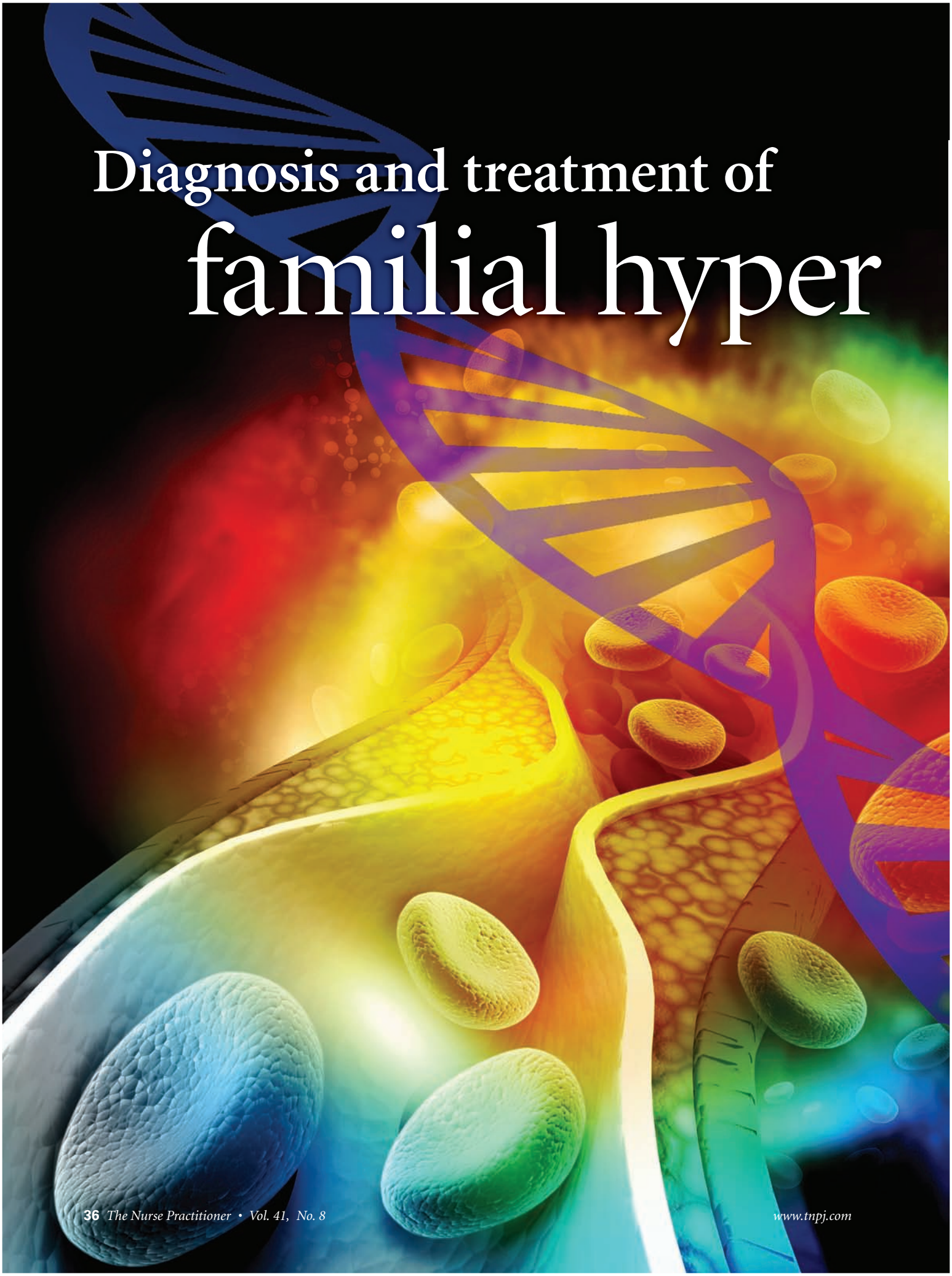
Diagnosis and treatment of familial hyper



