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Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an ad hoc expert panel.

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Contribution Author(s). VDS and AL contributed equally to the work as co-first authors Study concepts: VDS, AL, GB; Study design: VDS, AL, GB; Data acquisition: VDS, AL; Quality control of data and algorithms: GB; Data analysis and interpretation: VDS, AL, MoC, MiC, FDR, AF, MO, MTP, MR, RS GB; Manuscript preparation: VDS, AL, GB; Manuscript editing: VDS, AL, GB; Manuscript review: MoC, MiC, FDR, AF, MO, MTP, MR, RS. All authors approved the final version of the manuscript for submission.

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Abstract

The introduction of new therapeutic agents in multiple myeloma (MM), including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, has improved the outcomes of patients but, in parallel, has changed the frequency and epidemiology of thrombotic events. Now, thrombosis is a significant cause of morbidity and mortality in MM patients, and optimal thromboprophylaxis is far from being reached. Moving from the recognition that the above issue represents an unmet clinical need, an Expert Panel assessed the scientific literature and composed a framework of recommendations for improving thrombosis control in patients candidates for active treatment for MM. The Panel generated clinical key questions using the criterion of clinical relevance through a Delphi process. It explored four domains, i.e., thrombotic risk factors and risk stratification, primary thromboprophylaxis, management of acute thrombotic events, and secondary thromboprophylaxis. The issued recommendations may assist hematologists in minimizing the risk of thrombosis and guarantee adherence to treatment in patients with MM candidates to active treatment.

Key words

Antithrombotic prophylaxis; Immunomodulatory drugs; Multiple myeloma; Risk stratification; Thrombosis.

Introduction

Patients with multiple myeloma (MM) are at high risk of venous thromboembolism (VTE) whose incidence is more than 10% during the course of the disease.[1] After the introduction of new therapeutic agents, including proteasome inhibitors, immunomodulatory drugs (IMiDs) and monoclonal antibodies, thrombosis has become one of the major causes of morbidity and mortality. In particular, the IMiDs thalidomide and lenalidomide are well known to be associated with increased risk of thrombosis, especially when combined with high-dose steroids and other chemotherapy, with incidence approaching 26% in some studies.[2-4] In MM patients, VTE and arterial thrombosis are associated with a higher risk of death than patients without thrombosis.[5,6] Hence, the great strides in the indications and use of new treatments need parallel progress in the best approach to prophylaxis and supportive treatment for thrombosis. The International Myeloma Working Group (IMWG) and the American Society of Clinical Oncology published guidance on the prevention of IMiDs-associated thrombosis in MM.[7,8] These guidelines recommended that all patients should be risk assessed and offered aspirin or low molecular weight heparin (LMWH) thromboprophylaxis. However, in contrast with improvements in MM treatment, there has been little progress regarding VTE prevention, with a stable overall rate of events. A meta-analysis published in 2011 computed a rate of VTE in MM patients ranging from 3% to 12%, according to the drug employed or the phase of disease.[3] An analysis published in 2020 of patients enrolled in the phase III randomized controlled Myeloma XI trial, reported that in patients treated with IMiDs, the rate of venous thromboembolism (VTE) was still as high as 11.8%, despite 87.7% of the patients being on thromboprophylaxis at the time of thrombosis.[9] This highlights that the optimal thrombosis prevention strategy for patients with MM remains an unmet clinical need.

Many additional challenging problems complicate the choice of thromboprophylaxis in MM. It is not clear how well the guidelines are implemented in daily clinical practice, since most of the physicians tend to apply thromboprophylaxis based mostly on clinical experience.[10] A further problem is the definition of an effective and easy to use thrombosis risk stratification. Furthermore, emerging data suggest direct oral anticoagulants (DOACs) may be an option in MM thromboprophylaxis, but their use is a matter of uncertainty.[11]

In view of these considerations, a Panel of experts was convened to provide recommendations for the management of thrombotic risk in MM, with the intent of offering indications to minimize the thrombotic events, improving the quality of life and ensuring a

better adherence to treatment. The present publication represents a consensus document from email correspondence and a series of meetings held during 2020-2021.

Design and methods

Two chairmen (VDS and AL) appointed an Expert Panel (EP) of 8 members, selected for whom had previously published and/or expressed an interest in thrombotic complications in MM (hereafter called the Panel). A clinician with expertise in clinical epidemiology (GB) assured the methodological correctness of the process. During an initial meeting, the Panel agreed on the areas of major concern in the risk of thrombosis by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, i.e. impact on the management of patients and risk of inappropriateness, through a Delphi process.[12] The candidate key-questions that ranked highest formed the set of questions of the present document. During a second meeting, the Panel examined the current state of knowledge regarding thrombosis risk in MM. In the last phase of the project, each panelist drafted statements that addressed the preliminarily identified key questions. Subsequently, each panelist scored his agreement with the statements made by other panelists and provided suggestions for rephrasing. For exploiting this phase of the process, the EP was convened, and two consensus conferences were held. During the consensus meetings, participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote. If at least a ≥80% consensus on the statement was not achieved, the choices were discussed, and a second vote taken. If a ≥80% consensus was still not attained, the issue was declared undecidable, and no further attempt was made. It was determined that formal evidence grading could not be provided for individual recommendations due to a paucity of high grade evidence in this field.

