Cancer Associated Thrombosis
Approach to VTE recurrence

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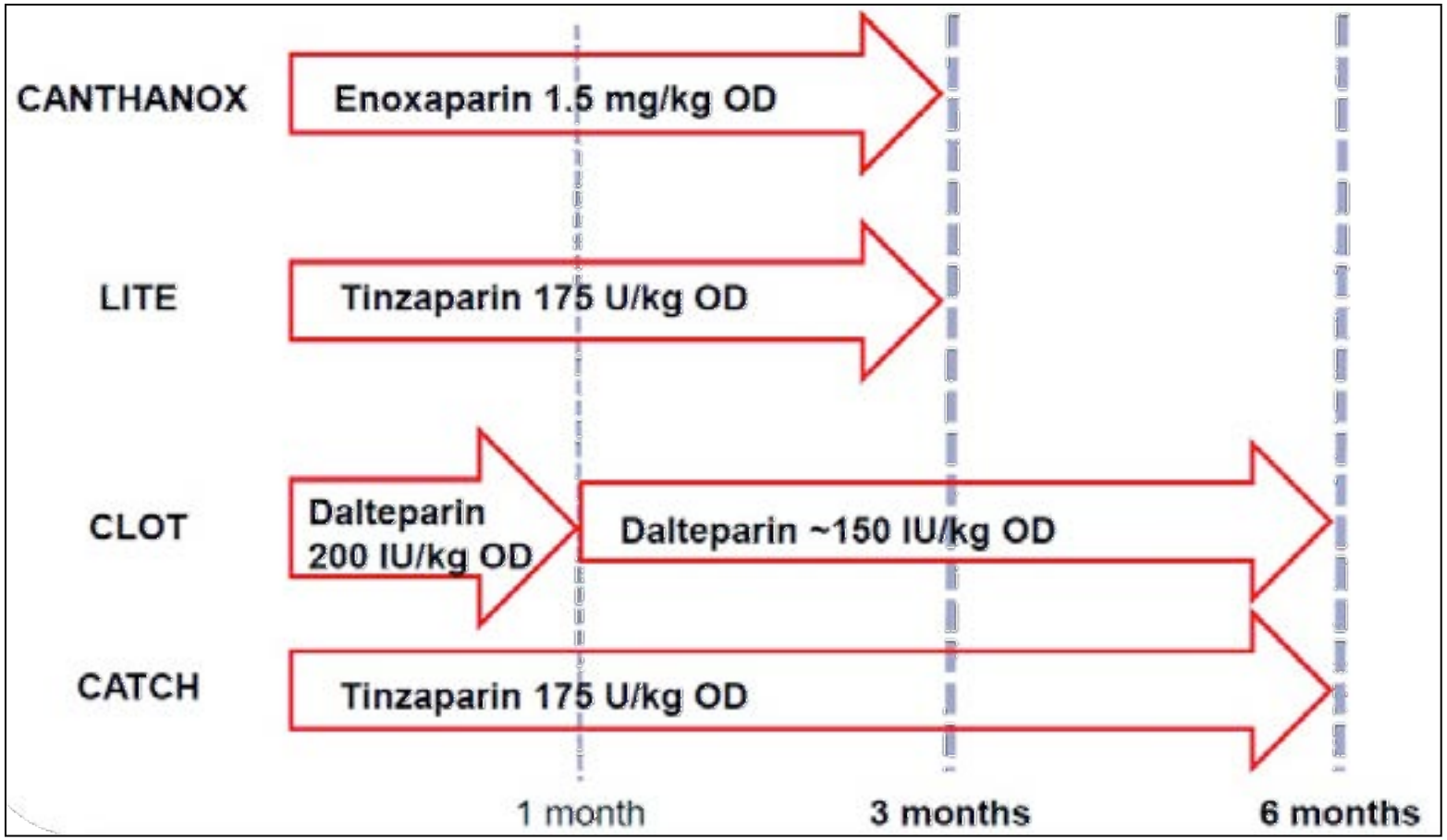
Cancer associated thrombosis

Initial treatment (first 6 months)

