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Review

Risk Factors and Risk Stratification of Thromboembolic Risk in Patients with Multiple Myeloma

Roza Chaireti [1,2,*] and Hareth Nahi [3]

[1] Department of Molecular Medicine and Surgery, Karolinska Institutet, 17177 Stockholm, Sweden
[2] Department of Hematology, Karolinska University Hospital, 17177 Stockholm, Sweden
[3] Center for Hematology and Regenerative Medicine, Department of Medicine, Huddinge, Karolinska Institutet, 17177 Stockholm, Sweden
* Correspondence: roza.chaireti@ki.se; Tel.: +46-8-524-800-00; Fax: +46-8-31-11-01

Abstract: Multiple myeloma (MM) is a hematological malignancy characterized by a high risk for thrombotic episodes, mainly venous thromboembolism (VTE). This risk is accentuated by cancer treatments such as immunomodulatory drugs (IMiDs). Cancer-associated thrombosis is one of the leading causes of mortality and morbidity, and the prevention of thrombosis is, therefore, of paramount significance. To this day, it is unclear which type of thromboprophylaxis is the most effective. This is partly due to the multifactorial etiology behind thrombosis since the compound of patient-, disease- and treatment-associated factors characterizing each patient with MM is unique. Additionally, the established risk scores are not reliable in patients with MM. The scope of this review is to summarize the factors contributing to increased thrombosis risk in MM, as well as the risk scores and thromboprophylaxis regimes available.

Keywords: multiple myeloma; thrombosis; anticoagulants

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1. Introduction

Cancer is the most studied and well-established risk factor for venous thromboembolism (VTE), namely cancer-associated thrombosis (CAT) [1]. The hypercoagulable state associated with cancer, according to the principles of the Virchow triad, leads to increased risk for thrombosis, mainly venous thrombosis, i.e., pulmonary embolism (PE) and deep vein thrombosis (DVT). Cancer-associated thrombosis is one of the leading causes of mortality and morbidity in patients suffering from cancer diseases, with an incidence of approximately 10% or higher [2]. The exact mechanisms behind CAT remain uncertain, but risk factors associated with the patient, tumor and treatment have been identified [3].

Most data on CAT come from studies on heterogeneous cohorts, where hematological malignancies are included. However, hematological cancers are distinct from solid tumors since they are characterized by bone marrow failure, both primary and secondary, as a result of both the effect of the malignancy and the chemotherapy. As such, risk factors for bleeding, such as thrombocytopenia, tend to be more pronounced. This leads to potentially severe complications when treatment with anticoagulants, either in therapeutic or prophylactic dosage, is required. Additionally, some types of chemotherapy and immunomodulatory drugs (IMiDs) can increase the thrombotic risk independently, contributing further to a hypercoagulable state.

One of the hematological malignancies with the highest risk for thrombosis is multiple myeloma (MM), which is characterized by neoplastic proliferation of plasma cells, typically leading to the production of monoclonal proteins [4]. Its prevalence varies, but the age-standardized incidence is circa 5/100,000 [5], and it is the second most common type of hematological malignancy following lymphoma [6].

The scope of this review is to offer an overview of the epidemiology, risk factors, including coagulation abnormalities, and prevention of CAT in patients with MM.

2. Epidemiology of CAT

It is established that patients with MM have a high risk for predominant VTE, shown in 1999 [7] and confirmed later by other studies [8–10]. The incidence of VTE varies in different studies depending heavily on the type of MM treatment. Zangari et al. reported that 24% of patients with newly diagnosed MM had a VTE during a 12-month follow-up; this was particularly evident among patients treated with thalidomide [11]. According to results from the ROADMAP-CAT-MM, over 10% of the patients with newly diagnosed MM had a thrombosis during a one-year follow-up, with the majority occurring during the first three months from diagnosis. Most of the patients (9/15) had either anticoagulants or platelet inhibitors as thromboprophylaxis at the time of the thrombosis, and the incidence of VTE was the same among the two groups [12]. Although venous thrombosis is the predominant type of thrombosis among these patients, arterial thrombosis has also been reported [8], albeit at a lower incidence.

For an overview of the risk for thrombosis in patients with MM, please refer to Table S1 in Supplementary Materials.

3. Hemostatic Abnormalities in Patients with Multiple Myeloma

The high incidence of CAT in MM has led to several studies investigating the hemostatic potential of the patients, both with and without treatment. The aim of these has been mainly to identify markers that could predict the risk for thrombosis in individual patients, thus sharpening the acuity of the current risk stratifications, which are based predominantly on clinical characteristics.

3.1. Primary Hemostasis

Increased levels of von Willebrand factor (vWF) have been reported as a common finding in patients with plasma cell dyscrasias [13–15]. Others have found that vWF, Vascular Endothelial Growth Factor (VEGF) and D-dimer correlate with disease phase, including the initiation of treatment, and are normalized if the patient responds to treatment, as well as that newly diagnosed patients have higher levels compared to patients who have relapsed [16].

