Challenges of Hemostasis in Cancer Patients

VTE Risk Assessment

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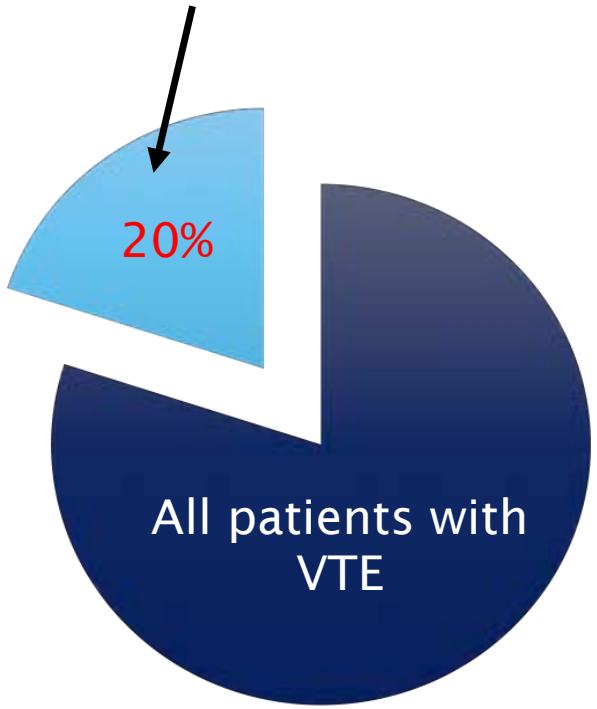
Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Example: company XYZ	x		x		x			

Thrombosis and Cancer

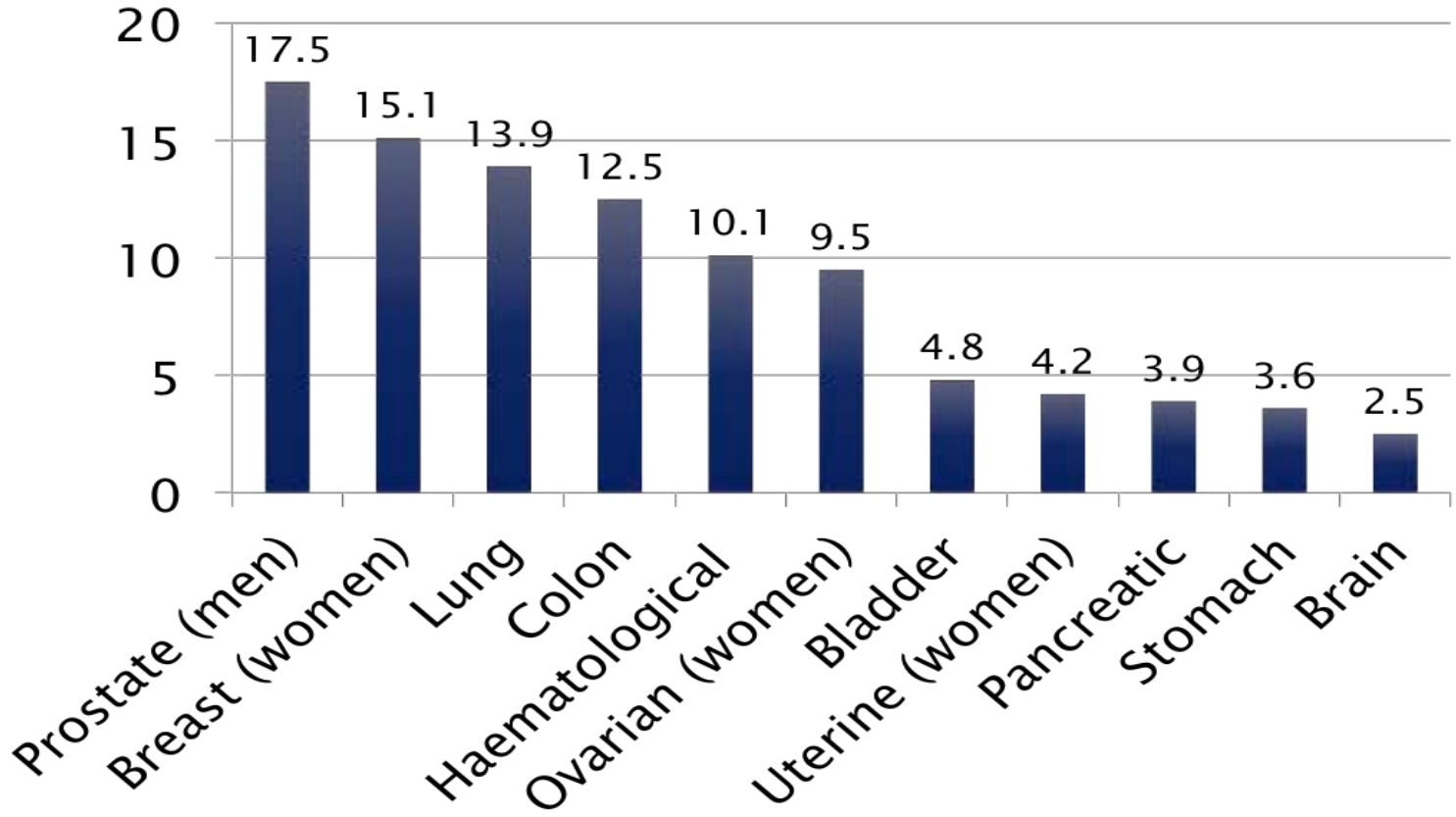
1 of 5 VTE events are related to cancer



Ay C, Pabinger I & Cohen AT. Thromb Haemost. 2017;117(2):219-230.

