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Thrombosis Associated with Immunomodulatory Agents in Multiple Myeloma

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1. Introduction

Patients with multiple myeloma (MM) are increasingly at risk for thromboembolic events (TEEs), usually venous thromboembolism (VTE) [1]. The introduction of thalidomide and lenalidomide has clearly improved outcomes in MM patients but these immunomodulatory agents (IMiDs) are also associated with higher rates of TEEs [2]. The pathogenesis of thalidomide/lenalidomide-associated thrombosis is multifactorial and poorly understood. Patients with MM who are being treated with schemes including combinations of either thalidomide or lenalidomide plus other agents should receive some form of thrombosis prophylaxis [3]. This chapter discusses the incidence, pathogenic mechanisms, prophylaxis and treatment of thalidomide/lenalidomide-associated TEEs.

2. Multiple myeloma and thrombosis

The risk of developing venous thrombotic complications for patients with cancer is approximately five times that of the general population (0.5 *vs.* 0.1%) [4]. Multiple myeloma (MM), characterized by the malignant proliferation of clonal plasma cells, accounts for approximately 10% of hematologic malignancies and affects older individuals (median age, 70 years) [5]. Thromboembolic events are a key concern in clonal plasma cells disorders, such as monoclonal gammopathy of undetermined significance (MGUS) as well as in MM. The exact incidence of VTE in MGUS is difficult to determine since reported VTE rates probably vary according to the level of diagnostic vigilance. The underlying medical problems that prompted laboratory testing for monoclonal may also increase the risk of VTE. Srkalovic et al [1] noted an increased incidence of VTE among patients with MGUS. They reported that 7.5% (13 of 174 patients) of patients with MGUS developed VTE at a median of 4 months (range, 0–67 months) after diagnosis. The cumulative VTE rate was 16% after 8 years of follow-up. A medical history of VTE, family history of VTE, immobility, low serum albumin level and an increase in leukocyte count were found to be correlated with increased incidence of VTE in patients with MGUS. In another retrospective study (310 patients with MGUS) the incidence of VTE was 6.1% after a median follow-up of 44 months [6]. Univariate analysis showed that age ≥ 65 years, M protein ≥ 16 g/l and disease progression to symptom MM were the significant risk factors for VTE. A retrospective review of U.S. Veterans Affairs hospital records from 1980–1996 reported an incidence of VTE of 0.9, 3.1 and 8.7% in veterans without a plasma cell dyscrasia, diagnosed to have

MGUS, and MM, respectively [7]. The incidence of VTE in MM patients is difficult to estimate and varies from 3–10%. On the other hand, the recent introduction of the anti-myeloma therapy class called immunomodulatory drugs (IMiDs), substantially increased risk of VTE in multiple myeloma.

The exact pathogenesis of thrombosis in plasma cell dyscrasia is multifactorial and poorly understood. Prothrombotic coagulation abnormalities are found in patients with newly diagnosed multiple myeloma, including elevated levels of von Willebrand antigen factor, factor VIII and tissue factor, as well as decreased protein S and thrombosposndin [8]. Proinflammatory and angiogenic cytokines such as interleukin-6, tumor necrosis factor and vascular endothelial growth factor (VEGF) are elevated in MM and could activate the coagulation system [9]. A recently described mechanism of hypercoagulability in cancer patients, including MM patients, is acquired activated protein C resistance (APC-R). APC-R, in the absence of factor V Leiden mutation, was present in almost one-quarter of newly diagnosed myeloma patients and significantly increased the risk of VTE [10]. The possible production of auto-antibodies against protein C in these patients could explain the transient APC resistance phenotype. However, to date, we know of no single prothrombotic abnormality that can be used to predict which patients with plasma cell dyscrasia will develop VTE. Other risk factors of MM-associated thrombosis are involved, such as older age, immobility, prior or family history of VTE and the presence of other medical comorbidities, immobility due to pain and/or surgery, indwelling central venous catheters, extrinsic venous compression by plasmacytomas, and the presence of inherited factors such as factor V Leiden. However, the dominant risk factor for VTE in MM is the type of drug administered.

