Cancer Associated Thrombosis
An update.

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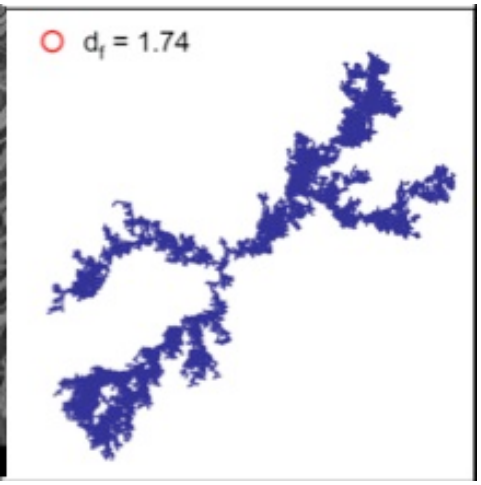
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Marie Curie
Care and support through terminal illness

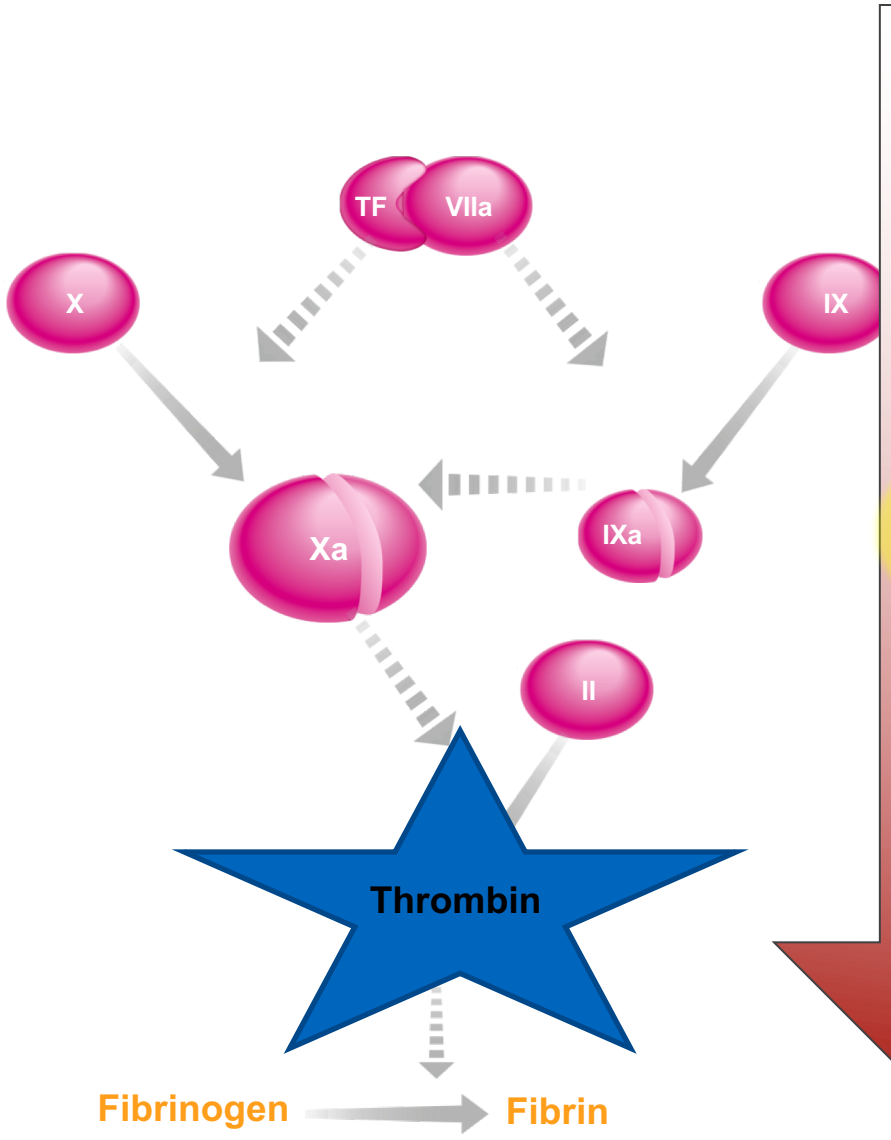
The coagulation pathway

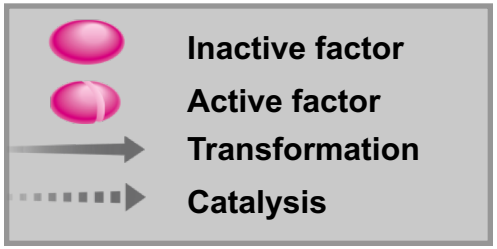


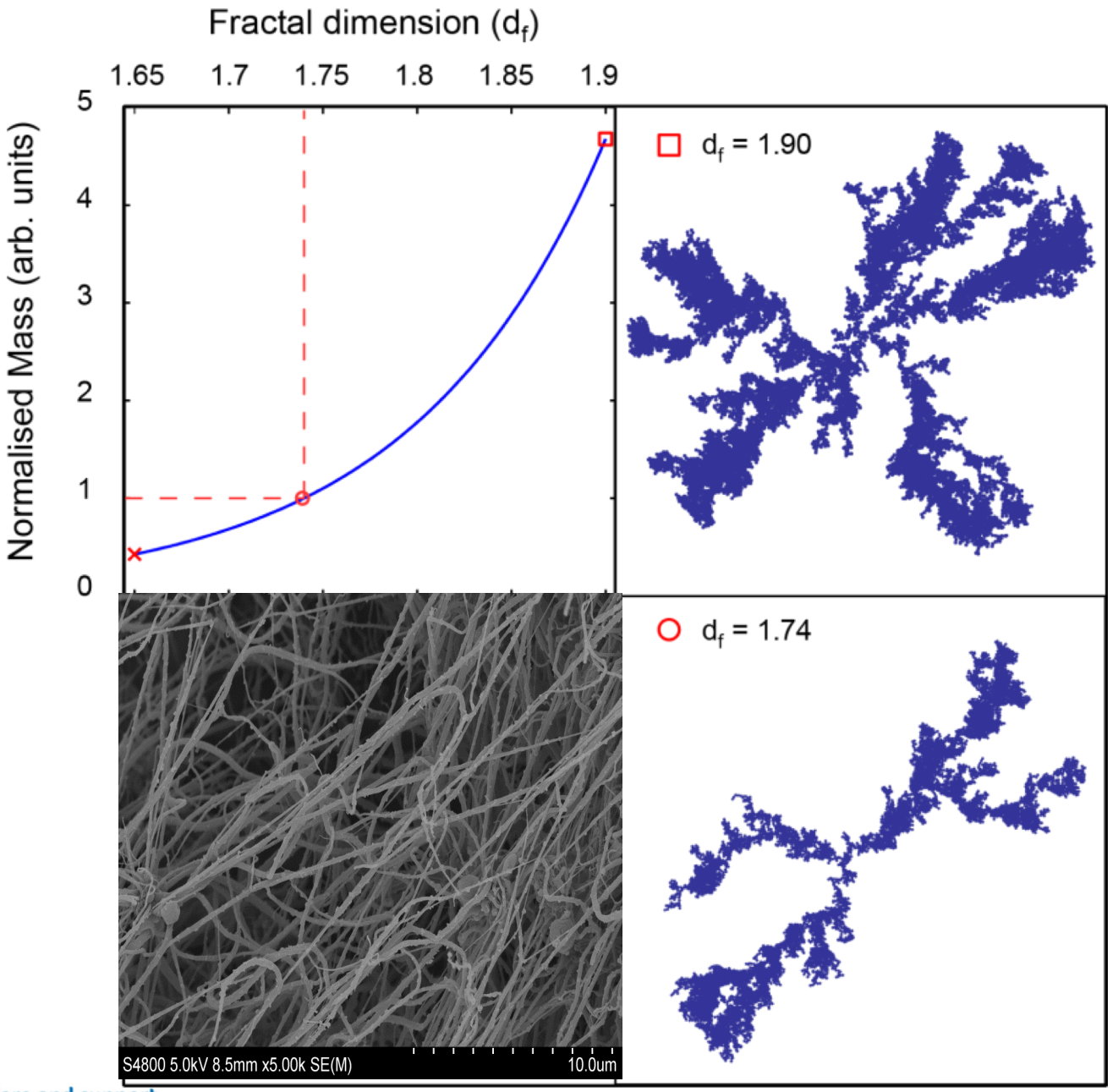
Initiation

Propagation

Clot formation



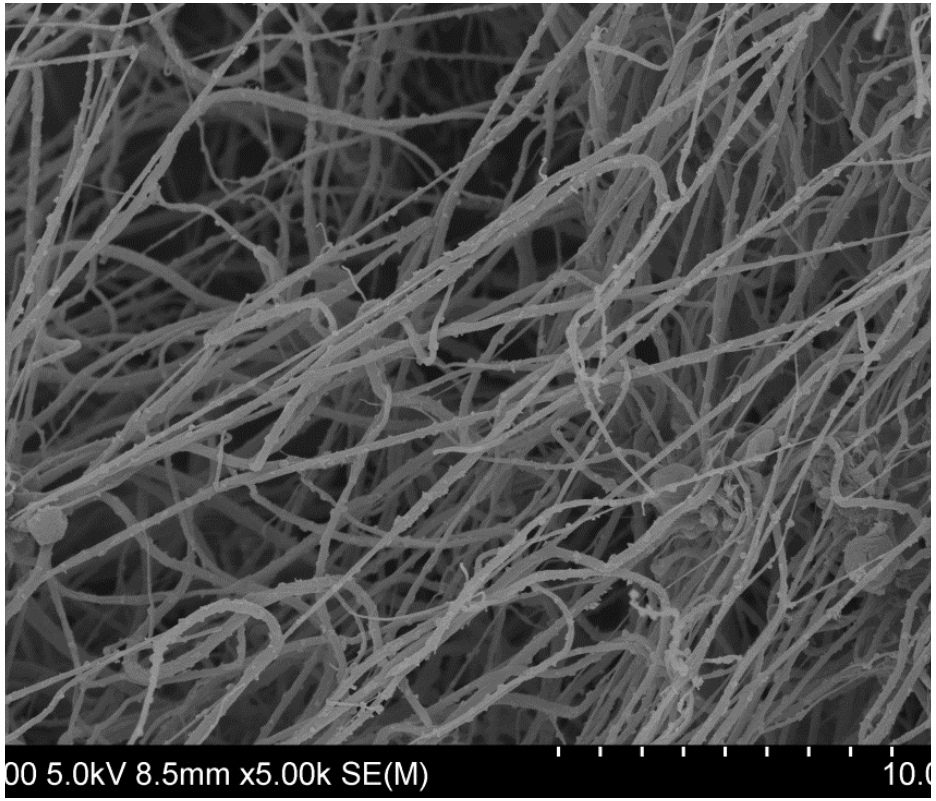




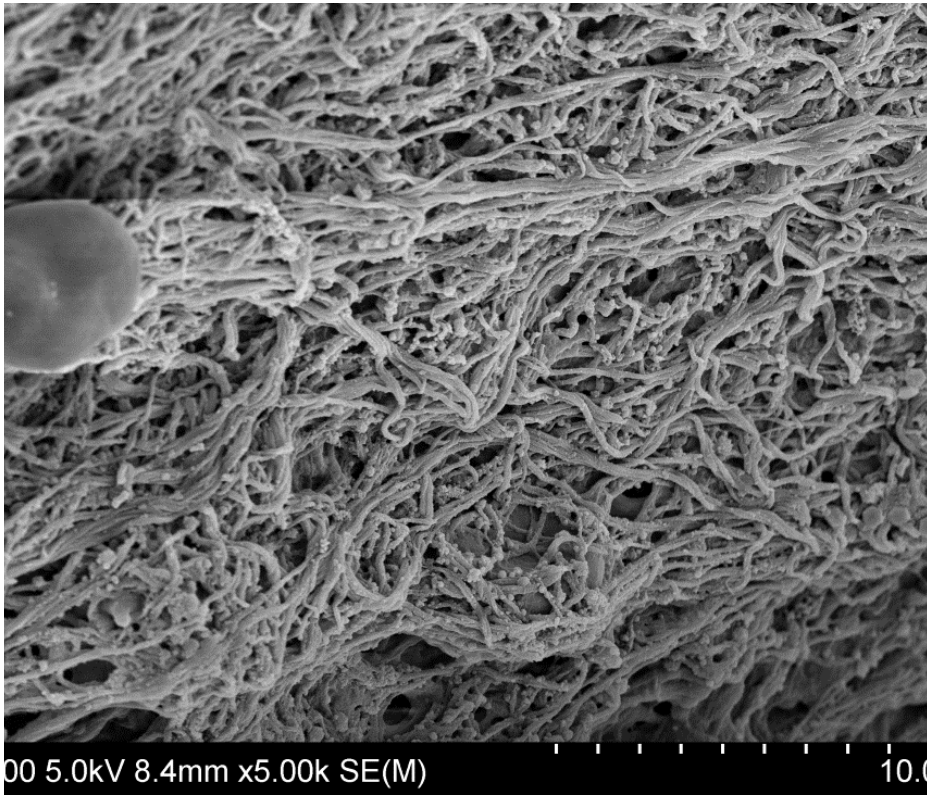
Lung cancer

Non-cancer

Electron microscopy

