



Overcoming challenges in cancer-associated thrombosis

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Outline

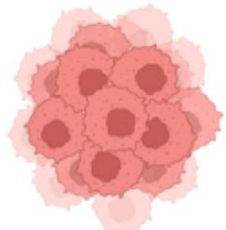
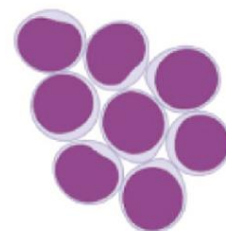
- Cancer patients with thrombocytopenia
- Patients with brain tumors
- Cancer patients with recurrent VTE despite anticoagulation

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Prevalence of thrombocytopenia in CAT

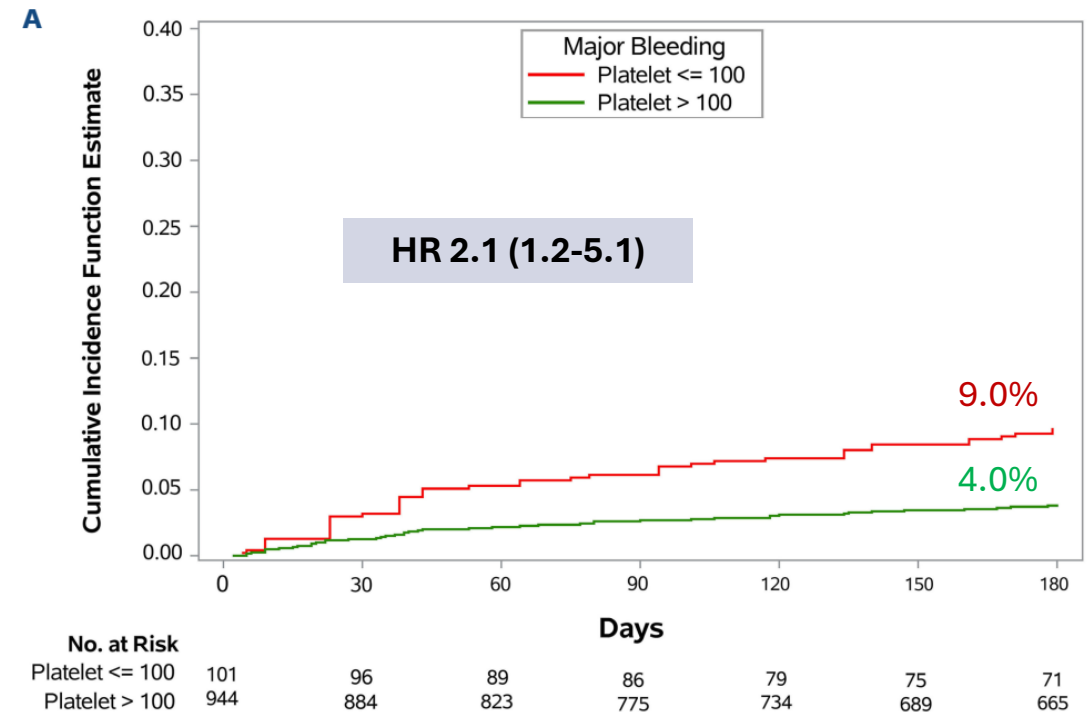
A retrospective cohort of adult patients with CAT
at Beth Israel Deaconess Medical Center, between 2010 and 2021

	Platelet Count <100K/ μ L	Platelet Count <50K/ μ L
 Solid Malignancies n = 2,902	22%	7%
 Hematologic Malignancies n = 647	47%	30%

Impact of thrombocytopenia on CAT

Hokusai VTE Cancer Study

- Post-hoc analysis
- Anticoagulant management protocol
- Dalteparin
 - Plt 50-100x10⁹/L
 - Dose reduction by 2500 IU
 - Plt <50x10⁹/L
 - Withheld
- Edoxaban
 - No dose adjustment based on Plt



Impact of thrombocytopenia on CAT

Hokusai VTE Cancer Study

Incidence at 6 months of **major bleeding** in patients with $\text{Plt} < 100 \times 10^9/\text{L}$

	Edoxaban	Dalteparin	P
All patients	8.3%	9.6%	0.80
Patients with GI malignancies	16.8%	0	<0.01
Patients with hematologic malignancy	0	19%	<0.01

Full-dose vs modified dose AC in thrombocytopenia

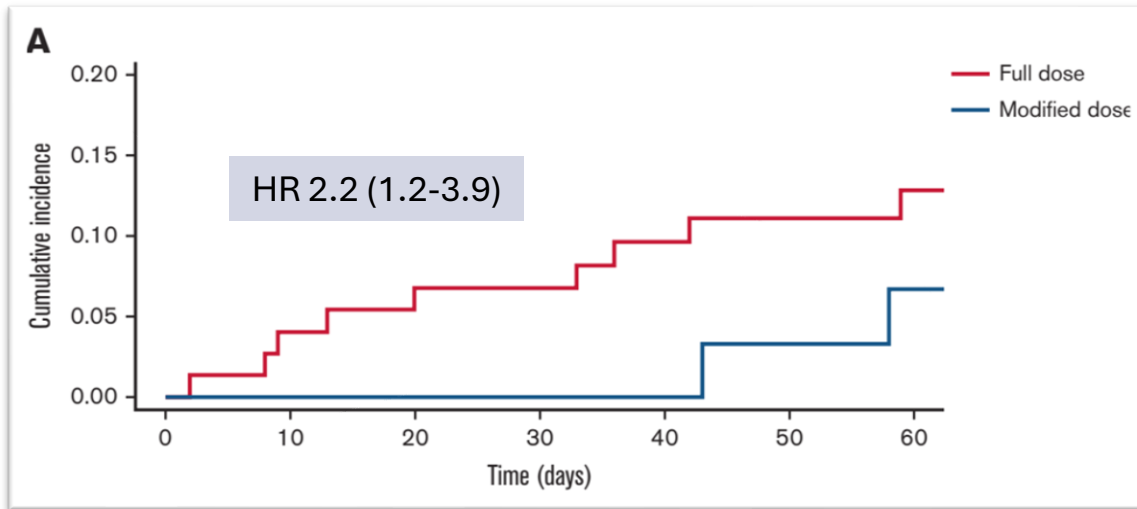
- Prospective study
 - Cancer patients with VTE
 - Plt < 100 x10⁹/L
- Anticoagulant management
 - Full-dose with platelet transfusion
 - Modified dose
 - Enoxaparin < 1.5 mg/kg/day
 - Apixaban 2.5 mg BID
 - Rivaroxaban 10 mg OD

Table 1. Baseline characteristics

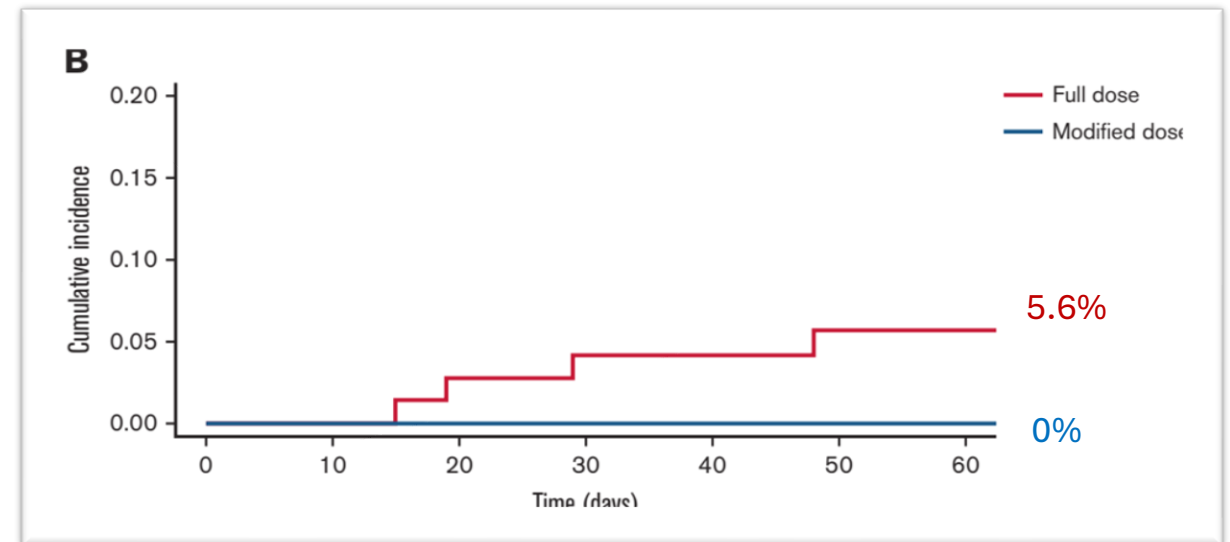
Characteristic	Full-dose (n = 75)	Modified-dose (n = 33)	None (n = 13)
Male sex, n (%)	39 (52)	16 (48)	10 (77)
Mean age at enrollment (range), y	59 (23-88)	60 (26-78)	65 (42-78)
Inpatient, n (%)	70 (93)	30 (91)	11 (85)
Cancer diagnosis, n (%)			
Hematologic malignancy	43 (57)	31 (94)	11 (85)
Solid tumor	32 (43)	2 (6)	2 (15)
Median baseline laboratory values (IQR)			
Hemoglobin, g/dL	8.7 (7.4-10.7)	7.9 (7.5-9.7)	7.4 (7.0-8.7)
Platelet count, K/ μ L	65 (47-88)	37 (24-48)	16 (14-32)
Anticoagulant, n (%)			
LMWH	40 (53)	26 (79)	0
Unfractionated heparin	23 (31)	3 (9)	0
Direct oral anticoagulant	12 (16)	4 (12)	0

