Internal and external validation of ThroLy score

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Thromboembolic complications in patients with hematological malignancies

Hematological malignancy	Incidence of thrombosis, %
Acute leukemia	2.1–21.1
– Acute promyelocytic leukemia	5.1–16
Myeloproliferative neoplasms	12–39
Lymphoproliferative neoplasms	1.5–14.6
Plasma cell disorders	
– MGUS	6.1–7.5
– Multiple myeloma	4–58[a]

Clin Chem Lab Med 2015;53(8): 1139-1147

Epidemiology

The rate of thrombotic complications in lymphoma patients ranges **from 1.5% up to 59.5%**

Lymphoma patients have a 10-fold higher risk for the development of venous thrombosis than patients with lung and gastrointestinal cancers

- meta-analysis on 18,018 lymphoma patients from 29 independent cohorts showed that the rate of VTE was 6.4%, being significantly higher in non-Hodgkin lymphoma (NHL) compared to Hodgkin lymphoma (HL) patients (6.5% vs. 4.7%)

The impact of venous thrombosis 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.

Epidemiology

- VTE risk is higher in high-grade NHL, especially in primary central nervous system lymphoma and in mediastinal B-cell lymphoma

- symptomatic VTE occur predominantly within the first 3 months, i.e. at presentation and during initial therapy

- Thrombotic episodes in patients with HL occur usually between chemotherapy cycles in the absence of clinically detectable tumor while in DLBCL lymphoma they occur primarily during the early phase

- the patients with relapsed disease experience VTE more frequently

Thromboembolic risk factors in lymphoma patients

Patient-related	Age
	Race
	Gender
	Pregnancy
	Comorbidities
	Performance status
	Thrombophilia
Lymphoma-related	Histology
	Localization
	Clinical stage
Treatment-related	Chemotherapy
	Surgery
	Suportive care agents
	Indwelling catheters
	Hospitalization

Antic et al. Blood Rev. 2018;32(2):144-158.

Thromboembolic risk factors in lymphoma patients

Patient-related	Age
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Lymphoma-[illegible]	[illegible]ilia
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	Localization
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	Chemotherapy
	Surgery
	Suportive care agents
	Indwelling catheters
	Hospitalization

Most patients have at least one risk factor for VTE

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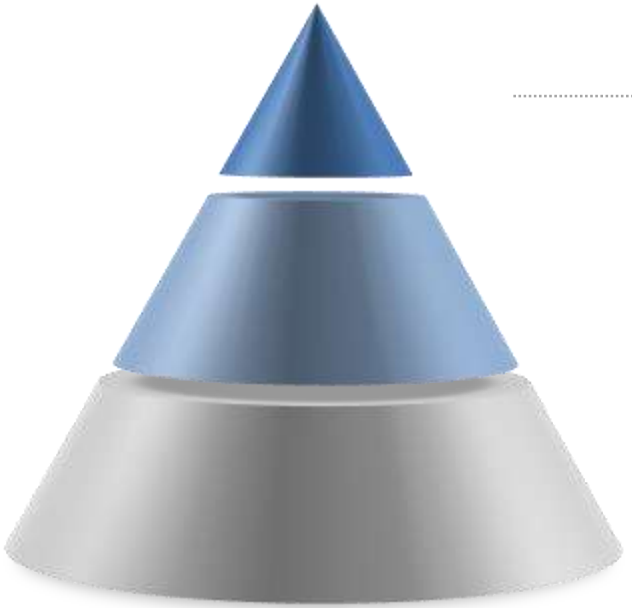
Current thromboprophylaxis guidelines for cancer patients

Thromboprophilaxis



Outpatient VTE Prophylaxis.

