Management of Cancer-Associated Thrombosis

Vicky Tagalakis MD FRCP

Division of General Internal Medicine

Jewish General Hospital

McGill University

Canadian Venous Thromboembolism Clinical Trials and Outcomes Research Network

Hôpital général juif Jewish General Hospital

CETAC Centre of Excellence in Thrombosis and Anticoagulation Care Centre d'excellence en thrombose et anticoagulation

McGill University

Disclosures

Advisory board

- Pfizer
- Bayer
- Sanofi
- Leo Pharma
- Servier

Investigator initiated research funding

- Pfizer
- Sanofi

Objectives

- Review the evidences of direct oral anticoagulants in the treatment of cancer-associated thrombosis
- Discuss the use of DOACs in the management of cancer-associated thrombosis
- Consider recent guidelines recommendation in clinical practice for the treatment of cancer-associated thrombosis

Paradigm shift in the treatment of acute VTE

Conventional

- LMWH + VKA----> VKA

New

- DOAC*

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

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

Can the same be said of DOACs for cancer associated VTE?

Cancer associated VTE: DOAC clinical studies

SELECT-D
Pilot study
(rivaroxaban)

Hokusai-VTE
Cancer
(edoxaban)

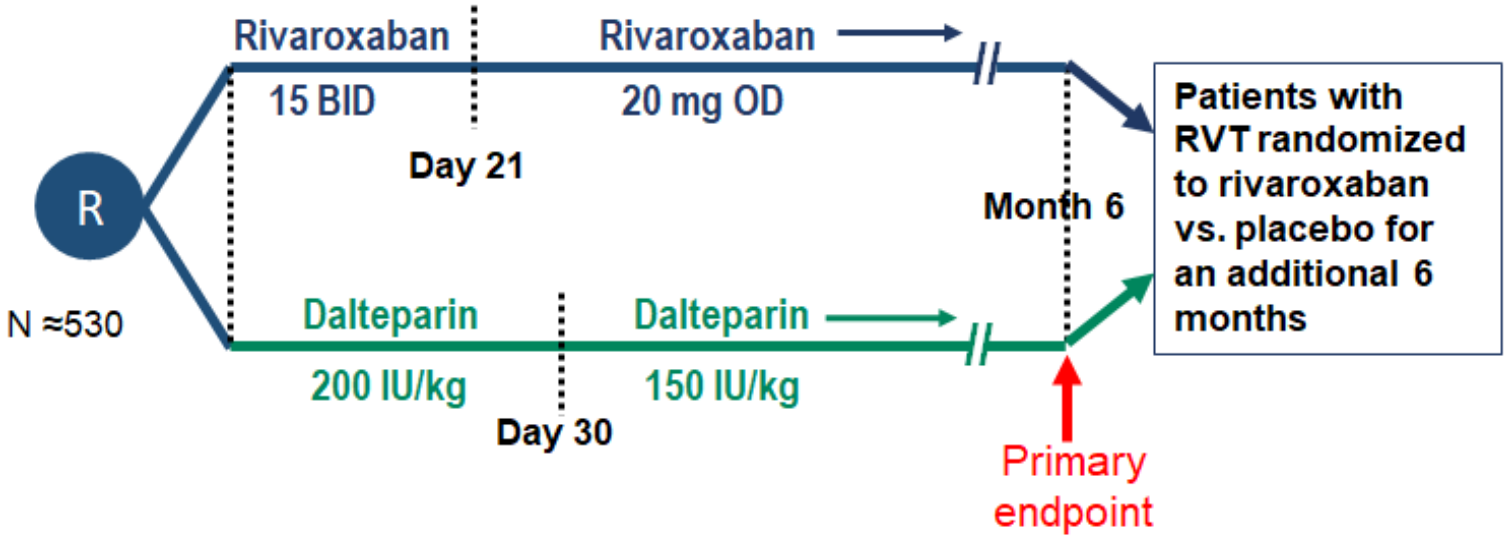
SELECT-D: Main research objectives

- 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 Pilot trial

SELECT-D pilot study

Primary outcome	Secondary outcomes
VTE recurrence at 6 months	Major bleeding, CRNMB



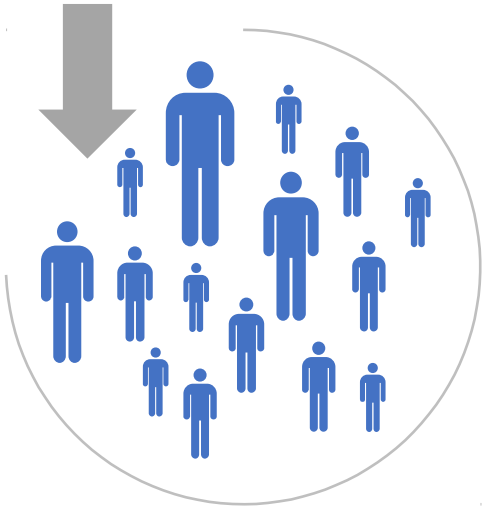
Adapted from Young A et al. *ASH* 2017; Abstract 625.
Young AM, *et al. J Clin Oncol* 2018; 36 https://doi.org/10.1200/JCO.2018.78.8034.

