VTE* und Tumorerkrankungen

*Venöse Thromboembolie

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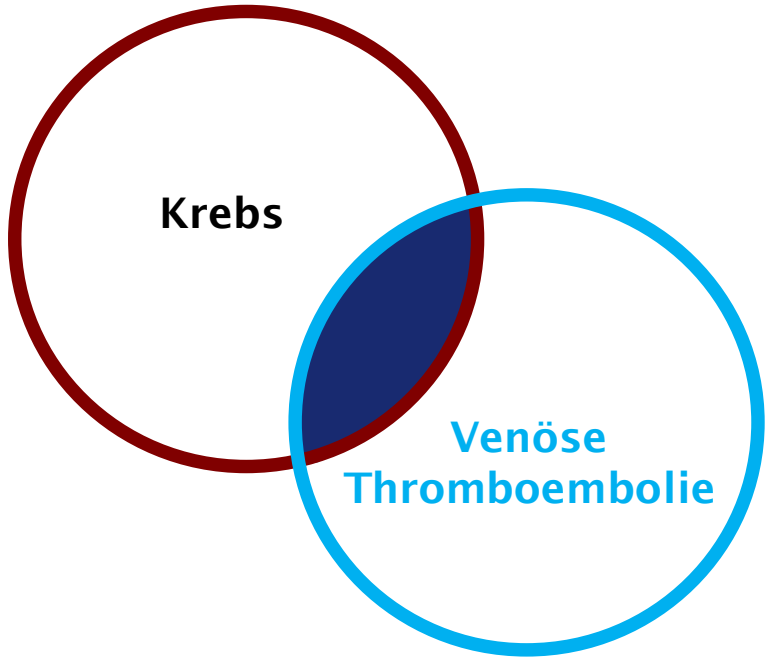
Tumor und Thrombose - Epidemiologie

- ~20% aller VTEs sind mit einer Tumorerkrankung assoziiert
  - Tumorerkrankungen sind ein starker VTE-Risikofaktor

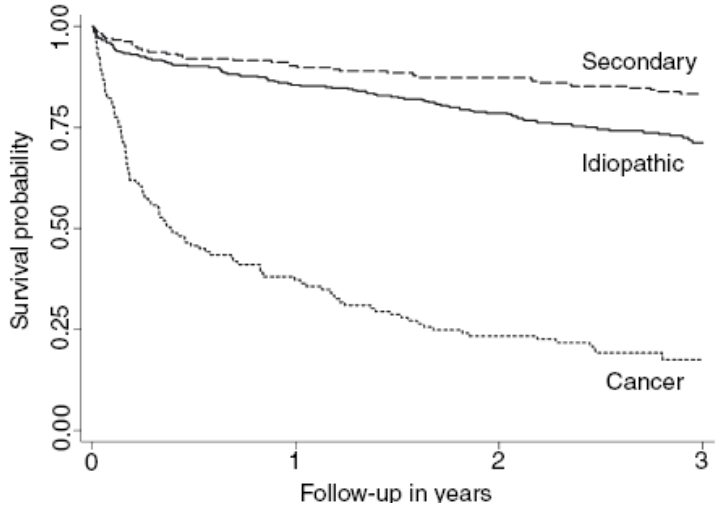
- 1 bis 30% der Patienten mit Tumoren erleiden eine VTE
  - Hohe Rate an “asymptomatischen” (inzidentellen) Pulmonalembolien (PE)



Ay C, Pabinger I & Cohen AT. Thromb Haemost. 2017;117(2):219-230.

Tumor und Thrombose - Folgen

- VTE erhöht Morbidität und Mortalität der Tumorpatienten
  - VTE eine führende Todesursache bei Tumorpatienten
  - Mortalitätsrisiko bei Patienten mit VTE 3.7-fach [95% CI: 1.3-14.4] erhöht
  - „Case-fatality rate“ nach 30 Tagen: ~25%

