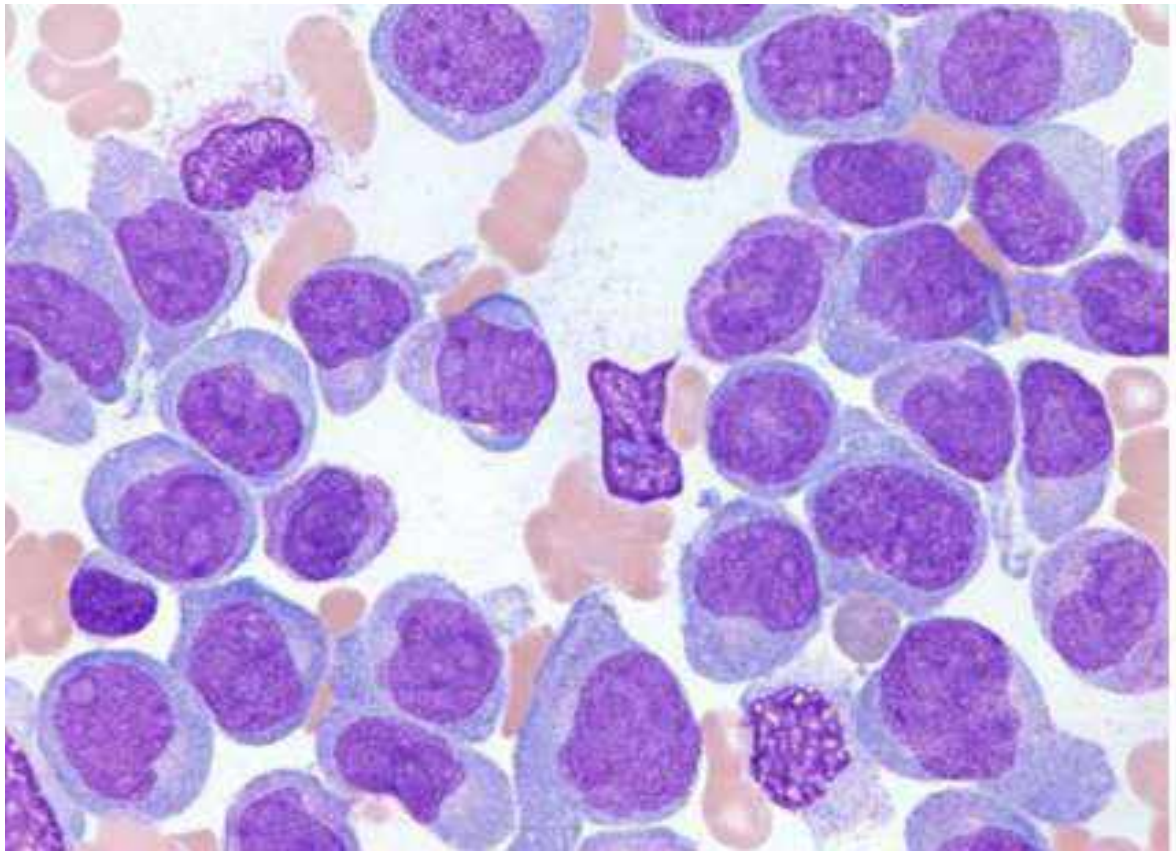
Complicanze trombotiche nelle leucemie acute



Marco Cerrano, MD

rete oncologica
PIEMONTE | VALLE D'AOSTA
si prende cura di te

AZIENDA OSPEDALIERO-UNIVERSITARIA
Città della Salute e della Scienza di Torino

S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

Con il patrocinio
dell'Università degli Studi di Torino

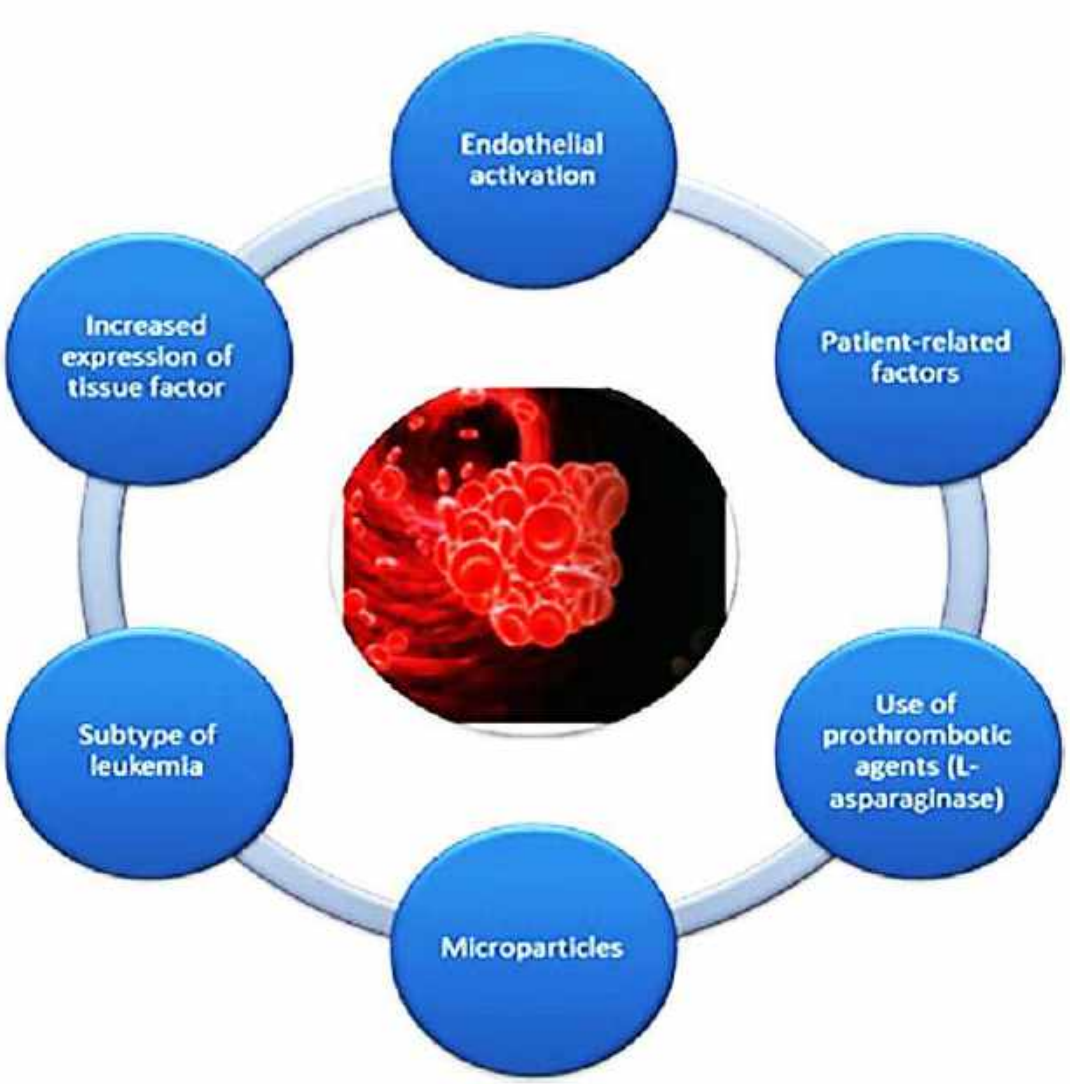
UNIVERSITÀ
DEGLI STUDI
DI TORINO

OUTLINE

- PATHOGENESIS
- THROMBOSIS IN ALL
- THROMBOSIS IN APL
- THROMBOSIS IN AML

OUTLINE

Pathogenesis of thrombosis in leukemias



Disease-related

- Subtype of leukemia
- CBC: WBC, PLTS

Treatment-related

- Type of chemo (ASP, CCS?)
- CVC
- Immobility

Patient-related

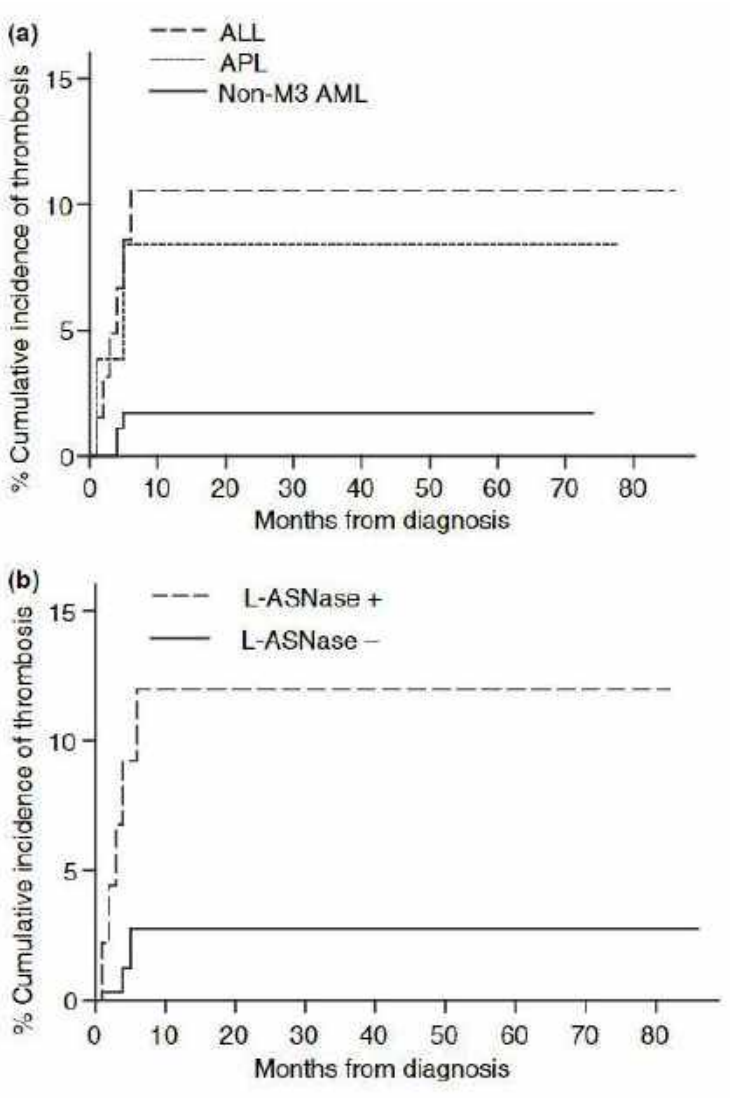
- Age
- BMI, diabetes
- Infection
- History of thrombosis
- Thrombophilia