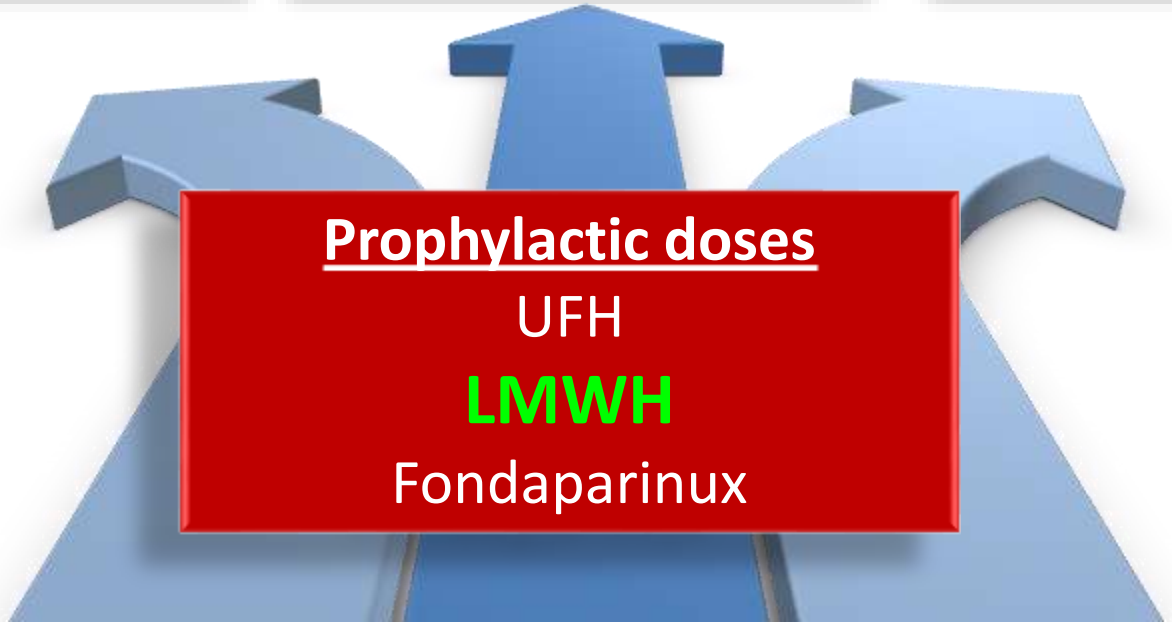
Inpatients : no surgery

Inpatients : surgery

Inpatient VTE prophylaxis: no surgery

*Note: These recommendations are all in the absence of contraindications to anticoagulation.

ITAC-CME	ACCP	ESMO
▪ High risk patients	Padua prediction score	▪ patients confined to bed with acute medical complication



Ambulatory VTE prophylaxis: not recommended routinely

*Note: These recommendations are all in the absence of contraindications to anticoagulation.

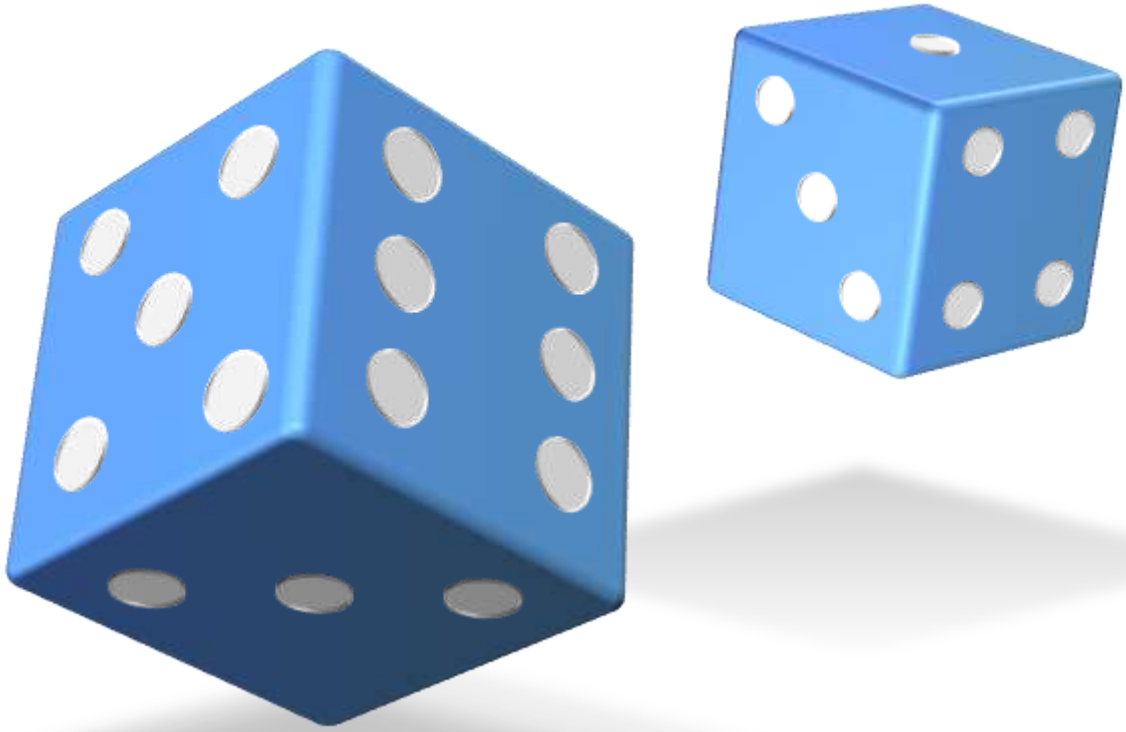
ITAC-CME	ASCO	ESMO
▪ pts with locally advanced or metastatic pancreatic cancer in low bleeding risk receiving CHT	▪ consider LMWH only in highly selected pts receiving CHT for solid tumors	▪ receiving paliative CHT for locally advanced and metastatic disease high-risk pts according to the Khorana risk score

