PREMATURE HEART ATTACKS: BAD LIFESTYLE, BAD LUCK, OR BAD GENES?

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ABSTRACT

Homozygous familial hypercholesterolaemia (HoFH), a rare inherited lipid disorder usually caused by bi-allelic defects in the *LDLR* gene, is characterised by marked elevation in low-density lipoprotein -cholesterol (LDL-C). Aggressive, early intervention with lipid-lowering therapy is warranted in patients with HoFH, and the recent introduction of new drug treatments including lomitapide and mipomersen has enabled physicians and their patients to achieve lower LDL-C levels than previously possible in this hard-to-treat condition. Understanding the overall impact of new interventions in HoFH requires a correct assessment of the true prevalence of the disease. Although it is rare, emerging studies suggest that HoFH may be more common than previously thought. We have reviewed data on the epidemiology and management of HoFH, with a focus on raising awareness on this condition so that clinicians can be made aware of the potential for genetic causes for presentation with premature cardiovascular disease. As classic clinical characteristics may be absent in HoFH patients, genetic status and/or family history should be part of the assessment of patients with significantly elevated LDL-C and premature atherosclerosis with a premature heart attack or clinical complications. As direct outcomes data for new treatments for HoFH are not yet available, intermediate phenotypes of arterial structure and function are being studied as endpoints in clinical trials. Novel therapies which enable lowering of LDL-C to levels that were, until recently, unachievable, have the potential to alter cardiovascular morbidity and mortality in this high-risk group of patients.

Keywords: Homozygous familial hypercholesterolaemia, prevalence, incidence, myocardial infarction, cardiovascular outcomes, premature mortality, lipid-lowering therapy, lomitapide, mipomersen.

INTRODUCTION

Patients with homozygous familial hypercholesterolaemia (HoFH) have extremely high cholesterol levels, and without treatment these patients often die from clinical complications of early atherosclerosis (AS) by the second decade of life.[1] Lifetime exposure to elevated levels of low-density lipoprotein cholesterol (LDL-C) drives premature AS and increases the likelihood of clinical events which can manifest in childhood or adulthood.[2,3] In addition to cardiac disease, aortic root disease with supravalvular aortic stenosis is a particularly feared complication.[2] Aggressive, early intervention with lipid-lowering therapy is warranted in patients with HoFH, and the introduction of new treatment options has led to the achievement of lower LDL-C levels. Although direct outcomes data for novel licensed therapies or agents in development are not yet available, intermediate phenotypes of arterial structure and function are being studied as endpoints in clinical trials.

Understanding the overall impact of new interventions in HoFH requires an appreciation of the real prevalence of the disease. Although it is rare, there is now evidence that HoFH may be more common than once thought. At the recent European Society of Cardiology (ESC) annual meeting in Barcelona, Spain, Aegerion Pharmaceuticals - a company that commercialises a product for HoFH (lomitapide) and is active in the research into the treatment of HoFH - sponsored a satellite symposium. The session was well attended by cardiologists, yet there remains a need to spread the message of this rare disease throughout the clinical community. In this article, we will reiterate the themes from the session at ESC and explore current thoughts on the epidemiology and management of HoFH, considering whether, for some patients with premature cardiac disease, there may be an underlying genetic cause.

WHAT IS THE TRUE PREVALENCE OF HOFH?

Although the incidence of sudden death in young people is relatively low, the majority of these deaths have been found to be of cardiac origin. In people aged <40 years, the incidence of sudden death in the general population has been estimated to be 2.07 per 100,000 person-years, and the incidence of sudden cardiac death to be 1.62 per 100,000 person-years.[4] These estimates were determined from death certificate data recorded by Statistics Netherlands from 1996-2006. From the reported data, it appears that AS may be the underlying pathology in approximately 40% of sudden deaths (Figure 1). As there is no dedicated International Classification of Diseases (ICD) code for 'sudden death', the authors first performed a literature analysis of causes of sudden death in the young, and from this they selected ICD-10 codes that could be used as a proxy for sudden death.