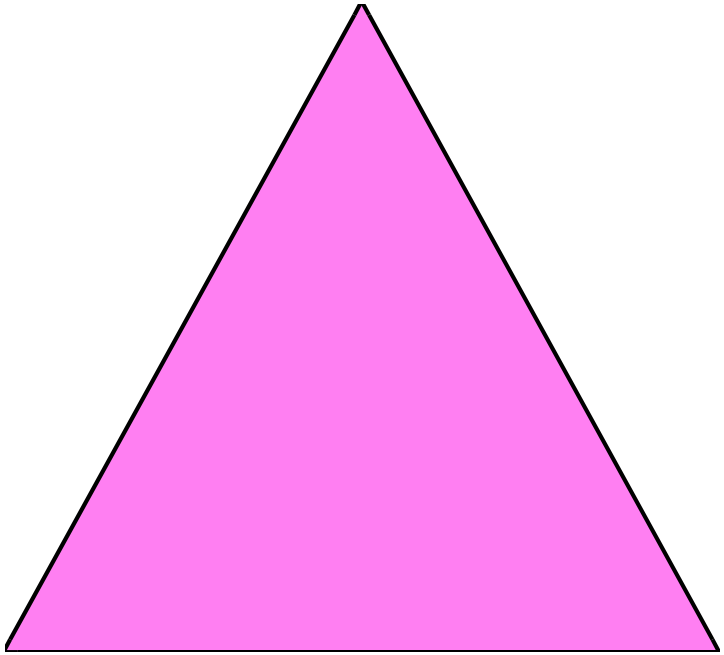


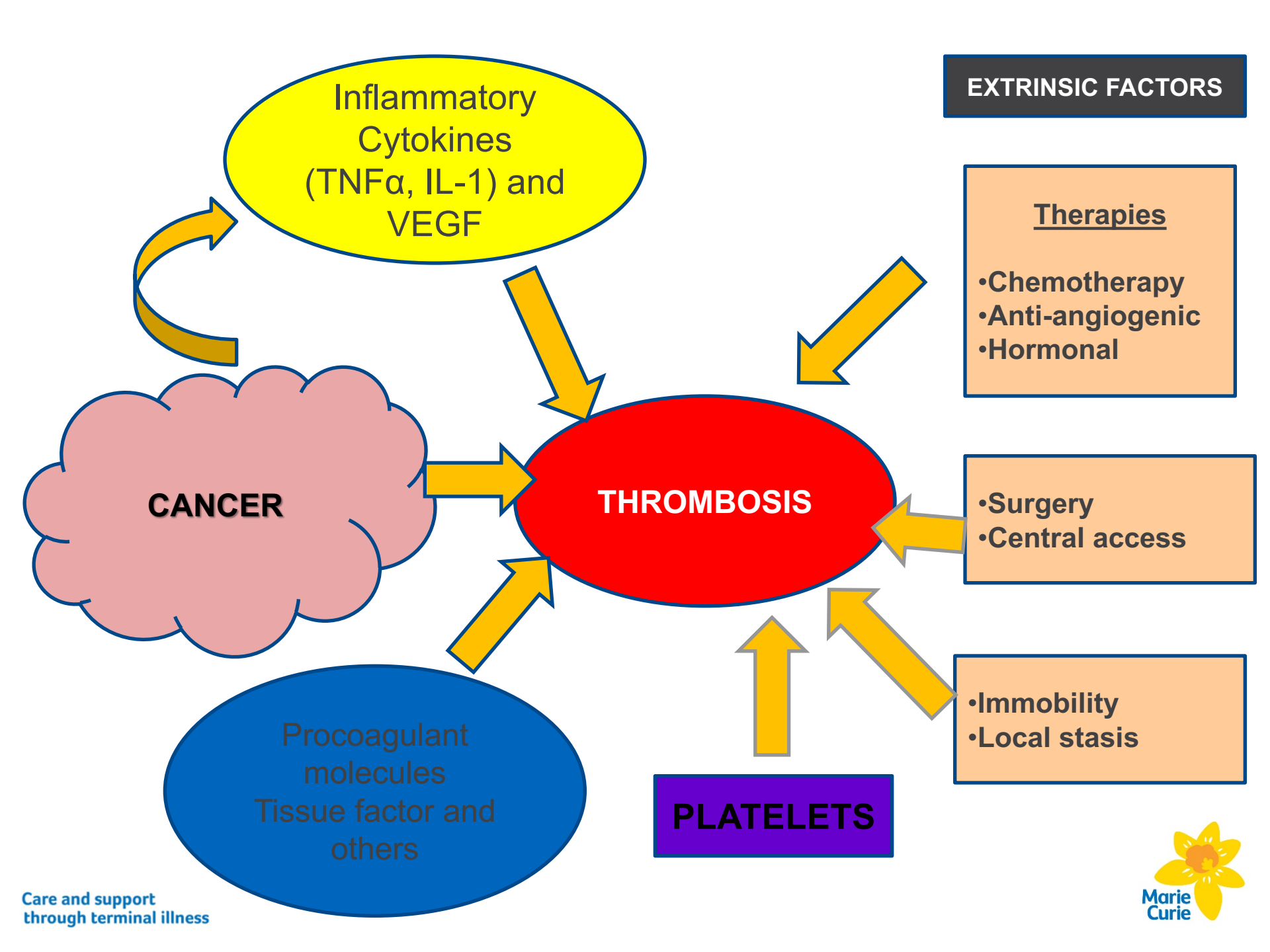
Healthy blood



Blood from patient with stage IV lung cancer

Virchow's triad




Inflammatory Cytokines (TNFα, IL-1) and VEGF
EXTRINSIC FACTORS
Therapies
•Chemotherapy
•Anti-angiogenic
•Hormonal
CANCER
THROMBOSIS
•Surgery
•Central access
Procoagulant molecules Tissue factor and others
PLATELETS
•Immobility
•Local stasis
Care and support through terminal illness
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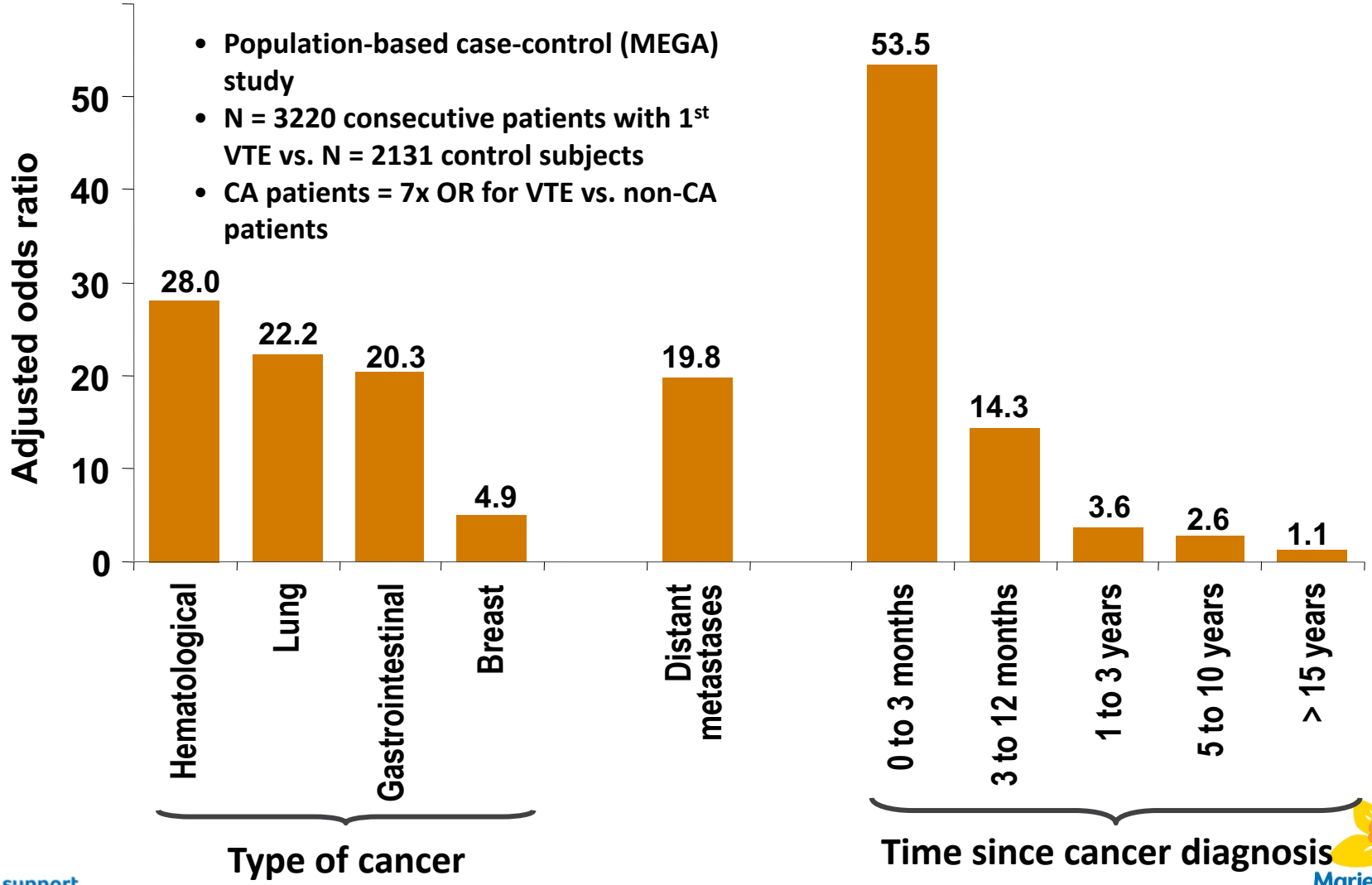
Effect of Malignancy on Risk of Venous Thromboembolism (VTE)

