substantial proportion of patients with FH are receiving no or inadequate lipid-lowering therapy. Statins remain the mainstay of treatment for patients with FH. Lipoprotein apheresis and newly approved lipid-lowering drugs are valuable adjuncts to statin therapy, particularly when the LDL-C–lowering response is suboptimal. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 provide an additional approximately 60% lowering of LDL-C levels and are approved for use in patients with FH. For homozygous FH, 2 new drugs that work independent of the LDL receptor pathway are available: an apolipoprotein B antisense oligonucleotide (mipomersen) and a microsomal triglyceride transfer protein inhibitor (lomitapide). This review attempts to critically examine the available data to provide a summary of the current evidence for managing patients with FH, including screening, diagnosis, treatment, and surveillance.

Familial hypercholesterolemia (FH), a relatively common Mendelian genetic disorder, is associated with markedly elevated low-density lipoprotein cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). In patients with untreated FH, life expectancy is significantly shortened, with sudden death and myocardial infarction (MI) as the principal causes of mortality. Timely and effective lipid-lowering treatment improves the life expectancy of patients with FH. Despite the availability of lipid-lowering drugs, most patients with FH do not achieve an LDL-C level less than 100 mg/dL. Newer drugs for FH are now available, however, long-term safety data are awaited. There is a need to develop systematic approaches to identify patients with FH and to conduct cascade screening of their

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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relatives and to increase awareness and control of FH. A significant amount of literature related to the prevalence, undertreatment, and underdiagnosis of FH has accumulated during the past several years. To provide an update on the current evidence for managing patients with FH, we reviewed original and research articles using PubMed and Google Scholar for the following search terms: *familial hypercholesterolemia, FH, prevalence, awareness, pathophysiology, low-density lipoprotein receptor gene, familial defective apoB-100, autosomal recessive, PCSK9, outcomes, aortic stenosis, atherosclerosis, screening, perception, models of care, assessment, registry, healthcare, guidelines, recommendations, statins, ezetimibe, bile acid sequestrants, niacin, lipoprotein apheresis, mipomersen, lomitapide, PCSK9 inhibitors, liver transplantation*, and *gene therapy*. Relevant articles identified were full-text papers in the English, French, German, and Russian languages. The final reference list includes selected research articles as well as relevant reviews that provide additional references.

AN ILLUSTRATIVE VIGNETTE

A 35-year-old woman is hospitalized with an inferior wall ST-segment elevation MI. Physical examination is remarkable for an early-peaking ejection systolic murmur (grade 2/6) at the left upper sternal border, bruits over the right carotid and subclavian arteries, and yellowish nodules on the tendons of the hands and the Achilles tendon. The lipid profile reveals a total cholesterol level of 338 mg/dL, an LDL-C level of 285 mg/dL, a high-density lipoprotein cholesterol (HDL-C) level of 31 mg/dL (to convert all to mmol/L, multiply by 0.0259), and a triglyceride level of 114 mg/dL (to convert to mmol/L, multiply by 0.0113). Coronary angiography revealed severe triple-vessel disease with right coronary artery occlusion. How should the patient be further evaluated and treated?

HISTORICAL ASPECTS

Familial hypercholesterolemia is a heritable disorder of lipid and lipoprotein metabolism classically transmitted in an autosomal dominant manner and associated with elevated levels of LDL-C. Pathogenic variants in 1 of 3 genes, ie, *LDLR, APOB*, or *PCSK9*, account for most cases. The reason for the relatively high prevalence of genetic variants that lead to FH is not clear, although it is speculated that the variants may have been advantageous from an evolutionary standpoint.[1–3] The first patients with FH were described almost 80 years ago by the Norwegian physician Muller.[4,5] Twenty-five years later, a single-gene codominant inheritance was postulated by Khachadurian[6] based on segregation analysis in Lebanese families. Research relating FH to disorders of LDL-C metabolism by Fredrickson et al[7] and deficiency in a cell surface receptor for LDL by Goldstein and Brown[8] established the molecular basis of the disease. Subsequently, the amino acid sequence of the LDL receptor was determined and the gene was cloned by Russell et al,[9] enabling a catalog of pathogenic variants in the gene.

PATHOGENESIS AND GENETICS

An outline of the molecular basis of FH is presented in Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org). Most of the circulating LDL-C is removed

from the blood by hepatic LDL receptor-mediated endocytosis.[8] Pathogenic variants in *LDLR* lead to impaired LDL receptor function and elevated LDL-C levels. A dominant mode of transmission with a gene-dosage effect explains higher cholesterol levels in patients who are homozygous (hoFH) for a mutant allele than in heterozygotes (heFH). Approximately 2000 *LDLR* genetic variants have been submitted to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk), of which approximately 60% are recognized to be pathogenic. Pathogenic variants in *LDLR* can be broadly categorized as loss-of-function/inactivating/null variants and variants that lead to impaired LDL receptor activity, the former being associated with higher LDL-C levels.[10] Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) lists genes encoding proteins implicated in the regulation of LDL metabolism.

Patients with pathogenic variants in *APOB* and *PCSK9* may have a less severe clinical presentation than those who have pathogenic variants in *LDLR*. Apolipoprotein B100 functions as a ligand that links the LDL particle to the LDL receptor. Of more than 200 *APOB* variants, only a few are known to impair function and are included in genetic testing panels for FH. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that regulates LDL-C levels by targeting LDL receptor for lysosomal degradation. More than 70 variants in *PCSK9* are associated with interindividual differences in LDL-C levels, with gain-of-function mutations resulting in increased clearance of LDL receptors and increased levels of LDL-C. Recently *APOE*, which encodes apolipoprotein E that directs removal of chylomicron and very low-density lipoprotein remnants from the circulation, has been implicated in the pathogenesis of FH.[11–13] Using family-based linkage analysis and whole exome sequencing, Fouchier et al[14] and Braenne et al[15] identified 5 variants in *STAP1*, which has been proposed as the fourth gene causing FH. Affected individuals had a relatively mild FH phenotype.

Homozygous FH results when a patient inherits a pathogenic variant from each of the heterozygous parents. Culprit variants most often occur in *LDLR* and less frequently in 2 different FH-related genes (double or compound heterozygotes). An autosomal recessive form of FH was described in 2001 in families of Sardinian origin carrying variations in *LDLRAP1*.[16] The presentation is somewhat similar to that of hoFH due to mutations in *LDLR*, but ASCVD presents later in life, and there is better response to lipid-lowering drugs.

