Clinical update

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

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Aims

Homozygous familial hypercholesterolaemia (HoFH) is a rare life-threatening condition characterized by markedly elevated circulating levels of low-density lipoprotein cholesterol (LDL-C) and accelerated, premature atherosclerotic cardiovascular disease (ACVD). Given recent insights into the heterogeneity of genetic defects and clinical phenotype of HoFH, and the availability of new therapeutic options, this Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society (EAS) critically reviewed available data with the aim of providing clinical guidance for the recognition and management of HoFH.

Methods and results

Early diagnosis of HoFH and prompt initiation of diet and lipid-lowering therapy are critical. Genetic testing may provide a definitive diagnosis, but if unavailable, markedly elevated LDL-C levels together with cutaneous or tendon xanthomas before 10 years, or untreated elevated LDL-C levels consistent with heterozygous FH in both parents, are suggestive of HoFH. We recommend that patients with suspected HoFH are promptly referred to specialist centres for a comprehensive ACVD evaluation and clinical management. Lifestyle intervention and maximal statin therapy are the mainstays of treatment, ideally started in the first year of life or at an initial diagnosis, often with ezetimibe and other lipid-modifying
Homozygous familial hypercholesterolaemia

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare and life-threatening disease originally characterized clinically by plasma cholesterol levels $>13$ mmol/L ($>500$ mg/dL), extensive xanthomas, and marked premature and progressive atherosclerotic cardiovascular disease (ACVD). Studies in cultured fibroblasts from these patients showed a severe defect in the ability to bind and internalize LDL particles, subsequently shown to be caused by mutations in both alleles of the gene encoding the LDL receptor (LDLR). Recent genetic insights, however, indicate that mutations in alleles of other genes, including APOB, PCSK9, and LDLRAP1, may be present in some individuals with HoFH.

Untreated, most patients with markedly elevated LDL-C levels develop overt atherosclerosis before the age of 20 years, and generally do not survive past 30 years. Thus, the primary goals of management are prevention of ACVD by early and comprehensive control of hypercholesterolaemia, and early detection of complications, with specific focus on ostial occlusion and aortic stenosis. Unfortunately, HoFH is typically diagnosed when considerable coronary atherosclerosis has already developed, emphasizing the need for optimization of treatment in childhood.

Recent advances have highlighted the (i) prevalence and (ii) phenotypic heterogeneity of the genetic defects underlying HoFH and its clinical phenotype, which are both more pronounced than originally believed. Therefore, this Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society (EAS) critically reviewed current and emerging data with the aim of providing clinical guidance for the recognition and management of HoFH patients. These recommendations are directed not only to cardiologists and lipid specialists, but also to a wide spectrum of clinicians, including primary care physicians, paediatricians, dermatologists, and endocrinologists, who are often the first to see and hopefully refer these patients. These recommendations will also be a useful reference when decisions are made about provision of healthcare for HoFH.

Prevalence of clinical and genetically confirmed homozygous familial hypercholesterolaemia

Historically, the frequency of clinical HoFH has been estimated at 1 in 1 000 000 and for heterozygous FH (HeFH) 1 in 500, although therapy. As patients rarely achieve LDL-C targets, adjunctive lipoprotein apheresis is recommended where available, preferably started by age 5 and no later than 8 years. The number of therapeutic approaches has increased following approval of lomitapide and mipomersen for HoFH. Given the severity of ACVD, we recommend regular follow-up, including Doppler echocardiographic evaluation of the heart and aorta annually, stress testing and, if available, computed tomography coronary angiography every 5 years, or less if deemed necessary.

Conclusion

This EAS Consensus Panel highlights the need for early identification of HoFH patients, prompt referral to specialized centres, and early initiation of appropriate treatment. These recommendations offer guidance for a wide spectrum of clinicians who are often the first to identify patients with suspected HoFH.

