Risk Stratification and Anticoagulation in Multiple Myeloma: Tailoring Venous Thromboembolism Prevention and Treatment

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Abstract

Purpose: Venous thromboembolism (VTE) is a serious complication for patients with multiple myeloma (MM), particularly those undergoing treatment with immunomodulatory drugs (IMiDs). This review aims to explore personalized strategies for managing VTE in MM, with a emphasis on risk stratification methods, emerging biomarkers, and advancements in therapeutic approaches to improve patient care.

Design: A thorough review of contemporary evidence was performed to assess the underlying pathophysiology, risk assessment tools, and therapeutic strategies for VTE in MM. Guidelines and multidisciplinary care practices were evaluated to identify shortcomings and propose individualized interventions.

Results: MM is associated with a substantially increased risk of VTE, particularly during the initial six months of diagnosis, driven by disease and treatment factors. Risk assessment models (RAMs) like the SAVED and IMPEDE VTE scores have been instrumental in identifying high-risk patients. For instance, the IMPEDE score, validated in multiple cohorts, demonstrates superior predictive capacity, achieving a C-statistic of 0.74 and outperforming traditional tools like the Padua score (AUC: 0.722 vs. 0.591). Moreover, biomarkers such as elevated D-dimer levels and tissue factor activity enhance the precision of VTE risk assessment.

Emerging evidence highlights the integration of genetic and acquired thrombophilia markers in VTE management. Hereditary mutations (e.g., Factor V Leiden, prothrombin G20210A) and acquired factors (e.g., dexamethasone use, immobility) significantly contribute to VTE risk. Pharmacological thromboprophylaxis tailored to individual risk profiles remains the cornerstone of VTE prevention. Direct oral anticoagulants (DOACs) offer comparable efficacy to aspirin and low molecular weight heparin (LMWH), with a favorable safety profile, particularly in patients with renal impairment or cancer. However, their cost and limited access in certain regions pose challenges.

Conclusion: Effective VTE management in MM demands a multidisciplinary, precision-focused approach. Although risk assessment tools have improved, further refinements are needed to overcome their limitations. Incorporating genetic and acquired thrombophilia markers with evidence-based prophylaxis, especially using DOACs, is a promising avenue for improving care. Future research should emphasize large-scale trials and real-world validation to better mitigate VTE risk and enhance survival in MM.

Keywords: Venous thromboembolism, multiple myeloma, risk assessment, prophylaxis, immunomodulatory drugs

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Introduction

Venous thromboembolism (VTE) is a common and potentially life-threatening complication among patients with multiple myeloma (MM), particularly in those treated with immunomodulatory drugs (IMiDs).[1].With recent advances in therapy leading to improved survival rates in MM, addressing the increased thrombotic risk has become more crucial than ever. Emerging research emphasizes the need for individualized strategies to manage VTE risk, especially in this patient population, which is inherently predisposed to cancer-related hypercoagulability.[2]

Risk stratification tools such as the SAVED and IMPEDE VTE scores have significantly improved clinicians ability to identify MM patients at elevated risk for thrombotic event. [3] Incorporating both genetic and acquired thrombophilia markers has further refined this precision, allowing for more tailored prophylactic and therapeutic decisions.[4] Current guidelines, including those from the Intergroupe Francophone du Myélome (IFM), recommend the use of anticoagulants, such as low-dose direct oral anticoagulants (DOACs), over antiplatelet agents for MM patients receiving IMiDs, thereby enhancing individualized care.[1,5]

Despite notable progress in VTE management, several aspects remain under continuous evaluation, particularly the balance between efficacy and safety in anticoagulant therapy. As new evidence emerges, the roles of clinicians and nurses in monitoring and managing VTE risk are paramount.[6] This review synthesizes recent findings and explores precision-based approaches to VTE management in MM, emphasizing the need for ongoing updates to clinical practice to optimize patient outcomes.

