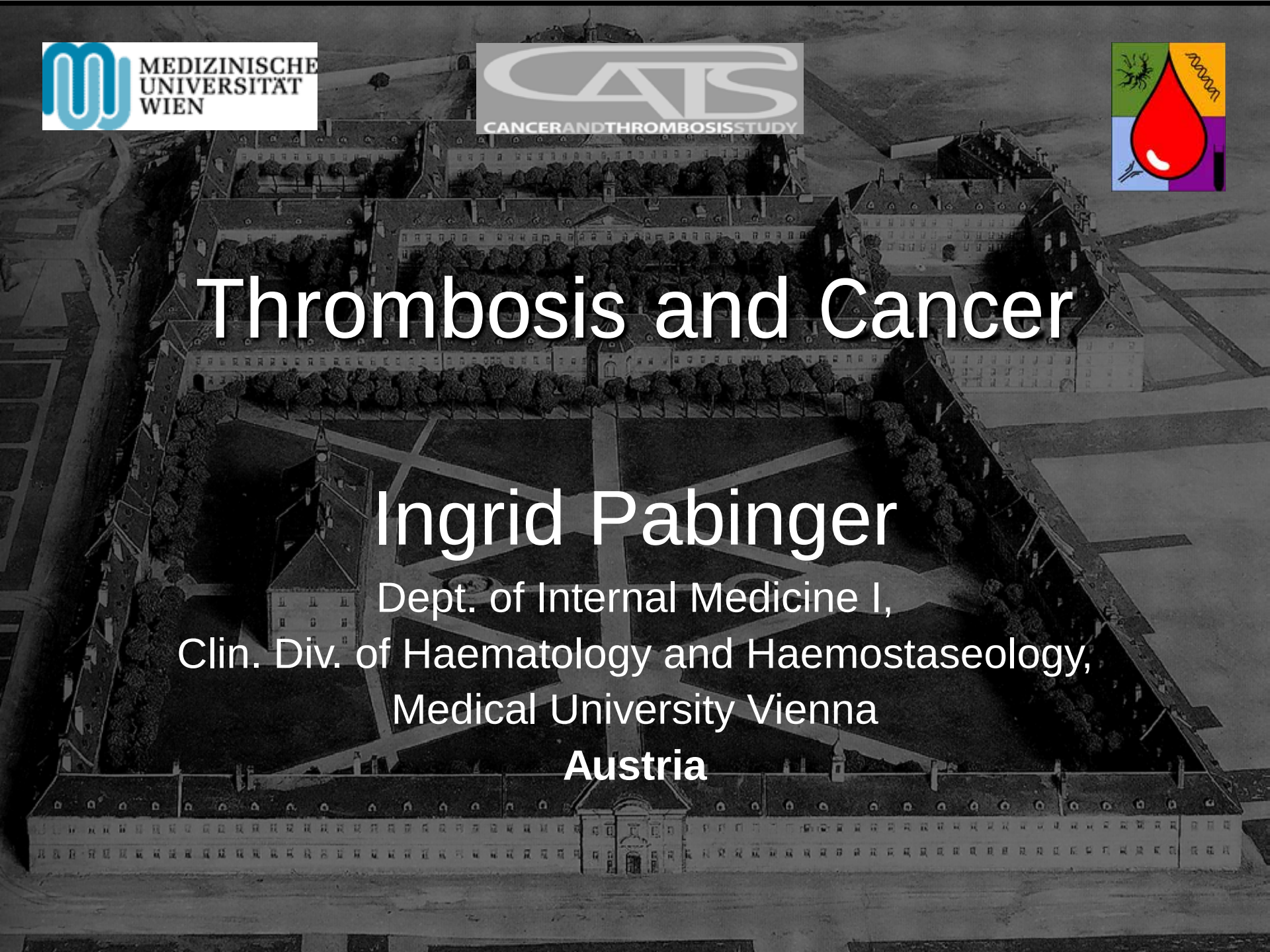

Thrombosis and Cancer

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Introduction

- A higher proportion of patients with venous thromboembolism (VTE) have underlying cancer compared to individuals without (VTE)
- Cancer patients have an increased risk of venous thromboembolism

Established risk factors for thrombosis in cancer patients

- Cancer related
  - Entity
  - Stage
  - Histological Grading
- Treatment related
  - Surgical procedure
  - Chemotherapy
    - Thalidomide + Chemotherapy + Dexamethasone
    - -platins
    - Tamoxifen (+ Chemotherapy)

Venous thrombosis or pulmonary embolism in a cancer patient

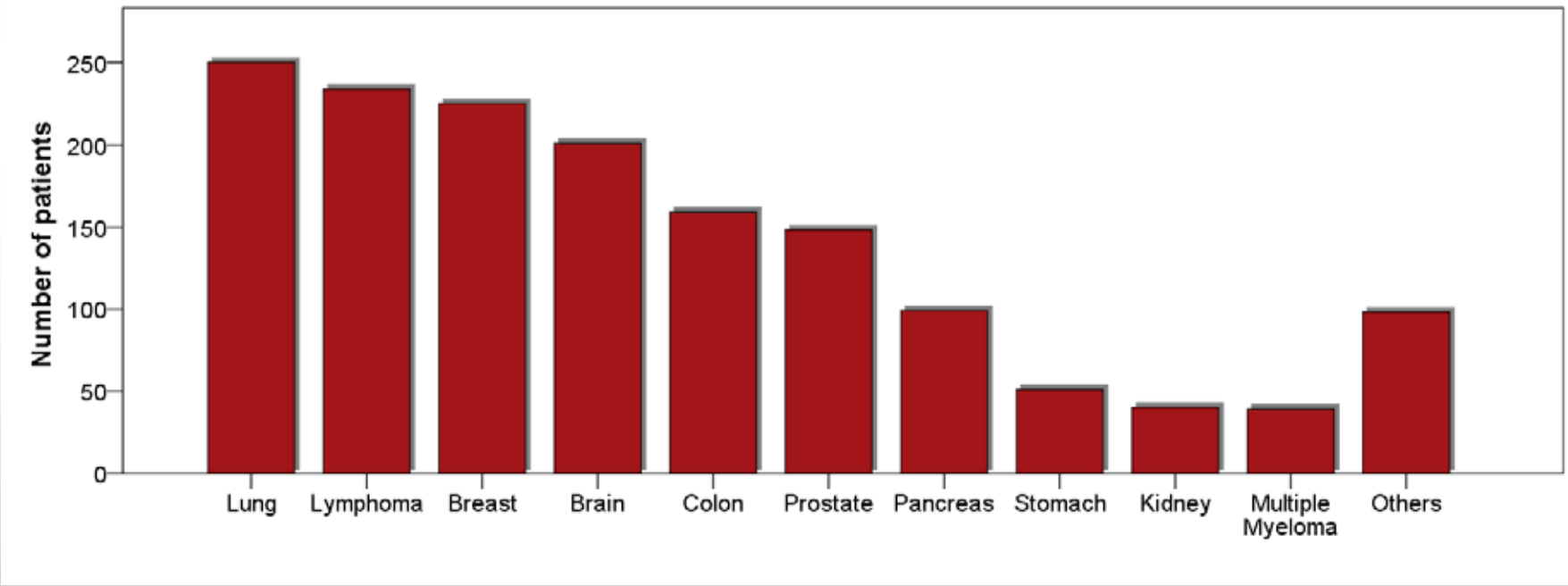
- Incidence in various cancer entities
- Risk factors for thrombosis in cancer
- Influence of cancer associated thrombosis on survival
- Haemostatic parameters for prognosis in cancer patients
- Prevention and treatment of cancer associated thrombosis

