Washington University in St. Louis
School of Medicine

Direct Oral Anticoagulants in Cancer: Cases Against

2018

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Disclosures

- BMS Speaker Bureau, 2017
- Pfizer Advisory Board, 2018
- NHLBI Funding, K01

Outline

- Absorption
- Obesity
- Risk of Hemorrhage
- Cost/Alternatives

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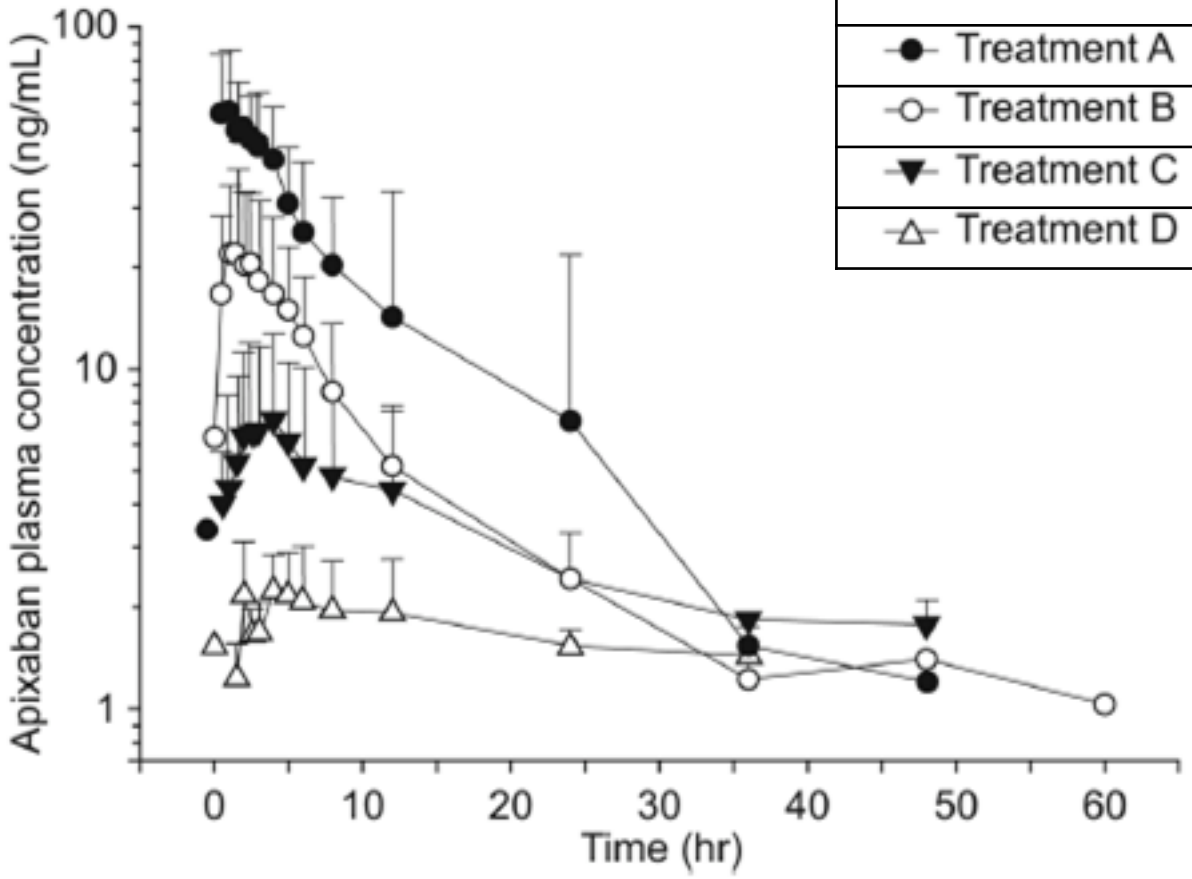
Absorption

- Location
  - Feeding tube (gastric vs. GJ tube)
  - Ostomy
  - Surgical History
- Timing
  - Concurrent with food

