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

Published in:
JAMA Cardiology

Publication status and date:
Published: 10/04/2024

DOI (link to publisher):
10.1001/jamacardio.2023.5597

Document Version
Peer reviewed version

Diagnosis, treatment, and cardiovascular outcomes in Homozygous Familial Hypercholesterolemia: a sex-specific analysis

Janneke W.C.M. Mulder[1], MD, Tycho R. Tromp[2], MD PhD, Mutaz Al-Khnifsawi[3], MD, Dirk J. Blom[4], MD PhD, Krysztof Chlebus[5], MD PhD, Marina Cuchel[6], MD PhD, Laura D'Erasmo[7], MD PhD, Antonio Gallo[8], MD PhD, G. Kees Hovingh[2], MD PhD, Ngoc Thanh Kim[9], MD, Jiang Long[10], MD PhD, Frederick J. Raal[11], MD PhD, Willemijn A.M. Schonck[2], MD, Handrean Soran[12], MD, Thanh-Huong Truong[13], MD PhD, Eric Boersma[14], PhD, and Jeanine E. Roeters van Lennep[1], MD PhD, and the Homozygous Familial Hypercholesterolemia International Clinical Collaborators*

[1] Department of Internal Medicine, Erasmus MC Cardiovascular Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands;

[2] Department of Vascular Medicine, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands;

[3] Al-Qadisiyah University, College of Medicine, Department of Internal Medicine, Diwaniya City, Iraq;

[4] Department of Medicine, Division of Lipidology and Cape Heart Institute, University of Cape Town, Cape Town, South Africa;

[5] 1st Department of Cardiology, Medical University of Gdansk, Poland and National Centre of Familial Hypercholesterolaemia in Gdańsk, Poland;

[6] Department of Medicine, Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA;

[7] Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy;

[8] Sorbonne Université, INSERM UMR1166, Lipidology and cardiovascular prevention Unit, Department of Nutrition, APHP, Hôpital Pitié-Salpètrière, F-75013, Paris, France;

[9] Vietnam National Heart Institute, Bach Mai Hospital, Vietnam *and* Department of Cardiology, Hanoi Medical University, Vietnam;

[10] Department of Atherosclerosis, Beijing Anzhen Hospital, Capital Medical University, The Key Laboratory of Remodeling–Related Cardiovascular Diseases, Ministry of Education, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China;

[11] Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa;

[12] Department of Diabetes, Endocrinology and Metabolism *and* Manchester National Institute of Health Research/Wellcome Trust Clinical Research Facility, Manchester University NHS Foundation Trust, Manchester, United Kingdom;

[13] Faculty of Medicine, Phenikaa University, Hanoi city, Vietnam *and* Vietnam Atherosclerosis Society;

[14] Department of Cardiology, Erasmus MC Cardiovascular Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands;

* The full list of authors is given in the online-only supplemental materials (eText 1).

Date minor revision: December 12, 2023
Manuscript word count = 2956

Corresponding author:

J.E. Roeters van Lennep, MD PhD

Department of Internal Medicine, Erasmus University Medical Center

Address: PO Box 2040, 3000 CA Rotterdam, The Netherlands

Tel.: +31 65 23 13 132

E-mail j.roetersvanlennep@erasmusmc.nl

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: An observational multi-national registry of 751 HoFH patients 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 the sexes.

Meaning: In women and men, HoFH remains responsible for an alarmingly high premature ASCVD risk without clear sex differences, except a higher incidence of MI in men.

Abstract

Importance Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition characterized by extremely increased LDL-cholesterol (LDL-C) levels and very premature atherosclerotic cardiovascular disease (ASCVD). Heterozygous familial hypercholesterolemia (HeFH) is much 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 HoFH patients.

Design, setting and participants Sex specific analyses were performed using data from the HoFH International Clinical Collaborators (HICC, NCT04815005) registry, the largest global dataset of HoFH patients.

Main Outcome(s) and Measure(s) Comparison between women and men with HoFH regarding: age at diagnosis, presence of risk factors, lipid lowering treatment, prevalence, onset and incidence of ASCVD morbidity (myocardial infarction (MI), aortic stenosis, and combined ASCVD outcomes) and mortality.

Results We analyzed data from 389 women and 362 men with HoFH from 38 countries. Women (W) and men (M) had similar age at diagnosis (median 13 [25^{th}-75^{th} percentile 6-26] vs 11 [5-27] years), untreated LDL-cholesterol levels (W: 579 (203), M: 596 (186) mg/dL), and cardiovascular risk factor prevalence, except smoking (W: 14.3%, M: 27.2%). Prevalence of MI was lower in women (8.0%) than men (16.3%), but age at first MI was similar (W: 39 (13), M: 38 (13) years). Treated LDL-cholesterol levels and lipid lowering therapy were similar in both sexes, in particular statins (W: 89.9%, M: 91.1%) and lipoprotein apheresis (W: 36.3%, M: 38.8%). Sixteen years after HoFH diagnosis, women had statistically significant lower cumulative incidence of MI (W: 5.0% versus M: 13.7%; HR 0.37 (95% CI 0.21-0.66)) and non-significantly lower all-cause (W: 3.0% versus M: 4.1%; HR 0.76 (95% CI 0.40-1.45)) and cardiovascular mortality (W: 2.6% versus M: 4.1%; HR 0.87 (95% CI 0.44-1.75)).

Conclusions and Relevance In this observational multi-national registry of individuals with known HoFH, MI was higher in men compared with women yet age at diagnosis and first ASCVD event were

similar. Early diagnosis and treatment are crucial in attenuating the excessive cardiovascular risk in both sexes.

Key words: homozygous familial hypercholesterolemia, cardiovascular disease, sex differences, treatment

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic bi-allelic disorder with a prevalence of 1 in 250.000-360.000[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 three of the causal genes, i.e. *LDLR, APOB* and *PCSK9,* display autosomal semi-dominant 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 (PCSK9) inhibition, microsomal triglyceride transfer protein (MTP) inhibition (lomitapide) or angiopoietin-like 3 (ANGPTL3) blockade (evinacumab)[8]. Reaching guideline recommended LDL-cholesterol (LDL-C) goals in patients with HoFH is challenging, even with intensive combination treatment[9].

The lifelong cholesterol burden and cardiovascular risk in HoFH patients is much higher compared to patients with heterozygous familial hypercholesterolemia (HeFH) in whom only one allele in the genes associated with semi-dominantly 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[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 contra-indicated in the conception, pregnancy and lactation period[18]. These factors may explain why the excess ASCVD morbidity and mortality associated with HeFH is greater in women than men compared to the general population[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.

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, and ASCVDs morbidity and mortality, and year when the ASCVD event and/or intervention occurred. Income status was defined based on country specific data according to the 2019 World Bank definition (eTable1)[21]. Detailed description of data collection methods was published previously[9].

Clinical endpoints

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: BMI in kg/m^2, smoking (ever or never), diabetes, hypertension, and chronic kidney disease (CKD).

We evaluated treatment based on the latest recorded data and analyzed the type, number and intensity of LLT utilized. For intensity of LLT, starting age and frequency of apheresis and statin intensity was investigated. Statin intensity was defined according to the ACC/AHA clinical practice guideline on cholesterol[22]. The proportion of women and men achieving recommended LDL-C goals at the last recorded visit was investigated, being <70 mg/dL for patients without ASCVD events and <55 mg/dL for patients with ASCVD[2].

