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ORIGINAL REPORT

Statins Are Associated With Reduced Mortality in Multiple Myeloma

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ABSTRACT

Purpose
The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) have activity in one of the pathways influenced by nitrogen-containing bisphosphonates, which are associated with improved survival in multiple myeloma (MM). To understand the benefit of statins in MM, we evaluated the association between statin use and mortality in a large cohort of patients with MM.

Patients and Methods
From the Veterans Administration Central Cancer Registry, we identified patients diagnosed with MM between 1999 and 2013. We defined statin use as the presence of any prescription for a statin within 3 months before or any time after MM diagnosis. Cox proportional hazards regression assessed the association of statin use with mortality, while controlling for known MM prognostic factors.

Results
We identified a cohort of 4,957 patients, of whom 2,294 received statin therapy. Statin use was associated with a 21% decrease in all-cause mortality (adjusted hazard ratio, 0.79; 95% CI, 0.73 to 0.86; $P < .001$) as well as a 24% decrease in MM-specific mortality (adjusted hazard ratio, 0.76; 95% CI, 0.67 to 0.86; $P < .001$). This association remained significant across all sensitivity analyses. In addition to reductions in mortality, statin use was associated with a 31% decreased risk of developing a skeletal-related event.

Conclusion
In this cohort study of US veterans with MM, statin therapy was associated with a reduced risk of both all-cause and MM-specific mortality. Our findings suggest a potential role for statin therapy in patients with MM. The putative benefit of statin therapy in MM should be corroborated in prospective studies.

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INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are widely used for treatment of dyslipidemia and prevention of coronary heart disease. In a recent trial of patients with perceived life expectancy of 1 to 12 months, there was no difference in 60-day mortality between patients randomly assigned to discontinue pre-existing statin therapy, and those randomly assigned to continue statin therapy.[1] Of the 381 patients enrolled, half of them had cancer as the principal diagnosis. Subgroup analyses of this population were not done, and cancer-specific outcomes were not assessed.

Because statins directly inhibit HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway,[2] they may have activity in multiple myeloma (MM).[3] Nitrogen-containing bisphosphonates, an adjunct therapy in MM, act downstream of statins in the mevalonate pathway through inhibition of farnesyl-diphosphate synthase (Fig 1). Modification of this pathway in a prospective, randomized trial found a 16% reduction in the risk of mortality in patients with MM randomly assigned to receive zoledronic acid (a nitrogen-containing bisphosphonate) versus clodronate (a non-nitrogen–containing bisphosphonate).[4] A similar association between zoledronic acid and survival was found in separate studies.[4,5] Preclinical data suggest this improvement is related to the nitrogen-containing class inhibition of the mevalonate pathway leading to a reduction in protein prenylation,[3] a process crucial for MM cell growth and survival.[6,7]

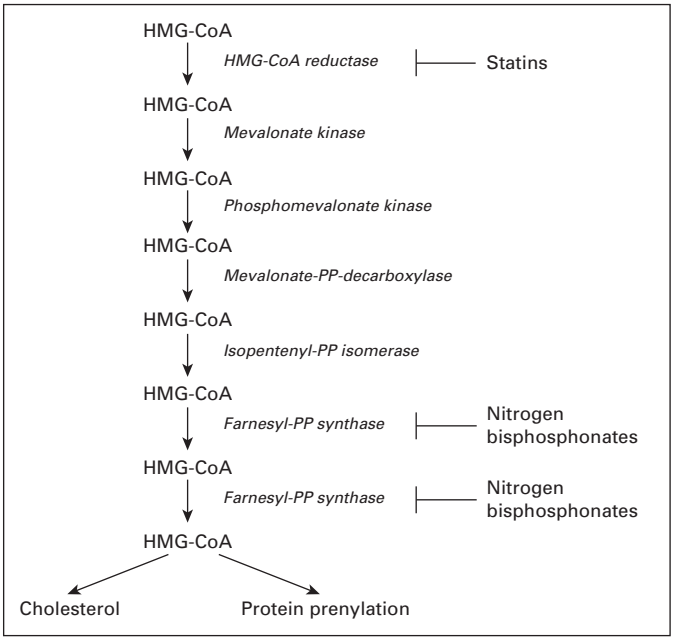

Fig 1. Statin and nitrogen-containing bisphosphonate mechanism of action on the mevalonate pathway. HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; PP, pyrophosphate.

In vivo and in vitro studies show acceleration of MM cell apoptosis and cell growth arrest with statin therapy.[8-12] Statins decrease angiogenesis[13] and reduce the metastatic potential of tumor cells.[14,15] In addition, statins have been shown to stimulate bone formation.[16] A randomized trial of lovastatin in MM found improved progression-free survival,[17] but enrolled only 91 patients and this practice has not been adopted. Thus, to understand the putative benefit of statins in MM, we quantified the association between statin use and mortality in a large cohort of patients with MM.

PATIENTS AND METHODS

Study Population

Patients diagnosed with MM within the Veterans Health Administration (VHA) between September 1, 1999, and December 31, 2013, were identified in the Veterans Administration (VA) Central Cancer Registry using International Classification of Diseases (ICD)–03 code 9732/3. The cohort was followed through October 2014. To remove patients who had monoclonal gammopathy of undetermined significance, solitary plasmacytoma, or smoldering MM, we excluded patients who did not receive treatment within 6 months of MM diagnosis. Before cohort assembly, the St Louis VHA Medical Center and Washington University School of Medicine institutional review boards approved this study.

