Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel

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Familial hypercholesterolaemia is common in individuals who had a myocardial infarction at a young age. As many as one in 200 people could have heterozygous familial hypercholesterolaemia, and up to one in 300 000 individuals could be homozygous. The phenotypes of heterozygous and homozygous familial hypercholesterolaemia overlap considerably; the response to treatment is also heterogeneous. In this Review, we aim to define a phenotype for severe familial hypercholesterolaemia and identify people at highest risk for cardiovascular disease, based on the concentration of LDL cholesterol in blood and individuals' responsiveness to conventional lipid-lowering treatment. We assess the importance of molecular characterisation and define the role of other cardiovascular risk factors and advanced subclinical coronary atherosclerosis in risk stratification. Individuals with severe familial hypercholesterolaemia might benefit in particular from early and more aggressive cholesterol-lowering treatment (eg, with PCSK9 inhibitors). In addition to better tailored therapy, more precise characterisation of individuals with severe familial hypercholesterolaemia could improve resource use.

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Introduction

Familial hypercholesterolaemia is an autosomal co-dominant disorder characterised by raised concentrations of LDL cholesterol in blood and an average 3–13 times greater risk of premature atherosclerotic cardiovascular disease, compared with individuals with normal blood concentrations of LDL cholesterol.[1–3] Familial hypercholesterolaemia has been subclassified into heterozygous and homozygous forms, depending on the presence of one or two affected alleles in genes encoding the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*).[1,3] Clinical diagnosis is made on the basis of raised concentrations of LDL cholesterol: patients with heterozygous familial hypercholesterolaemia usually present with LDL cholesterol concentrations two to three times higher than normal, and those with homozygous forms of the disease have LDL concentrations up to ten times higher.[3,4] With the exception of regions where founder effects are present (eg, South Africa, Quebec in Canada, and Lebanon), evidence suggests that heterozygous familial hypercholesterolaemia affects one in roughly 200–600 individuals.[2,5,6] Homozygous familial hypercholesterolaemia, which was initially reported to affect one in 1 000 000 people,[7] is probably three times more prevalent than previously thought.[4,8]

Patients with the homozygous familial hypercholesterolaemia phenotype are at highest risk for atherosclerotic cardiovascular disease.[7,9] However, with more widespread use of molecular diagnosis, findings show that some people carrying heterozygous mutations in genes associated with familial hypercholesterolaemia have LDL cholesterol concentrations that overlap those deemed characteristic of homozygous familial hypercholesterolaemia (usually ≥10–13 mmol/L [≥400–500 mg/dL]);[1,4] therefore, these individuals should also be judged at very high risk for atherosclerotic cardiovascular disease.[8,10,11] The converse also applies: patients with molecularly proven homozygous familial hypercholesterolaemia can present with LDL cholesterol concentrations in the range typical for heterozygotes (≥5–10 mmol/L [≥190–400 mg/dL]).[8,11–14] Reasons for phenotypic heterogeneity among individuals with the same familial hypercholesterolaemia genotype have become apparent: LDL cholesterol concentrations are affected not only by rare, large-effect monogenic variants but also by common, small-effect gene variants. This notion adds complexity to diagnostic classification of the disease.[15,16] Since concentrations of LDL cholesterol—and not the causative mutations in familial hypercholesterolaemia or range of variants—are the main drivers of risk for atherosclerotic hypercholesterolaemia,[17] a definition of the severe phenotype of familial hypercholesterolaemia, encompassing individuals at high risk, whether they have molecularly defined heterozygous or homozygous familial hypercholesterolaemia, needs to be considered for best clinical practice.[10] Patients with familial hypercholesterolaemia and previous manifestations of atherosclerotic cardiovascular disease,[18] those with advanced subclinical atherosclerosis,[19–21] and individuals with LDL cholesterol concentrations greater than 8 mmol/L (310 mg/dL),[22] associated or not with other risk conditions at initial presentation, are at especially high risk for atherosclerotic cardiovascular disease.

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Case identification is important in view of the availability of effective, standard, lipid-lowering drugs (mainly high-dose statins and ezetimibe)[1,4] and emerging, efficacious, but more expensive treatments such as mipomersen,[12,23] lomitapide,[13] and PCSK9 inhibitors.[24] Indeed, considering cost-effectiveness,[25,26] PCSK9 inhibitors could have particular benefits for patients with familial hypercholesterolaemia who are deemed at the highest risk for atherosclerotic cardiovascular disease and have persistent and recalcitrant raised concentrations of LDL cholesterol, despite treatment.

This Review arose from a need to address gaps in our knowledge about the familial hypercholesterolaemia phenotype. We now know that risk for atherosclerotic cardiovascular disease in people with familial hypercholesterolaemia is related directly to chronic exposure to raised concentrations of LDL cholesterol. Furthermore, genetic diagnosis of severe familial hypercholesterolaemia is difficult because the previous stratification of disease—non-mutated, heterozygous, or homozygous—no longer describes risk adequately in view of the overlap in LDL cholesterol concentrations across these categorisations. With availability of new drugs to lower LDL cholesterol effectively, and the scant evidence base that addresses the issue of genetic heterogeneity directly, the International Atherosclerosis Society convened an expert panel to establish consensus about clinical recommendations for this high-risk population, which we report here. In this Review, we discuss risk stratification for atherosclerotic cardiovascular disease and treatment recommendations for patients, including timing, intensification, goals, and choice of drug.

LDL cholesterol

Hypercholesterolaemia is an independent cause of atherosclerotic cardiovascular disease, as shown by findings of prospective observational studies,[27] genome-wide association studies,[28] and mendelian randomisation studies.[29,30] Definitive proof of this causal role derives from several clinical trials and surrogate interventional studies of cholesterol-lowering drugs, mainly statins,[31,32] in which a reduction in major atherosclerotic cardiovascular events and mortality has been reported.