For cardiovascular outcomes, we compared the prevalence and incidence of non-fatal myocardial infarction (MI), angina pectoris, aortic stenosis, ischemic stroke, transient ischemic attack (TIA), peripheral artery disease (PAD), 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 (CABG), carotid endarterectomy and PAD 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, CABG 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, PAD stenting, and PAD bypass.

Statistical analysis

Continuous data are shown as mean (SD) or median with interquartile range [25^{th}-75^{th} percentile] 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, are analyzed with a two-sample t-test or Mann-Whitney U test (continuous data) and Chi-squared test or Fischer's exact test (categorical data). Cardiovascular risk factors, LLT, ASCVD and 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 endpoints, the Fine-Gray subdistribution hazard model was employed, to account for (non-cardiovascular) death as competing risk[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 endpoints was assessed with the Gray's test and Fine-Gray subdistribution hazard regression, resulting in subdistribution hazard ratios (SHR)s with 95%

confidence interval (CI). The cumulative incidences of the ASCVD endpoints after HoFH diagnosis were compared between the sexes for the 75th percentile of MACCE+AVR follow-up duration. Subdistribution hazards ratios (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 statistical software (version 4.2.1). Statistical significance of all tests was set at 0.05 (2-sided).

Results

HoFH diagnosis: patient characteristics and presentation

The HICC registry included 389 women (W) and 362 men (M), who had similar median age at diagnosis (W: 13 [6-26], M: 11 [5-27] years; Table 1). Genetic information was available in 75.2% of the patients showing a similar proportion of women and men with two *LDLR* null variants (eTable 2). Mean untreated total cholesterol at a median age of 13 [5-29] years was similar in women and men (W: 645 (204), M: 650 (201) mg/dL), as were untreated LDL-C levels (W: 579 (203), M: 596 (186) mg/dL; Figure 1). Mean untreated HDL-C was significantly higher in women than men (W: 42 (17), M: 38 (16) mg/dL, *P*= .007), whereas median triglycerides were significantly lower (W: 100 [75-140], M: 115 [79-161] mg/dL, *P*= .013; eFigure 1 in the online-only supplement).

Latest clinical evaluation: patient characteristics, LLT, ASCVD prevalence, and age at ASCVD onset

The median clinical follow-up duration (n=709) of 9 [1; 20] years from the time of HoFH diagnosis was the same in the sexes (*P*= >.90, Table 2). At the latest clinical evaluation, the median age of registry participants was 28 [16-43] years (W: 29 [17-42], M: 27 [14-44], *P*= .68). Smoking was significantly less common in women than in men (W: 14.3%, M: 27.2%, *P*= <.001), the prevalence of other cardiovascular risk factors was similar in both sexes (Table 2).

Almost all women and men with HoFH were on LLT (W: 94.9%, M: 96.5%, *P*= .49). The most frequently used LLT for both women and men were statins (W: 89.9%, M: 91.1%, *P*= .74) and most

patients received high-intensity statin (W: 58.3%, M: 58.9%, *P*= .74). Ezetimibe was used equally in women and men (W: 61.6%, M: 63.6%, *P*= .70). No sex differences were observed for any form or number of LLT (Table 2). Only 37.3% of the women and 37.2% of the men used ≥ 3 LLT. Approximately one third of the women and men received apheresis treatment (W: 36.3%, M: 38.8%, *P*= .57). In both sexes, the median frequency of apheresis was every other week and the age of apheresis initiation was similar (W: 16 [10-32], M: 14 [9-22] years, *P*= .33).

Treated total cholesterol (W: 377 (184), M: 373 (184) mg/dL) and LDL-C (W: 321 (179), M: 323 (176) mg/dL) levels did not differ between the sexes at a median follow-up of 11 [4-23] years after HoFH diagnosis (Figure 1). Mean treated HDL-C values were significantly higher in women than men (W: 44 (18), M: 41 (16) mg/dL, *P*= .022). No sex difference was observed in median treated triglycerides (W: 91 [62-131], M: 96 [70-143] mg/dL; eFigure 1). Overall, women and men using LLT had a similar reduction of LDL-C after a median 12 [6-23] years between the untreated and most recent laboratory levels (eFigure 3). The vast majority of women and men did not reach the currently recommended LDL-C goals (W: 96.0%, M: 96.9% respectively, *P*= .82).

Fewer women than men had experienced a MI at the latest clinical evaluation (W: 8.0%, M: 16.3%; *P*= <.001). However, age at first MI did not differ between sexes (W: 39 (13), M: 38 (13) years, *P*= .81). There were no significant sex differences in the prevalence of aortic stenosis, angina pectoris, ischemic stroke and/or TIA, and PAD (Table 2). The ages of onset of aortic stenosis (W: 20 [14-30], M: 20 [11-33]), angina pectoris (W: 30 (15), M: 29 (14)), ischemic stroke and/or TIA (W: 33 [29-39], M: 43 [37-43]), and PAD (W: 33 [24-49], M: 36 [21-46]) were also comparable (eFigure 2 in the online-only supplement).

Although fewer women had undergone a PCI (W: 8.7%, M: 15.7%, *P*= .005), we observed no sex difference in prevalence of other ASCVD interventions: 14.4% women and 17.7% men underwent a CABG and AVR occurred in 6.2% women vs 7.7% men (Table 2). For all ASCVD interventions (PCI, CABG, AVR, and carotid intervention), the age of first ASCVD intervention was comparable in women and men (eFigure 2 in the online-only supplement). In total, 37 patients, 18 (5.3%) women and 19 (6.1%) men had died (*P*= .77). Median age at death was similar between the sexes (W: 32 [23-48] vs M: 43 [16-54] years, *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 significantly lower in women than in men (W: 5.0% (95% CI 2.2-7.8), M: 13.7% (95% CI 8.7-18.7); SHR 0.37 (95% CI 0.21-0.66)), as was the cumulative incidence of first PCI (W: 6.5% (95% CI 3.1-9.8), M: 15.0% (95% CI 9.8-20.2); SHR 0.42 (95% CI 0.26-0.69)) and first MACCE+AVR event (W: 27.7% (95% CI 21.5-34.0), M: 36.5% (95% CI 29.5-43.5); SHR 0.63 (95% CI 0.48-0.83); Figure 2A 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 (Figure 2B and 3). No statistical significant sex difference was observed for the cumulative incidence of all-cause mortality (HR 0.76 (95% CI 0.40-1.45), eFigure 6) and cardiovascular mortality post HoFH diagnosis (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: 1.002 (95% CI 1.000-1.003)) were significantly associated with MACCE+AVR events (eTable3). 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), eTable3).

Discussion

In our observational 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 statistical significant higher prevalence and incidence of MI and PCI and a non-significant 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 of 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 HeFH patients, the Familial Hypercholesterolemia Studies Collaboration (FHSC) reporting on 42167 patients of which 21999 (53.6%) women, showed that women were diagnosed on average 3 years later compared to men: 46 vs 43 years $P<.0001$[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 HoFH patients (13 women) and found no sex differences in plasma cholesterol[25]. However, sex-stratified data or a formal analysis was not performed. The currently available literature in HeFH patients 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 were lower in women with HoFH, which has also been observed in HeFH patients[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 very low (women 4.0% and men 3.1%) similar to previous findings in HoFH patients[27-29]. Therefore, it is important that HoFH patients are treated as early as possible with combination LLT. Moreover, this underscores the necessity of new LLT and access in all countries to these newer LLT, 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 less often with LLT[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 HoFH patients with regards to treatment is the severity of the condition and the intensiveness of required treatment, which is offered in specialized lipid clinics.

