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## 2 **Homozygous Familial Hypercholesterolaemia – Worldwide**

### 3 **Experience**

4

### 5 **Authors**

6 Tycho R. Tromp<sup>1</sup> MD, Merel L. Hartgers<sup>1,2</sup> PhD, Prof G. Kees Hovingh<sup>1</sup> PhD, Antonio J. Vallejo-Vaz<sup>3,4,5</sup>  
7 PhD, Prof Kausik K. Ray<sup>3</sup> FRCP, Handrean Soran<sup>6</sup> MD, Prof Tomas Freiburger<sup>7</sup> PhD, Prof Stefano  
8 Bertolini<sup>8</sup> MD, Mariko Harada-Shiba<sup>9</sup> PhD, Dirk J. Blom<sup>10</sup> PhD, Prof Frederick J. Raal<sup>11</sup> PhD, Marina  
9 Cuchel<sup>12</sup> PhD, and the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators  
10 (HICC)\*

11

12 \*The full list of authors is shown at the end of the manuscript.

13    **Correspondence to:**

14    Dr Marina Cuchel, MD PhD

15    Perelman School of Medicine at the University of Pennsylvania

16    Translational Medicine & Human Genetics

17    9th floor Maloney Building, Room 9017

18    3600 Spruce Street

19    Philadelphia, PA 19104

20

21    Email: mcuchel@pennmedicine.upenn.edu

22    Phone number: (215) 662-7188

23

24

25

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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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58 **Study registration:** ClinicalTrials.gov NCT04815005 ([link](#))

59 **Funding:** Detailed at end of paper (see Acknowledgements).

60 **Keywords**

61 Homozygous familial hypercholesterolaemia, low-density lipoprotein cholesterol, lipid-lowering

62 therapy, atherosclerotic cardiovascular disease, aortic valve stenosis, lipoprotein apheresis

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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.



## 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.<sup>1</sup> 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,<sup>2–5</sup> with a higher prevalence in populations with a founder effect.<sup>1</sup> 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.<sup>6</sup> 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,<sup>7,8</sup> 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.

[box]

## 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<sup>1</sup>

### *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*.<sup>9</sup>

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

150 ***[/box]***

## 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.<sup>1</sup> 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.<sup>1</sup>

### *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).<sup>12</sup>

### *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  $\geq 40$ mg or rosuvastatin  $\geq 20$ mg 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  $\geq 3$  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).<sup>13</sup>

### *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 ( $p=0\cdot21$ , 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.<sup>14</sup>

Prior studies of smaller sample size have reported on the severe cardiovascular consequences of HoFH.<sup>2,5,10,11,15–18</sup> 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.<sup>19</sup> 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.<sup>1</sup>

Cumulative exposure to extreme elevations of LDL-C drives the premature onset of ASCVD<sup>6</sup>, therefore guidelines recommend starting intensive lipid lowering immediately from the time of HoFH diagnosis.<sup>1,20,21</sup> 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<sup>16,22–24</sup>, although this option is invasive, not uniformly available<sup>25</sup> and associated with reduced quality of life.<sup>26</sup> Recently, medications such as lomitapide and evinacumab have emerged, which have been shown to reduce LDL-C independently of LDLR function<sup>7,8,27</sup>, and can be used in combination with PCSK9 inhibitors for patients with residual LDLR activity.<sup>28,29</sup> 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.<sup>27</sup>

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.<sup>30</sup>

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,<sup>18</sup> 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,

388 the scale and global reach of this study offer important insights into the contemporary nature of HoFH  
389 and its management.

390

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

399    **\* List of authors**

400    **Writing committee:**

401    Tycho R. Tromp<sup>1</sup> MD, Merel L. Hartgers<sup>1,2</sup> PhD, Prof G. Kees Hovingh<sup>1</sup> PhD, Antonio J. Vallejo-Vaz<sup>3,4,5</sup>  
402    PhD, Prof Kausik K. Ray<sup>3</sup> PhD, Handrean Soran<sup>6</sup> MD, Prof Tomas Freiburger<sup>7</sup> PhD, Prof Stefano Bertolini<sup>8</sup>  
403    PhD, Mariko Harada-Shiba<sup>9</sup> PhD, Dirk J. Blom<sup>10</sup> PhD, Prof Frederick J. Raal<sup>11</sup> PhD, Marina Cuchel<sup>12</sup>, PhD

