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# Thrombotic Complications of Myeloma Therapy

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**Patients with multiple myeloma are at relatively high baseline risk of developing thromboembolic events (TEE), usually deep vein thromboses. There are numerous contributing factors, among them certain treatment regimens that include thalidomide or related compounds such as lenalidomide combined with glucocorticoids and/or cytotoxic chemotherapy. The risk of developing TEE appears to be particularly high when these immunomodulatory agents are combined with anthracyclines as treatment of newly-diagnosed disease. Up-front combinations including thalidomide plus pulse dexamethasone and/or alkylating agents are associated with an intermediate risk, whereas the same regimens for relapsed/refractory myeloma seem to be associated with the lowest risk. Several different thromboprophylaxis strategies have been effective in lowering the risk of developing clots: daily aspirin (81-325 mg/day), full-intensity warfarin (INR 2-3), and prophylactic enoxaparin (40 mg SQ daily). Low, fixed-dose warfarin may also reduce the risk of TEE, but the data on this are disputable. None of these TEE prevention strategies have been prospectively compared head-to-head, so the choice often reflects physician and/or patient preferences. The available evidence upon which one might make such a decision is reviewed here.**

Individuals with multiple myeloma (MM) are at increased risk for developing thromboembolic events (TEE) compared to the general population.[1] The exact incidence is difficult to determine since reported TEE rates likely vary according to the level of diagnostic vigilance. For example, in one retrospective chart review at the Cleveland Clinic, which has an established imaging algorithm for evaluating patients with MM and monoclonal gammopathy of uncertain significance who have symptoms of a possible TEE, the reported rate was approximately 10%.[1] In contrast, the rates documented in patients treated with melphalan-prednisone or dexamethasone as part of large multicenter studies without uniform algorithms for documenting TEE were 5% and 3%, respectively.[2,3] It is likely the actual background incidence falls in the 5-10% range. Factors that have been suggested as contributory to the risk of TEE in people with MM include newly diagnosed disease status[4]; immobility due to pain and/or surgery; indwelling central venous catheters; extrinsic venous compression by plasmacytomas; acquired abnormalities in platelet function,[5] clotting factors,[6] and the coagulation cascade[7-9]; the presence of inherited factors such as Factor V Leiden; and treatment with immunomodulatory agents including thalidomide and lenalidomide. The risk of developing TEE during therapy with combination regimens containing thalidomide and lenalidomide will be discussed, followed by recommendations on prevention and treatment.

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## Thalidomide

Thalidomide has become one of the most widely used drugs to treat MM in the United States. While it is FDA approved for use in combination with high-dose dexamethasone (DEX) as treatment for newly diagnosed multiple myeloma (NDMM), single-agent therapy is commonly employed in the setting of relapsed/refractory multiple myeloma (RRMM). Increasingly, thalidomide is also being administered concurrently with cytotoxic chemotherapy. There have been numerous reports of TEE attributed to thalidomide therapy. The majority of thrombotic events described in patients receiving treatment with thalidomide have been venous, but occasional arterial thrombotic events have also been reported.[10] Thalidomide has a wide spectrum of biological effects, including some that have been hypothesized to promote thrombosis such as transient reduction of soluble thrombomodulin levels during the first month of therapy[11] and restoration of endothelial cell PAR-1 expression after damage from cytotoxic agents such as doxorubicin.[12] The latter finding may in part explain the markedly higher TEE risk apparent during thalidomide-anthracycline combination therapy compared to thalidomide monotherapy (see below), since immunomodulatory drugs do not appear to cause endothelial injury themselves.[13]

### *Single-agent thalidomide*

There is little evidence from prospective clinical trials or retrospective reviews that single-agent thalidomide significantly increases the risk of developing TEE. No definite TEE occurred among 84 patients with RRMM treated with thalidomide (200-800 mg/day).[14] In a follow-up report on 169 patients with RRMM, including extended follow-up on the original 84 patients, the incidence of Doppler-confirmed DVT was less than 2%.[15] Other investigators reported three nonfatal TEE and 1 transient ischemic attack occurring among 75 patients with RRMM treated with thalido-

