

# Venous Thromboembolism Risk Stratification and Prophylaxis in Multiple Myeloma

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*Estratificação de Risco e Profilaxia do Tromboembolismo Venoso no Mieloma Múltiplo*

*Estratificación del Riesgo y Profilaxis del Tromboembolismo Venoso en el Mieloma Múltiplo*

Renata Bourdette Ferreira<sup>1</sup>; Marcos Jose Pereira Renni<sup>2</sup>

## INTRODUCTION

Venous thromboembolism (VTE) is the second main cause of death of cancer patients and can be the first manifestation of neoplasms or occur at any time point of the course of the disease<sup>1-3</sup>. Subgroups have different risks with higher rates observed in specific cancers, including pancreas, stomach and multiple myeloma (MM)<sup>1</sup>.

Associated with higher risk of death, thrombotic events do have an important adverse impact as they may lead to treatment interruption, increased morbidity and economic burden<sup>4</sup>.

In this scenario, MM is challenging, it is the second most common hematologic cancer with a risk of VTE nine-fold higher than in the general population<sup>1,5</sup>. The high-risk results from patient, treatment and disease-related factors. The epidemiologic profile of the patient with MM favors the coexistence of additional thromboembolic risks, nevertheless, advances of oncologic treatment increased global survival and thrombotic risk<sup>4</sup>. It is known that 10% of the population with MM will develop VTE at some time point of the disease's course<sup>4,6</sup>, with high incidence in the first six months post-diagnosis<sup>5</sup>.

Inconsistencies in applying the current thromboprophylaxis recommendations have been found. Due to the lack of robust data and standardized models of risk stratification, many physicians tend to rely on their clinical experience<sup>7</sup>. The ideal thromboprophylaxis of MM remains unknown.

## DEVELOPMENT

Virchow's triad update on constituents of the blood and its complex interactions on the process of thrombogenesis is a useful tool to understand the etiopathogenesis of VTE in neoplasm<sup>3</sup> (Chart 1).

The association among cancer, thrombosis and inflammation is well-established. Platelets play a major role

Chart 1. Virchow's Triad

Pathogenesis: Virchow's triad	
Stasis	Prolonged bed rest and extrinsic compression of blood vessels
Constituents of the blood	Tumor procoagulant substances and inflammatory cytokines
Vascular injury	Direct invasion by tumors, central nervous catheter, chemotherapy or others

Source: Adapted from Chung I, Lip GYH<sup>8</sup>.

contributing to the oncogenesis leading to atherosclerosis, pro-thrombotic and pro-inflammatory activities through the same physiopathological mechanisms, the point of interconnection among cancer, inflammation and cardiovascular disease<sup>9</sup>.

The ideal and patient-centered prophylaxis strategy is to identify the contributive factors to thrombogenesis and intervene on those that are modifiable. Patient, disease and treatment related factors coexist in MM, some are modifiable, but others are not.

Patient-related modifiable factors are obesity, arterial hypertension, diabetes, dyslipidemia, sedentarism, heart failure, infection, frequent hospitalizations and pulmonary disease<sup>10</sup>. Ageing, ethnicity, genetics, previous history of VTE and thrombophilia are among non-modifiable factors<sup>10</sup>.

Timing of the disease onset is an important aspect. The active disease is associated with high-risk of thrombosis because increased levels of immunoglobulins, inflammatory cytokines and microparticles help to create the hypercoagulable environment<sup>4</sup>. In addition, while MM develops, pathologic fractures of the pelvis, femur and vertebrae can occur, leading to immobilization or surgeries and increased thrombotic risk<sup>6</sup>.