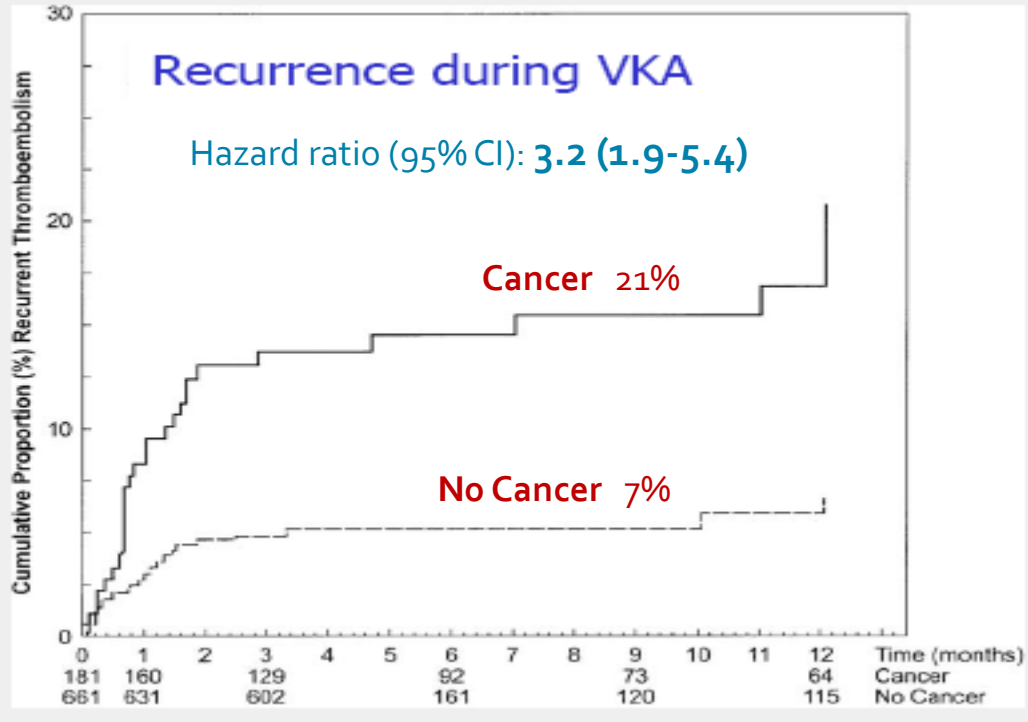


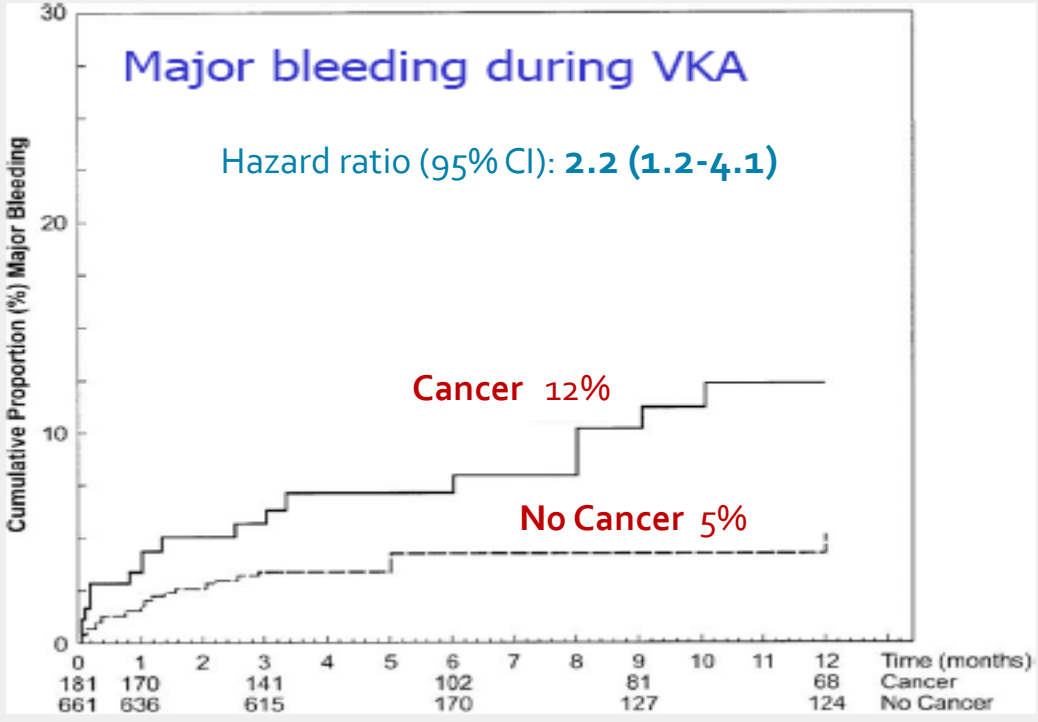
Khorana AA. J Thromb Haemost. 2007;5(3):632-4; Naess IA et al, J Thromb Haemost 2007;5(4):692-9; Chew HK. Arch Intern Med 2006;166(4):458-64

Behandlung der VTE bei Tumorpatienten

Oral Anticoagulation with Vitamin K Antagonists (Warfarin) for Treatment of VTE

- High risk of recurrence of VTE and bleeding during oral anticoagulation in patients with cancer

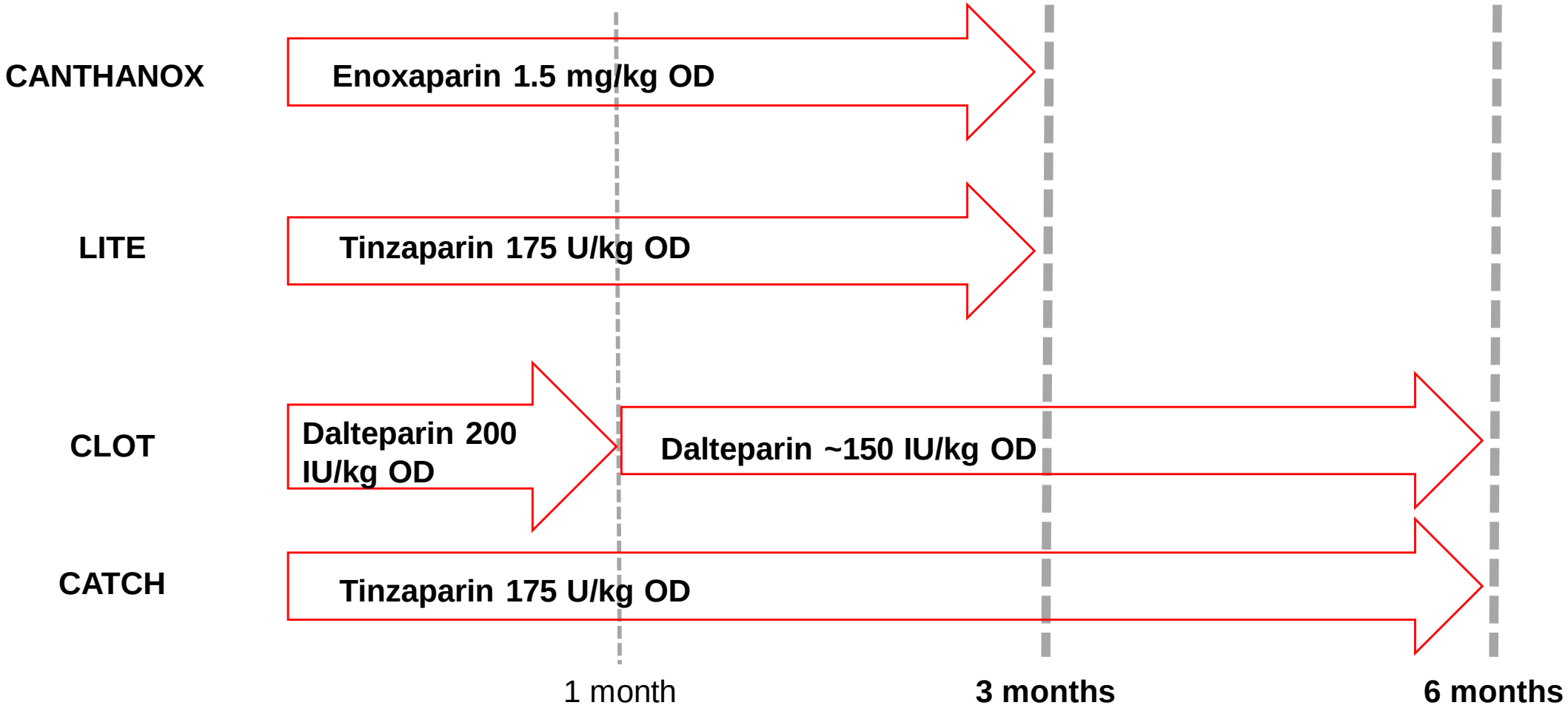




Prandoni P. Blood 2002; 100: 3484-8

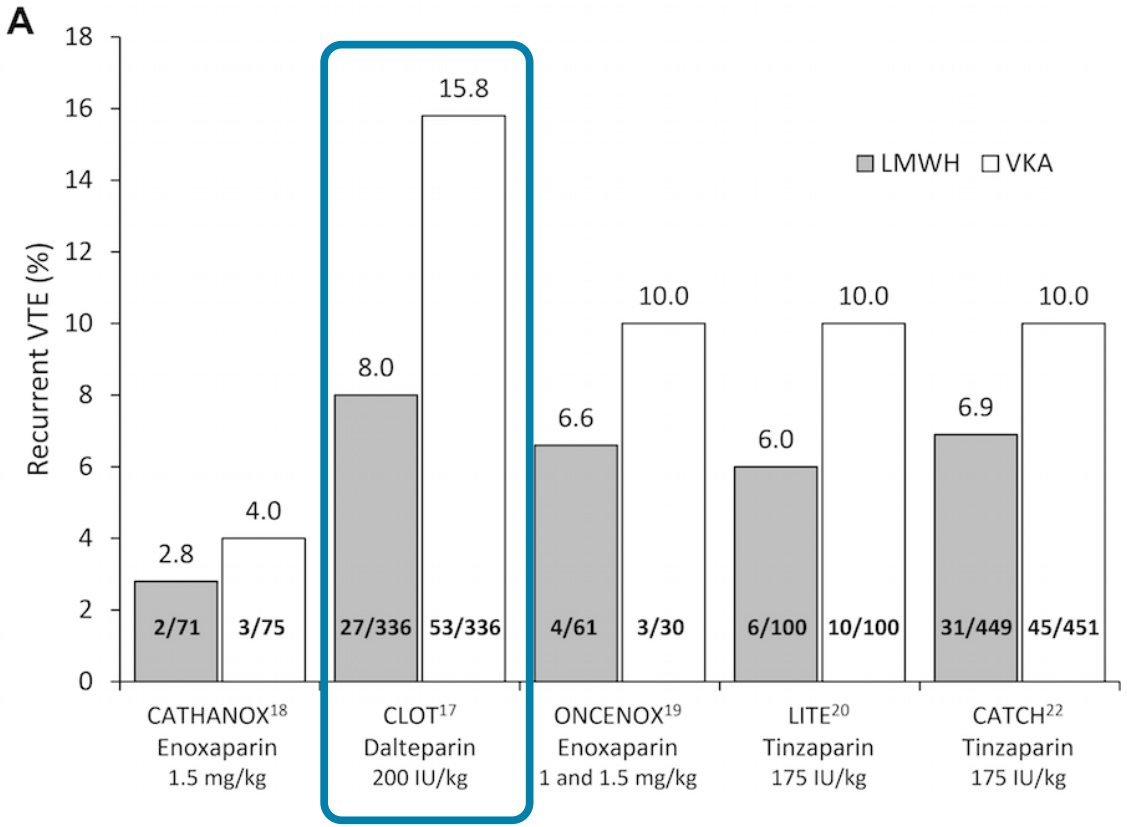
Treatment of cancer-associated VTE (CAT)

