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LDL cholesterol targets rarely achieved in familial hypercholesterolemia patients: A sex and gender-specific analysis

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ABSTRACT

Background and aims: Despite lipid lowering therapy (LLT), reaching LDL-C targets in patients with familial hypercholesterolemia (FH) remains challenging. Our aim was to determine attainment of LDL-C target levels and reasons for not reaching these in female and male FH patients.

Methods: We performed a cross-sectional study of heterozygous FH patients in five hospitals in the Netherlands and Norway. Clinical characteristics and information about LLT, lipid levels and reasons for not being on LDL-C treatment target were retrospectively collected from electronic medical records.

Results: We studied 3178 FH patients (53.9% women), median age 48.0 (IQR 34.0–59.9) years. Median LDL-C before treatment and on-treatment was higher in women compared to men (6.2 (IQR 5.1–7.3) and 6.0 (IQR 4.9–7.2) mmol/l (p=0.005) and 3.0 (IQR 2.4–3.8) and 2.8 (IQR 2.3–3.5) mmol/L (p<0.001)), respectively. A minority of women (26.9%) and men (28.9%) reached LDL-C target. In patients with CVD, 17.2% of women and 25.8% of men reached LDL-C target. Women received less often high-intensity statins and ezetimibe. Most common reported reasons for not achieving the LDL-C target were insufficient effect of maximum LLT (women 17.3%, men 24.3%) and side effects (women 15.2%, men 8.6%).

Conclusions: In routine practice, only a minority of women and men with FH achieved their LDL-C treatment target. Extra efforts have to be made to provide FH patients with reliable information on the safety of statins and their long-term effects on CVD risk reduction. If statin treatment is insufficient, alternative lipid lowering therapies such as ezetimibe or PCSK9-inhibitors should be considered.

1. Introduction

Heterozygous familial hypercholesterolemia (FH) is the most common codominant monogenic dyslipidemia, affecting about 1 in 250 individuals [1]. FH causing mutations in the LDL-receptor gene (*LDLR*), apolipoprotein B gene (*APOB*) or proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*) lead to high LDL-C levels already at young age. Lifelong elevation of plasma levels of LDL-C increases the risk for developing premature cardiovascular disease (CVD) [1]. Furthermore, FH patients who experienced a CVD event have a more than 2-fold risk of a recurrent event within one year [2]. Moreover, women with FH are even less likely to achieve treatment goals than men [3–5]. This is concerning, as standardized CVD morbidity in FH patients is higher in women than men [4,6–8].

CVD risk can be effectively reduced with timely and adequate LDL-C lowering therapy, underlining the importance of lipid-lowering

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treatment of LDL-C in these patients [9]. Statin therapy is considered the cornerstone of treatment to attain these recommendations. When target LDL-C levels are not reached, other lipid lowering medications can be added such as ezetimibe and PCSK9 inhibitors [10,11]. Previous studies showed that the majority of FH patients did not reach their LDL-C target with statin therapy [12,13]. To gain more insight into the previously described sex difference of FH patients in reaching LDL-C targets, our aim was to study LDL-C goal attainment in women and men with FH. For this, we investigated determinants for LDL-C goal attainment and the interaction with sex. Secondly, we investigated reasons for not reaching LDL-C treatment target for women and men, separately.

2. Patients and methods

2.1. Study design and patients

This cross-sectional, observational study was conducted in three academic centers (Erasmus MC, University Medical Centre Rotterdam, University Medical Center Utrecht, the Netherlands, and The Lipid Clinic and the National Advisory Unit on FH, Oslo university Hospital, Norway) and two non-academic teaching hospitals (Diakonessen Hospital Utrecht and Elisabeth TweeSteden Hospital Waalwijk, the Netherlands). The population consisted of patients 18 years and older with heterozygous FH (HeFH), based on either a pathogenic FH causing mutation or clinical FH criteria (DLCN score $\geq$6) [14]. Consecutive patients who attended the outpatient clinic of the participating centers between January 2011 and December 2017 were included. Ethical approval for this study was waived because of its non-interventional nature.

2.2. Data collection

Information was collected from patient files on sex, age, body mass index (BMI), history of CVD defined as a history of a cardiac (MI, PCI, CABG, angina), cerebrovascular (CVA, TIA) or peripheral artery event (claudication, PTA), smoking, presence of hypertension, having a FH causing mutation and use of lipid-lowering therapy. Of the patients included in the Netherlands, reasons for not being on LDL-C target were retrospectively collected.

