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Pharmacological Innovations in Familial Hypercholesterolemia Treatment

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Abstract

Familial Hypercholesterolemia (FH) represents a significant global health challenge, characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels and an increased risk of atherosclerotic cardiovascular disease (ASCVD). Traditional management strategies, including statins and lifestyle modifications, are often insufficient to achieve optimal LDL-C targets, necessitating the exploration of advanced pharmacological approaches. This review highlights the critical role of pharmacology in mitigating ASCVD risks associated with FH, focusing on the efficacy and safety of current therapies such as statins, PCSK9 inhibitors, and novel agents targeting ANGPTL3 and microsomal triglyceride transfer protein. Furthermore, the potential of emerging modalities, including RNA interference therapies, gene editing, and cholesterol metabolism vaccines, is explored. Advances in risk stratification, incorporating genetic testing and imaging techniques, complement pharmacological innovations by enabling personalized care. These developments underscore the necessity of integrated, multidisciplinary approaches to FH management, emphasizing the promise of pharmacological breakthroughs in addressing unmet clinical needs.

Keywords: pharmacology, Familial Hypercholesterolemia, treatment

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal semi-dominant disorder characterized by a lifelong elevation of low-density lipoprotein cholesterol (LDL-C) levels, which results from impaired hepatic clearance of LDL (Goldstein & Brown, 2009). The prevalence of heterozygous FH (HeFH) is approximately 1 in 250 individuals, making it one of the most prevalent monogenic disorders. Despite this, the overall prevalence of FH has not been widely documented in many countries. However, certain populations, such as the French Canadians in Canada, Christian Lebanese in Lebanon, Afrikaners, Asian Indians, and Johannesburg Jews in South Africa, as well as consanguineous populations in Tunisia (particularly in central and southern regions), exhibit a higher prevalence of FH (>1:200). If left untreated, individuals with FH are at risk of developing physical signs of cholesterol deposition, accelerated atherosclerosis, and premature atherosclerotic cardiovascular disease (ASCVD). It has been estimated that individuals with HeFH may have a coronary heart disease risk that is up to ten times greater than that of the general population. Despite the high risk of ASCVD associated with HeFH, there exists significant variability in LDL-C levels and the susceptibility to ASCVD, even among individuals with the same genetic variant and within families. Homozygous FH (HoFH), with a prevalence of approximately 1 in 300,000 individuals (or higher in gene founder populations and consanguineous marriages), presents with extremely elevated LDL-C levels (>10 mmol/L or 400 mg/dL), often resulting in early-onset ASCVD and aortic sclerosis by the teenage years, or earlier if left untreated (Cuchel et al., 2023).

The diagnosis of FH can be established phenotypically using criteria that incorporate personal and family histories of hypercholesterolemia or premature ASCVD, LDL-C levels, and clinical features such as tendon xanthomas, corneal arcus, and xanthelasmas. Various diagnostic frameworks, including the Dutch Lipid Clinic Network Criteria, Simon Broome system, US Make Early Diagnosis to Prevent Early Death (MED-PED) program, and guidelines set by the Japanese Atherosclerosis Society, are commonly used. Additionally, there are country-specific guidelines and recommendations for the diagnosis of FH. Upon confirmation of the diagnosis of FH, a comprehensive ASCVD risk assessment should be performed. Given that LDL-C is a causal factor for ASCVD, it is crucial to initiate early and aggressive LDL-C lowering strategies to minimize cumulative exposure. In recognition of this, numerous guidelines have set LDL-C targets and treatment thresholds. These recommendations are based on a synthesis of data from trials conducted in both FH and non-FH populations, which demonstrate the efficacy and safety of LDL-C reduction (Watts et al., 2023).

Early detection and management of familial hypercholesterolemia (FH) is crucial for reducing the cumulative lifelong exposure to LDL-C. Unfortunately, FH remains underdiagnosed and inadequately managed worldwide, leading to global calls for action (Vallejo-Vaz et al., 2021). Several strategies have been proposed for universal, targeted, systematic, and opportunistic screening to identify affected individuals. However, even with appropriate diagnosis, many patients with FH fail to reach LDL-C targets despite the availability of therapeutic options. Achieving optimal lifelong care for FH remains challenging, particularly for those with homozygous FH (HoFH), although emerging lipid-lowering therapies hold promise for closing the treatment gap. This review discusses current and emerging therapies for LDL-C reduction and the implementation of care for patients with FH. It also provides an overview of ASCVD risk-stratification in FH to guide treatment intensity strategies. However, topics such as FH screening, diagnosis, genetic foundations, and cascade testing are outside the scope of this review.

2. ASCVD Risk-Stratification

2.1. Genetic Testing

The presence of a pathogenic variant causing FH is associated with a higher cumulative exposure to LDL-C and is an independent predictor of ASCVD, likely due to lifelong exposure

to elevated LDL-C levels. In individuals with phenotypic FH, a monogenic cause is linked to a two-fold higher ASCVD risk, whereas individuals with polygenic hypercholesterolemia may not exhibit a significantly different risk compared to those without an identifiable genetic cause. The impact of specific genetic variants on ASCVD risk remains poorly understood, except for bi-allelic ("homozygous") compared to mono-allelic ("heterozygous") variants, as well as major insertion/deletion rearrangements, which are better predictors of outcome than missense mutations. In the Simon Broome Registry, the odds ratios for coronary heart disease were found to be higher in individuals carrying LDLR, APOB, and PCSK9 gene variants, compared to those without detectable FH-causing variants. These odds ratios were particularly elevated when LDL-C levels were higher. However, APOB variants in the sequence encoding the LDL receptor-binding domain of apolipoprotein B100 (apoB) can lead to a form of FH called familial defective apoB, which typically presents with a less severe phenotype than when variants occur in the LDLR gene. Therefore, the detection of pathogenic variants may assist in ASCVD risk-stratification and support the need for intensified treatment. The role of polygenic risk scores in ASCVD risk-stratification for FH is still unclear and requires further investigation. While polygenic risk scores for coronary artery disease are likely to provide more value than risk scores for hypercholesterolemia, this approach has not yet been widely adopted in clinical practice (Fahed et al., 2020; Trinder et al., 2020).

