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Association between metformin use and transformation of monoclonal gammopathy of undetermined significance to multiple myeloma in U.S. veterans with diabetes mellitus: a population-based cohort study

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Abstract

Background—Multiple myeloma (MM) is one of the most common hematologic malignancies in the United States and is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS).

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Conflict of Interests

None.

Disclaimer

The conclusions and opinions presented herein are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health, the Agency for Healthcare Research and Quality, the American Cancer Society, or the Barnes-Jewish Hospital Foundation.

Contributors

S.-H. Chang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chang, Colditz, Carson

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Methods—A retrospective cohort of patients in the U.S. Veterans Health Administration database diagnosed with MGUS between 1, October, 1999 and 31, December, 2009 and diabetes mellitus prior to their MGUS diagnosis was identified and followed through 6, August, 2013. Patient-level clinical data were reviewed to verify diagnoses and to abstract data on size of baseline M-protein and type of MGUS, i.e., immunoglobulin (Ig) subtype or light-chain, when available. Metformin users were defined as patients that were prescribed metformin for at least 4 years, with no single break between consecutive prescriptions $\geq$ 6 months. Kaplan-Meier curves and Cox models were used to analyze the association between metformin use and the progression of MGUS to MM.

Findings—The analytic cohort consisted of 2,003 MGUS patients with a median follow-up time of 69 months. Within the analytic cohort, 463 metformin users (23.1%) were identified. Among the metformin users, 13 patients progressed to MM, while 74 patients progressed to MM among the non-metformin users. Metformin use was associated with a reduced risk of transformation to MM (Hazard ratio, HR: 0.47; 95% confidence interval, CI: 0.25–0.87).

Interpretation—For diabetics diagnosed with MGUS, metformin use for 4 years or longer was associated with a reduced risk of transformation of MGUS to MM. Prospective studies are required to determine whether this association is causal and whether these results can be extrapolated to non-diabetics.

1. INTRODUCTION

Multiple myeloma (MM) is one of the most common hematologic malignancies in the United States.¹ It is generally considered incurable, with a 5-year relative survival rate of 43% for patients diagnosed between 2003 and 2009.¹ In 2013 there were 22,350 new cases of MM (1.3% of all new cancer cases) and 10,715 deaths from this cancer. As of 2014, approximately 78,000 people were living with MM in the United States.¹

MM is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS),² although in many cases MGUS is undiagnosed until development of MM. MGUS is a pre-malignant condition of excessive plasma cell growth, with an annual risk of progression to MM or a related malignant condition of $\sim$ 1%.^{3, 4} The prevalence of MGUS in the population over age 50 is $\sim$ 3%.⁵ By definition, patients with MGUS are asymptomatic and no treatment has demonstrated efficacy in reducing the risk of transformation of MGUS to MM.

Risk factors for the development of MM include older age, male sex, black race, obesity, family history of MM, and MGUS.⁶ However, little is known about predictors of progression of MGUS to MM.⁷ Previous studies reported that serum M-protein concentration $\geq$ 1.5 g/dL, immunoglobulin (Ig) subtype other than IgG, an abnormal serum-free light-chain ratio,^{3, 8} and reduced levels of one or two non-involved Ig isotypes⁹ were risk factors for progression. In addition, IgM MGUS does not typically transform into MM, but instead is associated with the development of Waldenström macroglobulinemia and other B-cell non-Hodgkin lymphomas.^{9, 10} Currently, there are no studies providing clear evidence of any modifiable risk factors that might be associated with progression of MGUS to MM or any preventive treatment that might deter progression.

Previous research has suggested that insulin-like growth factor-1 and insulin may be important in MM pathogenesis.¹¹ This suggests that an agent, e.g., metformin, which decreases insulin production, increases insulin sensitivity, and induces weight-loss,¹² could alter the progression of MGUS to MM. Furthermore, metformin activates the AMPK signaling pathway, which induces cell cycle arrest and apoptosis of myeloma cells.¹³ Additional studies have also suggested that metformin use may be associated with better outcomes in patients diagnosed with a variety of malignancies.^{14, 15} Moreover, some studies reported that metformin users were at a lower risk of cancer incidence.^{16–20} In MM, Wu and colleagues found that metformin use is associated with improved outcomes.¹⁵ However, no study has examined the role of metformin in the development of MM.

The goal of this study is to investigate the association between metformin use and the progression of MGUS to MM, using a cohort of U.S. veterans diagnosed and treated within the Veterans Health Administration (VHA) system. This study is the first to examine this association.

2. METHODS

2.1 Study population and design

Patients with a diagnosis of MGUS between 1, October, 1999 and 31, December, 2009 were identified in all 21 regional VHA districts throughout the United States using International Classification of Diseases, 9th Revision (ICD-9) code 273.1 and assembled into a retrospective cohort. Unique patient identifiers were then used to obtain ICD-9 data on comorbidities and outpatient prescriptions. Patients with at least one ICD-9 code for diabetes mellitus (DM) (249.00–250.93, V4585, V5391, V6546) and one treatment for their DM (e.g., metformin, sulfonylurea, insulin, thiazolidinedione) prior to MGUS diagnosis were included. Institutional Review Boards at both the Washington University School of Medicine and the Saint Louis VHA Medical Center approved the study.