3. Thalidomide and thrombosis

Thalidomide is a glutamic acid derivative that exerts potent anti-angiogenic and immunomodulatory activity and has revolutionized clinical management of patients with myeloma. Thalidomide is effective in relapsed or refractory and newly diagnosed MM. However, from experience with myeloma patients, VTE has recently emerged as the single most important complication. The anti-myeloma effect is mediated by several mechanisms in myeloma cells directly as well as by the microenvironment [11]. Thalidomide induces G1 growth arrest/apoptosis by inhibiting NF-KB [12] and activating caspase. It inhibits adhesion of myeloma cells to bone marrow stromal cells, and inhibits secretion of cytokines (VEGF, [13], βFGF, [14-16], HGF, [17], TNFa, [18], IL-6, [19] and soluble IL-6 receptor (sIL-6R) [20]); up-regulate ICAM-1, [21] VCAM-1, IL-10, [22-23] and IL-12, [24]. Finally, it induces T cell and NK cell anti-myeloma immunity and inhibits angiogenesis [25].

The occurrence of VTE with the use of thalidomide was reported for the first time by Osman and Rajkumar in two independent phase 2 trials [31] in 2001. The combination of thalidomide (100–200 mg/day), doxorubicin (36 mg/m^2 on the first day of each 28-day cycle,) and dexamethasone (40 mg daily on days 1–4, 9–12, and 17–20 of each cycle) produced symptomatic deep venous thrombosis in four of the first 15 enrolled patients (27%) and the trial was therefore stopped. The other phase 2 trial combined thalidomide and dexamethasone for the treatment of patients with newly diagnosed myeloma at the Mayo Clinic. Seven percent (3/45) had thrombotic events. Cavo [32] and Rajkumar [33] in another

two phase 3 trials confirmed the preliminary observations of increased incidence of VTE in newly diagnosed MM treated with thalidomide plus dexamethasone (16 and 17% of VTEs). (*table 1 below*).

Regimen	n	Status of disease	Incidence (%)
Thalidomide in monotherapy			
Barlogie, 2001 [26]	169	RR	< 2
Bennet, 2001 [27]	326	RR	4.6
Rajkumar, 2002 [28]	31	RR	3.4
Tosi, 2002 [29]	65	RR	1.5
Weber, 2002 [30]	28	ND	3
Thalidomide / Dexamethasone			
Cavo, 2004 [32]	71	ND	16
Rakjumar, 2006 [33]	103	ND	17
Palumbo, 2004 [34]	120	RR	2
Dimopoulos, 2001 [35]	44	RR	7
Thalidomide / Melphalan / Prednisone			
Palumbo, 2006 [36]	129	ND	20
Facon, 2007 [37]	125	ND	12
Thalidomide / Melphalan / Dexamethasone			
Dimopoulos 2006 [38]	50	ND	9
Thalidomide / Dexamethasone / CTX			
Sidra, 2006 [39]	62	ND / RR	3.2
García-Sanz, 2004 [40]	71	RR	7
Dimopoulos, 2004 [41]	53	RR	4
Kropff, 2003 [42]	60	RR	9
Moehler, 2003 [43]	56	RR	7
Thalidomide / Chemotherapy			
Baz, 2005 [44]	35	ND/RR	58
Zangari, 2004 [3]	87	ND	34
Zangari, 2002 [45]	232	RR	16
Barlogie, 2006 [46]	323	ND	34
Schutt, 2005 [47]	31	ND	26
Zervas, 2004 [48]	39	ND	10

RR: refractory / relapsed; ND: newly diagnosed.

Table 1. Incidence of thalidomide-associated venous thromboembolism without VTE prophylaxis

Similarly, when thalidomide was combined with melphalan and steroids, the incidence of VTE was 9–20% in newly diagnosed elderly patients [36-38]. In all of these studies, the major risk of thrombosis occurs early after initiation of the treatment, when the tumor load is maximal. Thus, this complication may be related to the release of thrombogenic factors from myeloma cells rather than to cumulative drug exposure [49].

