Cancer-associated thrombosis

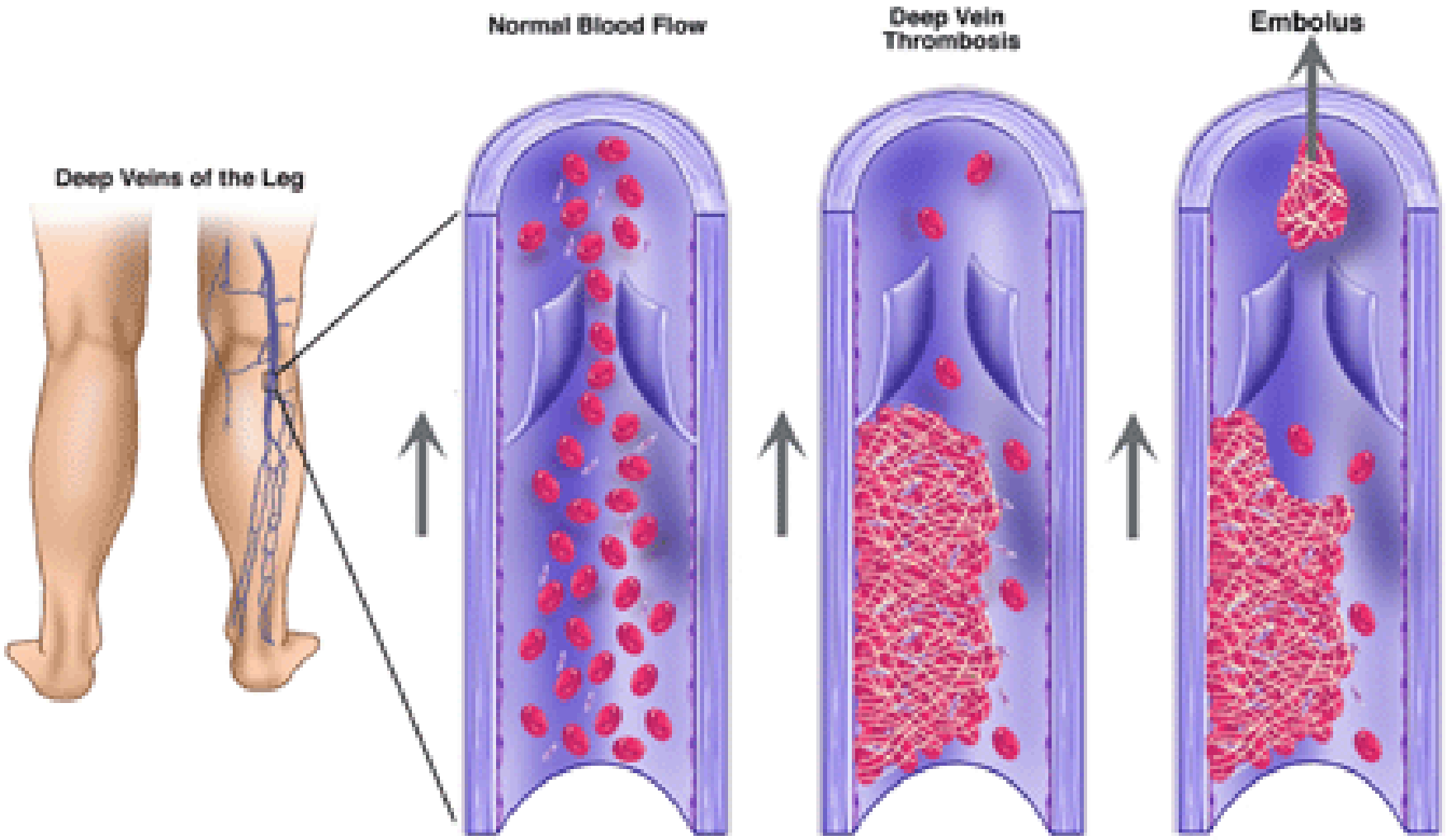
17th November 2016

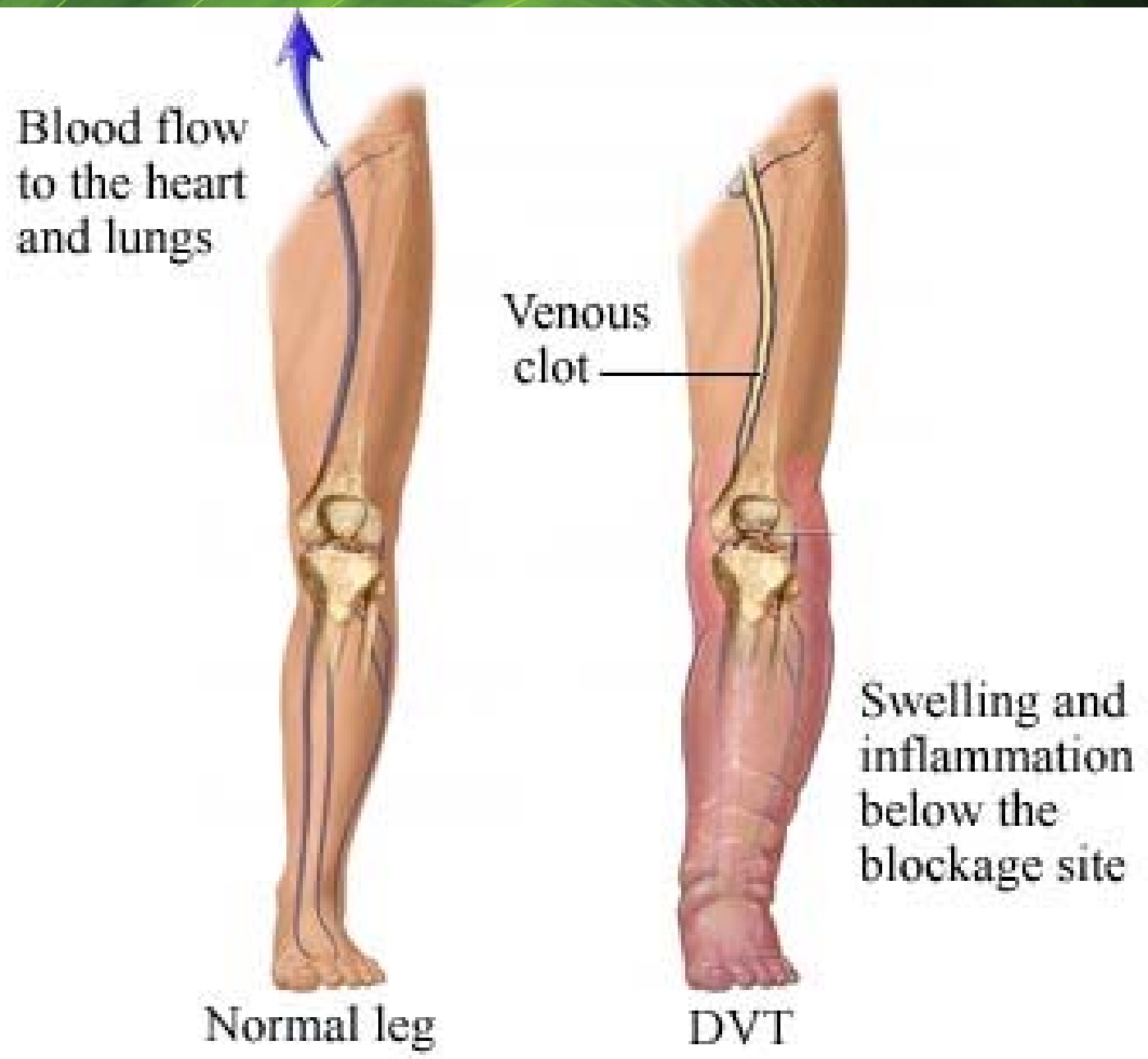
Simon Noble
Clinical Professor Palliative Medicine
Cardiff University
Wales, UK

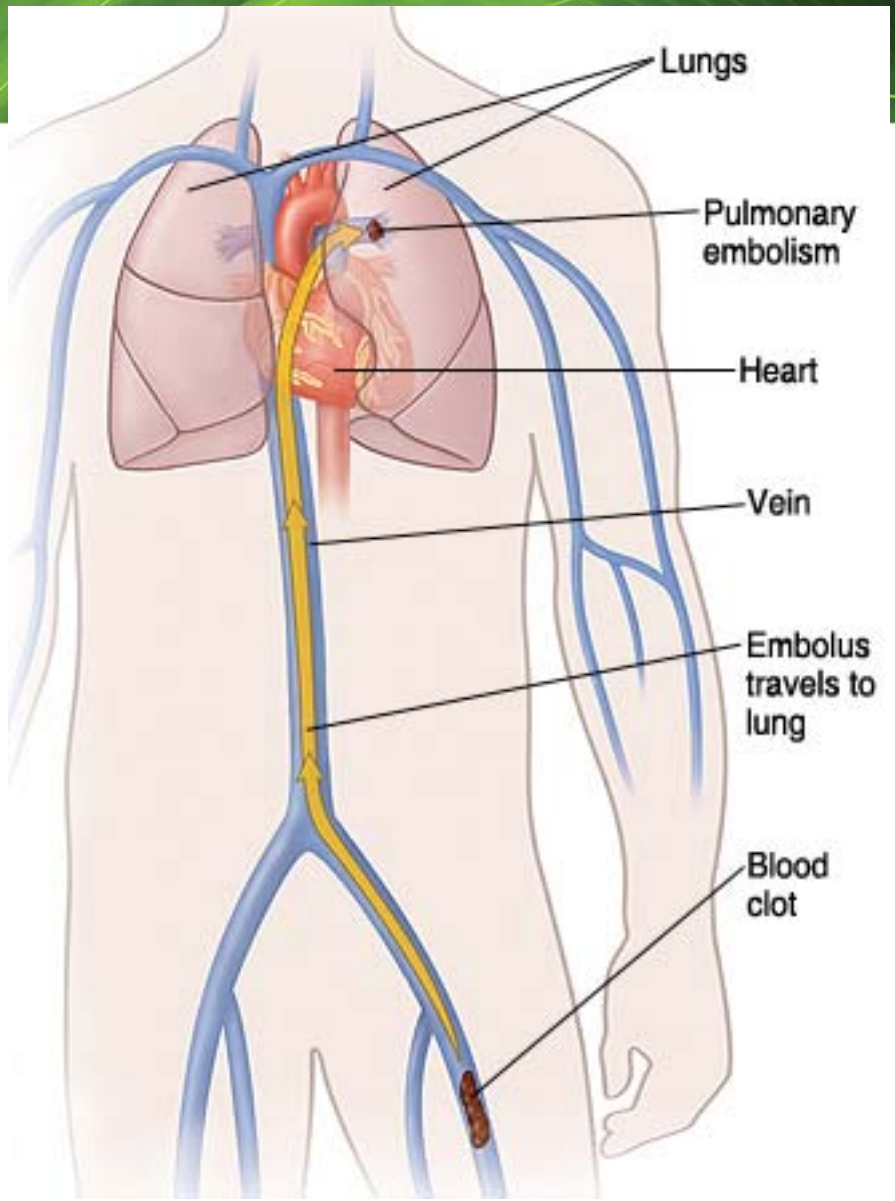
Today

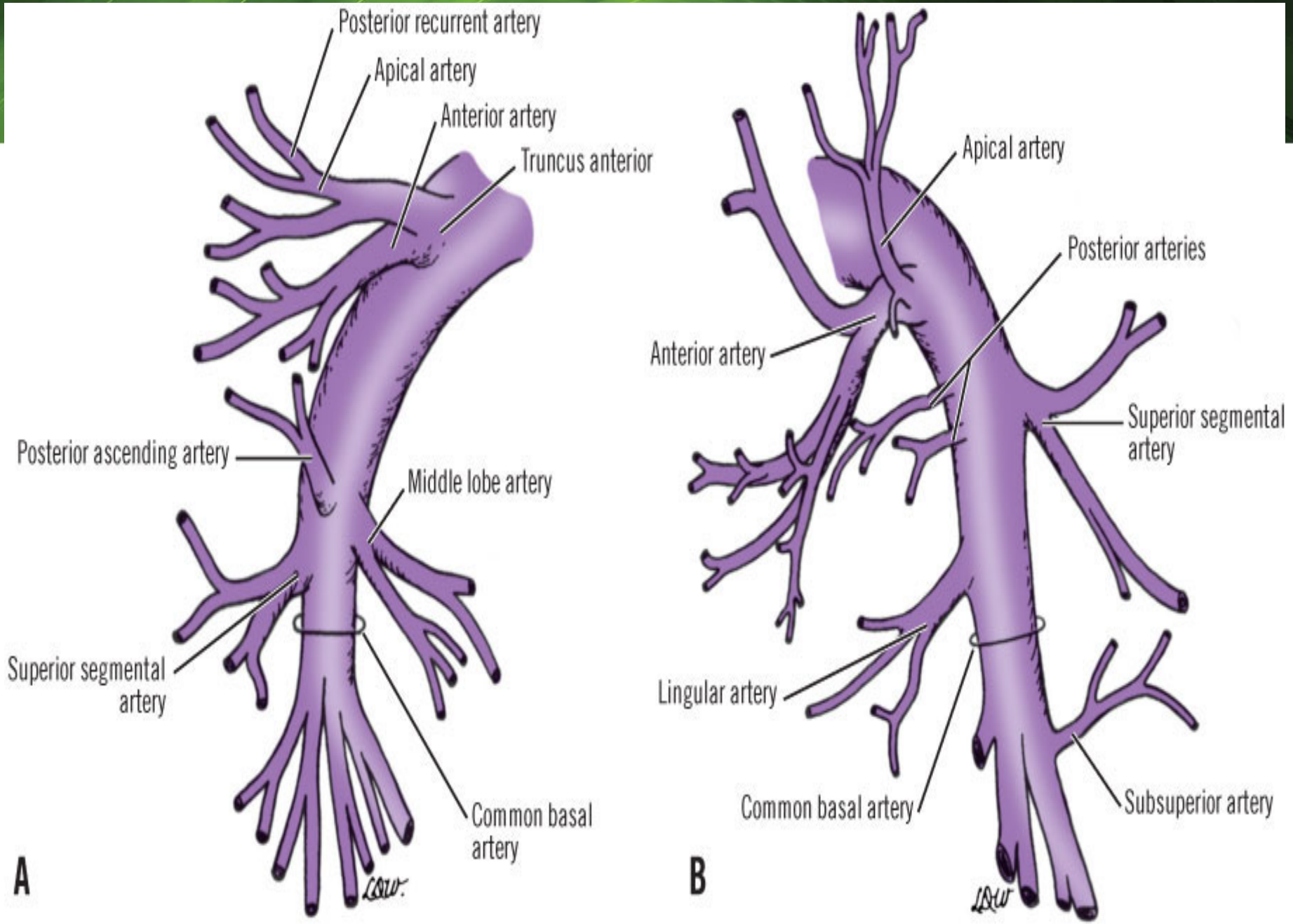
- What is VTE?
- How does CAT differ?
- Initial anticoagulation
- Anticoagulation at 6 months
- New oral agents and cancer
- Patient involvement in decision making

