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Patients with gastro-intestinal malignancies and anticoagulation due to thrombosis

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466-BE-2200054 - 10/22

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Patient Case

Patient initial presentation, diagnosis & management

43 years

Signet cell adenocarcinoma of the stomach with extensive peritoneal & liver metastases

Molecular testing

Microsatelite stability

HER2 -

PD-L1 CPS score = 12

Presented symptoms

Hematological

Iron deficiency anemia with hemoglobin of 8.2 gr/dl, suggesting certainly chronic blood loss

No melena or macroscopic blood loss

Thrombotic

Asymptomatic bilateral small pulmonary emboli were found,

No clinical signs of deep venous thrombosis in legs

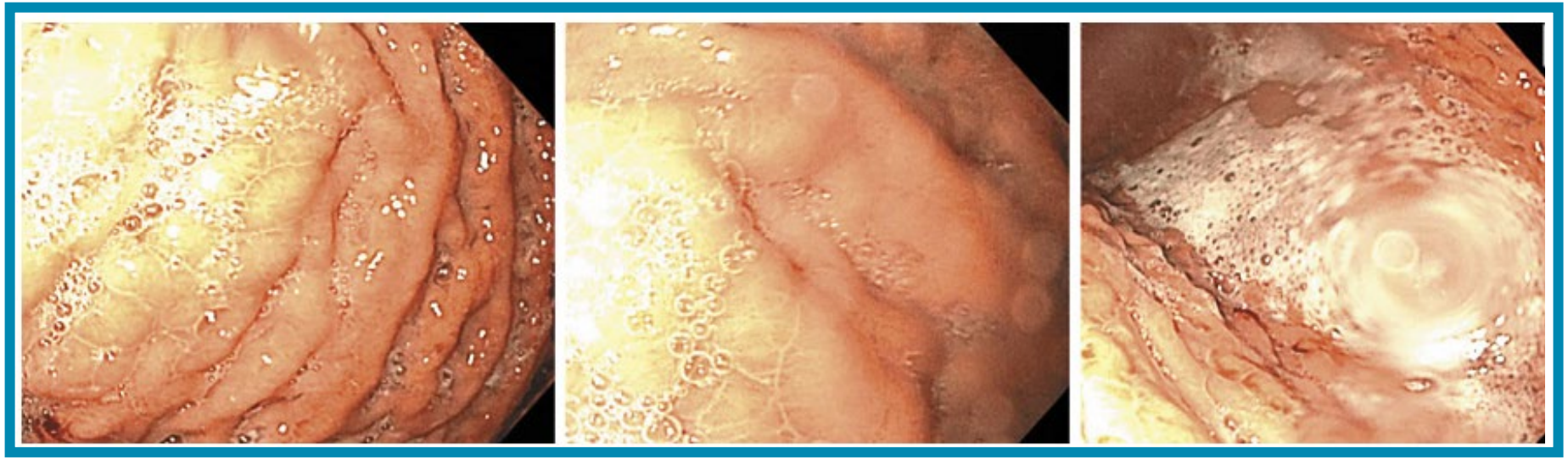
Management

Chemotherapy with FOLFOX + Nivolumab to be started

Patient initial presentation, diagnosis & management

Photographs of an initial upper endoscopy exam showing moderately diffuse inflammation and edema with stigmata of bleeding in the fundus of the stomach.

Biopsies reveal adenocarcinoma – poorly differentiated with signet ring cells.



Benesch M.G.K. Mathieson A.Case Rep Oncol 2022;15:114–119

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

Gary H. Lyman,[1,2,*] Marc Carrier,[3,*] Cihan Ay,[4] Marcello Di Nisio,[5] Lisa K. Hicks,[6] Alok A. Khorana,[7] Andrew D. Leavitt,[8,9] Agnes Y. Y. Lee,[10,11] Fergus Macbeth,[12] Rebecca L. Morgan,[13] Simon Noble,[14] Elizabeth A. Sexton,[15] David Stenehjem,[16] Wojtek Wiercioch,[13] Lara A. Kahale,[17,†] and Pablo Alonso-Coello[18,†]

"LMWH or direct oral anticoagulants (DOAC) in ambulatory patients with cancer receiving systemic therapy at high risk of VTE and LMWH or DOAC for initial treatment of VTE"

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Nigel S. Key, MB ChB[1]; Alok A. Khorana, MD[2]; Nicole M. Kuderer, MD[3]; Kari Bohlke, ScD[4]; Agnes Y.Y. Lee, MD, MSc[5]; Juan I. Arcelus, MD, PhD[6]; Sandra L. Wong, MD, MS[7]; Edward P. Balaban, DO[8]; Christopher R. Flowers, MD, MS[9]; Charles W. Francis, MD[10]; Leigh E. Gates[11]; Ajay K. Kakkar, MBBS, PhD[12]; Mark N. Levine, MD, MSc[13]; Howard A. Liebman, MD[14]; Margaret A. Tempero, MD[15]; Gary H. Lyman, MD, MPH[16]; and Anna Falanga, MD[17]

ASCO: "Caution with DOACs also warranted in other settings with high risk for mucosal bleeding"

Antithrombotic T… E Disease

Second Update of the … Expert Panel Report

Scott M. Stevens, MD; Scott C. …
Kevin Doerschug, MD; Geert-J…
Christopher S. King, MD; An…
Janine R. E. Vintch, MD; Ph…
… Bounameaux, MD;
…ive Kearon, MD, PhD;
… MD;

Check for updates

CHEST: Edoxa… risk of GI maj… malignancy … preferred …

…ated with a higher …al GI …ay be the

Inconsistency in guidelines on: How to treat CAT in Patients with GI-malignancies

2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19

Dominique Farge*, Corinne Frere*, Jean M Connors, Alok A Khorana, Ajay Kakkar, Cihan Ay, Andres Muñoz, Benjamin Brenner, Pedro H Prata, Dialina Brilhante, Darko Antic, Patricia Casais, María Cecilia Guillermo Esposito, Takayuki Ikezoe, Syed A Abutalib, Luis A Meillon-García, Henri Bounameaux, Ingrid Pabinger, James Douketis, the International Initiative on Thrombosis and Cancer (ITAC) advisory panel

ITAC: "direct oral anticoagulants for the initial treatment and maintenance treatment of cancer-associated thrombosis in patients who are not at high risk of gastrointestinal or genitourinary bleeding, in the absence of strong drug–drug interactions or of gastrointestinal absorption impairment"

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

Cancer-Associated Venous Thromboembolic Disease, Version 2.2021

NCCN: "DOACs (preferred for patients without gastric or gastroesophageal lesions)
Category 1: Apixaban Category 2A: Rivaroxaban"

Lyman GH, et al. Blood Adv. 2021 Feb 23;5(4):927-974; Key NS, et al. J Clin Oncol. 2020 Feb 10;38(5):496-520. doi: 10.1200/JCO.19.01461. Epub 2019 Aug 5; Stevens SM, et al. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. Epub 2021 Aug 2; Fargue D, et al. Lancet Oncol 2022; 23: e334–47; Streiff MB, J Natl Compr Canc Netw. 2021 Oct 15;19(10):1181-1201. doi: 10.6004/jnccn.2021.0047

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Types of anticoagulants used in the management of CAT

Types of anticoagulants used in the management of CAT

Characteristics	Direct Oral Anticoagulants				LMWH (Enoxaparin, Dalteparin)	Warfarin	Fondaparinux
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban			
Mechanism of action	Direct thrombin inhibitor, prodrug requires conversion by carboxylesterases	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Inhibition (through antithrombin III) of factor Xa and IIa	Inhibits formation of vitamin K dependent clotting factors (factors II, VII, IX, X) and proteins C and S	Inhibition (through antithrombin III) of factor Xa
Renal clearance	80	27%	50%	66% (30% as inactive metabolites)	R8%–40% (10% unchanged)	92%	77%
CYP metabolism	No	Mostly CYP3A4/5	Minimal	CYP3A4/5, CYP2J2	No	CYP2C9, CYP1A2, CYP3A4, CYP2C19	No
Impacted by P-glycoprotein Transporter system	Yes	Yes	Yes	Yes	No	No	No
Bioavailability	3%–7%, pH-dependent	50%	62%	66%–100% (increased with food for 15- to 20-mg dose)	80%–100% (subcutaneous)	100%	100% (subcutaneous)
Half-life	12–17 h	8–15 h	10-14 h	5–13 h	3–7 h	40 h (variable)	17–21 h
Dosing frequency	Twice daily	Twice daily	Daily	Daily	Twice daily or daily	Daily	Daily

- Anticoagulants recommended in current CAT treatment guidelines include low-molecular-weight heparin (LMWH), warfarin, and in recent years, the direct oral anticoagulants (DOACs)
- Fondaparinux is also occasionally used in outpatient CAT management

Schaefer JK, et al. J Natl Compr Canc Netw 2021;19(10):1203–1210.

European Labelling Information for DOAC Use in Cancer Patients

4.4 Special warnings and precautions for use

APIXABAN[1]	RIVAROXABAN[2]	DABIGATRAN[3]	EDOXABAN[4]
Patients with active cancer can be at high risk of both VTE and bleeding events. When apixaban is considered for DVT or PE treatment in cancer patients, a **careful assessment of the benefits against the risks** should be made	Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. **The individual benefit of antithrombotic treatment should be weighed against risk for bleeding** in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. **Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.** In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated	The efficacy and safety **have not been** established for DVT/PE patients with active cancer. There is **limited data** on efficacy and safety for **paediatric** patients with active cancer	Efficacy and safety of edoxaban in the treatment and/or prevention of VTE in patients **with active cancer have not been established**

It's important to note that apixaban is contraindicated in patients with malignant neoplasms at high risk of bleeding.[1]

Comparisons cannot be made between individual NOACs based on these data.

DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

1. European Summary of Product Characteristics, Eliquis® (apixaban); 2. European Summary of Product Characteristics, Xarelto® (rivaroxaban); 3. European Summary of Product Characteristics, Pradaxa® (dabigatran); 4. European Summary of Product Characteristics, Lixiana® (edoxaban).

