Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study

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Homozygous Familial Hypercholesterolaemia – Worldwide Experience

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Authorś contributions

The study was conceived, designed and implemented by four investigators with a longstanding interest in HoFH (GKH, FJR, DJB and MC) who, together, comprised the steering committee and had full access to the data. AJC and MLH constructed the electronic case report form. All authors contributed to the acquisition of data for the work. MLH and TRT acted as study coordinators. TRT curated the data, conducted the analysis and drafted the manuscript. The writing committee (TRT, MLH, GKH, AJVV, KKR, HS, TF, SB, MH-S, FJR, DJB and MC) provided critical interpretation and revision of the manuscript. All authors revised the manuscript and gave approval for submission.

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Abstract

Background: Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disorder resulting in extremely elevated low-density lipoprotein cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). Current guidance about its management and prognosis stems from relatively small studies, mostly from western countries. The objective of this study was to assess the clinical and genetic characteristics as well as the impact of current practice on health outcomes of HoFH patients globally.

Methods: The HoFH International Clinical Collaborators (HICC) registry collected data on patients with a clinical and/or genetic diagnosis of HoFH using a retrospective cohort study design.

Findings: Overall, 751 patients (52% female) from 38 countries were included, with 75% reporting bi-allelic pathogenic variants. Median age of diagnosis was 12·0 (IQR 5·5–27·0) years, with major manifestations of ASCVD or aortic stenosis already present in 9% at diagnosis of HoFH. Globally, pre-treatment LDL-C levels were 14·7 (IQR 11·6–18·4) mmol/L, with 92% of patients subsequently receiving statins, 64% ezetimibe and 39% lipoprotein apheresis. On-treatment LDL-C levels were lower in high-income versus non-high-income countries (3·93 [IQR 2·6–5·8] versus 9·3 [IQR 6·7–12·7] mmol/L), with greater use of three or more lipid-lowering therapies (LLT) (66% versus 24%) and consequently more patients attaining guideline-recommended LDL-C goals (21% versus 3% respectively). A first major adverse cardiovascular event occurred a decade earlier in non-high-income countries, at a median age of 24·5 (IQR 17·0–34·5) versus 37·0 (IQR 29·0–49·0) years in high-income countries (adjusted hazard ratio: 1·64 [95%CI 1·13–2·38]).

Interpretation: Worldwide, patients with HoFH are diagnosed too late, undertreated and at high premature ASCVD risk. Greater use of multi-LLT regimens associates with lower LDL-C levels and better outcomes. Significant global disparities exist in treatment regimens, control of LDL-C levels and cardiovascular event-free survival, which demands a critical re-evaluation of global health policy to reduce inequalities and improve outcomes for all patients with HoFH.

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Keywords

Homozygous familial hypercholesterolaemia; low-density lipoprotein cholesterol; lipid-lowering therapy; atherosclerotic cardiovascular disease; aortic valve stenosis; lipoprotein apheresis

Introduction

Familial hypercholesterolaemia (FH) is an inherited disorder resulting from pathogenic variants in genes involved in the metabolism of low-density lipoproteins, leading to markedly elevated LDL-C levels and an increased risk of premature atherosclerotic

cardiovascular disease (ASCVD) if not treated early and effectively.[1] The most severe form of FH is homozygous FH (HoFH) which broadly comprises simple homozygous as well as compound and double heterozygous cases (see box: “Definition and Diagnosis”).

The prevalence of HoFH was historically reported as 1 per million but has recently been estimated as 1 in ~300,000 persons worldwide,[2–5] with a higher prevalence in populations with a founder effect.[1] Plasma LDL-C levels may exceed 20 mmol/L depending on the variants carried; patients with an *LDLR* variant that leads to no residual functional protein (*LDLR* negative variant) in both alleles are generally the most severely affected. The magnitude and duration of exposure to extreme LDL-C levels largely determines prognosis.[6] Combination of commonly used lipid-lowering therapies (LLT), such as statins and ezetimibe, are often insufficient to control such high LDL-C levels, with many patients requiring extracorporeal removal of LDL by means of lipoprotein apheresis. Therapies that decrease LDL-C levels irrespective of residual LDLR function have recently emerged,[7,8] but their use is limited by cost and availability.

Our current view on the clinical characteristics and natural history of HoFH is largely based on studies of relatively small sample size comprising patients from high-income countries. Little is known about global differences in detection, management and cardiovascular outcomes in HoFH. To address these uncertainties, we created a global consortium of researchers and clinicians caring for HoFH patients. The objective of this study was to provide a contemporary, systematic assessment of the characteristics, diagnosis, treatment and outcomes of HoFH patients, both on a global scale and by country income status.

Methods

Participating centres and patient selection

The HoFH International Clinical Collaborators (HICC, NCT04815005) is a global consortium of clinicians and researchers involved in the care for HoFH patients. Patients were eligible for inclusion into the registry if they had received a clinical or genetic diagnosis of HoFH by the treating clinician.[1] Where genetic testing was reported, patients were considered HoFH if they were found to be simple HoFH, compound heterozygous or double heterozygous, consistent with current guidelines.[1]

Data collection

The present study has a retrospective cohort design. To reflect contemporary data, only patients with HoFH who were alive and being followed up in, or after, 2010 were eligible for inclusion. Baseline was defined as the point at which HoFH was diagnosed, and follow-up was defined as years post diagnosis. The method of data entry, variables collected and definitions of lipid targets, cardiovascular outcomes and aortic valve stenosis are described in the Supplementary Methods. For comparison between affluent and less affluent regions of the world, countries were grouped according to the 2019 World Bank definition of income category (Table S1).[12]

Genetic data

Genetic information was curated to a uniform nomenclature and independently validated by four clinical and molecular genetics experts (JCD, LZ, LT and TF) who confirmed the pathogenicity and assessed the functionality of the variants as detailed in the Supplementary Materials.