Statin intensity was categorized into low-, moderate- and high-intensity according to the American Heart Association classification [15]. Low-intensity statin treatment was defined as use of Simvastatin 10 mg, Pravastatin 10–20 mg, Lovastatin 20 mg, Fluvastatin 2–40 mg or Pitavastatin 1 mg. Moderate-intensity statin treatment was defined as Atorvastatin 10–20 mg, Rosuvastatin 5–10 mg, Simvastatin 20–40 mg, Pravastatin 40–80 mg, Lovastatin 40 mg, Fluvastatin 40 mg or Pitavastatin 2–4 mg. High-intensity statin treatment was defined as Atorvastatin 40–80 mg or Rosuvastatin 20–40 mg.

Maximum lipid-lowering therapy was defined a combination of the following lipid lowering therapy: 80 mg Simvastatin, 40 mg Rosuvastatin, 80 mg Atorvastatin, 40 mg Pravastatin or 80 mg Fluvastatin in combination with 10 mg ezetimibe and/or Colesevelam.

The primary aim was to analyze determinants for LDL-C goal attainment and their interaction with sex. Goal attainment was defined as LDL-C levels <2.5 mmol/l in patients without established CVD and <1.8 mmol/l in patients with CVD, based on the treatment targets according to the 2016 European guidelines on CVD prevention in clinical practice since they were the treatment goals at the time these patients were treated [16].

Table 1
Sex-specific baseline characteristics of FH patients treated with statins.

	Total (n = 3178)[a]	Women (n = 1713)	Men (n = 1465)	*p*-value
Age (median, IQR)	48.0 (34.0–59.9)	48.7 (33.0–61.0)	47.4 (36.9–58.1)	0.708
FH diagnosis (n, %)				0.941
Genetic	2564 (80.7)	1379 (80.5)	1185 (80.9)	
Clinical	608 (19.1)	331 (19.3)	277 (18.9)	
Missing	6 (0.2)	3 (0.2)	3 (0.2)	
CVD (n, %)	496 (15.6)	221 (12.9)	275 (18.8)	<0.001
Smoking (n, %)	471 (14.8)	222 (13.0)	249 (17.0)	0.002
Hypertension (n, %)	770 (24.2)	383 (22.4)	387 (26.4)	0.008
Diabetes (n,%)	152 (4.8)	69 (4.0)	83 (5.7)	0.031
HDL-C (mmol/l) (median, IQR)	1.3 (1.1 1.6)	1.4 (1.1–1.6)	1.2 (1.0–1.5)	<0.001
Triglycerides (mmol/l) (median, IQR)	1.2 (0.8–1.7)	1.1 (0.8–1.6)	1.2 (0.9–1.9)	<0.001
LDL-C before treatment (mmol/L) (median, IQR)	6.1 (5.0–7.3)	6.2 (5.1–7.3)	6.0 (4.9–7.2)	0.005
LDL-C on treatment (mmol/L) (median, IQR)	2.9 (2.4–3.7)	3.0 (2.4–3.8)	2.8 (2.3–3.5)	<0.001
LDL-C target reached (n, %)	884 (27.8)	460 (26.9)	424 (28.9)	0.102
Type of statin (n, %)				<0.001
No statin	207 (6.5)	151 (8.8)	56 (3.8)	
Atorvastatin	770 (24.2)	379 (22.1)	391 (26.7)	
Rosuvastatin	835 (26.3)	481 (28.1)	354 (24.2)	
Simvastatin	1284 (40.4)	663 (38.7)	621 (42.4)	
Pravastatin	44 (1.4)	20 (1.2)	24 (1.6)	
Fluvastatin	31 (1.0)	13 (0.8)	18 (1.2)	
Lovastatin	2 (0.1)	2 (0.1)	0 (0)	
Pitavastatin	2 (0.1)	1 (0.1)	1 (0.1)	
Statin treatment intensity (n, %)				<0.001
No statin	207 (6.5)	151 (8.8)	56 (3.8)	
Low	549 (17.3)	286 (16.7)	263 (18.0)	
Moderate	1262 (39.7)	684 (39.9)	578 (39.5)	
High	1160 (36.5)	592 (34.6)	568 (38.8)	
Ezetimibe use (n, %)	1850 (58.2)	908 (53.0)	942 (64.3)	<0.001
PCSK9i use (n, %)	189 (5.9)	99 (5.8)	90 (6.1)	0.776
Study site (n, %)				0.235
The Netherlands	2535 (79.8)	1353 (79.0)	1182 (80.7)	
Norway	643 (20.2)	360 (21.0)	283 (19.3)	

[a] Information on sex was missing in 17 patients.