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Studies showing efficacy & safety of NOAC use in CAT

DOACs for cancer-associated venous thromboembolism: a systematic review and meta-analysis

Study Characteristics								
Study name	Year	Treatment allocation*	Baseline characteristics indicated as No. (%)					
			Male	Age (mean/median with SD/IQR), a	Index-event PE ± DVT	Incidental VTE	Prior VTE	Metastatic disease	Gastro-intestinal cancer
Hokusai VTE Cancer	2018	Edoxaban, n = 522‡	277 (53.1)	64 ± 11	328 (62.8)	167 (32.0)	49 (9.4)	274 (52.5)	165 (31.6)
		Dalteparin, n = 524	263 (50.2)	63 ± 12	329 (62.8)	173 (33.0)	63 (12.0)	280 (53.4)	140 (26.7)
Select-D	2018	Rivaroxaban, n = 203	116 (57.1)	67 (22–87)	150 (73.9)	108 (53.2)	NR	118 (58.1)	94 (46.3)
		Dalteparin, n = 203	98 (48.3)	67 (34–87)	145 (71.4)	105 (51.7)	NR	118 (58.1)	86 (42.4)
ADAM-VTE§	2020	Apixaban, n = 150	72 (48.0)	64 ± 11	81 (54.0)	NR	8 (5.3)	96 (64.0)	48 (32.0)
		Dalteparin, n = 150	73 (48.7)	64 ± 11	75 (50.0)	NR	12 (8.0)	97 (64.7)	57 (38.0)
CARAVAGGIO	2020	Apixaban, n = 576	292 (50.7)	67 ± 11	304 (52.8)	116 (20.1)	45 (7.8)	389 (67.5)	188 (32.6)
		Dalteparin, n = 579	276 (47.7)	67 ± 11	334 (57.7)	114 (19.7)	61 (10.5)	396 (68.4)	187 (32.3)

Data are expressed as No. (%) unless otherwise indicated. IQR, interquartile range; NR, not reported; SD, standard deviation.
*Number of patients in (modified) intention-to-treat analysis.
‡A total of 122 (23.4%) patients receiving edoxaban met the criteria for dose reduction to 30 mg edoxaban once daily.
§ In the ADAM-VTE trial, baseline characteristics were presented for all 300 randomized patients, and the analysis was performed in the modified intention-to-treat population (n 5 145 in the rivaroxaban group, n 5 142 in the dalteparin group).
¶For the CARAVAGGIO study, this number also includes patients with recurrent locally advanced cancer.

IQR, interquartile range; NR, not reported; SD, standard deviation; VTE, venous thromboembolism.

Mulder FI et al. Blood 2020;136(12):1433–41.

DOACs for cancer-associated venous thromboembolism: a systematic review and meta-analysis

Cancer Type distribution across studies								
	CARAVAGGIO*		SELECT-D†		HOKUSAI VTE Cancer‡		ADAM-VTE	
	Apixaban (n=576)	Dalteparin (n=579)	Rivaroxaban (n=203)	Dalteparin (n=203)	Edoxaban (n=522)	Dalteparin (n=524)	Apixaban (n=150)	Dalteparin (n=150)
Colorectal	121 (21.0)	113 (19.5)	55 (27.0)	47 (23.0)	83 (15.9)	79 (15.1)	18 (12.2)	29 (19.6)
Upper GI	23 (4.0)	31 (5.4)	15 (7.0)	26 (12.0)	33 (6.3)	21 (4.0)	7 (4.8)	4 (2.7)
Lung	105 (18.2)	95 (16.4)	22 (11.0)	25 (12.0)	77 (14.8)	75 (14.3)	32 (21.8)	19 (12.8)
Breast	79 (13.7)	76 (13.1)	20 (10.0)	20 (10.0)	64 (12.3)	60 (11.5)	16 (10.9)	12 (8.1)
Genitourinary	66 (11.5)	73 (12.6)	25 (13.0)	17 (11.0)	65 (12.5)	71 (13.5)	13 (8.7)	14 (9.3)
Gynocological	60 (10.4)	59 (10.2)	18 (9.0)	25 (12.0)	47 (9.0)	63 (12.0)	14 (9.5)	15 (10.1)
Pancreatic or hepatobiliary	44 (7.6)	43 (7.4)	12 (10.0)	13 (6.0)	49 (9.4)	40 (7.6)	23 (15.6)	24 (16.2)
Head and neck$	14 (2.4)	8 (1.4)	0 (0.0)	0 (0.0)	—	—	0 (0.0)	0 (0.0)
Brain tumor	0 (0)	0 (0)	1 (1.0)	2 (1.0)	‖	‖	3 (2.0)	5 (3.4)
Bone/Soft issue	11 (1.9)	7 (1.2)	2 (1.0)	0 (0.0	—	—	3 (2.0)	1 (0.7)
Skin: melanoma	4 (0.7)	7 (1.2)	—	—	—	—	0 (0.0)	4 (2.7)
Hematological malignacy	33 (5.7)	52 (9.0)	14 (7.0)	17 (9.0)	56 (10.7)	55 (10.5)	13 (8.9)	14 (9.5)
Other	16 (2.8)	15 (2.6)	10 (5.0)	11 (7.0)	48 (9.2)	60 (11.5)	0 (0.0)	2 (1.4)

Values are n (%). *Basal cell or squamous cell carcinoma of the skin, primary brain tumor or known intracerebral metastases, and acute leukemia were not included in the CARAVAGGIO trial. †Basal cell or squamous cell carcinoma of the skin were not included in the SELECT-D trial. ‡Basal cell or squamous cell carcinoma of the skin were not included in the Hokusai VTE Cancer trial. $Other than brain tumors. ‖ Data not available, because brain tumors were included under “other tumors”.

Sabatino, J. et al. JACC.CardioOncology. 2020;2(3):428–40.

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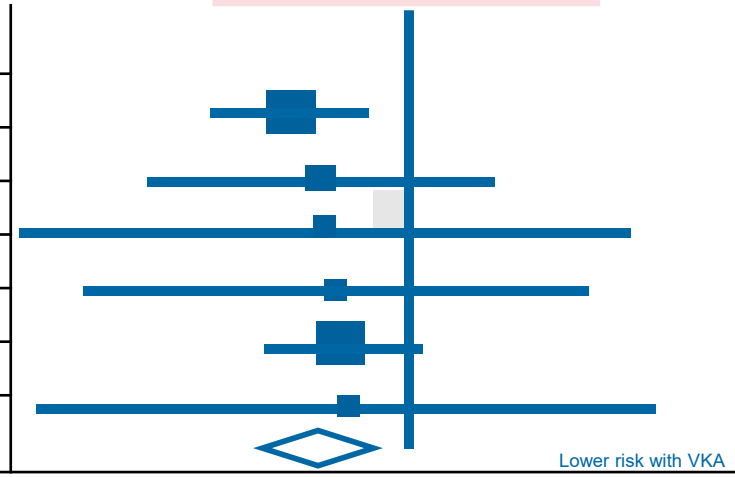
How to treat cancer-associated VTE: Does LMWH do a better job (vs. VKA)?

Efficacy and safety of LMWH vs VKA

LMWH vs.VKA (n=2078) — **Recurrent VTE**

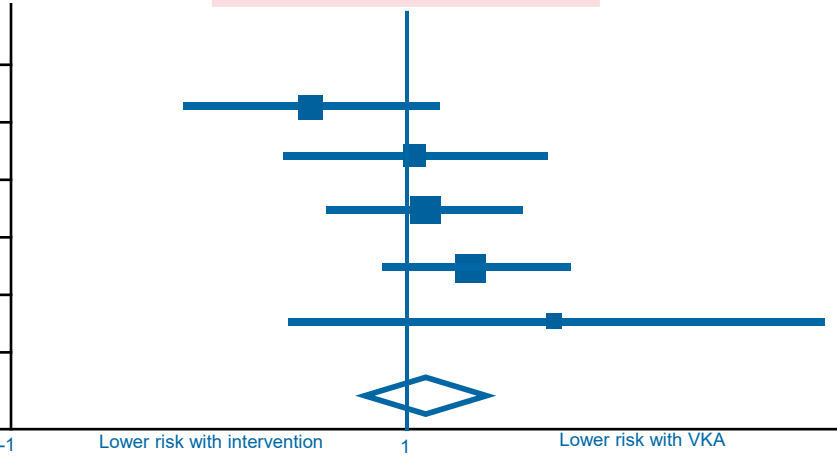


Study ID.	RR (95%)	Events, Intervention	Events, VKA	% Weight
CLOT	0.51 (0.33, 0.79)	27/336	53/336	41.31
LITE	0.60 (0.23, 1.59)	6/100	10/100	8.37
Romera	0.61 (0.11, 3.43)	2/36	3/33	2.66
ONCENOX	0.66 (0.16, 2.74)	4/61	3/30	3.87
CATCH	0.69 (0.45, 1.07)	31/449	45/451	41.24
CANTHANOX	0.70 (0.12, 4.09)	2/71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

Compared to VKA, the risk of VTE was in favor to LMWH

(RR = 0.60, 95%CI:, p<0.001)

LMWH vs.VKA (n=2020) — **Major bleeding**



Study ID.	RR (95%)	Events, Intervention	Events, VKA	% Weight
CANTHANOX	0.44 (0.16, 1.19)	5/71	12/75	18.83
LITE	1.00 (0.36, 2.75)	7/100	7/100	18.28
CATCH	1.09 (0.50, 2.36)	13/449	12/451	27.13
CLOT	1.57 (0.77, 3.18)	19/338	12/335	30.61
ONCENOX	3.04 (0.38, 24.28)	6/67	1/34	5.16
Subtotal: I^2 = 23.1%, p= 0.267	1.07 (0.66, 1.73)	50/1025	44/995	100.00

Compared to VKA, the risk of major bleeding was non significantly different with LMWH

(RR=1.07, 95%CI: 0.66-1.73, p=0.80)

SOC: 3-6m post-VTE LMWH, 6 -7.3 months treatment

LMWH, low molecular weight heparin; VKA, vitamin K antagonist

F. Posch et al. Thromb Res 136 (2015) 582–589.

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Do DOACs do a better job?

