Management of Cancer-Associated Venous Thromboembolism (VTE)

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Updates in anticoagulation management in AF and VTE

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Disclosures

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Educational aims

- Clinical practice guidelines on anticoagulation for VTE treatment
- Association between VTE and cancer
- Efficacy and safety of vitamin K antagonists and parenteral anticoagulants in cancer
- Clinical benefits and caveats for DOACs in patients with cancer
- Evolution of guideline recommendations 2019-2022

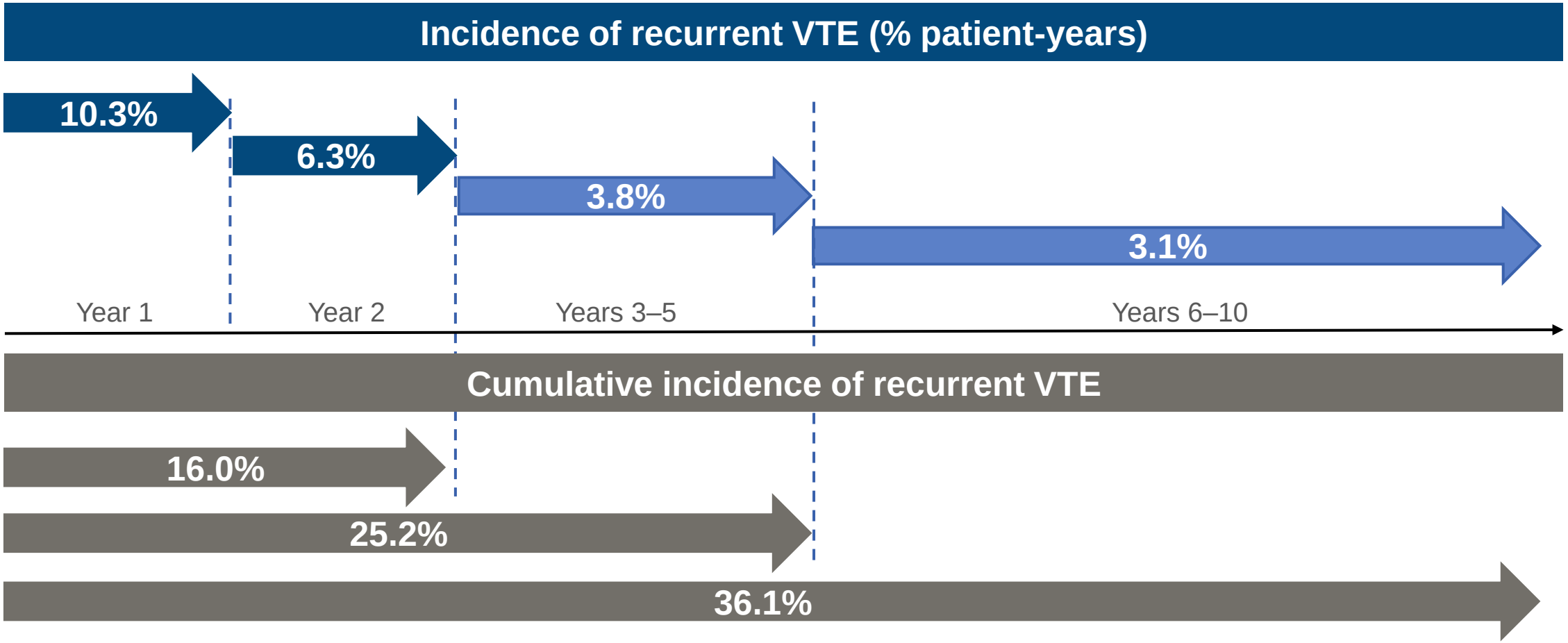
2019 ESC Guidelines: Anticoagulation for acute PE

Recommendation	Class	Level of evidence
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a **NOAC is recommended** in preference to a VKA.	I	A
NOACs are not recommended in patients with severe renal impairment, during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome.	III	C

Konstantinides SV *et al*. *Eur Heart J* 2019: doi:10.1093/eurheartj/ehz405

Risk of VTE recurrence after discontinuation of treatment

Meta-analysis of 18 studies, 7515 patients



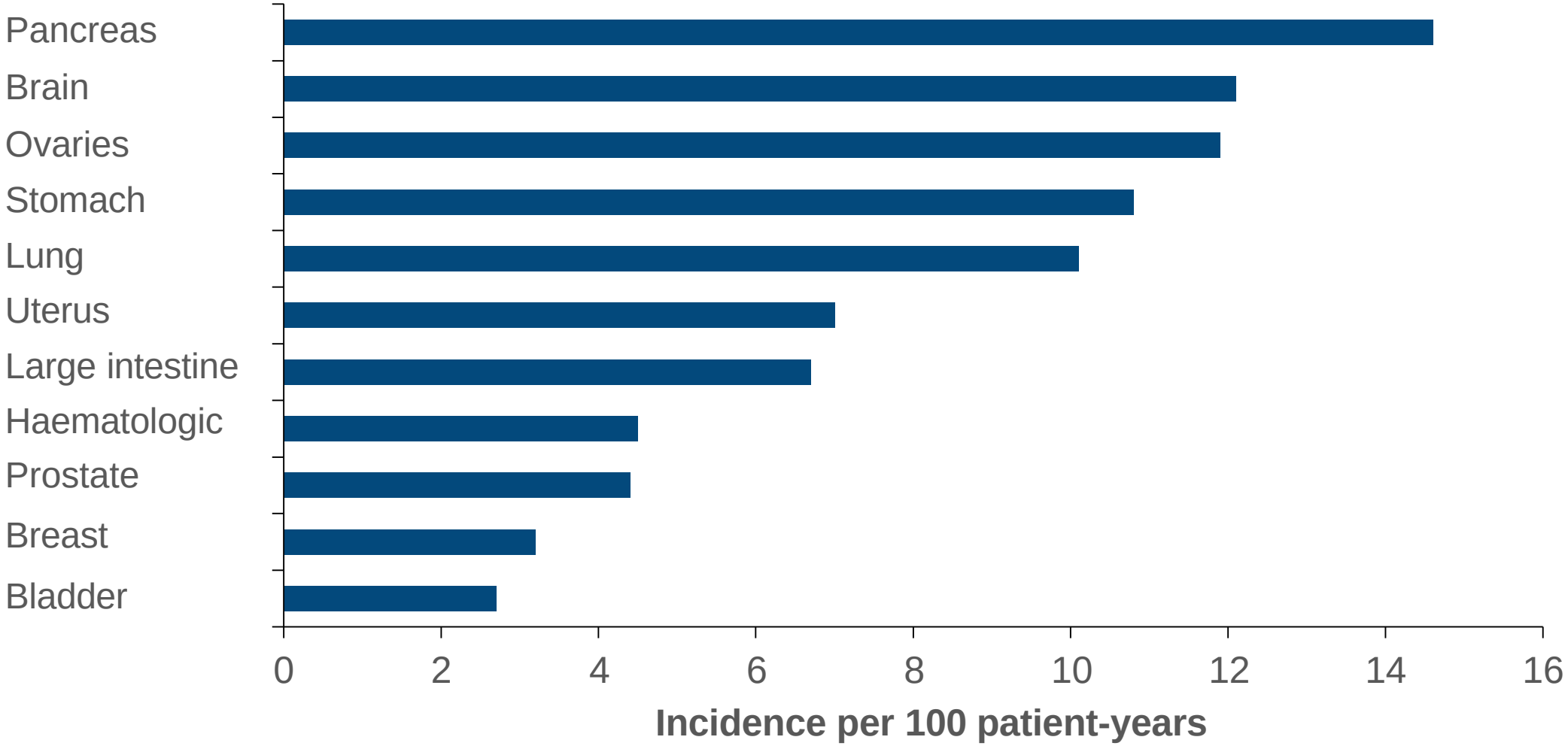
Kahn F *et al. BMJ* 2019;366:l4363.