Statistical analysis

Statistical analyses were performed using R software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). The primary outcome in the survival analyses was major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction (MI), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Descriptive estimates are presented as median and interquartile range (IQR) or mean (95% CI). We used bootstrapping (10,000 randomized samples) to estimate the 95% CIs around mean estimates using the percentile method. Due to the descriptive nature of the study, we did not impute missing data and performed available case analyses without formal hypothesis testing. Comparisons of survival times free from events between groups of interest were assessed using the Kaplan-Meier method and log-rank tests. Details on the generation of proportional hazard models are provided in the Supplementary Materials.

Ethics

Individual contributors were responsible for meeting local standards set by their institutional review board or ethics committee and obtaining approval. The study was conducted according to International Standards of Good Clinical Practice.

Role of the funding source

The HICC is an investigator-initiated project supported by funding from the academic institutions of the collaborators. The European Atherosclerosis Society provided funding to support a registry coordinator. The funders had no role in study design, data collection, data analysis, data interpretation, writing the manuscript or decision to submit for publication. The writing committee takes final responsibility for the content of the manuscript and the decision to submit for publication.

Results

Patient characteristics

Individual-level data on 751 patients from 88 institutions across 38 countries representing all seven World Bank regions were available. Twenty countries were classified as high-income, 12 as upper-middle income and six as lower-middle income countries; countries and number of patients per country are listed in Table S1. Patient demographic, clinical and genetic characteristic at the time of inclusion are presented in Table 1, overall and stratified by country income status. Median age of diagnosis was 12·0 (IQR 5·5–27·0) years, and 52% of patients were women. Race was reported in 527 patients; of these, 338 (64%) were White, 121 (23%) Asian, and 68 (13%) were Black or of mixed race. Patients from high-income

countries, compared with those from non-high-income countries, were older at the time of diagnosis (16·0 [IQR 6·0–33·0] versus 10·0 [5·0–20·0] years) and had fewer physical stigmata such as xanthomas (64% versus 74%) at the time of diagnosis.

Overall, untreated LDL-C levels were 14·7 (IQR 11·6–18·4) mmol/L, and lower in patients from high-income countries than those from non-high-income countries (13·5 [IQR 10·4–17·2] versus 15·8 [IQR 12·9–19·2] mmol/L, respectively). The prevalence of modifiable risk factors for cardiovascular disease such as smoking (8%), obesity (15%), diabetes mellitus (4%) and hypertension (15%) was comparable between high and non-high-income countries. Among 505 patients with data on family pedigree available, 150 (30%) had a first-degree family member with HoFH who was also entered in the registry.

Genetics

A genetic confirmation of HoFH was available for 565 of 751 patients (75%), with a higher proportion in high-income compared to non-high-income countries (92% versus 56%). Of note, two non-high-income countries (South Africa and Brazil) accounted for over half (54%) of genetic diagnoses reported in this income group. Patients who had a genetic diagnosis had lower untreated LDL-C levels (14·2 [IQR 11·3–17·6] versus 16·1 [IQR 12·9–19·7] mmol/L) and presented less frequently with xanthomas at diagnosis (66% versus 76%). The allele combinations and classification by *LDLR* residual function are presented in Table S2 and the individual genetic variants are listed in Table S3. Among patients with genetic information available, the majority were either simple homozygous or compound heterozygous carriers of *LDLR* mutations (471 patients, 83%). These patients had higher untreated LDL-C levels (14·7 [IQR 11·8–18·1] mmol/L) compared with patients with autosomal recessive hypercholesterolaemia (28 patients [5%]; LDL-C 12·0 [IQR 11·3–14·3] mmol/L) and with those carrying any other bi-allelic combination including *APOB* and/or *PCSK9* (66 patients [12%]; LDL-C 8·5 [IQR 6·8–13·2] mmol/L, Table S4). Of patients with bi-allelic variants in *LDLR* for whom the residual *LDLR* function was classified, 104 (23%) carried two *LDLR*-negative alleles and had higher untreated LDL-C levels compared with patients carrying any *LDLR*-defective allele (17·2 [IQR 14·2–22·2] versus 14·0 [IQR 11·3–17·1] mmol/L, Table S5).

Lipid-lowering therapy and LDL-C levels

Table 2 shows the type of LLT used at the time when the lowest on-treatment LDL-C levels were recorded. Nearly all patients (92%) were on statin therapy, usually high-intensity (311/379 [82%] defined as atorvastatin ≥40mg or rosuvastatin ≥20mg daily), where statin dosage was available. Ezetimibe was used by 72% of patients from high-income countries, while its use was 54% among patients from non-high-income countries. LLTs such as PCSK9 inhibitors, lomitapide and evinacumab were used infrequently and predominantly in patients from high-income countries. Among patients taking LLT, 78% were on combination therapy with two or more therapies and 42% used three or more types of LLT. Percentages of patients taking multi-LLT combinations were higher in high-income countries (Figure 1).

Lipoprotein apheresis (including plasma exchange) was conducted in 243 patients (39%), initiated at a median age of 15·0 [IQR 10·0–28·0] years, and performed weekly (25%)

or biweekly (54%) in the majority of patients. Patients on apheresis had higher untreated LDL-C at diagnosis compared with patients who were not on apheresis (Table S6, 17·2 [IQR 13·9–21·4] versus 13·5 [IQR 11·1–17·1] mmol/L).