Measurements and Covariates

International Classification of Diseases, 9th revision–Clinical Modification (ICD-9-CM) codes, Pharmacy Benefits Management records, and laboratory data were obtained using the VA Informatics and Computing Infrastructure platform. Records from Pharmacy Benefits Management included dates of administration of all MM-directed therapy, bisphosphonates, and statins (Appendix Table A1, online only). Height and weight were assessed within 1 month of diagnosis. Data on comorbidities present at the time of MM diagnosis were obtained using ICD-9-CM diagnostic codes for ischemic heart disease, diabetes mellitus, chronic kidney disease, peripheral vascular disease, cerebrovascular disease, and dyslipidemia.

Using ICD-9-CM codes, we calculated the Romano adaptation of the Charlson comorbidity index[18] for each patient at the time of diagnosis. Patients with skeletal-related events were identified using a combination of ICD-9-CM and Current Procedural Terminology codes, using previously described methods.[19,20] Hemoglobin and albumin levels were measured at the time closest to, but within 2 months of diagnosis, and before treatment initiation. We calculated the estimated glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration formula,[21] using data from immediately before treatment initiation.

Survival was measured from the date of MM diagnosis until death. Date of death was obtained using the VA vital status file (a VA database that combines death dates from the VA Beneficiary Identification and Records Locator Subsystem Death File, the Social Security Administration-Death Master File, the Medicare Vital Status File, and the Medical SAS Inpatient Datasets).[22,23] Cause-specific death information, including death from MM, was available for patients diagnosed up to December 31, 2009, and was obtained from the VHA National Death Index.

Statin Use

Statins available through the VHA during the study period included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Patients were identified as statin users if they had any prescriptions for statins in the 3 months before or any time after their date of MM diagnosis. To account for variation in statin use over time and adjust for immortal time bias,[24,25] we assessed statin use as a time-varying covariate (except in sensitivity analysis). To remove bias from medication changes that may occur at the end of life, we used a 3-month lag for the statin start and stop dates.[26,27] To account for differences in statin dosing and potency, we calculated the daily defined dose (DDD) as specified by the WHO.[28] The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Statistical Analyses

Baseline patient characteristics were compared between statin users and nonusers using χ^2 and Cochrane-Mantel-Haenszel tests for categorical variables. Unpaired Student *t* tests were used for continuous variables. A two-tailed α significance level of 0.05 was used for all analyses. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Primary Analyses

Our primary objective was to evaluate the association between statin use and all-cause mortality in patients with MM. A secondary objective of the study was to assess the association between statin use and MM-specific mortality. Cox proportional hazards regression controlled for the following baseline MM prognostic factors in both mortality analyses: body mass index (BMI), age, race, Charlson comorbidity index score, year of diagnosis, hemoglobin level, creatinine clearance, albumin level, and MM treatment (zoledronic acid, pamidronate, dexamethasone monotherapy, bortezomib, lenalidomide, thalidomide, and autologous stem cell transplantation [ASCT]). Dexamethasone monotherapy was defined as treatment with dexamethasone alone without receipt of other MM-specific therapies; for the remaining treatment categories, patients could receive any combination of MM-directed therapy. All prognostic factors were defined a priori. We used the same methods when quantifying the association between statin use and development of skeletal-related events.

Sensitivity Analyses

All sensitivity analyses were adjusted for the same MM prognostic factors as in the primary analyses. To assess the impact of race on the association between statin use and mortality, we stratified our initial results by race (white *v* black race).

To adjust for immortal time bias, we assessed the association between statin use and both all-cause and MM-specific mortality with a 12-month landmark analysis.[29,30] Patients were included in the landmark analysis if they survived at least 12 months from MM diagnosis, with statin users defined as

those who were on statin therapy at MM diagnosis, or who started within 12 months of MM diagnosis. All other patients in the cohort were considered nonstatin users. In addition, we performed a 12-month landmark analysis and assessed the association between cumulative duration of statin use and mortality by 3-month increments of increasing duration of statin use. Statin use for all landmark analyses was limited to the 12-month period following MM diagnosis.

Adjusting for variations in statin potency and dosing, we quantified the association between statin use and both all-cause and MM-specific mortality by DDD. In these analyses, we dichotomized patients into two groups: those who had received at least 365 DDDs and those who had received < 365 DDDs. To control for immortal time bias in the DDD analyses, we assessed statin use as a time-varying covariate.

Propensity score–matched analyses were used to adjust for baseline differences between statin users and nonusers.[31] Propensity scores were generated using logistic regression to estimate the probability that each patient in the cohort would be prescribed statin therapy conditional on baseline covariates.

Last, given the prognostic implications of cytogenetics and fluorescent in situ hybridization (FISH), we used Current Procedural Terminology codes to identify patients with results in either category. We then manually abstracted the results of testing in this population. Differences between the prevalence of high-, intermediate-, and standard-risk results between statin users and nonusers were assessed.

RESULTS

A total of 4,957 patients with MM met entry criteria into the all-cause mortality analytic cohort. Of these patients, 2,294 had prescriptions for statin therapy, and 2,663 patients did not (Appendix Fig A1, online only). The median follow-up for statin and nonstatin users was 34 months and 26 months, respectively. A total of 3,284 patients met entry criteria into the MM-specific mortality analytic cohort, of whom 1,415 patients received statin therapy (Appendix Fig A1). The median follow-up for statin and nonstatin users was 38 months and 24 months, respectively. In the MM-specific mortality cohort, 69% of patients died as a result of myeloma; remaining causes of death are listed in Appendix Table A2 (online only).