404    **HoFH Clinical Collaborators:**

405    **Australia:** Jing Pang<sup>13</sup>, PhD, Prof Gerald F. Watts<sup>13</sup>, DSc **Austria:** Prof Susanne Greber-Platzer<sup>14</sup>, PhD,  
406    Martin Mäser<sup>15</sup>, MD, Prof Thomas M. Stulnig<sup>16</sup>, MD, Prof Christoph F. Ebenbichler<sup>17</sup>, MD **Bahrain:**  
407    Khalid Bin Thani<sup>18</sup>, MD **Belgium:** Prof David Cassiman<sup>19</sup>, PhD, Olivier S. Descamps<sup>20</sup>, PhD, Daisy  
408    Rymen<sup>21</sup>, PhD, Peter Witters<sup>21</sup>, PhD **Brazil:** Raul D. Santos<sup>22</sup>, PhD **Canada:** Liam R. Brunham<sup>23</sup>, PhD, Prof  
409    Gordon A. Francis<sup>23</sup>, MD, Jacques Genest<sup>24</sup>, MD, Prof Robert A. Hegele<sup>25</sup>, MD, Brooke A. Kennedy<sup>26</sup>,  
410    Isabelle Ruel<sup>24</sup>, PhD, Mark H. Sherman<sup>24</sup>, MD **China:** Long Jiang<sup>27</sup>, PhD, Luya Wang<sup>27</sup>, MD **Croatia:** Prof  
411    Željko Reiner<sup>28</sup>, PhD **Czech Republic:** Prof Vladimir Blaha<sup>29</sup>, PhD, Prof Richard Ceska<sup>30</sup>, PhD, Jana  
412    Dvorakova<sup>31</sup>, MD, Lubomir Dlouhy<sup>32</sup>, Pavel Horak<sup>30</sup>, PhD, Prof Vladimir Soska<sup>33</sup>, MD, Lukas Tichy<sup>34</sup>, PhD,  
413    Robin Urbanek<sup>35</sup>, MD, Prof Helena Vaverkova<sup>36</sup>, MD, Prof Michal Vrablik<sup>30</sup>, PhD, Stanislav Zemek<sup>37</sup>, MD,  
414    Lukas Zlatohlavek<sup>30</sup>, PhD **Egypt:** Prof Sameh Emil<sup>38</sup>, MD, Tarek Naguib<sup>39</sup>, Prof Ashraf Reda<sup>40</sup>, MD **France:**  
415    Sophie Béliard<sup>41</sup>, MD, Prof Eric Bruckert<sup>42</sup>, MD, Antonio Gallo<sup>42</sup>, PhD **Greece:** Prof Moses S. Elisaf<sup>43</sup>,  
416    PhD, Genovefa Kolovou<sup>44</sup>, PhD **Israel:** Hofit Cohen<sup>45</sup>, MD, Prof Ronen Durst<sup>46</sup>, MD, Prof Eldad J. Dann<sup>47</sup>,  
417    MD, Prof Avishay Elis<sup>48</sup>, MD, Osama Hussein<sup>49</sup>, MD, Prof Eran Leitersdorf<sup>50</sup>, MD, Daniel Schurr<sup>50</sup>, MD  
418    **India:** Nitika Setia<sup>51</sup>, PhD, Prof Ishwar C. Verma<sup>51</sup>, FRCP **Iraq:** Mohammed D. Alareedh<sup>52</sup>, PhD, Mutaz  
419    Al-Khnifsawi<sup>53</sup>, MD, Ali F. Abdalsahib Al-Zamili<sup>54</sup>, PhD, Sabah H. Rhadi<sup>55</sup>, PhD, Foad K. Shaghee<sup>56</sup> **Italy:**  
420    Prof Marcello Arca<sup>57</sup>, MD, Prof Maurizio Averna<sup>58</sup>, MD, Andrea Bartuli<sup>59</sup>, MD, Marco Bucci<sup>60</sup>, MD, Paola  
421    S. Buonomo<sup>59</sup>, MD, Prof Paolo Calabrò<sup>61</sup>, PhD, Prof Sebastiano Calandra<sup>62</sup>, MD, Manuela Casula<sup>63</sup>,  
422    PhD, Prof Alberico L. Catapano<sup>63</sup>, PhD, Angelo B. Cefalù<sup>58</sup>, PhD, Arrigo F. Cicero<sup>64</sup>, PhD, Sergio  
423    D'Addato<sup>64</sup>, PhD, Laura D'Erasmo<sup>57</sup>, PhD, Alessia Di Costanzo<sup>57</sup>, PhD, Tommaso Fasano<sup>65</sup>, PhD, Marta

