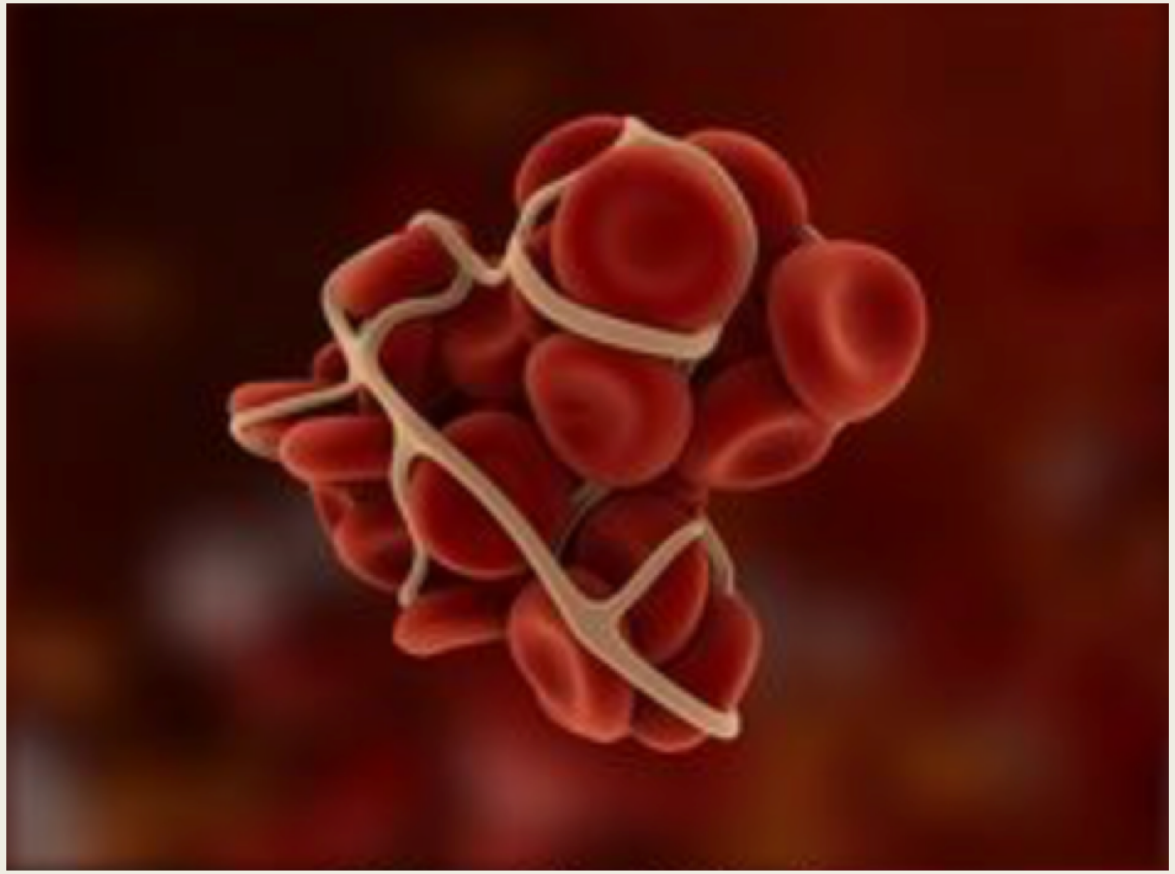
Cancer Associated Thrombosis: six months and beyond



Farzana Haque

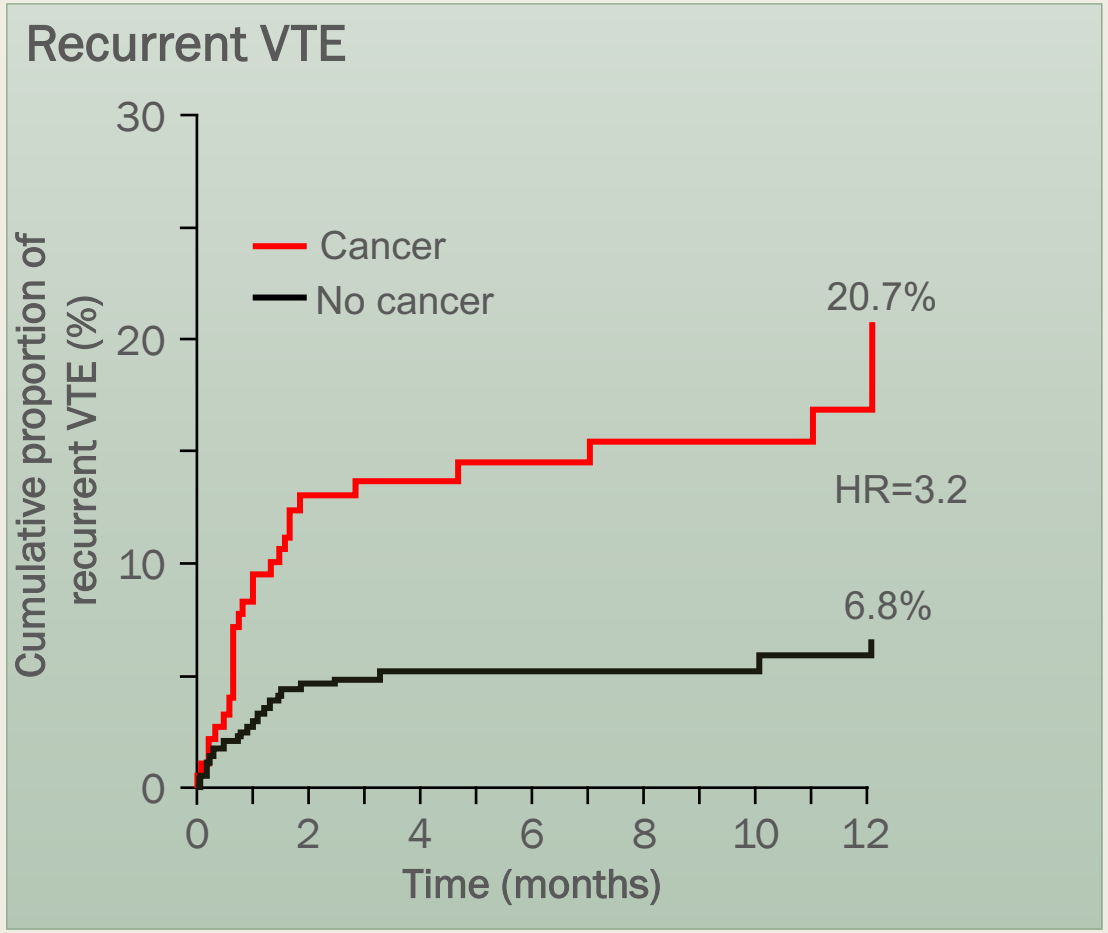
Hull York Medical School

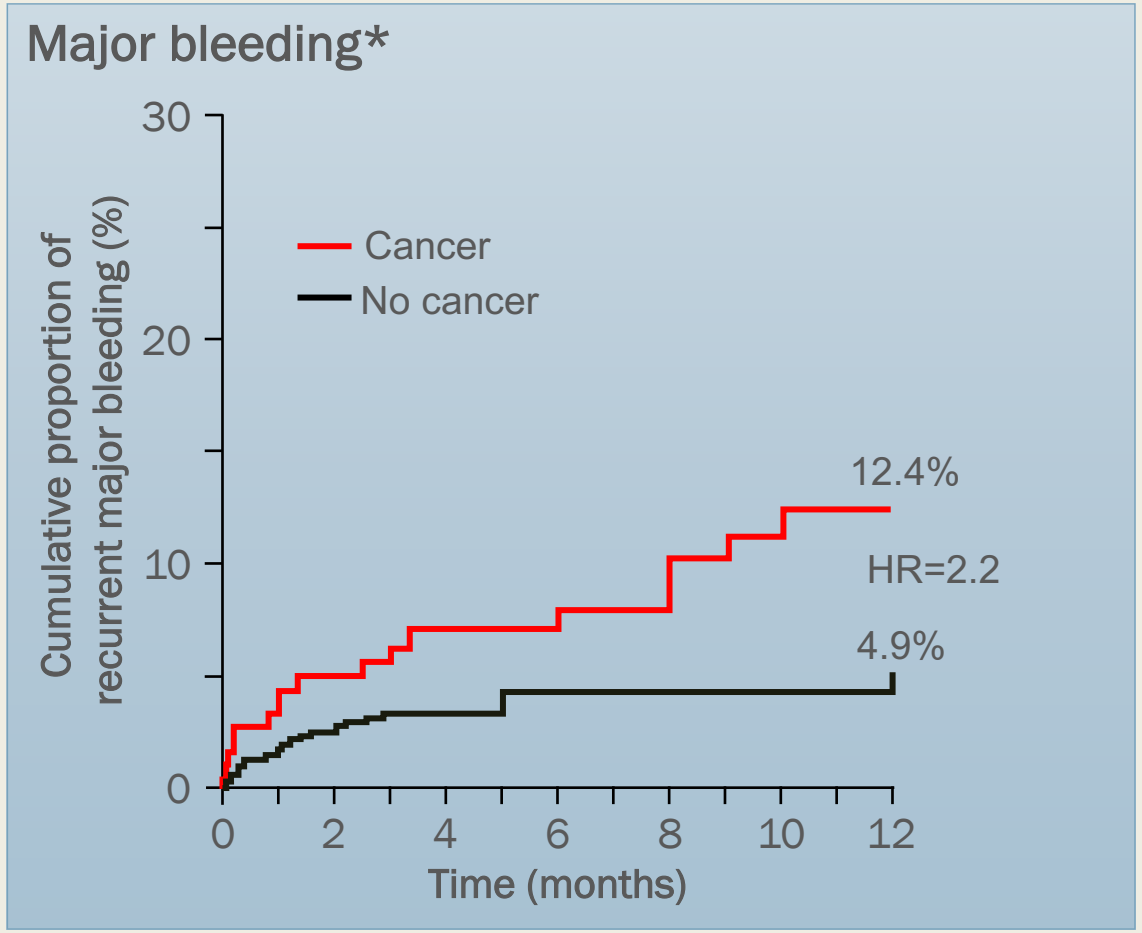
Disclosure

I have no disclosure

The Challenge of Anticoagulation in Patients with Venous Thromboembolism and Cancer

Risk of events in patients receiving anticoagulation therapy for VTE



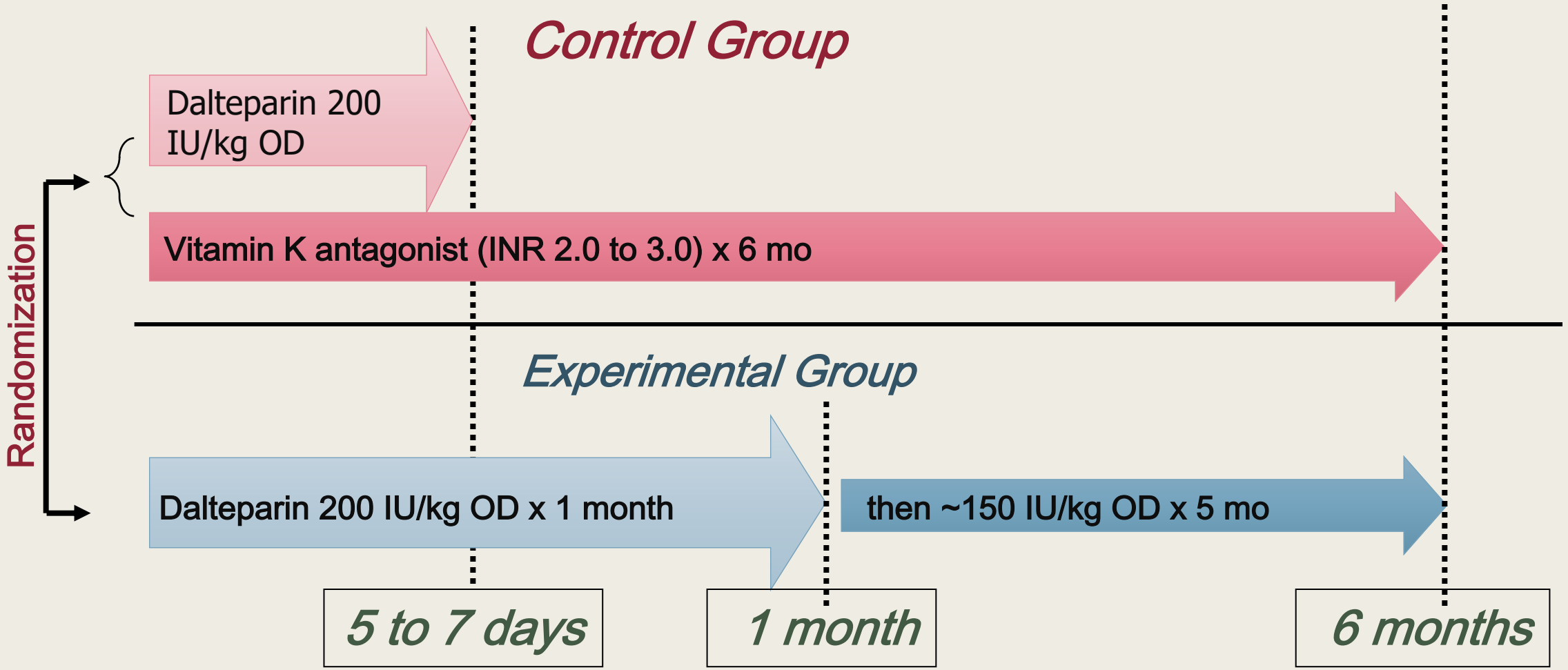


*Defined as overt and associated with either a decrease in the haemoglobin level (at least 2.0 g/dl) or the need for transfusion (≥2 units of blood), if it was retroperitoneal or intracranial, or if the treatment had to be discontinued permanently