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mide (median dose 600 mg/day; median duration of therapy, 22 weeks),[16] and in 1 of 28 patients with NDMM (thalidomide 100-600 mg/day),[17] respectively. Only 3 of 66 patients with RRMM treated with thalidomide (median dose 400 mg/day) plus celecoxib (800 mg/day) experienced thromboembolic complications,[18] which is noteworthy since COX-2 inhibitors themselves may be associated with thrombotic cardiovascular events.[19] Overall, the risk of TEE during thalidomide monotherapy for either RRMM or NDMM appears to be ≤ 5%.

### *Thalidomide plus dexamethasone*

In a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG) comparing thalidomide plus pulse dexamethasone (TD) to DEX alone as treatment for NDMM, there was an excess of TEE in the TD arm.[3] Seventeen episodes of TEE occurred amongst 102 patients (17%) treated with TD, versus 3 of 102 (3%) randomized to DEX alone. No specific thromboprophylaxis was mandated. This TEE incidence is consistent with the results of earlier phase II studies, in which TEE occurred in 12% to 15% of pts with NDMM treated with TD.[17,20] It is possible that the risk related to treatment with TD is slightly lower for patients with RRMM,[21] but whether this is a function of changing biology over the natural history of the disease is not established. One group of investigators reported that lowering the initial dose of thalidomide in patients with NDMM receiving TD induction reduced the incidence of early TEE.[22] Noting this, one must at least consider the possibility that the lower rates of TEE reported in patients with RRMM is related to their increased likelihood of being treated with lower dose thalidomide (i.e., 50-100 mg daily).

### *Thalidomide plus cytotoxic chemotherapy*

There appears to be a striking increase in the risk of developing TEE during treatment with thalidomide-anthracycline combination regimens, particularly during the first several months of therapy.[23] The risk of developing TEE during therapy with thalidomide-alkylating agent combination therapy may be increased as well, but not to the same degree as with anthracyclines.

In a phase II trial involving 43 patients treated with pulsed melphalan, dexamethasone, and thalidomide, the incidence of deep vein thrombosis was approximately 10%,[24] similar to the rate cited above for TD. In a randomized trial comparing MP to MP plus thalidomide (MPT; thalidomide dose 100 mg/day) as treatment for NDMM, the GIMEMA investigators observed an initial TEE incidence of 17% (11 of 65 pts) on the MPT arm, compared to only 2% in pts getting MP ($P = 0.001$).[25] As will be discussed below, the incidence of TEE was profoundly lowered by the addition of prophylactic enoxaparin, and the final overall incidence of TEE in the MPT arm was 12% (15 of 129). In a French study comparing MP, MPT, and intravenous MEL 100 mg/m$^2$ × 2, the incidence of TEE in

**Table 1. Incidences of thromboembolic events (TEE) reported in various trials utilizing thalidomide plus alkylating agents.**