424 Gazzotti<sup>63</sup>, MSc, Antonina Giammanco<sup>58</sup>, PhD, Gabriella Iannuzzo<sup>66</sup>, PhD, Anastasia Ibba<sup>67</sup>, MD,  
 425 Emanuele A. Negri<sup>68</sup>, MD, Andrea Pasta<sup>8</sup>, MD, Chiara Pavanello<sup>69</sup>, PhD, Livia Pisciotto<sup>8</sup>, PhD, Claudio  
 426 Rabacchi<sup>70</sup>, PhD, Carlo Ripoli<sup>71</sup>, MD, Tiziana Sampietro<sup>72</sup>, PhD, Francesco Sbrana<sup>72</sup>, MD, Fulvio Sileo<sup>73</sup>,  
 427 MD, Patrizia Suppressa<sup>74</sup>, PhD, Prof Patrizia Tarugi<sup>70</sup>, PhD, Chiara Trenti<sup>68</sup>, MD, Maria G. Zenti<sup>75</sup>, PhD  
 428 **Japan:** Mika Hori<sup>76,77</sup>, PhD **Jordan:** Mahmoud H. Ayesh<sup>78</sup>, MD **Lebanon:** Prof Sami T. Azar<sup>79</sup>, MD, Prof  
 429 Fadi F. Bitar<sup>80</sup>, MD, Akl C. Fahed<sup>81</sup>, MD, Elie M. Moubarak<sup>82</sup>, MD, Prof Georges Nemer<sup>83</sup>, PhD **Malaysia:**  
 430 Prof Hapizah Nawawi<sup>84</sup>, FRCPath **Mexico:** Ramón Madriz<sup>85</sup>, MD, Roopa Mehta<sup>86</sup>, PhD **Netherlands:**  
 431 Arjen J. Cupido<sup>1</sup>, MD, Joep C. Defesche<sup>87</sup>, PhD, M. Doortje Reijman<sup>88</sup>, MD, Jeanine E. Roeters-van  
 432 Lennep<sup>89</sup>, PhD, Prof Erik S. Strokes<sup>1</sup>, PhD, Albert Wiegman<sup>88</sup>, PhD, Linda Zuurbier<sup>87</sup>, PhD **Oman:** Khalid  
 433 Al-Waili<sup>90</sup>, MD **Pakistan:** Fouzia Sadiq<sup>91</sup>, PhD **Poland:** Krzysztof Chlebus<sup>92</sup>, PhD **Portugal:** Prof Mafalda  
 434 Bourbon<sup>93</sup>, PhD, Isabel M. Gaspar<sup>94</sup>, MD **Serbia:** Prof Katarina S. Lalic<sup>95</sup>, PhD **Russia:** Marat V. Ezhov<sup>96</sup>,  
 435 DMSc, Prof Andrey V. Susekov<sup>97</sup>, PhD **Slovenia:** Urh Groselj<sup>98</sup>, PhD **Taiwan:** Prof Min-Ji Charng<sup>99</sup>, PhD  
 436 **Thailand:** Prof Weerapan Khovidhunkit<sup>100</sup>, PhD **Turkey:** Melih Aktan<sup>101</sup>, MD, Prof Bulent B.  
 437 Altunkeser<sup>102</sup>, MD, Sinan Demircioglu<sup>103</sup>, MD, Melis Kose<sup>104</sup>, PhD, Prof Cumali Gokce<sup>105</sup>, MD, Prof  
 438 Osman Ilhan<sup>106</sup>, MD, Prof Meral Kayikcioglu<sup>107</sup>, MD, Leyla G. Kaynar<sup>108</sup>, MD, Prof Irfan Kuku<sup>109</sup>, MD,  
 439 Erdal Kurtoglu<sup>110</sup>, MD, Harika Okutan<sup>111</sup>, MD, Osman I. Ozcebe<sup>112</sup>, MD, Zafer Pekkolay<sup>113</sup>, MD, Saim  
 440 Sag<sup>114</sup>, PhD, Osman Z. Salcioglu<sup>115</sup>, MD, Prof Ahmet Temizhan<sup>116</sup>, MD, Mustafa Yenercag<sup>117</sup>, MD,  
 441 Mehmet Yilmaz<sup>118</sup>, MD, Hamiyet Yilmaz Yasar<sup>119</sup>, MD **Ukraine:** Prof Olena Mitchenko<sup>120</sup>, MD **United**  
 442 **Kingdom:** Alexander R. Lyons<sup>3</sup>, PhD, Christophe A. Stevens<sup>3</sup>, MSc **United States:** Julie A. Brothers<sup>121</sup>,  
 443 MD, Lisa C. Hudgins<sup>122</sup>, MD, Christina Nguyen<sup>12</sup>, MBS **Uzbekistan:** Rano Alieva<sup>123</sup>, MD, Prof Aleksandr  
 444 Shek<sup>123</sup>, MD **Vietnam:** Doan-Loi Do<sup>124,125</sup>, PhD, Ngoc-Thanh Kim<sup>124,125</sup>, MD, Hong-An Le<sup>126</sup>, MD, Thanh-  
 445 Tung Le<sup>124</sup>, MD, Mai-Ngoc T. Nguyen<sup>124</sup>, PhD, Thanh-Huong Truong<sup>124,125</sup>, PhD



## 446 Affiliations

- 447 1. Department of Vascular Medicine, Amsterdam UMC, location AMC, Meibergdreef 9, 1105 AZ  
448 Amsterdam, The Netherlands
- 449 2. Centre for Population Health Sciences (CePHaS), Lee Kong Chian School of Medicine, Nanyang  
450 Technological University, Singapore
- 451 3. Imperial Centre for Cardiovascular Disease Prevention (ICCP), Dept. of Primary Care and Public  
452 Health, School of Public Health, Imperial College London, London, United Kingdom
- 453 4. Clinical Epidemiology and Vascular Risk, Instituto de Biomedicina de Sevilla, IBiS/Hospital  
454 Universitario Virgen del Rocío/ Universidad de Sevilla/CSIC. Sevilla, Spain
- 455 5. Department of Medicine, Faculty of Medicine, University of Sevilla. Sevilla, Spain
- 456 6. Department of Diabetes, Endocrinology and Metabolism, Manchester University NHS  
457 Foundation Trust and National Institute of Health Research/Wellcome Trust Clinical Research  
458 Facility, Manchester, United Kingdom
- 459 7. Centre for Cardiovascular Surgery and Transplantation, Brno, Czech Republic; Medical Faculty,  
460 Masaryk University, Brno, Czech Republic
- 461 8. Department of Internal Medicine, University of Genova, Genova, Italy
- 462 9. Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research  
463 Institute, 6-1 Kishibe-Shinmachi, Suita, Osaka 564-8565 Japan
- 464 10. Department of Medicine, Division of Lipidology and Hatter Institute for Cardiovascular  
465 Research in Africa, University of Cape Town, Cape Town, South Africa
- 466 11. Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of  
467 Witwatersrand, Johannesburg, South Africa
- 468 12. Department of Medicine, Division of Translational Medicine and Human Genetics, Perelman  
469 School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
- 470 13. School of Medicine, University of Western Australia; Departments of Cardiology and Internal  
471 Medicine, Royal Perth Hospital, Perth, WA, Australia
- 472 14. Department of Pediatrics and Adolescent Medicine, Division of Pediatric Pulmonology,  
473 Allergology and Endocrinology, Medical University Vienna, Vienna, Austria
- 474 15. Department of Pediatrics, Academic Teaching Hospital, Landeskrankenhaus Feldkirch,  
475 Feldkirch, Austria
- 476 16. Third Department of Medicine and Karl Landsteiner Institute for Metabolic Diseases and  
477 Nephrology, Clinic Hietzing, Vienna Healthcare Group, Wokersbergernstrasse 1, 1130 Vienna,  
478 Austria
- 479 17. Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria
- 480 18. Salmaniya Medical Complex, Manama, Bahrain
- 481 19. Department of Hepatology and Center for Metabolic Diseases, University Hospital Leuven,  
482 Leuven, Belgium
- 483 20. Department of Internal Medicine, Centres hospitaliers Jolimont, Belgium
- 484 21. Department of Paediatrics and Center for Metabolic Diseases, University Hospital Leuven,  
485 Leuven, Belgium