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Can Edoxaban do a better job? (vs. LMWH)

Hokusai- VTE cancer, Study Design

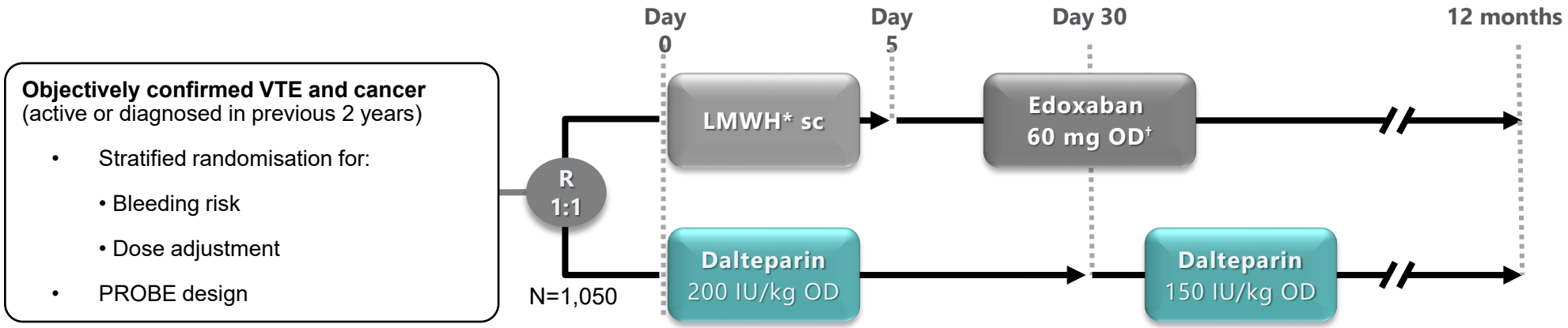
Prospective, randomized, open-label, multicenter noninferiority study comparing LMWH dalteparin with edoxaban for 12 months

Primary outcome

Composite of recurrent VTE or major bleeding regardless of duration of therapy

Secondary outcome

VTE, PE, DVT, major bleeding, CRNMB, all cause death, event free survival



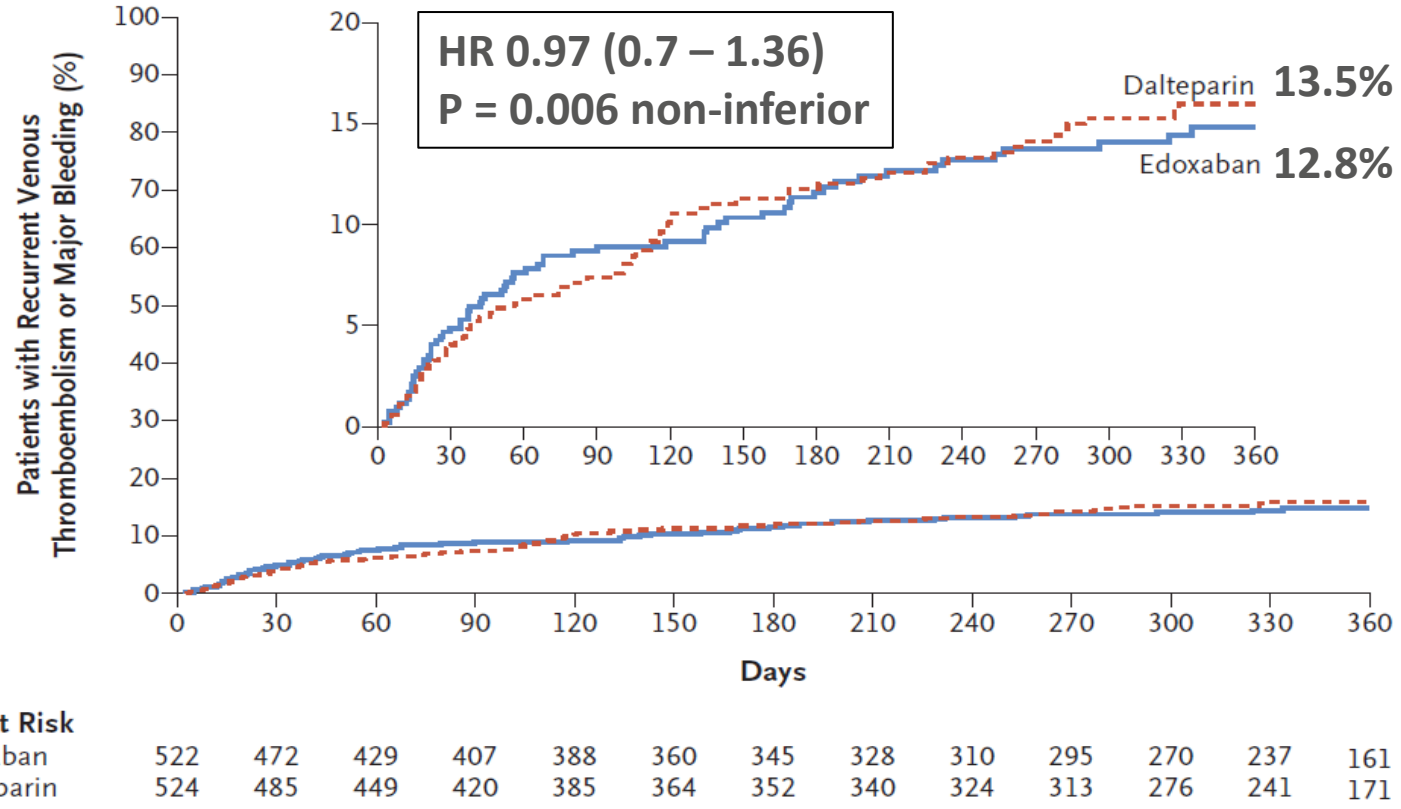
*≥5 days of LMWH. Choice of LMWH type and lead-in duration were left to treating physician;
†Edoxaban 30 mg OD for patients requiring dose adjustment for CrCl 30–50 mL/min, body weight ≤60 kg or concomitant P-gp inhibitor use.

CRNMB, clinically relevant nonmajor bleeding; DVT, deep vein thrombosis; EFS, event free survival; LMWH, low-molecular-weight heparins; PE, pulmonary embolism; VTE, venous thromboembolism, PROBE placebo controlled randomized, blinded endpoint.

Adapted from Raskob GE E et al.N Engl J Med 2018; 378,7: 615-624.

Primary study results: composite safety and efficacy

Composite of recurrent venous thromboembolism or major bleeding



VTE, venous thromboembolism

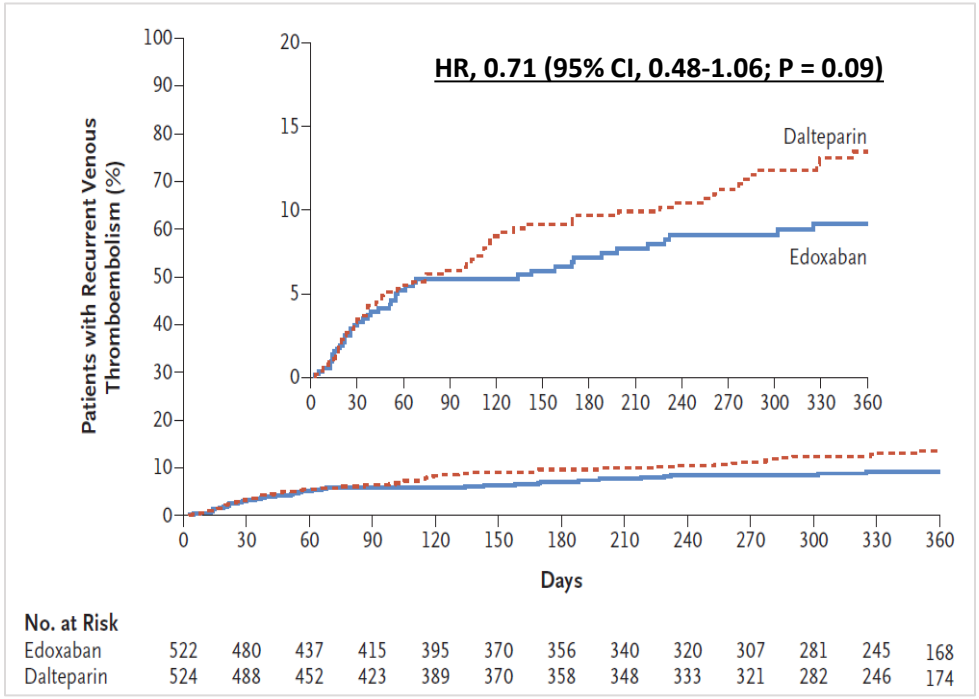
Raskob GE E et al.N Engl J Med 2018; 378,7: 615-624.

