CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Patterns of Statin Therapy Use and Associated Outcomes in Older Veterans Across Kidney Function

Grenita Gjyriqi, DO,[a,1] Adam Gross, MS,[b,1] Edith Burns, MD,[a] Eugenia Gianos, MD,[a] Mandeep S. Sidhu, MD, MBA,[c] Roy O. Mathew, MD[d]

[a]Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY; [b]Albany Medical College, NY; [c]Division of Cardiology, Department of Medicine and Department of Medical Education, Albany Medical College, Albany Med Health System, NY; [d]Department of Medicine, Loma Linda VA Health Care System, Calif.

ABSTRACT

BACKGROUND: Despite significant morbidity and mortality related to atherosclerotic cardiovascular disease, to date, most major clinical trials studying the effects of statin therapy have excluded older adults. The objective of this analysis was to evaluate the effect of initiating statin therapy on incident dementia and mortality among individuals 75 years of age or older across the complete spectrum of kidney function.

METHODS: We conducted a retrospective cohort study of 640,191 VA health system patients who turned 75 years of age between 2000 and 2018. Patients on statin therapy received the medication for an average of 6.3 years (standard deviation 4.6 years). The primary outcome of interest included incident dementia diagnosis during the study period. The secondary outcome was all-cause mortality. Cox proportional hazard analysis was used to evaluate the adjusted association of statin initiation with these outcomes.

RESULTS: There was a higher rate of incident dementia in the No Statin group (4.7%) vs the Statin group (3.2%). Additionally, we observed a 22% all-cause mortality benefit associated with statin therapy. We did not observe a treatment effect with respect to primary or secondary outcomes across varying levels of kidney function.

CONCLUSION: This large cohort study did not reveal an association between the initiation of statin therapy and incident dementia. A survival benefit was seen in statin users compared with nonusers. Prospective studies in more diverse populations including older adults will be needed to verify these findings.

 • The American Journal of Medicine (2024) 137:839–846

KEYWORDS: Atherosclerosis; Cerebrovascular disease; Chronic kidney disease; Incident dementia; Older adult population; Statin therapy

BACKGROUND

As individuals age, the incidence of atherosclerotic cardiovascular disease and chronic kidney disease increases.[1] Chronic kidney disease remains a strong risk factor for cardiovascular diseases, including atherosclerotic cardiovascular disease; thus, therapies reducing atherosclerotic cardiovascular disease risk remain a cornerstone of chronic kidney disease therapeutics.[2] While the use of statins in nonelderly adult patients with and without chronic kidney disease is well established for primary and secondary prevention of atherosclerotic cardiovascular disease, the guidelines are less clear when it comes to older adults.[3] This is due, in part, to the fact that there is a relative dearth of evidence about statin use in adults aged ≥75 years.[4,5]

Funding: This study has no funding sources to disclose.

Conflicts of Interest: None.

Authorship: All authors had access to the data and contributed to preparation of this manuscript. GG: Writing – review & editing, original draft, Project administration, Investigation, Formal analysis, Conceptualization; AG: Writing – review & editing, original draft, Project administration; EB: Writing – review & editing, original draft, Formal analysis, Conceptualization; EG: Writing – review & editing, original draft, Formal analysis, Conceptualization; MS: Writing – review & editing, original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization; RM: Writing – review & editing, original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Requests for reprints should be addressed to Adam Gross, MS, Albany Medical College, 43 New Scotland Avenue, Albany, NY 12208.

E-mail address: grossa4@amc.edu

[1] Authors contributed equally to this manuscript.

0002-9343/© 2024 Published by Elsevier Inc.
https://doi.org/10.1016/j.amjmed.2024.03.016

A leading therapeutic aim in the older adult population is to maintain functional status with acceptable levels of quality of life.[6] Secondary analyses of randomized clinical trials of statin therapies suggests that treating these patients with statins can improve their quality of life and increase disability-free survival.[7-14] Despite the mortality benefits related to statin therapy, there is concern that statin therapy may be associated with the development of dementia; however, the data would suggest that risk of worsening dementia is not present with statin use in older adults.[15-18]

Notwithstanding the controversies of diagnostic thresholds for chronic kidney disease in older adults, those with more stringent criteria (lower estimated glomerular filtration rate and higher amounts of albuminuria) continue to suffer higher rates of adverse kidney and cardiovascular events.[19] Statin therapy has become a mainstay of atherosclerotic cardiovascular disease risk reduction in the general chronic kidney disease population.[19] More specifically, in the older adult population, the effect of statin therapy is not well studied, and no definitive data support or contradict the use of statin therapy in older adults with chronic kidney disease.[19]

CLINICAL SIGNIFICANCE

- The benefit of statin therapy in older adults is unclear, especially in patients with lower kidney function.
- Statin therapy in older adults is associated with a decrease in all-cause mortality, without an increase in dementia.
- The treatment effect did not differ across the spectrum of kidney function.
- A greater degree of albuminuria was associated with higher all-cause mortality and dementia in the elderly.

It is critical to understand the current use patterns and outcomes associated with statin therapy in the older adult real-world population. Further elucidation of potential harms and benefits will be important to guide future and ongoing trials as well as to inform providers and patients. We describe the current practice patterns around use of statins among older adult patients across the spectrum of kidney function in the US Veterans Health Administration (VHA) national population, and explore outcomes related to statin use, including incident dementia. Our hypothesis was that statin use in older (≥75 years of age) individuals will be associated with longer dementia-free survival than in age-matched patients not initiated on statin therapy.

