Cancer associated thrombosis

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CARDIFF UNIVERSITY
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Marie Curie
Care and support through terminal illness

- **Cancer associated thrombosis becoming more complex**
  - Systemic anti cancer therapies
  - Patients living longer with metastatic disease
  - Increasing number of anticoagulants with CAT data
- **Individualised approach**
  - One size does not fit all
- **Advanced cancer different beast?**
  - Increased bleeding risk
  - VTE manifestation of advanced disease
  - ?biomarker of impending death?

Patient 1

- 58 year old male
- T3 N2 M0 carcinoma oesophagus
- Neoadjuvant chemotherapy: cisplatin/ 5FU
- 2nd cycle sudden onset SOB
- CTPA: multiple moderate volume pulmonary emboli

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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The NEW ENGLAND JOURNAL

ORIGINAL AR

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RESULTS

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CONCLUSIONS

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VTE Cancer ClinicalTrials.gov

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JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine

ABSTRACT

Purpose

Venous thromboembolism (VTE) is common in patients with cancer. Long-term daily subcutaneous low molecular weight heparin has been standard treatment for such patients. The purpose of this study was to assess if an oral factor Xa inhibitor, rivaroxaban, would offer an alternative treatment for VTE in patients with cancer.

Patient and Methods

In this multicenter, randomized, open-label, pilot trial in the United Kingdom, patients with active cancer who had symptomatic pulmonary embolism (PE), incidental PE, or symptomatic lower-extremity proximal deep vein thrombosis (DVT) were recruited. Allocation was to dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2-6) or rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months). The primary outcome was VTE recurrence over 6 months. Safety was assessed by major bleeding and clinically relevant nonmajor bleeding (CRNMB). A sample size of 400 patients would provide estimates of VTE recurrence to within ± 4.5%, assuming a VTE recurrence rate at 6 months of 10%.

Results

A total of 203 patients were randomly assigned to each group, 58% of whom had metastases. Twenty-six patients experienced recurrent VTE (dalteparin, $n = 18$; rivaroxaban, $n = 8$). The 6-month cumulative VTE recurrence rate was 11% (95% CI, 7% to 16%) with dalteparin and 4% (95% CI, 2% to 9%) with rivaroxaban (hazard ratio [HR], 0.43; 95% CI, 0.19 to 0.99). The 6-month cumulative rate of major bleeding was 4% (95% CI, 2% to 8%) for dalteparin and 6% (95% CI, 3% to 11%) for rivaroxaban (HR, 1.83; 95% CI, 0.68 to 4.96). Corresponding rates of CRNMB were 4% (95% CI, 2% to 9%) and 13% (95% CI, 9% to 19%), respectively (HR, 3.76; 95% CI, 1.63 to 8.69).

Conclusion

Rivaroxaban was associated with relatively low VTE recurrence but higher CRNMB compared with dalteparin.

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INTRODUCTION

Venous thromboembolism (VTE) is a common occurrence in patients with malignant disease. Acute VTE is treated with anticoagulant therapy to prevent recurrent thrombosis, including potentially fatal pulmonary embolism (PE). The risk of recurrent thrombosis is increased at least two-fold in patients with cancer compared with patients without cancer.[1] Furthermore, there is an increased risk of anticoagulant-induced bleeding in patients with cancer compared with patients without.[2] For more than a decade, low molecular weight heparin (LMWH) for at least 6 months has been the standard treatment for acute VTE in patients with cancer.[3,4] In cancer-associated thrombosis, there is limited evidence on the duration of anticoagulant therapy beyond 6 months. Guidelines recommend that treatment continue as long as the cancer is active.[5]

Over the last decade, a new class of anticoagulant, which directly inhibits a clotting factor and is not a vitamin K antagonist, has been developed.

Author affiliations and support information (if applicable) appear at the end of this article.

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Written on behalf of the SELECT-D Collaborative Group.

The opinions, results, and conclusions reported herein are those of the authors and are independent of the funding sources.

Clinical trial information: ISRCTN80712308; EudraCT 2012-000550-27.

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ASSOCIATED CONTENT

Appendix
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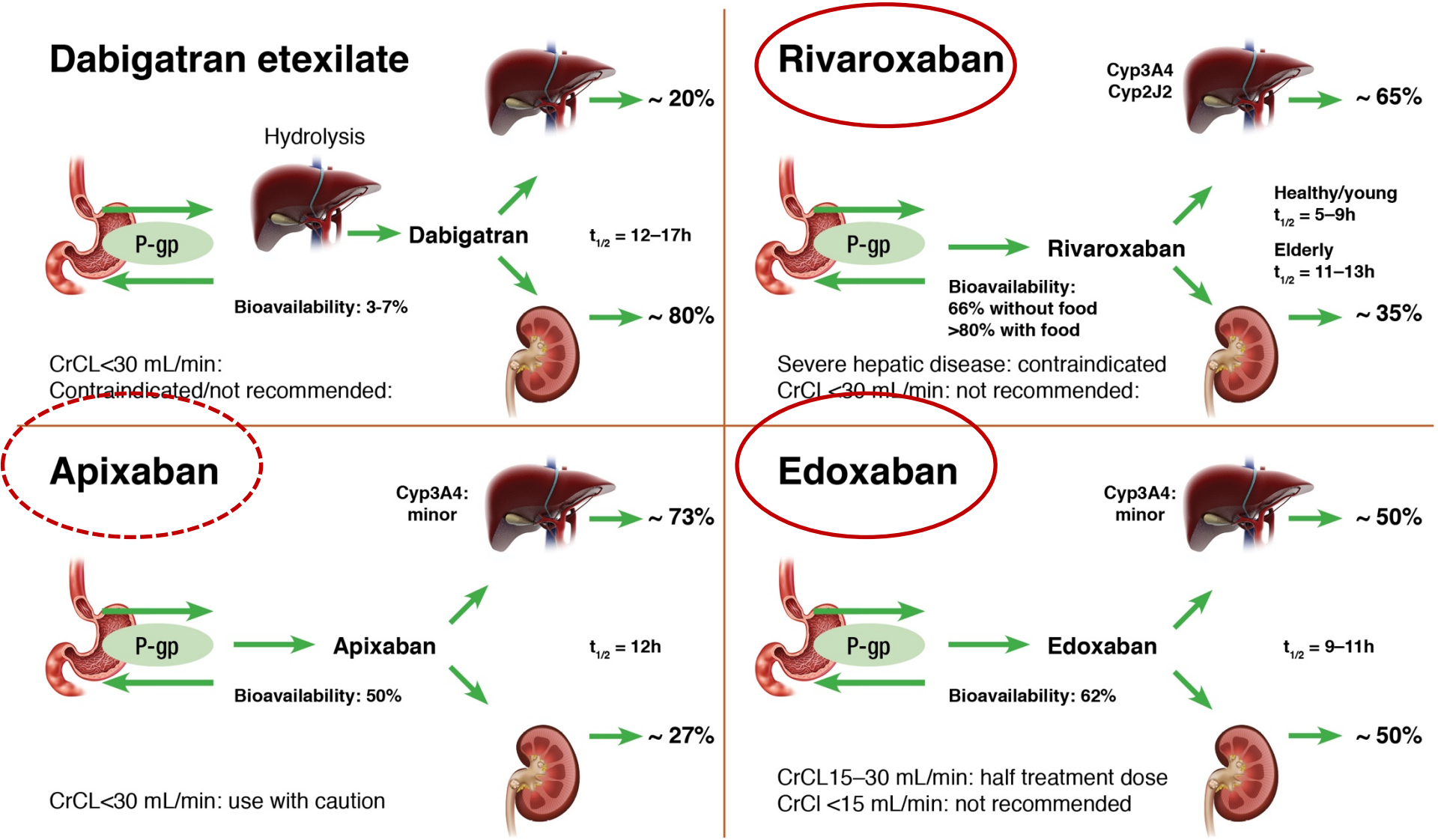
Data Supplement
DOI: https://doi.org/10.1200/JCO.2018.78.8034