Because of their very high concentrations of LDL cholesterol in blood, patients with homozygous familial hypercholesterolaemia are judged at highest risk for early atherosclerotic cardiovascular disease, which could be up to 100 times higher than the risk in the general population.[7,9] Individuals with homozygous familial hypercholesterolaemia frequently develop aortic or supra-aortic valve stenosis, in addition to atherosclerosis in the aorta, coronary, carotid, and peripheral arteries.[7]

The idea of the cholesterol-year score—a marker of exposure to high cholesterol levels over time—underpins the pathogenic relation between chronically increased concentrations of LDL cholesterol and extensive atherosclerosis in young patients with homozygous familial hypercholesterolaemia.[5,33–35] High concentrations in blood of LDL cholesterol are associated with worse prognosis in individuals with both homozygous and heterozygous familial hypercholesterolaemia.[22,35,36] If left untreated, familial hypercholesterolaemia is especially devastating among younger people, as shown in the pre-statin era, when increases in adjusted mortality rates were 125 times greater in women and 48 times greater in men aged 20–29 years compared with individuals with normal amounts of LDL cholesterol in blood.[37] Recently, Do and co-workers[38] sequenced the protein-coding regions of 9793 genomes from patients with early myocardial infarction and found that 2% of cases were caused by mutations in the LDL receptor gene. Similarly, Nanchen and colleagues[39] reported that 70 (5%) of 1451 individuals aged younger than 60 years and presenting with an acute coronary syndrome had either probable or definite familial hypercholesterolaemia.

Disappointingly, even among reports that include treatment with statins, individuals with the homozygous phenotype for familial hypercholesterolaemia still live with a very high risk of early atherosclerotic cardiovascular disease and premature mortality.[40,41] Raal and co-workers[40] assessed the occurrence of major atherosclerotic cardiovascular events in 149 patients from South Africa with homozygous familial hypercholesterolaemia. The prevalence of these events was reduced by 51% after 1990, which was the year statins were introduced in South Africa. Even so, the age at onset of the first major atherosclerotic cardiovascular event was delayed on average from 12·8 years to only 28·3 years, and by age 40 years almost 90% of patients in the study had had a vascular event. Thompson and colleagues[41] reported long-term outcomes of 43 patients with homozygous familial hypercholesterolaemia who had been treated at the Hammersmith Hospital in London, UK, over a period of 50 years. They compared patients who did or did not die during follow-up. The use of statins and apheresis was more frequent in survivors, and a clear temporal improvement was noted in the care of patients over this period. However, the prevalence of atherosclerotic cardiovascular disease was still high in surviving patients: aortic stenosis was recorded in 33%, aortic valve replacement was needed in 14%, and coronary heart disease was present in 37%. In both the South African and UK studies, on-treatment total cholesterol concentrations remained very high, with an average of 13·1 mmol/L (505 mg/dL) in the South African cohort[40] and 8·1 mmol/L (320 mg/dL) in the UK population.[41] These findings confirm the importance of high cholesterol concentrations as the driver of atherosclerotic cardiovascular disease in homozygous familial hypercholesterolaemia and the huge unmet treatment need for this population.

Many individuals with heterozygous familial hypercholesterolaemia are at high risk of atherosclerotic cardiovascular disease because they have very high concentrations of LDL cholesterol that are refractory to

current lipid-lowering treatments. LDL cholesterol concentrations greater than 8 mmol/L (310 mg/dL) before treatment could identify a more severe phenotype of heterozygous familial hypercholesterolaemia,[22] independent of the presence of traditional risk factors such as smoking, diabetes, hypertension, or a family history of early atherosclerotic cardiovascular disease. However, risk is increased if these other risk factors were also present. In a Dutch cohort with familial hypercholesterolaemia, raised LDL cholesterol concentrations were encountered in one in 3000 people, or 11% of the Dutch population with familial hypercholesterolaemia, and were associated with an odds ratio of 1·36 (95% CI 1·09–1·69) before treatment for atherosclerotic cardiovascular disease, compared with patients with lower amounts of LDL cholesterol.[22] An LDL cholesterol concentration greater than 8 mmol/L (310 mg/dL) that is refractory to maximally tolerated pharmaceutical therapy is an indication for reimbursement of apheresis (ie, plasmapheresis or selective lipoprotein apheresis) in patients without previous manifestations of atherosclerotic hypercholesterolaemia.[42]

Another important issue when assessing the severity of the familial hypercholesterolaemia phenotype is the age at initiation of treatment. Late treatment (eg, after age 40 years)[3,5,34] implies prolonged exposure of the arterial wall to high concentrations of LDL cholesterol and, thus, a greater risk of atherosclerotic cardiovascular disease.

Most guidelines endorse a minimum reduction in LDL cholesterol of 50% for patients with familial hypercholesterolaemia.[1,3–5] Specific absolute targets are sometimes recommended—eg, LDL cholesterol concentrations less than 2·5 mmol/L (100 mg/dL), or 1·8 mmol/L (70 mg/dL) in individuals presenting with clinical atherosclerotic cardiovascular disease.[1,3,5] In a cross-sectional assessment of 1249 Dutch patients with heterozygous familial hypercholesterolaemia undergoing lipid-lowering treatment, with 904 (72%) patients receiving a dose aimed to reduce LDL cholesterol by 50%,[43] only 261 (21%) participants attained levels of LDL cholesterol less than 2·5 mmol/L (100 mg/dL). In the SAFEHEART Spanish familial hypercholesterolaemia cohort, 2170 patients with a proven genetic diagnosis of heterozygous disease were followed up for an average of 5 years.[44] 1562 (72%) participants were on maximum lipid-lowering treatment, defined as a statin dose—alone or combined with ezetimibe—aiming to reduce LDL cholesterol by at least 50%. An LDL cholesterol concentration target less than 2·5 mmol/L (100 mg/dL) was reached in only 247 (11%) patients. Of 277 individuals presenting with previous atherosclerotic cardiovascular disease, only 13 (5%) attained a concentration of LDL cholesterol less than 1·8 mmol/L (70 mg/dL). These results show the immense deficit in controlling lipids in patients with familial hypercholesterolaemia, particularly for secondary prevention of atherosclerotic cardiovascular disease.