CATS – Cancer and Thrombosis Study

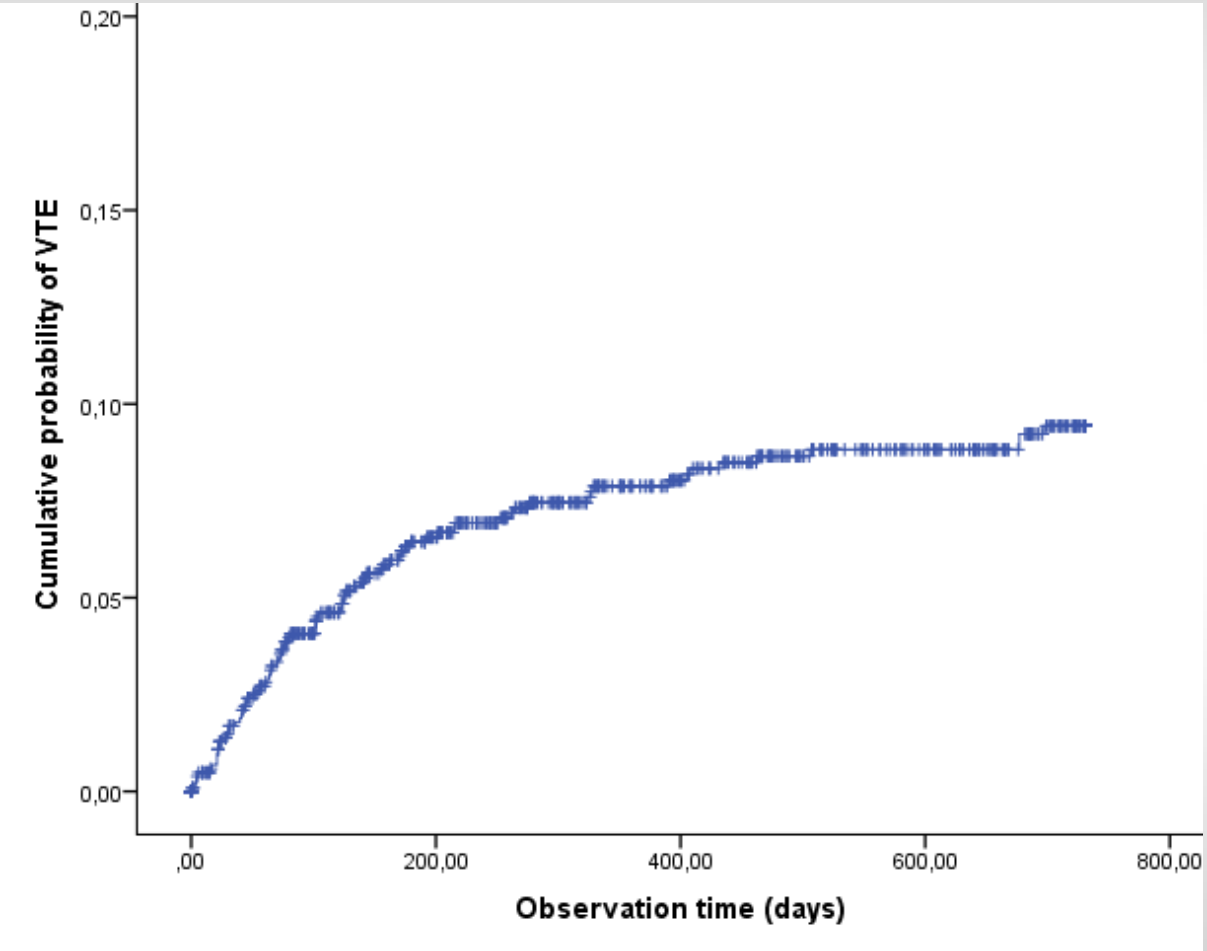
- **Aim**: To identify predictive parameters for occurrence of VTE in cancer patients
- **Design**: Prospective, observational and single center cohort study
- **Inclusion criteria:** Newly diagnosed cancer or progression of disease after complete or partial remission and written informed consent
- **Outcome measure**: Occurrence of VTE, either symptomatic or fatal and objectively confirmed

Vienna Cancer and Thrombosis Study
Patient population

- Approx. 2000 patients (45% women)
- Median age [IQR]: 62 [53-68] years
- 76% newly diagnosed



When do thrombotic events occur in patients with cancer?



Cumulative probability of VTE

3 months: 4.2%

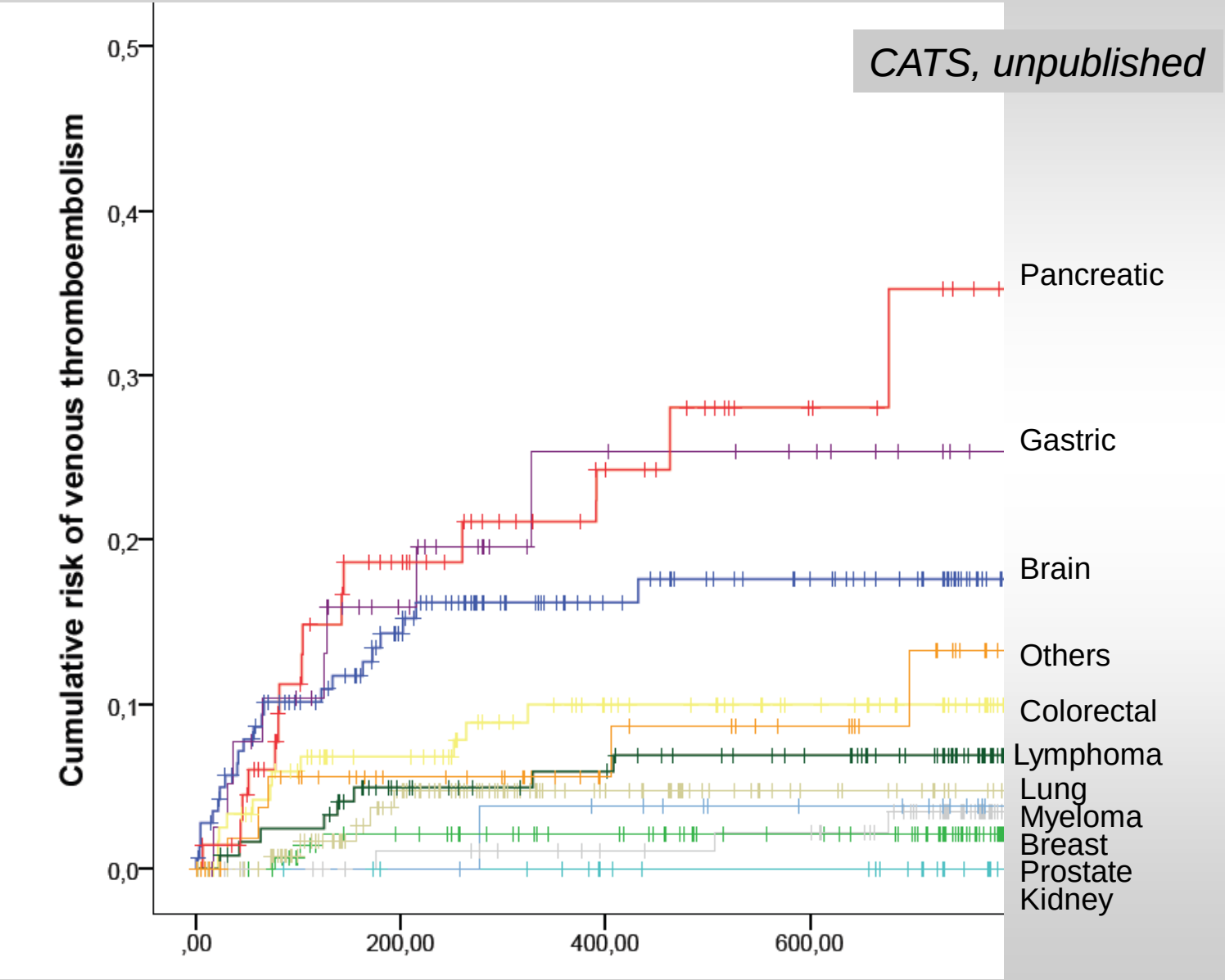
6 months : 6.1%

12 months : 8.1%

2 years: 9.4%

CATS (unpublished)

Cumulative VTE risk according to cancer type



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Biomarkers investigated to identify patients at high/low risk of VTE

Biomarkers and laboratory tests investigated for prediction of cancer-associated VTE in CATS		
Platelet count	Simanek et al, JTH 2009	+
soluble P-selectin	Ay et al, Blood 2008	+
D-Dimer		+
Prothrombinfragment 1+2	Ay et al, J Clin Oncol 2009	+
C-reaktive Protein	Kanz et al, JTH 2011	(+)
Factor VIII activity	Vormittag et al, ATVB 2009	+
Thrombin Generation Assay	Ay et al, J Clin Oncol 2011	+
Microparticles/Tissue factor bearing microparticles	Thaler et al, JTH 2012	-/+ ?
Fibrinogen	Tiedje et al, Thromb Haemost 2011	--