Full-dose vs modified dose AC in thrombocytopenia

Cumulative incidence of major bleeding



Cumulative incidence of recurrent VTE

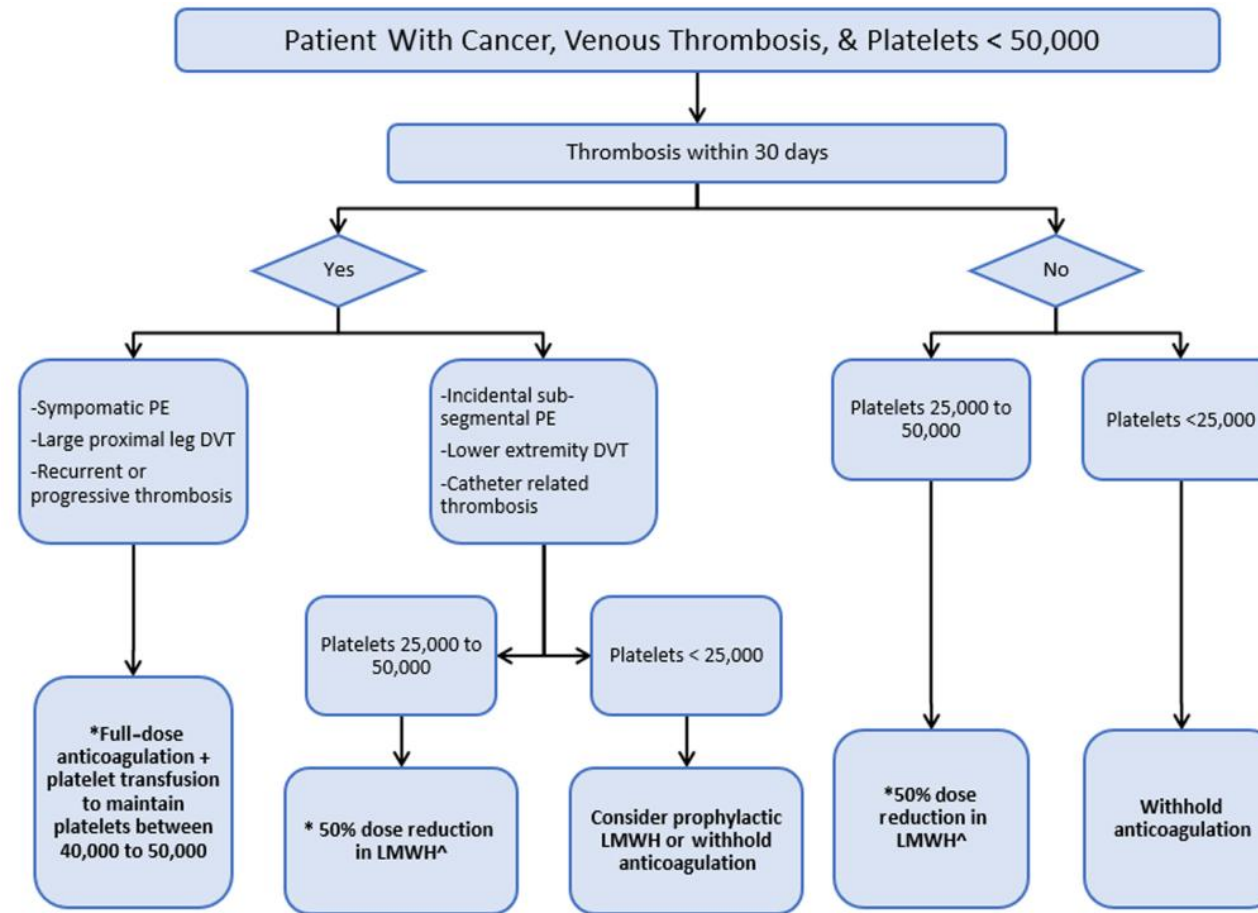


Impact of thrombocytopenia on CAT

Platelet $<50 \times 10^9/L$

Studies	Anticoagulant Management	Major bleeding	Recurrent VTE/clot progression
Khanal 2016	Prophylactic LMWH 47% Therapeutic LMWH 30% IVC filter 2% Observation 17%	6%	22%
Booth 2022	Prophylactic LMWH 16% Therapeutic LMWH 2% IVC filter 4% Observation 80%	8%	10%

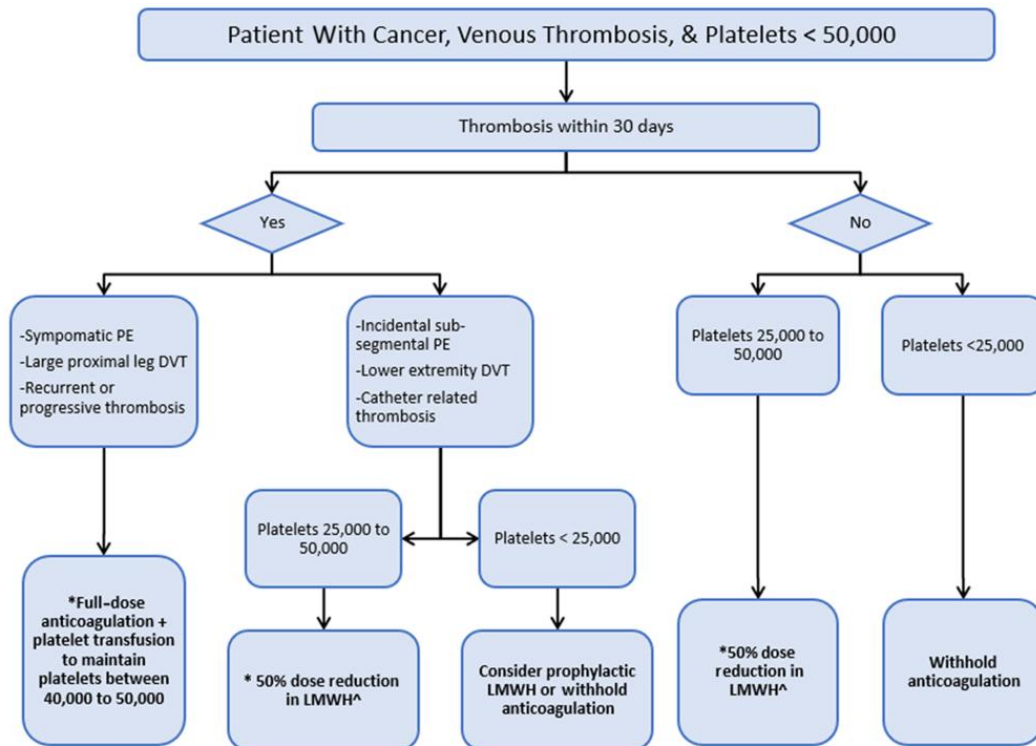
ISTH SSC guidance for CAT with thrombocytopenia