Patients with CAT : anticoagulant therapy

Studies comparing LMWH to VKA

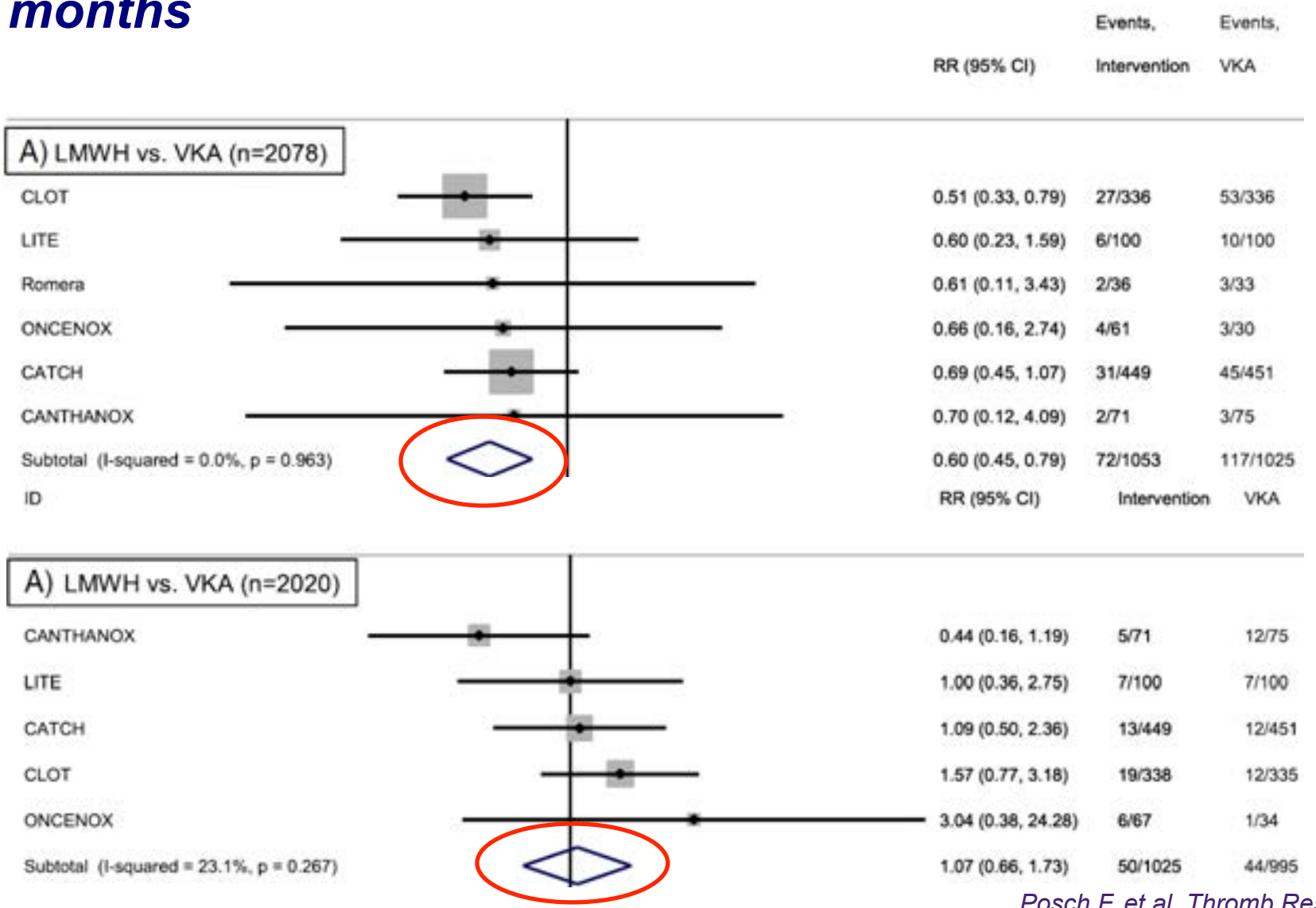


Patients with CAT

Studies comparing LMWH to VKA

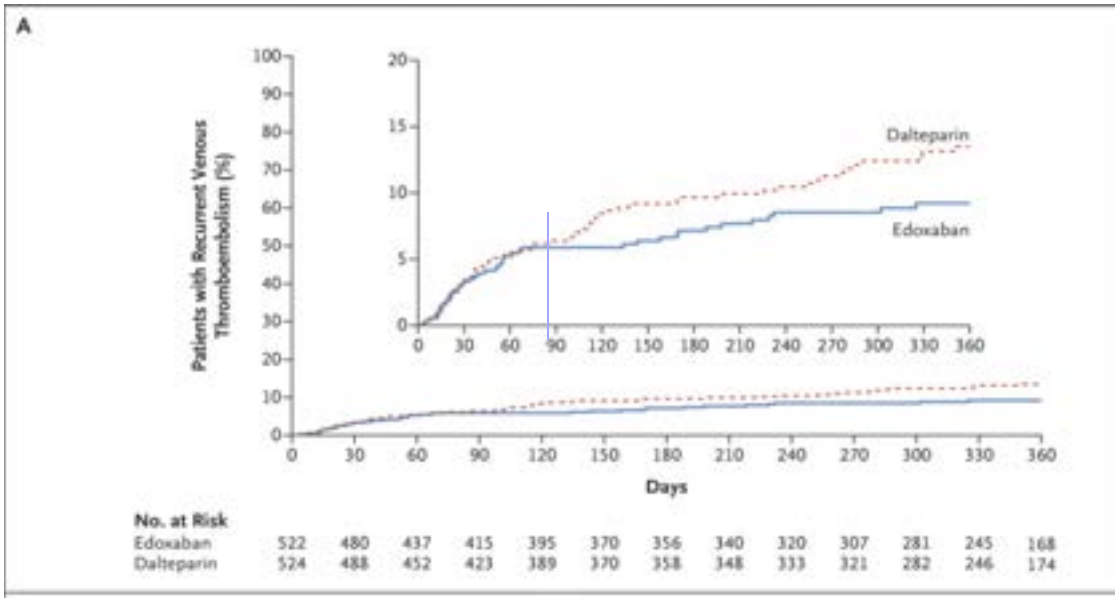
3-6 months

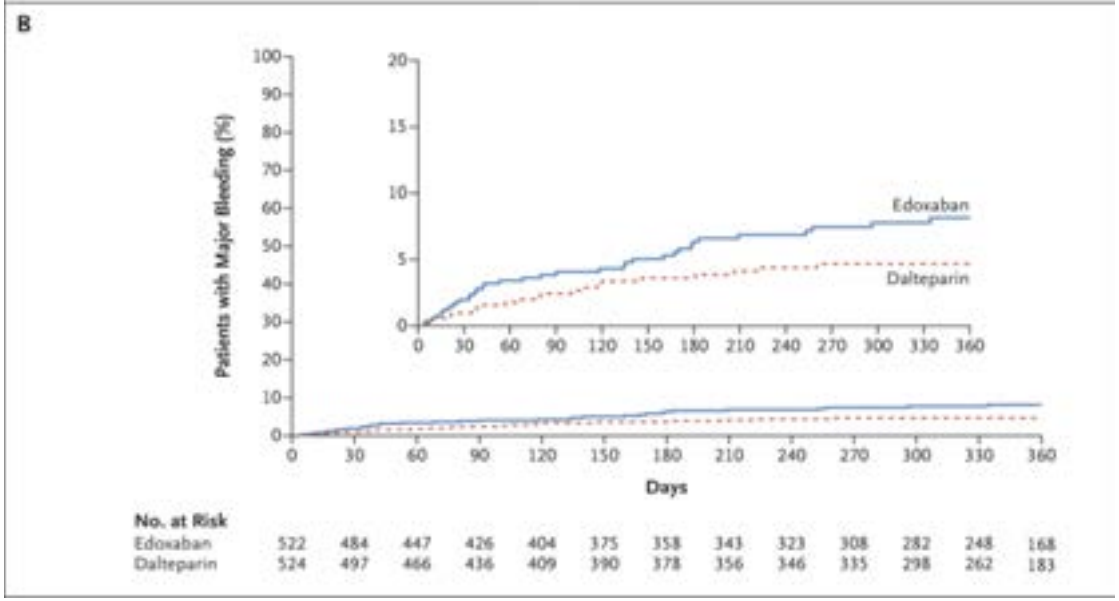
Dalteparin 200 and 150 UI/kg
Tinzaparin 175 UI/kg
Enoxaparin 1.5 mg/kg



Posch F. et al. Thromb Res 2015.

HOKUSAI Cancer : *VTE recurrences and MB*





Tendency to a better efficacy edoxaban vs dalteparin (p=0,09)

Significant increase of MB edoxaban vs dalteparin (p=0,04)

Raskob GE, NEJM 2018

Clinical prediction rule for risk stratification of recurrent VTE

Derivation study : a retrospective cohort - 543 patients with cancer

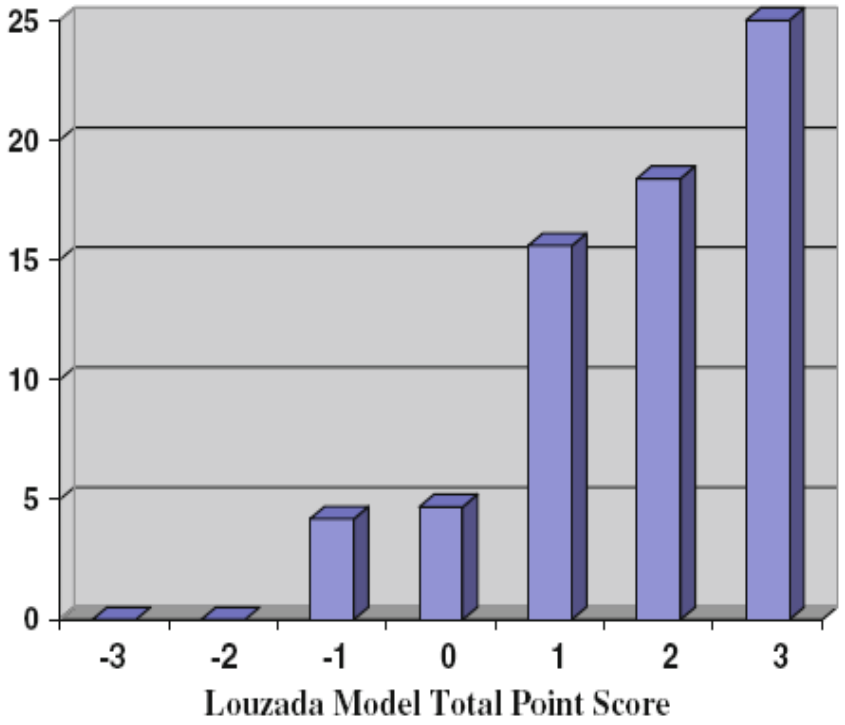
Validation study : 2 RCT comparing LWMH to VKA - 819 patients VTE+cancer

Table 2. Ottawa Score for Recurrent VTE Risk in Cancer-Associated Thrombosis

Variable	Regression Coefficient	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
Clinical probability		
Low (≤0)	. . .	−3 to 0
High (≥1)	. . .	1 to 3

VTE indicates venous thromboembolism.

*TNM (tumor-nodes-metastasis staging system) for solid tumors only.



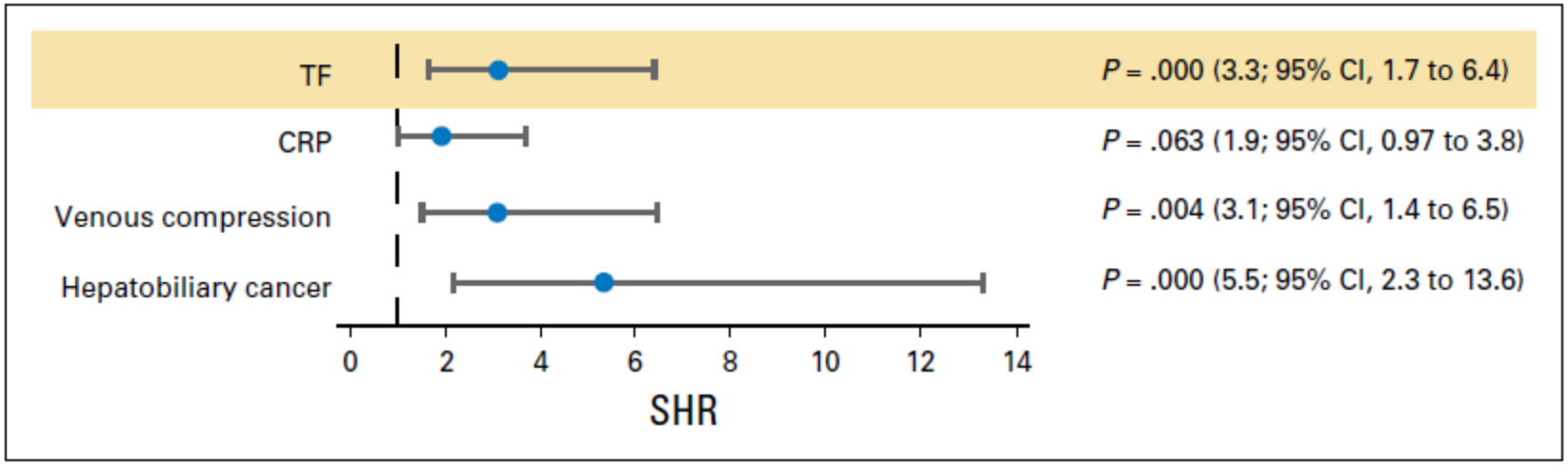
Louzada, Blood Coag Fibrinol 2011,
Louzada, Circulation 2012

NOT CONFIRMED IN PROSPECTIVE STUDIES

Van Es, Thromb Res 2018

Tissue Factor As a Predictor of Recurrent Venous Thromboembolism in Malignancy: Biomarker Analyses of the CATCH Trial

Alok A. Khorana, Pieter W. Kamphuisen, Guy Meyer, Rupert Bauersachs, Mette S. Janas, Mikala F. Jarner, and Agnes Y.Y. Lee



Khorana A, JCO 2016

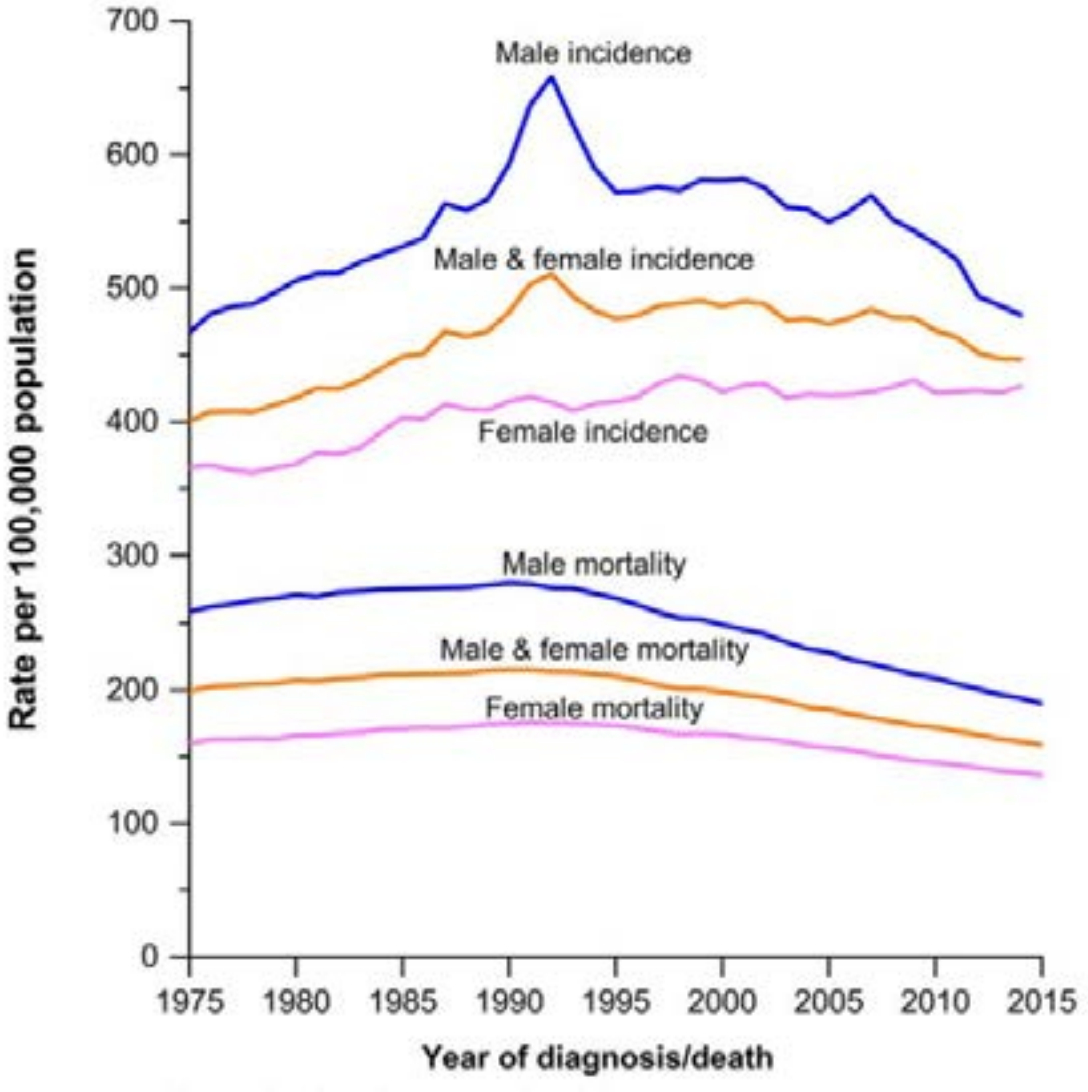
P-Sel at baseline : 4-fold higher risk in patients with high levels
HR 4.0 (95% CI, 1.114)

