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ORIGINAL ARTICLE

Initiation of lipid-lowering therapy as primary prevention of cardiovascular disease in the elderly

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Abstract

Aims: This study aimed to analyse the initiation adherence phase to lipid-lowering therapy for primary prevention of cardiovascular disease in a Spanish population aged 70 years or older. The secondary objective was to identify the determinants of initiation and early discontinuation.

Methods: This was an observational study conducted in the CArdiovascular Risk factors for HEalth Service research (CARhES) cohort. People aged 70 and older with a first prescription of a lipid-lowering drug and without a previous major adverse cardiovascular event (MACE) were selected (2018–2021). Data on sociodemographics, clinical conditions, drugs and use of health services were collected from clinical and administrative electronic databases. The study population was classified into: non-initiation, early discontinuation (i.e., discontinuation after the first dispensing) and initiation with more than one dispensing. Their characteristics were compared. Determinants of initiation and early discontinuation were explored.

Results: Among the 15 019 people studied, 80.2% initiated the medication, 11.2% showed an early discontinuation and 8.6% were non-initiators. An older age or conditions such as dementia, diabetes or depression reduced the likelihood of initiation, while obesity and a high pharmacological burden increased it. People over 90 years of age or those prescribed a statin in combination were more likely to have an early discontinuation.

Conclusions: Non-initiation and early discontinuation are common among older people prescribed lipid-lowering drugs as primary prevention of cardiovascular disease for the first time. The presence of chronic pathologies other than cardiovascular ones should be considered when assessing whether or not to prescribe these drugs in the elderly.

KEYWORDS
aged, cardiovascular primary prevention, hypolipidaemic agents, medication adherence, real-world data

The Principal Investigators of the CARhES cohort are Sara Malo and Isabel Aguilar-Palacio.

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1 | INTRODUCTION

The significance of lipid-lowering drugs in primary prevention of cardiovascular disease is underscored by their efficacy in modulating lipid profiles, thereby mitigating atherogenic processes and reducing the likelihood of adverse cardiovascular events. However, the evidence on the benefit–risk of using lipid lowering drugs in older people is uncertain.[1] This translates into nonspecific recommendations on the appropriateness of prescribing these drugs in the elderly.[2] Furthermore, once prescribed, their success in improving health outcomes depends on patient medication adherence.[3,4] Medication adherence in the elderly has been identified as suboptimal[5] and is influenced, among other factors, by the numerous morbidities and polypharmacy usually present at this age. Poor medication adherence may lead to worsening health status, increased healthcare costs, reduced quality of life or an increased cardiovascular risk, which will also increase as this population ages.[6,7]

Numerous attempts at an international level have been made to improve adherence to chronic treatments. The European-funded Ascertaining Barriers to Compliance (ABC) project proposed in 2012 a new medication adherence taxonomy aimed at overcoming potential confusion and misunderstanding in the terms and concepts related to medication adherence. Since their publication, the ABC taxonomy[8] has been widely adopted internationally and translated into different languages. It subdivides adherence into three essential elements: initiation, implementation and discontinuation. The process starts with initiation of the treatment, when the patient takes the first dose of a prescribed medication. After the initiation of a determined drug, the patient can continue taking it (persistence) as prescribed (implementation) and, in a determined moment, discontinue the treatment.[8] However, discontinuation after the first dispensing, or early discontinuation, as defined by the ABC taxonomy, is also possible[8] and constitutes probably a good indicator of subsequent drug utilization.[9] Analyses of both initiation and early discontinuation can help characterize the problem and identify its determinants. To date, few studies have investigated both processes in cardiovascular preventive drugs, especially among older people using chronic medications.[10] It may be of special interest in the case of lipid-lowering drugs, given the lack of clear recommendations on their indication and the scarcity of evidence on their use in real-world contexts.

This study aimed to analyse the initiation adherence phase to lipid-lowering therapy for primary prevention of cardiovascular disease in a Spanish population aged 70 years or older. The secondary objective was to identify the determinants of initiation and early discontinuation.

What is already known about this subject

- Medication adherence in older people with chronic diseases is, in general, poor, especially in asymptomatic conditions.
- There is limited evidence regarding the magnitude of medication initiation (i.e., when the patient takes the first dose of a prescribed medication) and its determinants.
- The identification of people who discontinue their treatment after the first dispensing and their determinants provides useful information to improve drug utilization.

What this study adds

- Of patients aged over 70 being prescribed lipid-lowering therapy for primary prevention of cardiovascular disease for the first time, 8.6% did not initiate it.
- Some 11.2% of patients discontinued their treatment after the first dispensing.
- Poor initiation was more prevalent in older patients, and in patients with comorbidities such as dementia, highlighting a need to reassess prescription patterns in certain groups.