Open-label, randomized controlled trials



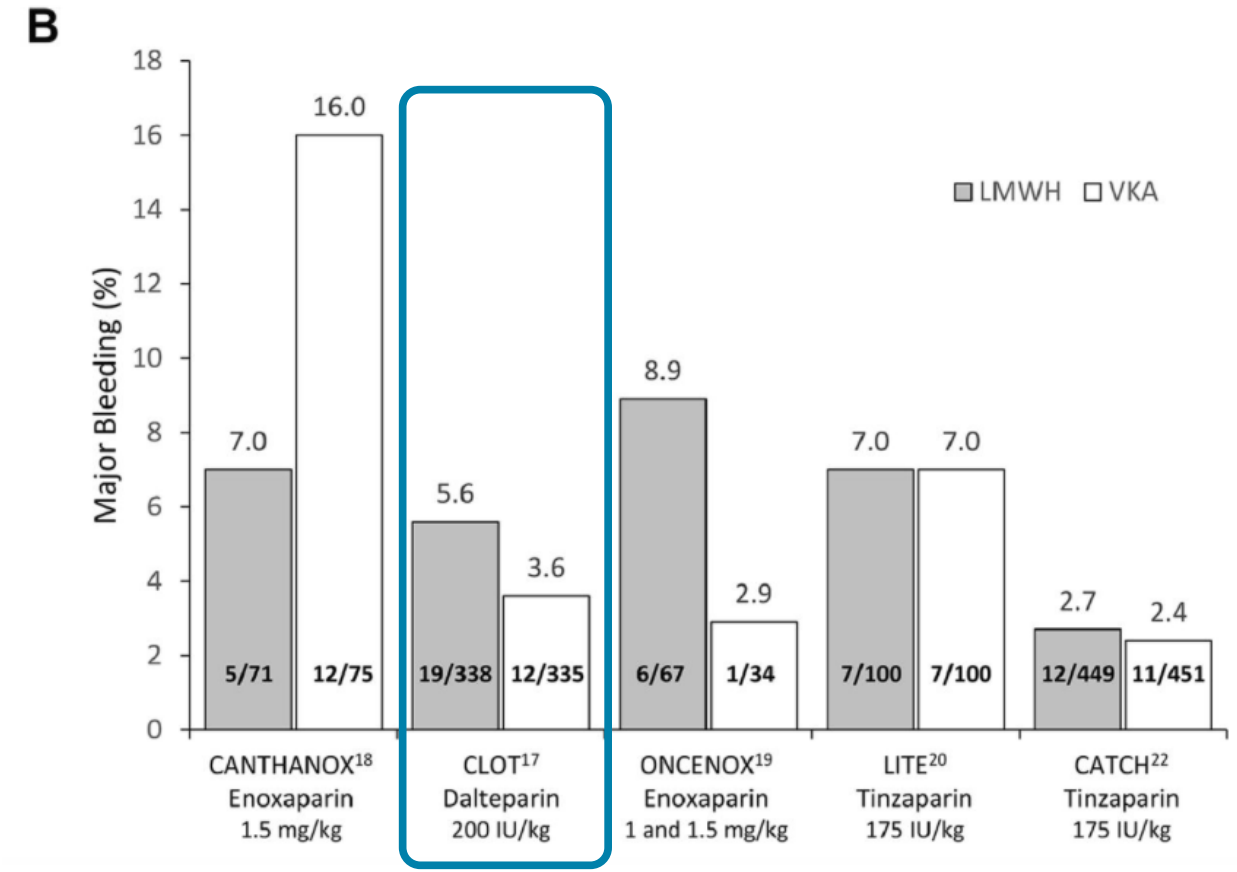
Meyer et al. Arch Intern Med 2002; 162: 1729–35.; Hull et al. Am J Med 2006; 119: 1062–72.; Lee et al. N Engl J Med 2003; 349: 146–53.; Lee et al. JAMA. 2015;314:677-86.

Incidence of **recurrent VTE** in randomized, clinical trials of LMWH vs. VKA for the treatment and secondary prevention of VTE in cancer patients



Ay C, Kamphuisen PW & Agnelli G. ESMO Open. 2017 Jun 8;2(2):e000188.

Incidence of **major bleeding** in randomized, clinical trials of LMWH vs. VKA for the treatment and secondary prevention of VTE in cancer patients



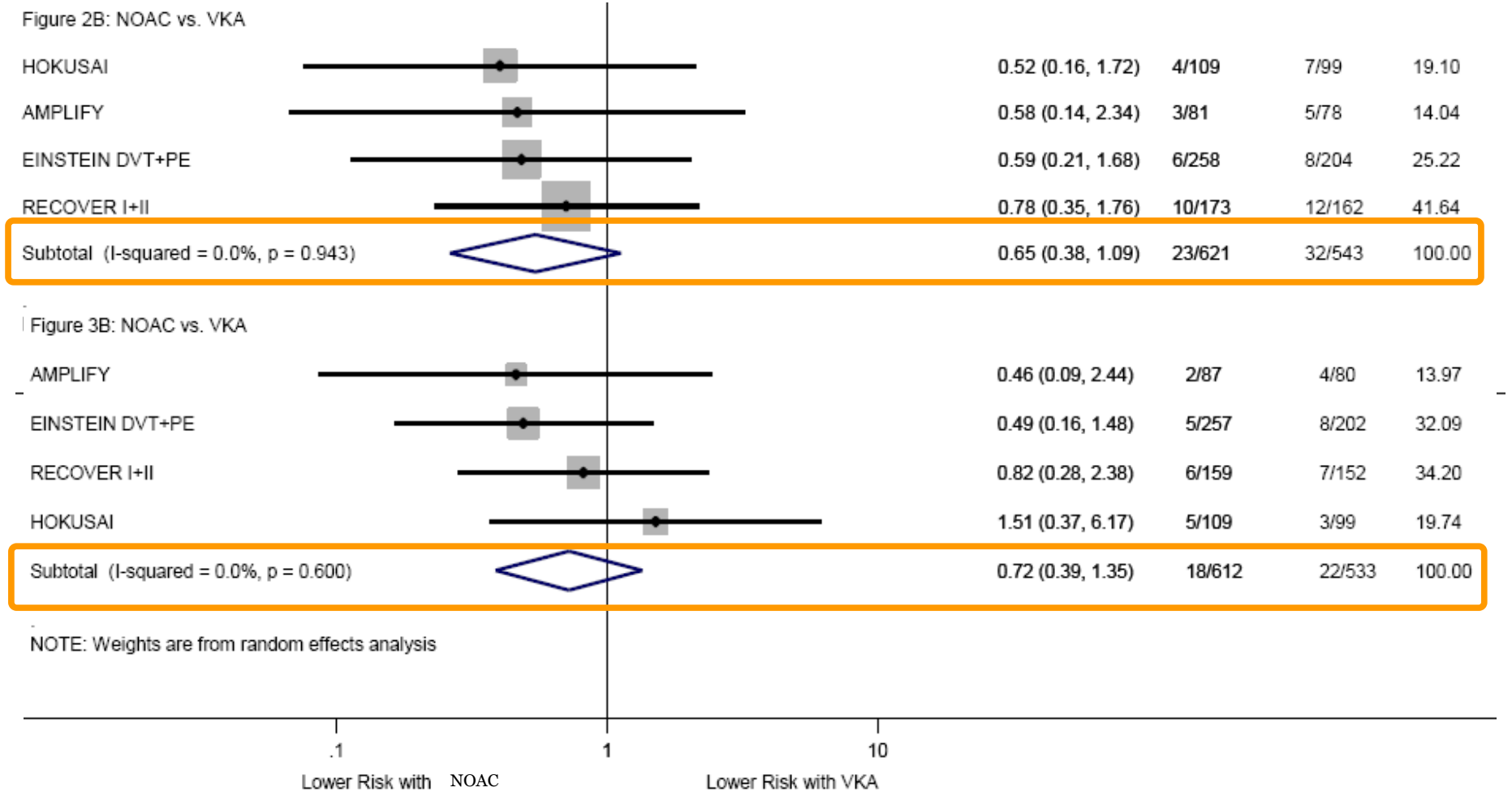
Ay C, Kamphuisen PW & Agnelli G. ESMO Open. 2017 Jun 8;2(2):e000188.

