

SPIF
21 novembre 2015

CANCER ET MALADIE VEINEUSE THROMBO-EMBOLIQUE

Philippe Girard

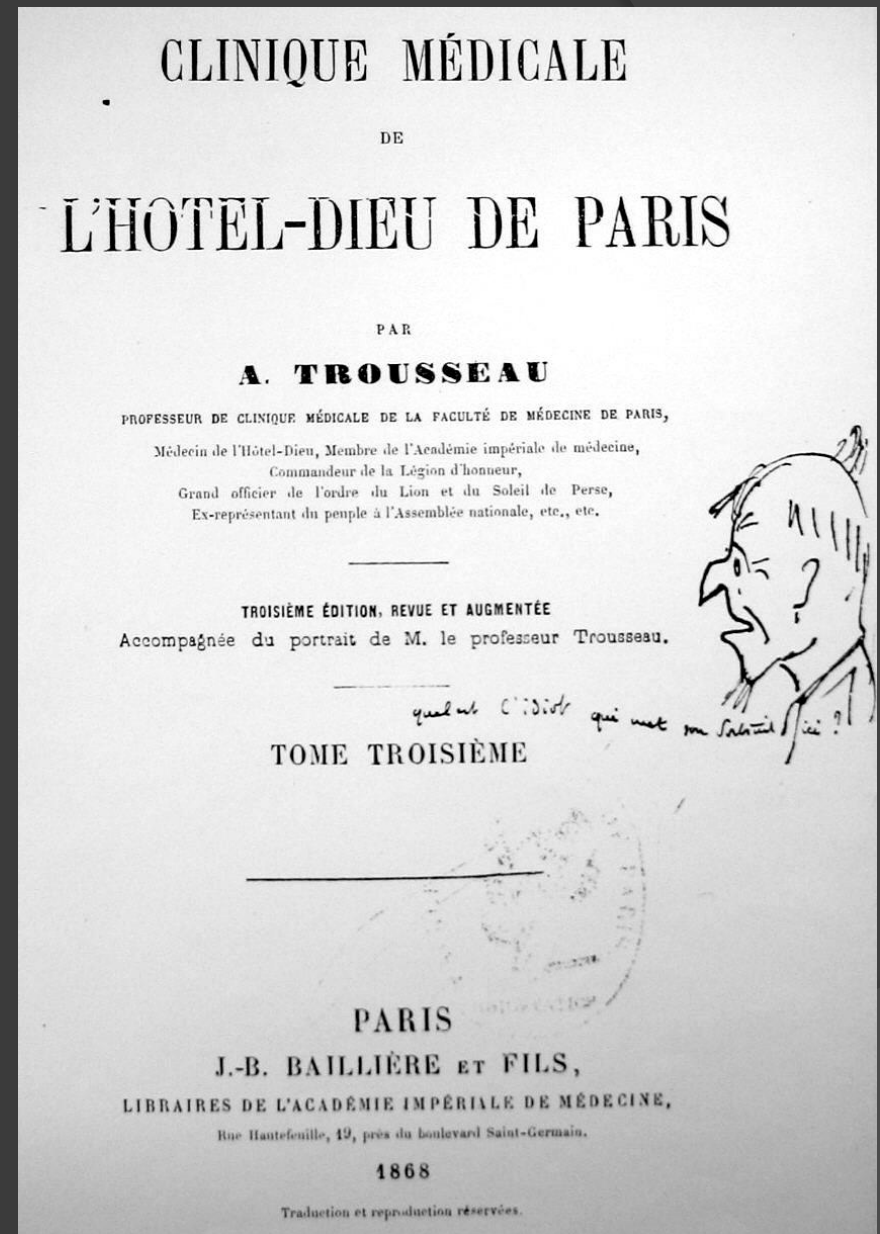


Armand Trousseau (1801-1867)



« Je suis perdu ! Depuis hier, j' ai une phlegmatia et ceci ne me laisse aucun doute sur la nature de ma maladie... »

(1er janvier 1867)



Cancer et MTEV

- Rappel épidémiologie/facteurs de risque MTEV
- Cancer et Prévention de la MTEV
- Cancer et Diagnostic de la MTEV
- Traitement curatif de la MTEV et cancer
- MTEV « non provoquée »: faut-il chercher un cancer?
- ~~● Chambres et cathéters~~
- ~~● Les anticoagulants anticancéreux ?~~

