

Prevention of Venous Thromboembolism in Multiple Myeloma

European Myeloma Network Clinical Practice Guidelines
2025



VTE in Multiple Myeloma

- VTE includes: DVT, PE, **atypical thrombosis-** cerebral or splanchnic vein thrombosis
- Incidence: 8-22 per 1000 person-years
- **9-fold increased risk vs. general population**
- VTE rates in MM clinical trials: 4-16%
- **Characteristics:**
 - ~50% present with distal DVT or CVC-related thrombosis
 - ~15% develop PE
 - >50% of events in NDMM occur within **first 3-6 months**
- Impact: Increased morbidity, mortality, treatment interruptions, reduced QOL

Primary prevention

- Patients should be assessed for VTE risk **at diagnosis, at relapse,** and systematically **during treatment**
- Patients should be educated about **early recognition** of symptoms and signs of VTE and hemorrhagic diathesis
- Patients **must be stratified as high-risk and intermediate/low-risk** for VTE, enabling targeted prevention strategies that balance the benefits of pharmacological thromboprophylaxis with the potential bleeding risk

The association between MM and VTE is multifactorial

Disease-Related Risk Factors

- Time since diagnosis-
newly diagnosed > Relapsed
- Tumor burden
- Immobilization
- Abnormal metaphase cytogenetics

Patient-related factors

- Age (>70)
- Female gender
- Obesity
- Comorbidities (such as cardiovascular disease, diabetes, and hypertension)
- Personal or family history of VTE
- Hereditary thrombophilia
- Immobilization
- Renal insufficiency

Treatment-Related Risk Factors

IMiDs

- Thalidomide/Lenalidomide monotherapy: 3-4% VTE rate
 - + High-dose dexamethasone: up to 26% VTE rate
 - + Low-dose dexamethasone: ~10% VTE rate
- **Pomalidomide:**
 - Lower VTE risk than lenalidomide
 - 3-7% VTE rate - dose-dependent

Bortezomib

- Low VTE risk

Carfilzomib

- Induces hypercoagulability → increased VTE risk
- KRd (carfilzomib/lenalidomide/dex): 8.9% VTE
- VRd (bortezomib/lenalidomide/dex): 6.2% VTE

Anti-CD38 Monoclonal Antibodies (Daratumumab):

- No amplification of thrombotic risk
- D-VRd: 10% cumulative VTE vs VRd: 15%

Bispesifics and CART: not associated with elevated risk of VTE

Other Triggering Risk Factors

- **Central Vein Catheters (CVC)**
- **Growth Factors:**
 - Erythropoietin/ESA
 - G-CSF
- **Immobilization:**
 - Bone disease
 - Any cause of immobility
- **Recent Healthcare Events:**
 - Hospitalization

TABLE 2 Risk assessment models available for the evaluation of VTE in patients with MM.

	IMPEDE-VTE	SAVED score ^a	PRISM	IMWG
Population	N = 4446	N = 2397	N = 783	
VTE history	+5	+3	+8	+1
Dexamethasone				
High dose (>160 mg/cycle)	+4	+2		+2 for >480 mg/cycle plus IMiD
Low dose (<160 mg/cycle)	+2	+1		+ 1 for <480 mg/cycle plus IMiD
IMiDs	+4		+2	+1
Fracture pelvis/hip/femur	+4			+1
Use of recombinant epoetin	+1			+1
Tunneled line/CVC	+2			+1
BMI	+1 For ≥ 25 kg/m ²			+1 for BMI > 30 kg/m ²
Race	-3 Asian/Pacific Islander	-3 Asian race	+1 Black race	+1 Caucasian
Age ≥ 80		+1		+1
Age > 75				
Surgery < 90 days		+2	+5	+1
Existing use of anticoagulant or antiplatelet therapy	-4 (-3 if prophylactic)			
Abnormal metaphase cytogenetics			+2	
Other therapy	+3 doxorubicin			+2 MiD plus multiagent chemo OR doxorubicin
New MM diagnosis evidence of hyperviscosity				+1 +1
Other comorbidity, hospitalization, PS > 1, thrombophilia				+1
Risk stratification	Score ≤ 3 : low-risk Score 4–7: intermediate-risk Score ≥ 8 : high-risk	Score ≤ 1 : low-risk Score ≥ 2 : high-risk	Score 0: low-risk Score 1–6: intermediate-risk Score ≥ 7 : high-risk	Score 0–1: low-risk Score > 1: high-risk

IMPEDE-VTE Risk Score

- **Risk Stratification:**

- Score ≤ 3 : Low-risk
- Score 4-7: Intermediate-risk
- Score ≥ 8 : High-risk

- **6-Month VTE Rates:**

- Low-risk: 3.3%
- Intermediate-risk: 8.3%
- High-risk: 15.2%

- **Advantages:**

- Derived from unselected, real-world MM population (N=4446)
- External validation (N=1747)

Predictor	Acronym	Score
Immunomodulatory drug	I	+ 4
Body Mass Index ≥ 25 kg/m ²	M	+ 1
Pelvic, hip or femur fracture	P	+ 4
Erythropoiesis-stimulating agent	E	+ 1
Doxorubicin	D	+ 3
Dexamethasone		
High-dose (>160 mg/month)		+ 4
Low-dose (≤ 160 mg/month)		+ 2
Ethnicity/race = Asian/Pacific Islander	E	- 3
History of Venous thromboembolism before MM	V	+ 5
Tunneled line/central venous catheter	T	+ 2
Existing thromboprophylaxis: therapeutic LMWH or warfarin	E	- 4
Existing thromboprophylaxis: prophylactic LMWH or aspirin		- 3

MM: multiple myeloma; LMWH: low molecular weight heparin.

