ROBERTO SANTI

Gestione del rischio trombotico ed emorragico nel paziente oncoematologico

Disclosures

No relevant conflicts of interest to declare related to this presentation

Table 2. Risk of Venous Thrombosis per Type of Malignancy for Patients With a Diagnosis of Malignancy Within 5 Years Before Diagnosis of Venous Thrombosis

Type of Malignancy	No. of Patients	No. of Control Participants	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
No malignancy			1.00	1.00
Men	1279	1038		
Women	1552	1024		
All malignancies†				
Lung	34	1	24.8 (3.4-181.1)	22.2 (3.6-136.1)
Hematological malignancies				
Non-Hodgkin lymphoma	13	1	9.5 (1.2-72.4)	10.2 (1.4-76.9)
Hodgkin disease	7	0	ND	ND
Leukemia	5	0	ND	ND
Multiple myeloma	12	0	ND	ND
All hematological cancer	37	1	26.2 (3.6-191.4)	28.0 (4.0-199.7)
Gastrointestinal malignancies				
Bowel	46	2	16.8 (4.1-69.1)	16.4 (4.2-63.7)
Pancreas	2	0	ND	ND
Stomach	2	0	ND	ND
Esophagus	2	0	ND	ND
All gastrointestinal cancer	52	2	18.9 (4.6-77.8)	20.3 (4.9-83.0)
Urinary/prostate malignancies				
Kidney	8	1	5.8 (0.7-46.6)	6.2 (0.8-46.5)
Bladder	10	0	ND	ND
Prostate‡	25	6	3.4 (1.4-8.3)	2.2 (0.9-5.4)
Female malignancies				
Breast‡§	43	8	3.5 (1.7-7.6)	4.9 (2.3-10.5)
Cervix‡	5	1	3.3 (0.4-28.3)	2.9 (0.3-25.3)
Ovarium‡	7	2	2.3 (0.5-11.1)	3.1 (0.6-15.3)
Endometrium‡	4	0	ND	ND
Brain	11	1	8.0 (1.0-62.1)	6.7 (1.0-45.4)
Skin (melanoma, squamous) cell	15	3	3.6 (1.1-12.6)	3.8 (1.1-12.9)
Ear, nose, and throat	6	3	1.5 (0.4-5.8)	1.6 (0.4-6.4)
Other	18	2	6.6 (1.5-28.3)	6.9 (1.6-29.6)

Blom et al, JAMA 2005

Table 1
Incidence of thromboembolic complications in hematologic malignancies.

Disease	Overall incidence	Reference
MGUS	6%	Sallah et al. [27]
	3%	Kristinsson et al. [29]
Myeloma	10%	Skralovic et al. [28]
	10%	Barlogie et al. [31]
Lymphoma	5-10%	Rickles et al. [2]
High-grade non-Hodgkin lymphoma	11%	Mohren et al. [22]
	7,5%	Sgarabotto et al. [71]
Low-grade non-hodgkin lymphoma	6%	Mohren et al. [22]
	3%	Sgarabotto et al. [71]
Hodgkin lymphoma	7%	Mohren et al. [22]
	3%	Sgarabotto 2008
Myelodysplastic syndromes	6,5%	Sgarabotto et al. [71]
Acute leukemia	6%	De Stefano et al. [6]
	2%	Ziegler et al. [4]
	12%	Mohren et al. [5]

Elice & Rodeghiero, Thromb Res 2012

Hematological Cancers: Risk of TE and Bleeding Outcome

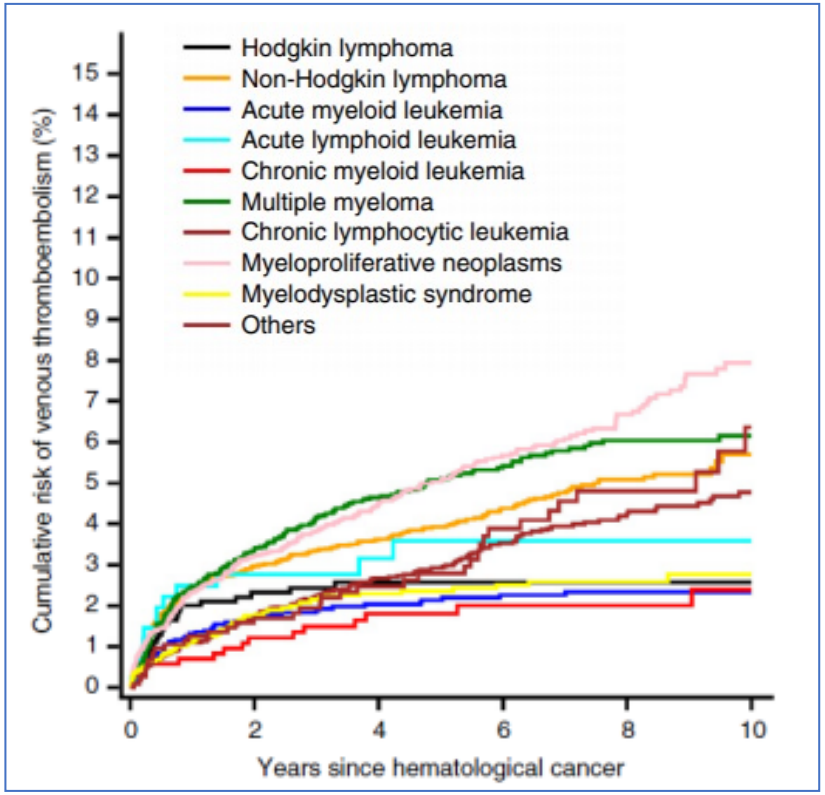
- Danish population-based cohort study (2000-2013) 32141 hematological cancers adult patients; each patient was matched with up to 5 controls.
- 10 years absolute risk for Thrombo-embolism or Bleeding complications – 19%
- VTE – 5.2%; MI – 3.3% ; Ischemic Stroke – 5.2%; Bleeding- 8.5%
- Hazard ratios compared to general population

MI-	1.36 (1.25-1.49)
Stroke –	1.22 (1.12-1.33)
VTE –	3.37 (3.13-3.64)
Bleeding –	2.39 (2.26-2.53)

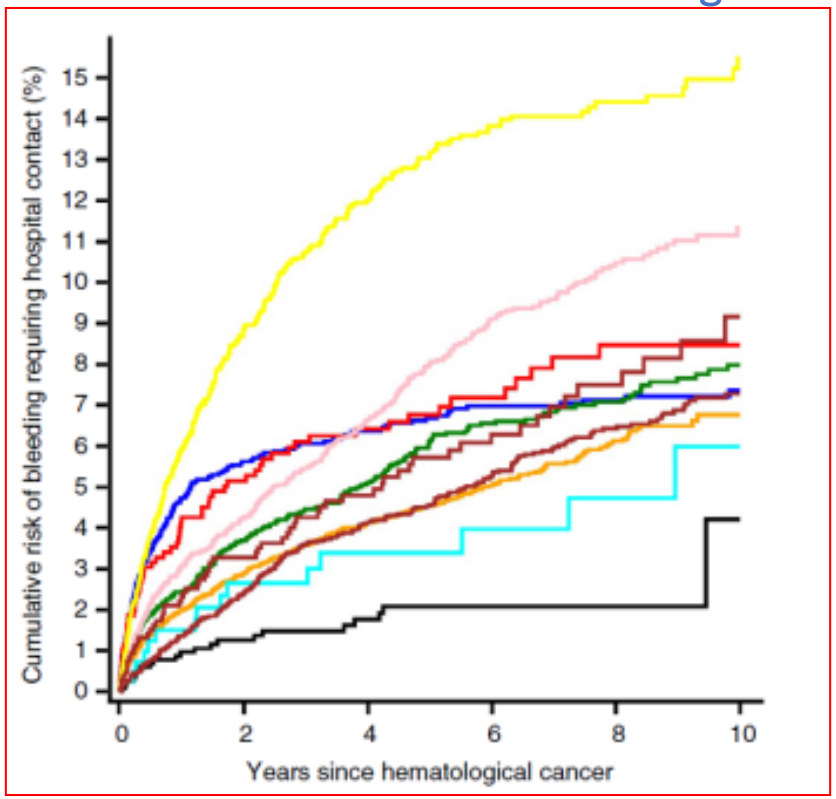
Adelborg JTH, 2019

Cumulative incidence curves of VTE and bleeding requiring hospital contact, by hematological cancer type

Cumulative risk of VTE



Cumulative risk of Bleeding



Population-based cohort study, N=32 141

VTE: venous tromboembolism

Adelborg K *et al.* J Thromb Haemost. 2019;17(8):1305-1318

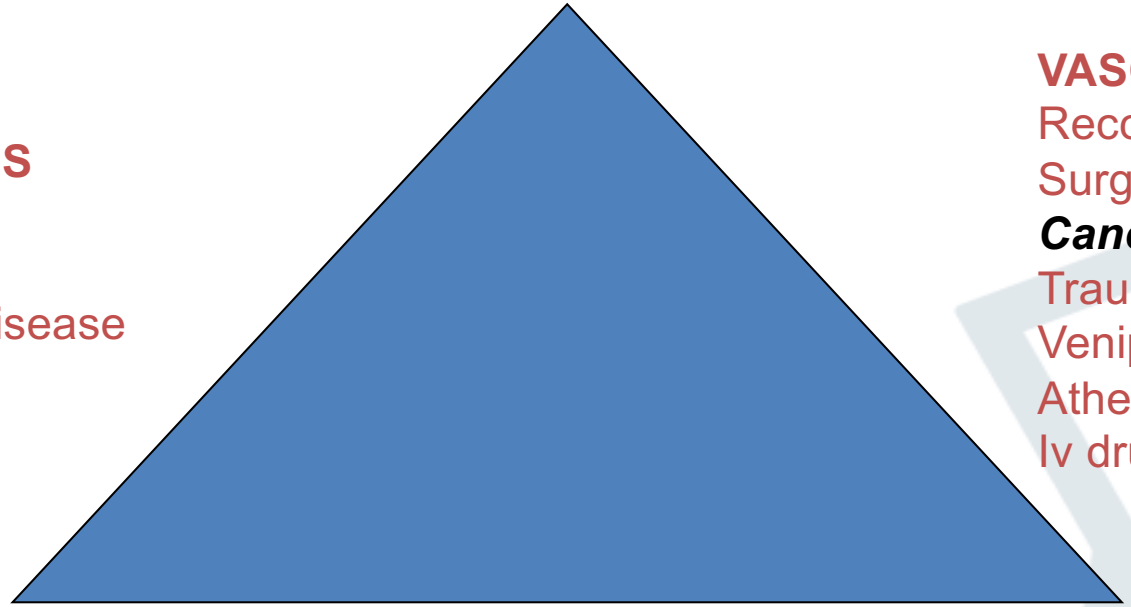
Pathogenesis of clotting activation in hematologic malignancies

