GUIDELINE ARTICLE

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

Valerio De Stefano,[1*] Alessandra Larocca,[2*] Monica Carpenedo,[3] Michele Cavo,[4] Francesco Di Raimondo,[5] Anna Falanga,[6,7] Massimo Offidani,[8] Maria Teresa Petrucci,[9] Marco Ruggeri,[10] Roberto Mario Santi[11] and Giovanni Barosi[12]

[1]Section of Hematology, Department of Radiological and Hematological Sciences, Catholic University, Fondazione Policlinico "A. Gemelli" IRCCS, Rome; [2]SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino; [3]Hematology and Transplant Unit, ASST Ospedale San Gerardo di Monza, Monza; [4]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università degli Studi, Bologna; [5]Section of Hematology, Department of General Surgery and Medical Specialties, University of Catania, and Division of Hematology, Policlinico "Rodolico", Catania; [6]Department of Medicine and Surgery, University of Milan Bicocca, Milan; [7]Department of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo; [8]Clinica di Ematologia Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona, Ancona; [9]Hematology, Azienda Policlinico Umberto I, Sapienza University, Rome; [10]Hematology Department, San Bortolo Hospital, Vicenza; [11]SSD Thrombosis and Hemostasis Center, Azienda Ospedaliera "SS Antonio e Biagio e C. Arrigo", Alessandria and [12]Center for the Study of Myelofibrosis, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

*VDS and AL contributed equally to this work as co-first authors.

Correspondence: V. De Stefano
valerio.destefano@unicatt.it

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Abstract

The introduction of new therapeutic agents for 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. Thrombosis is now 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 who are candidates for active treatment for MM. The panel generated key clinical 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 recommendations issued may assist hematologists in minimizing the risk of thrombosis and guarantee adherence to treatment in patients with MM who are candidates for active treatment.

Introduction

Patients with multiple myeloma (MM) are at high risk of venous thromboembolism (VTE). The incidence of VTE has been estimated to be more than 10% during the course of the disease.[1] Since the introduction of new therapeutic agents, including proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies, thrombosis has become one of the major causes of morbidity and mortality. In particular, the immunomodulatory drugs 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 the incidence of thrombosis approaching 26% in some studies.[2-4] In MM patients, VTE and arterial thrombosis are associated with a higher risk of death than that in patients without thrombosis.[5,6] Hence, the great strides in the indications for and use of new treatments need

parallel progresses 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 immunomodulatory drug-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 and 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 immunomodulatory drugs, the rate of 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 strategy for preventing thrombosis in 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 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 that direct oral anticoagulants (DOAC) 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 thrombotic events, thereby improving 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 of eight members, selected from among individuals who had previously published and/or expressed an interest in thrombotic complications in MM. A clinician with expertise in clinical epidemiology (GB) ensured the methodological correctness of the process. During an initial meeting, the panel of experts agreed on the areas of major concern in the risk of thrombosis by generating and rank-ordering key clinical questions using the criterion of clinical relevance, that is, 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 considered in 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. To exploit this phase of the process, the expert panel was convened, and two consensus conferences were held. During the consensus meetings, participants were first asked to comment in a 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.

Results

Thrombo-hemorrhagic risk factors and risk stratification (Box 1)

Thrombogenicity in MM is multifactorial, being the result of a combination of patient-, disease-, and treatment-related factors. Patient-related factors include advanced age, a 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, and neurological disease with limb paresis), immobility, presence of a central venous catheter, acute infection, hospitalization, blood clotting disorders, race (being 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 with newly diagnosed MM, genetic thrombophilic abnormalities were found in 5.3% of individuals, 3.2% carrying factor V Leiden (FVL) and 2.1% a prothrombin gene polymorphism (FII G20210A), with an incidence similar to that found in the general Caucasian population. The relative risk for VTE associated with inherited thrombophilia was 2.25 (95% confidence interval [95% 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 an increased risk of VTE in the general population, such as FVL and FII G20210A.[14]

Disease-related factors associated with a risk of thrombosis in MM include newly diagnosed disease, hyperviscosity, inhibition of natural anticoagulants and hypercoagulability induced by inflammatory cytokines, increased microparticle-associated tissue factor, elevated levels of von Willebrand factor, fibrinogen, or factor VIII, decreased protein S, acquired activated protein C resistance, hypofibrinolysis, and increased plasminogen activator inhibitor-1.[4]