Prevalence of VTE According to Cancer Types

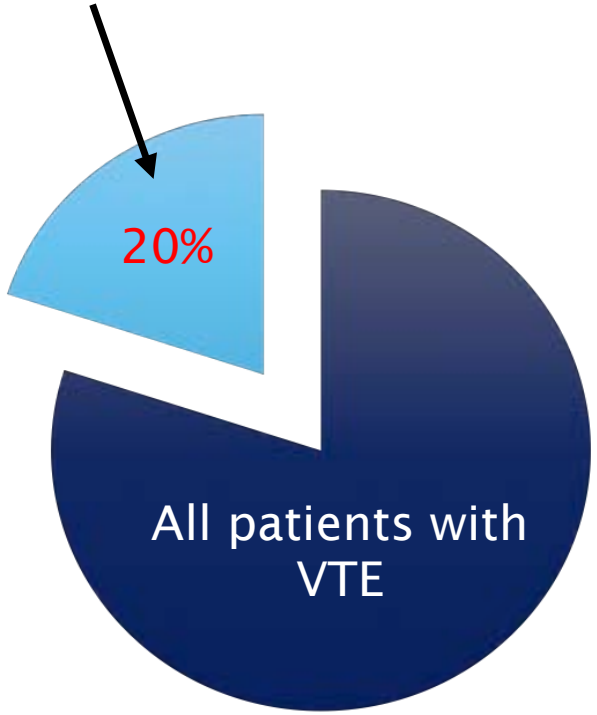
- Patients with active cancer and a first VTE (N=6592)



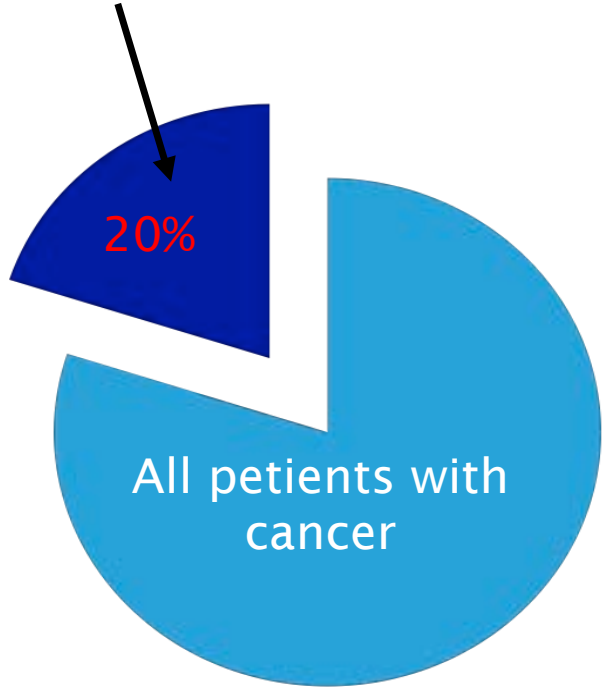
Cohen AT et al. Thromb Haemost. 2017;117(1):57-65

Thrombosis and Cancer - Cancer and Thrombosis

1 of 5 VTE events is related to cancer



1 in 5 patients with cancer will develop VTE*

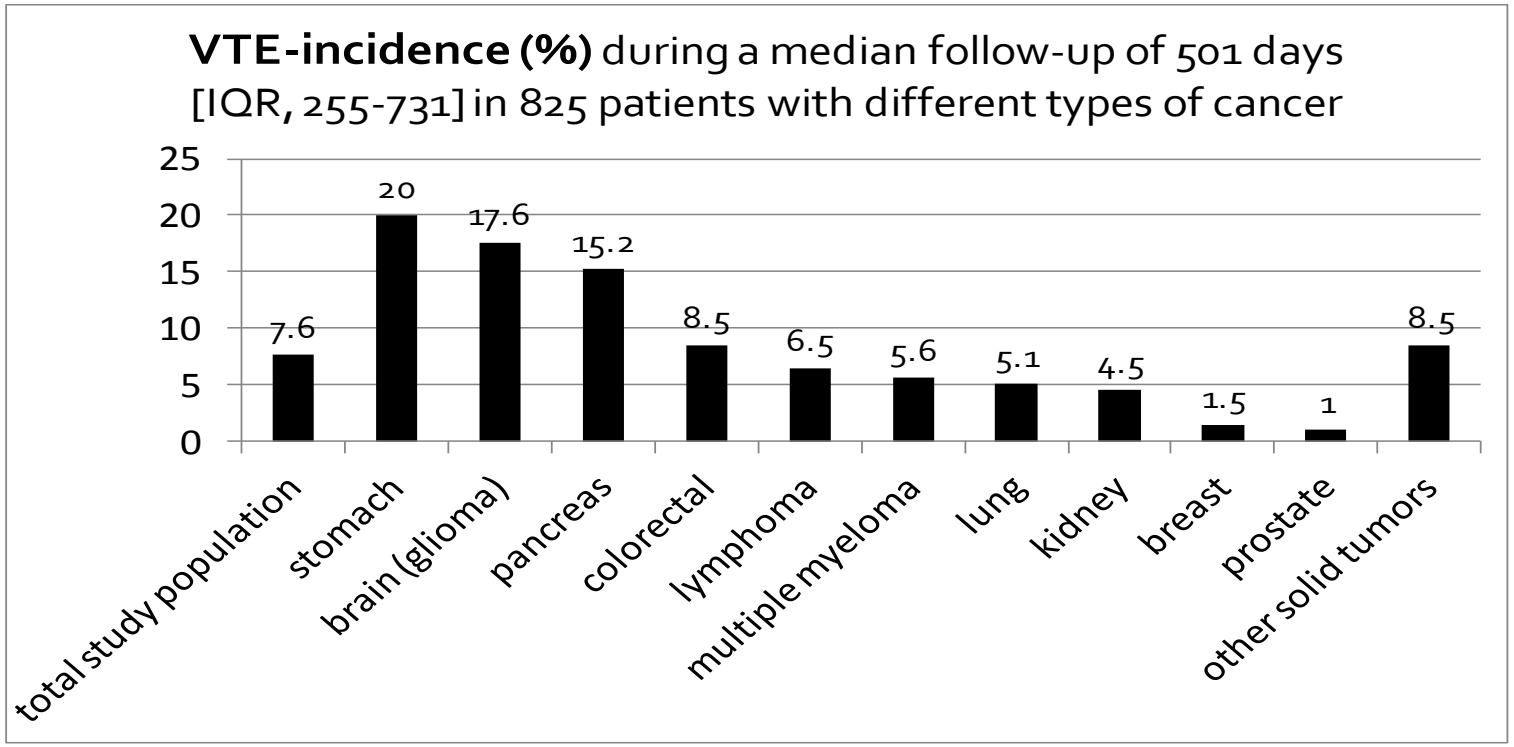


*High rates of „incidental“ (unuspected) pulmonary embolism (PE)

Ay C, Pabinger I & Cohen AT. Thromb Haemost. 2017;117(2):219-230.

