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New algorithms for treating homozygous familial hypercholesterolemia

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Purpose of review
We reviewed current and future therapeutic options for patients with homozygous familial hypercholesterolemia (HoFH) and place this evidence in context of an adaptable treatment algorithm.

Recent findings
Lowering LDL-C levels to normal in patients with HoFH is challenging, but a combination of multiple lipid-lowering therapies (LLT) is key. Patients with (near) absence of LDL receptor expression are most severely affected and frequently require regular lipoprotein apheresis on top of combined pharmacologic LLT. Therapies acting independently of the LDL receptor pathway, such as lomitapide and evinacumab, are considered game changers for many patients with HoFH, and may reduce the need for lipoprotein apheresis in future. Liver transplantation is to be considered a treatment option of last resort. Headway is being made in gene therapy strategies, either aiming to permanently replace or knock out key lipid-related genes, with first translational steps into humans being made. Cardiovascular disease risk management beyond LDL-C, such as residual Lp(a) or inflammatory risk, should be evaluated and addressed accordingly in HoFH.

Summary
Hypercholesterolemia is notoriously difficult to control in most patients with HoFH, but multi-LLT, including newer drugs, allows reduction of LDL-C to levels unimaginable until a few years ago. Cost and availability of these new therapies are important future challenges to be addressed.

Keywords
cardiovascular disease, homozygous familial hypercholesterolemia, lipid-lowering therapy

INTRODUCTION

Among the many forms of dyslipidaemia, homozygous familial hypercholesterolemia (HoFH) is by far the condition associated with the most severe elevations of LDL cholesterol (LDL-C) levels and, consequently, risk of premature cardiovascular disease [1]. HoFH is a rare disease with an estimated prevalence of approximately 1 in 300 000 [2–4], although higher prevalence is found in regions with a founder effect. HoFH is caused by bi-allelic pathogenic variants in *LDLR* or other genes affecting the LDL receptor pathway (*APOB, PCSK9, LDLRAP1*) [2]. If left untreated, HoFH invariably leads to premature onset of atherosclerotic cardiovascular disease (ASCVD) and aortic stenosis and sometimes death before the patient reaches adulthood [5,6]. International guidelines recommend early diagnosis and intensive lipid-lowering treatment to improve cardiovascular outcomes in HoFH [2]. A recent publication from the HoFH International Clinical Collaborators (HICC) registry, which combined data on an unprecedented number of 751 patients with HoFH worldwide, provided solid data in support of this concept [7▪▪]. Specifically, patients who were treated with three or more and five or more LLT were observed to have an LDL-C reduction of more than 65 and 85%, respectively (Fig. 1), allowing some patients to reach LDL-C levels within the acceptable range. Unfortunately, only about four in 10 patients were treated with three or more LLT and this number was even lower if only patients from non-high-income countries were considered. Thus, even

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Curr Opin Lipidol 2022, 33:326–335

DOI:10.1097/MOL.0000000000000853

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KEY POINTS

- HoFH is an ultra-rare disease of extremely elevated LDL-cholesterol levels, causing severe cardiovascular disease and aortic valve stenosis as early as in childhood if left untreated.
- Early diagnosis and treatment with combination lipid-lowering therapy with at least three and frequently more treatments, including lipoprotein apheresis, is crucial to reach LDL-C target and prevent the cardiovascular consequences of HoFH.
- Disease severity and response to treatment varies considerably between patients, due at least in part to the degree of residual LDL receptor activity, necessitating a personalized approach to management of HoFH driven by LDL-C target levels.
- Novel therapies added to the lipid-lowering armamentarium provide hope for attaining acceptable LDL-C levels, but are currently limited by cost and availability.
- CVD risk factors beyond LDL-C, related amongst others to lifestyle, Lp(a) levels, metabolic or inflammatory risk, need to be evaluated and treated accordingly.

despite treatment, LDL-C levels frequently remain far from controlled and the clinical course can be characterized by recurrent cardiovascular events and interventions [7▪▪,8].

