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ORIGINAL ARTICLE

Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma

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The incidence of venous thromboembolism (VTE) is more than 1‰ annually in the general population and increases further in cancer patients. The risk of VTE is higher in multiple myeloma (MM) patients who receive thalidomide or lenalidomide, especially in combination with dexamethasone or chemotherapy. Various VTE prophylaxis strategies, such as low-molecular-weight heparin (LMWH), warfarin or aspirin, have been investigated in small, uncontrolled clinical studies. This manuscript summarizes the available evidence and recommends a prophylaxis strategy according to a risk-assessment model. Individual risk factors for thrombosis associated with thalidomide/lenalidomide-based therapy include age, history of VTE, central venous catheter, comorbidities (infections, diabetes, cardiac disease), immobilization, surgery and inherited thrombophilia. Myeloma-related risk factors include diagnosis and hyperviscosity. VTE is very high in patients who receive high-dose dexamethasone, doxorubicin or multiagent chemotherapy in combination with thalidomide or lenalidomide, but not with bortezomib. The panel recommends aspirin for patients with ⩽1 risk factor for VTE. LMWH (equivalent to enoxaparin 40 mg per day) is recommended for those with two or more individual/myeloma-related risk factors. LMWH is also recommended for all patients receiving concurrent high-dose dexamethasone or doxorubicin. Full-dose warfarin targeting a therapeutic INR of 2–3 is an alternative to LMWH, although there are limited data in the literature with this strategy. In the absence of clear data from randomized studies as a foundation for recommendations, many of the following proposed strategies are the results of common sense or derive from the extrapolation of data from many studies not specifically designed to answer these questions. Further investigation is needed to define the best VTE prophylaxis.

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Introduction

Deep vein thrombosis (DVT) and its potentially lethal complication, pulmonary embolism (PE), are manifestations of venous thromboembolism (VTE). The age- and sex-adjusted incidence of VTE is more than 1‰ annually, including 0.5‰ for DVT and 0.7‰ for PE.[1] In cancer patients, the incidence of VTE is more than 7%.[2] Hematological neoplasia patients, in particular those with multiple myeloma (MM), have the highest risk of thrombosis.[3] The oral immunomodulatory drugs, thalidomide and lenalidomide, further increase the risk of VTE. Various VTE prophylaxis strategies have been investigated in clinical studies. This review summarizes the results of these trials and recommends a prophylaxis strategy according to a risk-assessment model.

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Incidence and risk factors in general population

VTE is a disease of older age, the incidence of which rises markedly from less than 2‰ in individuals younger than 55 years to more than 5‰ in those older than 65 years.[1] VTE may be a lethal disease, mostly due to PE: the 1-week survival rate after PE is 71%, and one-fourth of all cases of PE present as sudden death.[4] Patients at risk must be identified and must receive the appropriate prophylaxis to reduce the incidence of this serious adverse event. The most important risk factors can be categorized into individual and disease-related risk factors.[5–9] Individual factors include patients' general characteristics (such as age and body mass index), inherited thrombophilic abnormalities, central venous catheter (CVC), previous superficial vein thrombosis, pregnancy/puerperium and drug use. Major inherited prothrombotic conditions are antithrombin III deficiencies, protein C and protein S deficiencies, activated protein C resistance, factor V Leiden mutation, prothrombin gene (G20210A) mutation and high levels of homocysteine.[9] The presence of inherited thrombophilia should be evaluated, especially in patients with previous history of VTE. The disease-related factors include recent (generally less than 3 months) clinical conditions such as surgery, trauma or hospital admission, and chronic clinical conditions such as nursing home confinement, malignant neoplasm with or without chemotherapy and neurologic disease with extremity paresis[6] (Table 1). As shown in Table 1, the increased relative risk of these conditions is quite heterogeneous, varying from 2 to 40. The simultaneous presence of more than one risk factor exponentially increases the risk of thromboembolic complications.