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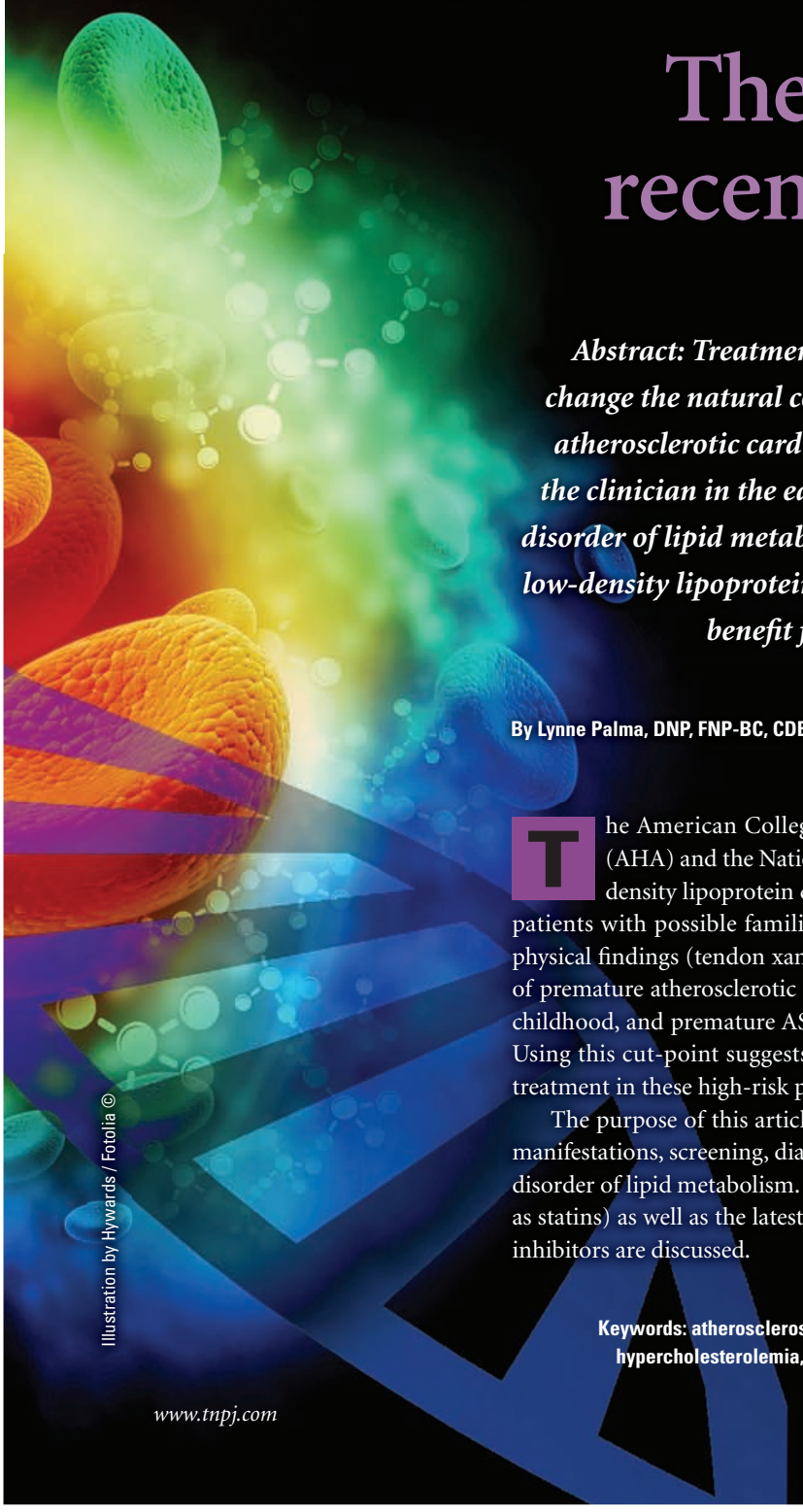
cholesterolemia:

The impact of recent guidelines



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Abstract: *Treatment of familial hypercholesterolemia can change the natural course of the disease to prevent premature atherosclerotic cardiovascular disease. New guidelines assist the clinician in the early identification of this common genetic disorder of lipid metabolism by placing individuals with elevated low-density lipoprotein cholesterol levels in high-risk groups who benefit from treatment with statins.*

