LE RAGIONI DEL RISCHIO TROMBOTICO NEI PAZIENTI CON CANCRO: FISIOPATOLOGIA E IMPLICAZIONI CLINICHE

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Verona 14.05.2024

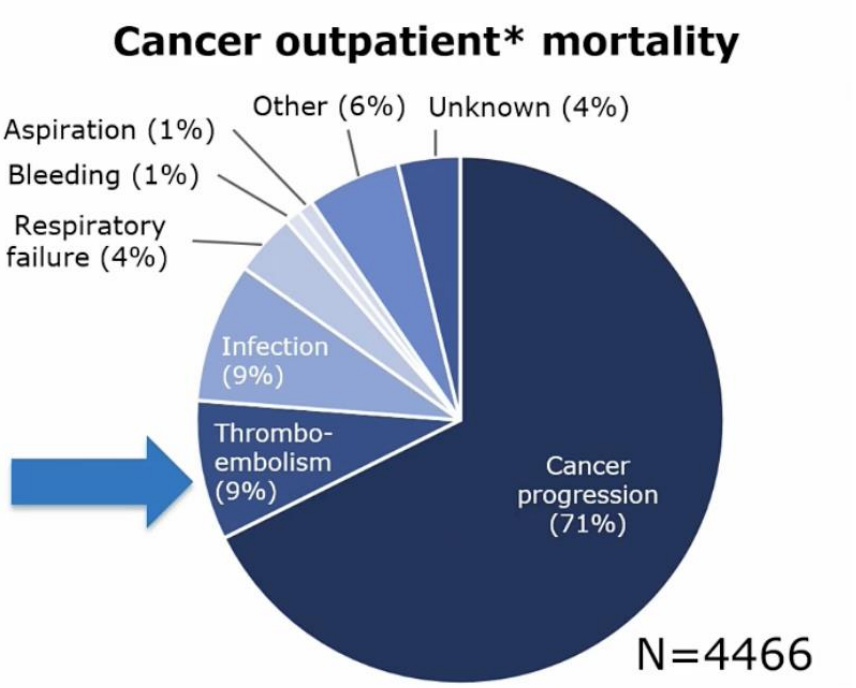
VTE IN CANCER PATIENTS

- VTE occurs in over 20% of cancer patients through their lifetime[1]
- VTE may be present in as much a 50% of patients at the time of death[2]

1. *Lyman GH, et al. J Clin Oncol. 2009;27:4821-46..*
2. *Gao S, et al. Expert Rev Anticancer Ther. 2004;4:303-20.*

VTE: why should we prevent it?

- Thromboembolism is the **second leading** cause of death in patients with cancer
- Patients (N=4466) from 117 US centres, receiving chemotherapy, were enrolled in a prospective observational study
- Annual death rate for VTE was 448 per 100,000 cancer outpatients
  - **47-fold increase** over the general population



**Receiving chemotherapy.*
Khorana AA et al. J Thromb Haemost 2007;5:632-634.

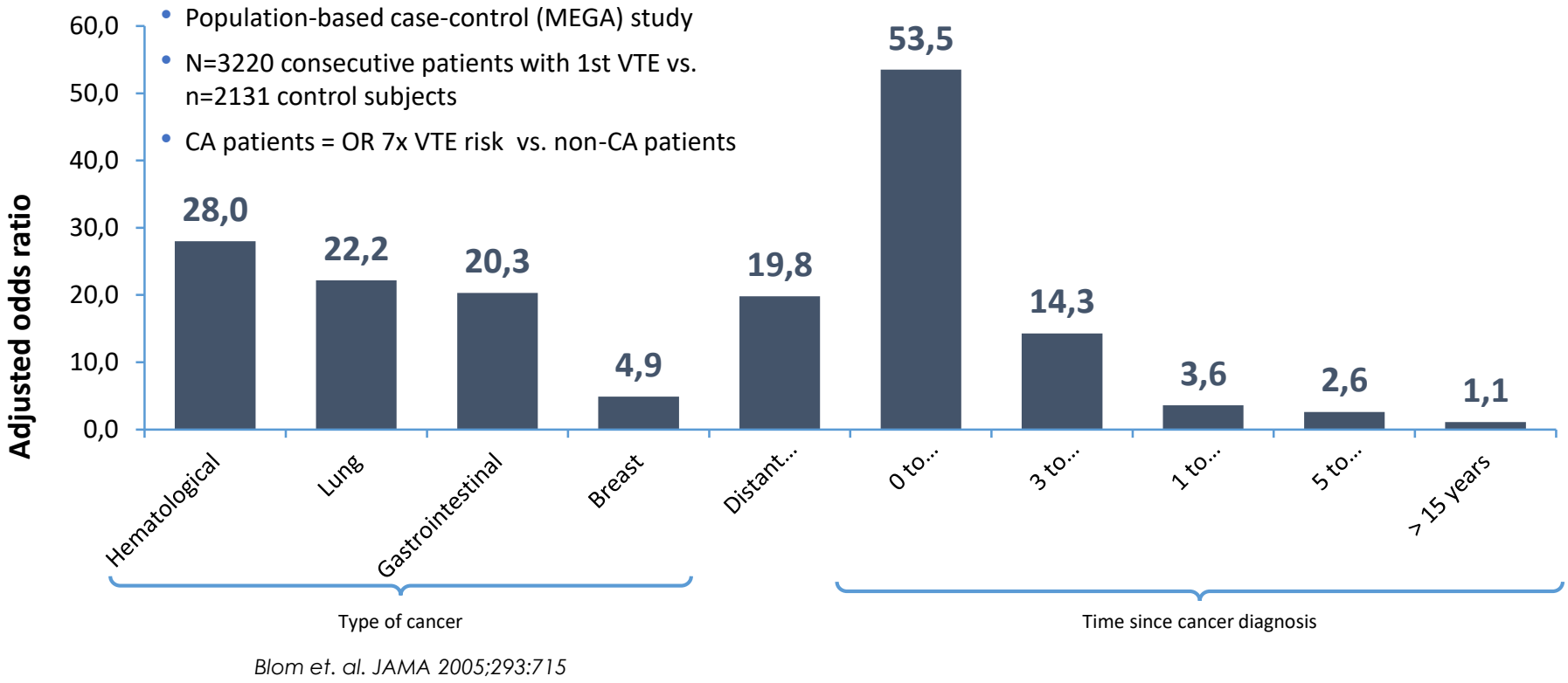
VTE: why should we prevent it?

CAT is related to a 30-fold increased risk of death

Exposure	Patient-years	Deaths	Mortality per 100 patient-years (95% CI)	HR (95% CI)
No VTE or cancer	2,777,713	1750	0.63 (0.60–0.66)	1.0 (reference)
VTE only	1317	67	5.1 (4.0–6.4)	2.6 (2.0–3.3)
Cancer only	5650	721	12.7 (11.9–13.7)	7.4 (6.8–8.2)
Cancer and VTE	131	72	55.0 (43.6–69.3)	31.2 (24.6–39.6)

**Receiving chemotherapy.*
Khorana AA et al. J Thromb Haemost 2007;5:632-634.

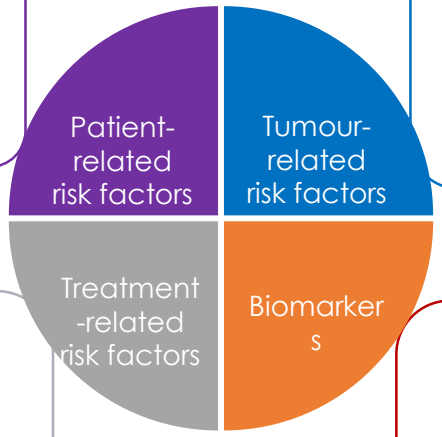
Effect of Malignancy on Risk of Venous Thromboembolism (VTE)



Blom et. al. JAMA 2005;293:715

Risk factors for developing VTE in cancer patients

- **Medical comorbidities (CCI ≥3)**
- **Presence of varicose veins**
- **Prior VTE**
- **Hereditary risk factors (e.g. factor V Leiden)**



- Site of cancer:
  - Very high: stomach, pancreas
  - High: lung, haematological, gynaecological, brain, renal, bladder
- Histological grade of a tumour
- Stage of cancer/metastases
- Time since cancer diagnosis

- Platinum-based and other chemotherapy
- Anti-angiogenesis agents
- Hormonal therapy
- Surgery
- Radiotherapy
- Blood transfusion
- Central venous catheters
- Immobility and hospitalisation

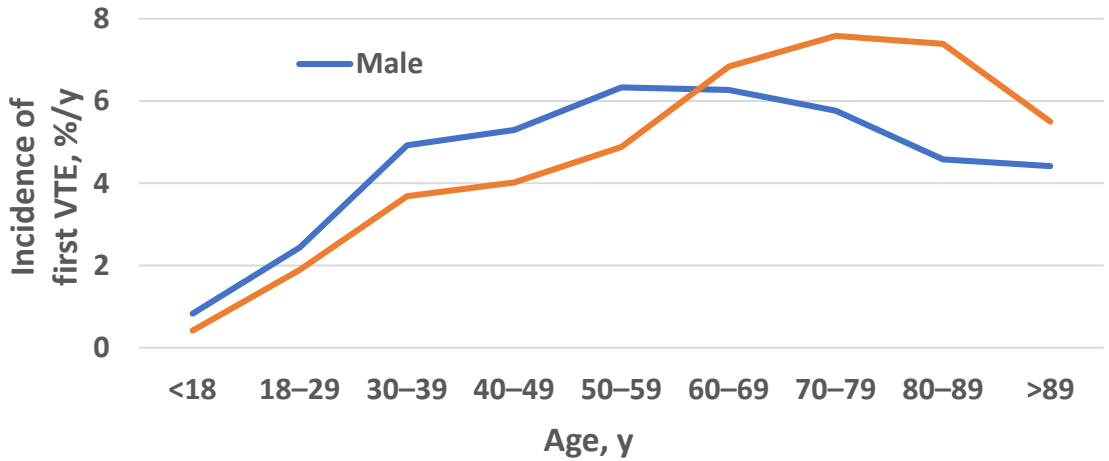
- Haematological biomarkers (e.g. platelet, haemoglobin, leukocyte counts)
- D-dimer, P-selectin,
- Prothrombin fragment 1 + 2
- Thrombin generation potential
- Microvesicle-tissue factor activity
- C-reactive protein

CCI: Charlson Comorbidity Index.