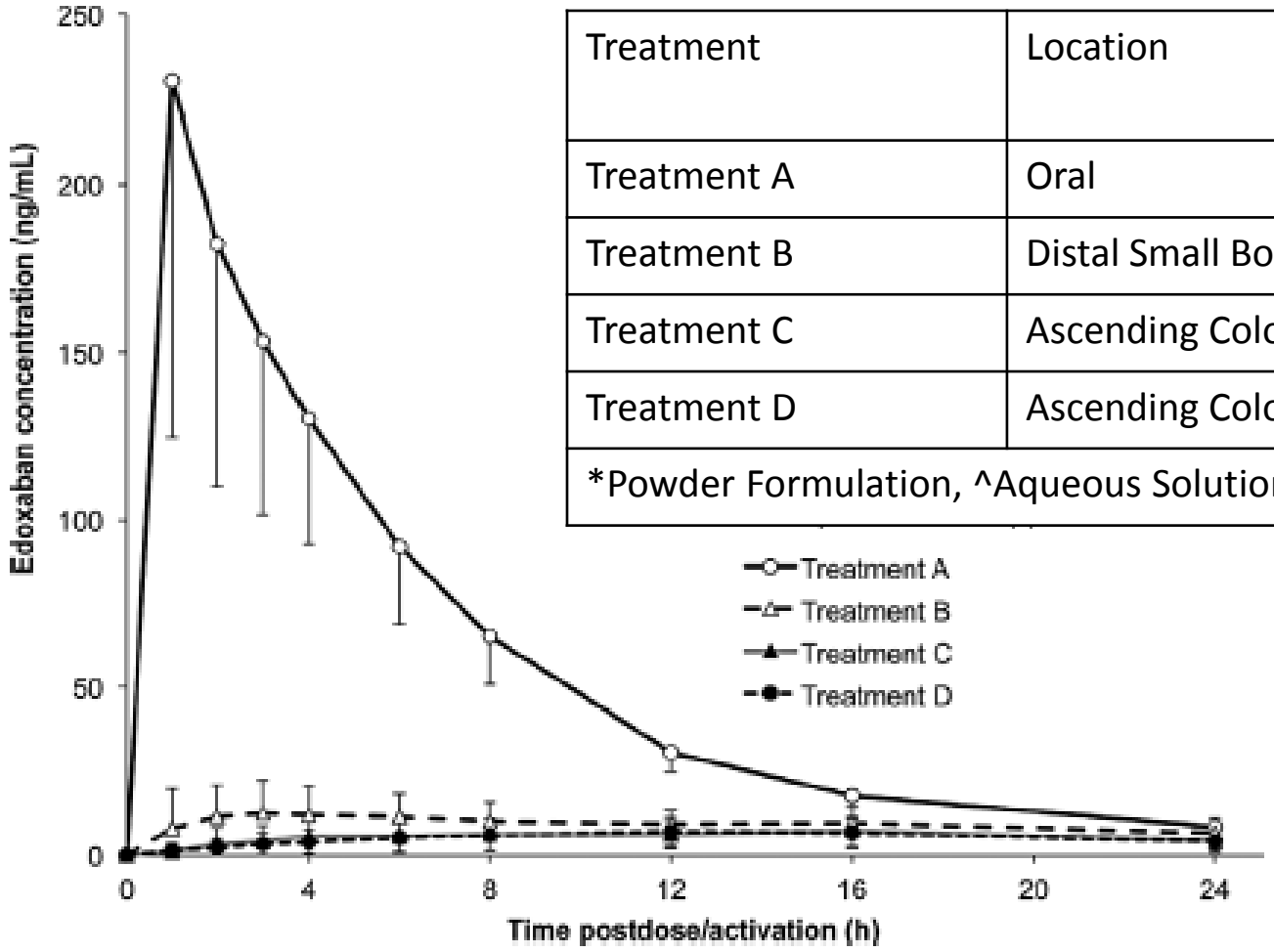
Absorption: Apixaban



Treatment	Location	Cmax Reduction
Treatment A	Oral	REF
Treatment B	Distal Small Bowel	62%
Treatment C	Ascending Colon	90%
Treatment D	Crushed, Ascending Colon	97%

