Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study

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Summary

Background Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disorder resulting in extremely elevated low-density lipoprotein cholesterol levels and premature atherosclerotic cardiovascular disease (ASCVD). Current guidance about its management and prognosis stems from small studies, mostly from high-income 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 registry collected data on patients with a clinical, or genetic, or both, diagnosis of HoFH using a retrospective cohort study design. This trial is registered with ClinicalTrials.gov, NCT04815005.

Findings Overall, 751 patients from 38 countries were included, with 565 (75%) reporting biallelic pathogenic variants. The median age of diagnosis was 12·0 years (IQR 5·5–27·0) years. Of the 751 patients, 389 (52%) were female and 362 (48%) were male. Race was reported for 527 patients; 338 (64%) patients were White, 121 (23%) were Asian, and 68 (13%) were Black or mixed race. The major manifestations of ASCVD or aortic stenosis were already present in 65 (9%) of patients at diagnosis of HoFH. Globally, pretreatment LDL cholesterol levels were 14·7 mmol/L (IQR 11·6–18·4). Among patients with detailed therapeutic information, 491 (92%) of 534 received statins, 342 (64%) of 534 received ezetimibe, and 243 (39%) of 621 received lipoprotein apheresis. On-treatment LDL cholesterol levels were lower in high-income countries (3·93 mmol/L, IQR 2·6–5·8) versus non-high-income countries (9·3 mmol/L, 6·7–12·7), with greater use of three or more lipid-lowering therapies (LLT; high-income 66% *vs* non-high-income 24%) and consequently more patients attaining guideline-recommended LDL cholesterol goals (high-income 21% *vs* non-high-income 3%). A first major adverse cardiovascular event occurred a decade earlier in non-high-income countries, at a median age of 24·5 years (IQR 17·0–34·5) versus 37·0 years (29·0–49·0) 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 is associated with lower LDL cholesterol levels and better outcomes. Significant global disparities exist in treatment regimens, control of LDL cholesterol 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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Introduction

Familial hypercholesterolaemia is an inherited disorder resulting from pathogenic variants in genes involved in the metabolism of LDL, leading to markedly elevated LDL cholesterol levels and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD) if not treated early and effectively.[1] The most severe form of familial hypercholesterolaemia is homozygous familial hypercholesterolaemia (HoFH), which broadly comprises simple homozygous as well as compound and double heterozygous cases (panel).

The prevalence of HoFH was historically reported as one per 1 million but has recently been estimated as 1 in approximately 300 000 people worldwide,[3,6–8] with a higher prevalence in populations with a founder effect.[1] Plasma LDL cholesterol levels might 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 cholesterol levels largely determines prognosis.[9] A combination of commonly used lipid-lowering therapies (LLT), such as statins and ezetimibe, are often insufficient to control such high LDL cholesterol levels, with many patients requiring extracorporeal removal of LDL by means of lipoprotein apheresis.

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See Online for appendix

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, limited to humans, from Jan 1, 2000, up to and including Feb 1, 2021, were included. Although the prevalence of homozygous familial hypercholesterolaemia (HoFH) was traditionally estimated to be approximately 1 in 1 million, 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, before advances in treatment strategies. Such studies have suggested that the clinical consequences of HoFH likely relate to untreated LDL cholesterol levels, type of genetic defect, and age at which treatments are started.

Added value of this study

To our knowledge, the HoFH International Clinical Collaborators registry is the first and only global HoFH registry. Initiated by physicians caring for HoFH patients in specialised centres across diverse health-care settings, it 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 health care and use of effective medications on health outcomes. The present study shows that patients with HoFH are often only diagnosed in the second decade of life with extreme LDL cholesterol 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 cholesterol 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 with patients from high-income countries.

Implications of all the available evidence

The findings from the HoFH International Clinical Collaborators 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 finding is particularly relevant to non-high-income countries where patients with HoFH require greater access to more effective combinations of lipid-lowering therapies to improve health outcomes.