Van Es N, Thromb Res 2018

Cancer associated thrombosis
Extended treatment (beyond 6 months):

an important and increasing unmet need

Cancer *An increasing incidence*
A longer survival



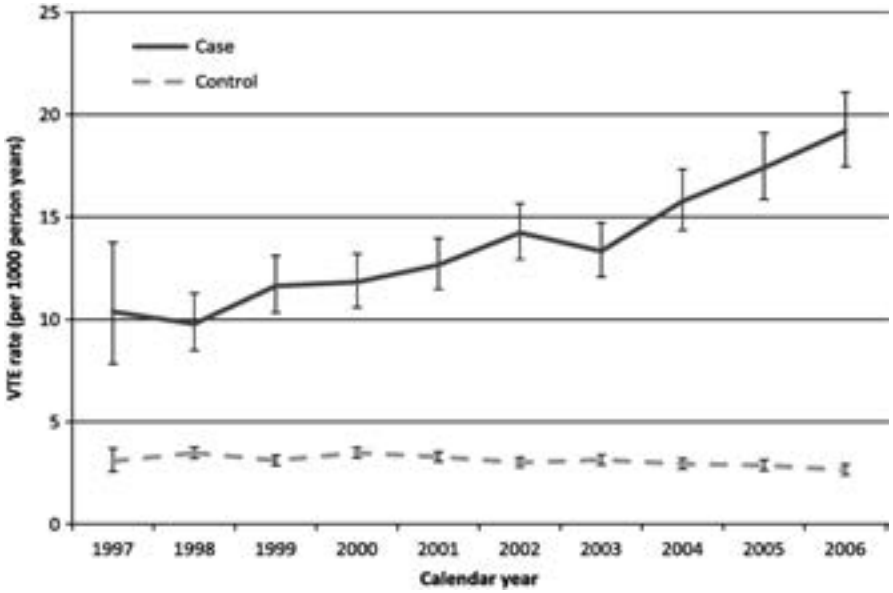
2006-2015
Deaths: -1.5%/y
Cancer-related death : -26%
(2 3787600 prevented events)

FIGURE 2. Trends in Cancer Incidence (1975 to 2014) and Death Rates (1975 to 2015) by Sex, United States.
Rates are age adjusted to the 2000 US standard population. Incidence rates also are adjusted for delays in reporting.

Siegel R,CA Cancer J Clin 2018

Patients with CAT, alive after 6 months

A frequent situation → ***Treatment options***



-STOP or not to stop?

-How long to treat?

-Which drug ? VKA, LMWH, DOACs

-Which dosage?

Walker AJ, Eur J Cancer 2013
Timp, Blood 2013

Patient with CAT : treatment duration?

ACCP 2016

11. In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), **or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B).

Kearon, Chest 2016

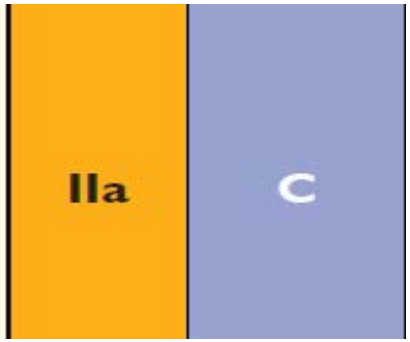
ISTH update2016

After 3–6 months, termination or continuation of anticoagulation (LMWH, VKA, or direct oral anticoagulants) should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance, in the absence of data).

Farge, Lancet Hematol 2016

ESC 2014

For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.



Konstantidines, Eur H J 2014

Active cancer: *a time-related risk of VTE rec and MB*

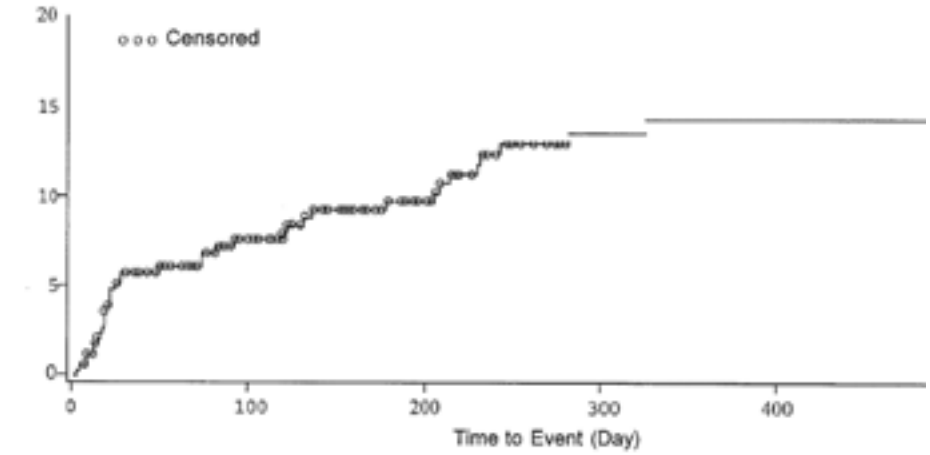
- Active cancer and newly diagnosed VTE (49,1% DVT, 38,9% PE, 12% both)
- Dalteparin 200 IU/kg daily SC for 1 month, followed by 150 IU/kg daily for the subsequent 11 months
- 334 patients: 55.4% 6 months; 33% 12 months
- 92% of the patients had solid tumors: lung (16.8%), breast (9.3%), or pancreas (9.3%)

PRIMARY AIM : safety of dalteparin between 6-12 months in CAT

5.7% M1, 3.4% pt-month M2-6, 4.1% pt-month M7-12

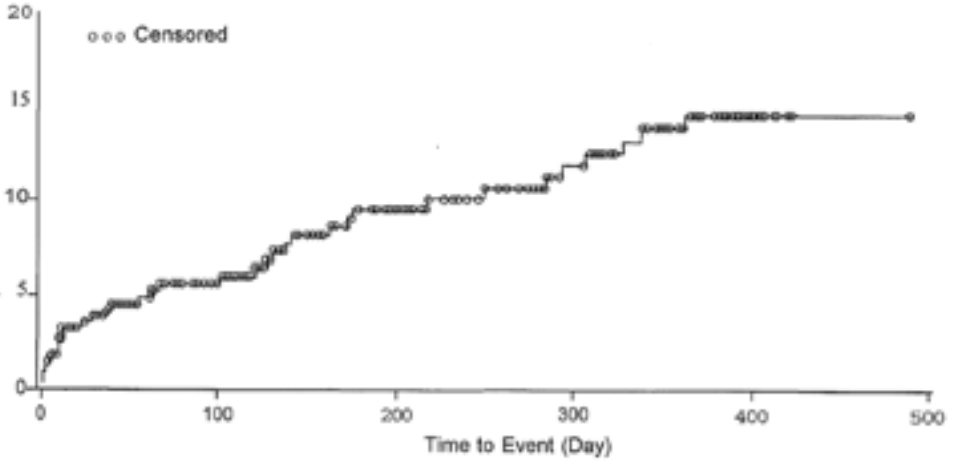
3.6% M1, 1.1% pt-month M2-6, 0.7% pt-month M7-12

Figure 2. Time to Recurrent VTE 11.1%



Time to venous thromboembolism. The Kaplan-Meier estimate of the time to first occurrence of new VTE is shown. Open circles represent censored points and the numbers of patients a risk are indicated.

Figure 1. First Occurrence of Major Bleeding 10.2%



Time to major bleeding. The Kaplan-Meier estimate of the time to the first occurrence of major bleeding is shown. Open circles represent censored points and the numbers of patients at risk are indicated.

116 deaths (4 recurrent VTE, 2 MB)

Kakkar, ISTH 2013
Francis, JTH 2015

CAT treatment beyond 6 months :
Heterogeneity, individual benefit to risk ratio

- **The question is not** : which treatment?
- **The question is** : which treatment for which patient?

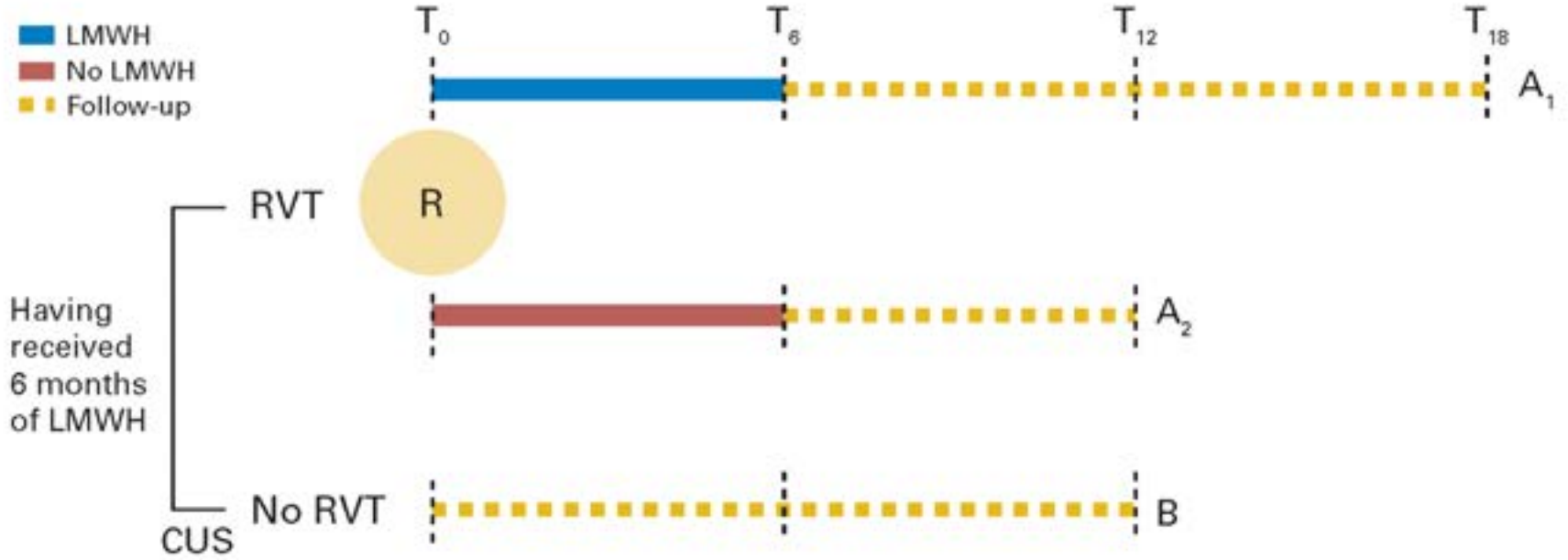
- **No clinical trial available**
- **Hypothesis : identify factors predictive for the risk of recurrence and bleeding**
- **Perspective : decide the treatment according to the risk of recurrence and the risk of bleeding**

