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Original article

Primary prevention in older adults: sex differences in statin persistence and cholesterol control

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ABSTRACT

Introduction and objectives: This study aimed to analyze sex differences in statin persistence and associated factors among individuals aged 70 years and older in Spain who initiated statin therapy for primary prevention of cardiovascular disease. Additionally, it assessed the role of sex in low-density lipoprotein cholesterol (LDL-C) control based on the intensity of statin therapy used.

Methods: This was an observational longitudinal study conducted within the CARhES (Cardiovascular risk factors for health services research) cohort. Individuals aged ≥ 70 years who initiated statin therapy for primary prevention of cardiovascular disease between 2018 and 2020 were included. Two-year statin persistence was assessed by sex. Considering major cardiovascular events and death as competing risks, the risk of statin discontinuation and its associated factors were estimated using cumulative incidence functions and Fine and Gray analysis. The proportion of men and women achieving LDL-C target levels was also calculated.

Results: A total of 4936 older adults (61.7% women) were included. Compared with men, women had higher mean LDL-C levels prior to statin initiation, a greater pharmacological burden, were less likely to receive high-intensity statins, and demonstrated lower persistence. No variables were statistically associated with discontinuation among women. In men, the adjusted HR for discontinuation was 1.03 (95%CI: 1.00-1.06) per 10 mg/dL increase in baseline LDL-C level. Among persistent statin users, women were less likely than men to achieve LDL-C targets, particularly when treated with low- to moderate-intensity statins.

Conclusions: Significant sex differences exist in statin persistence, associated factors, and achievement of LDL-C targets among older adults. These findings highlight the importance of considering sex-specific factors when evaluating the appropriateness of statin use in this population.

Prevención primaria en personas mayores: diferencias por sexo en la persistencia al tratamiento con estatinas y el control del colesterol

Palabras clave:
Personas mayores
Diferencias por sexo
Enfermedades cardiovasculares
Prevención primaria
Hipercolesterolemia
Fármacos hipolipemiantes
Persistencia al tratamiento
Datos de la vida real

RESUMEN

Introducción y objetivos: El objetivo de este estudio fue analizar las diferencias por sexo en la persistencia al tratamiento con estatinas y los factores asociados en una población española mayor de 70 años que inició tratamiento con estatinas para la prevención primaria de la enfermedad cardiovascular. Además, se evaluó el papel del sexo en el control del colesterol unido a lipoproteínas de baja densidad (cLDL) en función de la intensidad del tratamiento con estatinas.

Métodos: Estudio longitudinal observacional realizado en la cohorte CARhES *(Cardiovascular risk factors for health services research)* que incluyó a personas ≥ 70 años que iniciaron tratamiento con estatinas para la prevención primaria de enfermedades cardiovasculares entre 2018 y 2020. Se evaluó la persistencia al tratamiento con estatinas 2 años después en función del sexo. Se consideraron riesgos competitivos los

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eventos cardiovasculares mayores y la muerte, y se estimó el riesgo de interrumpir el tratamiento y sus factores asociados mediante funciones de incidencia acumulada y análisis de Fine y Gray. También se calculó la proporción de mujeres y varones que alcanzaron los niveles de cLDL recomendados.
Resultados: Se incluyó un total de 4.936 personas mayores (61,7% mujeres). En comparación con los varones, las mujeres presentaron valores medios de cLDL más elevados antes de iniciar el tratamiento con estatinas, mayor carga farmacológica, menor probabilidad de recibir estatinas de alta intensidad y menor persistencia al tratamiento, sin variables asociadas a la interrupción. En los varones, la HR ajustada de interrupción del tratamiento fue de 1,03 (IC95%, 1,00-1,06) por cada incremento de 10 mg/dl en el cLDL. Entre los pacientes que seguían en tratamiento con estatinas, las mujeres tuvieron menos probabilidad que los varones de alcanzar los objetivos de cLDL, en particular si recibían tratamiento con estatinas de intensidad baja-moderada.
Conclusiones: Existen diferencias significativas en función del sexo en la persistencia al tratamiento con estatinas, los factores asociados y el logro de los objetivos de cLDL entre las personas mayores. Estos hallazgos resaltan la importancia de considerar factores específicos de cada sexo el evaluar la idoneidad del uso de estatinas en esta población.

Abbreviations

CARhES: Cardiovascular risk factors for health services research
CVD: cardiovascular disease
LDL-C: low-density lipoprotein cholesterol
MACE: major adverse cardiovascular event

INTRODUCTION

Cardiovascular disease (CVD) remains a major public health concern. Dyslipidemia is one of the most well-established cardiovascular risk factors, and its management reduces the likelihood of major adverse cardiovascular events (MACE). Statins are the first-line therapy for dyslipidemia in high-risk individuals from the general population. However, their use for primary prevention of CVD in older adults is controversial due to limited evidence supporting a favorable benefit-risk balance in this age group. In individuals older than 70 years, factors such as multimorbidity, quality of life, and life expectancy should be carefully considered.[1]

When prescribed, chronic medications like statins should be both initiated and taken consistently to achieve therapeutic goals.[2] Nevertheless, population-based studies have reported decreased adherence to chronic treatments with advancing age.[3,4] In a recent study, we showed that approximately 20% of individuals older than 70 years who were newly prescribed lipid-lowering therapy for primary prevention did not initiate treatment. This behavior was influenced by factors such as older age and the presence of certain chronic conditions influenced this behavior.[5]

Statin use also displays notable sex differences. Women are less likely to be managed in accordance with clinical guidelines[6–9] and tend to have lower adherence to statin therapy compared with men.[8,10] Consequently, women are less likely to achieve recommended lipid targets.[9,11,12]

Given these patterns, it is reasonable to expect that older women may exhibit lower statin persistence (ie, treatment continuity) than men, which could negatively impact dyslipidemia control. However, this hypothesis has not yet been empirically confirmed. Improving the management of dyslipidemia in older adults—especially through equitable, sex-sensitive strategies—is essential to enhance cardiovascular outcomes in this population.