Efficacy and Safety Results

Cumulative event rates for recurrent VTE and major bleeding

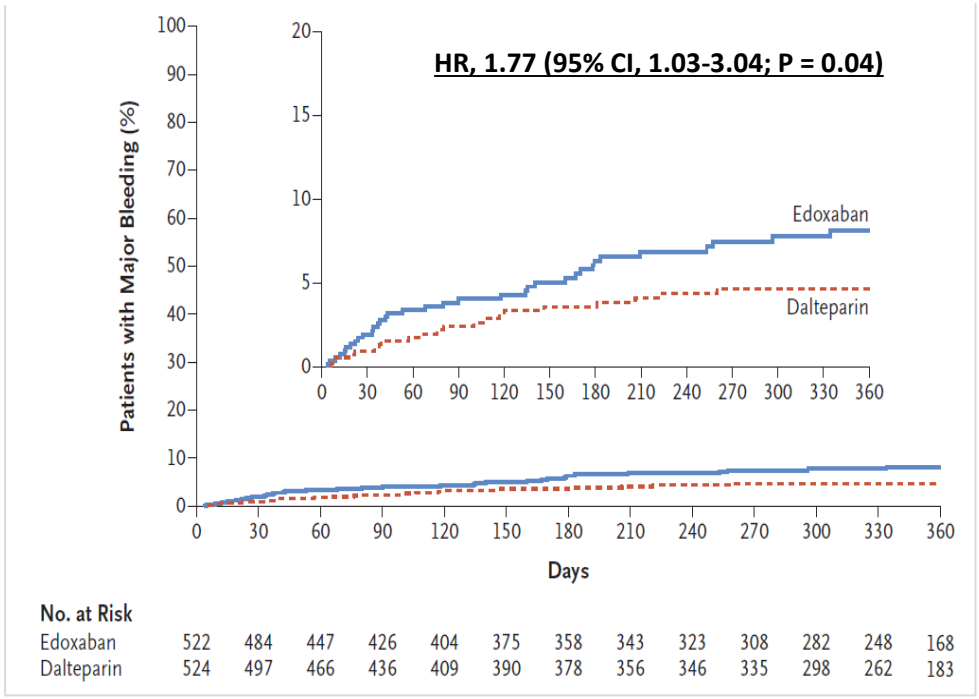
Recurrent VTE

Edoxaban **7.9%** vs Dalteparin **11.3%**



Major bleeding

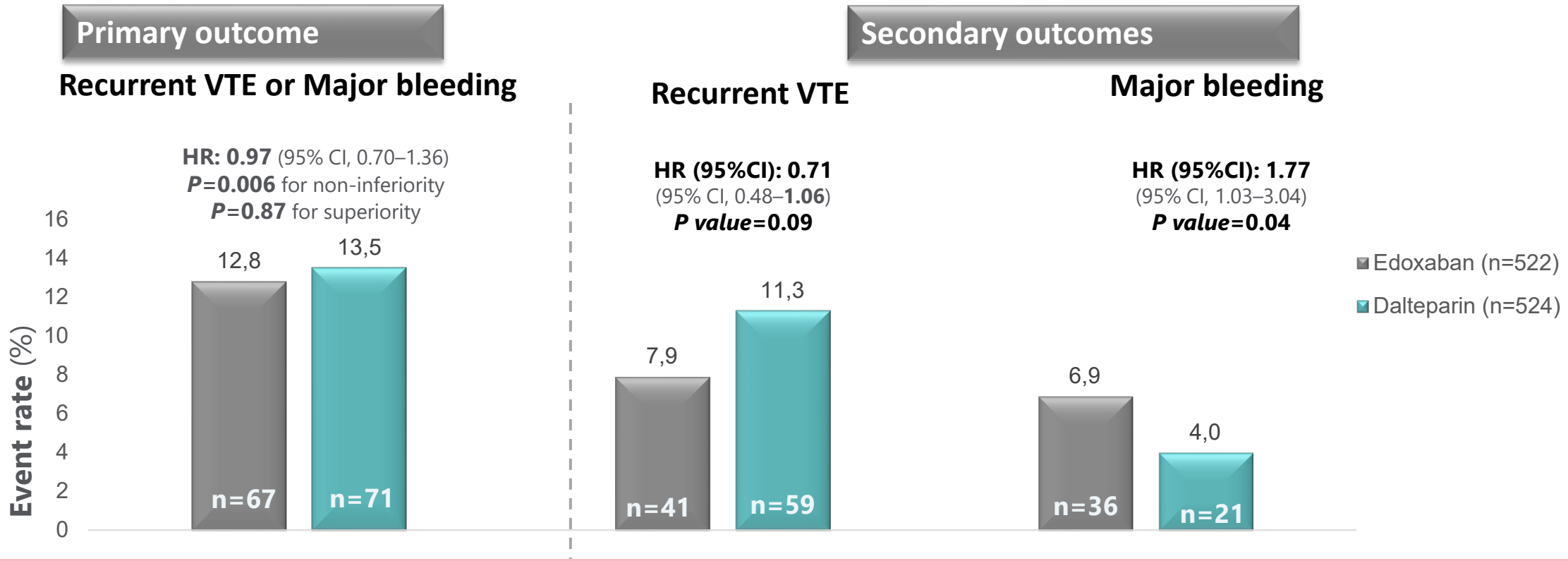
Edoxaban **6.9%** vs Dalteparin **4.0%**



VTE, venous thromboembolism

Raskob GE E et al.N Engl J Med 2018; 378,7: 615-624.

Composite, efficacy and safety results



- No statistically significant interactions between subgroup and treatment, **except for the subgroups gastrointestinal cancer at the time of randomization**
- Patients with gastrointestinal cancer were **more likely to have an increase in the risk of bleeding during treatment with edoxaban** than with dalteparin (P = 0.02 for interaction in the safety population)

HR, hazard ratio; VTE, venous thromboembolism

Adapted from Raskob GE E et al.N Engl J Med 2018; 378,7: 615-624.

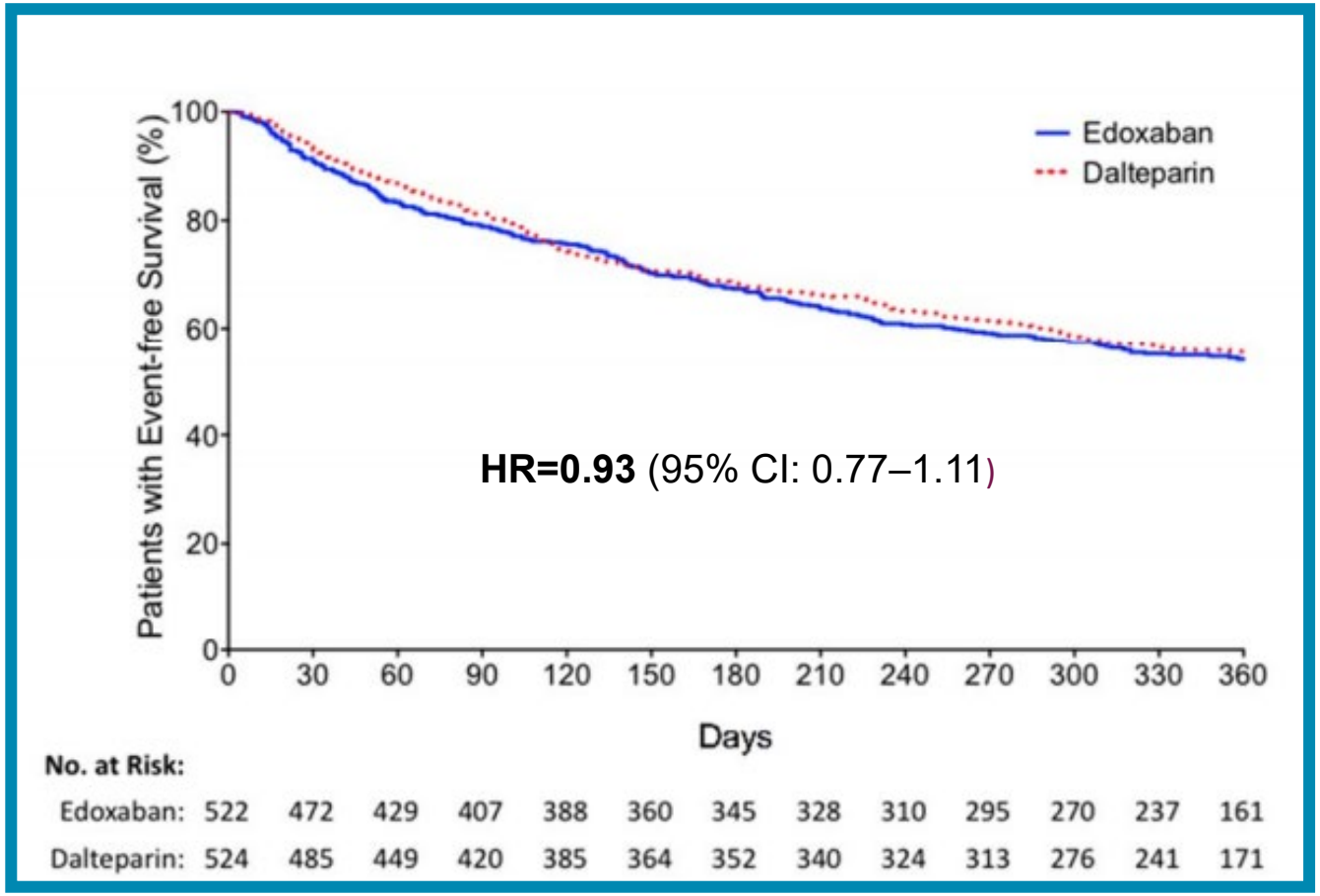
Sites of Major bleeding

	Edoxaban (N = 522)	Dalteparin (N = 524)
Major bleeding, n (%)	**33** (6.3)	17 (3.2)
Fatal†	0	2 (0.4)
Intracranial	2 (0.4)	2 (0.4)
Gastrointestinal	20 (3.8)	6 (1.1)
Upper	**17** (3.3)	3 (0.6)
Lower	3 (0.6)	3 (0.6)†
Urogenital	**5** (1.0)	0
Other	6 (1.1)	7 (1.3)
Severity of Major bleeding, n (%)‡		
1	0	0
2	21/33 (63.6)	5/17 (29.4)
3	12/33 (36.4)	11/17 (64.7)
4	0	1/17 (5.9)

† The site of fatal bleeding was intracranial in one patient and lower gastrointestinal in one patient.
‡ The severity of clinical presentation of major bleeding was adjudicated without knowledge of treatment assignment according to the predefined categories
1: Bleeding events presenting without any clinical emergency,
2: Bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency,
3: Bleeding events presenting with great medical urgency, such as bleeding with hemodynamic instability or intracranial bleeding presenting with neurologic symptoms,
4: Bleeding events already fatal before or almost immediately upon entering the hospital.

DVT,deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Event (major bleeding/ recurrent VTE/ death) free survival



Event-free survival was defined as the absence of recurrent venous thromboembolism, major bleeding or death

Raskob et al., N Engl J Med. 2018, 378,7: 615-624

Author’s conclusions

- Edoxaban was non-inferior to dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding
- The rate of recurrent VTE was lower but the rate of major bleeding was higher with edoxaban than with dalteparin

VTE, venous thromboembolism.