The question for cardiologists is clear: why are these young people developing cardiac conditions so early in life? To answer this question, a number of factors need to be considered. Sudden death may result from arrhythmia rather than myocardial infarction (MI). MI can be caused by a number of underlying conditions, of which atherosclerotic coronary disease is the most common. In young patients alternative conditions such as hypercoagulable states, recreational drug use, congenital coronary abnormalities, and coronary vasculitis all need to be considered.[5]

The aetiology of coronary heart disease (CHD) in young patients is generally different to that in older individuals. Importantly, there are genetic disorders that predispose young people to AS and consequent cardiac risk. A study of 200 patients (100 with premature CHD and 100 with late-onset CHD) revealed that while risk factors of smoking, hypertension, and diabetes were present in both groups, the largest proportional difference was for family history, which was evident in 39 of the younger patients versus only 11 of the older patients ($p<0.001$).[6] This study used a cut-off age of 45 years to define early versus late onset of CHD, and the findings provide a clue to the possible contribution of genetic abnormalities in LDL metabolism to death.

MI is a heritable phenotype and inheritance plays the greatest role in early-onset MI. Early-onset MI is associated with rare mutations in key

genes controlling lipid metabolism.[7,8] Deleterious mutations in the LDL-receptor and apolipoprotein A-V genes (*LDLR* and *APOA5*, respectively) occur significantly more frequently in early-onset MI patients than in non-MI controls.[6] The mutations in these genes are associated with elevations in LDL-C and triglycerides, respectively.[6] Among the diseases of lipid metabolism that can arise from genetic aberrations, heterozygous familial hypercholesterolaemia (HeFH) is the most prevalent, and is actually the most common autosomal dominant disease in man. It occurs when a mutation (usually in the *LDLR* gene) is inherited from one parent. HeFH can usually be managed adequately with statins (with or without ezetimibe), dietary modifications, and lifestyle changes.[9] However, HeFH has a sister condition, HoFH, in which defective genes controlling lipid metabolism are inherited from both parents. The genetic defect is usually, but not always, in the *LDLR* gene, and can also affect other genes controlling the LDLR pathway, such as *ApoB* and *PCSK9*.[2]

HoFH is a very severe disease characterised by extremely elevated LDL-C levels, xanthomas, and evidence of atherosclerotic valvular disease.[2] Historically, the incidence of HoFH in the general population has been estimated at 1:1,000,000.[2] However, these estimates were calculated from a 1973 study, which estimated the prevalence of HeFH based on the frequency of autosomal dominant hypercholesterolaemia among relatives of a small cohort of MI survivors.[10] Emerging studies suggest that the prevalence of HeFH, and consequently HoFH, may be higher than previously thought. For example, in a Dutch study that examined 104,682 medical records in the Netherlands' autosomal dominant hypercholesterolaemia database, 49 patients (0.05%) were identified as having HoFH.[9] Although mean lipid levels in these patients with molecularly defined disease were lower than generally assumed in HoFH patients, with mean (±SD) LDL-C level prior to lipid-lowering therapy of 12.9±5.1 mmol/L. These data place the estimation of the incidence of HoFH in the Dutch population at 1:300,000, and there are no logical reasons to suggest that this figure would not apply to the rest of Western Europe. In founder populations with little genetic admixture the incidence of HoFH is thought to be even higher.