- Tumor cell-derived procoagulant, fibrinolytic and proteolityc and inflammatory cytokines
- Cytotoxic therapies
- Infection complication

Virchow's triad

Risk factor are cumulative

VENOUS STASIS
Obesity
Immobility
Chronic Heart Disease
Age >40

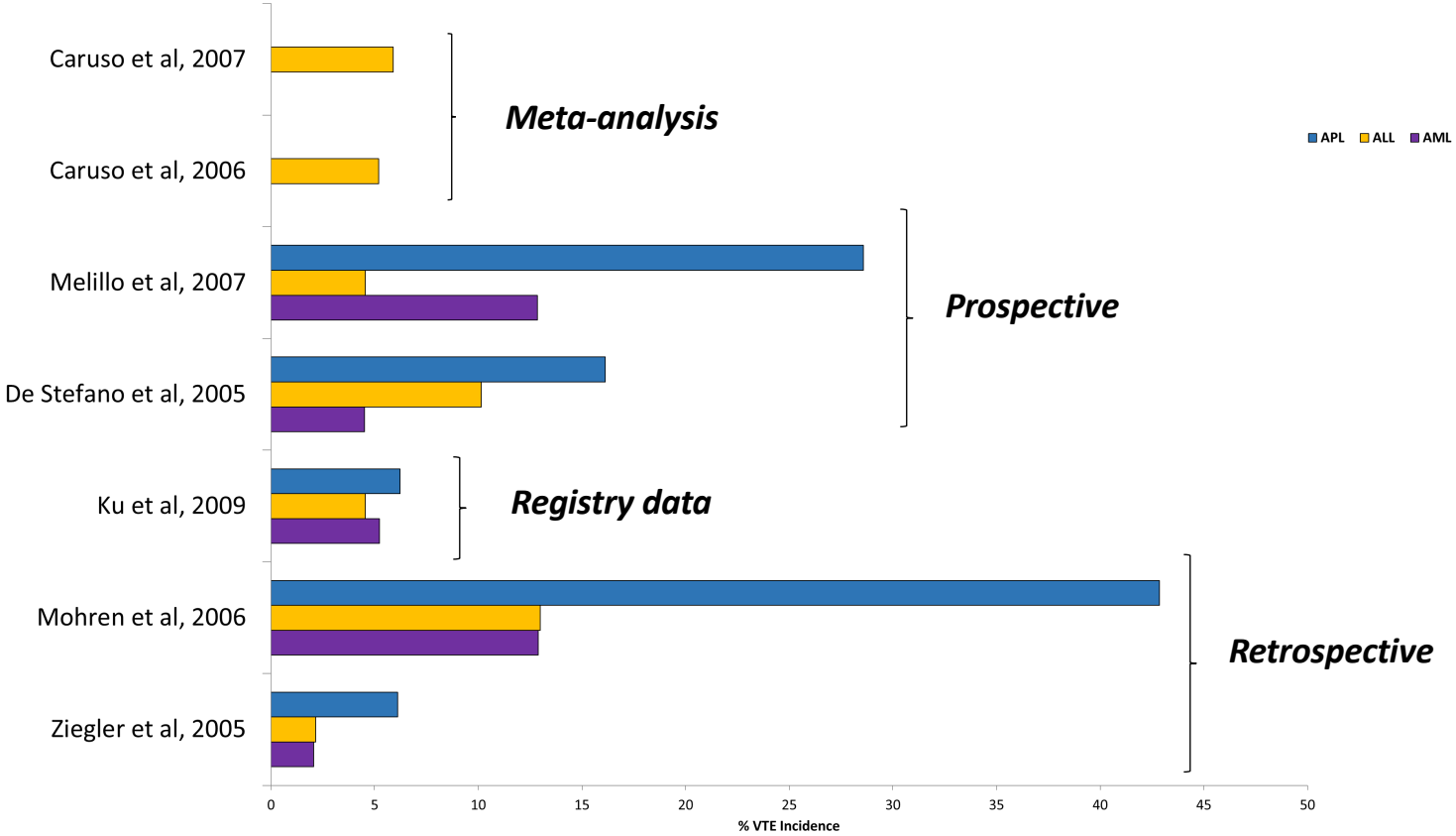


VASCULAR INJURY
Reccurent VTE
Surgery
Cancer treatment
Trauma
Venipuncture
Atherosclerosis
Iv drug administration

HYPERCOAGULABILITY
Malignancy
Bleeding disorders
Hereditary risk factors

Anderson FA, Jr.Spencer, Circulation, 2003 : 107 ;9-16

Incidence of venous thromboembolism (VTE) evaluated in clinical studies of patients with Acute Leukemias



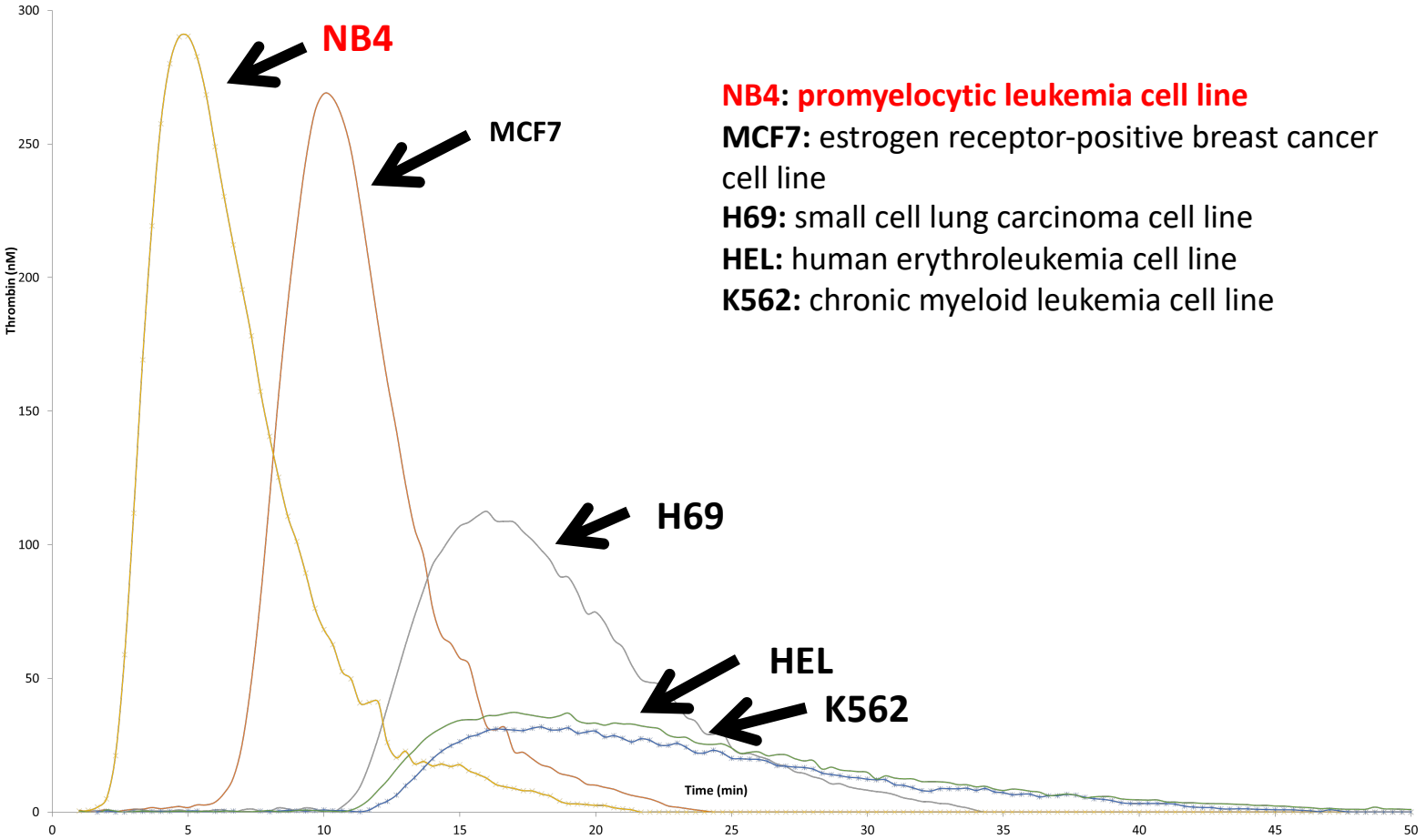
Falanga et al, Curr Op Oncol 2012

Risk of Thrombosis in Acute Leukemia

- Thrombotic events – **6.3%**
- 80% VTE; 20% arterial events
- At diagnosis 13/379 – **3.4%**
- ALL – 1.4%; **APL – 9.6%;** non-M3 AML – 3.2%