Byon et al. J Clin Pharmacol 2018

Absorption: Edoxaban



Treatment	Location	Cmax Reduction
Treatment A	Oral	REF
Treatment B	Distal Small Bowel*	93%
Treatment C	Ascending Colon*	96%
Treatment D	Ascending Colon^	97%
*Powder Formulation, ^Aqueous Solution		

Parasrampuria et al. J Clin Pharmacol 2015

Absorption

- Dabigatran
  - Absorbed in stomach/proximal small bowel
  - Cannot be crushed/broken (75% ↓ Cmax)
  - Concurrent with antacids (20% ↓ Cmax)
- Rivaroxaban
  - Absorbed in the stomach predominately
  - Cmax ↓ 56% when released in the proximal small bowel
  - 15mg and 20mg tablet, with food
    - Initial PK was studied with 750-1000 kcal meal
    - Dinner or largest meal of the day
  - 10mg tablet, with or without food

Package Insert, Boehringer 2018
Package Insert, Janssen 2017

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Obesity and DOACs

Drug	Pharmacokinetic Data, Weight > 120kg
Apixaban	30% ↓ Cmax ½-life 8.8 hours vs. 12 hours
Betrixaban	No Data
Dabigatran	21% ↓ mean concentration (weight > 100kg)
Edoxaban	No Data
Rivaroxaban	No change in Cmax No change in ½-life

Frost et al. Br J Clin Pharmacol 2013
Kubitza et al. J Clin Pharmacol 2007
Reilly et al. JACC 2013

ISTH DOAC in Obesity Guidelines

ISTH Recommendations DOAC use in Obesity and VTE	
BMI ≤ 40 kg/m2 Weight ≤ 120 kg	Standard Dosing
BMI > 40 kg/m2 Weight > 120 kg	Avoid Use (If using, measure drug-specific peak**)
** No currently defined therapeutic range	

Martin et al. J Thromb Haemost 2016

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Select-D Trial

- Esophageal and Gastro-esophageal excluded at 1st DSMC due to higher major bleed rate

