Statin Use in Older Adults for Primary Cardiovascular Disease Prevention Across a Spectrum of Cardiovascular Risk

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BACKGROUND: There remains uncertainty regarding optimal primary atherosclerotic cardiovascular disease (ASCVD) prevention practices for older adults.
OBJECTIVE: To assess statin treatment patterns and incident ASCVD among older patients for primary prevention across the spectrum of ASCVD risk.
DESIGN: Retrospective cohort study of participants without ASCVD aged 65–79 years. Patients were stratified by age (65–69, 70–75, > 75 years) and 10-year ASCVD risk category (low/borderline, intermediate, high) based on the Pooled Cohort Equations. Multivariable logistic regressions were used to identify predictors of moderate- or high-intensity statin prescriptions. Cox proportional models were used to estimate hazard ratios (HRs) for incident ASCVD.
PARTICIPANTS: Patients aged 65–79 years without ASCVD from a Northern California health system.
MAIN MEASURES: Statin prescriptions and incident ASCVD events.
KEY RESULTS: There were 54,066 patients, with 10,288 (19%) aged > 75 years and 57% women. Compared with younger groups, adults > 75 years were less likely to be prescribed moderate- or high-intensity statin prescriptions across ASCVD risk groups (all $p < 0.001$); this persisted after multivariable adjustment including for ASCVD risk (odds ratio [OR] 0.80, 95% confidence interval [CI] 0.74–0.86). Adults > 75 years were more likely to experience incident ASCVD (HR 1.42, 95% CI 1.23–1.63). Women (OR 0.85, 95% CI 0.81–0.89) and underweight older adults (OR 0.45, 95% CI 0.33–0.61) were also less likely to receive moderate- or high-intensity statins.
CONCLUSIONS: Among older adults aged 65–79 years without prior ASCVD, those > 75 years of age were less likely to receive moderate- or high-intensity statins regardless of ASCVD risk compared with their younger counterparts, while experiencing more incident ASCVD. Efforts are warranted to study the reasons for age-based differences in statin use in older adults, particularly those at highest ASCVD risk.

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BACKGROUND

Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of death in the United States of America (US). Age is the strongest predictor of ASCVD and older adults experience a disproportionate burden of events compared with younger patients.[1,2] Statin therapy is the cornerstone of ASCVD prevention and is associated with outcome benefits among older adults.[3–6] In a meta-analysis of older adults without cardiovascular disease, statin therapy was shown to decrease myocardial infarctions (MIs) and stroke.[3] Similarly, in a sub-analysis of the JUPITER (Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) and HOPE-3 (Heart Outcomes Prevention Evaluation) trials, participants over age 70 years experienced consistent statin outcome benefits, comparable to those of younger trial participants.[4] There are limited randomized clinical trial data for the benefits of statins in primary prevention in patients over age 75 years. A meta-analysis from the Cholesterol Treatment Trialists' Collaboration that included 14,483 patients over age 75 years suggested no significant benefit of statins among adults > 75 years of age for primary prevention.[7] In contrast, a retrospective cohort study of 326,981 US veterans over age 75 concluded that statin use was significantly associated with decreased all-cause and cardiovascular mortality.[8]

Although there is evidence of primary prevention benefit from statin use among older adults, there is also marked heterogeneity and uncertainty among major guideline recommendations regarding statin initiation and dosing. Adults over the age of 65, for example, are not included in the European Society of Cardiology (ESC)-recommended Systematic

Coronary Risk Evaluation (SCORE) system for risk-based primary prevention.[9] The American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equations (PCE) have been validated up to age 79, but ACC/AHA recommendations for statins remain less clear for adults over the age of 75, highlighting risk–benefit discussions that incorporate frailty, comorbidity, and life expectancy considerations.[10–12] This clinical uncertainty may translate to inconsistent real-world statin use among older adults for primary prevention even with elevated baseline ASCVD risk, particularly for patients over 75 years of age. Prior data from the Patient and Provider Assessment of Lipid Management (PALM) registry and the Medicare Expenditure Panel Survey suggested that patients aged 75 years or more were as likely or more likely, respectively, to use statins for primary prevention versus much younger patients including those below the age of 65 years.[13,14] However, these studies did not evaluate statin use by baseline ASCVD risk, a pivotal component of statin risk–benefit decisions, and provided limited data on statin use by dose intensity. Data remain lacking regarding statin use by baseline ASCVD risk and by statin intensity within the population of older patients above the age of 65 who likely experience the highest uncertainty regarding statin use for primary prevention. Clarifying and appropriately addressing statin therapy gaps in older patients, particularly among those at highest ASCVD risk, is necessary for guiding optimal ASCVD prevention.