Keywords

Homozygous familial hypercholesterolaemia • Diagnosis • Genetics • Phenotypic heterogeneity • Statins • Ezetimibe • Lipoprotein apheresis • Lomitapide • Mipomersen

Figure 1 Estimated number of individuals worldwide with homozygous familial hypercholesterolaemia by the World Health Organization region. Estimates are based on historical prevalence data (1 in a million with homozygous familial hypercholesterolaemia), as well as directly detected estimates of familial hypercholesterolaemia in the Danish general population ($\approx 1/160 000$). Data from Nordestgaard et al.4

Genetics of homozygous familial hypercholesterolaemia

The proteins known to affect LDL receptor function and their role are summarized in Figure 2. Most patients with genetically confirmed HoFH have two mutant alleles of the LDLR gene (MIM 606945) and their parents each have HeFH. Recently, mutations in alleles of three other genes were identified as causal in some cases with a severe phenotype resembling HoFH. These secondary genes are APOB (MIM 107730) encoding apolipoprotein (apo) B, PCSK9 (MIM 607786) encoding proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDLRAP1 (MIM 695747) encoding LDL receptor adapter protein 1, which uniquely causes a recessive phenotype, since carrier parents have normal lipid profiles.6 Patients are homozygotes, with the same higher frequencies in specific populations, such as French Canadians, Afrikaners in South Africa, or Christian Lebanese, have been reported due to founder effects.7 However, recent studies in unselected general populations suggest that the prevalence of HeFH based on the Dutch Lipid Clinic Network criteria may be as high as 1 in $\sim 200$ or, for molecularly defined HeFH, 1 in 244.5 Consequently, HoFH may affect as many as 1 in 160 000–300 000 people (Figure 1).
(A) Newly synthesized low-density lipoprotein receptor (LDLR) is transported to the cell membrane. After reaching the cell surface, the low-density lipoprotein receptor binds apolipoprotein B-100 (apoB-100), the main protein on LDL, forming a complex. (2) The low-density lipoprotein receptor–low-density lipoprotein complex, located in a clathrin-coated pit, is endocytosed via interactions that involve the low-density lipoprotein receptor Adaptor Protein 1 (LDLRAP1). (3) Inside the endosome, the complex dissociates: apoB-100 and lipids are targeted to the lysosome and degraded, the low-density lipoprotein receptor recycles to the cell membrane. (4) Pro-protein convertase subtilisin/kexin type 9 (PCSK9) acts as a post-transcriptional low-density lipoprotein receptor inhibitor and through an interaction with it, targets the low-density lipoprotein receptor for degradation, instead of recycling. (B) In the presence of loss-of-function mutations in the gene encoding for the low-density lipoprotein receptor, the low-density lipoprotein receptor is either not synthesized, not transported to the surface, or is present on the surface, but its function is altered. (C) In the presence of mutations in the low-density lipoprotein receptor-binding region of apoB, its ability to bind to low-density lipoprotein receptor is reduced, with consequent reduction in low-density lipoprotein particle uptake. (D) In the presence of gain-of-function mutations in the gene encoding PCSK9, more low-density lipoprotein receptors are targeted for degradation, with consequent reduction in the number of low-density lipoprotein receptors which recycle to the cell surface. (E) In the presence of loss-of-function mutations in the gene encoding for LDLRAP1, which facilitates the interaction between the low-density lipoprotein receptor and the cell machinery regulating the endocytic process, low-density lipoprotein receptor–low-density lipoprotein complex internalization is impaired.
mutation in both alleles of the same gene, or more commonly, compound heterozygotes with different mutations in each allele of the same gene, or double heterozygotes with mutations in two different genes affecting LDL receptor function (Figure 3).

**Genetic heterogeneity translates to phenotypic variability**

Irrespective of the underlying genetic defect, the severity of the HoFH phenotype depends on residual LDL receptor activity. Based on in vitro assays in their cultured fibroblasts, patients with clinically defined HoFH have been conventionally classified as either receptor-negative (<2% residual activity) or receptor-defective (2–25% residual activity).\(^1\) Homozygous familial hypercholesterolaemia patients who are LDLR-negative have higher LDL-C levels and poorer clinical prognosis than LDLR-defective patients.\(^2,7,8\)

Residual LDL receptor activity has not been systematically evaluated in patients carrying mutations in APOB and PCSK9 genes. In patients carrying LDLRAP1 mutations, LDL receptor activity in fibroblast culture is normal, although the cause remains unclear.\(^6\) Nevertheless, emerging data suggest that carriers of mutations in these genes may present a milder phenotype compared with that of receptor-negative subjects.\(^7\) Overall, mean LDL-C levels by genotype generally increase as follows: HeFH < double heterozygote (e.g. LDLR+PCSK9 gain-of-function or APOB mutation) < homozygous APOB or PCSK9 gain-of-function mutation < homozygous LDLRAP1 or LDLR-defective mutations < compound heterozygote LDLR-defective + LDLR-negative mutations < homozygous LDLR-negative mutations (see Supplementary material online and Figure 4).

