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REVIEW

Clinical update

Diagnosis and treatment of familial hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is an autosomal dominant genetic disorder, associated with elevated levels of low-density lipoprotein-cholesterol (LDL-C), which can lead to premature cardiovascular disease. Early diagnosis of FH is important to prevent morbidity and mortality. Familial hypercholesterolaemia is usually diagnosed using clinical characteristics, such as family history, and cholesterol levels; however, genetic testing may provide a definite diagnosis of FH by detecting a pathological mutation. Current guidelines highlight the importance of reducing LDL-C levels in patients with FH. Statins are the current standard treatment for the majority of these patients, and have been shown to be effective in reducing the incidence of cardiovascular heart disease in patients with FH. Nevertheless, many FH patients do not achieve their target LDL-C levels; as such, new treatment options are required to decrease LDL-C levels beyond those currently achieved. There are currently several new classes of pharmacotherapy under investigation to control LDL-C levels. These include agents which modify LDL-C production, such as inhibitors of apolipoprotein B, or those which affect LDL-C catabolism, such as inhibition of pro-protein convertase subtilisin/kexin 9, a protein which is responsible for the degradation of the LDL receptor. Therapies which raise high-density lipoprotein cholesterol are also being evaluated. In this article, we consider the diagnosis of FH and the goals of therapy and review the current and potential future treatment options for patients with FH.

Keywords Familial hypercholesterolaemia • Diagnosis • Treatment • Hyperlipidaemia

Introduction

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic disorder characterized by elevated plasma levels of low-density lipoprotein-cholesterol (LDL-C). Familial hypercholesterolaemia comprises a minimum of three separate genetic conditions due to mutations in the genes for: (i) the LDL receptor (LDLR), (ii) apolipoprotein B (ApoB), and (iii) pro-protein convertase subtilisin/kexin 9 (PCSK9). The clinical phenotype resulting from these mutations is variable, with, for example, ApoB mutations being the least severe of the three.[1] There are both 'heterozygous' (heFH) and 'homozygous' (hoFH) forms; total cholesterol and LDL-C concentrations in heFH patients often range between 350–550 mg/dL (9–14 mmol/L)[2] and 200–400 mg/dL (5–10 mmol/L), respectively,[3] whereas in hoFH patients levels can be 650–1000 mg/dL (17–26 mmol/L)[2] and >600 mg/dL (15.5 mmol/L), respectively.[4] Low-density lipoprotein-cholesterol deposits in the tissues cause external manifestations of FH, such as tendinous xanthomas and corneal arcus.[5] More importantly, LDL-C deposits in arteries can lead to premature cardiovascular disease (CVD). Historically, left untreated, clinical symptoms of CVD typically manifest in men in their fourth decade and in women in their fifth decade of life in heFH patients. In contrast, hoFH patients can experience serious cardiovascular events as early as childhood and, on average, in their twenties.[6,7] However, there has been a decline in CVD event rates in recent years, in part due to lifestyle changes,[8] which may also have an impact on the presentation of FH. Other traditional CVD risk factors, such as smoking, hypertension, and diabetes, add to the total risk in FH patients, and therefore all modifiable risk factors should be treated aggressively.[9]

Current pharmacotherapy with statins lowers LDL-C levels and as a consequence reduces cardiovascular mortality and morbidity.[10,11] An analysis of patients with heFH by the Simon Broome register group during the 1980s, a pre-statin era, identified a significantly elevated risk for CVD, specifically a 100-fold increase in mortality from coronary heart disease (CHD) vs. the general population in young adults aged 20–39.[12] With the introduction of HMG-coenzyme A reductase inhibitors (statins), a decline in

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the relative risk for coronary mortality in FH patients aged 20–59 has been shown.[11] The risk for CHD, however, still remained higher than that in the non-FH population. Additional evidence of the statin effect on CVD came from a large meta-analysis in 2010, by Baigent *et al.*,[10] of 26 randomized trials, which identified that intensive regimens of statin treatment produced a further 15% reduction in CHD incidence and ischaemic stroke—statistically significant compared with less intensive regimens or control. Furthermore, all-cause mortality was reduced by 10% per 1.0 mmol/L reduction in LDL-C.[10] In heFH patients, the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study, which used carotid intima-media thickness (cIMT) as a surrogate marker for cardiovascular endpoints, demonstrated the benefit of high-dose statins.[13] However, the ENHANCE study showed that cIMT was not improved with the addition of ezetimibe to simvastatin despite substantial reductions in LDL-C.[14] Despite the lack of data validating standard LDL-C targets in patients with FH, several national guidelines use the treatment target of reduction of LDL-C by at least 50% from baseline in patients with FH.[2,15]

Statins have proved a powerful tool in lowering LDL-C levels. However, recommended treatment goals to at least 50% from baseline[6] or reduction of LDL-C levels to $<$100 mg/dL (2.6 mmol/L; for patients at high risk of CVD) and $<$70 mg/dL (1.8 mmol/L; in those at very high risk)[3,16,17] fail to be achieved in a significant number of patients with FH, with only 21% of patients achieving target LDL-C levels in one study.[18] Of those not reaching target LDL-C levels, only 27% were receiving ezetimibe in combination with the maximum statin dose; primarily, this was due to acceptance of a higher target LDL-C level by the treating physician.[18] An audit of FH management in the UK demonstrated that 80% of patients were using ezetimibe, yet only 44% of patients achieved the target of 50% reduction from baseline.[19] New pharmacotherapies are in development to fulfil this treatment gap. We provide a comprehensive review of FH diagnosis and therapeutic goals and present potential future treatment options.