Figure 1 shows the untreated LDL-C levels and the lowest LDL-C levels achieved with the number of LLTs used, including apheresis. Fibrates, omega-3 fish oils, red yeast rice and plant stanols, which lower LDL-C levels modestly, were not included in this analysis. Five patients who had undergone liver transplantation were also excluded from this analysis. Despite multiple therapies, attainment of guideline-recommended LDL-C levels was low: overall, 12% of patients reached an LDL-C <2·6 mmol/L (primary prevention) or <1·8 mmol/L (secondary prevention). The LDL-C reduction was 30% in patients on monotherapy, 45% with 2 classes of LLT and over 65% in patients using ≥3 LLT (Figure 1). The percentage of patients who attained LDL-C goals increased with the number of LLTs, and were more frequently attained in patients from high-income countries compared to non-high-income countries (Table 1, 21% versus 3%). Only 5% of the overall population achieved the more recent lower LDL-C goals (<1·8 and <1·4 mmol/L, respectively).[13]

Cardiovascular Disease

Table 3 shows the proportion of patients reported to have cardiovascular disease overall and stratified by income. The median age at which MACE occurred was 31·0 [IQR 22·0–42·0] years, with 9% of patients already having suffered a non-fatal MI, having undergone PCI or CABG or with aortic valve stenosis at diagnosis of HoFH. There were 37 deaths of which 28 (76%) were from cardiovascular causes (median 28·0 [IQR 17·0–45·5] years). The earliest recorded age at which angina pectoris, MI, CABG or PCI were reported were 4, 10, 5 and 10 years old, respectively. Among those with a recorded non-fatal coronary event, a recurrent coronary event occurred in 28% of patients (29/102), where reported. Peripheral artery and cerebrovascular disease occurred in 42 (6%) and 22 (3%) patients, respectively.

(Supra-)valvular aortic stenosis (any severity) was reported in 29% (216/751) of patients. Where echocardiographic data were available (n=265), 35 (13%) patients had mild, 25 (9%) moderate, and 7 (3%) severe aortic stenosis. Aortic valve replacement had been performed in 52 (7%) patients (median 31·0 [24·8–41·0] years; youngest 5 years).

Figure 2A shows MACE-free survival, with an earlier occurrence in patients managed in non-high-income compared to high-income countries (24·5 [IQR 17·0–34·5] versus 35·0 [IQR 25·0–49·0] years, respectively), with a crude ratio (HR) of 2·01 (95%CI 1·40–2·88). Stepwise attenuation of the HR for incident MACE is shown in Figure 3; adjustment for treatment with three or more types of LLT, age of diagnosis and sex reduced the HR to 1·64 (95%CI 1·13–2·38), suggesting that a fifth of the excess risk might be mitigated through early diagnosis and use of three or more LLTs.

Figure 2B shows MACE-free survival stratified by tertiles of untreated LDL-C. A graded relationship was observed, with events occurring earlier among the highest tertile. Stepwise attenuation of the HR for incident MACE is shown in Figure 3; after adjustment for age of diagnosis and income status the HR for the highest versus lowest tertile with MACE fell from 3·60 (2·22–5·84) to 1·60 (0·96–2·67). Using country status as a proxy for use of

multi-LLT regimens suggests that as much as half of the excess risk could be attenuated by early diagnosis and better treatment.

MACE-free survival was shorter in males (Figure 2C), despite similar demographic characteristics compared to females (Table S7). In sensitivity analyses, the coefficient for sex changed little after addition of smoking to the model: the coefficient for male sex changed from 0·63 to 0·67. Event-free survival was also shorter for patients with a clinical diagnosis of HoFH (no genetic data) versus those genetically confirmed (Figure 2D). In patients with bi-allelic *LDLR* variants, there was a trend towards shorter survival free from MACE in patients carrying two *LDLR*-negative alleles compared with those carrying *LDLR*-defective variants (p=0·21, Figure S1).

Discussion

The present study reports the largest international cohort of HoFH patients to date. Our findings show that, although a rare disease, HoFH occurs worldwide with severe manifestations of cardiovascular diseases very early in life, contributing significantly to premature deaths and disability among those affected. We found clinically meaningful treatment inequalities between countries, with patients in less affluent countries less likely to receive three or more LLTs, resulting in higher on-treatment LDL-C levels and over a decade shorter survival free from cardiovascular events.

Assuming a prevalence of HoFH of about 1 in 300,000 and a global population of 7 billion, we expect approximately 23,000 cases worldwide with the majority residing in less affluent parts of the world, often in regions with high consanguinity or with founder effects, where the condition remains largely underdiagnosed and untreated. Although manyfold larger than previous reports, the 751 patients included in this study thus only comprise ~3% of the estimated total population of HoFH patients worldwide, highlighting the pressing need to increase the identification of these patients using systematic screening and genetic testing for FH globally.[14]

Prior studies of smaller sample size have reported on the severe cardiovascular consequences of HoFH.[2,5,10,11,15–18] Though in part confirmatory, the present report leverages data from 751 patients from 38 countries with a larger number of events, providing more robust information to better guide health-policy and improve patient care. We show that diagnosing HoFH in the second decade of life is too late, as by this age many patients have already experienced cardiovascular complications, supporting the need for more effective strategies to aid timely diagnosis, such as systematic cascade screening or universal screening at an early age. Despite the use of LLT, first MACE occurs early at a median age of 31 years, and in 4% even before the age of 18 years, in line with anecdotal evidence that cardiovascular events can occur in HoFH during childhood.[19] Additionally, one third of patients had (supra-)valvular aortic stenosis, which frequently required surgical intervention. Hence, systematic and more frequent image-guided assessment of aortic (valve) pathology in addition to ASCVD should be implemented in care pathways for HoFH patients.[1]

Cumulative exposure to extreme elevations of LDL-C drives the premature onset of ASCVD[6], therefore guidelines recommend starting intensive lipid lowering immediately from the time of HoFH diagnosis.[1,20,21] The backbone of LLT to date has been high-intensity statin therapy with ezetimibe. However, in the present study, very few patients achieved current LDL-C recommendations with this approach. Use of three or more LLTs (nearly exclusive to patients managed in high-income countries) were associated with lower LDL-C levels and greater likelihood of goal achievement. Our finding that use of five LLTs lowered LDL-C by more than 85% demonstrates that reaching acceptable LDL-C levels, and consequently better outcomes, is possible if a combination of drugs is used. For many patients, especially those without residual LDLR function, therapeutic approaches independent of LDLR function can significantly improve LDL-C levels. These approaches include frequent lipoprotein apheresis[16,22–24], although this option is invasive, not uniformly available[25] and associated with reduced quality of life.[26] Recently, medications such as lomitapide and evinacumab have emerged, which have been shown to reduce LDL-C independently of LDLR function[7,8,27], and can be used in combination with PCSK9 inhibitors for patients with residual LDLR activity.[28,29] Among those with the highest LDL-C levels, our study suggests that as much as half of excess risk could be attenuated through earlier diagnosis and greater use of multi-LLT combinations. Furthermore, as cardiovascular complications may already occur in childhood, it is imperative that existing and new LLTs are rapidly approved for use in the paediatric population.[27]