METHODS

Data Source: National Veterans Affairs (VA) data warehouse; access was permitted through the Veterans Informatics Networking and Computing Infrastructure. Currently, data cannot be shared outside of the VA system. If users would like to replicate these data, they can individually request access to VA data if this is accessible to them.

The Loma Linda VA Health Care System Institutional Review Board approved the protocol for this project under expedited review, with waiver of informed consent due to the retrospective nature of the study.

Cohort

Patients were identified for this analysis if they had turned 75 years of age between 2000 and 2018. Subsequently, from this population, patients who died prior to 80 years of age were excluded. The flow diagram (Figure 1) demonstrates the mechanism of patient selection for this analysis.

Variables

The statin prescriptions were collected for patients from the outpatient pharmacy records within the VHA Corporate Data Warehouse (CDW). In addition, statin prescriptions that were obtained from non-VA providers/pharmacies were searched in the NonVAMed file. Patients were segregated into several groups based on prescription patterns, with prescriptions filled at either VA or non-VA pharmacies: 1) prescription prior to age 75 and continued after age 75; 2) prescription prior to age 75 and stopped within 6 months prior to or after turning 75; 3) prescription starting at age 75 ± 6 months; 4) no statin prescription identifiable within the VHA record. For this analysis, patients with only a VA statin prescription starting at age 75 years were compared with patients without a VA, or Non-VA statins. The exposure of interest was statin prescription starting at age 75 years [group 3) above].

Clinical and laboratory variables were collected in reference to the age of 75 years. Medical diagnoses were collected based on codes provided in Supplementary Table 1 (available online). Other cardiovascular medications were collected at ±6 months from the age of 75, including renin-angiotensin system inhibitors, beta-blockers, calcium channel blockers, diuretics, aspirin, ezetimibe, medications with potential interactions with statins (fibrates, antiretrovirals, antifungal agents, St. John's wort). Laboratory parameters obtained included creatinine, lipid profile (total, low-density lipoprotein, and high-density lipoprotein cholesterols, and triglycerides), creatine phosphokinase, alanine transaminase, aspartate transaminase, and urinary microalbumin. Baseline glomerular filtration rate was estimated using the recently developed race-free equation utilizing only serum creatinine, age, and sex;[20] cystatin-C values were not adequately available for cystatin C-based glomerular filtration rate estimation. Vital signs were also collected. The future atherosclerotic cardiovascular disease risk was calculated using the American College of Cardiology pooled cohort equation (PCE)[21]; for the PCE estimation, all persons not Black or White were considered White.

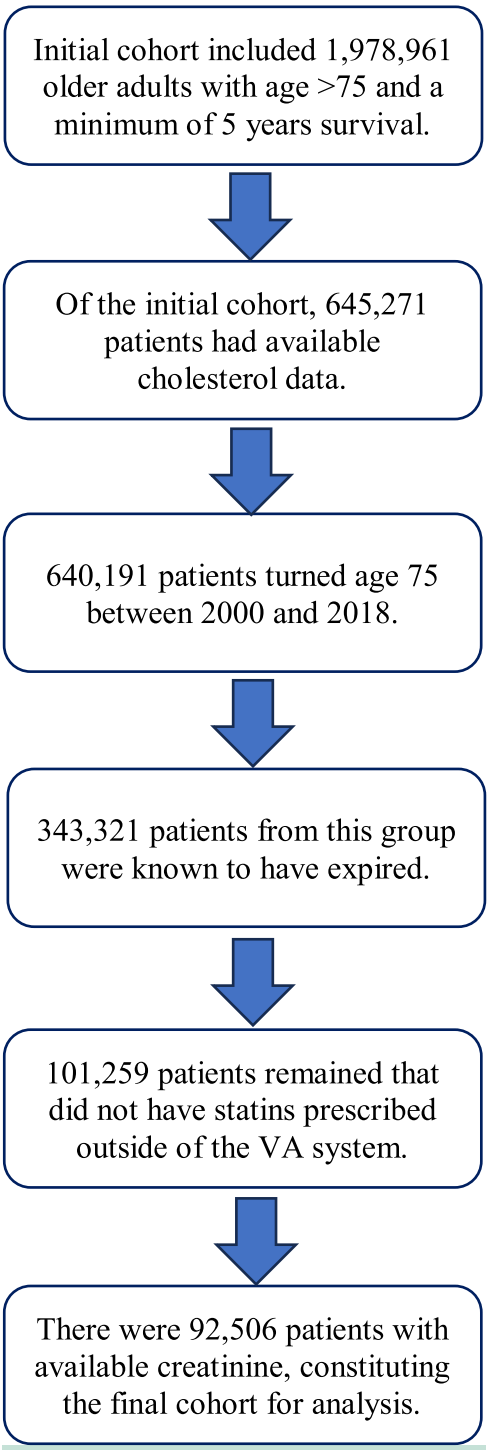

Figure 1 Process by which the study group was selected.
See Methods for Further Information.

Outcomes

Outcomes were identified using International Classification of Diseases (ICD)-9 and 10 codes (Supplementary Table 1, available online). The primary outcome of interest: incident dementia (patients with dementia diagnosis at baseline were excluded from this analysis). Secondary outcomes: For all patients, mortality was determined from the death notification within VHA CDW. Hospitalizations for myocardial infarction, heart failure, or stroke were identified within the VHA CDW.