As is the case in other malignancies, patients with MM also have an increased risk for bleeding. Factors such as disease- and treatment-mediated thrombocytopenia and renal insufficiency are important, but patients with MM have also exhibited coagulation abnormalities that exacerbate the bleeding risk. Despite increased vWF levels, there are reports of qualitative defects of vWF as well as acquired von Willebrand syndrome (AVWS). Patients with abnormal bleeding have been shown to have such abnormalities in vWF as well as longer closure times (CTs), as measured by the platelet function instrument PFA-100. Those defects are reversible upon treatment response [17].

Aside from thrombocytopenia, platelet function defects resulting in impaired aggregation have also been reported and increase the bleeding risk [18] in MM patients.

3.2. Secondary Hemostasis and Coagulation Inhibitors

Already in 1976, it was shown that factor VIII (FVIII), which has both hemostatic and inflammatory activity, is increased in patients with MM [19].

In a study on the patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering MM (SMM), and MM from the cohort of the Vienna Cancer and Thrombosis Study, patients had significantly higher D-dimer, FVIII and vWF compared to controls, with MM exhibiting higher levels of FVIII and von Willebrand (vWF) antigen compared to MGUS [13], which has been verified by other studies [14,15]. Tiong et al. showed that, in addition to increased vWF and FVIII at diagnosis with additional increases upon initiating MM treatment, protein C (PC) was higher in MM patients, whereas there was no difference in protein S and antithrombin. All three coagulation inhibitors increased gradually during treatment. Even though increased or higher levels of coagulation in-

hibitors are generally considered to lack clinical significance, they could be indicative of a prothrombotic state [15].

Acquired activated PC (APC) resistance has been associated with increased VTE risk in patients with MM; as shown in a study of 62 patients, those receiving regimes including thalidomide had the highest risk [20]. Newly diagnosed patients with MM have higher tissue factor (TFa), activated factor II (FVIIa), D-Dimer and fibrin monomers and significantly shorter procoagulant phospholipid clotting time [12].

Acquired hemophilia A (AHA) has been identified among patients with plasma cell disease, including MM. A total of 16 patients were reported, and, in the majority of those, treatment for both the plasma cell disease and AHA was necessary to achieve satisfactory patient outcomes [21]. Since 10–15% of patients with MM have light chain (AL)—amyloidosis [22], which is associated with acquired factor X deficiency [23], this acquired coagulopathy can lead to increased bleeding tendency.

3.3. Effect of Paraproteins on Coagulation Potential

Earlier studies have focused on the effect of MM paraproteins and increased immunoglobulin levels on fibrin structure. In 1992, it was reported that high immunoglobulin levels in the serum of patients with MM impair fibrinogen structure, leading to inadequate fibrin polymerization and subsequent interference with blinding to FXIII and exacerbation of bleeding tendency [24,25]. The effect of paraproteins in patients with MM results in the production of fibrin strands, which are thinner, weaker and resistant to plasmin [26–28].

It has also been reported that increased immunoglobulin levels compete with FXIII for binding to the lateral sites of fibrin monomers, leading to the production of clots that have difficulties retracting [29,30] and that increased blood viscosity interferes with fibrin polymerization and leads to the impairment of clot lysis times [31–33].

3.4. Other Tests

In an in vitro study, MM micro-vesicles (MVs) were isolated from the MM cell line RPMI 8226 (both treated and untreated with bortezomib), as well as from the blood and bone marrow of patients with MM and healthy controls. MM cells exhibited a high MV shedding rate, which was particularly evident following the addition of bortezomib. MM-MVs expressed TF and tissue factor pathway inhibitor (TFPI), as well as angiogenetic factors (VEGFR1, VEGFR2 and CD31) and procoagulant activity, most pronounced in the untreated cells [34].

Patients with MM have higher concentrations of extravascular vesicles (EVs) carrying TF and phospholipids as well as larger EV particles at baseline compared to controls, and the largest fraction was halved in patients with VCD compared to patients who received other treatment (MPV or lenalidomide and dexamethasone). Since EVs produced by malignant cells have a role in angiogenesis and immune escape, the authors hypothesized that EVs could be used as markers of procoagulant activity and disease activity, as well as treatment response [35].

3.5. Global Hemostatic Methods

Global hemostatic methods have been included both in routine and research analyses to evaluate the coagulation potential and subsequent risk for thromboembolism in different patient groups, such as patients with malignancies. This is because, despite disadvantages such as lack of standardization, the global hemostatic assays reflected the entirety of the coagulation cascade, in contrast to the traditional coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), which are indicative of merely the initial stage of thrombin generation and the forming of the clot [36].

In a study published in 2011, thrombin generation was evaluated in 1033 patients with cancer (Vienna Cancer and Thrombosis Study) and showed that increased peak thrombin concentration is a significant risk factor for thrombosis [37].

In a pilot study, three global hemostatic methods (overall hemostatic potential, OHP, calibrated automated thrombogram and thromboelastography, TEG) were studied in 29 patients with MM, 14 with SMM and 13 patients with MGUS and compared to controls. It was shown that both parameters of CAT (peak and velocity index) and TEG (maximum amplitude) were increased in patients with plasma cell dyscrasias compared to controls, thus rendering their coagulation profile prothrombotic. One patient suffered a LE and four cardiovascular events during the 14-month-long follow-up, and although the cohort was small, it showed that hypercoagulability is reproducible when evaluated with different methods [13].