Background to familial hypercholesterolaemia

Disease background

In 1938, the Norwegian scientist Dr Carl Müller recognized the link between elevated serum cholesterol levels, tendon xanthomas, and the lesions in coronary arteries in patients with FH.[20] In 1964, FH was defined as an autosomal dominant disease,[21] and a clinical distinction was made based on the phenotype severity of a heFH (mild) and hoFH (severe) form.

Brown and Goldstein[22] found that receptors on the cell surface mediate the uptake of the cholesterol-containing particles (LDL) that circulate in the blood. In 1986, they discovered that the molecular defect underlying FH (autosomal dominant hypercholesterolaemia—ADH) is a functional mutation in the gene that encodes for the LDLR.[23] These 'Nobel Prize' findings provided the foundation for current treatment and prevention practices to lower LDL-C levels.

Some patients with the clinical FH phenotype have been shown not to carry a mutation in LDLR, and in these cases, mutations in ApoB[24] and the (PCSK9) gene[25] may be present. Autosomal recessive hypercholesterolaemia (ARH) is caused by homozygosity for mutations in the gene encoding the LDLR adaptor protein 1 (LDLRAP1).[26]

Molecular pathways that cause familial hypercholesterolaemia

Low-density lipoprotein receptor gene

The LDLR is a glycoprotein expressed on the surface of hepatocytes (*Figure 1*),[27] that binds to the ApoB-100 protein on the surface of the LDL particle, thereby forming the LDL ligand–receptor complex, which then internalizes.[28] The most common cause of ADH is a mutation at the LDLR gene, which lies on the short arm of chromosome 19 (19p13).[29] More than 1700 LDLR mutations are recorded in the University College London database.[30] They can affect any domain of the LDLR protein and result in, e.g. impairment in binding to the LDL particle, failure to internalize into the cell after binding,[28] or a complete absence of the LDLR gene. Defects resulting from LDLR mutations lead to diminished catabolism of LDL-C, resulting in elevated plasma levels alongside normal levels of other lipoproteins.[7]

ApoB-100 gene

Familial defective ApoB-100 is a genetic disorder clinically indistinguishable from ADH that is characterized by a mutation in the ApoB-100 gene, located on chromosome 2p24-p23. A mutation in the ApoB-100 gene disables LDL-C from binding to the LDLR and leads to elevated LDL-C in the circulation.[24] Mutations in ApoB-100 are relatively uncommon compared with LDLR mutations.

Pro-protein convertase subtilisin/kexin 9

In 2003, two gain-of-function mutations in the PCSK9 gene were shown to be associated with ADH.[31] It was subsequently shown that PCSK9 was involved in the regulation of LDLR activity[32] and that PCSK9 loss-of-function mutations were associated with decreased LDL-C levels.[33] PCSK9 binds to the LDLR–LDL complex extracellularly and, following endocytosis, targets the LDLR for lysosomal degradation.[34]

Autosomal recessive hypercholesterolaemia

The extremely rare recessive form of hypercholesterolaemia is ARH,[35] which is caused by loss-of-function mutations in LDLRAP1,[26] which is located on chromosome 1p36-35.[36] The endocytosis of LDLR occurs within clathrin-coated pits and is facilitated by LDLRAP1. Internalization of the LDL-C ligand–receptor complex within hepatocytes cannot occur in ARH patients due to LDLRAP1 mutations, resulting in an impairment of LDL-C catabolism and increased LDL-C levels.[35]

