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BRIEF REPORT

Bleeding risk from anticoagulant thromboprophylaxis in patients with multiple myeloma: a MarketScan analysis

Diego Adrianzen-Herrera[1] | Katherine Giorgio[2] | Rob F. Walker[2] | Andrew D. Sparks[3] | Mansour Gergi[1] | Neil A. Zakai[1,4] | Pamela L. Lutsey[2]

[1]Department of Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

[2]Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, Minnesota, USA

[3]Biomedical Statistics Research Core, University of Vermont, Burlington, Vermont, USA

[4]Department of Pathology & Laboratory Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

Correspondence
Diego A. Adrianzen-Herrera, Department of Medicine, Larner College of Medicine at the University of Vermont, 89 Beaumont Avenue, Given Building, Suite E-214, Burlington, VT 05405, USA.
Email: dadrianz@med.uvm.edu

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Abstract

Background: Multiple myeloma (MM) is associated with high risk of venous thromboembolism (VTE). Anticoagulant prophylaxis is frequently recommended but underutilized partly due to the absence of studies assessing bleeding risk.

Objectives: To determine the rate of severe (hospitalized) bleeding from thromboprophylaxis in patients treated for MM and identify clinical risk factors for bleeding in this population.

Methods: Using the MarketScan database, we analyzed 6656 patients treated for MM between 2013 and 2021. Concomitant thromboprophylaxis was defined using prescription claims. Hospitalized bleeding was identified through the Cunningham algorithm. Bleeding rates were compared by thromboprophylaxis status, and Cox regression identified risk factors for bleeding.

Results: Anticoagulant thromboprophylaxis was used in 6.6% (436) patients treated for MM. Patients on thromboprophylaxis had a higher rate of immunomodulatory-based therapy (63.8% vs 46.7%; $P < .01$) and lower rate of antiplatelet use (2.1% vs 4.7%; $P < .01$). Bleeding occurred in 1.4% of them during median follow-up of 1.3 years. Rate of severe bleeding was not different between those on prophylaxis (7.8 per 1000 person-years) and those not on prophylaxis (10.1 per 1000 person-years). No association was identified between thromboprophylaxis and bleeding. Factors associated with increased bleeding included age (hazard ratio [HR], 1.38 per 10 years increase in age), comorbidity index (HR, 1.18 per SD increase), history of bleeding (HR, 1.54), hypertension (HR, 1.87), and renal disease (HR, 1.56).

Conclusion: Risk of serious bleeding from thromboprophylaxis in patients treated for MM was low, and concomitant anticoagulant therapy did not result in increased bleeding risk. Clinical risk factors for bleeding included age, comorbidity index, bleeding history, hypertension, and renal disease.

KEYWORDS
anticoagulants, hemorrhage, multiple myeloma, risk factors, venous thromboembolism

Essentials

- After median follow-up of 1.3 years, 1.4% of patients on thromboprophylaxis had severe bleeding.
- Rate of severe bleeding in patients receiving thromboprophylaxis was 7.8 per 1000 person-years.
- Bleeding rates are similar between myeloma patients on and off anticoagulant thromboprophylaxis.
- Clinical factors including hypertension and renal disease increased bleeding risk.

1 | INTRODUCTION

Venous thromboembolism (VTE) is an important source of morbidity and mortality in patients with multiple myeloma (MM) [1]. The combination of patient- (age and immobility) [2] and disease-specific (hypercoagulability, plasma viscosity, and endothelial inflammation) [3] risk factors and prothrombotic therapies (high dose dexamethasone and immunomodulatory drugs [IMiDs]) [4] increases thrombosis risk in a population perceived to be at high risk for bleeding. In the current era of novel triplet and quadruplet combinations and improved survival in MM, VTE still occurs in over 10% of patients, particularly in the first 6 months of treatment, and is associated with inferior survival [5].