Additional data were obtained including sex, race, height, weight, and level of glycated hemoglobin (HgbA1c). Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. The Romano adaptation of the Charlson comorbidity index was calculated based on comorbid conditions present before MGUS diagnosis.²¹

2.2 Primary outcome measure

The time from MGUS diagnosis to MM diagnosis was the primary outcome. Two investigators (KKO and TST) reviewed patient-level clinical data to verify both MGUS and MM diagnoses based on the criteria defined by the International Myeloma Working Group²² and the actual date of each diagnosis. Additional data were also abstracted, including size of baseline M-protein, type of MGUS, i.e., immunoglobulin (Ig) subtype or light-chain, when available. Patients without date of death information were assumed to be alive at the time of the last death recorded within the cohort, 6, August, 2013. This assumption is supported by previous studies showing that >97% of death events are captured in VHA vital status files.^{23, 24}

2.3 Analytic cohort and covariates

Metformin users were defined as DM patients treated with metformin consistently over a 4-year period after their DM diagnosis and before MM development, death, or censorship, to allow sufficient time for metformin to demonstrate an effect, if any. Four-year users were defined as patients with no single gap of 6 months between consecutive prescriptions during the 4-year exposure period. In the VHA system, metformin prescriptions are typically dispensed every 3 months via mail, thus we allowed no more than 3 additional months beyond when a prescription would be expected to be exhausted. Sensitivity analyses were also performed, varying the observation window of metformin use from 2 to 6 years.

While the etiology of the progression of MGUS to MM remains unclear, we considered a wide range of possible confounders in our adjusted analysis. These include sex, MGUS type, race, BMI, and level of HgbA1c, as well as age, serum M-protein, comorbidities, and serum creatinine, all measured at or shortly before MGUS diagnosis. Sex, MGUS type, race, and BMI were considered because they are known risk factors of MM.^{6, 25} Serum creatinine was included as an indicator of renal dysfunction and was included along with comorbidities because they could alter the timing of MGUS or MM diagnoses, if not the incidence of the diseases. HgbA1c levels measured after MGUS diagnosis were averaged. Serum M-protein was categorized as <1.5 g/dL and 1.5 g/dL. Serum creatinine was categorized as <1.5 mg/dL and 1.5 mg/dL. Mean BMI was calculated based upon height and weight measurements before MGUS diagnosis.²⁶ BMI was categorized as underweight (<18.5 kg/m²), normal-weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥30 kg/m²). Race was categorized as white, black, or other. When categorical variables were used, an unknown category was used for individuals with missing data.

The final analytic cohort was formed by excluding the following patients: (i) patients with alternative diagnosis; (ii) patients with missing diagnosis date or diagnosed with MGUS prior to 1999; (iii) IgM and IgD MGUS patients, because IgM MGUS typically does not progress to MM,^{9, 10} and IgD MGUS is exceptionally rare; (iv) underweight patients, because disease-driven weight loss might urge them to seek care and result in an earlier MGUS/MM diagnosis, and because they were more likely to die or become lost to follow-up before progression; (v) patients diagnosed with MM <6 months after their MGUS diagnosis, as these patients were more likely to have had smoldering myeloma instead of MGUS; (vi) patients with missing data on HgbA1c; and (vii) patients who either died, developed MM, or were censored <4 years after diabetes diagnosis, because they were not given an equal amount of time for potential metformin exposure.²⁷ The number of years for this last exclusion criterion changed with the length of the observation window in sensitivity analyses.

2.4 Statistical analyses

Chi-square tests were performed to examine differences between categorical variables. Analysis of variance was conducted to test the difference in the means of continuous variables. The percentage of patients without MM incidence was plotted against time to construct the Kaplan-Meier graph. The log-rank statistic was used to compare the Kaplan-Meier curves between metformin users and non-metformin users. Cox proportional hazards

models were used in both univariate and multivariate analyses. The proportional hazards assumption was tested using time-dependent covariate methodology,²⁸ but no violation of this assumption was detected. An alpha significance level of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

2.5 Role of the Funding Sources

The funding agencies had no role in the study design, or in the collection, analysis, or interpretation of data, or in the writing of the report.

3. RESULTS

We identified 3,287 diabetics diagnosed with MGUS (via at least 2 ICD-9 codes for MGUS) between 1, October, 1999 and 31, December, 2009 in the VHA dataset (Figure 1). From chart review, we found that 595 patients (18%) had an alternative diagnosis (e.g., MM rather than MGUS), and among 269 patients who had at least one ICD-9 code for MM, 183 patients (68%) did not develop MM. We further excluded 166 patients whose MGUS diagnosis dates were missing or before the study period. We also excluded 335 IgM and one IgD MGUS patients. Three underweight patients were excluded, in addition to 7 patients diagnosed with MM <6 months after MGUS diagnosis. Furthermore, 46 patients without HgbA1c information were also excluded from the analysis. Last, 131 individuals who died, developed MM, or were lost to follow-up within 4 years after diabetes diagnosis were excluded. In total, 1,284 patients were deemed ineligible and were excluded in the analyses. The final analytic cohort included 2,003 patients.

