Thrombosis and Treatment in Oncology

Simon Watt

- Epidemiology
- Causes of thrombosis and relevance to cancer
- Specific problems in malignancies
- In VTE who might have cancer?
- Treatment of VTE
- NOACS and the relevance in malignancy

VTE and Cancer: Epidemiology

- Of all cases of VTE:
  - About 20% occur in cancer patients
  - Patients with spontaneous VTE have a 4x risk of being diagnosed with cancer
- Of all cancer patients:
  - 15% will have symptomatic VTE
  - As many as 50% have VTE at autopsy
- Compared to patients without cancer:
  - Higher risk of first and recurrent VTE
  - Higher risk of bleeding on anticoagulants
  - Higher risk of dying

Lee AY, Levine MN. *Circulation*. 2003;107:23 Suppl 1:I17-I21

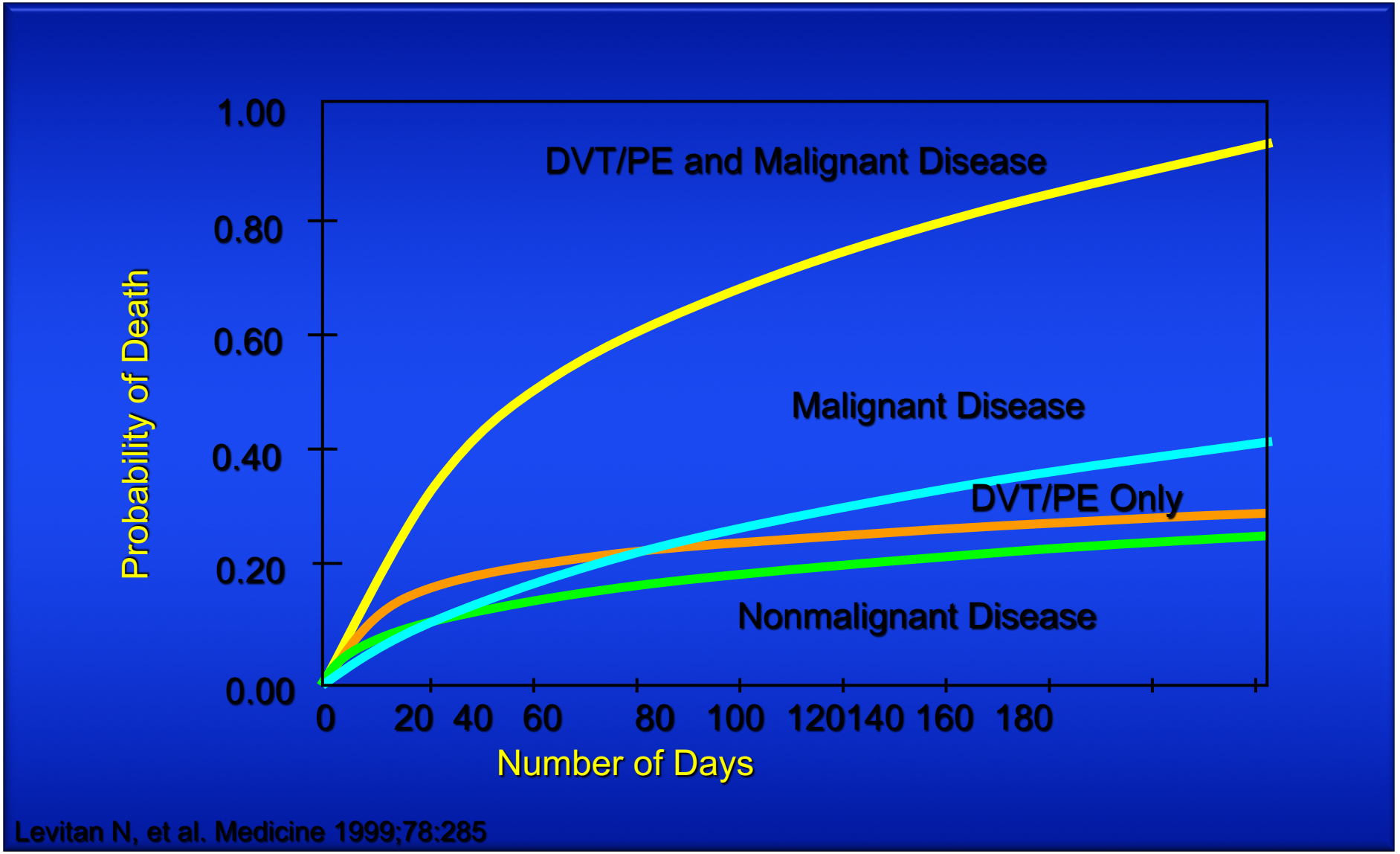
Clinical Features of VTE in Cancer

- VTE has significant negative impact on quality of life

- VTE may be the presenting sign of occult malignancy
  - 10% with idiopathic VTE develop cancer within 2 years
  - 20% have recurrent idiopathic VTE
  - 25% have bilateral DVT

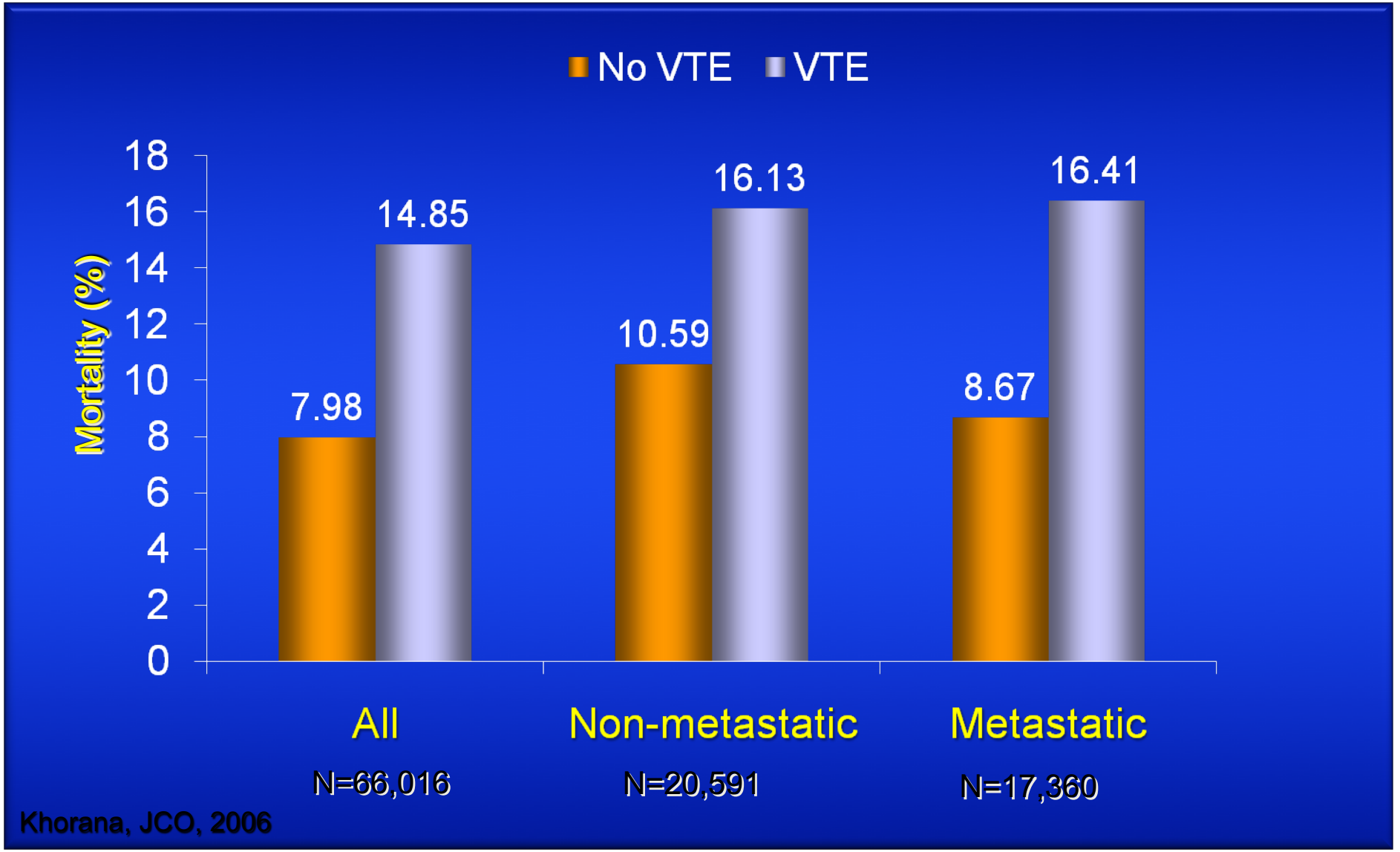
Bura *et. al., J Thromb Haemost* 2004;2:445-51

Likelihood of Death After Hospitalization



Levitan N, et al. Medicine 1999;78:285

Hospital Mortality With or Without VTE



WHAT CAUSES VTE ?

Three main components were identified by Rudolph Virchow,19th century German pathologist

- **A change in blood flow** due to immobility/paralysis resulting in **stasis**
- **Hypercoaguability** causing the blood to clot more readily, e.g. hormone replacement, clotting disorders or thrombophilias
- **Injury to the vessel wall,** e.g. trauma or infection

Risk factors for first thrombosis

- Age
- Active cancer/cancer treatment-20%
- Critical care admission
- Surgery
- Thrombophilia
- Family/personal history of VTE
- Obesity
- HRT/oestrogen-containing contraceptive pill
- Pregnancy/given birth within 6 weeks

Risk factors for recurrent thrombosis

- Previous thrombosis
- Spontaneous
- Male sex
- Antiphospholipid syndrome
- Active cancer

Natural History of DVT

Rare under 16 years

Annual incidence 30/100,000 40 years

Annual incidence 90/100,000 60 years

Annual incidence 260/100,000 80 years

Thrombophilia

Factor V Leiden (V resistant to cleavage by Protein C)

Prothrombin gene G20210A variant (high II)

Protein C

Protein S

Low Antithrombin

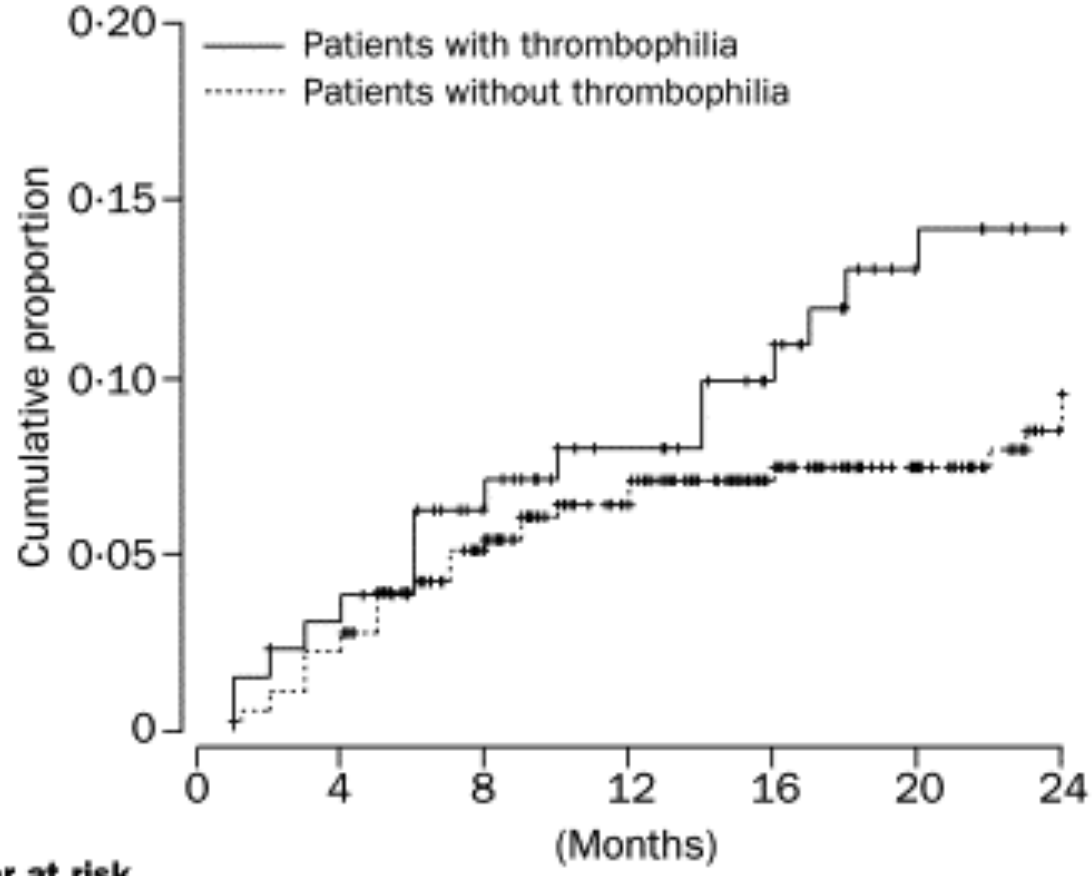
Thrombophilia

- Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia(1B).
- Decisions regarding duration of anticoagulation in unselected patients should be made with reference to whether or not a first episode of venous thrombosis was provoked or not, other risk factors, and risk of anticoagulant therapy-related bleeding, regardless of whether a heritable thrombophilia is known (1B)

Thrombophilia

- Adults who develop skin necrosis in association with oral VKAs should be tested for protein C and S deficiency when VKA treatment is withdrawn (2B).