Consensus guidelines from 2008 and 2015 favored anticoagulant thromboprophylaxis over aspirin, except in low-risk patients with none or 1 single myeloma/individual VTE risk factor [6,7]. Large multicenter observational studies and meta-analyses documented the validity of this approach [8,9]. However, more recent data suggest that criteria in these guidelines underestimated VTE risk [10]. Modern risk scores recognize larger proportions of high-risk patients [11–13], and their implementation in the National Comprehensive Cancer Network recommendations has identified more MM patients benefiting from warfarin, low-molecular-weight heparin (LMWH), fondaparinux, or direct oral anticoagulant (DOAC) prophylaxis. In particular, ease of administration has created a growing interest in DOACs for thromboprophylaxis [14], with reports of their safety and efficacy for VTE prevention in MM [15,16]. As more high-risk patients are identified and more anticoagulant options are available, current expert statements favor anticoagulants to antiplatelet agents for thromboprophylaxis in MM patients at high risk of VTE [17,18].

Regrettably, real-world adherence to these recommendations is poor [19], partially accounting for unacceptably high VTE rates in MM [20]. Among barriers to widespread adoption of anticoagulant thromboprophylaxis is an excessive perceived risk of bleeding [21]. Pathogenic pathways in MM include impaired platelet aggregation [22], altered fibrin polymerization [3], and acquired von Willebrand factor autoantibodies [23], causing altered *in vitro* platelet aggregation and prolonged coagulation times [3,22]. Though these hemostatic abnormalities have limited clinical correlation [24], they affect bleeding risk estimation and could alter clinicians' behavior [22,23].

Research aimed at defining bleeding complications in MM is scarce, and the bleeding risk associated with anticoagulant thromboprophylaxis is not defined. Characteristics inherent to MM suggest higher bleeding risk [23], but that has not been reported in clinical studies and factors associated with bleeding in this context are poorly documented. We conducted a real-world analysis of a large community-based cohort of ambulatory MM patients to study the risk of bleeding from anticoagulant thromboprophylaxis. A better understanding of this risk can inform the use of preventive measures and reduce VTE rates in MM.

2 | METHODS

2.1 | Data source

The Merative MarketScan Commercial Claims and Encounters and Medicare supplemental databases comprise healthcare claims from insured subjects in the US through participating programs, including most private and public health insurance. Individual-level information is available on healthcare enrollment, inpatient and outpatient visits, and prescriptions from US employers, healthcare plans, and hospitals. Data are deidentified and compliant with the Health Insurance Portability and Accountability Act. The study was exempted by the University of Minnesota's Institutional Review Board.

2.2 | Study population

Enrollees aged 18 to 99 years diagnosed and treated for MM from January 1, 2013, to December 31, 2021, were identified. MM diagnosis was defined as at least 1 inpatient or 2 outpatient claims at least 7 days apart using International Classification of Diseases (ICD)-9 or ICD-10 codes (88% sensitivity and 86% positive predictive value [PPV]) [25]. Eligible patients started MM-specific therapy between 7 days before and 90 days after diagnosis date, identified from Healthcare Common Procedure Coding System codes or prescription records. At least 90 days of continuous enrollment before MM-specific therapy initiation was required to acquire comorbidity information. Patients with VTE, atrial fibrillation, or stroke at any time prior to initial MM-specific therapy and those with anticoagulant use during the 90-day run-in period were excluded. Relevant administrative codes utilized are shown in Supplementary Table S1.

2.3 | Exposure and outcome ascertainment

Anticoagulant thromboprophylaxis was defined as at least 1 outpatient pharmacy claim for warfarin, LMWH, or DOAC (apixaban, rivaroxaban, dabigatran, and edoxaban) within 30 days of index date

of MM-specific therapy using National Drug Code and prescription fill dates (94% sensitivity and 99% PPV for warfarin identification [26]; validity studies for DOACs and LMWH are lacking). Severe bleeding was defined as any bleeding event requiring hospitalization using the Cunningham algorithm [27], which has 89% to 99% PPV to identify bleeding (intracranial, gastrointestinal, and others) and is validated to study bleeding complications from anticoagulation [28]. Enrollees with severe bleeding at any time prior to initiating MM-specific therapy were excluded. Study design is shown in Supplementary Figure S1.

2.4 | Prespecified covariates

Comorbidities and frequent prescription medications including antiplatelet agents (except aspirin) were ascertained. Validated algorithms and ICD codes were used to identify history of nonsevere bleeding [27] and Charlson comorbidity index (CCI) [29]. IMiD-containing therapy was defined using outpatient pharmacy claims.

