Optimizing Thromboembolism Prophylaxis for the Contemporary Age of Multiple Myeloma

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ABSTRACT

Venous thromboembolism (VTE) is a major complication in all patients with cancer. Compared with the general population, patients with multiple myeloma (MM) have a 9-fold increase in VTE risk, likely because of their malignancy, its treatments, and other additional patient-related factors. In MM, thromboembolism events tend to occur within 6 months of treatment initiation, regardless of treatment regimen; however, the use of immunomodulatory agents such as thalidomide or lenalidomide, especially in combination with dexamethasone or multi-agent chemotherapy, is known to create a significant risk for VTE. Currently, official recommendations for VTE prophylaxis in MM outlined in various national guidelines or multidisciplinary society panels are based on expert opinion, because data from randomized controlled trials are scarce. Large studies which have mainly focused on the efficacy of thromboprophylaxis in patients with cancer at higher risk for VTE either had a very low representation of patients with MM, or excluded them all together, limiting our ability to draw evidence-based conclusions on how to effectively protect MM population from VTE. In this brief perspective, we highlight some of the greatest challenges that have hampered the field concerning the availability of high-quality clinical trial data for the formulation of best VTE prophylaxis strategies in patients with newly diagnosed MM, as well as the rationale for the latest updates in the NCCN Guidelines on this topic.

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Thromboembolism, both arterial and venous (VTE), is a major complication in patients with cancer.¹ Compared with the general population, patients with multiple myeloma (MM) have a 9-fold increase in VTE risk, likely because of their malignancy, its treatment, and other additional patient-related factors.^{2,3} Besides interfering with optimal cancer care, thrombosis is a leading cause of mortality in patients with cancer,⁴ and the occurrence of deep vein thrombosis in the first year following a MM diagnosis triples the risk of mortality compared with patients with MM without VTE.⁵ A recent analysis of 2 phase III randomized controlled trials (RCTs) for newly diagnosed MM (NDMM) that included transplant-eligible and transplant-ineligible patients confirmed the significant risk of thrombosis, with nearly all events occurring within 6 months of treatment initiation, regardless of treatment regimen.⁶ It should be noted that the overall incidence of VTE in patients with any malignancy is on the rise in the contemporary era (increased 3-fold overall compared with the general population), fueled not only by the use of conventional cytotoxic drugs but also by many targeted agents and immunotherapy (6-fold increase in those using chemotherapy or targeted therapies).¹ In MM, the use of immunomodulatory agents such as thalidomide or lenalidomide, especially in combination with dexamethasone or multiagent chemotherapy, creates a significant risk for VTE.⁷ Lastly, considering further that the incidence of MM has uniformly increased over the last several decades,⁸ the question of optimal VTE prophylaxis is of even greater importance in this disease entity for successful long-term outcomes for all patients.

Currently, official recommendations for VTE prophylaxis in MM outlined in various national guidelines or multidisciplinary society panels are based on expert opinion, because data from RCTs are scarce. Importantly, the most recent American Society of Hematology guidelines for the management of VTE in patients with cancer stressed the need for prospective RCTs that would assess the full spectrum of VTE risk factors, and the effect of various thromboprophylaxis agents and decision aids through validated risk models for VTE in MM.⁹

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This brief perspective highlights some of the greatest challenges that have hampered the field concerning the availability of high-quality clinical trial data for the formulation of best VTE prophylaxis strategies in patients with NDMM, as well as the rationale for the latest updates in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on this topic.

Issues With Prior Clinical Trials on Thromboembolism Prophylaxis in MM

Considering that the relative benefit of routine thromboprophylaxis in unselected patients with cancer is of lower certainty, recent studies have mainly focused on the efficacy of thromboprophylaxis in patients at higher risk of VTE (ie, Khorana score ≥ 2).¹⁰ However, most trials, such as AVERT, either had a very low representation of patients with MM (2.6%),¹¹ or excluded them all together such as the CASSINI trial.¹² Meta-analyses have also contained equally few patients with MM, further limiting the ability to draw evidence-based conclusions on how to effectively protect this population from VTE. Even with studies that assessed the efficacy of aspirin (ASA), warfarin, or enoxaparin for thromboprophylaxis in NDMM, they excluded the patients at the highest risk for VTE, including those with a prior history of VTE.^{13,14} Trials have also excluded patients with significant renal impairment, which is common at diagnosis of myeloma. As such, most NDMM trials have suggested nonuniform, opinion-based VTE prophylaxis approaches, or left them to the investigator's discretion.