Treatment-related factors are key components of the thrombotic risk in MM: immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), in particular, have been associated with the rise in VTE occurrence in the MM population. Thalidomide or lenalidomide monotherapy does 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 that the incidence of VTE is almost three times higher in patients being treated with lenalidomide and dexamethasone than in those receiving dexamethasone alone.[18-23] Lenalidomide-related VTE was also influenced by the dose of dexamethasone: the incidence of VTE in patients treated with lenalidomide plus low-dose dexamethasone (<480 mg/month) was 12%, whereas it was 26% in those treated with lenalidomide plus high-dose dexamethasone (>480 mg/month).[18-23] In other studies, the incidence of VTE among patients treated with lenalidomide in combination with doxorubicin was 9% while it was 14% among patients treated with other forms of chemotherapy.[24-26]

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

There does not seem to a risk of VTE linked to the use of the monoclonal antibodies elotuzumab, daratumumab, and belantamab, or the proteasome inhibitor ixazomib,[1,35,36] while VTE events have been reported in patients who received the proteasome inhibitor carfilzomib. In the ASPIRE trial, the incidence of VTE in the patients treated with carfilzomib, lenalidomide and dexamethasone was 13%, whereas the incidence in those treated only with lenalidomide and dexamethasone was 6%.[37] In a retrospective study of 223 newly diagnosed MM patients receiving aspirin thromboprophylaxis, VTE rates in those treated with carfilzomib, lenalidomide and dexamethasone or bortezomib, lenalidomide, and dexamethasone were significantly different (16.1% *vs*. 4.8%), confirming a higher incidence of VTE when using carfilzomib, lenalidomide and dexamethasone induction.[38]

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 reportedly more frequent in the lenalidomide group than in the placebo group (6% *vs*. 2%, P=0.01).[40] Within the maintenance phase of the Myeloma XI trial significantly more patients in the lenalidomide maintenance group than in 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 for the prediction of thrombosis in cancer patients is well established. The Khorana risk score, based on the site of the cancer, hemoglobin <10 g/dL, use of an erythropoietin-stimulating agent, platelet count >350x10^9/L, leukocyte count >11x10^9/L, and body mass index >35 kg/m^2, accurately predicted cancer-associated thrombosis in non-hematologic 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 2,870 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 VTE at 3 or 6 months.[42] In a recent study of 332 MM patients, 32 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 analyses, 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 IMWG developed an MM-specific risk assess-

ment model 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 focused on special patient populations such as patients with renal disease, recurrent thrombosis, and spinal cord compression. However, in the Myeloma XI trial the IMWG risk assessment model did not predict the risk of thrombosis efficiently: before VTE, 54.7% had been assigned to the high-risk group and 45.3% to the low-risk group.[9]

Two MM-specific risk assessment models were published in 2019.[44,45] Sanfilippo and coworkers published the IMPEDE-VTE clinical risk score based on data from 4,446 patients in the Veterans Administration Central Cancer Registry.[44] The IMPEDE-VTE score included therapy with an immunomodulatory drug, body mass index, pathological fractures, treatment with an erythropoiesis-stimulating agent, dexamethasone or doxorubicin therapy, ethnicity, history of VTE, the presence of an indwelling tunneled line and existing thromboprophylaxis (Table 2). Three risk groups were identified. The 6-month cumulative incidence of VTE following treatment initiation was 3.3% for the low-risk group (scores ≤3), 8.3% for the intermediate-risk group (scores of 4-7), and 15.2% for the high-risk group (scores ≥8). The score was externally validated using the Surveillance, Epidemiology, End Results (SEER) Medicare database and 4,256 MM patients.[44]

A second group developed the SAVED risk assessment model for MM patients who receive immunomodulatory drug-based regimens using the SEER Medicare database to extract data retrospectively on 2,397 patients with MM.[45] The data were subsequently validated using the Veterans registry. Five variables were included in the SAVED score risk assessment model (prior surgery, Asian race, VTE history, age ≥80 years old, and dexamethasone dose) (Table 3). Patients were grouped into either low risk (score of 0-1) or high risk (score of ≥2) using this risk assessment model, 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:

Table 1. International Myeloma Working Group risk assessment model.[7]

Individual risk factors
Obesity (BMI ≥30 kg/m²)
Previous venous thromboembolism
Central venous catheter or pacemaker
Associated diseases
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/month)
Doxorubicin
Recommendations from the 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)

BMI: body mass index; IMWG: International Myeloma Working Group; LMWH: low molecular weight heparin; INR: International Normalized Ratio.