2.5 | Statistical analysis

Person-time at risk accumulated from end of prophylaxis assessment window (30 days after index date) until incident severe bleeding, death, or end of study follow-up (December 31, 2021). Incidence rates of severe bleeding were calculated, and the Kaplan–Meier method estimated unadjusted 1-year cumulative incidence. Cox proportional hazard models estimated the hazard ratios (HR) and 95% CIs for risk of bleeding associated with anticoagulant thromboprophylaxis and clinical risk factors, adjusted for age and biologic sex. The association with anticoagulant prophylaxis was further defined in a series of models adjusting for potential confounders, including a propensity score. Proportional hazards assumption was tested with an interaction term between exposure and time. Statistical significance was determined at $\alpha < .05$ without adjusting for multiple comparisons. Statistical analyses were performed with SAS, version 9.4 (SAS Institute).

3 | RESULTS AND DISCUSSION

We analyzed 6656 patients with incident MM who initiated cancer-directed therapy within 90 days of diagnosis. The study cohort flowchart is presented in Supplementary Figure S2. Mean age was 62.7 years (SD, 11.3), and 55.3% were female. Patients treated with IMiD-containing regimens accounted for 63.8% of the population. The frequency of individual myeloma therapies and prevalence of comorbidities and concomitant therapies for cardiovascular disease at the time of MM diagnosis are presented in Supplementary Table S2. The mean CCI was 4.4 (SD, 2.3), and there was a high burden of VTE-associated risk factors, including 63.7% patients with hypertension, 24.9% with diabetes, and 24.3% with chronic renal disease.

Although over half of the cohort had more than 1 VTE risk factor and would have been classified as high thrombotic risk by consensus guidelines [6,7], only 6.6% (436) received concurrent anticoagulant thromboprophylaxis with cancer-directed therapy, a utilization rate lower than that identified in the Medicare population [30]. Compared with those not receiving prophylaxis, patients treated with anticoagulants had lower burden of hypertension (56.4% vs 64.4%; $p = .001$), diabetes (20.9% vs 25.2%; $p = .04$), and renal disease (17.4% vs 24.8%; $p < .001$). They also had a higher rate of IMiD-containing therapy (83.9% vs 62.4%; $p < .001$) and lower rate of use of antiplatelet agents (2.1% vs 4.7%; $p = .01$). There were no differences in age and sex distribution, mean CCI, or precedent history of nonsevere bleeding within groups.

Among patients who received prophylaxis, the anticoagulant agent of choice was warfarin in 23.4% (102), LMWH in 38.8% (169), and DOACs in 37.8% (165) throughout the study period (2013-2021). The quarterly trends of anticoagulants prescribed as thromboprophylaxis in MM patients starting cancer therapy are shown in the Figure. There was a notable trend over time in favor of DOACs as the preferred anticoagulant prescribed, while warfarin utilization was minimal later in the study period. DOACs accounted for over 80% of prescriptions in the last 2 years of analysis (2020-2021).

With a median follow-up time of 1.3 years, the 1-year cumulative incidence and incidence rate of severe bleeding among MM patients starting cancer-directed therapy and receiving anticoagulant thromboprophylaxis were 0.8% (95% CI, 0.3%-2.5%) and 7.8 bleeding events per 1000 person-years, respectively. In patients not receiving anticoagulants, the cumulative incidence and incidence rate of severe bleeding were 1.0% (95% CI, 0.8%-1.4%) and 10.1 bleeding events per 1000 person-years, respectively. These differences were not statistically significant, and bleeding complications were similar across groups. We conducted a sensitivity analysis including subjects considered at higher risk of bleeding who were excluded from initial models (those with prior VTE, atrial fibrillation, or stroke). In this analysis, which included 784 additional high-risk subjects, 20% (163) of whom received anticoagulant prophylaxis (total, 7440 subjects), we also found no differences in the rate of hospitalized bleeding between subjects on prophylaxis and those not: 2.2% vs 2.1%.