2. Pathophysiology of VTE in MM

Venous thromboembolism in multiple myeloma results from a multifactorial interaction of patient-specific, disease-related, and treatment-induced risks, resulting in a markedly elevated incidence of thrombotic events. The highest occurrence is observed within the first year following diagnosis, particularly in patients undergoing immunomodulatory drug therapy. [7,8] Key components of the pathophysiology are depicted in Figure 1.

Procoagulant State

MM is linked to an upregulation of procoagulant factors, promoting thrombus formation[9] , and impaired fibrinolysis, which contributes to increased clot stability[10]

Risk Factors

Treatment with IMiDs, such as thalidomide and lenalidomide, significantly raises VTE risk.[8.11] Additionally, patient characteristics, including obesity and a history of thromboembolic events, further heighten susceptibility.[9]

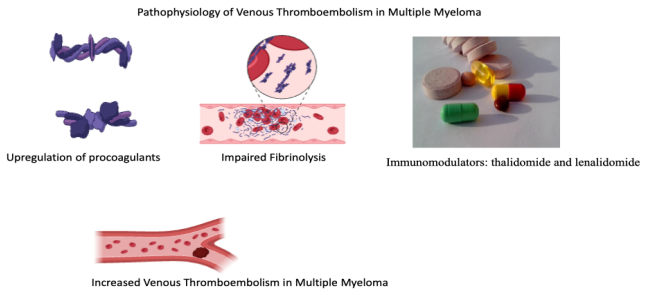

Fig. 1: Showing factors contributing to increased risk of thromboembolism in multiple myeloma

3. Risk Stratification in VTE for MM Patients

Risk stratification for venous thromboembolism in multiple myeloma is essential due to the high incidence of thrombotic events in this population. Various studies have developed and validated risk assessment models (RAMs) to effectively identify patients at elevated risk. For example, the IMPEDE VTE score has demonstrated strong predictive capacity, with a hazard ratio (HR) of 1.59 for VTE occurrence in high-risk groups.[12] In addition, a novel RAM for immunomodulatory drug (IMiD)-associated VTE in Chinese MM patients identified independent risk factors such as diabetes and prior VTE history, yielding a C-statistic of 0.64.[13] Biomarkers, including elevated D-dimer levels and increased tissue factor activity, have also been correlated with higher VTE risk, underscoring the value of a multifactorial approach to risk assessment.[14]

The SAVED and IMPEDE VTE scores are pivotal tools for assessing venous thromboembolism risk in patients with multiple myeloma. These tools are effective in identifying high-risk patients, with increased VTE rates observed in patients with SAVED scores ≥2.[15] The IMPEDE score, in particular, has

been validated in multiple studies, demonstrating robust efficacy in stratifying VTE risk among newly diagnosed MM patients. For example, in a cohort of 405 Chinese patients, the IMPEDE score achieved a C-statistic of 0.74, reflecting strong predictive accuracy, with a cumulative VTE incidence of 40.5% in high-risk groups.[3] Comparatively, the IMPEDE score outperformed the Padua score, with an area under the curve (AUC) of 0.722 versus 0.591, underscoring its superior sensitivity and specificity.[16] Additionally, the IMPEDE score remains applicable when accounting for treatment-related factors, such as the use of carfilzomib, which independently elevates VTE risk.[17] Another model PRISM includes variables likes prior VTE, race, and metaphase cytogenetics , predicts risk in community settings.[18] While the integration of clinical data and biomarkers enhances the precision of VTE risk stratification in MM patients, some studies suggest that traditional models like IMPEDE and SAVED may not always provide accurate predictions. This indicates a need for ongoing refinement of these tools. For instance, Campos et al. (2023) and Fotiou et al. (2020) have demonstrated variability in predictive performance, suggesting that refinements incorporating additional clinical and biomarker data may improve accuracy. [19,20]

Table 1: Comparison of VTE risk stratification models in multiple myeloma:

