

Executive Summary

Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients

Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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Abstract: The familial hypercholesterolemias (FH) are a group of genetic defects resulting in severe elevations of blood cholesterol levels and increased risk of premature coronary heart disease. FH is among the most commonly occurring congenital metabolic disorders. FH is a treatable disease. Aggressive lipid lowering is necessary to achieve the target LDL cholesterol reduction of at least 50% or more. Even greater target LDL cholesterol reductions may be necessary for FH patients who have other CHD risk factors. Despite the prevalence of this disease and the availability of effective treatment options, FH is both underdiagnosed and undertreated, particularly among children. Deficiencies in the diagnosis and treatment of FH indicate the need for greatly increased awareness and understanding of this disease, both on the part of the public and of healthcare practitioners. This document provides recommendations for the screening, diagnosis and treatment of FH in pediatric and adult patients developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia. This report goes beyond previously published guidelines by providing specific clinical guidance for the primary care clinician and lipid specialist with the goal of improving care of patients with FH and reducing their elevated risk for CHD. © 2011 National Lipid Association. All rights reserved.

Background and rationale

The familial hypercholesterolemias (FH) are a group of genetic defects resulting in severe elevations of blood cholesterol levels. Although the term FH has, in the past, been used to refer specifically to LDL receptor (LDLR) defects, this document will use a broader definition to reflect discoveries of defects in the genes for apolipoprotein (Apo) B, proprotein convertase subtilisin/kexin type 9 (PCSK9), and possibly others yet to be described, which produce severe hypercholesterolemia and increased risk of premature coronary heart disease (CHD). Total cholesterol concentrations in heterozygous FH patients (genetic defect inherited from one parent) are typically in the range of 350 to 550 mg/dL and in homozygotes (genetic defects inherited from both parents) range from 650 to 1000 mg/dL. FH is among the most commonly occurring congenital metabolic disorders. The heterozygous form occurs in approximately 1 in 300 to 500 people in many populations, although this ratio is much higher in certain populations in the U.S. The homozygous form is quite rare, occurring in approximately 1 out of every 1,000,000 individuals. Because FH is due to a genetic defect or defects, hypercholesterolemia is present from childhood, leading to early development of CHD. Of particular concern are FH homozygotes, in whom the severity of hypercholesterolemia usually results in severe atherosclerosis and even cardiovascular disease during childhood and adolescence.

FH is a treatable disease. Aggressive lipid lowering is necessary to achieve the target LDL cholesterol reduction of at least 50% or more. Even greater target LDL cholesterol reductions may be necessary for FH patients who have other CHD risk factors. In addition to diet and lifestyle modifications, safe and effective medical therapies are available, including statins and other lipid-lowering drugs, and LDL apheresis, (a method of removing LDL and other Apo B particles from the blood). Despite the prevalence of this disease and the availability of effective treatment options, FH is both underdiagnosed and undertreated,

particularly among children. Some estimates suggest that approximately 20% of patients are diagnosed and, of those, only a small minority receive appropriate treatment.

Deficiencies in the diagnosis and treatment of FH indicate the need for greatly increased awareness and understanding of this disease, both on the part of the public and of healthcare practitioners. Central to that education is comprehension of the importance of universal screening during childhood and cascade lipid screening of family members of known FH patients. This document provides recommendations for the screening, diagnosis and treatment of FH in pediatric and adult patients (including women of childbearing potential and during pregnancy) developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia. This report goes beyond previously published guidelines by providing specific clinical guidance for the primary care clinician and lipid specialist with the goal of improving care of patients with FH and reducing their elevated risk for CHD. The rationale and supporting evidence for these recommendations are published herein, but are not intended to be a comprehensive examination of the published literature.¹⁻⁵

1. Definition, prevalence, genetics, diagnosis and screening

1.1 Definition of familial hypercholesterolemias

- 1.1.1 The FH are a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations.
- 1.1.2 For purposes of this document, FH will refer to the autosomal dominant forms of severe hypercholesterolemia unless otherwise specified. However, causes of inherited high cholesterol are not restricted to autosomal dominant FH.

1.2 Prevalence of FH and associated risk

- 1.2.1 The prevalence of FH is 1 in 300 to 500 in many populations, making FH among the most common of serious genetic disorders.

- 1.2.2 There are approximately 620,000 FH patients currently living in the United States.
- 1.2.3 The risk of premature coronary heart disease (CHD) is elevated about 20-fold in untreated FH patients.
- 1.2.4 Approximately 1 in one million persons is homozygous (or compound heterozygous) for *LDLR* mutations and has extreme hypercholesterolemia with rapidly accelerated atherosclerosis when left untreated.
- 1.2.5 In a few populations (such as French Canadians and Dutch Afrikaners), the prevalence of FH may be as high as 1 in 100.

1.3 Genetics of FH

- 1.3.1 Currently, known causes of FH include mutations in the LDL receptor (*LDLR*), Apo B (*APOB*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes.
- 1.3.2 There are over 1600 known mutations of the *LDLR* gene documented to cause FH at the time of this writing, accounting for about 85 to 90% of FH cases.
- 1.3.3 The Arg3500Gln mutation in *APOB* is the most common cause of hypercholesterolemia due to an *APOB* mutation, accounting for 5 to 10% of FH cases in Northern European populations (rare in other populations).
- 1.3.4 Gain-of-function mutations in *PCSK9* cause fewer than 5% of cases in most studies.

1.4 Screening for FH

- 1.4.1 Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated fasting LDL cholesterol or non-HDL cholesterol levels are at or above the following:
 - Adults (≥ 20 years): LDL cholesterol ≥ 190 mg/dL or non-HDL cholesterol ≥ 220 mg/dL;
 - Children, adolescents and young adults (< 20 years): LDL cholesterol ≥ 160 mg/dL or non-HDL cholesterol ≥ 190 mg/dL.
- 1.4.2 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 before age 55 years and women before age 65 years).
- 1.4.3 Cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. All individuals should be screened by age 20.
- 1.4.4 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:

- Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons, but can also occur in patellar and triceps tendons).
 - Arcus corneae in a patient under age 45.
 - Tuberos xanthomas or xanthelasma in a patient under age 20 to 25.
- 1.4.5 At the LDL cholesterol levels listed below the probability of FH is approximately 80% in the setting of general population screening. These LDL cholesterol levels should prompt the clinician to *strongly* consider a diagnosis of FH and obtain further family information:
- LDL cholesterol ≥ 250 mg/dL in a patient aged 30 or more;
 - LDL cholesterol ≥ 220 mg/dL for patients aged 20 to 29;
 - LDL cholesterol ≥ 190 mg/dL in patients under age 20.

1.5 Diagnosis

- 1.5.1 Age at onset of CHD, even if approximate, is particularly important to note in the family history.
- 1.5.2 Physical signs of FH are insensitive but can be quite specific. The presence of tendon xanthomas should be sought for by careful palpation (not just visual inspection) of the Achilles tendon and finger extensor tendons. Corneal arcus (partial or complete) is only indicative of FH if present under age 45. Neither xanthelasma nor tuberos xanthomas are specific for FH but, if they are encountered in a younger patient, FH should be considered. Importantly, the absence of any of these physical findings does not rule out FH.
- 1.5.3 Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria [U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry]. It should be noted that LDL cholesterol cut points usually vary with age.
- 1.5.4 The clinical diagnosis of FH is most likely when two or more first-degree relatives are found to have elevated LDL cholesterol in the range noted above, when pediatric cases are identified in the family, or when the patient or a close relative has tendon xanthomas.
- 1.5.5 Once a family is diagnosed with FH, somewhat lower LDL cholesterol cut points can be applied to identify additional affected family members.
- 1.5.6 Patients with FH occasionally have elevated triglycerides, and high triglycerides should not exclude the diagnosis of FH.

1.6 Genetic screening

- 1.6.1 Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain.
- 1.6.2 Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.
- 1.6.3 Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods.

1.7 Cascade screening

- 1.7.1 Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.
- 1.7.2 As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.
- 1.7.3 Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved. General population screening of a young population (before age 16) is similarly cost-effective in terms of cost per year of life saved, given that effective cholesterol-lowering treatment is begun in all those identified.

2. Adult treatment recommendations and evidence for treatment

2.1 Rationale for treatment

- 2.1.1 Individuals with FH have a very high lifetime risk of CHD and are at very high risk of premature onset CHD.
- 2.1.2 Early treatment is highly beneficial. Long-term drug therapy of patients with FH can substantially reduce or remove the excess lifetime risk of CHD due to the genetic disorder and can lower CHD event rates in FH patients to levels similar to those of the general population.
- 2.1.3 FH requires lifelong treatment and regular follow-up.

2.2 Treatment

- 2.2.1 Both children and adults with LDL cholesterol ≥ 190 mg/dL [or non-high-density lipoprotein (HDL) cholesterol ≥ 220 mg/dL] after lifestyle changes will require drug therapy.
- 2.2.2 For adult FH patients (≥ 20 years of age), drug treatment to achieve an LDL cholesterol reduction $\geq 50\%$ should be initiated.
- 2.2.3 Statins should be the initial treatment for all adults with FH.

2.3 Intensified drug treatment

- 2.3.1 Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL cholesterol < 100 mg/dL and non-HDL cholesterol < 130 mg/dL).
- 2.3.2 Any of the following places FH patients at higher CHD risk: clinically evident CHD or other atherosclerotic cardiovascular disease, diabetes, a family history of very early CHD (in men < 45 years of age and women < 55 years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.
- 2.3.3 In FH patients without any of the characteristics listed above, intensification of drug therapy may be considered if LDL cholesterol remains ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL), or if an initial 50% reduction in LDL cholesterol is not achieved.
- 2.3.4 Ezetimibe, niacin, and bile acid sequestrants are reasonable treatment options for intensification of therapy, or for those intolerant of statins.
- 2.3.5 The potential benefit of multidrug regimens for an individual patient should be weighed against the increased cost and potential for adverse effects and decreased adherence.

2.4 Risk factors should be aggressively treated

- 2.4.1 Risk factors are the same in FH as in the general population and require aggressive management to reduce CHD risk, with special attention to smoking cessation.
- 2.4.2 Regular physical activity, a healthy diet and weight control should be emphasized.
- 2.4.3 Blood pressure should be treated to $< 140/90$ mm Hg (or $< 130/80$ mm Hg in those with diabetes). Low dose aspirin (75-81 mg per day) should be considered in those at high CHD or stroke risk.

2.5 Risk stratification algorithms should not be used

- 2.5.1 Individuals with FH are at high CHD risk. The 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools. Therefore, assessment of 10-year risk is not recommended.
- 2.5.2 All FH patients require lifestyle management, and very few will not require lipid-lowering drug therapy.

2.6 Consider referral to a lipid specialist

- 2.6.1 Consider referral to a lipid specialist with expertise in FH if LDL cholesterol concentrations are not reduced by $\geq 50\%$ or if patients are at high risk.
- 2.6.2 Cascade testing of first-degree relatives should be offered to all individuals with FH.

3. Management issues in pediatrics

3.1 Screening

- 3.1.1 Universal screening at age 9 to 11 years with a fasting lipid profile or nonfasting non-HDL cholesterol measurement is recommended to identify all children with FH. This age identifies individuals at the potential onset of advanced atherosclerosis, and provides the best discrimination between those with and without inherited dyslipidemias by avoiding confounding due to changes in lipid levels associated with puberty.
- 3.1.2 If a nonfasting non-HDL cholesterol concentration of ≥ 145 mg/dL is detected, then a fasting lipid profile should be performed.
- 3.1.3 Screening should occur earlier (≥ 2 years of age) in the presence of a positive family history for hypercholesterolemia or premature CHD or the presence of other major CHD risk factors.
- 3.1.4 Identifying FH in someone with other major CHD risk factors is critical for risk stratification.
- 3.1.5 Evaluation (history, physical examination, selected laboratory tests) of possible secondary causes of dyslipidemia should be performed. Secondary causes include hypothyroidism, nephrotic syndrome, and liver disease.

3.2 Diagnosis

- 3.2.1 Untreated fasting lipid levels at which FH may be suspected in children, adolescents and young adults (< 20 years) are LDL cholesterol concentration ≥ 160 mg/dL or non-HDL cholesterol ≥ 190 mg/dL. These levels are supported by family studies of affected individuals.
- 3.2.2 A second lipid profile should be performed to assess response to diet management, to account for regression to the mean, and to accurately classify those with levels close to classification thresholds.

3.3 Lipid specialists

- 3.3.1 Primary care clinicians should be responsible for screening and diagnosis.
- 3.3.2 For treatment of children with FH, either consultation with or referral to a lipid specialist is recommended. Pediatric lipid specialists include pediatric cardiologists, endocrinologists, or other health care providers with specialized lipidology training. Use of lipid lowering medications is currently not typically part of pediatric training.
- 3.3.3 Homozygous FH should always be managed by a lipid specialist.

3.4 Cardiovascular risk assessment

- 3.4.1 Comprehensive CHD risk assessment [including measurement of lipoprotein (a) levels] and management is critical. The presence of multiple

CHD risk factors is associated with dramatic acceleration of atherosclerosis development.

- 3.4.2 Primordial prevention, which includes counseling for the prevention of risk development (not smoking, low saturated fat diet, appropriate caloric intake and regular physical activity supporting the avoidance of diabetes), is an important component of treatment of patients with FH.

3.5 Treatment in children

- 3.5.1 Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.
- 3.5.2 Consideration should be given to starting treatment at the age of 8 years or older. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages.
- 3.5.3 Clinical trials with medium term follow up suggest safety and efficacy of statins in children.
- 3.5.4 The treatment goal of lipid lowering therapy in pediatric FH patients is a $\geq 50\%$ reduction in LDL cholesterol or LDL cholesterol < 130 mg/dL. There is a need in treatment of pediatric FH for balance between increased dosing and the potential for side effects vs. achieving goals. More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.

3.6 Homozygous FH

- 3.6.1 Initiation of therapy early in life and ongoing monitoring of homozygous FH is vital.
- 3.6.2 High dose statins may be effective in some homozygous FH patients, but the majority will require LDL apheresis. Liver transplantation is also being used in some centers.
- 3.6.3 Gene therapy is a potential new treatment in development and may be particularly beneficial for homozygous FH patients.

4. Management issues in adults

4.1 Lifestyle modifications

- 4.1.1 Patients with FH should be counseled regarding the following lifestyle modifications:
 - Therapeutic Lifestyle Changes and dietary adjuncts.
 - Reduced intakes of saturated fats and cholesterol: total fat 25-35% of energy intake, saturated fatty acids $< 7\%$ of energy intake, dietary cholesterol < 200 mg/d.
 - Use of plant stanol or sterol esters 2 g/d.
 - Use of soluble fiber 10-20 g/d.
 - Physical activity and caloric intake to achieve and maintain a healthy body weight.
 - Limitation of alcohol consumption.
 - Emphatic recommendation to avoid use of any tobacco products.

- 4.1.2 Clinicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for medical nutrition therapy.

4.2 Drug treatment of FH

- 4.2.1 For adult FH patients, initial treatment is the use of moderate to high doses of high-potency statins titrated to achieve an LDL cholesterol reduction $\geq 50\%$ from baseline. Low potency statins are generally inadequate for FH patients.
- 4.2.2 If the initial statin is not tolerated, consider changing to an alternative statin, or every-other-day statin therapy.
- 4.2.3 If initial statin therapy is contraindicated or poorly tolerated, ezetimibe, a bile acid sequestrant (colesevelam), or niacin may be considered.
- 4.2.4 For patients who cannot use a statin, most will require combination drug therapy.

4.3 Additional treatment considerations

- 4.3.1 If the patient is not at LDL cholesterol treatment goal with the maximum available and tolerable dose of statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred).
- 4.3.2 Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities.

4.4 Candidates for LDL apheresis

- 4.4.1 LDL apheresis is a U.S. Food and Drug Administration approved medical therapy for patients who are not at LDL cholesterol treatment goal or who have ongoing symptomatic disease.
- 4.4.2 In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:
- Functional homozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL-C ≥ 330 mg/dL).
 - Functional heterozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL-C ≥ 330 mg/dL) and 0-1 risk factors.
 - Functional heterozygous FH patients with LDL cholesterol ≥ 200 mg/dL (or non-HDL-C ≥ 230 mg/dL) and high risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.
 - Functional heterozygotes with LDL cholesterol ≥ 160 mg/dL (or non-HDL-C ≥ 190 mg/dL) and very high-risk characteristics (established CHD, other cardiovascular disease, or diabetes).

4.5 LDL apheresis referrals

- 4.5.1 Healthcare practitioners should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A list of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org).

4.6 Women of childbearing age

- 4.6.1 Women with FH should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, and niacin at least four weeks before discontinuing contraception and should not use these medications during pregnancy and lactation.
- 4.6.2 Consultation with her healthcare practitioner regarding continuation of any other lipid medications is recommended.
- 4.6.3 In case of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately and should consult with her healthcare practitioner promptly.