Prandoni P *et al*, *Blood* 2002;100:3484–3488

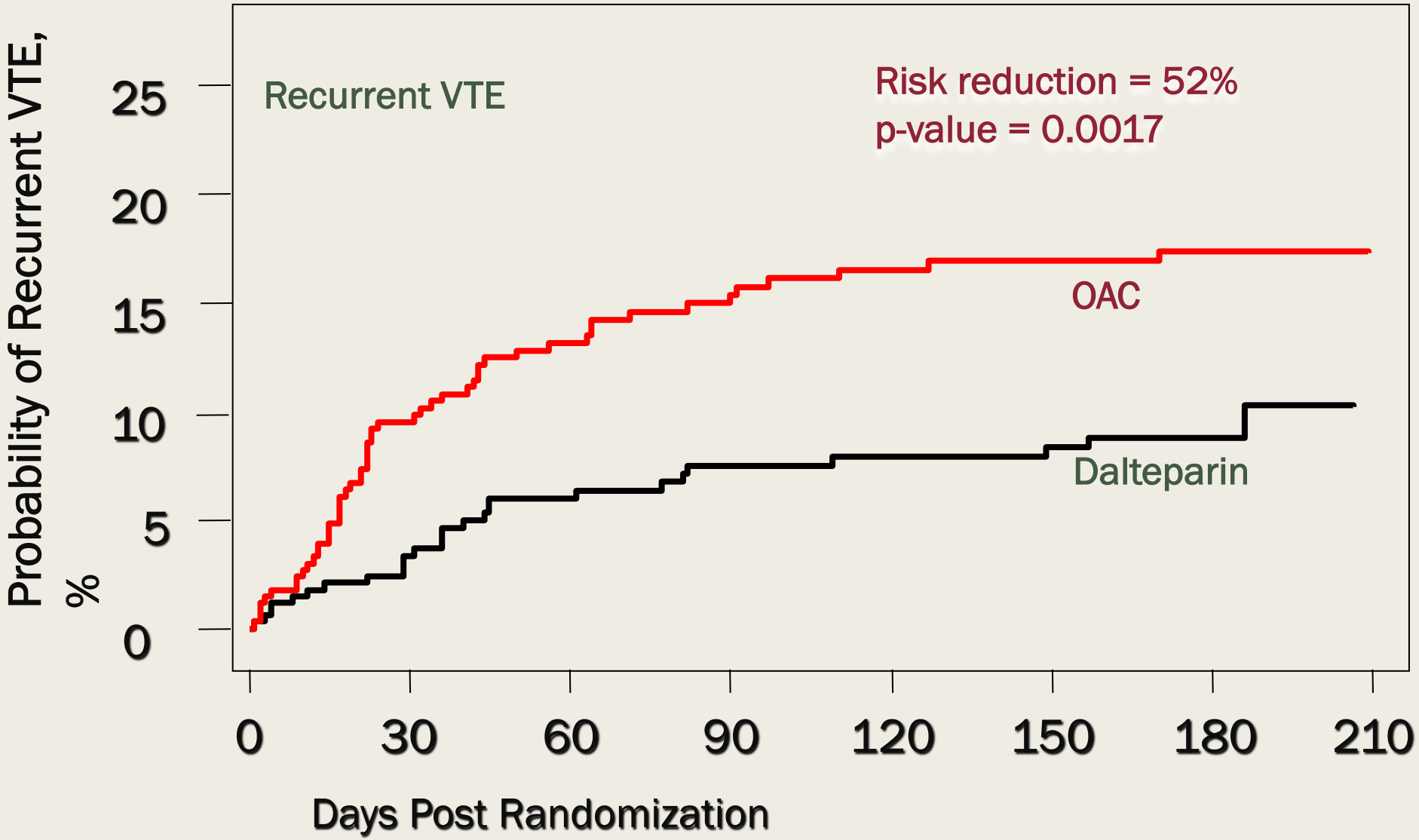
The CLOT Investigators Trial

Cancer patients with acute DVT or PE (n=677)



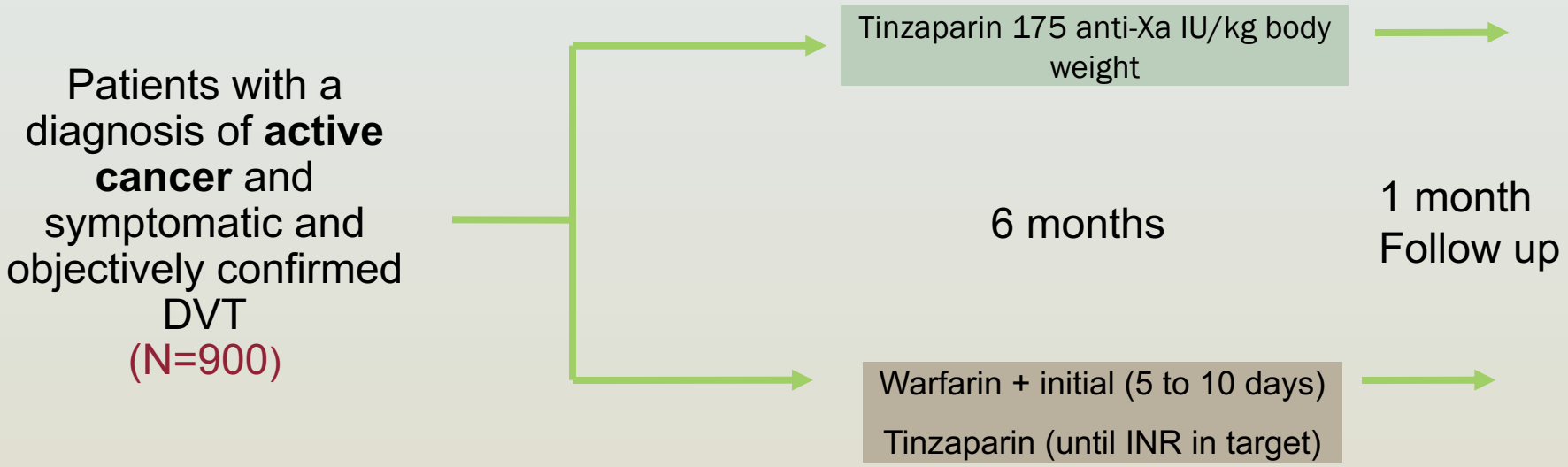
Lee AY, et al. N Engl J Med. 2003;349:146-153.

CLOT Study:Reduction in Recurrent VTE



Lee AY, et al. N Engl J Med. 2003;349:146-153.

CATCH STUDY: Phase 3, randomised, controlled, multi-centre Tinzaparin Vs VKA.



11 scheduled Clinic Visits:

- Screening Visit – up to 72 hours before randomisation
- Visit 1-3 - every 14 days
- Visit 4-9 - once a month
- Visit 10 - Follow-up visit, 1 month after end-of-study visit

All patients interviewed in between clinic visits by telephone

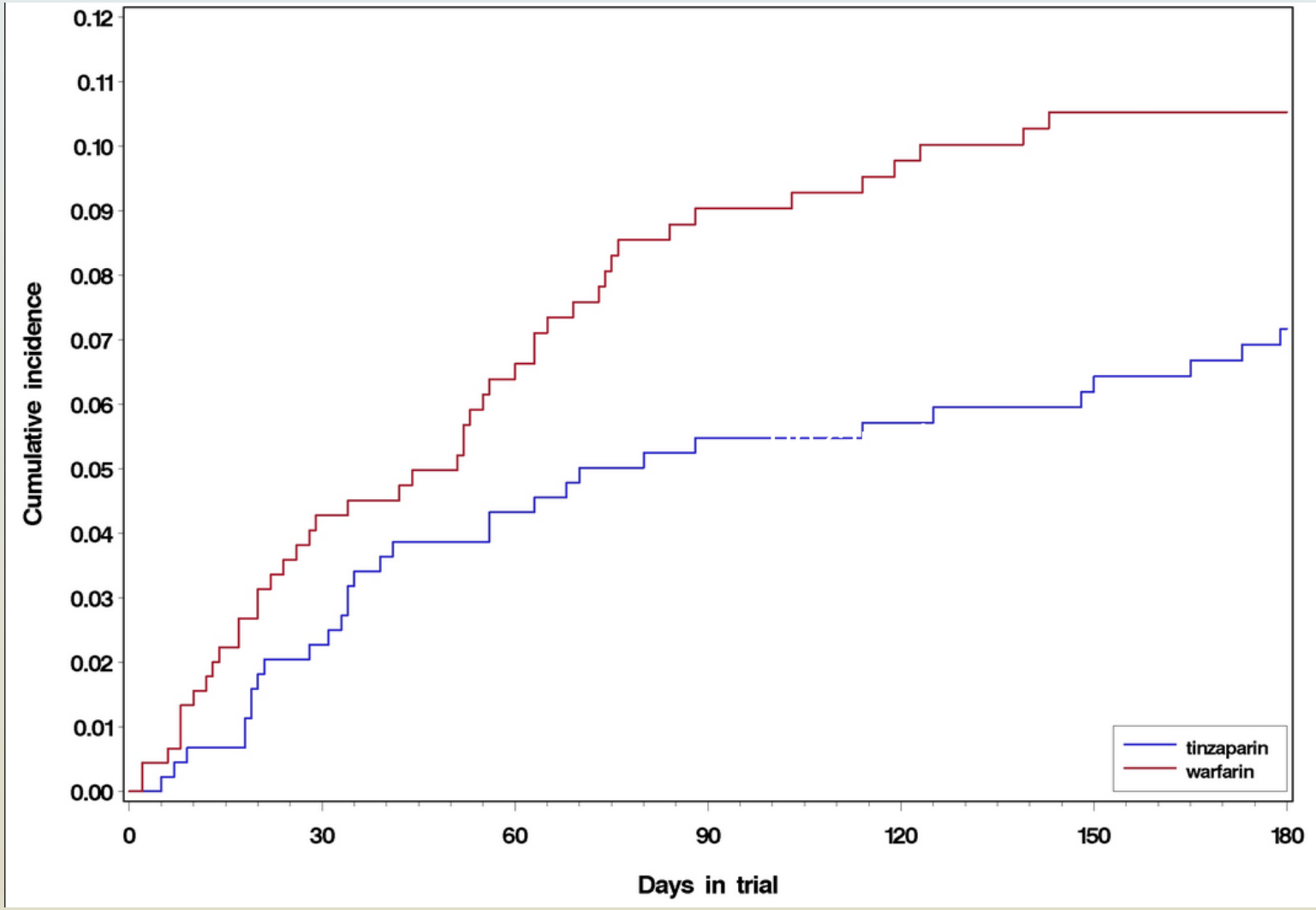
Lee, A.Y.Y., et al jco.org December 27,2016

CATCH STUDY: Results

- *Symptomatic DVT* : 12 patients (2.7%) in the Tinzaparin arm and 24 (5.3%) in the warfarin arm (HR 0.48 [95% CI 0.24–0.96]; *P*=0.04).
- *Symptomatic non-fatal PE:* 3 patients in the Tinzaparin arm and 2 in the warfarin arm (and *2 incidental VTE* in warfarin arm)
- *Fatal PE:* 17 (3.8%) patients in each arm (HR 0.96 [95% CI 0.49–1.88]; *P*=0.90).
- No difference in major bleeding events (n=13 [2.7%] in the Tinzaparin arm and 12 [2.4%] in the warfarin arm)
- Significantly less *clinically relevant non-major bleeding* with Tinzaparin than warfarin (50 [11%] and 73 [16%] patients, respectively; *P*=0.004, HR 0.58).