Thrombin generation (TG) was measured by the calibrated automated thrombogram in the presence of 1 pM and 5 pM TF in 24 patients with MM and 19 with MGUS both at baseline and at 1, 2 and 3 months following the initiation of treatment and the results were compared to those obtained from healthy controls. It was shown that, in the presence of 5 pM TF, ttPeak was decreased and velocity increased in subjects with MM, whereas peak thrombin concentration was similar and endogenous thrombin potential (ETP) was unexpectantly lower compared to controls. Most of those differences, with the exception for ETP, were retained even at the presence of 1 pM. TF. When thrombomodulin was added to the sample, total and peak thrombin as well as velocity were significantly higher in MM patients, indicating increased resistance to TM inhibition and thus to inactivation by APC [15]. During MM treatment, the ttPeak and lagtime were increased towards normalization, whereas ETP was constant, and thrombomodulin resistance was retained in patients with plasma cell dyscrasias. The authors attributed the surprisingly low ETP in patients (5 pM TF) to differences in the TG assays and noted that, in their study, it was the time (velocity) markers that could differentiate between the prothrombotic and normal coagulation potential rather than the most widely used concentration parameters. This is important when designing new studies and protocols to evaluate prothrombotic potential [15]. Although increased TG in patients with MM has been found by more groups, the findings of resistance to APC and TM have not been replicated in all studies [38].

Thrombin generation was measured in a small cohort of MM patients at 1, 2 and 3 months following diagnosis. Peak thrombin concentration was decreased and APC sensitivity was increased, but no changes in the time parameters were observed [39]. In a larger study, fibrin clot properties (permeability, turbidity and susceptibility to lysis) were improved after 3 months of primarily thalidomide-based therapy compared to baseline, and those findings are associated with lower peak thrombin but elevated FVIII [40].

Increased time and concentration parameters were increased in patients with MM compared to patients with MGUS and controls, which could be mediated by phospholipid and TF activity [41], which has been reported as increased even by others [35]. When measuring changes in TG parameters during 2 and 5 years from diagnosis, it was found that a continuing increase in TG concentration parameters was predictive of a VTE [42].

Another study showed that thrombin production is increased and takes place during a shorter period compared to controls and that total thrombin concentration was decreased in patients treated for MM [35].

In a small study comparing patients with MM, MGUS and without thrombophilia or previous thrombosis, the TEG parameters (r time, k time, alpha angle, maximum amplitude) were similar among all three groups. Since factors such as vWF and FVIII were increased in patients with plasma cell diseases, it was suggested that classical tests could be more efficient in differentiating between different groups, but the conclusions are limited by the small cohort [14].

For an overview of the hemostatic changes in patients with MM, please refer to Table S2.

4. Risk Factors Associated with the Patient

The MELISSE study aimed to evaluate the thrombotic risk in a cohort of >500 patients with MM treated with IMiDs, of which the majority received platelet inhibitors as thromboprophylaxis. Factors such as thrombophilias, obesity, co-morbidities (diabetes mellitus,

cardiac failure, renal failure), treatment with erythropoietin, presence of central venous catheter and recent surgery were included in a stratification algorithm. In this study, 6% of the patients suffered a VTE, and the patients in the intermediate- and high-risk groups were twice as likely to have a thrombosis compared to the patients in the low-risk group. Overall, the risk factors that have been recognized as significant, even in patients without VTE, were shown to affect the thrombotic risk even in patients with MM, but the individual variations, even in the same risk group, were notable [43].

5. Effect of Treatment on Thrombotic Risk

The addition of IMiDs as treatment choices for MM has led to improved overall and progression-free survival but also to an increased risk for thrombosis. Already in 1999, it was established that treatment was a risk factor for VTE in patients with MM [7] and that there are clear variations in the thrombotic risk depending on which treatment is administered. Treatment with prednisolone and melphalan has a varying reported risk, from 0–2% to 16% in elderly patients [44], whereas treatment with single thalidomide increases this risk to the highest interval of 2% [45] and generally doubles the risk compared to patients who are not treated with thalidomide [46]. The thrombotic risk increases when different drugs are combined, such as when thalidomide is combined with dexamethasone or cytotoxic chemotherapy, especially anthracyclines, with the highest risk observed for the combination of thalidomide with daunorubicin (4.3; $p \leq 0.001$) [47,48]. Patients treated with lenalidomide have been reported to have a risk for VTE up to 4.5%; this risk increases to 8.5% when lenalidomide is combined with dexamethasone [49]. Treatment with bortezomib does not increase the risk for VTE to the same extent as the other treatment regimens, even when it is combined with dexamethasone, with VTE rates of <5% [50,51].