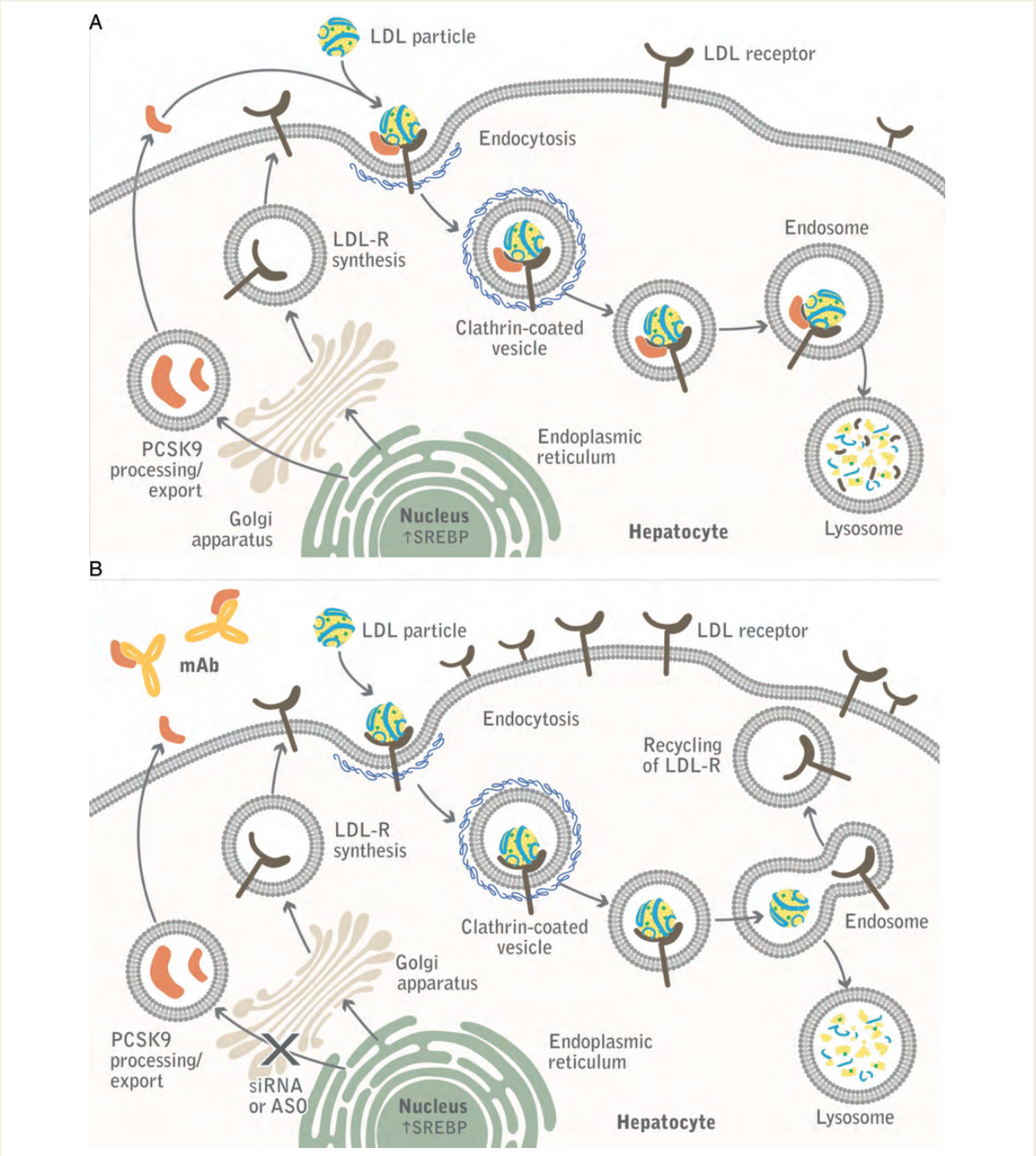

Figure 1 Catabolism of the LDL particle; the role of PCSK9 and antibody to PCSK9. (*A*) Intracellular cholesterol homeostasis is modulated by the LDLR pathway. The LDLR is a cell-surface glycoprotein that is synthesized in the ER and processed in the Golgi apparatus, and transported to the cell surface. The LDLR specifically binds ApoB in LDL particles. The resulting receptor–ligand complex is then internalized by endocytosis, which involves the LDLRAP1. PCSK9 binds the LDLR–LDL complex extracellularly and prevents it from dissociating within the vesicle, thus targeting the whole complex for degradation in the lysosomal compartment. (*B*) Antibody to PCSK9 prevents the binding of PCSK9 to the LDLR–LDL complex. The acidic environment of the internalized vesicle results in the dissociation of the complex. The receptor is recycled to the cell surface, whereas the LDL particle is degraded in the lysosomal compartment. Both LDLR and PCSK9 are transcriptionally regulated by SREBP.[27] Accumulation of free cholesterol released by hydrolysis of cholesteryl esters in the core of LDL inactivates SREBP. LDL, low-density lipoprotein; ApoB, apolipoprotein B; ER, endoplasmic reticulum; LDLR, LDL receptor; LDLRAP1, LDL receptor adaptor protein 1; PCSK9, pro-protein convertase subtilisin/kexin type 9; SREBP, sterol regulatory element-binding protein.

Consequences of familial hypercholesterolaemia

The consequences of LDLR gene mutations are high total serum cholesterol and high serum LDL-C.[37] Plasma levels of key lipoprotein particles, including LDL-C levels, are major determinants of the initiation of changes in vascular endothelial damage, of monocyte differentiation into macrophages and foam cell formation, leading to the development of atherosclerotic lesions,[38] premature coronary artery disease (CAD),[39] peripheral arterial disease,[40] and valvular disease (predominantly aortic stenosis).[41]

Familial hypercholesterolaemia often leads to accumulation of cholesterol in the skin, where xanthomas can occur (*Figure 2*). Xanthomas particularly affect the tendons: elbows, Achilles tendon, and hands.[37] Xanthelasmata are lipid depositions around the eyes. Deposition of lipid can also occur in the cornea, leading to presenile corneal arcus (*Figure 2*). Xanthomas and corneal arcus are pathognomonic for heFH and hoFH and their presence is associated with a three-fold higher risk of CVD in patients with FH.[42] Although xanthomas do not have any further clinical manifestations, corneal arcus is associated with an increased intraocular pressure and a lower central corneal thickness; however, any clinical implication for glaucoma is yet to be determined.[43]

Compared with heFH, these symptoms are much more severe and occur earlier in patients with hoFH. For example, xanthomas may be observed at birth or develop during early childhood in those with hoFH.[44]

Diagnosis of familial hypercholesterolaemia

Familial hypercholesterolaemia is underdiagnosed and undertreated, particularly among children. It is thought that ~20% of cases are diagnosed.[2] Familial hypercholesterolaemia patients are at a 20 times greater risk of premature CHD than the general population.[2] Early diagnosis of FH enables prompt treatment and prevention of consequent morbidity and mortality from premature CHD. Clinical findings are the first approach to diagnosis. A diagnosis of FH may comprise a combination of family history, clinical signs (specifically tendon xanthomas), and cholesterol concentration. Secondary causes of hypercholesterolaemia, such as diabetes, hypothyroidism, hepatic disease, and renal disease, should be excluded before a diagnosis of FH is considered.

There is no single internationally accepted set of criteria for the clinical diagnosis of FH. The most commonly used are the US (Make Early Diagnosis to Prevent Early Death) MEDPED,[45] the UK (Simon Broome),[12] and the Dutch Lipid Clinic[46] sets of criteria that have been statistically and genetically validated (*Table 1*). Criteria developed by groups in the UK and in the Netherlands include family and personal history, physical signs, and mutations, in addition to the cholesterol levels, which are classified in terms of a definite, probable, and possible diagnosis of FH (unlike the US criteria, which uses only lipid levels).[12,46]

Although clinical criteria for FH diagnosis are inexpensive and help to identify family members who may also have FH, they are not accurate in diagnosing index cases in the general population.[28] In some cases, it may not be apparent as to whether the elevated lipid levels are caused by FH or non-FH, such as secondary hypercholesterolaemia.