We thus sought to evaluate contemporary statin prescription patterns by intensity across the spectrum of ASCVD risk levels in a multiethnic, outpatient, and primary prevention cohort of older patients aged 65 years or more.

METHODS

Study Population

Patients 65 to 79 years of age without pre-existing ASCVD were identified from a large community-based outpatient healthcare organization in Northern California through electronic health records (EHR) data from 2007 to 2018. The Pooled Cohort Equations to calculate ASCVD risk have been validated for patients up to 79 years of age, and therefore, patients older than 79 years were excluded from the study cohort. To ascertain the absence of ASCVD, we imposed a 2-year wash-in period for each person beginning with their first visit date. During the wash-in period, included patients were required to have at least 2 visits with no evidence of any ASCVD event in the problem list or encounter diagnoses (ICD-9 410–414, V45.81, V45.82; ICD-10 I20–I25, Z95.5, Z98.61 (coronary artery disease), ICD-9 430–438; ICD-10 G45, G46, I60–I69 (cerebrovascular disease), ICD-9 440, 443.9; ICD-10 I74, I75 (peripheral artery disease)).[15]

Of these ASCVD-free individuals who were included in the study, the index date was defined as the first visit after the wash-in period. All the baseline demographic and clinical characteristics were defined as of the index date. We limited the final study cohort to those with at least one encounter in the healthcare system for the next 2 years to ensure that we captured the full clinical information of the study cohort.

Measures

Demographics and Comorbidities. For patients meeting inclusion criteria, demographic, clinical comorbidities, and healthcare utilization data were extracted from the EHR. Demographic data included age, sex, and race/ethnicity. Clinical comorbidities included smoking status, body mass index (BMI), history of diabetes, renal disease, malignancy, and dementia. Healthcare utilization variables included number of prescription medications excluding statins and number of medical visits in the preceding year, split into groups based on observed median value (less than or equal to the median and greater than the median). Frequency of outpatient visits during the year prior was also included in the multivariable analysis to adjust for clinical confounders that may have influenced statin prescription. Outpatient visits were categorized according to the observed median value[2] and split into three overall groups based on the range of observed values, with one group lower than the median value.

ASCVD Risk Classification. The ASCVD 10-year risk score (ASCVD10y) was computed with the PCE which incorporates age, diabetes, systolic blood pressure, antihypertensive medication, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and current smoking status and is specific to race and sex.[16] Multiple imputations, conditional on all comprehensive sets of clinical demographic characteristics available from the EHR data, were used to impute missing data for systolic blood pressure, smoking status, HDL-C, and total cholesterol. Although the PCE was developed with a population of age 40–75, it has been validated in adults up to 79 years old.[12] The equation for non-Hispanic white (NHW) was used for all races other than African American. Based on risk stratification as outlined in the ACC/AHA guidelines, patients were classified as follows: (1) low risk: ASCVD10y < 5%; (2) borderline risk: ASCVD10y ≥ 5% and < 7.5% and no diabetes; (3) intermediate risk: ASCVD10y ≥ 7.5% and < 20%; and (4) high-risk: ASCVD10y ≥ 20%.[7] Low and borderline risk groups were combined in the analysis.