The objectives of this study, conducted in a Spanish population aged 70 years and older initiating statin therapy for primary prevention of CVD, were: *a)* to analyze sex differences in statin persistence and associated factors, and *b)* to evaluate the impact of sex on low-density lipoprotein cholesterol (LDL-C) control, stratified by statin intensity.

METHODS

Study design and population

This observational longitudinal study was conducted within the CARhES cohort (Cardiovascular risk factors for health services research), which includes all adults in the Spanish Autonomous Community of Aragon (population: 1.3 million) with at least 1 cardiovascular risk factor (hypertension, diabetes, or dyslipidemia) since 2017.[13]

The study population comprised all CARhES participants aged ≥ 70 years who initiated statin therapy for primary prevention of CVD between 2018 and 2020. These individuals were followed for up to 2 years. Inclusion criteria were: having at least 2 statin dispensations (Anatomical Therapeutic Chemical code C10) within 180 days after initiation: at least 1 LDL-C measurement ≥ 100 mg/dL (off-target) within the 90 days prior to the first statin dispensation; and at least 1 follow-up LDL-C measurement within 2 years after statin initiation. The 100 mg/dL LDL-C threshold was chosen in accordance with current clinical guidelines[1] for individuals at moderate cardiovascular risk, such as those in primary prevention.

Data collection

Data were obtained from the CARhES cohort, whose follow-up is based on real-world data from the Aragon Health System. This is pseudonymized information on sociodemographic, clinical characteristics and healthcare services and pharmacological treatments utilization.

Socioeconomic status was inferred from annual income, which determines the level of pharmaceutical copayment. Participants were categorized as follows: income < €18 000 per annum; income ≥ €18 000 per annum; and other situations.

MACE were identified by ICD-10 codes for acute myocardial infarction (I21), nontraumatic intracranial hemorrhage, or cerebral infarction (I60-I63), recorded during hospital admissions or emergency visits.

Most sociodemographic and clinical variables were obtained from the year of the first statin dispensation, except for MACE and deaths (collected throughout the entire period). Institutionalization was considered if the participant was recorded as institutionalized at any point during follow-up. Baseline LDL-C level was based on the latest measurement within the 90 days prior to statin initiation.

The first dispensed statin was categorized according to clinical practice guidelines[14] into: low-to-moderate intensity statins (simvastatin, lovastatin, pravastatin, fluvastatin, pitavastatin, atorvastatin 10/20 mg, rosuvastatin 5/10 mg), high-intensity statins (atorvastatin 30/40/60/80 mg, rosuvastatin 15/20/30 mg), and combination therapies (simvastatin + ezetimibe, pravastatin + fenofibrate, atorvastatin + ezetimibe, rosuvastatin + ezetimibe, atorvastatin + amlodipine, and atorvastatin + aspirin + ramipril).

The care level from which the initial statin prescription originated (primary care or specialty care) was also recorded.

Pharmacological burden was estimated by counting the number of unique pharmacological subgroups (third level of the Anatomical Therapeutic Chemical classification) dispensed to each participant.

Statistical analyses

Descriptive analyses of sociodemographic, clinical, and therapeutic characteristics were conducted in the total study population and stratified by sex. Continuous variables are reported as mean ± standard deviation or median [interquartile range], and categorical variables as absolute frequencies and percentages. Differences between groups were assessed using the chi-square test or Fisher exact test for categorical variables, and the Student *t*-test for continuous variables.

Persistence was defined according to the Ascertaining Barriers to Compliance taxonomy developed by the International Society on Medication Adherence (ESPACOMP).[2] In this framework, persistence refers to the time from the first dose (initiation) to the last dose taken before discontinuation.

Persistence was analyzed using the AdhereR package (version 0.8.1) in R,[15] which enables transparent and reproducible medication adherence analyses using electronic health care data. Persistence to statin therapy was assessed over a maximum follow-up of 2 years. We applied the maximum gap method, whereby a patient is considered persistent as long as the interval between 2 dispensations does not exceed a predefined allowable gap. For statins, which are usually prescribed as 1 pill per day, the maximum gap was set as twice the number of pills supplied in the prior dispensation. Remaining pills from previous fills (carryover) were considered when calculating allowable gaps.

The analysis followed the Timelines-Events-Objectives-Sources (TEOS) framework[16] and the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE),[17] both of which are consensus-based standards for transparent reporting of medication adherence research.

Differences in median persistence time among population subgroups were evaluated using the Kruskal-Wallis test and the Wilcoxon rank-sum test.

To account for competing events, we performed a competing risk analysis, treating death or MACE, whichever occurred first, as a competing risk for statin discontinuation. The cumulative incidence function (CIF) was used to estimate the probability of each event (discontinuation, MACE, or death). CIF curves were stratified by sex and age group, and by sex and statin type, with differences assessed using Gray's test.

