Cancer Associated Thrombosis-Difficult Cases and DOACs-when to use

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Research Support/P.I.	**Leo Pharma, BMS**
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Consultant	**No relevant conflicts of interest to declare**
Major Stockholder	**No relevant conflicts of interest to declare**
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Disclosure of Commercial Support

- **This program has received financial support from Leo Pharma.**

- **<u>Potential for conflict(s) of interest</u>:**
  - Marc Carrier will receive an honorarium from CAGPO
  - Leo Pharma benefits from the sale of a product that will be discussed in this program: Tinzaparin (Innohep).

Objectives

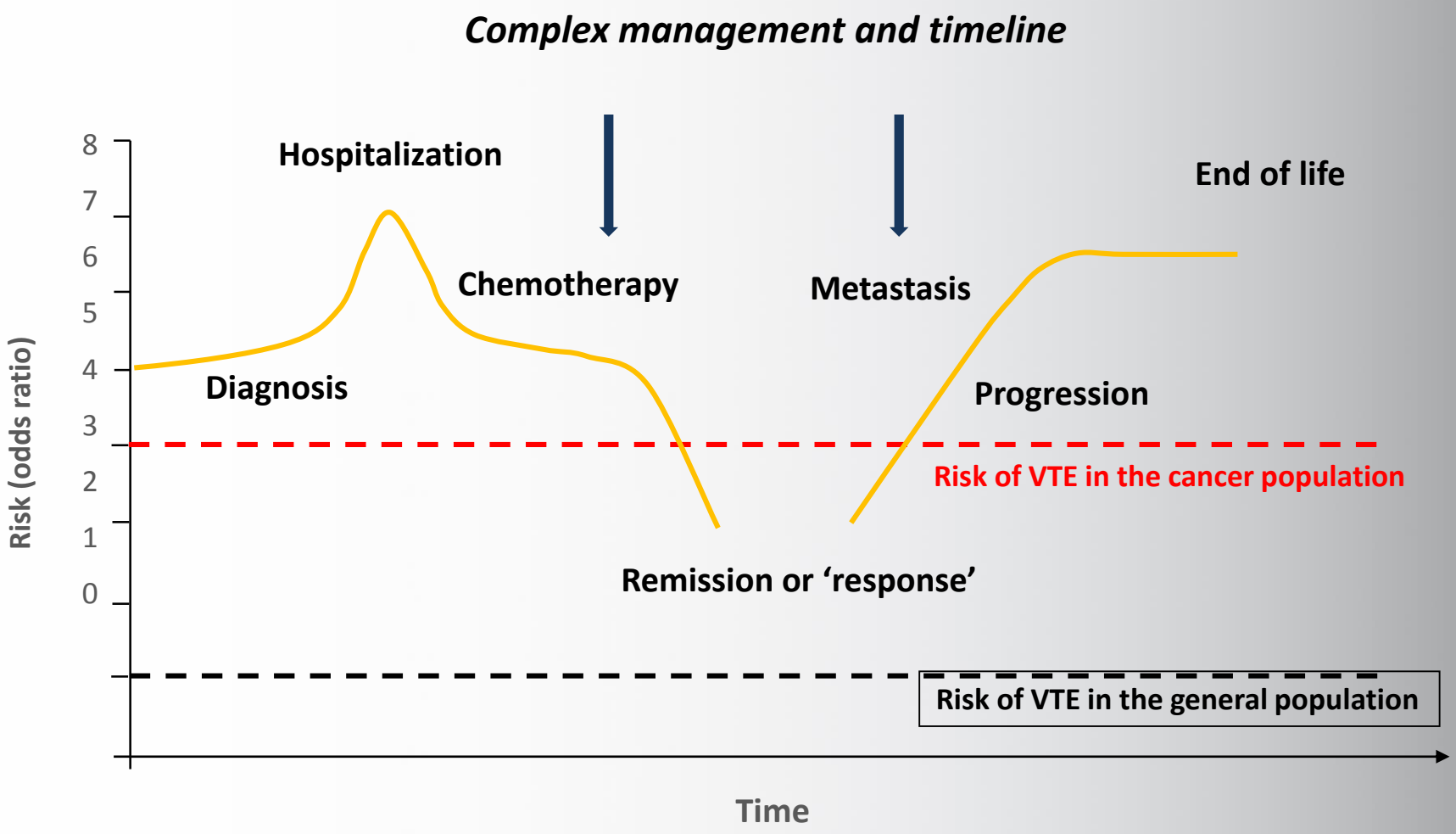
- To review the evidence for the acute and long-term treatment of CAT
- To discuss the use of DOACs for the management of CAT
- Review the management of patients with recurrent thrombosis despite anticoagulation.

Incidence

- Annual incidence of VTE in the general population is 117 per 100,000
  - Cancer alone was associated with a 4.1-fold risk of thrombosis
  - Chemotherapy increased the risk 6.5-fold
- Combining these estimates yields an approximate annual incidence of venous thromboembolism (VTE) of 1 per 200 in a population of cancer patients

Heit JA et al. Arch Intern Med. 2000; 160: 809–815.

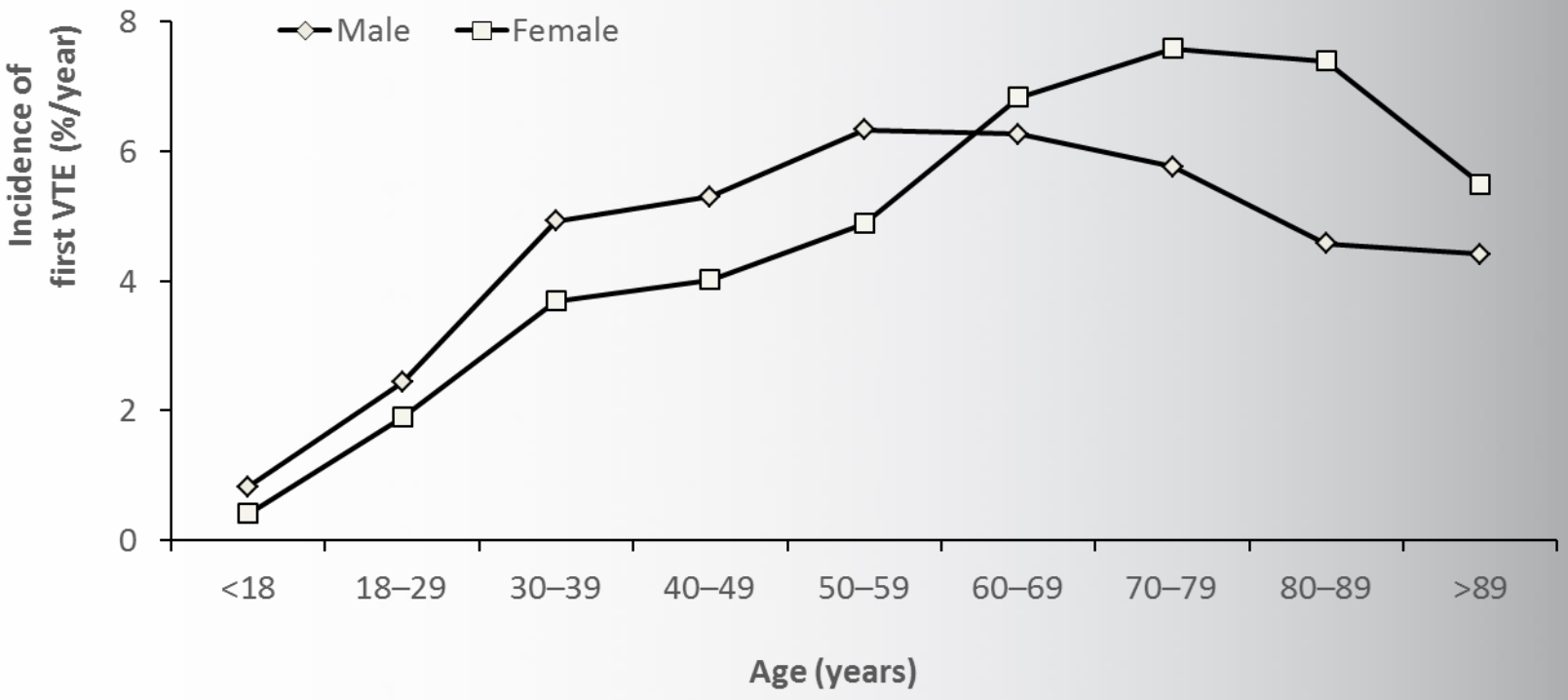
Cancer and VTE



Lyman GH, *Cancer* 2010;7:1334–1349

Incidence of CAT among patients with active cancer

- Incidence rate of a first VTE event in patients with active cancer**: 5.8 (95% CI 5.7–6.0)** per 100 person-years
- Incidence of a first VTE event was highest in the elderly population



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

Incidence rate of CAT by cancer type

Incidence rate (95% CI) of first VTE per 100 person-years by cancer type

Age	Bladder	Breast	Colon	Lung	Prostate	Uterus	Haem.	Brain	Ovary	Pancreas	Stomach
Total ≥18	2.7 (2.4–3.0)	3.2 (2.9–3.4)	6.7 (6.3–7.2)	10.1 (9.5–10.8)	4.4 (4.0–4.7)	7.0 (5.9–8.3)	4.5 (4.1–4.8)	12.1 (10.3–14.0)	11.9 (10.6–13.2)	14.6 (12.9–16.5)	10.8 (9.5–12.3)

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

Patient demographics

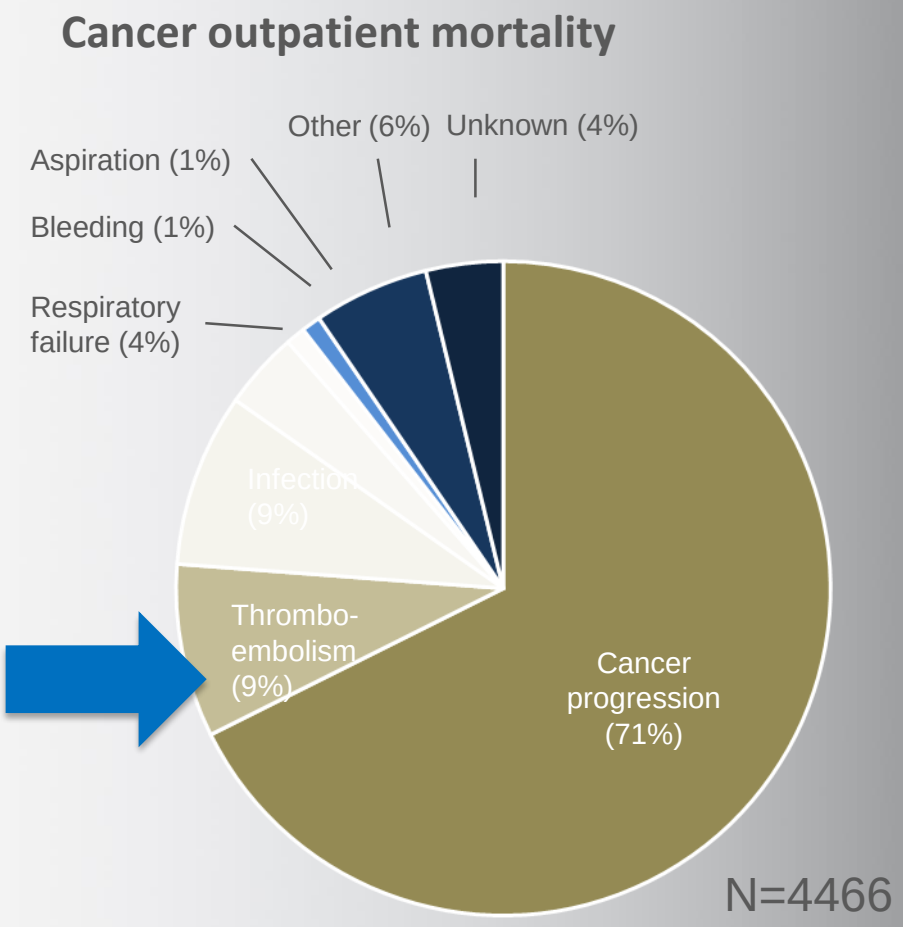
Patients with active cancer and a first VTE (N=6592)

	DVT (n=3055)	PE (n=3537)	Total (N=6592)
Common cancer types, n (%)			
Prostate (males)	278 (19.1)	287 (16.1)	565 (17.5)
Breast (females)	225 (14.0)	281 (16.0)	506 (15.1)
Lung	315 (10.3)	603 (17.0)	918 (13.9)
Colon	384 (12.6)	443 (12.5)	827 (12.5)
Haematological	360 (11.8)	309 (8.7)	669 (10.1)
Ovarian (females)	136 (8.5)	182 (10.3)	318 (9.5)
Bladder	186 (6.1)	133 (3.8)	319 (4.8)
Uterus (females)	83 (5.2)	58 (3.3)	141 (4.2)
Pancreas	129 (4.2)	131 (3.7)	260 (3.9)
Stomach	104 (3.4)	133 (3.8)	237 (3.6)
Brain	79 (2.6)	87 (2.5)	166 (2.5)

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

VTE as a cause of death

- Thromboembolism is the **second leading** cause of death in patients with cancer
- Annual death rate for VTE: 448 per 100,000 cancer outpatients
  - **47-fold increase** over the general population



1. Khorana AA *et al, J Thromb Haemost* 2007;5:632–634; 2. Khorana AA *et al, Thromb Res 2*010;125:490–493

Case 1

Ms. MT

- 85 yo woman (Looks much younger),
- LABC – ER/PE positive/Her2neu neg
- Neoadjuvant letrozole
- No significant response at time of mastectomy - large tumor, lots of positive nodes positives
- Placed on tamoxifen (because of lack of response to AI)

Ms. MT

- 6 weeks later:
  - New SOB/CP and right leg swelling
  - VSS
  - Hb: 100; Plt 150 and CrCl 35 cc/min
  - CTPA: extensive acute PE involving all lobes and and main pulmonary arteries. Evidence of right heart strain.

