Le rôle émergent des anticoagulants oraux directs pour la thrombose associée au cancer

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Disclosures

Advisory board

- Pfizer
- Bayer
- Sanofi
- Leo Pharma
- Servier

Investigator initiated research funding

- Pfizer
- Sanofi

Objectifs

- Revoir les évidences actuelles des anticoagulants oraux directs (AOD) pour la thrombose associée au cancer.

- Positionner la place des AOD dans l'arsenal thérapeutique des thromboses avec cancer.

- Connaître les lignes directrices actuelles pour le traitement des thromboses avec cancer.

Patients with Cancer and VTE
Anticoagulation therapy

- Treatment is warranted in all cancer patients with VTE
  - Untreated PE: 30% mortality
  - Untreated proximal DVT: 50% risk of PE

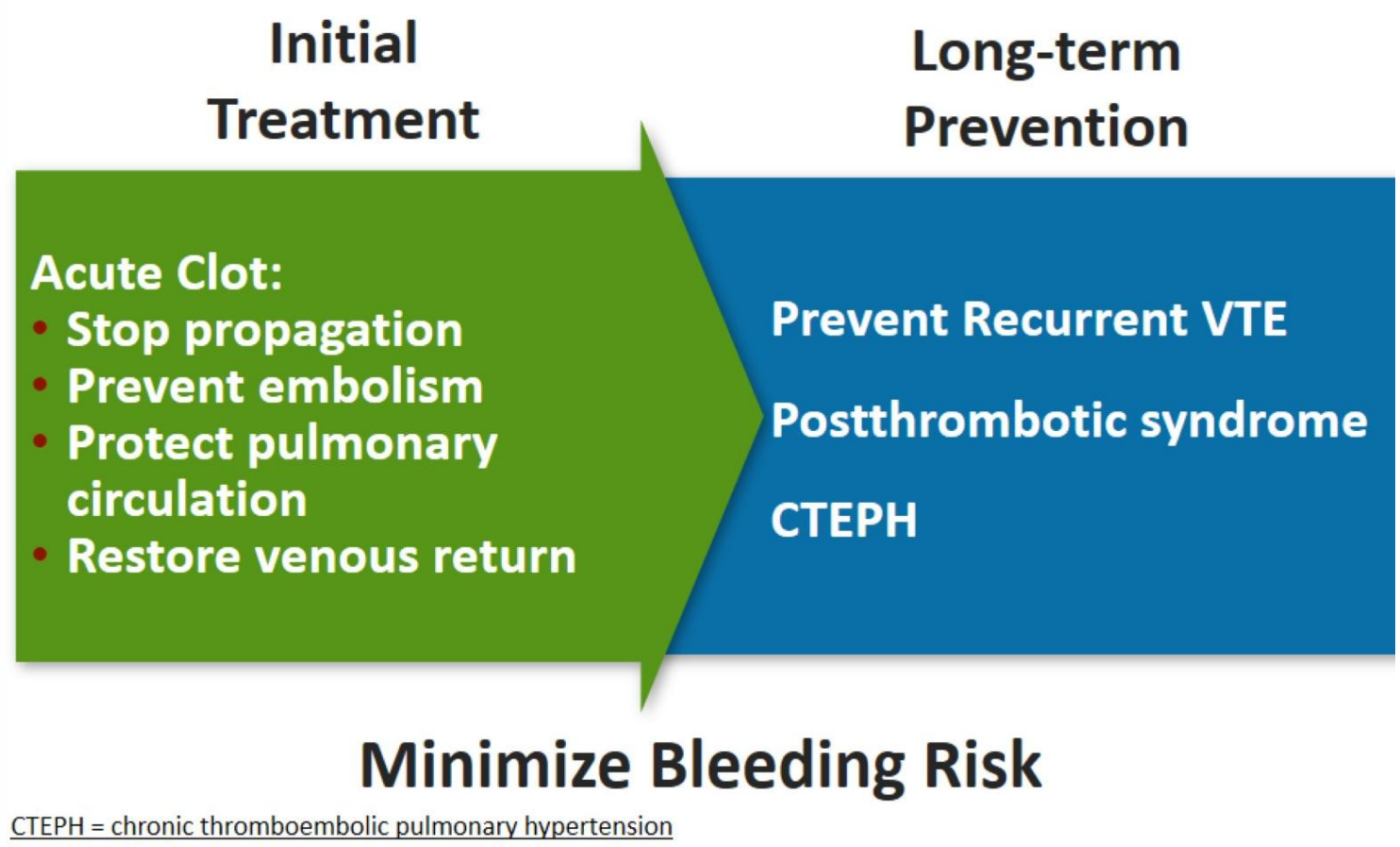
- Goal is to prevent extension, embolization and finally VTE recurrence while minimizing risk of bleeding

- However, AC in cancer patients with VTE is more complicated than in non-cancer patients with VTE
  1) higher risk of recurrence (up to 20-30%)
  2) higher risk of bleeding (8-18%)