<sup>1</sup>Pesquisadora Autônoma. Rio de Janeiro (RJ), Brazil. Orcid iD: <https://orcid.org/0009-0009-1432-6419>. E-mail: [rebourdette@yahoo.com.br](mailto:rebourdette@yahoo.com.br)

<sup>2</sup>Instituto Nacional de Câncer (INCA). Rio de Janeiro (RJ), Brazil. Orcid iD: <https://orcid.org/0000-0003-3381-7394>. E-mail: [mrenni@inca.gov.br](mailto:mrenni@inca.gov.br)

**Corresponding author:** Renata Bourdette Ferreira. Rua Agenor Rabello, 50, 301 – Recreio dos Bandeirantes. Rio de Janeiro (RJ), Brazil. CEP 22790-080. E-mail: [rebourdette@yahoo.com.br](mailto:rebourdette@yahoo.com.br)



Another challenge is light-chain amyloidosis (AL) found in nearly 10% of these patients when plasmacytes produce unstable immunoglobulins with tissue infiltration, potential damage of multiple organs and possibly leading to heart failure, atrial fibrillation and nephrotic syndrome, increasing the thrombotic risk. Additionally, hemorrhagic risk increases due to gastrointestinal involvement, deficiency of factor X and renal failure, making thrombotic and hemorrhagic risks particularly challenging<sup>11</sup>.

When treatment-related factors are analyzed, immunomodulating drugs (thalidomide, lenalidomide, pomalidomide) are a key topic of thrombotic risk, they are the base of MM therapy protocols and their thrombogenic potential increases when associated with high-dose dexamethasone, multiagent chemotherapy or anthracycline and possibly with a risk of 26% of thrombosis<sup>6,12</sup>.

The precise thrombogenic mechanism is unknown, but association studies so far have hypothesized a role for increased von Willebrand factor, factor VIII and tissue factor and growth of platelet activation<sup>4</sup>. The use of proteasome inhibitors, particularly carfilzomib and monoclonal antibody elotuzumab can also be associated with higher incidence of VTE in this population<sup>13</sup>.

Central venous catheter, surgeries and support therapies including erythropoietin and multiple transfusions contribute to the risk of VTE<sup>1</sup>.

### RISK STRATIFICATION AND PROPHYLAXIS

Khorana score widely used to evaluate risk of thrombosis associated with cancer was developed for solid tumors and not validated to MM patients as it does not accurately predict VTE in this population<sup>4,14</sup>.

An individual, disease and treatment-based model was proposed by Palumbo et al.<sup>13</sup> attempting to find a solution, which was incorporated into the algorithm recommended prophylaxis of the International Myeloma Working Group (IMWG)<sup>13,14</sup>, (Chart 2) widely used still<sup>14</sup>.

Later, two promising and recommended risk evaluation models have been developed for MM: IMPEDE VTE and SAVED<sup>1,15</sup>.

The European Society of Cardiology published the guidelines of cardio-oncology in 2022, recommending that every patient with cancer in treatment with potential cardiovascular toxicity should have basal risk evaluated, ideally when cancer is diagnosed and without delaying the oncologic treatment<sup>13</sup>.

The proposal is to utilize the HFA-ICOS (Heart Failure Association-International Cardio-Oncology Society)<sup>13</sup> cardiovascular toxicity risk stratification tool. This practice allows the identification of individuals with high-risk of thrombosis and refer them for cardio-oncology follow-up and maintain the oncologic treatment.

Detailed risk stratification is the starting point for an individualized prophylaxis involving changes of lifestyle,

**Chart 2.** Algorithm of recommended prophylaxis of the International Myeloma Working Group

<b>International Myeloma Working Group, European Myeloma Network and National Comprehensive Cancer Network</b>		
<b>Patient-related risk factors 1 point per item:</b>	<b>Disease-related factors 1 point per item:</b>	<b>Treatment-related factors Assign points as below:</b>
BMI > 25, age >75, Personal or family history of VTE, central venous catheter, acute infection or hospitalization, blood clotting disorders or thrombophilia, immobility with PS of >1, Comorbidities (liver, renal impairment, COPD, diabetes mellitus, chronic inflammatory bowel disease), Race (Caucasian is a risk factor)	Diagnosis of MM Evidence of hyperviscosity	IMiD in combination with low-dose dexamethasone (<480 mg/month) (1 point) IMiD plus high-dose dexamethasone (>480 mg/month) or doxorubicin or multiagent chemotherapy (2 points) IMiD alone (1 point) Erythropoietin use (1 point)
<p><b>Risk stratification and recommended thromboprophylaxis</b></p> <p>0 points: Low risk – no prophylaxis</p> <p>1 point: Intermediate risk – Aspirin (acetylsalicylic) 100 mg/day</p> <p>&gt; 1 point: High risk – Low molecular weight heparin at prophylactic dose or therapeutic dose of warfarin</p>		