Statin Intensity. Statin use was defined as the prescription of any statin on the index date and classified into three levels of intensity, according to ACC/AHA cholesterol treatment guidelines: (1) high intensity (daily dosage of atorvastatin 40–80 mg, rosuvastatin 20–40 mg, lovastatin 80 mg, simvastatin 80 mg); (2) moderate intensity (daily dosage of atorvastatin 10–39 mg, fluvastatin 80 mg, lovastatin 40–60 mg, pitavastatin 2–4 mg, pravastatin 40–80 mg, rosuvastatin 5–19 mg, simvastatin 20–40 mg); and (3) low intensity (daily

dosage of atorvastatin < 10 mg, rosuvastatin < 5 mg, fluvastatin < 80 mg, lovastatin < 40 mg, pravastatin < 40 mg, pitavastatin 1 mg, simvastatin < 20 mg).[10]

Incident ASCVD. In line with ACC/AHA Work Group guidelines, we defined ASCVD events as acute myocardial infarction (ICD-9 410.x; ICD-10 I21),[12,17] ischemic and hemorrhagic stroke events defined based on (ICD-9-CM codes 433.x, 434.x, or 436.0; ICD-10 I63, I67.89),[12,18] or coronary heart disease followed by death within a year. Death information was retrieved from the EHR data which were based on Social Security records.

Analysis

We identified the proportion of low-, moderate-, and high-intensity statins by ASCVD risk category in each age group (65–69, 70–75, and > 75 years). The groups reflect the various thresholds that have been used to define older adults in ESC and ACC/AHA guidelines and contemporary literature, i.e., 65 years, 70 years, or 75 years of age.[3–5,11,19] We used logistic regressions to identify predictors of moderate- or high-intensity statin prescriptions. The pre-specified predictors included in the model were patient ASCVD risk level, age, sex, race/ethnicity, selected comorbid conditions (weight status, renal disease, dementia, and cancer), number of concurrent medications, and the number of healthcare visits in the year preceding the index date. Age, sex, and race/ethnicity were included to assess residual associations even after adjustment for baseline ASCVD risk. We then assessed predictors of ASCVD incidence. Time-to-event analysis using Cox proportional hazard models was used to assess the ASCVD incidence associated with statin use as of index date, adjusting for indicators of moderate- or high-intensity statin prescriptions and other risk factors as listed above. The 65–69 years group was the referent for age comparisons.

Data management and statistical analyses were conducted with Stata 16.0 (College Station, TX) and a p value < 0.01 was considered statistically significant. The study was approved by the Internal Review Boards of Stanford University and Sutter Health.

RESULTS

Of a total of 54,066 patients, 10,288 (19.0%) were > 75 years of age (Fig. 1, Table 1). Compared with those aged 65–69 years, patients aged > 75 years were more likely to be classified as high-risk for ASCVD (14.9% versus 86.5%, respectively), more likely to identify as Asian (15.1 vs 17.7%, respectively), have diabetes (12.3 vs 15.1%, respectively), and have other comorbidities including heart failure, dementia, cancer, and renal failure (Table 1). Patients over 75 years of age had more prescriptions (median 5 versus 4) and a higher number of office visits (proportion with 11 or more visits, 11% versus 6.7%) compared with those aged 65 to 69 years.

In the high-risk ASCVD group, patients > 75 years of age were less likely to receive high intensity statins compared with those aged 65–69 (5.0% versus 7.7%, $p < 0.001$) or those aged 70–75 years (5.0% versus 6.1%, $p < 0.001$) (Fig. 2). High-risk patients > 75 years of age were also less likely to receive moderate intensity statin therapy compared with those aged 65–69 years (19.2 vs 22.3%, $p < 0.001$) or 70–75 years (19.2 vs 20.2%, $p < 0.001$). In multivariable analysis adjusting for ASCVD risk and additional clinical variables, patients aged > 75 years remained less likely to receive moderate- or high-intensity statins compared with those aged 65–69 years of age (odds ratio [OR] 0.80, 95% confidence interval [CI] 0.74–0.86, Table 2). Patients aged 70–75 years were also less likely to receive moderate- or high-intensity statins compared with those aged 65–69 years (OR 0.86, 95% CI 0.82–0.91).

Across the full cohort, underweight patients were less likely to receive moderate- or high-intensity therapy than those with a normal BMI (OR 0.45, 95% CI 0.33–0.61). Asian patients were more likely to receive moderate- or high-intensity therapy compared with NHW patients (OR 1.27, 95% CI 1.20–1.35). More annual clinic visits were associated with higher odds of receiving moderate- or high-intensity statin therapy (Table 2).