Other sources of variability in the HoFH phenotype may arise from small effect genetic variants (common single nucleotide polymorphisms), gene–gene and gene–environment interactions, and non-Mendelian and epigenetic influences.\(^6,9,10\) Greater access and wider clinical application of next generation sequencing are critical to defining such variability, as well as additional causative genes, all of which have important prognostic and therapeutic implications.

**Metabolic characteristics of homozygous familial hypercholesterolaemia**

Impaired functionality of the LDL receptor underlies the hypercholesterolaemia of HoFH. While defective hepatic LDL uptake is the main and most direct consequence, other metabolic perturbations may contribute to the metabolic characteristics and accelerated atherosclerotic disease associated with HoFH. ApoB metabolism in HoFH remains incompletely defined, although in vitro and in vivo studies suggest that LDLR-negative mutations are associated with hepatic oversecretion of apoB. In addition, while levels of triglycerides are frequently within the normal range, hypertriglyceridaemia has been observed, and may be more common with an increasing prevalence of the metabolic syndrome. Decreased catabolism of triglyceride-rich lipoproteins may result from deficient LDL receptor function and account for postprandial dyslipidaemia. Familial hypercholesterolaemia is also associated with increased plasma levels of lipoprotein(a) (Lp(a)) by an undefined mechanism that may not directly involve the LDL receptor pathway. Lipoprotein(a) levels tend to be higher in HoFH than HeFH, and are independent of genetic variation in apolipoprotein(a).\(^8\) Finally, HoFH patients frequently have low levels of high-density lipoprotein cholesterol (HDL-C), probably due to accelerated turnover of HDL apoA-I, and defective HDL-driven cholesterol efflux. These metabolic perturbations have been extensively reviewed.\(^11\)
Diagnosis of homozygous familial hypercholesterolaemia

Diagnosis of HoFH can be made on the basis of genetic or clinical criteria (Box 1). While genetic testing may provide a definitive diagnosis of HoFH, it is recognized that in some patients genetic confirmation remains elusive, despite exhaustive investigation; indeed, the existence of additional FH genes cannot be excluded. Historically, HoFH has been most commonly diagnosed on the basis of an untreated LDL-C plasma concentration $\geq 13$ mmol/L ($\sim 500$ mg/dL), or a treated LDL-C concentration of $\geq 8$ mmol/L ($\geq 300$ mg/dL), and the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents.

Plasma low-density lipoprotein cholesterol levels

Within a family, the plasma LDL-C level is the critical discriminator, being about four times and about two times higher in family members with HoFH or HeFH, respectively, compared with unaffected members. At the population level, however, the range of LDL-C levels may overlap significantly between HeFH and HoFH (Figure 4), and untreated LDL-C levels $< 13$ mmol/L ($< 500$ mg/dL) can be found in genetically confirmed HoFH. This is especially relevant for children, who tend to have lower LDL-C levels than adults. More than 50% of HoFH children identified in the Netherlands have LDL-C levels between 5.6 and 9.8 mmol/L (A Wiegman personal communication). Such phenotypic heterogeneity can be at least partly explained by the previously described genotypic heterogeneity. Thus, the LDL-C cut-offs given here should not be the sole guide for diagnosis. Indeed, the treated LDL-C cut-off of $> 8$ mmol/L ($> 300$ mg/dL) is now considered obsolete, given the multiplicity of lipid-lowering treatments that these patients typically receive. This point is clearly illustrated in a recent trial, in which HoFH patients with a confirmed genetic diagnosis had baseline LDL-C levels as low as 3.9 mmol/L ($\sim 150$ mg/dL) while on multiple LDL-C lowering agents, as well as in a recent report.

