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Association Between Intensity of Statin Therapy and Mortality in Patients With Atherosclerotic Cardiovascular Disease

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IMPORTANCE High-intensity statin therapy is recommended for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD). Nevertheless, statin therapy in general, and high-intensity statin therapy in particular, is underused in patients with established ASCVD.

OBJECTIVE To determine the association between all-cause mortality and intensity of statin therapy in the Veterans Affairs health care system.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort analysis was conducted of patients aged 21 to 84 years with ASCVD treated in the Veterans Affairs health care system from April 1, 2013, to April 1, 2014. Patients who were included had 1 or more *International Classification of Diseases, Ninth Revision* codes for ASCVD on 2 or more different dates in the prior 2 years.

EXPOSURES Intensity of statin therapy was defined by the 2013 American College of Cardiology/American Heart Association guidelines, and use was defined as a filled prescription in the prior 6 months. Patients were excluded if they were taking a higher statin dose in the prior 5 years.

MAIN OUTCOMES AND MEASURES The primary outcome was death from all causes adjusted for the propensity to receive high-intensity statins.

RESULTS The study sample included 509 766 eligible adults with ASCVD at baseline (mean [SD] age, 68.5 [8.8] years; 499 598 men and 10 168 women), including 150 928 (29.6%) receiving high-intensity statin therapy, 232 293 (45.6%) receiving moderate-intensity statin therapy, 33 920 (6.7%) receiving low-intensity statin therapy, and 92 625 (18.2%) receiving no statins. During a mean follow-up of 492 days, there was a graded association between intensity of statin therapy and mortality, with 1-year mortality rates of 4.0% (5103 of 126 139) for those receiving high-intensity statin therapy, 4.8% (9703 of 200 709) for those receiving moderate-intensity statin therapy, 5.7% (1632 of 28 765) for those receiving low-intensity statin therapy, and 6.6% (4868 of 73 728) for those receiving no statin ($P < .001$). After adjusting for the propensity to receive high-intensity statins, the hazard ratio for mortality was 0.91 (95% CI, 0.88-0.93) for those receiving high- vs moderate-intensity statins. The magnitude of benefit of high- vs moderate-intensity statins was similar, for an incident cohort hazard ratio of 0.93 (95% CI, 0.85-1.01). For patients aged 76 to 84 years, the hazard ratio was 0.91 (95% CI, 0.87-0.95). Patients treated with maximal doses of high-intensity statins had lower mortality (hazard ratio, 0.90; 95% CI, 0.87-0.94) compared with those receiving submaximal doses.

CONCLUSIONS AND RELEVANCE We found a graded association between intensity of statin therapy and mortality in a national sample of patients with ASCVD. High-intensity statins were associated with a small but significant survival advantage compared with moderate-intensity statins, even among older adults. Maximal doses of high-intensity statins were associated with a further survival benefit.

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Editor's Note page 55

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Statin therapy remains the cornerstone for the prevention of atherosclerotic cardiovascular disease (ASCVD). Many large, randomized trials have shown that the use of statins significantly reduces the likelihood of future cardiovascular events and mortality in diverse populations.[1,2] Despite this finding, statins continue to be underused, even in the populations at highest risk of cardiovascular events and mortality.[3-12]

Trials have also provided support that higher-intensity statin dosing may be more effective than lower-intensity statin therapy at reducing future cardiovascular events.[13-15] In fact, compared with moderate-intensity statin therapy (pravastatin, 40 mg), high-intensity statin therapy (atorvastatin, 80 mg) showed a reduction in atherosclerosis progression in patients with coronary artery disease.[16] Use of maximal doses of high-intensity statins (atorvastatin, 80 mg, and rosuvastatin, 40 mg) similarly resulted in regression of atherosclerosis in a large, randomized trial in patients with coronary artery disease.[17] Large meta-analyses have confirmed the safety and efficacy of the use of high-intensity statins to achieve very low levels of low-density lipoprotein cholesterol (LDL-C) in patients with coronary artery disease and cerebrovascular disease.[2]

