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Sex Differences in Diagnosis, Treatment, and Cardiovascular Outcomes in Homozygous Familial Hypercholesterolemia

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IMPORTANCE Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition characterized by extremely increased low-density lipoprotein (LDL) cholesterol levels and premature atherosclerotic cardiovascular disease (ASCVD). Heterozygous familial hypercholesterolemia (HeFH) is more common than HoFH, and women with HeFH are diagnosed later and undertreated compared to men; it is unknown whether these sex differences also apply to HoFH.

OBJECTIVE To investigate sex differences in age at diagnosis, risk factors, lipid-lowering treatment, and ASCVD morbidity and mortality in patients with HoFH.

DESIGN, SETTING, AND PARTICIPANTS Sex-specific analyses for this retrospective cohort study were performed using data from the HoFH International Clinical Collaborators (HICC) registry, the largest global dataset of patients with HoFH, spanning 88 institutions across 38 countries. Patients with HoFH who were alive during or after 2010 were eligible for inclusion. Data entry occurred between February 2016 and December 2020. Data were analyzed from June 2022 to June 2023.

MAIN OUTCOMES AND MEASURES Comparison between women and men with HoFH regarding age at diagnosis, presence of risk factors, lipid-lowering treatment, prevalence, and onset and incidence of ASCVD morbidity (myocardial infarction [MI], aortic stenosis, and combined ASCVD outcomes) and mortality.

RESULTS Data from 389 women and 362 men with HoFH from 38 countries were included. Women and men had similar age at diagnosis (median [IQR], 13 [6-26] years vs 11 [5-27] years, respectively), untreated LDL cholesterol levels (mean [SD], 579 [203] vs 596 [186] mg/dL, respectively), and cardiovascular risk factor prevalence, except smoking (38 of 266 women [14.3%] vs 59 of 217 men [27.2%], respectively). Prevalence of MI was lower in women (31 of 389 [8.0%]) than men (59 of 362 [16.3%]), but age at first MI was similar (mean [SD], 39 [13] years in women vs 38 [13] years in men). Treated LDL cholesterol levels and lipid-lowering therapy were similar in both sexes, in particular statins (248 of 276 women [89.9%] vs 235 of 258 men [91.1%]) and lipoprotein apheresis (115 of 317 women [36.3%] vs 118 of 304 men [38.8%]). Sixteen years after HoFH diagnosis, women had statistically significant lower cumulative incidence of MI (5.0% in women vs 13.7% in men; subdistribution hazard ratio [SHR], 0.37; 95% CI, 0.21-0.66) and nonsignificantly lower all-cause mortality (3.0% in women vs 4.1% in men; HR, 0.76; 95% CI, 0.40-1.45) and cardiovascular mortality (2.6% in women vs 4.1% in men; SHR, 0.87; 95% CI, 0.44-1.75).

CONCLUSIONS AND RELEVANCE In this cohort study of individuals with known HoFH, MI was higher in men compared with women yet age at diagnosis and at first ASCVD event were similar. These findings suggest that early diagnosis and treatment are important in attenuating the excessive cardiovascular risk in both sexes.

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Supplemental content

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Group Information: The Homozygous Familial Hypercholesterolemia International Clinical Collaborators appear in Supplement 2.

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Homozygous familial hypercholesterolemia (HoFH) is a rare genetic biallelic disorder with a prevalence of 1 in 250 000 to 360 000.[1,2] Pathogenic variants in genes associated with low-density lipoprotein receptor (LDLR) function result in severely increased LDL cholesterol (LDL-C) levels. Variants in 3 of the causal genes—*LDLR*, *APOB*, and *PCSK9*—display autosomal semidominant inheritance, while variants in the *LDLRAP1* gene underlie a rare recessive form of HoFH.[3,4] The cumulative LDL-C burden is substantial from birth onwards, giving rise to a very high risk of premature atherosclerotic cardiovascular disease (ASCVD).[5] Patients with HoFH may already experience an ASCVD event before reaching adulthood or before the condition is diagnosed and treatment can be initiated.[3,6,7] Treatment generally consists of a combination of lipid-lowering therapies (LLTs), such as statins and ezetimibe, but also lipoprotein apheresis, and novel treatment strategies, such as proprotein convertase subtilisin/kexin type 9 inhibition, microsomal triglyceride transfer protein inhibition (lomitapide), or angiopoietinlike 3 (ANGPTL3) blockade (evinacumab).[8] Reaching guideline-recommended LDL-C goals in patients with HoFH is challenging, even with intensive combination treatment.[9]