1. Ay C, et al. Thromb Haemost 2017;117(2):219 - 230.

VTE in Active Cancer by Gender and Age

- Incidence rate of a first venous thromboembolic event:
  - 5.8 (95% CI: 5.7, 6.0) per 100 person-years
- Incidence was highest in the elderly population



- Patients with active cancer and a first VTE (N = 6592). Active cancer was defined as a primary diagnosis of cancer (excluding non-melanoma skin cancer) as a hospital discharge diagnosis or treatment with radiation, chemotherapy or bone marrow transplantation during hospitalization.
- Cohen AT, et al. *Thromb Haemost* 2017;117:57-65.

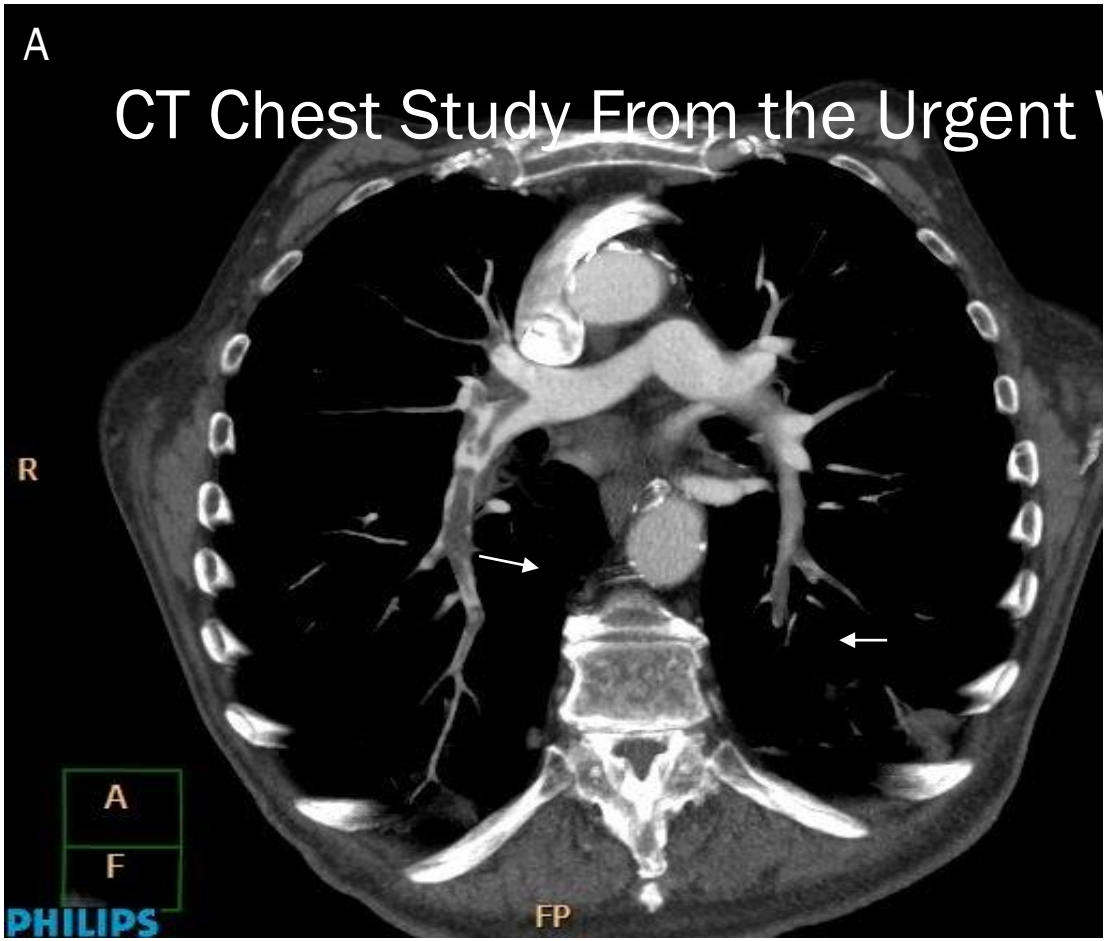
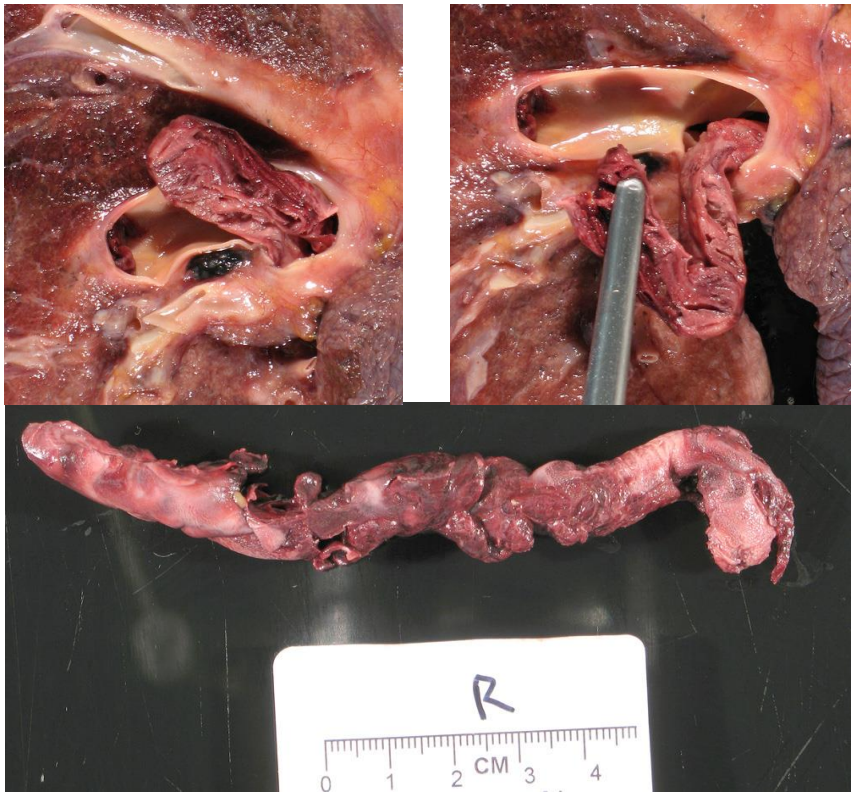


Image provided by
Prof A. Maraveyas.



Images provided by
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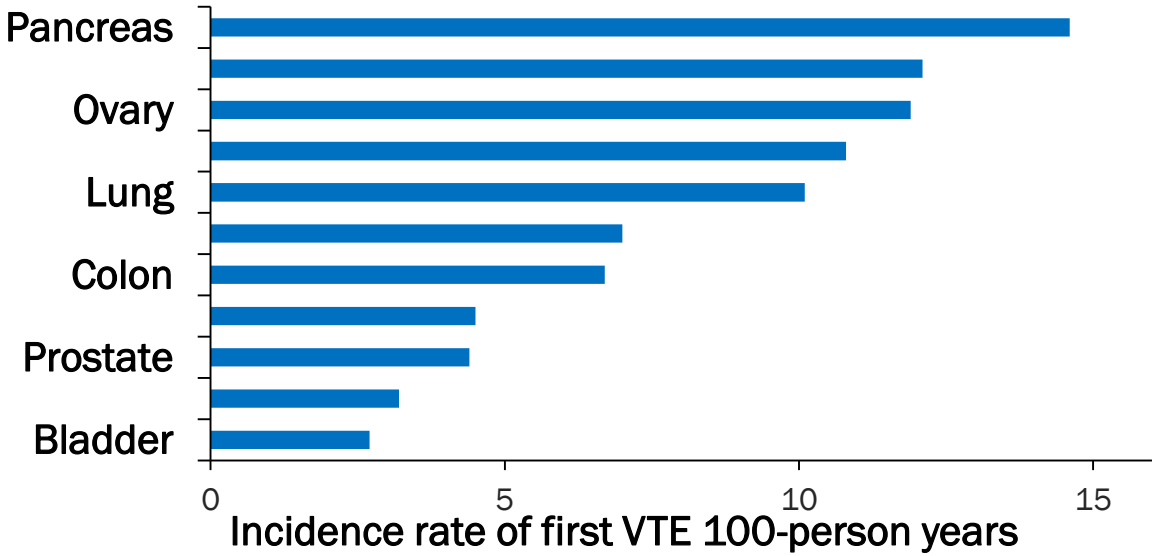
Incidence of VTE After Cancer Diagnosis



Age	Bladder	Breast	Colon	Lung	Prostate	Uterus	Haematological	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.

Prevalence of tumour types in active cancer-associated thrombosis

- Patients With Active Cancer* and a First VTE (N = 6592)

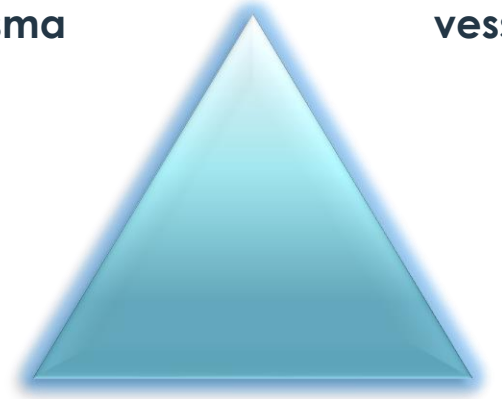
	DVT (n = 3055)	PE (n = 3537)	Total (n = 6592)
Common cancer types, %			
Prostate (men)	19.1	16.1	17.5
Breast (women)	14.0	16.0	15.1
Lung	10.3	17.0	13.9
Colon	12.6	12.5	12.5
Ovarian (women)	8.5	10.3	9.5
Haematological	11.8	8.7	10.1
Bladder	6.1	3.8	4.8
Uterus (women)	5.2	3.3	4.2
Pancreas	4.2	3.7	3.9
Stomach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

- *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.

