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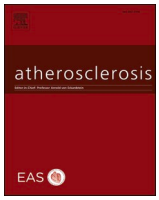

Sex differences in LDL-C control in a primary care population: The PORTRAIT-DYS study

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ABSTRACT

Background and aims: Cardiovascular (CV) diseases show clear differences in clinical manifestation and treatment outcomes between men and women. To reduce sex disparities in achieving lipid-lowering therapy (LLT) goals, a sex-focused assessment is essential and more studies are needed to bring new evidence to clinicians. This study aims to assess the role of sex in attaining low-density lipoprotein cholesterol (LDL-C) goals, after correction for age, CV risk category, LLT intensity, and presence of mental health disorder and social deprivation.
Methods: A retrospective cohort analysis of patients aged 40–85, followed in 1 hospital and 14 primary care centers in Portugal, using electronic health records from 1/1/2012 to 31/12/2020, was performed. The analysis considered an episode-based design, where exposure consists of any time when LLT was started or intensity changed. The likelihood of reaching the LDL-C goal according to contemporary ESC/EAS guidelines was modeled using multivariate Cox regression. LDL-C goal achievement at 180 days was defined as the outcome. The analysis was repeated at 30-day follow-up intervals up to 360 days, and also stratified by CV risk category.
Results: We identified 40,032 exposure episodes (LLT initiation or intensity change) in 30,323 distinct patients. Male sex, older age, lower CV risk and increasing LLT intensity were associated with improved LDL-C control. Women were 22% less likely to reach the LDL-C goal than men (HR = 0.78, 95% CI:0.73, 0.82) independently of covariates.
Conclusions: Women have a lower likelihood of attaining LDL-C goals than men after adjustment for LLT intensity, age, CV risk category, presence of mental health disorder and social deprivation. This finding underscores the need for further investigation and tailoring of LLT management strategies in women.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) causes four million deaths in Europe each year, killing more women than men (2.2 million compared to 1.8 million in men), and is the leading cause of death and disability worldwide [1–3]. The European Society of Cardiology (ESC)/European Society of Atherosclerosis (EAS) has defined low-density lipoprotein cholesterol (LDL-C) goals according to the patient's cardiovascular (CV) risk, with no specific recommendations concerning sex [2].

Women are less likely to be diagnosed appropriately, receive preventive care, or be treated as recommended for cardiovascular disease

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(CVD) [4]. There are sex differences in CVD clinical manifestations, outcomes and pharmacological treatment [5].

Although for many years it was thought that the prevalence of CVD in men was higher than in women, several studies concluded otherwise. Women with diabetes have a higher risk of cardiovascular complications than men, with a 50% higher risk of fatal coronary heart disease [6]. There has been a significant increase in the prevalence of ischemic heart disease in young women due to unfavorable lifestyle changes over the last decade [7] and women still have worse outcomes compared with men [8]. Mortality caused by coronary artery disease is significantly higher in women compared to men (51% *vs.* 42%) [9] and appears to be greater after some events, such as acute myocardial infarction and percutaneous coronary intervention [10,11].

Sex and gender differences in cardiovascular health and lipid control may be attributed to various factors. These differences may be biological (sex-related), such as hormonal factors like premature menopause, pregnancy-related risk factors, use of hormonal contraceptives and higher prevalence of thyroid dysfunction [12,13], or they may be due to social, environmental, and community factors (gender-related) [18], such as lower adherence and higher treatment dropout, associated depressive symptoms, and even lower perceived risk in women by patients and clinicians [8].

Given that lipid control, particularly LDL-C levels, is a key modifiable risk factor for the development and progression of CVD, it is crucial to understand sex differences in this area to address disparities in CVD outcomes [14,15].

The aim of this study was to estimate the effect of sex upon LDL-C control regardless of age, LLT regimen, CV risk category, presence of mental health disorder and social deprivation.