Cancer associated thrombosis beyond 6 months:

Criteria to take into account to predict the risk of recurrence :

- **Residual thrombus**
- **Cancer activity**
- **Site of cancer**

Residual thrombus : *DACUS Study*



	6 months				12 months				18 months			
	VTE	BI		F	VTE	BI		F	VTE	BI		F
Group		Major	Minor			Major	Minor			Major	Minor	
A1	4	4	2	108	10	2	4	91	8	1	3	78
A2	18	1	4	94	9	1	4	77				
B	2	1	3	97	1	1	2	91				

Napolitano M, J Clin Oncol 2014

Active cancer : *Definition*

CAT is considered as a VTE provoked by a persistent risk factor

Active cancer

Cancer is considered active if any of the following apply:

(1) has not received potentially curative treatment; or

(2) there is evidence that treatment has not been curative (e.g. recurrent or progressive disease)‡; or

(3) treatment is ongoing.

Kearon C, JTH 2016

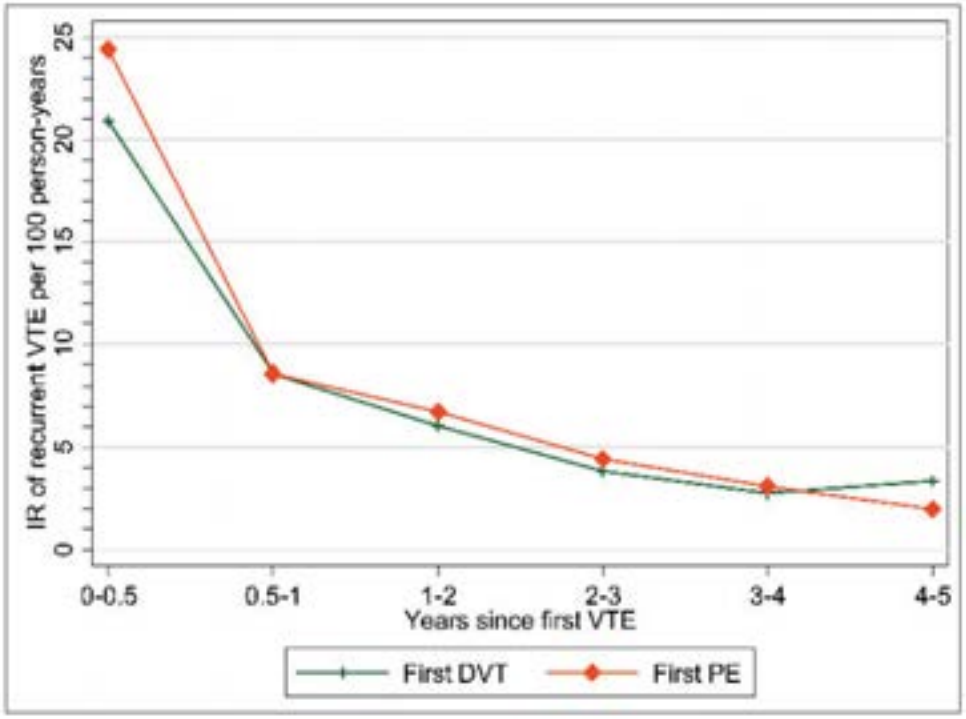
Active cancer and risk of recurrence

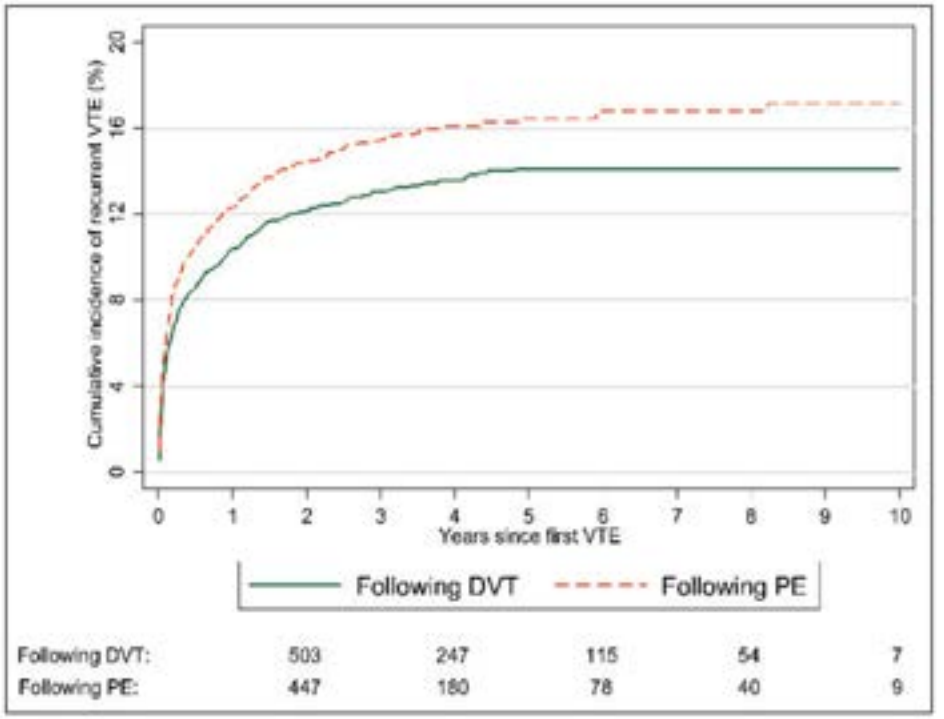
Source population: all patients in the UK Clinical Practice Research Datalink between 2001 and 2011

Active cancer associated VTE: cancer-related clinical DG or therapy within the 90 days before or after a VTE

Selected types of common cancers,[a] n (%)			
Prostate cancer in males	278 (19.1)	287 (16.1)	565 (17.5)
Breast cancer in females	225 (14.0)	281 (16.0)	506 (15.1)
Lung cancer	315 (10.3)	603 (17.0)	918 (13.9)
Colon cancer	384 (12.6)	443 (12.5)	827 (12.5)

6,592 patients with VTE in association with active cancer.

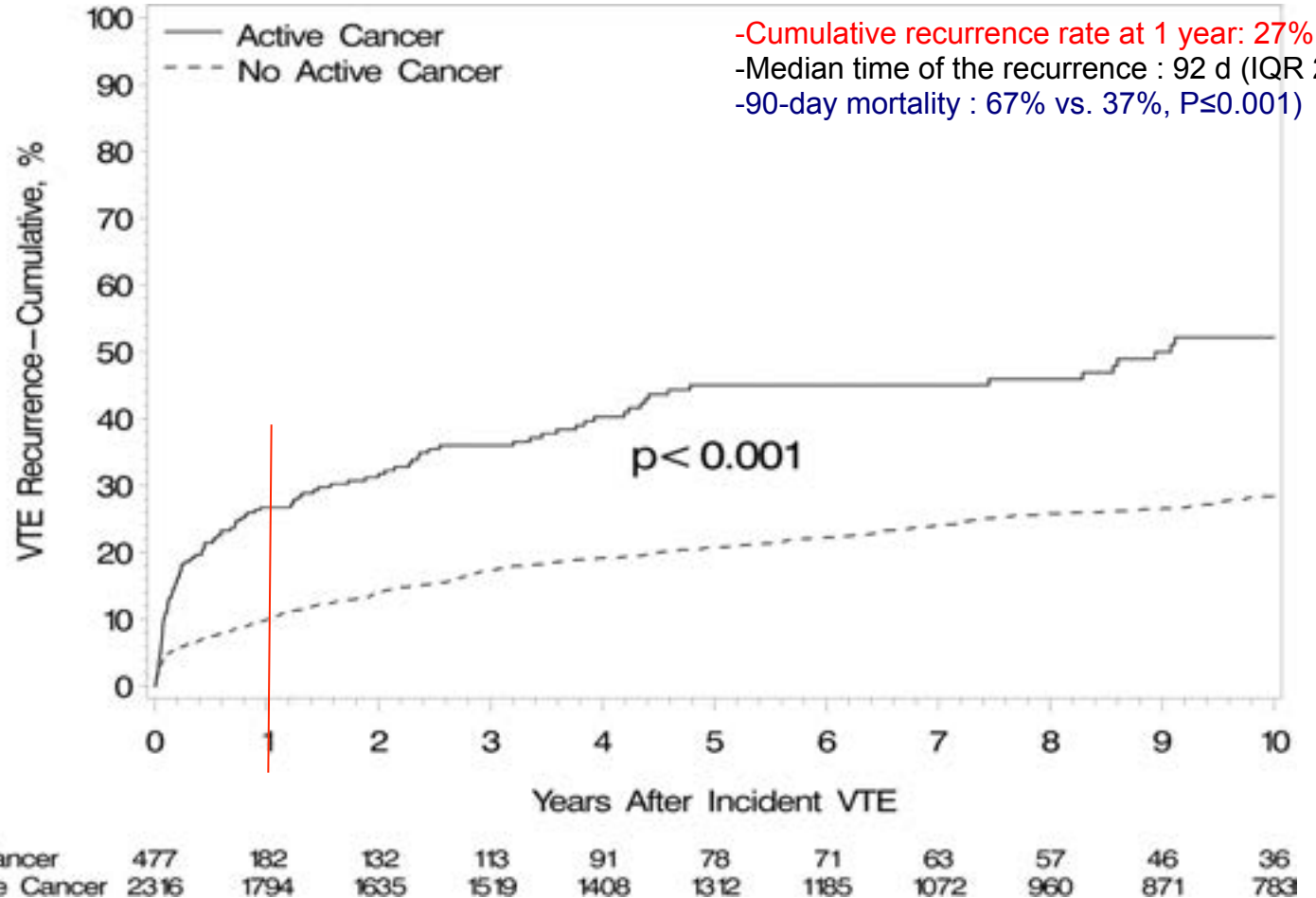




Cohen A, Thromb Haemost 2016

Active cancer : *a higher risk of VTE recurrence*

Population-based cohort study, Olmsted Count, Minnesota, 3385 patients with active cancer-related incident VTE from 1966-2000 who survived 1 day or longer, VTE recurrence, bleeding on ACG therapy, survival, Active cancer in the 3 months before or after the VTE event