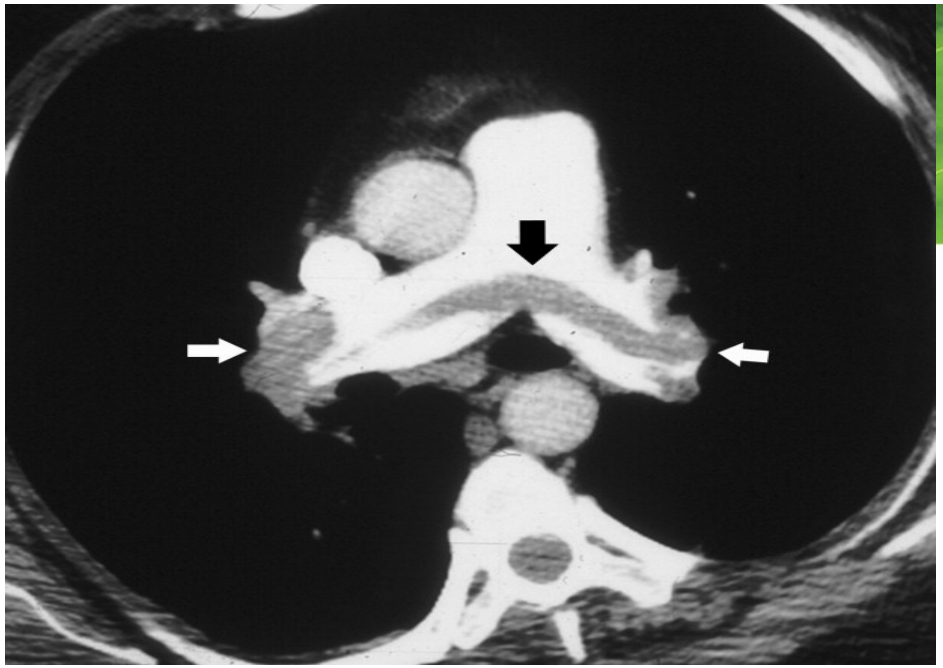
Deep Vein Thrombosis (DVT)



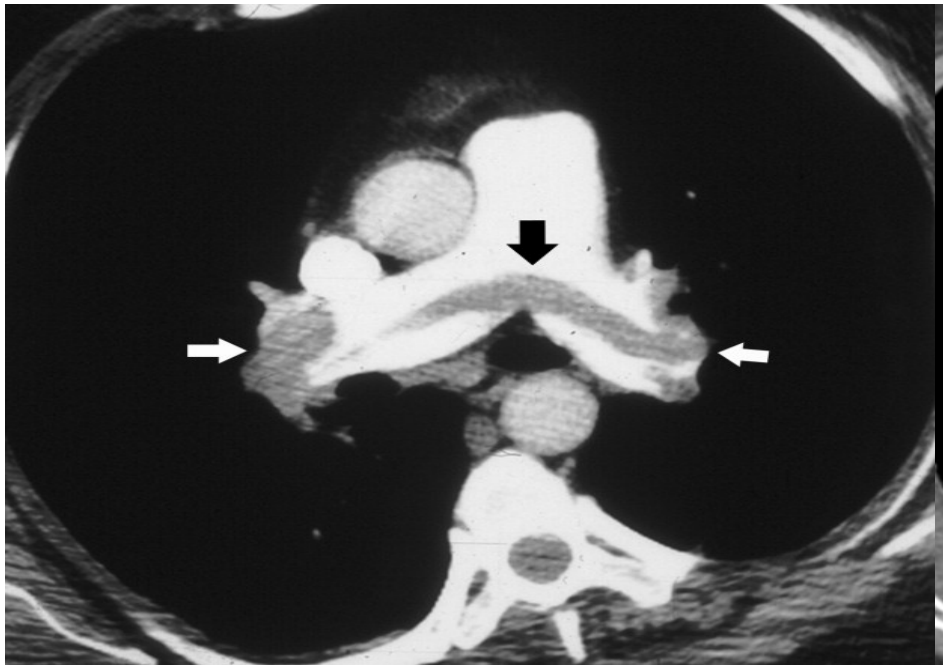

Blood flow to the heart and lungs
Venous clot
Swelling and inflammation below the blockage site
Normal leg
DVT


Lungs
Pulmonary embolism
Heart
Vein
Embolus travels to lung
Blood clot

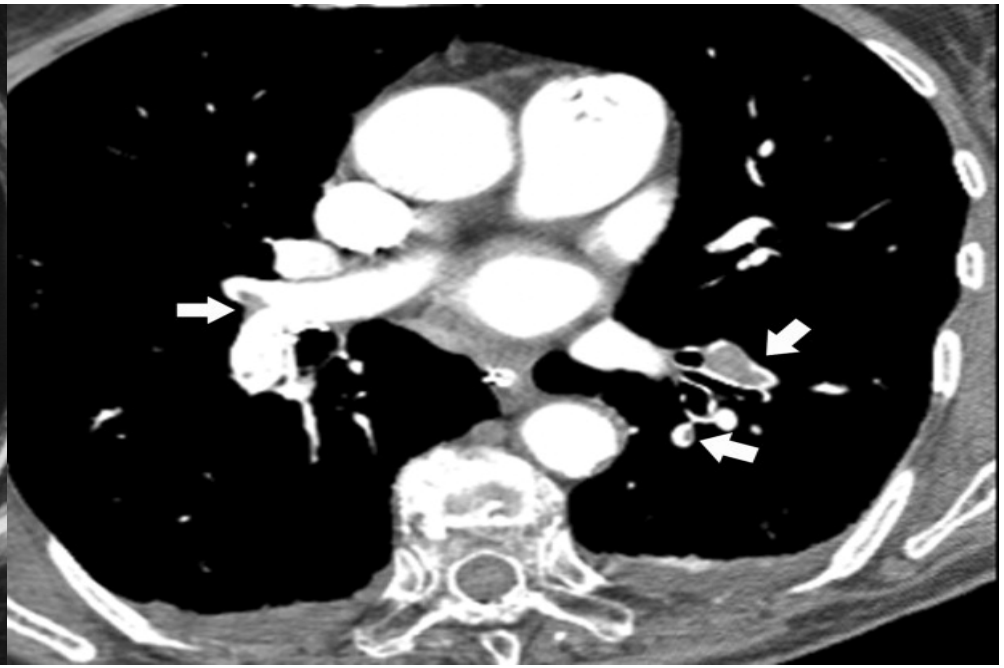

Posterior recurrent artery
Apical artery
Anterior artery
Truncus anterior
Posterior ascending artery
Middle lobe artery
Superior segmental artery
Common basal artery
A
Apical artery
Posterior arteries
Anterior artery
Superior segmental artery
Lingular artery
Common basal artery
Subsuperior artery
B