The lifelong cholesterol burden and cardiovascular risk in patients with HoFH is much higher compared to patients with heterozygous familial hypercholesterolemia (HeFH) in whom only 1 allele in the genes associated with semidominantly inherited FH is mutated. Sex differences have been observed in the diagnosis and management of HeFH. Women with HeFH are often diagnosed later[10-13] and LLT is started later in life.[12] Studies have also reported that women with HeFH receive less potent LLT,[10,11,13,14] and that combination LLT is used less frequently.[10] This results in women having higher untreated and treated LDL-C levels than men both at young and old ages[10,12,15] and lower rates of achieving LDL-C goals.[10,11,13,16,17] Furthermore, women with HeFH often have prolonged pregnancy-related off-statin periods, since LLT is contraindicated during conception, pregnancy, and lactation.[18] These factors may explain why the excess ASCVD morbidity and mortality associated with HeFH is greater in women than in men.[19,20]

Against this background, similar sex differences might be expected in patients with HoFH, but these have not been studied. Using the largest global HoFH registry, we explored whether differences in age at diagnosis, risk factors, treatment, and ASCVD outcomes exist between women and men with HoFH.

Key Points

Question Are there sex differences in presentation at diagnosis, management, and atherosclerotic cardiovascular diseases (ASCVD) outcomes in patients with homozygous familial hypercholesterolemia (HoFH)?

Findings This cohort study of 751 patients with HoFH revealed no sex differences in age at diagnosis, treatment, and cardiovascular risk factors, except for a higher smoking prevalence in men. Men had higher incidence of myocardial infarction (MI), while other incident expressions of ASCVD morbidity were similar between sexes.

Meaning The findings indicate that HoFH represents a very high risk of premature ASCVD without clear sex differences, except a higher incidence of MI in men.

Methods

Patients and Data

The HoFH International Clinical Collaborators (HICC) registry collected data of patients with a clinical or genetic diagnosis of HoFH from a total of 88 institutions across 38 countries.[9] Using a retrospective cohort design, patients with HoFH who were alive during or after 2010 were eligible for inclusion. Data entry occurred between February 2016 and December 2020. The collected retrospective data included age at diagnosis, most recently present cardiovascular risk factors, untreated and most recent lipid levels, genetic data, ASCVD morbidity and mortality, and year when the ASCVD event or intervention occurred. Income status was defined based on country-specific data according to the 2019 World Bank definition (eTable 1 in Supplement 1).[21] Detailed description of data collection methods was published previously.[9] Data were analyzed from June 2022 to June 2023. Individual contributors were responsible for meeting local standards set by their institutional review board or ethics committee and obtaining approval. This study was conducted according to International Standards of Good Clinical Practice.

Clinical End Points

We evaluated sex differences in diagnosis, treatment, and ASCVD outcomes. For presentation at diagnosis, the main outcomes were age at diagnosis in years, presence of xanthomas at diagnosis, availability of genetic testing, and untreated lipid levels (total cholesterol, LDL-C, HDL cholesterol [HDL-C], and triglycerides) in mg/dL. We assessed the following risk factors at the last follow-up recorded: body mass index (calculated as weight in kilograms divided by height in meters squared), smoking (ever or never), diabetes, hypertension, and chronic kidney disease.

We evaluated treatment based on the latest recorded data and analyzed the type, number, and intensity of LLT received. For intensity of LLT, starting age and frequency of apheresis and statin intensity were investigated. Statin intensity was defined according to the American College of Cardiology/American Heart Association clinical practice guideline on cholesterol.[22] The proportion of women and men achieving recommended LDL-C goals at the last recorded visit was investigated, namely, less than 70 mg/dL for patients without ASCVD events and less than 55 mg/dL for patients with ASCVD (to convert to mmol/L, multiply by 0.0259).[2]

For cardiovascular outcomes, we compared the prevalence and incidence of nonfatal myocardial infarction (MI), angina pectoris, aortic stenosis, ischemic stroke, transient ischemic attack, peripheral artery disease, and cardiovascular and all-cause mortality between the sexes. We analyzed the prevalence and incidence of cardiovascular interventions, such as percutaneous coronary intervention (PCI), coronary artery bypass grafting, carotid endarterectomy, and peripheral artery

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Table 1. Homozygous Familial Hypercholesterolemia Diagnosis: Demographic and Clinical Characteristics

Characteristic	No. (%)			*P* value
	Overall (N = 751)	Women (n = 389)	Men (n = 362)	
Diagnosis				
Age at diagnosis, median (IQR), y[a]	12 (5-27)	13 (6-26)	11 (5-27)	.53
Genetic information available	565 (75.2)	294 (75.6)	271 (74.9)	.89
Xanthomas at diagnosis	516 (68.7)	265 (68.1)	251 (69.3)	.78
Race[b]				
Asian	121 (16.1)	65 (16.7)	56 (15.5)	.39
Black	9 (1.2)	2 (0.5)	7 (1.9)	
White	338 (45.0)	181 (46.5)	157 (43.4)	
Multiple races	59 (7.9)	29 (7.5)	30 (8.3)	
Unknown	224 (29.8)	112 (28.8)	112 (30.9)	
Country income status				
High income	398 (53.0)	205 (52.7)	193 (53.3)	.92
Middle income	353 (47.0)	184 (47.3)	169 (46.7)	

[a] Total participants with age data = 711.