Thrombosis and cancer

The overall risk of VTE is increased 7- to 10-fold in patients with malignancy. In hematological cancer, the risk is increased as much as 28-fold.[3] The pathophysiology of thrombosis in cancer is a complex process. The interaction between malignant cells and monocyte/macrophage cells stimulates the release of tumor necrosis factor, interleukin-1 and -6, all causing endothelial damage. The interaction between tumor cells and macrophages also activates platelets, factor XII and X. Cysteine protease and tissue factor are highly expressed in cancer cells, have procoagulant activity, and can directly activate factor X and VII.[10,11] The risk of VTE is increased 4.1-fold in malignant neoplasms without chemotherapy, and 6.5-fold with chemotherapy. Patients are most likely to develop VTE in the first few months after diagnosis. In a recent study, the adjusted odds ratio within the first 3 months was found to be as high as 58.2, to decrease from the third month to the first year to 13.4 and to continue to decrease thereafter.[6] The conditions that increase the risk of VTE in cancer patients are active therapy, immobilization, surgery, CVC and erythropoiesis-stimulating agents. In two large clinical trials of women with node-negative breast cancer, the 5-year incidence of VTE was 0.2% in those who received placebo, 0.9% in those who received tamoxifen and 4.2% in those who received tamoxifen plus chemotherapy.[12,13] Cancer patients undergoing surgery have at least twice the risk of postoperative DVT and more than three times the risk of fatal PE than noncancer patients who are undergoing similar procedures.[14] In the general population, the presence of CVC is an independent risk factor for thrombosis in axillary/subclavian veins.[6] In cancer patients with indwelling CVC, the rate of thrombosis varied between 5 and 40%.[15–18] Recently, the Food and Drug Administration discussed concerns about risks of thromboembolic disease, promotion of tumor growth and decreased survival associated with the erythropoiesis-stimulating agents used to treat anemia caused by chemotherapy.[19] In two phase 3 clinical trials, an increased risk of sudden death or a cardiovascular or thromboembolic event was reported in patients with chronic renal failure who received

Table 1 The most important noninherited risk factors for deep vein thrombosis and pulmonary embolism[6]

Risk factors	*Univariate analyses*		*Multivariate analyses*	
	OR	*95% CI*	*OR*	*95% CI*
Individual				
Age (years)	1.38	1.09–1.74	NA	NA
Body mass index, kgm^{-2}	0.98	0.96–1.00	NA	NA
Previous superficial vein thrombosis	2.5	1.40–4.46	4.32	1.76–10.61
Previous central venous catheter or pacemaker	11.83	5.14–27.23	5.55	1.57–19.58
Disease-related				
All cardiac disease	1.57	1.18–2.08	NA	NA
Chronic renal disease	3	1.19–7.56	NA	NA
Neurologic disease with extremity paresis	5.17	2.78–9.59	3.04	1.25–7.38
Institutionalization within previous 90 days	18.44	11.48–29.64	NA	NA
Institutionalization without recent surgery	NA	NA	7.98	4.49–14.18
Institutionalization with recent surgery	NA	NA	21.72	9.44–49.93
Malignant neoplasm	7.67	4.69–12.53	NA	NA
Malignant neoplasm with chemotherapy	9.9	3.89–25.18	6.53	2.11–20.23
Malignant neoplasm without chemotherapy	6.9	3.92–12.17	4.05	1.93–8.52
General surgery	15	6.07–37.09	NA	NA
Orthopedic surgery	11.67	5.07–26.86	NA	NA
Neurosurgery	41	2.48–677.92	NA	NA
Any anesthesia	17.5	9.25–33.10	NA	NA
Trauma	20.5	7.51–55.93	12.69	4.06–39.66
Gynecologic surgery	11	1.42–85.20	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

erythropoiesis-stimulating agents to drive hemoglobin levels into the normal range (13.5 g dl^{-1} or higher), but was not shown in those treated to achieve levels in a subnormal range (10.5–11.5 g dl^{-1}).[20,21] In summary, cancer patients are at increased risk for developing hypercoagulable events, and this is confounded further by several factors, including therapy.

Thrombosis and plasma cell dyscrasia

In 310 patients with monoclonal gammopathy of undetermined significance (MGUS), the incidence of VTE was 6.1% after a median follow-up of 44 months.[22] By univariate analysis, age $\geqslant$65 years, M protein $\geqslant$16 g l^{-1} and disease progression were the significant risk factors for VTE. In another series of 174 MGUS patients, the incidence of VTE was 7.5%, and all events occurred within the first 6 months of follow-up. The risk of VTE was increased 8-fold if a personal history of VTE was present and 27-fold in immobilized patients.[23] However, it cannot be determined from these studies if there is a true increased risk of VTE with MGUS, since the risk may be solely related to the underlying medical problems that prompted laboratory testing for monoclonal proteins in the first place. The incidence of VTE in MM patients is difficult to estimate and varies from 3%[24] to 10%.[23] However, based on the available data using standard treatments for MM, the risk of VTE in the first 4 months following diagnosis is approximately 3–4% in patients receiving either dexamethasone alone[24] or melphalan/prednisone therapy.[25,26] This risk could be as high as 10% with nonbiologic therapy.[23] The exact mechanisms behind VTE in MM are not known. The type of drug therapy used to treat the disease is the dominant factor determining the risk of VTE. Procoagulant antibody formation, paraprotein interference with fibrin structure, activated protein C resistance and endothelial damage may play a significant role.[27] Furthermore, increased secretion of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor can activate coagulation pathways.[28] Elevated von Willebrand and factor VIII, as well as decreased protein S and activated protein C resistance, have been described.[29] Unfortunately, no single prothrombotic abnormality can be used to predict which patients will develop VTE.

