

FAMILIAL HYPERCHOLESTEROLEMIA: GENES AND BEYOND

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ABSTRACT

Genetic disorders resulting in familial hypercholesterolemia (FH) include autosomal dominant hypercholesterolemia (ADH), polygenic hypercholesterolemia, as well as other rare conditions such as autosomal recessive hypercholesterolemia (ARH). All of these disorders cause elevations in low-density lipoprotein (LDL)-cholesterol (LDL-C) and, as a result, greatly increase the risk of cardiovascular disease (CVD). Genetic loci involved in ADH include the *LDLR*, which codes for the LDL receptor (LDLR), *APOB*, which codes for apolipoprotein B-100 (apoB-100), the major protein component of LDL, *PCSK9*, which codes for Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), the low abundance circulatory protein that terminates the lifecycle of the LDLR, and apolipoprotein E (*APOE*), which is an important constituent of triglyceride rich lipoproteins. Importantly, a large percentage of people with the severe hypercholesterolemic phenotype do not possess a readily identifiable gene defect and many likely have polygenic hypercholesterolemia. Thus, identification of a specific genetic pathologic variant is not a necessary condition for the diagnosis of a genetic hypercholesterolemia. Several formal

diagnostic criteria exist for FH and include lipid levels, family history, personal history, physical exam findings, and genetic testing. As all individuals with severe hypercholesterolemia are at high risk for CVD, treatment is centered on dietary and lifestyle modifications and early institution of lipid-lowering pharmacotherapy. Treatment should initially be statin-based, but most patients require adjunctive medications such as ezetimibe and PCSK9 blocking monoclonal antibodies. Three large cardiovascular outcome trials have shown a reduction in atherosclerotic CVD when ezetimibe or PCSK9 blocking monoclonal antibodies were added to a background of statin therapy and consequently have assisted in shaping international guidelines and consensus recommendations. Novel therapeutics recently developed, include: inclisiran – a small interfering ribonucleic acid (siRNA)-based gene-silencing technology that inhibits PCSK9 production, bempedoic acid – an inhibitor of adenosine triphosphate (ATP)-citrate lyase with a large cardiovascular outcome trial demonstrating a reduction in CVD in patients with statin intolerance and is now FDA approved for a wide range of patients including heterozygous FH and patients with prior CVD (secondary prevention) or those at high-risk for CVD (primary prevention) and elevated LDL-C, and

evinacumab – a fully human monoclonal antibody inhibiting angiopoietin-like 3 (ANGPTL3) (FDA approved for homozygous FH only). Patients with extreme and unresponsive elevations in LDL-C will require more aggressive therapies such as lipoprotein apheresis and agents for the treatment of severe hypercholesterolemia such as microsomal triglyceride transfer protein (MTP) inhibitors and evinacumab.

INTRODUCTION

Genetic disorders resulting in familial hypercholesterolemia (FH) consist of autosomal dominant hypercholesterolemia (ADH), autosomal recessive hypercholesterolemia (ARH), and polygenic hypercholesterolemia. The genetic architecture of FH is more complex than previously recognized and in fact is now believed to be associated with at least nine different genes with thousands of variants, the details of which are beyond the scope of this chapter. But briefly, the term “autosomal dominant hypercholesterolemia” refers to those patients with dominantly inherited severe hypercholesterolemia – low-density lipoprotein (LDL)-cholesterol (LDL-C) greater than 190 mg/dL, who likely harbor mutations in genes regulating serum LDL levels. Historically, the more common causes of ADH include “classic” FH, which is a codominant disorder involving aberrations in the LDL receptor (*LDLR*), as well as other codominant forms of “nonclassical” FH, which involve defects in two other genes that regulate plasma clearance of LDL, apolipoprotein B (*APOB*), which is the main protein of LDL (a ligand for the *LDLR*), and Proprotein Convertase Subtilisin/Kexin Type 9 (*PCSK9*), which synthesizes a low abundance circulatory protein that limits the *LDLR* lifespan (1,2). Autosomal dominant forms of ADH include mutations in apolipoprotein E (*APOE*), which synthesizes the main protein of triglyceride rich lipoproteins and signal transducing adaptor family member 1 (*STAP1*), whose function in cholesterol homeostasis remains largely unknown (2,3). However, recent data have determined that mutations in *STAP1* are not a causative factor in

FH (4-7). An autosomal recessive form of FH, ARH, is very rare and results from pathogenic variants in *LDLR* accessory protein 1 (*LDL-RAP1*). Other forms may be due to defects in lysosomal acid lipase (*LIPA*), ATP-binding cassette sub-family G member 5 and 8 (*ABCG5/8*), and cholesterol 7 α -hydroxylase (*CYP7A1*) (2,8). Finally, a common form of FH is attributable to multiple variations in several genes each with minor effects on cholesterol regulation (more than 50 loci identified, as opposed to a single large effect as seen in the textbook version of FH). Polygenic causes are relatively common and likely explain many of the patients who are genotype negative. In fact, up to 50% of patients referred to lipid clinics for possible or probable HeFH have a polygenic basis (2). Additionally, only approximately 2% of patients with an LDL >190 mg/dL and no additional clinical or family history compatible with FH have a pathogenic variant in one of the FH genes (9,10). Thus, having an elevated LDL-C does not necessarily indicate that the patient has ADH due to a pathogenic variation in the *LDLR*, *APOB*, *PCSK9*, or *APOE* genes. All forms of FH result in very high levels of LDL-C and increase the risk of early and accelerated coronary artery disease (CAD) (8). Yet, FH remains vastly underdiagnosed and thus, undertreated, representing an extraordinary missed opportunity for maintenance of cardiovascular health and prevention of cardiovascular events. It has been estimated that less than 10% of the patients in the US with FH have been diagnosed (11,12). This chapter will largely focus on the canonical forms of FH involving the traditional genetic loci described above.

GENETICS

The *LDLR* is an 893-amino acid cell surface glycoprotein that binds and internalizes LDL particles, primarily in the liver. Mutations in *LDLR* (i.e., “classic” FH) give rise to nearly 90% of cases of clinical ADH (13). Over 2000 such mutations in *LDLR* have been identified, including deletions, insertions, missense, copy number variants, and nonsense mutations (2).

FH patients can be homozygous (traditionally with a prevalence thought to be 1 in 1,000,000 but based on contemporary genetic studies, the prevalence is thought to be closer to 1 in 300,000), carrying mutations in both alleles encoding for LDLR, or heterozygous (traditionally with a prevalence thought to be 1 in 500, with newer data suggesting as frequent as 1 in 200), possessing mutations in only one allele (2,14). Homozygous FH (HoFH) should be suspected when LDL-C exceeds 400 mg/dL, whereas heterozygous FH (HeFH) should be suspected when LDL-C is greater than 190 mg/dL in adults and 160 mg/dL in children (8). Patients with HoFH can be true FH homozygotes, with two identical mutations in each allele, versus compound heterozygotes, with a different mutation in each allele. In addition, FH can result in elevated levels of lipoprotein(a) (Lp[a]) through an unclear mechanism, not necessarily linked to the dysfunctional LDLR pathway (15-19). Elevated Lp(a), which historically was thought composed of 30-45% cholesterol by mass and reported as part of the LDL-C laboratory measurement, amplifies the already increased risk of incident CAD seen in those with FH (19). A more contemporary study suggests this range of cholesterol content contributed by Lp(a) to be more heterogeneous with a range of 9-57% with a median value of approximately 15-20% in individuals with elevated Lp(a) (20). A recent evaluation of Lp(a) levels in a Danish Lipid Clinic found that elevated Lp(a) levels were common, with approximately 27% of individuals fulfilling a clinical diagnosis of FH due in part to elevated Lp(a) (21). This data suggests the *LPA* gene should be considered in the realm of possible causes for phenotypic FH and emphasize the importance of Lp(a) testing. It is also important to be aware of "founder effects" in some populations. Founder effects influencing the type and frequency of mutations causing FH are seen among Afrikaners, French Canadians, Ashkenazi Jews, Christian Lebanese, and some Tunisian groups. Slimane et al. estimated the prevalence of individuals with HoFH and HeFH in Tunisia to be 1:125,000 and 1:165, respectively (22).