[b] Race data were collected through self-report by clinicians and reported to gain insights into the representativeness of this global patient cohort.

disease stenting. Age at first ASCVD event and ASCVD intervention were compared between the sexes. In addition, we compared composite outcomes: major adverse cardiovascular events (MACE), including cardiovascular mortality, MI, coronary artery bypass grafting, and PCI; major adverse cardiovascular and cerebrovascular events (MACCE), including MACE variables and ischemic stroke events; and a more comprehensive composite outcomes (MACCE + AVR) consisting of the MACCE variables plus aortic valve replacement (AVR), cerebrovascular disease stenting, carotid endarterectomy, peripheral artery disease stenting, and peripheral artery disease bypass.

Statistical Analysis

Continuous data are recorded as means (SDs) or medians with IQRs depending on the distribution, and categorical data as number with percentage. Differences between women and men in age at diagnosis, cardiovascular risk factors, LLT, ASCVD, and ASCVD intervention prevalence, age at first ASCVD event and intervention, were analyzed with a 2-sample *t* test or Mann-Whitney *U* test (continuous data) and χ^2 test or Fischer exact test (categorical data). Cardiovascular risk factors, LLT, ASCVD, ASCVD intervention prevalence, and age at onset were compared at the latest clinical evaluation recorded.

The cumulative incidence of all-cause mortality after HoFH diagnosis was studied with Kaplan-Meier and Cox proportional hazard regression. To estimate the cumulative incidence of cardiovascular end points, the Fine-Gray subdistribution hazard model was used to account for noncardiovascular death as competing risk (all-cause death was considered in relation to nonfatal end points).[23,24] Differences in cumulative incidence of all-cause mortality between the sexes were evaluated using the log-rank test and the hazard ratio (HR). Equality between the sexes for cardiovascular end points was assessed with the Gray test and Fine-Gray subdistribution hazard regression, resulting in subdistribution HRs (SHRs) with 95% CIs. The cumulative incidences of the ASCVD end points after HoFH diagnosis were compared between the sexes for the 75th percentile of MACCE + AVR follow-up duration. SHRs of possible influencing variables, such as untreated LDL-C, age at diagnosis, history of smoking, statin treatment, and country income status, were calculated per sex and for women and men combined for the maximum available follow-up duration. Analyses were performed using R version 4.2.1 (R Foundation). Statistical significance of all tests was set at 2-sided $P < .05$.

Results

HoFH Diagnosis: Patient Characteristics and Presentation

The HICC registry included 389 women and 362 men, who had similar median (IQR) age at diagnosis (13 [6-26] years in women and 11 [5-27] years in men) (**Table 1**). Genetic information was available in 565 of 751 patients (75.2%), showing a similar proportion of women and men with 2 *LDLR* null variants (eTable 2 in Supplement 1). Mean (SD) untreated total cholesterol at a median (IQR) age of 13 (5-29) years was similar in women and men (645 [204] mg/dL in women vs 650 [201] mg/dL in men), as were untreated mean (SD) LDL-C levels (579 [203] mg/dL in women vs 596 [186] mg/dL in men) (**Figure 1**). Mean (SD) untreated HDL-C was significantly higher in women than men (42 [17] mg/dL in women vs 38 [16] mg/dL in men; $P = .007$), whereas median (IQR) triglycerides were significantly lower (100 [75-140] mg/dL in women vs 115 [79-161] mg/dL in men; $P = .01$) (eFigure 1 in Supplement 1).