4.7 Treatment options during pregnancy

- 4.7.1 Statins, ezetimibe, and niacin should not be used during pregnancy. Use of other lipid lowering medications (e.g., colesevelam) may be considered under the guidance of the healthcare practitioner.
- 4.7.2 Consider LDL apheresis during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.

4.8 Hard to manage patients

- 4.8.1 If other treatment options are inadequate or the FH patient cannot tolerate pharmacotherapy or LDL apheresis, other treatment options include ileal bypass and liver transplantation (both are used rarely), and, potentially, new drugs in development.

5. Future issues, public policy, and public awareness

5.1 Screening

- 5.1.1 It is the responsibility of all primary health care providers and relevant specialists to screen all children and adults for hypercholesterolemia, and to initiate therapy in patients with FH and severe hypercholesterolemia.

5.2 Lipid specialists

- 5.2.1 Patients with FH who do not respond adequately to, or are intolerant of, initial statin therapy should be referred to a lipid specialist.
- 5.2.2 For children with FH, either consultation with or referral to a lipid specialist is recommended.
- 5.2.3 Patients who are candidates for more intensive therapy, or who have family histories of very

premature CHD (in men <45 years of age and women <55 years of age), should also be referred to a lipid specialist.

5.3 Payers

- 5.3.1 Patients with FH are at high lifetime risk of atherosclerotic cardiovascular disease and appropriate therapy is required.
- 5.3.2 Payers should cover initial screening, initiation of therapy with appropriate medications, and monitoring of response to therapy.
- 5.3.3 Payers should cover appropriate drugs including high potency statins and combination lipid drug therapy. They should also cover other drugs and combinations for patients with statin tolerance problems.
- 5.3.4 LDL apheresis and genetic testing, when appropriate, should be covered by payers.

5.4 Public and provider awareness

- 5.4.1 To promote early diagnosis of FH and the prevention, and treatment of CHD, public awareness of FH needs to be increased by a variety of methods.
- 5.4.2 Health care provider awareness needs to be increased through education at all levels and in multiple specialties, through partnering with professional organizations and through local, national and international health agencies.

5.5 Responsibility for education

- 5.5.1 Health systems, hospitals, pharmacy benefits management organizations, and insurance companies should contribute to patient and provider education.
- 5.5.2 Governmental agencies and other policy makers at local, state, national and international levels should be engaged in efforts to screen and treat FH.

5.6 Research needs

- 5.6.1 Research is needed in the following areas related to FH:
 - Agents to further lower LDL cholesterol;
 - Ways to improve adherence to and persistence with therapy;
 - Cost effective genetic screening;
 - Behavioral management of patients with FH;
 - Cost effectiveness analysis of various approaches to screening and treatment;
 - Cost effectiveness analysis of the benefits of aggressive therapy;
 - Long-term follow-up of patients with FH, including safety of long-term therapy with lipid lowering drugs;
 - Differences in drug metabolism by gender, ethnicity, and age;

- Long-term cardiovascular benefits of combination therapies;
- Management of FH in pregnancy;
- Mechanism and management of statin intolerance;
- Safety and effectiveness of dietary supplements and dietary adjuncts for LDL cholesterol reduction;
- Methods to enhance healthcare provider adherence to guidelines.

5.7 Funding

- 5.7.1 Funding for FH education and research should come from multiple sources including government, professional associations, industry, and private donations.

Concluding statements

FH is a difficult to treat but manageable disease. Primary care clinicians should be aware of the key role they play in the early detection and treatment of FH, and of the availability of additional support and guidance from lipid specialists who have undergone intensive training in the management of lipid disorders. Key elements for control of FH include reducing the LDL cholesterol concentration, management of additional CHD risk factors, such as elevated blood pressure and smoking, and improving adherence to and persistence with lifestyle modifications and pharmacotherapy. Screening first-degree relatives of patients with FH, including siblings, parents and children, facilitates early detection and treatment. Long-term drug therapy of patients with FH significantly reduces or removes the excess lifetime risk of CHD, lowering the level of risk to that of the general population.

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Familial Hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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Introduction

Familial hypercholesterolemia (FH) may be the most common serious genetic condition and is a well-known and frequent cause of premature coronary heart disease (CHD). About 5% of heart attacks under age 60 and as many as 20% under age 45 are due to FH.^{1–9} Too often, FH is diagnosed after the occurrence of a major coronary event; hence a population-based approach to identify affected individuals prior to the discovery of atherosclerosis is clearly

warranted.¹⁰ Implementation of appropriate screening can lead to early detection, diagnosis, and treatment of FH and makes a huge impact on the prevention of CHD and related detrimental sequelae.^{11,12}

Definition of Familial Hypercholesterolemias

The FH (www.ncbi.nlm.nih.gov/sites/GeneTests) are defined as a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations. FH is recognized clinically by an extreme elevation of low-density lipoprotein (LDL) cholesterol, which is characterized by an autosomal dominant or co-dominant transmission pattern with 90% or higher penetrance.^{13,14} The vast majority of families show only dominant transmission with heterozygous carriage of the causal gene. FH is, however, a co-dominant trait with the rare low-density lipoprotein receptor (*LDLR*) homozygote or compound heterozygote having extreme elevations in LDL cholesterol. In the Fredrickson classification, FH patients are most often type IIa, but IIb, and even type III hyperlipidemias may be seen.^{15–18} Affected subjects are at increased risk for all forms of atherosclerotic disease and premature death secondary to lifelong pathogenic elevations in serum LDL cholesterol.¹⁸

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Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

Definition of Familial Hypercholesterolemias

- The familial hypercholesterolemias are a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations.
- For purposes of this document, familial hypercholesterolemia (FH) will refer to the autosomal dominant forms of severe hypercholesterolemia unless otherwise specified. However, causes of inherited high cholesterol are not restricted to autosomal dominant FH.

Prevalence of FH and Associated Risk

- The prevalence of FH is 1 in 300 to 500 in many populations, making FH among the most common of serious genetic disorders.
- There are approximately 620,000 FH patients currently living in the United States.
- The risk of premature coronary heart disease (CHD) is elevated about 20-fold in untreated FH patients.
- Approximately 1 in one million persons is homozygous (or compound heterozygous) for low-density lipoprotein receptor gene (*LDLR*) mutations and has extreme hypercholesterolemia with rapidly accelerated atherosclerosis when left untreated.
- In a few populations (such as French Canadians and Dutch Afrikaners), the prevalence of FH may be as high as 1 in 100.

Genetics of FH

- Currently, known causes of FH include mutations in the *LDLR*, apolipoprotein (Apo) B (*APOB*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes.
- There are over 1600 known mutations of the *LDLR* gene documented to cause FH at the time of this writing, accounting for about 85 to 90% of FH cases.
- The Arg3500Gln mutation in *APOB* is the most common cause of hypercholesterolemia due to an *APOB* mutation, accounting for 5 to 10% of FH cases in Northern European populations (rare in other populations).
- Gain-of-function mutations in *PCSK9* cause fewer than 5% of cases in most studies.

Screening for FH

- Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated, fasting LDL cholesterol or non-high-density lipoprotein (HDL) cholesterol levels are at or above the following:
 - Adults (≥ 20 years): LDL cholesterol ≥ 190 mg/dL or non-HDL cholesterol ≥ 220 mg/dL;
 - Children, adolescents and young adults (< 20 years): LDL cholesterol ≥ 160 mg/dL or non-HDL cholesterol ≥ 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 before age 55 years and women before age 65 years).
- Cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. 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:
 - Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons, but can also occur in patellar and triceps tendons).
 - Arcus corneae in a patient under age 45.
 - Tuberos xanthomas or xanthelasma in a patient under age 20 to 25.
- At the LDL cholesterol levels listed below the probability of FH is approximately 80% in the setting of general population screening. These LDL cholesterol levels should prompt the clinician to *strongly* consider a diagnosis of FH and obtain further family information:
 - LDL cholesterol ≥ 250 mg/dL in a patient aged 30 or more;
 - LDL cholesterol ≥ 220 mg/dL for patients aged 20 to 29;
 - LDL cholesterol ≥ 190 mg/dL in patients under age 20.

Diagnosis

- Age at onset of CHD, even if approximate, is particularly important to note in the family history.
- Physical signs of FH are insensitive but can be quite specific. The presence of tendon xanthomas should be sought for by careful palpation (not just visual inspection) of the Achilles tendon and finger extensor tendons. Corneal arcus

(partial or complete) is only indicative of FH if present under age 45. Neither xanthelasma nor tuberous xanthomas are specific for FH but, if they are encountered in a younger patient, FH should be considered. Importantly, the absence of any of these physical findings does not rule out FH.

- Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria [U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry]. It should be noted that LDL cholesterol cut points usually vary with age.
- The clinical diagnosis of FH is most likely when two or more first-degree relatives are found to have elevated LDL cholesterol in the range noted above, when pediatric cases are identified in the family, or when the patient or a close relative has tendon xanthomas.
- Once a family is diagnosed with FH, somewhat lower LDL cholesterol cut points can be applied to identify additional affected family members.
- Patients with FH occasionally have elevated triglycerides and high triglycerides should not exclude the diagnosis of FH.

Genetic Screening

- Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain.
- Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.
- Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods.

Cascade Screening

- Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.
- As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.
- Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved. General population screening of a young population (before age 16) is similarly cost-effective in terms of cost per year of life saved, given that effective cholesterol-lowering treatment is begun in all those identified.

Heterozygous FH is caused by an inherited mutation from one parent only. Defective LDL receptors have either zero or a reduced capacity for LDL cholesterol uptake, which results in approximately twice the normal concentration of LDL cholesterol. Children of one heterozygote parent carrying the faulty gene have a 50% chance of inheriting it. In this document, use of the term FH refers to autosomal dominant heterozygous FH unless otherwise specified. However, causes of inherited high cholesterol are not restricted to autosomal dominant FH. Genetic defects classified as FH include defects in the LDLR, apolipoprotein B (Apo B), proprotein convertase subtilisin/kexin type 9 (PCSK9), and autosomal recessive hypercholesterolemia.

Children with two heterozygote FH carrier parents have a 25% chance of inheriting both defective genes and therefore developing homozygous FH. There is a gene dosage effect with homozygotes having markedly greater elevations of LDL cholesterol and earlier CHD onset than subjects who are heterozygotes.¹⁹ Homozygous FH is diagnosed when a person inherits exactly the same genetic mutation from both parents, whereas a person who inherits a different mutation from each parent will have compound heterozygous FH. Each of these defects leads to almost no LDL receptor activity, extremely high levels of LDL cholesterol, frequent and large tendon xanthomas, tuberous xanthomas, and a much greater probability of early onset CHD with an unusual

predilection for the coronary ostia, as well as valvular disease caused by xanthoma-like lesions.

Prevalence of FH and associated risk

According to the Centers for Disease Control and Prevention, based on data from the 2005 to 2008 National Health and Nutrition Examination Survey, there are an estimated 71 million (33.5%) adults in the United States aged ≥ 20 years with high LDL cholesterol.²⁰ These estimates include all persons with LDL cholesterol levels above recommended National Cholesterol Education Program goals, persons who report taking cholesterol-lowering medications, and all etiologies for hypercholesterolemia (e.g., obesity, uncontrolled hypothyroidism). The CDC report states that high LDL cholesterol increases with age with a prevalence of 11.7%, 41.2%, and 58.2% for ages 20 to 39, 40 to 64, and ≥ 65 years, respectively.²⁰

Heterozygous FH occurs with a frequency of about 1 in every 300 to 500 people and is therefore one of the most commonly occurring congenital metabolic disorders.^{2,21,22} Based on this estimate there are approximately 10 million people with FH worldwide. There are some populations with a much higher prevalence of FH, perhaps as high as 1 in 50 to 100 in communities with a 'founder gene',

such as Christian Lebanese, French-Canadians, and three populations in South Africa including Dutch Afrikaner, Ashkenazi Jews, and Asian Indians.^{21,23} Because those with heterozygous FH have only one normal gene, resulting in half the normal number of LDL receptors, their hepatocytes take up LDL cholesterol at approximately one-half the rate of those unaffected. Average, untreated LDL cholesterol levels are about 220 mg/dL in those with FH and serum total cholesterol levels are often in the range of 350-550 mg/dL; the risk of premature CHD is elevated about 20-fold without treatment.^{10,24} The excess risk for CHD has been estimated to be as high as 100-fold in untreated young men with FH.²³ The CHD risk in women with FH is lower than in FH men, and CHD development usually occurs about ten years later in women compared to men. Approximately 50% of males and at least 30% of females with FH will suffer fatal or non-fatal coronary events before ages 50 and 60 years, respectively.²⁵

Homozygous FH occurs in approximately 1 of every 1 million people and, due to a near total or total loss of LDL receptor functionality, cholesterol levels range from 650 to 1000 mg/dL.²¹ These patients develop rapidly accelerated atherosclerosis when left untreated. Patients with homozygous FH typically develop CHD by the second decade of life²⁶, but death may occur in the first years of life from severe CHD.²²

The genetics of Familial Hypercholesterolemias

FH is most commonly attributable to mutations (including deletion, missense, nonsense, and insertion types) in the *LDLR* gene, resulting in LDL receptors having functional reductions (partial to complete) in the capacity to clear LDL cholesterol from the circulation. Patients can be receptor negative, expressing little to no LDL receptor activity, or receptor defective, leading to the expression of *LDLR* isoforms with reduced affinity for LDL on the hepatocyte surface.²⁷⁻³² There are five major classes of *LDLR* defects:^{30,31}

- Class I: LDL receptor is not synthesized at all.
- Class II: LDL receptor is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface.
- Class III: LDL receptor does not properly bind LDL on the cell surface because of a defect in either apolipoprotein (Apo) B-100 (R3500Q) or in the LDL receptor.
- Class IV: LDL receptor bound to LDL does not properly cluster in clathrin-coated pits for receptor-mediated endocytosis.
- Class V: LDL receptor is not recycled back to the cell surface.

The gene for *LDLR* resides on the short arm of chromosome 19 (19p13.1-13.3). There are over 1600 mutations of the *LDLR* gene documented to cause FH at the time of this writing. These account for about 85 to 90% of FH cases.³³

A large number of *LDLR* mutations have been catalogued from around the world and resources listing these are available on the web (see websites at the end of the references).

Hypercholesterolemia due to an *APOB* mutation is referred to as Familial Defective Apo B (FDB).³⁴⁻³⁶ FDB is reportedly less severe than typical FH caused by *LDLR* mutations.^{37,38} The most common mutation *APOB* mutation is Arg3500Gln, accounting for 5 to 10% of FH cases in northern European populations (rare in other populations).³³

Another etiology for the FH phenotype is autosomal dominant hypercholesterolemia attributable to increased activity of PCSK9, which increases degradation of the LDL receptor.^{39,40} This is the least common cause of FH, accounting for fewer than 5% of cases in most series.³³ The causal gene, whether *LDLR*, *Apo B*, or *PCSK9*, cannot be determined clinically.

Autosomal recessive hypercholesterolemia has been attributed to reduced expression of the LDL receptor accessory protein 1 (*LDLRAP1*) that facilitates the association of LDL receptors with clathrin in cell surface coated pits.⁴¹⁻⁴³ Other rare forms of autosomal recessive hypercholesterolemia include sitosterolemia due to adenosine triphosphate (ATP)-binding cassette subfamily G member 5 (*ABCG5*) or *ABCG8* deficiency,⁴⁴ and deficiency of cholesterol 7- α hydroxylase (*CYP7A1*), which is the enzyme of the first step in bile acid synthesis, resulting in high intrahepatic cholesterol and reduced surface expression of LDL receptors. *CYP7A1* deficiency is the least common of the autosomal recessive conditions that can cause severe hypercholesterolemia.⁴³

Inherited high cholesterol may include other forms of hypercholesterolemia such as type III and familial combined hyperlipidemias, as well as polygenic hypercholesterolemia and mutations or variants in genes not yet identified.

