Statin use is associated with improved survival in multiple myeloma: A Swedish population-based study of 4315 patients

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Abstract
Statin use has been associated with reduced cancer-specific mortality among patients with several cancer types, including multiple myeloma (MM). We aimed to further elucidate the association of statin use and dose intensity with MM survival. Using Swedish population-based national health registers, we identified all incident MM diagnoses occurring January 1, 2007 to December 31, 2013 and their drug dispensations and comorbidities. We assessed statin exposure in 6-month periods pre- and post-diagnosis, treated diagnosis as baseline for calculating survival time, and calculated hazard ratios (HR) and 95% confidence intervals (CI) of exposure-related MM-specific and all-cause mortality using Cox regression. We assessed statin exposure during the entire follow-up and risk of MM-specific mortality in a nested case-control analysis. We classified dose intensity according to American College of Cardiology/American Heart Association recommendations. We ascertained 4315 MM cases during follow-up. Statin use was associated with reduced MM-specific mortality (pre-diagnosis use multivariate-adjusted HR, 95% CI: 0.83, 0.71-0.96; 6 months post-diagnosis: 0.73, 0.60-0.89; entire follow-up: 0.65, 0.52-0.80) and (more weakly) with all-cause mortality. Intensity analyses suggested a dose-response; MM-specific mortality decreased with increasing statin intensity in all time windows (eg, 6 months post-diagnosis: low [0.76 (0.56-1.03)], medium [0.73 (0.58-0.92)], high [0.33 (0.08-1.32)] intensity). However, relatively few patients received high intensity treatment, and the trend was statistically significant only for unadjusted pre-diagnosis use.

In this large population-based MM cohort, statin use was associated with improved MM-specific survival in both sexes. Randomized prospective studies are warranted to evaluate statins as adjuvant treatment in MM.

INTRODUCTION
Reduced cancer-specific mortality with statin use has been described in several solid cancer types, such as prostate, breast and colorectal cancer.1-5 The impact of statins on cholesterol and isoprenoid synthesis may have anticancer effects through several mechanisms important in carcinogenesis and tumor survival, which include decreased protein prenylation and interference with the cell membrane "lipid rafts" involved in cell signaling.6,7 Multiple myeloma (MM) arises in a complex tumor microenvironment characterized in...
part by cytokine and growth factor signaling that favors tumor proliferation and survival, angiogenesis and disease progression. Statins have pro-apoptotic, anti-angiogenic, anti-inflammatory and other immunomodulatory properties that are postulated to explain their observed anti-neoplastic effects. These include the downregulation of the nuclear factor-kappa-B (NF-kB) pathway, which is upregulated in MM cells and a target for many new MM treatments, supporting the plausibility that statin use may influence outcomes in MM patients. This is further supported by the report of improved MM-specific survival for statin users in a large study of American veterans. In vitro data also show that statins inhibit macrophage inflammatory protein-1a (MIP-1α) expression, which is considered important in MM-associated osteolysis, and that simvastatin reduces MM-induced hemostatic imbalances, suggesting an anti-thrombotic effect in the thrombosis-prone MM patients. These observations raise the question of whether statins could have an adjuvant role in MM treatment.

The aforementioned American veterans’ study included almost exclusively men and began enrollment in 1999, before most of the new anti-MM therapies were introduced. To our knowledge, no additional observational studies have been published to confirm or refute these findings. We aimed to further investigate the potential benefit of statins for MM survival in a more recent nationwide cohort of men and women with MM in Sweden, leveraging access to records of all dispensed statins to allow analysis of dose intensity according to the well validated statin intensity categories recommended by the American College of Cardiology/American Heart Association (ACC/AHA). Despite the improvements in MM treatment in recent years, disparities in MM survival, and in particular those related to socioeconomic factors, seem to have persisted. Identifying low-cost, safe cofactors for MM treatment would be highly beneficial to enhance MM survival for patients of all sociodemographic groups.