Recent years have seen significant advances concerning the treatment options available for patients with HoFH and, when given in combination, they are able to decrease LDL-C to levels unimaginable until a few years ago. Here, we aim to review current and emerging therapeutic approaches and to provide a treatment algorithm that can be adapted to the therapeutic needs of the patients as well as to the realities of different healthcare settings (Fig. 2).

EARLY DIAGNOSIS AND TREATMENT WITH COMBINATION LIPID-LOWERING THERAPY ARE CRITICAL

Clinically, HoFH is diagnosed by the presence of extremely elevated LDL-C levels (historically >13 mmol/l) in combination with the presence of cholesterol depositions under the skin (xanthomas) in childhood or the presence of heterozygous familial hypercholesterolemia in both parents [2]. A genetic diagnosis of HoFH is made when bi-allelic variants causing familial hypercholesterolemia are found, but considerable heterogeneity exists within the resulting phenotypic spectrum of HoFH [7▪▪,9], attributable in great part to residual activity of the LDL receptor [2]. Knowing the patient's genetic underpinning may have implications for treatment because therapies that upregulate the LDL receptor pathway (statins and PCSK9i) are poorly effective in patients carrying two *LDLR* null alleles. In addition, genetic screening may reveal variants in genes other than those causing familial hypercholesterolemia, such as *ABCG5* and *ABCG8* (causing sitosterolemia), *LIPA* (causing lysosomal acid lipase deficiency) or *CYP27A1* (causing cerebrotendinous xanthomatosis), which require a different therapeutic approach. It is important to realize that genetic analysis may not be available to all patients and absence of a genetic confirmation should not delay treatment.

Upon diagnosis, patients with HoFH should promptly be referred to a lipid specialist for treatment, preferably in an interdisciplinary care setting. Reverse cascade screening should be initiated, starting with both obligate heterozygous familial hypercholesterolemia parents. Patients and their families should receive counselling on familial hypercholesterolemia and its inheritance pattern, including informing parents of the 25% chance of a future child having HoFH. Clinicians should be aware of the potential psychological burden related to the treatment and consequences of HoFH, and consider psychosocial support tailored to patient-specific needs [10▪,11]. Such interventions are also an integral part of strategies to help maintain compliance to life-long needed therapies.

The recent report from the HICC registry highlighted that the combination of multiple therapies is key to approach LDL-C goals, which is important because the degree of LDL-reduction strongly determines survival in HoFH [7▪▪,12]. Unfortunately, most patients are still grossly undertreated and target levels are seldom attained especially in the less affluent parts of the world (Fig. 1) [7▪▪]. The following paragraphs discuss currently available and future LLT and the rationale for their use in HoFH.

LIPID-LOWERING THERAPIES

Statins and ezetimibe

High-intensity statins and ezetimibe are the cornerstone of LLT used by the majority of HoFH patients [7▪▪]. These drugs are readily available at low costs, are well tolerated and have been shown to reduce cardiovascular mortality in patients with HoFH [13]. Although statin efficacy may vary depending on the degree of residual LDLR activity, benefit is also seen in patients carrying *LDLR* null/null variants [14]. This may be explained by a possible normalization of increased production of ApoB-containing lipoproteins [15,16]. Red yeast rice, a herbal drug