Therapies that decrease LDL cholesterol levels irrespective of residual LDL receptor (LDLR) function have recently emerged,[10,11] 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 of 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 carry biallelic familial hypercholesterolaemia variants (either homozygous, 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 appendix (pp 9–10). For comparison between high-income and non-high-income regions of the world, countries were grouped according to the 2019 World Bank definition of income categories of high income, upper-middle income, or lower-middle income. (appendix p 11).[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; appendix p 3) who confirmed the pathogenicity and assessed the functionality of the variants as detailed in the appendix (pp 13–25).

Statistical analysis

Statistical analyses were performed using R, version 4.0.3. The primary outcome in the survival analyses was major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Descriptive estimates are presented as median (IQR) or mean (95% CI). We used bootstrapping (10 000 randomised 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 appendix (p 10).

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.

This trial is registered with ClinicalTrials.gov, NCT04815005.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing the manuscript, or decision to submit for publication.

Results

Individual-level data on 751 patients from 88 institutions across 38 countries representing all seven World Bank regions were available. 20 countries were classified as high-income, 12 as upper-middle-income, and six as lower-middle-income countries (hereafter, we will refer to these last two groups as non-high-income countries); countries and number of patients per country are listed in the appendix (p 11). Patient demographic, clinical, and genetic characteristic at the time of inclusion are presented in table 1, overall and stratified by country income status. The median age of diagnosis was 12·0 years (IQR 5·5–27·0), and of the 751 patients, 389 (52%) were female and 362 (48%) were male. Race was reported for 527 patients; 338 (64%) patients were White, 121 (23%) were Asian, and 68 (13%) were Black or mixed race. Patients from high-income countries, compared with those from non-high-income countries, were older at the time of diagnosis (16·0 years [IQR 6·0–33·0] in high-income countries *vs* 10·0 years [5·0–20·0] in non-high-income countries) and had fewer physical stigmata such as xanthomas (64% in high-income countries *vs* 74% in non-high-income countries) at the time of diagnosis.

Overall, untreated LDL cholesterol levels were 14·7 mmol/L (IQR 11·6–18·4), and lower in patients from high-income countries (13·5 mmol/L, 10·4–17·2) than those from non-high-income countries (15·8 mmol/L, 12·9–19·2). The prevalence of modifiable risk factors for cardiovascular disease such as smoking (43 [8%]), diabetes (23 [4%]), and hypertension (93 [15%]) was comparable between high-income 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.

A genetic confirmation of HoFH was available for 565 (75%) of 751 patients, with a higher proportion in

***Panel:* Definition and diagnosis**

Patients with homozygous familial hypercholesterolaemia (HoFH) have extremely high plasma LDL cholesterol 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 supravalvular aortic stenosis. Deposits of cholesterol in the skin or tendons, or both, called xanthomas, are the hallmark of the disease. The development and severity of ASCVD or aortic stenosis, or both, determine prognosis in HoFH. HoFH can be diagnosed clinically or genetically.

Clinical diagnosis

- Untreated LDL cholesterol levels >13 mmol/L (500 mg/dL), or LDL cholesterol ≥8 mmol/L (300 mg/dL) while on conventional lipid-lowering therapies; and,
- Presence of xanthomas before the age of 10 years, or the presence of heterozygous familial hypercholesterolaemia in both parents[1]

Genetic diagnosis

- Identification of biallelic 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 familial hypercholesterolaemia genes are termed double heterozygous. Autosomal recessive hypercholesterolaemia is a very rare form of HoFH caused by bi-allelic variants in *LDLRAP1*.[2] The phenotype of HoFH varies considerably and genetic testing has identified many patients with lower LDL cholesterol and less severe phenotypes.[3–5] Conversely, the absence of two pathogenic variants in the presence of a phenotype consistent with HoFH does not exclude the diagnosis.