DOI: https://doi.org/10.1200/JCO.2018.78.8034

DOAC Pharmacology



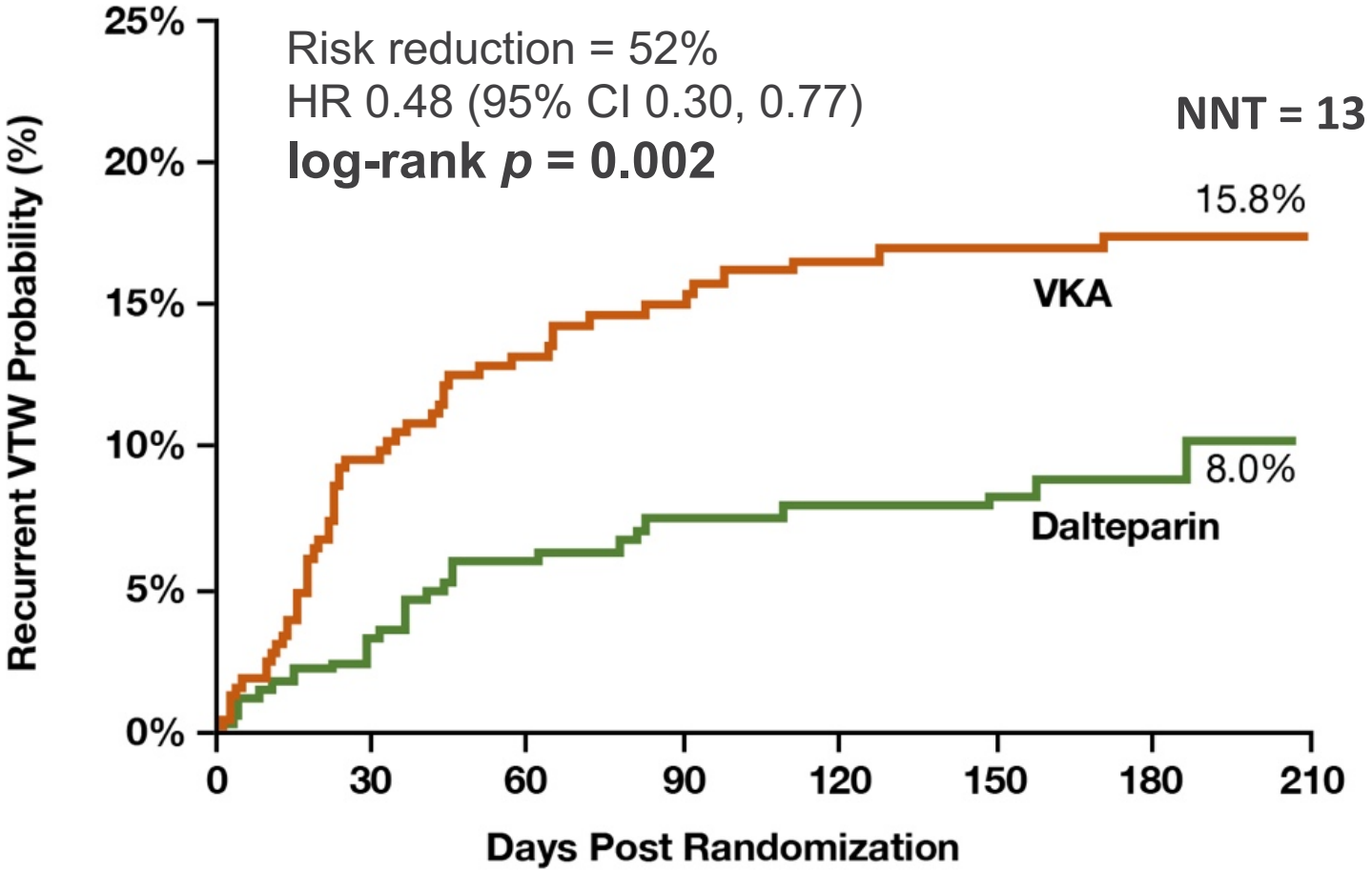
Adapted from: Heidbuchel H *et al. Europace* 2013; U.S., Canadian Prescribing Information CrCl = creatinine clearance

DOACs and the jobbing oncologist

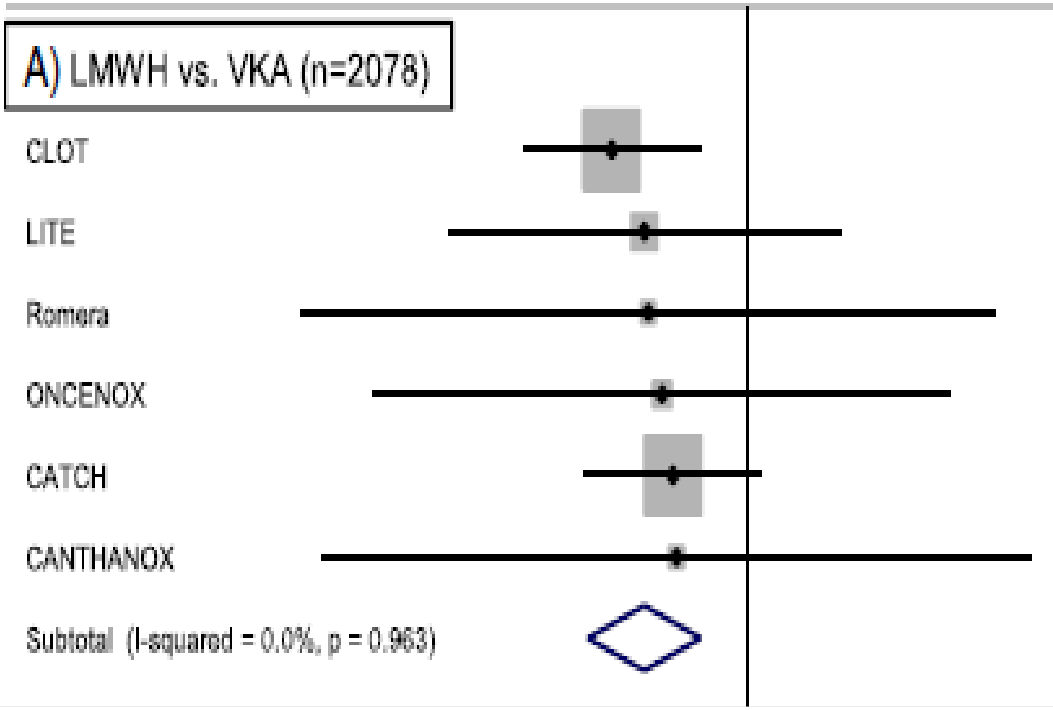
DOACs are only as safe as the stupidest person allowed to prescribe them

Current practice and recommendations

The CLOT Trial
Primary outcome: VTE recurrence



LMWH vs warfarin meta analysis



Study ID	RR (95% CI)	Events, Intervention	Events, VKA	% Weight
CLOT	0.51 (0.33, 0.79)	27/336	53/336	41.31
LITE	0.60 (0.23, 1.59)	6/100	10/100	8.37
Romera	0.61 (0.11, 3.43)	2/36	3/33	2.66
ONCENOX	0.66 (0.16, 2.74)	4/61	3/30	3.87
CATCH	0.69 (0.45, 1.07)	31/449	45/451	41.24
CANTHANOX	0.70 (0.12, 4.09)	2/71	3/75	2.56
Subtotal (I-squared = 0.0%, p = 0.963)	0.60 (0.45, 0.79)	72/1053	117/1025	100.00

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.

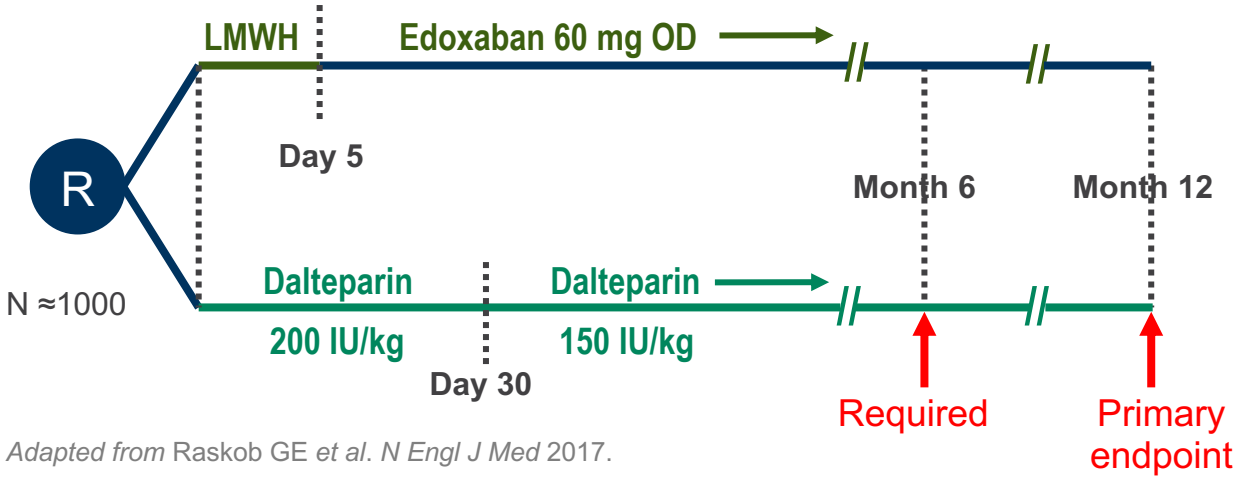
(Grade D)

Recent data challenges us to think about the needs and desires of individual patients

