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

### 3 **Experience**

4

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27 Abstract: 301 words

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32 **Abstract**

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

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

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

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

57

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

63

64 **Research in context**

65 *Evidence before this study*

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

69 While the prevalence of homozygous familial hypercholesterolaemia (HoFH) was traditionally  
70 estimated to be ~ 1 in 1,000,000, more recent studies have suggested a prevalence closer to 1 in  
71 300,000 in populations not subject to gene founder or consanguinity effects. Given its rarity, guidance  
72 for screening and treatment has relied on expert opinion and studies of small sample size, derived  
73 mostly from patients of European ancestry or from high-income countries, prior to advances in  
74 treatment strategies. Such studies have suggested that the clinical consequences of HoFH likely relate  
75 to untreated low-density lipoprotein cholesterol (LDL-C) levels, type of genetic defect, and age at which  
76 treatments are started.

77 *Added value of this study*

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

89 high-income countries have on average a more severe phenotype at diagnosis, are less likely to receive  
90 advanced treatments and have a decade shorter cardiovascular event-free survival compared to those  
91 from high-income countries.

## 92 *Implications*

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

100 **Introduction**

101 Familial hypercholesterolaemia (FH) is an inherited disorder resulting from pathogenic variants in  
102 genes involved in the metabolism of low-density lipoproteins, leading to markedly elevated LDL-C  
103 levels and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD) if not treated  
104 early and effectively.<sup>1</sup> The most severe form of FH is homozygous FH (HoFH) which broadly comprises  
105 simple homozygous as well as compound and double heterozygous cases (see box: “Definition and  
106 Diagnosis”).

107 The prevalence of HoFH was historically reported as 1 per million but has recently been estimated as  
108 1 in ~300,000 persons worldwide,<sup>2–5</sup> with a higher prevalence in populations with a founder effect.<sup>1</sup>  
109 Plasma LDL-C levels may exceed 20 mmol/L depending on the variants carried; patients with an *LDLR*  
110 variant that leads to no residual functional protein (*LDLR* negative variant) in both alleles are generally  
111 the most severely affected. The magnitude and duration of exposure to extreme LDL-C levels largely  
112 determines prognosis.<sup>6</sup> Combination of commonly used lipid-lowering therapies (LLT), such as statins  
113 and ezetimibe, are often insufficient to control such high LDL-C levels, with many patients requiring  
114 extracorporeal removal of LDL by means of lipoprotein apheresis. Therapies that decrease LDL-C levels  
115 irrespective of residual LDLR function have recently emerged,<sup>7,8</sup> but their use is limited by cost and  
116 availability.

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

124

125 [box]

126 **Definition and Diagnosis**

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

134 HoFH can be diagnosed clinically or genetically.

135 *Clinical diagnosis:*

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

138 AND

139 • Presence of xanthomas before the age of ten years, or the presence of heterozygous FH in  
140 both parents<sup>1</sup>

141 *Genetic diagnosis:*

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

143 Patients with identical variants in both alleles of the same gene are simple homozygous. Patients with  
144 non-identical variants in both alleles of the same gene are compound heterozygous and patients with  
145 variants in two different FH-genes are termed double heterozygous. Autosomal recessive  
146 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]***

151 **Methods**

152 *Participating centres and patient selection*

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

158 *Data collection*

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

166 *Genetic data*

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

170 *Statistical analysis*

171 Statistical analyses were performed using R software, version 4.0.3 (R Foundation for Statistical  
172 Computing, Vienna, Austria). The primary outcome in the survival analyses was major adverse  
173 cardiovascular events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial  
174 infarction (MI), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

175 Descriptive estimates are presented as median and interquartile range (IQR) or mean (95% CI). We  
176 used bootstrapping (10,000 randomized samples) to estimate the 95% CIs around mean estimates  
177 using the percentile method. Due to the descriptive nature of the study, we did not impute missing  
178 data and performed available case analyses without formal hypothesis testing. Comparisons of survival  
179 times free from events between groups of interest were assessed using the Kaplan-Meier method and  
180 log-rank tests. Details on the generation of proportional hazard models are provided in the  
181 Supplementary Materials.