"Nonclassical" FH, which phenotypically resembles classic FH in presentation and severity, involves dominantly inherited gene defects in *APOB*, *PCSK9*, and *APOE*, which code for proteins that modulate ligand-LDL/LDL-like receptor interaction (2,23,24). ApoB is the major protein constituent of LDL and acts as a ligand for LDLR. Mutations in ApoB (most commonly a single base change at a position near amino-acid 3,500) block the binding of LDL containing the apoB-100 to LDLR, resulting in severely elevated levels of LDL-C. This condition was originally defined as "familial defective APOB-100" or FDAB (25). PCSK9, on the other hand, is a circulating protein that terminates the lifecycle of LDLR by binding to it and targeting it to lysosomal degradation. Gain-of-function (GOF) mutations in PCSK9 lead to a FH phenotype, whereas loss-of-function (LOF) mutations lead to lower LDL-C and protection from coronary atherosclerotic events (26,27). Absence of circulating PCSK9 has been reported in a few subjects, who were reportedly healthy and had LDL levels around 20 mg/dL (28,29). Collectively, these observations spurred a frenzy of targeted research that led to the development and FDA approval of therapeutic antibodies against PCSK9 to reduce LDL levels in individuals with atherosclerotic cardiovascular disease (ASCVD) and/or in FH. Mutations in ApoE (an in-frame three base-pair deletion at position 167 in exon 4) block the binding of triglyceride rich lipoproteins (i.e., chylomicrons, chylomicron remnants, very low-density lipoprotein [VLDL-C], intermediate-density lipoprotein [IDL-C]) to the E receptor (belongs to the LDLR superfamily), and limits clearance of these particles from plasma (30). The prevalence of ADH resulting from mutations in *APOB*, *PCSK9*, and *APOE* has been difficult to estimate, but it is agreed that these are 5-10%, <1%, and <<1% respectively (2).

Finally, an additional ultra-rare recessive genetic disorder causing hypercholesterolemia bears mentioning. It involves a homozygous deletion mutation in the gene *CYP7A1*. This gene codes for the enzyme cholesterol 7 α -hydroxylase, which catalyzes the initial step in cholesterol catabolism and bile acid

synthesis. The mutation results in loss of enzymatic function and high levels of LDL-C, and was first identified in three homozygotes within a single kindred of English and Celtic descent (31). There are a number

of other rare recessive genetic disorders that are associated with hypercholesterolemia, see table 1 below and other Endotext chapters on these rare genetic disorders (32,33).

TABLE 1. RARE GENETIC DISORDERS THAT CAN BE CONFUSED WITH ADH	
Disorder	Description
Sitosterolemia	Autosomal recessive disorder due to mutations in <i>ABCG5/8</i> . Manifestations include hypercholesterolemia, marked elevations of plasma plant sterols, tendon and tuberous xanthomas, and premature ASCVD
Lysosomal acid lipase deficiency	Autosomal recessive disorder due to mutations in <i>LIPA</i> , which codes for lysosomal acid lipase. Manifestations include moderate hypercholesterolemia with depressed high-density lipoprotein cholesterol (HDL-C), accelerated atherosclerosis, and progressive liver disease.
Deficiency of LDL receptor adapter protein 1	Autosomal recessive disorder due to mutations in <i>LDL-RAP1</i> . Typically presents with very high LDL cholesterol levels.
Deficiency of cholesterol 7-alpha hydroxylase	Autosomal recessive disorder due to mutations in <i>CYP7A1</i> , which codes for the enzyme that catalyzes the first step in bile acid synthesis, resulting in high intrahepatic cholesterol and reduced surface expression of LDLR.

An important practical point is that 30-50% of people with the FH phenotype have no readily identifiable defects in any of the genes that have been mentioned here; thus, diagnosing an individual with the FH phenotype does not necessarily mean the presence of a monogenic defect in the LDLR pathway (34). The genetic confirmation for FH-causing mutations in ADH varies considerably (2,10). The rate of positive genetics is related to clinical criteria - in patients with definite FH based on clinical criteria 60-80% are positive whereas in patients with possible FH based on clinical criteria only 21-44% are positive (35). Additionally, the LDL-C level is crucial. When LDL-C is very high (i.e., >310 mg/dL), the frequency of monogenic pathogenic variants is as high as 92% (36). In patients without an identifiable pathologic

genetic variant the etiology may be due to an as-yet-unidentified genetic error or to polygenic, epigenetic, or non-genetic factors, including co-morbid and environmental modifiers. For those without a mutation, an elevated LDL-C still confers elevated cardiovascular disease (CVD) risk (37). However, for any given LDL-C strata, those with a causal mutation compared to those without have higher risk for CVD, likely due to lifelong exposure to high LDL-C (10,38). In addition, unintended consequences of genetic testing (i.e., genetic discrimination for life or long-term care insurance and increased expense) must be taken into account. For these reasons, genetic testing should not be mandated, but should involve a shared-decision making model between patient and provider, encompassing benefits and risks of genetic testing, as

well as patient values and preferences (39). On the other hand, others advocate for routine genetic testing citing as the rationale 1) facilitate a definitive diagnosis; 2) identify pathogenic variants with higher cardiovascular risk and therefore needing more aggressive treatment; 3) increase initiation of and adherence to therapy; 4) facilitate insurance approval for novel lipid-lowering therapies; and 5) cascade testing of first-degree relatives (25). Cascade screening on the basis of LDL-C alone (i.e., ≥ 190 mg/dL) has low sensitivity and specificity, however, identification of a pathogenic variant with genetic testing followed by cascade screening results in very high sensitivity and specificity. This is likely due to missed diagnoses of FH with reduced penetrance where LDL-C is < 190 mg/dL (35). Nonetheless, the reduced costs and more widespread availability of genetic testing warrant performance of this test to obtain information that can help the physician familiarize with genotype-phenotype correlations and identify subjects that can be studied for the discovery of novel pathways leading to severe hypercholesterolemia. It must be noted that the FDA does not mention genetic testing as a measure to define FH (either heterozygous or homozygous).

PATHOPHYSIOLOGY

Most circulating LDL particles end up in the liver. The LDLR pathway is the predominant method for LDL uptake (40,41). ApoB binds to a specific binding site on LDLR and the receptor-ligand complex is subsequently internalized from clathrin-coated pits on the cell membrane. The receptor-ligand complex undergoes endocytosis and is targeted to the lysosome, where LDL is released for degradation while the LDLR is recycled back to the cell surface approximately 100-150 times in its 24 hour life cycle (2). PCSK9 terminates LDLR lifespan by disallowing

its recycling, thus providing a physiologic mechanism of protein removal much different from, and stronger than, that caused by inducible degrader of LDL, an E3 ubiquitin ligase (26,42). There are other nonspecific and constitutively active pathways of LDL-C clearance as well (40,43). In HeFH, though transport through the LDLR pathway is reduced by 50%, LDL-C clearance is doubled through these other, non-LDLR pathways. The same holds true for HoFH, where despite a near-absolute reduction in LDLR transport, total LDL-C clearance via non-specific pathways is increased by 4-fold (44). Excess LDL-C, which accumulates in liver cells, is then re-exported via the apoB system back into the plasma, secreted into bile unchanged, or transformed into bile acids. This increased production of LDL adds to inefficient clearance via LDLR to cause elevated serum LDL levels typical of the FH phenotype (45).

ADH can thus be further classified into subtypes 1, 2, and 3, based on which protein of the LDLR pathway is causative (Figure 1). ADH-1 comprises mutations within *LDLR*, the canonical form of FH. There are six major classes of ADH-1 (see table 2 below), based on the type of mutation. These include those that: inhibit synthesis of LDLR; impede exit of mature LDLR from the endoplasmic reticulum; affect the binding site of LDLR to apoB-100; prevent the ligand-receptor interaction; prevent endocytosis of the LDLR-apoB-100 complex; or inhibit recycling of LDLR to the cell surface for further rounds of lipid uptake (not shown). ADH-2 comprises mutations of *APOB* that block the association of apoB-100 to LDLR. ADH-3 is due to GOF mutations of *PCSK9*, which reduce LDLR recycling and accelerate its lysosomal degradation (12). Some authors have suggested that mutations that affect binding of apoB-100 to LDLR carry a less severe phenotype than those that affect LDLR directly (46-50).