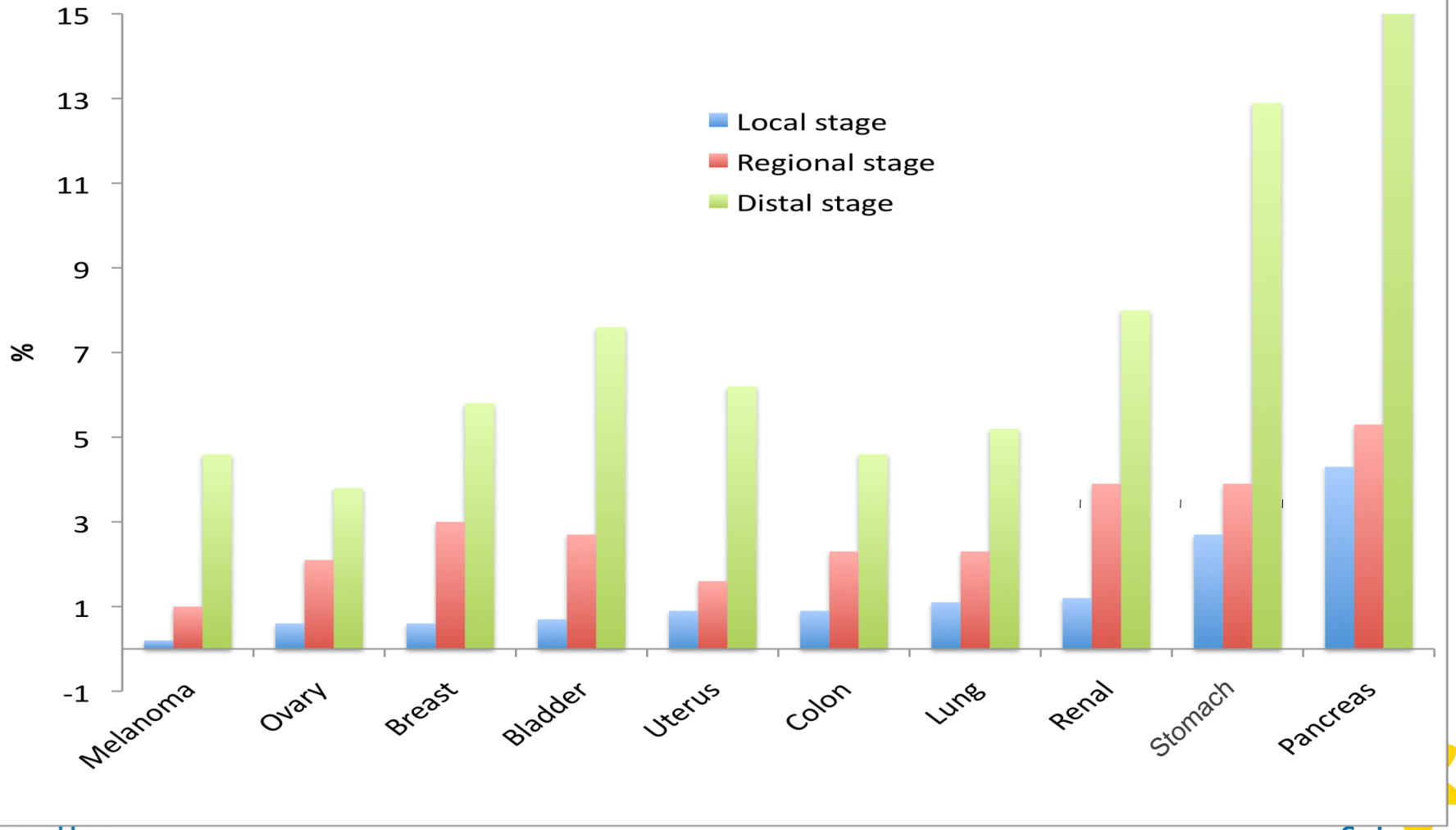


Care and support through terminal illness

Marie Curie

Silver *In:* The Hematologist - modified from Blom *et al. JAMA* 2005;293:715.

Incidence of symptomatic CAT according to the cancer type and stage



through terminal illness

Curie

Wun T, White RH. Best Pract Res Clin Haematol. 2009;22:9-23

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%

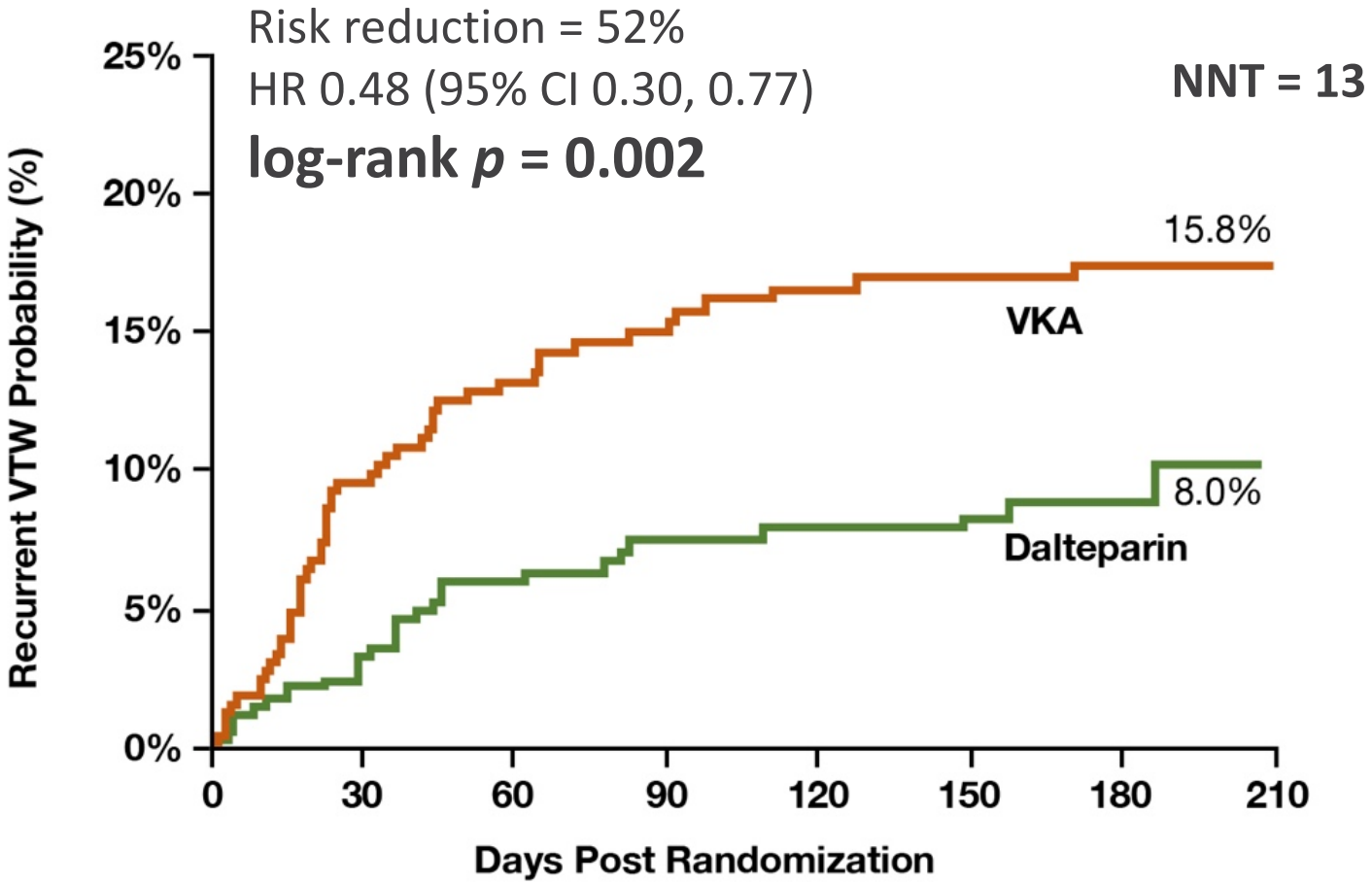
Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

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

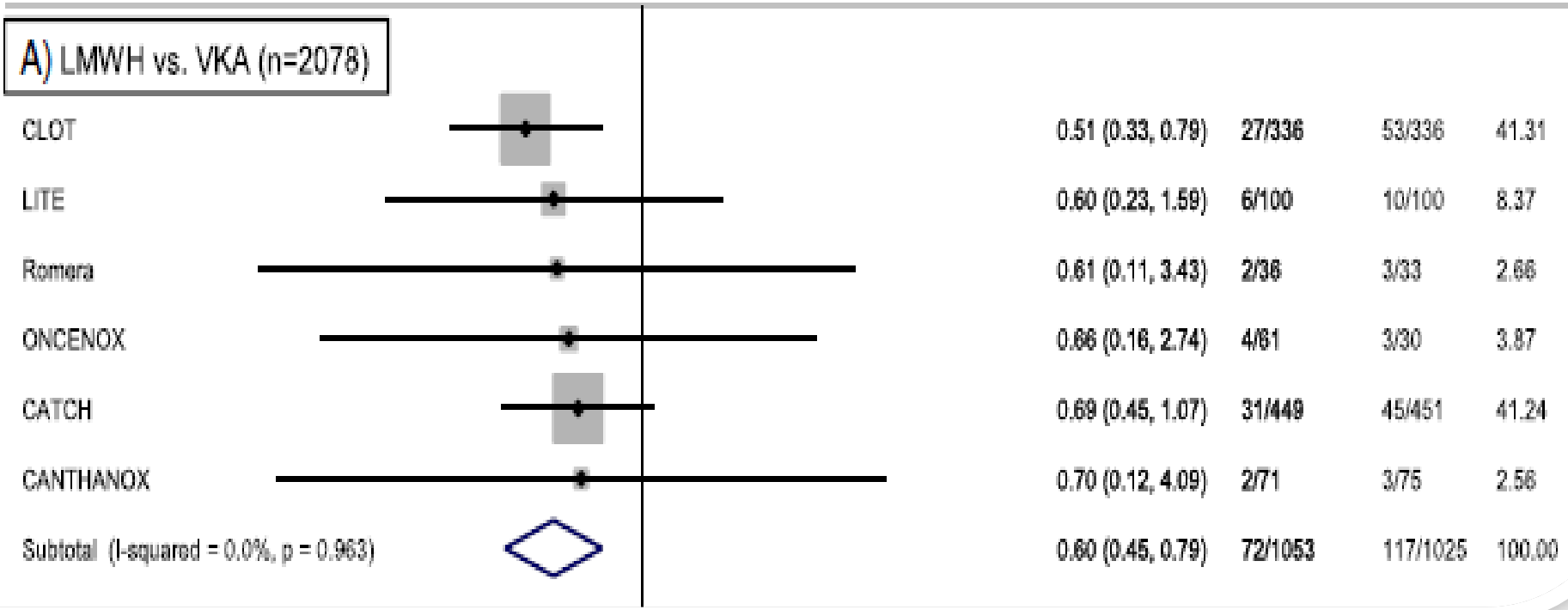
The CLOT Trial
Primary outcome: VTE recurrence



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

Lee AY *et al. N Engl J Med* 2003;349(2):146–153.