## 182 *Ethics*

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

## 186 *Role of the funding source*

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

192

193 **Results**

194

195 *Patient characteristics*

196 Individual-level data on 751 patients from 88 institutions across 38 countries representing all seven  
197 World Bank regions were available. Twenty countries were classified as high-income, 12 as upper-  
198 middle income and six as lower-middle income countries; countries and number of patients per  
199 country are listed in Table S1. Patient demographic, clinical and genetic characteristic at the time of  
200 inclusion are presented in Table 1, overall and stratified by country income status. Median age of  
201 diagnosis was 12·0 (IQR 5·5-27·0) years, and 52% of patients were women. Race was reported in 527  
202 patients; of these, 338 (64%) were White, 121 (23%) Asian, and 68 (13%) were Black or of mixed race.  
203 Patients from high-income countries, compared with those from non-high-income countries, were  
204 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  
205 stigmata such as xanthomas (64% versus 74%) at the time of diagnosis.

206 Overall, untreated LDL-C levels were 14·7 (IQR 11·6-18·4) mmol/L, and lower in patients from high-  
207 income countries than those from non-high-income countries (13·5 [IQR 10·4-17·2] versus 15·8 [IQR  
208 12·9-19·2] mmol/L, respectively). The prevalence of modifiable risk factors for cardiovascular disease  
209 such as smoking (8%), obesity (15%), diabetes mellitus (4%) and hypertension (15%) was comparable  
210 between high and non-high-income countries. Among 505 patients with data on family pedigree  
211 available, 150 (30%) had a first-degree family member with HoFH who was also entered in the registry.

212

213 *Genetics*

214 A genetic confirmation of HoFH was available for 565 of 751 patients (75%), with a higher proportion  
215 in high-income compared to non-high-income countries (92% versus 56%). Of note, two non-high-  
216 income countries (South Africa and Brazil) accounted for over half (54%) of genetic diagnoses reported

217 in this income group. Patients who had a genetic diagnosis had lower untreated LDL-C levels (14.2 [IQR  
218 11.3-17.6] versus 16.1 [IQR 12.9-19.7] mmol/L) and presented less frequently with xanthomas at  
219 diagnosis (66% versus 76%). The allele combinations and classification by *LDLR* residual function are  
220 presented in Table S2 and the individual genetic variants are listed in Table S3. Among patients with  
221 genetic information available, the majority were either simple homozygous or compound  
222 heterozygous carriers of *LDLR* mutations (471 patients, 83%). These patients had higher untreated LDL-  
223 C levels (14.7 [IQR 11.8-18.1] mmol/L) compared with patients with autosomal recessive  
224 hypercholesterolaemia (28 patients [5%]; LDL-C 12.0 [IQR 11.3-14.3] mmol/L) and with those carrying  
225 any other bi-allelic combination including *APOB* and/or *PCSK9* (66 patients [12%]; LDL-C 8.5 [IQR 6.8-  
226 13.2] mmol/L, Table S4). Of patients with bi-allelic variants in *LDLR* for whom the residual *LDLR* function  
227 was classified, 104 (23%) carried two *LDLR*-negative alleles and had higher untreated LDL-C levels  
228 compared with patients carrying any *LDLR*-defective allele (17.2 [IQR 14.2-22.2] versus 14.0 [IQR 11.3-  
229 17.1] mmol/L, Table S5).

230

### 231 *Lipid-lowering therapy and LDL-C levels*

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

241 Lipoprotein apheresis (including plasma exchange) was conducted in 243 patients (39%), initiated at a  
242 median age of 15·0 [IQR 10·0-28·0] years, and performed weekly (25%) or biweekly (54%) in the  
243 majority of patients. Patients on apheresis had higher untreated LDL-C at diagnosis compared with  
244 patients who were not on apheresis (Table S6, 17·2 [IQR 13·9-21·4] versus 13·5 [IQR 11·1-17·1]  
245 mmol/L).

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

257

### 258 *Cardiovascular Disease*

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

266 reported. Peripheral artery and cerebrovascular disease occurred in 42 (6%) and 22 (3%) patients,  
267 respectively.

268 (Supra-)valvular aortic stenosis (any severity) was reported in 29% (216/751) of patients. Where  
269 echocardiographic data were available (n=265), 35 (13%) patients had mild, 25 (9%) moderate, and 7  
270 (3%) severe aortic stenosis. Aortic valve replacement had been performed in 52 (7%) patients (median  
271 31.0 [24.8-41.0] years; youngest 5 years).