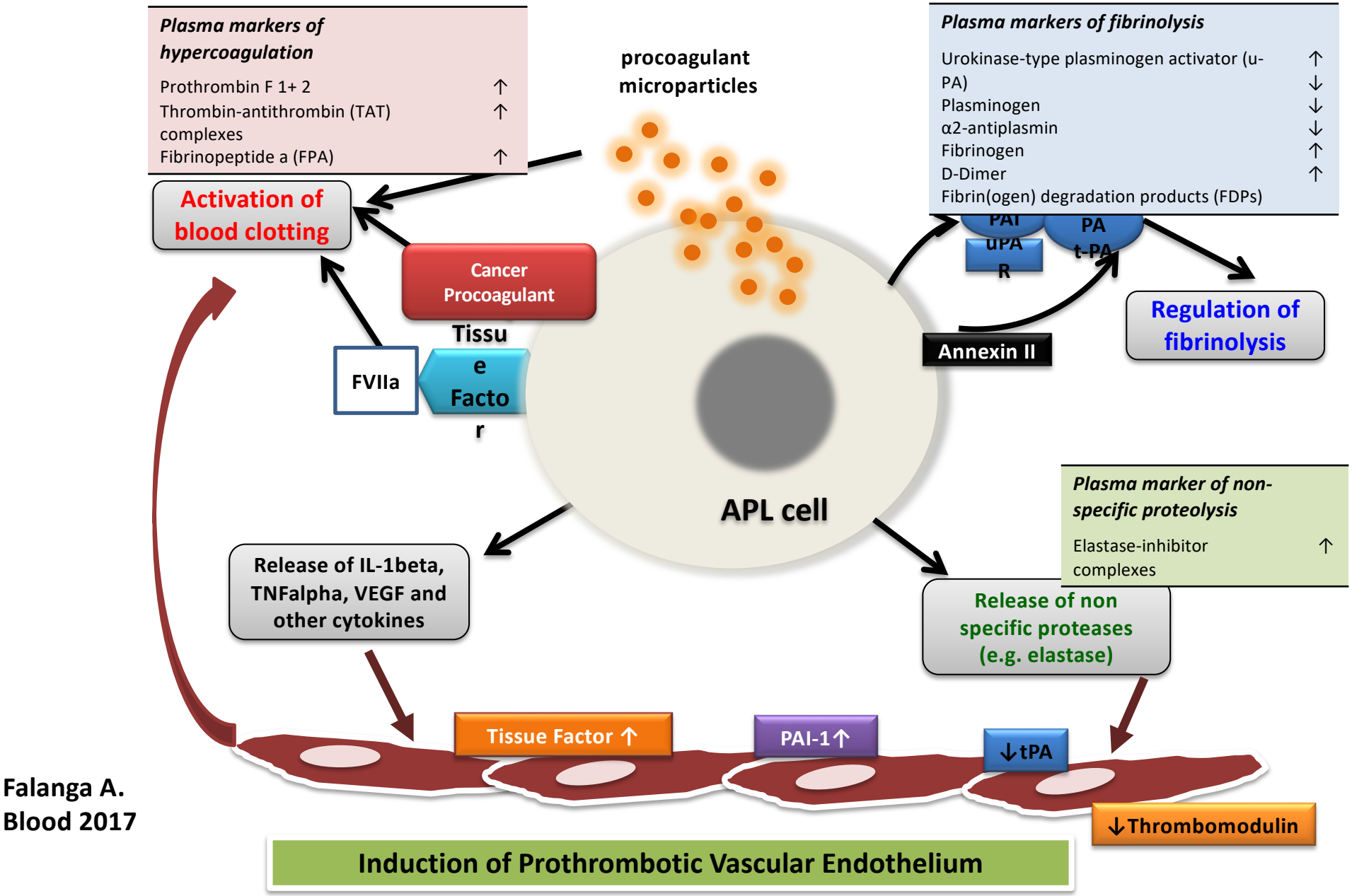
De Stefano J Thromb Haemost 2005

Human tumor cells induce thrombin generation



NB4: promyelocytic leukemia cell line
MCF7: estrogen receptor-positive breast cancer cell line
H69: small cell lung carcinoma cell line
HEL: human erythroleukemia cell line
K562: chronic myeloid leukemia cell line

Marchetti et al, Haematologica 2012.



Falanga A.
Blood 2017

Oncogenic events & the cellular procoagulant activity

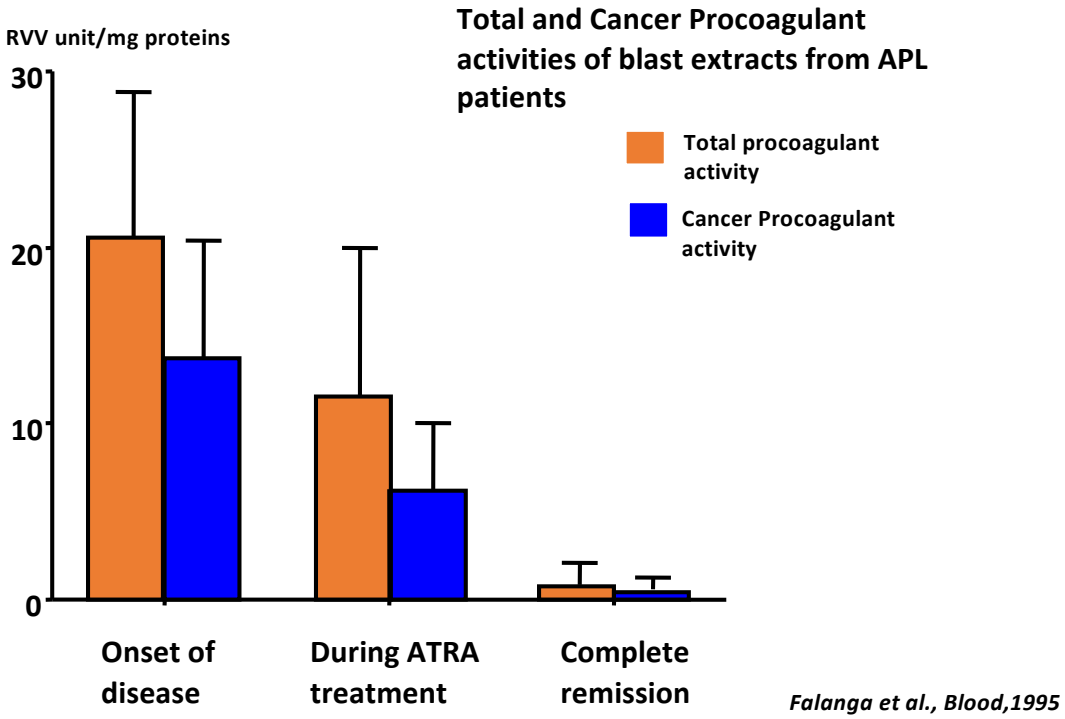
The example of Acute Promyelocytic Leukemia (APL)

- In APL cells the typical *PML/RARa* genetic lesion is associated with overexpression of procoagulant activity (i.e. Tissue Factor) and the occurrence of a severe coagulopathy.

- With the *leukemic cell differentiation into mature granulocytes* induced by all-*trans*-Retinoic Acid (ATRA) therapy, targeting the molecular lesion, the cellular procoagulant activity is lost and the coagulopathy resolves.

Falanga A, Barbui T, Rickles F. Sem. Thromb. Hemost. 2008

ATRA reduces acute promyelocytic leukemia cell procoagulant activities "in vivo"



Falanga et al., Blood,1995

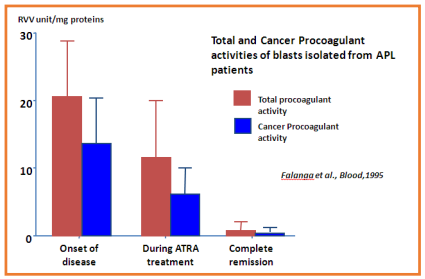
Differentiation of leukemic blasts

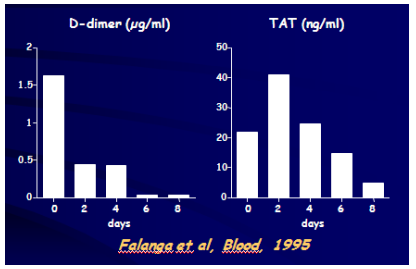
ATRA

Correction of thrombo-hemorrhagic syndrome

↓ procoagulant activity of APL cells

↓ plasma hypercoagulation markers





Remission Induction

However, the rate of early deaths due to the thrombo-hemorrhagic syndrome is still relevant in this disease

The characterization of the coagulopathy and the identification of predictive markers remain a critical issue

Arsenic Trioxide (ATO)

- ATO, another agent effective in the cure of APL, including the APL resistant to ATRA, also reduces the procogulant activities expression of APL blast cells in vitro and in vivo.

- ATO exerts a dose-dependent dual effects on APL cells:
  - at low concentrations (0.5 μM), induces partial differentiation by degrading the PML/RAR-alpha fusion protein;
  - at relatively high concentrations (0.5-2.0 μM), it triggers apoptosis.

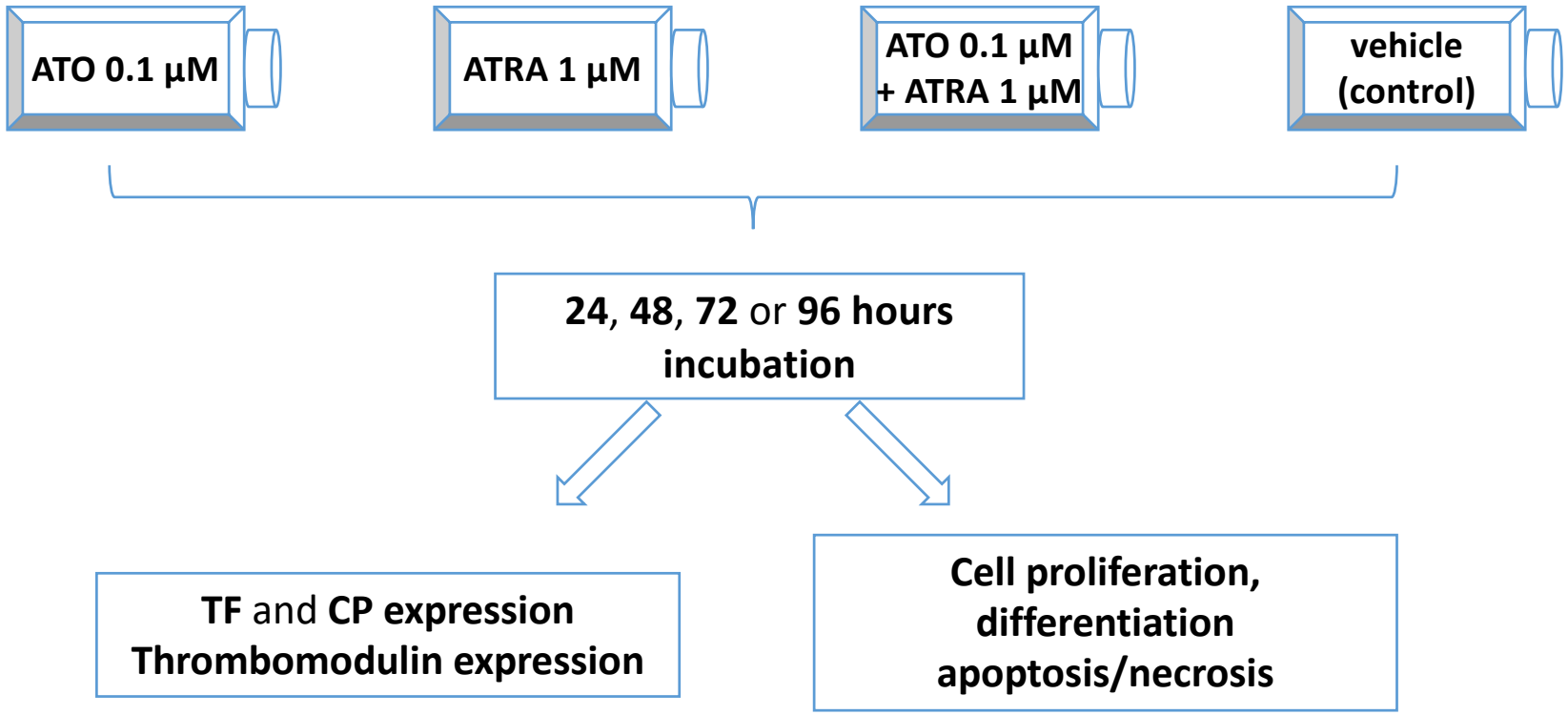
- ATO treatment can induce rapid loss of membrane procoagulant activity and TF mRNA leading to beneficial effect on the coagulopathy of APL.

- However, mechanisms by which ATRA or ATO lead to the rapid resolution of coagulopathy need further definition.