2.2. **Conventional ASCVD Risk Factors and Lipoprotein(a)**

The primary contributors to ASCVD risk in familial hypercholesterolemia (FH) are the cumulative exposure to elevated LDL-C from birth and delays in the initiation of therapeutic interventions. In line with this, clinical signs of cholesterol deposition, such as tendon xanthomas, are associated with an increased risk of ASCVD, irrespective of the presence of an FH-causing genetic variant. Variability in ASCVD risk also arises from the presence of co-existing cardiometabolic risk factors and the complex interaction between environmental, pathogenic, or protective genetic factors, beyond the FH-causing variants themselves. Conventional risk factors continue to serve as significant predictors of ASCVD, emphasizing the importance of a multifactorial approach to risk reduction in FH patients. Guidelines recommend considering asymptomatic individuals with FH who also have one additional major ASCVD risk factor as being at very high risk of ASCVD. The International Atherosclerosis Society has proposed a definition of "severe FH," which includes factors such as age, male sex, smoking, diabetes, hypertension, low high-density lipoprotein cholesterol (HDL-C), a family history of early ASCVD, chronic kidney disease, obesity, and elevated lipoprotein(a) [Lp(a)] levels. Lp(a) is a genetically determined LDL-like particle bound to apolipoprotein(a), and it is a recognized causal risk factor for ASCVD and aortic valve stenosis. In individuals with FH, elevated Lp(a) levels are commonly observed and remain a risk factor for ASCVD, independent of the specific LDLR gene variant. The measurement of Lp(a) should be incorporated into routine clinical evaluation, as it refines ASCVD risk-stratification, enhances the value of cascade screening, and because elevated Lp(a) levels can mimic the phenotype of FH. The potential role of other biomarkers, including those related to inflammation, oxidative stress, coagulation, blood group, and proteomics, for ASCVD risk-stratification in FH, requires further investigation (Bos et al., 2017).

2.3. **ASCVD Risk Equations**

Current ASCVD risk equations used in the general population have not been validated for FH, as they do not account for lifelong exposure to elevated LDL-C, leading to an underestimation of risk. FH-specific equations for calculating absolute ASCVD risk have been developed to assist with shared decision-making. The Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART) registry demonstrated that factors such as age, male sex, previous ASCVD, hypertension, obesity, smoking, LDL-C, and Lp(a) were significant predictors of ASCVD in

2404 adults with genetically-defined FH after an average follow-up of 5.5 years. The SAFEHEART risk equation (SAFEHEART-RE) was developed and showed high discriminatory power in predicting both first and recurrent ASCVD events. Interestingly, the presence of diabetes mellitus was not identified as a predictor of ASCVD in the SAFEHEART study, which may be due to its low prevalence (approximately 4%), although obesity and hypertension were consistently identified as predictive factors in this algorithm, which applied exclusively to genetically defined FH patients. Furthermore, the Montreal-FH-SCORE, derived from retrospective data in a French-Canadian cohort of 670 FH patients with an LDLR gene variant, indicated that age, male sex, HDL-C, hypertension, and smoking were independent predictors of ASCVD, regardless of LDL-C levels. More recently, the FH-Risk-Score was developed to estimate the 10-year risk of ASCVD in a multinational cohort of 3881 adults with HeFH who did not have clinical ASCVD. This score, incorporating factors such as male sex, age, HDL-C, LDL-C, hypertension, smoking, and Lp(a), was suggested to be a stronger predictor than the SAFEHEART-RE and could be used in FH patients even when the causative FH variant is not identified or when molecular diagnosis is unavailable (Paquette et al., 2021). However, the SAFEHEART-RE was derived solely from individuals with a monogenic cause of FH. These risk equations still require further validation across different FH populations. Additionally, equations derived from patient data in large electronic records, which may better reflect real-world conditions and incorporate artificial intelligence methods, have been developed. However, these populations were not genetically defined, and the resulting algorithms, with C-statistics below 0.8, may not be directly applicable to individuals with a confirmed diagnosis of FH. Future studies on the application of deep learning techniques, such as artificial neural networks, to enhance the prediction of ASCVD events in FH beyond conventional statistical methods are needed. It is important to note that patients with HoFH, due to their extremely elevated LDL-C levels and ASCVD risk from childhood, are considered to be at very high risk a priori, and the use of risk equations is not indicated in this population.