Elevated plasma LDL-C level is a complex genetic trait, and most cases are polygenic rather than due to a single gene disorder. It is estimated that 1 of 15 patients with severe hypercholesterolemia has clinical diagnosis of heFH (Safarova et al, 2015, unpublished data) and 1 of 50 carry a pathogenic mutation;[17] in the remainder a polygenic cause is invoked. Among patients with the same FH-causing mutation, such aggregative polygenic effects contribute to variability in LDL-C levels and heterogeneity in the clinical presentation.[18,19] In individuals clinically diagnosed as having FH who are mutation negative, whole genome/exome sequencing[20] is being utilized to identify novel monogenic causes.

EPIDEMIOLOGY

Prevalence

Homozygous FH is rare, ie, 1 in 1 million, although recent estimates suggest that the prevalence may be as high as 1 in 300,000.[10,21] Due to a founder effect, the prevalence is higher in certain populations, ie, Lebanese, South African Afrikaners, South African Jews, South African Indians, French Canadians, and Tunisians.[22] The reported prevalence of heFH varies across the globe,[22] with the most commonly cited estimate being 1 in 500.[23–25] One reason for variation in the estimates is that some are based on clinical criteria and others based on genetic testing. A summary of prevalence estimates across the globe is provided in Table 1. In 36,949 National Health and Nutrition Examination Survey (1999–2012) participants, the prevalence of FH was 0.40% (1 in 250), with similar rates in women and men but a higher frequency in white individuals compared with other races/ethnicities.[26] In a 2-year period (2009–2011), the Very Large Database of Lipids investigators identified 0.3% of individuals (1 in 340; 3829 of 1,320,581) meeting the National Lipid Association (NLA)-specified age-based screening LDL-C thresholds for FH.[35] A comprehensive community-based study addressing clinical and genetic heterogeneity of FH in the United States has yet to be reported.

Awareness and Control

In most countries, less than 20% of all estimated prevalent FH cases are diagnosed, and less than 1% of patients with FH are aware of their condition,[23] often not until after the first ASCVD event. Of the estimated 0.65 million to 1 million patients with FH in the United States (US Census; population of 323.4 million), less than 10% carry a diagnosis of FH. A 2011 survey of cardiologists indicated that less than 30% were able to recognize a typical case of FH.[36] In the US national FH registry,[37,38] only 42% of 1295 adult patients with FH were receiving high-intensity statin therapy, and of these, an LDL-C level less than 100 mg/dL was achieved in approximately 25% and an at least 50% reduction in LDL-C levels was seen in 41%.[39] A survey across 24 European countries revealed that 45% of patients with FH with coronary heart disease (CHD) were not receiving a high-intensity statin dose.[40] In Dutch patients with hoFH, an LDL-C level less than 100 mg/dL was not achieved, and a reduction of greater than 50% was noted in only 40%.[10] These data highlight the degree of underdiagnosis and undertreatment of FH worldwide.

At the national level, the FH Foundation, a patient-centered nonprofit organization, advocates proactive identification and treatment of patients diagnosed as having FH and brings together leading US academic centers through the CASCADE (CAscade SCreening for Awareness and DEtection, https://thefhfoundation.org/fh-research/registry/) registry for patients with FH.

CLINICAL PRESENTATION

The cardinal manifestations of FH are significantly elevated LDL-C levels, early-onset ASCVD, and pathognomonic signs of cholesterol deposits under the skin (xanthomas) and in the cornea (corneal arcus).

Hypercholesterolemia

Levels of LDL-C are typically elevated to greater than the 90th percentile for age and sex, whereas HDL-C and triglyceride levels are usually normal or modestly altered. Secondary causes of hypercholesterolemia, such as hepatic, renal, and thyroid dysfunction, should be excluded. Several drugs may result in an artificial increase in LDL-C levels (reviewed elsewhere[41]).

Premature ASCVD

Due to elevated plasma levels of LDL-C from birth, patients with FH are at high risk for ASCVD, in particular MI and sudden cardiac death. The risk of ASCVD in patients with FH is also influenced by traditional risk factors, such as male sex, smoking, obesity, diabetes, hypertension, and low HDL-C levels.[42,43] However, conventional risk stratification algorithms in individuals with FH do not take into account exposure to elevated LDL-C levels from birth and may, therefore, underestimate ASCVD risk. If left untreated, patients with hoFH develop ASCVD and die before age 20 years. In heFH, CHD occurs in early middle age, at approximately 35 years old, if untreated[44]; however, if treated from age 18 years, this threshold shifts toward age 48 years, and treatment from age 10 years postpones CHD development to age 53 years.[45,46] A community-based study in Australia found the odds of having CHD to be 17 to 22 times higher for individuals with FH.[32,47] The prevalence of overt CHD in individuals 45 years and younger with FH ranges from 8% to 19% and is estimated to be 9% if based on the frequency of pathogenic variants in *LDLR*. Nearly 14% of patients with an early-onset acute coronary syndrome have clinical FH.[48] The European Action on Secondary Prevention Through Intervention to Reduce Events (EUROASPIRE) IV study revealed an FH prevalence of 15% in individuals younger than 60 years with a less than 3-year history of an acute coronary event.[40] Men with FH develop CHD before women: nearly 50% of males experience ASCVD by age 50 years, and 30% of females by age 60 years.[22,49] Compared with individuals with normal LDL-C levels, FH is associated with a 5- to 10-fold greater odds of peripheral artery disease.[50,51]

Xanthomas and Arcus

A hallmark of FH is early-onset corneal arcus and xanthomas on the extensor tendons, especially thickening of the Achilles tendon. Corneal arcus occurs as a full or partial grayish-white ring opacity in the periphery of the cornea unilaterally or bilaterally and is not associated with visual impairment. A xanthoma appears as a nodule or bump associated with tendons and varies from no change in color of skin covering the lesion to yellowish-orange to reddish-brown papules. Painless masses grow slowly and can limit the range of motion of the affected joints. Ultrasound of the Achilles tendon can increase the sensitivity of detecting xanthomas by 80% and the specificity by up to 88%.[52] However, up to 10% to 25% of patients with xanthomas do not have an FH-specific pathogenic variant on genetic testing. The reported frequency of xanthomas varies from 33% in patients with mutations in *LDLR* to 19% when mutation is in *APOB*.[53] Tendon xanthomas are also seen in such rare genetic disorders as cerebrotendinous xanthomatosis and sitosterolemia due to mutations in *CYP27* and *ABCG5/ABCG8*, respectively.