Baseline characteristics of the analytic cohort are summarized in Table 1. Nearly 98% of the patients (1,961/2,003) were male. Approximately 23% of patients (463/2,003) were categorized as metformin users. These patients were younger than those who did not use metformin (mean age: 67.4 versus 69.8 years, $p<0.0001$). Moreover, metformin users had lower comorbidity scores (mean Charlson scores: 4.1 versus 5.5, $p<0.0001$) and consisted of more white patients (298/463, 64.4% versus 929/1,540, 60.3%) and fewer black patients (125/463, 27.0% versus 521/1,540, 33.8%) ($p<0.0001$), as well as more obese (258/463, 55.7% versus 736/1,540, 47.8%) and less overweight (145/463, 31.3% versus 548/1,540, 35.6%) individuals ($p=0.016$) than non-metformin users. Last, metformin users comprised a higher percentage of patients with low serum creatinine (<1.5 mg/dL) than non-metformin users (286/463, 61.8% versus 593/1,540, 38.5%, $p<0.0001$).

Figure 2 shows the Kaplan-Meier plots for the analytic cohort stratified by metformin use. Among the analytic cohort, 87/2,003 (4.3%) patients progressed to MM (Table 1) and 938/2,003 (46.8%) patients died before 6, August, 2013 (see Figure A1 in the Appendix for Kaplan-Meier plots with censoring marks). A significant decrease in MM incidence was noted among metformin users ($p=0.028$). The rate of progression at each time point is presented in Table A1 (see Appendix). The median time of progression to MM was 71 (interquartile range, IQR: 30) months for metformin users, and 47 (IQR: 46) months for non-metformin users. The median follow-up time was 73 (IQR: 45) months for metformin users and 67 (IQR: 48) months for non-metformin users.

Table 2 shows the results of univariate analysis, partially adjusted analyses, and fully adjusted analysis (adjusting for all covariates). Additionally adjusting for the level of HgbA1c in partially adjusted analysis B did not change the results of partially adjusted analysis A, in which age, gender, serum M-protein, MGUS type, and metformin use were controlled for, and the level of HgbA1c did not reach statistical significance (Table 2 and Table A2 in the Appendix). In fact, HgbA1c was not statistically significant in any of the analyses (also see other results in the Appendix, Table A3). The fully adjusted analysis demonstrated that metformin users were less likely to progress to MM (Hazard ratio, HR: 0.47; 95% confidence interval, CI: 0.25–0.87). As expected from previous studies, patients with serum M-protein concentration ≥ 1.5 g/dL at MGUS diagnosis (HR: 5.99; 95% CI: 3.21–11.16) or IgA MGUS (HR: 2.40; 95% CI: 1.45–3.96) had an increased risk of progression.

To understand how the change in the observation window affects our analysis and conclusion, we further explored metformin use over a period of 2–6 years after DM diagnosis. The hazard ratios for patients who used metformin were 0.76 (95% CI: 0.48–1.12) for 2 years, 0.63 (95% CI: 0.38–1.05) for 3 years, 0.50 (95% CI: 0.23–1.06) for 5 years, and 0.58 (95% CI: 0.24–1.40) for 6 years. These ratios indicate that metformin use over a period of time, in particular, at least 4 years, is protective in the transformation of MGUS to MM.

4. DISCUSSION

We observed that MGUS patients who used metformin for at least 4 years had a 53% lower risk of transformation of MGUS to MM than patients who did not, after removing IgM MGUS patients who are not at risk for developing MM and controlling for known risk factors for MGUS progression. To our knowledge, this is the first study to examine the association between metformin use and the transformation of MGUS to MM. The importance of this finding is that it provides the first evidence that a widely available, generally well-tolerated, and inexpensive medical intervention may alter the progression of MGUS to MM. This is similar to the finding that aspirin may reduce or delay the development of colon cancer in patients with Lynch syndrome, with aspirin now considered standard of care for those patients.²⁹ If our finding is confirmed by others, it may stimulate broader change in the detection and management of MGUS. MM is a unique malignancy since it is invariably associated with the pre-malignant condition MGUS, which typically precedes MM diagnosis by nearly a decade and in the vast majority of patients is detectable in the serum by protein electrophoresis or light chain assay.³⁰ Currently, MGUS is an incidental finding that warrants only regular follow-up. If early intervention alters the progression of MGUS to MM, then additional consideration might be given to population-based screening for MGUS to reduce the overall burden of MM in the population.

