



**HAL**  
open science

## Venous thromboembolism prophylaxis and multiple myeloma patients in real-life: Results of a large survey and clinical guidance recommendations from the IFM group

Laurent Frenzel, Olivier Decaux, Margaret Macro, Karim Belhadj-Merzoug, Salomon Manier, Cyrille Touzeau, Xavier Leleu, Corinne Frere, Thomas Lecompte, Aurore Perrot, et al.

### ► To cite this version:

Laurent Frenzel, Olivier Decaux, Margaret Macro, Karim Belhadj-Merzoug, Salomon Manier, et al.. Venous thromboembolism prophylaxis and multiple myeloma patients in real-life: Results of a large survey and clinical guidance recommendations from the IFM group. *Thrombosis Research*, 2024, *Thrombosis Research*, 233, pp.153-164. 10.1016/j.thromres.2023.11.021 . hal-04423951

**HAL Id: hal-04423951**

**<https://hal.science/hal-04423951>**

Submitted on 18 Apr 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Venous thromboembolism prophylaxis and multiple myeloma patients in real-life: results of a large survey and clinical guidance recommendations from the IFM group

Runnig title: IFM guidances for thromboprophylaxis in multiple myeloma

Laurent Frenzel<sup>1</sup>; Olivier Decaux<sup>2</sup>, Margaret Macro<sup>3</sup>, Karim Belhadj-Merzoug<sup>4</sup>, Salomon Manier<sup>5</sup>, Cyrille Touzeau<sup>6</sup>, Xavier Leleu<sup>7</sup>, Corinne Frère<sup>8</sup>, Thomas Lecompte<sup>9</sup>, Aurore Perrot<sup>10</sup>, Hervé Avet-Loiseau<sup>10</sup>, Philippe Moreau<sup>6</sup>, and Emilie Chalayer<sup>11</sup>

<sup>1</sup>Service d'Hématologie Adulte et unité d'hémostase clinique, Hôpital Necker, Institut IMAGINE - INSERM U 1163 / CNRS ERL 8254, Paris France

<sup>2</sup>Centre Hospitalier Universitaire Rennes,

<sup>3</sup> Institut d'Hématologie de Basse Normandie (IHBN), CHU Côte de Nacre, Caen, France

<sup>4</sup> centre hospitalier universitaire Mondor, Creteil, France

<sup>5</sup> Hematology department, CHU Lille, Lille University, INSERM UMR-S1277, Lille, France

<sup>6</sup>Department of Hematology, University Hospital Hôtel-Dieu, 44093 Nantes, France; Centre de Recherche en Cancérologie et Immunologie Intégrée Nantes Angers, INSERM UMR 1307, CNRS UMR 6075, Nantes, France

<sup>7</sup> Hématologie Biologique, Hôpital Pontchaillou University Hospital of Rennes, Rennes, France

<sup>8</sup>Service d'Hématologie Biologique, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France ;

<sup>9</sup>Centre Hospitalier Universitaire Poitiers, Poitiers

<sup>10</sup> Institut Universitaire du Cancer de Toulouse-Oncopole and Centre de Recherches en Cancerologie de Toulouse Institut National de la Sante et de la Recherche Medicale, Toulouse

<sup>11</sup>Hématologie clinique, Institut de Cancérologie Hématologie Universitaire, CHU St Etienne Unité INSERM SAINBIOSE, U1059, Université Jean Monnet, St-Etienne

Corresponding author : Laurent Frenzel Md, PhD, Service d'Hématologie Adulte et unité d'hémostase clinique, Hôpital Necker, Institut IMAGINE - INSERM U 1163 / CNRS ERL 8254, Paris France ; email : laurent.frenzel@aphp.fr ; tel +33 1 44 49 52 92 fax : +33 1 44 49 52 83

Words count = text : 4884 ; Abstract : 227 ; Figures = 5 ; Tables = 3 ; References = 58

Keywords: Prophylaxis, venous thromboembolism, multiple myeloma, direct oral anticoagulants, immunomodulatory drugs

### **Highlights:**

Venous thromboembolism pharmacological prophylaxis should be considered for all patients treated with immunomodulatory drugs in combination with dexamethasone despite low level of evidence in a well-structured approach

### **Abstract:**

Venous thromboembolism (VTE) remains a critical issue in the management of patients with multiple myeloma (MM), particularly when immunomodulatory drugs (IMiDs) combined with dexamethasone therapy are being prescribed as first-line and relapse therapy. One possible explanation for the persistent high rates of VTE, is the use of inappropriate thromboprophylaxis strategies for patients starting antimyeloma treatment. To tackle the issue, the *Intergroupe francophone du myélome* (IFM) offered convenient guidance for VTE thromboprophylaxis in MM patients initiating systemic therapy. This guidance is mainly supported by the results of a large survey on the clinical habits regarding VTE of physicians who are substantially involved in daily care of MM patients. VTE prophylaxis should be considered for all patients treated with IMiDs in combination with dexamethasone, in the absence of significant comorbidities, such as renal failure or bleeding risk. Anticoagulant should be preferred to antiplatelet agents for thromboprophylaxis. Despite the absence of large randomized controlled trials comparing those attitudes / options, available data on direct oral anticoagulants, which are already used in daily management of MM patients, are consistent with their potential usefulness for VTE prophylaxis in such patients. However, in order to implement a personalized continuous improvement strategy, clinicians must to be organized to collect all the data regarding this management. In other situations, thromboprophylaxis should be evaluated by using risk models and after careful evaluation of the risk/benefit ratio.

### **Introduction**

Multiple myeloma (MM) is associated with a high incidence of venous thromboembolic events (VTE), such as deep vein thrombosis (DVT) or pulmonary embolism (PE). A large study including millions of United States (US) veterans hospitalized at least once from October 1, 1980, to September 30, 1996, showed that the risk of developing DVT was nine-fold higher in MM patients compared with the entire study population<sup>1</sup>. A Swedish population-based study confirmed that MM patients display an increased risk of VTE compared with controls, especially during the first year after diagnosis<sup>2</sup>. Although the underlying mechanisms of VTE in MM are far from being understood, IMiD-based treatments in combination with dexamethasone were shown to be strongly associated with a higher risk of VTE<sup>3</sup>. As a result, in 2008, the International Myeloma Working Group (IMWG) proposed consensus-based guidelines for thromboprophylaxis in patients initiating IMiD-based drugs<sup>4</sup>. According to the thrombotic risk assessments proposed at that time, the IMWG suggested using aspirin (ASA) in low-risk patients, and using low-molecular-weight heparin (LMWH) in high-risk patients. However, the MM treatment landscape has evolved considerably since 2010, including the use of IMiD-based drugs, more frequently with triplet or quadruplet regimens, from first line therapy to late relapse. Recently, a post-hoc analysis of the randomized phase 2 GRIFFIN trial reported that VTE remains a critical complication in this patient population<sup>5</sup>. Indeed, the VTE incidence observed in the safety population of the GRIFFIN study was significantly higher (approximately 13%) under lenalidomide/bortezomib/dexamethasone (RVd) +/- daratumumab (D), despite thromboprophylaxis

with  $\geq 162$ mg ASA daily according to the IMWG guidelines. Such a high incidence could be explained by the long duration of IMiD-based treatments and a suboptimal thromboprophylaxis, as well<sup>6</sup>.

Because VTE can lead to MM treatment discontinuation, increased risk of anticoagulant-related bleeding, and long-term VTE complications, thereby negatively impacting patient prognosis, real-life management of VTE risks is critical to physicians' daily practice. While risk assessment models have been successively developed to stratify the risk of VTE and facilitate the decision-making process regarding appropriate thromboprophylaxis, routine practice remains challenging. Choice and duration of thromboprophylaxis, patient comorbidities such as renal failure or thrombocytopenia, and local practices are factors that may explain the trends toward using suboptimal thromboprophylaxis regimen. In addition, the emergence of new anticoagulant drugs such as direct oral anticoagulants (DOACs) call into question their use in MM thromboprophylaxis, especially in the absence of results from comparative studies.

To address those queries, the Intergroupe francophone du myélome (IFM) has elaborated guidance for thromboprophylaxis in MM patients, which are based on updated published data and the results of a large survey conducted among clinicians working in all IFM centers in France and Belgium regarding their thromboprophylaxis practices.

#### Results of the IFM survey

An anonymous internet survey was distributed through a google form link and sent by email to registered practitioners at IFM centers in France and Belgium between December 2021 and June 2022. The survey tool was approved by an internal review board within the IFM group, including MM and vascular medicine specialists. The survey was a 15-item questionnaire regarding the use of thromboprophylaxis in MM, which covered the following topics:

- 1) How do you assess the benefit of implementing thromboprophylaxis in a MM patient who requires specific treatments?
- 2) What do you consider to be relevant evaluation criteria or tools for stratifying the risk of VTE?
- 3) If thromboprophylaxis is indicated, in which cases and for how long do you recommend it? (*IMiD-based versus non-IMiD-based treatment*)
- 4) If you plan to start a treatment combining IMiD and dexamethasone, which one of the following thromboprophylaxis regimens do you prefer (creatinine clearance [CrCl]  $>30$ mL/min)? (LMWH, vitamin K antagonist [VKA], DOACs, aspirin [ASA], etc.)
- 5) What are your prescribing habits when ASA thromboprophylaxis is started? Or when LMWH thromboprophylaxis is started (CrCl  $>30$ mL/min)? Or if VKA thromboprophylaxis can be started? Or when DOAC thromboprophylaxis is started (CrCl  $>30$ mL/min)?
- 6) What are your limitations/fears regarding the use of LMWH for prophylaxis? Same question regarding VKA or DOACs for prophylaxis?
- 7) Do you consider this issue as critical in the care of your MM patients?
- 8) Do you manage the choice of treatment yourself or do you call upon a colleague specialized in vascular medicine or hemostasis?

Responses were analyzed using descriptive and frequency statistics.

A total of 86 respondents agreed to participate and completed the core survey. Demographics of the respondents are shown in Table 1. Overall, 86% (N=72) of respondents were working in the

public health system and 92 % (N=76) of them were considered as senior practitioners between 30 and 70 years old.