Thrombosis and thalidomide

As a single agent, thalidomide does not increase the risk of VTE compared to dexamethasone alone or melphalan/prednisone. The risk of VTE is highly variable, even within the same combination. This difference is likely to be related to both individual and therapy-related risk factors, including the dose of novel agents or, more importantly, the dose of dexamethasone. Thalidomide alone does not increase the risk of VTE: in newly diagnosed MM the incidence of VTE was 3–4%[30,31] and in relapsed/refractory MM it was 2–4%.[32–34] The combination of thalidomide with dexamethasone significantly increased the incidence of VTE to 14–26% in newly diagnosed MM patients[24,35,36] and to 2–8% in relapsed/refractory patients.[37,38] In a randomized trial comparing thalidomide/dexamethasone with placebo/dexamethasone, the incidence of VTE was 17% in the thalidomide arm versus 3% in the placebo arm. No specific thromboprophylaxis was mandated in this trial.[24] When thalidomide was combined with melphalan, the incidence of VTE was 10–20% in newly diagnosed patients[25,26,39] and 11% in relapsed/refractory patients.[40] In two independent phase III trials, the combination of melphalan, prednisone and thalidomide at diagnosis caused VTE in 12–20% of patients who did not received any prophylaxis.[25,26] Thalidomide plus doxorubicin and dexamethasone further increased the risk of VTE to 10–27% at diagnosis[41–43] and to 58% in a single study.[44] Table 2 summarizes the incidence of VTE as it relates to different agents and regimens.[24–26,30–53] No significant increase in incidence of VTE was reported in patients who received thalidomide alone, or in combination with prednisone as a maintenance therapy.[54] Overall, the median time to onset of a thrombotic event was around 3 months. The risk of VTE was higher in newly diagnosed patients.

To further define the relative risk of VTE as it relates to the different therapeutic agents, Zangari *et al*.[63] analyzed risk factors associated with the development of VTE in 535 patients treated either with thalidomide in combination with multiagent chemotherapy or with dexamethasone only. Overall, the incidence of VTE was 15%. By multivariate analysis, doxorubicin-containing regimens were associated with a 4.3-fold increase in VTE, while newly diagnosed disease was associated with a 2.5-fold increase of VTE in comparison with relapsed/refractory disease. In a retrospective analysis, erythropoietin did not increase the risk of VTE.[64]

Thrombosis and lenalidomide

Lenalidomide is an immunomodulatory drug that is structurally similar to thalidomide yet functionally distinct. As a single agent, lenalidomide did not significantly increase the risk of VTE at relapse.[55,56] By contrast, when lenalidomide was combined with dexamethasone, the incidence of VTE was 75% in a small group of newly diagnosed patients[57] and 8–16% in relapsed/refractory patients[59,60] (Table 2). In two large randomized trials in which relapsed patients received lenalidomide–dexamethasone or dexamethasone alone without mandatory prophylaxis, the incidence of VTE was 8–16 and 4%, respectively.[59,60] When lenalidomide was combined with cyclophosphamide in relapsed patients, the incidence of VTE was 14%.[61] The combination of lenalidomide–bortezomib did not increase the risk of VTE in relapsed/refractory patients.[62] The incidence of VTE according to different agents and regimens is summarized in Table 2. Risk factors associated with an increased risk of VTE were the dexamethasone dose and erythropoietin administration. In a recent report, lenalidomide was delivered at diagnosis with high-dose dexamethasone (480 mg per month) or low-dose dexamethasone (160 mg per month); the incidence of VTE was 23 and 8%, respectively.[58] In patients receiving lenalidomide and dexamethasone at relapse, the concomitant administration of erythropoietin significantly increased the risk of VTE (23 versus 5%) in one study,[65] and though the risk was also elevated in a second study, the difference failed to reach statistical significance (31 versus 14%).[54]

VTE prophylaxis in medical and surgical patients

Models to estimate risk on the basis of number and type of risk factors present in an individual patient have been proposed,[66,67] but none have been prospectively validated. Anticoagulant prophylaxis is generally considered reasonable for hospitalized patients who are older than 40 years, are limited in their mobility for more than 3 days, or have at least one risk factor. A meta-analysis,[68] including nine randomized studies comparing anticoagulant prophylaxis with no treatment in hospitalized medical patients, showed that anticoagulant prophylaxis is