Additional consideration

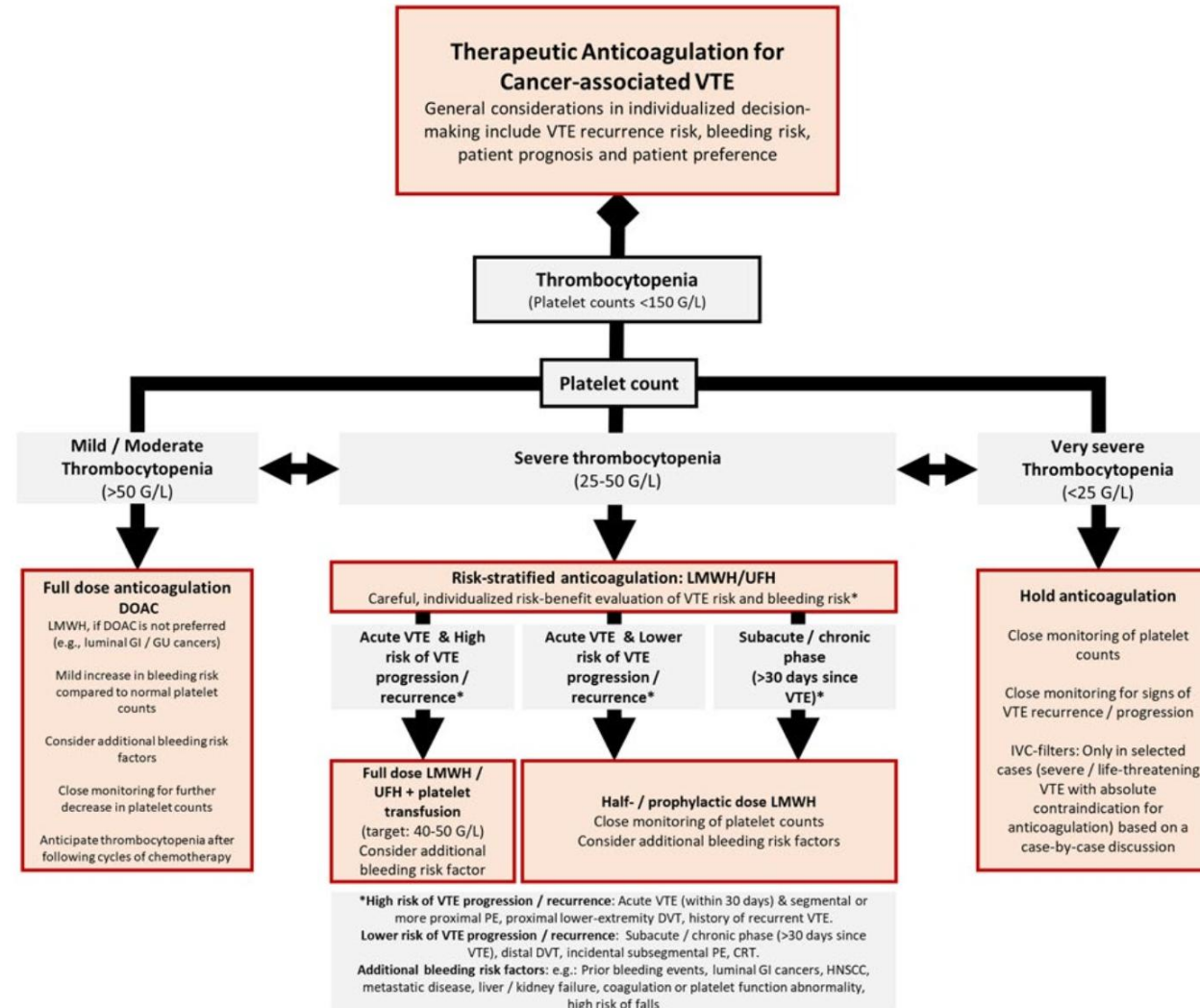
- Co-morbid diseases
 - Liver/renal dysfunction
 - Coagulopathy
 - Primary site of cancer: luminal GI cancer, brain cancer
 - Presence of intracerebral tumors/metastasis
- History of anticoagulant related bleeding
- Prognosis and performance status

Implementation of ISHT: CAT with thrombocytopenia



- 80 patients with CAT and thrombocytopenia
- Post-intervention period
 - Increased platelet transfusion
 - Increased major bleeding (8%)
 - Numerically less recurrent thrombosis (8%)

Summary #1

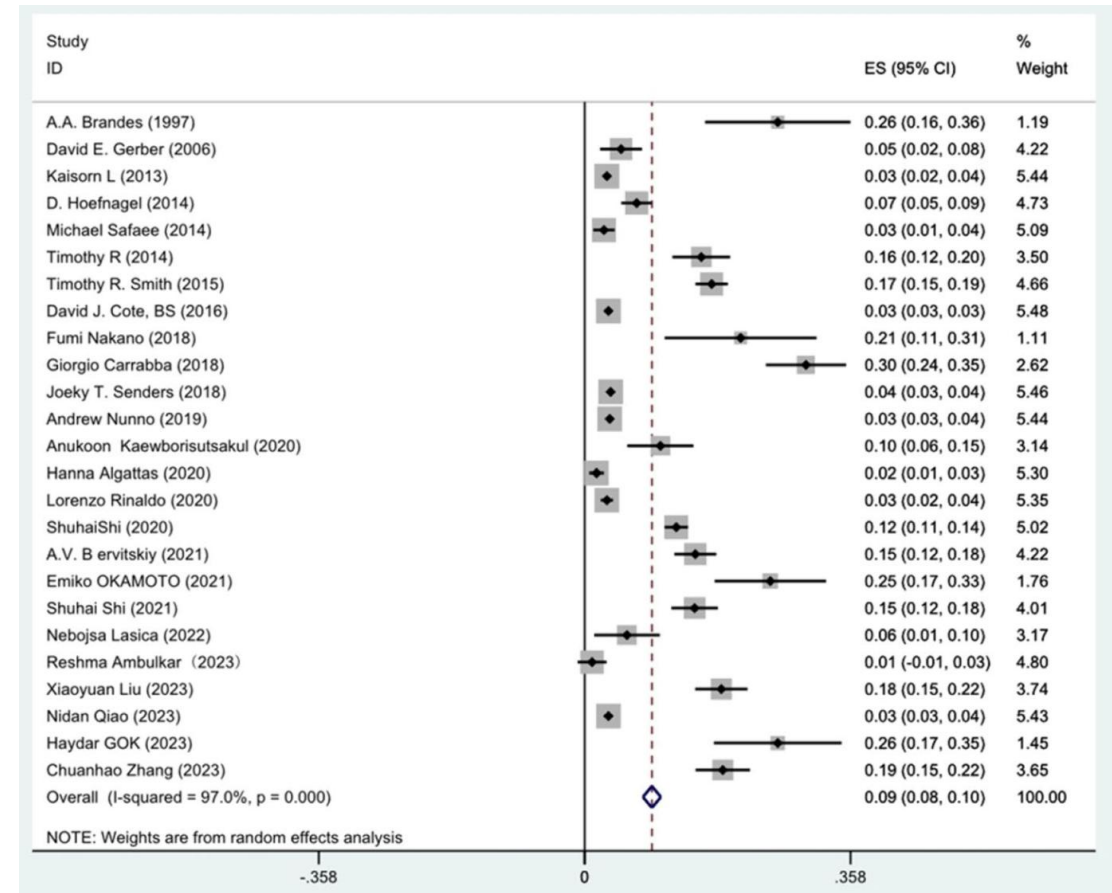


Outline

- Cancer patients with thrombocytopenia
- Patients with brain tumors
- Cancer patients with recurrent VTE despite anticoagulation

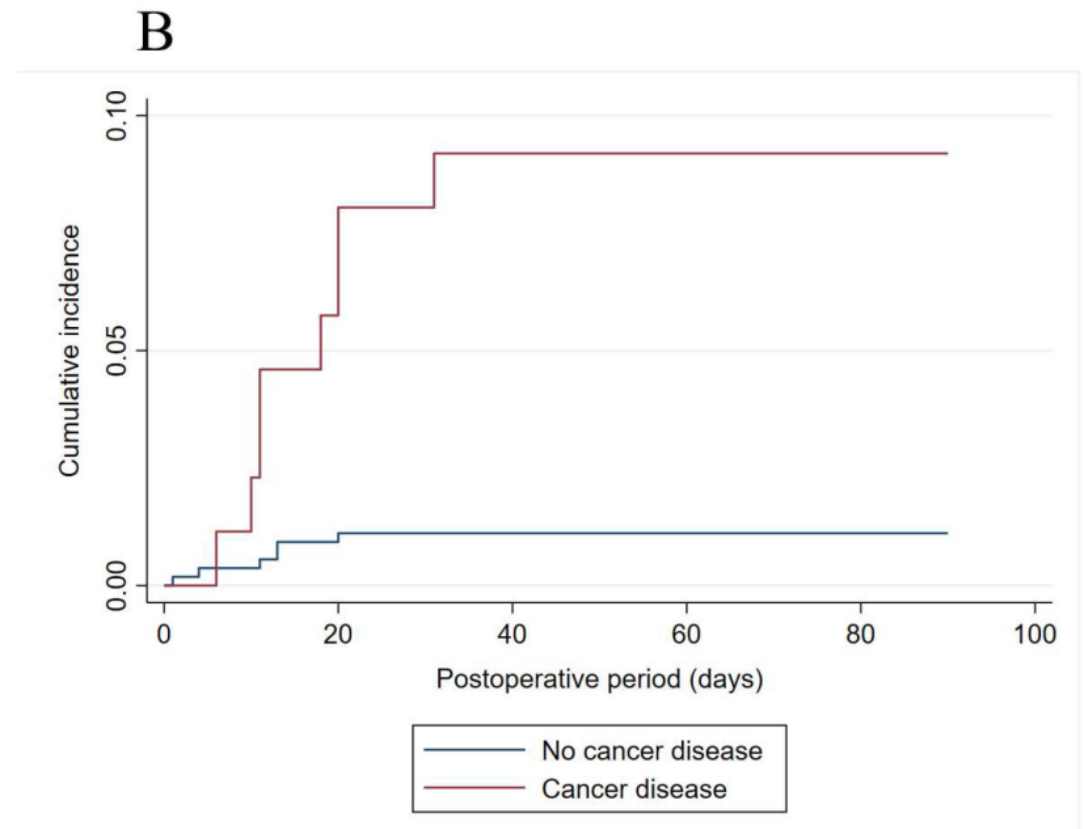
Prevalence of VTE in patients with brain tumors

- Meta-analysis of 25 studies
 - Primary brain tumors
 - Secondary brain tumors
- Pooled prevalence of VTE: 9% (8-10)
- Risk factors
 - Prior history of VTE
 - CHF, DM, HTN
 - Steroid use
 - High WBC, high fibrinogen