A meta-analysis of studies of thalidomide in MM, which involved 3,322 patients, showed that patients receiving thalidomide were 2.1 times as likely to have a VTE event compared with those who were not receiving thalidomide ($p<0.01$). Those receiving thalidomide plus dexamethasone were 3.1 times as likely to have a VTE event ($p<0.01$), and those receiving thalidomide in addition to other chemotherapy agents were 1.5 times as likely to have a VTE event ($p<0.01$) [2].

The pathogenesis of thalidomide-associated thrombosis has not yet been established. Zangari et al. [10] tested for hypercoagulability in 62 newly diagnosed MMs, and found that DVT was more frequent in those patients with acquired APC resistance (36 *vs.* 15%, $p<0.04$). The pre-existing elevated factor VIII coagulant activity and von Willebrand factor antigen have also been related with thalidomide-associated thrombosis [50]. In an experimental model, Kausahal et al. demonstrated that the addition of thalidomide to uninjured arterial endothelium did not cause any appreciable change, whereas thalidomide added to adriamycin-injured (8–24 h) endothelial cells resulted in endothelial dysfunction by altering the expression of PAR-1 in injured endothelium [51].

Cases of VTE that began shortly after the initiation of treatment with recombinant human erythropoietin in patients who had been receiving thalidomide for some time have been reported [52]. However, another study found no apparent increased risk of thrombosis in 199 cases of myeloma given thalidomide with or without erythropoietin. Of the 49 patients receiving both drugs, 8.1% developed thrombosis compared with 9.3% of the 150 patients on thalidomide who did not receive erythropoietin [53].

The genetic susceptibility to developing a VTE in response to thalidomide therapy has been also evaluated. The lack of a strong association with genetic variations in the coagulation cascade, such as factor V Leiden or G20210A prothrombin mutation, suggests that VTE risk is mediated via alternative mechanisms. Johnson et al [54] identified 18 SNPs, using a custom-built molecular inversion probe (MIP)-based single nucleotide polymorphism (SNP) chip. There were two "response to stress" groups: a response to DNA damage group, including *CHEK1*, *XRCC5*, *LIG1*, *ERCC6*, *DCLRE1B* and *PARP1*, and a cytokine response group containing *NFKB1*, *TNFRSF17*, *IL12B* and *LEP*. A third apoptosis-related group with *CASP3*, *PPARD* and *NFKB1* was also found.

Interestingly, no thromboembolic events were observed in a group of 30 patients with relapsed MM treated with a bortezomib, melphalan, prednisone and thalidomide (VMPT) combination despite the absence of any anticoagulant prophylaxis [55]. A recent review of phase 3 trials of bortezomib- and/or IMiD-based therapy in frontline MM, together with other studies of novel combination regimens concluded that bortezomib-based regimens were typically associated with DVT/PE rates of ≤ 5%, similar to those seen with melphalan-prednisone and dexamethasone, whereas IMiD-based bortezomib-free regimens were generally associated with higher rates [56]. These results suggested the existence of a protective effect of coadministration of thalidomide or lenalidomide with bortezomib [57-58]. Zangari et al prospectively described *in vivo* effects of bortezomib from routine tests of blood coagulation and platelet function in treated MM patients. This pilot clinical trial showed *in vivo* that even a short exposure to bortezomib can affect platelet function. Platelet aggregation was reduced after bortezomib infusion with most of the commonly agonists used (ADP, epinephrine and ristocetin) on both days of treatment [59].

The majority of thrombotic events described in patients receiving treatment with thalidomide have been venous, but occasional arterial thrombotic events have also been reported [60-63]. In a prospective analysis of arterial thrombosis risk, the incidence of arterial thrombosis in patients with newly diagnosed MM treated with three cycles of thalidomide, doxorubicin and dexamethasone (TAD group) was 4.5%. However, the true incidence of arterial thrombosis could have been underestimated in the TAD group due to prophylactic use of LMWH. High factor VIII:C levels, possibly reflecting disease activity, could contribute to the risk of arterial thrombosis especially in patients with known cardiovascular risk factors [64].

4. Lenalidomide and thrombosis

Lenalidomide, a more potent immunomodulatory derivative of thalidomide, was designed to increase the anti-myeloma efficacy of thalidomide, while possibly reducing side effects like neuropathy and thrombosis. However, although neuropathy is not an important lenalidomide-related side effect, thrombosis continues to be one of the most important side effects, especially when lenalidomide is given in combination with dexamethasone or chemotherapy (*table 2*).