2.4. **Imaging of Atherosclerosis**

Non-invasive imaging of subclinical atherosclerosis has the potential to become a highly valuable clinical tool for assessing ASCVD risk in FH, as it provides insight into an individual's lifetime exposure to both risk and resilience factors. Imaging techniques could aid in personalized risk assessment, support shared decision-making, optimize the use of preventive therapies, and improve adherence to treatment protocols. As statins are recommended for all adults with FH, the utility of imaging in asymptomatic patients lies in its ability to identify those who may require more intensive lipid-lowering therapy, some of which may be costly and reserved for the highest-risk individuals. In FH patients without additional ASCVD risk factors, detecting atherosclerosis can reclassify their risk from high to very high. Carotid ultrasonography is one imaging technique that can be employed to detect atherosclerosis, while in children with FH, measurement of carotid intima-media thickness can help determine the appropriate treatment intensity. Notably, early initiation of statin therapy in children with FH has been shown to reduce the progression of carotid intima-media thickness and prevent ASCVD events. For patients with HoFH, echocardiographic evaluation for supravalvular or valvular aortic stenosis at diagnosis and annually thereafter is essential, as these areas are especially susceptible to atherosclerosis (Bélanger et al., 2022).
Coronary imaging can provide valuable insight into the natural progression of atherosclerosis and the effects of lipid-lowering therapies. Cardiac computed tomography (CT) has emerged as a non-invasive method for detecting and quantifying coronary atherosclerosis, as well as for ASCVD risk-stratification. In adults with FH who are receiving statins, the coronary artery calcium (CAC) score shows significant variability; for example, a meta-analysis of 1176 asymptomatic middle-aged adults with HeFH found that 45% had a CAC score of zero. The CAC score is independently associated with ASCVD events and provides incremental

prognostic information when added to the SAFEHEART-RE, with one study showing that it could reclassify risk in nearly half of the individuals. The CAC score has been found to provide superior discrimination compared to conventional risk factors and Lp(a) in predicting ASCVD. For HeFH patients on statin therapy, a CAC score of zero may indicate a very low risk of ASCVD events. However, the clinical application of CAC scoring in HeFH patients to tailor therapy requires further research. In individuals with suspected FH, imaging findings such as the CAC score may help identify those most likely to have a monogenic form of FH, potentially guiding the targeted use of genetic testing (Clarke et al., 2013). Coronary computed tomography angiography (CCTA) can be used to detect and quantify both calcified and non-calcified coronary plaques. In a recent study of asymptomatic individuals from the general population, subclinical obstructive coronary atherosclerosis was found to be associated with an over eight-fold increased risk of myocardial infarction. In asymptomatic individuals with FH, the presence of atherosclerosis detected via CCTA is highly prevalent and is independently associated with increased ASCVD risk (Pérez de Isla et al., 2021; Tada et al., 2015). The identification of more advanced atherosclerotic disease on CCTA has been linked to intensification of therapy and a reduction in estimated risk. A recent study of CCTA in FH patients without clinical ASCVD showed that adding alirocumab to high-intensity statin therapy resulted in significant regression and stabilization of coronary plaque, indicating the potential value of imaging for assessing treatment responses in clinical practice. CCTA can also differentiate between coronary ostial stenosis and aortic stenosis in children with HoFH and should be considered at least once, even in asymptomatic individuals. Myocardial perfusion imaging for inducible ischemia is another tool that can be used to guide overall management. While the clinical value of cardiac imaging for identifying subclinical atherosclerosis in FH is promising, further studies are needed to fully establish its role.

3. Current treatments

3.1. Lifestyle modification

Guidelines for the prevention of atherosclerotic cardiovascular disease (ASCVD) emphasize the importance of modifications to diet, smoking habits, physical activity, weight management, alcohol consumption, and psychological stress, all of which are also applicable to familial hypercholesterolemia (FH). The management of comorbidities such as diabetes, hypertension, obesity, and ASCVD should adhere to disease-specific guidelines. For FH, a cardioprotective diet is recommended, one that is low in saturated fats and cholesterol, while favoring unsaturated fats, particularly within the context of the Mediterranean-style or DASH (Dietary Approaches to Stop Hypertension) diets. Additionally, supplementation with plant sterols or stanols may play a role in lowering LDL cholesterol (LDL-C) levels in FH patients. Referral to dietitians for personalized advice is also recommended. Registry data suggest that individuals with FH may adopt healthier lifestyle habits compared to their unaffected relatives when provided with proper education. Importantly, the adoption of healthier lifestyle behaviors is associated with a reduction in ASCVD risk in individuals with high genetic risk for the condition (Gidding, 2019). Lifestyle modifications are considered a critical component of treatment for all FH patients, including those under 8 years of age, pregnant women, and individuals with heterozygous FH (HeFH) who are unable to tolerate pharmacologic therapies.

3.2. Statins and ezetimibe

Statins, or 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors, are the cornerstone of therapy for reducing the cumulative burden of elevated LDL-C and preventing ASCVD, supported by extensive clinical trial evidence. In individuals with HeFH, high-intensity statins can lower LDL-C by more than 50%, and these should be prescribed to all FH patients at the maximum tolerated dose in conjunction with lifestyle modifications. Statins are also the foundational treatment for patients with homozygous FH (HoFH). Statin therapy

should be initiated as soon as possible following the diagnosis of HoFH, as well as in HeFH adults and children aged 8–10 years and older, based on shared decision-making. Large cohort and registry studies have shown that statin use is associated with significant reductions in both ASCVD events and mortality in FH patients. However, statins alone are frequently insufficient to achieve the desired LDL-C targets. Additional therapies may be required to adequately lower LDL-C levels in patients with HeFH and HoFH. Nonetheless, factors such as statin intolerance, non-adherence, and treatment inertia may lead to suboptimal dosing, thereby hindering the achievement of target LDL-C levels. Statin intolerance remains a significant issue in FH management and should be addressed according to established guidelines (Cheeley et al., 2022).