Lee, A.Y.Y., et al jco.org December 27,2016

CATCH: Recurrent VTE in the tinzaparin and warfarin groups



Lee, A.Y.Y., et al jco.org December 27,2016

Guideline Recommendations for the Treatment of CAT

Society	Recommendations
ESMO 2011[1]	◆ LMWH recommended for long-term (6 months) anticoagulant therapy ◆ Recommendations for duration of therapy depend on the type of cancer, stage of disease and cancer treatment
ACCP 2016[2]	◆ LMWH preferred over VKA or DOAC therapy ◆ There is no preference towards VKAs, dabigatran, rivaroxaban, apixaban or edoxaban ◆ Extended therapy (>3 months) recommended over 3 months of therapy
ESC 2014[3]	◆ LMWH should be considered for the first 3–6 months ◆ LMWH or VKAs should be considered for extended anticoagulation beyond the first 3–6 months
ASCO 2015[4,5]*	◆ LMWH recommended over UFH for the first 5–10 days ◆ LMWH preferred over VKAs for the first 6 months of treatment. VKAs are an acceptable alternative if LMWH is not available ◆ For extended anticoagulation (beyond 6 months) LMWH or VKAs may be considered for selected patients# with active cancer ◆ Use of DOACs is not currently recommended for patients with cancer and VTE owing to limited data

*Updated ASCO guidelines were published in 2015; reassessment of available new data did not prompt any changes from the 2013 recommendations[5]; #such as those with metastatic disease or receiving chemotherapy

1. Mandala M *et al*, *Ann Oncol* 2011;22:vi85–vi92; 2. Kearon C *et al*, *Chest* 2016;49:315–352; 3. Konstantinides S *et al*, *Eur Heart J* 2014;35:3033–3069; 4. Lyman GH *et al*, *J Clin Oncol* 2013;17:2189–2204; 5. Lyman GH *et al*, *J Clin Oncol* 2015;33:654–656

? Evidence for treating beyond 6 month

Treatment and 2° Prevention of VTE in Cancer

ASCO: Extended an[illegible]coagulation with LMWH or VKA may be considered beyond 6/12 for patients with metastatic di[illegible]ents who are receiving chemotherapy.

Length of second

LONGHEVA NCT011[illegible] (+6 m)

ALICAT ISRCTN[illegible]agulant (+6 m)– Funde[illegible]

Failed to Recruit
Downscaled to a Registry

Failed Feasibility –Trial Closed without achieving endpoint--

Long-term Management of VTE in Cancer Patients: The DALTECAN Study

Clinical Question

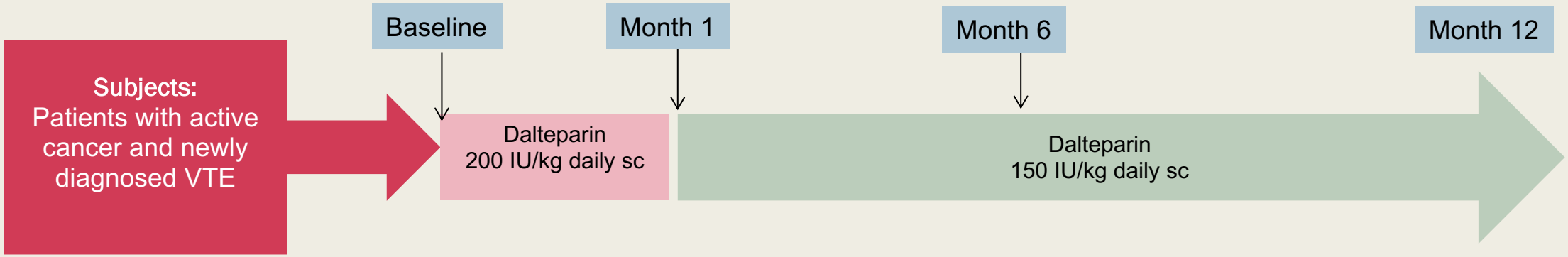
- Does extending anticoagulation therapy with dalteparin in cancer-associated VTE beyond 6 months have an acceptable safety and adherence profile?

Methods

- Single-arm prospective multi-centre phase IV study (cohort study)
- Determined incidence rates of bleeding and recurrent VTE at month 1, months 2-6, and months 7-12 following enrolment

Duration of therapy

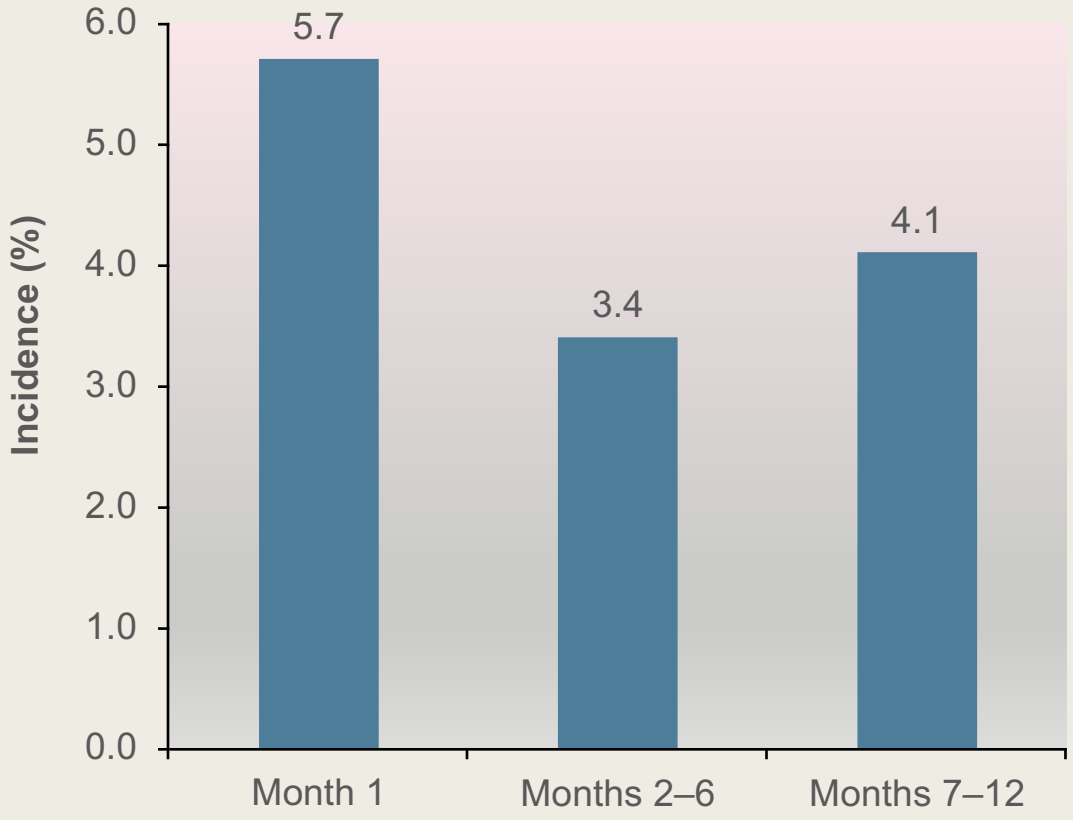
- 185 (55.4%) completed 6 months of therapy
- 109 (32.6%) completed 12 months of therapy
- Mean duration: 210 days



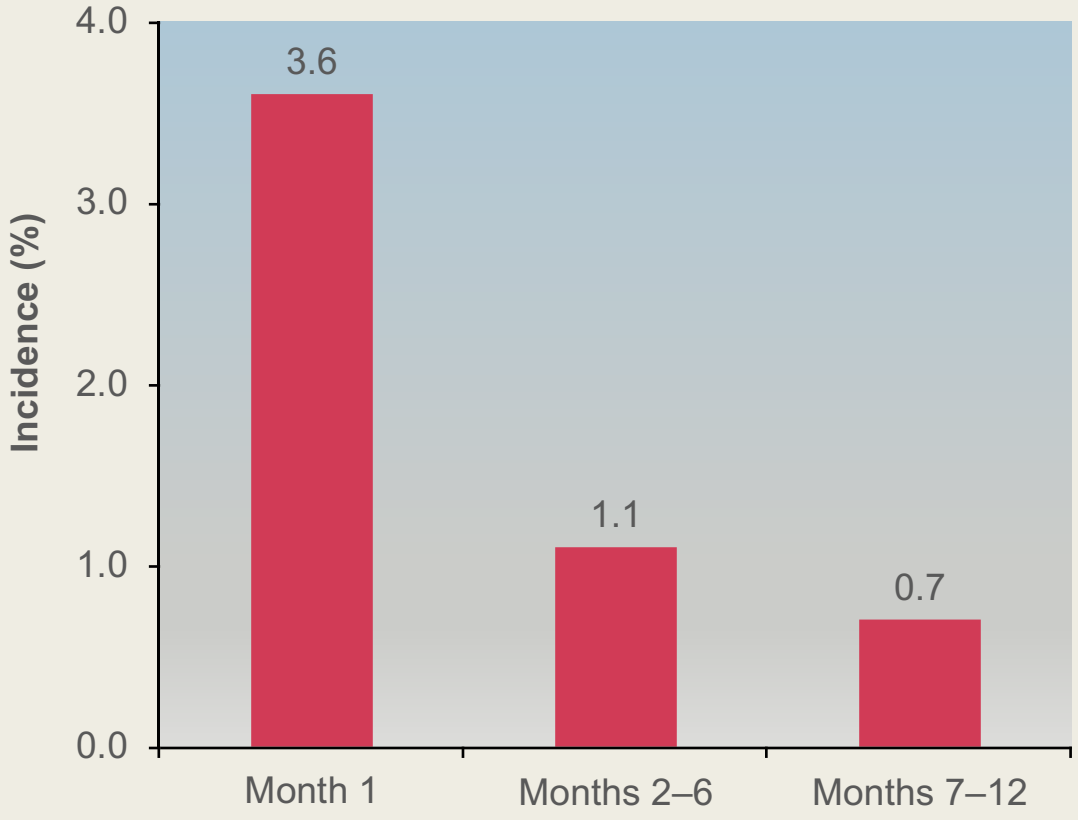
Adapted from Kakkar A, *et al. J Thromb Haemost.* 2013;11:AS12.3.