Management of Ms. MT

- IV heparin/ LMWH and warfarin
- LMWH only
- DOAC only

Acute anticoagulation treatment

ACCP guidelines

- In patients with DVT of the leg or PE and cancer (CAT), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over:
  - VKA therapy (Grade 2B)
  - Dabigatran (Grade 2C)
  - Rivaroxaban (Grade 2C)
  - Apixaban (Grade 2C)
  - Edoxaban (Grade 2C)

Kearon C *et al, Chest* 2016;149:315–352

Acute anticoagulation treatment

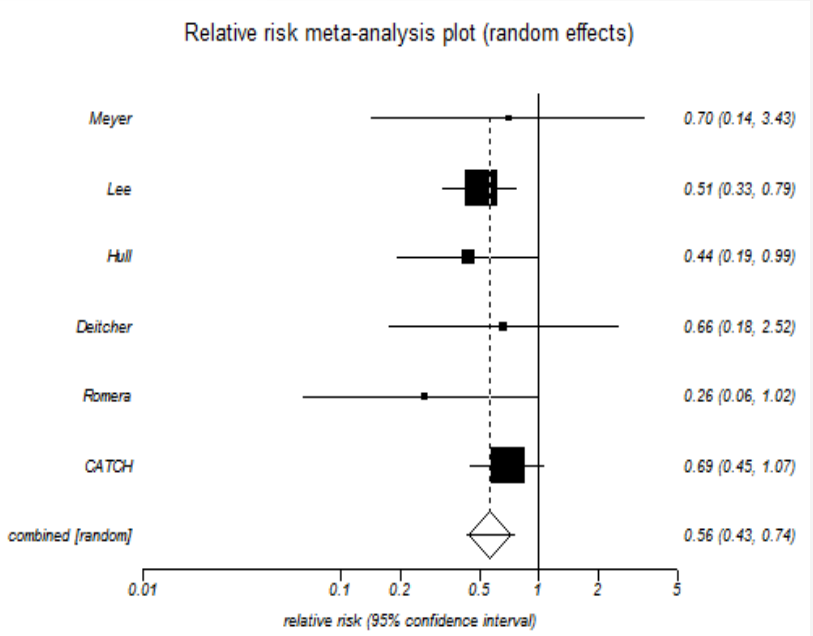
ITAC-CME

- LMWH is preferred over VKA therapy for the early treatment of CAT
  (Grade 1A)
- LMWH should be used for a minimum of 3 months to treat established CAT (Grade 1A)
- DOACs can be considered in patients with stable cancer not receiving systemic anti-cancer therapy, and in cases where VKA therapy is an acceptable, but not an available, option (Guidance)

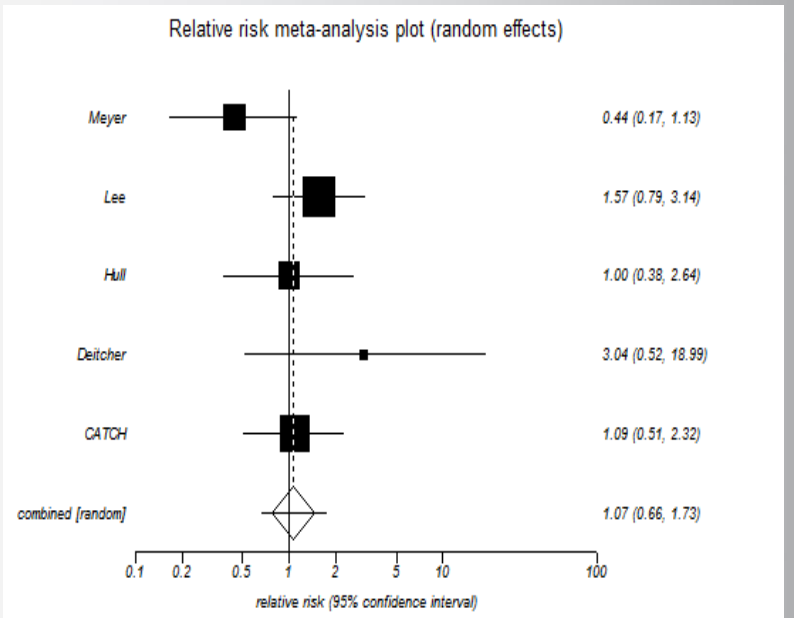
Farge D *et al, Lancet Oncol* 2016; 17:e452–466

Overall efficacy and safety of LMWH

Recurrent VTE



Major Bleeding



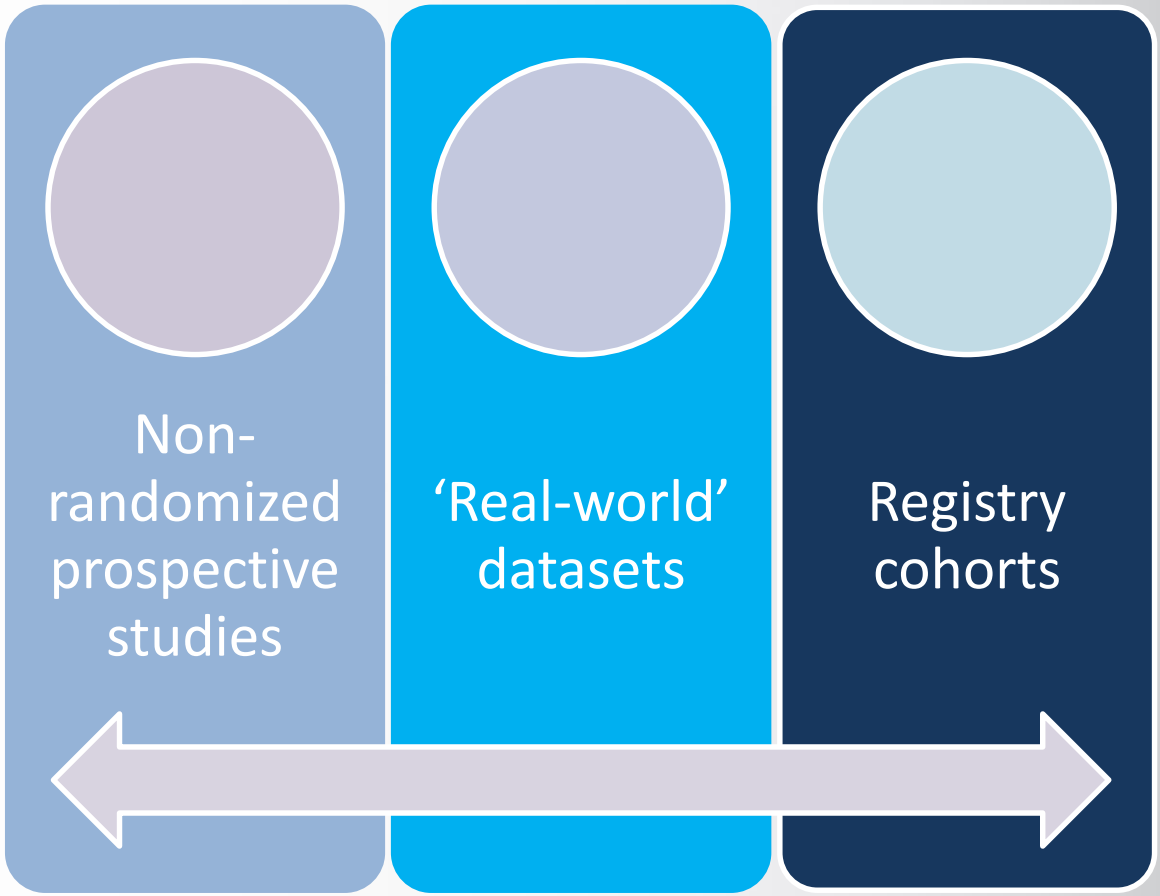
Recurrent VTE:
RR: 0.56
95% CI: 0.43-0.74

Major Bleeding:
RR: 1.07
95% CI: 0.66-1.73

Evidence for DOACs vs. VKA Cancer subgroups

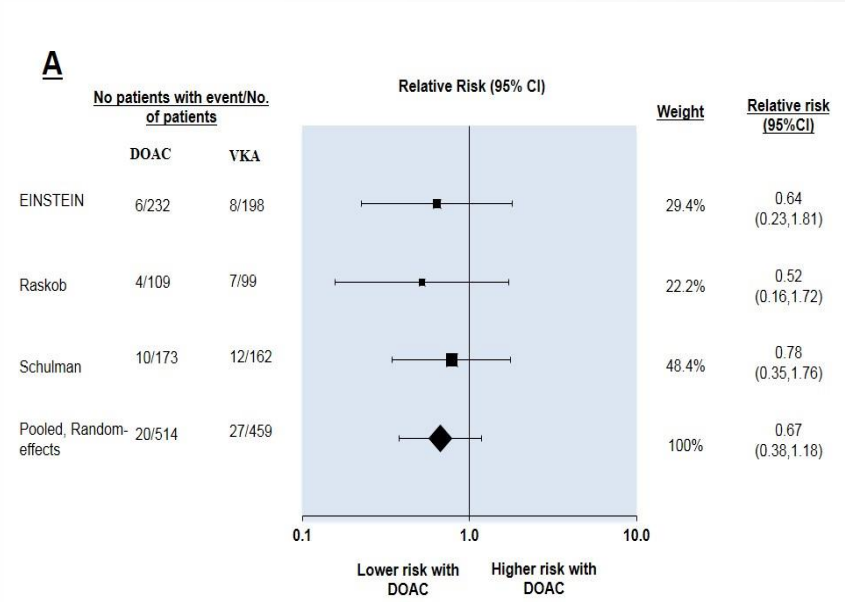
DOAC trial	Patients with active cancer	Recurrent VTE	Clinically relevant bleeding
EINSTEIN-DVT	Rivaroxaban 6.8%; enoxaparin/VKA 5.2%	Rivaroxaban 3.4%; enoxaparin/VKA 5.6%	Rivaroxaban 14.4%; enoxaparin/VKA 15.9%
EINSTEIN-PE	Rivaroxaban 4.7%; enoxaparin/VKA 4.5%	Rivaroxaban 1.8%; enoxaparin/VKA 2.8%	Rivaroxaban 12.3%; enoxaparin/VKA 9.3%
EINSTEIN-EXT	Rivaroxaban 4.7%; placebo 4.4%	Not Reported	Not Reported
AMPLIFY	Apixaban 2.5%; enoxaparin/warfarin 2.8%	Not Reported	Not Reported
AMPLIFY-EXT	placebo 2.2% 2.5 mg apixaban 1.8% 5 mg apixaban 1.1%	Not Reported	Not Reported
RE-COVER	Dabigatran 5%; warfarin 4.5%	Dabigatran 3.1%; warfarin 5.3%	Not Reported
RE-MEDY	Dabigatran 4.2%; warfarin 4.1%	Dabigatran 3.3%; warfarin 1.7%	Not Reported
Hokusai-VTE	Edoxaban 2.6%; warfarin 2.4%	Edoxaban 3.7%; warfarin 7.1%	Edoxaban 18.3%; warfarin 25.3%

DOACs in Cancer

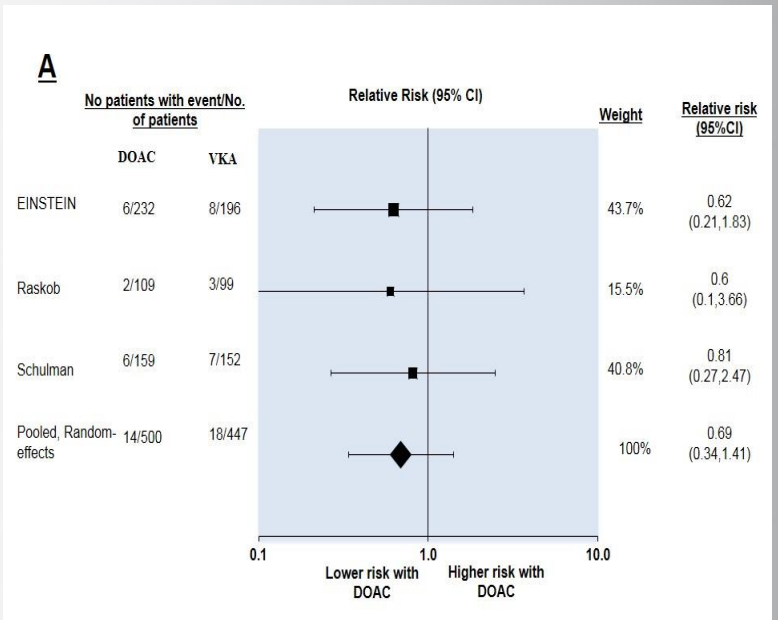


Overall efficacy and safety of DOAC

Recurrent VTE



Major Bleeding

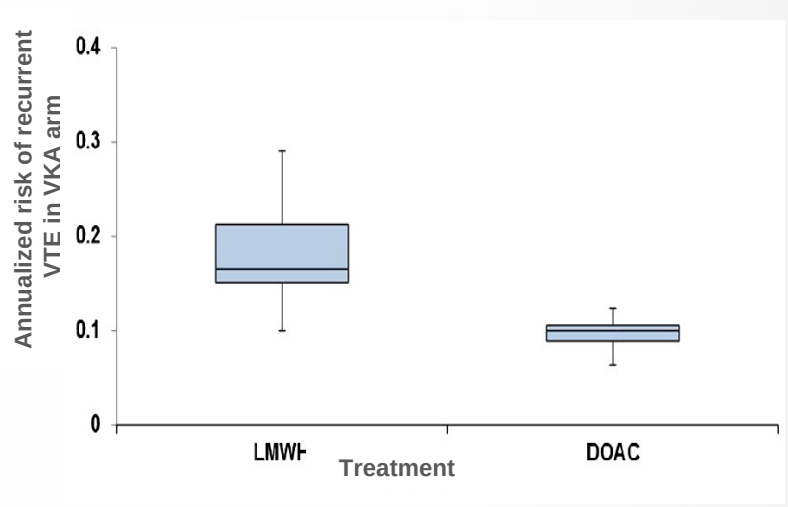


Recurrent VTE:
RR: 0.67
95% CI: 0.38-1.18

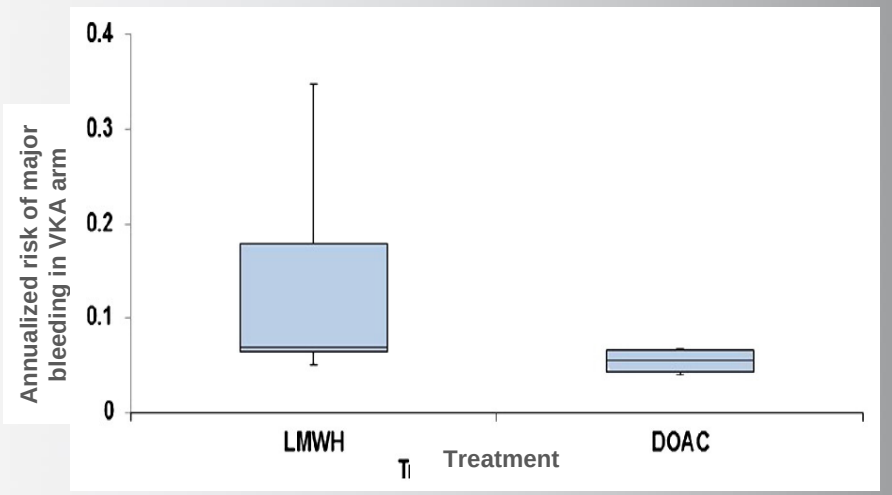
Major bleeding:
RR: 0.69
95% CI: 0.34-1.41

Lower risk cancer patients in DOAC trials?