Regimen	n	Status of disease	Incidence (%)
Lenalidomide in monotherapy			
Richardson, 2009 [65]	222	RR	4
Lenalidomide / Dexamethasone			
Dimopoulos, 2007 [66]	176	RR	11.4
Weber, 2007 [67]	177	RR	14.7
Zonder, 2005 [68]	38	ND	75
Rajkumar 2010 [69]	223	ND	26
Lenalidomide / Dexamethasone Low Dose			
Rajkumar, 2010 [69]	222	ND	12
Lenalidomide / Dexamethasone / Bortezomib			
Richardson, 2010 [70]	66	ND	6

RR: refractory / relapsed; ND: newly diagnosed.

Table 2. Incidence of lenalidomide-associated venous thromboembolism without VTE prophylaxis

In two large phase 3 trials comparing lenalidomide plus dexamethasone to dexamethasone alone without mandated thromboprophylaxis in patients with RRMM, the incidences of VTE in the LD arm were 11.4 and 14.7%, compared with 4.6 and 3.4% in the DEX alone arm [66-67]. The incidence was even higher in patients with newly diagnosed MM (up to 75%) who were treated with lenalidomide plus dexamethasone [68]. In all these trials conducted in RR and newly diagnosed MM patients, dexamethasone was given at high dose (three pulses of 40 mg for 4 days, total amount per cycle: 480 mg). Interestingly, the rate of VTE was significantly lower when lenalidomide was combined

with low-dose dexamethasone (40 mg weekly; total dose per cycle: 160mg) compared with high-dose (26 *vs.* 12%, p=0.0003) [69].

Similar to thalidomide, low rates of VTE have been reported in MM patients treated with lenalidomide in combination with bortezomib. In a phase 1/2 study of lenalidomide plus dexamethasone and bortezomib without thromboprophylaxis, thrombosis was rare (6% overall) [70].

The role of ESA and lenalidomide in thrombotic risk is controversial. An increased thrombotic risk has been observed in patients who received concomitant ESA with lenalidomide plus dexamethasone [71], although a third study showed no impact of ESA [72].

5. Pomalidomide and thrombosis

Pomalidomide (CC4047) is a new IMiD with high *in vitro* potency. In a phase 1 trial evaluating CC-4047 alone in 24 patients with RRMM, 4 (17%) developed a TEE during the first year of therapy [73]. Thromboprophylaxis was given in the phase 2 studies of pomalidomide and low-dose dexamethasone [74-78].

6. Prophylaxis of TEE-related IMiDs

Patients with MM being treated with IMiDs-based combinations should receive thromboprophylaxis [79-80]. There are data showing benefit of using low-molecular-weight heparin (LMWH), full-dose warfarin and daily aspirin in myeloma patients receiving IMiDs drugs [3, 44, 81]. However, fixed-dose warfarin (1 mg/d) was ineffective in reducing the VTE rate [3, 36]. Currently, outpatient VTE prophylaxis is recommended by the Italian Association of Medical Oncology, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the French National Federation of the League of Centers Against Cancer and the European Society of Medical Oncology only for medical oncology patients receiving highly thrombogenic thalidomide- or lenalidomide-based combination chemotherapy regimens [80].

The 2008 International Myeloma Working Group consensus statement on VTE prophylaxis in myeloma patients receiving thalidomide or lenalidomide [81], recommends a prophylaxis strategy according to a risk-assessment model. Individual risk factors for VTE associated with thalidomide and lenalidomide therapy include: advanced age, a history of VTE, an indwelling central venous catheter, comorbid conditions (e.g, infections, diabetes, cardiac disease, etc), current or recent immobilization, recent surgery and inherited thrombophilic abnormalities. Myeloma-related risk factors include diagnosis and hyperviscosity. Therapy-related risk factors include 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 little has been published about this strategy (see *figure 1 below).*