Table 2. IMPEDE VTE risk assessment model.[45]

Predictor	Acronym	Score
Immunomodulatory drug	**I**	+ 4
Body **M**ass Index ≥ 25 kg/m²	**M**	+ 1
Pelvic, hip or femur fracture	**P**	+ 4
Erythropoiesis-stimulating agent	**E**	+ 1
Doxorubicin	**D**	+ 3
Dexamethasone		
High-dose (>160 mg/month)		+ 4
Low-dose (≤160 mg/month)		+ 2
Ethnicity/race = Asian/Pacific Islander	**E**	– 3
History of **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

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

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 an Eastern Cooperative Oncology Group performance status of ≥2 as compared to the cohort without VTE (33% *vs*. 16%, P=0.001).

From these findings the 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 investigating VTE prophylaxis strategies in MM patients.

Primary antithrombotic prophylaxis (Box 2)

Data about prophylaxis of thromboembolic events in MM patients are limited. In a recent systematic review by the Cochrane Collaboration, four randomized controlled trials with 1,042 participants were appraised.[48]

Two of these trials compared aspirin to LMWH at 6 months of follow-up (Table 4). One 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 with regard to the composite primary endpoint 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 randomized controlled trial, aspirin 100 mg/day was compared to the LMWH enoxaparin 40 mg/day in MM patients receiving lenalidomide-based induction regimens. The incidence of VTE was not significantly different with aspirin (2.2%) with respect to the 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 symp-

Table 3. SAVED risk assessment model.[46]

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

Box 1. Recommendations regarding thrombo-hemorrhagic risk factors and risk stratification in patients with multiple myeloma.

- *All patients with multiple myeloma who are candidates for active anti-myeloma treatment need evaluation for risk of thrombosis in order to prevent thromboembolic complications appropriately.*
- *Patient-, disease- and treatment-related factors should be evaluated.*
- *Patient-related factors include advanced age, personal and family history of venous thromboembolism, obesity, immobility, central venous catheter, acute infection or hospitalization, comorbidities, race (being 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, i.e. with one first-degree relative <50 years with one episode of venous thromboembolism or two first-degree relatives with one episode of venous thromboembolism, 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 multiple myeloma, evidence of hyperviscosity, pathological fracture of the pelvis, femur or spine conditioning immobilization or requiring surgery.*
- *Treatment-related factors include immunomodulatory drugs, especially in combination with high-dose dexamethasone, multiagent chemotherapy, or exposure to erythropoietin-stimulating agents.*
- *Even though risk assessment models such as the International Myeloma Working Group model and the IMPEDE and SAVED scores were validated for use in clinical prospective studies, the panel of experts agreed that there are not sufficient data to recommend one specific risk assessment model in clinical practice. The panel recommended that application of a risk assessment model should be consistent in a single center for all the patients.*
- *Besides thrombotic risk, it is recommended that bleeding risk is also assessed before anti-myeloma therapy is started. An accurate history should be collected from the patient and bleeding history investigated; prothrombin time, partial thromboplastin time, platelet count and fibrinogen level should be evaluated.*
- *Patients with alterations of first-line diagnostic tests indicative of a bleeding predisposition, or with a history of bleeding should be carefully evaluated by second-line diagnostic tests in cooperation with an expert in coagulation.*

Table 4. Primary antithrombotic prophylaxis in multiple myeloma: results of two randomized clinical trials[49,50] and of studies addressing the use of apixaban or rivaroxaban.[38,54-57]