Sample size

On September 1, 2016, the second random assignment was closed,

with **only 92 patients recruited,**

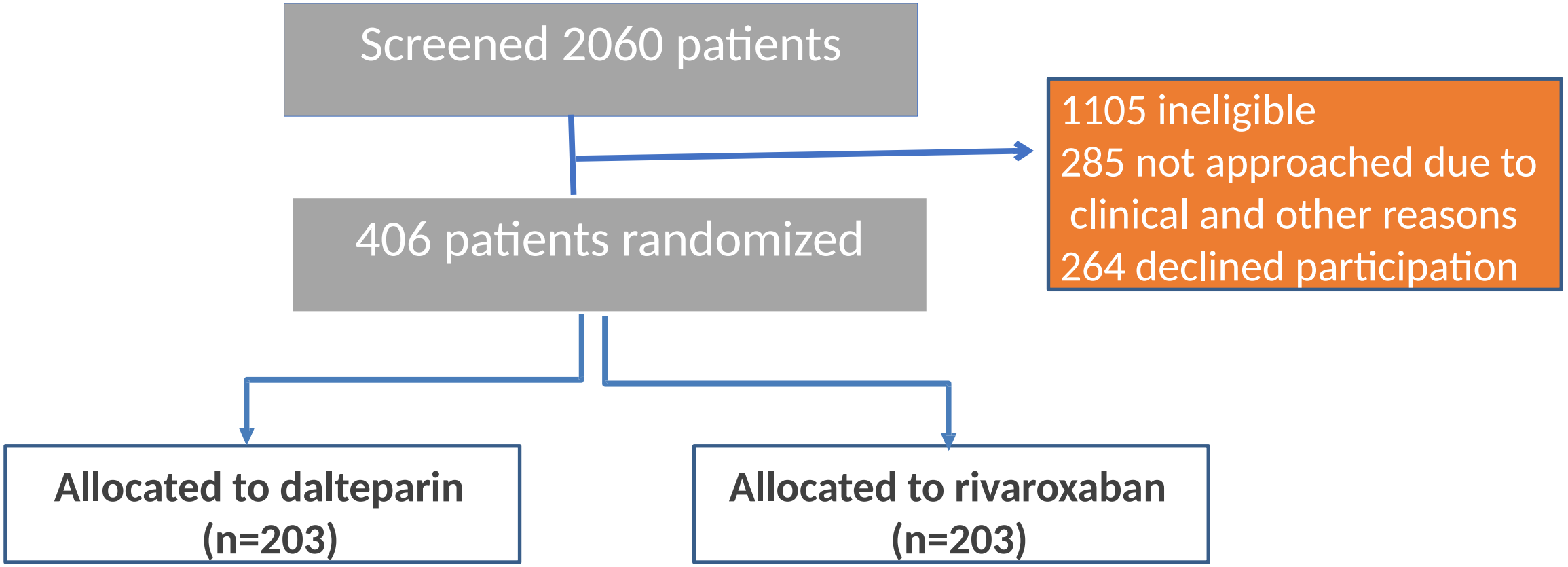
because it was considered futile to continue.



At the same time, the sample size for the trial was **reduced to a total of 400 patients.**

Still allow estimates of the primary outcome to be **within a 95% CI of 9%,instead of 8% as originally planned**

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
BMI, median (kg per m2)	26.7	26.6
Currently receiving cancer Rx: no (%)	142 (70)	140 (69)
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