By Lynne Palma, DNP, FNP-BC, CDE; Marguerite Welding, MS, FNP-BC; and Jennifer O'Shea, PharmD

The American College of Cardiology (ACC)/American Heart Association (AHA) and the National Lipid Association (NLA) utilize a cut-point of low-density lipoprotein cholesterol (LDL-C) of 190 mg/dL or greater to identify patients with possible familial hypercholesterolemia (FH). Other criteria, such as physical findings (tendon xanthomas and premature corneal arcus), a family history of premature atherosclerotic cardiovascular disease (ASCVD), elevated LDL-C since childhood, and premature ASCVD in the patient are used to confirm the diagnosis. Using this cut-point suggests the diagnosis of FH and paves the way for lifesaving treatment in these high-risk patients.

The purpose of this article is to discuss the prevalence, pathophysiology, clinical manifestations, screening, diagnosis, and treatment recommendations of this genetic disorder of lipid metabolism. The use of HMG CoA reductase inhibitors (also known as statins) as well as the latest proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are discussed.

Keywords: atherosclerosis, cascade screening, cholesterol guidelines, familial hypercholesterolemia, myopathy, PCSK9 inhibitors, rhabdomyolysis, statins

Case presentations

Ms. L is 8 years old at the time of her first serum cholesterol screening due to a family history of high cholesterol on her mother's side. She is a healthy second-grader with height and weight in the 50th percentile. Her physical exam is normal. Pertinent lab findings include:

Total cholesterol 317 mg/dL
LDL-C 251 mg/dL
Triglycerides 52 mg/dL
High-density lipoprotein cholesterol (HDL-C) 56 mg/dL
Cholesterol/HDL-C ratio 7.6

Mr. E is a 54-year-old White male with multiple comorbidities, including cerebral vascular disease, diabetes mellitus, depression, hypertension, hyperlipidemia, and peripheral artery disease (PAD). He is nonadherent to medications, including both a statin and insulin. Surgical history includes a right femoral popliteal bypass procedure, and social history includes a 30 pack/year history of tobacco use.

Pertinent findings on physical exam include:

- Eyes: Diminished visual acuity, cotton wool patches, mild arterial narrowing, corneal arcus
- Heart: 3/6 systolic murmur
- Peripheral vascular: 1+ bilateral midcalf edema, bilateral Achilles tendon xanthomas, diminished peripheral pulses

Pertinent lab findings include:

HgbA1c 10.3%
Total cholesterol 491 mg/dL
LDL-C 383 mg/dL
Triglycerides 228 mg/dL
HDL-C 63 mg/dL
Cholesterol/HDL-C ratio 7.6

Both patients presenting for care are at different stages in the disease process. Ms. L was discovered to have FH at an age whereby treatment may more significantly alter the natural course of the disease to prevent the complications seen in Mr. E, who has the same untreated condition with the resulting dire consequences.

Prevalence

FH occurs mainly in two general forms: when individuals inherit either one mutant allele or two mutant alleles that cause defective LDL metabolism. If one defective allele is inherited, the individual has heterozygous familial hypercholesterolemia (HeFH) and typically presents with cholesterol levels two- to three-fold higher than normal. Adults with HeFH characteristically have LDL-C levels of 190 mg/dL or greater, and in children, LDL-C levels are 160 mg/dL or greater.[1]

The prevalence of HeFH is predicted at 1:500 in the general population and is considered to be one of the most frequent autosomal dominate hereditary disorders in the general population.[1] Recent data indicate that the prevalence is closer to 1:200.[2] It is estimated that only 10% of individuals with FH have been detected, and only 5% are adequately treated.[3] The more obscure finding (1:300,000) of homozygous familial hypercholesterolemia (HoFH) occurs when individuals inherit two defective alleles that allow LDL-C to rise three to six times normal.[2] This article will focus on the more common HeFH (also known simply as FH).