Universal screening

All primary healthcare providers and relevant specialists are responsible for screening all children and adults for hypercholesterolemia and initiating therapy in patients with FH and other forms of severe hypercholesterolemia. Family history of high cholesterol and/or premature history of CHD in first-degree relatives (men <55 years of age and women <65 years of age) warrants suspicion of FH. Asking about early heart attacks or other coronary events in second degree relatives is also helpful, particularly in young patients. Universal screening at ages 9 to 11 years with a fasting lipid profile or non-fasting non-high-density lipoprotein (HDL) cholesterol measurement is recommended to identify all children with FH. At these young ages, LDL cholesterol discriminates those with and without FH particularly well.⁴⁵ Non-HDL cholesterol, which is a surrogate marker for Apo B-containing lipoprotein particles, is determined by subtracting HDL cholesterol from total cholesterol. A non-fasting non-HDL cholesterol result ≥ 145 mg/dL in a child indicates the need for follow-up and further evaluation of a fasting lipid profile. Screening should

occur earlier (≥ 2 years of age) in the presence of a positive family history for hypercholesterolemia or premature CHD, or the presence of other major CHD risk factors. The importance of identifying FH in children with other CHD risk factors is critical for appropriate risk stratification and treatment. Screening before 2 years of age is not recommended.⁴⁶

FH may be suspected in children, adolescents, or young adults when untreated fasting LDL cholesterol levels are ≥ 160 mg/dL or non-HDL cholesterol levels are ≥ 190 mg/dL. In adults >20 years, FH is suspected when fasting LDL cholesterol levels are ≥ 190 mg/dL or non-HDL cholesterol is ≥ 220 mg/dL. In the general population, the probability of FH is approximately 80% when LDL cholesterol levels are ≥ 250 mg/dL in patients aged 30 years or more, ≥ 220 mg/dL in patients aged 20 to 29 years, and ≥ 190 mg/dL in patients younger than 20 years of age.⁴⁷

The following physical findings should prompt the clinician to strongly suspect FH and obtain necessary lipid measurements if not already available:

- Tendon xanthomas at any age (most commonly in the Achilles tendon and finger extensor tendons but possibly in patellar and/or triceps tendons). These clinically detectable nodularities or areas of thickening of the tendons are caused by an infiltration of lipid-laden histiocytes (macrophages in connective tissue).
- Corneal arcus senilis in a patient less than 45 years of age.
- Yellow-orange tuberous xanthomas or xanthelasma in a patient aged 20 to 25 years.

Diagnosis

When hypercholesterolemia is found, it is initially important to seek and exclude possible secondary causes of the disorder (e.g., undiagnosed diabetes, hypothyroidism, nephrotic syndrome).⁴⁸ Patient history should emphasize any prior diagnosis of CHD (with age at onset), current cardiovascular symptoms, use of lipid-altering agents, and presence of other CHD risk factors with particular attention to the family history of cardiovascular disease. Age at onset of CHD in family members, even if approximate, is important to note.

Although this is an area of some controversy, the diagnosis of FH is straightforward in a family with obvious bimodal distribution of LDL cholesterol with unaffected members of the family having LDL cholesterol generally under 130 mg/dL and affected members having levels approximately two-fold higher, typically >190 to 220 mg/dL, depending on age. For any affected member of a pedigree, at least one of the parents will be affected. The diagnosis is certain if one of the family members or close relatives is confirmed to have a tendon xanthoma with high cholesterol.

Physical signs of FH are insensitive but can be quite specific. The presence of tendon xanthomas should be sought by careful palpation, not just visual inspection. They are most

commonly found in the Achilles tendons, less often in finger extensor tendons, and least often in the patellar tendon. Tendon xanthomas are essentially pathognomonic for FH; however, they occur in less than half of FH patients, and this seems to vary between populations. In a large group of Utah FH patients, prevalence was approximately equal to the patient's age minus 10, so that at age 30 years, prevalence is approximately 20 percent.⁴⁹ Tendon xanthomas are rare in younger children.⁵⁰ Achilles tendon xanthomas may be associated with tendinitis which occurs about six times more frequently among individuals with FH than among those in the general population.⁵¹ Triglyceride-rich lipoprotein remnant accumulation, which occurs in some heterozygotes, infrequently leads to tuberous xanthomas.^{15,16} In patients with homozygous FH, remnant accumulation is severe and tuberous xanthomas are frequent.^{21,52} It is important to note that cerebrotendinous xanthomatosis, which is said to cause xanthomas, may be mistaken for FH, but does not cause hypercholesterolemia. Sitosterolemia can also cause tuberous and tendon xanthomas.⁵³ Corneal arcus (partial or complete) is only indicative of FH if present under age 45. Neither xanthelasma nor tuberous xanthomas are specific for FH but if they are encountered in a younger patient, FH should be considered. Importantly, the absence of any of these physical findings does not rule out FH.

The presence of hypertriglyceridemia does not exclude the diagnosis of FH. However, a calculated LDL cholesterol measurement is typically unsuitable for patients with triglycerides ≥ 400 mg/dL and a more accurate direct measure of LDL cholesterol may be necessary to ensure proper diagnosis. Furthermore, cholesterol exchange with triglyceride-rich particles may reduce the amount of cholesterol per particle, resulting in decreased sensitivity (under-recognition) for diagnosing FH.

A variety of approaches have been developed for formally diagnosing FH by applying any one of several validated sets of criteria.^{24,54} The best characterized are the Simon Broome Register Diagnostic Criteria for FH,⁵⁵ the Dutch Lipid Clinic Network Diagnostic Criteria for FH⁵⁴ and the US Make Early Diagnosis Prevent Early Death (MEDPED) Program Diagnostic Criteria for FH.^{47,56} It should be noted that LDL cholesterol cut points usually vary with age. They may also differ when considering diagnosis of an individual within a previously well-defined FH pedigree as opposed to a new proband without a prior diagnosis of FH in the family. When considering diagnosis in first-degree relatives of a patient with *definite* FH, keep in mind that LDL cholesterol levels are usually about two-fold higher in affected as compared to unaffected family members. Some experts suggest applying age-specific 90 to 95th percentile LDL cholesterol cutpoints when diagnosing relatives of known FH patients while other criteria utilize somewhat higher LDL cholesterol cutpoints. Note that in the general population, even if all FH were included among those in the 95th percentile for LDL cholesterol, only 1 in 25 would have FH. Random variation, dietary effects, and familial polygenic influences on LDL cholesterol

can cause false-positives and false-negatives when applying any of the clinical criteria.

For a newly identified proband not known to be part of a previously identified FH family, examples of criteria for clinical diagnosis of *definite* FH (consistent with several definitions) are available (See below and Table 1). For example, the US MEDPED rules require multiple affected pedigree members (statistically similar to showing bimodality) with a few exceptions described below. Additional rules for diagnosing *definite* as well as *probable* FH are provided in the formal definitions for each of the different criteria. A website is being planned that will facilitate and automate diagnosis of FH and provide additional information for education and management.

Utilizing LDL categories defined in Table 1, criteria which can be used to diagnose *definite* FH in an individual patient without any additional family information include:

- Presence of a causal mutation for FH by DNA testing together with category 1 to 2 LDL cholesterol levels.
- Presence of a tendon xanthoma with category 2 LDL cholesterol levels.
- Patient age <20 years with category 5 LDL cholesterol levels (no requirement for multiple affected family members). Only *probable* diagnosis of FH is made in older persons with category 5 LDL cholesterol levels without additional family information.

Criteria which can be used to diagnose *definite* FH in a newly identified family requiring data for two or more relatives include:

- Category 4 LDL cholesterol levels in one family member together with category 2 cholesterol levels in a first-degree relative. Only a “probable” diagnosis of FH can be made for category 4 cholesterol levels without additional family information.
- Any two first-degree relatives with category 3 LDL cholesterol levels.
- First-degree relatives of a “definite” FH case with category 2 LDL cholesterol levels.

DNA evidence affirming the presence of a causal mutation in the *LDLR*, *APOB*, or *PCSK9* genes is the gold standard for

diagnosis if, and only if, a mutation has already been identified for the family. Due to incomplete mutation detection in newly identified families, DNA testing may actually be less sensitive than standard clinical criteria.⁵⁷

Cascade screening

The process of family tracing for identification of people at risk of a genetic condition is called cascade screening and involves screening of family members.⁵⁸ Too few FH patients are diagnosed. In any given population it is estimated that approximately 20% of patients with FH are diagnosed and less than 10% of patients with FH receive appropriate treatment.^{23,58} The most cost-effective strategy to diagnose patients with FH, initiated by the MEDPED program, is to screen close relatives of patients already diagnosed with FH.^{59–61} Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients. There is a 50% probability of detection in first-degree relatives, 25% probability in second-degree relatives, and a 12.5% probability in third-degree relatives. In families where the disease-causing mutation has been identified, genetic testing may also be a part of cascade screening. This method will help identify new cases of FH among those at highest risk for FH. As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening. Primary care practitioners are strongly encouraged to use cascade screening.

Genetic screening

Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain. Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment, with little evidence for psychological harm.^{62,63} In families with a previously identified causal mutation, genetic testing clearly provides a gold standard for diagnosis. It may be particularly useful in such a family for a relative with an equivocal or only suggestive

Table 1 LDL cholesterol categories often used for FH diagnosis*

| Category | Description | LDL cholesterol (mg/dL) [†] by age | | |
|----------|--|---|-----------|---------|
| | | Age <20 | Age 20–29 | Age 30+ |
| 1 | General population 95 th percentile | 130 | 160 | 190 |
| 2 | 80% have FH in first-degree relatives [‡] | 150 | 170 | 200 |
| 3 | 80% have FH in general population | 190 | 220 | 260 |
| 4 | 99% have FH in general population | 220 | 240 | 280 |
| 5 | 99.9% have FH in general population | 240 | 260 | 300 |

*These LDL cholesterol cut points were derived from analyses of Gaussian (normal) distributions in FH and general populations given the conditions in the descriptions. Fasting lipid levels are assumed. For diagnostic criteria, specifying one category implies all higher categories as well.

[†]To convert mg/dL to SI units, divide the results by 38.6.

[‡]This category is relevant for diagnosis of FH patients who are first-degree relatives of a known FH case. At the LDL cholesterol level shown, approximately 80% of first-degree relatives can be expected to have FH.

LDL cholesterol level. Genetic testing may also be reasonable for identifying a causal mutation in newly identified families strongly suspected of having FH. Individuals with no family contacts but who likely have FH may also be good candidates. However, genetic testing does have limitations. Among hypercholesterolemic patients with a diagnosis of *possible* FH, the mutation identification rate is 50% or less, whereas in patients with a more definite phenotypic FH, the mutation identification rate can be as high as 86%.^{64–66} However, considerably lower discovery rates have been reported even using current genetic methods.⁶⁷ An excellent recent review of genetic screening studies is available.³³ Importantly, a negative genetic test does not exclude FH. Furthermore, persons with high LDL cholesterol remain at high risk and should be treated according to accepted guidelines regardless of the results of genetic testing.

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Treatment of adults with Familial Hypercholesterolemia and evidence for treatment: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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Rationale for treatment

Patients with familial hypercholesterolemias (FH) are at greatly increased lifetime risk of cardiovascular disease (CVD). If left untreated, most individuals with FH will experience premature coronary heart disease (CHD) and/or stroke. The mean age of onset of a cardiovascular event in men with FH is in the early 40s and in women with FH in the early 50s.¹ Although fewer than 5% of acute myocardial infarctions (AMI) occur in individuals ≤ 40 years of age, FH is associated with a 24-fold increase in the risk of myocardial infarction by age 40.² In western countries, the prevalence of CVD in middle-aged individuals with FH ranges from 22% to 39%.^{3–8} Therefore, all individuals with FH, regardless of age, will require lifestyle and drug

treatment to remove the excess cardiovascular risk due to their genetic disease. Intensification of treatment is indicated in those with FH who already have clinically evident CVD, diabetes, or other cardiovascular risk factors.

Individuals with FH and established CHD or other atherosclerotic CVD are at the very highest risk of future cardiovascular events and death (Table 1).^{3,4,7,9–12} In non-FH patients, diabetes is considered a CHD risk equivalent according to current guidelines.¹³ The presence of diabetes therefore places individuals with FH at very high risk for CVD. FH patients with CVD or diabetes require more aggressive treatment of LDL cholesterol, non-HDL cholesterol, and other risk factors.

Risk factors for CVD in individuals with FH are similar to the risk factors of those without FH (Table 2).^{3,4,7,9–12} However, in the setting of high cholesterol levels, the effect of each risk factor is amplified, resulting in a greater increase in risk than occurs with lower cholesterol levels.^{14,15} Individuals with FH who have two or more cardiovascular risk factors are at very high risk of CVD and should receive intensive treatment of their cholesterol as well as the other modifiable cardiovascular risk factors. More intensive cholesterol treatment may be considered in individuals with FH who have only one cardiovascular risk factor, along with treatment of the modifiable risk factor.

Smoking markedly accelerates the atherosclerotic disease process in individuals with FH, and particularly accelerates risk in men. Therefore every effort should be made to encourage smokers to quit. Members of families

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Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

Rationale for Treatment

- Individuals with familial hypercholesterolemias (FH) have a very high lifetime risk of coronary heart disease (CHD) and are at very high risk of premature onset CHD.
- Early treatment is highly beneficial. Long term drug therapy of patients with FH can substantially reduce or remove the excess lifetime risk of CHD due to the genetic disorder and can lower CHD event rates in FH patients to levels similar to those of the general population.
- FH requires lifelong treatment and regular follow-up.

Treatment

- Both children and adults with low-density lipoprotein (LDL) cholesterol ≥ 190 mg/dL [or non-high-density lipoprotein (HDL) cholesterol ≥ 220 mg/dL] after lifestyle changes will require drug therapy.
- For adult FH patients (≥ 20 years of age), drug treatment to achieve an LDL cholesterol reduction $\geq 50\%$ should be initiated.
- Statins should be the initial treatment for all adults with FH.

Intensified Drug Treatment

- Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL cholesterol < 100 mg/dL and non-HDL cholesterol < 130 mg/dL).
- Any of the following places FH patients at higher CHD risk: clinically evident CHD or other atherosclerotic CVD, diabetes, a family history of very early CHD (in men < 45 years of age and women < 55 years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.
- In FH patients without any of the characteristics listed above, intensification of drug therapy may be considered if LDL cholesterol remains ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL) or if initial 50% reduction in LDL cholesterol is not achieved.
- Ezetimibe, niacin, and bile acid sequestrants are reasonable treatment options for intensification of therapy, or for those intolerant of statins.
- The potential benefit of multidrug regimens for an individual patient should be weighed against the increased cost and potential for adverse effects and decreased adherence.

Risk Factors Should be Aggressively Treated

- Risk factors are the same in FH as in the general population and require aggressive management to reduce CHD risk, with special attention to smoking cessation.
- Regular physical activity, a healthy diet and weight control should be emphasized.
- Blood pressure should be treated to $< 140/90$ mm Hg (or $< 130/80$ mm Hg in those with diabetes). Low dose aspirin (75-81 mg per day) should be considered in those at high CHD or stroke risk.

Risk Stratification Algorithms Should not be Used

- Individuals with FH are at high CHD risk. The 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools. Therefore, assessment of 10-year risk is not recommended.
- All FH patients require lifestyle management and very few will not require lipid-lowering drug therapy.

Consider Referral to a Lipid Specialist

- Consider referral to a lipid specialist with expertise in FH if LDL cholesterol concentrations are not reduced by $\geq 50\%$ or if patients are at high risk.
- Cascade testing of first-degree relatives should be offered to all individuals with FH.

with FH should also be counseled to avoid smoking initiation, and to avoid passive smoke exposure.

Individuals with metabolic syndrome (defined in Table 1) have a >2 -fold increase in cardiovascular risk and a 1.5-fold increased risk of overall mortality.¹⁶ The presence of metabolic syndrome therefore places individuals with FH at higher cardiovascular risk and indicates

the need for more aggressive modification of lifestyle and treatment of risk factors.^{13,17}

Recent large epidemiologic and genetic studies have found increased cardiovascular risk with elevated lipoprotein (a) [Lp(a)] levels in the general population and some studies of FH patients.¹⁸ Some evidence suggests the excess risk of high Lp(a) levels may be somewhat ameliorated when

Table 1 Characteristics placing FH patient at the highest CVD risk

Intensification of treatment and an LDL-C goal <100 mg/dL (non-HDL-C <130 mg/dL) is recommended for FH patients with any of these very high risk characteristics

| | |
|--|---|
| Established CHD or other CVD | History of acute myocardial infarction, stroke, peripheral arterial disease, resuscitated cardiac arrest, cardiovascular revascularization, stable or unstable angina, transient ischemic attack, carotid artery stenosis >50%, aortic abdominal aneurysm |
| Smokers | Male current smokers have >2-fold higher risk than female smokers – Encourage smoking cessation to reduce risk |
| Diabetes mellitus | Lifestyle or drug treated diabetes |
| Family history of very premature onset CHD | First or second degree male relative onset before age 45 First or second degree female relative onset before age 55 |
| 2 or more risk factors | See Table 2 |

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

LDL-C levels are <100 mg/dL.^{19,20} In extreme cases, LDL-apheresis effectively removes Lp(a), although randomized trials of CVD risk reduction are lacking. The majority of studies have not found an association for C-reactive protein or apolipoprotein (Apo) E genotype.³ Although genetic testing is not routinely recommended for most individuals with FH, an identified DNA mutation does place an individual at higher risk than when a DNA mutation is not confirmed.²⁰

Evidence drug treatment is beneficial

Treatment recommendations for adults with FH are outlined in Table 3. Evidence supporting these recommendations is discussed below.

