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Familial hypercholesterolemia: Detect, treat, and ask about family

ABSTRACT

Familial hypercholesterolemia is an autosomal dominant disorder that affects the metabolism of low-density lipoprotein cholesterol (LDL-C) through mutations in the gene for LDL receptor (*LDLR*), and less commonly in those for apolipoprotein B (*APOB*), proprotein convertase subtilisin-kexin type 9 (*PCSK9*), and others. Patients with these mutations have elevated plasma levels of LDL-C and, as a result, an increased risk of atherosclerotic cardiovascular disease beginning in childhood, leading to significant risk of illness and death.

KEY POINTS

Indices are available to help practitioners estimate a patient's likelihood of having familial hypercholesterolemia based on lipid values, clinical presentation, and family history. Patients who likely have the disease should have further evaluation considered.

If a patient is found to have familial hypercholesterolemia, family members should be screened for it in a cascading process.

A statin is generally the first-line treatment, and a non-statin therapy such as ezetimibe can be added. PCSK9 inhibitors should also be considered if adequate LDL-C lowering is not achieved by statins or if the patient is statin-intolerant. Patients with homozygous familial hypercholesterolemia may need LDL-C apheresis.

Dr. Tang has disclosed serving as a consultant for MyoKardia and Sequana Medical.

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FAMILIAL HYPERCHOLESTEROLEMIA is the result of mutations in genes for proteins involved in the metabolism of low-density lipoprotein cholesterol (LDL-C), and is inherited in an autosomal dominant fashion.^{1,2} Patients born with it can develop elevated LDL-C and atherosclerotic cardiovascular disease at a young age,³ which can often be detected in childhood.

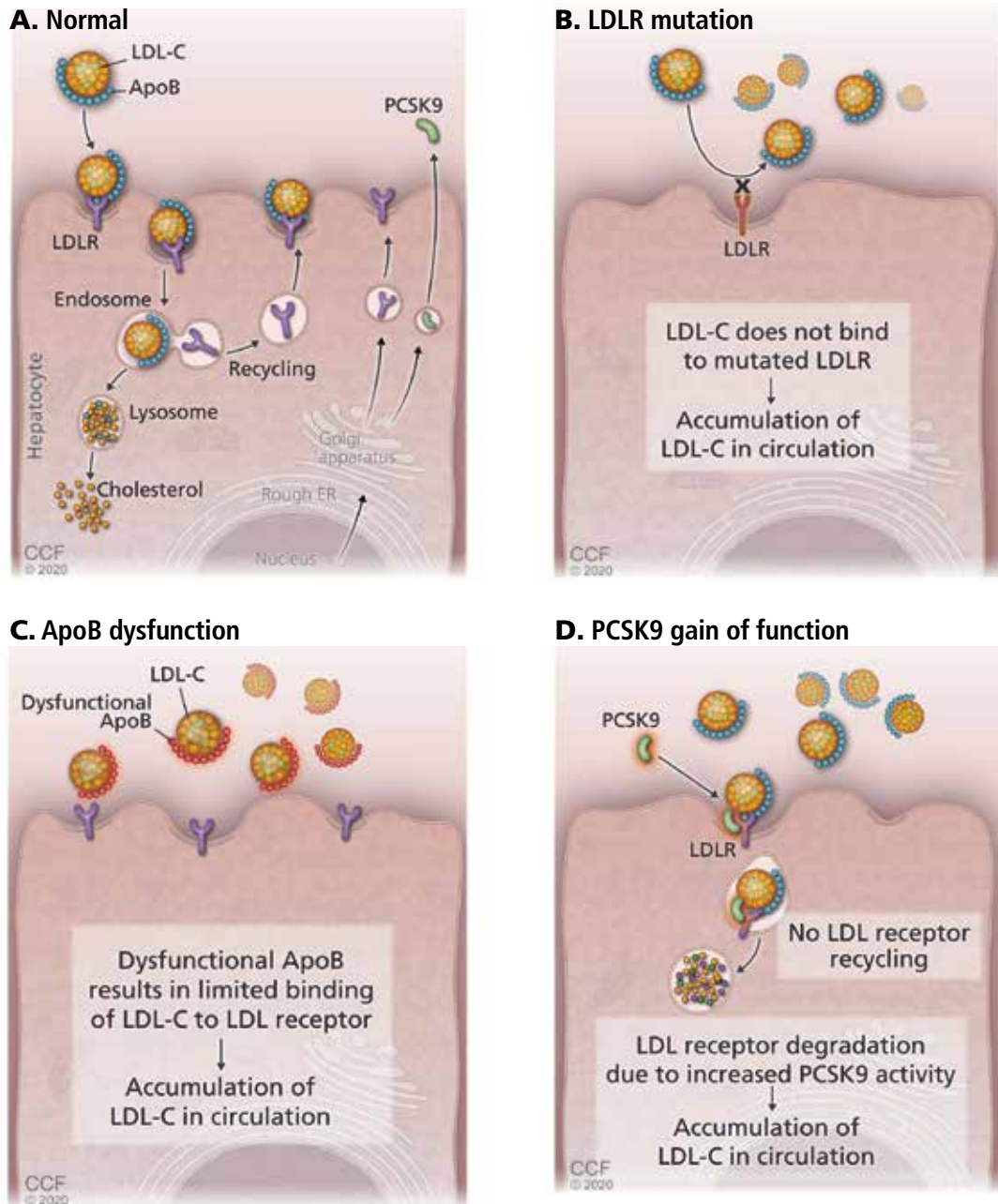
Strategies have been devised to detect the disease early for primary prevention, which is especially relevant now that novel lipid-lowering drugs are available.⁴⁻⁸ Often, the first opportunity for detection is during a routine checkup with the primary care physician.

Here, we provide an overview of familial hypercholesterolemia for general practitioners, including current diagnostic strategies, treatments, guidelines for management, and avenues for future research.