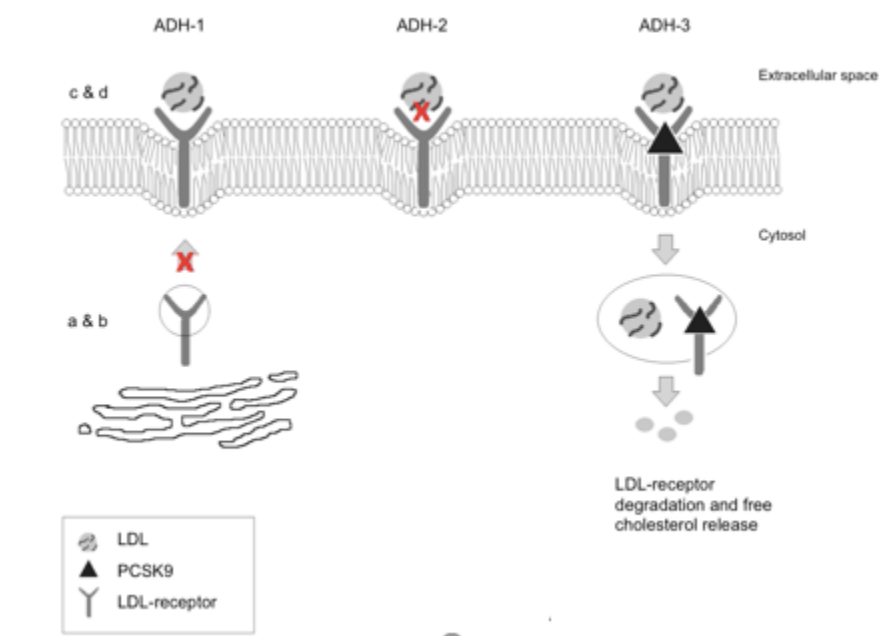


FIGURE 1 (24): ADH-1 comprises mutations within LDLR. There are six major classes of ADH-1, affecting: a) synthesis of LDLR; b) exit of mature LDLR from the endoplasmic reticulum; c) binding site of LDLR to apoB-100; d) endocytosis of LDLR-apoB-100 complex; and recycling of LDLR to the cell surface (not shown). ADH-2 comprises mutations in apoB that block the association of apoB-100 to LDLR. ADH-3 is due to GOF mutations of PCSK9, which reduce LDLR recycling and accelerate its lysosomal degradation. Adapted from Calandra et al. J. Lipid Research 2011; 52: 1885-926.

TABLE 2. THE SIX CLASSES OF LDLR MUTATIONS (51)	
Class 1: synthesis of receptor or precursor protein is absent	The so-called null allele is a prevalent class of mutations and is generally associated with very high LDL-C levels. The molecular basis of this type of mutation shows a wide variety: point mutations introducing a stop codon, mutations in the promoter region completely blocking transcription, mutations giving rise to incorrect excision of mRNA, and finally, large deletions preventing the assembly of a normal receptor.
Class 2: absent or impaired formation of receptor protein	This class comprises mutations in which the normal routing through the cell is not complete or is only very slowly completed. Usually, there is a complete blockade of transport, and LDL receptors are unable to leave the ER. The Golgi apparatus is not reached, and the increase of 40,000 Da in molecular weight does not take

	place. Truncated proteins, as a result of a premature stop codon, and misfolded proteins, as a result of mutations in cysteine-rich regions leading to free or unpaired cysteine residues, are retained in the ER. However, quality control by the ER is not perfect, given the observation that sometimes misfolded proteins leave the ER but are processed more slowly. Such mutations give rise to class 2B mutations, in contrast to class 2A mutations that cause complete retaining in the ER.
Class 3: normal synthesis of receptor protein, abnormal LDL binding	Receptors characterized by this class of alleles show the normal rate of synthesis, exhibit normal conversion into receptor protein, and are transported to the cell surface, but binding to LDL is impaired. It is obvious that mutations in the binding domain underlie this class of receptors.
Class 4: clustering in coated pits, internalization of the receptor complex does not take place	The receptors in this class lack the property to cluster in coated pits (class 4A). This phenomenon, which makes interaction of receptors with the fuzzy coat impossible, is caused by mutations in the carboxyterminal part of the receptor protein. These mutated receptors are synthesized normally, folding and transport are normal, but clustering in coated pits is impossible, and sometimes the receptors are secreted even after they have reached the cell surface (class 4B).
Class 5: receptors are not recycled and are rapidly degraded	All mutations in this class are localized in the EGF-precursor homologous domain of the LDL receptor protein. This domain seems to be involved in the acid-dependent dissociation of the receptor-ligand complex in endosomes, after which the receptor can be recycled. When the entire EGF-precursor homologous domain is deleted by site-directed mutagenesis or when such a deletion occurs naturally in a homozygous FH patient, the receptor is trapped in the endosomes, and rapid degradation subsequently is observed.
Class 6: receptors fail to be targeted to the basolateral membrane	The class of mutations was recently discovered and is caused by alterations in the cytoplasmic tail of the protein. Such receptors do not reach the liver cell membrane and are probably rapidly degraded.

*Adapted from Gidding SS, et al. *Circulation* 2015;132:2167-92.

CLINICAL MANIFESTATIONS

Lipid Abnormalities in Heterozygous Familial Hypercholesterolemia

LDL-C levels are frequently greater than the 90th percentile for age and gender. The magnitude of the LDL-C elevation is affected by the specific mutations causing FH with mutations in the LDLR leading to greater elevations in LDL-C levels than mutations in ApoB or PCSK9 (36,46-49,52). Null mutations in the LDLR are more severe than non-null mutations (53). Additionally, other genes that regulate LDL-C and environmental factors, such as diet, also influence the magnitude of the elevation in LDL-C (54,55). It should be recognized that a significant number of patients with genetically diagnosed FH have LDL-C <190 mg/dL. In some studies, approximately 50% of patients with genetically diagnosed FH have LDL-C levels <190 mg/dL (9,10). HDL-C and triglyceride levels are usually normal or only modestly altered (56-63). Elevated triglycerides and/or low HDL-C do not rule out the diagnosis of FH. Lp(a) levels are frequently elevated in patients with FH and may contribute to the increased risk of ASCVD (15-19). One should exclude secondary causes of marked elevations in LDL-C particularly hypothyroidism, renal disease, autoimmunity, and iatrogenic conditions (see chapter on Approach to the Patient with Dyslipidemia) (64). Another pertinent secondary cause that should be evaluated, particularly given escalating global rates of adiposity and the myriad treatment approaches at curtailing these trends, include dietary interventions that may induce a hyperlipidemic state. One such contemporary dietary fad that has garnered traction in the weight loss community is the ketogenic diet, which includes low level of carbohydrates (sufficient enough to induce the formation of ketones), moderate protein intake and high fat intake. It is well-documented that the ketogenic diet results in modest LDL-C elevations in most, but for some, can induce marked elevations

in LDL-C, to the degree of mimicking a FH phenotype (65).

Atherosclerotic Cardiovascular Disease in Heterozygous Familial Hypercholesterolemia

Patients with FH have a 3-13-fold higher risk of ASCVD, and a 20-fold higher risk for early onset ischemic heart disease (66,67). Untreated males with FH have a 50% risk for a fatal or non-fatal myocardial infarction by 50 years of age whereas untreated females have a 30% chance by age 60 (68,69). However, it should be recognized that there is heterogeneity of ASCVD risk and much of this risk is potentially modulated by variance in genetic factors (70,71). Other cardiovascular risk factors, such as male sex, BMI, diabetes, hypertension, smoking, low HDL-C levels, and Lp(a) levels modulate the risk of ASCVD (66). Patients with FH who have corneal arcus or xanthomas are more likely to have ASCVD (72-74). Of particular note, patients with mutations that result in FH have a greater ASCVD risk than patients with equivalent LDL-C levels (10,38). This is likely due to the LDL-C elevations being present from birth (lifelong exposure to elevated LDL-C). This concept is termed "cholesterol-years", which tabulates the cumulative exposure, both degree of cholesterol elevation and duration of cholesterol elevation, as a measure of area under the cholesterol curve. Those with a greater exposure (higher cholesterol for longer) of cholesterol, will go on to develop atherosclerosis at a much more aggressive rate (75,76). This concept also highlights an important framework for early FH detection and treatment as vital interventions for optimal ASCVD risk reduction (76).

Other Manifestations

Early onset corneal arcus (age < 45) and tendinous xanthomas, particularly the Achilles tendon and dorsum of hands, are classical abnormalities that

occur in patients with FH. Xanthelasma (xanthomas in eyelids) and tuberous xanthoma may also be seen. However, it should be recognized that in the modern era with the increased treatment of elevated LDL-C levels these abnormalities are no longer frequently seen (only 5-35% of patients have xanthoma or corneal arcus currently) (77,78).

Homozygous Familial Hypercholesterolemia

This is a rare disorder with untreated LDL-C levels that vary but are markedly elevated (usually > 300 mg/dL but often > 500 mg/dL) (79). Patients who are LDLR negative have higher LDL-C and a poorer clinical prognosis than LDLR defective patients (79). Lp(a) levels tend to be higher than observed in patients with HeFH (16). Additionally, HDL-C levels tend to be decreased in HoFH (79). Tendinous xanthoma, tuberous xanthomas, and arcus cornea may appear in childhood (79). If untreated >50% of patient with HoFH develop clinically significant ACVD by age of 30 and cardiovascular events can occur before age 10 in

some patients (80). Almost 90% of patients with HoFH suffered a cardiovascular event by age 40 (80). Cholesterol and calcium deposits can lead to aortic stenosis and occasionally to mitral regurgitation (79,81-83).