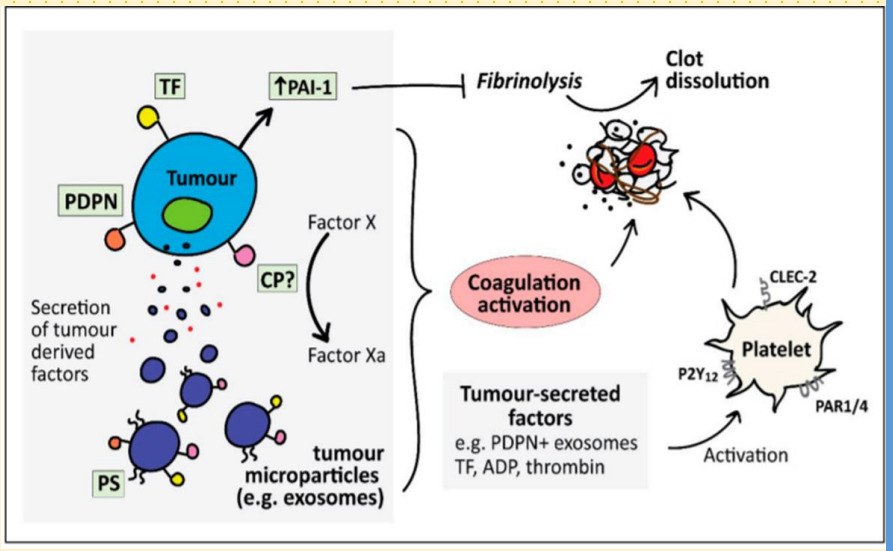
Pathogenesis of Thrombosis

Virchow – triad model 1856



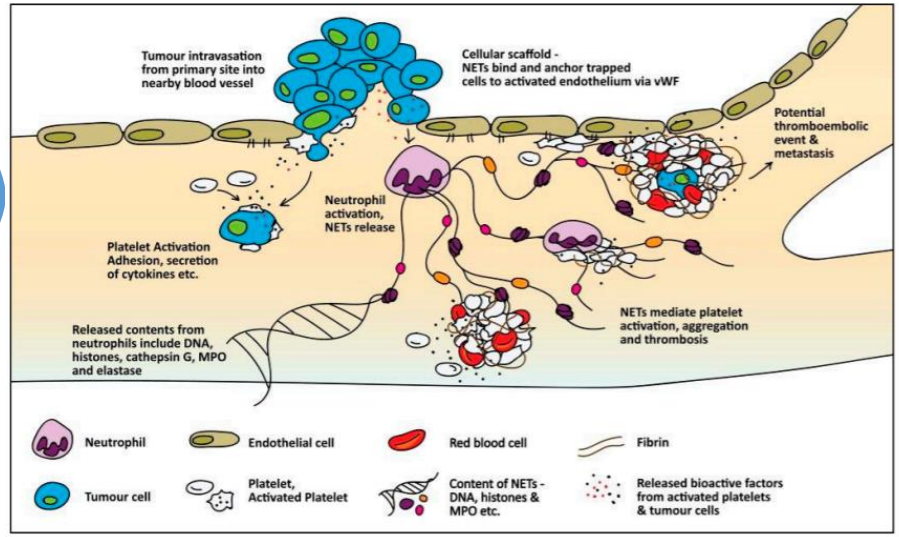
Direct mechanisms of thrombosis in cancer

Direct activation of coagulation and inhibition of fibrinolysis by cancer cells and secreted factors



Indirect mechanisms of thrombosis in cancer

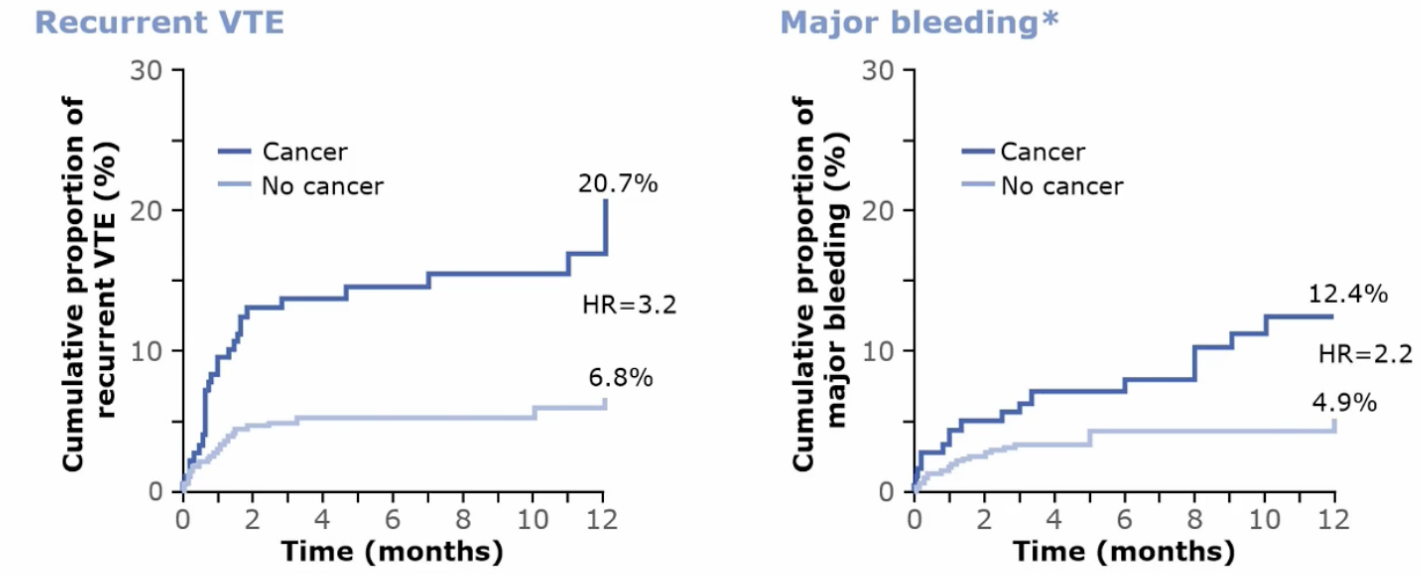
Indirect activation of coagulation through inflammation (CK release & neutrophil activation)



Abdol Razak et al, Cancers (Basel) 2018

VTE in cancer a challenging problem

Risk of events in patients receiving anticoagulation therapy for VTE

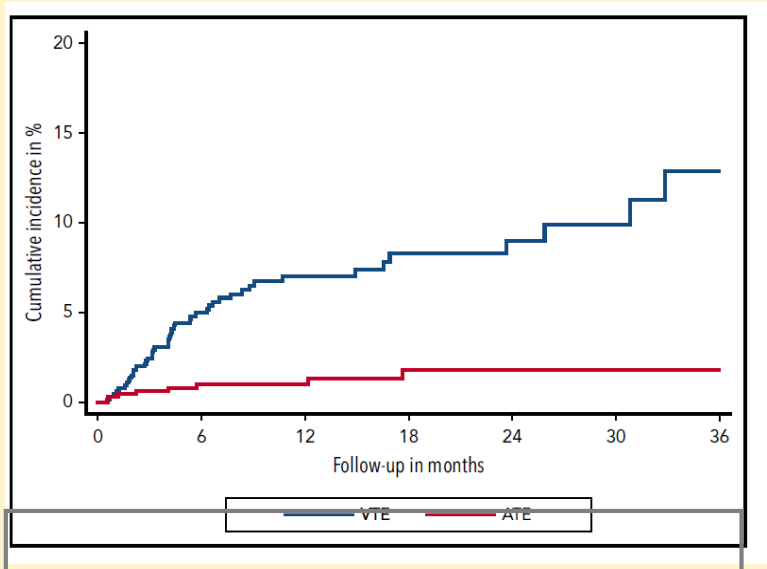


Data predates the introduction of the NOACs.

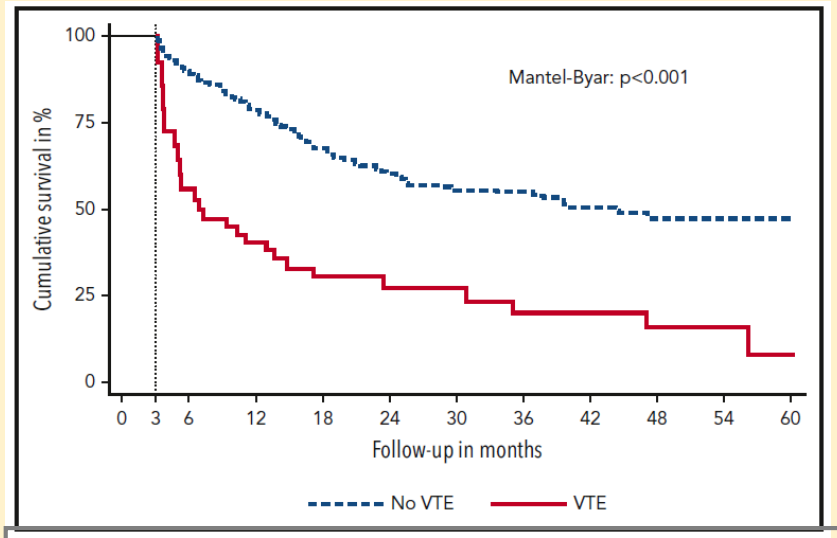
*Defined as overt and associated with either a decrease in the haemoglobin level (at least 2.0 g/dl) or the need for transfusion (≥2 units of blood), if it was retroperitoneal or intracranial, or if the treatment had to be discontinued permanently.

Prandoni P *et al*. *Blood* 2002;100:3484–3488.