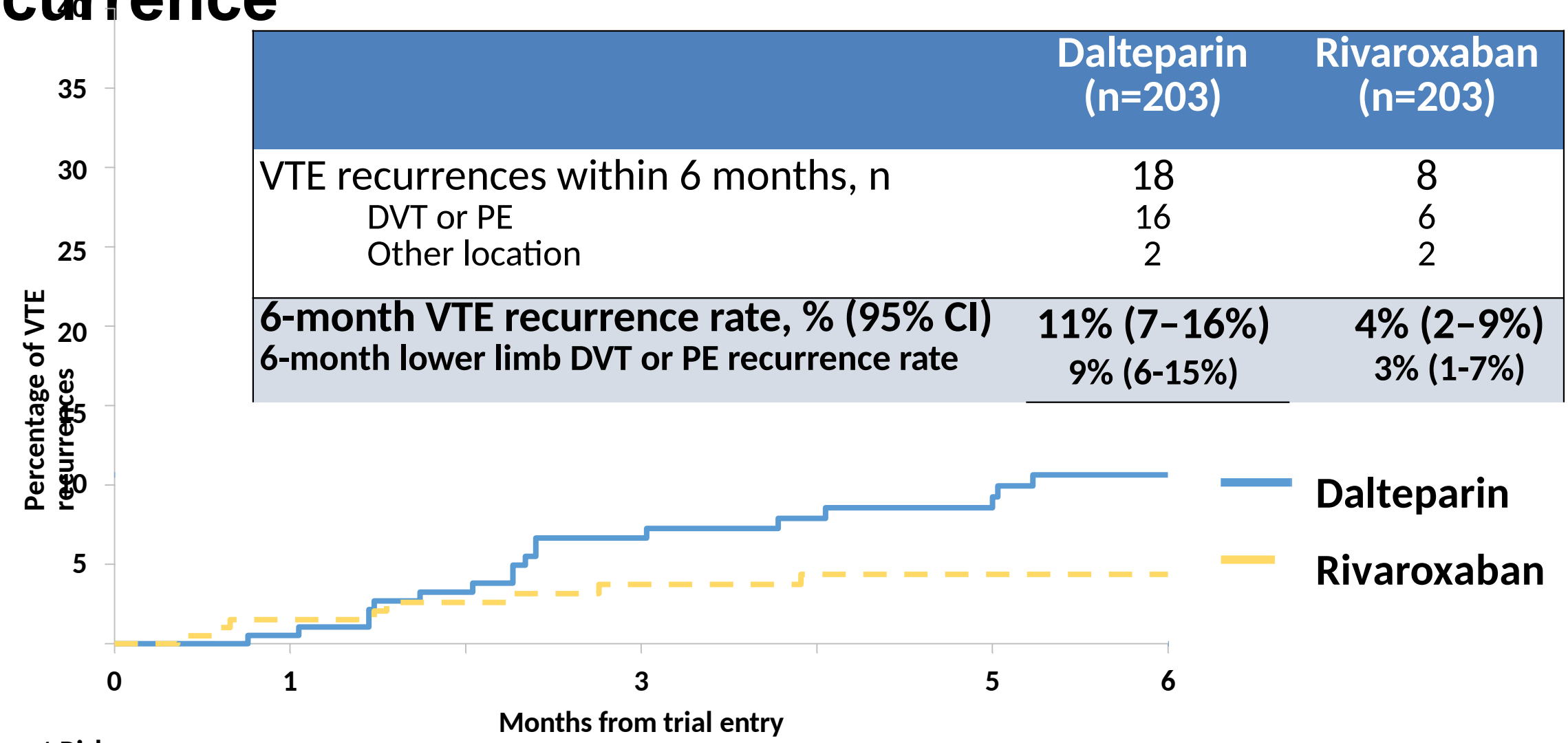
SELECT-D: Primary tumour type

	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

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

Category	Dalteparin (n=203)	Rivaroxaba n (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

- Most **major bleeds** were gastrointestinal
- Most **clinically relevant non major bleeds** were gastrointestinal and genitourinary

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.