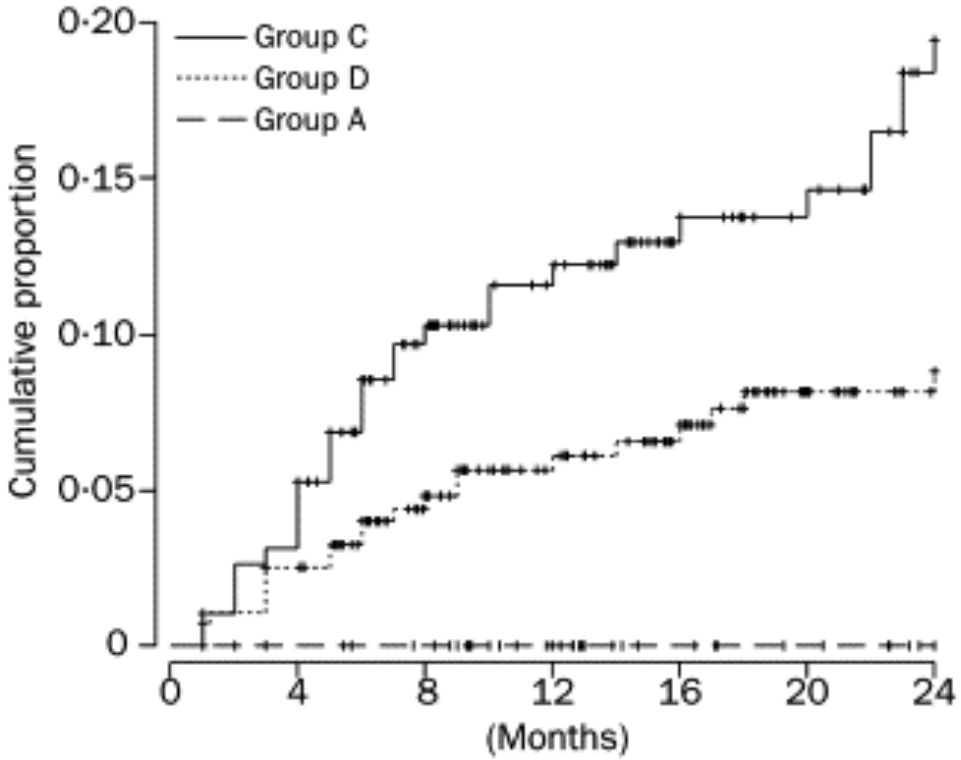
Thrombophilia?



Number at risk

Patients with thrombophilia	130	125	111	100	90	76	71
Patients without thrombophilia	359	350	308	272	230	201	174

Recurrence



Number at risk

Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

Figure 1: **Cumulative proportions of recurrent thrombosis after cessation of anticoagulant therapy**

Data for group B are not included because it was a small group with no recurrences.

Thrombophilia screening- Acquired

Antiphospholipid antibodies

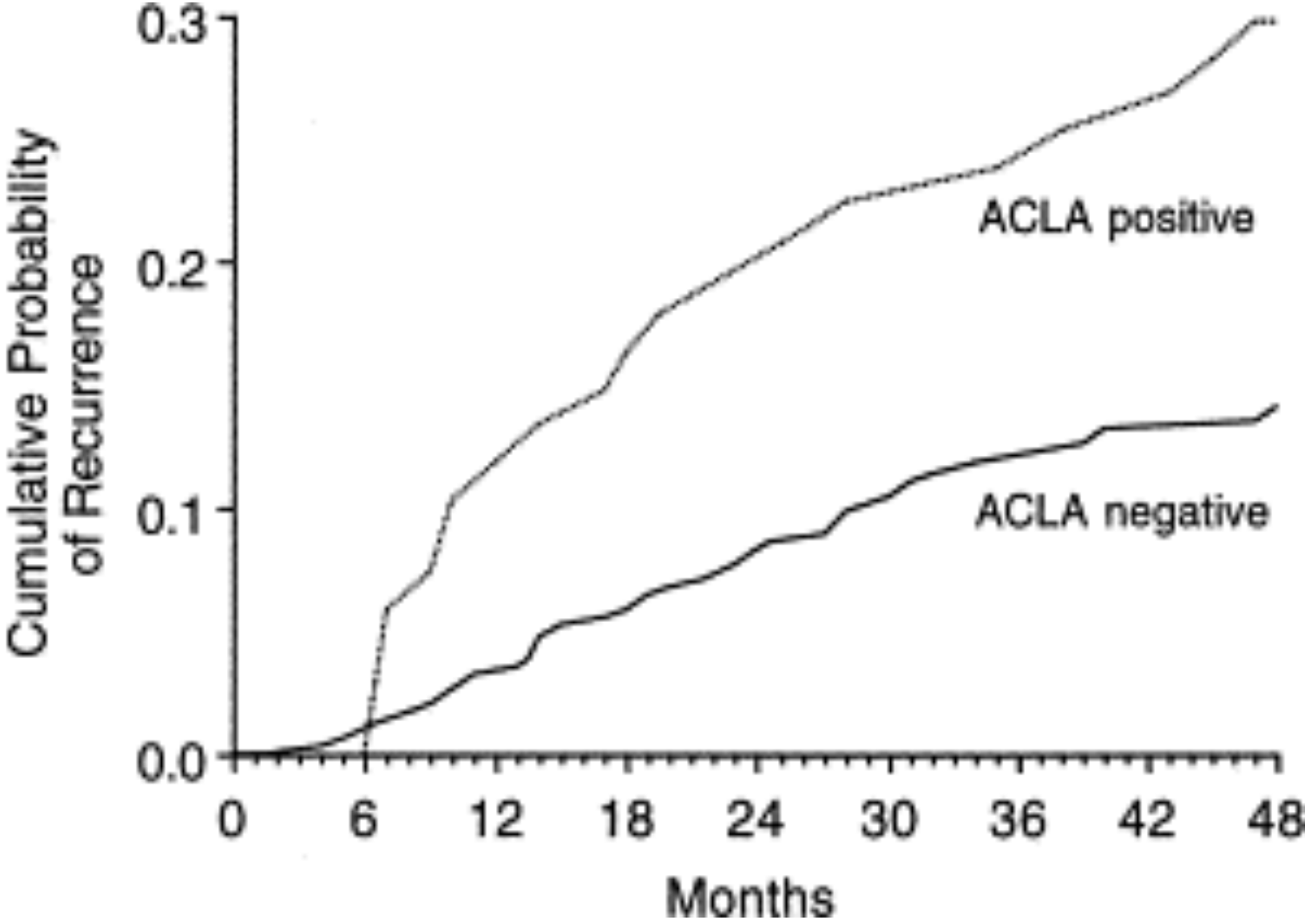
Anticardiolipin antibodies

Lupus anticoagulant

Anti-Beta2 glycoprotein I antibodies

High homocysteine

Schulman et al AJM 1998



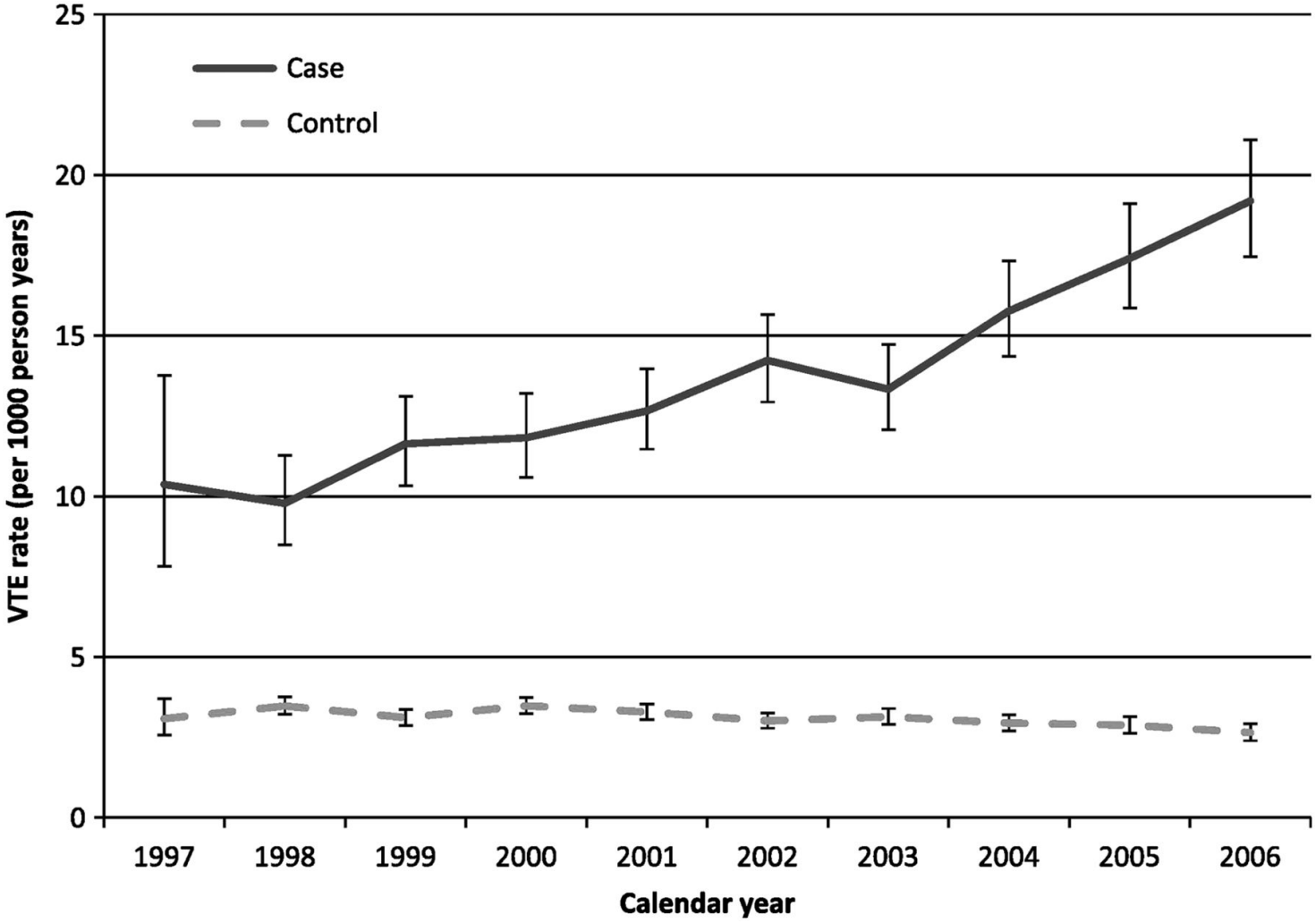
Cancer-Associated VTE

Elyamany G, et al. *Clin Med Insights Oncol*. 2014;8:129-137.