Table 2 Venous thromboembolism incidence in trials of thalidomide or lenalidomide without thromboprophylaxis

Treatment regimen	*Newly diagnosed patients*		*Relapsed/refractory patients*	
	VTE incidence (%)	*References*	*VTE incidence (%)*	*References*
Thalidomide				
Alone	3–4[a]	30,31	2–4	32–34
Plus dexamethasone	14–26	24,35,36	2–8	37,38
Plus melphalan	10–20	25,26,39	11	40
Plus doxorubicin	10–27	41–43	58[b]	44
Plus cyclophosphamide	3[b]–11	45,46	4–8	47–50
Plus multiagent chemotherapies	16–34	51,52	15	53
Lenalidomide				
Alone	—	—	0–33	55,56
Plus dexamethasone	8–75	57,58	8–16	59,60
Plus cyclophosphamide	—	—	14	61
Plus bortezomib	—	—	0	62

Abbreviations: VTE, venous thromboembolism; —, data not available.
[a]Asymptomatic newly diagnosed multiple myeloma patients.
[b]Both at diagnosis and relapse.

effective in preventing symptomatic VTE. All these trials included only patients considered to be at high risk for VTE because they had been hospitalized for such conditions as congestive heart failure, acute and chronic respiratory failure, acute infectious disease or rheumatologic disease. In the three largest randomized trials, the administration of anticoagulant prophylaxis in hospitalized patients decreased the risk of VTE 3-, 2- and two-fold, respectively. In the first randomized study (MEDENOX), 1102 patients were randomly assigned to receive enoxaparin or placebo.[69] Patients randomized to prophylaxis with 40 mg of enoxaparin daily had a significantly lower rate of VTE than the placebo group (5.5 versus 14.9%, $P<0.001$). In the second study, 3706 patients received deltaparin or placebo;[70] deltaparin significantly decreased the rates of VTE (2.8 versus 5.0%, $P=0.002$). In the third study, 849 hospitalized patients received fondaparinux or placebo.[71] Once again, fondaparinux significantly reduced the incidence of VTE (5.6 versus 10.5%, $P=0.03$).

No study has directly compared different commonly used anticoagulant regimens. A meta-analysis of eight trials comparing unfractionated heparin with low-molecular-weight heparin (LMWH) for prophylaxis in high-risk hospitalized patients[72] showed no significant differences between the two treatment groups in the rates of VTE, but patients receiving LMWH had a twofold decrease in the risk of major bleeding (relative risk, 0.48; 95% CI, 0.23–1.00).

Recent recommendations[73] are based on the above-summarized results and are consistent with the guidelines of the American College of Chest Physicians.[74] They strongly recommend the use of either unfractionated or LMWH in acutely ill hospitalized patients with heart failure, severe respiratory disease, acute stroke, immobility or multiple risk factors.

Like medical patients, surgical patients also derive significant benefit from thromboprophylaxis with LMWH.[74] Individual trials of antiplatelet therapy, usually used to prevent arterial thromboembolism, revealed discrepant results, but a meta-analysis indicated a reduction of about one quarter in the risk of VTE in surgical and high-risk medical patients who received antiplatelet therapy.[75] In a large randomized study, 17 444 patients undergoing orthopedic surgery were randomized to receive 160 mg per day of aspirin or placebo. VTE occurred in 1.6% of patients assigned aspirin compared with 2.5% of those assigned placebo, with an absolute reduction of the risks of VTE of about one third.[76]

VTE prophylaxis in cancer patients

Very few randomized studies in cancer patients who received anticoagulant prophylaxis or placebo are available. The previously described three studies on hospitalized patients included only a small number of cancer subjects, and they were not balanced for the additional risk factors that occur in cancer patients.[69–71] With these limitations, a subset analysis of cancer patients in the MEDENOX study reported that enoxaparin reduced by twofold the risk for VTE (relative risk 0.50, 95% CI 0.14–1.72) in the cancer cohort.[77]

In one randomized trial,[78] 311 women with stage IV breast cancer were randomized to receive low-dose warfarin or placebo for the duration of their multiagent chemotherapy. Warfarin was given at 1 mg daily for the first 6 weeks and then the dose was adjusted to maintain the international normalized ratio (INR) at 1.3–1.9. VTE was observed in 4% of patients receiving placebo and in 0.6% of those taking low-dose warfarin. The VTE risk was reduced by sixfold in warfarin patients ($P=0.03$). No difference in any major bleeding was found. Despite these results, the use of low-dose warfarin is not frequently used in cancer patients for a number of reasons. First, low-dose warfarin is poorly tolerated in some patients and the use of low-dose warfarin with INR monitoring is a laborious task often unattractive to both patients and physicians. Second, the relatively low risk of VTE of 4% in the control patients in this study raises the question of whether routine prophylaxis is warranted. Third, the influence of cytochrome P-450 CYP2C9 polymorphisms and warfarin-drug interactions may increase warfarin sensitivity and lead to over anticoagulation with higher risk of hemorrhage.[79] Finally, there has been no other study that confirms these findings.