Pathophysiology

The LDL receptor mutation in the allele in individuals with FH is one of loss of function. The receptors in the liver that clear LDL particles from the plasma are defective, allowing for markedly elevated LDL-C levels from birth. Currently, greater than 1,200 mutations of the LDL receptor have been documented.[4] Approximately 5% of genetically identified FH may be due to an apolipoprotein B-100 (APOB-100) gene mutation and approximately 1% of PCSK9 gain-of-function mutations.[4] The PCSK9 mutations are currently of interest as the basis of recently approved therapies for FH.

The risk of ASCVD is elevated about 20-fold in untreated patients with FH.[5] Cholesterol and triglycerides are hydrophobic fat that must be packaged in hydrophilic lipoproteins for transport in plasma. The amount of cholesterol and triglyceride carried by each of the lipoproteins varies by lifestyle choices, inherited lipid disease, other diseases, and certain medications. The lipoprotein particles are identified by their surface apo-lipoproteins and are either atherogenic or antiatherogenic.

Over the lifetime of an individual with FH, elevations of atherogenic LDL-C persist, and the LDL particles are retained in the arterial wall with subsequent foam cell formation within the intima of arteries. Plaque formation typically progresses to occlusive atherosclerosis with ensuing PAD, angina, plaque rupture, myocardial infarction, and stroke.[4]

Clinical manifestations

Patients with FH may present with typical clinical manifestations of ASCVD or more obscure findings, such as tendon xanthomas, eyelid xanthelasmas, and corneal arcus. Tendon xanthomas are pathognomonic for FH and result from deposition of cholesterol into the tendon, which changes its mechanical properties.

The accumulations of lipid-laden macrophages (foam cells) in tendons resemble the lesions found in atherosclerotic plaques and most commonly occur in the Achilles and finger extensor tendons.[6] Xanthelasmas are cholesterol deposits in the eyelids that may or may not be related to elevated LDL-C levels. If seen in individuals under age 25, FH should be considered. Corneal arcus occurs in older individuals and is a part of normative aging. If seen in an

individual under age 45, it may be due to elevated LDL-C levels.[6]

Screening and diagnosis

Universal screening for elevated serum cholesterol is recommended and should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. A family history of hypercholesterolemia and ASCVD in first-degree relatives increases the likelihood of FH if it occurs prematurely in men younger than age 55 and women younger than age 65. All individuals should be screened by age 20.[6-8]

Several groups have offered diagnostic criteria for FH and include the Make Early Diagnosis Prevent Early Death Program, the Simon Broome Register Group in the United Kingdom, and the Dutch Lipid Clinic Network.[6] These groups vary with their diagnostic criteria considering various metrics, such as very high LDL-C as well as family history of elevated LDL-C levels and early onset ASCVD. Tendon xanthomas and the presence of corneal arcus prior to age 45 are given a point value in the Dutch Lipid Clinic Network criteria.

The ACC, AHA, and NLA simplify the diagnosis of FH by using a level of LDL-C 190 mg/dL or greater as a possible indication of FH.[7,8] Children under age 20 should be suspected of having FH if their LDL-C is 160 mg/dL or greater. Genetic testing is not required unless the diagnosis is uncertain, and even when performed, it is insensitive.[6-8] If LDL-C is found to be elevated, a second profile after 2 to 3 months of dietary guidance along with other biochemical analyses to exclude secondary hypercholesterolemia should be performed. Dietary characteristics, certain disorders, and drugs can elevate LDL-C (see *Examples of drugs that may elevate LDL-C*).

Family history and cascade screening

Drawing a family pedigree can help confirm the FH diagnosis, and this awareness of the genetic nature of the disorder may improve the adherence to treatment for the parents and the child.[4] Once the diagnosis is made, patients identified with FH are recommended to have cascade screening. The subsequent screening of all first-degree relatives with a fasting lipid panel is "the cascade effect" and helps identify family members who are at risk for this genetic condition and assists with the early diagnosis and prevention of ASCVD (see *Genogram*).