Incidence of VTE in neurosurgery patients: CMU

- 626 patients underwent neurosurgeries
- 3-month incidence of VTE 2.24%
- Cancer increased risk of VTE
 - HR 8.5 (95%CI 2.9-24.6)



Natural history of VTE in patients with brain tumor

- 1:1 matched patients with cancer associated thrombosis
 - Brain tumor vs Non brain tumor
- 364 patients
 - Treated with LMWH 100%

	Incidence per 100-patient year (95 % CI)		Incidence rate ratio (95 % CI)	P-value
	Non-brain tumours	Brain tumours		
Recurrent VTE	13.5 (9.3–19.7)	11.0 (6.7–17.9)	0.8 (0.4–1.5)	0.43
Major bleeding	5.0 (2.8–9.2)	8.6 (4.8–14.7)	1.7 (0.7–4.1)	0.21
Clinically relevant bleeding	8.7 (5.5–13.8)	12.4 (7.8–19.7)	1.4 (0.7–2.9)	0.29

Natural history of VTE in patients with brain tumor

Site of major bleeding	Non-brain tumours (n=182)	Brain tumours (n=182)
Gastrointestinal tract	8 (4.4 %)	0
Intracranial site	0	9 (4.5 %)
Retroperitoneal	0	1 (0.5 %)
Genitourinary tract	2 (1.1 %)	1 (0.5 %)
Others	2 (1.1 %)	3 (1.5 %)

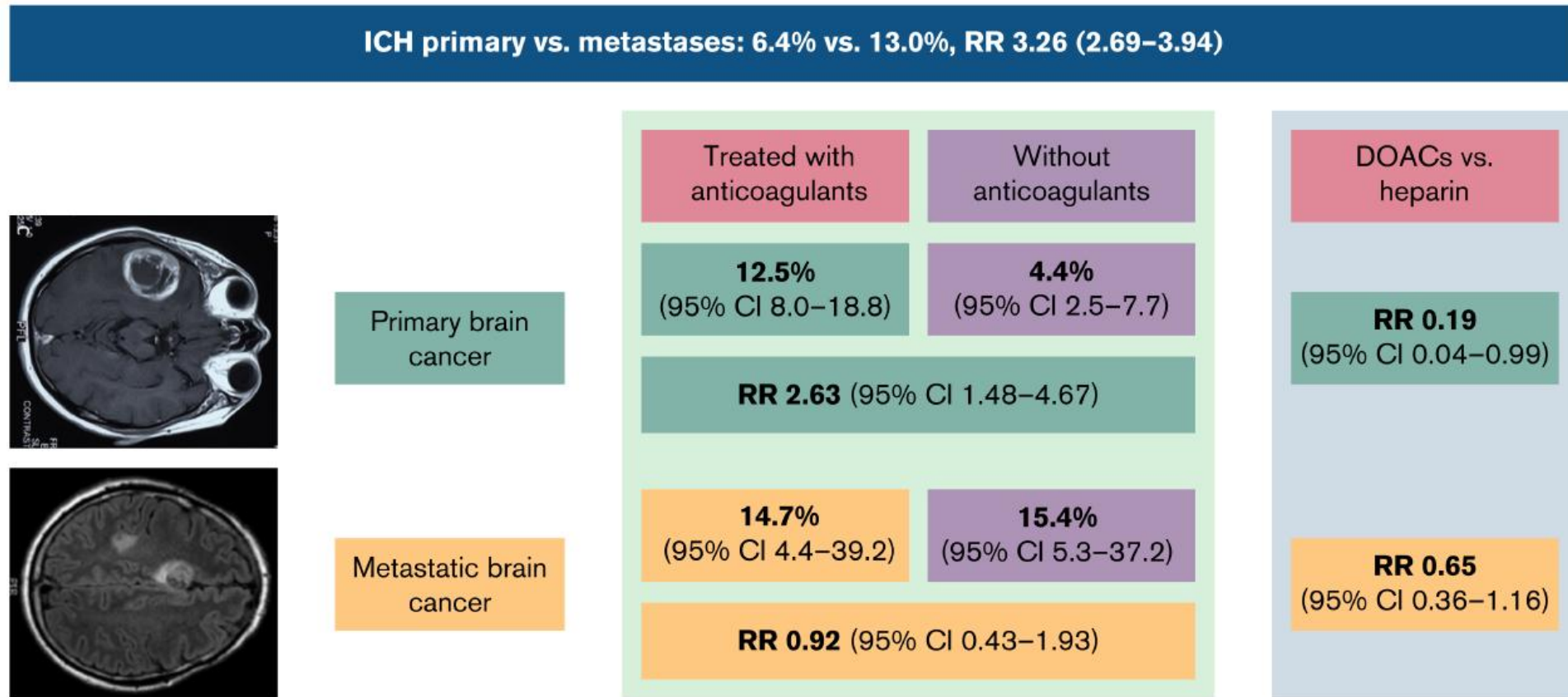
Bleeding complications: VTE in GBM patients

- 414 GBM patients
 - 15.7% had VTE
 - 94% treated with therapeutic anticoagulant
- Bleeding complications
 - **11.5% ICH**
 - **3.3% SDH**
 - 7.0% others

Cause of death	All patients, n = 414	Non-VTE cohort, n = 349	VTE cohort, n = 65
Tumor progression	283 (90.7%)	246 (92.8%)	37 (78.7%)
Bleeding	5 (1.6%)	4 (1.5%)	1 (2.1%)
Intracranial	4 (1.3%)	3 (1.1%)	1 (2.1%)
Gluteal muscle	1 (0.3%)	1 (0.4%)	0
Thromboembolic event, assumed cardiopulmonary failure	3 (1.0%)	0	3 (6.4%)

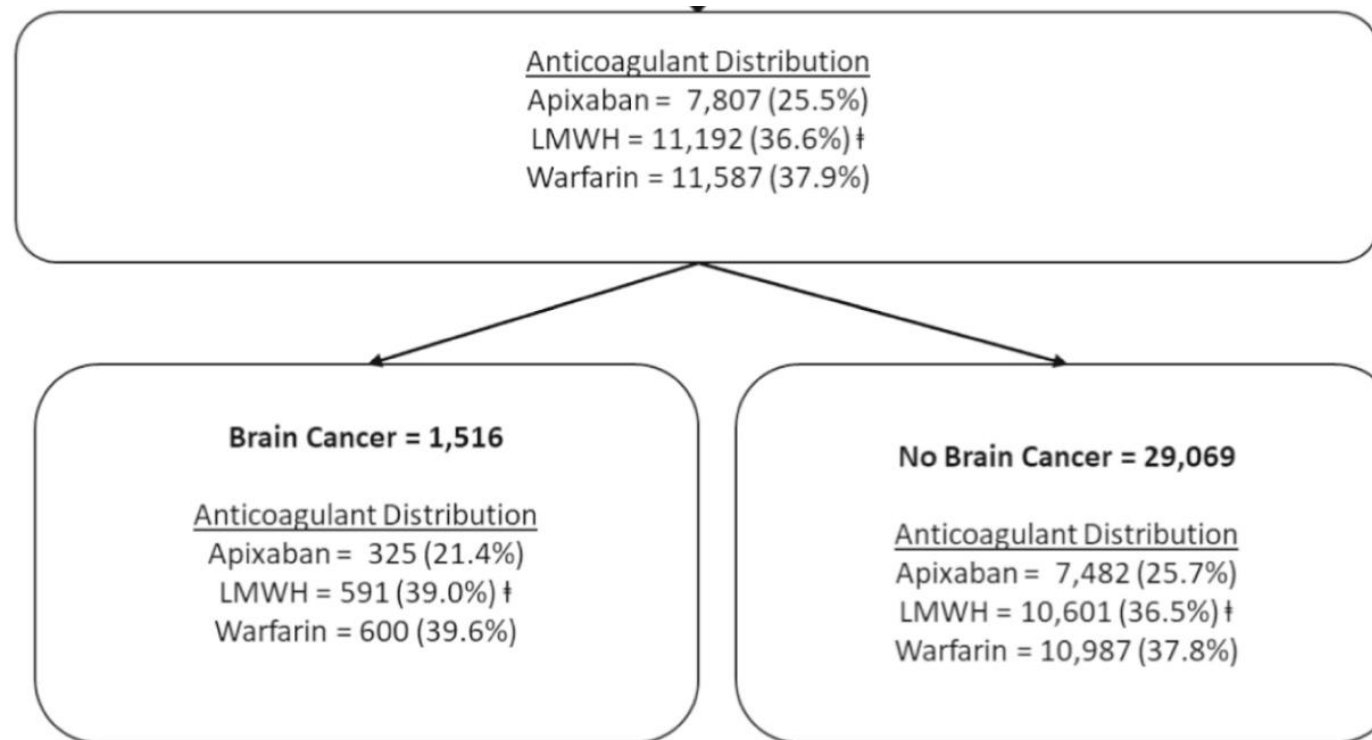
ICH in brain cancer patients with or without AC

