Consensus guidelines for the management of deep venous thrombosis (DVT) in multiple myeloma

Indication for DVT prophylaxis outline:

The efficacy of a regimen should always be balanced against its toxicity profile. The incidence of venous thromboembolism (VTE) is more than 1‰ annually in the general population and increases further in cancer patients (Silverstein et al., Arch Intern Med 1998). Though the introduction of novel agents has considerably improved efficacy in the treatment of multiple myeloma (MM), thalidomide and lenalidomide have increased the risk of VTE, thus increasing discontinuation rate. Appropriate prophylaxis for treatment-related VTE can decrease discontinuation rate, improve the safety profile of the regimen and optimize outcome.

1. The cause of VTE is multifactorial and is often a consequence of a combination of risk factors:

- The more important individual risk factors are: immobilization, which has repeatedly been observed to be an independent risk factor, as well as trauma and several chronic diseases (Heit et al., Arch Intern Med 2000); age, indeed the incidence of VTE rises markedly from less than 2 ‰ in individuals younger than 55 years to more than 5‰ in those older than 65 years (Silverstein et al., Arch Intern Med 1998); obesity; and previous history of VTE; inherited thrombophilic abnormalities, such as factor V Leiden, prothrombin G20210A mutation, protein C or protein S deficiency, and antitrhombin deficiency (Kristinsson, Hematology 2010). The presence of inherited thrombophilia should be carefully evaluated especially with patients who have previous history of VTE.

- Other individual risk factors are: central-venous catheter (CVC), comorbidities (diabetes, infections, cardiac diseases), surgical procedures (including vertebroplasty and kyophoplasty);
- 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;

The simultaneous presence of more than one of the risk factors described above exponentially increases the risk of VTE (Palumbo et al., Leukemia 2008). Patients may be divided into 2 subcategories based on both individual and myeloma-related risks of VTE: standard- vs high-risk patients. Based on this distinction, appropriate action should be taken and different prophylaxis (Aspirin or definitive anti-coagulation) should be used, as described in Table 1

Table 1. Risk assessment model for management of venous thromboembolism in MM patients.

Risk Factors	**Univariate analysis ***		**Thrombotic risk assessment and action**
	OR	**95% CI**	

Individual			**HIGH RISK**
Obesity	0.98	0.96-1.00	*Occurrence of at least one of the following risk factors*:
Age	1.38	1.09-1.74	
Hystory of VTE and/or	2.5	1.40-4.46	- Hystory of VTE and/or ypercoagulable state thrombophylia
hypercoagulable state thrombophylia	11.83	5.14-27.23	- cardiac disease
Central–venous catheter or pacemaker			- high degree and prolonged immobilization
Disease-related:			- major surgical procedures or trauma
- Diabetes	NA	NA	⇩
- Choronic renal disease	3	1.19-7.56	LMWH (equivalent of enoxaparin 40 mg once daily)
- Infection	NA	NA	Full dose Warfarin (target INR 2-3)
- Cardiac disease	1.57	1.18-2.08	
- High degree and prolonged Immobilization	NA	NA	**STANDARD RISK**
- Malignant neoplasm	7.67	4.69-12.53	*If none risk factor or any one of the other risk factors occur*
Major Surgical procedures (including Vertebroplasty and Kyphoplasty) or trauma	15-20.5	6.07-37.09	⇩
Medications (Erythropoietin)	NA	NA	Aspirine 81-325 mg once daily or other prophylaxis at physician's discretion
Blood clotting disorders	NA	NA	
Myeloma -related			
• Diagnosis and hyperviscosity			
• Therapy : High dose dexamethasone,Doxorubicin,			

Abbreviations: CI, confidence interval; OR, odds ratio
*Heit JA, et al .Arch Intern Med 2000

2. Focus on myeloma-related risk factors: multi-agent chemotherapies.

- Many clinical studies have found an increased risk of VTE in patients with MM; however, most of them were retrospective trials or were not designed to evaluate the risk of VTE. The incidence of VTE in patients with melphalan and prednisone is 2% to 8% (Facon et al., Lancet 2007; Palumbo et al., Blood 2008; Hulin et al., J Clin Oncol 2009), while in those receiving high-dose dexamethasone is 3% (Rajkumar et al., J Clin Oncol 2006). Novel agents have considerably increased response rates in MM patients, but the incidence of treatment-related VTE has increased as well, particularly in thalidomide- and lenalidomide-containing regimens.
- Before it became evident that treatment with thalidomide and lenalidomide was associated with an increased risk of VTE, investigators used not to require any thromboprophylaxis. Table 2 shows the incidence of VTE in both newly diagnosed

and relapsed/refractory patients with MM. Thalidomide alone does not seem to increase the risk for VTE in relapsed/refractory patients, but the risk increase when thalidomide is combined with dexamethasone, alkylating agents, anthracyclines,or as multi-agent chemotherapy. In most studies, the highest risk was observed during the first few months of therapy. Similarly, lenalidomide as single-agent treatment in relapsed/refractory patients does not increase the risk of VTE, while the incidence of VTE rises when lenalidomide is combined with dexamethasone or cyclophosphamide.