All but one respondent considered thromboprophylaxis to be relevant in MM patient care (Table 2). In general, the choice of drug for thromboprophylaxis seemed to depend on the clinical context. Fifteen (17.4%) respondents reported to always manage thromboprophylaxis by themselves, while others indicated that the decision regarding the choice of drug for thromboprophylaxis was based on consultant recommendation, especially in cases of prior VTE (26.7%), severe hemorrhage (30.2%), or concomitant antiplatelet drugs (20.9%). In these specific cases, practitioners would prefer to call upon a colleague specialized in vascular disease, though they could directly start treatment, in the absence of any specific risks in terms of comorbidities. Most participants reported that they preferred analyzing thromboembolism risk factors before prescribing any drug regardless of treatment line if an IMiD-dexamethasone-based therapy had been chosen (53.5%). Clinical situations, comorbidities, history of patients, and MM disease characteristics have been largely employed by clinicians as relevant risk analysis criteria to assess the risk of VTE, whereas very few of them seemed to apply a specific score (14%) or complementary assessments (3.5%).

Regarding the duration of thromboprophylaxis, more than two-thirds (70.9%) of clinicians participating to the survey indicated that they continue to use thromboprophylaxis until the end of IMiDs in first-line therapy or in relapsing situations. Only one-third did not prescribe thromboprophylaxis when a non IMiD-based treatment had been chosen (Figure 1).

We then asked participants about their preferred antithrombotic drugs in some frequent real-life situations (Figure 2). Interestingly, thromboprophylaxis with DOACs was likely the preferred option, followed by LMWH therapy and ASA alone, or after switching from parenteral treatment, irrespective of the patient age or concomitant VTE risk factors. In case of concomitant antiplatelet drugs, supervision by a cardiologist was more frequently chosen. Most patients with dual antiplatelet therapy did not receive additional anticoagulation therapy. As carfilzomib treatment can increase the incidence of vascular events<sup>7</sup>, anticoagulation therapy was preferentially given under systematic cardiac supervision.

Finally, we focused on dose management and administration schedule for each of the mostly used thromboprophylaxis agents by practitioners (Figure 3). Interestingly, 15% of clinicians indicated that they never prescribe ASA. Most clinicians using ASA prescribed a 75mg daily dose. In contrast with other countries, 80% of clinicians never proposed a VKA as thromboprophylaxis in MM patients. Two-thirds of clinicians usually prescribed enoxaparin 0.4mL daily, whereas one-third prescribed less than 175IU/Kg tinzaparin per day. Finally, regarding DOACs, 78% practitioners preferred prescribing 2.5mg apixaban twice daily, and 18% 10mg rivaroxaban daily. Only 13% of practitioners never considered DOACs for thromboprophylaxis. The answers concerning the limits or fears of using either DOAC or LMWH were quite different (Figure 4). LMWH limitations included the subcutaneous route of administration with subsequent difficulties encountered in patients after a long treatment, as well as their use in patients with severe renal failure. For DOACs, there were concerns about the lack of approval for MM patients, bleeding risks, absence of antidote, or renal impairment.

### Comprehensive analysis of the survey

The survey addressed several critical aspects, such as the assessment of thromboprophylaxis benefits, risk stratification for venous thromboembolism (VTE), drug choices, prescription habits, and the role of specialists in vascular medicine and hemostasis. The survey's findings highlight the relevance of thromboprophylaxis in MM patient care, with nearly all respondents recognizing its importance. The choice of thromboprophylaxis drugs was often context-dependent, reflecting the complex nature of MM treatment. While some practitioners managed thromboprophylaxis themselves, others sought consultant recommendations, particularly in cases involving prior VTE, severe bleeding, or concomitant use of antiplatelet drugs. In specific situations, practitioners preferred involving colleagues with expertise in vascular disease, although they were capable of initiating treatment independently in the absence of specific comorbidity-related risks. Risk analysis criteria, such as clinical context, comorbidities, patient history, and MM disease characteristics, played a prominent role in assessing VTE risk. Interestingly, the majority of respondents preferred analyzing thromboembolism risk factors before prescribing any drug, especially when adopting an IMiD-dexamethasone-based therapy.

Regarding the duration of thromboprophylaxis, the survey revealed that over two-thirds of clinicians continued its use until the end of IMiD-based therapy in first-line or relapsing scenarios. However, approximately one-third of respondents did not prescribe thromboprophylaxis when opting for non-IMiD-based treatments.

When considering antithrombotic drugs in real-life situations, DOACs emerged as a preferred option, followed by LMWH therapy and ASA, regardless of patient age or concomitant VTE risk factors. Cardiologist supervision was frequently chosen when antiplatelet drugs were involved, and most patients on dual antiplatelet therapy did not receive additional anticoagulation. Notably, the survey suggested a preference for systematic cardiac supervision when using carfilzomib, which can increase the incidence of vascular events.

Dose management and administration schedules varied for different thromboprophylaxis agents. Some clinicians did not prescribe ASA, while those who did often opted for a daily dose of 75mg. In contrast to other countries, VKAs were infrequently proposed as thromboprophylaxis for MM patients. LMWH choices included enoxaparin and tinzaparin, with variations in dosing. DOAC preferences were evident, with apixaban and rivaroxaban being common choices, while a small percentage of practitioners did not consider DOACs due to concerns such as approval status, bleeding risks, lack of antidotes, and renal impairment.

### **IFM clinical guidance for venous thromboprophylaxis in multiple myeloma patients**

The guidance recommendations are proposed to provide guidance in decision-making and implement optimal thromboprophylaxis in MM patients in a real-world setting (Figure 5). A practical algorithm based on easy decision steps, and enabling a prompt determination of the best course of action for any given patient based on her-his clinical scenario is an urgent need for practitioners involved in MM patient care. To develop these guidances (figure 5), a committee from the Intergroupe Français du Myélome (IFM) was assembled, comprising a team of experts in clinical medicine, clinical research, and healthcare services specializing in the fields of myeloma and thrombotic disease. All committee members are credited as authors of this work. The committee systematically reviewed the available evidence related to each clinical question and allocated writing tasks for each respective section. Further refinement of the guidance was achieved through

conferences and email correspondence. A total of three iterative rounds were undertaken, involving the core group initially, followed by hemostatic experts, and ultimately, myeloma experts. Each committee member contributed to drafting the guidance, which was subsequently circulated for review by the entire panel.

### **IMiD-dexamethasone therapy is key in decision-making for thromboprophylaxis: state of the art**

The choice of IMiD-dexamethasone-based therapy is a key step in the decision making for initiating thromboprophylaxis based on published data and real-world experience. Indeed, several studies have demonstrated that the risk of VTE is higher (up to 25%) with IMiD drugs, especially when used in combination with dexamethasone<sup>8-11</sup>. Moreover, the risk of VTE associated with IMiD in combination with dexamethasone was higher than with dexamethasone alone,<sup>12</sup> being directly correlated with the dexamethasone doses used<sup>13</sup>. In contrast, thalidomide or lenalidomide in monotherapy was not associated with any increase in VTE risk compared with the baseline VTE risk in MM patients<sup>15</sup>. Other therapies including alkylants, proteasome inhibitors, or monoclonal antibodies, without an IMiD-dexamethasone combination, did not cause any significant increase in VTE risk<sup>16-18</sup>. In addition, different route of administration of carfilzomib in combination with dexamethasone were shown to be unlikely to correlate with an increase in the risk of VTE<sup>19</sup>. However, carfilzomib in combination with both lenalidomide and dexamethasone clearly resulted in a higher VTE rate compared with the lenalidomide-bortezomib and dexamethasone combination (16.1% vs. 4.8%) when used without any pharmacological prophylaxis for VTE<sup>20</sup>. In most cases, IMiD-dexamethasone therapy is chosen either in the induction or relapse setting. In a recent study, univariable and multivariable analyses showed that 12% out of 672 newly-diagnosed MM patients who received a triplet or quadruplet lenalidomide-based induction therapy were diagnosed with a VTE within the first year of treatment<sup>21</sup>. Most of them were treated with aspirin as thromboprophylaxis regimen. This point highlights the urgent need of prescribing more effective thromboprophylaxis alternative to aspirin to reduce the risk of VTE. According to the IFM survey, most physicians already systematically propose thromboprophylaxis when prescribing an IMiD-dexamethasone combination until the end of treatment regardless of the therapy line. However, up to one-third of practitioners never use thromboprophylaxis in the absence of an IMiD-dexamethasone combination (Table 2 and Figure 1).

### **VTE risk assessment in multiple myeloma: should we use risk prediction models?**

Risk assessment models to stratify the risk of VTE in cancer patients are increasingly used since the publication of the Khorana score in 2008<sup>22</sup>. However, we can question the poor discriminative ability of this score to predict VTE in hematology malignancies, especially in MM. A recent study demonstrated that the Khorana score performed poorly in predicting VTE in a cohort of 2870 MM patients<sup>23</sup>. Among the currently available scores for VTE risk prediction in patients with MM, **four** have been externally validated, comprising the IMWG<sup>24</sup>, SAVED<sup>25</sup>, IMPEDE VTE<sup>26</sup> and PRISM models<sup>27</sup> (Table 3). In each score, the use of IMiD-dexamethasone based therapy is associated with an at least intermediate or high risk of VTE. According to our algorithm, a pharmacological prophylaxis of VTE is thus highly recommended in MM patients initiating IMiD-dexamethasone based therapy who do not exhibit renal impairment or bleeding risk factors. VTE risk should be assessed in all other situations to evaluate the need of thromboprophylaxis. Both patient- and disease-related risk factors must be genuinely assessed to evaluate the overall risk of VTE. Indeed, recent studies have highlighted some disease-related VTE risk factors, such as abnormal metaphase cytogenetics with the Prism Score<sup>27</sup> or “hyperviscosity” with serum gamma globulin levels >27g/L<sup>28</sup>. Furthermore, the survey analysis of

physicians' habits revealed that almost two-thirds of them carry out VTE risk analysis, with most of them considering disease- and patient-related risks factors to be most relevant for VTE risk assessment (Table 2). In contrast, very few practitioners were likely to employ any validated model, including the SAVED, IMPEVE VTE, or IMWG scores, in their daily practice.

### **Clinical situations to consider prior to thromboprophylaxis treatments**

According to our algorithm (figure 5), when initiating thromboprophylaxis is required (IMiD-dexamethasone therapy or presence of relevant risk factors), several comorbidities potentially associated with a higher risk of anticoagulant overdosing or bleeding events must be considered before thromboprophylaxis initiation. According to our survey (Figures 2 and 4) and clinical experience, in addition to published data, there are two common situations that may directly impact initiation and maintenance of thromboprophylaxis drugs in MM patients, including renal impairment and bleeding risks (especially in cases of thrombocytopenia or dual antiplatelet therapy).