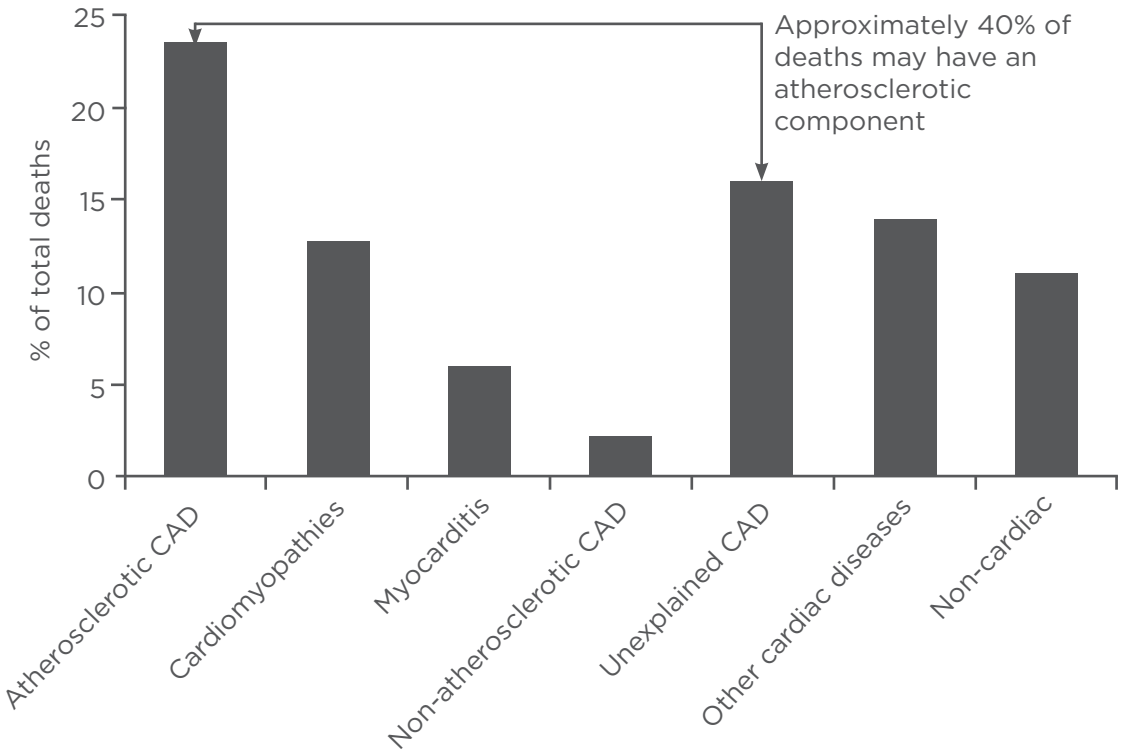

Figure 1: Incidence of SCD in a literature analysis of 17 publications, including 3,150 SCD victims <40 years old.

SCD: sudden cardiac death; CAD: coronary artery disease.

Adapted from Vaartjes I et al. Eur J Cardiovasc Prev Rehabil. 2009;16:592-96.[4]

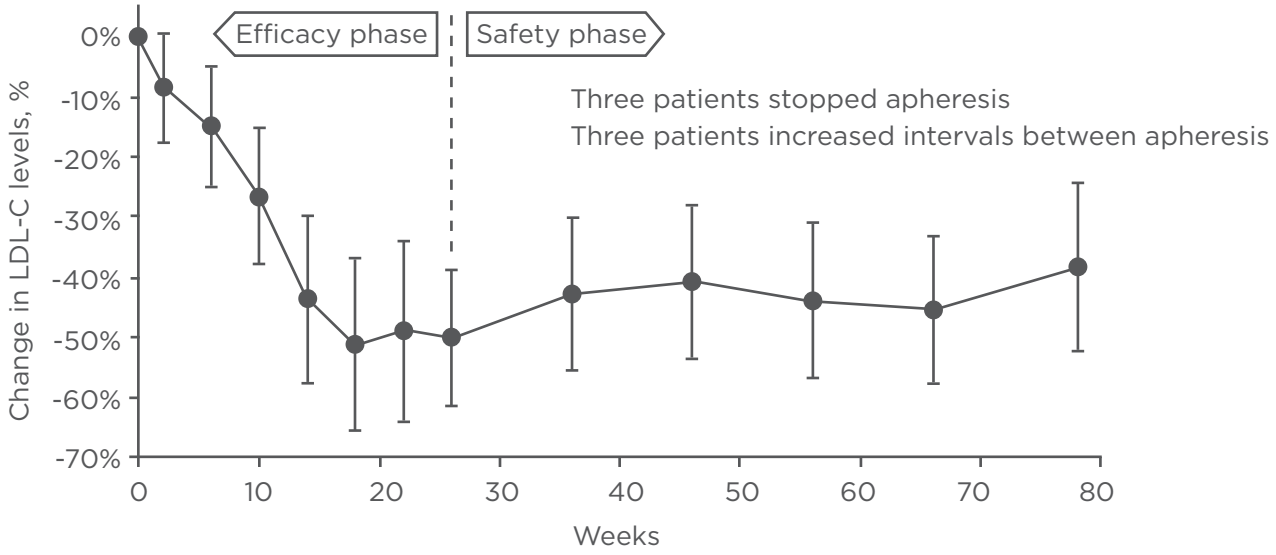

Figure 2: Mean change in low-density lipoprotein-C (LDL-C) from baseline (%) in lomitapide Phase III study.