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 Canadian study in HoFH patients 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, women experience their first ASCVD-event approximately 7-10 years later compared to men[31-34]. A reduced gap in age at onset of cardiovascular disease has been observed between women and men with HeFH in some[19,20], but not other studies[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 don't have a conclusive explanation for this finding. Considering the premenopausal age of the women we studied, 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 which observed that women more often had silent or missed MIs[38-40].

Strengths and weaknesses

Previous cohort studies consisted of small numbers of HoFH patients 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 HoFH patients who were diagnosed and received treatment from 2010 onwards. Therefore, we do not know if sex differences exist in undiagnosed, untreated or prematurely deceased HoFH patients. 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 ethnicities 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. Lastly, information on relevant non-lipid 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 over- and underestimated respectively.

Conclusions

This study, using data from the HICC registry, is the first to assess sex differences in patients with HoFH. We observed no sex-differences in diagnosis, most risk factors and treatment. Women and men with HoFH experience an excessive ASCVD risk caused by extreme hypercholesterolemia. Although prevalence and incidence of myocardial infarction and PCI was higher in men (comparable to findings from the general population), interestingly, the age at myocardial infarction and PCI was similar between the sexes.

Additionally, other ASCVD morbidity, interventions and age of 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.

Both women and men with HoFH have an extreme risk of premature ASCVD. Therefore, early diagnosis and treatment are crucial in attenuating the excessive cardiovascular risk in both sexes.

Author contributions:

JM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JM, TT, MAK, DJB, KC, MC, LD, AG, GKH, NTK, JL, FJR, WS, HS, THT, EB, JRvL. Acquisition, analysis or interpretation of data: JM, TT, MAK, DJB, KC, MC, LD, AG, GKH, NTK, JL, FJR, WS, HS, THT, EB, JRvL, HICC collaborators. Drafting of the manuscript: JM, EB, JRvL. Critical revision of the manuscript for important intellectual content: TT, MAK, DJB, KC, MC, LD, AG, GKH, NTK, JL, FJR, WS, HS, THT, EB, JRvL, HICC collaborators. Statistical analysis: JM, EB, JRvL. Supervision: EB, JRvL.

Funding/Support

In-house funding at each institution was used to cover effort of contributors for data collection and entry. The creation and the maintenance of the REDCap database and support of a study coordinator for bulk data entry was provided in house by MC at the University of Pennsylvania. MC acknowledges support from NIH/NHLBI grant P01HL059407. Support of the registry coordinators (WS and TT) was provided in house by GKH at Amsterdam UMC. The HICC is an investigator-initiated project supported by funding from the academic institutions of the collaborators. The European Atherosclerosis Society provided funding to support a registry coordinator. The writing committee takes final responsibility for the content of the Article and the decision to submit for publication.

Conflicts of interest / Disclosures

MAK received lecture fees and travel grants from Amryt and received research grants from IAS. 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 is supported in part by grant HL148769 from the National Institutes of Health and reports institutional research funding from Regeneron Pharmaceuticals and Regenxbio. LD reports honoraria, lecture fees or research grants from Amryt pharmaceuticals, Novartis, Sobi, Aurora biopharma, Daiichi sankyo, Amarin, Bayer. AG reports research grants from Amgen, Sanofi and Regeneron; honoraria for lectures, presentations, speakers bureaus or educational events from Amgen, Sanofi, Mylan, Ackea Therapeutics, Novartis, MSD, Ultragenyx, Servier. GKH reports research grants from the Netherlands Organization for Scientific Research (vidi 016.156.445), CardioVascular Research Initiative, European Union 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); GKH is part-time employment at Novo Nordisk and has stock in Novo Nordisk, Denmark. JL received research grant from the National Key R&D Program of China (No. 2021YFC2500600 and 2021YFC2500602, and 2022YFE0209900); The National Natural Science Foundation for Young Scientists of China (No. 81700792). FJR reports receiving advisory board fees and lecture fees from Amgen, Sanofi-Aventis, Regeneron Pharmaceuticals, Novartis, and LIB Therapeutics. HS reports research grants from Amgen, MSD, Synageva, Amryt, Alexion and Akcea; consulting fees from Amgen, Alexion, Daiichi-Sankyo, Pfizer, Akcea; speaker fees from Amgen, Daiichi-Sankyo, Sanofi and Akcea. JRvL received research grant from Novartis. The other authors JM, TT, KC, NTK, WS, THT, and EB do not have disclosures for this manuscript.

Data sharing statement

Data in the HICC registry is property of the individual contributors. Therefore, data cannot be shared without approval of all individual contributors. However, upon reasonable request, it can be expected that specific data will be shared to a qualified researcher in case of approval.

References

1. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome. *European Heart Journal*. 2014;36(9):560-565. doi:10.1093/eurheartj/ehu058
2. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. May 2 2023;doi:10.1093/eurheartj/ehad197
3. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. Aug 21 2014;35(32):2146-57.
4. Sturm AC, Knowles JW, Gidding SS, et al. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. Aug 7 2018;72(6):662-680. doi:10.1016/j.jacc.2018.05.044
5. Kramer AI, Akioyamen LE, Lee S, et al. Major adverse cardiovascular events in homozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Eur J Prev Cardiol*. May 5 2022;29(5):817-828. doi:10.1093/eurjpc/zwab224
6. Bertolini S, Calandra S, Arca M, Averna M, Catapano AL, Tarugi P. Homozygous familial hypercholesterolemia in Italy: Clinical and molecular features. *Atherosclerosis*. Nov 2020;312:72-78. doi:10.1016/j.atherosclerosis.2020.08.027
7. Raal FJ, Sjouke B, Hovingh GK, Isaac BF. Phenotype diversity among patients with homozygous familial hypercholesterolemia: A cohort study. *Atherosclerosis*. May 2016;248:238-44. doi:10.1016/j.atherosclerosis.2016.03.009
8. Tromp TR, Cuchel M. New algorithms for treating homozygous familial hypercholesterolemia. *Curr Opin Lipidol*. Oct 5 2022;doi:10.1097/mol.0000000000000853
9. Tromp TR, Hartgers ML, Hovingh GK, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *The Lancet*. 2022;399(10326):719-728. doi:10.1016/S0140-6736(21)02001-8
10. Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet*. Nov 6 2021;398(10312):1713-1725. doi:10.1016/s0140-6736(21)01122-3
11. Amrock SM, Duell PB, Knickelbine T, et al. Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry. *Atherosclerosis*. Dec 2017;267:19-26. doi:10.1016/j.atherosclerosis.2017.10.006
12. Iyen B, Qureshi N, Weng S, et al. Sex differences in cardiovascular morbidity associated with familial hypercholesterolaemia: A retrospective cohort study of the UK Simon Broome register linked

