# Management of Familial Hypercholesterolemia: A Review of the Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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## SUMMARY

Familial hypercholesterolemia (FH) is a genetic disorder of lipid metabolism that is characterized by a significant elevation in levels of low-density lipoprotein cholesterol (LDL-C), and patients are at very high risk for premature coronary heart disease (CHD). The etiology of FH includes known mutations in the gene of the LDL receptor, *LDLR*; the gene of apolipoprotein B, *apo B*; and the proprotein convertase subtilisin/kexin type 9 gene, *PCSK9*. The National Lipid Association Expert Panel on Familial Hypercholesterolemia has provided recommendations for the screening and treatment of patients with FH. Early identification and aggressive treatment of FH in individual patients, as well as screening of all first-degree relatives, are recommended to minimize the risk for premature CHD. Similar to patients with conventional hypercholesterolemia, patients with FH should receive statins as initial treatment, but patients with FH may require higher doses of statins, more potent statins, statin-based combination therapy, or adjunctive therapies. Patients with FH who have additional risk factors for, or existing, cardiovascular disease or those with an inadequate response to initial statin therapy should have access to higher doses of the most efficacious statins; statins used in combination with other LDL-C–lowering agents should also be supported by formularies; additional treatments, such as LDL-C apheresis or novel therapies, may also be required to achieve acceptable LDL-C levels. New treatment approaches include mipomersen, which was approved by the FDA in January 2013. Mipomersen is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis (called an antisense inhibitor) indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol (non-HDL-C) levels in patients with homozygous FH (HoFH). The microsomal transfer protein lomitapide has also received FDA approval for use only in patients with HoFH. Other novel treatments currently in development include *PCSK9* inhibitors. Therapies such as apheresis are likely more expensive than simple therapy with a statin but may be needed to achieve long-term reductions in complications from nonfatal and fatal cardiovascular events and hospitalizations related to myocardial infarction, cardiac revascularization, and stroke in FH patients. The cost-effectiveness of this more aggressive therapy has not been determined and should be studied. Utilization of published guidelines and the recommendations from the National Lipid Association will help to optimize the management of patients with FH.

Individuals with familial hypercholesterolemia (FH) are at significantly increased risk for premature cardiovascular disease (CVD). Patients with FH generally have significantly higher levels of low-density lipoprotein cholesterol (LDL-C) than most patients with severe hyperlipidemia. Patients with FH older than 30 years of age often have an LDL-C level of 250 milligrams per deciliter (mg/dL) or higher; patients between 20 and 29 years of age often have an LDL-C level of 220 mg/dL or higher; and those younger than 20 often have an LDL-C level of 190 mg/dL or higher.[1] Patients with FH may have thickening of the tendons called tendon xanthomas. Because FH is primarily an autosomal dominant disorder, family members of a person with FH may manifest a bimodal distribution of LDL-C.[1] FH is a disorder of LDL-C metabolism and may be the most common serious genetic disorder, with an estimated 620,000 individuals affected in the United States.[1,2] Heterozygous FH (HeFH) is the most common form of the disease (prevalence of approximately 1 in 300 to 500 persons worldwide and as high as 1 in 100 persons in some populations), with the majority of inheritance through an autosomal-dominant mechanism.[1-4] Homozygous FH (HoFH) is a very rare form of the disease (prevalence of 1 in 1 million persons). Some populations, such as French Canadians, Ashkenazi Jews, Lebanese, and Dutch Afrikaners, are at a higher risk for FH owing to an increased prevalence of HeFH-associated mutations in the LDL receptor gene, *LDLR*, in these founder populations.[1,5-8]

FH is characterized by severe hypercholesterolemia that results in premature CVD. Individuals with FH are at increased risk for cardiac events such as premature myocardial infarction and early death from premature coronary heart disease (CHD) especially in patients with severe forms of the disease if left untreated.[2,9,10] HeFH is characterized by 1 normally functioning gene and is less severe and more responsive to treatment such as statins than HoFH. The mean age for the onset of CVD in men with HeFH is 42 to 46 years and in women, onset is 51 to 52 years.[11,12] HoFH is a severe, aggressive form of FH, which is often unresponsive to traditional treatment for hypercholesterolemia owing to the patient's lack of functional LDL receptors.[10,12] In patients with HoFH, the mean age at the time of diagnosis of CVD is 20 years.[9]

More than 85% of FH cases are due to inherited mutations in the *LDLR* gene, with more than 1,600 mutations identified.[1] Mutation of the *LDLR* gene leads to defective uptake of LDL-C

from the blood. Less commonly, FH may also be caused by mutations in the gene encoding apolipoprotein B (*apo B*), the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene, or rare mutations in the *LDLRAP1* gene.[2] *Apo B* is important for lipid metabolism because serum lipoproteins, including LDL-C and very low-density lipoprotein (VLDL), contain *apo B* as a structural component. The level of *apo B* correlates with cardiovascular risk.[13,14] *Apo B* is also necessary for transport of VLDL from the liver into the plasma.[15] *PCSK9* is a convertase enzyme that mediates the degradation of the LDL receptor.[16] The importance of *PCSK9* is shown by significantly lower LDL-C levels and incidence of CHD in patients with nonsense mutations in the *PCSK9* gene.[17] The *LDLRAP1* gene encodes an adaptor protein for trafficking of LDL receptors in cells in the liver, and mutations have been identified in patients with either FH, an autosomal dominant disorder, or an autosomal recessive hypercholesterolemia.[18,19]