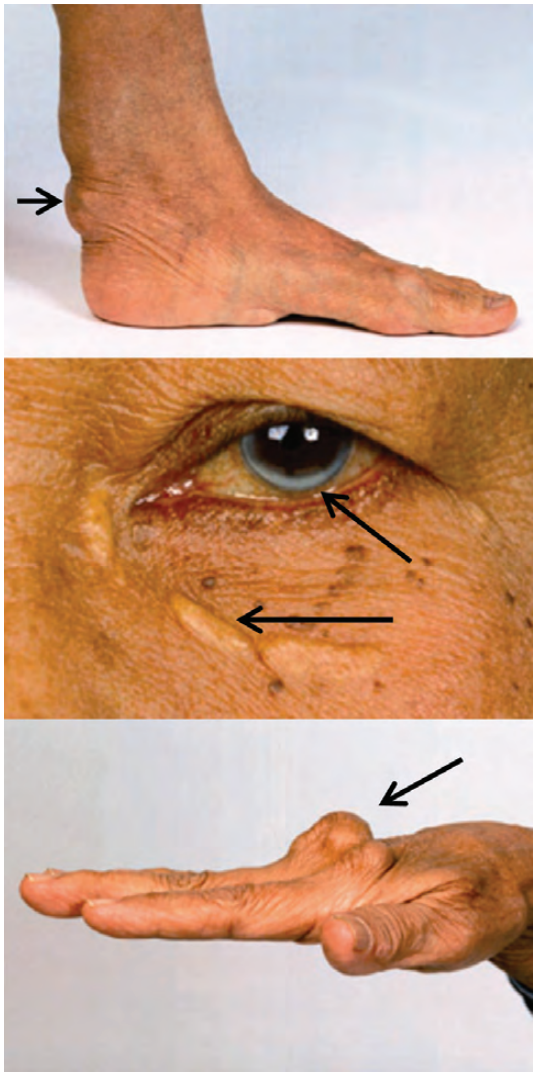

Figure 2 Examples of xanthomas in familial hypercholesterolaemia patients. (*A*) Achilles tendon xanthoma, (*B*) xanthelasmas and arcus corneae, (*C*) xanthomata of the extensor tendons. Reprinted from Liyanage *et al.*,[44] page 3, with permission from Informa Healthcare.

Genetic testing may give a definite diagnosis of FH by detection of a pathological mutation.[47] Furthermore, guidance from the National Institute of Clinical Excellence (NICE) in the UK states that comprehensive genetic analysis is more clinically effective than LDL-C screening and is also cost-effective for the diagnosis of FH.[48] Identification of the defective gene will dictate some aspects of the phenotype, allows for early diagnosis and treatment, and may be of prognostic value influencing management strategies. Patients with severe phenotypes are more likely to have a functional mutation.[49] Genetic testing is mandatory for the molecular

Table 1 Criteria for the clinical diagnosis of familial hypercholesterolaemia

USA: MEDPED criteria	Total cholesterol (and LDL-C) levels, mg/dL				Risk
Age (years)	First-degree relative	Second-degree relative	Third-degree relative	General population	
<18	220 (155)	230 (165)	240 (170)	270 (200)	
20	240 (170)	250 (180)	260 (185)	290 (220)	98% specificity
30	270 (190)	280 (200)	290 (210)	340 (240)	87% sensitivity
40+	290 (205)	300 (215)	310 (225)	360 (260)	
Total cholesterol (and LDL-C) levels	Plus				Risk
UK: Simon Broome criteria					
Adults: 290 (190) mg/dL	DNA mutation				Definite FH
Children: 260 (155) mg/dL					
	Tendon xanthomas in the patient or in a first- or second-degree relative				Definite FH
	Family history of myocardial infarction at age <50 in a second-degree relative or at age <60 in a first-degree relative or family history of total cholesterol >290 mg/dL in an adult first- or second-degree relative or 260 (155) mg/dL in a child or sibling aged <16 years				Possible FH
Rating	Feature				Risk
The Netherlands: Dutch Lipid Clinic criteria					
1 point	A first-degree relative with premature CVD or LDL-C >95th percentile, or Personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 and 189 mg/dL				
2 points	A first-degree relative with tendinous xanthoma or corneal arcus, or A first-degree relative child (<18 years) with LDL-C >95th percentile, or Personal history of CAD				
3 points	LDL-C between 190 and 249 mg/dL				Possible FH (3–5 points)
4 points	Presence of corneal arcus in patients <45 years old				
5 points	LDL-C between 250 and 329 mg/dL				
6 points	Presence of a tendon xanthoma				Probable FH (6–7 points)
8 points	LDL-C >330 mg/dL, or				Definite FH (≥8 points)
	Functional mutation in the LDLR gene				

Adapted from Fahed and Nemer,[28] page 7, with permission from Biomed Central.
LDL-C, low-density lipoprotein-cholesterol; LDLR, low-density lipoprotein receptors; FH, Familial hypercholesterolaemia.

diagnosis; however, a recent study showed the LDL-C level is the key determinant of CVD risk, and not the molecular defect *per se*.[50]

Epidemiology

In the general population, the prevalence of the heFH phenotype has been reported as 1 in 500 and the prevalence of the hoFH form is estimated to be 1 in 1 million.[44] Familial hypercholesterolaemia prevalence is higher in some populations such as the Afrikaners, the French Canadians (Québécois), the Finnish, and the Lebanese,[51] where there are founder effects and relatively isolated populations.[44,52] The highest prevalence of FH is seen in the Afrikaner population—estimated as 1 in 70 in the heFH form.[44] In French Canadians, 1 in 270 is estimated to have the heFH form.[53] There is a wide distribution and range of FH mutations in European populations, with some showing considerable heterogeneity (e.g. French and Italian), whereas others involve a narrow range of causative mutations and are relatively homogeneous.[54]

