Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study

Sigurdur Y. Kristinsson,1 Ruth M. Pfeiffer,2 Magnus Björkholm,1 Lynn R. Goldin,2 Sam Schulman,1,3 Cecilia Blincre,4 Ulf-Henrik Mellqvist,4 Anders Wahlin,5 Ingemar Turesson,6 and Ola Landgren1,2,7

1Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; 2Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; 3Department of Medicine, McMaster University, Hamilton, ON; 4Department of Medicine, Section of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden; 5Cancer Centre, Section of Hematology, Umea University Hospital, Umea, Sweden; and 6Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Patients with multiple myeloma (MM) have an increased risk of venous thrombosis. Interestingly, excess risk of venous thromboembolism has been observed among patients with monoclonal gammopathy of undetermined significance (MGUS). Using population-based data from Sweden, we assessed the risks of venous and arterial thrombosis in 18 627 MM and 5326 MGUS patients diagnosed from 1958 to 2006, compared with 70 991 and 20 161 matched controls, respectively. At 1, 5, and 10 years after MM diagnosis, there was an increased risk of venous thrombosis: hazard ratios (95% confidence intervals) were 7.5 (6.4-8.9), 4.6 (4.1-5.1), and 4.1 (3.8-4.5), respectively. The corresponding results for arterial thrombosis were 1.9 (1.8-2.1), 1.5 (1.4-1.6), and 1.5 (1.4-1.5). At 1, 5, and 10 years after MGUS diagnosis, hazard ratios were 3.4 (2.5-4.6), 2.1 (1.7-2.5), and 2.1 (1.8-2.4) for venous thrombosis. The corresponding risks for arterial thrombosis were 1.7 (1.5-1.9), 1.3 (1.2-1.4), and 1.3 (1.3-1.4). IgG/IgA (but not IgM) MGUS patients had increased risks for venous and arterial thrombosis. Risks for thrombosis did not vary by M-protein concentration (>10.0 g/L or <10.0 g/L) at diagnosis. MGUS patients with (vs without) thrombosis had no excess risk of MM or Waldenström macroglobulinemia. Our findings are of relevance for future studies and for improvement of thrombosis prophylaxis strategies. (Blood. 2010;115(24):4991-4998)

Introduction

Patients with multiple myeloma (MM) have an increased risk of venous thrombosis.1 During the past decade, the introduction of the oral immunomodulatory drugs (IMiDs) thalidomide and lenalidomide has improved clinical outcome of patients diagnosed with MM.2,3 However, an important complication related to IMiD therapy is the well-known risk of venous thromboembolism.4-17 Most studies have observed the most pronounced risk during the first months after MM diagnosis and when combining IMiDs with high-dose corticosteroids or chemotherapy.8-17 The underlying mechanisms for the excess of thromboembolism are largely unknown.

The risk of venous thromboembolism has also been explored among patients diagnosed with the precursor condition monoclonal gammopathy of undetermined significance (MGUS), with some,18,19 but not all,20 studies observing an increased risk. In a large study, based on more than 4 million veterans in the United States, we identified 2374 MGUS cases, of whom 31 developed deep vein thrombosis (DVT; crude incidence, 3.1 per 1000 person-years).21 Compared with non-MGUS cases, this translated to a statistically significant 3-fold increased risk of DVT among MGUS patients.

Although data are limited, there have been a few case reports indicating that the use of IMiDs in MM patients might also be associated with an increased risk of developing arterial thrombosis.22-27 To our knowledge, no large study has been conducted to evaluate the risk of arterial thrombosis among MGUS and MM patients.


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centralized nationwide Swedish Cancer Registry, which has a very high completeness and diagnostic accuracy.\textsuperscript{29,30} Using the Swedish Cancer Registry, we identified all MM patients diagnosed between 1958 and 2006. We also used a nationwide MGUS cohort established from a national hospital network, including MGUS patients diagnosed in Sweden between 1958 and 2006.\textsuperscript{29} When available, information on MGUS immunoglobulin (Ig) isotype and concentration of the M-protein at diagnosis was collected. To minimize the influence of a potentially undetected lymphoproliferative malignancy, MGUS patients who within 6 months of diagnosis developed a lymphoproliferative malignancy were excluded from the analysis.

