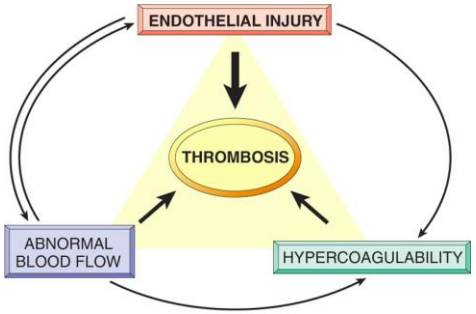
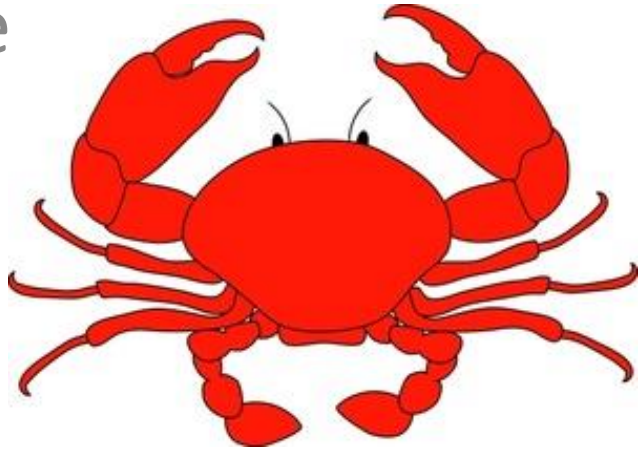
Journée scientifique en oncologie
TEV & Cancer

Sophie Savary Bélanger
Hémato-oncologue



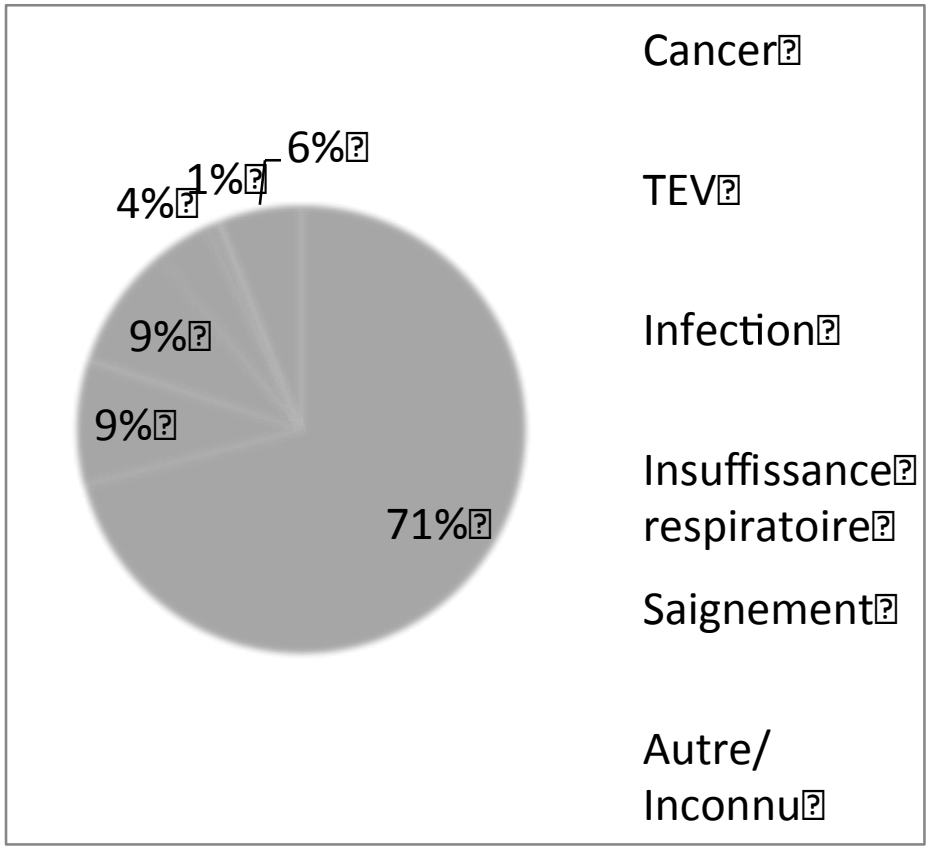



ISTH
2017
CONGRESS
JULY 8-13
BERLIN GERMANY
WWW.ISTH2017.ORG
TRANSCENDING SCIENTIFIC BOUNDARIES

Quelques statistiques

Très commun

Très mortel



Streiff. Thrombosis in the setting of cancer. ASH Ed Book 2016. 198-205.
Adapté de Khorana. Thrombosis Research. 2010;125(6): 490-3.

ISth™

International Society on Thrombosis and Haemostasis

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American Society of Clinical Oncology

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National Comprehensive Cancer Network®

Curr Oncol, Vol. 22, pp. 144-155; doi: http://dx.doi.org/10.3747/co.22.2587

PRACTICE GUIDELINE

Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment

J.C. Easaw MD PhD, M.A. Shea–Budgell MSc,* C.M.J. Wu MD,* P.M. Czaykowski MD,† J. Kassis MD,‡ B. Kuehl PhD,§ H.J. Lim MD PhD,‖*

ESMO

GOOD SCIENCE

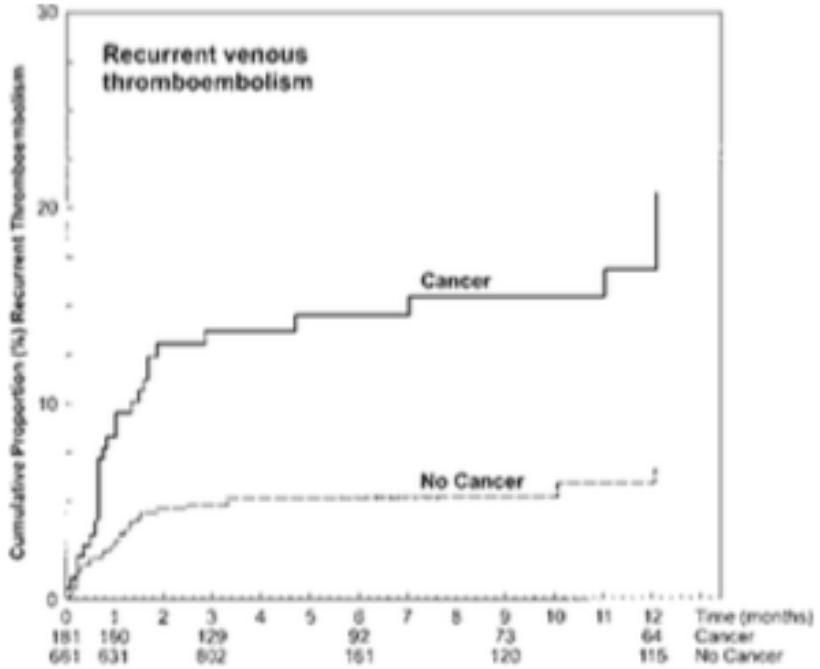
BETTER MEDICINE

BEST PRACTICE

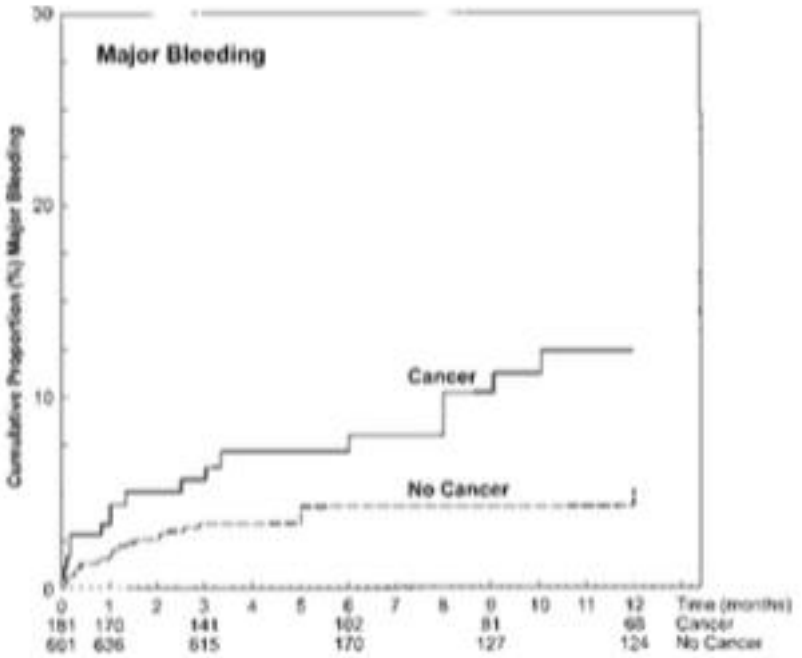
European Society for Medical Oncology

Pas facile…

Incidence cumulative TEV sous traitement



Incidence cumulative saignement cliniquement significatif sous traitement



Prandoni et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis . Blood. 2002; 100:3484-3488

ALL ANIMALS
CANCERS
ARE EQUAL
BUT SOME ANIMALS
CANCERS
ARE
MORE EQUAL
THAN OTHERS

Khorana score

Table I. Predictive model for chemotherapy-associated venous thromboembolism.

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Pre-chemotherapeutic platelet count ≥350 × 10^9/l	1
Haemoglobin concentration <100 g/l or use of erythropoiesis-stimulating agents	1
Pre-chemotherapeutic leucocyte count >11 × 10^9/l	1
Body mass index ≥ 35 kg/m^2	1

		Thrombosis rate per 2·5 months (%)
Low score	0	0·3–0·8
Intermediate score	1–2	1·8–2
High score	>2	6·7–7·1

This table has been modified from research originally published in *Blood*. Khorana, A.A., Kuderer, N.M., Culakova, E., Lyman, G.H. & Francis, C.W. (2008) Development and validation of a predictive model for chemotherapy associated thrombosis. *Blood*, **111**, 4902–4907. © the American Society of Hematology.

Prévention primaire
Études principales

FAMOUS	Mixed, III-IV	Dalteparin 5000 IU o.d.	374	1 year	• Placebo arm :3.3 % • LMWH arm : 2.4 %	(56)
SAVE-ONCO	Mixed, III-IV	Semuolparin 20 mg o.d.	3212	3.5 months	• Placebo arm :3.4 % • LMWH arm : 1.2 % • RR,0.36; 95 %CI, 0.21–0.60	(57)
PROTECHT	Mixed, III-IV	Nadroparin 3800 IU o.d.	1150	4 months	• Placebo arm : 3.9 % • LMWH arm : 2 % • P=0.02	(58)
FRAGEM-UK	APC	Dalteparin 200IU/kg o.d. for 4 weeks followed by 150 IU/kg o.d. for 8 weeks	123	3 months	• Placebo arm :28 % • LMWH arm : 12 % • RR,0.419; 95 %CI, 0.187–0.935	(59)
CONKO-04	APC	Enoxaparin 1 mg/Kg o.d.	312	3 months	• Placebo arm :15.1 % • LMWH arm : 6.4 % • HR,0.40; 95 %CI, 0.19–0.83; p=0.01	(60)
TOPIC-1	Breast	Certoparin 3000 IU o.d.	351	6 months	• Placebo arm :4 % • LMWH arm : 4 % • OR,1.02; 95 %CI, 0.30–3.48	(61)
TOPIC-2	NSCLC, III-IV	Certoparin 3000 IU o.d.	532	6 months	• Placebo arm :8.3 % • LMWH arm : 4.5 % • OR,0.52; 95 %CI, 0.23–1.12;	(61)
FRAGMATIC	Lung cancer, any stage and histology	Dalteparin 5000 IU o.d.	2202	24 weeks	• Placebo arm :9.7 % • LMWH arm : 5.5 % • HR,0.57; 95 %CI, 0.42–0.79; p=0.001	(62)

Frere et al. Clinical practice guidelines for prophylaxis of venous thromboembolism in cancer patients. Thromb Haemost, 2016;116:618-25.

Prévention primaire
Études principales

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Tous

2%

Pancréas

10-15%

Poumon

4%

Frere et al. Clinical practice guidelines for prophylaxis of venous thromboembolism in cancer patients. Thromb Haemost, 2016;116:618-25.