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

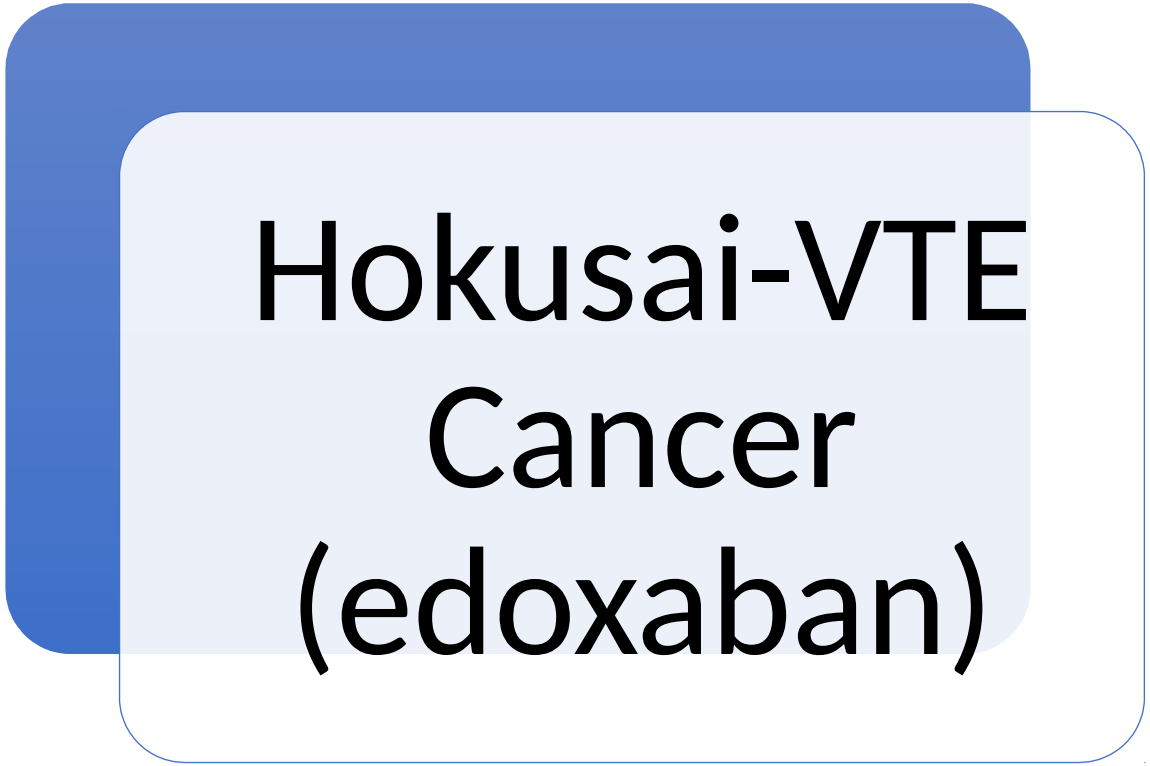
SELECT-D: Conclusions

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

LIMITATIONS

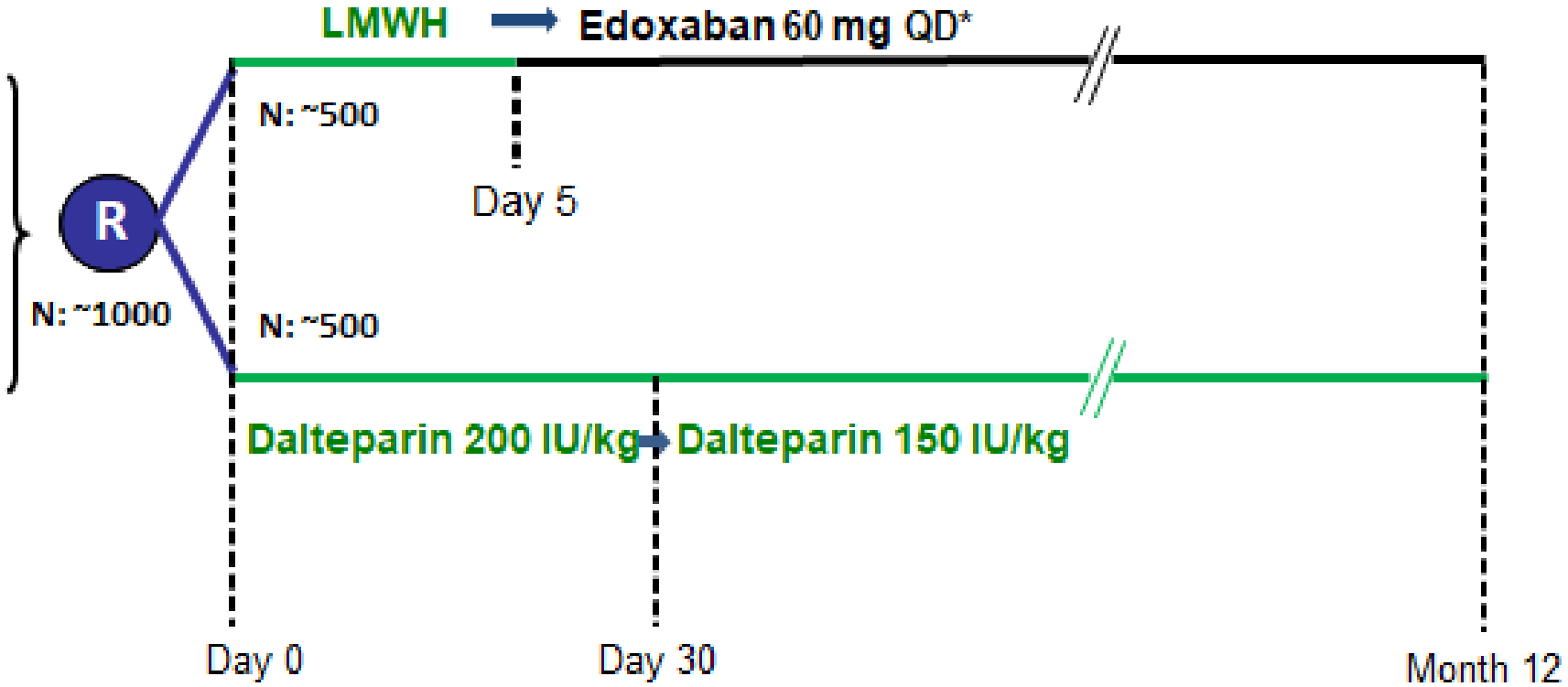
- Pilot feasibility study to detect point estimate for VTE recurrence around rivaroxaban
- Change in study design and sample size
- GI tumors excluded
- No data beyond 6 months

Cancer associated VTE: DOAC clinical studies



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.

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

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

Types of cancers

	Edoxaban (N = 522)	Dalteparin (N = 524)
Solid tumour – no. (%)	**465 (89.1)**	**467 (89.1)**
Colorectal	83 (15.9)	79 (15.1)
Lung	77 (14.8)	75 (14.3)
Genitourinary	65 (12.5)	71 (13.5)
Breast	64 (12.8)	60 (11.5)
Pancreatic or hepatobiliary	49 (9.4)	40 (7.6)
Gynecologic	47 (9.0)	63 (12.0)
Upper gastrointestinal	33 (6.3)	21 (4.0)
Other	48 (9.2)	60 (11.5)
Hematologic malignancy – no. (%)	**50 (10.7)**	**55 (10.5)**