- Meta-analysis of 13 studies



AC in patients with and without brain cancer

- 4 US commercial and Medicare databases

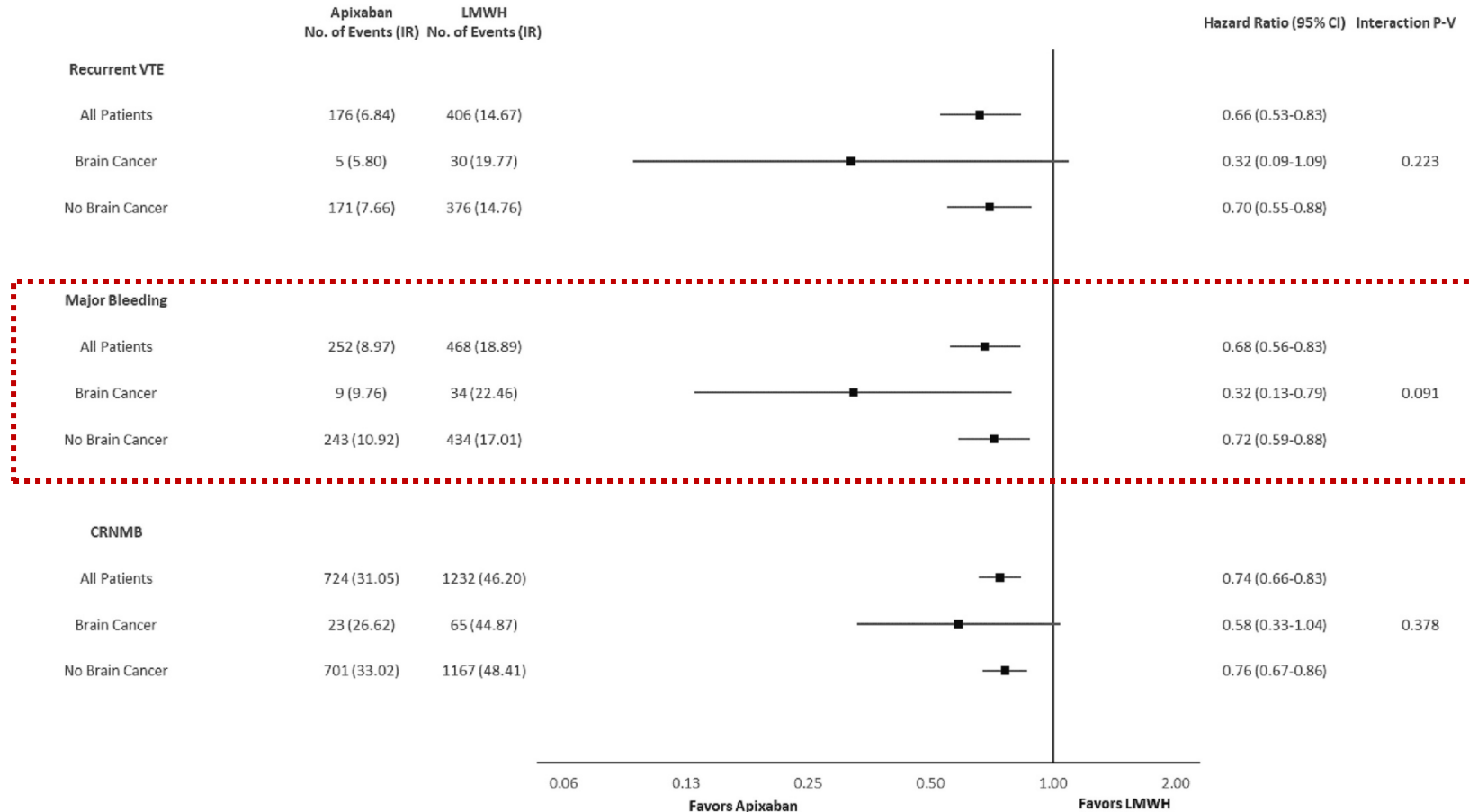


AC in patients with and without brain cancer

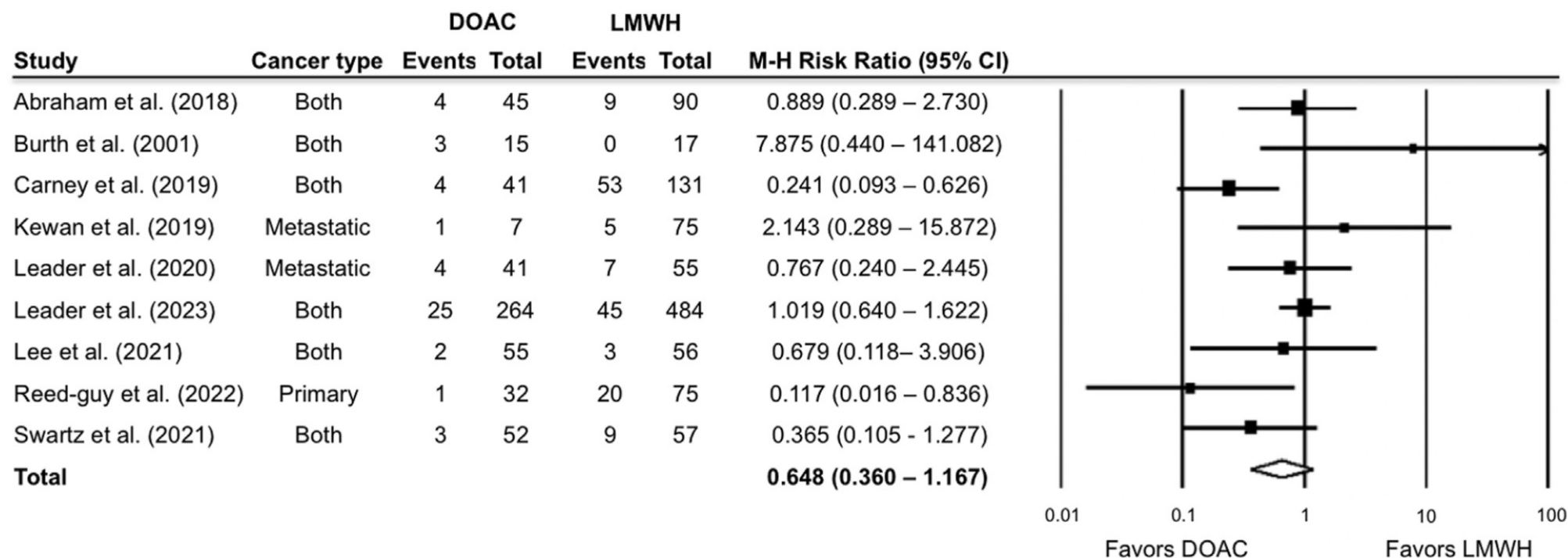
Recurrent VTE

Major bleeding

CRNMB

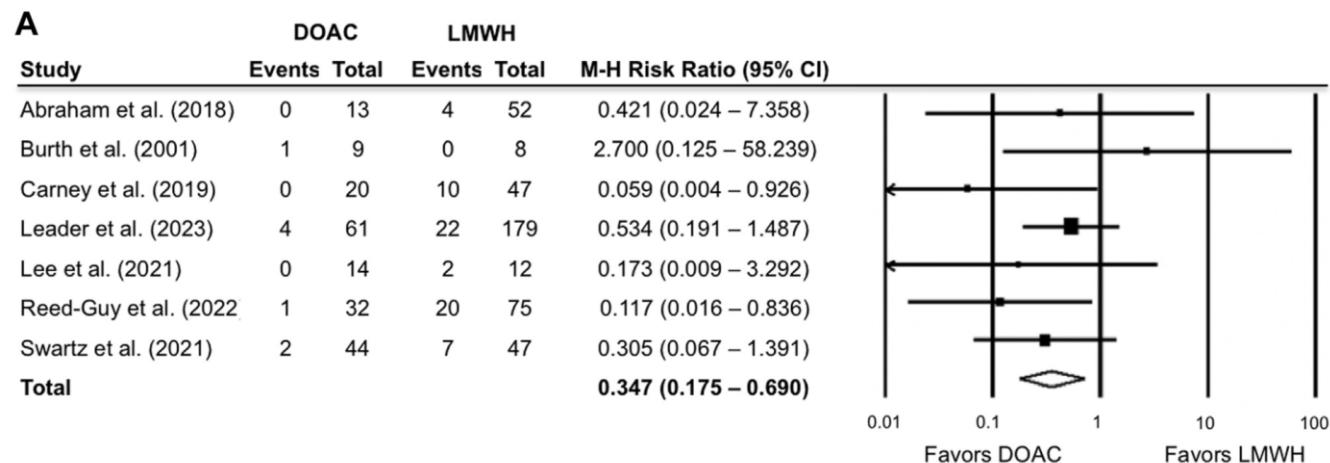


ICH in patients receiving DOAC vs LMWH

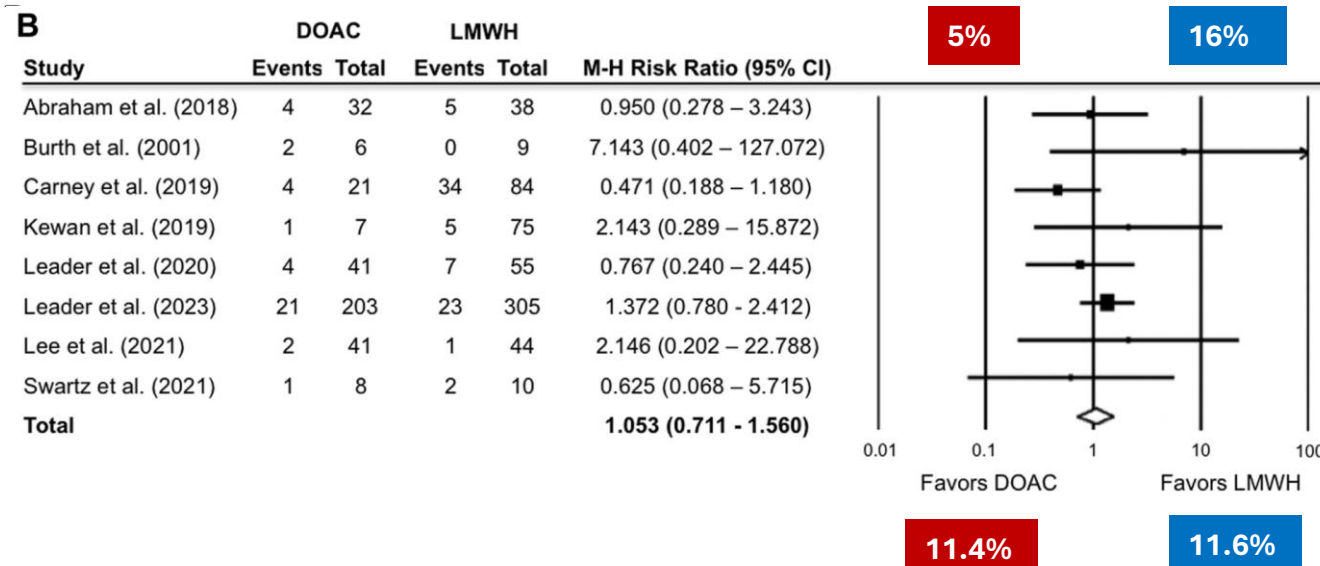


ICH in patients receiving DOAC vs LMWH

Primary brain tumor

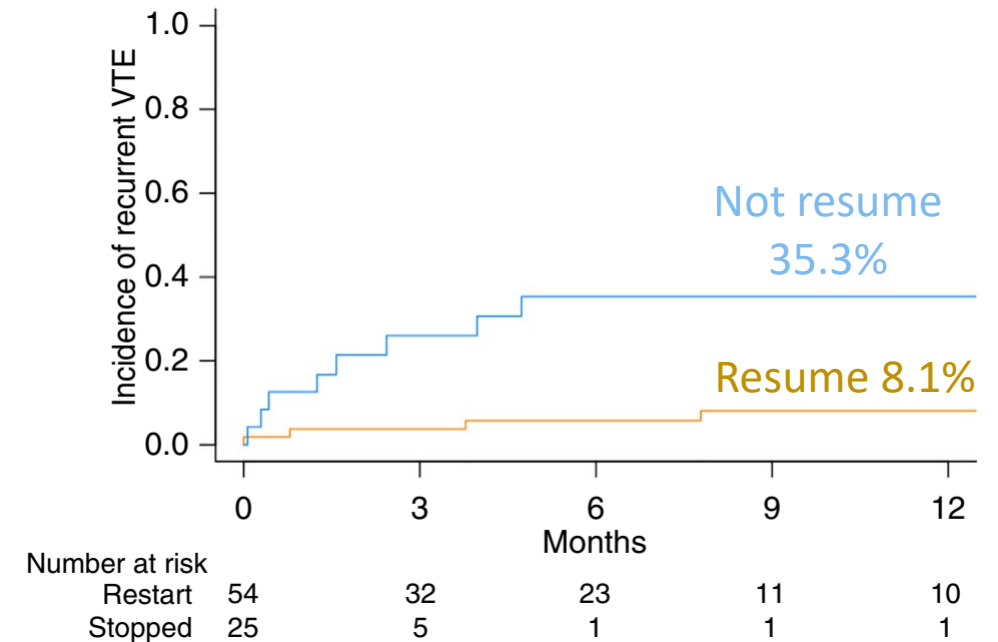


Metastatic brain tumor



AC after ICH in brain tumors