■ MUTATIONS IN *LDLR* AND OTHER GENES

In more than 75% of cases of familial hypercholesterolemia, the LDL receptor is defective, owing to mutations in the *LDLR* gene.⁹ Less often, the problem is a mutation in a gene for another molecule that interacts with the LDL receptor, such as apolipoprotein B (*APOB*), proprotein convertase subtilisin-kexin type 9 (*PCSK9*), or an unknown gene (**Figure 1**).^{2,9}

Because familial hypercholesterolemia is inherited in an autosomal dominant fashion, most patients who have it are heterozygous, possessing 1 normal allele and 1 mutated allele.¹⁰ The prevalence of heterozygous familial hypercholesterolemia is about 1 in 220, based on large genetic studies.¹¹ Homozygous familial hypercholesterolemia, in which the patient possesses 2 mutated alleles, is much less



Often, the first opportunity for detection is during a routine checkup with the primary care physician

Figure 1. (A) Low-density lipoprotein cholesterol (LDL-C) binds to its receptor (LDLR), using apolipoprotein B (ApoB) as its ligand. Defects in LDLR (B) or ApoB (C) result in less binding of LDL-C, raising LDL-C levels. (D) Proprotein convertase subtilisin kexin type 9 (PCSK9) binds to LDLR and escorts it into the interior of the hepatocyte, where it is destroyed, resulting in fewer receptors and higher LDL-C concentrations. Gain-of-function mutations in PCSK9 raise LDL-C levels.

prevalent, with a frequency estimated at 1 in 300,000.^{10,12} Patients with homozygous disease face a worse prognosis.

The prevalence of familial hypercholesterolemia differs across ethnic groups, with higher frequencies of mutations in various parts of the

world due to the founder effect. For instance, Finns, French-Canadians, Afrikaners, and Christian Lebanese populations have a higher prevalence of the disease.¹³ Racial differences have been shown as well; blacks have a slightly higher prevalence than whites or Hispanics.¹⁴



Figure 2. Xanthomas of the Achilles tendons. Note the position used for examination, with the patient kneeling on a chair.

From Sibley and Stone, reference 27.

Although cardiovascular events tend to occur at an earlier age in men than in women, the prevalence of familial hypercholesterolemia is similar between sexes.^{4,14}

■ ELEVATED RISK FROM AN EARLY AGE

Because people with familial hypercholesterolemia have elevated LDL-C levels from an early age, they also begin to have manifestations of atherosclerotic cardiovascular disease early.^{3,15–17} Children with familial hypercholesterolemia have greater carotid intimal thickness than unaffected children by age 8.¹⁸ Coronary artery disease is evident in patients with familial hypercholesterolemia from age 17 in males and age 25 in females, and up to 25% of adolescents with familial hypercholesterolemia have coronary artery calcification.^{19,20}

A study from Denmark showed an adjusted odds ratio for coronary artery disease of 3.3 in carriers of a familial hypercholesterolemia mutation.²¹ Similarly, the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART) found the prevalence of atherosclerotic cardiovascular disease to be 3 times higher in people with familial hyper-



Figure 3. Corneal arcus.

From Sibley and Stone, reference 27.

cholesterolemia than in unaffected people.²²

Clinical atherosclerotic cardiovascular disease is even more accelerated in patients with homozygous familial hypercholesterolemia, in whom the first cardiovascular event usually occurs before age 30.²³ Thus, early diagnosis of familial hypercholesterolemia is essential for risk stratification.

■ WHEN TO SUSPECT IT

Three sets of clinical criteria have been devised to identify patients with heterozygous familial hypercholesterolemia.^{24–26} Each is based on a combination of:

- **Lipid levels**, typically an LDL-C greater than 190 mg/dL
- **Family history** of premature coronary artery disease or familial hypercholesterolemia
- **Clinical history**
- **Physical signs** such as xanthelasma (cholesterol deposits in the skin of the eyelids); xanthoma (deposits in connective tissue in and around extensor tendons—pathognomonic for this disease) (Figure 2)²⁷ and arcus cornealis or corneal arcus (deposits along the corneal border) (Figure 3).²⁷

The Dutch Lipid Network Criteria

The Dutch Lipid Network Criteria,²⁴ the most widely used of the 3 sets of criteria, yields a score based on LDL-C level, physical findings, premature cardiovascular disease in relatives, and positive genetic testing if available (Table 1). A score higher than 8 makes the diagnosis “definite,” as 80% of people in that category were found to have a genetic mutation.²⁸ One purpose of developing this set of criteria was

Several mutations remain unknown, and not finding a mutation does not exclude the diagnosis

TABLE 1

The Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia

Criteria	Points
Family history	
First-degree relative with known premature atherosclerotic cardiovascular disease (age < 55 in men, age < 60 in women) or first-degree relative with LDL-C > 95th percentile	1
First-degree relative with tendon xanthomas or arcus cornealis, or child under age 18 with LDL-C > 95th percentile	2
Clinical history	
Premature coronary artery disease	2
Premature cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthomas	6
Arcus cornealis before age 45	4
LDL-C levels, mg/dL	
≥ 330	8
250–329	5
190–249	3
155–189	1
DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>APOB</i> , or <i>PCSK9</i> gene	8
Interpretation	
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6–8
Possible familial hypercholesterolemia	3–5
Unlikely familial hypercholesterolemia	< 3

From the World Health Organization, reference 24.

to identify patients with familial hypercholesterolemia who did not have a family member with an established diagnosis.

The Simon Broome Registrar criteria

The Simon Broome Registrar criteria,²⁵ developed in the United Kingdom, also rely on a combination of clinical, physical, and biochemical data (Table 2).^{13,16} Again, if certain clinical findings are met, a definite diagnosis can be made.

The MED-PED criteria

The Make Early Diagnosis and Prevent Early Deaths (MED-PED) criteria focus more on lipid levels and family history and less on clinical characteristics or genetic testing (Table 3).²⁶ They were developed to be broadly applicable and were found to achieve 54% sensitivity and 98% specificity in detecting heterozygous familial hypercholesterolemia in the general population.²⁶ The sensitivity improved to 88% when the criteria were used in patients with a first-degree relative with heterozygous familial hypercholesterolemia, 85% in those with an affected second-degree relative, and 81% in those with an affected third-degree relative. Thus, the authors suggested performing biochemical testing of relatives of patients found to have heterozygous familial hypercholesterolemia mutations, a process known as cascade screening.

Which set of criteria is best?