A clear trend towards extended anticoagulation

Recommendations	Class	Level
Patients in whom extension of anticoagulation beyond 3 months should be considered		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor	**IIa**	**A**
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than the antiphospholipid antibody syndrome	**IIa**	**C**
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor	**IIa**	**C**

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2020; 41(4):543-603

Annual incidence of VTE in patients with diagnosed cancer



Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Prevalence of tumour types in cancer-associated thrombosis

Patients with active cancer* and a first VTE

Common cancer types (%)	DVT (n=3055)	PE (n=3537)	Total (N=6592)
Prostate (men)	19.1	16.1	17.5
Breast (women)	14.0	16.0	15.1
Lung	10.3	17.0	13.9
Colon	12.6	12.5	12.5
Ovarian (women)	8.5	10.3	9.5
Haematological	11.8	8.7	10.1
Bladder	6.1	3.8	4.8
Uterus (women)	5.2	3.3	4.2
Pancreas	4.2	3.7	3.9
Stomach	3.4	3.8	3.6
Brain	2.6	2.5	2.5

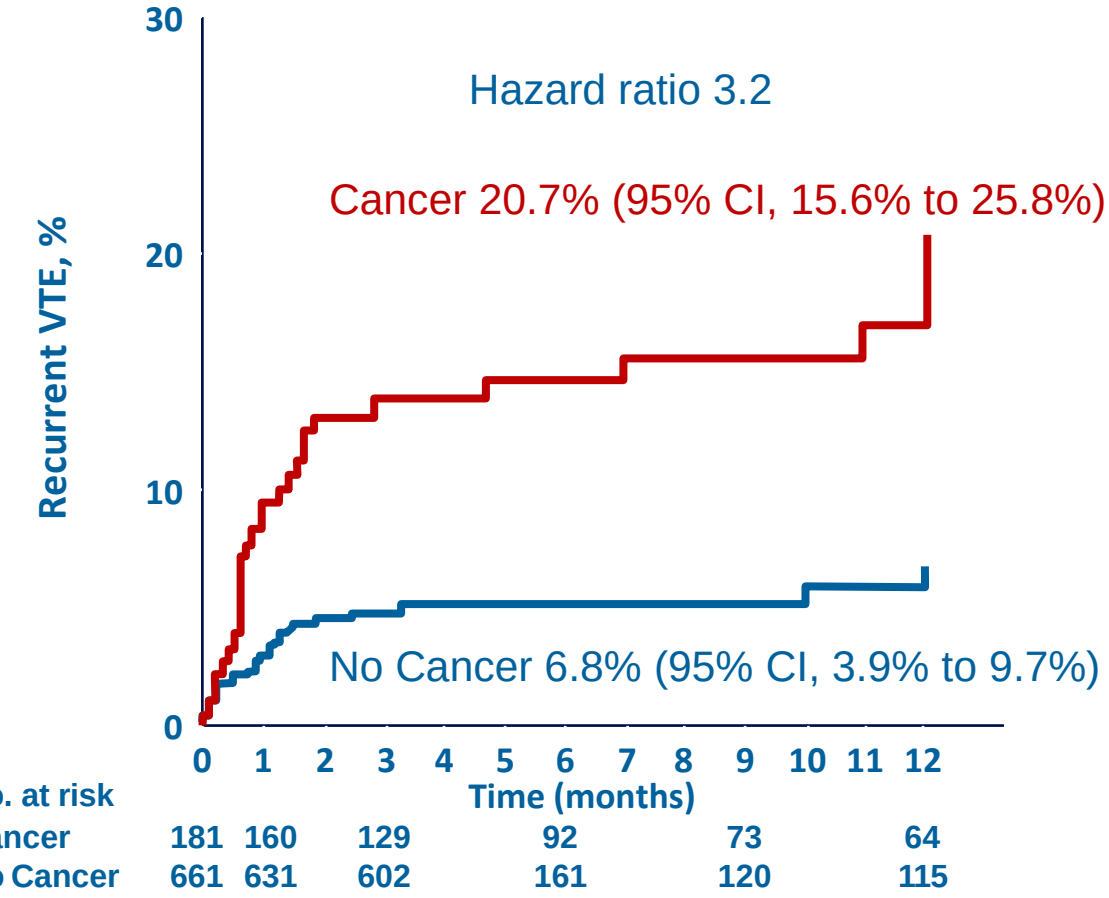
CAT, cancer associated thrombosis; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; HES, hospital episodes statistics

*Defined as an admission to hospital with a primary diagnosis of cancer (excluding non-melanoma skin cancer), or a recording of radiation, chemotherapy or bone marrow transplantation in HES records