- 486 22. Heart Institute (InCor) University of Sao Paulo and Hospital Israelita Albert Einstein, Sao Paulo,  
487 Brazil
- 488 23. Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
- 489 24. Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada
- 490 25. Department of Medicine, Schulich School of Medicine and Dentistry, Western University,  
491 London, ON, Canada
- 492 26. Robarts Research Institute, Schulich School of Medicine and Dentistry, Western University,  
493 London, ON, Canada
- 494 27. Department of Atherosclerosis, Beijing Anzhen Hospital, Capital Medical University, The Key  
495 Laboratory of Remodeling-Related Cardiovascular Diseases, Ministry of Education, Beijing  
496 Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China
- 497 28. Department of Internal medicine, University Hospital Centre Zagreb, School of Medicine  
498 University of Zagreb, Croatia
- 499 29. University Hospital Hradec Králové and Charles University, Faculty of Medicine in Hradec  
500 Králové, 3rd Department of Internal Medicine - Metabolism and Gerontology, Hradec Králové,  
501 Czech Republic
- 502 30. General University Hospital and 1st Faculty of Medicine, Charles University, 3rd Department of  
503 Internal Medicine – Endocrinology and Metabolism, Prague, Czech Republic
- 504 31. Department of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital,  
505 Prague, Czech republic
- 506 32. Laboratory Medicine Center, Regional Hospital Liberec, Czech Republic
- 507 33. Department of Clinical Biochemistry, St. Anne's University Hospital Brno, Czech Republic; 2nd  
508 Clinic of Internal Medicine, Faculty of Medicine, Masaryk University, Brno, Czech Republic
- 509 34. Center of Molecular Biology and Genetics, Department of Internal Medicine – Hematology and  
510 Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech  
511 Republic
- 512 35. Lipid Clinic, Zlin, Czech Republic
- 513 36. Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital  
514 Olomouc, Third Department of Internal Medicine – NRE, Olomouc, Czech Republic
- 515 37. Lipidová ambulance, Masarykovo namesti 155, Uherske Hradiste, Czech Republic
- 516 38. Military Academy, Cairo
- 517 39. Zagazig University, Zagazig
- 518 40. Menoufia University, Faculty of medicine, Cardiology department, Egypt
- 519 41. Department of Endocrinology and Nutrition, APHM, La Conception University hospital,  
520 Marseille, France
- 521 42. Department of Endocrinology and prevention of cardiovascular disease, Pitié-Salpêtrière  
522 University Hospital, Paris, France
- 523 43. Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece
- 524 44. Cardiometabolic Center, Lipid Clinic, LA apheresis Unit, Metropolitan Hospital, Athens, Greece
- 525 45. Bert W. Strassburger Lipid Center, the Chaim Sheba Medical Center, Tel Hashomer, Israel

- 526 46. Cardiology Dept. and Centre for Treatment and Prevention of Atherosclerosis, Hadassah  
527 Hebrew University Medical Centre, Jerusalem, Israel
- 528 47. Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus,  
529 Haifa, Israel
- 530 48. Department of Internal Medicine, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel
- 531 49. Internal Medicine department, Ziv Medical Center, Zfat, Israel
- 532 50. Internal Medicine department and Centre for Treatment and Prevention of Atherosclerosis,  
533 Hadassah Hebrew University Medical Centre, Jerusalem, Israel
- 534 51. Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, India
- 535 52. Kufa University, college of medicine, Iraq
- 536 53. Al-Qadisiyah University, Faculty of Medicine, Department of Internal Medicine, Diwaniya City,  
537 Iraq
- 538 54. Al-Diwaniya teaching hospital, Iraq
- 539 55. Al-Hussain teaching hospital, Thi-Qar, Iraq
- 540 56. Jabir Ibn Hayyan Medical University, faculty of medicine, Iraq
- 541 57. Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
- 542 58. Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical  
543 Specialties—University of Palermo, Italy
- 544 59. Rare Diseases and Medical Genetics, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
- 545 60. Internal Medicine Department, European Center of Excellence on Hypertension, Regional  
546 Reference Center for Dyslipidemias, SS Annunziata Hospital and University "G. d'Annunzio",  
547 Chieti, Italy
- 548 61. Division of Cardiology, A.O.R.N. "Sant'Anna and San Sebastiano", Caserta and Department of  
549 Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
- 550 62. Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio  
551 Emilia, Modena, Italy
- 552 63. Department of Pharmacological and Biomolecular Sciences, University of Milan and IRCCS  
553 Multimedica, Milan, Italy
- 554 64. IRCCS Policlinico S. Orsola-Malpighi, Hypertension and cardiovascular risk factor research  
555 center, University of Bologna, Bologna, Italy
- 556 65. Clinical Chemistry and Endocrinology Laboratory, Department of Diagnostic Imaging and  
557 Laboratory Medicine, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
- 558 66. Department of Clinical Medicine and Surgery, University "Federico II" of Naples, Naples, Italy
- 559 67. Pediatric Endocrine Unit and Newborn Screening Centre, Microcitemico Pediatric Hospital "A.  
560 Cao", AO Brotzu, Cagliari, Italy
- 561 68. Department of Internal Medicine, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
- 562 69. E. Grossi Paoletti Center, Department of Pharmacological and Biomolecular Sciences, University  
563 of Milan, Milan, Italy
- 564 70. Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy
- 565 71. Pediatric Diabetology Unit, Pediatric and Microcytemia Department, AO Brotzu, Cagliari, Italy