Guzmán-Uribe & Vargas-Ruíz. Curr Oncol Rep 2015

OUTLINE

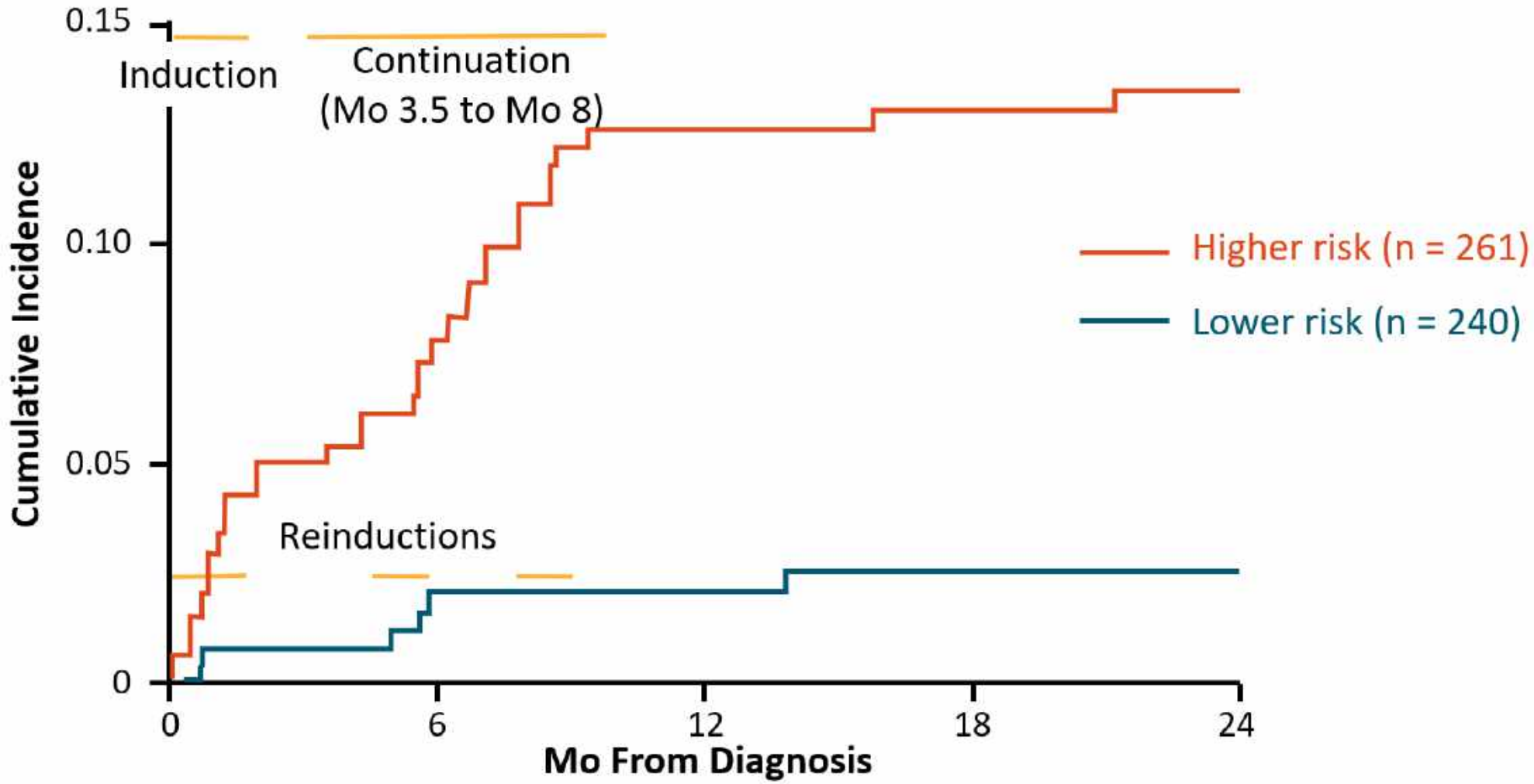
Thrombosis in acute leukemias

Thrombosis at diagnosis (incidence)	
ALL	1.4
APL	9.6
AML	3.2



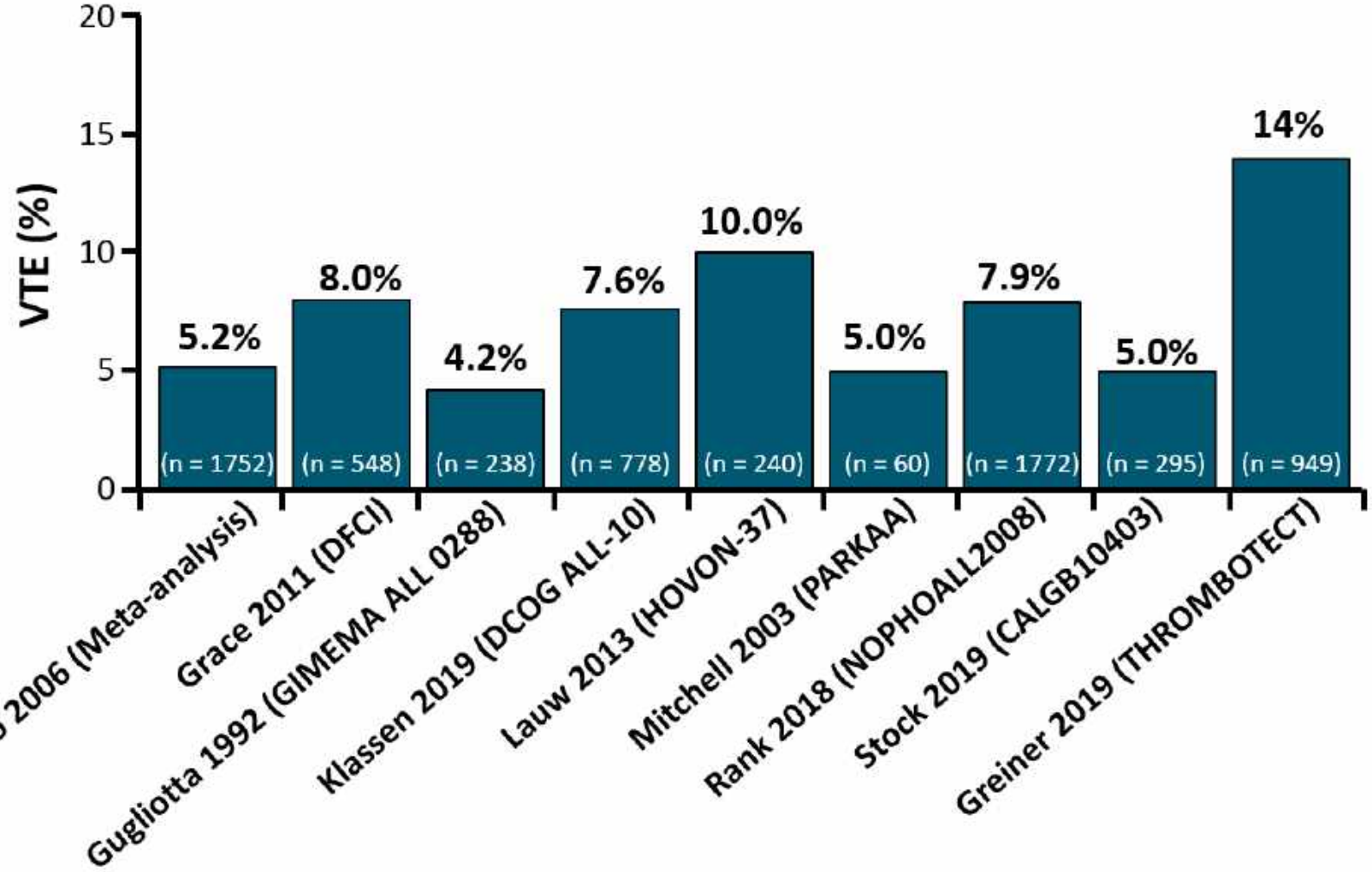
De Stefano, J Thromb Haemost 2005

Cumulative Incidence of Thrombosis in Patients With ALL by Risk Group



Pui. NEJM. 2009;360:2730.

Incidence of VTE With Pegaspargase in ALL Across Studies



Underwood. Int J Hematol Oncol. 2020;9:IJH28. Greiner. Haematologica. 2019;104:756.

Site of thrombosis in ALL

Pediatric patients

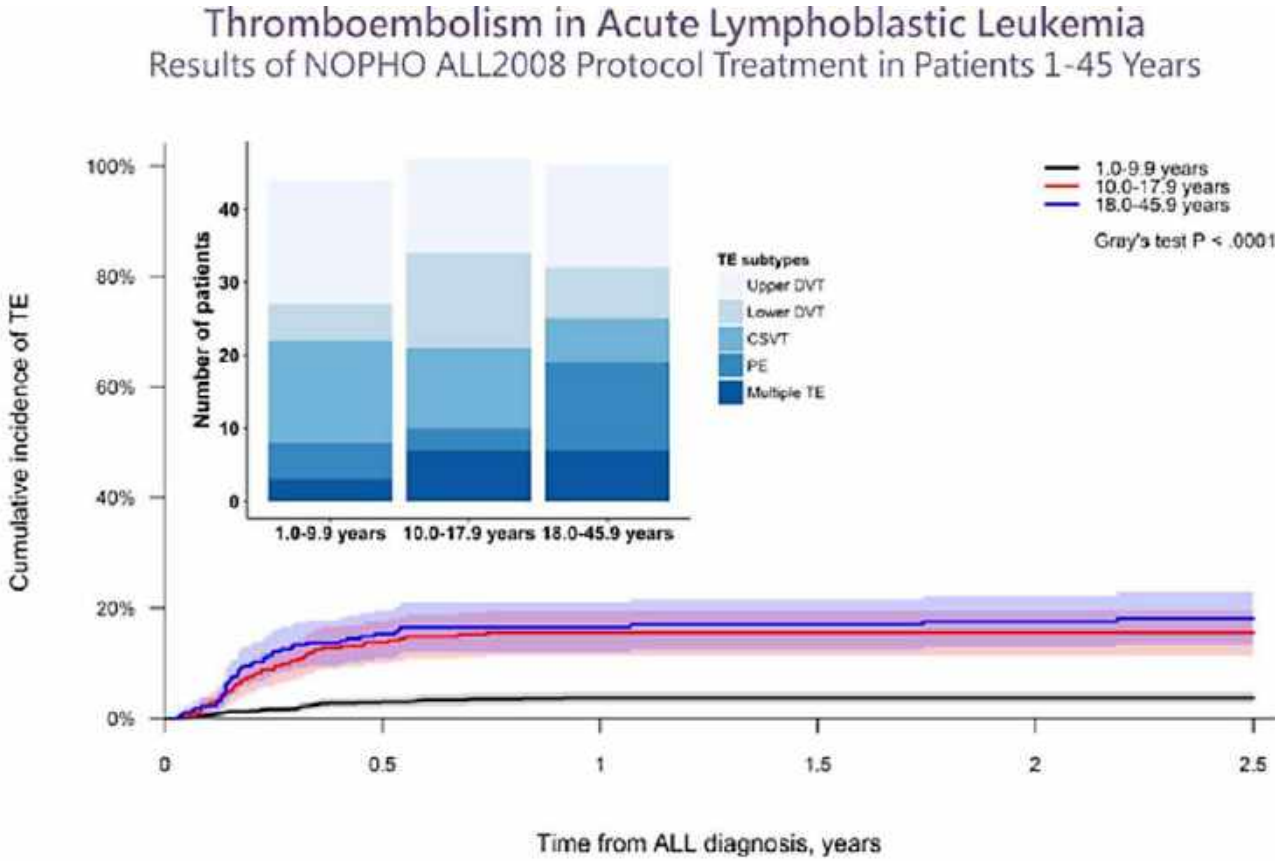
Table 2. Sites of thrombosis

Site of thrombosis, N = 91	No. of events (%)
Central nervous system	49 (53.8)
Cerebral venous thrombosis	26 (28.6)
Cerebral thrombosis (nonspecified)	5 (5.5)
Cerebral infarction	9 (9.9)
Stroke	9 (9.9)
Non-CNS venous thrombosis	39 (42.8)
Nonspecified DVT	3 (3.3)
DVT-lower limbs	7 (7.7)
DVT-upper limbs + CVC-associated thrombosis	25 (27.5)
Pulmonary embolism	1 (1.1)
Right atrium	1 (1.1)
Portal thrombosis	0
Superficial thrombosis	2 (2.2)
Nonspecified site of thrombosis	3 (3.3)

Adult patients

GRAAL

All (n = 784)	Any thrombosis (n = 112)	DVT/PE (n = 85)	CVT (n = 32)