Safety and Efficacy of Long-Term LMWH Therapy: The DALTECAN Study

Recurrent VTE



Major bleeding events

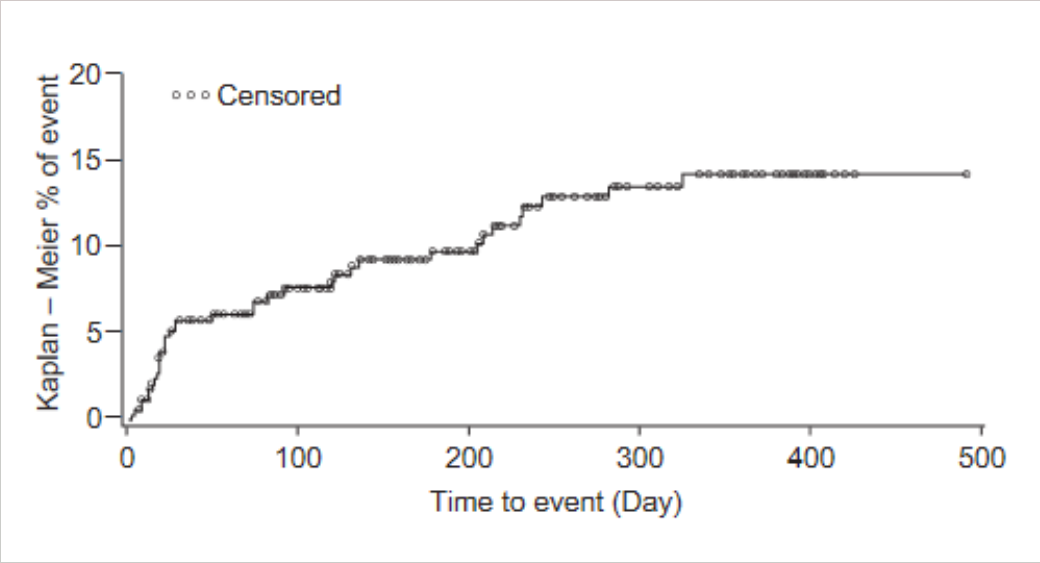


LMWH, low molecular weight heparin; VTE, venous thromboembolism

Francis CW *et al*, *J Thromb Haemost* 2015;13:1028–1035

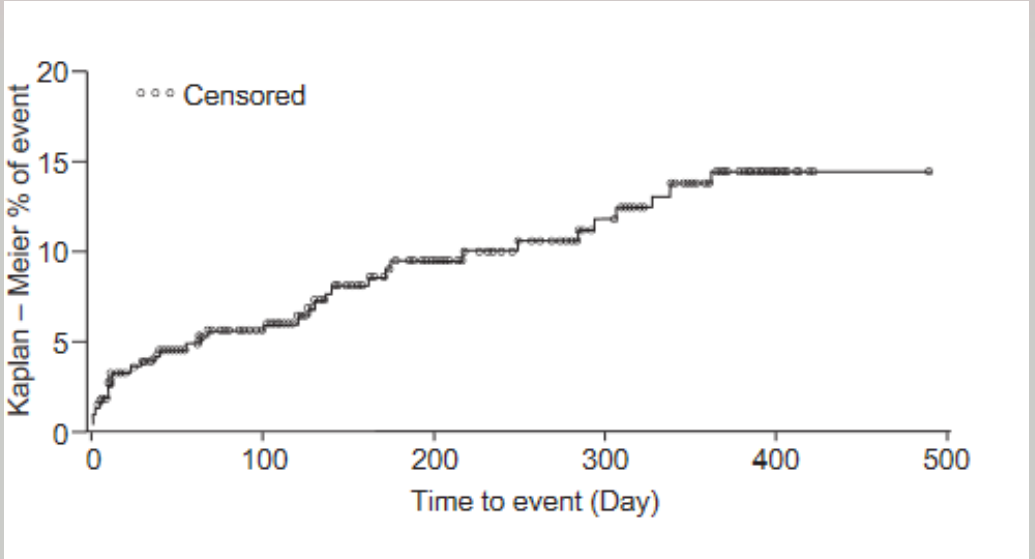
Safety and Efficacy of Long-Term LMWH Therapy: The DALTECAN Study

Recurrent VTE



- Incidence of new or recurrent VTE: **11.1%** **(1.4% per patient-month)**
- 154 (46.1%) patients died, 115 during the study period (4/115 due to VTE, 2/115 due to bleeding

Major bleeding events



Incidence of Major Bleeding Events
1.9% per patient month through the whole study (12 months)

Francis CW *et al*, *J Thromb Haemost* 2015;13:1028–1035

Long-term Management of VTE in Cancer Patients: The DALTECAN Study

Conclusions:

i. Risk of major bleed was ***greatest in first month*** of therapy and decreased over the following 11 months

ii. Risk of VTE recurrence was ***greatest in first month*** of therapy and decreased over the following 11 months

iii. Dalteparin ***beyond 6 months is not associated with increased bleeding*** compared to initial period of therapy

iv. ***Adherence to dalteparin was high*** (96% over entire cohort)

Kakkar A, *et al. J Thromb Haemost.* 2013;11:AS12.3.

Safety and Efficacy of Long-Term LMWH Therapy: The TiCAT Study

Design

- Prospective, multicentre, ***cohort study*** in patients with cancer-associated VTE treated with **tinzaparin** therapy (N=247)
- **Objective:** to evaluate the rate of clinically relevant bleeding events (major and non-major) and recurrent VTE with short-term versus long-term therapy

Duration of therapy

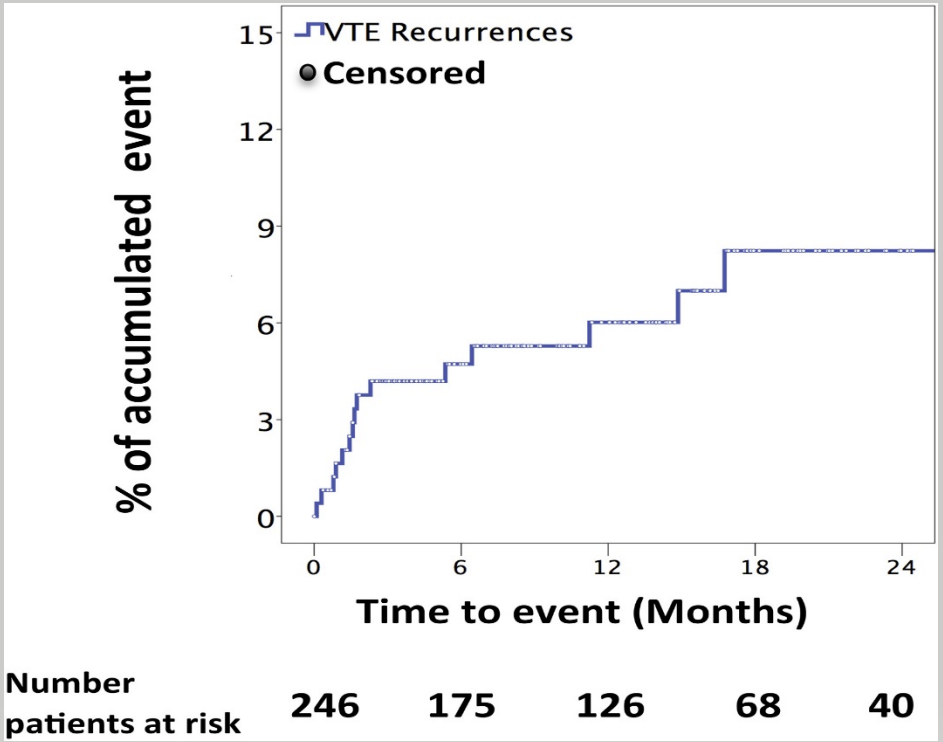
- 198 (80.2%) completed 6 months of therapy
- 136 (55.1%) completed 12 months of therapy
- Mean duration: 15.6 ± 13.2 months

LMWH, low molecular weight heparin; VTE, venous thromboembolism

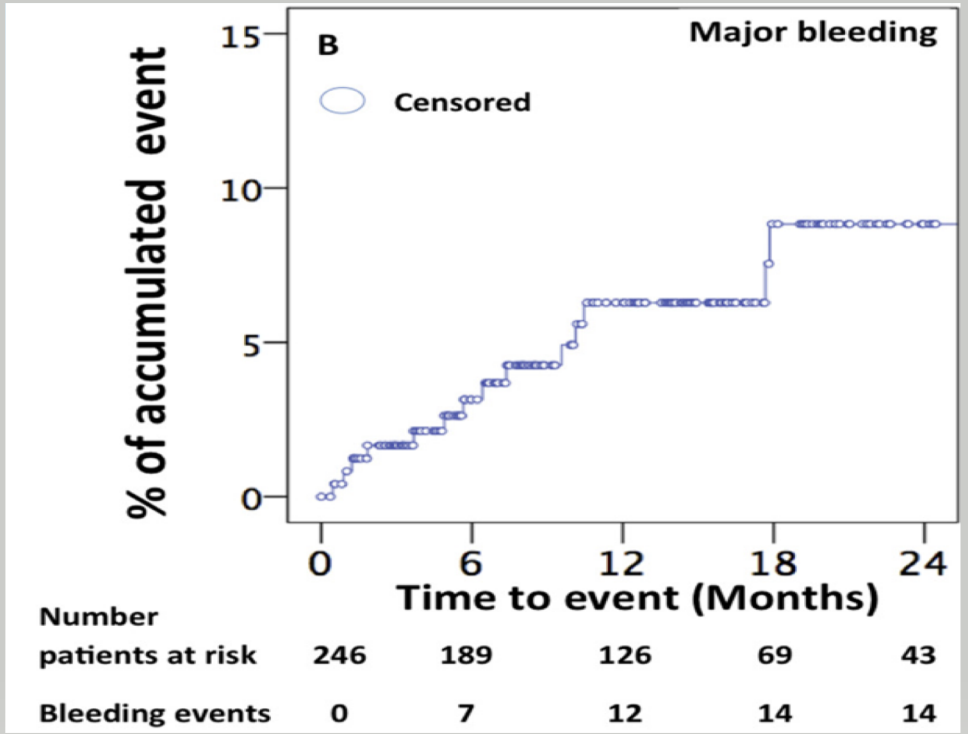
Jara-Palomares L *et al, J Thromb Res* 2017;157:90–96

Safety and Efficacy of Long-Term LMWH Therapy: The TiCAT Study

Recurrent VTE



Major bleeding events



LMWH, low molecular weight heparin; VTE, venous thromboembolism

Jara-Palomares L *et al, J Thromb Res* 2017;157:90–96

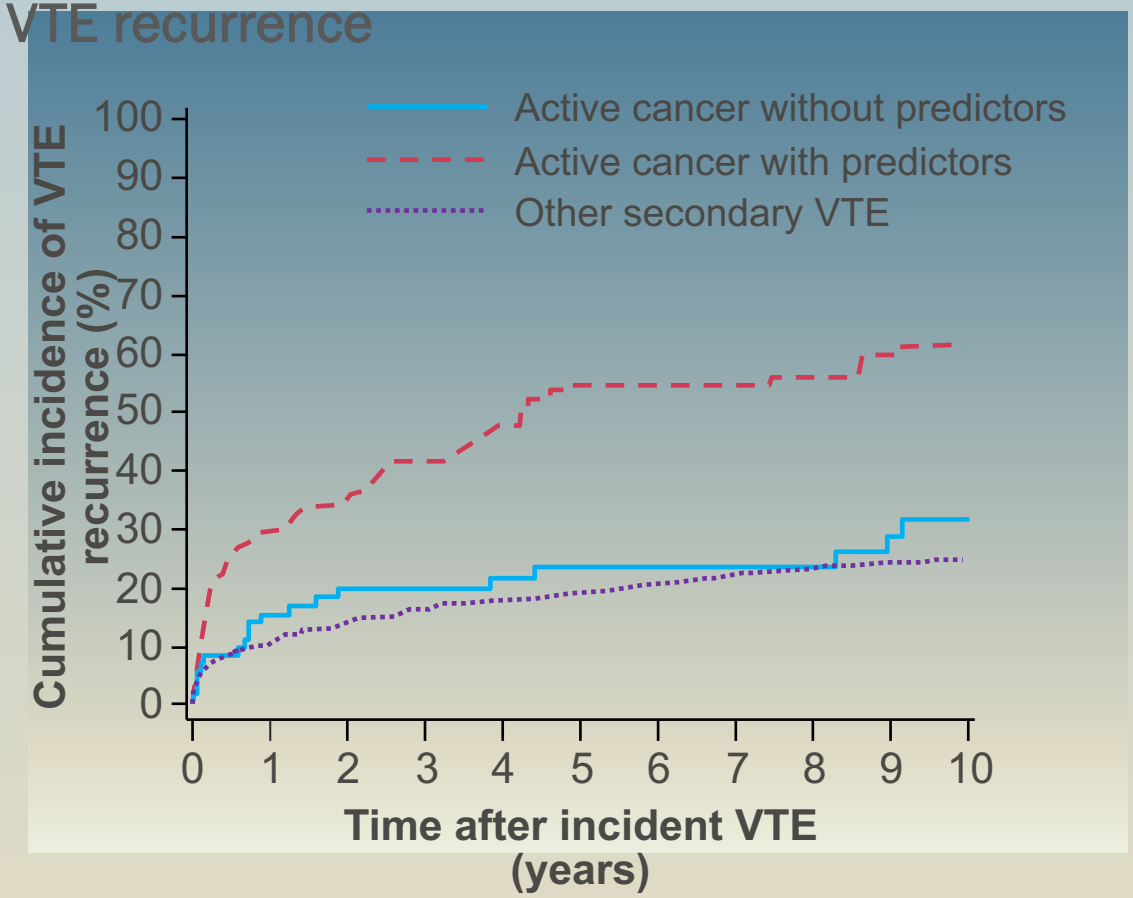
Any Predictors for VTE recurrence ?