DOAC in the treatment of cancer-associated VTE (CAT)

- In phase III clinical trials **dabigatran**, **rivaroxaban, apixaban** and **edoxaban** have shown non-inferiority to standard treatment (vitamin K antagonist: warfarin) in treatment of DVT and PE
  - Cancer patients comprised only ~4% to 9% of patients in these studies

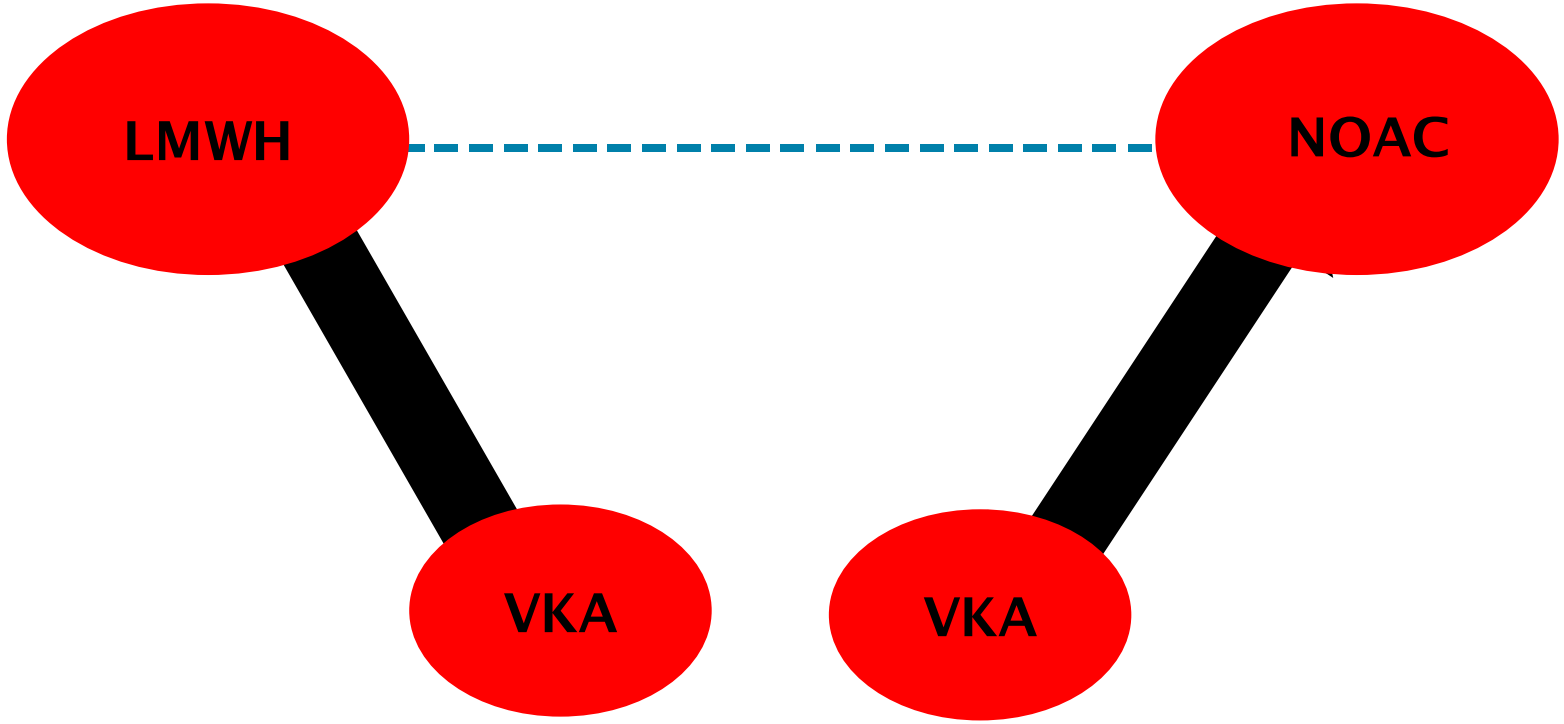
Schulman et al *NEJM* 2009, Bauersachs et al *NEJM* 2010, Buller et al *NEJM* 2012, Agnelli et al. NEJM 2013, Büller et al. NEJM 2013

What role do NOACs/DOACs play in treating cancer-associated VTE?
Meta-Analysis (subgroups): Efficacy and safety of NOACs vs VKA



Posch and Ay et al. Thromb Res. 2015;136(3):582-9.