Up to one-third of MM patients have renal impairment which requires dose adjustments of anticoagulant therapy, especially LMWH and DOACs. In patients with a CrCl of at least 30mL/min, no drug adjustment is required. Conversely, neither LMWH nor DOACs should be used in cases of CrCl below 15mL/min. Only unfractionated heparin (UFH) should be proposed for thromboprophylaxis at a dose of 0.2mL twice daily administered subcutaneously in these patients. Of note, clinicians are increasingly inclined to prescribe LMWH and DOAC in patients with severe renal impairment with a CrCl below 15mL/min, along with anti-factor Xa activity monitoring or dose reduction. Nevertheless, there is currently no approval for this indication, especially considering its prophylactic use<sup>29-30</sup>. For patients with a CrCl between 15 and 30mL/min, either LMWH or apixaban could be used at prophylactic doses, with an active surveillance of bleeding risk, especially in the presence of other associated risk factors for bleeding<sup>31</sup>.

The risk of bleeding has been poorly evaluated in MM patients. A recent publication attempted to evaluate the bleeding rates in a real-world computed analysis of nearly 1300 MM patients receiving therapeutic anticoagulation therapy<sup>32</sup>. As a result, the cumulative incidence of bleeding was less than 5%, depending on the anticoagulant drug, and was higher with VKA than with LMWH or DOAC, as in other cancer patients receiving therapeutic anticoagulant therapy. Comorbidities associated with an increased bleeding risk included age, Charlson comorbidities index, the concomitant use of antiplatelet drugs (aspirin being not considered), diabetes, and renal disease. According to our survey, most clinicians needed a thorough supervision in cases of simultaneous use of antiplatelet and anticoagulant prophylaxis agents, although an association of these two drug types is unlikely to increased bleeding rates. Even on using DOACs<sup>33</sup>, patients with dual antiplatelet drugs must be thoroughly evaluated before adding any anticoagulant therapy, especially if other risk factors coexist<sup>34</sup>. Age alone should not be considered as an exclusion criterion for initiating thromboprophylaxis. Based on our survey, age did not influence the choice of drug. More importantly, age itself was considered as a VTE risk factor, and a careful evaluation of benefits and risks is warranted in frail patients before initiating a prophylactic anticoagulation therapy.

In clinical practice, the management of anticoagulant therapy in case of thrombocytopenia is a common issue in patients with hematological malignancies. As individual platelet counts are poor predictors of bleeding risks, no clear recommendations pertaining the use of anticoagulation therapy in relation with platelet counts have been given so far. Usually, therapeutic anticoagulation in the presence of platelet counts  $<50 \times 10^9/L$  is a condition that requires specific care due to thrombocytopenia-related bleeding risk<sup>35</sup>. Given that prophylactic anticoagulation is associated with



a lower bleeding risk compared to therapeutic anticoagulation, as it is close to single antiplatelet therapy risk, a platelet count of  $>30 \times 10^9/L$  should be considered a reasonable cut-off for initiating or continuing an anticoagulant prophylactic regimen with a prophylactic anticoagulation<sup>36</sup>.

### **Why should aspirin not be considered as a valuable option for thromboprophylaxis in MM?**

Results from clinical trials comparing different options for thromboprophylaxis in MM patients are sparse. A recent Cochrane review systematically reviewed the available evidence on the efficacy and safety of aspirin, DOAC, LMWH, VKA to prevent VTE in MM patients<sup>37</sup>. A total of 1015 citations from 11 articles were identified with only four randomized clinical trials enrolling 1042 MM patients. No significant differences were reported in terms of bleeding risks among aspirin, LMWH, or DOAC upon a prophylactic use. Furthermore, data from the observational prospective MELISSE study generated the same conclusion about adapted thromboprophylaxis regimens<sup>38</sup>. In this study, VTEs were observed in 7% patients on aspirin and only 3% on LMWH prophylaxis. Only two randomized studies compared 100mg aspirin once daily (OD) versus 0.4mL enoxaparin once daily with or without warfarin. They did not demonstrate any significant differences between groups<sup>39-40</sup>. However, after 6-month follow-up, the VTE rate was about 4.5% in the aspirin group versus 2.7% in the LMWH group for patients treated with thalidomide; yet, this VTE rate in both groups was 2.2% versus 1.2%, respectively, for patients undergoing a lenalidomide-based treatment. Moreover, 1.7 % of patients in the ASA group were diagnosed with a pulmonary embolism compared with none in the LMWH group<sup>40</sup>. More recently, two observational studies have proposed ASA and DOAC as VTE prophylaxis in MM patients<sup>20,41</sup>. In newly-diagnosed MM patients treated with carfilzomib-lenalidomide-dexamethasone (KRd) regimen, the VTE rate exceeded 16% in the ASA (81 or 160 mg OD) group compared with only 4.8% in the rivaroxaban (10mg OD) group ( $p=0.0067$ )<sup>20</sup>. For relapsed patients treated with IMiD-based drugs, VTE was reported in 4% of patients receiving 75mg aspirin OD, whereas no VTE was observed in patients receiving 2.5 mg apixaban twice daily (BID) for thromboprophylaxis<sup>41</sup>.

Moreover, the superiority of anticoagulants in preventing VTE has been demonstrated in other situations than MM. In a large randomized trial involving patients requiring extended thromboprophylaxis after a prior VTE, rivaroxaban treatment (10 or 20mg OD) was associated with a significantly lower rate of recurrent VTE compared with aspirin therapy (100mg OD), without any significant increase in bleeding rates, particularly on 10mg rivaroxaban<sup>42</sup>.

### **DOACs are likely preferred for preventing thromboembolic complications in MM patients**

According to the survey, DOACs were more commonly prescribed by practitioners as anticoagulant agents than LMWH (Figure 2). The mostly chosen doses were 2.5mg BID apixaban followed by 10mg OD rivaroxaban (Figure 3). The recommendations for using apixaban 2.5 mg twice daily or rivaroxaban 10 mg daily are, of course, empirical due to limited available evidence. However, they are based on published data in a manner similar to the recommendations for aspirin or low molecular weight heparins (LMWHs). Similarly, if LMWH was recommended as anticoagulant agent, 0.4mL OD enoxaparin was mostly suggested after  $<175$  UI/Kg OD tinzaparin. Several dosing regimens involving tinzaparin have been suggested for prophylaxis, with daily fixed doses ranging from 4500 to 12000 UI<sup>43</sup>. Nevertheless, in the analysis of the IFM2009/DFCI study, the prophylactic dose of tinzaparin employed was 4500 IU per day<sup>28</sup>, and another recent study in oncology substantiates the efficacy of this dosage for primary prophylaxis<sup>44</sup>.

However, DOACs are currently not approved for the treatment and prevention of VTE in MM. This point has been highlighted by clinicians as a limitation to DOAC prescriptions, though being clearly surpassed by the difficulties inherent to subcutaneous injection requirements of LMWH prophylaxis (Figure 4). The French and Belgian trend in using DOACs as anticoagulant agents in MM has been recently confirmed in several studies<sup>32,45</sup>. Furthermore, the use of DOACs at a low dose for primary VTE prevention is considered off-label, it may not be covered by reimbursement in many healthcare systems.

To date, no large, randomized study in MM has compared efficacy and safety of either LMWH and standard of care versus DOAC as thromboprophylaxis in MM patients. The Caravaggio study was designed to compare apixaban versus dalteparin (LMWH) in cancer patients with acute VTE<sup>46</sup>, with up to 9% of these patients having a hematological malignancy. Apixaban met the non-inferiority efficacy endpoint in the curative VTE treatment versus LMWH regimen, without any increase in major bleedings. In ambulatory cancer patients at intermediate to high risk of VTE according to the Khorana score, two large randomized clinical trials compared DOAC versus placebo for VTE prevention<sup>47-48</sup>. Both 10mg OD rivaroxaban<sup>47</sup> and 2.5mg BID apixaban<sup>48</sup> demonstrated significant benefits in terms of VTE prevention without any increased major bleeding risks, except for gastric cancer patients.

Several non-randomized studies provided data on the efficacy and safety of DOACs as thromboprophylaxis for MM patients treated with IMiD-dexamethasone in first-line therapies or relapses<sup>49-51</sup>. All of them proposed 2.5mg BID apixaban as anticoagulant, suggesting its efficacy in VTE prevention with very low or no events during thromboprophylaxis in MM patients, regardless the use of thalidomide, lenalidomide, or pomalidomide as IMiDs. Moreover, a very low major bleeding rate was reported, with some minor bleeds identified without any consequence under MM treatments. Although antidote non-availability could be considered as a limitation by some clinicians (Figure 4), since unscheduled surgeries or traumatic events could be more complicated to manage with DOACs compared with LMWH when using prophylactic doses. However prophylactic DOAC doses are unlikely concerned when considering the quick need of an antidote activity.

## **Discussion**

We have herein proposed a guidance framework for thromboprophylaxis in MM patients based on an updated review of available data, expert opinions, and, most importantly, real-world practice of physicians involved in MM care (figure 5). VTE continue to be a crucial issue in this setting, the IMiD-dexamethasone strategy being currently among the most commonly used in both first-line therapy and relapse. With a daratumumab-RVd (Lenalidomide (R) + bortezomib (V) + dexamethasone (D)) treatment as induction and consolidation for transplant-eligible patients followed by lenalidomide as maintenance therapy, more than 90% of patients achieved a complete response in the Griffin trial<sup>5</sup>. Nevertheless, the efficacy endpoint was not met because of a high VTE rate (10%). In most cases, aspirin was used for thromboprophylaxis, whereas several patients exhibiting a VTE never received any thromboprophylaxis.

Simplified algorithms are urgently needed in view in order to optimize thromboprophylaxis. In cases where anticoagulation prophylaxis was quite mandatory, the VTE rate was lower than that observed in the Griffin trial, as seen in the IFM2009/DFCI trial with RVd induction, with less than 5,5% VTEs (Grade 3-4) in both arms<sup>52</sup>. In the IFM2013-04 study, only 1.8% of patients were diagnosed with a VTE (Grade 3-4) in the cyclophosphamide (VCD) or thalidomide (VTD) groups, in spite of thalidomide-dexamethasone being the induction regimen for newly-diagnosed MM patients<sup>53</sup>. In

both studies, LMWH was the mostly used thromboprophylaxis strategy, consisting of 0.4mg enoxaparin daily or less than 175IU/Kg tinzaparin, as proposed by clinicians (Figure 3). However, according to the survey, the burden of daily subcutaneous injections was clearly shown to be the major limiting factor for patients, especially upon using continuous regimens for years on end until progression (Figure 4). In addition to the subcutaneous injection burden, the long-term use of LMWHs can potentially lead to significant side effects, such as osteoporosis and the risk of heparin-induced thrombocytopenia (HIT). These side effects can be particularly detrimental to the management of myeloma patients who already have preexisting bone fragility and are undergoing treatments that induce cytopenias.