434 to national hospital records. *Atherosclerosis*. Dec 2020;315:131-137.
435 doi:10.1016/j.atherosclerosis.2020.10.895
436 13. Ryzhaya N, Cermakova L, Trinder M, et al. Sex Differences in the Presentation, Treatment,
437 and Outcome of Patients With Familial Hypercholesterolemia. *J Am Heart Assoc*. 2021:e019286. vol.
438 11.
439 14. Zamora A, Masana L, Comas-Cufí M, et al. Familial hypercholesterolemia in a European
440 Mediterranean population-Prevalence and clinical data from 2.5 million primary care patients. *J Clin*
441 *Lipidol*. Jul-Aug 2017;11(4):1013-1022. doi:10.1016/j.jacl.2017.05.012
442 15. Holven KB, Narverud I, van Lennep JR, et al. Sex differences in cholesterol levels from birth
443 to 19 years of age may lead to increased cholesterol burden in females with FH. *J Clin Lipidol*. May-
444 Jun 2018;12(3):748-755.e2. doi:10.1016/j.jacl.2018.02.021
445 16. Saadatagah S, Alhalabi L, Farwati M, et al. The burden of severe hypercholesterolemia and
446 familial hypercholesterolemia in a population-based setting in the US. *Am J Prev Cardiol*. Dec
447 2022;12:100393. doi:10.1016/j.ajpc.2022.100393
448 17. Schmidt N, Dressel A, Grammer TB, et al. Lipid-modifying therapy and low-density lipoprotein
449 cholesterol goal attainment in patients with familial hypercholesterolemia in Germany: The CaReHigh
450 Registry. *Atherosclerosis*. Oct 2018;277:314-322. doi:10.1016/j.atherosclerosis.2018.08.050
451 18. Klevmoen M, Bogsrud MP, Retterstøl K, et al. Loss of statin treatment years during pregnancy
452 and breastfeeding periods in women with familial hypercholesterolemia. *Atherosclerosis*. 2021;
453 19. Ahmad Z, Li X, Wosik J, et al. Premature coronary heart disease and autosomal dominant
454 hypercholesterolemia: Increased risk in women with LDLR mutations. *J Clin Lipidol*. Jan-Feb
455 2016;10(1):101-8.e1-3. doi:10.1016/j.jacl.2015.09.003
456 20. Krogh HW, Mundal L, Holven KB, Retterstøl K. Patients with familial hypercholesterolaemia
457 are characterized by presence of cardiovascular disease at the time of death. *Eur Heart J*. May 1
458 2016;37(17):1398-405. doi:10.1093/eurheartj/ehv602
459 21. The World Bank. Data World Bank national accounts. GNI per capita, Atlas method (current
460 US$) - high income, middle income, low income. https://data.worldbank.org/indicator/NY.GNP.PCAP.
461 CD?locations=XD-XP-XM. Accessed March 3, 2021,
462 22. Grundy SM, Stone NJ, Bailey AL, et al. 2018
463 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the
464 Management of Blood Cholesterol. *Journal of the American College of Cardiology*. 2019;73(24):e285-
465 e350. doi:doi:10.1016/j.jacc.2018.11.003
466 23. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of
467 Competing Risks. *Circulation*. Feb 9 2016;133(6):601-9. doi:10.1161/circulationaha.115.017719
468 24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk.
469 *Journal of the American statistical association*. 1999;94(446):496-509.
470 25. Moorjani S, Roy M, Torres A, et al. Mutations of low-density-lipoprotein-receptor gene,
471 variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial
472 hypercholesterolaemia. *Lancet*. May 22 1993;341(8856):1303-6. doi:10.1016/0140-6736(93)90815-x

26. Alonso R, Mata N, Castillo S, et al. Cardiovascular disease in familial hypercholesterolaemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. *Atherosclerosis*. Oct 2008;200(2):315-21. doi:10.1016/j.atherosclerosis.2007.12.024

27. Di Taranto MD, Giacobbe C, Buonaiuto A, et al. A Real-World Experience of Clinical, Biochemical and Genetic Assessment of Patients with Homozygous Familial Hypercholesterolemia. *J Clin Med*. Jan 14 2020;9(1)doi:10.3390/jcm9010219

28. Rodrigo Alonso and Jose Luis Díaz-Díaz and Francisco Arrieta and Francisco Fuentes-Jiménez and Raimundo and Pedro Saenz and Gema Ariceta and José IV-PaFAa. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: Insights from SAFEHEART registry. *Journal of Clinical Lipidology*. 2016;10(4):953-961. doi:https://doi.org/10.1016/j.jacl.2016.04.006

29. Kayikcioglu M, Tokgozoglu L, Yilmaz M, et al. A nation-wide survey of patients with homozygous familial hypercholesterolemia phenotype undergoing LDL-apheresis in Turkey (A-HIT 1 registry). *Atherosclerosis*. Mar 2018;270:42-48. doi:10.1016/j.atherosclerosis.2018.01.034

30. Saeed S, Dweck MR, Chambers J. Sex differences in aortic stenosis: from pathophysiology to treatment. *Expert Rev Cardiovasc Ther*. Feb 2020;18(2):65-76. doi:10.1080/14779072.2020.1732209

31. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation*. Feb 22 2022;145(8):e153-e639. doi:10.1161/cir.0000000000001052

32. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular Disease in Women: Clinical Perspectives. *Circ Res*. Apr 15 2016;118(8):1273-93. doi:10.1161/circresaha.116.307547

33. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. *Circulation*. Mar 1 2016;133(9):916-47. doi:10.1161/cir.0000000000000351

34. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. Jan 1 2016;37(1):24-34. doi:10.1093/eurheartj/ehv598

35. Allard MD, Saeedi R, Yousefi M, Frohlich J. Risk stratification of patients with familial hypercholesterolemia in a multi-ethnic cohort. *Lipids Health Dis*. Apr 8 2014;13:65. doi:10.1186/1476-511x-13-65

36. Hussain Y, Ding Q, Connelly PW, et al. G-protein estrogen receptor as a regulator of low-density lipoprotein cholesterol metabolism: cellular and population genetic studies. *Arterioscler Thromb Vasc Biol*. Jan 2015;35(1):213-21. doi:10.1161/atvbaha.114.304326

37. Yerly A, van der Vorst EPC, Baumgartner I, Bernhard SM, Schindewolf M, Döring Y. Sex-specific and hormone-related differences in vascular remodelling in atherosclerosis. *Eur J Clin Invest*. Jan 2023;53(1):e13885. doi:10.1111/eci.13885

38. van der Ende MY, Juarez-Orozco LE, Waardenburg I, et al. Sex-Based Differences in Unrecognized Myocardial Infarction. *J Am Heart Assoc*. Jul 7 2020;9(13):e015519. doi:10.1161/jaha.119.015519

39. de Torbal A, Boersma E, Kors JA, et al. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. *Eur Heart J*. Mar 2006;27(6):729-36. doi:10.1093/eurheartj/ehi707

40. Lichtman JH, Leifheit EC, Safdar B, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). *Circulation*. Feb 20 2018;137(8):781-790. doi:10.1161/circulationaha.117.031650

Tables and Figures

Table 1. HoFH diagnosis: demographic and clinical characteristics

	N	Overall (n=751)	Women (n=389)	Men (n=362)	*P-value*
Diagnosis					
Age at diagnosis (years)	711	12 [5-27]	13 [6-26]	11 [5-27]	.53
Genetic information available	751	565 (75.2%)	294 (75.6%)	271 (74.9%)	.89
Xanthomas at diagnosis	751	516 (68.7%)	265 (68.1%)	251 (69.3%)	.78
Ethnicity					
Asian	751	121 (16.1%)	65 (16.7%)	56 (15.5%)	.39
Black		9 (1.2%)	2 (0.5%)	7 (1.9%)	
Mixed		59 (7.9%)	29 (7.5%)	30 (8.3%)	
Unknown		224 (29.8%)	112 (28.8%)	112 (30.9%)	
White		338 (45.0%)	181 (46.5%)	157 (43.4%)	
Country income status					
High income	751	398 (53.0%)	205 (52.7%)	193 (53.3%)	>.90
Middle income		353 (47.0%)	184 (47.3%)	169 (46.7%)	

Continuous data are shown in median [IQR]. Categorical data are shown in No. (%).

