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Sex differences in efficacy and safety of PCSK9 monoclonal antibodies: A real-world registry

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ABSTRACT

Background and aims: Proprotein convertase subtilisin/kexin 9 monoclonal antibodies (PCSK9 mAbs) reduce low-density lipoprotein (LDL-c) with a favourable safety profile. Available data from PCSK9 antibody trials suggest LDL-c reduction is lower in women compared to men. Data in real-world setting is scarce. The aim of this study was to assess sex differences in efficacy and safety of PCSK9 antibodies in clinical care.

Methods: All patients starting with evolocumab or alirocumab in our lipid clinic were included in a prospective registry. We collected clinical information, including baseline and follow-up mean LDL-C levels after initiation of PCSK9 mAbs treatment. In addition, side effects and PCSK9 mAbs discontinuation were recorded.

Results: We analysed 436 patients (209 women), mean age 58 ± 11 years. Women had higher baseline LDL-c levels compared to men (4.7 ± 1.6 mmol/L *vs* 4.1 ± 1.4 mmol/L, $p < 0.01$). PCSK9 mAbs resulted in less relative LDL-c reduction in women compared to men (50% *vs* 61% $p < 0.01$), but equal absolute LDL-c reduction (respectively 2.3 ± 1.3 mmol/L *vs* 2.5 ± 1.1 mmol/L, $p = 0.087$). Women less often reached LDL-c target levels than men (50% *vs* 72%). No sex differences were observed in reporting of side effects (women 32% *vs* men 27% $p = 0.26$) or PCSK9 mAbs discontinuation (women 13% *vs* men 10%, $p = 0.46$).

Conclusions: In clinical practice, PCSK9 mAbs are less effective in reducing LDL-c levels in women compared to men and equally safe, implying the importance of sex differences in PCSK9 metabolism.

1. Introduction

Over time, LDL-cholesterol (LDL-c) is one of the main modifiable cardiovascular risk factors [1,2]. In addition to improving lifestyle, LDL-c can be lowered with lipid-lowering therapy (LLT), such as statins and ezetimibe. Since 2016, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors monoclonal antibodies (mAbs) have been developed as a new class of LLT. Previous trials showed that the PCSK9 mAbs evolocumab and alirocumab lower LDL-c levels with an average LDL-c reduction of 55–60%, leading to an improvement in cardiovascular outcomes [3–5]. Moreover, both PCSK9 mAbs have a favourable safety profile [3,4]. Sex-specific analysis of clinical trials showed that PCSK9 mAbs in women experienced slightly less reduction of LDL-c than men [6–8]. In addition, more side effects and discontinuation were reported in women [6,9]. In both the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY OUTCOMES (the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, no sex differences were observed in the association between PCSK9 mAbs and cardiovascular endpoints [6,9].

Some recent real-world studies reported that women showed less LDL-c reduction [10–14], consequently had less LDL-c target level achievement [12,14]. In contrast, other real-world studies found no differences in LDL-c reduction [15,16] and mentioned comparable side-effects in both sexes [12]. These previous real-world studies, have limitations as they consist of a small population, have a short follow-up, and an unbalanced sex distribution. Therefore, we aim to investigate sex differences in efficacy and safety of PCSK9 mAbs of women and men in a clinical real-world setting using a large registry.

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2. Patients and methods

2.1. Patient inclusion and registry

We have previously described in- and exclusion criteria of our registry [17]. In short, all consecutive patients ≥18 years who started a PCSK9 inhibitor at the Erasmus MC university hospital outpatient lipid clinic in Rotterdam, the Netherlands, as part of clinical care, were registered in an open-cohort prospective registry. According to the Dutch reimbursement criteria, patients qualify for reimbursement of a PCSK9 inhibitor when they fulfil the following requirements: 1) LDL-c target level is not reached with maximum tolerated LLT and 2) the patient is at very high risk for cardiovascular disease. Patients are considered very high risk in case of having: familial hypercholesterolemia (FH) (with or without atherosclerotic cardiovascular disease (ASCVD)), a history of two or more cardiovascular events, diabetes mellitus type 2 and a cardiovascular event, or a history of one or more cardiovascular event and a statin intolerance. FH diagnosis is based on the Dutch Lipid Clinic Network (DLCN) score or the presence of a pathogenic mutation in the *LDLR*, *APOB*, or *PCSK9* gene. Statin intolerance is defined as having documented side-effects for ≥3 different types of statins. For patients without history of ASCVD, the LDL-c target is < 2.5 mmol/L and in patients with a history of ASCVD <1.8 mmol/L according to the Dutch guideline [18].