Xanthomas and arcus corneae

Although not exclusively associated with HoFH, the presence of cutaneous or tuberous xanthomas in children is highly suggestive of diagnosis (Figure 5). Evidence of arcus corneae reinforces the clinical diagnosis. As seen for LDL-C levels, variability in the age at appearance and extension of xanthomas can be partly explained by the underlying mutations, with earlier appearance of xanthomas associated with receptor-negative vs. receptor-defective status. Cholesterol deposits in the tendons and joints may lead to tendinitis and joint pain, which impairs the quality of life of patients, and these may

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**Box 1** Criteria for the diagnosis of homozygous familial hypercholesterolaemia

- Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus
- An untreated LDL-C $> 13$ mmol/L (500 mg/dL) or treated LDL-C $\geq 8$ mmol/L (300 mg/dL) together with either:
  - Cutaneous or tendon xanthoma before age 10 years
  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents
- These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH
require surgical removal. In rare cases, patients may present with giant ectopic cholesterol xanthomas in the brain, mediastinum, and muscles of the buttock. As referral following the appearance of xanthomas in young children is frequently the key driver of HoFH diagnosis, prompt recognition is crucial to early diagnosis. The presence of markedly elevated LDL-C levels and the absence of neurological, cognitive, and ophthalmic symptoms in patients with HoFH distinguish them from patients with cerebrotendinous xanthomatosis.

Family history
A careful family history is essential for comprehensive assessment of possible FH in general, and HoFH in particular. In the case of autosomal dominant mutations (in LDLR, PCSK9, and APOB genes), both parents are obligate heterozygotes and therefore display elevated LDL-C levels (frequently >95th percentile by country-specific age and gender criteria) and a strong positive family history of premature ACVD (<55 years in men and <60 years in women among first-degree relatives). In the case of autosomal recessive hypercholesterolaemia (due to LDLRAP1 mutations), parents may exhibit LDL-C levels in the normal range, and determination of an extended family pedigree may reveal an autosomal recessive pattern of inheritance. Systematic cascade or opportunistic screening offers prospective parents with HeFH the possibility of making informed decisions prenatally, and identifying HoFH patients at birth, thereby allowing for early initiation of treatment. Identification of HoFH can also guide ‘reverse’ cascade screening for parents and relatives to identify patients with FH.

Differentiation from sitosterolaemia
Although in most cases the diagnosis of HoFH is relatively straightforward, another disorder of lipid metabolism, sitosterolaemia (alternatively termed ‘phytosterolaemia’), may have a very similar clinical presentation, with the presence of tendinous and/or tuberous xanthomas in childhood associated with a dramatic increase in plasma cholesterol and atherosclerotic complications. It is, however, of relevance that atherosclerotic disease is not always present in genetically defined sitosterolaemic subjects, as shown in a recent report. Similar to autosomal recessive hypercholesterolaemia, sitosterolaemia has an autosomal recessive pattern of inheritance and consequently parents may present with normal cholesterol levels. Two major features differentiate sitosterolaemia from HoFH: (i) markedly (>30-fold) increased plasma concentrations of plant sterols, and (ii) elevated cholesterol levels, which respond well to diet and bile acid sequestrants or ezetimibe and may not persist after the first two decades of life. Diagnosis is confirmed by genetic analysis, with mutations in two ATP binding cassette transporter genes, ABCG5 and/or ABCG8, shown to be causative for sitosterolaemia.

In summary, this Consensus Panel recommends that diagnosis is made by careful assessment of the clinical characteristics and family history, as well as genetic testing when the clinical diagnosis of HoFH is uncertain or to facilitate ‘reverse’ cascade screening. ‘Reverse’ cascade screening is in any case strongly recommended.

Cardiovascular complications and natural history
The burden of markedly elevated plasma LDL-C levels from birth underlies the sequelae of ACVD complications unique to HoFH. The cholesterol-year score, an integrated measure of the severity and the duration of hypercholesterolaemia, is directly associated with cholesterol deposition in vascular and extravascular compartments in HoFH patients, thus reinforcing the concept that absolute LDL-C levels affect the severity of the CV phenotype. In clinically diagnosed HoFH, the first major CV events often occur during adolescence, although angina pectoris, myocardial infarction and death have been reported in early childhood, typically in individuals who are LDLR-negative. Untreated HoFH patients who are LDLR-negative rarely survive beyond the second decade. While HoFH patients who are LDLR-defective have a better prognosis, almost all develop clinically significant ACVD by age of 30. Long-term studies are still needed to assess CV risk in genetically confirmed HoFH without the severe phenotype usually observed in clinically defined HoFH.