EVALUATION

History and Examination

In patients suspected of having FH, history of personal and family occurrence of premature ASCVD must be elicited. Details of previous therapy should be sought, including age at initiation of lipid-lowering therapy, use of novel lipid-lowering agents, and use of lipoprotein apheresis. One should also obtain a history of thyroid, renal, hepatic, or biliary disease as potential causes of hypercholesterolemia. Physical examination should evaluate peripheral pulses, the presence of bruits or aneurysms, xanthomas, and corneal arcus. One should look for signs of aortic valve stenosis, which is relatively common in individuals with high LDL-C and lipoprotein(a) (Lp(a)) levels.[54] In middle-aged patients with heFH, the prevalence of aortic valve calcification and stenosis varies from 30% to 40%,[55,56] in contrast to the prevalence of approximately 0.2% in the general population of adults aged 50 to 60 years.[57]

Clinical Criteria

Various clinical criteria have been proposed to establish a diagnosis of FH. Table 2 lists the criteria for diagnosing hoFH. In practice, 2 sets of validated clinical criteria, ie, the Dutch Lipid Clinic Network (DLCN) and the UK Simon Broome Register based on family and personal clinical history, physical examination, and lipid profile, are widely used to ascertain heFH. In Asian populations, modifications of the aforementioned sets of criteria have been advocated (Tables 3–5). These sets of criteria may miss patients with heFH with a mild phenotype and they are not applicable to the pediatric population.

Genetic Testing

A stepwise genetic testing approach to FH used at Mayo Clinic includes (1) sequencing of *LDLR* supplemented by large deletion/duplication analysis, (2) genotyping of 2 variants in *APOB* (R3500Q and R3500W), and (3) sequencing of *PCSK9*. Failure to identify a distinct variant in *LDLR*, *APOB* or *PCSK9* in a patient with a presentation suggestive of FH does not exclude the diagnosis. Molecular genetic analysis can be expanded to encompass *LDLRAP1* and *APOE*. With advances in next-generation sequencing additional novel genes for FH are likely to be identified. In patients with a clinical diagnosis of FH, the mutation detection rate varies from 50%[63] to 90% depending on the clinical criteria used and the genetic testing protocol.[23] In one study, the mutation detection rates in patients clinically ascertained as having definite, probable, and possible FH according to the DLCN criteria were 63%, 35%, and 22%, respectively.[53]

There is overlap in the distributions of LDL-C levels in mutation-positive and mutation-negative relatives of patients with heFH, suggesting that genotyping may be more reliable than LDL-C levels for screening.[58] A family pedigree with genetic testing extended to second- and third-degree relatives is a valuable tool to assess penetrance and identify affected individuals. Before testing, genetic counseling is helpful in addressing potentially sensitive family and ethical issues.[64] There is little evidence for stigmatization; however, education of health professionals and the public may be useful to avoid discrimination of those testing positive.[65,66] A centralized genetic screening service with guidelines for reimbursement by insurers can improve rates of genetic testing and cascade screening.[67,68]

Efforts are ongoing to develop curricula for genetic counselors and lipidologists about the genetics and genomics of FH.[69]

Advanced Lipid Testing

Often, Lp(a) levels are elevated in patients with FH[70] and should be measured. The mechanism for increased Lp(a) levels is not clear, although differences in Lp(a) levels in patients with FH may be related to the type of *LDLR* mutation.[71] A gene dosage effect is present because Lp(a) levels are higher in patients with hoFH than in those with heFH.[72] The incremental utility of advanced lipoprotein profiling, including measurement of apolipoprotein B (apoB) and the density of lipoprotein particles, is unclear. Direct LDL-C measurements may be useful in patients with hypertriglyceridemia (triglyceride level ≥200 mg/dL[73]), low calculated LDL-C levels in treated individuals (<70 mg/dL[74]) and in the nonfasting state.

Noninvasive imaging in the form of carotid ultrasound[75] or computed tomography for coronary calcification[76,77] may be helpful in assessing the presence and extent of atherosclerotic burden in FH. Measurement of carotid intima-media thickness has been used to track the effect of lipid-lowering medications through childhood and into adulthood.[78] However, monitoring response to lipid-lowering treatment in asymptomatic individuals is not recommended by the NLA guidelines.[79] Patients with FH, in particular those with elevated Lp(a) levels and a severe phenotype (defined as hoFH or heFH with an untreated LDL-C level >310 mg/dL), should be screened for valvular and supravalvular aortic stenosis using auscultation and echocardiography. In patients with exertional leg discomfort or diminished peripheral pulses, ankle brachial indexes should be measured. There is no consensus on screening for myocardial ischemia in patients with asymptomatic FH. Stress testing could be considered in patients with asymptomatic heFH (1) with late initiation of lipid-lowering treatment, (2) with a family history of early ASCVD, and (3) who intend to participate in competitive sports.[58] Patients who have undergone revascularization should be monitored for stent or graft patency.

SCREENING

Familial hypercholesterolemia is one of a few genetic diseases that meet the World Health Organization criteria for population-based screening programs aimed at early disease detection and treatment. The Centers for Disease Control and Prevention classifies FH as a tier 1 category, representing “genomic and family health history applications which have a base of synthesized evidence supporting implementation into practice.”[80] Three screening approaches have been proposed for FH: targeted (opportunistic), universal, and cascade. Targeted identification of FH implies screening of patients with family members who have premature ASCVD, tendon xanthomas, early corneal arcus, or elevated LDL-C levels. In adults with ASCVD, the American College of Cardiology/American Heart Association (ACC/AHA) guideline expert panel[81] suggests family screening for FH if the untreated LDL-C level is 190 mg/dL or greater (correction factors can be used to estimate the pretreated LDL-C levels of patients taking lipid-lowering medication[59]). However, targeted screening is subject to certain caveats. For example, using family history of premature

ASCVD as the entry point for screening fails to identify a high proportion of individuals with lipid abnormalities,[82] missing 30% to 60% of children with lipid disorders.[83]

The NLA guidelines recommend universal lipid screening[41] and eliciting family history of hypercholesterolemia and CHD in individuals with elevated levels.[84] Measuring plasma LDL-C levels in children and adolescents, in particular in children aged 1 to 9 years (before a physiologic 10%–20% decrease in LDL-C levels during puberty) had better discrimination than at other ages.[85,86] In reality, only 10% of children and adolescents aged 3 to 19 years have lipid testing.[87] A model of child-parent screening with immunization and cholesterol measurement at age 1 or 2 years followed by blood collection in parents of children with high cholesterol levels was shown to be feasible and effective.[88] Alert systems in clinical biochemistry laboratories reporting LDL-C–specific thresholds for FH have been shown to be effective.[45,89] Universal screening followed by cascade screening through genotyping has been considered the most cost-effective means.[90–94] In the US health care system, the optimal screening strategy has yet to be established.