VTE prophylaxis in myeloma patients receiving thalidomide or lenalidomide

Given the high risk of VTE with combination regimens including either thalidomide or lenalidomide, at least all newly diagnosed patients should receive thromboprophylaxis. To address this issue several studies have added anticoagulant prophylaxis to induction therapies (Table 3). In one study, the thalidomide–dexamethasone combination was delivered at diagnosis without

any prophylaxis and the incidence of VTE was 26%. The protocol was then amended, low-fixed-dose prophylactic warfarin (1.25 mg daily) was introduced and the incidence of VTE dropped to 13%.[35] In another study thalidomide, dexamethasone and low-fixed-dose warfarin were administered; the incidence of VTE, at 25%, did not appear to be impacted.[31] In a rather small series of 26 patients who received thalidomide–dexamethasone at diagnosis, either therapeutic LMWH or warfarin (INR 2.0-3.0) was used, and VTE was seen in 8%.[80]

In a randomized trial, melphalan, prednisone and thalidomide were administered as induction therapy. In the first 65 patients who did not receive anticoagulant prophylaxis, the incidence of VTE was 20%, but dropped to 3% when enoxaparin was introduced at 40 mg per day for the first 4 months of therapy. All thromboembolic events occurred within 2 months after the discontinuation of enoxaparin.[25] In a randomized study, 412 newly diagnosed patients received vincristine–doxorubicin–dexamethasone or thalidomide–doxorubicin–dexamethasone. Patients who received thalidomide were treated with nadroparin. The incidence of VTE was 5% in the control group and 9% in the thalidomide group, with all events occurring in the first 6 months of therapy.[81] In a smaller study, 50 patients received thalidomide, pegylated liposomal doxorubicin, dexamethasone and low-fixed-dose warfarin (1.25 mg per day), and the incidence of DVT was 14%.[82] In another study, 105 patients received a combination of pegylated doxorubicin, vincristine, thalidomide and dexamethasone at diagnosis without any prophylaxis; VTE incidence was 58%. The protocol was then amended and the remaining 58 patients received aspirin (81 mg per day), resulting in a VTE incidence of 18%.[44]

In one study, 256 newly diagnosed myeloma patients received multiagent chemotherapy (including doxorubicin, dexamethasone, etoposide, cyclophosphamide, cisplatin) with or without thalidomide. Without anticoagulant prophylaxis, VTE was 14% in patients who received chemotherapy only and 34% in those who received chemotherapy plus thalidomide. VTE was 31% in patients who received chemotherapy, thalidomide and low-fixed-dose warfarin (1 mg per day), but 15% in those who received chemotherapy, thalidomide and enoxaparin (40 mg per day).[83] In another study, the incidence of VTE among 162 patients randomly assigned to multiagent chemotherapy plus thalidomide versus no thalidomide was 34 versus 18%, respectively. The protocol was subsequently amended and LMWH was introduced, but VTE remained at 24% among the patients enrolled in the multiagent chemotherapy plus thalidomide group, and at 15% in the patients enrolled in the multiagent chemotherapy control group.[51] These data clearly show that the combination of multiagent chemotherapy with thalidomide causes the highest risk of VTE, and that LMWH at a prophylactic dose may not effectively prevent this adverse event.

Among 34 patients who received lenalidomide, dexamethasone and aspirin (80–325 mg per day) at diagnosis, VTE was as low as 3%.[84] In a larger randomized study, newly diagnosed patients received lenalidomide with high-dose dexamethasone (480 mg per month) or low-dose dexamethasone (160 mg per month); the incidence of VTE was 23 and 8%, respectively, without any prophylaxis, but dropped to 14 and 5%, respectively, after the introduction of aspirin.[58] This study clearly suggests both that high-dose dexamethasone by itself represents a major risk factor for VTE, and that aspirin prophylaxis seems appropriate in patients treated with low-dose dexamethasone. In another trial, patients received melphalan, prednisone and lenalidomide plus aspirin (100 mg per day), and VTE was 5%.[85] In a combination study of lenalidomide, doxorubicin and dexamethasone, 85% of patients received erythropoietin therapy; the incidence of VTE was 9% with the use of aspirin (81 mg per day).[86] Numbers are limited and only a few trials have addressed the question of VTE prophylaxis with lenalidomide-containing regimens. The dose of aspirin is still an open issue: on the one hand, the full dose (325 mg) inhibits both prostaglandins and prostacyclines, and on the other hand, the 81–162 mg dose inhibits only the prostaglandins, leaving the antiplatelet protective prostacycline levels intact.[87] With these limitations, aspirin nevertheless seems an effective anticoagulant prophylaxis for lenalidomide treatment.