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Can Rivaroxaban do a better job? (vs. LMWH)

Select-D, Study Design

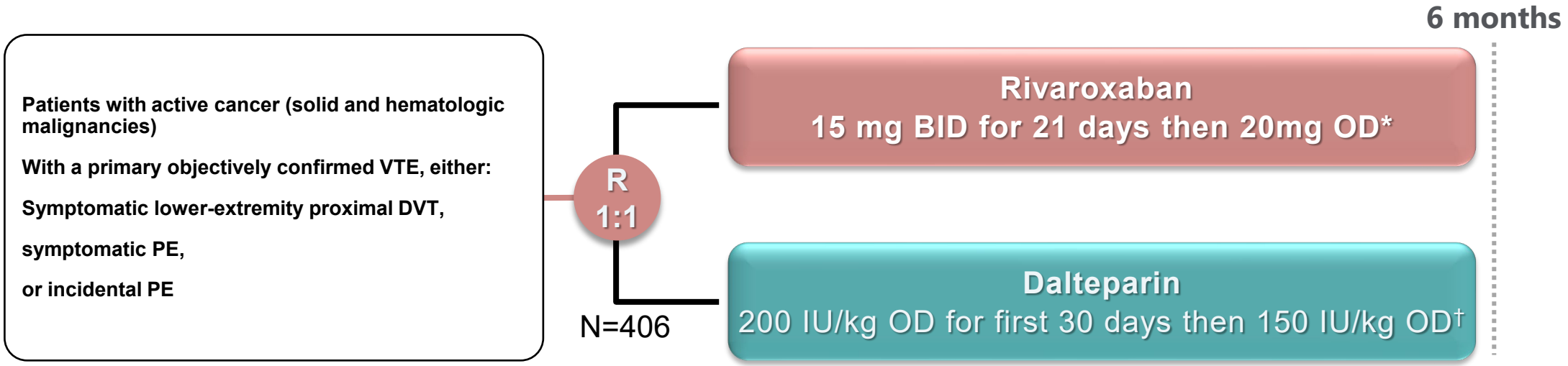
Multicenter, randomized, open-label, pilot trial comparing dalteparin vs rivaroxaban for 6 months

Primary outcome

VTE reccurence at 6 months

Secondary outcome

Major bleeding, CRNM Bleeding



A second random assignment for a further 6 months' treatment in this study was closed based on a recommendation from the DSMC

BID, twice daily; CRNM, clinically relevant non major; DSMC, data and safety monitoring committee; DVT, deep vein thrombosis; OD, once daily; PE, pulmonary embolism; VTE venous thromboembolism
*For patients with CrCl 30–49 mL/min dosing recommendations as in rivaroxaban SmPC; if a patient's platelet counts were <50,000/mm3, rivaroxaban was to be discontinued until platelet count recovered to >50,000/mm3;
†The dose was adjusted or discontinued for low platelet count and significant renal failure until recovery.

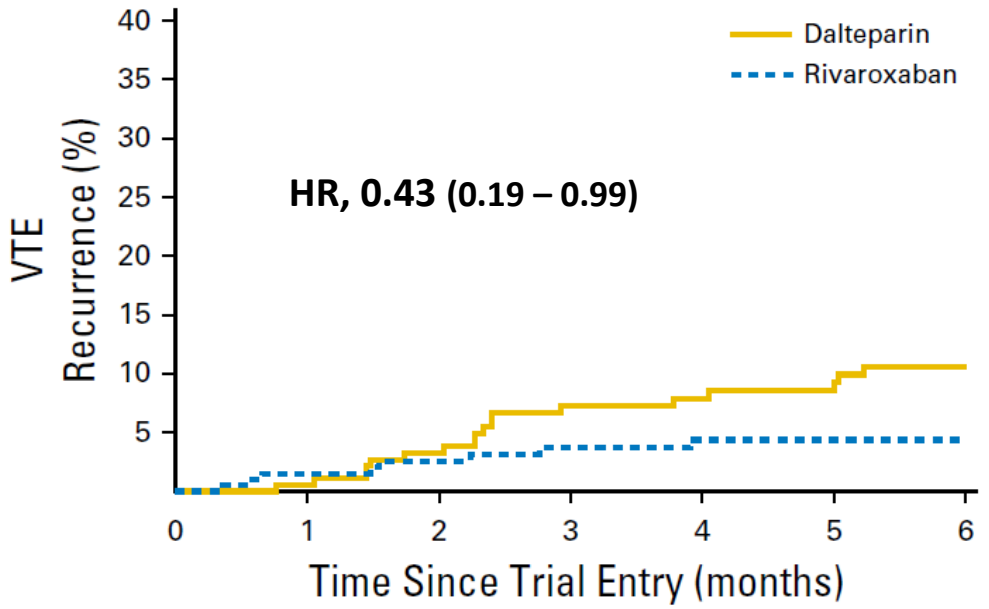
Adapted from Young A et al. J clin oncol. 2018; 36,20: 2017-2023.

Efficacy and Safety results

Cumulative VTE recurrence and major bleeding rate at 6 months

VTE recurrence

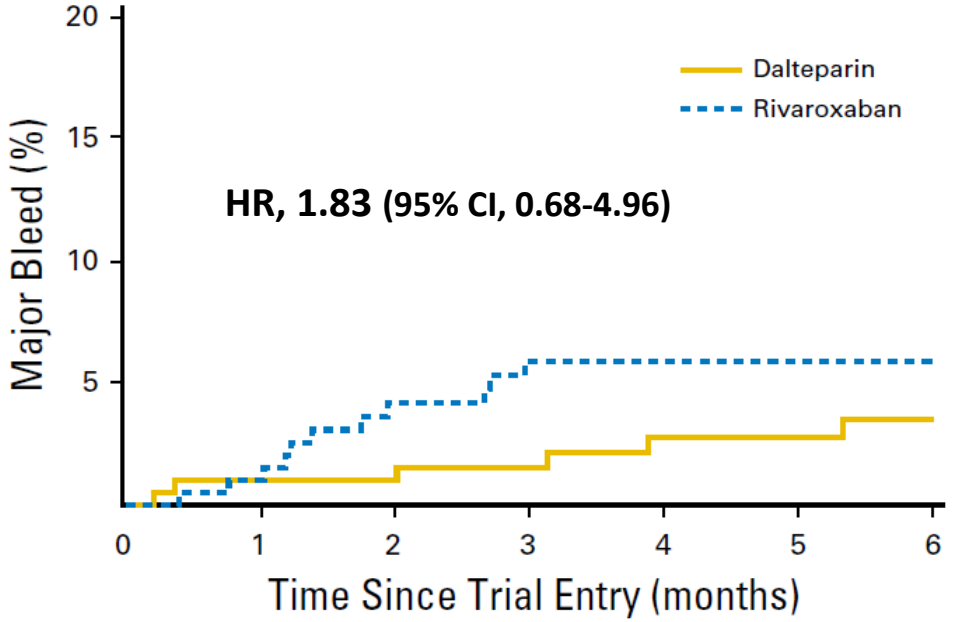
Rivaroxaban **4%** vs Dalteparin **11%**



No. at risk:				
Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

Major bleeding

Rivaroxaban **6%** vs Dalteparin **4%**



No. at risk:				
Dalteparin	203	176	147	122
Rivaroxaban	203	172	149	134

VTE, venous thromboembolism; CI, confidence interval; HR, hazard ratio

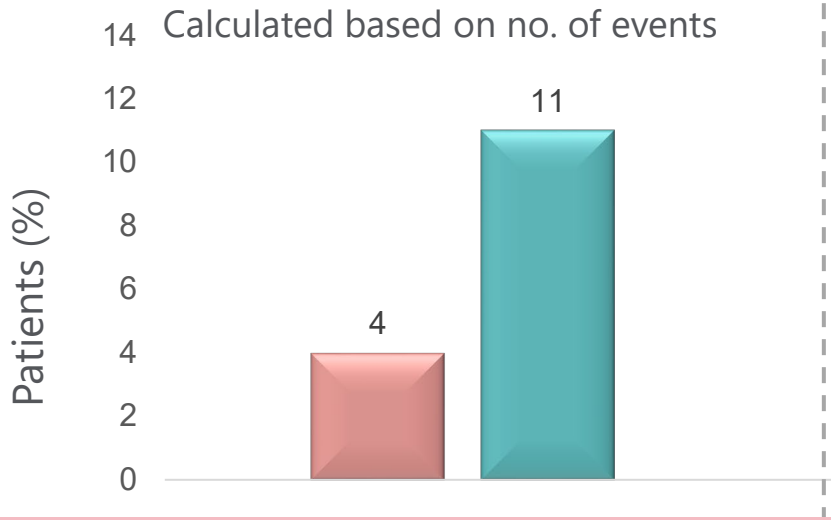
Young A et al. J clin oncol. 2018; 36,20: 2017-2023.

Efficacy and Safety results

Primary outcome

Recurrent VTE over 6 months

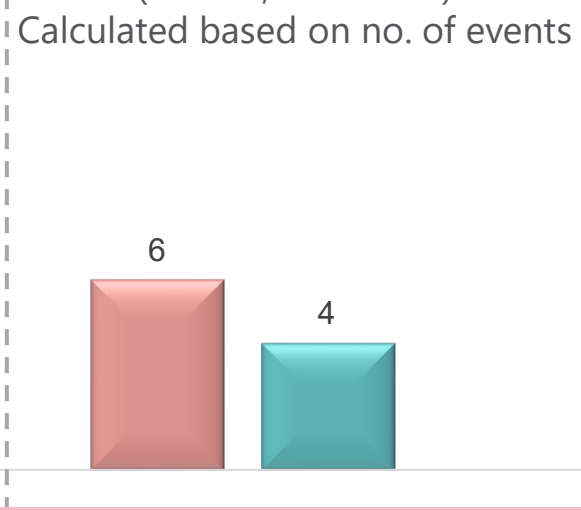
HR: 0.43 (95% CI, 0.19-0.99)
Calculated based on no. of events



Secondary outcomes

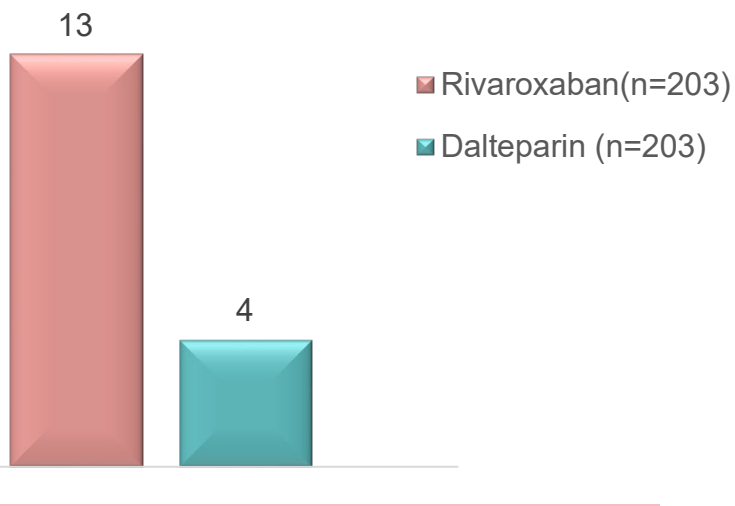
Major Bleeding

HR: 1.83
(95% CI, 0.68–**4.96**)
Calculated based on no. of events



CRNM Bleeding

HR: 3.76 (95% CI, 1.68–8.69)
Calculated based on no. of events



- **54%** of patients **completed** 6 months of trial treatment
- **Most major bleeding events were GI bleeds**
- Patients with **esophageal or gastroesophageal cancer tended to experience more major bleeds with rivaroxaban** than with dalteparin (4 (36%) of 11 versus 1 (11%) of 19)

CI, confidence interval; CRNM, clinically relevant non major; HR, hazard ratio; VTE, venous thromboembolism

Adapted from Young A et al. J clin oncol. 2018; 36,20: 2017-2023.

