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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

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Published online: 19 Oct 2021.

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Association between adherence to statin therapy and low-density lipoprotein cholesterol (LDL-c) response in first-time users of standard-dose and low-dose statins: the PharmLines initiative

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ABSTRACT

Objective: To investigate whether statin adherence (defined as proportion days covered, PDC) is associated with LDL-c response in statin initiators on standard and low starting doses of statins, and to detect a possible interaction with sex.

Methods: An inception cohort study was conducted using the PharmLines Initiative, a linkage between the Lifelines Cohort Study and the University of Groningen's IADB.nl (prescription database). First-time statin users were followed from baseline to follow-up measurement. We matched participants (1:1) between the standard-dose and the low-dose group of statin users on the duration of follow-up. Multiple linear regression analysis was used to model the association.

Results: In univariate analysis, PDC was significantly associated with LDL-c response similarly (slope = −0.021), in both the standard-dose group ($N = 115$, $p < .001$) and the low-dose group ($N = 115$, $p = .003$). In the standard-dose group, the same level of PDC appeared to be significantly associated with a greater LDL-c level reduction in women (slope = −0.027, $N = 48$, $p < .001$) than in men (slope = −0.017, $N = 67$, $p < .001$). Meanwhile, in the low-dose group, the reduction of LDL-c level from baseline seemed to be greater in men (slope = −0.023, $N = 56$, $p < .001$) than in women (slope = −0.020, $N = 59$, $p < .001$) for the same level of PDC. In multiple regression analysis, the significant association between PDC and LDL-c with a similar pattern to the univariate result was maintained only in the standard-dose group.

Conclusions: Adherence is significantly associated with LDL-c response to statins at follow-up. Sex appears to significantly modify this association. At a similar adherence level, women seem to experience a better LDL-c response to standard-dose statins compared to men in a real-world setting.

Introduction

Statin therapy can prevent cardiovascular (CV) events and death in individuals at risk[1,2]. Clinical guidelines[3,4] have been long recommending attainment of a certain target level of low-density lipoprotein cholesterol (LDL-c) after statin initiation, such as ≤ 2.5 mmol/L in the Dutch guideline[3]. However, in Dutch clinical practices, only a third of statin initiators reach their target[5]. A major cause may be the interaction between starting dose and adherence as shown in a study among patients with diabetes[6]. Furthermore, a meta-analysis showed sex disparities in statin adherence behavior in which women tend to be less adherent than men[7]. Here, we aimed to estimate the association between statin adherence and the LDL-c response in statin initiators on standard-dose and low-dose and to detect how adherence and sex interact with those dosing schemes.

Methods

We conducted an inception cohort study using the University Groningen PharmLines Initiative database in which data from the Lifelines Cohort Study and the IADB.nl community prescription database have been linked. Details on these databases are described elsewhere[8–12].

We included participants who had both the baseline and follow-up visit recorded in the Lifelines cohort database and had been dispensed with any statin monotherapy (Anatomical Therapeutic Chemical code: C10AA) for the first time in the IADB.nl since the baseline measurement. The date of the first statin prescription was defined as the index date. Participants were followed from the index date to the follow-up measurement. We excluded participants aged < 40 years at baseline, used statins < 90 days, and switched to different types of statins during the follow-up period. The participants were classified into two groups based on the

starting dose of statins: standard dose and low dose. The low doses of statins were simvastatin 10 and 20 mg, pravastatin 40 mg, and atorvastatin 10 mg. The standard doses of statins were simvastatin 40 and 60 mg, atorvastatin 20 mg, and rosuvastatin 5 and 10 mg[6]. Most participants were prescribed simvastatin 20 mg (41.6%) and simvastatin 40 mg (46.2%). Our primary outcome was the association between adherence to statin therapy and LDL-c, both LDL-c concentration (mmol/L) achieved at follow-up and percentage change of LDL-c from baseline to follow-up, in the standard-dose group compared to the low-dose group.

We defined adherence as the proportion of days covered (PDC) in a unit of percentage, where the number of days covered with statin prescriptions was divided by the number of days between index date and follow-up multiplied by 100. A higher value of PDC indicated a higher level of adherence. We could obtain the data needed to calculate these number of days from the Pharmlines database, as a result of data linkage between the Lifelines and IADB.nl databases[11]. Lifelines' data were initially obtained from questionnaire[8–10,12] while IADB.nl's were from the refilled-prescription data uploaded regularly by community pharmacies located in different parts of the Netherlands[9].