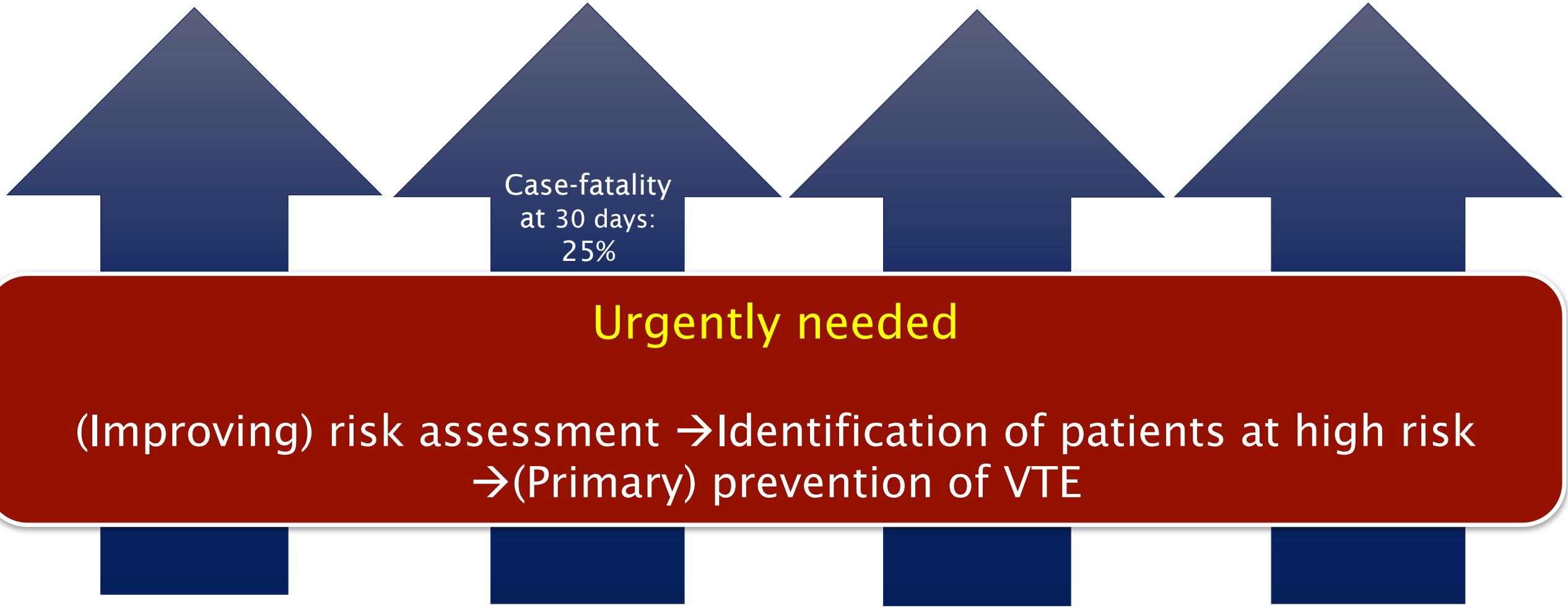
Rates of VTE in Patients With Cancer

- Vienna Cancer and Thrombosis Study (CATS)



Ay C. J Clin Oncol. 2009 Sep 1;27(25):4124-9.

Cancer and Thrombosis - Burden of Disease



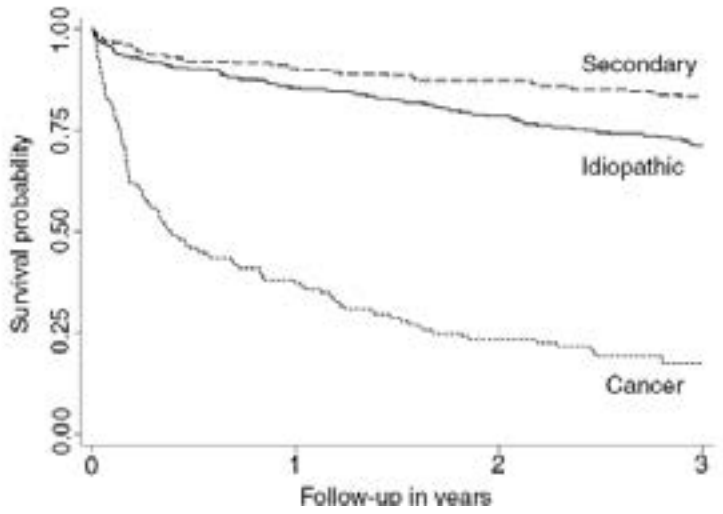
Urgently needed

(Improving) risk assessment →Identification of patients at high risk
→(Primary) prevention of VTE

Prandoni P. Blood 2002; 100: 3484-8; Khorana AA. J Thromb Haemost. 2007;5(3):632-4; Naess IA et al, J Thromb Haemost 2007;5(4):692-9; Chew HK. Arch Intern Med 2006;166(4):458-64

Cancer and Thrombosis - Burden of Disease

- VTE in patients with cancer increases the risk of morbidity and mortality
  - VTE is a leading cause of death in cancer
  - Risk of mortality 3.7-fold [95% CI: 1.3-14.4] higher in cancer patient with VTE (adjusted for tumor stage, age and ethnicity)
  - Case-fatality rate at 30-days: 25%