| Regimen | Disease Status | TEE Prophylaxis | TEE Incidence | Reference |
|---|---|---|---|---|
| MEL 8 mg/m$^2$ d 1-4<br>DEX 12 mg/m$^2$ d 1-4, 17-20<br>THAL 300 mg d 1-4, 17-20 | NDMM | None | 10% | Dimopoulos et al[24] |
| MEL 4 mg/m$^2$ d 1-7<br>PRED 40 mg/m$^2$ d 1-7<br>THAL 100 mg/day (until PD) | NDMM | None* | 20%* | Palumbo et al[25] |
| MEL 0.25 mg/kg d 1-4<br>PRED 2 mg/kg d 1-4<br>THAL ≤ 400 mg/d<br>(until end of MP) | NDMM | None | 12% | Facon et al[2] |
| CTX 500 mg P.O. d 1,8,15<br>DEX 40 mg d 1-4, 15-18<br>THAL 100-200 mg/day | NDMM (15)<br>RRMM (46) | None | 3% | Williams et al[26] |
| CTX 300 mg/m$^2$ q wk<br>DEX 40 mg/d × 4 d q mo.<br>THAL ≤ 300 mg/day | RRMM | Warfarin<br>1 mg/day | 11.5% | Kyriakou et al[27] |
| CTX 50 mg/day<br>DEX 40 mg/d × 4 d q 3 wks<br>THAL 200-800 mg/d | RRMM | None | 7% | Garcia-Sanz et al[28] |
| CTX 150 mg/m$^2$ P.O. q 12 hr × 5 d<br>DEX 20 mg/m$^2$ d 1-4, 15-18<br>THAL 400 mg/day d 1-5, 14-18 | RRMM | None | 4% | Dimopoulos et al[29] |
| CTX 100-150 mg/day<br>THAL 100-400 mg/day | RRMM | None | 3% | Hovenga et al[30] |
| CTX 300 mg/m$^2$ q 12 hrs × 6<br>DEX 20 mg/m$^2$ d 1-4, 9-12, 17-20<br>THAL 100-400 mg/day | RRMM | None | 9% | Kropff et al[31] |
| CTX 400 mg/m$^2$ CIV d 1-4<br>VP-16 40 mg/m$^2$ CIV d 1-4<br>DEX 40 mg/day d 1-4 q 28 d | RRMM | NR | NR | Moehler et al[32] |

*After addition of enoxaparin 40 mg daily, incidence decreased to 3%, resulting in overall incidence of 12% for patients receiving MP + thalidomide on this study.
Abbreviations: CTX, cyclophosphamide; DEX, dexamethasone; MEL, melphalan; MP, melphalan + prednisone; NDMM, newly diagnosed multiple myeloma; NR, not reported; PD, progressive disease; PRED, prednisone; RRMM, relapsed/refractory multiple myeloma; THAL, thalidomide

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the MPT arm was also 12% (compared to 4% and 8% in the MP and IV MEL arms, respectively).[2] In this trial, no TEE prophylaxis was used, but any associated risk of thrombosis may have been partially offset by a shorter duration of thalidomide exposure.

There is a smaller but consistent body of data regarding combination regimens incorporating thalidomide plus cyclophosphamide, in which the incidence of TEE generally ranges from 3-11%.[26-32] Please see **Table 1** for a summary of studies evaluating thalidomide-alkylator combinations. Overall, the available data suggest that the risk of TEE for patients with NDMM is similarly increased whether they are being treated with concurrent MPT or TD, whereas the risk for RRMM patients receiving thalidomide-cyclophosphamide combination therapy is minimally, if at all, increased over baseline.

The risk of TEE when thalidomide is added to anthracycline-containing chemotherapy combinations appears to be much higher. As shown in **Table 2**, in phase II studies evaluating thalidomide plus anthracycline-containing chemotherapy regimens without thromboprophylaxis, incidences of 10% to 58% have been reported.[5,33-35] The study with the highest reported incidence of TEE was a large phase II trial evaluating DVd-T in both RRMM and NDMM patients in which 58% of patients developed TEE prior to amendment of the protocol mandating low-dose aspirin thromboprophylaxis. As will be discussed in more detail below, the addition of ASA reduced the incidence of TEE by approximately two-thirds.[5] There is also a small amount of randomized data further implicating concurrent anthracycline and thalidomide administration as a risk factor for TEE development. Barlogie et al described 668 patients with NDMM who received chemotherapy with (323 patients) or without (345 patients) thalidomide.[23] The first 162 patients randomized to thalidomide received no TEE prophylaxis, and the remaining thalidomide-treated patients received once-daily enoxaparin. Cycles 1 and 3 of the four-cycle induction regimen contained doxorubicin. Prior to the introduction of enoxaparin prophylaxis, the incidence of TEE in the thalidomide arm was 34%, versus 18% in the chemotherapy-only arm ($P < 0.001$). The impact of introducing LMWH will be discussed below. In another report, the same investigators retrospectively compared the incidence of TEE among 232 patients treated with one of two thalidomide-chemotherapy regimens: T-DCEP and DT-PACE. Both regimens include thalidomide (400 mg/day), dexamethasone (40 mg days 1-4), cyclophosphamide, cisplatin, and etoposide; DT-PACE also includes doxorubicin (Adriamycin). TEE occurred in 1 of 40 (2%) subjects treated with T-DCEP, compared to 31 of 192 (16%) receiving DT-PACE, most frequently within the first 60 days of therapy.[36] This suggests that the risk of TEE was related to the addition of doxorubicin, rather than dose or duration of thalidomide or dexamethasone, which were identical in these two patient groups.