	Overall (N=751)	High-income countries (n=398)	Non-high-income countries (n=353)
Age of familial hypercholesterolaemia 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)
Sex			
Female	389 (52·1%)	205 (51·5%)	184 (52·9%)
Male	362 (47·9%)	169 (47·1%)	193 (48·5%)
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	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 cholesterol	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 cholesterol	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 cholesterol	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 cholesterol 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 cholesterol	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 cholesterol 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 (%), or median (IQR); bootstrapped means (95% CI). Classification of high-income and non-high-income countries is shown in the appendix (p 11). *This reflects the most recent measurement available after diagnosis and before data entry in the registry. †LDL cholesterol below guideline-recommended goals is defined as less than 2·5 mmol/L in primary prevention or less than 1·8 mmol/L in secondary prevention. ‡This reflects the lowest recorded LDL cholesterol measurement between untreated (at diagnosis) and most recent measurement. When unavailable, the most recent measurement itself was considered the lowest. §For details see the appendix (p 12).

Table 1: **Demographic, clinical, and genetic characteristics and plasma lipid levels in patients with homozygous familial hypercholesterolaemia, 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	9·7 (5·7–14·2)

Data are n (%), or bootstrapped mean (95% CI). Classification of high-income and non-high-income countries is shown in the appendix (p 11). NA=not applicable. PCSK9=proprotein convertase subtilisin/kexin type 9. *Evinacumab is an investigational product that has been recently approved by the US Food & Drug Administration but is not yet approved by other regulatory agencies. It was given as compassionate use, or open-label extension, or both, 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 were on apheresis were mainly from Turkey (n=87) and Lebanon (n=26). §Ileal bypass and portacaval shunt surgery are no longer considered treatments for homozygous familial hypercholesterolaemia, these entries reflect (abandoned) historic practice.

Table 2: **Lipid-lowering therapy at the time of the lowest on-treatment LDL cholesterol level recorded, overall, and stratified by country income status**

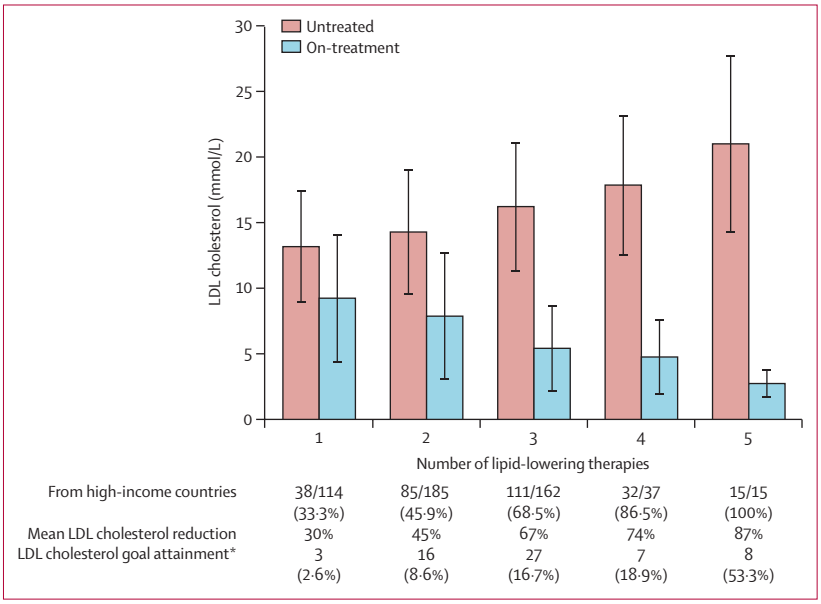
high-income (92%) compared with non-high-income (56%) countries. Two non-high-income countries (South Africa and Brazil) accounted for more than half (54%) of genetic diagnoses reported in this income group. Patients who had a genetic diagnosis had lower untreated LDL cholesterol levels (14·2 mmol/L, IQR 11·3–17·6) and presented less frequently with xanthomas at diagnosis (374 [66%] of 565), as compared with patients who had a clinical diagnosis only (LDL cholesterol 16·1 mmol/L, IQR 12·9–19·7; xanthomas at diagnosis 142 [76%] of 186). The allele combinations and classification by *LDLR* residual function and the individual genetic variants are presented in the appendix (p 12–25). Among patients with genetic information available, the majority were either simple homozygous or compound heterozygous carriers of