Elevations in LDL-C levels are a function of the severity of the genetic mutation and whether it is homozygous or compound heterozygous.[1] When left untreated, patients with HeFH typically have 2- to 3-fold higher levels of plasma LDL-C compared with healthy individual (about 200-400 mg/dL), whereas patients with HoFH have levels of LDL-C that are 6- to 10-fold higher than normal (> 600 mg/dL).[20]

Patients should initiate positive modifications to their lifestyle; however, drug therapy is almost always required to decrease LDL-C to the desired levels to reduce the risk of premature CVD.[21] Even though many patients with FH are treated using the current standard of care for hyperlipidemia, patients with FH should receive aggressive statin therapy to achieve more than a 50% reduction in LDL-C levels, which usually requires high doses of high-potency statins.[3,22] In patients with other forms of severe hyperlipidemia or FH with clinical CVD, diabetes, or additional risk factors, treatment should be intensified to decrease LDL-C levels to less than 100 mg/dL, if possible, according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines and reiterated in the National Lipid Association (NLA) FH Treatment statement.[23,24] LDL-C levels of less than 100 mg/dL have been identified as the treatment target for cholesterol-lowering therapy in patients at higher risk for CVD.[23,24]

A need exists for the increased awareness of early, aggressive treatment of patients with FH to prevent or slow the progression of CVD caused by exposure to high lipid levels since birth.[3,22] From a pharmacy perspective of the management of FH, high-dose statins and adjunctive LDL-C–lowering therapies need to be available on insurance and managed care formularies, with reduced copayments for patients with FH in order to improve utilization. Eliminating copayments has been shown to increase adherence to generic statin therapy.[25] Decreasing or eliminating copayments would likely increase

the use of statins or adjunctive therapies in patients with FH. Although statins are generally inexpensive, adjunctive therapies such as other LDL-C–lowering drugs and apheresis can be expensive and come with high patient out-of-pocket contribution requirements.[26] This review includes management options for FH and highlights the recommendations from the NLA Expert Panel on Familial Hypercholesterolemia regarding the need for early and aggressive treatment.

### Risk Factors for Cardiovascular Disease in Familial Hypercholesterolemia

Risk factors for CVD in patients with FH are similar to those in patients without FH, although FH itself is a significant CVD risk factor because it results in long-term exposure to high lipid levels.[1,11,12] Increasing age, elevated levels of total cholesterol and LDL-C, low levels of high-density lipoprotein cholesterol (HDL-C), male sex, smoking, metabolic syndrome, diabetes, hypertension, and a family history of early CVD are risk factors for developing CVD.[11,12,27-33] These factors accelerate the development of atherosclerosis in patients with and without FH and must be treated aggressively, especially in those with FH.[3] Smoking is an extremely important and modifiable risk factor in patients with FH, and smoking must be avoided due to the increased likelihood of developing very premature onset of CVD.[11,12,34] Additional factors that may put patients with FH at increased risk for CVD include lipoprotein(a) (Lp[a]) levels of 50 mg/dL or higher and the presence of 2 or more CVD risk factors.[3,35-37]
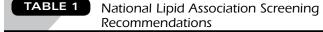
Risk stratification algorithms are often used to identify candidates for drug therapy on the basis of estimated CVD risk. However, risk stratification algorithms, such as the Framingham equations recommended by ATP III, underestimate the 10-year risk of CHD in patients with FH because of their lifelong exposure to severely elevated LDL-C levels. Therefore, risk stratification should not be used in patients with FH, who are already candidates for drug therapy on the basis of their genetic disorder.[3] Patients with severe HeFH and clinical CVD and those with HoFH are at very high CVD risk and require intensive LDL-C–lowering therapy.[3]

### Management Objectives for Patients with Familial Hypercholesterolemia

Early treatment of FH is highly beneficial for reducing CVD events.[3] According to NLA treatment recommendations, the goal of treatment in adults with FH is to achieve a 50% or greater decrease in LDL-C levels with statin therapy.[3,36] Patients with FH who are at a higher risk for CVD—including those with clinically evident CVD or atherosclerotic disease, diabetes, family history of early CVD, current smoking, 2 or more CVD risk factors, or an Lp(a) level of 50 mg/dL or higher—should be treated in an effort to achieve an LDL-C level of less than 100 mg/dL.[3] The highest doses of high-potency statins may be needed to achieve this reduction in LDL-C levels. For