- 566 72. Lipoapheresis Unit and Centre for Inherited Dyslipidaemias Fondazione CNR Toscana Gabriele  
567 Monasterio, Pisa, Italy
- 568 73. Division of Endocrinology, Papa Giovanni XXIII Hospital -ASST-PG23, Bergamo, Italy
- 569 74. Department of Internal Medicine and Rare Disease Centre “C. Frugoni” University Hospital of  
570 Bari, Bari, Italy
- 571 75. Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, UOC  
572 Endocrinologia, University Hospital of Verona, Verona, Italy
- 573 76. Department of Molecular Innovation in Lipidology, National Cerebral & Cardiovascular Center  
574 Research Institute, Japan
- 575 77. Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya  
576 University, Japan
- 577 78. Department of Internal Medicine, King Abdullah University Hospital, Faculty of Medicine,  
578 Jordan University of Science and Technology, Irbid, Jordan
- 579 79. Department of Internal Medicine, American University of Beirut, Beirut, Lebanon
- 580 80. Division of Pediatric Cardiology, Department of Pediatrics, American University of Beirut  
581 Medical Center, Beirut, Lebanon
- 582 81. Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston,  
583 Massachusetts, USA
- 584 82. National LDL Apheresis Center, Dahr El-Bashek Governmental University Hospital, Roumieh,  
585 Lebanon
- 586 83. Genomics and Translational Biomedicine Division, College of Health and Life Sciences, Hamad  
587 Bin Khalifa University, Doha, Qatar
- 588 84. Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Faculty of Medicine,  
589 Universiti Teknologi MARA (UiTM), Sungai Buloh, Selangor, Malaysia
- 590 85. Servicio de Endocrinología, Unidad de Especialidades Médicas de la Secretaría de la Defensa  
591 Nacional, Ciudad de México, Mexico
- 592 86. Unidad de Investigación de Enfermedades Metabólicas, Instituto Nacional de Ciencias Médicas  
593 y Nutrición "Salvador Zubirán", Mexico City, Mexico
- 594 87. Department of Clinical Genetics, Amsterdam UMC, Location AMC, University of Amsterdam,  
595 Amsterdam, the Netherlands
- 596 88. Department of Pediatrics, Amsterdam UMC, Location AMC, Amsterdam, the Netherlands
- 597 89. Department of Internal Medicine, Erasmus MC, Erasmus University Medical Center, Rotterdam,  
598 the Netherlands
- 599 90. Department of Clinical Biochemistry, Sultan Qaboos University Hospital, Muscat, Oman
- 600 91. Directorate of Research, Shifa Tameer-e-Millat University, Islamabad, Pakistan
- 601 92. 1st Department of Cardiology, Medical University of Gdansk, Poland and National Centre of  
602 Familial Hypercholesterolaemia in Gdańsk, Poland
- 603 93. Unidade de I&D, Grupo de Investigação Cardiovascular, Departamento de Promoção da Saúde  
604 e Prevenção de Doenças Não Transmissíveis, Instituto Nacional de Saúde Doutor Ricardo Jorge,  
605 Lisboa, Portugal; and BioISI – Biosystems & Integrative Sciences Institute, Faculdade de  
606 Ciências, Universidade de Lisboa, Lisboa, Portugal