Due to the differences in follow-up times between participants, we matched participants from the low-dose group 1 to 1 to a participant from the standard-dose group on the duration of follow-up within a range of 90 days. We used the duration of follow-up within that range because of the average repeat prescription duration for statins in the Netherlands in 90 days. We did not match participants based on other characteristics as we observed there were no significant differences in values or proportions of other baseline characteristics. Another reason was the small sample available for this study limited the possibility to match based on more than one or two variables.

Baseline variables were compared between standard-dose and low-dose statins using the Chi-square test for categorical variables, independent sample t-tests for normally distributed continuous variables, and Mann-Whitney-U tests for skewed variables. Multiple linear regression analyses were performed to model the association between the independent variable (PDC) and the dependent variable (LDL-c level at follow-up and percentage change of LDL-c from baseline), while also accounted the effect of the following covariates: sex, baseline LDL-c level, and other lipid parameters, and interaction between PDC and sex. Other baseline characteristics of participants that were significantly different in value or proportion between the standard- and the low-dose groups were also included as covariates. We reported the intercepts, slopes, standard errors (SEs), 95% confidence intervals (95% CIs), p values, and R^2 of the model. Multiple linear regression analyses were also performed separately in each dosing group comparing the sexes. Complete case analysis was performed to account for any sporadically missing data in the covariates and outcome variables. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.

Results

Among approximately 50,000 participants present in the linked database, 5366 were statin users. Of these, 571 participants initiated statin therapy and met the eligibility criteria. Among these participants, 406 (71%) individuals were dispensed with the same type of statins from the index date to the follow-up measurement, 132 and 266 participants were in the low-dose and standard-dose groups, respectively. After excluding participants with statistical outliers on covariate data ($N = 16$) and duration of follow-up matching, 238 individuals (119 in each dosing group) were analyzed. Median follow-up was 864 and 863 days for both groups.

Baseline characteristics showed no differences between both dosing groups to sex, age, blood pressure, lipid parameters, comorbidities, and the use of other CV medication as well as adherence rate to statin therapy (Appendix 1). However, the standard-dose group had a significantly higher proportion of patients with high 10-year CV risk and high BMI than the low-dose group ($p = .047$ and $p = .040$, respectively).

Univariate regression analysis showed a significant association between PDC and LDL-c level at follow-up and percentage change of LDL-c level from baseline. These associations remained significant after adjustment for covariates using multiple regression analysis (Table 1). Sex and the interaction between sex and PDC showed significant results in predicting the level of LDL-c at follow-up ($p = .019$ and $p = .023$, respectively) and percentage change of LDL-c level from baseline ($p = .004$ and $p = .010$, respectively).

In univariate analysis of both the low-dose and the standard-dose subgroups, the same level of PDC was associated with a similar slope of decline in LDL-c level at follow-up (slope $= -0.021$, figure not supplied). In the standard-dose group, the same level of PDC appeared to be significantly associated with a greater LDL-c level reduction in women (slope $= -0.027$, $N = 48$) than in men (slope $= -0.017$, $N = 67$). Meanwhile, in the low-dose group, the reduction of LDL-c level seemed to be greater in men (slope $= -0.023$, $N = 56$) than in women (slope $= -0.020$, $N = 59$) for the same level of PDC (Figure 1). Although the line depicted the association between PDC and LDL-c level at follow-up appeared to project the very broad range of PDC rates, most of these values were concentrated at the end of the line (close to 100%) due to the high rates of adherence in this study.

After adjusting for covariates in the multiple regression analysis of the standard-dose group, PDC was significantly associated with a reduction of LDL-c level at follow-up at a greater point in women (slope $= -0.029$) than in men (slope $= -0.014$). The slopes were not significantly different in the low-dose group between the sexes. Similar patterns were found for the percentage change in the LDL-c level from baseline.

Discussion

Our study lends support to previous studies that high adherence to statins is essential to reach the LDL-c target[5]. The

Table 1. Association of proportion days covered (PDC) with LDL-c at follow-up and percentage change in LDL-c (results from multiple regression analysis).