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

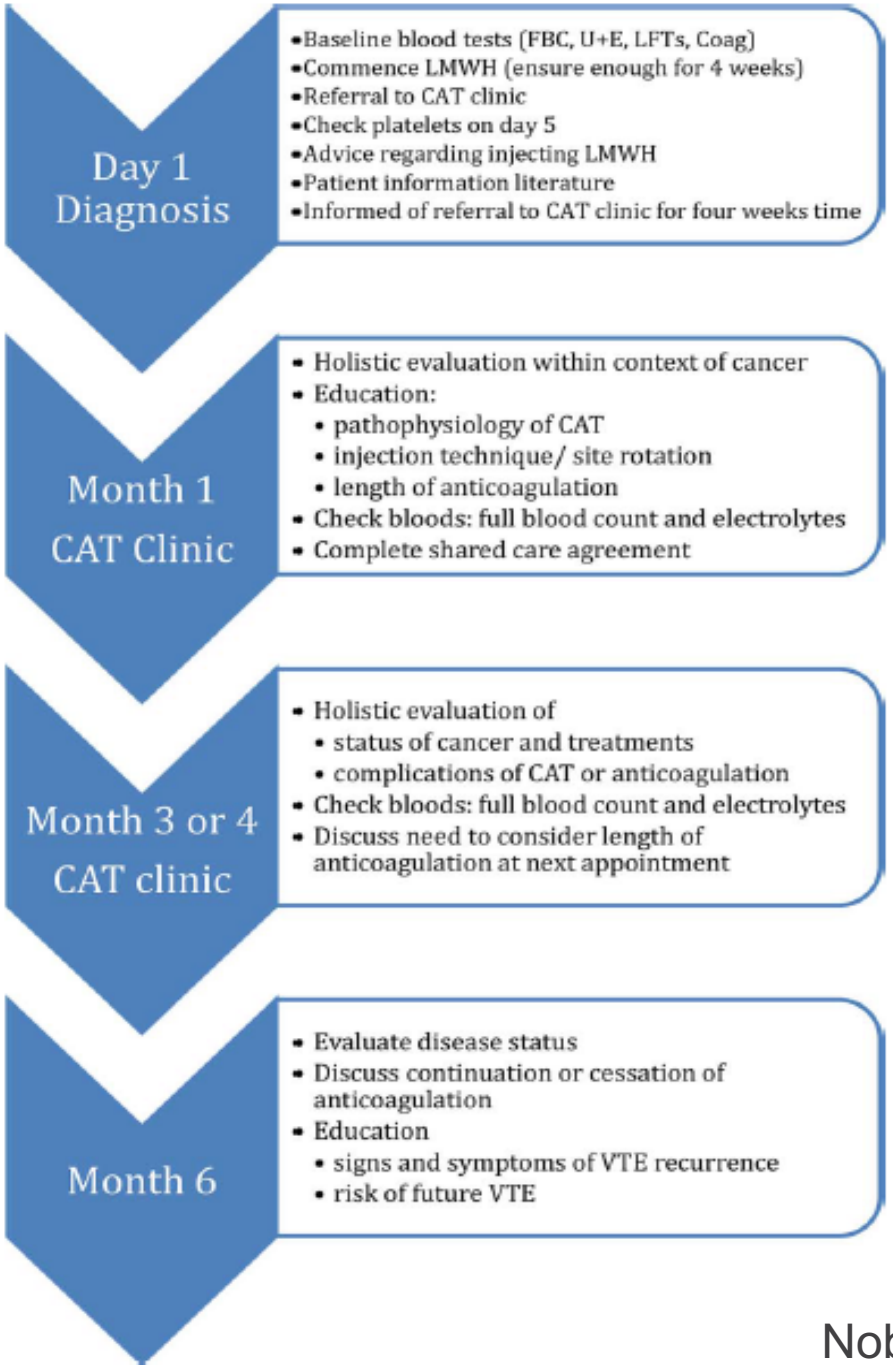
(Grade A)

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)

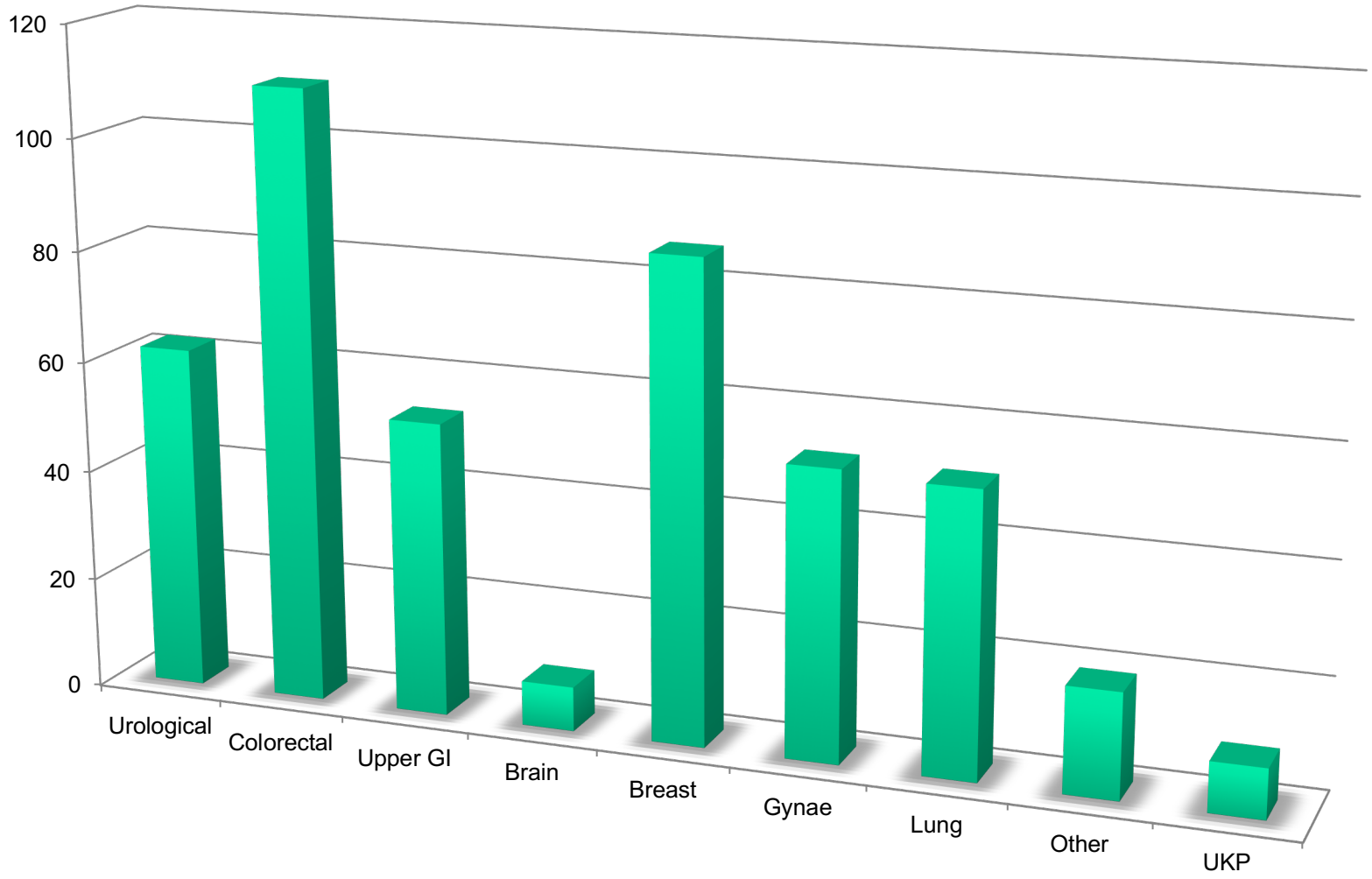
ISTH	LMWH	3 to 6 months then VKA or LMWH until cancer resolution

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



Noble et al BMJ Open 2017

Scope of patients



Patient spread

44% metastatic

60% during chemotherapy (majority palliative)

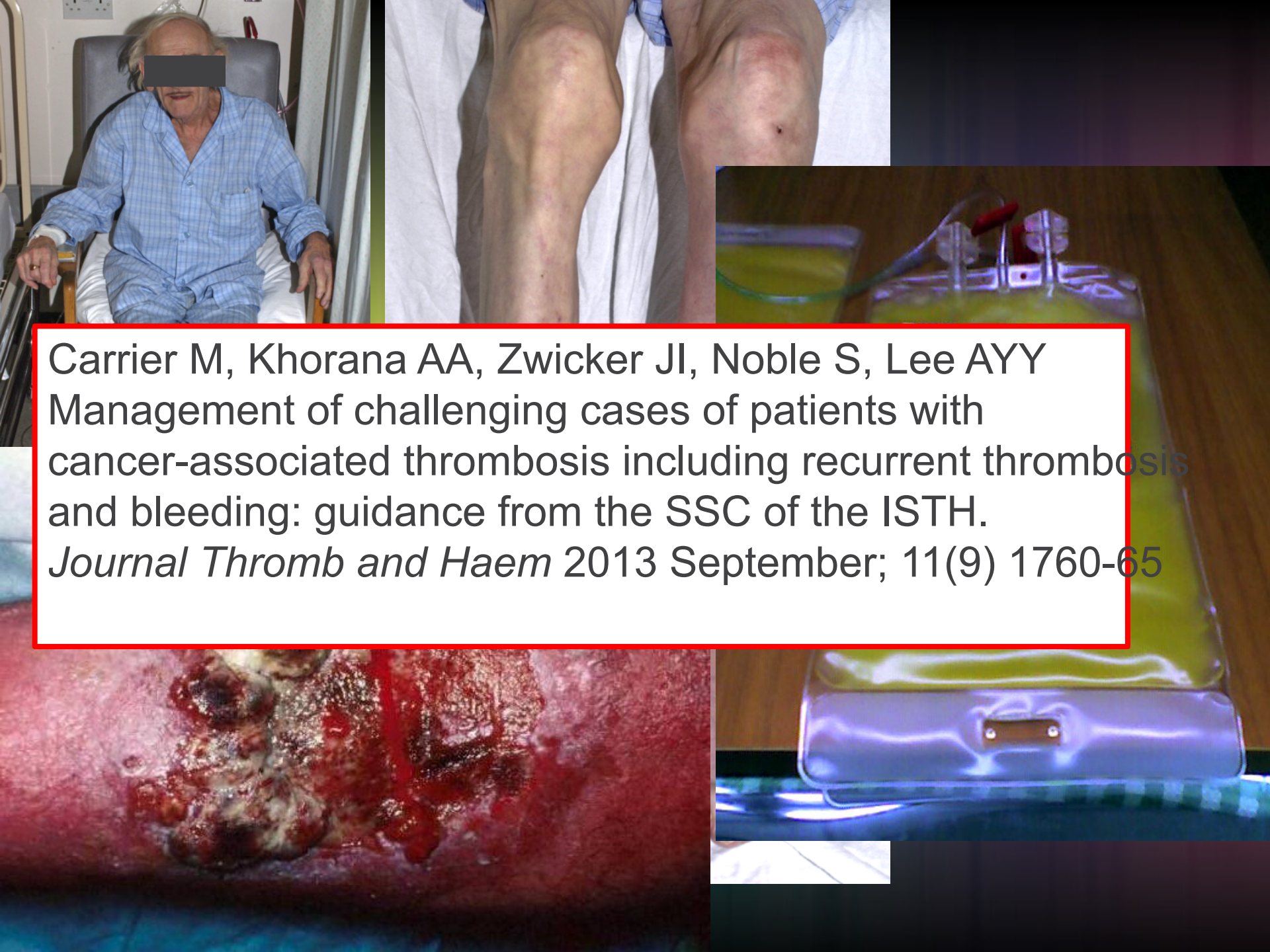
59% known to specialist palliative care services