HDL-C levels in our cohort of HoFH patients were relatively low compared to those expected in a general population. The cause for this known observation is unclear; however the magnitude of the effect of lifelong exposure to extreme LDL-C levels dwarfs any meaningful impact of lower HDL-C levels on cardiovascular outcomes.[30]

Our study also offers insights into the important role of genetics in HoFH diagnosis. Nearly all (~90%) patients from high-income countries were genetically confirmed versus just over half (56%) from non-high-income countries. Of these, more than half resided in South Africa or Brazil, where some local institutions have access to genetic testing. Patients from non-high-income countries had, on average, a more severe phenotype at diagnosis (higher untreated LDL-C levels and greater prevalence of xanthomas), despite being diagnosed at a younger age. These differences may be an artefact of healthcare systems and approaches to case finding, including screening affected relatives and use of genetic testing. Thus, it is possible that only patients with the most severe phenotypes are diagnosed clinically in non-high-income countries, while those with a less severe phenotype are diagnosed clinically as “severe heterozygous FH” or remain undiagnosed. This possibility is supported by the fact that in our cohort double heterozygous patients, who have a less severe phenotype, were almost exclusively reported from high-income countries.

The global nature of our study not only allows for a comparison of the impact of current practice between high and non-high-income countries, but also provides an opportunity to explore potential determinants of health outcomes. The most striking finding in this regard is that event-free survival in HoFH is on average a decade shorter among patients managed in non-high-income countries. These patients had significantly higher risk of MACE, even after adjustment for age of diagnosis, sex and LLT. Patients managed in non-high-income

countries had higher on-treatment LDL-C levels and were less likely to receive multi-LLT combinations. As on-treatment LDL-C levels are a major determinant of event-free survival for HoFH patients,[18] it is likely that this could in part explain the excess risk. Thus the uneven global health burden from HoFH cannot be addressed until less affluent countries have access to effective and affordable LLT regimens starting in childhood, with inevitable implications for healthcare systems and the pharmaceutical industry.

This study has several limitations. Patients entered in the registry may not reflect clinical practice or phenotypes outside of participating centres. That said, as a rare condition, HoFH is mostly managed in specialist and/or academic centres, such as those participating in this registry. Inevitably, those diagnosed reflect local healthcare systems, impacting referrals to specialist clinics and thus availability for inclusion. To generate contemporary data, this registry only included patients alive in 2010 or later. Survival bias is thus inevitable because patients with less severe phenotypes survive longer and are consequently more likely to be included. Collection of retrospective data reduces granularity and completeness of some variables of interest and missing data may also reflect clinical practice at country or institution level. For example, data on Lp(a) levels were not included in this analysis since they were only available in one third of patients, mainly from high-income countries, and measured using different laboratory assays. Although we included participants from 38 countries, more clinicians from other countries and sites were invited to this initiative than those who ultimately participated. Some regions (e.g. much of Latin America and Africa) remain underrepresented and more information is needed to further reduce existing data gaps. Furthermore, a significant proportion of the total number of patients came from three countries: Italy, Turkey and South Africa. However, patients from these countries were comparable to others in their respective income group, and sensitivity analyses excluding these countries did not change results. Finally, the observational nature of the study including survival analyses does not allow assessment of causality and we cannot exclude the possibility of unmeasured variable and residual confounding on outcomes. Despite these limitations, the scale and global reach of this study offer important insights into the contemporary nature of HoFH and its management.

In conclusion, this study reports on the largest international cohort of HoFH patients to date and highlights global disparities that result in clinically significant differences in their care and health outcomes. Our data strongly support the fact that patients with HoFH require early diagnosis and initiation of treatment within the first decade of life as well as more intensive lipid lowering using three or more types of LLT as standard of care in order to prevent the serious consequences of extreme LDL-C exposure. As the greatest global burden resides in less affluent regions of the world, a critical reappraisal of healthcare policy and funding is required at a global level to improve health outcomes for all patients with HoFH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Interests

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Data sharing statement

Data ownership for the data shared with the HICC registry remains the property of the individual contributors. Hence, the HICC Registry cannot share data with third parties without the respective contributors' approval.

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Research in context

Evidence before this study

Articles were identified by PubMed searches using terms related to “(homozygous) familial hypercholesterolaemia” and the reference list was expanded to include references cited in relevant articles. Articles published in English up to and including February 2021 were included.

While the prevalence of homozygous familial hypercholesterolaemia (HoFH) was traditionally estimated to be ~ 1 in 1,000,000, more recent studies have suggested a prevalence closer to 1 in 300,000 in populations not subject to gene founder or consanguinity effects. Given its rarity, guidance for screening and treatment has relied on expert opinion and studies of small sample size, derived mostly from patients of European ancestry or from high-income countries, prior to advances in treatment strategies. Such studies have suggested that the clinical consequences of HoFH likely relate to untreated low-density lipoprotein cholesterol (LDL-C) levels, type of genetic defect, and age at which treatments are started.

Added value of this study

The HoFH International Clinical Collaborators (HICC) registry (NCT04815005) is the first and only global HoFH registry. Initiated by physicians caring for HoFH patients in specialized centres across diverse healthcare settings, HICC offers a unique opportunity to not only provide a comprehensive assessment of the genetic profile and clinical characteristics of HoFH patients globally, but also to provide insights into the impact of policies and access to healthcare and use of effective medications on health outcomes. The present study shows that HoFH patients are often only diagnosed in the second decade of life with extreme LDL-C elevation and a prevalence of cardiovascular or aortic valve disease at diagnosis of almost one in ten. We found significant health inequalities in the management of patients with HoFH globally. Despite the development of newer, more effective therapies that have been demonstrated to result in significantly better control of LDL-C levels, guideline-recommended goal attainment is rare and largely restricted to patients from high-income countries. Patients from non-high-income countries have on average a more severe phenotype at diagnosis, are less likely to receive advanced treatments and have a decade shorter cardiovascular event-free survival compared to those from high-income countries.