For each MM and MGUS patient, 4 population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All controls had to be alive and free of any preceding hematologic malignancy at the time of MM or MGUS diagnosis for the corresponding case.

The centralized Swedish Patient Registry captures information on individual patient-based discharge diagnoses and discharge listings from inpatient (since 1964) and outpatient care (since 2000), with a very high coverage.\textsuperscript{31} Information on occurrence and date of arterial (coronary artery disease and cerebrovascular disease) and venous (DVT and pulmonary embolism [PE]) thromboembolism was obtained using the seventh, eighth, ninth, and 10th revisions of the International Classification of Diseases. All conditions were analyzed both individually and grouped into the categories coronary artery disease, cerebrovascular disease, and venous thromboembolism. Through linkage with the Cause of Death Register and the Register of Total Population, we collected information on vital status until December 31, 2006. From the Swedish Medical Products Agency, we gathered information on the number of patients who were prescribed thalidomide and lenalidomide, during the study period.

Approval was obtained from the Karolinska Institutional Review Board for this study. Informed consent was waived because we had no contact with study subjects. An exemption from institutional review board review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

**Results**

A total of 18,627 MM patients with 70,991 matched controls, and 5,326 MGUS patients with 20,161 controls were included in the study. Demographic and clinical characteristics of MM and MGUS patients and controls are shown in Table 1. The median age at diagnosis of MM as well as of MGUS was 71 years with almost equal sex distribution. A total of 1756 patients received thalidomide in Sweden 2000 to 2005 and fewer than 100 before the year 2000. Lenalidomide was prescribed to 130 patients 2003 to 2005.

**Arterial and venous thrombosis in MM patients**

Compared with controls, MM patients had an HR of 7.5 (95% CI, 6.4-8.9), 4.6 (95% CI, 4.1-5.1), and 4.1 (95% CI, 3.8-4.5) for venous thrombosis based on 1, 5, and 10 years of follow-up, respectively, after MM diagnosis (Figure 1). The same pattern was observed when DVT and PE were analyzed separately, and the risks were highest during the first year of follow-up after diagnosis (Table 2). Risks for arterial thrombosis were significantly increased at 1, 5, and 10 years of follow-up, with HR 1.9 (95% CI, 1.8-2.1), 1.5 (95% CI, 1.4-1.6), and 1.5 (95% CI, 1.4-1.5), respectively (Figure 1). The same pattern was seen in the hazard plots in Figure 2. When analyzed separately, the risks for coronary artery disease and cerebrovascular events were also increased at 1, 5, and 10 years of follow-up (Table 2). MM patients had a significantly increased risk of any thrombosis (venous and arterial) at 1, 5, and 10 years of follow-up after diagnosis, with HR 2.6 (95% CI, 2.4-2.8), 1.9 (95% CI, 1.8-2.0), and 1.8 (95% CI, 1.7-1.9), respectively. Analyses stratified by sex resulted in similar risk estimates (Table 2). When we allowed the impact of case-control status to differ for the first year using a time-dependent variable, risk was significantly higher during the first year after diagnosis than subsequently for all outcomes studied in Table 2 ($P < .001$).

The HR for venous thrombosis and arterial thrombosis in MM patients diagnosed before compared with after the year 2000 were not significantly different (data not shown).