Need for specialist input

334 CLOT regime

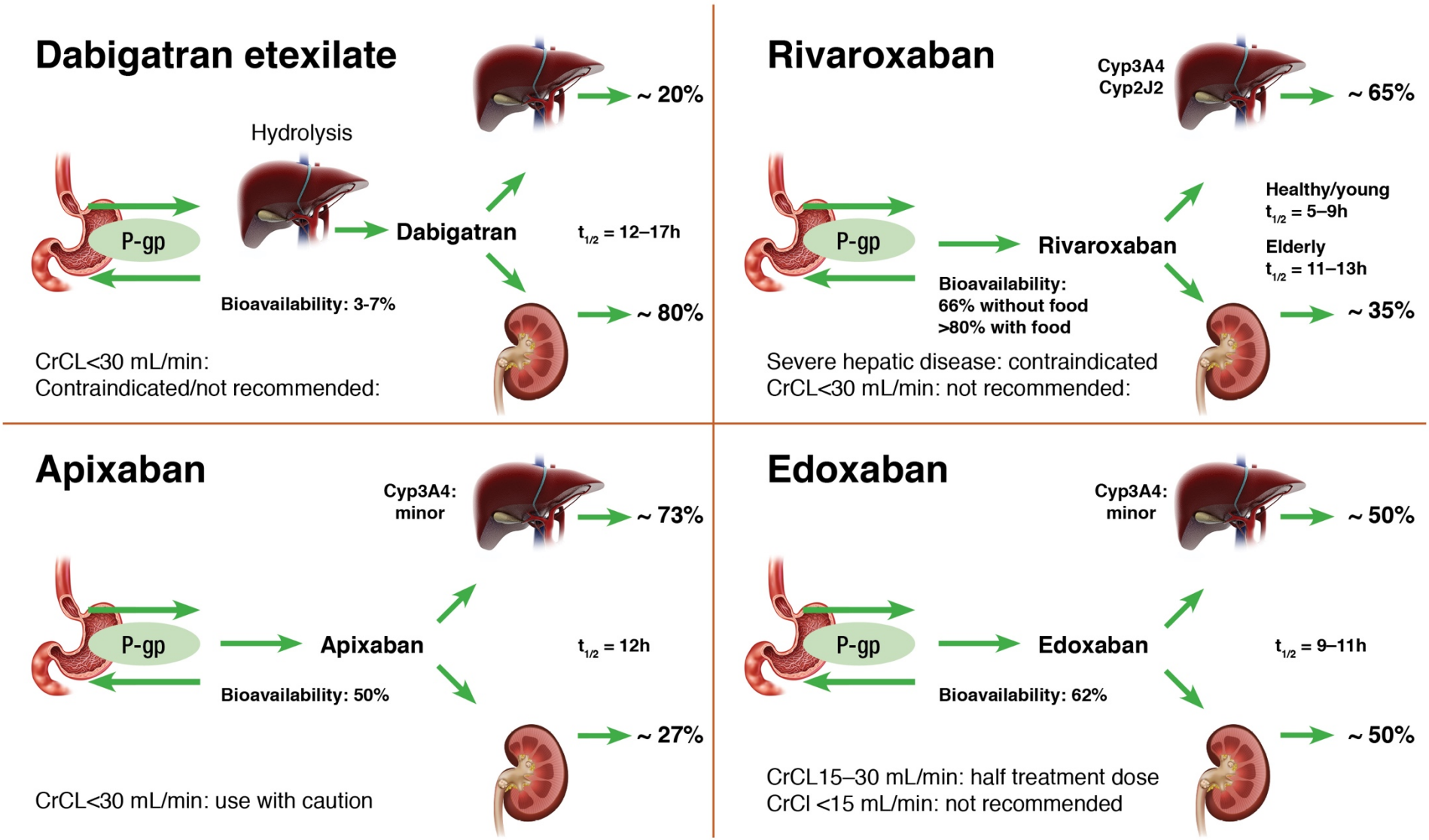
124 (27%) non CLOT

- Bleeding/ risk of bleeding
- Thrombus progression/ recurrence
- Renal impairment (EGFR<25)
- Intolerant injections
- Extremes of bodyweight



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

DOAC Pharmacology



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

VTE treatment studies - new oral anticoagulants

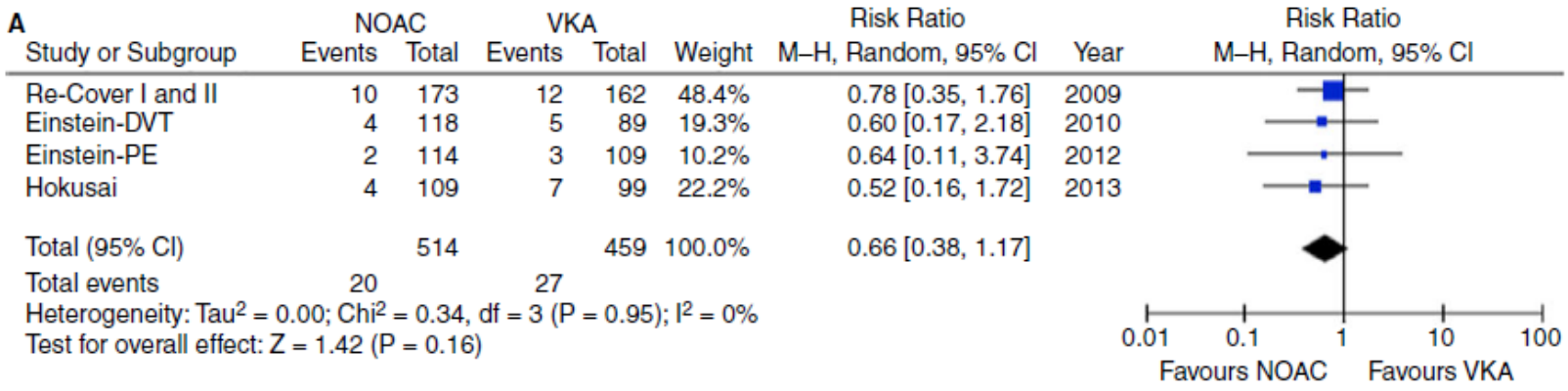
	Hokusai-VTE	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	RE-COVER I RE-COVER II
Drug	Edoxaban▼	Rivaroxaban▼	Apixaban	Dabigatran
Study design	Double-blind	Open-label	Double-blind	Double-blind
Heparin lead-in	At least 5 days	None	None	At least 5 days
Dose	60 mg qd 30 mg qd (CrCl, bw, P-gp)	15 mg bid x 3 wk then 20 mg qd	10 mg bid x 7 days then 5 mg bid	150 mg bid
Non-inferiority margin	1.5	2.0	1.8	2.75
Sample size	8,292	**EINSTEIN-DVT** 3,449 **EINSTEIN-PE** 4,832	5,400	**RE-COVER I** 2,564 **RE-COVER II** 2,568
Treatment duration	Flexible 3 to 12 months	Pre-specified 3, 6, or 12 months	6 months	6 months

Please note that there are no head to head RCTs between the NOACs. Results should not be directly compared because of important differences in the pharmacologic properties, the doses used, the patient populations, the quality of warfarin management or other aspects of the trial designs.

RCT	Total studied population	Patients with cancer
EINSTEIN Acute DVT	**Rivaroxaban** = 1731 **Enox/VKA**= 1718	**Rivaroxaban** = 6.8% **Enox/VKA** = 5.2%
EINSTEIN DVT extension	**Rivaroxaban**= 602 **placebo**= 594	**Rivaroxaban** = 4.5% **Placebo** = 4.4%
EINSTEIN-PE	**Rivaroxaban**= 2419 **Enox/VKA**= 2413	**Rivaroxaban** = 4.7% **Enox/VKA**= 4.5%
RECOVER	**Dabigatran** = 1274 **VKA** = 1265	**Dabigatran** = 5% **VKA** = 4.5%

DOACs in the treatment of CAT

Recurrent VTE



A

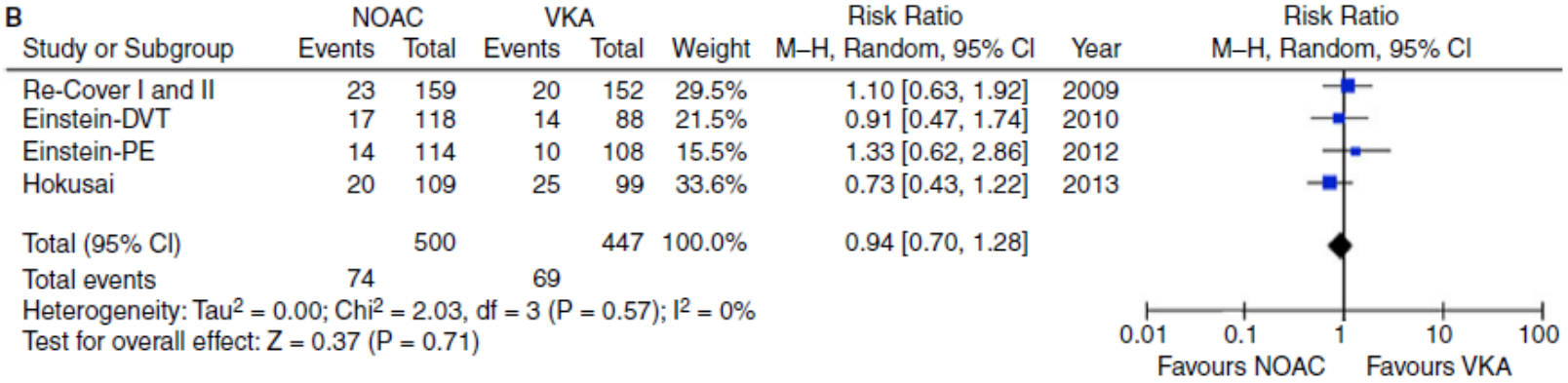
Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Re-Cover I and II	10	173	12	162	48.4%	0.78 [0.35, 1.76]	2009
Einstein-DVT	4	118	5	89	19.3%	0.60 [0.17, 2.18]	2010
Einstein-PE	2	114	3	109	10.2%	0.64 [0.11, 3.74]	2012
Hokusai	4	109	7	99	22.2%	0.52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

Care and through terminal illness

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

Proportion of metastatic patients

STUDY	LMWH	WARFARIN	RIVAROXABAN
CLOT	66%	69%	
LITE	47%	36%	
CATCH	55%	54%	
ONCENOX	54%	52%	
EINSTEIN DVT/PE		26%	19%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

ABSTRACT

BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for noninferiority; P=0.87 for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

CONCLUSIONS

Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. (Funded by Daiichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02073682.)