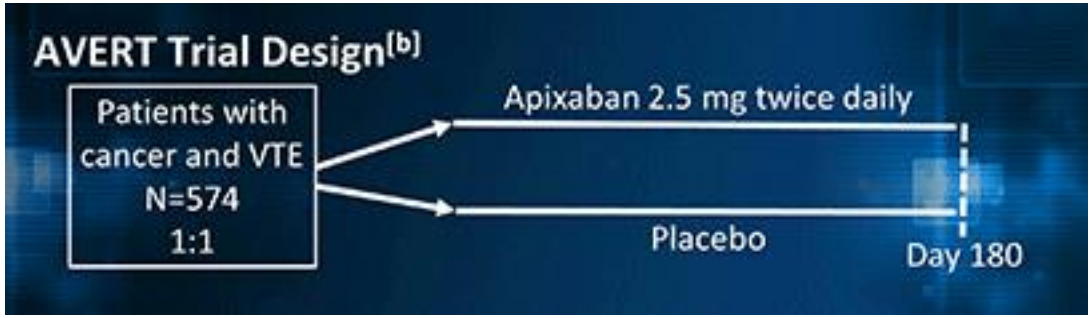
Prévention primaire

Hospitalisé

- Tous*

Ambulatoire

- Myélome multiple sous IMID+stéroides/chimio



clinicaltrials.gov/ct2/show/NCT02048865

Avant de commencer…

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2015 VOL. 373 NO. 8

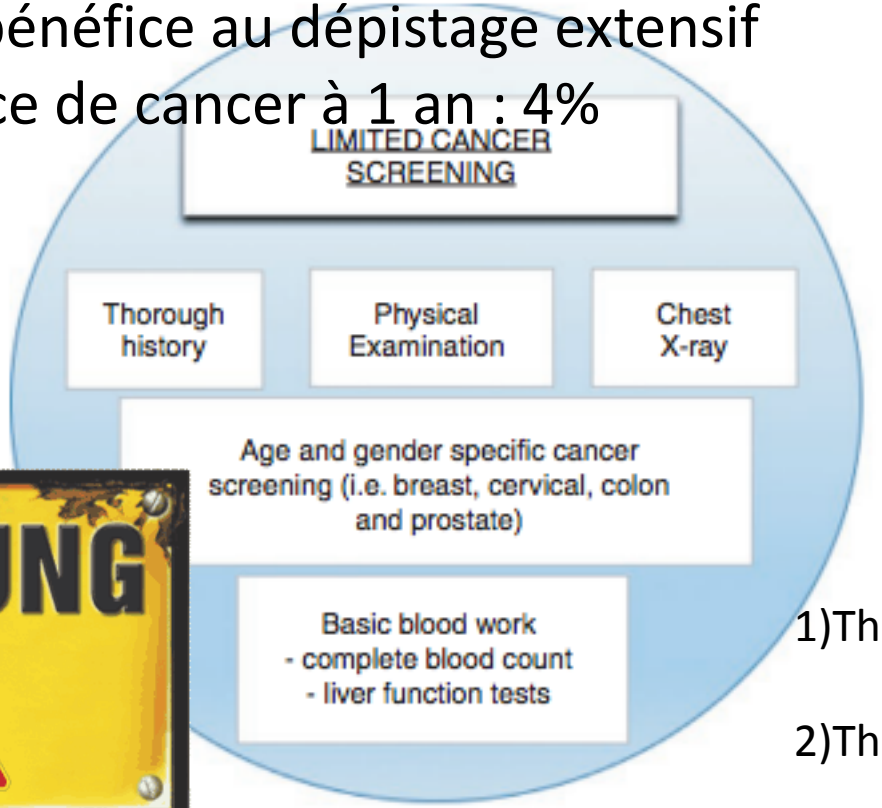
Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D., Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D., Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D., Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D., and Marc A. Rodger, M.D., for the SOME Investigators*

Conclusions

-Pas de bénéfice au dépistage extensif

-Incidence de cancer à 1 an : 4%

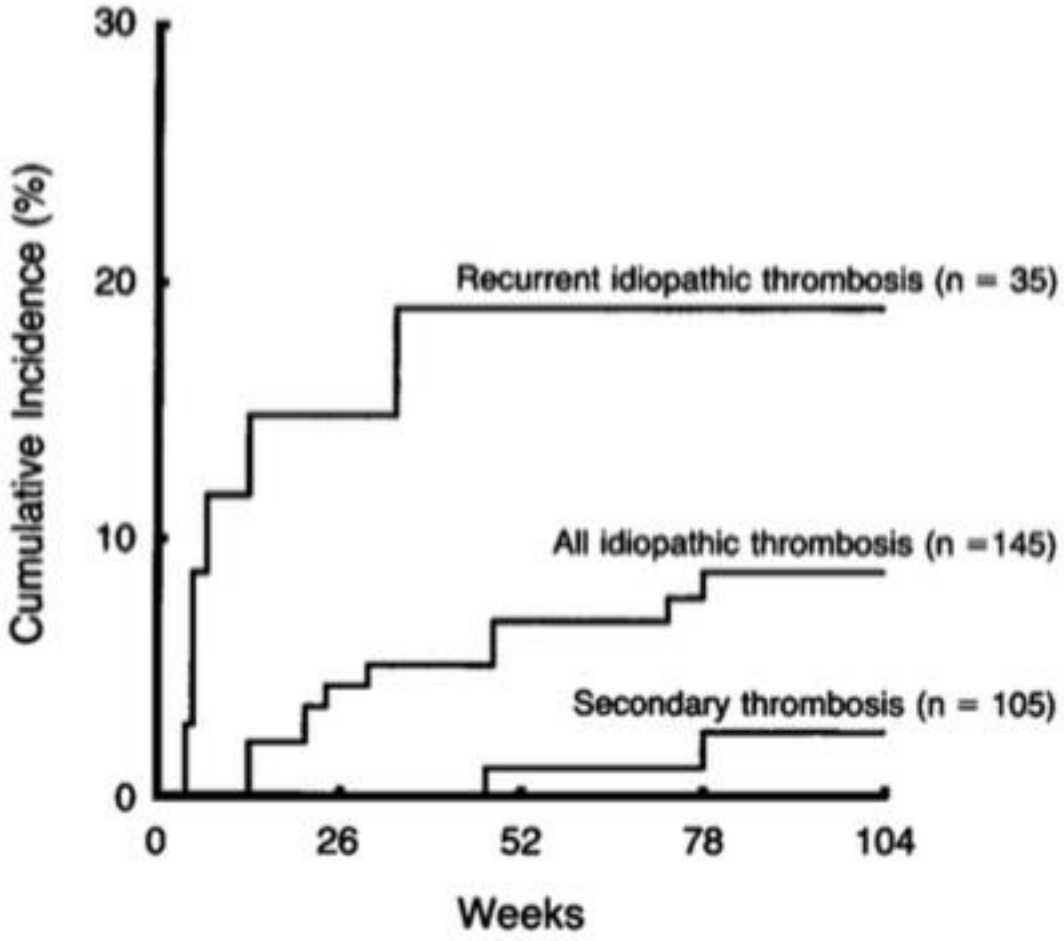


1)Thrombose site inhabituel

2)Thrombose récidivante

Khan et al. Occult cancer detection in venous thromboembolism: the past, the present, and the future. *Res Pract Thromb Haemost.* 2017;1:9–13.

Thrombose récidivante et Cancer



Prandoni et al. Deep vein thrombosis and the incidence of subsequent symptomatic cancer. NEJM. 1992;327:1128-33.

TEV & Cancer
Traitement standard

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

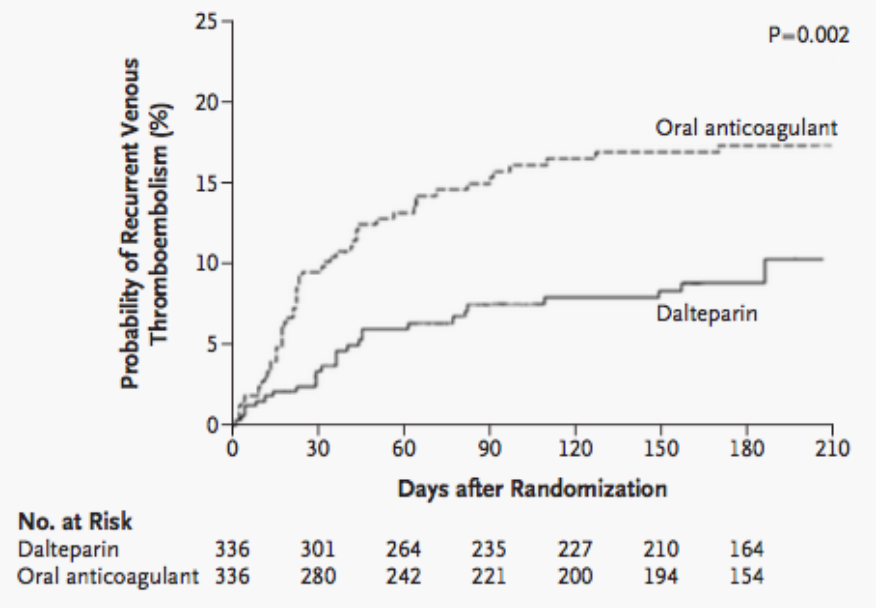
Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc., for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators*

N Engl J Med 2003;349:146-53.

CLOT

Characteristic	Dalteparin (N=338)	Oral Anticoagulant (N=338)
Mean age (yr)	62±12	63±13
Female sex (no. of patients)	179	169
ECOG performance score (no. of patients)		
0	80	63
1	135	150
2	118	122
3†	5	3
Hospitalization status (no. of patients)		
Outpatient	169	156
Inpatient	169	182
Hematologic cancer (no. of patients)	40	30
Solid tumor (no. of patients)		
No clinical evidence of disease	36	33
Localized disease	39	43
Metastatic disease	223	232
Antineoplastic treatment (no. of patients)‡	266	259
Current smoker (no. of patients)	33	42
History of DVT or PE (no. of patients)	39	36
Recent major surgery (no. of patients)	62	67
Central venous catheter (no. of patients)	46	40
Qualifying thrombotic event (no. of patients)		
DVT alone	235	230
PE, with or without DVT	103	108

Résultats



Lee et al. LMWH versus coumadin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.

Table 3 Comparison of trials on LMWH versus VKA for treatment of VTE in cancer patients

Trial Name	CANTHANOX	CLOT	MAIN-LITE	ONCENOX	CATCH
Year of Publication [Ref]	2002 [43]	2003 [44]	2006 [45]	2006 [46]	2015 [47]
Design	Open-label	Open-label	Open-label	Open-label	Open-label
Number of Patients	146	676	200	122	900
Treatment Protocol	Enoxaparin 1.5 mg/kg daily	Dalteparin 200 IU/kg once daily for the first month then 150 IU/kg for 5 months	Tinzaparin 175 IU/kg once daily	Enoxaparin 1 mg/kg every 12 h for 5 days then enoxaparin 1 mg/kg or 1.5 mg/kg daily	Tinzaparin 175 IU/kg once daily
Duration of Therapy (months)	3	6	3	6	6
Primary Efficacy Outcome LMWH vs VKA (%)	Combination of major bleeding or recurrent VTE: 10.5 vs 21.1	Recurrent symptomatic VTE: 9[a] vs 17	Recurrent symptomatic VTE: 7 vs 10	Recurrent symptomatic VTE: enoxaparin 1 mg vs. 1.5 mg vs VKA 6.8 vs 6.3 vs 10.0	Composite of recurrent symptomatic VTE, fatal PE, or incidental VTE: 7.2 vs 10.5
Safety Bleeding Outcomes LMWH vs VKA (%)	Major bleeding: 7 vs 16; Fatal bleeding: 0 vs 8[a]	Major bleeding: 6 vs 4; Any bleeding 14 vs 19	Major bleeding: 7 vs 7; Any bleeding: 27 vs 24	Major bleeding: enoxaparin 1 mg vs. 1.5 mg vs VKA : 6.5 vs 11.1 vs 2.9	Major bleeding: 2.7 vs 2.4 CRNM bleeding: 10.9[a] vs 15.3

CRNM clinically relevant non-major, *DOAC* direct oral anticoagulants, *LMWH* low-molecular weight heparin, *PE* pulmonary embolism, *VKA* vitamin K antagonists, *VTE* venous thromboembolism

[a]Statistically significant difference between the two groups

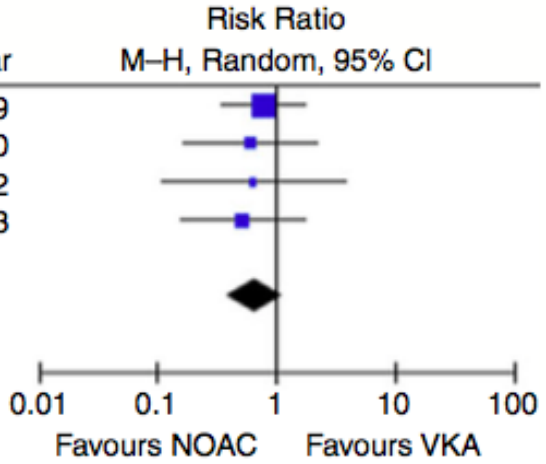
NACO?