6. Guidelines and Risk Scores

Patients with MM are not included in the established risk scores for the stratification of ambulatory patients at high risk for VTE and, therefore, risk scores, such as Khorana's risk score [52], cannot be employed since they have been proven insufficient [53,54]. The current guidelines recommend the usage of thromboprophylaxis in all patients with MM treated with IMiDs, except for the patient groups for which there is an absolute contraindication to anticoagulants. The guidelines issued by the international working myeloma group (IMWG) [55] and the European Myeloma network [56] recommend the usage of anticoagulants (parenteral or peroral) or platelet inhibitors as thromboprophylaxis in patients with MM treated with IMiDs, depending on the risk factors. The ASH guidelines from 2021 confirmed those recommendations [57]. There is still no agreement on which type of antithrombotic medication is optimal in preventing thrombosis. Additionally, there have been studies indicating that the guidelines are sometimes not adequate in preventing thrombosis. Since there have been reports that the adherence to guidelines is not optimal [58], the reasons behind this failure are open for discussion, but the hypercoagulability and high thrombogenicity of MM is probably a contributing risk factor.

The prospective ROADMAP-CAT-MM study identified procoagulant phospholipid clotting time and ETP as independent risk factors for venous thrombosis and proposed that those would be included in a risk score for MM patients. Additionally, the authors showed that patients in different risk categories indeed had a different risk for thrombosis [12].

Risk scores have been developed and evaluated in retrospective studies based on databases. In the IMPEDE VTE score, risk factors such as the usage of IMiDs, erythropoietin and dexamethasone and patient-specific factors such as BMI, race, previous thrombosis, etc., were included. The score identified three risk groups with distinctly different risks for thrombosis, as shown by the incidence of VTE [59]. In the SAVED score, the risk factors included were fewer and more patient- than therapy-centered (race, medical history of thrombosis, age, surgery within 90 days and treatment of dexamethasone) and two groups were identified with significantly different thrombotic risks [60]. Neither of these scores is used routinely since prospective validation has not yet been performed [61].

7. Thromboprophylaxis

As mentioned above, it is unclear which thromboprophylaxis regimen is ideal, and local traditions and preferences might affect the physician's choice to a certain extent.

Both low-molecular-weight heparin (LMWH) and warfarin have been shown to prevent thrombosis, and aspirin has also been used as an effective alternative in some studies [62–64]. Most guidelines recommend individual risk stratification of each patient according to patient-, disease- and treatment-associated risk factors and the administration of platelet inhibitors and anticoagulants for low- and high-risk patients, respectively.

LMWH is the standard of care for most centers, however, direct oral anticoagulants (DOAC) are gaining ground. Data are scarce, but the existing results are promising, showing effectiveness in preventing thrombosis with a low incidence of bleeding complications [64–66]. However, drug interactions, severe thrombocytopenia and impaired kidney function are factors that can potentially limit the usage of peroral anticoagulants and possibly favor the usage of low-dosage LMWH [58,67,68].

8. Conclusions

Despite progress in predicting and preventing CAT, there is a lack of consensus on risk stratification and optimal thromboprophylaxis for patients with MM, a hematological malignancy with a high risk for thrombosis. Those challenges can be expected to be even more pronounced in the future since improvements in the treatment of MM lead to increased survival and an aging patient population with more co-morbidities and a subsequent even higher thrombotic risk. DOAC is a promising choice for thromboprophylaxis, but clinical, real-world data on interactions are scarce, and complications commonly associated with MM such as thrombocytopenia and renal impairment can potentially limit its usage. However, the usage of global hemostatic methods has revolutionized our perception of the coagulation potential in, among others, patients with cancer, and new biomarkers emerge that can further refine personalized risk stratification.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/hemato3030036/s1, Table S1: Overview of the studies on risk for thromboembolism; Table S2: Overview of the differences in hemostatic markers and global hemostatic methods between patients with MM and controls.

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References

1. Goldenberg, N.; Kahn, S.R.; Solymos, S. Markers of coagulation and angiogenesis in cancer-associated venous thromboembolism. *J. Clin. Oncol.* **2003**, *21*, 4194–4199. [CrossRef] [PubMed]
2. Falanga, A.; Marchetti, M.; Vignoli, A. Coagulation and cancer: Biological and clinical aspects. *J. Thromb. Haemost.* **2013**, *11*, 223–233. [CrossRef] [PubMed]
3. Blom, J.W.; Doggen, C.J.; Osanto, S.; Rosendaal, F.R. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA* **2005**, *293*, 715–722. [CrossRef]
4. Matsui, W.; Wang, Q.; Barber, J.P.; Brennan, S.; Smith, B.D.; Borrello, I.; McNiece, I.; Lin, L.; Ambinder, R.F.; Peacock, C.; et al. Clonogenic multiple myeloma progenitors, stem cell properties, and drug resistance. *Cancer Res.* **2008**, *68*, 190–197. [CrossRef]
5. Sant, M.; Allemani, C.; Tereanu, C.; De Angelis, R.; Capocaccia, R.; Visser, O.; Marcos-Gragera, R.; Maynadiè, M.; Simonetti, A.; Lutz, J.M.; et al. Incidence of hematologic malignancies in Europe by morphologic subtype: Results of the HAEMACARE project. *Blood* **2010**, *116*, 3724–3734. [CrossRef] [PubMed]
6. Palumbo, A.; Anderson, K. Multiple Myeloma. *NEJM* **2011**, *364*, 1046–1060. [CrossRef] [PubMed]
7. Barlogie, B.; Jagannath, S.; Desikan, K.R.; Mattox, S.; Vesole, D.; Siegel, D.; Tricot, G.; Munshi, N.; Fassas, A.; Singhal, S.; et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. *Blood* **1999**, *93*, 55–65. [CrossRef]