TREATMENT

The management of patients with FH is summarized in Figure 1. Numerous imaging studies have confirmed an increased atherosclerotic burden in FH, which is significantly reduced after initiation of lipid-lowering therapy. Data on the effects of FH treatment are mainly derived from registry-based cohorts, cross-sectional studies, and post hoc analyses of clinical trials. The introduction of statins in the Simon Broome Register cohort of patients with heFH reduced CHD mortality by 48% in the primary prevention setting and by 25% in the secondary prevention setting.[93] Timely initiation of statin treatment can lower the risk of MI in patients with FH to that seen in the general population.[95] In a retrospective analysis covering a 50-year surveillance period of patients with hoFH, lower on-treatment cholesterol levels were associated with significantly lower rates of ASCVD, including CHD (37% vs 85%), myocardial revascularization procedures, and aortic stenosis (33% vs 77%).[96] Starting lipid-lowering therapy, including statins, lipoprotein apheresis, or surgery, at an early age is associated with better survival.

High-intensity lipid-lowering therapy, including maximum tolerable dose of a statin, is the cornerstone of management of patients with FH as well as patients with severe hypercholesterolemia (defined as an untreated fasting LDL-C level ≥190 mg/dL in adults [>20 years old] and ≥160 mg/dL in children and adolescents).[23,60,64,79,81,84,94,97,98,99] Treatment should be started as soon as the diagnosis has been made and should be continued throughout the lifetime. Figure 2 depicts LDL-receptor–mediated regulation of LDL-C levels and drugs that affect various steps in this pathway. The effects of novel drugs and conventional lipid-lowering strategies on lipid and lipoprotein levels are summarized in Table 6.

Lipid-Lowering Modalities

Response to statins varies widely in patients with FH and depends on several factors, including residual LDL receptor activity associated with each particular pathogenic variant. On average, in patients with heFH, LDL-C levels can be halved with statin therapy (Figure

2); thereafter, the 6% rule for doubling the dose of statins comes into effect. In patients with hoFH, statins reduce cholesterol synthesis and increase functional activity of residual LDL receptors. Treatment with high doses of atorvastatin and rosuvastatin reduced LDL-C levels up to 20% in hoFH.[108] In heFH, a combination of simvastatin with ezetimibe reduced LDL-C levels by 57% independent of the type of *LDLR* mutation.[100] When LDL-C targets cannot be reached by statin therapy alone, or in the case of statin intolerance, other drug treatments or combinations are recommended (Figure 1).

Although older studies showed reduction in CHD mortality with niacin monotherapy,[109] there are no randomized clinical trials testing niacin in patients with FH. The HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events)[110] found an increased incidence of diabetes and bleeding, leading to termination of another study evaluating extended-release niacin/laropiprant (Merck Sharp & Dohme Corp.) in adolescents with heFH (ClinicalTrials.gov Identifier: NCT01583647).

The bile acid sequestrants (cholestyramine, colestipol, and colesevelam) bind bile acids and thereby up-regulate LDL receptors and increase the rate of LDL-C clearance. There is more than 45 years' experience of using these drugs in the treatment of adults and children with heFH both as monotherapy and in combination.[103,111,112] The drugs should be avoided in patients with bowel or biliary obstruction.

Monoclonal antibodies targeting PCSK9 prevent binding of PCSK9 to the LDL receptor, therefore limiting LDL receptor degradation in lysosomes and promoting receptor recycling to the cell surface. Such therapy is a rational adjunct to statins, which up-regulate PCSK9. Data demonstrating the safety and efficacy of PCSK9 inhibitors (Table 6) led to the recent Food and Drug Administration (FDA) approval of alirocumab[113] (Praluent; Sanofi US and Regeneron Pharmaceuticals Inc.) and evolocumab[114] (Repatha; Amgen Inc) for the treatment of patients with heFH receiving maximally tolerated lipid-lowering therapy. Based on the results of TESLA (Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities) performed in 50 individuals with hoFH for 3 months, evolocumab 420 mg once monthly has been additionally approved for use in patients with hoFH with at least 2% of functioning LDL receptors.[115] In a meta-analysis of 24 trials, A decreased rate of ASCVD events was observed without an increase in adverse events, including events leading to premature drug discontinuation.[116] Although accompanied by a remarkable degree of LDL-C-lowering (w60%), the effect of PCSK9 antibodies on cardiovascular and all-cause mortality will be known after the completion of several ongoing trials.

Two new drug classes have been developed that work independent of the LDL receptor pathway. Mipomersen (Kynamro; Genzyme Corp) represents an apoB antisense oligonucleotide drug class that binds to *APOB* mRNA and inhibits subsequent synthesis of the protein, therefore decreasing the secretion of apoB-containing lipoproteins. Mipomersen is approved by the FDA as a once-a-week subcutaneous injection for patients with hoFH 12 years and older based on a 6-month phase 3 trial randomizing patients with hoFH receiving maximally tolerated therapy, but not lipoprotein apheresis, to receive mipomersen (n =34) and placebo(n =17).[117] Lomitapide (Juxtapid; Aegerion Pharmaceuticals Inc.) is indicated as an adjunct to lipid-lowering treatment in patients with hoFH 18 years and older. The drug

reduces the rate of secretion of apoB-containing lipoproteins by inhibiting an endoplasmic reticulum–localized microsomal triglyceride transfer protein, which participates in assembly of chylomicrons in the enterocytes and very low-density lipoprotein particles in the hepatocytes. In 29 patients with hoFH, lomitapide therapy led to a dose-dependent decrease in LDL-C and triglyceride levels, with additive efficacy when coadministered with other lipid-lowering drugs.[118] Both drugs have not yet been shown to reduce ASCVD events, are associated with risk of hepatotoxicity due to fat accumulation, and are included in the FDA's Risk Evaluation and Mitigation Strategies program.

There is almost half a century of treatment experience with therapeutic apheresis in patients with FH[119] demonstrating high efficacy and safety of extracorporeal elimination of atherogenic particles. The FDA-approved criteria for apheresis in patients receiving maximally tolerated lipid-lowering therapy are (1) an LDL-C level greater than 500 mg/dL in patients with hoFH, (2) an LDL-C level greater than 300 mg/dL in patients with heFH, and (3) an LDL-C level greater than 200 mg/dL in patients with heFH with ASCVD. The goal of treatment is to reduce the time-averaged LDL-C level by more than 60% from baseline.[120]

Surgical Intervention

Portacaval shunting and liver transplant[121] in patients with FH rapidly decrease LDL-C levels by approximately 25% and 80%, respectively. Both interventions are major surgeries with significant rates of complications and should be restricted to patients with severe FH who are not candidates for or who have no access to more efficacious therapies.