2.3. Statistical analysis

Continuous baseline characteristics that had non-normal distribution according to Shapiro-Wilk tests are presented as median (25th-75th percentiles). Categorical data are presented as numbers and percentages. Sex differences in continuous baseline characteristics were analyzed with Mann Whitney U tests, whereas categorical variables were analyzed with chi-square tests.

We reported the distribution of on-treatment LDL-C, as well as on the percentage of subjects reaching the treatment target in women and men separately. We studied sex, age, BMI, smoking, hypertension and LDL-C treatment intensity (low, moderate or high intensity statins, ezetimibe, PCSK9 inhibitors) as determinants of reaching LDL-C targets using (multivariable) logistic regression. The multivariable models were adjusted for age, smoking, hypertension, diabetes, BMI, LDL-C before treatment, PCSK9-inhibitor treatment and statin treatment intensity. By including sex*other determinants interaction terms, we studied differences in the contribution of these determinants between women and men. All analyses were stratified according to the presence of CVD.

Data were analyzed using SPSS Statistics, version 25.0 (IBM Corp). All *p*-values are two sided, and values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 3178 patients, 1713 women and 1465 men, with HeFH were analyzed, of whom 80% were treated in the Netherlands and 20% in Norway. Baseline characteristics of the patients are presented in Table 1. Median age was 48 (IQR 34–60) years. The majority (94%) used statin therapy, and more than half (58%) of the patients were treated with ezetimibe. PCSK9 inhibitors were prescribed in a minority of them (5.9%).

3.2. Achievement of LDL-C target levels in patients with and without CVD

In this HeFH population, a minority reached their LDL-C target (22.0% of patients with CVD and 28.9% without CVD). Patients with a history of CVD (OR 0.69, 95%CI 0.52–0.93) and those with high untreated LDL-C levels (OR 0.81 per mmol/l, 95%CI 0.76–0.86) had significantly lower odds of reaching the LDL-C target. In contrast, patients using ezetimibe (OR 1.41, 95%CI 1.15–1.72) and those using PCSK9-inhibitors (OR 6.49, 95%CI 4.57–9.21) had higher odds of reaching the LDL-C target (Table 2).

The percentage of patients on LDL-C target was lower in those with than without CVD (CVD: 22.0% *vs.* non-CVD 28.9%, $p = 0.002$). Mean