Risk factors in cancer

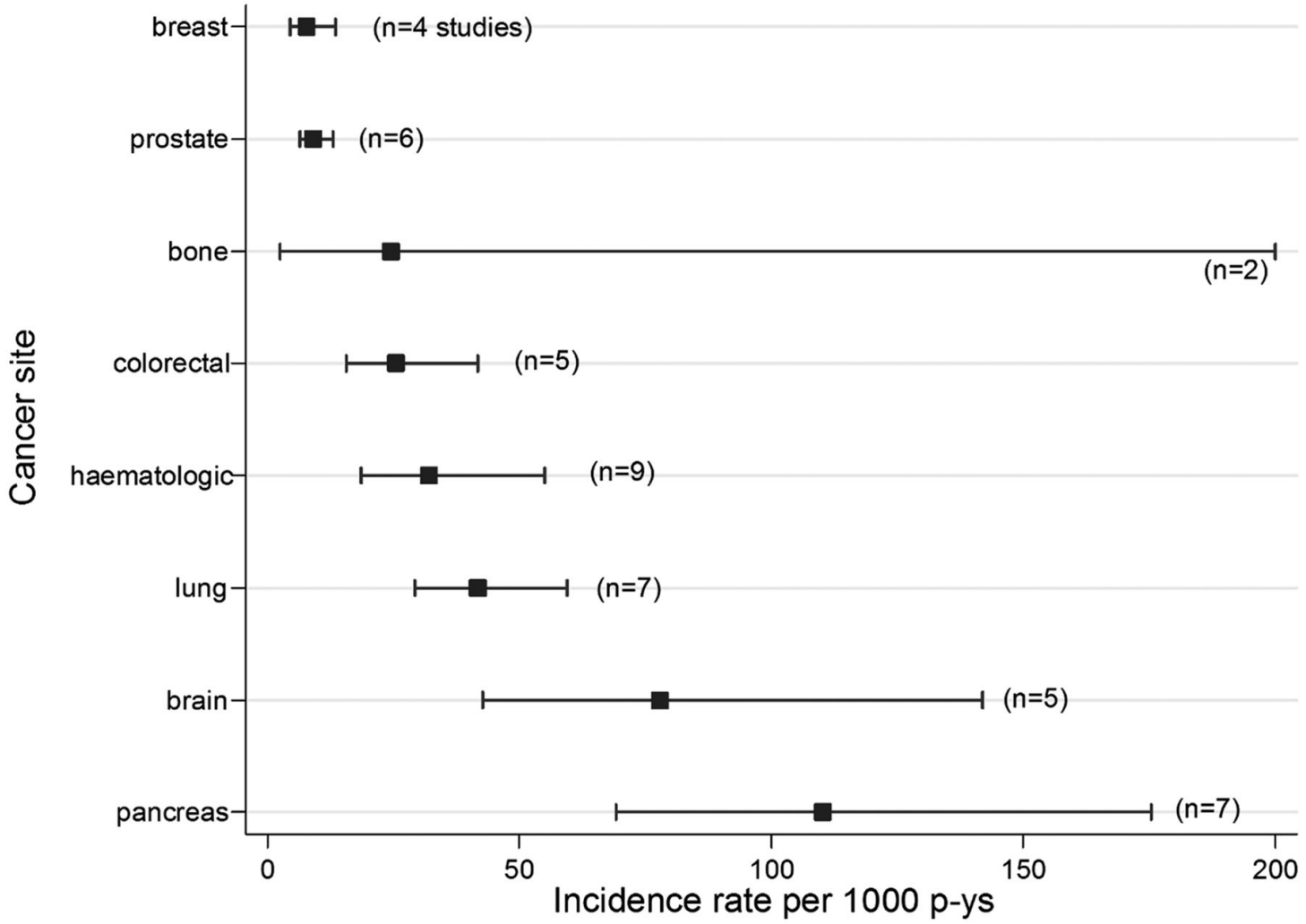
- Site
- Stage
- Aggressiveness
- Direct/mass effects of tumour
- Chemotherapy
- Central catheters
- Surgery
- Immobility

Absolute rates of venous thrombosis (per 1000 person-years) for individual calendar years between 1997 and 2006.



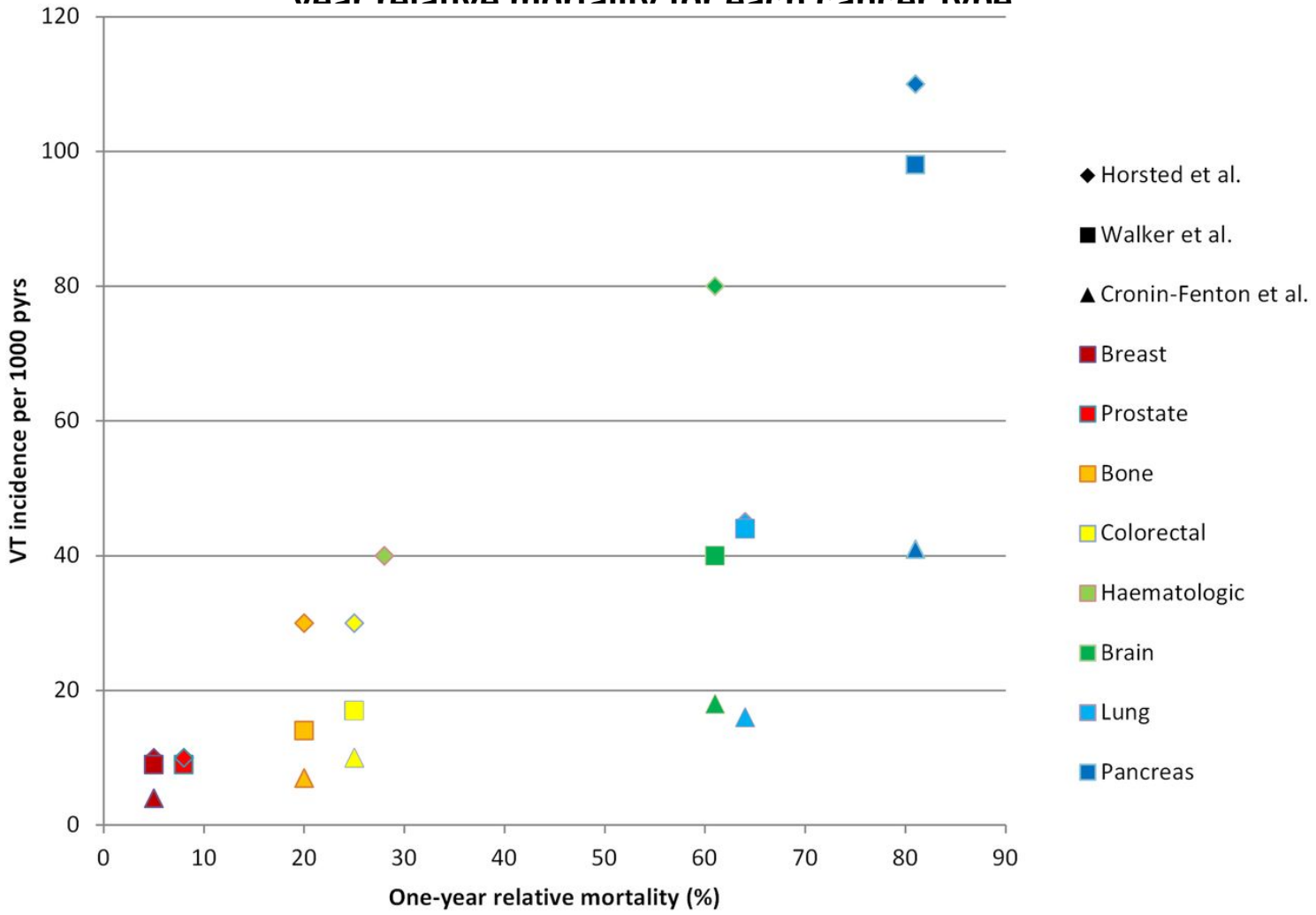
Jasmijn F. Timp et al. Blood 2013;122:1712-1723

Pooled incidence rates (per 1000 person-years) of venous thrombosis per type of cancer.



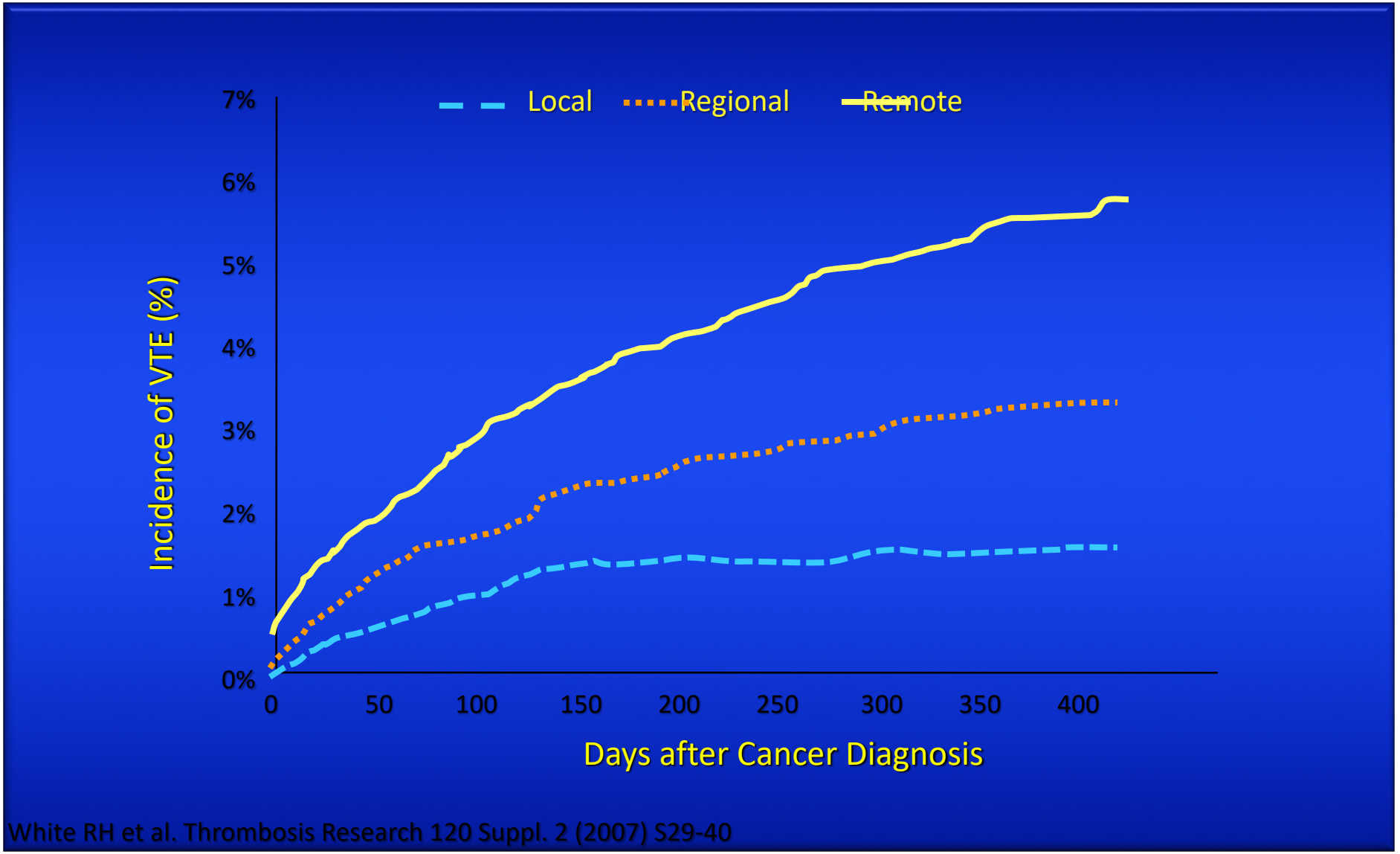
Jasmijn F. Timp et al. Blood 2013;122:1712-1723

Incidence rates of venous thrombosis (VT) (per 1000 person-years) per type of cancer (according to Horsted et al,17 Walker et al,13 and Cronin-Fenton et al11) plotted against the 1-year relative mortality for each cancer type