Genotype, LDL cholesterol, and risk discordance

High LDL cholesterol is the *sine qua non* for diagnosis of familial hypercholesterolaemia—eg, greater than 5 mmol/L (190 mg/dL) for adults with heterozygous disease. Diagnostic confidence is increased with a family history of hypercholesterolaemia, personal or family history of premature atherosclerotic cardiovascular disease, and physical features such as tendon xanthomas, arcus cornealis, and xanthelasmas.[1,5,45] Although future personalised medicine might benefit from knowledge about genomic background, and detection of the pathogenic mutation can support family screening, identification of a causative gene variant is not essential for either diagnosis or treatment decisions, since these are guided more appropriately by LDL cholesterol concentration and not by genotype. However, widespread use of genetic analysis to identify patients with familial hypercholesterolaemia has led to the discovery of a higher prevalence than expected of less severe forms of the disease,[4,5,8] with lower LDL cholesterol concentrations and less apparent physical findings. Several factors confound the genotype–phenotype relation in familial hypercholesterolaemia and make the simplistic distinction between homozygous and heterozygous disease inadequate for risk management. These include: heterogeneity of monogenic causes; heterogeneous variant classes; polygenic effects; gene–gene interactions; gene–environment interactions; modulatory roles for other unknown mendelian genes; and non-mendelian genetic mechanisms, including epigenetic effects.

Locus and mutation type heterogeneity

Familial hypercholesterolaemia is typically inherited as a co-dominant autosomal disease, caused by mutations in (in decreasing order of prevalence) *LDLR*, *APOB*, and *PCSK9*.[5,45] Next-generation sequencing has shown that the heterozygous phenotype of familial hypercholesterolaemia results very occasionally from dominant mutations in *APOE*, which encodes apolipoprotein E, or *STAP1*, which encodes signal-transducing adapting family member 1.[4,5] The *LDLR*, *APOB*, and *PCSK9* co-dominant genes also underlie the homozygous phenotype of familial hypercholesterolaemia, when two mutations are inherited.[4] For *LDLR* variants, the severity of the clinical phenotype depends on residual LDL receptor activity.[5,45] *LDLR* negative or *LDLR* null mutations are associated with less than 2% activity of LDL receptors, and *LDLR* defective mutations are associated with 2–25% activity.[4]

Furthermore, rare variants in *LDLRAP1*, which encodes LDL receptor adaptor protein 1, cause a purely autosomal recessive hypercholesterolaemia, in which heterozygous parents are phenotypically normal. Recessive forms of hypercholesterolaemia with a phenotype similar to homozygous familial hypercholesterolaemia have been reported with particular rare mutations in *LIPA*, which encodes lysosomal acid lipase, and *ABCG5* and *ABCG8*, which encode sterolin 1 and sterolin 2,

respectively. Homozygosity for *LIPA* mutations causes cholesterol ester storage disease (or Wolman's disease), and compound heterozygosity for mutations in ABC transporter genes causes sitosterolaemia (or phytosterolaemia).[46]

Genetic heterogeneity in homozygous familial hypercholesterolaemia underlies phenotypic variability (figure 1). Patients with *LDLR* null mutations and homozygous familial hypercholesterolaemia have higher levels of LDL cholesterol and poorer clinical prognosis than do individuals with *LDLR* defective mutations who are homozygous.[35,47] Across the range of phenotypes for familial hypercholesterolaemia, the mean amount of LDL cholesterol follows a decreasing gradient according to genotype. Thus, for example, patients with homozygous familial hypercholesterolaemia and an *LDLR* null mutation have higher amounts of LDL cholesterol than do those with a compound heterozygous *LDLR* null mutation and an *LDLR* defective mutation. Compound heterozygotes with *LDLR* null and *LDLR* defective mutations have higher values of LDL cholesterol than do individuals with homozygous familial hypercholesterolaemia and an *LDLR* defective mutation or a mutation in *LDLRAP1*, and they have greater values of LDL cholesterol than do people homozygous for a defective mutation in *APOB* or a *PCSK9* gain-of-function mutation. Furthermore, those levels of LDL cholesterol are greater than for people who are double heterozygous (eg, with *LDLR* and *PCSK9* gain-of-function mutations or defective *APOB*). Finally, people with heterozygous familial hypercholesterolaemia and an *LDLR* null mutation have LDL cholesterol levels greater than those of individuals with heterozygous disease and an *LDLR* defective mutation.[4]

Findings of population-based molecular studies showed that around 50% of people carrying two causative variants for familial hypercholesterolaemia had LDL cholesterol concentrations consistent with previous clinical diagnostic criteria for homozygous disease—ie, greater than 13 mmol/L (500 mg/dL).[4,8] The need for aggressive treatment—eg, lipoprotein apheresis, lomitapide, mipomersen, or PCSK9 inhibition—in such people depends on the LDL cholesterol concentration and not the molecular diagnosis. For instance, a carrier of two genetic variants who has an amount of LDL cholesterol in blood in the range of that for patients with heterozygous familial hypercholesterolaemia could be treated as a heterozygote, even though molecularly they have homozygous disease. Conversely, some patients with only one heterozygous mutation detected might present with LDL cholesterol concentrations consistent with the homozygous phenotype. Such genotype–phenotype discrepancies can be attributable to factors other than the major locus effect.

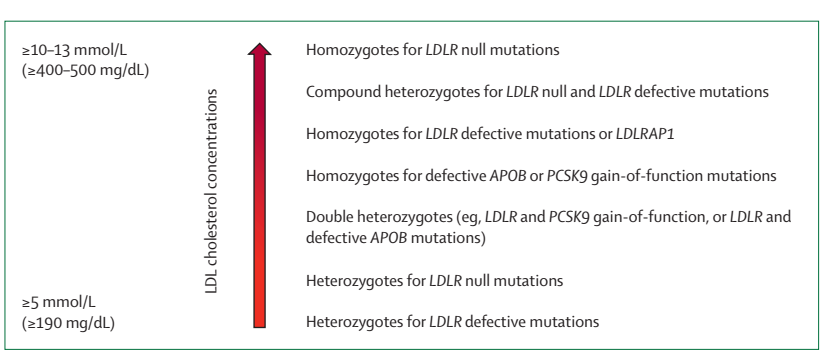

Figure 1: **Range of LDL cholesterol concentrations in severe hypercholesterolaemia, according to monogenic defects**
LDL cholesterol concentrations might overlap in individuals with different genetic defects.[1,4] They might also vary according to the presence or absence of small-effect gene variants.[15,16] Homozygotes have the same mutation in two alleles of the same gene. Double heterozygotes have different mutations, one on each allele of the same gene. Compound heterozygotes have mutations in two different genes. *LDLR* null mutations defined as LDL receptor activity <2% in fibroblasts. *LDLR* defective mutations defined as LDL receptor activity 2–25% in fibroblasts.