**Arterial and venous thrombosis in MGUS patients**

MGUS patients had an HR of 3.4 (95% CI, 2.5-4.6), 2.1 (95% CI, 1.7-1.5), and 2.1 (95% CI, 1.8-2.4) for venous thrombosis at 1, 5, and 10 years of follow-up, respectively (Figure 1). The risks of DVT and PE were also significantly increased for all follow-up periods (Table 3). Risks for arterial thrombosis were significantly increased, with HR 1.7 (95% CI, 1.5-1.9), 1.3 (95% CI, 1.2-1.4), and 1.3 (95% CI, 1.3-1.4) at 1, 5, and 10 years of follow-up after diagnosis, respectively (Figure 1). The same increased risks were seen in Figure 2. Risks for coronary artery disease and cerebrovascular events were increased for all follow-up periods (Table 3). MGUS patients had a significantly higher risk of any thrombosis than matched controls at 1, 5, and 10 years of follow-up after diagnosis, with HR 1.9 (95% CI, 1.7-2.1), 1.4 (95% CI, 1.3-1.5), and 1.4 (95% CI, 1.4-1.5). When we allowed the impact of case-control status to differ for the first year using a time-dependent variable, risk was significantly higher during the first year after diagnosis than subsequently for all outcomes reported in Table 3 ($P < .001$). In sensitivity analyses, excluding MGUS patients with thrombosis within the first 6 months after MGUS diagnosis, the observed risks remained significantly elevated. In addition, when restricted to MGUS patients diagnosed before age 40, risk was still significantly elevated (data not shown).
When we assessed risk by MGUS isotype (Table 4), patients with IgG/IgA MGUS had significantly increased risk of both venous and arterial thrombosis based on 1-year follow-up (HR 4.2; 95% CI, 2.6-6.8 and HR 1.6; 95% CI, 1.3-1.9, respectively) and 5-year follow-up after diagnosis (HR 2.1; 95% CI, 1.6-2.7 and HR 1.2; 95% CI, 1.1-1.4, respectively). Patients with IgM MGUS did not have an increased risk of venous or arterial thrombosis compared with controls (Table 4).

Risks for thrombosis did not vary by M-protein concentration (< 10.0 g/L or ≥ 10.0 g/L) at diagnosis (Table 5).

### MGUS, thrombosis, and subsequent MM

Ten years after MGUS diagnosis, there were 170 (6.2%) IgG/IgA patients who progressed to MM. The risk of progression to MM was not different in patients with venous or arterial thrombosis compared with those without (Table 6). A total of 28 (0.5%) patients progressed to Waldenström macroglobulinemia.

### Survival in relation to thrombosis in MM and MGUS

Survival in MM patients with versus without thrombosis was not statistically different at 5 (HR = 1.0; 95% CI, 0.3-3.5) or 10 years (HR = 0.8; 95% CI, 0.4-1.6). MGUS patients with thrombosis had inferior survival compared with MGUS patients without thrombosis at 5 (HR = 1.7; 95% CI, 1.3-2.2) and 10 years (HR = 1.6; 95% CI, 1.3-2.0).

### Discussion

In this large study, including more than 5000 MGUS patients, 18 000 MM patients, and their matched controls, we found that both MGUS and MM patients had an increased risk of venous as well as arterial thrombosis. Among MGUS patients, an excess risk of thrombosis was observed in patients with IgG/IgA MGUS, but not IgM. In contrast to a prior smaller study, we did not find thrombosis to predict for MM progression among patients diagnosed with MGUS. In accordance with other studies, thrombosis in MM patients had no effect on survival. However, thrombosis in MGUS patients was associated with an inferior survival. Our findings are important and provide novel clues for future studies designed to explore underlying mechanisms of myelomagenesis and thromboembolism. In addition, these results may impact the development of thrombosis prophylaxis strategies in MM and possibly MGUS patients.

In accordance with prior smaller studies as well as our recent study on veterans in United States, we found MGUS to be associated with an increased risk of DVT and PE. In the present study, we found a slightly higher risk of DVT during the first year and a stable increased risk thereafter. This pattern is quite consistent with the results from our previous study in which we found a constant excess risk of DVT over time. We found no difference in the risk of MM progression among MGUS patients with (vs without) a diagnosis of venous thrombosis, which is in contrast to the study by Sallah et al. Interestingly, we found that patients with IgM MGUS did not have an increased risk of thrombosis, whereas patients with IgG/IgA MGUS had a 4-fold increased risk of venous thrombosis. Although the exact mechanisms remain unclear, this is consistent with previous studies on patients with Waldenström macroglobulinemia treated with IMiDs, where no increased risk of venous thrombosis was observed.

Thus, our study and these prior observations suggest that there might be a biologic difference between IgG/IgA and IgM MGUS with regard to risk of thromboembolism. In contrast to the study by
Sallah et al., we found no association between concentration of M-protein and risk of thrombosis.