A total of 2076 (3.8%) patients experienced an ASCVD event during a mean follow-up period of 4.7 years (standard deviation 3.8 years) (Supplemental Table 1). In Cox hazard models adjusting for relevant factors including baseline ASCVD risk, age remained an independent predictor of ASCVD incidence such that compared with those aged 65–69 years, patients > 75 years of age (HR 1.42, 95% CI 1.23–1.63) and those aged 70–75 years (HR 1.15, 95% CI 1.03–1.28) were more likely to experience an ASCVD event during follow-up (Table 3). African American patients were more likely to experience an ASCVD event compared with NHW patients (HR 1.48, 95% CI 1.11–1.97).

DISCUSSION

In a multiethnic primary prevention cohort of older adults aged 65–79 years, we found that patients over 75 years of age were less likely to receive moderate- or high-intensity statin therapy compared with younger counterparts regardless of baseline ASCVD risk, while experiencing more incident ASCVD events. In addition, being underweight or female were associated with lower moderate- or high-intensity statin use, while Asian race and more frequent clinic visits were predictors of greater moderate- or high-intensity statin use. These results provide important insight into contemporary statin treatment patterns, differences, and primary prevention gaps in a real-world population of older adults for whom robust evidence is lacking regarding the role of statin therapy for primary prevention.[9,20]

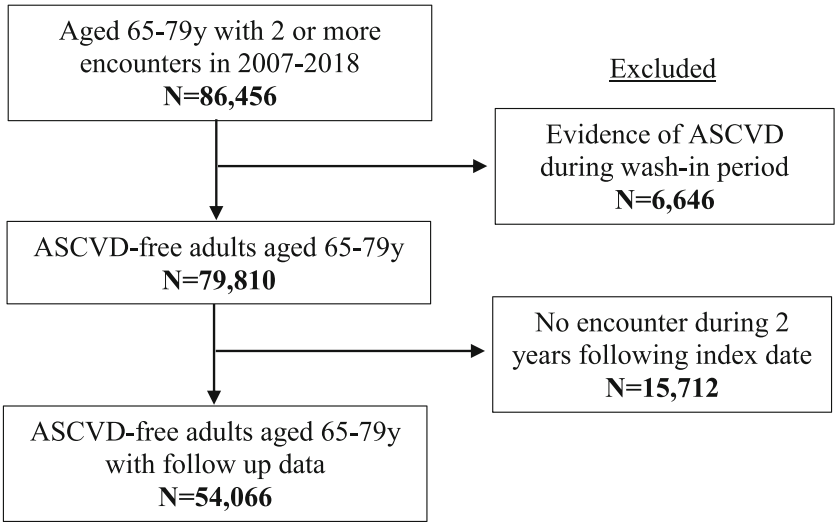

Figure 1 The CONSORT diagram. ASCVD, atherosclerotic cardiovascular disease; y, years.