In response to this growing body of evidence, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends against routine LDL-C targets and instead recommends use of high-intensity statin therapy among all patients 75 years or younger with ASCVD.[18] This paradigm shift has resulted in significant controversy as health care professionals determine the best metrics for lipid performance measures and patient outcomes.[5,19] The guidelines define high-intensity statins as rosuvastatin, 20 or 40 mg/d, and atorvastatin, 40 or 80 mg/d, but do not offer recommendations on a specific dose of these higher-intensity statins for patients with ASCVD.[18] On the other hand, the Veterans Affairs (VA) health care system has released separate dyslipidemia guidelines that recommend moderate-intensity statins for most patients with ASCVD, citing insufficient evidence for recommending high-intensity statin therapy except in some subgroups of patients at high risk for ASCVD.[20]

We thus sought to determine 1-year cardiovascular mortality by intensity of statin therapy for patients with ASCVD in the VA health care system and to assess whether any differences in mortality associated with intensity of statin treatment, if present, were observed in different age groups of patients.

Key Points

Question Is intensity of statin therapy associated with all-cause mortality in a large national sample of patients in the Veterans Affairs health care system with atherosclerotic cardiovascular disease?

Findings In this cohort study of 509 766 patients with atherosclerotic cardiovascular disease, there was an inverse association between intensity of statin therapy and mortality, with the greatest 1-year mortality reductions for patients receiving high-intensity statins. These findings were consistent across multiple subgroups, including adults older than 75 years.

Meaning Maximally tolerated doses of high-intensity statins may confer a survival advantage to patients with atherosclerotic cardiovascular disease, including older adults.

Methods

Study Population

Our study population included all outpatients within the VA health system between ages 21 and 84 years with established ASCVD, defined as coronary artery disease (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 410-414), cerebrovascular disease (*ICD-9* codes 430-438), or peripheral artery disease (*ICD-9* code 440), identified quarterly from April 1, 2013, through April 1, 2014, with at least 1 *ICD-9* code for ASCVD on at least 2 different dates and at least 1 outpatient visit in the VA health system during the study period in the prior 2 years. Patients with LDL-C levels of less than 50 mg/dL or more than 600 mg/dL (to convert to millimoles per liter, multiply by 0.0259) were excluded from the analyses. Patients were excluded if they filled no prescriptions from a VA health system clinician during the 6 months prior to the index date (42 363 [5%]), as this group of patients with ASCVD likely represents those receiving most of their primary or cardiovascular care outside the VA health system. To limit patients intolerant of statins and include patients receiving a stable dosage of statins, we excluded patients currently receiving a moderate-intensity statin who had previously been prescribed (in the prior 5 years) a higher-intensity statin, which excluded 70 439 patients (21%) receiving moderate-intensity statins, 30 377 receiving low-intensity statins (43%), and 127 921 of those not receiving a statin (48%). As a sensitivity analysis, we defined an incident cohort that included only patients with a first prescription for a statin in the prior 6 months. The study was approved by the Stanford University Institutional Review Panel for Human Subjects, which waived the need for patient consent.

Statin Classification

Intensity of statin therapy was classified according to the ACC/AHA cholesterol guidelines.[18] Statin use was defined as a statin prescription filled in the prior 6 months. For example, a patient identified from the January 1, 2014, cohort with 2 codes for ASCVD from January 1, 2012, through December 31, 2013, was defined as receiving statin therapy if a statin prescription was filled between July 1 and December 31, 2013. If a patient was identified in more than 1 cohort, we used the data from their first identification. Low-intensity statin therapy was defined as fluvastatin, 20 to 40 mg, lovastatin, 20 mg, simvastatin, 10 mg, pitavastatin, 1 mg, and pravastatin, 10 to 20 mg. Moderate-intensity statin therapy was defined as atorvastatin, 10 to 20 mg, fluvastatin, 40 mg twice a day or 80 mg once a day (extended-release formulation), lovastatin, 40 mg, pitavastatin, 2 to 4 mg, pravastatin, 40 to 80 mg, rosuvastatin, 5 to 10 mg, and simvastatin, 20 to 40 mg. High-intensity

statin therapy was defined as atorvastatin, 40 to 80 mg, or rosuvastatin, 20 to 40 mg. Although there were no new prescriptions for simvastatin, 80 mg, patients who continued to take this dose were included in the high-intensity statin group since this statin dosage typically lowers LDL-C levels by nearly 50%.[21] If patients were prescribed more than 1 type of statin during the prior 6 months, the highest intensity and dose were used in the analyses.