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

Type of cancer therapy

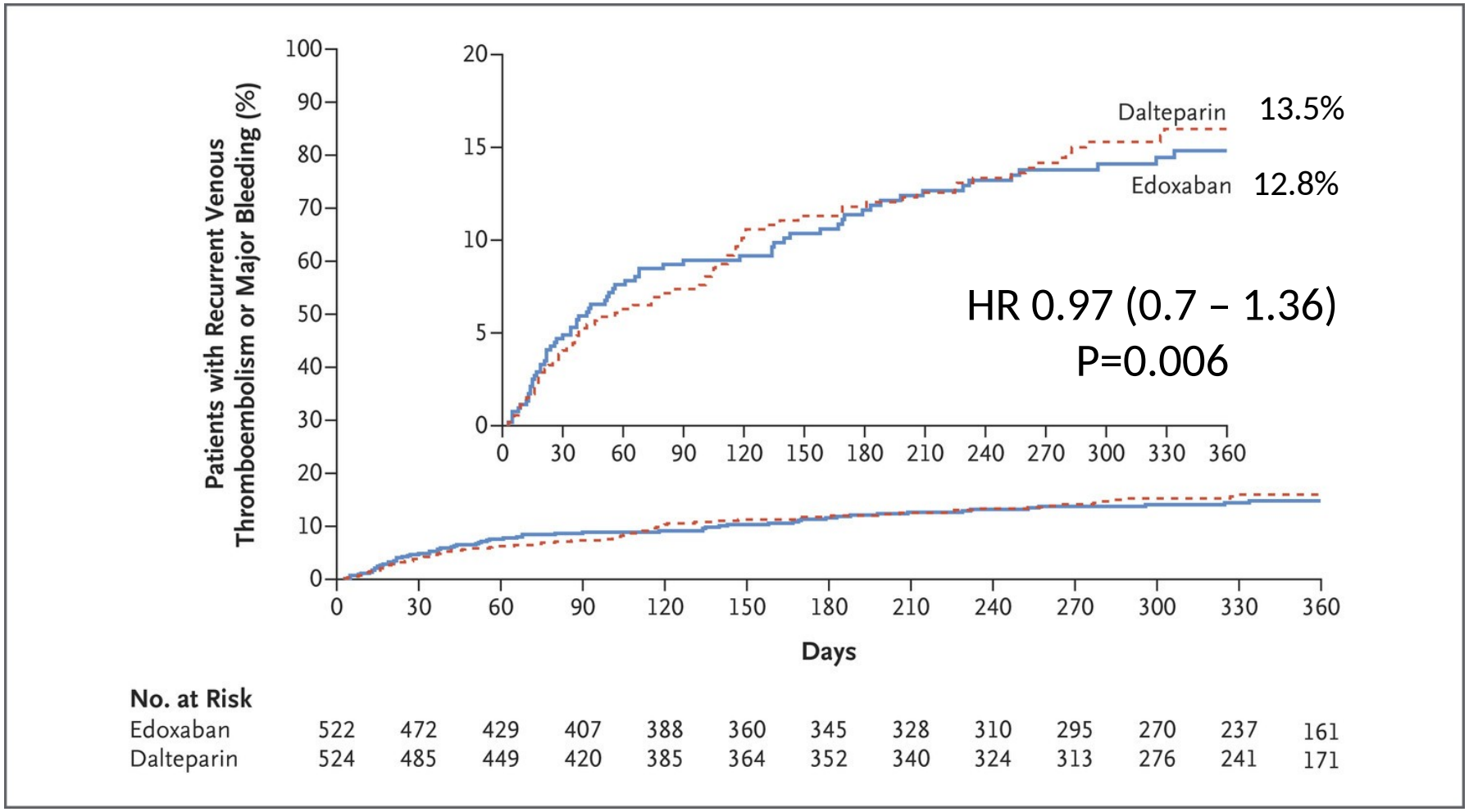
	Edoxaban (N = 522)	Dalteparin (N = 524)
Chemotherapies, no. (%)		
Antimetabolites	124 (23.8)	118 (22.5)
Platinum-based	105 (20.1)	107 (20.4)
Taxanes	40 (7.7)	47 (9.0)
Topoisomerase inhibitors	30 (5.7)	48 (9.2)
Alkylating agents	30 (5.7)	38 (7.3)
Anthracyclines	22 (4.2)	25 (4.8)
Vinca alkaloids	16 (3.1)	18 (3.4)
Anti-tumour antibiotics	5 (1.0)	5 (1.0)

	Edoxaban (N = 522)	Dalteparin (N = 524)
Targeted therapies, no. (%)		
Monoclonal antibodies	42 (8.0)	54 (10.3)
Bevacizumab	13 (2.5)	17 (3.2)
Kinase inhibitors	18 (3.4)	18 (3.4)
Proteosome inhibitors	7 (1.3)	8 (1.5)
Other therapies, no. (%)		
Hormonal therapies	41 (7.9)	37 (7.1)
Immuno-modulators	16 (3.1)	9 (1.7)
Miscellaneous	14 (2.7)	14 (2.7)

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

With permission from Dr Carrier

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



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

Primary outcome

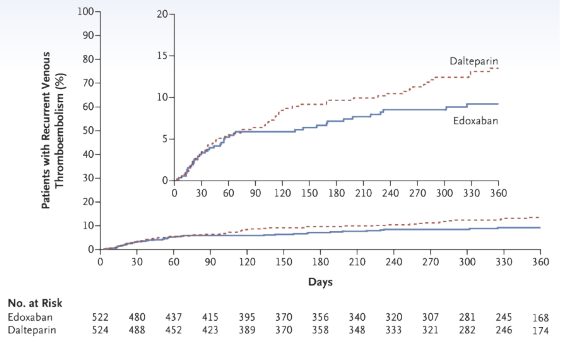
Analyses	Edoxaban (N = 522)	Dalteparin (N = 524)	HR (95% CI) for non-inferiority
Primary analysis	67 (12.8)	71 (13.5)	0.97 (0.70, **1.36**) *p* = 0.006
First 6 months	55 (10.5)	56 (10.7)	1.01 (0.69, **1.46)** *p* = 0.018
Per protocol	51 (10.4)	53 (10.4)	0.99 (0.68, **1.46**) *p* = 0.018