Studien zur Behandlung der VTE bei Tumorerkrankungen



Direkte Evidenz aus „Head-to-Head“ Studien

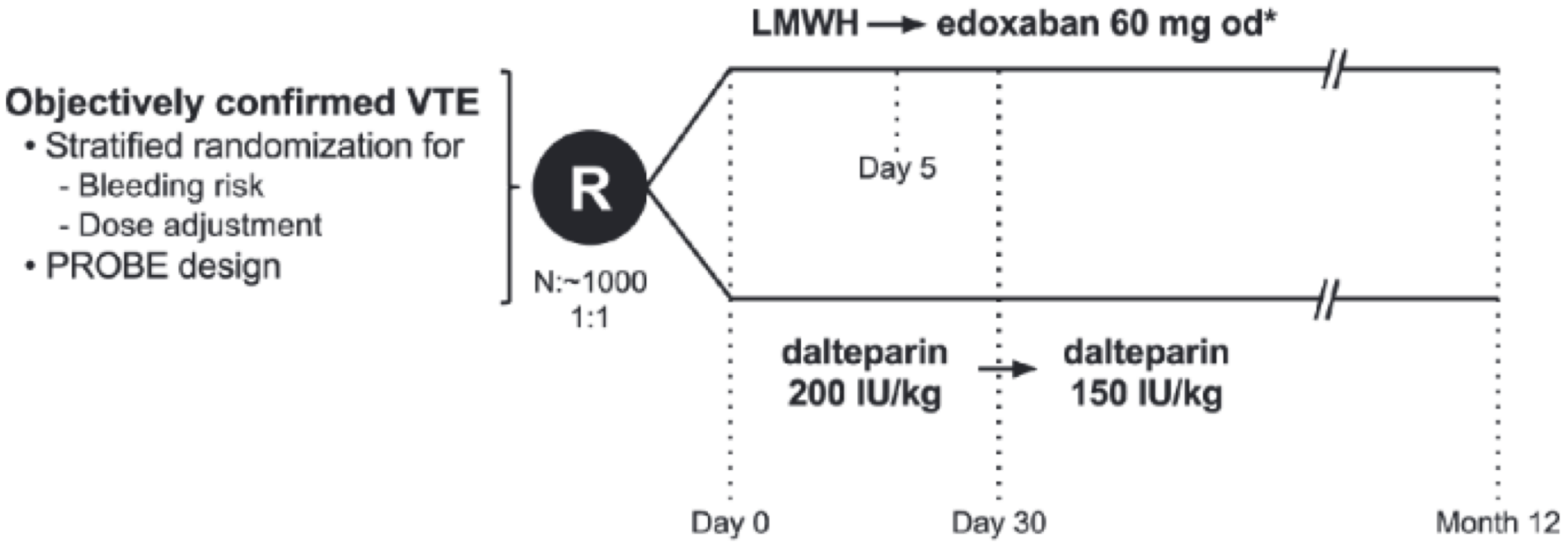
Kein direkter Vergleich bisher

Guidelines until 2017 (selection)

Class	Acute Treatment	Long-Term Treatment	Duration of Extended Treatment
ACCP	For acute and long-term treatment (first 3 months), LMWH is preferred over VKA (Grade 2B) or DOACs (Grade 2C) in cancer patients In cancer patients not treated with LMWH, ACCP states no preference for VKAs or DOACs and no DOAC is preferred over the others		Extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy Continued use of treatment should be reassessed at periodic intervals
ASCO	LMWH for the initial 5–10 days of anticoagulation for cancer patients with newly diagnosed VTE (strong recommendation)	LMWH (VKA is alternative when LMWH not available) (strong recommendation)	At least 6 months Select patients with active cancer (eg, metastatic disease or receiving chemotherapy) can continue beyond 6 months
International Clinical Practice Guidelines	LMWH (Grade 1B)	LMWH for at least 3 months (Grade 1A)	After 3–6 months, termination or continuation of anticoagulation should be based on individual evaluation of the benefit-risk ratio, tolerability, patient preference, and cancer activity
NCCN	LMWH (preferred)	LMWH (preferred)	Continue for ≥3 months or for as long as there is active cancer or persistent risk factors

HOKUSAI VTE Cancer Studie

- LMWH/**Edoxaban** vs. LMWH (CLOT Dosierungschema)



*Edoxaban 30 mg 1x täglich, wenn CrCL 30–50 mL/min, Gwicht ≤60 kg, und/oder gleichzeitig P-gp Inhibitor im Einsatz.

van Es N et al. Thromb Haemost. 2015;114(6):1268-76.

The NEW ENGLAND JOURNAL of MEDICINE

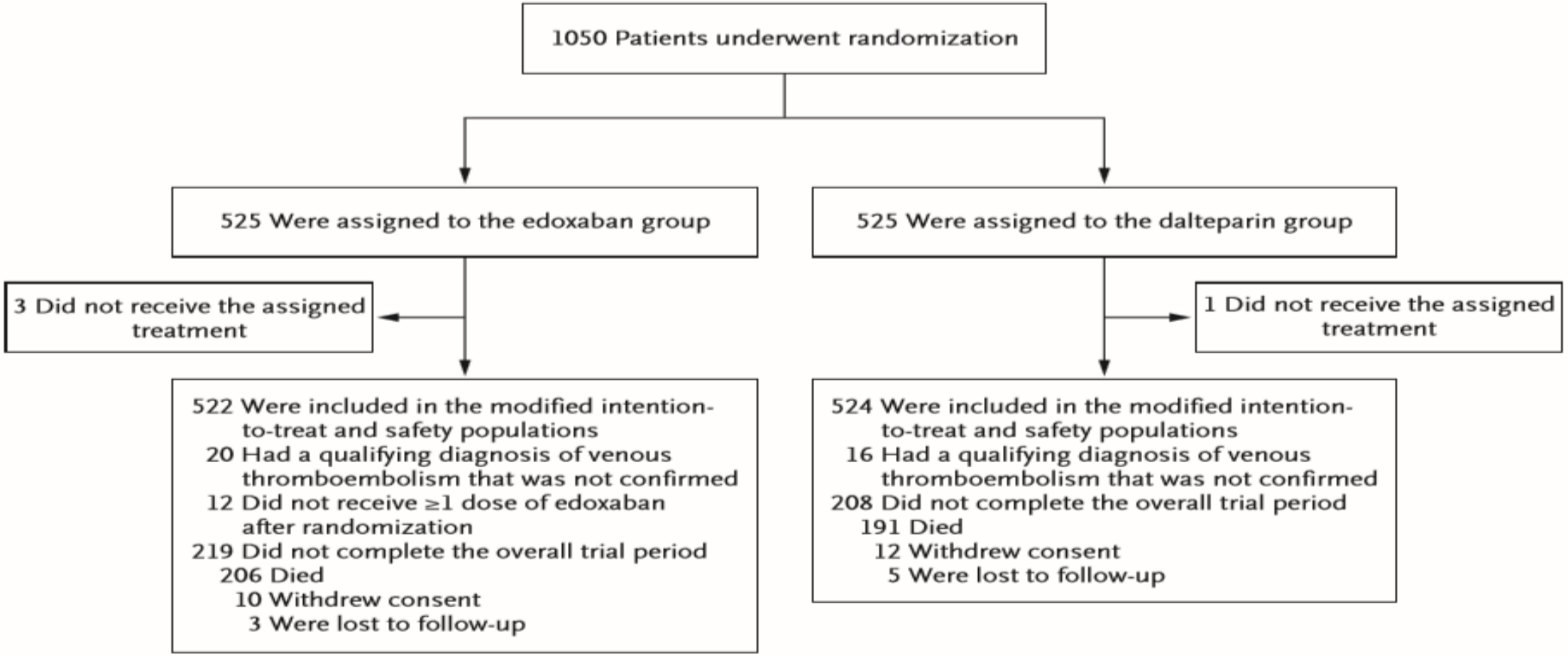
ORIGINAL ARTICLE

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*

N Engl J Med. 2017 Dec 12. doi: 10.1056/NEJMoa1711948.

Offene randomisierte Studie mit verblindeter Adjudizierung der Ereignisse



Raskob GE et al. N Engl J Med. 2017 Dec 12. doi: 10.1056/NEJMoa1711948.