Reference	N of pts	State of disease	MM treatment	Drug	Follow-up, months	DVT and/or PE, N (%)	SVT, N (%)	MB, N (%)	Non-MB, N (%)
Palumbo *et al.*, 2011[49] (RCT)	220	New diagnosis	Thal	ASA 100 mg od	6	10 (4.5) [ATE, 1 (0.4)]	NR	3 (1.3)	6 (2.7)
	219	New diagnosis	Thal	Enoxaparin 40 mg od	6	6 (2.7) [ATE 3, (1.4)]	NR	0	3 (1.4)
	220	New diagnosis	Thal	Warfarin 1.25 mg od	6	18 (8.2)	NR	0	1 (0.5)
Larocca *et al.*, 2012[50] (RCT)	176	New diagnosis	Lena	ASA 100 mg od	6	4 (2.2)	4 (2.2)	0	0
	166	New diagnosis	Lena	Enoxaparin 40 mg od	6	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	0 [ATE 2, (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	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	0	0	0	3 (6)
Piedra *et al.*, 2021[38]	124	New diagnosis	Lena (RVD)	ASA 81 mg od	3	6 (4.8)	NR	0	1 (0.8)
	99	New diagnosis	Lena (KRD)	ASA 81 mg od	3	16 (16.1)	NR	0	5 (5)
	82	New diagnosis	Lena (KRD)	Rivaroxaban 10 mg od	3	4 (4.8)	NR	0	1 (1.2)
Sayar *et al.*, 2022[57]	98	Relapse (81%)	IMID	ASA 75 mg od	NR	4 (4)	0	1 (1)	4 (4)
	82			Apixaban 2.5 mg bid	NR	0	0	1 (1.2)	7 (8.5)

MM: multiple myeloma; DVT: deep vein thrombosis; PE: pulmonary embolism; SVT: superficial vein thrombosis; MB: major bleeding; RCT: randomized controlled trial; ATE: arterial thrombotic event; ASA: aspirin; Thal: thalidomide; Lena: lenalidomide; Poma: pomalidomide; IMID: immunomodulatory drugs (thalidomide, lenalidomide or pomalidomide); RVD: lenalidomide, bortezomib, dexamethasone; KRD: lenalidomide, carfilzomib, dexamethasone; od: once daily; bid: twice daily; NR: not reported.

tomatic deep vein thrombosis (relative risk, 1.23; 95% CI: 0.49-3.08). The appraisal resulted in 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 those who did not receive any thromboprophylaxis (odds ratio = 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 (odds ratio = 2.60; 95% CI: 1.08-6.25). However, the authors claimed that the data were insufficient to confirm the superiority of LMWH over aspirin as thromboprophylaxis in MM patients.

In the prospective observational MELISSE study, VTE occurred in 7% of patients on aspirin *versus* 3% on LMWH prophylaxis, and none on vitamin K antagonists among patients being treated with immunomodulatory drugs.[52]

Current thrombosis guidelines recommend primary VTE prophylaxis with aspirin, warfarin or LMWH. In 2008, the IMWG recommended primary thromboprophylaxis for MM patients and specifically aspirin for patients with one or no risk factors for VTE and LMWH (equivalent to enoxaparin 40 mg/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 to maintain a therapeutic International Normalized Ratio 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 immunomodulatory drug therapy should receive appropriate anticoagulation for the duration of the treatment. In these patients, aspirin (100 mg) is considered sufficient 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 should be used. The use of LMWH should be continued for at least 4 months and then patients may be switched to aspirin prophylaxis.[53]

Box 2. Recommendations regarding primary antithrombotic prophylaxis in patients with multiple myeloma.

• All patients with multiple myeloma who are candidates for active anti-myeloma treatment should be considered for thromboprophylaxis.

• The type, intensity and duration of thromboprophylaxis should be tailored according to the individual's baseline thrombotic and hemorrhagic risk profiles.

• Severe thrombocytopenia (platelet count <20x10^9/L), active bleeding, congenital bleeding disorders (hemophilia, von Willebrand disease, severe deficiency of coagulation factors), and acquired coagulopathy that cannot be corrected (e.g. severe liver disease) are absolute contraindications to thromboprophylaxis.

• Mild thrombocytopenia (platelet count <50x10^9/L), a history of bleeding, and acquired coagulopathy with a chance of correction are relative contraindications to thromboprophylaxis.

• To ensure appropriate, safe and effective thromboprophylaxis and to avoid the risks of bleeding and potential thrombotic complications, it is recommended that the drug-drug interactions of antithrombotic agents and anti-myeloma drugs are considered.