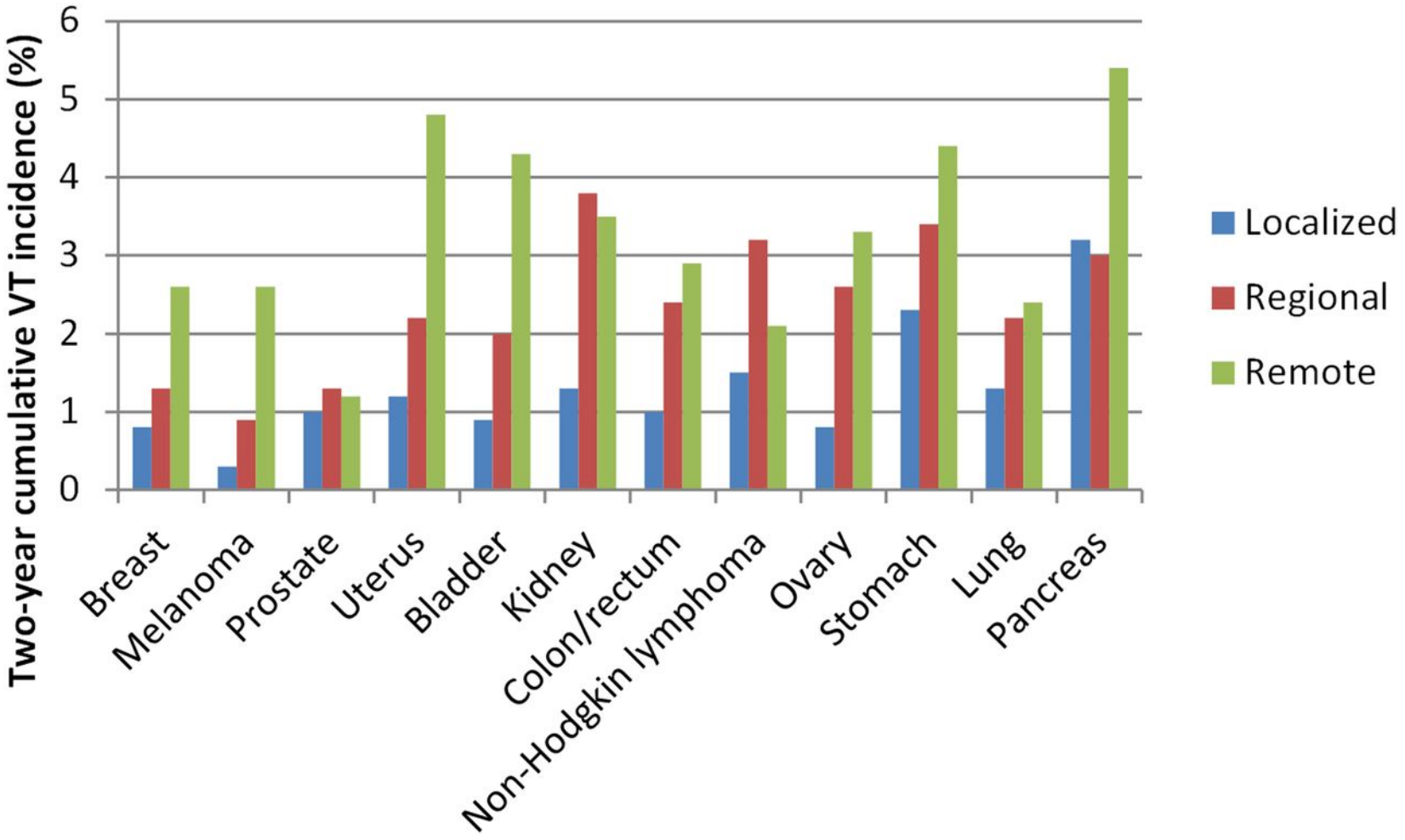
Jasmijn F. Timp et al. Blood 2013;122:1712-1723

Incidence of VTE and Colon Cancer Stage

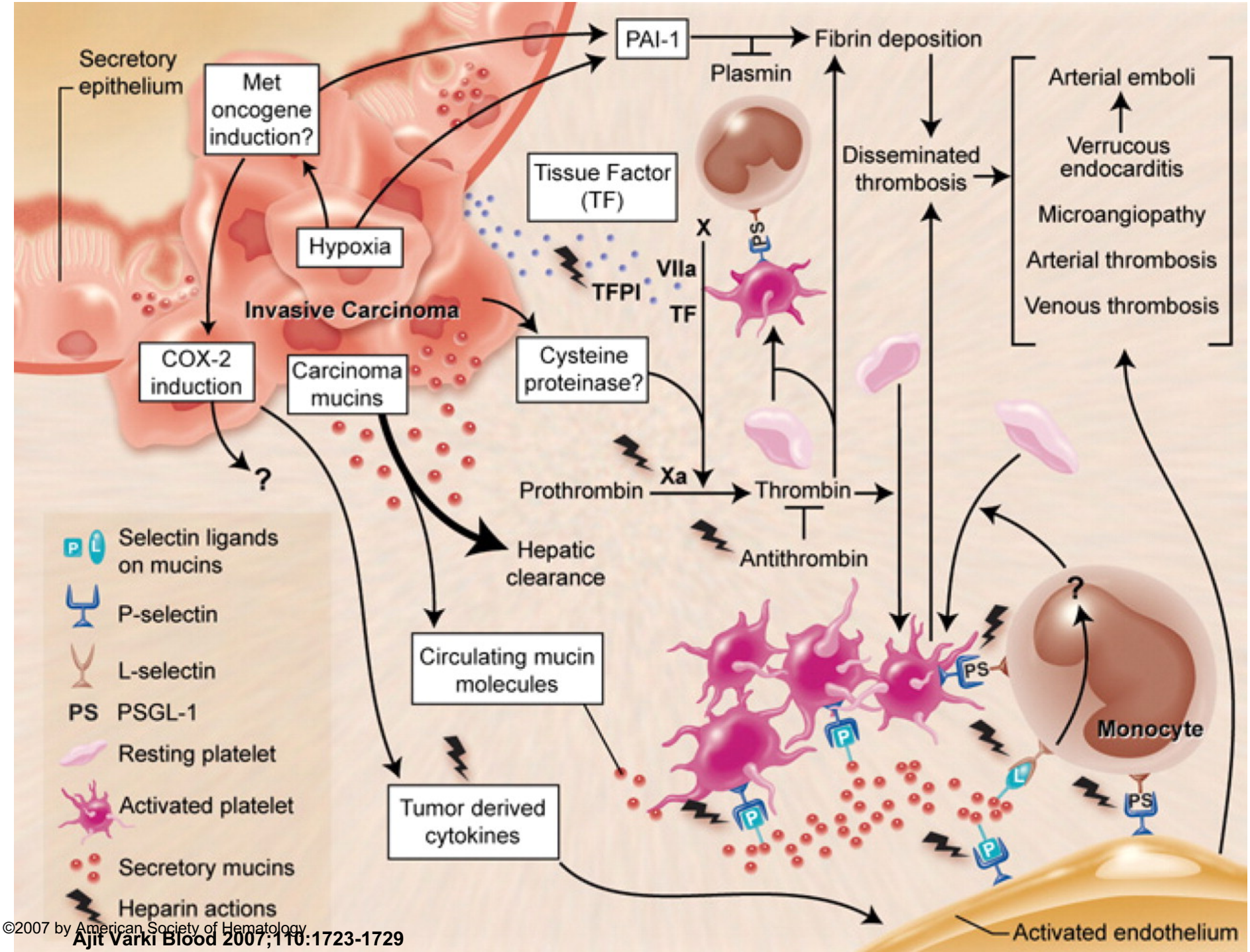


White RH et al. Thrombosis Research 120 Suppl. 2 (2007) S29-40

Two-year cumulative incidence (%) of venous thrombosis per type and stage of cancer.



Jasmijn F. Timp et al. Blood 2013;122:1712-1723



Ajit Varki Blood 2007;110:1723-1729

Thalidomide and Lenalidomide

- In myeloma increased thrombosis
- Rates 3% as single agent
- Up to 17% as combination treatment
- ?worse with anthracyclines

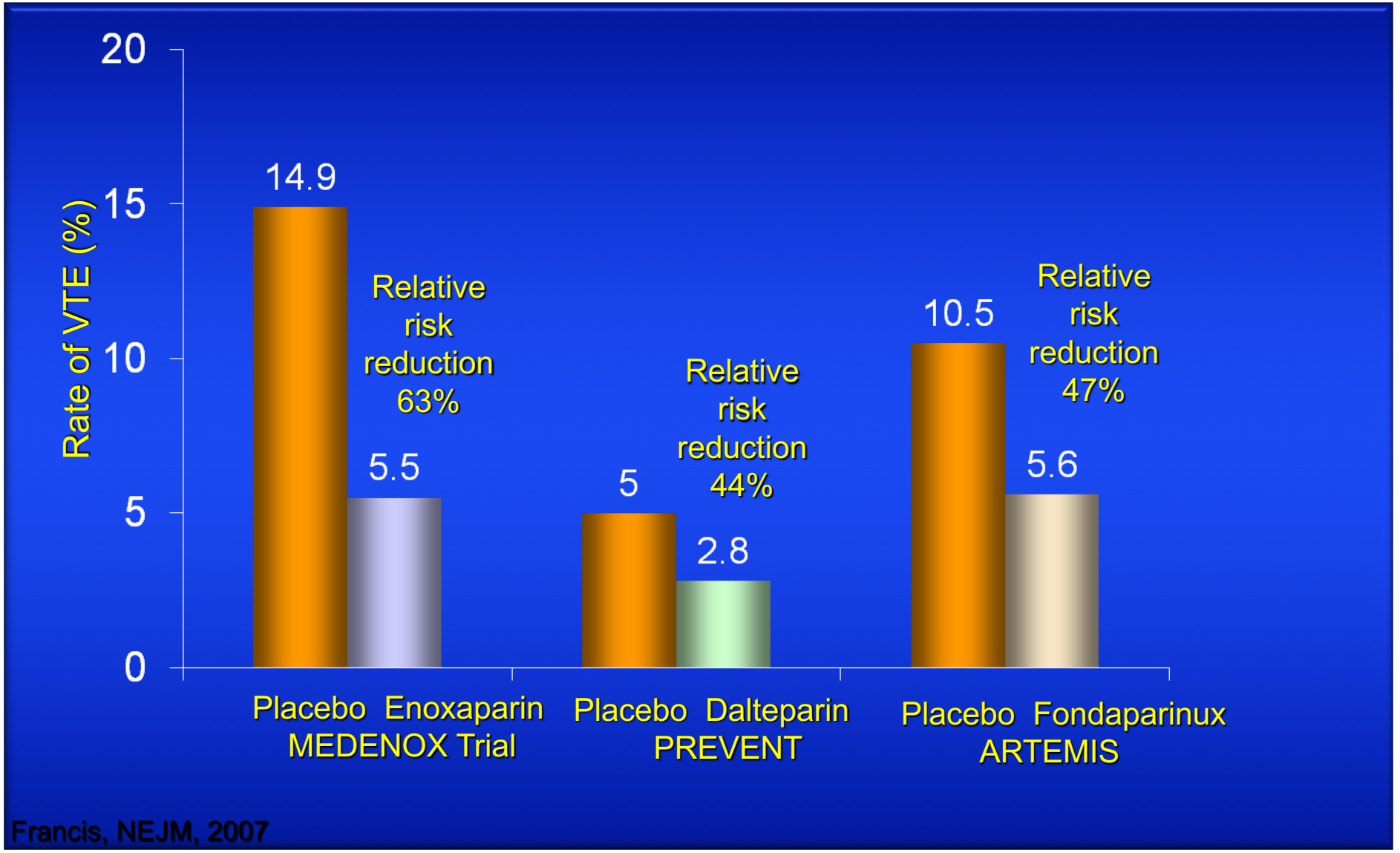
Thalidomide and Lenalidomide

- Increased tissue factor and vascular endothelial growth factor
- Downregulate thrombospondin causing cytokine-mediated, activated protein C resistance.
- Increase the levels von Willebrand factor and factor VIII.
- Regulates the level of the prothrombotic factor COX-2

Prevention

- Treatment of choice -LMWH
- Aspirin?
- Warfarin?