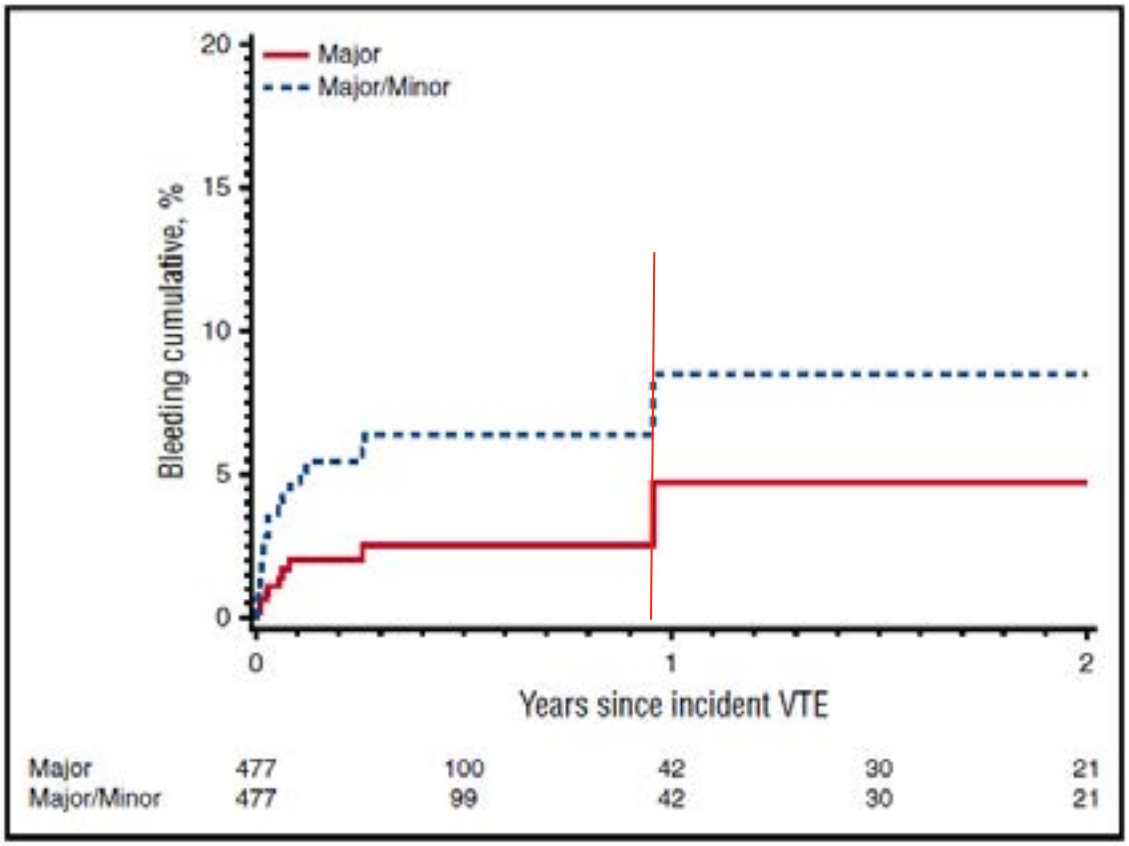
-Cumulative recurrence rate at 1 year: 27% vs.10%; P<0.001
-Median time of the recurrence : 92 d (IQR 26-751)
-90-day mortality : 67% vs. 37%, P≤0.001)

Chee CE, Blood 2014

Predictors of venous thromboembolism recurrence and bleeding among active cancer patients

Population-based cohort study, Olmsted Count, Minnesota, 3385 patients with active cancer-related incident VTE from 1966-2000 who survived 1 day or longer, VTE recurrence, bleeding on ACG therapy, survival, Predictors Cox proportional hazards modelling, Active cancer in the 3 months before or after the VTE event,

Cumulative incidence of major bleeding at 1 year: 4,7%
Cumulative incidence of total bleeding at 1 year: 8,5%
50% of bleedings occurred within the first 7 days of treatment



Chee CE, Blood 2014

Independent predictors of VTE recurrence among patients with active cancer

Characteristic	HR	95% CI	*P* value
Stage IV pancreatic cancer*	6.38	2.69, 15.13	<.0001
Brain cancer*	4.57	2.07, 10.09	.0002
Myeloproliferative or myelodysplastic disorder*	3.49	1.59, 7.68	.002
Ovarian cancer*	3.22	1.57, 6.59	.001
Stage IV cancer (non pancreas)*	2.85	1.74, 4.67	<.0001
Lung cancer*	2.73	1.63, 4.55	.0001
Neurological disease with leg paresis	2.38	1.14, 4.97	.02
Cancer stage progression	2.14	1.30, 3.52	.003
Multiple active cancers	1.78	0.87, 3.63	.12
Gastrointestinal (noncolorectal) cancer*	1.94	0.90, 4.17	.09
Stage III cancer, ALL or AML*	1.47	0.95, 2.27	.09
Warfarin therapy	0.43	0.28, 0.66	<.0001

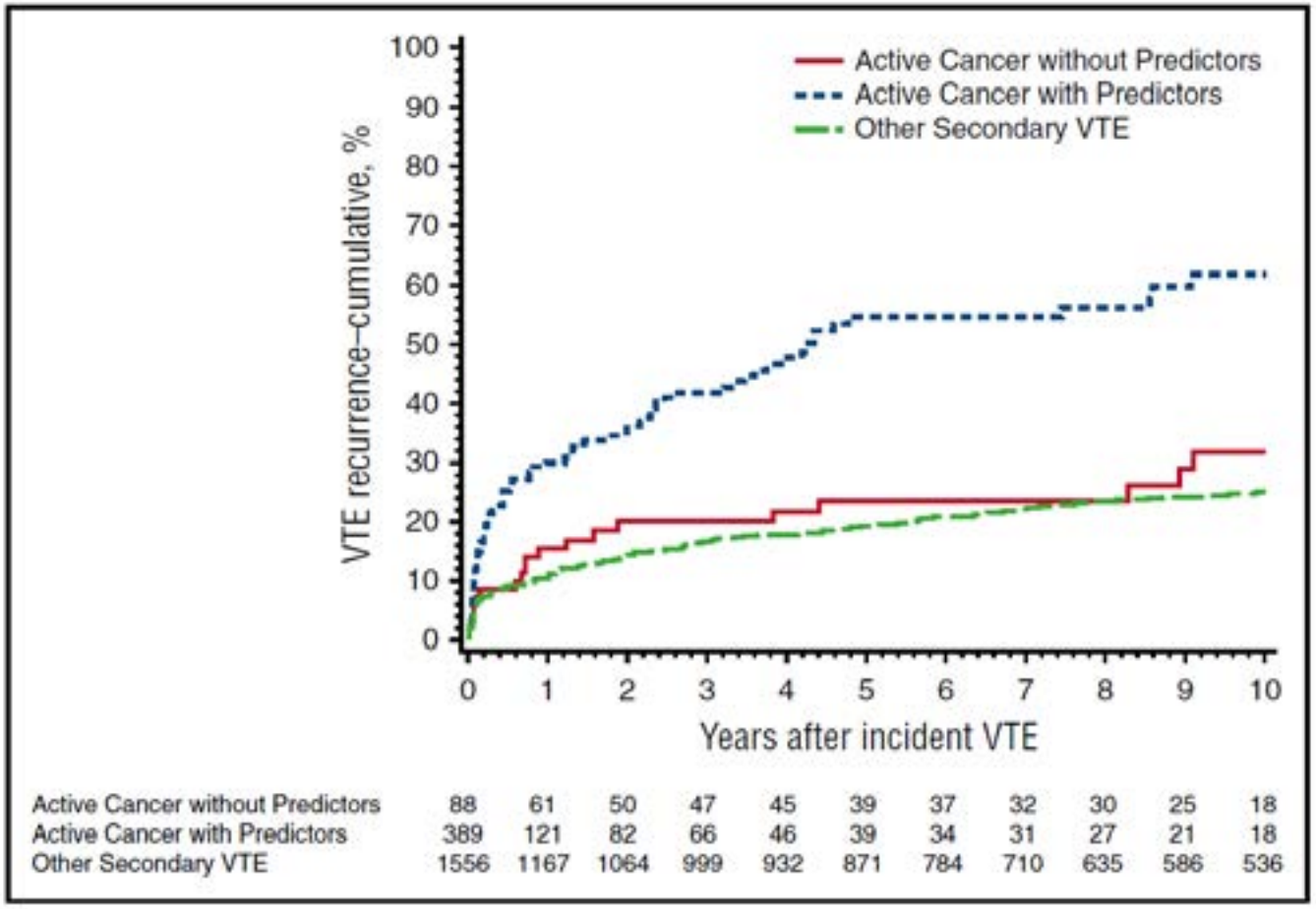
38%: tt failure at the time of recurrence

Recurrent VTE increased the HR of death: adjusted HR 2,7

Chee CE, Blood 2014

Cumulative incidence of first VTE recurrence among residents with cancer-associated VTE and 1 or more predictor of VTE recurrence