Patients with cancer under immune checkpoint inhibitor therapy are at high risk of thromboembolism, associated with increased mortality



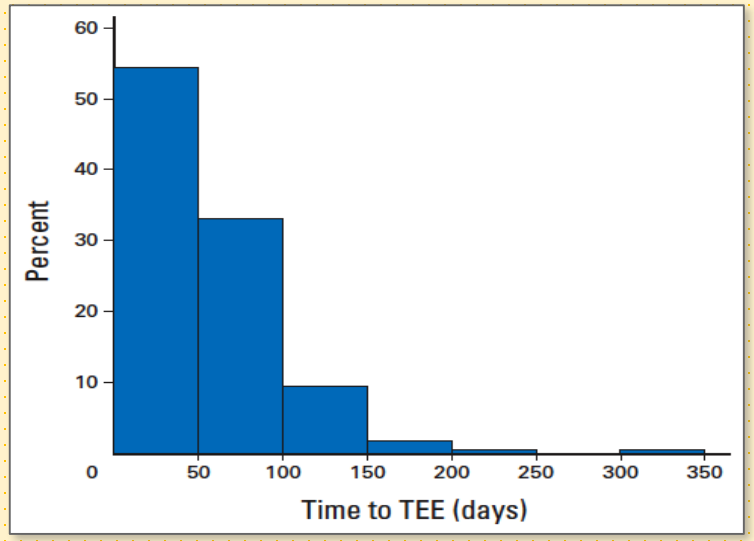
Cumulative incidence functions of VTE and ATE.
obtained within a competing risk framework, considering all-cause mortality as the competing event of interest



Landmark analysis of OS.
Patients are stratified by the occurrence of **VTE in the first 3** months of immune checkpoint inhibitor therapy.

Risk of VTE with Platinum Based chemo

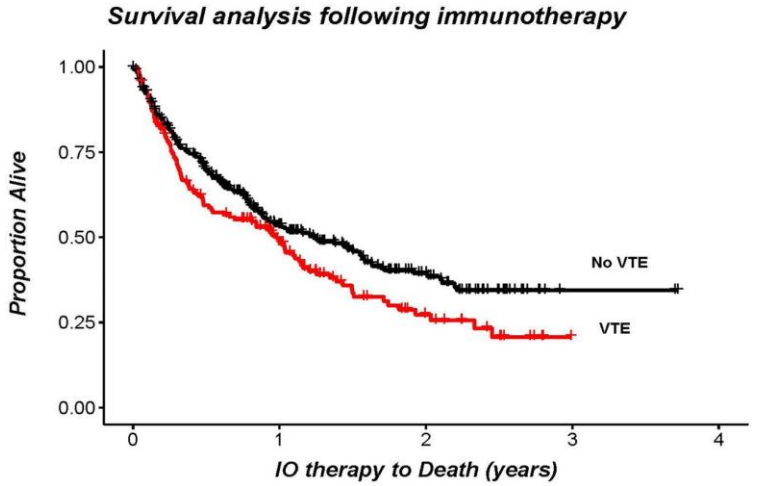
- 18.1% experienced a TEE during treatment
- 44% of all events were incidental
- 88% of events occurred within the first 100 days



J Clin Oncol 2011; 29: 3466–73.

VTE is common in cancer patients receiving immunotherapy

either as single-agent or in combination regimens, affecting nearly one-third of all patients and may potentially be associated with worsened survival



Roopkumar J. et al. Blood. 2018; 132:2510

PATIENT AWARENESS

ESMO VTE GUIDELINES : Ann Oncol 2023

- Patient education materials on CAT including risk factors, signs and symptoms and information on positive lifestyle factors, should be one component of the information package provided to all ambulatory patients scheduled to receive systemic anti-cancer treatment [III, A].
- Cancer patients should be offered a CAT risk assessment and have an opportunity to discuss their particular risk [III, B].

ESMO GL Falanga Ann Oncol 2023

ESMO VTE GUIDELINES : Ann Oncol 2023

- VTE risk assessment should be based on validated RAMs such as the KRS, COMPASS-CAT or the Vienna-CATS nomogram score [III, C].

- An estimated risk of VTE >8%-10% at 6 months is suggested as threshold for discussing primary thromboprophylaxis [II, C].

ESMO GL Falanga Ann Oncol 2023

Should hospitalized patients with active cancer receive anticoagulation for thromboprophylaxis?

Hospitalized patients who have active malignancy and acute medical illness or reduced mobility **should be offered pharmacologic thromboprophylaxis** in the absence of bleeding or other contraindications

Recom. ASCO 2019

Ambulatory cancer patients receiving chemotherapy

WHO'S AT RISK FOR THROMBOSIS

Khorana risk score per la CAT

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Cancer-Associated Venous Thromboembolic Disease

NCCN Guidelines Index
Table of Contents
Discussion

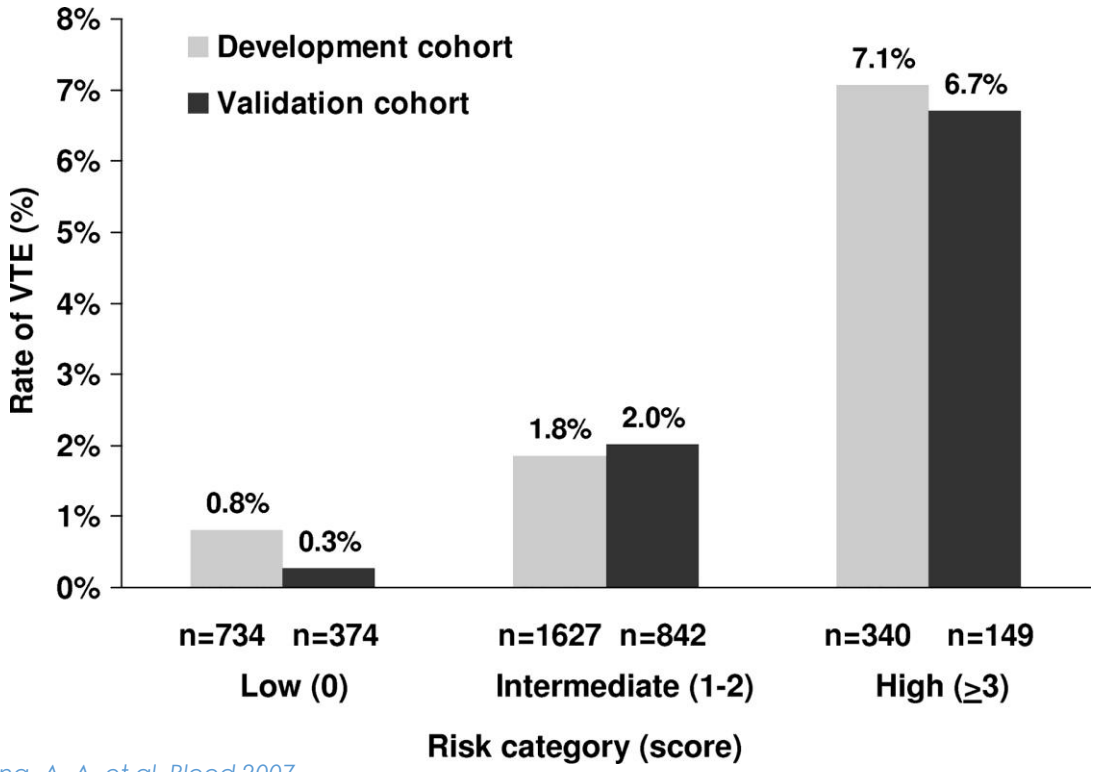
VTE RISK ASSESSMENT IN CANCER OUTPATIENTS

Khorana Predictive Model for Chemotherapy-Associated VTE[1]

Patient Characteristic	Risk Score
• Site of primary cancer	
▸ Very high risk (stomach, pancreas)	2
▸ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count 350 x 10^9/L or higher	1
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count higher than 11 x 10^9/L	1
• BMI 35 kg/m^2 or higher	1

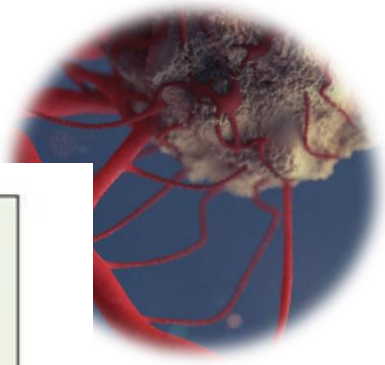
Total Score	Risk Category	Risk of Symptomatic VTE[2]
0	Low	0.3–1.5%
1, 2	Intermediate	2.0–4.8%
3 or higher	High	6.7–12.9%

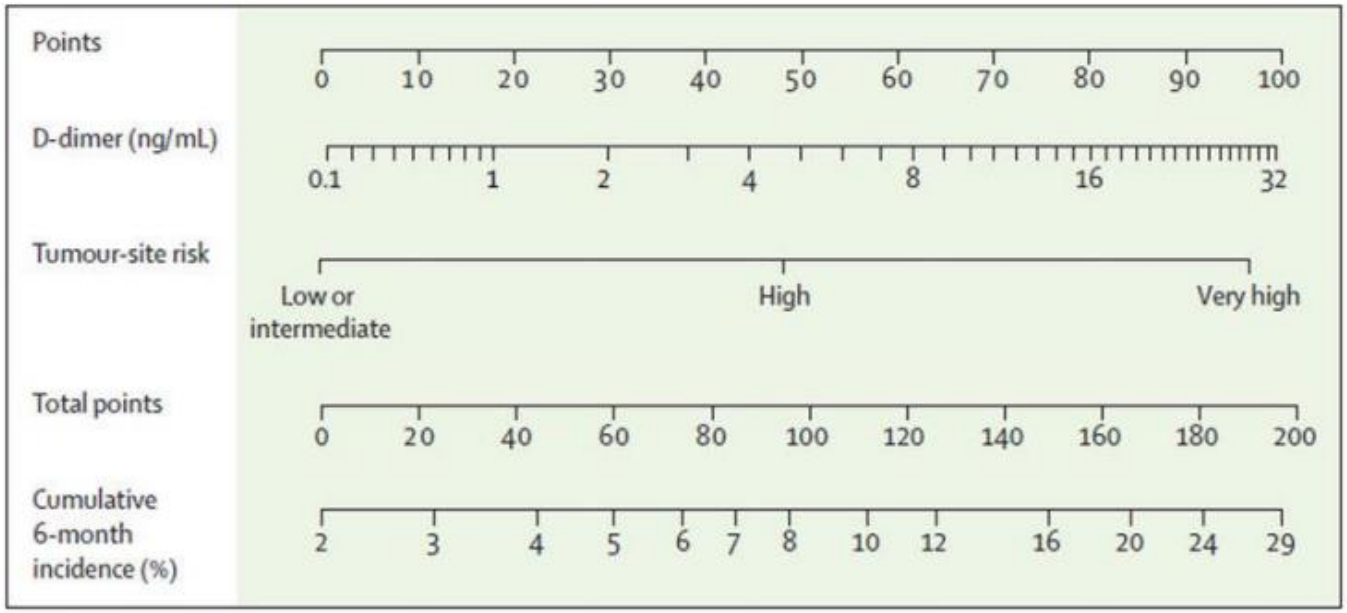
Rate of VTE: clinical score



Khorana, A. A. et al. Blood 2007

RAMs: Risk Assessment Models



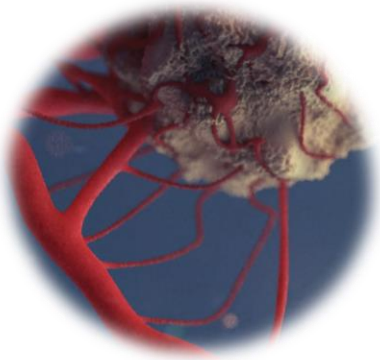


Vienna-CATS, Vienna Cancer and Thrombosis Study.