Model Name	Key Features	Performance Metrics
IMPEDE	Includes variables such as age, IMiD use, and comorbidities	C-statistic: 0.68-0.74; Predicts VTE risk within 6 months of treatment initiation
SAVED	Incorporates variables such as age, BMI, and diabetes	C-statistic: 0.74; Outperforms other models in predicting VTE risk
PRISM	Includes variables such as prior VTE, race, and metaphase cytogenetics	C-statistic: 0.759; Predicts VTE risk in community settings

The integration of genetic and acquired thrombophilia markers is essential for personalized management of venous thromboembolism risk in multiple myeloma patients. Research demonstrates that both hereditary and acquired factors contribute significantly to VTE risk, necessitating a comprehensive approach to risk assessment. Key considerations include:

Genetic Factors

Hereditary mutations such as Factor V Leiden and prothrombin G20210A increase VTE in carriers.[21] Additionally, while genetic variants like rs5985 (factor XIII) may offer protection, others, including serpinA10, are linked to elevated thrombotic risk.[4] Recent evidence indicates that VTE risk in MM patients arises from a complex interplay of hereditary and acquired factors. While traditional thrombophilic mutations such as Factor V Leiden and Factor II G20210A are well recognized, they represent only a portion of the genetic predisposition to thrombosis. According to study by Cini. Et.al additional inherited conditions such as deficiencies in natural anticoagulants (protein C, protein S, and antithrombin) and the presence of antiphospholipid antibodies also significantly contribute to thrombosis risk .[22]

Acquired Factors

Risk factors such as immobility, aggressive lymphoma, and treatment with dexamethasone contribute to increased VTE incidence.[4] Elevated D-dimer levels and reduced total protein S activity also serve as important biomarkers for thrombosis.[4] Although genetic testing can reveal predispositions, it does not always translate directly into clinical outcomes or dictate management strategies, underscoring the complexity of VTE risk in MM. [23] Beyond the genetic factors, acquired elements play a crucial role. Patient-specific risk factors such as advanced age, obesity, reduced mobility, and systemic inflammation further predispose individuals to VTE. Moreover, disease-related factors in MM—including high tumor burden and altered cytokine profiles—create a prothrombotic environment that is compounded by the effects of treatment.

Treatment regimens are particularly influential in modifying VTE risk. The use of immunomodulatory drugs (IMiDs), proteasome inhibitors, and corticosteroids has been shown to elevate thrombotic risk independently, necessitating a careful and tailored approach to prophylaxis. [22] This comprehensive view highlights the need to assess VTE risk in MM patients using multifactorial models that integrate both genetic and acquired factors alongside the impact of specific treatment protocols.

4. Current Guidelines for VTE Prevention in MM

Current evidence-based guidelines for venous thromboembolism (VTE) prevention in multiple myeloma (MM) patients emphasize the importance of pharmacological thromboprophylaxis, particularly in those receiving immunomodulatory drugs (IMiDs). The National Comprehensive Cancer Network (NCCN) guidelines recommend the use of risk assessment tools, such as the SAVED and IMPEDE VTE scores, to stratify patients based on their VTE risk. Key recommendations include:

Pharmacological Options

Low-risk patients are those without additional clinical risk factors beyond the diagnosis of MM—for example, patients who do not exhibit prior VTE, significant comorbidities, or other established thrombogenic factors. Whereas, High-risk patients include those with one or more additional risk factors such as a history of VTE, obesity, advanced age, renal impairment, or those receiving high-risk treatment regimens (e.g., immunomodulatory drugs combined with high-dose corticosteroids).