VTE=venous thromboembolism, AC=anticoagulation

[1]Hutten et al. *Journal of Clinical Oncology* 2000; 18, 3078-3083

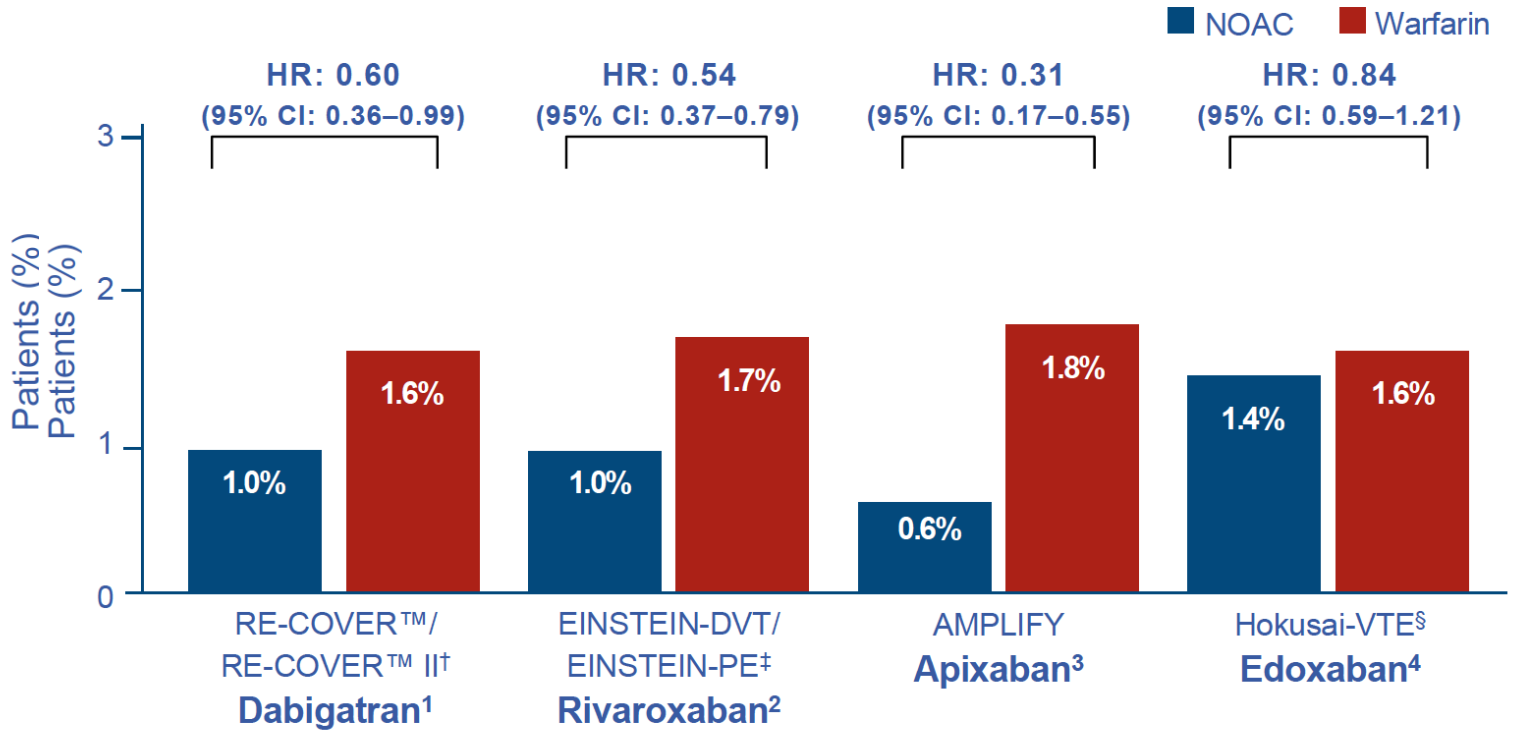
Goals of Treatment



CTEPH = chronic thromboembolic pulmonary hypertension

Parac … ite VTE

Treatment of acute DVT/PE: NOACs associated with less major bleeding than warfarin in Phase III trials*



Direct comparisons cannot be made as no head-to-head data are available

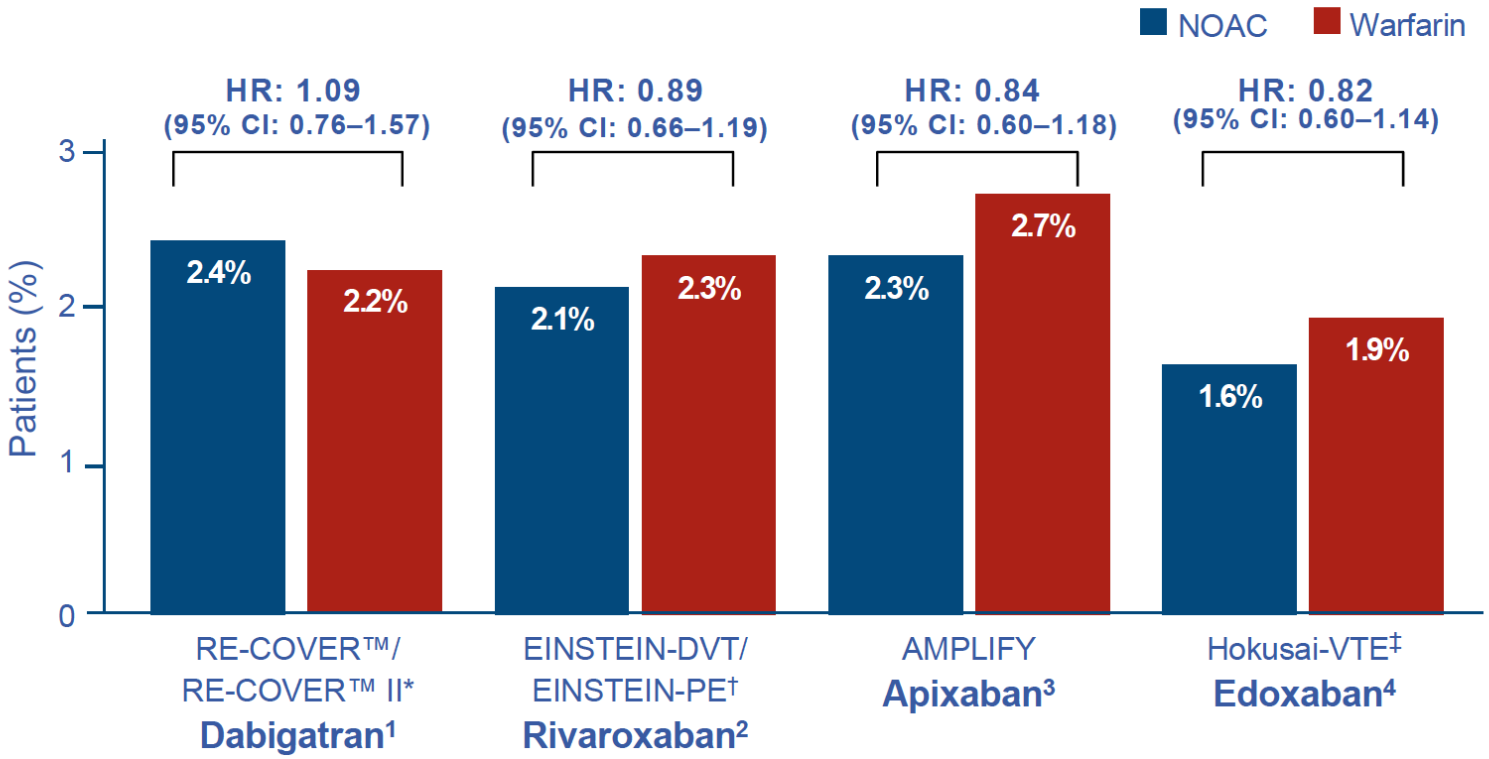
*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin; †Pooled data from RE-COVER™ and RE-COVER™ II; oral drug treatment period only; ‡Pooled analysis; §On treatment

1. Schulman S et al. Circulation 2014;129:764–72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799–808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

- Higher initial dose

*Rivaroxaban and apixaban (Edoxaban and Dabigatran require an initial 5 days of LMWH)

Treatment of acute DVT/PE: NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in Phase III trials



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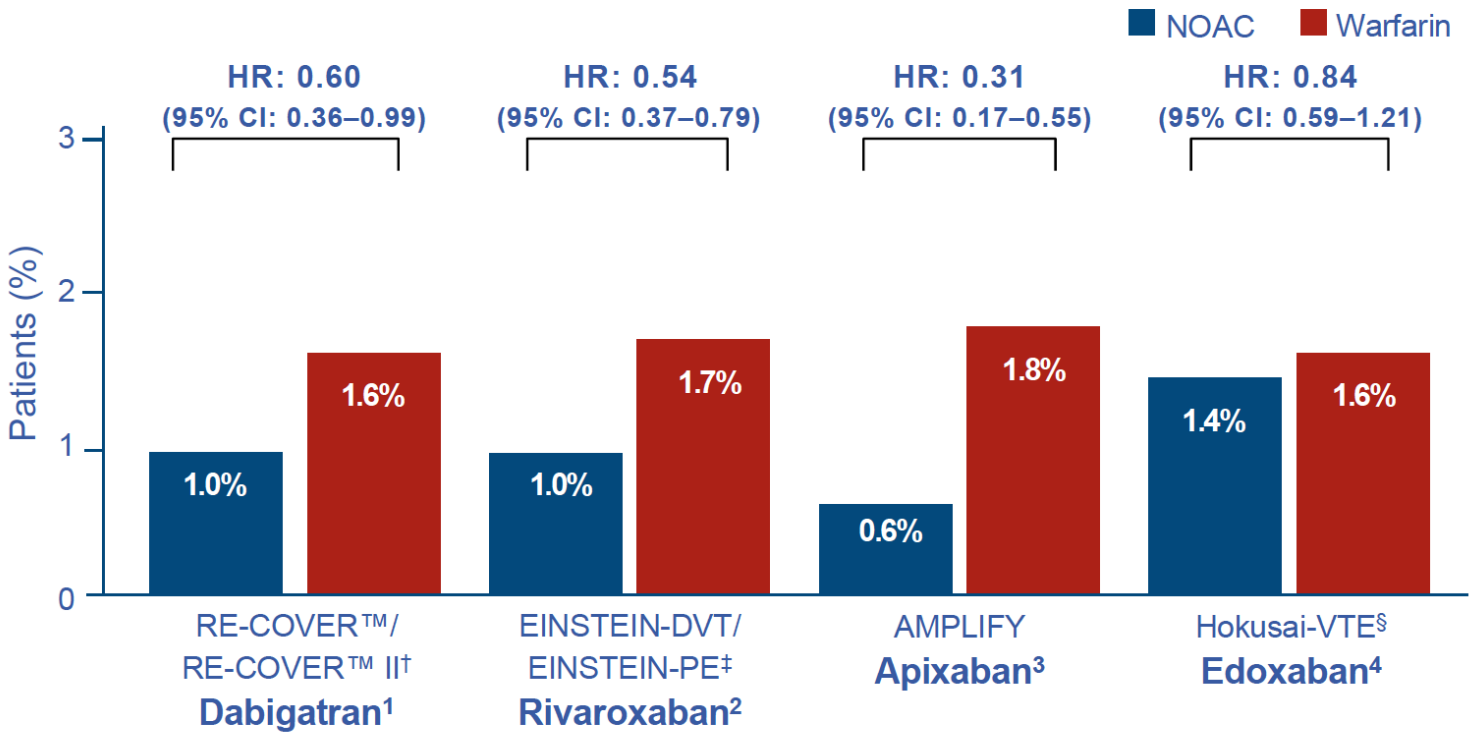