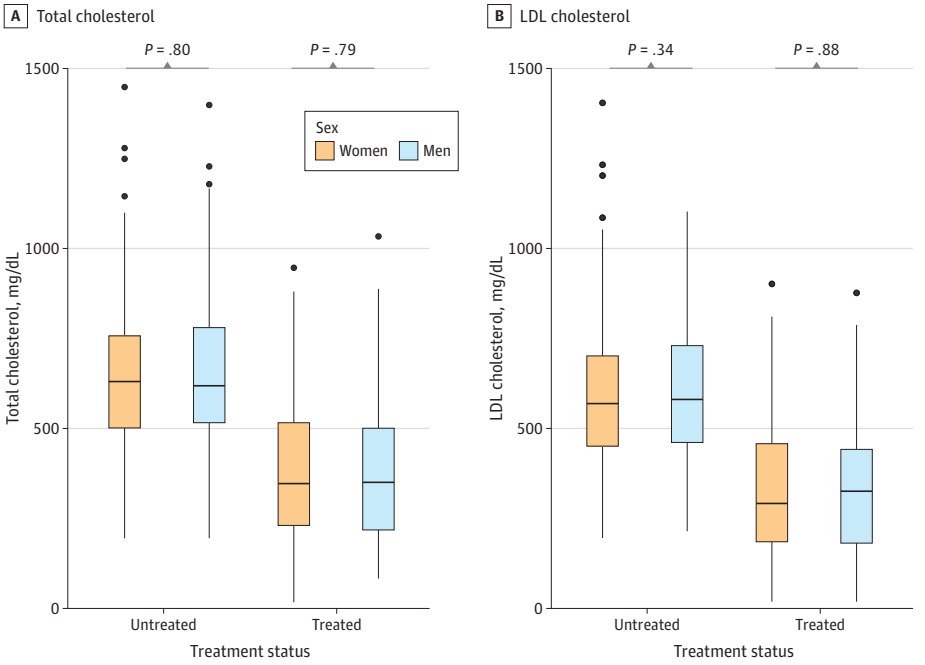
Latest Clinical Evaluation: Patient Characteristics, LLT, ASCVD Prevalence, and Age at ASCVD Onset

The median (IQR) clinical follow-up duration (n = 709) of 9 (1-20) years from the time of HoFH diagnosis was the same in the sexes (**Table 2**). At the latest clinical evaluation, the median (IQR) age of registry participants was 28 (16-43) years (29 [17-42] years for women and 27 [14-44] years for men; $P = .68$). Smoking was significantly less common in women than in men (38 of 266 [14.3%] vs 59 of 217 [27.2%], respectively; $P < .001$), and the prevalence of other cardiovascular risk factors was similar in both sexes (Table 2).

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Figure 1. Untreated and Treated Total Cholesterol and Low-Density Lipoprotein (LDL) Cholesterol Levels



Values are shown in median (IQR) in mg/dL (to convert to mmol/L, multiply by 0.0259).

Almost all women and men with HoFH were receiving LLT (262 of 276 women [94.9%] and 249 of 258 men [96.5%] $P = .49$). The most frequently used LLT for both women and men were statins (248 of 276 women [89.9%] and 235 of 258 men [91.1%]; $P = .74$), and most patients received high-intensity statin (161 of 276 women [58.3%] and 152 of 258 men [58.9%]; $P = .74$). Ezetimibe was used equally in women and men (170 of 276 [61.6%] and 164 of 258 [63.6%], respectively; $P = .70$). No sex differences were observed for any form or number of LLTs (Table 2). A total of 103 of 276 women (37.3%) and 96 of 258 men (37.2%) received 3 or more LLTs. Approximately one-third of the women and men received apheresis treatment (115 of 317 [36.3%] and 118 of 304 [38.8%], respectively; $P = .57$). In both sexes, the median frequency of apheresis was every other week, and the median (IQR) age of apheresis initiation was similar (16 [10-32] years in women vs 14 [9-22] years in men; $P = .33$).

Mean (SD) treated total cholesterol levels (377 [184] mg/dL in women and 373 [184] mg/dL in men) and LDL-C levels (321 [179] mg/dL in women and 323 [176] mg/dL in men) did not differ between the sexes at a median (IQR) follow-up of 11 (4-23) years after HoFH diagnosis (Figure 1). Mean (SD) treated HDL-C values were significantly higher in women than men (44 [18] mg/dL vs 41 [16] mg/dL, respectively; $P = .02$). No sex difference was observed in median (IQR) treated triglycerides (91 [62-131] mg/dL in women vs 96 [70-143] mg/dL in men) (eFigure 1 in Supplement 1). Overall, women and men receiving LLTs had a similar reduction of LDL-C after a median (IQR) 12 (6-23) years between the untreated and most recent laboratory levels (eFigure 3 in Supplement 1). Most women and men did not reach the currently recommended LDL-C goals (261 of 272 women [96.0%] and 246 of 254 men [96.9%]; $P = .82$).

Fewer women than men had experienced a MI at the latest clinical evaluation (31 of 389 [8.0%] vs 59 of 362 [16.3%], respectively; $P < .001$). However, mean (SD) age at first MI did not differ between sexes (39 [13] years for women and 38 [13] years for men; $P = .81$). There were no significant sex differences in the prevalence of aortic stenosis, angina pectoris, ischemic stroke or transient ischemic attack, or peripheral artery disease (Table 2). The age at onset of aortic stenosis (median [IQR], 20 [14-30] years for women and 20 [11-33] years for men), angina pectoris (mean [SD], 30 [15] years for women and 29 [14] years for men), ischemic stroke or transient ischemic attack (median [IQR], 33 [29-39] years for women and 43 [37-43] years for men), and peripheral artery disease (median [IQR], 33 [24-49] years for women and 36 [21-46] years for men) were also comparable (eFigure 2 in Supplement 1).