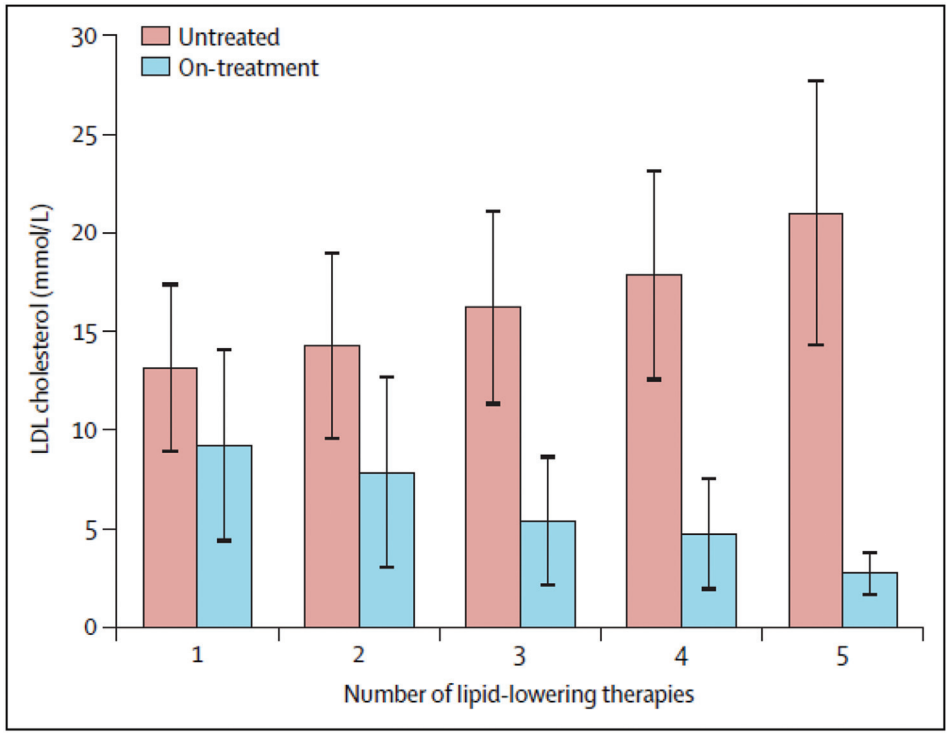

FIGURE 1. Combination lipid-lowering therapy in treating HoFH. Reprinted with permission from [7▪▪].

containing monacoline K (lovastatin, a low-intensity statin), is used instead of other statins by some patients with HoFH in China [17▪]; however, use of a high-intensity statin is preferred. Ezetimibe inhibits uptake of cholesterol in the intestine and has been shown to reduce LDL-C levels and cardiovascular events when given on top of a statin [18]. In patients with HoFH, the LDL-lowering response to ezetimibe is estimated to be nearly 10% [19].

These two medications combined are nearly always insufficient to adequately lower LDL-C levels and add-on treatments such as PCSK9 inhibitors, lomitapide, evinacumab and/or lipoprotein apheresis are needed and should be started with or shortly after statin and ezetimibe. The choice may depend on patient-specific effectiveness, tolerability, accessibility and cost of treatment.

PCSK9 inhibition

mAbs directed against PCSK9 are frequently used as first choice add-on LLT in patient with HoFH, because they are well tolerated and less costly compared with lomitapide or evinacumab. Their effectiveness has been established in multiple trials with average observed LDL-C reductions of around 25% [20–23,24▪]. However, this effect is variable and depends on residual LDLR expression [24▪,25]. Patients with *LDLR* null/null genotype are generally completely unresponsive to PCSK9 inhibitors [23]. Therefore, the effect on LDL-C levels should be carefully evaluated and PCSK9 inhibitors stopped if found to be ineffective. Inclisiran, an siRNA therapy aimed at blocking translation of *PCSK9* mRNA, showed LDL-C reductions comparable to PCSK9-inhibition using mAbs in four patients with HoFH, with the benefit of less frequent dosing [26]. Results of a subsequent phase III trial in HoFH are expected in the near future (NCT03851705).