LDLR variants (471 [83%] patients). These patients had higher untreated LDL cholesterol levels (14·7 mmol/L, IQR 11·8–18·1) compared with patients with autosomal recessive hypercholesterolaemia (28 [5%] patients; LDL cholesterol 12·0 mmol/L, IQR 11·3–14·3) and with those carrying any other biallelic combination including *APOB* or *PCSK9*, or both (66 [12%] patients; LDL cholesterol 8·5 mmol/L, IQR 6·8–13·2; appendix p 26). Of patients with biallelic variants in *LDLR* for whom the residual *LDLR* function was classified, 104 (23%) carried two *LDLR*-negative alleles and had higher untreated LDL cholesterol levels (17·2 mmol/L, IQR 14·2–22·2) compared with patients carrying any *LDLR*-defective allele (14·0 mmol/L, 11·3–17·1; appendix p 28).

The type of LLT used at the time when the lowest on-treatment LDL cholesterol levels were recorded is shown in table 2. Of 534 patients for whom detailed information on LLT was available, nearly all patients (491 [92%]) were on statin therapy, usually high intensity (311 [83%] of 379 where statin dosage was available), defined as atorvastatin 40 mg or more or rosuvastatin 20 mg or more per day. Ezetimibe was used by 212 (72%) of 293 patients from high-income countries, and 130 (54%) of 241 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 513 patients with known LLT and lipid values, 399 (78%) were on combination therapy with two or more therapies and 214 (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 done in 243 (39%) patients, initiated at a median age of 15·0 years (IQR 10·0–28·0), and performed once per week (27 [25%]) or every other week (58 [54%]) in the majority of 108 patients for whom apheresis frequency was available. Patients on apheresis had higher untreated LDL cholesterol at diagnosis (17·2 mmol/L, IQR 13·9–21·4) compared with patients who were not on apheresis (13·5 mmol/L, 11·1–17·1; appendix p 29).

The untreated LDL cholesterol levels and the lowest LDL cholesterol levels achieved with the number of LLTs used, including apheresis, are shown in figure 1. Fibrates, omega-3 fish oils, red yeast rice, and plant stanols, which lower LDL cholesterol 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 cholesterol levels was low; overall, 61 (12%) of 513 patients reached an LDL cholesterol of less than 2·6 mmol/L (primary prevention) or less than 1·8 mmol/L (secondary prevention). The LDL cholesterol reduction was 30% in patients on monotherapy, 45% with two classes of LLT, and more than 65% in patients using three or more LLT (figure 1). The percentage of patients



	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 cholesterol reduction	30%	45%	67%	74%	87%
LDL cholesterol goal attainment*	3 (2·6%)	16 (8·6%)	27 (16·7%)	7 (18·9%)	8 (53·3%)

***Figure 1*: Untreated LDL cholesterol levels and lowest on-treatment LDL cholesterol levels achieved, as a function of number of LLTs (including apheresis)**
Data are shown as mean (SD) or n (%). LLT included statins, ezetimibe, PCSK9 inhibitors, lipoprotein apheresis, lomitapide, evinacumab, and mipomersen. Five patients who had undergone liver transplantation were excluded from this analysis. LLT=lipid-lowering therapy. *LDL cholesterol below guideline-recommended goals is defined as an LDL cholesterol level of less than 2·5 mmol/L in primary prevention or less than 1·8 mmol/L in case of secondary prevention.

who attained LDL cholesterol goals increased with the number of LLTs, and were more frequently attained in patients from high-income countries (21%) compared with non-high-income countries (3%; table 1). Only 5% of the overall population achieved the more recent lower LDL cholesterol goals (<1·8 mmol/L in case of primary prevention and <1·4 mmol/L in case of secondary prevention).[13]

The proportion of patients reported to have cardiovascular disease overall and stratified by income is shown in table 3. The median age at which MACE occurred was 31·0 years (IQR 22·0–42·0), with 65 (9%) of 751 patients already having suffered a non-fatal myocardial infarction, 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 years, IQR 17·0–45·5). The earliest recorded age at which angina pectoris, myocardial infarction, CABG, or PCI were reported were 4 years (angina pectoris), 10 years (myocardial infarction), 5 years (CABG), and 10 years (PCI). Among patients with a recorded non-fatal coronary event, a recurrent coronary event occurred in 29 (28%) of 102 patients. Peripheral artery disease occurred in 42 (6%) patients and cerebrovascular disease in 22 (3%) patients.