3.3. Bile Acid Sequestrants

Bile acid sequestrants lower LDL-C moderately by binding bile acids in the intestine, disrupting their enterohepatic circulation. This action depletes intra-hepatic cholesterol levels and enhances LDL receptor activity. Post-hoc analysis has demonstrated that cholestyramine, in combination with a dietary regimen, can reduce the progression of coronary atherosclerosis in FH. However, the use of bile acid sequestrants is limited due to their gastrointestinal side effects and their impact on the absorption of fat-soluble vitamins and other medications (Huijgen et al., 2010).

3.4. ATP Citrate Lyase Inhibitors

Bempedoic acid is an ATP citrate lyase inhibitor, acting upstream of HMG-CoA reductase, the enzyme targeted by statins, to reduce hepatic cholesterol synthesis. Administered orally once daily, bempedoic acid is also available in combination with ezetimibe. Approved for use in the US and Europe in 2020, bempedoic acid has shown in phase III trials involving individuals with ASCVD or HeFH on maximally tolerated statins that it reduces LDL-C by 15–20% after 12 weeks of treatment, although it increases the risk of gout. Data from an open-label extension study demonstrated sustained efficacy with up to 2.5 years of treatment, with a safety profile similar to that observed in the initial trials. A recent ASCVD outcome trial involving more than 14,000 individuals with statin intolerance and ASCVD or ASCVD risk factors indicated that bempedoic acid led to an approximate 0.8 mmol/L (30 mg/dL) reduction in LDL-C. This resulted in a 13% reduction in the risk of primary major adverse cardiovascular events over a median follow-up period of nearly 3.5 years (Nissen et al., 2023). Thus, bempedoic acid may offer benefits to patients with FH and statin intolerance. However, its role in treating HoFH remains unclear, with the possibility that those with residual LDL receptor activity may respond to this therapy.

3.5. Therapies Targeting PCSK9

PCSK9, a proprotein convertase subtilisin/kexin type 9, binds to LDL receptors on hepatocytes, leading to their lysosomal degradation. Inhibition of PCSK9 upregulates LDL receptor activity, thereby reducing LDL-C levels. This mechanism is supported by the observation that carriers of loss-of-function variants in the PCSK9 gene exhibit low LDL-C levels and reduced ASCVD risk. Monoclonal antibodies targeting PCSK9, such as alirocumab and evolocumab, are administered subcutaneously every two to four weeks and have been shown to reduce LDL-C by 50–60% on top of statin therapy. These agents also lower lipoprotein (a) by 20–30% and have demonstrated efficacy in reducing ASCVD events in secondary prevention. Phase III clinical trials have confirmed the efficacy of these antibodies in individuals with HeFH receiving lipid-lowering therapy. The response to therapy appears to be similar across various HeFH mutations, with many patients achieving LDL-C goals and reducing the need for lipoprotein apheresis. In HoFH, alirocumab and evolocumab have been shown to lower LDL-C by 20–35%, though efficacy varies depending on residual LDL receptor activity. These monoclonal antibodies have proven long-term durability and safety, with injection site

reactions being the primary adverse effect (Hovingh et al., 2017; Santos et al., 2020). As a result, they are recommended as third-line therapy in FH, following statin and ezetimibe.

Inclisiran, a triantennary N-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA), targets PCSK9 synthesis by binding to its messenger RNA and inhibiting translation. Due to its prolonged action, inclisiran is administered subcutaneously on days one and 90, with subsequent doses every six months, offering convenience to patients. In individuals with HeFH, a phase III clinical trial demonstrated that inclisiran reduced LDL-C by approximately 40–50%, with 65% of patients achieving LDL-C levels <2.6 mmol/L (100 mg/dL). A meta-analysis showed no significant difference in efficacy between inclisiran and monoclonal antibodies targeting PCSK9 in lowering LDL-C in HeFH, with similar results across genotypes. Inclisiran has also been studied in individuals with ASCVD, showing the ability to lower lipoprotein (a). Adverse effects associated with inclisiran are similar to those of placebo, except for injection-site reactions and nasopharyngitis, with favorable safety observed over five years of follow-up. A proof-of-concept open-label study in HoFH involving four individuals receiving maximally tolerated statin and ezetimibe demonstrated that inclisiran was safe, though LDL-C response was variable (Hovingh et al., 2020). A phase III clinical trial for HoFH is ongoing (NCT03851705), as well as ASCVD outcome (NCT03705234 and NCT05030428) and longer-term follow-up studies (NCT03814187).

3.6. Lomitapide

Lomitapide, a small molecule inhibitor of microsomal triglyceride transfer protein (MTP), is approved for the treatment of HoFH, where the LDL receptor is either drastically reduced or absent. MTP plays a crucial role in the assembly of very low-density lipoprotein (VLDL) by transferring triglycerides onto apoB. Inhibiting MTP disrupts the secretion of VLDL and decreases circulating levels of apoB-containing lipoproteins. As MTP is also required for chylomicron assembly and secretion in the intestine, lomitapide can cause steatorrhea and deficiencies in fat-soluble vitamins. Consequently, low-fat diets and supplementation of fat-soluble vitamins are recommended to mitigate gastrointestinal side effects and prevent vitamin deficiency (Cuchel et al., 2007).