Patients with 1 or more predictors of recurrence:



blood

Chee CE, Blood 2014

Active cancer : *anticoagulant interruption?*

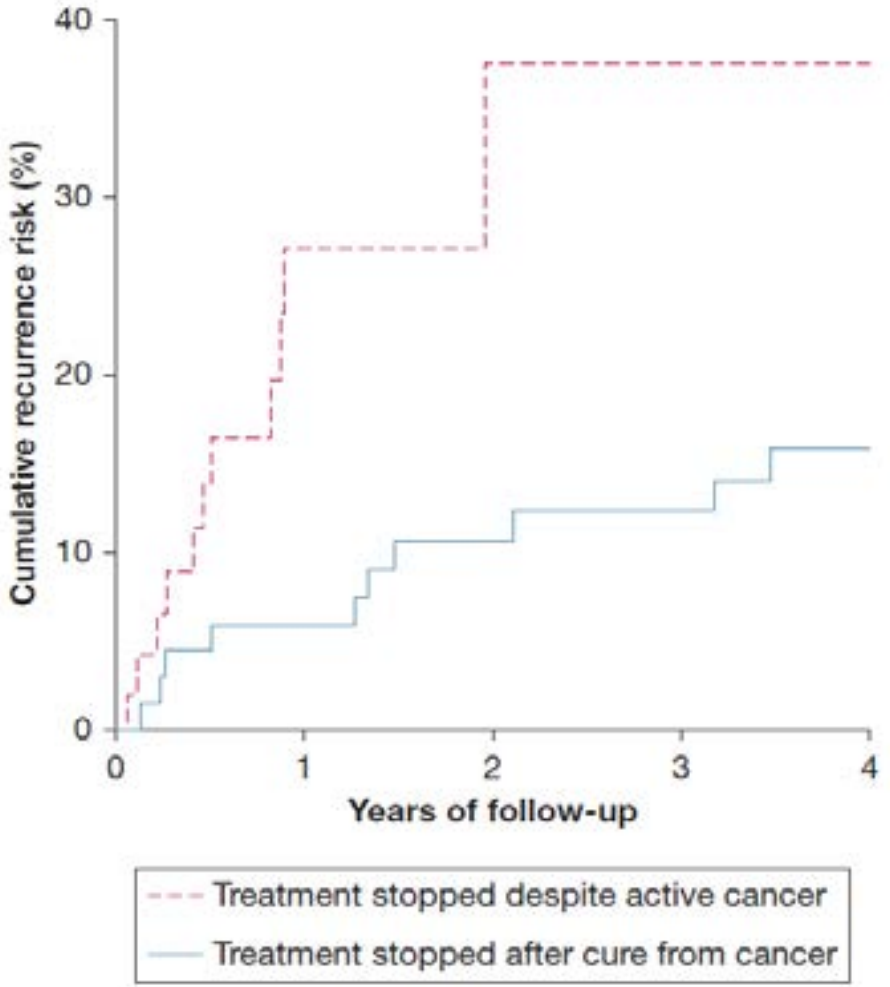
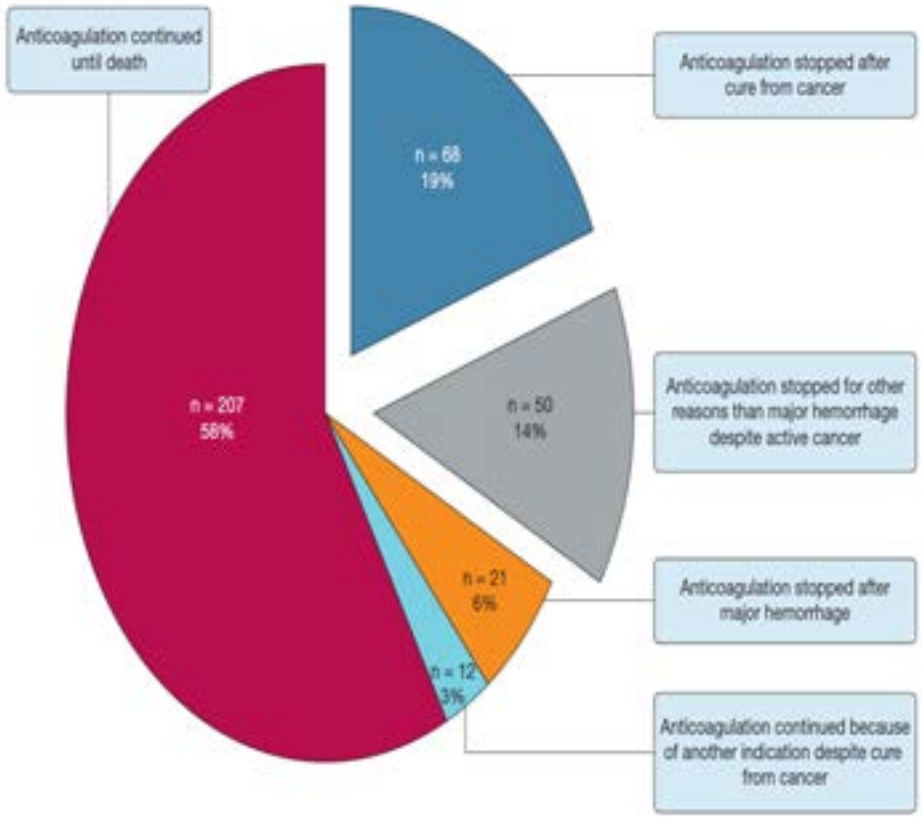


Figure 2 – *Shown is the cumulative incidence rate of recurrent VTE in patients who stopped anticoagulation therapy after being cured of cancer (solid line) and after stopping anticoagulation for reasons other than major hemorrhage despite active cancer (dotted line).*



Van der Hulle, Chest 2016

Cancer associated thrombosis
Extended treatment (beyond 6 months):

Site of cancer : impact
-on the risk of recurrence and
-on the risk of bleeding

The Clinical Course of Venous Thromboembolism May Differ According to Cancer Site

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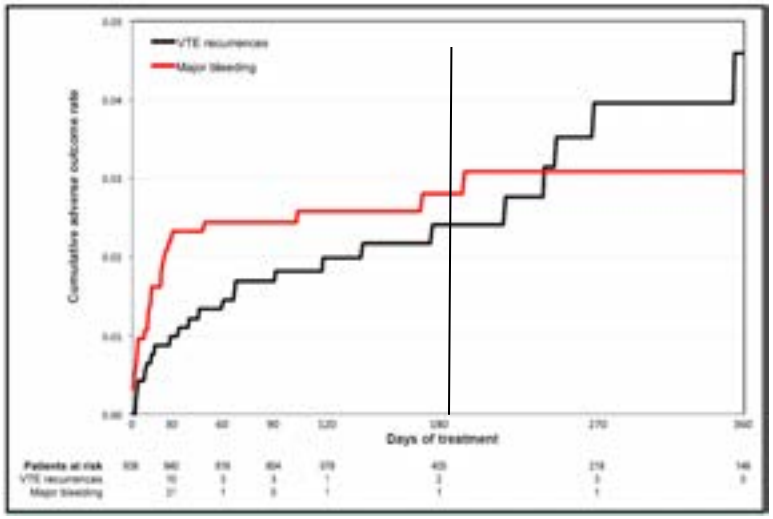
Isabelle Mahé, MD, PhD,[a] Jean Chidiac, MD,[a] Laurent Bertoletti, MD, PhD,[b] Carme Font, MD, PhD,[c] Javier Trujillo-Santos, MD, PhD,[d] Marisa Peris, MD,[e] Cristina Pérez Ductor, MD,[f] Santiago Nieto, MD,[g] Elvira Grandone, MD, PhD,[h] Manuel Monreal, MD, PhD,[i] the RIETE investigators