Supravalvular aortic stenosis (any severity) was reported in 216 (29%) of 751 patients. Where echocardiographic data were available (n=265), 35 (13%) patients had mild, 25 (9%) moderate, and seven (3%) severe aortic stenosis. Aortic valve replacement had been

	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, years	28·0 (17·0–45·5); 31·5 (25·5–37·6); 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 myocardial infarction, years	37·5 (30·0–50·0); 38·8 (35·6–42·0); 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 angina pectoris onset, years	30·0 (20·0–39·0); 30·4 (27·3–33·7); 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)
Coronary artery bypass grafting	120 (15·8%)	60 (14·9%)	60 (16·9%)
Age at first coronary artery bypass grafting, years	30·0 (22·5–40·0); 31·5 (28·9–34·2); 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)
Percutaneous coronary intervention	91 (12·1%)	54 (13·4%)	37 (10·2%)
Age at first percutaneous coronary intervention, years	39·5 (28·0–48·5); 38·5 (35·5–41·5); 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 aortic valve replacement, years	31·0 (24·8–41·0); 33·0 (28·6–37·4); 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 peripheral artery disease diagnosis, years	34·5 (20·5–47·3); 35·5 (27·5–44·0); 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, years	37·0 (28·0–48·0); 40·9 (33·9–48·7); 23–71	38·0 (29·0–53·0); 42·5 (34·6–50·8)	28·5 (27·3–29·8); 26, 31, NA, NA‡
MACE§	216 (28·8%)	110 (27·2%)	106 (29·9%)
Age of first MACE, years	31·0 (22·0–42·0); 33·0 (30·9–35·0); 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 plus¶	267 (35·6%)	137 (34·4%)	130 (36·7%)
Age of first MACE plus, years	30·0 (21·0–41·0); 32·0 (30·0–33·9); 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 n (%), or median (IQR); bootstrapped mean (95% CI); and range (minimum–maximum). 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. ‡ Two patients had a first cerebrovascular disease event at age 26 years and 31 years, and for two patients the age was missing. §MACE is a composite of cardiovascular death, non-fatal myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. ¶MACE plus is a composite of cardiovascular death, non-fatal myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting, angina pectoris, non-fatal ischaemic stroke, carotid stenting, carotid endarterectomy, and peripheral artery disease.

Table 3: **Cardiovascular disease in the overall population and stratified by country income status**

performed in 52 patients (7%; median 31·0 years, 24·8–41·0; youngest 5 years).

MACE-free survival is shown in figure 2, with an earlier occurrence in patients managed in non-high-income (24·5 years, IQR 17·0–34·5) compared with high-income countries (35·0 years, 25·0–49·0), with a hazard 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.

MACE-free survival stratified by tertiles of untreated LDL cholesterol is shown in figure 2. 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 (95% CI 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 2), despite similar demographic characteristics compared with females (appendix p 31). 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 2).