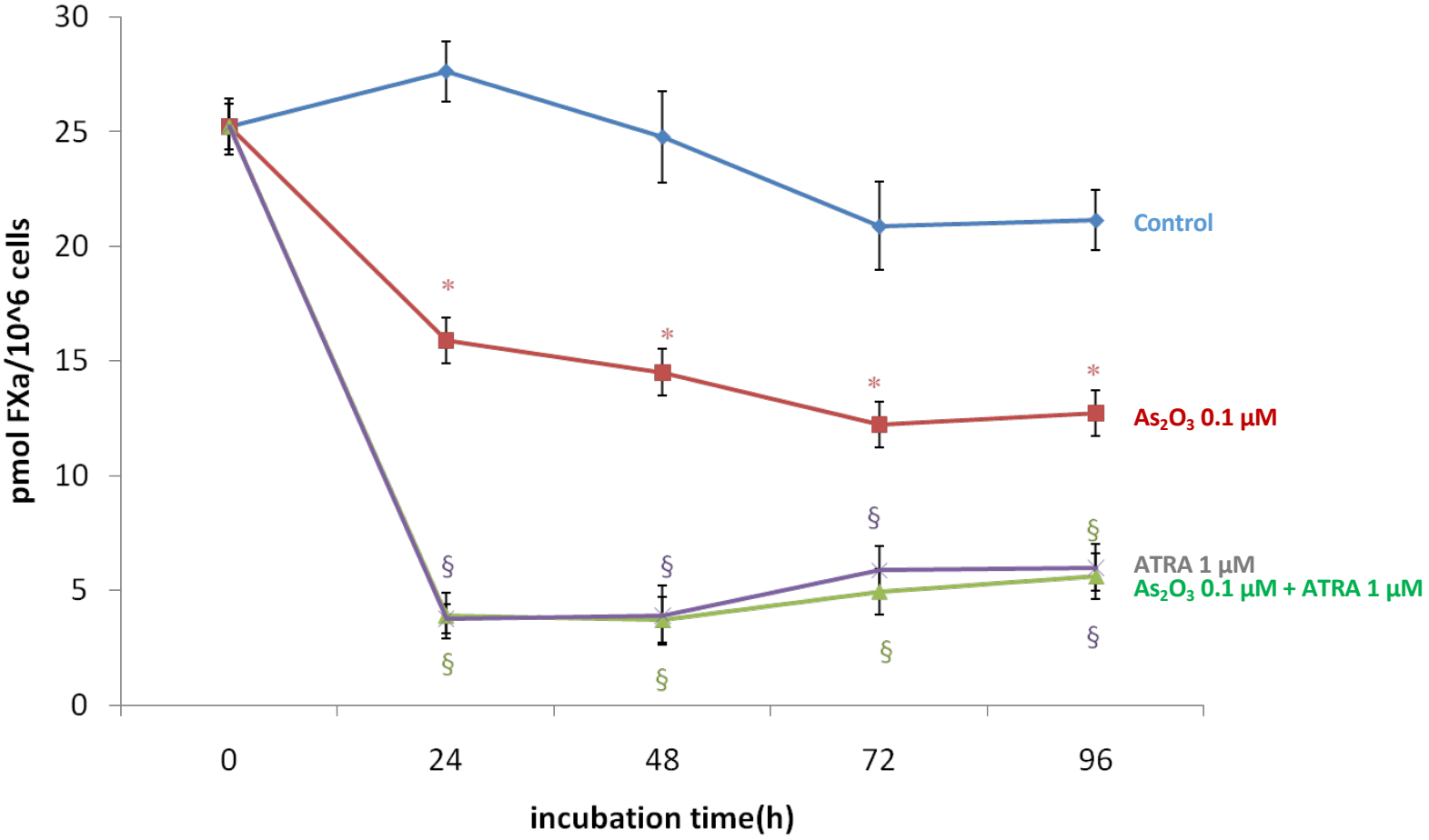
Experimental system

APL NB4 cell line:

- Has the t(15;17) chromosomal translocation
- Expresses chimerical protein PML-RARα
- Is sensitive to ATRA-induced differentiation



ATO and ATRA affects Tissue Factor activity in NB4 cells



* = p<0.05 *vs* Control
§ = p<0.01 *vs* Control

ALL

Table 1. Incidence of venous thromboembolism in adult acute lymphoblastic leukemia

Reference	Design	Number of patients	Thrombosis incidence	Site	Risk factors
De Stefano *et al.* [68]	Retrospective	69	1.4% at diagnosis, 10.6% at 6 months	DVT of legs, DVT of arm, CNS thrombosis	L-ASP
Guzman-Uribe *et al.* [69]	Retrospective	83	8.4%	DVT, CVC,	L-ASP (nonsignificant)
Couturier *et al.* [70]	Prospective	708	3.1%	Only CNS thrombosis	L-ASP, low level of AT, male, T-phenotype
Musgrave *et al.* [71]	Retrospective	3126	1.4%	Only CNS thrombosis	L-ASP, immobility, infection, dehydration
Ku *et al.* [72]	Retrospective	2482	4.5%	DVT	CVC, older age, comorbidity

AT, antithrombin; CNS, central nervous system; CVC, central venous catheter; DVT, deep-venous thrombosis; L-ASP, L-asparginase.

blood®
Regular Article

LYMPHOID NEOPLASIA

CME Article

Thromboembolism prophylaxis in adult patients with acute lymphoblastic leukemia treated in the GRAALL-2005 study

Corentin Orvain,[1-3] Marie Balsat,[4] Emmanuelle Tavernier,[5] Jean-Pierre Marolleau,[6] Thomas Pabst,[7,8] Patrice Chevallier,[2,9] Noémie de Gunzburg,[10] Victoria Cacheux,[11] Françoise Huguet,[12] Sylvain Chantepie,[13] Denis Caillot,[14] Yves Chalandon,[8,15,16] Jamilé Frayfer,[17] Caroline Bonmati,[18] Véronique Lheritier,[19] Norbert Ifrah,[1-3] Hervé Dombret,[20] Nicolas Boissel,[20,*] and Mathilde Hunault-Berger,[1-3,*] for the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)

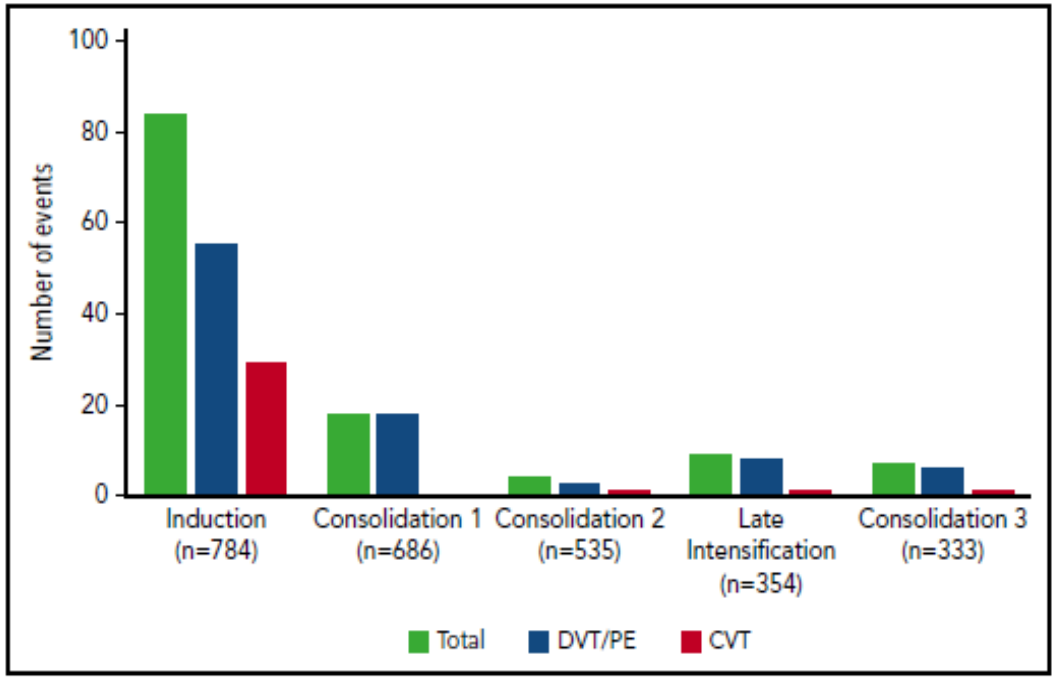
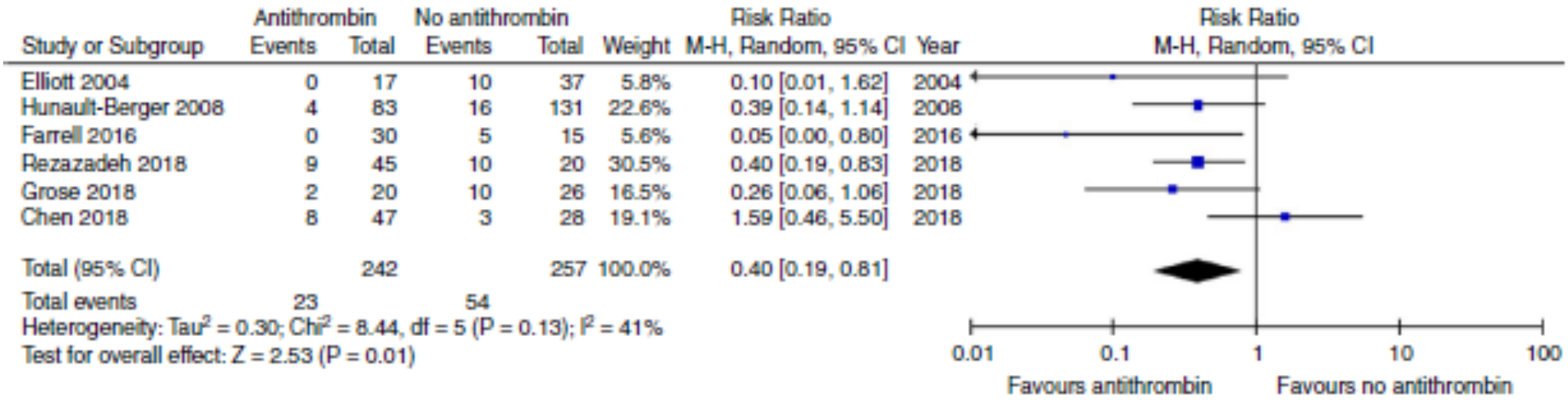


Figure 1. Number of thrombosis per treatment phase. Seven patients developed VTE at different sites (3 patients with DVT and CVT, 2 with PE and CVT, 1 with DVT and PE during induction therapy, and 1 with DVT and PE during consolidation), and 3 patients with DVT experienced relapse of DVT during a subsequent phase of treatment.