Small-effect variants in hypercholesterolaemia

Causative variants are not identified by DNA sequencing in 20–40% of patients who meet clinical criteria for probable or definite heterozygous familial hypercholesterolaemia.[15] Some of this missing variability is now attributable to polygenic effects, which are quantifiable by risk scores for high LDL cholesterol.[15] Polygenic risk scores are established by tallying the patient's burden of common alleles that raise LDL cholesterol levels, identified by single nucleotide polymorphisms (SNPs) recorded in genome-wide association studies of normolipidaemic populations.

Some common small-effect loci are identical to large-effect monogenic loci for familial hypercholesterolaemia—eg, *LDLR*, *APOB*, *PCSK9*, *ABCG5*, and *ABCG8*. Other small-effect loci have a mechanistic link (eg, *HMGCR*, which encodes HMG-CoA reductase) and some loci suggest new mechanisms (eg, *SORT1*, which encodes sortilin 1).[15] Polygenic scores can be weighted according to effect sizes;[15,16] for instance, LDL cholesterol concentration is increased by about 0·25 mmol/L (10 mg/dL) by common *LDLR* and *APOE* SNP alleles, but only by about 0·07 mmol/L (3 mg/dL) by *PCSK9* SNP alleles. A high polygenic risk score accounts for some—but not all—heterozygous patients who do not have a monogenic large-effect mutation. Moreover, a high polygenic risk burden probably worsens the phenotype in large-effect mutation carriers. However, more than 95% of children and adolescents diagnosed clinically with familial hypercholesterolaemia carry a large-effect mutation in a known related gene, yet, polygenic effects are not noticeable in this age-group.[48]

Gene–gene and gene–environment interactions and epigenetic effects

The severity of the familial hypercholesterolaemia phenotype among carriers of the same gene variant can be modulated by variation at other loci. For instance, the combined effect of single *LDLR* and *APOB* mutations produces a phenotype intermediate between

heterozygous and homozygous familial hypercholesterolaemia.[49] Also, *APOE* genotype can modulate phenotypic expression in carriers of the same heterozygous familial hypercholesterolaemia mutation.[50] By contrast, inheriting a hypobetalipoproteinaemia *APOB* mutation returned the lipid profile to normal in a patient with a causative heterozygous familial hypercholesterolaemia *LDLR* mutation.[51] Furthermore, the trend towards higher LDL cholesterol concentrations among index cases of familial hypercholesterolaemia, compared with more distant relatives, suggests interaction with background polygenic or environmental effects.[52]

Other examples of gene–environment interactions include variable risk of death among patients with heterozygous familial hypercholesterolaemia in multigenerational families.[53,54] Such variability points to interactions with environmental factors; generational changes in activity level and dietary composition were judged key modulatory influences.[53,54] Finally, a patient with heterozygous familial hypercholesterolaemia had very low amounts of LDL cholesterol because of chronic hepatitis C virus infection, providing a different mechanism for external modulation of the familial hypercholesterolaemia phenotype.[55] Other possible sources of phenotypic variability in familial hypercholesterolaemia include epigenetic modifications—eg, DNA methylation, which could be associated with perturbations of key lipoprotein metabolism genes and variable amounts of lipid in blood in people carrying identical heterozygous familial hypercholesterolaemia mutations.[56]

Genotype–drug interactions

The response of LDL cholesterol levels to statin treatment is highly variable according to the genotype status of patients with familial hypercholesterolaemia.[57] For instance, attainment of target LDL cholesterol concentrations was greatest in heterozygous patients with no mutation (presumed polygenic), intermediate in patients with *LDLR* defective mutations, and worst in patients with *LDLR* null mutations, although patients with a null mutation had the highest baseline LDL cholesterol concentrations.[58] Other genetic determinants of response to statins have been reported.[59]

Genetic factors also modulate the response to PCSK9 inhibitors. Studies in patients with heterozygous familial hypercholesterolaemia who received subcutaneous alirocumab or evolocumab showed similar relative reductions in LDL cholesterol from baseline as did patients with high cholesterol without familial hypercholesterolaemia.[24] Heterozygous patients with *LDLR* null mutations responded equally well to evolocumab (around 55% reductions in LDL cholesterol), as did those with either *LDLR* defective mutations or *APOB* mutations,[14] suggesting that response depends mainly on upregulation of the normal *LDLR* allele, with the mutant receptor contributing negligibly. By contrast, in individuals with homozygous familial hypercholesterolaemia, PCSK9 inhibitors had no effect on LDL cholesterol in those with two *LDLR* null alleles, but if at least one allele had residual LDLR activity, PCSK9 inhibitors lowered LDL cholesterol by about 35%.[60] Thus, genotype can predict response to PCSK9 inhibition in patients with homozygous familial hypercholesterolaemia.[14,60]

Cardiovascular risk heterogeneity and stratification

Patients with familial hypercholesterolaemia and a history of an atherosclerotic cardiovascular event are at the highest risk for event recurrence and mortality, as shown by Neil and colleagues[18] in 3382 heterozygous patients from UK clinics who were followed up for 26 years. Notwithstanding an overall reduction in coronary heart disease mortality by 37% with statin therapy, the excess standardised mortality ratio in patients receiving secondary prevention with lipid-lowering agents was still four times higher than that of the general population. The benefit of secondary prevention was half that reported in patients with familial hypercholesterolaemia receiving primary prevention. This finding emphasises the need for early diagnosis and intervention in people with familial hypercholesterolaemia, which is achievable with efficient cascade screening programmes.