- 607 94. Department of Cardiogenetics, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal and Lisbon  
608 Medical School, Genetics Laboratory, University of Lisbon, Lisbon, Portugal
- 609 95. Faculty of Medicine University of Belgrade, Clinic for Endocrinology, Diabetes and Metabolic  
610 Diseases, Belgrade, Serbia
- 611 96. National Medical Research Centre of Cardiology of Ministry of Health of the Russian Federation,  
612 Moscow, Russia
- 613 97. Academy for Postgraduate Medical Education, Faculty of Clinical Pharmacology and  
614 therapeutics, Ministry of Health, Moscow, Russian Federation, Russia
- 615 98. University of Ljubljana, Faculty of Medicine and UMC - University Children's Hospital Ljubljana,  
616 Ljubljana, Slovenia
- 617 99. Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei,  
618 Taiwan
- 619 100. Endocrinology and Metabolism Unit, Department of Medicine, Faculty of Medicine,  
620 Chulalongkorn University and King Chulalongkorn Memorial Hospital, Patumwan, Bangkok,  
621 Thailand
- 622 101. Istanbul University Istanbul Medical Faculty, Department of Hematology, Turkey
- 623 102. Selcuk University Medical Faculty, Department of Cardiology, Turkey
- 624 103. Necmettin Erbakan University Meram Medical Faculty, Department of Hematology, Turkey
- 625 104. Izmir Katip Çelebi University Medical Faculty Department of Pediatrics, Division of Inborn  
626 Errors of Metabolism, Turkey
- 627 105. Erdem Hospital, Department of Endocrinology and Metabolic Diseases, Turkey
- 628 106. Ankara University Medical Faculty Ibn-i Sina Hospital, Department of Hematology, Turkey
- 629 107. Ege University Medical Faculty, Department of Cardiology, Turkey
- 630 108. Erciyes University Medical Faculty, Department of Hematology, Turkey
- 631 109. Inonu University Medical Faculty, Department of Hematology, Turkey
- 632 110. Antalya Training and Research Hospital, Department of Hematology, Turkey
- 633 111. LOSANTE Children's and Adult Hospital, Department of Hematology, Turkey
- 634 112. Hacettepe University Medical Faculty, Department of Hematology, Turkey
- 635 113. Dicle University Medical Faculty, Department of Endocrinology, Turkey
- 636 114. Uludag University Medical Faculty, Department of Cardiology, Turkey
- 637 115. Kanuni Sultan Suleyman Training and Research Hospital, Department of Pediatric Hematology,  
638 Turkey
- 639 116. Ankara State Hospital, Department of Cardiology, Turkey
- 640 117. Ordu University Medical Faculty, Department of Cardiology, Turkey
- 641 118. Sanko University, Department of Internal Diseases, Turkey
- 642 119. Tepecik Training and Research Hospital, Department of Endocrinology and Metabolism, Turkey
- 643 120. Dyslipidemia Department State Institution National Scientific Centre "The M.D. Strazhesko  
644 Institute of Cardiology National Academy of Medical Sciences of Ukraine", Kyiv, Ukraine
- 645 121. Children's Hospital of Philadelphia, Philadelphia, USA

- 646 122. The Rogosin Institute/Departments of Medicine and Pediatrics, Weill Cornell Medical College,  
647 New York, New York, USA
- 648 123. Republican Specialized Scientific and Practical Medical Center of Cardiology, Tashkent,  
649 Uzbekistan
- 650 124. Vietnam National Heart Institute, Bach Mai Hospital, Vietnam
- 651 125. Department of Cardiology, Hanoi Medical University, Vietnam
- 652 126. Vietnam National University, University of Medicine and Pharmacy, Vietnam

653 **Declaration of Interests**

654 Authors listed alphabetically by last name. **AFAAZ** has nothing to disclose. **MA** Melih Aktan PENDING  
655 FORMS. **MDA** has nothing to disclose. **RA** has nothing to disclose. **MAK** has nothing to disclose. **BBA**  
656 has nothing to disclose. **KAW** reports lecture fees and personal fees from Abbot, Amgen, AstraZeneca,  
657 Merck, Pfizer and Sanofi. **MA** reports research grants from Novartis, Akcea, Amryt, Regeneron, Daiichi-  
658 Sankyo; consulting fees from Amryt, Akcea and Pfizer; lecture fees from Amryt, Akcea, Daiichi-Sankyo,  
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660 advisory boards for Novartis, Amryt, Akcea, Amarin, Pfizer, Alfasigma and Daiichi-Sankyo. **MHA** has  
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663 to disclose. **DJB** reports research grants from Amgen, Amryt, AstraZeneca, Sanofi, and Regeneron;  
664 lecture fees and personal fees from Amgen, Sanofi-Aventis and Novartis; participation in advisory  
665 board for Amryt (Chair of the LOWER study steering committee) and being member of the executive  
666 committee of the Lipid and Atherosclerosis Society of South Africa. **MB** has nothing to disclose. **JAB**  
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## **Authors' 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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782     **Data sharing statement**

783     Data ownership for the data shared with the HICC registry remains the property of the individual  
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872

873 **Table 1 – Demographic, clinical and genetic characteristics and plasma lipid levels in HoFH patients,**  
874 **overall and stratified by country income status**

	<b>Overall</b>	<b>High-income countries</b>	<b>Non-high-income countries</b>
	N=751	N=398	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 <sup>2</sup> )	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%)
<b>Lipids (mmol/L)</b>			
<i>Untreated</i>			
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)
<i>Most recent**</i>			
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%)
<i>Lowest recorded level†</i>			
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%)
<b>Genetic information available††</b>	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

901 additional information was available on other lipid-lowering therapies. Patients from non-high-  
902 income countries who are on apheresis were mainly from Turkey (n=87) and Lebanon (n=26).  
903 †† Ileal bypass and portacaval shunt surgery are no longer considered treatments for HoFH, these  
904 entries reflect (abandoned) historic practice.

