
Mini-Review

Management of Familial Hypercholesterolemia: Current Status and Future Perspectives

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Abstract

Familial hypercholesterolemia (FH) is the most common monogenic disorder associated with premature atherosclerotic cardiovascular disease. Early diagnosis and effective treatment can significantly improve prognosis. Recent advances in the field of lipid metabolism have shed light on the molecular defects in FH and new therapeutic options have emerged. A search of PubMed database up to March 2020 was performed for this review using the following keywords: “familial hypercholesterolemia,” “diagnosis,” “management,” “guideline,” “consensus,” “genetics,” “screening,” “lipid lowering agents.” The prevalence rate of heterozygous FH is approximately 1 in 200 to 250 and FH is underdiagnosed and undertreated in many parts of the world. Diagnostic criteria have been developed to aid the clinical diagnosis of FH. Genetic testing is now available but not widely used. Cascade screening is recommended to identify affected family members, and the benefits of early interventions are clear. Treatment strategy and target is currently based on low-density lipoprotein (LDL) cholesterol levels as the prognosis of FH largely depends on the magnitude of LDL cholesterol-lowering that can be achieved by lipid-lowering therapies. Statins with or without ezetimibe are the mainstay of treatment and are cost-effective. Addition of newer medications like PCSK9 inhibitors is able to further lower LDL cholesterol levels substantially, but the cost is high. Lipoprotein apheresis is indicated in homozygous FH or severe heterozygous FH patients with inadequate response to cholesterol-lowering therapies. In conclusion, FH is a common, treatable genetic disorder, and although our understanding of this disease has improved, many challenges still remain for its optimal management.

Key Words: familial hypercholesterolemia, LDL receptor, genetic testing, cascade screening

Familial hypercholesterolemia (FH) is a common hereditary disorder of lipid metabolism characterized by high circulating levels of low-density lipoprotein (LDL). The underlying cause is mainly due to defects in genes related

to the clearance of LDL. Chronic exposure to high levels of circulating LDL leads to the development of premature atherosclerotic cardiovascular disease (ASCVD). FH is a treatable disorder, and the discovery of statins has

significantly improved the prognosis of individuals with FH. However, in those with a more severe phenotype, adequate LDL-cholesterol (LDL-C) reduction remains difficult to achieve. With the development of novel molecular diagnostic techniques and more potent LDL-C lowering therapies, there has been a renewed impetus to reduce the clinical and public health burden of this familial lipid disorder, and a global call to action has just been released [1]. Recent updates on the epidemiology and advances in the genetics and management of FH will be reviewed in this article.

Epidemiology of FH

Recent studies have shown that FH is underdiagnosed in many parts of the world, and it has been estimated that less than 10% of patients worldwide with FH have been diagnosed with the condition [2-4]. Earlier studies have suggested that heterozygous FH (HeFH) affects 1 in 500 individuals, and that homozygous FH (HoFH) affects 1 in 1 000 000 individuals [5-8]. More recent studies have shown that the prevalence of HeFH is in fact up to 2-fold higher than previously reported. The 2016 US NHANES study reported a prevalence rate of 1:250 for HeFH [9] and the SEARCH study using electronic health care records observed a rate of 1:310 in a US population [10]. Recent data from Europe showed prevalence rates of 1:217 in a Danish general population sample [11], and 1:192 in a Catalan database sample [12]. In Australia, the prevalence rate was 1:267 [13]. For HoFH, the prevalence rate was approximately 1:300 000 based on a Dutch population sample [14]. Differences in prevalence rates in various populations are partly attributed to the inherent genotypic/phenotypic variability of FH and to the discrepancy in the criteria used to identify FH individuals in the studies. Some countries like South Africa have higher prevalence rates due to founder effects [15]. National and international registries are being formed to advance clinical research and improve healthcare planning and patient care [4,16].

Genetic Basis of FH

Monogenic dominant inherited form of FH is caused by mutations in 3 main genes: the LDL-receptor (*LDLR*) gene accounting for over 90% of the cases, the apolipoprotein (apo) B-100 (*APOB*) gene accounting for 5 to 10% of the cases, and the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene accounting for up to 3% of the cases [17,18]. A rare cause of autosomal dominant FH is due to pathogenic variants in the *APOE* gene [19-21], and a mutation in the LDLR adaptor protein 1 (*LDLRAP1*) gene causes an extremely rare autosomal recessive form of FH [22]. It

has been estimated that at least 20% of FH patients diagnosed by clinical criteria do not have identifiable causative mutations in any of the known FH-associated genes [23]. Although this may be due to the involvement of yet unknown genes, a substantial subset of these “mutation-negative” FH patients may have polygenic causes, and they carry a disproportionately high burden of multiple small effect common variants that raises plasma LDL-C [23-25].