The prevention and management of asparaginase-related venous thromboembolism in adults: Guidance from the SSC on Hemostasis and Malignancy of the ISTH



Study or Subgroup	Antithrombin Events	Total	No antithrombin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Elliott 2004	0	17	10	37	5.8%	0.10 [0.01, 1.62]	2004
Hunault-Berger 2008	4	83	16	131	22.6%	0.39 [0.14, 1.14]	2008
Farrell 2016	0	30	5	15	5.6%	0.05 [0.00, 0.80]	2016
Rezazadeh 2018	9	45	10	20	30.5%	0.40 [0.19, 0.83]	2018
Grose 2018	2	20	10	26	16.5%	0.26 [0.06, 1.06]	2018
Chen 2018	8	47	3	28	19.1%	1.59 [0.46, 5.50]	2018
Total (95% CI)		242		257	100.0%	0.40 [0.19, 0.81]	
Total events	23		54				

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 8.44$, df = 5 (P = 0.13); $I^2 = 41\%$

Test for overall effect: Z = 2.53 (P = 0.01)

In the majority of studies, the threshold for antithrombin repletion was either 50% to 60% (with a threshold of 70% in two studies). There were fewer VTE in the antithrombin cohorts in all but one study, yielding an overall summary risk ratio of 0.40 (95% CI, 0.19-0.81) by a random effects model.

Zwicker JI et al., JTH 2020

The prevention and management of asparaginase-relatedvenous thromboembolism in adults: Guidance from the SSC on Hemostasis and Malignancy of the ISTH

Despite the lack of randomized data, based on current best available evidence on antithrombin monitoring and repletion in adults with ALL, we formulated the following guidance statements:

1. Based on an approximate 60% reduction in VTE when implementing an antithrombin repletion regimen, we suggest monitoring antithrombin levels during asparaginase therapy.

2. Where the decision has been made to monitor antithrombin levels, we suggest measurement on a weekly basis for the duration of asparaginase therapy.

3. We suggest infusion of antithrombin concentrate for levels below 50% to 60%. The optimal antithrombin concentration is not established but we suggest a repletion target in the 80% to 120% range.

Zwicker JI et al., JTH 2020

The prevention and management of asparaginase-related venous thromboembolism in adults: Guidance from the SSC on Hemostasis and Malignancy of the ISTH

Despite limited data regarding efficacy, due to the high rate of VTE in adults and existing guidelines regarding thromboprophylaxis during hospitalization, we formulated the following guidance statements:

1. We suggest LMWH thromboprophylaxis during induction phase of ALL therapy that includes asparaginase.

2. Outpatient LMWH thromboprophylaxis is suggested in those patients considered especially high risk due to concomitant risk factors such as obesity or prior history of thrombosis (during induction and intensification phases of therapy).

3. We suggest withholding LMWH thromboprophylaxis in cases of severe thrombocytopenia (ie, platelet count < 30 × 109/L).29

Zwicker JI et al., JTH 2020

BACKGROUND

Table 1. Characteristics and Incidence Rates of VTE in 25 studies published between 2000 and 2019.

First Author	Year	Country	Ref. No.	Type of Study	No. Pts	Histologies	Median Age	Identification of Events	Median Time	No. VTE	Cumulative Incidence
Sanfilippo	2016	USA	25	registry	2730	DLBCL FL	64	ICD codes	28.4 mo.	246	DLBCL 10% at 6 mo.
Santi	2017	Italy	22	clinical trials	1717	NHL	57	pharmacovigilance	6 mo.	53	2.9% at 6 mo.
Antic	2016	Serbia	7	retrospective single center	1820	NHL, HL, CLL	53	records review	9 mo,	73	5.3% during therapy
Rupa-Matysek	2018	Polonia	12	retrospective single center	428	DLBCL, HL	50	records review	37 mo.	64	15%
Rupa-Matysek	2018	Polonia	13	retrospective single center	428	DLBCL, HL	50	records review	37 mo.	64	15%
Hohaus	2018	Italy	8	retrospective single center	857	NHL, HL	51	records review	15 mo.	95	11.1% at 9 mo.
Park	2012	Korea	30	prospective single center	686	NHL, HL, CLL	51	records review	21.8 mo.	54	7.9% at 1 yr
Mohren	2005	Germany	14	retrospective single center	1038	NHL, HL,	59	records review	n.a.	80	7.7%
Zhou	2010	USA	15	retrospective single center	422	NHL, HL	57	records review	2 yrs	80	17.1% at 2 yrs
Mahajan	2014	USA	27	population-based databases	16755	NHL	n.a.	ICD codes	2 yrs	670	4% at 2 yrs
Lund	2015	Denmark	28	population-based databases	10375	NHL, HL	n.a.	ICD codes	2 yrs	355	3.9%at 2 yrs
Caruso	2010	International	23	meta-analysis	18018	NHL, HL	n.a.	published studies	n.a.	1149	6.4% during therapy
Lim	2016	Korea	6	prospective single center	322	DLBCL	56	not specified	41.9 mo.	34	10.6% at 1 yr
Komrokji	2006	USA	16	retrospective single center	211	DLBCL	57	records review	n.a.	27	12.7% during therapy
Borg	2016	Denmark	6	retrospective single center	289	DLBCL	67	ICD codes	16 mo.	32	11.1% at 2 yrs
Yokoyama	2012	Japan	19	retrospective single center	142	DLBCL	63	records review	n.a.	15	11% during therapy
Goldschmidt	2003	Israel	18	retrospective single center	42	PCNSL	61	records review	n.a.	25	59.5% at 3 mo.
Byun	2019	Korea	20	retrospective multicenter	235	PCNSL	63	records review	21 mo.	33	11.7% at 1 yr
Lekovic	2010	Serbia	10	retrospective single center	42	PMBCL	34	records review	47 mo.	15	35.7% at 6 mo.
Borchmann	2019	Germany	9	clinical trials	573	HL	36	trial data	12 mo.	173	3.3%
Gebhart	2014	Austria	21	retrospective multicenter	70	SMZL	n.a.	records review	n.a.	9	13%
Hultcrantz	2014	Sweden	29	population-based databases	2190	WM/LPL	74	ICD codes	10 yrs	92	2.1% at 1 y
Gangaraju	2019	USA	26	registry	734	NHL	49	patient questionaire	8.1 yrs	58	8.1% at 10 yrs
Yamshon	2018	International	24	meta-analysis	1433	NHL	66	published studies	n.a.	77	4.5% at 6 mo.
Zhang	2016	China	11	retrospective single center	565	lymphoma	n.a.	not specified	n.a.	40	7.1% PICC-related

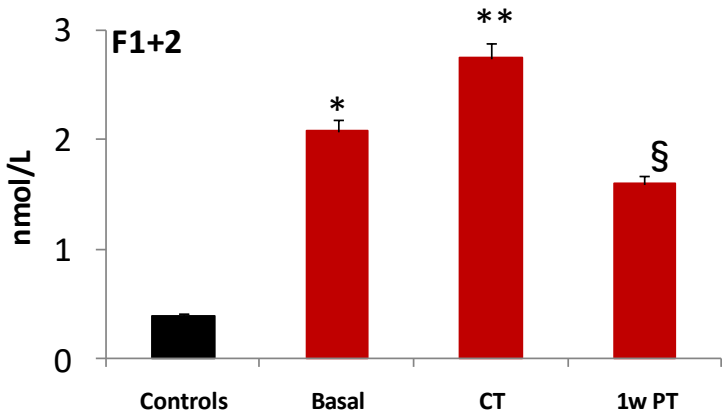
Abbreviations: No., number: pts, patients; VTE, venous thromboembolism; mo., months; yrs, years; DBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; NHL, Non-Hoddgkin lymphoma,; HL Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; SMZL, splenic marginal zone lymphoma; PCNSL, primary central nervous system lymphoma; PMBCL, primary mediastinal B cell lymphoma; WM, Waldenstroems macroglobulinemia; LPL, lymphoplasmocytic lymphoma; ICD, international classification of diseases; IR, incidence rate; CI cumulative incidence; PICC, peripherally-inserted central catheter.

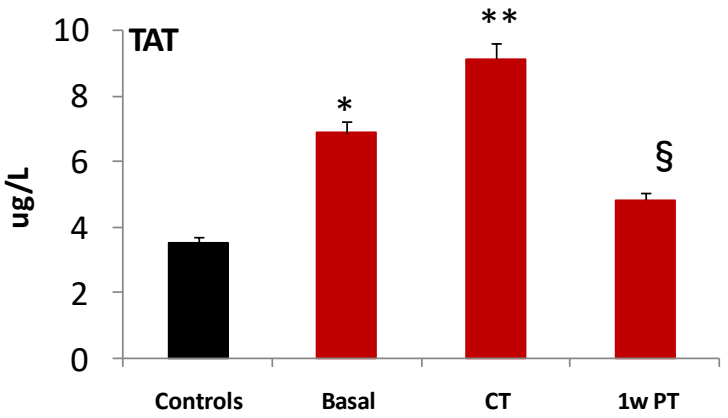
Hohaus, Cancers 2020

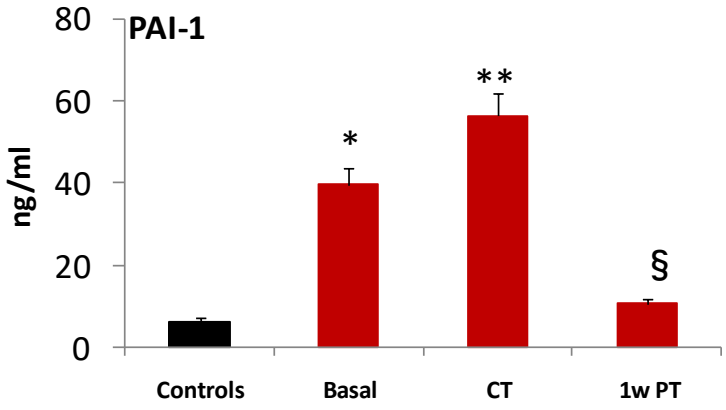
The hypercoagulable state in Lymphoma

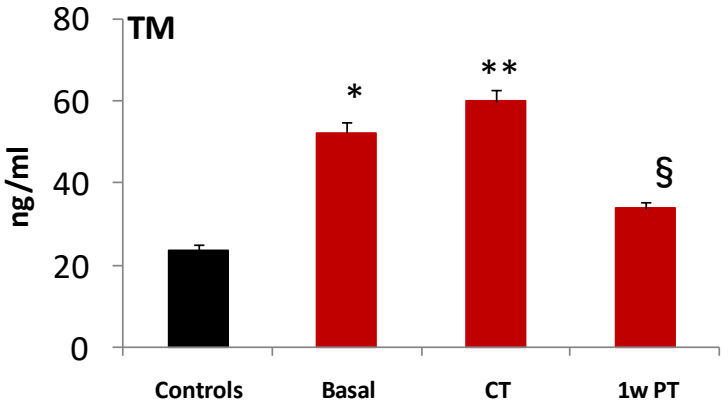
- Non-Hodgkin and Hodgkin Lymphomas carry a significant risk for venous and arterial thrombosis, particularly during chemotherapy treatments
- However, hemostatic alterations underlying a hypercoagulable condition, even in the absence of overt thrombosis, are commonly found in patients with lymphomas