Although fewer women had undergone a PCI (34 of 389 [8.7%] vs 57 of 362 men [15.7%]; $P = .005$), we observed no sex difference in prevalence of other ASCVD interventions: 56 of 389 women (14.4%) and 64 of 362 men (17.7%) underwent a coronary artery bypass grafting and AVR occurred in 24 of 389 women (6.2%) vs 28 of 362 men (7.7%) (Table 2). For all ASCVD interventions (PCI, coronary artery bypass grafting, AVR, and carotid intervention), the age at first ASCVD intervention was comparable in women and men (eFigure 2 in Supplement 1). In total, 37 patients died, 18 women (5.3%) and 19 men (6.1%) ($P = .77$). Median (IQR) age at death was similar between the sexes (32 [23-48] years in women vs 43 [16-54] years in men; $P = .89$).

Cumulative Incidence of ASCVD After HoFH Diagnosis

At 16 years (75th percentile of MACCE + AVR follow-up) after HoFH diagnosis, the cumulative incidence of first MI was

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Table 2. Clinical Characteristics at Latest Evaluation

Characteristic	No.	No. (%)			*P* value
		Overall (N = 751)	Women (n = 389)	Men (n = 362)	
Birth year, median (IQR)	745	1983 (1972-1997)	1984 (1972-1997)	1986 (1971-1999)	.72
Latest age, median (IQR), y	727	28 (16-43)	29 (17-42)	27 (14-44)	.68
Time since diagnosis, median (IQR), y	709	9 (1-20)	9 (1-20)	9 (1-20)	>.99
Risk factors					
BMI, mean (SD)	386	23.9 (6.1)	23.8 (6.0)	24.1 (6.3)	.61
Smoking (ever)	483	97 (20.1)	38 (14.3)	59 (27.2)	<.001
Diabetes	603	23 (3.8)	9 (2.9)	14 (4.8)	.29
Hypertension	590	93 (15.8)	46 (14.9)	47 (16.7)	.62
Chronic kidney disease	421	6 (1.4)	3 (1.4)	3 (1.5)	>.99
Type of LLT					
Statin	534	483 (90.4)	248 (89.9)	235 (91.1)	.74
Ezetimibe	534	334 (62.5)	170 (61.6)	164 (63.6)	.70
Apheresis	621	233 (37.5)	115 (36.3)	118 (38.8)	.57
PCSK9 inhibitor	534	108 (20.2)	56 (20.3)	52 (20.2)	>.99
Lomitapide	534	41 (7.7)	21 (7.6)	20 (7.8)	>.99
Evinacumab	534	13 (2.4)	7 (2.5)	6 (2.3)	>.99
Mipomersen	534	1 (0.19)	0 (0)	1 (0.39)	.48
Resins	534	31 (5.8)	16 (5.8)	15 (5.8)	>.99
Fibrates	534	6 (1.12)	1 (0.36)	5 (1.94)	.11
LLTs					
0	534	23 (4.3)	14 (5.1)	9 (3.5)	.84
1		120 (22.5)	62 (22.5)	58 (22.5)	
2		192 (35.9)	97 (35.1)	95 (36.8)	
≥3		199 (37.3)	103 (37.3)	96 (37.2)	
Mean (SD)	534	2 (1)	2 (1)	2 (1)	.51
Statin intensity					
High	534	313 (58.6)	161 (58.3)	152 (58.9)	.74
Moderate		60 (11.2)	28 (10.1)	32 (12.4)	
Low		6 (1.1)	2 (0.7)	4 (1.6)	
Unknown dose		104 (19.5)	57 (20.7)	47 (18.2)	
No statin		51 (9.6)	28 (10.1)	23 (8.9)	
ASCVD prevalence					
Angina pectoris	751	95 (12.6)	46 (11.8)	49 (13.5)	.55
Percutaneous coronary intervention	751	91 (12.1)	34 (8.7)	57 (15.7)	.005
Coronary artery bypass grafting	751	120 (16.0)	56 (14.4)	64 (17.7)	.26
Myocardial infarction	751	90 (12.0)	31 (8.0)	59 (16.3)	<.001
Carotid intervention[a]	751	15 (2.0)	5 (1.3)	10 (2.8)	.19
Ischemic stroke or TIA	751	13 (1.7)	8 (2.1)	5 (1.4)	.58
Peripheral artery disease	634	42 (6.6)	17 (5.0)	25 (8.4)	.12
Aortic valve disease prevalence					
Aortic stenosis	751	169 (22.5)	90 (23.1)	79 (21.8)	.73
Aortic valve replacement	751	52 (6.9)	24 (6.2)	28 (7.7)	.48

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin-kexin type 9; TIA, transient ischemic attack.