Recurrent VTE



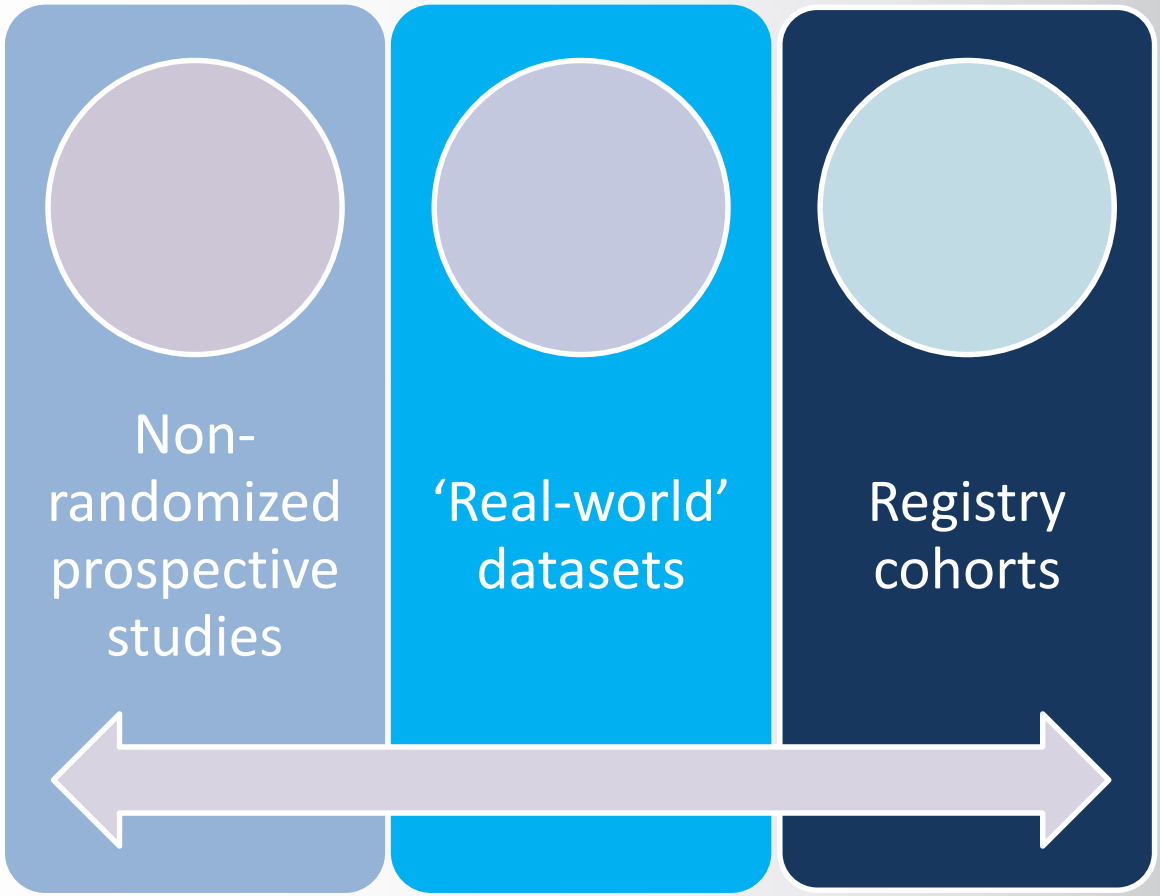
Major bleeding events



The higher annualized risk of recurrent VTE and major bleeding in LMWH trials suggests a higher-risk cancer population were enrolled in these studies

Carrier M *et al*, *Thromb Res* 2014;134:1214–1219

DOACs in Cancer



Mayo Clinic experience

Mayo Thrombophilia Clinic DOAC Registry (2013–2015)

- Consecutive patients treated with rivaroxaban for DVT or PE and had ≥3 months of follow-up (N=296)
  - n=118 with active cancer
- Genitourinary (23.6%), gastrointestinal (20.3%) and lung (13.5%)
- Recurrent VTE rate: 3.3%
  - n=4 only

Variable	Cancer (n=118)	No cancer (n=178)	*p*-value
VTE recurrence, n (%)	4 (3.3)	5 (2.8)	0.53
DVT, n	3	4	1.00
PE, n	1	1	1.00
Major bleeding, n (%)	3 (2.5)	0	0.06
NMCR bleeding, n (%)	4 (3.4)	1 (0.6)	0.08
Major and NMCR bleeding, n (%)	7 (5.9)	1 (0.6)	0.008
Minor bleeding, n (%)	3 (2.5)	3 (1.7)	0.69
Death, n (%)	37 (31.0)	0	<0.0001

Bott-Kitslaar DM *et al*, *Am J Med* 2016;129:615–619

MSKCC experience

Quality assessment initiative

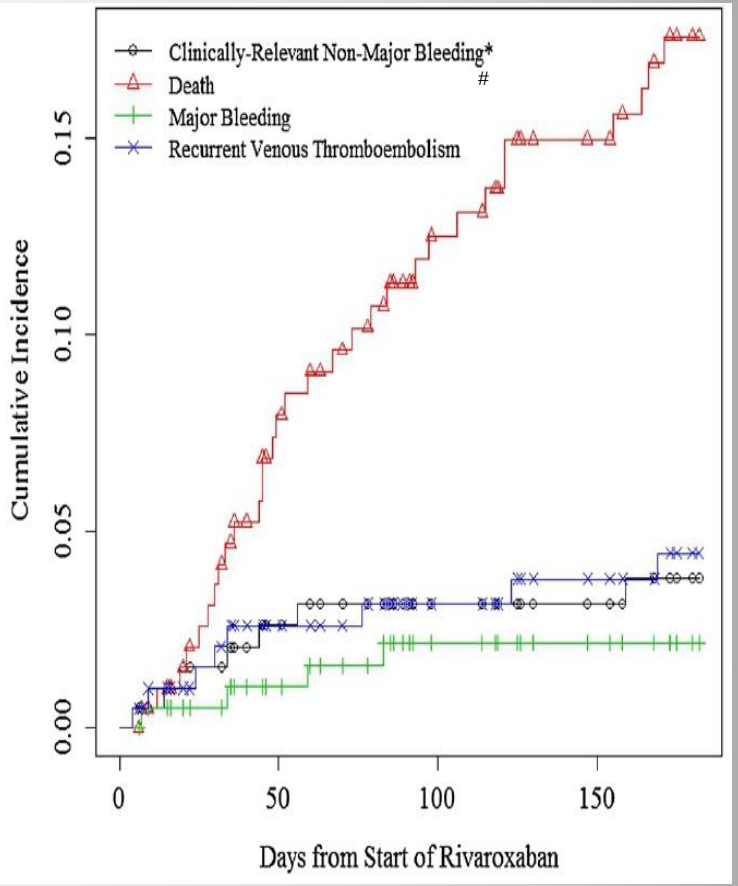
- 200 patients with active cancer and CAT treated with rivaroxaban
  - Intended to receive ≥6 months of therapy
- Several exclusions:
  - CrCl <30 ml/min
  - Liver function tests >3 × ULN
  - Expected malabsorption at stomach or small bowel
  - Active GU or GI lesions
  - Untreated primary CNS neoplasm
  - A body weight <50 or >150 kg
  - Any antiplatelet agent other than ASA 81 mg daily and any significant drug interaction
- Empirically dose-reduced: patients ≥75 years old received rivaroxaban 10 mg bid for 3 weeks followed by 15 mg od

Mantha S *et al, J Thromb Thrombolysis* 2017;43:166–171

MSKCC experience

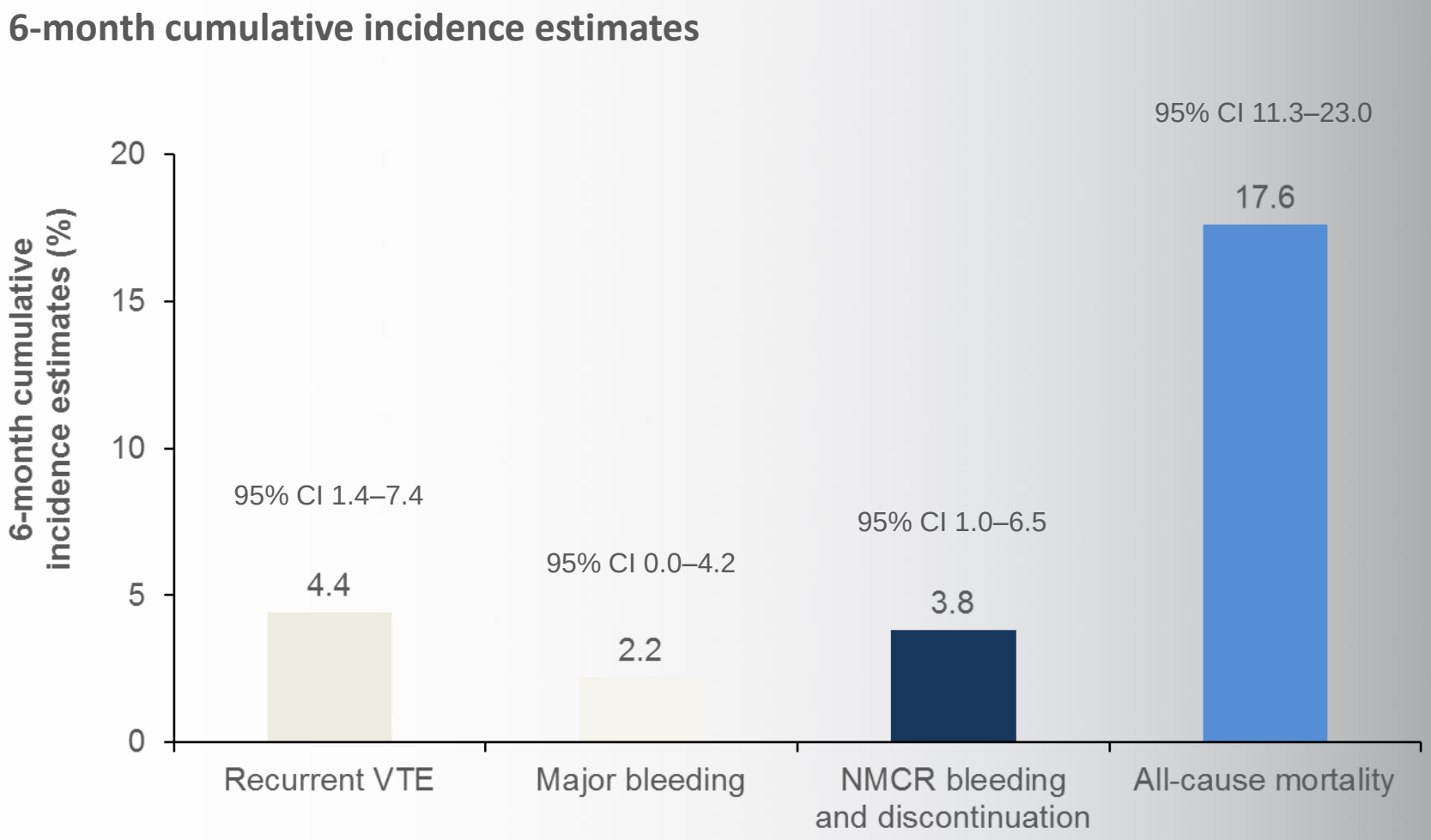
Characteristic	N
Cancer stage (of solid tumours, excluding brain)	
0–2	15
3	23
4	142
Cancer types	
Pancreas	34
Gynaecological	26
Lung	23
Breast	22
Genitourinary/prostate	21
Colorectal	18
Haematological	17
Stomach/oesophagus	6
Other	33

Cumulative incidence for competing risks



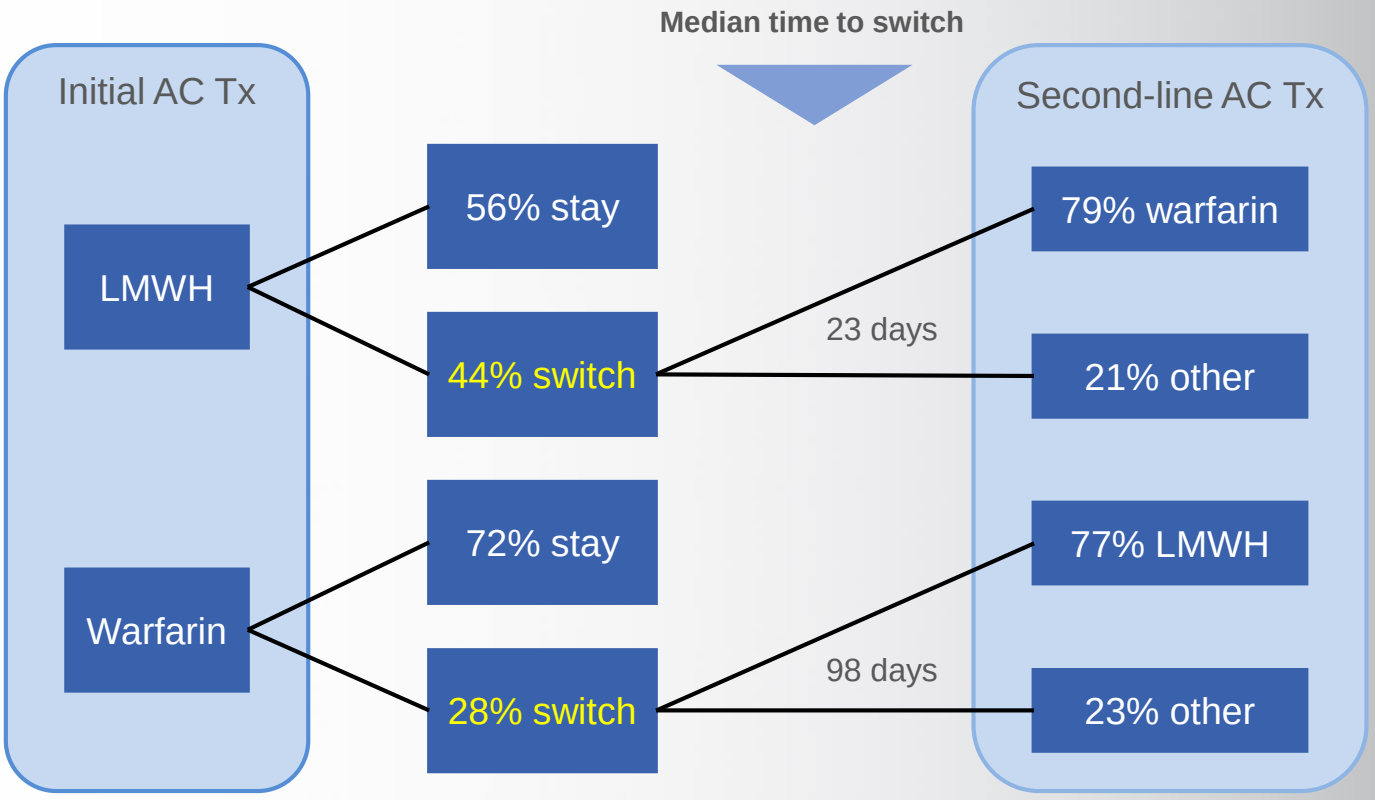
Mantha S *et al, J Thromb Thrombolysis* 2017;43:166–171