A

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M–H, Random, 95% CI	Year	Risk Ratio M–H, Random, 95% CI
Re-Cover I and II	10	173	12	162	48.4%	0.78 [0.35, 1.76]	2009	
Einstein-DVT	4	118	5	89	19.3%	0.60 [0.17, 2.18]	2010	
Einstein-PE	2	114	3	109	10.2%	0.64 [0.11, 3.74]	2012	
Hokusai	4	109	7	99	22.2%	0.52 [0.16, 1.72]	2013	
Total (95% CI)		514		459	100.0%	0.66 [0.38, 1.17]		
Total events	20		27					

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0\%$

Test for overall effect: Z = 1.42 (P = 0.16)



van der Hulle et al. Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. J Thromb Haemost 2014; 12: 1116–20.

NACO?

- Not just yet…
  - Études de sous-groupe
  - Vs coumadin
  - Inquiétudes
    - Intéractions médicamenteuses
    - Absorption
    - Arrêt/Antidote
  - **Non représentatif**

Burnett et al. Guidance for the practical management of direct oral anticoagulants in VTE treatment. J Thromb Thrombolysis 2016;41:206–232

NACO?

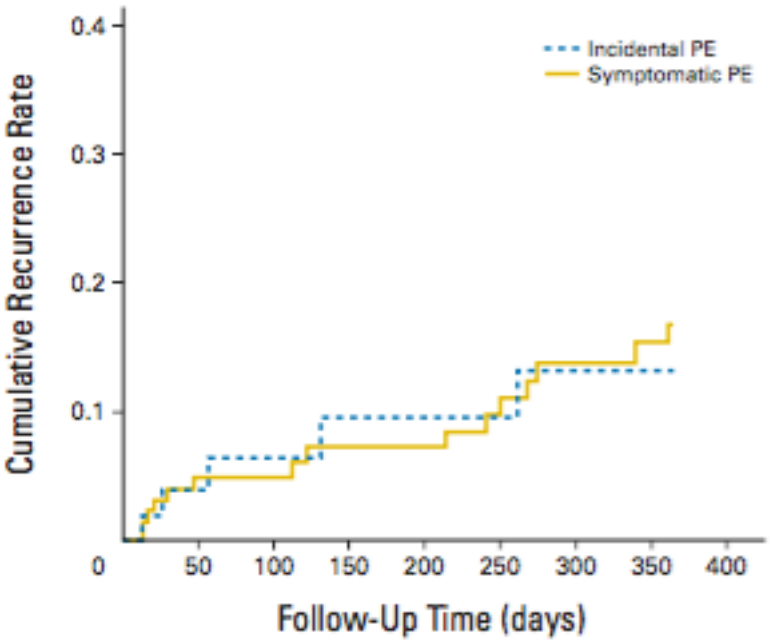
- Not just ye
  - Études de
  - Vs couma
  - Inquiétudes
    - Hokusai
    - VTE
    - camenteuses
    - select-d
  - **Non représentatif**

59th ASH® Annual Meeting and Exposition
December 9-12 • Atlanta, Georgia

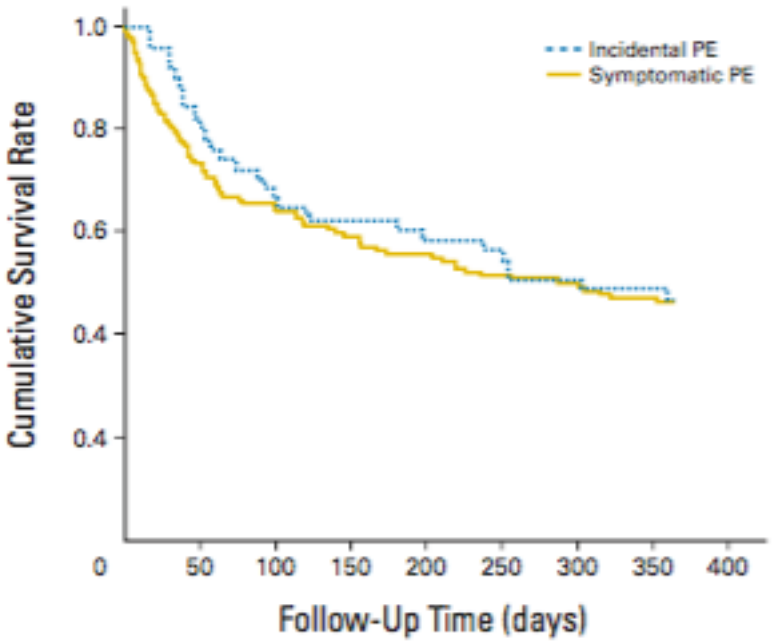
Burnett et al. Guidance for the practical management of direct oral anticoagulants in VTE treatment. J Thromb Thrombolysis 2016;41:206–232

Mais si… Découverte fortuite

Récidive



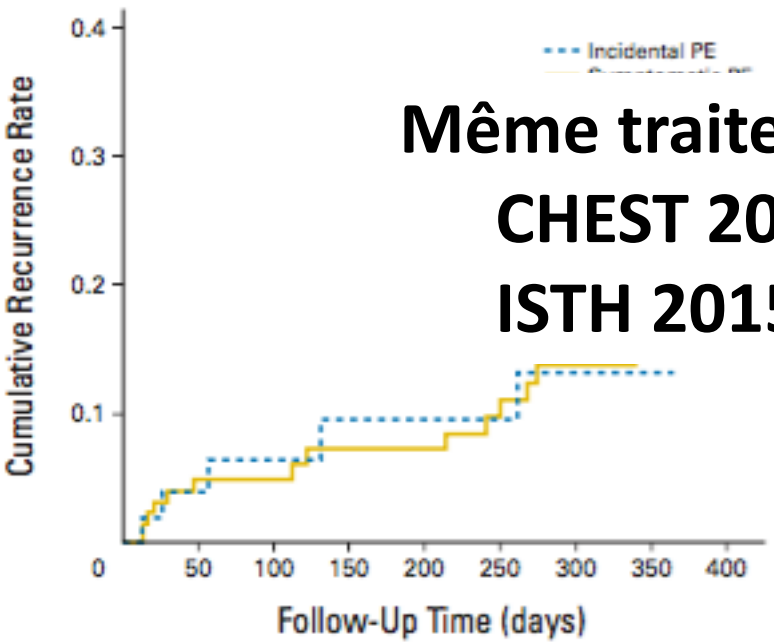
Mortalité



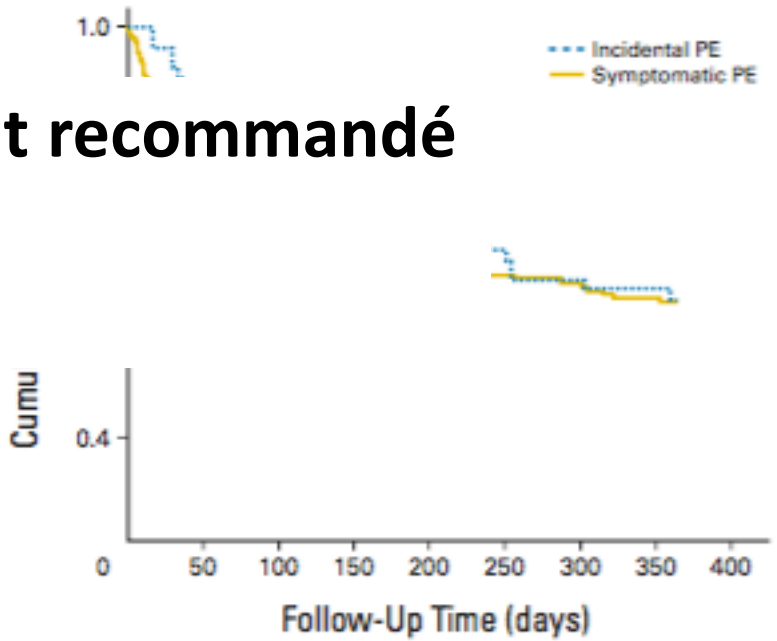
denExter et al. Risk of Recurrent Venous Thromboembolism and Mortality in Patients With Cancer Incidentally Diagnosed With Pulmonary Embolism: A Comparison With Symptomatic Patients. *J Clin Oncol 2011;29:2405-2409.*

Mais si… Découverte fortuite

Récidive



Mortalité



Même traitement recommandé

CHEST 2016

ISTH 2015

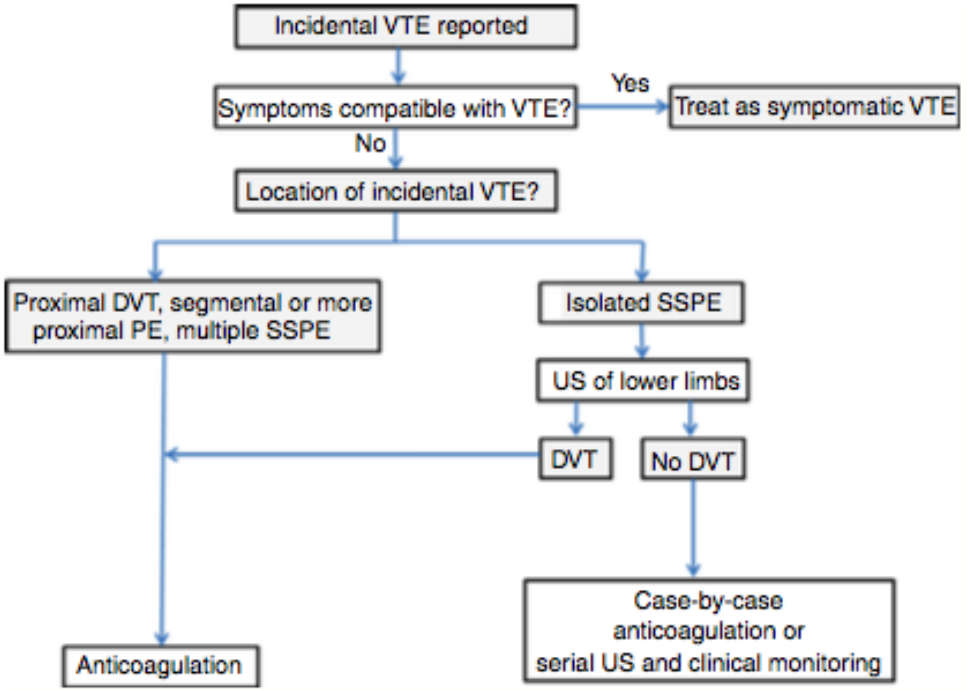
denExter et al. Risk of Recurrent Venous Thromboembolism and Mortality in Patients With Cancer Incidentally Diagnosed With Pulmonary Embolism: A Comparison With Symptomatic Patients. *J Clin Oncol 2011;29:2405-2409.*

Mais si… Découverte fortuite ET sous-segmentaire

CHEST 2016

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C), **and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).