The 3 sets of clinical screening criteria were compared in a retrospective study²⁹ in 408 patients from 1995 through 2003. None outperformed the others, but when patients deemed to be in the “definite” diagnosis categories underwent genetic testing, the mutation detection rate was as low as 30% to 40%. The authors²⁹ acknowledged that perhaps not all mutations were tested for, and polygenetic factors may have been overlooked. Regardless, they emphasized that the phenotype (ie, elevated LDL-C value, physical findings, and clinical history) confers enough of a cardiovascular risk to justify treatment, and that negative genetic testing should not stratify patients to lower risk categories.

This notion is endorsed by the International Atherosclerosis Society, which has proposed criteria for severe familial hypercholesterolemia based on LDL-C levels and evidence of subclinical or clinical atherosclerotic cardiovascular disease.³⁰

What about homozygous disease?

The clinical criteria do not apply to patients who may have homozygous familial hypercholesterolemia, which is much less common and more serious. However, the diagnosis can be suspected clinically if the patient has very high LDL-C levels (> 500 mg/dL if untreated, or > 300 mg/dL if on maximal lipid-lowering

treatment) and has cholesterol deposits in the first decade of life, especially if both parents have heterozygous familial hypercholesterolemia.⁴

■ WHAT IS THE PATIENT'S RISK?

The Montreal FH Score³¹ predicts cardiovascular risk in patients with familial hypercholesterolemia. It was devised by Paquette et al, based on a study in which they identified age, hypertension, low levels of high-density lipoprotein cholesterol, male sex, and smoking as independent risk factors (Table 4).³¹ A score higher than 20 points was associated with a cardiovascular risk 10 times greater than a score lower than 20 (odds ratio 10.3, 95% confidence interval 6.7–15.5, $P < .001$). The Montreal FH Score was validated in an independent cohort with familial hypercholesterolemia.³²

■ GENETIC TESTING IS THE GOLD STANDARD

Genetic testing is the gold standard for diagnosing familial hypercholesterolemia. Most of the known mutations are in *LDLR*, but *APOB*, *PCSK9*, and potentially other genes involved in LDL-C catabolism can also have mutations. Several mutations remain unknown, and not finding a genetic mutation does not exclude the diagnosis, especially if there is strong phenotypic evidence.⁹

Finding a mutation also has prognostic value. At any LDL-C level, a gene-positive individual carries a higher risk of atherosclerotic cardiovascular disease than does a gene-negative one.³³ The type of *LDLR* mutation also carries its own risk.³⁴ Thus, if you strongly suspect that a patient has the disease based on clinical diagnostic criteria, then genetic testing can be considered, with appropriate genetic counseling.³⁵

Genetic testing may be particularly helpful in younger patients, especially if they have relatives with confirmed familial hypercholesterolemia. Though familial hypercholesterolemia can be diagnosed clinically based on lipid profile, patients with it have a higher burden of lifelong LDL-C exposure, which is likely a reason that gene-positive patients have a higher risk of atherosclerotic cardiovascular disease.

TABLE 2

The Simon Broome diagnostic criteria for familial hypercholesterolemia

Criterion ^a	Description
A	Total cholesterol level > 290 mg/dL or LDL-C > 190 mg/dL in adults (age ≥ 16) Total cholesterol level > 260 mg/dL or LDL-C > 155 mg/dL in children (age < 16)
B	Tendon xanthomas in the patient or in a first- or second-degree relative
C	DNA-based evidence of a mutation in <i>LDLR</i> , <i>APOB</i> , or <i>PCSK9</i>
D	Family history of myocardial infarction before age 50 in a second-degree relative, or before age 60 in a first-degree relative
E	Total cholesterol > 290 mg/dL in a first- or second-degree relative

^a "Definite" familial hypercholesterolemia requires criterion C by itself, or criterion A plus B; "probable" familial hypercholesterolemia requires either A plus D, or A plus E.

Information from the Simon Broome Register Group, reference 25.

Genetics may also explain some degree of phenotypic heterogeneity, as more deleterious mutations (*LDLR* null) are associated with higher LDL-C levels and higher cardiovascular risk.^{30,36} Moreover, patients with severe heterozygous familial hypercholesterolemia can have LDL-C concentrations that overlap with those of patients who have homozygous familial hypercholesterolemia, and vice versa, leading to alternative therapeutic approaches.³⁰ Polygenetic factors, gene-environment interactions, and gene-gene interactions can also allow for variations in familial hypercholesterolemia without extreme elevations in LDL-C, making genetic testing even more important for risk stratification.³⁰

Rarely, genetic testing can also help in guiding therapy, as particular mutations (eg, null mutations of *LDLR* in homozygous patients) can make certain therapies ineffective.

■ CASCADE SCREENING OF RELATIVES

Identifying affected relatives is important so that they can be treated and potentially avoid atherosclerotic cardiovascular disease. Unfor-

At any LDL-C level, a gene-positive individual carries a higher risk than a gene-negative individual

TABLE 3

MED-PED diagnostic criteria for probable heterozygous familial hypercholesterolemia

Age	Closest relative with familial hypercholesterolemia							
	First-degree		Second-degree		Third-degree		None	
	Threshold cholesterol level (mg/dL) in the patient							
	Total	LDL-C	Total	LDL-C	Total	LCL-C	Total	LDL-C
< 20	220	155	230	165	240	170	270	200
20–29	240	170	250	180	260	185	290	220
30–39	270	190	280	200	290	210	340	240
≥ 40	290	205	300	215	310	225	360	260

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Cascade screening in the United States can be challenging, given barriers in the health-care system

Unfortunately, many remain unaware of their risk.³⁷ Thus, screening strategies have been developed in the hope of rapid and cost-effective diagnosis.

This is primarily done through cascade screening, in which LDL-C measurement, genetic testing, or both are done in consenting relatives of patients (proband) identified with the disease. As more probands are identified, the process repeats itself by targeting more relatives. These strategies have been implemented in many European countries,³⁸ and data from the SAFEHEART registry have indicated that identifying 9,000 cases of familial hypercholesterolemia in 10 years could prevent 847 coronary events and 203 coronary deaths, and could add 767 quality-adjusted life years.³⁹

Cascade screening can be implemented in several ways, with outreach cascade screening in relatives of patients who have:

- A worrisome lipid profile on a routine health screen but no symptoms
- Early-onset atherosclerotic cardiovascular disease and who meet clinical criteria for familial hypercholesterolemia
- Persistently elevated lipid levels despite treatment, and a family history that raises the suspicion of familial hypercholesterolemia.