Reviewed in: Pabinger, Thaler and Ay, Blood 2013

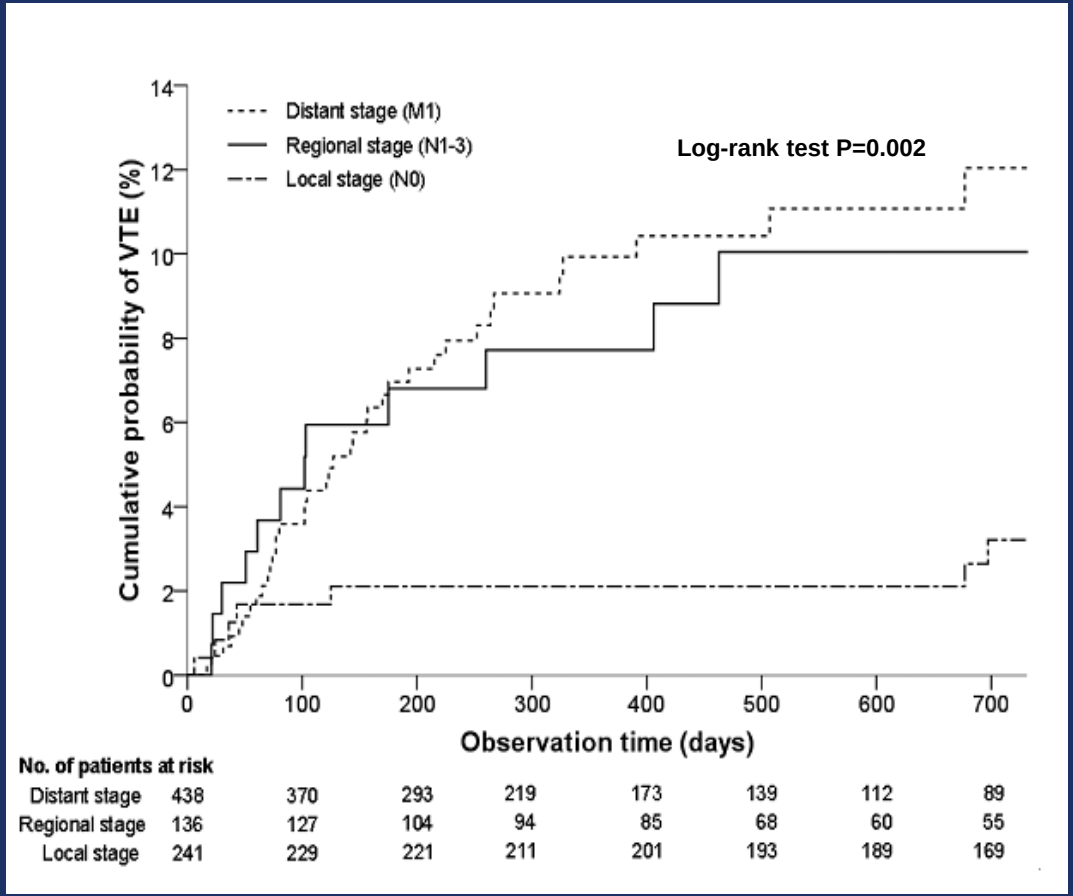
Association with stage

Cumulative probability after 6 months:

2% local

7% regional LN

7% distant metastasis



Dickmann et al, in revision

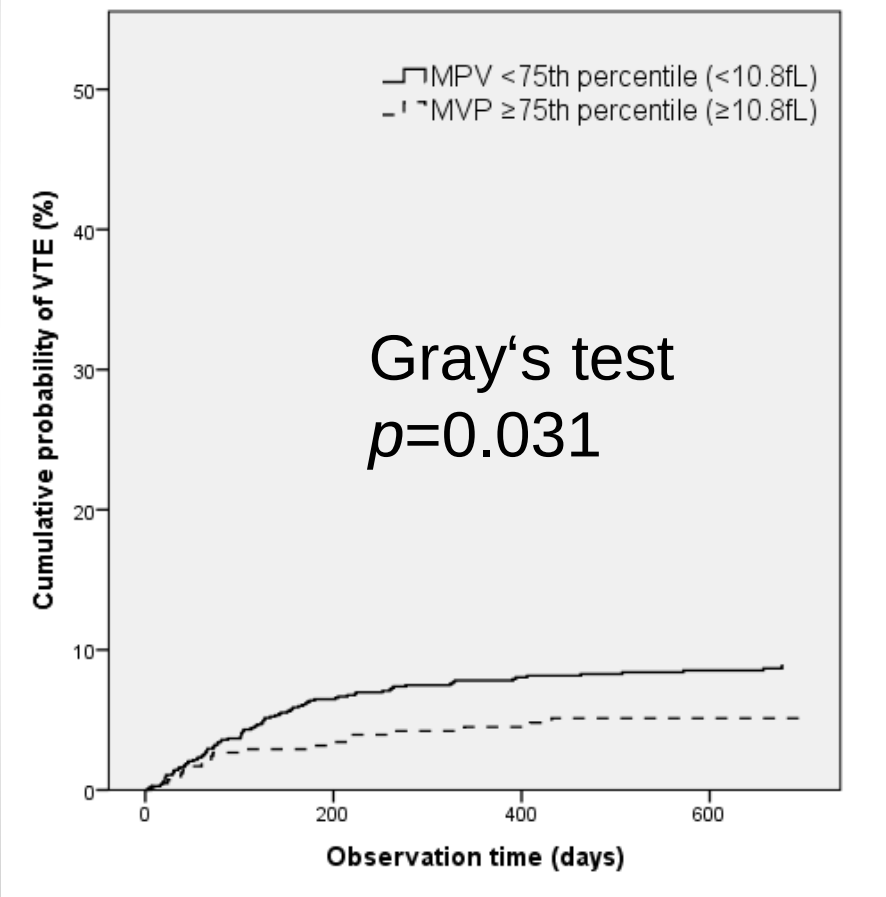
Mean platelet volume (MPV) is associated with risk of VTE

Multivariable* hazard ratio (HR)
0.6 [95% CI: 0.37-0.98]

* including age, sex, different groups of cancer (glioblastoma, hematological malignancy, solid tumor without metastasis or solid tumor with metastasis), newly diagnosed vs. recurrent disease, platelet count and levels of soluble P-selectin

Cumulative probability of VTE after 2 years:

5.5% for high MPV
9% for lower MPV



Riedl et al., Thromb Haemost 2014

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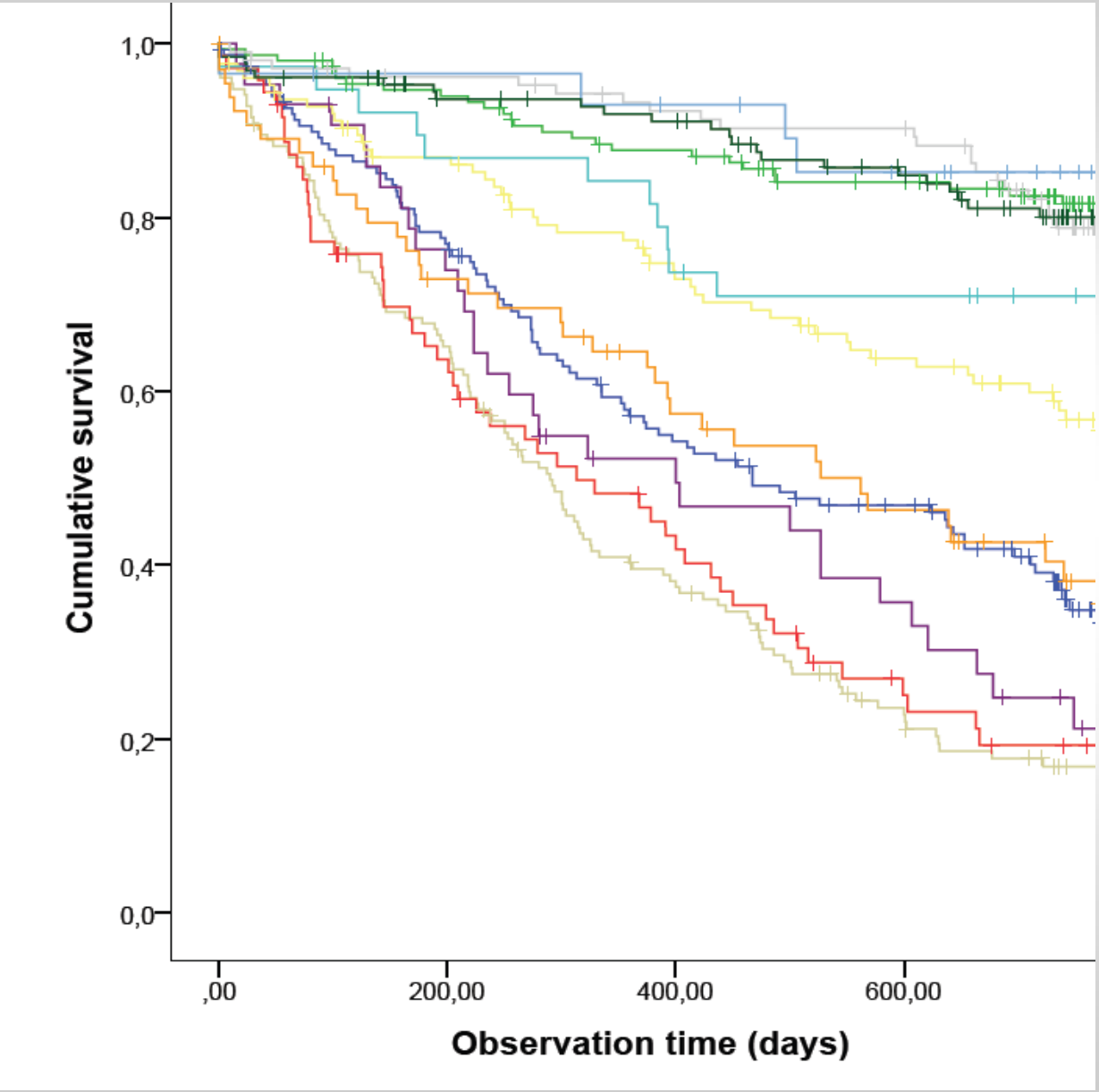
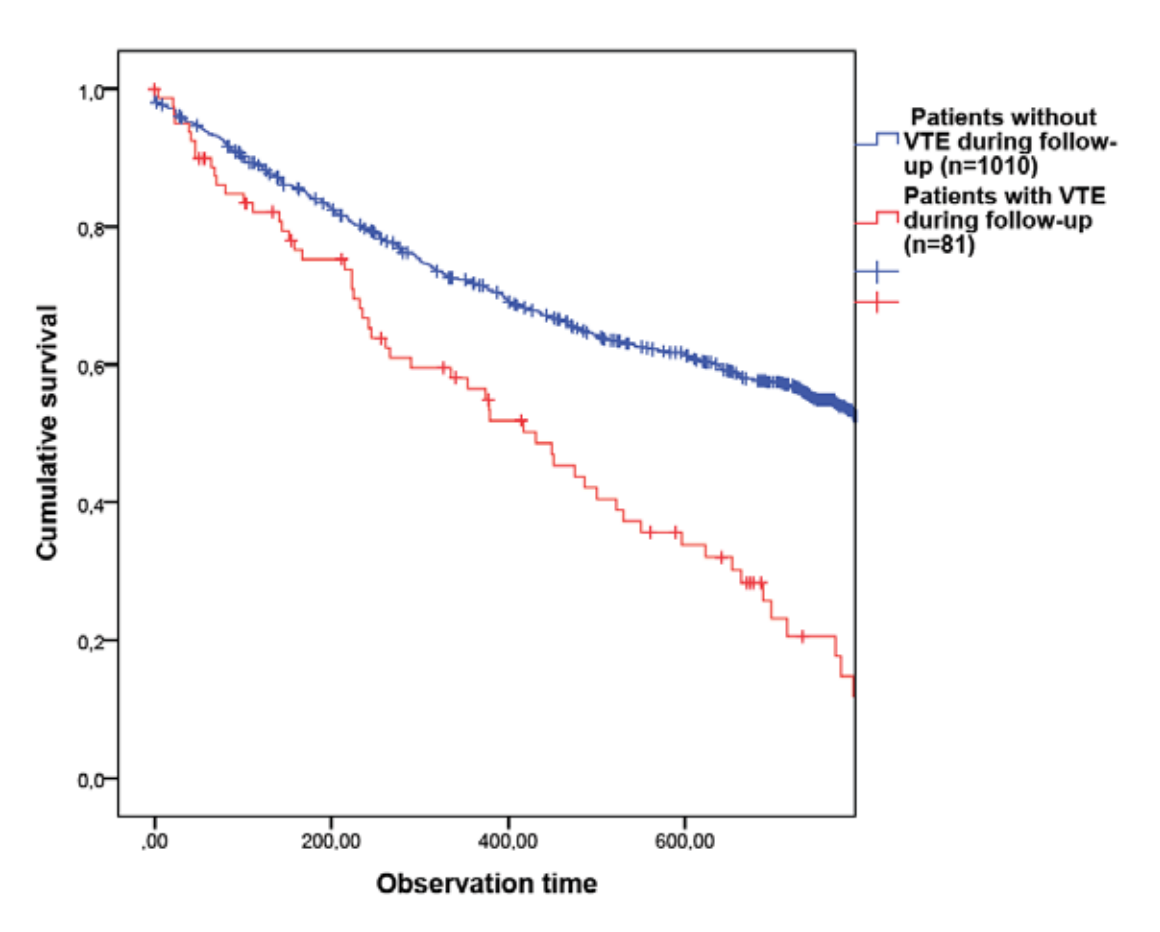
Cumulative survival according to cancer type



CATS, unpublished

Probability of survival in cancer patients without and with VTE during follow up



Multivariable HR (including stage) in patients with VTE
HR: 2.2 (95% CI: 1.7-2.8; p<0.001)

CATS, unpublished

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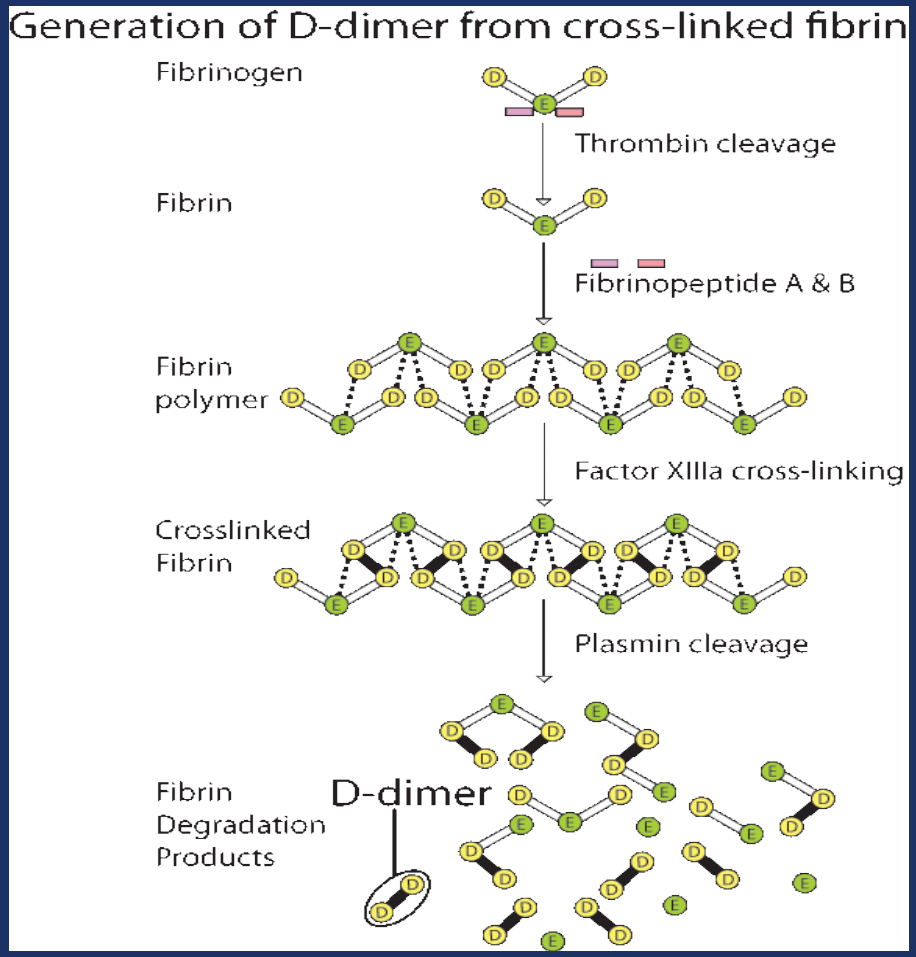
CANCERANDTHROMBOSISSTUDY