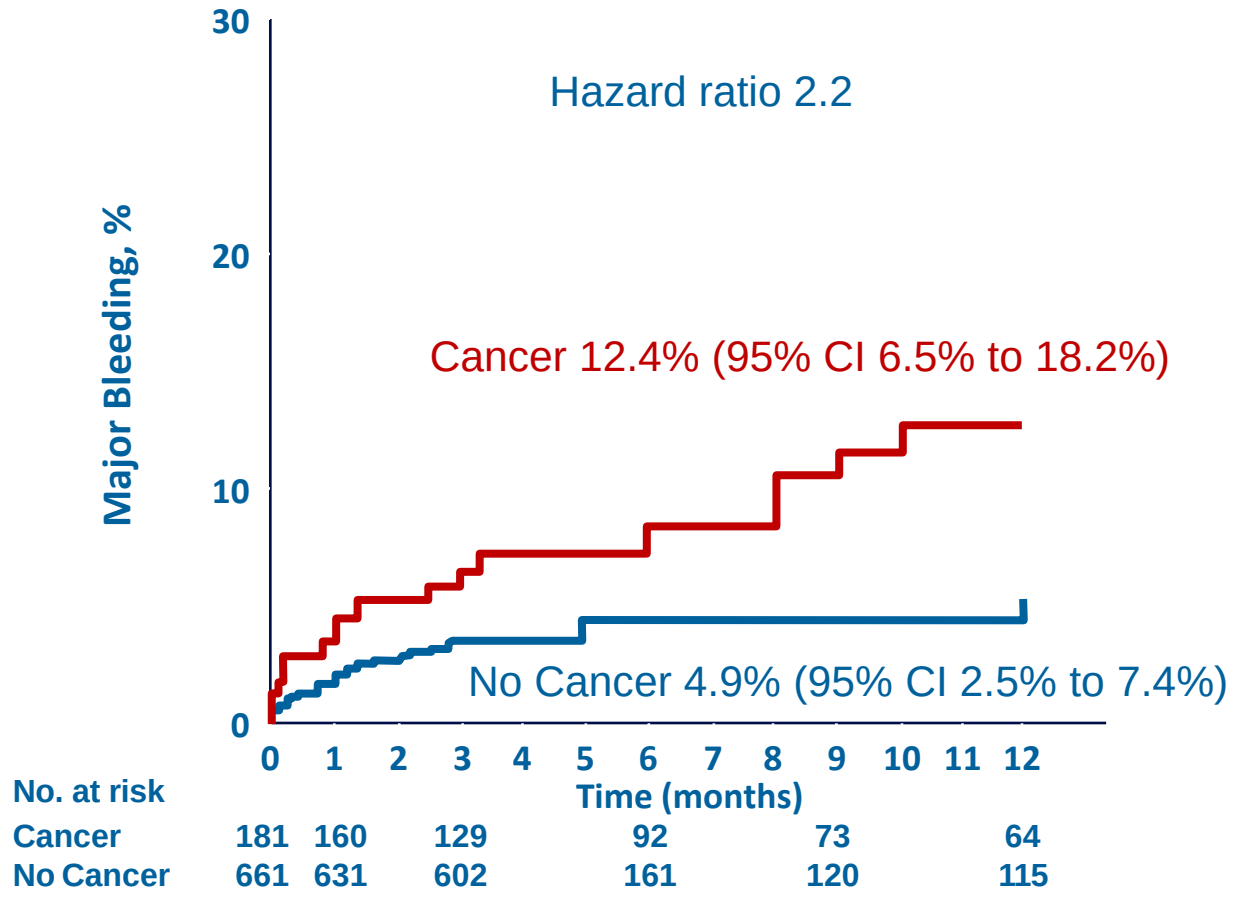
Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Efficacy and safety of VKA in patients with cancer

12 Month cumulative incidence of recurrent VTE during anticoagulation therapy in DVT patients with *vs* without cancer



12-month cumulative incidence of major bleeding during anticoagulation therapy in DVT patients with *vs* without cancer