Screening for familial hypercholesterolaemia

Because FH is a highly prevalent disease, screening is warranted. Cascade screening employs genealogy to identify people at risk of FH. The index patient is diagnosed first through clinical criteria, such as by measurement of serum LDL-C, followed by a DNA test to confirm the mutation. Screening for the same mutation is undertaken in first-degree relatives to identify new cases, and any resulting new cases then have their first-degree relatives screened for the mutation.[55] Started in 1994, a national genetic cascade screening programme in the Netherlands proved to be highly

effective in identifying patients with FH.[56,57] DNA analysis and measurement of cholesterol levels were used to screen families in which a functional mutation in the LDLR gene had been detected. Similar screening strategies are being employed by Norway,[58] Spain, Wales, Australia, New Zealand, and Denmark.[28] There is an active community approach in some countries, including the Netherlands, Spain, and Wales, involving home visits to relatives by health workers offering routine lipid and genetic testing.[59,60]

Currently, national programmes determined by genetic cascade screening are implemented in the Netherlands, Spain, and Wales; regional programmes are ongoing in Australia, Brazil, the Czech Republic, Ireland, New Zealand, Norway, the Slovak Republic, and Slovenia; and local initiatives have been successful in Austria, Germany, Ireland, Italy, Malaysia, Poland, Portugal, Switzerland, Taiwan, and the UK (excluding Wales).[59] Molecular diagnosis of FH patients through genetic cascade screening in the Netherlands has achieved a significantly increased proportion of patients using cholesterol-lowering medication; however, only a minority of treated patients (22%) were able to achieve treatment targets.[55] It was reported in 2010 that screening programmes in 39 countries have identified 50 000 FH patients so far. However, within those countries, it is estimated that there are 4.4 million patients with FH, indicating that further work and intensification of screening programmes is required.[59]

Treatment for hypercholesterolaemia in familial hypercholesterolaemia

Treatment targets

Guidelines from the US National Lipid Association (NLA) and NICE in the UK recommend a reduction in LDL-C concentration of >50% from levels before treatment in patients with FH.[2,15] Guidelines from Canada and Europe recommend lowering LDL-C levels to <3.0 mmol/L (<116 mg/dL) in patients at moderate risk of CVD; to <2.5 mmol/L (<97 mg/dL) in patients at high risk; and to <1.8 mmol/L (<70 mg/dL) in patients at very high risk. The risk levels are defined according to the SCORE system, which is recommended by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS).[3,16,17] These targets are for patients with hypercholesterolaemia; however, the ESC/EAS guidelines state that targets should be the same for HeFH. If targets cannot be reached due to high pre-treatment levels, the recommended target is the maximal reduction of LDL-C that can be achieved without side effects.[3]

Current treatment

Heterozygous familial hypercholesterolaemia

There is now uniform consensus that lipid-lowering drug therapy is the cornerstone of management in adults (*Table 2*).[61] First-line treatment for patients with heFH is with statins,[2,6,62] which can lower risk of CHD in heFH by up to 80% when started as a preventive treatment in early adulthood.[63] Statins have beneficial effects on the incidence of cardiovascular events and coronary atherosclerosis in patients with CAD.[64–66]

Statin doses may be increased to the maximum licensed or tolerated dose to achieve the recommended reduction in LDL-C concentration. Higher risk patients, such as those with clinically evident CHD or other atherosclerotic CVD, a family history of very early CHD, two or more CVD risk factors, or high lipoprotein (a) [Lp(a)], may need intensification of drug treatment to achieve more aggressive treatment goals. Indeed, a study in patients with FH showed that elevated Lp(a) was a risk factor for CVD[9] and a consensus statement from EAS concludes that screening for Lp(a) should be performed in those at high or intermediate risk of CVD/CHD. Niacin is currently recommended to reduce Lp(a) levels in these patients.[67] Familial hypercholesterolaemia patients without these risk factors may also require intensification of drug therapy if their treatment targets are not achieved.[2] It is often necessary to use statins in combination with other agents, such as ezetimibe, bile acid sequestrants (e.g. colesevalam), or stanol esters, which may improve the LDL-C-lowering response.[7]

Ezetimibe use results in a compensatory increase in hepatic LDLRs and an ~20% reduction in LDL-C.[7] Ezetimibe may be used as a monotherapy treatment for adults who are unable to take statins or in combination therapy.[6] Bile acid sequestrants also have a strong LDL-C-lowering effect and are frequently used at high doses in monotherapy when statins are not well tolerated or in combination with statins when statins alone are not able to achieve the LDL-C target. Nicotinic acid, along with fibric acid derivatives, is an agent with one of the greatest triglyceride-lowering effects.[68] By displacing cholesterol from bile salt micelles and interfering with cholesterol absorption,[69] stanol esters also have a cholesterol-lowering effect.[70] Of note, despite the LDL-C-lowering effect observed, there is currently no evidence to support a reduction in CVD events with ezetimibe, stanol esters, or combination therapy, although there are some data to support reductions in CVD events with niacin and fenofibrate monotherapy.[71] Due to interactions with statins, fibrates should only be prescribed with caution.