ISTH 2015 (Cancer)



Carrier et al. Symptomatic subsegmental pulmonary embolism: what is the next step? J Thromb Haemost 2012; 10: 1486–90.
Kearon et al. Antithrombotic therapy for VTE. CHEST 2016; 149(2):315-352.
Di Nisio et al. for the Subcommittee on Haemostasis and Malignancy. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost 2015; 13: 880–3.

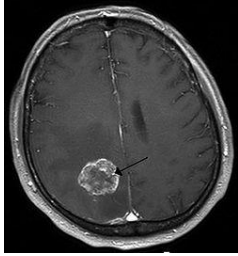
Mais si… Indication de thrombolyse

Contraindications to fibrinolytic therapy for deep venous thrombosis or acute pulmonary embolism

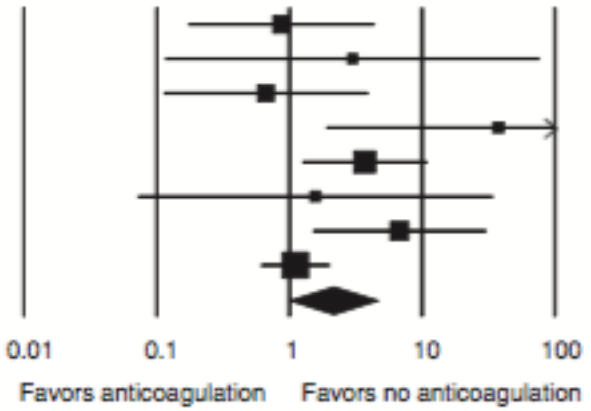
Absolute contraindications
Prior intracranial hemorrhage
Known structural cerebral vascular lesion
Known malignant intracranial neoplasm
Ischemic stroke within three months (excluding stroke within three hours*)
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head trauma or facial trauma within three months

Adapté de utdol.com. CHEST2012.

Mais si… Lésion(s) cérébrale(s)

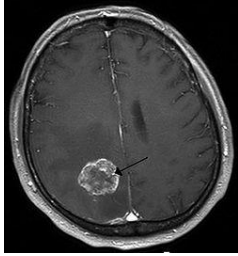


Study name	Subgroup within study	Statistics for each study					ICH / Total	
		Odds ratio	Lower limit	Upper limit	*Z*-Value	*P*-Value	Anticoagulation	No anticoagulation
Ruff, 1983	Glioma	0.88	0.17	4.42	–0.16	0.87	2 / 103	6 / 272
Olin, 1987	Both	3.00	0.12	77.31	0.66	0.51	1 / 25	0 / 24
Schiff, 1994	Mets	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
Khoury, 2015	Glioma	6.77	1.50	30.59	2.48	0.01	15 / 97	2 / 76
Donato, 2015	Mets	1.11	0.61	2.04	0.35	0.73	21 / 104	35 / 189
		2.13	1.00	4.57	1.95	0.05		



Zwicker et al. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. J Thromb Haemost 2016; 14: 1736–40.

Mais si… Lésion(s) cérébrale(s) 1)Métastases

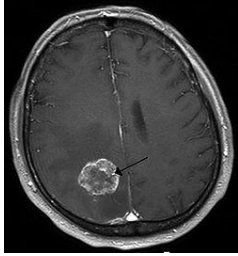


- Matched control cohort

- Hémorragies intracrâniennes
- Hémorragies IC mesurables (>1cc)
- Hémorragies IC significatives (>10cc ou sx ou chx)

Characteristic	Enoxaparin (N = 104)	Controls (N = 189)
Males, n (%)	55 (52.9%)	94 (49.7%)
Mean age at time of brain metastasis, y (range)	60.9 (31.1-84.6)	60 (21.9-92.1)
Stage 4 at time of cancer diagnosis, n (%)	46 (44.2%)	91 (48.1%)
Number of brain lesions when first recognized, n (%)		
1-2	63 (60.6%)	107 (56.6%)
3-4	10 (9.6%)	29 (15.3%)
5 or more	16 (15.4%)	25 (13.2%)
Primary malignancy, n (%)		
Non-small cell lung cancer	56 (53.8%)	97 (51.3%)
Breast cancer	12 (11.5%)	25 (13.2%)
Renal cell carcinoma	10 (9.6%)	20 (10.6%)
Melanoma	10 (9.6%)	20 (10.6%)
Colorectal cancer	5 (4.8%)	9 (4.8%)
Small cell lung cancer	2 (1.9%)	6 (3.2%)
Comorbidities, n (%)		
Hypertension	40 (38.5%)	76 (40.2%)
Chronic kidney disease	5 (4.8%)	18 (9.5%)
Treatment of brain metastasis, n (%)		
Chemotherapy after brain met diagnosis	72 (69.2%)	115 (60.8%)
Brain radiation*	82 (78.8%)	163 (86.2%)
Neurosurgery	30 (28.8%)	44 (23.3%)
Corticosteroids for cerebral edema	74 (71.2%)	162 (85.7%)
Neurosurgery or brain radiation	83 (79.8%)	168 (88.9%)
Concomitant medications		
Aspirin use, n (%)	5 (4.8%)	29 (15.3%)†
Antiangiogenic agents	14 (13.5%)	10 (5.2%)‡

Donato et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin : A matched cohort study. Blood. 2015;126(4):494-499



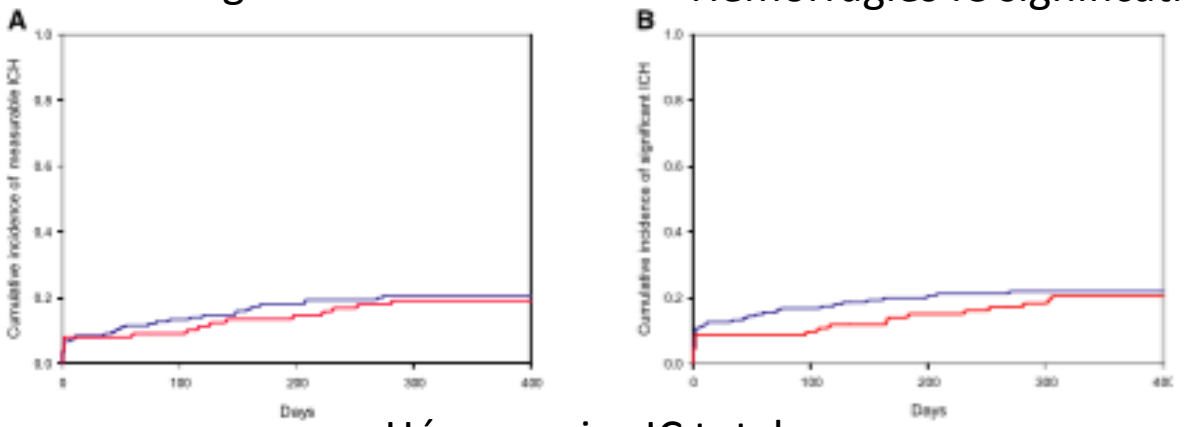
Mais si… Lésion(s) cérébrale(s)

1)Métastases

Incidence cumulative à 1 an

Hémorragies IC mesurables

Hémorragies IC significatives



Hémorragies IC totales

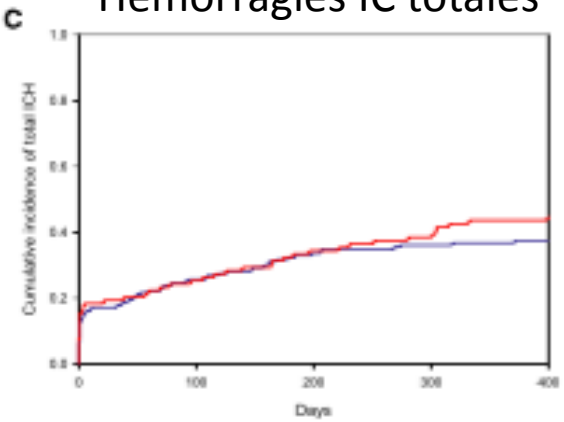
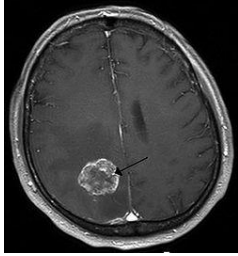


Figure 1. Cumulative incidence of intracranial hemorrhage (ICH) in patients with metastatic brain tumors. No differences between enoxaparin and control cohorts were observed in the cumulative incidence of intracranial hemorrhage for any category (Gray test, $P > .05$) including measurable (A), significant (B), and total (C) hemorrhages. Enoxaparin cohort shown in red and controls in blue.

Donato et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin : A matched cohort study. Blood. 2015;126(4):494-499



Mais si… Lésion(s) cérébrale(s)

1)Métastases

HIC significatives : Incidence cumulative à 1 an

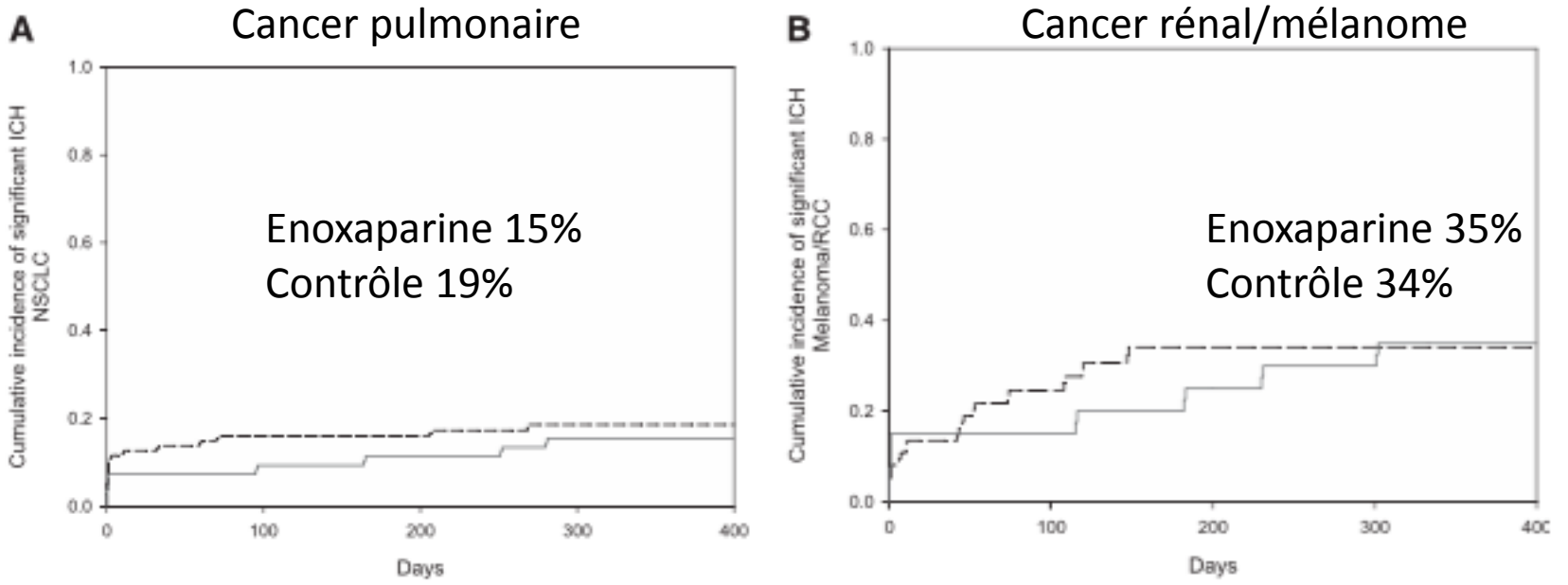
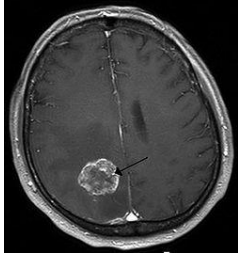


Figure 3. Cumulative incidence of significant intracranial hemorrhage (ICH) in the non-small cell lung cancer and melanoma/renal cell carcinoma subgroups. (A) The cumulative incidence of significant intracranial hemorrhage in patients with non-small lung cancer at 1 year was 15% in the enoxaparin cohort compared with 19% in the control cohort (Gray test, $P = .93$). (B) In the melanoma plus renal cell carcinoma subgroup, the cumulative incidence of significant intracranial hemorrhage at 1 year was 35% for the enoxaparin cohort vs 34% for the controls (Gray test, $P = .86$). Enoxaparin cohort shown in solid gray line and controls in hatched black line. NSCLC, nonsmall lung cancer; RCC, renal cell carcinoma.