At baseline, patients in the all-cause mortality cohort receiving statin therapy were significantly older, more likely to be white, had higher BMIs, were more likely to be diagnosed after 2006, and had differences in baseline albumin and hemoglobin levels. In addition, they were more likely to have medical comorbidities, including diabetes mellitus, chronic kidney disease, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and dyslipidemia. Compared with nonstatin users, statin users had a higher frequency of lenalidomide, bortezomib, and pamidronate use, and were less likely to be treated with dexamethasone monotherapy. After propensity score matching, demographic data and clinical characteristics were well balanced in the all-cause mortality cohort (except for baseline hemoglobin level; Table 1). Baseline differences in the MM-specific mortality cohort were similar to those in the all-cause mortality cohort, with the additional observation that statin users were more likely to receive treatment with zoledronic acid and thalidomide compared with nonstatin users. All demographic data and clinical characteristics were well balanced after propensity score matching in the MM-specific mortality cohort (Appendix Table A3, online only).

Primary Analyses

Patients with MM receiving statin therapy had a significant reduction in all-cause mortality (Fig 2A). The median survival among statin users was 39.5 months compared with 27 months in nonusers. After adjusting for potential confounders, statin users had a 21% reduction in the risk of all-cause mortality compared with nonusers (adjusted hazard ratio [aHR], 0.79; 95% CI, 0.73 to 0.86; $P < .001$; Table 2). Several factors were associated with increased all-cause mortality, including older age, BMI < 18.5 kg/m^2, higher Charlson comorbidity index score, hemoglobin < 10 g/dL, eGFR < 30 mL/min/1.73 m^2, albumin < 3 g/dL, and treatment with pamidronate. In contrast, ASCT, first-line treatment with a novel agent (lenalidomide, bortezomib, or thalidomide), treatment with zoledronic acid, diagnosis after 2006, black race, and BMI ≥ 25 kg/m^2 were each associated with a reduced risk of all-cause mortality (Table 2).

Patients with MM receiving statin therapy also had a significant reduction in MM-specific mortality (Fig 2B). Statin use was associated with a 24% reduction in the risk of MM-specific mortality (aHR, 0.76; 95% CI, 0.67 to 0.86; $P < .001$; Table 2). Older age, BMI < 18.5 kg/m^2, higher comorbidity score, hemoglobin < 10 g/dL, eGFR < 30 mL/min/1.73 m^2, and use of pamidronate were all associated with increased MM-specific mortality. First-line treatment with a novel agent, ASCT, treatment with zoledronic acid, black race, and BMI ≥ 25 kg/m^2 were all associated with reduced MM-specific mortality.

Users of statin therapy had a 31% reduction in the risk of developing a skeletal-related event (aHR, 0.69; 95% CI, 0.59 to 0.80; $P < .001$). In this analysis, being a recipient of a stem-cell transplantation was associated with a decreased risk of skeletal-related events, whereas treatment with pamidronate was associated with an increased risk of skeletal-related events.

Sensitivity Analyses

When stratifying our results on the basis of race, statin use remained associated with a significant reduction in all-cause mortality in black (aHR, 0.73; 95% CI, 0.62 to 0.86; $P < .001$) as well as white (aHR, 0.83; 95% CI, 0.76 to 0.92; $P < .001$) patients. Similarly, statin use was associated with a reduced risk of MM-specific mortality in black (aHR, 0.67; 95% CI, 0.51 to 0.86; $P = .002$) and white (aHR, 0.81; 95% CI, 0.70 to 0.95; $P = .007$) patients.

In the 12-month landmark analyses, statins remained associated with a significant reduction in risk of all-cause mortality (aHR, 0.86; 95% CI, 0.78 to 0.94; $P = .001$), as well as MM-specific mortality (aHR, 0.83; 95% CI, 0.71 to 0.96; $P = .01$; Table 3). In addition, patients prescribed statins for longer durations had greater reductions in all-cause mortality by 12% (95% CI, 0.80 to 0.96; $P = .004$), 16% (95% CI, 0.76 to 0.92; $P < .001$), and 18% (95% CI, 0.74 to 0.92; $P = .003$) for at least 3-, 6-, and 9-month use, respectively.

Using DDD, patients with < 365 DDDs had a 20% reduction (aHR, 0.80; 95% CI, 0.73 to 0.89; $P < .001$), whereas patients with ≥ 365 DDDs of statin use had a 22% reduction in risk of all-cause mortality (aHR, 0.78; 95% CI, 0.70 to 0.87; $P < .001$; Appendix Table A4, online only). MM-specific mortality in patients with < 365 DDDs was reduced by 22% (aHR, 0.78; 95% CI, 0.68 to 0.91; $P = .001$), whereas patients with ≥ 365 DDDs of statin use had a 28% reduction in risk of death from MM (aHR, 0.72; 95% CI, 0.59 to 0.86; $P < .001$; Appendix Table A4, online only).

When further adjusting for baseline differences between statin users and nonusers with propensity score matching, statin use remained similarly associated with both a reduction in all-cause

Table 1. Demographic Data and Clinical Characteristics Stratified by Statin Use Among US Veterans Diagnosed With Multiple Myeloma Between 1999 and 2013: All-Cause Mortality Cohort