In accordance with the literature, we found MM patients to have a significantly increased risk of venous thromboembolism, with the highest risk during the first year after diagnosis. The reason for the observed increased risk of venous thrombosis in MM is not completely understood. Factors such as immobilization, surgery, infections, indwelling central venous catheters, use of erythropoietin, and acquired and inherited hypercoagulable state are known risk factors for venous thrombosis and have probably contributed to the excess risk. However, because the highest risk of venous thrombosis was observed during the first year after diagnosis, it seems reasonable that the hypercoagulable state, at least in part, also reflects accelerated neoplastic

**Figure 1. Cumulative risk of arterial and venous thrombosis in patients with MM and MGUS compared with matched controls.**

**Table 2. HRs and 95% CIs for selected arterial and venous thrombosis among 18 627 MM patients versus 70 991 matched controls**

<table>
<thead>
<tr>
<th>Category</th>
<th>1-year follow-up</th>
<th>5-year follow-up</th>
<th>10-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MM patients</td>
<td>Controls</td>
<td>HR* (95% CI)</td>
</tr>
<tr>
<td>Thrombosis by location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>252</td>
<td>146</td>
<td>8.0 (6.5-9.9)</td>
</tr>
<tr>
<td>PE</td>
<td>152</td>
<td>97</td>
<td>7.3 (5.6-9.4)</td>
</tr>
<tr>
<td>Coronary artery disease†</td>
<td>537</td>
<td>1137</td>
<td>2.2 (2.0-2.5)</td>
</tr>
<tr>
<td>Cerebrovascular‡</td>
<td>203</td>
<td>655</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td>Arterial thrombosis§</td>
<td>712</td>
<td>1699</td>
<td>1.9 (1.8-2.1)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>384</td>
<td>227</td>
<td>7.5 (6.4-8.9)</td>
</tr>
<tr>
<td>Any thrombosis (combined)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1065</td>
<td>1892</td>
<td>2.6 (2.4-2.8)</td>
</tr>
<tr>
<td>Males</td>
<td>612</td>
<td>1163</td>
<td>2.5 (2.2-2.7)</td>
</tr>
<tr>
<td>Females</td>
<td>453</td>
<td>729</td>
<td>2.8 (2.5-3.2)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and calendar period at diagnosis.
†Angina pectoris, unstable angina, and myocardial infarction.
‡Cerebral infarction, transient ischemic attack, and cerebral hemorrhage.
§Angina pectoris, unstable angina, myocardial infarction, transient ischemic attack, and cerebral infarction.
||DVT and PE.
activity, high tumor burden, and perhaps active MM therapy. Indeed, studies focusing on IMiDs and risk of venous thrombosis in MM have reported the cumulative incidence to vary between approximately 2% and 75%, with the greatest risk in previously untreated patients receiving combination therapy. The fact that we observed no increase in risk of thrombosis in the period after 2000 (compared to before) is probably explained by the fact that very few MM patients in Sweden have received treatment with IMiDs, as first-line therapy during the study period as, in accordance with national guidelines, younger patients were treated with the VAD regimen until the year 2005, when cyclophosphamide and dexamethasone became standard.

Table 3. HRs and 95% CIs for selected arterial and venous thromboses among 5326 MGUS patients versus 20 161 matched controls

<table>
<thead>
<tr>
<th>Category</th>
<th>1-year follow-up</th>
<th>5-year follow-up</th>
<th>10-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS Controls</td>
<td>HR* (95% CI)</td>
<td>MGUS patients</td>
<td>HR* (95% CI)</td>
</tr>
<tr>
<td>DVT</td>
<td>51</td>
<td>52</td>
<td>3.7 (2.5-5.5)</td>
</tr>
<tr>
<td>PE</td>
<td>34</td>
<td>36</td>
<td>3.6 (2.3-5.8)</td>
</tr>
<tr>
<td>Coronary artery disease†</td>
<td>232</td>
<td>490</td>
<td>2.0 (1.7-2.4)</td>
</tr>
<tr>
<td>Cerebrovascular‡</td>
<td>109</td>
<td>305</td>
<td>1.4 (1.0-1.7)</td>
</tr>
<tr>
<td>Type of thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thrombosis§</td>
<td>325</td>
<td>763</td>
<td>1.7 (1.5-1.9)</td>
</tr>
<tr>
<td>Venous thrombosis§</td>
<td>73</td>
<td>83</td>
<td>3.4 (2.5-4.6)</td>
</tr>
<tr>
<td>All patients</td>
<td>601</td>
<td>829</td>
<td>1.9 (1.7-2.1)</td>
</tr>
<tr>
<td>Males</td>
<td>339</td>
<td>528</td>
<td>1.9 (1.6-2.2)</td>
</tr>
<tr>
<td>Females</td>
<td>262</td>
<td>301</td>
<td>1.9 (1.6-2.4)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and calendar period at diagnosis.
†Angina pectoris, unstable angina, and myocardial infarction.
‡Cerebral infarction, transient ischemic attack, and cerebral hemorrhage.
§Angina pectoris, unstable ischemic attack, and cerebral infarction.
||DVT and PE.
Table 4. HRs and 95% CIs for selected arterial and venous thromboses among MGUS patients versus matched controls, stratified by MGUS isotype