Implications

The findings from HICC provide a framework to inform the development of clinical practice guidelines and public health policies concerning HoFH and help establish a uniform world-wide approach to the management of this high-risk condition. Greater awareness and changes in health policy, including restructuring approaches to screening and diagnosis, are urgently required to improve early detection and treatment of HoFH. This is particularly relevant to non-high-income countries where patients with HoFH require greater access to more effective combinations of lipid-lowering therapies, in order to improve health outcomes.

Definition and Diagnosis

Patients with HoFH have extremely high plasma LDL-C levels that causes accelerated atherosclerotic cardiovascular disease (ASCVD). Manifestations of ASCVD most notably include fatal and non-fatal myocardial infarction as well as occlusive vascular disease requiring surgical or percutaneous revascularisation. Similarly, deposition of cholesterol in and around the aortic valve can cause severe (supra-)valvular aortic stenosis. Deposits of cholesterol in the skin and/or tendons, called xanthomas, are the hallmark of the disease. The development and severity of ASCVD and/or aortic stenosis determine prognosis in HoFH.

HoFH can be diagnosed clinically or genetically.

Clinical diagnosis:

- Untreated LDL-C levels >13 mmol/L (500 mg/dL), or LDL-C ≥8 mmol/L (300 mg/dL) while on conventional LLT

  AND

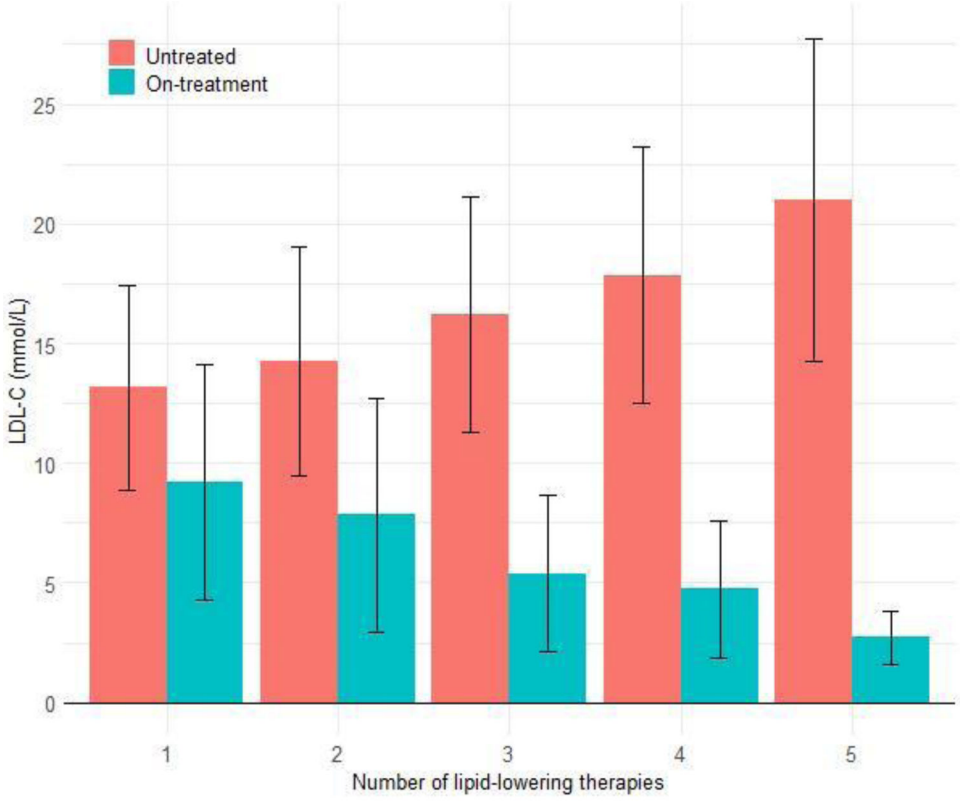
- Presence of xanthomas before the age of ten years, or the presence of heterozygous FH in both parents[1]

Genetic diagnosis:

- Identification of bi-allelic pathogenic variants at the *LDLR*, *APOB*, *PCSK9* or *LDLRAP1* gene locus

Patients with identical variants in both alleles of the same gene are simple homozygous. Patients with non-identical variants in both alleles of the same gene are compound heterozygous and patients with variants in two different FH-genes are termed double heterozygous. Autosomal recessive hypercholesterolaemia is a very rare form of HoFH caused by bi-allelic variants in *LDLRAP1*.[9]

Importantly, the phenotype of HoFH varies considerably and genetic testing has identified many patients with less severe phenotypes.[2,10,11] Conversely, the absence of two pathogenic variants in the presence of a phenotype consistent with HoFH does not exclude the diagnosis.



Number of LLT	1	2	3	4	5
From high-income countries	38/114 (33·3%)	85/185 (45·9%)	111/162 (68·5%)	32/37 (86·5%)	15/15 (100%)
Mean LDL-C reduction (%)	30%	45%	67%	74%	87%
LDL-C goal attainment*	3 (2·6%)	16 (8·6%)	27 (16·7%)	7 (18·9%)	8 (53·3%)

Figure 1 - Untreated LDL-C levels and lowest on-treatment LDL-C levels achieved, as a function of number of LLTs (including apheresis)

Data are shown as mean (±SD) or n (%), as appropriate. LLT included statins, ezetimibe, PCSK9 inhibitors, lipoprotein apheresis, lomitapide, evinacumab and mipomersen. Five patients who had undergone liver transplantation were excluded from this analysis. LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy

* LDL-C below guideline-recommended goals is defined as an LDL-C level < 2·5 mmol/L in primary prevention or < 1·8 mmol/L in case of secondary prevention.