Lifestyle changes to reduce CHD risk, such as smoking cessation, regular physical activity, weight and blood pressure control, and moderation of alcohol intake, should also be emphasized.[2,6] Furthermore, dietary changes are also important. A low-saturated fat diet has been shown to result in ~8–10% reduction in LDL-C, whereas consuming <200 mg/day of dietary cholesterol may result in ~3–5% reduction in LDL-C.[72] Indeed, NLA guidelines suggest that patients with FH should reduce their intake of saturated fatty acids to <7% of energy intake and reduce dietary cholesterol to <200 mg/day.[2]

Homozygous familial hypercholesterolaemia

Statins may be effective in some hoFH patients,[2] although generally, even high doses of HMG-CoA reductase inhibitors have only modest effects on plasma levels of LDL-C, as there is a diminished response to statins in HoFH patients, with reductions in LDL-C of ~20 vs. ~40–60% reductions in other patients with

Table 2 Current lipid-lowering therapies and future management

Lipid–lowering therapy	Mechanism of action	Effects
Current therapies		
HMG-CoA reductase inhibitors (statins)	Inhibition of HMG-CoA reductase	Increases LDLR activity. FH patients should initially be treated with more potent statins, which have been shown to reduce LDL-C levels by 50–60% at their maximum proved doses
Ezetimibe	Inhibition of cholesterol absorption by interfering Niemann–Pick C1-like 1 protein, responsible for transluminal cholesterol transport	Reduces cholesterol absorption, which reduces the delivery of intestinal cholesterol to the liver
Bile acid sequestrants (colesevelam, colestipol, cholestyramine)	Decrease of the hepatocyte cholesterol content, resulting in an up-regulation of the LDLR	Increases LDLR activity, increased clearance of LDL-C from the circulation by up to 20%
Nicotinic acids (niacin)	Unclear	Reduces VLDL synthesis, favourably affects VLDL, LDL-C, and increases HDL-C
Fibrates (bezafibrate, ciprofibrate, gemfibrozil, fenofibrate)	Probably mediated by agonizing PPAR-α	Decreased production of VLDL-C and an increased clearance of triglycerides. Fibrates have also been shown to lower total cholesterol and LDL-C and elevate HDL-C
Stanol esters	Decreases cholesterol absorption by displacing cholesterol from mixed micelles	Reduces cholesterol absorption
Low fat, low cholesterol diet	Reduces cholesterol intake	Increases LDLR activity
LDL apheresis	Filters LDL particles from the circulation through extracorporeal binding to either dextran sulfate or heparin	Removes LDL, resulting in an LDL-C reduction of ∼60%
Therapies in development		
MTP inhibitors	Inhibition of MTP, thereby interfering in the assembly of plasma lipoproteins in the liver by mediating the transfer of triglycerides and on to VLDL (liver) and chylomicron (intestine)	
ApoB synthesis inhibitors (mipomersen)	Inhibition of ApoB production	
Thyroid mimetics (eprotirome)	Selective affinity for thyroid receptor β, which is expressed in the liver. Induction of metabolic beneficial pathways	
PCSK9 inhibitors	Inhibition of PCSK9, protease which inhibits the expression of LDL receptors	
CETP inhibitors (torcetrapib, dalcetrapib, anacetrapib)	Inhibition of CETP, which mediates the exchange of cholesteryl esters from HDL to LDL particles	

Adapted from Rader *et al.*,[7] page 1798, with permission from the American Society for Clinical Investigation, and Sjouke *et al.*,[93] page 532, with permission from Springer.
C, cholesterol; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; MTP, microsomal triglyceride transfer protein; PCSK9, pro-protein convertase subtilisin/kexin type 9; PPAR-α, peroxisome proliferator-activated receptor-α; VLDL, very low density lipoprotein.

hypercholesterolaemia.[73,74] However, one study demonstrated that ezetimibe combined with a statin resulted in clinically important reductions in LDL-C concentrations in patients with hoFH.[75] Nevertheless, the current treatment offered to patients with hoFH is weekly or biweekly LDL-C apheresis.[2,6] This therapy removes LDL particles from the circulation by their binding to dextran sulphate or heparin, and can promote regression of xanthomas and slow the progression of atherosclerosis.[76,77] Low-density lipoprotein-cholesterol apheresis typically results in a 50–70% reduction in LDL-C levels that can last for up to 2 weeks. Although effective, it is time-consuming, costly, and limited in certain regions.[76,77] Adverse events (AEs) associated with LDL-C apheresis are uncommon; however, these can include hypotension, nausea, headache, anaemia, chest pain, arrhythmias, and blood loss. Liver transplantation to bring about normal functional LDLRs is an alternative for severe cases, whereas other surgical techniques such as portacaval shunt surgery limit cholesterol absorption and promote bile acid loss.[41,78–80]

New treatments: realizing achievable goals

A study in 1249 patients with heFH found that of the 96% of patients on a statin, 47% of them reached >50% of LDL-C

lowering, and only 21% of them reached LDL-C levels of <2.5 mmol/L (97 mg/dL).[18] Almost a third (27%) of patients who did not reach the target of LDL-C levels of <2.5 mmol/L were on combination therapy of maximum statin dose and ezetimibe.[18] The study suggests that only a small proportion of patients with FH reach the LDL-C targets recommended by current guidelines,[2,15] often because they are not treated to the maximum extent, they are statin intolerant, or because their levels are too high to be controlled with currently available lipid-lowering therapies. This indicates the need for better monitoring and use of available therapies, and for new treatment options to decrease LDL-C levels beyond those currently achieved. Control of cholesterol concentrations should also be based on individualized risk assessment for CVD, concomitant medications, and the presence of other disease conditions. Moreover, for paediatric cases of FH, the balance between increased dosing and the potential for side effects vs. achieving goals must be evaluated. There are several new classes of pharmacotherapy providing new opportunities to effectively control LDL-C levels (*Table 2*).