The genetic diversity of FH leads to considerable variability in phenotype. On the whole, pathogenic variants in the *LDLR* gene tend to be associated with higher plasma LDL-C levels than binding defective variants in the *APOB* or gain-of-function variants in the *PCSK9* gene. The severity of the phenotype is inversely proportional to the residual LDLR activity [26,27]. Individuals with receptor-negative or receptor-null mutations tend to have a more severe phenotype with significantly higher LDL-C and also higher risk of ASCVD than those with receptor-defective mutations [26]. The presence of other cholesterol-raising and lowering genes, as well as dietary habits and lifestyle are also important factors which modulate the magnitude of LDL-C elevation.

The spectrum of mutations of FH has been extensively studied, and with the widespread use of next-generation sequencing, new variants are constantly being reported. A recent update provided by the ClinGen consortium has shown that there are 2314, 353, and 216 reported unique variants in the *LDLR*, *APOB*, and *PCSK9* gene, respectively [28]. However, functional studies have not been performed for the great majority of variants reported. When the American College of Medical Genetics and Genomics algorithm is applied, around 50% of all worldwide FH-associated variants are classified as variants of unknown significance [29]. As a result, the ClinGen FH Variant Curation Expert Panel is developing an FH-specific algorithm to classify FH variants based on the American College of Medical Genetics and Genomics algorithm to improve variant curation and to standardize interpretation [30].

Making a Diagnosis of FH

Diagnosis of FH can be made by using either clinical and/or molecular criteria after ruling out secondary causes of hypercholesterolemia. Clinical diagnosis of FH can sometimes be difficult because LDL-C levels in younger individuals or those with a milder phenotype can overlap with polygenic causes of raised LDL-C. A number of clinical diagnostic criteria have been developed over the years to facilitate diagnosis. They are mainly based on lipid levels and various combinations of physical signs and personal or family history of hyperlipidemia or premature ASCVD [31], and some of these diagnostic criteria use a scoring

algorithm. The major available diagnostic systems for FH include the US Make Early Diagnosis to Prevent Early Death (MEDPED) [6], the UK Simon Broome system [32], the Dutch Lipid Clinic Network Criteria [33], and the Japanese FH diagnostic criteria [34]. They can be used as a first step to identify those who may benefit the most from undergoing genetic testing when resources are limited. Although all these diagnostic systems may differ on the proposed lipid cut-off values and entail slightly different combination of clinical criteria, their prediction value is, in general, relatively similar. They tend to have high specificity but low sensitivity, and there is no consensus on which set of criteria is superior [31].

A simpler and more functional classification to diagnose FH has been proposed by the American Heart Association. In the absence of genetic testing, HeFH is diagnosed if LDL-C is ≥ 160 mg/dL (4.1 mmol/L) in a child or ≥ 190 mg/dL (4.9 mmol/L) in an adult confirmed on 2 occasions, with a first-degree relative similarly affected, or with premature coronary artery disease (CAD), or with an FH-causing mutation [35]. HoFH is diagnosed if LDL-C > 400 mg/dL (10 mmol/L) and 1 or both parents have FH diagnosed clinically or by genetic testing. If an individual has an untreated LDL-C is > 560 mg/dL (14 mmol/L) or if LDL-C is > 400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata before age 20 years, HoFH is highly likely [35]. The LDL-C levels for the clinical diagnosis of HoFH in the European Atherosclerosis Society guidelines is an untreated LDL-C of > 500 mg/dL (13 mmol/L) or treated LDL-C of ≥ 300 mg/dL (8 mmol/L), together with either cutaneous or tendon xanthoma before age 10 years or untreated elevated LDL-C levels consistent with HeFH in both parents [36]. The results of population-based studies of genetic screening for FH have demonstrated that there is no fixed LDL-C threshold for making the diagnosis of HoFH. Although an untreated LDL-C of > 400 mg/dL (10 mmol/L) should lead to a consideration of the diagnosis of HoFH, LDL-C levels of < 400 mg/dL (10 mmol/L) have also been documented in patients with genetically confirmed HoFH [14,36].