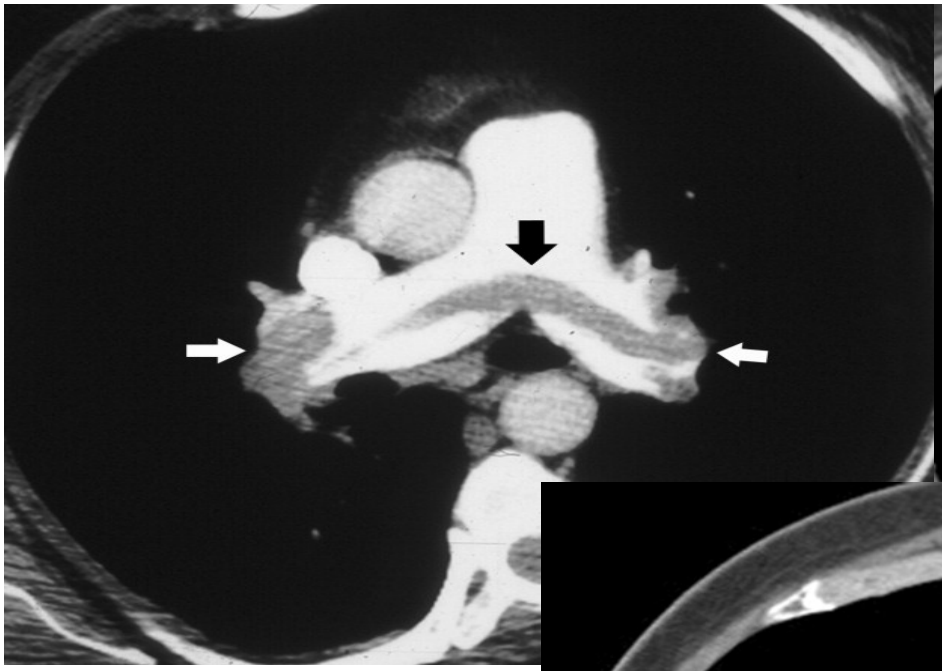
Saddle PE

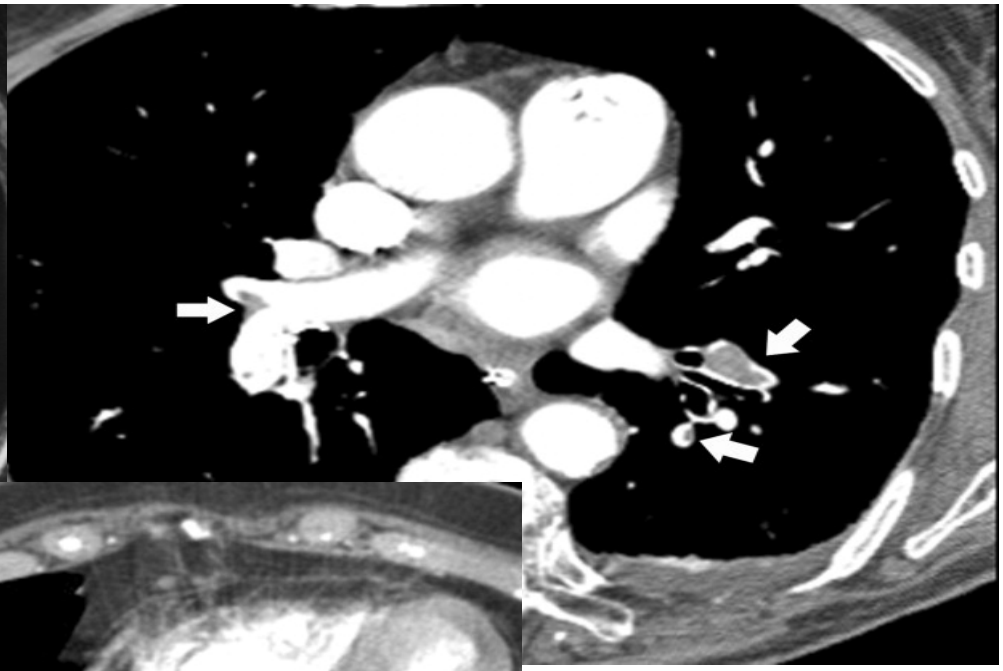


Saddle PE



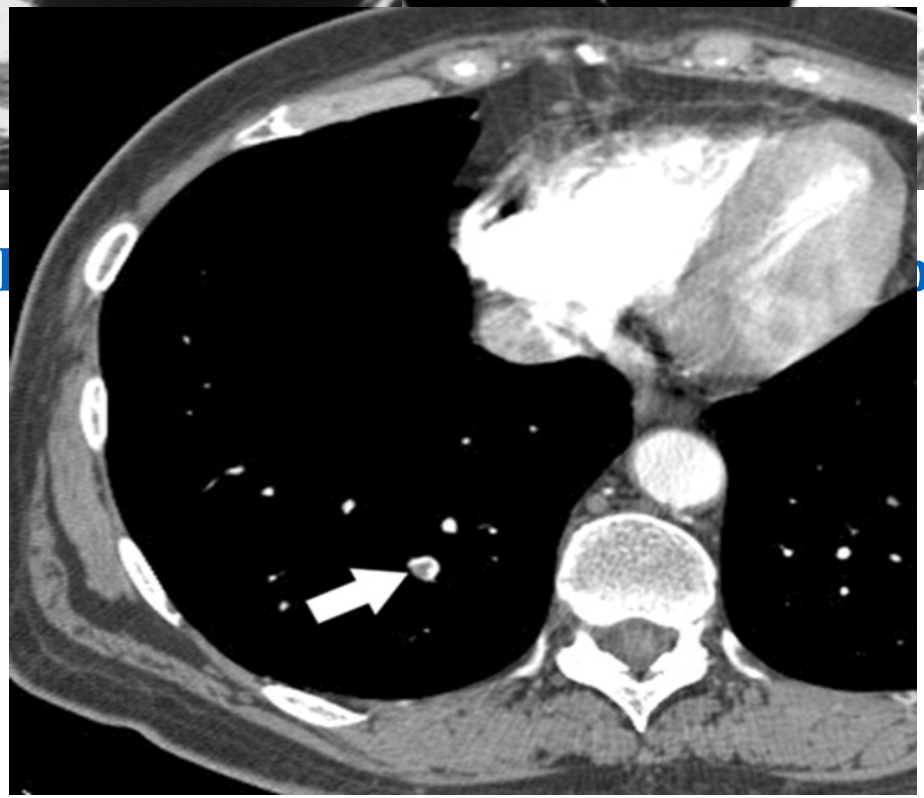
Multiple PE



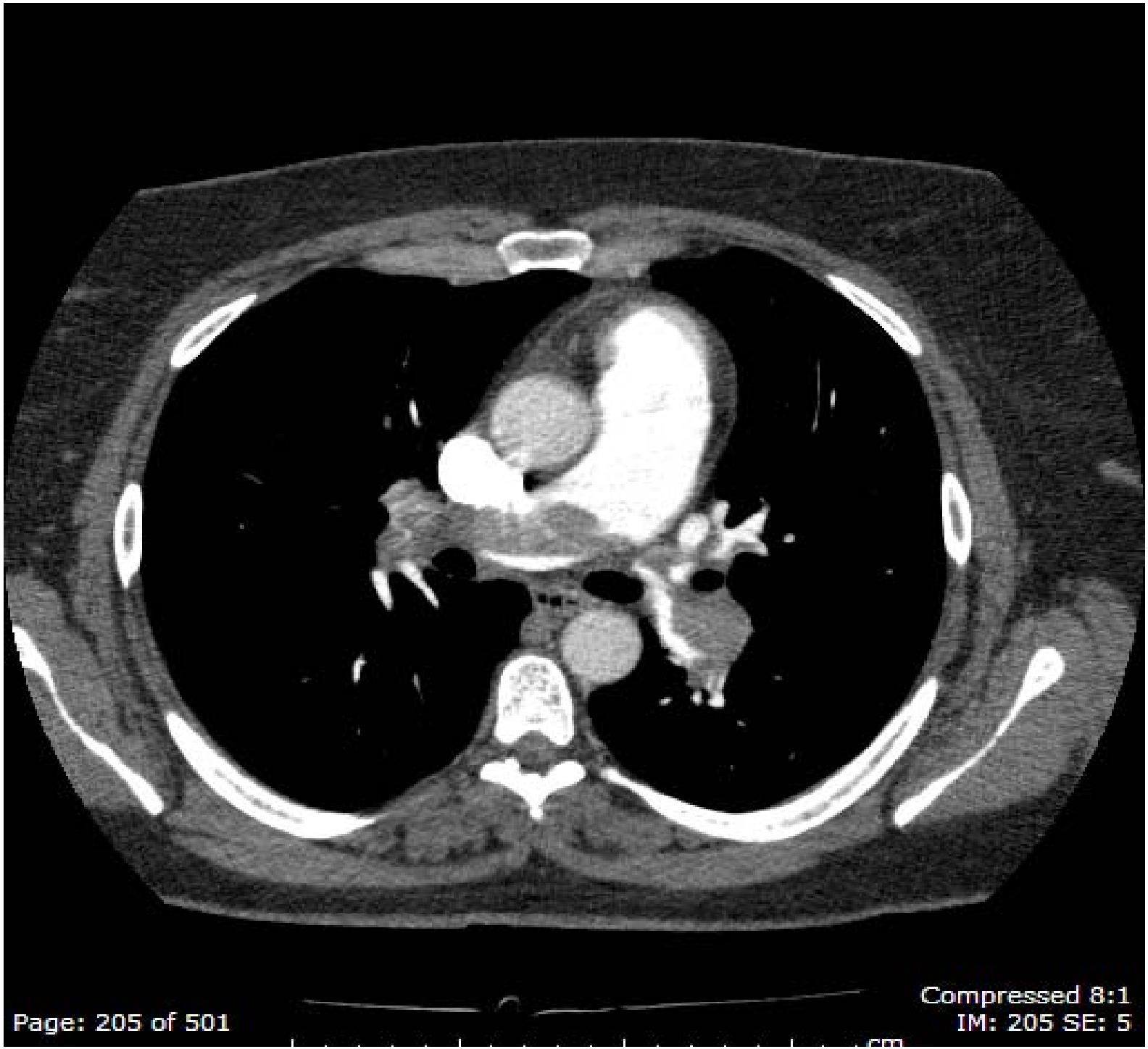


Saddle PE

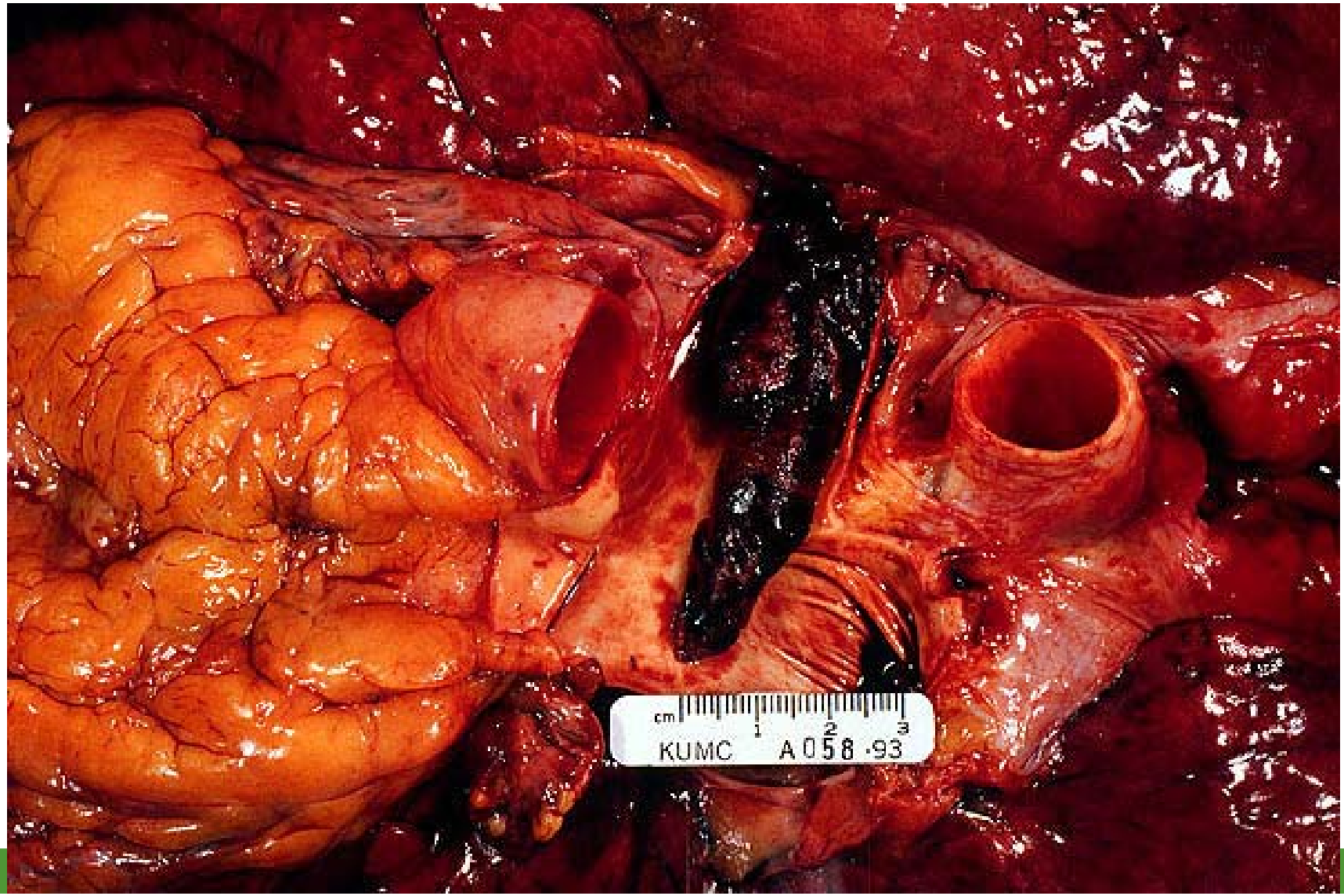
ble PE



Isolated segmental PE


Page: 205 of 501
Compressed 8:1
IM: 205 SE: 5

PE responsible for 10% of deaths in hospital




Mmmm…A sudden massive PE is a nice way to go!

Post mortem study

- 92 patients where PE identified as cause of death
- 27 (30%) died within 10 minutes of symptoms
- 9 (10%) had no symptoms

Havig (1977)

60% of patients: “gradual deterioration dominated by dyspnoea, tachycardia and fever”

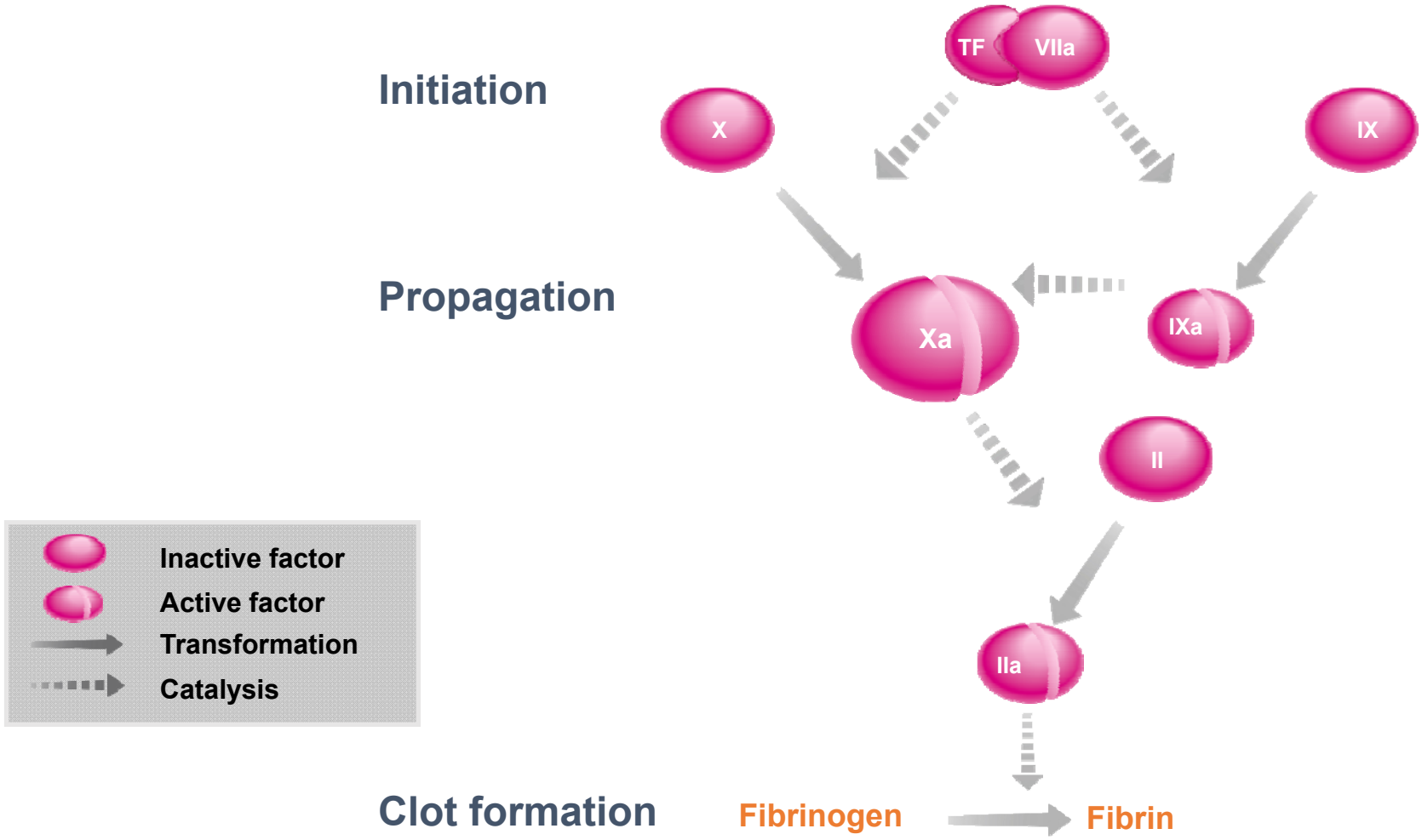
- Correct diagnosis of PE in 10% of cases
- Approximately 2 hours to die
- Treated with diuretics, digoxin, antibiotics

VTE in cancer

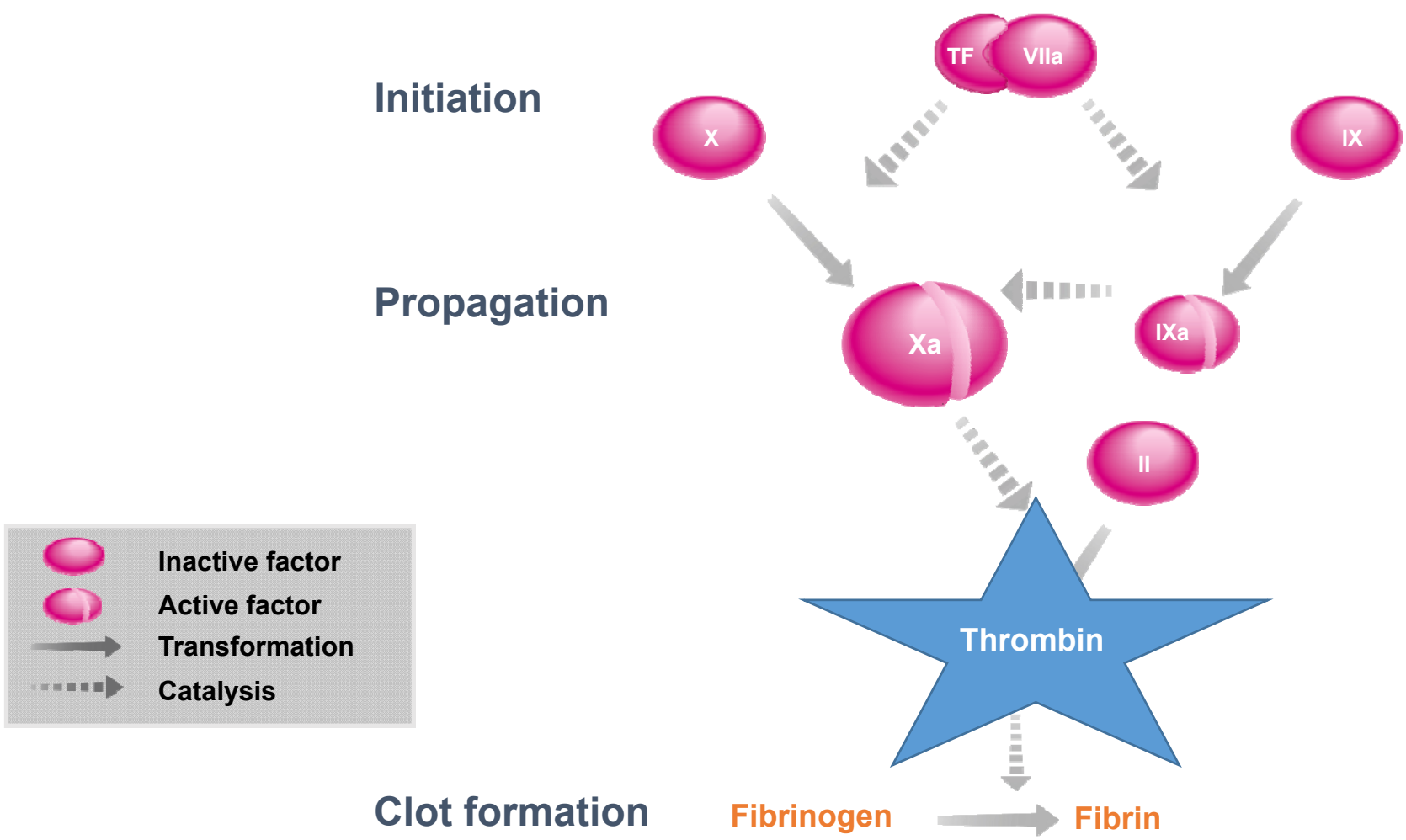
- VTE is commonest cause of death in cancer patients undergoing chemotherapy
- VTE is considered to the second leading cause of death in cancer patients
- VTE occurs in ≥ 20% of cancer patient through their lifetime
- VTE may be present in as much as 50% of patients at the time of autopsy series.

Lyman et al JCO 2009;
Khorana et al J. Thromb. Hemost. 2007;
Lyman et al JCO 2007
Johnson Clin Lab HaemJ 1999