Statistical Analysis

Descriptive statistics were utilized to evaluate baseline variables. Continuous variables were described using either mean ± standard deviation or median (interquartile range) for normal or skewed distribution, respectively. Univariate Kaplan-Meier evaluations of statin prescription and the outcomes were performed using *ggsurvplot*. An initial evaluation of the propensity score distribution between the 2 groups demonstrated an adequate overlap of scores (data not shown). Thus, a standard adjusted outcome analysis with time-to event analysis used un-matched treatment and control grouping. Cox proportional hazard analysis was utilized to evaluate effect of statin prescription on the time to the primary outcome, adjusting for sex, age, race, history of hypertension, history of prior stroke, history of prior coronary artery disease, history of peripheral arterial disease, history of heart failure, history of diabetes, current or prior tobacco use, baseline estimated glomerular filtration rate-creatinine based, baseline microalbuminuria, PCE 10-year risk estimate, baseline ejection fraction, baseline low-density lipoprotein cholesterol, total cholesterol, and baseline systolic and diastolic blood pressures. Visual inspections of Schoenfeld residual plots revealed no violation of the proportionality assumption. A 2-tailed P value of $< .05$ was considered statistically significant. All analyses were performed using R 4.1.2 statistical software.

RESULTS

Baseline Features

Table 1 displays the demographics and comorbidity data for the study population. The total duration of statin therapy in the cohort prescribed statins was a mean of 2298 days.

Supplementary Table 2 (available online) displays the baseline physiology and laboratory features of each cohort. The majority of patients were classified as Chronic Kidney Disease stages G2 and G3a, and the mean estimated glomerular filtration rate was 63.9 mL/min/1.73 m^2 in the statin therapy group and 67.12 mL/min/1.73 m^2 in the No Statin group ($P < .001$).

Comorbidities at Time of New Statin Therapy

Factors associated with new statin prescription are displayed in Table 2. Patients newly prescribed statin therapy were more likely to have pre-existing coronary artery disease (odds ratio [OR] 3.03; 95% confidence interval [CI], 2.06-4.49; $P < .001$] and dementia (OR 1.64; 95% CI, 1.09-2.49; $P < .019$). However, baseline estimated glomerular filtration rate (OR 0.99; 95% CI, 0.98-0.9969; $P < .011$), and ejection fraction (OR 0.98; 95% CI, 0.97-0.99;

Table 1 Baseline Demographic Features of Those On and Not On Statins at Age 75

	Statin	No Statin	*P* Value
n	55,203	37,303	
Demographics			
Sex (male)	54,691 (99.1)	36,775 (98.6)	< .001
Marital status			< .001
Divorced	8083 (14.6)	6100 (16.4)	
Married	33,352 (60.4)	22,796 (61.1)	
Widowed/ single	13,314 (24.1)	8025 (21.5)	
Unknown	454 (0.8)	382 (1.0)	
Race			< .001
Black	4310 (7.8)	2716 (7.3)	
White	41,273 (74.8)	27,472 (73.6)	
Other	9620 (17.4)	7115 (19.1)	
Ethnicity			< .001
Hispanic or Latino	2393 (4.7)	1175 (3.4)	
Not Hispanic or Latino	46,502 (91.0)	31,535 (92.4)	
Unknown/ declined	2199(4.3)	1424 (4.2)	
Comorbidities			
Hypertension	51,916 (94.0)	31,931 (85.6)	< .001
Cerebrovascular accident	21,255 (38.5)	8032 (21.5)	< .001
Coronary artery disease	26,366 (47.8)	6342 (17.0)	< .001
Peripheral artery disease	15,791 (28.6)	6279 (16.8)	< .001
HIV/AIDS	94 (0.2)	87 (0.2)	.04
Heart failure	18,596 (33.7)	7477 (20.0)	< .001
Diabetes mellitus	27,530 (49.9)	11,274 (30.2)	< .001
History of dementia	18,383 (33.3)	10,636 (28.5)	< .001
History of tobacco use	8230 (14.9)	5152 (13.8)	< .001
Current tobacco use	11,098 (20.1)	8240 (22.1)	< .001
Medications			
Angiotensin converting enzyme inhibitors	26,004 (47.1)	12,184 (32.7)	< .001
Angiotensin receptor blockers	3878 (7.0)	1938 (5.2)	< .001
Beta-blockers	18,234 (33.0)	7741 (20.8)	< .001
Dihydropyridine calcium channel blockers	11,903 (21.6)	6284 (16.8)	< .001
Loop diuretics	7289 (13.2)	3198 (8.6)	< .001
Thiazide	11,754 (21.3)	6358 (7.0)	< .001
Diltiazem	3535 (6.4)	1820 (4.9)	< .001
Verapamil	1673 (3.0)	957 (2.6)	< .001
Aspirin	16,147 (9.3)	8980 (4.1)	< .001
Ezetimibe	178 (0.3)	77 (0.2)	.001
Fibrate	3450 (6.2)	1466 (3.9)	< .001
Statins prescribed at VA			
Simvastatin	42,780 (77.5)	NA	
Lovastatin	5156 (9.3)	NA	
Atorvastatin	4315 (7.8)	NA	
Pravastatin	2052 (3.7)	NA	
Other	863 (1.6)	NA	
Duration of statin therapy (days)	2297.73 (1667.40)	NA	NA
Presence of statin allergy in chart	4254 (7.7)	345 (0.9)	< .001

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; VA = Veterans Affairs.