To examine factors associated with statin discontinuation, we fitted Fine and Gray subdistribution hazard models, both crude and adjusted. The proportional subdistribution hazards assumption was verified using Schoenfeld residuals. *P*-values for hazard ratios (HRs) were calculated via Gray's test, and omnibus *P*-values were reported for categorical variables with multiple categories.

Sensitivity analyses were conducted by re-estimating the cumulative incidence functions and Fine and Gray models using an alternative allowable gap of 3 months.

Finally, the proportion of men and women achieving on-target LDL-C levels (≤ 100 mg/dL) was estimated for various time windows, both overall and stratified by statin intensity. The lowest LDL-C value recorded for each patient during each time window was used. Differences in proportions were tested using the chi-square test.

All analyses were performed using R Statistical Software, version 4.1.3 (R Foundation for Statistical Computing, Austria).

RESULTS

Baseline characteristics

A total of 4936 participants met the inclusion criteria and were included in the analyses. Their baseline characteristics are summarized in table 1. Most participants (72.1%) were aged 70-79 years. The most prevalent comorbidities were hypertension (68.9%), diabetes mellitus (29.5%), chronic kidney disease (19.0%), and depression (18.6%). Women accounted for 61.7% of the study population.

Compared with men, women had a significantly lower socioeconomic status and were more frequently institutionalized. They also had higher rates of obesity, dementia, and depression, but a lower prevalence of diabetes mellitus, ischemic heart disease, and chronic obstructive pulmonary disease.

Women exhibited significantly higher mean LDL-C levels prior to statin initiation (165 vs 152 mg/dL; $P < .001$), a greater pharmacological burden, and were more frequently prescribed low-to-moderate intensity statins. Among women, prescriptions were more often initiated in primary care. In contrast, men had higher incidences of death and a slightly greater incidence of MACE during follow-up.

Persistence with statin therapy

Overall, 39.9% of participants discontinued statin therapy within the 2-year follow-up period. The median time to discontinuation was 181 [89-347] days (table 2).

Among those who initiated statins and did not experience a MACE or die during follow-up (2991 women and 1822 men), 57.7% of women and 61.5% of men remained persistent over 2 years. Permanent discontinuation (no re-initiation) occurred in 12.2% of women and 11.7% of men, while 30.1% of women and 26.8% of men discontinued and later restarted therapy. Among those who reinitiated, 16.8% of women and 12.9% of men switched to a different statin.

Cumulative incidence curves revealed significant sex differences in persistence, with women remaining on treatment for a shorter duration than men ($P = .003$; figure 1). Participants aged ≥ 90 years and those prescribed combination statin therapies showed higher discontinuation rates than other groups, although these differences did not reach statistical significance. When stratified by sex and statin intensity, differences in persistence were evident among women: those on high-intensity statins were more likely to persist, whereas those on combination therapies showed the lowest persistence rates ($P = .059$; figure 2).

Table 1
Baseline characteristics of the study population

Characteristics	Total	Women	Men	*P*
Total	4936	3047 (61.7)	1889 (38.3)	
Age, y				<.001*
70-74	2248 (45.5)	1312 (43.1)	936 (49.6)	
75-79	1314 (26.6)	815 (26.7)	499 (26.4)	
80-84	814 (16.5)	530 (17.4)	284 (15.0)	
85-89	438 (8.9)	299 (9.8)	139 (7.4)	
≥90	122 (2.5)	91 (3.0)	31 (1.6)	
Socioeconomic level				<.001*
<€18 000/y	3446 (69.8)	2368 (77.7)	1078 (57.1)	
≥€18 000/y	1437 (29.1)	649 (21.3)	788 (41.7)	
Other	53 (1.07)	30 (0.98)	23 (1.2)	
Institutionalization	225 (4.6)	158 (5.2)	67 (3.6)	.007*
Type of area				.005*
Rural	1308 (26.5)	765 (25.1)	543 (28.7)	
Urban	3628 (73.5)	2282 (74.9)	1346 (71.3)	
Chronic pathologies	5.32 ± 2.5	5.51 ± 2.5	5.02 ± 2.4	<.001*
Comorbidities				
Hypertension	3396 (68.9)	2089 (68.7)	1307 (69.2)	.743
Diabetes mellitus	1453 (29.5)	772 (25.4)	681 (36.1)	<.001*
Obesity	771 (15.6)	510 (16.8)	261 (13.8)	.006*
Ischemic heart disease	311 (6.3)	163 (5.4)	148 (7.8)	.001*
Heart failure	279 (5.7)	175 (5.8)	104 (5.5)	.760
Chronic kidney disease	935 (19.0)	548 (18.0)	387 (20.5)	.035*
Dementia	201 (4.1)	151 (5.0)	50 (2.7)	<.001*
Depression	915 (18.6)	741 (24.4)	174 (9.2)	<.001*
COPD	378 (7.7)	122 (4.0)	256 (13.6)	<.001*
LDL-C before statin initiation	160.0 ± 29.5	165.0 ± 29.2	152.0 ± 28.4	<.001*
HDL-C before statin initiation	56.0 ± 14.3	59.5 ± 14.5	50.4 ± 11.9	<.001*
Pharmacological burden	9.3 ± 4.6	9.9 ± 4.7	8.4 ± 4.3	<.001*
Type of statin				<.001*
Low-moderate intensity statin	4208 (85.3)	2666 (87.5)	1542 (81.6)	
High intensity statin	461 (9.3)	220 (7.2)	241 (12.8)	
Statin in combination	267 (5.4)	161 (5.3)	106 (5.6)	
Level of care				.001*
Specialty care	165 (3.3)	80 (2.6)	85 (4.5)	
Primary care	4771 (96.7)	2967 (97.4)	1804 (95.5)	
MACE during follow-up	66 (1.3)	34 (1.1)	32 (1.7)	.112
Death during follow-up	57 (1.2)	22 (0.7)	35 (1.9)	<.001

COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events.
The results are expressed as No. (%) or mean ± standard deviation.
* Statistically significant result.
Pharmacological burden was based on the number of different pharmacological subgroups dispensed in the baseline year.
The frequency of deaths corresponds to deaths occurring in individuals without a previous MACE (participants experiencing a MACE were included in the frequency of MACE).