Outcomes

The primary outcome was all-cause mortality during a mean follow-up of 492 days. Secondary outcomes were 1-year mortality, 1-year hospitalization for any cause, acute myocardial infarction, ischemic cerebrovascular disease, chronic obstructive pulmonary disease, and malignant neoplasms. All-cause mortality during follow-up was extracted from the VA Vital Status file. Survival was evaluated at 1 year and throughout the available follow-up period using Cox proportional hazards regression analyses. Incident diabetes (type 1 and type 2) was defined as having at least 1 *ICD-9* code for diabetes during the follow-up period when there were no codes for diabetes in the prior 2 years.

Our main subgroups of interest were patients older than 75 years and 75 years or younger. We repeated the analysis of outcomes separately in these groups.

Patient and Hospital Characteristics

Race/ethnicity was self-reported in the VA health system records. Participants were classified as white, Hispanic, black, Asian, Pacific Islander, or other race. Participant age and sex were also included. High-intensity statin use by ASCVD classification, including coronary artery disease, peripheral artery disease, and cerebrovascular disease, was also assessed. Clinical comorbidities included the presence of heart failure, diabetes, hypertension, or renal disease. Mean LDL-C levels were compared between each of the statin intensity groups and were adjusted for in the regression models. To account for adherence to statin therapy in our adjustment model, medication possession ratios were calculated by dividing the number of days of outpatient statin supplied during a 2-month period divided by the number of days not hospitalized and alive during the 12-month period.[22] This total was multiplied by 100% and expressed as a percentage. A medication possession ratio during follow-up was calculated for all patients taking a statin during follow-up regardless of their baseline statin use.

Hospital characteristics were obtained from the American Hospital Association database. These characteristics included geographical region (divided into Northeast, Midwest, South, and West) and academic teaching status, defined as membership in the Council of Teaching Hospitals and Health Systems (COTH).

Statistical Analysis

All statistical testing was 2-sided, with $P < .05$ considered significant. Analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc). Baseline characteristics of participants were compared by use of statins (no statin, low intensity, moderate intensity, and high intensity) using either analysis of variance for continuous variables or the χ^2 test for categorical variables.

Missing race/ethnicity was treated as a separate category. Missing laboratory test values were imputed with the mean by statin category. Missing hospital COTH data were imputed using the most common category. For multivariable analyses, we imputed continuous variables using the mean and most common value for categorical variables.

We performed unadjusted Cox proportional hazards regression analysis to determine the association of high-intensity statin use with survival. We then modeled the propensity to receive a high-intensity statin prescription using all available patient-level and facility variables, including demographics (age, sex, and race/ethnicity), Charlson Comorbidity Score (prior myocardial infarction, peripheral artery disease, cerebrovascular disease, diabetes, heart failure, renal disease, liver disease, pulmonary disease, connective tissue disease, hemiparesis, malignant neoplasms [including metastases], and AIDS), filled prescriptions (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), laboratory test values (baseline LDL-C, high-density lipoprotein cholesterol, total cholesterol, triglycerides, and creatinine), region of the country, COTH membership, and time period for entry into the cohort (year and quarter). The Cox proportional hazards regression analysis was then repeated using inverse probability weighting with the propensity score. Adjusted survival curves were created with weighting using the propensity score. The main comparison of interest was confounding between the groups receiving high- and moderate-intensity statins (other characteristics associated with mortality may lead to not prescribing a statin or prescribing it in low doses). In a sensitivity analysis, we further adjusted for potential clustering of patients within VA health system facilities using a robust sandwich covariance matrix estimate. Secondary outcomes (1-year death rates and several 1-year hospitalization rates) were also adjusted using inverse probability weighting with the propensity score to receive a high-intensity statin prescription. An additional adjusted Cox proportional hazards regression analysis was limited to patients receiving high-intensity statin therapy and examined survival for those receiving a maximal dose of high-intensity statin therapy (atorvastatin, 80 mg, or rosuvastatin, 40 mg) compared with those receiving a submaximal dose (atorvastatin, 40 mg, or rosuvastatin, 20 mg).