*Categorical values are presented as n (%) and continuous variables are presented as mean (standard deviation [SD]) unless otherwise specified. Chi-square statistical testing was utilized for group comparisons of categorical variables. For normally distributed continuous variables, one-way analysis of variance testing was utilized. For non-normally distributed continuous variables, the Kruskal-Wallis test was utilized.

Table 2 Baseline Characteristics That Are Associated with New Statin Prescription at Age 75 vs Not Being Prescribed Statin Therapy at Age 75

	OR (95% CI)	*P* Value
Favored prescription of a statin		
Coronary artery disease	3.03 (2.06-4.49)	< .001
Dementia	1.64 (1.09-2.49)	.019
10-year atherosclerotic cardiovascular disease risk by the pooled cohort equation	>100 (3.06->1000)	.04
Less likely to be prescribed a statin		
Heart failure	0.60 (0.40-0.89)	.011
Baseline estimated glomerular filtration rate	0.99 (0.98-0.997)	.011
Baseline ejection fraction	0.98 (0.97-0.99)	.004

CI = confidence interval; OR = odds ratio.
Logistic regression was utilized for statistical analysis.

$P < .004$) were inversely associated with a new statin prescription at age 75.

Outcomes

Table 3 displays raw outcomes within the cohort. Incident dementia was less frequent in the Statin Therapy group (3.2%) vs the No Statin group (4.7%), $P < .001$. The mean days to dementia diagnosis was 3924 in the Statin Therapy group vs 3489 in the No Statin group ($P < .001$). There

Table 3 Observed Outcomes by Statin Therapy Group

	Statin	No Statin	*P* Value
n	55,203	37,303	
Age at death, years; mean (SD)	85.96 (3.83)	84.78 (3.53)	< .001
Outcomes, n (%)			
New dementia diagnosis	1790 (3.2)	1738 (4.7)	< .001
Days to dementia diagnosis	3924.15 (1488.63)	3488.98 (1376.26)	< .001
Hospitalization for acute coronary syndrome	9 (0.0)	5 (0.0)	.937
Hospitalization for cerebrovascular accident	78 (0.1)	37 (0.1)	.091
Hospitalization for peripheral arterial disease	49 (0.1)	28 (0.1)	.553

Chi-square testing for categorical outcome (Yes/No). One-way analysis of variance for days to outcome comparison.

Table 4 Adjusted* Hazard Ratios for the primary outcome of incident dementia in those without a dementia diagnosis at baseline.

	HR (95% CI)	*P* Value
New statin prescription at 75 y vs no statin prescription at 75 y	0.81 (0.25-2.61)	.73
History of tobacco use	3.12 (1.05-9.21)	.04
Urinary albumin:creatinine ratio	1 (1-1)	.02
Diastolic blood pressure	1.06 (1.00-1.13)	.04

CI = confidence interval; HR = hazard ratio.
*Adjusted for baseline demographic parameters, comorbidities, laboratory, and physiologic parameters.Time-to-event analysis using Cox proportional hazard.

were very few hospitalizations for acute coronary syndrome, cerebrovascular accident, or peripheral arterial disease identified, and the differences between groups were not statistically significant.

Multivariable Cox proportional hazard analysis for incident dementia diagnosis (censored for death) and mortality (after age 80) are demonstrated in Tables 4 and 5, and the graphical, unadjusted representation is shown in Figures 2 and 3. On multivariable analysis, adjusting for baseline demographic characteristics, comorbidities, and available laboratory and physiology parameters, the prescription of a new statin at age 75 was not associated with a lower incidence of new dementia diagnosis (hazard ratio [HR] 0.81; 95% CI, 0.25-2.61; $P = .73$). Factors that were associated with new dementia diagnosis included history of tobacco use (HR 3.12; 95% CI, 1.05-9.21), urinary albumin:creatinine ratio ($P = 0.02$), and diastolic blood pressure ($P = .04$).

Table 5 Adjusted* Hazard Ratios for Mortality

	HR (95% CI)	*P* Value
New statin prescription at age 75 vs no statin prescription	0.778 (0.677-0.893)	< .001
Race (reference Black)		
Other	1.34 (1.05-1.70)	.017
White	1.24 (1.03-1.50)	.023
Coronary artery disease	0.86 (0.76-0.98)	.019
Baseline urinary albumin: creatinine ratio	1 (1-1)	.011
Baseline ejection fraction	0.995 (0.991-0.999)	.009

CI = confidence interval; HR = hazard ratio.
*Adjusted for baseline demographic parameters, comorbidities, laboratory, and physiologic parameters.Time-to-event analysis using Cox proportional hazard.

Mortality was significantly lower on univariate (Figure 3) and multivariable analysis for new statin prescription (Table 5). New statin prescription was associated with a 22% lower hazard (HR 0.78; 95% CI, 0.68-0.89; $P < .001$) for mortality.

DISCUSSION

This nationwide, retrospective cohort study of VA health system patients characterized demographics and outcomes associated with initiation of statin therapy in older adults across all levels of kidney function. Within this predominantly Caucasian male cohort, initiation of statin therapy was more likely in patients with coronary artery disease and dementia, whereas factors such as higher baseline ejection fraction and baseline kidney function were associated with a lower likelihood of statin therapy. With respect to the primary outcome, statin therapy was not associated with incident dementia. However, statin therapy was associated with a significant reduction in all-cause mortality. There was no effect modification associated with kidney function and statin use on outcomes.