Hokusai VTE Cancer

Primary outcome: composite of recurrent VTE or major bleeding regardless of duration of therapy

Secondary outcomes: VTE, PE, DVT, major bleeding, CRNMB, all cause death, EFS

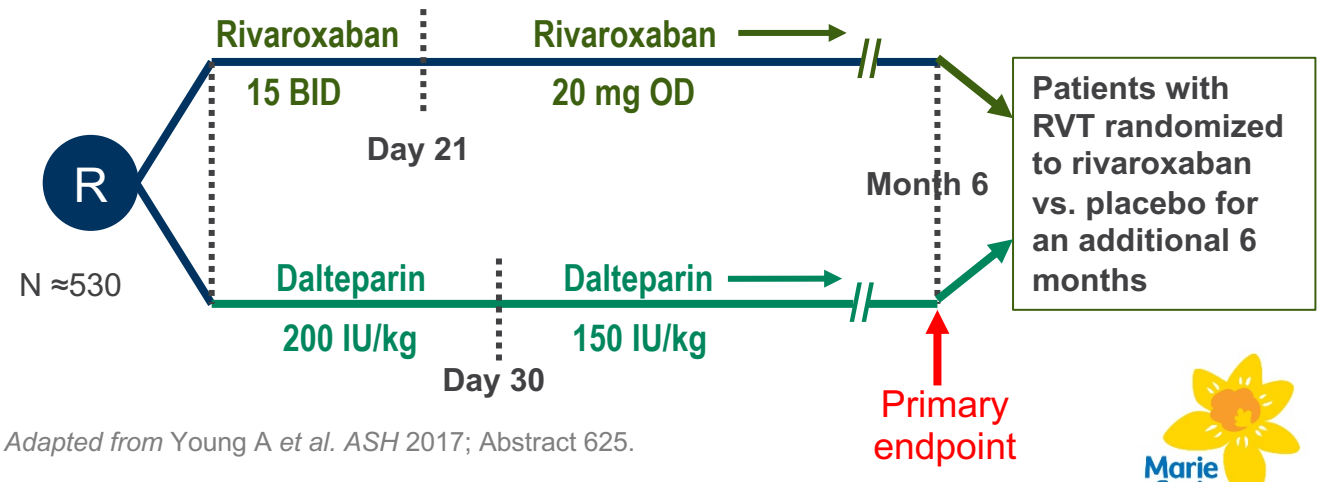


Adapted from Raskob GE *et al. N Engl J Med* 2017.

SELECT-D pilot study

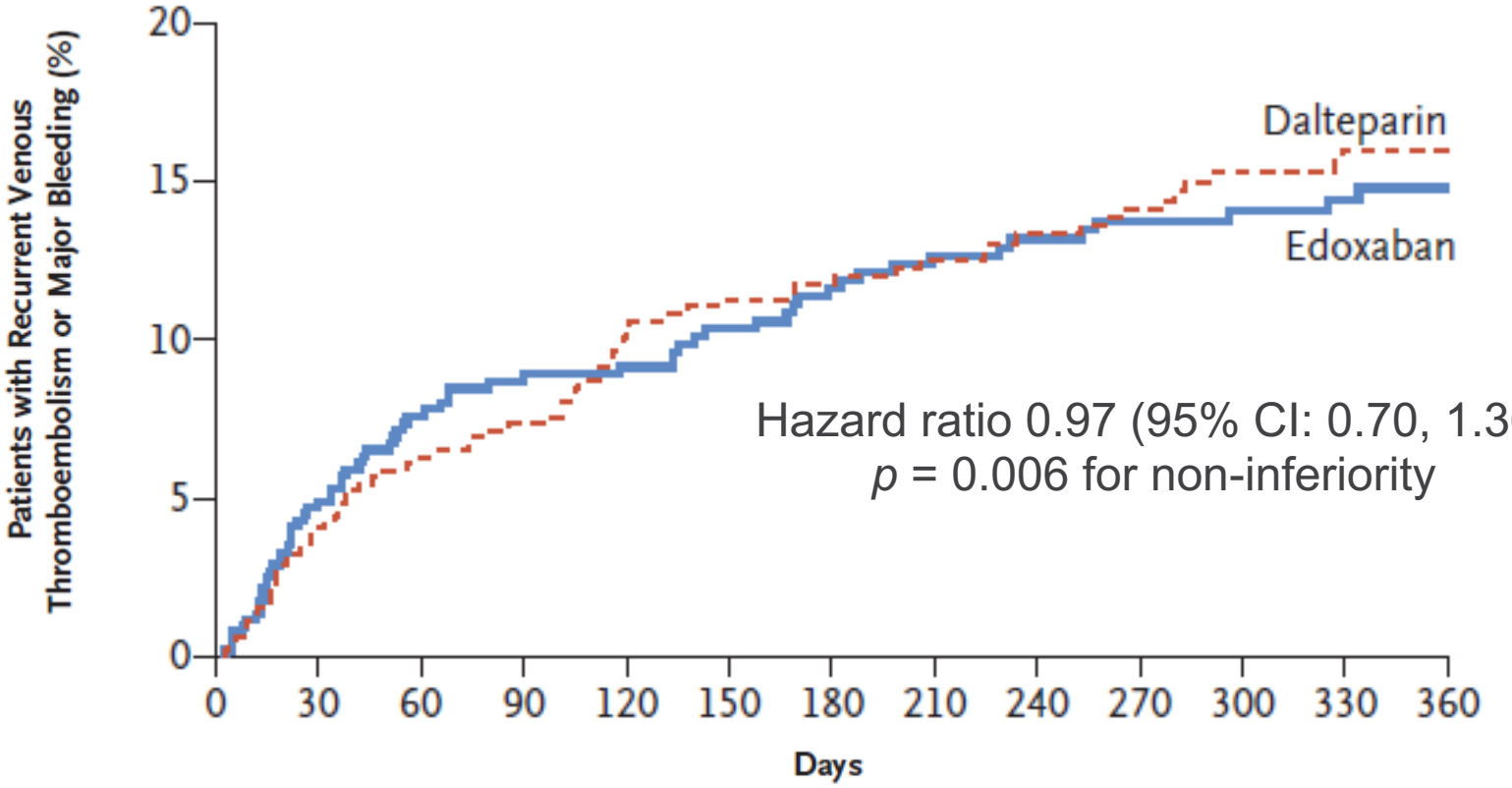
Primary outcome: VTE recurrence at 6 months

Secondary outcomes: major bleeding, CRNMB



Adapted from Young A *et al. ASH* 2017; Abstract 625.

Hokusai VTE-Cancer: Primary endpoint
Recurrent VTE or major bleeding



No. at Risk

Edoxaban	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin	524	485	449	420	385	364	352	340	324	313	276	241	171

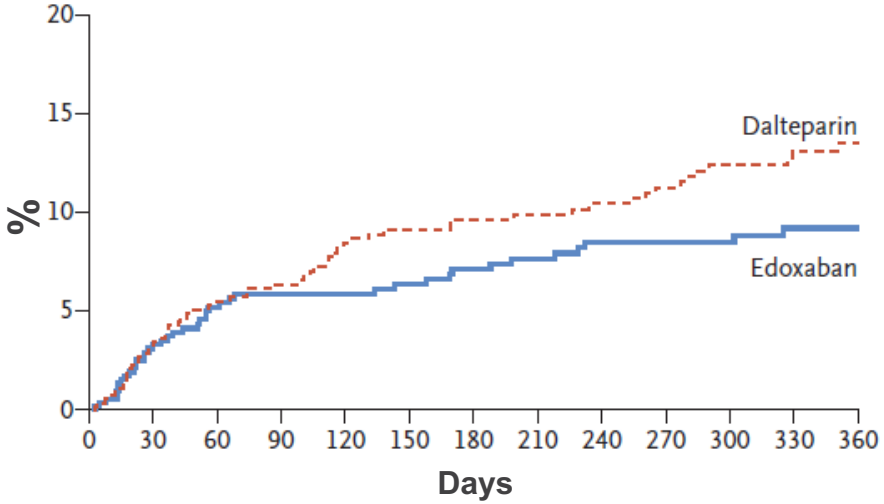
Raskob GE *et al. N Engl J Med* 2017; [Epub ahead of print].