Table 1 Baseline Characteristics of Patients by Age

N (% by column) unless specified	All (*N* = 54,066)	Age 65–69 years (*N* = 23,489)	Age 70–75 years (*N* = 20,289)	Age > 75 years (*N* = 10,288)
Statin intensity at baseline				
No statin	39,962 (73.9%)	17,743 (75.5%)	14,882 (73.4%)	7337 (71.3%)
Low	2712 (5.0%)	1068 (4.5%)	1062 (5.2%)	582 (5.7%)
Moderate	9096 (16.8%)	3733 (15.9%)	3472 (17.1%)	1891 (18.4%)
High	2296 (4.2%)	945 (4.0%)	873 (4.3%)	478 (4.6%)
10-year ASCVD risk level at baseline*				
Low (< 5%)	1973 (3.6%)	1959 (8.3%)	14 (0.1%)	0 (0.0%)
Borderline (5 to < 7.5%)	4934 (9.1%)	4420 (18.8%)	514 (2.5%)	0 (0.0%)
Intermediate (7.5 to < 20%)	26,057 (48.2%)	13,614 (58.0%)	11,050 (54.5%)	1393 (13.5%)
High (20% or greater)	21,102 (39.0%)	3496 (14.9%)	8711 (42.9%)	8895 (86.5%)
Demographic and clinical variables				
Female	30,756 (56.9%)	13,178 (56.1%)	11,620 (57.3%)	5958 (57.9%)
Race/ethnicity				
NHW	33,995 (62.9%)	15,030 (64.0%)	12,709 (62.6%)	6256 (60.8%)
African American	763 (1.4%)	348 (1.5%)	287 (1.4%)	128 (1.2%)
Asian	8666 (16.0%)	3545 (15.1%)	3301 (16.3%)	1820 (17.7%)
Hispanic	3286 (6.1%)	1452 (6.2%)	1259 (6.2%)	575 (5.6%)
Other	1017 (1.9%)	418 (1.8%)	397 (2.0%)	202 (2.0%)
Missing	6339 (11.7%)	2696 (11.5%)	2336 (11.5%)	1307 (12.7%)
History of diabetes	7224 (13.4%)	2895 (12.3%)	2773 (13.7%)	1556 (15.1%)
Current smoker	2134 (4.0%)	1110 (4.8%)	732 (3.7%)	292 (2.9%)
History of HTN	19,661 (36.4%)	7717 (32.9%)	7565 (37.3%)	4379 (42.6%)
BMI category				
Underweight	619 (1.1%)	229 (1.0%)	231 (1.1%)	159 (1.5%)
Normal weight	15,333 (28.4%)	6633 (28.2%)	5728 (28.2%)	2972 (28.9%)
Overweight	17,250 (31.9%)	7611 (32.4%)	6434 (31.7%)	3205 (31.2%)
Obese	20,864 (38.6%)	9016 (38.4%)	7896 (38.9%)	3952 (38.4%)
Heart failure	795 (1.5%)	220 (0.9%)	319 (1.6%)	256 (2.5%)
Renal disease	3561 (6.6%)	1307 (5.6%)	1390 (6.9%)	864 (8.4%)
Dementia	296 (0.5%)	41 (0.2%)	91 (0.4%)	164 (1.6%)
Cancer	9540 (17.6%)	3920 (16.7%)	3635 (17.9%)	1985 (19.3%)
Total cholesterol, median (IQR), mg/dl	189 (162, 215) (*n* = 37,455)	192 (166, 218) (*n* = 16,887)	188 (161, 213) (*n* = 13,771)	182 (156, 210) (*n* = 6797)
LDL, median (IQR), mg/dl	107 (85, 129) (*n* = 37,126)	110 (89, 132) (*n* = 16,718)	106 (84, 128) (*n* = 13,673)	101 (80, 124) (*n* = 6735)
SBP, median (IQR), mmHg	128 (118, 140) (*n* = 54,066)	127 (118, 138) (*n* = 23,489)	129 (119, 140) (*n* = 20,289)	130 (120, 142) (*n* = 10,288)
Prescriptions (excluding statins) ≥ 6	22,942 (42.4%)	9087 (38.7%)	8936 (44.0%)	4919 (47.8%)
Outpatient visits in the previous year				
0–2	28,800 (53.3%)	13,225 (56.3%)	10,669 (52.6%)	4906 (47.7%)
3–10	20,920 (38.7%)	8679 (36.9%)	7986 (39.4%)	4255 (41.4%)
11+	4346 (8.0%)	1585 (6.7%)	1634 (8.1%)	1127 (11.0%)

All p values < 0.01 for differences in baseline characteristics between age groups; total age range 65–79 years
IQR interquartile range, NHW non-Hispanic White, BMI body mass index, LDL low-density lipoprotein, SBP systolic blood pressure, HTN hypertension
**Calculated by the American College of Cardiology/American Heart Association Pooled Cohort Equations of 10-year ASCVD risk*