Genetic testing, when positive, allows very accurate cascade testing. However, ge-

netic testing must follow established recommendations³⁵ to maximize efficacy and minimize risk.⁴⁰ Privacy and ethical issues are also raised, including questions about appropriate informed consent.⁴⁰

In the United States, cascade screening can be challenging due to barriers in our healthcare system.⁴¹ Moreover, privacy policies mandate that the proband make first contact with family members, but the proband may have difficulty locating and getting in touch with them.⁴¹

Universal cholesterol screening of adults could help identify more people with familial hypercholesterolemia, but this strategy has not been fully implemented or recommended.⁴² Further, universal cholesterol screening is more common in adults than in children, whereas we need to diagnose the disease as early in life as possible.

Other strategies are being implemented to identify patients who may have familial hypercholesterolemia. For example, artificial intelligence systems that use machine learning techniques can explore electronic health records, billing codes, and laboratory data.⁴³ Large-scale DNA sequencing may also help in finding cases that would not be detected.⁴⁴ Though these novel techniques are intriguing, whether they would be cost-effective remains unclear.

TREATMENT SHOULD START EARLY

Starting lipid-lowering therapy early is as important as early detection of disease. In untreated heterozygous patients, the first coronary event occurs about 20 years earlier than in the general population.⁴⁵ In untreated homozygous patients, the prognosis is even worse, with the first event often occurring in childhood.⁴⁶

The type of mutation also affects treatment response. For instance, *LDLR* mutations can result in either a defective but somewhat functional LDL receptor or one with no functionality (null *LDLR*).³⁵ Thus, cases of null *LDLR* mutations are more likely to be medically refractory, as lipid-lowering therapy often relies on somewhat functional LDL receptors.³⁵

Lipid-lowering therapy in familial hypercholesterolemia can be with statins, non-statin drugs (eg, ezetimibe, PCSK9 inhibitors), and, rarely, LDL-C apheresis. Lifestyle modifications such as dietary changes and exercise should accompany any medical therapy, even though they reduce LDL-C only modestly in adults with this disease.⁴⁷

Statins are the first-line treatment

Reducing LDL-C levels is the primary goal, and high-dose statins are the first-line treatment. Statins inhibit the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, resulting in decreased cholesterol production and increased LDL receptor expression on the surface of hepatocytes, which further reduces plasma LDL-C.⁹

Statin therapy should be started as soon as possible to help prevent cardiovascular events. In homozygous familial hypercholesterolemia patients, statin therapy is often started in the first decade of life.²³ Of note, however, homozygous patients are more likely to have null *LDLR* mutations, which make statin therapy less effective.

Thanks to statin therapy, the prognosis for patients with familial hypercholesterolemia has improved in the last 30 years.^{48,49} In a randomized controlled trial in heterozygous patients, atorvastatin 80 mg lowered LDL-C levels by 50%.⁴⁹ In another study,⁴⁸ statin therapy reduced the 10-year risk of atherosclerotic cardiovascular disease from 60% at baseline to 10% (adjusted hazard ratio 0.18, 95% confi-

TABLE 4

The Montreal FH score to predict cardiovascular risk in familial hypercholesterolemia

Cutoff	Points
Age	
≤ 21	0
22–28	4
29–35	8
36–42	12
43–49	16
50–56	20
57–63	24
> 63	28
High-density lipoprotein cholesterol, mg/dL	
≤ 23	12
23–34	9
35–46	6
47–58	3
> 58	0
Hypertension	
Yes	2
No	0
Smoking	
Yes	1
Never	0
Sex	
Male	3
Female	0

A score > 20 is associated with a 10-fold higher cardiovascular risk.

Reprinted from Paquette M, Brisson D, Dufour R, Khoury É, Gaudet D, Baass A. Cardiovascular disease in familial hypercholesterolemia: validation and refinement of the Montreal-FH-SCORE. *J Clin Lipidol* 11(5):1161–1167.e3. Copyright 2017, with permission from Elsevier.

dence interval 0.13–0.25). With statin therapy, the risk of atherosclerotic cardiovascular disease in heterozygous patients was only slightly higher than in the general population (6.7 vs

4.1 events per 1,000 patient-years).⁴⁸ Therefore, statin therapy has proven to be highly effective in terms of cost, morbidity, and mortality.^{4,48,49}

Nonstatin therapies can be added

In cases in which statins do not effectively lower LDL-C, other lipid-lowering drugs can be considered as adjunctive therapy. The CASCADE, SAFEHEART, and other registries suggest that many patients with familial hypercholesterolemia cannot achieve their lipid goals with statins alone. Up to 50% require a second-line agent, and 20% require a PCSK9 inhibitor.⁵⁰

Ezetimibe is a selective cholesterol absorption inhibitor that blocks uptake of cholesterol at both the enterocyte lumen and the hepatobiliary system.⁹ This leads to depletion of cholesterol stores and increased expression of LDL receptor, which further reduces plasma LDL-C.⁹ In patients already taking a statin, ezetimibe can further reduce LDL-C by 15% to 20% and is generally well tolerated in combination with statin therapy.^{1,51} National and international guidelines suggest ezetimibe as a second-line agent when LDL-C goals are not met with statins alone.⁵⁰

Combination therapy with ezetimibe and simvastatin was shown to significantly reduce the risk of atherosclerotic cardiovascular disease events after myocardial infarction.⁵² Though this study did not specifically target familial hypercholesterolemia patients, it further supports the benefit of lowering LDL-C in general in all high-risk populations.

Nonstatin therapies such as bile acid sequestrants, niacin, and fibrates are not well studied in patients with familial hypercholesterolemia.

Bile acid sequestrants form insoluble complexes of bile acid and cholesterol molecules that avoid capture by enterocytes.⁴⁹ These complexes are then excreted. With less substrate for LDL-C, plasma levels can be decreased by 13% to 19%.⁴ Unfortunately, these medications are not well tolerated, which limits their use.