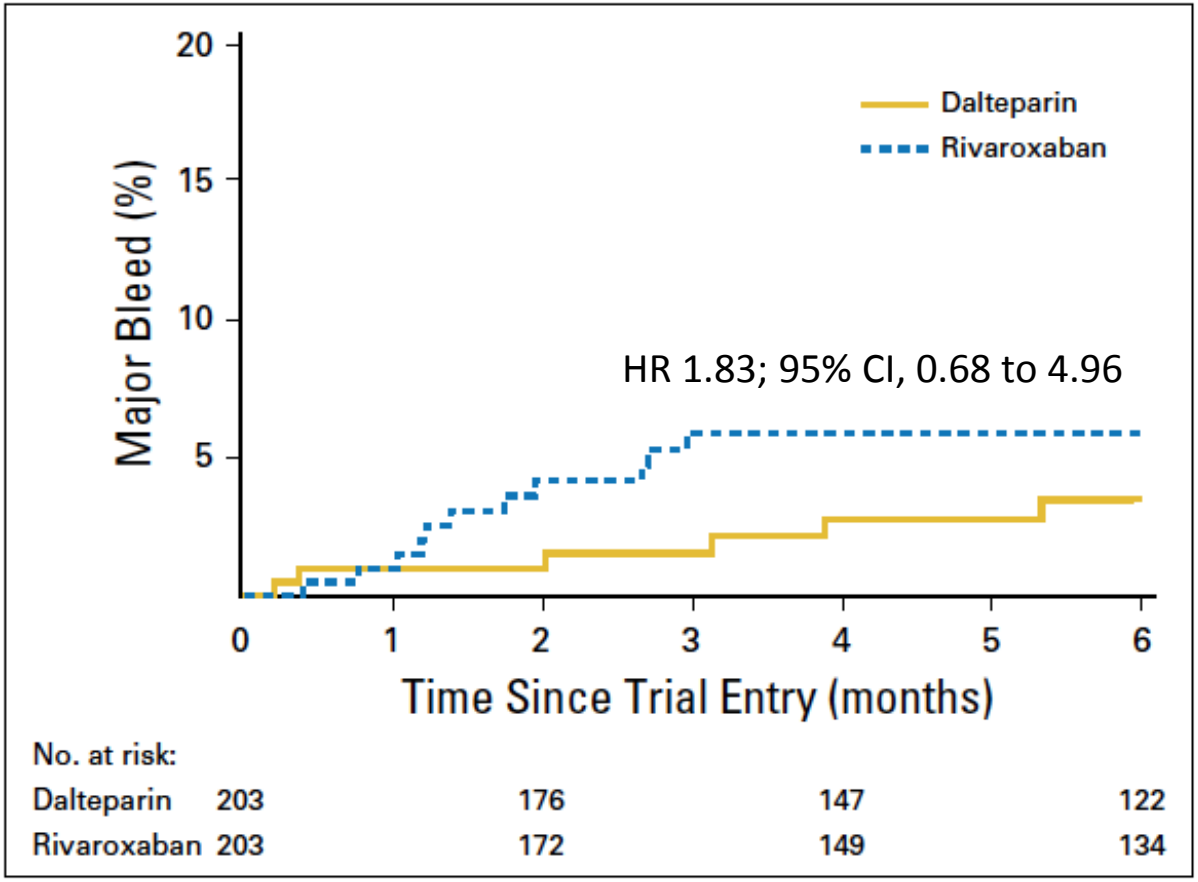


Fig 3. Time to major bleed within 6 months.

Select-D Trial

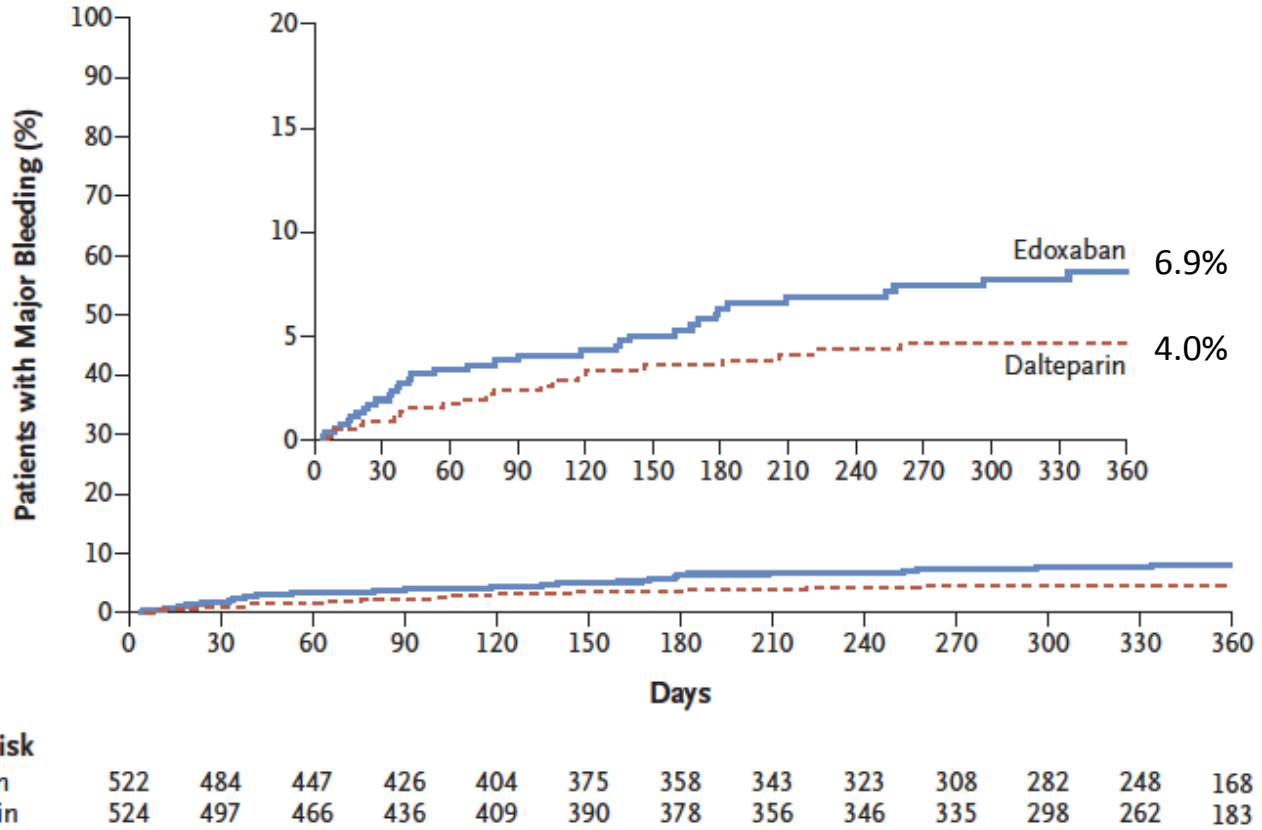
Table A3. Bleeding Events by Primary Tumor Type