8. Kristinsson, S.Y.; Pfeiffer, R.M.; Björkholm, M.; Goldin, L.R.; Schulman, S.; Blimark, C.; Mellqvist, U.H.; 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**, *115*, 4991–4998. [CrossRef]
9. De Stefano, V.; Za, T.; Rossi, E. Venous thromboembolism in multiple myeloma. *Semin. Thromb. Hemost.* **2014**, *40*, 338–347.
10. Kristinsson, S.Y. Thrombosis in multiple myeloma. *Hematol. Am. Soc. Hematol. Educ. Program* **2010**, *2010*, 437–444. [CrossRef]
11. Zangari, M.; Anaissie, E.; Badros, A. Thrombotic complications in myeloma patients receiving thalidomide in combination with chemotherapy. *Thromb. Haemost.* **2001**, P2192, (Abstract).
12. Fotiou, D.; Sergentanis, T.N.; Papageorgiou, L.; Stamatelopoulos, K.; Gavriatopoulou, M.; Kastritis, E.; Psaltopoulou, T.; Salta, S.; Van Dreden, P.; Sangare, R.; et al. Longer procoagulant phospholipid dependent clotting time, lower endogenous thrombin potential and higher tissue factor pathway inhibitor concentrations are associated with increased VTE occurrence in patients with newly diagnosed multiple myeloma: Results of the prospective ROADMAP-MM-CAT study. *Blood Cancer J.* **2018**, *8*, 102. [PubMed]
13. Lim, H.Y.; Brook, R.; Krishnamoorthi, B.; Tacey, M.; Leung, T.; Donnan, G.; Nandurkar, H.; Ho, P. Global coagulation assays in patients with multiple myeloma and monoclonal gammopathy of unknown significance. *Thromb. Res.* **2019**, *183*, 45–48. [CrossRef]
14. Crowley, M.P.; Quinn, S.; Coleman, E.; Eustace, J.A.; Gilligan, O.M.; Shea, S.I.O. Differing coagulation profiles of patients with monoclonal gammopathy of undetermined significance and multiple myeloma. *J. Thromb. Thrombolysis* **2015**, *39*, 245–249. [CrossRef] [PubMed]
15. Tiong, I.S.; Rodgers, S.E.; Lee, C.H.S.; McRae, S.J. Baseline and treatment-related changes in thrombin generation in patients with multiple myeloma. *Leuk. Lymphoma* **2017**, *58*, 941–949. [CrossRef]
16. Sokol, J.; Hrncar, M.; Nehaj, F.; Stasko, J. Plasma Levels of Vascular Endothelial Growth Factor and Selected Hemostatic Parameters in Association with Treatment Response in Multiple Myeloma. *Clin. Appl. Thromb. Hemost.* **2019**, *25*, 1–6. [CrossRef]
17. Hinterleitner, C.; Pecher, A.-C.; Kreißelmeier, K.-P.; Budde, U.; Kanz, L.; Kopp, H.-G.; Jaschonek, K. Disease progression and defects in primary hemostasis as major cause of bleeding in multiple myeloma. *Eur. J. Haematol.* **2020**, *104*, 26–35. [CrossRef]
18. Eby, C.S. Bleeding and Thrombosis Risks in Plasma Cell Dyscrasias. *Hematol. Am. Soc. Hematol. Educ. Program* **2007**, *1*, 158–164. [CrossRef]
19. Gomperts, E.D.; Shulman, G.; Lynch, S.R. Factor VIII and factor- VIII-related antigen in multiple myelomatosis and related conditions. *Br. J. Haematol.* **1976**, *32*, 249–255. [CrossRef]
20. Zangari, M.; Saghafifar, F.; Anaissie, E.; Badros, A.; Desikan, R.; Fassas, A.; Mehta, P.; Morris, C.; Toor, A.; Whitfield, D.; et al. Activated protein C resistance in the absence of factor V Leiden mutation is a common finding in multiple myeloma and is associated with an increased risk of thrombotic complications. *Blood Coagul. Fibrinolysis* **2002**, *13*, 187–192. [CrossRef]
21. Jalowiec, K.A.; Andres, M.; Mansouri Taleghani, B.; Musa, A.; Dickenmann, M.; Angelillo-Scherrer, A.; Rovó, A.; Kremer Hovinga, J.A. Acquired hemophilia A and plasma cell neoplasms: A case report and review of the literature. *J. Med. Case Rep.* **2020**, *14*, 206. [CrossRef] [PubMed]
22. Röllig, C.; Knop, S.; Bornhäuser, M. Multiple myeloma. *Lancet* **2015**, *385*, 2197–2208. [CrossRef]
23. Choufani, E.B.; Sanchorawala, V.; Ernst, T.; Quillen, K.; Skinner, M.; Wright, D.G.; Seldin, D.C. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: Incidence, bleeding manifestations, and response to high-dose chemotherapy. *Blood* **2001**, *97*, 1885–1887. [CrossRef] [PubMed]
24. Gabriel, D.A.; Muga, K.; Boothroyd, E.M. The effect of fibrin structure on fibrinolysis. *J. Biol. Chem.* **1992**, *2367*, 24259–24263. [CrossRef]
25. Gabriel, D.A.; Smith, L.A.; Folds, J.D.; Davis, L.; Cancelosi, S.E. The influence of immunoglobulin (IgG) on the assembly of fibrin gels. *J. Lab. Clin. Med.* **1983**, *101*, 545–552. [PubMed]
26. Frick, P.G. Inhibition of conversion of fibrinogen to fibrin by abnormal proteins in multiple myeloma. *Am. J. Clin. Pathol.* **1955**, *25*, 12634–12637. [CrossRef] [PubMed]
27. Lopaciuk, S.; Snigurowicz, J.; Rostkowska, J.; Pniejnia-Olszynski, W.; Powiertowska-Rezmer, M. Disorders in the conversion of fibrinogen to fibrin in patients with multiple myeloma. *Acta Haematol. Pol.* **1978**, *9*, 157–164.
28. Cohen, L.; Amir, J.; Bern Shaul, Y.; Pick, A.; De Vries, A. Plasma cell myeloma associated with an unusual myeloma protein causing impairment of fibrin aggregation and platelet function in a patient with multiple malignancy. *Am. J. Med.* **1970**, *48*, 766–776. [CrossRef]
29. Carr, M.E.; Dent, R.M.; Carr, S.L. Abnormal fibrin structure and inhibition of fibrinolysis in patients with multiple myeloma. *J. Lab. Clin. Med.* **1996**, *128*, 83–88. [CrossRef]
30. Carr, M.E.; Zrekert, S.L. Abnormal clot retraction, altered fibrin structure and normal platelet function in multiple myeloma. *Am. J. Physiol.* **1994**, *266*, H1195–H1201. [CrossRef]
31. O'Kane, M.J.; Wisdom, G.B.; Desai, Z.R.; Archbold, G.P. Inhibition of fibrin monomer polymerization by myeloma immunoglobulin. *J. Clin. Pathol.* **1994**, *47*, 266–268. [CrossRef] [PubMed]
32. Panzer, S.; Thaler, E. An acquired cryoglobulinemia which inhibits fibrin polymerization in a patient with IgG kappa myeloma. *Haemostasis* **1993**, *23*, 69–76. [CrossRef] [PubMed]
33. Coleman, M.; Vigiliano, E.M.; Weksler, M.E.; Nachman, R.L. Inhibition of fibrin monomer polymerization by lambda myeloma globulins. *Blood* **1972**, *39*, 210–223. [CrossRef]