The hypercoagulable profile in patients with NHL









CT: after high-dose chemotherapy; 1w PT: 1 week post-transplantation

**p< .05 vs Controls, **p <.05 vs Basal, § p<.05 vs CT*

Falanga A et al, Cancer Invest. 2008

Thrombosis Research(2012):130(3);e6-e12

Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: Results from a prospective cohort study with Asian population

Lee Chun Park[1], Sook-young Woo, Seonwoo Kim, Hyejin Jeon, Young Hyeh Ko, Seok Jin Kim, Won Seog Kim

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

-cohort of 686 lymphoma pts (NHL + HL)
-VTE incidence 7.9% (NHL > HL)
-median time of VTE development: 1.97 months
-risk factors for VTE:

- **age > 60 years**
- **CNS involvement**
- **chemotherapy (no VTE in untreated pts)**

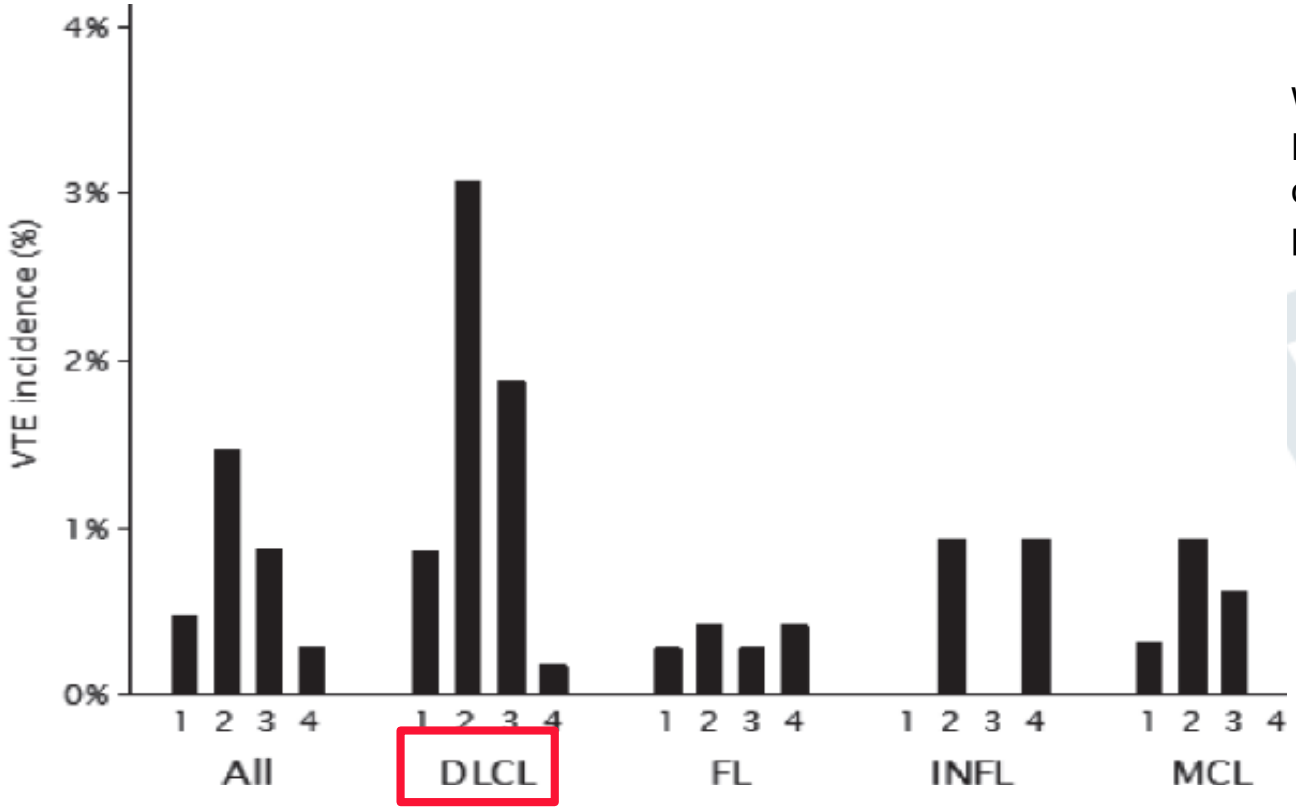
The impact of VTE on mortality in lymphoma patients

Analysis of 16,755 NHL patients (significant predictors of death within 2 years)

- **diagnosis of acute VTE,**
- advanced stage of disease,
- increased number of comorbidities,
- age over 75,
- intermediate- or high-grade histopathology.
- This study also reported that as the time between the lymphoma diagnosis and VTE diagnosis increased, the effect of VTE on death increased as well (HR = 1.7 95%CI:1.5–1.9 for VTEs < 6 months; HR= 6.5 95%CI:4.7–8.9 for VTEs 12–24 months)

Mahajan A: Thromb Res 2014:S23-8.

VTE incidence by grade and NHL histotype



We stratified VTE incidence according to NHL histotype, observing an increased overall incidence of VTE episodes in patients affected by DLBCL

Santi et al, Thromb Haemost 2017

RISK ASSESSMENT MODELS

blood®
2008 111: 4902-4907
doi:10.1182/blood-2007-10-116327 originally published online January 23, 2008

Development and validation of a predictive model for chemotherapy-associated thrombosis

Al[illegible] [illegible]rancis

Table 1. Khorana Score

Khorana Score	Risk score
Site of cancer	
very high risk (stomach, pancreas)	2
high risk (lung, lymphoma, etc)	1
PLTs ≥ 350 x 10^9/l pre-chemo	1
Hb < 10 g/dl or use of r-EPO	1
WBC > 11 x 10^9/l pre-chemo	1
BMI 35 kg/m^2 or more	1
Low risk	0 points
Intermediate risk	1-2 points
High risk	≥ 3 points

validated in solid tumors for risk of VTE development

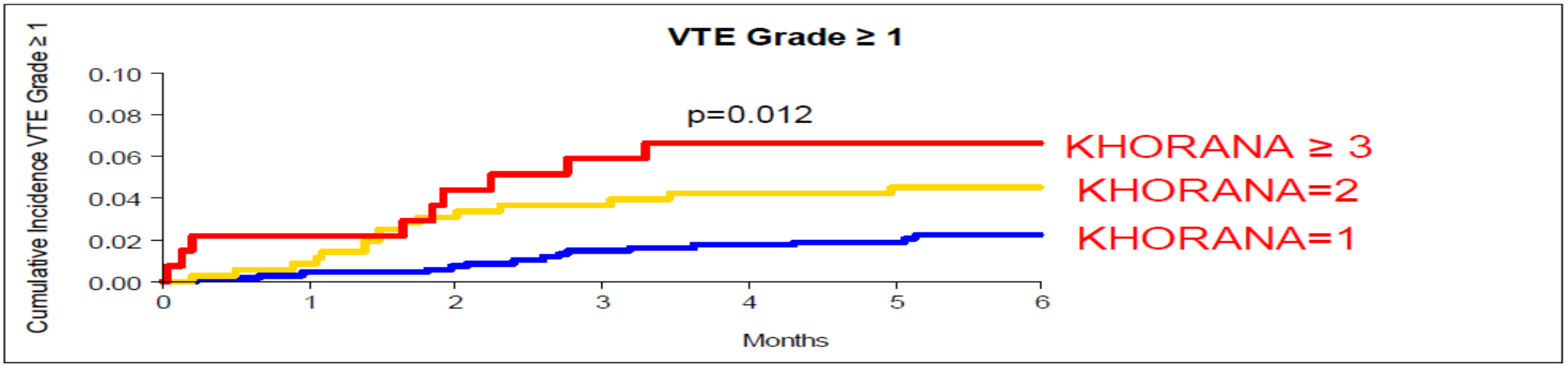


Table 8. Cumulative incidence of VTE of any grade at 6 months

VTE grade ≥ 1	Cumulative incidence at 6 months (CI 95%)	Gray test p
Total pts (n° = 1717)	2.9% (2.1 – 3.8)	-
Pts with available KS (n° = 1189)	3.4% (2.4 – 4.4)	-
KS = 1 (n° = 689)	2.2% (1.1 – 3.3)	p = 0.012
KS = 2 (n° = 359)	4.5% (2.3 – 6.7)	
KS ≥ 3 (n° = 141)	6.6% (2.4 – 10.8)	

Table 9. Cumulative incidence of VTE grade ≥ 3 at 6 months

VTE grade ≥ 3	Cumulative incidence at 6 months (CI 95%)	Gray test p
Total pts (n° = 1717)	1.1% (0.6 – 1.6)	-
Pts with available KS (n° = 1189)	1.3% (0.6 – 1.9)	-
KS = 1 (n° = 689)	0.7% (0.1 – 1.4)	p = 0.048
KS ≥ 2 (n° = 500)	2.0% (0.8 – 3.3)	

Santi et al, Thromb Haemost 2017

Arterial and venous thrombosis in MM during follow up

Table 2. HRs and 95% CIs for selected arterial and venous thrombosis among 18 627 MM patients versus 70 991 matched controls

	1-year follow-up			5-year follow-up			10-year follow-up		
Category	**MM patients**	**Controls**	**HR* (95% CI)**	**MM patients**	**Controls**	**HR* (95% CI)**	**MM patients**	**Controls**	**HR* (95% CI)**
Thrombosis by location									
DVT	252	146	8.0 (6.5-9.9)	459	581	5.2 (4.6-5.8)	528	1035	4.6 (4.1-5.1)
PE	152	97	7.3 (5.6-9.4)	263	403	4.2 (4.1-5.1)	304	714	3.8 (3.3-4.4)
Coronary artery disease†	537	1137	2.2 (2.0-2.5)	1079	4176	1.8 (1.6-1.9)	1263	6756	1.7 (1.6-1.8)
Cerebrovascular‡	203	655	1.5 (1.3-1.8)	475	2830	1.2 (1.1-1.3)	601	4956	1.2 (1.1-1.3)
Type of thrombosis									
Arterial thrombosis§	712	1699	1.9 (1.8-2.1)	1471	6413	1.5 (1.4-1.6)	1751	10 490	1.5 (1.4-1.5)
Venous thrombosis‖	384	227	7.5 (6.4-8.9)	678	904	4.6 (4.1-5.1)	777	1602	4.1 (3.8-4.5)
Any thrombosis (combined)									
All patients	1065	1892	2.6 (2.4-2.8)	2039	7073	1.9 (1.8-2.0)	2384	11 558	1.8 (1.7-1.9)
Males	612	1163	2.5 (2.2-2.7)	1156	4159	1.8 (1.7-1.9)	1338	6653	1.8 (1.7-1.9)
Females	453	729	2.8 (2.5-3.2)	883	2914	2.0 (1.8-2.1)	1046	4905	1.9 (1.8-2.0)

*Adjusted for age, sex, and calendar period at diagnosis.
†Angina pectoris, unstable angina, and myocardial infarction.
‡Cerebral infarction, transient ischemic attack, and cerebral hemorrhage.
§Angina pectoris, unstable angina, myocardial infarction, transient ischemic attack, and cerebral infarction.
‖DVT and PE.