Primary Tumor Type	No. (%)					
	Dalteparin			Rivaroxaban		
	Total	Major Bleeds	CRNMB	Total	Major Bleeds	CRNMB
Total patients	203	6 (3)	7 (3)	203	11 (5)	25 (12)
Bladder	4 (2)	0	1 (25)	10 (5)	1 (10)	5 (50)
Brain	2 (1)	0	0	1 (1)	0	1 (100)
Breast	20 (10)	1 (5)	0	20 (10)	0	2 (10)
Cancer unknown primary	3 (2)	0	0	3 (1)	0	0
Chronic lymphoid leukemia	2 (1)	0	0	1 (1)	0	0
Colorectal	47 (23)	4 (9)	1 (2)	55 (27)	4 (7)	6 (11)
Gallbladder	2 (1)	0	0	2 (1)	0	0
Gastric	7 (3)	0	0	4 (2)	0	0
Gynecologic	7 (3)	0	0	6 (3)	0	0
Kidney	5 (3)	0	0	2 (1)	0	0
Lung	25 (12)	0	2 (8)	22 (11)	1 (5)	2 (9)
Lymphoma	12 (6)	0	0	11 (5)	0	2 (18)
Multiple myeloma	3 (2)	0	0	2 (1)	0	0
Esophageal/gastroesophageal	19 (9)	1 (5)	0	11 (5)	4 (36)	0
Ovarian	18 (9)	0	2 (11)	12 (6)	0	3 (25)
Pancreatic	11 (5)	0	0	19 (9)	0	1 (5)
Prostate	8 (4)	0	1 (13)	13 (7)	0	1 (8)
Sarcoma	0	0	0	2 (1)	0	1 (50)
Other*	5 (3)	0	0	6 (3)	1 (20)	1 (20)
Unknown	3 (2)	0	0	1 (1)	0	0

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.
*Other cancers: anal cancer with major bleed (n = 1); sacral chordoma with CRNMB (n = 1). Patients with CNS tumors (n = 3).