Genetic Testing in FH

A deoxyribonucleic acid diagnosis remains the gold standard for the diagnosis of FH, and recent advances on molecular techniques have facilitated the identification of the underlying genetic defects. Various diagnostic platforms have been developed including deoxyribonucleic acid array-based chip [37] and next-generation sequencing [38,39]. Although the cost of genetic testing has come down, genetic testing is still not widely available and is not reimbursed in many countries [40]. The diagnostic yield of genetic testing varies widely by population settings and

testing platforms used. The mutation detection rate is much higher when genetic testing is performed in those with clinically suspected FH. In a clinically ascertained sample with severe hypercholesterolemia, the percentage of individuals with an identifiable genetic cause was 57% and increased to 92% when LDL-C level rose from 194 to > 310 mg/dL (5.0 to > 8.0 mmol/L) [41]. When individuals were ascertained solely on the basis of a single elevated LDL-C level > 190 mg/dL (4.9 mmol/L) in population cohort studies, the mutation detection rate was much lower at $< 5\%$ [42].

Overall, genetic testing is underutilized in many parts of the world [40]. For instance, data from the Cascade Screening for Awareness and Detection of FH Registry in the United States showed that genetic testing had only been performed in 3.9% of individuals with a clinical diagnosis of FH [43]. The need for genetic testing has been contested, and it has been argued that genetic testing may not always be necessary or cost-effective as patients with high LDL-C levels must be treated regardless of the genetic test results [40]. Furthermore, the absence of a known mutation does not exclude a diagnosis of FH, particularly in those with a strong phenotype. There is also a potential concern for genetic discrimination. However, detection of a pathogenic variant can improve identification and patient care. Genetic testing provides prognostic information and refines risk stratification. Presence of a mutation signifies the higher ASCVD risk of these individuals due to lifelong exposure to elevated LDL-C and indicates the need for more aggressive lipid-lowering therapy [43-45]. Documentation of a genetic cause has also been shown to increase an individual's motivation and adherence to therapy [46]. Moreover, genetic testing facilitates the definitive diagnosis (especially in children) and enables unambiguous and more cost-effective cascade screening of relatives [47]. International and European guidelines on FH recommend that genetic testing should be performed if available after making a clinical diagnosis [35,48-50], and the US FH Foundation recently also recommended that molecular diagnosis should be offered to all FH individuals [51]. The National Lipid Association in the United States has published a scientific statement on genetic testing in dyslipidemia as well, which addressed the indications and important limitations of genetic testing in FH [52].

Screening of FH

Even though FH is underdiagnosed globally, universal screening for FH is currently not feasible nor cost-effective. The most effective means to identify new cases of FH is by cascade screening of family members of a known index case [53,54]. The reported yield in the number of relatives identified with FH per index case

varies from 2 to as high as 8 in the Netherlands where genetic cascade screening has been highly successful [55-57]. Once an individual is diagnosed to have FH, screening should be offered to all his or her first-degree relatives. Screening of relatives can be done by measuring LDL-C, genetic analysis, or both, and FH has been designated as a tier 1 genomics application for family screening by the US Centers for Disease Control and Prevention Office of Public Health Genomics [58]. In patients with a clinical diagnosis of FH in whom the mutation is unknown, lipid measurements can be used for screening relatives. It has been estimated that around 20% of relatives with *LDLR* mutations but modestly raised LDL-C may be missed if only LDL-C levels are used in screening [46]. The total cholesterol and LDL-C cut-offs used in the diagnosis of an FH proband from the general population is not used in diagnosing relatives in family screening because of the greater prior probability of a first-degree relative having FH. Age- and sex-specific LDL-C cut-offs for the diagnosis of FH in relatives have been developed and can be used in cascade screening in FH families where the genetic basis is unknown [6,59].

Universal pediatric screening coupled with reverse cascade screening has been proposed as another strategy to identify new FH cases as the discrimination power between FH and non-FH cases based on LDL-C levels is better during childhood [60,61]. The implementation and cost-effectiveness of such an approach are being studied [62]. In most countries, children with FH are currently identified through cascade testing in families where an index case has been identified. In these families, testing for FH in a child is recommended from the age of 5 years onward, or earlier if HoFH is suspected. If a genetic defect has already been identified in the affected parent, the diagnostic LDL-C level for the child is ≥ 135 mg/dL (3.5 mmol/L), and genetic testing should be offered [50,63].