2 | METHODS

2.1 | Study setting and population

This was an observational study conducted in the CArdiovascular Risk factors for HEalth Service research (CARhES) cohort.[11] This is a dynamic population cohort which includes all people aged ≥16 years old registered as users of the public health system and with a diagnosis of dyslipidaemia, hypertension and/or diabetes in the Spanish region of Aragón (with approximately 1.5 million inhabitants). For the present study, we selected those aged ≥70 years with a first prescription of a lipid-lowering drug for primary prevention of cardiovascular disease, that is, without a previous major adverse cardiovascular event (MACE). The study period was 2018–2021.

The STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) checklist was followed in this study.

2.2 | Ethical considerations

The use of the CARhES cohort data was approved by the Clinical Research Ethics Committee of Aragon (CEICA PI21/148). This Committee waived informed consent.

2.3 | Data sources and variables

Data were obtained from BIGAN, a data lake that integrates data on sociodemographic, clinical and drugs and health services utilization information of all users of the Aragón health system, linked at the

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patient level through a pseudonymized individual code.[12] Data derives from different information systems: the users' database (BDU), with sociodemographic information including age, sex and basic health area (i.e., the administrative health unit); the electronic prescribing system and the dispensing database, with prescribing and dispensing data of any drug covered by the public health system; the hospital discharge records (CMBD) database, with information for each hospitalization; the primary care (OMI-AP) database, on visits to primary care and the corresponding medical diagnoses; the emergency care (PCH) database, with information obtained for each visit; and the adjusted morbidity groups (GMA) database, with summarized information on the diagnosed morbidities registered at the hospital, the primary and the emergency care settings for each patient and their individual morbidity burden. The latter is an index adapted to the Spanish healthcare system that consists of the aggregation of all the patient's diagnoses.[13]

To select patients who had been prescribed lipid-lowering therapy for primary prevention of cardiovascular disease, we identified and excluded those with one of the following diagnosis codes before the first prescription date: myocardial infarction [International Classification of Diseases (ICD)-10 code I21; ICD-9 code 410], subarachnoid, intracerebral and other nontraumatic haemorrhage (ICD-10 codes I60–I62; ICD-9 codes 430–432), or acute ischaemic stroke (ICD-10 code I63; ICD-9 code 433; ICD-9 code 434), in the hospital discharge records or in the emergency care database. These codes to describe a MACE were agreed among the clinicians in our group.

Pharmacological burden was estimated based on the number of medications belonging to different pharmacological subgroups, (i.e., the third level in the Anatomic Therapeutic Chemical classification),[13] that each patient was prescribed and dispensed during the year when the lipid-lowering therapy was first prescribed.[14]

Socioeconomic level of each patient was categorized into: < €18 000 per annum (p.a.), >€18 000 p.a. and other, this latter category including both mutualists and people uninsured.

2.4 | Analyses

Initiation was analysed as an adherence phase, by assessing the concordance between the first prescription of a lipid-lowering drug and its subsequent dispensing.[8] In Aragón, each prescription indicates a treatment starting and ending date, both registered in the Electronic prescribing system. The maximum time lapse between these two dates is 12 months, time during which the patient can fill the prescription according to his/her needs. After that, the prescription must be renewed by the prescriber in the case of chronic treatments.

For each patient, lipid-lowering drug prescriptions were followed up 180 days after the first one. Following these criteria, our study population was classified into three groups: non-initiators (i.e., without any dispensing of a lipid-lowering drug within the 30 days after its first prescription), initiators with early discontinuation (i.e., with a lipid-lowering drug dispensed within the 30 days after its first prescription, but with no refills within the following 180 days) and initiators (i.e., with a lipid-lowering drug dispensed within the 30 days after its first prescription, and at least one refill within the following 180 days).

The frequency of non-initiation, early discontinuation and initiation was estimated. Sociodemographic, clinical and treatment characteristics of patients in the three groups were analysed and compared by descriptive and bivariate analyses. Logistic regression analyses were then conducted to identify determinants of initiation (*vs.* non-initiation) and early discontinuation (*vs.* initiation with more than one dispensing).

A sensitivity analysis was conducted. Analyses were replicated by considering window periods extended until 90 and 180 days after the first prescription date.

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

3 | RESULTS

A total of 15 019 patients over 70 years of age with a first prescription of a lipid-lowering drug were studied (Table 1). Of these, 12 044 (80.2%) initiated the treatment within the 30 days after its first prescription and 1687 (11.2%) had an early discontinuation. There were 1288 (8.6%) non-initiator patients. Women represented 59.6% (8944) of the total patients and showed a similar distribution to men in the three study groups. Regarding age, initiation was more frequent in the youngest groups, while early discontinuation and non-initiation were more common among those aged over 90 years (15.0% with early discontinuation and 14.0% of non-initiators). Non-initiators showed a lower mean number of chronic conditions as well as a lower pharmacological burden. Also, non-initiation was more frequent among people with dementia. On the contrary, initiation was more commonly found in people with hypertension, diabetes mellitus, heart failure and obesity. Regarding the drug type, those treated with a single statin, both low/moderate and high intensity, showed higher frequency of initiation and lower frequency of early discontinuation, compared with people treated with a statin in combination or with a lipid-lowering drug other than a statin.