Lomitapide

In contrast to other drugs that promote lipoprotein catabolism, lomitapide is an oral small molecule inhibitor of MTTP, an enzyme that facilitates the production of VLDL in the liver and chylomicrons in the intestine. By lowering production of its precursor VLDL, lomitapide thus lowers LDL independent of the LDL receptor pathway. However, given this mechanism of action, lomitapide increases liver fat so that patients have to be closely monitored for steatohepatitis [27▪▪]. Strict dose-titration combined with adherence to a fat-restricted diet is required to improve gastrointestinal tolerability and fat-soluble vitamins need to be supplemented. LDL-C reductions of about 50% were observed in a clinical trial at maximal tolerated dose [28], but recent real-world data have shown that lomitapide has a similar efficacy at lower doses with improved tolerability [27▪▪,29]. Limited evidence indicates that long-term

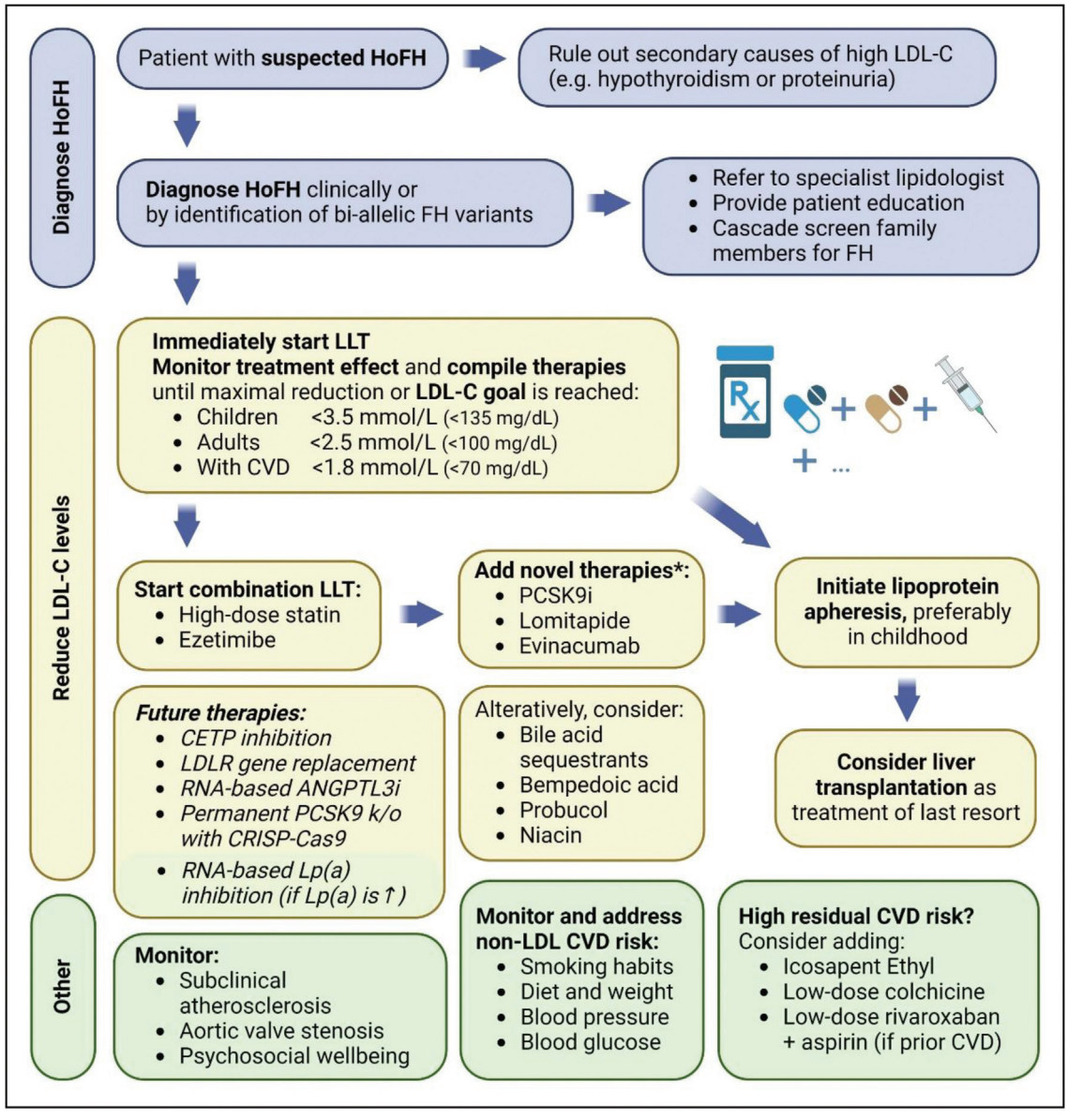

FIGURE 2. Treatment algorithm for HoFH. *Depending on cost, availability and patient's residual LDLR activity. ANGPTL3i, angiopoietin-like protein 3 inhibition; CETP, cholesterol ester transfer protein; CVD, cardiovascular disease; HoFH, homozygous familial hypercholesterolemia; k/o, knockout; LDL-C, LDL cholesterol; LDLR, LDL receptor; LLT, lipid lowering therapy; Lp(a), lipoprotein(a); PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibition.

LDL-C lowering with lomitapide results in stabilization and/or regression of the carotid intima-media thickness as a marker of ASCVD risk [30▪]. Given these results and the fact that lomitapide lowers LDL-C independently of the LDL receptor pathway, it may be considered as an alternative to lipoprotein apheresis and as a first-line treatment for HoFH in combination with statins and ezetimibe [31▪].

ANGPTL3 inhibition

Ever since loss of function variants in *ANGPTL3* were shown to be associated with a phenotype of combined hypolipidaemia [32], angiopoietin-like 3 (ANGPTL3) has been a promising candidate for lipid-lowering therapies. Although its precise role in affecting LDL-C levels is still uncertain, ANGPTL3 is a known inhibitor of lipoprotein lipase and endothelial lipase and inhibition of ANGPTL3 by mAbs, in turn, promotes catabolism of large VLDL particles and leads to faster clearance of their remnants by non LDLR-mediated pathways [33,34]. Evinacumab is a human mAb dosed at 15 mg/kg/iv monthly that is directed against ANGPTL3 that has been shown to lower LDL-C levels by approximately 50% on top of background LLT, irrespective of residual LDLR activity [35▪▪]. It is