Can we predict TE risk in our lymphoma patients?

Can we identify which patients may benefit most from prophylaxis?

Can we predict events?

- Padua score?
- Khorana score?
- Or something different?



PADUA prediction score

Table 1 Risk assessment model (high risk of VTE: ≥4)

Baseline features	Score
Active cancer*	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility†	3
Already known thrombophilic condition‡	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30)	1
Ongoing hormonal treatment	1

Barber S et al. J Thrombosis and Haemostasis, 2010

What is the risk of thrombosis during CHT ?

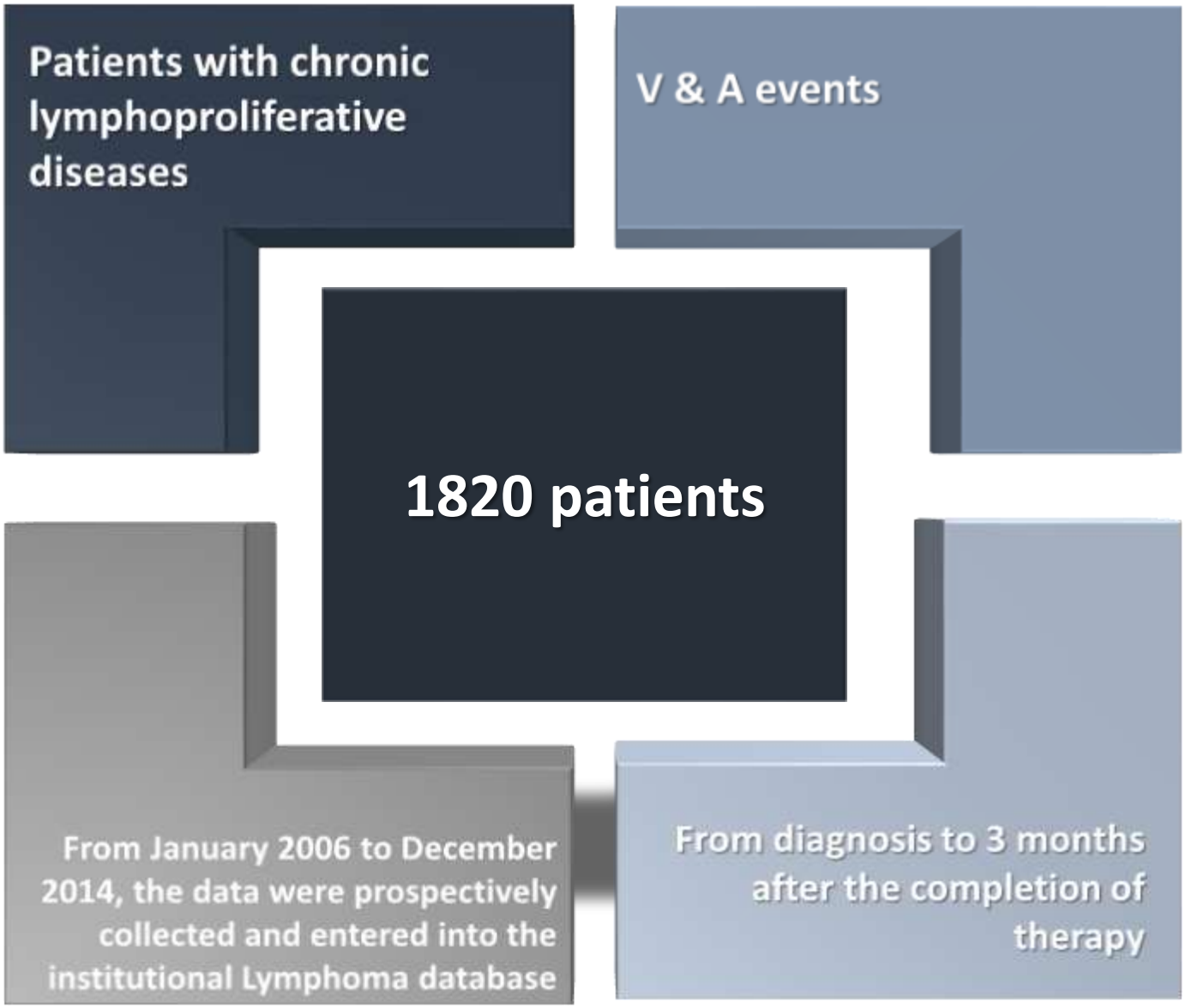
ASCO: Khorana score

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350 × 10^9/L or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11 × 10^9/L	1
BMI 35 kg/m^2 or more	1

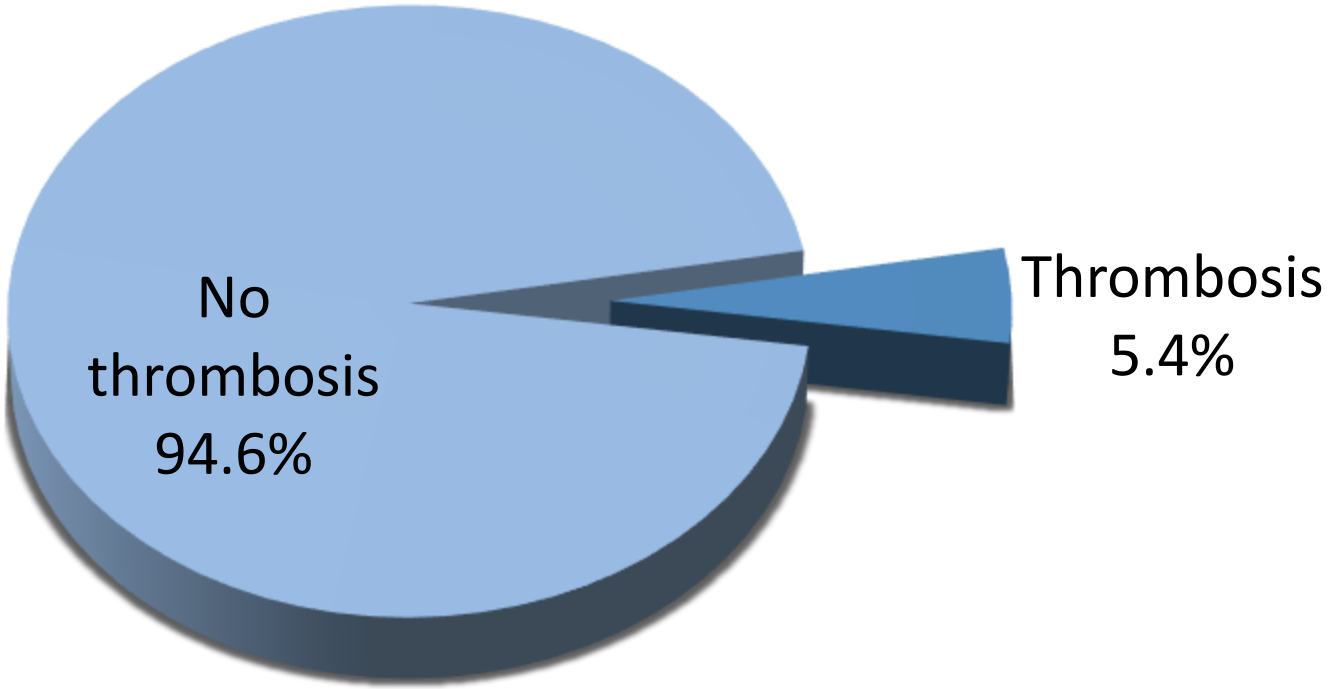
Khorana et al. Blood, 2008

DECODING THE RISK OF THROMBOEMBOLIC EVENTS IN LYMPHOMA PATIENTS

Methodology



Patients with no thrombosis = 99



*The total number of thromboses was 107

Methodology

- the derivation cohort: 1236 patients (67.9%)
- the validation cohort: 584 patients (32.1%)