Table 2 shows the predictors of initiation, *vs.* non-initiation, in both the univariate and multivariate analysis. Predictors that significantly reduced the likelihood of initiation in the univariate analysis were age ≥85, dementia and ischaemic heart disease, while those associated with a higher likelihood of initiation were hypertension, obesity and pharmacological burden. After adjustment, the higher possibility of initiation was found in men, those living in urban areas, with obesity and a high pharmacological burden. On the contrary, a decreasing likelihood was found with increasing age and conditions such as dementia, diabetes, heart failure, chronic obstructive pulmonary disease (COPD), depression, ischaemic heart disease and chronic kidney disease. With respect to the type of drug, receiving a lipid-lowering drug other than a statin was related with a higher probability of non-initiation, compared with low/moderate intensity statins.

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TABLE 1 Comparison of sociodemographic, clinical and therapy characteristics of the three study groups.

	Initiation (>1 dispensing) *n* (%)	Early discontinuation *n* (%)	Non-initiation *n* (%)	Total
Total	12 044 (80.2)	1687 (11.2)	1288 (8.6)	15 019
Sex				
Women	7153 (80.0)	1010 (11.3)	781 (8.7)	8944
Men	4891 (80.5)	677 (11.1)	507 (8.3)	6075
Age				
70–74	4970 (80.8)	710 (11.5)	472 (7.7)	6152
75–79	3197 (81.1)	432 (11.0)	314 (8.0)	3943
80–84	2146 (80.8)	273 (10.3)	236 (8.9)	2655
85–89	1310 (78.2)	183 (10.9)	183 (10.9)	1676
90+	421 (71.0)	89 (15.0)	83 (14.0)	593
Socioeconomic level				
<€18 000 p.a.	8167 (82.1)	1072 (10.8)	704 (7.1)	9943
≥€18 000 p.a.	3403 (80.6)	507 (12.0)	314 (7.4)	4224
Other	374 (56.7)	31 (4.7)	255 (38.6)	660
Type of healthcare area				
Rural	3387 (81.4)	414 (9.9)	360 (8.7)	4161
Urban	8557 (80.2)	1196 (11.2)	913 (8.6)	10 666
Number of chronic pathologies	5.2 (2.6)	5.2 (2.7)	4.8 (2.7)	5.2 (2.6)
Dementia				
Yes	585 (79.2)	66 (8.9)	88 (11.9)	739
No	11 270 (81.0)	1507 (10.8)	1135 (8.2)	13 912
Hypertension				
Yes	7900 (82.3)	962 (10.0)	738 (7.7)	9600
No	3955 (78.3)	611 (12.1)	485 (9.6)	5051
Diabetes mellitus				
Yes	3177 (82.4)	371 (9.6)	307 (8.0)	3855
No	8678 (80.4)	1202 (11.1)	916 (8.5)	10 796
Heart failure				
Yes	770 (83.5)	65 (7.0)	87 (9.4)	922
No	11 085 (80.7)	1508 (11.0)	1136 (8.3)	13 729
COPD				
Yes	1025 (82.6)	117 (9.4)	99 (8.0)	1241
No	10 830 (80.8)	1456 (10.9)	1124 (8.4)	13 410
Depression				
Yes	2192 (81.4)	292 (10.8)	210 (7.8)	2694
No	9663 (80.8)	1281 (10.7)	1013 (8.5)	11 957
Ischaemic heart disease				
Yes	982 (80.1)	114 (9.3)	130 (10.6)	1226
No	10 873 (81.0)	1459 (10.9)	1093 (8.1)	13 425
Chronic kidney disease				
Yes	2162 (81.0)	278 (10.4)	228 (8.5)	2668
No	9693 (80.9)	1295 (10.8)	995 (8.3)	11 983
Obesity				
Yes	1740 (84.8)	198 (9.7)	113 (5.5)	2051
No	10 115 (80.3)	1375 (10.9)	1110 (8.8)	12 600
Pharmacological burden	9.4 (4.6)	9.0 (4.8)	5.9 (4.9)	9.0 (4.8)

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TABLE 1 (Continued)

	Initiation (>1 dispensing) *n* (%)	Early discontinuation *n* (%)	Non-initiation *n* (%)	Total
Type of lipid-lowering drug				
Low/moderate intensity statin	9032 (81.7)	1087 (9.8)	936 (8.5)	11 055
High intensity statin	1622 (81.3)	199 (10.0)	173 (8.7)	1994
Statin in combination	547 (76.7)	109 (15.3)	57 (8.0)	713
Other lipid-lowering drug	843 (67.1)	292 (23.2)	122 (9.7)	1257

Note: Categorical variables expressed as number (%) and continuous variables as mean (standard deviation).
Abbreviations: COPD, chronic obstructive pulmonary disease.