Treatment using evidence-based guidelines

There are differences between the ACC/AHA and NLA guidelines (in general) regarding LDL-C targets, use of non HDL-C measurements, and ASCVD risk calculators.[7,8] In spite of the differences, there is consensus that individuals with an LDL-C 190 mg/dL or greater are in a high-risk category that benefits from statins. These patients often have FH and need lifelong treatment. The NLA recommends that patients with FH be treated to a target goal of LDL-C less than 100 mg/dL, and the ACC/AHA recommends 50% lowering of LDL-C from baseline regardless of the initial measurement.[7,8] If a patient with FH also has ASCVD, the target LDL-C is less than 70 mg/dL, according to the NLA.[8]

Both organizations identify individuals at high risk and make recommendations for treatment, which include lifestyle changes and statins. Individuals who do not fit into high-risk groups are further assessed using risk assessment calculators. Both the NLA and the ACC/AHA use the Pooled Cohort Equation to assess for risks with different cutoffs.[7,8] Statins are recommended if the 10-year risk of a cardiovascular event exceeds 7.5% in the ACC/AHA and 15% for the NLA guideline.

The NLA also uses the Framingham Risk Assessment calculation from older cholesterol guidelines (Adult Treatment Panel III). Using this risk calculator, if the patient has a 10% risk of having a cardiovascular event in the next 10 years, statins are recommended. It is important to understand that if the patient is in a high-risk group, such as a patient with ASCVD, diabetes mellitus, and FH (LDL-C 190 mg/dL or greater), no further risk assessment is needed, and treatment with statins is recommended. In other words, the 10-year ASCVD risk in the patient with FH is not adequately predicted by any conventional risk assessment tools, and thus not needed nor recommended.[7,8]

Examples of drugs that may elevate LDL-C[8]

- Synthetic progestins
- Anabolic steroids
- Synthetic steroids (danazol)
- Glucocorticoids
- Immunosuppressive agents (cyclosporine)
- Amiodarone
- Diuretics (thiazide diuretics in high doses)
- Thiazolidinediones
- Fibric acids (in patients with severe hypertriglyceridemia)
- Long-chain omega-3 fatty acids (in patients with severe hypertriglyceridemia)

Lifestyle changes

Lifestyle therapies are an important element of risk and have been shown to have an impact on atherogenic cholesterol and other related disturbances, such as obesity, hypertension, and insulin resistance.[7,8] Although drug therapy will

be needed, patients with FH are encouraged to maintain a diet low in saturated fat (less than 7% of energy), moderate- or higher-intensity physical activity (at least 150 minutes per week), and weight loss (5% to 10% of body weight) for those who are overweight or obese.[8]

A 3-month trial of lifestyle changes may be recommended before or with concurrent treatment with lipid-lowering agents. Plant stanols/sterols (2 g/day) increase in viscous fiber intake (10 to 20 g/day); in addition, referral to a nutritionist is helpful.[5] Tobacco cessation is recommended, and advising children and adolescents to never start smoking is important.

High-intensity statins

The ACC/AHA and the NLA guidelines consider statins as first-line therapy for patients with FH.[7,8] Within hepatocytes, cholesterol is recycled or newly made with the help of an enzyme called 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. Statins block hepatic cholesterol synthesis by inhibiting HMG CoA reductase and have been shown to reduce serum LDL-C levels by 18% to 55%.[8]

A large body of evidence demonstrates that statins are safe and generally well tolerated and have the ability to reduce the risk of ASCVD events. Patients with FH should receive aggressive statin therapy to achieve 50% reduction in LDL-C levels. This typically requires high doses of high-intensity statin therapy.[5,7,8]