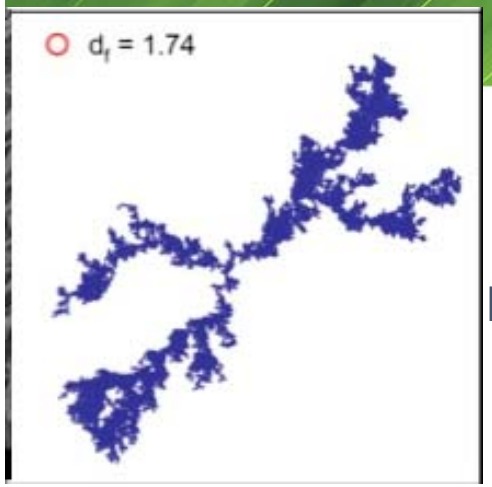
The coagulation pathway



The coagulation pathway



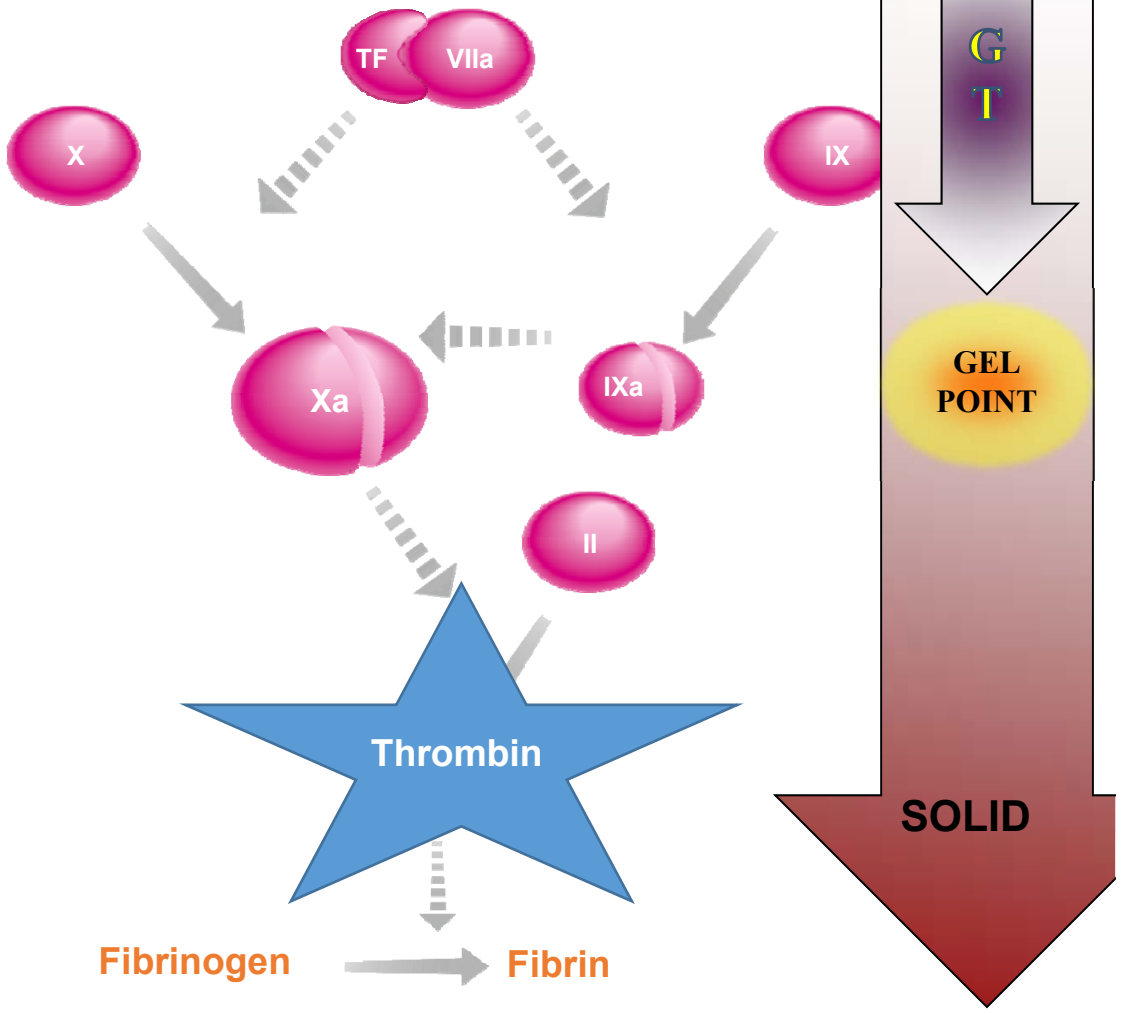
The coagulation pathway

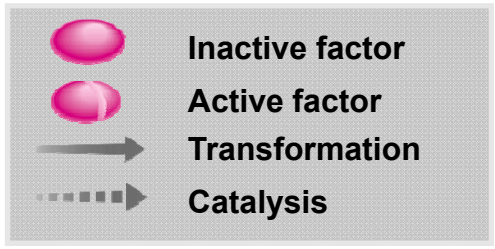


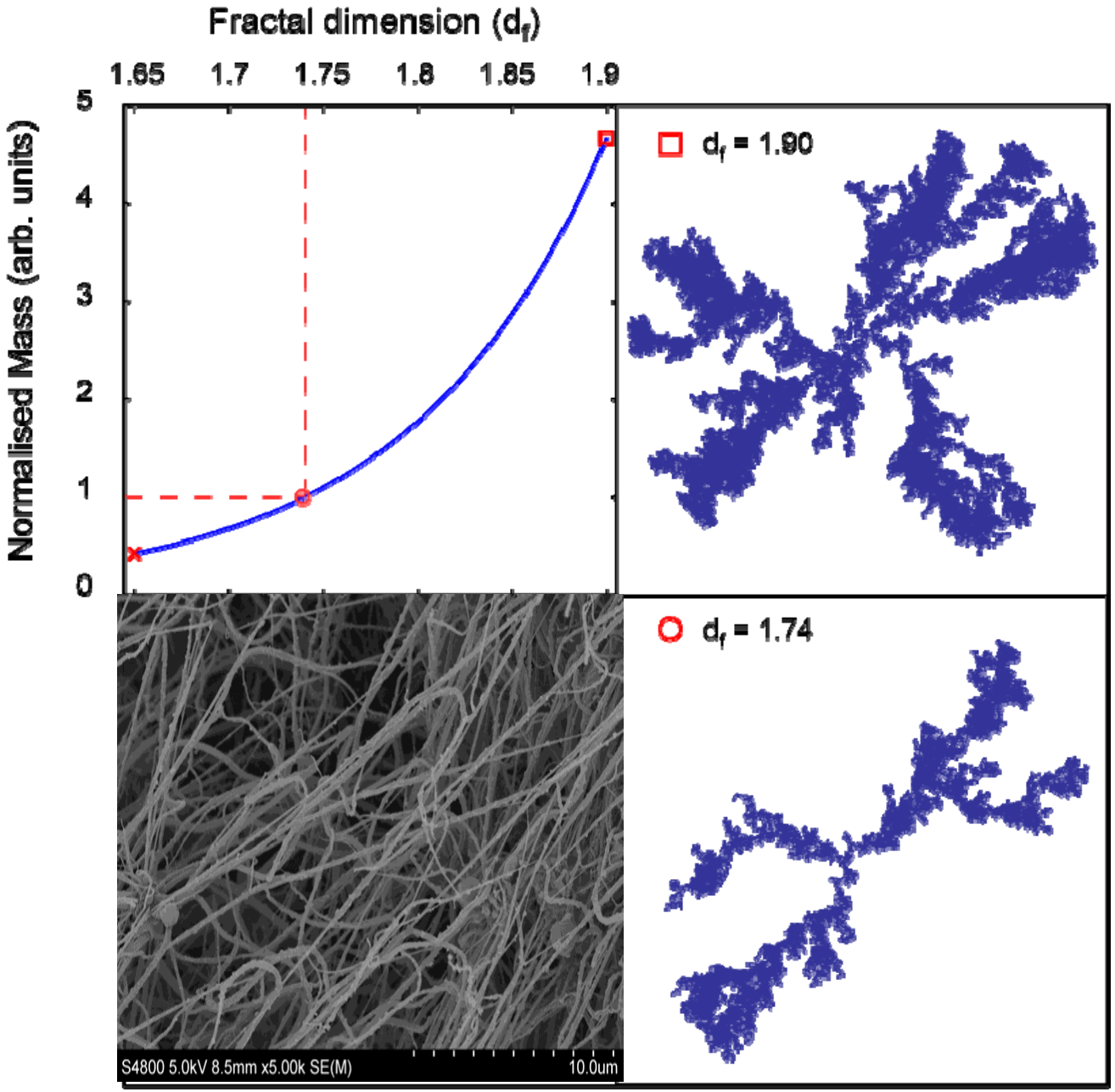
Initiation

Propagation

Clot formation



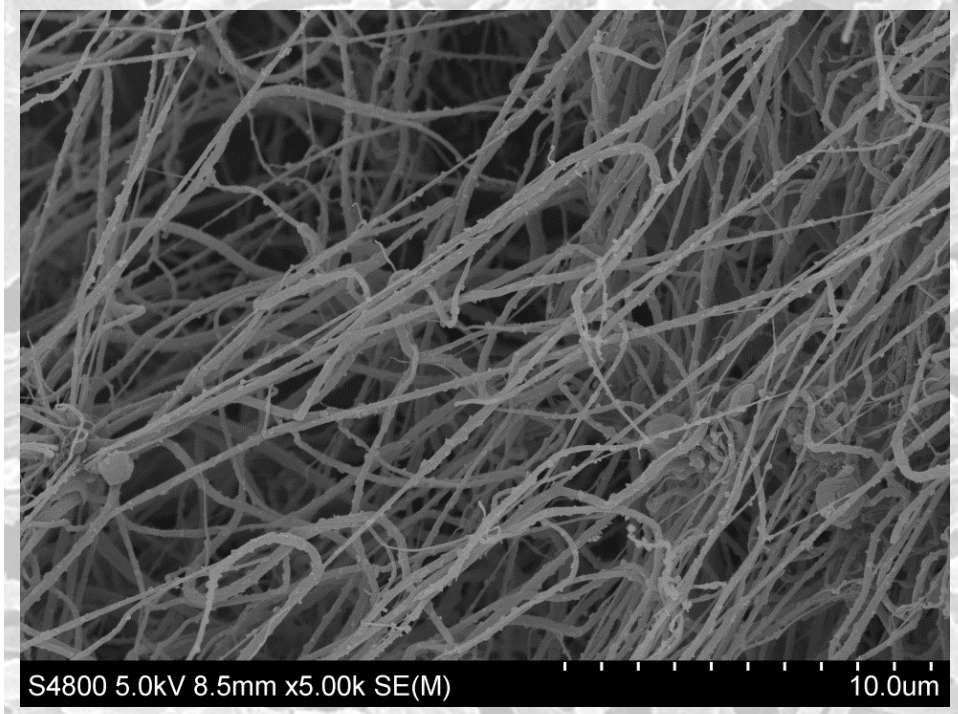


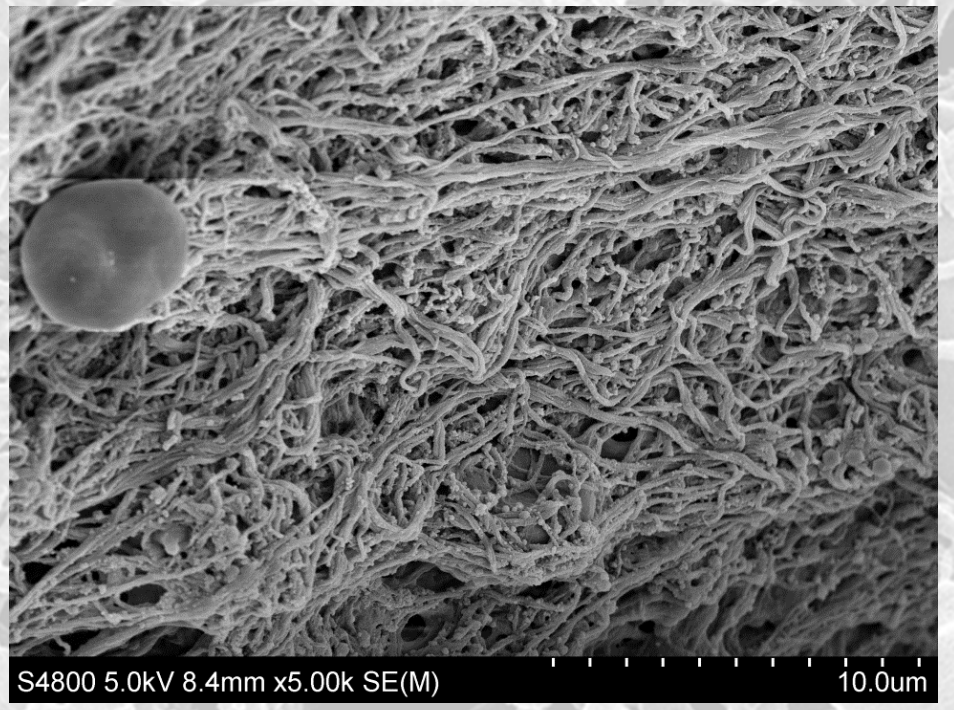


Lung cancer

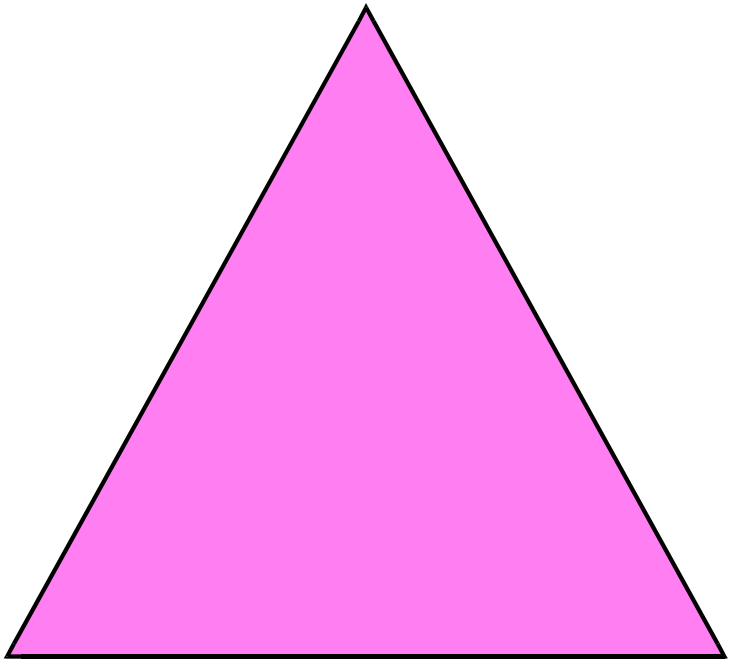
Non-cancer

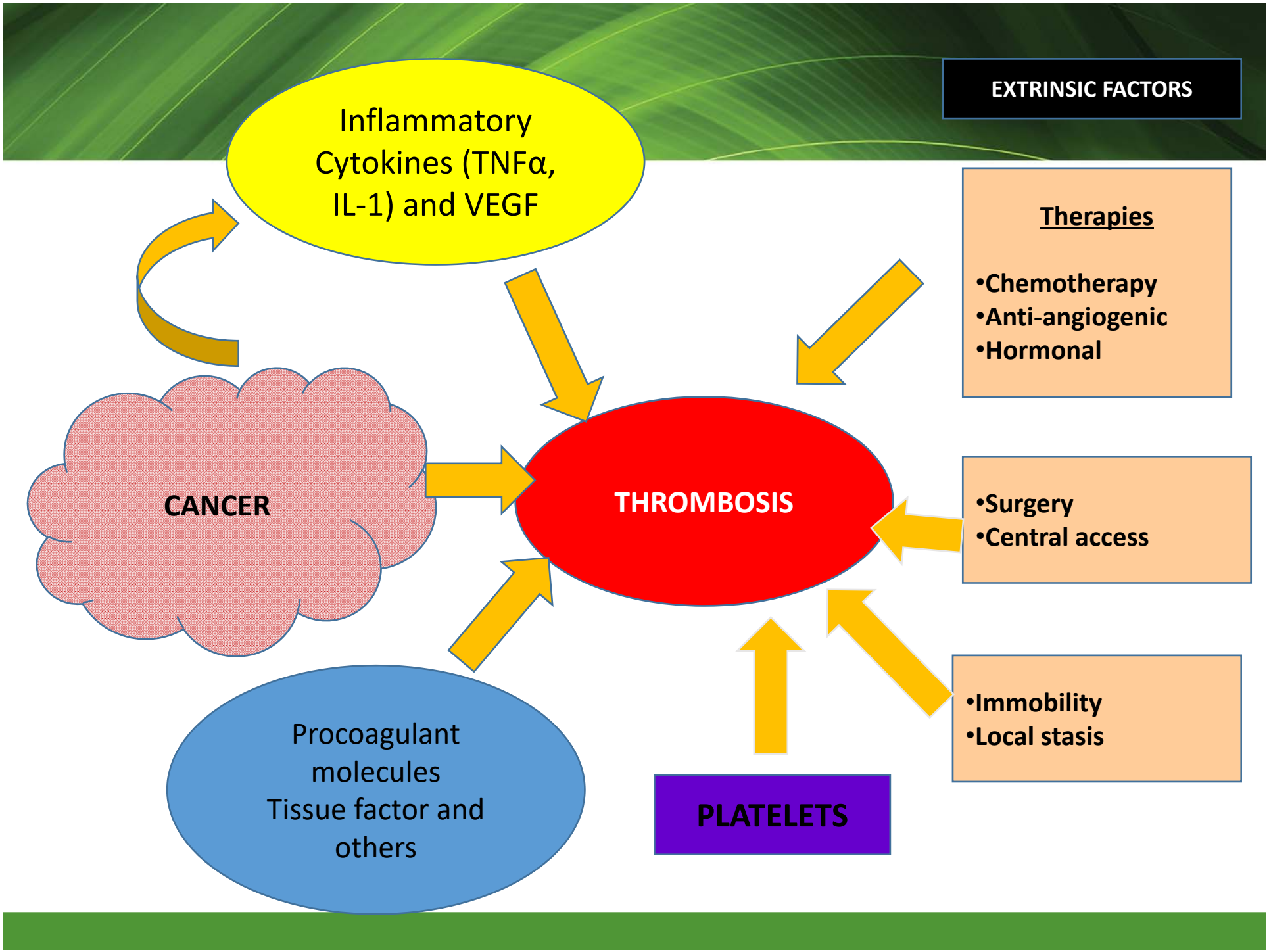
Healthy vs Cancer



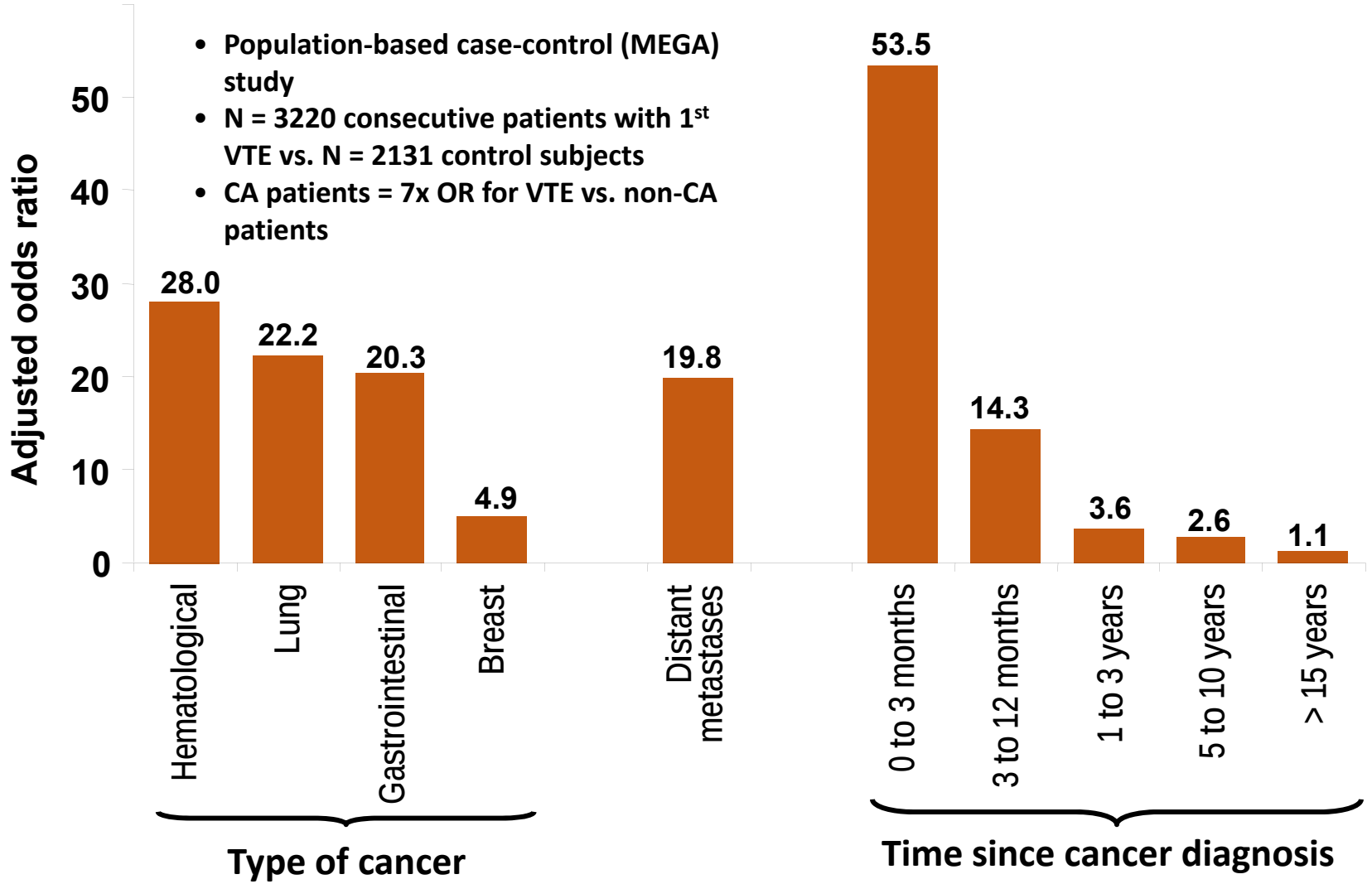


Virchow's triad




EXTRINSIC FACTORS
Inflammatory Cytokines (TNFα, IL-1) and VEGF
Therapies
•Chemotherapy
•Anti-angiogenic
•Hormonal
CANCER
THROMBOSIS
•Surgery
•Central access
•Immobility
•Local stasis
Procoagulant molecules Tissue factor and others
PLATELETS

Effect of Malignancy on Risk of Venous Thromboembolism (VTE)



Treatment impact on VTE Incidence In Various Tumors

Oncology Setting	VTE Incidence
Breast cancer (Stage I & II) w/o further treatment	0.2%
Advanced cancer (1-year survival=12%)	9%
High-grade glioma	26%
Multiple myeloma	3-5%
Renal cell carcinoma	43%
Solid tumors (anti-VEGF + chemo)	47%

Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

Treatment impact on VTE Incidence In Various Tumors

Oncology Setting	VTE Incidence
Breast cancer (Stage I & II) w/o further treatment	0.2%
Breast cancer (Stage I & II) w/ chemo	2%
Breast cancer (Stage IV) w/ chemo	8%
Advanced cancer (1-year survival=12%)	9%
High-grade glioma	26%