- Conversely, the novel proteasome inhibitor bortezomib does not increase VTE risk either alone or in combination with dexamethasone and/or chemotherapy. When bortezomib is administered with thalidomide or lenalidomide, the incidence of VTE is low, and bortezomib seems to have a protective role against VTE, as shown in the table below..

Table 2 Incidence of VTE in MM trials without thrombo-prophylaxis

Treatment	Newly diagnosis VTE incidence (%)	References	Relapsed/refractory VTE Incidence (%)	References
Melphalan-prednisone	2-8	Facon et al (2007). Hulin et al. (2009) Palumbo et al (2006) Ludwig et al (2011)	-	
Dexamethasone	3	Rajkumar et al. (2006)	-	
Thalidomide	4	Weber et al (2003)	2-3	Barlogie et a l(2001) Kumar et al (2003)
Single agent	17- 26	Rajkumar et al(2006) Cavo et al(2004)	2-8	Palumbo et al (2004) Anagnostopoulos et al(2003)
Dexamethasone	12- 20	Facon et al(2007), Palumbo et al (2006)	11	Offidani et al (2004)
Mephalan and prednisone	10-34	Zarvas et al (2004), Barlogie et al (2006)	58	Baz et al (2005)
Doxorubicina combination	11	Wu et al(2006)	7-8	Garcia-Sanz et al (2004) Kropff et al (2008)
Cyclophosphamide				

Lenalidomide				
Single agent	-		0	Richardson et al (2002)
High dose Dexamethasone	26	Rajkumar et al(2010) Zonder et al (2006)	11-15	Dimopoulos et al (2007) Weber et al(2007)
Low dose dexmethasone	12	Rajkumar et al(2010)	-	
Cyclophosphamide	-		14	Morgan et al(2007)
Bortezomib				
Melphalan and prednisone	1-5	San Miguel et al(2008) Palumbo et al (2010)	0	Palumbo et al(2007) Richardson et (2005)
Dexamethasone	0	Harousseau et al(2006)	1	Jagannath et al(2004)
Thalidomide and dexamethasone	3	Shen et al (2011)	-	

As reported in Table 3, the incidence of VTE decreases when thromboprophylaxis is used in regimens including thalidomide and lenalidomide

Table 3

Treatment	**Incidence of venous thromboembolism (%)**				**References**
	Aspirin	**LWMH**	**Low-dose warfarin**	**Full-dose Warfarin**	
Thalidomide					
Thalidomide-dexamethasone	7		13-25	8	Niesvisky et al (2007), Cavo et al (2004), Weber et al (2003), Wang et al (2005)
Melphalan-prednisone-thalidomide		3-5			Baz et al (2005), Palumbo et al (2006)

Thalidomide multiagente chemtherapy, including anthracycline	18	5-24	14-31	8	Zangari et al (2004), Baz et al (2005), Minnema et al (2004), Offidani et al (2006), Barlogie et al (2006), Palumbo et al (2011)
Lenalidomide					
Lenalidomide-dexamethasone	3-14	2			Rajkumar et al (2005), Zonder et al (2006), Klein et al (2009)
Lenalidomide multiagent chemotherapy including anthracycline	6-9				Schey et al (2010), Baz et al (2006)

3. Here follow the data on arterial thrombosis:

Table 4: Risk of arterial thrombosis with 3 different therapies:

Treatment	Thromboprophylaxis	Incidence of arterial thromboembolism (%)
Thalidomide, doxorubicin and dexamethasone (TAD)	Yes (LMWH)	4.5
Vincristine -AD (VAD)	No	6
Bortezomib, doxorubicin and dexamethasone(PAD)	No	6.4

Libourel et al Blood 2010

Table 5: Causes of arterial thrombosis in MM patients treated with TAD or PAD or VAD regimens

Risk factor	Univariate analysis, HR (95% CI)	Multivariate analysis,[*] HR (95% CI)
Factor VIII:C[‡]	1.92 (1.17-3.14)	1.85 (0.99-3.47)
Hypertension	3.70 (1.13-12.2)	11.7 (2.23-61.2)
Smoking	6.25 (1.61-24.2)	15.2 (1.78-130)

Chronic arterial fibrillation (AF) was an additional cardiovascular risk factor.