Thrombo-hemorrhagic risk factors and risk stratification

Thrombogenicity in MM is multifactorial, due to a combination of patient-, disease-, and treatment-related factors. Patient-related factors include advanced age, history of VTE, comorbidities (such as heart failure, hypertension, liver, renal impairment, chronic obstructive pulmonary disorder, diabetes mellitus, chronic inflammatory bowel disease, autoimmune diseases, multiple sclerosis, neurological disease with limb paresis), immobility, central venous catheter, acute infection or hospitalization, blood clotting disorders, race (Caucasian is a risk factor), surgery, and hormone therapy.[1]

Genetic thrombophilia as a risk factor for thrombosis in MM has been investigated in two observational studies. In a series of 190 patients younger than 65 years and with newly diagnosed MM, genetic thrombophilic abnormalities were found in 5.3% of individuals, 3.2% carrying factor V Leiden (FVL) and 2.1% prothrombin gene (FIIG20210A) polymorphism, with an incidence similar to that found in the general Caucasian population. The relative risk for VTE associated with inherited thrombophilia resulted 2.25 (95% confidence interval (CI) 0.51-9.84) providing a small and not significant increase of risk in carriers versus non-carriers.[13] A series of 200 consecutive, unselected MM patients treated with lenalidomide-based regimens had a VTE incidence of 6%: none of them had common genetic variants that are associated with increased risk of VTE in the general population, such as FVL and FIIG20210A.[14]

Disease-related factors of thrombotic risk in MM include newly diagnosed disease, hyperviscosity, inhibition of natural anticoagulants and hypercoagulability induced by inflammatory cytokines, increased microparticle-associated tissue factor, elevated von Willebrand factor, fibrinogen, or factor VIII, and decreased protein S, acquired APC-resistance, hypofibrinolysis, increased PAI-1.[4]

Treatment-related factors represent the key ones for the thrombotic risk in MM: in particular, IMiDs (thalidomide, lenalidomide, pomalidomide) have been associated with the rise in VTE occurrence in the MM population. Thalidomide or lenalidomide monotherapy do not contribute significantly to the baseline VTE risk, reported to be around 3%-4%.[15-17] However, the risk increases up to 26% with the addition of dexamethasone or multiagent chemotherapy or anthracyclines.[18-26] Several studies demonstrated the incidence of VTE to be almost three times higher in lenalidomide and dexamethasone-treated patients than in those receiving dexamethasone alone.[18-23] Lenalidomide-related VTE was also influenced by the dose of dexamethasone: lenalidomide plus low-dose dexamethasone (<480 mg/month) had an incidence of VTE of 12% with respect to 26% of lenalidomide with high-dose dexamethasone (>480 mg/month).[18-23] The incidence of VTE of lenalidomide in combination with doxorubicin was 9% while with other forms of chemotherapy was 14%.[24-26]

Fewer data exist regarding the thrombogenic potential of pomalidomide. In a multicenter, open-label, randomized phase 2 study of pomalidomide with and without low-dose dexamethasone in patients with relapsed/refractory MM, the incidence of VTE was low (2%) with pomalidomide plus low-dose dexamethasone with respect to 3% with pomalidomide alone.[27] In a phase 2 multicenter, open-label study with pomalidomide-

dexamethasone in early refractory or resistant MM patients with del(17p) and/or t(4;14) only one pulmonary embolism was reported in 50 treated patients, knowing that use of a thromboprophylaxis was mandatory in this study.[28]

With older conventional therapies such as melphalan and prednisone, the incidence of VTE during frontline therapy was 1-2%.[29] In a meta-analysis comparing the efficacy of melphalan, prednisone, and thalidomide *versus* melphalan and prednisone, with five prospective randomized controlled trials (RCTs) identified, the odds ratio (OR) for VTE was 2.4 in favor of melphalan-prednisone.[30]

The first-generation proteasome inhibitor bortezomib was associated with a very low rate of VTE, as demonstrated by the randomized VISTA [31] and APEX trials [32,33], as well as preclinical studies.[34]