Lipid-lowering therapy is a key component of management in patients at risk for atherosclerotic cardiovascular disease and for the prevention of major adverse cardiovascular events.[3] Prevailing literature supports the use of statin therapy in patients under 75 years of age.[3] Consensus guidelines, including the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease recommends continuation of statin therapy beyond 75 years of age for patients already prescribed these drugs, however, the data about the initiation of therapy in patients 75 years of age and older is lacking.[3] Best practices in this population include shared decision-making based on myriad factors such as the risks and benefits of therapy, the patient's life expectancy, and the patient's desired quality of life.[22]

One of the concerns associated with statin therapy is that these drugs have been linked to cognitive decline and the development of dementia.[15-17] Our results, however,

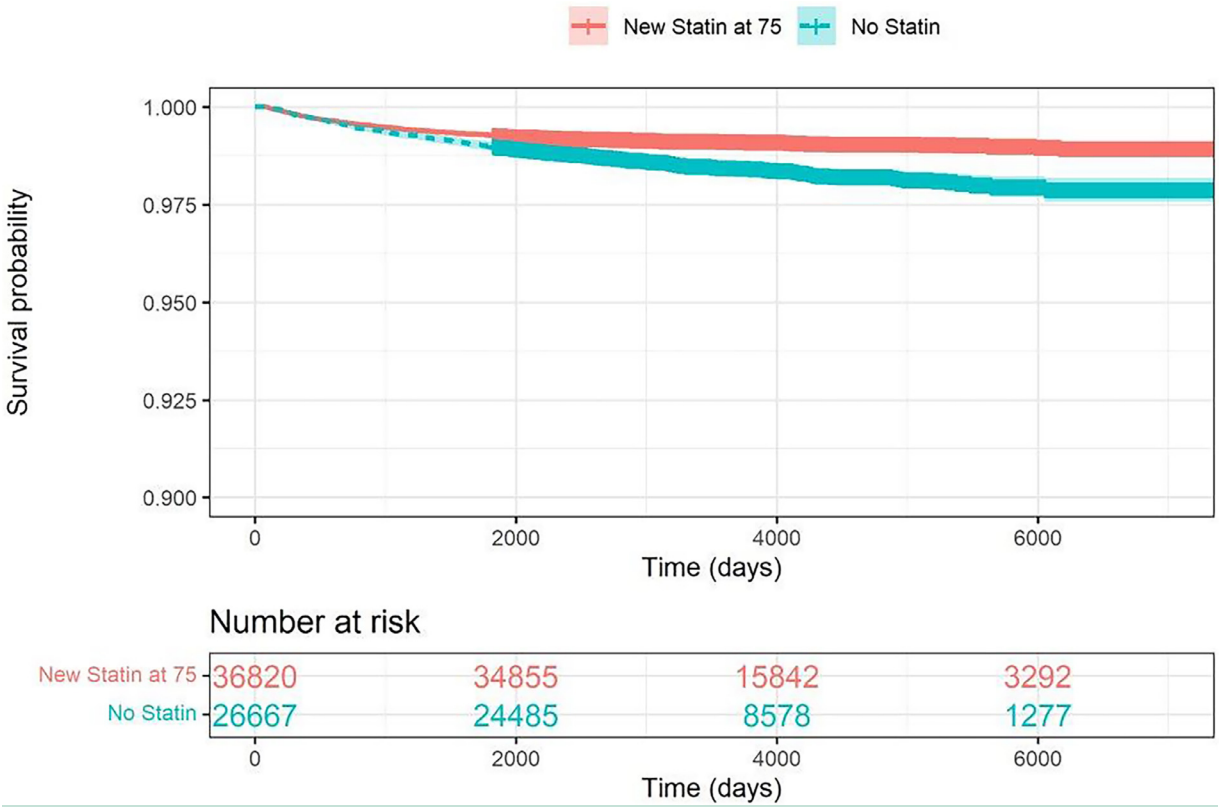

Figure 2 Unadjusted probability for survival free of incident dementia diagnosis. Lower probability of the diagnosis of dementia during the study period in the statin group.
Incident dementia probability curve shows likelihood of developing dementia as early as ~4000 days in patients not taking statin therapy. Number at Risk indicates total patients in each cohort at the indicated time points.

demonstrated that incident dementia occurred less frequently in the statin therapy group. This finding is consistent with the results of other observational and randomized studies, such as HOPE-3, which did not demonstrate worsening cognitive function in patients taking statin therapy and is supported by a recent American Heart Association Scientific Statement.[18,23]

In addition to a lower rate of incident dementia, results from the statin therapy group in this analysis also demonstrated a reduced risk for all-cause mortality. This finding is consistent with the data from a Danish nationwide cohort study by Andersson et al.[24] In this retrospective study of lipid-lowering therapy for primary prevention of cardiovascular disease, there was a 23% risk reduction for major vascular events with respect to patients aged ≥70 years.[24] This did not differ significantly from the 22% risk reduction achieved in the group of patients <70 years of age.[24] Taken together, there is a growing body of evidence supporting the extended use of statin therapy in the older adult population to derive similar benefits compared with those seen in younger patient cohorts.[5,25,26]

We believe that the decision to include a population of patients who lived to at least 80 years of age is an important component supporting the applicability of these results in clinical practice. This age range provides a population with a reasonable life expectancy and allows for a more appropriate determination of the clinical utility associated with the initiation of statin therapy at or after age 75.[27-29] It is important to study these therapies over an appropriate time course to best inform patients and providers about the burden of medication administration and possible adverse effects to determine a patient's expected quality of life. We await the results of randomized trials of statin therapy within the older adult population, such as the PREVENTABLE trial, which will help to quantify the therapeutic benefit and better describe possible harms.[30]

With respect to the spectrum of kidney function, the effects of statin therapy were similar across estimated glomerular filtration rate values. Our results demonstrate that there was no interaction between the treatment effect and kidney function. There is a physiologic framework that underlies the relationship between chronic kidney disease and atherosclerotic disease, and statin therapy has been repeatedly demonstrated to reduce atherosclerotic cardiovascular disease events in patients with chronic kidney disease.[31,32] This is an important consideration in older adults in whom reduced kidney function is more prevalent, representing an opportunity for prospective study.