Homozygous familial hypercholesterolaemia is characterized by accelerated atherosclerosis, typically affecting the aortic root, compromising the coronary ostia, but also other territories, including the carotid, descending aorta, and ilio-femoral and renal arteries. Cholesterol and calcium deposits, as well as fibrosis and inflammation in both the aortic root and aortic valve cusps, can lead to supravalvular aortic stenosis (Figure 6). These manifestations often occur within the first and second decades of life. Patients may be initially asymptomatic, presenting only with cutaneous and tendinous xanthomas and possibly, a cardiac murmur in the aortic area. Early involvement of the ascending and descending thoracic aorta is frequently observed, accompanied by premature severe aortic calcification in adult patients. Cholesterol deposition on valve leaflets may also cause mitral regurgitation.

Importantly, valvular and supravalvular aortic diseases may progress even when cholesterol levels are reduced, as a result of hemodynamic stress and progressive fibrosis over affected territories. Dyspnoea, diastolic and systolic left ventricle heart failure, and sudden cardiac death are also common. In young children, the...
HoFH is characterized by accelerated atherosclerosis, typically affecting the aortic root, although other vascular territories may also be affected. The first major cardiovascular events often occur during adolescence, possibly younger when patients are LDLR-negative and/or untreated. In young children, early symptoms and signs are often linked to aortic stenosis and regurgitation, due to massive accumulation of cholesterol at the valvular levels. As aortic and supra-valvular aortic valve diseases may progress even when cholesterol levels are reduced, regular screening for subclinical aortic, carotid, and coronary heart disease is indicated.

Current treatment for homozygous familial hypercholesterolaemia

Given the ACVD complications associated with HoFH, reducing the burden of elevated LDL-C levels is critical. A low-saturated fat, low-cholesterol, heart-healthy diet should be encouraged in all patients with HoFH, but even with strict adherence, diet has little impact on the severity of hypercholesterolaemia. Patients should be encouraged to be active. As aortic stenosis may precipitate angina and syncope on exertion, a careful assessment of the aortic and ostial involvement is recommended before sport activities are initiated. While other risk factors such as smoking, hypertension, and diabetes should be aggressively targeted, aspirin is of value in asymptomatic patients, the most important aim of therapy is to reduce LDL-C levels as much as possible.

Pharmacotherapy

This Consensus Panel strongly recommends that lipid-lowering therapy should be started as early as possible, based on evidence that treatment can delay the onset of clinically evident ACVD. In accordance with recently published guidelines, LDL-C targets in HoFH are <2.5 mmol/L (<100 mg/dL) [<3.5 mmol/L (<135 mg/dL) frequently if clinically indicated, taking into account the radiation exposure and severity of subclinical disease. Computed tomography coronary angiography can detect luminal obstruction by calcified and non-calcified plaques and results can be combined with those from myocardial stress testing, provided the age of the child permits consent. Stress testing, although not optimal for detecting subclinical disease, may be used in case of limited access to CTCA or cardiac magnetic resonance imaging (MRI). Owing to concerns about the exposure of young individuals to radiation, CTCA must be performed in CT scanners with at least 64 and preferably 320 detectors or dual source scanners, with radiation exposure adapted for body weight. The atherosclerotic burden of the aorta can be also evaluated by MRI or trans-oesophageal echocardiography.

Stress testing and invasive coronary angiography are indicated in patients with clinical symptoms suggestive of ischaemia or valve malfunction, or in the presence of findings from non-invasive cardiac evaluation. Given the high rate of ostial stenosis, risk of sudden death and inability to undertake stress testing due to age, invasive angiography may be indicated in severely affected young children. This should be performed by an experienced paediatric invasive cardiologist. Coronary revascularization is indicated for severe CHD, and aortic valve replacement for severe left ventricle outflow obstruction. For either surgery, care must be taken with the aortic root as it is usually severely compromised by atherosclerotic plaques and calcification. Reconstruction of the aortic root might be necessary with aortic valve replacement. These patients should be followed by a team of experts including a lipidologist and cardiologist working in close collaboration to optimize therapeutic measures, including pharmacological antiplatelet treatment, prevention of endocarditis especially in those with valve prosthesis or aortic grafts, and surgical intervention to correct valvular and coronary impairment.