Despite the raised lifetime risk of atherosclerotic cardiovascular disease in people with familial hypercholesterolaemia, the risk of having a cardiovascular event is heterogeneous in individuals undergoing primary prevention, with some having higher risk than others,[9,22,37] even among those with the same mutation causing familial hypercholesterolaemia.[61] In addition to higher LDL cholesterol concentrations and late treatment or refractoriness to treatment, conventional risk factors account in part for this heterogeneity in atherosclerotic cardiovascular disease risk.[22,62–64]

Risk factors for atherosclerosis other than raised LDL cholesterol

Atherosclerosis is a multifactorial disease, and several conditions are associated independently with risk of atherosclerotic cardiovascular disease in patients with heterozygous familial hypercholesterolaemia.[22,62–65] These risk conditions include commencing lipid-lowering treatment at age 40 years or older, male sex, smoking, low HDL cholesterol (<1 mmol/L [40 mg/dL]), diabetes mellitus, hypertension, a family history of early atherosclerotic cardiovascular disease in first-degree relatives (younger than 55 years for men and 60 years for women), BMI greater than 30 kg/m², and chronic kidney disease (defined as an estimated glomerular filtration rate <60 mL/min per 1·73 m²).

Raised concentrations of lipoprotein(a) in blood are especially deleterious for patients with familial hypercholesterolaemia.[62–64,66,67] High levels of this class of lipoprotein have been associated independently with

coronary heart disease, ischaemic stroke, and aortic stenosis in meta-analyses of prospective studies,[68] genome-wide association studies,[69] and in mendelian randomisation studies in the general population.[70] Lipoprotein(a) is proatherogenic because it not only is a cholesterol-rich particle but also has prothrombotic and proinflammatory properties.[71,72] Concentrations of this molecule are raised in patients with familial hypercholesterolaemia compared with individuals with normal lipid levels,[62,66,72] and very high levels are seen usually in those with homozygous familial hypercholesterolaemia.[72,73] However, definitive evidence of a crucial role of the LDL receptor in lipoprotein(a) clearance from blood is scant.[72,74] Evidence associating lipoprotein(a) with increased risk of atherosclerotic cardiovascular disease in familial hypercholesterolaemia[63,64,66,67] is supported by observations in patients in the SAFEHEART cohort,[62] and from prospective follow-up of the Copenhagen General Population Study.[67] In these studies, lipoprotein(a) levels greater than 0·5 g/L (75 nmol/L) were associated with onset of atherosclerotic cardiovascular disease. Moreover, in asymptomatic patients with familial hypercholesterolaemia treated with statins, high amounts of lipoprotein(a) were an independent risk factor for aortic valve calcification, pointing at potential additional cardiac disease outside the coronary problems in long-term treated patients.[75]

Panel: Proposed criteria for definition of severe familial hypercholesterolaemia and LDL cholesterol treatment goals

At presentation (untreated LDL cholesterol)

- Severe familial hypercholesterolaemia diagnosed if LDL cholesterol >10 mmol/L (400 mg/dL); or LDL cholesterol >8·0 mmol/L (310 mg/dL) and one high-risk feature;* or LDL cholesterol >5 mmol/L (190 mg/dL) and two high-risk features*
- Realistic goal is to reduce LDL cholesterol by ≥50%; the ideal goal is to achieve LDL cholesterol <2·5 mmol/L (100 mg/dL)

Presence of advanced subclinical atherosclerosis

- Advanced subclinical atherosclerosis diagnosed with a coronary artery calcium score >100 Agatston units, or >75th percentile for age and sex;† or CT angiography with obstructions >50% or presence of non-obstructive plaques in more than one vessel
- Realistic goal is to reduce LDL cholesterol by ≥50%; the ideal goal is to achieve LDL cholesterol <1·8 mmol/L (70 mg/dL)

Presence of clinical atherosclerotic cardiovascular disease

- Clinical atherosclerotic cardiovascular disease defined as previous myocardial infarction, angina, coronary revascularisation, non-embolic ischaemic stroke, or transitory ischaemic attack, and intermitent claudication
- Realistic goal is to reduce LDL cholesterol by ≥50%; the ideal goal is to achieve LDL cholesterol <1·8 mmol/L (70 mg/dL)

*High-risk features are: age >40 years without treatment; smoking; male sex; lipoprotein(a) >75 nmol/L (50 mg/dL); HDL cholesterol <1 mmol/L (40 mg/dL); hypertension; diabetes mellitus; family history of early cardiovascular disease in first-degree relatives (age <55 years in men and <60 years in women); chronic kidney disease (ie, estimated glomerular filtration rate <60 mL/min per 1·73 m^2; and BMI >30 kg/m^2. †Calcium scores calculated using criteria from the Multi-Ethnic Study of Atherosclerosis.[86]

Advanced subclinical coronary atherosclerosis burden

A high burden of subclinical atherosclerosis in the coronary arteries is an independent marker of risk for atherosclerotic cardiovascular disease in the general population.[19,20,76] Evidence from robust prospective studies shows that advanced coronary-artery calcification detected by cardiac CT (defined mainly as a coronary calcium score >100 Agatston units) identifies individuals at high relative and absolute risk of coronary heart disease events and mortality.[19,77] Coronary calcium scores greater than the 75th percentile for age and sex can also be used to identify individuals with a raised atherosclerotic plaque burden and at augmented risk of atherosclerotic cardiovascular disease.[78]

The presence of either obstructive (>50% luminal obstruction) coronary plaques in one vessel or non-obstructive coronary plaques in at least two vessels, detected by cardiac CT angiography, are also independent markers of death and myocardial infarction.[20,79–81] Indeed, advanced subclinical atherosclerosis can be detected in patients with familial hypercholesterolaemia by cardiac CT.[82–85] Tada and colleagues[21] prospectively assessed 101 individuals with molecularly defined, heterozygous, familial hypercholesterolaemia, of whom 65–70% took statins for 7–9 years. After median follow-up of 941 days, 21 major atherosclerotic events had occurred and an increased coronary atherosclerotic plaque score was associated independently with coronary events (hazard ratio 3·65, 95% CI 1·32–25·84).