Donato et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin : A matched cohort study. Blood. 2015;126(4):494-499

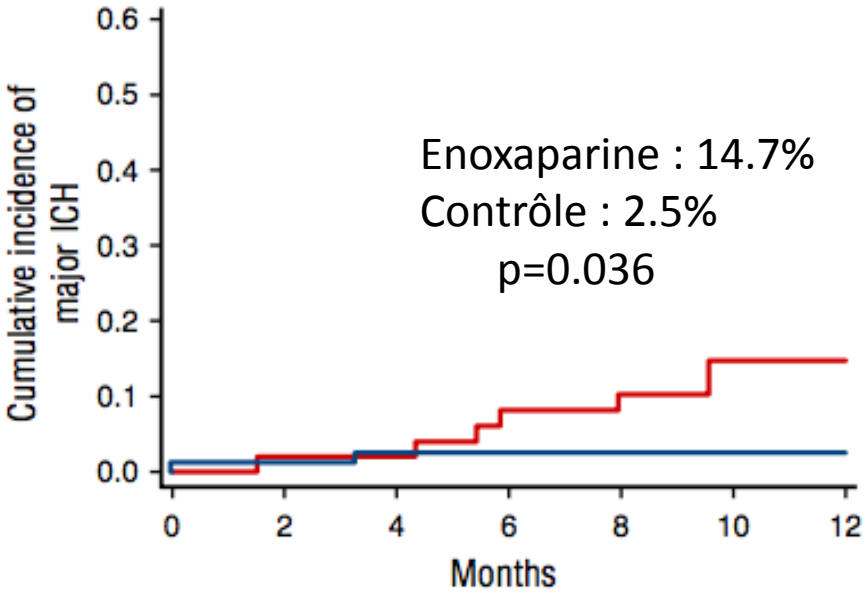
Mais si… Lésion(s) cérébrale(s) 2)Gliome



Patients

Patient characteristics	Enoxaparin (N = 50), n (%)	Control (N = 83), n (%)	*P*
Male	33 (66)	48 (58)	.37
Age at diagnosis, y (range)	62 (26-89)	61 (24-82)	.84
Type of glioma			.18
Anaplastic astrocytoma	5 (10)	2 (2)	
Anaplastic oligodendroglioma	4 (8)	10 (12)	
Glioblastoma	41 (82)	71 (86)	
Hypertension	13 (26)	41 (49)	.01
Chronic kidney disease	1 (2)	2 (2)	1.00
Glioma treatment			
Involved field radiation	49 (98)	82 (99)	1.00
Stereotactic radiosurgery	19 (38)	20 (24)	.12
Surgical resection	33 (66)	56 (67)	1.00
Any antineoplastic drug	48(96)	81 (98)	.63
Antiangiogenic agents	23 (46)	42 (51)	.72
Aspirin use	5 (10)	11 (13)	.78

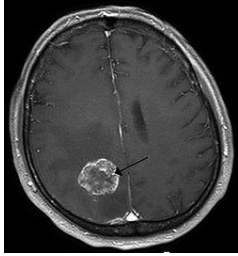
Résultats

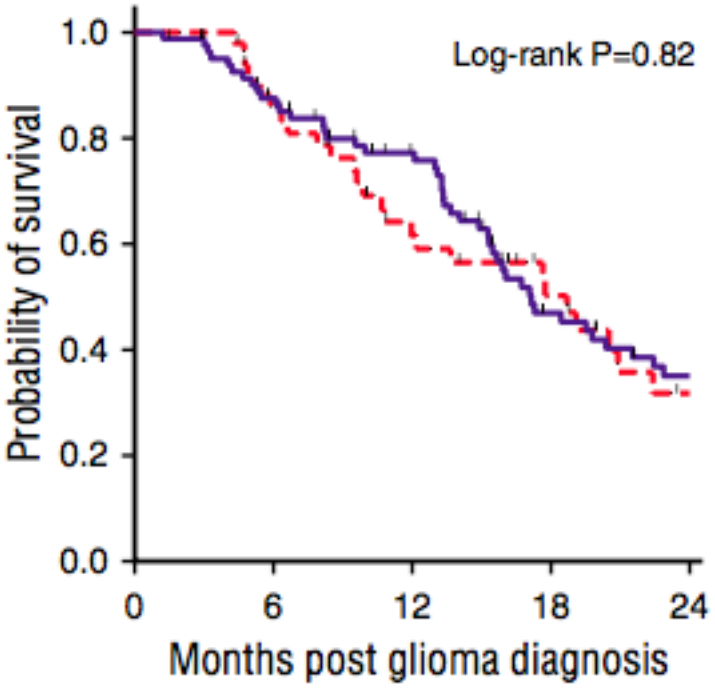


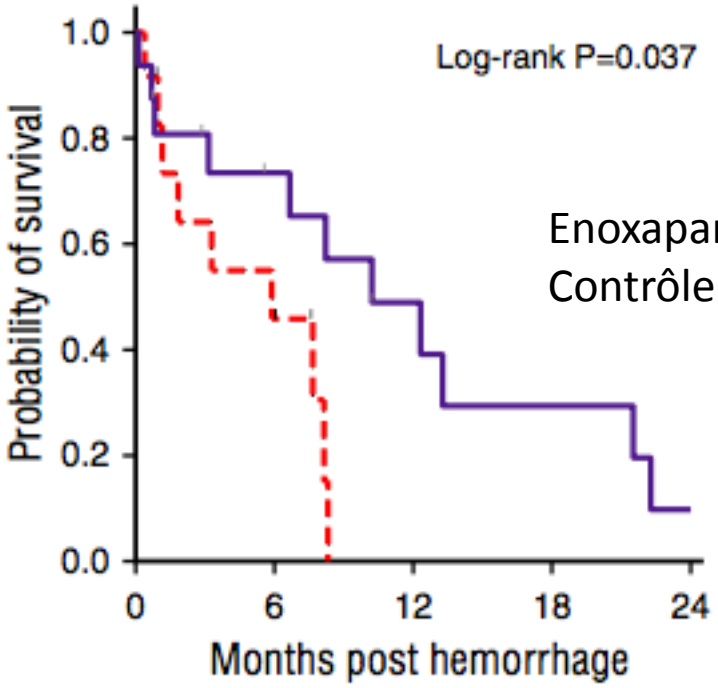
Enoxaparine : 14.7%
Contrôle : 2.5%
p=0.036

Mantia et al. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin Blood. 2017;129(25):3379-3385.

Mais si… Lésion(s) cérébrale(s) 2)Gliome





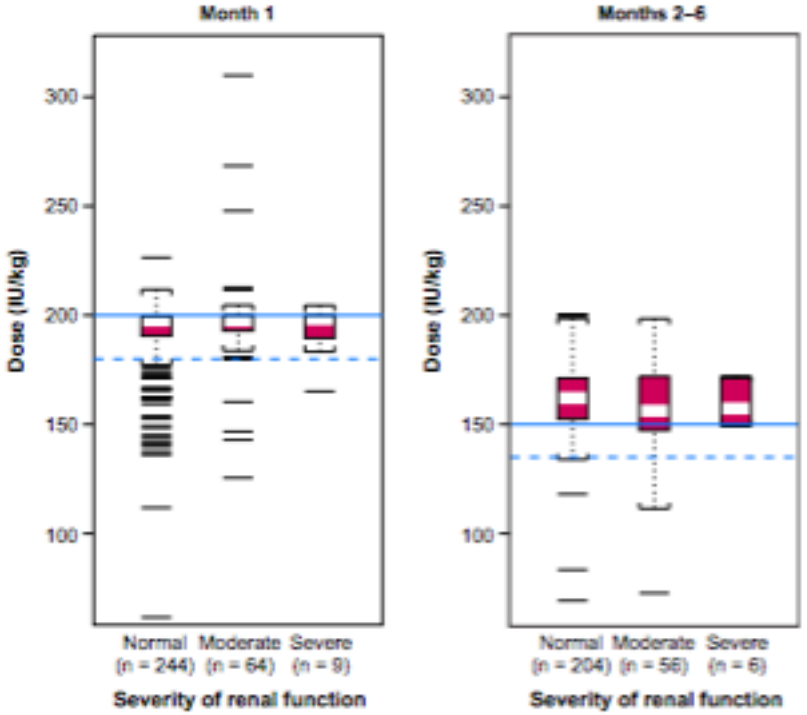


Enoxaparine 3.3m
Contrôle 10.2m

Mantia et al. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin Blood. 2017;129(25):3379-3385.

Mais si… Insuffisance rénale

- L’expérience CLOT
  - Exclusion : Créatinine > 3XULN



Woodruff et al. A post hoc analysis of dalteparin versus oral anticoagulant (VKA) therapy for the prevention of recurrent venous thromboembolism (rVTE) in patients with cancer and renal impairment. J Thromb Thrombolysis 2016;42:494–504 .

Mais si… Insuffisance rénale

CLOT : Analyse *posthoc* sous-groupe IR

Variable	Treatment	Patients at risk (no.)	Events	%	*p* value[a]	Hazard ratio (95 % CI)
VTE (n = 162)[b]	Dalteparin	74	2	2.7	0.0111	0.148 (0.034–0.647)
	VKA	88	15	17.0		
Any bleeding (n = 161)[c]	Dalteparin	74	15	20.3	0.4658	0.781 (0.402–1.517)
	VKA	87	21	24.1		
Major bleeding (n = 161)[c]	Dalteparin	74	7	9.5	0.6511	1.287 (0.432–3.834)
	VKA	87	6	6.9		

Woodruff et al. A post hoc analysis of dalteparin versus oral anticoagulant (VKA) therapy for the prevention of recurrent venous thromboembolism (rVTE) in patients with cancer and renal impairment. J Thromb Thrombolysis 2016;42:494–504 .

Mais si… Insuffisance rénale

- L'expérience CATCH

	ClCr>60 Coumadin n=378	ClCr>60 Tinzaparin n=355	ClCr<60 Coumadin n=62	ClCr<60 Tinzaparin n=67
VTE	36 (10%)	22 (6%)	9 (15%)	13 (9%)
CRB	65 (17%)	46 (13%)	15 (24%)	11 (16%)

CRB : Clinically relevant bleeding

Bauersachs et al on behalf of the CATCH Investigators .ISTH 2015 Abstract AS214 Long-term tinzaparin versus warfarin for treatment of venous thromboembolism (VTE) in cancer patients – analysis of renal impairment (R

Mais si… Insuffisance rénale

- Recommendations
  - HBPM de plus haut poids moléculaire
  - Anti-Xa?

Medscape® www.medscape.com

Heparin Formulation	Mol Wt (D)	Anti-Xa/Anti-IIa Ratio	Halflife (mins)
ardeparin (Normiflo)†	6000	2.0:1	200
dalteparin (Fragmin)	5000	2.0:1	119–139
enoxaparin (Lovenox)	4200	3.7:1	129–180
nadroparin‡	4300	3.5:1	210
tinzaparin (Innohep)	6500	2.8:1	180–240
unfractionated	10,000–15,000	1:1	30–150§

* Based on data from studies reported in references 4, 15, 33, and 36.
Abbreviation: mol wt = molecular weight.
† No longer marketed.
‡ Available in Europe only.
§ Unfractionated heparin has saturable binding and its halflife increases with doses greater than 400 U/kg.

