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RESEARCH LETTER

Sex Differences in the Presentation, Treatment, and Outcome of Patients With Familial Hypercholesterolemia

Natalia Ryzhaya, BSc; Lubomira Cermakova, MSc; Mark Trinder, MSc; Isabelle Ruel, PhD; Thais Coutinho, MD; Jacques Genest, MD; Liam R. Brunham, MD, PhD

Heterozygous familial hypercholesterolemia (FH) is the most common genetic disorder with a prevalence of 1 in 311 and is associated with a high risk of premature cardiovascular disease (CVD). As an autosomal dominant condition, it affects men and women equally. However, little is known about sex-specific differences in prescription of lipid-lowering therapy (LLT) and response to therapy in patients with FH.[1,2] The objective of this study was to investigate sex-related differences in the presentation, treatment, response, and clinical outcomes of patients with HF.

This study was approved by the Research Ethics Board of the Providence Health Care Research Institute. All patients provided written informed consent. We included participants within the British Columbia FH Registry with a diagnosis of "probable" or "definite" FH according to Dutch Lipid Clinic Network Criteria (DLCN)[3]. We examined baseline characteristics, LLT, attainment of lipid targets (defined as LDL-C<2.00 mmol/L or a>50% reduction from baseline)[4], and CVD rates. Baseline was defined as the first available medical record, while follow-up was defined as the last clinic visit as of August 2019. Baseline characteristics, CVD rates, LLT prescription, and response were analysed using a 2-sample t-test and χ^2 test. Paired t-test, Wilcoxon matched-pairs signed rank test, and Mann-Whitney U-test were used to analyze LLT response as appropriate. The authors declare that all supporting data are available within this article.

Women comprised 52.5% of our cohort and were diagnosed later than men (Table), even after excluding participants with a history of prior CVD (mean age 45.5 versus 41.5 years, P=0.003). Most participants were of European or East Asian descent. The prevalence of cardiovascular risk factors was similar between sexes (Table). However, men had a higher prevalence of CVD events prior to enrolment in the registry (20.7% versus 9.9%, P<0.001), defined as acute coronary syndrome, coronary artery bypass grafting, myocardial infarction (MI), percutaneous coronary intervention (PCI), stroke, and transient ischemic attack. Women had higher HDL-C (1.53 mmol/L versus 1.31 mmol/L, P<0.001) and lower triglycerides (1.34 mmol/L versus 1.50 mmol/L, P=0.01) at baseline. Other baseline lipid levels were similar between sexes.

Statin use at baseline was higher in men (19.3% versus 12.2%, P=0.01). After a median follow-up of 8 years, statin use was similar between sexes, with 89.0% of patients receiving statins. However, women were less likely to be prescribed high-potency statins, defined as atorvastatin ≥40 mg per day or rosuvastatin ≥20 mg per day (45.0% versus 55.0%, P=0.03), and ezetimibe (41.0% versus 51.5%, P=0.02). PCSK9 inhibitor use was numerically lower in women.

The less intensive treatment was associated with a lower rate of target achievement in women. Women experienced a lesser reduction in both LDL-C (–52.7% versus –59.0%, P=0.001) and apoB-100 (–29.7% versus –42.3%, P=0.008). Fewer women reached an LDL-C<2.00mmol/L (16.4% versus 33.3%, P<0.001).

We next examined the prevalence of premature MI in patients ≤55 years of age. Rates of premature MI were 1115/100 000-patient-years in men and

Correspondence to: Dr. Liam R. Brunham, Centre for Heart Lung Innovation, Room 166-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada. E-mail: liam.brunham@ubc.ca

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Table. Sex Differences in the British Columbia Familial Hyperlipidemia Cohort

Variable	Men No.*	Men	Women No.*	Women	*P* Value
Baseline characteristics					
Age, y, mean (SD)	275	43.9 (14.1)	304	46.6 (15.8)	0.03
DLCNC Score mean (SD)		11.2 (5.3)		11.2 (5.0)	0.9
Age of first cardiovascular event, y (SD)		47.1 (10.3)		52.7 (11.7)	0.01
Years of follow-up (IQR)		8 (13.5)		8 (13)	0.5
Baseline cardiovascular risk factors					
BMI, kg/m^2 (SD)	275	26.7 (3.9)	304	25.9 (5.5)	0.049
Current Smoker, %		10 (3.6%)		19 (6.2%)	0.2
Hypertension, %		59 (21.4%)		68 (22.4%)	0.8
DM, %		21 (7.6%)		27 (8.9%)	0.8
Prior cardiovascular event(s), %		57 (20.7%)		30 (9.9%)	<0.001
Baseline medications					
Statin	275	54 (19.6%)	304	37 (12.2%)	0.01
ACE inhibitor/ARB	228	31 (13.6%)	249	20 (8.0%)	0.004
Antiplatelet		43 (18.9%)		32 (12.8%)	0.07
Beta blocker		19 (8.3%)		12 (4.8%)	0.1
Calcium channel blocker		4 (1.8%)		3 (1.2%)	0.8
Baseline patient lipid profiles					
LDL-C mean, mmol/L (SD)	270	6.81 (2.3)	304	6.95 (2.3)	0.5
HDL-C mean, mmol/L (SD)	269	1.31 (1.3)	295	1.53 (0.5)	0.008
NONHDL mean, mmol/L (SD)	268	6.92 (2.3)	290	7.18 (2.0)	0.2
Triglycerides median, mmol/L (IQR)	273	1.50 (1.0)	303	1.34 (1.1)	0.01
ApoB-100 mean, g/L (SD)	99	1.54 (0.5)	120	1.63 (0.5)	0.2
Lp(a) median, mg/L (IQR)	65	376 (641)	86	395 (578)	0.9
Lipid lowering therapies received					
Statin, %	231	207 (89.6%)	249	220 (88.4%)	0.7
High-potency statin, %		127 (55.0%)		112 (45.0%)	0.03
Statin drug+ezetimibe, %		107 (46.3%)		94 (37.8%)	0.06
Ezetimibe, %		119 (51.5%)		102 (41.0%)	0.02
PCSK9 inhibitor, %		40 (17.3%)		31 (12.4%)	0.1
Treatment response					
LDL-C (mmol/L)	231		250		
Baseline mean (SD)		6.93 (2.0)		6.83 (2.2)	0.6
Last follow-up mean (SD)		2.71 (1.7)		3.09 (1.2)	6.7E-03
Average % change		−59.01% (0.2)		−52.69% (0.2)	1.3E-03
Target LDL-C reached					
<2.00 mmol/L (%)	231	77 (33.3%)	250	41 (16.4%)	<0.001
>50% reduction, %		164 (71.0%)		161 (64.4%)	0.1
Either target		165 (71.4%)		164 (65.6%)	0.2
HDL-C, mmol/L					
Baseline mean, SD	226	1.23 (0.3)	224	1.53 (0.5)	<0.001
Last follow-up mean, SD		1.35 (0.4)		1.62 (0.5)	<0.001
Average % change		9.01% (0.3)		9.16% (0.3)	0.9
non HDL-C, mmol/L					
Baseline mean, SD	225	6.86 (2.3)	238	7.12 (1.9)	0.2
Last follow-up mean, SD		3.27 (1.8)		3.67 (1.3)	7.1E-03
Average % change		−47.26% (0.4)		−44.86% (0.2)	0.5