the most recently approved therapy for the treatment of HoFH and, given the paucity of adverse events and its remarkable efficacy, can be considered a game changer for some patients who do not tolerate or have access to apheresis or lomitapide. Using computed tomography (CT) coronary angiography, it has been reported that intensive LDL-C lowering with evinacumab even led to soft plaque regression in the coronary arteries of two young HoFH patients [36▪]. An RNA-based therapy targeting ANGPTL3 mRNA in the liver is under investigation in a phase 2 trial in HoFH (NCT05217667) and, if effective, it may have the advantage of a less frequent dosing.

Lipoprotein apheresis

In the absence of other lipid-lowering therapies, lipoprotein apheresis (including nonselective plasma exchange) has for decades been a lifeline for patients with HoFH and it continues to have an important role in their management. Although it is invasive, time-consuming and has been associated with reduced quality of life [11], lipoprotein apheresis remains a main-stay therapy when LDL-C levels remain elevated despite combination LLT, or when access of other effective drugs is limited by cost or availability. Furthermore, lipoprotein apheresis may be the best option for young children, for whom safety of some of the newer treatments has not yet been established [37▪,38]. There are various methods of lipoprotein apheresis (e.g. adsorption-based, filtration-based), which are roughly equally effective at clearing LDL-particles from the circulation [40▪]. Depending on the volume of blood or plasma filtered and on the treatment modality used, lipoprotein apheresis clears approximately 60% of LDL from the circulation per session [38]. Immediately following this, however, LDL-C levels rise again meaning that sessions need to be repeated at regular intervals, usually weekly or bi-weekly [41]. Equitable access to lipoprotein apheresis is ensured through reimbursement by national public healthcare systems in some countries, but remains limited in many others [42,43]. Although lipoprotein apheresis is expensive, its costs are lower than those of lomitapide and evinacumab [31▪,44]. Some data suggest that reduction in lipoprotein apheresis frequency following addition of a PCSK9 inhibitor treatment was accompanied with estimated overall cost-saving to the health system [45▪]. Economic evaluations of lomitapide or evinacumab to either supplement or supplant lipoprotein apheresis are lacking [31▪]. If response to first-line drug treatment is poor and apheresis is the only available add-on therapy, its initiation should not be delayed until onset of CVD symptoms [39].