Outcomes	Independent variable	Slope, SE	95% CI	p value	R^2	N
LDL-c level at follow-up (mmol/L)	PDC	−0.017, 0.003	−0.022, −0.011	**<.001**	0.480	220
	Sex	0.822, 0.349	0.134, 1.510	**.019**		
	Baseline LDL-c	0.343, 0.047	0.251, 0.436	**<.001**		
	Baseline HDL-c	0.013, 0.162	−0.307, 0.332	.938		
	Baseline Tg	0.123, 0.059	0.007, 0.239	**.038**		
	Baseline BMI	−0.011, 0.012	−0.035, 0.013	.377		
	High CV-risk	−0.021. 0.095	−0.209, 0.166	.823		
	Sex*PDC	−0.009, 0.004	−0.017, −0.001	**.023**		
	Constant	2.947, 0.536	1.891, 4.002	**<.001**		
Percentage change of LDL-c level from baseline (%)	PDC	−0.415, 0.076	−0.565, −0.265	**<.001**	0.458	220
	Sex	28.224, 9.817	8.872, 47.575	**.004**		
	Baseline LDL-c	−10.205, 1.324	−12.814, −7.596	**<.001**		
	Baseline HDL-c	−0.826, 4.553	−9.801, 8.150	.856		
	Baseline Tg	3.049, 1.657	−0.217, 6.315	.067		
	Baseline BMI	−0.237, 0.348	−0.923, 0.449	.497		
	High CV-risk	1.166, 2.678	−4.113, 6.446	.664		
	Sex*PDC	−0.286, 0.110	−0.503, −0.069	**.010**		
	Constant	50.256, 15.059	20.570, 79.942	**.001**		

BMI, body mass index; CI, confidence interval; CV, cardiovascular; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; N, number of participants included in the analysis; PDC, proportion days covered; SE, standard error; Tg, triglycerides.
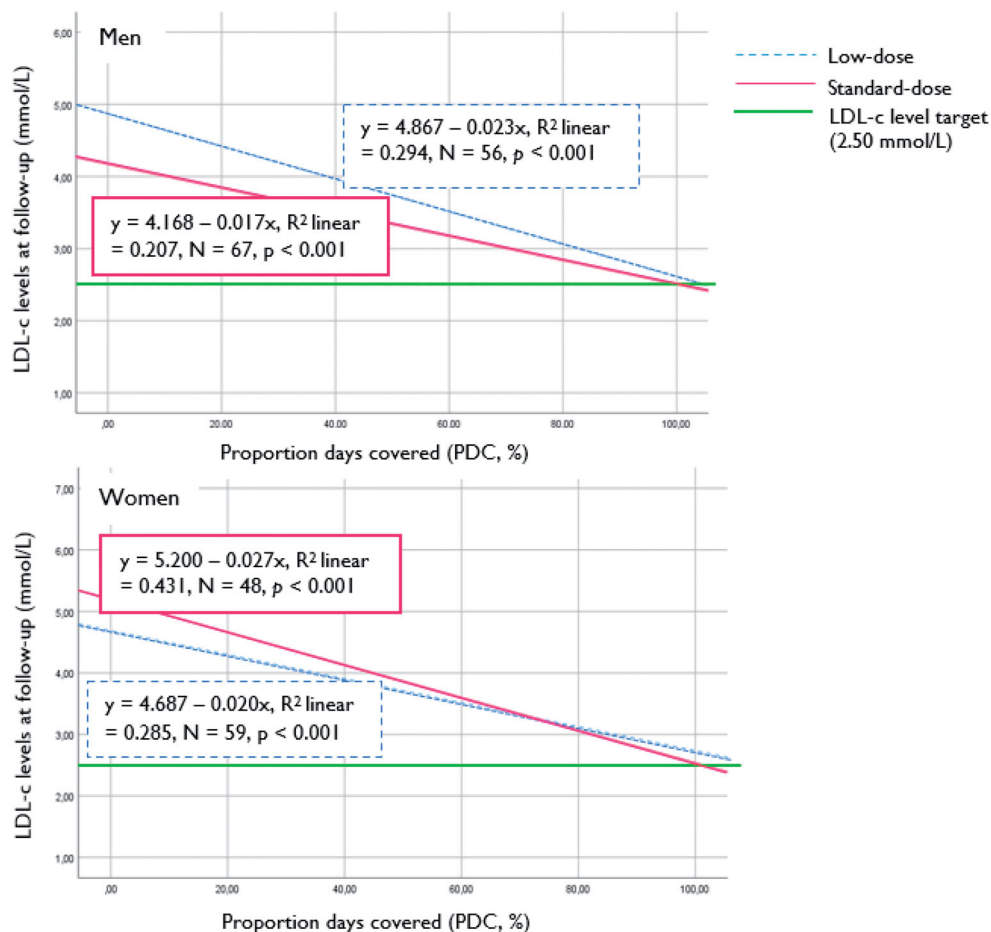Bold values represent statistically significant $p < .05$.