CI = confidence interval; VTE = venous thromboembolism

Hokusai VTE-Cancer: Secondary outcomes
Recurrent VTE and major bleeding

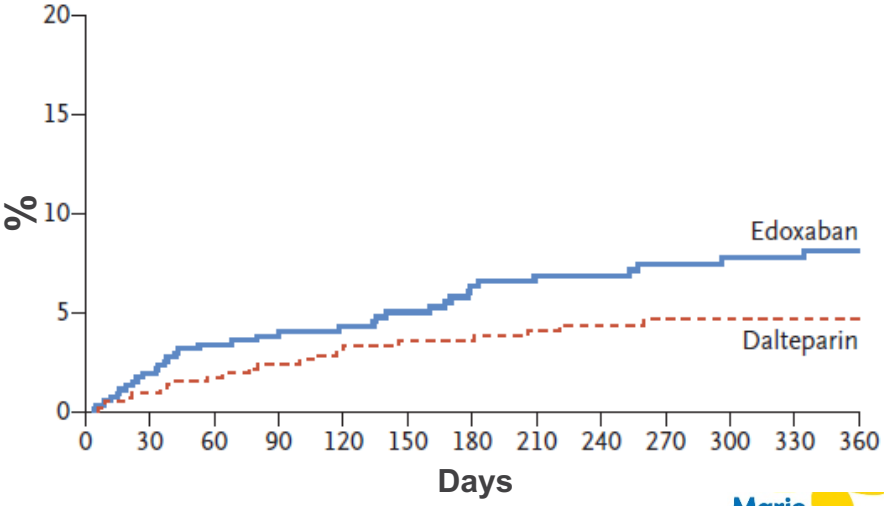
Recurrent VTE

	Edoxaban N = 522	Dalteparin N = 524	*p* – value (HR, 95% CI)
VTE, n (%)	41 (7.9)	59 (11.3)	**0.09 (0.71, 0.48–1.06)**
PE, n (%)	27 (5.2)	28 (5.3)	**(0.56, 0.59–1.69)**
DVT, n (%)	19 (3.6)	35 (6.7)	**(0.56, 0.32–0.97)**



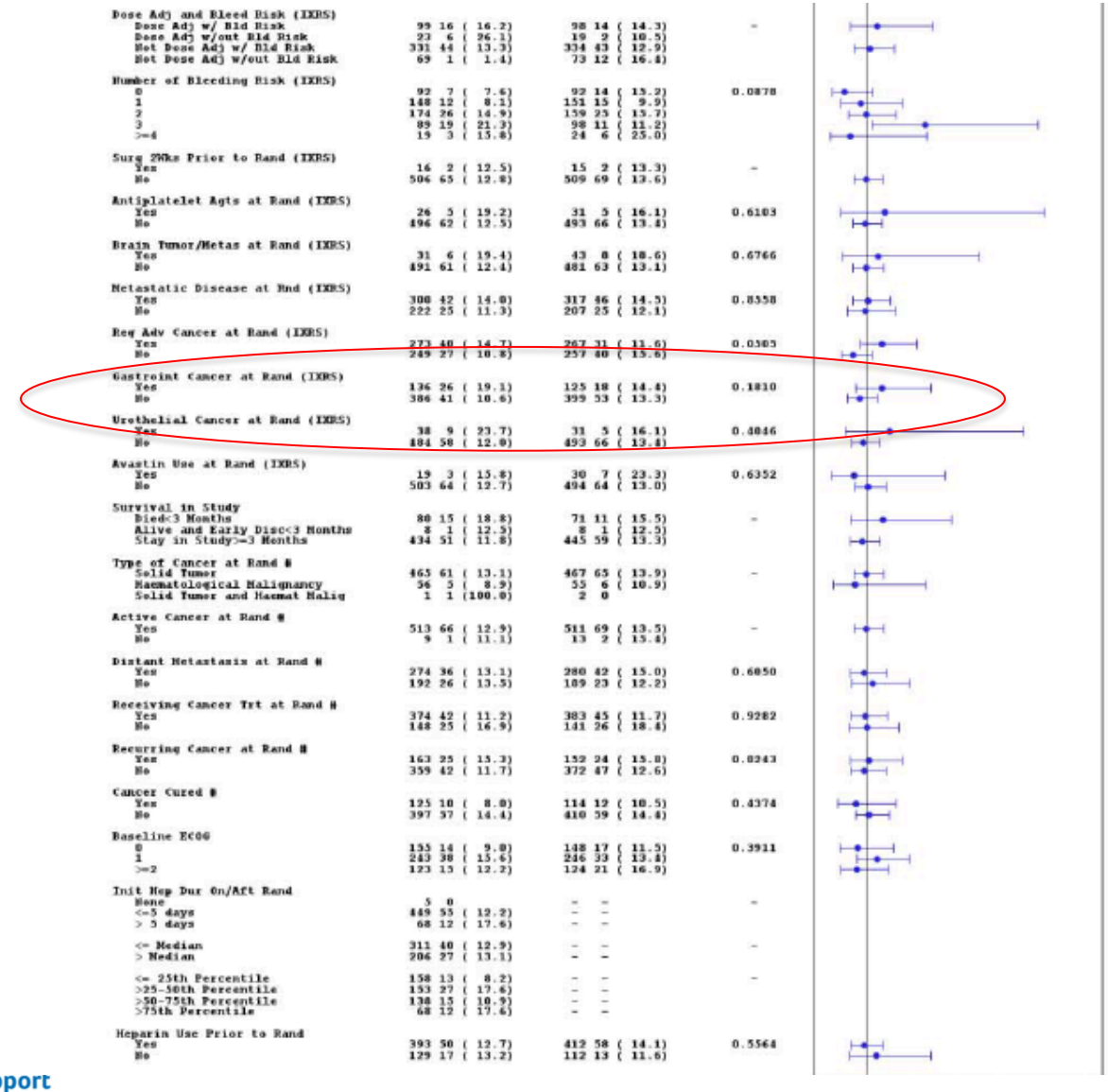
Major bleeding

	Edoxaban N = 522	Dalteparin N = 524	*p* – value (HR, 95% CI)
All, n (%)	36 (6.9)	21 (4.0)	**0.04 (1.77, 1.03–3.04)**
Gr 2, n (%)	**21 (4.0)**	**5 (0.1)**	
Gr 3/4, n (%)	**12 (2.3)**	**12 (2.3)**	

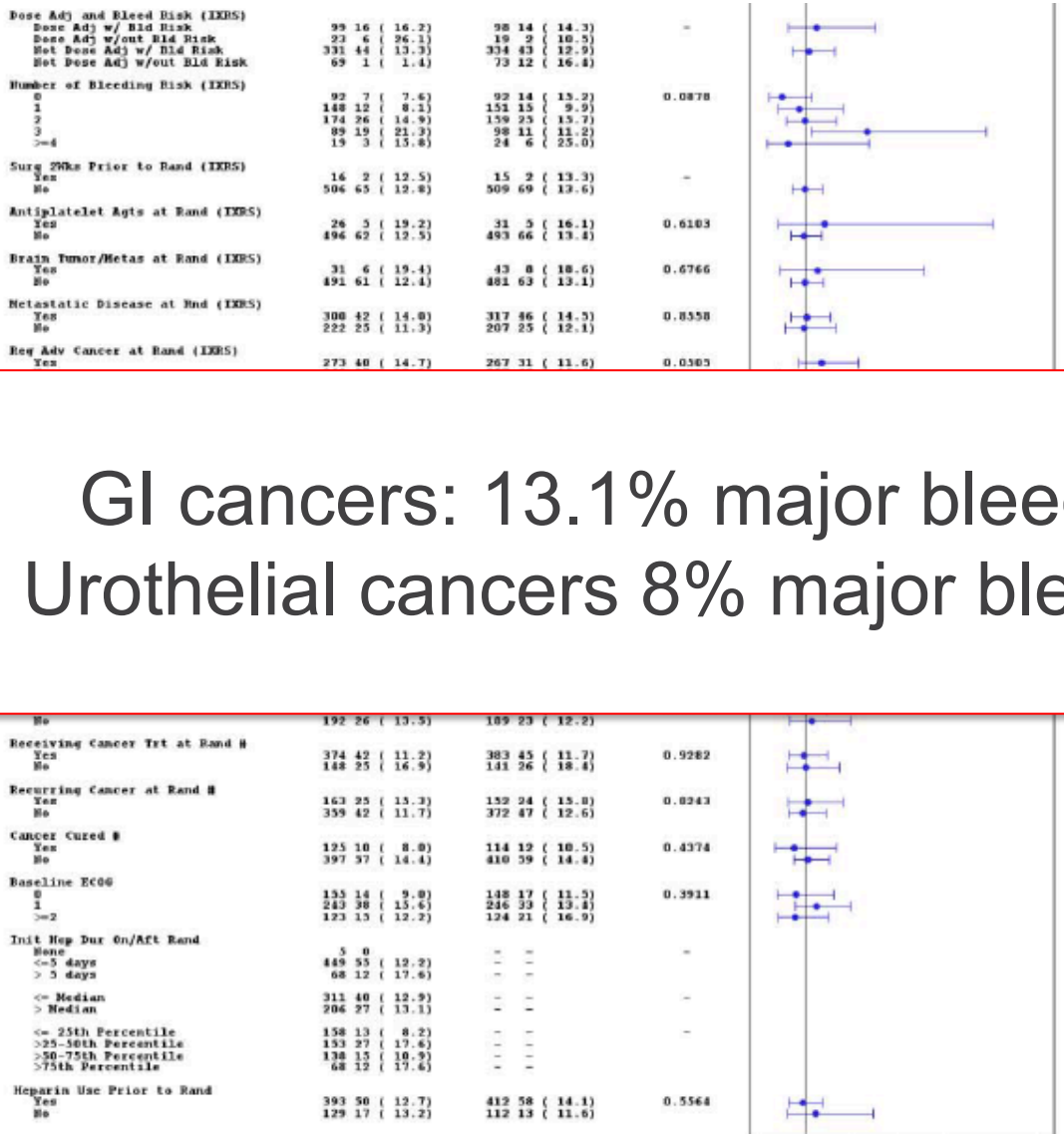


Raskob GE et al. *N Engl J Med* 2017; [Epub ahead of print].