Baseline Characteristic	Unadjusted Data, Statin Use			Propensity Score Matched, No Statin Use		
	Yes (n = 2,294)	No (n = 2,663)	*P*	Yes (n = 1,328)	No (n = 1,328)	*P*
Mean age, years	69.3	67.6	< .001	68.6	68.3	.40
Male sex, %	98.3	97.6	.08	97.9	97.9	1.00
Race, %						
White and other	73.1	68.5		71.9	72.2	
Black	26.9	31.5	< .001	28.1	27.8	.86
BMI, kg/m^2, %						
< 18.5	1.1	4.1		1.4	1.6	
18.5 to < 25	23	33.2		26.9	26.5	
25 to < 30	36.9	33.2		36.6	37.7	
≥ 30	31.8	20.7		27.9	26.1	
Unknown	7.2	8.8	< .001	7.2	8.2	.56
Diagnosis year, %						
1999-2002	9.1	20.6		11.7	13	
2003-2006	26	28.1		26.7	26.8	
2007-2010	38.5	29.1		37.5	33.3	
2011-2013	26.4	22.2	< .001	24.2	27	.98
Charlson comorbidity index score, mean	3.6	2.6	< .001	3.2	3.1	.59
Diabetes mellitus, %	42.0	21.9	< .001	34	32.9	.54
Chronic kidney disease, %	25.4	18.6	< .001	23	23.3	.86
Ischemic heart disease, %	45.3	18.6	< .001	31.2	28.6	.15
Cerebrovascular disease, %	11.9	6.3	< .001	9.1	8.5	.58
Peripheral vascular disease, %	16.3	7.2	< .001	12.3	10.3	.11
Dyslipidemia, %	81.1	34.5	< .001	67.5	67.3	.93
Transplantation, %	14	13.6	.65	15.2	13.9	.35
Melphalan, %	34.1	34.9	.56	32.7	31.9	.68
Lenalidomide, %	40	32.4	< .001	37.4	39.6	.23
Thalidomide, %	38.6	37	.24	36.9	39.3	.20
Dexamethasone, %	7	9.1	.008	8.3	7.2	.31
Bortezomib, %	48	42.2	< .001	46.8	48.3	.46
Zoledronic acid, %	41.8	39.1	.06	40.6	41.6	.61
Pamidronate, %	43	48.5	< .001	44.2	42.7	.44
Hemoglobin, g/dL, mean	10.8	10.5	< .001	10.9	10.6	.002
eGFR, %						
≥ 30 mL/min/1.73 m^2	53.3	44.4		50.6	49.8	
< 30 mL/min/1.73 m^2	14.9	12.8		14.4	15.5	
Unknown	31.8	42.9	.75	35	34.7	.42
Albumin, d/dL, mean	3.3	3.2	< .001	3.3	3.3	.21

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.

mortality (aHR, 0.78; 95% CI, 0.70 to 0.87; $P < .001$), as well as with MM-specific mortality (aHR, 0.79; 95% CI, 0.67 to 0.94; $P = .007$).

Cytogenetic and FISH data were not available for the majority of the cohort. A subgroup of 988 patients with results of either routine cytogenetic or FISH testing was identified. All 988 patients had cytogenetic testing results, whereas only 374 also had FISH testing results. There was no difference in the prevalence of high- or intermediate-risk results between statin users and nonusers (Table 4). There was a significant difference in the prevalence of translocation (11;14), a favorable FISH test result, with a higher prevalence noted in statin nonusers.

DISCUSSION

In this multicenter, population-based cohort study of patients with newly diagnosed MM, statin use was associated with a 21% reduction in all-cause mortality and a 24% reduction in MM-specific mortality. These reductions were statistically significant across all analyses, with the reduction in mortality persisting after adjustment for immortal time bias and propensity score. In addition, statin use was associated with a decreased risk of developing skeletal-related events, even after adjusting for bisphosphonate use.

Statins directly inhibit HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway.[2] This enzyme is upstream of the mechanism of action of bisphosphonates on the same pathway. Bisphosphonates are associated with a reduction in the risk of mortality in MM.[4,5] Our findings support an association between statin use and reduced risk of mortality even after adjusting for bisphosphonate use.

Interestingly, pamidronate (a nitrogen-containing bisphosphonate) was associated with increased risk of mortality in several analyses. One hypothesis to explain this observation is confounding by indication. In 1995, pamidronate was approved by the Food and Drug Administration for treatment of patients with MM with at least one lytic bone lesion. In 2002, the year zoledronic acid was approved for the same indication, ASCO released clinical treatment guidelines for bisphosphonates in MM.[32] These guidelines reinforced the efficacy of bisphosphonates (either pamidronate or zoledronic acid) in patients

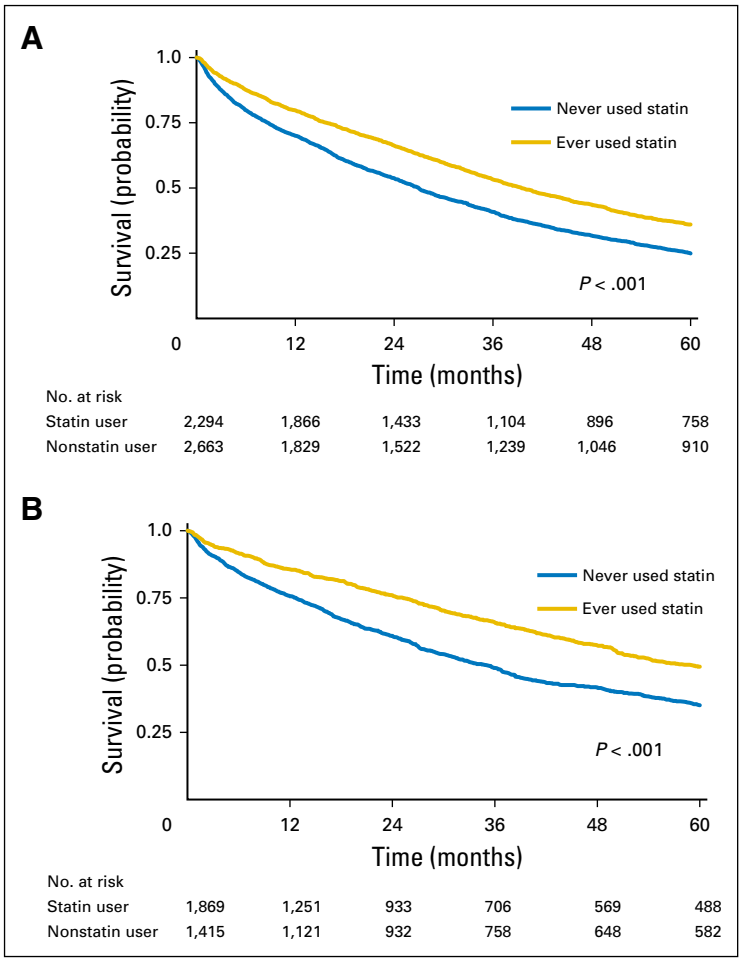

Fig 2. Kaplan-Meier curves. Survival for patients with multiple myeloma treated with statin versus no statin therapy. (A) All-cause survival; (B) multiple myeloma–specific survival.