Treatment of Adults

Patients with FH should be counseled on lifestyle changes, including reduced intake of saturated and trans fats and cholesterol; use of soluble fiber, plant stanol, or sterol esters; limitation of alcohol consumption; smoking cessation and regular physical activity[84]; and blood pressure and glucose control. Patients should be assessed for compliance with lifestyle measures and drug therapy and to assess for the onset of or change in symptoms. To improve life expectancy, high-intensity lipid-lowering therapy, including maximum tolerable dose of statin, should be administered. Figure 1 outlines a stepwise treatment algorithm for FH. In adults, statin therapy should be initiated as soon as the diagnosis of FH is made. The 2013 ACC/AHA guidelines do not mandate specific targets for LDL-C levels but consider a decrease by more than 50% from baseline to be a therapeutic success even if the level remains greater than 100 mg/dL.[81] However, NLA guidelines advocate levels less than 100 mg/dL in all patients with FH and less than 70 mg/dL in those who have ASCVD or a CHD equivalent.[79] Results of trials evaluating the effects of new therapies on ASCVD outcomes are expected in the near future and may lead to a revision of the guidelines. Patients with ASCVD are at high risk for recurrent events, and current management of these patients focuses on the use of a combination of potent statins and ezetimibe to achieve at least a 50% reduction.

Treatment of Children and Adolescents

Statins are the cornerstone of treatment in children with FH and do not seem to affect growth, maturation, and educational levels.[78] Guidelines advocate initiation of statins as early as 8 (pravastatin) and 10 (simvastatin, lovastatin, atorvastatin, fluvastatin, and rosuvastatin) years of age.[90,122] Pitavastatin, a newer lipophilic statin with fewer drug-drug interactions via cytochrome competition than other statins,[123] has been extensively studied in children (10–15 years old), in particular of Asian descent.[124] The statin dose should be up-titrated according to the LDL-lowering response and tolerance. The goal of LDL-lowering therapy is to decrease the LDL-C level to less than the 95th percentile (≤130 mg/dL)[90] or greater than 50% from pretreatment levels.[122] In a 10-year follow-up of a placebo-controlled study (median patient age, 13 years; 60% younger than 14 years) with pravastatin (20–40 mg) there was a direct association between age at statin initiation and carotid intima-media thickness.[125] Indeed, early treatment initiation should be considered in severe cases. Although data on the safety (during 3 months) and efficacy of ezetimibe monotherapy in children 6 to 10 years of age diagnosed as having heFH exist,[126] ezetimibe is not approved for use in children younger than 10 years. The only bile acid sequestrant approved for use in children with heFH is colesevelam,[127] with the caveat that it has not been studied in children younger than 10 years or in premenarchal girls. Performing lipoprotein apheresis in children is technically challenging but can be a lifesaving procedure[128] in patients with hoFH and undetectable LDL receptor activity.[129,130] Initiation of apheresis has been reported at ages as early as 2[128] and 3 years.[131]

Treatment of Pregnant Women

Women with FH who desire to become pregnant should have preconceptional assessment and frequent antenatal follow-up.[132] Statins should be discontinued 3 months before planned conception and should not be used during pregnancy and lactation. During pregnancy, LDL-C levels can rise to extreme levels,[133] increasing risk for compromised uteroplacental perfusion with subsequent placental infarctions and insufficiency. The only lipid-lowering drug currently assigned to category B by the FDA is colesevelam.[133] A case series level of evidence suggests the feasibility of lipoprotein apheresis in pregnant women with FH as well as its safety for both maternal and fetal health. In treated patients, histologic examination of the placenta and the umbilical vessels revealed no atherosclerotic changes.[134] Studies of outcomes of pregnancy in women with FH and in newborns to mothers with FH are needed.[135]

FUTURE DIRECTIONS

There is a need for rapid and automated case identification, supplemented by clinical decision support systems to assist health care providers in managing patients and families with FH. The introduction of FH-specific codes in practice, ie, codes for heFH, hoFH, and family history of FH, in the *International Classification of Diseases, 10th Revision* may help increase detection, awareness, and control of FH. Improving the knowledge and skills of providers in the realm of genetics, addressing variations in reimbursement for genetic testing, and developing electronic health record–based tools to disclose genetic testing results will facilitate cascade screening for FH. Studies that elucidate cost-effectiveness and

logistics of screening can inform systems for the detection and surveillance of patients with FH. There is a need for greater understanding of sequence variations in FH-related genes, including functional assays of variants of uncertain significance.

Patients with FH and their family members should be treated by a multidisciplinary team. At Mayo Clinic, the Cardiovascular Genomics Clinic staffed by a cardiovascular specialist, a genetic counselor and a medical geneticist, provides specialized evaluation and genetic testing and facilitates cascade screening of family members.

RECOMMENDATIONS

The patient described in the vignette developed MI at an early age in the setting of a marked increase in the levels of atherogenic lipoproteins, including an Lp(a) level of 190 mg/dL. Based on a family and personal history of early-onset CHD, tendon xanthomas, and elevated LDL-C levels, the patient had a DLCN score of 14, which indicates definite FH. Given the presence of a systolic murmur, echocardiography was performed and showed mild aortic valve stenosis. She should be started on a high-intensity statin and followed closely for the effect of CHD and aortic valve disease on her functional capacity and quality of life. Lower LDL-C levels (<70 mg/dL) are desirable in this patient and can be achieved with combination lipid-lowering therapy. Genetic testing to identify the causal variant followed by testing this variant in family members should be encouraged.