2 | METHODS

2.1 | Study population

We conducted a nationwide retrospective cohort study using Swedish population-based health-care registers held at the National Board of Health and Welfare. We used the unique personal identification number assigned to all Swedish residents to link the databases. We identified all patients with a first diagnosis of MM from January 1, 2007 until December 31, 2013 in the Cancer Register. Patients not residing in Sweden during the periods 6 months before and after diagnosis were excluded due to lack of dispersion data for the periods of interest.

To permit assessment of statin use across the entire study period, we also performed a nested case-control analysis within the cohort of MM patients. In this analysis, all MM-specific deaths (ICD10 codes C90.0, C90.1, C90.2 or C90.3 as main cause of death) were defined as cases. Each case was matched to five controls, defined as cohort members still alive at the index date (e.g., case date of death). Controls were sampled with replacement and matched on time since MM diagnosis.

2.2 | Statin use

We used the Prescribed Drug register, established in July 2005 and containing data on all dispensed prescriptions at Swedish pharmacies, to retrieve data on all dispensed statins and other selected concomitant medications during the study period. Of note, statins are not available over-the-counter in Sweden, and by pharmacy practice, one dispensation typically covers 3 months’ use of the drug. We included all statins on the market during the follow-up period: simvastatin, rosuvastatin, pravastatin, fluvastatin and atorvastatin (Table S1). Statin use was defined in two ways in the cohort analyses: (a) users before diagnosis had at least one dispensed statin prescription recorded during the 6-month period preceding the MM diagnosis, and (b) users after diagnosis had at least one dispensed statin prescription recorded within 6 months after the diagnosis. We viewed the pre-diagnosis use as a proxy for use at baseline, that is, at diagnosis.

In the case-control analysis, all statin dispensations were assessed from date of MM diagnosis until 6 months before index date (death of the case). We excluded the last 6 months before death to avoid reverse causation by changes in medication patterns towards end of life.

Statin dose intensity was classified according to the ACC/AHA guidelines into high, moderate and low intensity statin therapy based on average mg/day dispensed during the corresponding period. High-intensity therapy on average lowers low-density lipoprotein cholesterol (LDL-C) levels by approximately ≥50%, moderate-intensity by 30 to <50% and low-intensity by <30% (Table S2). For participants changing statin ATC-code, an average dose intensity was assessed for the respective period. In the case-control analysis, a cumulative duration of statin use was also calculated from date of the first dispensation after diagnosis to 6 months after the last dispensation, allowing for a gap of up to 6 months between dispensations to account for missed doses. If a new statin prescription occurred after that, the periods were added to the cumulative duration.

2.3 | Covariates

We used the Patient Registers, which include all outpatient visits and inpatient discharge diagnoses in Sweden during the study period, to collect information on previous diagnoses of monoclonal gammopathy of undetermined significance (MGUS), and number of outpatient doctor visits during the three-year period before diagnosis. Socioeconomic data was added from the longitudinal integration database for health insurance and labor market studies. Information about concomitant use of anticoagulants, beta-blockers, diuretics, ACE inhibitors, calcium channel blockers and diabetes medications was retrieved from the Prescribed Drug register to account for related comorbidities (Table S3). For descriptive purposes, we also gathered information on use of thalidomide or lenalidomide during follow-up. Because the Swedish Drug register includes prescribed medications dispensed in pharmacies but not medications administered at hospitals, information
about bortezomib, which is administered by injection at a hospital, could not be obtained.

### 2.4 | Assessment of MM-specific and all-cause mortality

Information on deaths was added from the Cause-of-Death Register. A diagnosis of any malignant plasma cell disorder (MM, plasma cell leukemia or extramedullary or solitary plasmacytoma; ICD10 codes C90.0, C90.1, C90.2 or C90.3) as main cause of death was considered MM-specific mortality.

We validated the classification of MM-specific mortality in a random patient subset (N = 68, 5%) through medical record review. In this review, the cause of death was regarded as MM-specific if death was due to progressive disease or was treatment-related. The positive predictive value (PPV) was calculated with the medical record review classification as gold standard. (Table S4).