For the current study, patients were excluded if they had: 1) participated in a PCSK9 inhibitor trial, 2) homozygous FH, or 3) inclisiran as PCSK9 inhibitor.

Patients were prescribed alirocumab 75 mg/2 weeks subcutaneously, alirocumab 150 mg/2 weeks subcutaneously, or evolocumab 140 mg/2 weeks subcutaneously.

Index date was the first PCSK9 mAb injection, which occurred after instructions and with supervision of a trained healthcare professional. At baseline and at every follow-up visit, blood measurements (total cholesterol, LDL-c, apolipoprotein B, HDL-cholesterol (HDL-c), triglycerides, and glucose), change in LLT, side-effects, and general information (e.g. age, weight, height, blood pressure, ASCVD-events) were recorded. At baseline, descriptive variables, such as FH diagnosis and ASCVD presence, were also noted.

Menopausal status was based on clinical information on surgical ovariectomy or age. Women <45 years without surgical ovariectomy were defined as premenopausal and women >55 years were considered as postmenopausal. Women between 45 and 55 years of age were classified as unknown menopausal status unless history of ovariectomy was known.

Statin use was defined as: high intensity statin (rosuvastatin ≥20 mg, atorvastatin ≥40 mg, simvastatin 80 mg), moderate intensity statin (rosuvastatin 5 to <20 mg, atorvastatin 10 to <40 mg, simvastatin 20 to ≤40 mg, pravastatin ≥40 mg, fluvastatin ≥80 mg), and low intensity statin (rosuvastatin ≤2.5 mg, simvastatin <20 mg, fluvastatin <80 mg, pravastatin <40 mg). Statin intolerance is defined as reporting severe side effects of at least 3 different statins. Hypo- or non-responders were defined as having an LDL-c decrease ≤25% and hyper-responders as having an LDL-c decrease >75% after 6 months of PCSK9 inhibitor use.

In addition, for the efficacy analyses, patients without lipid levels available at ≥6 months were excluded, resulting in 390 patients at 6 months, 296 patients at 12 months, and 155 patients at 24 months follow-up.

This study was conducted in accordance with the 1975 Declaration of Helsinki. According to the Medical Ethical Research Committee (METC), this study was not subject to the medical research involving Human Subjects Act and received a waiver (MEC-2016-698). All patients gave informed consent for use of their clinical data.

2.2. Statistical analyses

Data cleaning and analyses were performed in SPSS version 28.0 and R version 4.2.1. Categorical data are shown as count (%) and continuous data as mean and standard deviation (SD) or median and interquartile range (25th percentile; 75th percentile) depending on the distribution. Data was stratified by sex and differences were assessed with Chi-squared test or Fischer's exact test and two-sided t-tests or Mann-Whitney U tests. LDL-c was assessed at 6, 12 and 24 months of follow-up. Stability of LDL-c levels and LDL-c reduction over time were assessed with the ANOVA or Friedman test depending on the distribution. For assessing influencing factors on percentage LDL-c reduction and side-effects reported, univariate and multivariable linear and logistic regression analysis was performed. A *p*-value of 0.05 was considered significant.

Main outcomes were the comparison of percentage LDL-c change compared to pre-PCSK9 mAbs levels and reported side-effects between women and men at 6 months. Secondary outcomes were comparisons of absolute and percentage change in LDL-c reduction over time, other blood measurements (e.g. total cholesterol, triglycerides, glucose, liver tests), specific side effects, and discontinuation between women and men.

3. Results

A total of 436 patients of whom 209 (48%) women, mean age 58 ± 11 years, started either with evolocumab (47%) or alirocumab (53%) in addition to maximal tolerated LLT. The baseline characteristics of the patients are presented stratified by sex in Table 1.