Table 2
Frequency of discontinuation, MACE or death (whichever occurred first) in the study population and median time to event. Total and by sex

Study population and final events	Discontinuation		MACE		Death		Total
Total	1967 (39.9)	181 [89-347]	66 (1.3)	244 [66-433]	57 (1.2)	523 [268-645]	4936
Women	1265 (41.5)	181 [89-348]	34 (1.1)	172 [48-432]	22 (0.7)	492 [188-582]	3047
Men	702 (37.2)	180 [89-346]	32 (1.7)	266 [67-436]	35 (1.9)	545 [348-648]	1889

IQR, interquartile range; MACE, major adverse cardiovascular event; No., number.
The results are expressed as No. (%) or median [interquartile range]. The percentages were calculated with respect to the total population, women, or men. The median times were estimated in each case considering people who experienced the respective event (discontinuation, MACE, or death).

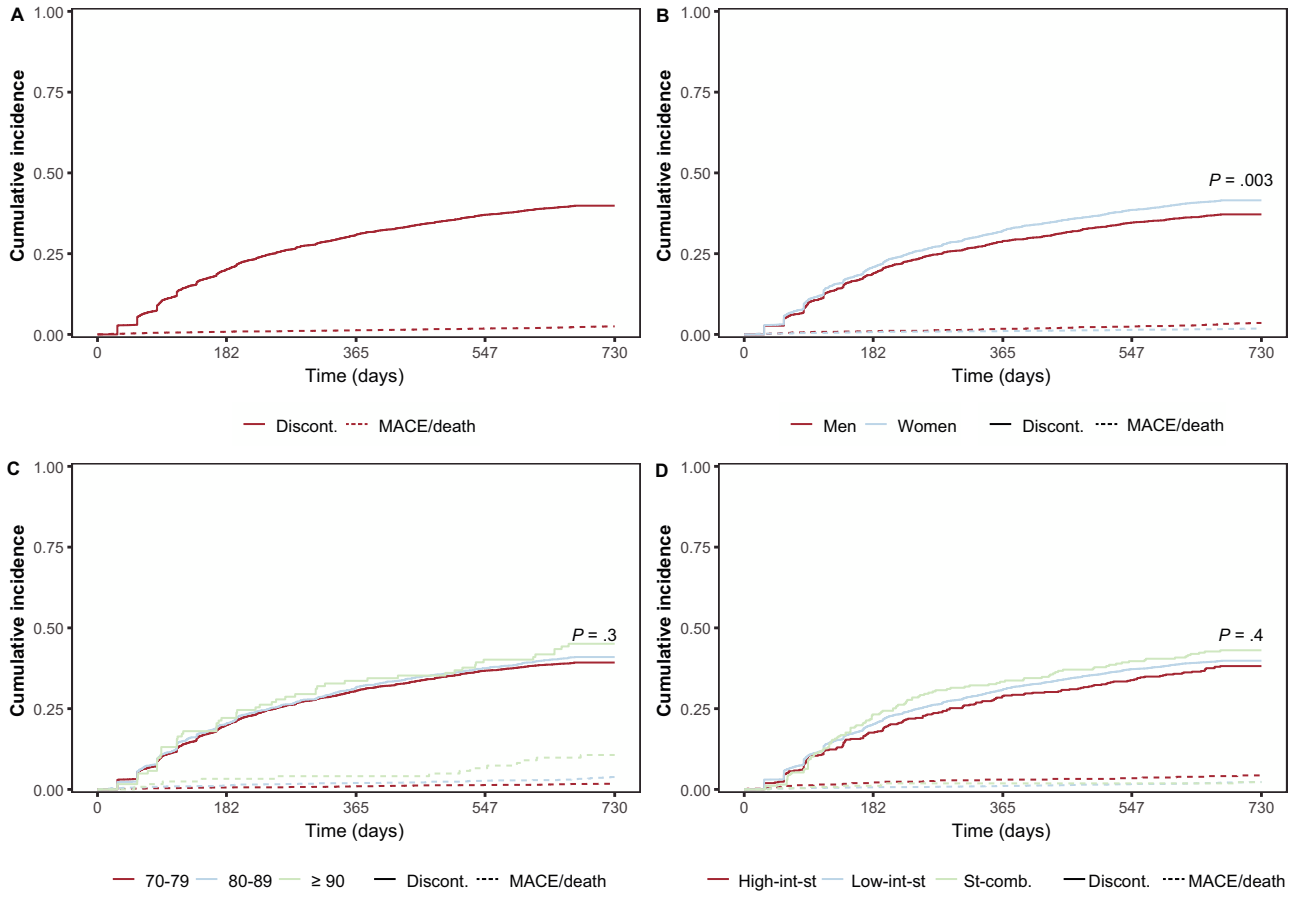

Figure 1. Cumulative incidence curves of statin discontinuation and competing risks (MACE and death) (A) for the study population, (B) by sex, (C) by age group, (D) by type of statin. Discont., discontinuation; High-int-st, high-intensity statin; Low-int-st, low-intensity statin; MACE, major adverse cardiovascular event; St-comb, statin in combination.