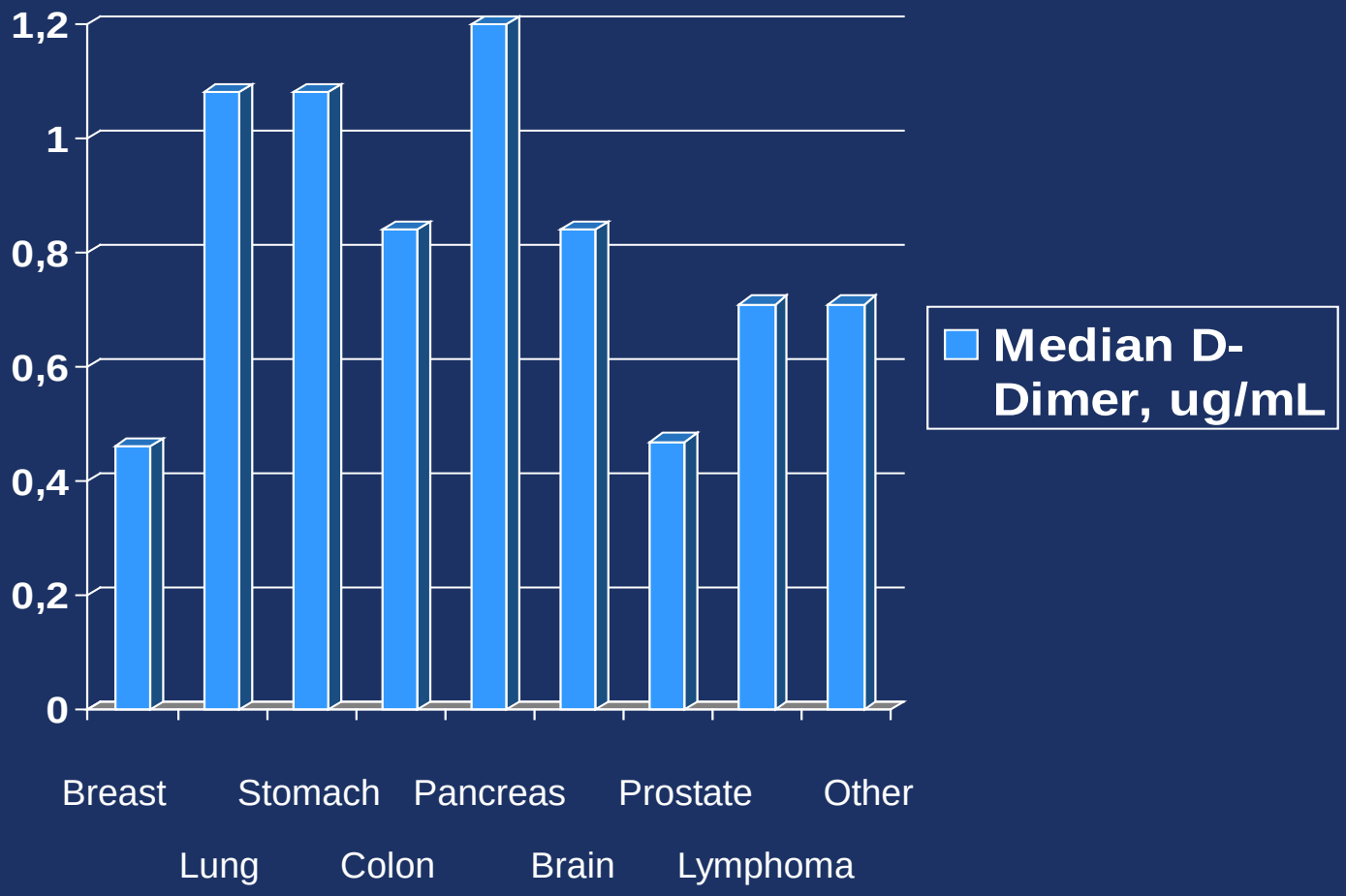
D-Dimer



- global marker of coagulation activation
  - •degradation product of cross-linked fibrin, formed after thrombin-generated fibrin has been degraded by plasmin
  - •diagnosis of acute VTE
  - •higher levels in cancer patients

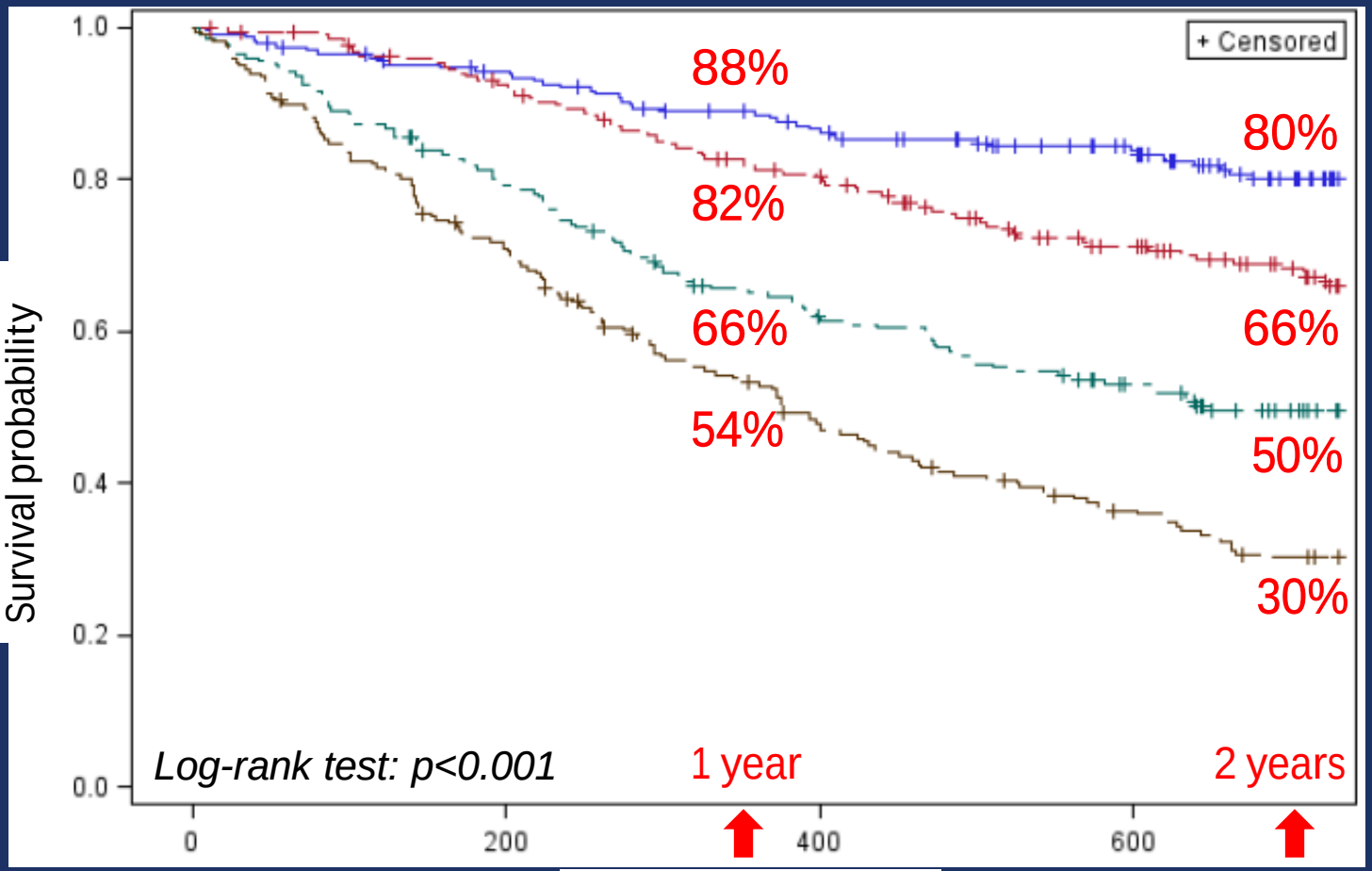
reviewed in: Pabinger and Ay, Arterioscler Thromb Vasc Biol. 2009