Relevant studies

- Retrospective analysis using the Olmstead county database
- Development of risk adaptive models- Ottawa Prognostic Score
- The Cancer DACUS study
- Biomarker Analyses of the CATCH trial
- RIETE registry

Risk of VTE Recurrence May Depend on Tumour Type, Stage of Disease and Co-morbidities

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

- A total of 139 recurrences were identified with an estimated 10-year cumulative rate of **28.6%**
- Highest recurrence risk in first month of treatment

Population-based cohort study performed using the Olmstead county database; 477 patients (1533 person-years of follow-up) with cancer and VTE were identified

Chee CE *et al*, *Blood* 2014;123:3972–3978

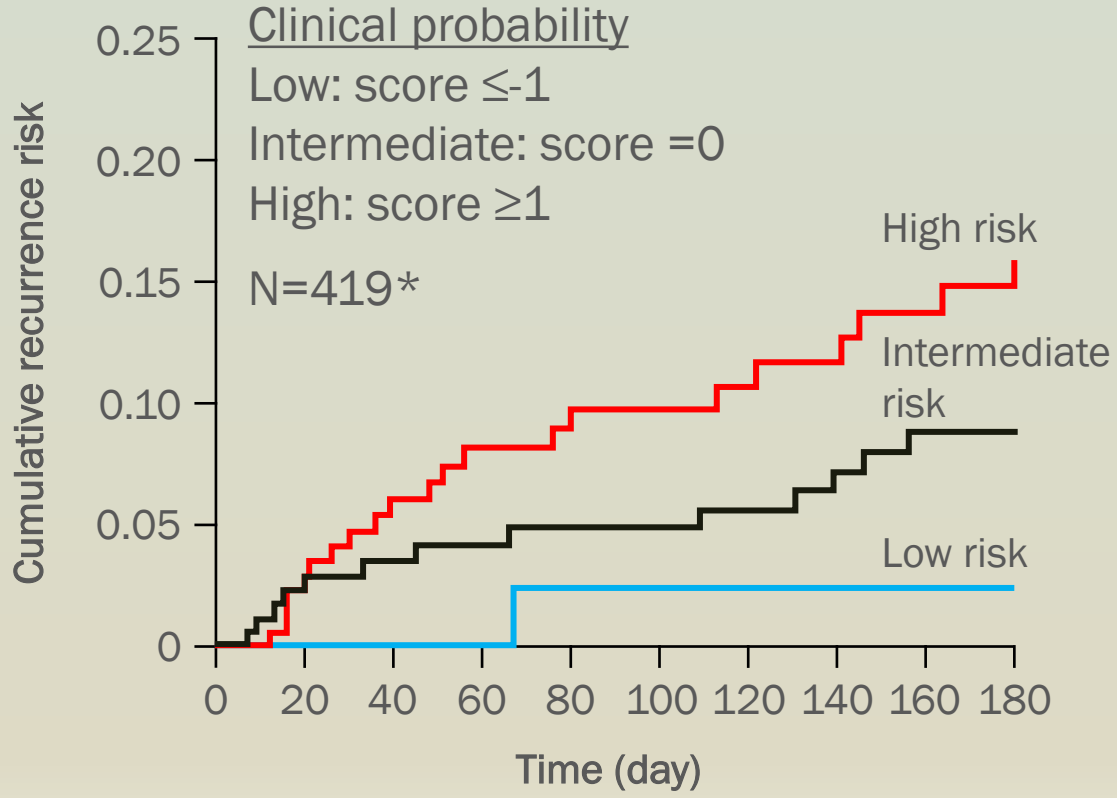
Extended Treatment of VTE in Cancer Associated Thrombosis: Predicting the Risk of Recurrence

Ottawa prognostic score for recurrent VTE risk in CAT[1]

Variable	Regression co-efficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	-0.76	-1
TNM stage I	-1.74	-2
Previous VTE	0.40	1

- Clinical probability low: score ≤0 (-3–0)
- Clinical probability high: score ≥1 (1–3)

Cumulative risk of recurrent VTE according to Ottawa risk class[2]

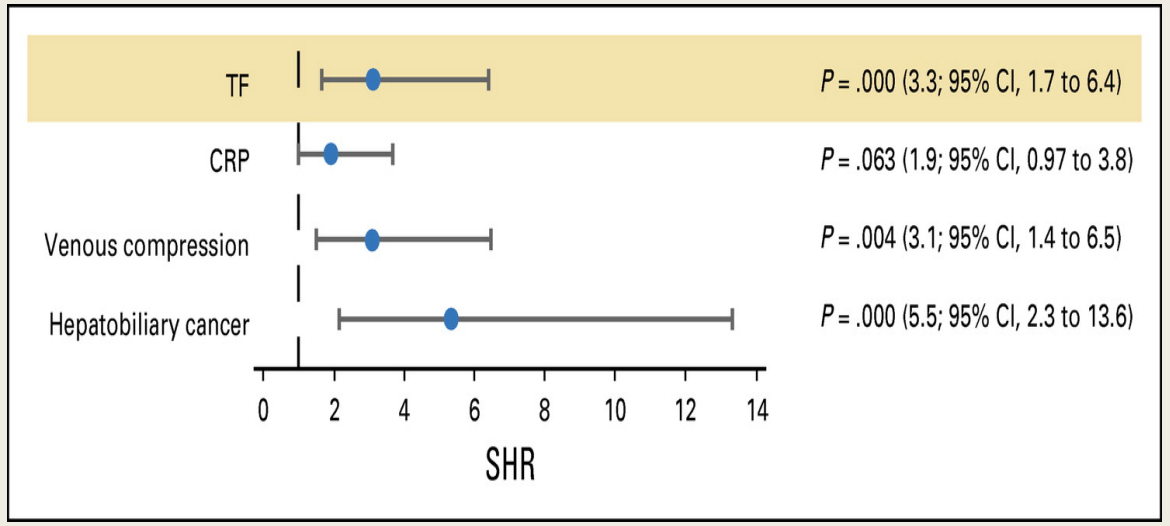


*Retrospective analysis of 419 adult patients with VTE and concomitant active cancer from a multicentre observational cohort study (2001–2010)

1. Louzada ML *et al*, *Circulation* 2012;126:448–454; 2. Den Exter PL *et al*, *J Thromb Haemost* 2013;11:998–1000

Tissue Factor As a Predictor of Recurrent Venous Thromboembolism in Malignancy: Biomarker Analyses of the CATCH Trial

- CATCH- multicentre RCT that investigated Tinzaparin or dose adjusted warfarin for 6 month.
- 805 patients had had sample for TF assay.
- Patients in the highest quartile of TF experienced the greatest VTE recurrence (> 64.6 pg/mL; 38 [19%] of 203 patients *v* 34 [6%] of 602 patients; relative risk, 3.3; 95% CI, 2.1 to 5.1; *P* < .001).

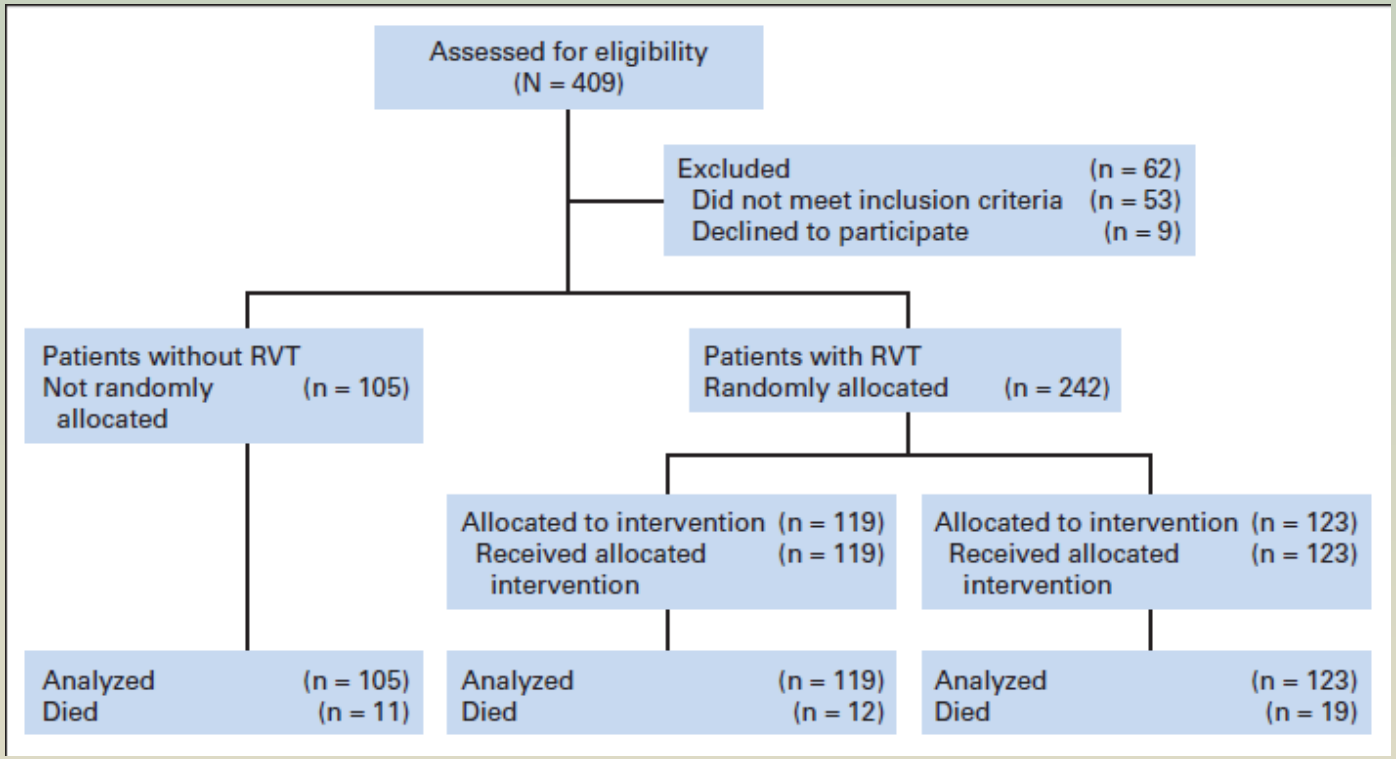


Subdistributional hazard ratios (SHRs; and 95% CIs) in the combined competing risk regression model.