1. Aspirin

For patients deemed to be at low risk, aspirin is advised as a prophylactic agent. Its antiplatelet effects are sufficient in patients who do not exhibit additional thrombogenic risk factors beyond the MM diagnosis .[24]

2. Low Molecular Weight Heparin (LMWH)

High-risk patients benefit from the use of LMWH. The anticoagulant properties of LMWH make it a suitable option for patients with established risk factors, including those receiving high-risk regimens. Its efficacy in reducing VTE events has been well-documented in this subgroup.[3,24]

3. Direct Oral Anticoagulants (DOACs)

Emerging data have positioned DOACs as an attractive alternative for VTE prophylaxis in MM. Studies have shown that DOACs demonstrate comparable efficacy to aspirin, with no significant increase in bleeding risk. Newly diagnosed MM patients are at heightened risk for VTE, particularly within the first six months of treatment, especially when treated with immunomodulatory drugs (IMiDs). [25] Studies show that DOACs offer similar efficacy to traditional therapies such as aspirin, with no significant differences in VTE rates—21% of patients experience VTE within six months, regardless of treatment.[25] Additionally, DOACs have proven effective alternatives to low-molecular-weight heparin and vitamin K antagonists, offering a favorable safety profile.[26] Risk assessment using tools like the SAVED and IMPEDE scores remains essential in determining patient-specific prophylactic strategies.[25]

Efficacy of DOACs in VTE Prophylaxis

In a cohort of 347 newly diagnosed MM patients, 21% experienced VTE within six months.

VTE rates were comparable between patients on DOACs (21.4% for apixaban, 21.7% for rivaroxaban) and those on aspirin (20.2%).

A SAVED score ≥2 was strongly associated with higher VTE rates ($p < 0.0006$) .[25]

Safety and Tolerability

DOACs exhibit fewer adverse effects compared to traditional anticoagulants, making them a preferred choice.[26] Furthermore, they are effective across various patient populations, including those with renal impairment and cancer.[26]

Clinical Implications

While DOACs offer a promising option for VTE prophylaxis in MM, further trials are needed to optimize thromboprophylaxis strategies.[25] Cost remains a significant barrier to their widespread adoption, particularly in certain regions. [27] Additionally, increased education among healthcare providers is necessary to fully realize the benefits of DOACs in this patient population.

Aspirin plays a notable role in venous thromboembolism (VTE) prevention for patients with multiple myeloma (MM), though its efficacy relative to other agents, such as heparin, remains under investigation. Some studies suggest that aspirin may serve as an independent factor in reducing VTE risk, especially when integrated with risk stratification tools like the IMPEDE-VTE score for more precise patient assessment. [28] Additionally, aspirin has demonstrated effectiveness in reducing VTE incidence across various cancer populations, including trauma and gynecological cancer patients, though results are mixed.[29,30] While aspirin remains a valuable option for thromboprophylaxis, further research is necessary to delineate its comparative effectiveness against other anticoagulants.

Nonetheless, some evidence suggests that long-term aspirin use may not significantly impact VTE rates in certain cancer populations, highlighting the need for larger, more definitive studies to validate these findings.[29] A balanced approach to VTE prevention necessitates the concurrent evaluation of bleeding risk factors, including the use of concomitant antiplatelet therapy, underlying coagulopathies, and other individual patient-specific conditions that may predispose to hemorrhage. This integrated risk–benefit assessment is essential for the individualized tailoring of thromboprophylaxis strategies, ensuring optimal patient outcomes while mitigating the risk of adverse bleeding events.

5. Therapeutic Management of VTE in MM

The management of venous thromboembolism (VTE) in multiple myeloma (MM) presents substantial challenges due to the heightened thrombotic risk associated with various treatments. In particular, therapies such as lenalidomide and carfilzomib have been linked to increased VTE rates, underscoring the need for enhanced risk assessment models, including the IMPEDE-VTE score. [17] Although this score shows promise in stratifying patients based on VTE risk, the absence of a fully validated Risk Assessment Model (RAM) complicates the implementation of personalized thromboprophylaxis strategies .[17]

Key Treatment Challenges

High VTE Incidence: Approximately 16% of MM patients experience VTE, particularly within the first three months of therapy [17]

Ineffective Risk Models: The IMWG score is insufficient, with VTE occurring in roughly 15% of patients[17]