A black box warning was recently added to the package inserts for thalidomide and lenalidomide, indicating that patients treated with these drugs and dexamethasone may benefit from VTE prophylaxis.[88,89] The American College of Chest Physicians recommends the use of LMWH for VTE prophylaxis in high-risk cancer patients and strongly recommends against the use of aspirin.[74] Randomized trials are urgently needed to define the best anticoagulant prophylaxis. On the one hand, full-dose warfarin with a target INR of 2.0–3.0 and LMWH are both highly effective, but are cumbersome and require close monitoring, in the case of warfarin, or subcutaneous injections, in the case of LMWH. Moreover, elderly patients may have difficulty complying with and following these strategies. On the other hand, aspirin as well as low-fixed-dose warfarin are quite simple options, but their efficacy must be validated.

In the absence of clear data from randomized studies as a foundation for recommendations, many of the following proposed strategies are the results of common sense or derive from the extrapolation of data from many studies not specifically designed to answer these questions. The treatment decision needs to be individualized based on the type of therapy and patients' individual risk factors.

Recommendations in myeloma patients receiving thalidomide or lenalidomide

The choice of thromboprophylaxis needs to be modified depending on the baseline risk of VTE associated with a given regimen. The goal should be to use the safest and least cumbersome form of thromboprophylaxis that reduces the risk of VTE to at least below 10%.

Thalidomide

In published articles, thalidomide alone as induction therapy or maintenance after chemotherapy has consistently shown an incidence of VTE below 5%.[30,31,54] In accordance with these data, anticoagulant prophylaxis is not recommended for patients receiving single-agent thalidomide. In newly diagnosed patients, who received the combination of thalidomide and dexamethasone, the risk of VTE was effectively reduced by full-dose warfarin, while low-fixed-dose warfarin was ineffective[31,35,80] and no report is available for either LMWH or aspirin. For newly diagnosed patients treated with combinations including melphalan, LMWH was quite effective, but no other anticoagulant prophylaxis has been studied.[25] Low-fixed-dose warfarin and full-dose aspirin were ineffective in patients who received thalidomide plus doxorubicin or multiagent chemotherapies.[44,83] LMWH was equally ineffective for the combination of thalidomide and doxorubicin, except when used in a regimen

Table 3 Venous thromboembolism incidence in trials of thalidomide or lenalidomide with thromboprophylaxis in newly diagnosed patients

Treatment regimen	*VTE incidence (%)*				*References*
	LMWH	*Low-fixed-dose warfarin*	*Full-dose warfarin*	*Aspirin*	
Thalidomide					
Plus dexamethasone	—	13–25	8	—	31,35,80
Plus melphalan	3	—	—	—	25
Plus doxorubicin	9	14	—	18	44,81,82
Plus multiagent chemotherapies	15–24	31	—		51,83
Lenalidomide					
Alone	—	—	—	—	—
Plus dexamethasone	—	—	—	3–14	58,84
Plus melphalan	—	—	—	5	85
Plus doxorubicin	—	—	—	9	86

Abbreviations: LMWH, low-molecular-weight heparin; VTE, venous thromboembolism; —, data not available.

containing bortezomib.[90] LMWH with the combination of thalidomide and multiagent chemotherapies was not effective, with a 24% incidence of VTE.[51] The heterogeneity of data reported in the literature does not allow a precise recommendation. In the majority of studies, both LMWH and full-dose warfarin were effective, while results with aspirin were negative or not available. In relapsed/refractory patients, very limited data are available on the efficacy of thromboprophylaxis. The risk of VTE (2–15%) at relapse is much lower than at the time of diagnosis (3–34%). For these reasons, anticoagulant prophylaxis in relapsed patients may be suggested only in those with a high risk of VTE.

Lenalidomide

Lenalidomide alone does not induce a high risk of VTE and thromboprophylaxis is not suggested when lenalidomide is used as a single agent. In the reported studies, aspirin has been appropriate prophylaxis in patients who received lenalidomide in combination with low-dose dexamethasone, melphalan or doxorubicin, reducing the incidence of VTE to less than 10%.[59,84–86] High-dose dexamethasone is an additional risk factor and may mandate the delivery of more aggressive prophylaxis, such as LMWH or full-dose warfarin.