Our finding that metformin may deter the development of MM is supported by findings in other cancers. Using a cohort of diabetics in the United Kingdom, Currie et al. found that compared to other diabetes treatments metformin monotherapy carried the lowest risk of colon and pancreatic cancer.¹⁶ The protective effect of metformin against cancer (no specific site) was also found in over 300,000 diabetics in Scotland.¹⁷ In Asia, several studies

reported decreased cancer incidence among metformin users.^{18, 20} In contrast to those studies evaluating metformin and the risk of common solid tumors, this study evaluated exclusively patients known to be at high risk for the development of MM due to the pre-malignant condition MGUS. There is little previous evidence that metformin reduces the incidence of hematologic malignancies, though there is evidence that diabetics with acute lymphoblastic leukemia and MM who are treated with metformin have better outcomes than those treated with other medications.^{15, 31, 32}

The mechanism through which metformin might deter the progression of MGUS to MM cannot be assessed in this study, as we had no access to biological specimens. If the effect of metformin on circulating insulin levels is responsible, however, then one would expect a clear relationship between DM, HgbA1C, and MM incidence. While DM is associated with an increased overall risk of cancer incidence, a meta-analysis of ten studies reporting data on the association between DM and MM found a positive but not significant association (odds ratio: 1.22; 95% CI: 0.98–1.53).³³

Our findings on metformin use could be beneficial to populations at higher risk for MGUS and MM. These populations include populations characterized by older age, male sex, black race, obese BMI, or family history of MM.⁶ If this study motivates future clinical trials, which further confirm the protective effect of metformin on the transformation of MGUS to MM, a preventative strategy could be promoted to reduce MM incidence in these populations. This strategy could be regular screening for MGUS followed by metformin treatment for at least 4 years upon diagnosis.

Since the outcome of interest was progression of MGUS to MM, we excluded IgM MGUS patients who tend to develop Waldenström macroglobulinemia and other B-cell non-Hodgkin lymphomas, rather than MM.^{9, 10} Nonetheless, because all MGUS types represent a premalignant condition in cells of B-lymphocyte origin, it is conceivable that metformin would similarly reduce transformation of IgM MGUS to malignant conditions other than MM. Further study will be required to understand how metformin might influence the progression of IgM MGUS to a lymphoid malignancy.

Our study has several strengths that should be highlighted. First, the large number of patients in the VHA database allowed this research to have sufficient statistical power to examine associations between metformin use and the relatively uncommon outcome of MM in patients with MGUS. Second, instead of relying on the ICD-9 codes and the diagnosis dates appearing in the administrative database, we carefully verified MGUS and MM diagnoses and the dates of diagnoses by reviewing electronic medical records for each patient. Therefore, our study captures the time of transformation more precisely than other studies using only VHA administrative data. Third, with a review of patient level data we were able to differentiate MGUS patients by MGUS type, removing IgM MGUS patients, who tend to develop lymphoid malignancies other than MM, and IgD MGUS patients, who are exceptionally rare. We were then able to control for differences in the risk of MM progression for the remaining patients by IgG, IgA, or light-chain MGUS, and serum M-protein concentration. Last, to avoid potential biases,²⁷ we carefully assembled the analytic cohort and defined metformin use, followed by sensitivity analyses, in which the length of

the observation window of metformin use was varied. The frequency of metformin use over a period of time was chosen over the duration of metformin use to reduce potential bias arising from reverse causality, i.e., individuals who did not develop MM might live longer, increasing treatment duration. Metformin dose was not used due to the expected biases resulting from individual-level variables that drive metformin dosing decisions and the expected increase in dose needed over time.

This study also has limitations that should be noted. First, MGUS is an asymptomatic condition for which patients are not routinely screened and which can last for many years before MM diagnosis. Thus, determining an actual date of MGUS incidence is not feasible nor can it be controlled for in statistical models. In this study, we assumed that there was no systematic difference in the elapsed time between MGUS incidence and diagnosis between metformin users and non-users. In fact, the lower mean comorbidity score and the higher percentage of patients with lower serum creatinine level (<1.5 mg/dL) observed in the metformin users would likely result in less frequent medical provider visits, potentially delaying the MGUS diagnosis. Such a delay would then tend to shorten the time between MGUS diagnosis and progression to MM among metformin users, biasing against a significant finding in our study. Had this comorbidity-dependent delay been controlled for, a lower hazard ratio for metformin users would have been observed. Second, although the large VHA database allowed us to observe a statistically significant association between metformin use and MM development, the associations in the sensitivity analyses were not statistically significant, although metformin use of at least 3 years ($p=0.074$) and 5 years ($p=0.070$) almost reached statistical significance. For shorter metformin exposure periods, this could be due to a threshold effect, where by 4 years of metformin exposure is required for clinical benefit. With longer exposure periods, and thus smaller numbers of exposed patients (the numbers of metformin users dropped from 463 for the 4 years criterion to 325 for the 5 years criterion and 246 for the 6 years criterion), even a large dataset like the VHA does not have sufficient statistical power to demonstrate a significant association given the low rate of transition of MGUS to MM. Third, although we designed our study to minimize potential biases, some sources of bias could remain. For example, bias arising from different distributions of follow-up time among metformin users and non-users²⁷ could have been controlled if the cohort size were sufficiently large such that it allowed us to select the metformin and non-metformin users with similar distributions of follow-up time. In fact, in our analytic cohort, the difference in median follow-up time between metformin patient group (73 months) and non-metformin patient group (67 months) was only 0.5 years. Therefore, the bias should be relatively small. Future studies using a large dataset could consider conducting a nested case-control study adjusting for all possible confounders if a large difference in the follow-up time between the two groups is observed. Moreover, bias resulting from metformin being a first-line therapy²⁷ cannot be completely eliminated if the severity of DM is associated with MM incidence. Nonetheless, our analysis did control for patients' age at MGUS diagnosis and duration between DM diagnosis and MGUS diagnosis, which might mitigate the bias. Furthermore, metformin was a first-line therapy for only 23% (461/2,003) of our MGUS patients with DM. Fourth, we did not consider how insulin or insulin secretagogues (i.e., sulfonylureas) may influence transition to MM independent of metformin. This was an operational decision based on the fact that many patients in this