- High risk of VTE recurrence in patients with cancer (3-fold)
- High risk of bleeding during anticoagulation (2-fold)

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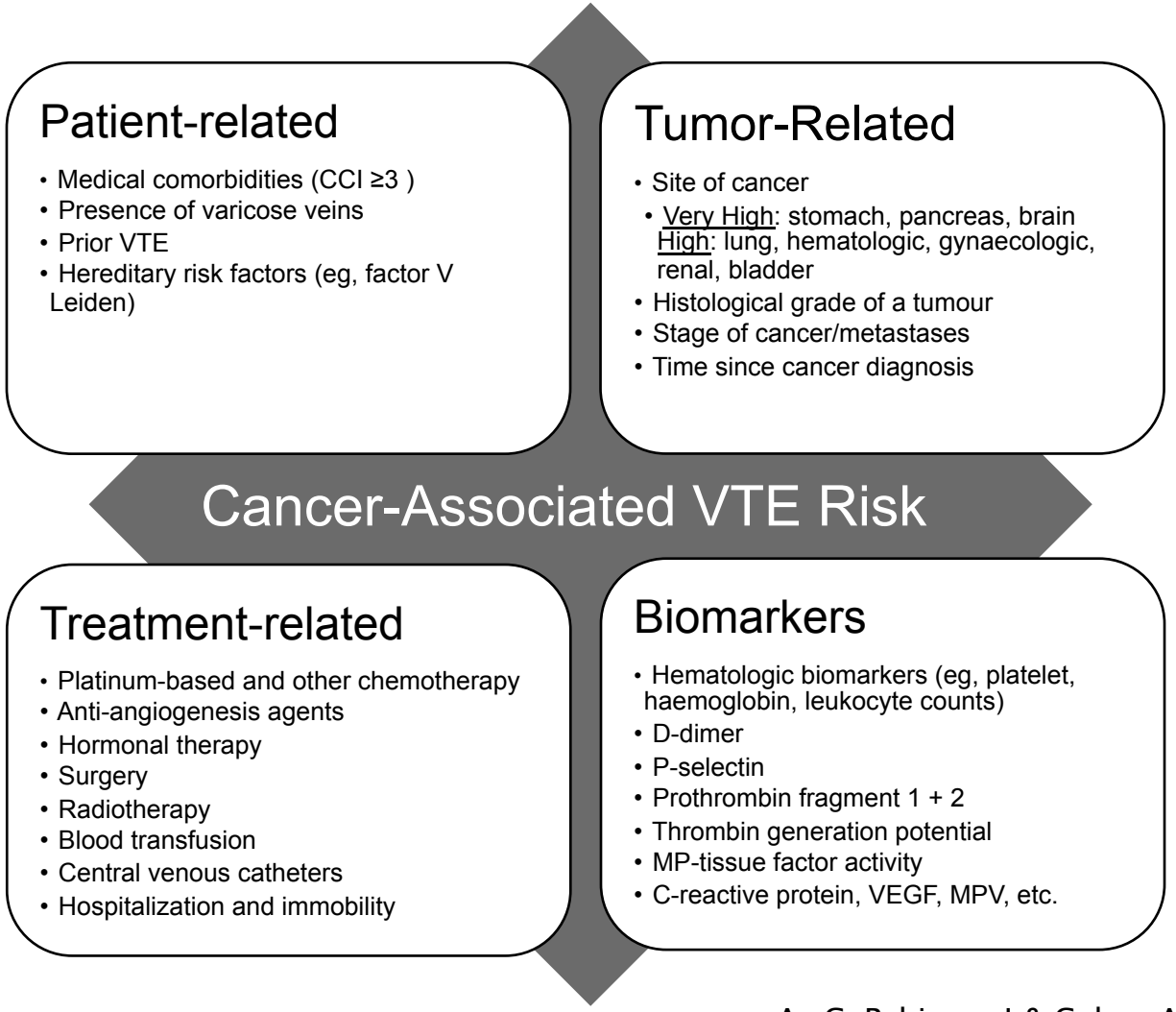
Risk Factors for VTE in Cancer Patients



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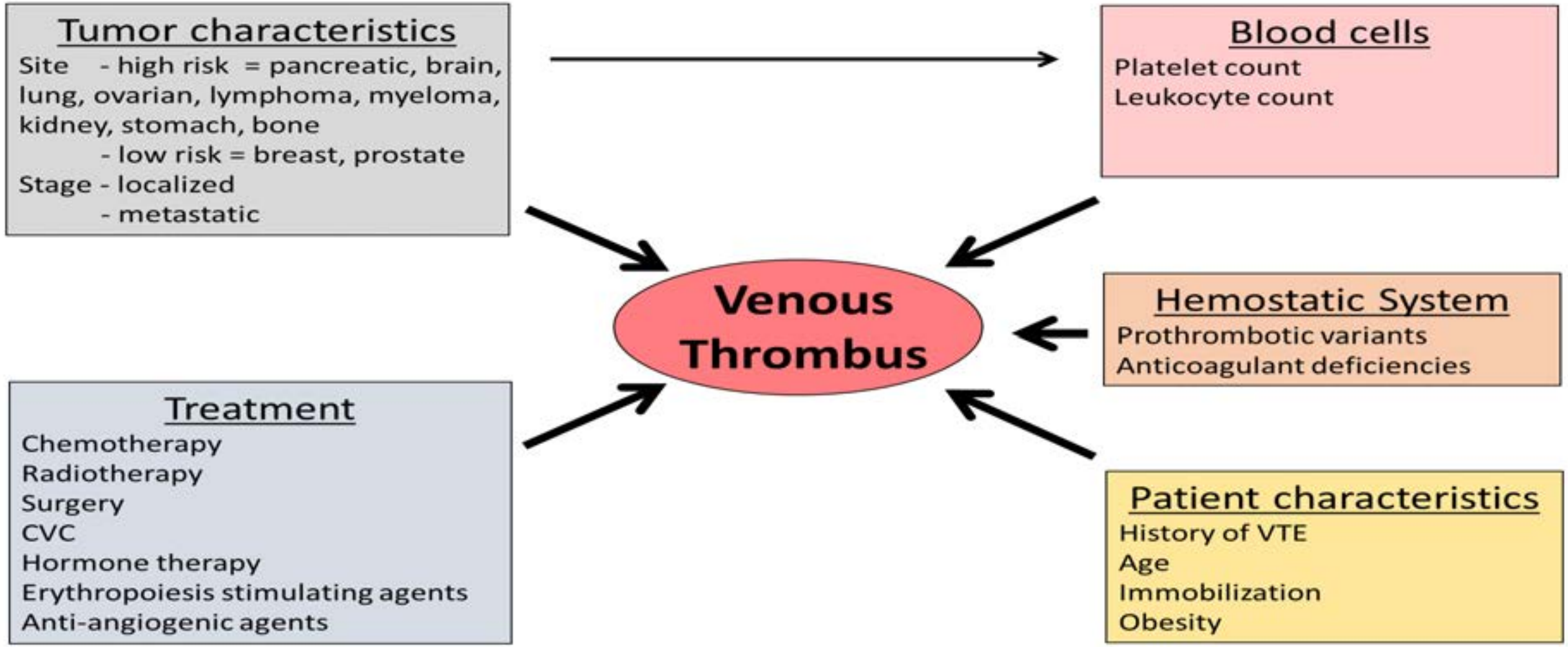
Risk Factors for Cancer-associated VTE