2. Patients and methods

2.1. Study design

This is an observational cohort study using electronic health records (EHR) of patients followed at the Unidade Local de Saúde de Matosinhos (ULSM). ULSM is a large healthcare institution that includes 14 primary care centers supported by 1 hospital that provides secondary and tertiary care services to the region of Matosinhos, reflecting the activity of more than 1000 doctors from different background specialties. An 8-year time window from 01/01/2012 to 31/12/2020 to scan EHRs for eligible patients was considered, encompassing the 2011, 2016 and 2019 revisions of the ESC/EAS guidelines [2,16,17]. The index date was defined as the first time upon which LLT was initiated or changed. In order for a patient to be included and analyzed in the study, the following criteria had to be met at the same point in time: i) age between 40 and 85 years; ii) at least one appointment with a ULSM primary care physician in the three years preceding the index date, in line with the official government indicator used to determine whether a patient is routinely followed or not; iii) at least one record in the last year before the index date and iv) enough information to categorize the patient according to the contemporary ESC/EAS guidelines. These inclusion criteria maximize the overlap of the study population with the resident population, which accounts for approximately 90% of the resident population of Matosinhos within the selected age group, according to the 2021 Portuguese Census. Matosinhos is the eighth most inhabited municipality in the country and the fourth in the northern region.

Only patients aged between 40 and 85 years were included in the analysis because the evidence upon which the ESC/EAS guidelines were built to recommend usage of the Systematic Coronary Risk Estimation (SCORE), CV risk category calculation and LLT initiation are not as widely accepted outside this age group and thus allow greater room for clinician discretion regarding patient assessment and treatment.

This study was approved by the Ethical Committee of ULSM (translated from *Comissão de Ética para a Saúde da Unidade Local de Saúde de Matosinhos*). All data processing and analysis were performed exclusively by analytic programs developed for this purpose and sent for execution at ULSM datacenter. No data was extracted outside ULSM, and no direct access to the data took place. As an additional degree of security, processed data were de-identified by the ULSM Information Technology Department prior to the analytic code execution according to the Health Insurance Portability and Accountability Act (HIPAA) safe harbor standard [18].

2.2. Key variable definition

CV risk categories were constructed considering the contemporary ESC/EAS Guidelines for Dyslipidemia from 2011, 2016 and 2019 at the index date. Firstly, risk categories were decomposed in independent risk criteria sufficient to classify the patient in a given CV risk category. Then, each criteria was broken down into smaller sub-criteria, and then further refined into the most granular EHR data available among clinical measurements, laboratory results and conditions recorded at ULSM.

Relevant conditions at primary care were originally coded using International Classification of Primary Care, version 2 (ICPC-2), and inpatient and outpatient hospital appointments coded using International Classification of Disease, 9th Revision (ICD-9) and International Classification of Disease, 10th Revision (ICD-10) codes. Laboratory and clinical measurements were coded using ad-hoc vocabularies that were standardized to the systematized nomenclature of medicine clinical terms (SNOMED CT). In order to compute family history of relevant diseases, familial relationships were reconstructed from primary care family information.

Neither carotid or coronary imaging data, nor ankle brachial index, were used to assert the presence of ASCVD as these were not retrievable from the EHR at the time of this study. Furthermore, familial hypercholesterolemia was classified as definite or possible according to Simon and Broome criteria [19].

Prescription data registered according to the Anatomical Therapeutic Chemical Classification System [20] and corresponding dosage information were used to compute LLT regimens. The statin intensity group, considering both the drug and the dosage, was attributed according to the classification of the American College of Cardiology and the American Heart Association [21]. A total of 6 groups for LLTs were defined according to statin intensity (low, moderate, high) and the addition of ezetimibe. Prescriptions of fixed or single-pill combinations of the LLTs were considered. In case a patient switched statins or doses within the same intensity range, it would remain in the same LLT category.

To account for socioeconomic and mental health factors, the presence of mental health disorders and social deprivation was defined using ICPC-2, ICD-9 and ICD-10 codes (Supplementary Table S5 provides further details on these definitions). The patient's sex was determined from the administrative record available in the EHR.

Prior to analysis, the source data was harmonized according to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version 5.3 [22]. A detailed definition for all study variables is present as Supplementary Materials (Tables S1–S5).

2.3. Exposure and outcome definitions

Exposure was defined as any time point in which an LLT regimen was initiated or its intensity was changed. Upon cohort entry date, baseline CV risk category was computed according to the current version of the ESC/EAS guidelines [2,16,17]. The outcome of interest was defined as the attainment of the LDL-C target according to baseline CV risk category and contemporary version of the ESC/EAS guidelines 180 days after exposure. This time frame was chosen considering that in the Portuguese National Health System it is recommended that patients are reevaluated 60–180 days after LLT regimen is initiated or its intensity is changed. Additional sensitivity analyses were performed for each 30-day period from baseline until 360 days, and repeated for LLT events

occurring after entering each CV risk category.