Niacin, also known as vitamin B₃ or nicotinic acid, reduces free fatty acid mobilization from adipose tissue, which impairs the liver's ability to synthesize cholesterol and triglycer-

ide-containing particles.⁹ Unfortunately, the medication is not well tolerated and has not shown clinical efficacy in large randomized clinical trials in patients without familial hypercholesterolemia.^{53,54}

Fibrates are typically used to lower triglyceride levels. Caution must be used when combining them with statins, as they can cause myopathies and other drug interactions.¹

Newer agents have been developed that are currently reserved for homozygous familial hypercholesterolemia patients, who commonly have null *LDLR* mutations.

Lomitapide is a microsomal triglyceride transfer protein inhibitor that prevents assembly of lipids onto proteins.⁹

Mipomersen is an antisense oligonucleotide that binds *APOB* mRNA and further decreases LDL-C generation in the liver.³

Both of these medications are poorly tolerated due to adverse effects, and thus they are reserved for patients at very high risk of atherosclerotic cardiovascular disease, such as those with homozygous familial hypercholesterolemia.⁹

PCSK9 inhibitors

Perhaps the most effective therapies in reducing LDL-C independently and in combination with statins are PCSK9 inhibitors.⁸ The US Food and Drug Administration and the European Medicines Agency have approved 2 of these medications—evolocumab and alirocumab.

PCSK9 inhibitors are monoclonal antibodies that target circulating PCSK9, which normally degrades LDL receptor. More LDL receptor is therefore recycled to the hepatocyte surface and is available to remove more LDL-C from circulation.⁵⁵

These medications are recommended when traditional lipid-lowering therapy cannot effectively lower LDL-C.⁵⁵ They lower LDL-C levels by another 50% to 60% in addition to the reduction achieved by statins.^{56,57} They have also been shown to decrease LDL-C levels modestly (up to 20%) in patients with homozygous familial hypercholesterolemia who have almost no LDL receptor activity.⁵⁸

Overall, these agents reduce major cardiovascular events in patients at high risk of atherosclerotic cardiovascular disease, like

Thanks to statins, the prognosis in familial hypercholesterolemia has improved in the last 30 years

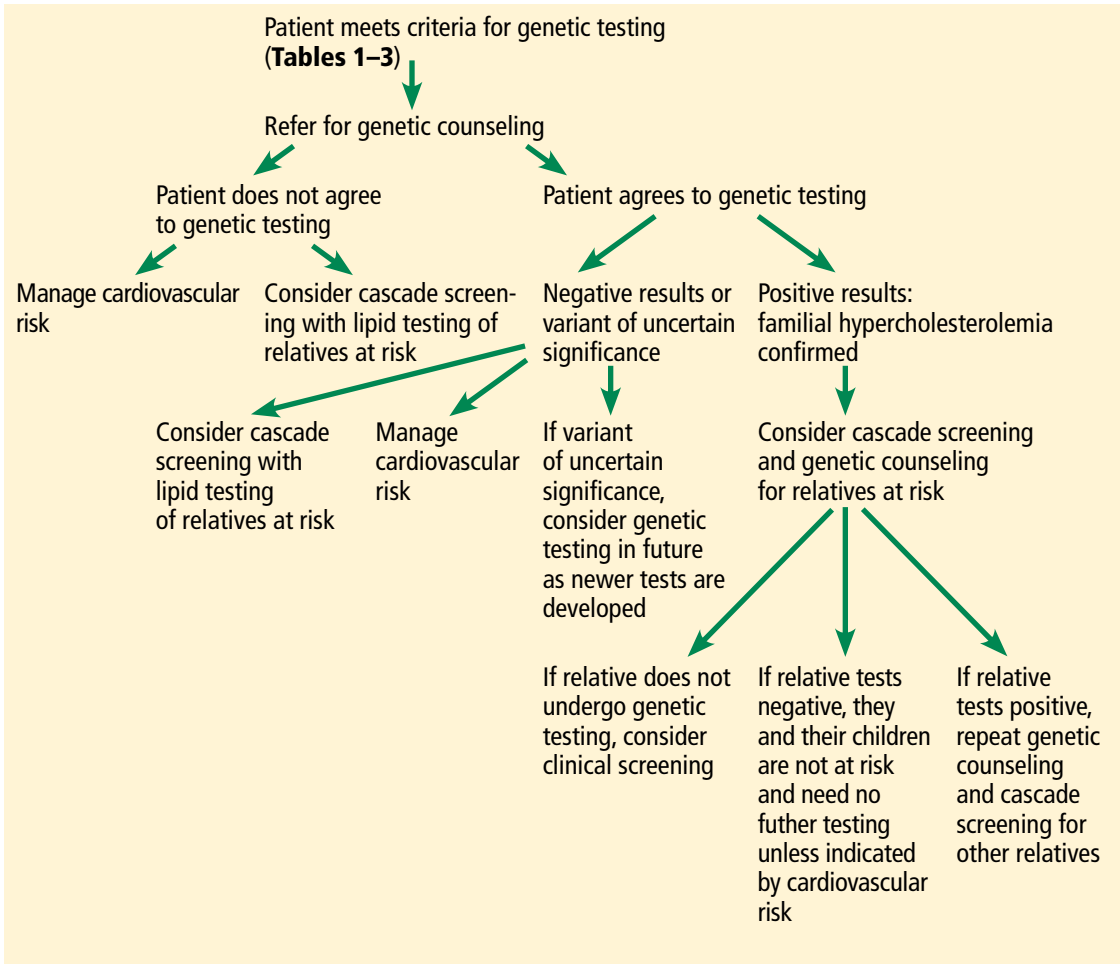


Figure 4. Algorithm for cascade screening.

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those with familial hypercholesterolemia.^{59,60} Further, they are generally well tolerated, but unfortunately, their cost can pose a barrier to both patients and providers.⁶¹ However, approvals from insurance companies are increasing, given the available evidence noted above.

LDL-C apheresis

LDL-C apheresis involves extracorporeal filtering of lipoproteins, using an indwelling venous catheter, either weekly or twice a week.⁴⁴ It is usually reserved for patients at extremely high risk in whom medical therapies have been ineffective, or in those with homozygous familial hypercholesterolemia who have a null *LDLR* mutation and no response to conventional lipid-lowering therapy.⁴⁴ In fact, it is one of the only therapies shown to prolong survival in this group of patients.⁶²

Factors to consider before referring patients for apheresis are cost, problems with venous access, and time. Despite its benefit in homozygous familial hypercholesterolemia, there is still a scarcity of evidence on its use, precluding standardized guidelines and limiting its use to a case-by-case basis.⁶³

WHAT DO THE GUIDELINES SAY?