Prophylaxis Studies in Medical Patients



Francis, NEJM, 2007

Thromboprophylaxis

- For hospitalised medical or surgical patients
- No specific cancer patient trials for inpatients
- Not for outpatients unless assessed as high risk
- Cochrane review of 9 RCTs
- relative risk (RR) 0.66
- However, this analysis identified that 60 patients needed to be treated to prevent 1 episode of thrombosis
- Not for CV catheter patients- no proven benefit

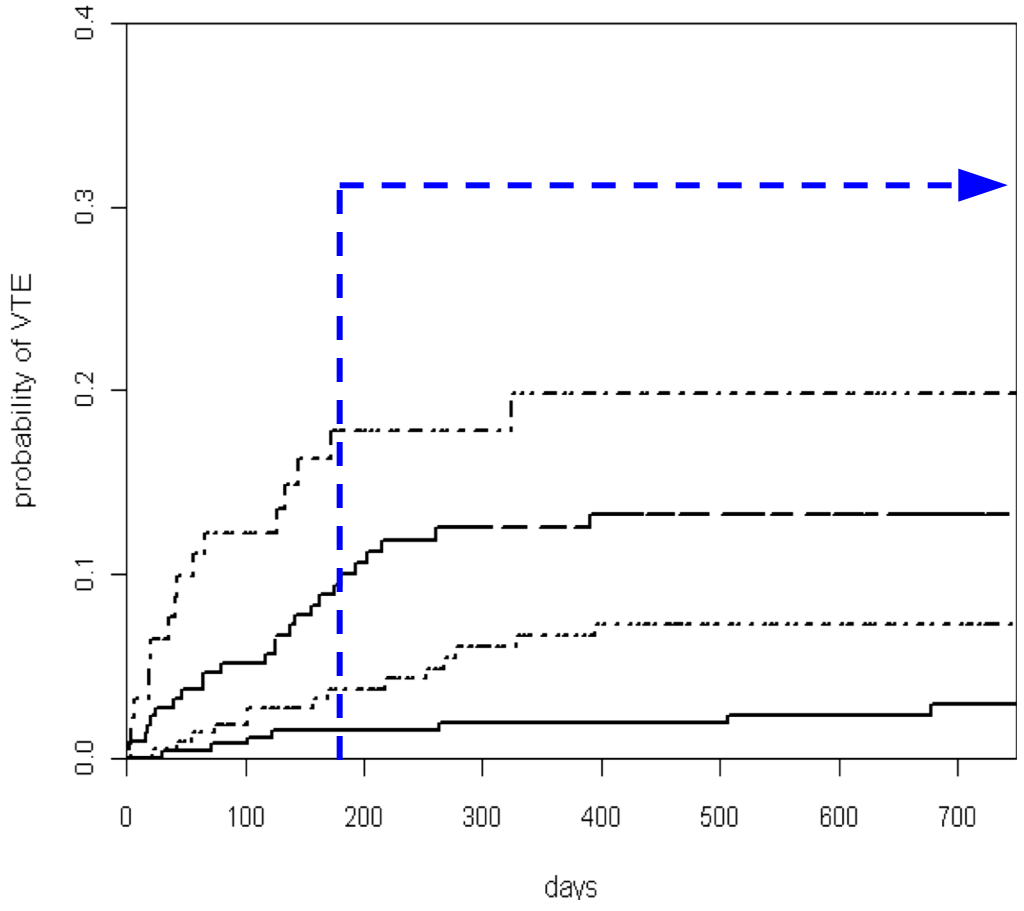
Khorana Model for Outpatients

Patient Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Pre-chemotherapy platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Prechemotherapy leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

Khorana et al. Blood 2008.

Khorana Model Validation

- Prospective follow up of 819 patients
- Median observation time/follow-up: 656 days



6-mo cumulative VTE rates:

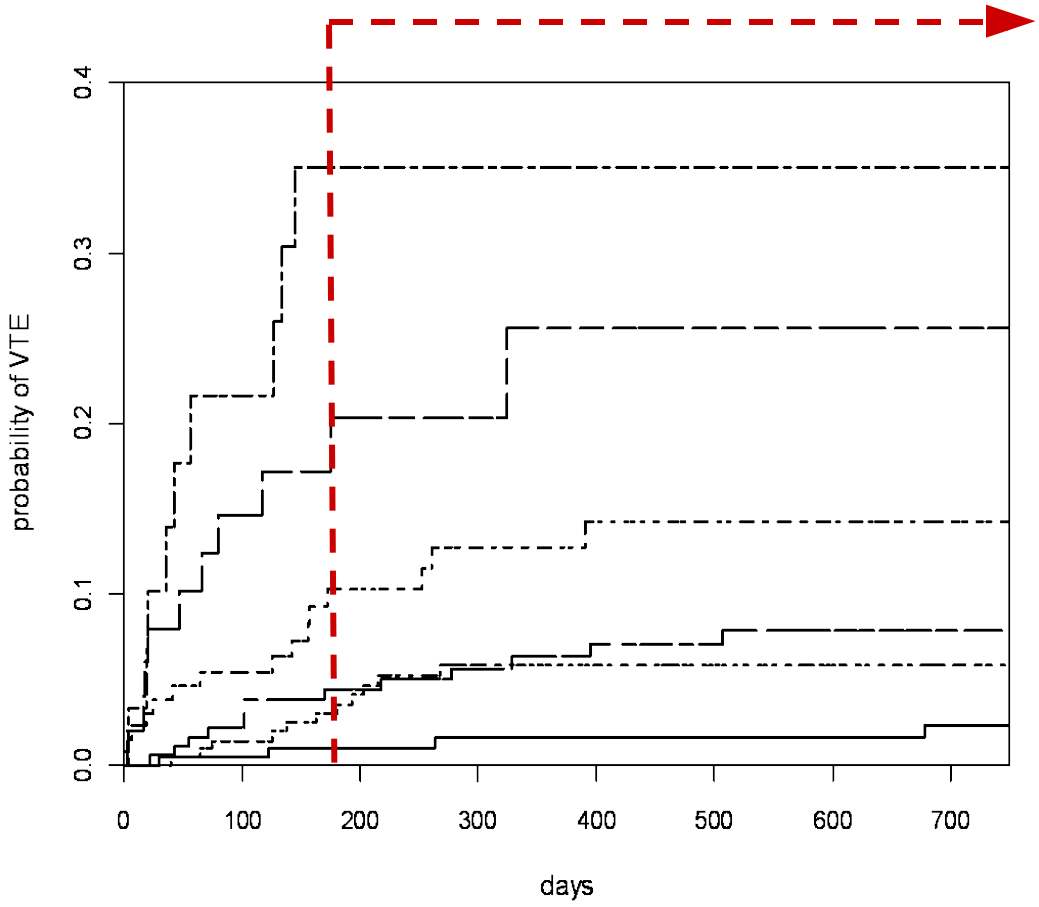
	Patients n	Events %
Score ≥3	93	17.7%
Score 2	221	9.6%
Score 1	229	3.8%
Score 0	276	1.5%

CANCERANDTHROMBOSISSTUDY

Ay et al Blood 2010.

Ay Model for Outpatients

- Addition of D-dimer and soluble P-selectin to Khorana model:



6-mo cumulative VTE rates:

	Patients, n	Events, %
Score ≥5	30	35%
Score 4	51	20.3%
Score 3	130	10.3%
Score 2	218	3.5%
Score 1	190	4.4%
Score 0	200	1.0%

CANCERANDTHROMBOSISSTUDY

Validation of score

- PROTECHT high risk patients were 11.1 % in the placebo arm and 4.5 %
- SAVE-ONCO, NNT was 25 for high-risk patients but 333 in low risk patients

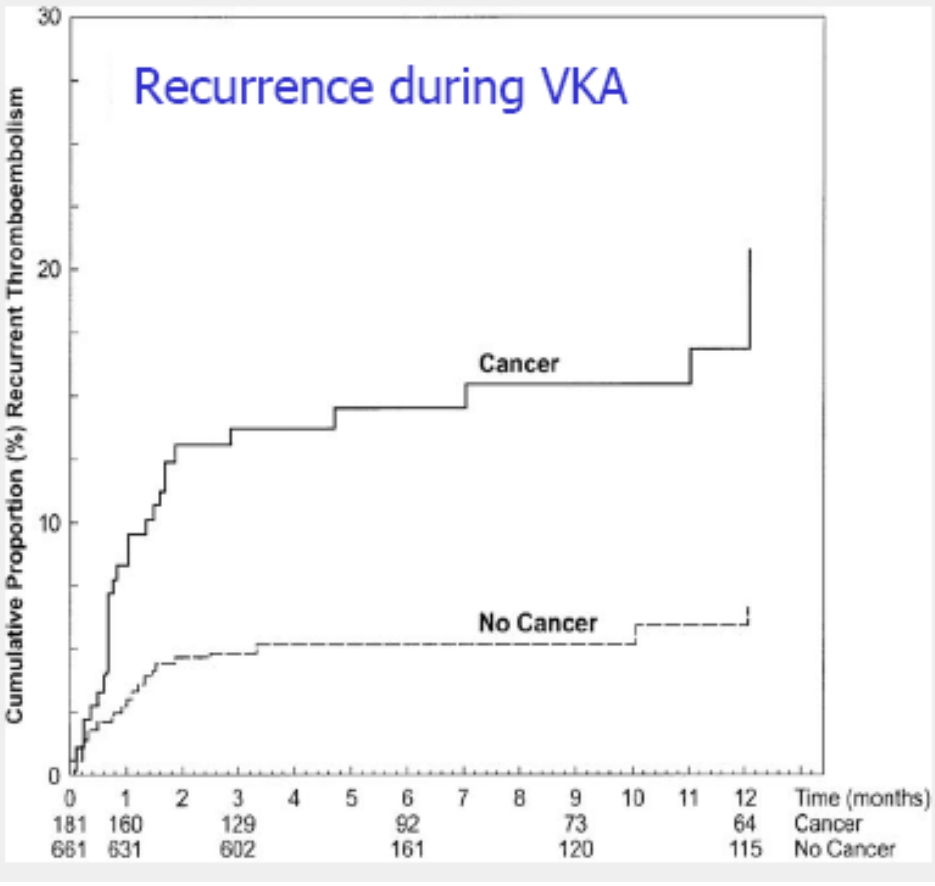
Treatment

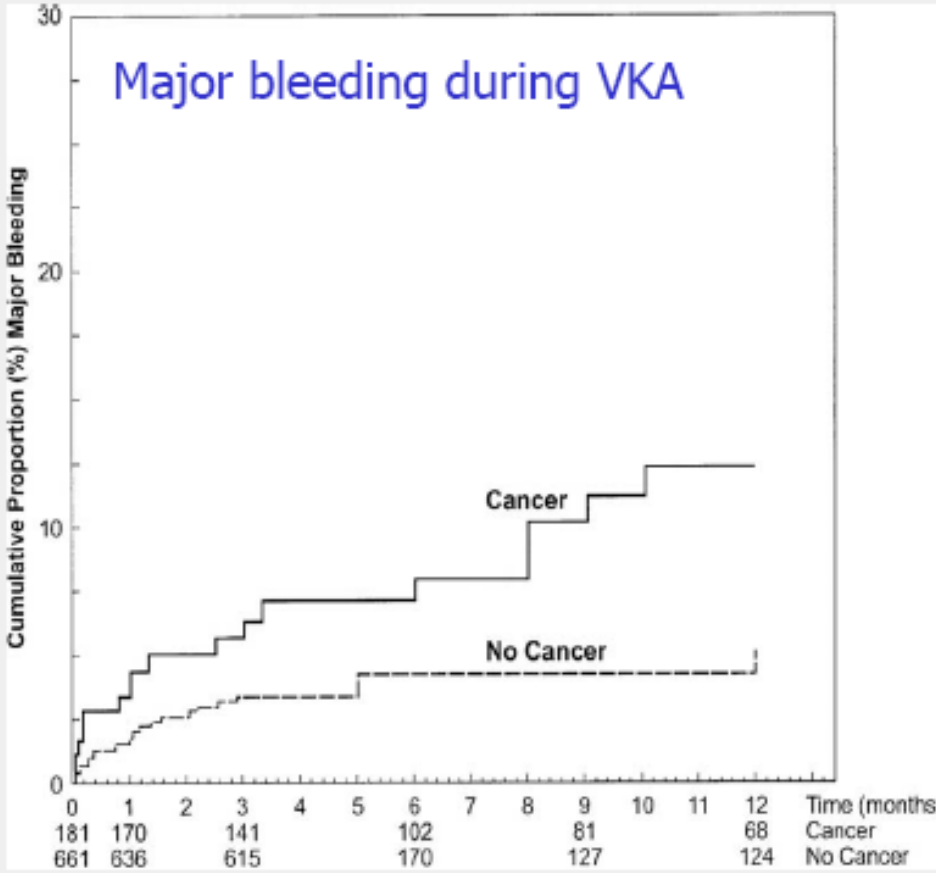
- American College of Chest Physicians (ACCP)
- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Network (NCCN)
- European Society for Medical Oncology (ESMO)
- International Clinical Practice Guidelines
- **Guidelines**Management and treatment of VTE* in cancer patients
- BSH