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The reasons for the paradigm shift in VTE treatment

- DOACs have similar efficacy to and are safe or safer than LMWH/VKA ? VKA
- Extended therapy with DOACs is effective and relatively safe (based on extension DOAC studies)
- DOACs have less drug-drug interactions and are less patient-burdensome compared to VKA

Debate regarding treatment of VTE in cancer patients: LMWH vs DOACs

LMWH superior to VKA	• CLOT trial is relatively old data • CATCH trial did not reach statistical significance
No RCT comparing DOAC vs LMWH	• BUT, cancer subgroup analyses of DOAC vs VKA studies show similar efficacy and bleeding in cancer patients • Over 1100 cancer patients included in subgroup meta-analyses
Guidelines recommend LMWH monotherapy	• Real world data suggest that less than 50% of patients persist with LMWH at 3 months (US data)

Cancer associated VTE: DOAC clinical studies

- SELECT-D (rivaroxaban)
- Hokusai-VTE Cancer (edoxaban)

SELECT D Study

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

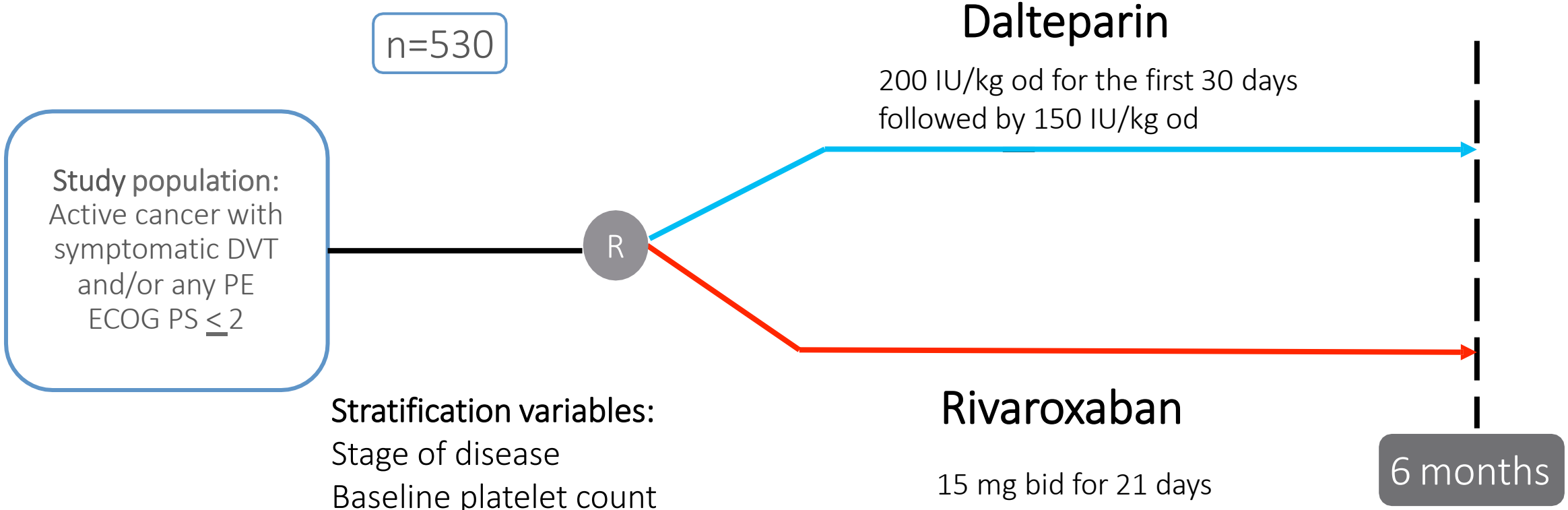
J Clin Oncol 36.

SELECT-D
Main research objectives

- To assess VTE recurrence in cancer patients with a first VTE treated with rivaroxaban or dalteparin
- To assess rates of major and clinically relevant non-major bleeding
- To assess extended anticoagulation treatment beyond 6 months in selected patients