ADDITIONAL THERAPIES WHEN LDL-CHOLESTEROL ARE NOT AT TARGET

Although currently not frequently prescribed, other drugs can be used if LDL-C levels are not yet at goal, or if cost and availability limit use of other add-on therapies. In the HICC database, about 6% of patients are treated with bile acid sequestrants [7▪▪], which are estimated to reduce LDL-C levels by approximately 10% in patients with HoFH [19]. Their use is limited by the large pill burden, occurrence of gastrointestinal side effects and the emergence of more potent LLT. Second-generation bile acid sequestrants (colesevelam and colestilan) have improved tolerability [46▪] and may be considered as alternative add-on therapies. Other LLTs reported in the HICC registry are fibrates, stanols, red yeast rice and omega-3 fish oil, collectively accounting for about 3–4% of the patients [7▪▪].

Bempedoic acid is a small molecule inhibitor of ATP citrate lyase, an enzyme in the cholesterol biosynthesis pathway that acts upstream of HMG-CoA. It was recently approved by the FDA and EMA and has been shown to lower LDL-C by approximately 18% on top of maximally tolerated LLT [47,48]. Bempedoic acid has never been evaluated in patients with HoFH, but given its mechanism of action, it is not expected to benefit patients with no residual LDLR activity. Apart from the increased risk of gout, bempedoic acid was well tolerated, but effects on cardiovascular outcome and long-term safety remain to be established.

Probucol, an antioxidative drug with pleiotropic effects including reduction in LDL-C and HDL-C [49], has been largely abandoned in western countries, but is still prescribed in Japan [42] and China [17▪]. A recently published Japanese study randomized 876 patients with CHD and dyslipidaemia to probucol or placebo and reported consistent yet modest reduction in LDL-cholesterol levels and a trend towards lower cardiovascular endpoints [aHR 0.746, 95% confidence interval (95% CI) 0.741–1.182, $P = 0.1839$] [50▪].

Finally, niacin, one of the oldest LLT that modestly lowers LDL-C, is now rarely used because of frequent side effects such as flushing [19] and lack of robust observed cardiovascular benefit [51–53]. Mipomersen, an antisense oligonucleotide directed against *APOB* mRNA, was the first gene-based silencing therapy to receive regulatory approval for the treatment of dyslipidaemia. Although providing approximately 28% reduction in LDL-C levels in patients with HoFH [54], its use was offset by side effects and frequent drug discontinuation [55]. It was withdrawn from the market in 2019. Gemcabene, a peroxisome proliferation-activated receptor (PPARα) agonist, modestly lowered LDL-C levels in

three patients with HoFH [56], but development of this drug was halted.

Liver transplantation

Liver transplantation was reported in less of 1% of the patients enrolled in the HICC database [7▪▪]. It is performed in select cases and often as treatment of last resort, when ASCVD progresses despite maximal lipid-lowering therapy [37▪,57]. Anecdotal evidence shows that coronary artery disease may regress [58], whereas aortic valve stenosis may continue to progress after liver transplantation, even after LDL-C levels have reached a normal range [59]. In some patients, posttransplant LLT is still required, suggesting that liver transplantation cannot be universally considered 'curative' for HoFH [60▪].