The risk of VTE seems not to be linked with monoclonal antibodies elotuzumab, daratumumab, belantamab, or proteasome inhibitor ixazomib[35-37], whilst VTE events have been reported in patients who received the proteasome inhibitor carfilzomib. In the ASPIRE trial, carfilzomib/lenalidomide/dexamethasone (KRD) had a VTE incidence of 13% while lenalidomide/dexamethasone (DR) had 6%.[38] In a retrospective study of 305 newly diagnosed MM patients, VTE rates in those treated with KRD or bortezomib, lenalidomide, and dexamethasone (RVD) were significantly different (16.1% vs. 4.8%), confirming a higher incidence of VTE when using KRD induction.[35]

As far as the role of the disease phase, a recent meta-analysis reported that the rate of VTE was comparable in trials of newly diagnosed and refractory/relapsed MM.[39] In phase III trials of lenalidomide maintenance, thromboembolic complications were reported more frequently in the lenalidomide group than in the placebo group (6% vs. 2%, P = 0.01).[40] In the Myeloma XI trial, within the maintenance phase, significantly more patients in the lenalidomide maintenance group than the observation group had a VTE (4.1% *vs* 0.6%, p <0.0001). Arterial events were also more frequent in those receiving lenalidomide maintenance than in those under observation (1.3% *vs* 0.3%, p=0.022).[9]

The importance of risk assessment models (RAMs) for the prediction of thrombosis in cancer patients is well established. The Khorana risk score based on site of cancer, hemoglobin <10 g/dL, use of erythropoietin stimulating agent, platelet count > 350 x 10^9/L, leukocyte count > 11 x 10^9/L, and body mass index (BMI) > 35 kg/m^2, accurately predicted cancer-associated thrombosis in non-hematological malignancies.[41]

Retrospective cohort analyses of newly diagnosed MM patients documented that the Khorana score is not predictive of VTE in MM patients. In a cohort of 2870 MM patients,

128 patients developed VTE within 6 months of MM diagnosis (4.4%). The Khorana score did not discriminate between patients who did and did not develop VTEs at 3 or 6 months.[42] In a recent study of 332 MM patients, thirty-two patients (9.6%) were diagnosed with VTE, 39% of them (9 of the 23 patients with available data) suffered VTE during their induction chemotherapy. When individual variables from the Khorana score were subjected to univariate and multivariate analysis, the white blood cell count was the only variable that retained predictive significance.[43].

Some MM-specific risk models have been published. In 2008, the International Myeloma Working Group (IMWG) developed an MM-specific RAM based on the presence of individual- disease and therapy-related risk factors (Table 1).[7]

In 2018, Swan et al[11] proposed an amended risk stratification starting from the IMWG model and proposed an additional group of very high risk patients (patients with a previous thrombosis, and those with antithrombin deficiency) and focusing on special patient populations such as patients with renal disease, recurrent thrombosis, spinal cord compression.

However, in the Myeloma XI trial the IMWG RAM did not predict efficiently the risk of thrombosis: before VTE, 54.7% had been assigned to the high-risk group and 45.3% to the low-risk group.[9] Two MM-specific RAMs were published in 2019.[44.45] Sanfilippo and coworkers published the IMPEDE-VTE risk clinical score based on data from the Veterans Administration Central Cancer Registry in 4446 patients.[44] The IMPEDE-VTE score included therapy with an IMiD, BMI, pathologic fractures, treatment with erythropoiesis-stimulating agents, dexamethasone or doxorubicin therapy, ethnicity, history of VTE, the presence of an indwelling tunnelled line and existing thromboprophylaxis (Table 2). Three risk groups were identified. The respective six-month cumulative incidence of VTE following treatment initiation was 3.3% for the low-risk group (scores $\leq$3), 8.3% for intermediate-risk group (score of 4–7), and 15.2% for the high-risk group ($\geq$8 score). The score was externally validated using the Surveillance, Epidemiology, End Results (SEER)–Medicare database and 4256 MM patients.[44]

A second group developed a RAM for MM patients who receive IMiD-based regimens using the SEER Medicare database to extract data retrospectively on 2397 patients with MM.[45] The data were subsequently validated using the Veterans registry. Five variables were included in the SAVED Score RAM (prior surgery, Asian race, VTE history, eighty years old, dexamethasone dose) (Table 3) . Patients were grouped into either low (score of 0-1) or high risk (score of $\geq$2) using this RAM, and the model stratified approximately

30% of patients in both the derivation and the validation cohorts as high-risk. The hazard ratios reported for high versus low VTE risk were 1.85 (P<0.01) and 1.98 (P<0.01) in the derivation and validation cohorts, respectively.