Agents modifying low-density lipoprotein-cholesterol production: inhibitors of very low density lipoprotein-cholesterol secretion

Microsomal triglyceride transfer protein (MTP) plays an important role in the formation of ApoB-containing lipoproteins in hepatocytes and intestinal enterocytes[81] and its inhibition prevents very low density lipoprotein-cholesterol (VLDL-C) secretion, leading to reductions in cholesterol and triglyceride levels.[82] Lomitapide is an oral MTP inhibitor that is intended to treat hoFH. In a dose-ranging study, lomitapide demonstrated decreases of 50.9 and 55.6% in LDL-C and ApoB, respectively, at 1.0 mg/kg/day compared with baseline levels.[83] However, in this study, lomitapide was associated with transaminase elevations in four of the six patients enrolled, and hepatic fat was also increased in four patients.[83] A recent analysis of a Phase III study of lomitapide, which enrolled 29 patients with hoFH, showed that elevations in transaminases, between 5 and 11 times the upper limit of normal, were observed in four patients. Liver fat count also increased from 0.9 $\pm$ 1.0% at baseline to 7.3 $\pm$ 8.2% at week 56.[84] The transaminase rise associated with lomitapide may limit its clinical use.

Apolipoprotein B is essential for the production of VLDL-C (the precursor of LDL-C) and for the subsequent clearance of cholesterol.[85] Mipomersen, an oligonucleotide antisense inhibitor directed against ApoB mRNA, was associated with decreases from baseline in LDL-C of up to 37% in subjects with heFH and hoFH.[86–88] An average reduction of LDL-C >100 mg/dL with mipomersen was observed in patients with hoFH and severe hypercholesterolaemia.[86] The most common AEs were transient, mild-to-moderate injection-site reactions, and flu-like symptoms. In some patients, increases in liver transaminase levels (three or more times the upper limit of normal) and the fat content of the liver were observed,[86,88] which tended to stabilize or decrease with continued treatment.[89] A large study in severe heFH is currently underway to assess long-term safety and efficacy of mipomersen (Focus FH; www.clinicaltrials.gov, NCT01475825).

Agents affecting low-density lipoprotein-cholesterol catabolism

Thyroid hormone analogues lower cholesterol via increased clearance of LDL-C, caused by increased expression of the LDLR protein.[90,91] Owing to their mechanism of action, thyroid mimetics are unlikely to work in patients with hoFH, but have been assessed in patients with hypercholesterolaemia. Operating through thyroid receptor-β, the beneficial effect of one of these hormone analogues, eprotirome, has been explored in a 12-week placebo-controlled trial.[92] Given in addition to a statin, eprotirome (25, 50, and 100 μg daily) resulted in a decrease of LDL-C levels by 22, 28, and 32%, respectively, vs. placebo (7%).Very recently, the eprotirome programme in heFH (AKKA) was discontinued due to unexpected side effects in a pre-clinical model after long-term chronic dosing (www.clinicaltrials.gov, NCT01410383). Sobetirome and MB07811, which act similarly, have not yet been tested for their effect on dyslipidaemia in humans.[93]

Pro-protein convertase subtilisin/kexin 9 is involved in the degradation of LDLR.[25] Interest in PCSK9, as a target for lipid lowering, stems from reports of the associations between PCSK9 gain-of-function mutations and ADH, and between PCSK9 loss-of-function mutations and reduced LDL-C levels.[1,94] In African Americans, two nonsense mutations in PCSK9 (*PCSK9*^{142X} and *PCSK9*^{679X}) led to a 28% reduction in LDL-C levels, which were associated with an 88% risk reduction in CHD. In white subjects, the *PCSK9*^{46L} loss-of-function mutation was associated with a 15% reduction in LDL-C, and a 47% risk reduction in CHD.[95] A mouse model with PCSK9 deficiency has shown abnormal pancreatic islets and is also hyperglycaemic and hypoinsulinaemic[96]; however, this has not been observed in humans.

Several strategies to lower PCSK9 activity are under investigation, including antisense nucleotide-based therapy (e.g. ISIS BMS-PCSK-9$_{Rx}$, ALN-PCS02, and ID01),[97,98] monoclonal antibodies binding to PCSK9 (e.g. REGN727/SAR236553, AMG 145, 1D05-IgG2, and RN316),[98–101] and small interfering RNAs.[93] A few are in the early stages of development. REGN727/SAR236553, a fully human monoclonal antibody to PCSK9, has proved well tolerated in Phase I studies when administered subcutaneously, with no significant elevations of liver transaminases, but a dose-dependent decrease in LDL-C, Apo-B, and non-high-density lipoprotein (HDL)-C.[99] When added to statins, REGN727/SAR236553, at doses of 50–150 mg, demonstrated dose-dependent LDL-C reductions of 41–58% in patients with FH, and 38–65% in those without FH vs. placebo.[99]

Three Phase II trials assessing REGN727/SAR236553 have also been completed.[102,103] The first evaluated REGN727/SAR236553 in hypercholesterolaemic patients taking atorvastatin treatment.[102] Patients were randomized to placebo or one of the REGN727/SAR236553 regimens (50, 100, or 150 mg every 2 weeks, or 200 or 300 mg every 4 weeks) for 12 weeks. A dose-dependent decrease in LDL-C (40–72%), non-HDL-C, Apo-B, and Lp(a) was observed after 12 weeks of REGN727/SAR236553 treatment. Adverse events were similar for all treatment groups, with no dose relationship observed. The most common AEs observed in the treated recipients were mild injection-site reactions. There