Warfarin

- Warfarin therapy is complicated by:
  - Difficulty maintaining tight therapeutic control, due to anorexia, vomiting, drug interactions, etc.
  - Frequent interruptions for thrombocytopenia and procedures
  - Difficulty in venous access for monitoring
  - Increased risk of both recurrence and bleeding

Warfarin


Recurrence during VKA
Cumulative Proportion (%) Recurrent Thromboembolism
30
20
10
0
Cancer
No Cancer
0 1 2 3 4 5 6 7 8 9 10 11 12 Time (months)
181 160 129 92 73 64 Cancer
661 631 602 161 120 115 No Cancer


Major bleeding during VKA
Cumulative Proportion (%) Major Bleeding
30
20
10
0
Cancer
No Cancer
0 1 2 3 4 5 6 7 8 9 10 11 12 Time (months
181 170 141 102 81 68 Cancer
661 636 615 170 127 124 No Cancer

Treatment of Cancer-Associated VTE-LMWH

Study	Design	Length of Therapy (Months)	N	Recurrent VTE (%)		Major Bleeding (%)		Death (%)	
CLOT Trial (Lee 2003)	Dalteparin OAC	6	336 336	9 17	0.002	6 4	NS	39 41	NS
CANTHENOX (Meyer 2002)	Enoxaparin OAC	3	67 71	11 21	0.09	7 16	0.09	11 23	0.03
LITE (Hull ISTH 2003)	Tinzaparin OAC	3	80 87	6 11	0.03	6 8	NS	23 22	NS
ONCENOX (Deitcher ISTH 2003)	Enox (Low) Enox (High) OAC	6	32 36 34	3.4 3.1 6.7	NS		NS		NR

LMWH

- In recurrence 90% response to increasing LMWH dose by 25-50%
- LMWH dose reduction is effective in patients with thrombocytopenia ($< 50 \times 10^9/L$)
  - consider platelet transfusion if VTE is acute
  - reduce dose to 50% if count $20 – 50 \times 10^9/L$
  - prophylactic or withhold dose if count $<20 \times 10^9/L$

IVC filters

- Not recommended in initial treatment of DVT or PE
- Routine insertion of filters in patients who are also anticoagulated does not alter the frequency of recurrent VTE or total mortality
- Venous thrombosis at the site of filter insertion sites is common- 10%
- If anticoagulant therapy contra-indicated, insert temporary filter and anticoagulate when contra-indication over

IVC filters

- Recurrence- Should only be considered after increasing the target INR/LMWH in recurrence on anti-coagulation
- Can be considered if surgery required within a month of VTE

BRIDGE study

- AF Bridging v no bridging with LMWH in surgery
- No increase in thrombosis in those not given LMWH
- Increase in bleeding 3.2 v 1.3%

What about the reverse?

- Should we be looking for cancer in those with VTE?
- Evidence is weak, guidance varies
- NICE says to consider an abdo pelvis CT and mammography
- No trials have shown a mortality benefit
- Simple lab tests CXR and clinical examination may be as good as more extensive investigations
- Expense, radiation, anxiety, low yield and unnecessary investigations should be considered

NOACS/OACS/DOACS

Novel/Direct/non Vitamin K oral anticoagulants

Current licensed drugs

- Direct thrombin inhibitors
- Dabigatran
- Xa inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

Current position

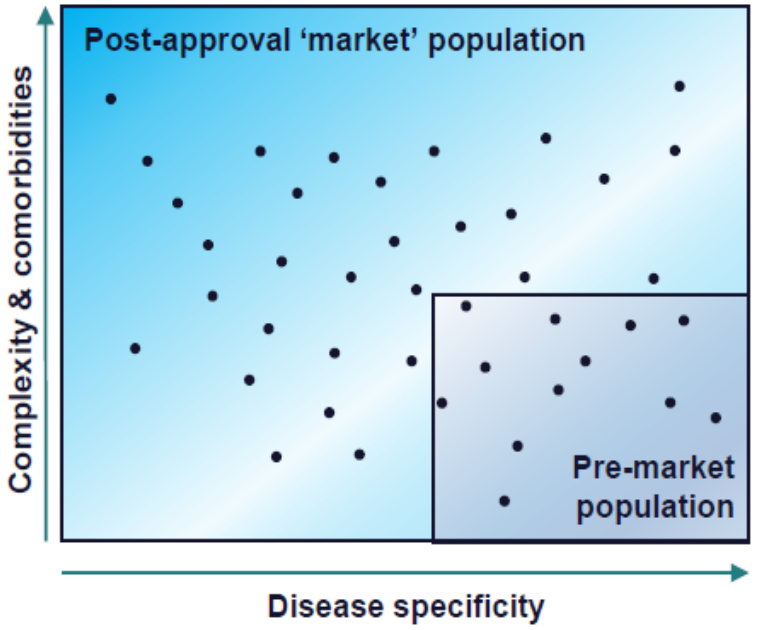
- Apixaban Dabigatran and Rivaroxaban licensed for THR and TKR, AF and VTE
- Edoxaban AF and VTE
- Rivaroxaban-licence for ACS reduction in stent thrombosis and cardiovascular death
- Apixaban failed to show benefit in ACS or medical admissions

DVT

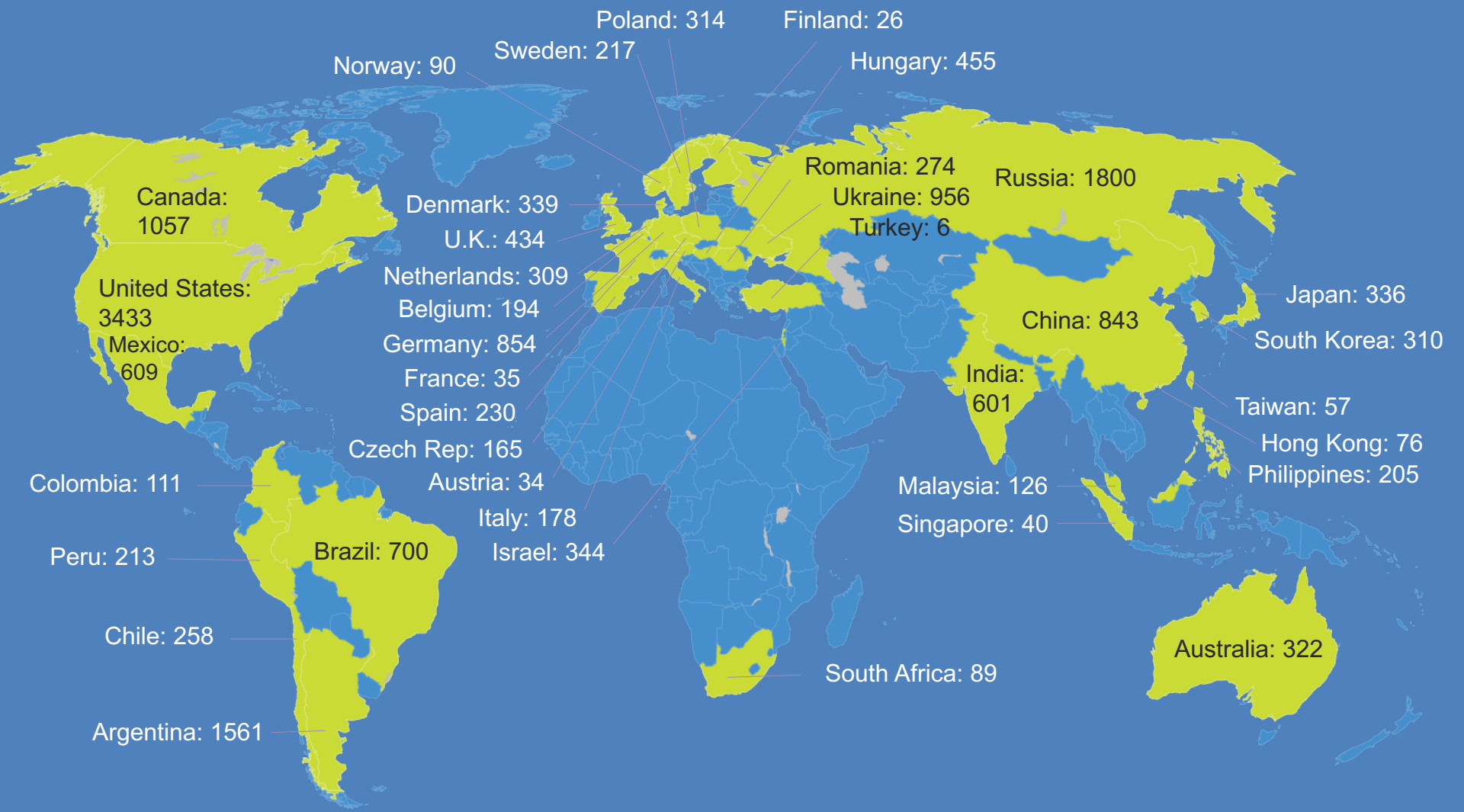
- Warfarin v NOAC
- Numbers comparible. Possibly slightly less bleeding

Challenges today:
Targeting innovative therapies at appropriate patients

- Patient populations vary greatly within disease groups, and this diversity is not always reflected in controlled clinical trials
- Innovative therapies should be assessed in representative sub-groups before implementation in diverse populations
- Understanding and targeting patients at greatest risk is necessary to reduce overall burden of disease most efficiently



Enrollment
18,201 patients, 1034 sites, 39 countries



Precautions

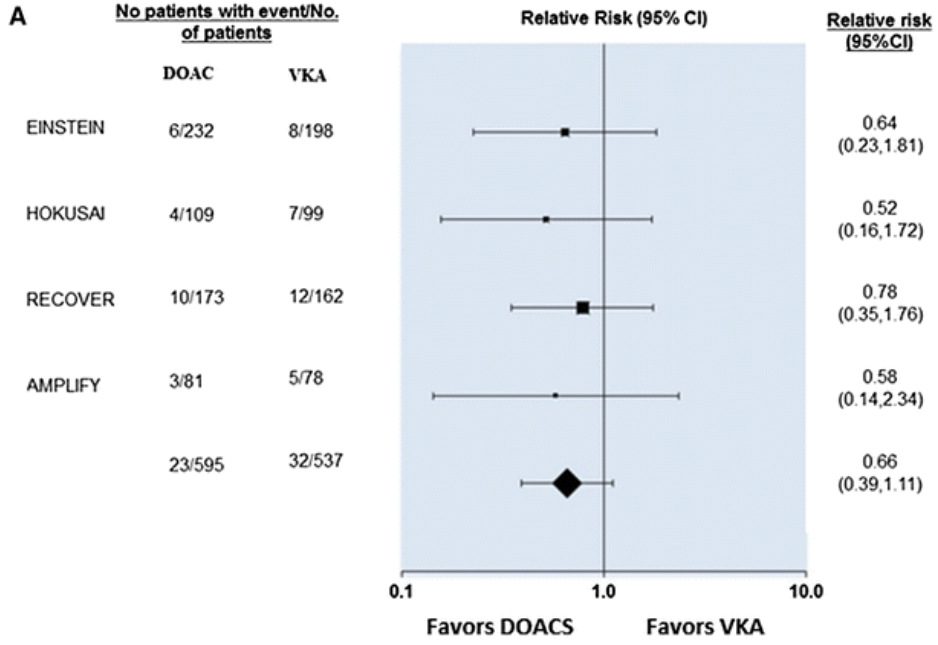
- Renal impairment CC<30ml/min
- Limited data on subgroups eg anti-phospholipids
- Not licensed for heart valves
- Apixaban, Rivaroxaban study didn’t show to LMWH equivalence in medical patients