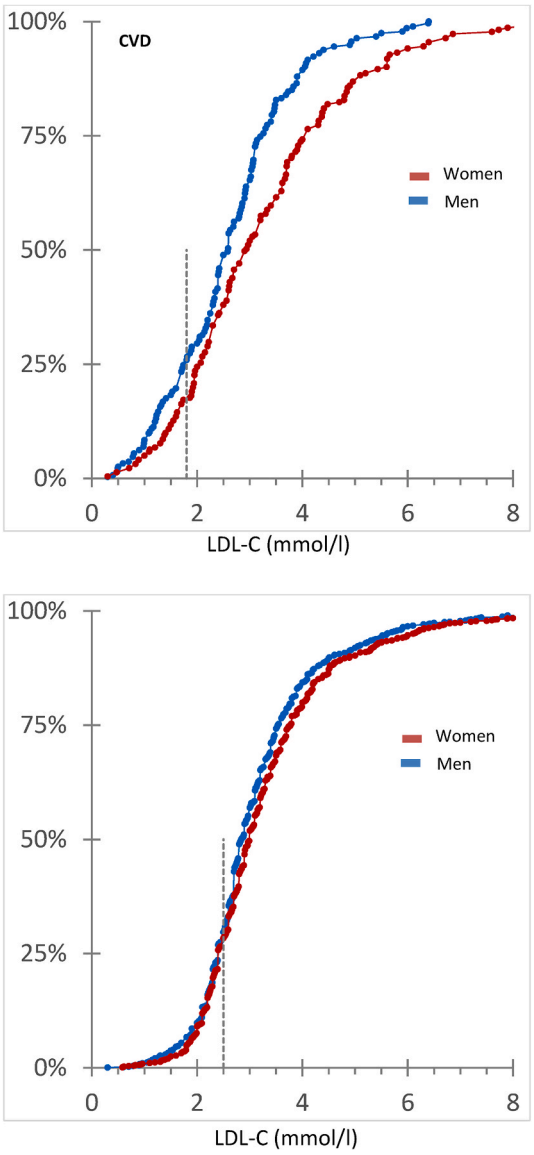

Fig. 1. LDL-C distribution.
(A) LDL-C distribution in FH women and men with CVD, 17.2% of women and 25.8% of men reached LDL-C target. (B) LDL-C distribution in FH women and men without CVD, 28.3% of women and 29.7% of men reached LDL-C target. LDL-C = low density lipoprotein cholesterol, FH = familial hypercholesterolemia.

Table 2
Determinants of reaching LDL-C target in FH patients.

	OR (95%CI)	*p* value
Age (per year)	1.00 (1.01–1.02)	0.155
Women	1.01 (0.83–1.23)	0.906
CVD	0.69 (0.52–0.93)	0.013
Genetic FH	0.87 (0.70–1.09)	0.230
Smoking	0.84 (0.64–1.10)	0.196
BMI (per kg/m^2)	0.99 (0.97–1.01)	0.250
Hypertension	1.30 (1.04–1.62)	0.023
Diabetes	1.41 (0.99–2.02)	0.058
LDL-C before treatment (per 1 mmol/l)	0.81 (0.76–0.86)	<0.001
Ezetimib	1.41 (1.15–1.72)	0.001
PCSK9-inhibitor	6.49 (4.57–9.21)	<0.001
Low intensity statin treatment	-ref-	
Medium intensity statin treatment	1.29 (0.98–1.69)	0.071
High intensity statin treatment	1.20 (0.96–1.50)	0.110
Dutch study site	0.83 (0.69–1.01)	0.060

FH = familial hypercholesterolemia, CVD = cardiovascular disease, LDL-C = low density lipoprotein cholesterol.

Table 3
(A) Sex differences of determinants on reaching LDL-C targets in FH patients with CVD. (B) Sex differences of determinants on reaching LDL-C targets in FH patients without CVD.

A	CVD					
	Women		Men		*p* for interaction	
	Univariate (OR)	Multivariate (OR)[a]	Univariate (OR)	Multivariate (OR)[a]	*p* value univariate	*p* value multivariate
Age (per year)	1.28 (0.15–10.69)	0.96 (0.91–1.02)	0.78 (0.09–6.51)	0.99 (0.94–1.04)	0.837	0.526
Smoking	1.09 (0.58–2.08)	0.86 (0.35–2.10)	0.49 (0.29–0.82)	3.80 (0.98–14.79)	0.127	0.079
Hypertension	1.07 (0.59–1.93)	0.79 (0.26–2.35)	2.52 (1.09–5.82)	4.38 (1.14–16.81)	0.101	0.052
Diabetes		[b]		[b]		–