Alok A. Khorana; Pieter W. Kamphuisen; Guy Meyer; Rupert Bauersachs; Mette S. Janas; Mikala F. Jarner; Agnes Y.Y. Lee; *JCO* **2017,** 35, 1078-1085.
DOI: 10.1200/JCO.2016.67.4564

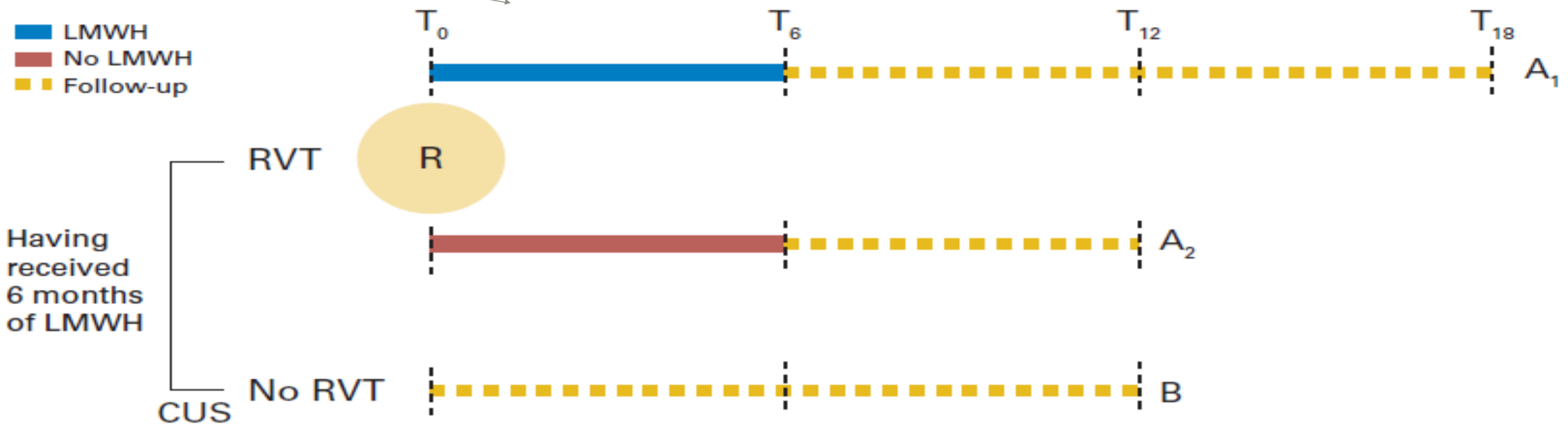
Long-term Management of VTE in Cancer Patients: The Cancer-DACUS Study

Pure DVT study (No PE)



Long-term Management of VTE in Cancer Patients: The Cancer-DACUS Study

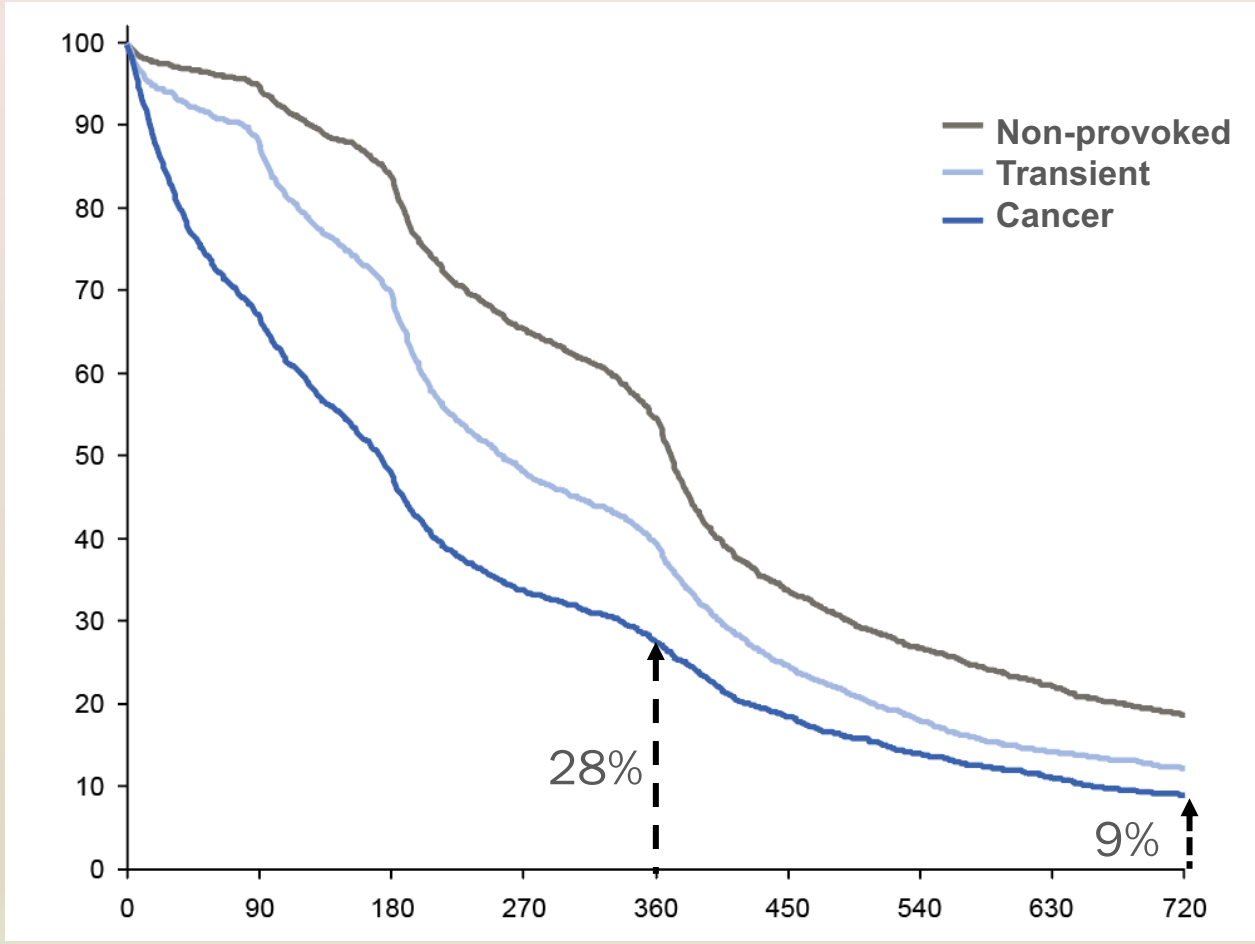
Nadroparin maintained at 75% dose. BD regimen



	6 months				12 months				18 months			
	VTE	BI		F	VTE	BI		F	VTE	BI		F
Group		Major	Minor			Major	Minor			Major	Minor	
A1	4	4	2	108	10	2	4	91	8	1	3	78
A2	18	1	4	94	9	1	4	77				
B	2	1	3	97	1	1	2	91				

Extended Treatment in Cancer Associated Thrombosis: Challenges in the Real World

RIETE Registry: Duration of anticoagulant therapy by risk factors for VTE



Ageno W *et al*, *Thromb Res* 2015;135:666–672

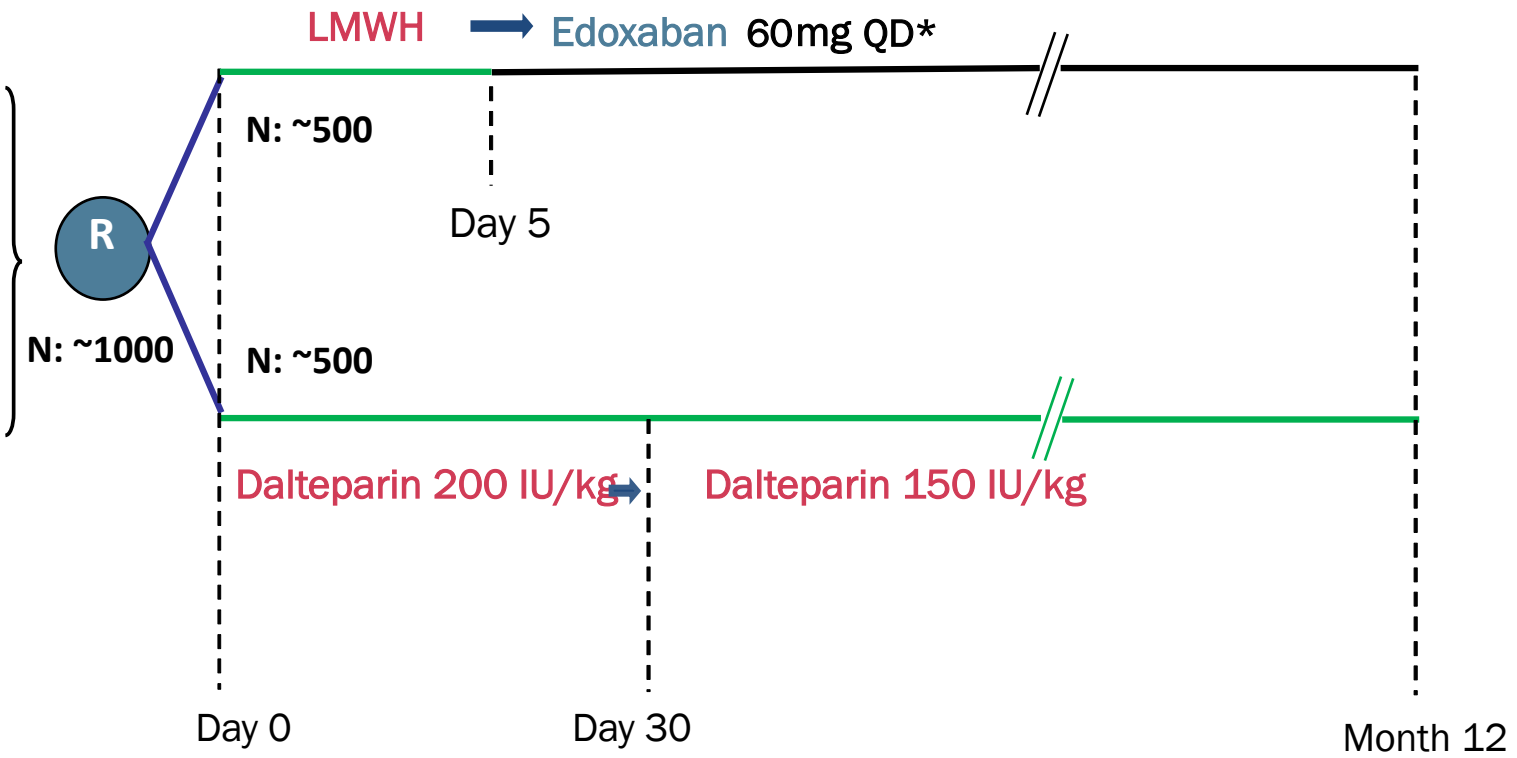
DOAC for CAT

?For how long

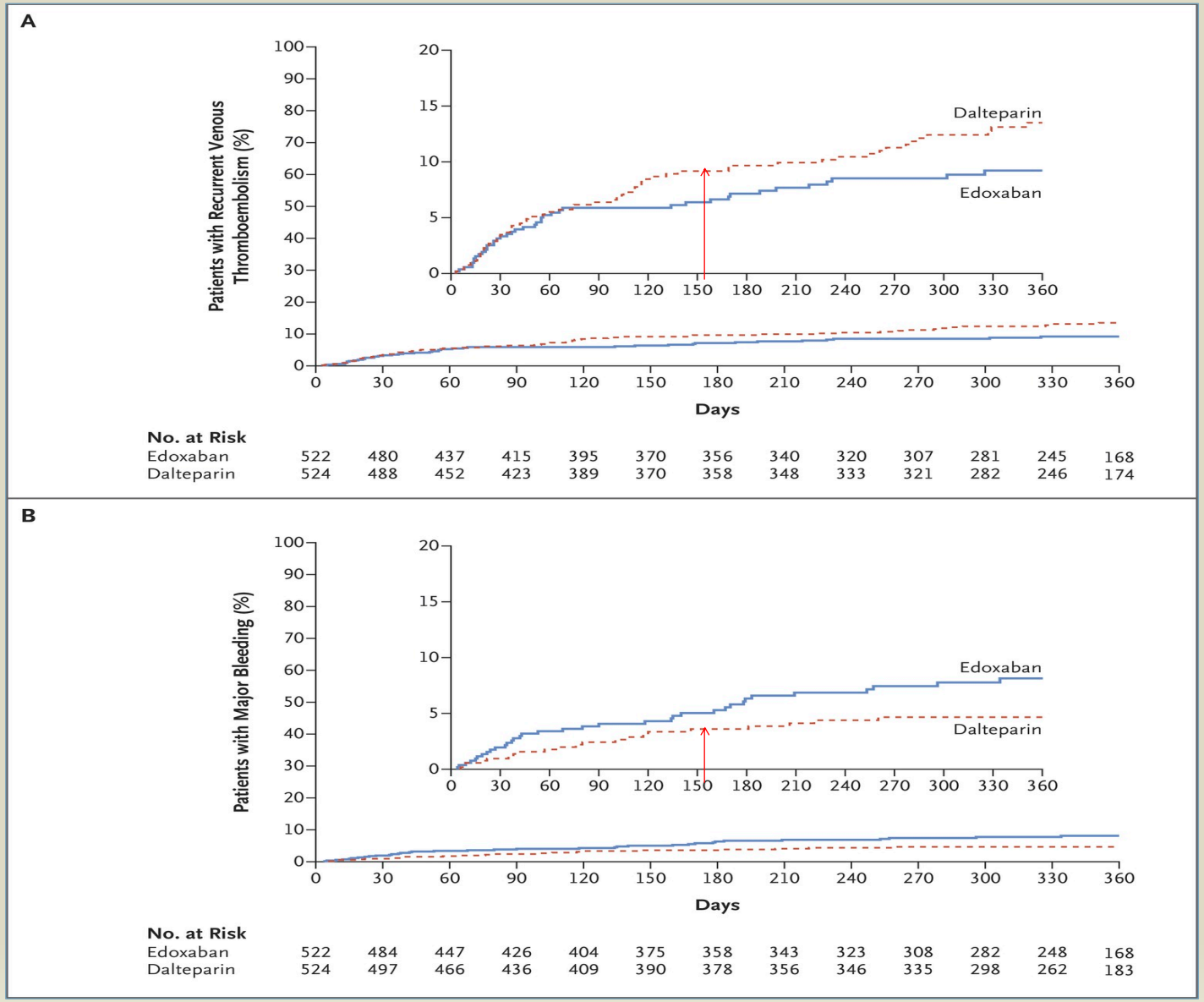
Hokusai VTE - Cancer Study Design

Objectively Confirmed VTE

- Stratified randomization for
  - Bleeding Risk
  - Dose Adjustment
- PROBE design
- 114 sites North America, Europe, Australia, New Zealand