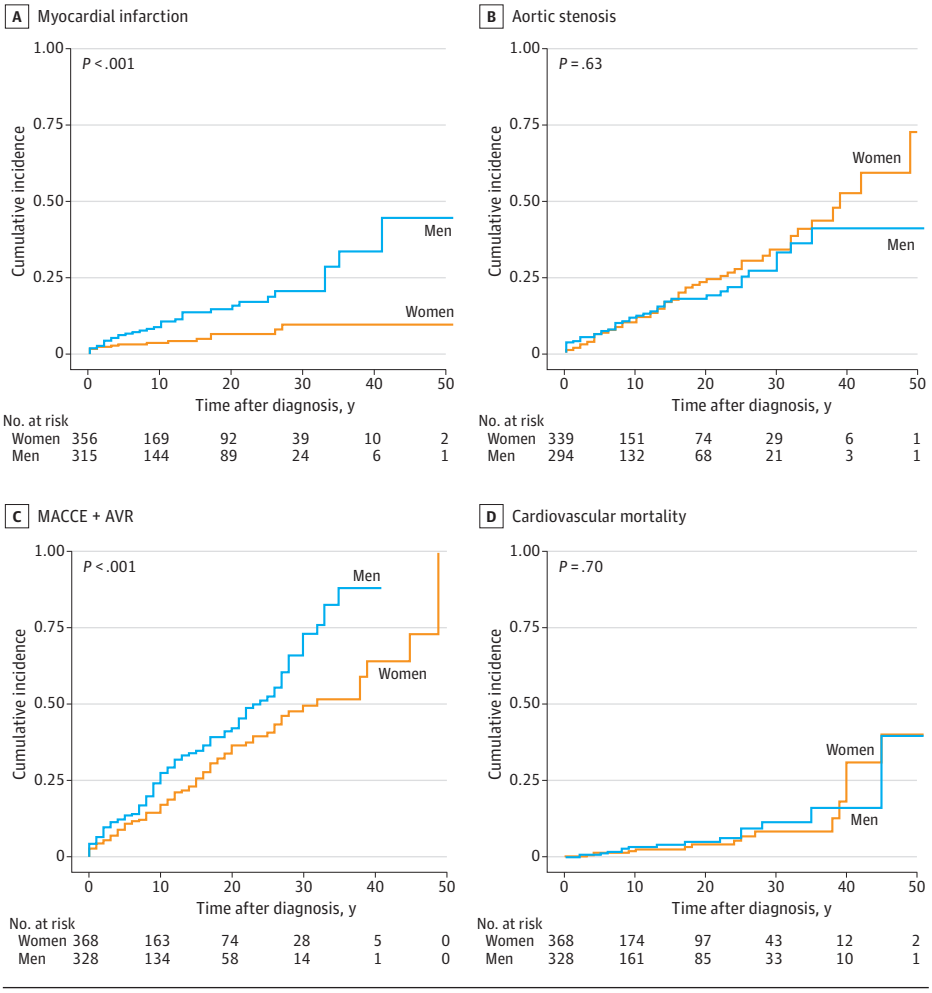
[a] Carotid intervention contains carotid endarterectomy and carotid stenting.

significantly lower in women than in men (5.0% in women; 95% CI, 2.2-7.8 vs 13.7% in men; 95% CI, 8.7-18.7; SHR, 0.37; 95% CI, 0.21-0.66), as was the cumulative incidence of first PCI (6.5% in women; 95% CI, 3.1-9.8 vs 15.0% in men; 95% CI, 9.8-20.2; SHR, 0.42; 95% CI, 0.26-0.69) and first MACCE + AVR event (27.7% in women; 95% CI, 21.5-34.0 vs 36.5% in men; 95% CI, 29.5-43.5; SHR, 0.63; 95% CI, 0.48-0.83) (**Figures 2** and 3). The cumulative incidence functions of other MACCE + AVR outcomes including aortic stenosis (SHR, 1.11; 95% CI, 0.75-1.63) were comparable between women and men (Figures 2 and 3). No statistically significant sex difference was observed for the cumulative incidence of all-cause mortality (3.0% in women vs 4.1% in men; HR, 0.76; 95% CI, 0.40-1.45) (eFigure 6 in Supplement 1) and cardiovascular mortality

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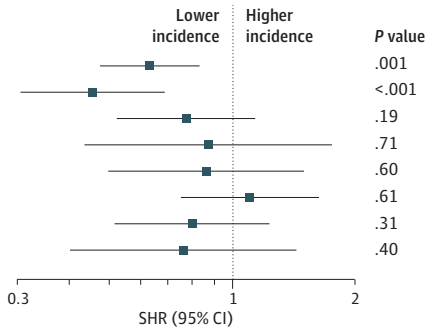
Figure 2. Cumulative Incidence of First Event After Diagnosis of Homozygous Familial Hypercholesterolemia



AVR indicates aortic valve replacement; MACCE, major adverse cardiovascular and cerebrovascular events.