**TABLE 1** National Lipid Association Screening Recommendations

- Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated fasting LDL-C or non-HDL-C levels are at or above the following:
  o Adults (age ≥ 20 years): LDL-C ≥ 190 mg/dL or non-HDL-C ≥ 220 mg/dL
  o Children, adolescents, and young adults (age <20 years): LDL-C ≥ 160 mg/dL or non-HDL-C ≥ 190 mg/dL.
- For all individuals with these levels, a family history of high cholesterol and heart disease in first-degree relatives should be collected. The likelihood of FH is higher in individuals with a positive family history of hypercholesterolemia or of premature CHD (onset in men aged < 55 years and women aged < 65 years).
- Cholesterol screening should be considered beginning at age 2 for children with a family history of premature CVD or elevated cholesterol levels. All individuals should be screened by age 20.
- Although not present in many individuals with FH, the following physical findings should prompt the clinician to strongly suspect FH and obtain necessary lipid measurements, if not already available:
  o Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons but can also occur in patellar and triceps tendons)
  o Arcus corneae in patients aged < 45 years
  o Tuberous xanthomas or xanthelasma in patients aged < 20 years
- At the LDL-C levels listed below, the probability of FH is approximately 80% in the setting of general population screening. These LDL-C levels should prompt the clinician to strongly consider a diagnosis of FH and obtain further family information:
  o LDL-C ≥ 250 mg/dL in patients aged ≥ 30 years
  o LDL-C ≥ 220 mg/dL in patients aged 20 to 29 years
  o LDL-C ≥ 190 mg/dL in patients aged < 20 years

*Adapted from Goldberg AC, Hopkins PN, Toth PP et al. Familial hypercholesterolemia.[3]*

*CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter.*

**TABLE 2** Criteria for Total Cholesterol and Low-Density Lipoprotein Cholesterol for the Diagnosis of Probable Heterozygous Familial Hypercholesterolemia (HeFH)[a]

| Ages | First-Degree Relative | Second-Degree Relative | Third-Degree Relative | General Population |
|---|---|---|---|---|
| < 18 years | 220 (155) | 230 (165) | 240 (170) | 270 (200) |
| 20-29 years | 240 (170) | 250 (180) | 260 (185) | 290 (220) |
| 30-39 years | 270 (190) | 280 (200) | 290 (210) | 340 (240) |
| ≥ 40 years | 290 (205) | 300 (215) | 310 (225) | 360 (260) |

*Adapted from Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics.[39]*

*[a]Total cholesterol levels in milligram per deciliter (low-density lipoprotein cholesterol levels in parentheses) expected to diagnose HeFH with 98% specificity. First-degree relatives are parents, offspring, brothers, and sisters; second-degree relatives are aunts, uncles, grandparents, nieces, and nephews; third-degree relatives are first cousins and siblings of grandparents.*

those who do not achieve at least a 50% reduction in LDL-C levels with maximally tolerated statin therapy or who continue to have an LDL-C level of at least 160 mg/dL (or a non-HDL-C level of at least 190 mg/dL), other LDL-C–lowering therapies should be added.[3] Similarly, multiple LDL-C–lowering therapies will typically be required in patients with FH at highest risk for CHD to achieve the more aggressive goal for LDL-C levels of less than 100 mg/dL and the goal for non-HDL-C levels of less than 130 mg/dL.[3,36] HDL-C is not considered a target for therapy in these patients.[36,38]

## Screening and Diagnosis

Early identification of FH is best achieved by the initiation of screening between the ages of 9 and 11 years in children and no later than 20 years in adults (Table 1).[3,24] In families with a history of FH or premature-onset CHD, screening should begin at age 2 years.[3] Formal diagnosis of FH is made by using 1 of several validated criteria, including the U.S. Make Early Diagnosis Prevent Early Death (MEDPED; Table 2), the Dutch Lipid Clinic Network, and the Simon Broome Registry.[3,39] A family history of 2 or more family members with elevated

LDL-C levels, along with a family history of pediatric cases of FH, or the presence of tendon xanthomas in the patient or a first-degree relative permit a clinical diagnosis.[3] Physical signs of the disease are often specific but not exclusive to FH, including tendon xanthomas and corneal arcus, although their absence does not rule out a diagnosis of FH.[3]

The NLA recommends that cascade screening, a process for identifying family members at risk for a genetic condition, should be performed in all first-degree relatives of patients with FH for the early diagnosis and prevention of CVD in family members.[1,40,41] In cascade screening, all first-degree relatives of a patient diagnosed with FH undergo lipid screening for evidence of FH.[1,40,41] The probability of detecting FH in first-degree relatives of these patients is 50%; the probability in second-degree relatives is 25%; and the probability in third-degree relatives is 12.5%.[1,40,41] The cascade effect comes from the subsequent screening of all first-degree relatives from patients with FH identified in the initial testing with continuing spread of the testing to additional first-degree relatives as each patient is diagnosed with FH.[23] Cascade screening has been shown to be cost-effective in identifying additional patients with FH.[42,43] The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines also recommend the use of cascade screening as a diagnostic tool, along with DNA testing and cholesterol measurement.[40] The NLA guidelines summarized in this review do not require genetic testing or DNA testing for a diagnosis of FH or selection of treatment, but genetic testing can be used if the diagnosis is uncertain.[1,3]

## Therapeutic Options

Patients with FH should adopt lifestyle modifications, including a healthy diet, exercise, weight control, blood pressure

| TABLE 3 | Differing Efficacies of Statins Based on Their Abilities to Decrease LDL-C Levels[a] |
|---|---|

| Statin/Decreased LDL-C Level By: | | |
|---|---|---|
| **30%-40%** | **>50%** | **>60%** |
| Atorvastatin 10 mg | Atorvastatin 40-80 mg | |
| Fluvastatin 80 mg | | |
| Lovastatin 40-80 mg | | |
| Pitavastatin 2-4 mg | | |
| Pravastatin 40-80 mg | | |
| Rosuvastatin 5-10 mg | Rosuvastatin 20 mg | Rosuvastatin 40 mg |
| Simvastatin 20-40 mg | Simvastatin/ezetimibe 20-40 mg/10mg | Simvastatin/ezetimibe 80/10 mg |