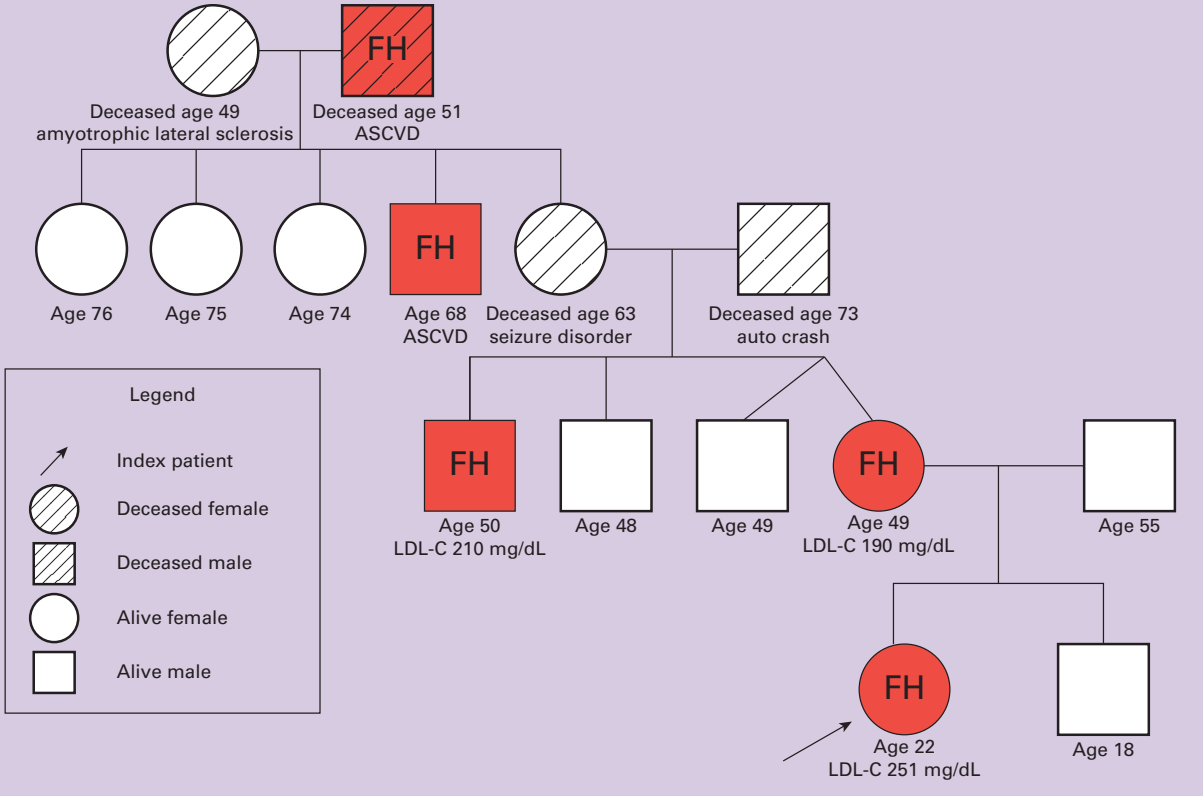
Starting statin therapy requires effective communication and shared goals between the clinician and patient. Treatment goals, time span of treatment (lifelong), adverse reactions, and potential drug or dietary interactions need to be clearly communicated. Sometimes, especially in younger individuals, the starting dose may be lower than what is recommended.

It might be more effective to start at a lower dose than to have the patient experience an adverse reaction, which often puts them in the category of "statin intolerant." Because patients often discontinue statin therapy when they experience adverse reactions, it is important for the clinician to apply a strategy that produces the greatest likelihood of long-term adherence.

Use of statins in children

Use of lipid-lowering medications has been shown to be safe and effective in children with FH; however, it is not commonly part of pediatric training, and referral to a lipid

Genogram



Genogram courtesy of the author.

specialist is common.[5,9] Long-term effects of the use of high-intensity statins starting at an early age are unknown and the recommended age of initiation of statins varies.[3] The ACC/AHA guideline recommends statin therapy at age 21 if the patient has not already been diagnosed and treated earlier.[7] Recommendations endorsed by the NLA recommend that initial treatment with statins for pediatric patients with FH should be considered beginning at age 8 to 10 depending on severity of the LDL-C elevation.[3,6,9]

The goal for pediatric patients with FH is LDL-C below the 95th percentile (<130 mg/dL) or a reduction in the LDL-C of 50%, and does not need to be as low as in adults.[3,9] Statin use should be initiated at the lowest available dose in children.[9] Monitoring statins in children is the same as in adults.[9]