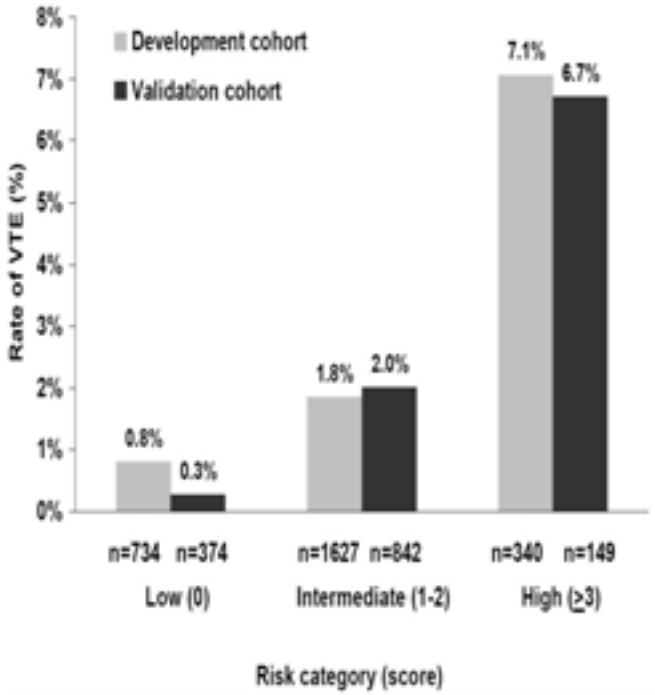


Hisada Y, Geddings J, Ay C and Mackman N. J Thromb Haemost 2015

Risk Assessment of VTE in Patients With Cancer

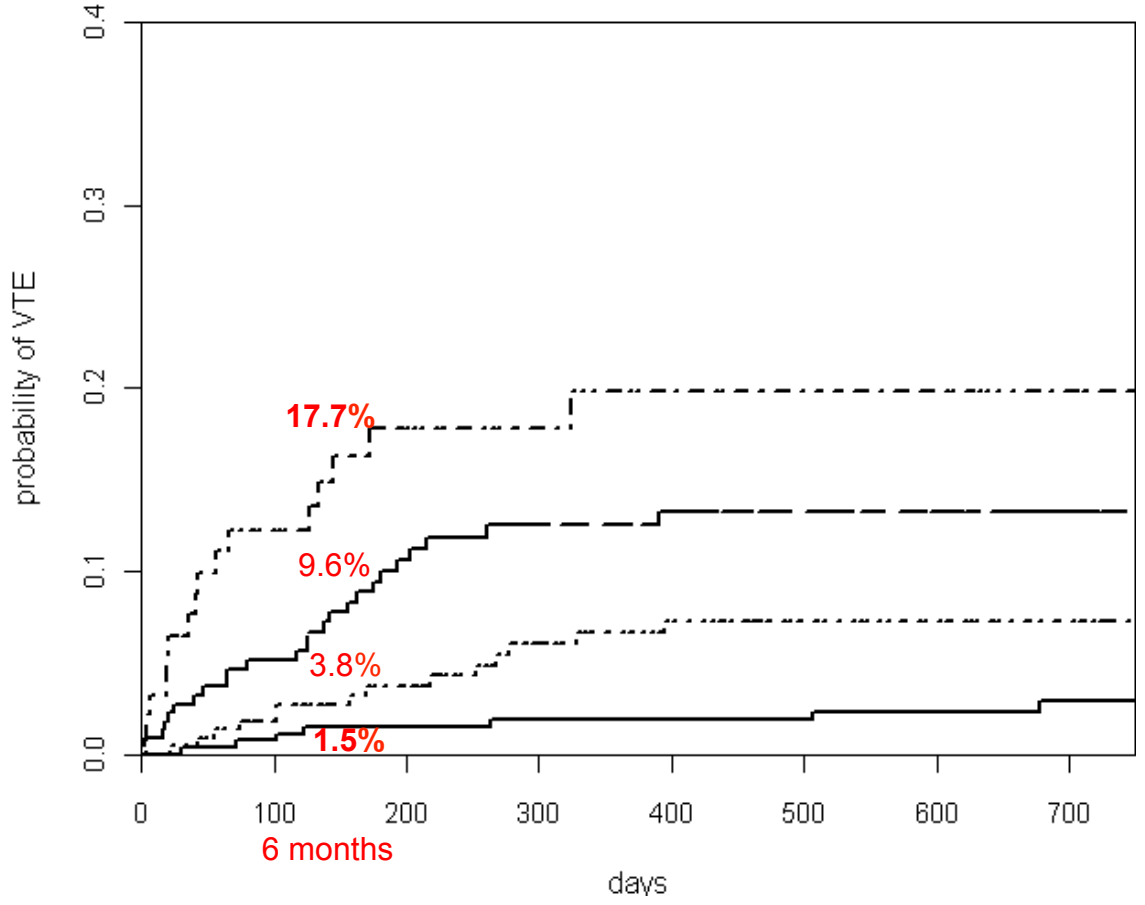
- Prediction of cancer-associated VTE during chemotherapy with the „Khorana-Score“ (follow-up 2.4 months)