The study was approved by the regional ethics review board at Karolinska Institutet.

### 2.5 | Statistical analysis

Participants were followed from MM diagnosis (baseline) until death, emigration or December 31, 2013, whichever came first. We used Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) of MM-specific mortality (primary outcome) and all-cause mortality (secondary outcome) among statin users, compared to non-users during the 6-month periods before (baseline) and after diagnosis. Multivariable models were adjusted for age at diagnosis (<60, 60-<70, 70-<80, 80-<90, 90+ years), sex, year of diagnosis, highest attained education (elementary school, high school, college/university) and comorbidity

### TABLE 1  Characteristics of nationwide cohort of patients with multiple myeloma (MM) 2007-2013 in Sweden by statin use before diagnosis

| No statin use before MM diagnosis | MM-specific death | Statin use before MM diagnosis | MM-specific death |
|----------------------------------|--------------------|--------------------------------|--------------------|
| All patients n = 3408 N (%) or median [range] | All patients n = 1122 N (%) or median [range] | All patients n = 907 N (%) or median [range] | All patients n = 274 n (%) or median [range] |
| Sex | | | |
| Female | 1555 (46) | 556 (50) | 342 (38) | 102 (37) |
| Male | 1853 (54) | 566 (50) | 565 (62) | 172 (63) |
| Age at MM diagnosis | Years | 70 [19-98] | 74 [32-97] | 74 [46-95] | 76 [47-95] |
| Education level | Elementary school | 1210 (36) | 469 (42) | 393 (43) | 143 (52) |
| College/University | 805 (24) | 200 (18) | 162 (18) | 42 (15) |
| Missing | 39 (1.1) | 19 (1.7) | 10 (1.1) | 5 (1.8) |
| Previous MGUS diagnosis<sup>a</sup> | | 180 (5.3) | 47 (4.2) | 50 (5.5) | 15 (5.5) |
| Other medications before MM diagnosis<sup>b</sup> | Beta blockers | 825 (24) | 291 (26) | 535 (59) | 168 (61) |
| Diuretics | 725 (21) | 287 (26) | 353 (39) | 113 (41) |
| ACE inhibitors | 848 (25) | 281 (25) | 543 (60) | 147 (54) |
| Calcium blockers | 518 (15) | 170 (15) | 320 (35) | 75 (27) |
| Anticoagulants | 783 (23) | 297 (26) | 622 (69) | 203 (74) |
| Diabetes medications | 184 (5.4) | 86 (7.7) | 214 (24) | 63 (23) |
| PPI | 680 (20) | 251 (22) | 254 (28) | 79 (29) |
| SSRI | 230 (6.8) | 92 (8.2) | 85 (9.4) | 28 (10) |
| No. of outpatient doctor visits before MM diagnosis | During a 3-year period | 4.00 [0-480] | 4.00 [0-480] | 6.00 [0-339] | 6.00 [0-70] |
| Length of Follow-up, years | 1.96 [0.0-6.99] | 1.53 [0.0-6.77] | 1.68 [0.0-6.92] | 1.31 [0.0-6.63] |
| Treatment with Thalidomide and/or Lenalidomide at any time during follow-up | 1337 (39.2) | 524 (39.2) | 360 (39.7) | 128 (35.6) |

Note: Categorical variables presented as counts and percent, continuous variables as median [range].

Abbreviations: ACE, Angiotensin-Converting Enzyme; MM, multiple myeloma; MGUS, Monoclonal gammopathy of undetermined significance; PPI, Proton pump inhibitors; SSRI, Selective Serotonin Reuptake Inhibitors.

<sup>a</sup>Diagnosis of MGUS during the period from five years to 6 months before diagnosis of MM.