TVP et EP: Facteurs de risque

- 2218 patients, 1966-1990

	OR	95% CI
Hospitalisation/chirurgie		
- ni hosp. ni chir.	1,0	(référence)
- hosp. sans chir.	8,0	(4,5-14,2)
- hosp avec chir.	21,7	(9,4-49,9)
Trauma	12,7	(4,1-39,7)
Cancer sans chimio	4,1	(1,9-8,5)
Cancer avec chimio	6,5	(2,1-20,2)
Maladie hépatique grave	0,1	(0,01-0,7)

TVP et EP: Facteurs de risque

Strong
(OR >10)

Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous venous thromboembolism
Spinal cord injury

Moderate
(OR 2-9)

Arthroscopic knee surgery
Auto-immune diseases
Blood transfusion
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
<i>In vitro</i> fertilization
Infection (specifically pneumonia, urinary tract infection and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Oral contraceptive therapy
Paralytic stroke
Postpartum period
Superficial vein thrombosis
Thrombophilia

Weak
(OR <2)

Bed rest >3 days
Diabetes mellitus
Hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

TVP/EP et cancer: Impact Pronostique

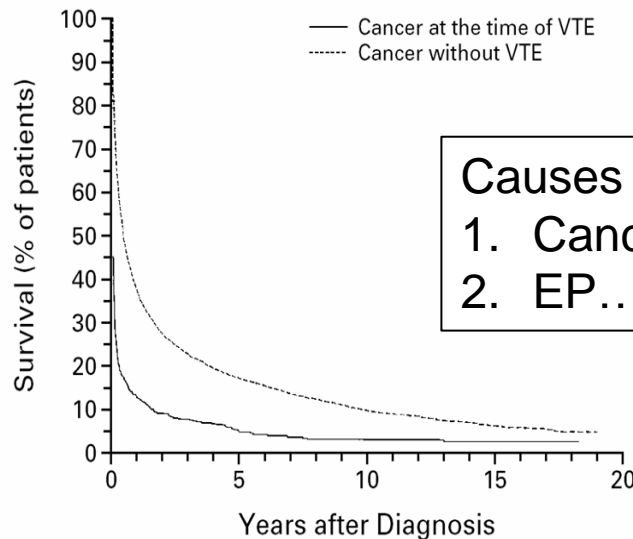
Registre cancers Danemark

1228 pts TVP/EP

vs

12.254 «contrôles» (cancers sans TVP/EP)

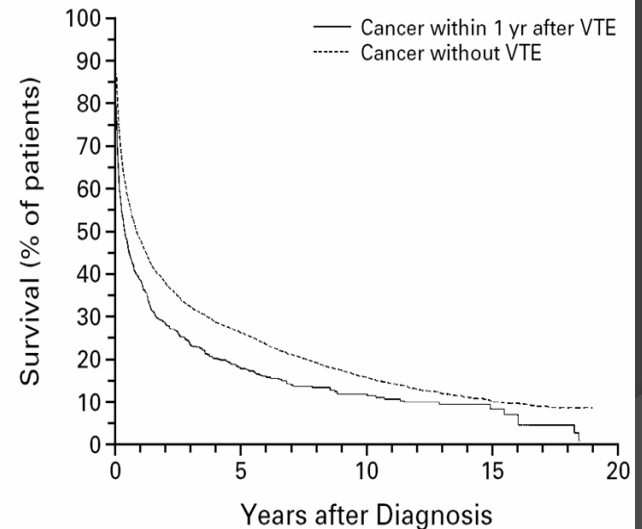
Poumon	16, 1%
Prostate	9,0%
Pancréas	8,8%
Colon/rectum	7,6%
...Sein...	...3,9%...



Causes de décès:
1. Cancer (>90%)
2. EP...

No. AT RISK

Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87



NO. AT RISK

Cancer within 1 yr after VTE	560	72	37	7
Cancer without VTE	5586	1181	419	106

TVP/EP selon Cancer Primitif

Registre Californie

235.249 cancers

TVP/EP:
3.775 (1,6%)

Poumon	822 (21,8%)
Colon-rect.	601 (16,1%)
Prostate	460 (12,2%)
Sein	375 (11,9%)
Pancréas	231 (6,1%)

...