In a phase III clinical trial involving 29 individuals with HoFH, lomitapide reduced LDL-C by 50% after 26 weeks and by 38% at week 56, with a median oral dose of 40 mg daily. However, lomitapide's use is limited by tolerability issues, including nausea and diarrhea, which are the most common reasons for discontinuation. Furthermore, the drug can increase hepatic fat and transaminase levels, limiting its prescribing. Data from the phase III study, extension phase clinical trial, the Lomitapide Observational Worldwide Evaluation Registry (LOWER), and real-world evidence from Italy suggest that lomitapide does not result in clinically significant elevations in hepatic biomarkers or other new safety concerns over up to nine years of follow-up. A more patient-centric approach to dosing, including reductions as needed to address safety and tolerability issues, along with diet modification, has been shown to effectively lower LDL-C. In a retrospective study across nine European countries, a median daily dose of 20 mg led to a 60% reduction in LDL-C, with more than one-third of patients discontinuing lipoprotein apheresis. Initiating lomitapide treatment at age 18 in HoFH is estimated to increase life expectancy by 11.2 years and delay the time to the first ASCVD event by 5.7 years (Leipold et al., 2017).

3.7. Evinacumab

Angiopoietin-like 3 (ANGPTL3) is a liver-derived protein that plays a crucial role in regulating lipoprotein metabolism by inhibiting lipoprotein lipase and endothelial lipase. Genetic deficiency of ANGPTL3, such as in familial combined hypolipidaemia, has been associated with a lower risk of atherosclerotic cardiovascular disease (ASCVD). As a result, ANGPTL3 has become an important target for therapeutic interventions. Evinacumab is a fully human

monoclonal antibody that inhibits ANGPTL3 and has been approved for use in patients with homozygous familial hypercholesterolemia (HoFH) aged 12 years and older. Its mechanism of action does not alter the expression, binding, or activity of the LDL receptor in individuals with HoFH, as evidenced by lymphocyte analysis of participants in a phase II clinical trial (Gaudet et al., 2017).

In a phase III clinical trial involving 65 individuals with HoFH, evinacumab, administered as a one-hour intravenous infusion every four weeks, resulted in a ~50% reduction in LDL cholesterol (LDL-C) after 24 weeks, with no significant differences in adverse effects compared to placeb. Notable reductions in LDL-C were observed in individuals with HoFH, including those with null/null variants, and the effect was consistent across various background lipid-lowering therapies. The long-term safety of evinacumab is currently under evaluation in an open-label extension of the trial (NCT03409744); however, real-world data support the long-term efficacy and safety of evinacumab in HoFH patients. While evinacumab has proven to be a promising addition to the treatment options for HoFH, concerns related to its cost, access, and overall impact remain unresolved. Although it is not approved for use in heterozygous familial hypercholesterolemia (HeFH), evinacumab has also been investigated in this patient population. In a phase II clinical trial, 272 individuals with refractory hypercholesterolemia (including those with HeFH) were treated with subcutaneous evinacumab (300 or 450 mg weekly, or 300 mg every two weeks), intravenous evinacumab (5 or 15 mg/kg every four weeks), or placebo. The greatest reductions in LDL-C at 16 weeks were observed with weekly subcutaneous doses, as well as with the intravenous administration of 15 mg/kg every four weeks, with reductions greater than 50% compared to placebo. These results suggest that subcutaneous administration of evinacumab may be more feasible and preferred by HeFH patients compared to intravenous dosing. Further studies with larger sample sizes in both HeFH and HoFH populations are necessary to better understand the long-term efficacy, safety, cost-effectiveness, and outcomes related to ASCVD.

3.8. Apheresis

Lipoprotein apheresis is often required for patients with HoFH or severe HeFH who cannot achieve their LDL-C targets with available therapies or who lack access to the most potent lipid-lowering agents. This extracorporeal procedure involves circulating blood outside the body through an adsorber column that selectively removes apoB-containing lipoproteins. Although lipoprotein apheresis is the preferred method due to its specificity for lipoproteins, plasma exchange should be considered when alternative treatments are unavailable. Apheresis is typically performed on a weekly or biweekly basis, requiring sufficient vascular access and appropriately trained personnel. Limitations include the procedure’s availability, cost, and the inconvenience for patients. Although no randomized controlled trials have assessed the efficacy of lipoprotein apheresis, several retrospective studies have demonstrated its effectiveness in reducing LDL-C levels and mitigating ASCVD risk. An analysis from the UK Lipoprotein Apheresis Registry, which included 129 HoFH patients undergoing apheresis, revealed a mean 43% reduction in LDL-C immediately after each session compared to pre-procedure levels. Furthermore, a review of five studies involving HoFH patients undergoing long-term apheresis (up to five years) reported LDL-C reductions between 22% and 36%. In a systematic review of 76 studies involving 209 pediatric HoFH patients, apheresis was associated with mean LDL-C reductions of up to 71% following a session, and xanthomas resolved in 83% of cases. The UK Lipoprotein Apheresis Registry also indicated a 65% reduction in ASCVD events in the two-year period following the initiation of apheresis compared to the two years prior. Another benefit of lipoprotein apheresis is its ability to lower lipoprotein(a) [Lp(a)], potentially further reducing ASCVD risk (Drouin-Chartier et al., 2016).

3.9. Liver Transplantation

Liver transplantation is considered the definitive treatment for HoFH, although it has been performed in a limited number of rare cases. A recent review documented 44 cases of liver transplantation in HoFH patients since the first reported case in 1984, noting that LDL-C levels decreased by up to 80% following the transplant. In a study of pediatric HoFH patients who underwent liver transplants, four children aged between 3 and 17 years were followed for four to six years after surgery. During this period, coronary artery disease regressed in two of the patients who initially had >50% stenosis. However, in two patients, aortic valve stenosis continued to progress, supporting the hypothesis that once calcific aortic valve disease develops, it does not regress even with LDL-C reduction. The risks and complications associated with liver transplantation, the need for long-term immunosuppressive therapy, and the associated costs and limited access make this treatment option highly rare. A recent review of nine HoFH patients who underwent liver transplantation, with 22 years of follow-up, highlighted the significant challenges involved. Three of the patients died due to surgical complications, and one was awaiting a third transplant due to graft failure at the time of the review (Al Dubayee et al., 2022).