with lytic bone disease in MM. However, they also suggested that use was reasonable in patients with MM with osteoporosis/osteopenia, expanding use of bisphosphonates. In 2007, the National Comprehensive Cancer Network released guidelines that recommended bisphosphonate use for any patient with active MM, regardless of lytic bone lesions.[33] Thus, it is probable that patients who received pamidronate were more likely to have lytic bone disease at time of treatment compared with those treated with zoledronic acid. Lytic bone lesions have been associated with reduced survival in patients with MM because they are probably a sign of more advanced and/or aggressive disease.[34]

Three prior studies have investigated the role of statins in patients with MM.[17,35,36] The first trial, containing 16 patients, found a decrease in treatment resistance with the addition of simvastatin to MM-directed therapy.[36] The second study, a retrospective analysis, assessed statin use in 146 patients with MM undergoing ASCT.[35] In that study, there was a trend toward increased overall response rates among patients taking a statin; however, there was no change in progression-free or overall survival. Last, a trial of 91 patients receiving thalidomide and dexamethasone with or without lovastatin found improved progression-free survival with lovastatin and a trend toward improved overall survival.[17] Although these prior studies suggest a possible benefit of statins in MM, they are limited by small sample sizes. In addition, MM-specific mortality was not assessed.

Our population-based study has notable strengths and limitations. The VHA is the largest integrated health care system in the United States with facilities in all 50 states and Puerto Rico providing care to a diverse population of patients. Given the comprehensive benefits provided by the VHA, records of survival status are well maintained and accurate.[23] Prior work has shown the accuracy of VHA vital status files for survival status, with $>$ 97% of death events accurately captured in the database.[22,23] Misclassification of statin use was possible as a result of patient noncompliance; however, the 3-month lag, and the duration-of-use analysis requiring multiple statin prescriptions, make misclassification of less concern. Additionally, misclassification of statin use, if present, would be expected to bias our results toward a null finding.

The robust data within the Veterans Administration Central Cancer Registry allowed for the adjustment of known prognostic factors associated with survival in MM, including baseline comorbidities, year of diagnosis, baseline laboratory data, MM-specific therapy, and transplantation status. Although we used propensity score analyses in an attempt to adjust for unmeasured confounding, it is plausible that there were residual, unmeasured differences between the two groups, resulting in confounding. Cytogenetic and

Table 2. Association Between Statin Use and All-Cause and Multiple Myeloma–Specific Mortality

Variable	All-Cause Mortality			Multiple Myeloma–Specific Mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Statin use	0.79	0.73 to 0.86	< .001	0.76	0.67 to 0.86	< .001
BMI, kg/m^2						
< 18.5	1.40	1.15 to 1.70	< .001	1.41	1.07 to 1.86	.015
18.5 to < 25	Referent	0.77 to 0.92	< .001	Referent	0.72 to 0.93	.002
25 to < 30	0.84	0.73 to 0.88	< .001	0.82	0.63 to 0.84	< .001
≥ 30	0.80	0.71 to 0.95	.009	0.73	0.71 to 1.05	.13
Unknown	0.82			0.86		
Age, per year increase	1.02	1.01 to 1.02	< .001	1.01	1.01 to 1.02	< .001
Race						
White	Referent	0.77 to 0.90	< .001	Referent	0.78 to 0.99	.03
Black	0.84			0.88		
Charlson comorbidity index	1.06	1.05 to 1.08	< .001	1.03	1.01 to 1.05	.01
Diagnosis in 2006 or later	0.86	0.78 to 0.95	.004	0.99	0.86 to 1.14	.85
Baseline laboratory data						
Hemoglobin < 10 g/dL	1.23	1.12 to 1.35	< .001	1.41	1.21 to 1.65	< .001
Hemoglobin unknown	1.08	0.95 to 1.23	.22	1.30	1.06 to 1.60	.01
Creatinine clearance < 30 mL/min	1.32	1.18 to 1.46	< .001	1.45	1.22 to 1.73	< .001
Albumin ≤ 3 g/dL	1.34	1.21 to 1.47	< .001	1.16	0.99 to 1.36	.06
Multiple myeloma–specific therapy						
Transplantation	0.49	0.43 to 0.57	< .001	0.51	0.42 to 0.62	< .001
Upfront therapy with novel agent	0.54	0.50 to 0.59	< .001	0.56	0.49 to 0.62	< .001
Bisphosphonate therapy						
Zoledronic acid	0.73	0.67 to 0.78	< .001	0.70	0.62 to 0.78	< .001
Pamidronate	1.09	1.01 to 1.17	.03	1.22	1.10 to 1.36	< .001

Abbreviations: BMI, body mass index; HR, hazard ratio.

FISH analyses were unavailable for the majority of the cohort. However, an analysis of the group of patients with cytogenetic information found no significant difference in the presence of high- or intermediate-risk cytogenetics between statin users and nonusers.