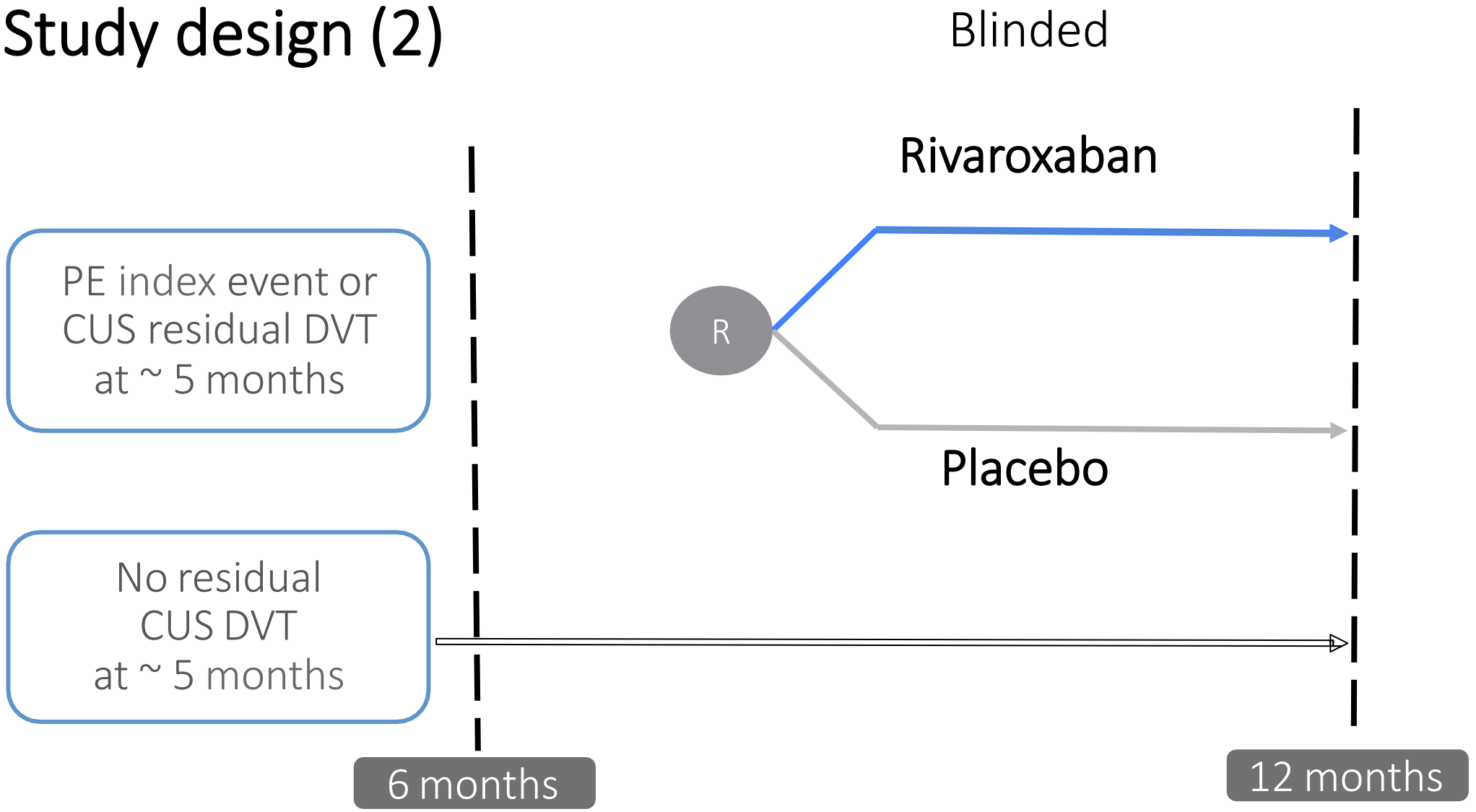
SELECT D
Study design (1)

Prospective, randomised, open-label, multicentre pilot phase III



Stratification variables:
Stage of disease
Baseline platelet count
Type of VTE
Risk of clotting by tumour type

SELECT- D
Study design (2)



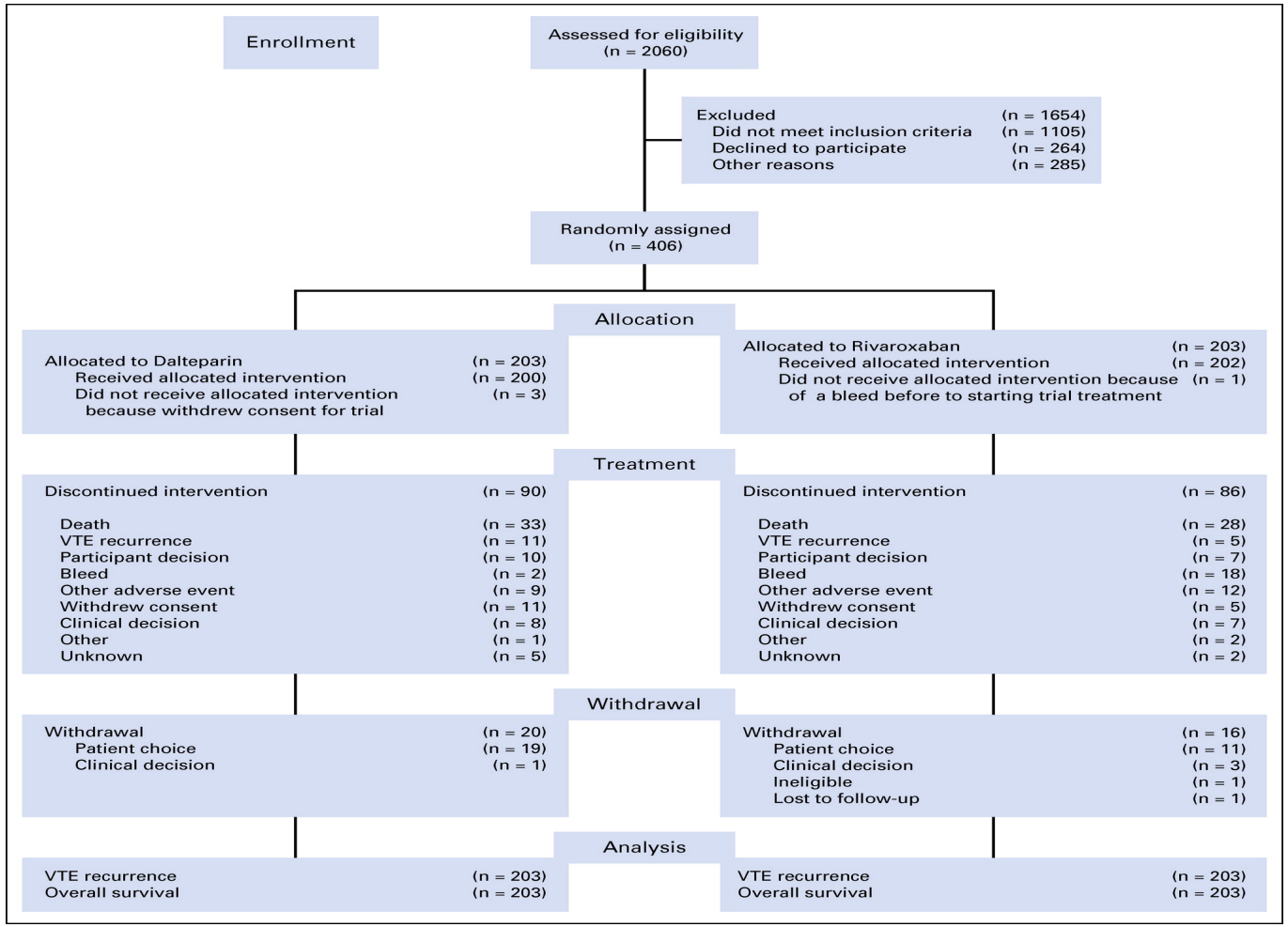
Statistical considerations

- A sample size of 530 patients would provide:
  - estimates of VTE recurrence rates at 6 months to within +/- 4% assuming a VTE recurrence rate at 6 months of 10%
  - 300 patients for the second randomisation, assuming 70% eligible at 6 months and 80% agreed to participate