272 Figure 2A shows MACE-free survival, with an earlier occurrence in patients managed in non-high-  
273 income compared to high-income countries (24.5 [IQR 17.0-34.5] versus 35.0 [IQR 25.0-49.0] years,  
274 respectively), with a crude ratio (HR) of 2.01 (95%CI 1.40-2.88). Stepwise attenuation of the HR for  
275 incident MACE is shown in Figure 3; adjustment for treatment with three or more types of LLT, age of  
276 diagnosis and sex reduced the HR to 1.64 (95%CI 1.13-2.38), suggesting that a fifth of the excess risk  
277 might be mitigated through early diagnosis and use of three or more LLTs.

278 Figure 2B shows MACE-free survival stratified by tertiles of untreated LDL-C. A graded relationship was  
279 observed, with events occurring earlier among the highest tertile. Stepwise attenuation of the HR for  
280 incident MACE is shown in Figure 3; after adjustment for age of diagnosis and income status the HR  
281 for the highest versus lowest tertile with MACE fell from 3.60 (2.22-5.84) to 1.60 (0.96-2.67). Using  
282 country status as a proxy for use of multi-LLT regimens suggests that as much as half of the excess risk  
283 could be attenuated by early diagnosis and better treatment.

284 MACE-free survival was shorter in males (Figure 2C), despite similar demographic characteristics  
285 compared to females (Table S7). In sensitivity analyses, the coefficient for sex changed little after  
286 addition of smoking to the model: the coefficient for male sex changed from 0.63 to 0.67. Event-free  
287 survival was also shorter for patients with a clinical diagnosis of HoFH (no genetic data) versus those  
288 genetically confirmed (Figure 2D). In patients with bi-allelic *LDLR* variants, there was a trend towards  
289 shorter survival free from MACE in patients carrying two *LDLR*-negative alleles compared with those  
290 carrying *LDLR*-defective variants ( $p=0.21$ , Figure S1).

291 **Discussion**

292

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

299

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

307

308 Prior studies of smaller sample size have reported on the severe cardiovascular consequences of  
309 HoFH.<sup>2,5,10,11,15-18</sup> Though in part confirmatory, the present report leverages data from 751 patients  
310 from 38 countries with a larger number of events, providing more robust information to better guide  
311 health-policy and improve patient care. We show that diagnosing HoFH in the second decade of life is  
312 too late, as by this age many patients have already experienced cardiovascular complications,  
313 supporting the need for more effective strategies to aid timely diagnosis, such as systematic cascade  
314 screening or universal screening at an early age. Despite the use of LLT, first MACE occurs early at a

315 median age of 31 years, and in 4% even before the age of 18 years, in line with anecdotal evidence  
316 that cardiovascular events can occur in HoFH during childhood.<sup>19</sup> Additionally, one third of patients  
317 had (supra-)valvular aortic stenosis, which frequently required surgical intervention. Hence, systematic  
318 and more frequent image-guided assessment of aortic (valve) pathology in addition to ASCVD should  
319 be implemented in care pathways for HoFH patients.<sup>1</sup>

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

338

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

343

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

356

357 The global nature of our study not only allows for a comparison of the impact of current practice  
358 between high and non-high-income countries, but also provides an opportunity to explore potential  
359 determinants of health outcomes. The most striking finding in this regard is that event-free survival in  
360 HoFH is on average a decade shorter among patients managed in non-high-income countries. These  
361 patients had significantly higher risk of MACE, even after adjustment for age of diagnosis, sex and LLT.  
362 Patients managed in non-high-income countries had higher on-treatment LDL-C levels and were less  
363 likely to receive multi-LLT combinations. As on-treatment LDL-C levels are a major determinant of

364 event-free survival for HoFH patients,<sup>18</sup> it is likely that this could in part explain the excess risk. Thus  
365 the uneven global health burden from HoFH cannot be addressed until less affluent countries have  
366 access to effective and affordable LLT regimens starting in childhood, with inevitable implications for  
367 healthcare systems and the pharmaceutical industry.