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

Time to recurrent VTE, major bleeding survival

Recurrent VTE

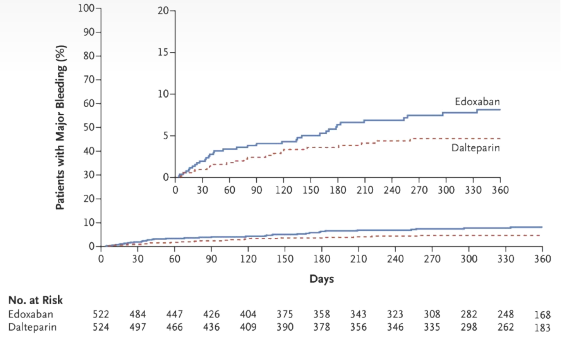
E 7.9% vs D 11.3%



HR 0.71 (0.48 – 1.06)
p = 0.09

Major bleeding

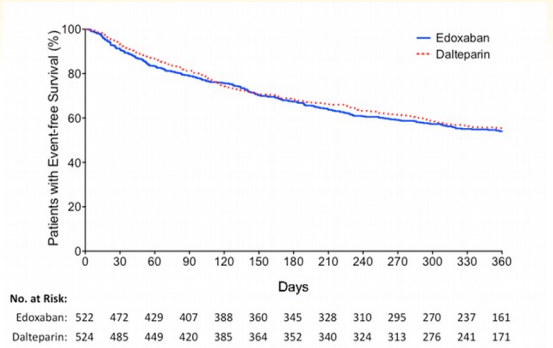
E 6.9% vs D 4.0%



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	17	3	
Lower GI	3	3	
Severity of Bleeding			
2	24 (67%)	8 (38%)	
3	12 (33%)	12 (57%)	
4	0	1 (5%)	

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

Hokusai VTE-Cancer: Other key outcomes

Length of therapy

- Median duration of treatment was significantly shorter in the dalteparin arm
- Appears to be due to patient preference for drug discontinuation when permitted at 6 months (edoxaban 21 [4%] vs. dalteparin 78 [14.9%])

	Edoxaban (N = 522)	Dalteparin (N = 524)	*p* – value
Treatment duration (median)	211 days	184 days	0.01
Patients completing 12 months (n)	200	154	

Patients at highest risk for major bleeding on Edoxaban

- Patients with GI cancer at entry were at particularly high risk of bleeding
- The majority of major bleeds were upper GI

GI cancer	Edoxaban (N = 522)	Dalteparin (N = 524)	*p* – value
Yes, n/N (%)	18/136 (13.2)	3/125 (2.4)	0.02
No, n/N (%)	4/386 (3.6)	13/399 (3.3)	