Of the thrombophilic risk factors, only FVIII:C was associated with arterial thrombosis (HR = 1.92 for each IU/mL increase of FVIII:C; 95% CI = 1.17-3.14). No association was found between fibrinogen, VWF:Ag, antithrombin levels, protein C and protein S activity, the presence of prothrombin 20210G>A, or factor V Leiden mutation and arterial thrombosis. (Libourel et al Blood 2010)

Table 6: Risk of arterial thrombosis in MM Sweden patients

Time	OR	95% confidence interval
1 year	1.9	1.8-2.1
5 year	1.5	1.4-1.6
10 year	1.5	1.4-1.5

Kristinsson et al Blood 2010

4. Prophylaxis in maintenance therapy. Data on VTE incidence in maintenance/consolidation are reported in Table 6.

- So far there are only limited data available. Although some late cases of VTE could occur, we do not have clear evidence to say whether to treat or not.
- At present with aspirin use a very low frequency of DVT 2% in MPR-R in maintenance period. The French trial, DVT in maintenance was also low.
- Schedules for prophylaxis: LMWH equivalent to Enoxaparin 40 mg/day; ASA 100 mg/day for at least 4-6 months.
- Data on the incidence of DVT and time of occurrence: 6 months of antithrombotic prophylaxis are enough, but for high-risk patients longer prophylaxis is needed

Table 7 Incidence of VTE in MM trials using consolidation/maintenance with thalidomide or lenalidomide

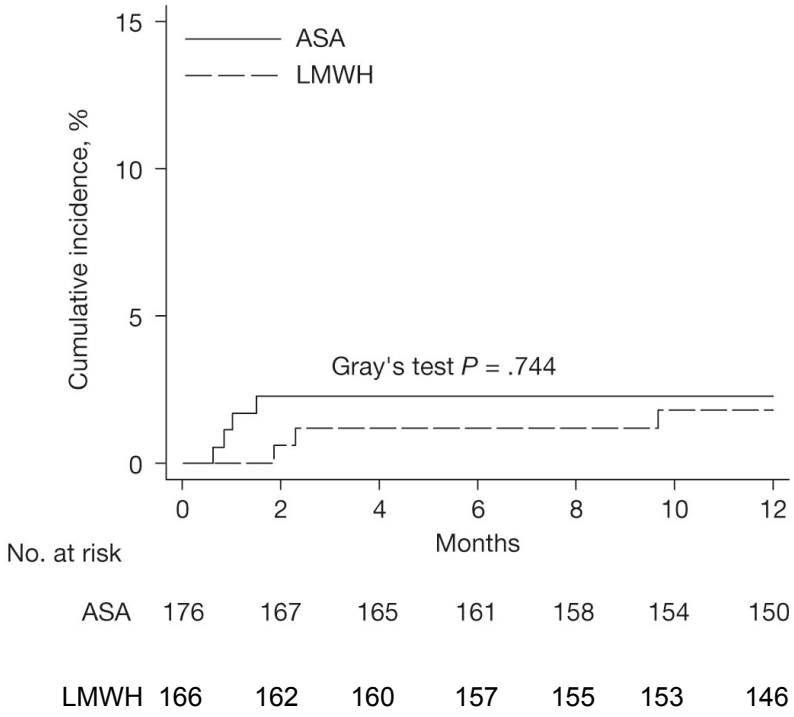
Treatment	N	Thromboprophylaxis	VTE incidence (%)	References

Thalidomide				
Consolidation/maintenance	314	NO	20 (6)	Barlogie et al.NEJM (2006)
+ Pamidronate	201	NO	4 (2)	Attal et al. Blood (2006)
+ Prednisone	114	NO	6 (5)	Spencer et al. JCO (2009)
+ dexamethasone	52	3 pts used Warfarin	0 (0)	Offidani et al BJH (2009)
+ interferon	64	Not mandatory	2 (3)	Ludwig et al Haematologica (2010)
Lenalidomide				
Consolidation/maintenance (LP-L)	80	Aspirin	2 (2)	Palumbo et al JCO (2009)
Consolidation (L)	307	NA	1	Attal IFM trial 2005-02 ASCO (2010)
Maintenance (L)	NA	NA	4 (1)	Mc Carthy et al ASH (2010)

Table 8. Data on VTE incidence in relation to time.