Recently 575 patients with newly diagnosed MM were included in an analysis to validate the IMPEDE score.[46] The 6-month cumulative incidence of VTE was 5.0% (95% CI: 2·1-7·9) in the low-risk group, compared to 12.6% (95% CI: 8.9-16.4%) and 24.1% (95% CI: 12.2-36.1) in the intermediate- and high-risk groups (P < 0·001 for both). In addition, a higher proportion of patients in the VTE cohort had ECOG performance status of ≥2 as compared to the no VTE cohort (33% *vs* 16%, P = 0.001).

From these findings IMPEDE score and SAVED score were recommended to be utilized as a VTE risk stratification tool.[47] Moreover, they should be employed in prospective studies looking into investigating VTE prophylaxis strategies in MM patients.

Recommendations

All MM patient candidate to an active anti-myeloma treatment need evaluation of the risk for thrombosis in order to appropriately prevent thromboembolic complications.
Patient, disease and treatment-related factors should be evaluated.
Patient-related factors include advanced age, personal and family history of VTE, obesity, immobility, central venous catheter, acute infection or hospitalization, comorbidities, race (caucasian is a risk factor), recent surgery, and ongoing hormone therapy.
There is no evidence to recommend universal laboratory testing for inherited thrombophilia. However, in the presence of a strong family history of venous thromboembolism (VTE), i.e. with one first-degree relative <50 years with 1 episode of VTE or 2 first-degree relatives with 1 episode of VTE, laboratory investigation for genetic thrombophilia should be considered, i.e. deficiency of antithrombin, protein C, protein S, factor V Leiden mutation, prothrombin G20210A mutation.
Disease-related factors include: active MM, evidence of hyperviscosity, pathologic fracture of the pelvis, femur or spine conditioning immobilization or requiring surgery.
Treatment-related factors include immunomodulatory drugs (IMiDs), especially in combination with high dose dexamethasone, multiagent chemotherapy, or exposure to erythropoietin stimulating agents (ESAs).
Even though risk assessment models (RAMs) like IMWG, IMPEDE, SAVED were validated for their use in clinical prospective studies, the Panel agreed there are no

sufficient data to recommend one specific RAM in the clinical practice. The Panel also recommended application of a RAM should be consistent in a single center for all the patients.
Besides the thrombotic risk, the bleeding risk assessment is recommended before starting anti-myeloma therapy. An accurate patient history should be collected and bleeding history investigated; PT, PTT, platelet count and fibrinogen, should be evaluated.
Patients with alterations of first-line diagnostic tests for bleeding predisposition, or with a history of bleeding should be carefully evaluated by second-line diagnostic tests in cooperation with an expert in coagulation.

Primary antithrombotic prophylaxis

Data about prophylaxis of thromboembolic events in MM patients are limited. In a recent systematic review of Cochrane Collaboration, four randomized controlled trials (RCTs) with 1042 participants were appraised.[48]

Two RCTs compared aspirin to LMWH at six months follow-up (Table 4). One RCT compared aspirin, fixed low-dose warfarin (1.25 mg/day), and LMWH (enoxaparin 40 mg/day) in 667 newly diagnosed MM patients who received thalidomide. This trial did not demonstrate a significant difference among the three agents as regards the composite primary end point including serious thromboembolic events, acute cardiovascular events, or sudden deaths- The rate of VTE was 4.5% in the aspirin group, 8.2% in the warfarin group, and 2.7% in the LMWH group.[49] In another RCT, aspirin 100 mg/d was compared with LMWH enoxaparin 40 mg/d in MM patients receiving lenalidomide-based induction regimens. The incidence of VTE was not significantly different with aspirin (2.2%) with respect to LMWH (1.2%). Pulmonary embolism was observed in 1.7% of patients in the aspirin group and none in the LMWH group.[50] However, in these trials, patients at very high risk (those with a previous history of arterial or venous thromboembolism) were excluded.

The pooled data did not confirm or exclude a beneficial or detrimental effect of aspirin relative to LMWH on symptomatic DVT (RR, 1.23, 95% CI, 0.49 to 3.08). Appraisal resulted in a very low-certainty evidence.[48]

Further evidence on the efficacy of the most commonly used thromboprophylactic agents in MM relies on non-randomized observational studies. In a systematic review of studies comparing aspirin versus other interventions in patients with MM, ten studies were included with 1,964 participants (1,257 treated with aspirin, 640 with LMWH and 67 with no

thromboprophylaxis).[51] Patients treated with aspirin had a significantly lower risk of VTE compared to no intervention (OR= 0.20; 95%CI: 0.07-0.61). The use of aspirin was associated with a higher VTE risk compared to LMWH in longitudinal studies (OR = 2.60; 95%CI: 1.08-6.25). However, the authors claimed data are insufficient to confirm superiority of LMWH over aspirin as thromboprophylaxis in MM patients.