Results

Patient Characteristics and Adherence

We identified 509 766 adults with documented ASCVD (mean [SD] age, 68.5 [8.8] years) who had not had their statin dose lowered. This cohort included 150 928 patients (29.6%) receiving high-intensity statin therapy, 232 293 (45.6%) receiving moderate-intensity statin therapy, 33 920 (6.7%) receiving low-intensity statin therapy, and 92 625 (18.2%) receiving no statin therapy (**Table 1**). Those receiving

Table 1. Baseline Characteristics of Patients With ASCVD by Intensity of Statin Therapy

Characteristic	Value[a]			
	High Intensity (n = 150 928)	Moderate Intensity (n = 232 293)	Low Intensity (33 920)	No Statin (92 625)
Age, mean (SD), y	67.5 (8.3)	69.0 (8.7)	69.4 (9.0)	68.7 (9.9)
Male	148 258 (98.2)	228 314 (98.3)	33 038 (97.4)	89 988 (97.2)
ASCVD category				
CAD only	107 711 (71.4)	154 195 (66.4)	20 417 (60.2)	55 794 (60.2)
Cerebrovascular disease only	12 534 (8.3)	32 373 (13.9)	6905 (20.4)	21 459 (23.3)
PAD only	1048 (0.7)	2787 (1.2)	691 (2.0)	2096 (2.3)
≥1 Vascular bed	29 635 (19.6)	42 938 (18.5)	5907 (17.4)	13 186 (14.2)
Race/ethnicity[b]				
White	120 157 (80.4)	186 132 (80.8)	26 665 (79.3)	71 553 (78.2)
Black	18 955 (12.7)	27 413 (11.9)	4474 (13.3)	13 518 (14.8)
Hispanic	6433 (4.3)	11 106 (4.8)	1653 (4.9)	3986 (4.4)
Pacific Islander	1800 (1.2)	2594 (1.1)	369 (1.2)	968 (1.1)
Asian	651 (0.4)	954 (0.3)	109 (0.3)	376 (0.4)
Native American	574 (0.4)	1016 (0.4)	178 (0.5)	578 (0.5)
Other	867 (0.6)	1251 (0.5)	163 (0.5)	510 (0.6)
Region				
Midwest	35 134 (23.3)	54 621 (23.5)	8140 (24.0)	20 845 (22.5)
Northeast	24 154 (16.0)	33 678 (14.5)	4492 (13.2)	15 050 (16.3)
South	65 140 (43.2)	102 216 (44.0)	14 963 (44.1)	40 782 (44.0)
West	26 498 (17.6)	41 776 (18.0)	6325 (18.7)	15 947 (17.2)
Academic teaching hospital[c]	62 451 (44.2)	96 538 (43.7)	13 561 (42.0)	37 103 (42.6)
Clinical comorbidities				
Heart failure	31 620 (21.0)	45 600 (19.6)	6706 (19.8)	13 881 (15.0)
Diabetes	73 390 (48.6)	106 408 (45.8)	14 496 (42.7)	33 959 (36.7)
Hypertension	132 695 (87.9)	202 313 (87.1)	29 288 (86.3)	73 741 (79.3)
Renal disease	23 099 (15.3)	35 569 (15.3)	5541 (16.0)	12 146 (13.1)
Chronic obstructive pulmonary disease	40 895 (27.1)	64 757 (27.9)	10 192 (30.1)	24 329 (26.2)
Malignant neoplasm	16 999 (11.3)	28 949 (12.5)	4585 (13.5)	12 370 (13.4)
Charlson Comorbidity Score, mean (SD)	2.31 (1.92)	2.33 (1.93)	2.59 (2.05)	2.41 (2.04)
Medication possession ratio, mean (SD), %	0.83 (0.23)	0.84 (0.24)	0.81 (0.26)	NA
Creatinine, mean (SD), mg/dL[d]	1.18 (0.69)	1.19 (0.74)	1.25 (0.91)	1.24 (1.00)
LDL-C, mean (SD), mg/dL[e]	85.9 (34.5)	81.5 (30.7)	84.7 (32.3)	95.0 (35.9)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; PAD, peripheral artery disease.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; LDL-C to millimoles per liter, multiply by 0.0259.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. All differences across cholesterol groups are statistically significant ($P < .001$).