In summary, patients with FH are at high risk for adverse cardiovascular events. Those with definite and probable FH should undergo genetic testing and genetic counseling. Management involves the treatment of CHD risk factors and intensive lipid-lowering therapy starting early in life. Patients should be observed for compliance with drug and lifestyle changes as well as signs and symptoms suggestive of ASCVD or aortic valve disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ACC/AHA	American College of Cardiology/American Heart Association
ApoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
CHD	coronary heart disease

DLCN	Dutch Lipid Clinic Network
FAMCAT	an FH prediction model
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
HDL-C	high-density lipoprotein cholesterol
heFH	heterozygous FH
hoFH	homozygous FH
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MI	myocardial infarction
MTP	microsomal triglyceride transfer protein
NLA	National Lipid Association
NPC1L1	Niemann-Pick C1-like 1 protein (located in the plasma membrane on the luminal side of the enterocyte in the small intestine)
PCSK9	proprotein convertase subtilisin/kexin type 9
SC	subcutaneous
TG	triglycerides

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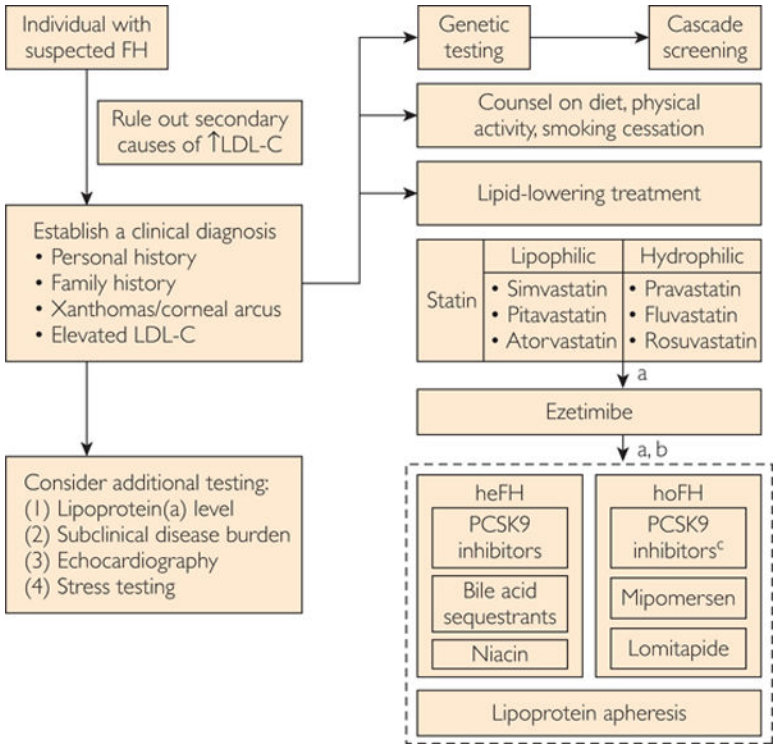

Figure 1.

Evaluation and treatment of patients with familial hypercholesterolemia (FH). [a]Not at goal or intolerant. [b]In patients with FH in whom maximally tolerated lipid-lowering therapy, including a statin and ezetimibe, does not lead to achievement of target low-density lipoprotein cholesterol (LDL-C) levels. [c]Currently, only evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, is approved for clinical use in homozygous FH. heFH = heterozygous FH; hoFH = homozygous FH.

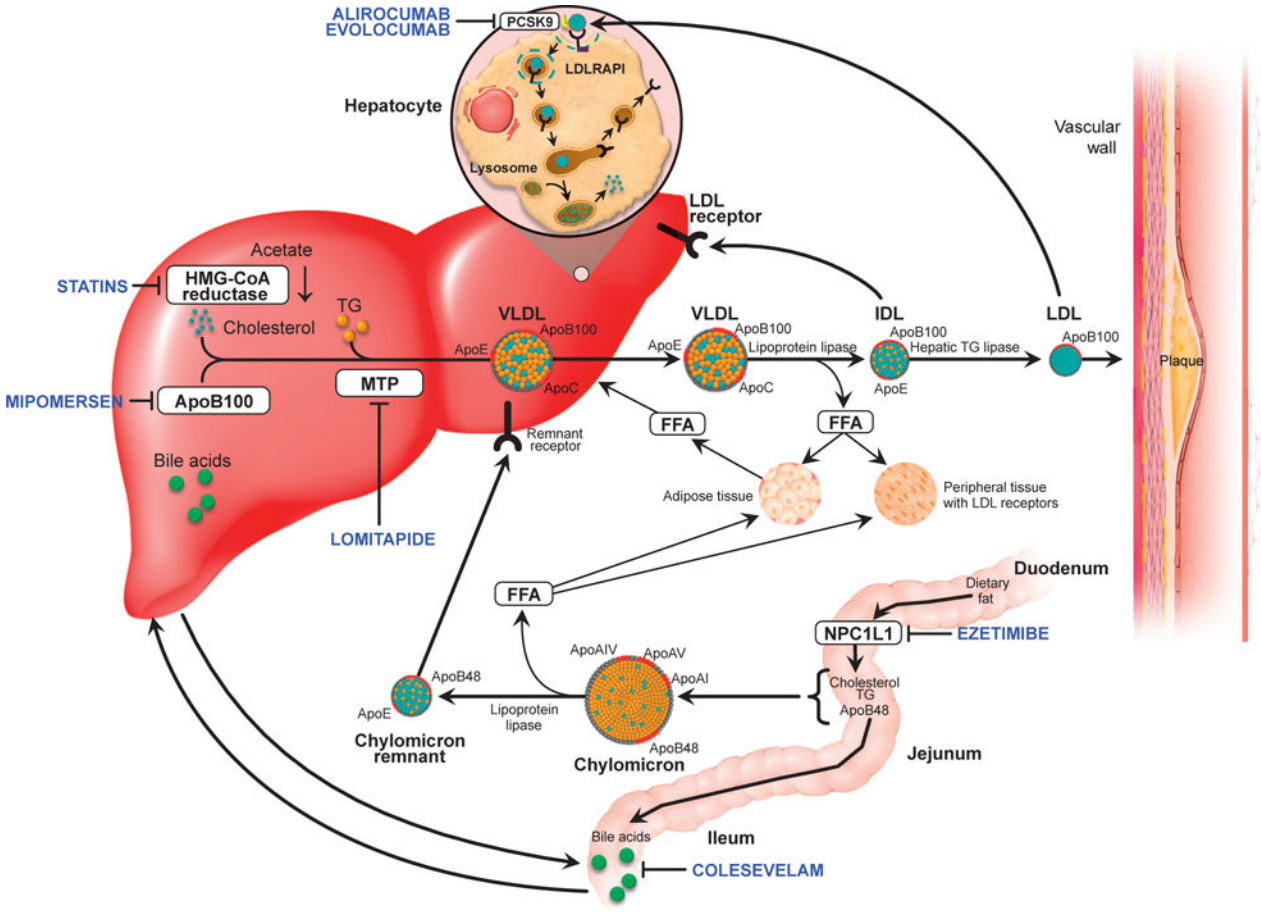

Figure 2.