Firm recommendations for detection of advanced subclinical coronary atherosclerosis do not exist for either the general population or individuals with familial hypercholesterolaemia. At one extreme, those with homozygous familial hypercholesterolaemia and LDL cholesterol greater than 10 mmol/L (400 mg/dL), generally detected in childhood, need frequent monitoring for atherosclerosis.[1,4] In other people who meet the definition we propose here for severe familial hypercholesterolaemia, testing for subclinical atherosclerosis could help to identify those with advanced atherosclerosis,[76] for whom more intense lipid-lowering treatment (LDL cholesterol <1·8 mmol/L [70 mg/dL], depending on treatment availability and toxic effects) would be appropriate. Examples of individuals who should be tested for subclinical atherosclerosis include people diagnosed with familial hypercholesterolaemia in adulthood and, thus, untreated for many years, and those with multiple risk factors for atherosclerotic cardiovascular disease. Absence of subclinical disease should not preclude initiation of lipid-lowering treatment with statins.

Risk stratification

The panel depicts the proposed definition of and lipid goals for patients with severe familial hypercholesterolaemia. Those with prevalent atherosclerotic cardiovascular disease are at the highest risk for cardiovascular disease. Detection of advanced subclinical atherosclerosis, depending on availability of such testing, indicates the need for more intensive LDL cholesterol-lowering therapy. Advanced subclinical atherosclerosis is defined as an increased burden of subclinical atherosclerosis detected in the coronary arteries (panel). In the absence of atherosclerotic cardiovascular disease[18] or subclinical atherosclerosis,[20,21,80,87] LDL cholesterol is the greatest driver of onset of atherosclerotic cardiovascular disease.[22] Risk factors are additive; thus, risk needs to be stratified according to LDL cholesterol thresholds and a concomitant risk condition algorithm. The expert panel chose three values of LDL cholesterol to identify a patient with severe familial hypercholesterolaemia: greater than 10 mmol/L (400 mg/dL); greater than 8·0 mmol/L (310 mg/dL) and one high-risk condition; and greater than 5 mmol/L (190 mg/dL) and two high-risk conditions (panel). These criteria were chosen based on previously discussed clinical epidemiology and considering the possible additive costs of new treatments.

Treatments for severe familial hypercholesterolaemia

Figure 2 shows the expert panel's proposed treatment algorithm for patients with severe familial hypercholesterolaemia. The table presents information about the effectiveness, indications, dosage, and side-effects of lipoprotein apheresis and approved pharmacological treatments for severe forms of familial hypercholesterolaemia. In most situations, patients with severe familial hypercholesterolaemia have very high concentrations of LDL cholesterol; thus, goals should be regarded as either realistic or ideal (panel), depending on baseline LDL cholesterol, treatment availability, toxic effects, and costs. A realistic goal for these patients would be to achieve at least a 50% reduction in LDL cholesterol. Generally, a reduction in LDL cholesterol to less than 2·5 mmol/L (100 mg/dL) would be an ideal target in adults. However, in the presence of a previous atherosclerotic cardiovascular event, or advanced subclinical atherosclerosis, a lower ideal treatment goal (<1·8 mmol/L [70 mg/dL])[4,5] is proposed, based on epidemiological findings[88] and data from clinical trials that included patients with familial hypercholesterolaemia but were not specific for this population.[31]

Considering the available evidence,[31] reduction of LDL cholesterol must be attained initially with the highest tolerated dose of a potent statin (preferentially, atorvastatin or rosuvastatin) with addition of ezetimibe.[32] Other drugs—eg, bile acid sequestrants and niacin—are optional, depending on availability and tolerability, with the aim of reducing cholesterol in refractory patients who have not reached their target reduction in LDL cholesterol.

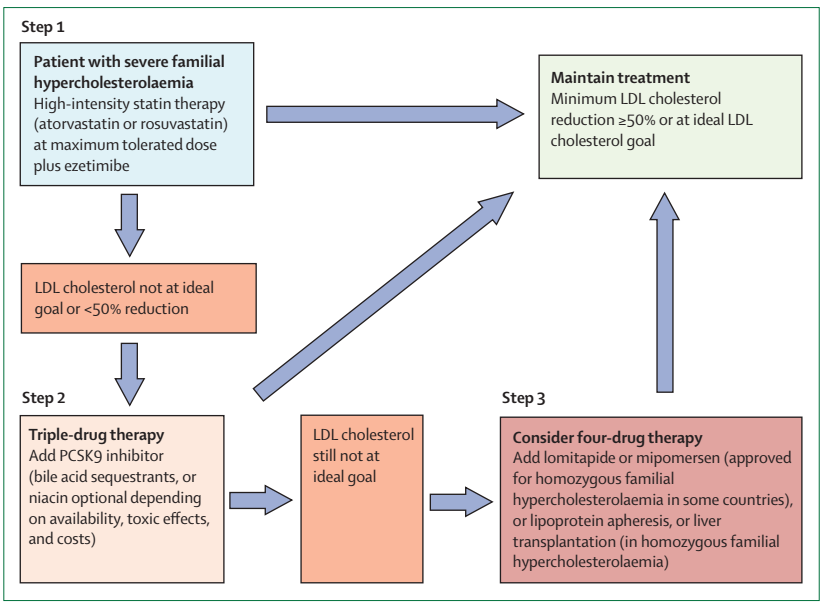

Figure 2: **Treatment algorithm for severe familial hypercholesterolaemia**
The therapeutic strategy is based on refractoriness of treatment, drug or procedure availability, reimbursement, and approval by local regulatory agencies.

PCSK9 inhibitors

If patients with severe familial hypercholesterolaemia are judged refractory to conventional treatment (ie, reduction in LDL cholesterol <50% and not at the ideal goal), PCSK9 inhibitors can be prescribed for reasons of efficacy, tolerability, and lower costs, by comparison with mipomersen and lomitapide (which are approved only for patients with homozygous familial hypercholesterolaemia)[13,14,24–26,60,87] and lipoprotein apheresis.[89] PCSK9 inhibitors should be started as soon as refractoriness to conventional treatment is detected, and they should be maintained indefinitely, if well tolerated, until proven otherwise (ie, adverse effects arise or benefit is lost). PCSK9 inhibitors have great potential to control LDL cholesterol concentrations in people with severe familial hypercholesterolaemia. In patients with heterozygous disease who were refractory to standard lipid-lowering treatment, a concentration of LDL cholesterol lower than 1·8 mmol/L (70 mg/dL) was attained in 61–66% of those treated with evolocumab[14] and 60–68% in those receiving alirocumab.[24] In both these studies, alirocumab and evolocumab were well tolerated, and the frequency and severity of side-effects were not different from placebo (or ezetimibe, when used as a comparator). The potential of PCSK9 inhibitors to prevent atherosclerotic disease, and the long-term safety of these drugs, is being tested in studies enrolling high-risk patients with a background of statin therapy—eg, FOURIER (NCT01764633), ODYSSEY Outcomes (NCT01663402), SPIRE-1 (NCT01975376), and SPIRE-2 (NCT01975389).[90]