[a]Data from package inserts.
LDL-C = low-density lipoprotein cholesterol; milligram = mg.

| TABLE 4 | Alternative Treatment Options to Reduce LDL-C, Non-HDL-C, or *apo B* Levels in Patients with Familial Hypercholesterolemia Unresponsive to Initial Statin Therapy |
|---|---|

| | Changes in Levels | | | | |
|---|---|---|---|---|---|
| **Drug** | **LDL-C** | **Non-HDL-C** | **Triglycerides** | **HDL-C** | ***apo B*** |
| Double statin dose | -6% to -7% | -6% | -2% to -6% | -2% to +2% | -5% to -6% |
| Ezetimibe[a] 10 mg | -19% to -20% | -17% to -19% | -8% to -13% | +5% to +7% | -14% to -15% |
| ER niacin 2 g | -14% | -25% | -28% | +22% | -16% |
| Bile acid-binding agents[b] | -15% to -18% | -10% to -13% | +9% to +10% | +3% | -12% |

Adapted from Robinson JG. Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin;[66] Moga C, Hastall C. Low density lipoprotein apheresis for the treatment of familial hypercholesterolemia;[74] Stoffel W, Borberg H, Greve V. Application of specific extracorporeal removal of low density lipoprotein in familial hypercholesterolaemia;[75] Thompson GR. LDL apheresis;[76] Thompson GR, Catapano A, Saheb S, et al. Severe hypercholesterolaemia;[77] and Marais AD, Naoumova RP, Firth JC, et al. Decreased production of low density lipoprotein by atorvastatin after apheresis in homozygous familial hypercholesterolemia.[78]
[a]Ezetimibe in combination with statin therapy.
[b]Colesevelam 6 tablets (3.75 g/suspension, 3.75 g packet once daily, or 1.875 g packet twice daily).
apo B = apolipoprotein B; ER = extended release; g = gram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg = milligram.

control, and smoking cessation.[3,36] Similarly, the NICE guidelines recommend lifestyle modifications and smoking cessation.[4] A number of drug treatment options are available for FH. The increased risk for CVD and unique treatment needs of these patients may require managed care organizations to offer expanded formulary options, including allowing the highest doses of statins, more potent statins, newly approved drugs, and unique combination therapies.[3]

Statins should be the first-line therapy for patients with FH, according to the NLA recommendations, the NCEP ATP III guidelines, and the NICE guidelines.[3,24,40] Low-potency statins are generally inadequate to reduce LDL-C levels by 50% or greater in patients with FH (Table 3).[3] In a comparative dose efficacy study, a moderate dose of a higher-potency statin (atorvastatin 10 mg and 20 mg) was more efficacious than lower-potency statins (simvastatin, pravastatin, lovastatin, or fluvastatin) in patients with hypercholesterolemia yet still did not lower LDL-C levels by 50% or more.[44] Therefore, even higher doses of high-potency statins are often needed in patients with FH. A review of clinical trials of high-dose statins in coronary artery disease reported that, compared with moderate-dose statins, high-dose statins reduced the death rate due to coronary death or myocardial infarction by 16%, and in patients with acute coronary syndrome, high-dose statins decreased the risk of all-cause mortality by 22% and of cardiovascular mortality by 25% over treatment periods of 2 to 5 years.[45] One study showed that in patients with FH, moderate-dose statins reduced the risk for CVD by up to 80%.[46] High-dose statins are generally well tolerated.[47] In large, long-term clinical trials in secondary prevention in patients with hyperlipidemia, but not specifically FH, atorvastatin 80 mg was efficacious and was associated with low rates of serious adverse musculoskeletal (<0.6%) and hepatic (<1.3%) events.[47] Rosuvastatin 20 mg was used over a shorter period in a large primary prevention population and was also associated with very low rates of serious muscle and liver adverse events.[48] Fewer long-term data are available for rosuvastatin 40 mg. In contrast, 1.4% of patients

receiving simvastatin 80 mg in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial developed myopathy compared with 0.2% of patients receiving simvastatin 20 mg in the placebo group; however, clinicians are advised to be aware of the potential increased risk for muscle injury according to a U.S. Food and Drug Administration (FDA) advisory from March 2010.[49,50] High-dose statins are associated with a somewhat higher rate of discontinuation, ranging from 3.2% to 9.6% due to drug-related adverse events.[47] High-dose statins are, therefore, a well-tolerated treatment option for the large majority of high risk patients. The main question about the long-term safety of high-intensity statins arises from the increased risk for type 2 diabetes with these agents. High-intensity statins increase the risk for diabetes in those with increasing numbers of risk factors for diabetes (levels of fasting blood glucose higher than 100 mg/dL or glycated hemoglobin A1c higher than 6%, fasting triglyceride level higher than 150 mg/dL, body mass index greater than 30 milligram per kilogram squared [mg/kg²], hypertension, or metabolic syndrome) but not in those without such risk factors.[51,52] For individuals with FH, diabetes risk factors markedly increase CVD risk, as previously discussed. However, analyses have not been performed to estimate the trade-offs in terms of long-term CVD risk reduction compared with the risk of diabetes complications.