<sup>b</sup>Numbers may add to >100% because patients can contribute to several categories when using several types of medications concomitantly.
measured as ATC groups of concomitant medications used for diabetes and for ischemic heart, peripheral vascular and cerebrovascular disease. The timescale was time since diagnosis; of note, when modeling post-diagnosis statin exposure, we applied a one-year delayed entry to account for the left truncation introduced by the 6-month exposure period and subsequent exposure lag. Grambsch-Therneau tests based on Schoenfeld residuals from the Cox models confirmed the validity of the proportional hazards assumption.

We utilized Kaplan-Meier survival curves to visualize survival differences across patient groups. For comparison to those covariate-unadjusted graphs, we also obtained adjusted survival curves after fitting a flexible parametric survival model (adjusted for the same covariates as the fully adjusted Cox regression model described above).24

In the nested case-control analysis, conditional logistic regression was used, conditioned on the matched sets, to estimate HRs and 95% CIs. Only patients surviving more than 1 year were included in these models, for consistency with the exposure definition. To assess dose intensity and cumulative duration, a trend test was applied by assuming a linear association between these variables and the outcomes in the regression models. We also performed sex-stratified analyses and used a likelihood ratio test to formally check for possible effect modification by sex.

### 2.6 | Sensitivity analyses

To assess a possible “healthy user bias,” ie, whether patients with more frequent doctors’ visits were also prescribed more statins and/or diagnosed and treated earlier for MM, we fitted additional regression models adjusted for use of proton pump inhibitors (PPIs) and selective serotonin reuptake inhibitors (SSRIs), two frequently prescribed medications for common symptoms, and number of doctor visits in the three-year period before diagnosis of MM. A Swedish study has shown improved survival for MM patients with an earlier MGUS diagnosis.25 Thus, to assess possible different associations of MM survival with statins by known MGUS status, we performed separate analyses for patients with or without known MGUS 5 years to 6 months before MM diagnosis. To investigate possible reverse causation from

| TABLE 2 | Hazard ratios (HR) and 95% confidence intervals (CI) for the association of statin use and multiple myeloma (MM)-specific and all-cause mortality in Sweden 2007-2013 |
| --- | --- | --- |
| **Cohort analysis** | **MM-specific mortality** | **All-cause mortality** |
|  | N subjects /n-deaths | HR (95% CI) | N subjects /n-deaths | HR (95% CI) |
| Statin use vs no use before diagnosis<sup>b</sup> | 4315/1396 | 1.00 (0.88, 1.15) | 4315/1913 | 1.13 (1.01, 1.26) |
| Crude |  | 0.88 (0.77, 1.00) |  | 0.96 (0.86, 1.07) |
| Adjustede |  | 0.83 (0.71, 0.96) |  | 0.85 (0.75, 0.97) |
| Adjustedg |  | 0.82 (0.71, 0.96) |  | 0.85 (0.75, 0.96) |
| Statin use vs no use after diagnosis<sup>b</sup> | 2955c/855 | 0.89 (0.74, 1.06) | 2955c/1123 | 1.03 (0.89, 1.19) |
| Crude |  | 0.77 (0.64, 0.93) |  | 0.87 (0.74, 1.01) |
| Adjustede |  | 0.73 (0.60, 0.89) |  | 0.81 (0.69, 0.95) |
| Adjustedg |  | 0.74 (0.61, 0.90) |  | 0.81 (0.69, 0.95) |
| Nested Case-Control analysis | N subjects (cases/controls)<sup>e</sup> | 5130 (855/4275) | 5130 (855/4275) | 5130 (855/4275) |
| Statin use vs no use during follow-up |  | 0.90 (0.75, 1.09) |  | 0.90 (0.75, 1.09) |
| Crude |  | 0.79 (0.65, 0.95) |  | 0.79 (0.65, 0.95) |
| Adjustede |  | 0.65 (0.52, 0.80) |  | 0.65 (0.52, 0.80) |
| Adjustedg |  | 0.65 (0.53, 0.80) |  | 0.65 (0.53, 0.80) |