Multiple myeloma	3-5%
Renal cell carcinoma	43%
Solid tumors (anti-VEGF + chemo)	47%

Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

Treatment impact on VTE Incidence In Various Tumors

Oncology Setting	VTE Incidence
Breast cancer (Stage I & II) w/o further treatment	0.2%
Breast cancer (Stage I & II) w/ chemo	2%
Breast cancer (Stage IV) w/ chemo	8%
Advanced cancer (1-year survival=12%)	9%
High-grade glioma	26%
Multiple myeloma	3-5%
Multiple myeloma (thalidomide + chemo)	28%
Renal cell carcinoma	43%
Solid tumors (anti-VEGF + chemo)	47%

Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

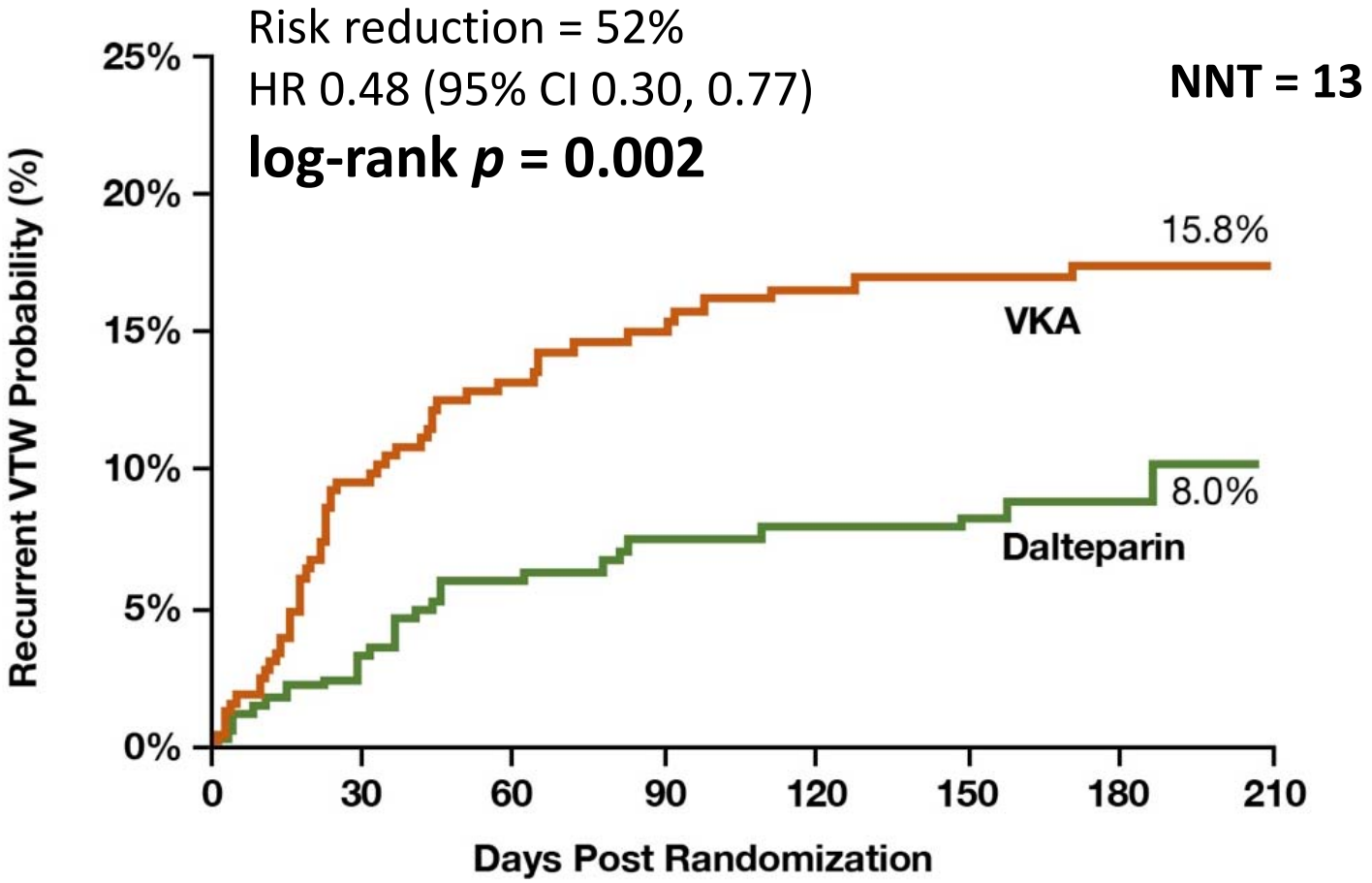
TREATMENT OF VTE

Warfarin

- High rate of bleeding in palliative care setting[1]
- Difficulty controlling INR[1]
- Multiple drug-drug interactions with commonly used symptom control drugs[2]
- Impaired quality of life[3]

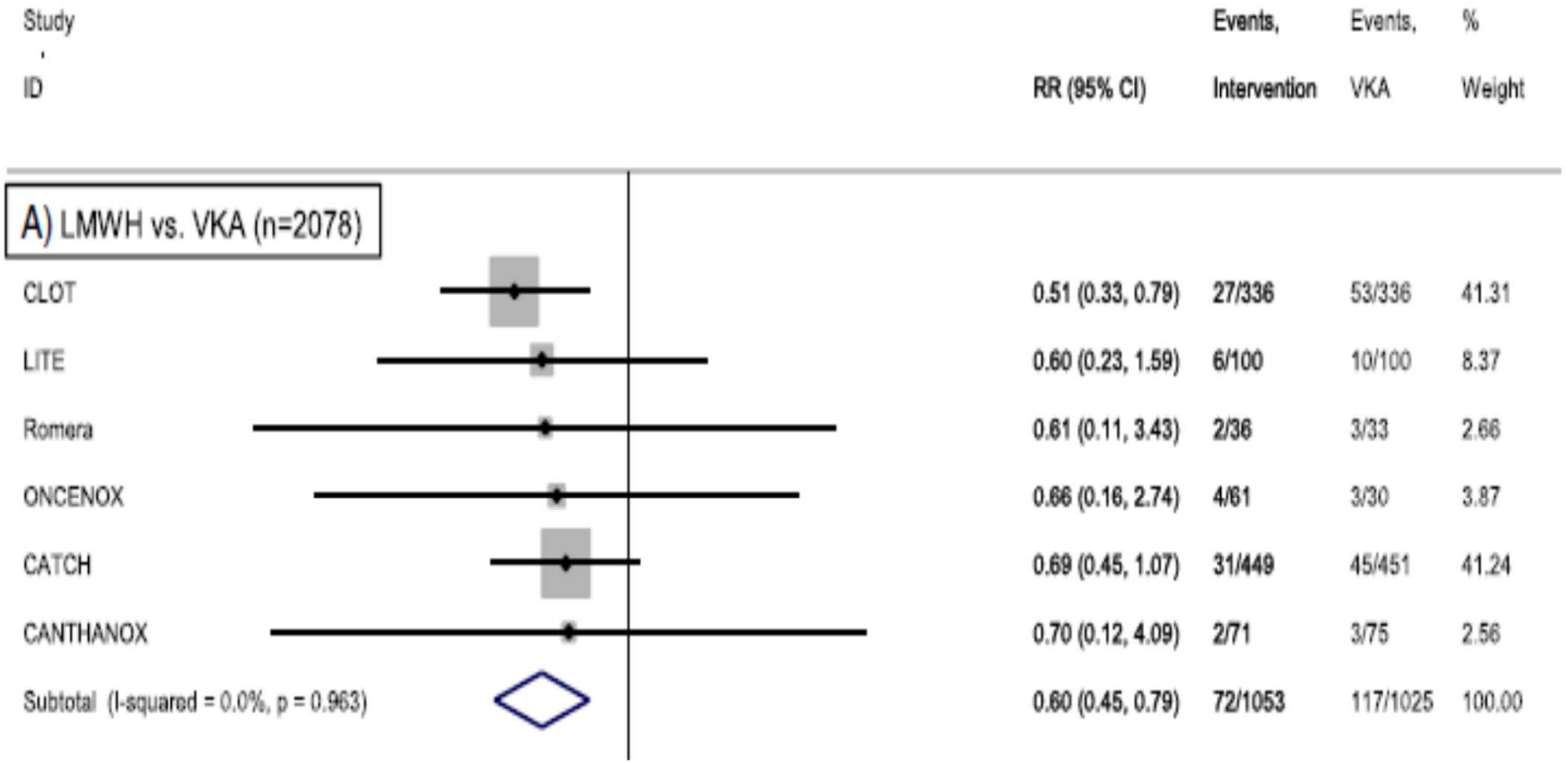
1. Johnson. Palliative Medicine 1997
2. Noble. Palliative Medicine 2004
3. Noble and Finlay. Palliative Medicine 2004

The CLOT Trial
Primary outcome: VTE recurrence



HR = hazard ratio; NNT = number needed to treat; VKA = vitamin K antagonist; VTE = venous thromboembolism

LMWH vs warfarin meta analysis



Florian Posch et at, Thrombosis Research 136 (2015) 582–589

Guideline recommendations

Guideline recommendations:

Standard of treatment for cancer-associated thrombosis is three to six months LMWH

(Grade A)

In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference.