DIAGNOSIS

FH, despite its different underlying gene abnormalities, leads to severe hypercholesterolemia and a distinct FH phenotype with markedly increased risk of developing CAD. In general, there are five major clinical criteria for diagnosing FH (see table 3): a family history of early CAD (less than age 55 in a first-degree relative in men, and less than age 65 in women), early CAD in the index case, elevated LDL-C (greater than 190 mg/dL), tendon xanthomas (especially in the Achilles and finger extensor tendons), and corneal arcus (which is highly specific in younger patients, but overall an insensitive finding). Mutations in any of the aforementioned genes of the LDLR pathway, when they are identified, are diagnostic.

TABLE 3. MAJOR CLINICAL CRITERIA FOR DIAGNOSING FH
When to Suspect FH
If LDL-C levels are > 190 mg/dL (4.92 mMol/L) or non-HDL-C levels are >220 mg/dL (5.70mMol/L)
Patients with premature ASCVD (<55 years of age in male and <65 years of age in females)
Family history of hypercholesterolemia
When there is a positive family history of premature ASCVD (<55 years of age in male and <65 years of age in females)
When tendon xanthomas or corneal arcus (< age 45) are present on physical exam

As has been mentioned in other chapters of this text, when evaluating a patient suspected of having FH, it is critical to rule out secondary causes of hypercholesterolemia, such as hypothyroidism, nephrotic syndrome, and liver disease. Another extremely rare cause of non-FH has been described, involving autoantibodies to LDLR that inhibit receptor-mediated binding and catabolism of LDL-C (84).

There are three sets of statistically validated criteria that are most commonly used in the diagnosis of FH: the Dutch Lipid Network criteria, Simon Broome Register criteria, and Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria (85,86). These are summarized in Table 4, below (87).

TABLE 4. SCORING SYSTEMS FOR DIAGNOSING FH				
MEDPED Criteria (USA)				
	FH diagnostic if total cholesterol (LDL-C) levels exceed these cut points in mg/dL			
Age	1 st degree relative	2 nd degree relative	3 rd degree relative	General population
< 18	220 (155)	230 (165)	240 (170)	270 (200)
20	240 (170)	250 (180)	260 (185)	290 (220)
30	270 (190)	280 (200)	290 (210)	340 (240)
> 40	290 (205)	300 (215)	310 (225)	360 (260)
Simon Broome Criteria (UK)				
Total cholesterol (LDL-C) 290 (190) mg/dL in adults, or 260 (155) mg/dL in children	AND	DNA mutation	Definite FH	
		Tendon xanthomas in patient or 1 st or 2 nd FH degree relative	Probable	
		Family history of MI at age < 50 in 2 nd FH degree relative or < 60 in 1 st degree relative OR Family history of total cholesterol > 290 mg/dL in 1 st or 2 nd degree relative	Possible	
Dutch Criteria (Netherlands)				
1 point	1 st degree relative with premature CVD or LDL-C > 95 th percentile, OR Personal history of premature peripheral or cerebrovascular disease, OR LDL-C 155-189 mg/dL			Definite FH (8 points or more)
2 points	1 st degree relative with tendon xanthoma or corneal arcus, OR 1 st degree relative child (< 18 years) with LDL-C > 95 th percentile, OR Personal history of CAD			Probable FH (6-7 points)
3 points	LDL-C 190-249 mg/dL			Possible FH (3-5 points)
4 points	Presence of corneal arcus in patient < 45 years old			
5 points	LDL-C 250-329 mg/dL			
6 points	Presence of a tendon xanthoma			
8 points	LDL-C > 330 mg/dL, OR Functional mutation of the <i>LDLR</i> gene			

Adapted from Fahed et al., Nutrition & Metabolism 2011;8:23.

Unlike MEDPED criteria, which use only lipid levels, the Simon Broome and Dutch criteria also use family history, personal history, physical exam findings, and genetic testing to establish an FH diagnosis. Again, however, it should be emphasized that FH should be diagnosed phenotypically, as opposed to genetically—most FH patients are genotype-negative and do not possess a clear genetic substrate for their hyperlipidemic phenotype, but they clearly warrant aggressive intervention.

It is important to note that in the modern era of earlier recognition, wide-spread statin use and possibly improved dietary messages, it is often difficult to make a definitive or probable diagnosis of FH using clinical criteria (i.e., treatment reduces the development of xanthomas and corneal arcus and reduces or delays the occurrence of ASCVD events in patients and relatives). Similarly, it is often very difficult to know the before treatment LDL-C levels (35).

While genetic screening is not required for clinical management, lipid screening in family members should be undertaken in all individuals by age 20, starting as early as age 2 (42). Cascade screening—i.e., lipid screening of first-degree relatives of the proband—is infrequently employed but is recommended as the most economical method of identifying new cases of FH (43). It is the responsibility of the examining clinician to attempt identification of other cases when making the diagnosis of FH in any given patient.

A potential novel solution to the underdiagnosis and undertreatment issues that plague the FH community lies in leveraging health information technology. The FIND FH study demonstrated the use of a machine learning algorithm can successfully utilize medical profiles within the electronic health record to

consistently identify individuals with probable FH (88). This new approach possesses the promise of identifying FH patients on a national scale and will hopefully lead to increased initiation of effective preventive therapies and at an earlier time-point as well.

TREATMENT

Goals of Therapy

In genetic disorders causing hypercholesterolemia, aggressive lipid-lowering through lifestyle modification, pharmacologic treatment, and invasive treatments such as apheresis has been shown to decrease angiographically-apparent CAD and reduce cardiovascular events (80,89,90). However, traditional risk assessment tools like the Framingham risk score or pooled cohort equation do not apply to FH patients. Recent guidelines suggest that drug therapy should be initiated when LDL-C is greater than 190 mg/dL in all patients, including children over the age of eight (91,92). Most recommend at least a 50% reduction in LDL-C with initiation of high-intensity statin therapy as a starting goal, with some advocating for targeting LDL-C less than 100 mg/dL without ASCVD, less than 70 mg/dL with ASCVD, and even less than 55 mg/dL with ASCVD and at very high-risk (92-95). Additionally, consideration of non-statin options (ezetimibe, bile-acid sequestrants, bempedoic acid, and PCSK9 inhibiting [PCSK9i] therapeutics – including both monoclonal antibodies preferentially but also small interfering RNA should these thresholds not be met (92-94). The European Atherosclerosis Society suggests LDL-C goals of less than 135 mg/dL in pediatric patients, less than 100 mg/dL in adults, and less than 70 mg/dL in adults with known CAD or diabetes mellitus(11).

TABLE 5. GUIDELINE RECOMMENDATIONS FOR TREATING FH				
	NLA Expert panel on pediatric FH(91)	AHA/ACC 2018 cholesterol guideline(92) and ACC non-statin ECDP(94)	NLA Expert panel on adult FH(93)	EAS guideline on FH(11)
Age to initiate treatment	≥ 8 years (earlier in special cases i.e., HoFH)	≥ 20 years	Not specified – “After a confirmatory diagnosis of FH ...adult FH patients should receive initial treatment”	≥ 8 years
Agent recommended	<p>Statins are preferred</p> <p>Non-statin options (ezetimibe, BAS, fibrates, niacin) are discussed but not routinely recommended due to lack of FDA approval or adverse drug events</p>	<p>Statins are preferred</p> <p>Non-statin options (ezetimibe, BAS, bempedoic acid, PCSK9i therapeutics) are also recommended as add on therapy</p>	<p>Statins are preferred</p> <p>Non-statin options (ezetimibe, BAS, niacin) or LDL apheresis are also recommended as add on therapy or in statin intolerant patients</p>	<p>Statins are preferred</p> <p>Non-statin options (ezetimibe, BAS) or LDL apheresis are also recommended as add on therapy or in statin intolerant patients</p>
Goal of therapy	≥ 50% reduction in LDL-C or LDL-C < 130 mg/dL	≥ 50% reduction in LDL-C or LDL-C < 100 mg/dL in those without ASCVD, < 70 mg/dL with ASCVD, and < 55 mg/dL with ASCVD and at very high-risk	≥ 50% reduction in LDL-C	LDL-C < 135 mg/dL in pediatrics, < 100 mg/dL in adults, < 70 mg/dL in adults with CAD or diabetes

AHA / ACC: American Heart Association / American College of Cardiology; EAS: European Atherosclerosis Society; ECDP: Expert Consensus Decision Pathway; NLA: National Lipid Association; BAS: bile-acid sequestrants.