To compensate for the delay in implementing the latest version of the guidelines in clinical practice, the goals set out in the guidelines were assumed to take effect from January 1st of the year following the publication.

A patient may become eligible for multiple cohorts as their LLT changes over time. When a patient already being followed in one cohort becomes eligible for another cohort, they will begin to be followed in the new cohort while still keeping follow-up in the former cohort. A graphical representation of the cohort identification and follow-up strategy, illustrating examples of different patient's trajectory scenarios with respect to the exposure and the outcome is available in the Supplementary Materials (Fig. S1).

2.4. Statistical analysis

Continuous variables were reported as median and interquartile range (IQR). Categorical variables were presented as absolute and relative frequencies. In order to estimate the risk for LDL-C control, we modeled cohorts using a Cox proportional hazards model adjusted at baseline for age, sex, CV risk category, mental health condition and social deprivation, and LLT intensity. To correct for the dependent observations resulting from having a patient in more than one cohort at different points in time, the standard errors of the estimated hazard ratios (HR) were adjusted to account for correlations between the same patient by applying the cluster method available in the Survival package. The resulting variance is what is known as the working independence variance in a generalized estimating equation. Overall, this design ensures that risk estimates are kept as conservative as possible.

To further account for potential differences in LDL-C target achievement between age groups and between primary care and hospital settings, we conducted additional subanalyses focused on patients categorized by age group and by their outpatient appointment history. Specifically, we examined whether or not they had attended any Cardiology, Endocrinology, or Internal Medicine outpatient appointments within the 365 days prior to the index date.

We used Apache Spark Framework version 2.4.5 for engineering the source data into the final dataset, R version 4.0.3 to perform the statistical analysis using the Survival package [23], and Vega-lite to generate result figures [24].

3. Results

3.1. Episode and exposed patient characterization

30,323 distinct patients were eligible for the study, which contributed to 40,032 episodes of LLT initiation or intensity changes meaning that, on average, each distinct patient contributed to 1.3 eligible episodes of LLT initiation or intensity changes.

The median age at the time of entering the cohort was 63 years (IQR = 14). There was a predominance of females in the low-intensity statin (57.3%), moderate-intensity statin (53.2%) and low intensity statin associated with ezetimibe (55.2%) cohorts. Further details on CV risk level distribution and context covariates by LLT use at the time of entry into the cohort are depicted in Table 1.

4437 (11.1%) episodes were identified for low intensity statin use, 22944 (57.3%) episodes for moderate intensity statin, 6491 (16.2%) episodes for high intensity statin, 1108 (2.8%) episodes for low intensity statin associated with ezetimibe, 3546 (8.9%) episodes for moderate-intensity statin associated with ezetimibe, and 1506 (3.8%) episodes for high-intensity statin associated with ezetimibe.

3.2. Achievement of LDL-C target at 180 days

For the analysis at 180 days of follow-up, LDL-C control was reached for 7349 episodes (18%) across all cohorts. The median time to reach LDL-C control varied between 52 and 84 days.

Regression results indicate that women had a 22% lower likelihood of reaching their LDL-C goal (HR = 0.78, 95% CI = [0.73, 0.82]) when compared to men (Fig. 1), independently of age, LLT intensity, CV risk category, and social or mental health status. The likelihood of reaching LDL-C control increased with age and LLT intensity and decreased with increased CV risk category. Further details for this model are available in the Supplementary Materials (Table S6).

The subanalyses exploring LLT events among distinct age groups and outpatient appointment categories are presented in Figs. S2 and S3 within the Supplementary Materials. The sex disparity in reaching LDL-C control remained true for most of these groups.

3.3. LDL-C target achievement at additional time points and CV risk category

Women are significantly less likely than men to reach LDL-C goals for all follow-up times and for LLT events within all CV risk categories (Fig. 2). The sex disparity found for the likelihood of reaching LDL-C goals was greater among patients with low CV risk compared to those with high CV risk. Tables in the Supplementary Materials provide baseline cohort characteristics (Tables S7–S10) and model estimates for each CV risk group (Tables S11–S14).

4. Discussion

The results of this study show relevant sex differences in the management of hypercholesterolemia. Women are 22% less likely to achieve the LDL-C target, 180 days after starting or changing LLT, regardless of the intensity of the LLT used, CV risk category, age, mental health

Table 1
Cohort characteristics at baseline for the time-to-event analysis to estimate the effect of sex in LDL-C achievement after starting or switching LLT.