Abbreviations: CI, Confidence interval; HR, Hazard Ratio; MM, Multiple myeloma.
<br><sup>a</sup>HRs: In the cohort analyses the HRs were calculated with Cox regression. In the case-control analysis ORs were calculated and estimated to HRs given that incidence density sampling was used when sampling the controls.
<br><sup>b</sup>During the 6-month periods before and after diagnosis, respectively.
<br><sup>c</sup>Only patients still alive 365 days after diagnosis were included in the analysis of statin use after diagnosis (due to 6 months exposure classification and 6 months exposure lag).
<br><sup>d</sup>Numbers may add to more than 100% of the cohort because some individuals may be both a case and a control, and/or sampled more than once as a control, if resampled.
<br><sup>e</sup>Adjusted for age category, sex, year of diagnosis, highest education level.
<br><sup>f</sup>Adjusted for age category, sex, year of diagnosis, highest education level, medication (yes/no) for: diabetes, anticoagulants, diuretics, beta-blockers, ACE inhibitors, Calcium channel blockers during same period as statin exposure.
<br><sup>g</sup>Same as f plus use of PPI, SSRI during same period as statin exposure, and number of outpatient doctor visits during the three-year period before MM diagnosis.
end-of-life medication changes in the case-control analysis, we ran additional analyses restricted to statin dispensations up until 1 year before the index date (instead of 6 months).

All statistical tests were two-sided, and $P$ values <.05 were considered significant. Most data analyses were performed with SAS version 9.3 (SAS Institute, Inc., Cary, NC); survival analyses utilized Cox proportional hazards regression analysis.

**FIGURE 1**  
A. Multiple myeloma-specific survival, Kaplan–Meier (unadjusted analysis). B. Multiple myeloma-specific survival, multivariate-adjusted model*. C. All-cause survival, Kaplan–Meier (unadjusted analysis). D. All-cause survival, adjusted model*. For statin users during the period 6 months after diagnosis of MM compared to non users of statins, with 6 months lag. *Models adjusted for age category, sex, year of diagnosis, highest education level, medication (yes/no) for: diabetes, anticoagulants, diuretics, beta-blockers, ACE inhibitors, Calcium channel blockers [Color figure can be viewed at wileyonlinelibrary.com]
| Intensity | n (%) | MM-specific mortality | All-Cause mortality |
|-----------|-------|-----------------------|---------------------|
|           | n     | HR crude (CI)         | HR adjusted (CI)    |
|           | HR    | CI                    | HR adjusted CI      |

### Cohort analysis (N = 4315)

#### Statin before diagnosis

| No use   | 3408 (79) | 1122 | ref | ref | 1500 | ref | ref |
|----------|-----------|------|-----|-----|------|-----|-----|
| Low      | 274 (6.4) | 102  | 1.19 (0.97, 1.46) | 0.93 (0.75, 1.15) | 139 | 1.21 (1.01, 1.44) | 0.88 (0.73, 1.05) |
| Medium   | 605 (14.0)| 168  | 0.93 (0.79, 1.10) | 0.78 (0.65, 0.93) | 268 | 1.11 (0.97, 1.26) | 0.85 (0.73, 0.98) |
| High     | 28 (0.7)  | 4    | 0.59 (0.22, 1.57) | 0.65 (0.24, 1.75) | 6   | 0.65 (0.29, 1.44) | 0.67 (0.30, 1.50) |

*P* trend = 0.025, 0.097, 0.18, 0.51

#### Statin after diagnosis

| No use   | 2848 (81) | 865  | ref | ref | 1605 | ref | ref |
|----------|-----------|------|-----|-----|------|-----|-----|
| Low      | 198 (5.7) | 63   | 1.00 (0.74, 1.35) | 0.76 (0.56, 1.03) | 118 | 1.18 (0.93, 1.51) | 0.86 (0.67, 1.10) |
| Medium   | 424 (12)  | 110  | 0.87 (0.70, 1.07) | 0.73 (0.58, 0.92) | 184 | 0.98 (0.82, 1.18) | 0.80 (0.66, 0.97) |
| High     | 25 (0.7)  | 3    | 0.38 (0.10, 1.54) | 0.33 (0.08, 1.32) | 6   | 0.59 (0.22, 1.58) | 0.48 (0.18, 1.28) |