TABLE 2 Predictors of initiation within the 30 days after the first prescription of a lipid-lowering drug in primary prevention of cardiovascular disease.

	Univariate estimate (95% CI)	*P*-value	Multivariate estimate (95% CI)	*P*-value
Sex				
Women	1		1	
Men	1.05 (0.94–1.18)	0.407	1.35 (1.18–1.55)	<0.001
Age				
70–74	1		1	
75–79	0.96 (0.83–1.12)	0.594	0.81 (0.69–0.95)	0.009
80–84	0.85 (0.72–1.00)	0.054	0.70 (0.58–0.84)	<0.001
85–89	0.68 (0.57–0.81)	<0.001	0.52 (0.42–0.64)	<0.001
≥90	0.51 (0.40–0.66)	<0.001	0.46 (0.34–0.63)	<0.001
Socioeconomic level				
<€18 000 p.a.	1		1	
≥€18 000 p.a.	0.95 (0.83–1.09)	0.456	0.96 (0.82–1.11)	0.562
Other	0.12 (0.10–0.14)	<0.001	0.19 (0.16–0.23)	<0.001
Type of healthcare area				
Rural	1		1	
Urban	1.01 (0.89–1.15)	0.858	1.19 (1.03–1.37)	0.015
Pathologies				
Dementia	0.66 (0.52–0.83)	<0.001	0.60 (0.46–0.78)	<0.001
Hypertension	1.28 (1.13–1.44)	<0.001	0.95 (0.83–1.08)	0.428
Diabetes mellitus	1.07 (0.94–1.23)	0.316	0.81 (0.69–0.94)	0.004
Heart failure	0.87 (0.69–1.10)	0.217	0.49 (0.38–0.65)	<0.001
COPD	1.06 (0.86–1.31)	0.622	0.66 (0.52–0.84)	0.001
Depression	1.09 (0.94–1.28)	0.251	0.73 (0.62–0.87)	<0.001
Ischemic heart disease	0.75 (0.62–0.91)	0.003	0.58 (0.46–0.72)	<0.001
Chronic kidney disease	0.97 (0.84–1.13)	0.682	0.83 (0.70–0.99)	0.035
Obesity	1.66 (1.36–2.03)	<0.001	1.27 (1.03–1.58)	0.031
Pharmacological burden	1.22 (1.20–1.24)	<0.001	1.25 (1.23–1.28)	<0.001
Type of lipid-lowering drug				
Low/moderate intensity statin	1		1	
High intensity statin	0.97 (0.82–1.16)	0.758	0.82 (0.68–1.00)	0.046
Statin in combination	1.06 (0.81–1.42)	0.660	1.04 (0.77–1.44)	0.789
Other lipid-lowering drug	0.86 (0.71–1.05)	0.138	0.65 (0.52–0.81)	<0.001

Note: Non-adjusted ($n = 15\,019$) and adjusted ($n = 14\,651$) regression models (initiation during the 30 days following the first prescription *vs.* non-initiation).
Abbreviations: 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease.

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Among all people who filled the first dispensing (Table 3), we observed in both the univariate and multivariate analyses that people aged 90 years and older showed an early discontinuation more frequently than people aged 70–74 years. The same was found for those prescribed a statin in combination or a lipid-lowering drug other than a statin, compared with a low/moderate intensity statin. Conversely, having hypertension, diabetes or heart failure statistically reduced the probability of showing an early discontinuation, after adjusting by other factors.

Figure 1 shows the distribution of the study population into the three groups (initiation, early discontinuation and non-initiation) when applying window periods of 30, 90 and 180 days. Tables S1 and S2 present the results on the predictors of initiation obtained by applying window periods of 90 and 180 days after the first prescription date (sensitivity analyses).

4 | DISCUSSION

To the best of our knowledge, this population-based study provides the most comprehensive characterization of lipid-lowering therapy initiation in the elderly to date. Our results showed a higher frequency

TABLE 3 Predictors of early discontinuation within the 30 days after the first prescription of a lipid-lowering drug in primary prevention of cardiovascular disease.