368

369 This study has several limitations. Patients entered in the registry may not reflect clinical practice or  
370 phenotypes outside of participating centres. That said, as a rare condition, HoFH is mostly managed in  
371 specialist and/or academic centres, such as those participating in this registry. Inevitably, those  
372 diagnosed reflect local healthcare systems, impacting referrals to specialist clinics and thus availability  
373 for inclusion. To generate contemporary data, this registry only included patients alive in 2010 or later.  
374 Survival bias is thus inevitable because patients with less severe phenotypes survive longer and are  
375 consequently more likely to be included. Collection of retrospective data reduces granularity and  
376 completeness of some variables of interest and missing data may also reflect clinical practice at  
377 country or institution level. For example, data on Lp(a) levels were not included in this analysis since  
378 they were only available in one third of patients, mainly from high-income countries, and measured  
379 using different laboratory assays. Although we included participants from 38 countries, more clinicians  
380 from other countries and sites were invited to this initiative than those who ultimately participated.  
381 Some regions (e.g. much of Latin America and Africa) remain underrepresented and more information  
382 is needed to further reduce existing data gaps. Furthermore, a significant proportion of the total  
383 number of patients came from three countries: Italy, Turkey and South Africa. However, patients from  
384 these countries were comparable to others in their respective income group, and sensitivity analyses  
385 excluding these countries did not change results. Finally, the observational nature of the study  
386 including survival analyses does not allow assessment of causality and we cannot exclude the  
387 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.

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763 The study was conceived, designed and implemented by four investigators with a longstanding interest  
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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%)

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

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

881 **\*\*\* LDL-C below guideline-recommended goals is defined as an LDL-C level < 2.5 mmol/L in primary**  
882 **prevention or < 1.8 mmol/L in case of secondary prevention.**

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

886 **†† For details see Table S2 in the online supplement.**

887

888

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

	<b>Overall</b> N=534	<b>High-income countries</b> N=293	<b>Non-high-income countries</b> N=241
<b>Medication</b>			
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%)
<b>Surgeries</b>			
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

891  
 892 **Data are shown as n (%) for categorical variables, as bootstrapped mean (95%CI) for quantitative**  
 893 **variables. Classification of high- and non-high-income countries is shown in Table S1. NA, not**  
 894 **applicable; PCSK9, proprotein convertase subtilisin/kexin type 9**

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

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

899 **† Apheresis includes all lipoprotein apheresis types including plasma exchange. For 87 patients**  
 900 **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**

	<b>Overall</b>	<b>High-income countries</b>	<b>Non-high-income countries</b>
	N=751	N=398	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.**

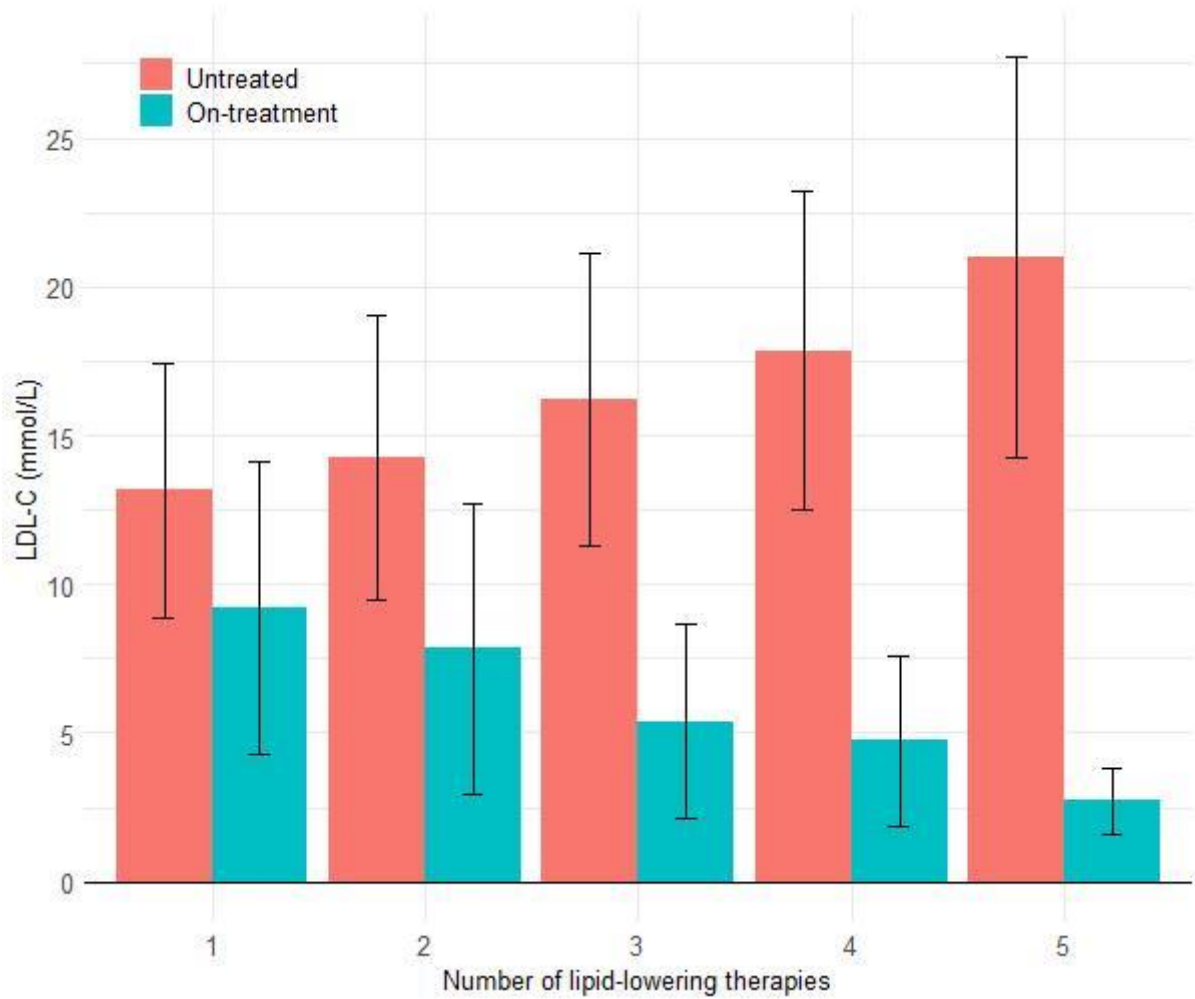
917 <sup>§</sup> **MACE is a composite of cardiovascular death, non-fatal MI, PCI and CABG.**