SELECT-D: Trial progress

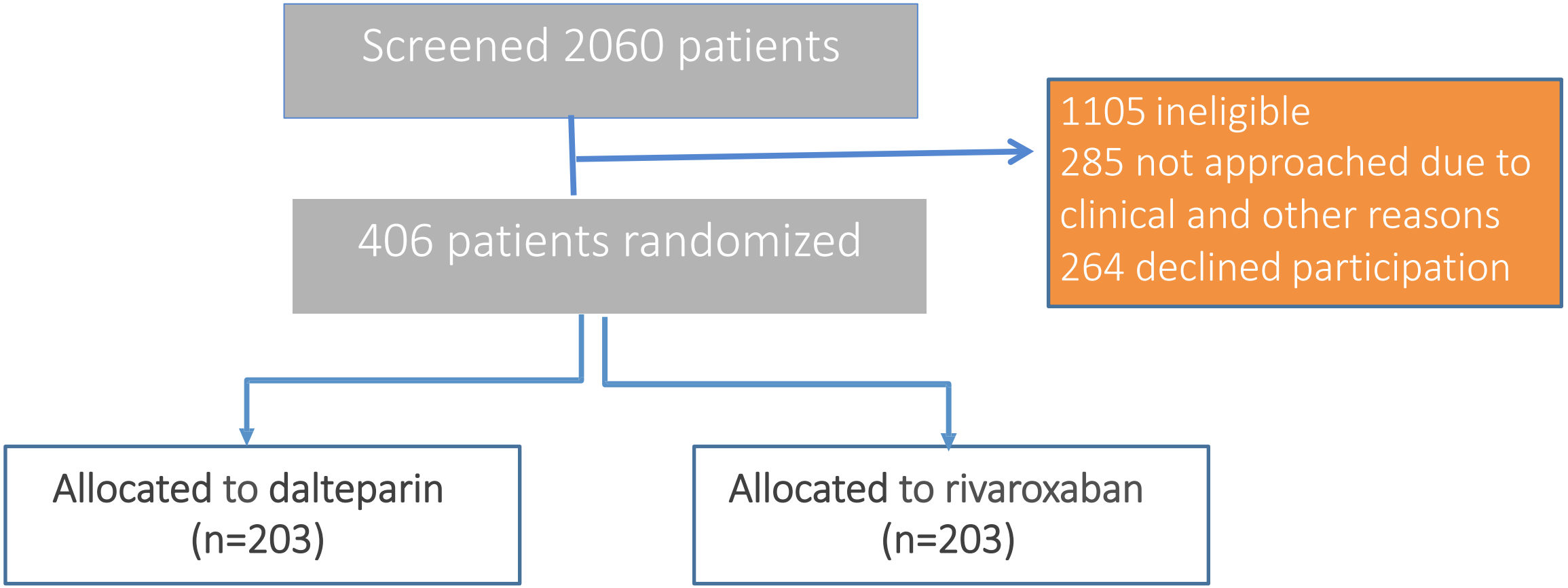
- First patient randomised in October 2013
- Changes to protocol based on DMC recommendations in June 2016
  - The second randomisation was closed to patients randomised into the trial after 31st August 2016 due to low recruitment (n=92)
  - Sample size reduced from 530 to 400 patients (increased the width of the 95% CI for VTE recurrence rate from 8% to 9%)
  - Patients with oesophageal and gastro-oesophageal cancer were excluded due to apparent imbalance in major bleeding rates compared to other tumour types
- Final bleeding adjudication committee, 24th November 2017

Fig 1. CONSORT diagram, including enrollment and outcomes. VTE, venous thromboembolism.



Published in: 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; Mark Levine; *JCO* Ahead of Print
DOI: 10.1200/JCO.2018.78.8034

SELECT-D: Recruitment



- Recruitment between October 2013 and December 2016 from 58 sites across the UK

SELECT-D: Baseline characteristics

Factor	Dalteparin % (n=203)	Rivaroxaban % (n=203)
Age: years, median (range)	67 (34–87)	67 (22–87)
Gender: male	48	54
Stage of Cancer: - metastatic	59	59
ECOG PS: - 0,1 - 2	 76 21	 72 26
Qualifying VTE: - symptomatic VTE - incidental PE	 48 52	 46 54

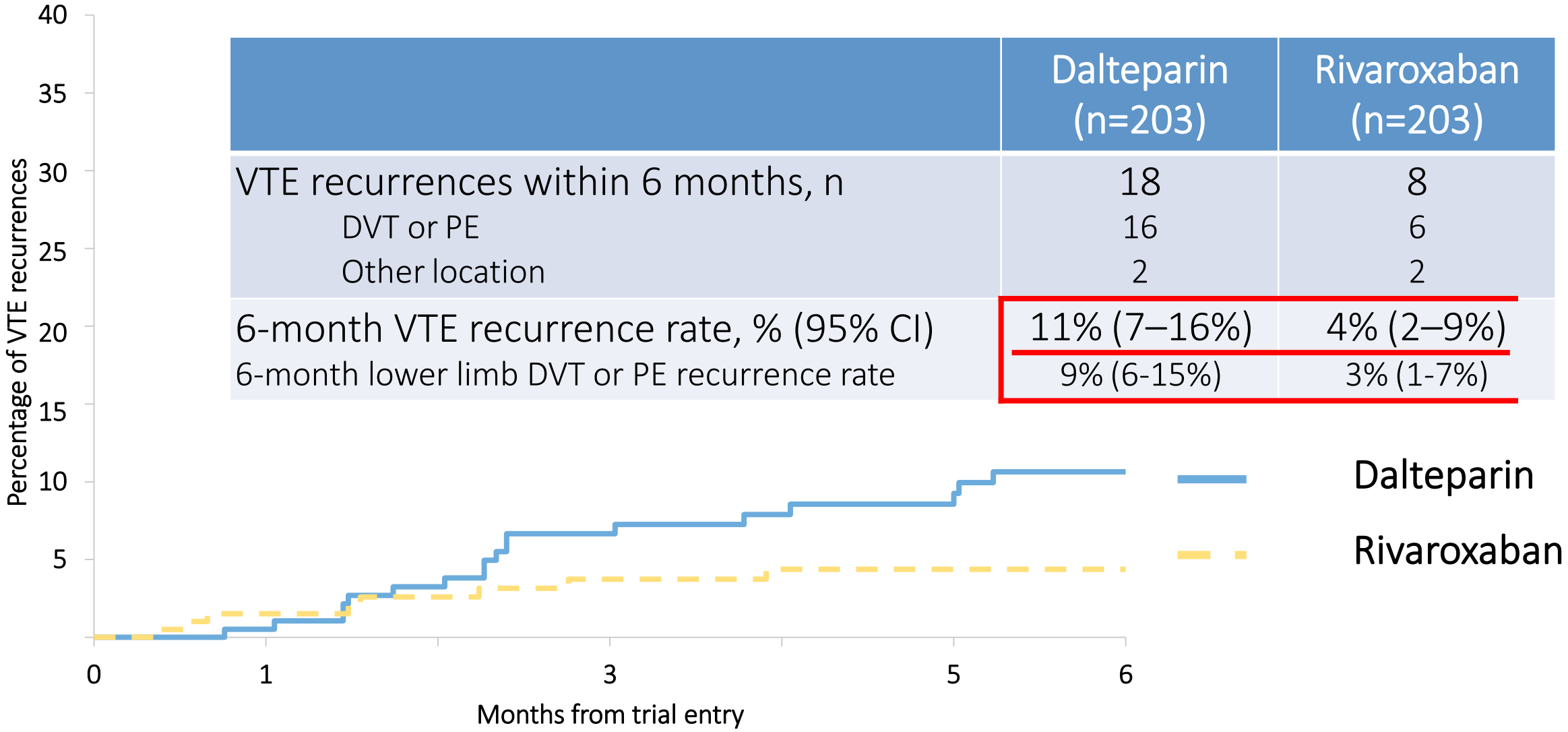
SELECT-D: Primary tumour type

	Dalteparin, % (n = 203)	Rivaroxaban, % (n = 203)
Colorectal	23	27
Lung	12	11
Breast	10	9
Ovarian	9	5
Pancreatic	5	9
Lymphoma	6	5
Oesophageal/gastro-oesophageal	9	5
Prostate	3	6
Bladder	2	5
Other	21	18

SELECT-D: VTE recurrence

HR 0.43; 95% CI 0.19-0.99

	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%)



Numbers at Risk:

Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

Recurrent VTE

Table 2. Recurrent VTE

Thrombosis	No. (%)* Dalteparin (n = 203)	No. (%)* Rivaroxaban (n = 203)
VTE recurrence	18	8
Location of recurrence		
Lower extremity	7 (39)	3 (38)†
Femoral vein	5	2
Popliteal vein	3	1
Iliac vein	2	2
IVC	0	1
PE	9 (50)	4 (50)
Other	2 (11)	2 (25)
Brachial, subclavian, or jugular	1	1
Renal plus IVC	1	0
Extrahepatic portal vein	0	1
Type of PE		
Symptomatic	2 (11)	2 (25)
Incidental	6 (33)	1 (13)
Fatal PE	1 (6)	1 (13)

Abbreviations: IVC, inferior vena cava; PE, pulmonary embolism; VTE, venous thromboembolism.
*Percentages are out of the total with VTE recurrence.
†One patient had deep vein thrombosis and PE.