Best VTE Risk Assessment Models in MM

Three risk assessment models have been developed to predict VTE in NDMM receiving therapy: an early International Myeloma Working Group (IMWG) score historically adopted by NCCN,¹⁵ and more recently the SAVED¹⁶ and the IMPEDE VTE¹⁷ scoring models. Unfortunately, both the accuracy of the IMWG/NCCN model for predicting the development of VTE, as well as its use outside of clinical trials, have been poor.^{18,19} Furthermore, recent attempts at validating the IMWG/NCCN model in 2 large cohorts—SEER-Medicare and Veterans Administration Healthcare System—demonstrated that the model's discriminatory performance as measured by Harrell's c-statistic (measured from 0.5–1.0 as the best “fit” of a propensity score model assessing the risk) was suboptimal in both groups, at 0.52 and 0.55, respectively.^{16,17} On the other hand, both the SAVED and the IMPEDE VTE models performed slightly better, with external validations at 0.60 and 0.64, respectively.²⁰ Lastly, the IMPEDE model additionally takes into consideration baseline use of ASA or anticoagulants when assessing the VTE risk. Given the advantages of the latter 2 risk prediction models, the updated NCCN Guidelines for VTE prophylaxis in NDMM have preferentially focused on the SAVED and IMPEDE risk models.²¹ Importantly, although these prediction models perform well, they offer no consensus regarding recommendations for thromboprophylaxis based on different VTE risk groups. For this reason, the NCCN MM panel has actively addressed this knowledge gap based on the available body of evidence, albeit limited, to optimize decision-making regarding the choice of anticoagulant and duration of thromboprophylaxis.

Table 1. Common VTE Prophylaxis Choices in Various Myeloma Settings^a

Type of Myeloma Therapy	Myeloma Treatment Stages			
	NDMM	Consolidation	Maintenance	RRMM
Doublets (eg, Vd, Rd, Kd)	ASA or ppx AC	ASA or ppx AC	ASA	ASA or ppx AC
Triplets (eg, VRd, VTd, KRd, ^b DRd)	ASA or ppx AC	ASA or ppx AC	ASA	ASA or ppx AC
VCd ^c	ASA or ppx AC	ASA or ppx AC	ASA	ASA or ppx AC
Quads (eg, DVMP, DVTd, DVRd)	ppx AC	ppx AC	ASA or ppx AC	ppx AC
Multiagent (eg, VTd-PACE) ^d	ppx AC	N/A	N/A	ppx or full? dose AC
Any regimen + prior unprovoked VTE or prior provoked VTE with persistent high-risk VTE factor	Full-dose AC			

Abbreviations: AC, anticoagulation; ASA, aspirin; DOAC, direct oral anticoagulant; DRd, daratumumab/Rd; DVMP, daratumumab/bortezomib/melphalan/dexamethasone; DVRd, daratumumab/VRd; DVTd, daratumumab/VTd; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; LMWH, low-molecular-weight heparin; N/A, not applicable; NDMM, newly diagnosed multiple myeloma; Plt, platelets; ppx, prophylaxis; Rd, lenalidomide/dexamethasone; RRMM, relapsed/refractory multiple myeloma; VCd, bortezomib/cyclophosphamide/dexamethasone; Vd, bortezomib/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; VTd-PACE, bortezomib/thalidomide/dexamethasone/cisplatin/doxorubicin/cyclophosphamide/etoposide; VTE, venous thromboembolism.

^aDecision regarding the choice of VTE ppx (ASA, LMWH, DOAC, or warfarin) needs to be carefully individualized based on IMPEDE VTE risk score and other clinical factors for each patient. For patients with thrombocytopenia assuming no other coagulopathy: Plt $>50,000/\text{mL}$: deliver full-dose AC; Plt $30,000\text{--}50,000/\text{mL}$: deliver 50% therapeutic dose AC; Plt $<30,000/\text{mL}$: hold all AC.

^bLimited data suggest that patients treated with KRd may preferentially benefit from being on a ppx AC with a DOAC.

^cOften used in patients with myeloma and acute kidney injury or end-stage renal disease.