*P* trend = 0.09, 0.38

### Nested case-control analysis (N = 5130)

#### Statin during follow-up

| No use   | 4015 (78) | 681  | ref | ref |
|----------|-----------|------|-----|-----|
| Low      | 200 (3.9) | 40   | 1.23 (0.86, 1.75) | 0.80 (0.55, 1.18) |
| Medium   | 870 (17)  | 130  | 0.86 (0.70, 1.05) | 0.62 (0.50, 0.79) |
| High     | 45 (0.9)  | 4    | 0.48 (0.17, 1.33) | 0.35 (0.12, 1.91) |

*P* trend = 0.09, 0.38

**Abbreviations:** ACC/AHA, American College of Cardiology/American Heart Association; CI, Confidence interval; HR, Hazard ratio; MM, Multiple myeloma.

*a* Hazard ratio (HR) with 95% confidence interval computed in Cox regression models in the cohort analysis and estimated with Odds Ratios using logistic regression in the case-control analysis given that incidence-density sampling was used when sampling the controls.

*b* During the period 6 months before and after diagnosis respectively.

*c* Adjusted for age category, sex, year of diagnosis, highest education level, medication (yes/no) for: diabetes, anticoagulants, diuretics, beta-blockers, ACE inhibitors, Calcium channel blockers during same period as statin exposure.

*d* Only statin users included in the trend test.

*e* Number larger than total cohort because participants can be included both as case and control and/or more than once as a control, if resampled.
Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3 | RESULTS

3.1 | Patient characteristics

We identified 4315 patients with a first incident MM diagnosis in the Cancer Register. The median age at diagnosis was 71 years, and the patients were followed for a median of 1.9 years (range, 0-7 years) (Table 1). Among all patients, 230 (5.3%) had a prior diagnosis of MGUS. There were 1496 MM-specific deaths, representing 78% of all 1913 deaths during the follow-up period (Table S5). During follow-up, 1341 patients (31.1%) filled prescriptions for thalidomide and 718 (16.6%) for lenalidomide, and a total of 1697 (39.3%) used at least one or both of these medications during follow-up. In the cohort, 907 (21%) used statins during the 6-month period preceding MM diagnosis (eg, “at baseline”). Among these patients there were a total of 1699 statin dispensations, the vast majority being simvastatin (86%) (Table S1). Seventy-two percent of the baseline users (n = 651) also continued statin use during the 6-month period after diagnosis. During the 6-month period after diagnosis, 728 patients (17%) used statins (Table S6). Of these patients, only 77 (2%) were new users. Statin users were somewhat older (median 74 vs 70 years at the time of diagnosis), more often male (62 vs 54%) and less educated than non-users (highest education level elementary school for 43% vs 36%). Statin users also had a considerably higher use of concomitant medications and more frequent doctor visits in the three-year period before MM diagnosis (Table 1).

3.2 | Statin use within 6 months before/after MM diagnosis

Baseline (pre-diagnosis) use of statins was associated with a 17% reduction in MM-specific mortality (HR, 95% CI: 0.83, 0.71-0.96) and a 15% reduction in all-cause mortality (HR, 95% CI: 0.85, 0.75-0.97) after adjusting for potential confounders (Table 2). Additional adjustment for use of PPI, SSRI and number of doctor visits before diagnosis did not alter the results. Use of statins during the 6-month period after diagnosis was associated with a 27% reduction in MM-specific mortality (0.73, 0.60-0.89) and a 19% reduction in all-cause mortality (0.81, 0.69-0.95) (Table 2, Figure 1). In sex-stratified analyses statin use was significantly associated with a lower mortality in women (statin use after diagnosis; 0.57, 0.42-0.79) but not in men (0.87, 0.68-1.11). When assessed formally, no statistically significant interaction by sex was observed (P = .094) (Table S7). Similar results were obtained when patients with a previous MGUS diagnosis were excluded (Table S8).