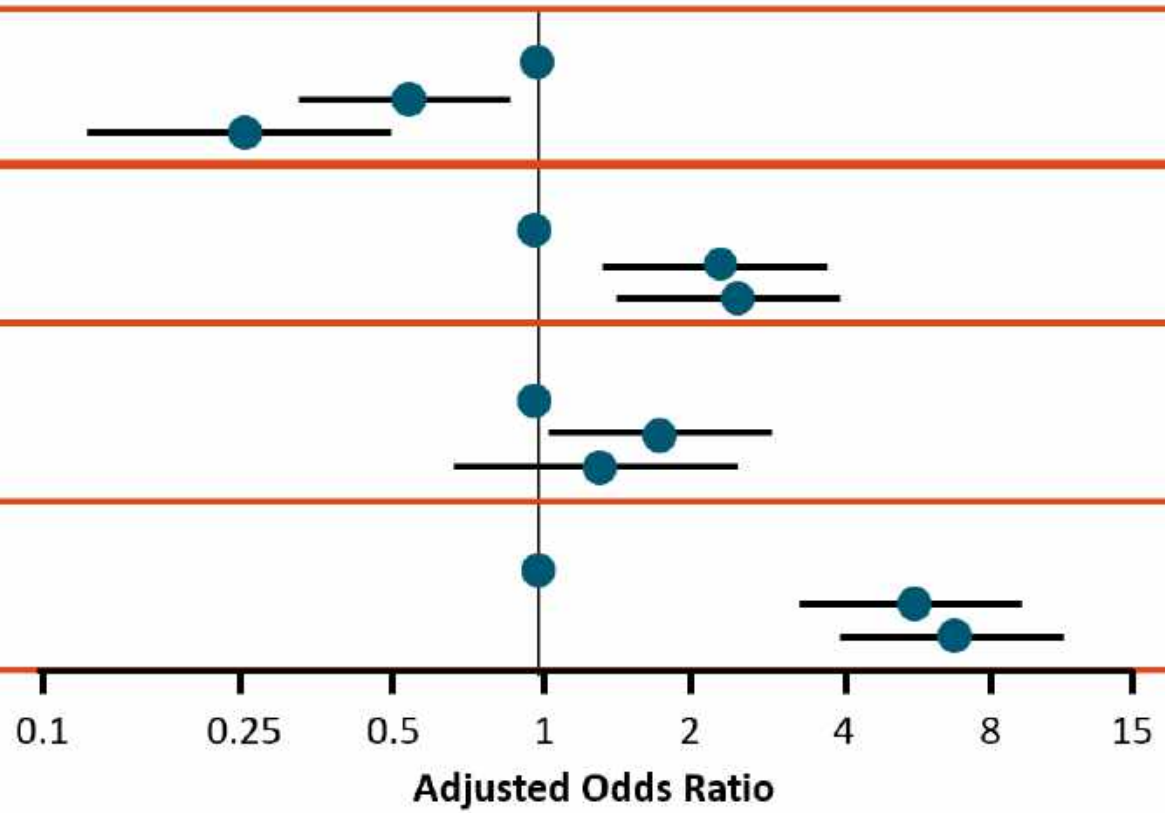


Caruso. Blood 2006; Orvain, Blood 2020; Rank, Blood 2018

Age and Asparaginase-Associated Toxicities

Risk of Common Asparaginase-Associated Toxicities by Age

Age Range	Y/N (%)	OR (95% CI)	*P*	*P* Trend
Anaphylactic reaction to asparaginase				
1-9	146/863 (14.5)	1.0 (1.0-1.0)		<.001
10-17	25/237 (9.5)	0.6 (0.4-0.9)	.016	
18-45	11/201 (5.2)	0.3 (0.1-0.5)	<.001	
Pancreatitis				
1-9	60/949 (5.9)	1.0 (1.0-1.0)		<.001
10-17	29/233 (11.1)	2.2 (1.3-3.5)	.001	
18-45	24/188 (11.3)	2.4 (1.4-4.0)	.001	
Hyperlipidemia				
1-9	72/937 (7.1)	1.0 (1.0-1.0)		.12
10-17	26/236 (9.9)	1.7 (1.0-2.8)	.027	
18-45	15/197 (7.1)	1.3 (0.7-2.3)	.37	
Thrombosis				
1-9	36/973 (3.6)	1.0 (1.0-1.0)		<.001
10-17	40/222 (15.3)	5.0 (3.1-8.2)	<.001	
18-45	37/175 (17.5)	6.0 (3.6-10.1)	<.001	



- Prospective database analysis of 1509 consecutive patients (aged 1-45 yr) with Ph-negative ALL receiving treatment at Nordic and Baltic centers from July 2008 to December 2014

Toft. Leukemia. 2018;32:606.

CALGB 10403 vs COG AALL0232: Grade 3/4 AEs During Induction Therapy in AYA Patients With ALL

Grade 3/4 AE, n (%)	CALGB 10403 (n = 289)	COG AALL0232 (n = 158)	*P* Value*
Hyperglycemia	90 (31.1)	36 (22.8)	.06
AST	37 (12.8)	9 (5.7)	.02
ALT	83 (28.7)	28 (17.7)	.01
Hyperbilirubinemia	55 (19.0)	11 (7.0)	<.001
Anaphylaxis	4 (1.4)	1 (0.6)	.66
Pancreatitis	8 (2.8)	2 (1.3)	.51
Thrombosis	**15 (5.2)**	**3 (1.9)**	**.13**
Febrile neutropenia	69 (23.9)	9 (5.7)	<.001
Infection	71 (24.6)	36 (22.8)	.67

*$\chi 2$ or Fisher's exact test.

- Grade 3/4 thrombosis with postremission therapy: 10.1% vs 2.0% (*P* = .002)

Anjali. Blood Adv. 2021;5:504.

Risk factors for thrombosis in ALL

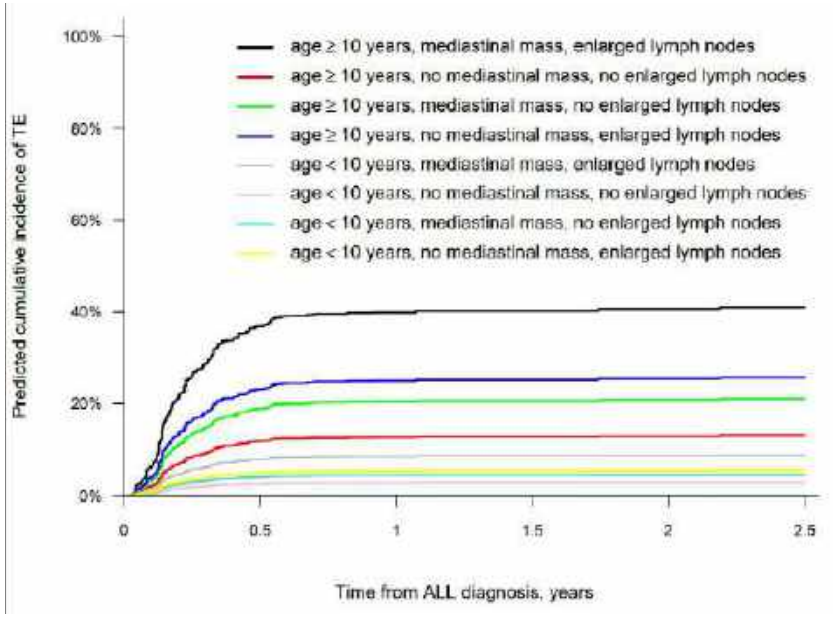


Table 2. Univariable analysis of risk factors for DVT/PE and CVT

	Univariable analysis of risk factors for any thrombosis		
	OR	95% CI	P
Age	1.02	1.00-1.03	.03
Female	1.50	1.00-2.23	.05
BMI	1.04	1.00-1.08	.05
Smoking	.98	.92-1.04	.5
Contraception	.63	.40-1.75	.63
B-cell phenotype	1.24	.82-1.88	.31
CNS involvement	.58	.23-1.49	.26
WBC count at diagnosis, $\times 10^9$/L	.99	.99-1.00	.46
Hemoglobin level at diagnosis, g/dL	1.05	.98-1.12	.19
Platelet count at diagnosis/100 $\times$ 10^9/L	1.02	1.00-1.04	.03

Multivariable analysis

Clinical factor	*P*	OR (95% CI)
Age ≥10 years	0.036	1.97 (1.05–3.72)
Mediastinal mass	0.017	2.89 (1.21–6.95)
Weight < 5th or > 95th centile at diagnosis	0.001	2.94 (1.54–5.59)

TABLE 4 Multivariable analysis of risk factors associated to VTE

Risk factor	Odds ratio	p
T-cell ALL phenotype	1.26 (0.44–3.61)	.663
High-risk group	1.59 (0.77–2.35)	.206
Mediastinal mass	2.29 (0.93–5.64)	.07
Non-O blood group	1.57 (0.78–3.18)	.201
Family history of thrombosis	4.12 (0.94–18.09)	.06
Heritable thrombophilia	3.25 (1.57–6.71)	.001

Rank, Blood 2018; Orvain, Blood 2020; Mateos, Thromb Research 2019; Ruiz-Llobet, J Thromb Haemost 2022

ASP-related toxicityes in adults

Table 1. The rate and risk factors for pegasparaginase toxicities in adults

Toxicity	Any grade (%)	High grade (≥ 3) (%)	Risk factors
Hypersensitivity	7-22	4-10	Second dose and future doses, HLA-DRB1*07:01 polymorphism, no concurrent rituximab administration, younger age, no pre-medications
Hyperbilirubinemia	86	24-39	During the induction cycle, older age, obesity, higher dose of pegasparaginase, low albumin, low platelet count, CC genotype of rs4880 polymorphism
Pancreatitis	24	5-13	Older age, high-risk ALL stratification, germline polymorphisms in *ULK2* variant rs281366 and *RGS6* variant rs17179470
Hypertriglyceridemia	77	11-51	Beyond first cycle, high BMI, younger age
Thrombosis		11-27	First cycle, older age, obesity, mediastinal mass, cryoprecipitate replacement
Hypofibrinogenemia (<100)		48-51	First cycle, severe obesity (BMI >35)
Hyperglycemia	91	31-33	Concomitant use of steroid

BMI, body mass index.

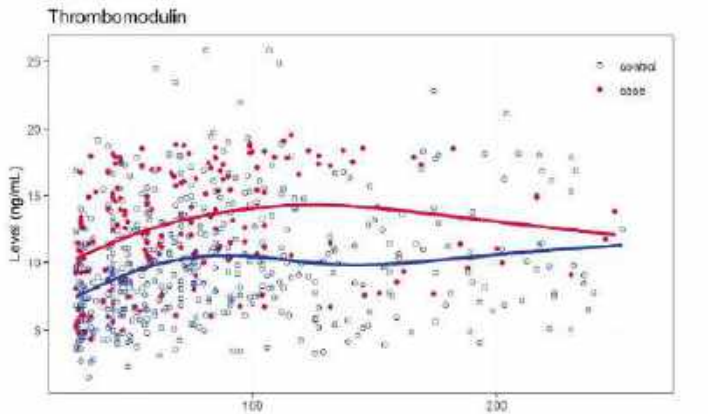
Aldoss & Douer. Blood 2020

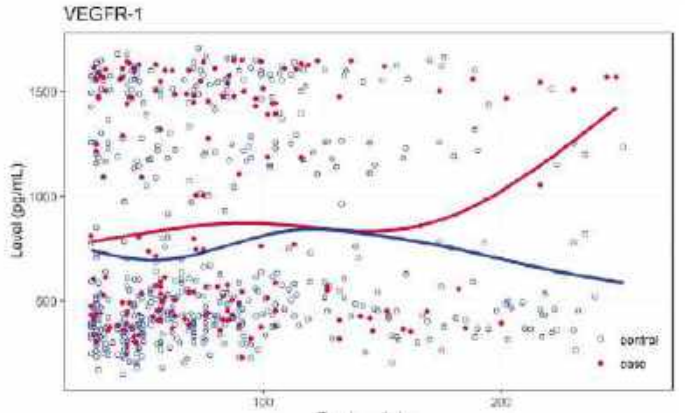
Biomarkers of thrombosis in ALL

Thrombomodulin and VEGFR-1

	N	TE-specific OR	95% CI	*P*
Model with TM				
Median TM level (per 1 ng/mL)	220	1.37	1.20–1.56	<0.0001
Sex				
Male	118	1.0 [ref.]		
Female	102	4.69	1.72–12.77	0.003
Age groups				
1.00–9.9 y	128	1.0 [ref]		
10.0–17.9 y	51	2.69	1.09–6.62	0.03
18.0–45.9 y	41	6.79	2.52–18.31	0.0002
Risk group				
Non-HR	188	1.0 [ref]		
HR	32	2.20	0.75–6.45	0.15