Factors associated with statin persistence

Fine and Gray competing risk analyses showed differences between men and women (figure 3), after confirming the proportionality assumption on the subdistribution hazard scale. In women, neither the crude nor the adjusted analyses showed a statistically significant association with any of the variables studied. In men, the crude HRs for statin discontinuation were significantly lower in participants with hypertension, diabetes mellitus, heart failure, chronic obstructive pulmonary disease, and high pharmacological burden, while higher HRs were observed in those whose statins were prescribed in primary care or who had higher high-density lipoprotein cholesterol and LDL-C levels prior to statin initiation. After adjustment, only heart failure, primary care prescribing, and baseline LDL-C levels remained significantly associated with discontinuation.

In the sensitivity analyses, median times to discontinuation (table 1 of the supplementary data), based on a 3-month allowed gap, were slightly higher than those previously estimated. The results of the original Fine and Gray models were confirmed for both women (table 2 of the supplementary data) and men (table 3 of the supplementary data).

Attainment of LDL-C target by sex and type of statin

Overall, 66.1% of patients attained LDL-C targets within 6 months of statin initiation. The proportions increased over time: 68.6% at 12 months, 69.7% at 18 months, and 70.4% at 24 months.

This upward trend was observed in both women and men. However, among all time windows, women achieved LDL-C targets less frequently than men: 62.8% of women vs 71.3% of men at 6 months and 66.1% vs 77.3% at 24 months. These differences were statistically significant at all time points ($P < .001$; figure 2).

When statin intensity was considered, sex differences in LDL-C control persisted. Statistically significant differences across all time points were found only for low-to-moderate intensity statins ($P < .0001$). In addition, both women and men treated with low-moderate intensity statins had lower rates of LDL-C target attainment than those on high-intensity statins ($P \leq .05$). For example, 6 months after initiation, 59.6% of women and 69.2% of men on low-to-moderate intensity statins were on target vs 78.3% of women and 84.3% of men on high-intensity statins.

Among those on statin combination therapy, women had a higher proportion of LDL-C target attainment than men, although the number of patients in this group was small (figure 4). Sex differences in LDL-C target attainment remained consistent after stratifying by both baseline LDL-C levels and statin intensity (data not shown).

DISCUSSION

In this population-based study conducted in an elderly population, sex differences in statin use patterns were found.

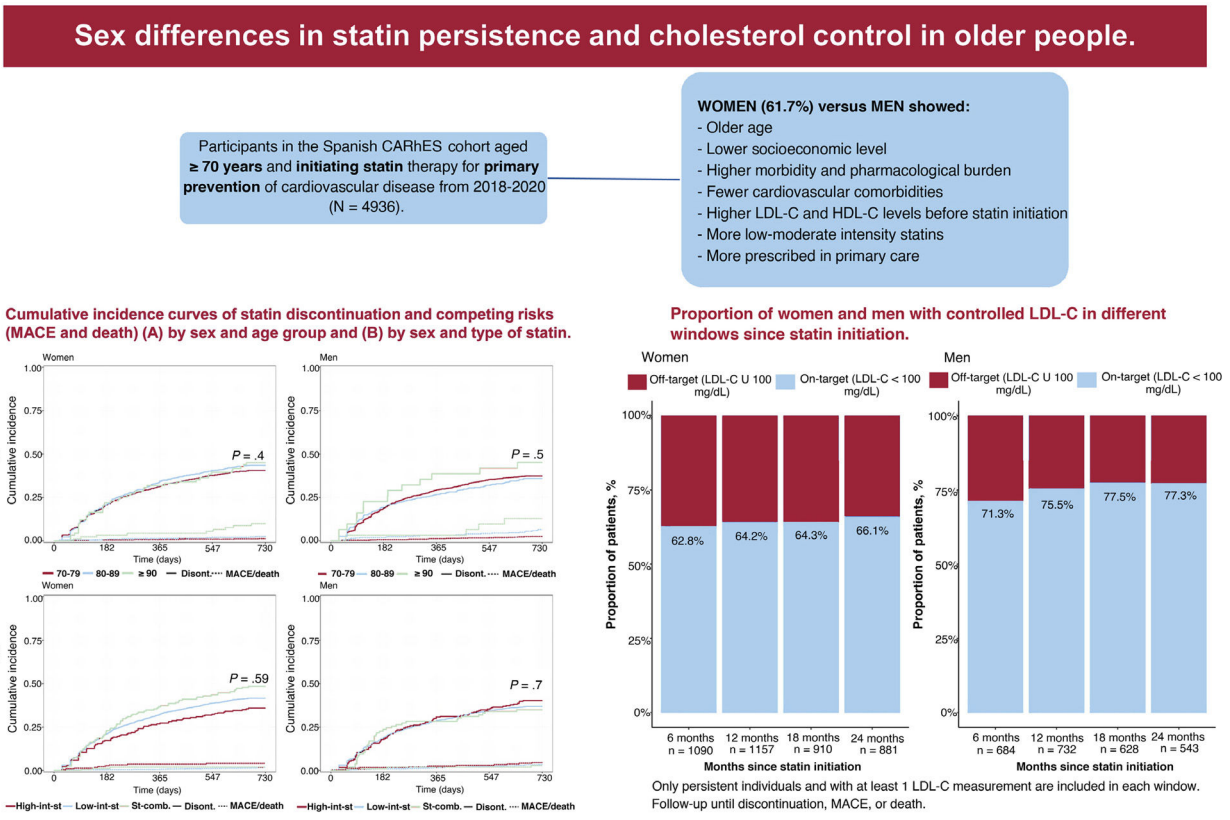

Figure 2. Central illustration. Sex differences in baseline characteristics, statin discontinuation incidence, and LDL-C control over time in an elderly population prescribed statins as primary prevention of cardiovascular disease. Discont., discontinuation; HDL-C, high-density lipoprotein cholesterol; High-int-st, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; Low-int-st, low-intensity statin; MACE, major adverse cardiovascular event; St-comb, statins in combination.