THE FUTURE: NEW, BRIGHT AND NOT-SO-DISTANT?

Gene therapy

As a rare monogenic condition, HoFH is an promising candidate for gene therapy. After an early attempt to provide a correct copy of the *LDLR* gene using an ex-vivo approach [61], rapid improvements of in-vivo gene delivery using adeno-associated virus (AAV) as a vector have allowed development of several gene therapies for rare monogenic diseases, two of which have already gained regulatory approval [62]. With regards to HoFH, successful preclinical AAV-mediated delivery of the correct *LDLR* for incorporation into the liver [63,64▪] has provided the basis for a phase 1/2a clinical trial (NCT02651675). Although results on LDL-lowering from this recently completed study are pending, early data showed a dose-dependent elevation in liver transaminases [65,66], which could be mitigated by prophylactic steroid treatment [65]. Transaminase elevations have also been observed in other AAV-mediated gene transfer trials and has been attributed to a Tcell immune response to the vector capsid [67].

Base editing

Since the discovery of the CRISPR-Cas9 system, giant steps have been made in the development of somatic gene editing. Familial hypercholesterolemia is at the forefront of this approach, which, as opposed to AAV-mediated gene transfer, aims to modify endogenous genes directly at the DNA level [68▪]. Utilizing a modified CRISPR-Cas9 system that is able to edit a single base in a DNA strand (base editing) and lipid nanoparticles as a delivery vector, Musunuru *et al.* [69] were able to successfully knockdown *PCSK9* in primates. This study opened the door for the recently launched first-in-man clinical trial using CRIPR-Cas9 to permanently knock out PCSK9 using base editing (NCT05398029). First results are expected in 2023. Although PCSK9 can already be adequately targeted by mAbs or inclisiran, this approach might theoretically reduce the burden of different medications that have to be taken at a regular basis by patients with HoFH. Preclinical studies targeting the knockdown of ANGPTL3 were also successful [70–72] and this may be a more effective target for HoFH.

Cholesteryl ester transfer protein inhibition

Cholesteryl ester transfer protein (CETP), amongst others, facilitates transfer of cholesterol esters from HDL to LDL particles [73]. The premise that inhibiting CETP lowers LDL-C levels and ASCVD risk is supported by genetic evidence from Mendelian randomization studies [73,74]. Obicetrapib is a novel CETP inhibitor that has recently been shown to reduce LDL-C levels in a phase II placebo-controlled study [75]. Two phase III studies are currently underway (NCT05142722; NCT05202509), but patients with HoFH are excluded. Whether CETP-inhibitors can be added to the LLT armamentarium for HoFH remains to be established.

CONSIDERATIONS FOR POPULATIONS OF SPECIAL INTEREST

Children and pregnant women with HoFH are populations that require special attention. We provide brief highlights of these topics rather than an in-depth discussion.

Children

Use of new therapies is almost always first tested in adults and, if found to be well tolerated, use in children lags behind by several years. This is no exception for lipid-lowering treatments [37▪]. The fact that not all LLTs are registered for use in children of all ages, is particularly problematic for HoFH children, as guidelines recommend starting intensive treatment at the time of diagnosis, including statins and apheresis once technically possible [2,6,39,76,77]. Although there is limited experience from off-label use [78], more advanced LLTs are not yet approved for use in young children, but several clinical trials are ongoing with inclusion age as young as 7 years [79,80].

Pregnant women

Management of hypercholesterolemia in pregnant patients may pose challenges that have recently been

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expertly addressed elsewhere [81,82]. Female HoFH patients may benefit from a multidisciplinary approach that includes a lipidologist, cardiologist and gynaecologist before, during and after pregnancy [81,83]. Considerations need to be made to carefully balance benefits of LLT for the mother against possible risks to the foetus, as well as to assess any hazard of stress imposed by pregnancy and labour on a potentially at-risk cardiovascular system. To avoid potential foetal toxicity, most pharmacological LLT has been historically discontinued before conception and during pregnancy, leaving resins and lipoprotein apheresis as the only treatment options. However, in 2021, the FDA removed the strongest warning against statins in pregnancy recognizing that they may provide benefits that outweigh risks in high-risk pregnant patients such as those with HoFH [84]. The use of statins is thus no longer contraindicated in high-risk pregnant patients, including HoFH. This recommendation is based on mounting evidence that the theoretical risk of gestational exposure to statins has not been observed in large cohort studies [85–87].