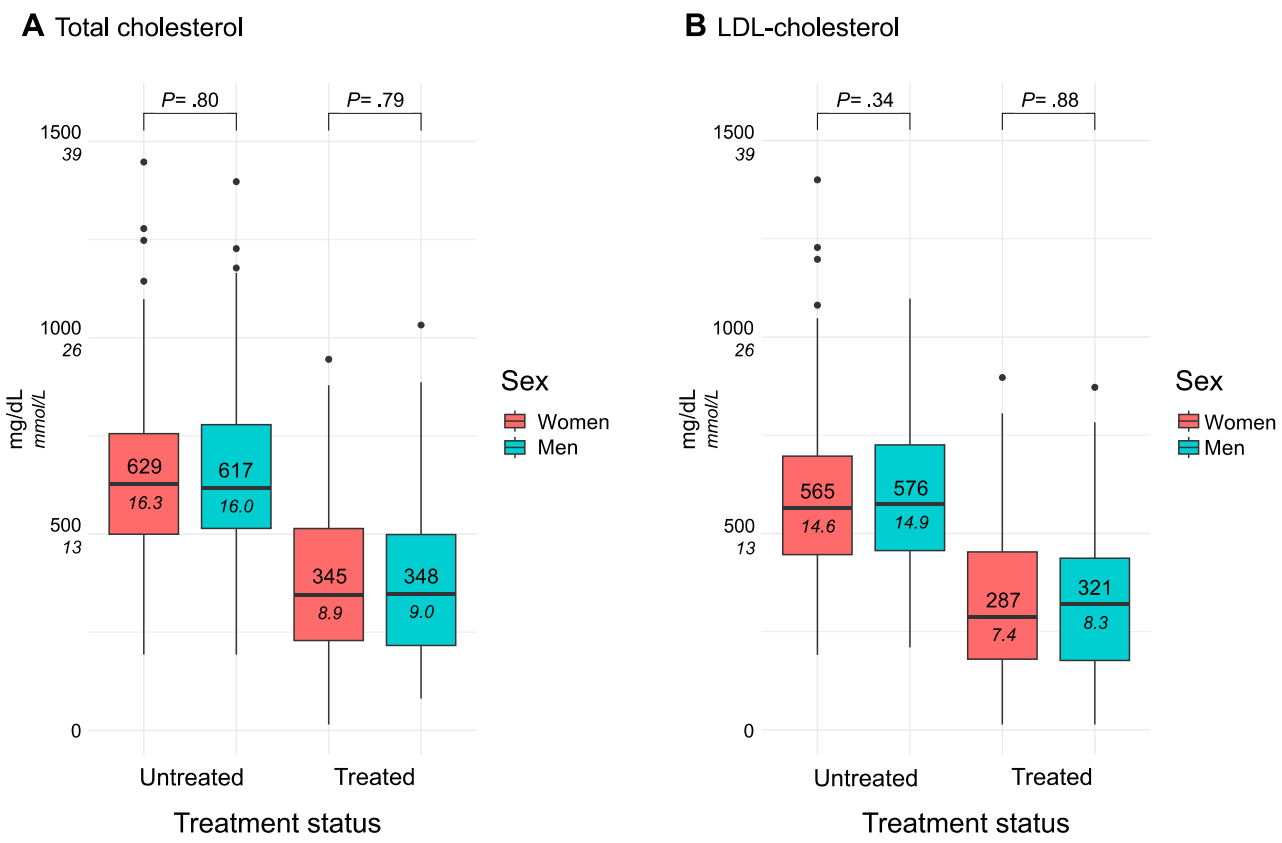
Table 2. Clinical characteristics at latest evaluation

	N	Overall (n=751)	Women (n=389)	Men (n=362)	*P-value*
Birthyear	745	1983 [1972-1997]	1984 [1972-1997]	1986 [1971-1999]	.72
Latest age (years)	727	28 [16-43]	29 [17-42]	27 [14-44]	.68
Time since diagnosis (years)	709	9 [1-20]	9 [1-20]	9 [1-20]	>.90
Risk factors					
BMI (kg/m^2)	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 mellitus	603	23 (3.8%)	9 (2.9%)	14 (4.8%)	.29
Hypertension	590	93 (15.8%)	46 (14.9%)	47 (16.7%)	.62
CKD	421	6 (1.4%)	3 (1.4%)	3 (1.5%)	>.90
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%)	>.90
Lomitapide	534	41 (7.7%)	21 (7.6%)	20 (7.8%)	>.90
Evinacumab	534	13 (2.4%)	7 (2.5%)	6 (2.3%)	>.90
Mipomersen	534	1 (0.19%)	0 (0%)	1 (0.39%)	.48
Resins	534	31 (5.8%)	16 (5.8%)	15 (5.8%)	>.90
Fibrates	534	6 (1.12%)	1 (0.36%)	5 (1.94%)	.11
Nr. of LLT					
Mean number	534	2 (1)	2 (1)	2 (1)	.51
Per nr. of LLT:					
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%)	
LLT intensity					
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
PCI	751	91 (12.1%)	34 (8.7%)	57 (15.7%)	**.005**
CABG	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	751	15 (2.0%)	5 (1.3%)	10 (2.8%)	.19
Ischemic stroke and/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
AVR	751	52 (6.9%)	24 (6.2%)	28 (7.7%)	.48

Continuous data are shown in mean (SD) or median [IQR] depending on the distribution. Categorical data are shown in No. (%). BMI = Body Mass Index, CKD = chronic kidney disease, PCSK9-inhibitor = Proprotein Convertase Subtilisin-Kexin type 9-inhibitor, LLT = Lipid Lowering Therapy, ASCVD = Atherosclerotic

538 Cardiovascular Disease, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Grafting,
539 TIA = Transient Ischemic Attack, AVR = Aortic Valve Replacement. Carotid intervention contains carotid
540 endarterectomy and carotid stenting.

Figure 1. Untreated and treated total cholesterol and LDL-cholesterol levels



Values are shown in median [interquartile range] in mg/dL and *mmol/L* (conversion factor 0.0259) for: (A) total cholesterol, and (B) LDL-cholesterol.