Of all patients, 64% had a history of ASCVD, mainly coronary artery disease (93%). ASCVD was less often diagnosed in women than men (57% *vs* 71%, $p = 0.003$). The majority (71%) of the patients were diagnosed with FH. More women than men had a diagnosis of FH (78% *vs* 65%, $p = 0.002$).

An equal number of women and men (44% and 48%, $p = 0.41$) used a statin and ezetimibe as co-LLT, of whom the majority (58%) were treated with high-intensity statin therapy, which was equal for women and men (55% and 59%, $p = 0.68$). There was no difference in the prescription of type of PCSK9 mAb between women and men.

At baseline, women had a higher mean total cholesterol level than men; 6.7 ± 1.7 mmol/L *vs* 5.8 ± 1.5 mmol/L ($p < 0.001$), a higher LDL-c 4.7 ± 1.6 mmol/L *vs* 4.1 ± 1.4 mmol/L ($p < 0.001$), and ApoB 1.4 ± 0.4 g/L *vs* 1.3 ± 0.3 g/L ($p = 0.026$).

3.1. Efficacy

After 6 months, addition of PCSK9 mAb therapy showed a mean LDL-c decrease of 55% ± 22% in the total population (Table 2A). Women had less LDL-c decrease than men; 50% ± 25% *vs* 61% ± 18% ($p < 0.001$). LDL-c decrease remained stable over time until 24 months in both sexes ($p = 0.18$, Fig. 1).

LDL-c reduction in women with evolocumab was lower than in men (48% *vs* 62%, $p < 0.001$). In the group who received alirocumab, a similar sex difference in LDL-c reduction was seen (51% *vs* 60%, $p = 0.003$). Overall, no differences were seen in average LDL-c reduction between alirocumab and evolocumab.

Women with FH showed less LDL-c decrease compared to men with FH (48% *vs* 61%, $p < 0.001$). LDL-c decrease in women and men without FH showed a similar significant difference (55% *vs* 62%, $p = 0.015$). Within one sex, no significant differences in LDL-c decrease were observed (women with *vs* without FH $p = 0.063$; men with *vs* without FH $p = 0.64$). In women with CVD, less LDL-c reduction was observed in comparison to men with CVD (50% *vs* 63%, $p < 0.001$).

At 6-month follow-up, premenopausal women (n = 21) were compared to postmenopausal women (n = 131), showing similar percentage and absolute LDL-c reduction (percentage change −55% *vs* −53% $p = 0.89$ and absolute change −2.4 mmol/L (−3.4; −1.4) *vs* −2.3 mmol/L (−2.9; −1.8) $p = 0.53$, respectively).

After initiation of PCSK9 mAb therapy, mean LDL-c levels remained

Table 1
General characteristics of patients starting PCSK9 inhibitors at baseline N = 436.

	Total n = 436	Women n = 209 (48%)	Men n = 227 (52%)	*p*
Age (years) mean ± SD	58 ± 11	59 ± 11	57 ± 10	0.068
Postmenopausal[b]	NA	144 (69%)	NA	NA
History of ASCVD, n (%)	280 (64%)	119 (57%)	161 (71%)	**0.003**
Cardiovascular risk factors, n (%)				
Ever smoker	225 (52%)	100 (48%)	125 (55%)	0.17
Current smoker	49 (11%)	17 (8%)	32 (14%)	0.069
BMI median	27.2 (24.4; 30.0)	27.0 (24.1; 30.0)	27.3 (24.8; 30.1)	0.53[a]
History of hypertension	202 (47%)	98 (47%)	104 (46%)	>0.9
DM type 1 or 2	67 (15%)	35 (17%)	32 (14%)	0.53
FH	310 (71%)	164 (78%)	146 (65%)	**0.002**
Lipid lowering therapy, n (%)				
Statin use	202 (46%)	92 (44%)	110 (48%)	0.41
High intensity	118 (58%)	51 (55%)	67 (59%)	0.68
Moderate intensity	70 (34%)	33 (36%)	37 (33%)	0.75
Low intensity	17 (8%)	8 (9%)	9 (8%)	>0.9[a]
Ezetimibe	436 (100%)	209 (100%)	227 (100%)	NA
Prescribed PCSK9 inhibitor, n (%)				0.12[a]
Evolocumab 140 mg/2wks sc	207 (47%)	89 (43%)	118 (52%)	
Alirocumab 150 mg/2wks sc	220 (51%)	116 (56%)	104 (46%)	
Alirocumab 75 mg/2 wks sc	9 (2%)	4 (2%)	5 (2%)	
Baseline lipid values, mean ± SD or median (IQR)				
Total cholesterol (mmol/L)	6.2 ± 1.7	6.7 ± 1.7	5.8 ± 1.5	< **0.001**
LDL cholesterol (mmol/L)	4.4 ± 1.5	4.7 ± 1.6	4.1 ± 1.4	< **0.001**
Apo B (g/L)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	**0.026**
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.5 ± 0.4	1.2 ± 0.3	< **0.001**
Triglyceride (mmol/L)	1.6 (1.2; 2.3)	1.6 (1.1; 2.2)	1.6 (1.2; 2.4)	0.26[a]
Glucose (mmol/L)	5.7 (5.2; 6.4)	5.7 (5.2; 6.2)	5.8 (5.2; 6.5)	0.18[a]