NCCN 2024

Table 2 NCCN Treatment Guideline Recommendations for VTE Prophylaxis in Multiple Myeloma	
VTE risk tool score	Guideline recommendation
IMPEDE score ≤ 3	Aspirin 81-325 mg/d
SAVED score < 2	
IMPEDE score ≥ 4	Apixaban 2.5 mg twice daily or LMWH (equivalent to enoxaparin 40 mg/d) or Fondaparinux 2.5 mg/d or Rivaroxaban 10 mg/d or Warfarin daily (target INR, 2-3)
SAVED score ≥ 2	

INR indicates international normalized ratio; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
Source: National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): multiple myeloma. Version 1.2025. September 17, 2024.

Primary Thromboprophylaxis: Recommendations

3. *We recommend the implementation of the IMPEDE-VTE score for VTE risk assessment in all patients with MM; given its comprehensive inclusion of relevant risk factors, applicability across treatment regimens, and reliance on universally available clinical parameters. The IMPEDE-VTE score should be applied within the context of its limitations (Grade 1B).*
4. *We recommend the stratification of patients into two risk groups as either high/intermediate or low risk for VTE (Grade 2A).*
5. *Patients who receive IMiD-based regimens or carfilzomib combinations should be stratified as high/intermediate risk for VTE (Grade 2B).*
6. *We suggest risk assessment for VTE upon primary diagnosis and antimyeloma treatment initiation, following induction completion or disease remission, at diagnosis of disease progression or recurrence, when modifications of therapeutic lines are scheduled (Grade 2B).*

VTE prophylaxis During Acute Illness

Recommendations

We recommend to administer prophylactic doses of LMWH or fondaparinux to patients with active MM and acute medical illness, either hospitalized or receiving care in the primary healthcare setting or at home (Grade 1A).

Case 1

- A 56-year-old Caucasian male is diagnosed with high-risk MM (t[4;14] and 1q gain) and about to start induction treatment with DVRd (low-dose dexamethasone). He is transplant eligible
- His ECOG status is 1. The patient is fully ambulatory with no prior history of DVT and no other high-risk features for thrombosis

What are the most important aspects to consider when choosing thromboprophylaxis for this patient?

Using the risk scores for this patient

SAVED- 1 (LD dexta) = Low risk = 6m risk of VTE- 7%

IMPEDE-VTE- 6 (LD dexta+IMiDs) = Intermediate risk = 6m risk of VTE- 8.3%

PRISM- 2 (IMiDs) = Intermediate risk = 12m risk of 10.8%

Clinical judgment remains important in determining the optimal thromboprophylaxis agent

Case 2

- A 65-year-old African American woman was recently diagnosed with MM and is starting treatment with KRd (low-dose dexamethasone). The plan is to continue induction treatment for 8–12 cycles and transition to lenalidomide maintenance, with auto-transplant reserved for 1st relapse
- She also had an arthroplasty for a hip fracture 2 months prior to diagnosis

Which is the best VTE regimen to consider for this patient?

Using the risk scores for this patient

IMPEDE-VTE -10 (IMiDS, recent fracture, surgery, dexamethasone)- High risk- 6m risk 15.2%

SAVED- 3 (surgery, dexamethasone)- High risk- 6m risk 11-12%

PRISM- 8 (race, IMiDs, surgery)- High risk- 12m risk 36.5%

The patient is also receiving carfilzomib, which increases the risk of thrombosis as shown in the phase 3 ENDURANCE trial comparing KRd vs. VRd in NDMM patients, which found increased grade 3–5 VTE rates for the KRd arm (5% vs. 2%, respectively)

Case 3

- A 60-year-old Caucasian male is considering maintenance options after an ASCT for standard-risk MM with normal metaphase-cytogenetics
- The physician's choice is lenalidomide (10 mg/day) until progression
- He has no prior history of VTE, and no surgery, with an ECOG of 0 and a BMI of 24

Should the patient be considered for thromboprophylaxis?

Using the risk scores for this patient

- IMPEDE-VTE, PRISM, and SAVED suggests a low risk for VTE at diagnosis
- **These risk models are not applicable for patients on maintenance** and thus, should not be used to guide decisions for this patient
- Due to the low risk of VTE in the maintenance setting, it remains unclear whether VTE prophylaxis is required during IMiD-based maintenance therapy
- The consideration for low-dose aspirin is substantiated by studies that involved more than 1,000 patients and examined the use of lenalidomide maintenance after transplant. These studies reported VTE rates of up to 6% when prophylaxis was not used but less than 1% when a risk-adapted approach to prophylaxis was employed

Considering the patient's low-risk profile as per the IMPEDE, PRISM, and SAVED models at diagnosis and the low risk of VTE in the maintenance setting overall, either low-dose aspirin or no thromboprophylaxis can be considered reasonable

Key Takeaways

- VTE is a frequent, serious complication in MM with significant morbidity/mortality impact
- Systematic VTE risk assessment using IMPEDE-VTE score recommended at diagnosis, relapse, and with treatment changes
- All patients receiving IMiD or carfilzomib-based therapy require thromboprophylaxis (after bleeding risk evaluation)
- LMWH and direct anti-Xa agents are first-line for high/intermediate-risk patients