MSKCC experience



Mantha S *et al*, *J Thromb Thrombolysis* 2017;43:166–171

Real World

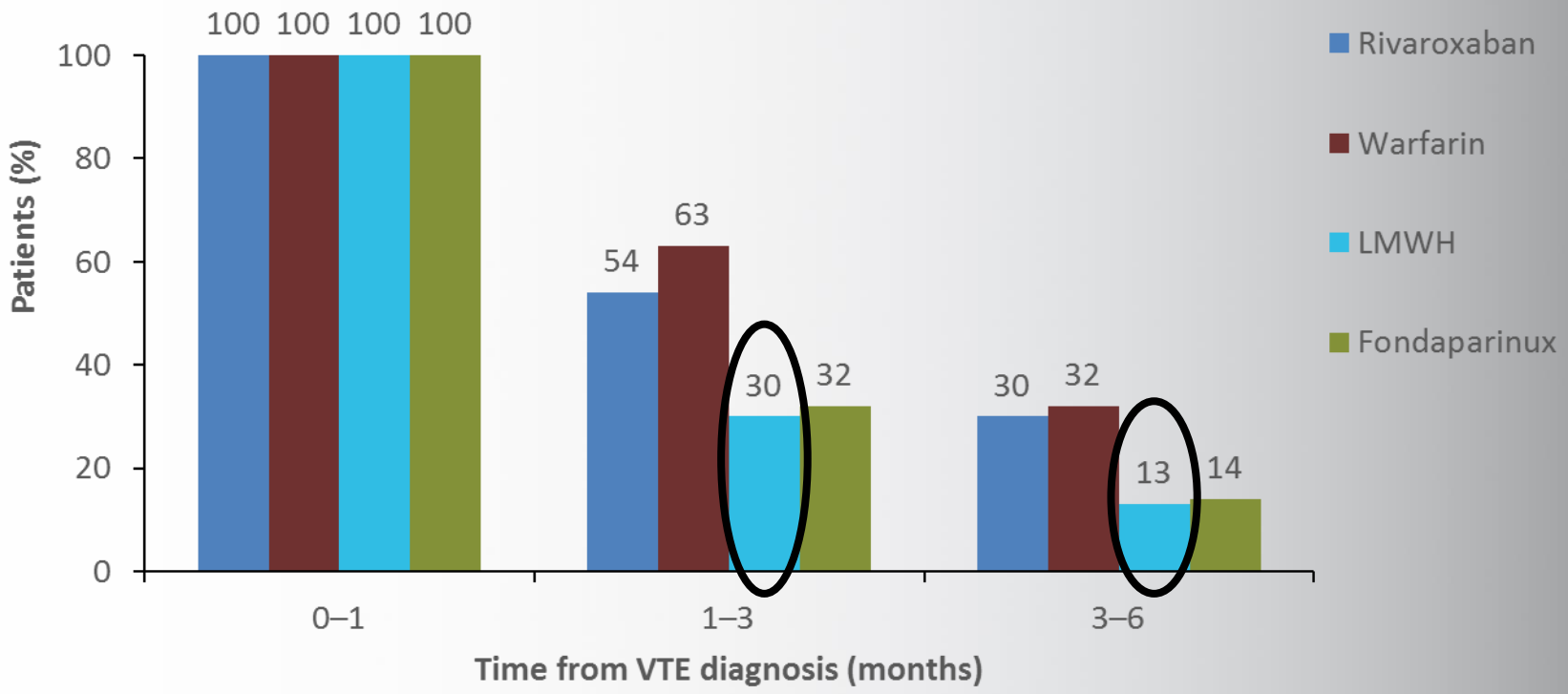


N=52,911 cancer patients with VTE in the USA, 2009–2014

Khorana AA *et al, Throm Res* 2016;145:51–53

Real-world anticoagulant use: duration

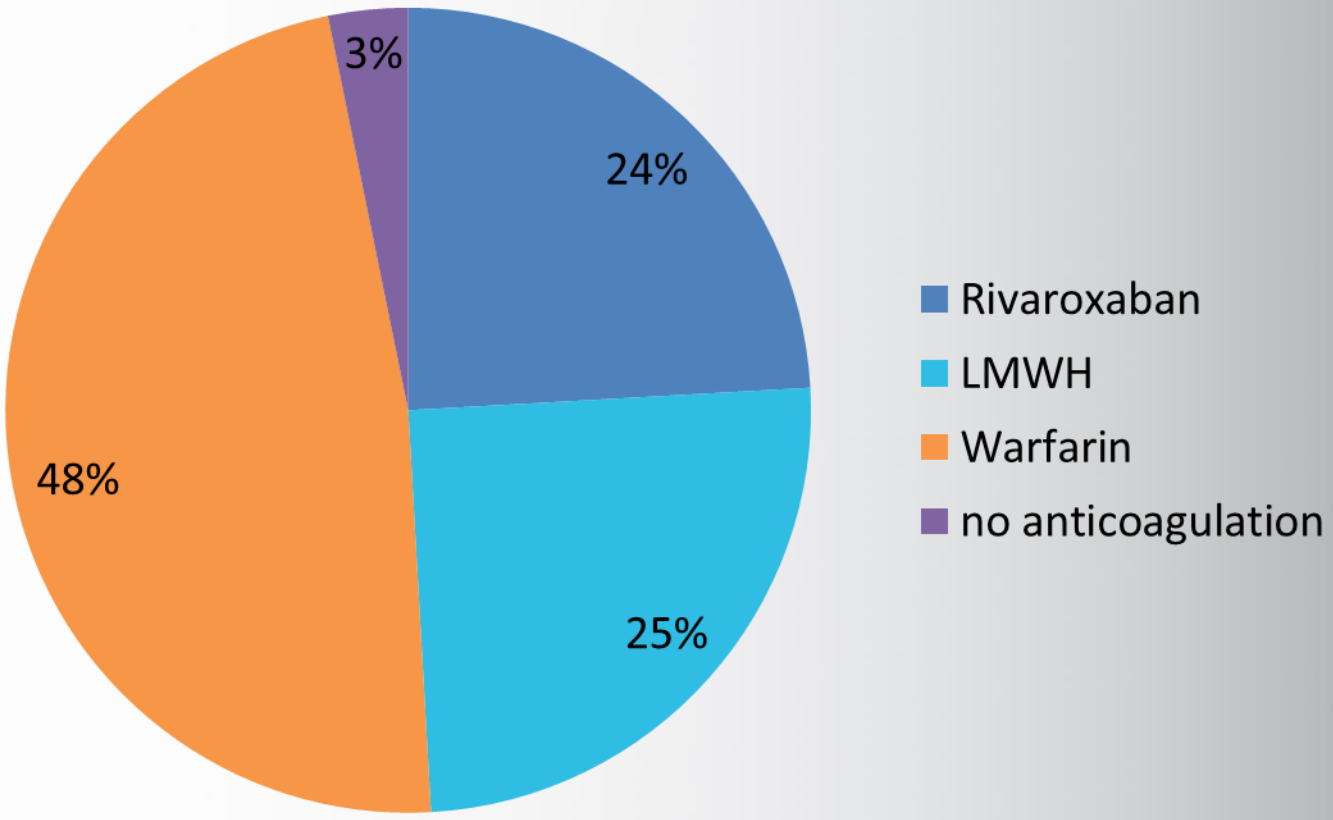
Percentage of patients who remained on anticoagulant therapy



N=52,911 cancer patients with VTE in the USA, 2009–2014

Khorana AA *et al, Throm Res* 2016;145:51–53

Initial treatment: US prescriptions



N=2,941 patients with new VTE and cancer (Humana Database, 2007–2014)

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

Acute anticoagulation treatment DOACs vs. LMWH

- **Rivaroxaban versus dalteparin**
  - Select-d trial: N=530
    - ISRCTN86712308
  - CASTA-DIVA: N=200
    - NCT02746185
  - COSIMO: N=500
    - NCT02742623
  - CONKO-011: N=450
    - NCT02583191
- **Edoxaban versus dalteparin**
  - HOKUSAI VTE-Cancer: N=1000
    - NCT02073682
- Apixaban versus dalteparin
  - CARAVAGGIO: N=1168
    - NCT03045406

Treatment: A risk-adapted approach?

- **Individualize approach**
  - Drug to drug interaction
  - Nausea/vomiting

- **Risk/benefit ratio**
  - Risk of recurrent VTE
  - Risk of bleeding

Drug to drug interactions

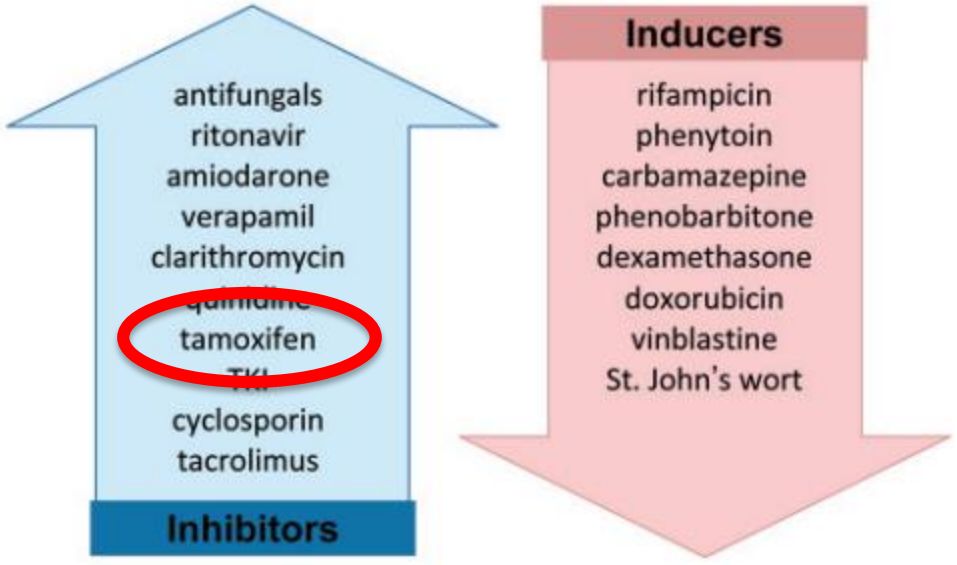
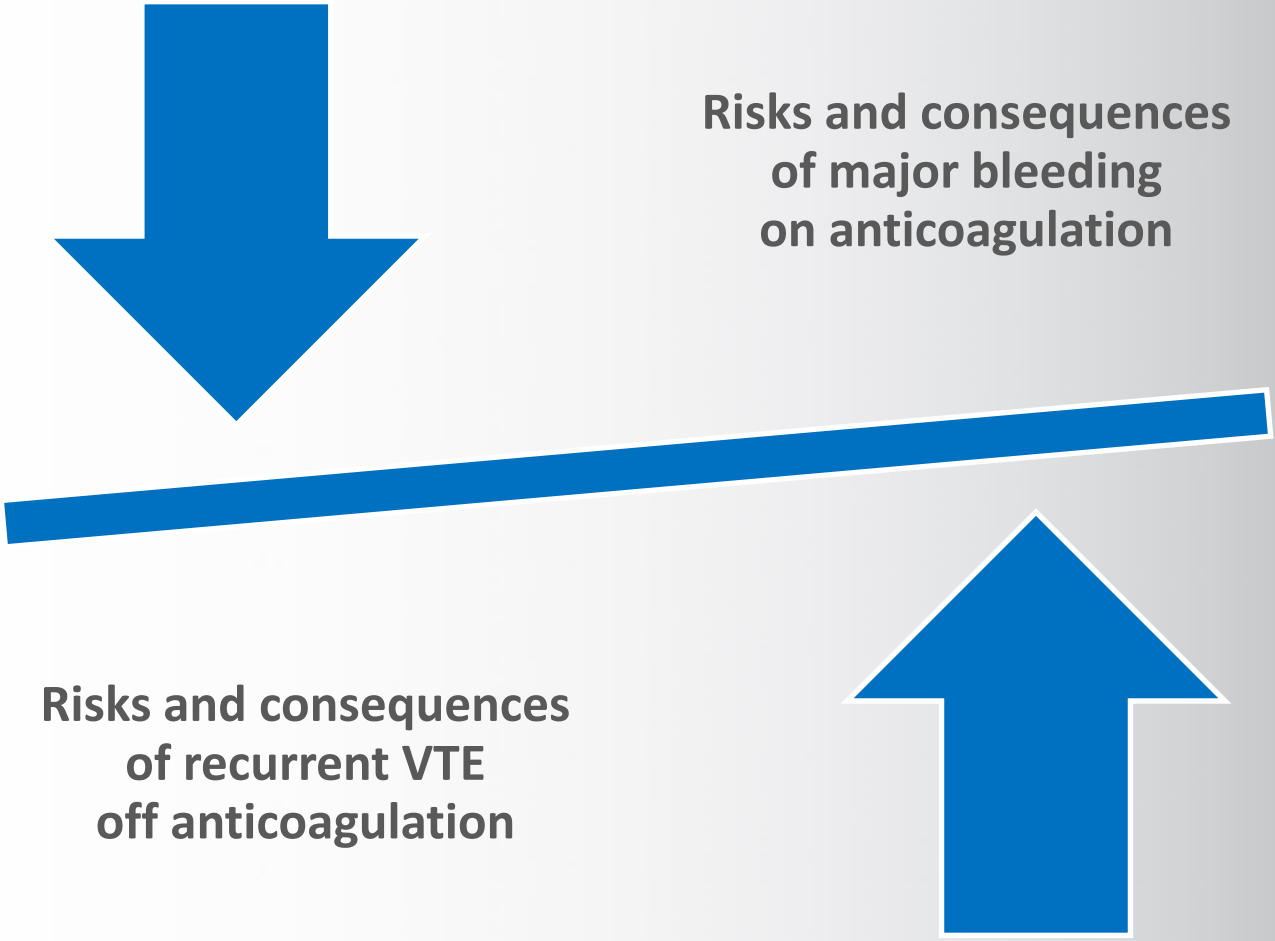


Fig. 1. Effect of Inhibitors and Inducers of P-Glycoprotein or CYP-3A4 Pathways on Plasma Levels of Novel Oral Anticoagulants (NOAC). TKI, tyrosine kinase inhibitor.

Lee AY, Carrier M, Thromb Res. 2014 May;133 Suppl 2:S167-71.

Treatment: A risk-adapted approach?



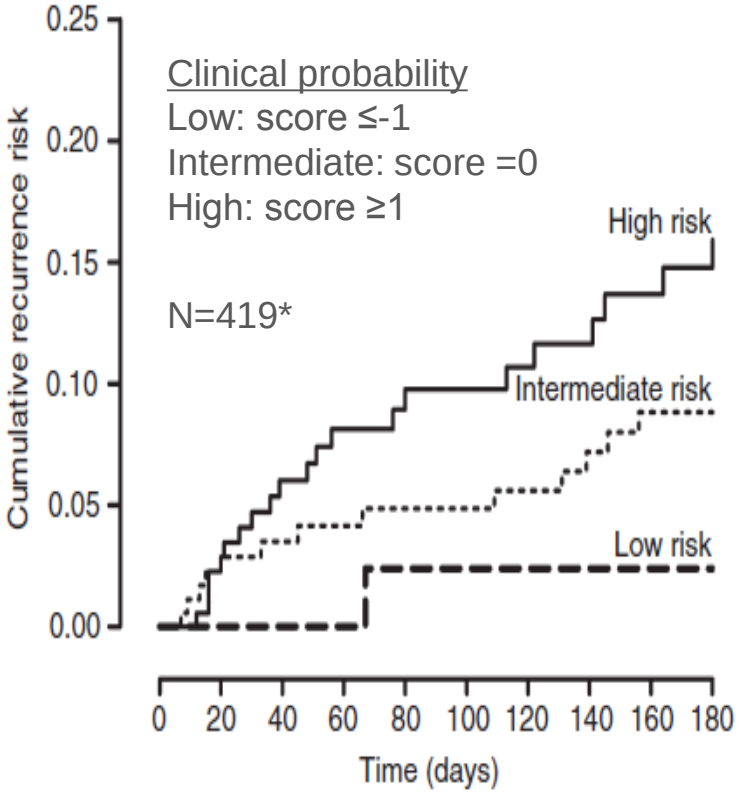
VTE, venous thromboembolism

Predicting the risk of recurrent CAT

Ottawa prognostic score for recurrent VTE risk in CAT

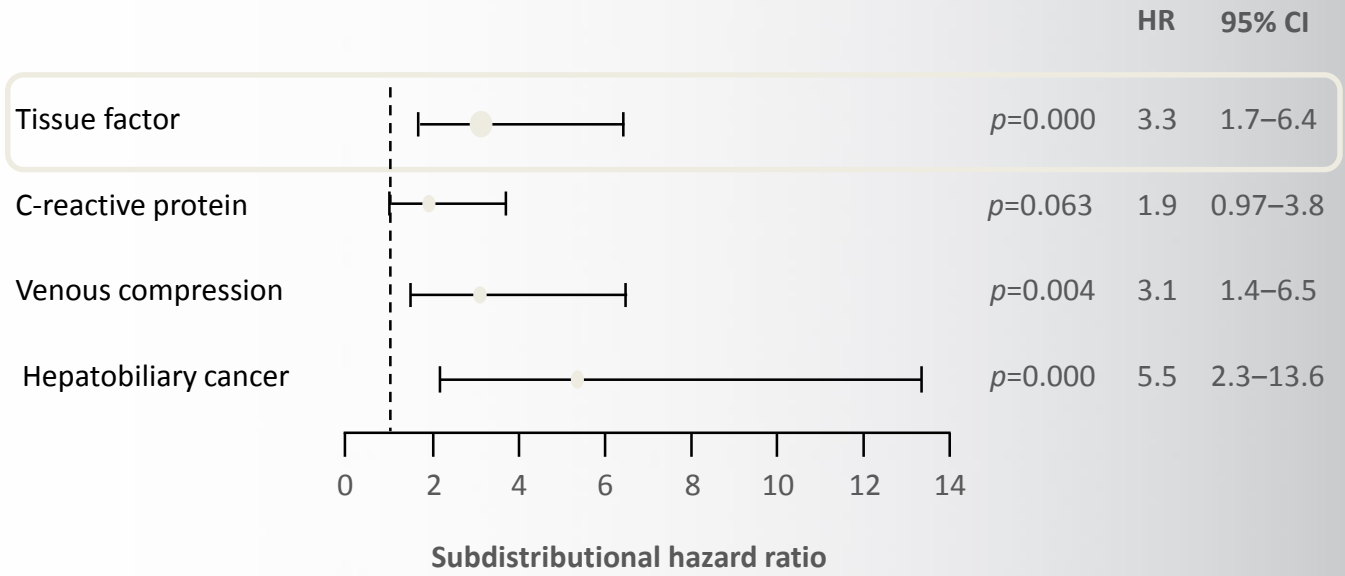
Variable	Regression co-efficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	-0.76	-1
TNM stage I	-1.74	-2
Previous VTE	0.40	1