• Patients' compliance and patients' preferences should be considered in the choice of thromboprophylaxis, and patients should be adequately informed about their thrombotic risk.

• Patients at low risk of thrombosis, i.e. those aged less than 75 years, with a normal body mass index, without fractures, a central venous catheter, or co-morbidities and not planned to receive therapy with immunomodulatory drugs, should not be given thromboprophylaxis or can be given thromboprophylaxis with low-dose aspirin. The criterion for the choice is the individual hemorrhagic risk.

• All other patients should receive thromboprophylaxis, with low molecular weight heparin as the first choice.

• Patients without other risk factors for thrombosis except for a planned therapy containing an immunomodulatory drug and with a contraindication, strong aversion or documented poor compliance to low molecular weight heparin therapy, could be given aspirin as thromboprophylaxis.

• Preliminary data on the efficacy and safety of apixaban and rivaroxaban as primary thromboprophylaxis in patients receiving immunomodulatory drugs are promising. However, there is no strong evidence in favor of direct oral anticoagulants instead of a low molecular weight heparin.

• Off-label prescription of apixaban as primary antithrombotic prophylaxis in patients with contraindications to low molecular weight heparin (e.g., for allergy) should be considered.

• The duration of thromboprophylaxis should be modulated according to the length of anti-myeloma treatment and 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 multiple myeloma 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 than during newly diagnosed disease. In these patients, prophylactic aspirin 100 mg/day is recommended.

• In patients with renal insufficiency, the most appropriate prophylaxis should be chosen according to the degree of renal function. For patients with a creatinine clearance below 30 mL/min, low molecular weight heparin with dose adjustments is the preferred prophylaxis. Dose adjustments of low molecular weight heparin according to creatinine clearance value are recommended (Table 5).

• During antithrombotic prophylaxis, the platelet count should be monitored, particularly in patients receiving anti-myeloma therapeutic combinations that are at high risk of causing thrombocytopenia.

• Thromboprophylaxis should be stopped if the platelet count decreases to less than 20-30x10^9/L. Dose reductions should be applied when the platelet count is 30-50x10^9/L. Full-dose thromboprophylaxis can be used when the platelet count is over 50x10^9/L.

• Primary thromboprophylaxis should be stopped in the case of clinically relevant or major bleeding. In this circumstance, the cause of bleeding should be evaluated and eventually corrected before restarting thromboprophylaxis.

The National Comprehensive Cancer Network guidelines included guidance on the prevention of VTE in MM patients. The recommended VTE prophylaxis for patients with an IMPEDE score of ≤3 points or a SAVED score of <2 points is aspirin at a dose of 81 to 325 mg once daily. For those with an IMPEDE score of ≥4 points or a SAVED score of ≥2 points, the recommendation is enoxaparin (40 mg/day subcutaneously), warfarin (target International Normalized Ratio, 2.0–3.0), fondaparinux (2.5 mg/day subcutaneously), or a DOAC, such as rivaroxaban at a dose of 10 mg/day orally or apixaban at a dose of 2.5 mg orally twice daily.[47] Thus, alternative thromboprophylaxis strategies for MM under consideration at present include the use of a DOAC licensed for the treatment of cancer-associated thrombosis. These drugs are inhibitors of clotting factor Xa, 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 immunomodulatory drugs (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 deep vein thrombosis. In the latter case, apixaban had been stopped 14 days before the event. The pooled data revealed three episodes of major hemorrhage (1%).[54-57] This bleeding frequency seems comparable to that reported in a population of 1,605 MM patients with 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 DOAC 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 a DOAC, respectively.[58]

A retrospective study of 305 newly diagnosed MM patients showed that the use of low-dose rivaroxaban thromboprophylaxis can mitigate the risk of deep vein thrombosis without an observable increase in bleeding rates (Table 4).[38]

Early treatment of acute thrombotic events, secondary antithrombotic prophylaxis, and re-exposure to anti-myeloma drugs (Box 3)