Figure 3. Subdistribution Hazard Ratios (SHRs) by Sex for Cardiovascular End Points After Diagnosis of Homozygous Familial Hypercholesterolemia (HoFH)

Outcome	Cumulative incidence (%)		SHR (95% CI), women vs men	P value
	Women	Men		
MACCE + AVR	27.7	36.5	0.63 (0.48-0.83)	.001
Myocardial infarction and PCI	10.0	22.0	0.46 (0.30-0.69)	<.001
CABG	16.3	20.9	0.77 (0.52-1.14)	.19
Cardiovascular mortality	2.6	4.1	0.87 (0.44-1.75)	.71
Other MACCE + AVR components[a]	6.5	5.6	0.86 (0.50-1.50)	.60
Aortic stenosis	19.8	17.8	1.11 (0.75-1.63)	.61
Angina pectoris	10.8	13.3	0.80 (0.52-1.23)	.31
All-cause mortality[b]	3.0	4.1	0.76 (0.40-1.45)	.40



The cumulative incidence is shown for 16 years' follow-up post-HoFH diagnosis (75th percentile). The SHRs are calculated for the full follow-up duration. Aortic stenosis includes all patients with a clinical diagnosis of aortic stenosis with and without aortic valve replacement. AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACCE, major adverse cardiovascular and cerebrovascular events.

[a] Contains AVR, cerebrovascular disease stenting, carotid endarterectomy, and peripheral artery disease stenting or bypass.

[b] Shown as normal hazard ratio based on a Cox regression model.

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post-HoFH diagnosis (2.6% in women vs 4.1% in men; SHR 0.87; 95% CI, 0.44-1.75). As shown in Figure 3, the significantly lower hazard of women compared to men with regards to MACCE + AVR seems to be driven by MI and PCI, whereas the probability of occurrence of other ASCVD morbidity were comparable in the sexes (Figure 3).

In unadjusted and age-adjusted models investigating the influence of variables on the cumulative incidence function of women and men combined, age at diagnosis in years (model 2 SHR age-adjusted, 1.07; 95% CI, 1.04-1.10), high-income country (model 2 SHR age-adjusted, 0.56; 95% CI, 0.34-0.92), and untreated LDL-C in mg/dL (model 2 SHR age-adjusted per 20 mg/dL, 1.03; 95% CI, 1.01-1.06) were significantly associated with MACCE + AVR events (eTable 3 in Supplement 1). Patients with prior or current smoking had an increased risk of MACCE + AVR events in the age-adjusted model 1 (SHR age-adjusted, 1.59; 95% CI, 1.07-2.37) (eTable 3 in Supplement 1).

Discussion

In this cohort study we showed that the age at diagnosis and untreated LDL-C levels did not differ between women and men in the largest international registry of HoFH patients. Apart from smoking, which was less common in women, the prevalence of other cardiovascular risk factors did not differ by sex. Treatment selection and intensity, and subsequently treated LDL-C levels at 9 years after diagnosis were similar for women and men. Both women and men with HoFH have an extremely high risk of premature ASCVD and showed a similar age at onset of the first ASCVD event. Men showed a statistically significant higher prevalence and incidence of MI and PCI and a nonsignificant higher incidence of all-cause and cardiovascular mortality. The prevalence and incidence of other cardiovascular outcomes was comparable between the sexes.

In the HICC registry, median age at diagnosis was in the early teenage years and comparable between women and men (13 vs 11 years respectively). This contrasts with several HeFH studies which observed that women with HeFH were diagnosed later in life than men.[10-13] The largest cohort of patients with HeFH, the Familial Hypercholesterolemia Studies Collaboration (FHSC), reporting on 42 167 patients (21 999 [53.6%] women) showed that women were diagnosed on average 3 years later compared to men: 46 vs 43 years $P < .001$.[10] HoFH is usually diagnosed in childhood or adolescence, as the extreme hypercholesterolemia frequently is accompanied by skin and tendon xanthomata. Both for women and men with HoFH in our study, delayed diagnosis was significantly associated with an increased incidence of MACCE + AVR outcomes. This further underlines the importance of early screening, diagnosis, and treatment in both sexes.