Low-density lipoprotein (LDL) receptor–mediated regulation of LDL cholesterol levels and drugs that affect various steps in these pathways. Apo = apolipoprotein; FFA = free fatty acids; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IDL = intermediate-density lipoprotein; MTP = microsomal triglyceride transfer protein; NPC1L1 = Niemann-Pick C1-like 1; PCSK9 = proprotein convertase subtilisin/kexin type 9; TG = triglyceride; VLDL = very low-density cholesterol.

Table 1

Summary of Recently Reported Rates of Prevalence of Heterozygous FH[a,b]

Country	United States		The Netherlands	Denmark		Finland		China	Australia		United Kingdom		Russia
Frequency[c]	1:250[26]	1:310[d]	1:319[e]	1:200[f]	1:650[f]	1:600[g]	1:150[g]	1:357[h]	1:353[i]	1:229[j]	1:375[k]	1:500[l]	1:300[m]
Prevalence, %	0.33	0.32	0.31	0.73	0.15	0.16	0.67	0.28	0.28	0.44	0.27	0.20	0.3
Cohort (×1000)	59.4	131.0	104.7	69.0	13.8	28.5		0.93	10.9	0.73	280.0	2228.6	18
Diagnosis	DLCN criteria		Genetic testing	DLCN criteria	Genetic testing (*LDLR, APOB*)	Genetic testing (*LDLR*)	LDL-C >250 mg/dL	DLCN criteria	DLCN criteria		DLCN criteria	FAMCAT	DLCN criteria

[a] DLCN = Dutch Lipid Clinic Network; FAMCAT = an FH prediction model[27]; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

[b] SI conversion factor: To convert LDL-C to mmol/L, multiply by 0.0259.

[c] In studies not using genetic testing, the prevalence of FH may be overestimated.

[d] Safarova MS et al, 2015, unpublished data.

[e] Genetic screening of 104,682 individuals identified 178 (0.17%) carriers of 2 biallelic mutations in *LDLR* or *APOB*. The prevalence of heterozygous FH was estimated assuming Hardy-Weinberg equilibrium, in which p^2 accounts for homozygotes, 2pq for heterozygotes, and q^2 represents unaffected individuals, with a simplified estimation of p + q = 1.

[f] Genetic testing results were available in only 20% of the definite/probable FH cases.[28]

[g] Finnish *LDLR* mutation data set.[29]

[h] In the Jiangsu Nutrition Study, the prevalence of FH based on the modified DLCN criteria among those older than 50 years was as high as 0.65%.[30]

[i] Data on the prevalence of clinically defined definite/probable FH were collected in 1999 and 2000 in an unselected Australian population.[31]

[j] Study cohort was randomly sampled from the Australian community undergoing cardiovascular risk evaluation on a voluntary basis from 2005 to 2012.[32] No genetic testing was performed.[32]

[k] Interim analysis of general practices in the United Kingdom ascertaining FH based on the DLCN criteria.[33]

[l] Assessment of data from the UK Clinical Practice Research Datalink over 14 years.[27]

[m] A randomly selected cohort from the Russian population assessed for the DLCN criteria.[34]

Table 2

Criteria for Diagnosing Homozygous FH[a,b]

Plasma LDL-C levels[c]: ≥500 mg/dL or >300 mg/dL with lipid-lowering treatment21 and • Family history of hypercholesterolemia: LDL-C level >95th percentile for age and sex in both parents or • Onset of tendon or cutaneous xanthomas at age <10 y
Plasma LDL-C levels ≥400 mg/dL[58] and • Aortic valve disease or • Onset of tendon or cutaneous xanthomas at age <20 y
Biallelic mutation in FH-related genes, ie, *LDLR, APOB, PCSK9*, or *LDLRAP1*

[a] FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

[b] SI conversion factor: To convert LDL-C to mmol/L, multiply by 0.0259.

[c] A caveat to be considered when only cholesterol levels are analyzed: In the Dutch population of homozygotes, almost half were found to have LDL-C levels less than 500 mg/dL, and approximately 80% had LDL-C levels less than 300 mg/dL with lipid-lowering treatment,[10] therefore not meeting the clinical criteria.

Table 3

Dutch Lipid Clinic Network Clinical Criteria for Diagnosing Heterozygous FH[a–c]

Criteria	Points[d]
Family history	
A first-degree relative (parent, offspring, or sibling of the patient) aged 18–55 y, women 18–60 y with	
coronary or vascular disease *or*	1
LDL-C level >95th percentile for age and sex	1
Children aged <18 y with LDL-C level >95th percentile for age and sex *or*	2
A first-degree relative with tendon xanthomas or arcus cornealis	2
Personal history of premature ASCVD	
Coronary heart disease	2
Cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthomas	6
Arcus cornealis at age <45 y	4
Plasma levels of LDL-C (mg/dL)	
>325	8
251–325	5
191–250	3
155–190	1
Molecular genetic testing	
Pathogenic variants in *LDLR, APOB, PCSK9*	8

[a] ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; FH = familial hypercholesterolemia.

[b] SI conversion factor: To convert LDL-C to mmol/L, multiply by 0.0259.

[c] In the Chinese population, modified Dutch Lipid Clinic Network criteria have been proposed: (1) family history of premature CHD or vascular disease manifesting before age 60 years in first-degree relatives, (2) personal history of premature CHD or cerebrovascular disease documented in men younger than 55 years and women younger than 65 years, and (3) corresponding thresholds for LDL-C as follows: greater than 230 mg/dL, 190 to 230 mg/dL, 135 to 189 mg/dL, and 100 to 130 mg/dL. The Welsh FH criteria weight the Dutch Lipid Clinic Network score depending on age at CHD onset in the index case, his or her first- and second-degree relatives, and the levels of triglycerides, deducting 2, 3, and 4 points, if triglyceride levels are in the range of 220 to 300, 310 to 434, and greater than 440 mg/dL, respectively.[59]

[d] The highest applicable score should be chosen in each diagnostic group. Definite heterozygous FH is considered present if the total score is greater than 8 points, probable FH if the score is 6 to 8 points, and possible FH if the score is 3 to 5 points; if the score is 0 to 2 points, FH is unlikely.

Table 4

British Simon Broome Register Criteria[a–d]

Plasma levels (mg/dL): • Total cholesterol >290 (adult) or >260 (child aged <16 y) or • LDL-C >190 (adult) or >155 (child aged <16 y)	
Tendon xanthomas in the patient or any of the patient's first- (parent, offspring, or sibling) or second-degree (grandparent, grandchild, nephew, niece or half-sibling) relatives	Family history of myocardial infarction: • In a first-degree relative before age 60 y • In a second-degree relative before age 50 y
Molecular genetic testing: pathogenic variant in *LDLR, APOB, PCSK9*	Family history in any first- or second-degree relative of plasma total cholesterol level >290 mg/dL in an adult or >260 mg/dL in a child
Definite HeFH	**Probable HeFH**

[a] heFH = heterozygous FH.