Management of FH

The aim of treatment of FH is to reduce the cumulative burden of elevated LDL-C levels and prevent or delay the development of ASCVD. The risk of developing CAD is increased up to 13-fold in untreated FH subjects [64], and 22-fold when an FH mutation is present [42]. Effective control of LDL-C significantly reduces the cardiovascular morbidity and mortality of FH, and treatment should start as early as possible [2,65]. Since the prognosis of FH largely depends on the LDL-C levels, the treatment strategy is based on LDL-C levels. Most guidelines recommend LDL-C targets of <100 mg/dL (<2.6 mmol/L) for adults with FH (or at least 50% reduction), <70 mg/dL (<1.8 mmol/L) for those with ASCVD or diabetes, and <135 mg/dL (<3.5 mmol/L) for children >10 years of age

[35,48,49]. In the latest European Society of Cardiology guideline, LDL-C targets have been lowered to 70 mg/dL (1.8 mmol/L) for FH adults without other major risk factors and 55 mg/dL (1.4 mmol/L) for those with ASCVD or another major risk factor and therefore considered to have very high risk [50]. To improve risk assessment, noninvasive cardiovascular imaging techniques to detect asymptomatic atherosclerosis can be considered [35,50,66].

Statins are the mainstay of treatment of FH, in addition to dietary and lifestyle modifications and smoking cessation, which are the cornerstone in the management of FH and for which all patients should be counseled [67]. Patients with FH benefit from a low saturated fat/low-cholesterol diet, which lowers cholesterol and improves cardiovascular outcomes [68]. When the LDL-C goal is not achieved despite high-intensity statin therapy in adults, ezetimibe is recommended as the second-line therapy and can further reduce LDL-C levels by 24% when used in combination with a statin [35,48,49]. In children with FH, recent European guidelines suggested that low dose statin therapy can be started at the age of 6 to 10 years and increased to reach goals if required [35,50,63,69], whereas in the United States, treatment is recommended to be started at the age of 8 to 10 years, consistent with the US Food and Drug Administration (FDA)-approved use of statins in children with FH [70]. If LDL-C remains high despite using statin doses licensed in children, ezetimibe can be added in children from 10 years of age [63, 71].

If LDL-C is still above goal in adult FH patients, bile acid sequestrants or niacin can be used as third-line agents. However, these drugs are poorly tolerated and have limited efficacy in lowering LDL-C. A major breakthrough in the treatment of FH has been the advent of PCSK9-based therapies [72]. In FH patients with ASCVD or with other major risk factors, treatment with an anti-PCSK9 monoclonal antibody (mAb) is recommended if LDL-C remains above target despite maximally tolerated statin plus ezetimibe [50]. The current approach to the management of FH is summarized in Table 1.

Lomitapide and mipomersen were approved by the FDA for use in adults with HoFH in late 2012 and early 2013, respectively. However, mipomersen is no longer available after the termination of distribution in 2018. In subjects with HoFH or severe HeFH who are unable to achieve LDL-C targets with pharmacotherapy, lipoprotein apheresis should be considered for further LDL-C lowering [36,73]. Acute reduction in LDL-C, up to 60% to 80%, can be achieved after each procedure. Lipoprotein apheresis is not available in many parts of the world, and plasmapheresis may be used. Lipoprotein apheresis is costly, and the eligibility criteria differ between countries, and the availability of PCSK9 inhibitors has reduced the need for lipoprotein apheresis [74,75].

Table 1. Summary of the current approach to the management of familial hypercholesterolemia

1. **Consider diagnosis of FH**
 - Premature ASCVD (<55 years men, <60 years women)
 - Family history of premature ASCVD
 - Family history of hypercholesterolemia and/or tendon xanthoma
 - LDL > 190 mg/dL (4.9 mmol/L) in adults
 - LDL > 150 mg/dL (3.9 mmol/L) in children
2. **Confirm diagnosis of FH**
 - Exclude secondary causes
 - Apply clinical diagnostic criteria
 - Genetic testing if available
 - Assess other cardiovascular risk factors
 - Cascade screening of family members
 - by lipid levels
 - by genetic analysis if causative mutation identified
3. **Management of FH**
 - LDL-C goals
 - Adults without ASCVD: <70 mg/dL (<1.8 mmol/L) or ≥50% reduction
 - Adults with ASCVD: <55 mg/dL (<1.4 mmol/L)
 - Children >10 years of age: <135 mg/dL (<3.5 mmol/L)
 - Dietary and lifestyle measures and statin as first line
 - Add ezetimibe if LDL-C goal not achieved despite maximal tolerated dose of statin
 - Add PCSK9 inhibitor if LDL-C goal not achieved despite statin plus ezetimibe

Latest Pharmacological Therapies in FH

Monoclonal antibodies to PCSK9

Evolocumab and alirocumab are fully human immunoglobulin (Ig) IgG2 and IgG1 anti-PCSK9 mAb, respectively, and are administered subcutaneously. These mAbs prevent PCSK9 from interacting with the LDLR and thereby increase the recycling of LDLR to the cell surface of hepatocytes and increases the clearance of LDL particles from the circulation [76]. In addition to lowering LDL, plasma levels of lipoprotein (a) are also reduced by 12% to 32 [77].