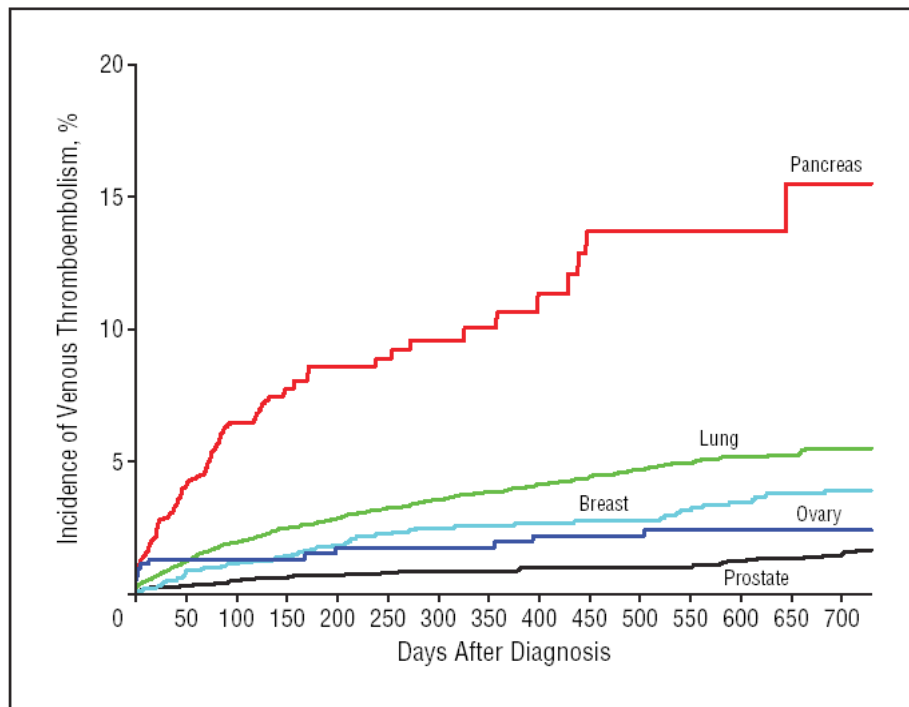
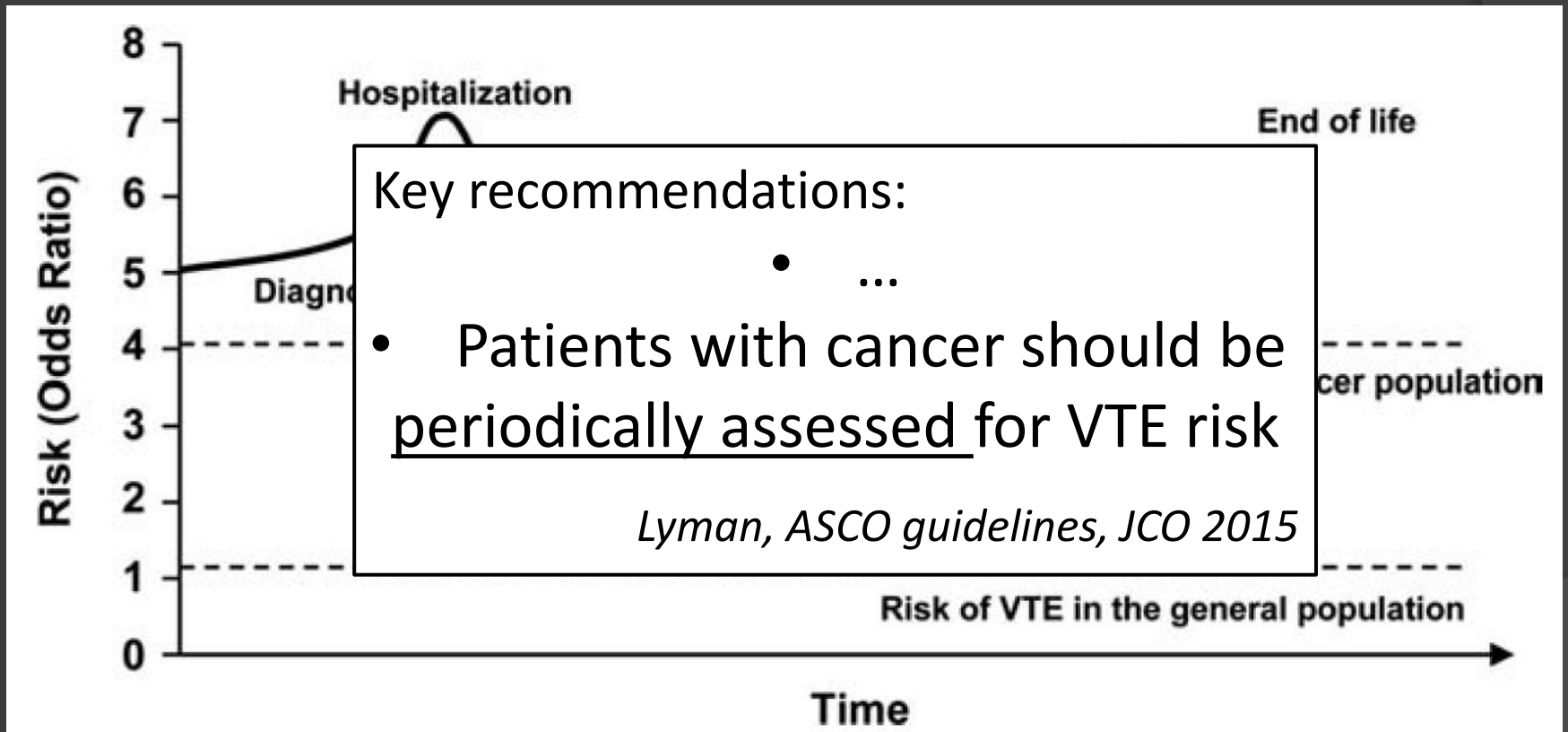