TE events:

- the derivation cohort: 65 patients (5.3%)
- the validation cohort: 34 patients (5.8%)

Significant Padua variables

Variable	Univariate	Multivariate
Previous VTE	<0.001	<0.001
Reduced mobility	<0.001	<0.001
Recent trauma/surgery	<0.001	0.002
Heart/respiratory failure	0.016	/
Previous AMI/stroke	<0.001	<0.001
Infection/rheumatoid disorder	0.020	/
Obesity (BMI≥30kg/m^2)	<0.001	<0.001

Significant Khorana variables

Variable	Univariate	Multivariate
Tr ≥ 350	0.001	/
Hb < 100	<0.001	<0.001
Le > 11	<0.001	<0.001

Significant additional lymphoma variables

Variable	Univariate	Multivariate
Extranodal	<0.001	<0.001
Bulky	0.049	/
B symptoms	0.009	/
Mediastinum	<0.001	<0.001
Neutropenia	<0.001	<0.001

Significant variables in multivariate logistic regression model

Variable	p	OR
Previous VTE	<0.001	>10
Reduced mobility	<0.001	5.7
Previous AMI/stroke	<0.001	>10
Obesity (BMI>25kg/m^2)	<0.001	>10
Extranodal	<0.001	2.7
Mediastinum	<0.001	>10
Neutropenia	<0.001	3.4
Hb<100	<0.001	3.9

Thro(MBOSIS) Ly(MPHOMA) score

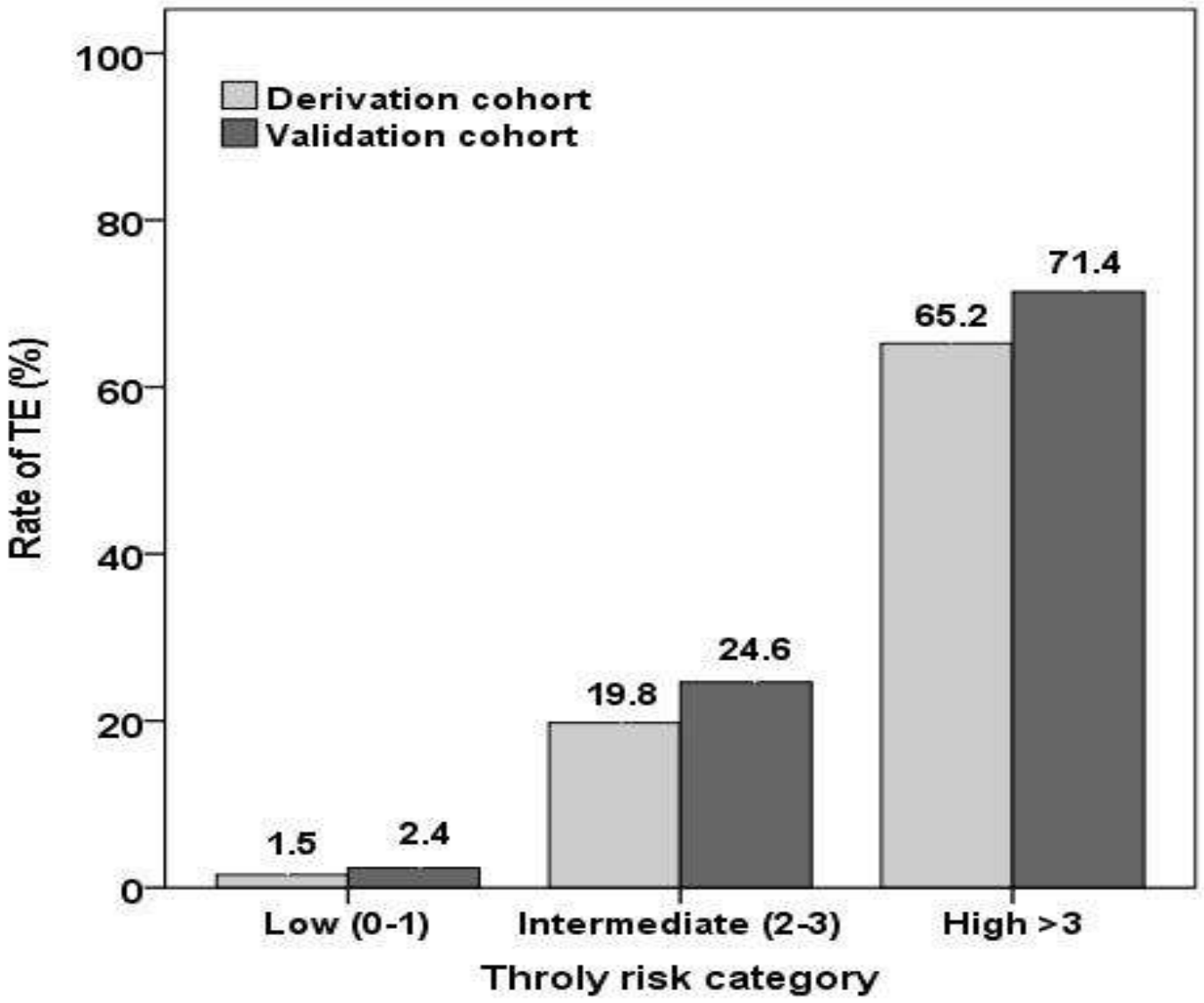
Variable	points
Previous VTE	2
Reduced mobility	1
Previous AMI/stroke	2
Obesity (BMI>25)	2
Extranodal	1
Mediastinum	2
Neutropenia	1
Hb<100	1