observational study received numerous sequential single agent or combination treatments over time, complicating these analyses. However, if insulin or sulfonylurea increases MM risk, as reported in other types of cancer, we may have found a smaller reduction in MM incidence associated with metformin use. Fifth, our study cannot explore sex differences in the association, because the VHA population is overwhelmingly male. Last, we note that the VHA population is different from the general population of the United States, in that the patients served by the VHA are frequently from lower socioeconomic strata, older, and more likely to be unemployed than the general population.^{34–36} However, it is likely that our findings can be extrapolated to other populations with similar characteristics.

5. CONCLUSION

Our results provide evidence that metformin treatment for at least 4 years reduces the risk of progression of MGUS to MM in diabetics. Prospective studies will be needed to confirm this finding and determine if the lower risk of progression found in this study is less prominent in non-diabetics without elevated levels of insulin.

6. RESEARCH in CONTEXT

6.1 Systematic Review

We performed a systematic review as part of the planning for this study. We searched MEDLINE and used the following search terms: metformin, (multiple) myeloma, monoclonal gammopathy of undetermined significance, and MGUS. We restricted our searches by using the following exclusion criteria: animal studies; languages other than English; no metformin intervention; lack of outcomes of interest (MM incidence or progression); and not population of interest (adults age >18 years). We found studies investigating how metformin is associated with survival outcomes of MM, but did not find any existing evidence suggesting the association of metformin treatment with the risk of progression of MGUS to MM.

6.2 Interpretation

Currently, there are no strategies to prevent progression to MM in MGUS patients. Our study provides evidence that metformin use for at least 4 years reduces the risk of progression of MGUS to MM in patients diagnosed with MGUS.

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APPENDIX

Figure A1.

Kaplan-Meier curves (with censoring marks) for metformin users ($n = 463$) and non-metformin users ($n = 1,540$) from the analytic cohort of U.S. veterans with diabetes mellitus diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Table A1

Rate of progression to MM in metformin patient group and non-metformin patient group among U.S. veterans with DM diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Non-metformin patient group				Metformin patient group			
Time from MGUS diagnosis to MM diagnosis (months)	Number at risk	Number who progressed to MM	Fraction progressing to MM	Time from MGUS diagnosis to MM diagnosis (months)	Number at risk	Number who progressed to MM	Fraction progressing to MM
7	1,525	2	0.0013	14	460	1	0.0022
8	1,522	1	0.0020	21	450	1	0.0044
9	1,520	1	0.0026	38	426	1	0.0067
11	1,510	3	0.0046	52	369	1	0.0094
12	1,502	1	0.0053	54	362	1	0.0122
15	1,481	1	0.0059	60	317	1	0.0153
18	1,461	2	0.0073	71	246	1	0.0193
19	1,453	1	0.0080	78	214	1	0.0239
20	1,447	1	0.0087	79	208	1	0.0286
22	1,442	1	0.0094	82	196	1	0.0335
23	1,436	1	0.0100	89	162	1	0.0395
24	1,424	1	0.0107	93	144	1	0.0461