In the prospective observational MELISSE study, VTE occurred in 7% on aspirin *vs* 3% on LMWH prophylaxis, and none on vitamin K antagonists (VKA) in IMiDs treated patients.[52]

Current thrombosis guidelines recommend primary VTE prophylaxis for patients with aspirin, warfarin or LMWH. The International Myeloma Working Group (IMWG) in 2008 recommended primary thromboprophylaxis for MM patients and specifically: aspirin for patients with ≤1 risk factor for VTE, LMWH (equivalent to enoxaparin 40 mg per day) for those with two or more individual/myeloma-related risk factors and for all patients receiving concurrent high-dose dexamethasone or doxorubicin (Table 1). Full-dose warfarin targeting a therapeutic INR of 2–3 is an alternative to LMWH.[7]

In 2015, the European Myeloma Network provided recommendations for the management of the most common complications of MM. It was recommended that patients who are due to start IMiD therapy should receive appropriate anticoagulation during the treatment duration. In these patients, aspirin (100 mg) is enough for VTE prophylaxis in low-risk patients (i.e. without risk factors, or only one myeloma/individual risk factor present), unless contraindicated. Otherwise, LMWH or full-dose warfarin has to be used. The use of LMWH has to be continued for at least four months and then patients may be switched to aspirin prophylaxis.[53]

The National Comprehensive Cancer Network (NCCN) guidelines, included guidance on the prevention of VTE in MM patients. The VTE prophylaxis recommendation for patients with ≤3 points by IMPEDE score or <2 points by SAVED score is aspirin at 81 to 325 mg once daily. For those with ≥4 points by IMPEDE score or ≥2 points by SAVED score, the recommendation is enoxaparin (40 mg/d subcutaneously), warfarin (target international normalized ratio, 2.0–3.0), fondaparinux (2.5 mg/d subcutaneously), or a DOAC, such as rivaroxaban at 10 mg/d orally or apixaban at 2.5 mg orally twice daily.[47] Thus, alternate thromboprophylaxis strategies for MM under consideration at present include the use of DOACs licensed for the treatment of cancer-associated thrombosis. They are inhibitors of clotting factors Xa or IIa, are administered orally, do not require blood monitoring at standard doses, and have fewer drug-drug interactions compared to warfarin.

Data are accumulating regarding the use of apixaban in primary VTE prevention in MM patients treated with IMiDs (Table 4).[54-57]

Four recent studies comprising 306 patients in total have evaluated VTE and bleeding rates with the use of apixaban at 2.5 mg twice daily for at least 6 months, with only two recorded VTE events (0.6%): an asymptomatic proximal deep vein thrombosis and a symptomatic distal DVT; in the latter case, apixaban was stopped 14 days before). The pooled data revealed three episodes of major haemorrhage (1%).[54-57] This bleeding frequency seems comparable to the frequency of bleeding reported in a population of 1605 MM patients and an incident VTE requiring treatment. The cumulative incidence of major bleeding was 4.8% in the warfarin group and 3.2% in the LMWH and DOACs groups. The incidence rate of bleeding was 25.7, 20.1, and 25.2 per 1,000 person-years for patients treated with warfarin, LMWH, and DOACs, respectively.[58]

A retrospective study of 305 newly diagnosed MM patients, revealed that the use of low-dose rivaroxaban thromboprophylaxis can mitigate the DVT risk without an observable increase in bleeding rates.[35]

Recommendations

All MM patents candidate to an active anti-myeloma treatment should be considered for thromboprophylaxis.
Type, intensity and duration of thromboprophylaxis should be tailored according to the baseline individualized thrombotic and hemorrhagic risk profile.
Severe thrombocytopenia (PLT < 20.000/mcl), active bleeding, congenital bleeding disorders (hemophilia, von Willebrand disease, severe deficiency of coagulation factors), and acquired coagulopathy that cannot be corrected (e.g. severe hepatic disease), are absolute contraindications to thromboprophylaxis.
Mild thrombocytopenia (PLT < 50.000/mcl), history of bleeding, acquired coagulopathy with chance of correction are relative contraindications to thromboprophylaxis.
To ensure an appropriate safe and effective thromboprophylaxis, avoid bleeding risk and potential thrombotic complication, it is recommended to consider the drug-drug interactions of antithrombotic agents and anti-myeloma drugs.
Patient's compliance and patient's preferences should be considered in the choice of thromboprophylaxis, and patients should be adequately informed about his/her thrombotic risk.
Patients at low-risk of thrombosis, i.e. those with an age lower than 75 years, a normal

