Familial Hypercholesterolemia: Although Identification Advances, Appreciation and Treatment Lag

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Familial hypercholesterolemia is one of the most common autosomal dominant inherited genetic disorders, yet it is frequently undiagnosed, leading to a markedly increased risk for cardiovascular events. Understanding the pathophysiology of the disease as well as the importance of cascade screening is critical to appropriate treatment of patients. Though the mainstay of therapy for heterozygous familial hypercholesterolemia remains statins, many patients require additional therapy including ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies to achieve adequate low-density lipoprotein cholesterol (LDL-C) lowering. Access to PCSK9 inhibitors remains a significant clinical problem.

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KEY WORDS

Familial hypercholesterolemia • PCSK9 antibodies • Elevated LDL cholesterol

In 1972, Brown and Goldstein described the root cause of familial hypercholesterolemia (FH), a mutation in the key low-density lipoprotein cholesterol (LDL-C) regulatory enzyme, HMG CoA reductase. Within a year, they recognized their error and correctly identified the LDL receptor as the culpable protein in the genesis of FH.[1] Loss of function mutations result in impaired LDL receptor function, causing blunted degradation of LDL particles and LDL-C. Afflicted individuals experience markedly elevated LDL-C levels beginning in utero (Figure 1). This lifelong exposure to high LDL-C results in extraordinary risk of myocardial infarction (MI), cerebrovascular accident (CVA; stroke), and peripheral arterial disease (PAD).[2] Some studies have estimated this risk to be >20 times that of the "normal" population.[3,4]

Original prevalence estimates were that 1/1,000,000 people carried mutations in both alleles for the LDL receptor (homozygote), whereas 1/500 carried just one allele mutation (heterozygote).[5] Over the past few years, genetic studies have revealed that the prevalence is much higher, with approximately 1/200-250 people having a single

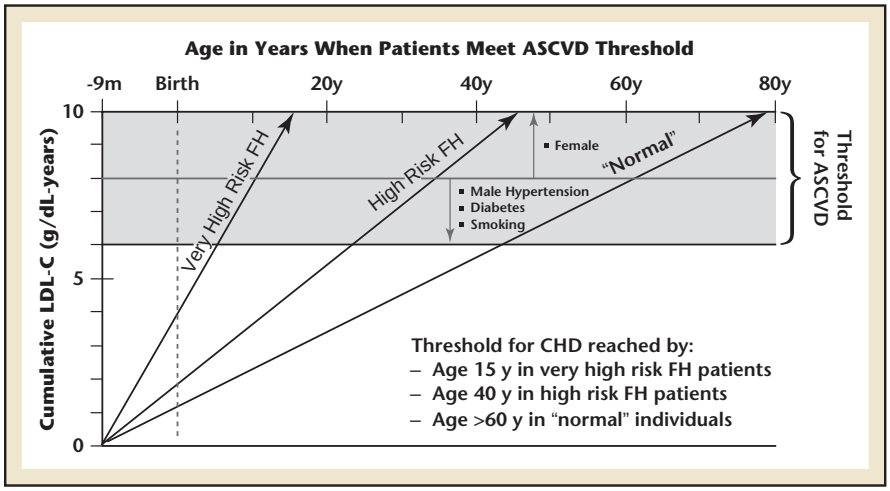

Figure 1. Threshold for atherosclerotic cardiovascular disease (ASCVD) as a function of cumulative low-density lipoprotein cholesterol (LDL-C) exposure. This adaptation emphasizes the genetic aspect of familial hypercholesterolemia (FH), bringing the start point of LDL-C accumulation into the in utero period. Exposure to markedly elevated LDL-C levels occurs even prior to birth, further explaining the prematurity of ASCVD in such individuals. Additionally, the figure introduces the suggested terminology *very high risk* and *high risk* FH. Adapted from Horton JD et al. *J Lipid Res.* 2009;50(suppl):S172-S177.

mutation and 1/160,000-200,000 possessing two.[6] Populations that have historically experienced high rates of consanguinity have been found to have prevalence rates of single FH mutations as high as 1/67. These "founder" groups include South African Ashkenazi Jews,[7] South African Afrikaners,[8] French Canadians,[9] Christian Lebanese,[10] and others. It is important to recognize these populations, as clinicians' index of suspicion for FH must always be on high alert when they enter our practices.