Sites of bleeding

	Rivaroxaban (N = 203)	Dalteparin (N = 203)
Major bleeding*, n	**11**	6
Gastrointestinal	**8**	4
Esophageal	3	1
Stomach	2	3
Lower GI	1	0
Site unkown	2	0
Genitourinary- Hematuria	1	0
Other	2	0
CRNM Bleeding*, n	**25**	7
Gastrointestinal	9	3
Upper GI	2	0
Lower GI	0	1
Other	5	2
Genitourinary	**11**	2
Other	7	3

*Patients could have more than one reason or site of bleed; one patient receiving rivaroxaban had two CRNMBs

CRNM, clinically relevant non major

Young A et al. J clin oncol. 2018; 36,20: 2017-2023.

Author’s conclusions

- Rivaroxaban is an effective alternative to LMWH for the treatment of VTE in cancer
- Rivaroxaban reduced the rate of recurrent VTE compared with LMWH, but at the cost of more bleeding
- Oral administration is more convenient than daily subcutaneous injections
- It should be used with particular caution in patients with esophageal cancer
- At the end of the day, a patient’s preference for a specific anticoagulant is based on a careful discussion between patient and physician about the benefits and risks of the treatment alternatives

Young A et al. J clin oncol. 2018; 36,20: 2017-2023.

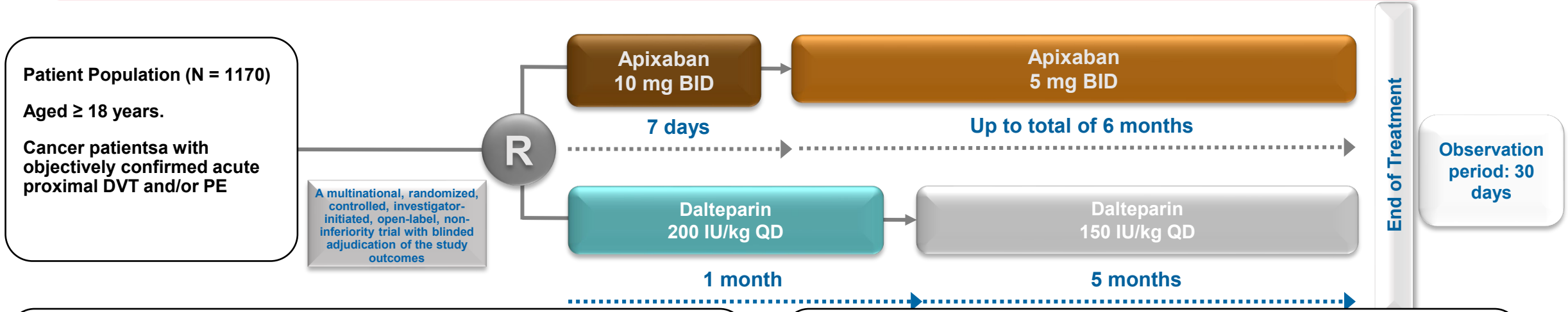
ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Can Apixaban do a better job? (vs. LMWH)

CARAVAGGIO, Study Design

Aim:
To assess whether oral apixaban would be non-inferior to subcutaneous dalteparin, a LMWH, for the prevention of recurrent VTE in patients with cancer without increasing the risk of major bleeding



Primary Outcome: Objectively confirmed recurrent VTE (proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, and PE (symptomatic, incidental, or fatal) occurring during the 6-month trial period.

Principle Safety Outcome: Major bleeding (ISTH definition* plus bleeding resulting in surgical intervention) in the trial period through to 72 hours after the last dose.

Secondary Outcomes

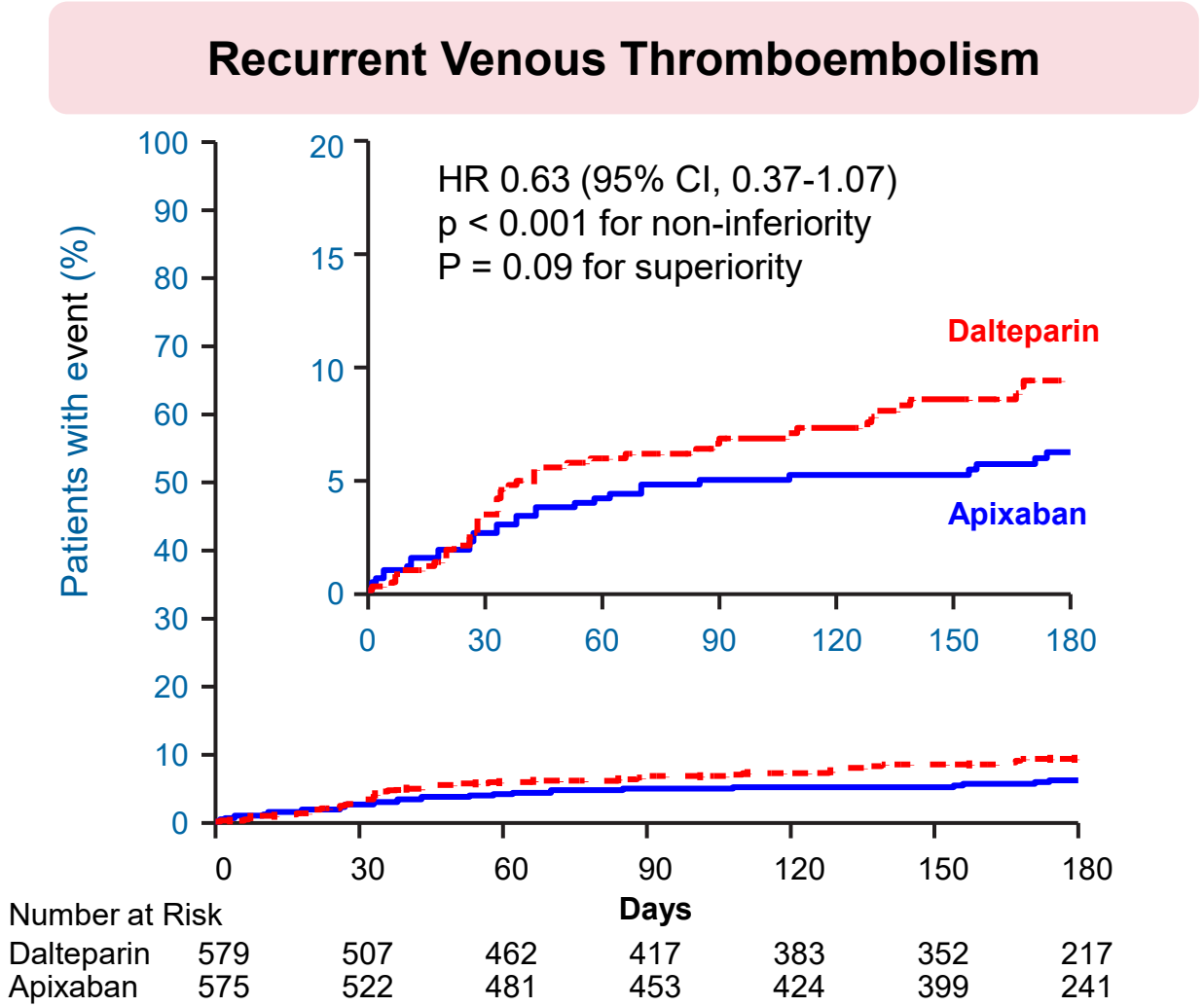
Individual components of the primary efficacy outcome; symptomatic recurrence of VTE; all-cause death; composite of the primary efficacy outcome plus major bleeding; composite of the primary efficacy outcome plus major bleeding plus all-cause death; composite of the primary efficacy outcome plus all-cause death; CRNM bleeding; major plus CRNM bleeding; MACE; all VTE events; QoL according to ACTs; permanent discontinuation due to safety.

The maximum daily dose allowed for dalteparin was 18 000 IU. During the trial, the protocol was amended to allow dose adjustments for dalteparin on the basis of the platelet count according to the country-specific labeling of the drug.
Trial drugs could be temporarily withheld in case of a platelet count lower than 50 000/mm^3 or any condition associated with an increased risk of bleeding, including surgery, invasive procedures, or deterioration of renal function.
*ISTH definition of major bleeding is clinically overt bleeding associated with one or more of the following: a decrease in the hemoglobin level of at least 2 g per deciliter, a transfusion of 2 or more units of red cells, bleeding occurring at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding

ACTS, Anti-Clot Treatment Scale; BID, twice daily; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; ISTH; International Society on Thrombosis and Haemostasis; MACE; major cardiovascular event; PE, pulmonary embolism; QD, once daily; QoL, quality of life; VTE, venous thromboembolism.

Agnelli G et al. N Engl J Med. 2020;382:1599-1607 and supplementary appendix available online.