(*Continued*)

Table. Continued

Variable	Men No.*	Men	Women No.*	Women	*P* Value
Triglycerides (mmol/L)					
Baseline median (IQR)	229	1.50 (1.1)	248	1.39 (1.2)	0.046
Last follow-up median (IQR)		1.08 (0.8)		1.17 (0.8)	0.6
Average % change		–12.11% (0.5)		–7.80% (0.4)	0.3
ApoB-100, g/L					
Baseline mean, SD	52	1.53 (0.5)	56	1.58 (0.4)	0.6
Last follow-up mean, SD		0.83 (0.3)		1.04 (0.3)	<0.001
Average % change		–42.27% (0.2)		–29.72% (0.3)	7.7E-03
Cardiovascular event rate (per 100 000 patient-years)†					
Any cardiovascular Event	275	1597	304	548	<0.001
MI		588		198	<0.001
Age stratified					
Any cardiovascular event≤55, y		2211		673	<0.001
Any cardiovascular event>55, y		1288		982	<0.001
MI≤55, y		1115		229	<0.001
MI>55, y		204		186	0.4

ACE Inhibitors indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ApoB-100, apolipoprotein B; BMI, body mass index; DLCNC, Dutch Lipid Clinic Network Criteria Score; DM, diabetes mellitus; FRS, Framingham Risk Score; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; IQR, interquartile range; LLT, lipid-lowering therapy; MI, myocardial infarction; NONHDL, non-high-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9 inhibitors.

*N varies due to the availability of data within the database.

†Only follow-up years/events analyzed. Expressed in events/100 000 patient-years.

229/100 000-patient-years in women. Relative to the background population MI rates in this age group in the province of BC (95.16/100 000 for men and 22.66/100 000 for women)[5], this represents an 11.7X increased risk in men and 10.4X increased risk in women (*P*=0.6). Notably, the CVD rates in FH population are considerably higher than would be predicted by risk calculators such as the Framingham Risk Score.[3]

These results point to important and previously unrecognized sex-related differences in the presentation and treatment of FH. To our knowledge, this is the first Canadian study to assess statin intensity, treatment response, and premature MI rates among men and women with FH. On average, women were diagnosed 4 years later, and this was not accounted for by a lesser prevalence of prior CVD. Despite similarly high levels of LDL-C and apoB-100, women received less intensive LLT and were less likely to reach guideline-recommended lipid targets. While the absolute rate of premature MI was higher in men, the excess risk relative to the general population was equivalent in men and women, highlighting a critical need to equally and aggressively treat FH in both sexes. However, it is also important to note that statins and most other LLT are contraindicated during pregnancy, thereby requiring careful attention when managing women with FH during the reproductive years. These findings point to important gaps in the treatment of FH in women, and the need to investigate potential factors contributing to management disparities.

This study has limitations. Multiparity, postmenopausal status of women, as well as sex-related differences in statin intolerance were not assessed. Future studies will be important to determine the reasons for less intensive treatment of women with FH, and to what extent this reflects a hesitancy of providers to prescribe LLT to women of childbearing potential.

In conclusion, our findings identify important sex-related differences in the presentation, treatment, and lipid target attainment in FH, highlighting the need for further sex-specific analyses and improvements in the management of this common cause of premature atherosclerotic CVD.

ARTICLE INFORMATION

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Affiliations

Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada (N.R., M.T., L.R.B.); Healthy Heart Program Prevention Clinic, St. Paul's Hospital, Vancouver, BC, Canada (L.C., L.R.B.); Research Institute of the McGill University Health Center, Montreal, QC, Canada (I.R., J.G.); Division of Cardiac Prevention & Rehabilitation, Division of Cardiology, Canadian Women's Heart Health Centre - University of Ottawa Heart Institute, Ottawa, ON, Canada (T.C.); and Departments of Medicine and Medical Genetics, University of British Columbia, Vancouver, BC, Canada (L.R.B.).

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None.

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