LDL = low density lipoprotein; HDL = high density lipoprotein; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; DM = diabetes mellitus; FH = familial hypercholesterolemia; LLT = lipid lowering therapy.

[a] Fischer's exact test or Mann Whitney *U* test.

[b] Menopausal status available in 169 women (81%).

higher in women compared to men; LDL-c 2.4 ± 1.4 mmol/L *vs* 1.6 ± 1.0 mmol/L ($p < 0.001$) after 6-month follow-up. Mean LDL-c levels remained stable over time in women ($p = 0.42$) and in men ($p = 0.30$) (Fig. 1).

In total, 61% of the patients were on-target after addition of PCSK9 mAb therapy, women significantly less often than men (50% *vs* 72%, $p < 0.001$).

Univariate determinants of percentage LDL-cholesterol reduction are shown in Table 3A. In a multivariable model, only two determinants remained significantly associated with percentage LDL-c change: female sex (β 12.0, $p = 0.001$) and concomitant use of high-intensity statin (β −13.7, $p < 0.001$).

No sex differences were observed in achievement of treatment goal in patients without ASCVD (LDL-c ≤2.5 mmol/L). However, women with ASCVD less often reached treatment target of LDL-c ≤1.8 mmol/L than men (46% *vs* 74%, $p < 0.001$). One hundred eighteen patients with ASCVD (48%) reached LDL-c levels ≤1.4 mmol/L, with again a lower percentage of women than men achieving this target (32% *vs* 59%, $p < 0.001$).

Women were more hypo- or non-responders having <25% LDL-C decrease. On the other hand, men more often were hyper-responder and had a >75% LDL-c decrease following PCSK9 mAbs (Table 2B).

3.2. Adherence and side effects

All patients were able to use the auto-injector without any problems. Remembering the unusual interval of administration of the PCSK9 mAb every two weeks was mainly implemented through reminders on mobile phone and calendars by patients themselves. All patients confirmed that they were fully adherent in using PCSK9 mAb therapy.

After 6 months, one or more side effects of PCSK9 mAbs were reported by an equal number of women and men (32% *vs* 27%, $p = 0.26$, Table 2B). Women and men with statin intolerance had more side effects of PCSK9 mAbs compared to patients with statin therapy (36% *vs* 19%, $p = 0.005$). In logistic regression, statin intolerance was significantly associated to reporting of any side effect (OR 1.7 (95% CI 1.1–2.7), $p = 0.014$, Table 3B).

In total, 51 (12%) patients discontinued PCSK9 mAb treatment, mainly because of side effects (Table 2B). This was similar in women and men (13% *vs* 10%, $p = 0.46$).