Both alirocumab and evolocumab have been approved for the treatment of FH as an add-on therapy to conventional lipid-lowering agents [78]. In double-blind placebo-controlled trials involving HeFH patients, a further 60% LDL-C reduction was observed when anti-PCSK9 mAb was added to conventional maximally tolerated lipid-lowering therapies, and over 60% of the patients were able to achieve LDL-C of <70 mg/dL (<1.8 mmol/L) [79,80] (Table 2). The reduction in LDL-C in HeFH patients was consistent and durable up to 4 years, as demonstrated in the Odyssey Open-Label Extension (Odyssey OLE) trial [81]. In HeFH patients with more severe phenotype and LDL-C levels of ≥160 mg/dL (≥4.1 mmol/L) despite maximally tolerated lipid-lowering therapies, alirocumab further reduced LDL-C levels by 39% (Odyssey High FH study) [82].

The reductions in LDL-C levels by anti-PCSK9 mAb were more or less comparable among HeFH patients with a variety of underlying genetic mutations [83]. However,

the effectiveness of anti-PCSK9 mAb in HoFH appears to be partly determined by the underlying genetic abnormality [84]. In the Trial Evaluating PCSK9 antibody in Subjects with LDL Receptor Abnormalities (TESLA) Part B study, evolocumab 420 mg every 4 weeks significantly reduced LDL-C by 31% in HoFH patients. Analysis according to LDLR function revealed that patients with a receptor-defective mutation in 1 or both alleles had the best response, whereas patients with autosomal recessive hypercholesterolemia had moderate response and those carrying receptor-negative mutations in both alleles did not respond to evolocumab [84]. In HoFH patients with or without lipoprotein apheresis in the Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders (TAUSSIG), evolocumab treatment resulted in sustained reduction of mean LDL-C by 21% at 4 years [85].

Both evolocumab and alirocumab are generally well tolerated. Common reported side effects included nasopharyngeal problems, nausea, and injection site reactions [86]. The prospective Evaluating PCSK9 Binding antiBody Influence on coGNitive HeALTH in High cardiovascular Risk Subjects (EBBINGHAUS) trial showed no significant adverse neurocognitive changes with evolocumab over a median follow-up of 19 months [87]. Antidrug antibodies were observed in 5.1% in patients treated with alirocumab and in 0.3% of patients treated with evolocumab, but these antibodies were not associated with attenuation of LDL-C lowering effects [88,89].

Large cardiovascular outcome trials in subjects with established ASCVD (Further Cardiovascular Outcomes

Table 2. Key clinical trials of PCSK9 inhibitors, lomitapide and bempedoic acid in familial hypercholesterolemia

Drugs	Clinical Trials	Population	Effects on lipid parameters (vs placebo) (%)		
			LDL-C	Lp(a)	TG
Evolocumab	RUTHERFORD-2 [79]	HeFH	-59 to -61	-28 to -32	-12 to -20
	TESLA Part B [84]	HoFH	-31	No effect	No effect
	TAUSSIG [85]	HoFH	-24 ^a	-14 ^a	—
Alirocumab	ODYSSEY FH I and FH II [80]	HeFH	-51 to -58	-18 to -20	-11 to -16
	ODYSSEY HIGH FH [82]	HeFH	-39	-15	-9
	ODYSSEY LONG TERM [92]	High risk patients (including HeFH)	-56	-26	-17
	ODYSSEY OLE [139]	HeFH	-48 ^a	-27 ^a	-2 ^a
Lomitapide	Blom et al [97]	HoFH	-46 ^a	—	—
Bempedoic acid	CLEAR Harmony [116]	High risk patients (including HeFH)	-17	—	No effect
	CLEAR Wisdom [117]		-15		
	Ballantyne et al [118]		-17		

^aCompared to baseline.

Research with PCSK9 Inhibition in Subjects with Elevated Risk [FOURIER]) and in patients with acute coronary syndrome (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab, Odyssey Outcomes) reported a significant 15% relative risk reduction in the primary cardiovascular endpoint [90,91]. Although cardiovascular outcome trials of anti-PCSK9 mAb have not been carried out in FH patients, a post-hoc analysis of the Odyssey Long Term study, which included patients with HeFH, showed a lower rate of major adverse cardiovascular events (MACE) with alirocumab treatment compared with placebo (1.7% vs 3.3%, nominal $P = 0.02$) [92].