mass body index, without fractures, central venous catheter, co-morbidites and without a planned therapy with IMIDs, should receive no thromboprophylaxis or thromboprophylaxis with low-dose aspirin. The criterion for the choice is the individual hemorrhagic risk.
All other patients should receive thromboprophylaxis with LMWH as first choice.
Patients without other risk factors for thrombosis except for a planned IMiDs-containing therapy and with contraindication or strong aversion to LMWH therapy, or with documented poor compliance to LMWH therapy, could use aspirin as thromboprophylaxis.
Preliminary data on the efficacy and safety of apixaban and rivaroxaban as primary thromboprophylaxis in patients receiving IMiDs are promising. However, there is no strong evidence in favor of DOACs instead of LMWH.
Off-label prescription of apixaban as primary antithrombotic prophylaxis in patients with contraindications to LMWH (e.g. for allergy) should be considered.
The duration of thromboprophylaxis should be modulated according to the length of anti-myeloma treatment and the evolving risk factors. Prophylaxis should continue as long as a thrombotic risk is present (e,g. active disease or assumption of drugs with a thrombotic risk).
Patients with relapsed MM should receive thromboprophylaxis during the treatment according to the indications recommended for newly diagnosed patients.
For patients under lenalidomide maintenance, thromboprophylaxis is indicated even if thromboembolic events are less frequent compared to newly diagnosed diseases. In these patients, prophylactic aspirin 100 mg is recommended.
In patients with renal insufficiency, the most appropriate prophylaxis should be chosen according to the grade of renal function. For patients with creatinine clearance below 30 mL/min, LMWH with dose adjustments is the preferred prophylaxis. LMWH dose adjustments according to creatinine clearance value are recommended (Table 5).
During antithrombotic prophylaxis, the platelet count should be monitored particularly for anti-myeloma therapeutic combinations that are at high risk of thrombocytopenia.
Thromboprophylaxis should be stopped when platelet count decrease to less than 20-30 x 10^9/L. Dose reductions should be applied when the platelet count is 30-50 x 10^9/L. Full-dose thromboprophylaxis can be used when the platelet count is over 50 x 10^9/L.
Primary thromboprophylaxis should be stopped in case of clinically relevant or major bleeding. In this circumstance, the cause of bleeding should be evaluated and eventually corrected to restart thromboprophylaxis.

Early treatment of acute thrombotic events, secondary antithrombotic prophylaxis, and re-exposure to anti-myeloma drug

Treatment of acute VTE in the setting of cancer is well established. LMWH has been the standard of care for treatment of acute VTE for many years and has more recently been slowly transitioning to DOACs as evidence suggests that these newer drugs can be safe and effective. DOACs (apixaban, edoxaban, rivaroxaban, and dabigatran), have emerged as the preferred treatment option for VTE in the general population.[59] Recently, factor Xa-inhibitors (xabans: edoxaban, apixaban, rivaroxaban) have been tested for the treatment and secondary prevention of VTE in patients with cancer head-to-head against LMWH in 4 studies.[60-63] A meta-analysis of such 4 trials, including 2894 cancer patients showed that xabans significantly reduced recurrent VTEs compared to LMWHs (5.2% vs. 8.2%; RR, 0.62 [95% CI, 0.43-0.91]), but were associated with a non-significant increase in major bleedings (4.3% vs. 3.3%; RR, 1.31 [95% CI, 0.83-2.08]) and a significant increase in clinically relevant non-major bleedings (10.4% vs 6.4%; RR, 1.65 [95% CI, 1.19-2.28]).[64] However, in such studies hematological malignancies accounted for no more than 10%.

Current thrombosis and oncology guidelines recommend treatment of VTE in cancer for 3 to 6 months or longer if cancer therapy is ongoing or malignancy remains present.[65] As in cancer therapy in general, for VTE occurring in the context of anti-MM therapy, patients should be on anticoagulants for at least 6 months provided there is no high bleeding risk. The choice of anticoagulant medication depends on patient renal function, ability to perform subcutaneous self-injection when using LMWH, and public or private funding for DOACs.

Recommendations

Patients with MM on secondary prophylaxis with long-term oral anticoagulation with VKA or DOAC, should continue during anti-myeloma therapy with their anticoagulation treatment.
Patients on anti-platelet therapy (single or double agents) because of previous arterial ischemic event, should continue the ongoing anti-platelet prophylaxis. They should add LMWH after a careful evaluation of risk-benefit ratio during the anti-myeloma treatment. LMWH should be considered until the MM disease burden remains high.
Patients with a history of provoked venous thromboembolism or of thrombosis of superficial veins not receiving oral anticoagulation, should receive a short-term