## Lenalidomide (Revlimid) and CC-4047 (Actimid)

Lenalidomide and CC-4047 are members of a class of drugs called IMiDs® that are structurally related to thalidomide, but which have relatively increased potency and differing side effect profiles. Although the sedation, constipation, and neuropathy associated with thalidomide are not commonly seen with these agents, the risk of developing TEE during therapy with IMiD-containing combinations may be similar to that ascribed to thalidomide combinations.

### *Lenalidomide monotherapy*

In phase I and II studies of lenalidomide monotherapy in patients with RRMM or myelodysplastic syndrome, no increase in TEE was observed,[37-39] even in the absence of routine thromboprophylaxis. Data regarding the risk of TEE in patients with NDMM treated with single-agent lenalidomide are lacking.

### *Lenalidomide plus dexamethasone*

There is ample data suggesting that when lenalidomide is combined with dexamethasone (LD) the risk of TEE is increased. In a large phase III trial comparing LD to DEX alone without mandated thromboprophylaxis in patients with RRMM, the incidence of TEE in the LD arm was 16%, compared to 4% in the DEX alone arm.[40] In a second identically designed study the incidence of clots was lower in the LD arm (8.5%), but this was still significantly increased compared to the dexamethasone-only arm.[41] As will be discussed below, concurrent use of recombinant erythropoietin (rHuEPO) may have contributed to the difference in TEE rates between the LD arms of the two studies. On SWOG protocol S0232, in which patients with NDMM are randomized to dexamethasone (40 mg daily on days 1-4, 9-11, and 17-20 of three 35-day induction cycles) with or without lenalidomide (25 mg/day days 1-28 of each cycle), 9 of the first 12 patients randomized to LD (without thromboprophylaxis) developed TEE after a median duration of less than 2 months therapy.[42] In contrast, among 34 patients enrolled on a phase II study of lenalidomide + DEX as treatment of NDMM, Rajkumar et al observed only one DVT (incidence: 3%).[43] In this trial, aspirin (ASA) 80-325 mg/day was used as thromboprophylaxis. Three of 22 evaluable pts (14%) treated with the BiRD (biaxin/revlimid/dexamethasone) regimen and no thromboprophylaxis developed TEE.[44] Although higher doses of dexamethasone have been implicated as contributory to the risk of TEE,[45] this cannot be the sole explanation for the increased rates seen in the SWOG protocol compared to Rajkumar's study, since the dexamethasone doses were identical in these trials. It is possible that the prolonged LEN schedule in the SWOG trial was a factor. Currently, both the ECOG and SWOG trials have been amended to include mandatory aspirin thomboprophylaxis (325 mg/day; see below for data regarding ASA prophylaxis).

