RESEARCH LETTER

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

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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 χ² 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<2.00 mmol/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

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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/m² (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, %                         | 231      | 127 (55.0%)              |            | 112 (45.0%)                | 0.03    |
| Statin drug+ezetimibe, %                       | 231      | 107 (46.3%)              |            | 94 (37.8%)                 | 0.06    |
| Ezetimibe, %                                   | 231      | 119 (51.5%)              |            | 102 (41.0%)                | 0.02    |
| PCSK9 inhibitor, %                              | 231      | 40 (17.3%)               |            | 31 (12.4%)                 | 0.1     |
| **Treatment response**                         |          |                          |            |                            |         |
| LDL-C (mmol/L)                                 | 231      | 6.93 (2.0)               | 250        | 6.83 (2.2)                 | 0.6     |
| Baseline 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, %                             | 231      | 164 (71.0%)              |            | 161 (64.4%)                | 0.1     |
| Either target                                  | 231      | 164 (71.4%)              |            | 164 (65.6%)                | 0.2     |
| **HDL-C, mmol/L**                              | 226      | 1.23 (0.3)               | 224        | 1.53 (0.5)                 | <0.001  |
| Baseline 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)
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), 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.

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