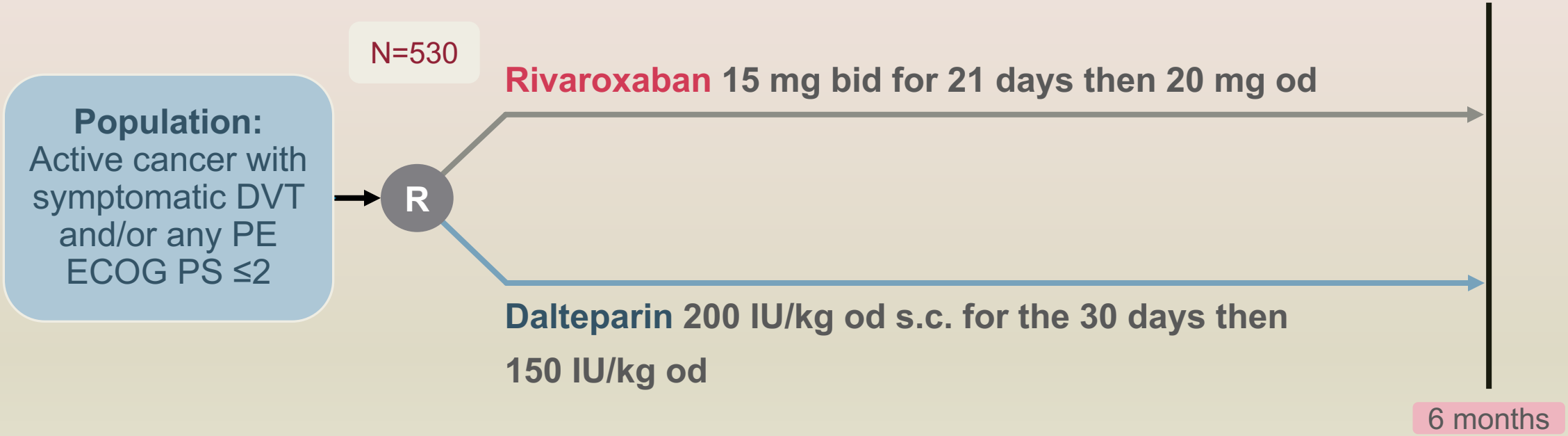


Hokusai VTE Cancer Recurrent VTE and Major Bleeding – 12 Months



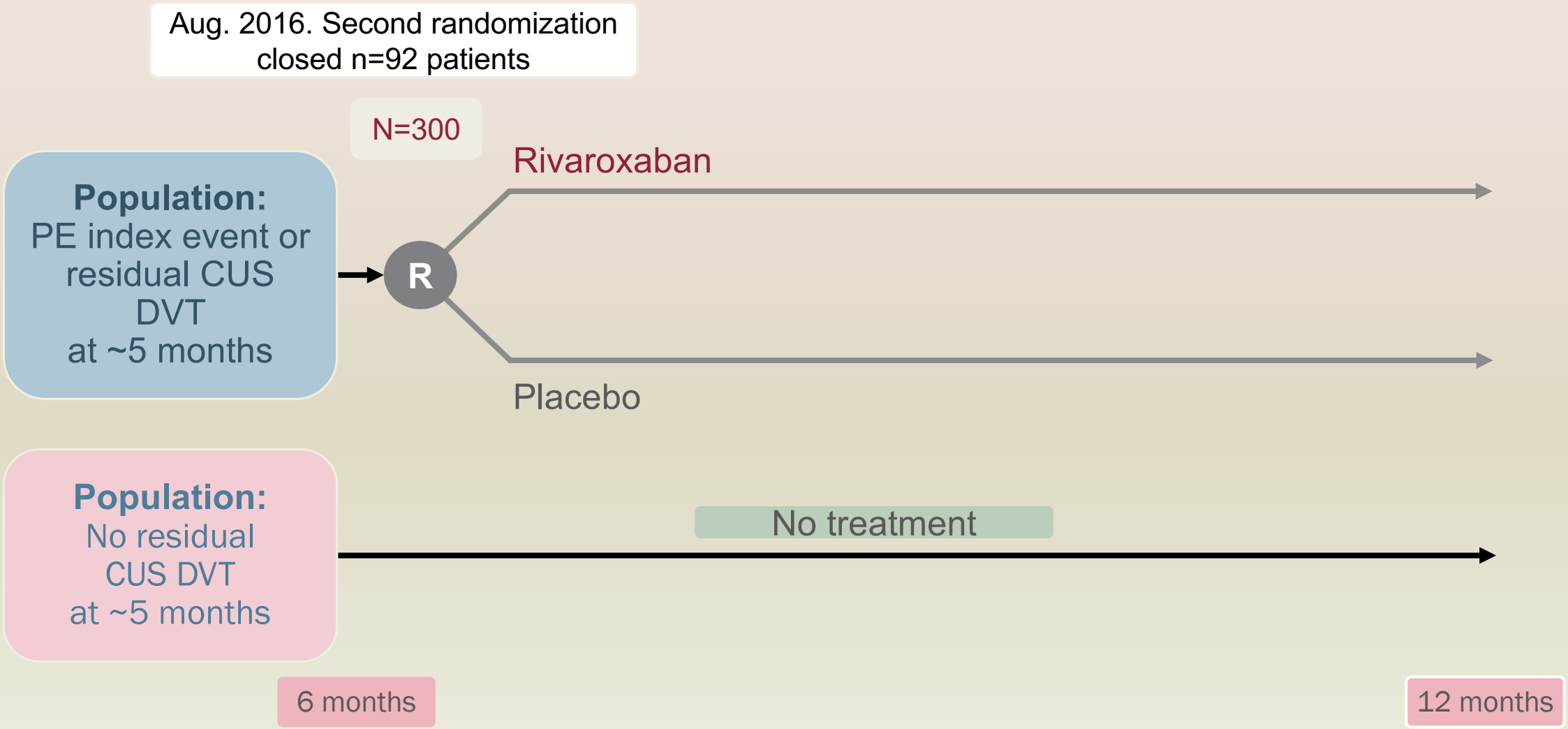
Raskob GE et al. N Engl J Med 2018;378:615-624

SELECTeD: Study Design (1)
Randomized, Open-Label, Multi-Centre, Pilot trial



Young A *et al*, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/; select-d protocol. https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/select-d/select-d_protocol_v2.0_09-apr-2013.pdf [accessed 21 Mar 2018]

SELECTeD: Study Design (2)

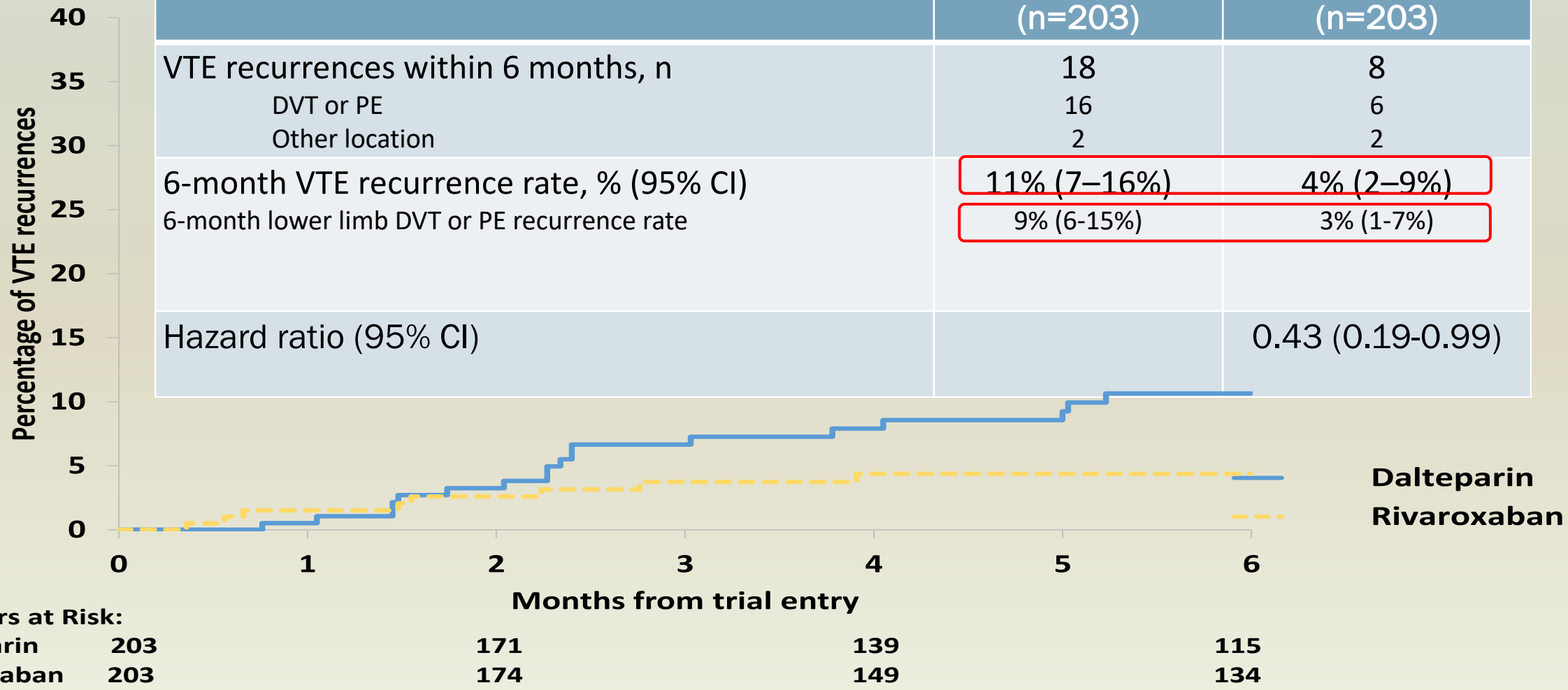


Young A *et al*, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/; select-d protocol. https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/select-d/select-d_protocol_v2.0_09-apr-2013.pdf [accessed 21 Mar 2018]