4. Discussion

We demonstrated that in clinical setting addition of PCSK9 mAbs to maximum tolerated LLT resulted in less relative LDL-c reduction in women than in men at 6 months of follow-up. Absolute LDL-c decrease was similar in women and men, however, women had higher baseline LDL-c compared to men. Women were less likely than men to reach LDL-c treatment targets. We observed no sex-differences in safety of the use of PCSK9 mAbs as reporting of side effects and discontinuation of treatment was similar for women and men. However, women and men with statin intolerance did experience more side effects.

4.1. Sex differences in efficacy of PCSK9 mAbs

In the FOURIER, the ODYSSEY OUTCOMES, and a pooled analysis of 10 ODYSSEY phase 3 trials, the reduction of cardiovascular endpoints associated with PCSK9 mAbs was similar between the sexes [6,7,9]. In several clinical trials, female participants had a lower relative response to PCSK9 mAbs in LDL-c reduction compared to male participants [6–8]. As patients participating in clinical trials may fail to reflect the entire population who will use a drug in daily practice amongst others because of specific inclusion and exclusion criteria, "real-world data" are a valuable additional source to evaluate efficacy and safety in clinical practice [19]. In addition, women are often underrepresented in cardiovascular randomized controlled trials [20–22]. For example, also in the aforementioned FOURIER and ODYSSEY OUTCOMES trials, approximately 75% of participants were men [6,23]. In real-world studies, similar underrepresentation has been reported, as women are more often undertreated and are prescribed PCSK9 mAbs less often than

Table 2
(A) Efficacy of PCSK9 mAbs after 6 months of follow-up 2. (B) Reported side-effects and discontinuation of PCSK9 mAbs after 6 months of follow-up.

A	Total n = 390	Women n = 185 (47%)	Men n = 205 (53%)	*p*
PCSK9 inhibitors, n (%)				0.17[a]
Evolocumab 140 mg/2wks sc	183 (47%)	78 (42%)	105 (51%)	
Alirocumab 150 mg/2wks sc	198 (51%)	103 (56%)	95 (46%)	
Alirocumab 75 mg/2wks sc	9 (2%)	4 (2%)	5 (2%)	
Lipid levels, mean ± SD or median (IQR)				
Total cholesterol (mmol/L)	3.8 ± 1.4	4.3 ± 1.5	3.3 ± 1.1	< **0.001**
LDL cholesterol (mmol/L)	2.0 ± 1.3	2.4 ± 1.4	1.6 ± 1.0	< **0.001**
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.6 ± 0.4	1.3 ± 0.3	< **0.001**
Apo B (g/L)	0.7 ± 0.3	0.8 ± 0.4	0.6 ± 0.3	< **0.001**
Triglyceride (mmol/L)	1.4 (1.0; 2.0)	1.4 (0.9; 2.0)	1.4 (1.0; 2.1)	0.24[a]
LDL-c percentage decrease (% mean ± SD)	55 ± 22	50 ± 25	61 ± 18	< **0.001**
Hypo or non-responders	31 (8%)	24 (13%)	7 (3%)	< **0.001**[a]
Hyper responders	63 (16%)	22 (12%)	41 (20%)	**0.044**
LDL-c absolute decrease (absolute mean ± SD)	2.4 ± 1.2	2.3 ± 1.3	2.5 ± 1.1	0.087
LDL-c by treatment goal, n (%)	239 (61%)	92 (50%)	147 (72%)	< **0.001**
LDL-c ≤ 2.5 mmol/L (without ASCVD), n (%)	85 (60%)	44 (55%)	41 (67%)	0.20
LDL-c ≤ 1.8 mmol/L (with ASCVD), n (%)	154 (62%)	48 (46%)	106 (74%)	< **0.001**
LDL-c ≤ 1.4 mmol/L (with ASCVD), n (%)	118 (48%)	33 (32%)	85 (59%)	< **0.001**
FH with and without ASCVD (≤1.8 mmol/L or 2.5), n (%)	165 (58%)	73 (49%)	92 (69%)	**0.001**