Non-metformin patient group				Metformin patient group			
Time from MGUS diagnosis to MM diagnosis (months)	Number at risk	Number who progressed to MM	Fraction progressing to MM	Time from MGUS diagnosis to MM diagnosis (months)	Number at risk	Number who progressed to MM	Fraction progressing to MM
26	1,402	2	0.0122	137	32	1	0.0760
31	1,358	2	0.0136				
33	1,340	1	0.0143				
34	1,318	1	0.0151				
37	1,302	1	0.0158				
38	1,290	1	0.0166				
39	1,280	1	0.0174				
41	1,249	4	0.0205				
42	1,238	2	0.0221				
43	1,225	1	0.0229				
44	1,214	1	0.0237				
46	1,186	1	0.0245				
47	1,163	2	0.0262				
48	1,142	4	0.0296				
49	1,116	1	0.0305				
51	1,085	2	0.0323				
53	1,041	1	0.0332				
54	1,021	3	0.0361				
56	978	1	0.0370				
57	969	1	0.0380				
59	923	1	0.0391				
60	917	1	0.0401				
65	803	1	0.0413				
66	792	1	0.0425				
74	680	2	0.0453				
77	628	1	0.0469				
78	608	1	0.0484				
79	598	1	0.0500				
80	587	1	0.0516				
81	569	1	0.0533				
82	553	1	0.0550				
84	523	1	0.0568				
85	511	1	0.0587				
91	430	1	0.0609				
92	424	1	0.0631				
95	392	1	0.0655				
109	252	1	0.0692				

Non-metformin patient group				Metformin patient group			
Time from MGUS diagnosis to MM diagnosis (months)	Number at risk	Number who progressed to MM	Fraction progressing to MM	Time from MGUS diagnosis to MM diagnosis (months)	Number at risk	Number who progressed to MM	Fraction progressing to MM
111	227	1	0.0733				
113	218	1	0.0775				
118	185	1	0.0825				
133	102	1	0.0915				
134	90	1	0.1016				
140	68	1	0.1148				
169	13	1	0.1829				

Table A2

Univariate and multivariate adjusted hazard ratios for developing multiple myeloma among U.S. veterans with DM diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Parameter	Univariate			Partially adjusted model A			Partially adjusted model B		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.00	0.97–1.02	0.67	0.99	0.97–1.02	0.60	0.99	0.97–1.02	0.60
Gender									
Male		REF			REF			REF	
Female	1.44	0.46–4.57	0.53	1.46	0.46–4.69	0.53	1.46	0.46–4.69	0.53
Serum M-protein									
<1.5 g/dL		REF			REF			REF	
1.5 g/dL	5.60	3.04–10.33	<0.0001	6.05	3.28–11.16	<0.0001	6.05	3.27–11.17	<0.0001
MGUS type									
IgG		REF			REF			REF	
IgA	2.19	1.22–3.60	0.0020	2.37	1.44–3.90	<0.0001	2.37	1.44–3.90	<0.0001
Light-chain	2.78	0.68–11.42	0.16	2.62	0.63–10.99	0.19	2.62	0.62–10.99	0.19
HgbA1c	1.00	0.83–1.20	0.97	--	--	--	1.00	0.84–1.20	0.99
Metformin use									
Non-metformin user		REF			REF			REF	
Metformin user	0.52	0.29–0.94	0.030	0.49	0.27–0.89	0.019	0.49	0.27–0.89	0.019
BMI category									
Normal-weight		REF		--	--	--	--	--	--
Overweight	0.96	0.44–2.09	0.91	--	--	--	--	--	--
Obese	0.88	0.41–1.88	0.74	--	--	--	--	--	--
Race									
White		REF		--	--	--	--	--	--

Parameter	Univariate			Partially adjusted model A			Partially adjusted model B		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Black	1.24	0.81–1.92	0.33	--	--	--	--	--	--
Other race	0.84	0.28–2.69	0.77	--	--	--	--	--	--
Comorbidity score	0.98	0.91–1.05	0.51	--	--	--	--	--	--
Serum creatinine									
<1.5 mg/dL		REF		--	--	--	--	--	--
1.5 mg/dL	1.25	0.77–2.04	0.37	--	--	--	--	--	--
Months between DM and MGUS diagnoses	1.00	1.00–1.01	0.65	--	--	--	--	--	--

All models are presented in Table 2. Univariate analyses was conducted using age, gender, serum M-protein, MGUS type, metformin use, BMI category, race, HgbA1c, comorbidity, serum creatinine, and months between DM and MGUS diagnoses one by one as the covariate. Covariates in partially adjusted model A include age, gender, serum M-protein, MGUS type, and metformin use. Covariates in partially adjusted model B include HgbA1c in addition to all covariates in partially adjusted model A. DM: diabetes mellitus; MGUS: monoclonal gammopathy of undetermined significance; HR: hazard ratio; CI: confidence interval; Ig: immunoglobulin; BMI: body mass index; HgbA1c: glycated hemoglobin; REF: reference group; --: estimate not available.