In conclusion, in this cohort study of United States veterans with MM, statin therapy was associated with a reduced risk of both all-cause and MM-specific mortality. Our findings suggest a potential role for statin therapy in patients with MM. The putative

Table 3. Association Between Statin Use and All-Cause and Multiple Myeloma–Specific Mortality: Landmark Analyses

Variable	All-Cause Mortality			Multiple Myeloma–Specific Mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Statin use	0.86	0.78 to 0.94	.001	0.83	0.71 to 0.96	.01
BMI, kg/m^2						
< 18.5	1.37	1.03 to 1.81	.03	1.44	0.96 to 2.18	.08
18.5 to < 25	Referent	0.71 to 0.88	< .001	Referent	0.70 to 0.96	.02
25 to < 30	0.79	0.69 to 0.87	< .001	0.82	0.63 to 0.91	.003
≥ 30	0.78	0.68 to 0.95	.01	0.76	0.61 to 1.00	.05
Unknown	0.80			0.78		
Age, per year increase	1.02	1.02 to 1.03	< .001	1.02	1.01 to 1.03	< .001
Race						
White	Referent	0.77 to 0.93	< .001	Referent	0.82 to 1.09	.45
Black	0.85			0.95		
Charlson comorbidity index	1.06	1.04 to 1.08	< .001	1.01	0.98 to 1.04	.59
Diagnosis in 2006 or later	0.94	0.83 to 1.07	.36	1.05	0.87 to 1.26	.60
Baseline laboratory data						
Hemoglobin < 10 g/dL	1.23	1.10 to 1.39	< .001	1.39	1.13 to 1.71	.002
Creatinine clearance < 30 mL/min	1.22	1.05 to 1.40	.007	1.38	1.07 to 1.77	.01
Albumin ≤ 3 g/dL	1.07	0.95 to 1.21	.28	0.91	0.74 to 1.13	.39
Multiple myeloma–specific therapy						
Transplantation	0.68	0.59 to 0.78	< .001	0.69	0.56 to 0.84	< .001
Upfront therapy with novel agent	0.75	0.67 to 0.83	< .001	0.80	0.68 to 0.94	.006
Bisphosphonate therapy						
Zoledronic acid	0.91	0.83 to 0.99	.03	0.89	0.78 to 1.01	.08
Pamidronate	1.30	1.18 to 1.42	< .001	1.62	1.40 to 1.87	< .001

Abbreviation: BMI, body mass index; HR, hazard ratio.

Table 4. Cytogenetic and Fluorescent In Situ Hybridization Abnormalities Between Statin Users and Nonusers

Abnormality	Statin Use, n = 126 (%)	No Statin Use, n = 99 (%)	*P*
High risk			
FISH deletion 17p	2.4	4	.70
FISH translocation (14;16)	0.8	0	1.00
FISH translocation (14;20)	0	0	
Intermediate risk			
FISH translocation (4;14)	0	2	.19
Cytogenetic deletion 13q	4.0	2.2	.47
Hypodiploidy	2.4	1	.63
Standard risk			
FISH translocation (11;14)	1.6	7.1	.05
FISH translocation (6;14)	0.0	0	

benefit of statin therapy in MM should be corroborated in a prospective study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Statins Are Associated With Reduced Mortality in Multiple Myeloma

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Appendix

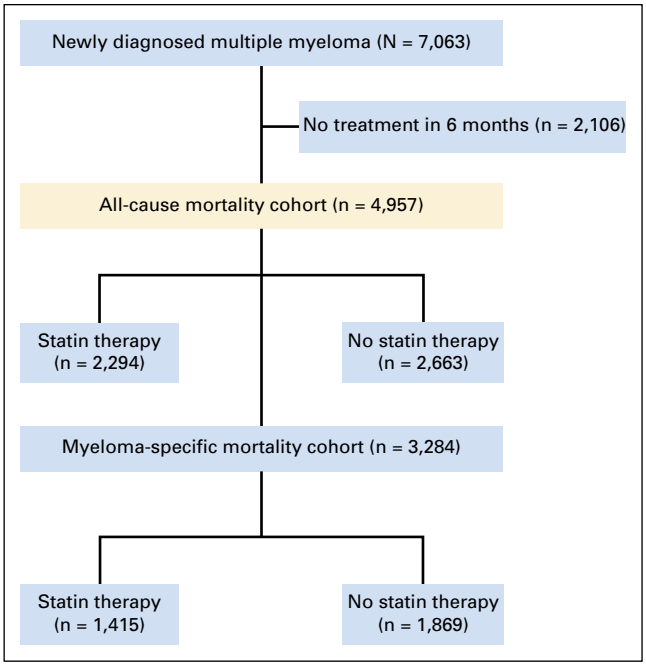

Fig A1. Strengthening the reporting of observational studies in epidemiology (STROBE) diagram.