^dVTE rate in this group can be elevated at 15% despite prophylactic-dose LMWH; careful and detailed risk/benefit assessment and discussion should be conducted on individual basis with respect to the potential choice of higher-level (full-dose) AC in select cases.

Table 2. Features for Consideration Among Different Prophylaxis Agents

Agent	Route	Reversal ^a	Cost	Benefits	Possible Issues ^b
Aspirin	Oral	None (platelets)	Low	<ul style="list-style-type: none"> No monitoring Mostly tolerable 	<ul style="list-style-type: none"> Complications uncommon Adults aged ≥70 years have increased risk for major bleeding
UFH	IV or SC	Protamine sulfate	Low	<ul style="list-style-type: none"> Easily adjustable (short $t_{1/2}$) Reversal readily available Safe in AKI/ESRD Highly reliable Cost 	<ul style="list-style-type: none"> Inconvenient modes for delivery for outpatient use (including every-8-hours SC dosing schedule) Inconvenient for some (eg, fear of needles) Contraindicated in recent/acute HIT Relative contraindication with past history of HIT
LMWH	SC	Protamine sulfate	Medium-high	<ul style="list-style-type: none"> Highly reliable Reversal readily available No need for monitoring 	<ul style="list-style-type: none"> CrCl <30 mL/min: recommended dosing 30 mg daily Not dialyzable Inconvenient for some (eg, fear of needles) Contraindicated in recent/acute HIT Relatively contraindicated with past history of HIT
Warfarin ^c	Oral	Vitamin K 4F-PCC	Low	<ul style="list-style-type: none"> Reversal readily available Safe in AKI/ESRD Cost Oral 	<ul style="list-style-type: none"> Less reliable with INR fluctuations (diet, absorption from GI symptoms, drug interactions, low albumin) Blood draws for INR monitoring Relative contraindication with concomitant inhibitors and inducers of CYP2C9, 1A2, or 3A4
Apixaban	Oral	Andexanet (specific) or 4F-PCC (nonspecific)	High	<ul style="list-style-type: none"> No monitoring Oral 	<ul style="list-style-type: none"> Azole interactions Lack of data at extreme weights Avoid if CrCl ≤15^d mL/min or Child-Pugh class B/C Andexanet may not be readily available on formulary
Rivaroxaban	Oral	Andexanet (specific) or 4F-PCC (nonspecific)	High	<ul style="list-style-type: none"> No monitoring Oral 	<ul style="list-style-type: none"> Azole interactions Lack of data at extreme weights Avoid if CrCl ≤30 mL/min or Child-Pugh class B/C Doses ≥15 mg recommended with food Andexanet may not be readily available on formulary

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; AKI, acute kidney injury; CrCl, creatinine clearance; ESRD, end-stage renal disease; GI, gastrointestinal; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; PRN, as needed; SC, subcutaneous; $t_{1/2}$, half-life; UFH, unfractionated heparin; VTE, venous thromboembolism.

^aReversal of prophylactic anticoagulation may often not be necessary due to the short half-life of many of the drugs.

^bAll anticoagulants carry increased risk of bleeding; careful consideration needs to be made regarding risks and benefits for each patient.

^cWarfarin at INR 2–3 for VTE prophylaxis is not directly comparable to the other agents listed at prophylactic doses with respect to bleeding or thrombotic risks.

^dSome data available for safety in hemodialysis patients at 2.5-mg twice-daily dosing.

Optimizing the Predictive Power of Myeloma VTE Prophylaxis Models With Serologic Biomarkers

To date, the full spectrum of host- and disease-specific thrombophilic factors mechanistically driving the high rates of both arterial and VTE in MM has not yet been elucidated. As summarized in a recent review by Fotiou et al,²² an expanding body of literature has identified several serologic biomarkers that may help in predicting VTE risk in MM. Recently, a study examining the combination of the common VTE marker D-dimer and the IMPEDE VTE score in patients with NDMM starting chemotherapy demonstrated improvement in the identification of patients at high risk of VTE: patients in the highest quartile (>75th percentile) of D-dimer levels had a 2-fold increase in the risk of VTE after adjusting for IMPEDE VTE score (adjusted hazard ratio, 2.04; 95% CI, 1.03–4.02; $P=.04$).²³