Low risk – 0,1

Intermediate risk – 2,3

High risk – ≥ 4

VTE rates based on the ThroLy risk categories



Model performance original group

	ThroLy (%)				K≥ 3 (%)		P≥ 4(%)	
	Deriv. cohort		Valid. cohort		Deriv. cohort	Valid. cohort	Deriv. cohort	Valid. cohort
	≥ 2	≥ 3	≥ 2	≥ 3				
sensitivity	75	52	65	38	16	10	42	40
specificity	88	95	90	97	96	96	87	87
PPV	25	38	29	42	15	11	13	15
NPV	98	97	98	96	96	95	97	87

External validation cohort prospective analysis

- 9 Institutions
- 8 completed results

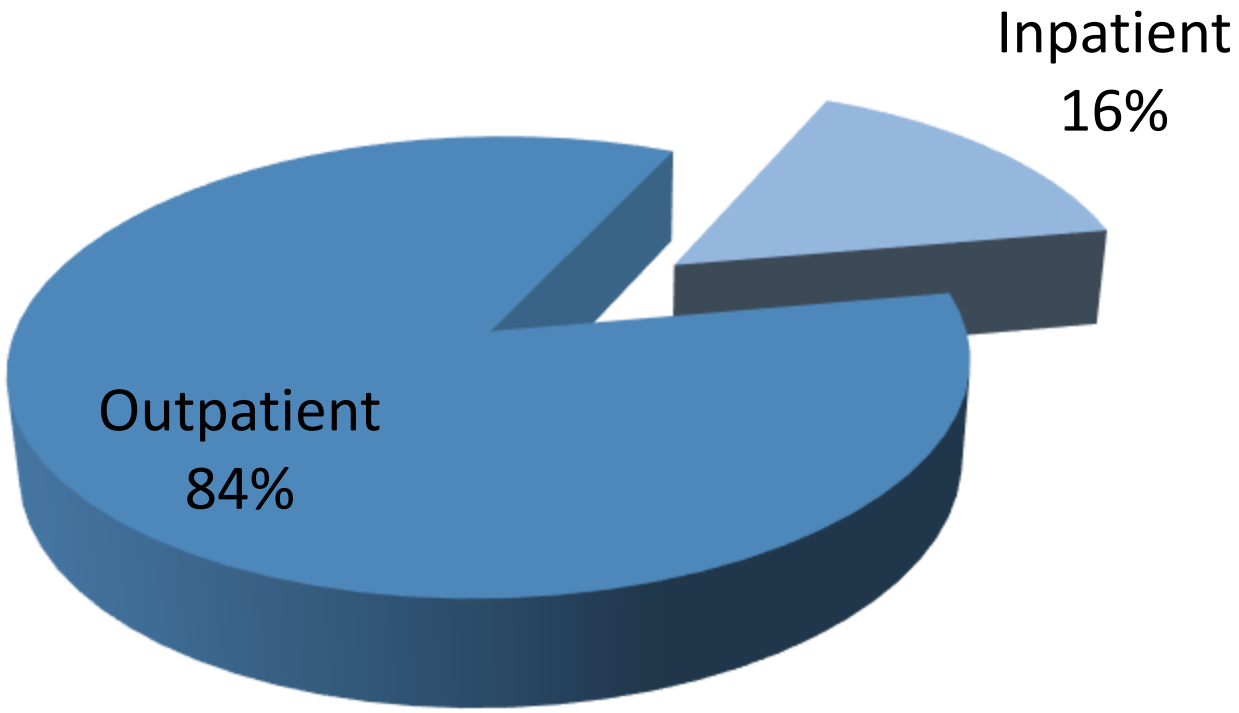
External validation cohort

Country	Number of pts
USA	200
France	153
Swiss	168
Croatia	303
Austria	77
Spain	170
Jordan	332
Macedonia	320
Total	1723