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 although there has recently been a slow transition to DOAC as evidence suggests that these newer drugs can be safe and effective. DOAC (apixaban, edoxaban, rivaroxaban, and dabigatran) have emerged as the preferred treatment option for VTE in the general population.[59] Recently, factor Xa-inhibitors (the so-called xabans: edoxaban, apixaban, and rivaroxaban) have been tested head-to-head against LMWH in four studies on the treatment and secondary prevention of VTE in patients with cancer.[60-63] A meta-analysis of these four trials, which included 2,894 cancer patients, showed that the xabans significantly reduced the incidence of recurrent VTE compared to that in patients treated with LMWH (5.2% *vs.* 8.2%; relative risk, 0.62; 95% CI: 0.43-0.91), but were associated with a non-significant increase in major bleeding (4.3% *vs.* 3.3%; relative risk, 1.31; 95% CI: 0.83-2.08) and a statistically significant increase in clinically relevant non-major bleeding (10.4% *vs.* 6.4%; relative risk, 1.65; 95% CI: 1.19-2.28).[64] However, less than 10% of the patients in these studies had hematologic malignancies.

Current thrombosis and oncology guidelines recommend treatment of VTE in cancer for 3 to 6 months or longer if cancer therapy is ongoing or the malignancy remains present.[65] As for VTE in patients receiving 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 they do not have a high bleeding risk. The choice of anticoagulant medication depends on the individual patient's renal function and ability to perform subcutaneous self-injections when using LMWH, as well as public or private funding for DOAC.

Table 5. Dose adjustments of low molecular weight heparin and fondaparinux in renal insufficiency.

Low molecular weight heparins
CrCl ≥30 mL/min: no dose adjustments
CrCl <30 mL/min: dose reduction of 25-30%
Dialysis: dose reduction of 50%
Fondaparinux
CrCl <20 mL/min: use not recommended
CrCl 20-50 mL/min: 1.5 mg/day
CrCl >50 mL/min: no dose adjustments

CrCl: creatinine clearance.

Discussion

In the light of new therapies for MM, key clinically relevant questions regarding MM-associated thrombosis were identified, and recommendations were formulated by a panel of experts in the field. Although several scientific bodies have provided guidance on how to optimize thromboprophylaxis in MM patients, the panel highlighted the high degree of uncertainty regarding risk stratification and thromboprophylaxis in MM patients. Since the existing scientific literature about thromboprophylaxis in MM does not allow evidence-based recommendations, consensus was a critical part of the production of the present recommendations.

Box 3. Recommendations regarding early treatment of acute thrombotic events, secondary antithrombotic prophylaxis, and re-exposure to anti-myeloma drug in patients with multiple myeloma.

• Patients with multiple myeloma on secondary prophylaxis with long-term oral anticoagulation with vitamin K antagonists or direct oral anticoagulants, should continue with their anticoagulation treatment during anti-myeloma therapy.

• Patients on anti-platelet therapy (single or double agents) because of previous arterial ischemic events should continue their ongoing anti-platelet prophylaxis. They should add a low molecular weight heparin after a careful evaluation of the risk-benefit ratio during anti-myeloma treatment. The use of low molecular weight heparin should be considered as long as the myeloma 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 course of prophylactic low molecular weight heparin (4-6 months) followed by aspirin 100 mg/day during anti-myeloma treatment.

• Patients with a history of unprovoked venous thromboembolism not receiving oral anticoagulation who have normal renal function may be treated with a low molecular weight heparin, vitamin K antagonist or a direct oral anticoagulant (apixaban). The choice should be based on pharmacological interactions and risk of bleeding.

• In patients with a history of unprovoked venous thromboembolism who have started low molecular weight heparin or oral anticoagulation as thromboprophylaxis after a diagnosis of multiple myeloma, the decision to change to aspirin after 6 months or to continue with oral anticoagulation during long-term treatment with immunomodulatory drugs should be evaluated case by case.

• In general, the treatment of acute thrombosis during active treatment for multiple myeloma should not be different from that usually recommended.

• Patients with multiple myeloma and non-life-threatening venous thromboembolism during therapy with immunomodulatory drugs should continue the therapy and receive long-term anticoagulation.

• In the case of life-threatening venous thromboembolism or arterial thrombosis during treatment with immunomodulatory drugs, a careful case-by-case evaluation should be made, considering the response of the multiple myeloma disease to immunomodulatory drugs, the severity of the thrombosis, and the patient's risk profile for future events.

• In multiple myeloma patients with acute venous thromboembolism, the duration of anticoagulant treatment should be at least 6 months or indefinite in the case of ongoing treatment with immunomodulatory drugs.