34. Zarfati, M.; Katz, T.; Avivi, I.; Brenner, B.; Aharon, A. The role of microvesicles in multiple myeloma progression. PO-45 Abstracts. *Thromb. Res.* **2016**, *140*, S168–S200. [CrossRef]
35. Nielsen, T.; Kristensen, S.R.; Gregersen, H.; Teodorescu, E.M.; Christiansen, G.; Pedersen, S. Extracellular vesicle-associated procoagulant phospholipid and tissue factor activity in multiple myeloma. *PLoS ONE* **2019**, *14*, e0210835. [CrossRef] [PubMed]
36. Lancé, M.D. A general review of major global coagulation assays: Thrombelastography, thrombin generation test and clot waveform analysis. *Thromb. J.* **2015**, *13*, 1. [CrossRef]
37. Ay, C.; Dunkler, D.; Simanek, R.; Thaler, J.; Koder, S.; Marosi, C.; Zielinski, C.; Pabinger, I. Prediction of venous thromboembolism in patients with cancer by measuring thrombin generation: Results from the Vienna Cancer and Thrombosis Study. *J. Clin. Oncol.* **2011**, *29*, 2099–2103. [CrossRef]
38. Legendre, P.; Verstraete, E.; Poinsard, A.; Martin, M.; Perrin, J.; Perrot, A.; Hulin, C.; Faure, G.; Latger-Cannard, V. Hypocoagulability as assessed by thrombin generation test in newly-diagnosed patients with multiple myeloma. *Blood Cells Mol. Dis.* **2017**, *66*, 47–49. [CrossRef]
39. Crowley, M.P.; Kevane, B.; O'Shea, S.I.; Quinn, S.; Egan, K.; Gilligan, O.M.; Ni Áinle, F. Plasma thrombin generation and sensitivity to activated protein C among patients with myeloma and monoclonal gammopathy of undetermined significance. *Clin. Appl. Thromb. Hemost.* **2016**, *22*, 554–562. [CrossRef]
40. Undas, A.; Zubkiewicz-Usnarska, L.; Helbig, G.; Woazczyk, D.; Kozinska, J.; Dmoszynska, A.; Debski, J.; Podolak-Dawidziak, M.; Kuliczkowski, K. Induction therapy alters plasma fibrin clot properties in multiple myeloma patients: Association with thromboembolic complications. *Blood. Coagul. Fibrinolysis.* **2015**, *26*, 621–627. [CrossRef]
41. Nielsen, T.; Risom Kristensen, S.; Gregersen, H.; Teodorescu, E.M.; Pedersen, S. Prothrombotic abnormalities in patients with multiple myeloma and monoclonal gammopathy of undetermined significance. *Thromb. Res.* **2021**, *202*, 108–118. [CrossRef] [PubMed]
42. Leiba, M.; Malkiel, S.; Budnik, I.; Rozic, G.; Avigdor, A.; Duek, A.; Nagler, A.; Kenet, G.; Livnat, T. Thrombin generation as a predictor of thromboembolic events in multiple myeloma patients. *Blood Cells Mol. Dis.* **2017**, *65*, 1–7. [CrossRef] [PubMed]
43. Leleu, X.; Rodon, P.; Hulin, C.; Daley, L.; Dauriac, C.; Hacini, M.; Decaux, O.; Eisemann, J.-C.; Fitoussi, O.; Lioure, B.; et al. 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**, *110*, 844–851. [CrossRef] [PubMed]
44. Rus, C.; Bazzan, M.; Palumbo, A.; Bringhen, S.; Boccadoro, M. Thalidomide in front line treatment in multiple myeloma: Serious risk of venous thromboembolism and evidence for thromboprophylaxis. *J. Thromb. Haemost.* **2004**, *2*, 2063–2065. [CrossRef]