For those patients with FH who are unable to tolerate statins at the highest intensity, or who are completely intolerant to statins, access to alternative LDL-C–lowering therapies is needed. Several non-statin LDL-C–lowering agents are available (Table 4).

Ezetimibe, combined with statins, such as atorvastatin and simvastatin, significantly reduces LDL-C levels by an additional 17% to 23% compared with a statin alone.[53,54] Depending on the dose of statin, the addition of ezetimibe, which inhibits absorption of cholesterol from the intestine, can reduce LDL-C levels by approximately 43% to 70% in patients with HeFH and by 21% (a difference of approximately 14% from statins) in patients with HoFH.[53-57] In several studies, the addition of ezetimibe to statin therapy was well tolerated, with a rate of adverse events similar to that for statin therapy alone, although statin-ezetimibe therapy more frequently causes persistent elevations in hepatic transaminase levels compared with moderate-dose statin monotherapy.[54,57] The combination of simvastatin-ezetimibe has been shown to reduce CVD events compared with placebo;[58,59] however, the incremental CVD risk reduction benefit of adding ezetimibe to statin therapy has yet to be determined.[60]

The bile acid sequestrant cholestyramine has been shown to reduce the risk for CVD in severely hypercholesterolemic patients.[57] Cholestyramine and colestipol have gastrointestinal adverse effects, such as constipation; the newer bile acid sequestrant, colesevelam, is generally better tolerated with fewer drug interactions.[61] In a phase 4 trial of 86 patients with FH, the addition of colesevelam to combination therapy with ezetimibe and a statin significantly lowered LDL-C levels by an additional 12% at 12 weeks compared with ezetimibe or a statin alone.[62] No significant differences in adverse events were observed between the colesevelam treatment and control arms.[62] Cholestyramine monotherapy has been shown to reduce CVD events in a primary prevention population of men with severe hypercholesterolemia;[63] however, no CVD outcomes data are available for bile acid sequestrants combined with statin therapy.

Niacin combined with statins is a safe and effective LDL-C–lowering therapy in patients with severe hypercholesterolemia but has not been tested in clinical trials exclusively enrolling patients with FH or in combination with high-dose statins. Other than LDL-C apheresis, niacin is the only known therapy that has a significant impact on Lp(a) levels, although the clinical impact of lowering Lp(a) levels with niacin has not been established.[64,65] A dose of 1.5 grams (g) to 2 g of niacin is typically required to achieve a 15% lowering of LDL-C levels; however, the efficacy and safety of these high doses in combination with high-dose statins has not been evaluated. Patients receiving high doses of niacin often experience intolerable flushing and are likely to discontinue treatment, making the use of high doses of niacin difficult to apply in clinical practice.[64] In a review of niacin and moderate-dose statin combination therapy

in hyperlipidemic patients, reductions in LDL-C levels ranging from 25% to 57% and Lp(a) levels of 37% were reported.[65] In this analysis of 293 patients, no cases of myopathy and minimal hepatic toxicity were reported; however, 53% and 42% of patients experienced elevations in alanine aminotransferase and aspartate aminotransferase levels, respectively. The percentage of patients experiencing flushing was not reported. In another review of 4 clinical trials evaluating extended-release niacin 1,000 to 2,000 mg and simvastatin 20 mg to 80 mg, this combination lowered LDL-C levels, with reductions ranging from 2% to 24% and reductions in Lp(a) levels from 0% to 29%.[66] The combination was well tolerated, with liver and muscle toxicities similar to those of niacin and simvastatin monotherapies. Although cutaneous adverse effects may limit the use of niacin in some patients, adherence to therapy can be improved with extended-release niacin. Extended-release niacin is contraindicated in patients with active liver disease or unexplained hepatic dysfunction, and the dose should not exceed 2 g daily due to concerns about hepatotoxicity.[67]

Niacin monotherapy has been shown to reduce CVD events in men with CHD.[68,69] Niacin when combined with simvastatin has been shown to reduce CVD risk similar to simvastatin (plus ezetimibe) when similar levels of LDL-C of about 70 mg/dL were achieved.[11] In addition, a recent trial of niacin combined with laropiprant did not demonstrate an incremental reduction in CVD events when added to statin therapy.[70]

## Therapeutic Options for Patients with Severe LDL-C Elevations on Maximal Drug Therapy

Ideally, patients who have high lipid levels that are difficult to control or who are at high risk for cardiac complications should be referred to a lipid specialist.[4] Regardless of aggressive lipid management, some patients with severe HeFH (LDL-C levels of 200 mg/dL or higher, either after maximum tolerated lipid-lowering therapy or with evidence of CVD) and the majority of patients with HoFH will not achieve sufficient reductions in LDL-C levels even with the maximal doses of statin and non-statin therapies. These patients often require additional therapy such as LDL-C apheresis (Table 4).[3,57,66,67,71-73] LDL-C apheresis is an effective way to lower LDL-C levels in patients with FH who are not responsive to or are intolerant of drug therapy. Unlike statins, apheresis also lowers Lp(a) levels.[74-76] Apheresis is a procedure to physically remove plasma lipoproteins from the blood using dextran sulfate cellulose adsorption (DSA), heparin-induced extracorporeal LDL cholesterol precipitation (HELP), immunoadsorption, double filtration plasmapheresis (DFPP), or direct adsorption of lipoproteins.[77] Unfortunately, many patients with FH do not achieve the desired reduction of lipoproteins with apheresis and with all methods of removing the LDL, and the LDL-C levels return to pre-treatment levels within 2 to 4 weeks.[77]

Apheresis and statins may effectively be combined to lower LDL-C levels in patients with HeFH as well as in those with

**TABLE 5** National Lipid Association Recommendations for Identifying Candidates for LDL Apheresis

LDL apheresis is an FDA-approved medical therapy for patients who are not at LDL cholesterol treatment goal or who have ongoing symptomatic disease.