VTE recurrence

SELECTeD

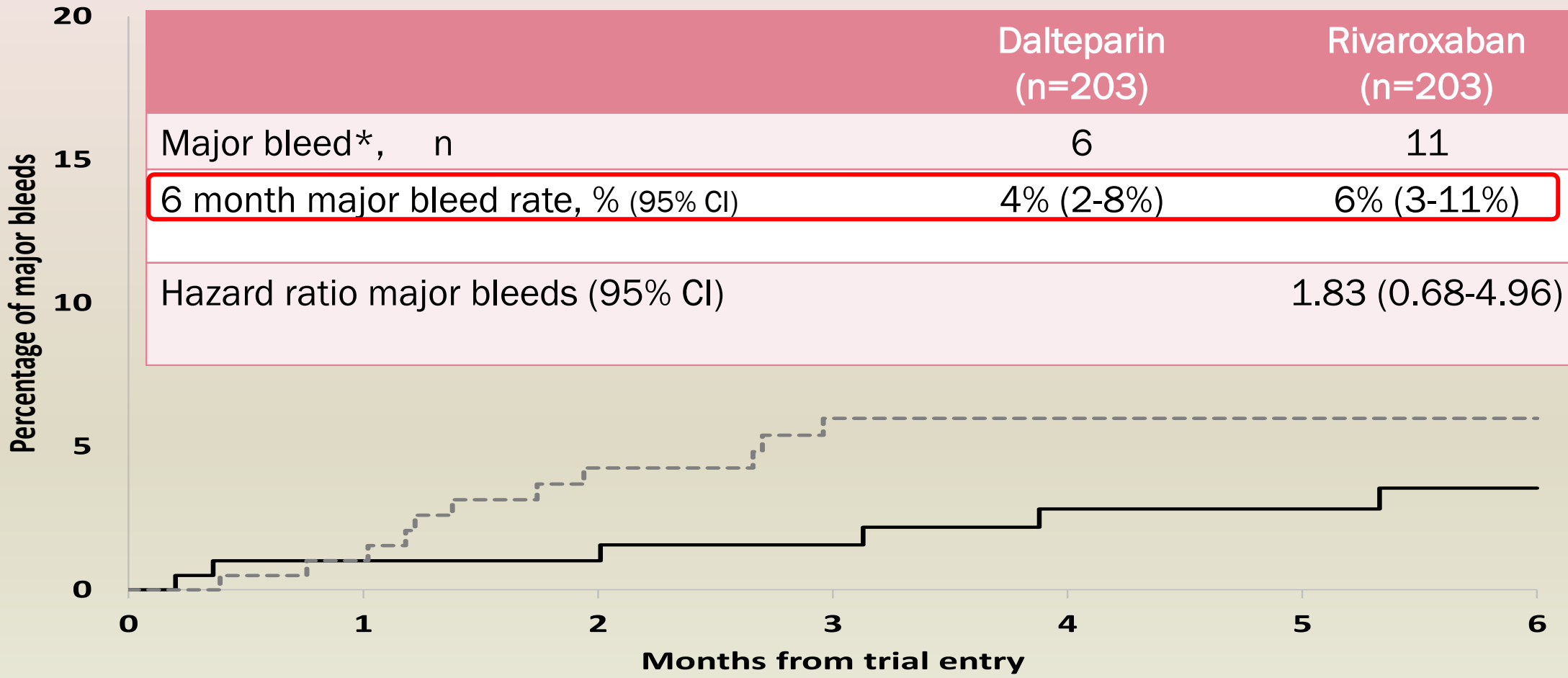
	Dalteparin (n=203)	Rivaroxaban (n=203)
VTE recurrences within 6 months, n	18	8
DVT or PE	16	6
Other location	2	2
6-month VTE recurrence rate, % (95% CI)	11% (7–16%)	4% (2–9%)
6-month lower limb DVT or PE recurrence rate	9% (6-15%)	3% (1-7%)
Hazard ratio (95% CI)		0.43 (0.19-0.99)



SELECTeD

Major bleeds

	Dalteparin (n=203)	Rivaroxaban (n=203)
Major bleed*, n	6	11
6 month major bleed rate, % (95% CI)	4% (2-8%)	6% (3-11%)
Hazard ratio major bleeds (95% CI)		1.83 (0.68-4.96)



Numbers at Risk:

Dalteparin	203	176	147	122
Rivaroxaban	203	172	149	134

*1 fatal bleed in each arm

Summary

	Hokusai-VTE-Cancer[1]	select-d[2–4]
Design	Non-inferiority	Randomized pilot
Patients	Active cancer	Active cancer
Rx	◆ LMWH 5 days edoxaban po od ◆ Dalteparin s.c. od ◆ 6 months and up to 12 months	◆ Rivaroxaban po od ◆ Dalteparin s.c. od ◆ 6 months and second randomization
Outcome	Composite of recurrent VTE or major bleeding	Primary: recurrent VTE Secondary: major bleeding and CRNM bleeding
Sample size	1050	406
Results (difference % between NOAC and LMWH)	◆ Recurrent VTE: 3.4% in favour of edoxaban ◆ Major bleeding: 2.9% in favour of dalteparin	◆ Recurrent VTE: 7.0% in favour of rivaroxaban ◆ Major bleeding: 2.0% in favour of dalteparin

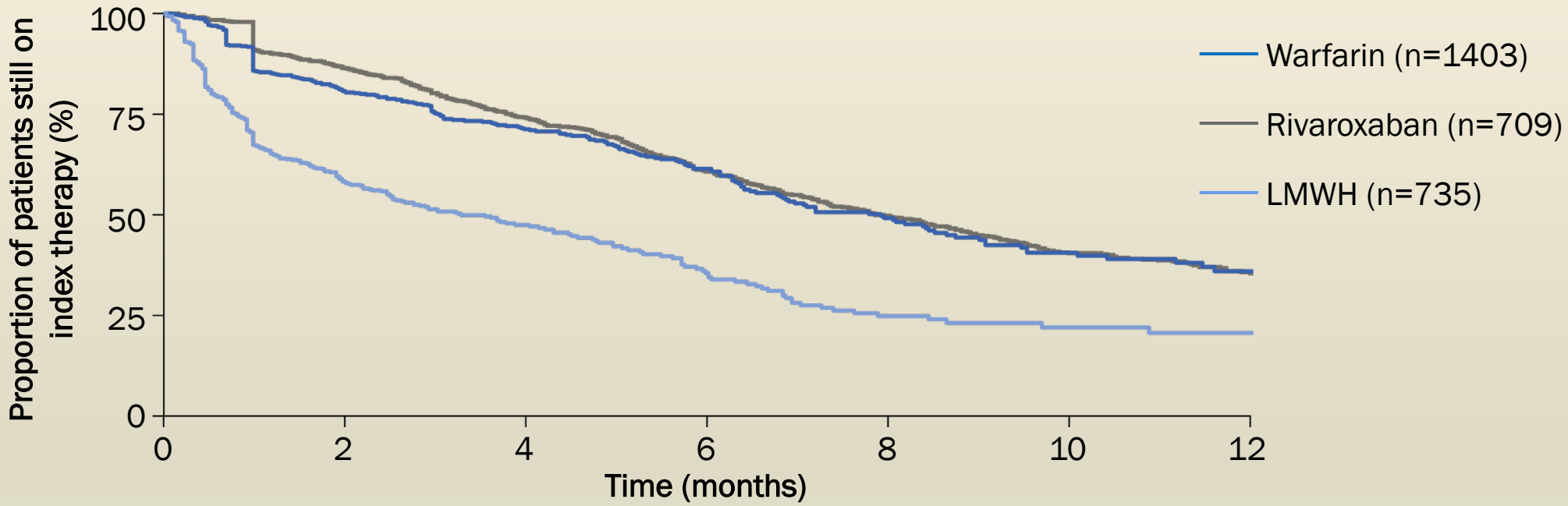
Median duration of treatment: 211 days for edoxaban and 184 days for dalteparin, p=0.01

NOT INTENDED FOR DIRECT COMPARISON

1. Raskob G *et al*, *N Engl J Med* 2018;378:615–624; 2 ...lresults.org/; 3. select-d protocol. https://warwick.ac.uk/fac/med/research/ctu/trials/ca... 018]; 4. select-d trial summary. https://warwick.ac.uk/fac/med/research/ctu/trials/ca... [accessed 21 Mar 2018]

Real World Data

Higher Persistence on Index Therapy in Cancer Patients Using Rivaroxaban or Warfarin versus LMWH



Cohort	Median treatment duration	Kaplan–Meier rates	
		6 months	12 months
LMWH	3.3	37%	21%
Warfarin	7.9	61%	35%
Rivaroxaban	7.9	61%	36%

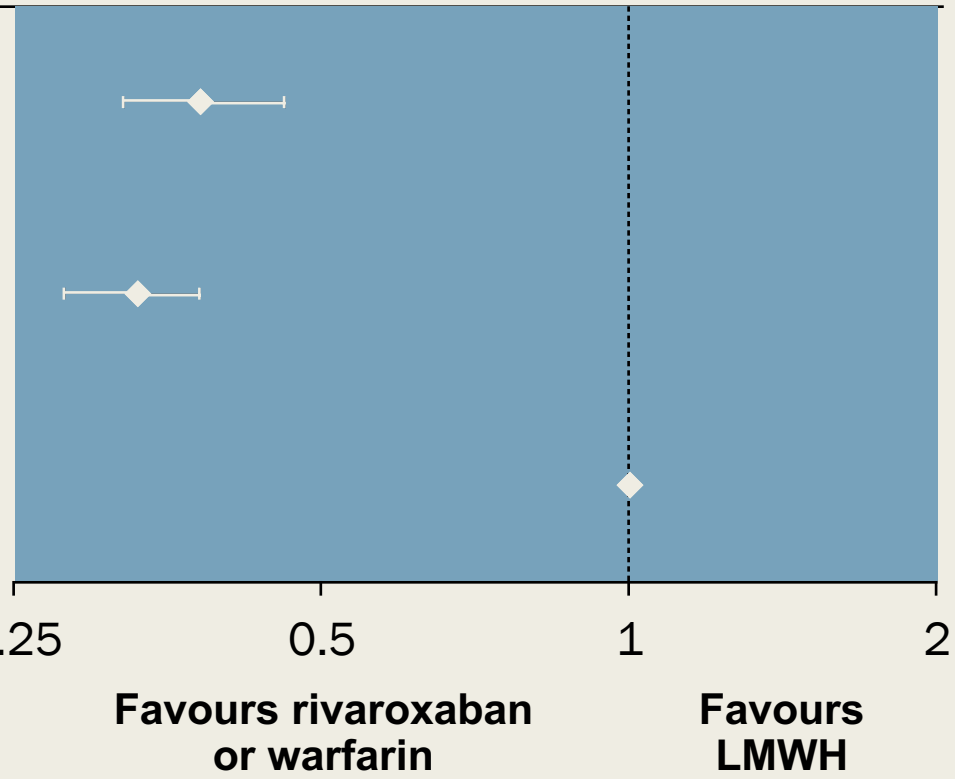
*Discontinuation was defined as a gap of no more than 60 days between the end of the days of supply of a dispensing and the start date of he next dispensing of the index therapy, if any

Khorana AA *et al*, *Res Pract Thromb Haemost* 2017;1:14–22

Higher Risk of Discontinuation of Index Therapy on LMWH versus Rivaroxaban or Warfarin

Risk of discontinuation with rivaroxaban or warfarin versus LMWH

Drug	HR	95% CI
Rivaroxaban	0.38	0.32–0.46
Warfarin	0.33	0.28–0.38
LMWH	N/A	N/A



Khorana AA *et al*, *Res Pract Thromb Haemost* 2017;1:14–22

Real World Data

- Warfarin is still the most commonly used anticoagulant.
- Rivaroxaban is as commonly used as LMWH despite guideline recommendation
- Patients On LMWH had significantly lower persistence and shorter duration
- Patients initiating on oral agents are at significantly lower risk to discontinue therapy relative to LMWH

Inconveniences of Long-Term LMWH Therapy

- Reluctance of patients to have a drug injected parenterally beyond the first weeks
- Reluctance of physicians to prescribe such an expensive therapy beyond the first weeks
- Country-based regulations that may not reimburse LMWH treatment beyond the initial treatment

LMWH, low molecular weight heparin

Kearon C *et al, Chest* 2016;149:315–352; Author's opinion

To conclude -

- Current guidelines are expected to change .
- Data that may help to individualize treatment is still lacking and risk adaptive models are not validated
- Evidence for both LMWH and DOAC identifies the first month to be at greatest risk for recurrent VTE and major bleed
- Not much difference in the rate composite outcome of recurrent venous thromboembolism or major bleeding between DOAC and LMWH.

Thank you