Table A3

Fully adjusted hazard ratios for developing multiple myeloma among U.S. veterans with DM diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Parameter	Fully adjusted model A			Fully adjusted model B		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.99	0.97–1.02	0.50			
<70 years	--	--	--		REF	
70 years	--	--	--	0.85	0.54–1.34	0.49
Gender						
Male		REF			REF	
Female	1.55	0.48–5.02	0.47	1.51	0.46–4.91	0.49
Serum M-protein						
<1.5 g/dL		REF			REF	
1.5 g/dL	5.99	3.21–11.16	<0.0001	6.23	3.34–11.65	<0.0001
MGUS type						
IgG		REF			REF	
IgA	2.40	1.45–3.96	<0.0001	2.40	1.45–3.98	<0.0001
Light-chain	2.42	0.57–10.21	0.23	2.43	0.58–10.29	0.23
HgbA1c	0.99	0.82–1.18	0.90			
<6.5%	--	--	--		REF	
6.5%	--	--	--	1.21	0.77–1.92	0.41
Metformin use						
Non-metformin user		REF			REF	
Metformin user	0.47	0.25–0.87	0.016	0.48	0.26–0.88	0.018
BMI category						
Normal-weight		REF			REF	

Parameter	Fully adjusted model A			Fully adjusted model B		
	HR	95% CI	p-value	HR	95% CI	p-value
Overweight	1.01	0.46–2.23	0.98	1.01	0.46–2.23	0.98
Obese	0.94	0.43–2.05	0.88	0.94	0.43–2.04	0.88
Race						
White		REF			REF	
Black	1.07	0.68–1.68	0.79	1.07	0.68–1.68	0.78
Other race	0.87	0.27–2.81	0.81	0.86	0.27–2.78	0.80
Comorbidity score	0.94	0.87–1.02	0.14			
<mean	--	--	--		REF	
mean	--	--	--	0.77	0.47–1.24	0.28
Serum creatinine						
<1.5 mg/dL		REF			REF	
1.5 mg/dL	1.24	0.73–2.10	0.42	1.18	0.70–1.98	0.53
Months between DM and MGUS diagnoses	1.01	1.00–1.01	0.083	1.00	1.00–1.01	0.18

Fully adjusted model A is presented in Table 2. DM: diabetes mellitus; MGUS: monoclonal gammopathy of undetermined significance; HR: hazard ratio; CI: confidence interval; Ig: immunoglobulin; BMI: body mass index; HgbA1c: glycated hemoglobin; REF: reference group; --: estimate not available.

Figure 1. Consort diagram

DM: diabetes mellitus; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; Ig: immunoglobulin; BMI: body mass index; HgbA1c: glycated hemoglobin

Figure 2. Kaplan-Meier curves of metformin users (n = 463) and non-metformin users (n = 1,540) from the analytic cohort of U.S. veterans with diabetes mellitus diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Table 1

Demographic and clinical characteristics stratified by metformin use (yes/no) among U.S. veterans with DM diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Demographic clinical characteristics	Metformin use			p-value
	Overall N=2,003	Yes (n=463)	No (n=1,540)	
Age (years)	69.2 (9.5)	67.4 (9.5)	69.8 (9.5)	<0.0001 [†]
Male	1,961/2,003 (97.9%)	455/463 (98.3%)	1,506/1,540 (97.8%)	0.53 [*]
Race				<0.0001 [*]
White	1,227/2,003 (61.3%)	298/463 (64.4%)	929/1,540 (60.3%)	
Black	646/2,003 (32.3)	125/463 (27.0%)	521/1,540 (33.8%)	
Other	92/2,003 (4.6%)	34/463 (7.3%)	58/1,540 (3.8%)	
Unknown	38/2,003 (1.9%)	6/463 (1.3%)	32/1,540 (2.1%)	
Average BMI				0.016 [*]
18.5–24.9 kg/m ²	209/2,003 (10.4%)	43/463 (9.3%)	166/1,540 (10.8%)	
25–29.9 kg/m ²	693/2,003 (34.6)	145/463 (31.3%)	548/1,540 (35.6%)	
30 kg/m ²	994/2,003 (49.6%)	258/463 (55.7%)	736/1,540 (47.8%)	
Unknown	107/2,003 (5.3%)	17/463 (3.7%)	90/1,540 (5.8%)	
Co-morbidities (mean Charlson score)	5.2 (3.2)	4.1 (2.9)	5.5 (3.3)	<0.0001 [†]
Serum creatinine				<0.0001 [*]
<1.5 mg/dL	879/2,003 (43.9%)	286/463 (61.8%)	593/1,540 (38.5%)	
1.5 mg/dL	676/2,003 (33.8%)	61/463 (13.2%)	615/1,540 (39.9%)	
Unknown	448/2,003 (22.4%)	116/463 (25.1%)	332/1,540 (21.6%)	
Serum M-protein concentration (%)				0.54 [*]
<1.5 g/dL	1,008/2,003 (50.3%)	240/463 (51.8%)	840/1,540 (54.6%)	
1.5 g/dL	81/2,003 (4.0%)	18/463 (3.9%)	63/1,540 (4.1%)	
Unknown	842/2,003 (42.0%)	205/463 (44.3%)	637/1,540 (41.4%)	
MGUS type				0.51 [*]
IgA	289/2,003 (14.4%)	71/463 (15.3%)	218/1,540 (14.2%)	
IgG	1635/2,003 (81.6%)	377/463 (81.4%)	1258/1,540 (81.7%)	
Light-chain	26/2,003 (1.3%)	3/463 (0.7%)	23/1,540 (1.5%)	
Unknown	53/2,003 (2.7%)	12/463 (2.6%)	41/1,540 (2.7%)	
Average HgbA1c (%)	7.1 (1.2)	7.1 (1.0)	7.1 (1.2)	0.69 [†]
Incidence of MM	87/2,003 (4.3%)	13/463 (2.8%)	74/1,540 (4.8%)	<0.0001 [*]

DM: diabetes mellitus; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; Ig: immunoglobulin; BMI: body mass index; HgbA1c: glycated hemoglobin;

^{*} Chi-square test;

[†] ANOVA test; Age, comorbidities, and average HgbA1c are presented in means and standard deviations in parentheses.