4. Special Groups

4.1. Care of Children

Early diagnosis and the initiation of LDL-C-lowering treatments in children with familial hypercholesterolemia (FH) have the most substantial impact on reducing the risk of atherosclerotic cardiovascular disease (ASCVD) over their lifetime, potentially extending life expectancy by several decades. Screening programs and detection protocols have proven to be a cost-effective strategy for the early identification of FH in children. Early identification is particularly crucial for children with homozygous FH (HoFH), especially in populations where the condition is prevalent due to gene founder effects or consanguinity. Once diagnosed, guidelines recommend aiming for an LDL-C level of < 3.5 mmol/L (130 mg/dL) or a 50% reduction in LDL-C in children aged 10 years and older. For children with heterozygous FH (HeFH), statins should be considered from ages 8–10, following heart-healthy lifestyle modifications. Extensive research has reaffirmed the safety and efficacy of statins in reducing ASCVD events and mortality in genetically confirmed FH cases, with 20 years of observational follow-up supporting these findings. Ezetimibe and bile acid sequestrants have also been reported to effectively lower LDL-C in children with FH, both as monotherapies and as adjunct therapies. Additionally, monoclonal antibodies targeting PCSK9 are now approved for use in children with FH aged 10 years and older, with recent studies confirming their safety and efficacy in children and adolescents receiving lipid-lowering therapy. Management of children with FH should be multidisciplinary, emphasizing shared decision-making in a developmentally appropriate and comprehensive manner. Addressing barriers to treatment and ensuring proper transition to adult care via specialized clinics is highly recommended (Horton et al., 2022; Langslet et al., 2021).

For children with HoFH, management should occur in specialized centers, with imaging assessments of the coronary arteries, aorta, and aortic valve. Lipid-lowering therapy should commence as soon as HoFH is diagnosed in children. However, achieving adequate LDL-C reduction in HoFH remains challenging, particularly for individuals with LDL receptor-negative (null/null) variants, who have little to no functional LDL receptors and therefore exhibit poor responses to therapies aimed at increasing LDL receptor activity. Lipoprotein apheresis, which is recommended as early as age 5, is a key treatment for children with HoFH, as it is safe, effectively lowers LDL-C, and may reduce ASCVD events. The addition of monoclonal antibodies targeting PCSK9 is also supported by clinical trials, though long-term data are still required. Lomitapide may be considered as adjunctive therapy, with one study

demonstrating its safety and tolerability in children with HoFH, and phase III clinical trials indicating positive outcomes, though full results are pending (NCT04681170). A recent phase III clinical trial of evinacumab in children with HoFH has been completed (NCT04233918), with results pending. Evinacumab has recently received FDA approval for use in children aged 5 and older with HoFH. Compassionate use of novel therapies should be evaluated on a case-by-case basis. Since there is no one-size-fits-all treatment for HoFH, an individualized approach that incorporates a combination of lipid-lowering therapies, factoring in tolerability, cost, and access, is essential.

4.2. Care of Women During Pregnancy

Guidelines continue to advise against the use of statins in women who are planning to become pregnant, as well as during pregnancy or breastfeeding, due to the risks of teratogenesis and the toxic effects of statins. Statins should be discontinued at least three months prior to conception, but prolonged cessation may increase the risk of ASCVD due to elevated LDL-C levels. The loss of LDL-C life-years should be considered; for instance, the median duration of statin discontinuation during pregnancy and breastfeeding in women with FH has been estimated to be 2.3 years. While bile acid sequestrants are considered safe during pregnancy, their efficacy is modest, and they are often poorly tolerated. Additionally, these drugs may impair the absorption of fat-soluble vitamins, particularly vitamin K. Ezetimibe lacks established safety data for use during pregnancy, and monoclonal antibodies targeting PCSK9 or ANGPTL3 are contraindicated during this period. Therefore, women of childbearing age with FH should receive individualized pre-pregnancy counseling and contraception advice while on cholesterol-lowering therapies. The thrombotic risks associated with contraceptives, especially those containing high doses of estrogen, should be considered, as these are generally contraindicated for women with HoFH for this reason (Roos-Hesselink et al., 2015).

While myocardial infarction is uncommon in women of reproductive age, pregnancy is associated with a three- to four-fold increased risk of myocardial infarction in the general population. Moreover, LDL-C levels increase by approximately 30% during pregnancy, further elevating ASCVD risk. Therefore, a tailored approach to managing FH during pregnancy should account for the severity of hypercholesterolemia, the presence of ASCVD, and the risks and benefits of cholesterol-lowering treatments. Imaging for atherosclerosis may be useful in this context. Lipoprotein apheresis can be safely performed during pregnancy and should be considered for women with HoFH or severe HeFH, particularly when ASCVD risk is elevated. The recommendations against statin use during pregnancy have recently been reevaluated, with the U.S. FDA requesting the removal of the “Pregnancy Category X” label for statins, as evidence of congenital anomalies has not been confirmed in cohort studies. Statin use in pregnant women with HoFH or severe HeFH may be justified if apheresis is unavailable, as recent reports suggest that statins may be safe after the first trimester of pregnancy in HoFH cases. Data from prospective cohort registries indicate favorable pregnancy outcomes for women with FH, as these women do not appear to have an increased risk of preterm delivery, low birth weight infants, or congenital malformations (Toleikyte et al., 2011). A multidisciplinary approach involving lipidologists, obstetricians, and cardiologists is recommended for managing FH during pregnancy.