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Nomenclature

The definition of FH is complex, and therefore requires detailed explanation. Homozygous FH (HoFH) necessitates two mutations, whereas heterozygous FH (HeFH) only one. HoFH can be further subdivided. Simple HoFH is the presence of two mutations, one from each parent. Both mutations are identical, making this form of HoFH quite rare. Compound heterozygous FH, also a form of HoFH, occurs when one mutation in a single gene is inherited from each parent, but the mutations differ. This form of HoFH is the most common and involves the LDL receptor, as over 1700 mutations in the LDL receptor have been identified to date. Finally, there is the situation when two genes responsible for FH are involved. In this case, the patient has inherited one mutation from each parent, but the mutations affect different genes. For example, the patient may inherit an LDL receptor mutation from mother, and a gain of function (GOF) proprotein convertase subtilisin/kexin type 9 (PCSK9) from father. This form of HoFH has been dubbed *double heterozygous* and is not quite as common as the compound heterozygous form of HoFH. Understanding nomenclature is vital but grasping the physiology of FH is more consequential. To comprehend this, one must also have a working knowledge of LDL metabolism.

The hepatocyte manufactures very-low-density lipoproteins (VLDL) to transport lipids in the circulation. VLDL carries triglycerides (TG) and cholesterol with approximately 5 times as much TG as cholesterol. As VLDL travels through the capillaries of tissues such as skeletal muscle, the TGs are removed by the action of lipoprotein lipase in the capillaries and converted into free fatty acids to be used as energy. As it does so, the particle shrinks and becomes PCSK9, more cholesterol laden with less TG content. Its intermediary form is called intermediate-density lipoprotein (IDL), a particle with a particularly short residence time under normal conditions. IDL is rapidly degraded in the liver by hepatic lipase, or after removal of virtually all TG in the circulation it becomes LDL. LDL contains approximately 98% cholesterol. In humans, kinetic studies have demonstrated that LDL-C is removed from the circulation via LDL receptors on the liver as its primary mode of metabolism. It is not used for steroidogenesis, and it does not cross the blood-brain barrier to nourish the brain. Each of these organs manufactures cholesterol or receives cholesterol via delivery from HDL and therefore are not dependent on circulating blood levels of LDL cholesterol. Thus, in humans, LDL-C in the circulation is likely not necessary for bodily function and its excess causes atherosclerotic vascular disease through penetration of the vascular intima, oxidation, and promotion of inflammation of the vasculature, leading to cardiovascular events. The higher the LDL-C level, and the longer one experiences a high LDL-C level, the greater the risk of vascular events. For this reason,

patients with FH, having high LDL-C beginning in utero, have a high incidence of premature and severe vascular disease.

Diagnosis

There are three diagnostic systems that have been developed to help determine the diagnosis of FH. These include the Dutch Lipid Clinic Network (DLCN), Simon Broome, and MEDPED, or Make Early Diagnosis, Prevent Early Death.[6]

At the LDL-C levels listed below, the probability of FH is approximately 80% in the setting of general population screening. These LDL-C levels should prompt the clinician to strongly consider a diagnosis of FH and obtain further family information[11]:

LDL-C >250 mg/dL in a patient aged 30 years or more
LDL-C >220 mg/dL for patients aged 20 to 29 years
LDL-C >190 mg/dL in patients under age 20 years

Most clinicians make the diagnosis on clinical grounds, using an LDL-C >95% for age- and gender-matched controls in conjunction with a family history of either very high cholesterol or premature vascular disease in a first-degree relative. The American Heart Association statement by Gidding and colleagues is consistent with this form of diagnosing FH.[12] Physical examination can at times be useful as two signs are pathognomonic for FH: a corneal arcus in someone under age 45 years, and tendon xanthomas, typically involving the Achilles, independently secure the diagnosis of FH. Because of the more prevalent use of statins, these two signs have become less common. Another sign pathognomonic for FH, specifically HoFH, is supravalvular aortic stenosis in the setting of markedly elevated LDL-C. This too is a rare finding.