Screening for subclinical atherosclerosis

Given the extremely high risk of early onset of severe ACVD and its rapid progression in HoFH, regular screening for subclinical aortic and coronary heart disease (CHD) is indicated. This Consensus Panel recommends that patients receive a comprehensive CV evaluation at diagnosis, with subsequent Doppler echocardiographic evaluation of the heart and aorta annually, and, if available, computed tomography coronary angiography (CTCA) every 5 years, or more frequently if clinically indicated, taking into account the radiation exposure and severity of subclinical disease. Computed tomography coronary angiography can detect luminal obstruction by calcified and non-calcified plaques and results can be combined with those from myocardial stress testing, provided the age of the child permits consent. Stress testing, although not optimal for detecting subclinical disease, may be used in case of limited access to CTCA or cardiac magnetic resonance imaging (MRI). Owing to concerns about the exposure of young individuals to radiation, CTCA must be performed in CT scanners with at least 64 and preferably 320 detectors or dual source scanners, with radiation exposure adapted for body weight. The atherosclerotic burden of the aorta can be also evaluated by MRI or trans-oesophageal echocardiography.

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in children], or <1.8 mmol/L (<70 mg/dL) in adults with clinical ACVD. However, such targets are ambitious and careful evaluation of the benefit vs. risk of therapeutic options is needed. The Panel also recognizes that the genetic and phenotypic heterogeneity of HoFH may translate to broad variability in the response to conventional and novel lipid-lowering therapies.

Statins have proven efficacy as the mainstay of treatment in HoFH, even in individuals who are receptor-negative, and have been shown to reduce CV and all-cause mortality. Even at the highest doses of the most efficacious statins, however, only modest reductions in LDL-C plasma levels, of 10–25%, are observed in most patients. Autosomal recessive hypercholesterolaemia seems relatively more responsive to treatment. Addition of the cholesterol absorption inhibitor ezetimibe further lowers LDL-C levels by 10–15%, thus providing 30–40% reduction in LDL-C levels, with minimal adverse events and relative low costs (Figure 7). Combinations of statins with other cholesterol-lowering medications, including bile acid sequestrants, niacin, fibrates, and probucol have been used successfully in HoFH and can be considered to further lower LDL-C levels, although their use may be limited by tolerability and availability.

**Lipoprotein apheresis**

Where available, extracorporeal removal of LDL-C, although an expensive and time-consuming therapeutic approach, is an important adjunctive treatment for HoFH. The initial unselective approach of plasma exchange (plasmapheresis) has been replaced by several methods for selective elimination of atherogenic lipoproteins. A single treatment can decrease plasma LDL-C levels by 55–70% relative to pre-treatment levels, with close to normal LDL-C levels achieved with apheresis on a once weekly basis. Long-term treatment frequently results in regression of cutaneous xanthomas (Figure 8). Side effects of apheresis include hypotension, abdominal pain, nausea, hypocalcaemia, iron-deficiency anaemia, and allergic reactions. These are rarely serious but can be debilitating. Depending on the technique used, particularly with dextran sulphate LDL adsorption and haemoperfusion methods, concomitant therapy with an angiotensin-converting enzyme inhibitor is contraindicated due to the risk of severe hypotension.

Despite the lack of randomized studies, there is clinical evidence that long-term lipoprotein apheresis can contribute to plaque regression and/or stabilization and improve prognosis, as extensively reviewed, and is cost-effective in HoFH, especially in severe phenotypes (see Supplementary material online). Whether other effects, including marked reduction in Lp(a), add benefit to the CV prognosis remains to be established. Accumulating data strongly suggest that the earlier apheresis is initiated, the better the prognosis. In practice, the age of starting and the frequency of treatment represent a compromise between practical feasibility, cost and the clinical need to achieve LDL-C target. In very young patients (~2 years), venous access can be an issue, although this can be achieved with a peripheral venous cannula. While the theoretical optimal frequency is one procedure per week, most centres treat patients every 2 weeks. Lipoprotein apheresis can be continued during pregnancy.

In line with current guidelines, this Consensus Panel recommends that lipoprotein apheresis be considered in patients with HoFH. Treatment should be started as soon as possible, ideally by...
age 5 and not later than 8 years, although this and the frequency of
treatment represent a compromise between access to centres, the
severity of the disease, affordability, and the patient’s choice.