In our view in FH patients without clinical ASCVD one should aim for an LDL-C level <100 mg/dL (2.59 mMol/L). In FH patients with clinical ASCVD the goal, at a minimum should be an LDL-C level <70 mg/dL (1.81 mMol/L) with many experts recommending LDL-C levels <55 mg/dL (1.4 mMol/L), particularly when patients have additional risk factors (acute coronary syndrome, diabetes, polyvascular disease, etc.) (96,97). In patients without ASCVD but who are at high risk due to other risk factors such as diabetes, Lp(a) >50 mg/dL, smokers, a strong family history of premature ASCVD, etc. many experts would recommend an LDL-C goal of <70 mg/dL (1.81 mMol/L). While LDL-C goals continue to decline, attainment of these goals is increasing more difficult and seldom attained in most FH patients.

Treatment of Patients with Heterozygous Familial Hypercholesterolemia

As with almost all metabolic disorders we should encourage the patient to follow a lifestyle that will reduce disease manifestations. However, lifestyle changes are very rarely sufficient to lower LDL-C levels to the desired range in patients with FH and therefore cholesterol lowering drugs will be required (see figure 2 and tables 6 and 7) (for detailed information on cholesterol lowering drugs see the chapter on cholesterol lowering drugs (98). In patients with HeFH, statins are a mainstay of treatment, despite the dearth of randomized clinical trials of statin efficacy focused on this special population. Statins are FDA approved for use in pediatric FH patients beginning at age 8-10 years for HeFH and in the first year of life or at initial diagnosis for HoFH (51,79,96,99-103). Data from longitudinal observational studies suggest statin initiation in childhood is both safe and effective, reducing LDL-C burden and corresponding atherosclerosis rates over follow-up of up to 20 years (51,104). The major early statin trials (4S and WOSCOPS) likely had study populations that were enriched with FH patients, given

that mean baseline LDL-C ranged from 189 to 216 mg/dL (105,106). Patients should be treated with atorvastatin 40-80 mg per day or rosuvastatin 20-40 mg per day (i.e., high-intensity statin therapy). As monotherapy, statins can reduce LDL-C by up to 60% in HeFH patients but typically display a blunted response (10-25%) in HoFH patients depending on LDLR functionality (79,95,107). Updated guidance on statin therapy during pregnancy was issued by the FDA during a drug safety communication in 2021, removing the strongest warning against using statins during pregnancy (108). Though statins should still be avoided in most women attempting contraception during pregnancy, particular during the first trimester, the available evidence suggest that statins are likely not teratogenic. The updated guidance allows for more flexibility for treating pregnant women as part of a shared decision-making process, particular those at the highest ASCVD risk, including those with FH (109).

The vast majority of patients, however, require additional pharmacotherapy. When intensive statin therapy does not result in an LDL-C level in the desired range additional therapy should be added. Given that ezetimibe is generic, relatively inexpensive, well tolerated, and has evidence for ASCVD risk reduction in a large cardiovascular outcome trial, this is frequently the next drug used (110). One can anticipate that ezetimibe 10 mg per day added to intensive statin therapy will result in an approximate 20% further reduction in LDL-C. If this is not sufficient one can then use a PCSK9i monoclonal antibody to achieve the desired cholesterol goal. Adding a PCSK9i monoclonal antibody will result in a further 50-60% decrease in LDL-C levels and in most patients will result in LDL-C levels in the desired range. In some instances, if the LDL-C level is far from goal (>25%) on intensive statin therapy one can skip treating with ezetimibe and proceed directly to adding a PCSK9i monoclonal antibody. Bempedoic acid (discussed in more detail below) is an acceptable third- or fourth-line add-on agent if additional LDL-C lowering is needed. It is worth noting that bempedoic acid also comes as a

combination product with ezetimibe providing approximately 40% LDL-C reduction in one tablet. This may be pertinent for patients with FH for whom

pill burden is a real concern. In certain instances, bile resin binders may be useful in the treatment of FH (for example pregnant and lactating patients).

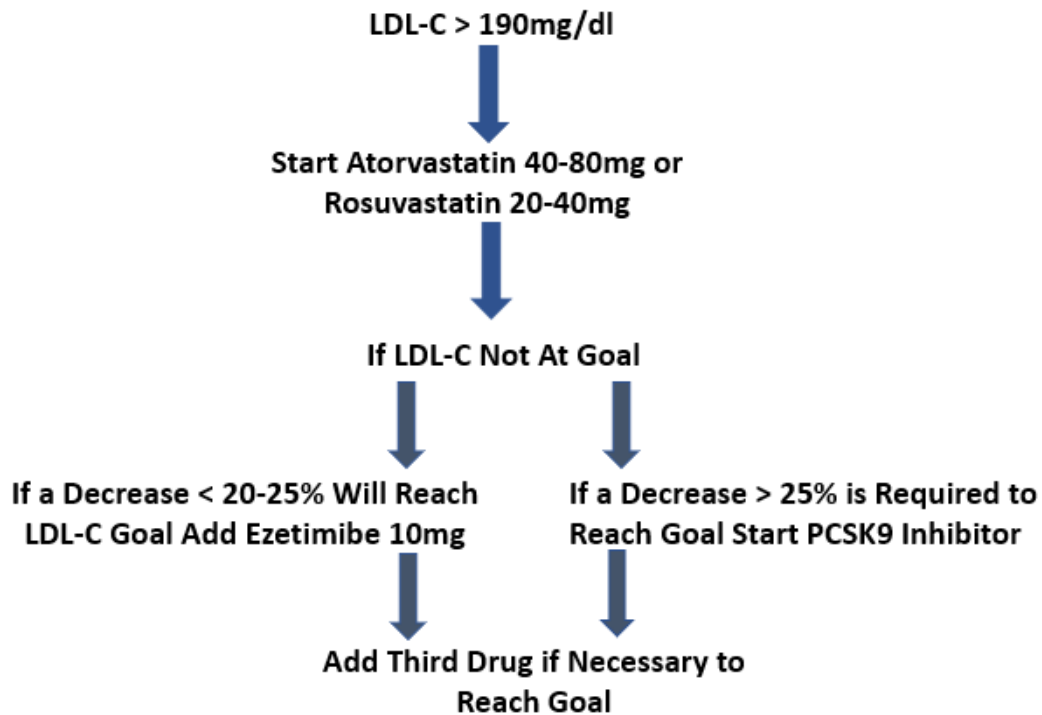


FIGURE 2. Approach to the Pharmacologic Treatment of Patients with Heterozygous Familial Hypercholesterolemia.

PCSK9 inhibitors consist of two therapeutic modalities, 1) monoclonal antibodies (alirocumab and evolocumab) that work extracellularly to sequester the PCSK9 protein, and 2) inclisiran, a novel, small interfering ribonucleic acid (siRNA)-based gene-silencing technology that inhibits mRNA translation and intracellular production of PCSK9 by the liver (111).

The effect of PCSK9i monoclonal antibodies in patients with HeFH has been extensively studied and consistently demonstrate potent LDL-C lowering on the order of 50-60% (63,112-126). An analysis of the ODYSSEY trials (FH I, FH II, LONG TERM, and HIGH FH) evaluated alicumab use (75 or 150 mg

subcutaneously every 14 days) in 1,257 HeFH patients. The primary endpoint was LDL-C at 24 weeks; alicumab resulted in a more than 55% reduction in LDL-C compared with placebo (122). In another trial, alicumab 150 mg every 14 days in 62 apheresis patients reduced the primary endpoint, rate of apheresis treatments over 12 weeks, by 75%, with 63.4% of patients completely discontinuing apheresis treatments due to well controlled LDL-C values (121). The RUTHERFORD-2 trial evaluated more than 300 patients with HeFH randomized to evolocumab (140 mg subcutaneously every 2 weeks or 420 mg subcutaneously monthly) versus placebo. At both dosing regimens, evolocumab resulted in significantly reduced LDL-C at 12 weeks compared with placebo

(>60%) (63). In all trials, PCSK9i monoclonal antibodies were well tolerated, with most demonstrating treatment-emergent adverse events (TEAEs) similar to placebo. Clinically, the most common adverse events include: injection site reactions, mild cold or flu-like symptoms, nasopharyngitis, and myalgias (127). Thus, PCSK9i monoclonal antibodies are very effective at lowering LDL cholesterol levels and safe in HeFH patients.