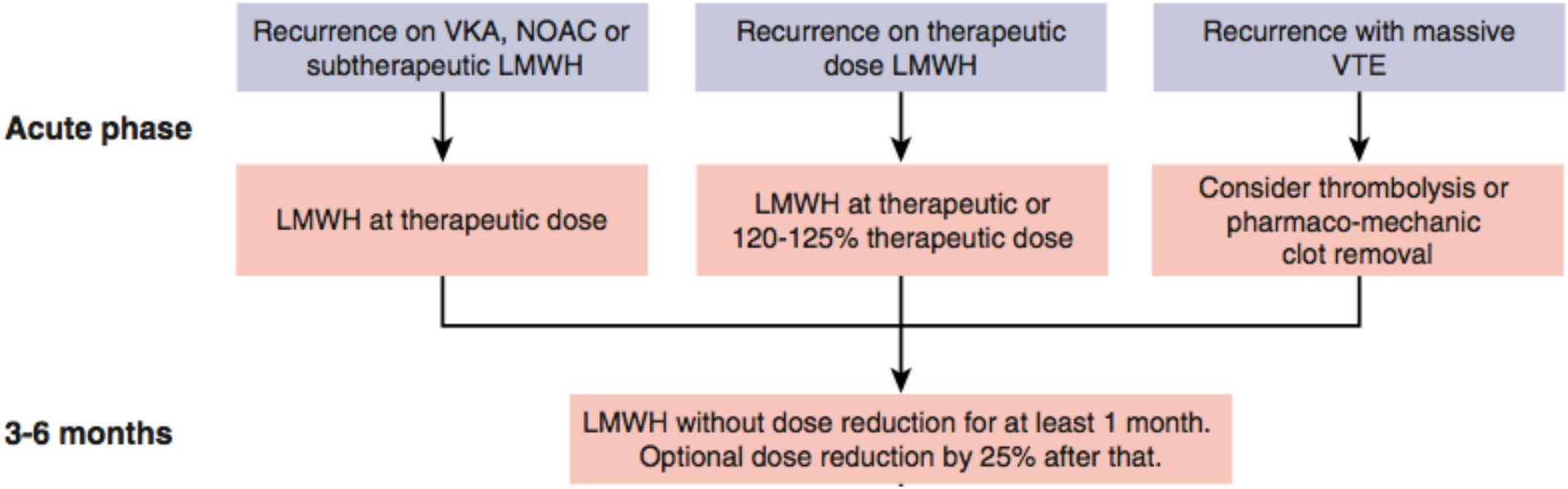
Mais si… Thrombopénie

- Pas de RCT (évidemment)
  - 2 écoles : Ajustement de dose vs Transfusion
  - Études rétrospectives

- Suggestions
  - 25-50 : ½ dose
  - <25 : Suspendre
  - *Si 1er mois : FVCI? Transfusion?*

Watson et al. Guideline on aspects of cancer-related venous thrombosis. British Journal of Haematology. 2015; 170: 640–8.

Mais si… Récidive sous traitement



Schulman. How I treat recurrent VTE in patients receiving anticoagulant therapy. Blood. 2017; 129(25):3285-3293

Et après 6 mois?

- Pas de RCT

Table 3 Comparison of trials on LMWH versus VKA for treatment of VTE in cancer patients

Trial Name	CANTHANOX	CLOT	MAIN-LITE	ONCENOX	CATCH
Year of Publication [Ref]	2002 [43]	2003 [44]	2006 [45]	2006 [46]	2015 [47]
Design	Open-label	Open-label	Open-label	Open-label	Open-label
Number of Patients	146	676	200	122	900
Treatment Protocol	Enoxaparin 1.5 mg/kg daily	Dalteparin 200 IU/kg once daily for the first month then 150 IU/kg for 5 months	Tinzaparin 175 IU/kg once daily	Enoxaparin 1 mg/kg every 12 h for 5 days then enoxaparin 1 mg/kg or 1.5 mg/kg daily	Tinzaparin 175 IU/kg once daily
Duration of Therapy (months)	3	6	3	6	6
Primary Efficacy Outcome LMWH vs VKA (%)	Combination of major bleeding or recurrent VTE: 10.5 vs 21.1	Recurrent symptomatic VTE: 9[a] vs 17	Recurrent symptomatic VTE: 7 vs 10	Recurrent symptomatic VTE: enoxaparin 1 mg vs. 1.5 mg vs VKA 6.8 vs 6.3 vs 10.0	Composite of recurrent symptomatic VTE, fatal PE, or incidental VTE: 7.2 vs 10.5
Safety Bleeding Outcomes LMWH vs VKA (%)	Major bleeding: 7 vs 16; Fatal bleeding: 0 vs 8[a]	Major bleeding: 6 vs 4; Any bleeding 14 vs 19	Major bleeding: 7 vs 7; Any bleeding: 27 vs 24	Major bleeding: enoxaparin 1 mg vs. 1.5 mg vs VKA : 6.5 vs 11.1 vs 2.9	Major bleeding: 2.7 vs 2.4 CRNM bleeding: 10.9[a] vs 15.3

CRNM clinically relevant non-major, *DOAC* direct oral anticoagulants, *LMWH* low-molecular weight heparin, *PE* pulmonary embolism, *VKA* vitamin K antagonists, *VTE* venous thromboembolism

[a]Statistically significant difference between the two groups

Piran et al. Management of venous thromboembolism : an update. Thrombosis Journal 2016, 14(Suppl 1):23

Et après 6 mois?

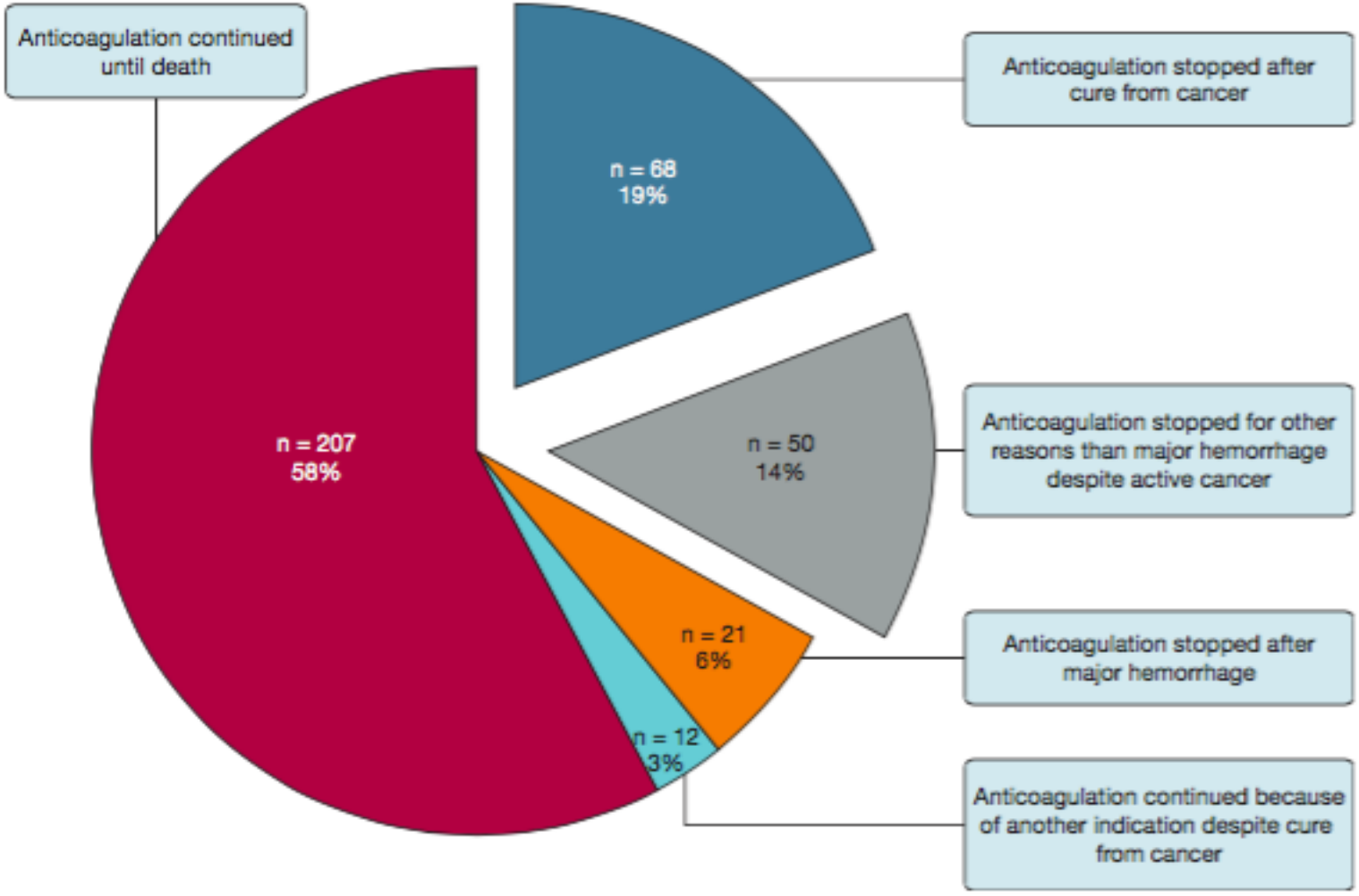
- Risque de récidive

Cause de TEV	Récidive à 5 ans
Chirurgie	3%
FR non-chirurgical transitoire	15%
Idiopathique	30%
Cancer	15%/an*

- Risque de saignement

Kearon et al. Antithrombotic Therapy for VTE Disease; CHEST Guideline and Expert Panel Report. CHEST 2016; 149(2):315-352.

Expérience de Leiden 2001-2010

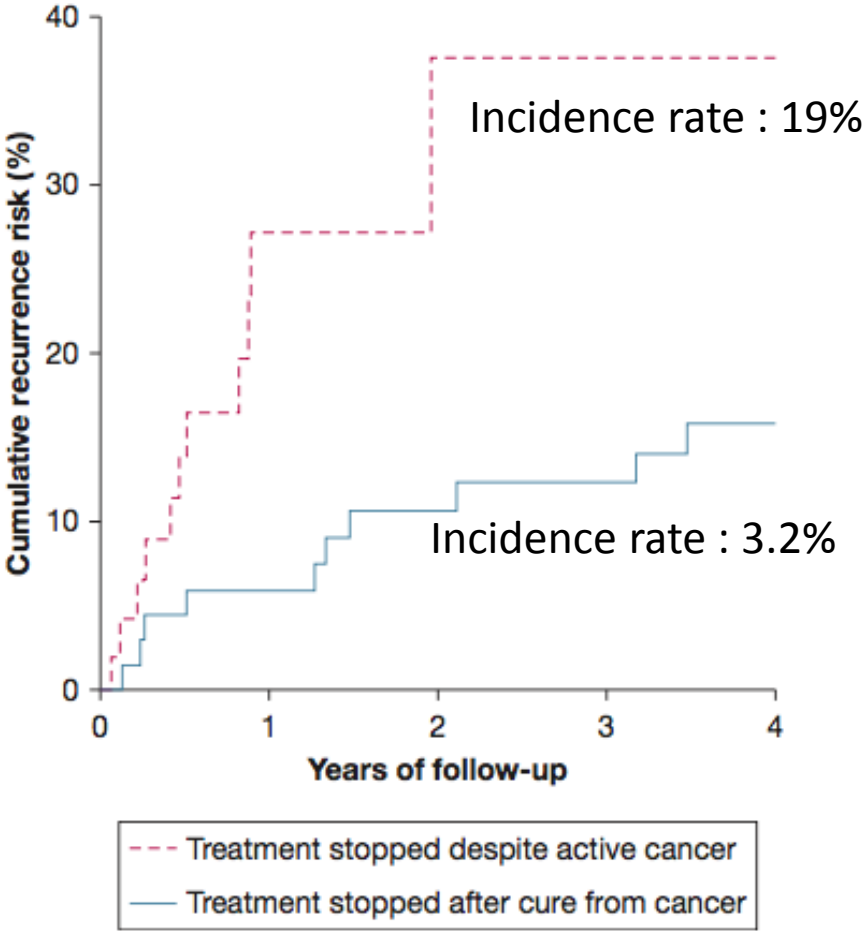


Van der Hulle et al. Cohort Study on the Management of Cancer-Associated Venous Thromboembolism Aimed at the Safety of Stopping Anticoagulant Therapy in Patients Cured of Cancer. CHEST 2016; 149(5):1245-1251.