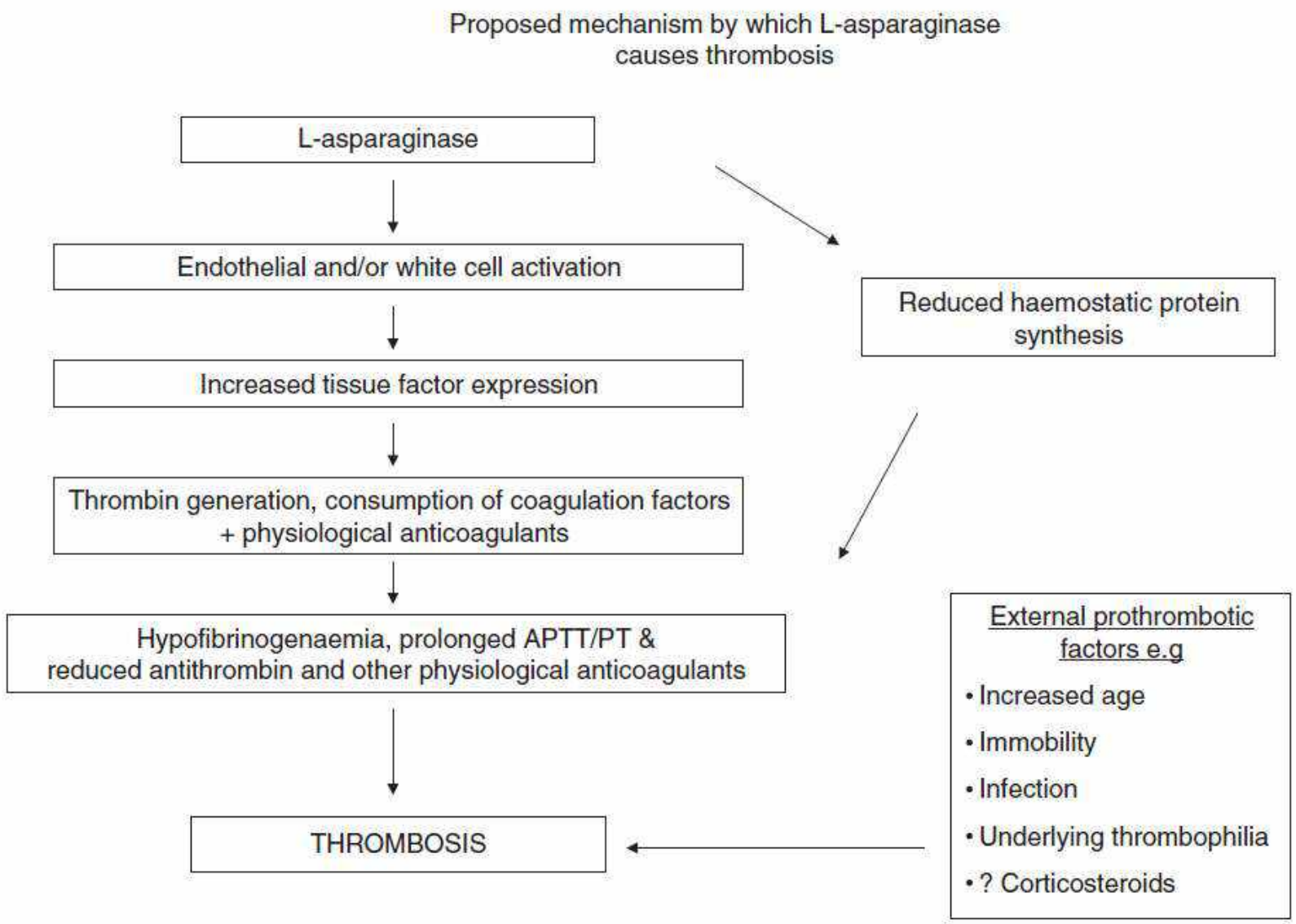
	N	TE-specific OR	95% CI	*P*
Model with VEGFR-1				
Median VEGFR-1 level (per 100 pg/mL)	220	1.12	1.04–1.21	0.005
Sex				
Male		1.0 [ref]		
Female		1.95	0.93–4.09	0.08
Age groups				
1.00–9.9 y		1.0 [ref]		
10.0–17.9 y		3.28	1.47–7.35	0.004
18.0–45.9 y		9.10	3.67–22.53	<0.0001
Risk group				
Non-HR		1.0 [ref]		
HR		1.25	0.48–3.21	0.6





Andrés-Jensen, Leukemia

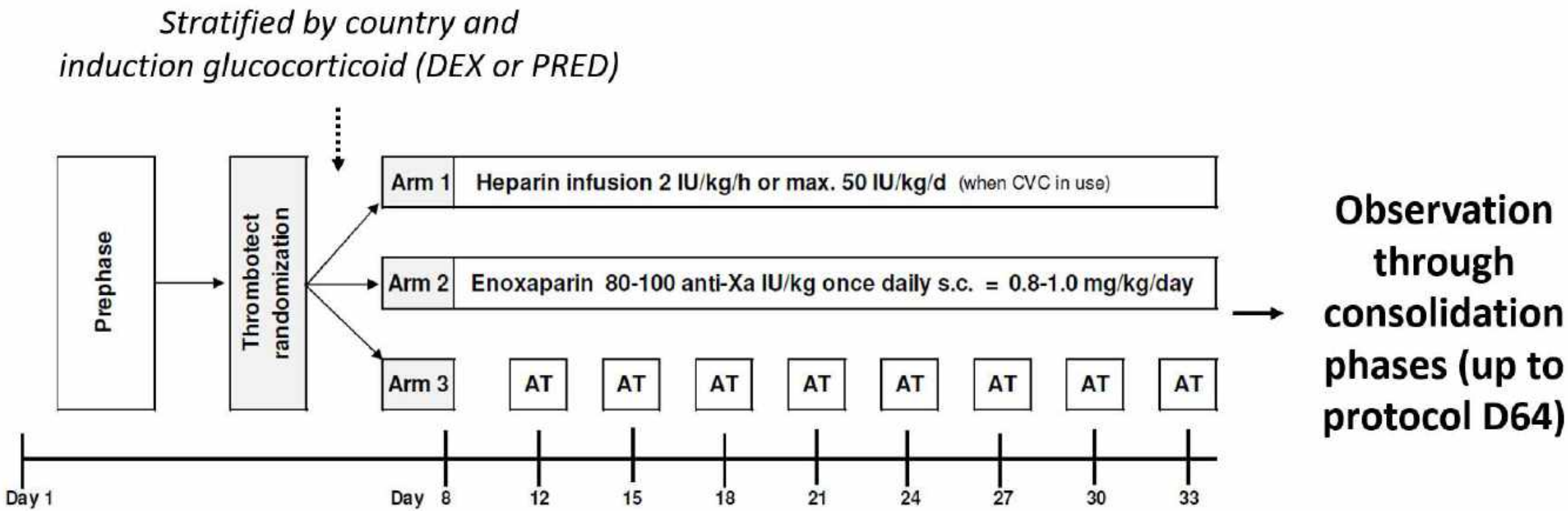
Mechanism of L-ASP-induced thrombosis



Coagulation factors affected
Depleted
Factor XI, IX, VIII, von Willebrand, V, X, II, fibrinogen, antithrombin, heparin cofactor II, protein C, protein S, plasminogen, α2-antiplasmin
Increased
Factor VII, t-PA, PAI-1

Truelove, Leukemia 2013; Guzmán-Uribe & Vargas-Ruíz. Curr Oncol Rep 2015

THROMBOTECT: Thromboprophylaxis During Induction Therapy for ALL in Children and Adolescents

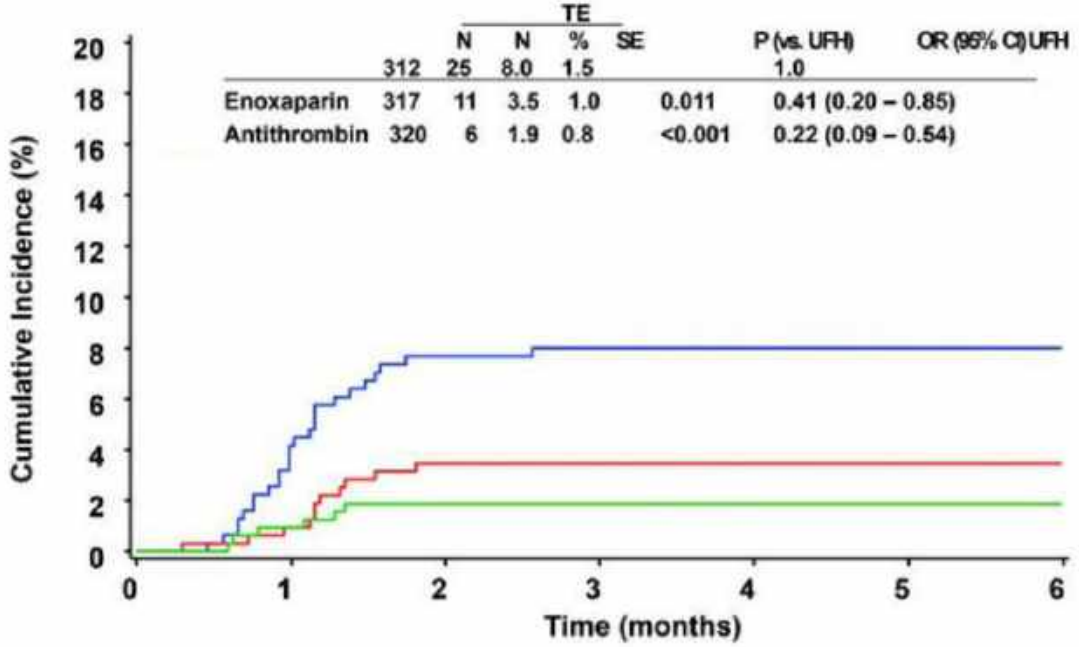


D33 = end of interventional phase

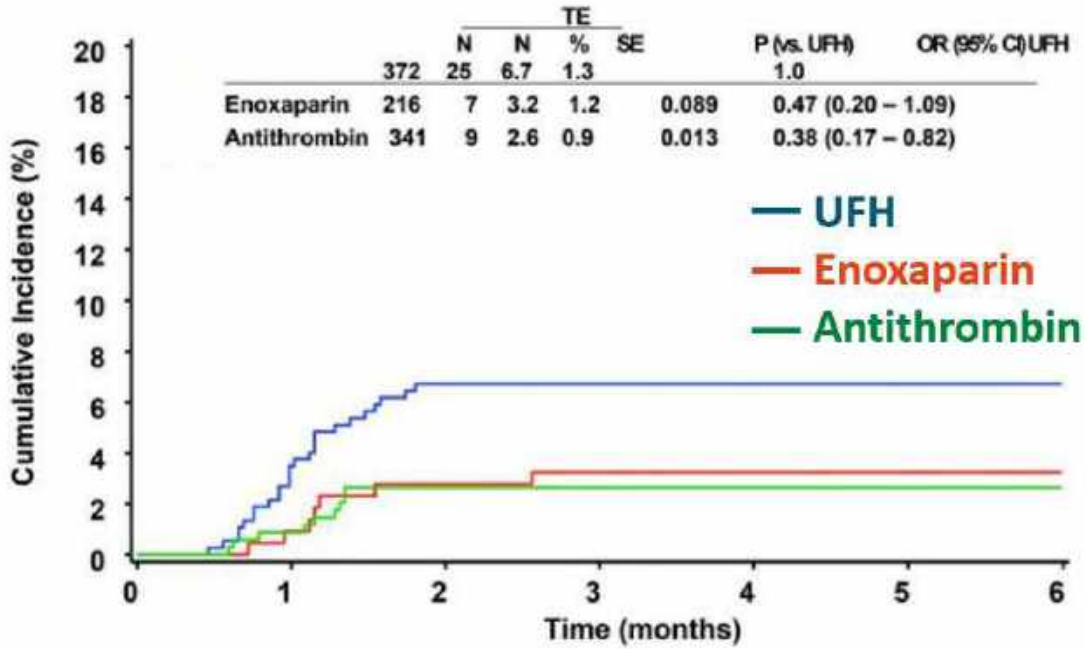
Greiner. Haematologica. 2019;104:756.