Additional avenues for future research and validation include the use of nontraditional predictors of outcomes.

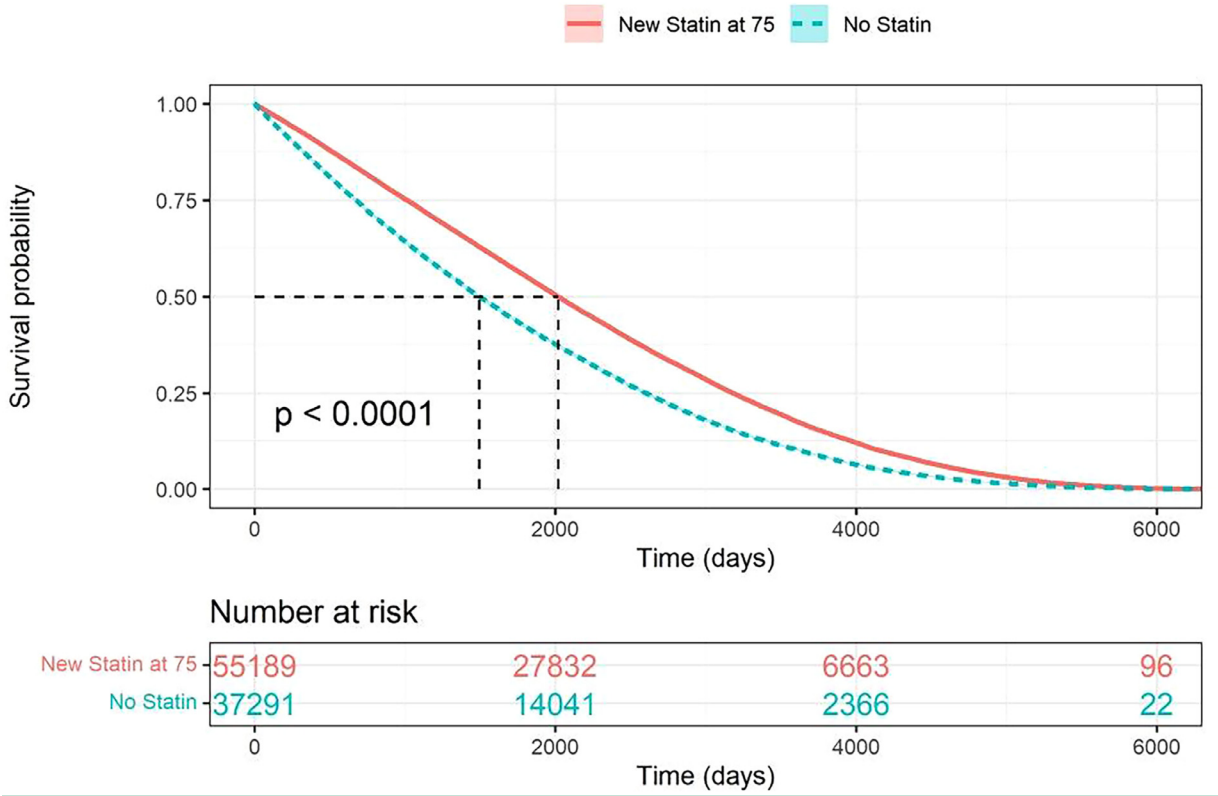

Figure 3 Unadjusted survival probability. Significant difference in the probability of survival after age 80 years in patients taking statins as compared with those not taking statin therapy.
See Methods for statistical methods used. Number at risk indicates total patients in each cohort at the indicated time points.

These factors, including albumin:creatinine ratio, have not been used consistently in the population for risk stratification or prognostication of atherosclerotic cardiovascular disease and statin therapy.[33,34] In the current study, higher baseline urinary albumin:creatinine ratio, albuminuria, was associated with a greater risk of all-cause mortality. This is consistent with recent literature that found albuminuria to be associated with adverse outcomes such as increased rates of hospitalization, myocardial infarction, cardiovascular mortality, and heart failure, as well as an increased risk of all-cause mortality.[33] The degree to which albuminuria is predictive of dementia remains a possible area for investigation.[33,34]

Limitations

Our study should be considered in the context of some limitations. First, the VA population demographics include predominantly Caucasian males, limiting the generalizability of the results to other populations. Next, incident dementia was likely underreported, as the current analysis relied on ICD designations and diagnostic coding. Regarding kidney function, estimated glomerular filtration rate and chronic kidney disease staging were noted only at the timepoint of study inclusion, and changes in kidney function were not assessed. Additionally, given the observational nature of the study, despite multivariable adjustment of findings, residual confounding cannot be completely excluded. Finally, non-VA-prescribed statin therapy in the No Statin arm that was not captured in the VA medical record may have led to an underestimation of the true effects of statin therapy.