Appendix: page 16/32



Appendix: page 16/32



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

ISTH definition major bleeding

Major bleeding event

A major bleeding event will be confirmed when it is a clinically overt bleeding event that meets at least one of the following:

a) Fatal bleeding

b) Bleeding in a critical area or organ such as:

- Retroperitoneal
- Intracranial
- Intraocular
- Intraspinal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

c) A clinically overt bleeding event

- that is associated with a fall in hemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or
- leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood.

Classification of clinical presentation

Category	Description
1	Bleeding events presenting without any clinical emergency
2	All bleeding events that could not be classified to any of the other three
3	Bleeding events presenting with great medical emergency
4	Bleeding events already fatal before or almost immediately upon entering the hospital

Bleker SM, et al. Thromb Haemost 2017;117:1944–51

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Stroke, Systemic or Venous Thromboembolism

Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists

An individual patient data meta-analysis

Suzanne M. Bleker[1*]; Marjolein P.A. Brekelmans[1*]; Elise S. Eerenberg[1]; Alexander T. Cohen[2]; Saskia Middeldorp[1]; Gary Raskob[3]; Harry R. Büller[1]

[1]Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; [2]Department of Haematological Medicine, Guy's and St Thomas' Hospitals, King's College London, London, UK; [3]College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

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Summary

LMWH/VKA patients. The clinical presentation was classified as cat

SELECT-D

430 patients randomized.

A protocol change was implemented to exclude patients with esophageal and gastro-esophageal cancer by the safety committee due to excessive bleeding in the rivaroxaban arm.

Second randomization was deemed not feasible.

Will not proceed to large study.

Six-month outcomes	Rivaroxaban (N = 203)	Dalteparin (N = 203)
Recurrent VTE, n (%)	8 (4)	18 (11)
Major bleeding, n (%)	11 (5)	6 (3)
CRNMB, n (%)	25 (12)	6 (3)
Major and CRNMB, n (%)	36 (17)	12 (6)

Young A *et al.* Presented at ASH 2017; Abstract 625.

ASH = American Society of Hematology; CRNMB = clinically-relevant non-major bleeding; VTE = venous thromboembolism

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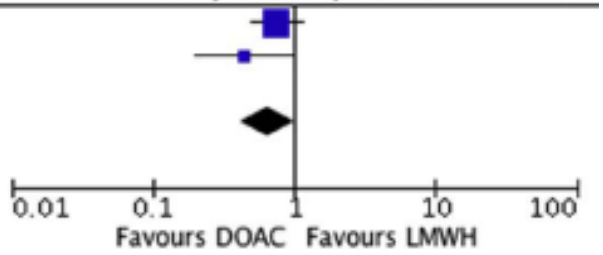
ASH = American Society of Hematology; CRNMB = clinically-relevant non-major bleeding; VTE = venous thromboembolism

Similar outcomes in Hokusai and SELECT-D
Six-month results

Recurrent VTE

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob 2017	34	522	46	524	73.4%	0.74 [0.48, 1.14]
Young 2017	8	203	18	203	26.6%	0.44 [0.20, 1.00]
Total (95% CI)		**725**		**727**	**100.0%**	**0.65 [0.42, 1.01]**
Total events	42		64			

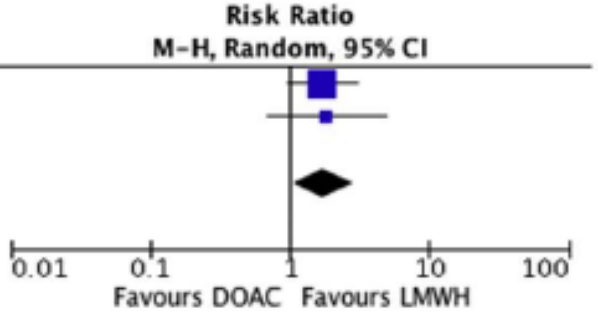
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.21$, df = 1 (P = 0.27); $I^2 = 17\%$
Test for overall effect: Z = 1.92 (P = 0.06)



Major bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob 2017	29	522	17	524	73.5%	1.71 [0.95, 3.08]
Young 2017	11	203	6	203	26.5%	1.83 [0.69, 4.86]
Total (95% CI)		**725**		**727**	**100.0%**	**1.74 [1.05, 2.88]**
Total events	40		23			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0\%$
Test for overall effect: Z = 2.17 (P = 0.03)



Li A *et al*. *Thromb Res* 2018; [in press].

CI = confidence interval; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; VTE = venous

Inducers and inhibitors of CYP3A4 and P-gp

Kinase inhibitors	CYP3A4	P-gp
Afatinib		↓
Alectinib		↓
Ceritinib	↓	
Crizotinib	↓	
Dasatinib	↓	
Ibrutinib		↓
Idelalisib	↓	↓
Imatinib	↓	
Lapatinib	↓	↓
Nilotinib	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑

Chemotherapy	CYP3A4	P-gp
Doxorubicin	↓	
Topotecan	↓	
Vinblastine	↓	
Mitotane	↑	
Venetoclax		↓

Supportive care	CYP3A4	P-gp
Aprepitant	↓	
Methylpred	↓	
Dexamethasone	↑	↑

Product Prescribing Information

CYP = Cytochrome P450; P-gp = p-glycoprotein; ↓ = inhibitor; ↑ = inducer

ISTH SSC DOACS

1. We recommend individualized treatment regimens after shared decision-making with patients.
2. We suggest the use of specific DOACs for cancer patients with an acute diagnosis of VTE, a **low risk of bleeding**, and **no drug–drug interactions** with current systemic therapy. LMWHs constitute an acceptable alternative.
3. We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and **a high risk of bleeding**, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis.

Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, Carrier M. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018 Jun 29. doi: 10.1111/jth.14219

Patient 2

- 68 year old female
- Metastatic ovarian cancer
- Last scan showed disease progression on post chemo scan
- General deterioration past 3 months
- Reduced mobility due to weakness/ pain
- Poor appetite, constipation
- Admitted to optimize symptom control

- What about thromboprophylaxis?