[b] Data on race/ethnicity available for the following groups: high, 149 437; moderate, 230 269; low, 33 611; and none, 91 489.

[c] Data on academic teaching hospital available for the following groups: high, 141 387; moderate, 221 002; low, 32 302; and none, 87 104.

[d] Data on creatinine level available for the following groups: high, 118 681; moderate, 177 003; low, 26 106; and none, 66 658.

[e] Data on LDL-C level available for the following groups: high, 115 190; moderate, 118 681; low, 24 039; and none, 58 198.

high-intensity statin therapy were slightly younger, more likely to be male, and of white race compared with patients receiving other doses of statins. Adherence to statin therapy during the subsequent 12 months ranged from 81% to 83% as measured by medication possession ratios. Baseline characteristics of patients with ASCVD by statin intensity after weighting by propensity score showed similar results (eTable in the Supplement).

Mortality

Patients receiving high-intensity statin therapy had a 1-year mortality rate of 4.0% compared with 4.8% for those receiving moderate-intensity statin therapy, 5.7% (1632 of 28 765) for those receiving low-intensity statin therapy, and 6.6% (4868 of 73 728) for those receiving no statin therapy ($P < .001$). After adjusting for the propensity to receive a high-intensity statin prescription, similar patterns of survival were observed during a mean follow-up of 492 days (median, 147 days) (**Figure 1**).

High- vs Moderate-Intensity Statins

When the sample was limited to patients receiving high- or moderate-intensity statins, the unadjusted hazard ratio for mortality was 0.82 (95% CI, 0.80-0.84) for those taking high-intensity statins vs those taking moderate-intensity statins (**Table 2**). After adjustment using inverse probability weighting of the propensity to receive a high-intensity statin, the association with mortality and high-intensity statin use was attenuated but remained significant (hazard ratio, 0.91; 95% CI, 0.88-0.93). Adjustment for potential clustering of patients within VA health system facilities produced similar results (hazard ratio, 0.91; 95% CI, 0.88-0.93).

When the sample was further limited to patients receiving high-intensity statins, those treated with maximal doses (atorvastatin, 80 mg, or rosuvastatin, 40 mg) had a lower mortality (adjusted hazard ratio, 0.90; 95% CI, 0.87-0.94) compared with those receiving submaximal doses (atorvastatin, 40 mg, rosuvastatin, 20 mg, and simvastatin, 80 mg).

Other Outcomes

Table 2 shows unadjusted and adjusted outcomes at 1 year for mortality, hospitalization, and a new diagnosis of diabetes. The results suggest that patients receiving high-intensity statins were more likely to have more severe coronary artery disease (higher risk of acute myocardial infarction) but slightly less likely to have malignant neoplasms. These differences were attenuated but persisted with adjustment. There was no significant difference in new diagnosis of diabetes, admission for pulmonary disease, or admission for stroke. The effect sizes were similar for the incident cohort, but these differences were not significant except for 1-year mortality.

Age Groups

The primary and secondary outcomes (adjusted for the propensity to receive a high-intensity statin) for those 75 years or younger and those between 76 and 84 years are shown in **Table 3** and **Figure 2**. In general, the directions of the effects of high-intensity statins were similar for both age groups except for malignant neoplasms, with hospitalizations for malignant neoplasms more common for patients in the younger group receiving moderate-intensity statins (Table 3).