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

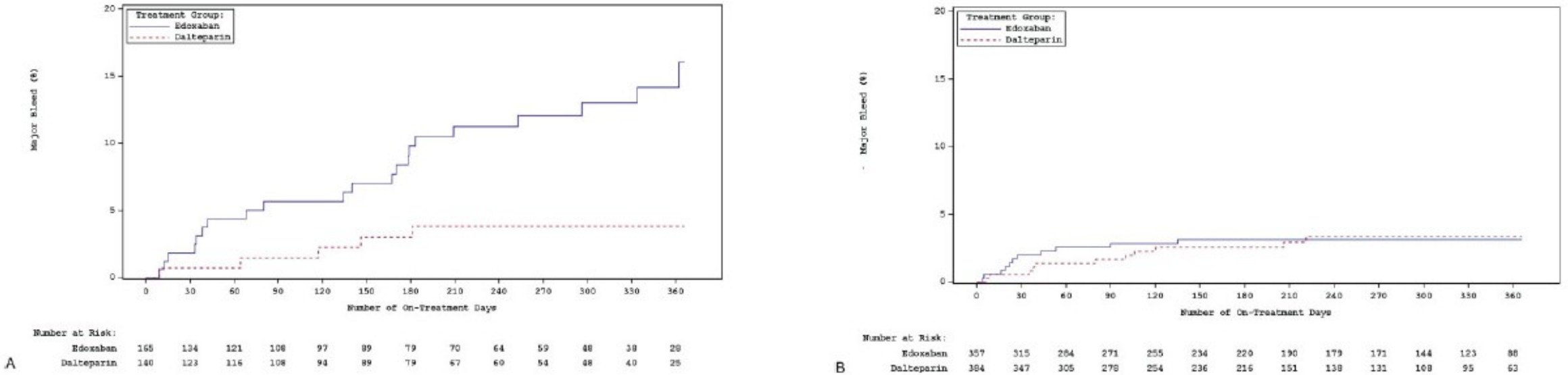
With permission from Dr Carrier

Clinical Presentation of Major Bleeding Events

	Edoxaban (n = 32)	Dalteparin (n = 16)
Site of major bleeding – no. (%)		
Gastrointestinal		
Upper	18 (56.2)	3 (18.8)
Lower	4 (12.5)	2 (12.5)
Intracranial	2 (6.3)	3 (18.8)
Genitourinary	2 (6.3)	0
Cutaneous/soft tissue	1 (3.1)	1 (6.3)
Retroperitoneal	1 (3.1)	1 (6.3)
Epistatix	1 (3.1)	0
Intra-muscular	0	2 (12.5)
Intraspinal	0	1 (6.3)
Other	3 (9.4)	3 (18.8)
Associated with surgery, trauma or other procedures– no. (%)	0	5 (31.1)
Time from Randomization to major bleeding, d, (IQR)	61 (23-174)	91 (37-134)

Kraaijpoel et al., Thromb Haemost 2018;118:1439–1449.

Major bleeding in GI cancer vs non-GI cancer



Cumulative event rates of major bleeding in gastrointestinal cancer and non-gastrointestinal cancer. Shown are cumulative event rates for major bleeding with edoxaban and dalteparin in patients with gastrointestinal cancer (A) and non-gastrointestinal cancer (B).

Kraaijpoel et al., Thromb Haemost 2018;118:1439–1449.

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)

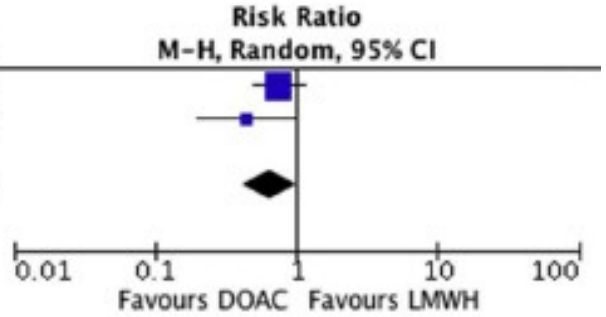
Similar outcomes in Hokusai and SELECT-D

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			

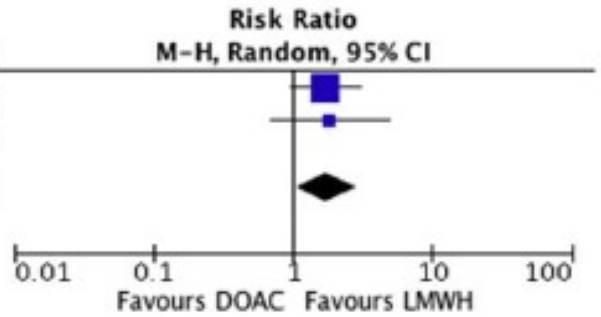
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.21$, df = 1 (P = 0.27); $I^2 = 17\%$
Test for overall effect: Z = 1.92 (P = 0.06)



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)



With permission from Dr Carrier

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

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

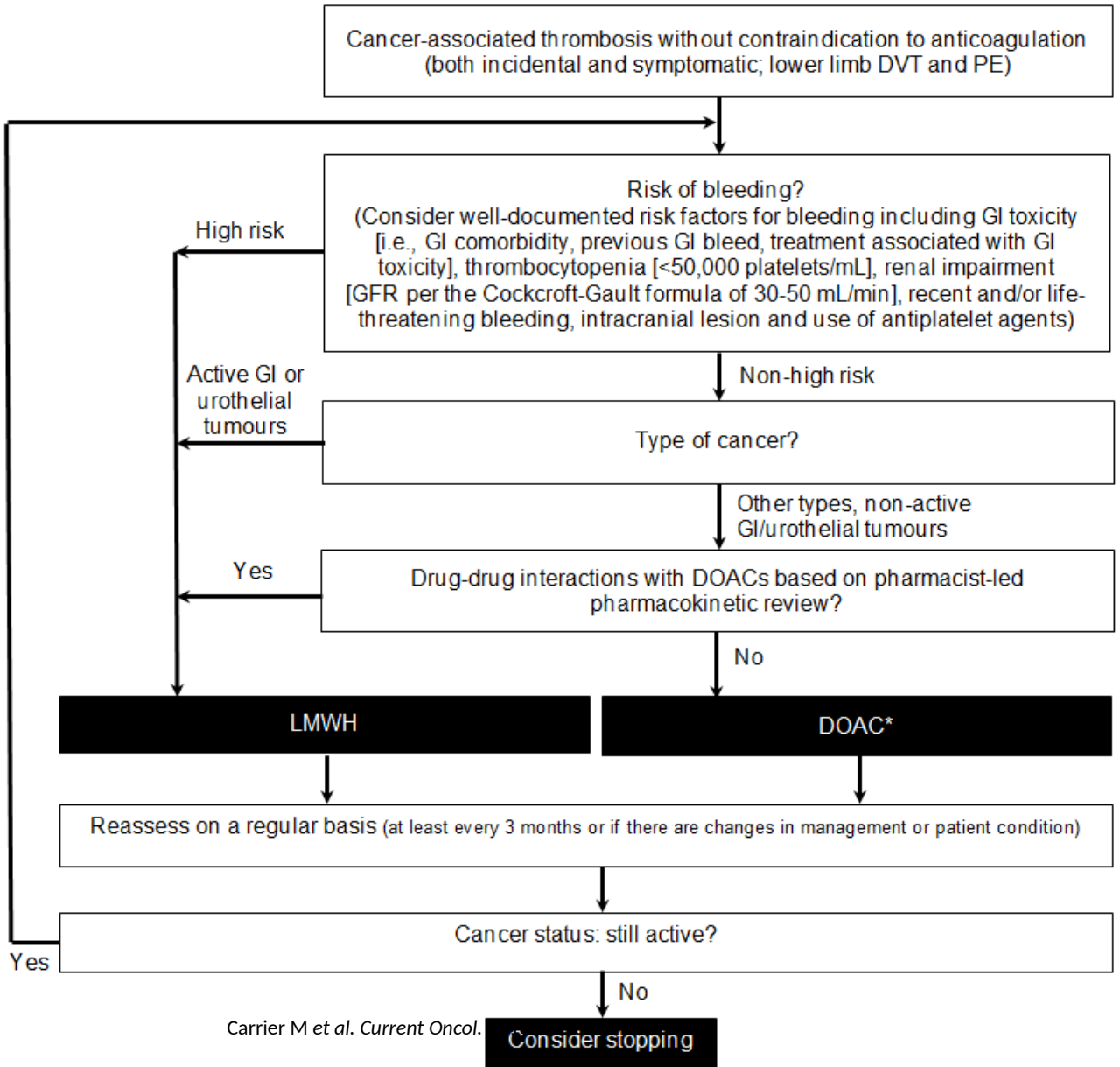
- No data (or known on-going prospective studies) supporting the use of the direct thrombin inhibitor dabigatran for cancer associated thrombsois