	Low Intensity		Moderate Intensity		High Intensity Statin		Low Intensity + Ezetimibe		Moderate Intensity + Ezetimibe		High Intensity Statin + Ezetimibe	
Episodes (n)	4437		22,944		6491		1108		3546		1506	
Female (n, %)	2540	57.3%	12,199	53.2%	3001	46.2%	612	55.2%	1748	49.3%	637	42.3%
Age, years (P50, IQR)	63	16	60	16	64	15	63	15	64	14	64	13
CV Risk category	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Low risk	534	12.0%	3193	13.9%	272	4.2%	99	8.9%	184	5.2%	24	1.6%
Intermediate risk	1169	26.4%	6036	26.3%	781	12.0%	222	20.0%	539	15.2%	124	8.2%
High risk	1189	26.8%	5902	25.7%	1392	21.5%	262	23.7%	834	23.5%	233	15.5%
Very high risk	1317	29.7%	6517	28.4%	3955	60.9%	452	40.8%	1904	53.7%	1112	73.8%
Unknown	228	5.1%	1296	5.6%	91	1.4%	74	6.7%	85	2.4%	13	0.9%
Context covariates	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Mental health disorder present	1570	35.4%	7778	33.9%	3036	46.8%	412	37.2%	1555	43.9%	781.0	51.9%
Social deprivation present	42	1.0%	264	1.2%	130	2.0%	7	0.6%	50	1.4%	33	2.2%

CV - Cardiovascular; IQR - Interquartile range.