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*A complete list of Hokusai VTE Cancer Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Primary end point

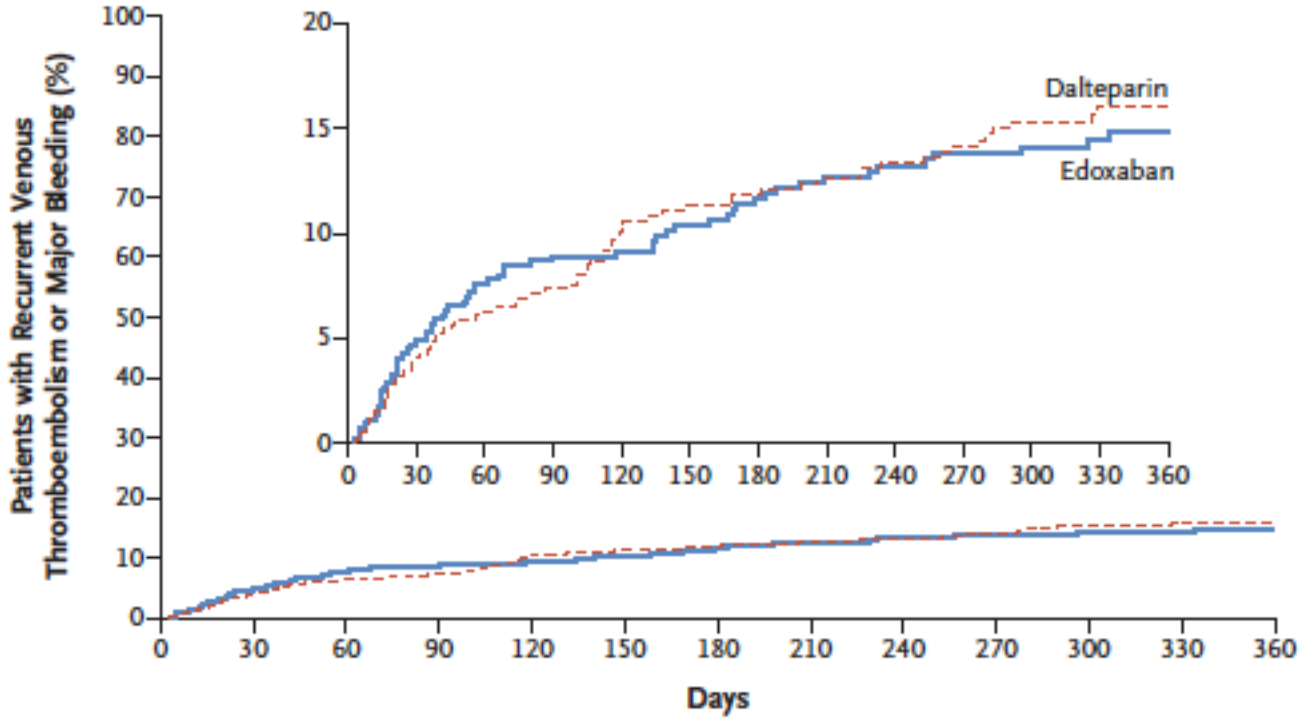
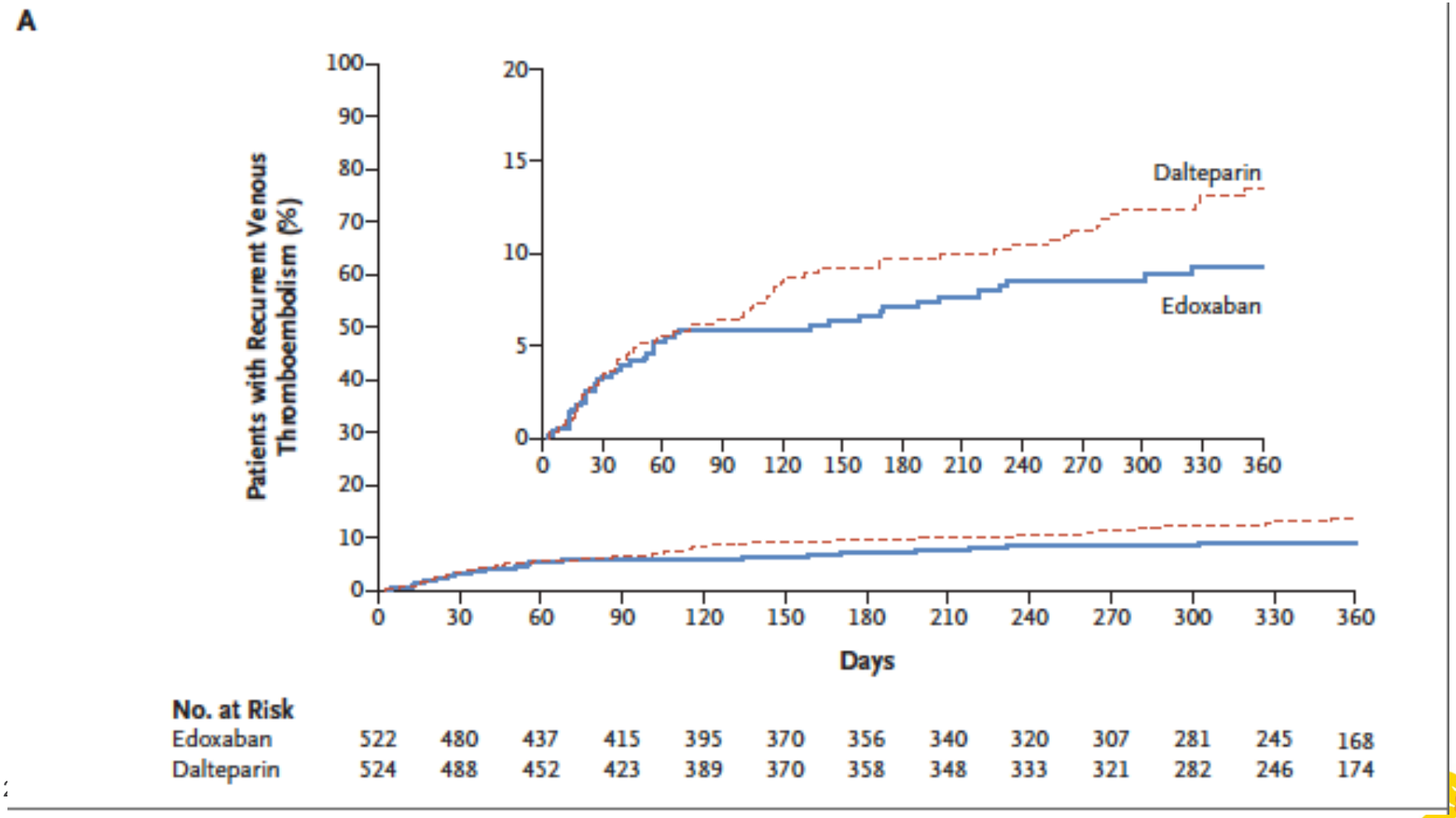


Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.

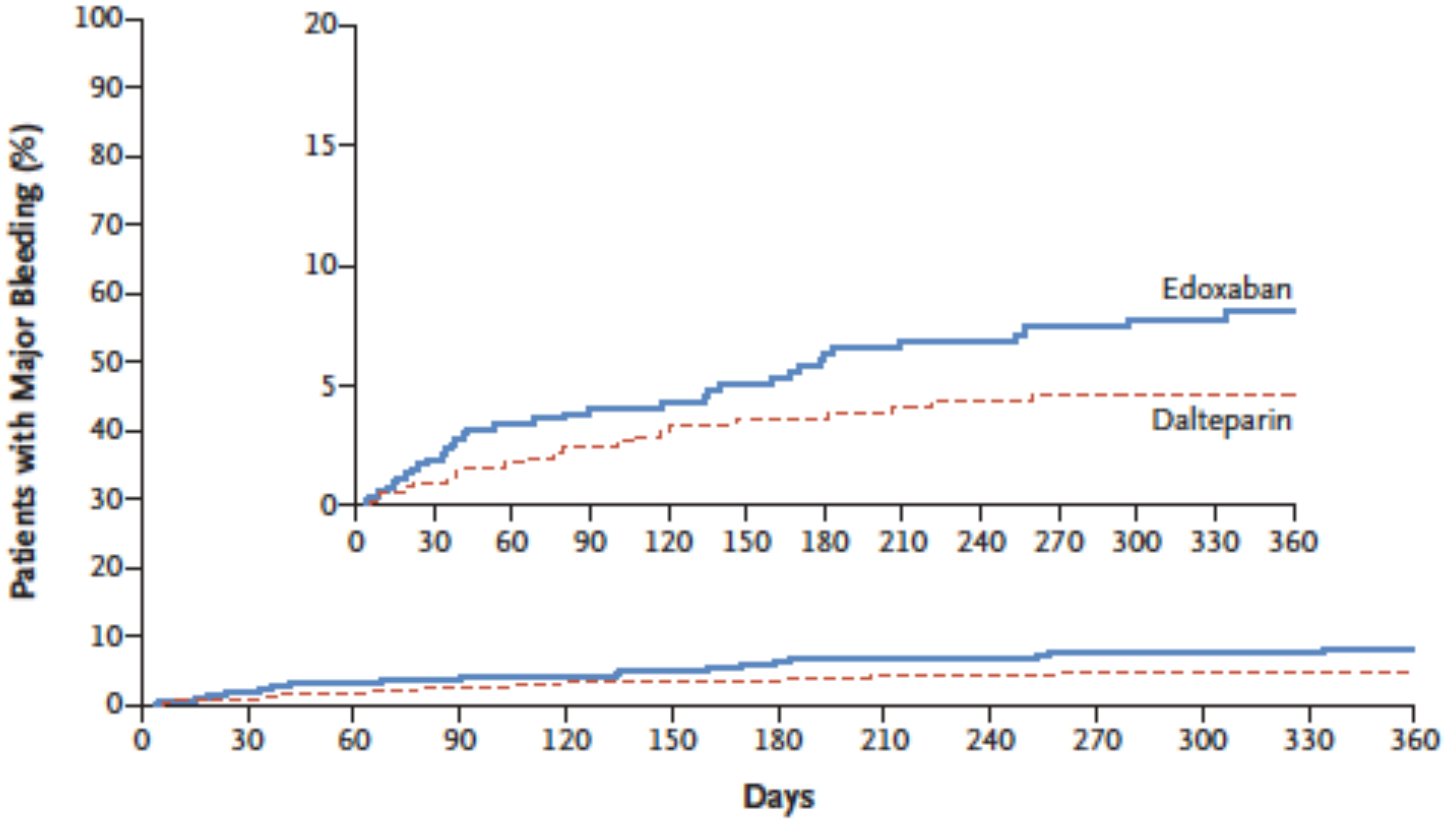
The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