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SELECT-D: Bleeding - number of patients (%)

Category	Dalteparin (n=203)	Rivaroxaban (n=203)
Major*	6 (3%)	11 (5%)
Clinically relevant non-major	6 (3%)	25 (12%)
Total	12 (6%)	36 (17%)

*1 fatal bleeding event in each arm
Most major bleeding events were gastrointestinal bleeding; no CNS bleeds
Most CRNMBs were gastrointestinal or urological

Bleeding Events

Table 3. Bleeding Events

Type of Bleed	Dalteparin (n = 203)	Rivaroxaban (n = 203)
Major bleeding	6	11
Criteria to define major bleeding*		
Clinically overt and decrease in hemoglobin level of ≥ 2 g/dL over 24 hours	5	6
Clinically overt and transfusion of ≥ 2 units of packed red cells	3	10
Clinically overt and critical site (eg, intracranial, retroperitoneal)	0	0
Clinically overt and contributes to death	1	1
Sites of major bleed*		
GI		
Esophageal	1	3
Stomach	3	2
Lower GI	0	1
Site unknown	0	2
Genitourinary		
Hematuria	0	1
Other		
Epistaxis	0	1
Intraoperative hemorrhage	0	1
Hematoma	1	0
Abdominal hematoma related to surgical clip	1	0
CRNMB	7	25
Criteria to define CRNMB*		
Overt bleeding with medical intervention	0	8
Unscheduled contact with a physician	2	15
Interruption or discontinuation of a study drug	4	22
Discomfort or impairment of activities of daily life	2	11
Site of CRNMB*		
GI		
Oral	0	1
Upper GI	0	2
Lower GI	1	0
Colon and rectum	2	1
Anus	0	3
Hemorrhoidal	0	2
Genitourinary		
Hematuria	1	9
Vagina	0	1
Menorrhagia	0	1
Penis	1	0
Other		
Bronchopulmonary	0	2
Epistaxis	1	1
Bruising	1	1
Hematoma	1	0
Subconjunctival	0	2
Joint effusion	0	1

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.
*Patients could have more than one reason or site of bleed; one patient receiving rivaroxaban had two CRNMBs.

GI related MB
-66% with D
-55% with R

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SELECT-D: Overall survival

	Dalteparin	Rivaroxaban
6-months overall survival, % (95% CI)	70% (63–76%)	75% (69–81%)

- Overall 104 (26%) patients died
- 92 (88%) died from progressive cancer
- 2 (2%) fatal PEs

SELECT-D: Conclusions

- Treating with rivaroxaban was associated with a relatively low recurrence rate but a higher bleeding rate compared with dalteparin

- High mortality
  - overall survival at 6 months was 70% (95% CI, 63-76%) and 63% (95% CI, 68-80%) on dalteparin and rivoraxban respectively

LIMITATIONS

- Small #s
- Pilot design

The NEW ENGLAND JOURNAL of MEDICINE

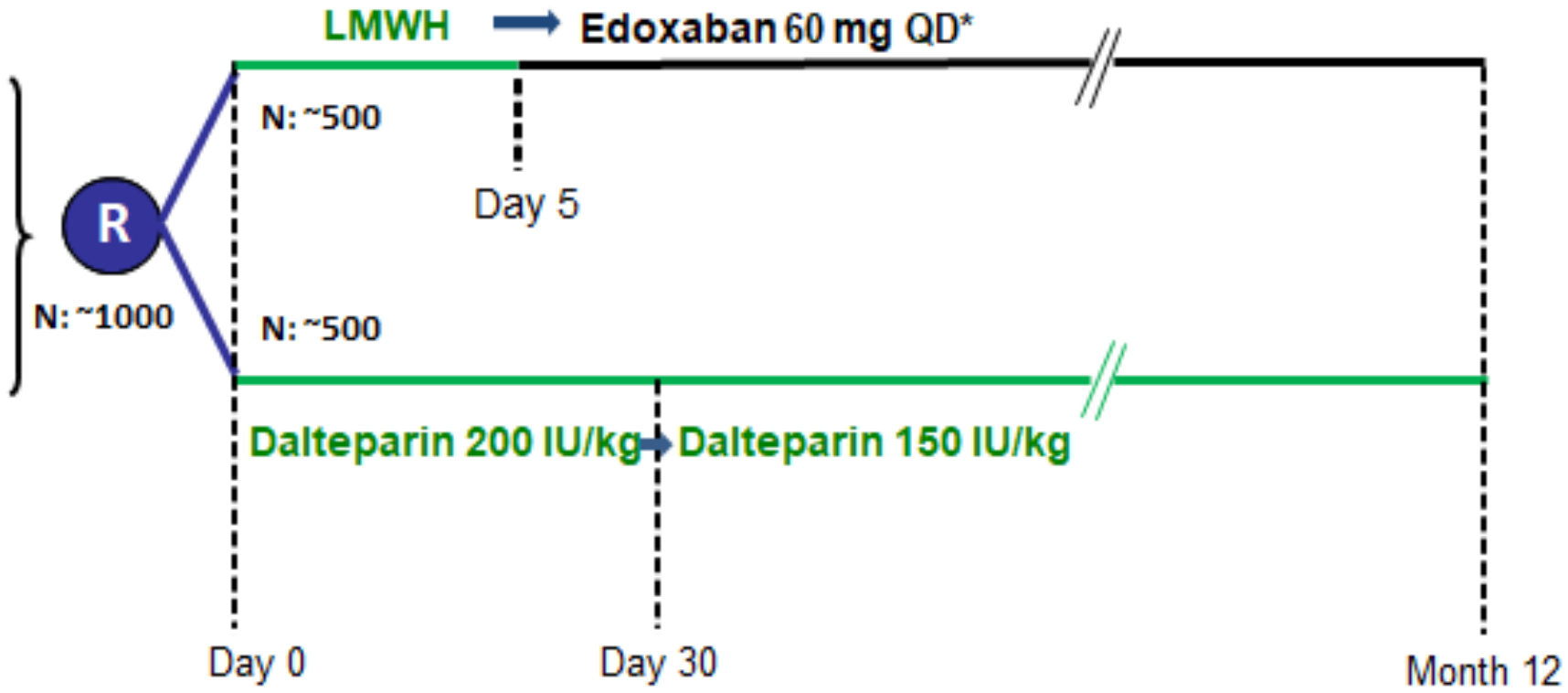
ORIGINAL ARTICLE

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*

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



- Treatment for up to 12 months (at least 6 months; physician discretion for >6 months)
- Efficacy and safety data collected during the entire 12 month study period
- Independent blind adjudication of all suspected outcomes
- Severity of major bleeding at presentation also adjudicated

Raskob et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1711948.