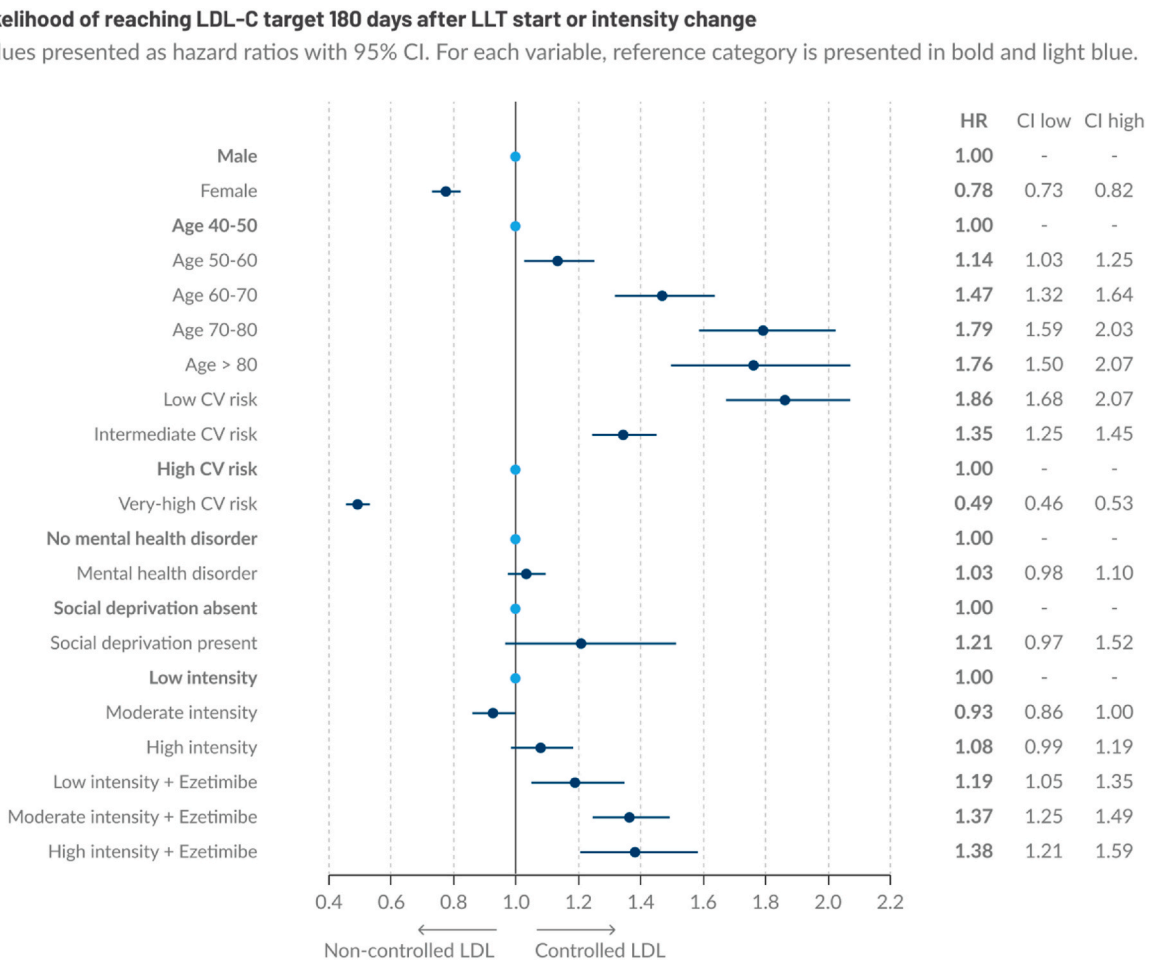

Fig. 1. Forest plot of the likelihood of reaching LDL-C target 180 days after LLT start or intensity change, based on adjusted hazard ratios (HRs) derived from the constructed multivariate model.
CI - Confidence Interval; CV - Cardiovascular; HR - Hazard ratio; LLT - Lipid-lowering therapy.

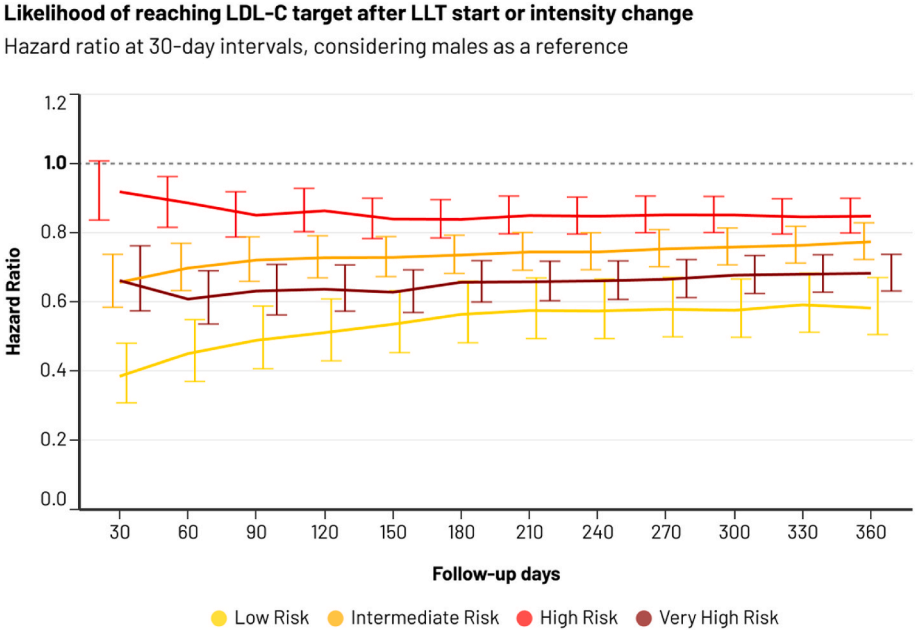

Fig. 2. Likelihood of reaching LDL-C target after LLT start or intensity change at 30-day intervals by CV risk group.
LLT - lipid-lowering therapy.

condition or social deprivation. This study focused specifically on patients prescribed LLT and, by using an episode-based approach to model multiple changes in LLT over time, was able to estimate the likelihood of achieving LDL-C goals. In addition, this study considered the CV risk definitions and LDL-C goals of contemporary guidelines, minimizing potential bias resulting from guideline changes over time.

Our results are in agreement with other studies. A cross-sectional study of primary care patients aged 40–79 years in Switzerland found that women had higher LDL-C values than men in both primary and secondary prevention and lower LDL-C assessment rates [25]. The EUROASPIRE III study concluded that women are less likely to achieve their LDL-C target in secondary prevention than men under the same treatment [26] and the EUROASPIRE IV study showed that only 16% of women had an LDL-C <70 mg/dL compared to 21% in men [27]. The DISGEN-LIPID study, conducted in Portugal, analyzed a total of 368 patients, of whom 73% had a high or very high CV risk SCORE. Women had higher TC ($p<0.001$), LDL-C (not significant) and HDL-C ($p<0.001$), and lower TG ($p=0.002$) levels; 57% of men and 63% of women had LDL-C>100 mg/dL ($p=0.28$), and 58% of men and 47% of women had LDL-C>70 mg/dL ($p=0.933$) [28]. Two more studies showed different results, although they were not designed specifically to estimate the likelihood of control of LDL-C after LLT initiation or change, which may partially explain the differences from our study [29,30].