BMI (per kg/m^2)	1.00 (0.93–1.08)	1.01 (0.91–1.12)	1.06 (0.99–1.13)	1.12 (0.95–1.31)	0.287	0.267
LDL-C before treatment (per 1 mmol/l)	0.72 (0.59–0.87)	0.35 (0.23–0.55)	0.89 (0.70–1.12)	0.64 (0.47–0.86)	0.169	0.020
Ezetimib	3.53 (1.34–9.29)	[b]	14.80 (1.98–110.70)	[b]	0.208	–
PCSK9-inhibitor	36.23 (14.79–88.75)	11.99 (6.03–23.87)	12.11 (5.23–28.02)	32.23 (7.56–137.34)	0.080	0.211
Statin treatment intensity						
Low intensity	-ref-					
Medium intensity	1.23 (0.89–1.69)	2.27 (0.67–7.74)	0.91 (0.55–1.51)	3.24 (0.50–20.90)	0.837	0.749
High intensity	1.40 (1.01–1.92)	1.87 (0.63–5.54)	1.15 (0.71–1.89)	4.89 (0.70–1.33)	0.727	0.368
B	no CVD					
	Women		Men		*p* for interaction	
	Univariate (OR)	Multivariate (OR)[a]	Univariate (OR)	Multivariate (OR)[a]	*p* value univariate	*p* value multivariate
Age (per year)	1.01 (1.00–1.02)	1.01 (0.99–1.02)	1.24 (0.73–2.11)	1.01 (1.00–1.02)	0.277	0.700
Smoking	1.11 (0.92–1.33)	0.67 (0.42–1.06)	1.02 (0.72–1.44)	0.94 (0.60–1.48)	0.168	0.296
Hypertension	1.92 (1.40–2.64)	1.76 (1.14–2.73)	1.38 (1.03–2.64)	1.35 (0.89–2.04)	0.129	0.363
BMI (per kg/m^2)	1.00 (0.97–1.02)	0.96 (0.93–1.00)	1.01 (0.99–1.03)	0.97 (0.94–1.00)	0.514	0.805
Diabetes	2.20 (1.23–3.93)	1.94 (0.82–4.57)	1.63 (0.88–3.01)	0.77 (0.33–1.78)	0.481	0.127
LDL-C before treatment (per 1 mmol/l)	0.78 (0.72–0.86)	0.70 (0.63–0.78)	0.87 (0.82–0.94)	0.83 (0.76–0.91)	0.055	0.013
Ezetimib	1.33 (1.03–1.73)	1.02 (0.73–1.44)	1.63 (1.30–2.05)	1.37 (0.99–1.88)	0.250	0.209
PCSK9-inhibitor	9.10 (4.55–18.21)	11.99 (6.03–23.87)	4.05 (2.29–7.16)	5.23 (2.28–2.93)	0.077	0.078
Statin treatment intensity						
Low intensity	-ref-					
Medium intensity	1.40 (1.13–1.72)	2.13 (1.34–3.38)	1.49 (1.24–1.78)	1.74 (1.16–2.62)	0.663	0.518
High intensity	1.50 (1.21–1.86)	1.95 (1.22–3.12)	1.54 (1.28–1.86)	1.94 (1.25–1.94)	0.842	0.990