Given that the global incidence of HoFH is likely to have been underestimated, it is ever more important to ask the right questions when a patient with significantly elevated LDL-C presents with a premature atherosclerotic disease or MI. Genetic status and/or family history should be part of the examination and workup. Classic features of HoFH may be absent in the patient phenotype, thus making genetic assessment even more important. LDL-C levels are classically >300 mg/dL, but examination of baseline characteristics of clinical trials in HoFH have revealed a much wider variation from 150–500 mg/dL.[11]

AFTER DIAGNOSIS OF HOFH, WHAT ARE THE TREATMENT OPTIONS?

Early and aggressive reduction of LDL-C is the foundation of the successful management of HoFH.[3,12] Prompt intervention with effective lipid-lowering therapies will reduce the lifelong exposure to elevated LDL-C, and thereby has the potential to improve outcomes. Treatment should be started immediately after diagnosis in infancy, but treatments that rely on a functioning LDL receptor may be of limited efficacy in HoFH patients.[13] Such treatments, which are frequently used with success in other forms of hypercholesterolaemia, include statins, ezetimibe, and bile acid sequestrants.[14] The limited success of pharmacotherapy for HoFH has established LDL apheresis as standard treatment; however, this mode of therapy is complex and expensive, and access is not universal.[15] The treatment challenges in HoFH have been highlighted by Raal et al.,[16] who reported findings in 149 patients with HoFH in clinics in Cape Town and Johannesburg. Although treatment with modern lipid-lowering therapies, available in 1990s, resulted in a 26% reduction in LDL-C and prolonged survival, lipid levels were still considerably higher than currently recommended targets, with life expectancy remaining considerably shortened.[3,16] A number of novel therapeutic approaches are being explored to fulfil the unmet medical need for additional HoFH treatments, including reduction of lipoprotein synthesis (lomitapide, mipomersen), upregulating LDL-receptor function (monoclonal antibodies against proprotein convertase subtilisin/kexin Type 9 [PCSK9]), and inhibiting cholesterol ester transfer protein (anacetrapib). Evacetrapib, lomitapide, and mipomersen have been approved by the US FDA for use in patients with HoFH,[17,18] and additionally lomitapide has received approval from the European Commission.[19]

Lomitapide

Lomitapide, an oral agent indicated for the treatment of adults with HoFH as an adjunct to low-fat diets and other lipid-lowering therapies (with or without apheresis), inhibits microsomal triglyceride transfer protein in enterocytes and hepatocytes and reduces synthesis of chylomicrons and very low-density lipoproteins (VLDL). In a Phase III, open-label, single-arm dose-escalation

study involving 29 patients with HoFH receiving lomitapide (median dose 40 mg/day), the mean LDL-C reduction at 26 weeks was 40% in the intent-to-treat analysis, and 50% in the patients who completed the first 26 weeks of the study (range 20-90%) and was maintained out to the end of the Phase III trial at 78 weeks (Figure 2).[17,19,20] The statistically significant reduction from baseline in LDL-C levels was maintained after 126 weeks of lomitapide treatment in 17 patients who participated in a long-term extension phase of the study.[20]

Lomitapide is active in the liver and intestine, and most prevalent adverse effects of lomitapide relate to its mechanism of action. High fat meals can provoke bloating, diarrhoea, and other gastrointestinal tract symptoms, and these can often be ameliorated by restricting dietary fat/triglyceride intake and dose titration.[17,19] Patients should receive dietary counselling before starting treatment with lomitapide. Adverse hepatic effects include altered liver function tests (such as increased plasma levels of transaminases) and liver fat accumulation. Altered liver function tests can generally be managed with dose interruption/reduction while hepatic fat content, as measured by nuclear magnetic resonance spectroscopy, generally stabilises over time.[17,19,20] In the Phase III study, four patients had alanine aminotransferase more than 5-times the upper limit of normal - all elevations were managed either by dose reduction or temporary interruption of lomitapide - and high alcohol intake was a contributory factor in three of the four cases.[20] It is also important for patients and healthcare professionals to be vigilant for potential drug-drug interactions and to follow liver monitoring recommendations.[17,19]

A worldwide observational registry study of lomitapide (Lomitapide Observational Worldwide Evaluation Registry; LOWER) is currently recruiting patients, and will document the real-world efficacy and safety of lomitapide. LOWER is now established in the US, Europe, Canada, Taiwan, Brazil, and Argentina. As of the time this manuscript was finalised, 54 patients were enrolled; 300 enrolled patients are expected by March 2018. A vascular imaging sub-study of the LOWER registry (CAPTUre) will evaluate aortic and carotid AS by magnetic resonance imaging (MRI) at baseline and years 1, 2, and 5. Lomitapide is currently only licensed for use in adults,[17,19] but a study involving children and adolescents is expected to commence recruitment in late 2014. In common with the adult Phase III trial, the study will have an efficacy and a safety phase; however, in contrast with the pivotal trial, the efficacy phase of the paediatric study will be placebo-controlled, with all patients switching to lomitapide in the safety phase. Also, importantly, the paediatric study will include the results of vascular imaging procedures as surrogate outcomes endpoints.