Cumulative risk of recurrent VTE according to Ottawa risk class[2]



*Louzada ML *et al*, *Circulation* 2012;126:448–454; 2. Den Exter PL *et al, J Thromb Haemost* 2013;11:998–1000

Predictors of recurrent CAT in CATCH



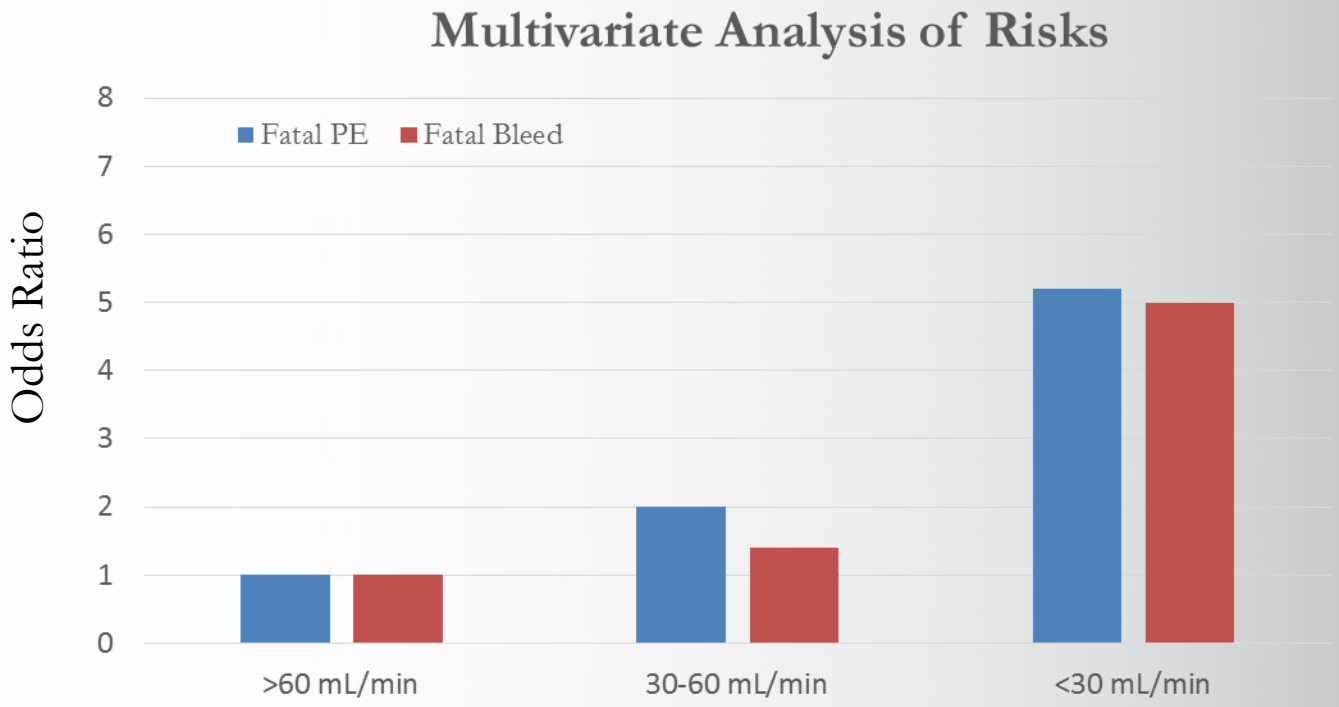
74% of patients who experienced recurrent VTE had at least 1 of the 4 risk factors

67% had 1 of 3 risk factors

Khorana AA *et al, J Clin Oncol* 2017;35:1078–1085

Renal failure increases risk of fatal PE and fatal bleeding

Patients with VTE who have renal insufficiency had an increased incidence of both fatal PE and fatal bleeding, but the risk of fatal PE exceeded that of fatal bleeding.



Monreal M, et al. Am J Med. 2006;119(12):1073-9

CLOT Study — *post-hoc* analysis

Outcomes: Patients with RI vs. total CLOT

		Total CLOT population[1]		CLOT population with renal insufficiency[2]	
Endpoint	Treatment	%	p - value	%	p - value
VTE (ITT) (n = 162)	Dalteparin	8.0	0.002	2.7	0.0111
	VKA	15.7		17.0	
Any bleeding (AT) (n = 161)	Dalteparin	20.1	0.4658	20.1	0.4658
	VKA	24.1		24.1	
Major bleeding (AT) (n = 161)	Dalteparin	5.6	0.27	9.5	0.6511
	VKA	3.6		6.9	

- Results in patients with renal insufficiency were consistent with those in the overall CLOT study.
- Major bleeding was increased in patients with RI in both arms.

Woodruff S *et al*. *J Thromb Thrombolysis* 2016;42(4):494–505.

CATCH Study — *post-hoc* analysis

Outcomes: Patients with RI

	Clinically relevant bleeding		
	CrCl <60 n/N (%)	**CrCl ≥60 n/N (%)**	**RR (95% CI)**
Tinzaparin	10/67 (14.9)	45/355 (12.7)	1.18 (0.62, 2.22)
Warfarin	15/62 (24.2)	60/378 (15.9)	1.52 (0.93, 2.51)

No statistically significant differences in CRB between tinzaparin and warfarin within each renal function group

Bauersachs R *et al*. *J Thromb Haemost* 2015;13(Suppl. 2):76;

Bauersachs R *et al*. Abstract Symposium Presentation, ISTH 2015. Abstract AS214

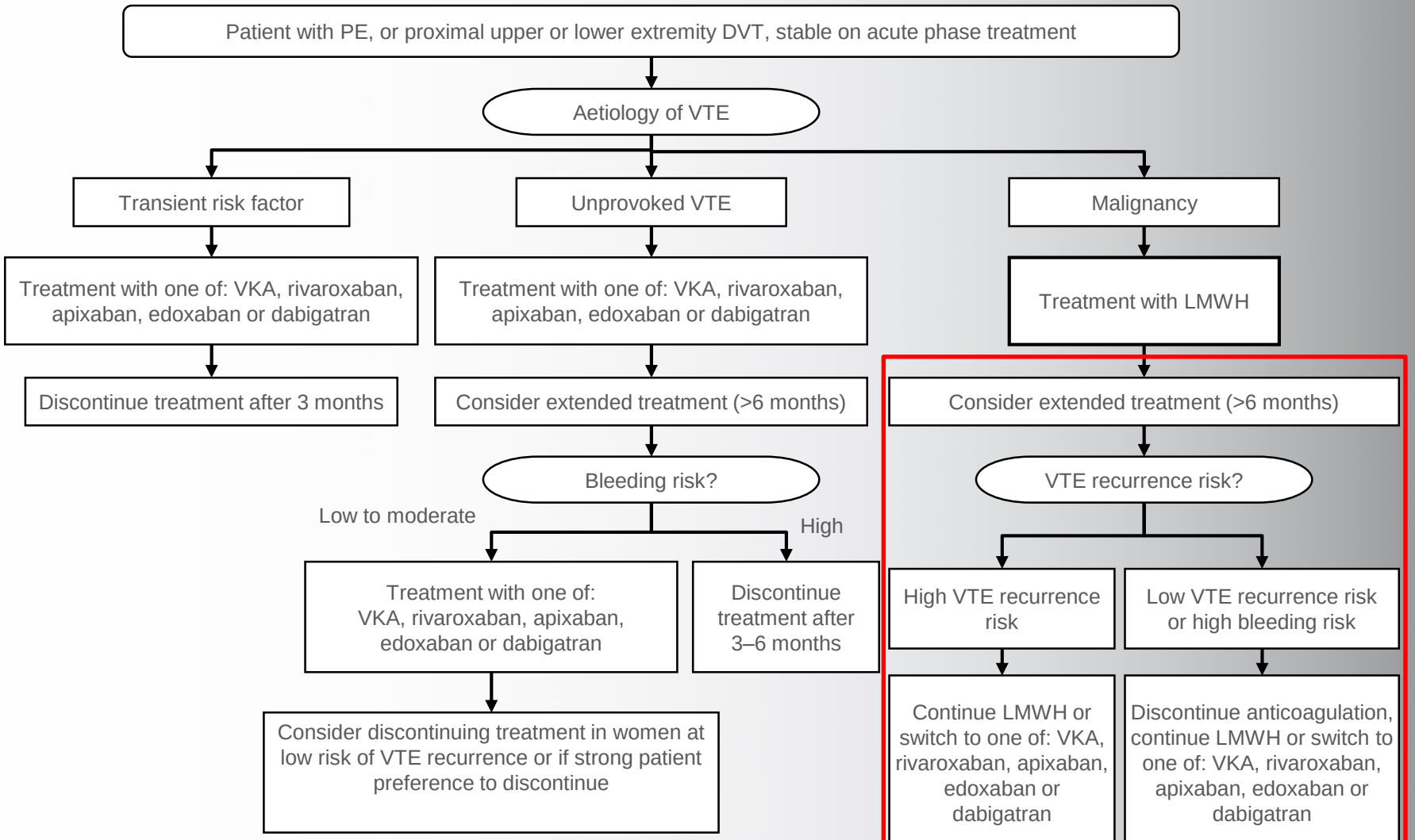
Treatment: A risk-adapted approach?

- Individualize approach
  - Drug to drug interaction
  - Nausea/vomiting
- Emphasize use of LMWH and long-term anticoagulation in patients at high risk
- Consider DOACs (or, less preferably, warfarin) in patients at lower risk,
  those refusing or unable to afford LMWH or
  after 6 months of treatment

Management of Ms. MT

- IV heparin/ LMWH and warfarin
- **LMWH only**
- DOAC only

Extended anticoagulation therapy



Wells PS *et al*, *JAMA* 2014;311:717–728

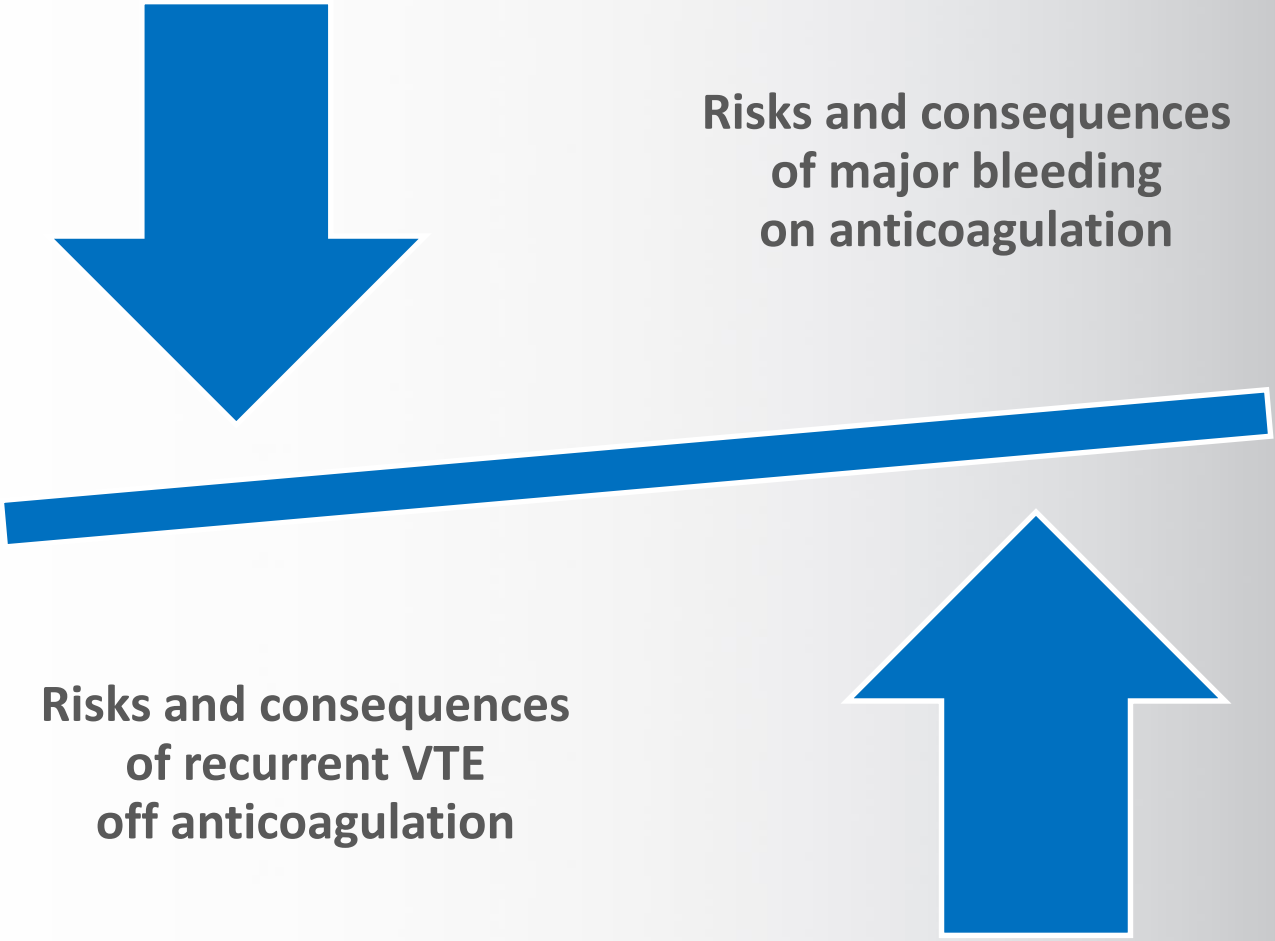
Extended anticoagulation therapy

ITAC-CME

- After 3–6 months, termination or continuation of anticoagulation (LMWH, VKA or DOAC) should be based on individual assessment of the:
  - Benefit-to-risk ratio
  - Tolerability
  - Drug availability
  - Patient preference
  - Cancer activity
- (Guidance, in the absence of data)

Farge D *et al*, *Lancet Oncol* 2016; 17:e452–466

Extended anticoagulation therapy



VTE, venous thromboembolism

Who should probably continue anticoagulation?