Thromboprophylaxis in hospices and specialist palliative care units

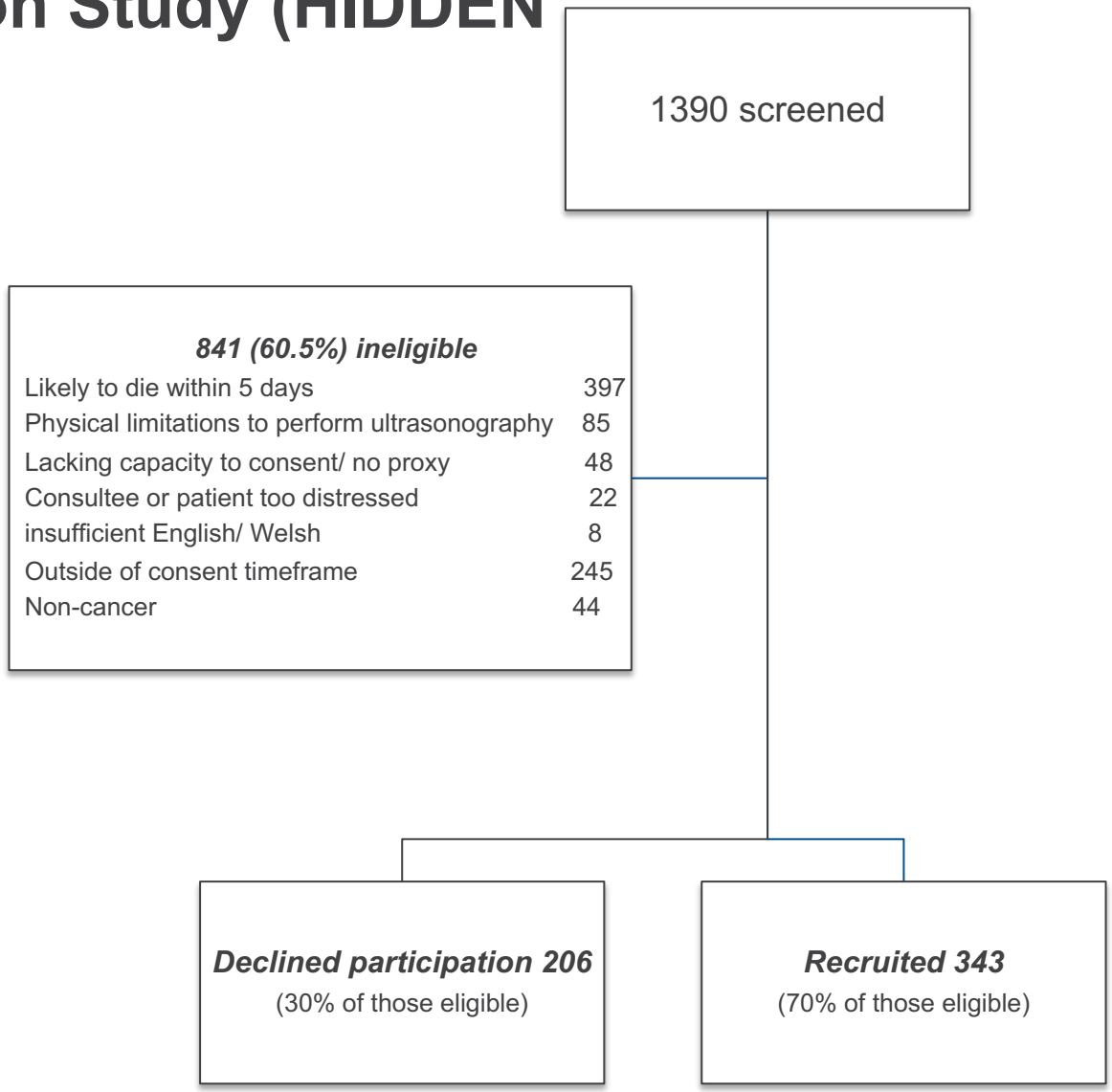
- Variable practice across UK hospices
- “not a big problem”
- “population in thromboprophylaxis studies not representative”
- “large PE a nice way to go”
- “clinical outcomes not appropriate”

Thromboprophylaxis: Hospice Inpatient DVT Detection Study (HIDDEN

- Setting: Patients admitted to UK hospice/ SPCU
- Compression ultrasonography on admission and weekly
- Screened for symptoms attributable to VTE
- Primary outcome
  - Prevalence of radiological apparent DVT
- Secondary outcomes
  - Attributable symptoms
  - Incidence of VTE and symptoms
  - Associated variables
  - Survival

White C et al 2019 Lancet Haem

Thromboprophylaxis: Hospice Inpatient DVT Detection Study (HIDDEN



Demographics

- Average AKPS =49
- Mean survival = 44 days

White C et al 2019 Lancet Haem

Results: 273 evaluable scans

- **92/273 (34%, CI 28% to 40%) showed DVT.**
- **Excluding early scans, 64/232 (28%, 22% to 34%)**
- **Associated with**
  - Previous thromboembolism,
  - bedbound ≤12 weeks for any reason (p=0·003)
  - lower limb oedema (p=0.009)

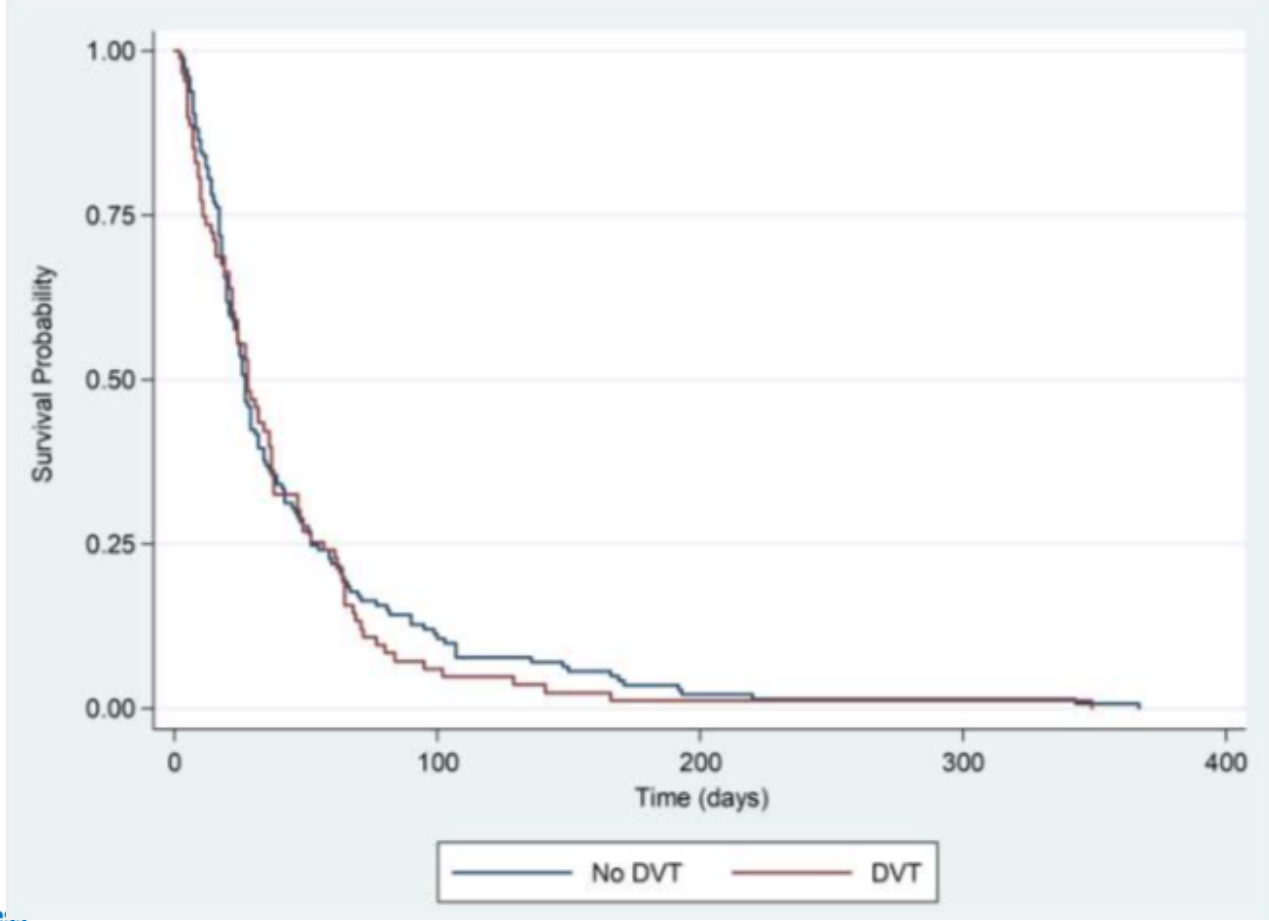
No significant attributable symptom burden difference

) **White C et al 2019 Lancet Haem**

No association with

- Serum albumin (p =0·430),
- Thromboprophylaxis (p = 0·173) and

No impact on survival (p = 0·473)



RHESO study

- 22 SPCUs, 1199 patients
- CRB 9.8% (95% CI 8.3-11.6)

Clinically relevant bleeding = Major Bleeding

+

Clinically Relevant Non Major Bleeding

Tardy B, et al J Thromb Haemost. 2017 Mar;15(3):420-428

Characteristics of patients

Reason for admission to the palliative unit	0/1199	
Cancer		1091 (91.0)
Metastatic cancer		929 (77.5)
Neurologic disease		52 (4.3)
Cardiac or respiratory disease		49 (4.1)
AIDS*		7 (0.6)

Treatments received within 4 weeks prior to admission		
Cancer treatment	0/1199	
Chemotherapy		257 (21.4)
Targeted cancer therapy		35 (2.9)
Radiotherapy		91 (7.6)
Growth factors	0/1199	32 (2.7)
Anticoagulant therapy		
At prophylactic (low) dose**	0/1199	527 (44.0)
At therapeutic (high) dose††	0/1199	69 (5.7)
Antiplatelet therapy	3/1196	167 (14.0)
Corticosteroids	6/1193	620 (52.0)
Antidepressive agents	0/1199	304 (25.4)
Serotonin reuptake inhibitors		208 (17.3)

Risk factors for bleeding

Table 4 Univariate and multivariate analyses of potential risk factors for clinically relevant bleeding at 3 months

Patient factor	With bleeding (n = 116)	Without bleeding (n = 1075)	Multivariate analysis*	
			HR (95% CI)	P value
Male sex	63 (54.3)	479 (44.6)	1.31 (0.91–1.90)	0.15
Cancer	114 (98.3)	970 (90.2)	5.65 (1.40–22.9)	0.01
Previous surgery†	2 (1.7)	67 (6.2)	0.21 (0.05–0.87)	0.03
Previous bleeding†	38 (32.8)	134 (12.5)	3.36 (2.28–4.97)	< 0.0001
Anticoagulant prophylaxis	69 (59.5)	561 (52.2)	1.48 (1.02–2.15)	0.04
Antiplatelet therapy‡	44 (37.9)	288 (26.9)	1.67 (1.15–2.44)	0.007

Only factors with a P value ≤ 0.15 in the univariate analysis are presented. Because data were available in less th
index (univariate Hazard Ratio, HR = 2.38 [1.05–5.40]) and moderate or severe renal insufficiency (univariate H
included in the multivariate analysis. *According to the Fine and Gray method. †Within 4 weeks prior to incl
4 weeks prior to inclusion or during hospitalization in the palliative care unit.