Young et al. J Clin Oncol 2018

Hokusai VTE Cancer



$p = 0.04$

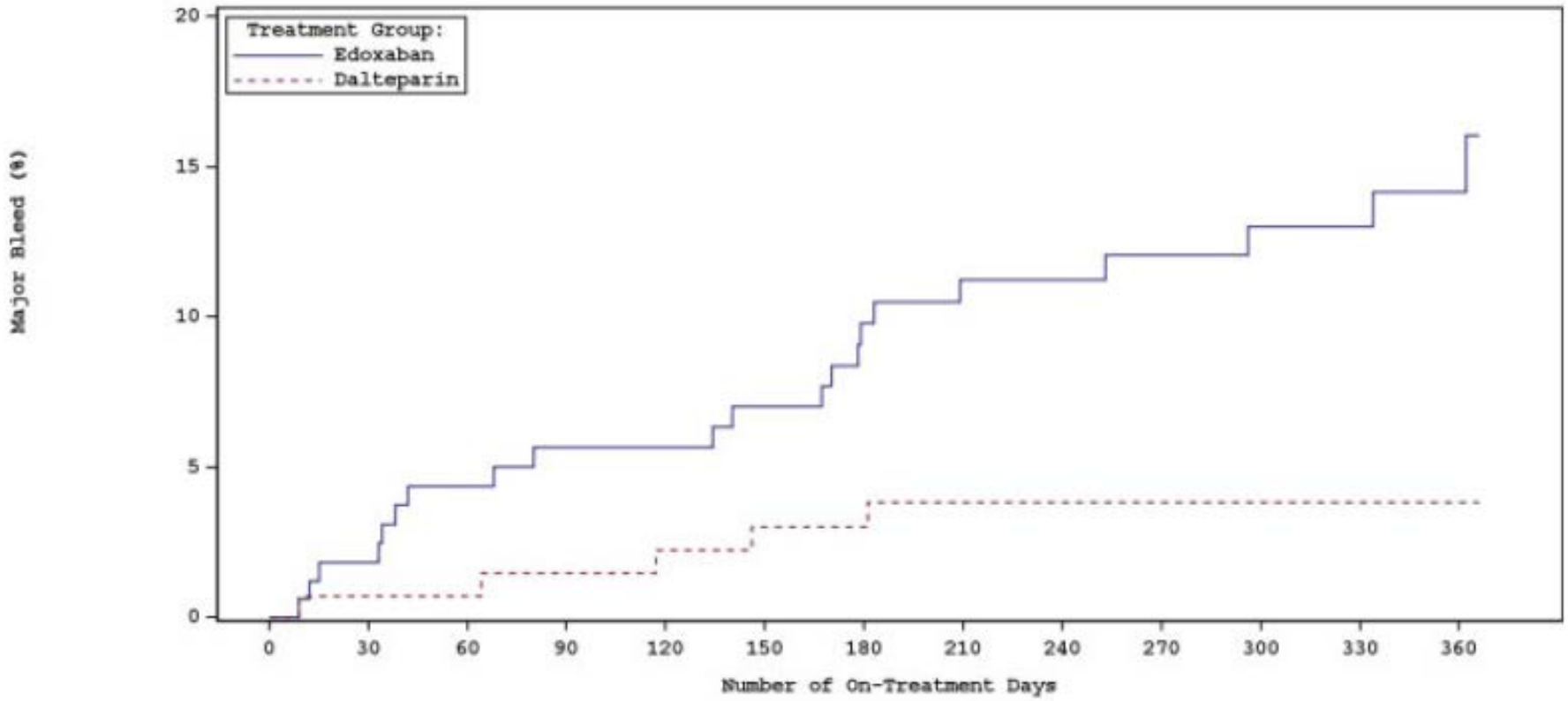
Figure 3. Kaplan–Meier Cumulative Event Rates for Secondary Outcomes.

Shown are cumulative event rates for recurrent venous thromboembolism (Panel A) and major bleeding (Panel B). The insets show the same data on an enlarged y axis.

Hokusai VTE Cancer

Major Bleeding Cases Edoxaban vs. Dalteparin, 12 months		
	Edoxaban (n=522)	Dalteparin (n=524)
Fatal (%)	0	2 (0.4)
Intracranial	2 (0.4)	4 (0.8)
Gastrointestinal Upper Lower	20 (3.8) 17 (3.3) 3 (0.6)	6 (1.1) 3 (0.6) 3 (0.6)
GU	5 (1.0)	0
Other	6 (1.1)	7 (1.3)