Krinstinnson et al. Blood. 2010;115(24):

Risk factors for VTE in MM

Patient related	Disease related		Treatment related
	MC related	MC unrelated	
Age	Hyperviscosity	Increased MP-TF	CVC
Previous VTE	Thinner fibrin fibers	Increased Fbg	Doxorubicin
Obesity	LAC-like activity	Increased VWF	Dexamethasone
Immobility	PC inhibition	Increased FVIII	Thalidomide
Major illnesses	PS inhibition	Decreased PS	Lenalidomide
Limb paresis		Acquired APC-Res	Erythropoietin
Orthopedic surgery		Hypofibrinolysis	
		Increased PAI-1	

Abbreviations: APC-Res, activated protein C-resistance; CVC, central venous catheter; Fbg, fibrinogen; FVIII, factor VIII; LAC, lupus anticoagulant; MP-TF, microparticle-associated tissue factor; MC, monoclonal component; PAI, plasminogen activator inhibitor; PC, protein C; PS, protein S; VTE, venous thromboembolism; VWF: von Willebrand factor.
Note: Inherited thrombophilia is not listed among the patient-related risk factors given the uncertainty of association with VTE in this setting.

De Stefano et al, Semin Thromb Hemost 2014;40:338–347

THALIDOMIDE AND VTE IN MYELOMA

New DX Myeloma

R

Desa + Chemo+ Thalidomide

Desa + Chemo

VTE

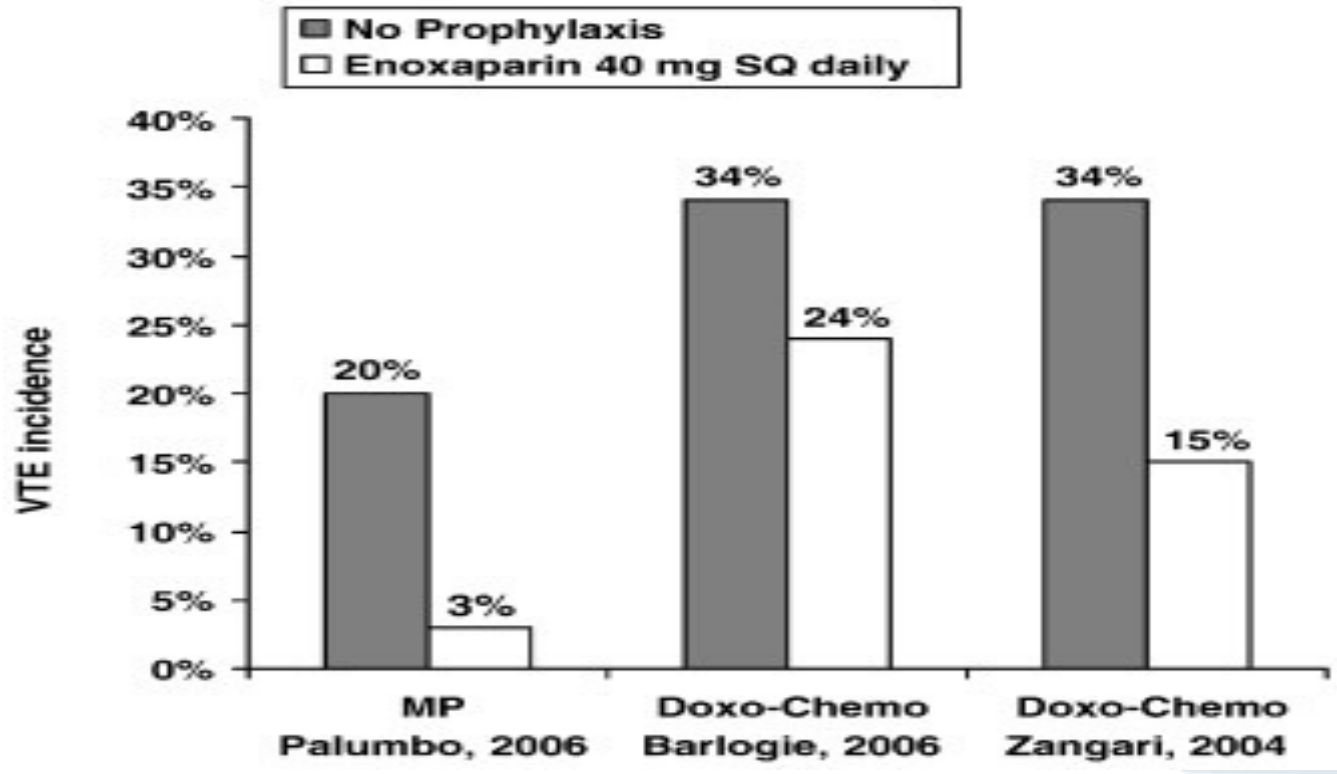
14/50 (28 %)

P=.002

2/50 (4 %)

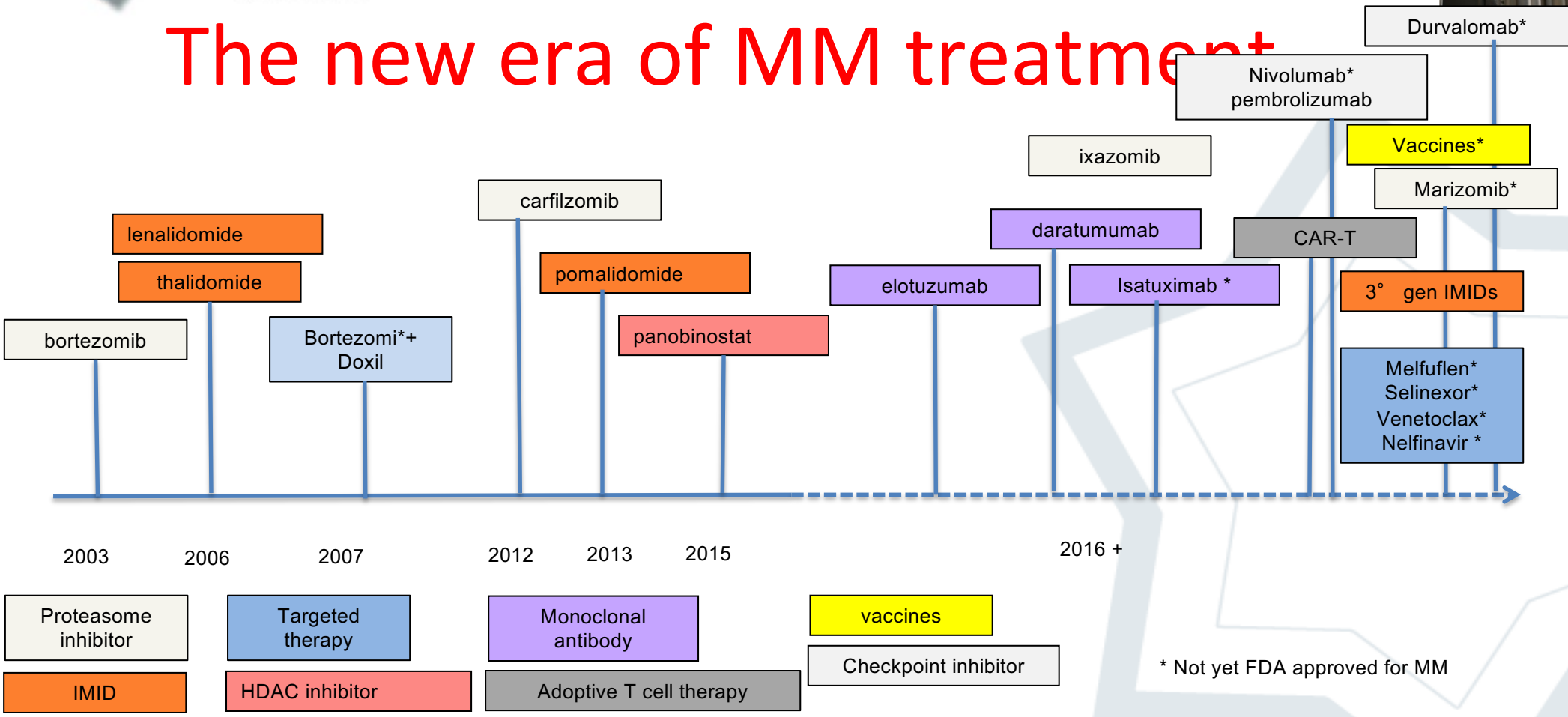
Zangari M Blood 2001,98:1614-1615

Incidence of VTE with and without LMWH in NDMM patients receiving thalidomide-containing regimens



Khaled M. , *Thrombosis Research, Volume 123, Issue 5, March 2009, Pages 679-686*

The new era of MM treatment



Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an ad hoc expert panel.

* Valerio De Stefano[1], * Alessandra Larocca[2], Monica Carpenedo[3], Michele Cavo[4], Francesco Di Raimondo[5], Anna Falanga[6,7], Massimo Offidani[8], Maria Teresa Petrucci[9], Marco Ruggeri[10], Roberto Mario Santi[11], Giovanni Barosi[12].

Haematologica, 2022

Recommendations

All MM patents candidate to an active anti-myeloma treatment should be considered for thromboprophylaxis.
Type, intensity and duration of thromboprophylaxis should be tailored according to the baseline individualized thrombotic and hemorrhagic risk profile.
Severe thrombocytopenia (PLT < 20.000/mcl), active bleeding, congenital bleeding disorders (hemophilia, von Willebrand disease, severe deficiency of coagulation factors), and acquired coagulopathy that cannot be corrected (e.g. severe hepatic disease), are absolute contraindications to thromboprophylaxis.
Mild thrombocytopenia (PLT < 50.000/mcl), history of bleeding, acquired coagulopathy with chance of correction are relative contraindications to thromboprophylaxis.
To ensure an appropriate safe and effective thromboprophylaxis, avoid bleeding risk and potential thrombotic complication, it is recommended to consider the drug-drug interactions of antithrombotic agents and anti-myeloma drugs.
Patient's compliance and patient's preferences should be considered in the choice of thromboprophylaxis, and patients should be adequately informed about his/her thrombotic risk.

Patients at low-risk of thrombosis, i.e. those with an age lower than 75 years, a normal mass body index, without fractures, central venous catheter, co-morbidites and without a planned therapy with IMIDs, should receive no thromboprophylaxis or thromboprophylaxis with low-dose aspirin. The criterion for the choice is the individual hemorrhagic risk.
All other patients should receive thromboprophylaxis with LMWH as first choice.
Patients without other risk factors for thrombosis except for a planned IMiDs-containing therapy and with contraindication or strong aversion to LMWH therapy, or with documented poor compliance to LMWH therapy, could use aspirin as thromboprophylaxis.
Preliminary data on the efficacy and safety of apixaban and rivaroxaban as primary thromboprophylaxis in patients receiving IMiDs are promising. However, there is no strong evidence in favor of DOACs instead of LMWH.
Off-label prescription of apixaban as primary antithrombotic prophylaxis in patients with contraindications to LMWH (e.g. for allergy) should be considered.