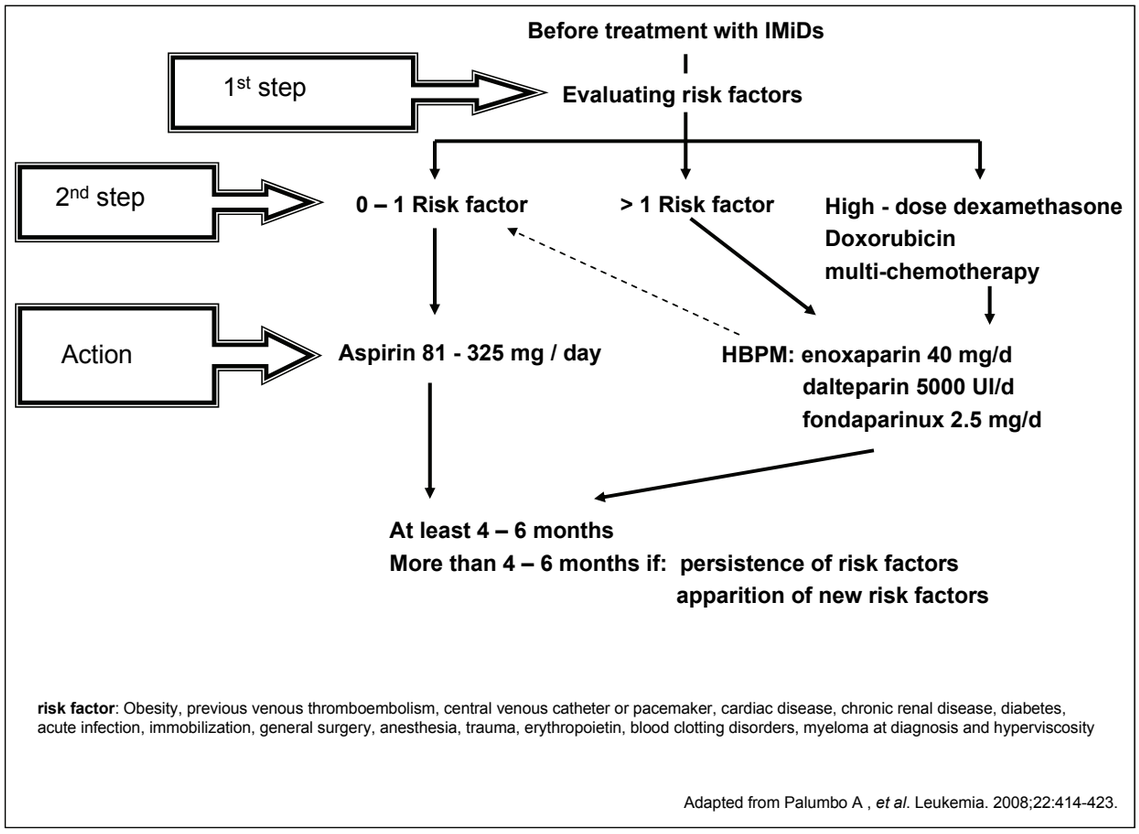

Fig. 1. International Myeloma Working Group consensus statement on VTE prophylaxis in myeloma patients receiving thalidomide or lenalidomide (2008).

Two direct comparison trials between thromboprophylaxis agents have recently been conducted. In the first phase 3 Italian Myeloma Network GIMEMA study [82], which prospectively assessed the impact of LMWH, aspirin or low-dose warfarin in newly diagnosed patients receiving thalidomide as part of either VMPT, VTD or TD regimens, the risk of VTE was similar in all three thromboprophylactic therapies after 6 months of follow up (5.0, 6.4 and 8.2%, respectively), and all were considered likely to be effective.

The second phase 3 trial compared the efficacy and safety of thromboprophylaxis with low-dose aspirin (ASA) or low-molecular-weight heparin (LMWH) in newly diagnosed MM patients, treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone lenalidomide consolidation. The incidence of VTE was 2.27% in the ASA group and 1.20% in the LMWH group. The authors concluded that aspirin could be an effective and less expensive alternative to LMWH thromboprophylaxis during treatment with lenalidomide [83].