Expérience de Leiden 2001-2010
Résultats

Arrêt en rémission

Si récidive TEV :



Van der Hulle et al. Cohort Study on the Management of Cancer-Associated Venous Thromboembolism Aimed at the Safety of Stopping Anticoagulant Therapy in Patients Cured of Cancer. CHEST 2016; 149(5):1245-1251.

DALTECAN

- Étude prospective internationale
  - EP ou TPP proximale symptomatique
  - Cancer actif
- Traitement
  - Mois 1 : Dalteparine 200 u/kg
  - Mois 2-12 : Dalteparine 150 u/kg
- Issue primaire
  - Saignement majeur mois 6-12

Francis et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 2015; 13: 1028–35.

DALTECAN : Résultats

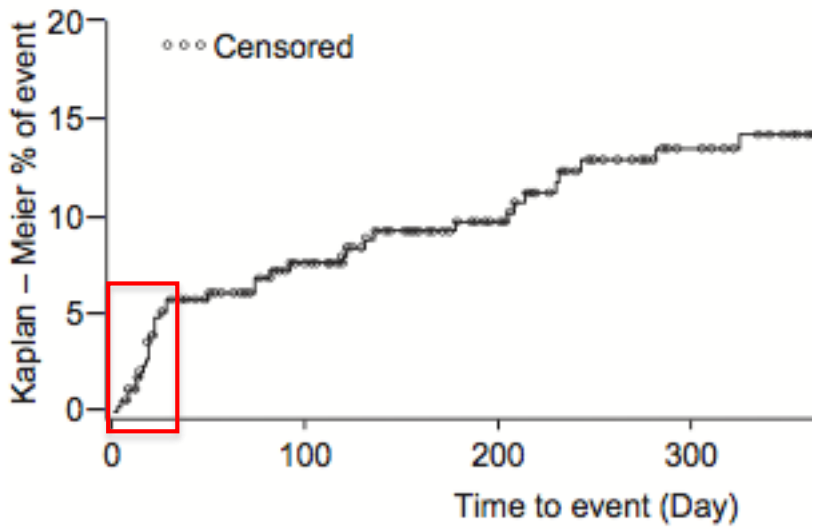
Table 2 Incidence of major bleeding*

Total (N = 334)

Time period	Incidence n/subject months at risk[b]	%	95% confidence interval[a]
1–6 months	26/1571	1.7	1.1, 2.4
7–12 months	8/1086	0.7	0.3, 1.4
1–12 months	34/2657	1.3	0.9, 1.8
2–6 months	14/1237	1.1	0.6, 1.9
2–12 months	22/2323	0.9	0.6, 1.4
By month*			
1st month	12/334	3.6	1.9, 6.2
2nd month	3/301	1.0	0.2, 2.9
3rd month	2/266	0.8	0.1, 2.7
4th month	2/244	0.8	0.1, 2.9
5th month	4/221	1.8	0.5, 4.6
6th month	3/204	1.5	0.3, 4.2
7th month	0/192		0, 1.6
8th month	1/172	0.6	0, 3.2
9th month	1/160	0.6	0, 3.4
10th month	2/153	1.3	0.2, 4.6
11th month	2/139	1.4	0.2, 5.1

Francis et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 2015; 13: 1028–35.

DALTECAN : Temps à récidive TEV



32% des patients complètent 12 mois tx

Francis et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 2015; 13: 1028–35.

Patients avec cancer
RIETE Registry

- 1502 patients consécutifs traités 6 mois HBPM pour thrombose associée à cancer
  - HBPM : 763 Coumadin : 739 (non randomisé)

Figure 1. Recurrent venous thromboembolism

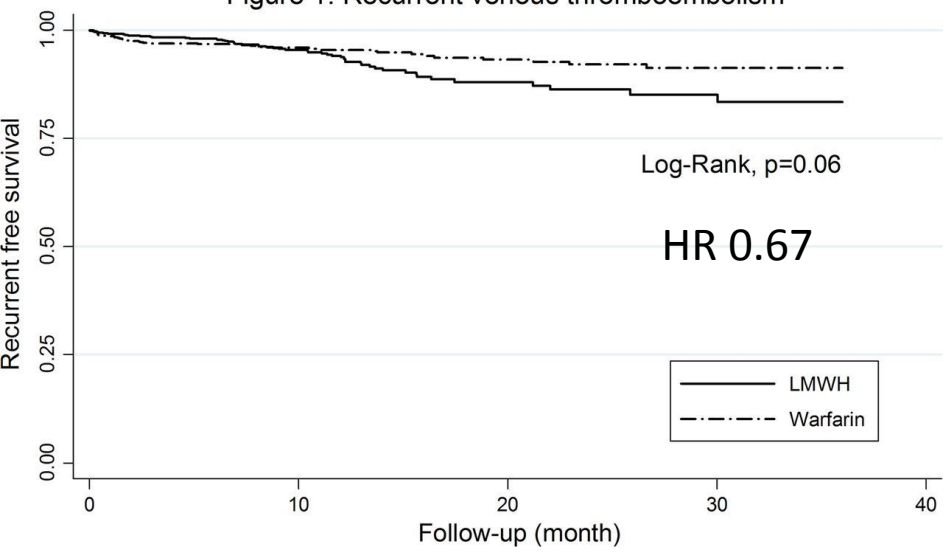
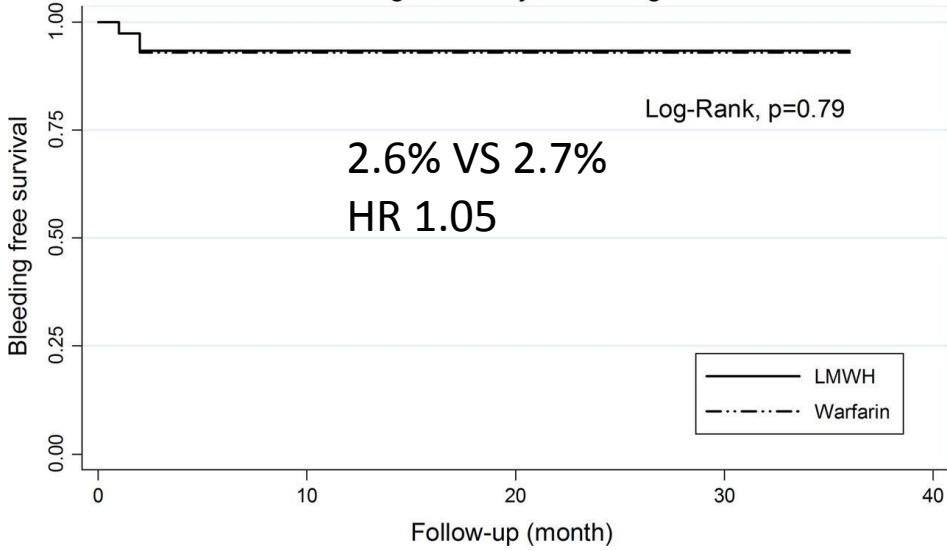


Figure 2. Major bleeding



Chai-Adisaksopha et al. Switching to Warfarin after 6-Month Completion of Anticoagulant Treatment for Cancer-Associated Thrombosis. Blood 2015;126:430

Population générale
RCT avec NACO

Table 4 Comparison of extended duration DOAC trials

Trial Name	EINSTEIN-EXTENSION	AMPLIFY-EXT	RE-MEDY	RE-SONATE
Year of Publication [Ref]	2010 [17]	2013 [50]	2013 [51]	2013 [51]
Design	Double-blinded	Double-blinded	Double-blinded	Double-blinded
Comparison Arm	Placebo	Placebo	Warfarin	Placebo
Number of Patients	1197	2486	2866	1353
Treatment Protocol	Rivaroxaban 20 mg once daily	Apixaban 5 mg or 2.5 twice daily	Dabigatran 150 mg twice daily	Dabigatran 150 mg twice daily
Duration of Therapy (months)	6 to12	12	6 to 36	6
Primary Efficacy Outcome DOAC vs VKA or Placebo (%)	Recurrent symptomatic VTE: 1.3[a] vs 7.1	Recurrent symptomatic VTE or all-cause mortality: 3.8[a] vs 4.2[a] vs 11.6	Recurrent symptomatic VTE or related mortality: 1.8[a] vs 1.3	Recurrent symptomatic VTE or related mortality: 0.4[a] vs 5.6
Major Bleeding DOAC vs VKA or Placebo (%)	0.7 vs 0	0.2 vs 0.1 vs 0.5	0.9 vs 1.8	0.3 vs 0
Major and CRNM Bleeding DOAC vs VKA or Placebo (%)	6.0[a] vs 1.2	3.2 vs 4.3 vs 2.7	5.6[a] vs 10.2	5.3[a] vs 1.8

DOAC direct oral anticoagulant, *CRNM* clinically relevant non-major, *DOAC* direct oral anticoagulants, *VKA* vitamin K antagonists, *VTE* venous thromboembolism
[a]Statistically significant difference between the two groups

Piran et al. Management of venous thromboembolism : an update. Thrombosis Journal 2016, 14(Suppl 1):23

Population générale
EINSTEIN CHOICE

- 3396 patients post anticoagulation pour 6-12 mois
- Randomisation double aveugle
- Issue primaire : récidive symptomatique TEV

	Rivaroxaban 20mg die n=1107	Rivaroxaban 10mg die n=1127	ASA 100mg die n=1131
TEV	17 (1.5%)	13 (1.2%)	50 (4.4%)
Saignement majeur	0.5%	0.4%	0.3%
Saignement cliniquement significatif	2.7%	2.0%	1.8%

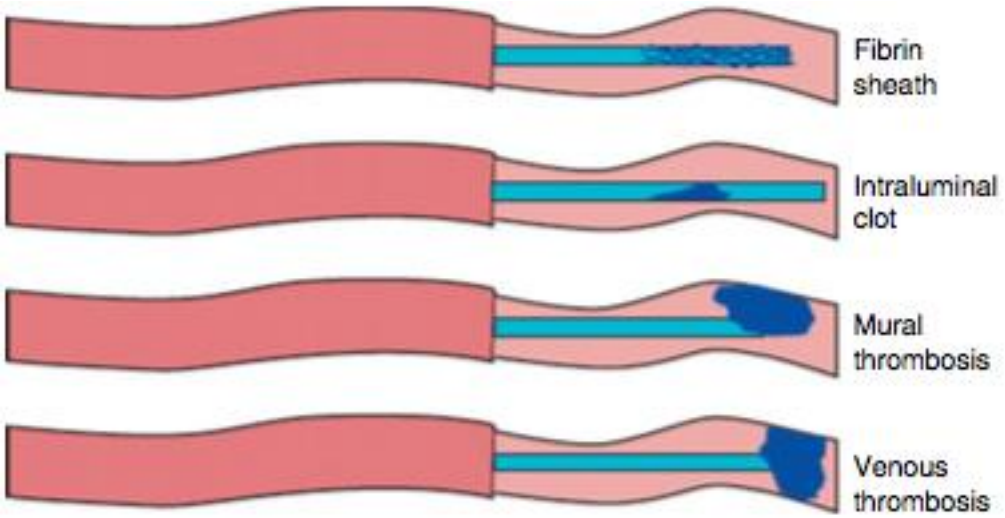
Weitz et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N Engl J Med 2017; 376:1211- 22.

Et après 6 mois?

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 et al. Antithrombotic therapy for VTE. CHEST 2016; 149(2):315-352.