	Univariate estimate (95% CI)	*P*-value	Multivariate estimate (95% CI)	*P*-value
Sex				
Women	1		1	
Men	0.98 (0.88–1.09)	0.707	0.94 (0.84–1.06)	0.339
Age				
70–74	1		1	
75–79	0.95 (0.83–1.07)	0.393	0.98 (0.86–1.12)	0.797
80–84	0.89 (0.77–1.03)	0.126	0.99 (0.84–1.16)	0.892
85–89	0.98 (0.82–1.16)	0.800	1.14 (0.94–1.37)	0.179
≥90	1.48 (1.16–1.88)	0.001	1.78 (1.36–2.30)	<0.001
Socioeconomic level				
<€18 000 p.a.	1		1	
≥€18 000 p.a.	1.14 (1.01–1.27)	0.028	1.10 (0.97–1.24)	0.138
Other	0.63 (0.43–0.90)	0.015	0.59 (0.40–0.85)	0.007
Type of healthcare area				
Rural	1		1	
Urban	1.14 (1.02–1.29)	0.027	1.13 (1.00–1.28)	0.058
Pathologies				
Dementia	0.84 (0.64–1.09)	0.200	0.80 (0.61–1.04)	0.106
Hypertension	0.79 (0.71–0.88)	<0.001	0.81 (0.72–0.91)	<0.001
Diabetes mellitus	0.84 (0.74–0.95)	0.007	0.87 (0.76–0.98)	0.028
Heart failure	0.62 (0.47–0.80)	<0.001	0.61 (0.46–0.80)	<0.001
COPD	0.85 (0.69–1.03)	0.107	0.91 (0.74–1.12)	0.372
Depression	1.00 (0.88–1.15)	0.944	0.99 (0.86–1.14)	0.923
Ischemic heart disease	0.87 (0.70–1.05)	0.159	0.94 (0.76–1.16)	0.593
Chronic kidney disease	0.96 (0.84–1.10)	0.586	1.04 (0.90–1.20)	0.590
Obesity	0.84 (0.71–0.98)	0.027	0.91 (0.77–1.07)	0.259
Pharmacological burden	0.98 (0.97–0.99)	0.004	0.99 (0.98–1.01)	0.387
Type of lipid-lowering drug				
Low/moderate intensity statin	1		1	
High intensity statin	1.02 (0.87–1.19)	0.814	1.02 (0.86–1.21)	0.802
Statin in combination	1.66 (1.33–2.04)	<0.001	1.67 (1.33–2.08)	<0.001
Other lipid-lowering drug	2.88 (2.48–3.33)	<0.001	3.13 (2.68–3.64)	<0.001

Note: Non-adjusted ($n = 13\,731$) and adjusted ($n = 13\,428$) regression models (early discontinuation *vs*. initiation with ≥2 dispensings during the 180 days following the first prescription).
Abbreviations: 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease.

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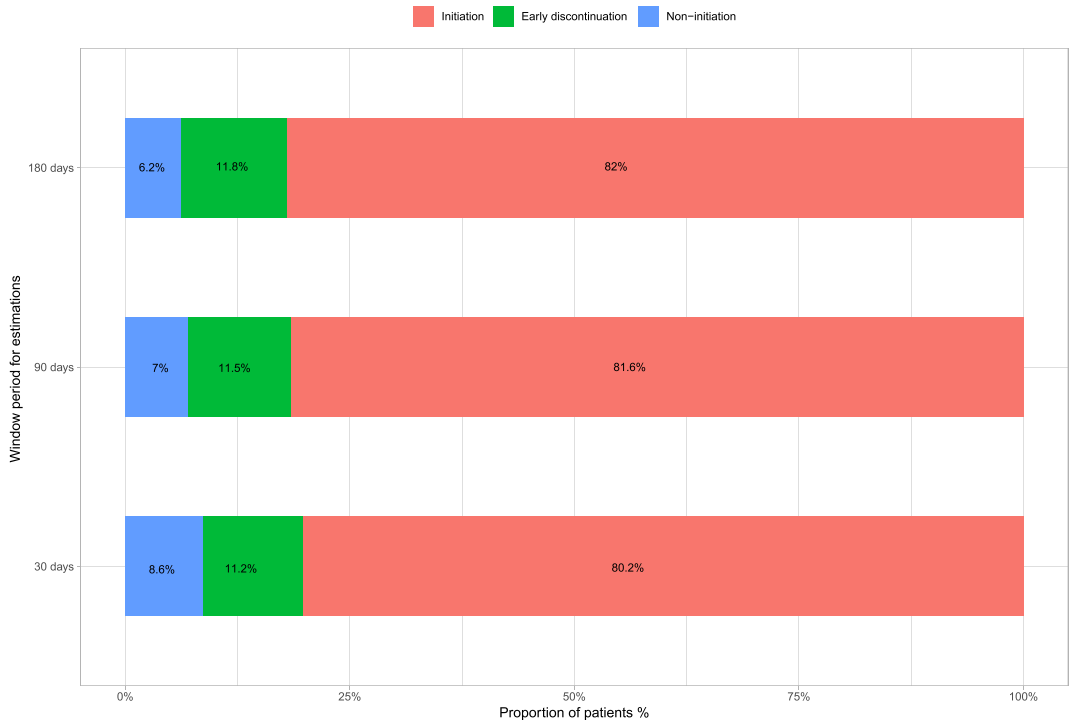