D-dimer in various tumour entities



Ay et al, JCO 2009 and Ay et, Haematologica 2012

Cumulative probability of survival



D-dimer levels

1.quartile

2.quartile

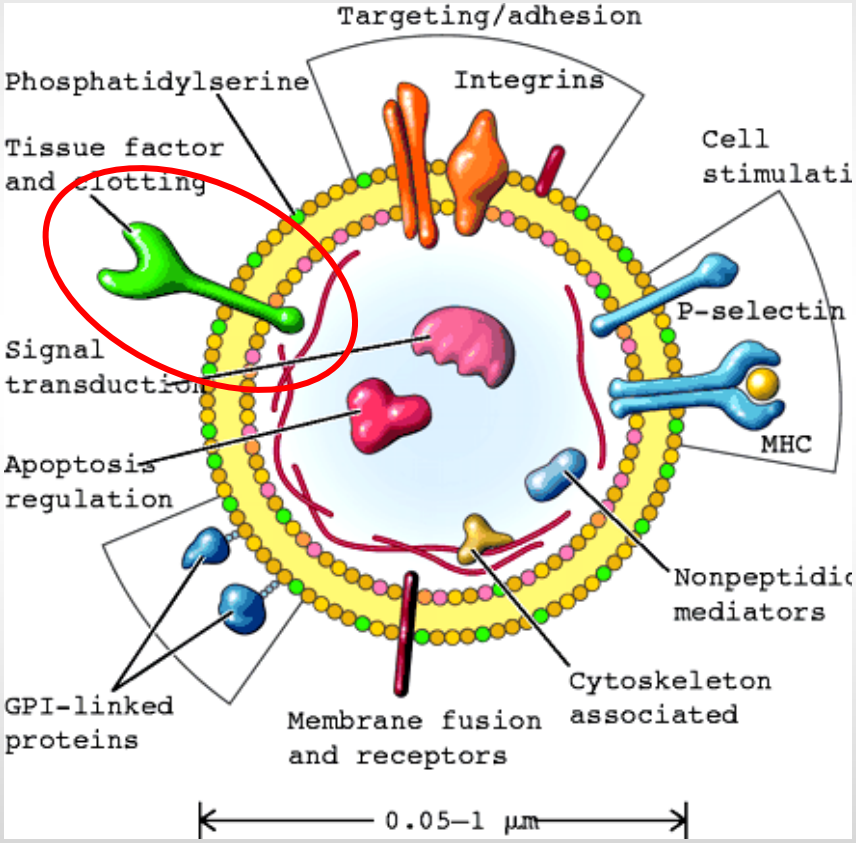
3.quartile

4.quartile

Ay et al, Haematologica 2012

Microparticles

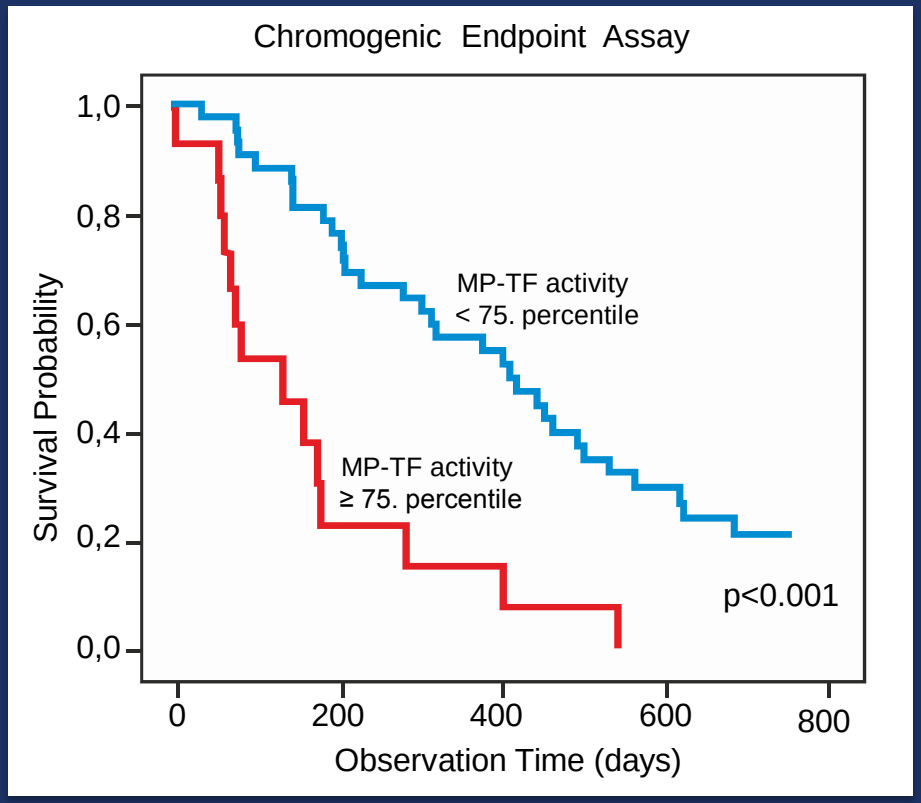
On their surface microparticles bear antigens of their parental cells and may **transfer/receive** surface molecules to/from other cell types

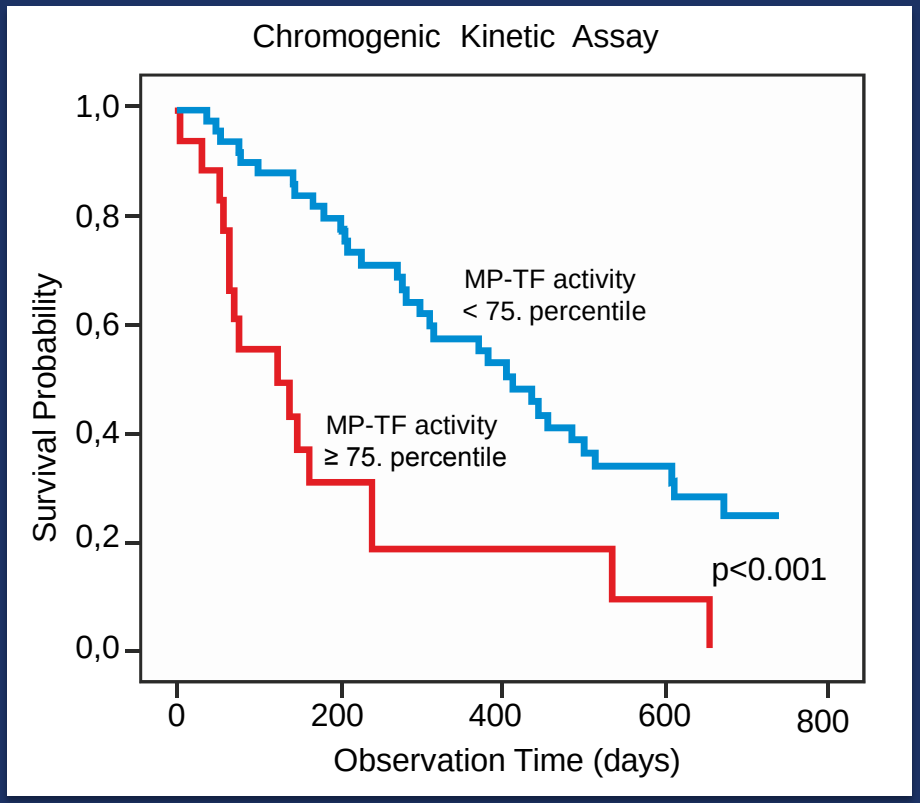


From: Hugel B et al, Membrane Microparticles: Two sides of the coin. Physiology 20:22-27, 2005.

TF-positive MPs and prognosis in CATS

Cumulative survival probability in pancreatic cancer patients





Probabilty of survival after 6 months: 82% versus 31 %

Thaler et al. JTH 2012

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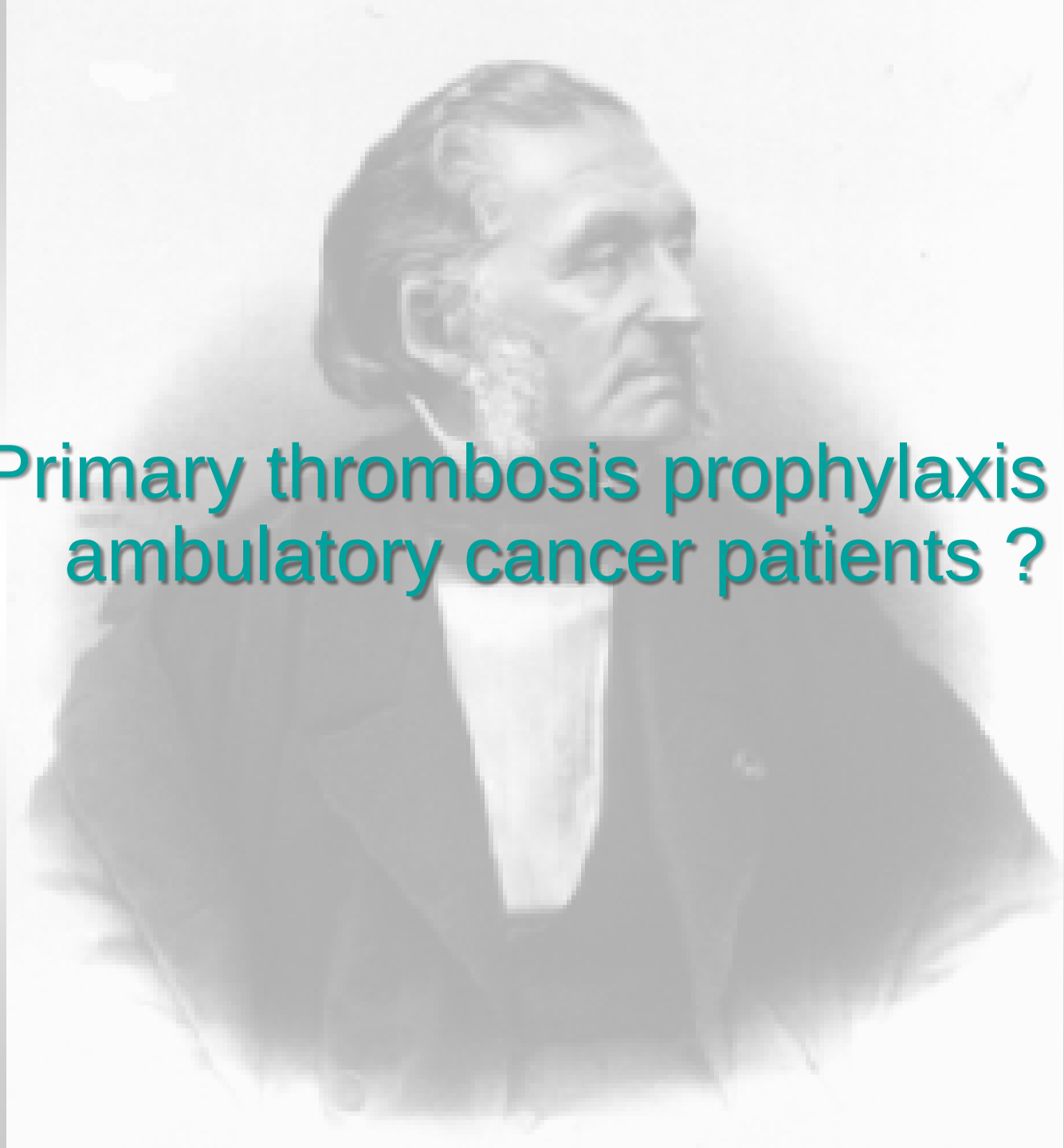
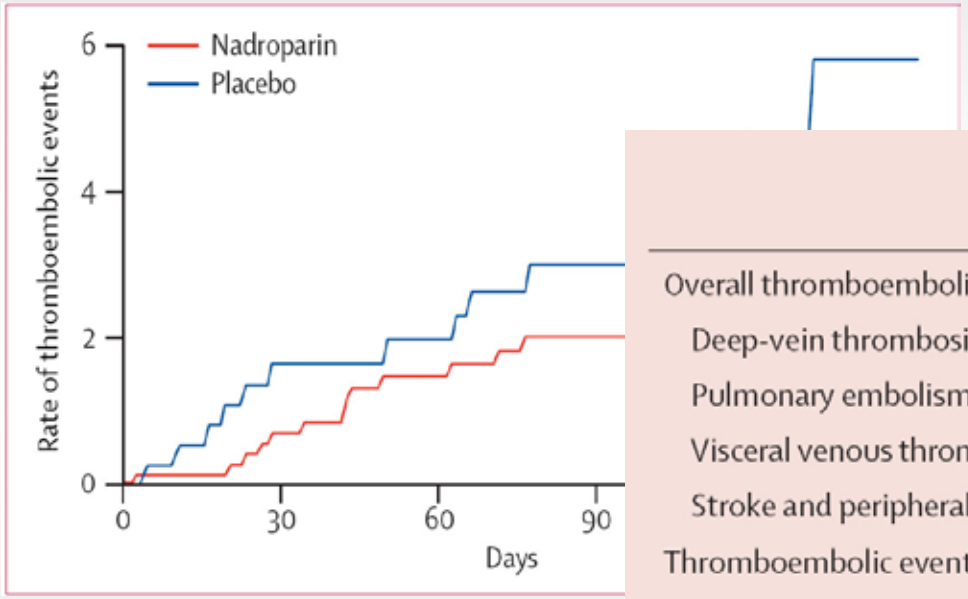