Hokusai VTE Cancer

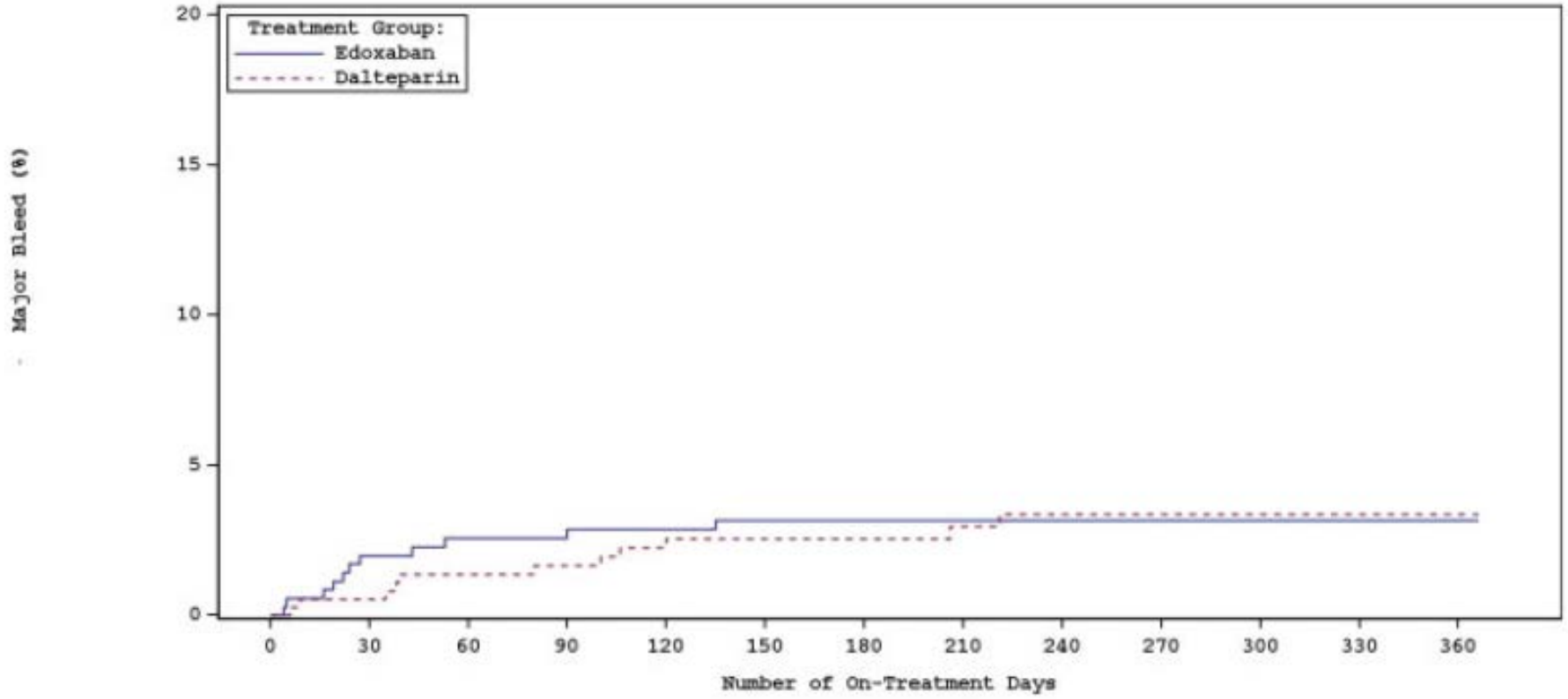


Number at Risk:													
Edoxaban	165	134	121	108	97	89	79	70	64	59	48	38	28
Dalteparin	140	123	116	108	94	89	79	67	60	54	48	40	25

A

Kraaijpoel et al. Thromb Haemost 2018

Hokusai VTE Cancer



B

Number at Risk:													
Edoxaban	357	315	284	271	255	234	220	190	179	171	144	123	88
Dalteparin	384	347	305	278	254	236	216	151	138	131	108	95	63