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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921

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



924

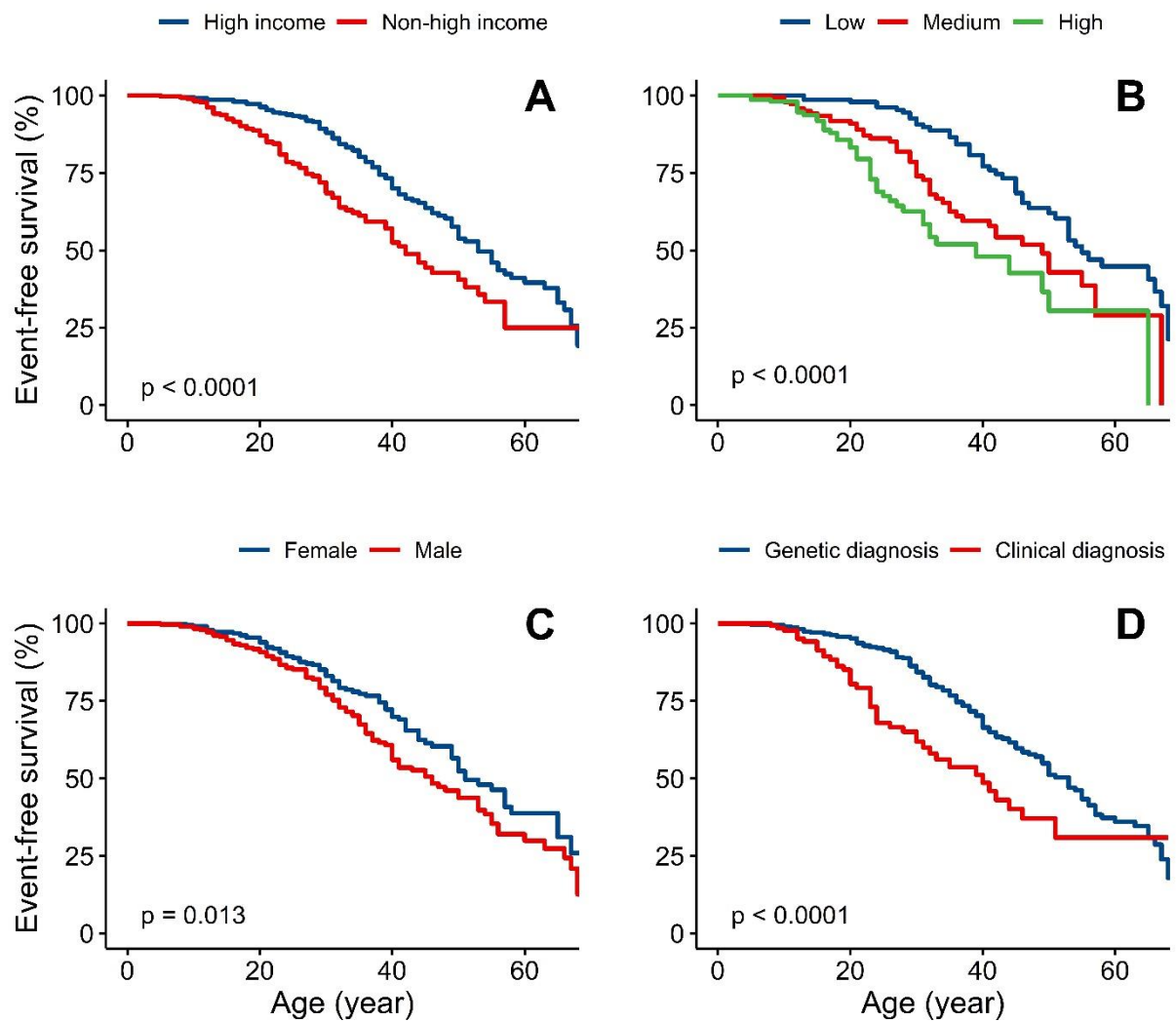
Number of LLT	1	2	3	4	5
From high-income countries	38/114 (33.3%)	85/185 (45.9%)	111/162 (68.5%)	32/37 (86.5%)	15/15 (100%)
Mean LDL-C reduction (%)	30%	45%	67%	74%	87%
LDL-C goal attainment*	3 (2.6%)	16 (8.6%)	27 (16.7%)	7 (18.9%)	8 (53.3%)