Several professional societies have published guidelines to help providers diagnose and manage familial hypercholesterolemia.^{6,35,64-66}

American professional societies generally agree on considering genetic testing for familial hypercholesterolemia in patients with elevated plasma LDL-C (usually > 190 mg/dL [> 4.9 mmol/L]), a family history of familial hypercholesterolemia, or who meet clinical

PCSK9 inhibitors lower LDL-C by another 50% to 60% in addition to the reduction achieved with statins

criteria.^{35,65–67} The National Lipid Association⁶⁴ and International Familial Hypercholesterolemia Foundation⁶⁵ also recommend cascade screening when a mutation is identified (**Figure 4**).³⁵

For management, the American guidelines recommend lifestyle modifications in addition to lipid-lowering therapy.^{24,35,65,66} First-line drugs for patients with suspected familial hypercholesterolemia are high-intensity statins, which have class I recommendation (evidence or general agreement that the treatment is beneficial, useful, and effective) and a level of evidence of B-R (moderate, derived from 1 or more randomized controlled trials or meta-analyses of moderate-quality randomized controlled trials).^{50, 65–67} The general consensus is that the initial LDL-C value should decrease by at least 50% in primary prevention settings. Alternative lipid-lowering therapies can be added if this goal is not reached, with the preferred second-line agent being ezetimibe, which has a class IIa recommendation (the weight of evidence or opinion is in favor of usefulness or efficacy), and a level of evidence of B-R.⁵⁰

If patients strongly suspected of having familial hypercholesterolemia are on maximally tolerated statin therapy and ezetimibe and still have an LDL-C level of 100 mg/dL or higher or are statin-intolerant, then PCSK9 inhibitors can be considered (class IIb recommendation, level of evidence B-R).⁵⁰ In secondary prevention cases, LDL-C goals should be 70 mg/dL or less, according to the 2018 American College of Cardiology and American Heart Association cholesterol guidelines, and 55 mg/dL or less according to the American Association of Clinical Endocrinologists and American College of Endocrinology (recom-

mendation grade A, best level of evidence 1 [strong evidence]).⁶⁶

These recommendations were primarily aimed at those with heterozygous familial hypercholesterolemia. However, similar treatment algorithms exist for homozygous familial hypercholesterolemia. Childhood diagnosis is essential, and there are lower thresholds for LDL-C apheresis.^{65,66} Referral to specialized centers for familial hypercholesterolemia should be strongly considered as soon as a diagnosis of heterozygous or homozygous familial hypercholesterolemia is established to aid in further screening, risk stratification, and treatment.

■ CALL FOR EARLIER DIAGNOSIS

Familial hypercholesterolemia is a genetic disease process that is associated with significant morbidity and mortality. The US Centers for Disease Control and Prevention has designated familial hypercholesterolemia as a tier 1 genomic application, indicating that it imposes a significant public health burden.⁶⁷ Thus, early diagnosis and treatment are essential to help reduce the burden of cardiovascular disease in these patients.

Unfortunately, a large percentage of people remain undiagnosed and at risk of cardiovascular events.^{68,69} Efforts are being made to identify patients earlier, through cascade screening, genome-wide DNA sequencing, or screening algorithms in large electronic health records.⁶⁹ Earlier diagnosis should increase understanding of the disease and allow collaborations across specialties as we work to improve our care of familial hypercholesterolemia.

The Familial Hypercholesterolemia Foundation at www.thehfoundation.org provides resources for patients and families. ■

■ REFERENCES

1. Turgeon RD, Barry AR, Pearson GJ. Familial hypercholesterolemia: review of diagnosis, screening, and treatment. *Can Fam Physician* 2016; 62(1):32–37. PMID:26796832
2. Faiz F, Hooper AJ, van Bockxmeer FM. Molecular pathology of familial hypercholesterolemia, related dyslipidemias and therapies beyond the statins. *Crit Rev Clin Lab Sci* 2012; 49(1):1–17. doi:10.3109/10408363.2011.646942
3. Nanchen D, Gencer B, Auer R, et al. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *Eur Heart J* 2015; 36(36):2438–2445. doi:10.1093/eurheartj/ehv289
4. Alonso R, Perez de Isla L, Muñoz-Grijalvo O, Diaz-Diaz JL, Mata P. Familial hypercholesterolaemia diagnosis and management. *Eur Cardiol* 2018; 13(1):14–20. doi:10.15420/scr.2018:10:2
5. Mata P, Alonso R, Pérez de Isla L. Atherosclerotic cardiovascular disease risk assessment in familial hypercholesterolemia: does one size fit all? *Curr Opin Lipidol* 2018; 29(6):445–452. doi:10.1097/MOL.0000000000000553
6. Nordestgaard BG, Chapman MJ, Humphries SE, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus Statement of the European Atherosclerosis Society. *Eur Heart J* 2013; 34(45):3478–3490a. doi:10.1093/eurheartj/ehv273
7. Wierzbicki AS, Humphries SE, Minhas R; Guideline Development Group. Familial hypercholesterolaemia: summary of NICE guidance. *BMJ* 2008; 337:a1095. doi:10.1136/bmj.a1095
8. Ahmed HM, Nissen SE. Nonstatin therapy for dyslipidemia. *Circ Res*