Mipomersen

Mipomersen is an antisense oligonucleotide that inhibits the transcription of apoB100 mRNA, thereby reducing VLDL synthesis. In the Phase III trial of mipomersen, the mean LDL-C reduction at week 26 achieved by HoFH patients treated with mipomersen 200 mg/week subcutaneously was 24.7% (range 2–82%).[21] Data from the long-term extension study showed that these reductions were sustained for up to 104 weeks.[22] The most common side-effects of mipomersen are injection site reactions, flu-like reactions, elevations in transaminases, and hepatic steatosis.[18] In common with lomitapide, mipomersen is being studied in a long-term patient registry. Mipomersen is only approved for use in the US. In the US, access to both lomitapide and mipomersen are covered by a Risk Evaluation and Mitigation Strategy (REMS) programme, which recognises the potential for drug-induced toxicity.

Therapies Currently in Development

Evolocumab, a monoclonal antibody directed against PCSK9, was evaluated in the TESLA trial,[23] which randomised 49 patients with HoFH to evolocumab (n=33) or placebo (n=16). Evolocumab resulted in a 23.1% reduction in LDL-C from baseline at week 12, which was a 30.9% reduction over placebo. Another PCSK9 inhibitor (alirocumab) has been studied as an agent to lower elevated LDL-C,[24] but has not been specifically evaluated in HoFH. A Phase III study evaluating the cholesteryl ester transfer protein inhibitor anacetrapib in HoFH (NCT01841684) was planned but never started.

Current Position and Future Direction

Significant therapeutic advances have been achieved for patients with HoFH, with mechanisms of action that decrease LDL production and increase LDL catabolism. Novel treatments may improve outcomes but currently there are no cardiovascular (CV) outcome data for novel therapies. The availability of outcomes data in HoFH will be hindered by the rarity of the disease,

and physicians should not wait for these data, but treat patients promptly with the current therapeutic armamentarium. Looking to the future, optimal management of HoFH may require multi-agent combinations, involving multiple lipid-lowering mechanisms at low doses, which will also hopefully minimise off-target toxicity.

WHAT WILL EFFECTIVE TREATMENT MEAN FOR THE HOFH PATIENT POPULATION?

An improved understanding of the molecular pathophysiology of HoFH has led to the development of promising new therapies in a disease that has been historically difficult to treat. Although there are as yet no direct data on CV outcomes and survival for any of the novel therapies, better management of LDL-C is anticipated to translate into improved CV outcomes. The lomitapide and mipomersen registries should provide additional information of this type.

Evidence from a South African cohort of 149 HoFH subjects has shown that cholesterol lowering with statins is associated with markedly improved survival.[16] However, assessing the benefits of treatments on outcomes in this way is challenging in such a rare disorder. Early intervention is required to maximise lifetime gains,[12] and intermediate phenotypes of arterial structure and function are therefore valuable as endpoints in clinical trials. Endothelial dysfunction is an early event in the process of atherogenesis, and endothelial function can be measured non-invasively from childhood. In children with FH, impairment of endothelial function has been found from the age of 7.[25] In HeFH, the rate of increase of carotid intima-media thickness, a measure of structure arterial disease, is also accelerated from the first decade of life. In children with HeFH, statin therapy has been shown to improve endothelial function and to slow or even reverse progressive arterial wall thickening.[26] More recently, the size, composition, and morphology of carotid plaques have been evaluated non-invasively using MRI.[27] Novel therapies that substantially lower LDL-C levels in addition to statins are being evaluated in terms of their effects on these endpoints. Patients receiving lomitapide who are enrolled in CAPTure, the vascular imaging sub-study of the LOWER registry, will be evaluated for aortic and carotid AS by MRI at baseline and at years 1, 2, and 5. Global recruitment is planned from Q1 2015, and the estimated sample size is 60.