Multivariable analyses adjusted for age and sex accounting for important bleeding risk factors are presented in Table 1. Anticoagulant thromboprophylaxis was not associated with increased risk of severe bleeding (HR, 0.84; 95% CI, 0.37-1.92). Clinical risk factors significantly associated with bleeding included older age (HR, 1.38 per 10-year increase; 95% CI, 1.18-1.61), higher CCI (HR, 1.18 per SD increment; 95% CI, 1.01-1.40), previous history of bleeding (HR, 1.54; 95% CI, 1.01-2.37), hypertension (HR, 1.87; 95% CI, 1.21-2.89), and renal disease (HR, 1.56; 95% CI, 1.06-2.29). Interestingly, IMiD-containing regimens were associated with a decreased risk of severe bleeding (HR, 0.69; 95% CI, 0.48-0.99) despite higher rate of anticoagulant prophylaxis in patients treated with IMIiDs. The estimated bleeding risk associated with anticoagulant thromboprophylaxis vs no anticoagulant use was further analyzed across several models, as shown in Table 2. No statistically significant association was identified after accounting for comorbidities, bleeding history, and IMiD therapy across several models. Results from similar models in the sensitivity

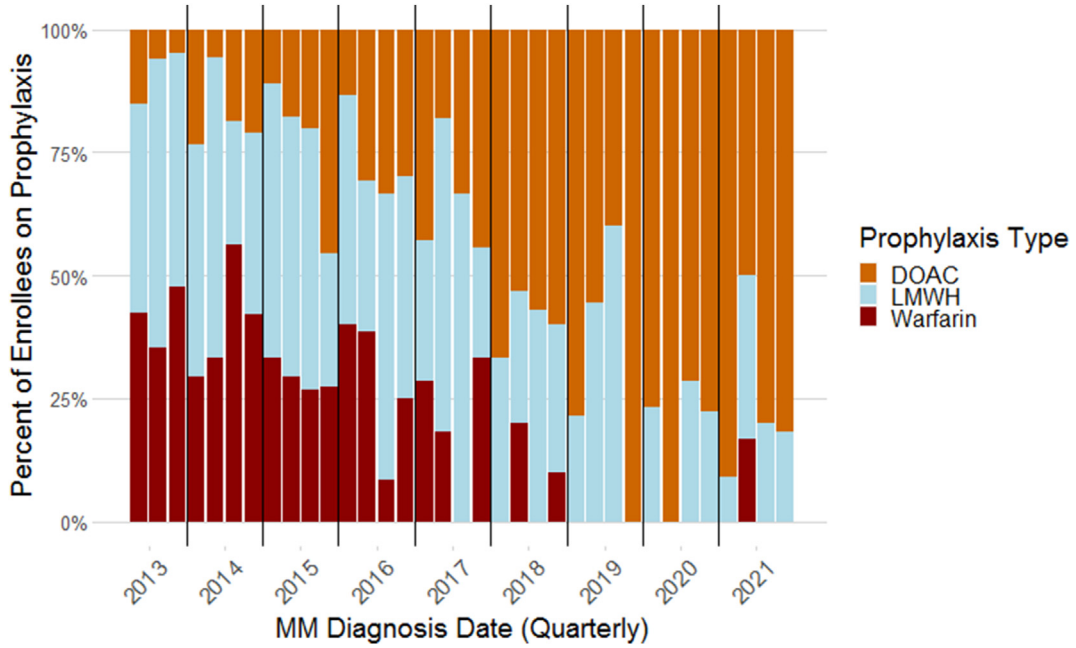

FIGURE Quarterly trends in anticoagulant thromboprophylaxis prescribed for multiple myeloma (MM) patients who start cancer-directed therapy. *Source:* MarketScan 2013-2021. DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin.

analysis population including subjects with prior VTE, atrial fibrillation, or stroke are presented in Supplementary Tables S3 and S4.