Recurrent VTE

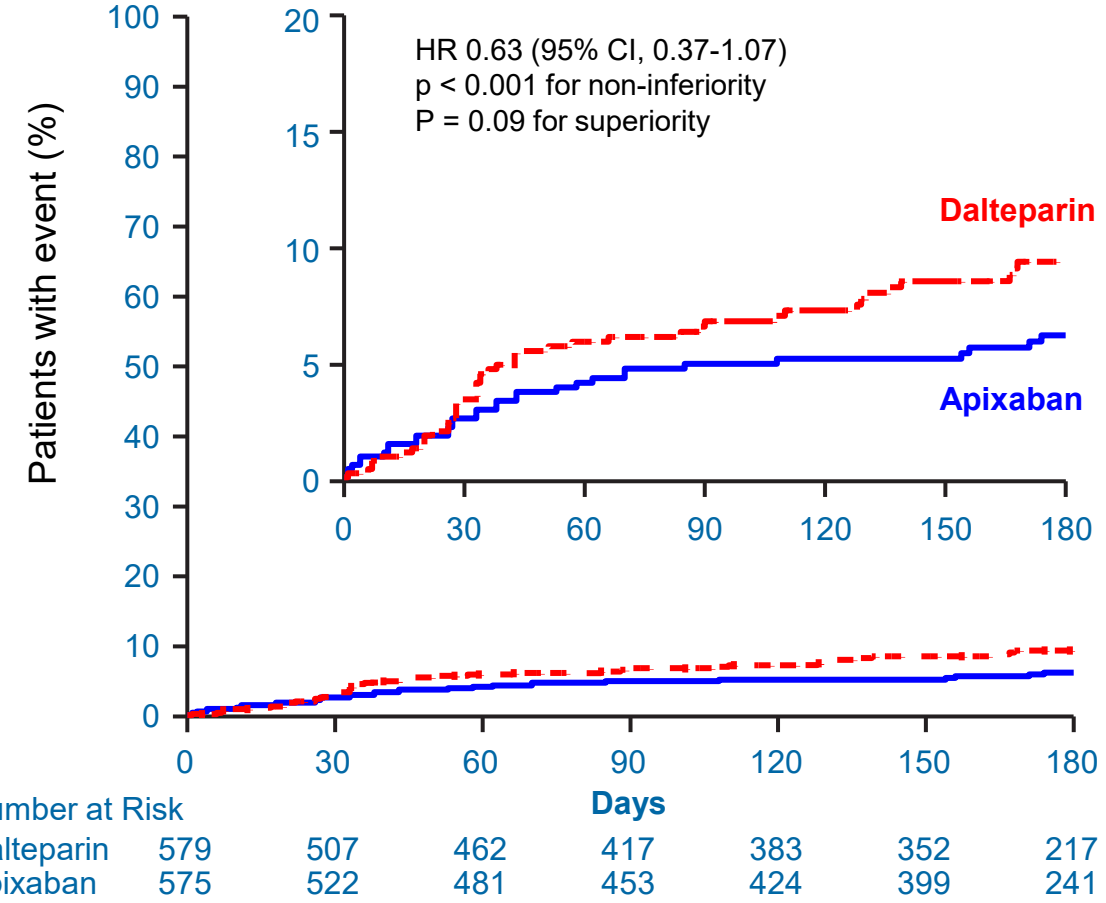


DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

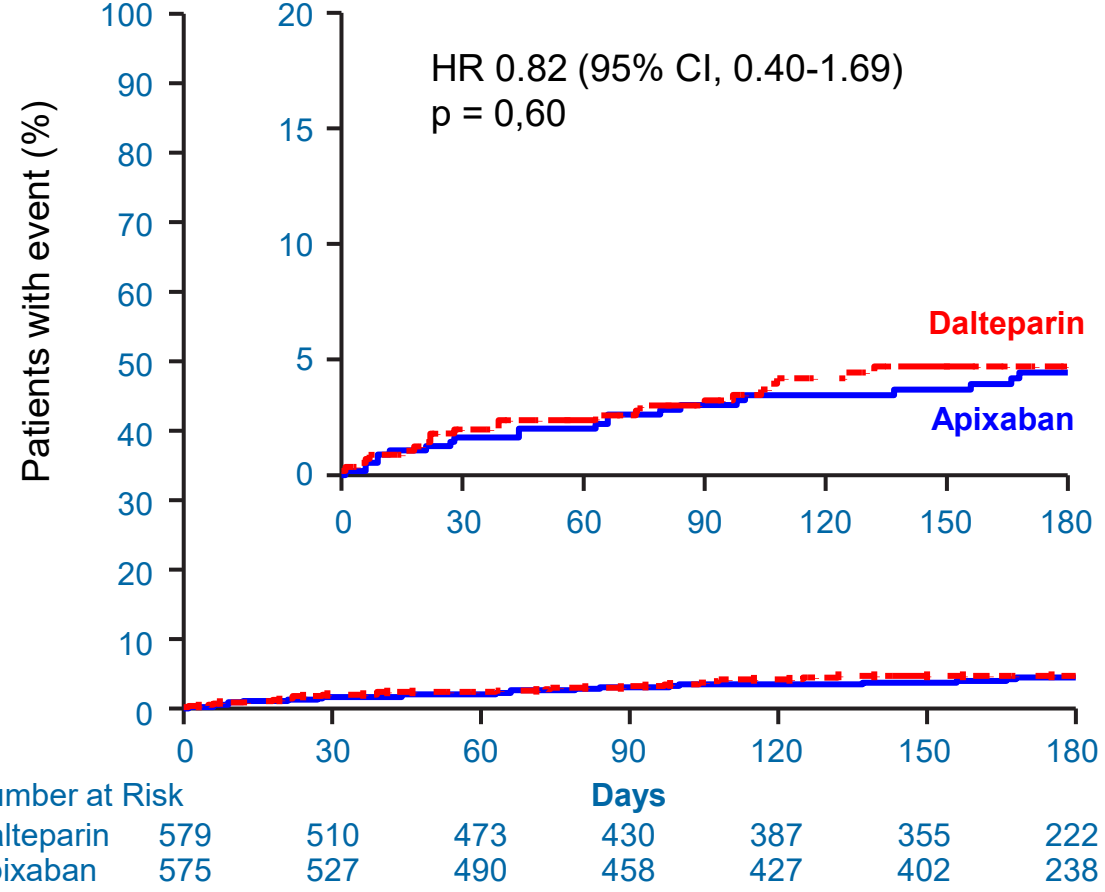
Agnelli G et al. *N Engl J Med*. 2020;382:1599-1607

Recurrent VTE and Major Bleeding

Recurrent VTE



Major Bleeding



DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Agnelli G et al. N Engl J Med. 2020;382:1599-1607

Results: Clinical Outcomes During the Trial Period*

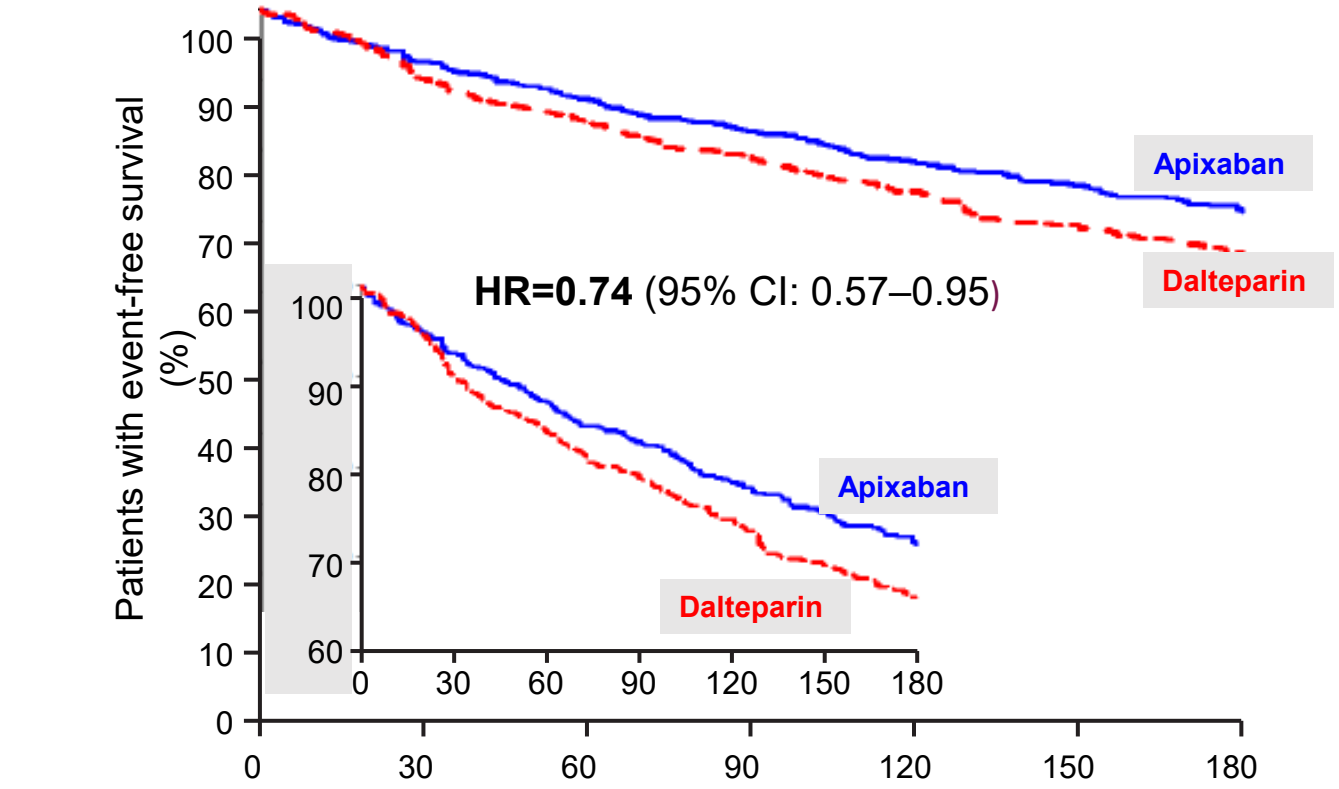
Outcome	Apixaban n = 576	Dalteparin n = 579	Hazard Ratio 95% CI	P Value
Primary efficacy outcome, n (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37 to 1.07)	< 0.001 for non-inferiority; 0.09 for superiority
Recurrent deep vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34 to 2.21)	
Recurrent pulmonary embolism	19 (3.3)	32 (5.5)	0.54 (0.29 to 1.03)	
Fatal pulmonary embolism§	4 (0.7)	3 (0.5)	1.93 (0.40 to 9.41)	
Primary safety outcome, n (%)				
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40 to 1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44 to 2.50)	
Major non-gastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21 to 2.20)	
Secondary outcomes, n (%)				
Recurrent venous thromboembolism or major bleeding	51 (8.9)	66 (11.4)	0.70 (0.45 to 1.07)	
Clinically relevant non-major bleeding	52 (9.0)	35 (6.0)	1.42 (0.88 to 2.30)	
Major or clinically relevant non-major bleeding‖	70 (12.2)	56 (9.7)	1.16 (0.77 to 1.75)	
Death from any cause (assessed up to 210 days after randomization)	135 (23.4)	153 (26.4)	0.82 (0.62 to 1.09)	
Event-free survival††	422 (73.3)	397 (68.6)	1.36 (1.05 to 1.76)	