	Mechanism of action	Dosage	Remarks
Lipoprotein apheresis[42]	Extracorporeal removal of proatherogenic apolipoprotein B-containing lipoproteins; reduces concentrations of apolipoprotein B, LDL, VLDL, and lipoprotein(a)	One session a week or every 2 weeks; current apheresis methods transitorily reduce apolipoprotein B-containing lipoproteins, including LDL, VLDL, and lipoprotein(a), by 60–80%	Approved by the FDA for three indications (values of LDL cholesterol are after 6 months of diet and maximum tolerated drug therapy): (1) homozygous, functional, familial hypercholesterolaemia and LDL cholesterol >13 mmol/L (>500 mg/dL); (2) heterozygous, functional, familial hypercholesterolaemia and LDL cholesterol >8·0 mmol/L (>310 mg/dL); (3) heterozygous, functional, familial hypercholesterolaemia, LDL cholesterol >5·0 mmol/L (>190 mg/dL), and documented coronary heart disease
Mipomersen[12,87]	Antisense oligonucleotide that binds to mRNA to block translation of apolipoprotein B	200 mg subcutaneously every week (160 mg if bodyweight <50 kg); reduces LDL cholesterol, apolipoprotein B, and lipoprotein(a) by 25%, 27%, and 31%, respectively, in patients with homozygous familial hypercholesterolaemia	Approved in the USA for homozygous familial hypercholesterolaemia; main side-effects are injection-site reactions (77%), influenza-like symptoms (29%), and increases in aminotransferase levels more than three times ULN (12%); increments in liver fat usually stabilise with time and revert with drug suspension; prescription follows a REMS programme
Lomitapide[13]	Microsomal triglyceride transfer protein inhibitor; reduces the synthesis of VLDL and chylomicrons	5–60 mg orally every day (average clinical trial dose was 40 mg); the maintenance dose of lomitapide should be personalised; reduces LDL cholesterol, apolipoprotein B, and triglycerides by 50%, 49%, and 45%, respectively	Approved in the USA, Canada, and Europe for homozygous familial hypercholesterolaemia; because fat absorption by the gut is inhibited, a low-fat diet should be started (<20% of energy from fat) and the dose should be titrated based on safety and tolerability; fat-soluble vitamin supplementation should be started; main side-effects are gastrointestinal (nausea, vomiting, bloating; 30%) and increases in aminotransferase levels more than three times ULN (33%); increments in liver fat usually stabilise with time and revert with drug suspension; drug can be used in patients submitted for lipoprotein apheresis; drug is metabolised by CYP3A4 (check for drug interaction); maximum dose of atorvastatin should not exceed 30 mg/day; in the USA, prescription follows a REMS programme
Evolocumab[14,60]	Binds to plasma PCSK9, reducing endosomal degradation of the LDL receptor; increases LDL cholesterol clearance from plasma	420 mg subcutaneously (approved dose for homozygous familial hypercholesterolaemia) every 4 weeks, or 140 mg subcutaneously every 2 weeks; reduces LDL cholesterol by 31% in patients with homozygous familial hypercholesterolaemia, compared with placebo; however, response depends on the type of *LDLR* mutation (from no response to 40% LDL cholesterol-lowering depending if mutations are null or defective); reduces LDL cholesterol, apolipoprotein B, and lipoprotein(a) by 60%, 49%, and 30%, respectively, in patients with heterozygous familial hypercholesterolaemia	Approved for familial hypercholesterolaemia, including homozygous disease, in the USA and Europe; most frequent side-effects (not different from placebo) are nasopharyngitis (5–10%), headache (4%), and injection-site reactions (5–7%)
Alirocumab[24]	Binds to plasma PCSK9, reducing endosomal degradation of the LDL receptor; increases LDL cholesterol clearance from plasma	75 mg subcutaneously, up-titrated to 150 mg subcutaneously every 2 weeks; reduces LDL cholesterol, apolipoprotein B, and lipoprotein(a) by 51–58%, 39–41%, and 20–30%, respectively	Approved in the USA and Europe for familial hypercholesterolaemia; most frequent side-effects (not different from placebo) are nasopharyngitis (11·2–12·6%), headache (4%), and injection-site reactions (11·4–12·4%)

FDA=Food and Drug Administration. REMS=risk evaluation and mitigation strategy. ULN=upper limit of normal. *For adult patients who are taking standard lipid-lowering drugs but persist with uncontrolled lipid levels.

Table: **Treatments approved for severe familial hypercholesterolaemia***

Mipomersen and lomitapide

Mipomersen is an antisense oligonucleotide that reduces the production of apolipoprotein B; lomitapide is a microsomal transfer protein inhibitor. Both these drugs are approved (mipomersen in the USA and lomitapide in both North America and Europe) for treatment of patients with homozygous familial hypercholesterolaemia. These drugs can lower LDL cholesterol amounts by 25–50% in homozygous patients[12,13] and can be used in homozygous patients who are refractory to statins, ezetimibe, and PCKS9 treatment (eg, individuals who are homozygous because of null *LDLR* mutations).[60] Use of mipomersen and lomitapide is limited by their side-effects and very high costs.[13,26,87] Studies are necessary to investigate combined treatment with either mipomersen or lomitapide and PCSK9 inhibitors.