Choice of thromboprophylaxis

Thromboprophylaxis should be tailored to the presence of risk factors that may increase the risk of VTE, as shown in Table 4. The relative risk of these factors is quite heterogeneous, varying from 2 to 40. Accordingly, the hazard ratio of a specific risk should be taken in account in the choice of the appropriate anticoagulant prophylaxis.

Risk factors

- Individual risk factors, such as, age, obesity, history of VTE, central-venous catheter, comorbidities (diabetes, infections, cardiac diseases), surgical procedures (including vertebroplasty and kyophoplasty) and inherited thrombophilia;
- myeloma-related risk factors such as diagnosis *per se* as well as hyperviscosity;
- therapy-related risks such as high-dose dexamethasone, doxorubicin or multiagent chemotherapies.
- Both individual and myeloma-related risks of VTE should be taken into account in determining the type of thromboprophylaxis. Therapy-related risk factors should be considered, *per se*, high-risk factors.

Table 4 Risk assessment model for the management of venous thromboembolism in multiple myeloma patients treated with thalidomide or lenalidomide

	Actions
Individual risk factors	
Obesity[a]	If no risk factor or any one risk factor is present:
Previous venous thromboembolism	Aspirin 81–325 mg once daily
Central venous catheter or pacemaker	
Associated disease	If two or more risk factors are present:
Cardiac disease	LMWH (equivalent of enoxaparin
Chronic renal disease	40 mg once daily)
Diabetes	Full-dose warfarin (target INR 2–3)
Acute infection	
Immobilization	
Surgery	
General surgery	
Any anesthesia	
Trauma	
Medications	
Erythropoietin	
Blood clotting disorders	
Myeloma-related risk factors	
Diagnosis	
Hyperviscosity	
Myeloma therapy	
High-dose dexamethasone[b]	LMWH (equivalent of enoxaparin 40 mg once daily)
Doxorubicin	Full-dose warfarin (target INR 2–3)
Multiagent chemotherapy	

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.
[a]Obesity was defined as body mass index $\geqslant 30\,kgm^{-2}$.
[b]$\geqslant 480$ mg per month.

Thromboprophylaxis

- Although aspirin is more appealing because of its convenience and ease of administration, the rate of thrombosis, especially in patients treated with thalidomide-based

combinations is relatively high when full-dose is used. Until further evidence becomes available, aspirin should only be recommended for low-risk patients, such as those with no risk factor or one individual/myeloma-related risk factor;
- LMWH or full-dose warfarin should be recommended in the presence of at least two individual/myeloma-related risk factors;
- LMWH or full-dose warfarin should be considered in all patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy, independent of the presence of additional risk factors.

Given the limitations of the data upon which these recommendations are made, they should not be considered firm guidelines. The specific form of thromboprophylaxis recommended for a given patient ultimately should be based on the treating physician's best clinical judgment.

Without a published direct comparison of different anticoagulants in this setting, the choice may be based on specific clinical factors. For example, the initiation of anticoagulant prophylaxis and, more importantly, of antiplatelet agents, warrants exclusion of acquired von Willebrand disease, a rare but typical complication of lymphoproliferative diseases. Full-dose warfarin might best be avoided in patients in whom severe thrombocytopenia is likely to develop, such as with thalidomide or lenalidomide combined with chemotherapy. Note, though, that since such combinations are associated with a relatively high risk of VTE, LMWH (with its lower risk of secondary bleeding and a short half-life) is a more suitable option than either warfarin or aspirin. The most widely used schema of LMWH prophylaxis employ enoxaparin 40 mg once daily or deltaparin 5000 U once daily. Renal failure may limit the use of LMWH since renal clearance is the primary mode of elimination for this drug. In patients with reduced creatinine clearance ($<30\,ml\,min^{-1}$), LMWH is not an optimal choice because it may accumulate and increase the risk of bleeding. The best choice in this situation could therefore be full-dose warfarin.[91,92]

The duration of prophylaxis may vary according to length of treatment. In cancer patients, the majority of VTE appear within 12 months from diagnosis.[6] In myeloma, the vast majority of VTE has been reported in the first 6 months of treatment and all episodes occurred within the first 12 months.[25,52,83] It may be reasonable to deliver anticoagulant prophylaxis for 4–6 months, while longer periods may be considered in the presence of additional patient- or treatment-specific risk factors.