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

Vienna Cancer and Thrombosis Study (CATS)



Total number of patients included in this analysis: 819

Score ≥3 (n=93)

Score 2 (n=221)

Score 1 (n=229)

Score 0 (n=276)

Ay et al, Blood 2010

External Validation of the Khorana Risk Score

Table 5. Multivariate Analysis of Baseline and Treatment Variables

Variable	Odds Ratio	95% CI	Adjusted *P*
Sex			.15
Male	1		
Female	1.31	0.91 to 1.88	
Age (per 10-year increase)	1.19	1.02 to 1.39	.03
Race/ethnicity			.51
White	1		
Asian	0.87	0.41 to 1.85	
African American	1.43	0.74 to 2.76	
KPS (per 10-unit increase)	0.92	0.86 to 0.98	.02
Central venous catheter/pacemaker	1.61	1.10 to 2.36	.01
Stage			.57
Early	1		
Locally advanced	0.84	0.41 to 1.72	
Metastatic	1.03	0.50 to 2.13	
Khorana risk group			.04
Low	1		
Intermediate	1.33	0.81 to 2.16	
High	2.06	1.16 to 3.65	

Abbreviation: KPS, Karnofsky performance status.

Table 4. Venous thromboembolism according to age, time from first tumor diagnosis, Khorana score and the use of antiangiogenic agents: multivariate analysis

Covariates	Chi-square	*P*-value	HR (95% CI)
Age	2.3749	0.1233	1.019 (0.995–1.044)
Time from first tumor diagnosis (years)	2.1908	0.1388	0.921 (0.825–1.027)
Khorana score			
High (≥3)	15.9257	<0.0001	7.876 (2.858–21.704)
Intermediate (1–2)	6.6582	0.0099	2.747 (1.275–5.919)
Low (0)	—	—	1*
Antiangiogenic with cytotoxic			
Yes	1.6730	0.1959	1.617 (0.781–3.352)
No	—	—	1*

*Reference class.

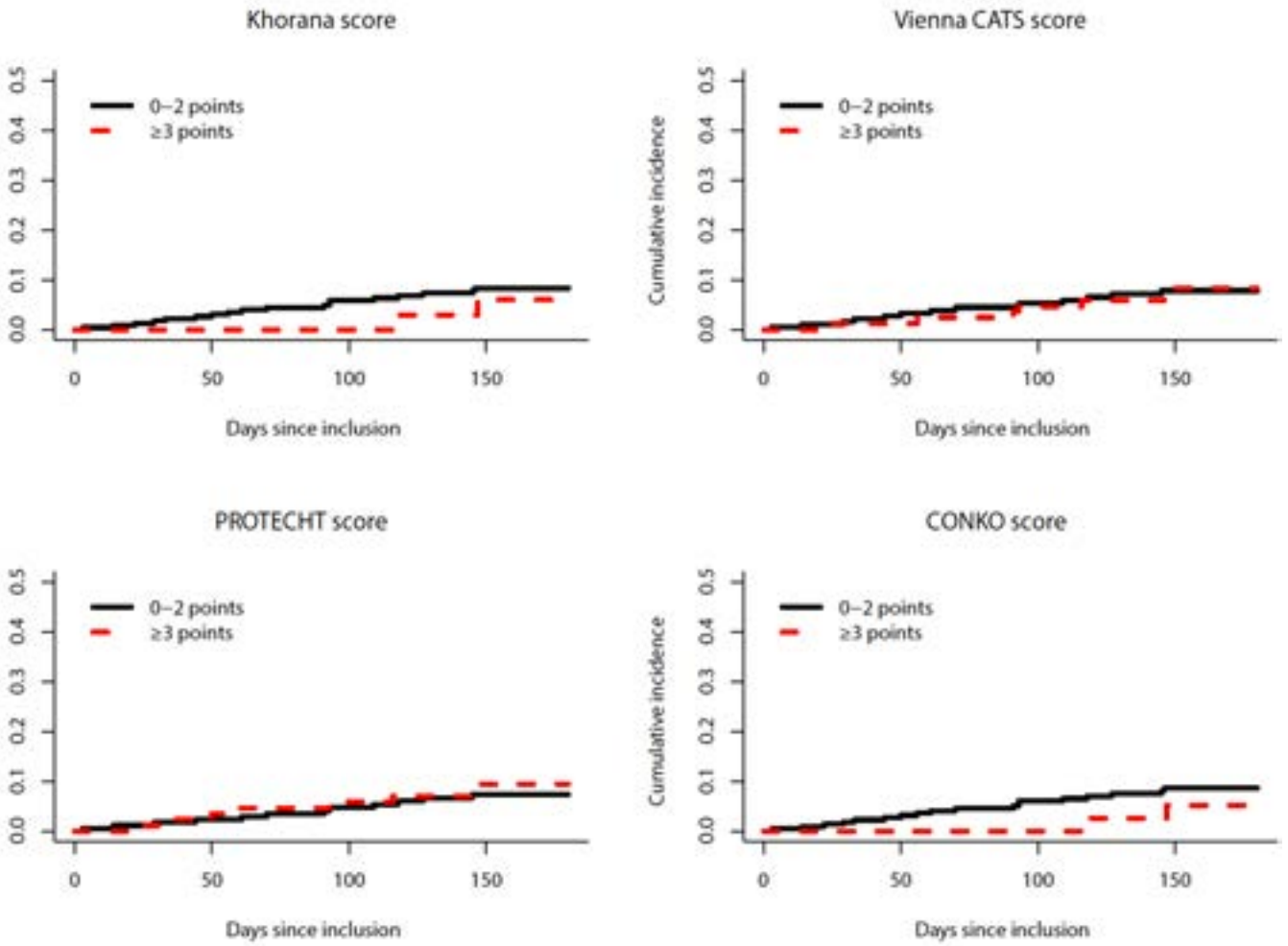
Moore et al, *J Clin Oncol* 2011, Mandala et al, *Ann Onc* 2012