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### *Lenalidomide + chemotherapy*

Relatively few studies combining lenalidomide with cytotoxic chemotherapy have been conducted to date. As a result, little data are available regarding the risk of TEE associated with such treatment. In a phase I study evaluating lenalidomide plus MP with daily aspirin prophylaxis, the incidence of TEE was only 4% (1 of 24).[46] In a phase I study of lenalidomide plus bortezomib without thromboprophylaxis, no TEE were observed.[47] In one trial combining lenalidomide with an anthracycline, the incidence of TEE was in the same range (9%), but all patients in this report received 81 mg ASA daily as thromboprophylaxis.[48]

### *CC-4047*

In a phase I trial evaluating CC-4047 in 24 patients with RRMM, 4 (17%) developed TEE during the first year of therapy. There was no concurrent glucocorticoid therapy in this trial.[49]

### *Erythropoietin*

Recombinant human erythropoietin (rHuEPO) is widely used to treat anemia in MM patients undergoing concomitant antimyeloma therapy. rHuEPO therapy has been hypothesized to increase the risk of thrombosis by enhancing the thrombogenicity of endothelial cells' extracellular matrix via increased tissue factor expression,[50] as well as inducing TAFI expression and an associated hypofibrinolytic state.[51] While the early termination of a phase I/II study in which 3 of 7 patients with MDS treated with thalidomide and rHuEPO developed TEE[52] may lend credence to this notion, a randomized study comparing darbepoietin to placebo in 344 anemic patients with lymphoproliferative diseases (approximately half myeloma) getting concomitant chemotherapy did not show an increased risk of thrombosis related to darbepoietin use.[53] Subsequent reports on the risk of TEE during treatment with concurrent rHuEPO and thalidomide/lenalidomide in MM pts have varying results. A retrospective analysis of 199 patients with MM being treated with thalidomide showed no increased risk of developing TEE related to concomitant rHuEPO administration (annual incidence of 7.8% in patients receiving thalidomide plus rHuEPO vs 7.4% among those patients taking thalidomide only [$P$ = NS]).[54] More recently, an analysis of a large North American trial of LD as treatment for RRMM revealed a statistically significant difference in the incidence of TEE in patients getting LD plus concomitant rHuEPO (20/87; 23%) compared to those not receiving rHuEPO (4/83; 5%), leading the authors to recommend, "EPO . . . should be used with caution in patients receiving lenalidomide and high-dose dexamethasone."[55] The results of a preliminary analysis of the relationship between TEE incidence and rHuEPO use among the first 76 patients treated on SWOG protocol S0232 were consistent with these findings (31% with rHuEPO vs 14% without it), but this difference was not statistically significant due to smaller sample size ($P$ = 0.25) (unpublished data).

## Thrombosis Prophylaxis for Patients on Thalidomide or Lenalidomide

Given the risk of TEE described above, patients with MM being treated with combination therapy incorporating either thalidomide or lenalidomide should receive some form of thrombosis prophylaxis. There are data showing benefit from low-molecular-weight heparin (LMWH), full-dose warfarin, and daily aspirin, but no direct comparison between these agents has been conducted to date.

### *LMWH*

As discussed previously, 12% of NDMM patients were treated with MP + thalidomide as part of a randomized GIMEMA trial comparing MP to MP + thalidomide. Initially, when the trial did not mandate any form of TEE prophylaxis, 13 of 65 pts (20%) receiving MP + thalidomide developed TEE. This number decreased dramatically to 2 of the next 64 patients (3%) with the addition of enoxaparin 40 mg SQ daily ($P$ = 0.005).[57] After a 34% cumulative TEE incidence was noted amongst 162 patients treated with anthracycline-containing chemotherapy plus thalidomide at the University of Arkansas as part of a phase III study, thromboprophylaxis with enoxaparin 40 mg subcutaneously daily was added. Only 36 of the next 152 patients (24%) developed TEE, a statistically significant reduction in TEE incidence.23 Although the degree of TEE reduction with enoxaparin prophylaxis was not as impressive as in previous reports from the same institution,[58] this does provide strong evidence that LMWH reduces the risk of thalidomide associated clots. Finally, 9% of 211 pts with NDMM treated with thalidomide/adriamycin/dexamethasone (TAD) plus prophylactic LMWH (nadroparine, 2850-5700 IE anti-Xa) developed TEE, compared to 5% of 201 patients treated with VAD and no prophylaxis ($P$ = NS),[59] suggesting the addition of LMWH abrogated excess risk of developing TEE related to the addition of thalidomide.