However, some questions remain unanswered: the outcome of the use of thromboprophylaxis in patients already in remission receiving thalidomide or lenalidomide as maintenance therapy during prolong periods of time is not well understood. A recent meta-analysis of the use of thalidomide as maintenance after autologous transplantation found the incidence of thromboembolic events to be 4–6%, and the risk of thromboembolism

was 1.95 times that of patients who did not receive thalidomide [84]. The use of ASA for a longer period may reduce the risk of late thromboembolism. Future studies should address this possibility.

7. Management of IMiD-associated VTE

No studies or guidelines are available to guide treatment of established thalidomide/lenalidomide-associated VTE. Although the use of LMWH has improved VTE management in patients with solid tumors [85], no similar experience has been built up in patients with MM. The recommended treatment for thalidomide- or lenalidomide-associated thrombosis is either LMWH or warfarin. However, the use of LMWH is more attractive because of the lack of need for laboratory monitoring and the reduced variability (compared with warfarin) caused by interference from drugs and food. Also, in patients with solid tumors, LMWH administered for 6 months after a first VTE episode (1 month at full dose and 5 months at approximately 75% of the full dose) has proved to be safe and superior to warfarin in preventing VTE recurrence [85]. However, the optimal duration of anticoagulation therapy in oncology patients remains controversial.

The optimal doses of the most commonly used LMWH are 100 U/kg every 12 h or 200 U/kg daily for dalteparin, 1 mg/kg every 12 h or 1.5 mg/kg daily for enoxaparin, and 86 U/kg every 12 h or 171 U/kg daily for nadroparin. In patients with a high risk of hemorrhage (thrombocytopenia or renal failure), association of monitoring of peak anti-factor Xa levels to maintain a range of 0.5 to 1.0 IU/mL could be very attractive. In addition, a reduction of 50% of the therapeutic dose of LMWH for platelet counts less than 50 $x10^9/\mu L$, and a temporary discontinuation of LMWH for platelet counts less than 20,000 $x10^9/\mu L$ can be performed [86]. Also, UFH followed by warfarin remains a sensible alternative for VTE treatment in patients with CrCl <30 ml/min [87].

Zangari et al reported the treatment of 14 patients who developed thalidomide-related VTE. In 75% of them, administration of thalidomide was safely resumed after appropriate anticoagulation therapy was initiated. This consisted of low-molecular-weight heparin followed by warfarin, the target being the international normalized ratio of 2.5 to 3. Both anticoagulant and thalidomide treatments were continued as long as they were clinically indicated [88].

Alternative anti-myeloma treatment with an IMiS-free scheme should be seriously considered in patients who develop a VTE receiving LMWH or warfarin therapy with an appropriate INR [89]. However, if the use of IMiDs which produced the VTE is absolutely necessary, an alternative anticoagulant scheme could be used. In this setting, in patients with cancer-associated thrombosis while on warfarin therapy, with an appropriate INR, a recommended practice is to switch them to LMWH because it is more efficacious than warfarin [90]. On the other hand, dose escalation appears to be effective in patients who develop a cancer-associated thrombosis while on LMWH. In a small cohort study of oncology patients with recurrent thrombosis while on LMWH or warfarin, escalating the dose of LMWH by 20–25% or switching to LMWH, respectively, prevented further thrombotic episodes [91].

8. References

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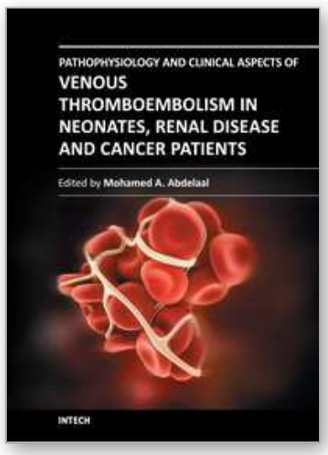

Pathophysiology and Clinical Aspects of Venous Thromboembolism in Neonates, Renal Disease and Cancer Patients

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Venous Thromboembolism remains a major health challenge in many countries because of the morbidity and mortality it inflicts, mainly in hospitalized patients. This book, with contributions from distinguished experts in the field, depicts some hot aspects on aetilogics of VTE, the disease burden in neonates, renal disease and cancer patients as well as issues relevant to prophylaxis and the concept of VTE as patient injury content.

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