CVD = cardiovascular disease, LDL-C = low density lipoprotein cholesterol.
[a] Adjusted for age, smoking, hypertension, diabetes, BMI, LDL-C before treatment, PCSK9-inhibitor treatment, statin treatment intensity.
[b] Too few cases for analyses.

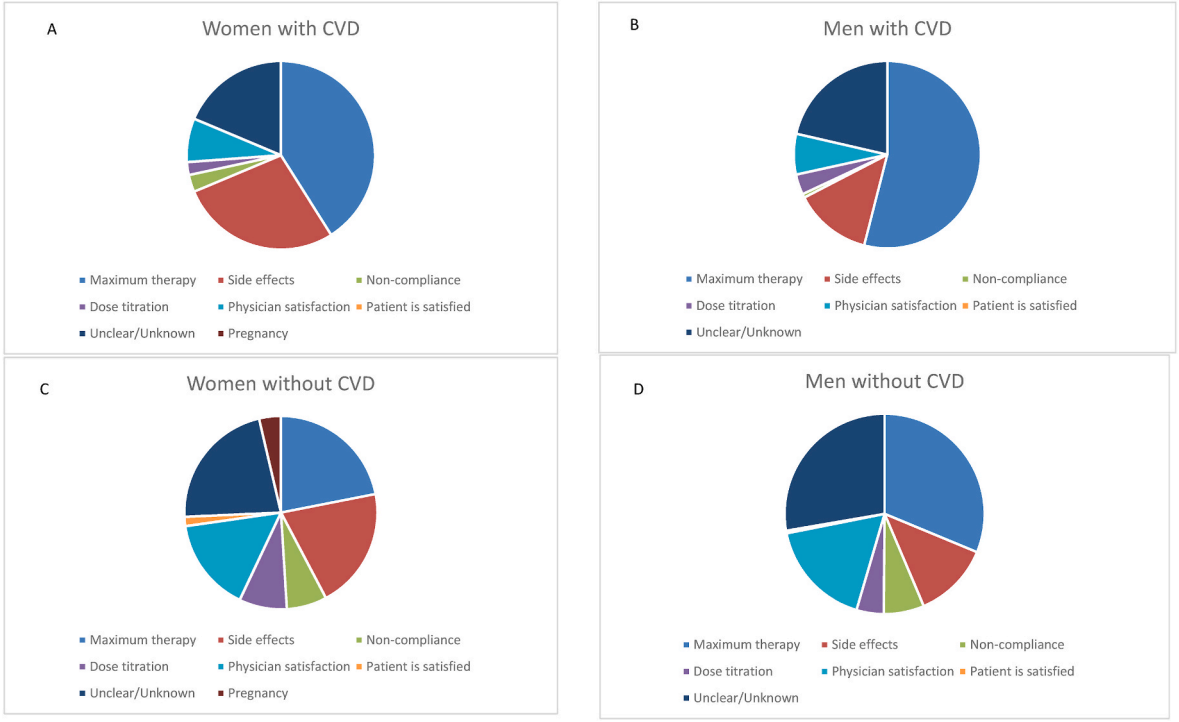

Fig. 2. Reasons for not reaching LDL-C in FH women with CVD (A), FH men with CVD (B), FH women with CVD (C) and FH men without CVD (D).

treated LDL-C in these groups was 2.7 (IQR 1.94–3.67) mmol/L and 2.9 (IQR 2.40–3.70) mmol/L, respectively. In patients without CVD, the use of PCSK9-inhibitors was more strongly associated with reaching the LDL-C target than in those without CVD, after adjustment for pre-treatment LDL-C values (OR 34.24 and 95%CI 17.25–67.96 *vs.* OR 6.47 and 95%CI 4.04–10.36, p for interaction = 0.002) (Supplementary Table 1). Also, patients without CVD were significantly more likely to reach their LDL-C target with high intensity statin treatment than patients with CVD (OR 1.67 and 95%CI 1.26–2.22 per mmol/l *vs.* OR 1.38 and 95%CI 1.14–2.02 per mmol/l, p for interaction <0.001).

3.3. Sex-specific analyses

Over the years, on-treatment LDL-C decreased, meaning that patients are more adequately treated over time. However, we observed that LDL-C level decrease over time is more pronounced in men than in women (Supplementary Fig. 1).

Considering determinants that might cause this, firstly women had a lower prevalence of CVD than men (12.9% *vs.* 18.8%, p<0.001). Moreover, women less often had traditional risk factors, including smoking (13.0% *vs.* 17.0%, p = 0.002), hypertension (22.4% *vs.* 26.4%, p = 0.008) and diabetes (4.0% *vs.* 5.7%, p = 0.031). Median LDL-C before treatment was higher in women than in men (6.2 *vs.* 6.0 mmol/l, p = 0.005) (Table 1).

Women less often received high and low intensity statin treatment, but more often received medium intensity than men (p<0.001). The use of ezetimibe was also lower in women (53.0% *vs.* 64.3%, p<0.001). Treatment with PCSK9 inhibitors was quite low in this population, but similar in women and men (5.8% *vs.* 6.1%, p = 0.78) (Table 1).

In patients without and with CVD, median LDL-C on-treatment levels were significantly higher in women than in men (without CVD 3.0 *vs.* 2.8 mmol/l, p<0.001 and with CVD 2.9 *vs.* 2.6 mmol/l, p<0.001). The overall OR for treatment target attainment was 1.01 (95%CI 0.83–1.23) for women compared to men.

In patients with CVD, 17.2% of women and 25.8% of men reached LDL-C target and, in patients without CVD, 28.3% of women and 29.7% of men reached LDL-C target (Fig. 1A and B). The multivariably adjusted odds for treatment target attainment was OR 1.08 (95%CI 0.86–1.36) for women with CVD compared to men; and OR 0.86 (95%C 0.49–1.53) for women without CVD compared to men (p-for-interaction = 0.47) (Supplementary Table 1). Higher LDL-C before treatment was significantly associated with not reaching LDL-C targets in women and men, regardless of CVD status (CVD: women OR 0.35 and 95%CI 0.23–0.55 per mmol/l, men OR 0.64 and 95%CI 0.47–0.86 per mmol/l, no CVD: women OR 0.70 and 95%CI 0.63–0.78 per mmol/l, men OR 0.83 and 95%CI 0.76–0.91 per mmol/l) (Table 3A and B). However, the relation between higher untreated LDL-C level and not reaching the treatment target was significantly stronger in women than men (CVD: p for interaction 0.020, no CVD: p for interaction 0.013).