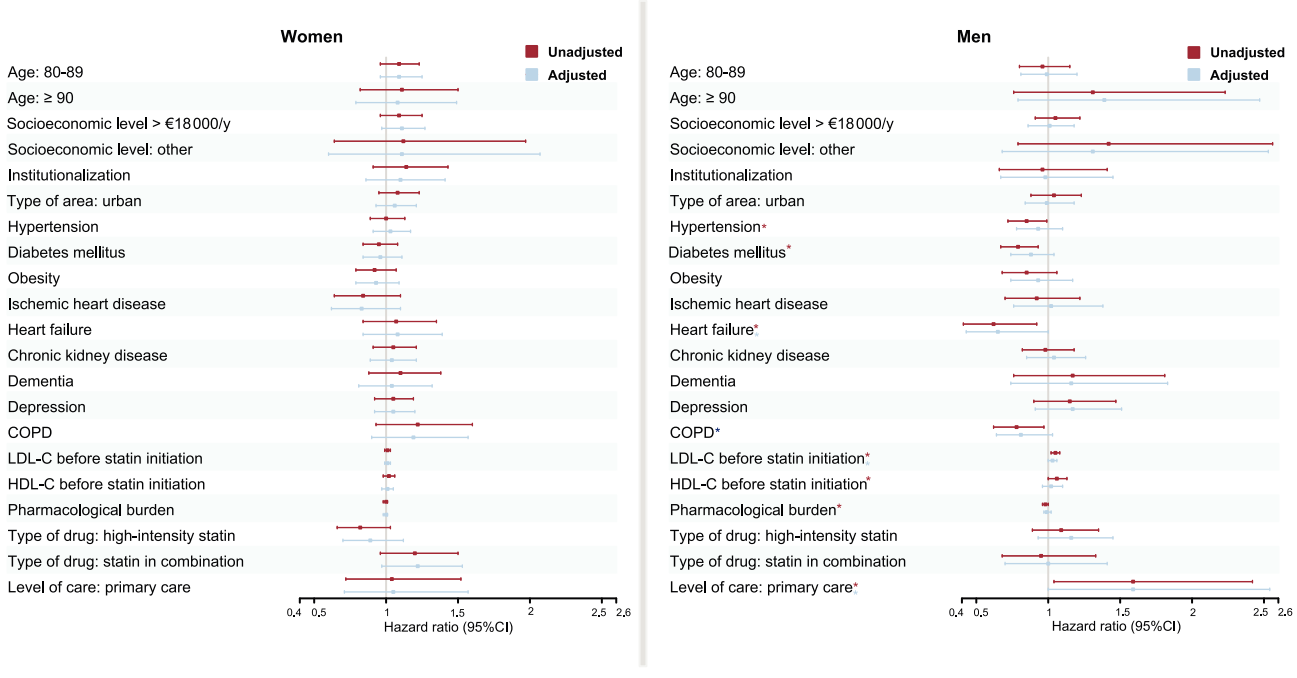

Figure 3. Crude and adjusted Fine and Gray competing risk analyses for discontinuation of statin therapy in primary prevention of cardiovascular disease in women and men older than 70 years, Aragon (Spain). Reference categories: age 70-79 years; socioeconomic level < €18 000/y; institutionalization: no; type of area: rural; comorbidities: no; type of drug: low-intensity statin; level of care: specialty care. The LDL-C and HDL-C variables were transformed so that the HRs obtained for them indicate the increase in risk as LDL-C or HDL-C increased by 10 mg/dL. The adjusted models included as covariates all the other variables presented. Women Omnibus *P* values for age = .36; socioeconomic level = .40; type of drug = .06. Men Omnibus *P* values for age = .53; socioeconomic level = .45; type of drug = .66. 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol. $^{*}P \leq .05$.