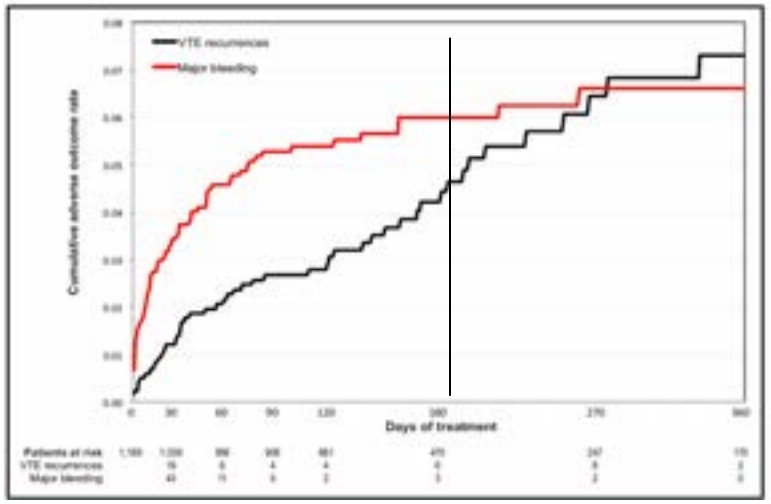
Mahé I, Am J Med 2017



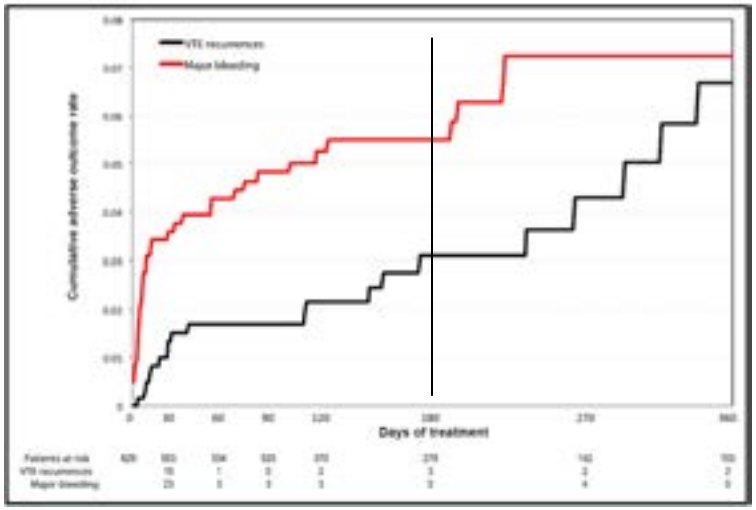
BREAST CANCER N=938

International RIETE Registry

-3947 patients with CAT,
-55% at metastatic stage
-On anticoagulant treatment



COLORECTAL CANCER N=1189



PROSTATE CANCER N=629

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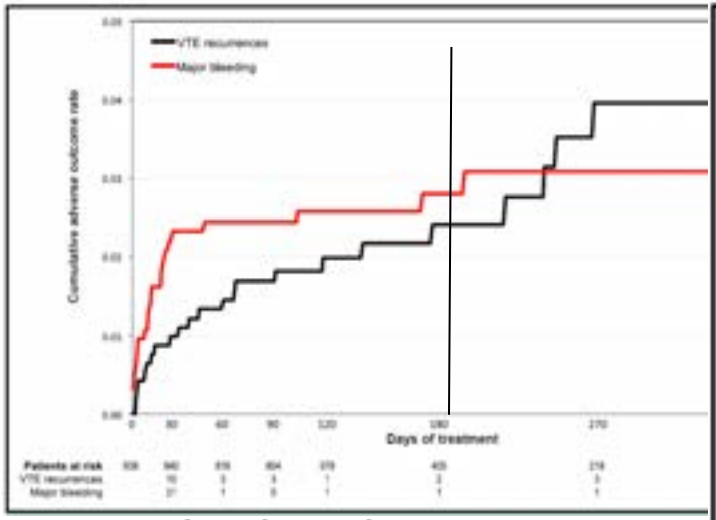
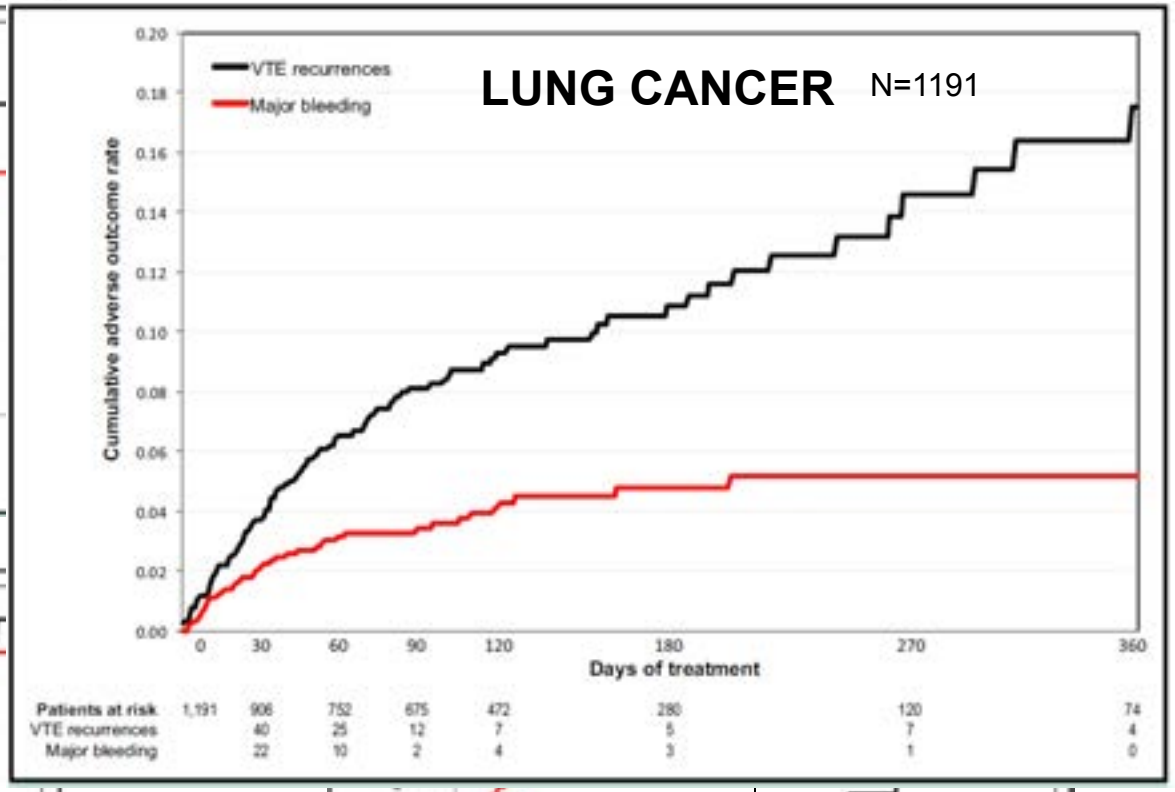
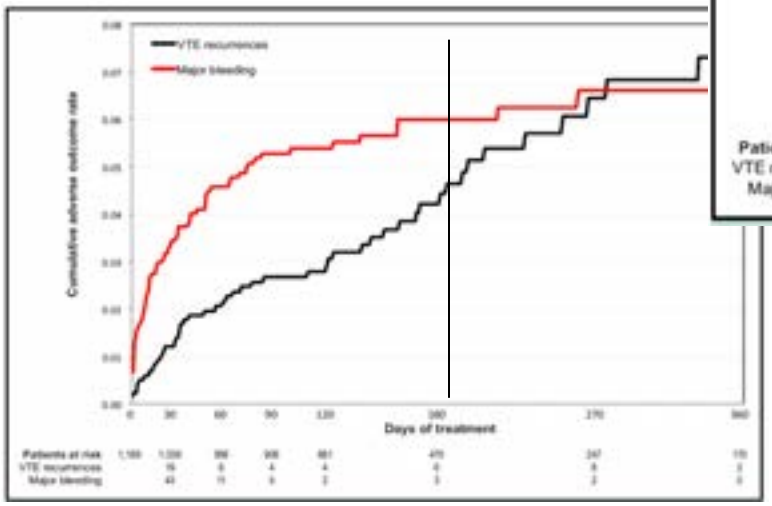
Mahé I, Am J Med 2017



BREAST CANCER N=938





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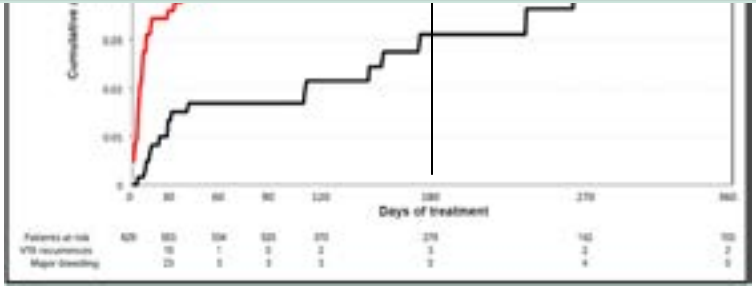

PROSTATE CANCER N=629

Cancer associated thrombosis
Extended treatment (beyond 6 months):

-No clinical trial
-A significant of VTE recurrence and bleeding

Interest of scores to predict the risk of VTE recurrence and the risk of bleeding?

Risk factors for predicting the risk of VTE recurrence

Study	Clinical Factor or Biomarker	Estimated Risk (95% CI)
Prandoni 2002[4]	Extensive cancer	HR 4.6 (2.3 – 9.0)*
	Lung cancer	HR 6.9 (3.0 – 15.9)*
	Gastrointestinal cancer†	HR 5.1 (2.3 – 11.3)*
	Genitourinary cancer‡	HR 3.7 (1.7 – 8.0)*
Trujillo-Santos 2008[5]	Age < 65	OR 3.0 (1.9 – 4.9) for rPE OR 1.6 (1.0 – 2.4) for rDVT
	Diagnosis less than 3 months earlier	OR 2.0 (1.2 – 3.2) for rPE OR 2.4 (1.5 – 3.6) for rDVT
	Clinically overt PE	1.9 (1.2 – 3.1)
Louzada 2011[23]	Metastatic cancer	RR 1.36 (1.06 – 1.74)
Chee 2014[10]	Stage IV pancreatic cancer	HR 6.38 (2.69 – 15.13)
	Brain cancer	HR 4.57 (2.07 – 10.09)
	MPN or MDS	HR 3.49 (1.59 – 7.68)
	Ovarian cancer	HR 3.22 (1.57 – 6.59)
	Stage IV (non-pancreas) cancer	HR 2.85 (1.74 – 4.67)
	Lung cancer	HR 2.73 (1.63 – 4.55)
	Neurological disease with leg paresis	HR 2.38 (1.14 – 4.97)
	Cancer stage progression	HR 2.14 (1.30 – 3.52)
Mahe 2017[11]	Lung cancer	HR 3.8 (2.6 – 5.6)[§]
Khorana 2017[26]	Hepatobiliary cancer	sHR 5.5 (2.3 – 13.6)
	Venous compression	sHR 3.1 (1.4 – 6.5)
	Tissue factor antigen	sHR 3.3 (1.7 – 6.4)
	C-reactive protein	sHR 1.9 (1.0 – 3.8)

*as compared with patients without cancer.
†colorectal, stomach or esophagus, pancreas, liver or gallbladder.
‡uterus, kidney, ovary or testicle, bladder, prostate.
§as compared with patients with breast cancer.

Lee A, Blood 2017

Risk factors for predicting the risk of MB

Study	Clinical Factor or Biomarker	Estimated Risk
Prandoni 2002[4]	Genitourinary cancer*	HR 4.5 (2.1 – 9.9)†
	Extensive cancer	HR 4.8 (2.3 – 10.1)†
Trujillo-Santos 2008[5]	Metastatic cancer	OR 1.6 (1.1 – 2.3)
	Immobility ≥ 4 days	OR 1.8 (1.2 – 2.7)
	Creatinine clearance < 30 mL/min	OR 2.2 (1.5 – 3.4)
	Recent major bleeding	OR 2.4 (1.1 – 5.1)
Kamphuisen 2015[15]	Metastatic cancer	RR 1.6 (1.1 – 2.3)
	Intracranial lesion	RR 1.6 (1.1 – 3.5)
	Age > 75 years	RR 2.8 (1.2 – 2.7)
Mahe 2017[11‡]	Lung cancer	HR 1.8 (1.1 – 3.0)‡
	Colorectal cancer	HR 2.1 (1.3 – 3.4)‡
	Prostate cancer	HR 2.1 (1.3 – 3.5)‡
	Cancer diagnosis within past 3 months	HR 1.6 (1.1 – 2.3)
	Platelet count less than 100×10^9/L	HR 2.0 (1.4 – 3.0)
	Recent major bleeding	HR 5.0 (3.1 – 7.9)

*uterus, kidney, ovary or testicle, bladder, prostate.

†as compared with patients without cancer.

‡study included only patients with breast, prostate, colorectal or lung cancer. Risk is relative to patients with breast cancer.