<table>
<thead>
<tr>
<th>Type of thrombosis</th>
<th>1-year follow-up</th>
<th>5-year follow-up</th>
<th>1-year follow-up</th>
<th>5-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MGUS patients</td>
<td>Controls</td>
<td>HR* (95% CI)</td>
<td>MGUS patients</td>
</tr>
<tr>
<td>Arterial thrombosis†</td>
<td>139 (2724)</td>
<td>337 (10 348)</td>
<td>1.6 (1.3-1.9)</td>
<td>359 (530)</td>
</tr>
<tr>
<td>Venous thrombosis‡</td>
<td>35 (95% CI)</td>
<td>32 (10 348)</td>
<td>4.2 (2.6-6.8)</td>
<td>88 (530)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and calendar period.
†Arterial thrombosis includes angina pectoris, unstable angina, myocardial infarction, transient ischemic attack, and cerebral infarction.
‡DVT and PE.

Similarly, elderly patients in Sweden, not included in clinical trials, have been treated with the MPT regimen only for the last 3 to 4 years.41

Our findings of an increased risk of arterial thrombosis in both MM and MGUS are novel. More specifically, we found the risk of coronary artery disease and cerebrovascular disease to be elevated among MGUS and MM patients. In patients with MM, the risk of arterial thrombosis was significantly elevated throughout the study period and did not differ statistically significantly between the time period before and after the introduction of the IMiDs. However, further investigations with longer follow-up are needed.

For the first time, we show that thrombosis is a predictor of survival in MGUS patients diagnosed in a clinical setting. The same did not apply to MM patients, as in accordance with another study.33 In our previous study, we found life expectancy in MGUS patients to be decreased compared with the general population, and predictors of poor survival were high age at diagnosis and IgG or IgA isotype. Furthermore, the risk for death in ischemic heart disease was 30% higher than in matched controls.52 Thrombosis in MGUS is thus a new predictor of survival but not MM progression.

Our study adds substantially to the limited literature on thrombosis among patients with plasma cell dyscrasias. For the first time, we provide a quantitative measure of arterial and venous thrombosis risk among patients with MGUS and MM. We have speculated that the elevated risk of thrombosis among MGUS patients is less likely caused by accelerating neoplastic activity but is rather a result of ongoing clonal plasma cell activities, as has been suggested by other authors.39 Factor VIII and von Willebrand factor levels were found to be increased among MGUS cases in a recent study; and in good accordance with our clinical findings, the observed increase was similar to that of untreated MM patients.39

Our observations of an excess risk of arterial thromboembolism among MGUS and MM patients may influence clinical management and the development of improved prophylactic regimens. Furthermore, they are of importance for our understanding of the pathogenesis of thromboembolism in plasma cell dyscrasias.

Indeed, the observed excess risk of both arterial and venous thrombosis suggests that there might be some shared biologic features, most probably involving platelet activation. This is further supported by the indication that aspirin is an effective prophylactic agent in venous thrombosis in MM.17,43,44 In addition, some studies have found evidence of platelet aggregation43 and activation caused by thalidomide, which is abrogated by aspirin.45 Future investigations are needed to clarify underlying mechanisms of our observations.