„Expanded“ Risk Prediction Scores for VTE in Cancer Patients

Item	Khorana score (points)	Vienna CATS score (points)	PROTECHT score (points)	CONKO score (points)
Pancreatic or gastric cancer (very high-risk tumors)	+2	+2	+2	+2
Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)	+1	+1	+1	+1
Pre-chemotherapy hemoglobin <10 g/dL or use of erythropoietin stimulating agents	+1	+1	+1	+1
Pre-chemotherapy white blood cell count >11 x 10^9/L	+1	+1	+1	+1
Pre-chemotherapy platelet count ≥350 x 10^9/L	+1	+1	+1	+1
Body Mass Index >35 kg/m²	+1	+1	+1	–
D-dimer >1.44 µg/L	–	+1	–	–
Soluble P-selectin >53.1 ng/L	–	+1	–	–
Gemcitabine chemotherapy	–	–	+1	–
Platinum-based chemotherapy	–	–	+1	–
WHO performance status ≥2	–	–	–	+1

van Es et al. Haematologica 2017;102(9):1494-1501.

Cumulative Incidence of Venous Thromboembolism in Low and High Risk Patients



van Es et al. Haematologica 2017;102(9):1494-1501.

HOT OFF THE PRESS!

A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts

Ingrid Pabinger, Nick van Es, Georg Heinze, Florian Posch, Julia Riedl, Eva-Maria Reitter, Marcello Di Nisio, Gabriela Cesarman-Maus, Noémie Kraaijpoel, Christoph Carl Zielinski, Harry Roger Büller, Cihan Ay

Pabinger I et al. Lancet Haematol. 2018 Jun 7 [Epub ahead of print]

Development of the model (in CATS)

Penalized regression approach (LASSO, R library glmnet)* with cause-specific VTE hazards over 12 months (in order to increase model stability) for selection of prognostic variables for the clinical prediction model from a large pool of clinical and laboratory candidate variables

*Simon et al, J Stat Software 2011, 39:1-13

Clinical Prediction Rule

- **Tumour site category**

  "Low/intermediate"

  Breast, prostate

  "high"

  Lung, colorectal, lymphoma, genitourinary excluding prostate, gynecologic excluding breast, esophageal, others

  "Very high"

  Stomach, pancreas

Multivariable SHR 1.96
(95% CI 1.41-2.72)