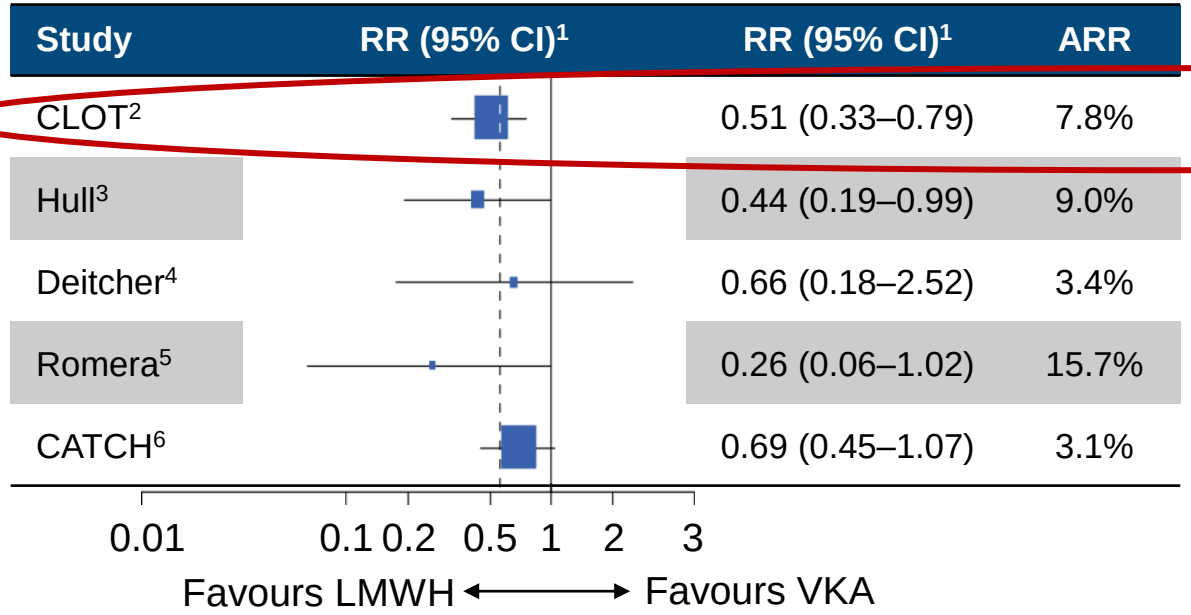


CI, confidence interval

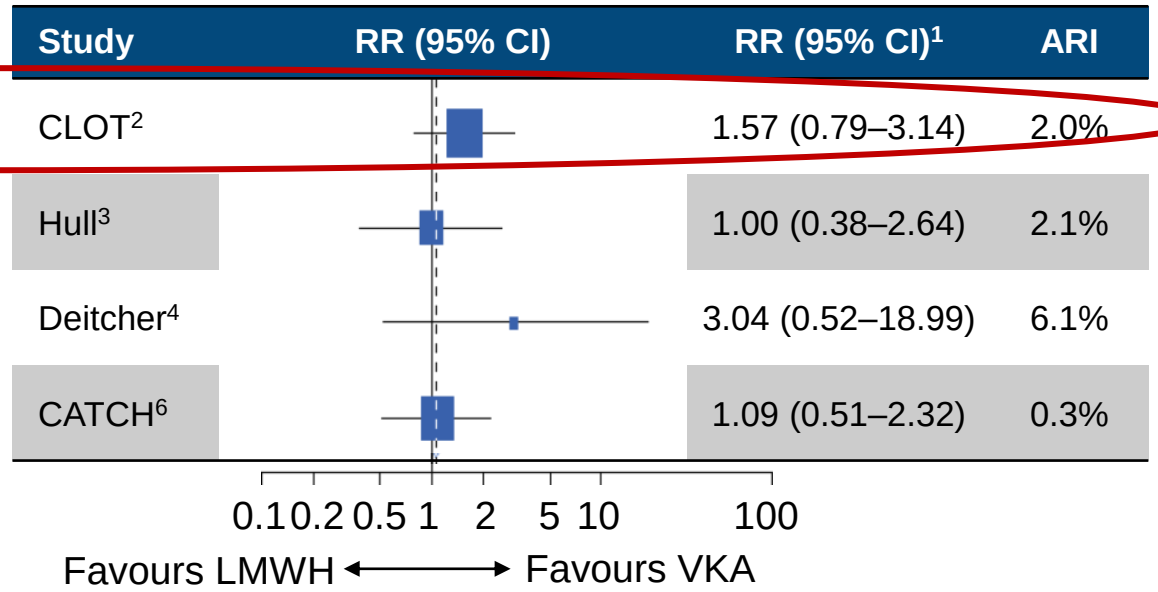
Prandoni P *et al*, *Blood* 2002;100:3484-3488

LMWH versus VKAs in cancer-associated thrombosis

Recurrent VTE



Major bleeding events

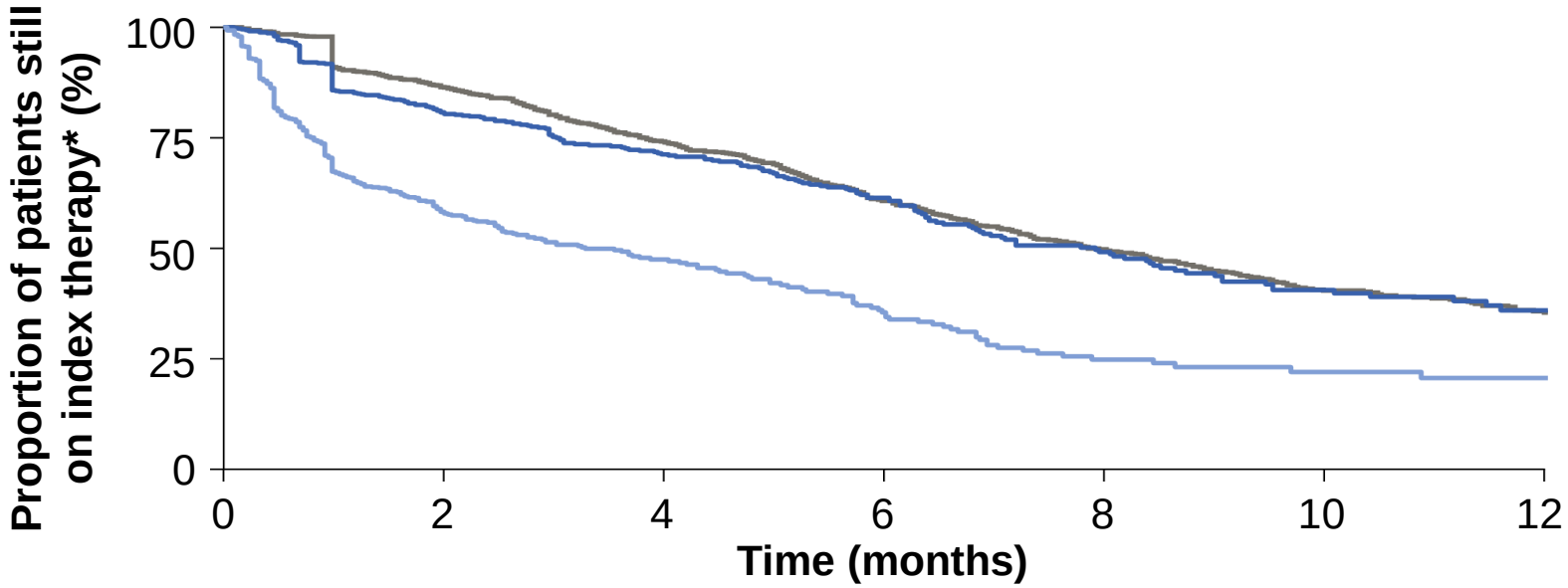


LMWH was associated with a significant reduction in the risk of recurrent VTE without a significant increase in major bleeding events versus VKA

ARI, absolute risk increase; ARR, absolute risk reduction; CI, confidence interval; LMWH, low molecular weight heparin; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism. *Random effects model

1. Carrier M, Prandoni P, *Expert Rev Hematol* 2017;10:15–22; 2. Lee AYY *et al, New Engl J Med* 2003;349:146–153; 3. Hull RD *et al, Am J Med* 2006;119:1062–1072; 4. Deitcher SR *et al, Clin Appl Thromb Hemost* 2006;12:389–396; 5. Romera A *et al*, *Eur J Vasc Endovasc Surg* 2009;37:349–356; 6. Lee AYY *et al, JAMA* 2015;314:677–686

Persistence on index therapy in patients with cancer



Warfarin (n=1403)

Rivaroxaban (n=709)

LMWH (n=735)