Table 2

Univariate and multivariate adjusted hazard ratios for developing multiple myeloma among U.S. veterans with DM diagnosed with MGUS between 1, October, 1999 and 31, December, 2009

Parameter	Univariate				Partially adjusted model A				Partially adjusted model B				Fully adjusted model			
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR
Age	1.00	0.97–1.02	0.67	0.99	0.97–1.02	0.60	0.99	0.97–1.02	0.60	0.99	0.97–1.02	0.50	0.99	0.97–1.02	0.50	0.99
Gender																
Male		REF			REF			REF			REF			REF		
Female	1.44	0.46–4.57	0.53	1.46	0.46–4.69	0.53	1.46	0.46–4.69	0.53	1.46	0.46–4.69	0.53	1.55	0.48–5.02	0.47	1.55
Serum M-protein																
<1.5 g/dL		REF			REF			REF			REF			REF		
1–5 g/dL	5.60	3.04–10.33	<0.0001	6.05	3.28–11.16	<0.0001	6.05	3.27–11.17	<0.0001	5.99	3.21–11.16	<0.0001	5.99	3.21–11.16	<0.0001	5.99
MGUS type																
IgG		REF			REF			REF			REF			REF		
IgA	2.19	1.22–3.60	0.0020	2.37	1.44–3.90	<0.0001	2.37	1.44–3.90	<0.0001	2.40	1.45–3.96	<0.0001	2.40	1.45–3.96	<0.0001	2.40
Light-chain	2.78	0.68–11.42	0.16	2.62	0.63–10.99	0.19	2.62	0.62–10.99	0.19	2.42	0.57–10.21	0.23	2.42	0.57–10.21	0.23	2.42
HgbA1c	1.00	0.83–1.20	0.97	--	--	--	1.00	0.84–1.20	0.99	0.99	0.82–1.18	0.90	0.99	0.82–1.18	0.90	0.99
Metformin use																
Non-metformin user		REF			REF			REF			REF			REF		
Metformin user	0.52	0.29–0.94	0.030	0.49	0.27–0.89	0.019	0.49	0.27–0.89	0.019	0.47	0.25–0.87	0.016	0.47	0.25–0.87	0.016	0.47
BMI category																
Normal-weight		REF		--	--	--	--	--	--	--	--	--	--	REF	--	--
Overweight	0.96	0.44–2.09	0.91	--	--	--	--	--	--	--	--	--	1.01	0.46–2.23	0.98	1.01
Obese	0.88	0.41–1.88	0.74	--	--	--	--	--	--	--	--	--	0.94	0.43–2.05	0.88	0.94
Race																
White		REF		--	--	--	--	--	--	--	--	--	--	REF	--	--
Black	1.24	0.81–1.92	0.33	--	--	--	--	--	--	--	--	--	1.07	0.68–1.68	0.79	1.07
Other race	0.84	0.28–2.69	0.77	--	--	--	--	--	--	--	--	--	0.87	0.27–2.81	0.81	0.87
Comorbidity score	0.98	0.91–1.05	0.51	--	--	--	--	--	--	--	--	--	0.94	0.87–1.02	0.14	0.94
Serum creatinine																
<1.5 mg/dL		REF		--	--	--	--	--	--	--	--	--	--	REF	--	--

Parameter	Univariate			Partially adjusted model A			Partially adjusted model B			Fully adjusted model		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
1.5 mg/dL	1.25	0.77–2.04	0.37	--	--	--	--	--	--	1.24	0.73–2.10	0.42
Months between DM and MGUS diagnoses	1.00	1.00–1.01	0.65	--	--	--	--	--	--	1.01	1.00–1.01	0.083

Univariate analyses was conducted using age, gender, serum M-protein, MGUS type, metformin use, BMI category, race, HgbA1c, comorbidity, serum creatinine, and months between DM and MGUS diagnoses one by one as the covariate. Covariates in partially adjusted model A include age, gender, serum M-protein, MGUS type, and metformin use. Covariates in partially adjusted model B include HgbA1c in addition to all covariates in partially adjusted model A. Covariates in fully adjusted model include all listed in the table. DM: diabetes mellitus; MGUS: monoclonal gammopathy of undetermined significance; HR: hazard ratio; CI: confidence interval; Ig: immunoglobulin; BMI: body mass index; HgbA1c: glycated hemoglobin; REF: reference group; --: estimate not available.