(Grade D)

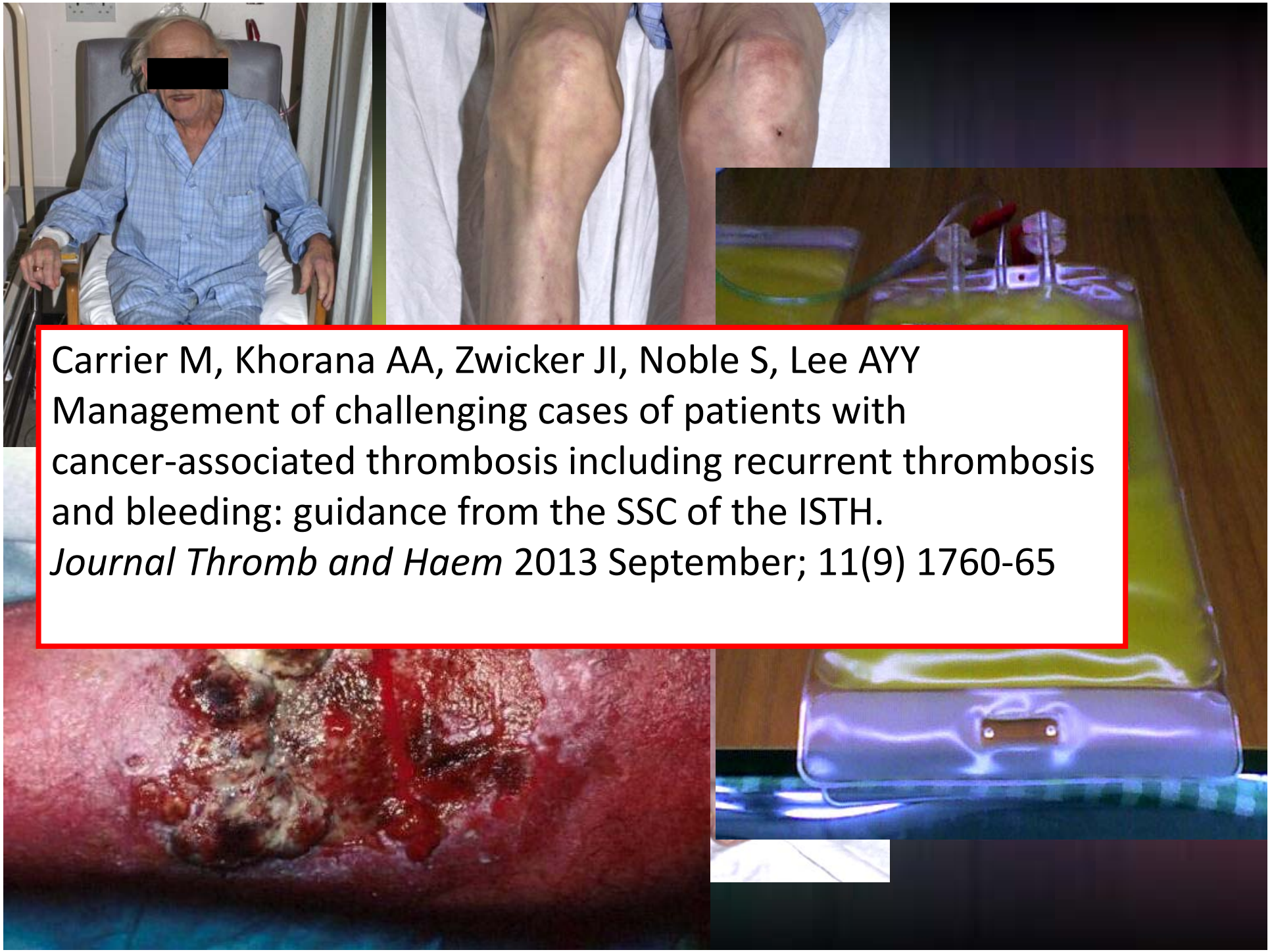
DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist

What the evidence covers

- Metastatic disease
- Performance status 0-2
- Estimated prognosis > 3 months
- Platelet count >75,000 mm^3
- Weight > 40kg
- No active bleeding

Range of disease

- CLOT:
  - 65% metastatic
- Meyer:
  - 40% not receiving active treatment
  - 50% metastases
- LITE
  - 47% metastatic disease



Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AYY
Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH.
Journal Thromb and Haem 2013 September; 11(9) 1760-65

Data in palliative care population

- 2 case series describe use of LMWH for treatment of VTE in advanced cancer patients [1,2]
- One qualitative study suggests LMWH to be acceptable to palliative care patients [3]
- LMWH now drug of choice for cancer associated VTE in palliative care [4]
- LMWH does not accumulate over time [5]

1. Noble SIR, Hood K, Finlay IG. Palliative Medicine 2007
2. Soto-Cárdenas MJ et al . Palliative Medicine 2008
3. Noble SIR, Finlay IG. Palliative Medicine 2005
4. Noble et al Lancet Oncology 2008
5. Kovacs et al T&H 2005

Is LMWH still acceptable?

- Original paper 2005
- Selection bias?
  - LMWH not custom and practice
  - Most interviewed on LMWH due to warfarin failure
- Representative timeframe?
  - On LMWH for a month
  - Same after 6 months?

Study repeated using same methods

- LMWH for at least 3 months

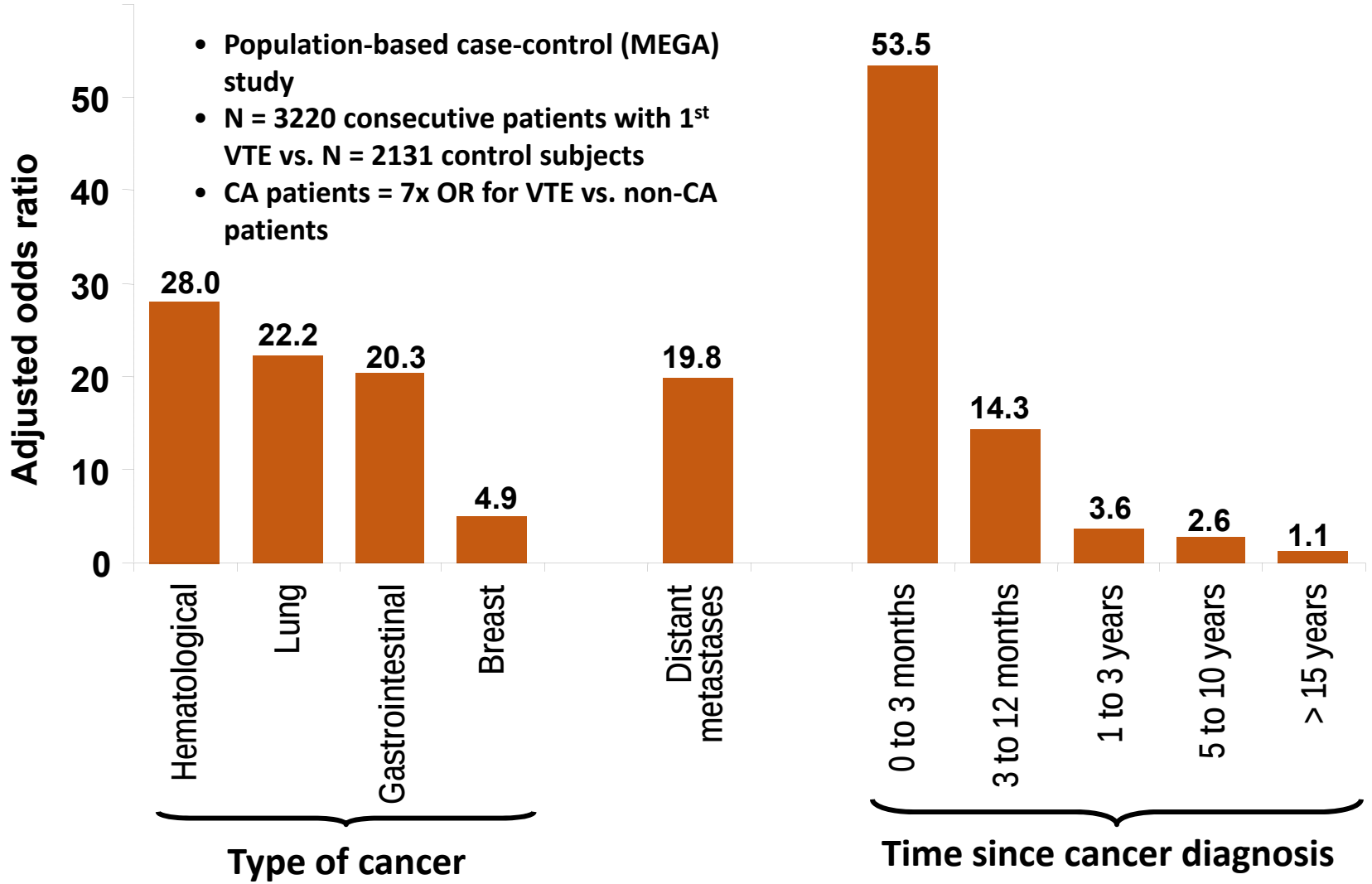
Major themes

- Symptoms/ experience of VTE “worse than cancer”
  - o Impact on cancer journey
  - o Impact on ADLs
- LMWH acceptable within context of illness
  - o Necessary inconvenience
  - o Fear of recurrence
- Adaptive behaviours and routine

Seaman Pat Pref Adh (2014)

What evidence is there to guide management beyond 6 months?

Effect of Malignancy on Risk of Venous Thromboembolism (VTE)



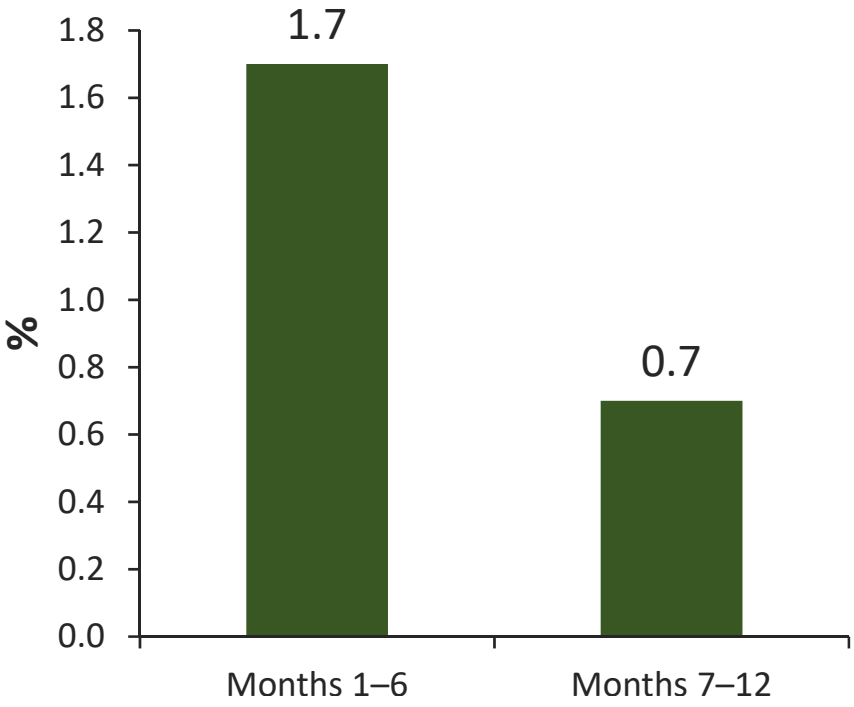
DALTECAN

- Prospective observational safety study of dalteparin at 6 and 12 months anticoagulation for CAT
- 334 patients enrolled,
  - 55.4% (155) completed 6 months of therapy
  - 33% (109) completed 12 months.

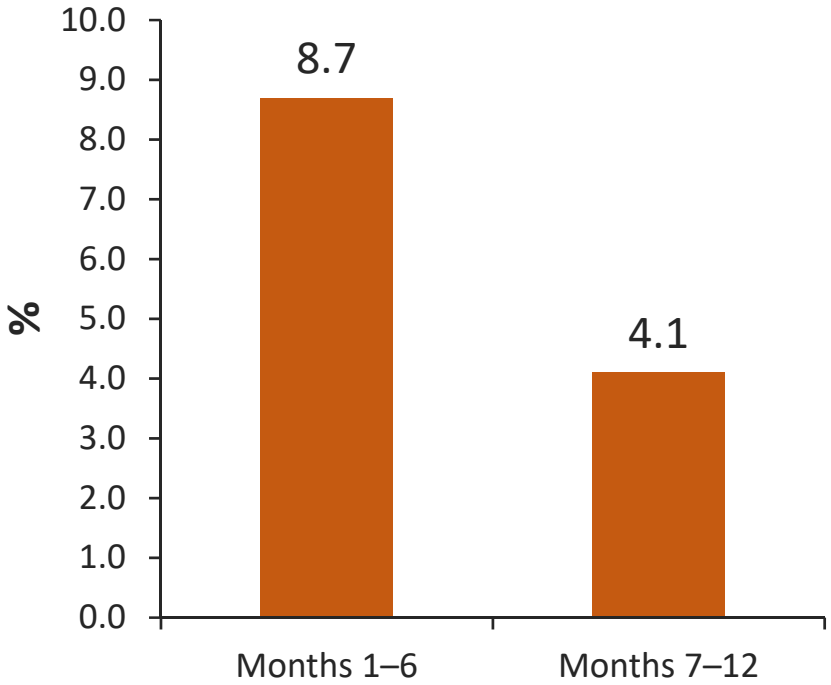
CAT = cancer-associated thrombosis

DALTECAN
Efficacy and safety of long-term therapy

Major bleeding rate per month



Total VTE recurrence rate

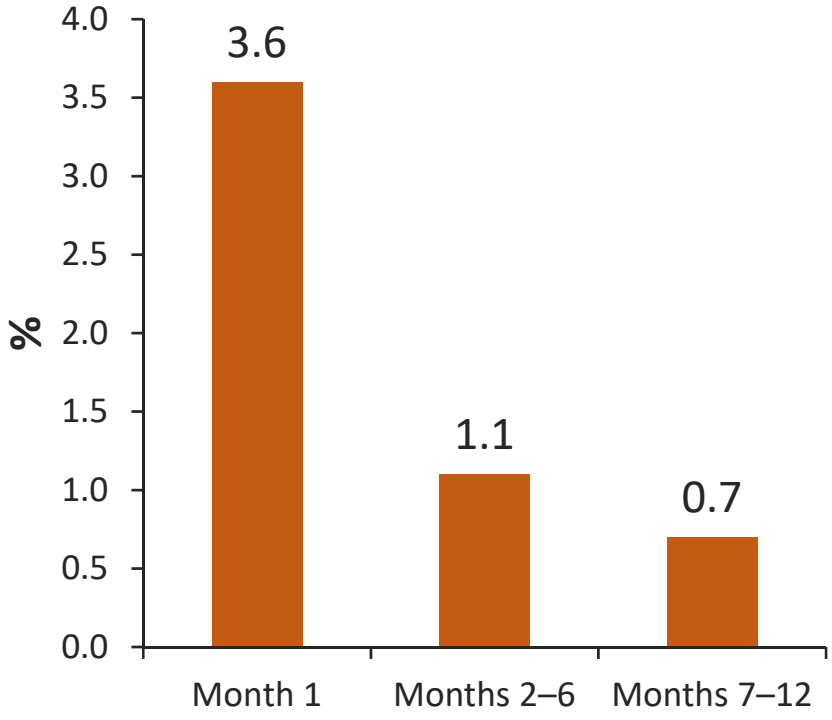


- 116 deaths – 105 due to cancer
  – 4 due to recurrent PE
  – 2 due to hemorrhage

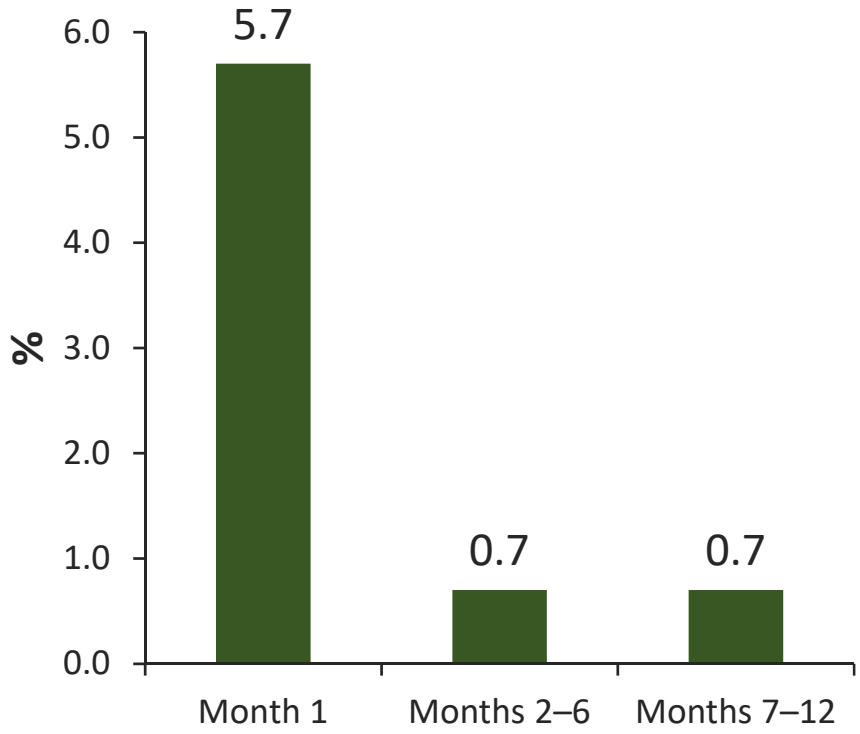
PE = pulmonary embolism; VTE = venous thromboembolism

DALTECAN
Efficacy and safety of long-term therapy

Major Bleeding Rate per Month



Rate of VTE Occurrence per Month



- Bleeding was not increased in Months 6–12 compared to Months 2–6.