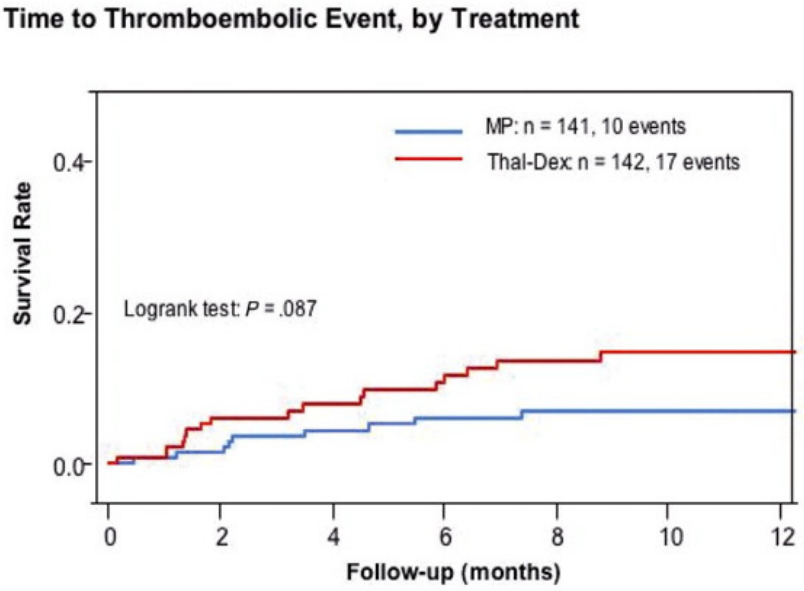
Thalidomide regimens (Palumbo et al JCO 2011)	**VTE incidence (%) during the first 6 months**	**VTE incidence (%) in the entire follow-up**
ASA (n=220)	3.6	5.5
WAR (n=220)	6.4	7.7
LMWH (n=210)	2.7	4.6
Lenalidomide plus low dose deaxamethasone (Palumbo et al ASH 2010)		
ASA (n=176)	1	NA
LMWH (n=166)	1	NA
Thalidomide plus dexamethasone (Ludwig et al Blood 2009)		
LMWH (n=145)	9	15

Figure 1. Cumulative incidence of VTE adjusted for competing risks (any cause of death) by treatment group (Rd)



Palumbo et al. ASH 2010

Figure 2. Time to thromboembolic event by treatment



Ludwig et al Blood 2009

Data from Austrian authors (Ludwig et al Blood 2009) show that the cumulative incidence rate of thromboembolic events was 15% in TD (thalidomide plus dexamethasone) group when LMWH was used as prophylaxis for the first 6 months; this resulted in a 35% relative risk reduction of thromboembolic complications within the first 6 months of TD therapy from 12.4% to 9%.

5. Concluding remarks and considerations

- investigation – currently none advocated unless Coumadin use
- Antithrombotic prophylaxis increases the risk of thrombocytopenia and hence bleeding in MM patients. Conflicting results have been reported on the risk of bleeding with ASA prophylaxis (Agnelli G et al. Lancet Oncol 2009; Levine M et al. Lancet 1994; Zangari M et al. J Clin Oncol 2009), further evaluation is needed. For MM patients, constant monitoring for platelet count during treatment and antithrombotic prophylaxis is necessary: If thrombocytopenia develops, ASA

000/μL (Kristinsson SY. Hematology Am Soc Hematol Educ Program 2010).

- In standard-risk patients, ASA antithrombotic prophylaxis should be considered.
- In high-risk patients, LMWH should remain mandatory for the first 4-6 months of therapy; thereafter, ASA should be considered to reduce the occurrence of late thromboembolic event during treatment.
- Some studies support interruption of anticoagulation in patients who completed a standard duration of anticoagulation therapy and demonstrate recanalization of the venous system using the ultrasound to detect residual thrombus. A landmark prospective cohort study monitored patients with serial ultrasound (6, 12, 24, and 36 months) after 3 months of anticoagulation for initial DVT. Veins were defined recanalized if they were < 2 mm on a single measurement or < 3mm on two consecutive measurements (Prandoni P et al. Ann Intern Med 2002)
- The use of D-dimer is also important to monitor patients who developed DVT, in particular some studies demonstrated that patients with persistently low D-dimer following a 3 to 6 months course of anticoagulation for idiopatic DVT may safely discontinue anticoagulation with an acceptable risk of recurrent thromboembolic events. Patients who have an initially abnormal D-dimer or convert from normal to abnormal have a significantly increase risk of recurrent disease and would benefit from extended duration of anticoagulation (Verhovsek M et al. Ann Intern Med 2008; Palareti G et al. New Engl J of Med 2006).