B	Total n = 436	Women n = 209(48%)	Men n = 227(52%)	*p*
Side effects of PCSK9 inhibitors, n (%)				
Side effects	128 (29%)	67 (32%)	61 (27%)	0.26
Flu like symptoms	37 (8%)	13 (6%)	24 (11%)	0.15
Neurological symptoms	12 (3%)	8 (4%)	4 (2%)	0.25[a]
Gastrointestinal symptoms	12 (3%)	8 (4%)	4 (2%)	0.25[a]
Headache	13 (3%)	7 (3%)	6 (3%)	0.78[a]
Psychological symptoms	2 (0.5%)	2 (1%)	0	0.23[a]
Other	48 (11%)	27 (13%)	21 (9%)	0.29
Injection site reaction	37 (8%)	19 (9%)	18 (8%)	0.79
Discontinuation of PCSK9 mAbs, n (%)	51 (12%)	28 (13%)	23 (10%)	0.46
Discontinuation due to side effects	43 (10%)	22 (11%)	21 (9%)	0.27[a]

ASCVD: atherosclerotic cardiovascular disease. Hypo or non-responders were defined as having a LDL-cholesterol decrease of ≤25% and hyper-responders as having a LDL-c decrease >75%.
[a] Fischer's exact test.

men [24–27]. We found less relative LDL-c reduction in women compared to men, which has been previously observed in some observational studies [10–14] but not in others [15,16,28].

Our results are comparable to a recent Canadian real-world study of 259 PCSK9 mAb users, 99 (38%) women [14]. The Spanish LIPID-REAL registry of 652 mAb users, of whom 161 (25%) women, also showed that LDL-c reduction was lower in women (47% *vs* 57%; $p = 0.0002$) [12]. The lower LDL-c reduction in women was observed both for evolocumab and alirocumab users, but especially for women who received the lower dose of 75 mg/2wks sc alirocumab. In the LIPID-REAL study, the majority of the alirocumab users (89% for women and 93% for men) used this dose while this was in our study only 2% for both women and men. Similar to our study, LDL-c target was less often reached by women compared to men [12].

An explanation for the unequal relative LDL-c reduction between sexes could be the sex difference in circulating levels of PCSK9, suggesting that the effect of PCSK9 inhibitors may have different impacts according to sex [29,30]. Several studies, including the IMPROVE study; a large-scale multicentre study encompassing several European countries with the centralized measurement of PCSK9 levels, showed that women have higher circulating PCSK9 concentrations than men [29]. Since PCSK9 levels fluctuate in the menstrual cycle and with menopause status, PCSK9 levels are presumed to be influenced by oestrogen, possibly through G-protein coupled oestrogen receptor (GPER) activation on hepatocytes [30,31]. Due to the decrease of oestrogen, especially postmenopausal, women have higher PCSK9 concentrations resulting in higher LDL-c levels [32]. In our study, 71% of the women were postmenopausal, which could explain the difference in LDL-c reduction compared to men. However, we did not observe a difference in LDL-c decrease between pre- and postmenopausal women, similar to findings of the aforementioned Canadian study [14]. However, we also had an unequal distribution of menopause status and were not able to confirm menopausal status in a substantial number of women in our population.

If one focusses on absolute LDL-c decrease, the lesser response of PCSK9 mAbs is masked. Women had higher baseline LDL-c levels compared to men, which was also observed in other cohorts [12,14]. As in other observational studies, also we found that the absolute LDL-c reduction was similar in women and men [14]. However, similar to previous studies, we observed that women less often reach LDL-c treatment targets.

All in all, the reduced LDL-c response to PCSK9 mAbs is clinically relevant.

4.2. *Sex differences in safety of PCSK9 mAbs*

Randomized controlled trials studying PCSK9 mAbs showed a very favourable safety profile [3,4,33]. Both the FOURIER and ODYSSEY OUTCOMES trials observed that women experienced more side effects attributed to PCSK9 inhibitors [6,9]. However, in the placebo arm of the FOURIER trial, women also reported more side effects compared to men [6]. In the pooled analysis of the 10 ODYSSEY phase 3 trials, no sex differences were observed in the safety profile [7]. In the FOURIER, women more often discontinued PCSK9 mAbs treatment [6].