Lipoprotein apheresis

Apheresis—either non-selective plasmapheresis or, preferably, selective LDL apheresis or lipopheresis—is approved and reimbursed in some countries for lowering LDL cholesterol and lipoprotein(a) concentrations in high-risk individuals with refractory dyslipidaemia.[91] Study findings have associated the use of lipoprotein apheresis with reduction in progression, or regression, of anatomical coronary disease.[42,91,92] In a 10-year, non-randomised, Japanese study of 130 patients with heterozygous familial hypercholesterolaemia,[93] apheresis decreased cardiovascular events when added to lipid-lowering drugs. Lipoprotein apheresis is indicated when pharmacological treatment is not effective in controlling severe familial hypercholesterolaemia.[4,42]

Future developments

Orthotopic liver transplantation is associated with striking correction and resolution of the homozygous familial hypercholesterolaemia phenotype.[4] The disadvantages and risks of transplantation and long-term immunosuppression have restricted the viability of this approach, but liver transplantation has provided a rationale for development of novel therapeutic approaches—eg, liver-directed gene delivery or stem-cell transplantation.

After decades of preclinical research,[94] a gene therapy trial using an adeno-associated virus (AAV)-based vector carrying an *LDLR* transgene has been initiated (NCT02651675). Autologous transplantation of genetically corrected cells derived from human-induced pluripotent stem cells is also being tested, although this approach is still at the preclinical stage.[95]

Cost-effectiveness issues

Use of statins to prevent cardiovascular events in patients with familial hypercholesterolaemia has been proven cost effective. However, treatments for more severe cases of the disorder can be very costly. The yearly cost of weekly, intensive, lipoprotein apheresis has been estimated at US$100 000.[89] Mipomersen and lomitapide cost, respectively, $176 000 and $235 000–295 000 per year,[26] whereas PCSK9 monoclonal antibodies cost around $14 000 per year in the USA (but about half this cost in Europe and Canada).[25] Use of these expensive treatments can impose an augmented burden on health systems, particularly for developing countries, where familial hypercholesterolaemia is severely underdiagnosed.[5] Therefore, characterisation of individuals at high risk, maximisation of standard treatment use, and judicious use of those treatments by following a step-by-step protocol (figure 2) could attenuate these costs, as long as intensive reduction in LDL cholesterol reduces the risk of these events effectively.

Concluding remarks

Everyone with familial hypercholesterolaemia has an increased lifetime risk for atherosclerotic cardiovascular disease, but a group with enhanced risk can be identified. In addition to patients with symptomatic atherosclerotic cardiovascular disease, this group includes individuals with the highest levels of LDL cholesterol (irrespective of a molecular diagnosis of heterozygous or homozygous familial hypercholesterolaemia), those with advanced subclinical coronary atherosclerosis, and people with additional risk factors for atherosclerotic cardiovascular disease. For patients with severe familial hypercholesterolaemia, as defined in our report, treatment should be initiated with statins and ezetimibe, and other conventional treatments as tolerated. If treatment goals are not met, new agents (including PCSK9 inhibitors, lomitapide, and mipomersen) should be considered. Other risk factors for atherosclerotic cardiovascular disease—eg, smoking or a sedentary lifestyle—must also be addressed aggressively in this high-risk population. To achieve LDL cholesterol targets in individuals with familial hypercholesterolaemia and existing atherosclerotic cardiovascular disease, early institution of treatment with new agents is probably necessary.

Search strategy and selection criteria

We searched PubMed for reports published only in English from Jan 1, 1980, to February, 2016, with the terms "familial hypercholesterolaemia", "hypercholesterolemia", "subclinical atherosclerosis", and "cholesterol lowering treatment". We also identified relevant publications by consensus of opinion of an international panel of specialists in dyslipidaemia, which was convened by the International Atherosclerosis Society from March, 2015, to March, 2016. We must emphasise that prospective data in populations with familial hypercholesterolaemia are scarce; most studies cited are observational, cross-sectional, or historical cohorts of patients. Also, because of the shortage of specific studies, some recommendations made by the expert panel come from consensus opinions derived from studies done in the general population. The expert panel met in May, 2015, in Amsterdam, Netherlands, to present and discuss available data; thereafter, they worked electronically to finalise this expert opinion consensus.

Contributors

RDS, SSG, RAH, MAC, and GFW were members of the writing committee. PJB, SJB, ALC, MJC, JCD, EF, TF, JG, GKH, MH-S, SEH, ASJ, PM, PMM, FJR, KA-R, KKR, ZR, EJGS, and SY revised the paper, discussed its contents, and suggested changes. The International Atherosclerosis Society Severe Familial Hypercholesterolaemia Panel was chaired by RDS, with help from SSG, MAC, ASJ, EF, and PJB. RDS, SSG, RAH, GFW, MAC, and GKH have reviewed the literature and presented the findings at the meeting in Amsterdam, Netherlands, in May, 2015.

Declaration of interests

KA-R has received grants from Pfizer; advisory board fees from Sanofi; and speaker's honoraria from AstraZeneca, Pfizer, and Sanofi. PJB has received personal fees from Amgen, Sanofi-Regeneron, Pfizer, and Merck; and grants from Pfizer. SJB has received advisory board fees from Aegerion, Merck, and Sanofi-Regeneron; speaker's honoraria from Aegerion, Amgen, and Merck; and consulting fees from Amgen. MJC has received honoraria for service on advisory boards, speaker's honoraria, and research funding from Amgen, AstraZeneca, CSL, Kowa, Sanofi-Regeneron, and Unilever. MAC has received grants from the National Heart, Lung, and Blood Institute (P01-HL-0594-07-14), Regeneron Pharmaceuticals, Sanofi-Aventis, and Aegerion; and personal fees from Sanofi-Aventis and Aegerion. ALC has received grants from Amgen, Pfizer, and Sanofi; and personal fees from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Mediolanum, Merck, Pfizer, Recordati, Rottapharm, and Sanofi. EF and ASJ are executive directors of the International Atherosclerosis Society. TF has received speaker's honoraria from Amgen, Sanofi, and Pfizer. JG has received grants from Amgen, Sanofi, Pfizer, and Aegerion. SSG is a member of the scientific advisory board of the FH Foundation. MH-S has received grants from the Japanese Ministry of Health and Welfare, the Japan Agency of Medical Research and Development, Astellas Pharma, and Kaneka Medix; and personal fees from Sanofi, Astellas Pharma, Kowa, Astellas Amgen, AstraZeneca, Boehringer Ingelheim, BML, Bayer, MSD, and Aegerion. RAH has received grants and personal fees from Aegerion, Amgen,

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