Although DOACs are not approved for MM patients, their use at prophylactic doses appears very comfortable for patients, without any significant safety concerns, while being highly efficient in preventing VTE, as based on the results of the most recent studies<sup>46-49</sup>. Randomized studies comparing DOACs with LMWH could be interesting for MM patients in first-line therapy or relapse settings, though ethic issues could limit patient (receiving either daily subcutaneous injections or oral drugs) participation. Developing new targets in thromboprophylaxis like factor XI (FXI) monoclonal antibody could be even more challenging in view of a new MM randomized trial, comparing patients receiving an intravenous injection twice monthly, such as abelacimab, with those treated with daily oral DOACs<sup>54</sup>. Another issue with using DOACs is their likely interaction with MM drugs. In this context, an ancillary study was proposed based on the IFM2020-05 / BENEFIT trial questioning the pharmacokinetics of 2.5mg BID apixan employed in non-transplant eligible newly-diagnosed patients receiving isatuximab, lenalidomide, and dexamethasone in both arms, with or without bortezomib. While this study is still ongoing, final analyses of apixaban pharmacokinetics and safety reports should be made available within the next months.

As primary VTE thromboprophylaxis has been largely discussed, questions about treatment of acute VTE appear to be less controversial. In general, acute VTE therapy has been well-established in cancer patients,<sup>55</sup> consisting of a progressive use of DOACs versus LMWH based on the results of large randomized controlled trials<sup>44</sup>. The same trend was observed for acute VTE therapy upon MM care, with a special focus on bleeding risk factors<sup>56</sup>. However, acute VTE therapy in patients already on ongoing anticoagulant prophylaxis is a hazardous situation, which requires further discussions involving vascular experts with respect to changing the anticoagulation drug or using a metal device as vena cava filter.

In addition, an arterial thromboembolic risk has been described in some MM trials, which was, however, less relevant than VTE<sup>43</sup>. While IMiD use and classical cardiovascular risk factors are linked to this issue, this risk appears to be quite low in the MM population, with an incidence ranging from 1.3 to 2.4%, as observed in the myeloma XI trial<sup>57</sup>. While no evidence of arterial thromboprophylaxis has been found in MM cohorts, both LMWH and DOACs were associated with a decrease in arterial events in cancer treated populations<sup>45,58</sup>. However, no preventive measures for arterial thromboembolic risk are provided in this guidance and would require future evaluation.

Finally, following this guidance (figure 5), the majority of patient could be protected against any VTE with a favorable safety risk assessment. However, there may probably persist a very small minority of MM patients that might experience a VTE, even if this guidance has been correctly applied. Actually, these “very high-risk” patients are very tricky to spot, and no clear definition is currently available, neither from different risk assessment models nor from guidelines<sup>37</sup>. Moreover, no available data support any specific therapeutic approach for these very high-risk patients, especially with respect to therapeutic doses of LMWH or DOAC. In response, continuing to provide

specific registers and clinical studies is mandatory to better identify individual VTE risk factors and optimize the anticoagulation options for these patients.

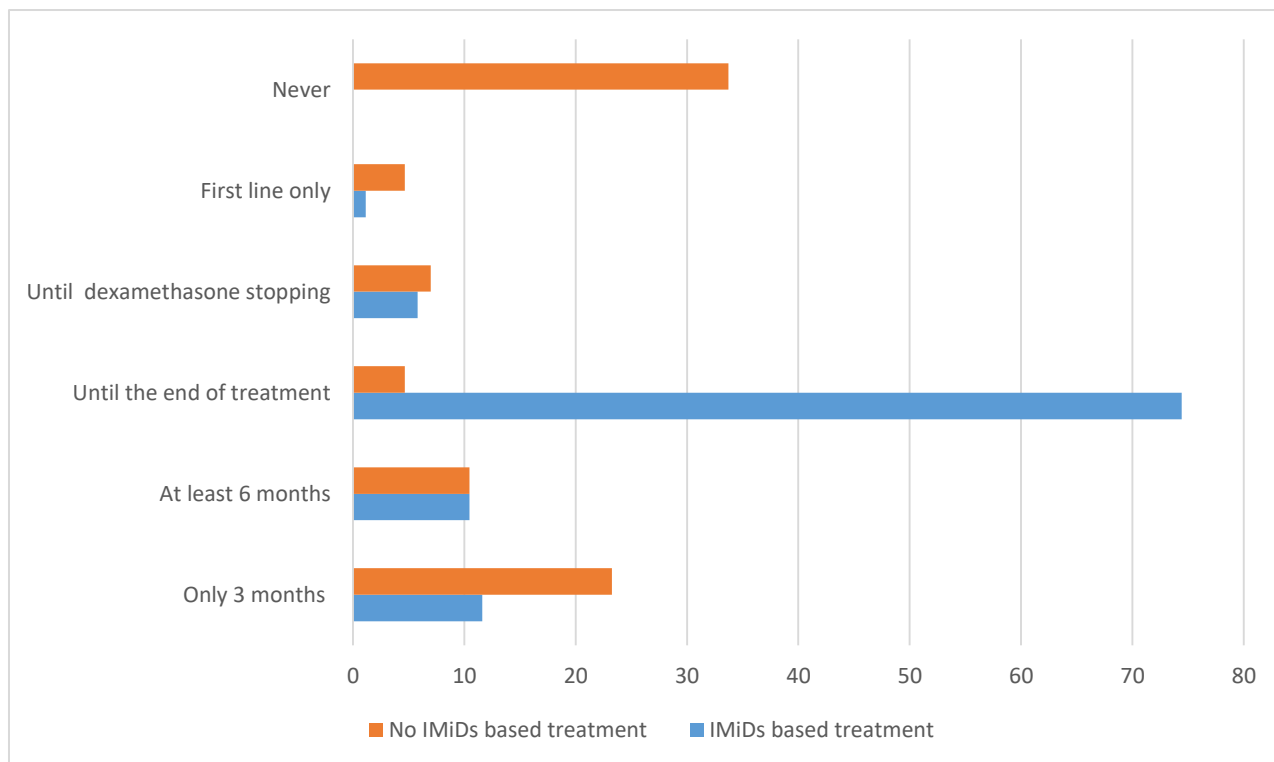
In conclusion, initiating a new treatment for MM patients is highly time-consuming for each physician in routine clinical practice. Choosing the best drug association and treatment duration for each patient, anticipating the side-effects, starting antibiotics prophylaxis and bone-related disease drugs, considering patient's preferences, and scheduling biological tests and hospitalizations, as well, are essential acts required by practitioners. Adding a holistic reflection on managing VTE thromboprophylaxis is clearly unnecessary, bearing the risks of underestimated and undertreated patients. These real-life adapted guidance recommendations (Figure 5) are built to help physicians adapt their daily care of MM patients in need of appropriate treatments. The most common context pertaining to IMiD-dexamethasone therapies consists in the initiation of anticoagulant prophylaxis with either LMWH or DOAC using prophylactic doses, provided that no comorbidities exist, including severe renal impairment, thrombocytopenia, or antiplatelet drug requirement. In less complicated situations, risk/benefit assessments are required to evaluate the VTE risk score using appropriate tools and an adapted anticoagulant strategy, such as decreasing doses or switching to other drugs.

Responses % (N=84)	
<b>Practice settings</b>	
University hospital	44% (37)
Regional public hospital	41.7% (35)
Hybrid public/private hospital	4.8% (4)
Others	9.5% (8)
<b>Practice experience</b>	
Professor	8.3% (7)
Hospital practitioner	83.3% (70)
Fellow in hematology	7.31% (7)
Medicine resident	1.1% (1)
<b>Age</b>	
Between 25 and 40 years	40.5% (34)
Between 41 and 55 years	35.7% (30)
Between 56 and 70 years	22.6% (19)
Over 70 years	1.2% (1)