Lomitapide

Lomitapide is an orally administered small molecule inhibitor of microsomal triglyceride transfer protein, an enzyme primarily expressed in the endoplasmic reticulum of hepatocytes and enterocytes. Microsomal triglyceride transfer protein is responsible for transferring triglyceride onto apo B during the assembly and secretion of apo B-containing lipoproteins in the liver (VLDL) and intestine (chylomicrons). Its inhibition leads to reduced synthesis of VLDL and chylomicrons [93,94], resulting in LDL-C lowering independent of LDLR function. In phase 3 studies, lomitapide resulted in significant (42%–50%) reduction of LDL-C in HoFH patients on standard lipid-lowering therapies [95,96], and a sustained efficacy up to 5 years of therapy was demonstrated in long-term extension studies [97,98] (Table 2). Results from a recent trial also suggested that lomitapide was more effective than LDL apheresis in terms of reduction in time-averaged LDL-C level in HoFH [99]. The effect of lomitapide on cardiovascular morbidity

and mortality has not been determined. Potential theoretical benefits have been suggested. Post-hoc and modeling analyses have shown that lomitapide reduced MACE (1.7 vs 21.7 events per 1000 patient-months), delayed the time to the first MACE by 5.7 years and increased life expectancy by 11.2 years in HoFH patients [100,101].

Gastrointestinal intolerance is the most common side effect of lomitapide. A possible mechanism is due to reduced dietary fat absorption and accumulation of intracellular triglyceride in enterocytes. Deficiencies of fat-soluble vitamins may also occur as a result of impaired fat absorption or due to an inadequate amount of lipoproteins as vitamin E transporter in the circulation [102]. Significant transaminase elevation and hepatic steatosis are side effects of lomitapide in view of its mechanism of action. Transaminase increases often normalized with dosage reduction without treatment discontinuation [94]. Increased hepatic fat content returned to baseline as soon as 4 weeks after stopping lomitapide [96,103]. As the long-term clinical consequences of these hepatic effects remain unknown [95–98], the FDA has stipulated the need of risk evaluation and mitigation strategies as well as postmarketing observational registries.

Mipomersen

Mipomersen is a second-generation antisense single-strand oligonucleotide that binds to *APOB* messenger ribonucleic acid (mRNA) transcript in the liver and triggers its degradation, thus inhibiting the synthesis of apo B-100 containing lipoproteins such as VLDL, LDL, and lipoprotein (a) through an LDLR-independent pathway [104,105]. In the pivotal 26-week phase 3 study, mipomersen resulted in a significant reduction of LDL-C by 21% in HoFH patients

on standard lipid-lowering therapy (excluding LDL apheresis) [106]. It also demonstrated similar efficacy in HeFH [107-109] and pediatric HoFH patients [110], and the addition of mipomersen could reduce the need of apheresis in HeFH patients with CAD [111]. A 2-year open-label extension trial confirmed that mipomersen offered a sustained reduction in atherogenic lipoproteins [112]. The most common adverse events were injection site reactions and influenza-like symptoms [106,108,109,112]. Significant transaminase elevation and hepatic steatosis were also reported [112]. Mipomersen is no longer available after its distribution was terminated in 2018.

Bempedoic acid

Bempedoic acid is an oral small-molecule inhibitor of adenosine triphosphate citrate lyase (ACL), a key enzyme involved in cholesterol biosynthesis by catalyzing acetyl-CoA synthesis. It is a pro-drug and requires activation to bempedoic acid-CoA by very long-chain acyl-CoA synthetase-1 which is highly expressed in the liver but not in skeletal muscle. Inhibition of hepatic ACL by bempedoic acid-CoA leads to depletion of intracellular cholesterol and upregulation of LDLR, thus increasing LDL-C clearance [94,113]. It has been shown in phase 3 studies that bempedoic acid significantly reduced LDL-C as monotherapy (21.4%) [114] or as a combination with ezetimibe (28.5%) in patients with statin intolerance [115]. In hypercholesterolemic patients already receiving guideline-recommended statin therapy, bempedoic acid 180 mg daily further reduced LDL-C levels by 17% (Cholesterol Lowering via Bempedoic Acid and ACL-Inhibiting Regimen [CLEAR] Harmony trial) [116], and the CLEAR Wisdom trial confirmed a similar efficacy of bempedoic acid in patients at high cardiovascular risk requiring additional LDL-C lowering [117]. The bempedoic acid-ezetimibe combination effectively lowered LDL-C by 36% in a similar patient population [118]. All 3 trials included a small proportion of HeFH patients, in which bempedoic acid demonstrated comparable lipid-lowering efficacy [116-118] (Table 2). Bempedoic acid is generally safe and well-tolerated with a similar overall incidence of adverse events as placebo, except for a small increase in the incidence of gout [114-118]. The CLEAR Outcomes trial (NCT02993406) is ongoing to assess the efficacy of bempedoic acid for reducing cardiovascular events in 12 600 patients. Bempedoic acid, both as a standalone drug and as a fixed-dose combination with ezetimibe, have received regulatory approval from the FDA and from the European Medicines Agency in 2020 for the treatment of adults with HeFH or established ASCVD in combination with diet and maximally tolerated statin therapy.