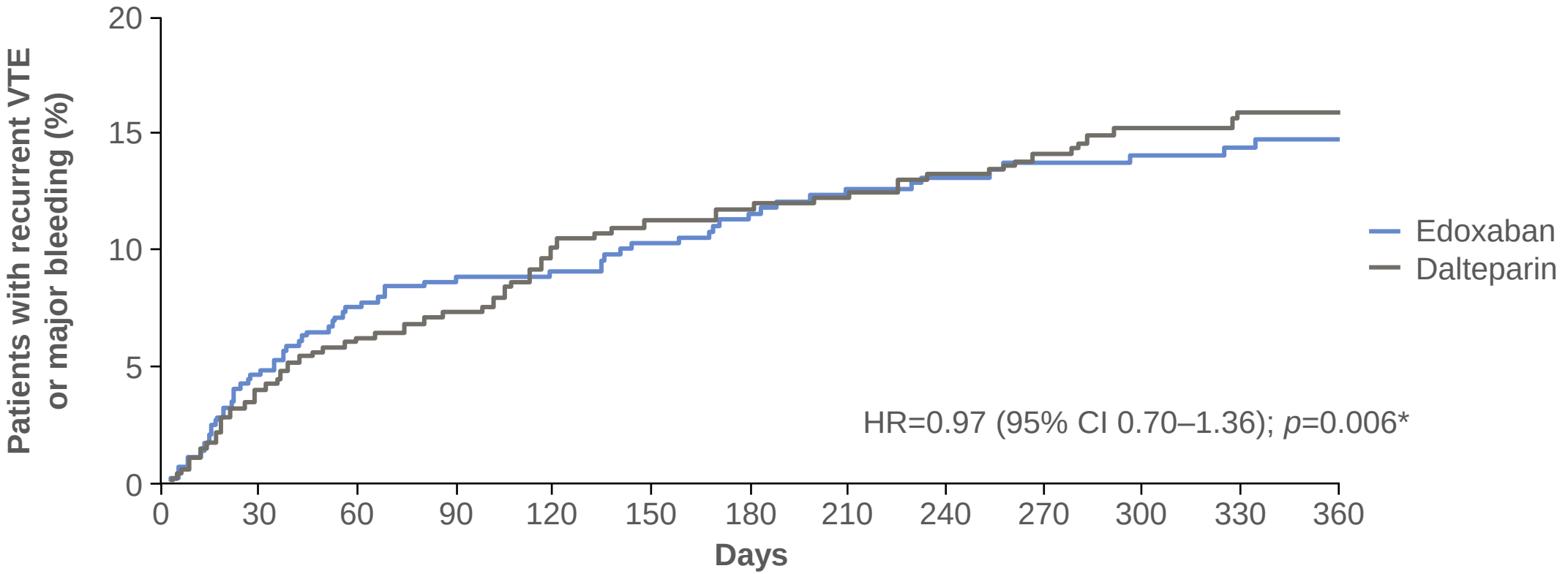
Cohort	Median treatment duration (months)	Kaplan–Meier rates	
		6 months	12 months
LMWH	**3.3**	**37%**	**21%**
Warfarin	7.9	61%	35%
Rivaroxaban	7.9	61%	36%

LMWH, low molecular weight heparin

*Discontinuation was defined as a gap of no more than 60 days between the end of the days of supply of a dispensing and the start date of the next dispensing of the index therapy, if any

Khorana AA *et al, Res Pract Thromb Haemost* 2017;1:14–22

Hokusai-VTE-Cancer: Composite primary outcome



Number of patients at risk

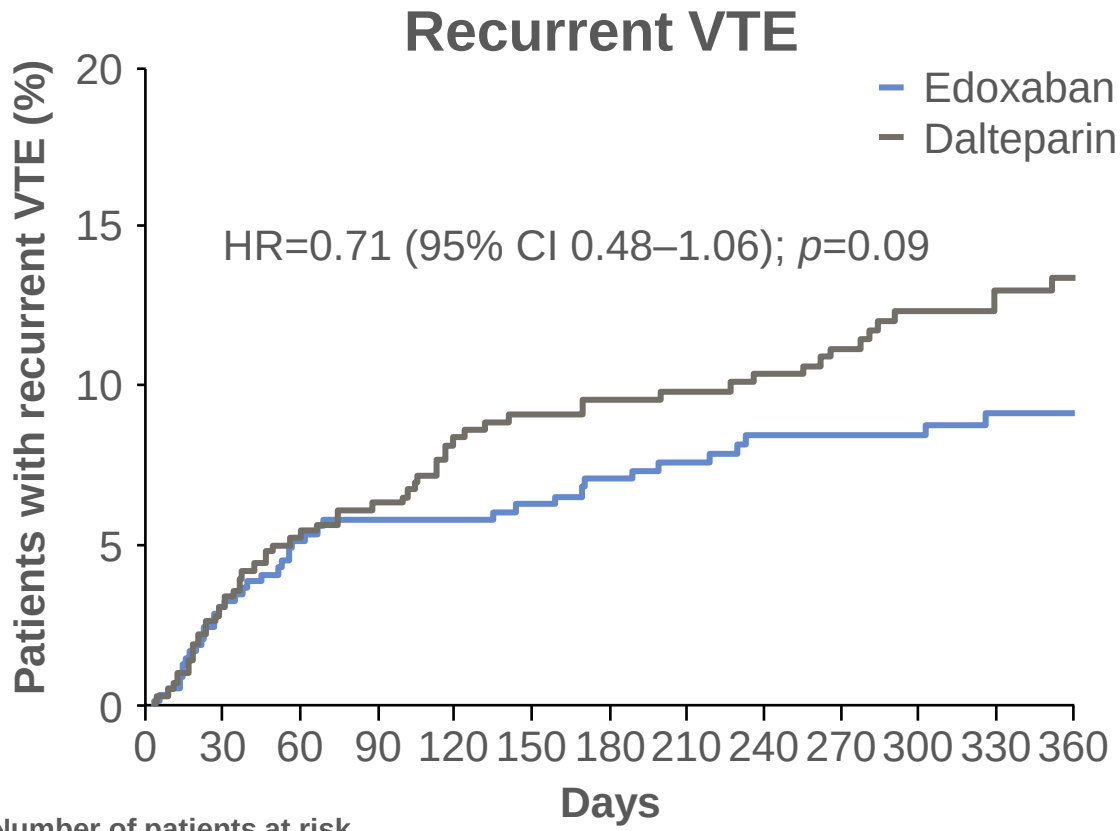
Dalteparin	522	472	429	407	388	360	345	328	310	295	270	237	161
Edoxaban	524	485	449	420	385	364	352	340	324	313	276	241	171