FIGURE 1 Proportion of elderly patients with initiation, early discontinuation and non-initiation of lipid-lowering therapy in primary prevention of cardiovascular disease when applying window periods of 30, 90 and 180 days (sensitivity analysis).

of first prescription of these drugs than would be expected, given the lack of evidence on the benefits of initiating this therapy in primary prevention of cardiovascular disease at this age. They accounted for 7% of the entire population over 70 years of age in Aragón,[15] ranging from 9% (in the 70–74 age group) to 3% (in the ≥90 age group). Current European clinical practice guidelines, which are the reference to be followed in Spain, do not issue very concrete recommendations for statin prescribing in the elderly. They state that dyslipidaemias in older people without a prior MACE should be managed individually, through non-pharmacological interventions.[2,15] The use of lipid-lowering drugs should be restricted to patients with a high or very high cardiovascular risk, always considering their frailty, quality of life and life expectancy.[16]

Additionally, about one fifth of the study population discontinued their treatment after its first prescription. This figure includes both initiators who had multiple dispensings after the first one and people who discontinued their treatment after the first dispensing. This approach seems relevant in medication adherence research because showing an early discontinuation corresponds, in practice, to being a non-initiator. Previous research has indicated that 10%–30% of adult patients fail to fill their initial statin prescription.[17] Other studies have also shown elevated figures of chronic patients with an early discontinuation of statins.[18,19] These figures are, however, not specific to the elderly, where the literature is, to the best of our knowledge, non-existent. In any case, our findings require special attention, given the clinical and economic consequences of medication non-adherence.

We found that the percentage of initiators decreased as age increased. Research on medication adherence has traditionally shown that older people are more adherent than younger people.[20] However, our results support previous findings reported by other authors who demonstrated that, when focusing only on elderly people, being older reduces the likelihood of being adherent.[21] Some possible reasons for this may be attributable to a misbalance between the perceived necessity for treatment and concerns,[22] including higher presence of concerns of side effects, such as muscle-related events or even rhabdomyolysis, scepticism about effectiveness, lack of awareness of its usefulness, or prioritizing other treatments related to other comorbidities.[23]

Being male was associated with a higher likelihood of initiating lipid-lowering therapy, after adjusting for other variables. Some reviews have shown that the existing lower statin adherence in women could be related to higher rates of statin intolerance, women being older at the time of diagnosis of a high cardiovascular risk, and potentially greater caregiving responsibilities that make them prioritize other actions over medication taking.[24] However, the reasons for gender disparities in lipid management and outcomes are still to be completely understood.

In relation to comorbidities, those related to the central nervous system, such as dementia or depression, reduced the probability of initiation. These conditions have been classically related to poor medication adherence, not only with lipid-lowering drugs. Reconsidering the prescription of certain treatments in these patients seems imperative.[25] If this therapy is strictly necessary, increased efforts to improve adherence are required, through actions other than the usual ones. These may involve healthcare professionals and caregivers, as well as the use of new adherence enhancing technologies.[26] When suffering

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from cardiovascular conditions, such as ischaemic heart disease, heart failure or diabetes, initiation was also reduced after adjusting by other factors. These results contrast with the review of Karr[17] who noted better adherence to statin treatment in those patients with a history of myocardial infarction or stroke, hypertension or diabetes. These were not, however, only older people. In our study population we also found that, once the lipid-lowering therapy was initiated, presenting heart failure, diabetes or hypertension was associated with a reduced probability of having an early discontinuation. This was in line with the findings reported by Vilaplana et al.,[19] who followed a Spanish cohort of patients who received a first prescription of different cardiovascular preventive medications. They demonstrated that a diagnosis of diabetes, hypertension or a recent cardiovascular disease decreased the probability of early discontinuation of statins. It seems reasonable that older patients with multimorbidity are reluctant to initiate a therapy such as the lipid-lowering one, because they prioritize the treatment of other, more severe comorbidities or those with symptoms. However, once initiated, they are less likely to discontinue it. Another finding that coincided with those of Vilaplana et al.[19] was the association between having obesity and initiating the lipid-lowering therapy. This could be attributable to the higher risk perception that an obese patient may have and, therefore, their better adherence to both lifestyle and medication recommendations, aligning with the healthy adherer effect.[27]

The type of lipid-lowering drug also influenced initiation and early discontinuation, with predictors somewhat different for both processes. Being prescribed a low/moderate intensity statin increased the likelihood of initiation and reduced the likelihood of early discontinuation, compared with a lipid-lowering drug other than a statin. When compared with a statin in combination, these latter showed a higher probability of discontinuing after the first dispensing. This finding represents an additional argument for not recommending initiation with statins in combination in the elderly. Current guidelines are clear in this regard and, when needed at this age, lipid-lowering drugs should be incorporated using a stepwise approach, due to the common appearance of pharmacological interactions and adverse effects.[28]