CONCLUSION

At the time of new statin therapy for dyslipidemia, many veterans have multiple comorbidities, including pre-existing dementia, abnormal kidney function, coronary artery disease, or increased atherosclerotic cardiovascular disease risk. Our findings suggest that statin therapy showed no signal for increased incident dementia despite previous reports. Lower all-cause mortality in the cohort receiving statin therapy was also noted in this study, which serves as the basis for extending the use of statin therapy in the older adult population. The observed treatment effects were independent of baseline kidney function. Confirmation is needed in broader and more diverse cohorts with prospective interventions such as the ongoing PREVENTABLE trial.[30] In terms of primary prevention in older adults, use of statin therapy requires better risk estimation that should incorporate life expectancy, medication tolerance, polypharmacy, patients' frailty, functional status, and shared decision-making.

References

1. Gupta K, Kakar TS, Jain V, et al. Comparing eligibility for statin therapy for primary prevention under 2022 USPSTF recommendations and the 2018 AHA/ACC/multi-society guideline recommendations: from National Health and Nutrition Examination Survey. *Prog Cardiovasc Dis* 2022;75:78–82.
2. Ren H, Zhao L, Zou Y, et al. Association between atherosclerotic cardiovascular diseases risk and renal outcome in patients with type 2 diabetes mellitus. *Ren Fail* 2021;43(1):477–87.
3. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2019;140(11):e649-e650; *Circulation*. 2020;141(4):e60; *Circulation*. 2020;141(16):e774]. *Circulation* 2019;140(11):e596–646.
4. Fleg JL, Forman DE, Berra K, et al. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. *Circulation* 2013;128(22):2422–46.
5. Singh S, Zieman S, Go AS, et al. Statins for primary prevention in older adults-moving toward evidence-based decision-making. *J Am Geriatr Soc* 2018;66(11):2188–96.
6. 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):261–6.
7. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003;41(1):47–55.
8. Nanna MG, Navar AM, Wang TY, et al. Statin use and adverse effects among adults >75 years of age: insights from the Patient and Provider Assessment of Lipid Management (PALM) registry. *J Am Heart Assoc* 2018;7(10):e008546.
9. Orkaby AR, Driver JA, Ho YL, et al. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older [published correction appears in *JAMA*. 2020;324(14):1468]. *JAMA* 2020;324(1):68–78.
10. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary JUPITER and HOPE-3 randomized trials. *Circulation* 2017;135(20):1979–81.
11. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360(9346):1623–30.
12. Zhou Z, Ofori-Asenso R, Curtis AJ, et al. Association of statin use with disability-free survival and cardiovascular disease among healthy older adults. *J Am Coll Cardiol* 2020;76(1):17–27.
13. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359(21):2195–207.
14. Foody JM, Rathore SS, Galusha D, et al. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: evidence for an age-statin interaction. *J Am Geriatr Soc* 2006;54(3):421–30.
15. Kim MY, Jung M, Noh Y, et al. Impact of statin use on dementia incidence in elderly men and women with ischemic heart disease. *Biomedicines* 2020;8(2):30.
16. Olmastroni E, Molari G, De Beni N, et al. Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies. *Eur J Prev Cardiol* 2022;29(5):804–14.
17. Zhang X, Wen J, Zhang Z. Statins use and risk of dementia: a dose-response meta analysis. *Medicine (Baltimore)* 2018;97(30):e11304.
18. Bosch J, O'Donnell M, Swaminathan B, et al. Effects of blood pressure and lipid lowering on cognition: results from the HOPE-3 study. *Neurology* 2019;92(13):e1435–46.
19. Mathew RO, Rosenson RS, Lyubarova R, et al. Concepts and controversies: lipid management in patients with chronic kidney disease. *Cardiovasc Drugs Ther* 2021;35(3):479–89.
20. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;385(19):1737–49.
21. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(25 suppl 2):S74-S75]. *Circulation* 2014;129(25 suppl 2):S49–73.
22. Strandberg TE. Role of statin therapy in primary prevention of cardiovascular disease in elderly patients. *Curr Atheroscler Rep* 2019;21(8):28.
23. Goldstein LB, Toth PP, Dearborn-Tomazos JL, et al. Aggressive LDL-C lowering and the brain: impact on risk for dementia and hemorrhagic stroke: a scientific statement from the American Heart Association [published correction appears in Arterioscler Thromb Vasc Biol. 2023 Nov;43(11):e490]. *Arterioscler Thromb Vasc Biol* 2023;43(10):e404–42.
24. Andersson NW, Corn G, Dohlmann TL, Melbye M, Wohlfahrt J, Lund M. LDL-C reduction with lipid-lowering therapy for primary prevention of major vascular events among older individuals. *J Am Coll Cardiol* 2023;82(14):1381–91.
25. US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2022;328(8):746–53.
26. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. *Ann Intern Med* 2015;162(8):533–41.
27. Arias E. United States life tables, 2008. *Natl Vital Stat Rep* 2012;61(3):1–63.
28. Centers for Disease Control and Prevention (CDC). Life expectancy at birth, age 65, and age 75, by sex, race, and Hispanic origin: United States, selected years. Health, United States, 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK569311/table/ch3.tab4/. Accessed April 5, 2024. National Library of Medicine; 2019.
29. Murrow S, Desmon S. Life expectancy gains threatened as more older Americans suffer from multiple medical conditions. *Johns Hopkins University HUB* 2014; July 23. Available at https://hub.jhu.edu/2014/07/23/life-expectancy-gains-threatened/. [Accessed April 5, 2024.
30. Joseph J, Pajewski NM, Dolor RJ, et al. Pragmatic evaluation of events and benefits of lipid lowering in older adults (PREVENTABLE): Trial design and rationale. *J Am Geriatr Soc* 2023;71(6):1701–13.
31. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377(12):1119–31.
32. Ridker PM, Devalaraja M, Baeres FMM, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2021;397(10289):2060–9.
33. Writing Group for the CKD Prognosis Consortium, ME Grams, Coresh J, et al. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *JAMA* 2023;330(13):1266–77.
34. Matsushita K, Jassal SK, Sang Y, et al. Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. *EClinicalMedicine* 2020;27:100552.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2024.03.016.