Novel Emerging Therapies

Inclisiran

Another approach to inhibit PCSK9 is by using small interfering ribonucleic acid. Inclisiran is a long-acting synthetic small interfering ribonucleic acid targeting the mRNA precursor for PCSK9. By causing PCSK9 mRNA degradation, inclisiran inhibits the translation of PCSK9. With its unique mechanisms of action, inclisiran can concomitantly reduce both intracellular and extracellular PCSK9 protein levels, leading to a substantial, durable reduction of LDL-C levels in patients with hyperlipidemia [119]. The ORION-9 trial enrolled 482 HeFH patients with LDL-C levels of ≥ 100 mg/dL (≥ 2.6 mmol/L) while on maximally tolerated doses of statins with or without ezetimibe, randomized to receive subcutaneous injection of inclisiran 300 mg or placebo on days 1, 90, 270, and 450. LDL-C was reduced by 39.7% in the inclisiran group, with similar efficacy across different genotypes [120] (Table 3). Adverse events were comparable between inclisiran and placebo groups except for injection-site reactions, which occurred in 17.0% of patients on inclisiran compared with 1.7% of those on placebo, and these reactions were generally mild and transient. Four patients with HoFH were included in the ORION-2 trial, and 2 doses of inclisiran 300 mg given at day 1 and day 90 were effective in 3 of the patients resulting in LDL-C reductions averaging 30% [121], a magnitude similar to that seen in TESLA Part B with evolocumab [84]. However, the HoFH patients must have LDL mutations with residual LDLR activity for the treatment to be effective, as previously shown with the anti-PCSK9 mAb [84]. A phase 3 trial to evaluate the effectiveness of inclisiran (ORION-5) in 45 HoFH patients is ongoing [122]. Inclisiran has been granted orphan drug designation for HoFH by the FDA [123], and the drug is not yet approved for clinical use.

Angiotensin-like protein 3 inhibitors

Angiotensin-like protein 3 (ANGPTL3) is a protein synthesized and secreted by the liver. It inhibits lipoprotein lipase and endothelial lipase, which are responsible for hydrolyzing triglyceride in VLDL and phospholipid in high-density lipoproteins (HDL), respectively, thereby reducing clearance of VLDL and HDL [94,124]. Population studies have shown that loss-of-function variants in ANGPTL3 were associated with significantly lower levels of triglyceride, LDL-C, HDL-C, and the risk of CAD [125, 126]. Evinacumab, a humanized mAb to ANGPTL3, caused a dose-dependent placebo-adjusted reduction in fasting triglyceride levels of up to 76% and

Table 3. Novel emerging therapies in familial hypercholesterolemia

Drugs	Mechanism of action	Population	Dosage / Route	Effects on lipid parameters (%)					Adverse events
				LDL-C	HDL-C	TG	Apo B	Lp(a)	
Inclisiran	Small interfering RNA inhibiting PCSK9 synthesis in the liver	HeFH	300 mg subcutaneous on days 1, 90, 270 and 450 [120]	-40	—	—	—	—	Injection site reactions
Evinacumab	Humanized monoclonal antibody blocking ANGPTL3	HoFH	300 mg subcutaneous on days 1 and 90 [121]	-30 (among the three responders)	—	—	—	—	Influenza-like illness and rhinorrhea
		HoFH	250 mg subcutaneous at baseline and 15 mg/kg intravenous at week 2 [127]	-49	-36	-47	-46	-11	
Gemcabene	Enhances clearance of VLDL via reduction of hepatic apoC-III mRNA	HeFH HoFH	300 mg daily oral for 4 weeks, then 600 mg daily for 4 weeks, then 900 mg daily [131]	-39 -11	No effect No effect	No effect No effect	-23 -15	— —	Mild diarrhea and headache