*Non-inferiority

Adapted from Raskob G *et al*, *N Engl J Med* 2018;378:615–624

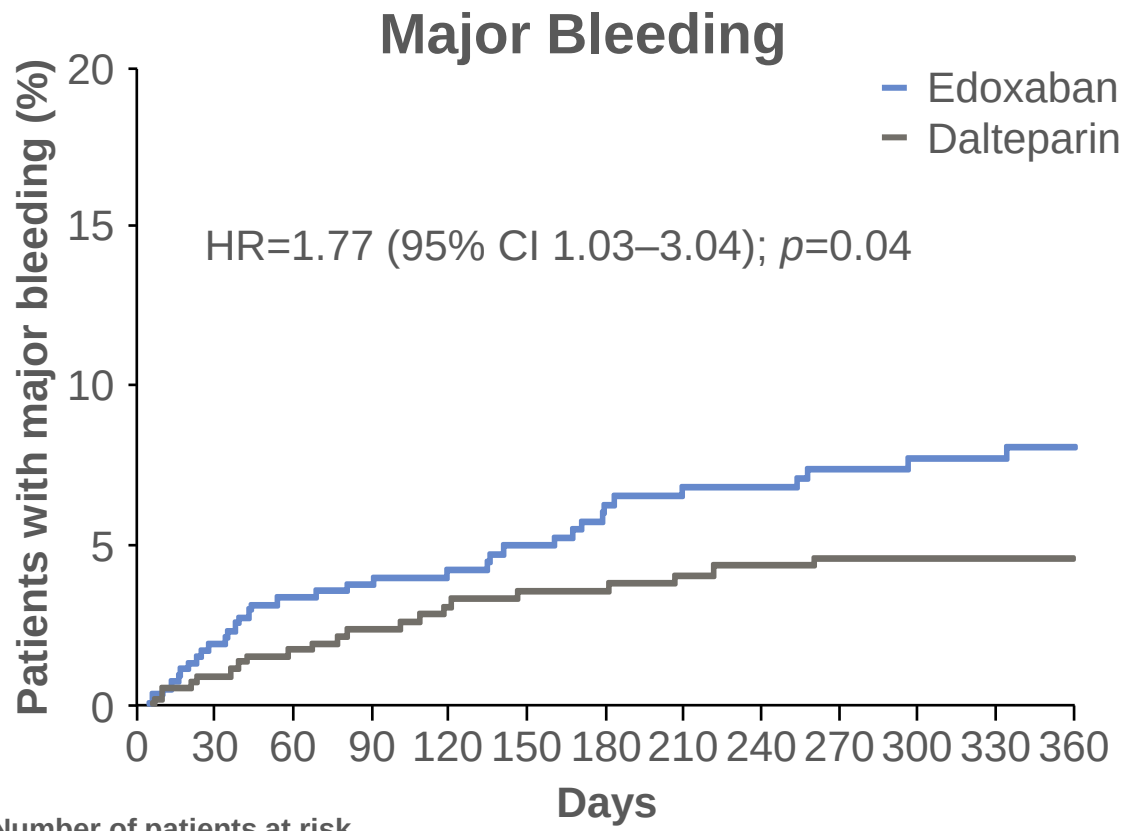
Hokusai VTE CANCER

Hokusai-VTE-Cancer: Secondary outcomes



Number of patients at risk

Dalteparin	522	480	437	415	395	370	356	340	320	307	281	245	168
Edoxaban	524	488	452	423	389	370	358	348	333	321	282	246	174



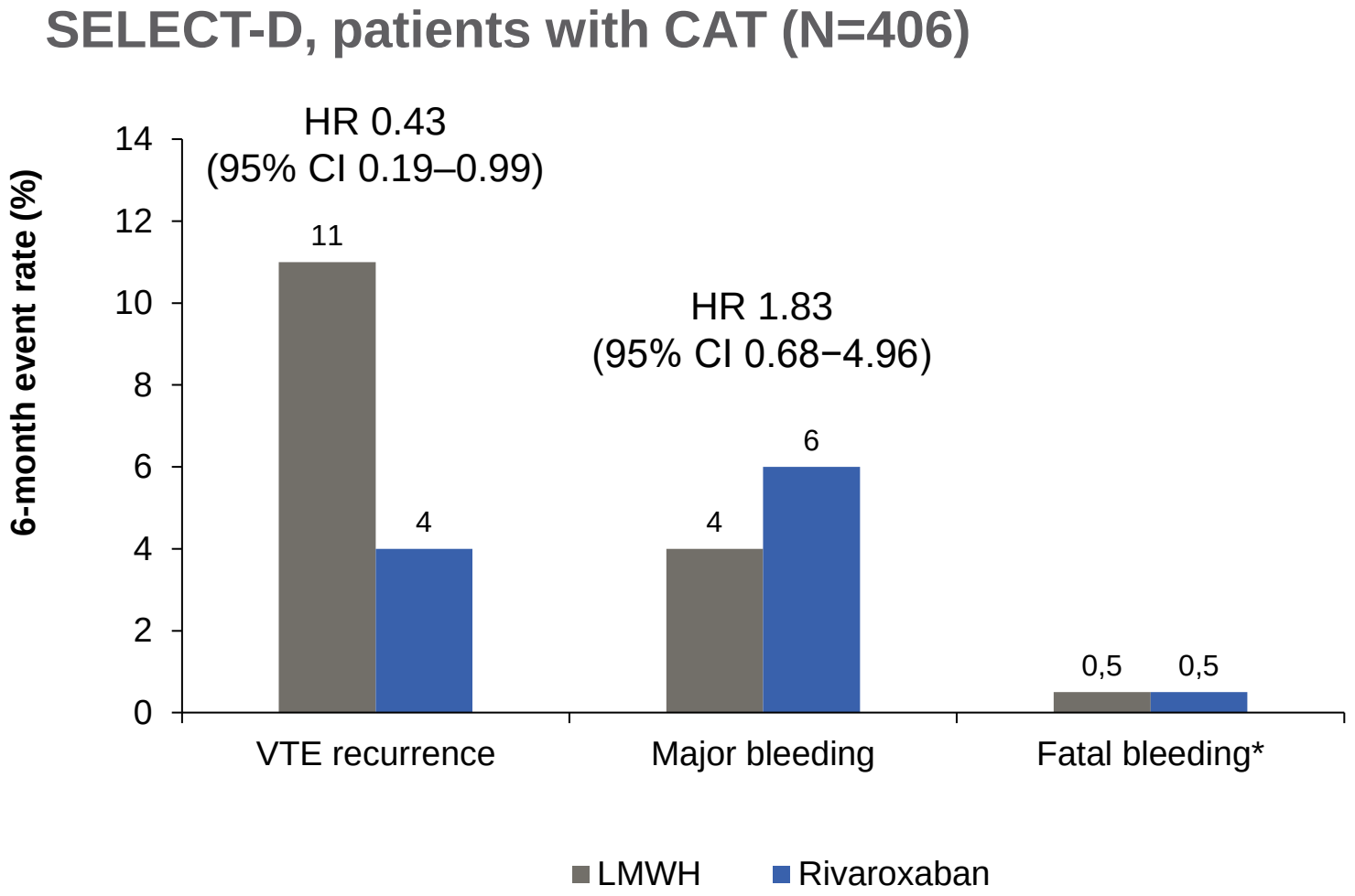
Number of patients at risk

Dalteparin	522	484	447	426	404	375	358	343	323	308	282	248	168
Edoxaban	524	497	466	436	409	390	378	356	346	335	298	262	183

Adapted from Raskob G *et al*, *N Engl J Med* 2018;378:615–624

Hokusai VTE CANCER

select-d: Efficacy and safety of rivaroxaban



*One fatal bleeding event in each arm.

Young A et al. *J Clin Oncol* 2018;36:2017–2023.