**Table 1. Demographic data of the survey respondents**

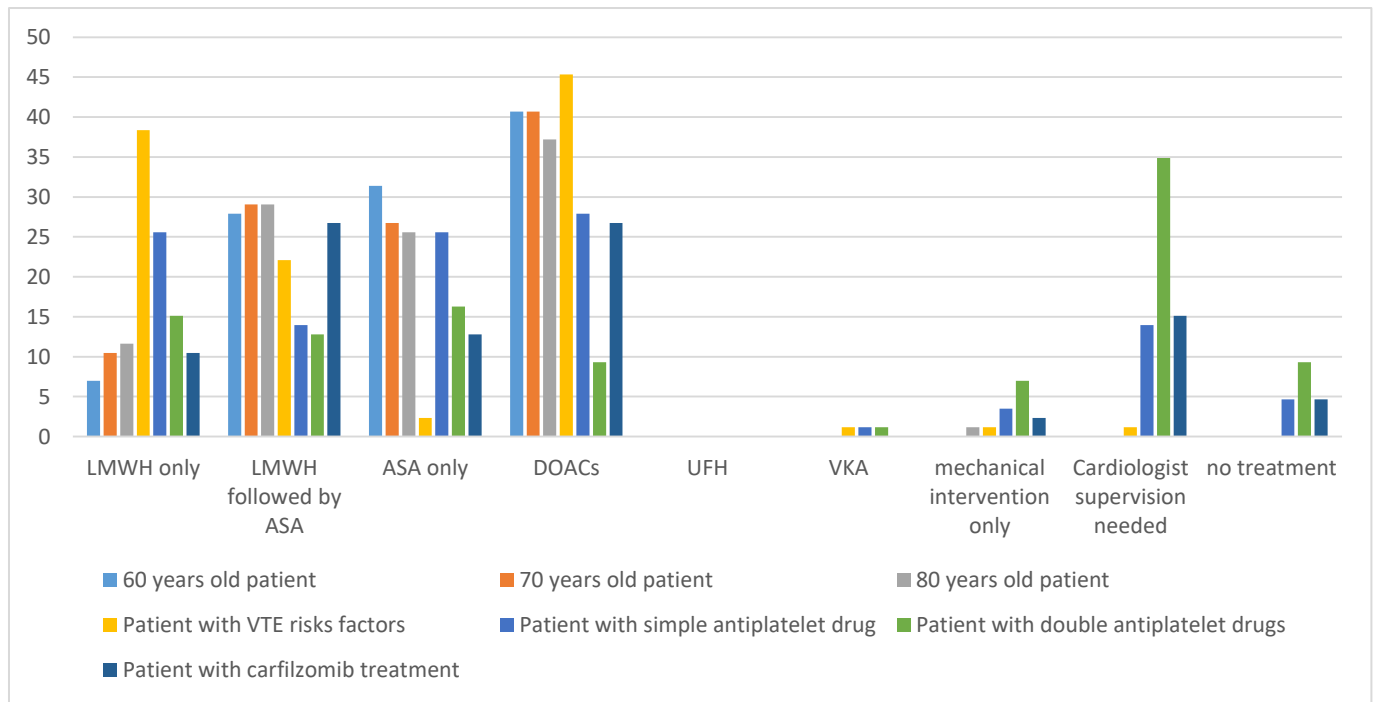
	Responses % (N=86)
<b><u>Do you consider thromboprophylaxis to be important in patient care?</u></b>	
Yes	98.8% (85)
No	1.2% (1)
<b><u>Do you manage the choice of treatment yourself or do you call upon a colleague specialized in vascular medicine or hemostasis?</u></b>	
Always by myself	17.4% (15)
Never by myself	19.8% (17)
Ask advice only if renal failure	16.3% (14)
Ask advice only if history of thromboembolic events	26.7% (23)
Ask advice only if history of severe hemorrhage	30.2% (26)
Ask advice only if patient has been already treated with an antiplatelet therapy	20.9% (18)
<b><u>How do you assess the benefit of implementing thromboprophylaxis in a multiple myeloma patient requiring specific treatments?</u></b>	
No interest	0% (0)
Only at times in first-line therapy	0% (0)
Whatever the line of treatment	70 % (61)
Whatever the class of treatment	12.8% (11)
Only in case of IMiDs-dexamethasone treatments	53.5% (46)
Without using any thromboembolism risk factor analysis	3.5% (3)
After using a thromboembolism risk factor analysis	62.8% (54)
<b><u>What do you consider relevant as evaluation criteria or tools for the analysis of venous thromboembolism risks?</u></b>	
Criteria related directly to the myeloma disease (hyperviscosity, high R-ISS score, high risk cytogenetics, etc.)	70.9% (61)
Criteria related to an adjuvant symptomatic treatment (EPO, G-CSF, etc.)	54.7% (47)
Criteria without any relation to myeloma disease (thrombophilia, obesity, history of thrombosis, etc.)	89.5% (77)
High-risk situations of thromboembolism (immobilization, surgery, infection, etc.)	90.7% (78)
Based on IMWG guidelines	15.1% (13)
Based on use of VTE risk models (Khorana, IMPEDE VTE, Palumbo score, etc.)	14% (12)
Based on complementary assessments (D-dimer dosing, systematic venous Doppler ultrasound, etc.)	3.5% (3)

**Table 2:** Analysis of usual consideration and practice before initiating thromboprophylaxis for MM patients. R-ISS=Revised multiple myeloma international staging system (R-ISS); EPO=Erythropoietin; G-CSF= Granulocyte-colony stimulating factor.



**Figure 1:** Management of thromboprophylaxis duration and indications with or without IMiD-based treatments (% of respondents)

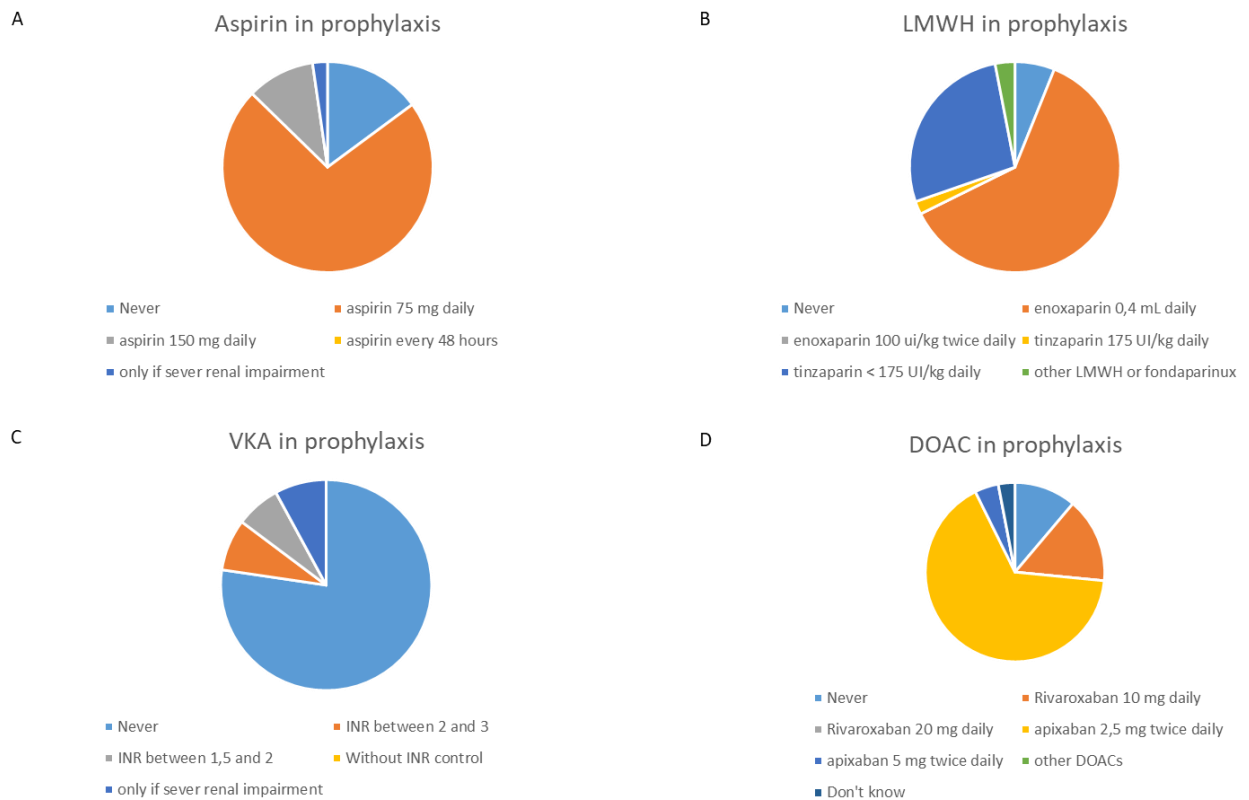
IMiDs= immunomodulatory drugs



**Figure 2:** Common clinical situations and thromboprophylaxis habits from survey participants (% of respondents).

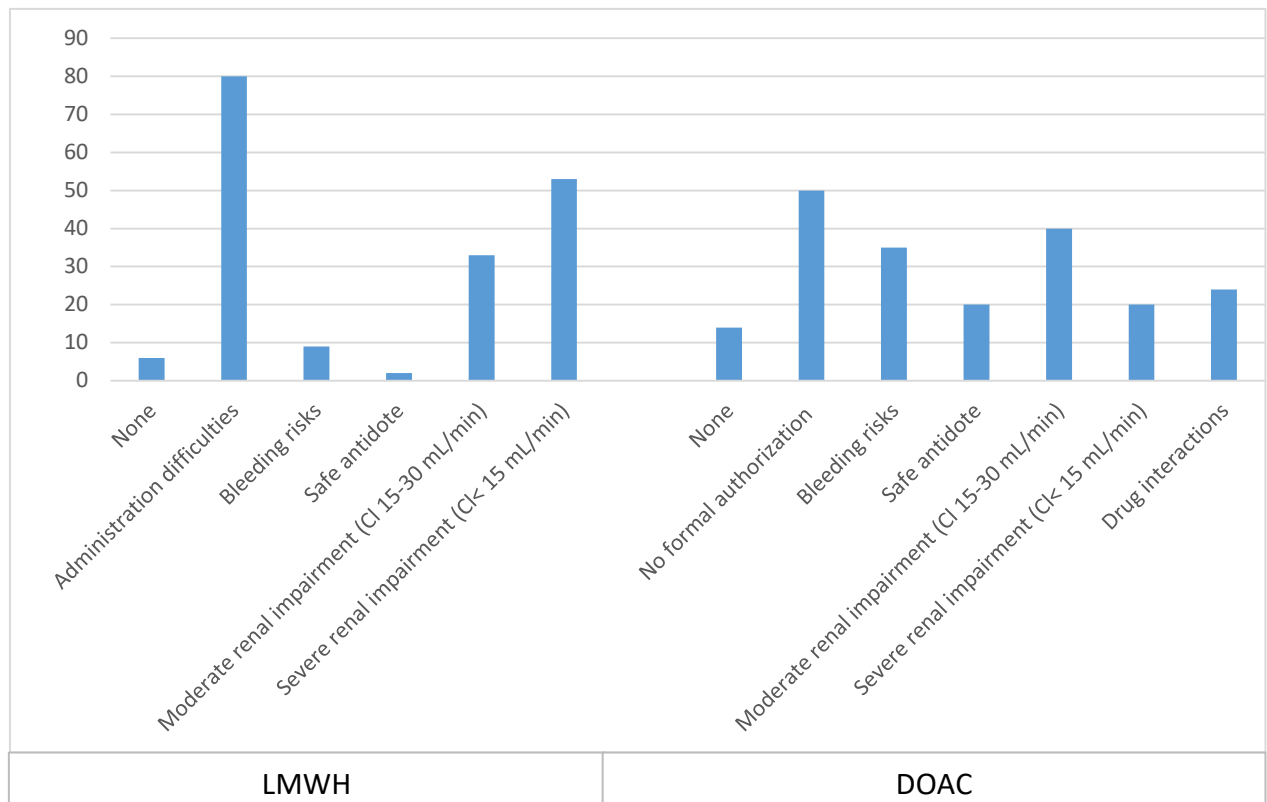
LMWH: Low-molecular-weight heparin; ASA: Aspirin; DOACs: Direct-acting oral anticoagulants; UFH: Unfractionated heparin; VKA: Vitamin K antagonist