- 79 patients with brain tumors + ICH on AC
 - 68% resumed
- Major ICH (**ICH>10 cm, symptoms, requiring intervention**)
 - Recurrent ICH 14.5%
- Smaller ICH
 - Recurrent ICH 2.6%
- Recurrent VTE
 - 8.1% vs 35.3% in resumed VS not resume



Prophylactic dose AC in patients with ICH

Prophylactic dose LMWH

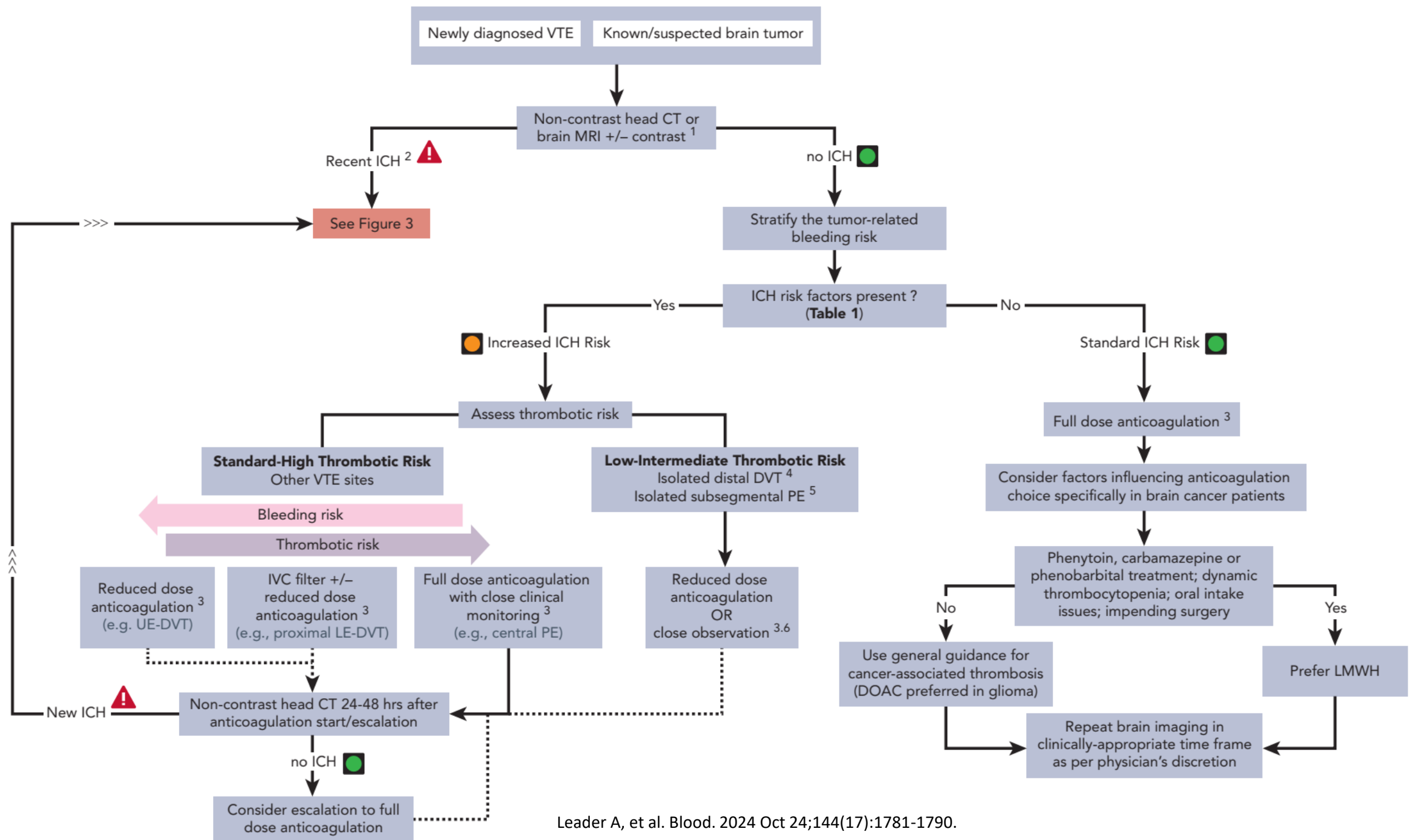
Study	Patients	Early vs late prophylaxis	ICH expansion or Rebleeding	P
Ianosì 2019	134 patients with spontaneous ICH	≤ 48 hr vs >48 hr	14.5% vs 26%	0.16
Faust 2017	400 patients with spontaneous ICH	≤ 48 hr vs >48 hr	5.6% vs 5%	0.80