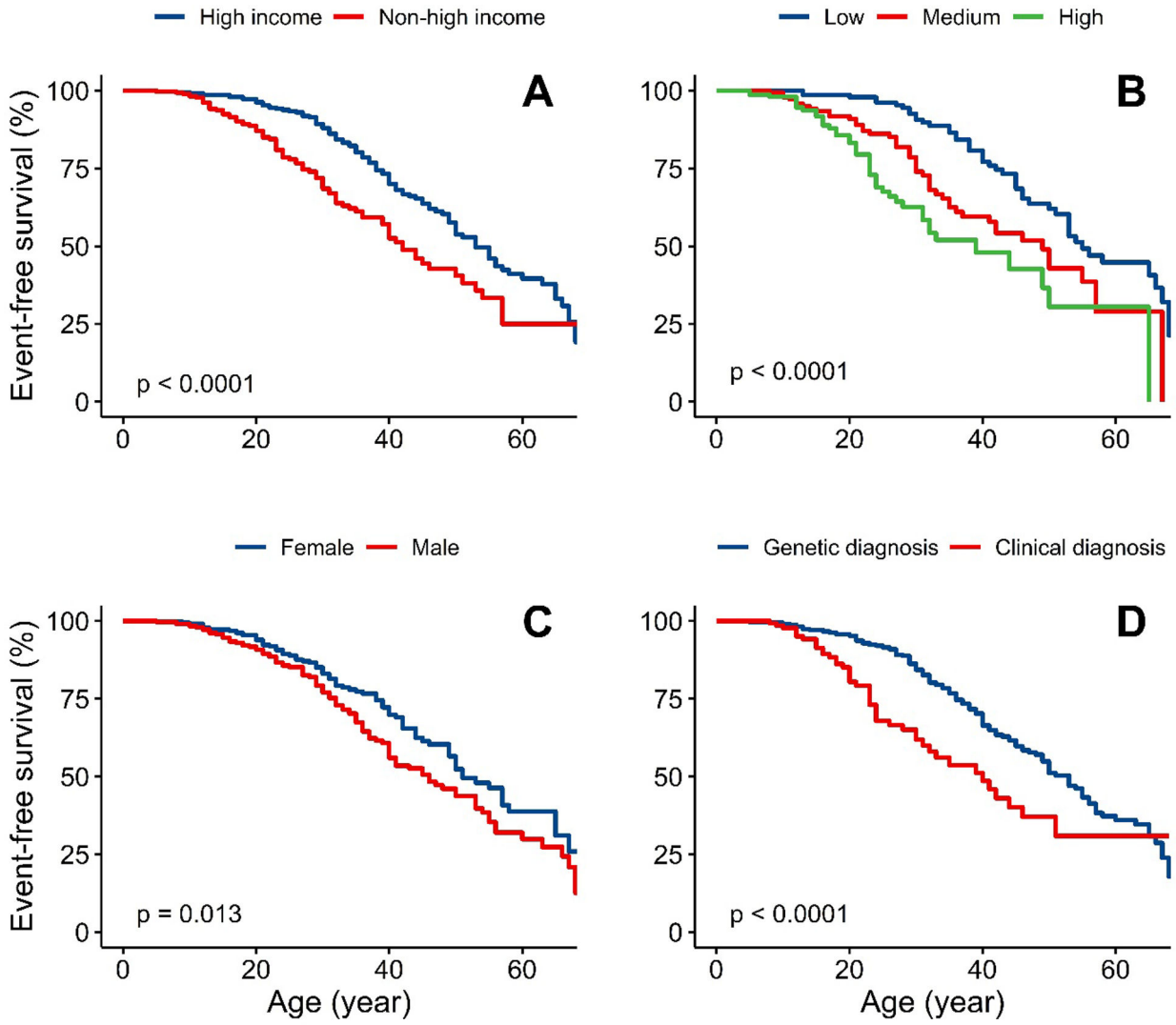


Figure 2 –. Survival-time free from major adverse cardiovascular events

Panel: event-free survival stratified by A) High-income vs non-high-income countries B) Untreated LDL-C tertiles, lowest (4·9–12·5 mmol/L), middle (12·6–17·1 mmol/L) and highest (17·1–36·3 mmol/L) C) Sex D) Clinical diagnosis only versus genetic diagnosis Statistical test for comparison between groups is Log-rank test.

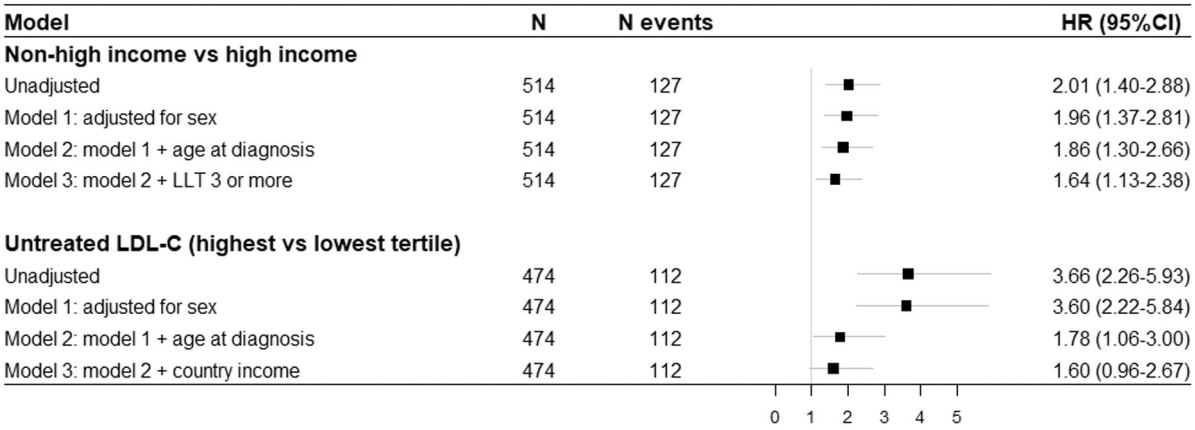


Figure 3 –. Forest plot showing unadjusted and adjusted hazard ratios for occurrence of major adverse cardiovascular events between specific groups of interest

LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LLT, lipid-lowering therapy; HR, hazard ratio; CI, confidence interval

Major adverse cardiovascular events were defined as cardiovascular death, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention that occurred after the diagnosis of HoFH was made. Presented data are based on complete case analysis.