THROMBOTECT: Thromboembolic Events Overall

Thromboembolic Events in ITT Population



Thromboembolic Events in Total Population

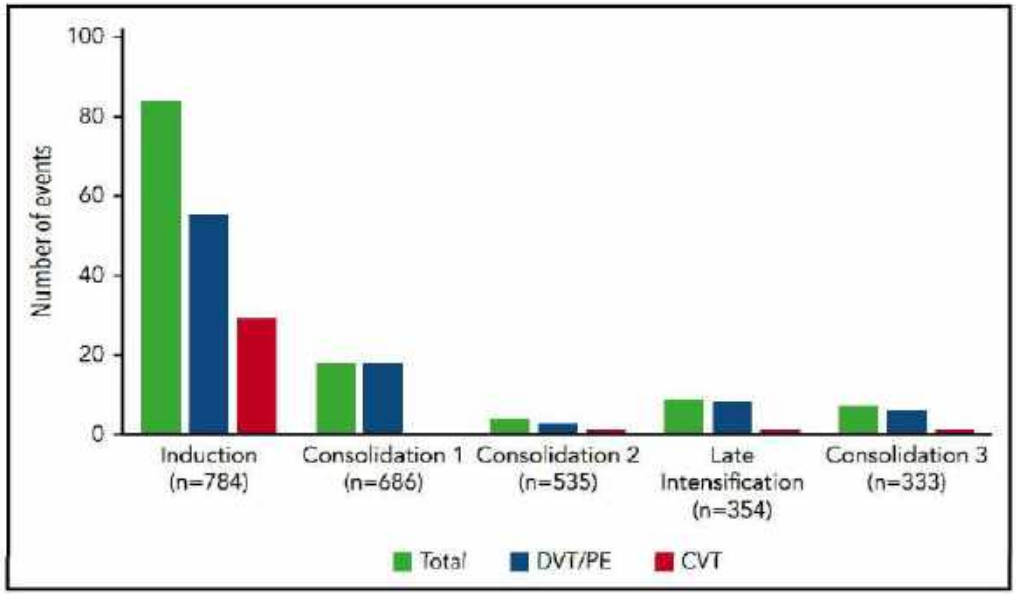


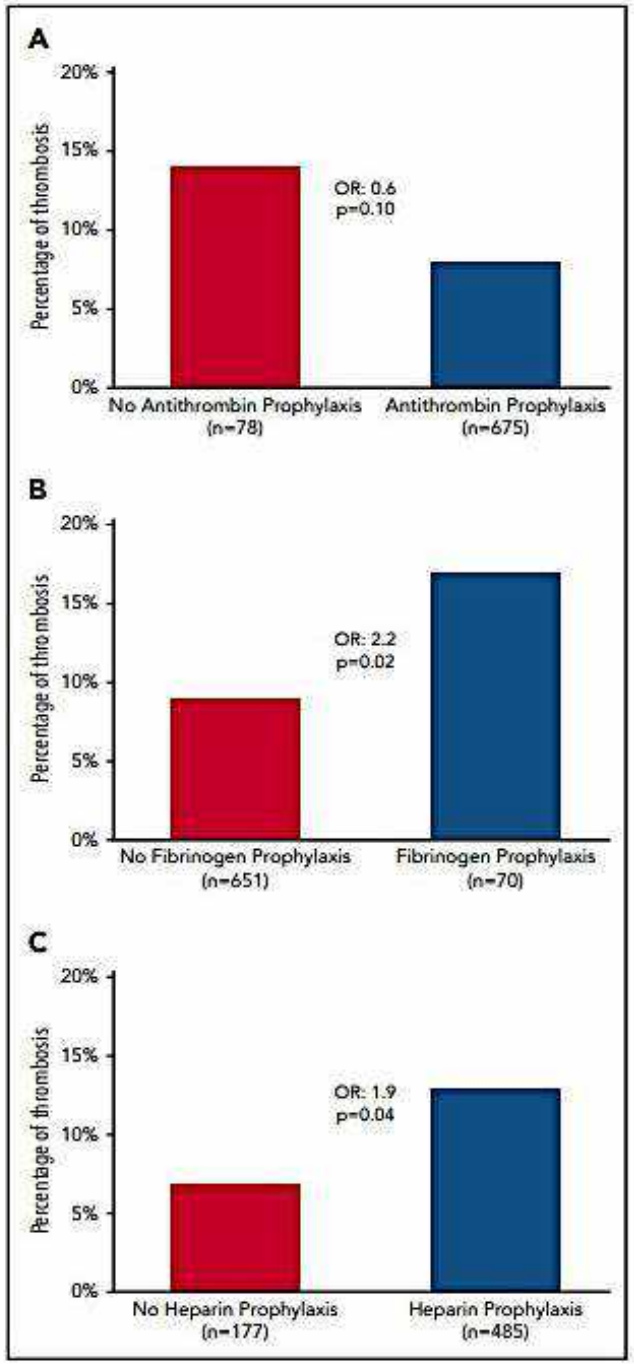
- Enoxaparin or AT prophylaxis from D8 to D33 reduces thrombosis by half when compared with UFH

Greiner. Haematologica. 2019;104:756.

Thromboses in ALL: GRAAL 2005

Incidence of VTE 16% (122 VTEs in 112 patients)

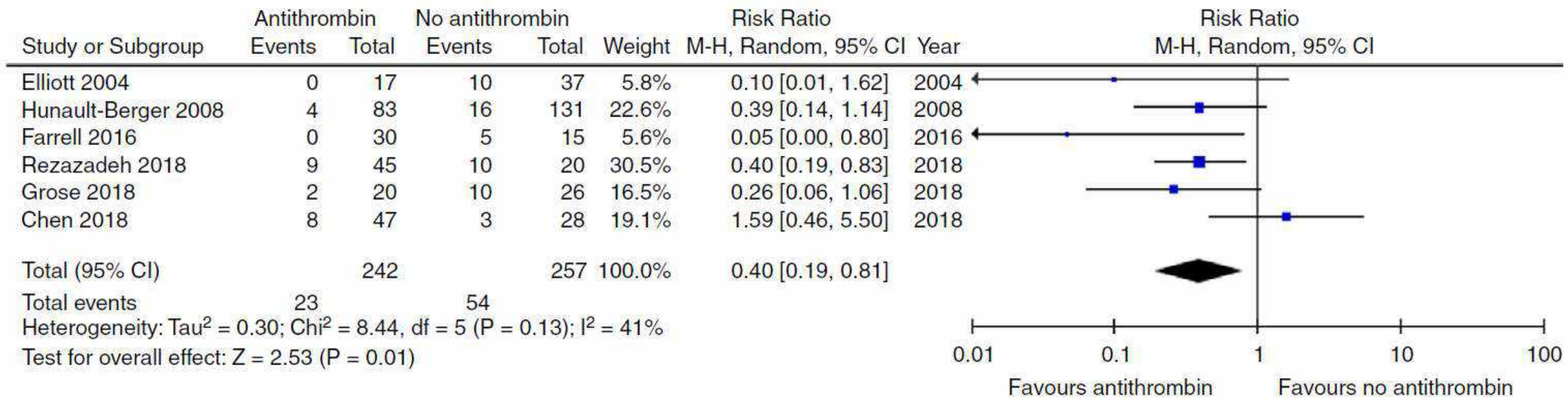




MOST PATIENTS RECEIVED UFH

Orvain, Blood 2020

AT III replacement in ALL



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)

FIGURE 1 Pooled analyses of cohort studies in adults comparing VTE rates with or without antithrombin repletion

Zwicker *(ISHT), J. Thromb. Haemost.* 2020

Guidance statements

1. We suggest monitoring and repletion of AT following L-asparaginase therapy per ISTH guidance.[2]

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

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 < 30×10^9/L).[29]

1. In adults, we suggest against routine infusion of FFP to prevent VTE during asparaginase therapy in patients with ALL.

2. In patients undergoing L-asparaginase treatment, we suggest replacement of fibrinogen for a level <0.5 g/L. In patients with active bleeding, we suggest targeting a higher fibrinogen level.

WANG et al (ISHT), J. Thromb. Haemost. 2020; Zwicker *(ISHT), J. Thromb. Haemost.* 2020

Guidance statements

1. We suggest LMWH for the acute management of VTE related to asparaginase therapy if severe thrombocytopenia (ie, platelet count < 50 x 10^9/L) is anticipated. Following resolution of severe thrombocytopenia, DOAC may be considered in the absence of other relative contraindications such as major drug interactions.
2. We recommend therapeutic dosing of LMWH and suggest monitoring of anti-Xa levels due to increased variability in the setting of decreased plasma antithrombin concentrations (see Management of anticoagulation with severe thrombocytopenia per ISTH SSC Hemostasis and Malignancy guidance[44]).
3. For life-threatening VTE such as cerebral venous thrombosis or central PE, we suggest short-term concurrent administration of antithrombin concentrate until therapeutic anticoagulation and clinical stability is established.
4. We recommend therapeutic anticoagulation for a catheter-related deep vein thrombosis (DVT) and nonremoval of a functioning catheter in accordance with prior ISTH guidance.[45]
5. For high-risk thrombotic events such as cerebral venous or sinus thrombosis, central PE, proximal DVT, or arterial thrombosis we recommend holding asparaginase therapy, at least temporarily.
6. We suggest the consideration to resume asparaginase following successful stabilization of the acute thrombotic event (approximately 4 weeks). There is limited literature on the safety of resumption of asparaginase following a cerebral venous thrombosis and resumption should be considered on a case-by-case basis accounting for number of asparaginase doses missed, resolution of thrombosis and symptomatology, and ongoing VTE risk factors, and only under the cover of anticoagulation.
7. We recommend at least 6 months of therapeutic anticoagulation for treatment of VTE associated with asparaginase. Shorter duration may be considered on a case-by-case basis with the minimum duration extending 4 to 6 weeks following completion of asparaginase therapy. In those patients who developed a life-threatening VTE such as cerebral venous thrombosis, central PE, proximal DVT, or arterial thrombosis and are not otherwise considered at increased risk for hemorrhage, we suggest continuation of anticoagulation until completion of chemotherapy and achievement of complete remission.

Zwicker *(ISHT), J. Thromb. Haemost.* 2020

RACCOMANDAZIONI SIE

Nei pazienti con LAL in trattamento con asparaginasi si raccomanda la profilassi del TEV con EBPM e si suggerisce di infondere antitrombina con l'obiettivo di raggiungere un livello target di 80-120%	
POSITIVA CONDIZIONATA	EVIDENZA BASSA

Astenuti per COI = 0/8

Si raccomanda una rivalutazione periodica clinica e di laboratorio del rischio trombotico ed emorragico del singolo paziente con LAL in terapia con asparaginasi, comprensiva anche del dosaggio di fibrinogeno e dell'antitrombina	
POSITIVA CONDIZIONATA	EVIDENZA MOLTO BASSA

Astenuti per COI = 0/8

Linee guida SIE profilassi TEV 2021

OUTLINE

Risk factors for thrombosis in APL

Incidence: 11/124 (8.9%)

Table 3 Comparison of presenting features in APL patients with and without thrombosis

Features	*Patients with thrombosis*	*Patients without thrombosis*	*P-value*
Sex (M/F)	4/7	48/55	NS
Age	55	37.3	NS
FAB M3/M3v	8/3	85/18	NS
WBC	17	2.8	0.002
bcr1-2/bcr3	2/9	46/44	0.01
FIT3-ITD	7/11	26/77	0.02
CD2+	6/11	17/87	0.0001
CD15+	4/11	8/95	0.016

Breccia, Leukemia 2007

Can we differentiate thrombohemorragic disorders in APL?

Univariate and multivariate regression analysis of risk factors for thrombosis in high-risk APL patients.