*The overall trial period for the primary efficacy outcome was the time from randomization through 6 months.
†The primary efficacy outcome (objectively confirmed recurrent venous thromboembolism) during the 6-month trial period was also the primary outcome.
‡Two of the recurrences of venous thromboembolism in the apixaban group were upper-extremity deep vein thrombosis.
§A total of 3 patients in the apixaban group and 3 patients in the dalteparin group died from unexplained causes for which pulmonary embolism could not be ruled out.
¶One patient in the apixaban group had an event that was categorized as major bleeding since it resulted in a surgical intervention.
‖In patients who had more than one event, only the first event was counted.
††Event-free survival was defined as the absence of recurrent venous thromboembolism, major bleeding, or death.

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Agnelli G et al. N Engl J Med. 2020;382:1599-1607

Event (recurrent VTE, major bleeding or death) Free Survival



No at Risk							
Apixaban	575	515	478	446	416	392	234
Dalteparin	579	497	454	412	374	343	213

Event-free survival was defined as the absence of recurrent venous thromboembolism, major bleeding or death.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Agnelli G et al. N Engl J Med. 2020;382:1599-1607 and supplementary appendix available online

Sites of Major Bleeding

Primary Safety Outcome	Apixaban n = 576	Dalteparin n = 579
Major bleeding, n (%)	22 (3.8%)	23 (4.0%)
Fatal†	0	2
Abdominal	1	0
Intracranial	0	2
Intraspinal	0	1
Pericardial	1	0
Intra-articular	0	1
Retroperitoneal	0	1
Cutaneous	1	1
Genito-urinary	4	1
Lung	1	1
Muscle	0	2
Upper airways	1	2
Gastrointestinal	11	10
Upper	5	6
Lower	6	4
Undetermined site	2	2

†The site of fatal bleeding was intracranial in 1 patient and retroperitoneal in 1 patient.

CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Sites of Clinically Relevant Non-Major Bleeding

Clinically Relevant Non-Major Bleeding	Apixaban n = 576	Dalteparin n = 579
CRNM bleeding, n (%)	52 (9.0%)	34 (5.9%)
Abdominal	1	1
Intramuscular	1	1
Cutaneous	6	4
Genito-urinary	19	10
Hematuria	**15**	7
Vaginal bleeding	4	3
Lung	3	2
Upper airways	**12**	3
Gastrointestinal	11	15
Upper	2	8
Lower	9	7
Undetermined site	1	0

CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Agnelli G et al. N Engl J Med. 2020;382:1599-1607 supplementary appendix available online.

Authors' Conclusions

- The favorable safety profile found for apixaban is in agreement with the results of previous randomized trials of this drug with respect to the treatment of atrial fibrillation & VTE in the general population
- Taken together, these findings may expand the proportion of patients with both cancer and VTE who would be eligible for treatment with apixaban, including patients with gastrointestinal cancer
- Oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of cancer-associated VTE without an increased risk of major bleeding

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

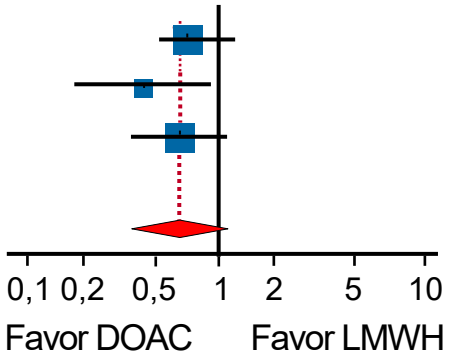
Agnelli G et al. N Engl J Med. 2020;382:1599-1607.

DOACs for cancer-associated venous thromboembolism: a systematic review and meta-analysis

Recurrent VTE

Recurrent VTE with DOAC and LMWH

Study	DOAC	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	Risk ratio	RR	95%-CI	Weight
Hokusai VTE Cancer	Edoxaban	522	34	524	46		0.74	[0.48; 1.14]	45.4%
SELECT-D	Rivaroxaban	203	7	203	17		0.41	[0.17; 0.97]	11.2%
Caravaggio	Apixaban	576	32	579	46		0.70	[0.45; 1.08]	43.4%
		1301	**73**	**1306**	**109**		**0,68**	**[0.39; 1.17]**	**100.0%**



Random effects model

Heterogeneity: $I^2 = 0\%$ $\tau^2 = 0.0001$, $p = 0.48$

- Lower risk of recurrent VTE with DOAC vs. LMWH

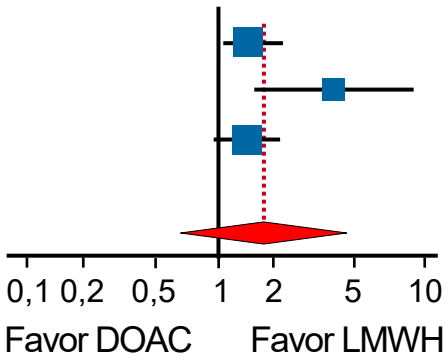
CI, confidence interval;DOAC, direct oral anticoagulant; LMWH, low molecular weight heaprin; RCT, randomized controlled trails; RR, relative risk; VTE, venous thromboembolism

Mulder FI et al. Blood 2020;136(12):1433–41.

DOACs for cancer-associated venous thromboembolism: a systematic review and meta-analysis

Clinically relevant non-major bleeding with DOAC and LMWH1

Study	DOAC	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	Edoxaban	522	64	524	43	1,49	[1,04; 2,16]	43,2%
SELECT-D	Rivaroxaban	203	25	203	7	3,57	[1,58; 8,07]	17,5%
Caravaggio	Apixaban	576	52	579	35	1,49	[0,99; 2,26]	39,3%
		1301	**124**	**1306**	**145**	**1,74**	**[0,64; 4,77]**	**100,0%**



Random effects model

Heterogeneity: I^2 = 49%, τ^2 = 0,0589, p = 0,14

- Increased risk of clinically relevant non-severe bleeding under DOAC vs. LMWH

CI, confidence interval;DOAC, direct oral anticoagulant; LMWH, low molecular weight heaprin; RCT, randomized controlled trails; RR, relative risk; VTE, venous thromboembolism

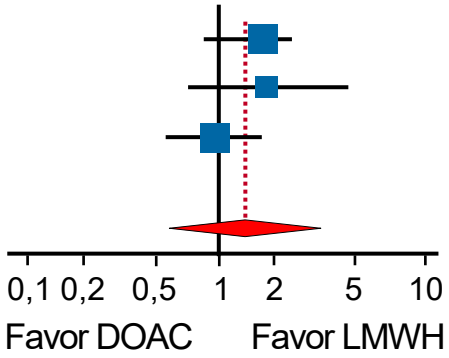
Mulder FI et al. Blood 2020;136(12):1433–41.

DOACs for cancer-associated venous thromboembolism: a systematic review and meta-analysis

Major bleeding

Major bleeding

Study	DOAC	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	Risk ratio	RR	95%-CI	Weight
Hokusai VTE Cancer	Edoxaban	522	29	524	17		1,71	[0,95; 3,08]	40,3%
SELECT-D	Rivaroxaban	203	11	203	6		1,63	[0,69; 4,86]	18,0%
Caravaggio	Apixaban	576	22	579	23		0,96	[0,54; 1,71]	41,7%
		1301	**62**	**1306**	**46**		**1,36**	**[0,55; 3,35]**	**100,0%**



Random effects model

Heterogeneity: I^2 = 15%, τ^2 = 0,0379, p = 0,31

- Increased risk of major bleeding under DOAC vs. LMWH?

CI, confidence interval;DOAC, direct oral anticoagulant; LMWH, low molecular weight heaprin; RCT, randomized controlled trails; RR, relative risk; VTE, venous thromboembolism

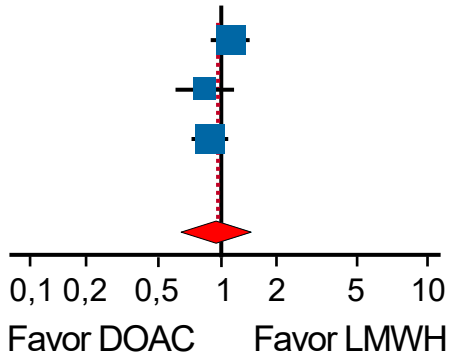
Mulder FI et al. Blood 2020;136(12):1433–41.

DOACs for cancer-associated venous thromboembolism: a systematic review and meta-analysis

All-cause mortality with DOAC and LMWH1

All-cause mortality

Study	DOAC	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	Risk ratio	RR	95%-CI	Weight
Hokusai VTE Cancer	Edoxaban	522	140	524	127		1,11	[0,90; 1,36]	39,2%
SELECT-D	Rivaroxaban	203	48	203	56		0,86	[0,61; 1,20]	20,1%
Caravaggio	Apixaban	576	135	579	153		0,89	[0,73; 1,08]	40,7%
		1301	**323**	**1306**	**336**		**0,96**	**[0,68; 1,36]**	**100,0%**



Random effects model

Heterogeneity: I^2 = 30%, τ^2 = 0,0074, p = 0,24

- **Comparable** risk of all-cause mortality with DOAC vs. LMWH

CI, confidence interval;DOAC, direct oral anticoagulant; LMWH, low molecular weight heaprin; RCT, randomized controlled trails; RR, relative risk; VTE, venous thromboembolism

Mulder FI et al. Blood 2020;136(12):1433–41.