In patients who, after 6 months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresisis is indicated according to these guidelines:

1. Functional homozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL).

2. Functional heterozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL) and 0-1 risk factors.

3. Functional heterozygous FH patients with LDL cholesterol ≥ 200 mg/dL (or non-HDL cholesterol ≥ 230 mg/dL) and high risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.

4. Functional heterozygotes with LDL cholesterol ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).

*Adapted from Ito MK, McGowan MP, Moriarty PM. Management of familial cholesterolemias in adult patients.[105]*

*CHD = coronary heart disease; FDA = U.S. Food and Drug Administration; FH = familial hypercholesterolemia; HDL = high-density lipoprotein; LDL = low-density lipoprotein; mg/dL = milligram per deciliter.*

HoFH.[78] In a study of 7 patients with HoFH, the combination of apheresis and atorvastatin 80 mg produced on average a 31% additional reduction in LDL-C levels over apheresis alone.[78] In a prospective, 10-year follow-up study of 18 patients receiving the combination of apheresis and statin therapy, a delay was observed in the progression of coronary artery disease, with evidence for the prevention of major cardiac events.[79] Little change was observed in coronary stenosis and ejection fraction. However, the use of apheresis is limited by high cost, difficult access, and the inconvenience of treatment (> 3 hours required for treatment every 1-2 weeks).[21] The yearly cost of LDL apheresis has been estimated at $45,000 to $100,000.[80] An estimated 400 patients receive apheresis in the United States; however, access remains a challenge, with only approximately 40 centers providing care.[21] The number of patients who qualify and may benefit from this treatment is thought to be significantly higher.[21] The FDA has approved LDL-C apheresis for patients with HoFH and an LDL-C level greater than 500 mg/dL and in patients with HeFH after failing a 6-month trial of diet therapy and maximally tolerated combination drug therapy and either an LDL-C level higher than 300 mg/dL without CVD or an LDL-C level higher than 200 mg/dL with known CVD. Insurers may choose other guidelines. The NLA recommendations for apheresis are listed in Table 5.[3] Recently published guidelines from the German Apheresis Working Group identify lower LDL-C thresholds for initiating apheresis. The German guidelines recommend that patients with FH should start lipid apheresis within 3 months of failure of diet and lipid-lowering therapies as follows: as primary prevention in patients with LDL-C levels higher than 160 mg/dL;

as secondary prevention in patients with progressive cardiovascular events with LDL-C levels higher than 120 mg/dL to 130 mg/dL; and in patients with progressive CVD with Lp(a) levels higher than 60 mg/dL.[81,82]

In the past, surgical approaches to the lowering of LDL-C have been used. Ileal bypass surgery has been shown to reduce LDL-C levels by approximately 40% and reduce cardiovascular events in patients with severely elevated LDL-C levels. Ileal bypass surgery is also associated with an 18% reduction in overall mortality over a 25-year follow-up period.[83,84] Liver transplantation has been performed very rarely in selected patients with severe FH.[85,86]

## New Treatment Options for Familial Hypercholesterolemia

Over the last few years, clinical development has led to the emergence of a number of novel therapies for lowering LDL-C levels. Because of the lower LDL-C levels and reduced incidence of CHD observed in patients with a specific allele of *PCSK9*,[17,26] a protease gene involved in the degradation of LDL-C, *PCSK9* is another potential therapeutic target. AMG 145 is a monoclonal antibody to *PCSK9* that was recently tested in a multicenter, double-blind, placebo-controlled, randomized, phase 2 trial in patients with HeFH unable to achieve an LDL-C level of less than 100 mg/dL despite therapy with statins with or without ezetimibe.[87] Patients receiving AMG 145 had a significant reduction in mean LDL-C levels of up to 55% compared with a 1% increase in the placebo arm, with no significant toxicity ($P < 0.001$).[87] REGN727/SAR236553 is a monoclonal antibody against *PCSK9* that inhibits binding to the LDL receptor.[88] REGN727 has been tested in a randomized, double-blind, placebo-controlled trial of patients with HeFH with LDL-C levels of 100 mg/dL or higher despite lipid-lowering therapy with diet therapy and a stable dose of statin with or without ezetimibe.[88] Patients receiving REGN727 had a rapid reduction in LDL-C levels, with a mean decrease of 29% to 68% compared with a mean reduction of 11% with placebo.[88]