		Multivariate analysis	
Factors	Unfavorable category	HR (95% CI)	P value
PT(s)	<15.8		
FIB (g/L)	<1.30		
PLT(×109/L)	<9.5		
WBC (×109/L)	>37.94		
D-dimer (mg/L)	<8.52		
WBC/D-dimer	>5.12	16.77(2.91–96.55)	**0.002**
FDP/FIB	<85.4		
D-dimer/FIB	<5.14	6.20(1.20–32.14)	**0.03**
FLT3-ITD mutation	Yes		

Xiao, Thromb Res 2022

RACCOMANDAZIONI SIE

Raccomandazione P1

La profilassi del TEV non è routinariamente raccomandata nei pazienti con APL per l'elevato rischio di eventi emorragici severi: il bilancio tra i rischi e i benefici della profilassi del TEV va valutato in ogni singolo paziente	
NEGATIVA FORTE	QUALITA' EVIDENZA MOLTO BASSA

Astenuti per COI = 0/8

Linee guida SIE profilassi TEV 2021

Management of APL coagulopathy

Management of coagulopathy

1.5. Treatment with ATRA should be started immediately when a diagnosis of APL is suspected

1.6. Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately upon suspicion of the diagnosis, and then daily or more than once a day if needed, to maintain the fibrinogen concentration above 100-150 mg/dL, the platelet count above 30×10^9/L to 50×10^9/L, and the INR below 1.5

1.7. Platelet counts and routine coagulation parameters, prothrombin time, activated partial thromboplastin time, and thrombin time, as well as levels of fibrinogen and fibrinogen-fibrin degradation products, should be monitored at least daily and more frequently if required, until disappearance of all clinical and laboratory signs of the coagulopathy

1.8. The benefit of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy remains questionable and should not be used routinely outside of the context of clinical trials

1.9. Central venous catheterization, lumbar puncture, and other invasive procedures (eg, bronchoscopy) should be avoided before and during remission induction therapy due to high risk of hemorrhagic complications

Management of hyperleukocytosis (WBC count >10 × 10^9/L) at presentation

1.10. Cytoreductive chemotherapy should be started without delay, even if the molecular results are still pending:

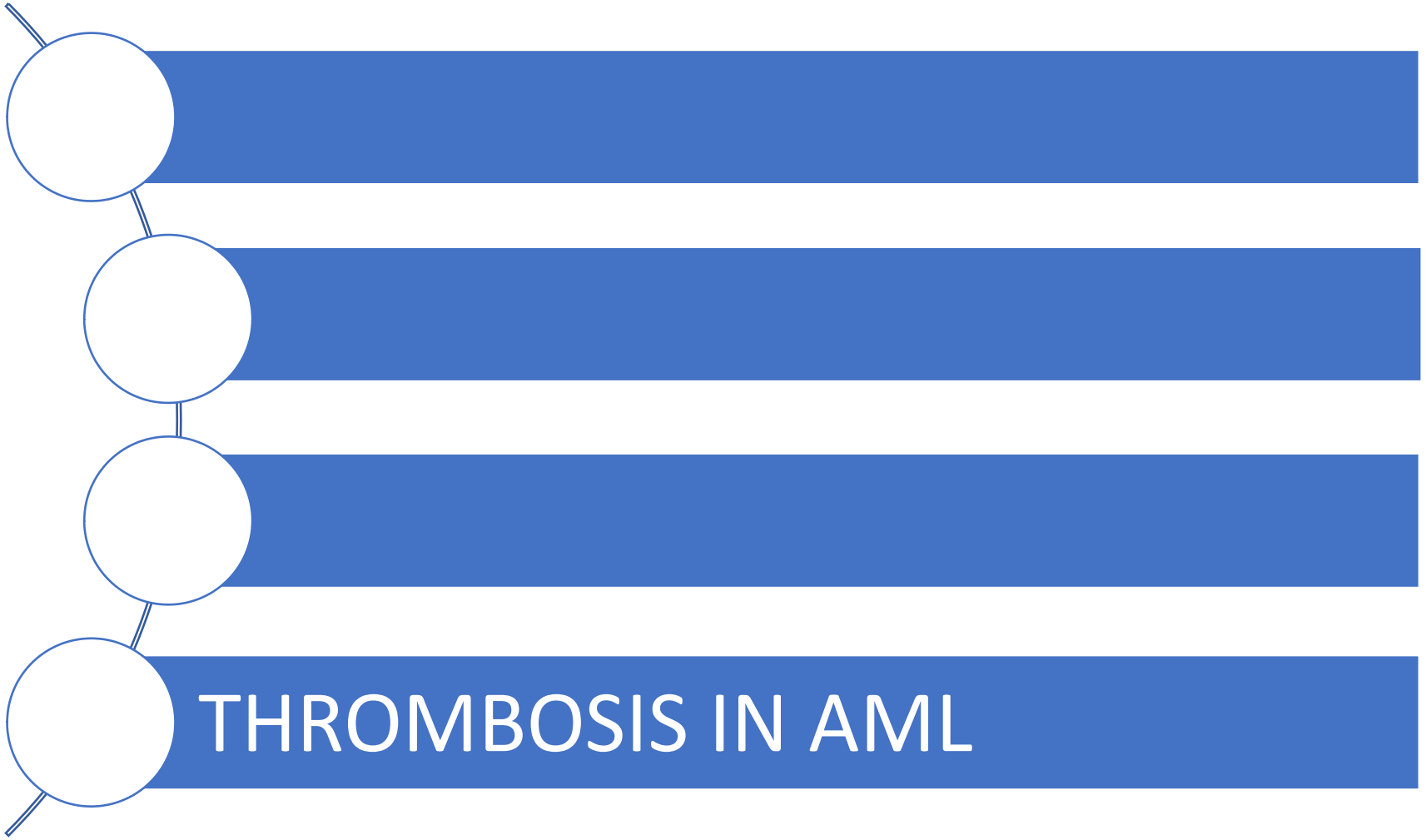
- For patients to be treated with ATRA + chemotherapy, idarubicin or daunorubicin alone or combined with cytarabine should be given
- For patients to be treated with ATRA + ATO, cytoreduction can be done with idarubicin (12 mg/m^2) or GO (6-9 mg/m^2)

1.11. Leukapheresis should be avoided due to risk of precipitating fatal hemorrhage

1.12. Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome

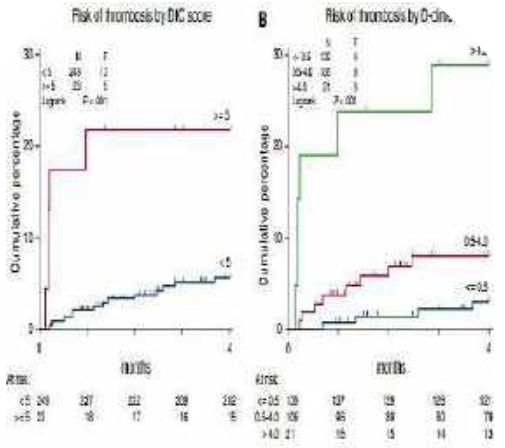
Sanz, Blood 2019

OUTLINE



Thrombosis in AML

- The incidence of venous thromboembolism (VTE) ranged from 2 to 14.4% in different studies
- Prognostic impact is not firmly established
- Different risk factors in different reports
  - ➢ Infections increase the risk of catheter-related thrombosis (CRT)
  - ➢ Female gender, older age, n° of chronic comorbidities, CVC
  - ➢ Age and cytogenetics risk
- Khorana score did not seem to work in this context
- **DIC score** was predictive, but it is not validated yet



Ziegler, *Thromb Res* 2005; De Stefano, *J Thromb Haemost* 2005; Ku, *Blood* 2009; Del Principe, *Thromb Res* 2013; Libourel, *Blood* 2016; Mirza, *Thrombosis Journal* 2019; Paterno, *EHA* 2020

Frequency and risk factors for thrombosis in acute myeloid leukemia treated with intensive chemotherapy: a two centers observational study

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Study Design

Endpoints

- To evaluate the frequency of thrombosis in AML patients treated with intensive chemotherapy
- To assess the ability of genetic and clinical factors to predict the risk of thrombosis
- To validate DIC and Khorana score
- To assess the potential prognostic impact of thrombosis in AML

Methods

- Retrospective analysis of adult patients with newly diagnosed AML (and HR-MDS), excluding APL
- Consecutively treated with intensive chemotherapy between January 2013 and February 2020
- Clinical and laboratory data at diagnosis were collected, including complete coagulation parameters

DIC SCORE		
Variable	Value	Points
Platelets (10^9/L)	>100	0
	50-100	1
	<50	2
Prolonged PT (s)	<3	0
	3-6	1
	>6	2
Fibrinogen level (mg/dl)	>100	0
	<100	1
D dimer (mg/L)	No increase (<0.5)	0
	Moderate increase (0.5-4)	1
	High increase (>4)	2

Khorana SCORE		
Variable	Value	Points
Platelets (10^9/L/L)	≥350	1
	<350	0
White blood cells (10^9/L)	>11	1
	≤11	0
Hemoglobin (g/dL)	<10	1
	≥10	0
Body max index (kg/m^2)	≥35	1
	<35	0

Khorana, *Blood* 2008; Libourel, *Blood* 2016; Mirza, *Thrombosis Journal* 2019

Patients' charachteristics

		N (%)	Median (range)
OVERALL		**222**	
Gender	Male	115 (52)	
	Female	107 (48)	
Age, years			**59.5 (20-78)**
AML		**210 (94.6)**	
	De novo	157 (74.8)	
	Secondary	44 (20.9)	
	Therapy-related	9 (4.3)	
HR-MDS		**12 (5.4)**	
Leucocytes (x 10^9/L)			36.5 (0.36-313)
Platelets (x 10^9/L)			88 (3-421)
Bone marrow blasts, %			60 (4-95)
AML Risk ELN 2010	Favorable	41 (19.5)	
	Intermediate-1	**82 (39)**	
	Intermediate-2	33 (16)	
	High	43 (20.5)	
	NA	11 (5)	
Induction therapy	**3+7 like**	**159 (72.6)**	
	Fludarabine-based	58 (26.1)	
	Other	5 (2.3)	

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Thrombotic episodes

Median follow-up, months IQR				43.5	23-58.2
Patients with thrombosis, n %	**Yes**			**49***	22.1
	No			173	77.9
Thromboses		**Venous, n %**		**45**	**90**
			DVT leg	6	13.3
			DVT upper	5	11.1
			Pulmonary	3	6.7
			CRT	**28**	**62.2**
			-PICC	26	
			-Hohn	1	
			-other	1	
			Other	3	6.7
		Arterial, n %		**5**	**10**
			Myocardial	2	40
			CVA	3	60
Median time to thrombosis, days IQR				84	22-224
Thromboses before day 100, n %				26	52
Thromboses before chemotherapy, n %				6	12
Thromboses preceded by sepsis, n %				20	40

DVT: deep venous thrombosis, CRT: catheter-related thrombosis; CVA: cerebral vascular accident

*1 patient developed both a venous and an arterial thrombosis

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Risk Factors of Thrombosis

		Thrombosis	No event	p-value	VTE	p-value	ATE	p-value
OVERALL		**49**	**173**		**45**		**5**	
Gender, n (%)	Male	29 (59)	86 (39)	0.2414				
Age, y (range)	<60	29 (59)	90 (52)	0.3749				
	>60	20 (41)	83 (48)					
Leukocytes, mean (range)		7.39 (0.53-261)	8.44 (0.36-393)	0.8554				
Platelets, n (%)	**>100*10^9/L**	**24 (49)**	**54 (31)**	**0.036**	**23 (51)**	**0.028**	2 (40)	0.94
	<100*10^9/L	25(51)	119 (69)		22 (49)		3(60)	
DIC score, n (%)	>5	7 (14)	30 (17)	0.6214				
	<5	42 (86)	143 (83)					
Hemoglobin, mean (%)		9.2 (3.9-16.1)	8.9 (4-15)	0.4663				
BM blasts, mean (%)		60 (12-90)	70 (4-95)	0.6227				
LDH, mean (range)		691	780	0.8388				
BMI, n (%)	**<25**	**38 (77.6)**	**136 (78.6)**	**0.87**				
	>25	11 (22.4)	37 (21.4)					
Active smoking, n (%)	No	40 (81.69	160 (92.5)	**0.025**	39 (86.7)	0.389	4 (80)	**0.001**
	Yes	9 (18.4)	13 (7.5)		6 (13.3)		1 (20)	
Previous thrombosis, n (%)	**Yes**	**8 (16)**	**12 (7)**	**0.0427**	8 (18)	**0.0214**	1 (20)	0.38
	No	41 (84)	161 (93)		37 (82)		4 (80)	
Previous VTE	**Yes**	**5 (10)**	**3 (2)**	**0.0053**	5 (11)	**0.003**	0 (0)	0.66
	No	44 (90)	170 (98)		40 (89)		5 (100)	
Khorana score, n (%)	Low	7 (22.5)	24 (13.9)	0.7606				
	Intermediate	42 (77.5)	146 (84.4)					
	High	0 (0)	3 (1.7)					
ELN Risk 2010 (AML), n (%)	Favorable	9 (20)	32 (19.4)	0.1697				
	Intermediate-1	24 (53.3)	58 (35.2)					
	Intermediate-2	5 (11.1)	28 (16.9)					
	High	6 (13.3)	37 (22.4)					