To our knowledge, this is the first study of real-world data to perform elaborate sex-specific analyses on safety outcomes. Our data did not show sex differences in reporting of side effects to PCSK9 mAbs, which was also seen in the LIPID-REAL registry [12]. However, they did not specify side effects per sex. Women and men reported similar number and type of side effects. Moreover, discontinuation of PCSK9 mAbs was also similar for women and men. However, both women and men with

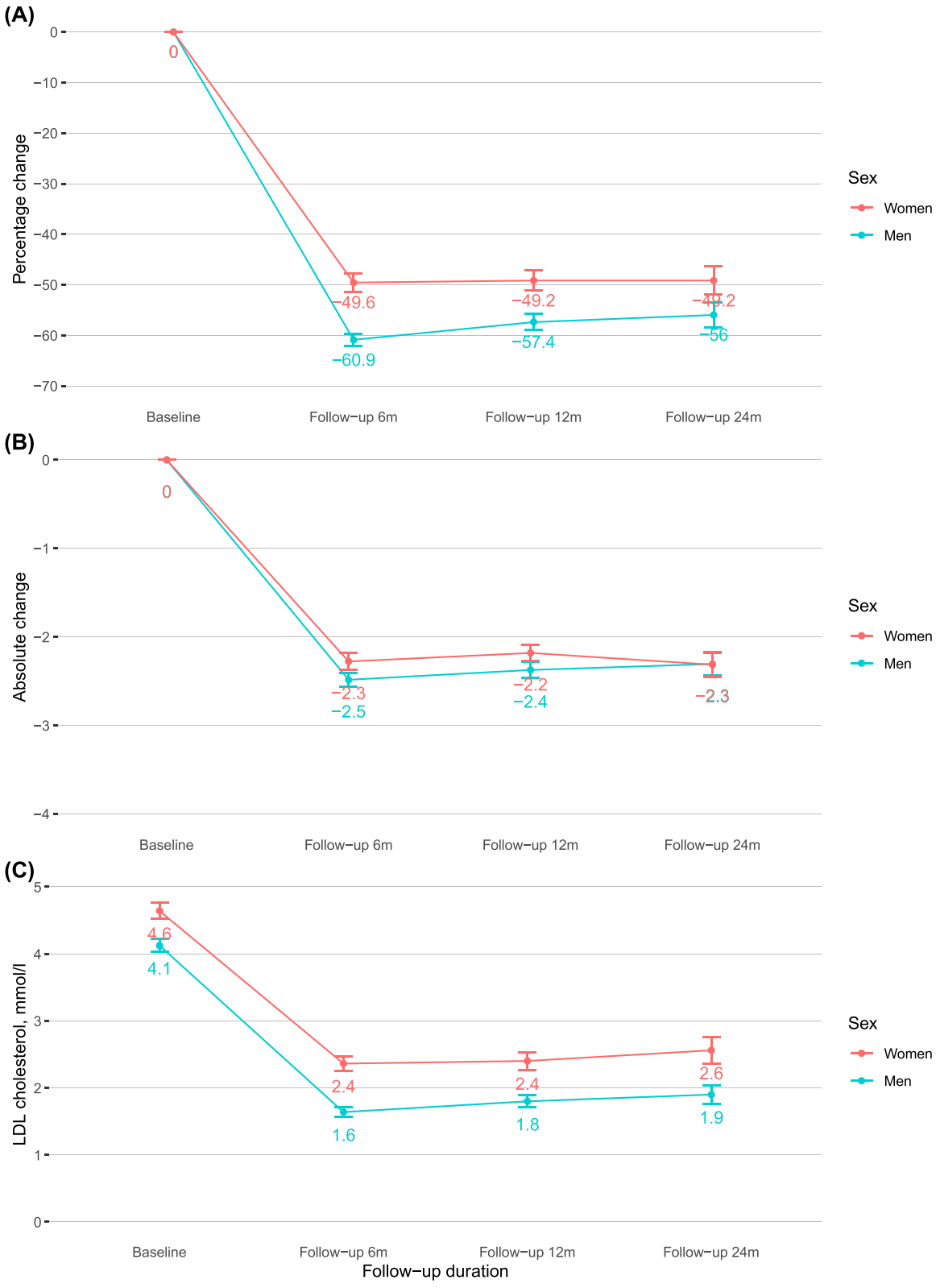

Fig. 1. LDL-cholesterol during follow-up in months, mean ± SE: (A) percentage change, (B) absolute change, (C) absolute levels.

statin intolerance reported more side effects of PCSK9 inhibitors compared to patients with statin therapy, suggesting that patients with a higher susceptibility to statin-associated adverse events are also more sensitive to side effects of PCSK9 mAbs.