Reproduced with permission from Pabinger I, et al

RAMs: Risk Assessment Models

COMPASS-CAT score for VTE prediction in ambulatory patients with cancer



Predictors for VTE	Score[a]
Cancer-related risk factors	
Anti-hormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment	6
Time since cancer diagnosis ≤6 months	4
CVC	3
Advanced stage of cancer	2
Predisposing risk factors	
Cardiovascular risk factors (composed by at least two of the following predictors: personal history of peripheral artery disease, ischaemic stroke, coronary artery disease, hypertension, hyperlipidaemia, diabetes, obesity)	5
Recent hospitalisation for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelet count ≥350 x 10^9/l	2

COMPASS-CAT, Prospective Comparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real-life patients-Cancer-Associated Thrombosis; CVC, central venous catheter; VTE, venous thromboembolism.

RAMs: Risk Assessment Models

The Hypercan Score in Lung cancer

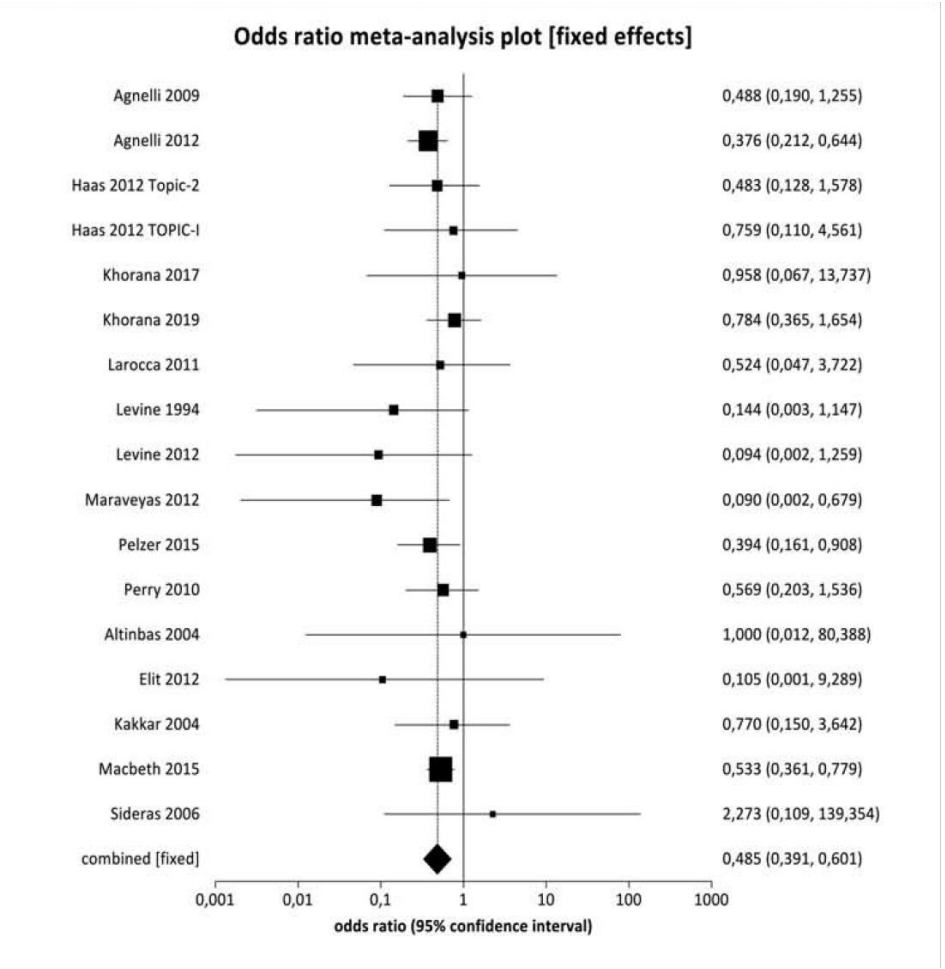
Table 4. Cumulative incidence of VTE and death, and accuracy of RAMs.

		6-Month VTE							6-Month Death						
RAM	**Risk Category**	**Cumulative Incidence (95% CI)**	**Log-Rank (*p*-Value)**	**ROC AUC (*p*-Value)**	**Sen (%)**	**Spe (%)**	**PPV (%)**	**NPV (%)**	**Cumulative Incidence (95% CI)**	**Log-Rank (*p*-Value)**	**ROC AUC (*p*-Value)**	**Sen (%)**	**Spe (%)**	**PPV (%)**	**NPV (%)**
HYPERCAN • D-dimer/ECOG 2	Low High	6 (4–10) 25 (24–42)	< 0.001	0.734 (<0.001)	63	74	25	93	19 (15–23) 55 (47–63)	<0.001	0.726 (<0.001)	56	80	55	81
KRS • Cancer site/BMI $\geq$ 35 kg/m^2 • Hemoglobin < 100g/L • Platelet > 350 $\times$ 10^9/L • Leukocyte > 11 $\times$ 10^9/L	Low Int-High	11 (9–15) 16 (9–30)	0.089	0.543 (0.290)	21	86	16	89	26 (22–30) 49 (39–62)	<0.001	0.609 (<0.001)	25	89	49	74
New-Vienna CATS * • Cancer site/D-dimer	Low-Int High	9 (5–13) 14 (12–22)	0.008	0.642 (0.001)	70	43	14	92	15 (11–20) 40 (35–46)	<0.001	0.670 (<0.001)	79	50	40	85
PROTECHT • Cancer site/BMI $\geq$ 35kg/m^2 • Hemoglobin < 100g/L • Platelet > 350 $\times$ 10^9/L • Leukocyte > 11 $\times$ 10^9/L • Gemcitabine/Platinum	Low-Int High	11 (8–17) 12 (9–18)	0.730	0.527 (0.504)	59	42	12	89	24 (18–30) 34 (29–40)	0.012	0.584 (0.002)	66	46	34	76
CONKO • Cancer site/WHO $\geq$ 2 • Hemoglobin < 100g/L • Platelet > 350 $\times$ 10^9/L • Leukocyte > 11 $\times$ 10^9/L	Int High	10 (8–14) 19 (13–36)	0.004	0.558 (0.156)	26	85	19	90	25 (21–29) 57 (48–69)	<0.001	0.647 (<0.001)	31	90	56	75

Data shows the cumulative incidence of VTE and death of the five RAMs at different risk stratification. The accuracy of the RAMs by ROC curve and the sensibility, specificity, PPV, and NPV. RAM: risk assessment model; VTE: venous thromboembolism; HYPERCAN: hypercoagulation in cancer; KRS: Khorana risk score; BMI: body mass index; WHO: World Health Organization; ROC: receiver operating characteristics; AUC: area under the curve; Sen: sensitivity, Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; Int: intermediate. * The New-Vienna CATS score set at a VTE cumulative incidence of 10%.

WHY PROPHYLAXIS IS NOT ROUTINE?

New meta-analysis on VTE in ambulatory cancer patients



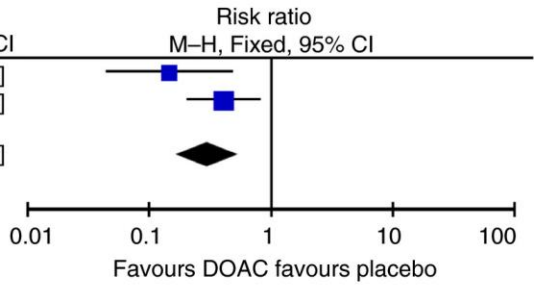
Becattini Hematologica 2019

Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: a systematic review and meta-analysis

A Risk ratio for overall VTE (during on-treatment period: sensitivity analysis)

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Fixed, 95% CI
AVERT	3	291	20	283	42.9%	0.1459 [0.0438, 0.4855]
CASSINI	11	420	27	421	57.1%	0.4084 [0.2053, 0.8125]
Total (95% CI)		711		704	100.0%	0.2957 [0.1644, 0.5317]
Total events	14		47			

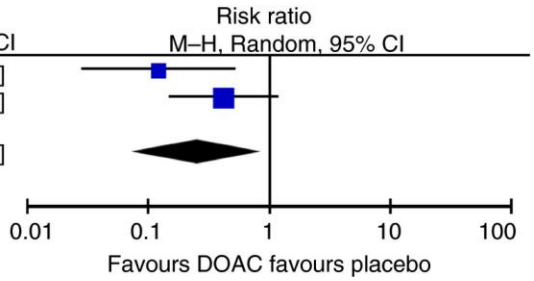
Heterogeneity: $\chi^2 = 2.17$, df = 1 ($P = .14$); $I^2 = 54\%$
Test for overall effect: $Z = 4.07$ ($P < .0001$)



B Risk ratio for symptomatic VTE (during on-treatment period: sensitivity analysis)

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Random, 95% CI
AVERT	2	291	16	283	41.2%	0.1216 [0.0282, 0.5239]
CASSINI	5	420	12	421	58.8%	0.4177 [0.1484, 1.1751]
Total (95% CI)		711		704	100.0%	0.2511 [0.0747, 0.8441]
Total events	7		28			