[b] SI conversion factor: To convert total cholesterol and LDL-C to mmol/L, multiply by 0.0259.

[c] Clinical criteria adopted in the Japanese population differ mainly in a lower bar for the LDL-C levels and a different cutoff for defining early-onset CHD in women. These criteria for the diagnosis of heFH in patients 15 years and older include (1) pretreatment LDL-C levels of at least 180 mg/dL, (2) tendon xanthomas and/or Achilles tendon thickening (≥9 mm), (3) family history of FH or premature CHD (in males and females <55 and <65 years old, respectively) in first- and second-degree relatives.[60]

[d] A diagnosis of FH is based on a combination of clinical criteria with biochemical results (obligatory), except when there is a positive genetic test.

Table 5

US Make Early Diagnosis to Prevent Early Deaths (MEDPED)[a,b]

	Plasma LDL-C (mg/dL)			
	Degree of relatedness			
Age group	First	Second	Third	General population
<20	155	165	170	200
20–29	170	180	185	220
30–39	190	200	210	240
40+	205	215	225	260

[a] Diagnostic accuracy of using MEDPED[61] LDL-C thresholds developed and validated in the US population increases when one family member has a molecular diagnosis of FH compared to screening in the general population. In relatives of patients with the heterozygous form, FH is diagnosed if LDL-C level exceeds these cutoff points, with 98% specificity and 88%, 85%, and 81% sensitivity for the first-, second-, and third-degree relatives. If there is no diagnosis of FH in the family, then using the LDL-C threshold for the general population will detect heterozygous FH with 98% specificity and 54% sensitivity.

[b] Compared with the gold standard, MEDPED criteria adjusted for age and sex in first-degree relatives demonstrated relatively low sensitivity,[62] emphasizing the role of DNA-based diagnostic tests for efficient cascade testing.

Table 6

Lipid-Lowering Modalities in Patients With FH[a,b]

	Mechanism	Use	Route	Form	LDL-C, Δ%	Lp(a), Δ%	HDL-C, Δ%	TG, Δ%
Ezetimibe[c]	Inhibits NPCILI protein	Daily 10 mg	Oral	HeFH HoFH	−17 to −25 −5 to −14	−10 to −20	0 to 5	−7 to −10
Niacin	Multilocus	Daily 1.5–2 g	Oral	HeFH	−15 to −20	−20 to −30	22 to 30	−29 to −40
Bile acid séquestrants	Bind bile acids and salts	Daily	Oral	HeFH HoFH	−5 to −28 0 to −10	2 to 10	0 to 3	0 to 10
Alirocumab[d,e]	Monoclonal antibody to PCSK9	Biweekly 75–150 mg	SC	HeFH	−63 to −45	−30 to −25	6 to 9	−30 to −25
Evolocumab[d,e]	Monoclonal antibody to PCSK9	Biweekly 140 mg, monthly 420 mg Monthly 420 mg	SC SC	HeFH HoFH	−65 to −50 −32 to −15	−28 to −17 −18 to −1	2 to 11 −2 to 10	−21 to 0 −11 to 8
Mipomersen[e,f]	Antisense oligonucleotide to ApoB	200 mg/160 mg (<50 kg) weekly	SC	HoFH	−36 to −18	−39 to −21	3 to 27	−36 to −4
Lomitapide[e,g]	MTP inhibitor	10–60 mg	Oral	HoFH	−52 to −24	−17 to 1	−13 to 3	−54 to −8
Lipoprotein apheresis[h]	Immunoadsorption of ApoB-containing particles	Biweekly	—	HeFH HoFH	−82 to −54	−72 to −51	−27 to −7	−34 to −49

[a] ApoB = apolipoprotein B; FDA = Food and Drug Administration; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; heFH = heterozygous FH; hoFH = homozygous FH; LDL = low-density lipoprotein cholesterol, Lp(a) = lipoprotein(a); MTP = microsomal triglyceride transfer protein; NPC1L1 = Niemann-Pick C1-like 1 protein (located in the plasma membrane on the luminal side of the enterocyte in the small intestine); PCSK9 = proprotein convertase subtilisin/kexin type 9; SC = subcutaneous; TG = triglyceride; Δ% = percentage change from baseline.

[b] Lipid levels are presented as minimal and maximal ranges based on review of original investigations, systematic analyses, meta-analyses, and review articles.[100–105]

[c] The net LDL-C reduction due to coadministration of ezetimibe varies between −39% and −5%, with the best response seen in carriers of an R174H variant in *NPC1L1*, which is associated with high cholesterol absorption.[100] A between-group difference of 17% was observed in a randomized 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in 720 patients with FH.[106] No difference in adverse events related to treatment was found.

[d] The HAUSER-RCT assessing the efficacy, safety, and tolerability of PCSK9 inhibition in 150 pediatric patients (aged 10–17 years) with heFH is anticipated to be completed in 2017 (NCT02392559). In ODYSSEY ESCAPE (NCT02326220), alirocumab will be tested in 63 adults with FH undergoing lipoprotein apheresis. The currently ongoing TAUSSIG (NCT01624142) evaluating long-term use (during years 2012–2020) of PCSK9 inhibitors in patients with severe FH will further assess the tolerability and safety of this drug class. Clinical trials to test the effects of PCSK9 monoclonal antibodies on ASCVD are under way (ODYSSEY OUTCOMES, NCT01663402; FOURIER, NCT01764633) and expected to be reported starting 2018.

[e] Genotyping to determine the efficacy of treatment could be mandated in the future, if further analysis shows its association with the drug response.

[f] The use of mipomersen is associated with hepatic steatosis (similar to that in patients with familial hypobetalipoproteinemia) and increased levels of liver transaminases.[107] A long-term safety study with enhanced pharmacovigilance program monitoring reports of malignancy, immune-mediated reactions, and hepatic abnormalities in treated patients is under way (NCT00694109). Also, safety data from an open-label extension study with 300 patients with FH are awaited (FOCUS FH study, NCT01475825).

[g] Adverse gastrointestinal effects are reduced with a low-fat diet.

[h] Regimen could be tailored to each patient depending on the rates of cholesterol synthesis and catabolism.