Hokusai VTE- Cancer: Study Design

- STRATIFICATION: **Risk factors for bleeding** included surgery within prior 2 weeks, use of antiplatelet therapy, primary or metastatic brain cancer, regionally advanced or metastatic cancer, GI or urothelial cancer diagnosed within prior 6 months, or treatment with bevacizumab within prior 6 weeks

- **Edoxaban**: ≥5 days of therapeutic LMWH followed by
  - 60 mg daily
  - 30 mg/d if CrCl 30-50 ml/min, body weight ≤60 kg, or receiving P-gp inhibitors

- **Dalteparin**: 200 IU/kg SC daily for 30 days, then reduced to 150 IU/kg/d.
  - capped at 18,000 IU per day.
  - temporarily reduced if the platelet count declined to <100K.

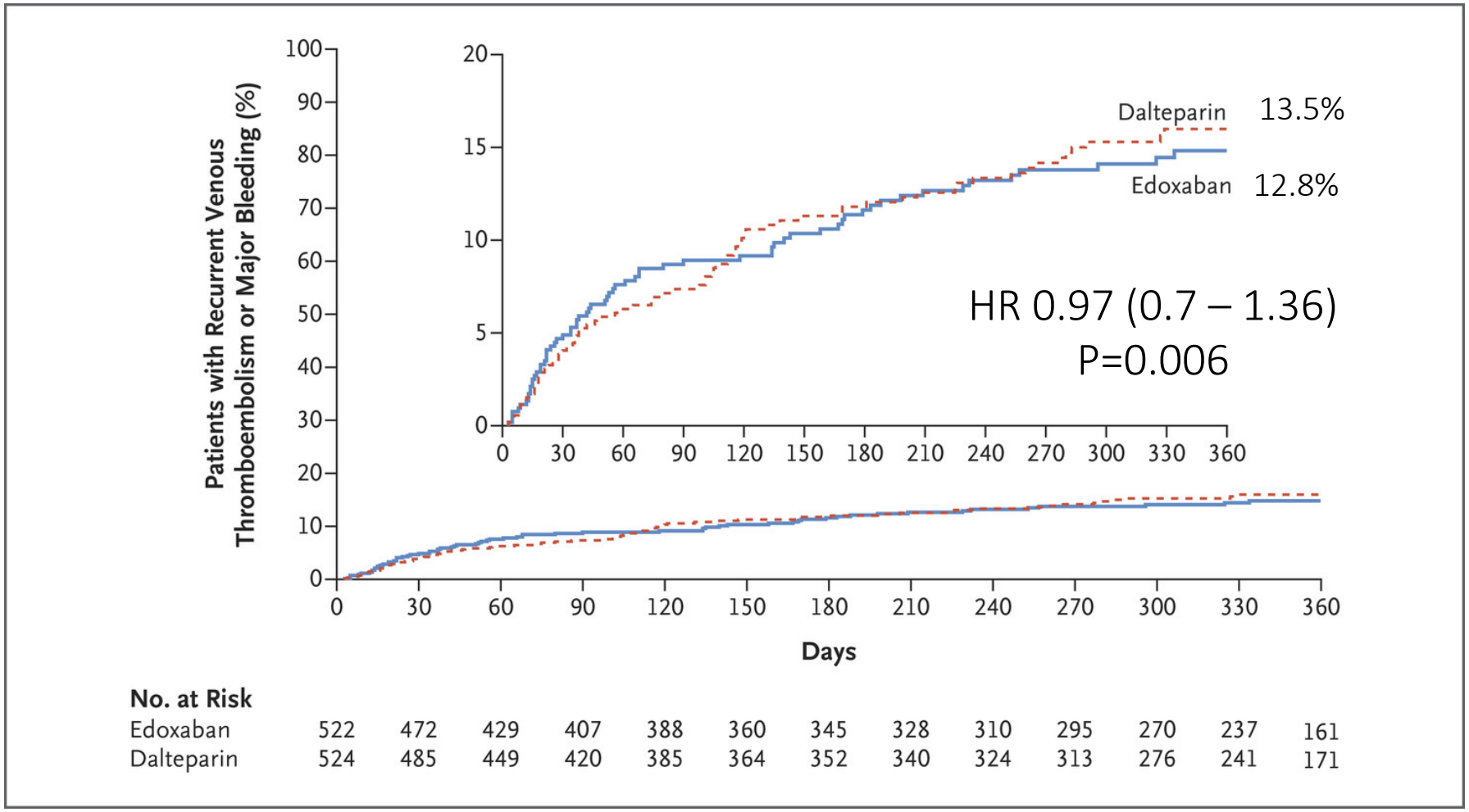
Hokusai-VTE Cancer: Exclusion criteria

- Treatment of VTE with thrombectomy, IVC filter placement, or fibrinolytic therapy
- Anticoagulation for ≥72 hours prior to randomization
- Therapeutic anticoagulation for a non-VTE indication prior to randomization
- Active bleeding or contraindication to study drug
- ECOG PS 3-4 at the time of randomization
- CrCl <30 mL/min
- History of HIT
- Acute hepatitis, chronic active hepatitis, liver cirrhosis
- AST/ALT >3×ULN and bilirubin >2×ULN in the absence of a clinical explanation
- Life expectancy <3 months
- Platelets <50K
- Uncontrolled hypertension
- Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breastfeeding
- NSAID therapy anticipated during the study
- Aspirin >100 mg/d or dual antiplatelet therapy anticipated during the study
- Treatment with P-gp inhibitors (eg, ritonavir) anticipated during the study
- Systemic use of P-gp inhibitors (eg, ketoconazole) at the time of randomization; subsequent use permitted

Patient characteristics and treatment duration

Characteristic	Edoxaban (N = 522)	Dalteparin (N = 524)
Age	64 +/- 11	64 +/- 12
Male sex	277 (53%)	263 (50%)
PE +/- DVT	328 (63%)	329 (63%)
Symptomatic VTE	355 (68%)	351 (67%)
Active cancer	513 (98%)	511 (98%)
Metastatic disease	274 (53%)	280 (53%)
Treatment duration	211 days	184 days

Primary outcome:
Time to first occurrence of recurrent VTE or major bleeding



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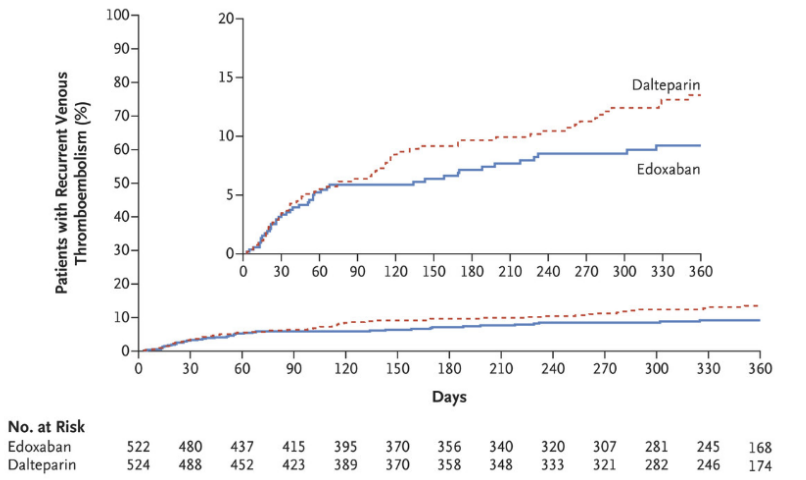
Time to recurrent VTE, major bleeding, survival