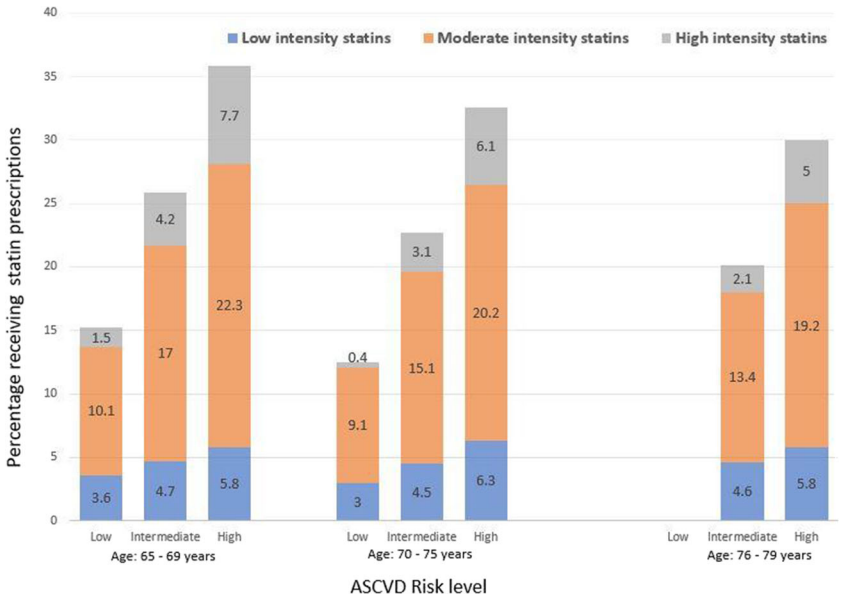

Figure 2 Rates of statin prescription in a primary prevention cohort of patients aged 65 through 79 years by statin intensity and ASCVD risk level. Within each ASCVD risk group, all $p < 0.001$ for differences in high-intensity, moderate-intensity, and low-intensity statin prescriptions between age categories. ASCVD risk level was calculated by the American College of Cardiology/American Heart Association Pooled Cohort Equations of 10-year ASCVD risk: (1) low risk (including "borderline" risk from the ACC/AHA guidelines): < 7.5%; (2) intermediate risk: ≥ 7.5% and < 20%; and (3) high risk: ≥ 20%. Rx, prescriptions; ASCVD, atherosclerotic cardiovascular disease.

Although older adults experience a disproportionate burden of ASCVD events, prior work has indicated suboptimal guideline-directed statin use in this population. Older veterans with severely elevated cholesterol were less likely to be on high-intensity statin therapy compared to younger patients in a retrospective analysis.[21] Our results add to prior literature by assessing statin use by baseline ASCVD risk and statin intensity in a large, multiethnic population of older adults. We show that adults > 75 years of age are the least likely to prescribed moderate- or high-intensity statins for primary prevention, irrespective of ASCVD risk. No patients aged 75 years or more were classified as low risk by the PCE, which suggests that age remains a primary determinant of CV risk among older adults. Prior work has described statin use rates among older adults versus much younger patients including those 40 to 65 years of age.[13,14] We now provide data regarding comparative statin use and age-based differences across the ASCVD risk spectrum within the population of older patients aged 65 years or more who experience the highest therapeutic uncertainty regarding statins for primary prevention. While not specifically investigated in this study, possible explanations include concerns regarding side effects in older populations[22], unmeasured comorbidities, and less well-defined considerations such as frailty and functional decline that have been included in recent guidelines.[23] Further research is urgently needed to understand the real-world patient or provider factors which may affect statin decisions in older adults and help explain the age-based differences seen in our study, including provider practice, cholesterol trends, side effects, frailty, or multimorbidity.

Our study suggests that older patients at highest ASCVD risk—who may benefit the most from statin therapy—may represent a missed opportunity for risk reduction interventions. Recent meta-analyses have shown that statin use is

Table 2 Predictors of Moderate- or High-Intensity Statin Use for Primary Prevention in Patients Aged 65 Through 79 Years