Heterogeneity: $\tau^2 = 0.37$, $\chi^2 = 1.89$, df = 1 ($P = .17$); $I^2 = 47\%$
Test for overall effect: $Z = 2.23$ ($P = .03$)



Journal of Thrombosis and Haemostasis, Volume: 17, Issue: 12, Pages: 2141-2151, First published: 17 August 2019, DOI: (10.1111/jth.14613)

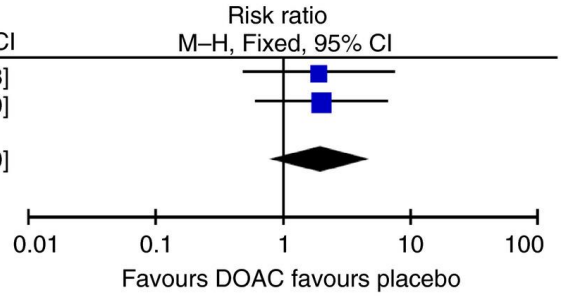
Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: a systematic review and meta-analysis

A Risk ratio for major bleeding (during on-treatment period)

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Fixed, 95% CI
AVERT	6	288	3	275	43.4%	1.9097 [0.4824, 7.5608]
CASSINI	8	405	4	404	56.6%	1.9951 [0.6056, 6.5730]
Total (95% CI)		693		679	100.0%	1.9580 [0.7953, 4.8210]
Total events	14		7			

Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = .96$); $I^2 = 0\%$

Test for overall effect: $Z = 1.46$ ($P = .14$)

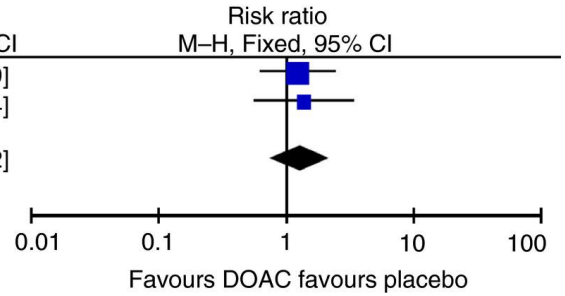


B Risk ratio for clinically relevant non-major bleeding (during on-treatment period)

Study or Subgroup	DOCA Events	DOCA Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Fixed, 95% CI
AVERT	18	288	14	275	64.1%	1.2277 [0.6228, 2.4199]
CASSINI	11	405	8	404	35.9%	1.3716 [0.5575, 3.3744]
Total (95% CI)		693		679	100.0%	1.2793 [0.7442, 2.1992]
Total events	29		22			

Heterogeneity: $\chi^2 = 0.04$, df = 1 ($P = .85$); $I^2 = 0\%$

Test for overall effect: $Z = 0.89$ ($P = .37$)



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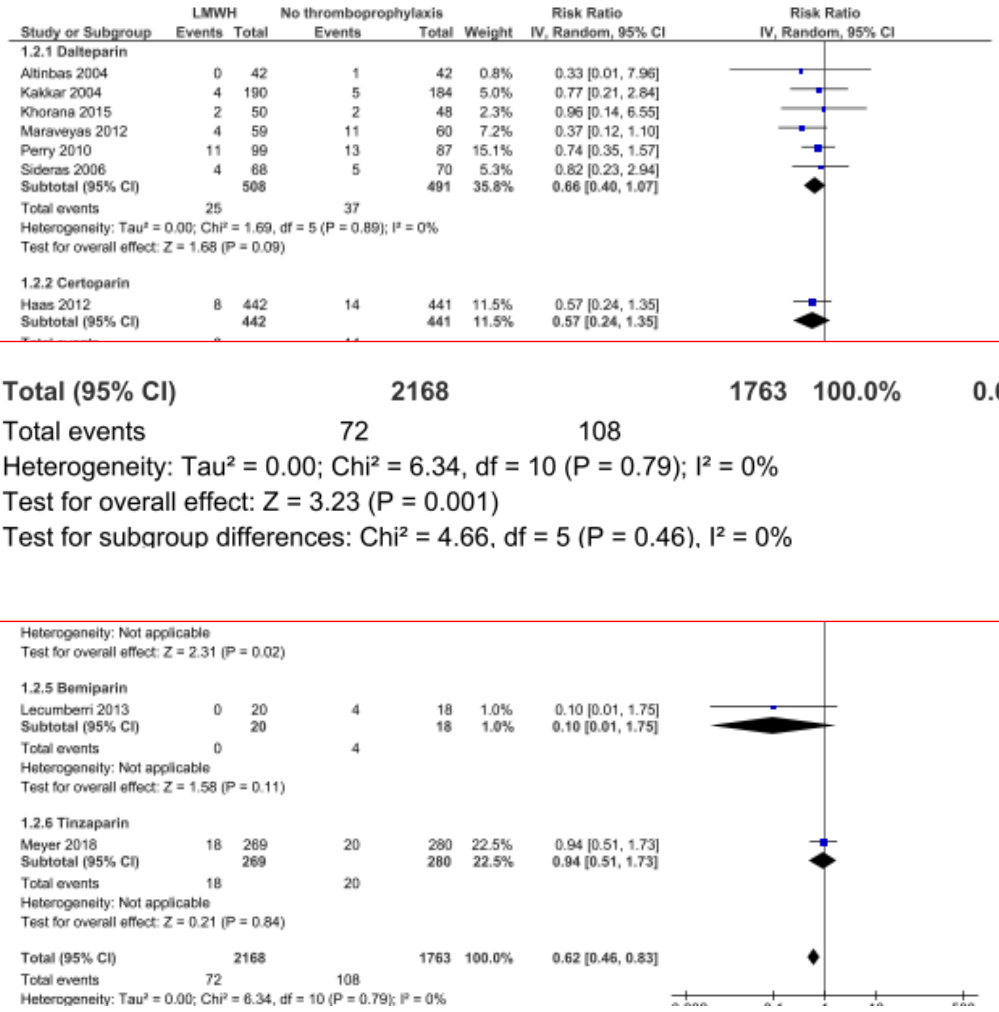
Recommendations

ASCO 2019	• Routine pharmacologic thromboprophylaxis should not be offered • Khorana score 2 may be offered apixaban, rivaroxaban, or LMWH
ITAC 2022*	• LMWH, VKAs, or DOACs not recommended routinely • LMWH or DOACs (rivaroxaban or apixaban) in locally advanced or M+ ***pancreatic cancer*** treated with systemic anticancer therapy with low bleeding risk • DOACs (rivaroxaban or apixaban) recommended intermediate-to-high risk of VTE (*Khorana* ♦
SSC of the ISTH	• DOACs suggested if **Khorana** ♦, no interactions, and no high risk for bleeding (e.g. GI cancer) • LWMH, if concerns for safety of DOAC • If DOACs were to be used, iadministered for up to 6 months
ASH 2021	• Intermediate risk: DOAC (apixaban or rivaroxaban) - no LMWH • High risk: parenteral thromboprophylaxis (LMWH) DOAC (apixaban or rivaroxaban)
ESMO 2023	• For ambulatory pancreatic cancer patients on first-line systemic anticancer treatment , **LMWH** given at a higher dose (150/IU/kg dalteparin or 1 mg/kg enoxaparin) for a maximum of 3 months may be considered [II, C] • In ambulatory cancer patients starting systemic anticancer treatment who have a high thrombosis risk, **apixaban, rivaroxaban or LMWH** may be considered for primary thromboprophylaxis for a maximum of 6 months [I, B]

*International Initiative on Thrombosis and Cancer

Key NS, et al. J Clin Oncol 2019; Farge D, et al. Lancet Oncol 2022; Wang TF, et al. JTH 2019; Lyman G, et al. Blood Adv 2021; Falanga A, et al. Ann Oncol 2023