Discussion

This study reports, to our knowledge, 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 cholesterol 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 non-high-income parts of the world, often in regions with high consanguinity or with founder effects, where the condition remains largely underdiagnosed and untreated. Although many times larger than previous reports, the 751 patients included in this study thus only comprise approximately 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 familial hypercholesterolaemia globally.[14]

Earlier studies of smaller sample size reported on the severe cardiovascular consequences of HoFH.[3–5,8,15–18]

Although 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, because by this age many patients have already had 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% of patients 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 supravalvular 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 cholesterol drives the premature onset of ASCVD;[9] 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 cholesterol recommendations with this approach. Use of three or more LLTs (nearly exclusive to patients managed in high-income countries) were associated with lower LDL cholesterol levels and greater likelihood of goal achievement. Our finding that use of five LLTs lowered LDL cholesterol by more than 85% shows that reaching acceptable LDL cholesterol 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 cholesterol 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 cholesterol independently of LDLR function,[10,11,27] and can be used in combination with PCSK9 inhibitors for patients with residual LDLR activity.[28,29] Among those with the highest LDL cholesterol 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,

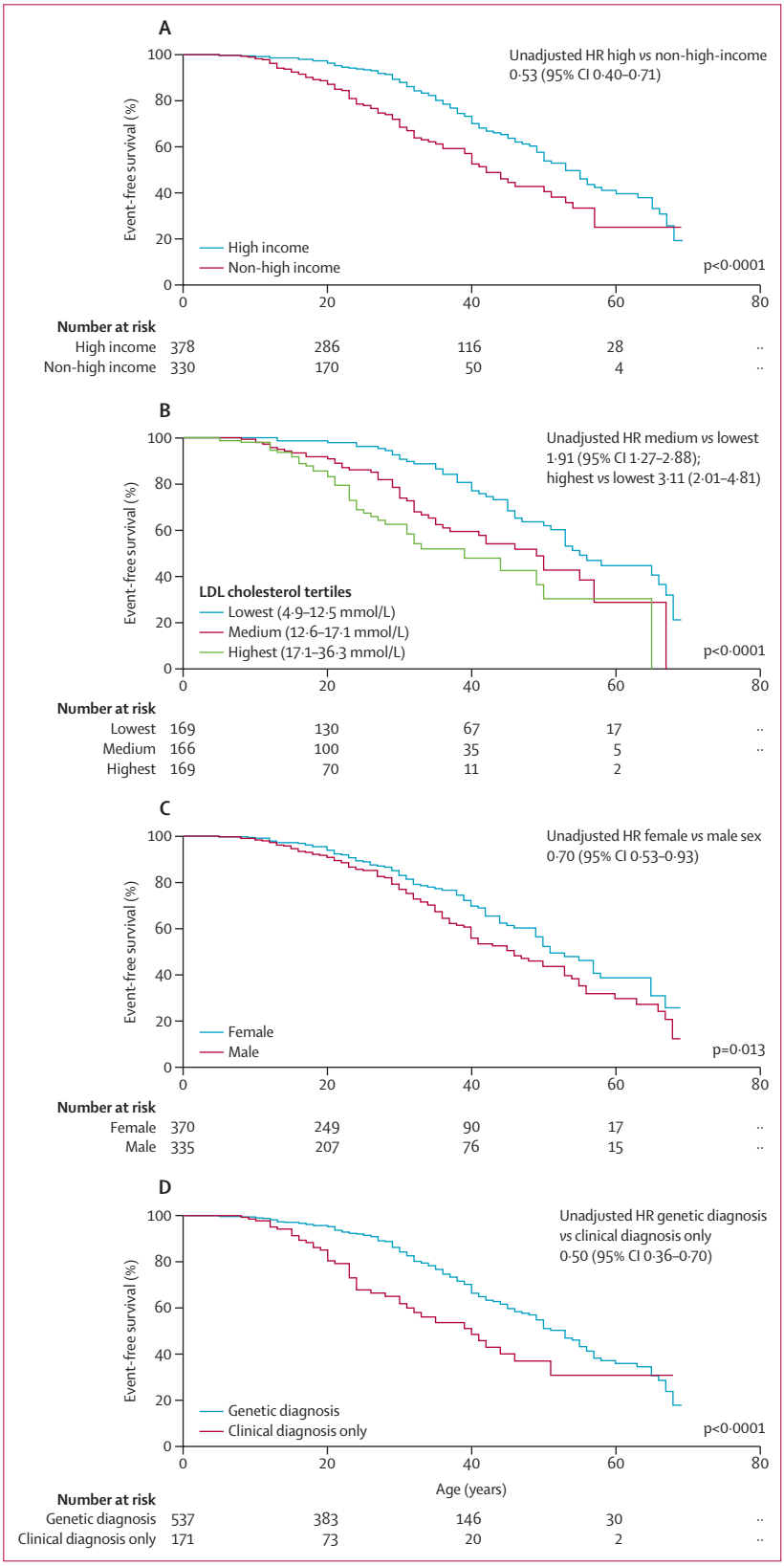


Figure 2: **Survival-time free from major adverse cardiovascular events**
Event-free survival stratified by high-income versus non-high-income countries (A), untreated LDL cholesterol tertiles (B), sex (C), and genetic diagnosis versus clinical diagnosis only (D). The statistical test for comparison between groups was a log-rank test. HR=hazard ratio.