- No contraindications to anticoagulation and:
  1. Active advanced cancer *or*

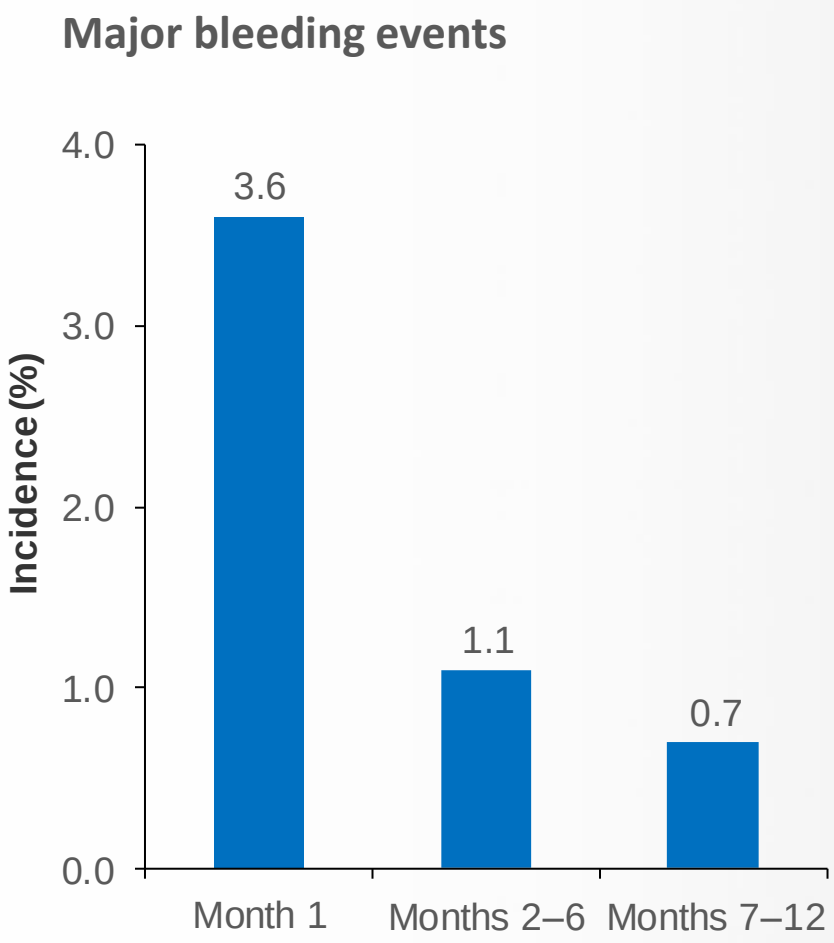
  2. Advanced cancer in complete remission, and for whom the short-term risk of cancer recurrence is high or in the presence of other ongoing major risk factors for thrombosis

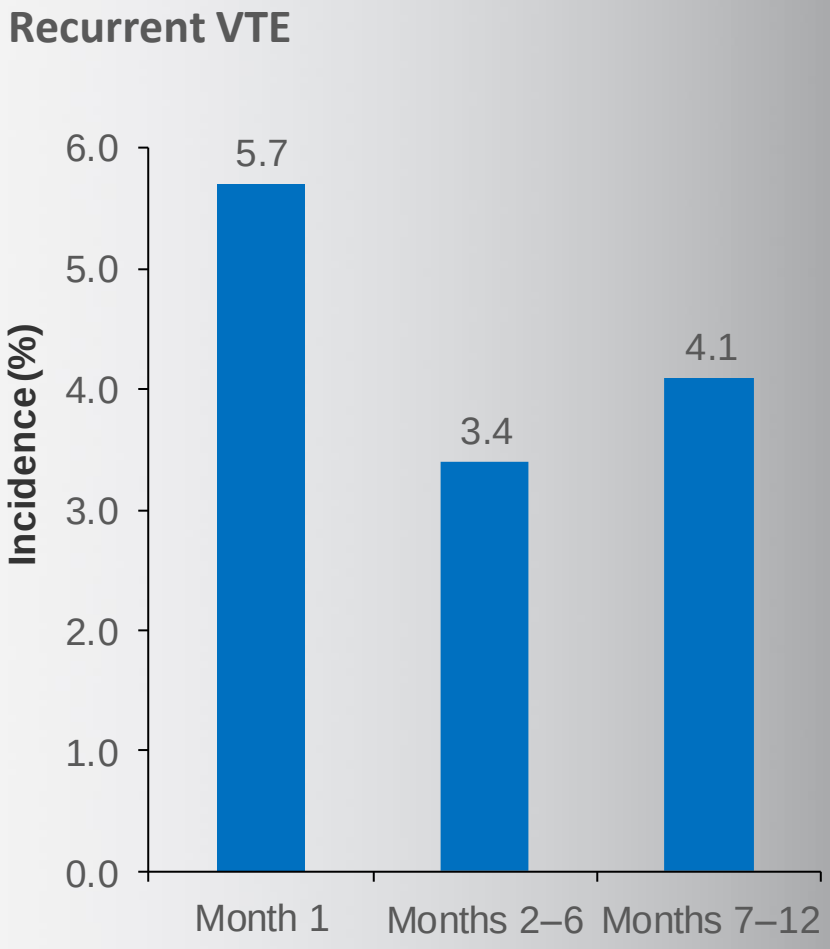
Selection of therapy?

- There is little prospective data, aside from the DALTECAN and TiCAT studies to guide selection of therapy
  - Continuation of LMWH at the current dose is a reasonable option
  - However, individualization of therapy (including DOACs and VKA) may also be reasonable in certain settings after considering patient preference and other
    clinical factors

1. Francis CW *et al*, *J Thromb Haemost* 2015;13:1028–1035
2. Jara-Palomares et al (2017) Thrombosis Research 157 90-96,

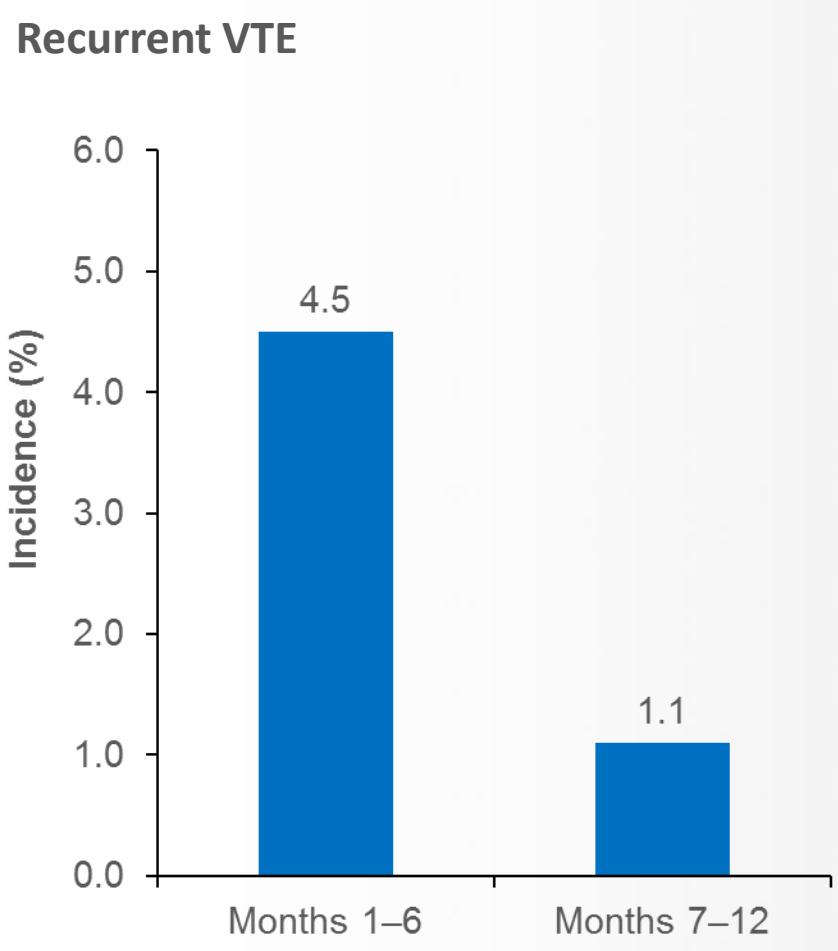
DALTECAN study

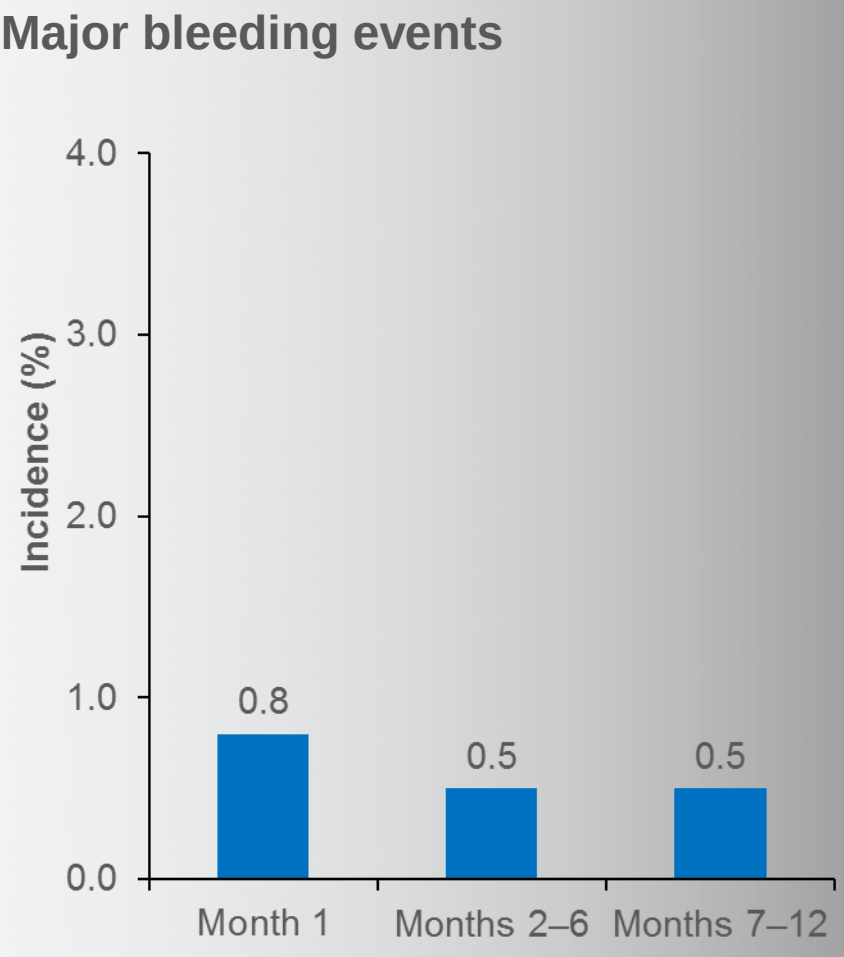




Francis CW *et al*, *J Thromb Haemost* 2015;13:1028–1035

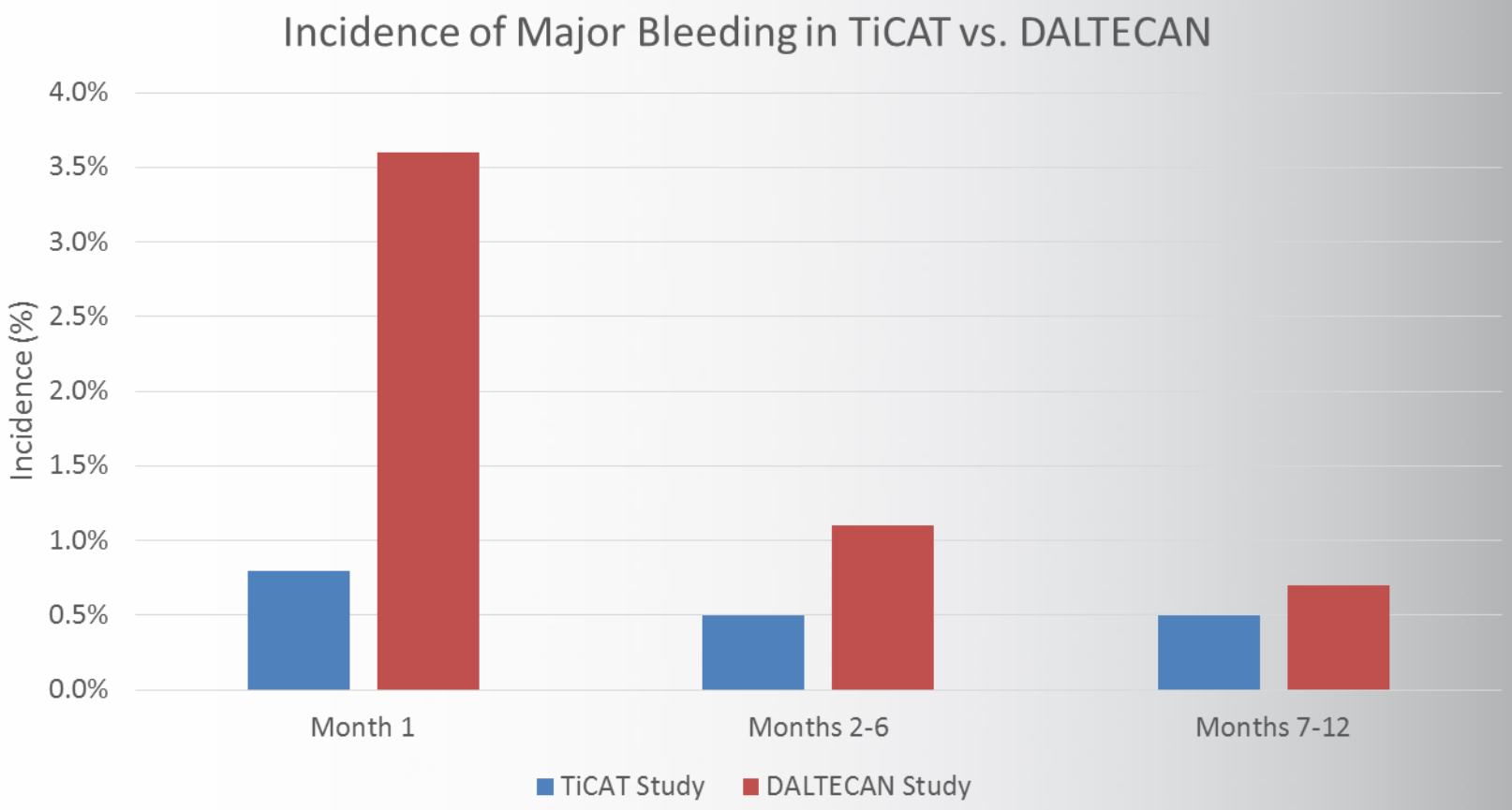
TiCAT Study





Jara-Palomares L *et al, J Thromb Res* 2017;157:90–96

Major Bleeding DALTECAN vs. TiCAT



1. Jara-Palomares et al (2017) Thrombosis Research 157 90-96,
2. Francis et al (2015) Journal of Thrombosis and Haemostasis 13 1028-1035

When Can Anticoagulation Be Stopped?

Anticoagulation can be stopped when:

1. The underlying cancer has been treated with curative intent **and**
2. Any ongoing therapy is associated with a low risk of thrombosis

May or may not stop?

- Complete remission with a low or moderate risk of recurrence of cancer and VTE
- Options:
  1. Stop anticoagulation therapy
  2. Continue anticoagulation therapy until the risk of cancer/VTE recurrence is felt to be low
     - LMWH
     - DOACs
     - VKA

Patient's perspective

- Most important attributes for anticoagulation choices:

    1. Does not interfere with cancer treatment.
    2. Efficacy and safety
    3. Route of administration

Noble SI et al. Haematologica. 2015;100:1486–1492.