prophylactic LMWH (4-6 months) followed by aspirin 100 mg during anti-myeloma treatment .
Patients with a history of unprovoked venous thromboembolism not receiving oral anticoagulation and a normal renal function may be treated with LMWH or VKA or DOAC (apixaban). The choice should be based on pharmacological interactions and risk of bleeding.
In patients with a history of unprovoked venous thromboembolism having started LMWH or oral anticoagulation as thromboprophylaxis after diagnosis of MM, the decision of shifting to aspirin after 6 months or continuing oral anticoagulation during long-term treatment with IMIDs should be evaluated case-by-case.
In general, the treatment of acute thrombosis during active treatment for MM should not be different from the usual recommendations
Patients with non life-threatening venous thromboembolism during IMiDs anti-MM therapy should continue the therapy and receive long-term anticoagulation.
In the case of life-threatening venous thromboembolism or arterial thrombosis during treatment with IMiDs, a careful case-by-case evaluation should be assessed, considering the response of the MM disease to IMiDs, the severity of the thrombosis, and the patient's risk profile for future events.
In MM patients with acute VTE, the duration of anticoagulant treatment should be at least 6 months or indefinite in the case of ongoing treatment with IMIDs.
In active MM with a high burden of disease, patients should continue the anticoagulant treatment even after 6 months until response of the MM disease.
As regards the platelet count during secondary thromboprophylaxis, the same recommendations as for primary thromboprophylaxis should be followed.
In case of acute VTE and severe thrombocytopenia, the placement of a retrievable IVC filter is suggested until a safe anticoagulation is possible, and the IVC filter removed.
In patients with renal insufficiency (with or without ongoing dialysis) the most appropriate secondary antithrombotic prophylaxis after venous thromboembolism is adjusted dose LMWH or VKA.

Discussion

In this paper, relevant key questions for the MM-associated thrombosis were identified, and recommendations addressed by a Panel of experts in the field. Even though several scientific bodies have provided guidance on how to optimize thromboprophylaxis in MM

patients, the Panel highlighted high degree of uncertainty on answering the questions on the risk stratification and thromboprophylaxis in MM patients. Since existing scientific literature about thromboprophylaxis in MM does not allow evidence-based recommendations, the consensus was a critical part of the present recommendation production.

During the discussion for the production of the recommendations on thromboprophylaxis, the Panel highlighted that two issues on treatment-emergent thrombotic events in MM require further investigation. The definition of the level of risk for thrombosis, particularly that during IMiD therapy, is a critical determinant in the thromboprophylaxis in MM. Understanding the complex procoagulant profile of the MM patient has been recognized by the Panel as critical for a personalized risk stratification. To date, the understanding of the underlying reasons that lead to enhanced coagulation in the MM patient has not been delineated. It has been shown that serum levels of the anticoagulant cofactor thrombomodulin decrease in people treated with thalidomide.[66] Moreover, extremely high levels of von Willebrand factor antigen and factor VIII have been documented in people with MM receiving thalidomide, dexamethasone, and chemotherapy.[67] Most groups have reported abnormal thrombin generation in multiple parameters of the assay compared to healthy controls.[68,69] However, biomarkers that accurately reflect prothrombotic risk in these patients and can be combined with clinical factors to enhance risk stratification have not been identified. The Panel argued that the search for a useful biomarker is a prime objective in the research in MM through the exploration of the complex coagulation.

The results with xabans in MM are encouraging; however, no a definite recommendation of use has been provided. The Panel agreed that evidence on benefits and risks of xabans for prevention of VTE recurrence in patients with MM needs new knowledge to be acquired with a direct clinical experimentation. The major issue for clinical trials with DOACs in MM patients is trial feasibility. In the setting of MM the Panel agreed that a pragmatic pivotal randomized comparison of DOACs to the standard-treatment control could facilitate the trial feasibility.

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Individual risk factors
Obesity (BMI ≥ 30 kg/m^2)
Previous venous thromboembolism
Central venous catheter or pacemaker
Associated disease
Cardiac disease
Chronic renal disease
Diabetes
Acute infection
Immobilization
Blood clotting disorders
Surgery
General surgery
Any anesthesia
Trauma
Medications
Erythropoietin
Myeloma-related risk factors
Diagnosis
Hyperviscosity
Myeloma therapy
High-dose dexamethasone (≥ 480 mg per month)
Doxorubicin
Recommendations from IMWG: *If no risk factor or any one risk factor is present:* Aspirin 81–325 mg once daily *If two or more risk factors are present:* LMWH (enoxaparin 40 mg once daily) Full-dose warfarin (target INR 2–3)

Table 1

International Myeloma Working Group Risk Assessment Model (ref. 7).