- 2018; 123(9):1036–1038. doi:10.1161/CIRCRESAHA.118.313829
9. Benito-Vicente A, Uribe K, Jebari S, Galicia-Garcia U, Ostolaza H, Martin C. Familial hypercholesterolemia: the most frequent cholesterol metabolism disorder caused disease. *Int J Mol Sci* 2018; 19(11): pii:E3426. doi:10.3390/ijms19113426
 10. EAS Familial Hypercholesterolaemia Studies Collaboration; Vallejo-Vaz AJ, Akram A, Kondapally Seshasai SR, et al. Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration. *Atheroscler Suppl* 2016; 22:1–32. doi:10.1016/j.atherosclerossup.2016.10.001
 11. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018; 50(9):1219–1224. doi:10.1038/s41588-018-0183-z
 12. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J* 2015; 36(9):560–565. doi:10.1093/eurheartj/ehu058
 13. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest* 2003; 111(12):1795–1803. doi:10.1172/JCI18925
 14. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* 2016; 133(11):1067–1072. doi:10.1161/CIRCULATIONAHA.115.018791
 15. Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease. *CMAJ* 2006; 174(8):1124–1129. doi:10.1503/cmaj.051313
 16. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis* 1999; 142(1):105–112. pmid:9920511
 17. Pérez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation* 2017; 135(22):2133–2144. doi:10.1161/CIRCULATIONAHA.116.024541
 18. Kusters DM, Wiegman A, Kastelein JJ, Hutten BA. Carotid intima-media thickness in children with familial hypercholesterolemia. *Circ Res* 2014; 114(2):307–310. doi:10.1161/CIRCRESAHA.114.301430
 19. Mabuchi H, Koizumi J, Shimizu M, Takeda R. Development of coronary heart disease in familial hypercholesterolemia. *Circulation* 1989; 79(2):225–232. doi:10.1161/01.cir.79.2.225
 20. Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. *Circulation* 1998; 98(23):2580–2583. doi:10.1161/01.cir.98.23.2580
 21. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016; 37(17):1384–1394. doi:10.1093/eurheartj/ehw028
 22. Pérez de Isla L, Alonso R, Mata N, et al; SAFEHEART Investigators. Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: insights from the SAFEHEART Registry (Spanish Familial Hypercholesterolaemia Cohort Study). *Arterioscler Thromb Vasc Biol* 2016; 36(9):2004–2010. doi:10.1161/ATVBAHA.116.307514
 23. Cuchel M, Bruckert E, Ginsberg HN, et al; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014; 35(32):2146–2157. doi:10.1093/eurheartj/ehu074
 24. World Health Organization. Familial hypercholesterolaemia (FH): report of a second WHO consultation, Geneva, 4 September 1998. <https://apps.who.int/iris/handle/10665/66346>. Accessed September 4, 2019.
 25. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991; 303:893–899.
 26. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol* 1993; 72(2):171–176. doi:10.1016/0002-9149(93)90155-6
 27. Sibley C, Stone NJ. Familial hypercholesterolemia: a challenge of diagnosis and therapy. *Cleve Clin J Med* 2006; 73(1):57–64. doi:10.3949/ccjm.73.1.57
 28. Fouchier SW, Defesche JC, Umans-Eckenhuis MA, Kastelein JP. The molecular basis of familial hypercholesterolemia in The Netherlands. *Hum Genet* 2001; 109(6):602–615. doi:10.1007/s00439-001-0628-8
 29. Damgaard D, Larsen ML, Nissen PH, et al. The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. *Atherosclerosis* 2005; 180(1):155–160. doi:10.1016/j.atherosclerosis.2004.12.001
 30. Santos RD, Gidding SS, Hegele RA, et al; International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol* 2016; 4(10):850–861. doi:10.1016/S2213-8587(16)30041-9
 31. Paquette M, Dufour R, Baass A. The Montreal-FH-SCORE: a new score to predict cardiovascular events in familial hypercholesterolemia. *J Clin Lipidol* 2017; 11(1):80–86. doi:10.1016/j.jacl.2016.10.004
 32. Paquette M, Brisson D, Dufour R, Khoury É, Gaudet D, Baass A. Cardiovascular disease in familial hypercholesterolemia: validation and refinement of the Montreal-FH-SCORE. *J Clin Lipidol* 2017; 11(5):1161–1167.e3. doi:10.1016/j.jacl.2017.07.008
 33. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol* 2016; 67(22):2578–2589. doi:10.1016/j.jacc.2016.03.520
 34. Huijgen R, Kindt I, Defesche JC, Kastelein JJ. Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29,365 individuals tested for 64 specific low-density lipoprotein-receptor sequence variants. *Eur Heart J* 2012; 33(18):2325–2330. doi:10.1093/eurheartj/ehs038
 35. Sturm AC, Knowles JW, Gidding SS, et al; Convened by the Familial Hypercholesterolemia Foundation. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2018; 72(6):662–680. doi:10.1016/j.jacc.2018.05.044
 36. Sun YV, Damrauer SM, Hui Q, et al. Effects of genetic variants associated with familial hypercholesterolemia on low-density lipoprotein-cholesterol levels and cardiovascular outcomes in the Million Veteran Program. *Circ Genom Precis Med* 2018; 11(12): pii:e002192. doi:10.1161/CIRCGEN.118.002192
 37. Neil HA, Hammond T, Huxley R, Matthews DR, Humphries SE. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 2000; 321(7254):148. doi:10.1136/bmj.321.7254.148
 38. Mata P, Alonso R, Pérez-Jiménez F. Screening for familial hypercholesterolemia: a model for preventive medicine. *Rev Esp Cardiol (Engl Ed)* 2014; 67(9):685–688. doi:10.1016/j.rec.2014.01.015
 39. Lázaro P, Pérez de Isla L, Watts GF, et al. Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. *J Clin Lipidol* 2017; 11(1):260–271. doi:10.1016/j.jacl.2017.01.002
 40. Tiller J, Lacaze P. Regulation of internet-based genetic testing: challenges for Australia and other jurisdictions. *Front Public Health* 2018; 6:24. doi:10.3389/fpubh.2018.00024
 41. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA* 2017;