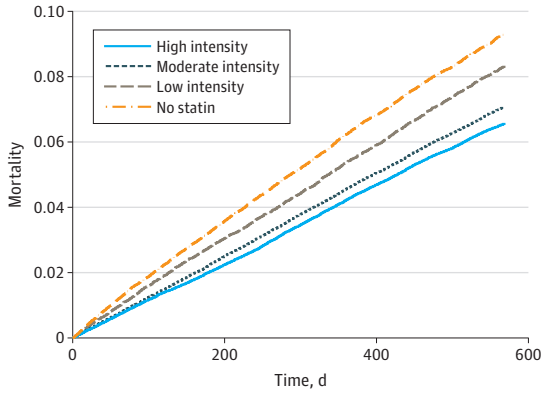
Incident Cohort

When the cohort was limited to patients with a first prescription for a statin within the prior 6 months, the sample size was decreased by 91.6% (14 454 patients receiving high-intensity statins and 28 168 receiving moderate-intensity statins). The propensity-weighted hazard ratio for mortality with high-intensity statins in this incident cohort was 0.93 (95% CI, 0.85-1.01) (Table 2).

Discussion

In this national study of patients in the VA health system, we found a consistent, graded association between intensity of statin therapy and mortality, with the greatest reductions for patients receiving high-intensity statins. We also found that

Figure 1. Adjusted Mortality Curves for Different Intensities of Statin Therapy



No. at risk			
High	150 928	146 474	120 559
Moderate	232 293	223 664	190 147
Low	33 920	32 389	26 997
None	92 625	87 322	68 474

Curves are adjusted for the propensity to receive a high-intensity statin. Differences are significant ($P < .001$).

Table 2. Outcomes for Patients Receiving High- vs Moderate-Intensity Statins

	Unadjusted, No./Total No. (%)			Adjusted (Propensity Score)[a]			Adjusted Incident Cohort[a]		
Outcome	High	Moderate	*P* Value	High	Moderate	*P* Value	High	Moderate	*P* Value
1-y Mortality	5103/126 139 (4.0)	9703/200 709 (4.8)	<.001	4.3	4.7	<.001	3.8	4.4	.007
1-y Hospitalization									
Acute myocardial infarction	1266/127 333 (1.0)	1515/203 196 (0.8)	<.001	0.9	0.8	<.001	1.0	1.0	.78
Ischemic cerebrovascular disease	1125/127 333 (0.9)	1740/203 196 (0.9)	.41	0.9	0.8	.01	1.2	1.2	.90
Chronic obstructive pulmonary disease	994/127 333 (0.8)	1625/203 196 (0.8)	.55	0.8	0.8	.97	0.6	0.7	.12
Malignant neoplasm	637/127 333 (0.5)	1195/203 196 (0.6)	<.001	0.5	0.6	<.001	0.5	0.6	.06
Any cause	21 154/127 333 (16.6)	33 170/203 196 (16.3)	.03	16.3	16.4	.37	17.0	19.0	<.001
1-y New diagnosis of diabetes	460/64 894 (0.7)	777/109 381 (0.7)	.97	0.7	0.7	.27	0.8	0.9	.66
Survival, hazard ratio (95% CI)	0.82 (0.80-0.84)		<.001	0.91 (0.88-0.93)		<.001	0.93 (0.85-1.01)		.09