All contemporary guidelines recommend using statins as the first line therapy for cardiovascular risk reduction in FH and other patients with hypercholesterolemia.^{1,17,20–23} Extensive clinical trial evidence supports the use of statins to reduce cardiovascular events in all patient populations, including those with FH. Moderate and high dose statins have an excellent record of safety.^{24–27} Statins also reduce total mortality in high risk populations.

Placebo-controlled CVD endpoint trials have not been performed specifically in individuals with a diagnosis of FH since it is considered unethical to withhold treatment from patients with inborn errors of metabolism.^{28,29} Therefore, estimates of the true efficacy of long-term statin treatment of individuals with FH are not available. However, observational data from large cohorts of FH patients in Europe suggest

Table 2 Cardiovascular risk factors in individuals with FH

| Risk factor | Cut-points for risk factors If >2 risk factors present intensification of therapy is recommended |
|---------------------------------------|---|
| Increasing age | Men >30 years of age Women >40 years of age |
| Baseline LDL-C level | >250 mg/dL |
| Male sex | Male sex |
| Smoking | Current smoker |
| Family history of premature onset CHD | First degree male relative onset before age 55 First degree female relative onset before age 65 |
| Metabolic syndrome | 3 of 5 characteristics: <ul style="list-style-type: none"> • Increased waist circumference: <ul style="list-style-type: none"> Men >40" (>37" in some populations) and women >35" • Blood pressure ≥130 mm Hg/or ≥80 mm Hg or drug treatment • Triglycerides ≥150 mg/dL or drug treatment • Low HDL-C: <ul style="list-style-type: none"> Men <40 mg/dL and women <50 mg/dL • Elevated glucose ≥100 mg/dL or drug treatment |
| Low HDL-C level | HDL-C <40 mg/dL |
| Hypertension | Blood pressure >140/or >90 mm Hg or drug treatment |
| High lipoprotein (a) | ≥50 mg/dL using an isoform insensitive assay |
| Physical findings | Tendon xanthoma |

Abbreviations: CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3 Adult FH treatment recommendations

1. **All** adult FH patients should receive long-term cholesterol-lowering therapy to reduce LDL-C by >50%
 - Almost all will require a high dose statin
2. Intensification of cholesterol-lowering therapy should be considered in higher risk FH patients (see Table 1)
 - Clinically evident CHD or other cardiovascular disease
 - Diabetes
 - Family history of very premature onset CHD (first degree relative male <45 years or female <55 years)
 - Current smoking (strongly encourage smoking cessation)
 - Two or more cardiovascular risk factors other than smoking (see Table 2)
 - Most will require ezetimibe or another drug in combination with a high dose statin
 - The potential benefit for an individual patient should be weighed against the potential for adverse effects, cost, and decreasing adherence with multidrug regimens.
3. Intensification of therapy may be considered in lower risk FH patients after the initial >50% reduction in LDL-C
4. Treat other cardiovascular risk factors
 - Emphasize a healthy diet, regular physical activity and weight control
 - Avoid tobacco
 - Control blood pressure <140/<90 mm Hg (Diabetes: <130/<80 mm Hg)
 - Low-dose aspirin for those with cardiovascular disease or diabetes; consider for those with ≥ 2 risk factors
5. Consider referral to a lipid specialist
 - More aggressive lipid management
 - Cascade testing to identify relatives with FH

Abbreviations: CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

long-term statin treatment removes the excess lifetime risk of CVD disease due to FH to a level similar to that of the general population. A Dutch study evaluating a cohort of over 2100 FH patients who did not have CVD in 1990 (prior to availability of the first statin) found that in those who later took statin therapy, the risk of myocardial infarction was reduced by 76% over the next 8+ years to a rate similar to that of an age-matched general population.³⁰ Similarly, an analysis of the U.K. Simon Broome database (n = 3382) of asymptomatic FH patients who used statins had rates of CHD death similar to the general population. Moreover, all-cause mortality was 33% lower than in the general population, primarily due to a 37% lower risk of fatal cancer.³¹

Although no randomized cardiovascular outcomes trials of exclusively FH patients are available, several outcomes trials in populations of severely hypercholesterolemic persons have been performed. Two placebo-controlled statin trials in populations with severely elevated LDL cholesterol levels >170 mg/dL found moderate dose simvastatin or pravastatin reduced the risk of nonfatal coronary events and CVD death.^{32,33} The Scandinavian Simvastatin Survival Study, performed in a secondary prevention population, found a significant 30% reduction in both stroke and total mortality over five years of treatment.³² The West of Scotland trial of a largely primary prevention population also found a trend toward reduced total mortality (-22%; p = 0.051).³³ The MEGA Study was the only trial in a severely hypercholesterolemic population performed outside the US and Europe. This five-year primary prevention trial of hypercholesterolemic Japanese, primarily female, patients found a lower statin dose (pravastatin 10 to 20 mg) combined with diet reduced cardiovascular risk by 25% over diet alone.³⁴

An individual-level meta-analysis of 14 randomized placebo-controlled trials of statin therapy (n > 90,000) found that individuals with baseline LDL cholesterol >175 mg/dL (>4.5 mmol/L) experienced the same 23% relative risk reduction as those with lower LDL cholesterol levels.³⁵ It should be noted that individuals with high LDL cholesterol levels are at higher risk of CVD, and therefore have a greater reduction in the absolute risk of CVD. A subsequent individual-level meta-analysis that included an additional 12 trials further found that high dose statins reduce risk more than moderate dose statins regardless of LDL cholesterol level.³⁶

Non-statin treatments have also been found to reduce CVD events in severely hypercholesterolemic populations, although none have been shown to reduce CVD deaths or total mortality. Individually, each of four small dietary trials (three evaluated polyunsaturated fats), in men with CHD failed to show a significant reduction in CVD events, but overall the reduction in CVD events was proportionate to the fairly modest reductions in LDL cholesterol level of <20%.³⁷⁻⁴⁰ Two larger placebo-controlled trials of the bile acid sequestrants, colestipol and cholestyramine, also found reductions in CVD over a five-year period proportionate to the degree of LDL cholesterol lowering of 13 to 21% in primary prevention and CHD populations.^{41,42} A placebo-controlled trial of niacin (2 grams) in men with CHD also found a reduction in CHD events (17%) proportionate to the magnitude of non-HDL cholesterol reduction (17%).^{43,44} A trial of ileal bypass surgery in CHD patients lowered LDL cholesterol by 38% and CVD events by 30%.⁴⁵ A placebo-controlled primary prevention trial of gemfibrozil found a significant 34% reduction in CHD events in hypertriglyceridemic men, which was somewhat

greater than that expected from the magnitude of non-HDL cholesterol (16%) or LDL cholesterol (10%) lowering.^{44,46} However, an ancillary study to this trial, that evaluated men with CHD, found no benefit from gemfibrozil compared to placebo.⁴⁷

No cardiovascular event outcomes trials of ezetimibe or a fibrate in combination with statin therapy have been performed in severely hypercholesterolemic populations, nor are any planned at this time. The results of cardiovascular endpoint trials evaluating statins used in combination with other drugs in less severely hypercholesterolemic populations are discussed below.

Evidence for >50% LDL cholesterol reduction

High dose statins reduce cardiovascular risk more than moderate dose statins, regardless of the baseline LDL cholesterol level.³⁶ Two trials using a non-invasive endpoint of carotid intimal thickness (CIMT) have been performed in FH patients. The first trial, [Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP)], found more aggressive LDL cholesterol lowering with atorvastatin 80 mg (54%) resulted in regression of CIMT over two years compared to progression of CIMT in those receiving less aggressive treatment with simvastatin 40 mg (42% LDL cholesterol lowering).⁴⁸ Regression in the atorvastatin group occurred despite a mean on-treatment LDL cholesterol level of 150 mg/dL. After the simvastatin group had been switched to atorvastatin 80 mg for two more years of treatment, CIMT progression was arrested although no regression was observed.⁴⁹ The second CIMT trial [Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerotic Regression (ENHANCE)] in FH patients evaluated the addition of ezetimibe 10 mg to simvastatin 80 mg.⁵⁰ Despite the 27% lower LDL cholesterol level with the addition of ezetimibe, no difference in CIMT was observed after two years of treatment. Since 80% of ENHANCE participants had received long-term statin therapy prior to trial entry, these findings were not surprising given the results of the four-year follow-up of patients switched to atorvastatin 80 mg in the earlier ASAP trial.⁴⁹ Notably the 20% of ENHANCE participants who were not receiving statins at study entry did have evidence of CIMT progression. The most important finding of ENHANCE was that long-term statin therapy had normalized the CIMT at study entry for the ENHANCE participants (who were on average 46 years old at baseline), to the level of a 32 year old male with an LDL cholesterol of 134 mg/dL.⁵¹ Another Dutch study observed similar results in FH patients treated with LDL cholesterol lowering medication for at least five years.⁵² These patients experienced 59% reductions in LDL cholesterol from baseline and had both LDL cholesterol levels (145 mg/dL) and CIMT similar to their spouses. A second drug (predominantly ezetimibe) was used in addition to a moderate to high dose statin in 25% of FH patients in this study.

Taken together, these findings suggest long-term reductions in LDL cholesterol of >50% essentially normalizes the adverse consequences of this genetic disorder to the level of the general population and therefore should be the initial goal of therapy in all adult FH patients. However, the general population still has significant cardiovascular risk. U.S. guidelines have identified an LDL cholesterol goal <100 mg/dL (and non-HDL cholesterol <130 mg/dL) for individuals at moderately high to very high cardiovascular risk.¹⁷ Therefore, it is reasonable to intensify therapy in FH patients who are at particularly high risk due to the presence of clinical or subclinical CVD, diabetes, 2 or more cardiovascular risk factors, or are smokers (Table 2). Although it is also reasonable to attempt to achieve an LDL cholesterol <100 mg/dL in many of these high risk FH patients, it may be very difficult. The potential benefit for an individual patient should be weighed against the potential for adverse effects, cost, and decreasing adherence with multidrug regimens. It should be noted that no clinical trial data are yet available on the long-term efficacy and safety of high dose statins used in combination with other drugs.

Statin combination therapy

No large cardiovascular endpoint trials of statins used in combination with another drug have been performed in FH or severely hypercholesterolemic populations. However, several of the completed trials of a statin combined with ezetimibe, niacin, fibrates and omega-3 fatty acids have implications for the treatment of FH patients.

The primary actions of ezetimibe are LDL cholesterol and non-HDL cholesterol lowering. Used as monotherapy or in addition to a statin, ezetimibe lowers LDL cholesterol and non-HDL cholesterol on average by 15–20%.⁵³ Two cardiovascular endpoint trials have been completed, and a third is underway. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial was a placebo-controlled trial performed in a primary prevention population of individuals with aortic stenosis and baseline LDL cholesterol levels of 140 mg/dL.⁵⁴ After 4.4 years of treatment with simvastatin 40 mg/ezetimibe 10 mg, the 22% reduction in ischemic CVD events was less than expected based on the 50% reduction in LDL cholesterol, based on a previous meta-analysis of statin trials.³⁵ However, a subsequent *post hoc* analysis did find the expected magnitude of CVD event reduction in the lowest two tertiles of aortic stenosis severity.⁵⁵ The Study of Heart and Renal Protection (SHARP) compared simvastatin 20 mg/ezetimibe 10 mg to placebo in a primary prevention population of individuals with chronic kidney disease and a mean LDL cholesterol of 108 mg/dL.⁵⁶ Major CVD events were reduced by 17% in the simvastatin/ezetimibe group, a degree of risk reduction predicted by the 32 mg/dL reduction in LDL cholesterol.^{35,57} In a prespecified analysis of the approximately two-thirds of participants who were not receiving dialysis, CVD risk was significantly reduced by 20%. Therefore, there is some evidence that the addition of

ezetimibe to moderate dose statin therapy provides additional risk reduction benefit in patients without other severe or end-stage diseases. Given its record of tolerability and apparent safety when used in combination with statins,^{53,58} it is reasonable to consider the addition of ezetimibe to a maximal dose of statin in FH patients who require intensification of therapy, or who are intolerant of statins.

Several very small surrogate endpoint trials have evaluated niacin used in combination with a moderate dose statin in populations without severe hypercholesterolemia. Unfortunately, although meta-analyses of niacin trials overall show cardiovascular risk reduction benefit, no definitive conclusions can be drawn regarding the additional cardiovascular event reduction benefit of niacin added to statin therapy, or the benefit of HDL cholesterol and triglyceride alterations *per se*.^{59,60} The results of the ongoing cardiovascular endpoint trials Niacin Plus Statin to Prevent Vascular Events (AIM-HIGH) and Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) are needed to address these questions.^{61,62} No trials evaluating the safety and efficacy of niacin combined with the highest doses of statins are anticipated.⁶³

The only trial of statin plus fibrate, Action to Control Cardiovascular Risk in Diabetes (ACCORD), did not find any additional cardiovascular risk reduction benefit in the trial as a whole when fenofibrate was added to simvastatin therapy in diabetic patients.⁶⁴ Subgroup analyses did find a trend toward benefit with the addition of fenofibrate in those with triglycerides ≥ 204 mg/dL and HDL cholesterol ≤ 34 mg/dL, whereas no benefit was found in the large majority not meeting these conditions (interaction $p = 0.06$). On the other hand, the addition of fenofibrate *increased* cardiovascular risk in women (interaction $p = 0.01$). ACCORD has several important implications for the treatment of FH patients for the reduction of cardiovascular risk. First, treatment of diabetes with lifestyle and hypoglycemic drugs is an excellent strategy for lowering LDL cholesterol and triglycerides in diabetic patients. Both the usual care and aggressive diabetes treatment groups had improvements in both lipid parameters over the course of the trial. Second, on the basis of extensive evidence, high dose statins are preferable to a low or moderate dose statin used in combination with a fibrate for cardiovascular prevention. Although ACCORD did suggest benefit in high triglyceride/low HDL cholesterol patients, no benefit was observed in the rest of the study participants. This is in contrast to high dose statins, which reduce cardiovascular risk in all subgroups of individuals regardless of concomitant triglyceride or HDL cholesterol abnormalities or LDL cholesterol levels.³⁶ Therefore, fibrates are not indicated in FH patients with genetic disorders manifested primarily as increased LDL cholesterol levels, without elevated triglyceride levels. However, severely hypertriglyceridemic FH patients, such as those with Familial Combined Hyperlipidemia, may need treatment with a triglyceride-lowering agent in addition to lifestyle and statin therapy.

Omega-3 fatty acids in pharmacologic doses are primarily used to lower triglycerides rather than LDL cholesterol. The largest trial ($n > 18,000$) of omega-3 fatty acid supplementation was performed in Japan, where fish consumption is high. This trial found an additional 20% reduction in CHD events with eicosapentaenoic acid (EPA) 1800 mg in statin treated hypercholesterolemic patients with and without CVD.⁶⁵ EPA did not influence LDL cholesterol level in this population without significant HDL cholesterol (58 mg/dL) or triglyceride (153 mg/dL) abnormalities. Interestingly, the main effect of EPA was to decrease nonfatal CHD events without decreasing the risk of sudden death. The most recent trials of omega-3 supplementation in US and European countries have not found evidence of cardiovascular benefits from moderate doses of either marine omega-3 fatty acid (EPA and docosahexaenoic acid) or plant omega-3 (alpha-linolenic) supplementation in high-risk patients with high levels of utilization of lipid-modifying, antihypertensive, and antithrombotic therapies.⁶⁶⁻⁶⁸ For FH patients, it is therefore reasonable to emphasize aggressive risk factor treatment and reserve omega-3 fatty acids for the treatment of severely hypertriglyceridemic patients.