Figure 1. Kaplan-Meier plot of the incidence of venous thromboembolism within 2 years of diagnosis of 5 different types of cancer with metastatic-stage disease at the time of diagnosis.

Thrombose et Cancer: Evolution du Risque



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- ~~○ Les anticoagulants anticancéreux ?~~

MTEV et Cancer: Recommandations

- Juin 2008
- Février 2012



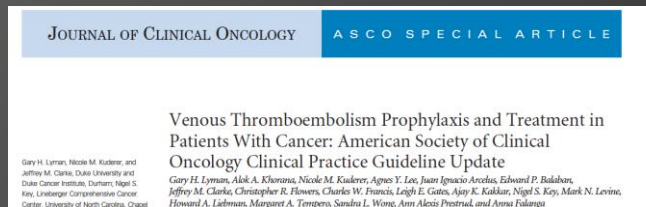
Antithrombotic Therapy for Venous Thromboembolic Disease*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Clive Kearon, MB, PhD; Susan R. Kahn, MD; Giancarlo Agnelli, MD; Samuel Goldhaber, MD, FCCP; Gary E. Raskob, PhD; and Anthony J. Comerota, MD

(CHEST 2008; 133:454S–545S)

- Octobre 2009
- Mai 2013
- Fevrier 2015



Lyman, JCO 2013;31:2189-204

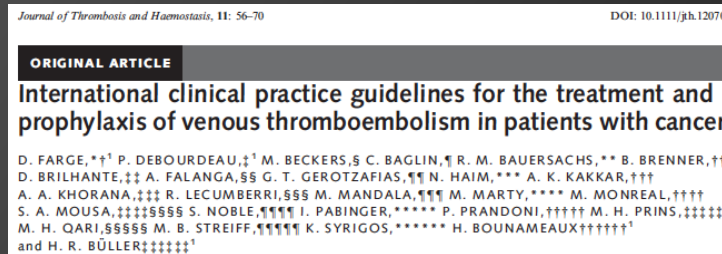
- Octobre 2009



Recommandations de bonne pratique Prévention et traitement de la MTEV en médecine

<http://www.afssaps.fr/>

- ISTH Juin 2013



Farge, JTH 2013;11:56-70
Debourdeau, JTH 2013, 11:71-80

- ESC Aout 2014

<http://www.escardio.org/guidelines>

Konstantinides, Eur Heart J 2014

MTEV et Cancer: Prévention

⊙ Patients Médicaux Hospitalisés

- Enoxaparine (Lovenox®) 40 mg /j
- Dalteparine (Fragmine®) 5000 U /j.
- Fondaparinux (Arixtra®) 2,5 mg /j
- Héparine calcique (Calciparine®) 5000 U X 2 /j.

Grade IA

⊙ Patients Chirurgicaux (chirurgie oncologique majeure)

- Prolonger la prévention jusqu'à 4-5 semaines post-op?

Grade IA-C

⊙ Patients Ambulatoires ?