Lee A, Blood 2017

Conclusion: *what we have to do*

- In patients with active cancer
  - Criteria for choosing the regimen have to be tested prospectively
  - Patients profile have to be proposed using risk factors for VTE recurrence and for bleeding
    - Related to the site of cancer
    - Related to the VTE disease
    - Related to the patient
  - Anticoagulant strategies have to be individualized

APIxaban Cancer Associated Thrombosis
French ISR – Multicenter- Double blind Trial – Long Term VTE TT

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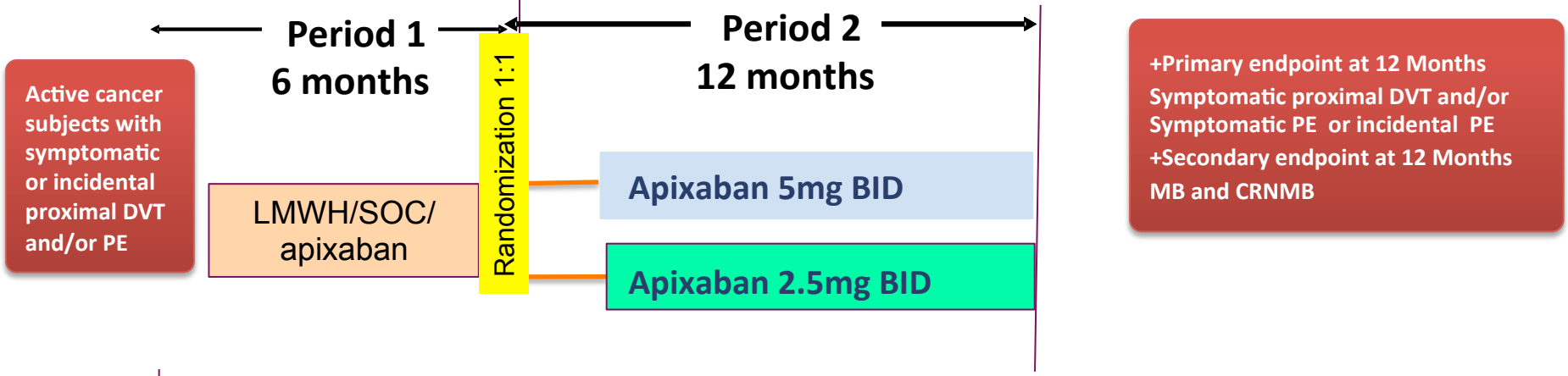


Target Population	Active cancer subjects with symptomatic or incidental proximal DVT and/or PE already treated by a LMWH/SOC/apixaban
# Patients/# Arms	750/Arm
Dosing	Apixaban 5mg BID vs Apixaban 2;5 mg BID
Study drug/Comparator	Apixaban
Treatment duration	12 months
Primary/secondary endpoints	Adjudicated Symptomatic proximal DVT and/or Symptomatic PE or incidental PE Adjudicated bleeding (major or clinically relevant non-major)
Statistic	-efficacy : non-inferiority with an estimated incidence of VTE recurrences of 4% in the control group and an estimated relative risk of 1 and a non-inferiority margin of 1.75 and then -safety : superiority with an estimated incidence of MB+CRNMB of 6% in the control group and an estimated risk reduction of 50% in the 2.5mg bid as compared with the 5mg bid (alpha 5%, beta 20%)
Study regions	Europe

Active cancer: *a time-related risk of VTE rec and MB*

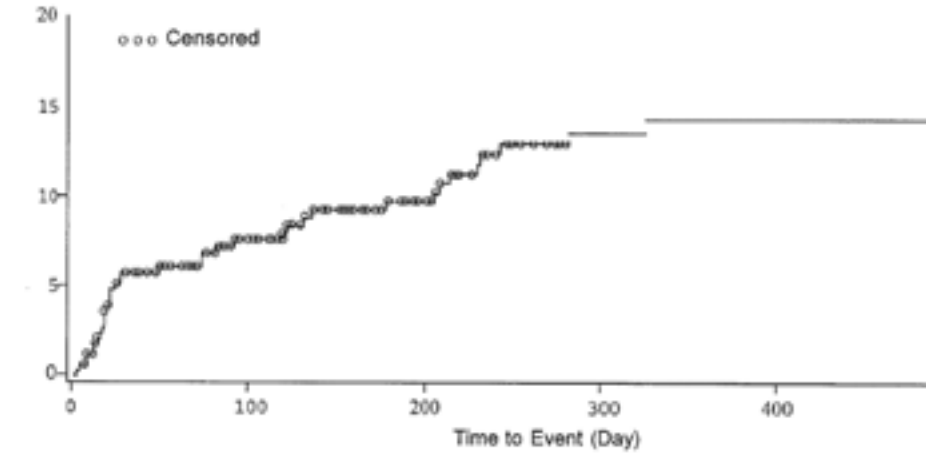
- Active cancer and newly diagnosed VTE (49,1% DVT, 38,9% PE, 12% both)
- Dalteparin 200 IU/kg daily SC for 1 month, followed by 150 IU/kg daily for the subsequent 11 months
- 334 patients: 55.4% 6 months; 33% 12 months
- 92% of the patients had solid tumors: lung (16.8%), breast (9.3%), or pancreas (9.3%)

PRIMARY AIM : safety of dalteparin between 6-12 months in CAT

5.7% M1, 3.4% pt-month M2-6, 4.1% pt-month M7-12

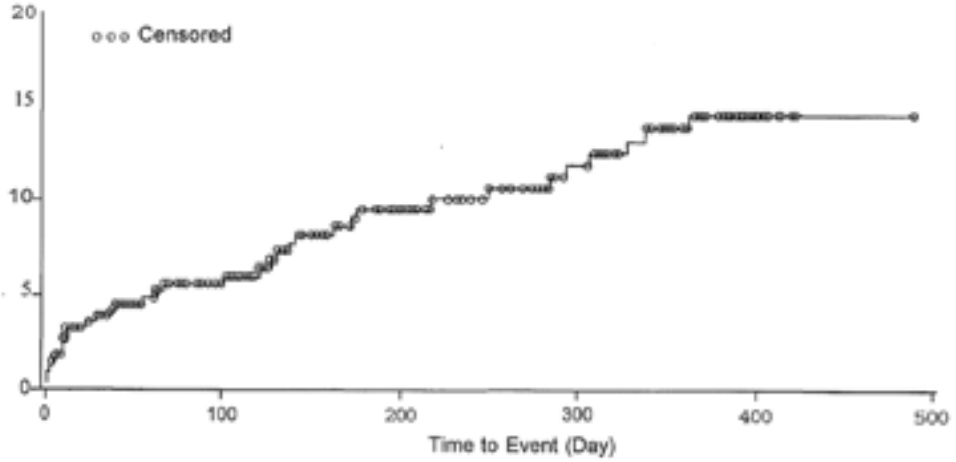
3.6% M1, 1.1% pt-month M2-6, 0.7% pt-month M7-12

Figure 2. Time to Recurrent VTE 11.1%



Time to venous thromboembolism. The Kaplan-Meier estimate of the time to first occurrence of new VTE is shown. Open circles represent censored points and the numbers of patients a risk are indicated.

Figure 1. First Occurrence of Major Bleeding 10.2%



Time to major bleeding. The Kaplan-Meier estimate of the time to the first occurrence of major bleeding is shown. Open circles represent censored points and the numbers of patients at risk are indicated.

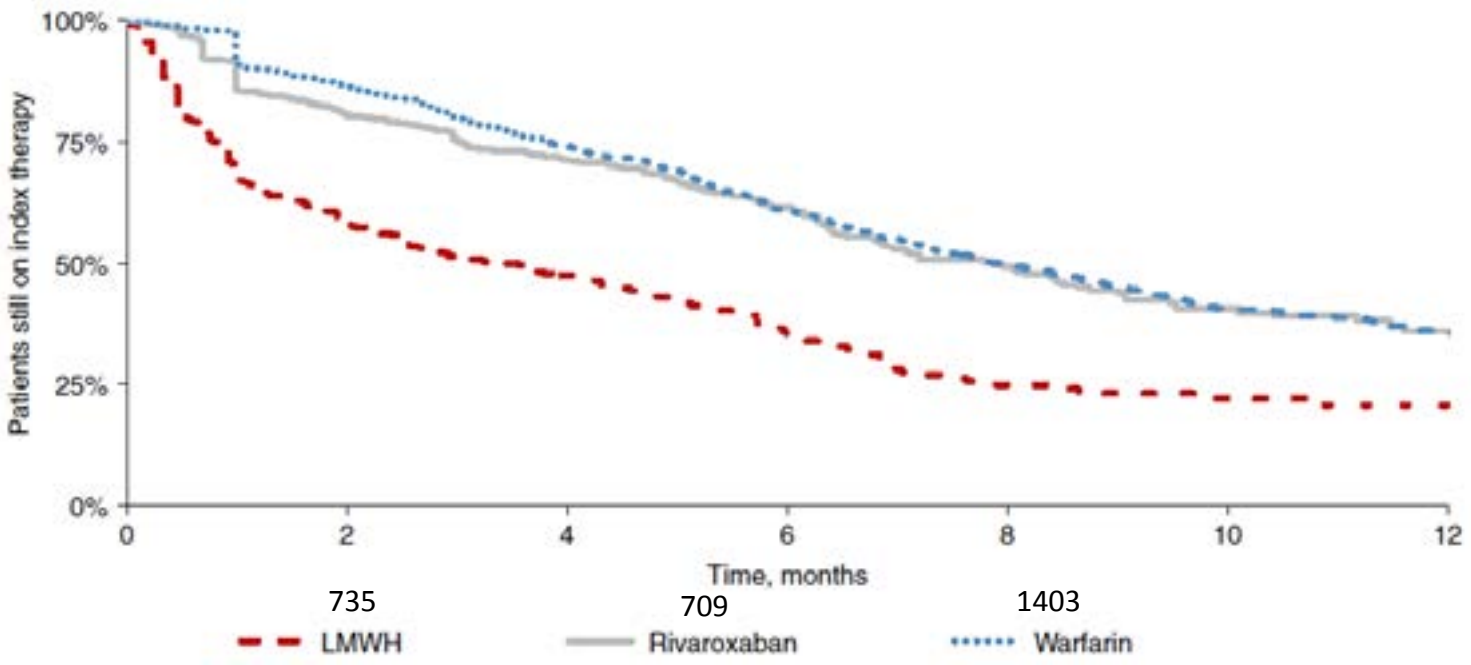
116 deaths (4 recurrent VTE, 2 MB)

Kakkar, ISTH 2013
Francis, JTH 2015

Current treatment patterns

Khorana A, TPTH 2017

Medical and pharmacy data base (2007-2014)



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

*Discontinuation was defined has a gap of 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.

Synthesis : *what we know*

- In patients with cured cancer
  - Anticoagulant therapy interruption can be considered
- In patients with active cancer
  - Anticoagulant therapy should be continued
  - Type of drug and dosage remain to be determined
  - Extended treatment using LMWH seems not a reasonable option
  - Place of DOACS to be addressed