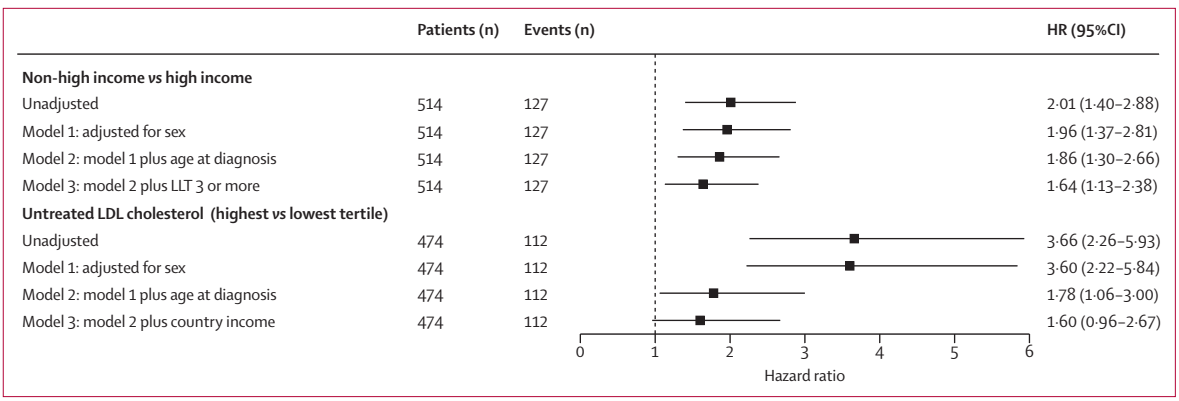


Figure 3: **Forest plot showing unadjusted and adjusted hazard ratios for occurrence of major adverse cardiovascular events between specific groups of interest**

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. LLT=lipid-lowering therapy. HR=hazard ratio.

because cardiovascular complications might already occur in childhood, it is imperative that existing and new LLTs are rapidly approved for use in the paediatric population.[27]

HDL cholesterol levels in our cohort of HoFH patients were low compared with 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 cholesterol levels overshadows any meaningful impact of lower HDL cholesterol levels on cardiovascular outcomes.[30]

Our study also offers insights into the role of genetics in HoFH diagnosis. Nearly all (approximately 90%) patients from high-income countries were genetically confirmed versus just over half (56%) from non-high-income countries. Of these patients, 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 cholesterol levels and greater prevalence of xanthomas), despite being diagnosed at a younger age. These differences might be an artefact of health-care 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, whereas patients with a less severe phenotype are diagnosed clinically as having severe heterozygous familial hypercholesterolaemia 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-income 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 cholesterol levels and were less likely to receive multi-LLT combinations. Because on-treatment LDL cholesterol levels are a major determinant of event-free survival for HoFH patients,[18] it is possible that this could in part explain the excess risk. Thus, the uneven global health burden from HoFH cannot be addressed until non-high-income countries have access to effective and affordable LLT regimens starting in childhood, with inevitable implications for health-care systems and the pharmaceutical industry.