Table A1. Pharmacy Benefits Management: List of Variables Abstracted

Variable	Type	Length	Format	Label
Inpatient intravenous prescription data				
DISP	Num	8		
DISP_OCCUR	Num	3		disp_occur
FORMULARY	Char	3		formulary
GENERIC	Char	25		
IV_IND	Char	1		
IV_ORDER	Char	3		
IV_PRN	Char	40		
IV_TYPE	Char	1		
NDC	Char	14		
OP_IV	Char	1		
ORDER_IND	Char	1		order_ind
SCRSSN	Num	6		
SIG	Char	36		
START_DATE	Num	8	DATETIME18.	start_date
STN_CLASS	Char	5		stn_class
STN_MATCH	Char	52		stn_match
STN_NAME	Char	30		
STN_NUM	Char	5		
STN_STRG	Char	5		
STOP_DATE	Num	8	DATETIME18.	stop_date
VA_PRODUCT	Char	52		va_product
VISN	Char	2		
Inpatient oral prescription data				
DSP_UNT	Char	10		
NDC	Char	14		
PRICE_DSP	Num	8		price_dsp
SCHEDULE	Char	35		
SCRSSN	Num	6		
START_DATE	Num	8	DATETIME18.	start_date
STN_CLASS	Char	5		stn_class
STN_MATCH	Char	61		stn_match
STN_NAME	Char	40		
STN_NUM	Char	5		
TL_QTY	Num	4		
UD_ORDER	Char	8		
UNITS_DOSE	Num	3		units_dose
VA_PRODUCT	Char	61		va_product
Outpatient prescription data, all				
CMOP_IND	Char	1		
DAY_SUPPLY	Num	4		Day_supply
DSP_UNT	Char	8		
FRP_DATE	Char	10		
GENERIC	Char	34		
MONTH_KEY	Num	6		month_key
NDC	Char	14		
NRP_IND	Char	1		
PRE_NUM	Char	10		
PRICE_DSP	Num	8		Price_dsp
PROV_TYPE	Char	1		Prov_type
REL_DATE	Char	10		
SCRSSN	Num	6		
SIG	Char	157		
STN_NUM	Char	5		
TL_COST	Num	8		
TL_QTY	Num	8		
VA_CLASS	Char	70		
VA_PRODUCT	Char	61		Va_product
VISN	Char	2		

Abbreviations: char, characters; num, numerals.

Table A2. Listed Causes of Death: Multiple Myeloma–Specific Mortality Cohort

Cause of Death	%
Multiple myeloma	69.4
Malignancy other than multiple myeloma	7.9
Lymphoid leukemia	
Myeloid leukemia	
Unspecified leukemia	
Unspecified malignant neoplasm, lymphoid, or hematopoietic	
Unspecified malignant neoplasm	
Non-Hodgkin lymphoma	
Malignant neoplasm of unspecified site	
Neoplasm of pharynx	
Neoplasm of esophagus	
Neoplasm of colon	
Neoplasm of rectosigmoid junction/rectum	
Neoplasm of liver	
Neoplasm of intrahepatic bile duct	
Neoplasm of pancreas	
Neoplasm of undefined digestive organ	
Neoplasm of larynx	
Neoplasm of trachea/bronchus/lung	
Neoplasm of bone	
Malignant melanoma	
Neoplasm of skin	
Neoplasm of other mesothelial or soft tissue	
Neoplasm of ovary	
Neoplasm of prostate	
Neoplasm of kidney	
Neoplasm of bladder	
Neoplasm of brain	
Neoplasm of unknown behavior/site	
Aplastic anemia	
Infection	3.2
Intestinal infection, not specified	
Septicemia	
Unspecified infectious/parasitic disease	
HIV resulting in neoplasm	
HIV resulting in other specified disease	
Unspecified viral disease	
Pneumonia	
Acute/subacute endocarditis	
Infection of skin and subcutaneous system	
Urinary tract infection	
Immune system and endocrinopathies	1.3
Certain disorders of immune mechanism	
Disorders of thyroid gland	
Diabetes mellitus	
Metabolic disorders	
Bleeding disorders	0.1
Coagulation defect, purpura, and hemorrhagic conditions	
Renal disorders	2.2
Unspecified glomerular disease	
Renal tubule-interstitial diseases	
Renal failure	
Volume depletion	
Neurologic/cerebrovascular	1.1
Parkinson's disease	
Alzheimer's dementia	
Epilepsy	
All other diseases of the nervous system	
Subarachnoid hemorrhage	
Intracerebral and/or intracranial hemorrhage	
Cerebrovascular accident	
Spina bifida	

(continued in next column)

Table A2. Listed Causes of Death: Multiple Myeloma–Specific Mortality Cohort (continued)

Cause of Death	%
Cardiovascular	9.2
Rheumatic mitral valve disease	
Essential primary hypertension	
Hypertensive heart disease	
Hypertensive renal disease and secondary hypertension	
Hypertensive heart and renal disease	
Acute myocardial infarction	
Other acute ischemic heart disease	
Other chronic ischemic heart disease	
Atherosclerotic cardiovascular disease	
All other forms of ischemic heart disease	
Nonrheumatic aortic valve disease	
All other diseases of the endocardium	
Cardiomyopathy	
Conduction disorder and cardiac dysrhythmias	
Congestive heart failure	
Other and unspecified heart failure	
Other cardiovascular disease	
Aortic aneurysm and dissection	
Other diseases of the arteries, arterioles, and capillaries	
Pulmonary	2.4
Emphysema	
Chronic obstructive pulmonary disease	
Pneumonitis as a result of solids/liquids	
All other diseases of the respiratory system	
Pleural effusion and plaque	
Pulmonary embolism	
Other pulmonary heart disease or disease of pulmonary circulation	
GI	1.0
Diseases of the esophagus	
Duodenal ulcer	
Diseases of the appendix	
Vascular disorder and obstruction of the intestine	
Diverticular disease	
Other diseases of the intestine/peritoneum	
Alcohol liver disease	
Cirrhosis of the liver	
Other diseases of the liver	
Disorders of the biliary tract and pancreas	
All other diseases of the digestive system	
Self-harm, intentional and unintentional, including substance use	1.5
Mental/behavioral disorder as a result of psychoactive substance use	
Organic dementia	
Unspecified motor vehicle accident	
Unspecified land transport accident	
Fall	
Accidental inhalation and ingestion of food/object causing obstruction	
Accidental exposure to smoke, flames, and fire	
Accidental poisoning by exposure to drugs/biologic substances	
All other unspecified accidents	
Suicide by discharge of firearms	
Iatrogenic	0.1
Complications of medical and surgical care	
Musculoskeletal	0.1
Arthropathies and related disorders	
Osteopathies, chondropathies, and disorders of connective tissue	
Miscellaneous	0.5
All other symptoms, signs, and abnormal clinical and laboratory findings	
Other ill-defined and unknown causes of mortality	