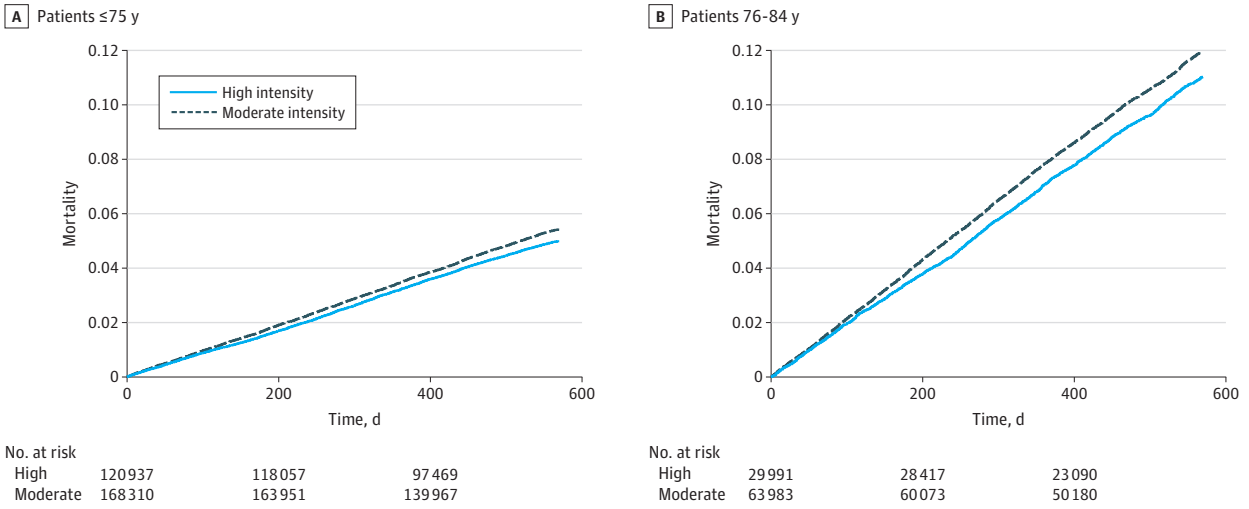
[a] The adjusted outcomes do not have unique patients and therefore do not have numbers of patients. Denominators for the adjusted (propensity score) cohort are the same as the unadjusted cohort. Denominators for the adjusted incident cohort are as follows: 1 year-mortality, high dose, 9116; moderate dose, 21 015; other 1-year outcomes: high dose, 9188; moderate dose, 21 201.

Table 3. Outcomes for Patients Receiving High- vs Moderate-Intensity Statins by Age Group[a]

Outcome	Age ≤75 y, No./Total No. (%)			Age 76-84 y, No./Total No. (%)		
	High	Moderate	*P* Value	High	Moderate	*P* Value
1-y Mortality	101 147 (3.3)	145 691 (3.6)	.002	24 992 (7.2)	55 018 (8.1)	<.001
1-y Hospitalization						
Acute myocardial infarction	101 898 (1.1)	147 081 (0.9)	<.001	25 435 (0.6)	56 115 (0.5)	.39
Ischemic cerebrovascular disease	101 898 (1.0)	147 081 (0.9)	.04	25 435 (0.7)	56 115 (0.6)	.15
Chronic obstructive pulmonary disease	101 898 (0.8)	147 081 (0.8)	.95	25 435 (0.8)	56 115 (0.8)	.94
Malignant neoplasm	101 898 (0.5)	147 081 (0.6)	<.001	225 435 (0.6)	56 115 (0.6)	.98
Any cause	101 898 (17.3)	147 081 (17.3)	.84	25 435 (13.4)	56 115 (13.8)	.07
1-y New diagnosis of diabetes	51 081 (0.8)	77 994 (0.8)	.19	13 813 (0.5)	31 387 (0.5)	.61
Survival, hazard ratio (95% CI)	0.90 (0.88-0.93)		<.001	0.91 (0.87-0.95)		<.001

[a] All results adjusted for propensity to be prescribed a high-intensity statin.

Figure 2. Adjusted Mortality Curves for High- vs Moderate-Intensity Statins by Age



A, Patients 75 years or younger. B, Patients aged 76 to 84 years. Curves are adjusted for the propensity to receive a high-intensity statin prescription.

the maximal doses of high-intensity statins (atorvastatin, 80 mg, and rosuvastatin, 40 mg) conferred the greatest survival advantage compared with submaximal doses of high-intensity statins. The benefits of high-intensity statins were consistent for those older than 75 years compared with younger patients.

Despite the growing evidence that statins consistently improve outcomes for the secondary prevention of ASCVD, these medications continue to be underused in clinical practice.[23-27] Although the reasons for this underuse are not clear, one cause may be an assumption that higher-intensity statins do not confer an important benefit.