3.4. Reasons for not reaching LDL-C target

The reasons for not reaching their LDL-C target were collected for the 1353 women and 1182 men enrolled in the Netherlands (Fig. 2, Supplementary Table 2). In 29.5% of patients not on target, the reason was that maximum LLT was already provided. Of these patients, 84.4% used high intensity LLT, 99.2% used ezetimibe and 9.0% used PCSK9 inhibition. The second most important reason was side effects (17.2%), followed by physician satisfaction with LLT (14.9%) and patients related reasons such as non-compliance (5.8%). The administration of maximum dose of LLT was more often reported to be a reason for not reaching LDL-C targets in patients with CVD and men (15.6% of women and 22.0% of men without CVD and 27.9% of women and 33.8% of men with CVD). Physicians were more often satisfied with LLT in patients without CVD compared to those with CVD, without relevant differences between women and men (11.2% of women and 12.2% of men without CVD and 5.1% of women and 4.4% of men with CVD) (Fig. 2A–D). Regardless of CVD status, women were more likely than men to not reach their LDL-C target due to side effects (14.5% of women and 8.7% of men without CVD and 18.8% of women and 8.4% of men with CVD).

4. Discussion

Our study shows that only a minority of FH patients (27.7%) in the Netherlands and Norway reach their guideline recommended LDL-C treatment target of <2.5 mmol/L for patients without CVD and <1.8 mmol/L for patients with CVD. The main determinants associated with reaching the LDL-C target were a lower LDL-C level before treatment and treatment with ezetimibe and PCSK9 inhibitor. Moreover, sex-specific analyses showed that women have higher LDL-C levels before treatment and high pre-treatment LDL-C was a more significant determinant in women than in men. In addition, women less often receive (high-intensity) statins and ezetimibe. The most common reason for not attaining target was maximum dose of LLT being administered. Furthermore, side effects were more often reported as a reason for not attaining target in women than in men.

4.1. Treatment targets in FH

Despite the availability of low cost and effective LLT in clinical practice, achievement of LDL-C targets in these two countries was low [12,13,17–19]. Compared to a previous large Dutch study assessing LDL-C treatment targets, which was conducted a decade ago, the number of FH patients on-treatment target only slightly increased from 21% to 28% [20]. This may be partly caused by the lowering of the LDL-C target for patients with CVD to <1.8 mmol/L in the 2011 ESC guidelines, since 31.1% of all patients (with and without CVD) reached the former LDL-C target of <2.5 mmol/l in this study [21].

In our study, the most common reasons for not being on LDL-C target were use of maximum LLT Notably, maximum LLT was defined as oral LLT; only few patients used PCSK9-inhibitors because these were only recently available in the period when we conducted our study. Other reasons for not reaching the LDL-C target were patient-related factors (e.g. side effects) and also physician satisfaction.with LLT Previous studies reported that physician satisfaction was an important reason for not attaining treatment target, meaning that there has been little improvement concerning this topic [20,22]. An important clinical implication of this study is that physicians awareness of guidelines and appropriate treatment according to the guidelines should be improved.

4.2. Lipid lowering treatment in women and men with FH

Women with FH are less likely to reach their LDL-C targets and are less often treated with the guideline-recommended high intensity statin therapy than men [23]. Although we did not observe a difference in the odds ratio of attaining treatment target between men and women, we did find that women less often received (high intensity) statins and ezetimibe.

The CASCADE-FH registry analyzed 3167 HeFH patients (61% women) in the USA and showed that women were less likely than men to achieve treated LDL-C <2.5 mmol/l (OR 0.68, 95% CI, 0.57–0.82). Women with FH were also less often treated with statins and did not receive high-intensity statin doses as often as men [3,24]. Moreover, similar to our study, in the CASCADE-FH registry, the pre-treatment LDL-C level was higher in women than in men.

Recently the Familial Hypercholesterolaemia Studies Collaboration (FHSC) study including 42,167 adult FH patients (54% women) from 56 countries, also showed higher LDL-C levels in women compared to men both treated and untreated with LLT (*vs.* 4.18 mmol/l, 5.50 *vs.* 5.35 mmol/l mmol/l, p<0.001). It was reported that men more often used the highest statin doses and more often used non-statin LLT, such as ezetimibe or PCSK9 inhibitors. Interestingly, even after adjusting for age,

baseline characteristics, and type of LLT the odds ratios of having LDL-C <1.8 mmol/L were lower for women than for men (OR 0.63, 95% CI 0.48–0.82; $p = 0.0007$) [5]. This implies that unmeasured factors such as differences in prescription and patient related factors such as side effects and non-adherence play an important role [6,7]. However, in this study the odds ratios were not adjusted for pre-treatment LDL-C.