Kraaijpoel et al. Thromb Haemost 2018

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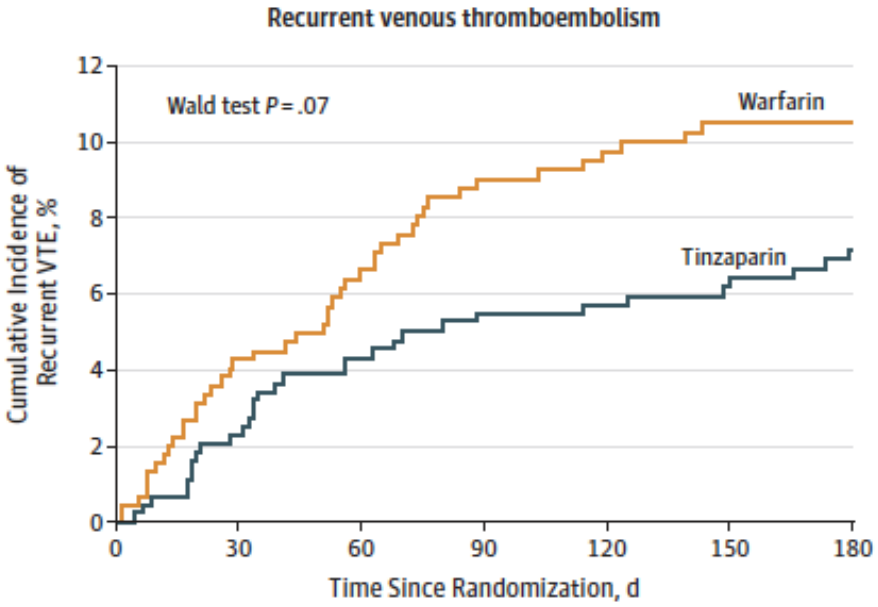
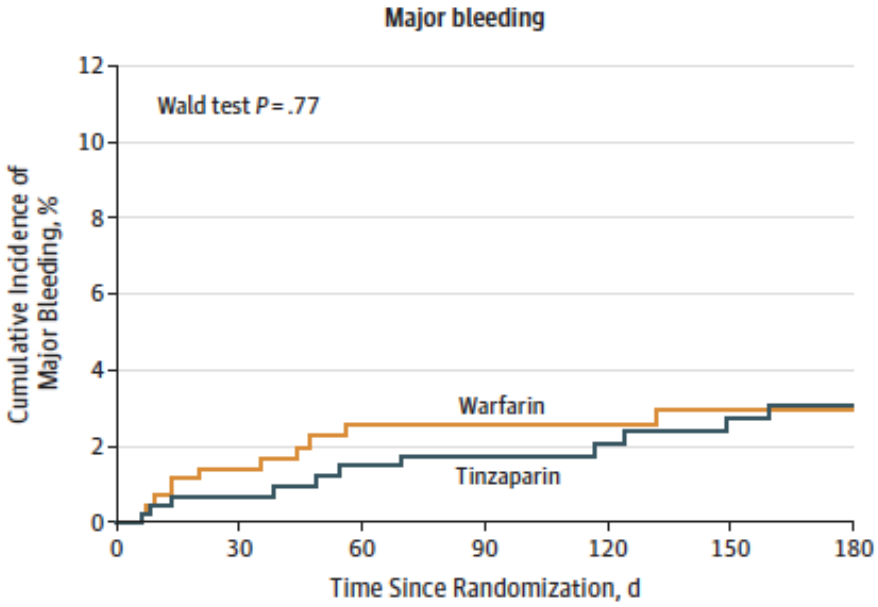
LWMH vs. Warfarin: CATCH Trial

Figure 2. Cumulative Incidence Among Patients With Active Cancer According to Treatment With Tinzaparin vs Warfarin





VTE indicates venous thromboembolism. Source: The left panel of Figure 2 was reproduced with permission from the American Society of Hematology.[24]

Lee et al. JAMA 2015

LWMH vs. Warfarin: CATCH Trial

Key Differences between the CLOT and CATCH Trial		
	CATCH Trial (Tinzaparin)	CLOT Trial (Daletparin)
Metastatic Disease (%)	55	67
ECOG PS 2 (%)	23	36
Anti-Cancer Therapy (%)	53	78
History of VTE (%)	6	11

Lee et al. JAMA 2015
Lee et al. NEJM 2003

ISTH CAT Guidelines

- Acute VTE, Low Risk of Bleeding
  - DOAC (if no drug-drug interactions) (1)
  - LMWH is an acceptable alternative
- Acute VTE, High Risk of Bleeding
  - e.g. luminal GI cancers with an intact primary, GU cancers, nephrostomy tubes, active GI mucosal abnml (gastritis, esophagitis, colitis)
  - LWMH (1)
  - DOAC (edoxaban and rivaroxaban) as an alternate
- Edoxaban and Rivaroxaban are the only DOACs that have been compared to LWMH in RCT (more at ASH)