Table 1 –

Demographic, clinical and genetic characteristics and plasma lipid levels in HoFH patients, overall and stratified by country income status

	Overall N=751	High-income countries N=398	Non-high-income countries N=353
Age of FH diagnosis (years)	12·0 [5·5–27·0] *18·0 (16·8–19·2)*	16·0 [6·0–33·0] *20·7 (18·9–22·5)*	10·0 [5·0–20·0] *15·1 (13·6–16·7)*
Women	389 (52·1%)	205 (51·5%)	184 (52·9%)
Xanthomas at diagnosis	516 (68·7%)	255 (64·1%)	261 (73·9%)
Body mass index (kg/m^2)	24·0 (23·4–24·6)	24·0 (23·2–24·8)	24·0 (23·1–24·9)
Diabetes mellitus	23 (3·6%)	15 (5·2%)	8 (2·3%)
Hypertension	93 (14·5%)	41 (14·0%)	52 (14·9%)
Chronic kidney disease	6 (1·2%)	5 (2·2%)	1 (0·4%)
Current smoker	43 (7·8%)	25 (8·7%)	18 (6·8%)
Previous smoker	54 (9·8%)	31 (10·8%)	23 (8·7%)
Lipids (mmol/L)			
Untreated			
Total cholesterol	16·2 [13·1–20·0] *16·8 (16·3–17·2)*	15·5 [12·4–19·3] *16·4 (15·8–17·0)*	17·2 [14·6–20·6] *17·6 (16·9–18·2)*
LDL-C	14·7 [11·6–18·4] *15·2 (14·8–15·6)*	13·5 [10·4–17·2] *14·2 (13·6–14·9)*	15·8 [12·9–19·2] *16·2 (15·6–16·7)*
HDL-C	1·00 [0·78–1·26] *1·05 (1·01–1·09)*	1·03 [0·80–1·27] *1·05 (1·00–1·09)*	0·93 [0·70–1·21] *1·05 (0·97–1·13)*
Triglycerides	1·20 [0·88–1·70] *1·41 (1·33–1·50)*	1·19 [0·85–1·65] *1·38 (1·27–1·51)*	1·23 [0·90–1·79] *1·46 (1·33–1·60)*
*Most recent***			
Total cholesterol	9·0 [5·8–13·0] *9·7 (9·3–10·1)*	6·7 [4·9–9·1] *7·4 (7·0–7·9)*	12·3 [8·9–15·4] *12·3 (11·7–12·9)*
LDL-C	7·7 [4·6–11·5] *8·3 (8·0–8·7)*	4·9 [3·0–7·5] *5·7 (5·3–6·1)*	10·1 [7·4–13·2] *10·5 (11·0–10·9)*
LDL-C below guideline-recommended goals****	42 (7·2%)	38 (14·6%)	4 (1·2%)
Lowest recorded level†			
Total cholesterol	7·6 [4·9–11·1] *8·7 (8·2–9·1)*	5·6 [4·1–7·6] *6·3 (5·9–6·7)*	10·7 [7·9–14·7] *11·3 (10·7–11·9)*
LDL-C	6·6 [3·6–10·4] *7·5 (7·1–7·9)*	3·9 [2·6–5·8] *4·7 (4·3–5·0)*	9·3 [6·7–12·7] *9·8 (9·3–10·3)*
LDL-C below guideline-recommended goals****	64 (10·9%)	56 (21·4%)	8 (2·5%)
Genetic information available††	565 (75·2%)	367 (92·2%)	198 (56·1%)

Data are shown as n (%) for categorical variables or as median [IQR]. In addition, numbers in italic describe quantitative variables as bootstrapped means (95%).Classification of high- and non-high-income countries is shown in Table S1. FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

** This reflects the most recent measurement available after diagnosis and prior to data entry in the registry.

*** LDL-C below guideline-recommended goals is defined as an LDL-C level< 2·5 mmol/L in primary prevention or < 1·8 mmol/L in case of secondary prevention.

[†]This reflects the lowest recorded LDL-C measurement between untreated (at diagnosis) and most recent measurement. When unavailable, the most recent measurement itself was considered the lowest.

[††]For details see Table S2 in the online supplement.

Table 2 –

Lipid-lowering therapy at the time of the lowest on-treatment LDL-C level recorded, overall and stratified by country income status

	Overall N=534	High-income countries N=293	Non-high-income countries N=241
Medication			
Statins	491 (91·9%)	262 (89·4%)	229 (95·0%)
Ezetimibe	342 (64·0%)	212 (72·4%)	130 (53·9%)
PCSK9 inhibitors	118 (22·1%)	76 (25·9%)	42 (17·4%)
Lomitapide	45 (8·4%)	40 (13·7%)	5 (2·1%)
Evinacumab *	13 (2·4%)	13 (4·4%)	0
Mipomersen	5 (0·9%)	0	5 (2·1%)
Bile acid sequestrants	33 (6·2%)	31 (10·6%)	2 (0·8%)
Fibrates	6 (1·1%)	2 (0·7%)	4 (1·7%)
Other **	17 (3·2%)	9 (3·1%)	8 (3·3%)
Lipoprotein apheresis †	243/621 (39·1%)	118/293 (39·7%)	125/328 (38·1%)
Surgeries			
Liver transplantation	5 (0·8%)	4 (1·3%)	1 (0·3%)
Age at liver transplantation (years)	19·4 (10·5–30·0)	10, 16, 24, 36	11
Ileal bypass surgery ††	1 (0·2%)	1 (0·3%)	0
Age at Ileal bypass surgery (years)	21	21	NA
Portacaval shunt surgery ††	6 (1·1%)	0	6 (2·9%)
Age at Portacaval shunt surgery (years)	9·7 (5·7–14·2)	NA	5, 5, 7, 11, 12, 18