N = 54,066	OR	95% CI
ASCVD risk [ref = low/borderline][†]		
Intermediate	1.82**	1.67–1.99
High	2.55**	2.31–2.82
Demographic and clinical variables		
Age, years [ref = 65–69]		
70–75	0.86**	0.82–0.91
> 75 years of age	0.80**	0.74–0.86
Female	0.85**	0.81–0.89
Race/ethnicity [ref = NHW]		
African American	1.09	0.92–1.29
Asian	1.27**	1.20–1.35
Hispanic	1.07	0.98–1.17
Other race	1.26*	1.08–1.46
Missing	0.90*	0.84–0.96
BMI category [ref = normal, 18.5 to < 25.0 kg/m^2]		
Underweight (< 18.5)	0.45**	0.33–0.61
Overweight (25.0 to < 30)	1.48**	1.40–1.57
Obese (≥ 30.0)	1.35**	1.28–1.43
Renal disease	1.22**	1.12–1.32
Dementia	1.01	0.76–1.33
Cancer, current	0.99	0.94–1.05
# RXs, excl. LLA ≥ 6 [ref = 0–5]	1.68**	1.61–1.76
# visits last year [ref = 0–2]		
3–10	1.62**	1.54–1.69
11+	1.44**	1.33–1.55

ASCVD atherosclerotic cardiovascular disease, NHW non-Hispanic White, BMI body mass index, RXs prescriptions, excl. excluding, LLA lipid-lowering agents, OR odds ratio, CI confidence interval
**p < 0.001, **p < 0.01*
[†]ASCVD risk level was calculated by the American College of Cardiology/American Heart Association Pooled Cohort Equations of 10-year ASCVD risk: (1) low risk (including "borderline" risk from the ACC/AHA guidelines): < 7.5%; (2) intermediate risk: ≥ 7.5% and < 20%; and (3) high risk: ≥ 20%

Table 3 Predictors of ASCVD Incidence Across a Primary Prevention Cohort of Patients Aged 65 Through 79 Years

$N = 54{,}066^{\dagger}$	HR	95% CI
Statins, moderate or high intensity	1.08	0.98–1.19
ASCVD risk [ref = low/borderline][‡]		
Intermediate	1.40*	1.15–1.70
High	1.93*	1.55–2.40
Demographic and clinical variables		
Age, years [ref = 65–69]		
70–75	1.15	1.03–1.28
> 75 years of age	1.42*	1.23–1.63
Female	0.90	0.81–0.99
Race/ethnicity [ref = NHW]		
African American	1.48*	1.11–1.97
Asian	0.85	0.75–0.98
Hispanic	1.08	0.91–1.29
Other race	1.33	0.97–1.82
Missing	0.99	0.84–1.17
BMI category [ref = normal, 18.5 to < 25.0 kg/m^2]		
Underweight (< 18.5)	1.24	0.80–1.91
Overweight (25.0 to < 30)	1.10	0.98–1.24
Obese (≥ 30.0)	1.08	0.96–1.21
Renal disease	1.27*	1.09–1.49
Dementia	0.68	0.32–1.44
Cancer, current	0.90	0.81–1.02
# RXs (excl. LLA) ≥ 6	1.28*	1.17–1.41
# visits last year [ref: 0–2]		
3–10	0.79*	0.72–0.87
11+	0.91	0.78–1.05

ref reference, ASCVD atherosclerotic cardiovascular disease, NHW non-Hispanic White, BMI body mass index, RXs prescriptions, excl. excluding, LLA lipid-lowering agents, OR odds ratio, CI confidence interval

**p < 0.001*

†Total ASCVD events 2076 (3.8%), with a mean follow-up period of 4.7 years (standard deviation 3.8 years)

‡ASCVD risk level was calculated by the American College of Cardiology/American Heart Association Pooled Cohort Equations of 10-year ASCVD risk: (1) low risk (including "borderline" risk from the ACC/AHA guidelines): < 7.5%; (2) intermediate risk: ≥ 7.5% and < 20%; and (3) high risk: ≥ 20%

associated with a decreased risk of ASCVD (myocardial infarction in particular) among older adults.[3,4,24] Our findings also show evidence of the treatment–risk paradox among older adults for primary prevention. Adults over 75 were less likely to receive moderate- or high-intensity statin treatment although being more likely to experience incident ASCVD compared with their younger counterparts. Prior studies of secondary prevention have demonstrated the treatment–risk paradox of statin therapy in older adults.[21,25,26] Although statins were not clearly protective in Table 3, this finding is inconsistent with protective effects demonstrated in prior work and must be interpreted with caution based on the observational nature of the present study.