Figure 1. Association between PDC and LDL-c level at follow-up stratified by statin dose level in men and women. LDL-c, low-density lipoprotein cholesterol; PDC, proportion days covered.

association between PDC and LDL-c levels is similar for those on standard and low-dose statins, although more adherence is needed for the low-dose group to attain the same target level. Sex appears to modify the association between PDC and LDL-c response to statins, both the LDL-c level at follow-up and the percentage change of LDL-c from baseline. At a

similar level of adherence to the standard-dose statins, women seem to have a greater reduction of LDL-c than men.

The effect of different types of statin on the rate of LDL-c level reduction in both dose groups could not be observed since more than 90% of participants in this study were

prescribed with simvastatin. Different types of statin have different potencies, for example, atorvastatin is about twice as potent as simvastatin. Most participants in the standard- and low-dose group in our study were prescribed simvastatin 40 mg (equivalent to atorvastatin 20 mg) and simvastatin 20 mg (equivalent to atorvastatin 10 mg), which could lower the LDL-c level 34% and 41%, respectively[13]. Since the baseline, LDL-c level of our participants was around 4 mmol/L and more than a third of participants had high baseline CVD risk, a more potent statin seemed to be required to reach the LDL-c level target of 2.5 mmol/L at a faster rate. As intensive-dose simvastatin (80 mg and above) has a higher risk of adverse drug reactions, other intensive-dose statins (atorvastatin >30 mg or rosuvastatin >10 mg) could bring a greater reduction of LDL-c level[13].

Two studies support the importance of starting with more potent statins or higher dose simvastatin to increase the possibility of reaching the LDL-c treatment target earlier in patients with high CV risk[14,15]. The first study by Ferrieres et al.[14] showed that being treated with a statin equivalent to >20 mg/day atorvastatin had significantly higher odds of attaining LDL-c goal (<1.8 mmol/L). This study also analyzed other factors positively associated with LDL-c goal attainment were having comorbidities like chronic kidney disease and type 2 diabetes while factors negatively associated with the goal attainment were sex (women), smoking status (current smoker), having stable angina, and having a history of congestive heart failure. However, the mean baseline LDL-c in this study (2.31 mmol/L) was already lower than the LDL-c treatment goal used in our study. The second study by Reiner and Tedeschi-Reiner[15] described the proportion of patients achieving LDL-c target in atorvastatin users as significantly higher than in simvastatin users.

The use of standard-dose simvastatin was still in line with the 2011 Dutch practice guideline on cardiovascular risk management applied at that period. All patients (with and without the cardiovascular disease [CVD]) should be started with simvastatin 40 mg if treatment with a lipid-lowering agent is selected. A step-by-step plan has been included in statin treatment[3]. Nevertheless, the 2019 Dutch guideline on cardiovascular risk management recommends starting with intensive-dose statins, especially in patients who have already had CVD and are still ≤70 years old. The recommendation to combine a lower dose statin with ezetimibe is also included when the LDL-c level is ≥1.8 mmol/L[16].

High adherence to statin therapy is required to attain the LDL-c treatment target. In our study, sex seems to influence and modify this association. With a similar level of adherence between sexes, women seem to have a better LDL-c response to standard-dose statins than men. However, baseline LDL-c levels in our study were higher than in the previous study[14]. Higher baseline LDL-c predicts better LDL-c response to statins and the more potent statins also leads to a greater reduction of LDL-c levels at follow-up[13,17], therefore, the magnitude of the effect modification by sex might be different at the intensive-dose use of statins.

One study conducted in a real-world population with a baseline LDL-c level similar to our study also found that women predicted a greater LDL-c response to statins than men after adjusting for confounding variables. Other significant predictors were statin dose (defined as defined daily dose, DDD), age, statin type (simvastatin or pravastatin compared to lovastatin), having diabetes, smoking, and being East Asian (compared to European/caucasian). This study analyzed the association between statin dose and LDL-c response in the first statin users who were adherent to statin therapy. Most participants (63%) used older types of statins (lovastatin) which is equal to a low-to-standard dose of statins. Interestingly, in all dosing categories (low-to-high), women seemed to also experience a greater LDL-c reduction than men. Nevertheless, this study did not include baseline lipid parameters into their model and the adherence was defined based on only two refills of statin prescription[18]. Our findings confirm the influence of sex on the LDL-c response to statins at the standard dose and longer duration of follow-up.