In this analysis, the incidence of severe bleeding among MM patients treated with anticoagulants alongside cancer-directed therapy was low. Our results suggest that there is no significant increase in the risk of severe bleeding with the use of anticoagulants as VTE prophylaxis. Bleeding rates appear to be comparable between MM patients with concurrent anticoagulant therapy and those receiving antiplatelet agents alone or no VTE prophylaxis. Though bleeding is an important complication of anticoagulant treatment and MM is associated with hemostatic abnormalities [3,22], these results are in line with previous reports demonstrating that bleeding complications should not limit efforts to prevent thrombosis in MM [24]. In a real-world modern cohort including a high proportion of commercially insured patients and DOAC as VTE prophylaxis strategy, our results are similar to those of older clinical trials using warfarin and LMWH in selected populations, which showed bleeding rates below 1% [31,32].

Our findings are important because balancing the increased and competing risk of bleeding in MM patients can be difficult for clinicians and the risk of bleeding associated with anticoagulant thromboprophylaxis has not been thoroughly investigated. Despite widespread awareness of VTE as a significant problem in MM, our results suggest that adherence to thromboprophylaxis recommendations remains poor in real-world practice, as has been previously reported [19]. It is possible that a disproportionally high perceived risk of bleeding affects clinicians' perceptions and contributes to underutilization of anticoagulants [21]. Documenting the safety of this prophylaxis strategy may persuade clinicians and build on the efficacy data supporting anticoagulants over antiplatelet agents as VTE prophylaxis [17,18].

A significant trend showed that DOACs are increasingly prescribed as anticoagulant thromboprophylaxis over warfarin and LMWH in recent years. Though this use is not currently standard of care, the convenience of DOACs appears to be compelling in real-world practice. While warfarin falling out of favor is not surprising, this trend could represent clinicians' preference over LMWH. Indeed, DOACs accounted for over 80% of anticoagulants prescribed in 2020 and 2021. Though availability over time, not prescriber preference, could also explain this finding and direct comparisons with LMWH are lacking, it is worth considering this trend and the growing evidence of DOACs' safety and efficacy as VTE prophylaxis in MM [15,16]. Though more evidence on the benefits and risks of DOACs for VTE prevention in MM is needed, particularly in high-risk patients, promoting DOACs as a viable option could improve adherence to thromboprophylaxis recommendations.

Unlike the growing number of scores aimed at predicting VTE [11–13], risk models for bleeding complications in MM are lacking. While the risk of severe bleeding from anticoagulants was low, we identified increasing age, previous bleeding history, higher comorbidity burden, hypertension, and renal disease as clinical risk factors significantly associated with increased risk, while IMiD-based therapy was associated with decreased risk of bleeding. These clinical factors could be included in risk assessment models to help clinicians identify a selective group of MM patients with excessively high individual risk for whom anticoagulant thromboprophylaxis may be withheld.

We acknowledge several study limitations. First, bleeding may be underestimated by a study design that excluded subjects with previous history of severe bleeding and by relying on administrative claims data, which limit severe events to those requiring hospitalization and define time at risk after an exposure assessment window. However,

TABLE 1 Risk factors for severe bleeding in patients starting therapy for multiple myeloma.

	Event frequency[a]		Adjusted analysis[b]	
Characteristic	***N***	**%**	**HR**	**(95% CI)**
Anticoagulant prophylaxis				
No	112	1.8	Ref	
Yes	6	1.4	0.84	(0.37-1.92)
Sex				
Female	45	1.51	Ref	
Male	76	2.07	1.41	(0.97-2.03)
Age (per 10-y increase)	—	—	1.38	(1.18-1.61)
CCI (per 1 SD increase)	—	—	1.18	(1.01-1.40)
History of bleeding				
No	26	1.39	Ref	
Yes	95	1.98	1.54	(1.01-2.37)
MM treatment				
Other regimens[c]	61	2.51	Ref	
IMiD-containing regimen	60	1.42	0.55	(0.39-0.79)
Comorbidities				
Heart failure	16	2.25	1.49	(0.87-2.56)
Hypertension	93	2.19	1.87	(1.21-2.89)
Myocardial infarction	3	1.13	0.63	(0.20-2.00)
Peripheral artery disease	16	2.16	1.21	(0.70-2.06)
Diabetes	38	2.29	1.33	(0.91-1.96)
Chronic pulmonary disease	22	1.45	0.79	(0.49-1.25)
Renal disease	40	2.47	1.56	(1.06-2.29)
Liver disease	15	1.95	1.31	(0.76-2.25)
Alcohol abuse	1	1.49	1.11	(0.16-7.96)
Depression	14	1.48	1.07	(0.61-1.88)