The major adverse event of thromboprophylaxis is bleeding. Prophylactic doses of LMWH or aspirin confer very little risk of major bleeding. The vitamin K antagonist warfarin may slightly increase the risk of bleeding, especially, in patients who develop thrombocytopenia due to chemotherapy. Mechanical methods of prophylaxis including graduated compression stockings, the use of intermittent pneumatic compression devices and the venous foot pump reduce stasis within the leg veins and reduce the frequency of VTE. Unfortunately, no data from large studies are available. For patients in whom anticoagulant prophylaxis may carry excessive bleeding risk because of coexisting conditions such as active gastrointestinal or intracranial bleeding, the use of mechanical prophylaxis is a reasonable alternative.[93,94]

Management of thromboembolism

Diagnosis of venous thromboembolism

DVT typically originates in the distal deep veins of the lower extremities but occasionally originates in the proximal veins, usually in response to trauma or surgery. Approximately 25% of untreated distal thromboses extend into the proximal veins, usually within a week after presentation.[95] Proximal-vein thrombosis is complicated by PE, either symptomatic or asymptomatic, in approximately 50% of patients.[96] In the case of suspect VTE, the diagnostic test of choice is compression ultrasonography, which has sensitivity and specificity of more than 95%. When PE is suspected, imaging remains the mainstay for diagnosis. Computed tomography pulmonary angiography is now the most widely used diagnostic test. Nuclear medicine techniques are used much less frequently. Magnetic resonance pulmonary angiography may be considered an alternative to computed tomography pulmonary angiography in patients who have contraindications to iodinated contrast media.[97]

Treatment of venous thromboembolism

All patients should be instructed to promptly inform the physician if clinical symptoms of VTE, such as, redness of the skin, pain in the extremities and/or chest, shortness of breath or rapid heartbeat occur. When deep-vein thrombosis is diagnosed, the goals of treatment are relief of symptoms and prevention of embolization and recurrence. The appropriate initial therapy for outpatients is LMWH. The optimal doses of the most commonly used LMWH are $100\,U\,kg^{-1}$ every 12 h or $200\,U\,kg^{-1}$ daily for deltaparin; $1\,mg\,kg^{-1}$ every 12 h or $1.5\,mg\,kg^{-1}$ daily for enoxaparin; $86\,U\,kg^{-1}$ every 12 h or $171\,U\,kg^{-1}$ daily for nadroparin. If the risk of concomitant thrombocytopenia is low, oral anticoagulation should generally be started on the first day of treatment. Heparin should be given for a minimum of 5 days and not stopped until the patient's INR has been from 2.0 to 3.0 for 2 consecutive days. The optimal duration of therapy remains controversial. However, in cancer patients who have had a VTE, the risk of recurrence in the year after discontinuation of anticoagulant therapy is more than 10%.[98] A randomized trial showed that long-term maintenance therapy with LMWH resulted in halving the recurrence risk as compared to maintenance with coumarin derivatives.[99] On the basis of these results, extended therapy with LMWH should be considered in cancer patients balancing its advantages with such possible disadvantages as cost, the need for daily injections and the risk of osteoporosis.

In myeloma patients treated with thalidomide or lenalidomide who develop VTE, it is reasonable to briefly discontinue thalidomide or lenalidomide and resume the treatment when full anticoagulation has been established.[81] As with other cancer patients, long-term therapy with LMWH, or with warfarin if heparin is not practical, should be continued for the total duration of thalidomide or lenalidomide therapy.

Conclusion

Myeloma patients treated with thalidomide or lenalidomide in combination with steroids or chemotherapy have an increased risk of VTE and hence require routine thromboprophylaxis. LMWH, full-dose warfarin and aspirin (especially lower dose) have all been shown to be effective in reducing the incidence of VTE. Although attractive, low-fixed-dose warfarin needs more extensive investigation. On the basis of available data, we recommend specific thromboprophylaxis strategies according to the type of therapy and the individual risk of patients (Table 4). Aspirin alone is recommended for patients who have either no risk factor or only one individual/myeloma-related risk factor. Patients who have at least two individual/myeloma-related risk

factors or therapy-related (high-dose dexamethasone, doxorubicin or multiagent chemotherapy) should receive LMWH (equivalent to enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2–3) as thromboprophylaxis. All patients with therapy-related risks (high-dose dexamethasone, doxorubicin or multiagent chemotherapy) should receive LMWH or full-dose warfarin. The ongoing randomized trials comparing aspirin, warfarin and LMWH will soon determine the optimal prophylaxis strategy. The goal remains to define a strategy that will reduce the risk of VTE below 10% in patients receiving thalidomide or lenalidomide.

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