### *Warfarin*

Several groups, after failing to demonstrate a reduction in risk of thalidomide-associated TEE with fixed-dose warfarin (1 mg/day),[17,20,58] have concluded that this thromboprophylaxis strategy is not effective. Others have seen some efficacy. In one study, after 5 of 19 patients (26%) with NDMM treated with TD induction developed DVTs, fixed-dose warfarin was added and the incidence of TEE was lowered to 13% of the next 52 patients enrolled.[60] Since the overall incidence of TEE in this protocol was 16%, essentially the expected number of TEE for patients with NDMM treated with TD and no thromboprophylaxis,[17,20] the apparent difference before and after the addition of warfarin may have been happenstance. In a retrospective review, Ikhlaque et al found that only 1 of 37 patients with MM receiving thalidomide-containing therapy developed TEE when treated with low fixed-dose warfarin (1-2 mg/day), compared with 2 of 18 patients receiving full-intensity warfarin (target INR: 2-3).[61] While there was no statis-

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tical difference in the incidence of TEE between patients receiving full-intensity warfarin compared to those getting fixed-dose warfarin, 4 of the patients receiving full-intensity warfarin had bleeding complications (usually in association with a supra-therapeutic INR), compared to 0 of 37 patients getting low-dose warfarin. In another report involving NDMM patients being treated with TD a part of a phase II trial, the addition of full-intensity warfarin completely eliminated TEE (25% prior to adding warfarin vs 0% after).[17] Zero of 18 patients with RRMM treated with bortezomib, thalidomide and dexamethasone (VTD) developed TEE when full-intensity warfarin was used as thromboprophylaxis.[62] Other investigators reported that only 2 of 36 patients with NDMM treated with VTD developed TEE when either *therapeutic* LMWH or full-intensity warfarin was used as thromboprophylaxis.[63] Zangari et al have suggested that adding bortezomib to thalidomide-containing combination regimens may abrogate the excess risk of developing TEE,[64] a finding which—if true—complicates interpretation of some of the above data.

### *ASA*

Aspirin, an agent that is not effective in other settings as venous thromboprophylaxis, was initially explored for this purpose in MM patients being treated with thalidomide after it was observed that platelet aggregation studies became abnormal and von Willebrand factor levels increased in the subset of non-prophylaxed patients who developed TEE during treatment.[5] In this study, the addition of low-dose ASA (81 mg/day) reduced the incidence of TEE from 58% to 18% ($P = 0.001$) among MM patients treated with DVd plus thalidomide.[5] This TEE incidence is in significant excess to that seen in another report using a virtually identical regimen in which only 10% of NDMM patients developed TEE.[34] The authors of the former study speculate that the aggressive TEE screening algorithm utilized at their center likely identified DVTs which would not have been clinically evident, thus contributing to a higher-than-expected incidence of TEE. Other factors likely contributed to this incidence, since the same screening algorithm was presumably utilized in a phase II study of DVd + lenalidomide with ASA (81 mg daily) conducted by the same investigators, in which the overall incidence of TEE was only 9%.[48] Also, a high incidence of TEE (75% without thromboprophylaxis; 19% with ASA 325 mg daily, $P = 0.0002$) was noted in NDMM patients treated with DEX plus lenalidomide as part of SWOG S0232, even though there was no defined TEE screening algorithm in this protocol. In contrast, as mentioned above, Rajkumar et al reported an extremely low (3%) incidence of TEE in a phase II trial of lenalidomide + DEX in NDMM when ASA (81-325 mg daily) was used as thromboprophylaxis.[43] In summary, the explanation for the extremely high initial incidence of thrombosis and the less complete protection afforded by aspirin prophylaxis in the SWOG trial and phase II trial of DVd-T compared to other studies involving similar regimens and patients is likely multifactorial, and unaccounted for clinical factors such as rHuEPO use must be considered.