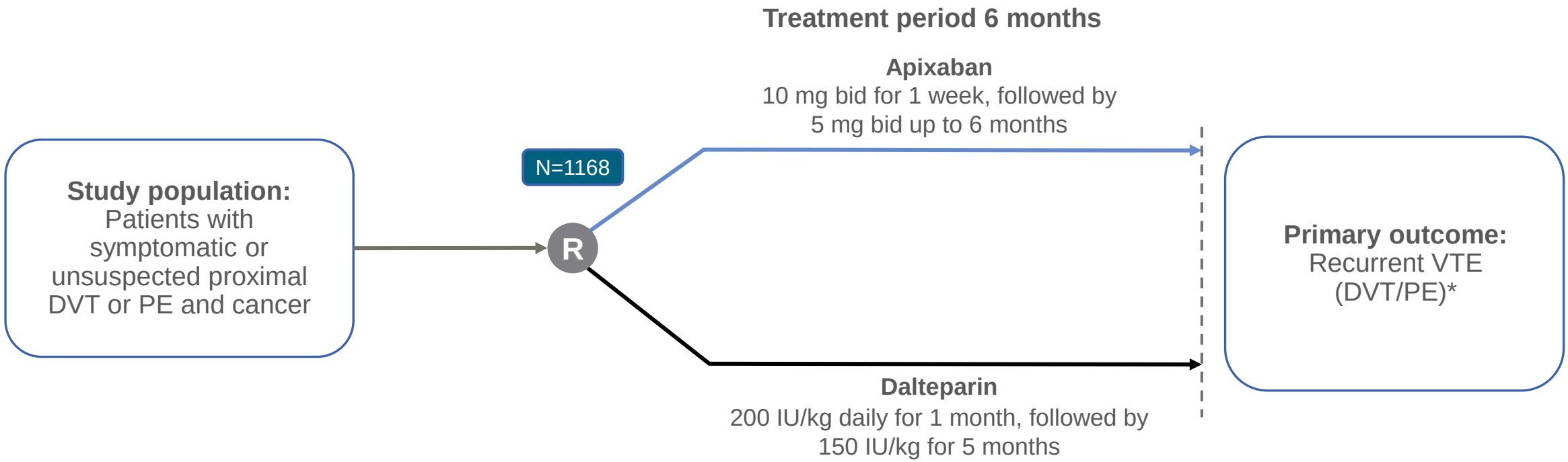
2019 ESC clinical practice guideline update

Recommendations for the regimen and the duration of anticoagulation after pulmonary embolism in patients with active cancer[2]	Class of recommendation
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.	IIa
Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with a word of caution for patients with gastrointestinal cancer due to the increased bleeding risk with NOACs.	IIa

1. Konstantinides SV *et al*, *Eur Heart J* 2014;35:3033–3069;
2. Konstantinides SV *et al*, *Eur Heart J* 2019: doi:10.1093/eurheartj/ehz405

CARAVAGGIO: Apixaban[1,2]

Phase III open-label, randomized, PROBE design study



Short design: Prospective, multicentre, randomized, open-label

Indication: VTE treatment in patients with CAT

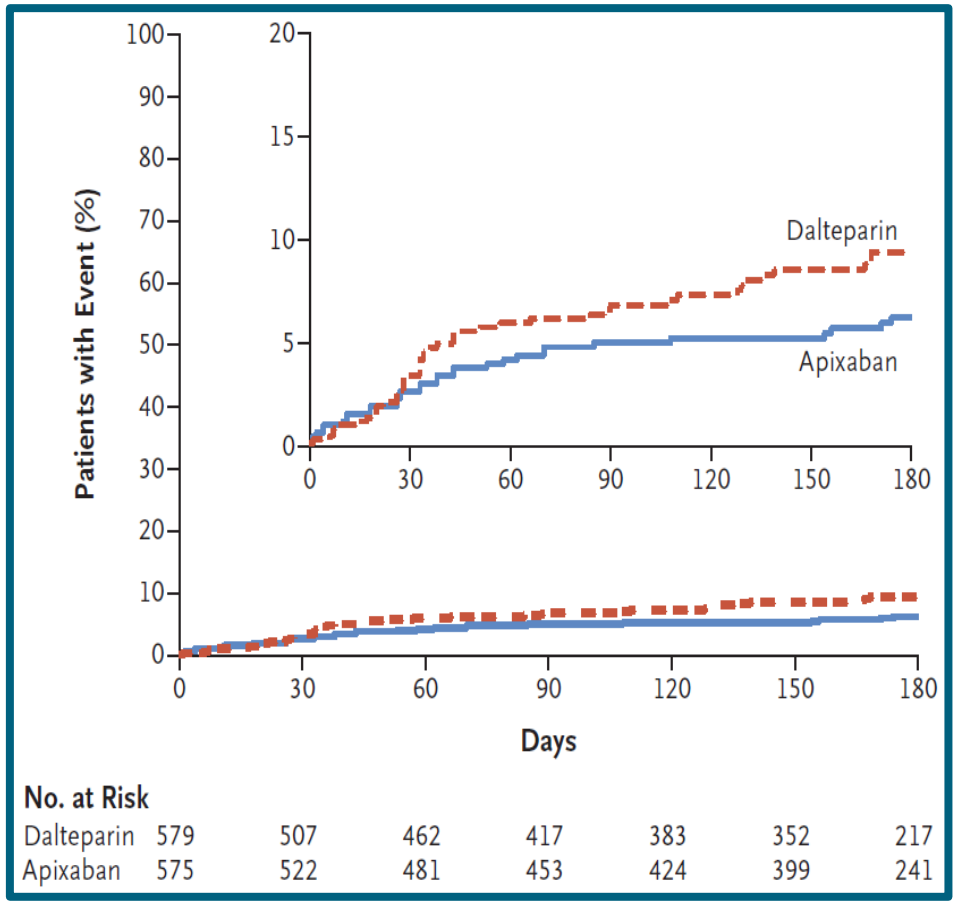
FPFV[2]: Q2-2017
LPLV[2]: Q2-2019

*Symptomatic or unsuspected DVT of the lower limbs, symptomatic DVT of the upper limbs and symptomatic or unsuspected PE[2]