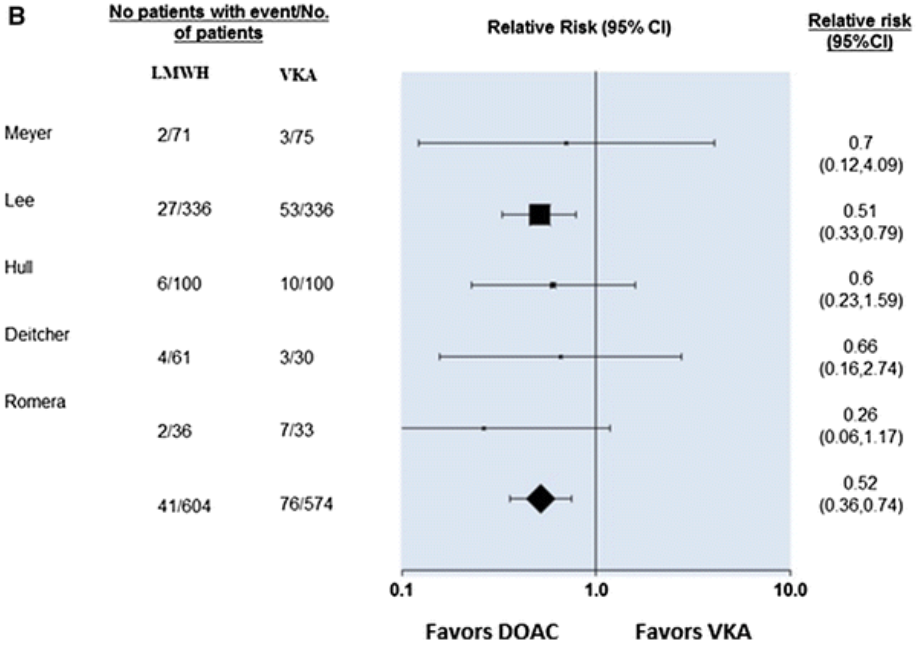
Reversal

- Relatively short half lives
- Only dabigatran has a specific reversal agent
- Idarucizumab
- For surgery, consult SPCs, consider renal function

In cancer

- Apixaban appears safe for primary prophylaxis in a phase 2 study- Not clear how this could be taken forward as no standard therapy for this group
- Phase 3 trial with apixaban- oral presentation, but not yet published

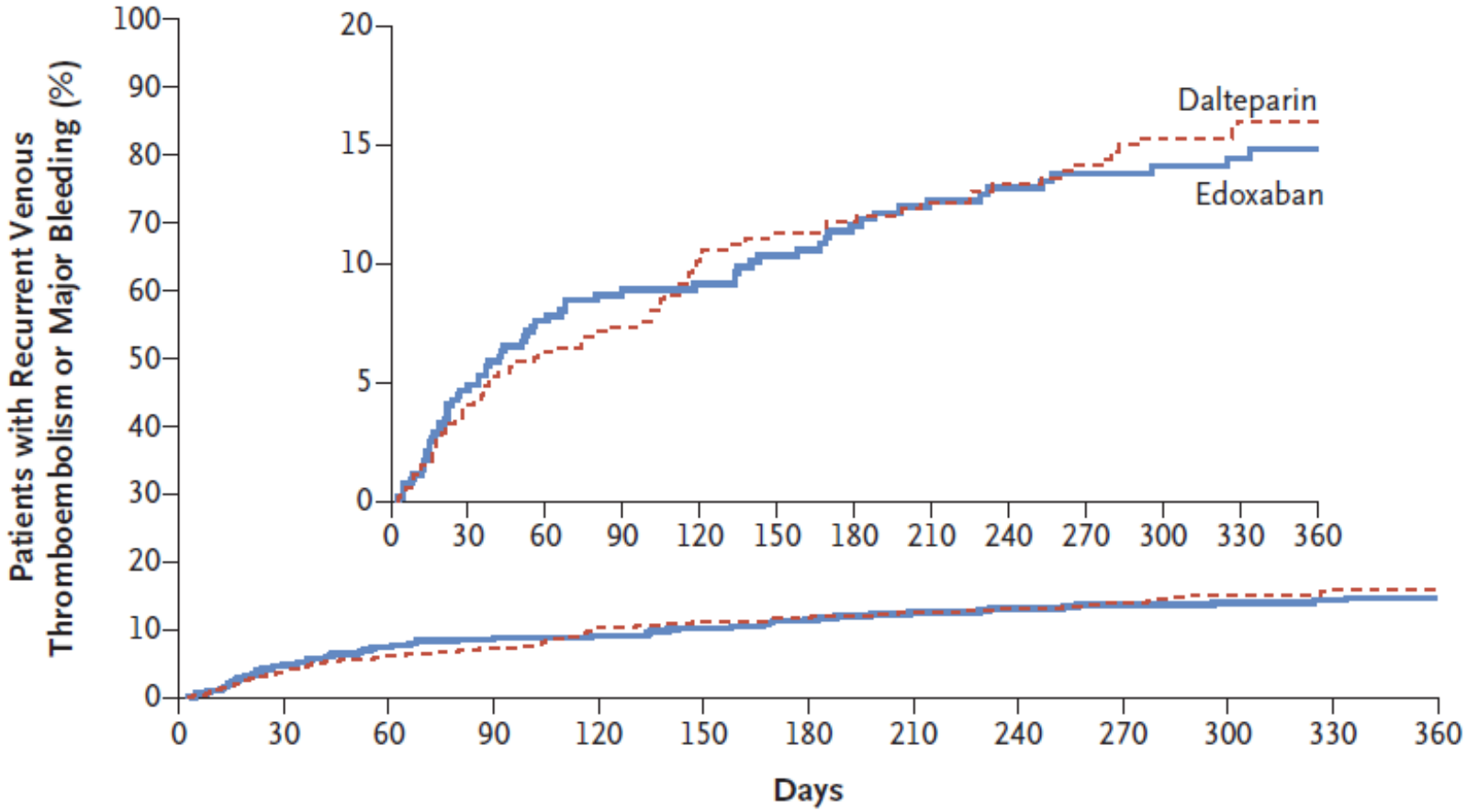

A
No patients with event/No. of patients
DOAC
VKA
Relative Risk (95% CI)
Relative risk (95%CI)
EINSTEIN
6/232
8/198
0.64 (0.23,1.81)
HOKUSAI
4/109
7/99
0.52 (0.16,1.72)
RECOVER
10/173
12/162
0.78 (0.35,1.76)
AMPLIFY
3/81
5/78
0.58 (0.14,2.34)
23/595
32/537
0.66 (0.39,1.11)
0.1
1.0
10.0
Favors DOACS
Favors VKA

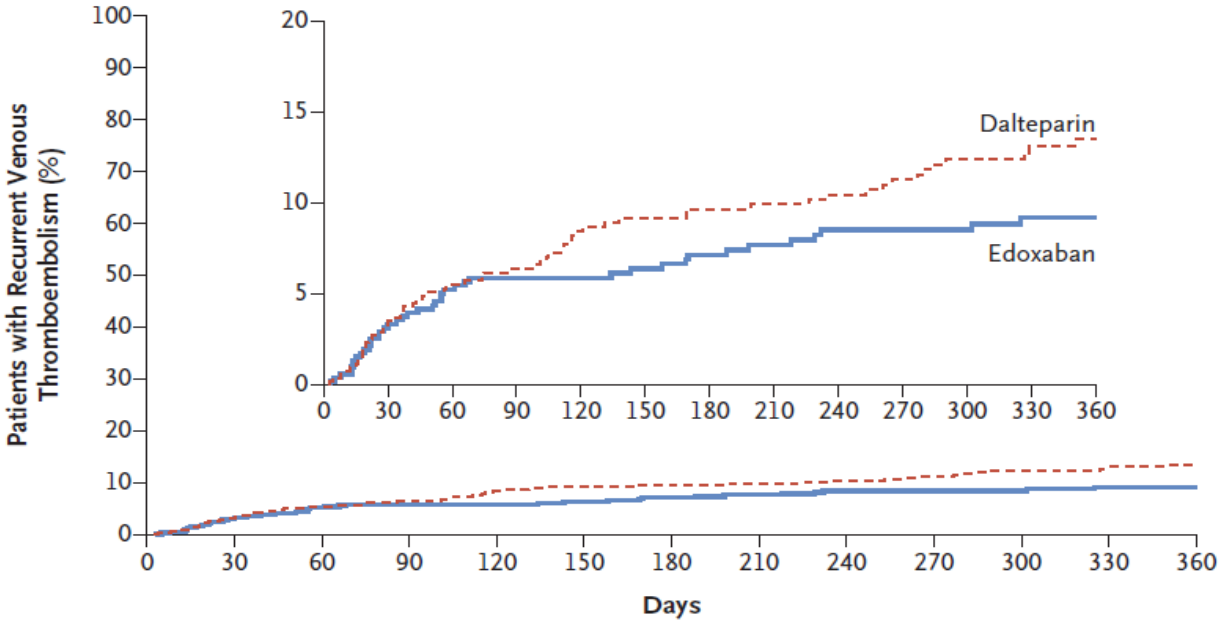

B
No patients with event/No. of patients
LMWH
VKA
Relative Risk (95% CI)
Relative risk (95%CI)
Meyer
2/71
3/75
0.7 (0.12,4.09)
Lee
27/336
53/336
0.51 (0.33,0.79)
Hull
6/100
10/100
0.6 (0.23,1.59)
Deitcher
4/61
3/30
0.66 (0.16,2.74)
Romera
2/36
7/33
0.26 (0.06,1.17)
41/604
76/574
0.52 (0.36,0.74)
0.1
1.0
10.0
Favors DOAC
Favors VKA

Meta-analysis of subgroups v VKA with cancer

- Trend towards less bleeding
- Similar recurrence rates
- BUT, not compared with standard of care in UK LMWH

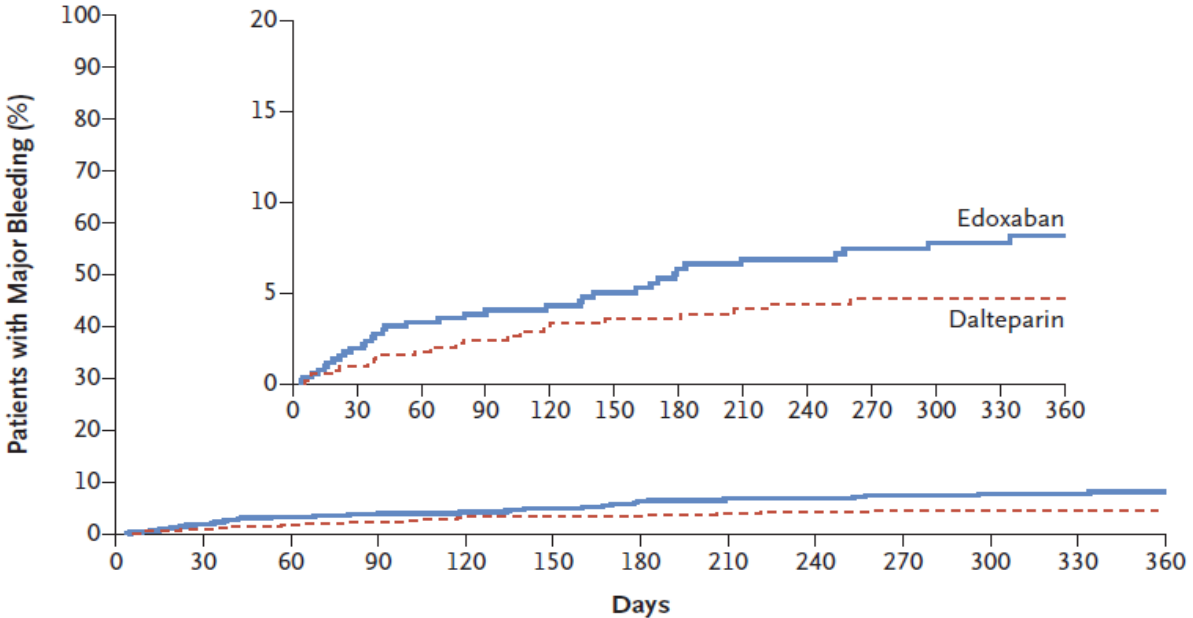
Edoxaban


Patients with Recurrent Venous Thromboembolism or Major Bleeding (%)
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
210
240
270
300
330
360
Days
20
15
10
5
0
Dalteparin
Edoxaban



o. at Risk

doxaban	522	480	437	415	395	370	356	340	320	307	281	245	168
alteparin	524	488	452	423	389	370	358	348	333	321	282	246	174



Current position with NOACS

- Not standard of care
- Could be considered where LMWH not appropriate
- Consider renal function and absorption
- Increased GI bleeding in trials, but decreased CNS bleeding
- Potential interaction with various chemo/drugs
- No routine monitoring of levels
- Further significant trials unlikely in view of going off patent 2019-20

Patients with AF and cancer

Both are common!