5. Emerging Therapies

5.1. RNA Therapies Targeting ANGPTL3

Evinacumab has demonstrated both efficacy and a favorable safety profile, establishing ANGPTL3 as a promising therapeutic target for individuals with familial hypercholesterolemia (FH). In addition to monoclonal antibody approaches, there are RNA-targeted therapies currently under development aimed at inhibiting ANGPTL3 synthesis, though the long-term safety and efficacy of these therapies remain to be fully established. Vupanorsen, an antisense oligonucleotide directed at ANGPTL3, showed significant reductions in non-HDL cholesterol

(non-HDL-C) and triglyceride levels in a dose-ranging study involving statin-treated individuals. However, the effect on LDL cholesterol (LDL-C) was modest, and there were safety concerns, particularly dose-dependent increases in hepatic fat and hepatic enzymes, leading to the discontinuation of its development. On the other hand, ARO-ANG3, a GalNAc-conjugated small interfering RNA (siRNA), inhibits the translation of ANGPTL3 protein from messenger RNA. In a dose-ranging study with healthy volunteers, administering ARO-ANG3 on day 1 and day 29 resulted in a 45–54% reduction in LDL-C levels within four to six weeks following the second dose. Preliminary results from a study of ARO-ANG3 in 17 individuals with heterozygous FH (HeFH) on statin therapy demonstrated a reduction in LDL-C by 23–37% after two subcutaneous doses administered 28 days apart (Watts et al., 2020). An open-label phase II study of ARO-ANG3 in individuals with homozygous FH (HoFH) is currently underway (NCT05217667).

5.2. Oral PCSK9 Inhibitors

Although injectable PCSK9 monoclonal antibodies and siRNA therapies targeting PCSK9 have proven effective in lowering LDL-C, their use is often limited by patient reluctance to undergo injections, cost concerns, and accessibility. MK-0616, a once-daily oral PCSK9 inhibitor, demonstrated a reduction of LDL-C by more than 60% in a recent phase II trial. Additionally, an oral antisense oligonucleotide targeting PCSK9 was found to have sufficient bioavailability in animal models, with a once-daily dosing regimen (Gennemark et al., 2021).

5.3. CETP Inhibitors

Cholesteryl ester transfer protein (CETP) inhibition was initially proposed as a potential therapy for reducing atherosclerotic cardiovascular disease (ASCVD) risk by increasing high-density lipoprotein cholesterol (HDL-C) levels. Early CETP inhibitors led to a substantial increase in HDL-C, up to 130%, but their trials failed to demonstrate a reduction in ASCVD risk. Specifically, torcetrapib was associated with increased risk for both all-cause mortality and ASCVD events, and trials for dalcetrapib and evacetrapib were prematurely halted for futility. In contrast, anacetrapib demonstrated a 9% reduction in ASCVD events over a median follow-up of 4.1 years in a phase III trial, with an additional 20% reduction during an extended follow-up period (median 2.2 years). While further development of anacetrapib was not pursued, the study highlighted the variability among CETP inhibitors. Anacetrapib caused a greater reduction in LDL-C (17%) than the other CETP inhibitors, suggesting that the reduction in LDL-C may be the primary factor driving the observed reduction in ASCVD events, rather than changes in HDL-C levels. Notably, in individuals with HeFH receiving stable lipid-lowering therapy, anacetrapib reduced LDL-C by nearly 40% compared to placebo after one year of treatment. Obicetrapib is the only CETP inhibitor currently in development, and in a phase II clinical trial, it produced a 51% reduction in LDL-C after eight weeks. A phase III outcomes trial is currently in progress (NCT05202509).

5.4. Gene Transfer with Viral Vectors

Gene therapy, aimed at correcting the underlying molecular defect affecting LDL receptor activity and thus LDL-C metabolism in FH, holds promise for potentially reducing the severity of the disease and possibly providing a curative approach. Specifically, adeno-associated virus (AAV) vectors have been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of inherited retinal dystrophy and more recently for spinal muscular atrophy. The EMA has also approved AAV-based gene therapy for hemophilia A, with the therapy currently under review by the US FDA. Preclinical studies involving AAV8-mediated LDL receptor (LDLR) gene therapy in Ldlr knockout mice have demonstrated success in restoring LDL receptor activity in hepatocytes, thereby reducing LDL-C and leading to the regression of atherosclerotic lesions in the aorta. A phase I/II first-in-human clinical trial of AAV8-mediated hLDLR gene therapy in nine individuals with HoFH

was recently completed (NCT02651675), though the results are still pending. Preliminary reports from the trial indicated dose-dependent elevations in liver transaminases, which have been observed in other AAV-based gene therapy trials. These elevations are thought to result from a T-cell immune response to the vector capsid. In previous studies, this issue was successfully managed with steroid treatment, and the elevations were mitigated by initiating a prophylactic steroid regimen prior to the administration of the vector (Tromp & Cuchel, 2022).