Cascade Screening

FH is an autosomal dominant disorder; having a single mutation causes disease. Thus, the inheritance pattern is that each offspring of an FH patient has a 50% chance of being affected.[13] By screening the family—cascade screening—starting with first-degree relatives and moving outward, many undiagnosed FH individuals can be identified.[6] In the Netherlands, the touchstone for cascade screening, each index case (first identified FH patient) was attached to an additional eight patients who were identified during cascade screening. To date, we have identified only 10% of FH patients in the United States. Thus, effective cascade screening is gravely needed in America.

Treatment

Treatment for patients with the likely diagnosis of FH was addressed in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[14] Patients with a baseline LDL-C of >190 mg/dL are candidates for high-intensity statin therapy with the recommendation to achieve a minimum 50% reduction in LDL-C levels. More recently, the ACC consensus pathway on the use of nonstatin therapy,[15] suggested that if LDL-C levels remained > 100 mg/dL despite high-intensity statin therapy, consideration for additional agents such as ezetimibe and/or PCSK9 inhibitors was an option. Both documents recommend maximizing statin therapy as an initial step with consideration of the addition of nonstatins if adequate LDL-C lowering is not obtained.

Early treatment of FH is essential to mitigate the associated risk of vascular events. Current guidelines recommend statin therapy as early as age 8 years in appropriate children. The focus on early treatment in patients with FH has developed because of the realization that these patients have >22 times the average risk for an atherosclerotic event compared with the general population. Patients with LDL-C >190 mg/dL in adulthood who by genetic testing do not show a mutation, in contrast have a sixfold increase in risk.[16] Obviously, both groups are at extremely high risk but those with a mutation have a remarkably greater risk, possibly due to lifetime exposure to elevated LDL-C levels (Figure 1).[17]

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Over the past 5 years, therapeutic options have grown. In the case of HoFH, two novel therapies were approved, mipomersen and lomitapide. Mipomersen is an antisense oligonucleotide to the mRNA for apoB 100, the large surface protein on all LDL and VLDL particles. By partially blocking the translation of apoB 100, mipomersen diminishes hepatic production of VLDL, in turn decreasing LDL-C levels by approximately 30%.[6] Lomitapide is a microsomal triglyceride transport protein (MTP) inhibitor and blocks the production of VLDL and downstream LDL-C through this novel mechanism. Lomitapide has been shown to decrease LDL-C

in the HoFH population by nearly 50%. Both drugs have potential hepatic toxicity and require verification of HoFH using a Risk Evaluation and Mitigation Strategy (REMS).[6] They should be utilized only in the HoFH patient population, and both drugs require intensive clinician supervision. PCSK9 monoclonal antibodies (mAb) are inhibitors of the hepatic-derived protein PCSK9. Thus, they are also known as PCSK9i.