HOKUSAI VTE Cancer - Patient characteristics

Characteristic	Edoxaban (N=522)	Dalteparin (N=524)
Age — yr	64.3±11.0	63.7±11.7
Male sex — no. (%)	277 (53.1)	263 (50.2)
Weight		
Mean — kg	78.8±17.9	79.1±18.1
≤60 kg — no. (%)	83 (15.9)	78 (14.9)
Creatinine clearance of 30–50 ml/min — no. (%)	38 (7.3)	34 (6.5)
Platelet count of 50,000–100,000 per μl — no. (%)	32 (6.1)	23 (4.4)
Met criteria to receive lower dose of edoxaban — no. (%)†	122 (23.4)	117 (22.3)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without deep-vein thrombosis	328 (62.8)	329 (62.8)
Deep-vein thrombosis only	194 (37.2)	195 (37.2)
Symptomatic deep-vein thrombosis or pulmonary embolism	355 (68.0)	351 (67.0)
Incidental deep-vein thrombosis or pulmonary embolism‡	167 (32.0)	173 (33.0)
Active cancer — no. (%)	513 (98.3)	511 (97.5)
Metastatic disease — no. (%)	274 (52.5)	280 (53.4)
Recurrent cancer — no. (%)	163 (31.2)	152 (29.0)
Cancer treatment within previous 4 wk — no. (%)§	374 (71.6)	383 (73.1)

Raskob GE et al. N Engl J Med. 2017 Dec 12. doi: 10.1056/NEJMoa1711948.

HOKUSAI VTE Cancer - Study outcomes

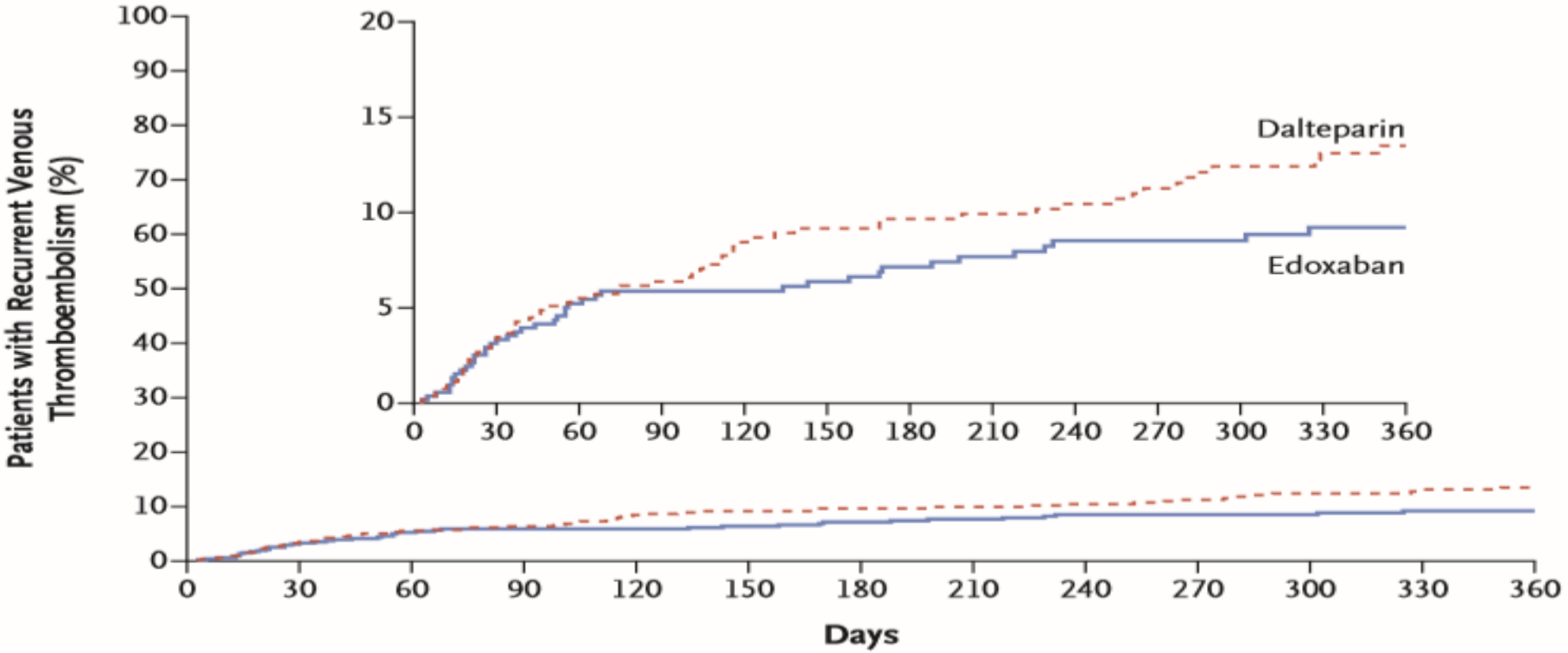
Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority
Secondary outcomes				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%)†	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%)‡				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)	
Event-free survival — no. (%)‖	287 (55.0)	296 (56.5)	0.93 (0.77–1.11)	

[a]Category 1 = bleeding events that were not considered to be a clinical emergency; category 2 = bleeding events that could not be classified in any of the other categories because they led to some treatment but were not considered to be a clinical emergency; category 3 = bleeding events that were considered to be a clinical emergency, such as bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms; category 4 = bleeding events that led to death before or almost immediately after the patient entered the hospital.

Most major bleedings (edoxaban) events were Gastrointestinal Bleedings

Raskob GE et al. N Engl J Med. 2017 Dec 12. doi: 10.1056/NEJMoa1711948.

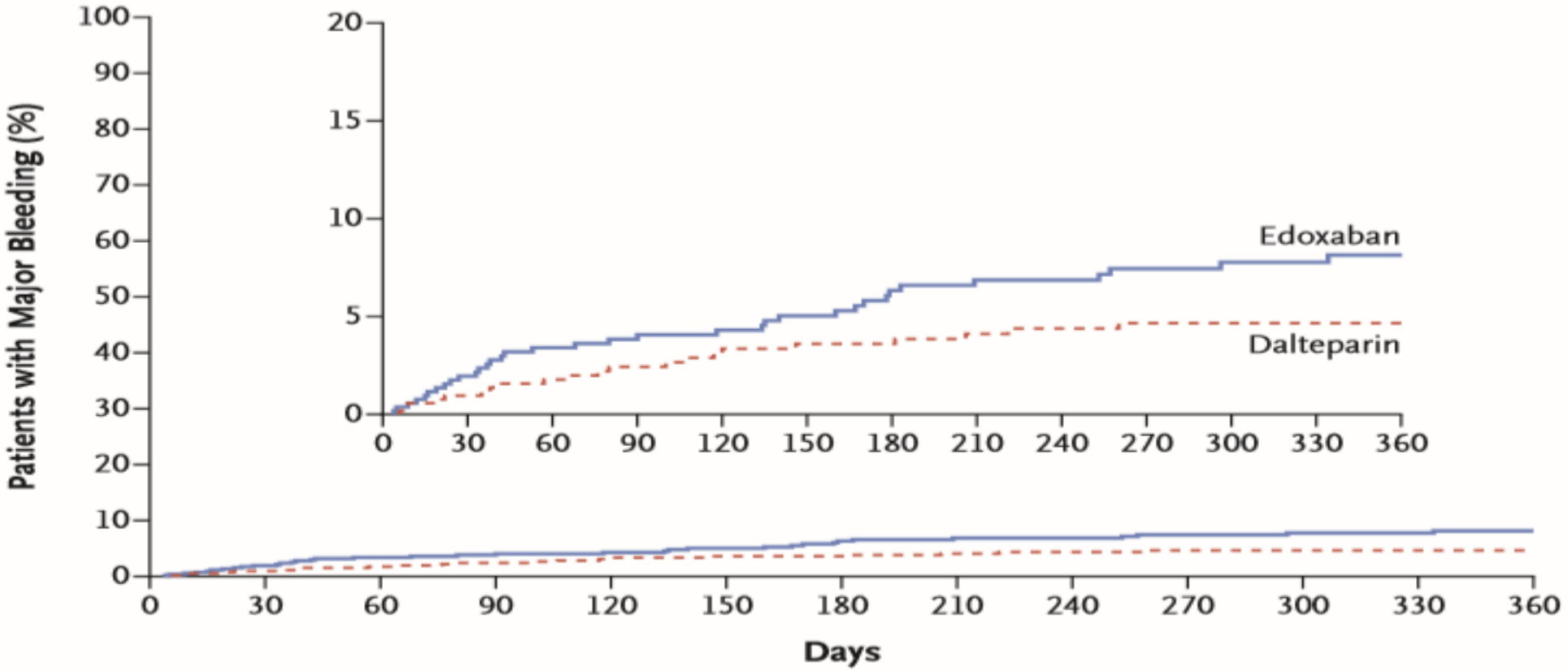
HOKUSAI VTE Cancer - Probability of recurrent VTE