Recurrent VTE



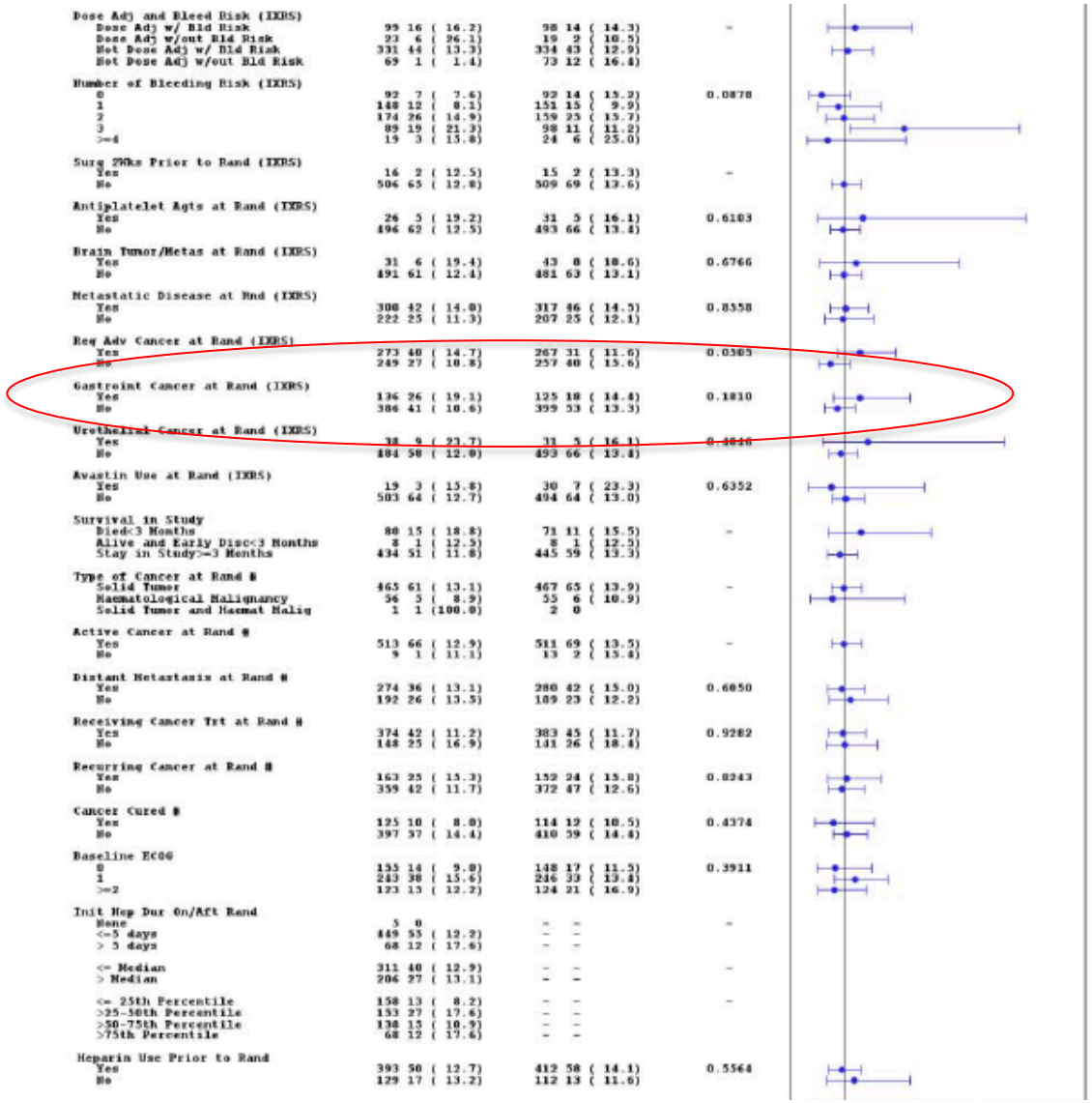
Bleeding

B



No. at Risk													
Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

Appendix: page 16/32



Dose Adj and Bleed Risk (IXRS)			
Dose Adj w/ Bld Risk	99 16 (16.2)	98 14 (14.3)	-
Dose Adj w/out Bld Risk	22 6 (26.1)	19 2 (10.5)	
Not Dose Adj w/ Bld Risk	331 44 (13.3)	334 43 (12.9)	
Not Dose Adj w/out Bld Risk	69 1 (1.4)	73 12 (16.4)	
Number of Bleeding Risk (IXRS)			
0	92 7 (7.6)	92 14 (15.2)	0.0878
1	148 12 (8.1)	151 15 (9.9)	
2	174 26 (14.9)	159 25 (15.7)	
3	89 19 (21.3)	98 11 (11.2)	
>=4	19 3 (15.8)	24 6 (25.0)	
Surg 2Wks Prior to Rand (IXRS)			
Yes	16 2 (12.5)	15 2 (13.3)	-
No	506 65 (12.8)	509 69 (13.6)	
Antiplatelet Agts at Rand (IXRS)			
Yes	26 5 (19.2)	31 5 (16.1)	0.6103
No	496 62 (12.5)	493 66 (13.4)	
Brain Tumor/Metas at Rand (IXRS)			
Yes	31 6 (19.4)	43 8 (18.6)	0.6766
No	491 61 (12.4)	481 63 (13.1)	
Metastatic Disease at Rnd (IXRS)			
Yes	308 42 (14.0)	317 46 (14.5)	0.8558
No	222 25 (11.3)	207 25 (12.1)	
Req Adv Cancer at Rand (IXRS)			
Yes	273 40 (14.7)	267 31 (11.6)	0.0305
No	249 27 (10.8)	257 40 (15.6)	
Gastroint Cancer at Rand (IXRS)			
Yes	136 26 (19.1)	125 18 (14.4)	0.1810
No	386 41 (10.6)	399 53 (13.3)	
Urothelial Cancer at Rand (IXRS)			
Yes	38 9 (23.7)	31 5 (16.1)	0.4016
No	484 58 (12.0)	493 66 (13.4)	
Avastin Use at Rand (IXRS)			
Yes	19 3 (15.8)	30 7 (23.3)	0.6352
No	503 64 (12.7)	494 64 (13.0)	
Survival in Study			
Died<3 Months	80 15 (18.8)	71 11 (15.5)	-
Alive and Early Disc<3 Months	8 1 (12.5)	8 1 (12.5)	
Stay in Study>=3 Months	434 51 (11.8)	445 59 (13.3)	
Type of Cancer at Rand #			
Solid Tumor	465 61 (13.1)	467 65 (13.9)	-
Haematological Malignancy	56 5 (8.9)	55 6 (10.9)	
Solid Tumor and Haemat Malig	1 1 (100.0)	2 0	
Active Cancer at Rand #			
Yes	513 66 (12.9)	511 69 (13.5)	-
No	9 1 (11.1)	13 2 (15.4)	
Distant Metastasis at Rand #			
Yes	274 36 (13.1)	280 42 (15.0)	0.6050
No	192 26 (13.5)	189 23 (12.2)	
Receiving Cancer Trt at Rand #			
Yes	374 42 (11.2)	383 45 (11.7)	0.9282
No	148 25 (16.9)	141 26 (18.4)	
Recurring Cancer at Rand #			
Yes	163 25 (15.3)	152 24 (15.8)	0.8243
No	359 42 (11.7)	372 47 (12.6)	
Cancer Cured #			
Yes	125 10 (8.0)	114 12 (10.5)	0.4374
No	397 57 (14.4)	410 59 (14.4)	
Baseline ECOG			
0	155 14 (9.0)	148 17 (11.5)	0.3911
1	243 38 (15.6)	246 33 (13.4)	
>=2	123 15 (12.2)	124 21 (16.9)	
Init Hep Dur On/Aft Rand			
None	5 0	- -	-
<=5 days	449 55 (12.2)	- -	
> 5 days	68 12 (17.6)	- -	
<= Median	311 40 (12.9)	- -	-
> Median	206 27 (13.1)	- -	
<= 25th Percentile	158 13 (8.2)	- -	-
>25-50th Percentile	153 27 (17.6)	- -	
>50-75th Percentile	138 15 (10.9)	- -	
>75th Percentile	68 12 (17.6)	- -	
Heparin Use Prior to Rand			
Yes	393 50 (12.7)	412 58 (14.1)	0.5564
No	129 17 (13.2)	112 13 (11.6)	