CH A_2DS_2 VASC

- Heart failure/LV dysfunction
- Hypertension
- Age >65 1 >75 2
- Diabetes
- Stroke/TIA/thromboembolism 2
- Vascular disease
- Female

Risk of stroke

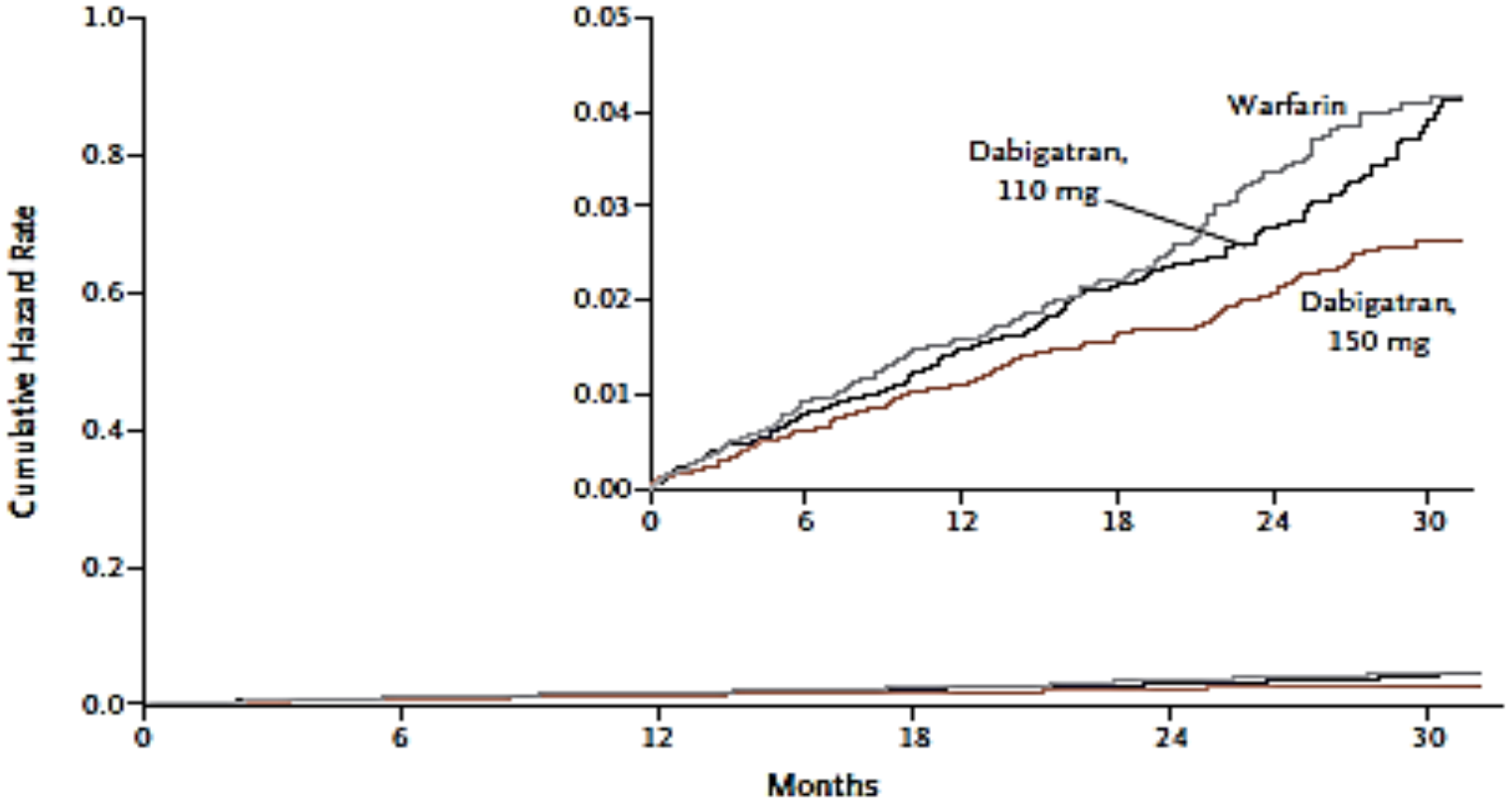
Score	% / yr
0	0
1	1.2
2	2.2
3	3.2
4	4
5	6.7
6	9.8

HAS-BLED score

Table 2. Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

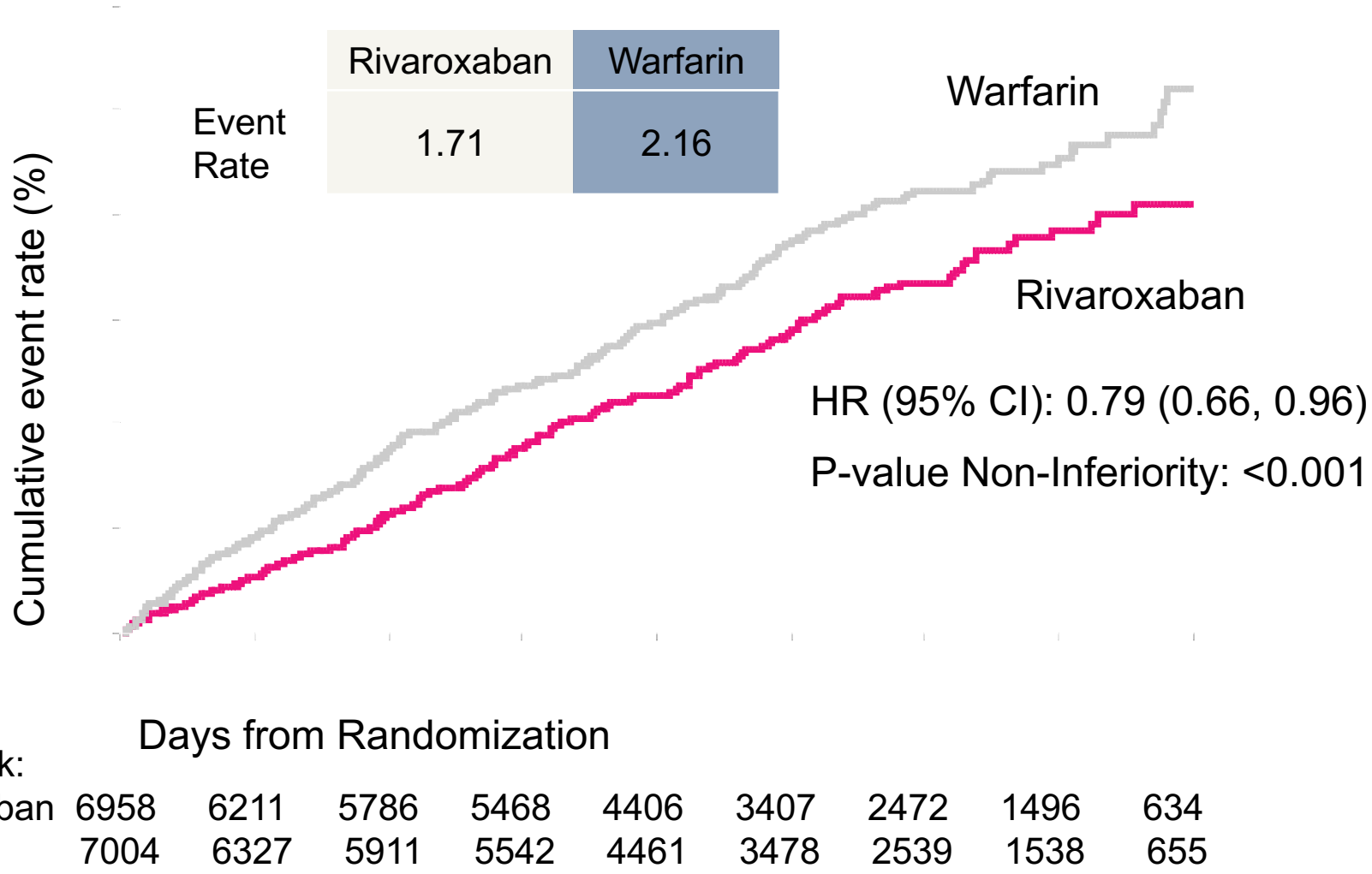
Dabigatran



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Rivaroxaban



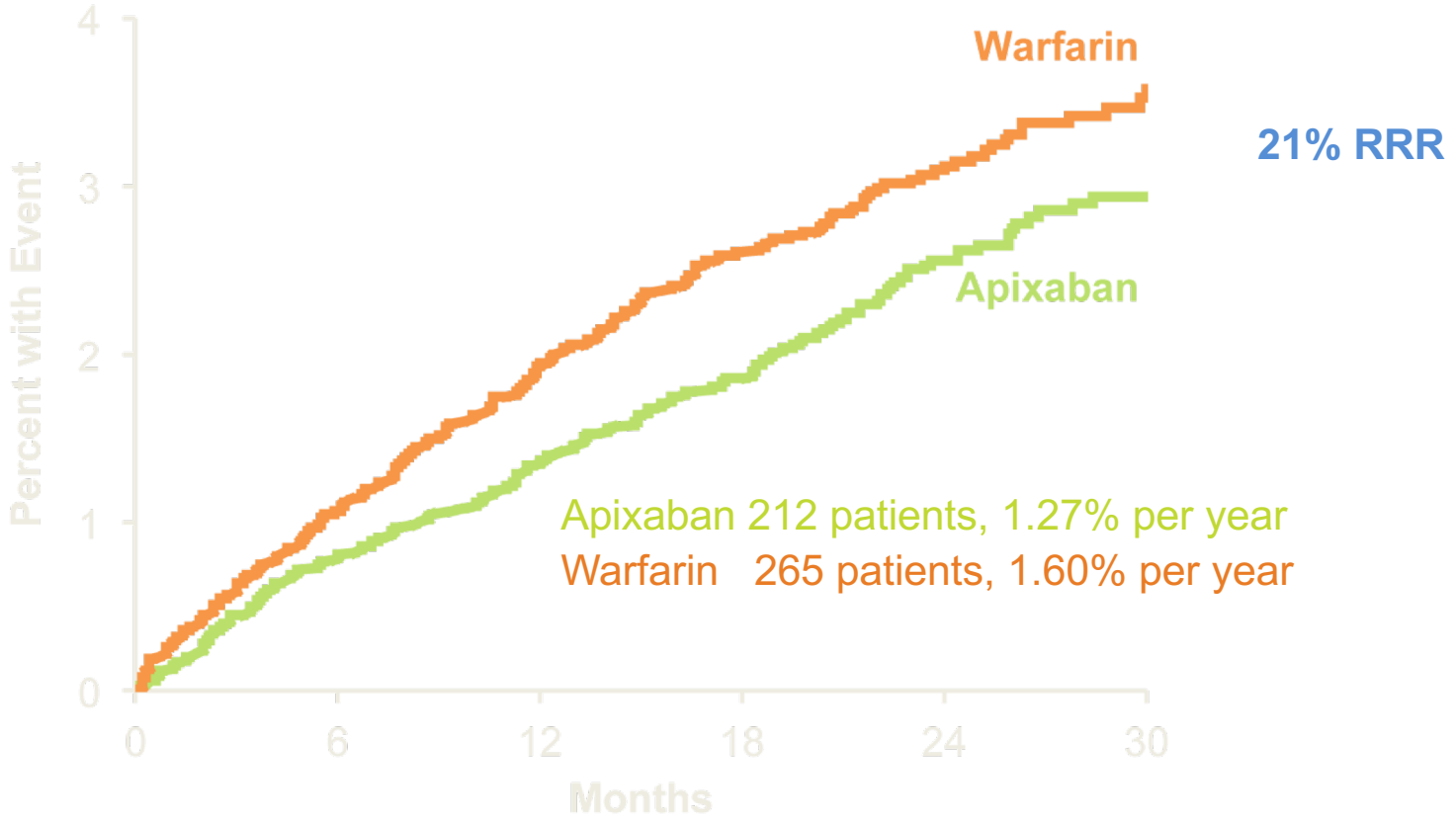
No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Apixaban

Stroke (ischemic or hemorrhagic) or systemic embolism



Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Thoughts?

- Individualised decisions
- Consider thrombosis risk, bleeding risk and overall prognosis
- Less evidence for LMWH
- ? Effect on cancer and risk of embolus

Thrombosis in Cancer

- VTE is a very common complication that increase morbidity and mortality in cancer patients
- Should we be using a risk model to estimate risk of VTE in ambulatory patients with new or progressive disease?
- Selected cancer patients benefit from extended prophylaxis after surgery
- Prophylaxis in hospitalized patients is a patient safety priority
- LMWH is the “best” agent available for prevention and treatment