No. at Risk													
Edoxaban	522	480	437	415	395	370	356	340	320	307	281	245	168
Dalteparin	524	488	452	423	389	370	358	348	333	321	282	246	174

Raskob GE et al. N Engl J Med. 2017 Dec 12. doi: 10.1056/NEJMoa1711948.

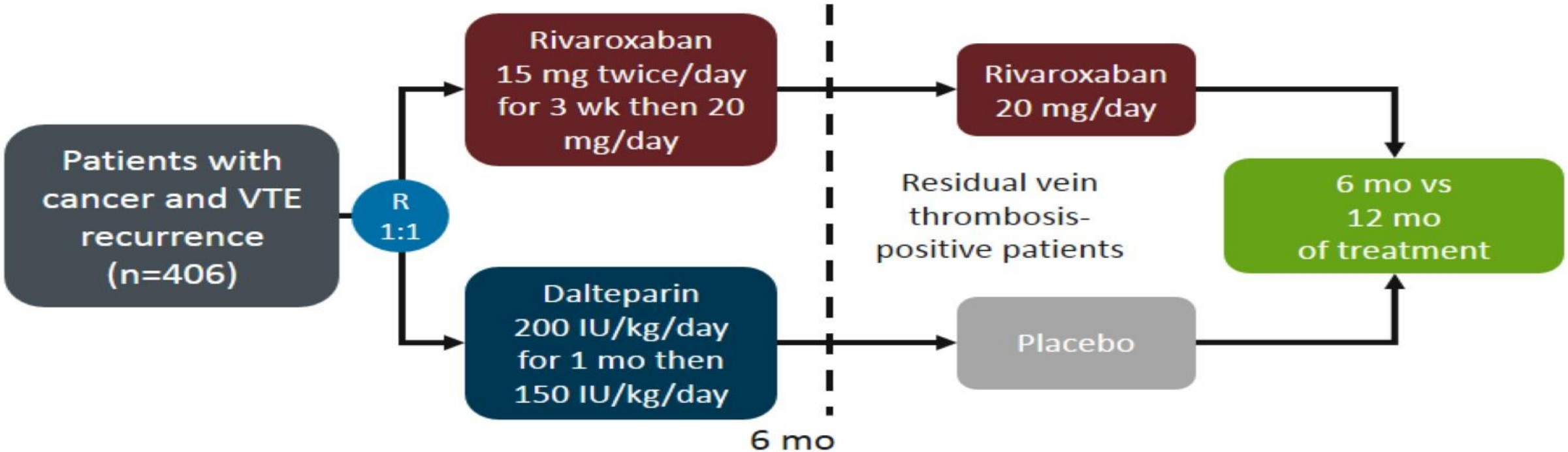
HOKUSAI VTE Cancer - Probability of major bleeding



No. at Risk													
Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

Raskob GE et al. N Engl J Med. 2017 Dec 12. doi: 10.1056/NEJMoa1711948.

SELECT-D Trial: Design

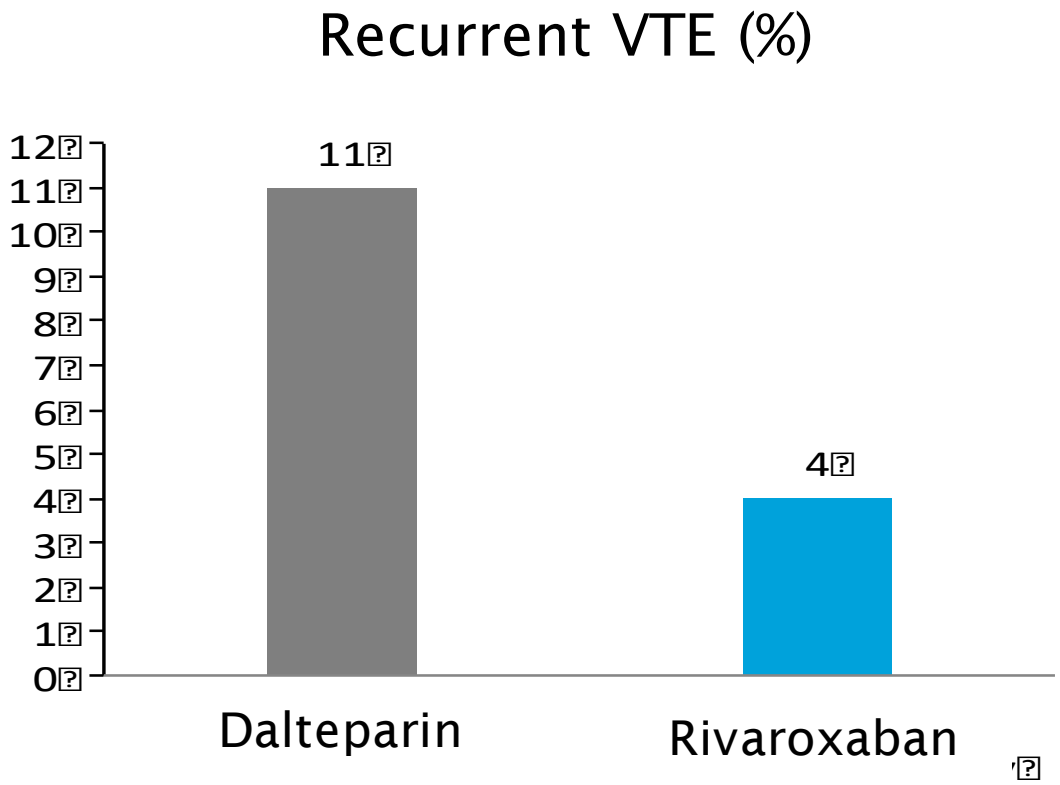


- Primary outcome: recurrent VTE

Young A, et al. *Thromb Res.* 2016;140:S172-S173.