PCSK9i

PCSK9 is a hepatic-derived protein that is made in the endoplasmic reticulum (ER) as a zymogen. It begins with five segments and during ER cleavage, the first two units are removed. The prosegment then binds the catalytic site on PCSK9, removing all enzymatic activity and rendering the protein a binding protein alone. After PCSK9 moves to the Golgi apparatus and into the blood, it nearly exclusively binds hepatic LDL receptor, and in so doing targets them for degradation. As each LDL receptor has the capacity to remove 150 LDL particles from circulation, destruction of LDL receptors will cause circulating LDL-C to rise. PCSK9 was discovered in 2003 and, as its importance in LDL metabolism was already understood, it was rapidly considered to be an important potential therapeutic target. Pharmaceutical companies began PCSK9 research, and in 2007 Amgen and Pfizer published the protein's crystal structure. By 2010, human mAb to PCSK9 had been developed and human clinical trials begun. In 2015, enough data from phase 2 and 3 clinical trials had been derived to enable the US Food and Drug Administration (FDA) to approve two PCSK9i, alirocumab and evolocumab. Both were approved for patients with HeFH or clinical atherosclerotic cardiovascular disease (ASCVD) on maximally tolerated statin therapy but still requiring greater LDL-C reduction. Evolocumab was given the additional indication for HoFH after the TESLA trial showed that most HoFH patients had significant reductions in LDL on evolocumab.[18] The drugs work by rapidly and irreversibly binding circulating PCSK9, rendering it unable to bind the LDL receptor. By so doing, LDL receptors are preserved, enabling them to work to their full potential and bring more LDL particles intracellularly for hepatic degradation.

Access

As PCSK9i had been shown to lower LDL-C approximately 60% on top of maximally tolerated statin therapy, they were immediately embraced by preventive cardiologists and other lipid specialists. Remarkably though, prescriptions for PCSK9i were denied at unprecedented rates, exceeding 80%. The appeal process was equally troublesome with ultimate approval rates well under 50%. The unparalleled rejection rates for PCSK9i catalyzed multiple studies evaluating this issue. Access to PCSK9 antibodies for patients has been a significant issue.[19] Payers have employed a high rate of prescription denials and required strict documentation criteria making access for PCSK9 antibodies a major issue both for patients and physicians alike. Interestingly, there has been a higher frequency of approval under Medicare compared with commercial payers for reasons that are unclear, but might relate to Medicare oversight.[20] Navar and coworkers demonstrated the use of high copays and burdensome prior authorizations (PA) as the main factors causing poor uptake of PCSK9i.[21] Hess and associates found that the single most important determinant of PCSK9i approval or denial was the type of insurance carried. Medicare again far surpassed approvals from commercial carriers.[22] The other key factor in determining approval was whether the prescriber was a primary care physician or specialist. Specialist approval rates exceeded those of primary care clinicians.

MAIN POINTS

- Familial hypercholesterolemia is one of the most common autosomal dominant inherited genetic disorders, yet it is frequently undiagnosed, leading to a markedly increased risk for cardiovascular events.
- Understanding the pathophysiology of the disease as well as the importance of cascade screening is critical to appropriate treatment of patients.
- Though the mainstay of therapy for heterozygous familial hypercholesterolemia remains statins, many patients require additional therapy including ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies to achieve adequate low-density lipoprotein cholesterol lowering.
- Access to PCSK9 inhibitors remains a significant clinical problem.

Again, Hess determined that LDL-C level had absolutely no bearing on PCSK9i, drugs whose purpose is to reduce LDL-C.[22] Knowles and colleagues published their findings in *Circulation*, and revealed that patients with FH, LDL-C >190 mg/dL, |and on maximal statin therapy (some also taking ezetimibe) experienced a rejection rate of 63.3%.[23] The FH population not only meets the FDA indications for PCSK9 inhibition, but also is more likely to require this therapy more so than any other cohort because of their extremely high baseline LDL-C levels and risk for cardiovascular events.

The FH Foundation, through its CASCADE FH Registry, and FOCUS (FH Optimal Care for the US) initiatives, have further informed us about the PCSK9i barrier difficulty. Not only is there a payer problem regarding PCSK9i access for FH patients; there is also a significant problem for the clinician as well. As of May 2017, 109,224 individuals had been prescribed a PCSK9i. In the same time frame, 110,577 patients had been diagnosed with FH through the new ICD 10 code created through the FH Foundation's efforts. Remarkably, only 1188 of these prescriptions were for FH patients (Figure 2). Thus, it appears that patients with FH are suffering in multiple ways—they often suffer from lack of diagnosis, they are often denied access by payers to needed PCSK9 antibody therapy, and they are also frequently inadequately treated by their clinicians with medications at low dose or with inadequate LDL-C lowering potency. From the clinician side, however, in addition to having the FDA's indications for PCSK9i, support is available from the ACC and the National Lipid Association who have established guidance about the use of nonstatin therapy. In the case of FH, PCSK9i and/or ezetimibe are recommended when LDL-C lowering on maximally tolerated statin therapy has been deemed inadequate. Thus, advice for the practicing clinician is readily available.