**Source:** Adapted from Fotiou D, Gavriatopoulou M, Terpos E<sup>16</sup>.

**Captions:** BMI = body mass index; VTE = venous thromboembolism; PS = performance status; COPD = chronic obstructive pulmonary disorder; DM = diabetes mellitus, MM = multiple myeloma, IMiD = immunomodulating agent.

satisfactory treatment of comorbidities and drugs as acid acetylsalicylic and anticoagulants.

The role of the cardio-oncologist in this context is to identify patient-related modifiable factors and intervene to eliminate or minimize the risks and ensure the continuation of the antineoplastic treatment and reduction of cardiovascular events.

The action on lifestyle factors as tobacco use, physical activity and weight control, making the patient aware about the adherence to the measures proposed and treatment of system arterial hypertension (SAH), diabetes *mellitus* (DM), dyslipidemia and heart failure ensures the feasibility of the oncologic therapy.

#### USE OF ACID ACETYLSALICYLIC AND ANTICOAGULANTS

The recent European cardio-oncology guideline recommends the patients with MM and VTE risk factors to receive low molecular weight heparin (LMWH) at a prophylactic dose at least in the first six months of treatment. In case of previous history of VTE, therapeutic dose of LMWH is recommended<sup>13</sup>. Acid acetylsalicylic can be considered an alternative to LMWH with only one risk factor, except previous VTE<sup>13</sup>.

These recommendations are grounded on limited evidences and it is unclear how deliverable these guidelines are in the real world<sup>17</sup>. The use of acid acetylsalicylic is based on data that indicate increase of platelet activation induced by immunomodulating drugs and the disease itself<sup>4</sup>. However, its use is controversial and discouraged in the first month of treatment, when thrombosis risk is higher but it remains an option for later timepoints during disease remission<sup>4</sup>.

Currently, LMWH is the standard prophylaxis drug, however, its cost, parenteral use and necessity of adjustment for renal disorder are challenging in clinical practice<sup>4</sup>.

Emerging data suggest that thromboprophylaxis with apixaban can be an option but additional studies are necessary to validate its use<sup>14,17,18</sup>. The study AVERT (Apixabana to Prevent Venous Thromboembolism in Patients with Cancer) investigated the efficacy and safety of apixaban 2.5 mg 12/12h in ambulatory patients with high risk of VTE, including MM. The result showed significant reduction of VTE with apixaban compared with placebo, but with increased bleeding in the apixaban group and similar mortality rate<sup>1</sup>. Other trials, as MYELAXAT (Evaluation of an oral direct anti-Xa anticoagulant, apixaban, for the prevention of venous thromboembolism in patients with myeloma treated with IMiD compounds: A pilot study) have investigated the safety and efficacy of apixaban in the primary prophylaxis of MM with encouraging results.

There are scarce data to support the choice of the ideal prophylaxis in specially relevant situations as renal failure and thrombocytopenia<sup>4</sup>.

#### CONCLUSION

The ideal prophylaxis strategy of thrombosis in MM remains debatable. Robust studies validating an ideal anticoagulation agent and monitoring tools of thrombotic risk and conduct in special occasions are necessary.

Understand that cancer and cardiovascular disease share inflammatory cascades that favor thrombotic events can be an additional opportunity for prevention through the identification and intervening on the contributing factors that activate these cascades. The cardio-oncologist within this context can help cancer treatment through correct management of the cardiovascular disease to reduce thrombotic events and facilitate the treatment of cancer.

#### CONTRIBUTIONS

Renata Bourdette Ferreira contributed substantially to the study design, acquisition, analysis and interpretation of the data and wording of the manuscript. Marcos Jose Pereira Renni contributed substantially to the acquisition, analysis and interpretation of the data and critical review. Both authors approved the final version to be published.

#### DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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