Monitoring statin therapy

Monitoring LDL-C provides evidence of patient adherence and can help motivate patients to reach their LDL-C goal. The NLA recommends further treatment when LDL-C and non-HDL goals are not met.[8] Adding a second cholesterol-lowering agent or referral to a lipid specialist is recommended in these situations. There is currently no evidence that dropping LDL-C to less than 40 mg/dL is harmful, although most clinicians have a tendency to lower statin dosage when the level is this low unless the patient is at very high risk for an ASCVD event.[8]

Adverse reactions of statins

All cholesterol-lowering drugs can potentially be hepatotoxic and myotoxic, but this risk is very low as evidenced by the advice of the FDA that routine monitoring of liver transaminases in patients on statins is not necessary.[10] A baseline measurement is required and is advised to be repeated only if clinically indicated. If liver transaminases are found to be elevated three times the upper limit of normal on two occasions, the statin should be discontinued.

Myopathy

Symptoms reported with statin use include mainly muscle-related complaints (myalgia) that are usually mild and reversible and often associated with higher doses. Rarely, life-threatening rhabdomyolysis can occur as muscle breakdown leads to the release of toxic intracellular constituents into the bloodstream, which can cause acute kidney failure. Approximately 60% of the cases of statin-related rhabdomyolysis are related to drug interactions.[11]

Musculoskeletal complaints are common in older adults, and it is important to assess other possible causes before attributing such symptoms to statin therapy. Older age, frailty, reduced overall skeletal mass, chronic kidney disease, diabetes, hypothyroidism, alcohol abuse, and underlying muscle disorders all increase the risk of myopathy.[11,12] A baseline creatine kinase level is recommended in patients at risk for myopathy and may be repeated if a patient becomes symptomatic. Drug-drug and food interactions such as grapefruit juice can also increase the risk of myopathy (see *Drug classes that increase statin levels and adverse reactions*).

Drug classes that increase statin levels and adverse reactions[11]

Drugs classes that inhibit CYP3A4	Examples
Macrolide antibiotics	Erythromycin, clarithromycin (azithromycin does not inhibit CYP3A4)
Azole antifungal agents	Ketoconazole, itraconazole
HIV protease inhibitors	Ritonavir
Antiarrhythmics	Amiodarone
Immunosuppressants	Cyclosporine
Nondihydropyridine calcium channel blockers	Diltiazem and verapamil
Antidepressants	Nefazodone

There are several proposed mechanisms by which statins cause myopathy; one theory suggests the breakdown of cholesterol caused by statins may also result in the breakdown of muscle tissue. A second proposed mechanism involves isoprenoid reduction, which promotes myofiber apoptosis. A third mechanism suggests that the depletion of ubiquinone (CoQ10) may cause myopathy.[11-13] CoQ10 is available as a dietary supplement and is sometimes recommended to help reduce the adverse reactions of statins, even though there is very little evidence of efficacy and it is not actively regulated by the FDA.[11-13]

Stopping the statin to determine if the complaints resolve, changing to another statin, decreasing the dose, or giving the statin every other day (or even once a week) can be helpful. Although it is a class effect, there seem to be fewer muscular events with extended-release fluvastatin and other hydrophilic statins, such as pravastatin and rosuvastatin.[11]

Nonstatin therapy may be the only other option and can include fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors, long-chain omega-3 fatty acid concentrates, and nicotinic acid. Adding another agent can provide a "statin-sparing" effect; however, the addition of some of these agents can increase the risk of myopathy. If a statin/fibrate acid derivative combination is necessary, fenofibrate is the preferred option over gemfibrozil.[11]

Cognitive dysfunction

There is controversy regarding the use of statins and cognitive dysfunction. The FDA released label changes in 2012 noting case reports of statin-associated ill-defined memory loss and confusion, which were reversible after medication discontinuation and were not restricted to a particular age group.[10]

Studies to date have debatable and controversial results requiring more randomized control trials if an association is to be made.[14] Until then, the benefits of statins must be weighed against the risk of cognitive impairment on an individual basis. If cognitive impairment is suspected, discontinuing the statin typically results in prompt resolution. Switching from a lipophilic to hydrophilic statin may also resolve the impairment.