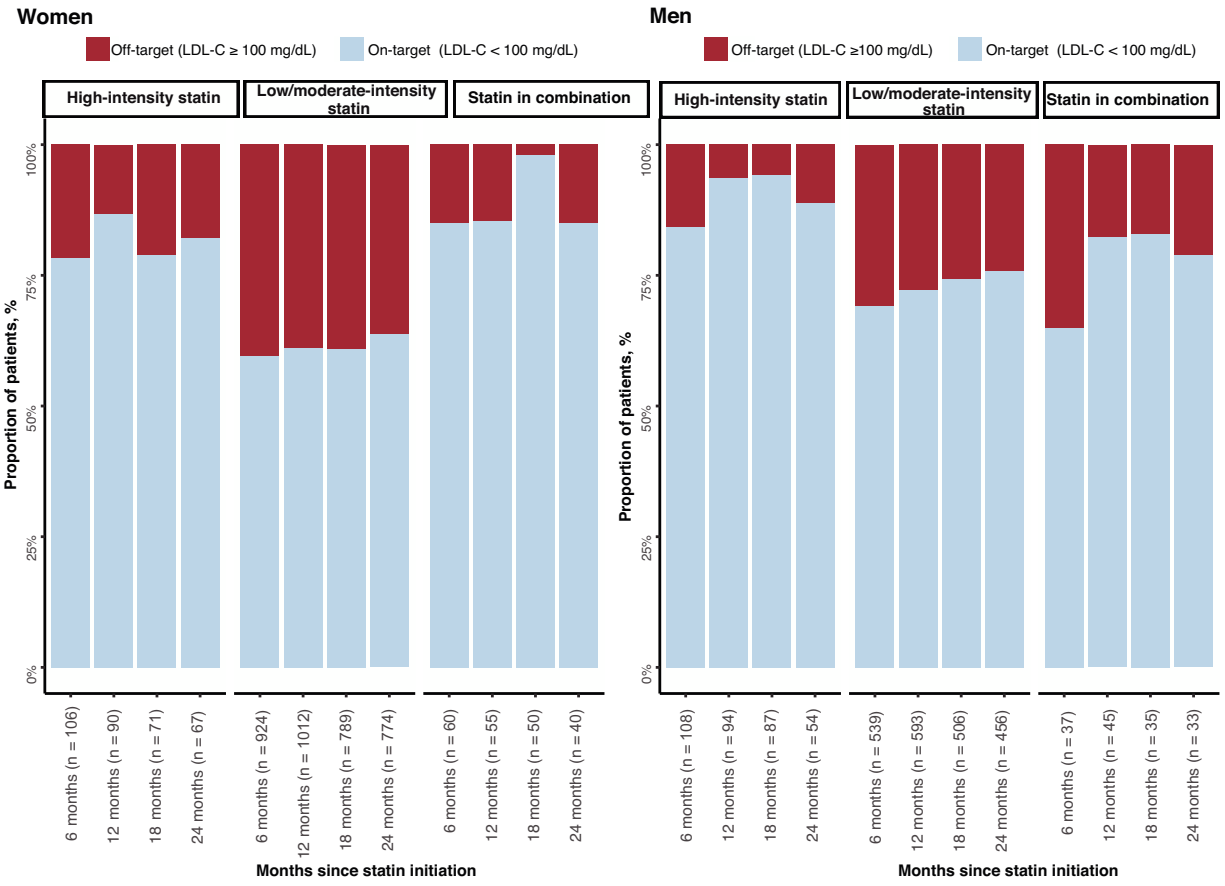

Figure 4. Proportion of women and men with controlled LDL-C (on target) in different window periods (months) since statin initiation, by type of statin. Only participants persistent and with at least 1 LDL-C measurement are considered in each window. Follow-up until discontinuation, MACE, or death. LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events.

Almost half of the individuals aged 70 years and older who started statin therapy for primary prevention of CVD had discontinued it after two years, with women and the oldest participants at higher risk of discontinuation. The role of the factors associated with discontinuation, although rarely statistically significant, also differed between women and men. Moreover, among persistent users, LDL-C control was better in a higher proportion of men than women, regardless of the time since initiation.

Other population-based studies have shown that around 40% to 50% of people discontinue statin therapy within 1 year of initiation.[18–20] These figures may seem to contrast with ours, which estimate almost 60% persistence after 2 years. However, these studies had shorter follow-up periods, and it has been shown that the largest drop in adherence to CVD preventive drugs occurs within the first year after initiation.[18] In addition, our study population consisted entirely of older adults, who have consistently shown better medication adherence than younger adults, likely due to greater risk awareness.[18,19,21]

With regard to age, one interesting finding, also supported by previous research, was its role in statin persistence. Individuals older than 90 years showed the highest risk of statin discontinuation. Although older age is generally considered a predictor of better adherence, when analyses are limited to elderly populations, the oldest individuals tend to be less adherent to chronic treatments.[3,18,19]

Women were less likely to receive high-intensity statins, despite having higher baseline LDL-C levels. This may indicate a lower therapeutic effort in women, as shown in previous studies,[22] with negative consequences for women's health. A greater inclination to protect women due to their underrepresentation in clinical trials—and thus the lack of evidence—could explain the different statin use patterns between men and women.[23] Conversely, in men, a higher prevalence of diagnoses associated with increased cardiovascular risk, such as diabetes, ischemic heart disease, or chronic kidney disease, may have influenced the type of statin prescribed. Men more frequently received prescriptions from specialist physicians compared with women. This could reflect a higher cardiovascular risk in men, leading to more frequent specialist visits. However, prior research has shown that women with chronic conditions are less likely than men to access specialty care.[24] It would therefore be important to confirm whether, under similar conditions, women are less often monitored by specialists other than family medicine physicians and whether men are prescribed statins earlier in specialty settings.

Sex differences in statin persistence and its determinants were identified, consistent with previous studies.[21,25] A higher proportion of women had several characteristics that placed them in a more vulnerable position compared with men: they were older, had lower socioeconomic status, a greater disease burden (particularly neurological conditions), and a higher pharmacological burden.