Additionally, there are two cardiovascular outcomes trials that evaluated the FDA approved monoclonal antibodies targeting PCSK9. The FOURIER trial evaluated almost 28,000 subjects with stable vascular disease (CAD, stroke, peripheral arterial disease) on optimized statin therapy and randomized them to either placebo or evolocumab. Evolocumab therapy was associated with a 60% reduction in LDL-C and a 15% reduction in the primary 5-point major adverse cardiovascular event (MACE) rate (128). The FOURIER had an open-label extension trial (FOURIER-OLE) which followed 6,635 patients from the parent trial and allocated all patients (those originally assigned placebo or evolocumab) to evolocumab and followed over a median and maximal exposure of 7.1 years and 8.4 years respectively. Those originally assigned evolocumab in the parents study continued to display significant reductions in ASCVD events and even cardiovascular death as compared to those assigned placebo - establishing the important notion of a legacy effect with PCSK9i, where earlier initiation of therapy provides cardiovascular prevention that cannot be achieved when delayed. This study represents the longest follow-up to date of PCSK9i monoclonal antibodies and confirms that attainment of low LDL (30 mg/dL) is both safe and effective for preventing cardiovascular events (129).

ODYSSEY OUTCOMES enrolled approximately 18,000 subjects with recent acute coronary syndrome (1-12 months prior to enrollment in the trial) who were on high-intensity statin therapy at baseline and randomized them to placebo or alirocumab.

Alirocumab was also associated with a 15% reduction in the primary outcome, in this case a 4-point composite of MACE (130). Major guidelines, consensus documents, and expert recommendations suggest consideration of a PCSK9 inhibitor (in addition to background statin +/- ezetimibe therapy) in high-risk patients with established ASCVD and/or in patients with severe hypercholesterolemia when LDL-C values exceed 55/70 or 100 mg/dL respectively (92,94,96,97,131-134). Both monoclonal antibodies have an FDA labeled indication for ASCVD risk reduction in patients with established ASCVD. Despite potent LDL-C lowering, a good safety profile, and robust clinical data demonstrating cardiovascular benefit, PCSK9i monoclonal antibodies are significantly underutilized among both patients with established ASCVD and those with FH, with reports suggesting only 1% to 2% of eligible patients currently prescribe PCSK9 inhibitors (135,136).

Inclisiran has been thoroughly studied in the ORION clinical development program, a series of phase 1 to 3 trials designed to investigate the pharmacokinetics, pharmacodynamics, optimal dose, efficacy, and safety of inclisiran in specific populations (111). ORION-9 was a phase 3, randomized, double-blinded, placebo-controlled trial evaluating use of inclisiran 300 mg given subcutaneously on days 1, 90, 270, and 540, in 482 HeFH patients with baseline LDL-C of ≥ 100 mg/dL (137). Treatment with inclisiran produced a placebo-corrected LDL-C reduction of 47.9% ($P < 0.001$) at day 510. Response based on genotype was as expected, with LDL-C reductions of 41.2% to 59.2% for all except PCSK9 GOF variants which were associated with dramatic LDL-C reduction of 89.7%. Pre-specified exploratory cardiovascular event (CV death, cardiac arrest, non-fatal MI, or non-fatal stroke) rates were comparable in both treatment groups (4.1% inclisiran vs. 4.2% placebo). Inclisiran was tolerated well during the trial with adverse events similar between treatment groups, with most adverse reactions mild to moderate in nature. The most common adverse event was injection site reactions, which was 10-fold higher in the inclisiran group (17%)

compared to placebo (1.7%), however, 90% of these were graded as mild severity. Future studies will evaluate inclisiran in an adolescent HeFH population in the ORION-16 trial (138). Inclisiran was FDA approved in December 2021 as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including HeFH, to reduce LDL-C (139). Pooled analyses of ORION-9 (patients with HeFH), ORION-10 (patients with ASCVD), and ORION-11 (patients with ASCVD or ASCVD risk equivalents) demonstrated durable LDL-C reduction of approximately 50% with a good safety profile with only injection site reactions, predominantly mild, and bronchitis as potentially drug-induced adverse effects (140,141). Additionally, prespecified exploratory analysis of MACE which was a non-adjudicated outcome and a safety event, and which should be regarded as hypothesis generating only, hinted at a reduction in atherosclerotic events with inclisiran (141). The question of whether inclisiran reduces cardiovascular events will be definitively determined with two large cardiovascular outcome trials – ORION-4 and VICTORIAN 2P, with estimated completion dates in 2026 and 2027 respectively (111). Though PCSK9 inhibition by monoclonal antibodies and inclisiran are comparable in LDL-C reducing capacity, there are important differences to acknowledge 1) inclisiran has a long biological half-life allowing for twice yearly dosing and possible medication adherence advantages, 2) PCSK9i monoclonal antibodies are administered by patients in their home and inclisiran is to be administered by a healthcare professional in a healthcare setting, and 3) while PCSK9i monoclonal antibodies have robust data proving reduction in ASCVD events, clinical outcome trials with inclisiran are still in progress. Additional considerations with the in-clinic administration of inclisiran include a new medication use process which includes procurement, storage, administration, and billing, which is a new workflow to the cardiovascular community and may take time to acclimate to. There are also the financial implications from the patient perspective as inclisiran is billed under medical insurance, not pharmacy benefits, which has the

potential for reduced out-of-pocket expense for Medicare recipients specifically (142,143).

Novel approaches to inhibit PCSK9 action, termed third-generation PCSK9 inhibitors, are currently in various stages of clinical development. These include once orally administered macrocyclic peptide agents (i.e., MK-0616), monthly subcutaneous injection fusion protein binders (i.e., Lerodalcicrep), CRISPR-based gene editing (i.e., VERVE-101), and PCSK9 vaccines (144). New PCSK9 modalities offer potential advantages such as oral administration, storage at room temp, and less frequent administration. The magnitude of LDL-C reduction with these technologies is similar to currently existing PCSK9 therapeutics, approximately 40%-60% lowering, except for vaccination, which appears less robust with approximately 10%-30% LDL-C reduction. Time will tell if and how these newer therapies position themselves among the ever-changing lipid-lowering landscape.

Bempedoic acid, a novel inhibitor of adenosine triphosphate (ATP)-citrate lyase (ACL), an enzyme upstream from 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) in the cholesterol synthesis pathway, is the newest orally administered lipid-lowering therapy (145). Bempedoic acid is a prodrug, that is converted into its active form (bempedoyl-CoA) by very long-chain acyl-CoA synthetase 1 (ACSVL1), which is expressed in hepatocytes but is undetectable in muscle. Development of this agent was designed to circumvent the myotoxicity commonly associated with historical lipid-lowering therapies, primarily statins. Bempedoic acid was FDA approved on February 21, 2020 for use in patients with established ASCVD and/or HeFH who require additional LDL-C lowering as an adjunct to dietary intervention and maximally tolerated statin therapy (146). Bempedoic acid was evaluated in over 3,600 patients in the phase 3 CLEAR program trials, of which, only 3.7% were HeFH patients (145). A pooled analysis from two phase 3 trials, CLEAR Harmony and CLEAR Wisdom,

demonstrated a similarly modest placebo-corrected LDL-C reduction at 12 weeks of bempedoic acid treatment in the HeFH cohort (22.3%) as compared to the overall population (18.3%) (147). Overall bempedoic acid was well tolerated in the phase 3 trials but occurrence of TEAEs was higher in the HeFH cohort compared to those without HeFH but was not increased with bempedoic acid versus placebo. Similar reports of efficacy and safety were seen in an updated analysis of phase 3 data in HeFH as well (148). In a real-world analysis of bempedoic acid, which was enriched in patients with HeFH (64%) and statin intolerance (74%), the drug was associated with clinically meaningful LDL-C lowering (mean reductions 20.3% to 36.7%), but high rates of TEAEs (50%) and drug discontinuations (35.9%)(149). Bempedoic acid completed a large cardiovascular outcome trial in 2023 with publication of the CLEAR OUTCOMES (150). The trial enrolled 13,970 patients with established cardiovascular disease (70%) or at high risk for cardiovascular disease (30%) who were deemed statin intolerant. Over a median follow-up of 40.6 months, the mean baseline LDL-C was reduced from 139 mg/dL to a time-averaged, placebo-adjusted reduction of 22 mg/dL in the bempedoic acid group. It is important to note there was a larger drop in LDL-C levels in the placebo arm than usually observed in clinical trials, which may have diluted the difference in LDL-C reduction between the 2 groups. Nevertheless, the primary endpoint which consists of a 4-point MACE including death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary vascularization was reduced from 11.7% in the placebo group vs. 13.3% in the bempedoic acid group, HR 0.87 (95% CI 0.79 to 0.96), with statistically significant reductions seen in the non-mortality outcome measures. Interestingly, the greatest relative risk reduction was seen in the primary prevention cohort (32%) as compared to the secondary prevention cohort (9%), however the clinical significance of this remains to be seen. Bempedoic acid was well-tolerated with small increases in biomarkers such as serum creatinine, blood urea nitrogen, hemoglobin, aminotransaminases, and uric acid, and rates of gout

(3.2% vs 2.2%), and cholelithiasis (2.2% vs 1.2%) (151). In response to the CLEAR OUTCOMES data, the FDA updated the label for bempedoic acid which now includes “to reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy, including those not taking a statin, with established ASCVD or at high risk for ASCVD” (146).