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

Treatment: A risk-adapted approach?

Individualize approach	Risk/benefit ratio
• Drug to drug interaction	• Risk of recurrent VTE
• Nausea/vomiting	• Risk of bleeding

Treatment of cancer associated thrombosis: individualized approach



Carrier M *et al. Current Oncol.*

Shift in therapy from a universal to an individualized approach while taking into consideration the risk and benefits of therapy

Drug-drug interactions

- DOACs and warfarin are substrates of key metabolic and transport pathways
- Some DDIs are well documented; clinical relevance of many potential DDIs is unknown
  - Unknowns are further complicated by polytherapy

Anticoagulants as substrates for major pathways			
Anticoagulant	CYP3A4 (metabolic)	P-gp (transport)	Other CYP metabolizing enzymes (2C9, 2C19, 2C8, 2C18, 1A2)
LMWH	No	No	No
VKA	Major	No/Minor	All (Major: CYP2C9)
Apixaban	Major	Major	Minor: 1A2, 2C8, 2C9, 2C19
Edoxaban	Minor	Major	No
Rivaroxaban	Major	Major	No
Dabigatran	No	Moderate	No

With permission from Dr Carrier

Drug-drug interactions:

Inducers and inhibitors of CYP3A4 and P-gp

Inhibitors of CYP3A4 and/or P-gp may increase risk of bleeding on DOACs

Chemotherapies	CYP3A4	P-gp
Doxurubicin	↓	
Topotecan	↓	
Vinblastine	↓	
Mitotane	↑	
Venetoclax		↓

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

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

With permission from Dr Carrier

Patient's perspective

Most important attributes for anticoagulation choices

1. Does not interfere with cancer treatment
2. Efficacy and safety
3. Route of administration

Noble SI et al. *Haematologica.* 2015; 100:1486–1492.

Other factors to consider

- Drug coverage
- Body weight (consider LMWH in patients with BMI >40 kg/m^2 or weight >120 kg)
- Burden of cancer and burden of VTE (consider LMWH for patients with severe symptoms, e.g., ileofemoral DVT, extensive PE, submassive PE, any thrombolysed patient)
- Renal impairment (consider LMWH for patients with GFRper the Cockcroft-Gault formula of 30-50 mL/min)
- Significant GI surgery or absorption disorders (consider LMWH for patients with impaired GI absorption)
- Pre-existing conditions and co-medication (e.g., ASA, other antiplatelet medications)
- Severe thrombocytopenia

Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH

A. A. KHORANA,* S. NOBLE,† A. Y. Y. LEE,‡ G. SOFF,§ G. MEYER,¶ C. O'CONNELL** and M. CARRIER††

1. Recommend individualized treatment regimens after shared decision-making with patients

2. 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.
Currently, edoxaban and rivaroxaban are the only DOACs that have been compared with LMWH in RCTs in cancer populations.

3. Suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding*.
Specific DOACs (edoxaban and rivaroxaban) are acceptable alternatives if there are no drug–drug interactions with current systemic therapy.

*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,

THANK YOU!

Canadian Venous Thromboembolism
Clinical Trials and Outcomes Research Network

Hôpital général juif
Jewish General Hospital

CETAC
Centre of Excellence in Thrombosis and Anticoagulation Care
Centre d'excellence en thrombose et anticoagulation

McGill
UNIVERSITY