Recently, mipomersen, a second-generation antisense oligonucleotide, was approved by the FDA as an adjunct to lipid-lowering medications and diet to reduce LDL-C, *apo B*, total cholesterol, and non-HDL-C in patients with HoFH.[89] *Apo B* is important for the structure and receptor binding of lipoproteins, including LDL-C.[90,91] In a phase 3 trial of patients with HoFH randomly assigned to receive either mipomersen or placebo, patients receiving mipomersen had a mean reduction in LDL-C levels of 24.7% compared with 3.3% in patients receiving placebo ($P = 0.0003$).[91] The most common adverse effect in patients receiving mipomersen was injection-site reactions.[92]

The microsomal triglyceride transfer (MTP) inhibitor lomitapide is another agent recently approved by the FDA for the treatment of HoFH. The MTP protein is responsible for transferring triglycerides onto *apo B*, a necessary step for the production of LDL-C.[92] In a clinical trial of lomitapide in patients with HoFH, a significant dose-dependent reduction in LDL-C

levels was observed; however, adverse effects included increased aminotransferase levels and fat in the liver.[92] Lomitapide has received FDA approval for use only in patients with HoFH, with the requirement of use through a restricted program called the JUXTAPID Risk Evaluation and Mitigation Strategy administered by the manufacturer.[93]

Effective novel therapies alone or in combination with statins, particularly agents that may provide additive reduction in LDL-C levels, may allow for elongated intervals between apheresis sessions—and perhaps may even completely eliminate the need for apheresis, as well as surgical treatment, while preventing early CVD and related comorbid conditions. Furthermore, novel therapies may provide clinicians with alternative or additional treatment options for lowering LDL-C or Lp(a) levels, particularly in patients who are intolerant of statins.

## Pediatric Considerations for the Management of Familial Hypercholesterolemia

Specific recommendations exist for the management of children and adolescents with FH.[94] Children aged 9 to 11 years should have a fasting lipid profile or a nonfasting non-HDL-C measurement as a universal screening for FH so that a diagnosis can be made before atherosclerosis develops. In the setting of a positive family history for FH, children should be screened at 2 years of age. FH should be suspected in children, adolescents, and young adults with LDL-C levels of 160 mg/dL or greater or with non-HDL-C levels of 190 mg/dL or greater.[94] The NLA Expert Panel on Familial Hypercholesterolemia recommends initial treatment for pediatric patients with statin therapy beginning at the age of 8 years, although patients with HoFH may require treatment at an earlier age. The treatment goal for pediatric patients is a reduction in LDL-C levels of at least 50% or an LDL-C level of less than 130 mg/dL. Many pediatric patients with severe FH will not reach their target goals for LDL-C levels or be able to tolerate high doses of statins. The majority of pediatric patients with HoFH will require apheresis to achieve adequate control of LDL-C levels. Despite the use of high-dose statins or apheresis, some pediatric patients with severely elevated LDL-C levels may benefit from liver transplantation because the transplanted liver will have functional LDL receptors, thereby lowering LDL-C levels.[94] Liver transplantation may be a curative therapy for children with HoFH, particularly those who have not developed cardiovascular complications.[95] In 1 case series, 4 patients with HoFH and progressive coronary atherosclerotic disease received orthotopic liver transplantation after failure of medical treatment.[86] Two patients are well 4, 9, and 11 years after transplantation, with 1 of these patients requiring no immunosuppression to prevent rejection for the last 6 years. The third patient died 2 years after transplantation due to a myocardial infarction.[86] At the last follow-up, all 4 patients had normal

| TABLE 6 | Research Needs for the Cost-Effectiveness of Screening and Treatment for Familial Hypercholesterolemia Based on Recommendations from the National Lipid Association |
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**Research Needs**

Cost-effectiveness analysis of genetic screening

Cost-effectiveness analysis of various approaches to screening and treatment

   Cascade screening

   Low-density lipoprotein apheresis

Cost-effectiveness analysis of the benefits of aggressive therapy, including use of high-dose statins and new agents to treat patients to lower-than-usual target LDL-C levels.

*Adapted from Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia.[3]*

*LDL-C = low-density lipoprotein cholesterol.*

serum cholesterol levels.[86] However, this therapy should typically be avoided due to major complications such as operative complications, transplant rejection, infection, chronic hepatitis, and vascular and biliary complications, along with the need for lifelong immunosuppressive therapy.[95,96]

## Cost-Effectiveness of Therapy

Both the acute and long-term costs associated with cardiovascular events are high.[97-100] For example, in a managed care setting, the total first-year health care cost per patient after acute coronary syndrome was estimated at $22,529.[97] In another managed care study, the total average annualized health care costs for the treatment of peripheral artery disease was $5,955.[98] Limited cost-effectiveness data are available for the treatment of patients with FH, and additional research is needed (Table 6). In a model evaluating the effectiveness of high-dose statins in a non-FH population, long-term therapy with these agents was cost-effective for decreasing LDL-C levels and minimizing the risk for CVD.[40] Cost-effectiveness models compare the incremental cost per quality-adjusted life-years to determine whether the intervention falls within a given threshold.[40] Cost-effectiveness models have not been evaluated to determine whether treatment with high-dose statins in patients with FH is cost-effective. However, it is likely that the cost-effectiveness of high-dose statin treatment in patients with FH is similar to, if not greater than, that in individuals without FH, given the very high risk for CVD in patients with FH. Furthermore, the cost-effectiveness of statins will generally continue to decrease as the patents for these drugs expire.[99] Indeed, over a longer-term period of treatment of more than 10 years, generic high-intensity statin therapy to lower LDL-C levels by 50% is more cost-effective than lower doses of statins in primary prevention in those without FH.[101] As previously

stated, the early identification and aggressive treatment of FH minimizes the risk for CVD.