3.3 | Statin use at any time during follow-up

The case-control analysis included 5130 individuals (855 cases with MM-specific mortality and 4275 controls) (Table 2). Patients using statins at least once during follow-up had 35% lower MM-specific mortality (HR 0.65; 95% CI 0.52-0.80) compared to non-users. The sensitivity analysis that sought to minimize possible reverse causality by restricting statin exposure to medications dispensed until 1 year (rather than 6 months) before the death of the case yielded similar results (Table S9).

3.4 | Statin dose intensity

A majority (67%) of baseline statin users received moderate intensity statin therapy as categorized by the ACC/AHA guidelines (vs 30% low intensity and 3% high intensity) (Table S2). The intensity category distribution was similar during the 6-month period after diagnosis. In the nested case-control analysis accounting for any statin exposure during follow-up, an even larger proportion used moderate intensity statin therapy (78% vs 18% low and 4% high intensity, respectively) (Table S2).

In analyses of statin treatment intensity and MM-specific mortality, the point estimates consistently suggested a dose-response, with lower mortality observed among higher-intensity users in all time windows assessed. However, a statistically significant trend was observed only for the unadjusted analysis of statin intensity at baseline (Table 3). No significant trends were seen for duration of statin use (Table S10).

3.5 | Cause of death validation

Of the 68 patients reviewed to validate the MM-specific mortality determination, medical record review confirmed 61. Only two had a cause of death clearly unrelated to their MM diagnosis; cause of death for the remaining five patients could not be evaluated due to lack of information in the medical records. The PPV in evaluable patients was thus (61 / (61 + 2)) = 97% (Table S11).

4 | DISCUSSION

In this population-based study including all incident cases of MM in Sweden from 2007-2013, we found a 27% reduction in MM-specific mortality associated with statin use during the 6-month period after diagnosis. Similar statistically significant reductions were seen both for statin use before diagnosis (baseline) and in the nested case-control analysis assessing any statin use during follow-up. Statin use was also associated with a statistically significantly reduced risk of all-cause mortality.

Our results are consistent with the American veterans’ study, which included mostly men and found a reduced MM-specific mortality of a similar magnitude for statin users (HR, 95% CI: 0.76, 0.67 to 0.86). Thus, our study extends these findings to both men and women, using a nationwide cohort ascertained from high-coverage population-based registers. Our results represent the era of the novel MM treatment agents, which were introduced in Sweden gradually during the beginning of the follow-up period and in which bortezomib, thalidomide or lenalidomide was included in first-line therapies for the
majority of patients from 2009 onwards. Although the Swedish Drug register provides no information on bortezomib use in these patients, the fact that approximately 40% of the patients in our study used thalidomide and/or lenalidomide shows that these patients were treated with novel agents, consistent with current clinical guidelines. Of interest, we found similar risk reductions for statin users of both sexes. Further, higher intensity statin users consistently had lower mortality in all exposure intervals, although few deaths occurred among high intensity users, and trend tests were not statistically significant after covariate adjustment.

Apart from the American veterans' study, statin use and MM prognosis has been investigated in a few other small studies (n = 9 to 146 MM patients) of relapsed and refractory MM; those showed high tolerance when combining statins with other therapies. Regarding statin use and risk of developing MM, two observational studies have also suggested a protective effect. In addition to the suggested general anti-cancer properties of statins, the biologic rationale for anti-MM effects of statins includes several possible immunomodulatory pathways, most notably the ability of statins to down-regulate NF-κB signaling, which is a therapeutic target of interest in MM. In vivo evidence that statins regulate mesenchymal stromal cell-induced T-cell suppression and B-lymphocyte survival also suggests a possible therapeutic role through interactions with the tumor microenvironment, that would render MM cells more susceptible to the host immune response. Moreover, in vitro studies showed that statins affect the same anti-osteoclast mechanisms as bisphosphonates, which are given to prevent osteolytic lesions in MM patients, further strengthening the plausibility for an improved MM prognosis with statin use.