Figure 2. Cumulative incidence of first event after diagnosis of homozygous familial hypercholesterolemia: (A) Myocardial infarction, (B) Aortic stenosis, (C) MACCE+AVR, (D) Cardiovascular mortality

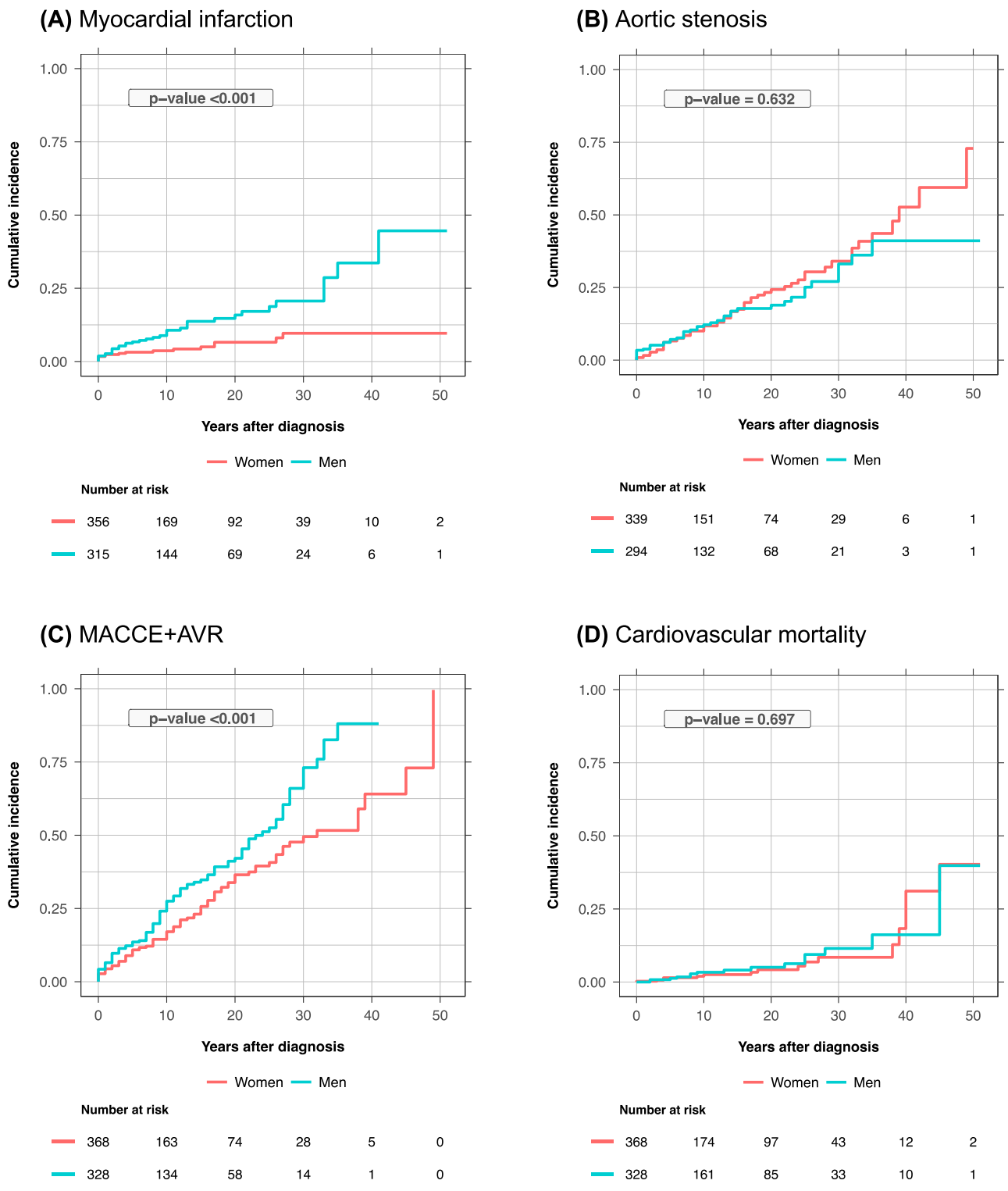
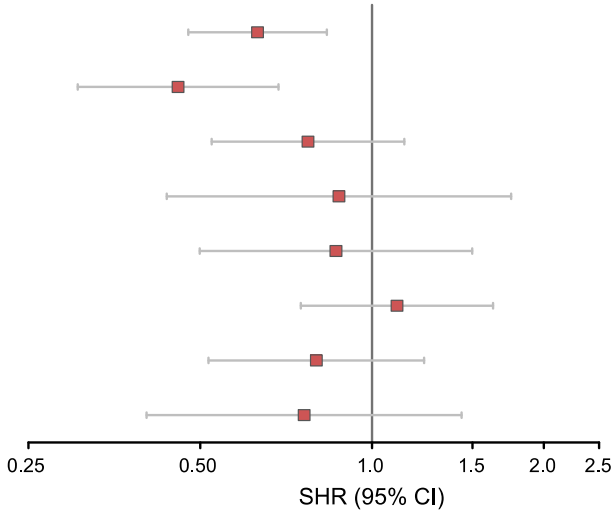


Figure 3. Forest plot of (subdistribution) hazard ratios by sex for cardiovascular endpoints after diagnosis of homozygous familial hypercholesterolemia

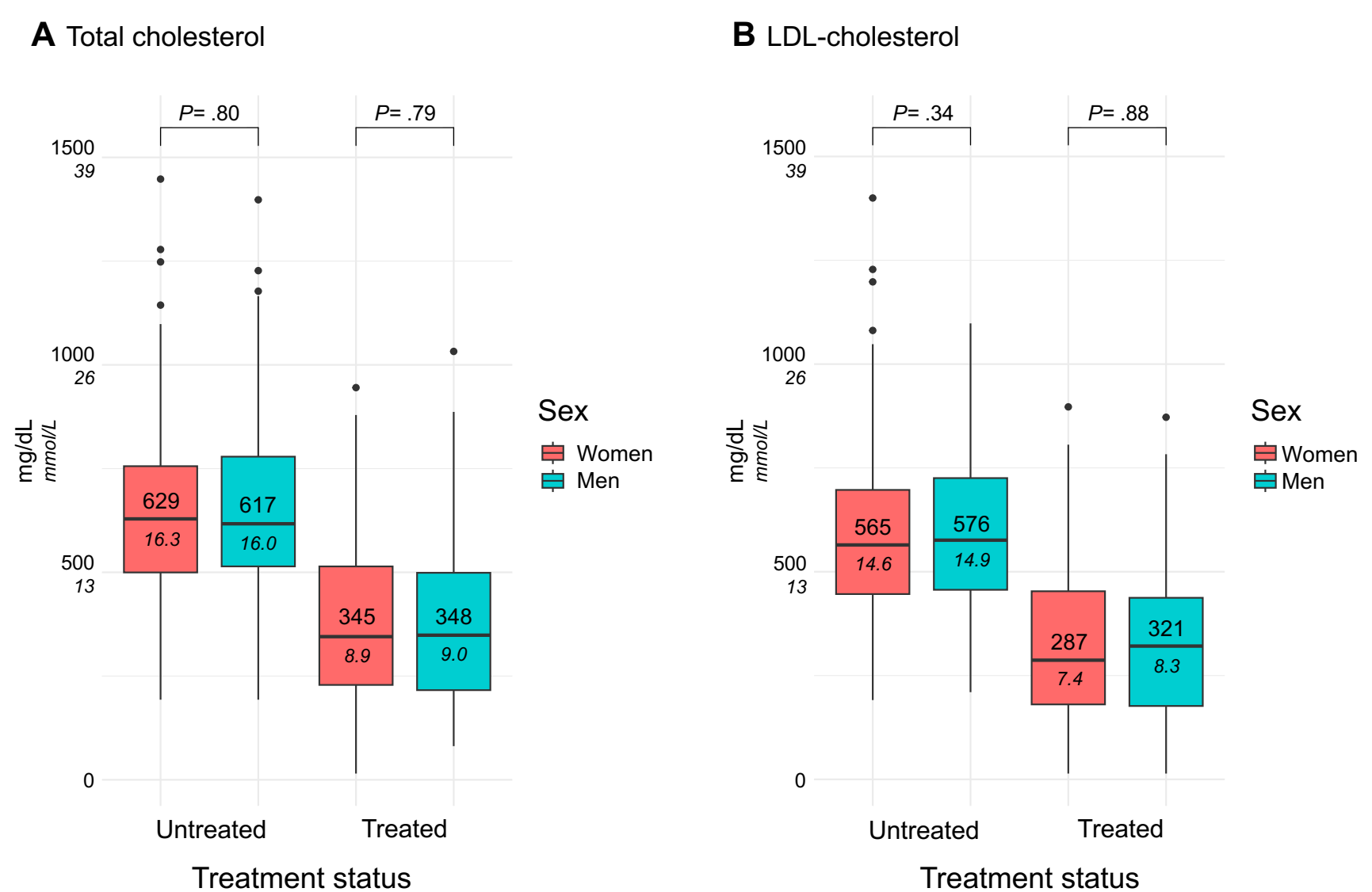
	Cumulative incidence (%)		SHR (95% CI)	
	Women	**Men**	**Women vs Men**	***P***
MACCE+AVR	27.7	36.5	0.63 (0.48-0.83)	**.001**
Myocardial infarction & PCI	10.0	22.0	0.46 (0.30-0.69)	**<.001**
CABG	16.3	20.9	0.77 (0.52-1.14)	.19
Cardiovascular mortality	2.6	4.1	0.87 (0.44-1.75)	.71
Other MACCE+AVR components[a]	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