Risk of diabetes

A small risk of developing diabetes has been noted in patients prescribed a statin, occurring more often in patients with prediabetes, obesity, or a family history of type 2 diabetes mellitus.[15-17] Most experts agree that the benefits of taking a statin far outweigh the risk of developing diabetes. Statins lower plasma LDL-C, and as a result, there may be direct inflammation and oxidation within beta cells (resulting in impairment in insulin secretion). A baseline HbA1c is recommended before treatment with a statin in individuals at risk and then periodically thereafter.[8]

Pregnancy risk category

The current pregnancy risk category for statins is X. Statins have been identified as potentially teratogenic; however, available evidence is far from conclusive. Despite the lack of data, it is still advisable to avoid the use of statins in pregnancy.[18] Women of reproductive age should be counseled to stop statins, ezetimibe, and niacin therapy 3 months prior to conception.[3] Statins, ezetimibe, and niacin should not be given during pregnancy and lactation.

Bile acid sequestrants can be used when appropriate. LDL apheresis can be used during pregnancy in high-risk patients with atherosclerotic disease. Low estrogen-containing oral agents, intrauterine devices, and barrier techniques are the preferred methods of contraception for women with FH.[3] Genetic counseling for families with FH regarding risk and follow-up treatment for their children should be considered.[3]

Newly approved treatments for FH-PCSK9 inhibitors

The FDA recently approved alirocumab and evolocumab for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH or patients with clinical ASCVD who require additional lowering of LDL-C. Alirocumab is given by subcutaneous injection and has been shown to reduce LDL-C by 36% to 59% compared with placebo.[19] Evolocumab is given by subcutaneous injection and has been shown in clinical trials to reduce LDL-C by 60%.[20] The most common adverse reactions for both drugs include nasopharyngitis, influenza, and injection site reactions, although more severe hypersensitivity reactions were reported.[19,20]

Alirocumab and evolocumab are antibodies that target a specific protein called proprotein convertase subtilisin-kexin type 9 and represent a new class of lipid-lowering agents called PCSK9 inhibitors. The PCSK9 protein regulates the expression of the LDL receptor. It binds to the LDL receptors on the hepatocytes forming a complex. The LDL receptor/PCSK9 complex that forms is internalized in the liver via endocytosis followed by degradation in the lysosome. When the PCSK9 is attached to the LDL receptor, both are degraded, and the LDL receptor is not recycled. This leads to fewer LDL receptors to remove excess LDL-C from the plasma.

Mutations exist within the PCSK9 that can alter the function of this regulating protein. "Gain of function" mutation of PCSK9 increases the activity of the protein that ultimately leads to fewer LDL receptors because of the joint degradation of the LDL receptor/PCSK9 complex. With fewer LDL receptors on the hepatocytes, LDL-C increases. Patients with "gain of function" mutation of PCSK9 have elevated LDL-C levels and increased ASCVD risk.

Some patients with FH have this mutation. With "loss of function" PCSK9, there are more LDL receptors recycled to capture and degrade LDL-C. Patients who have the "loss of function" mutation of PCSK9 enjoy lifelong low LDL-C levels. Drug treatment with the new monoclonal antibodies (alirocumab and evolocumab) blocks binding of PCSK9 to the LDL receptor, lowers LDL-C, and is now approved for FH. Long-term effects are not yet available, and thus these drugs should be reserved for patients who cannot tolerate statins.[19]

Implications for practice

Societal changes to promote healthy lifestyles are needed for individuals with or without FH. Evolutionary genetics were not made for the current surfeit of calories, obesity, tobacco, and inactive lifestyle. This being said, lifestyle changes alone are not sufficient for patients with FH, and in order to disrupt the decades-long process of plaque formation, pharmacologic treatment is required.

Typically, lipid abnormalities are treated only after disease presentation. Early identification with early and adequate treatment is the goal, and this is accomplished when clinicians are informed about the diagnosis and treatment of FH. NP

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Lynne Palma is an NP and program coordinator at Florida Atlantic University, Boca Raton, Fla.

Marguerite Welding is an NP at George Azar, MD, Ft. Lauderdale, Fla.

Jennifer O'Shea is a clinical pharmacist at United Healthcare, Miramar, Fla.

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