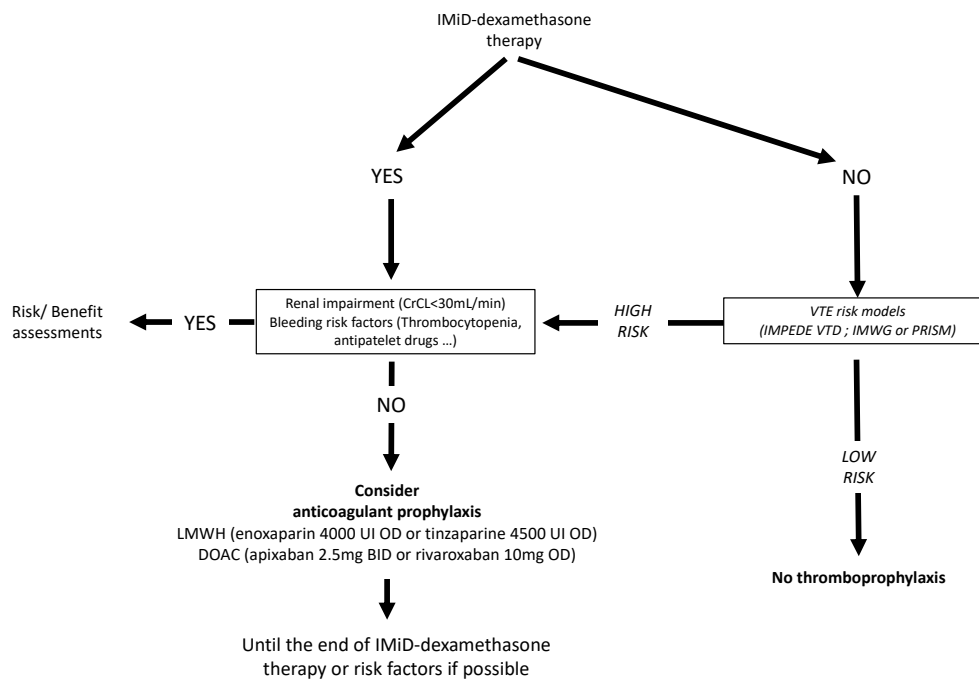
**Figure 3:** Doses and scheduled management of each mostly used thromboprophylaxis regimen in multiple myeloma patients by physician with aspirin (A), LMWH (B), VKA (C) and DOAC (D). (% of respondents)

LMWH: Low-molecular-weight heparin; ASA: Aspirin; DOACs: Direct-acting oral anticoagulants; UFH: Unfractionated heparin; VKA: Vitamin K antagonist



**Figure 4:** Limits and fears of LMWH or DOAC thromboprophylaxis for myeloma patients (% of respondents)

LMWH: Low-molecular weight heparin; DOACs: Direct-acting oral anticoagulants



**Figure 5:** Algorithm of thromboprophylaxis initiation for MM patients undergoing antimyeloma treatments. **The dosages of DOACs or LMWHs are based on empirical data due to the limited available evidence.**

LMWH: Low-molecular-weight heparin; VTE: venous thromboembolic events; DOACs: Direct-acting oral anticoagulants ; IMiD= immunomodulatory imide drug.

IMWG VTE risk assessment model†A2:E44		IMPEDE VTE risk assessment model		
Context of use : MM patients starting any therapy		Context of use : newly diagnosed MM starting any therapy		
Items	Score	Items	Score	
Obesity (BMI ≥30Kg/m <sup>2</sup> )	+1	I = Immunomodulatory drug	+4	
Previous VTE	+1	M = Body Mass index > 25 mg/m <sup>2</sup>	+1	
Central venous catheter or pacemaker	+1	P = Pelvic, hip or femur fracture	+4	
Cardiac disease	+1	E = Erythropoiesis-stimulating agent	+1	
Chronic renal disease	+1	D = Doxorubicin	+3	
Diabetes	+1	= Dexamethasone high dose		
Acute infection	+1	(> 160 mg/month)	+4	
Immobilization	+1	= Dexamethasone low dose		
Blood clotting disorders	+1	(≤ 160 mg/month)	+2	
Diagnosis of MM	+1	E = Ethnicity/race (Asian/Pacific)	-3	
Hyperviscosity	+1	V = History of VTE before MM	+5	
High-dose dexamethasone (≥480mg/month)	+1	T = Tunneled line/ central catheter	+2	
IMiD	+1	E = Existing thromboprophylaxis		
Doxorubicin	+1	therapeutic LMWH or VKA	-4	
Erythropoietin use	+1	= Existing thromboprophylaxis		
General surgery / trauma	+1	prophylactic LMWH or aspirin	-3	
Any anesthesia	+1			
<b>Risk stratification</b>		<b>Risk stratification</b>		<b>Thomboprophylaxis recommended</b>
Low risk	0	Low risk	≤3	None / aspirin
Intermediate risk	1	Intermediate risk	4 - 7	Aspirin / anticoagulant
High risk	> 1	High risk	>7	anticoagulant prophylactic/ curative

SAVED risk assessment model		PRISM risk assessment model		
Context of use : newly diagnosed MM started IMiD-containing therapy		Context of use : newly diagnosed MM starting any therapy		
Items	Score	Items	Score	
S = Surgery (within last 90 days)	+2	P = Prior history of VTE	+8	
A = Asian race	-3	R = Race (Black vs others)	+1	
V = VTE history	+3	I = IMiD use in induction therapy	+2	
E = Eighty (age >80 years)	+1	S = Surgery (within 90 d)	+1	
D = Dexamethasone		M = Abnormal Metaphase cytogenetics	+2	
Standard (≤160mg/cycle)	+1			
High (>160mg/cycle)	+2			
<b>Risk stratification</b>		<b>Risk stratification</b>		<b>Thomboprophylaxis recommended</b>
Low risk	≤1	Low risk	0	None / aspirin
Intermediate risk		Intermediate risk	1 to 6	Aspirin / anticoagulant
High risk	≥ 2	High risk	≥ 7	anticoagulant prophylactic/ curative

Table 3: IMWG, IMPEDE, SAVED VTE and PRISM risk assessment models with each item, stratification and thromboprophylaxis recommendation

## References:

1. Kristinsson SY, Fears TR, Gridley G, Turesson I, Mellqvist UH, Björkholm M, Landgren O. Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. *Blood*. 2008 Nov 1;112(9):3582-6. doi: 10.1182/blood-2008-04-151076. Epub 2008 Jun 17. PMID: 18559977; PMCID: PMC2572787.
2. Kristinsson SY, Pfeiffer RM, Björkholm M, Goldin LR, Schulman S, Blimark C, Mellqvist UH, Wahlin A, Turesson I, Landgren O. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. *Blood*. 2010 Jun 17;115(24):4991-8. doi: 10.1182/blood-2009-11-252072. Epub 2010 Mar 18. Erratum in: *Blood*. 2011 Apr 7;117(14):3938. PMID: 20299513; PMCID: PMC2890150.
3. Hicks LK, Haynes AE, Reece DE, Walker IR, Herst JA, Meyer RM, Imrie K; Hematology Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care. A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma. *Cancer Treat Rev*. 2008 Aug;34(5):442-52. doi: 10.1016/j.ctrv.2008.02.003. Epub 2008 Apr 1. PMID: 18381234.
4. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, Harousseau J, Zonder JA, Cavo M, Zangari M, Attal M, Belch A, Knop S, Joshua D, Sezer O, Ludwig H, Vesole D, Bladé J, Kyle R, Westin J, Weber D, Bringhen S, Niesvizky R, Waage A, von Lilienfeld-Toal M, Lonial S, Morgan GJ, Orłowski RZ, Shimizu K, Anderson KC, Boccadoro M, Durie BG, Sonneveld P, Hussein MA; International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008 Feb;22(2):414-23. doi: 10.1038/sj.leu.2405062. Epub 2007 Dec 20. PMID: 18094721.
5. Sborov DW, Baljevic M, Reeves B, Laubach J, Efebera YA, Rodriguez C, Costa LJ, Chari A, Silbermann R, Holstein SA, Anderson LD Jr, Kaufman JL, Shah N, Pei H, Patel S, Cortoos A, Bartlett JB, Vermeulen J, Lin TS, Voorhees PM, Richardson PG. Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma: Analysis of vascular thrombotic events in the GRIFFIN study. *Br J Haematol*. 2022 Nov;199(3):355-365. doi: 10.1111/bjh.18432. Epub 2022 Sep 16. PMID: 36111391.
6. Mai EK. Vascular thrombotic events in the era of modern myeloma therapy. *Br J Haematol*. 2022 Dec;199(5):642-644. doi: 10.1111/bjh.18452. Epub 2022 Sep 19. PMID: 36120817.
7. Chari A, Hajje D. Case series discussion of cardiac and vascular events following carfilzomib treatment: possible mechanism, screening, and monitoring. *BMC Cancer*. 2014 Dec 4;14:915. doi: 10.1186/1471-2407-14-915. PMID: 25471129; PMCID: PMC4289164.
8. Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Geyer SM, Kabat B, Zeldenrust SR, Kumar S, Greipp PR, Fonseca R, Lust JA, Russell SJ, Kyle RA, Witzig TE, Gertz MA. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005 Dec 15;106(13):4050-3. doi: 10.1182/blood-2005-07-2817. Epub 2005 Aug 23. PMID: 16118317; PMCID: PMC1895238.
9. Fouquet G, Tardy S, Demarquette H, Bonnet S, Gay J, Debarri H, Herbaux C, Guidez S, Michel J, Perrot A, Serrier C, Miljkovic D, Avet Loiseau H, Facon T, Hulin C, Leleu X. Efficacy and safety profile of long-term exposure to lenalidomide in patients with recurrent multiple myeloma. *Cancer*. 2013 Oct 15;119(20):3680-6. doi: 10.1002/cncr.28274. Epub 2013 Aug 6. PMID: 23921945.

10. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, San Miguel J, Hellmann A, Facon T, Foà R, Corso A, Masliak Z, Olesnyckyj M, Yu Z, Patin J, Zeldis JB, Knight RD; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007 Nov 22;357(21):2123-32. doi: 10.1056/NEJMoa070594. Erratum in: *N Engl J Med*. 2009 Jul 30;361(5):544. PMID: 18032762.
11. Leleu X. Thrombosis in myeloma treated with IMiDs. *Thromb Res*. 2012 Oct;130 Suppl 1:S63-5. doi: 10.1016/j.thromres.2012.08.279. PMID: 23026667.
12. Zonder JA, Crowley J, Hussein MA, Bolejack V, Moore DF Sr, Whittenberger BF, Abidi MH, Durie BG, Barlogie B. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). *Blood*. 2010 Dec 23;116(26):5838-41. doi: 10.1182/blood-2010-08-303487. Epub 2010 Sep 27. PMID: 20876454; PMCID: PMC3031379.
13. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, Abonour R, Siegel DS, Katz M, Greipp PR; Eastern Cooperative Oncology Group. 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 Jan;11(1):29-37. doi: 10.1016/S1470-2045(09)70284-0. Epub 2009 Oct 21. Erratum in: *Lancet Oncol*. 2010 Jan;11(1):14. PMID: 19853510; PMCID: PMC3042271.
14. Palumbo A, Palladino C. Venous and arterial thrombotic risks with thalidomide: evidence and practical guidance. *Ther Adv Drug Saf*. 2012 Oct;3(5):255-66. doi: 10.1177/2042098612452291. PMID: 25083240; PMCID: PMC4110867.
15. Richardson P, Jagannath S, Hussein M, Berenson J, Singhal S, Irwin D, Williams SF, Bensinger W, Badros AZ, Vescio R, Kenvin L, Yu Z, Olesnyckyj M, Zeldis J, Knight R, Anderson KC. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood*. 2009 Jul 23;114(4):772-8. doi: 10.1182/blood-2008-12-196238. Epub 2009 May 26. PMID: 19471019.
16. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, Cangialosi C, Grasso M, Rossini F, Galli M, Catalano L, Zamagni E, Petrucci MT, De Stefano V, Ceccarelli M, Ambrosini MT, Avonto I, Falco P, Ciccone G, Liberati AM, Musto P, Boccadoro M; Italian Multiple Myeloma Network, GIMEMA. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet*. 2006 Mar 11;367(9513):825-31. doi: 10.1016/S0140-6736(06)68338-4. PMID: 16530576.
17. Lonial S, Richardson PG, San Miguel J, Sonneveld P, Schuster MW, Bladé J, Cavenagh J, Rajkumar SV, Jakubowiak AJ, Esseltine DL, Anderson KC, Harousseau JL. Characterisation of haematological profiles and low risk of thromboembolic events with bortezomib in patients with relapsed multiple myeloma. *Br J Haematol*. 2008 Oct;143(2):222-9. doi: 10.1111/j.1365-2141.2008.07321.x. Epub 2008 Aug 18. PMID: 18713253.
18. Wang J, Park C, Arroyo-Suarez R. Venous thromboembolism in patients with multiple myeloma receiving daratumumab-based regimens: a post hoc analysis of phase 3 clinical trials. *Leuk Lymphoma*. 2021 Sep;62(9):2219-2226. doi: 10.1080/10428194.2021.1910687. Epub 2021 Apr 9. PMID: 33836624.
19. Moreau P, Stewart KA, Dimopoulos M, Siegel D, Facon T, Berenson J, Raje N, Berdeja JG, Orłowski RZ, Yang H, Ma H, Klippel Z, Zahlten-Kumeli A, Mezzi K, Iskander K, Mateos MV. Once-weekly (70 mg/m<sup>2</sup>) vs twice-weekly (56 mg/m<sup>2</sup>) dosing of carfilzomib in patients with relapsed or refractory multiple myeloma: A post hoc analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials. *Cancer Med*. 2020 May;9(9):2989-2996. doi: 10.1002/cam4.2945. Epub 2020 Feb 28. PMID: 32108443; PMCID: PMC7196059.

20. Piedra K, Peterson T, Tan C, Orozco J, Hultcrantz M, Hassoun H, Mailankody S, Lesokhin A, Shah U, Lu S, Patel D, Derkach A, Wilkins CR, Korde N. 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. *Br J Haematol.* 2022 Jan;196(1):105-109. doi: 10.1111/bjh.17772. Epub 2021 Aug 15. PMID: 34396516; PMCID: PMC9527668.
21. Charalampous C, Goel U, Kapoor P, Binder M, Buadi FK, Dingli D, Dispenzieri A, Fonder AL, Gertz MA, Gonsalves W, Hayman SR, Hobbs MA, Hwa YL, Kourelis T, Lacy MQ, Leung N, Lin Y, Warsame R, Kyle RA, Rajkumar SV, Kumar S. Thrombosis in multiple myeloma: Risk estimation by induction regimen and association with overall survival. *Am J Hematol.* 2023 Mar;98(3):413-420. doi: 10.1002/ajh.26806. Epub 2023 Jan 1. PMID: 36588396.
22. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008 May 15;111(10):4902-7. doi: 10.1182/blood-2007-10-116327. Epub 2008 Jan 23. PMID: 18216292; PMCID: PMC2384124.
23. Sanfilippo KM, Carson KR, Wang TF, Luo S, Edwin N, Kuderer N, Keller JM, Gage BF. Evaluation of the Khorana score for prediction of venous thromboembolism in patients with multiple myeloma. *Res Pract Thromb Haemost.* 2022 Jan 9;6(1):e12634. doi: 10.1002/rth2.12634. PMID: 35028491; PMCID: PMC8742966.\*
24. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, Landgren O, Hajek R, Einsele H, Anderson KC, Dimopoulos MA, Richardson PG, Cavo M, Spencer A, Stewart AK, Shimizu K, Lonial S, Sonneveld P, Durie BG, Moreau P, Orłowski RZ. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol.* 2014 Feb 20;32(6):587-600. doi: 10.1200/JCO.2013.48.7934. Epub 2014 Jan 13. PMID: 24419113; PMCID: PMC3918540.
25. Dima D, Li A, Granat LM, Dhillon P, Chamseddine F, Yalamanchali A, Mirzai S, Wei W, Samaras CJ, Valent J, Anwer F, Khouri J. External validation of the SAVED score for venous thromboembolism risk stratification in patients with multiple myeloma receiving immunomodulatory drugs. *Br J Haematol.* 2023 Jan 5. doi: 10.1111/bjh.18630. Epub ahead of print. PMID: 36604838.
26. Sanfilippo, K.M.; Luo, S.; Wang, T.F.; Fiala, M.; Schoen, M.; Wildes, T.M.; Mikhael, J.; Kuderer, N.M.; Calverley, D.C.; Keller, J.; et al. Predicting venous thromboembolism in multiple myeloma: Development and validation of the IMPEDE VTE score. *Am. J. Hematol.* 2019, 94, 1176–1184.
27. Chakraborty R, Rybicki L, Wei W, Valent J, Faiman BM, Samaras CJ, Anwer F, Khorana AA. Abnormal metaphase cytogenetics predicts venous thromboembolism in myeloma: derivation and validation of the PRISM score. *Blood.* 2022 Dec 8;140(23):2443-2450. doi: 10.1182/blood.2022015727. PMID: 35772005.
28. Chalayer E, Talbot A, Frenzel L, Karlin L, Collet P, Guyotat D, Attal M, Leleu X, Tardy B. Prediction of venous thromboembolism in patients with multiple myeloma treated with lenalidomide, bortezomib, dexamethasone, and transplantation: Lessons from the substudy of IFM/DFCI 2009 cohort. *J Thromb Haemost.* 2022 Aug;20(8):1859-1867. doi: 10.1111/jth.15758. Epub 2022 May 24. Erratum in: *J Thromb Haemost.* 2022 Oct;20(10):2446-2447. PMID: 35557490.
29. Parker K, Choudhuri S, Lewis P, Thachil J, Mitra S. UK prescribing practice of anticoagulants in patients with chronic kidney disease: a nephrology and haematology-based survey. *BMC*

- Nephrol. 2023 Jan 12;24(1):9. doi: 10.1186/s12882-022-03041-w. PMID: 36635661; PMCID: PMC9837988.
30. White BN, Van Berkel Patel M, Ware J, Cutshall T, Sakaan S, Sawyer AJ. A Description of Apixaban Dosing Patterns for Treatment or Prevention of Thrombotic Events in Hospitalized Patients on Dialysis. *Hosp Pharm*. 2023 Feb;58(1):49-56. doi: 10.1177/00185787221115311. Epub 2022 Sep 8. PMID: 36644745; PMCID: PMC9837318.
  31. Ifeanyi J, See S. A Review of the Safety and Efficacy of Apixaban in Patients With Severe Renal Impairment. *Sr Care Pharm*. 2023 Mar 1;38(3):86-94. doi: 10.4140/TCP.n.2023.86. PMID: 36803700.
  32. Adrianzen-Herrera D, Lutsey PL, Giorgio K, Walker RF, Zakai NA. Bleeding risk in patients with multiple myeloma treated for venous thromboembolism: a MarketScan analysis. *Res Pract Thromb Haemost*. 2022 Dec 23;7(1):100024. doi: 10.1016/j.rpth.2022.100024. PMID: 36873562; PMCID: PMC9982328.
  33. Zhou T, Gong Y, Li J, Wang Y, Wang X. Efficacy and safety of rivaroxaban plus clopidogrel versus aspirin plus clopidogrel in patients with coronary atherosclerotic heart disease and gastrointestinal disease undergoing percutaneous coronary intervention: study protocol for a non-inferiority randomized controlled trial. *Trials*. 2023 Mar 21;24(1):209. doi: 10.1186/s13063-023-07236-w. PMID: 36945020; PMCID: PMC10031942.
  34. Mhanna M, Beran A, Al-Abdouh A, Jabri A, Al-Aaraj A, Sajdeya O, Abuhelwa Z, Khokher W, Bhuta S, Burmeister CJ, Eltahawy EA. Single Versus Dual Antiplatelet Therapy following Left Atrial Appendage Occlusion in Patients With High Bleeding Risk. *Curr Probl Cardiol*. 2022 Sep;47(9):101269. doi: 10.1016/j.cpcardiol.2022.101269. Epub 2022 May 26. PMID: 35644502.
  35. Paoletti M, Azizi MA, Efthymiou A. Quel anticoagulant ou antiagrégant chez le patient oncologique présentant une thrombocytopénie ? [Which anticoagulant or antiplatelet treatment for cancer patients with thrombocytopenia ?]. *Rev Med Suisse*. 2023 Feb 8;19(813):281-285. French. doi: 10.53738/REVMED.2023.19.813.281. PMID: 36753345.
  36. Leader A, Gurevich-Shapiro A, Spectre G. Anticoagulant and antiplatelet treatment in cancer patients with thrombocytopenia. *Thromb Res*. 2020 Jul;191 Suppl 1:S68-S73. doi: 10.1016/S0049-3848(20)30400-X. PMID: 32736782.
  37. Kahale LA, Matar CF, Tsolakian I, Hakoum MB, Yosuco VE, Terrenato I, Sperati F, Barba M, Hicks LK, Schünemann H, Akl EA. Antithrombotic therapy for ambulatory patients with multiple myeloma receiving immunomodulatory agents. *Cochrane Database Syst Rev*. 2021 Sep 28;9(9):CD014739. doi: 10.1002/14651858.CD014739. PMID: 34582035; PMCID: PMC8477647.
  38. Leleu X, Rodon P, Hulin C, Daley L, Dauriac C, Hacini M, Decaux O, Eisemann JC, Fitoussi O, Lioure B, Voillat L, Slama B, Al Jijakli A, Benramdane R, Chaletteix C, Costello R, Thyss A, Mathiot C, Boyle E, Maloysel F, Stoppa AM, Kolb B, Michallet M, Lamblin A, Natta P, Facon T, Elalamy I, Femand JP, Moreau P. MELISSE, a large multicentric observational study to determine risk factors of venous thromboembolism in patients with multiple myeloma treated with immunomodulatory drugs. *Thromb Haemost*. 2013 Oct;110(4):844-51. doi: 10.1160/TH13-02-0140. Epub 2013 Aug 1. PMID: 23903204
  39. Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F, Rossi D, Gentilini F, Crippa C, Galli M, Nozzoli C, Ria R, Marasca R, Montefusco V, Baldini L, Elice F, Callea V, Pulini S, Carella AM, Zambello R, Benevolo G, Magarotto V, Tacchetti P, Pescosta N, Cellini C, Polloni C, Evangelista A, Caravita T, Morabito F, Offidani M, Tosi P, Boccadoro M. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with




- thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol*. 2011 Mar 10;29(8):986-93. doi: 10.1200/JCO.2010.31.6844. Epub 2011 Jan 31. PMID: 21282540.
40. Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, Cavalli M, Stanevsky A, Corradini P, Pezzatti S, Patriarca F, Cavo M, Peccatori J, Catalano L, Carella AM, Cafro AM, Siniscalchi A, Crippa C, Petrucci MT, Yehuda DB, Beggiato E, Di Toritto TC, Boccadoro M, Nagler A, Palumbo A. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. *Blood*. 2012 Jan 26;119(4):933-9; quiz 1093. doi: 10.1182/blood-2011-03-344333. Epub 2011 Aug 11. PMID: 21835953.
  41. Sayar Z, Gates C, Bristogiannis S, Patel A, Ogunbiyi MO, Tailor A, Yong K, Thomas M. Safety and efficacy of apixaban as thromboprophylaxis in myeloma patients receiving chemotherapy: A prospective cohort study. *Thromb Res*. 2022 May;213:27-29. doi: 10.1016/j.thromres.2022.03.001. Epub 2022 Mar 3. PMID: 35278887.
  42. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P; EINSTEIN CHOICE Investigators. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med*. 2017 Mar 30;376(13):1211-1222. doi: 10.1056/NEJMoa1700518. Epub 2017 Mar 18. PMID: 28316279.
  43. Christopoulou A, Ardavanis A, Papandreou C, Koumakis G, Papatsimpas G, Papakotoulas P, Tsoukalas N, Andreadis C, Samelis G, Papakostas P, Aravantinos G, Ziras N, Sougglari M, Kalofonos C, Samantas E, Makrantonakis P, Pentheroudakis G, Athanasiadis A, Stergiou H, Bokas A, Grivas A, Tripodaki ES, Varthalitis I, Timotheadou E, Boukovinas I. Prophylaxis of cancer-associated venous thromboembolism with low-molecular-weight heparin-tinzaparin: Real world evidence. *Oncol Lett*. 2022 Apr;23(4):115. doi: 10.3892/ol.2022.13235. Epub 2022 Feb 9. PMID: 35251346; PMCID: PMC8850961.
  44. Abu Saadeh F, Marchocki Z, O'Toole SA, Ibrahim N, Gleeson N, Norris LA. Extended thromboprophylaxis post gynaecological cancer surgery; the effect of weight adjusted and fixed dose LMWH (Tinzaparin). *Thromb Res*. 2021 Sep 7;207:25-32. doi: 10.1016/j.thromres.2021.08.027. Epub ahead of print. PMID: 34530386.
  45. Fotiou D, Dimopoulos MA, Kastritis E. Approach to Contemporary Risk Assessment, Prevention and Management of Thrombotic Complications in Multiple Myeloma. *Cancers (Basel)*. 2022 Dec 16;14(24):6216. doi: 10.3390/cancers14246216. PMID: 36551701; PMCID: PMC9777181.
  46. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M; Caravaggio Investigators. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med*. 2020 Apr 23;382(17):1599-1607. doi: 10.1056/NEJMoa1915103. Epub 2020 Mar 29. PMID: 32223112.
  47. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani CP, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane R, Bauer KA, Kuderer NM, Lyman GH; CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med*. 2019 Feb 21;380(8):720-728. doi: 10.1056/NEJMoa1814630. PMID: 30786186.
  48. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N Engl*

J Med. 2019 Feb 21;380(8):711-719. doi: 10.1056/NEJMoa1814468. Epub 2018 Dec 4. PMID: 30511879.

49. Storrar NPF, Mathur A, Johnson PRE, Roddie PH. Safety and efficacy of apixaban for routine thromboprophylaxis in myeloma patients treated with thalidomide- and lenalidomide-containing regimens. *Br J Haematol.* 2019 Apr;185(1):142-144. doi: 10.1111/bjh.15392. Epub 2018 May 22. PMID: 29785771.
50. Pegourie B, Karlin L, Benboubker L, Orsini-Piocelle F, Tiab M, Auger-Quittet S, Rodon P, Royer B, Leleu X, Bateau B, Cluquennois M, Fuzibet JG, Voog E, Belhadj-Merzoug K, Decaux O, Rey P, Slama B, Leyronnas C, Zarnitsky C, Boyle E, Bosson JL, Pernod G; IFM Group. Apixaban for the prevention of thromboembolism in immunomodulatory-treated myeloma patients: Myelaxat, a phase 2 pilot study. *Am J Hematol.* 2019 Jun;94(6):635-640. doi: 10.1002/ajh.25459. Epub 2019 Apr 1. PMID: 30859608.
51. Cornell RF, Goldhaber SZ, Engelhardt BG, Moslehi J, Jagasia M, Harrell S, Rubinstein SM, Hall R, Wyatt H, Piazza G. Primary prevention of venous thromboembolism with apixaban for multiple myeloma patients receiving immunomodulatory agents. *Br J Haematol.* 2020 Aug;190(4):555-561. doi: 10.1111/bjh.16653. Epub 2020 Apr 21. PMID: 32314352.
52. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, Arnulf B, Macro M, Belhadj K, Garderet L, Roussel M, Payen C, Mathiot C, Femand JP, Meuleman N, Rollet S, Maglio ME, Zeytoonjian AA, Weller EA, Munshi N, Anderson KC, Richardson PG, Facon T, Avet-Loiseau H, Harousseau JL, Moreau P; IFM 2009 Study. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med.* 2017 Apr 6;376(14):1311-1320. doi: 10.1056/NEJMoa1611750. PMID: 28379796; PMCID: PMC6201242.
53. Boyle EM, Leleu X, Petillon MO, Karlin L, Doyen C, Demarquette H, Royer B, Macro M, Moreau P, Fostier K, Marie-Lorraine C, Zarnitsky C, Perrot A, Herbaux C, Poulain S, Manier S, Beauvais D, Walker BA, Wardell CP, Vincent L, Frenzel L, Caillon H, Susanna S, Dejoie T, Avet-Loiseau H, Mohty M, Facon T; IFM2014-04 investigators. Daratumumab and dexamethasone is safe and effective for triple refractory myeloma patients: final results of the IFM 2014-04 (Etoile du Nord) trial. *Br J Haematol.* 2019 Nov;187(3):319-327. doi: 10.1111/bjh.16059. Epub 2019 Jun 19. PMID: 31218679.
54. Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, Raskob GE, Weitz JI; ANT-005 TKA Investigators. Abacimab for Prevention of Venous Thromboembolism. *N Engl J Med.* 2021 Aug 12;385(7):609-617. doi: 10.1056/NEJMoa2105872. Epub 2021 Jul 19. PMID: 34297496.
55. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol.* 2020 Feb 10;38(5):496-520. doi: 10.1200/JCO.19.01461. Epub 2019 Aug 5. PMID: 31381464.
56. De Stefano V, Larocca A, Carpenedo M, Cavo M, Di Raimondo F, Falanga A, Offidani M, Petrucci MT, Ruggeri M, Santi RM, Barosi G. Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an ad hoc expert panel. *Haematologica.* 2022 Nov 1;107(11):2536-2547. doi: 10.3324/haematol.2022.280893. PMID: 35861017; PMCID: PMC9614522.
57. Bradbury CA, Craig Z, Cook G, Pawlyn C, Cairns DA, Hockaday A, Paterson A, Jenner MW, Jones JR, Drayson MT, Owen RG, Kaiser MF, Gregory WM, Davies FE, Child JA, Morgan GJ, Jackson GH. Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials. *Blood.* 2020 Aug 27;136(9):1091-1104. doi:

10.1182/blood.2020005125. Erratum in: *Blood*. 2020 Oct 22;136(17):1994. PMID: 32438407; PMCID: PMC7453153.

58. Agnelli, G.; Gussoni, G.; Bianchini, C.; Verso, M.; Mandala, M.; Cavanna, L.; Barni, S.; Labianca, R.; Buzzi, F.; Scambia, G.; et al. Nadroparin for the Prevention of Thromboembolic Events in Ambulatory Patients with Metastatic or Locally Advanced Solid Cancer Receiving Chemotherapy: A Randomised, Placebo-Controlled, Double-Blind Study. *Lancet. Oncol.* 2009, 10, 943–949.



## **Declaration of interests**

All The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Highlights

1. Proposed guidance for thromboprophylaxis in MM.
2. VTE remains a significant issue in MM care.
3. Long-term LMWH use has notable side effects.
4. DOACs offer comfort, efficacy, but need studies.
5. Holistic VTE management approach is essential.