Both untreated levels at diagnosis and treated total cholesterol and LDL-C levels at the latest clinical evaluation were similar for women and men in this HoFH registry. Apart from a Canadian study published in 1993, there are no published data on sex-related differences in HoFH. The Canadian study included 21 patients with HoFH (13 women) and found no sex differences in plasma cholesterol.[25] However, they did not sex-stratify data or conduct a formal analysis. The currently available literature in patients with HeFH report contradicting data regarding sex differences in cholesterol levels with some reporting higher[10,12,15] and some similar[11,20] LDL-C levels in women compared to men, but none reporting higher LDL-C levels in men. HDL-C levels were higher and triglycerides lower in women with HoFH, which has also been observed in patients with HeFH.[11,13,20,26]

We observed no sex differences in LLT type and potency at the latest clinical evaluation. In addition, LDL-C goal achievement was comparable in both sexes albeit low (4.0% in women and 3.1% in men), similar to previous findings in patients with HoFH.[27-29] Therefore, it is important that patients with HoFH are treated as early as possible with combination LLT. Moreover, this underscores the necessity of new LLTs and access in all countries to these newer LLTs, such as lomitapide and evinacumab, to further reduce the LDL-C levels to get more patients to goal.

In contrast to our finding that women and men with HoFH receive equal LLT, numerous studies reported that women with HeFH were treated with LLT less often,[10,11,13] at a later age,[12] with less potent or combination LLT,[10,11,13,14] and less often achieve LDL-C goals than men with HeFH.[10,11,13,16,17] A possible explanation for the lack of sex differences in patients with HoFH with regard to treatment is the severity of the condition and the intensiveness of required treatment, which is offered in specialized lipid clinics.

In this study, MI and PCI prevalence and incidence were higher in men. We observed no sex differences in other ASCVD morbidities. The age at onset of the different ASCVD end points, including MI and aortic stenosis, was similar for women and men. The previously mentioned study in patients with HoFH stated that there were no sex differences observed in coronary heart disease, although a formal analysis was not performed.[25] In the general population, women have a lower risk of ASCVD before menopause.[30,31] Consequently, on average, women experience a first ASCVD event approximately 7 to 10 years than men.[31-34] A reduced gap in age at onset of cardiovascular disease has been observed between women and men with HeFH in some studies[19,20] but not others.[11,12,26,35] Except for prevalence and incidence of PCI, we did not observe a difference in AVR or other cardiovascular intervention treatments between women and men with HoFH. While age at onset of MI did not differ between the sexes, prevalence and incidence of MI was higher in men than women, comparable to the sex difference in MI event rate in the general population. We do not have a conclusive explanation for this finding. Considering the premenopausal age of the women in this study, they may still have experienced some hormonal cardiovascular protection in relation to the development of MI. For instance, estrogens have been linked to increased LDLR activity and plaque stability.[36,37] At the other hand, we do not exclude the possibility that the diagnosis of MI is more often missed in women, similar to previous reports of general population studies that observed that women more often had silent or missed MIs.[38-40]

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Strengths and Limitations

Previous cohort studies consisted of small numbers of patients with HoFH and therefore were not powered to analyze women and men separately. The HICC registry is the largest and most detailed registry with contemporary clinical worldwide data on HoFH. Therefore, the HICC registry is the first and only dataset in which detailed sex-specific analyses could be performed. In addition, survival analyses could be performed in which competing risk was accounted for to prevent overestimation of the outcome.

A limitation is that the HICC registry only captures patients with HoFH who were diagnosed and received treatment from 2010 onwards. Therefore, we do not know if sex differences exist in undiagnosed, untreated, or prematurely deceased patients with HoFH. Also, not all world regions are currently covered in the HICC registry. In particular our findings might not be representative for low-income countries. In addition, not all racial and ethnic groups were adequately represented. Furthermore, sex-specific risk factors were not part of the dataset and therefore female-specific risk factors, such as age at menarche, could not be investigated. For the Turkish subgroup, only living patients at data entry were included, and therefore mortality might be higher and underestimated. Information on relevant nonlipid risk factors (in particular smoking) were lacking in substantial numbers of patients, as data were not systematically collected at standard follow-up intervals after HoFH diagnosis. This especially hampered the ASCVD analyses. There were some missing data in follow-up time of the ASCVD outcome. Therefore, age at onset and cumulative incidence of ASCVD outcomes might be overestimated and underestimated, respectively.

Conclusions

To our knowledge, this is the first study to assess sex differences in patients with HoFH. We observed no sex differences in diagnosis, most risk factors, or treatment. Women and men with HoFH experience an excessive risk of ASCVD caused by extreme hypercholesterolemia. Although prevalence and incidence of MI and PCI was higher in men (comparable to findings from the general population), the age at MI and PCI onset was similar between the sexes. Other ASCVD morbidity, interventions, and age at occurrence were comparable in women and men. Additional research is needed to better understand this phenomenon, with particular focus on female-specific ASCVD risk factors. The findings indicate that both women and men with HoFH have a very high risk of premature ASCVD, suggesting that early diagnosis and treatment are important steps in attenuating excessive cardiovascular risk in both sexes.

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