was one case of treatment-related leucocytoclastic vasculitis.[102] The second study compared REGN727/SAR236553 in combination with a high-dose atorvastatin (80 mg) or atorvastatin 10 mg vs. high-dose atorvastatin plus placebo in patients with LDL-C ≥2.6 mmol/L (≥100 mg/dL) who had received atorvastatin 10 mg for at least 6 weeks prior to randomization.[103] After 8 weeks, patients receiving atorvastatin 80 mg alone achieved a mean LDL-C reduction of 17.7, vs. 72.3% for those receiving atorvastatin 80 mg plus REGN727/SAR236553 ($P < 0.0001$). Patients receiving REGN727/SAR236553 plus atorvastatin 10 mg had a mean LDL-C reduction of 66.7%.[103] This study suggests that PCSK9 inhibition provides an additive effect to statin-induced LDL-C lowering and can potentially be used as combination treatment in hypercholesterolaemic subjects. No new safety concerns were recorded.[103] A third Phase II trial assessed REGN727/SAR236553 in adults with heFH on a stable diet and a daily stable statin dose (with or without ezetimibe).[104] Patients were randomized to REGN727/SAR236553 150, 200, or 300 mg every 4 weeks, or 150 mg every 2 weeks, or placebo every 2 weeks. Administration of REGN727/SAR236553 was associated with dose-dependent least squares mean reductions of LDL-C from baseline to week 12 of 28.9–67.9 vs. 10.7% with placebo.[104] Of those receiving REGN727/SAR236553 150 mg every 2 weeks, 94 and 81% of patients achieved target levels of LDL-C <2.6 mmol/L (<100 mg/dL) and LDL-C <1.8 mmol/L (<70 mg/dL), respectively, vs. 27 and 13% of those receiving placebo. The safety profile was similar to that observed in the other Phase II trials.[104] A number of studies are also in the planning phase to assess long-term safety of REGN727/SAR236553 in heFH.

AMG 145, a fully human monoclonal antibody to PCSK9, has been evaluated in an ascending single-dose study in healthy subjects. Relative to placebo, administration of AMG 145 (subcutaneously or intravenously) dose-dependently decreased mean LDL-C levels by up to 64%.[100] AMG 145 was administered to patients with LDL-C 70–200 mg/dL (1.8–5 mmol/L) receiving low/moderate- or high-dose statin therapy in a Phase I, ascending, multiple-dose study. Patients received AMG 145 between once-weekly (a total of six doses) to once every 4 weeks (two doses). Mean LDL-C decreases of up to 75% vs. placebo were observed after three biweekly doses of AMG 145.[105] In the Phase I studies, there were no serious AEs or discontinuations due to an AE. The incidence of AEs was similar between patients receiving AMG145 and those receiving placebo.[100,105]

High-density lipoprotein-cholesterol-raising therapies

High-density lipoprotein scavenges cholesterol from peripheral tissues and transports it to the liver for excretion or recycling. This process, called reverse cholesterol transport, is anti-atherogenic and is found to promote atherosclerosis regression.[106] Studies indicate a strong inverse correlation between plasma levels of HDL and CVD; thus, emerging therapies aim to enhance HDL levels. The HDL-bound enzyme cholesterol ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL particles to pro-atherogenic lipoproteins, including ApoB-containing particles.[107] The addition of the CETP inhibitor torcetrapib to atorvastatin significantly reduced LDL-C (21%) and increased HDL-C (52%).[108] A Phase III clinical trial with patients at high cardiovascular risk, receiving either torcetrapib in combination with atorvastatin or atorvastatin alone, was terminated early due to increased morbidity and mortality in patients receiving torcetrapib.[109] This study demonstrated potential off-target effects of torcetrapib (plasma sodium increase, potassium decrease, and blood pressure increase); however, it did not rule out the cardioprotective effect of CETP inhibition. Therefore, other CETP inhibitors, anacetrapib and evacetrapib, are being evaluated, which have thus far been shown to effectively increase HDL-C levels—without the off-target toxicity.[110,111] The development of another CETP inhibitor, dalcetrapib, has been terminated due to a lack of efficacy in terms of reduction of cardiovascular events.

In FH patients, low HDL-C levels have been shown to be an independent risk factor to the development of CVD. HDL-C levels are affected by risk factors such as sex, obesity, smoking, diet, alcohol consumption, and exercise, as well as genetic polymorphisms leading to variations of HDL-C levels in FH patients.[112] A Phase III study of anacetrapib is currently underway in a large cohort of heFH patients (REALIZE; www.clinicaltrials.gov; NCT01524289).

Therapy targeting plaque regression

Subjects with FH develop premature CVD and might therefore benefit from interventions potentially affecting plaque regression. Reconstituted HDL (rHDL) shows promise in this respect in pre-clinical and clinical data. Intravenous administration of rHDL particles has been associated with regression of coronary atherosclerosis in humans and improvement in plaque characteristics,[113] with indications that it may promote reverse cholesterol transport.[114] The CER-001 developed by Cerenis™ Therapeutics mimics pre-beta HDL and has been shown in Phase I studies to mobilize cholesterol from the vasculature and is well tolerated. Ongoing Phase III studies are evaluating CER-001 in the regression of coronary atherosclerotic plaque (CHI SQUARE; www.clinicaltrials.gov; NCT01201837)[115] and in hoFH (MODE; NCT01412034).

Gene replacement therapy

The ultimate treatment of a genetic disease is gene replacement. Gene replacement for dyslipidaemia regarding LDLRs, ApoB inhibition, and lipoprotein lipase deficiency, plus gene transfer strategies for reducing LDL-C levels are currently being explored.[114]

Conclusions

Patients with FH are at severe risk for premature CVD and need to be treated early. The biggest difficulty is diagnosing the disorder in the asymptomatic population in order to commence early treatment. Current treatments are not always successful in lowering LDL-C levels to target; therefore, new treatments are urgently needed. Promising agents for heFH include PCSK9 inhibitors and CETP inhibitors. For severe FH, potential novel therapies include inhibitors of MTP and ApoB mRNA and infusion of pre-beta HDL (CER-001), whereas PCSK9 inhibitors and CETP inhibitors still require investigation in this condition. This review of FH will

be a valuable reference for use in the guideline projects currently in preparation.

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