45. Barlogie, B.; Desikan, R.; Eddlemon, P.; Spencer, T.; Zeldis, J.; Munshi, N.; Badros, A.; Zangari, M.; Anaissie, E.; Epstein, J.; et al. Extended survival in advanced and refractory multiple myeloma after single- agent thalidomide: Identification of prognostic factors in a phase 2 study of 169 patients. *Blood* **2001**, *98*, 492–494. [CrossRef]
46. Carrier, M.; Le Gal, G.; Tay, J.; Wu, C.; Lee, A.Y. Rates of venous thromboem- bolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: A systematic review and meta-analysis. *J. Thromb. Haemost.* **2011**, *9*, 653–663. [CrossRef]
47. Zangari, M.; Barlogie, B.; Thertulien, R.; Jacobson, J.; Eddleman, P.; Fink, L.; Fassas, A.; Van Rhee, F.; Talamo, G.; Choon-Kee, L.; et al. Thalidomide and deep vein thrombosis in multiple myeloma: Risk factors and effect on survival. *Clin. Lymphoma* **2003**, *4*, 32–35. [CrossRef]
48. Zangari, M.; Siegel, E.; Barlogie, B.; Anaissie, E.; Saghafifar, F.; Fassas, A.; Morris, C.; Fink, L.; Tricot, G. Throm bogenic activity of doxorubicin in myeloma patients receiving thalidomide: Implications for therapy. *Blood* **2002**, *100*, 1168–1171. [CrossRef]
49. Dimopoulos, M.; Spencer, A.; Attal, M.; Prince, H.M.; Harousseau, J.L.; Dmoszynska, A.; San Miguel, J.; Hellmann, A.; Facon, T.; Foá, R.; et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **2007**, *357*, 2123–2132. [CrossRef]
50. Lonial, S.; Richardson, P.G.; San Miguel, J.; Sonneveld, P.; Schuster, M.W.; Bladè, J.; Cavenagh, J.; Rajukumar, S.V.; Jakubowiak, A.J.; Esseltine, D.-L.; et al. Characterisation of haematological profiles and low risk of thromboembolic events with bortezomib in patients with relapsed multiple myeloma. *Br. J. Haematol.* **2008**, *143*, 222–229. [CrossRef]
51. Zangari, M.; Fink, L.; Zhan, F.; Tricot, G. Low venous thromboembolic risk with bortezomib in multiple myeloma and potential protective effect with thalidomide/lenalidomide-based therapy: Review of data from phase 3 trials and studies of novel combination regimens. *Clin. Lymphoma Myeloma Leuk.* **2011**, *11*, 228–236. [CrossRef] [PubMed]
52. Khorana, A.A.; Kuderer, N.M.; Culakova, E.; Lyman, G.H.; Francis, C.W. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* **2008**, *111*, 4902–4907. [CrossRef]
53. Sanfilippo, K.M.; Wang, T.F.; Luo, S.; Thomas, T.S.; Carson, K.R.; Keller, J.W.; Kuderer, N.M.; Calverley, D.; Gage, B. Predictive ability of the khorana score for venous thromboembolism (VTE) in multiple myeloma (MM). *J. Clin. Oncol.* **2018**, *36*, e18733. [CrossRef]
54. Sanfilippo, K.M.; Carson, K.R.; Wang, T.-F.; Luo, S.; Edwin, N.; Kuderer, N.; Keller, J.M.; Gage, B.F. Evaluation of the Khorana score for prediction of venous thromboembolism in patients with multiple myeloma. *Res. Pract. Thromb. Haemost.* **2022**, *6*, e12634. [CrossRef]
55. Palumbo, A.; Rajkumar, S.V.; Dimopoulos, M.A.; Richardson, P.G.; San Miguel, J.; Barlogie, B.; Harousseau, J.; Zonder, J.A.; Cavo, M.; Zangari, M.; et al. Prevention of thalidomide- and lenalidomide- associated thrombosis in myeloma. *Leukemia* **2008**, *22*, 414–423. [CrossRef]