Primary thrombosis prophylaxis in ambulatory cancer patients ?

A prospective randomized placebo-controlled trial of Tinzaparin in patients with advanced cancer with chemotherapy



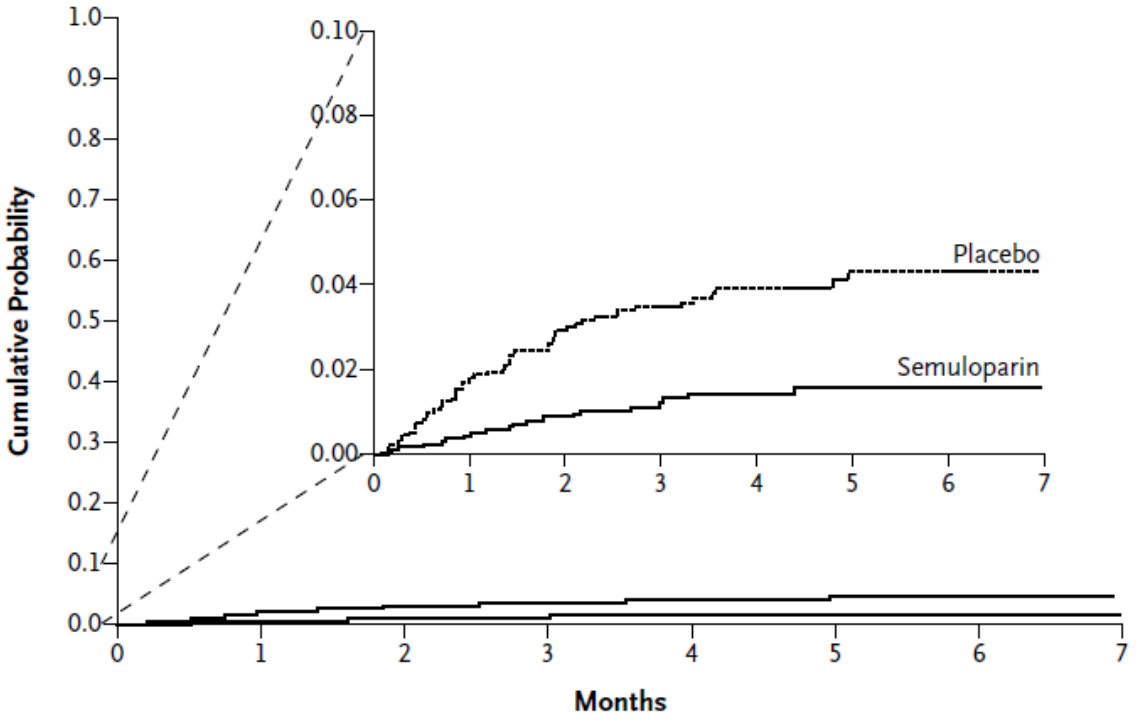
	Nadroparin (N=769)	Placebo (N=381)
Overall thromboembolic events	15 (2·0)	15 (3·9)
Deep-vein thrombosis	8 (1·0)	8 (2·1)
Pulmonary embolism	3 (0·4)	3 (0·8)
Visceral venous thrombosis	1 (0·1)	1 (0·3)
Stroke and peripheral thrombosis	3 (0·4)	3 (0·8)
Thromboembolic event by cancer site		
Lung	7/199 (3·5)	7/80 (8·8)
Gastrointestinal	4/272 (1·5)	4/148 (2·7)
Pancreas	3/36 (8·3)	1/17 (5·9)
Other	1/262 (0·4)	3/136 (2·2)

Data are n (%).

Agnelli et al, Lancet/onc. 2009

Semuloparin versus Placebo

Any VTE or VTE-related death



No. at Risk								
Semuloparin	1608	1410	1227	986	681	384	197	77
Placebo	1604	1375	1212	985	689	403	201	92
No. of Events								
Semuloparin	0	7	13	17	19	20	20	20
Placebo	0	26	42	49	53	55	55	55

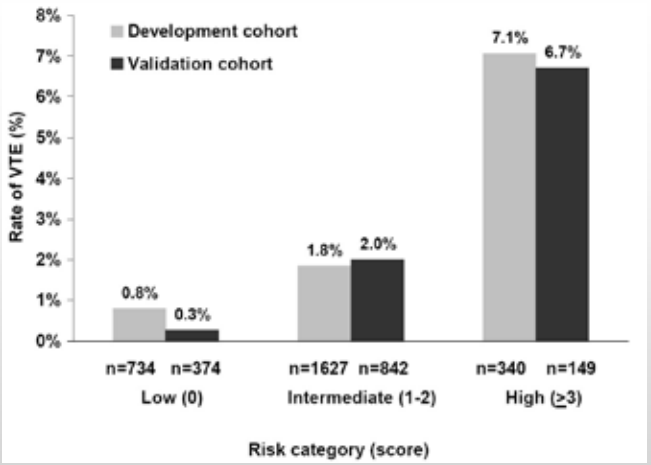
Agnelli et al, NEJM 2012, 366:601

Risk score model to predict VTE in a cohort of 2 701 cancer patients

Patient Characteristic	β	Odds Ratio* (95% CI)
Site of Cancer		
Very high risk (stomach, pancreas)	1.46	4.3 (1.2-15.6)
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	0.43	1.5 (0.9-2.7)
Low risk (breast, colorectal, head and neck)	0.0	1.0 (reference)
Pre-chemotherapy platelet count ≥ 350,000/ mm^3	0.60	1.8 (1.1-3.2)
Hemoglobin < 10g/dL or use of red cell growth factors	0.89	2.4 (1.4-4.2)
Pre-chemotherapy leukocyte count > 11,000/mm^3	0.77	2.2 (1.2-4)
Body mass index ≥ 35 kg/m^2	0.90	2.5 (1.3-4.7)