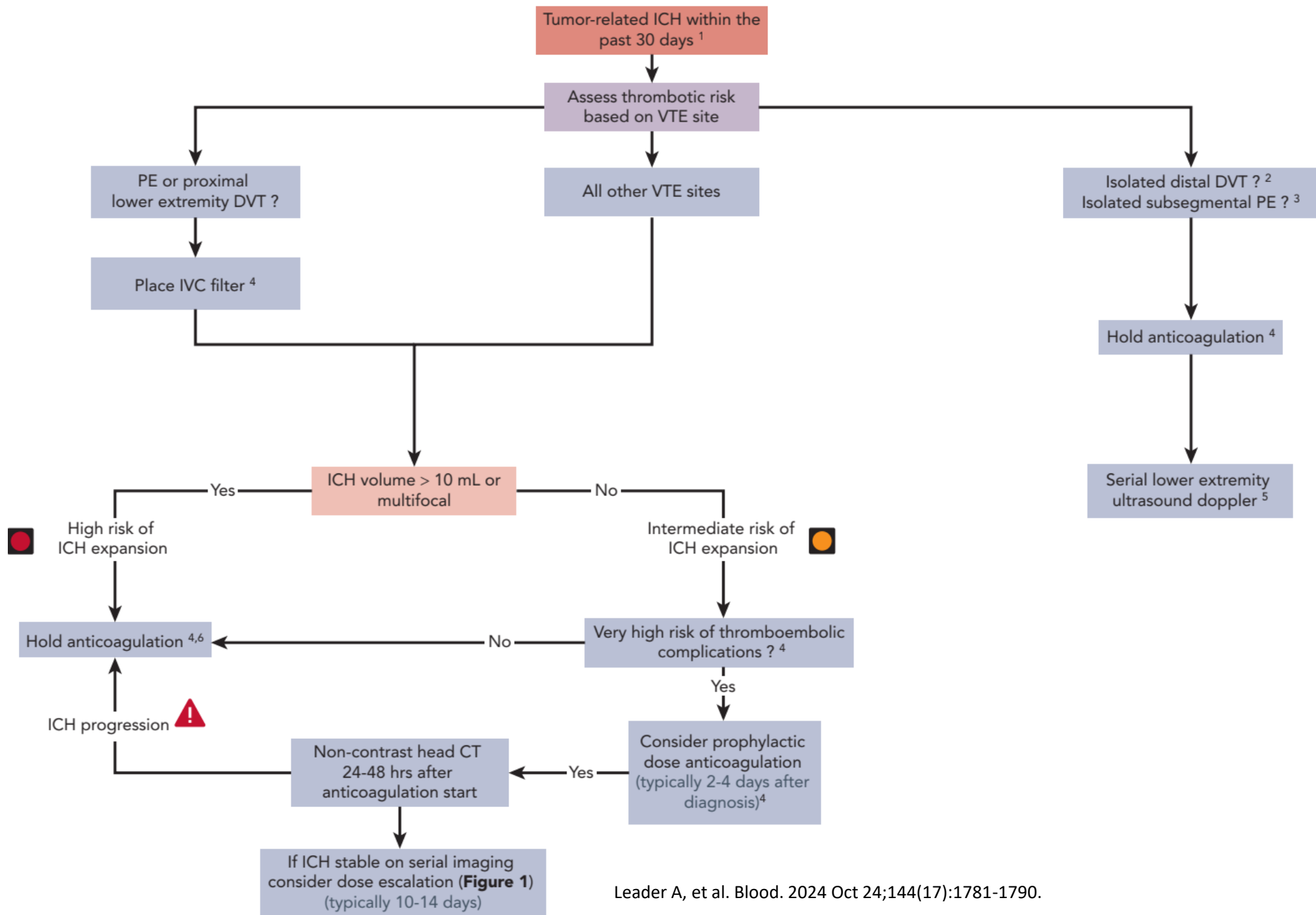
Management by thrombotic risk

- Standard-high thrombotic risk
- Low-intermediate thrombotic risk
 - Isolated distal DVT
 - Isolated subsegmental PE

Management by risk of ICH

- Higher risk of ICH
 - Prior ICH with large volume (≥ 10 ml volume)
 - Platelet count $< 50 \times 10^9/L$
- Intermediate risk of ICH
 - High-grade glioma
 - Platelet count $< 100 \times 10^9/L$
 - Antiplatelet use





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Recurrent VTE in anticoagulated cancer patients

- Prevalence
 - 2% at 1 year; prospective trials
 - 4-17% at 6 months: registry
- Impact of recurrent VTE in cancer patients
 - 52% increased risk of mortality
- Risk factors: type of anticoagulant
 - Warfarin: highest risk
 - LMWH: HR 0.6 (0.45-0.79)
 - DOAC: HR 0.63 (0.47-0.86)

Diagnosis for recurrent DVT

- Presence of a new non-compressible venous segment
- Established abnormal proximal vein segment
 - **Increase in diameter by >4 mm → diagnosis of recurrent DVT**
 - If the diameter increases between 2 and 4 mm
 - subsequent CUS at day 7
 - If the diameter increase is <2 mm
 - serial CUS only in cases of high clinical probability

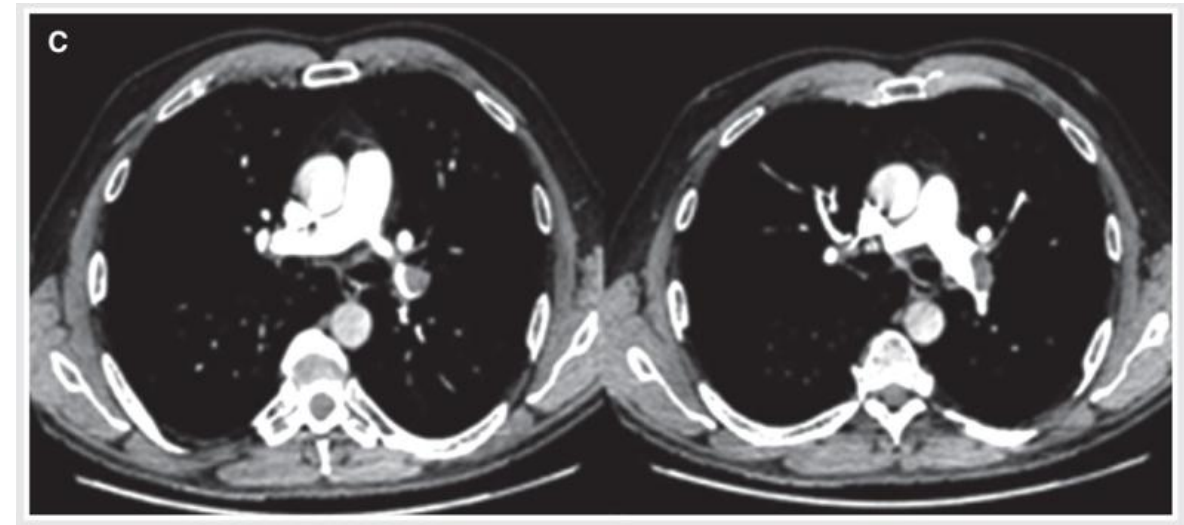
Diagnostic criteria for recurrent PE-CTPA

Suspected PE

- One or more new filling defects observed in segmental or more proximal arteries
- A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter
- If CT-PA cannot be performed, demonstration of a new or recurrent proximal DVT in the lower extremities by colour Doppler U/S, venography or MRI allows a diagnosis of recurrent PE to be made

Tumor thrombus

- Common tumors → tumor thrombus
 - Renal cell carcinoma
 - Hepatocellular carcinoma
 - Thyroid cancer
 - Metastatic disease
- (FDG-PET) can be useful to distinguish a tumor from bland thrombi
- The value of anticoagulation in cases of tumor thrombus is uncertain



Assessment for potential causes of recurrent VTE

- Extrinsic compression by tumor masses
- Cancer progression
- Anticoagulant administration
 - Poor compliance
 - Temporary interruption
 - Drug-drug interaction
 - Decreased absorptions
- Others
 - Intravascular devices
 - APS
 - HIT

Class	Strong CYP3A4 inducers	Moderate CYP3A4 inducers
Antineoplastic	Enzalutamide Apalutamide Mitotane Ivosidenib	Dabrafenib Lorlatinib Pexidartinib Sotorasib
Other	Carbamazepine Phenytoin Rifampin	