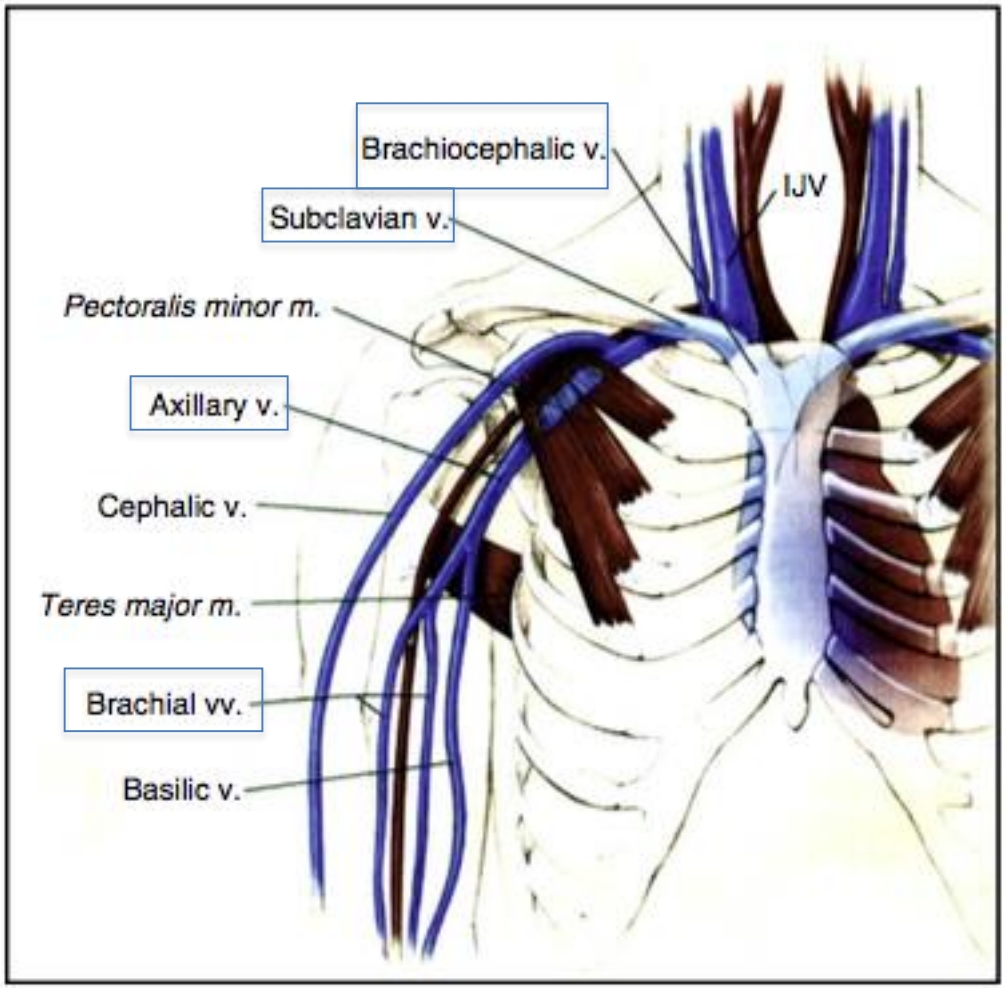
Thrombose de cathéter



Rajasekhar et al. How I treat central venous access device-related upper extremity deep vein thrombosis. Blood. 2017;129(20):2727-36.

Thrombose de cathéter

Veine profonde



Rajasekhar et al. How I treat central venous access device-related upper extremity deep vein thrombosis. Blood. 2017;129(20):2727-36.

Thrombose de cathéter

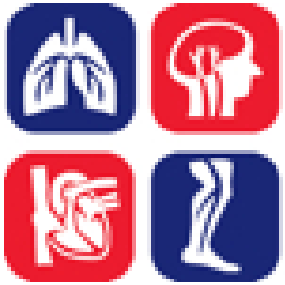
- Traitement préféré : HBPM et garder KT

- Si retrait KT
  - WAIT
  - HBPM pour 3 mois

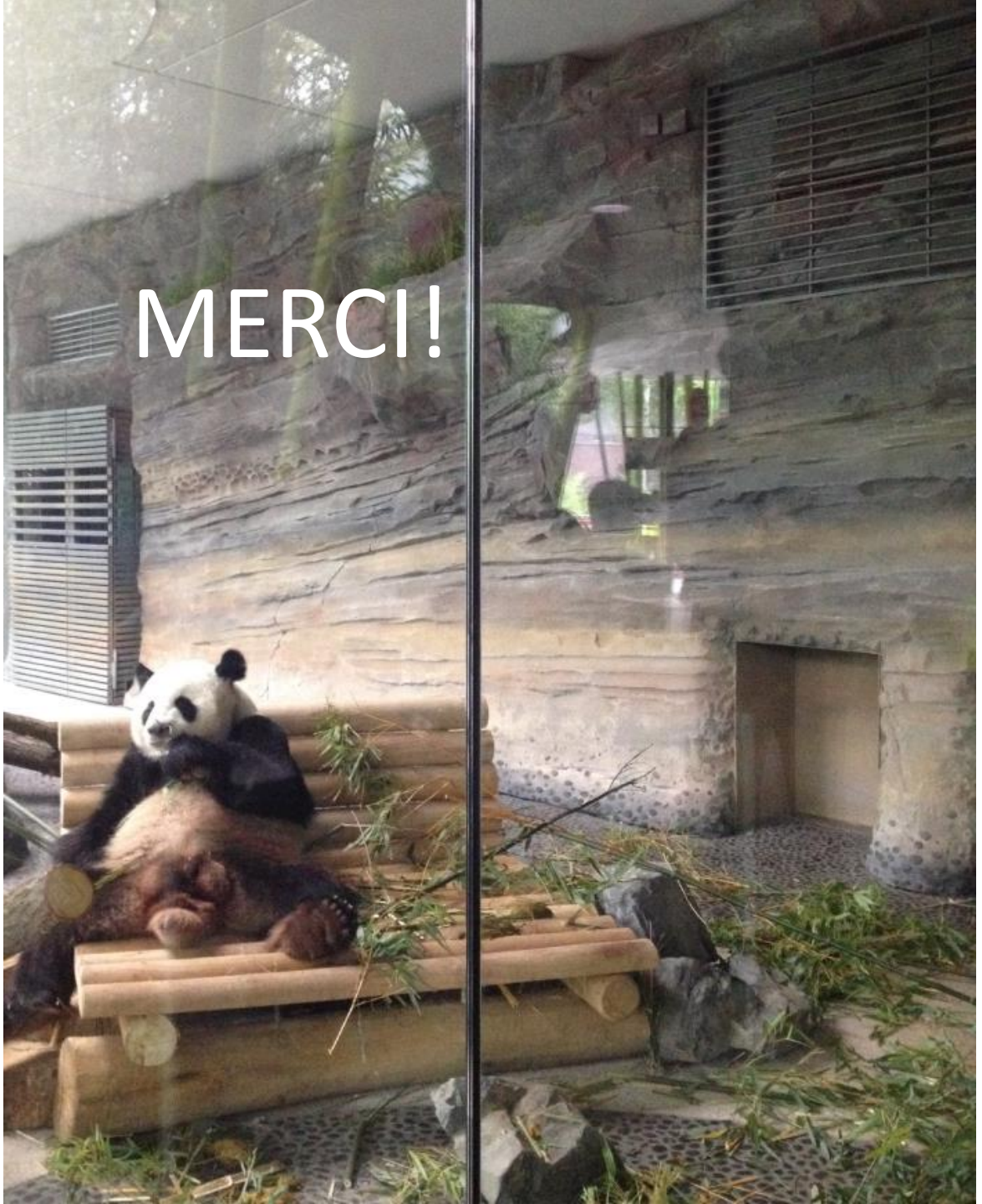
Rajasekhar et al. How I treat central venous access device-related upper extremity deep vein thrombosis. Blood. 2017;129(20):2727-36.

App

- Thrombose Canada
  - thrombosiscanada.ca/clinicalguides/clinical-guides-web-app/



- International initiative on thrombosis and cancer
  - itaccme.com/app


MERCI!

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Thrombose récidivante

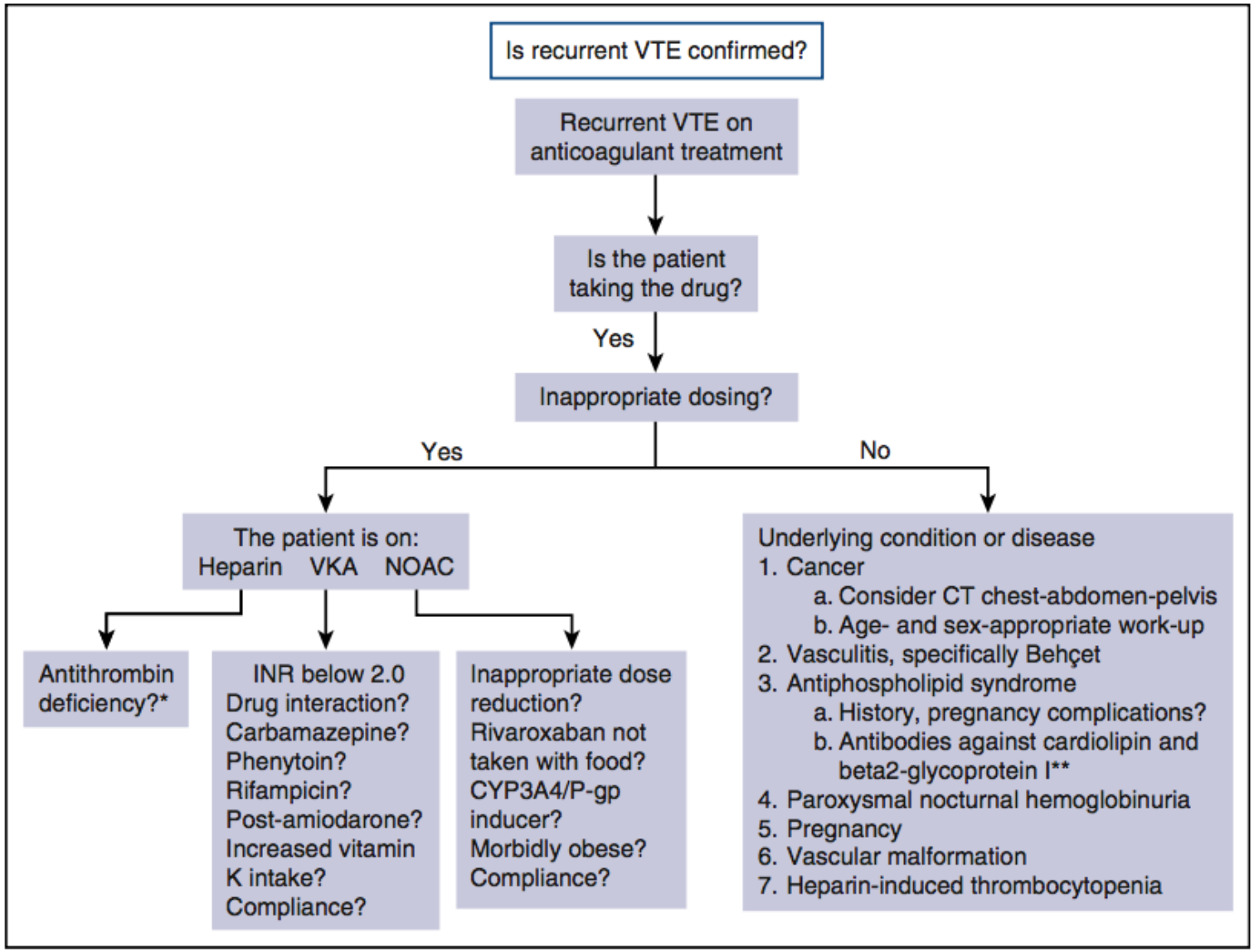

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Table 3. Primary Model Showing the Factors Independently and Significantly Associated With ICH

Factors	χ^2	HR	95% CI	*P* Value
Race (vs white or other)	19.18			<0.001
Asian		2.02	(1.39–2.94)	
Black		3.25	(1.43–7.41)	
Randomized to rivaroxaban (vs warfarin)	10.39	0.60	(0.44–0.82)	0.001
Age (HR for 10-year increase)	10.35	1.35	(1.13–1.63)	0.001
Albumin (HR for 0.5 g/dL decrease)	8.89	1.39	(1.12–1.73)	0.003
Platelets <210×10⁹/L (HR for each 10×10⁹/L ↓ below 210×10⁹/L)	8.43	1.08	(1.02–1.13)	0.004
History of CHF	7.27	0.65	(0.47–0.89)	0.007
Previous stroke or TIA	4.41	1.42	(1.02–1.96)	0.036
Diastolic BP (HR for 10 mm Hg increase)	4.13	1.17	(1.01–1.36)	0.042