Is an RCT feasible?

- ALICAT
  - RCT is not feasible because:
    - Patients have fixed views regarding their treatment wishes
    - Clinicians have fixed opinions about anticoagulation
- Longheva
  - Terminated early due to poor enrolment

Noble SI *et al, Health Technol Assess* 2015;19:vii-xxiii, 1–93

Let’s go back to Ms. MT

- Treated with therapeutic doses of LMWH
- Presents to the ED 2 weeks later with new contralateral limb swelling
- Doppler US: occlusive thrombus in the pop. vein.
- Hb: 110; Plt 145 and CrCl 40 cc/min

Management

- IVC filter only
- IVC filter and same dose of LMWH
- IVC filter and dose escalation of LMWH
- Escalation of the dose of LMWH
- Switch to a DOAC

IVC filters

- PREPIC 1: Permanent filters and anticoagulation
  - N= 400
  - ↓ PE; ↑ DVT; ↔ survival
- PREPIC 2: Temporary filters and anticoagulation
  - N= 398
  - ↔ PE; ↔ DVT; ↔ survival

Decousus H et l. N Engl J Med 1998; 338:409-416
Mismetti P et al, *JAMA.* 2015;313(16):1627-1635

IVC filters in cancer patients

- Large California database (N=14,000 CAT)
  - 2747 IVC filters (19.6%)
  - Survival: HR: 1.13 (95%CI: 0.99-1.26)
  - DVT: HR: 2.1 (95%CI: 1.53-2.69)
  - PE: HR: 0.81 (95%CI: 0.52-1.27)
- Subgroup analyses
  - Bleeding cancer patients:
    - HR: 0.99 (95%CI: 0.73-1.35)

Wun T et al. Thromb Res 2016;140S1:S66-S70.

ACCP 2016

- Antithrombotic Therapy for VTE Disease: CHEST Guidelines

In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an inferior vena cava (IVC) filter (Grade 1B).

Kearon C et al. Chest. 2016 Feb;149(2):315-52

ACCP 2016

- Antithrombotic Therapy for VTE Disease: CHEST Guidelines

In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

Kearon C et al. Chest. 2016 Feb;149(2):315-52

ACCP 2016

- Antithrombotic Therapy for VTE Disease: CHEST Guidelines

In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).

Kearon C et al. Chest. 2016 Feb;149(2):315-52

Recurrent CAT despite anticoagulation

	Ihaddadene et al. 2014	Carrier et al. 2009
Sample	55	70
Recurrent VTE	7.3% 95% CI: 2.0-17.6%	8.6% 95% CI: 4.1-17.5%
Major bleeding	5.5% 95% CI: 1.1-15.1%	4.3% 95% CI: 1.5-11.9%

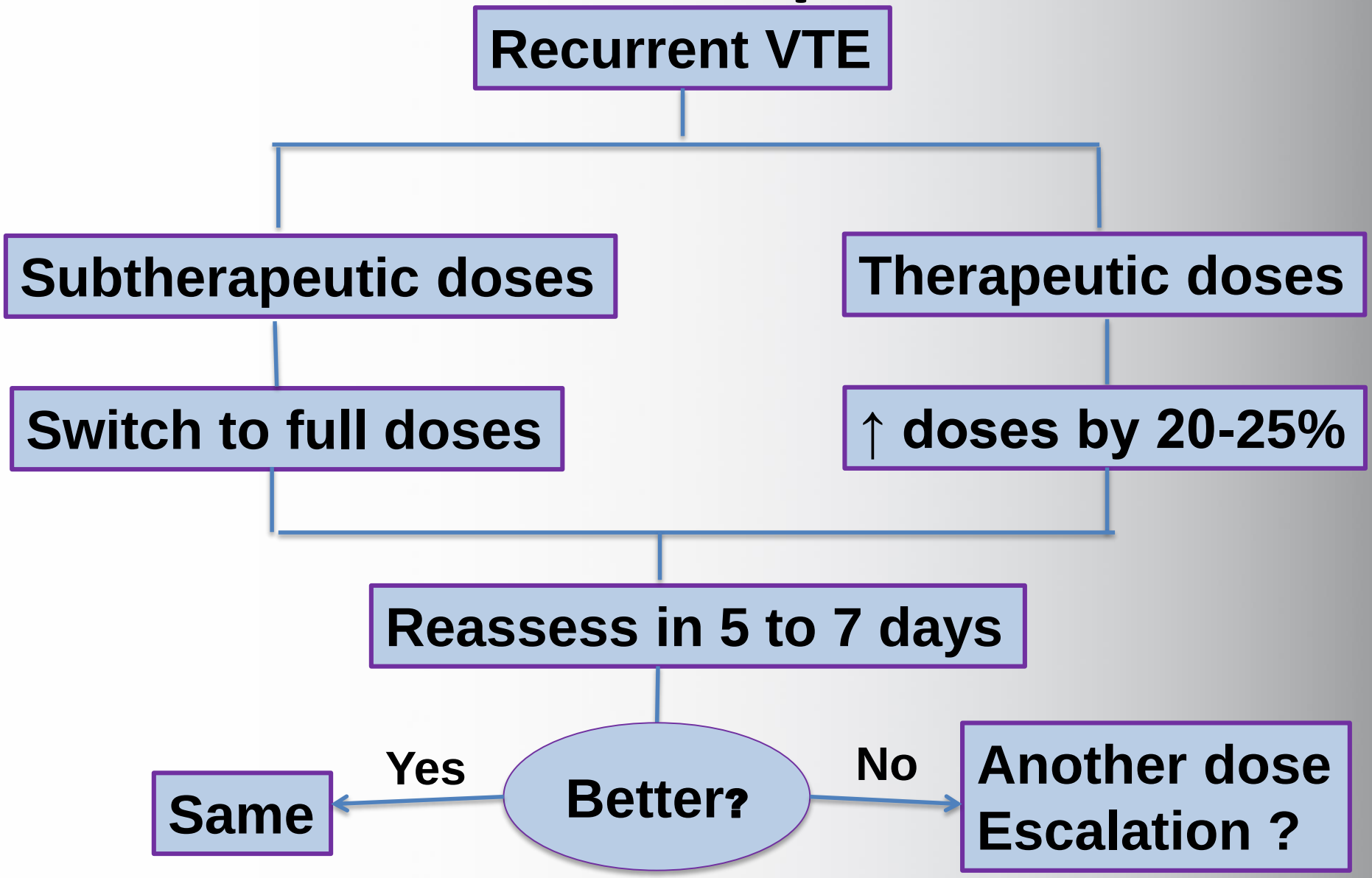
Ihaddadene et al. Thromb Res. 2014 Jul;134(1):93-5.
Carrier M et al. J Thromb Haemost 2009;7(5):760-765.

ISTH Registry

- 212 patients with recurrent cancer-associated thrombosis despite anticoagulation followed for 3 months
  - 70% LMWH; 30% VKA.
  - Acute phase:
    - 25% switched anticoagulant (VKA → LMWH)
    - 31% dose escalation and 25% same dose
  - Overall risk of recurrent VTE 11% (3 months)
  - ↔ risk of recurrent VTE: dose escalation *vs.* same dose

Schulman S et al. J Thromb Haemost. 2015;13:1010-1018.

Recurrent VTE despite LMWH



Ms MT.

- Dose of LMWH was increased by 25%
- Symptoms improved significantly within 7 days.
- Doing well – ongoing follow-up

Case 2

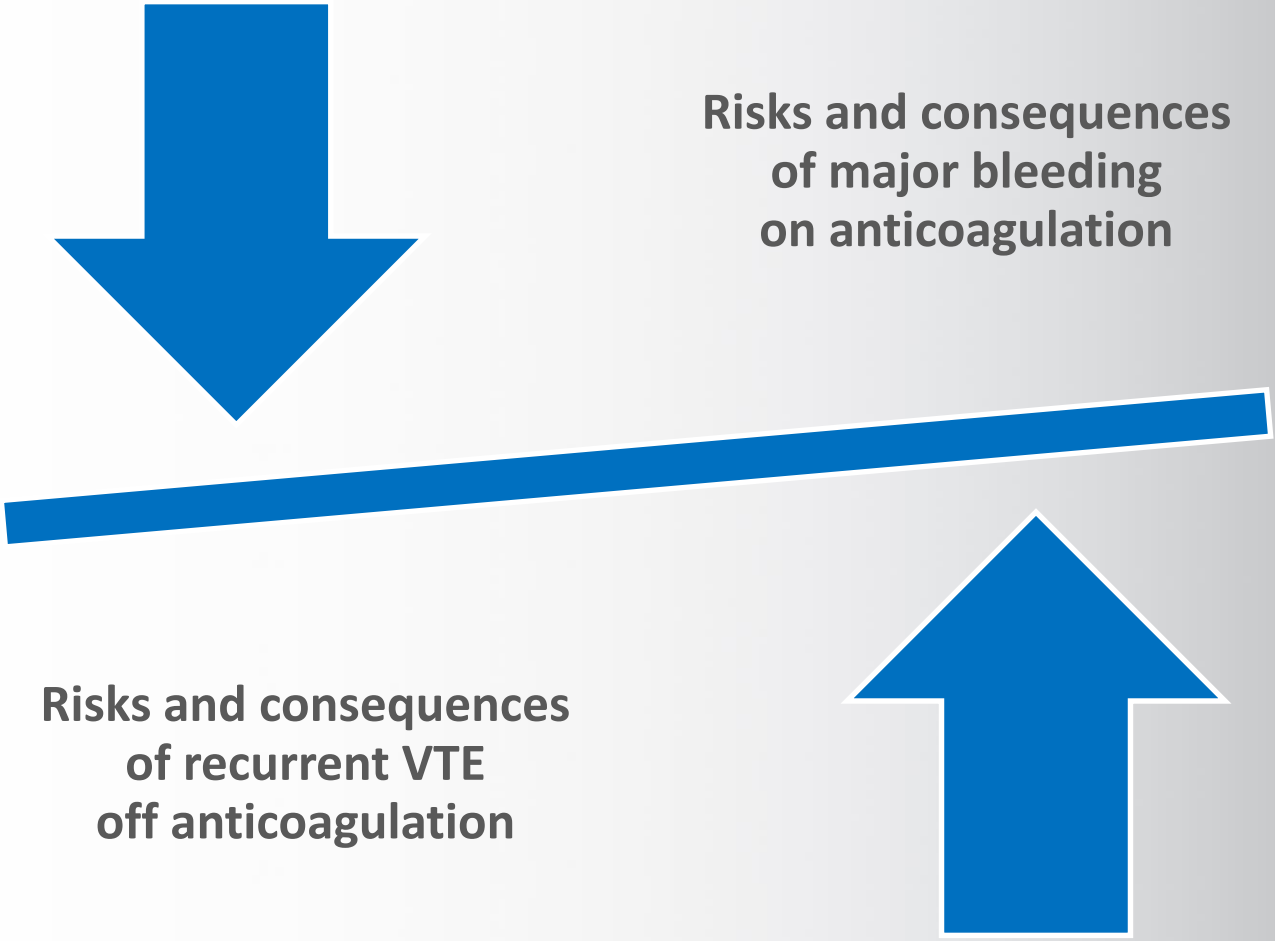
Ms. MC

- 60 yo female
- Stage 2 colon ca
- Surgical resection of primary and 12 cycles of adjuvant folfox
- Staging CT abdomen/pelvis showed partially thrombosed portal vein and completely occluded superior mesenteric vein thrombosis

Management of Ms. MC

- No anticoagulation: Serial US only
- IV heparin/ LMWH and warfarin
- LMWH only
- DOAC only

Treatment: A risk-adapted approach?



VTE, venous thromboembolism

Important considerations

- Acute vs. chronic
- Risk factors now and longitudinally
- Patient preference
- Morbidity of PVT\HPVT
- Risk of bleeding

Splanchnic vein thrombosis

SVT includes:

- portal vein thrombosis (PVT)
- mesenteric vein thrombosis (MVT)
- splenic vein thrombosis (SVT)
- Budd-Chiari syndrome (BCS)

- Incidence of PVT and MVT is reported to range between 0.7 and 2.7/100,000 person-years.

Risk Factors
Abdominal disorders and interventions Acute • pancreatitis, peritonitis/intraabdominal sepsis, diverticulitis, general abdominal surgery, abdominal trauma Chronic • cirrhosis, abdominal cancer, portal hypertension, hematologic disorders
Philadelphia chromosome negative chronic MPNs • Polycythemia vera, essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria (PNH)
Inherited thrombophilic state
Hormones • Oral contraceptives, hormone replacement therapy
Virus (cytomegalovirus)
Autoimmune disorders • Behçet's disease

Ageno W, et al. Blood. 2014;124(25):3685.

Splanchnic vein thrombosis

- Quality of evidence guiding the treatment of SVT is low as it is based on the results of observational studies only

Therapeutic strategies according to the site of thrombosis in real life from the International Registry on Splanchnic Vein Thrombosis study

Strategy	BCS (N = 51)	PVT (N = 244)	MVT (N = 67)	SpVT (N = 19)	Multiple sites (N = 232)
No treatment	31.4%	33.2%	9.0%	15.8%	12.9%
UFH	15.7%	4.9%	9.0%	—	16.4%
LMWH/fonda	49.0%	58.6%	83.6%	84.2%	71.8%
VKA	47.1%	31.6%	61.2%	63.2%	60.8%
Thrombolysis	3.9%	—	1.5%	—	2.6%
Surgery	—	—	7.5%	—	6.5%
Antiplatelets	—	1.6%	—	—	—
Interventional procedures	7.8%	1.6%	—	—	0.9%

- **Of 176 patients with incidentally diagnosed SVT, 110 (62.5%) received anticoagulant treatment.**

Ageno W, et al. Blood. 2014;124(25):3685-3691.

What should be used?

Symptom	Suggested Anticoagulant Therapy
Noncirrhotic, symptomatic SVT with no signs of active bleeding	Consider full therapeutic dose LMWH
Cancer-associated SVT	Full therapeutic dose LMWH for at least 3-6 months
GFR <30 mL/min	LMWH or UFH: • Dose adjust tinzaparin and dalteparin <20 mL/min • Dose adjustment of enoxaparin <30 mL/min
Platelet count >25 000 and <50 000 per mm^3	LMWH at 50% dose can be administered with close follow-up for possible bleeding
Platelet count <25 000 per mm^3	Prophylactic doses of LMWH can be tolerated with associated resolution of thrombotic symptoms (based on limited evidence)
Cirrhotic, symptomatic PVT patient	Consider full therapeutic dose LMWH after careful assessment (and treatment, if necessary) of esophageal varices
Incidentally detected SVT	Consider full therapeutic dose LMWH unless: thrombosis is nonocclusive, likely not recent, and limited to a single vein segment; no permanent risk factors or not recent (<1 mo) removable risk factors for thrombosis are identified; bleeding risk is moderate to high; and prognosis of underlying disease is poor

Ageno W, et al. Blood. 2014;124(25):3685-3691
Carrier M, et al. J Thromb Haemost. 2013;11:1760-1765.

ISTH Guidance

- In patients with incidental splanchnic vein thrombosis, we suggest anticoagulant therapy in patients with thrombosis that appears to be acute, or that shows progression or extension over time, and in those who are neither actively bleeding nor have a very high risk of bleeding.

DI Nisio M et al. J Thromb Haemost. 2015 May;13(5):880-3

ISTH Guidance

In cancer patients with evidence of disease or ongoing systemic or locoregional therapy, we suggest periodic reevaluation of the risks of bleeding and VTE recurrence, as well as patient preferences, to guide the decision of whether to extend LMWH beyond 6 months.