Young A et al. ASH 2017; Abstract 625

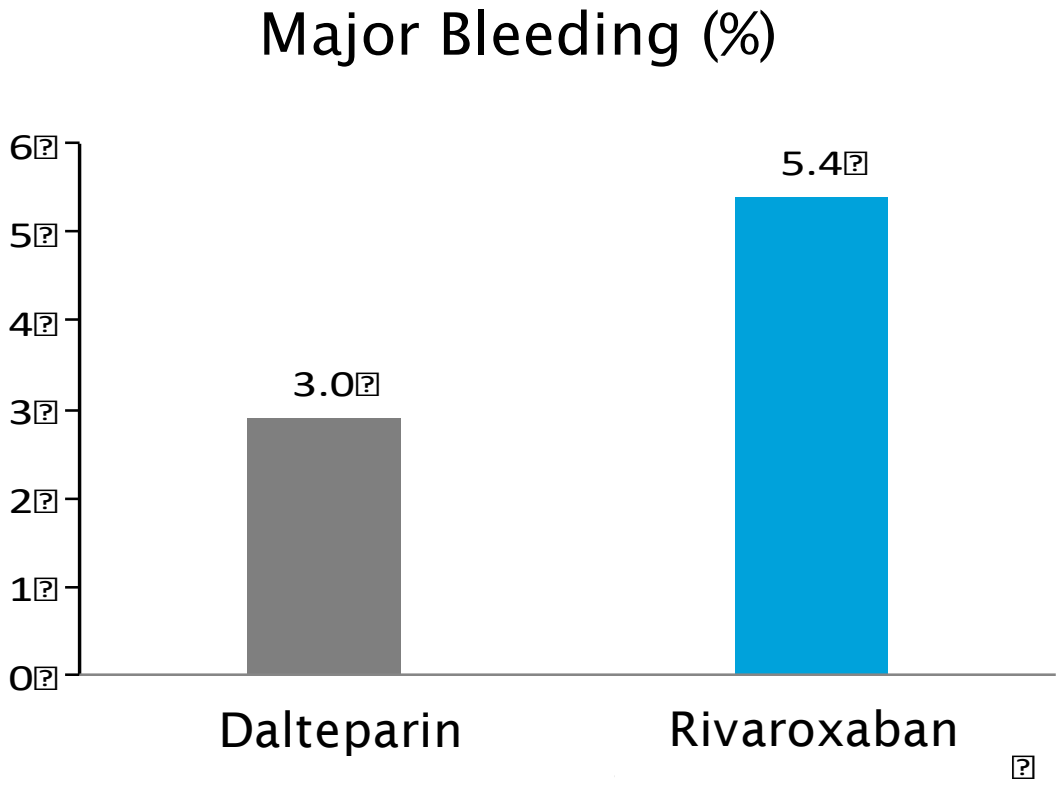
SELECT-D



- 54% of patients completed 6 months of trial treatment
  - 52% on dalteparin
  - 55% on rivaroxaban

Young A et al. ASH 2017; Abstract 625

SELECT-D (n=406)



- Most Major Bleeding events were Gastrointestinal Bleeding
- No Central Nervous System Bleeding was observed.

Young A et al. ASH 2017; Abstract 625

Zusammenfassung

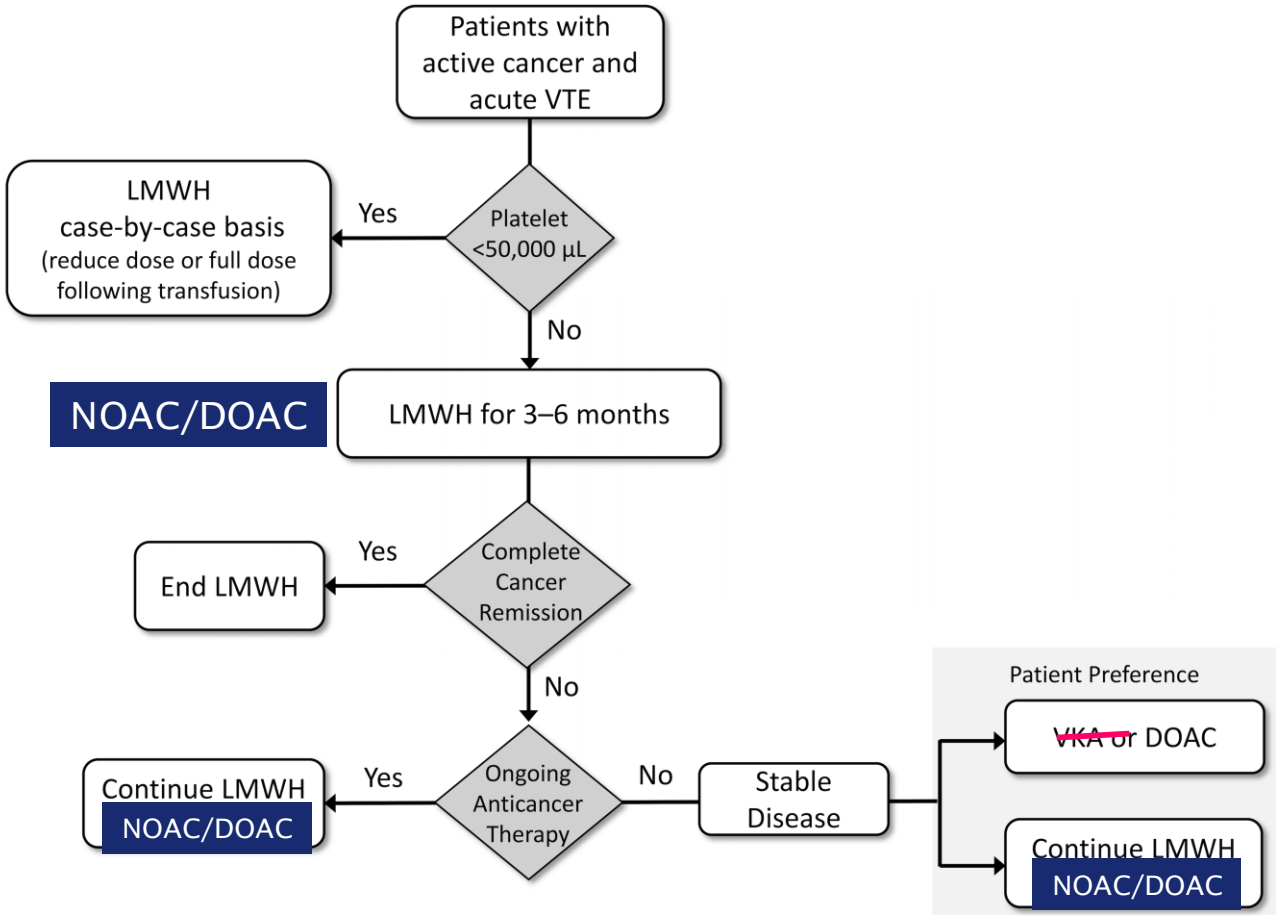
- Tumor-assoziierte VTE ist häufig

- Therapeutisches Management herausfordernd

- Therapie der Tumor-assoziierten VTE im Wandel
  - Monotherapie mit niedermolekularen Heparinen (LMWH) war bisher “standard-of-care” für die Behandlung
  - Neue Daten für DOAK/NOAK für die Therapie der Tumor-assoziierten VTE
    - Effektive Therapie (weniger VTE-Rezidive)
    - Höheres Blutungsrisiko (GI-Blutungen) – keine tödlichen Blutungen

Vielen Dank für Ihre Aufmerksamkeit!

Treatment and secondary prevention strategy for VTE in patients with active cancer based on the treatment guidelines for cancer-associated VTE



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