5.5. CRISPR Gene Editing

CRISPR (clustered regularly interspersed short palindromic repeats) technology, a precise method of gene editing, has gained attention for its potential in correcting genetic disorders. In recent years, CRISPR-based genome editing has demonstrated early clinical success across various conditions. A phase I human trial targeting the transthyretin (TTR) gene, responsible for amyloid transthyretin cardiomyopathy (ATTR), a hereditary form of cardiomyopathy, reported excellent safety and tolerability, achieving a 90% reduction in circulating TTR levels. Furthermore, CRISPR technology has proven successful in the treatment of sickle cell disease and beta-thalassemia. In the context of lipid-lowering, CRISPR-based approaches are being explored to target multiple cholesterol metabolism pathways, including genes such as PCSK9, ANGPTL3, LPA, and APOC3. A CRISPR base editor targeting PCSK9, delivered via lipid nanoparticles (LNPs), demonstrated significant efficacy in non-human primates, achieving a 90% reduction in PCSK9 enzyme levels and a 60% reduction in LDL-C, with effects sustained for up to eight months post-treatment. A phase I first-in-human trial of this CRISPR base editor for individuals with heterozygous familial hypercholesterolemia (HeFH) and atherosclerotic cardiovascular disease (ASCVD) has been initiated, with the first participant recently treated in New Zealand (NCT05398029). Additionally, a CRISPR base editor targeting ANGPTL3, developed with a GalNAc targeting ligand to bypass the LDL receptor, has shown promise in non-human primates with homozygous familial hypercholesterolemia (HoFH), demonstrating nearly 90% reduction in circulating ANGPTL3 levels. While these early results are promising, further clinical evaluation is necessary to determine their efficacy in humans.

5.6. Vaccines

Vaccines targeting key proteins involved in cholesterol metabolism are currently undergoing pre-clinical and early clinical trials. The goal of these vaccines is to induce the body's immune response to produce antibodies against the target proteins, thereby offering a longer-lasting effect compared to monoclonal antibody therapies and reducing the need for frequent dosing. One vaccine candidate targeting PCSK9, AT04A, has been tested in a phase I placebo-controlled trial with 72 healthy participants. Following three injections over 90 weeks, this candidate resulted in a 7.2% mean reduction in LDL-C levels. Another vaccine targeting ANGPTL3 is currently in pre-clinical development and has shown promise in reducing atherosclerosis in a mouse model of severe FH.

6. Implementation Practice

Implementation science plays a crucial role in improving the management of familial hypercholesterolemia (FH) by designing and applying evidence-based strategies. The International Atherosclerosis Society has recently provided guidance on the implementation of care for FH. Risk stratification methods can be utilized to integrate various services that support FH management, including cardiology, apheresis, and treatment for diabetes and hypertension. The use of digital technologies to apply risk prediction algorithms and imaging data can help develop personalized treatment plans for patients. These plans must be communicated in a manner that considers socio-cultural, psychological, and health literacy challenges. Medication adherence remains a significant issue in FH treatment, and overcoming barriers at the patient, clinician, and healthcare system levels is essential. Numerous interventions aimed at improving medication adherence have been identified. Additionally, conducting regular audits based on reliable registry data can help enhance service delivery. Registries are particularly valuable in

evaluating the outcomes of treatments such as lipoprotein apheresis and liver transplantation. Lipoprotein apheresis should be performed in specialized units with adequately trained staff, and it is important that only those patients who are physically and psychologically suitable undergo the procedure. Existing healthcare infrastructure, such as dialysis and transfusion medicine facilities, should be leveraged to improve the effectiveness and quality of apheresis services. Clinics specializing in FH should collaborate within a network to share knowledge, training, and clinical expertise. Ultimately, service outcomes should guide the development of sustainable financing models. The management of FH will benefit significantly from the active involvement of patient advocacy and peer-support groups within both the healthcare system and the community.

7. Conclusion

Substantial evidence from classical epidemiology, Mendelian randomization studies, clinical trials focused on cholesterol-lowering in primary prevention, and experimental research supports the effectiveness of significant LDL-C reduction through medications and lifestyle interventions in patients with familial hypercholesterolemia (FH). The primary aim is to reduce the cumulative burden of LDL-C and the associated risk of atherosclerosis. Therapeutic targets for LDL-C are grounded in extensive evidence and are reflected in current international guidelines. However, despite the availability of potent statins and ezetimibe, most patients are unable to achieve very low LDL-C goals, even with maximally tolerated doses, necessitating alternative treatments targeting PCSK9 or ANGPTL3. Treatment inertia at the patient, clinician, and healthcare system levels remains a significant barrier that must be addressed, with shared decision-making being a core component of all treatment recommendations. The management of homozygous familial hypercholesterolemia (HoFH) is considerably more challenging than that of heterozygous familial hypercholesterolemia (HeFH). Recent advancements in therapies targeting the LDL receptor, as well as those that can lower LDL-C through mechanisms independent of the LDL receptor, have led to treatment strategies that enable more patients with HoFH to approach recommended treatment targets. These therapies are most effective when combined with lipoprotein apheresis, although they have also reduced the need for apheresis in many patients. Emerging therapies for HoFH, including liver-directed gene transfer of the LDL receptor and CRISPR-based editing of PCSK9 and ANGPTL3, hold promise but require further clinical trials to establish their efficacy. In cases of severe HoFH with progressive atherosclerosis at a young age, liver transplantation remains a last-resort treatment. Risk stratification methods, particularly cardiovascular imaging, are essential in guiding the use of interventional therapies for FH. To improve clinical outcomes for all patients with FH, cost-minimization strategies and enhanced access to novel therapies are necessary. However, access to accurate diagnosis and emerging therapies remains a significant issue, which may be influenced by the higher prevalence of FH in founder populations or disparities in healthcare resources across countries. Effective management of FH requires an integrated healthcare system approach that utilizes both established and novel implementation strategies, along with their ongoing evaluation. Implementation science, encompassing both practice and research, is essential for addressing global challenges in the management of patients and families affected by FH.

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