905 **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%)
<i>Age at cardiovascular death</i>	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%)
<i>Age at first MI</i>	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%)
<i>Age at AP onset</i>	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%)
<i>Age at first CABG</i>	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%)
<i>Age at first PCI</i>	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%)
<i>Age at first AVR</i>	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%)
<i>Age at PAD diagnosis</i>	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%)

<i>Age at first cerebrovascular disease event</i>	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
<i>Composite outcomes</i>			
MACE <sup>§</sup>	216 (28·8%)	110 (27·2%)	106 (29·9%)
<i>Age of first MACE</i>	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+ <sup>§§</sup>	267 (35·6%)	137 (34·4%)	130 (36·7%)
<i>Age of first MACE+</i>	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)

906

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

912 **\* Cardiovascular death was physician reported death from cardiovascular causes. "Sudden death"**  
913 **and periprocedural death due to cardiac surgery necessitated by consequences of**  
914 **hypercholesterolaemia was additionally considered cardiovascular death.**

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

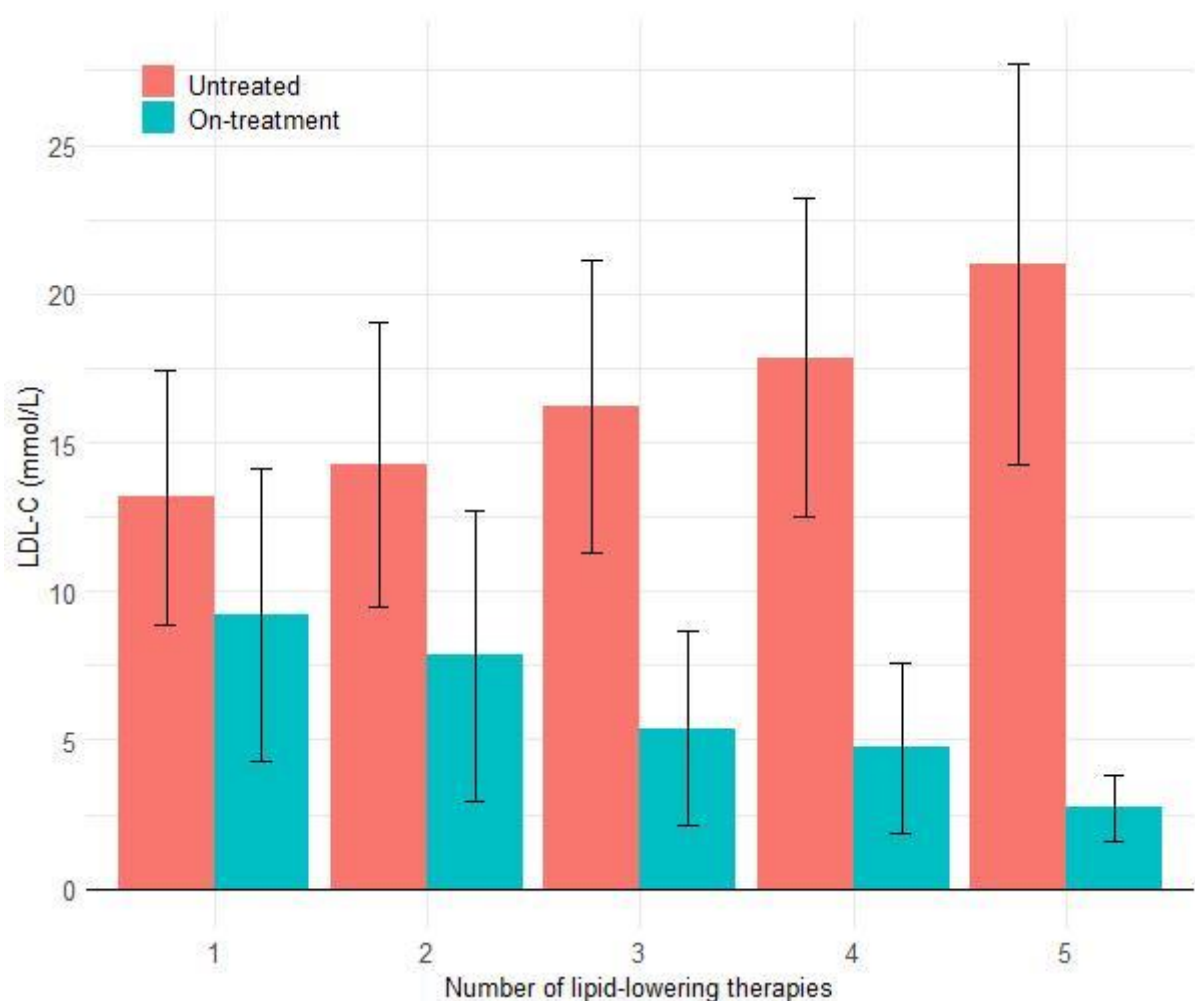
917 **<sup>§</sup> MACE is a composite of cardiovascular death, non-fatal MI, PCI and CABG.**

918 **<sup>§§</sup> MACE+ is a composite of cardiovascular death, non-fatal MI, PCI and CABG, AP, non-fatal**  
919 **ischemic stroke, carotid stenting, carotid endarterectomy and peripheral artery disease.**