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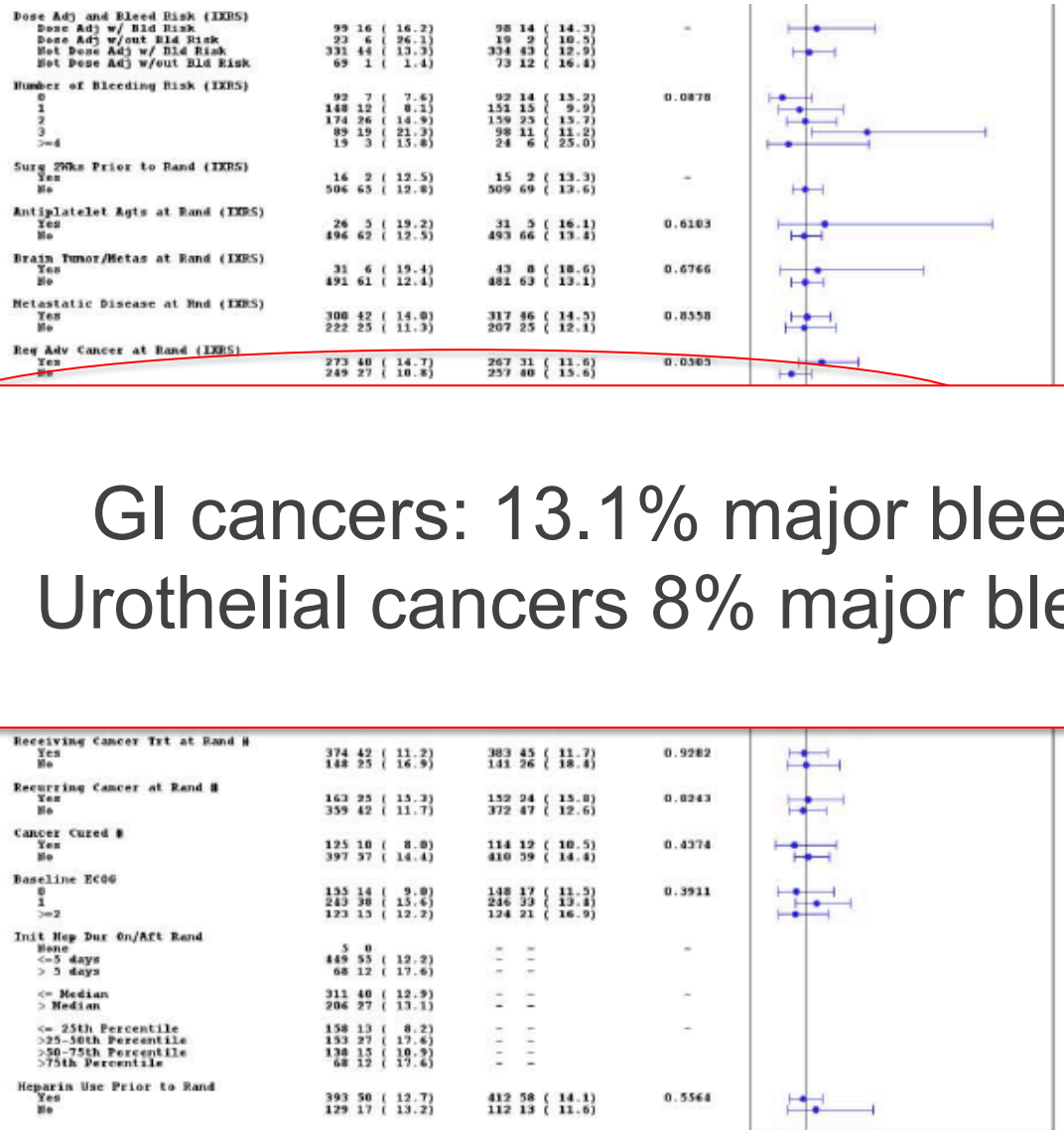


GI cancers: 13.1% major bleeding
Urothelial cancers 8% major bleeding

Select-D

Rivaroxaban vs dalteparin

400 patients: 90% metastatic disease, 83% chemo

4% vs 11% (95% CI 7-17%) recurrent VTE

4% vs 3% major bleeds

11% vs 2% CRNMB

Drug interations

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

Lee, AY, Peterson EA. *Blood* 2013.

Special circumstances

	LMWH	DOACs
Extremes of body weight	Commonly used	Not recommended
Chemotherapy	Few drug-drug interactions	Avoid in strong inducers/ inhibitors of p-GP or CYP3A4
Renal impairment	Dose adjustment	Dose adjustment
Thrombocytopenia	Dose adjustment	Dose adjustment

	LMWH	DOACs
Heparin induced thrombocytopenia	Contraindicated	Not contraindicated
Upper GI/ urothelial cancers	Commonly used	Increased bleeding risk: avoid
Needle phobia	Not advised	Acceptable
Liver disease	Used with caution	Used with caution

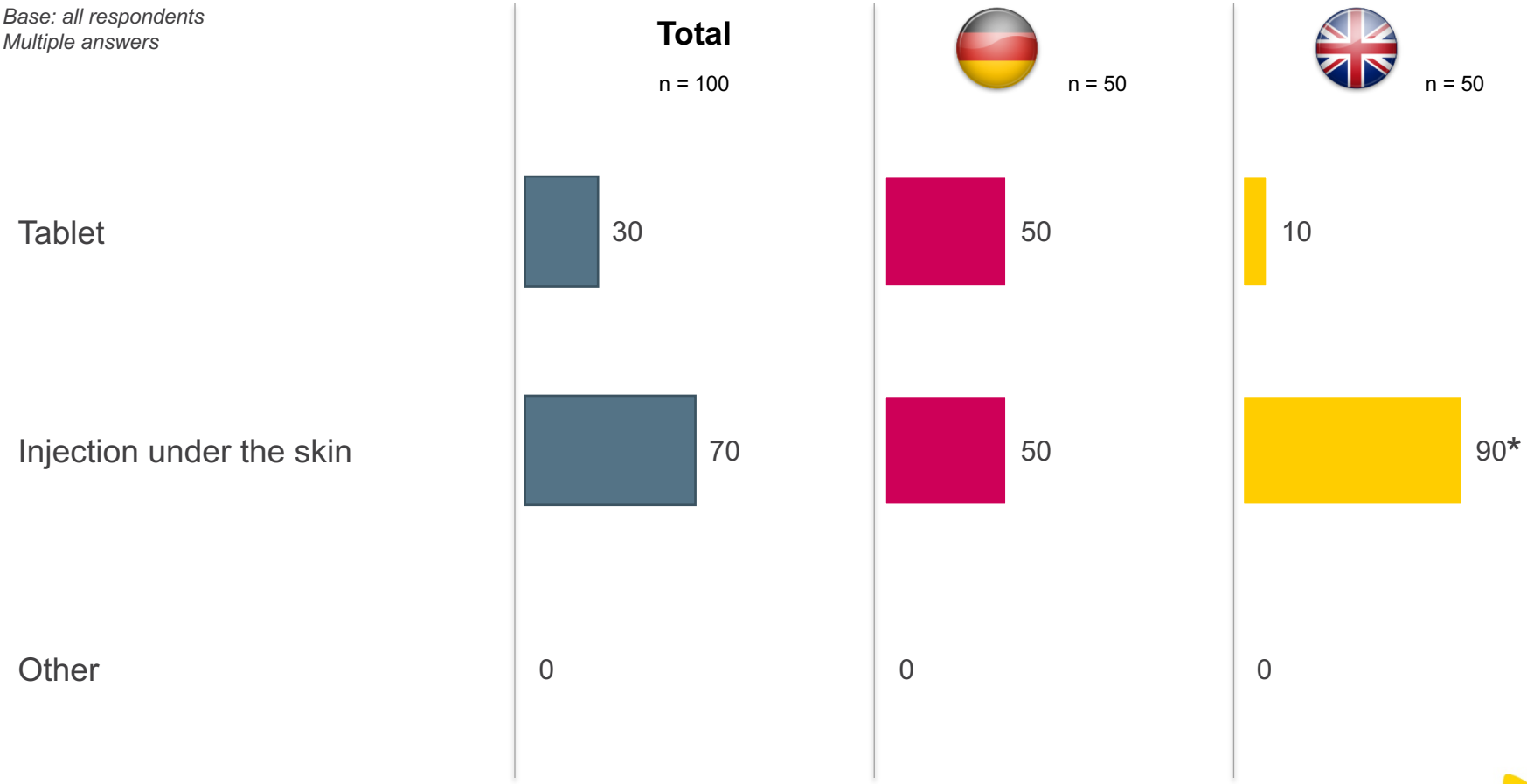
Renal impairment

	Apixaban	Edoxaban	Dabigatran	Rivaroxaban
Renal Clearance	27%	50%	80%	35%
CrCL <30ml/min	Use with caution	Dose reduction	Do not use	Do not use

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

Administration of medication (%)

Base: all respondents
Multiple answers



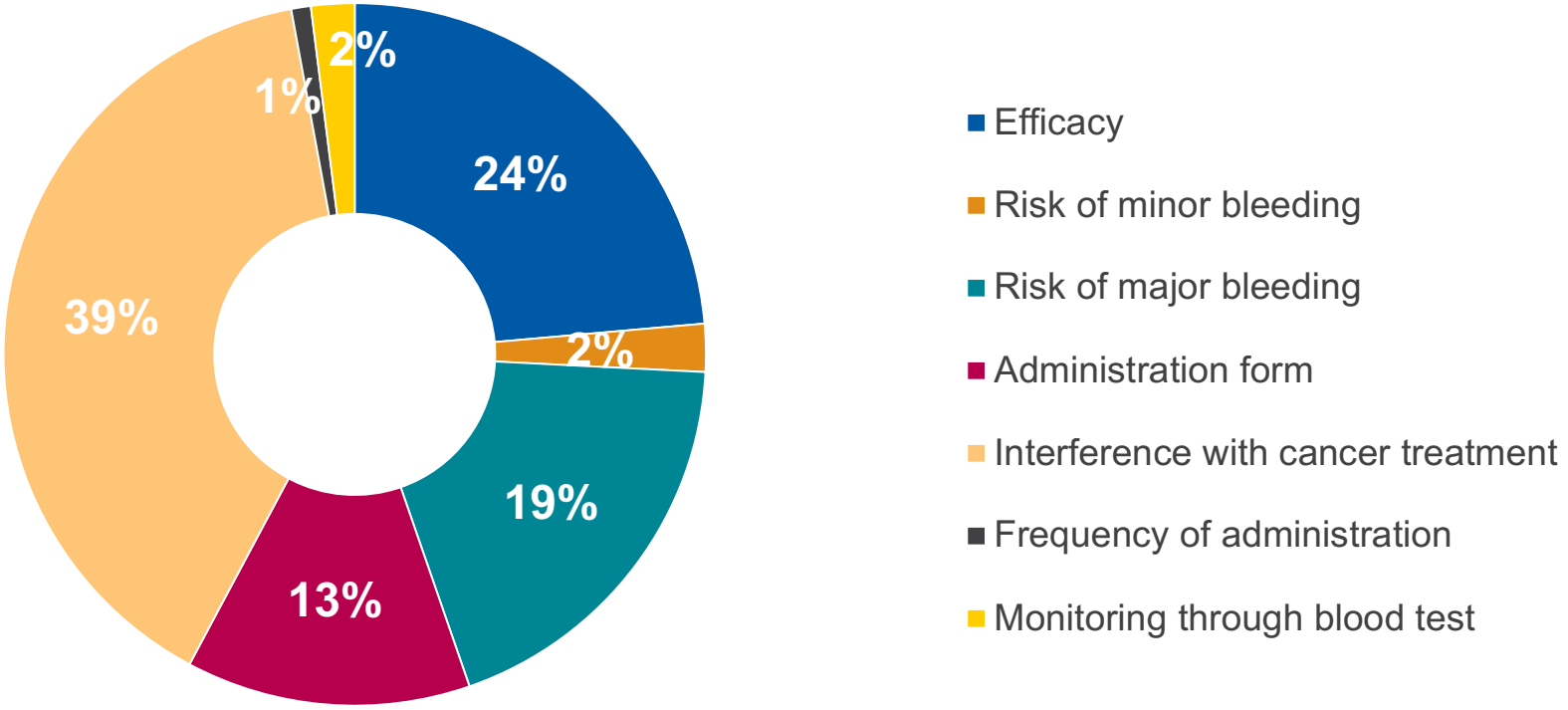
* Significant difference to Germany

Care and support through terminal illness

Marie Curie

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

Care and support through terminal illness

Marie Curie

To conclude

1. DOACs non inferior to LMWH for CAT
2. Better in preventing VTE recurrence
3. Increased bleeding risk (GI/ urothelial)
4. Drug drug interations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Care and support
through terminal illness