The differences in reaching the LDL-C target between women and men may have several reasons, most of them gender-related.

One often proposed hypothesis is lower adherence to therapy and higher therapy abandonment by women, which this study could not account for. In the study by Cangemi et al., response to therapy was comparable between sexes, with slightly more abandonment of therapy in women due to adverse events [5]. Women were more dissatisfied with their statin therapy and with how their doctor explained their cholesterol treatment [31]. In the study by Nanna et al., women more often reported discontinuing their statin because of a side effect (7.9% *vs* 3.6%; $p<0.001$) and less often believed that statins were safe (47.9% *vs* 55.2%; $p<0.001$) or effective (68.0% *vs* 73.2%; $p<0.001$). This study also concluded that women were more likely to discontinue and to decline statin therapy when offered, and less likely to report having been offered statin therapy [32]. In a more recent study by Brown et al., women were more likely than men to not accept the initial statin therapy recommendation and to never initiate a statin during the study. Female sex was found to be an independent risk factor associated with a longer time to achieve LDL cholesterol control, and women were less likely to achieve LDL cholesterol control within 12 months [33].

Other possibilities are psychosocial differences, such as associated depressive symptoms and socioeconomic status, conditioning the sense of responsibility and health care seeking in women [8,25], all of which were accounted for in this study that still showed a sex gap regardless of these conditions.

In our study, there was a predominance of women in the low-intensity statin (57.3%), moderate-intensity statin (53.2%) and low intensity statin associated with ezetimibe (55.2%) cohorts. Many studies have shown that women, despite having higher LDL-C, less frequently receive statin therapy than men, particularly high-intensity therapy [5,31,34–36]. Virani et al. showed that women with CVD (n = 13371) were less likely than men to receive statins (57.6% *vs* 64.8%, $p<0.0001$) or high-intensity statins (21.1% *vs* 23.6%, $p<0.001$), although their mean LDL-C levels (99 *vs* 85 mg/dL) were higher ($p<0.0001$) [36]. In the ESC-EORP EUROASPIRE V survey, after hospitalization for a coronary event women were treated less often with LLT (80.3% *vs* 85.6%) and received high-intensity LLT less often than men (46.0% *vs* 51.3%), even with higher levels of TC, LDL-C and non-HDL-C [37]. These results are complementary to the ones in our study as only patients receiving LLT were studied. In another study by Peters et al., among patients following hospital discharge for myocardial infarction, women were less likely than men to fill high-intensity statins and the disparity was the largest in the youngest and oldest adults and in those without comorbid conditions [38]. This is a factor that may contribute to explain these findings as the analysis focuses only on whether LLT was prescribed and not if it was actually filled.

The prescription differences between sexes are evident and deserve careful consideration. One reason for therapeutic inertia toward women may also be the biased belief that they have a lower risk of CVD and less need for preventive intervention [39].

There may also be sex-related issues justifying a differential response to LLT. In addition to the difference in the treatment of women, differences were also found in the response to statins compared to men. Mombelli et al. conducted an observational study to evaluate sex-related differences in statin responses and obtained, after adjusting the dose and statin intensity, a significantly greater reduction in total cholesterol and LDL-C after 1 year of treatment in men [34]. According to the BARI 2D trial, women with type 2 DM and established CAD, even when treated as aggressively as men, were less likely to achieve LDL-C targets, suggesting the existence of a sex-targeted response to lipid-lowering drugs [40]. In Petretta's meta-analysis, statins were found to be less effective in women than in men [41].

The fact that women more often have side effects due to statins, such as muscle symptoms, than men may also condition a less interventionist medical attitude towards hypercholesterolemia [42]. The onset or worsening of muscle symptoms was reported in 31% of women compared with 26% of men ($p<0.01$). However, it is important to note that most reported side effects of statins are a result of the nocebo effect, as evidenced by recent studies [43,44]. Although some adverse effects of statins, such as toxic skeletal muscle damage and diabetes mellitus, appear to be more common in women, there is no mechanistic data to prove that statins may be more harmful to women than to men [5]. A better understanding of the nocebo effect and its implications on reported side effects could help improve the clinical management of muscle symptoms in patients taking statins, regardless of gender.