Patients Ambulatoires Recevant une Chimiothérapie

Table 2. Comparison of Recommendations Regarding Prophylaxis against Venous Thromboembolism.*

Potential Indication	Recommended Use of Prophylaxis			
	Author	ACCP	ASCO	NCCN
Treatment of multiple myeloma with thalidomide or lenalidomide with doxorubicin, and other risk factors	Yes†	Suggest	Yes	Yes
Myelome + Thalidomide = prévention				
Cancer associated with high risk of venous thromboembolism (pancreatic or gastric)				
With other risk factors	Yes†	Suggest	Consider	Consider
Without other risk factors	Consider‡	No	Consider	Consider
Cancer associated with intermediate risk of venous thromboembolism (lung, ovarian, primary central nervous system, bladder, lymphoma)				
With other risk factors	Consider‡	Suggest	Consider	No
Without other risk factors	No‡	No	Consider	No
Cancer associated with low risk of venous thromboembolism				
With other risk factors	Consider‡	Suggest	Consider	No
Without other risk factors	No	No	Consider	No



Patients Ambulatoires Recevant une Chimiothérapie

		n	EP/TVP	NNT	Hem. Maj.
PROTECHT*	nadroparine vs placebo	769	1,4%	66	0,7%
	(≤ 4 mois)	381	2,9%		0
		poumon, colon...	($p=0,02$)		
SAVE- ONCO**	semuloparine vs placebo	1.608	1,2%	45	1,2%
	(médiane= 3,5 mois)	1.604	3,4%		1,1%
		poumon, colon...	($p<0,001$)		

*Agnelli, *Lancet Oncol* 2009;10:943-9

**Agnelli, *NEJM* 2012;366:601-9

TVP/EP: risque sous chimiothérapie

- Cohorte prospective de 4066 patients externes

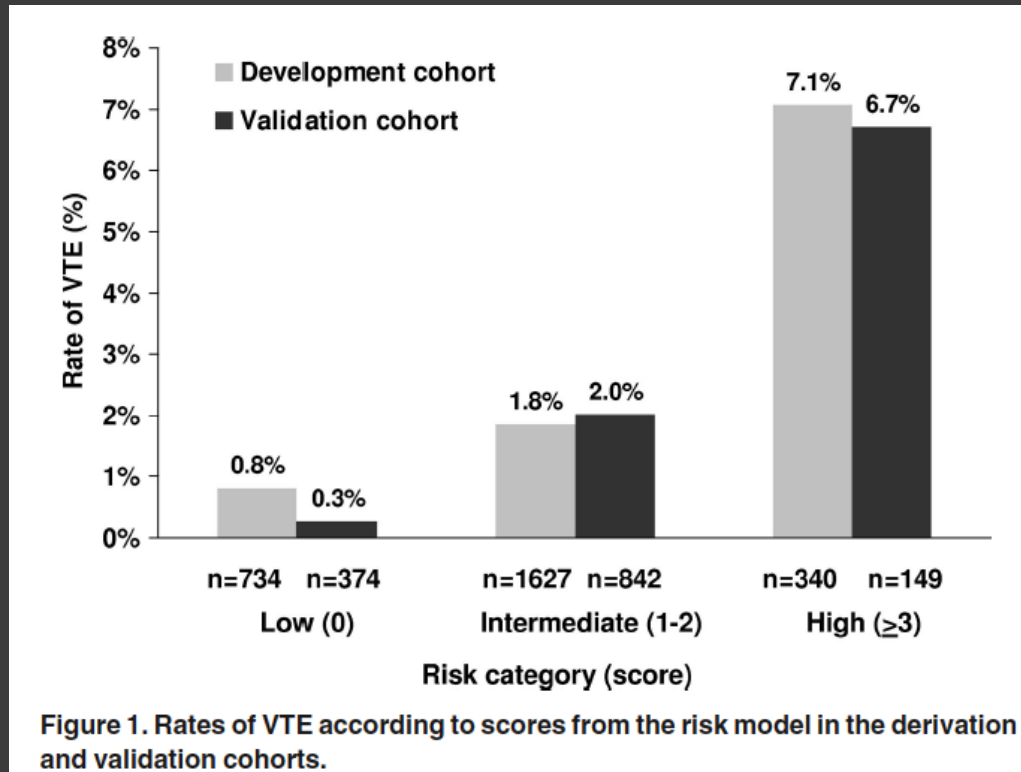
Table 3. Predictive model for chemotherapy-associated VTE

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $350 \times 10^9/L$ or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than $11 \times 10^9/L$	1
BMI 35 kg/m^2 or more	1

Khorana: 0= risque faible, 1-2= risque intermédiaire, ≥ 3 = risque élevé

*Khorana, Blood. 2008;111:4902-4907
(Thaler, Pabinger, Thromb Haemost 2012, 108(6):1042-8)*

TVP/EP et cancer: traitement préventif



- Risque à 3 mois
- calculable seulement AVANT traitement
- Tous primitifs et stades...
- % adjuvant inconnu...