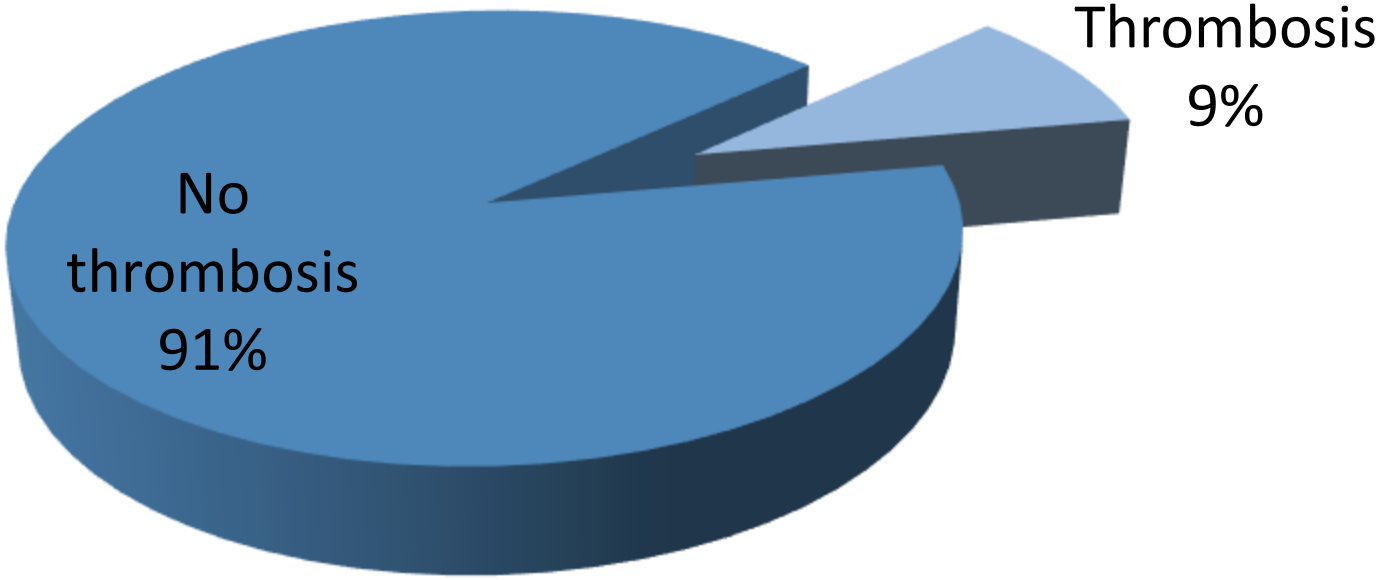
External validation cohort

Type of lymphoma	Number of pts (%)
Indolent NHL	467 (27.1%)
Agressive NHL	647 (37.6%)
CLL/SLL	235 (13.6%)
Hodgkin lymphoma	366 (21.2%)
Other	8 (0.5%)
Total	1723

Inpatient/outpatient population



Patients with thrombosis=158



venous thrombosis n=121 (7%)

External validation group

Risk group Throly score	Thrombosis	
	n	%
Low (0,1)	18 of 440	4.1
Intermediate (2,3)	51 of 586	8.7
High ≥ 4	73 of 440	16.6

Model performance external validation cohort

	ThroLy≥ 4	K≥ 3	P≥ 4
PPV	17%	11%	13%
NPV	93%	92%	95%
SN	51%	42%	70%
SP	72%	64%	52%

Multivariate logistic regression analysis for thrombosis prediction by different scores

Score	Original			External validation		
	p	OR	95%CI for OR	p	OR	95%CI for OR
Padua	/	/	/	0.006	1.823	1.192-2.789
Khorana	/	/	/	/	/	/
ThroLy	<0.001	4.217	3.370-5.276	<0.001	2.671	1.710-4.171