Evolving Landscape of VTE Incidence in the Modern Era of MM

Early trials in NDMM with thalidomide and lenalidomide + high-dose dexamethasone (ie, >40 mg weekly)

resulted in a very high frequency of VTE, between 17% and 26%, with negative implications for cumulative toxicity and short-term overall survival.^{24,25} Since then, the myeloma field has moved on to lower doses of dexamethasone in all phases of disease treatment, particularly in elderly patients (age ≥75 years). Yet, VTE rates remain unacceptably high. In the Myeloma XI trial, despite using IMWG-guided VTE thromboprophylaxis for a minimum of 3 months with low-molecular-weight heparin (LMWH) for high-risk patients and ASA for low-risk patients, the cumulative incidence of VTE was still 12% (notably, nearly half of the patients who developed VTE were not classified as high-risk).²⁶ When utilizing intensive combinational treatments, as was the case in a study that assigned patients with NDMM to multiagent chemotherapy + thalidomide versus no thalidomide, VTE was as high as 34% in the thali-domide group, and remained at 24% versus 15%, respectively, in the 2 groups with and without thalidomide, despite the protocol amendment that added prophylactic-dose LMWH, raising a question regarding whether these patients require full-dose anticoagulation.^{7,27}

Lastly, it remains unclear if the incidence of VTE in the modern era has improved significantly, given that some of the recent trials, such as ENDURANCE, that randomized patients with NDMM to bortezomib/lenalidomide/dexamethasone (VRd) versus carfilzomib/lenalidomide/dexamethasone (KRd) reported only grade ≥ 3 VTE events (2% vs 5%, respectively).²⁸ Indeed, recent retrospective data indicate that the frequency of VTE rates in patients with NDMM treated with KRd + ASA, RVd + ASA, and KRd + prophylactic rivaroxaban was significantly higher in some groups (ie, the KRd + ASA group), at 16%, 5%, and 5%, respectively.²⁹ Importantly, all patients who experienced VTE on ASA as thromboprophylaxis in this study received the lower, 81-mg dose. Furthermore, the recent GRIFFIN study that also used modern induction regimens—a quadruplet of daratumumab with VRd (DVRd) versus VRd—similarly demonstrated much higher all-grade cumulative rates of VTE, at 10% versus 15%, respectively.³⁰ Importantly, retrospectively calculated median SAVED scores in both groups were in the low-risk VTE category (< 2 points): 0 (range, 0–3) and 0.5 (range, 0–4) in the D-RVd and RVd groups, respectively, implying that despite low predicted VTE risk, the observed incidence of VTE in both groups was relatively high.³⁰

New Strategies to Address the Gaps

Significant obstacles remain in providing optimal VTE prevention to patients with NDMM. The first, and potentially most important obstacle is that use of thromboprophylaxis is not routinely incorporated for all patients with MM. Although current evidence favors the use of evidence-based VTE risk assessment models, such as IMPEDE-VTE or SAVED, over the IMWG guidelines, many patients with MM are not receiving risk-appropriate prophylaxis. A real-world study of VTE prophylaxis in NDMM demonstrated that only 19% of patients received appropriate prophylaxis per the IMWG guidelines.¹⁸ A recent analysis of the GRIFFIN trial similarly showed that only 60% of patients treated with DRVd and 67% of those treated with RVd were receiving antithrombotic prophylaxis at the time of their VTE (ASA in 40% and 60% of patients, and LMWH in 10% and 7% of patients, respectively), suggesting that use of antithrombotic prophylaxis

remains suboptimal even among mostly academic centers.³⁰ Finally, prospective validation of the SAVED and IMPEDE-VTE models is needed in order to determine the ideal thromboprophylaxis strategy based on baseline risk stratification and treatment regimen, ideally also incorporating biomarkers predictive of VTE risk.

In the meantime, to fill this care gap, we propose a simplified expert-based approach to VTE prophylaxis at various stages of MM, treated with various contemporary MM regimens (Table 1). We provide Table 2 as a guide to properties of specific anticoagulants, which may in turn facilitate selection of an appropriate agent for any individual MM patient deemed at risk for VTE. We conclude that the evidence surrounding unacceptably high VTE rates in patients with NDMM, particularly in those modeled to carry very high risk for VTE in the first 6 to 12 months of diagnosis, indicates an urgent need for prospective RCTs that can optimally inform best risk-driven VTE protection practices for all patients with MM.