## Patients with Disease-Related Thrombocytopenia and/or Renal Failure

Patients with MM may develop thrombocytopenia due to heavy disease burden in the marrow or extensive prior cytotoxic therapy (particularly melphalan), thus being at increased risk for bleeding complications from thromboprophylaxis. The risk of hemorrhagic complications will be highest with full-dose warfarin anticoagulation; therefore, this should be avoided if possible in patients with a platelet count under 30,000/mm$^3$. Low-dose ASA (81 mg daily) has been shown to be feasible in this setting.[5,35] Prophylactic dose enoxaparin (40 mg subcutaneously once daily) has been used without excessive complications during the period of profound cytopenias following stem cell transplant,[65] suggesting it may be considered in thrombocytopenic MM patients, particularly if the duration of thrombocytopenia is expected to be short.

**Table 2. Thromboemolic events (TEE) incidences in trials of thalidomide plus anthracycline combination regimens without thromboprophylaxis.**

| Regimen | Disease Status | TEE Incidence | References |
|---|---|---|---|
| Liposomal DOX 30 mg/m$^2$ d 1<br>Vincristine 2 mg d 1<br>DEX 40 mg daily d 1-4<br>THAL 50-400 mg/day | 55 NDMM<br>50 RRMM | 58%* | Baz et al[5] |
| Total Therapy II<br>Thalidomide 400 mg/day | NDMM | 34%** | Barlogie et al[23] |
| Vincristine 1.5 mg d 1<br>Epirubicin 30 mg/m$^2$ day 1-2<br>DEX 20 mg/m$^2$ days 1-4<br>THAL 200-400 mg/day | NDMM | 26% | Schutt et al[33] |
| DEX 40 mg/day d 1-4<br>THAL 400 mg/day<br>Cisplatin 10 mg/m$^2$ CIV d 1-4<br>CTX 400 mg/m$^2$ CIV d 1-4<br>VP-16 40 mg/m$^2$ CIV d 1-4<br>DOX 10 mg/m$^2$ CIV d 1-4 | NDMM | 16% | Zangari et al[36] |
| Liposomal DOX 40 mg/m$^2$ d 1<br>Vincristine 2 mg d 1<br>DEX 40 mg daily d 1-4, 15-18<br>THAL ≥ 200 mg/day | NDMM | 10% | Zervas et al[34] |

*addition of ASA 81 mg/day decreased the incidence to 18%
**addition of enoxaparin 40 mg/day decreased the incidence to 24%
Abbreviations: CTX, cyclophosphamide; DOX, doxorubicin; DEX, dexamethasone; THAL, thalidomide; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/relapsed multiple myeloma; TEE, thromboembolic event

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Occasionally, patients with MM will *develop* new thrombocytopenia while on enoxaparin prophylaxis. In addition to disease progression or therapy-related myelosuppression, the clinician needs to consider the possibility of heparin-induced thrombocytopenia (HIT), which is a prothrombotic state. Current published recommendations for full anticoagulation with direct thrombin inhibitors[66] need to be weighed against the clinician's degree of suspicion and the perceived risk of bleeding with such therapy. If HIT is a possibility, then at the least, while a heparin-induced antibody assay is being checked, alternate thromboprophylaxis with fondaparinux or a direct thrombin-inhibitor such as argatroban should be administered. Fondaparinux is easier to use since it is administered subcutaneously and does not require aPTT monitoring if the creatinine clearance is > 30 mL/min. Importantly, if HIT is being considered at all, patients should not be switched to full-dose warfarin as either thromboprophylaxis or treatment of a TEE, as this can induce thrombotic complications such as limb gangrene in patients who actually have HIT.[67]

With regards to renal dysfunction, the manufacturer of enoxaparin recommends dose adjustment for patients with a creatinine clearance < 30 mL/min requiring thromboprophylaxis to 30 mg subcutaneously once daily. Even after adjusting the enoxaparin dose, clinicians should monitor anti-Xa levels closely in these patients to minimize risk of over-anticoagulation.[68] Fondaparinux (Arixtra®), another FDA-approved agent for DVT prophylaxis, does not offer any advantage in this setting, since its clearance is also reduced in the setting of severe renal dysfunction.