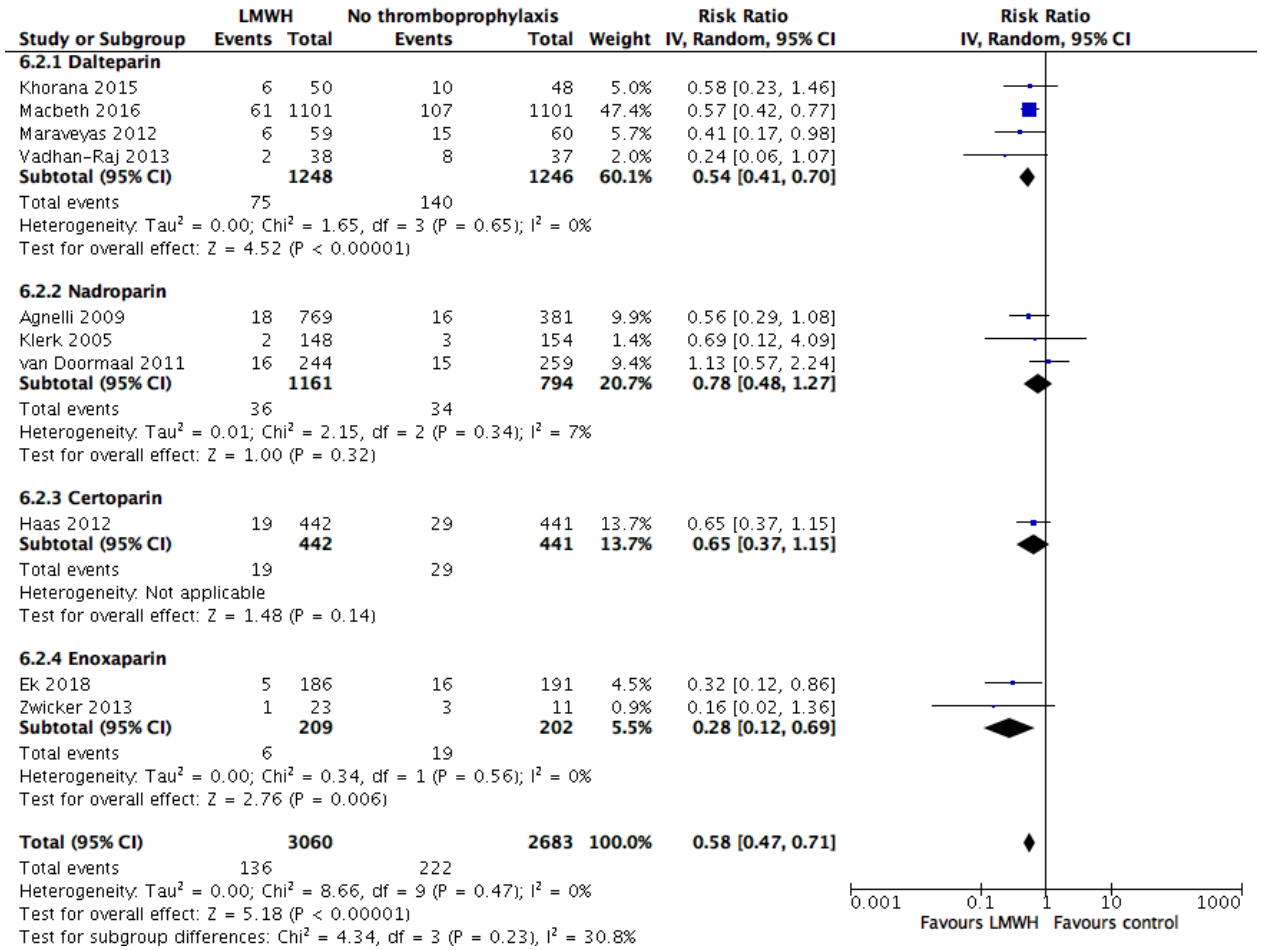
Symptomatic VTE

LMWH vs. placebo/no LMWH

3.3% vs. 6.1%

NNT = 37

Rutjes AWS, et al. Cochrane 2020

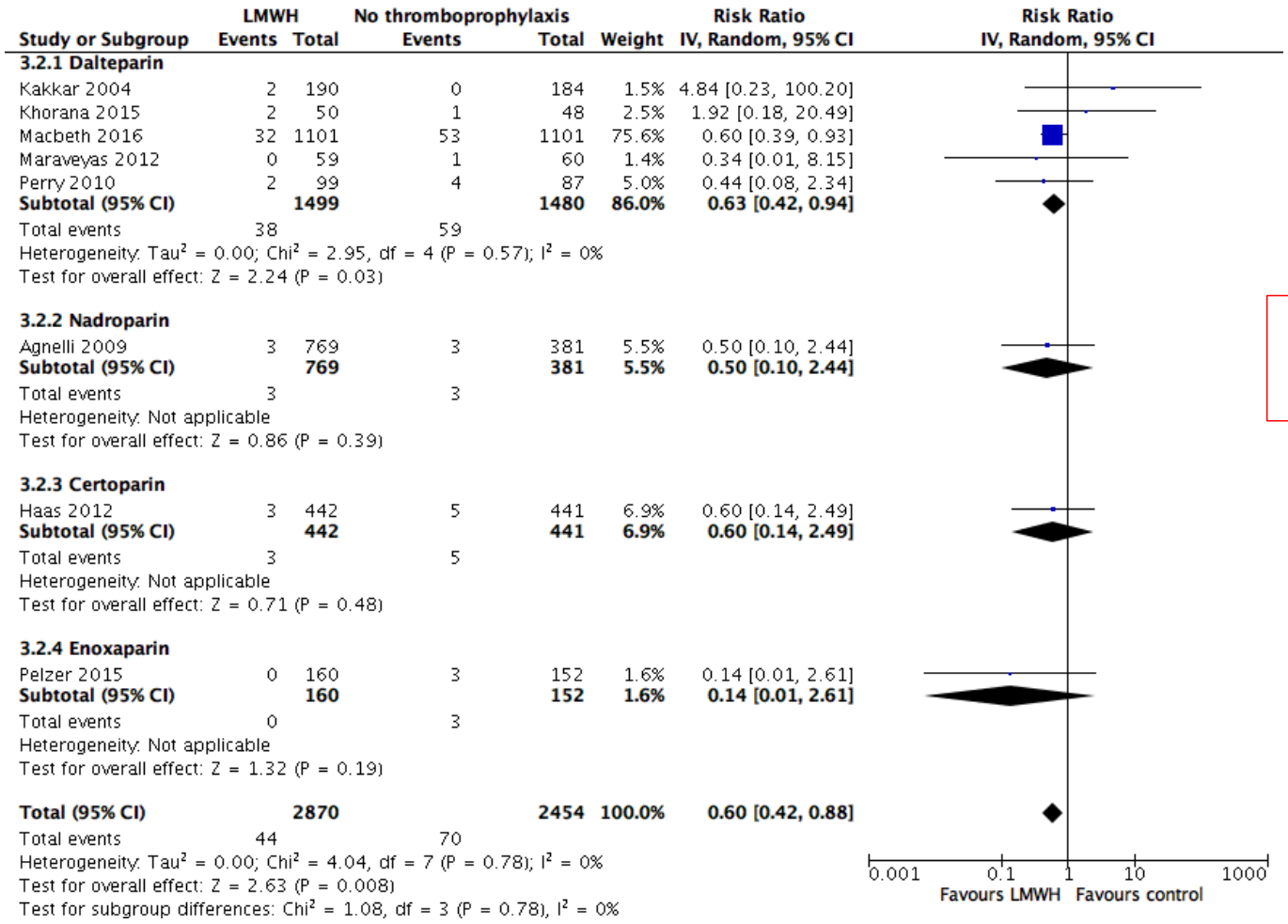


Any VTE

4.4% vs 8.27%

NNT 27

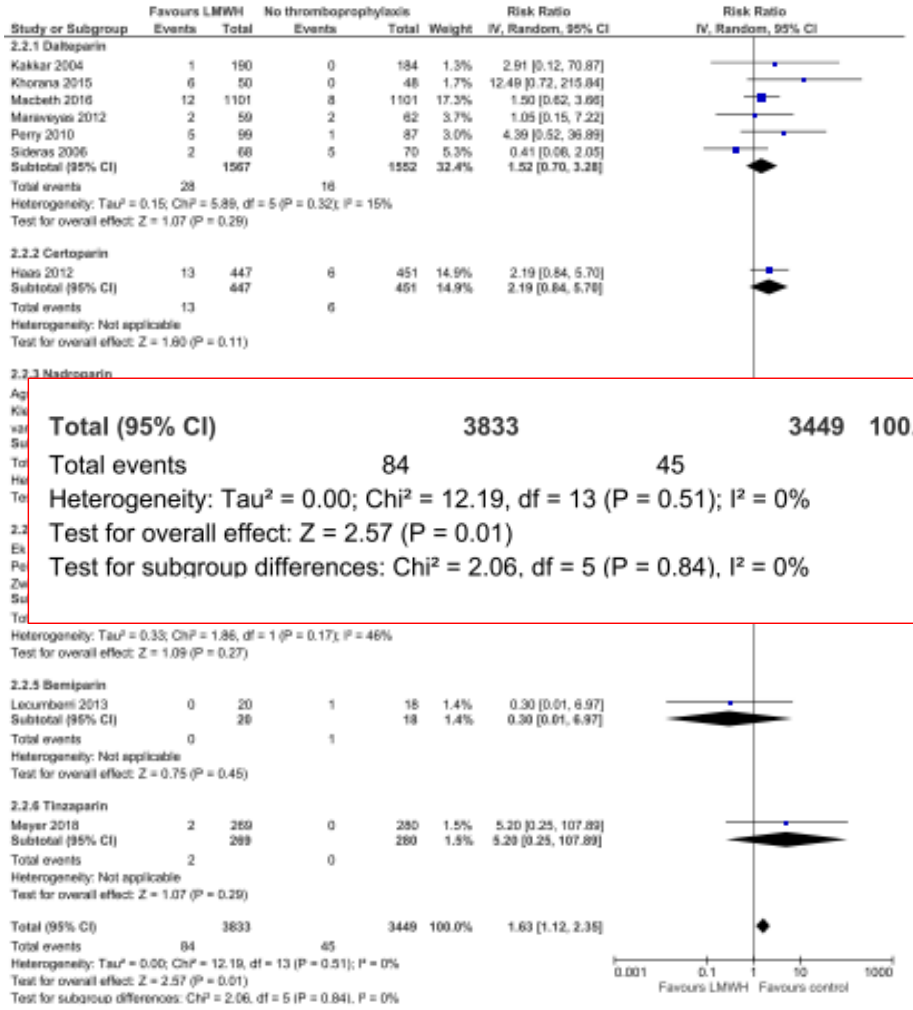
Rutjes AWS, et al. Cochrane 2020



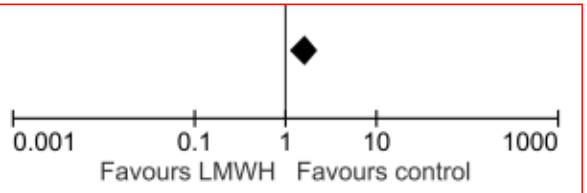
Symptomatic PE

NNT 138

Rutjes AWS, et al. Cochrane 2020



Total (95% CI) 3833 3449 100.0% 1.63 [1.12, 2.35]
Total events 84 45
Heterogeneity: Tau² = 0.00; Chi² = 12.19, df = 13 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)
Test for subgroup differences: Chi² = 2.06, df = 5 (P = 0.84), I² = 0%