VTE = venous thromboembolism

What data can guide us?

- CLOT subgroup analysis
- Independent risk factors of VTE recurrence:
  - Lung cancer (HR, 3.51; 95% CI, 1.62–7.62)
  - Metastases (HR, 2.59; 95% CI, 1.29–5.60)
- Lower risk
  - Breast cancer (HR, 0.59; 95% CI, 1.62–7.62)

CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism

Risk Model for Recurrent VTE in CAT
The Ottawa score

Variable	Regression Coefficient	Point
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	-0.76	-1
TNM Stage I	-1.74	-2
Previous VTE	0.4	1
Clinical probability: Low (≤0) Clinical probability: High (≥1)		-3 – 0 1 – 3

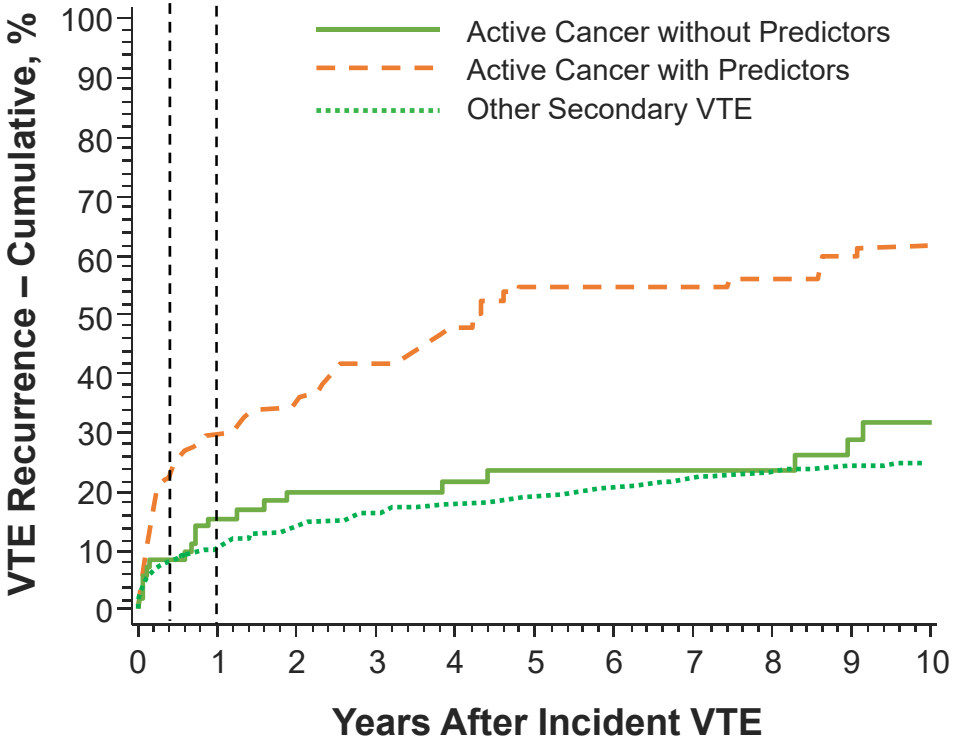
- Outcome:
  - Patients with a score <0 had a low risk of recurrence: **5.1%**
  - Patients with a score of 0 had an intermediate risk of recurrence: **9.8%**
  - Patients with a score ≥1 had a high risk of recurrence: **15.8%**
- Results have not been fully validated

Louzada ML *et al. Circulation* 2012. TNM = tumor, node, metastases; VTE = venous thromboembolism

Recurrent VTE Risk in Active Cancer
Population-based cohort Olmstead County

- 477 patients with active cancer and VTE (eligible between 1966 and 2000)

Cumulative Incidence of First VTE Recurrence



Multivariate Predictors of VTE Recurrence

Characteristic	HR	95% CI	*P*-value
Stage IV pancreatic cancer	6.38	2.69, 15.13	<0.0001
Brain cancer	4.57	2.07, 10.09	0.0002
Myeloproliferative or myelodysplastic disorder	3.49	1.59, 7.68	0.002
Ovarian cancer	3.22	1.57, 6.59	0.001
Stage IV cancer (non pancreas)	2.85	1.74, 4.67	<0.0001
Lung cancer	2.73	1.63, 4.55	0.0001
Neurological disease with leg paresis	2.38	1.14, 4.97	0.02
Cancer stage progression	2.14	1.30, 3.52	0.003
Warfarin therapy	0.43	0.28, 0.66	<0.0001

Chee CE *et al. Blood* 2014.

CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism

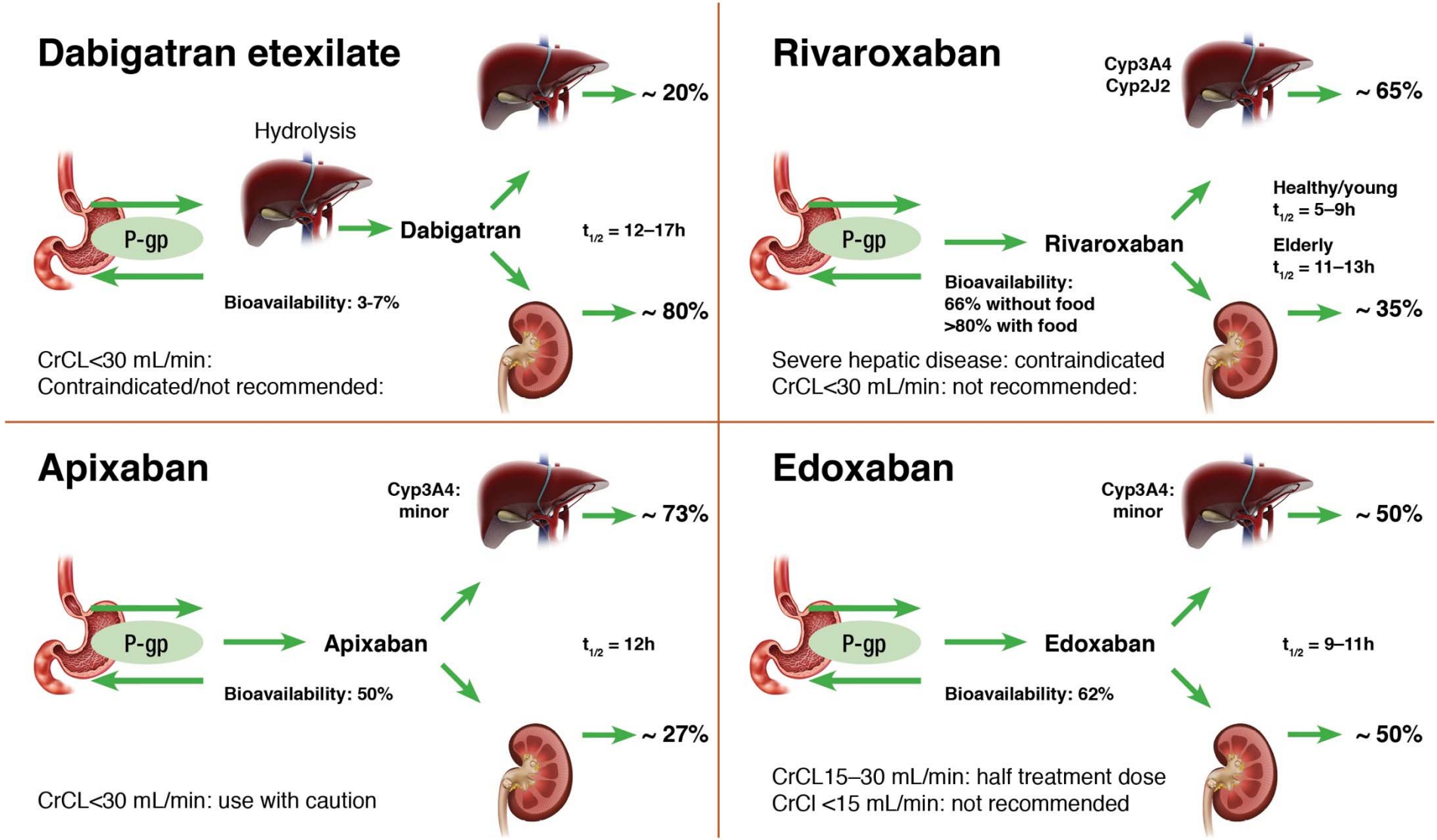
Factors influencing decision whether to extend anticoagulation in CAT

Factor	Favors continuing anticoagulation	Favors stopping anticoagulation
Patient preference	• 1^0 concern recurrence	• 1^0 concern hemorrhage
Malignancy specific	• Active malignancy • High risk cancer e.g., lung • Ongoing chemo or ESA	• No evidence of disease • Low risk cancer e.g., breast
Previous history of VTE	• Yes	• No
Nature of initial VTE	• Life-threatening PE • DVT with severe postphlebitic syndrome	• Non life-threatening PE • No residual symptoms
Risk of hemorrhage	• No	• Yes
Additional risk factors	• Obesity • Sex • Poor performance status • Central venous catheter	• Risk factors other than malignancy when diagnosed e.g., surgery

1^0 = primary; CAT = cancer-associated thrombosis; DVT = deep vein thrombosis; ESA = erythropoiesis stimulating agent; PE = pulmonary embolism

Can we use DOACs yet?

DOAC Pharmacology



Adapted from: Heidbuchel H *et al. Europace* 2013; U.S., Canadian Prescribing Information CrCl = creatinine clearance

Oral direct IIa and Xa inhibitors

	dabigatran	rivaroxaban	apixaban
Target	IIa	Xa	Xa
t½	12-17 h	9 h	12 h
Dose / frequency	150mg bd 110mg bd	20mg od	5mg bd
Renal clearance	85%	33%	27%
Peak	2 h	2-4 h	2-4 h

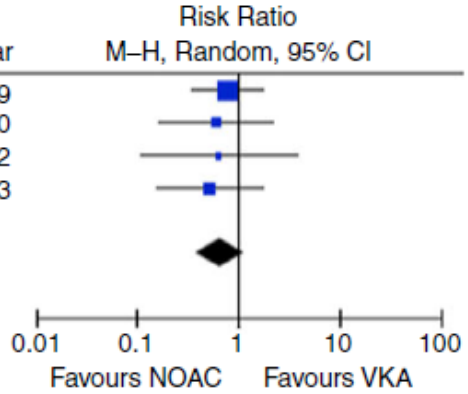
DOACs in the treatment of CAT

Recurrent VTE

A

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Re-Cover I and II	10	173	12	162	48.4%	0.78 [0.35, 1.76]	2009
Einstein-DVT	4	118	5	89	19.3%	0.60 [0.17, 2.18]	2010
Einstein-PE	2	114	3	109	10.2%	0.64 [0.11, 3.74]	2012
Hokusai	4	109	7	99	22.2%	0.52 [0.16, 1.72]	2013
Total (95% CI)		514		459	100.0%	0.66 [0.38, 1.17]	
Total events	20		27				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 1.42 (P = 0.16)



Pooled incidence rates: 4.1% (2.6–6.0) for DOACs
6.1% (4.1–8.5) for VKAs [RR 0.66 (0.38–1.2)]

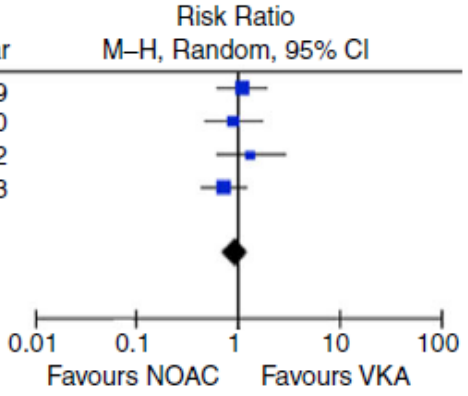
Recurrent VTE warfarin
Lee A *et al*. 2003: 16%
Meyer G *et al*. 2002 17%

Major bleeding or CR-NMB

B

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Re-Cover I and II	23	159	20	152	29.5%	1.10 [0.63, 1.92]	2009
Einstein-DVT	17	118	14	88	21.5%	0.91 [0.47, 1.74]	2010
Einstein-PE	14	114	10	108	15.5%	1.33 [0.62, 2.86]	2012
Hokusai	20	109	25	99	33.6%	0.73 [0.43, 1.22]	2013
Total (95% CI)		500		447	100.0%	0.94 [0.70, 1.28]	
Total events	74		69				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.03$, df = 3 (P = 0.57); $I^2 = 0\%$
Test for overall effect: Z = 0.37 (P = 0.71)



van der Hulle T *et al. J Thromb Haemost* 2014. CRNMB = clinically-relevant non-major bleeding

Drug-Drug Interactions with DOACs
Chemotherapeutic agents and immunosuppressants

	Dabigatran	Rivaroxaban	Apixaban
Interaction effect*	P-glycoprotein	P-glycoprotein CYP3A4	P-glycoprotein CYP3A4
Increases DOAC plasma levels†	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
Reduces DOAC plasma levels‡	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

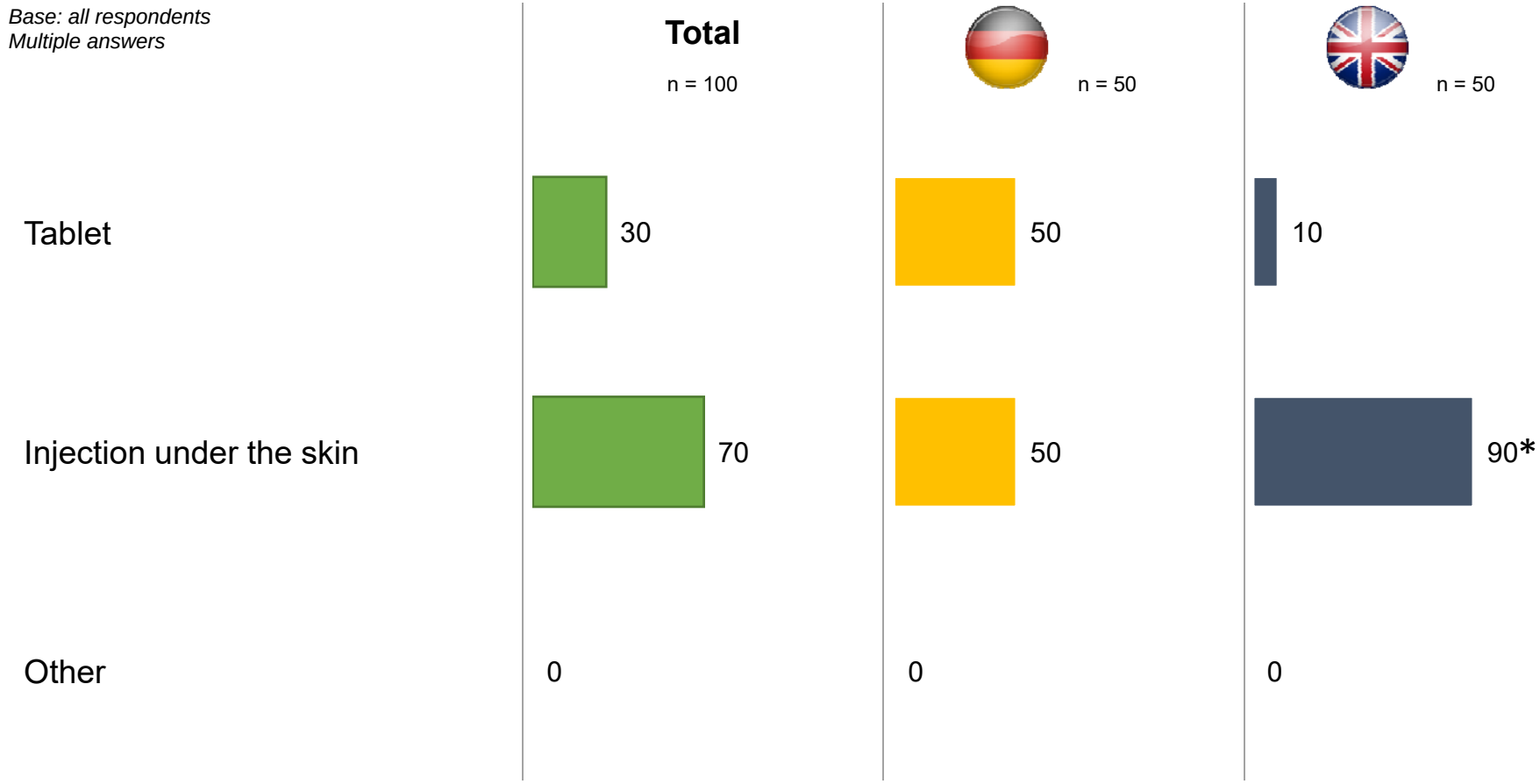
*Clinicians should consult pharmacist; †Drugs that inhibit P-GP or CYP3A4 can increase DOAC levels; ‡Drugs that induce P-GP or CYP3A4 can lower DOAC levels.