Treatment of Patients with Homozygous Familial Hypercholesterolemia

The initial therapy in patients with HoFH is identical to the treatment of patients with HeFH. However, statins and ezetimibe may prove relatively ineffective in the treatment of HoFH because the mode of action of these drugs largely depends on the upregulation of functional LDLR in the liver. In HoFH, measurable activity of both copies of the LDLR is absent or greatly reduced (80). Drug-induced LDL-C lowering is diminished by more than 50% comparing HeFH to HoFH – high intensity statins lower LDL-C 50-60% vs 10-25% and ezetimibe lowers LDL-C by 15-25% vs <10%, respectively (see table 6) (95,152).

In patients with HoFH, response to PCSK9i monoclonal antibodies varies depending on the specific gene defect. In the TESLA-B trial, 49 patients with HoFH were treated with evolocumab or placebo every four weeks for 12 weeks. LDL-C in the evolocumab treatment arm was significantly reduced by almost 31% compared with placebo. In addition to overall reduction in LDL-C, the trial investigators examined the treatment effect by *LDLR* mutation status. They found that the response to evolocumab aligns with the genetic cause of HoFH, with a greater reduction in LDL-C observed in subjects with two *LDL* receptor-defective mutations (i.e., abnormal receptor functionality in both alleles) when compared with those patients with even just one *LDL* receptor-negative mutation (i.e., nonexistent receptor functionality in one allele). Evolocumab was well tolerated among the HoFH patients (153). Similar results were seen in

other HoFH trials examining the PCSK9i monoclonal antibody (alirocumab) and over longer follow up durations, providing confirmation of durable LDL-C efficacy and safety with this therapeutic class (154-156).

Inclisiran, dosed as 300 mg subcutaneously on days 1 and 90 (or 104 if PCSK9 level was suppressed by >70%), was evaluated in 4 HoFH patients enrolled in the ORION-2 trial (157). Patients were ages 50, 46, 23, and 29 years, 50% female, and had baseline LDL-C 540 mg/dL, 547 mg/dL, 614 mg/dL, and 189 mg/dL, respectively. All had biallelic causative genetic variants in *LDLR*, and all were on high-intensity statins and ezetimibe. Inclisiran-induced LDL-C reductions ranged 11.7% to 33.1% at day 90, and 17.5% to 37.0% at day 180 in three of the four patients, similar to results in prior trials of PCSK9i monoclonal antibodies in HoFH patients with residual *LDLR* function. One patient (*LDLR* c.681C/G [defective]) who had a history of hypo-responsiveness to both PCSK9i monoclonal antibodies (<20% lowering), also exhibited no change in LDL-C with inclisiran treatment. No adverse events were recorded over a 10 month follow up. A second, larger study of inclisiran use within the HoFH population was evaluated in a 2-part, phase 3 ORION-5 trial (158). Part 1 is a double-blind randomized study where patients were randomized in a 2-1 fashion to inclisiran and placebo respectively at days 1 and 90. Part 2 consisted of an 18-month open label single-arm extension trial in which all patients received inclisiran at day 180 and every 6 months thereafter until end of study at day 720. The study included 56 HoFH adults on stable lipid-lowering therapies including high-intensity statin 100%, ezetimibe 66.1%, and apheresis 35.7%. The median age was 42.7 years, 60.7% were women, and 67.9% had established ASCVD. The baseline mean LDL-C was 315.3 mg/dL with a higher value in the placebo group (356.7 mg/dL) as compared to the inclisiran group (294 mg/dL). Notably, more patients in the inclisiran group displayed the null/null *LDLR* genotypes which are known to produce blunted response to PCSK9 inhibition (27% versus 15.8%) – an important

difference that may have confounded the treatment results. The primary endpoint, placebo-corrected percent change in LDL-C from baseline to day 150 was not statistically significant (-1.68%; $P=0.90$). The absolute placebo-corrected change in LDL-C level from baseline to day 150 was 6.47 mg/dL ($P=0.87$). The lack of statistically significant change in LDL values occurred despite a 60.6% reduction in plasma PCSK9 levels with inclisiran use. There were wide fluctuations in LDL-C reduction based on genotype: +26.6% with homozygous *LDLR*, -26.6% with compound heterozygous *LDLR*, and -22.5% with other genetic types. A post-hoc sensitivity analysis excluding patients with *LDLR* null/null genotypes and undergoing lipoprotein apheresis revealed greater reduction in LDL-C from 12.9% to 30%, indicating that inclisiran requires sufficient residual *LDLR* function to be effective within this population. There were no statistically significant changes in other proteins including apoB, non-HDL C, lipoprotein (a) and total cholesterol. Similar to prior evaluations of inclisiran, the medication was well-tolerated. The lack of positive treatment results from the ORION-5 cannot exclude a small sample size compared to those enrolled in the PCSK9i monoclonal antibody trials, an imbalance in genotypes in the present study, or differing mechanisms for PCSK9 intubation (159). The upcoming study of inclisiran in adolescent (ORION-13) HoFH patients, Which is estimated to be completed by December 2024, will shed further light on the use inclisiran in HoFH. (160).

Standard triple drug therapy (statin, ezetimibe, PCSK9 inhibitor) often does not result in a sufficient lowering of LDL-C due to the combination of the very high baseline LDL-C and the relative resistance of patients with HoFH to drug therapy. Currently, there are no published reports of bempedoic acid use within the HoFH population. Novel agents approved specifically for the treatment of severe hypercholesterolemia include microsomal triglyceride transfer protein (MTP) inhibitors and apoB-100 antisense oligonucleotides (ASO). MTP is involved in the transfer of lipid droplets to apoB as well as assembly and secretion of apoB-

containing lipoproteins in the liver and gut. MTP inhibition thus reduces production and secretion of chylomicrons and VLDL-C. In one study, 29 patients with HoFH were treated with the MTP inhibitor lomitapide for 26 weeks and were followed until week 78. Average LDL-C reductions were 50% (to 166 mg/dL) at week 26, 44% (to 197 mg/dL) at week 52, and 38% (to 208 mg/dL) at week 78 (161). Real-world observational data of lomitapide from the LOWER registry suggest slightly less robust LDL-C lowering (33%) and LDL-C goal attainment (65.4% attaining LDL-C <100 mg/dL, 41.1% attaining LDL-C <70 mg/dL), likely a result of inadequate dose titration (mean dose 10 mg/d, range 5-40 mg/d) due to a high burden of adverse effects with nearly quarter of patients discontinuing treatment due to side effects (162). Though lomitapide displays potent LDL-C lowering capacity, use is limited as a result of a significant side effect profile consisting of severe gastrointestinal complications and hepatotoxicity risk, as well as high medication cost.

Anti-sense oligonucleotide (ASO) molecules bind to specific mRNAs and target them for degradation, reducing protein synthesis in the process. Mipomersen, which was removed from the market in June 2018, is an ASO that binds to apoB-100 mRNA and thus prevents the formation of apoB-100. Mipomersen results in decreased synthesis of apoB-containing lipoproteins, mostly VLDL-C, eventually leading to a drastic reduction of LDL-C levels in plasma. In one trial, 51 patients with either genetically defined HoFH, untreated LDL-C levels of >500 mg/dL plus xanthomas, or evidence of HeFH in both parents were randomized to placebo versus mipomersen for a treatment duration of 26 weeks. In the placebo group, baseline LDL-C was 402 mg/dL and declined to 390 mg/dL; in the treatment group, baseline LDL-C dropped from 440 mg/dL to 324 mg/dL (163).