Our study has several strengths, including its large size as well as the application of high-quality data from Sweden, with its stable population with access to standardized medical care during the entire study period. In our study, we used a register-based cohort design, which ensured a population-based setting and generalization of our findings. As reported previously,46 the MGUS patients in our study were diagnosed at hematology/oncology outpatient units. In accordance with clinical practice in Sweden, most MGUS patients typically underwent a bone marrow examination as part of the clinical workup. In a recent validation study, we have reported that ascertainment and diagnostic accuracy for lymphoproliferative disorders are very high (> 90%-95%) in Sweden.30 Limitations include the lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, and geography), and lack of detailed clinical data, including information on subtype of MM and underlying diseases. Because our data do not come from an MGUS screening study, some of the controls might have an undiagnosed MGUS, and also the observed excess risks among MGUS patients may partly reflect various underlying medical illnesses that lead to the medical workup and the detection of the M-protein. To minimize such influences, MGUS patients with a diagnosis of a lymphoproliferative malignancy within 6 months after MGUS diagnosis were excluded from our analyses. In addition, when excluding MGUS patients with a thrombosis within 6 months after MGUS diagnosis, the risks were still elevated. Another limitation is the potential inaccuracy and

Table 5. HRs and 95% CIs for selected arterial and venous thromboses among MGUS patients versus matched controls, stratified by M-protein concentration at diagnosis

<table>
<thead>
<tr>
<th>Type of thrombosis</th>
<th>Concentration of M-protein less than 10 g/L</th>
<th>Concentration of M-protein more than 10 g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year follow-up</td>
<td>5-year follow-up</td>
</tr>
<tr>
<td></td>
<td>MGUS patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Arterial thrombosis†</td>
<td>84 (1732)</td>
<td>219 (6585)</td>
</tr>
<tr>
<td>Venous thrombosis‡</td>
<td>16 (10 348)</td>
<td>18 (6585)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and calendar period.
†Arterial thrombosis includes angina pectoris, unstable angina, myocardial infarction, transient ischemic attack, and cerebral infarction.
‡DVT and PE.
lack of independent validation of thromboembolic diagnosis obtained from the centralized Patient Registry. However, because we compared MM/MGUS cases to matched controls, using data from the same registries, the ascertainment should be nondifferential and any bias should be toward a null association.

In conclusion, in a population-based clinical setting (compared with controls), we found patients with MM and IgG/IgA MGUS to have a significantly increased risk of both arterial and venous thrombosis. In contrast, IgM MGUS patients had no excess risk of thrombosis. MGUS patients with thrombosis had an inferior survival compared with those without. We did not find thromboembolism to be a predictor of MM progression among patients diagnosed with MGUS. Future studies are needed to clarify underlying mechanisms of our findings. Such efforts will be of relevance for physicians managing MGUS and MM patients and have potential implications for the development of better thrombosis prophylaxis strategies.

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Authorship

Contribution: S.Y.K., M.B., I.T., and O.L. designed the study, obtained data, and initiated this work; R.M.P. performed all statistical analyses; S.Y.K., R.M.P., and O.L. wrote the report; all the authors were involved in the interpretation of the results; read, gave comments, and approved the final version of the manuscript; had full access to the data in the study; and take responsibility for the accuracy of the data analysis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Sigurdur Y. Kristinsson, Department of Medicine, Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden; e-mail: sigurdur.kristinsson@karolinska.se.

References


Table 6. HRs and 95% CIs for MM development among IgG/IgA MGUS patients with thrombosis versus those without

<table>
<thead>
<tr>
<th>MM transformation</th>
<th>Venous thrombosis* (n = 144)</th>
<th>Venous thrombosis (n = 2580)</th>
<th>Arterial thrombosis* (n = 547)</th>
<th>Arterial thrombosis (n = 2177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>9</td>
<td>86</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>10 years</td>
<td>13</td>
<td>157</td>
<td>1.2 (0.7-2.1)</td>
<td>1.4 (0.8-2.4)</td>
</tr>
</tbody>
</table>

*DVT and PE.
†Adjusted for age, sex, and calendar period.
‡Angina pectoris, unstable angina, myocardial infarction, transient ischemic attack, and cerebral infarction.


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