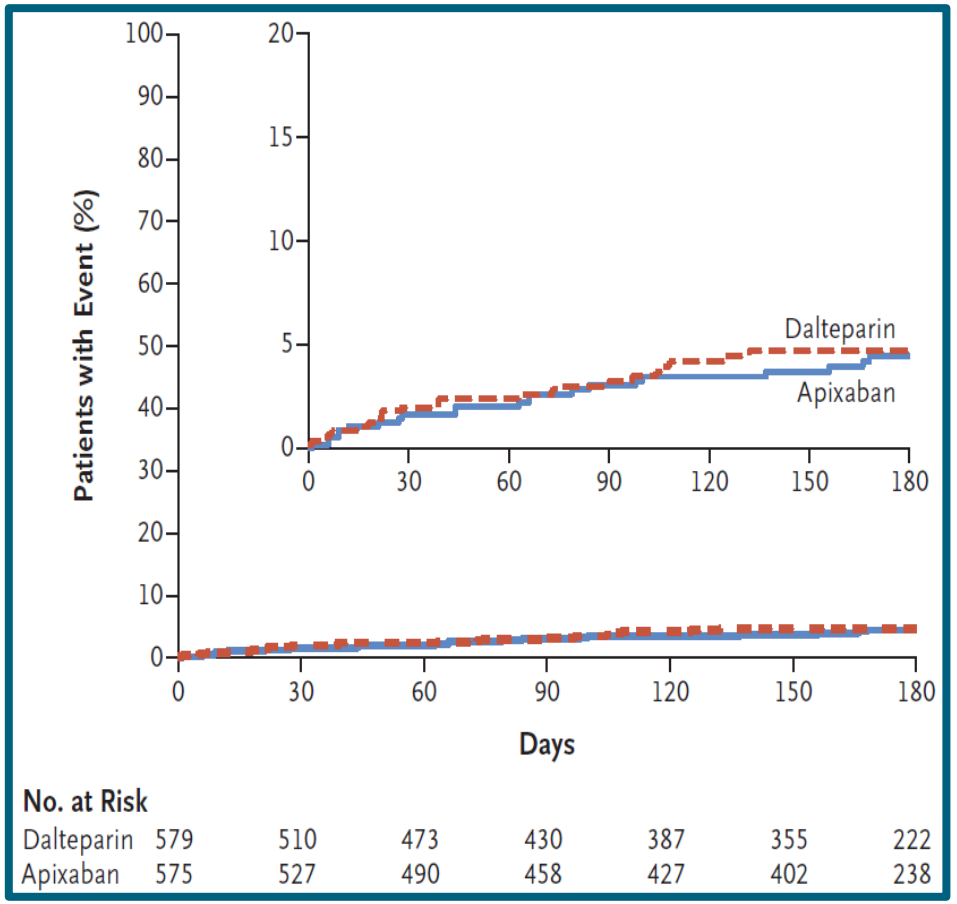
1. Agnelli G *et al*, *Thromb Haemost* 2018;118:1668–1678; 2. Fadoi Foundation, Italy. https://clinicaltrials.gov/ct2/show/NCT03045406 [accessed 9 Dec 2019]

Efficacy and safety of DOAC treatment of proximal DVT/PE in cancer confirmed in CARAVAGGIO trial

Recurrent VTE



Major Bleeding



Agnelli G, *et al*. 2020. *N Engl J Med*. DOI: 10.1056/NEJMoa1915103

2021 ASH guidelines

- For patients with cancer and VTE, the ASH guideline panel suggests that DOACs (apixaban or rivaroxaban) or LMWH be used for *initial* treatment

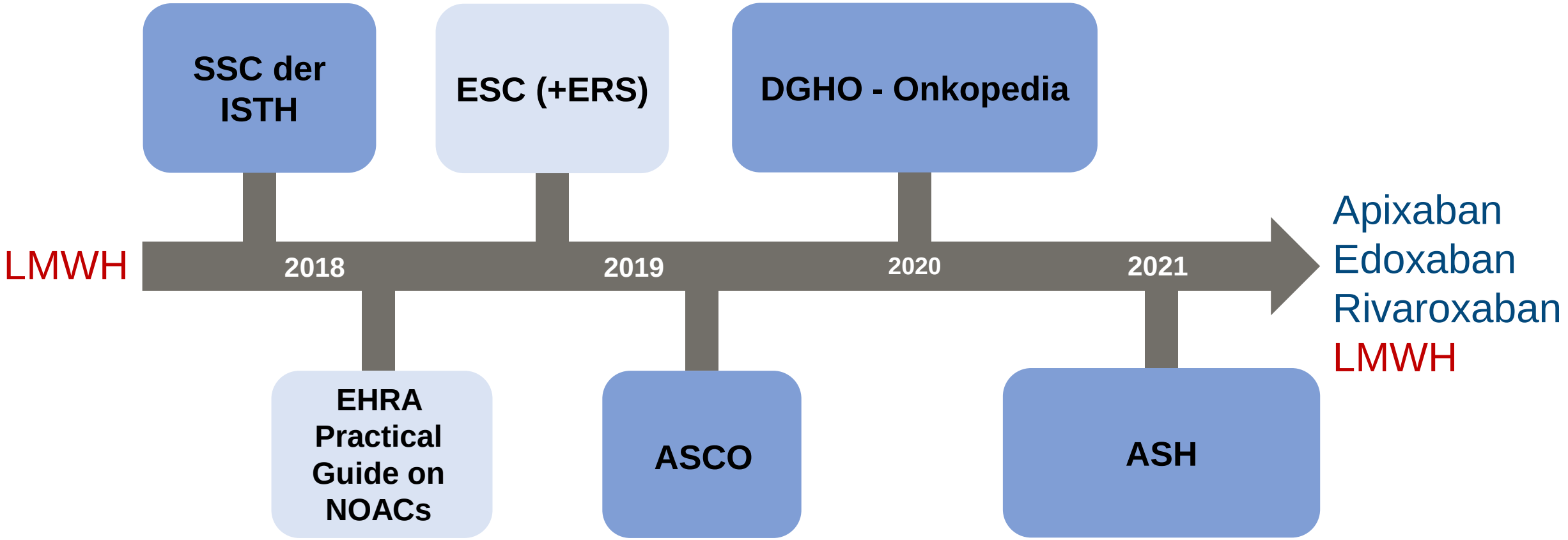
  DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding.

- For the *short-term* treatment of VTE (first 3-6 months) for patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH.

DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding.

Lyman, GH *et al*. *Blood Adv* 2021;5:927-974.

Evolution of guidelines on cancer-associated thrombosis



Take home messages

- There is a close association between cancer, thrombosis, and VTE.
- Vitamin K antagonists are less efficacious and also less safe for VTE treatment in cancer patients. Low molecular weight heparins possess superior efficacy, but persistence on therapy may be poor in patients with cancer.
- Direct oral anticoagulants have replaced VKAs as first-line therapy for VTE in the general population.
- Recently, randomized controlled trials demonstrated the efficacy and overall safety of DOACs in the treatment of VTE in cancer.
- Guidelines now recommend the DOACs apixaban and rivaroxaban in the initial treatment, and the DOACs apixaban, edoxaban and rivaroxaban over the first 3-6 months after VTE in cancer, with a caveat for the risk of bleeding in those with (intraluminal) gastrointestinal tumours.