Anticoagulation at the end of life

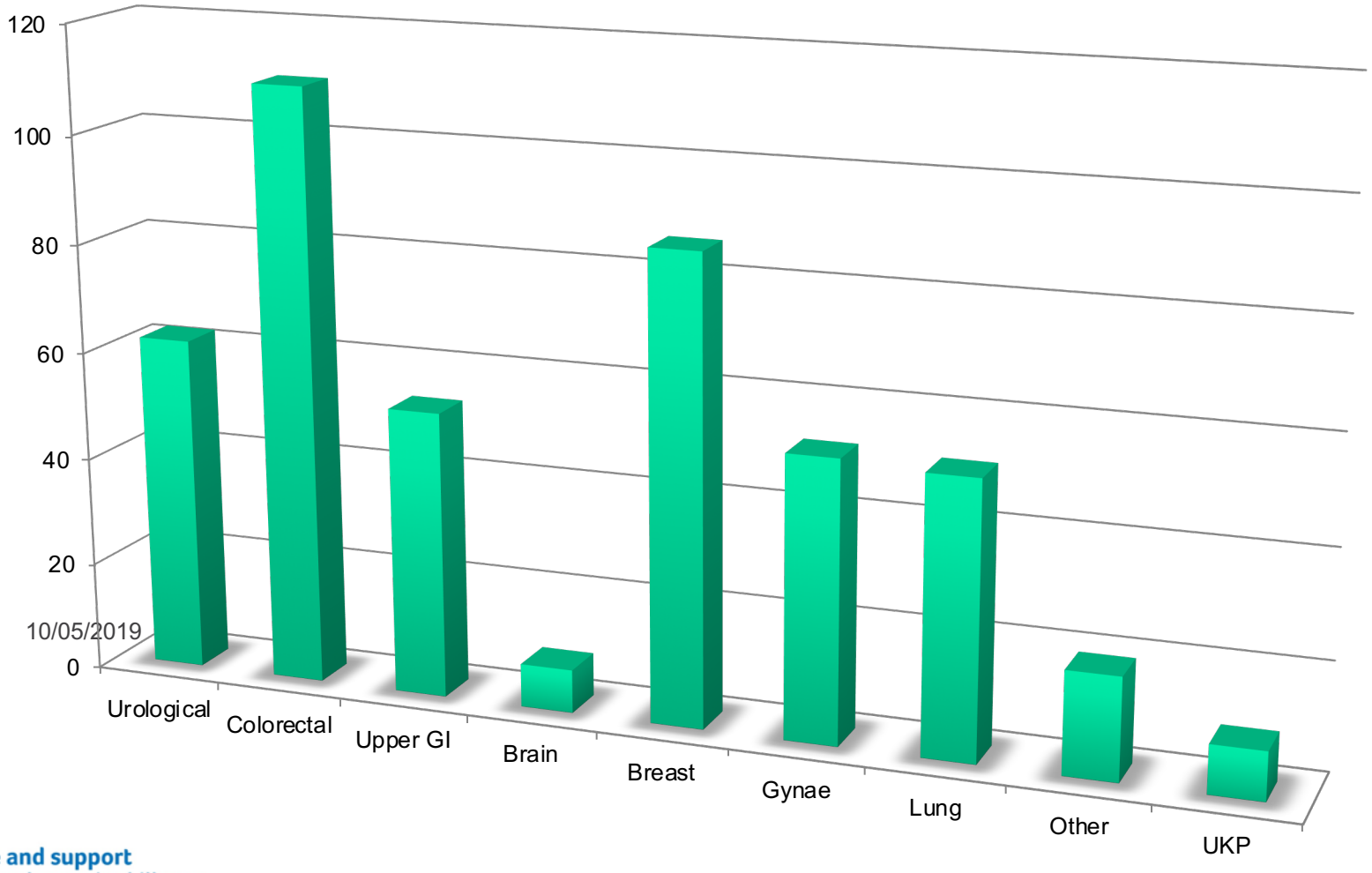
In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference.

Study to identify current practice in patients with cancer associated thrombosis at the end of life

- Setting: Patients attending a regional cancer associated thrombosis clinic
- Follow up over two years
- Notes review of patients at end of life
- Demographics, when anticoagulation stopped, bleeding/ thrombotic complications,
- Place of death

38 Noble S, Banerjee S, Pease N. Anticoagulation for Cancer Associated Thrombosis at the End of Life: Review of a Case Series of 214 Patients. *Palliative Medicine* 32(1S) 47-48

Cancer diagnoses: n=450



Patient spread at initial review

- 44% metastatic
- 60% during chemotherapy (majority palliative)