- 318(4):381–382. doi:10.1001/jama.2017.8543
42. **US Preventive Services Task Force; Bibbins-Domingo K, Grossman DC, Curry SJ, et al.** Screening for lipid disorders in children and adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; 316(6):625–633. doi:10.1001/jama.2016.9852
 43. **Safarova MS, Liu H, Kullo IJ.** Rapid identification of familial hypercholesterolemia from electronic health records: The SEARCH Study. *J Clin Lipidol* 2016; 10(5):1230–1239. doi:10.1016/j.jacl.2016.08.001
 44. **Abul-Husn NS, Manickam K, Jones LK, et al.** Genetic identification of familial hypercholesterolemia within a single US health care system. *Science* 2016; 354(6319). pii:aaf7000. doi:10.1126/science.aaf7000
 45. **Stone NJ, Levy RI, Fredrickson DS, Verter J.** Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation* 1974; 49(3):476–488. doi:10.1161/01.cir.49.3.476
 46. **Raal FJ, Pilcher GJ, Panz VR, et al.** Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation* 2011; 124(20):2202–2207. doi:10.1161/CIRCULATIONAHA.111.042523
 47. **Broekhuizen K, van Poppel MN, Koppes LL, Kindt I, Brug J, van Mechelen W.** No significant improvement of cardiovascular disease risk indicators by a lifestyle intervention in people with familial hypercholesterolemia compared to usual care: results of a randomised controlled trial. *BMC Res Notes* 2012; 5:181. doi:10.1186/1756-0500-5-181
 48. **Cholesterol Treatment Trialists’ (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, et al.** Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; 376(9753):1670–1681. doi:10.1016/S0140-6736(10)61350-5
 49. **Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF.** Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; 357(9256):577–581. doi:10.1016/S0140-6736(00)04053-8
 50. **Grundy SM, Stone NJ, Bailey AL, et al.** 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019; 73(24):e285–e350. doi:10.1016/j.jacc.2018.11.003
 51. **Stanworth SJ, Estcourt LJ, Powter G, et al; TOPPS Investigators.** A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med* 2013; 368(19):1771–1780. doi:10.1056/NEJMoa1212772
 52. **Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators.** Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; 372(25):2387–2397. doi:10.1056/NEJMoa1410489
 53. **HPS2-THRIVE Collaborative Group; Landray MJ, Haynes R, Hopewell JC, et al.** Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014; 371(3):203–212. doi:10.1056/NEJMoa1300955
 54. **AIM-HIGH Investigators; Boden WE, Probstfield JL, Anderson T, et al.** Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; 365(24):2255–2267. doi:10.1056/NEJMoa1107579
 55. **Robinson JG, Huijgen R, Ray K, Persons J, Kastelein JJ, Pencina MJ.** Determining when to add nonstatin therapy: a quantitative approach. *J Am Coll Cardiol* 2016; 68(22):2412–2421. doi:10.1016/j.jacc.2016.09.928
 56. **Raal FJ, Stein EA, Dufour R, et al; RUTHERFORD-2 Investigators.** PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 385(9965):331–340. doi:10.1016/S0140-6736(14)61399-4
 57. **Kastelein JJ, Ginsberg HN, Langslet G, et al.** ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J* 2015; 36(43):2996–3003. doi:10.1093/eurheartj/ehv370
 58. **Raal FJ, Hovingh GK, Blom D, et al.** Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. *Lancet Diabetes Endocrinol* 2017; 5(4):280–290. doi:10.1016/S2213-8587(17)30044-X
 59. **Schwartz GG, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Committees and Investigators.** Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018; 379(22):2097–2107. doi:10.1056/NEJMoa1801174
 60. **Ridker PM, Rose LM, Kastelein JJ, et al; Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) Investigators.** Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab. *J Clin Lipidol* 2018; 12(4):958–965. doi:10.1016/j.jacl.2018.03.088
 61. **Cohen JD, Cziraky MJ, Jacobson TA, Maki KC, Karalis DG.** Barriers to PCSK9 inhibitor prescriptions for patients with high cardiovascular risk: results of a healthcare provider survey conducted by the National Lipid Association. *J Clin Lipidol* 2017; 11(4):891–900. doi:10.1016/j.jacl.2017.04.120
 62. **Thompson GR, Catapano A, Saheb S, et al.** Severe hypercholesterolaemia: therapeutic goals and eligibility criteria for LDL apheresis in Europe. *Curr Opin Lipidol* 2010; 21(6):492–498. doi:10.1097/MOL.0b013e3283402f53
 63. **Gidding SS, Champagne MA, de Ferranti SD, et al; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health.** The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation* 2015; 132(22):2167–2192. doi:10.1161/CIR.0000000000000297
 64. **Watts GF, Gidding S, Wierzbicki AS, et al; International Familial Hypercholesterolemia Foundation.** Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Eur J Prev Cardiol* 2015; 22(7):849–854. doi:10.1177/2047487314533218
 65. **Goldberg AC, Hopkins PN, Toth PP, et al.** Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011; 5(3):133–140. doi:10.1016/j.jacl.2011.03.001
 66. **Jellinger PS, Handelsman Y, Rosenblit PD, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease—executive summary. *Endocr Pract* 2017; 23(4):479–497. doi:10.4158/EP171764.GL
 67. **Centers for Disease Control and Prevention (CDC).** Genomics Implementation. <https://www.cdc.gov/genomics/implementation/index.htm>. Accessed September 3, 2019.
 68. **Abul-Husn NS, Manickam K, Jones LK, et al.** Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science*. 2016; 354(6319). pii:aaf7000. doi:10.1126/science.aaf7000
 69. **Banda JM, Sarraju A, Abbasi F, et al.** Finding missed cases of familial hypercholesterolemia in health systems using machine learning. *NPJ Digit Med* 2019; 2:23. doi:10.1038/s41746-019-0101-5

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Familial hypercholesterolemia

The article, “Familial hypercholesterolemia: Detect, treat, and ask about family” by Drs. N. P. Shah, H. M. Ahmed, and W. H. Tang in the February 2020 issue (*Cleve Clin J Med* 2020; 87(2):109–120. doi:10.3949/ccjm.87a.19021) contained an error.

On page 118, first column, the last paragraph stated: “If patients strongly suspected of having familial hypercholesterolemia are on maximally tolerated statin therapy and ezetimibe and still have an LDL-C level of 100 mg/dL or higher or are statin-intolerant, then PCSK9 inhibitors can be considered (class IIb recommendation, level of evidence B-R).⁵⁰ In second-

ary prevention cases, LDL-C goals should be 70 mg/dL or less, according to the 2018 American College of Cardiology and American Heart Association cholesterol guidelines, and 55 mg/dL or less according to the American Diabetes Association (class IIa recommendation, level of evidence A [clear evidence]).⁵⁰”

The recommendation for a lower LDL-C goal of 55 mg/dL or less in secondary prevention is not from the American Diabetes Association but rather from the American Association of Clinical Endocrinologists and American College of Endocrinology (recommendation grade A, best level of evidence 1 [strong evidence]), reference 66 in the article. The error has been corrected online.