Anticoagulant management in recurrent VTE despite anticoagulant

- Dose continuation
- Dose escalation
- Switch class of anticoagulant

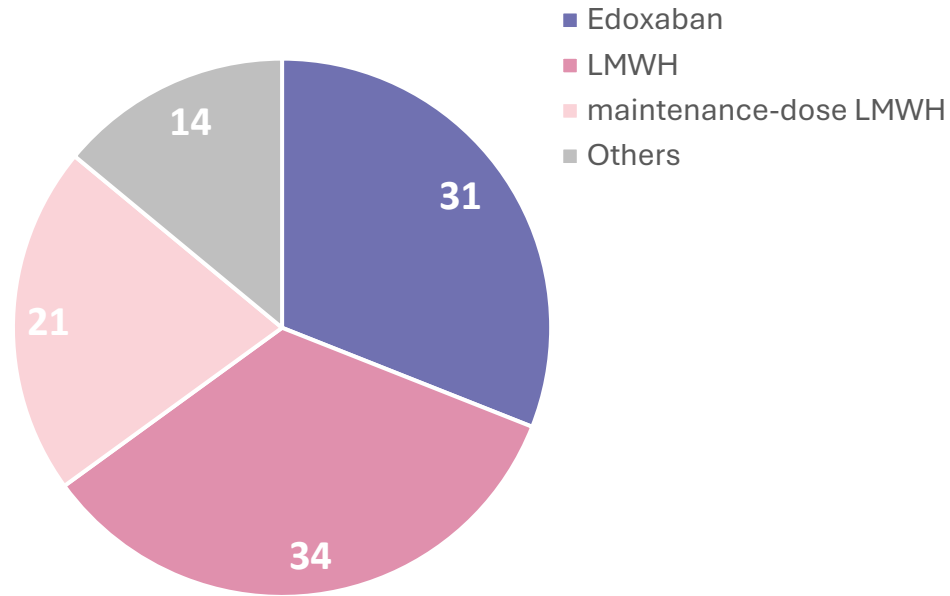
Dose escalation LMWH in cancer patients

- 70 cancer patients with recurrent VTE despite anticoagulant
- Anticoagulant management
 - Warfarin → therapeutic LMWH
 - Low dose LMWH → therapeutic LMWH
 - Therapeutic LMWH → 20-25% increased dose for at least 4 weeks
- 3-month outcomes
 - Second recurrent VTE 8.6%
 - 50% therapeutic LMWH
 - 50% increased dose LMWH
 - Bleeding complication 4.3%

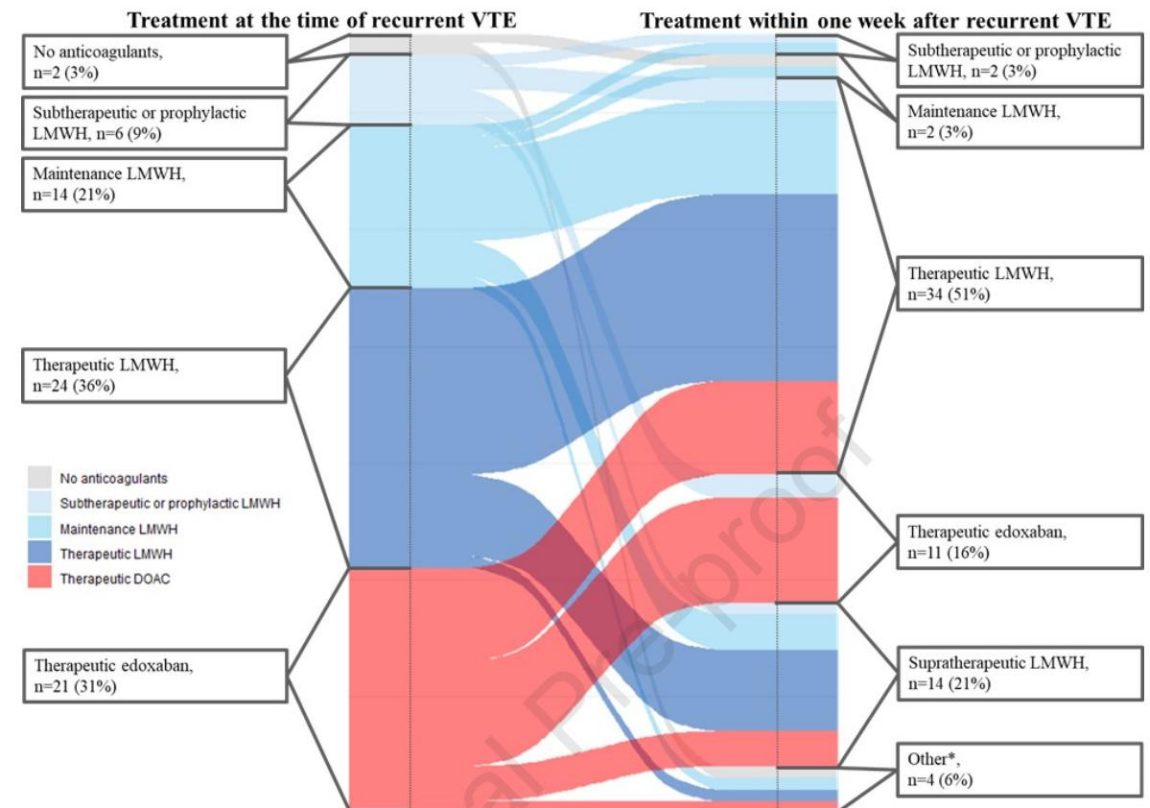
Recurrent VTE after on-treatment

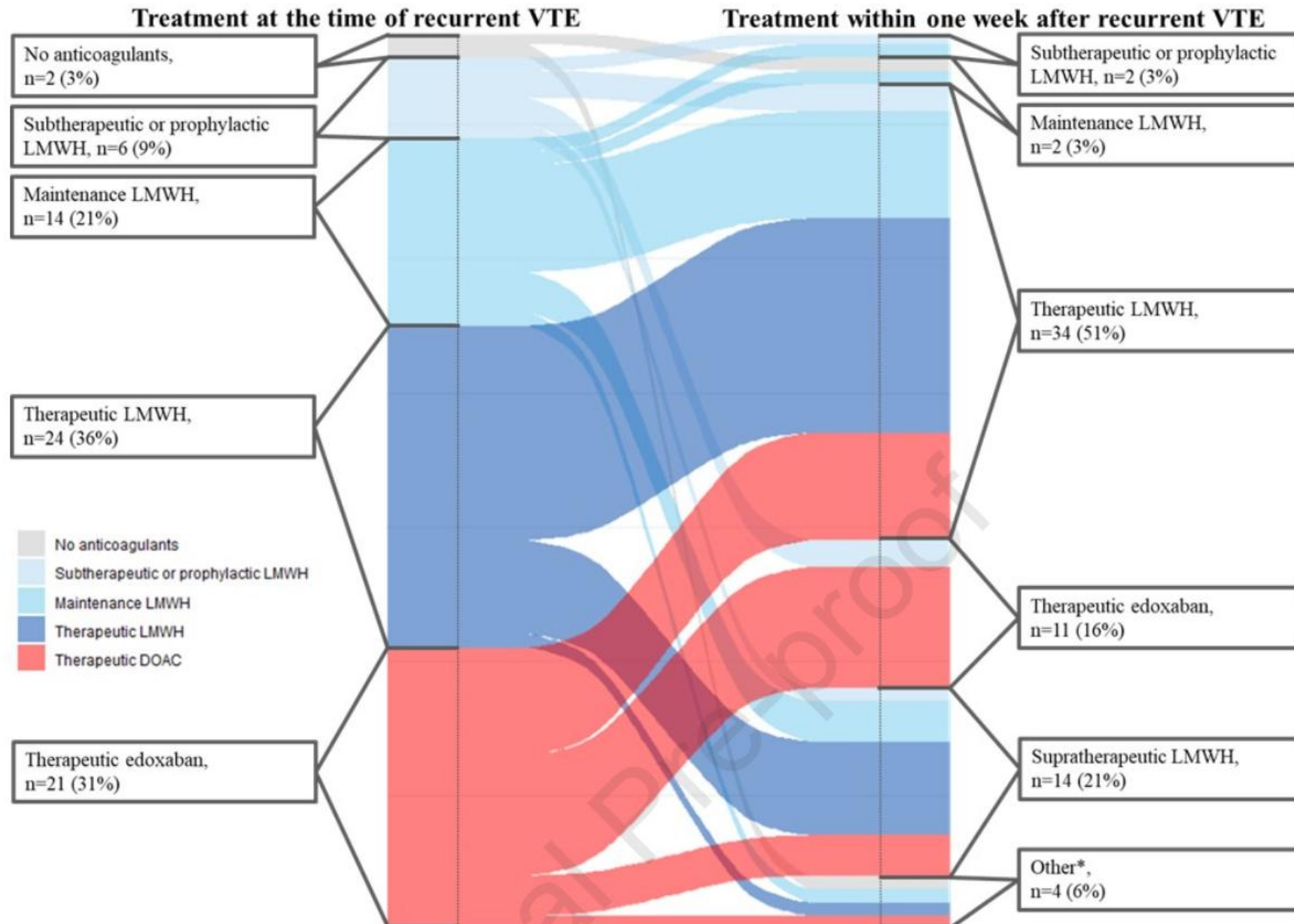
Hokusai VTE cancer study

- 67 patients with VTE after on-treatment



- Anticoagulant management





Recurrent VTE after on-treatment

Hokusai VTE cancer study

3-month outcomes after recurrent VTE

	Increased dose (n=28)	Unchanged (n=35)	P-value
Second recurrent VTE	7.1%	11.4%	0.86
Major bleeding	10.7%	2.9%	0.47
All-cause mortality	17.9%	40.0%	0.14

Summary #3

- Objectively confirmed recurrent VTE
- Clinical assessment for potential causes of recurrent VTE
- Therapeutic management
 - Warfarin → Therapeutic LMWH
 - Subtherapeutic LMWH → Therapeutic LMWH
 - Therapeutic LMWH → 20-25% increased dose LMWH or switch to DOAC
 - Subtherapeutic DOAC → Therapeutic DOAC or therapeutic LMWH
 - Therapeutic DOAC → Therapeutic LMWH or 20-25% increased dose LMWH

Thank you