## Management of Thalidomide- and Lenalidomide-Associated TEE

If a patient on either daily ASA or prophylactic dose LMWH develops a TEE during thalidomide or lenalidomide therapy, the immunomodulatory agent should be held while full anticoagulation with either full-intensity warfarin or therapeutic LMWH is initiated. It has been shown that, in most cases, thalidomide or lenalidomide can be safely reintroduced after the patient is fully anticoagulated.[58,60] When a TEE develops in a patient who is already on full-intensity anticoagulation, management is less straightforward. If the patient has been on therapeutic warfarin, but the INR is below 2 when the TEE develops, reinstitution of thalidomide or lenalidomide once therapeutic anticoagulation is established (warfarin with INR consistently between 2 and 3, or full-intensity LMWH) seems reasonable. Alternative anti-myeloma treatment without immunomodulatory agents should be strongly considered in patients who develop a TEE on therapeutic LMWH or warfarin with an appropriate INR. Patients often remain on full anticoagulation following a thalidomide- or lenalidomide-associated TEE for the entire duration of time they are on these drugs, despite the fact that the ongoing risk of TEE appears to diminish over time. This cautious approach is appropriate. A more challenging management issue is whether to continue full-intensity warfarin indefinitely if it was selected as the initial empiric thromboprophylaxis strategy in a patient who has no history of TEE prior to or during immunomodulatory therapy. Given the apparently decreased risk of TEE after the first year of therapy and the known risk of bleeding attributable to full-intensity warfarin, one could rationally consider switching to either prophylactic LMWH or daily ASA.

## Summary

Patients with MM being treated with glucocorticoid and/or combination chemotherapy therapy plus thalidomide or its analogues are at sufficiently increased risk of developing TEE that thromboprophylaxis is warranted. A high degree of vigilance for TEE is required when evaluating patients being treated with such regimens. Prophylactic-dose LMWH, full-dose warfarin, and ASA have all been shown to reduce the incidence of TEE associated with immunomodulatory therapies for MM. Factors that appear to have an impact on the risk of developing TEE during thalidomide or lenalidomide combination therapy, such as concurrent rHuEPI use and dexamethasone dose intensity, vary from study to study, making it difficult to compare the relative efficacy of the different thromboprophylaxis strategies discussed herein. While full-intensity warfarin and prophylactic LMWH have been advocated by some as preferable to ASA (largely due to the inefficacy of ASA as TEE prophylaxis in other settings), there is little data to support this. Full-intensity warfarin, while consistently shown to be highly effective at preventing TEE, is associated with the highest risk of bleeding complications and requires close monitoring of the PT/INR. Efficacy outcomes with either LMWH or ASA are more variable, but many physicians view these as more attractive options. In contrast to warfarin, LMWH does not generally require monitoring of coagulation parameters. ASA is by far the easiest to administer and costs the least. Ultimately, most physicians recommend a specific thromboprophylaxis strategy after taking cost, compliance, and individual risk for bleeding and clotting into account. For example, I am more likely to recommend warfarin in patients with a prior history of DVT or some other risk factor for developing a TEE on therapy, or who I plan to treat with concurrent immunomodulatory drugs plus an anthracycline-containing chemotherapy regimen. Also, I minimize usage of rHuEPO in MM patients initiating combination therapy involving either thalidomide or lenalidomide. Hopefully, a prospective randomized trial comparing warfarin, ASA, and LMWH will be conducted to determine the optimal prophylaxis strategy for patients with MM being treated with thalidomide or lenalidomide.

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