- **D-Dimer (μg/mL)**

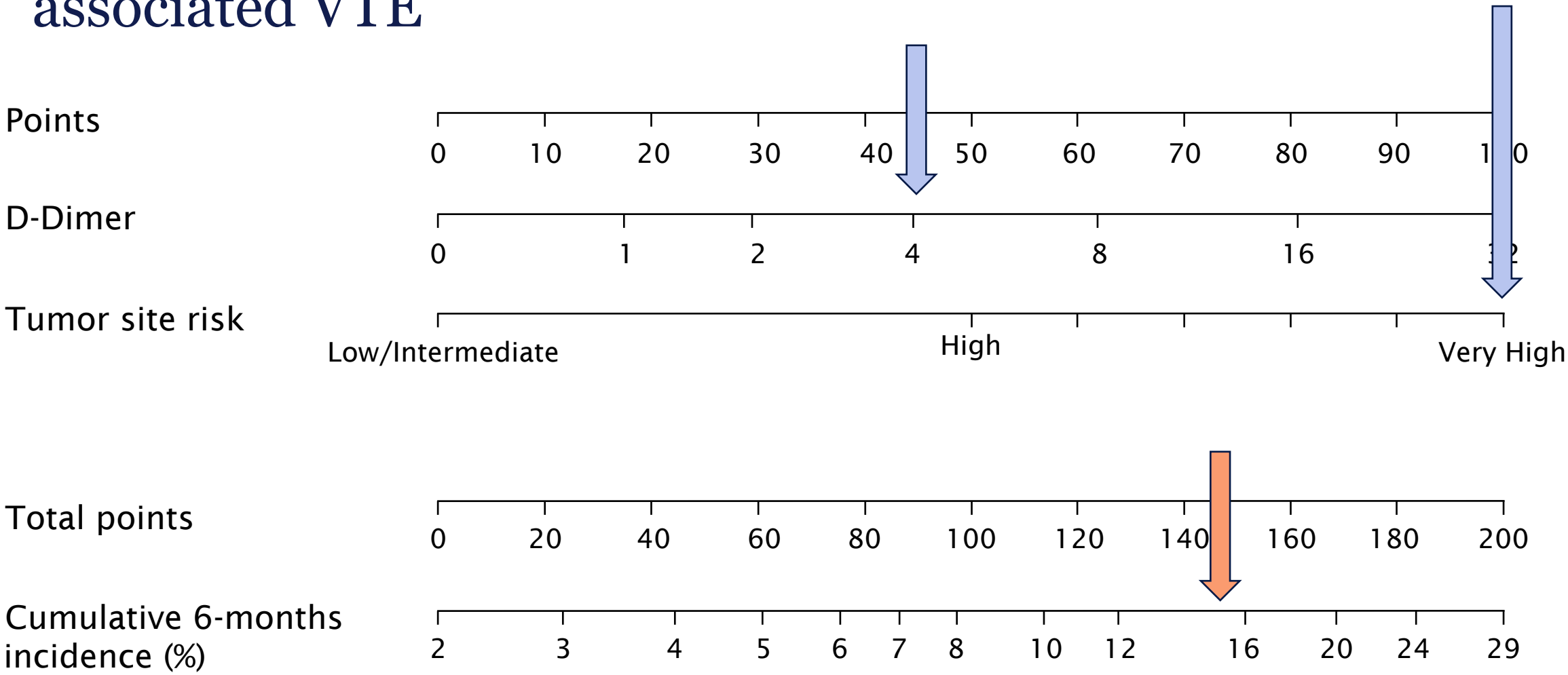
  as continuous variable

Multivariable SHR 1.32
(95% CI 1.12-1.56)

*This model compared to Khorana score:
Population-weighted net reclassification improvement (NRI)=0.31

Pabinger I et al. Lancet Haematol. 2018 Jun 7 [Epub ahead of print]

Nomogram for predicting the 6-month risk of cancer-associated VTE



For more on the risk calculator see: **catscore.meduniwien.ac.at**

Pabinger I et al. Lancet Haematol. 2018 Jun 7 [Epub ahead of print]

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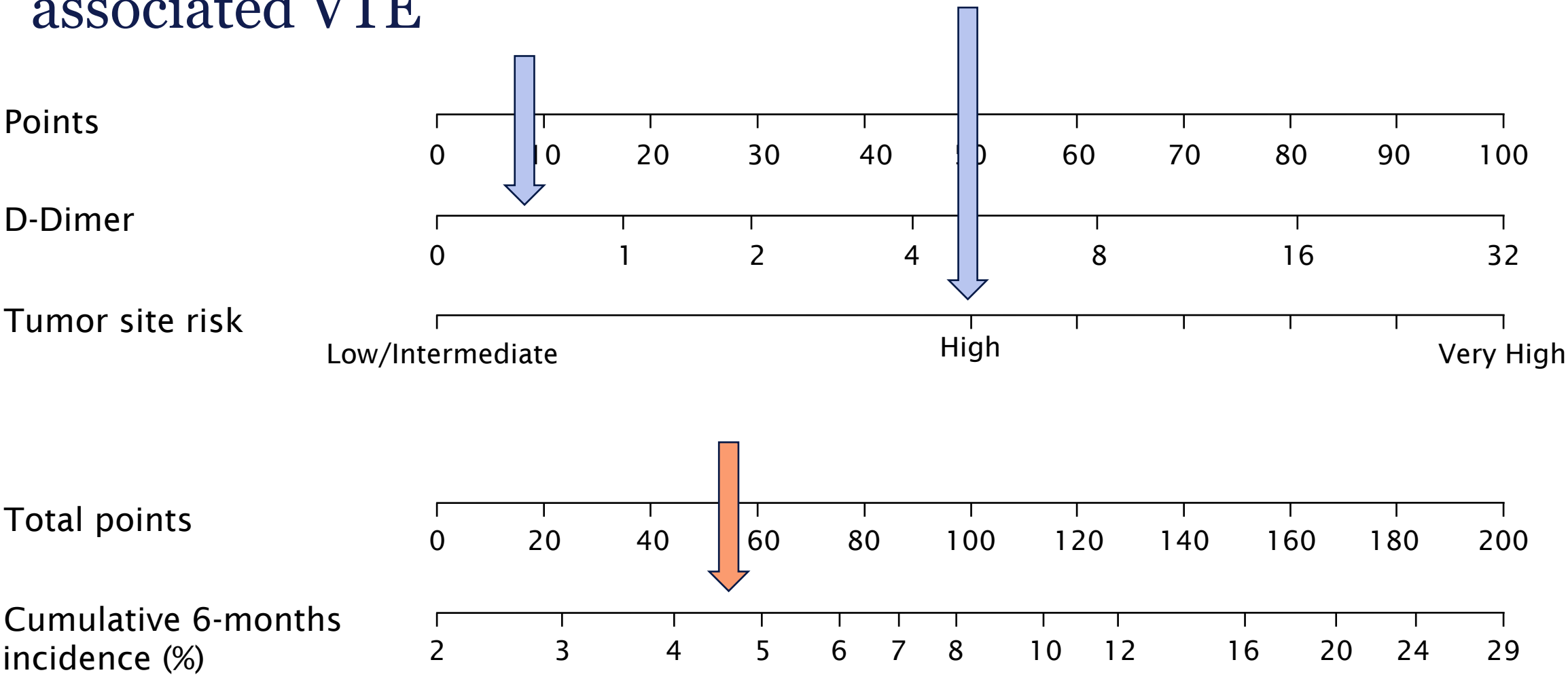

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Risk Assessment for VTE
ASCO Guidelines Recommendation

CLINICAL QUESTION 6

What is known about risk prediction and awareness of VTE among patients with cancer?

Recommendation 6.1

Based on consensus, the Panel recommends that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. Individual risk factors, including biomarkers and cancer site, do not reliably identify patients with cancer at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool (Table 5).

Recommendation 6.2

Based on consensus, the Panel recommends that oncologists educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy.

Lyman GH et al, J Clin Onc 2013

Summary & Take Home Messages

- VTE is frequent in subgroups of patients with cancer
- Multiple risk factors contribute to occurrence of VTE in patients with cancer

- It is possible to identify high risk patients by clinical and laboratory parameters

- Risk assessment models seem to be promising

- Advances in risk assessment since the publication of the „Khorana Score“
  - A **novel (**externally validated) **clinical prediction model** includes two variables: **tumour site category** (“low/intermediate” , “high” and “very high” VTE-risk tumor site) and **D-Dimer**.

- Improving risk prediction might facilitate decision making on primary thromboprophylaxis





Thank you for your attention!

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