In the multivariate analysis in men, clinical conditions such as hypertension, diabetes mellitus, heart failure, or chronic obstructive pulmonary disease were associated with a lower risk of discontinuation, while higher baseline LDL-C levels and being prescribed statins by family medicine physicians were associated with increased discontinuation. Although not statistically significant, receiving a high-intensity statin compared with a low-

moderate intensity statin was associated with a higher likelihood of discontinuation in men. Conversely, in women, the trend was reversed. Several factors were related to statin persistence in women, but none reached statistical significance. This suggests that key predictors of statin persistence in women may not have been captured in this study. These could include preferences for dietary or lifestyle modifications over medication use, lower confidence in statin effectiveness, or higher sensitivity to adverse effects, as noted in other research.[8,26] Indeed, elderly women are particularly vulnerable to statin-induced muscle-related adverse effects.[27] Psychosocial, economic, and cultural factors also affect women and men differently. Women often assume caregiver roles and are more likely to manage the health and medication needs of others, but not always their own.[8,26]

Regarding the effect of statins, LDL-C levels were on target in over half of the treated participants within six months of initiation, rising to 70% at 2 years. Although women had higher baseline LDL-C levels, it could be expected that statin effects would eventually equalize LDL-C control between sexes. However, sex differences persisted, with women significantly less likely to achieve LDL-C targets, especially when treated with low-moderate intensity statins. The application of the same LDL-C target levels for both men and women, as endorsed by current guidelines, remains a topic of debate. This consideration is particularly relevant given that persistent women consistently show lower rates of LDL-C goal attainment.[26]

Evaluating the risk-benefit balance of statin use and preventing future MACE should be a priority in older adults. In this regard, studies with longer follow-up periods may provide a more comprehensive understanding of the role of long-term statin adherence in reducing CVD risk. In addition, future research should explore psychosocial and cultural predictors of adherence in older men and women and integrate these insights into strategies aimed at improving cardiovascular health from a gender perspective.

Strengths and limitations

The main strength of the present study is its population-based nature. The findings obtained using real-world data provide a comprehensive picture of actual statin use for the primary prevention of CVD in the elderly. While there is growing evidence from observational studies on the use and effects of these drugs in clinical practice, limited evidence exists for this specific population group. It is even less common to find studies highlighting sex differences among the elderly. Data were collected from BIGAN, a platform that integrates information from the Aragon Health Service systems for secondary use in research and policy-making.[28] The use of a competing risks approach enhances the validity of the results, as discontinuation is influenced by death and MACE, which are competing events that may preclude the occurrence of the event of interest.

This study also has some limitations. First, as is common in adherence studies, it was assumed that a statin was taken if it was dispensed, though this cannot be guaranteed. Nonetheless, this is currently considered a valid and reliable method for assessing persistence.[29] Second, the persistence indicator calculated could yield variable and potentially non-comparable results. However, it was defined following the Ascertaining Barriers to Compliance consensus taxonomy and estimated using the AdhereR package. Consensus-based guidelines for best practices in the definition and reporting of adherence measures were followed. Furthermore, the available data did not allow us to distinguish whether discontinuation was a patient- or prescriber-driven decision.

Incorporating interval-censored survival techniques could produce more accurate estimates since both statin persistence and LDL-C target attainment were inferred from intervals. However, this approach cannot be used in conjunction with the competing risks method, which was preferred due to the short 2-month intervals, minimizing the impact of interval censoring, particularly in older populations where mortality and MACE are key competing events.

The selection and follow-up of the study population during the coronavirus disease 2019 (COVID-19) pandemic may have influenced the results. However, the 2-year follow-up period is considered sufficient to appropriately capture and assess the variables of interest. Finally, the sensitivity analyses conducted confirmed the consistency of the findings.

CONCLUSIONS

Sex differences in statin persistence were observed in this Spanish older population. Women discontinued therapy earlier than men, and none of the analyzed factors were significantly associated with persistence in women. Our findings also suggest that women receive statin therapy later, are prescribed fewer high-intensity statins, and, when treated, achieve LDL-C control at lower rates compared with men. These differences highlight the need for a gender-based approach to further explore the barriers and facilitators of statin treatment.

WHAT IS KNOWN ABOUT THE TOPIC?

The use of statins in older adults for the primary prevention of CVD remains controversial. Moreover, sex differences in statin persistence and associated factors have been demonstrated in the general population. It is unclear whether these differences in statin use and in their effects on cholesterol levels also apply to older populations.

WHAT DOES THIS STUDY ADD?

In a Spanish population-based cohort, real-world data analysis shows that, compared with men, women begin statin therapy later and are prescribed high-intensity statins less frequently. Women also discontinue statins earlier, have more unknown associated factors, and are less likely to achieve LDL-C control when taking statins.

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ETHICAL CONSIDERATIONS

This study used data from the CARhES cohort, whose protocol was approved by the Ethics Committee for Clinical Research in Aragon (CEICA PI21/148). As it was a population-based study using real-world data, no direct contact or interaction with participants was required, and informed consent was waived by the Ethics Committee. Sex and gender variables were considered in accordance with the SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this study.

AUTHORS' CONTRIBUTIONS

S. Malo, M.J. Rabanaque, and I. Aguilar-Palacio contributed to the conception and design of the study. S. Malo and I. Aguilar-Palacio collected the data. S. Malo, A. Gamba, and J.M. Vinuesa-Hernando developed and designed the methodology. A. Gamba performed the statistical analysis. S. Malo wrote the first draft of the manuscript. M.J. Rabanaque, A. Gamba, J.M. Vinuesa-Hernando, A. Moreno-Juste, M.J. Lallana, J. Cebollada, and I. Aguilar-Palacio reviewed and revised the manuscript and approved the submitted version.

CONFLICTS OF INTEREST

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

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2025.05.007.

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