CYP3A4 = cytochrome P450 3A4; DOAC = direct oral anticoagulant

Around one third of patients are currently treated with oral medication for their VTE

Administration of medication (%)

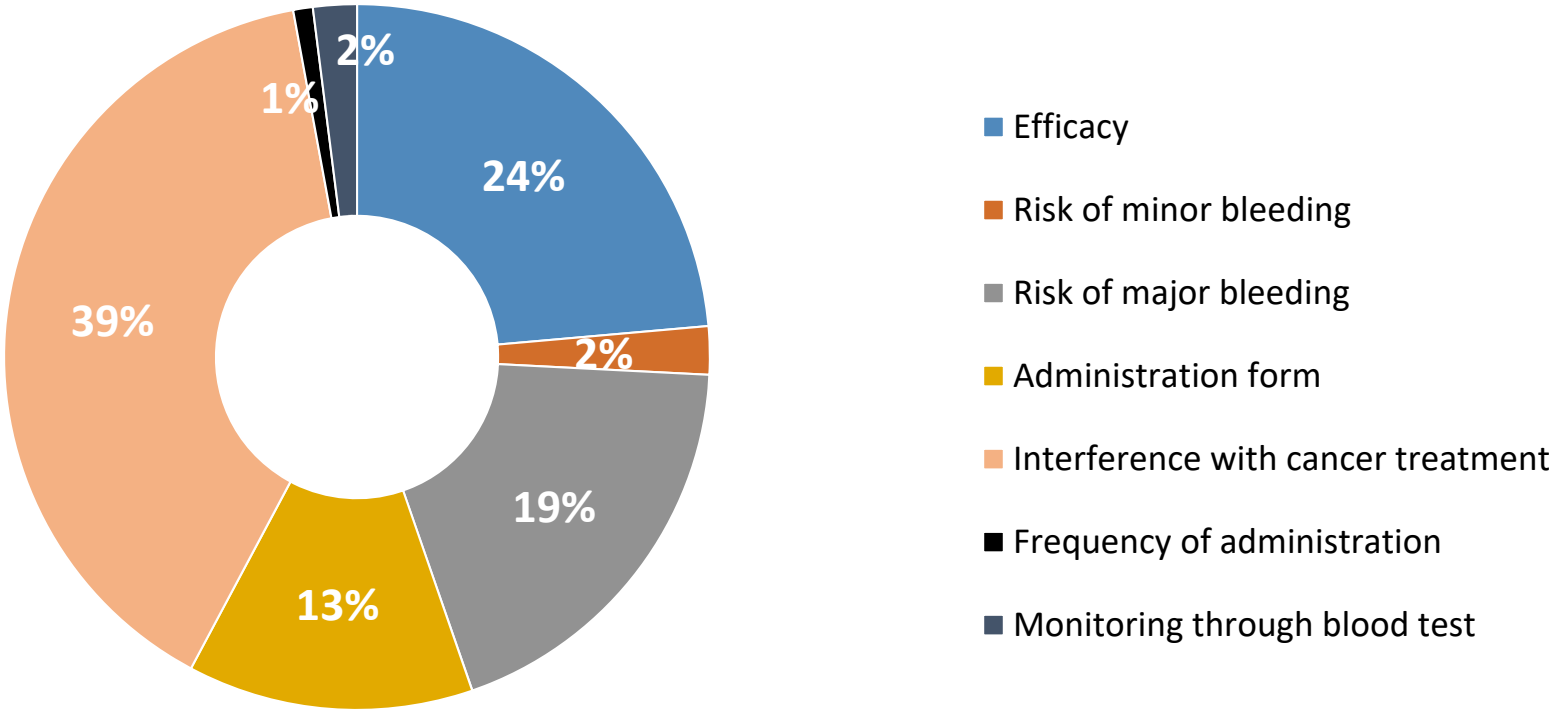
Base: all respondents
Multiple answers



* Significant difference to Germany

Interference with cancer treatment is the most important attribute to patients, followed by efficacy of VTE therapy

Relative importance of attributes* - Total



n = 100

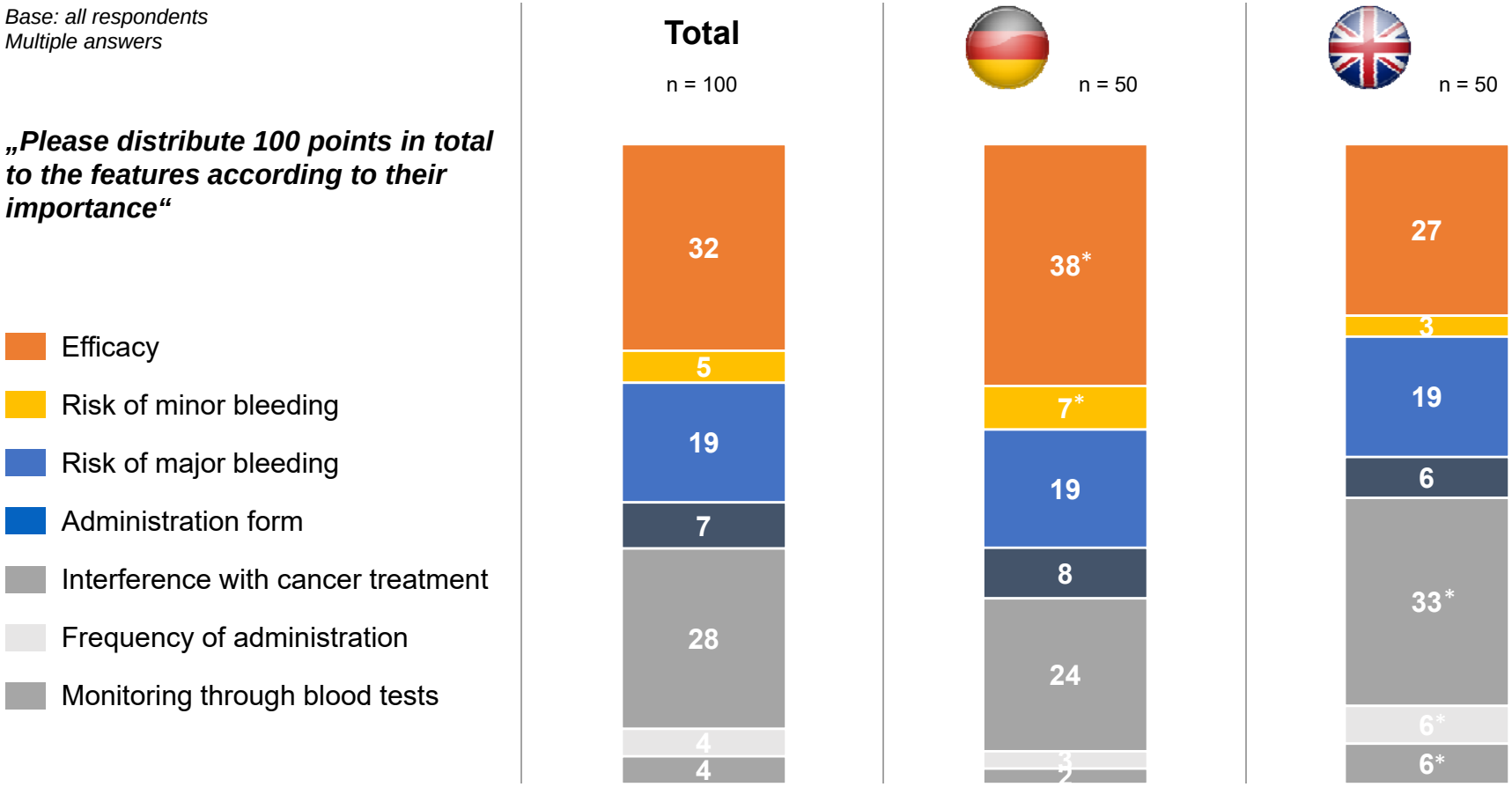
* Impact / weight of each attribute on the overall preference / choice behavior

When asked directly, patients allocate almost the same importance to efficacy and interference with cancer treatment

Direct importance of characteristics for treatment decision (means)

Base: all respondents
Multiple answers

„Please distribute 100 points in total to the features according to their importance“



* Significant difference to UK / Germany

What may the future hold for choosing anticoagulation for cancer-associated thrombosis?

- Current guidelines recommend LMWH for the treatment of patients with cancer and VTE.
- There are four active phase III trials of direct Xa inhibitors vs. LMWH that should be completed in the next 2–3 years.

Drug	Comparator	Study design elements	1° Endpoint
Edoxaban[1,2]	Dalteparin	Outcomes measured after both 6 months and 12 months of therapy	Composite of recurrent VTE and major bleeding
Rivaroxaban[3]	Dalteparin	After randomization of active therapy for 6 months, patients are randomized to rivaroxaban vs. placebo for a further 6 months	Recurrent VTE
Rivaroxaban[4]	Any LMWH	Randomized for 3 months	Patient-reported treatment satisfaction
Apixaban[5]	Dalteparin	Randomized for 6 months	Safety

1. Clinical.trials.gov NCT02073682; 2. van Es N *et al. Thromb Haemost* 2015; 3. IRCTN Registry ISRCTN86712308; 4. Clinicaltrials.gov NCT02583191; 5. Clinicaltrials.gov NCT02585713

LMWH = low molecular weight heparin; VTE venous thromboembolism.

Decision making

- Patients place great reliance on their doctors advice regarding treatment of CAT.[1]
- Discussing options with patients should include:
  - Strength of evidence
  - Potential benefits
  - Potential complications

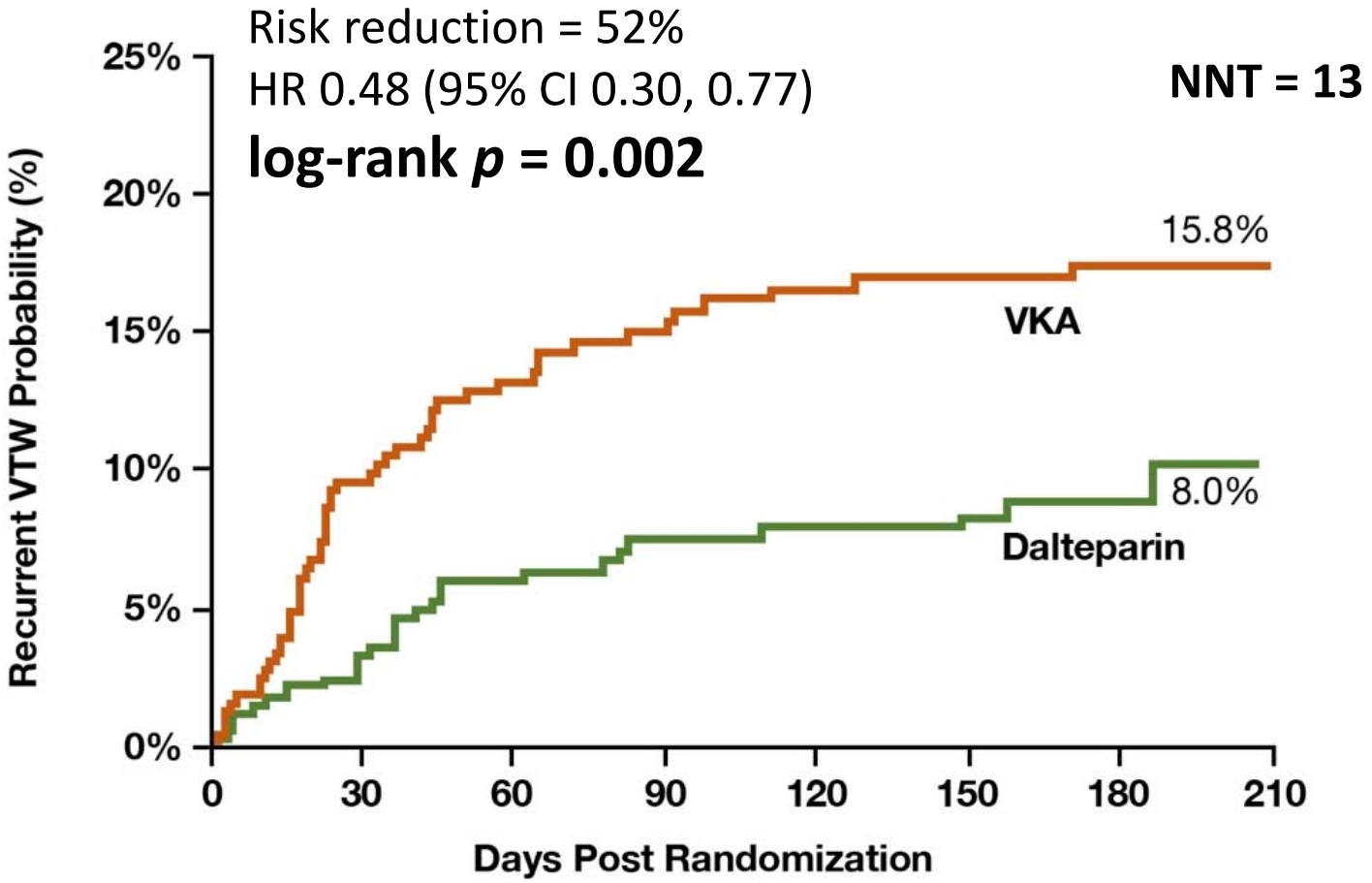
CAT = cancer-associated thrombosis

1. Noble S *et al Haematologica* 2015 Aug 20.

So is there any role for DOACs in cancer now?

- Efficacy of LMWH most marked in first 3 months

The CLOT Trial
Primary outcome: VTE recurrence



HR = hazard ratio; NNT = number needed to treat; VKA = vitamin K antagonist; VTE = venous thromboembolism

So is there any role for DOACs in cancer now?

- Efficacy of LMWH most marked in first 3 months
- No studies have demonstrated superiority after 6 months
- Arguably, one can justify any of the anticoagulants

My practice

- At six months (if patient warrants indefinite anticoagulation)
- DOAC if
  - Patient wants to stop injections
  - Not receiving chemo
  - Renal function satisfactory

CAT = Cancer-associated thrombosis

When the evidence is lacking:

- Management should be guided by an appreciation of
  - Pathophysiology of CAT
  - Thrombogenicity of respective cancer
  - Thrombogenicity of respective chemotherapy
  - Bleeding risks
  - Patient views

CAT = Cancer-associated thrombosis

THANKYOU