DI Nisio M et al. J Thromb Haemost. 2015 May;13(5):880-3

Case 3

Ms. MT

- 63 yo woman
  - Prior history of Crohn's disease
- Admitted to hospital with ICH
  - Right temporal-parietal cranitomy and evacuation of hematoma and resection of tumor
  - GBM
- Discharged home:
  - Azathioprine and phenytoin

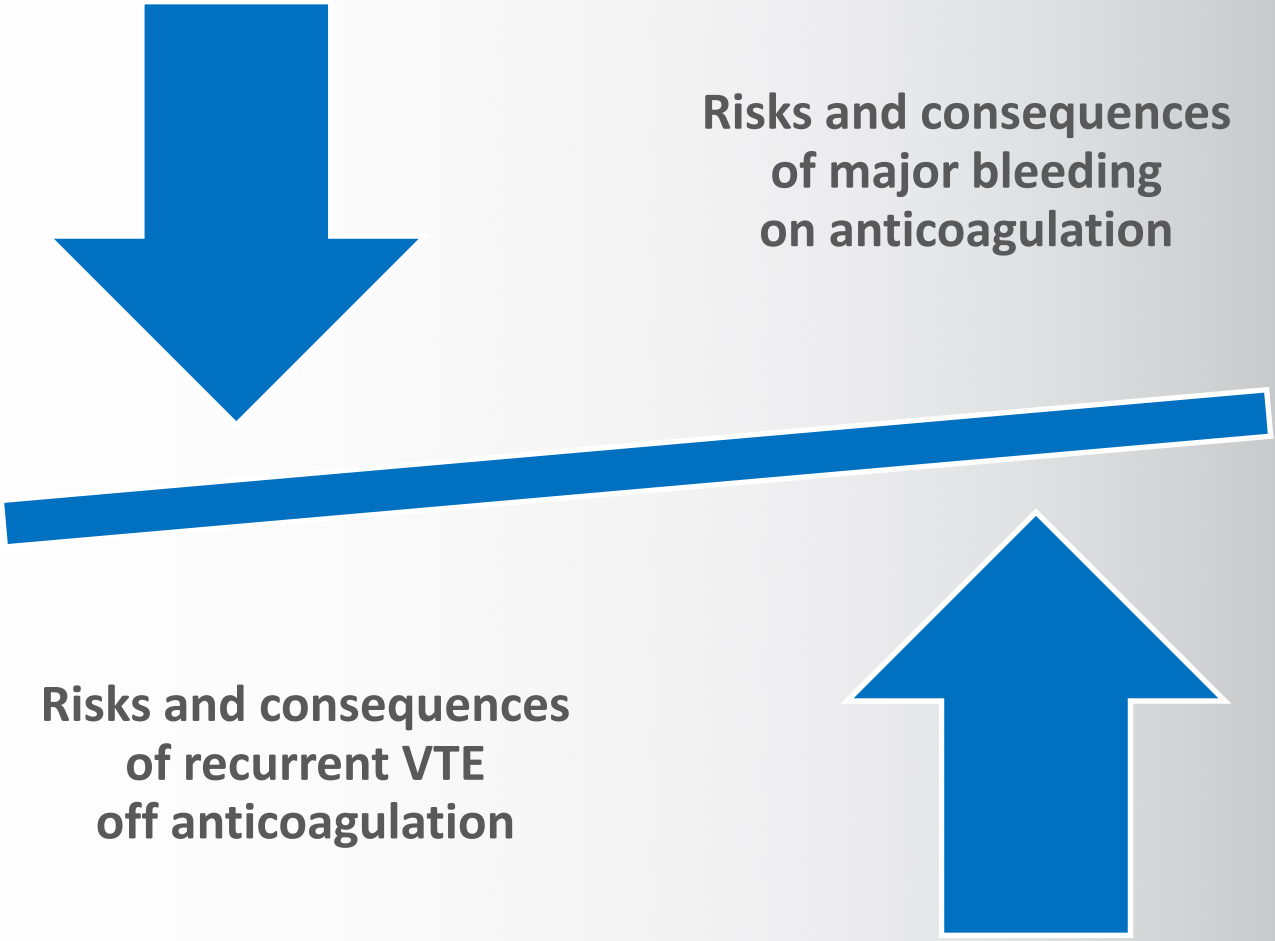
Ms. MT

- 6 weeks later:
  - New SOB/CP and right leg swelling
  - VSS
  - Hb: 100; Plt 150 and CrCl > 50 cc/min
  - CTPA: extensive acute PE involving all lobes and and main pulmonary arteries. Evidence of right heart strain.
  - CT head: Post-op changes only – No evidence of bleeding
  - Doppler US: Right proximal DVT

Management

- IVC filter only
- IVC filter and IV heparin/LMWH and warfarin
- IVC filter and LMWH
- IVC filter and therapeutic DOACs
- IV heparin/ LMWH and warfarin
- LMWH only
- DOAC only

Treatment: A risk-adapted approach?



VTE, venous thromboembolism

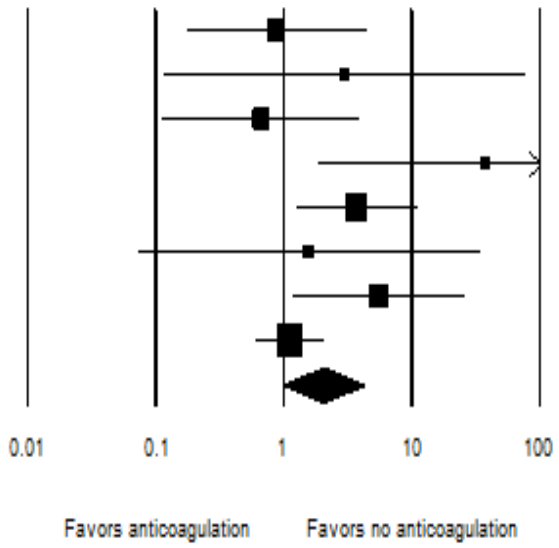
Meta-analysis: ICH and brain tumours with anticoagulation

Study	Malignancies	Retrospective cohort?	Both cohorts with VTE?	Number on anticoagulant (type of long-term anticoagulant)	Number without anticoagulation	Blinded radiology review?
Ruf et al, 1983[12]	Glioma	Yes	No	N=103 (warfarin)	N=272	No
Olin et al, 1987[7]	Both*	Yes	Yes	N=25 (warfarin)	N=24 (IVC filter)	No
Choucair et al, 1987[13]	Glioma	Yes	Yes	N=22 (warfarin)	N=14	No
Shiff et al, 1994[9]	Metastatic	Yes	Yes	N=42 (warfarin)	N=10 (IVC filter)	No
Pan et al, 2009[11]	Glioma	Yes	No	N=25 (LMWH/warfarin)	N=121	No
Norden et al, 2012[10]	Glioma	Yes	No	N=64 (LMWH/warfarin)	N=218	No
Alvarado, et al 2012[8]	Metastatic (melanoma)	Yes	Yes	N=57 (LMWH/warfarin)	N=17	No
Edwin et al, 2014[6]	Glioma	Yes	Yes	N=61 (LMWH/warfarin)	N=39	No
Donato et al, 2015[2]	Metastatic	Yes	No	N=104 (LMWH)	N=189	Yes

Zwicker JI *et al*, *J Thromb Haemost* 2016;14:1736–1740

ICH on anticoagulation

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	ICH / Total: Anticoagulation	ICH / Total: No Anticoagulation
Ruff, 1983	Glioma	0.88	0.17	4.42	-0.16	0.87	2 / 103	6 / 272
Olin, 1987	Both	3.00	0.12	77.31	0.66	0.51	1 / 25	0 / 24
Schiff, 1994	Mets	0.67	0.11	3.93	-0.45	0.65	6 / 42	2 / 10
Pan, 2009	Glioma	37.80	1.89	757.06	2.38	0.02	3 / 25	0 / 121
Norden, 2012	Glioma	3.70	1.25	10.99	2.36	0.02	7 / 64	7 / 218
Alvarado, 2012	Mets	1.58	0.07	34.43	0.29	0.77	2 / 57	0 / 17
Edwin, 2014	Glioma	5.51	1.18	25.78	2.17	0.03	14 / 61	2 / 39
Donato, 2015	Mets	1.11	0.61	2.04	0.35	0.73	21 / 104	35 / 189
		2.04	0.98	4.22	1.91	0.06		



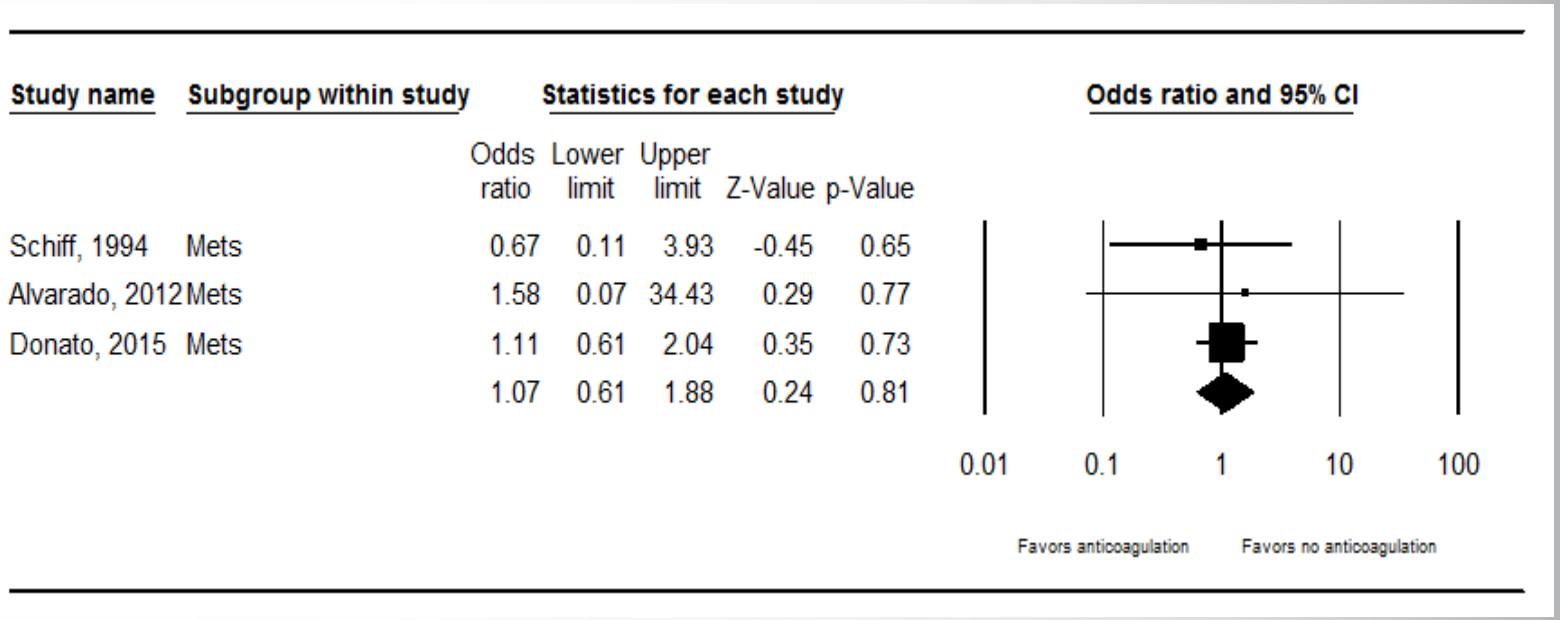
OR=2.13 (95% CI 1.00–4.57; *p*=0.051; I^2=46%)

Not influenced by administration of LMWH versus warfarin:

OR=0.75 (95% CI 0.24–32.33; *p*=0.62; I^2=0%)

Zwicker JI *et al*, *J Thromb Haemost* 2016;14:1736–1740

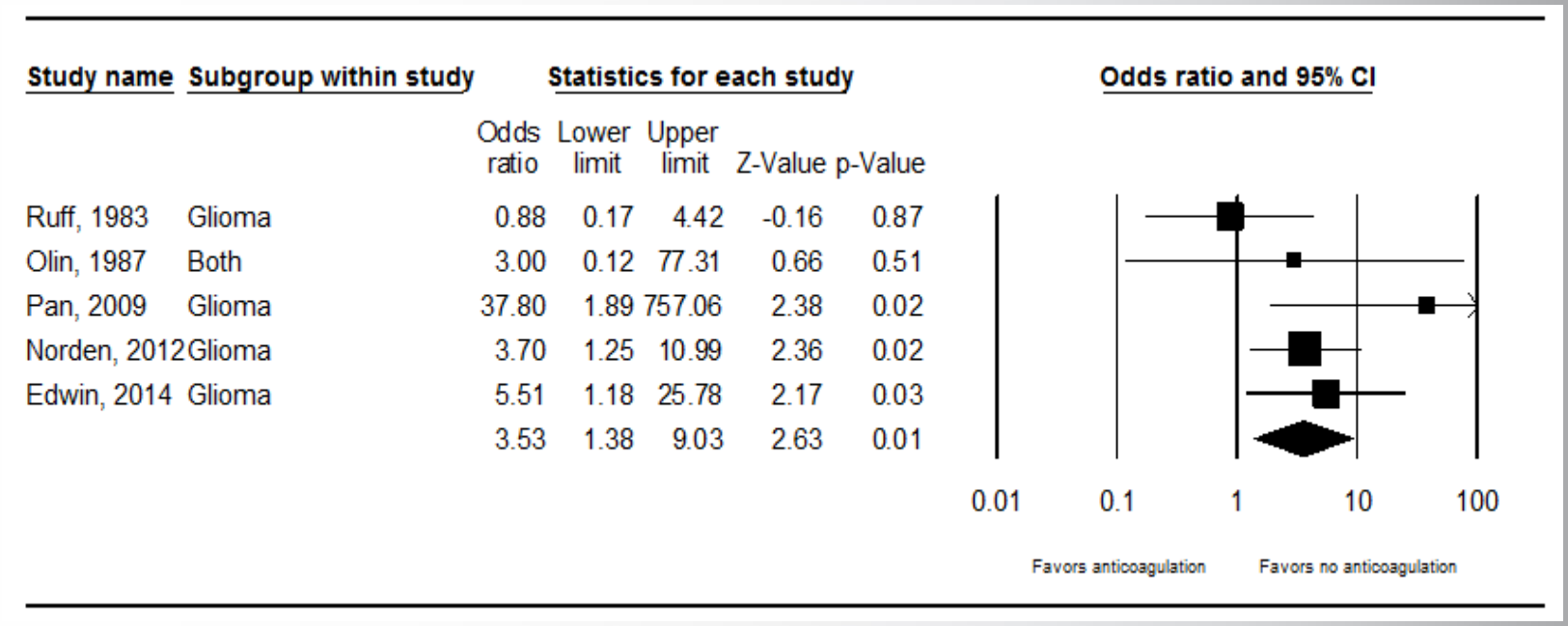
Metastatic brain disease on anticoagulation



OR=1.07 (95% CI 0.61–1.88; *p*=0.81; I^2=0%)

Zwicker JI *et al*, *J Thromb Haemost* 2016;14:1736–1740

Glioblastoma on anticoagulation



OR=3.75 (95% CI 1.42–9.95; *p*=0.01; I^2=33%)

Zwicker JI *et al*, *J Thromb Haemost* 2016;14:1736–1740

ASCO Recommendations

Recommendation 4.5

For patients with primary CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications

Lyman GH *et al*, *J Clin Oncol* 2013;31:2189–2205
Lyman GH *et al*, *J Clin Oncol* 2015;33:654–656

Thank you

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