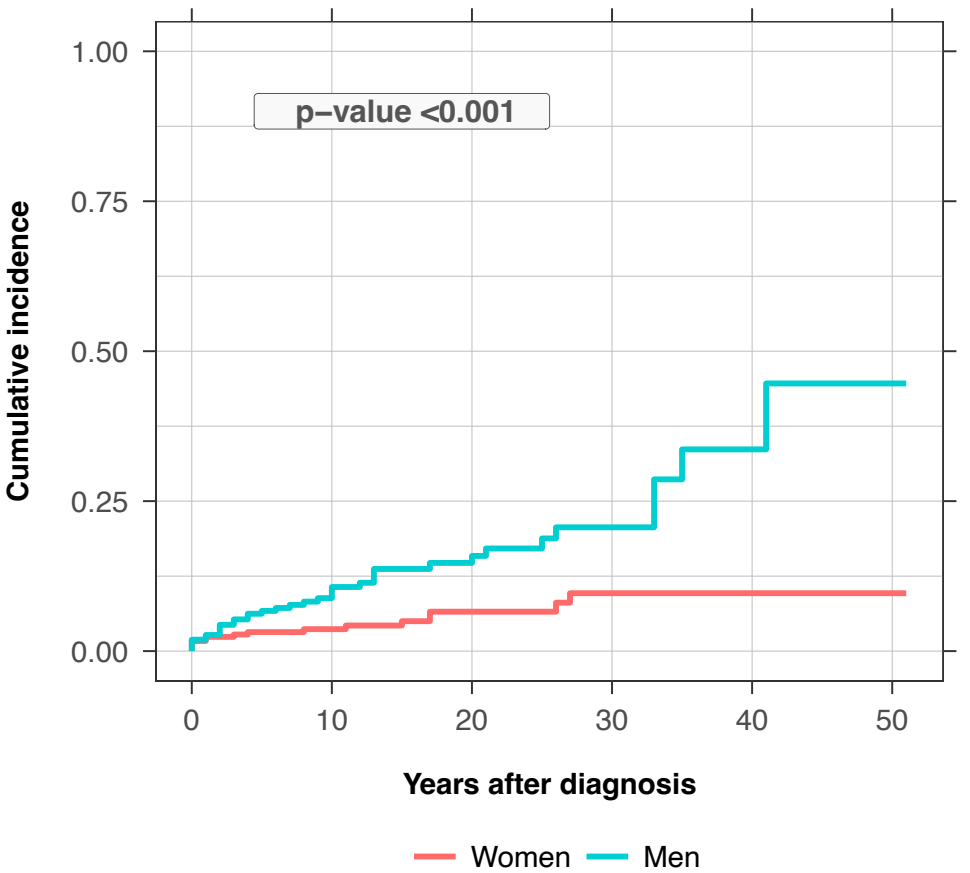
[a] Contains AVR, cerebrovascular disease stenting, carotid endarterectomy, and PAD stenting or bypass.
[b] Is shown as normal hazard ratio based on a Cox regression model.

The cumulative incidence is shown for 16 years follow-up post HoFH diagnosis (75th percentile). The subdistribution hazard ratios (SHR)s 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.

HoFH = homozygous familial hypercholesterolemia; SHR = subdistribution hazard ratio; CI = confidence interval. PCI = percutaneous coronary intervention. CABG = coronary artery bypass grafting. AVR = aortic valve replacement. MACCE+AVR = major adverse cardiovascular event, containing myocardial infarction, PCI, CABG, cardiovascular mortality, AVR, cerebrovascular disease stenting, carotid endarterectomy, and PAD stenting or bypass.


A Total cholesterol
P= .80
P= .79
1500
39
1000
26
500
13
0
mg/dL
mmol/L
629
16.3
617
16.0
345
8.9
348
9.0
Untreated
Treated
Treatment status
Sex
Women
Men
B LDL-cholesterol
P= .34
P= .88
1500
39
1000
26
500
13
0
mg/dL
mmol/L
565
14.6
576
14.9
287
7.4
321
8.3
Untreated
Treated
Treatment status
Sex
Women
Men