LDL-C levels of up to 23% in healthy subjects with elevated levels of triglycerides or LDL-C [126]. A single-arm, open-label study in 9 patients with HoFH or compound HeFH showed that evinacumab significantly reduced LDL-C by a mean of 49% after 4 weeks of treatment, and it was also effective in 3 patients with null/null LDLR genotypes [127] (Table 3). Similarly, an antisense oligonucleotide targeting ANGPTL3 mRNA achieved a significant and dose-dependent reduction of LDL-C up to 33% and other atherogenic lipoproteins in healthy subjects [128]. Hence, ANGPTL3 inhibition that achieves lipid modification independent of LDLR function appears to be a promising therapeutic strategy, especially in HoFH patients. Intriguingly, the observation that PCSK9 level dropped by 26% after evinacumab treatment suggested that an LDLR-dependent pathway may also play a role in evinacumab-mediated lipid modification [127]. Evinacumab (Regeneron Pharmaceuticals, Inc.) has been granted orphan drug designation for HoFH by FDA [129]. Recent topline results of the phase 3 trial in HoFH (ELIPSE HoFH, NCT03399786) released in August 2019 reported a 49% reduction of LDL-C compared to placebo when evinacumab was administered intravenously every 4 weeks at a dose of 15 mg/kg. Adverse events more commonly reported with evinacumab were influenza-like illness and rhinorrhea.

Gemcabene

Gemcabene is an orally administered lipid regulating small molecule, which enhances the clearance of VLDL via the reduction of hepatic apo C-III mRNA [130]. Results from a 12-week, open-label, dose-finding study in FH showed that gemcabene achieved meaningful LDL-C reduction in both HeFH (up to 39%) and HoFH patients (up to 11%) in a dose-dependent manner without major safety signals [131] (Table 3). The FDA has granted gemcabene (NeuroBo Pharmaceuticals, Inc.) orphan drug status for HoFH [132].

Liver-directed LDLR gene therapy

HoFH patients, especially those with receptor-negative or receptor-null mutations, fail to respond adequately to standard lipid-lowering therapies, which mainly act through upregulation of LDLR. Gene therapy, which replaces the defective gene with an intact and functional LDLR gene, can potentially restore effective hepatic LDL clearance in FH patients and hence achieve significant improvement in lipid profile. In a pilot study involving 5 HoFH patients, ex-vivo gene therapy demonstrated significant and prolonged LDL-C reduction, as well as persistent LDLR gene expression for at least 4 months after treatment

[133,134]. In vivo gene therapy avoids the invasive procedures of liver resection/hepatocyte isolation and directly transduces hepatocytes with LDLR genes through plasmid or viral vectors. Preclinical trials of in vivo gene therapy in murine models using adeno-associated virus serotype 8 as vector demonstrated impressive LDL-C reduction and prevention or regression of atherosclerosis [135-137]. Although promising animal data have been published, in vivo gene therapy for humans with HoFH is still in the very early stages of experimental treatment. An ongoing phase 1/2 study (NCT02651675) is now evaluating the safety and efficacy of adeno-associated virus serotype 8-mediated LDLR gene replacement RGX-501 (Regenxbio, Inc.) in HoFH patients [138].

Conclusions

If left untreated, FH is the most common genetic condition with potentially life-threatening cardiovascular consequences. Early intervention to lower LDL is the key to reduce the associated cardiovascular burden. Despite advances in genetic testing in FH and the availability of more potent lipid-lowering therapies, FH remains underdiagnosed and undertreated globally. At present, both phenotype- and genotype-based definitions of FH should continue to be used. Genetic testing for FH is likely to become more widely available in future, and this will enable more efficient family screening and precise genetic counseling. However, results of genetic testing should not be used to restrict access to indicated treatments for FH patients. This is because not all patients with phenotypic FH have identifiable pathogenic variants. In the context of precision medicine, more research is required to evaluate and compare the efficacy of different treatment in the setting of specific pathogenic variants. With regard to therapy, effective cholesterol-lowering therapy is available, and there are also a number of investigational agents undergoing evaluation for the treatment of FH. How to improve treatment adherence in this chronic disorder is not adequately addressed. The high cost of PCSK9 inhibitors has so far impeded access and limited their widespread use. The approval of bempedoic acid will provide another alternative treatment option for HeFH patients who require additional lowering of LDL-C. Although bempedoic acid is less potent than PCSK9 inhibitors in lowering LDL-C, it has the advantage of oral administration, and the price is expected to be lower and more affordable. In the near future, patient and payer preferences are likely to determine the order of these nonstatin LDL-C-lowering therapies before the availability of cardiovascular outcome data of bempedoic acid and its incorporation into treatment guidelines. The value

of patient registries has been recognized, and a number of national and international FH registries have been set up. Data collected from these registries have helped to identify knowledge and service gaps, inform clinical practice, and facilitate research. Concerted efforts are necessary to raise awareness of the condition and improve patient care.

Additional Information

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