Our results provide insights into determinants of medication adherence, allowing healthcare professionals, especially at the primary care level, to identify subgroups that may benefit from specific therapeutic strategies or need additional support or intervention to improve adherence rates. Nevertheless, the high prescribing frequency of these drugs in the elderly, together with the variations found in initiation based on different patient factors, emphasize the importance of reconsidering the prescription of lipid-lowering drugs in some groups (such as the very elderly) and the need to design personalized approaches for medication management.[29]

The main strength of this study is its population-based nature. The analysis of real-world data from the entire elderly population in a Southern European region gives the findings a high value. Also, the classification of these people according to their initiation adherence pattern, differentiating those with an early discontinuation and investigating their determinants represents a novelty with respect to previous studies. It provides relevant knowledge for the improvement of medication adherence and, consequently, of health outcomes. Lastly, the sensitivity analyses carried out by applying different window periods to classify the people into the study groups did not lead to conflicting results. Both the percentage of people classified in each group, their characteristics and the associated factors in the regression analyses showed consistent results. The few differences found were in variables that, when significant, did so with a low strength of association, which gives robustness to the method used.

The study has also some limitations. First, the use of electronic health databases is limited by the quality of the data recorded. The data used in the present study, however, are obtained from BIGAN and are subjected to rigorous quality control procedures that enhance the reliability and validity of the CARhES cohort data for research purposes from its origin. Moreover, as usual in adherence studies, we were not able to ascertain whether dispensed medications were consumed. Nor was it possible to find out all the factors that determined the decision to prescribe or not to fill the medication.

5 | CONCLUSIONS

In this large-scale pharmacoepidemiological study we found that, despite not being explicitly recommended by current guidelines, a high number of elderly people are prescribed a lipid-lowering drug for the first time as primary prevention of cardiovascular disease. Moreover, one fifth of them either did not initiate their treatment or showed an early discontinuation after the first prescription. Being over 90 years old reduced the likelihood of initiation and increase the likelihood of early discontinuation. Also, suffering from conditions such as dementia, diabetes or depression decreased the likelihood of initiation, while once the first prescription was filled, presenting diabetes, hypertension or heart failure decreased the likelihood of early discontinuation. The type of drug also influenced the initiation.

These findings reflect the need to reconsider the prescription of lipid-lowering drugs in the elderly, taking into account their general clinical status and personal situation. When the expected benefit–risk balance is positive, and therefore the therapy needed, adherence improvement efforts should be focused on these specific groups.

AUTHOR CONTRIBUTIONS

J.M. Vinuesa-Hernando, I. Aguilar-Palacio, M.J. Rabanaque and S. Malo contributed to conception and design of the study. I. Aguilar-Palacio and S. Malo performed the data collection. J.M. Vinuesa-Hernando and S. Malo developed and designed the methodology. A. Gamba performed the statistical analysis. J.M. Vinuesa-Hernando and S. Malo wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are curated as part of the CARhES cohort, extracted from the BIGAN information platform for secondary use of health data of the Aragon Health System, Spain. The permission obtained to setup the CARhES cohort do not allow data redistribution without the express approval of the BIGAN management body, the Institute of Health Science in Aragon (https://www.iacs.es/bigan/). Nonetheless, proposals for collaborations to exploit CARhES data are welcome. Interested researchers can contact the CARhES principal investigators (Sara Malo—smalo@unizar.es—and Isabel Aguilar-Palacio—iaguilar@unizar.es–).