Other treatments

Plasma exchange has been shown to prolong the lives of children with homozygous FH.⁶⁹ Plasma exchange has been largely replaced with LDL apheresis. LDL apheresis lowers LDL cholesterol similarly to maximal lipid-lowering drug therapy, and is the only treatment that substantially lowers Lp(a). No randomized trials of LDL apheresis have been performed, but it is reasonable to assume reductions in CVD events are proportional to the degree of LDL cholesterol lowering.^{70,71} LDL apheresis should be considered in high risk adult FH patients, such as those with overt CVD who are refractory to therapy and in those who are intolerant to drug therapy.⁷²

Cost-effectiveness

Long-term high dose statin therapy in adult FH patients is cost-effective for both primary and secondary prevention of CVD well below the threshold of \$50,000 per quality adjusted life year (QALY). An analysis performed for the U.K. National Institute for Health and Clinical Excellence (NICE) found simvastatin 80 mg, atorvastatin 80 mg, or rosuvastatin 40 mg were cost-effective over simvastatin 40 mg (£13,500/QALY or \$21,000 in 2011 US dollars) in FH patients without clinical CVD.²⁹ The cost-effectiveness models were sensitive to age in the case of asymptomatic FH *diagnosed after* age 60, with atorvastatin 80 mg becoming less cost-effective over simvastatin 40 mg (£26,250/QALY or \$40,400 in 2011 US dollars). It should be noted that atorvastatin 80 mg will become more cost-effective when it becomes generic in the U.S. in late 2011. In general, statins used for secondary prevention are about twice as

Table 4 National and international guidelines for the treatment of FH patients

| U.S. Guidelines | European Guidelines | United Kingdom Guidelines | Canadian Guidelines |
|--|---|--|--|
| ATP III (2002,2004) ^{13,17} AHA/ACC (2006) ⁷⁸ | 4 th European Cardiovascular Prevention Guidelines (2007) ²² | UK NICE Familial Hypercholesterolemia Guidelines (2008) ^{1,20} | Canadian Dyslipidemia Guidelines (2009) ²³ |
| No specific treatment recommendations for FH patients | FH patients: Aggressive statin treatment starting at a young age | Offer lifestyle advice, especially on smoking cessation | Low risk (FRS<10%) |
| Very high risk (CVD + diabetes, multiple risk factors) | High Clinical Priority includes: | Start treatment with high intensity statin to achieve a >50% reduction in LDL-C (such as simvastatin 80 mg or appropriate doses of atorvastatin or rosuvastatin) | Drug therapy recommended: |
| • LDL-C goal <100 mg/dL & optional LDL-C goal <70 mg/dL | • Patients with established CVD | • Increase to maximum dose if necessary | • LDL-C 5.0 mmol/L (>190 mg/dL) usually reflecting a genetic lipoprotein disorder (class I, level C) |
| | - Multiple risk factors and ≥5% 10-year risk CVD death | Consider ezetimibe | • TC/HDL-C ratio >6.0 (class IIb, level C), especially with severe hypertriglyceridemia to prevent pancreatitis |
| | - Diabetes type 2 and type 1 with microalbuminuria | • As monotherapy if statin use is limited by intolerance | • Goal: ≥50% ↓ LDL-C (Class IIa, level A) |
| | - Markedly increased single risk factor, especially if associated with end-organ damage | • As combination therapy if LDL-C not appropriately controlled | |
| | • Close relatives of individuals with premature CVD or at particularly high risk | Refer patients to a specialist with expertise in FH if | Moderate risk (FRS 10-19%) |
| High risk (CHD risk equivalent) | • LDL-C goal <100 mg/dL | • LDL-C concentrations not reduced by >50% | • Initiate treatment if LDL-C > 3.5 mmol/L (130 mg/dL); TC/HDL-C > 5.0; hs-CRP > 2 mg/dL in men >50 or women >60 years; family history or elevated CRP (RRS) |
| • LDL-C goal <100 mg/dL | • Optional LDL-C goal <80 mg/dL | At high risk (established CHD, family history of early disease, or ≥risk factors) | • Goal: LDL-C <77 mg/dL or ≥50% ↓ LDL-C [alternate Apo B <0.80 g/L] (Class IIa, level A) |
| • Optional/reasonable* LDL-C goal <70 mg/dL | | Offer referral to a cardiologist for evaluation of CHD if family history early CHD or ≥risk factors | High risk (CHD, other CVD, most patients with diabetes, FRS ≥20%, RRS ≥20%) |
| | Objectives of CVD prevention | Do NOT use risk estimation tools (such as Framingham Risk Score, Reynolds Risk Score, SCORE or others) | • Consider drug treatment for all high risk patients |
| Moderately high risk (≥2 RF & 10-20% CHD risk*) | • Maintain or achieve low lifetime CVD risk | | • Goal LDL-C <77 mg/dL or ≥50% ↓ LDL-C [alternate Apo B <0.80 g/L] (Class I, level A) |
| • LDL-C goal <130 mg/dL | • No smoking | | |
| Optional LDL-C goal <100 mg/dL | • Healthy food choices | | |
| | • Physical activity 30 min moderate activity daily | | |

| | | |
|---|--|--|
| <p>Low risk (0–1 risk factor & <10% CHD risk*)</p> <ul style="list-style-type: none"> • Add drugs if LDL-C > 190 mg/dL (optional > 160 mg/dL) <p>LDL-C goal < 160 mg/dL</p> <p>Non-HDL-C goal is 30 mg/dL higher than LDL-C goal when triglycerides 200–500 mg/dL</p> <p>Treat other cardiovascular risk factors</p> | <ul style="list-style-type: none"> • BMI < 25 kg/m² and avoidance of central obesity • Blood pressure < 140/90 mm Hg • Total cholesterol < 5 mmol/L (190 mg/dL) LDL-C < 3 mmol/L (115 mg/dL) • Fasting blood glucose < 6 mmol/L (110 mg/dL) <p>Achieve more rigorous risk factor control in high risk individuals, if feasible</p> <ul style="list-style-type: none"> • Blood pressure < 130/80 mm Hg • Total cholesterol < 4.5 mmol/L (175 mg/dL); option < 4 mmol/L (155 mg/dL) • LDL-C < 2.5 mmol/L (100 mg/dL); option < 2 mmol/L (80 mg/dL) • Fasting blood glucose < 6 mmol/L and HbA1c < 6.5% | <p>Encourage healthy behaviors</p> <ul style="list-style-type: none"> • Smoking cessation • Diet (reduced saturated fats and refined sugars) • Weight reduction and maintenance • Exercise (daily) • Stress management |
| <p>Metabolic syndrome</p> <ul style="list-style-type: none"> • Intensify lifestyle therapy | <p>Consider cardioprotective drug therapy in high risk individuals, especially those with established atherosclerotic CVD</p> | <p>See report for additional recommendations for FH diagnosis, referral, specialist care, and special considerations for women and children</p> |
| <p>Offer referral for cascade testing to identify relatives with FH</p> <p>Offer a structured review at least annually</p> <ul style="list-style-type: none"> • Measure fasting lipid profile • Assess for symptoms of CHD and smoking status • Discuss medication adherence & possible side effects • Update family pedigree with CHD events & cascade testing • Use a low threshold for urgent referral for evaluation of sign & symptoms of CHD | <p>Offer referral for cascade testing to identify relatives with FH</p> <p>Offer a structured review at least annually</p> <ul style="list-style-type: none"> • Measure fasting lipid profile • Assess for symptoms of CHD and smoking status • Discuss medication adherence & possible side effects • Update family pedigree with CHD events & cascade testing • Use a low threshold for urgent referral for evaluation of sign & symptoms of CHD | <p>Encourage healthy behaviors</p> <ul style="list-style-type: none"> • Smoking cessation • Diet (reduced saturated fats and refined sugars) • Weight reduction and maintenance • Exercise (daily) • Stress management |

Abbreviations: Apo, apolipoprotein; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; FRS, Framingham Risk Score; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; RRS, Reynolds Risk Score; TC, total cholesterol.

*No specific mention about whether or not to perform Framingham Risk Scoring (FRS) in FH patients; FRS or other risk stratification algorithms are NOT recommended in FH patients due to their very high short and long-term cardiovascular risk due to elevated LDL-C and/or non-HDL-C levels.

cost-effective as when used for primary prevention.⁷³ Cost-effectiveness evaluations of the addition of other drugs to statin therapy have not yet been performed. Nor has the cost-effectiveness of LDL-apheresis been formally evaluated.²⁰

Targets of treatment

FH is a condition characterized by elevated LDL cholesterol concentrations. Those with Familial Combined Hyperlipidemia may also have elevations in non-HDL cholesterol as well as abnormalities in triglycerides and HDL cholesterol. Evidence supports the recommendation to use LDL cholesterol as the primary target of therapy and non-HDL cholesterol as the second target of therapy in those with elevated triglyceride levels.^{13,36,44,74} However, there is insufficient evidence at this time for drug treatment targeting triglycerides or HDL cholesterol for cardiovascular prevention in FH or other patient populations.⁶⁰ Nor is there yet evidence that further targeting Apo B, after LDL cholesterol or non-HDL cholesterol, improves cardiovascular outcomes.⁷⁴

Aggressive lipid lowering to achieve >50% LDL cholesterol reduction is recommended for FH patients.¹ High dose statins reduce CVD risk more than moderate dose statins regardless of LDL cholesterol level and are therefore appropriate for almost all FH patients.³⁶ Lower doses of statins may be more appropriate for some FH patients, such as those of Japanese or other Asian ancestry, due to safety concerns with higher doses.^{75–77,78}

International guidelines have identified LDL cholesterol and, in some cases, non-HDL cholesterol or Apo B as targets for therapy (Table 4).^{1,13,17,20,23,78} The U.K. NICE Familial Hypercholesterolemia Guidelines are the most comprehensive guidelines addressing the diagnosis and treatment of FH patients and were based on an extensive evidence review.^{1,20} Evidence supports drug treatment of lower risk patients with or without FH when LDL cholesterol is >190 mg/dL with a >50% reduction in LDL cholesterol recommended. Those with established CHD, other atherosclerotic CVD, diabetes, or multiple risk factors should be more aggressively treated to achieve LDL cholesterol <100 mg/dL. More aggressive optional LDL cholesterol goals <70–80 mg/dL are suggested for the highest risk patients, although this level of LDL cholesterol is very difficult to achieve in patients with FH.

Attainment of an LDL cholesterol <100 mg/dL is a problem for FH patients unless high dose statins and/or statin combination therapy is used. In a recent Dutch study of three academic and two regional medical centers (n = 1249), 96% were on a statin and 47% achieved >50% LDL cholesterol reduction.⁷⁹ However, only 21% had LDL cholesterol <100 mg/dL (2.5 mmol/L). Of those with LDL cholesterol ≥100 mg/dL, 27% were on maximum statin dose plus ezetimibe. Physician reluctance to intensify therapy was reported in 32% of those with LDL cholesterol ≥100 mg/dL. Another report on a Spanish

cohort (n = 881) with FH (mean age of 47 years and 22% with clinical CVD) also identified underutilization of intensive therapy.³ Baseline mean LDL cholesterol was 336 mg/dL and non-HDL cholesterol was 365 mg/dL. Over 80% reported statin use at the time of the study but <30% were receiving the highest dose of simvastatin or atorvastatin alone or in combination with a resin.

Non-invasive testing

Noninvasive testing in asymptomatic middle-aged (45–50 years) individuals with FH reveals a substantial burden of subclinical atherosclerosis, related to cholesterol level and risk factor burden.¹² In one study, approximately half had plaques on coronary CT angiography (CTCA) compared to 14% of age and sex-matched controls; 19% had stenosis >50% on CTCA compared to 3% in age and sex-matched controls. Mean calcium scores were also higher in FH patients (55 vs. 38 in age/sex-matched controls). However, about 50% of those with FH had a zero calcium score. Similarly, when present, Achilles tendon xanthomas may indicate a greater atherosclerotic burden^{12,80} and are associated with a three-fold greater CVD risk.⁸¹ However, most FH patients will not have xanthomas, xanthelasma, or corneal arcus despite being at high cardiovascular risk. Carotid IMT does not correlate well with the presence of coronary plaque or stenosis and so is less useful in FH patients for whom CHD is usually the first manifestation.^{12,20,82}

Therefore, although subclinical atherosclerosis is common even in young adult FH patients, routine noninvasive screening of FH patients is not recommended. All FH patients should receive lifestyle and drug therapy to reduce cardiovascular risk. In the few highly selected FH patients who undergo non-invasive testing, a negative non-invasive test should not determine the intensity of therapy. Other considerations such as smoking, family history, severity of LDL cholesterol elevation, and the presence of other cardiovascular risk factors should determine intensity of therapy. The same considerations should also guide intensity of therapy in those with a positive non-invasive test. Since assessment of noninvasive imaging in drug-treatment trials does not predict cardiovascular events, these tests should not be used for monitoring response to treatment.^{83,84}

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Pediatric aspects of Familial Hypercholesterolemias: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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Introduction

Cardiovascular disease is a leading cause of death and morbidity in the United States.¹ Results from autopsy studies of children and young adults (2 to 39 years of age), including the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study^{2,3} and the Bogalusa Heart Study,^{4,5} show that the process of atherosclerosis begins in childhood with the development of the fatty streak.^{2,3,4–6} A fatty streak is an accumulation of lipid-filled macrophages within the arterial intima.⁷ Continued accumulation of lipid-filled macrophages combined with smooth muscle cell proliferation can eventually progress to an atherosclerotic lesion or fibrous plaque.⁷ Rupture of the plaque or blockage of the arterial lumen by the fibrous plaque, usually with an overlying

thrombus, leads to the clinical outcomes seen in cardiovascular disease: myocardial infarction and stroke.

The PDAY and Bogalusa Heart Study investigators showed that elevated plasma/serum cholesterol concentrations during childhood and adolescence, specifically low-density lipoprotein (LDL) and non-high-density lipoprotein (HDL) cholesterol, were associated with increased fatty streaks and plaques.^{2,3,5,6,8–10} The Cardiovascular Risk in Young Finns Study investigators¹¹ examined the association between LDL cholesterol concentration measured during childhood and adolescence and carotid intima-media thickness, a marker of subclinical atherosclerosis, measured in adulthood. LDL cholesterol levels in boys aged 12 to 18 years were positively associated with adult carotid intima-media thickness.¹¹

In addition to the association between lipid levels during childhood and the development of cardiovascular disease, epidemiologic evidence indicates that total and LDL cholesterol concentrations during childhood are strong predictors of adult cholesterol concentrations.^{12–20} In the Bogalusa Heart Study, 50% of the children with elevated cholesterol (>75th percentile) during childhood had hypercholesterolemia as adults.^{14–16} This is more than twice the proportion that would be predicted to have hypercholesterolemia by chance alone.²¹

The familial hypercholesterolemias (FH) are defined as a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations. FH is one of the two most frequently diagnosed lipid disorders in children and adolescents (the other is familial combined hyperlipidemia).

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Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia**Screening**

- Universal screening at age 9 to 11 years with a fasting lipid profile or nonfasting non-high-density lipoprotein (HDL) cholesterol measurement is recommended to identify all children with familial hypercholesterolemias (FH). This age identifies individuals at the potential onset of advanced atherosclerosis, and provides the best discrimination between those with and without inherited dyslipidemias by avoiding confounding due to changes in lipid levels associated with puberty.
- If a nonfasting non-HDL cholesterol concentration of ≥ 145 mg/dL is detected, then a fasting lipid profile should be performed.
- Screening should occur earlier (≥ 2 years of age) in the presence of a positive family history for hypercholesterolemia or premature coronary heart disease (CHD) or the presence of other major CHD risk factors.
- Identifying FH in someone with other major CHD risk factors is critical for risk stratification.
- Evaluation (history, physical examination, selected laboratory tests) of possible secondary causes of dyslipidemia should be performed. Secondary causes include hypothyroidism, nephrotic syndrome, and liver disease.

Diagnosis

- Untreated fasting lipid levels at which FH may be suspected in children, adolescents and young adults (<20 years) are low-density lipoprotein (LDL) cholesterol concentration ≥ 160 mg/dL or non-HDL cholesterol ≥ 190 mg/dL. These levels are supported by family studies of affected individuals.
- A second lipid profile should be performed to assess response to diet management, to account for regression to the mean, and to accurately classify those with levels close to classification thresholds.

Lipid Specialists

- Primary care clinicians should be responsible for screening and diagnosis.
- For treatment of children with FH, either consultation with or referral to a lipid specialist is recommended. Pediatric lipid specialists include pediatric cardiologists, endocrinologists, or other health care providers with specialized lipidology training. Use of lipid lowering medications is currently not typically part of pediatric training.
- Homozygous FH should always be managed by a lipid specialist.

Cardiovascular Risk Assessment

- Comprehensive CHD risk assessment [including measurement of lipoprotein (a) levels] and management is critical. The presence of multiple CHD risk factors is associated with dramatic acceleration of atherosclerosis development.
- Primordial prevention, which includes counseling for the prevention of risk development (not smoking, low saturated fat diet, appropriate caloric intake and regular physical activity supporting the avoidance of diabetes), is an important component of treatment of patients with FH.

Treatment

- Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.
- Consideration should be given to starting treatment at the age of 8 years or older. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages.
- Clinical trials with medium term follow up suggest safety and efficacy of statins in children.
- The treatment goal of lipid lowering therapy in pediatric FH patients is a $\geq 50\%$ reduction in LDL cholesterol or LDL cholesterol < 130 mg/dL. There is a need in treatment of pediatric FH for balance between increased dosing and potential for side effects vs. achieving goals. More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.

Homozygous FH

- Initiation of therapy early in life and ongoing monitoring of homozygous FH is vital.
- High dose statins may be effective in some homozygous FH patients, but the majority will require LDL apheresis. Liver transplantation is also being used in some centers.
- Gene therapy is a potential new treatment in development and may be particularly beneficial for homozygous FH patients.