4.3. Strengths and weaknesses

The main strength of our study is that we have long term follow-up of both efficacy and safety outcomes in a registry of consecutive patients who started PCSK9 mAbs in a real-world setting. Moreover, as we have an equal distribution of women and men, this allows us to perform relevant sex-specific analyses. Our study has several limitations. In the efficacy analysis, we lack information about menopausal status in 18% of the women in our study and most women (71%) are postmenopausal, which hampers the analysis regarding the effect of menopause. Moreover, we have no measurements of PCSK9 levels due to the observational nature of our study. Lastly, this study is performed in a single centre. However, as all patients were treated according to the national PCSK9 mAbs reimbursement criteria, we consider our results representative for female and male patients using PCSK9 mAbs in the Netherlands.

4.4. Conclusions, clinical implications and future directions

In our large real-world data registry, we confirmed that women had less LDL-c reduction and a similar safety profile compared to men after initiation of PCSK9 mAb inhibition. As women have higher baseline LDL-c levels and less often reach treatment targets, it could be argued to start with the full dose PCSK9 mAb (e.g. in case of alirocumab 150 mg/2wks sc instead of 75 mg/2wks sc). Moreover, as we showed that using high intensity statin was associated with increased efficacy of PCSK9 mAbs, it is important to up titrate statins in all patients who start a PCSK9 inhibitor, but especially for women.

More research is needed to clarify the effect of oestrogens and menopause on PCSK9 metabolism and its effect on PCSK9 inhibitor response and presence of sex differences in LDL-c reduction should be analysed.

Table 3
(A) Univariate and multivariable linear regression model of relative LDL-c percentage response to PCSK9 mAbs. (B) Univariate and multivariable logistic regression model of reporting of any side effects.

A	Beta coefficient	*p*
Univariate		
Age, years	−0.002	>0.9
BMI, kg/m^2	−0.1	0.79
Female sex	11.3	< **0.001**
Premenopausal status	1.3	0.83
Familial hypercholesterolemia	5.2	**0.041**
History of ASCVD	−4.9	**0.038**
Concomitant statin use	−4.9	**0.032**
Concomitant high-intensity statin use	−13.3	< **0.001**
Baseline LDL-cholesterol level, mmol/L	1.7	**0.021**
Multivariable		
Female sex	12.0	**0.001**
Concomitant high-intensity statin use	−13.7	< **0.001**
History of ASCVD	−0.6	0.66
Baseline LDL-cholesterol level, mmol/L	0.6	0.89
Familial hypercholesterolemia	5.5	0.37
B	**Beta coefficient**	***p***
Univariate		
Age, years	0.1	0.73
BMI, kg/m^2	0.01	0.41
Female sex	0.3	0.22
Premenopausal status	0.6	0.23
Familial hypercholesterolemia	−0.1	0.54
History of ASCVD	0.3	0.16
Statin intolerance	0.6	**0.004**
Baseline LDL-cholesterol level, mmol/L	0.2	**0.012**
Multivariable		
Baseline LDL-cholesterol, mmol/L	0.1	< **0.001**
Statin intolerance	0.6	**0.014**

LDL = low density lipoprotein; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index.LDL = low density lipoprotein; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index.

Data statement

Upon reasonable request, it can be expected that specific anonymous data will be shared to a qualified researcher.

CRediT authorship contribution statement

Annette M.H. Galema-Boers: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Investigation. **Janneke W.C.M. Mulder:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Investigation. **Kim Steward:** Conceptualization, Data curation, Writing – review & editing, Project administration, Investigation. **Jeanine E. Roeters van Lennep:** Conceptualization, Methodology, Writing – review & editing, Investigation, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JGB received funding from Sanofi outside the submitted work for education purposes. JRVL received research grants from Novartis and Amryt. JM and KS do not have any disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.03.013.

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