Supplementary Table 1 Diagnosis: International Classification of Disease Codes

Hypertension	
ICD 9	401.x, 402.x, 403.x, 404.x, 405.x
ICD 10	I10.x, I11.x, I12.x, I13.x, I15.x, I16.x
Cerebrovascular accident	
ICD 9	43[0-8].x
ICD 10	I6[0-9].x
Coronary artery disease	
ICD 9	410.x, 414.x
ICD 10	I2[0-5].x
Peripheral arterial disease	
ICD 9	440.20, 440.21, 440.23, 250.70, 443.9, 444.22
ICD 10	I702.13, I73.9
HIV	
ICD 9	V08.x, 042
ICD 10	Z21.x, B2[0-4].x
Heart failure	
ICD 9	428.x
ICD 10	I50.x
Dementia	
ICD 9	291, 290, 292, 294, 331, 797
ICD 10	F01.50, F01.51, F02.80, F03.90, F03.91, G30.0, G30.1, G30.8, G30.9, G31.01, G31.09, G31.1, G31.2, G31.83, G31.84
Diabetes	
ICD 9	250.x
ICD 10	E08.x E09.x, E10.x, E11.x, E13.x
History of tobacco use	
ICD 9	V15.82
ICD 10	Z87.891
Current tobacco use	
ICD 9	305.1
ICD 10	F17.2, Z72.0

ICD = International Classification of Diseases.

Supplementary Table 2 Baseline Physiologic and Laboratory Parameters*

Chronic Kidney Disease (CKD) Stage†	Statin	No Statin	< .001
n	55,203	37,303	
CKDG1	5183 (9.4)	5364 (14.4)	
CKDG2	33,678 (61.0)	23,250 (62.3)	
CKDG3a	11,193 (20.3)	6032 (16.2)	
CKDG3b	4144 (7.5)	2030 (5.4)	
CKDG4	615 (1.1)	325 (0.9)	
CKDG5	390 (0.7)	302 (0.8)	
Estimated glomerular filtration rate (CKD-EPI without race) (mL/min/1.73 m^2)	63.90 (15.68)	67.12 (15.81)	< .001
Creatinine (mg/dL)	1.18 (0.34)	1.13 (0.33)	< .001
Total cholesterol (mg/dL)	182.64 (35.86)	172.40 (31.02)	< .001
Low density lipoprotein-cholesterol (mg/dL)	110.03 (31.53)	101.40 (27.09)	< .001
High density lipoprotein-cholesterol (mg/dL)	44.03 (12.89)	46.84 (15.38)	< .001
Alanine amino transferase (IU/L)	24.66 (13.73)	24.24 (15.39)	< .001
Aspartate aminotransferase (IU/L)	23.64 (9.60)	24.58 (13.13)	< .001
Hemoglobin A1c (%)	6.61 (2.00)	6.14 (0.97)	< .001
Urinary albumin/creatinine ratio (mg/gm)	97.47 (701.98)	107.48 (1262.67)	0.61
Systolic blood pressure (mm Hg)	139.03 (16.39)	135.97 (15.93)	< .001
Diastolic blood pressure (mm Hg)	73.48 (9.21)	73.84 (9.17)	< .001
Weight (kg)	76.35 (11.36)	75.55 (11.09)	< .001
Ejection fraction (%)	49.78 (14.98)	51.98 (14.31)	< .001
Estimated 10-year atherosclerotic cardiovascular disease risk by pooled cohort equation	0.15 (0.04)	0.13 (0.04)	< .001
10-year atherosclerotic cardiovascular disease risk category			< .001
Low risk (<5%)	203 (0.4)	401 (1.1)	
Borderline risk (5-<7.5%)	811 (1.5)	1391 (3.9)	
Intermediate risk (7.5-<20%)	50,010 (93.7)	33,624 (93.3)	
High risk (≥20%)	2355 (4.4)	610 (1.7)	

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

*Categorical values are presented as n (%) and continuous variables are presented as mean (standard deviation [SD]) unless otherwise specified. Chi-square statistical testing was utilized for group comparisons of categorical variables. For normally distributed continuous variables, one-way analysis of variance testing was utilized. For non-normally distributed continuous variables, the Kruskal-Wallis test was utilized.

†Chronic kidney disease stage based on the Kidney Disease: Improving Global Outcomes estimated glomerular filtration-based staging criteria (G1: ≥90 mL/min/1.73 m^2; G2: 60-89 mL/min/1.73 m^2; G3a: 45-59 mL/min/1.73 m^2; G3b: 30-44 mL/min/1.73 m^2; G4: 15-29 mL/min/1.73 m^2; G5: <15 mL/min/1.73 m^2).