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REFERENCES

1. Marcellaud E, Jost J, Tchalla A, Magne J, Aboyans V. Statins in primary prevention in people over 80 years. *Am J Cardiol*. 2023;187:62-73. doi:10.1016/j.amjcard.2022.10.015
2. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
3. Ofori-Asenso R, Ilomäki J, Tacey M, et al. Predictors of first-year non-adherence and discontinuation of statins among older adults: a retrospective cohort study. *Br J Clin Pharmacol*. 2019;85(1):227-235. doi:10.1111/bcp.13797
4. Malo S, Maldonado L, Rabanaque MJ, et al. Patterns of statin adherence in primary cardiovascular disease prevention during the pandemic. *Front Pharmacol*. 2022;13:980391. Published 2022 Nov 14. doi:10.3389/fphar.2022.980391
5. Menditto E, Cahir C, Aza-Pascual-Salcedo M, et al. Adherence to chronic medication in older populations: application of a common protocol among three European cohorts. *Patient Prefer Adherence*. 2018;12:1975-1987. Published 2018 Oct 5. doi:10.2147/PPA.S164819
6. Kang JH, Choi SE, Xu H, Park DJ, Lee JK, Lee SS. Non-adherence to methotrexate was associated with high disease activity and poor health-related outcomes during a 4-year follow-up of rheumatoid arthritis patients. *Clin Exp Rheumatol*. 2022;40(9):1744-1753. doi:10.55563/clinexprheumatol/ir6yds
7. Chang PY, Chien LN, Lin YF, Chiou HY, Chiu WT. Nonadherence of oral antihyperglycemic medication will increase risk of end-stage renal disease. *Medicine (Baltimore)*. 2015;94(47):e2051. doi:10.1097/MD.0000000000002051
8. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705. doi:10.1111/j.1365-2125.2012.04167.x
9. Crockett KB, Wen Y, Overton ET, et al. One-year statin persistence and adherence in adults with HIV in the United States. *J Clin Lipidol*. 2021;15(1):181-191. doi:10.1016/j.jacl.2020.11.001
10. Morotti K, Lopez J, Vaupel V, Swislocki A, Siegel D. Adherence to and persistence with statin therapy in a veteran population. *Ann Pharmacother*. 2019;53(1):43-49. doi:10.1177/1060028018792702
11. Aguilar-Palacio I, Rabanaque M, Castel S, et al. Cohort profile: the CArdiovascular risk factors for hEalth services research (CARhES) cohort study. *Int J Epidemiol*. 2024;53(2):dyae015. doi:10.1093/ije/dyae015
12. Institute of Health Science in Aragon (IACS). Big Data in Healthcare. https://bigan.iacs.es/en/home. [accessed 04 March 2024]
13. World Health Organization. Anatomical Therapeutic Chemical (ATC) Classification. https://www.who.int/tools/atc-ddd-toolkit/atc-classification. Accessed June 20, 2024.
14. Monterde D, Vela E, Clèries M, grupo colaborativo GMA. Los grupos de morbilidad ajustados: nuevo agrupador de morbilidad poblacional de utilidad en el ámbito de la atención primaria [Adjusted morbidity groups: a new multiple morbidity measurement of use in Primary Care]. *Aten Primaria*. 2016;48(10):674-682. doi:10.1016/j.aprim.2016.06.003
15. Gobierno de Aragón. Padrón Municipal de Habitantes. Pirámides de Población, Aragón. Published online November 13, 2023. https://www.aragon.es/-/piramides-de-poblacion.-aragon. [accessed 04 March 2024]
16. Kleipool EE, Dorresteijn JA, Smulders YM, Visseren FL, Peters MJ, Muller M. Treatment of hypercholesterolaemia in older adults calls for a patient-centred approach. *Heart*. 2020;106(4):261-266. doi:10.1136/heartjnl-2019-315600
17. Karr S. Epidemiology and management of hyperlipidemia. *Am J Manag Care*. 2017;23(9 Suppl):S139-S148.
18. Lemstra M, Blackburn D. Nonadherence to statin therapy: discontinuation after a single fill. *Can J Cardiol*. 2012;28(5):567-573. doi:10.1016/j.cjca.2012.03.018
19. Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, et al. Initiation and single dispensing in cardiovascular and insulin medications: prevalence and explanatory factors. *Int J Environ Res Public Health*. 2020;17(10):3358. doi:10.3390/ijerph17103358
20. Ge L, Heng BH, Yap CW. Understanding reasons and determinants of medication non-adherence in community-dwelling adults: a cross-sectional study comparing young and older age groups. *BMC Health Serv Res*. 2023;23(1):905. doi:10.1186/s12913-023-09904-8
21. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2019;4(3):206-213. doi:10.1001/jamacardio.2018.4936
22. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PLoS One*. 2013;8(12):e80633. Published 2013 Dec 2. doi:10.1371/journal.pone.0080633
23. Spinler SA, Cziraky MJ, Willey VJ, et al. Frequency of attainment of low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol goals in cardiovascular clinical practice (from the National Cardiovascular Data Registry PINNACLE registry). *Am J Cardiol*. 2015;116(4):547-553. doi:10.1016/j.amjcard.2015.05.011
24. Goldstein KM, Zullig LL, Bastian LA, Bosworth HB. Statin adherence: does gender matter? *Curr Atheroscler Rep*. 2016;18(11):63. doi:10.1007/s11883-016-0619-9
25. El-Saifi N, Moyle W, Jones C, Tuffaha H. Medication adherence in older patients with dementia: a systematic literature review. *J Pharm Pract*. 2018;31(3):322-334. doi:10.1177/0897190017710524
26. van Boven JFM, Tsiligianni I, Potočnjak I, et al. European network to advance best practices and technology on medication adherence:

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mission statement. *Front Pharmacol*. 2021;12:748702. doi:10.3389/fphar.2021.748702
27. Bernardini F, Gostoli S, Marchetti G, et al. A survey on lifestyle and awareness of the use of statins in a sample of cardiopathic patients. *Psychol Health Med*. 2020;25(8):1004-1012. doi:10.1080/13548506.2020.1717555
28. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
29. Cai T, Abel L, Langford O, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ*. 2021;374:n1537. Published 2021 Jul 14. doi:10.1136/bmj.n1537

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