Since the release of the 2013 ACC/AHA cholesterol guidelines,[18] more attention has been placed on the use of high- vs moderate-intensity statins. However, the VA dyslipidemia practice guidelines,[20] which were released following the ACC/AHA guidelines, favor the use of moderate-intensity statins, even for secondary prevention, concluding that the evidence for use of high-intensity statins is lacking, with a consideration for titration to high-intensity statins among patients with recurrent coronary artery disease or those with acute coronary syndrome. Our finding that high-intensity statins were associated with a significant survival benefit compared with moderate-intensity statins instead supports the use of high-intensity statins for patients with ASCVD, as recommended by the ACC/AHA guidelines. As documented in the landmark PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22)[13] and TNT (Treating to New Targets)[15] randomized clinical trials, high-intensity statins are more efficacious at reducing cardiovascular end points compared with moderate-intensity statins.[13-15] Our study found that, when examined separately, CVD and non-CVD mortality were each associated with a comparable nonsignificant reduction in mortality. We can posit that the observed mortality risk reduction is mostly attributable to reductions in LDL-C levels, although reduction in inflammation may play an additional role and may lead to both improved CVD and non-CVD mortality. The maximal doses of high-intensity statins conferred the greatest mortality advantage, supporting the notion that physicians should prescribe the maximally tolerated doses of atorvastatin or rosuvastatin for patients with ASCVD.

The finding that adults older than 75 years are also more likely to benefit from high- vs moderate-intensity statins and that maximum high-intensity dosing was associated with greater survival than submaximal high-intensity dosing in this age group warrants special mention. The ACC/AHA cholesterol guidelines[18] recommend use of high-intensity statins only up to age 75 years given the inadequacy of existing data for older adults, with no clinical trials including adults older than 80 years.[28,29] The ACC/AHA guidelines[18] argue that there is no clear additional benefit from the use of high- vs moderate-intensity statins for patients older than 75 years. In addition, there is concern among health care professionals about geriatric-specific adverse effects of high-intensity statins, including myalgias and drug-drug interactions. Ko and colleagues[30] have coined this dilemma the *treatment-risk paradox*, highlighting that patients at the greatest cardiovascular risk should be, but are often not, treated most aggressively. Physicians may overemphasize the risk of treatment in the elderly, particularly in the setting of multiple comorbidities.[31,32] Our findings suggest that high-risk older adults may experience a survival benefit from treatment with high-intensity statins, although drug adverse effects must be considered on an individual basis and should be part of the risk discussion between a patient and a health care professional.

Our study has several strengths, including our sample size and the use of a large, well-characterized patient cohort from the VA health system, which offers a unique opportunity to study both administrative and clinical variables. We excluded a large number of patients who were previously treated with high-intensity statins, which helped to exclude patients who may be intolerant of high-intensity statins. However, we were unable to fully adjust for potential confounders, which likely affected our results, which suggests that patients treated with high-intensity statins were at higher risk of coronary events compared with those receiving moderate-intensity statins, given that we observed a small but significantly higher rate of admission for acute myocardial infarction in those receiving high-intensity statins. We were also unable to determine the cause of death. Although most studies of secondary prevention have consistently shown a reduction in coronary heart disease deaths with statins, in the PROVE-IT TIMI 22 trial[13] among patients receiving high-intensity statins, deaths not associated with coronary heart disease were reduced to a similar degree (27%) as deaths associated with coronary heart disease (30%).[13] Both differences were individually nonsignificant but together produced a significant decrease in total mortality. In addition, we were unable to determine if patients received statin treatment outside of the VA health system, although we excluded patients who did not fill a nonstatin medication prescription 6 months before the index period of interest. This limitation would likely bias our results toward the null. We adjusted for baseline LDL-C levels, which may bias the results toward the null, as higher-intensity treatment will lead to lower LDL-C values at baseline. Medication possession ratios were used as a proxy for adherence, although, as with all pharmacy databases, we can only determine if the prescription was dispensed and not if the patient actually took the medication. Medication possession ratios have a high specificity for medication adherence and are widely used in the literature.[22] Since we relied on *ICD-9* administrative codes for diagnosis of ASCVD, coding errors may have affected our findings, although these errors are likely to be nondifferential by statin intensity group. Furthermore, our mean duration of follow-up was less than 2 years, yet during that period, we were able to detect significant differences in mortality by intensity of statin therapy.

Conclusions

We evaluated the real-world practice of statin use by intensity and its association with all-cause mortality in a national sample of patients with ASCVD in the VA health system. We found an inverse graded association between intensity of statin therapy and mortality. These findings suggest there is a substantial opportunity for improvement in the secondary prevention of ASCVD through optimization of intensity of statin therapy.

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