Cascade screening is a cost-effective method for identifying patients with FH compared with primary prevention screening strategies.[43] A lipid panel is sufficient for most cascade screening. In families at high risk for FH and with diagnostic uncertainty, DNA analysis may be performed. As described previously, NLA guidelines for the management of patients with FH do not recommend DNA testing for making a diagnosis. Once a mutation has been identified in a patient with FH, DNA analysis of the mutation and measurement of LDL-C levels in first-degree relatives have a specificity and sensitivity of almost 100% for the identification of relatives with FH. A cascade screening strategy that incorporates DNA diagnosis in the index case to guide testing of mutation-positive patients, but also LDL-C-based cascade screening in patients with either a clinically definite or a probable history of FH, has been shown to be more cost-effective than a strategy based on LDL-C levels alone.[102] An analysis by Nherera et al. (2010) compared 4 cascade screening methods: (1) cholesterol only; (2) DNA analysis of the index patient and first-degree relatives and cascade screening only in the patient with the mutation; (3) DNA testing of the index case and cascade testing in all mutation-positive index cases and also relatives of patients with definite clinical evidence of FH with no mutation using LDL-C levels only to test for mutation; and (4) DNA testing of the index case and cascade testing in all mutation-positive index cases and also relatives of patients with definite or probable clinical evidence of FH with no mutation using LDL-C levels only to test for mutation.[102] Screening method 4 was found to be the most cost-effective compared with current screening practices.[102]

Although LDL-C apheresis is costly, this procedure decreases levels of LDL-C and other atherogenic particles, including Lp(a), with a reduction in the risk for CVD.[74] However, numerous factors must be seriously considered when the benefits of apheresis are being weighed against its high cost,[73] including the patient's quality of life, disease severity, and the potential lack of access to the procedure due to the scarcity of facilities.[73] Research into the cost-effectiveness of several areas in the screening and treatment of FH is still needed (Table 5). The NLA recommendations suggest that initial screening, initiation of therapy, and follow-up should be covered by health care insurance.[103] According to the NLA, payers should also cover high-potency statins, combination therapies, LDL-C apheresis, and genetic testing.[33]

■ **Conclusions**

In addition to the NLA recommendations for the management of dyslipidemias in patients with FH, the European Society of Cardiology and the European Atherosclerosis Society have recently published guidelines on the management of patients with dyslipidemias, including patients with HeFH or HoFH.[104] Older guidelines on the management of patients with FH include NCEP ATP III.[24]

FH is the most common genetic disease in the world but is also treatable. Early screening, early diagnosis, reduction of risk factors, and aggressive treatment are important for the optimal care of these patients. In particular, aggressive therapy can significantly lower the risk for premature CVD and prevent or delay the incidence of CVD-related events.

Effective treatment for FH requires an early clinical diagnosis; therefore, FH should be suspected and tested for in patients aged 20 years and older who have LDL-C levels of at least 190 mg/dL or non-HDL-C levels of at least 220 mg/dL; in patients younger than aged 20 years who have LDL-C levels of at least 160 mg/dL and non-HDL-C levels of at least 190 mg/dL; and in patients with these levels who have a family history of high cholesterol levels and heart disease in a first-degree relative.[3] In the managed care setting, clinicians need to be aware that patients with FH may need more aggressive treatment to lower LDL-C levels, including higher doses of statins, a more potent statin, or combination drug therapy, and to minimize the risk for CVD. Managed care organizations should optimize disease management by covering initial screening, treatment, and monitoring of patients for response, as well as more extensive coverage for payments related to drug therapy so as to include high-potency statins, combination therapies, and therapies for those patients who are intolerant of or unresponsive to statins.[3]

Unfortunately, even high-dose statin therapy or combination therapy often does not reduce LDL-C and other atherogenic particles to adequate levels; consequently, patients with FH continue to be at an increased risk for CVD. This leaves a significant unmet need for additional therapies for patients with severe FH (patients with HeFH and LDL-C levels greater than 200 mg/dL after maximum tolerated lipid-lowering therapy who also have CAD, and patients with HoFH). Despite the often rigid formularies of managed care organizations, proper management of patients with FH requires their ability to receive currently approved therapies, such as higher doses of statins, combinations of other LDL-C–lowering therapies, and lipid apheresis. Patients will also need access to recently approved and emerging treatments, including *apo B* antisense inhibitors, MTP inhibitors, *PCSK9* inhibitors, and other LDL-C–lowering agents. Mipomersen, an antisense inhibitor, has recently been granted approval by the FDA and, along with other novel agents, has been shown in initial clinical trials to effectively lower LDL-C levels when added to statin therapy. Some agents are in late-phase clinical trials. Some of these therapies have also shown the potential for lowering levels of Lp(a) and other atherogenic particles. These therapies may offer patients with severe FH additional options in addition to currently available therapies.

# Management of Familial Hypercholesterolemia: A Review of the Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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