The genetic defects in FH arise from mutations affecting the LDL receptor,²² apolipoprotein B (Apo B)²³ or proprotein convertase subtilisin kexin type 9 (PCSK9; an enzyme involved in LDL receptor degradation).²⁴ Heterozygous FH affects approximately one of every 500 persons in the United States, whereas homozygous FH is rare with a prevalence of one of every million individuals in the United States.^{22,25} Throughout this document, the term FH refers to the heterozygous (autosomal dominant) form of FH, unless otherwise indicated. Children with FH, particularly the homozygous form, are at extremely high risk for developing premature coronary heart disease (CHD). This document provides the rationale for the consensus reached by the National Lipid Association Familial Hypercholesterolemia Panel with regards to recommendations for the treatment of FH in pediatric patients.

Screening

Screening for hypercholesterolemia in childhood allows for early and accurate identification of FH. Because FH confers lifelong risk of atherosclerosis beginning in childhood, and is associated with premature CHD, early screening is justified. Previous national guidelines have recommended targeted screening for children who either 1) have a family history of premature cardiovascular disease or high blood cholesterol concentrations, or 2) have unknown family history or have other risk factors for cardiovascular disease such as obesity, hypertension or diabetes mellitus.^{21,26–28} Because FH is a genetic disorder, acknowledging the role that family history may have in the development of disease is important; however, reliance on family history as the basis for screening decisions has several limitations. Methods for collecting family history information are not standardized, and often family history and/or family members' cholesterol levels are unknown.^{21,29} Furthermore, a negative family history of premature CHD should not rule out a diagnosis of FH. It has been reported that application of targeted screening approaches may fail to indicate screening for 30 to 60% of children and adolescents with elevated cholesterol concentrations.^{21,30–32}

Due to the lack of sensitivity and specificity of targeted screening for detecting elevated cholesterol in children, we recommend universal screening of all children between the ages of 9 and 11 years to identify children with FH. This screening measurement should include a fasting lipid profile or a non-fasting non-high-density lipoprotein (HDL) cholesterol assessment, which is an estimate of the cholesterol content of all Apo B-containing lipoproteins calculated by subtracting HDL cholesterol from total cholesterol. If a non-fasting non-HDL cholesterol concentration ≥ 145 mg/dL is reported, then a fasting lipid profile should be obtained. The age range between 9 and 11 years was selected in order to allow the best discrimination between those with and without FH at the potential onset of advanced atherosclerosis, while avoiding confounding by pubertal-related unstable lipid levels. Lipid levels, particularly levels of LDL cholesterol, are reduced during pubertal development and then increase in

late adolescence and early adulthood.^{19,33} Screening should occur earlier (≥ 2 years of age) in the presence of a positive family history for hypercholesterolemia or premature CHD or the presence of other major CHD risk factors, including obesity, hypertension and diabetes. The cut point of ≥ 2 years is suggested because serum lipids and lipoprotein levels increase during the first two years of life, becoming stable around age 2.^{34–36}

Although cholesterol screening has been recommended for several decades in children and adolescents, there is significant under-screening, based on family history or the presence of other risk factors, and lack of adherence by practitioners in prescribing recommended treatments in children identified with lipid disorders.²¹ The importance of adherence to dietary and drug management of hypercholesterolemia should be strongly emphasized to parents and young patients identified with FH.

Hypercholesterolemia can be secondary to other diseases that affect lipoprotein metabolism. An important part of the screening process is to rule out possible secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, hepatic disease, or renal disease or dysfunction) through evaluation of history, physical examination or selected laboratory tests. Identifying FH in someone with other major CHD risk factors is also critical for risk management as described in greater detail in the Risk Management section below.

Diagnosis

Childhood and adolescent levels of total, LDL and non-HDL cholesterol categorized according to acceptable, borderline, and high classifications from Bogalusa Heart Study data,³⁷ as described by the National Cholesterol Education Program Expert Panel on Cholesterol Levels in Children and Lipid Research Clinics Prevalence Study¹² are shown in Table 1.

Several standardized criteria for the diagnosis of FH are used clinically, including the Simon Broome Criteria,³⁸ Dutch Lipid Clinic Network Criteria,³⁹ and Make Early Diagnosis Prevent Early Deaths (MEDPED) criteria.⁴⁰ These diagnostic criteria are described in detail elsewhere in this supplement. Genetic testing is an important element for making a diagnosis according to these criteria. Because confirmation of the presence of a genetic mutation is not necessary to identify individuals with hypercholesterolemia, and is unlikely to modify the approach to management in the current state of knowledge, a simplified approach to FH diagnosis can be taken (Table 2). FH may be suspected in a child, adolescent, or young adult (< 20 years of age) if he/she has an untreated fasting LDL cholesterol level ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL). These levels are substantially above the 95th percentile as supported by population studies and family studies of affected individuals.⁴¹ A second lipid profile (following dietary counseling) should be performed to assess response to diet management, account for regression to the mean, and confirm classification for those with levels close to

Table 1 Levels of plasma lipid concentrations (mg/dL)* in children, adolescents and young adults

| | Acceptable | Borderline High | High |
|---|------------|-----------------|------|
| Children and Adolescents[†] | | | |
| Total Cholesterol | <170 | 170–199 | ≥200 |
| LDL Cholesterol | <110 | 110–129 | ≥130 |
| Non-HDL Cholesterol | <120 | 120–144 | ≥145 |
| Young Adults[‡] | | | |
| Total Cholesterol | <190 | 190–224 | ≥225 |
| LDL Cholesterol | <120 | 120–159 | ≥160 |
| Non-HDL Cholesterol | <150 | 150–189 | ≥190 |

*To convert mg/dL to SI units, divide the results by 38.6.

[†]Values for plasma lipid levels are in agreement with the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children.²⁶ Non-HDL-C values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut-points for LDL cholesterol.³⁷ The cut-points for high and borderline-high represent approximately the 95th and 75th percentiles, respectively.^{26,37}

[‡]Values provided are from the Lipid Research Clinics Prevalence Study.¹² The cut points for total, LDL and non-HDL cholesterol represent the 95th percentile for subjects aged 20–24 years and are not identical with the cut points used in the most recent NCEP ATP III⁴² which are derived from combined data on adults of all ages. The age-specific cut-points given here are provided for pediatric care providers to use in managing this young adult age group. For total, LDL, and non-HDL cholesterol, borderline high values are between the 75th and 94th percentiles, whereas acceptable values are <75th percentile.

thresholds. Decisions regarding the need for prescription lipid drug therapy should be based on the average of results from at least two fasting lipid profiles. The amount of time between initial dietary counseling and decisions to start lipid drug therapy may vary between patients, depending on age, family history and baseline LDL cholesterol levels.

Lipid specialists

Primary care clinicians are at the front line of responsibility for the screening and diagnosis of FH in the pediatric population. However, because the use of lipid lowering medications is not typically part of pediatric medical training, if heterozygous FH is suspected or diagnosed, the primary care clinician should either consult a lipid specialist for guidance in treatment or refer the child directly to the lipid specialist. A pediatric patient with homozygous FH should always be managed by a lipid specialist. Pediatric lipid specialists include pediatric cardiologists, endocrinologists, or other health care providers with specialized lipidology training (see www.learnyourlipids.com/resources.php for a lipid specialist locator).

Cardiovascular risk assessment

Hypercholesterolemia is an established risk factor for the development of atherosclerosis.^{42,43} Other major CHD risk

factors and risk equivalents include family history of premature heart disease, increased age, male sex, hypertension, diabetes, smoking, and reduced high-density lipoprotein (HDL) cholesterol concentration. Children with chronic kidney disease, Kawasaki disease with coronary aneurysms, and possibly other chronic inflammatory conditions such as lupus are at risk for coronary artery disease as young adults.⁴⁴ The presence of additional CHD risk factors is associated with a dramatic acceleration of atherosclerosis in the FH patient, and should therefore be assessed comprehensively. When other CHD risk factors are present, they should be treated aggressively. If other CHD risk factors are not present, lifestyle intervention should be initiated to prevent the development of other risk factors. CHD risk assessment, including measurement of lipoprotein (a), and management of identified risk factors is integral to the treatment of FH.

Treatment

Primordial prevention, which includes counseling for the prevention of risk development (not smoking, low saturated fat diet, appropriate caloric intake, and regular physical activity supporting the avoidance of diabetes), is an important component of the treatment of patients with FH.⁴² All FH patients require primordial prevention, but it is unlikely that diet and lifestyle changes alone will be enough to achieve the target of ≥50% reduction in LDL cholesterol or LDL cholesterol <130 mg/dL. More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.⁴⁴ Almost all FH patients, including children and adolescents, will ultimately require lipid-lowering drug therapy to achieve LDL cholesterol treatment goal, but diet and lifestyle modifications, which may reduce LDL cholesterol by 10 to 15%,^{45,46} should not be abandoned with the initiation of drug therapy. These are important in long-term management, may affect non-cholesterol and cardiovascular disease risk factors, and may lower the required pharmacotherapy dose.⁴²

After initiation of diet (including dietary adjuncts of plant sterols/stanols and soluble fiber),⁴² statins are the

Table 2 Recommended screening indicators and treatment targets for pediatric FH

| Screening | |
|--|--|
| Non-fasting non-HDL cholesterol ≥145 mg/dL | → Perform fasting lipid profile |
| Fasting LDL cholesterol ≥160 mg/dL or non-HDL cholesterol ≥190 mg/dL | → Suspect FH in patients <20 years of age |
| Treatment | |
| Target for FH patients | ≥50% ↓ LDL cholesterol or LDL cholesterol <130 mg/dL |

preferred initial pharmacologic treatment in children with FH. Consideration should be given to starting medical treatment at the age of 8 years or older. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages. Six statins (rosuvastatin, atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin) are FDA approved as an adjunct to diet to lower markedly elevated LDL cholesterol levels in children 10 years of age and older (ages 8 years and older for pravastatin).^{47,48} Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate limiting enzyme for endogenous synthesis of cholesterol, and by doing so lower hepatocyte cholesterol concentration leading to LDL receptor upregulation and improved clearance of circulating LDL cholesterol.

Numerous clinical trials of the safety and efficacy of statins for lowering LDL cholesterol have been conducted in children and adolescents with severe dyslipidemia or FH.^{49–60} Although these clinical trials had short- to medium-term follow up, all suggested that statins are well tolerated, safe and efficacious for lowering LDL cholesterol in young people with hypercholesterolemia. While there have been no randomized clinical trials designed to address whether treating FH with drugs in children and adolescents will reduce cardiovascular disease events later in life, there is evidence from non-invasive vascular endothelial function testing and carotid intima-media thickness measurements that lipid-lowering with statins may delay the atherosclerotic disease process.^{57,61,62} In general, statins reduce LDL cholesterol levels in children with FH by 23 to 40%.⁶⁰ Adverse event profiles for statins in youth are similar to those reported in adult studies⁶³ and include rare instances of myopathy and hepatic enzyme elevation.⁶⁰ Routine monitoring of liver and muscle enzymes and symptoms of muscle toxicity, according to the timing described by the Scientific Statement from the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing⁶⁴ is strongly recommended for children and adolescents receiving statin therapy.

Children who are not able to reach the LDL cholesterol treatment goal with the initial statin dose, or who have additional CHD risk factors, may require intensification of statin therapy, or the addition of a second lipid medication under the guidance of a lipid specialist. Therapeutic management of FH in the pediatric population requires a careful balance between increased dosing and potential side effects vs. achieving treatment goals.

Bile acid sequestrants (colesevelam, cholestyramine, colestipol) bind bile salts in the intestinal lumen preventing their enterohepatic recirculation. This depletion of hepatic bile acids signals the need for increased production of bile acids from cholesterol. Bile acid sequestrants lower LDL cholesterol by 10 to 20%, but cholestyramine and colestipol are associated with significant gastrointestinal side effects (constipation) and low palatability, which reduce their tolerability.^{65,66} Although bile acid sequestrants are

generally considered safe in childhood (despite being poorly tolerated), cholestyramine and colestipol do not have pediatric indications. Colesevelam is indicated for use in pediatric populations (boys and postmenarchal girls aged 10 to 17 years with FH) as monotherapy or combined with a statin. This agent is available as a tablet or powder and is associated with only relatively minor side effects.⁶⁷

Ezetimibe is a cholesterol absorption inhibitor that acts to specifically inhibit cholesterol absorption in the intestine. Although ezetimibe is absorbed, most remains within the enterohepatic circulation. Ezetimibe has been shown to reduce LDL cholesterol by an additional 20% when added to a statin,⁶⁸ and recent studies support its use as monotherapy or in combination with a statin in children and adolescents.^{69,70} Currently, ezetimibe is not approved by the FDA for use in children with hypercholesterolemia.

There is limited published experience in children with the use of niacin or fibrates,^{48,71,72} and neither is used routinely for the treatment of pediatric FH. Niacin can be effective in lowering LDL cholesterol, lipoprotein (a), and triglycerides while increasing HDL cholesterol. However, its adverse effects make it difficult to use in pediatric clinical practice (flushing, hepatic dysfunction, myopathy, glucose intolerance, and hyperuricemia). The primary actions of fibric acid derivatives (gemfibrozil and fenofibrate) are to lower triglycerides and raise HDL cholesterol, and they do not reliably lower LDL cholesterol. Furthermore fibrates (particularly gemfibrozil) may increase the risk of statin-induced myositis.⁷³ Therefore, fibrates are not recommended for routine use in pediatric patients with FH, unless triglyceride levels are elevated, and then they should be used with caution.

Children should receive at least three nutrition counseling sessions in the six months after initial diagnosis, and then have clinic visits every one to two years until the age at which statins are recommended, unless lifestyle issues indicate that more frequent nutrition/lifestyle behavior visits are necessary. After lipid medication is initiated, clinic visits should occur every 3 to 6 months with a fasting lipid profile and comprehensive assessment by history and laboratory testing for side effects (hepatic enzyme elevation and muscle toxicity), other cardiovascular risk factors, and to reassess lifestyle behaviors.

Homozygous FH

Homozygous FH is very rare, with a prevalence of approximately one in every one million persons in the United States.^{22,25} It is associated with extremely high LDL cholesterol levels (650 to 1000 mg/dL). Homozygous FH most commonly manifests in infancy and early childhood as a history of skin lesions (xanthomas). In fact, initial identification of homozygous FH is often made by a dermatologist or by an astute family member. Initiation of therapy in childhood and ongoing monitoring is vital because patients with homozygous FH often develop cardiovascular disease in their 20s, or even earlier in severe cases.²⁵

A pediatric patient with homozygous FH should always be managed by a lipid specialist. A complete cardiologic investigation, including an electrocardiogram and echocardiogram or vascular imaging, at the time of diagnosis is useful for assessment of ongoing cardiovascular disease and may be beneficial for further educating the homozygous FH patient and parents regarding their disease risk. However, these findings do not typically alter decisions regarding treatment. Thus, there are no specific recommendations for performing these tests in children. The follow up of patients with homozygous FH is also not standard, and there are no generally accepted guidelines. Repeat echocardiograms to evaluate supravalvular aortic stenosis are useful and stress testing using nuclear medicine or stress echocardiography may be indicated. Regular assessment of coronary arteries for plaque formation may be important. This can be accomplished by coronary artery angiography sometimes accompanied by intracoronary ultrasound, or computed tomography angiogram using lower radiation protocols in experienced institutions. Significant atherosclerosis may develop outside the coronary system, including renal artery stenosis and carotid disease.

There are no randomized controlled trials of treatment for homozygous FH (for ethical reasons). Despite severely reduced LDL cholesterol receptor level/activity in homozygous FH patients, high doses of statins may be somewhat effective for lowering LDL cholesterol concentrations.²⁵ However, the majority will require LDL apheresis, which is an FDA-approved process of selectively removing Apo B-containing particles from the circulation through extracorporeal precipitation.⁷⁴ The procedure is performed at medical centers with this expertise and must be repeated every 1 to 2 weeks. A listing of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org). Liver transplantation may also be considered, and is being performed in some centers. The surgery is associated with considerable risks, but because a new liver provides functional LDL receptors, it can dramatically decrease LDL cholesterol concentrations. Gene therapy is a potential new treatment in development that may be particularly beneficial for patients with homozygous FH who require lifelong therapy and monitoring yet remain at significant risk for the development of cardiovascular disease.^{75–77}

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Management of Familial Hypercholesterolemias in adult patients: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in the United States.¹ Hypercholesterolemia, specifically elevated level of low-density lipoprotein (LDL) cholesterol, is a major coronary heart disease (CHD) risk factor.² While environmental factors such as diet and physical activity have important roles in determining an individual's level of circulating cholesterol, there is also a genetic component. The familial hypercholesterolemias (FH) are a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations. The genetic defects in FH arise from mutations affecting the LDL receptor,³ apolipoprotein (Apo) B⁴ or proprotein convertase subtilisin kexin type 9

(PCSK9; an enzyme involved in LDL receptor degradation)⁵. Heterozygous FH is a common genetic defect affecting approximately one of every 500 persons in the United States, although this ratio is much higher in certain subpopulations in the U.S. Homozygous FH is quite rare, affecting one of every one million individuals in the United States.^{6–9} Throughout this document, the term FH refers to the heterozygous form of FH, unless otherwise indicated.