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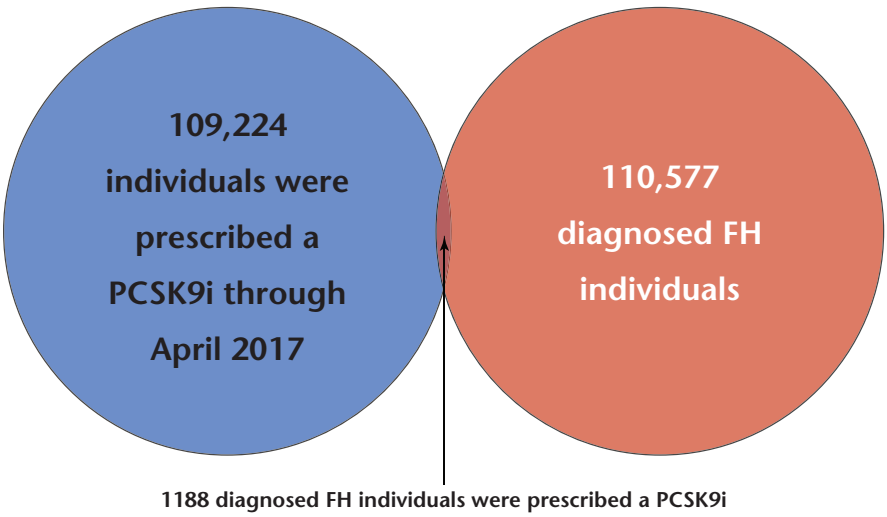

Figure 2. Very few patients diagnosed with familial hypercholesterolaemia (FH) are prescribed a PCSK9i. Unpublished data, The FH Foundation.

Conclusions

The message to treat FH earlier in life and more aggressively has not been adequately conveyed or received. The importance of recognition of this extremely high-risk disorder early in life and the importance of cascade screening of affected families need further emphasis. Clinicians must become familiar with appropriate approaches to therapy in FH patients and understand the importance of achieving adequate LDL-C lowering as well as helping patients get access to necessary medications. Efforts by the FH foundation, the American Society for Preventive Cardiology, the National Lipid Association, the American College of Cardiology, and others have made an impact, but more needs to be done to engage primary care physicians to diagnose FH and provide treatment to patients and their families. Much work remains to achieve optimal therapy for those with FH, a genetic disorder that when treated early and aggressively can usually minimize risk for cardiovascular events, nearly to the point of "cure." ■

Dr. Baum serves as a consultant for Amgen, Sanofi, Cleveland Heart Lab, GLG Group, Guidepoint Global, Regeneron, Novo Nordisk, and Akcea; serves on the Speakers Bureau for Amgen, Aralez, Boehringer ingelhelm. Novo Nordisk, and Akcea; and has received research grants from Esperion Therapeutics, Inc., Madrigal Pharmaceuticals, inc., Gemphire Therapeutics, Inc., Amgen, Inc., Boehringer ingelhelm Pharmaceuticals, Inc., lonis Pharmaceuticals, Astra Zeneca, Akcea, and Regeneron. His spouse owns Vital RemedyMD. Dr. Brown is a consultant for Akcea, Amgen, Kastle, Kowa, Merck, Regeneron, and Sanofi; and serves on the Speakers Bureau for Amgen, Regeneron, and Sanofi.

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