LOOKING BEYOND LDL-CHOLESTEROL LOWERING

Ultimately, the goal of treating patients with HoFH is preventing cardiovascular disease including aortic valve stenosis. To this end, attention should also be paid to treat any other CVD risk factor, including residual metabolic, inflammatory or Lp(a)-associated risks, with lifestyle or pharmacological interventions as appropriate. Clinicians should discourage smoking and encourage a heart-healthy lifestyle, including exercise, healthy diet and weight (Fig. 2). A careful evaluation of the atherosclerotic vascular burden should be made in concert with the cardiologists to assess the need to further reduce other CVD risks, including the evaluation of a pro-inflammatory and pro-thrombotic status [2,88]. Although no data on their use in HoFH exist, therapies such as icosapent ethyl [89] or low-dose colchicine [90] may be considered, as stated in the European guidelines [88].

Lipoprotein(a)

Lp(a) levels merit a special consideration. Lp(a) is an LDL-like particle whose plasma levels are independently associated with an increased risk of ASCVD and aortic valve stenosis [91], compounding existing risk due to familial hypercholesterolemia [92]. Although some studies report higher plasma levels of Lp(a) in patients with familial hypercholesterolemia, no clear consensus exists regarding the role of the LDL receptor in clearing Lp(a) from the circulation [93]. Lp(a) reduction using RNA-based therapies are being investigated in a phase 3 cardiovascular outcomes trial (NCT04023552). Provided the results are positive, this therapy would be a valuable addition to patients with HoFH and concomitantly elevated levels of Lp(a), especially in light of reducing the risk of developing aortic valve stenosis.

CONCLUSION AND FUTURE PERSPECTIVES

Given the extremely elevated LDL-C levels and the impossibility to reach target levels with only statins and ezetimibe, combination LLT with three or more treatments is a must to lower LDL-C levels and improve survival in patients with HoFH. Therapeutic goals for LDL-C lowering are the same as those established for other high-risk patients [2,94] and advances in treatment, such as the recently approved evinacumab, make these goals attainable, which was thought to be unimaginable until only a few years ago.

Unfortunately, access to recently approved powerful LLT (PCSK9 inhibitors, lomitapide and evinacumab) is frequently limited by regulatory approval and high cost, creating treatment inequity both between and within countries. As an ultra-rare disease with unique therapeutic challenges, HoFH should be recognized as such by regulatory agencies and legislators worldwide to ensure equitable access to treatment and best available care, irrespective of the economic status of the patient. Given the heterogeneity of the HoFH phenotype and the country-specific healthcare systems, there is no one-size-fits-all approach to its management. Although LDL-C levels should guide the need for starting additional therapies, clinicians should strive for an individualized approach taking into account availability and relative effectiveness of medication, patient preference and compliance. Beyond LDL-C lowering, a comprehensive evaluation and treatment of other CVD risk factors, such as lifestyle, Lp(a) and residual inflammatory risk, needs to be taken into account.

The development of novel therapeutic approaches, such as gene therapy and genome editing, is at the horizon and is poised to transform how we treat patients with HoFH in the future. Until that time, the greatest benefit to the largest number of patients must be gained from affordable and equitable access to existing add-on LLT.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

T.R.T. declares no conflicts of interest. M.C. reports institutional support for the conduction of clinical trials from Regeneron Pharmaceuticals and Regenxbio; consulting fees from Amryt Pharma.

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