FH is associated with a high risk for premature coronary heart disease (>50% risk in men by age 50 and >30% in women by age 60).^{8,9} In untreated individuals, symptoms of coronary disease may manifest in men in their 40s and in women 10 to 15 years later. There is a substantial body of evidence from large-scale clinical trials supporting the benefit of lowering LDL cholesterol with statins to reduce cardiovascular disease morbidity and mortality.^{2,10} Although no randomized placebo-controlled outcome trials of statin therapy have been conducted in FH cohorts (for ethical reasons) due to their high LDL cholesterol levels and associated cardiovascular disease risk, observational studies provide compelling evidence that statins alter the clinical course of the disease.¹¹ Thus, aggressive lipid management in men and women with FH is vital in order to prevent or slow the progression of coronary atherosclerosis. This document provides the rationale for the consensus reached by the National Lipid Association Familial Hypercholesterolemia Panel with regards to recommendations for the treatment of FH in adult patients.

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Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia**Lifestyle Modifications**

- Patients with familial hypercholesterolemias (FH) should be counseled regarding the following lifestyle modifications:
 - Therapeutic Lifestyle Changes and dietary adjuncts.
 - Reduced intakes of saturated fats and cholesterol: total fat 25-35% of energy intake, saturated fatty acids <7% of energy intake, dietary cholesterol <200 mg/d.
 - Use of plant stanol or sterol esters 2 g/d.
 - Use of soluble fiber 10-20 g/d.
 - Physical activity and caloric intake to achieve and maintain a healthy body weight.
 - Limitation of alcohol consumption.
 - Emphatic recommendation to avoid use of any tobacco products.
- Clinicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for medical nutrition therapy.

Drug Treatment of FH

- For adult FH patients, initial treatment is the use of moderate to high doses of high-potency statins titrated to achieve low-density lipoprotein (LDL) cholesterol reduction $\geq 50\%$ from baseline. Low potency statins are generally inadequate for FH patients.
- If the initial statin is not tolerated, consider changing to an alternative statin, or every-other-day statin therapy.
- If initial statin therapy is contraindicated or poorly tolerated, ezetimibe, a bile acid sequestrant (colesevelam) or niacin may be considered.
- For patients who cannot use a statin, most will require combination drug therapy.

Additional Treatment Considerations

- If the patient is not at LDL cholesterol treatment goal with the maximum available and tolerable dose of statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred).
- Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities.

Candidates for LDL Apheresis

- LDL apheresis is a U.S. Food and Drug Administration approved medical therapy for patients who are not at LDL cholesterol treatment goal or who have ongoing symptomatic disease.
- In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:
 - Functional homozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL).
 - Functional heterozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL) and 0-1 risk factors.
 - 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.
 - 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).

LDL Apheresis Referrals

- Healthcare practitioners should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A listing of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org).

Women of Childbearing Age

- Women with FH should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, and niacin at least four weeks before discontinuing contraception and should not use them during pregnancy and lactation.
- Consultation with her healthcare practitioner regarding continuation of any other lipid medications is recommended.
- In case of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately and should consult with her healthcare practitioner promptly.

Treatment Options During Pregnancy

- Statins, ezetimibe, and niacin should not be used during pregnancy. Use of other lipid lowering medications (e.g., colesevlam) may be considered under the guidance of the healthcare practitioner.
- Consider LDL apheresis during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.

Hard to Manage Patients

- If other treatment options are inadequate or the FH patient cannot tolerate pharmacotherapy or LDL apheresis, other treatment options include ileal bypass and liver transplantation (both are used rarely), and, potentially, new drugs in development.

Lifestyle modifications

The goal of treatment for patients with FH is to achieve an LDL cholesterol reduction of at least 50% from baseline.^{8,9} In patients with FH, lifestyle modifications should always be instituted, but usually these changes alone are insufficient to achieve the LDL cholesterol treatment goal.^{12,13} The degree of LDL cholesterol reduction with dietary and lifestyle changes is quite variable, depending on the patient's original diet, compliance, and genetic responsiveness. A decrease of 10 to 15% is achievable in many individuals.^{13,14}

Clinicians are encouraged to refer FH patients to registered dietitians or other qualified nutritionists for medical nutrition therapy and counseling in order to achieve the maximum possible diet-mediated reduction in LDL cholesterol. The National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATP III) Therapeutic Lifestyle Changes (TLC) diet, which restricts intakes of total fat (25 to 35% of energy intake), saturated fatty acids (<7% of energy intake), and cholesterol (<200 mg/d) is recommended for patients with FH.² Patients should also be instructed to incorporate dietary adjuncts including 2 g/d of plant stanol or sterol esters and 10 to 20 g/d of soluble fiber, both of which decrease cholesterol absorption.^{2,15,16}

In addition to following the TLC diet, patients with FH should be encouraged to achieve and maintain a healthy body weight through physical activity and appropriate caloric intake.² If an individual is overweight or obese, significant weight loss will improve lipid levels. Each kilogram of weight loss produces a reduction of about 0.8 mg/dL in the LDL cholesterol concentration.¹⁷ Limiting alcohol consumption and avoiding or stopping tobacco use (smoking cessation has been shown to increase HDL cholesterol levels¹⁸) is recommended in order to reduce the burden of additional cardiovascular risk factors among FH patients who are already at high risk by virtue of their severe hypercholesterolemia. Assistance in stopping smoking should be offered.

Dietary modifications should not be discounted in FH patients undergoing pharmacological therapy, because the effects on LDL cholesterol reduction are directly additive to those of lipid-lowering medications.¹⁹⁻²² The importance

of complying with dietary management of hypercholesterolemia should be strongly emphasized during counseling of patients with FH, and the added negative effects of smoking should be thoroughly explained.

Drug treatment of FH

Management of FH in women of childbearing potential and in breastfeeding women requires specific guidance, due to the risks to the child of certain types of drug therapies during pregnancy and breastfeeding (see sections below for Women of Childbearing Age and Treatment During Pregnancy). The recommendations for drug treatment of FH in the present section refer to women who are using contraception or who are not of childbearing potential.

After a confirmatory diagnosis of FH (excluding secondary causes of hypercholesterolemia), adult FH patients should receive initial treatment with higher potency statins (atorvastatin, rosuvastatin, pitavastatin, simvastatin) titrated to achieve an LDL cholesterol reduction $\geq 50\%$ from baseline (pitavastatin and simvastatin have lower probability of achieving a 50% reduction from baseline).^{8,9,23} Low potency statins (fluvastatin, lovastatin, pravastatin) are generally inappropriate as initial therapy for FH patients. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, causing a reduction in hepatic cholesterol and leading to upregulation of hepatic LDL receptors. Increased LDL receptor activity results in a reduction in circulating LDL cholesterol concentration. With 50% functional LDL receptors, heterozygous FH patients typically have an excellent response to statins. Even some FH homozygotes who have LDL receptor defective mutations have sufficient LDL receptor activity to respond favorably to statin therapy, although generally to a degree insufficient to achieve their LDL cholesterol goal.^{24,25} In individuals with hypercholesterolemia (not necessarily FH), statins have been shown to reduce LDL cholesterol concentrations by 50 to 60% at their maximum approved doses.²⁶⁻²⁹ Many randomized, placebo-controlled trials have demonstrated that lowering LDL cholesterol with statins reduces coronary morbidity and mortality.^{2,10}

Statins are generally well tolerated and have an excellent safety profile.^{30–32} The potential adverse effects of statins in FH patients are the same as in other treated patients, notably myopathy and elevated liver enzymes. Certain low potency statins, such as fluvastatin and pravastatin, may be less likely to cause severe myopathy,³² but they are not the preferred choice for patients with FH due to their lower ability to reduce LDL cholesterol levels.^{27,28,33}

Some patients do not tolerate statin therapy. In these cases, possible alternatives include changing to a different statin, instituting every-other-day statin therapy, or using very low dose statin therapy in combination with other LDL cholesterol lowering medications. Alternative lipid-lowering medications to consider, if initial statin therapy is either contraindicated or poorly tolerated, include ezetimibe (cholesterol absorption inhibitor), a bile acid sequestrant, most often colestevlam, or niacin.^{8,9,29} For patients who cannot use a statin, combination therapy of these other LDL cholesterol lowering agents will likely be required. Even among patients who tolerate the maximum doses of the higher efficacy statins, the addition of one or more non-statin cholesterol-lowering medications is often necessary to achieve the recommended LDL cholesterol reduction of $\geq 50\%$.

Ezetimibe specifically inhibits cholesterol and phytosterol absorption by binding to intestinal enterocytes and interfering with the activity of the Niemann-Pick C1-Like 1 sterol transporter. The reduced flow of cholesterol from the intestine to the liver leads to a compensatory increase in the hepatic LDL receptor resulting in increased uptake of circulating LDL and other lipoprotein particles. Ezetimibe reduces LDL cholesterol by approximately 15 to 20% when given alone or when combined with a statin. It can be administered in combination with other lipid medications in FH patients who do not tolerate statins.^{34–39}

Bile acid sequestrants (colesevelam, cholestyramine, colestipol) are anion-exchange compounds that prevent reabsorption of bile acids in the intestine. They have been shown to decrease LDL cholesterol concentrations by up to 20%⁴⁰ and can be added to statin therapy in FH patients requiring additional LDL cholesterol lowering.⁴¹ Because they are not absorbed systemically, they are generally considered safer than other lipid-lowering drugs. Cholestyramine and colestipol are associated with significant adverse gastrointestinal side effects, particularly constipation and multiple drug-drug interactions; and patient compliance is often an issue. The newest bile acid sequestrant on the market is colestevlam, a polymer available as a tablet or as a powder for oral suspension. Compared with cholestyramine and colestipol, colestevlam has fewer gastrointestinal side effects and drug-drug interactions and is effective at a lower dose. Its use may be associated with improved adherence compared with cholestyramine and colestipol. Colestevlam is also approved by the U. S. Food and Drug Administration for improving glycemic control in patients with type 2 diabetes mellitus. Colestevlam is therefore the recommended bile acid sequestrant for

use in patients with FH. Colesevelam can produce up to 20% further LDL cholesterol reductions when added to a statin.⁴¹

Niacin or nicotinic acid is available in immediate-release, extended-release, and sustained-release forms. The extended-release prescription product is preferred and most sustained-release non-prescription forms are not recommended due to increased potential for liver toxicity. Niacin is a water-soluble B vitamin which lowers very low-density lipoprotein and LDL cholesterol while raising HDL cholesterol, but its use is typically associated with troublesome side effects of flushing or hot flashes due to vasodilatation.^{42–44} Extended-release niacin, dosing not to exceed 2 g/d, when added to a stable dose of statin therapy has been shown to be effective in lowering LDL cholesterol.^{45–46}

Fibric acid derivatives (gemfibrozil, fenofibric acid, and fenofibrate) primarily act to lower triglycerides and raise HDL cholesterol, but do not reliably lower LDL cholesterol. Furthermore, fibrates (particularly gemfibrozil) may increase the risk of statin-induced myositis.⁴⁷ Therefore, fibrates should be used with caution. However, fenofibric acid is FDA approved for use in combination with low to moderate doses of statins. Prescription omega-3 fatty acid esters can also be used if concurrent high triglyceride levels are present.

Additional treatment considerations

As described above, if an individual with FH is not at LDL cholesterol treatment goal with the maximum available and tolerable dose of statin, then the statin should be combined with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred). The risk for myopathy with statin therapy appears to be positively associated with the dose and potency of the statin.³² Because doubling the dose of a statin further lowers LDL cholesterol by only 6 to 7%,²⁸ addition of another agent (such as ezetimibe, niacin, or colestevlam) is often necessary to achieve the amount of LDL cholesterol reduction required in FH patients. However, the risk for myopathy is also increased by certain drug combinations, such as that of a fibrate (particularly gemfibrozil) with a statin.^{32,47} Decisions regarding the selection of drug combinations should be based on concomitant risk factors for myopathy. Polypill forms of simvastatin combined with extended-release niacin (Simcor) and simvastatin combined with ezetimibe (Vytorin) are attractive options for patients with FH, reducing the number of pills required, which lowers cost and may improve adherence.

Another important factor to consider in the selection of combination drug therapies is potential concomitant medication interactions. Drug interactions with statins are primarily related to cytochrome P450 metabolism, drug transporters, and glucuronidation. Thus, caution should be used with a statin in combination with fibrates (mainly gemfibrozil), antifungals (except terbinafine which can be used with a statin), macrolide antibiotics,

antiarrhythmics, cyclosporine, protease inhibitors, or in patients who routinely drink grapefruit juice. Because it is not metabolized by cytochrome 3A4, rosuvastatin, unlike atorvastatin and simvastatin, may be less likely to produce interactions with other medications. Bile acid sequestrants may decrease the absorption of some medications, and the timing of dosing in conjunction with other medications is important, particularly with cholestyramine and colestipol. Ezetimibe, on the other hand, has a specific mechanism of action to inhibit cholesterol absorption, and therefore does not interfere with the absorption of other drugs.

Other major considerations when selecting drug combinations for treating FH are the presence of additional lipid abnormalities and other disease conditions, particularly hypertension, diabetes (type 1 or 2), and obesity, which also increase CHD risk. In addition to treating hypercholesterolemia, other cardiovascular risk factors should be identified and treated aggressively in patients with FH. The prognosis of FH patients depends heavily on the amount of LDL cholesterol reduction that can be achieved, but treatment of other modifiable risk factors such as hypertension, diabetes, and smoking, further decreases the risk of heart disease.

Candidates for LDL apheresis

In patients where LDL cholesterol reduction has been inadequate despite diet and maximum drug therapy (after 6 months), or if drug therapy is not tolerated or contraindicated, LDL apheresis may be considered for the following individuals: 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, and 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).

LDL apheresis is a U.S. FDA-approved process of selectively removing Apo B-containing particles from the circulation through extracorporeal precipitation with either dextran sulphate cellulose or heparin.⁴⁸⁻⁵¹ The procedure must be repeated every 1 to 2 weeks. In a single procedure, LDL apheresis typically removes at least 60% of the Apo B-containing lipoproteins.⁵⁰ Higher baseline lipid levels appear to exhibit a greater response to LDL apheresis treatment. Due to the cyclical nature of Apo B synthesis and circulation, recurrent hypercholesterolemia occurs in approximately 12 to 13 days with a rebound to pre-treatment levels of Apo B particles.⁵² Concomitant treatment with a statin enhances the efficacy of LDL apheresis.⁵³ Long-term therapy has been shown to result in a 20 to 40%

reduction in LDL cholesterol from pre-treatment levels.^{54,55} Few adverse effects are associated with LDL apheresis, mostly noncritical episodes of hypotension.

Several clinical trials have confirmed the benefits of LDL apheresis for prevention and slowing the progression of cardiovascular disease,^{50,56-62} and for other cardiovascular effects such as improvements in endothelial function,⁶³ coronary vasodilation,⁶⁴ microvascular flow,⁶⁵ and myocardial perfusion.⁶⁶ LDL apheresis has also been shown to promote regression of xanthomas⁵⁰ and modify a number of markers associated with vascular disease, including lipoprotein (a), an atherothrombotic marker.⁶⁷ LDL apheresis is the only treatment shown to consistently reduce lipoprotein (a) levels by more than 50%.⁶⁸ Although LDL apheresis is effective for retarding the development of atherosclerosis, and is often the only viable option for certain patients such as those with homozygous FH, the procedure is time consuming (more than 3 hours every 1 to 2 weeks) and expensive.^{62,69}

LDL apheresis referrals

Physicians should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A listing of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org). Currently, there are more than 400 patients in North America receiving LDL apheresis therapy at more than 40 centers. While new facilities are added regularly, there is a significant gap between the number of patients receiving LDL apheresis therapy and the number that, according to FDA guidelines,⁷⁰ may qualify for LDL apheresis.

Women of childbearing age

Statins, ezetimibe, and niacin are not approved for use by pregnant or breastfeeding women. Women with FH should receive pre-pregnancy counseling and instructions to stop use of statins, ezetimibe, and niacin at least four weeks prior to discontinuing contraception, and should not use these drugs during pregnancy and lactation. It is recommended that a woman of childbearing age consult her physician regarding continuation of any other lipid medications. In cases of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately, and she should consult with her physician promptly.