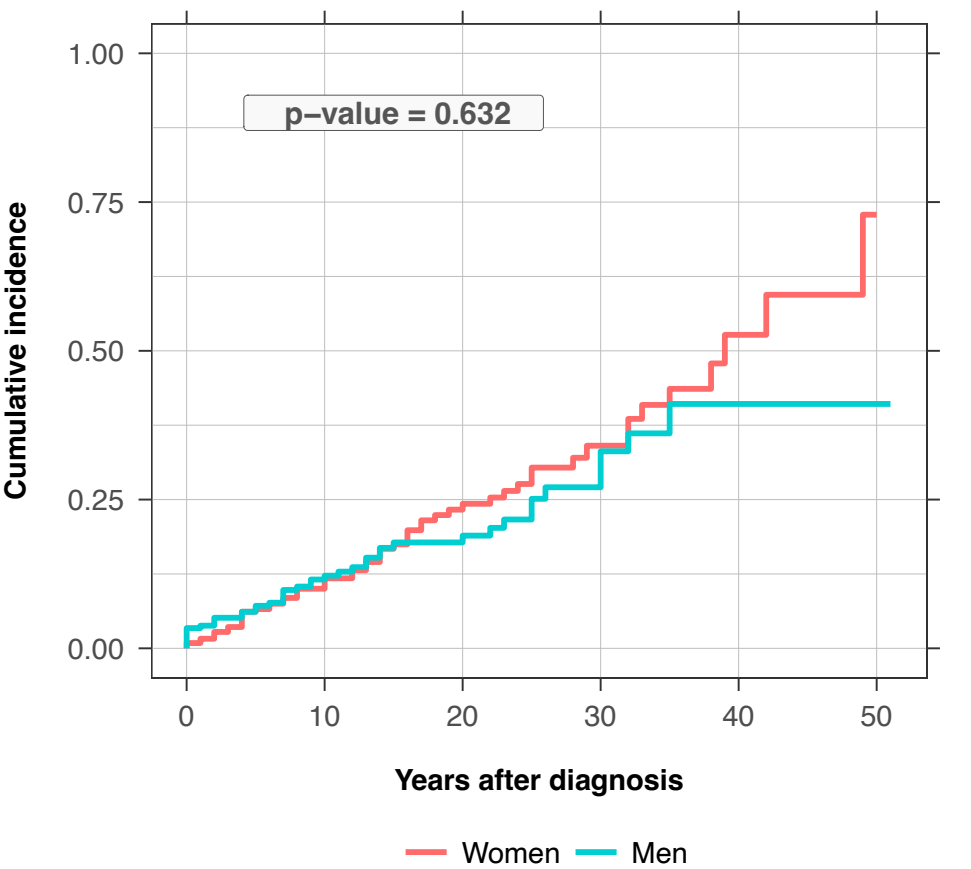
(A) Myocardial infarction



Number at risk

Women	356	169	92	39	10	2
Men	315	144	69	24	6	1

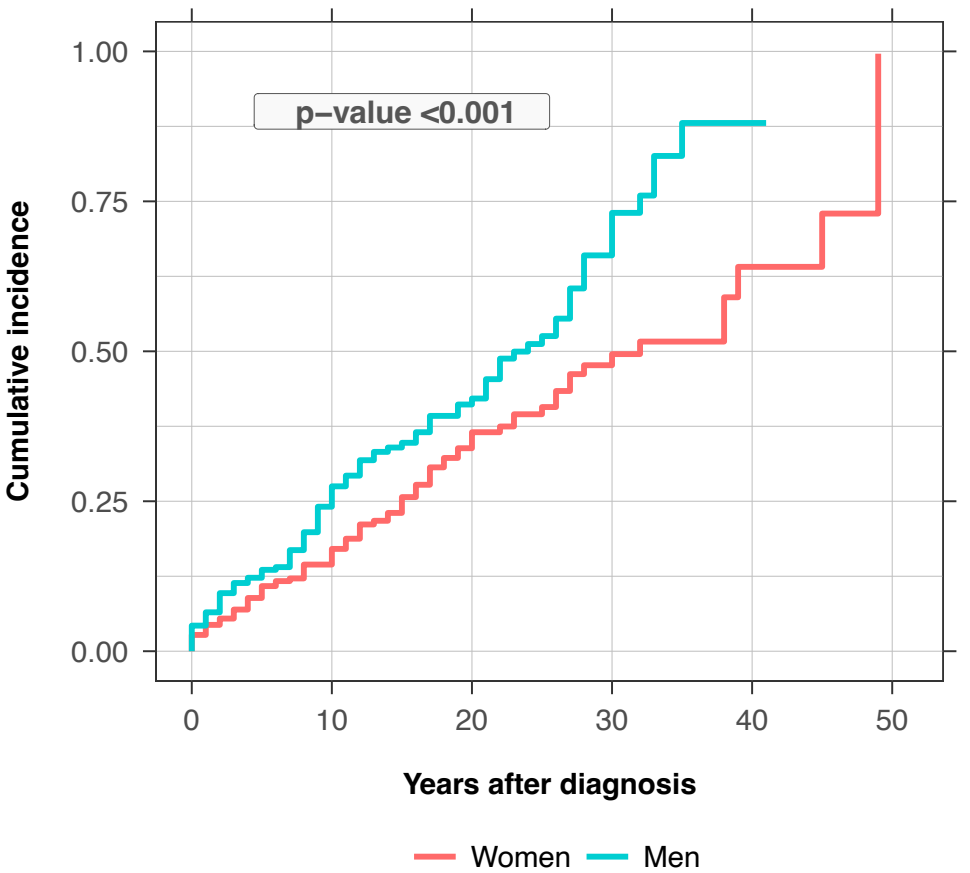
(B) Aortic stenosis



Number at risk

Women	339	151	74	29	6	1
Men	294	132	68	21	3	1

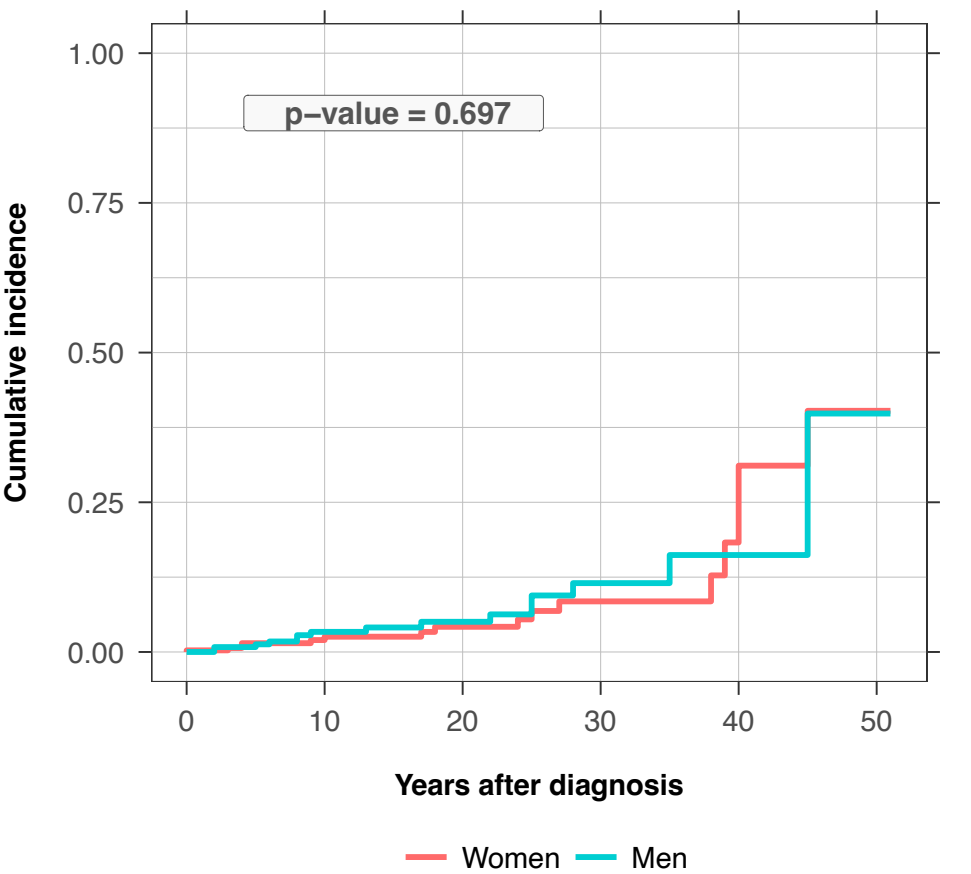
(C) MACCE+AVR



Number at risk

Women	368	163	74	28	5	0
Men	328	134	58	14	1	0

(D) Cardiovascular mortality



Number at risk

Women	368	174	97	43	12	2
Men	328	161	85	33	10	1

	Cumulative incidence (%)		SHR (95% CI)	
	Women	**Men**	**Women vs Men**	***P***
MACCE+AVR	27.7	36.5	0.63 (0.48-0.83)	**.001**
Myocardial infarction & 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