Data are shown as n (%) for categorical variables, as bootstrapped mean (95%CI) for quantitative variables. Classification of high- and non-high-income countries is shown in Table S1. NA, not applicable; PCSK9, proprotein convertase subtilisin/kexin type 9

* Evinacumab is an investigational product that has been recently approved by FDA but is not yet approved by other regulatory agencies. It was given as compassionate use and/or open label extension as part of a clinical trial

** Other therapies were red yeast rice, omega-3 fish oils and plant stanols

† Apheresis includes all lipoprotein apheresis types including plasma exchange. For 87 patients from non-high-income countries it was only known that they were on lipoprotein apheresis but no additional information was available on other lipid-lowering therapies. Patients from non-high-income countries who are on apheresis were mainly from Turkey (n=87) and Lebanon (n=26).

†† Ileal bypass and portacaval shunt surgery are no longer considered treatments for HoFH, these entries reflect (abandoned) historic practice.

Table 3 –

Cardiovascular disease in the overall population and stratified by country income status

	Overall N=751	High-income countries N=398	Non-high-income countries N=353
Cardiovascular death *	28 (3·7%)	10 (2·5%)	18 (5·1%)
Unknown or non-cardiovascular death	9 (1·2%)	6 (1·5%)	3 (0·8%)
Age at cardiovascular death	28·0 [17·0–45·5] *31·5 (25·5–37·6)* Range 5–58	49·5 [32·0–50·8] *37·0 (26·1–46·6)*	24·0 [17·0–40·3] *28·4 (21·2–36·2)*
Myocardial infarction	90 (11·9%)	48 (11·9%)	42 (11·9%)
Age at first MI	37·5 [30·0–50·0] *38·8 (35·6–42·0)* Range 10–68	39·0 [32·0–50·0] *39·9 (36·2–43·6)*	32·5 [28·5–42·5] *35·4 (29·2–41·9)*
Angina pectoris	95 (12·5%)	63 (15·6%)	32 (9·0%)
Age at AP onset	30·0 [20·0–39·0] *30·4 (27·3–33·7)* Range 4–75	32·0 [20·8–42·3] *33·2 (29·0–37·5)*	24·0 [20·0–32·0] *25·3 (21·6–29·1)*
CABG	120 (15·8%)	60 (14·9%)	60 (16·9%)
Age at first CABG	30·0 [22·5–40·0] *31·5 (28·9–34·2)* Range 5–69	32·0 [28·0–46·0] *36·7 (32·9–40·6)*	24·0 [17·3–32·8] *26·0 (23·0–29·0)*
PCI	91 (12·1%)	54 (13·4%)	37 (10·2%)
Age at first PCI	39·5 [28·0–48·5] *38·5 (35·5–41·5)* Range 10–75	42·5 [36·3–52·8] *42·9 (39·4–46·6)*	30·0 [21·0–40·0] *31·2 (26·8–35·5)*
Aortic valve replacement	52 (6·9%)	36 (8·9%)	16 (4·5%)
Age at first AVR	31·0 [24·8–41·0] *33·0 (28·6–37·4)* Range 5–69	31·5 [27·0–43·8] *36·1 (30·3–42·1)*	30·0 [22·0–35·3] *27·9 (21·9–33·5)*
Peripheral artery disease	42 (6·2%)	8 (2·4%)	34 (9·8%)
Age at PAD diagnosis	34·5 [20·5–47·3] *35·5 (27·5–44·0)* Range 7–74	51·0 [34·5–64·0] *49·9 (35·1–63·7)*	21·0 [17·0–38·0] *27·8 (19·8–36·4)*
Cerebrovascular disease **	22 (2·9%)	18 (4·5%)	4 (1·1%)
Age at first cerebrovascular disease event	37·0 [28·0–48·0] *40·9 (33·9–48·7)* Range 23–71	38·0 [29·0–53·0] *42·5 (34·6–50·8)*	28·5 [27·3–29·8] *26, 31, NA, NA*
Composite outcomes			
MACE§	216 (28·8%)	110 (27·2%)	106 (29·9%)
Age of first MACE	31·0 [22·0–42·0] *33·0 (30·9–35·0)* Range 5–75	37·0 [29·0–49·0] *38·1 (35·4–40·9)*	24·5 [17·0–34·5] *26·8 (24·3–29·3)*
MACE+§§	267 (35·6%)	137 (34·4%)	130 (36·7%)
Age of first MACE+	30·0 [21·0–41·0] *32·0 (30·0–33·9)* Range 4–75	35·5 [25·0–48·3] *36·5 (33·8–39·2)*	24·0 [17·0–32·0] *26·2 (23·9–28·6)*

Data are shown as n (%) for the prevalence of cardiovascular events, and as median [IQR] and range (minimum, maximum) for ages at cardiovascular events. In addition, ages at cardiovascular events are shown in italic as bootstrapped mean (95%CI). MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; AP, angina pectoris; AVR, aortic valve replacement; NA, not available; MACE, major adverse cardiovascular event

* Cardiovascular death was physician reported death from cardiovascular causes. “Sudden death” and periprocedural death due to cardiac surgery necessitated by consequences of hypercholesterolaemia was additionally considered cardiovascular death.

** Cerebrovascular disease was defined as ischemic stroke, carotid artery stenting or carotid endarterectomy.

§ MACE is a composite of cardiovascular death, non-fatal MI, PCI and CABG.

§§ MACE+ is a composite of cardiovascular death, non-fatal MI, PCI and CABG, AP, non-fatal ischemic stroke, carotid stenting, carotid endarterectomy and peripheral artery disease.