Treatment options during pregnancy

LDL cholesterol concentrations increase during the course of pregnancy due to hormonal changes.⁷¹⁻⁷³ This is considered beneficial in non-FH patients because cholesterol is necessary for embryonic and fetal nervous system development. However, in women with FH, the hormonal

increase in cholesterol combined with the need to stop taking statins (category X), ezetimibe (category C), and niacin (category C) in order to prevent potential birth defects, may put them at increased cardiovascular risk. Colesevelam is a pregnancy category B lipid-lowering medication indicating that it can be used during pregnancy when the need is clearly established. However, controlled trials during pregnancy have not been conducted. LDL apheresis should be considered during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH. Although not specifically recommended, case studies have provided evidence supporting the safety of LDL apheresis for pregnant women with FH.⁷⁴

Hard to manage patients

In the general population of hypercholesterolemic patients, a subset fails to achieve their NCEP ATP III LDL cholesterol goal.^{75,76} Many of these are patients with FH and patients who are resistant to lipid-lowering therapies. These hard-to-manage patients, particularly those with homozygous FH, cannot achieve target LDL cholesterol levels with currently available medications and will require alternative methods for cholesterol reduction.⁷⁷ For those who cannot tolerate drug therapy or LDL apheresis, other potential treatment options include partial ileal bypass and liver transplantation. Liver transplantation is beneficial because it can provide normal LDL receptors and often leads to a significant lowering of LDL cholesterol, but it is rarely used because of the risks associated with transplant surgery. Partial ileal bypass is also rarely used to treat FH. Gene therapy is another potential treatment option, but it is still in the investigational stage, as issues regarding potential side effects and long-term safety need to be resolved.^{78–81}

Investigation into better methods to treat patients with FH in order to decrease the morbidity and mortality associated with this inherited disorder is ongoing. Several other potential approaches to LDL cholesterol lowering are currently in development, including Apo B antisense oligonucleotides (prevent the production of Apo B-containing particles from the liver), microsomal triglyceride transfer protein inhibitors (inhibit the transfer of nascent Apo B to very low-density lipoprotein and chylomicrons), PCSK9 inhibitors (prevent the degradation of the LDL receptor), and thyroid hormone analogues (which like natural thyroid hormone, would regulate cholesterol metabolism).⁸¹

In addition to plant sterols/stanols and soluble fiber, which are recommended as adjuncts to the TLC diet, use of other non-pharmacologic lipid-altering substances may be helpful for some individuals with hypercholesterolemia.^{14,82,83} The following herbal products and supplements may have modest effects on LDL cholesterol levels, but these products should be used with caution, particularly in FH patients receiving multi-drug therapy: soy (has an FDA approved labeling health claim for cholesterol reduction, but recent studies suggest the effect may be quite small), red yeast rice

(some products may contain the active ingredient lovastatin, and should be treated as lovastatin and should never be used in conjunction with a statin), and green tea (suggestive epidemiologic data, but inconclusive clinical trial data, of its cholesterol lowering ability).⁸⁴

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Future issues, public policy, and public awareness of Familial Hypercholesterolemias: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

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Introduction

Heterozygous familial hypercholesterolemia (FH) occurs with a frequency of about 1 in every 300 to 500 people and is therefore one of the most commonly occurring congenital metabolic disorders.^{1–3} It is estimated that at least 620,000 Americans are affected with FH.^{2,4} Unfortunately, large numbers of the populace with FH are undiagnosed and consequently remain at increased risk for coronary heart disease (CHD).⁵ Furthermore, even though

highly effective lipid-lowering drugs are available, FH is often inadequately treated.⁴

In order to prevent premature CHD, avoid early death, and reduce costs to patients and society, there is a need to increase public and provider awareness, foster research, and develop national policies to improve diagnostic and treatment services for those with FH. The following discussion reflects the opinion of the members of the National Lipid Association's Expert Panel on Familial Hypercholesterolemia based on their experience as lipid specialists and evaluation of scientific evidence. It is intended to describe, from a clinical perspective, the current procedures for screening, diagnosis, and management of FH and areas for improvement. The panel acknowledges that policy statements such as these are not simply a matter of the scientific evidence, but also have political and social implications, particularly since FH is a genetic disorder.

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Screening

Because it is a relatively common, but treatable, disorder associated with high risk for CHD, FH meets the World

Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia**Screening**

- It is the responsibility of all primary health care providers and relevant specialists to screen all children and adults for hypercholesterolemia, and to initiate therapy in patients with familial hypercholesterolemias (FH) and severe hypercholesterolemia.

Lipid Specialists

- Patients with FH who do not respond adequately to, or are intolerant of, initial statin therapy should be referred to a lipid specialist.
- For children with FH, either consultation with or referral to a lipid specialist is recommended.
- Patients who are candidates for more intensive therapy, or who have family histories of very premature coronary heart disease (in men <45 years of age and women <55 years of age), should also be referred to a lipid specialist.

Payers

- Patients with FH are at high lifetime risk of atherosclerotic cardiovascular disease and appropriate therapy is required.
- Payers should cover initial screening, initiation of therapy with appropriate medications, and monitoring response to therapy.
- Payers should cover appropriate drugs including high potency statins and combination lipid drug therapy. They should also cover other drugs and combinations for patients with statin tolerance problems.
- Low-density lipoprotein (LDL) apheresis and genetic testing, when appropriate, should be covered by payers.

Public and Provider Awareness

- To promote early diagnosis of FH and the prevention, and treatment of CHD, public awareness of FH needs to be increased by a variety of methods.
- Health care provider awareness needs to be increased through education at all levels and in multiple specialties, through partnering with professional organizations and through local, national and international health agencies.

Responsibility for Education

- Health systems, hospitals, pharmacy benefits management organizations, and insurance companies should contribute to patient and provider education.
- Governmental agencies and other policy makers at local, state, national and international levels should be engaged in efforts to screen and treat FH.

Research Needs

- Research is needed in the following areas related to FH:
 - Agents to further lower LDL cholesterol;
 - Ways to improve adherence to and persistence with therapy;
 - Cost effective genetic screening;
 - Behavioral management of patients with FH;
 - Cost effectiveness analysis of various approaches to screening and treatment;
 - Cost effectiveness analysis of the benefits of aggressive therapy;
 - Long-term follow-up of patients with FH, including safety of long-term therapy with lipid lowering drugs;
 - Differences in drug metabolism by gender, ethnicity and age;
 - Long-term cardiovascular benefits of combination therapies;
 - Management of FH in pregnancy;
 - Mechanism and management of statin intolerance;
 - Safety and effectiveness of dietary supplements and dietary adjuncts for LDL cholesterol reduction;
 - Methods to enhance healthcare provider adherence to guidelines.

Funding

- Funding for FH education and research should come from multiple sources including government, professional associations, industry, and private donations.

Health Organization criteria for systematic screening.⁶ Various FH screening approaches have been implemented in different countries. In the United States, screening for FH involves assessment of blood cholesterol concentrations, accompanied by an inspection for physical signs of FH such as xanthomas, and evaluation of family history. After an individual has been diagnosed with FH, cascade screening should be implemented where possible, which involves testing lipid levels in all available first-degree relatives of the index case.

Although several U.S. national health organizations encourage screening for FH beginning in childhood,^{7–10} a widespread universal screening initiative has not been implemented. This panel believes it is the responsibility of primary healthcare providers and relevant specialists to screen all children and adults for hypercholesterolemia, and to initiate therapy in patients with FH and severe hypercholesterolemia. Individuals with FH have a mortality risk, particularly as young adults, that is disproportionately higher than that which would be predicted for individuals with the same cholesterol level, but without FH.¹¹ This increased risk is due to the exposure of people with FH to very high low-density lipoprotein (LDL) cholesterol concentrations from birth.¹¹ Without treatment, more than half of all men with FH and 30% of women with FH are expected to have a myocardial infarction before 60 years of age.¹² Early detection of FH is paramount to the successful treatment of the disease.

The late professor Roger Williams at the University of Utah recognized the importance of a systematic approach to identify individuals with FH more than 20 years ago.^{4,13–15} His commitment and worldwide activism for this cause led to the development of the Make Early Diagnosis Prevent Early Death (MEDPED, www.medped.org/index.html) program, a non-profit humanitarian organization to help diagnose and treat children and adults with high cholesterol disorders. MEDPED is supported internationally by over 40 countries.

Typically, FH is diagnosed on the basis of clinical and biological signs, but another aspect to diagnosis is identifying the causal genetic mutation.¹⁶ Genetic testing is generally not needed for clinical management or diagnosis, but may be useful when the diagnosis is uncertain. Identification of the causal mutation may also provide additional motivation for some patients to adhere to treatment. Population-based genetic screening for FH is generally impractical due to the large number of possible causal mutations (over 1600 known mutations of the LDL receptor gene alone at the time of this writing). The cost of genetic testing may also limit its use, but since the test is performed once in a lifetime and multiple affected relatives can then be identified, the benefits might outweigh the cost.^{17–19} The use of genetic information may also raise ethical concerns.²⁰ So, in cases where genetic testing is undertaken, the implications of the test results should be carefully explained to the patient. Another important point to note is that a negative genetic test does not necessarily exclude a diagnosis of FH, since about 20% of patients who have

been diagnosed as having definite FH do not have an identifiable mutation when tested with current methods.

In some countries, currently the Netherlands, Spain, and Wales, national screening programs exist which include genetic cascade screening.^{21–23} Records from the Lipid Clinic Network in the Netherlands indicate that with the use of the genetic cascade screening approach, 4500 to 6000 relatives of FH patients can be contacted yearly, resulting in identification of 1500 to 2000 new cases of FH per year.⁴ A long-term follow-up study of patients identified using this program also provided compelling evidence for the benefits of statin treatment.²⁴ In this follow-up (mean 8.5 years) study of 2146 patients with FH, statin use reduced CHD risk by approximately 80%, to a level similar to that of an age-matched sample from the general population. This suggests that statin treatment may substantially reduce or eliminate the CHD risk associated with FH.

Not only are cascade screening programs (both those that incorporate genetic testing and those that do not) effective in reducing disease risk, they have been shown to be cost-effective.^{6,25–30} Cascade screening is the most cost-effective means of finding a previously undiagnosed FH patient, particularly in children.³¹ Cost effectiveness will continue to improve as drug costs for certain statins, the drugs of choice for FH treatment, decrease due to the expiration of patents. Furthermore, as DNA diagnostic technology advances, the cost of genetic testing may also decrease.

Role of the front line provider

Primary care practitioners are on the front line of identifying individuals with hypercholesterolemia and FH, and in some cases successfully diagnose and manage the lipid treatment for FH patients. Primary care practitioners include family practitioners, internists, pediatricians, obstetrician-gynecologists, and nurse practitioners, physician assistants, pharmacists and others providing primary care. Cardiologists and neurologists may overlook a potential FH diagnosis in a person who has had a cardiovascular or cerebrovascular event, due to their focus on the acute event and the rapid discharge of the patient from the hospital.³² Achilles tendon xanthomas and premature corneal arcus are often overlooked during a routine physical examination. Unfortunately, there are many cases when patients with FH are not given an accurate diagnosis unless they visit a physician interested in lipid disorders.¹⁵

Role of the lipid specialist

Some FH patients require specialized care and should be referred to a lipid specialist. These include patients with FH who do not respond adequately to or are intolerant of initial statin therapy; children with FH (consultation with or referral to a lipid specialist is always recommended); and patients who are candidates for more intensive therapy

because of higher CHD risk, or who have family histories of very premature CHD (in men <45 years of age and women <55 years of age). Lipid specialists include physicians and other healthcare providers who have received specialized lipidology training. Such training has been recognized by the American Board of Clinical Lipidology or the Accreditation Council for Clinical Lipidology. An important part of the lipid specialists' approach to the management of FH, which may be different from the approach of the general practitioner, is the awareness of the familial nature of the condition and implementation of cascade screening of first-degree relatives of index cases.^{11,31}

Payers

Patients with FH are at very high lifetime risk of atherosclerotic cardiovascular disease and appropriate therapy is required. It is the opinion of this panel that initial screening, initiation of therapy with appropriate medications, and follow up monitoring should be covered by payers. It is understood that support for this proposition may be difficult to achieve. With no cure for FH on the horizon, long-term coverage of lipid-altering agents, including high potency statins and combination therapy, should be covered by payers. Other, non-statin, lipid altering agents for FH patients with statin intolerance or those refractory to statin therapy should also be covered. Patients with severe forms of FH may require coverage of LDL apheresis, and coverage of this procedure should not be denied for patients who meet criteria for LDL apheresis.

Although genetic testing is not recommended as a universal screening measure, and is not generally needed for clinical management or diagnosis, there are cases when genetic testing has an important role, such as when the diagnosis of FH is uncertain. The panel recommends that genetic testing should be covered by payers under those circumstances. Genetic testing has social implications and is an important policy issue.^{4,16,20,33,34} Issues regarding its use and impact on eligibility for health insurability have to be addressed.³³⁻³⁵ Patients who do have genetic testing for FH need to have legal safeguards in place to protect them from discriminatory practices. In the Netherlands and U.K. there has been preliminary research into the ethical, legal, and social issues related to genetic testing, but research in the U.S. is needed.^{33,36,37}

Public and provider awareness and education

FH is a significant, but poorly identified and underestimated, problem in the U.S. For early diagnosis of FH and for prevention and treatment of CHD, increased public awareness is necessary. Awareness by the general public is lacking, and even patients diagnosed with FH often have limited understanding of the nature of the condition.

According to an examination of 74 patients with FH who were administered a questionnaire about knowledge of FH, most patients knew about cholesterol, prevention, and the reason for drug treatment, but had very little knowledge about the risk of genetic transmission and the importance of family history.³⁸ The public needs to know the signs of FH, and that FH is a treatable condition with therapies that can markedly reduce the risk of early CHD, premature death, and other complications from atherosclerotic disease. Furthermore, FH patients and their families need to understand that this is a genetic disorder that is typically passed down from one generation to the next as a dominant trait. A variety of methods, including news media stories and public service announcements should be utilized to increase public and patient awareness. Also useful might be an FH patient/family organization or support group to assist in the dissemination of educational information.

Not only is there an apparent lack of awareness among the general public and FH patients, but also healthcare providers have often had limited training regarding the importance of screening and of appropriate treatment of FH. A follow-up study of the Netherlands genetic cascade screening program indicated that even after diagnosis of FH, patients who were receiving cholesterol-lowering medication(s) and being followed by their physicians were undertreated, and a minority reached their treatment goal.^{4,22,39} This indicates that not only should the importance of screening be emphasized in provider education, but also the need for aggressive therapy. Primary healthcare practitioners and relevant specialists should receive education regarding screening of all children and adults for hypercholesterolemia and the appropriate management of patients with FH and severe hypercholesterolemia. This education needs to be provided initially in medical and allied health professional schools, internship, residency, and fellowship programs, and thereafter through continuing education, in multiple specialties, through partnering of professional organizations and through local, national, and international health agencies. Furthermore, government agencies and other policy makers at local, state, national, and international levels should all be engaged in efforts to screen and treat patients with FH appropriately. Healthcare systems, hospitals, pharmacy benefits management organizations, and insurance companies should contribute to the education of both the public and healthcare practitioners.

Research

Since the development of MEDPED over 20 years ago, there have been great strides in the identification of FH through genetic testing and publication of diagnostic criteria and the treatment of high cholesterol with the development of safe, high potency statins. However, several areas in the field of FH require further research. In the United States, better data are needed regarding the percentage of individuals in the general population who are diagnosed

with and treated for FH, as well as information on CHD risk status and event rates for patients with FH; the cost effectiveness of various approaches to screening and treatment, including genetic screening; and the benefits and risks of aggressive therapy. Several areas of study are important in order to improve the care of FH patients including:

- behavioral management of patients with FH;
- patient adherence to medications and ways to improve adherence to therapy;
- adherence to guidelines by healthcare practitioners;
- long term follow up of patients with FH, including safety of long term therapy with lipid lowering drugs and long-term cardiovascular benefits of combination therapies;
- additional agents/methodologies for further lowering of LDL cholesterol;
- differences in drug metabolism by gender, ethnicity, and age;
- management of FH in pregnancy;
- mechanisms and treatment of statin intolerance; and
- safety and effectiveness of over-the-counter preparations and dietary adjuncts for lowering LDL cholesterol.

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It has been the experience of this panel, that funding for FH education and research is obtainable from multiple sources, including government agencies such as the National Institutes of Health, professional associations like the American Heart Association, various industries, and non-profit foundations. Together, fiscal support from multiple donors for public awareness campaigns, education, and research can greatly facilitate the implementation of appropriate screening, which can then lead to early detection and treatment of FH and make an enormous impact on the prevention of CHD and other atherosclerotic sequelae.^{40,41}

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