An observational study to assess a potential association of common medications with cancer outcome is prone to several biases. It has been suggested that medication use at baseline (before cancer diagnosis) may be a less biased exposure period, a pharmaco-epidemiological equivalent to the intention-to-treat approach used in randomized controlled trials. Disadvantages of using this time window for statin exposure is that the degree of exposure misclassification most likely is higher, especially for longer-term outcomes like MM-specific mortality.

Assessing statin exposure after cancer diagnosis imposes other challenges. Ideally, a new user design should be used; however when studying rare malignancies like MM, numbers do not allow for that even in a nationwide study. An active comparator design would also be preferable, but there is no such drug available for statins. We have, however, carefully addressed other potential sources of bias. For example, in the analysis of statin use during the 6-month period after diagnosis, we used a 6-month period for exposure assessment before start of follow-up, to avoid immortal time bias. Also, to avoid reverse causation due to discontinuation of prophylactic medications towards the end-of-life period, we used a 6-month lag between statin exposure assessment and end of follow-up and tested the sensitivity of those findings by imposing a one-year lag in additional analyses.

Concern has been raised by other authors that statin users may be more health-aware, with more physician appointments and prophylactic medication use, resulting in the so-called "healthy user bias." However, in Sweden, prescribed medications are subsidized by universal health care, and in our study, statin users had a lower education level than non-users, possibly reflecting a higher burden of cardiovascular disease and higher cholesterol levels in lower socioeconomic groups. Further, additional adjustment for other frequently prescribed medications (PPIs and SSRIs) and number of outpatient doctor visits during the three-year period before MM diagnosis did not alter our results, neither for baseline nor post-diagnosis use, arguing against a pronounced healthy user bias.

The statin users in our cohort were older and had significantly more comorbidity than the non-users, as expected and consistent with other studies. We adjusted for potential confounding by comorbidity by assessing all concomitant prescribed drugs related to cardiovascular disease. Any remaining residual confounding caused by increased cardiovascular morbidity in the statin group would likely bias our results towards a less protective association with statins. The somewhat greater reduction noted for MM-specific mortality than for all-cause mortality speaks against cardiovascular effects of statins as the primary driver of the observed results.

The major strengths of our study are the national scale and high-quality linked registers, in particular, access to the Swedish drug register, which has complete information on all dispensed prescriptions from Swedish pharmacies. This enabled assessment of statin therapy intensity according to the ACC/AHA guidelines, for which the degree of cholesterol reduction in the different intensity categories is based on extensive evidence. Although not directly validated in cancer, it is reasonable to believe that the putative effect and dose-response relationship between statins and MM tumor cells could be correlated with the resulting level of cholesterol reduction in the blood, equivalent to what has been shown in cardiovascular disease. The use of defined daily doses (DDDs) to assess statin therapy intensity, a common approach in cancer research, is less precise; the different types of statins are not equipotent, statin treatment intensity has increased steadily over time, and the WHO has changed the statin DDDs twice (last 2009), making intensity comparisons between the different statins inconsistent over time. Further strengths of our study include the validation of MM-specific deaths in the Swedish Cause-of-death register, which, reassuringly, showed very high concordance with medical records.

Limitations of our study include lack of clinical data on MM baseline characteristics and treatment, as well as more detailed outcome measures, such as partial or complete response. Also, because of the limited follow-up period, the results describe short-term rather than long-term survival. Furthermore, despite the large size overall, the study had limited power for analyses of high- and low-intensity statin treatment and insufficient size to explore potential combined effects of intensity and duration of statin use.

In summary, our results concur with earlier observational, clinical and in vitro studies, adding further evidence that statin use may improve MM-specific survival. Additional investigations in randomized prospective settings are needed to establish whether statins should have a role as adjuvant treatment in MM. An improved MM survival with statin use would provide an option for adjuvant MM treatment at a low cost and with few side effects and would be an appealing addition to the current treatment options, especially in the presence of disparities.
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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