Liver transplantation and other surgical approaches

Liver transplantation corrects the molecular defect in the organ most
active in the clearance of LDL, resulting in a marked improvement of
LDL-C levels.\(^1\) Although a successful therapeutic strategy, either
alone or in combination with a heart transplant\(^{47–49}\) there are
obvious disadvantages, including the high risk of post-transplantation
surgical complications and mortality, the paucity of donors, and the
need for life-long treatment with immunosuppressive therapy.\(^50\)
Partial ileal bypass or portocaval shunting is not recommended, but
may be considered where there is limited access to more efficacious
treatments for patients with very severe phenotypes.

In conclusion, this Consensus Panel emphasizes the need for a
combination of lifestyle, statin treatment (with or without other
lipid-lowering drugs) and lipoprotein apheresis to manage HoFH.

New therapeutic approaches affecting low-density lipoprotein
production

Lomitapide and mipomersen were recently approved by the Food
and Drug Administration (FDA) as adjunct therapy for HoFH in
patients aged \(\geq 18\) and \(\geq 12\) years, respectively; lomitapide is also
approved by the European Medicines Agency. Although targeting dif-
ferent proteins via different strategies, both drugs affect the produc-
tion and secretion of apoB-containing lipoproteins\(^{51,52}\) rather than
increasing their removal from circulation. As HoFH is characterized
by severely impaired removal of LDL from the bloodstream, these
new agents represent a promising approach for treatment of hyper-
cholesterolaemia.

Lomitapide

Lomitapide is an oral inhibitor of the microsomal triglyceride trans-
port protein (MTP), which is responsible for transferring triglycerides
and phospholipids onto chylomicron and VLDL during their assembly
in the intestine and the liver, respectively.\(^53\) Inhibiting MTP leads to
reduced secretion of these lipoproteins into the circulation. In an
open-label trial in HoFH patients, lomitapide at maximally tolerated
doses, in addition to the standard of care including LDL apheresis,
reduced plasma LDL-C and apoB levels by \(~50\%\) and Lp(a) by
\(~15\%\) at 26 weeks, with durable LDL-C lowering over a further 12
months follow-up. The most frequently observed adverse events were gastrointestinal symptoms and liver fat accumulation. Gastrointestinal adverse events (e.g., nausea, flatulence, and diarrhoea) were reduced by a gradual dose-escalation regimen combined with adherence to a low-fat diet (<20% of energy from fat) and dosing outside of mealtimes.

Elevations in alanine aminotransaminase (ALT) >3 × upper limit of normal (ULN) were reported for 10 patients (34%). Accumulation of liver fat up to a median level of 9% (range 0–13%) at 26 weeks and 8% (0–19%) at 78 weeks was observed.

Mipomersen

Mipomersen is a second generation antisense oligonucleotide, administered by subcutaneous injection, that targets the messenger ribonucleic acid (mRNA) of apoB, the main protein of LDL, and its precursor, VLDL. Mipomersen reduces translation of apoB mRNA and the synthesis of apoB by the ribosome, leading to reduced secretion of VLDL. In a placebo-controlled double-blind trial in HoFH patients, mipomersen (weekly 200 mg, on top of standard lipid-lowering therapy), resulted in further reductions from baseline at 26 weeks in plasma levels of LDL-C (mean 25%), apoB (27%), and Lp(a) (31%) vs. placebo.

The most frequently reported adverse events were injection site reactions (76% of patients), some of which were long-lasting, and flu-like symptoms, typically appearing 2 days after injection. Elevations in ALT have been reported during mipomersen treatment; in 12% of patients, increases >3 × ULN, with or without concomitant increases in liver fat content, were observed most although subsequently decreased while continuing treatment. Liver fat content was not routinely measured in the HoFH study with mipomersen, although in hypercholesterolaemic patients, including those with HeFH, a median increase of ~5% (range ~1 to 37%) after 28 weeks treatment was observed.

Increased liver fat content observed during both lomitapide and mipomersen treatment may be correlated with the degree of efficacy. The limited available data suggest that this effect is reversible following suspension of treatment. Owing to the potential risk for hepatic toxicity, both agents have been approved for restricted use. Although the potential CV benefits associated with substantial LDL-C lowering possibly outweigh the theoretical increased risk of steatohepatitis and fibrosis in such very high-risk patients, a systematic evaluation of long-term efficacy, outcome and hepatic safety is clearly necessary. Additionally, both drugs have adverse events that may limit long-term use. Lomitapide is also contraindicated with strong and moderate CYP3A4 inhibitors. Furthermore, as lomitapide has not been evaluated in HoFH patients aged <18 years, and mipomersen in those <12 years or receiving apheresis, treatment in such patients should only be considered via a special access scheme in the event of rapidly progressive atherosclerosis and if other options have been utilized.