These disparities reflect the limited understanding of the physiology of sex differences, which is substantially related to the lack of female-specific data, especially in primary prevention trials [4,5]. The results of these studies are sometimes inconsistent, as women with ASCVD are typically older, with more comorbidities and risk factors than men, such as hypertension and DM [45]. Moreover, women are underrepresented in clinical trials, challenging the assessment of sex-related disparities in dyslipidemia and response to LLT [46].

In summary, despite documented efficacy of treatments in both sexes and international guidelines, women are less likely to receive guideline-based primary and secondary prevention and to be assessed for their CV risk, with the majority not adhering to adequate primary prevention care and instead resorting to non-evidence-based therapies [8,47,48]. In this regard, our study also showed that despite the LLT intensity, men were still more likely to attain the LDL-C treatment target.

An in-depth assessment, taking into account both biological sex and gender, is essential to adapt CVD prevention strategies. Further research is needed to explore factors influencing disparities in LLT goal attainment across sex and gender. Such studies may include investigating sex-specific pharmacokinetics and pharmacodynamics of LLT, examining the impact of sociocultural factors and gender roles on adherence to LLT, and exploring potential interactions between sex, gender, and other comorbidities in achieving LLT targets.

4.1. Strengths and limitations

This study yields important information on long-term trends of a large cohort with limited selection bias, loss to follow-up, and small amount of missing data. Considering the high usage rate of ULSM by the resident population, the low population migration rates, and the large data collection period, the authors believe that these findings can be generalized to the population served in this region, and to populations of comparable profile. This statistical analysis approach, allowing patients

to be followed in more than one cohort, not censoring on new cohort inclusion, and including covariates that frequently account for competing risk of death, enabled a conservative estimation of risks, which were still shown to be of high clinical magnitude.

Still, there are limitations in this study. ULSM serves a predominantly urban population with broad primary healthcare coverage, and thus may not be representative of other regions of Portugal. This analysis was based on retrospective EHR data with their unavoidable potential for quality and completeness issues, and thus vulnerable to bias or residual confounding that hinders causal inference. Furthermore, the study only considers patients between 40 and 85 years, who started or changed their LLT intensity, and therefore does not account for differences in control among patients who did not use LLTs. This may limit the generalizability of the findings to the broader population of patients with dyslipidemia. Also, the patient's sex was determined from the administrative record available in the EHR, which did not allow for direct capture of any other aspects of gender identity. Consequently, it is likely that these results better reflect sex-related differences.

4.2. Conclusion

Women have a lower likelihood of attaining LDL-C goals than men after adjustment for LLT intensity, age, risk category, presence of mental health disorder and social deprivation. This finding underscores the need for further investigation and tailoring of LLT management strategies in women.

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Data availability statement

All aggregate statistical results are incorporated into the article and its online Supplementary Materials. Patient level data used in this study is not publicly available.

CRediT authorship contribution statement

Cristina Gavina: Conceptualization, Methodology, Writing – review & editing, Supervision. **Francisco Araújo:** Conceptualization, Writing – review & editing. **Carla Teixeira:** Conceptualization, Writing – review & editing. **Jorge A. Ruivo:** Conceptualization, Writing – review & editing. **Ana Luísa Corte-Real:** Writing – original draft, Writing – review & editing. **Leonor Luz-Duarte:** Writing – original draft, Writing – review & editing. **Mariana Canelas-Pais:** Validation, Formal analysis, Writing – review & editing. **Tiago Taveira-Gomes:** Conceptualization, Methodology, Software, Validation, Supervision, Formal analysis, Writing - review & editing.

Declaration of competing interest

C.G. declares speaker and consulting fees from AstraZeneca, Bayer, BIAL, Boehringer-Ingelheim, Daiichi Sankyo, Lilly, MSD, Novartis and Novo Nordisk. F.A. declares speaker and consulting fees from AstraZeneca, Bayer, BIAL, Daiichi Sankyo, Ferrer, MSD, Novartis, Novo Nordisk and Servier. T.T.-G. declares speaker and consulting fees from AstraZeneca, BIAL, Daiichi Sankyo, MSD and Medinfar. T.T.-G. holds shares in MTG. C.T. and J.R. are employees of Daiichi Sankyo.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.05.017.

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