Older adults may have multimorbidity, frailty, and life expectancy considerations that may affect statin use decisions. Thus, age-based differences in statin use may also reflect shared appropriate decision-making between older patients and their clinicians based on individual risk–benefit analysis. Our findings suggest a strong need to clarify these considerations and rigorously evaluate the clinical significance of age-based differences in statin use in older adults for primary prevention, particularly in the context of the age-based differences in ASCVD incidence that we observed. Future work should prospectively assess the impact of statin use in older adults on relevant clinical outcomes versus adverse effects. Ongoing clinical trials of primary prevention in older adults may help address this crucial unanswered question in ASCVD prevention. The STAREE trial (a Study of STAtins for Reducing Events in the Elderly, NCT02099123) randomizes adults 70 years or older to atorvastatin 40 mg or placebo daily to assess disability-free survival. The PREVENTABLE trial (Pragmatic Evaluation of Events and Benefits of Lipid-lowering in Older Adults, NCT04262206) randomizes adults aged 75 years or more to atorvastatin 40 mg daily or placebo to assess effects on new dementia or disability, with secondary outcomes of cardiovascular mortality and cognitive disability.

We found that increased healthcare utilization as defined by more frequent clinical encounters was associated with higher moderate- or high-intensity use and decreased ASCVD incidence. Complementary to our findings, a recent study investigating statin dosing by cardiologists versus primary care providers found that high intensity statin prescriptions increased with number of yearly clinic visits.[27] A potential target for interventions to optimize statin use in older adults may be to explore frequent patient follow-up. Our findings are also consistent with previously described sex and racial/ethnic disparities in statin use in older adults over 65 years of age. Female patients in all age groups are often undertreated with statins for primary prevention.[28,29] Asian patients were more likely to receive moderate- or high-intensity therapy, whereas African American patients were more likely to experience incident ASCVD. Disaggregated data across Asian subgroups may provide additional insight into this finding.

Our study should be interpreted in the context of its limitations. The cohort consisted of mostly insured patients from Northern California and our findings may be not generalizable to other patient groups. Patients above the age of 79 were not studied given that we aimed to assess statin use by ASCVD risk, and the Pooled Cohort Equations for primary prevention are not formally validated beyond the age of 79 years. Ongoing trials of statin use in older adults including the STAREE and PREVENTABLE trials may help clarify the impact of statin use in this very old population of those greater than 80 years of age. Reasons for statin non-prescription, including patient and provider factors, and measures of functional status, were not available in our data. Low-density lipoprotein (LDL) cholesterol changes were not analyzed given incomplete data availability. Since this study was from one organization, albeit a large one with multiple sites, we aimed to ensure regular health system use prior to cohort entry to exclude patients who may switched health systems after the index date. This may have excluded healthy people who rarely use the healthcare system or very sick patients who did not survive to a second encounter. To select a primary prevention population, we used a limited "wash-in" period to ensure the absence of ASCVD for at least 2 encounters. While this facilitated more accurate selection of primary prevention patients, we may have excluded some patients with a single health system encounter or

those with events between the first and second encounters. We did not capture events outside the health system. Future studies using claims data such as Medicare/Medicaid or National Death Index data may help capture outside events, particularly for non-regular users of our health system who may have been excluded from the cohort. As is inherent to observational studies, findings may be affected by unobserved confounders and associations may not indicate causality.

In conclusion, in a large multiethnic primary prevention cohort of older adults aged 65–79 years, we found that adults > 75 years of age were less likely to receive moderate- or high-intensity statins regardless of baseline ASCVD risk and more likely to experience incident ASCVD compared with their younger counterparts. These findings indicate that age-based differences in statin treatment in older adults may persist regardless of baseline ASCVD risk. We also observed statin prescription differences by sex, race/ethnicity, and healthcare utilization in older adults. Together, these results emphasize a strong need for efforts to study the reasons for these age-based statin use differences and ensure appropriate, patient-centered statin therapy for the primary prevention of ASCVD in older adults.

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Declarations:

Conflict of Interest: *F. Rodriguez has received consulting fees from Novartis and NovoNordisk and has served on an advisory board for Novartis. No other authors report disclosures.*

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