Evinacumab is the newest addition to the lipid-lowering treatment armamentarium, receiving FDA approval in February 2021 as an adjunct to other LDL-

lowering therapies for treatment of adults and pediatric patients originally ≥ 12 years of age with HoFH, with the age being reduced to ≥ 5 years of age in March 2023 (152). Evinacumab is a fully human IgG4 isotype monoclonal antibody targeting a novel, non-LDLR pathway for LDL-C lowering by inhibiting angiopoietin-like 3 (ANGPTL3) (164). ANGPTL3 inhibition overrides the inhibitory effect on lipoprotein lipase (LPL) and endothelial lipase (EL) increasing the activity of these enzymes, producing a panlipid-lowering effect of apo-B containing lipoproteins (with the exception Lp[a]), reducing lipoproteins by approximately 50% from baseline (152). Specifically, evinacumab promotes LDL-C lowering through EL-dependent VLDL-C processing and clearance by LDLR independent pathways, thereby decreasing formation of LDL-C from VLDL-C.(165) The magnitude of LDL-C lowering was seen in both HoFH and HeFH populations and was similar regardless of genotype. Serial coronary computed tomography angiography (CCTA) evaluations of two HoFH patients enrolled in the ELIPSE HoFH trial demonstrated reductions in coronary total plaque volume (TPV) of 76% to 85% over 10 months of treatment with evinacumab (166). Evinacumab is dosed at 15 mg/kg of body weight given over a 60 minute intravenous infusion (152). The drug is well tolerated with adverse effects being infrequent, mild, and transient, consisting primarily of injection site reactions, flu/cold-like symptoms, pain, and fatigue. The long-term safety of evinacumab remains unknown. A recent real-world analysis of evinacumab use across six US academic medical centers, demonstrated good tolerability, potent LDL-C lowering (50.8%), and LDL-C goal attainment (30.4% achieving LDL-C goals of <70 mg/dL) among 24 patients followed for up to 63 weeks (167). Additionally, a real-world analysis demonstrated that evinacumab can be a complementary therapy to apheresis. A single center US academic medical institution described the use of two patients undergoing apheresis for whom evinacumab was added achieving LDL-C lowering of 42% to 58%, and LDL-C goal attainment of <55 mg/dL in one patient. The study concluded that evinacumab presents a

major advancement in the treatment of HoFH and will allow for improved LDL-C goal attainment. Evinacumab will be complementary to ongoing lipoprotein apheresis in many, but for those with less severe residual LDL-C elevation, may allow for reduced apheresis frequency or potentially replace its use altogether (168). The most recent study of evinacumab was published January 2024 and included an open-label 3-part series evaluating evinacumab use in pediatric patients age 5 to 11 years of age with HoFH (169). Part A was a pharmacokinetic study of 6 patients which determined that the 15 mg/kg intravenously administered dose utilized within the adult patient population was appropriate for pediatric patients. Part B was a phase 3, single-arm, 24-week open-label study assessing the efficacy, safety, and pharmacokinetics of evinacumab in 14 patients. Part C is an ongoing, phase 3, 48-week open-label extension study with a 24-week follow-up designed to assess the long-term safety and efficacy of evinacumab and will include all 20 patients from parts A and B. The mean age for patients in the part B trial was 9.1 years, 57.1% of which were females with 71% of patients having biallelic different *LDLR* variance, with 5 patient's carrying null/null alleles. Additionally, 11 of the 14 of patients already had aortic stenosis at this young age. Baseline LDL-C was 263.7 mg/dL, 85.7% were on any statin, 50% were on high-intensity statin, 100% were taking non-statins (none on PCSK9 inhibitor), 14.3% were taking lomitapide, and 50% were on apheresis. The primary endpoint, mean LDL-C percent change from baseline was reduced by 48.3% with an absolute LDL-C lowering of 131.9 mg/dL at week 24. LDL-C reduction was seen as early as week 1 with near full response witnessed by week 2. Response was independent of age, sex, ethnicity, *LDLR* genotype, or baseline apheresis use. Evaluation of other lipoprotein parameters included reductions of 41.3% in apoB, 48.9% in non-HDL-C, 49.1% in total cholesterol, and 37.3% in Lp(a). Similar

to that seen in the adult population, evinacumab was well-tolerated with no treatment-related serious or severe TEAEs noted and no drug discontinuations due to adverse effects. Immunogenicity potential was minimal with only 1 patient developing treatment emergent antidrug antibodies but no neutralized antibodies. Evinacumab is poised to play a significant role in HoFH management as it offers one of the most potent LDL-C lowering capabilities among existing treatments. Use in HoFH will likely be as an add-on therapy after high-intensity statin, ezetimibe, and PCSK9 inhibition. However, potential barriers to use may include high cost, intravenous administration, and requirement for administration in a healthcare or home infusion setting. Future use of evinacumab may extend beyond HoFH and could entail use in other therapeutic areas such as HeFH and severe hypertriglyceridemia.

In patients in which drug therapy is either not successful at lowering LDL-C or not well tolerated one can consider lipoprotein apheresis or potentially even liver transplantation (170). The FDA has approved lipoprotein apheresis for subjects with CVD and LDL-C >200 mg/dL or without CVD and LDL-C >300 mg/dL (171). This threshold has been moved to 160 mg/dL, and more recently to 100 mg/dL with FH and ASCVD, thus increasing the target population for cholesterol dialysis at a time when arrival of stronger medications is curtailing patient entry into this therapeutic program. The process, which involves removing apoB-containing lipoproteins from plasma, is usually performed every two weeks and results in a 60-70% reduction of LDL-C and Lp(a) in the immediate post-procedure period, with time-averaged reductions of 20-50%. Levels tend to revert to baseline within two weeks. For more detailed information on lipoprotein apheresis see the Endotext chapter on this topic (172).

TABLE 6. COMMON LIPID-LOWERING TREATMENTS FOR FH					
Agent	Niacin	BAS	Fibrate	Statin	Ezetimibe
FDA approval date	1997*	1973	1981† 1993	1987	2002
Administration	PO	PO	PO	PO	PO
Dosing	Daily	Daily	Daily	Daily	Daily
LDL-C lowering (HeFH)	10%-25%	15%-30%	10%-20%	20%-60%	15%-25%
LDL-C lowering (HoFH)	<10%	<10%	<10%	10%-25%	<10%
Lp(a) lowering	20-30%	N/A	N/A	N/A	N/A
Relative cost	+ / ++	++	+	+	+
Safety concerns	Flushing, moderate GI intolerance (abd pain, nausea, vomiting, peptic ulcer), hyperglycemia, gout, hepatotoxicity	Moderate GI symptoms (abd pain, constipation, bloating, nausea), hypertriglyceridemia, fat-soluble vitamin deficiencies	Myalgia, mild GI symptoms (abd pain, diarrhea), cholelithiasis, increased LFT	LFT elevation, myalgia, DM risk	Mild GI symptoms (loose stool, diarrhea, cramping), myalgia, increased LFT
Other considerations		High pill burden, separate from other meds (binding)	Primarily used for triglyceride lowering, renal dose adjustments	Usually well tolerated	

Adapted from Warden BA, et al. *Expert Rev Cardiovasc Ther.* 2021;1-13.

*Approval date is for niacin extended-release. Niacin has been used clinically for hypercholesterolemia since the 1950's.

†Gemfibrozil FDA approved in 1981, fenofibrate in 1993.

TABLE 7. ADVANCED LIPID-LOWERING TREATMENTS FOR FH					
Agent	Lipoprotein apheresis	Lomitapide	PCSK9i*	Bempedoic acid	Evinacumab
FDA approval date	1996	2012	2015	2020	2021
Administration	IV	PO	SQ	PO	IV
Dosing	2-4x monthly	Daily	1-2x monthly	Daily	Monthly
LDL-C lowering (HeFH)	50-85% (acute) 23-50% (time-average)	N/A	50%-60%	15%-25%	49%
LDL-C lowering (HoFH)	50-85% (acute) 23-50% (time-average)	20%-50%	zero-30%†	Unknown	49%
Lp(a) lowering	50-75% (acute) 20-40% (time-average)	zero-30%	20-30%	N/A	N/A
Relative cost	++++	++++	+++	++/+++	+++++
Safety concerns	IV access issues, hypotension, vasovagal episodes, fatigue, bleeding, hypocalcemia, anemia	Severe GI intolerance (diarrhea, nausea, vomiting, abdominal pain, cramping), fat malabsorption, hepatic steatosis, hepatotoxicity (REMS)	ISR, flu/cold-like symptoms	Mild GI symptoms (diarrhea, abdominal discomfort), gout, tendon injury, transient lab changes (SCr, BUN, LFT, Hgb, HCT, uric acid)	Nasopharyngitis, ISR, flu-like symptoms, fatigue, pain, headache, rare hypersensitivity reaction
Other considerations	Lengthy and frequent treatments, need for patient travel, DDI (heparin, ACEi)	Significant DDI, renal dose adjustments	Access and cost issues	Improves glycaemia, option for patients with SAMS	Reduces all non-Lp(a) apoB-containing lipoproteins

Adapted from Warden BA, et al. *Expert Rev Cardiovasc Ther.* 2021;1-13.

*PCSK9i: represent PCSK9 blocking monoclonal antibodies and inclisiran, a novel small interfering ribonucleic acid (siRNA)-based medication.

†Response aligns with genetic cause of HoFH with no reduction was seen in those with null-null LDLR mutations.

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