Table A3. Demographic Data and Clinical Characteristics Stratified by Statin Use Among US Veterans Diagnosed with Multiple Myeloma Between 1999 and 2009: Multiple Myeloma–Specific Mortality Cohort

	Unadjusted Data, Statin Use			Propensity Score Matched, No Statin Use		
Baseline Characteristic	Yes (n = 1,415)	No (n = 1,869)	*P*	Yes (n = 844)	No (n = 844)	*P*
Mean age, years	69.3	67.8	< .001	68.8	68.8	1.00
Male sex, %	98.2	97.8	.41	97.4	97.5	.88
Race, %						
White and other	74.4	68.5		72.6	73.8	
Black	25.6	31.5	< .001	27.4	26.2	.58
BMI, kg/m^2, %						
< 18.5	1.1	4.3		1.9	1.7	
18.5 to < 25	23.7	34.1		27.4	26.4	
25 to < 30	37.2	34		36.4	36.5	
≥ 30	30.3	18.4		25.5	26.3	
Unknown	7.6	9.2	< .001	8.9	9.1	.55
Diagnosis year, %						
1999-2002	14.6	29.1		18.3	19.4	
2003-2006	41.1	33.4		41.4	41.6	
2007-2010	44.2	31.6	< .001	40.4	40	.47
2011-2013	NA	NA		NA	NA	
Charlson comorbidity index score, mean	3.4	2.5	< .001	3	2.9	.62
Diabetes mellitus, %	39.4	20.7	< .001	31.5	30.8	.75
Chronic kidney disease, %	22	16.3	< .001	20.7	20.9	.95
Ischemic heart disease, %	46.1	18.6	< .001	33.9	30.6	.14
Cerebrovascular disease, %	11.7	5.9	< .001	9.5	8.4	.44
Peripheral vascular disease, %	15.0	7	< .001	11.6	10.2	.35
Dyslipidemia, %	77.4	29.2	< .001	62.3	62	.88
Transplantation, %	13.6	12.5	.35	14.5	11.4	.06
Melphalan, %	43.8	42.9	.60	41.1	41.2	.96
Lenalidomide, %	33.5	24	< .001	30	30.8	.71
Thalidomide, %	53.1	48.1	.004	50.6	52	.56
Dexamethasone, %	6.8	9.7	.003	8.7	8.1	.66
Bortezomib, %	38.2	30.7	< .001	34.7	35.9	.61
Zoledronic acid, %	41.3	34.8	< .001	37.7	38.2	.84
Pamidronate, %	51.7	58.3	< .001	55.6	51.7	.11
Hemoglobin, g/dL, mean	10.8	10.5	.004	10.7	10.5	.08
eGFR ,%						
≥ 30 mL/min/1.73 m^2	47	36.1		42.2	42.1	
< 30 mL/min/1.73 m^2	11.8	10.3		11.6	13	
Unknown	41.2	53.6	.27	46.2	44.9	.45
Albumin, d/dL, mean	3.3	3.2	.03	3.3	3.3	.99

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; NA, not applicable.

Table A4. Association Between Statin Use and All-Cause and Multiple Myeloma–Specific Mortality Adjusted by Daily Defined Dose

Variable	All-Cause Mortality			Multiple Myeloma–Specific Mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Statin use, DDD						
< 365	0.80	0.73 to 0.89	< .001	0.78	0.68 to 0.91	.001
≥ 365	0.78	0.70 to 0.87	< .001	0.72	0.59 to 0.86	< .001
BMI, kg/m^2						
< 18.5	1.40	1.15 to 1.70	< .001	1.41	1.07 to 1.86	.01
18.5 < 25	Referent	0.77 to 0.92	< .001	Referent	0.72 to 0.93	.002
25 < 30	0.84	0.73 to 0.88	< .001	0.82	0.63 to 0.84	< .001
≥ 30	0.80	0.71 to 0.95	.009	0.73	0.71 to 1.05	.13
Unknown	0.82			0.86		
Age, per year increase	1.01	1.01 to 1.02	< .001	1.01	1.01 to 1.02	< .001
Race						
White	Referent	0.77 to 0.90	< .001	Referent	0.78 to 0.99	.03
Black	0.84			0.88		
Charlson comorbidity index	1.06	1.05 to 1.08	< .001	1.03	1.01 to 1.05	.01
Diagnosis in 2006 or later	0.86	0.78 to 0.95	.004	0.99	0.86 to 1.14	.86
Baseline laboratory data						
Hemoglobin < 10 g/dL	1.23	1.12 to 1.35	< .001	1.41	1.21 to 1.65	< .001
Hemoglobin unknown	1.08	0.95 to 1.23	.22	1.30	1.06 to 1.61	.01
Creatine clearance < 30 mL/min	1.32	1.18 to 1.46	< .001	1.45	1.22 to 1.73	< .001
Albumin ≤ 3 g/dL	1.34	1.22 to 1.47	< .001	1.16	1.00 to 1.36	0.06
Multiple myeloma–specific therapy						
Transplantation	0.49	0.43 to 0.57	< .001	0.51	0.42 to 0.62	< .001
Upfront therapy with novel agent	0.54	0.50 to 0.59	< .001	0.56	0.49 to 0.62	< .001
Bisphosphonate therapy						
Zoledronic acid	0.73	0.67 to 0.78	< .001	0.70	0.62 to 0.78	< .001
Pamidronate	1.09	1.01 to 1.17	.03	1.22	1.10 to 1.36	< .001

Abbreviations: BMI, body mass index; DDD, daily defined dose; HR, hazard ratio.