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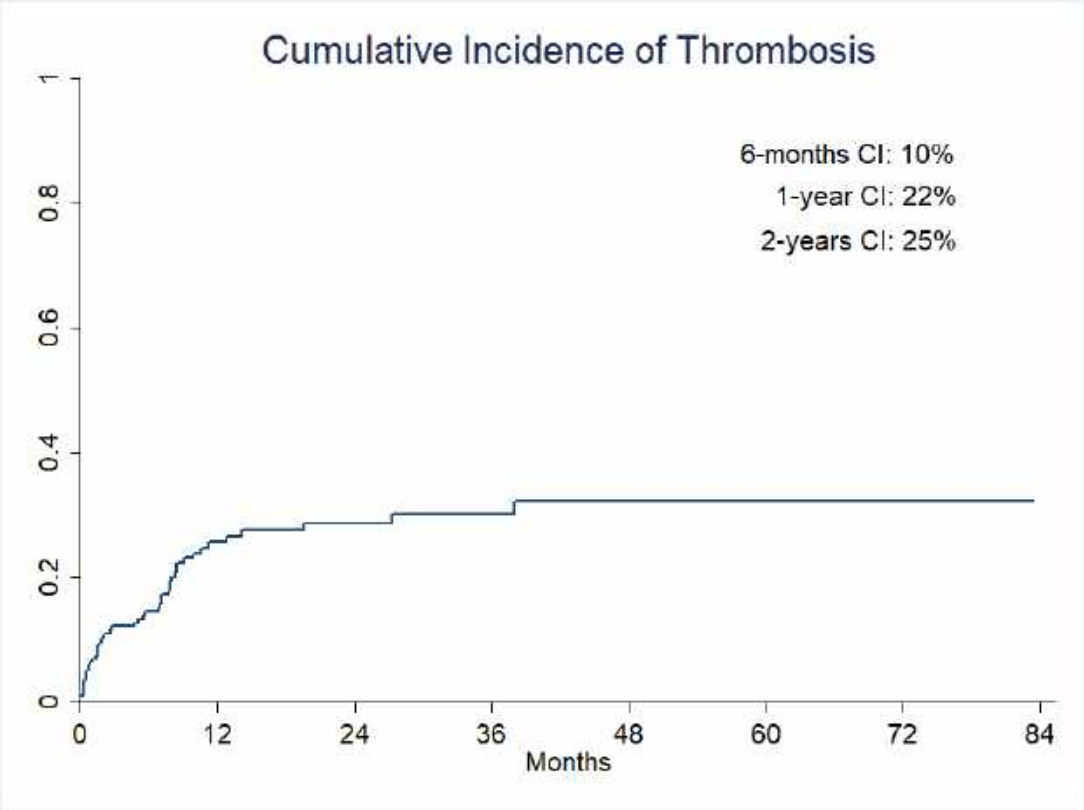
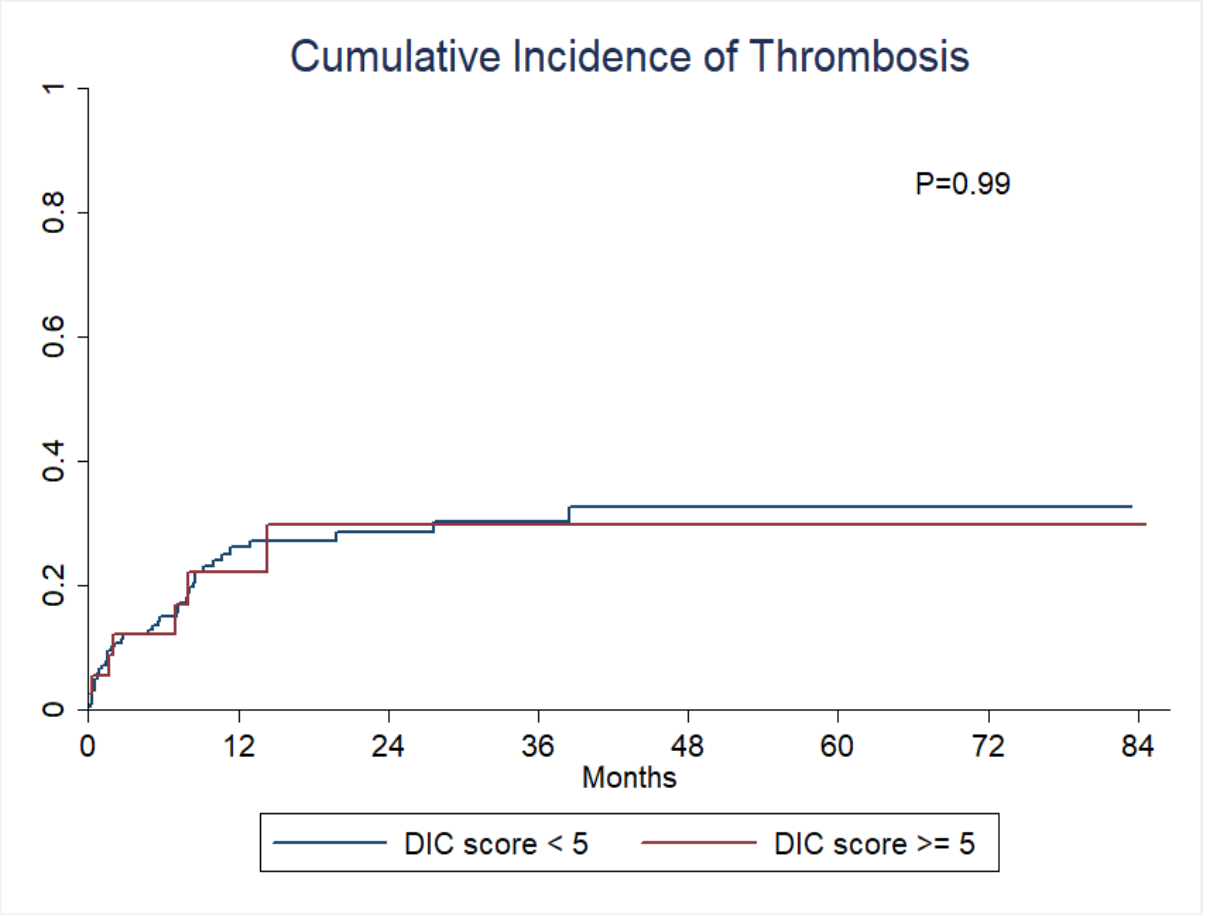
Cumulative Incidence of Thrombosis





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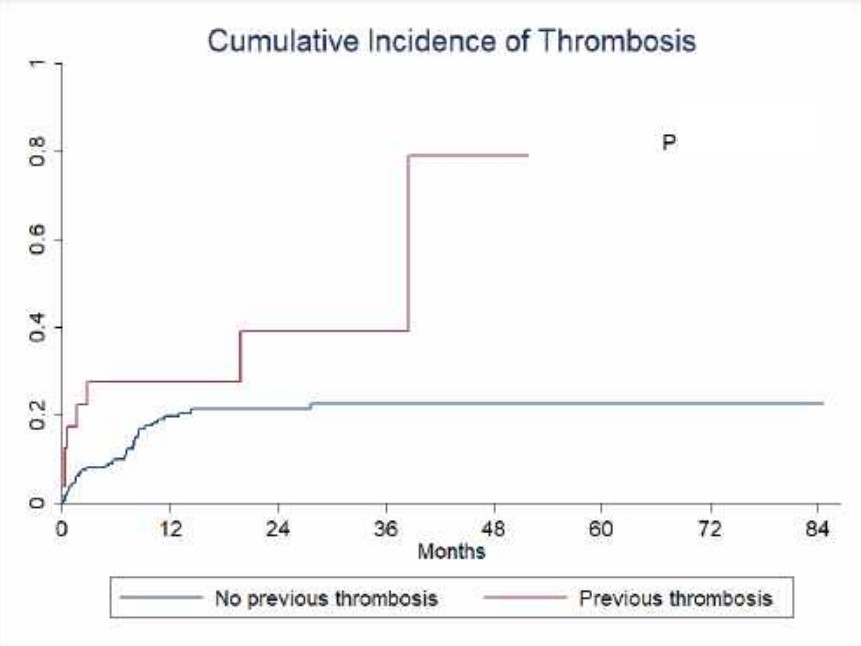
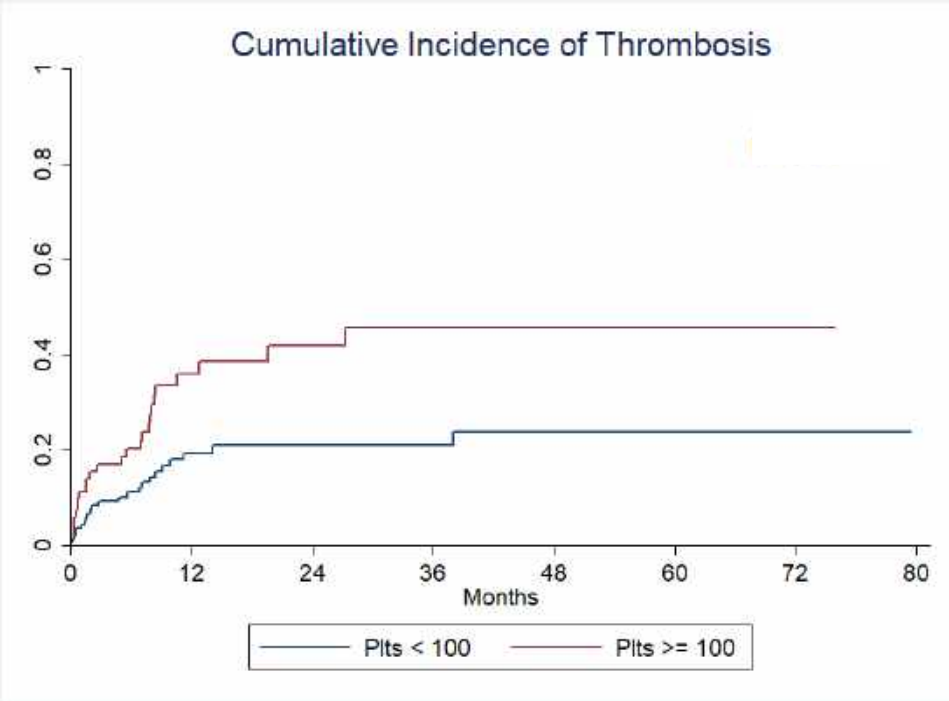
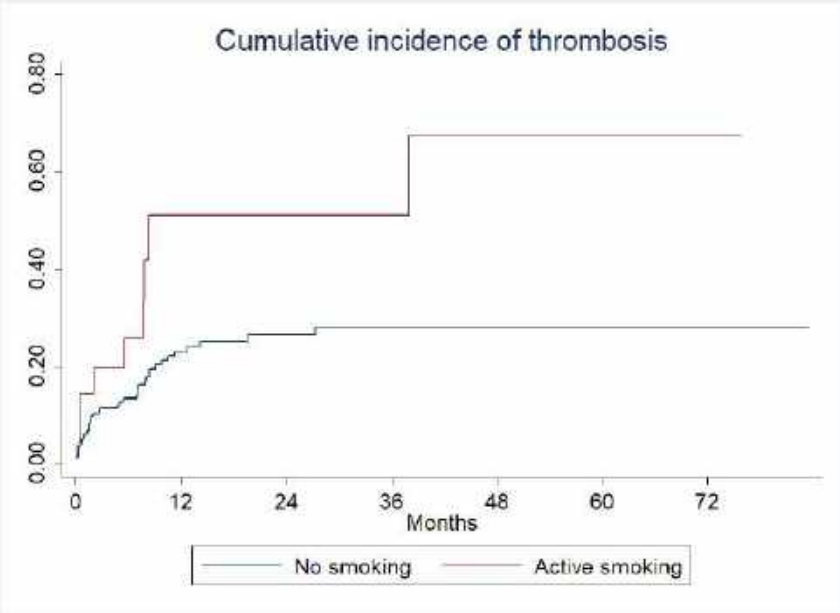
Cumulative Incidence of Thrombosis