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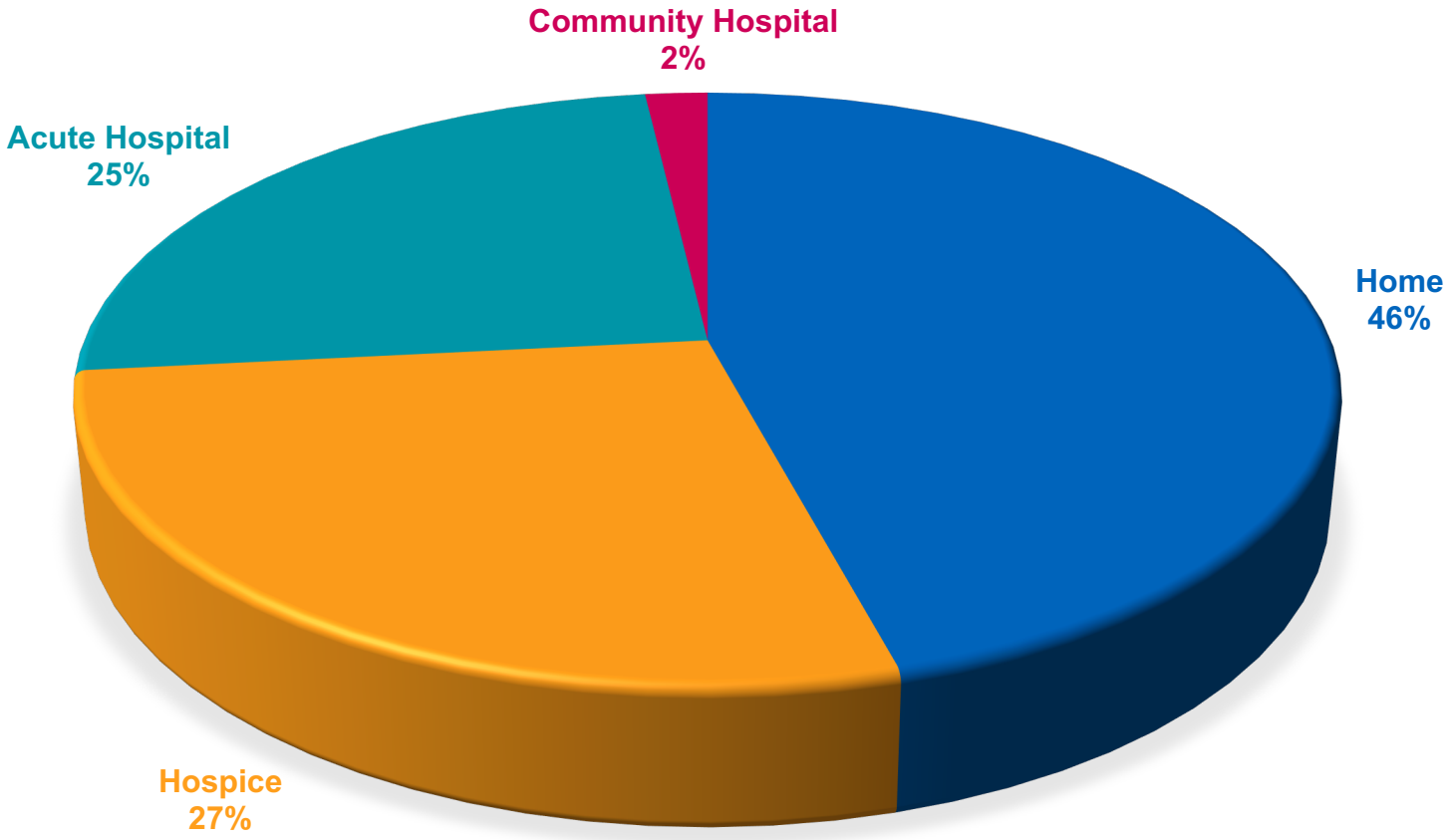
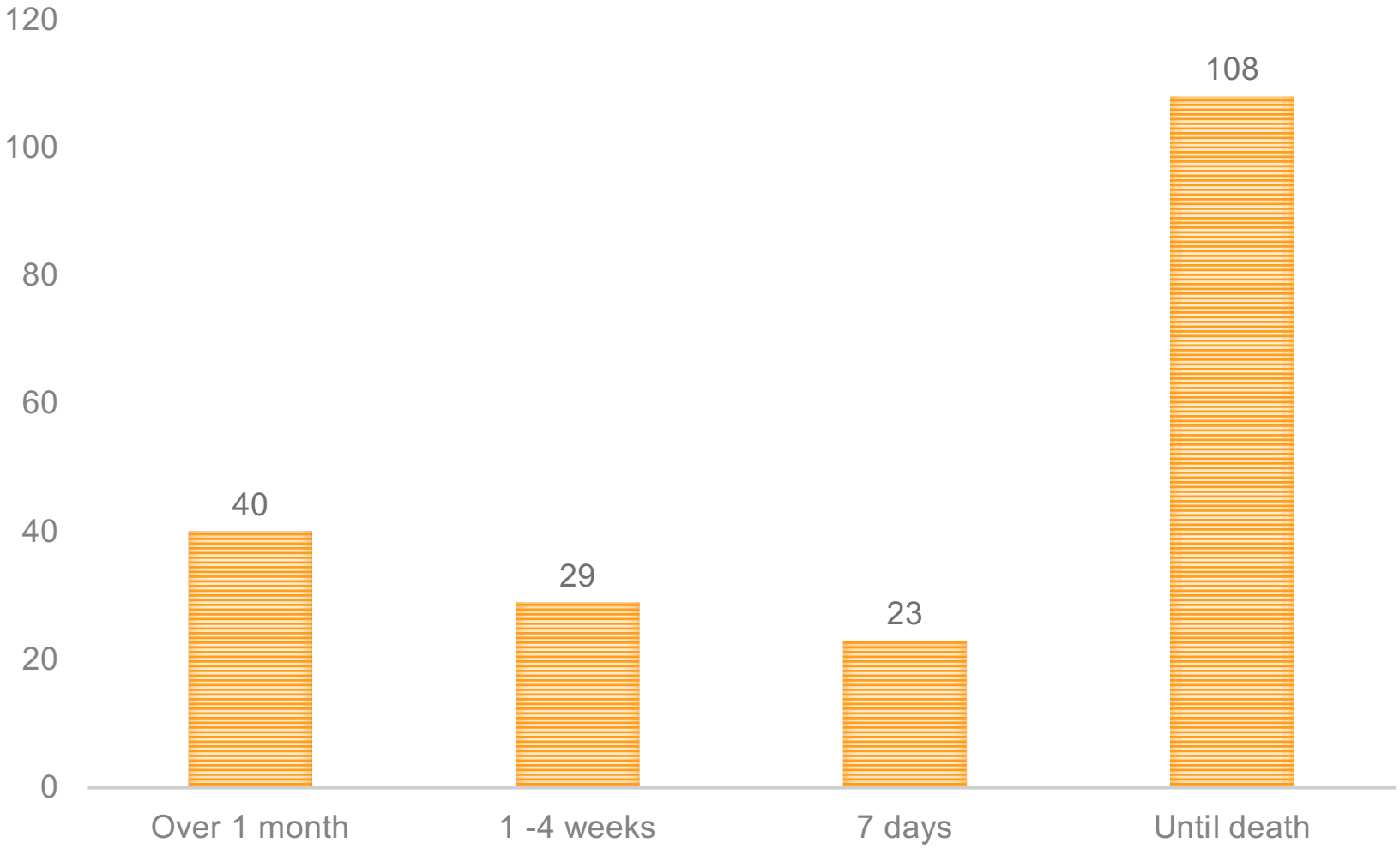
Noble S, Banerjee S, Pease N. Anticoagulation for Cancer Associated Thrombosis at the End of Life: Review of a Case Series of 214 Patients. *Palliative Medicine* 32(1S) 47-48

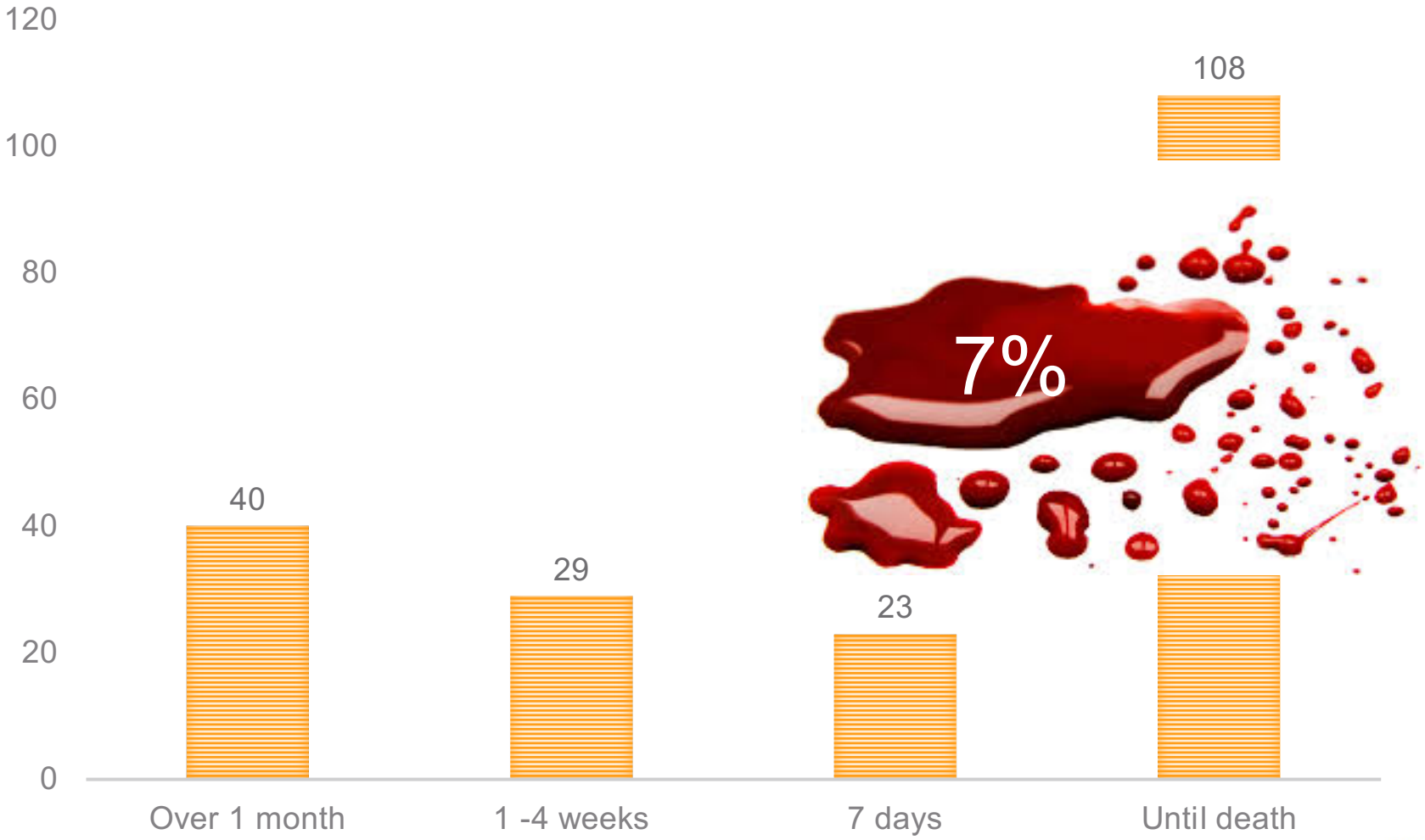
Place of death



When anticoagulation stopped



When anticoagulation stopped



To conclude

- **Cancer associated thrombosis becoming more complex**
  - Systemic anti cancer therapies
  - Patients living longer with metastatic disease
  - Increasing number of anticoagulants with CAT data
- **Individualised approach**
  - One size does not fit all
- **Advanced cancer different beast?**
  - Increased bleeding risk
  - VTE manifestation of advanced disease
  - ?biomarker of impending death?


Marie
Curie
Care and support
through terminal illness