	Antithrombotic therapy management †		
	Hold	**Continue full**	**Continue reduced-dose**
AC for DVT or PE, n (% of total) [N=115] *	28 (24)	41 (36)	46 (40)
PLT Tx threshold changed, n (%) †	1 (3.6)	24 (58.5)	12 (26.1)
New PLT Tx threshold ‡ (x 10^9/L), *median [IQR]*	20 [20-20]	30 [30-30]	27.5 [22.5-30]
VTE, % (95% CI) ¶	7.1 (0.1-20.7)	2.4 (0.2-11.2)	4.3 (0.8-13.2)
Arterial thrombosis, % (95% CI) ¶	3.6 (0.2-15.7)	0 (0)	2.2 (0.2-10.1)
Major bleeding, % (95% CI) § ¶	3.6 (0.2-15.7)	2.4 (0.2-11.2)	4.3 (0.8-13.2)
CRNMB, % (95% CI) § ¶	3.6 (0.2-15.7)	4.9 (0.9-14.7)	8.7 (0.2-15.7)
AC for atrial fibrillation, n (% of total) [N=55]	16 (29)	16 (29)	23 (42)
PLT Tx threshold changed, n (%) †	1 (6.3)	8 (50.0)	1 (4.4)
New PLT Tx threshold ‡ (x 10^9/L), *median [IQR]*	20 [20-20]	30 [30-40]	30 [30-30]
VTE, % (95% CI) ¶	0 (0)	0 (0)	0 (0)
Arterial thrombosis, % (95% CI) ¶	0 (0)	0 (0)	0 (0)
Major bleeding, % (95% CI) § ¶	0 (0)	0 (0)	0 (0)
CRNMB, % (95% CI) § ¶	26.1 (7.5-49.9)	18.7 (4.3-41)	0 (0)
APT for any indication, n (% of total) [N=80]	34 (42)	46 (58)	0 (0)
PLT Tx threshold changed, n (%) †	2 (5.9)	16 (34.8)	NA
New PLT Tx threshold ‡ (x 10^9/L), *median [IQR]*	10 [10-20]	10 [10-25]	NA
VTE, % (95% CI) ¶	9.1 (2.7-21.9)	0 (0)	NA
Arterial thrombosis, % (95% CI) ¶	0 (0)	2.2 (1.7-10.1)	NA
Major bleeding, % (95% CI) § ¶	0 (0)	0 (0)	NA
CRNMB, % (95% CI) § ¶	3 (0.2-13.6)	9.1 (2.8-19.9)	NA

† At study index, defined as first day of concurrent hematological malignancy, indication for antithrombotic treatment and PLT < 50 x 10^9/L
‡ Only calculated for patients with a change in PLT Tx threshold at study index †, after the change in threshold
§ ISTH definition
¶ 30-day cumulative incidence (95% CI) with death as a competing risk
* Median days [IQR] from VTE/PE to index = 78 [30-164], 36 [3.5-138] and 30 [10-112] in hold, continue full and reduced groups, respectively
AC, anticoagulation; *APT*, antiplatelet therapy; *CI*, confidence interval; *CRNMB*, clinically relevant non-major bleeding; *DVT*, deep vein thrombosis; *IQR*, interquartile range; *NA*, not applicable; *PE*, pulmonary embolism; *PLT*, platelet; *Tx*, transfusion; *VTE*, venous thromboembolism

EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2022 HYBRID VIRTUAL

HemaSphere 2022

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Guideline Article – Consensus based

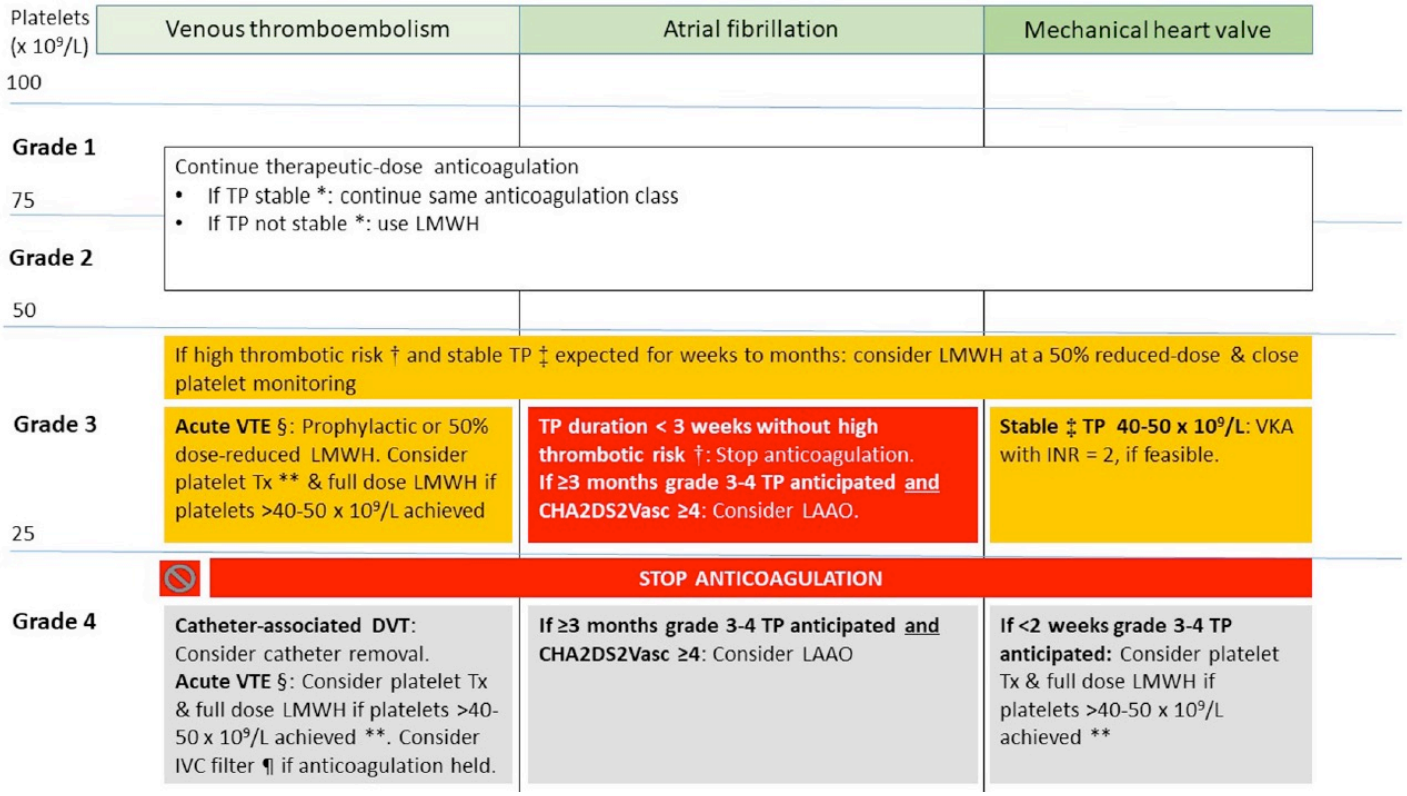
Open Access

EHA Guidelines on Management of Antithrombotic Treatments in Thrombocytopenic Patients With Cancer

Anna Falanga[1,2], Avi Leader[3,4], Chiara Ambaglio[2], Zsuzsa Bagoly[5,6], Giancarlo Castaman[7], Ismail Elalamy[8,9], Ramon Lecumberri[10,11], Alexander Niessner[12], Ingrid Pabinger[13], Sebastian Szmit[14,15], Alice Trinchero[16], Hugo Ten Cate[17,18], Bianca Rocca[19]

Correspondence: Anna Falanga (annafalanga@yahoo.com).

EHA GUIDELINES



Outcomes of VTE in Patients with Hematologic Malignancies compared with Solid Tumors RIETE Study

R. Lecumberri, P. Ruiz Artacho, I. Tzoran, B. Brenner, D. Farge-Bancel, V. Rosa, I. Francisco, L. Hernández-Blasco, J. Trujillo-Santos, M. Monreal, RIETE Investigators.

Outcomes During the Course of Anticoagulation

	Hematologic malignancies		Solid tumors		Rate ratio (95% CI)	p value
	N	Events per 100 patient-years	N	Events per 100 patient-years		
Patients, N		*1,062*		*15,632*		
Patient-years of treatment		756.19		9,625.86		
Median days (IQR)		150 (92-292)		127 (70-243)		
PE recurrences	19	2.51 (1.51-3.92)	461	4.79 (4.36-5.25)	0.52 (0.33-0.83)	0.003
DVT recurrences	39	5.16 (3.67-7.05)	552	5.74 (5.27-6.23)	0.90 (0.65-1.24)	0.261
VTE recurrences	58	7.67 (5.82-9.92)	1,013	10.52 (9.89-11.19)	0.73 (0.56-0.95)	0.009
Major bleeding	43	5.69 (4.12-7.66)	763	7.93 (7.37-8.51)	0.72 (0.53-0.98)	0.017
Gastrointestinal	16	2.12 (1.21-3.44)	338	3.51 (3.15-3.91)	0.60 (0.37-0.99)	0.023
Intracranial	6	0.79 (0.29-1.73)	123	1.28 (1.06-1.53)	0.62 (0.27-1.41)	0.125
Ischemic stroke	7	0.93 (0.37-1.91)	117	1.22 (1.01-1.46)	0.76 (0.36-1.63)	0.241
Myocardial infarction	4	0.53 (0.14-1.35)	43	0.45 (0.32-0.60)	1.18 (0.43-3.30)	0.373
Death	152	20.10 (17.03-23.56)	3,984	41.39 (40.11-42.69)	0.49 (0.41-0.57)	<0.001
Fatal PE	17	2.25 (1.31-3.60)	224	2.33 (2.03-2.65)	0.97 (0.59-1.58)	0.445
Fatal bleeding	4	0.53 (0.14-1.35)	81	0.84 (0.67-1.05)	0.63 (0.23-1.72)	0.180
Disseminated cancer	64	8.46 (6.52-10.81)	2,556	26.55 (25.53-27.60)	0.32 (0.25-0.41)	<0.001

In patients with VTE associated with hematological malignancies, a lower rate of **recurrent VTE**, **major bleeding** and **mortality** is observed compared to patients with solid tumors.

CONCLUSIONS

- MM and DLBCL have a high rate of VTE (>7 %)
- Thromboembolic risk is higher up to 6-12 months after starting chemotherapy
- Absolute risk for bleeding complications is high
- There are no evidence-based recommendation for VTE prophylaxis in patients undergoing anti-neoplastic treatment. Individual evaluation of the risk-benefit ratio considering the individual risks factors is the current strategy
- There are no evidence-based reccomandation for VTE treatment in oncohematology
- Thrombocytopenia represents the most important clinical problem in the management of antithrombotic therapy