In non-FH patients, a prospective meta-analysis of data conducted by the Cholesterol Treatment Trialists' (CTT) Collaborators concluded that, overall, for each mmol/L reduction in LDL-C achieved with statin therapy the 5-year incidence of major coronary events, coronary revascularisation, and stroke was reduced by about one-fifth.[28]

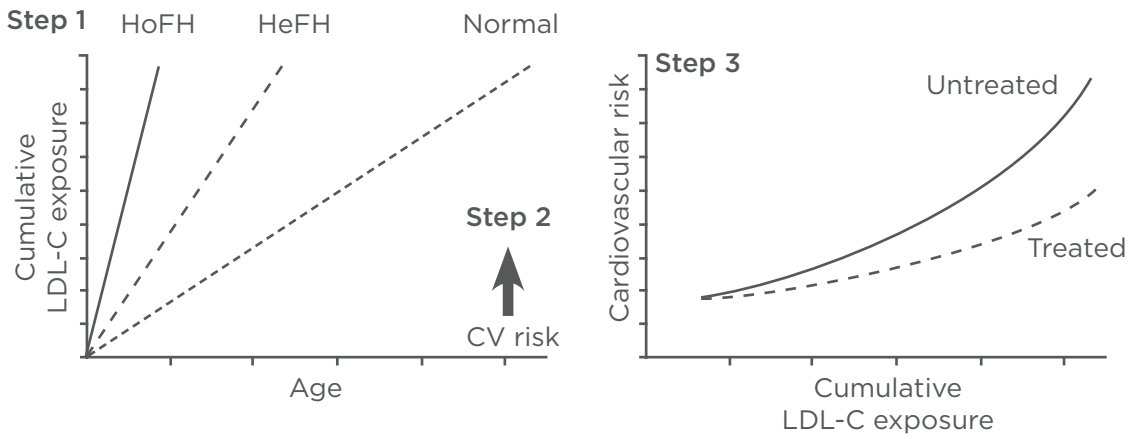

Figure 3: Development of a cumulative exposure model to predict survival benefits.
Step 1: Calculate cumulative LDL-C exposure as a function of age; Step 2: use the relationship between cardiovascular risk and cumulative LDL-C exposure to calculate cardiovascular risks as a function of age; Step 3: use the cardiovascular risks as a function of age to construct survival curves for untreated and treated scenarios.
HoFH: homozygous familial hypercholesterolaemia; HeFH: heterozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein-C; CV: cardiovascular.

Overall, statin therapy also produced a clear reduction in all-cause mortality. However, the CTT data underestimate survival benefits of cholesterol lowering in populations with genetic diseases such as FH. Exposure to risk factors over time is key, and in FH risk is driven by exposure to LDL-C. Thus, early intervention may prevent or delay the progression of atherosclerotic disease and improve the clinical benefit that is achievable with lipid-lowering therapies. In a meta-analysis of data from 312,321 participants, naturally random allocation to prolonged exposure to lower LDL-C levels beginning early in life was associated with a reduction in CHD risk of 54.5% per mmol/L (38.7 mg/dL) of LDL-C lowering.[29] This represents a 3-fold greater reduction in risk of CHD for each unit of LDL-C lowering than that observed with statin treatment started later in life.[29] This concept of 'cumulative exposure' and the leveraged lifetime gains from early risk factor lowering has been incorporated into the new UK JBS3 guidelines,[30] which provide CV prevention recommendations for the general population.

Although survival data are lacking, especially for the latest novel treatment approaches (lomitapide and mipomersen), modelling could be used to estimate the potential benefits of lipid-lowering therapy from an early age in rare diseases such as HoFH. A cumulative exposure model can be developed to try to predict the survival benefits of a new treatment; Figure 3 is an example of one possible way to do this. It would work as follows: first, cumulative LDL-C exposure as a function of age is calculated, and the relationship between CV risk and cumulative LDL-C exposure is used to calculate CV risks as a function of age. The CV risks as a function of age are then used to construct survival curves for untreated and treated scenarios.

In this new era, the development of novel therapeutic approaches has meant that lower LDL-C levels are becoming achievable. In many heterozygous patients with FH, combination therapy with statins and newer lipid-lowering therapies can result for the first time in normalisation of LDL-C levels. The impact of this approach in HoFH is currently being evaluated, and results of this research are so far very encouraging.

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