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References

- Mulder FJ, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood* 2021;137:1959–1969.
- Kristinsson SY, Fears TR, Gridley G, et al. Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. *Blood* 2008;112:3582–3586.
- Kristinsson SY, Pfeiffer RM, Björkholm M, et al. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. *Blood* 2010;115:4991–4998.
- Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;5:632–634.
- Kristinsson SY, Pfeiffer RM, Björkholm M, et al. Thrombosis is associated with inferior survival in multiple myeloma. *Haematologica* 2012;97:1603–1607.
- Bradbury CA, Craig Z, Cook G, et al. Bradbury CA, Craig Z, Cook G, et al. Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials. *Blood* 2020;136(9):1091–1104. *Blood* 2020;136:1994.

7. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008;22:414–423.
8. Cowan AJ, Allen C, Barac A, et al. Global burden of multiple myeloma: a systematic analysis for the Global Burden of Disease Study 2016. *JAMA Oncol* 2018;4:1221–1227.
9. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv* 2021;5: 927–974.
10. Wang TF, Zwicker JI, Ay C, et al. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2019;17: 1772–1778.
11. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med* 2019;380:711–719.
12. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med* 2019; 380:720–728.
13. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol* 2011;29: 986–993.
14. Larocca A, Cavallo F, Bringhen S, et al. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. *Blood* 2012;119:933–939.
15. Streiff MB, Holmstrom B, Angelini D, et al. NCCN Guidelines Insights: Cancer-Associated Venous Thromboembolic Disease, Version 2.2018. *J Natl Compr Canc Netw* 2018;16:1289–1303.
16. Li A, Wu Q, Luo S, et al. Derivation and validation of a risk assessment model for immunomodulatory drug-associated thrombosis among patients with multiple myeloma. *J Natl Compr Canc Netw* 2019;17:840–847.
17. Sanfilippo KM, Luo S, Wang TF, et al. Predicting venous thromboembolism in multiple myeloma: development and validation of the IMPEDE VTE score. *Am J Hematol* 2019;94:1176–1184.
18. Baker HA, Brown AR, Mahnken JD, et al. Application of risk factors for venous thromboembolism in patients with multiple myeloma starting chemotherapy, a real-world evaluation. *Cancer Med* 2019;8:455–462.
19. Palmaro A, Rougé-Bugat ME, Gauthier M, et al. Real-life practices for preventing venous thromboembolism in multiple myeloma patients: a cohort study from the French health insurance database. *Pharmacoepidemiol Drug Saf* 2017;26:578–586.
20. Sanfilippo KM. Assessing the risk of venous thromboembolism in multiple myeloma. *Thromb Res* 2020;191(Suppl 1):S74–78.
21. Kumar SK, Callander NS, Adekola K, et al. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 1.2022. Accessed September 21, 2001. To view the most recent version, visit NCCN.org
22. Fotiou D, Gavriatopoulou M, Terpos E. Multiple myeloma and thrombosis: prophylaxis and risk prediction tools. *Cancers (Basel)* 2020;12: E191.
23. Sanfilippo KM, Fiala MA, Tathireddy H, et al. D-dimer improves risk prediction of venous thromboembolism in patients with multiple myeloma [abstract]. *Blood* 2020;136(Suppl 1):26–27. Abstract 332.
24. Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2006;24: 431–436.
25. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2010;11:29–37.
26. Bradbury CA, Jenner MW, Striha A, et al. Thrombotic events in patients with myeloma treated with immunomodulatory drugs; results of the Myeloma XI study [abstract]. *Blood* 2017;130(Suppl 1):553. Abstract 331.
27. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; 354:1021–1030.
28. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2020;21: 1317–1330.
29. Piedra K, Peterson T, Tan C, et al. Comparison of venous thromboembolism incidence in newly diagnosed multiple myeloma patients receiving bortezomib, lenalidomide, dexamethasone (RVD) or carfilzomib, lenalidomide, dexamethasone (KRD) with aspirin or rivaroxaban thromboprophylaxis [published online August 15, 2021]. *Br J Haematol*, doi: 10.1111/bjh.17772
30. Sborov DW, Baljevic M, Reeves B, et al. Daratumumab (DARA) plus lenalidomide, bortezomib, and dexamethasone (RvD) in newly diagnosed multiple myeloma (NDMM): analysis of vascular thrombotic events (VTEs) in the GRIFFIN study [abstract]. *Clin Lymphoma Myeloma* 2021;21 (Suppl 2):S135–136. Abstract P-180.