Predictor	***Acronym***	**Score**
Immunomodulatory Drug	**I**	+ 4
Body **M**ass Index ≥ 25 kg/m^2	**M**	+ 1
Pelvic, Hip or Femur Fracture	**P**	+ 4
Erythropoiesis-Stimulating Agent	**E**	+ 1
Doxorubicin	**D**	+ 3
Dexamethasone		
High-Dose (> 160 mg monthly)		+ 4
Low-Dose (≤ 160 mg monthly)		+ 2
Ethnicity/Race = Asian/Pacific Islander	**E**	− 3
History of **V**enous Thromboembolism before MM	**V**	+ 5
Tunneled Line/Central Venous Catheter	**T**	+ 2
Existing Thromboprophylaxis: Therapeutic LMWH or Warfarin	**E**	- 4
Existing Thromboprophylaxis: Prophylactic LMWH or Aspirin		- 3

Table 2

IMPEDE Risk Assessment Model (ref. 45)

Predictor	***Acronym***	**Score**
Surgery (within 90 days)	**S**	+ 2
Asian race	**A**	- 3
History of **V**enous Thromboembolism	**V**	+ 3
Eigthy (age ≥ 80 years)	**E**	+ 1
Dexamethasone	**D**	
High-Dose (> 160 mg/cycle)		+ 2
Standard Dose (120-160 mg/cycle)		+ 1

Table 3

SAVED Risk Assessment Model (ref. 46)

Reference	*N pts.*	*State of disease*	*MM treatment*	*Drug*	*Follow-up*	*DVT and/or PE (%)*	*SVT (%)*	*MB %*	*Non-MB (%)*
Palumbo et al, 2011[49] (RCT)	220	New diagnosis	Thal	ASA 100 mg od	6 months	10 (4.5%) [1 ATE, 0.4]	n.r.	3 (1.3%)	6 (2.7%)
	219	New diagnosis	Thal	Enoxaparin 40 mg od	6 months	6 (2.7%) [3 ATE, 1.4%]	n.r.	0	3 (1.4%)
	220	New diagnosis	Thal	Warfarin 1.25 mg od	6 months	18 (8.2%)	n.r.	0	1 (0.5%)
Larocca et al, 2012[50] (RCT)	176	New diagnosis	Lena	ASA 100 mg od	6 months	4 (2.2%)	4 (2.2%)	0	0
	166	New diagnosis	Lena	Enoxaparin 40 mg od	6 months	2 (1.2%)	0	0	1 (0.6%)
Storrar et al, 2019[54]	70	New diagnosis [prev. PE in 2]	Thal (78.5%) Lena (21.5%)	Apixaban 2.5 mg bid	6 months	0 [2 ATE, 2.8%]	0	1 (1.4%)	0
Pegourie et al, 2019[55]	104	Relapse (89.4%) [prev. VTE in 15]	Thal or Lena	Apixaban 2.5 mg bid	6 months	2 (1.9%)	0	1 (0.9%)	10 (9%)
Cornell et al, 2020[56]	50	All stages (relapse 18%)	Lena (58%) Poma (42%)	Apixaban 2.5 mg bid	6 months	0	0	0	3 (6%)
Piedra et al, 2021[35]	124	New diagnosis	Lena (RVD)	ASA 81 mg od	3 months	6 (4.8%)	n.r.	0	1 (0.8%)
	99	New diagnosis	Lena (KRD)	ASA 81 mg od	3 months	16 (16.1%)	n.r.	0	5 (5%)
	82	New diagnosis	Lena (KRD)	Rivaroxaban 10 mg od	3 months	4 (4.8%)	n.r.	0	1 (1.2%)
Sayar et al, 2022[57]	98	Relapse (81%)	IMIDs	ASA 75 mg od	n.r.	4 (4%)	0	1 (1%)	4 (4%)
	82			Apixaban 2.5 mg bid	n.r.	0	0	1 (1.2)	7 (8.5%)

Table 4

Primary antithrombotic prophylaxis in multiple myeloma: results of two randomized clinical trials [50,51] and of studies addressing the use of apixaban or rivaroxaban [35,55-58]

ATE: arterial thrombotic event; DVT: deep vein thrombosis; MB: major bleeding; PE: pulmonary embolism; SVT: superficial vein thrombosis; IMIDs: immunomodulatory drugs (Thal or Lena or Poma); Thal: thalidomide; Lena: lenalidomide; Poma: pomalidomide; RVD: Lenalidomide, Bortezomib, Dexamethasone; KRD: Lenalidomide, Carfilzomib, Dexamethasone; n.r.: not reported

LMWH
≥30 mL/min: no dose adjustments
<30 mL/min: dose reduction from 25-30%
Dialysis: 50% dose reduction
Fondaparinux
<20 mL/min: not recommended the use
20-50 mL/min: 1.5 mg/day
> 50 mL/min: no dose adjustments

Table 5

Dose adjustments of low-molecular weigth heparin and fondaparinux in renal insufficiency