56. Terpos, E.; Kleber, M.; Engelhardt, M.; Zweegman, S.; Gay, F.; Kastritis, E.; van de Donk, N.W.; Bruno, B.; Sezer, O.; Broijl, A.; et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. *Haematologica* **2015**, *100*, 1254–1266. [CrossRef] [PubMed]
57. Lyman, G.H.; Carrier, M.; Ay, C.; Di Nisio, M.; Hicks, L.K.; Khorana, A.A.; Leavitt, A.D.; Lee, A.Y.Y.; Macbeth, F.; Morgan, R.L.; et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. *Blood. Adv.* **2021**, *5*, 927–974. [CrossRef]
58. Baker, H.A.; Brown, A.R.; Mahnken, J.D.; Shireman, T.I.; Webb, C.E.; Lipe, B.-C. Application of risk factors for venous thromboembolism in patients with multiple myeloma starting chemotherapy, a real-world evaluation. *Cancer Med.* **2019**, *8*, 455–462. [CrossRef]
59. 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. [CrossRef]
60. Li, A.; Wu, Q.; Luo, S.; Warnick, G.S.; Zakai, N.A.; Libby, E.N.; Gage, B.F.; Garcia, D.A.; Lyman, G.H.; Sanfilippo, K.M. Derivation and Validation of a Risk Assessment Model for Immunomodulatory Drug-Associated Thrombosis Among Patients With Multiple Myeloma. *J. Natl. Compr. Cancer Netw.* **2019**, *17*, 840–847. [CrossRef]
61. Fotiou, D.; Gavriatopoulou, M.; Terpos, E. Multiple Myeloma and Thrombosis: Prophylaxis and Risk Prediction Tools. *Cancers* **2020**, *12*, 191. [CrossRef] [PubMed]
62. Baz, R.; Li, L.; Kottke-Marchant, K.; Srkalovic, G.; McGowan, B.; Yiannaki, E.; Karam, M.A.; Faiman, B.; Abou Jawde, R.; Andresen, S.; et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo. Clin. Proc.* **2005**, *80*, 1568–1574. [CrossRef] [PubMed]
63. Palumbo, A.; Cavo, M.; Bringhen, S.; Zamagni, E.; Romano, A.; Patriarca, F.; Rossi, D.; Gentilini, F.; Crippa, C.; Galli, M.; et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: A phase III, open-label, randomized trial. *J. Clin. Oncol.* **2011**, *29*, 986–993. [CrossRef]
64. Larocca, A.; Cavallo, F.; Bringhen, S.; Di Raimondo, F.; Falanga, A.; Evangelista, A.; Cavalli, M.; Stanevsky, A.; Corradini, P.; Pezzatti, S.; et al. Aspirin or enoxaparin thromboprophylaxis for newly-diagnosed multiple myeloma patients treated with lenalidomide. *Blood* **2012**, *119*, 933–939. [CrossRef] [PubMed]
65. Cornell, R.F.; Goldhaber, S.Z.; Engelhardt, B.G.; Moslehi, J.; Jagasia, M.; Harrell, S.; Rubinstein, S.M.; Hall, R.; Wyatt, H.; Piazza, G. Primary prevention of venous thromboembolism with apixaban for multiple myeloma patients receiving immunomodulatory agents. *Br. J. Haematol.* **2020**, *190*, 555–561. [CrossRef]
66. Storrar, N.P.F.; Mathur, A.; Johnson, P.R.E.; Roddie, P.H. Safety and efficacy of apixaban for routine thromboprophylaxis in myeloma patients treated with thalidomide- and lenalidomide-containing regimens. *Br. J. Haematol.* **2018**, *185*, 142–144. [CrossRef] [PubMed]
67. Napolitano, M.; Saccullo, G.; Marietta, M.; Carpenedo, M.; Castaman, G.; Cerchiara, E.; Chistolini, A.; Contino, L.; De Stefano, V.; Falanga, A.; et al. Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: An expert consensus. *Blood Transfus.* **2018**, *17*, 171–178. [CrossRef]
68. Lutz, J.; Jurk, K.; Schinzel, H. Direct oral anticoagulants in patients with chronic kidney disease: Patient selection and special considerations. *Int. J. Nephrol. Renovasc. Dis.* **2017**, *10*, 135–143. [CrossRef]