HR, hazard ratio; CCI, Charlson comorbidity index; IMiD, immunomodulatory drug; MM, multiple myeloma; Ref, reference.
[a]Severe bleeding events were identified by Cunningham algorithm.
[b]Analysis adjusted for age and sex.
[c]Breakdown of myeloma-specific therapies, including proteasome inhibitors, monoclonal antibodies, and dexamethasone, shown in Supplementary Table S2.

the algorithms used to identify hospitalized bleeding and anticoagulant prescriptions have high PPV and are widely utilized to study bleeding complications from anticoagulation. Additionally, the bleeding rates in our cohort are consistent with the limited literature assessing bleeding risk in MM [33]. Second, it is possible that uncontrolled confounding may remain despite our attempts at adjustment. Given the nonrandomized design, causal inference is limited. Nevertheless, the bleeding risk factors identified are consistent with those reported in previous studies [16]. Third, we cannot exclude selection bias explaining the absence of difference in bleeding rates between subjects who received prophylaxis and those who did not, particularly if individuals at substantial risk of bleeding did not receive prophylaxis. However, comorbidities were generally equally distributed and we adjusted for differences between groups in our multivariable models. Fourth, MM-specific factors were not available, with important missing information including survival, coexisting thrombocytopenia, and stem cell transplantation status. These factors affect bleeding risk and should be accounted for in future studies. Fifth, differences in the risk of major bleeding could not be compared across different anticoagulants due to lack of power and aspirin use was not fully accounted for as administrative claims cannot reliably identify medications available over the counter. Lastly, we were unable to evaluate individual DOACs due to small sample numbers, resulting in poor precision.

TABLE 2 Risk of severe bleeding associated with anticoagulant thromboprophylaxis.

Model	HR	(95% CI)
Unadjusted	0.78	0.34-1.77
Model 1: age and sex	0.84	0.37-1.92
Model 2: model 1 + CCI	0.84	0.37-1.92
Model 3: model 2 + history of bleeding	0.86	0.38-1.95
Model 4: model 3 + IMiD therapy	1.00	0.44-2.31
Model 5: propensity score[a]	1.03	0.45-2.36
Model 6: model 5 + age and sex	1.06	0.46-2.44
Model 7: model 6 + history of bleeding and IMiD therapy	1.07	0.46-2.45

HR, hazard ratio; CCI, Charlson comorbidity index; IMiD, immunomodulatory drug.
[a]Propensity score includes all covariates listed in Table 1 + year of multiple myeloma diagnosis.

Despite these limitations, our results suggest that bleeding complications from anticoagulant therapy in MM are rare, with bleeding rates that may be similar to those of other prophylaxis strategies. Perceived risk of bleeding and lack of studies assessing bleeding in MM likely contribute to poor adherence to anticoagulant recommendations, which in turn may add to unacceptably high rates of VTE. Our results build on existing data demonstrating safety and support the use of anticoagulant prophylaxis in MM. Clinical risk factors can help assess individual bleeding risk and guide therapy decisions in selected cases.

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ETHICS STATEMENT

This study was reviewed by the University of Minnesota's IRB and determined to constitute research that does not involve human subjects under 45 CFR 46.102(f).

AUTHOR CONTRIBUTIONS

D.A.-H., P.L.L., N.A.Z., and K.G. designed the study. P.L.L. contributed to the acquisition of the data. K.G. and R.W. performed the statistical analysis. D.A.-H., P.L.L., and N.A.Z. interpreted the results. D.A.-H. wrote the manuscript. All authors critically revised the manuscript and approved the final version.

RELATIONSHIP DISCLOSURE

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

ORCID

Diego Adrianzen-Herrera https://orcid.org/0000-0003-0168-2165

X

Diego Adrianzen-Herrera @diegoah66
Pamela L. Lutsey @plutsey

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SUPPLEMENTARY MATERIAL

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