Women had higher on-treatment LDL-C levels, mainly because they had higher pre-treatment levels, in combination with the fact that they less often received statin treatment at the highest available dose. Although if FH remains untreated, men have a higher absolute risk for developing atherosclerotic CVD than women (50% at the age of 50 years), still 30% of the women will develop atherosclerotic CVD at 60 years if they are not adequately treated with lipid lowering therapies [25–27]. Moreover, a previous study has shown that women with FH have a higher relative mortality rate when compared to healthy controls than men with FH at a young age group. Between 20 and 29 years old the standardized mortality ratio for women with FH was 125 (95%CI 15–451) and of men 48 (95%CI 18–105) [28]. In addition, from birth until adolescence, girls with FH have already higher LDL-C levels than boys with FH [29]. Lastly, women are more likely to have interruption in their LLT during their reproductive years as most LLT is contraindicated during pregnancy. Pregnancy leads to a temporary rise in lipid levels, which is relatively similar to non-FH pregnant women, but is larger in absolute numbers because of the higher baseline levels in FH women due to the discontinuation of cholesterol-lowering agents during pregnancy [30,31]. This interruption of therapy often leads to years of statin missing.

In previous studies, the reasons for not reaching LDL-C targets were not specified. We demonstrated that the main reason for this was maximum use of LLT, followed by side effects and physician satisfaction. In line with our findings, women more often report statin-related side-effects compared to men [24,32]. However, taking into account the n-of-1 studies such as the SAMSON study and StatinWISE, it is likely that most of the statin-related side effects can be ascribed to “nocebo” effects, but is not clear whether this nocebo effect is stronger in women than in men [33,34]. However, in placebo controlled-randomized clinical statin trials, women also reported side-effects in the placebo arm more often than men [35]. Also, a previous study showed that women more often than men reported that their physician did not provide them information about their risk for heart disease and its relation to cholesterol levels. Moreover, women were more often dissatisfied with their physicians explanation about cholesterol treatment [32]. As statins are very effective in decreasing cardiovascular risk, are safe for both men and women and have low costs, it is important that health care providers take the time to inform especially women about the importance of statin treatment for cardiovascular risk prevention and provide reassurance about the safety of statins.

4.3. Strengths and limitations

We have examined a large multinational population of FH patients. Although previous studies in FH patients have reported a sex difference in intensity of statin therapy and fewer women on LDL-C treatment goals, we are the first to assess what are the underlying reasons why women are undertreated which can be very useful information in order to improve healthcare in women with FH.

A limitation is that this study was predominantly performed just before until right after the introduction of PCSK9-inhibitors and were not widely available at the time of our study, reflected in the lower number of patients using these drugs [36]. Therefore, the percentage of FH patients reaching target levels might currently be higher.

In conclusion, in our study only a minority of the FH patients reached their LDL-C target. The main determinants associated with reaching the LDL-C target were a lower LDL-C before treatment and treatment with a PCSK9 inhibitor. Women had higher LDL-C before treatment, were less likely to be treated with (high-intensity) statins or ezetimibe, and reported to have more side effects than men. Our study suggests that extra efforts have to be made to provide women and men with reliable information on the safety of statins and their long-term effects on CVD risk reduction. If statin treatment is insufficient, alternative LLT such as ezetimibe or PCSK9-inhibitors should be considered.

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CRediT authorship contribution statement

M.M. Schreuder: Data curation, Writing – original draft, Investigation, Software, Validation, Visualization. **S. Hamkour:** Data curation, Writing – original draft, Investigation. **K.E. Siegers:** Writing – review & editing. **K.B. Holven:** Conceptualization, Methodology, Supervision. **A. K. Johansen:** Writing – review & editing. **M.A. van de Ree:** Writing – review & editing. **B. Imholz:** Writing – review & editing. **E. Boersma:** Writing – review & editing. **L. Louters:** Data curation, Writing – original draft, Investigation. **M.P. Bogsrud:** Writing – review & editing. **K. Retterstøl:** Writing – review & editing. **F.L.J. Visseren:** Conceptualization, Methodology. **J.E. Roeters van Lennep:** Conceptualization, Methodology, Supervision. **C. Koopal:** Conceptualization, Methodology, Supervision.

Declaration of competing competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.03.022.

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