This study has several limitations. Patients entered in the registry might not reflect clinical practice or phenotypes outside of participating centres. That said, as a rare condition, HoFH is mostly managed in specialist or academic centres, such as those participating in this registry. Inevitably, patients diagnosed reflect local health-care 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 might 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 (eg, much of Latin America and Africa) remain under-represented

and more information is needed to further reduce existing data gaps. Furthermore, a substantial proportion of the total number of patients came from three countries; namely, 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 to prevent the serious consequences of extreme LDL cholesterol exposure. As the greatest global burden resides in less affluent regions of the world, a critical reappraisal of health-care policy and funding is required at a global level to improve health outcomes for all patients with HoFH.

Contributors

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. MLH let the creation of the electronic case report form. All authors contributed to the acquisition of data for the work. MLH and TRT acted as study co-ordinators. TRT curated the data, conducted the analysis, and drafted the Article. The writing committee (TRT, MLH, GKH, AJV-V, KKR, HS, TF, SB, MH-S, FJR, DJB, and MC) provided critical interpretation and revision of the Article. All authors revised the Article and gave approval for submission.

Declaration of interests

SB declares no competing interests. DJB reports research grants from Amgen, Amryt, AstraZeneca, Sanofi, and Regeneron; lecture fees and personal fees from Amgen, Sanofi-Aventis and Novartis; participation in advisory board for Amryt (Chair of the LOWER study steering committee); and being member of the executive committee of the Lipid and Atherosclerosis Society of South Africa. MC reports institutional support for the conduction of clinical trials from Regeneron Pharmaceuticals, Akcea, and Regenxbio; consulting fees from Amryt Pharma; and support from NIH/NHLBI grant (P01HL059407). TF reports personal fees from Novartis, Sanofi, and Amgen; and that he was partly supported by the Ministry of Health, Czech Republic, grant number NU20-02-00261. MH-S reports research grants from Recordati and Kaneka; personal fees from Amgen, Astellas, Recordati, Merck Sharp & Dohme, and Sanofi; being on the advisory board for New Amsterdam Pharma and Medicine Company and Scilence Therapeutics; being chairperson Primary Hyperlipidemia, Research on Measures against Intractable Diseases by the Japanese Ministry of Health, Labor, and Welfare; being chairperson of the Working Group by Japan Atherosclerosis Society for Making Guidance of Familial Hypercholesterolemia; and owning stock options of Liid Pharma. MLH reports lecture fees from Sanofi, outside the submitted work. GKH reports research grants from the Netherlands Organization for Scientific Research (vidi 016.156.445), CardioVascular Research Initiative, EU, and the Klinkerpad fonds; institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; speaker's bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron until April 2019 (fees paid to the academic institution); and part-time employment at Novo Nordisk, Denmark since April, 2019. FJR reports consulting fees, lecturing fees, and advisory board fees from Amgen, Sanofi-Aventis, Regeneron, Novartis and Lib Therapeutics outside the submitted work; and being member of the International Atherosclerosis Society. KKR reports institutional research grants from Amgen, Sanofi, Daiichi Sankyo, Regeneron, and Pfizer; consulting fees and lecturing fees from Amgen, Sanofi, Novartis, Pfizer, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Kowa, Silence Therapeutics, New Amsterdam, Esperion, Daiichi Sankyo, Bayer, Abbott, Resverlogix, Medicines Company, Eli Lilly, Algorithm, Merck, Sharp & Dohme, AbbVie, and Viatris, outside the submitted work. HS reports research grants from Amgen, Merck, Sharp & Dohme, Synageva, Amryt, Alexion, and Akcea; consulting fees from Amgen, Alexion, Daiichi Sankyo, Pfizer, and Akcea; and speaker fees from Amgen, Daiichi Sankyo, Sanofi, and Akcea. TRT declares no competing interests. AJV-V reports participation in research grants to Imperial College London or European Atherosclerosis Society, or both, from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron; personal fees for consulting from Bayer and Regeneron; and honoraria for lectures from Amgen, Mylan, and Akcea; outside the submitted work.

Data sharing

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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