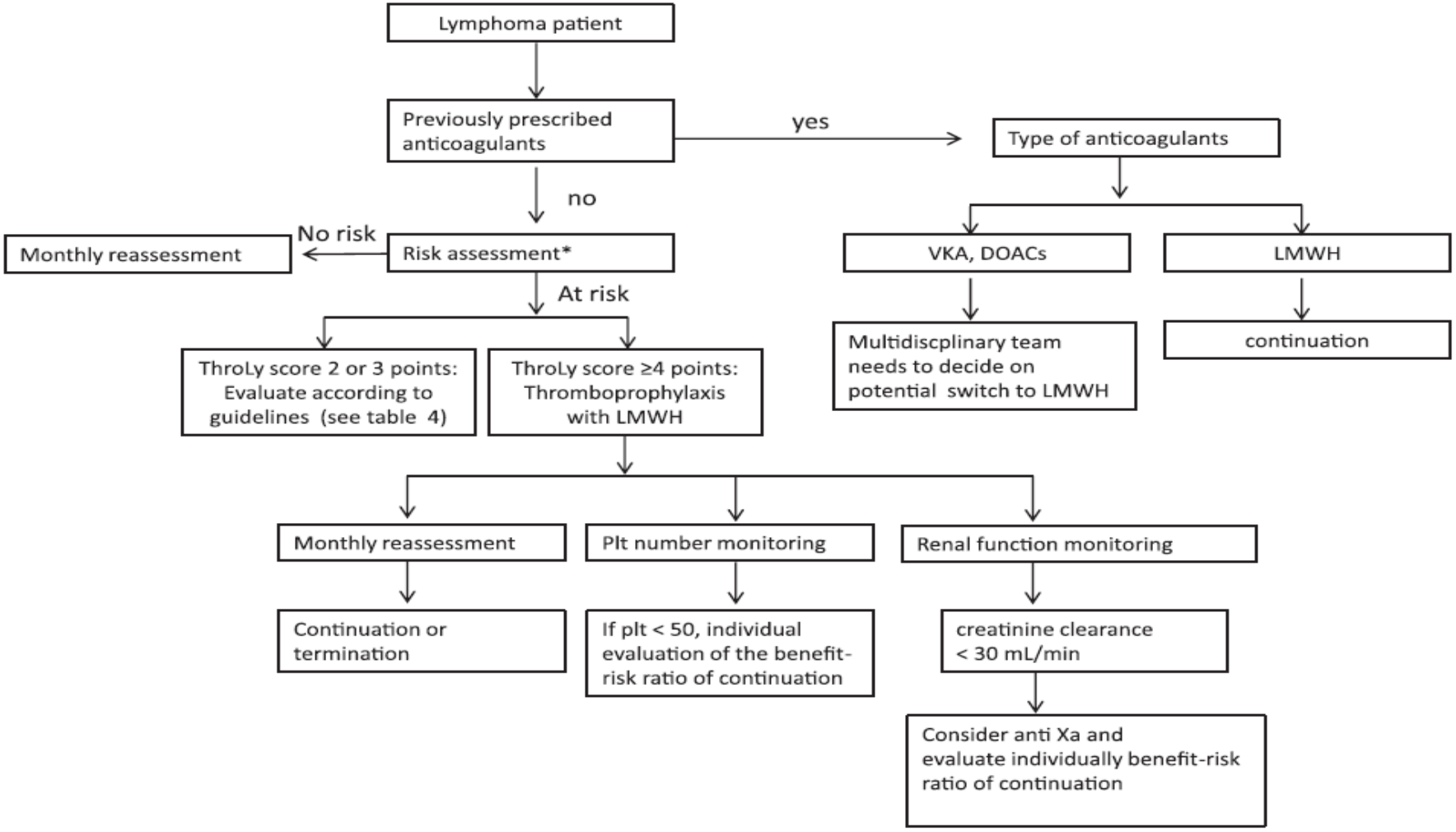
ThroLy will probably be updated...

Instead of a conclusion...
Recommendations for clinical practice

Review

Venous thromboembolic events in lymphoma patients: Actual relationships between epidemiology, mechanisms, clinical profile and treatment

Darko Antic[a,b,*], Jelena Jelicic[a], Vojin Vukovic[a], Srdjan Nikolovski[a], Biljana Mihaljevic[a,b]



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