925

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

930 **\* LDL-C below guideline-recommended goals is defined as an LDL-C level < 2.5 mmol/L in primary**  
 931 **prevention or < 1.8 mmol/L in case of secondary prevention.**

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



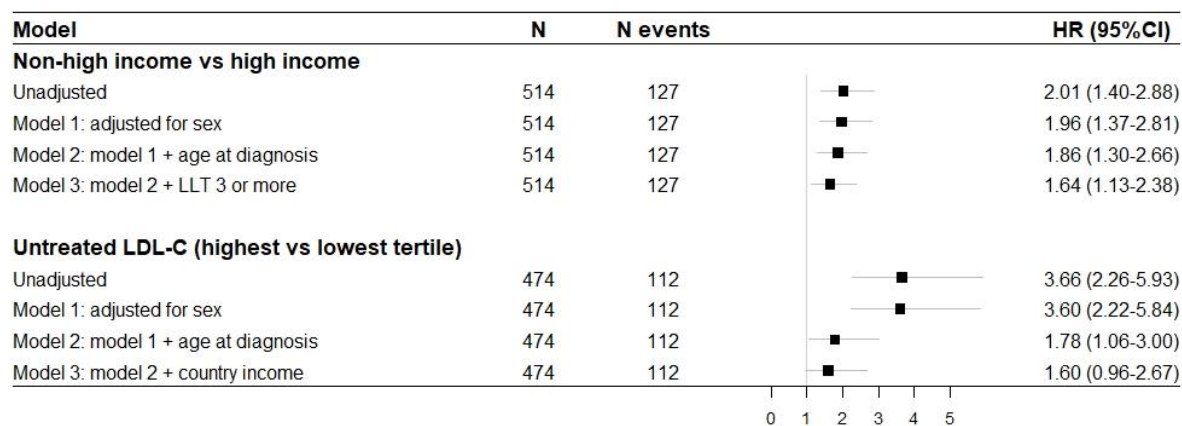
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935 **Panel: event-free survival stratified by A) High-income vs non-high-income countries B) Untreated**  
936 **LDL-C tertiles, lowest (4.9–12.5 mmol/L), middle (12.6–17.1 mmol/L) and highest (17.1–36.3**  
937 **mmol/L) C) Sex D) Clinical diagnosis only versus genetic diagnosis**

938 Statistical test for comparison between groups is Log-rank test.

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



941

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

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