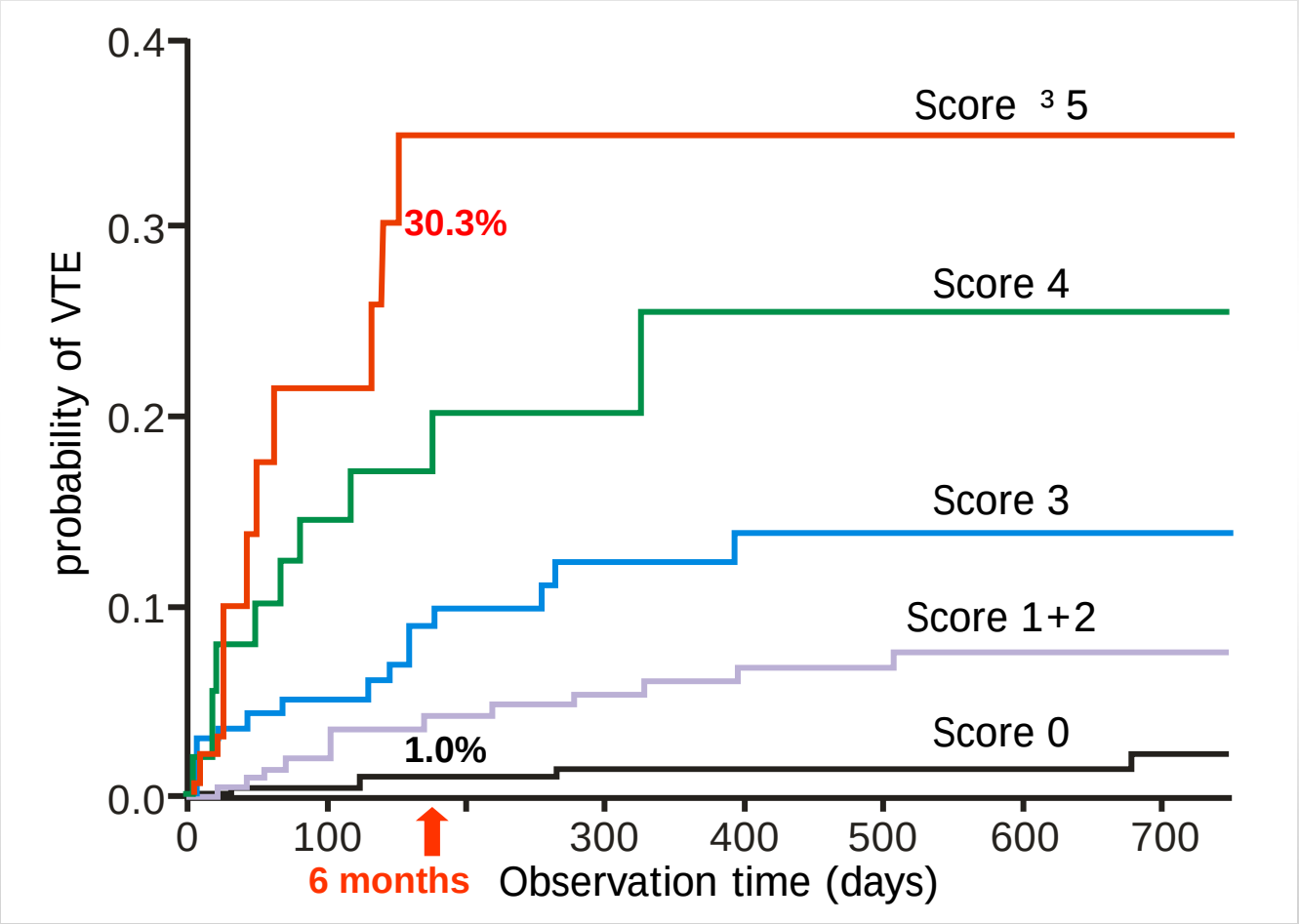
*Odds ratios are adjusted for stage.

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, 111:4902

Risk score including clinical parameters (tumour type, body weight), blood count and biomarkers (elevated D-Dimer and elevated sP-selectin)



Ay C, Pabinger et al, Blood 2010

Novel international guidelines JTH 2013

Journal of Thrombosis and Haemostasis, **11**: 56–70 DOI: 10.1111/jth.12070

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

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and H. R. BÜLLER‡‡‡‡‡‡[1]

Treatment
Perioperative prophylaxis
Prophylaxis in medical patients

International Good Clinical Practice Guidelines (GCPG) for Antithrombotics in cancer Patients

Treatment

Low molecular weight heparin (LMWH) for initial treatment and for at least 3 months (1A) – after 3-6 months “case based” treatment

Farge et al, JTH 2013

International Good Clinical Practice Guidelines (GCPG) for Antithrombotics in cancer Patients

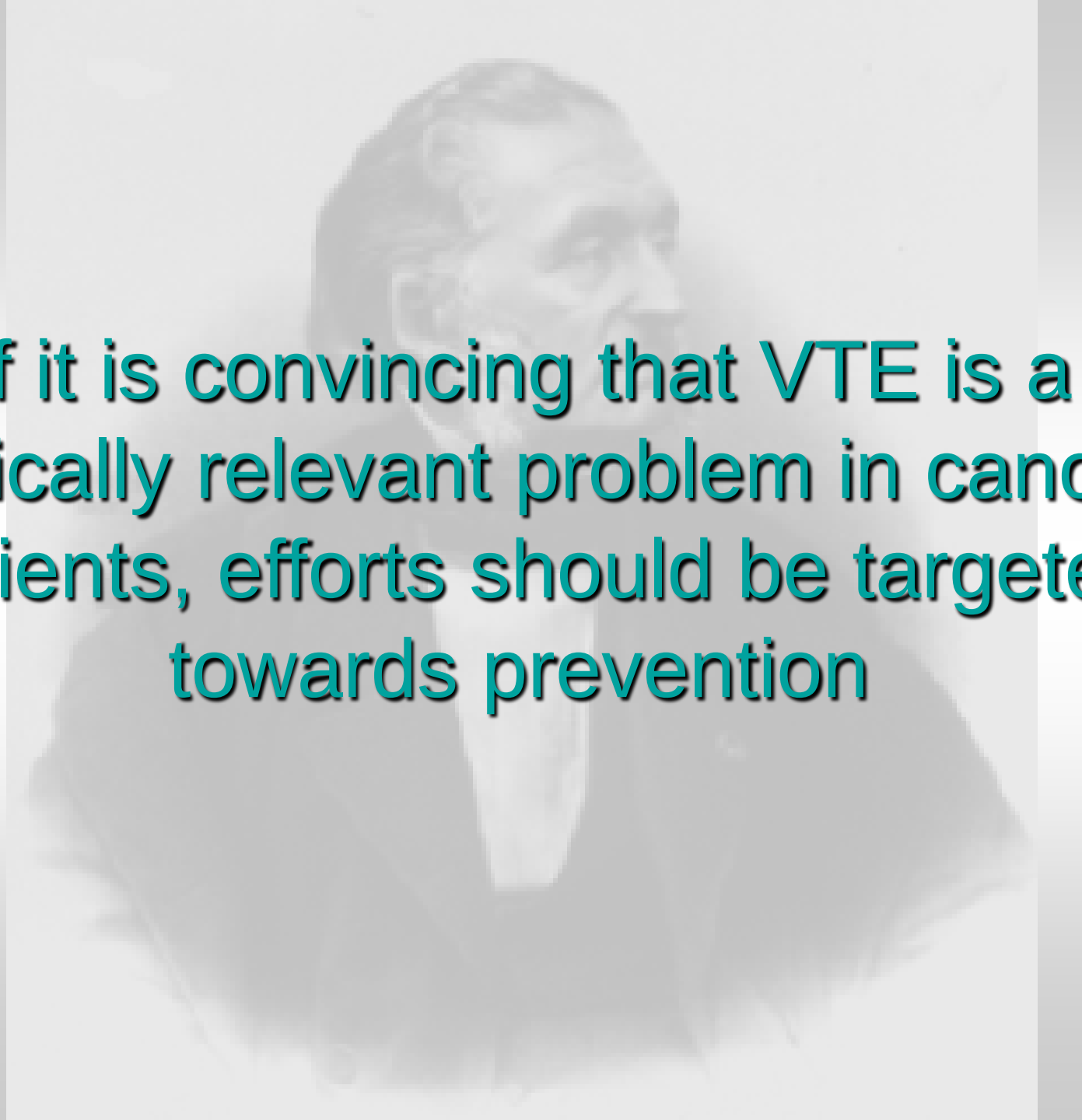
Prophylaxis in medical patients

We recommend prophylaxis with LMWH, UFH or fondaparinux in hospitalized medical patients with cancer and reduced mobility [Grade 1B].

In patients receiving chemotherapy, prophylaxis is not recommended routinely [Grade 1B].

Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy and having a low bleeding risk [Grade 1B].

Farge et al, JTH 2013



If it is convincing that VTE is a clinically relevant problem in cancer patients, efforts should be targeted towards prevention

Venous thromboembolism in cancer – Prevention in ambulatory patients -

Primary prevention of cancer associated VTE

- Efficacy in relative and absolute terms
- Influence on the overall survival
- Side effects (bleeding and other side effects)
- Costs for the health care system and the patients

Summary/Conclusion

- VTE is frequent in subgroups of cancer patients
- It is possible to identify high risk patients by clinical and laboratory parameters
- Part of the patients with VTE have a decreased survival
- There is an interrelation between hemostatic parameters and prognosis
- Advances have been made in the treatment of cancer associated VTE
- Primary prophylaxis is still a matter of debate

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Clinical Division of Oncology

Department of Laboratory Medicine

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Clinical Division of Haematology and Haemostaseology

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Nigel Mackman (Chapel Hill, NC, USA) and Rogier Bertina (Leiden, NL)


Thank you
for your attention


CANCERANDTHROMBOSISSTUDY
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