Undoubtedly, statins and other conventional lipid-lowering drugs are available worldwide and affordable, compared with apheresis and recent therapeutic options. Although the high costs of these approaches may be a concern, the overall cost to adequately treat HoFH remains low due to its rarity and may be counterbalanced by the cost of treating associated CV complications.

Future options

A number of novel agents may also offer therapeutic options for HoFH. Monoclonal antibody therapies targeting PCSK9 are being developed (Figure 9). In HoFH patients, this therapy reduced plasma LDL-C levels by up to 65% on top of concomitant lipid-lowering therapy. Subsequently, a proof of concept study showed that evolocumab (AMG 145, 420 mg subcutaneously every 2 weeks), reduced plasma LDL-C levels by 26% (mean 3.0 mmol/L) in HoFH patients who were receptor defective; in a placebo-controlled phase 3 trial evolocumab reduced LDL-C levels by 31%. Given that markedly elevated PCSK9 levels are associated with HoFH, either untreated or treated with statins, the use of PCSK9 inhibitors as adjunct therapy in subjects with LDLR defective mutations or PCSK9 gain-of-function mutations offers an additional therapeutic approach to optimizing LDL-C reduction. Moreover, inhibitors of cholesteryl ester transfer protein (CETP) have been shown to significantly lower LDL-C and Lp(a) levels by increasing the clearance of apoB-containing lipoproteins. Preliminary findings suggest that combination with a statin may be effective in HoFH.

Finally, rapid resolution of severe hypercholesterolaemia following liver transplantation in HoFH provides compelling support for the hypothesis that liver expression of LDLR via gene replacement may not only decrease LDL-C levels, but also make HoFH patients more responsive to existing or novel therapeutics. Indeed, early attempts investigating gene replacement therapy resulted in a transitory expression of the LDLR in some HoFH patients. Recent successes in humanized mouse models of HoFH using an AAV8-based gene therapy approach support further development.

Other issues

In addition to pharmacological treatment of hypercholesterolaemia, management of the HoFH patient should address other issues (Box 3). Diagnosis of HeFH can impact psychosocial functioning and quality of life, even more so for HoFH patients, implying the need for integration of psychological support into routine patient care. Thus, this Panel recommends that parents and children should be appropriately educated about HoFH, thereby providing a basis for shared decision-making regarding their treatment.

Contraception and pregnancy should be appropriately discussed for female patients; as hormonal control is generally contraindicated in HoFH, other contraceptive methods are strongly recommended (Box 3). The consequences of pregnancy, i.e. aggravation of hypercholesterolaemia due to discontinuation of pharmacotherapy, coupled with the effects of high levels of oestrogen and progesterone on lipoprotein metabolism, also merit consideration. In the absence of appropriate studies and on the basis of current experience, this Consensus Panel recommends a full discussion and detailed CV assessment in women who wish to become pregnant. Where pregnancy is not contraindicated, lipoprotein apheresis is strongly recommended.
Early diagnosis of HoFH and early initiation of lipid-lowering therapy are paramount. While genetic testing can usually provide a definitive diagnosis of HoFH, clinicians should be aware that in some patients, genetic confirmation remains elusive. Plasma levels of LDL-C should not be the sole criterion for diagnosis given emerging evidence that the genetic heterogeneity of HoFH translates to phenotypic variability to a greater level than previously thought.

Current management of HoFH should focus on lifestyle intervention, together with maximal statin therapy, often in combination with ezetimibe and other lipid-modifying therapy, and adjunctive lipoprotein apheresis (Figure 10), consistent with recent guidance. Despite this multiplicity of treatments, it is recognized that most patients with HoFH do not achieve recommended LDL-C targets and therefore remain at high CV risk. For these patients, the recent approval of lomitapide and mipomersen as adjunctive therapy specifically for HoFH, considered together with the potential of new CETP inhibitors and PCSK9 immunotherapy, offers the possibility of further LDL-C lowering on top of current standards of care. Subject to consideration of benefit vs. risk and cost, which may differ from country to country, such pharmacotherapies may ultimately translate to improved clinical outcome for patients with this rare, life-threatening genetic disease.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Appendix

European Atherosclerosis Society (EAS) Consensus Panel

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