The mechanism behind sex difference in the LDL-c response to statins has yet to be elucidated. Men and women have different anthropometric parameters and hormonal- and non-hormonal-related pharmacokinetic pathways of statins that may influence the LDL-c response. How these factors interact with one another to produce the overall LDL-c response is still unexplained. For example, although women have a higher rate of statin metabolism, especially lipophilic statins (simvastatin, lovastatin), women also have lower renal elimination of statins than men. The net results of this contradictory mechanism on the LDL-c response in men and women need further study[19].

Since the IADB.nl database only lists medicines dispensed by community pharmacists to be taken by patients thereafter, we could not know whether a patient is actually taking their medicines. We also did not know the actual reasons for non-adherence when a patient failed to refill their medicines. Our study showed the non-significant difference in adherence (PDC) between the standard- and the low-dose group with a median of 98.03% and 97.63%, respectively. The shorter duration of follow-up compared to the longer period participants had been present in the database in this study might contribute to the high level of adherence. Another study using the IADB.nl database reported that the rates of non-adherence in diabetic patients who initiated and used statins persistently were increasing the longer statins were used i.e. 13.4% in the first year, 15.6% in the second year, and 18.1% in the third year. These numbers were still higher compared to a previous study in the Netherlands[20].

Conclusions

High adherence to statin therapy is required to reach the LDL-c treatment target recommended by clinical guidelines. Sex seems to modify the association between adherence and LDl-c response to statins. At similar rates of adherence,

women appear to have a better LDL-c response to standard-dose statins compared to men.

Transparency

Declaration of funding

Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

EH and RAdB contributed to the conception or design of the work. SI drafted the manuscript. SDV and SI contributed to the statistical analysis of the data. JHJB prepared the data for the analysis. All authors contributed to the acquisition, analysis, or interpretation of the data. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgements

Data availability statement

De-identified individual participant data that underlie the results reported in this study (text, tables, figures, appendices) can be made available upon request immediately following article publication for researchers whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose. The proposal should be directed to: e.hak@rug.nl.

Ethics approval

The Lifelines study protocol is approved by the medical ethical committee of the University Medical Center Groningen and all Lifelines participants have each signed an informed consent stating that he/she approves use of his/her (anonymized) data and material for scientific purposes. Data of the IADB.nl is collected according to the national and European guidelines on privacy with human data valid at the time of collection.

Consent to participate

Informed consent was obtained from all participants included in the study.

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Appendix 1.

Baseline characteristics of participants based on starting dose of statins

Variables	Mean ± SD or Median (Q_3, Q_4) or n (%)		p value	Percentage of missing observation (%)
	Standard dose ($N = 119$, 50.0%)	Low dose ($N = 119$, 50.0%)		
Women	50 (42.0)	62 (52.1)	.119	0
High CV risk (10-y risk $\geq$ 20%)	52 (45.6)	37 (32.7)	**.047**	5
Age (years)	57.65 ± 10.59	57.50 ± 10.14	.910	0
BMI (kg/m2)	27.20 (25.40, 30.70)	26.50 (24.40, 29.20)	**.040**	0
Systolic blood pressure (mmHg)	135.18 ± 17.93	131.48 ± 17.64	.111	0
Diastolic blood pressure (mmHg)	77.00 (70.00, 84.00)	75.00 (69.00, 83.00)	.191	0
Total cholesterol (mmol/L)	6.05 ± 1.18	6.13 ± 1.04	.575	0
LDL-c (mmol/L)	4.14 ± 1.07	4.17 ± 0.96	.799	0
HDL-c (mmol/L)	1.37 ± 0.37	1.41 ± 0.37	.497	0
TG (mmol/L)	1.50 (0.99, 2.11)	1.50 (1.00, 2.21)	.565	0
Current-smokers	18 (18.9)	16 (17.4)	.783	21
Non diabetes	107 (91.5)	113 (95.0)	.284	1
Hypertension	43 (38.1)	46 (40.4)	.936	5
History of CVD	27 (22.7)	18 (15.1)	.136	0
Use of other cardiovascular medications	96 (80.7)	90 (75.6)	.347	0
Duration of statin use from index date until follow-up (days)	864.00 (564.00, 1183.00)	863.00 (598.00, 1130.00)	.891	
Adherence (PDC, %)	98.09 (75.54, 100.00)	97.63 (80.28, 100.00)	.885	0

BMI, body mass index; CVD, cardiovascular disease; HDL-c, high-density lipoprotein cholesterol; LDL-c; low-density lipoprotein cholesterol; N, number of total participants; n, number of participants included in the analysis; PDC, proportion days covered; Q_3, the third quartile; Q_4, the fourth quartile; SD, standard deviation; TG, triglyceride; y, year.
Bold values represent statistically significant $p < .05$.