Therapeutic Factors: Treatments with lenalidomide and carfilzomib markedly increase VTE risk, with carfilzomib monotherapy showing a 24% VTE rate at six months .[17]

Direct Oral Anticoagulants (DOACs): These agents have emerged as alternatives to low-molecular-weight heparin (LMWH), offering convenience and rapid onset of action. [31,32] The study by Costa and colleagues provides compelling evidence that DOACs are superior to aspirin for the prevention of VTE in multiple myeloma patients.[33] This finding is significant as it suggests a more effective treatment option for reducing the risk of thromboembolic events. However, there is a notable lack of high-quality evidence for VTE management in hematologic malignancies, highlighting the need for further research.[32]

6. Role of Multidisciplinary Care in VTE Management

Multidisciplinary care is essential for effectively managing venous thromboembolism (VTE) in multiple myeloma (MM) patients, given the complex interactions between disease pathology and treatment regimens. This approach necessitates collaboration among healthcare professionals to address the multifaceted needs of MM patients. Key elements include:

Nursing Management

Nurses play a critical role in patient monitoring, providing education about VTE risks, and ensuring adherence to prophylactic treatments.[6,34] Continuous professional development is crucial for equipping nurses with the skills needed to manage VTE in MM patients effectively.[6]

Multidisciplinary Collaboration

Incorporating palliative care, social work, and psychological support into patient care ensures that the diverse needs of MM patients are addressed.[35] Initiatives like the "Allo-Thrombosis Cancer" program have demonstrated improvements in guideline adherence and patient quality of life.[34]

While multidisciplinary care significantly benefits MM patients, challenges in standardizing protocols and ensuring consistent implementation across healthcare settings persist. Ongoing research and adaptation of care models are necessary to optimize outcomes for patients with multiple myeloma.

7. Ongoing Challenges and Research Gaps

Venous thromboembolism (VTE) management in multiple myeloma (MM) remains challenging due to the intricate interplay of patient-specific, disease-related, and treatment-induced risk factors. Despite established guidelines and available risk assessment tools, VTE incidence remains unacceptably high, underscoring the need for further research into more effective prophylactic strategies and enhanced risk stratification methods.

Patients with MM face a 20-fold increased risk of VTE compared to the general population, with the highest risk occurring within the first six months of diagnosis.[8] Even with prophylactic measures, VTE rates exceed 10%, pointing to the inadequacy of current risk assessments. [1,8]

Limitations of Current Risk Assessment Tools

Traditional models, such as the IMWG score, have proven insufficient, as VTE events still occur in approximately 15% of patients. [17] Although newer models like the IMPEDE-VTE score hold potential, they require further validation across diverse patient populations .[8,17]

Need for Robust Clinical Trials

A significant gap in the literature is the absence of large-scale randomized controlled trials focusing on VTE prophylaxis in MM, particularly regarding the efficacy of direct oral anticoagulants (DOACs).[9,24] While current guidelines advocate for pharmacological thromboprophylaxis, the optimal agents and strategies remain unclear.[24]

Despite advancements in understanding VTE risk factors in MM, persistently high thromboembolic event rates highlight the ongoing need for research. Future studies should prioritize refining risk stratification tools and evaluating the real-world efficacy of prophylactic strategies to improve patient outcomes.

Conclusion

In managing venous thromboembolism in multiple myeloma, precision approaches focusing on individualized risk assessment and tailored prophylaxis are of utmost importance. Tools like the SAVED and IMPEDE VTE scores, together with genetic and acquired thrombophilia markers, have enhanced our ability to identify high-risk patients, supporting more targeted prevention. Clinical practice benefits from these tools and updated guidelines, particularly the preference for direct oral anticoagulants (DOACs) in high-risk MM patients. Future research should prioritize refining these risk assessment models, exploring new biomarkers, and conducting large-scale trials to optimize VTE management further, ensuring improved outcomes through a more personalized, multidisciplinary approach.

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