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

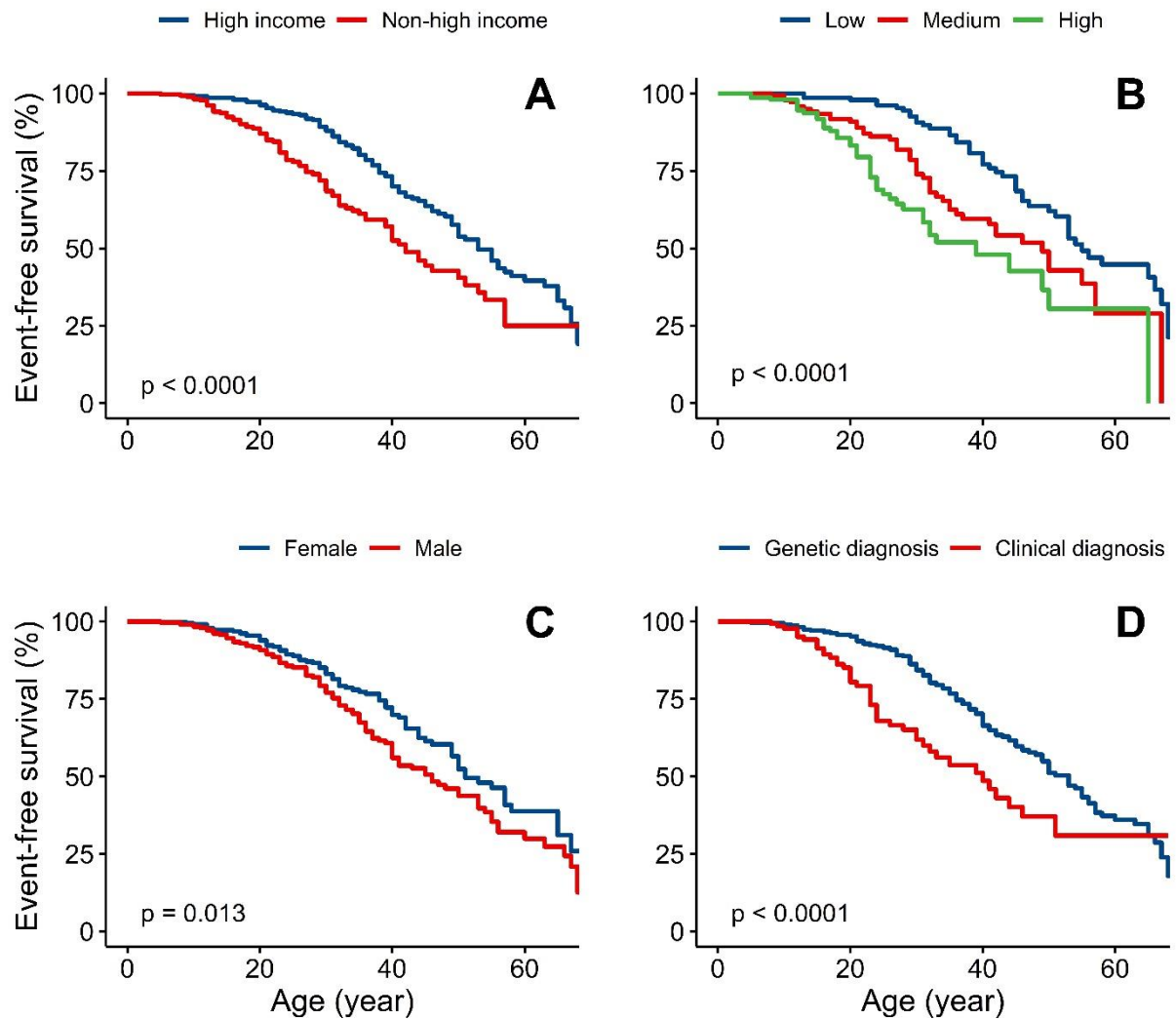


Number of LLT	1	2	3	4	5
From high-income countries	38/114 (33.3%)	85/185 (45.9%)	111/162 (68.5%)	32/37 (86.5%)	15/15 (100%)
Mean LDL-C reduction (%)	30%	45%	67%	74%	87%
LDL-C goal attainment*	3 (2.6%)	16 (8.6%)	27 (16.7%)	7 (18.9%)	8 (53.3%)

Data are shown as mean ( $\pm$ 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.

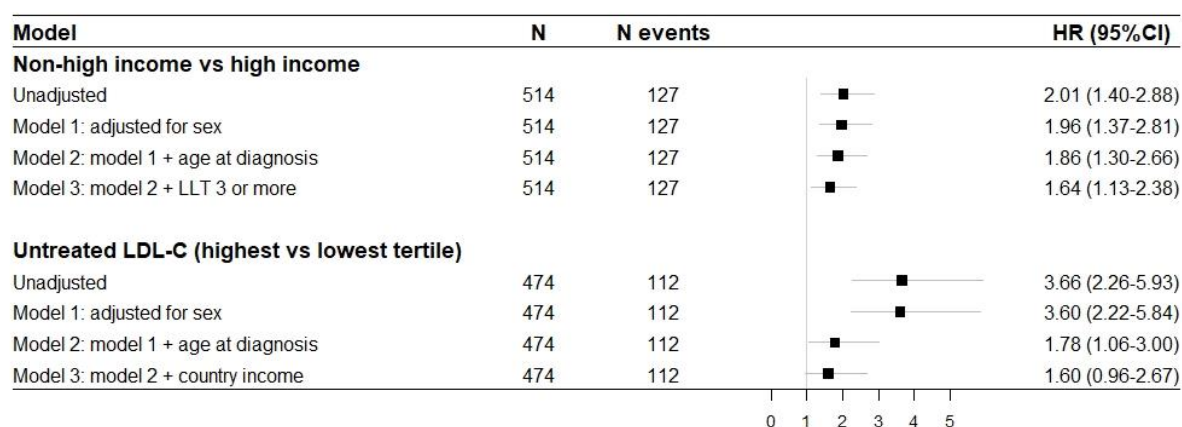
**Figure 2 – Survival-time free from major adverse cardiovascular events**



**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.