• In active multiple myeloma with a high burden of disease, patients should continue the anticoagulant treatment even after 6 months until response of the myeloma disease.

• As regards the platelet count during secondary thromboprophylaxis, the same recommendations as for primary thromboprophylaxis should be followed.

• In the case of acute venous thromboembolism and severe thrombocytopenia, the placement of a retrievable inferior vena cava filter is suggested until safe anticoagulation is possible, and the filter can be removed.

• In patients with renal insufficiency (with or without ongoing dialysis) the most appropriate secondary antithrombotic prophylaxis after venous thromboembolism is adjusted-dose low molecular weight heparin or a vitamin K antagonist.

During the discussion to formulate 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 therapy with immunomodulatory drugs, is a critical determinant in thromboprophylaxis in MM. Understanding the complex procoagulant profile of the MM patient was recognized by the expert panel as critical for a personalized risk stratification. To date, the underlying causes that lead to enhanced coagulation in the MM patient have 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 multiple abnormal parameters of the thrombin generation assay in patients with MM compared to those in 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 MM research through exploration of the complex mechanism of coagulation in this disease.

The results with xabans in MM are encouraging; however, no definite recommendation on their use has been provided. The panel agreed that new evidence on the benefits and risks of xabans for prevention of VTE recurrence in

patients with MM needs to be acquired through direct clinical experimentation. The major issue for clinical trials with DOAC in MM patients is trial feasibility. In the setting of MM the panel agreed that a pragmatic pivotal randomized comparison of DOAC to the standard-treatment control could facilitate trial feasibility.

Disclosures

VDS has received honoraria for participation in speakers bureau and advisory boards from AbbVie, Alexion, Amgen, AOP Health, BMS Celgene, Grifols, GSK, Leo Pharma, Novartis, Sanofi, Sobi, and Takeda, and has received research grants from Novartis. AL has received honoraria for participation in speakers bureau and advisory boards from Amgen, BMS Celgene, GSK, Janssen-Cilag, Oncopeptides, Sanofi, and Takeda. MoC has received honoraria for participation in speakers bureau and advisory boards from Amgen, Argenx, Novartis, and Sobi. MiC has received honoraria from AbbVie, Adaptative, Amgen, BMS Celgene, GSK, Janssen-Cilag, Sanofi, and Takeda, and has served on speakers bureau for BMS Celgene and Janssen-Cilag. FDR has received honoraria for participation in speakers bureau and advisory boards from Amgen, BMS Celgene, GSK, Janssen-Cilag, and Takeda. AF has received honoraria for participation in speakers bureau and advisory boards from Bayer, Instrumentation Laboratory, Kedrion, Leo Pharma, Pfizer, Sanofi, and Stago, and has received a research grant from Italfarmaco. MO has received honoraria for participation in speakers bureau and advisory boards from AbbVie, Amgen, BMS, Celgene, GSK, Janssen-Cilag, Sanofi, and Takeda. MTP has received honoraria for participation in speakers bureau and advisory boards from Amgen, BMS-Celgene, GSK, Janssen-Cilag, Karyopharm, Roche, Sanofi, and Takeda, and has received support for attending meetings and/or travel from Amgen, BMS, Celgene, Janssen-Cilag, Sanofi, and Takeda. RMS has received honoraria for participation in speakers bureau and advisory boards from Amgen, Boheringher, Kedrion, Novartis, and Roche. MR and GB declare no conflicts of interest. Furthermore, some authors have received honoraria from companies that produce drugs used to treat multiple myeloma, including Amgen (carfilzomib), BMS Celgene (elotuzumab, thalidomide, lenalidomide, pomalidomide), GSK (belantamab mafodotin), Janssen-Cilag (bortezomib, daratumumab), Sanofi (isatuximab), and Takeda (ixazomib).

Contributions

VDS, AL, and GB conceived and designed the study, and prepared and edited the manuscript. VDS and AL acquired the data. GB was responsible for the quality control of the data and algorithms. VDS, AL, MoC, MiC, FDR, AF, MO, MTP, MR, RS, and GB were responsible for analyzing and interpreting the data. MoC, MiC, FDR, AF, MO, MTP, MR, and RS reviewed the manuscript. All authors approved the final version of the manuscript for submission.

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