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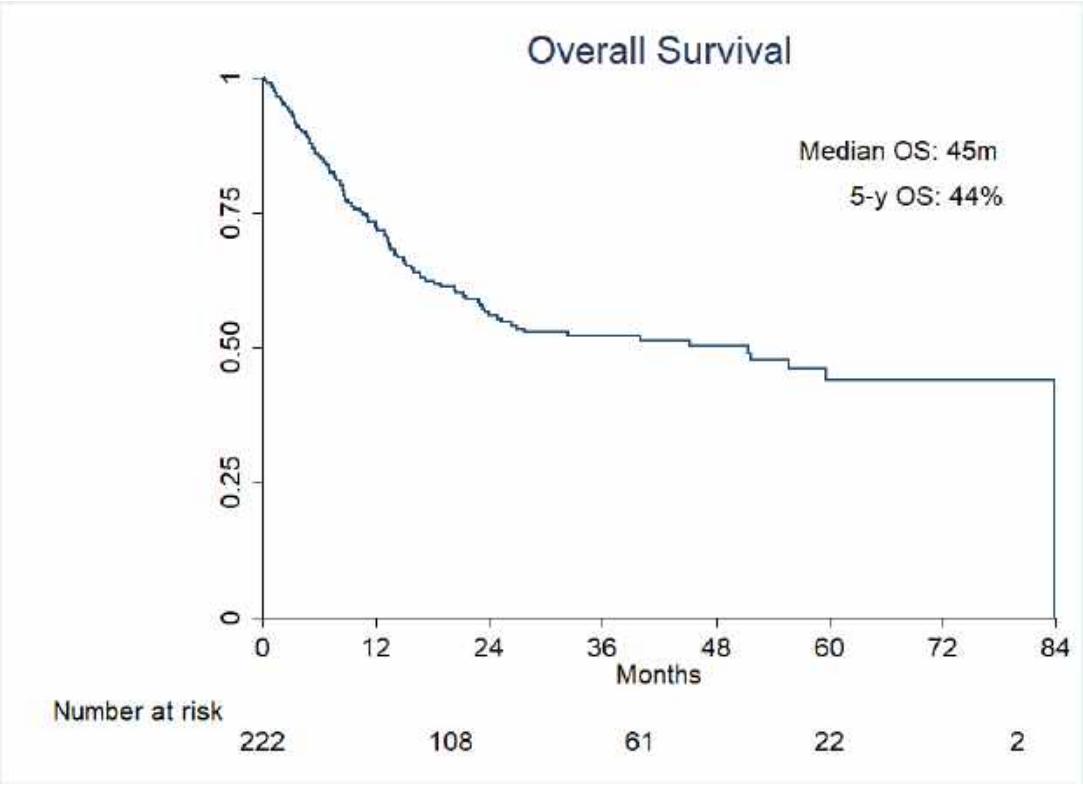
Overall Survival



Multivariate analysis			
Variable	**HR=**	**95% CI**	**P=**
Age	1.05	1.02 – 1.07	**0.0001**
DIC score > 5	2.08	1.2 – 3.61	**0.004**
LDH	1.001	1.001 – 1.001	**0.001**
ELN2010			
Intermediate-1	4.09	1.71 – 9.8	**0.002**
Intermediate-2	6.27	2.49 – 15.8	**0.0001**
Adverse	9.85	4.01 – 24.3	**0.0002**
Secondary AML	1.03	0.82 – 1.31	0.750
WBC>50k	1.02	0.59 – 1.76	0.89

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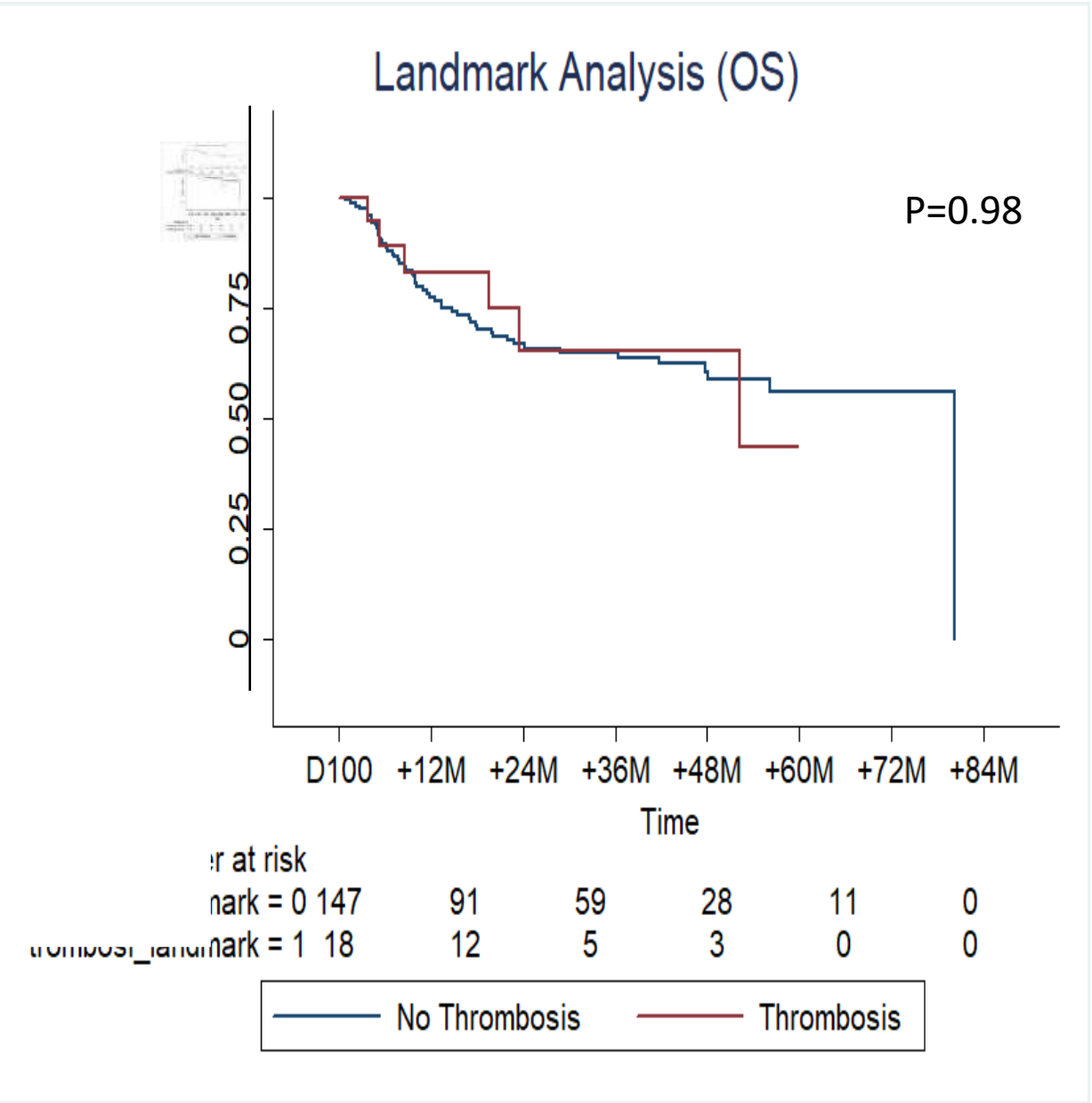
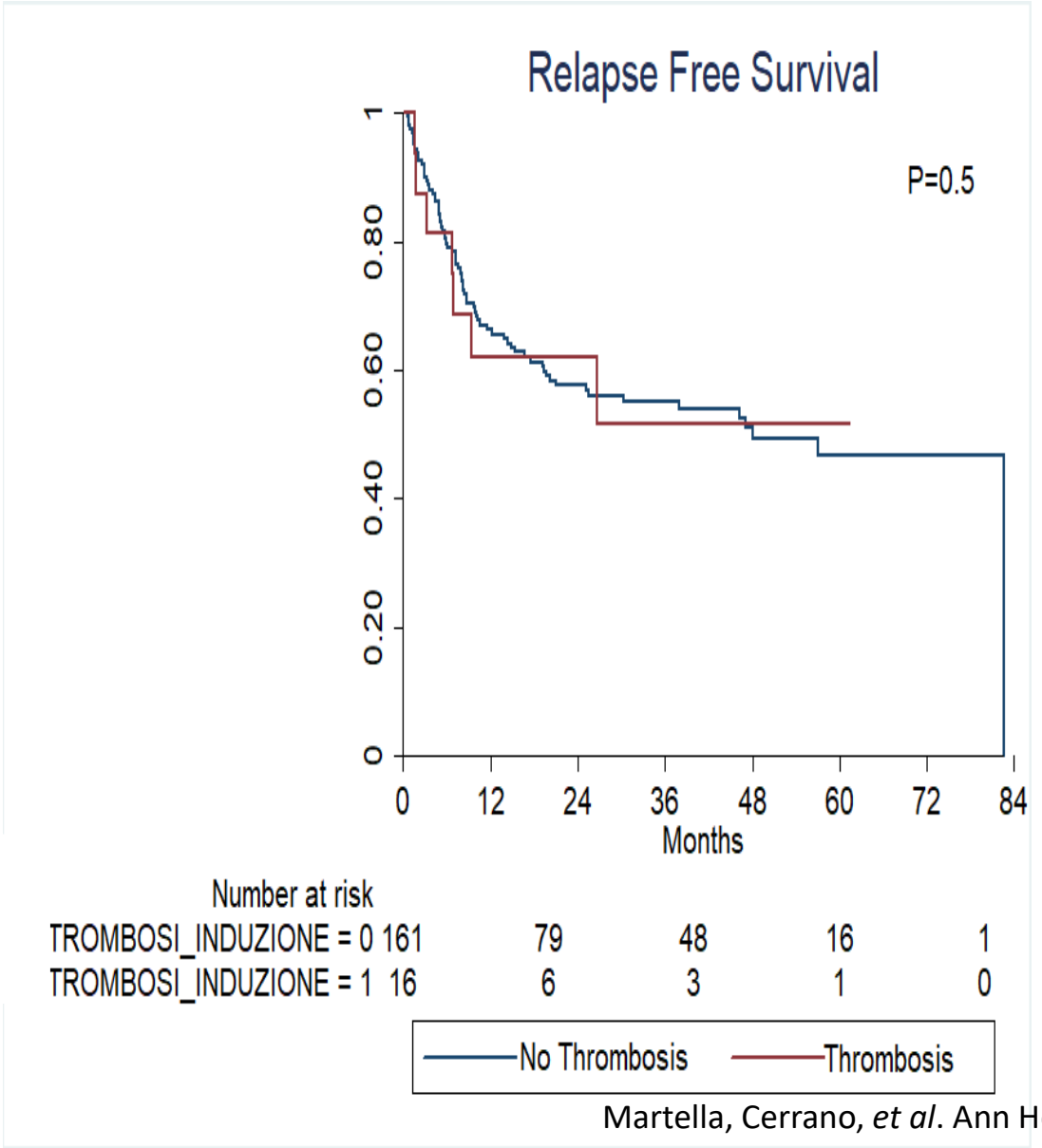
Impact of Thrombosis on Survival: RFS





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Conclusions of the study

- **Thromboses are a frequent complication in AML**, especially during chemotherapy, mostly VTE. The higher frequency (50 episodes in 222 pts) might be due to longer follow-up and type of CVC used

- **Previous thrombosis**, especially VTE, baseline **platelet count above 100*10^9/L** and **active smoking** could **predict thrombotic risk,** while AML genetic profile did not significantly affect thrombosis occurrence.

- We confirmed that **Khorana score is not a robust tool in this setting**, and **we could not validate the association of DIC** score with thromboses

- **No impact of thrombosis on survival** was observed, both on RFS and on OS in a landmark analysis. Interestingly, high **DIC score was independently associated with worse OS** in our cohort

- **Further studies** are need to develop a **reliable score** to predict thrombosis occurrence in AML, possibly including a detailed **genetic disease characterization**

- Trials prospectively **testing therapeutic measures** to prevent thrombosis in AML, e.g. in high-risk subgroups, are warranted

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