Recurrent VTE

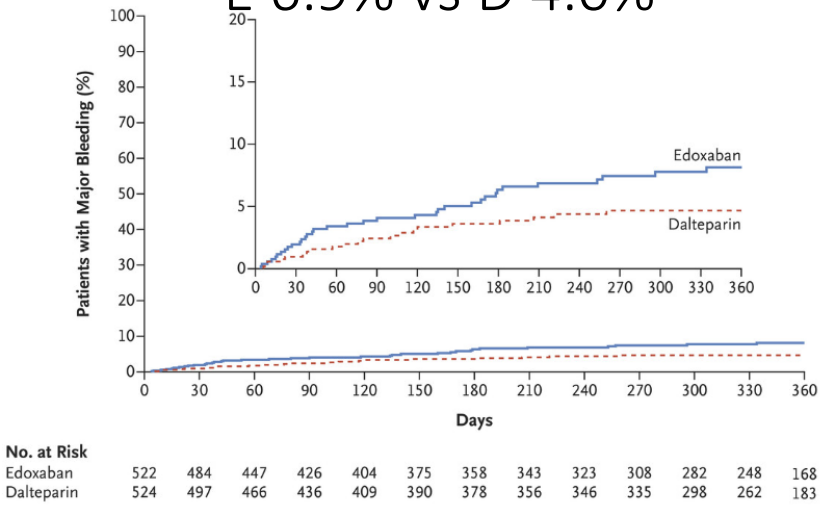
E 7.9% vs D 11.3%



HR 0.71 (0.48 – 1.06)
p = 0.09

Major Bleeding

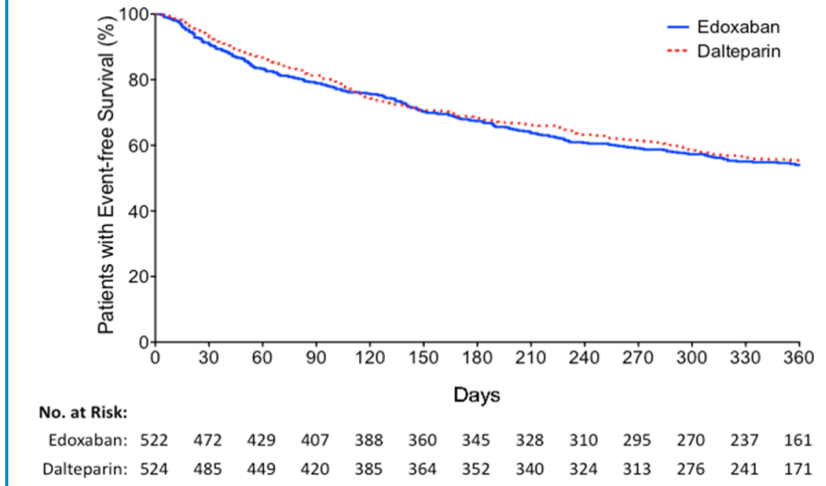
E 6.9% vs D 4.0%



HR 1.77 (1.03 – 3.04)
p = 0.04

Event-free Survival

E 55.0% vs D 56.5%



HR 0.93 (0.77 – 1.11)
p = NS

Raskob et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1711948.

Major bleeding and severity

	Edoxaban (N = 522)	Dalteparin (N = 524)	Hazard Ratio (95% CI)
Major bleeding	**36 (6.9%)**	**21 (4.0%)**	**1.77 (1.03 – 3.04)**
Fatal	0	2	
ICH	2	4	
Upper GI		3	
Lower GI		3	
Severity of Bleeding			
2	(67%)	8 (38%)	
3	12 (33%)	12 (57%)	
4	0	1 (5%)	

55% of all MB are GI

28% of all MB are GI

Raskob et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1711948.

Hokusai-VTE Cancer: Conclusions

- Edoxaban noninferior to dalteparin for primary outcome of recurrent VTE or major bleeding
- Lower rate of recurrent VTE observed with edoxaban offset by similar increase in risk of major bleeding
- More upper GI bleeding with edoxaban, mainly in patients with GI cancer
- Survival free of recurrent VTE or major bleeding similar

LIMITATIONS

- Open label
- Anticoagulation was stopped after 12 months (and after 6 months left to the discretion of treating physician)
- Findings in part may be due to better adherence to edoxaban

Gastrointestinal bleeding considerations with DOACs

- 47% of all MB involved upper GI system for patients on edoxaban compared to 14% of patients on dalteparin
  - Mostly upper GI tract and mostly in patients with esophageal or gastroesophageal tumours
- 55% of all MB for patients on rivaroxaban related to GI tract
- Most CRNB of patients on rivaroxaban seemed to be related to GI or GU tract

Subgroup analyses – other high risk features of major bleeding??

- Uroepithelial cancer (13.2% E vs 0% D)
- CrCl 30-50 ml/min (10.5% E vs. 2.9% D)
- Platelets 50,000-100,000/ml (12.5% E vs. 4.3% D)
- Antiplatelet use (11.5% E vs 3.2 % D)

Summary: DOACs and cancer associated VTE

- Based on trial data to date:
  - DOACs non-inferior to LMWHs
  - Edoxaban has the strongest evidence base

- Similar results seen in SELECT-D and HOKUSAI-VTE Cancer suggest a DOAC class effect rather than a drug effect

- No data (or known on-going prospective studies) supporting the use of the direct thrombin inhibitor dabigatran for cancer associated thrombsois

- Ongoing trials with apixaban should clarify whether this DOAC is also effective in cancer associated thrombosis

Clinical implications

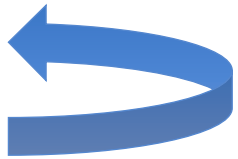
- DOACs (edoxaban > rivaroxaban) and LMWHs should be equally considered when contemplating anticoagulant therapy for acute VTE in a cancer patient

- We no longer have a “one drug fits all” approach

- MUST: Risk-benefit assessment at the start of anticoagulation and regularly throughout the duration of therapy to avoid major bleeding complications

DOACs: several advantages

- Oral
- Ease of use
- Effective
- Better adherence
- Cost



Clinical implications

- LMWH should be considered over DOACs for the initial management of cancer associated thrombosis in the context of:

  - GI malignancy, GU malignancy
  - Recent or prior GI bleed
  - GI mucositis
  - Significant GI surgery or malabsorption
  - Thrombocytopenia (<100,000/ml)
  - Renal impairment (30-50 ml/min)
  - Antiplatelet use
  - Drug interactions with anti-cancer therapy

  **catheter associated thrombosis
  **thrombolysed PE/DVT

Debate regarding treatment of VTE in cancer patients: LMWH vs DOACs

LMWH superior to VKA

- CLOT trial is relatively old data
- CATCH trial did not reach statistical significance

2 RCT comparing DOAC vs LMWH

- BUT, cancer subgroup analyses of DOAC vs VKA studies show similar efficacy and bleeding in cancer patients
- Over 1100 cancer patients included in subgroup meta-analyses

Guidelines recommend LMWH monotherapy

- Real world data suggest that less than 50% of patients persist with LMWH at 3 months (US data)

Debate regarding treatment of VTE in cancer patients: LMWH vs DOACs

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- Over 1100 cancer patients included in subgroup meta-analyses

Guidelines will reflect the latest data

- Real world data suggest that less than 50% of patients persist with LMWH at 3 months (US data)

THANK YOU!

Canadian Venous Thromboembolism
Clinical Trials and Outcomes Research Network

Hôpital général juif
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Centre of Excellence
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