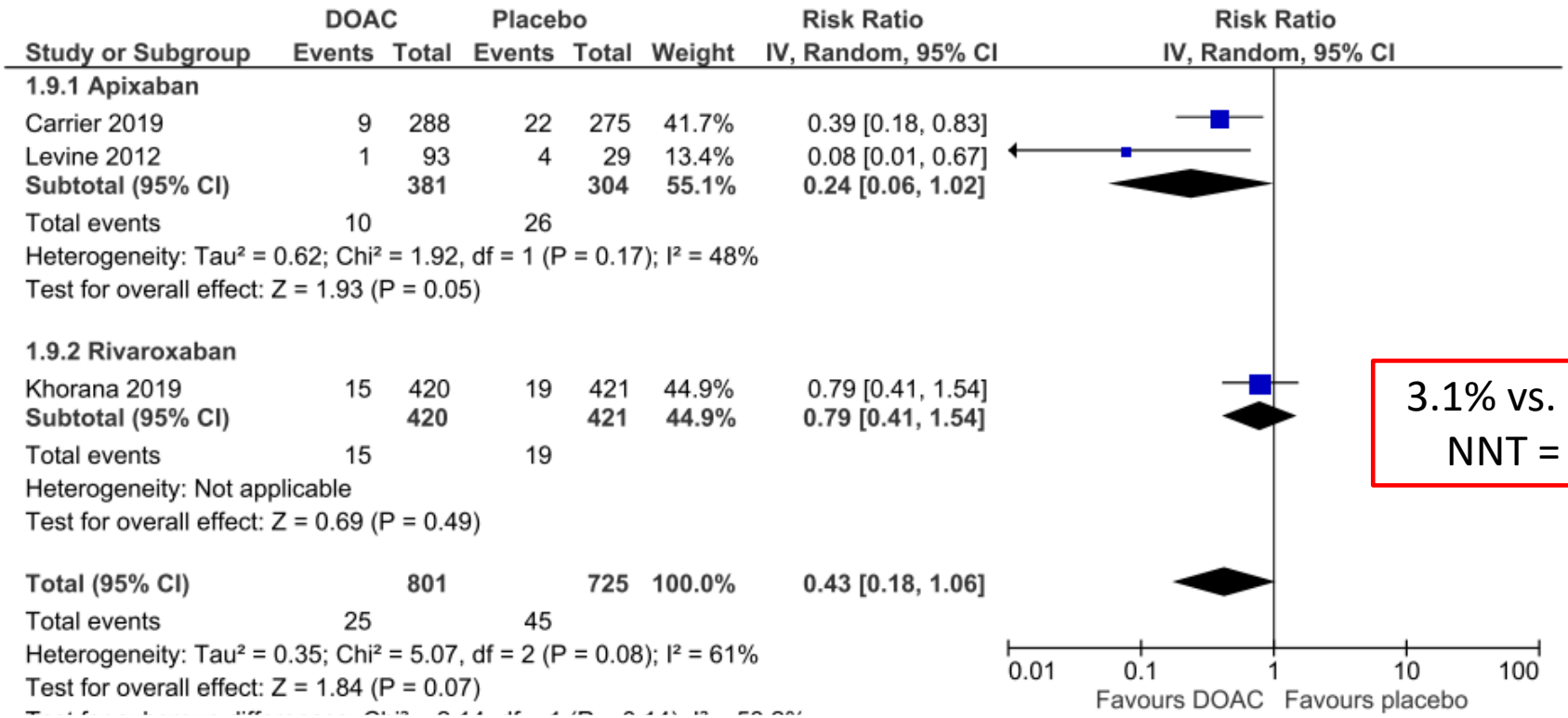
Major bleeding

LMWH vs. placebo/no LMWH

2.2% vs. 1.3%
NNH = 144

Rutjes AWS, et al. Cochrane 2020

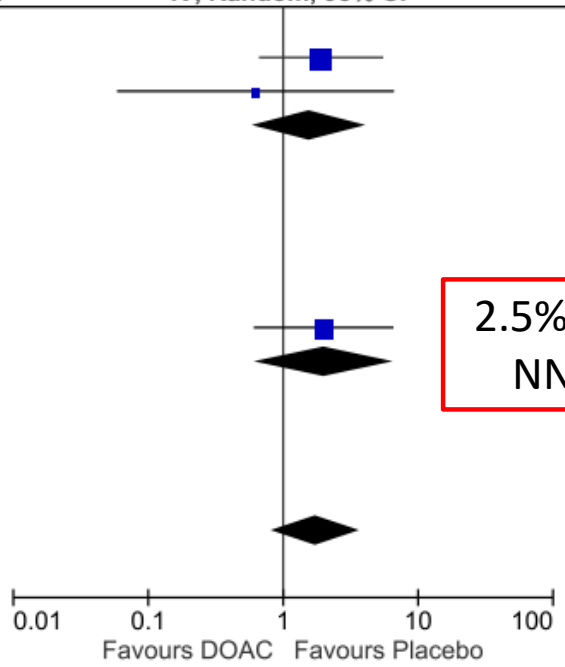
DOAC: Symptomatic VTE



3.1% vs. 6.2%
NNT = 32

DOAC: Major bleeding

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
2.10.1 Apixaban						
Carrier 2019	10	288	5	275	50.2%	1.91 [0.66, 5.52]
Levine 2012	2	93	1	29	10.1%	0.62 [0.06, 6.63]
Subtotal (95% CI)		**381**		**304**	**60.3%**	**1.58 [0.60, 4.17]**
Total events	12		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.10.2 Rivaroxaban						
Khorana 2019	8	405	4	404	39.7%	2.00 [0.61, 6.57]
Subtotal (95% CI)		**405**		**404**	**39.7%**	**2.00 [0.61, 6.57]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.26)						
Total (95% CI)		**786**		**708**	**100.0%**	**1.74 [0.82, 3.68]**
Total events	20		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						



2.5% vs. 1.4%
NNH = 91

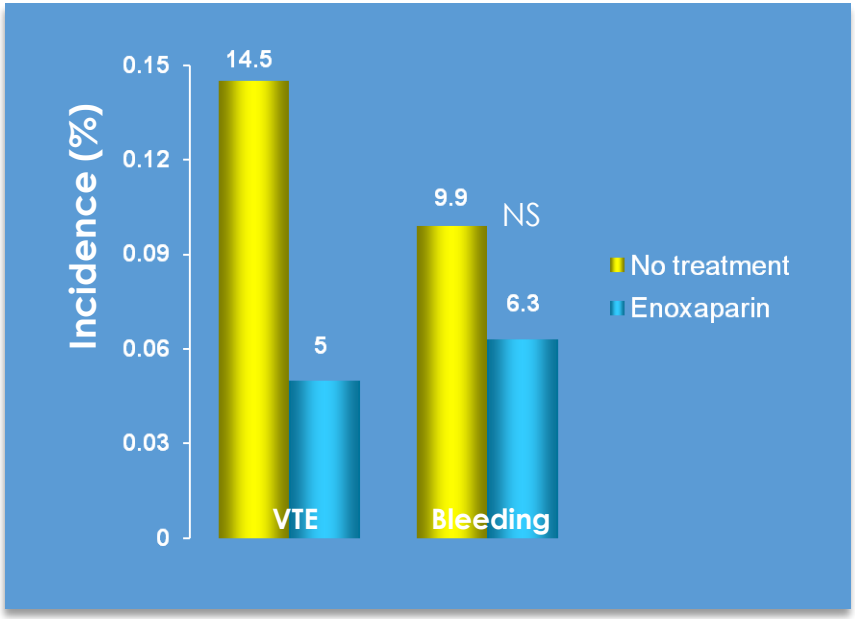
PROSPECT-CONKO 004

Study design

- RCT, 312 patients
- Pancreatic cancer
- GFFC vs Gem chemo
- Enoxaparin 1 mg/kg/day* vs none

Results

- 12 week incidence of VTE: 14.5% (control) vs 5% (enoxaparin)
- RR: 65% reduction
- No difference in PFS, OS

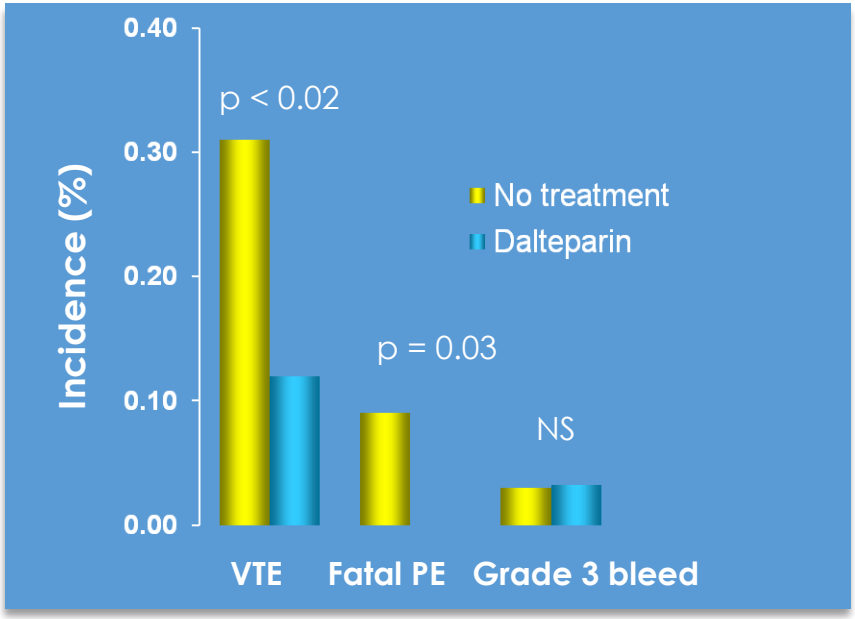


*1 mg/kg once daily s.c. for the first 12 weeks, thereafter 40 mg once daily.
GFFC = gemcitabine, cisplatin, 5-fluorouracil, folinic acid.

Riess HB, et al. J Thromb Haemost. 2009;7(Suppl 2):[abstract LB-MO-003].

UK – FRAGEM Study

- 123 patients receiving chemotherapy for APC
- Randomized to gemcitabine or gemcitabine + dalteparin
- Dalteparin 200 IU/kg once daily x 4 weeks, then
  150 IU/kg × 8 weeks
- Primary outcome: all TE (arterial, venous, incidental) at 3 months



APC *= metastatic pancreatic cancer.*

Maraveyas A, et al. Eur J Cancer. 2012.

Gaps on Oncologists awareness

- Complex: it requires the management of both the cancer and the thrombosis
- Anticoagulant treatment is viewed as less critical than the antineoplastic treatment
- When the oncologist is the referring physician, no referent may be found for the management of the thrombosis
- Following the VTE diagnosis, there is therefore a risk that no one is accountable or the follow-up, dose adaptation, prolongation or discontinuation of the anticoagulant treatment

Thromboprophylaxis in oncology patients still seems a neglected clinical issue!

Journal of Thrombosis and Haemostasis, 14: 2107–2113, 2016

CONCLUSIONS

INCREASING AWARENESS IS A TOPIC

PROPHYLAXIS MAY BE CONSIDERED IN HIGH RISK PATIENTS

DISEASE ORIENTED STUDIES NEEDED