Khorana, Blood. 2008;111:4902-4907

➔ Recherche: séparer primitifs, stades avancés, pendant chimio, autres facteurs de risque...

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Diagnostic EP/TVP et Cancer

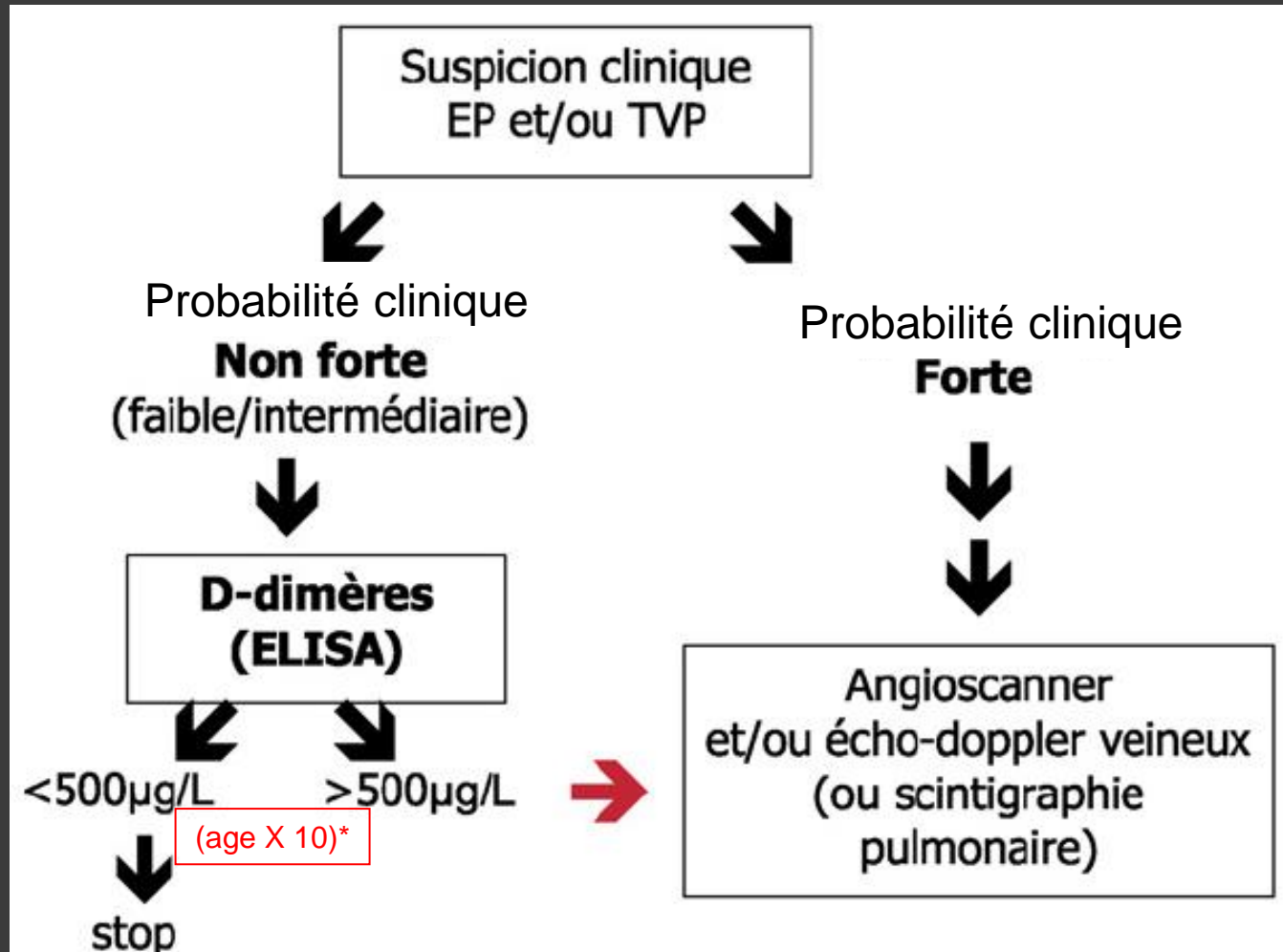
Cancer

+ TVP proximale et/ou EP

= traitement anticoagulant « à vie »

➔ **Rigueur diagnostique ++++**

Stratégies Diagnostiques EP/TVP



D-dimères et Cancer

1718 patients suspicion EP, probabilité clinique **non forte**

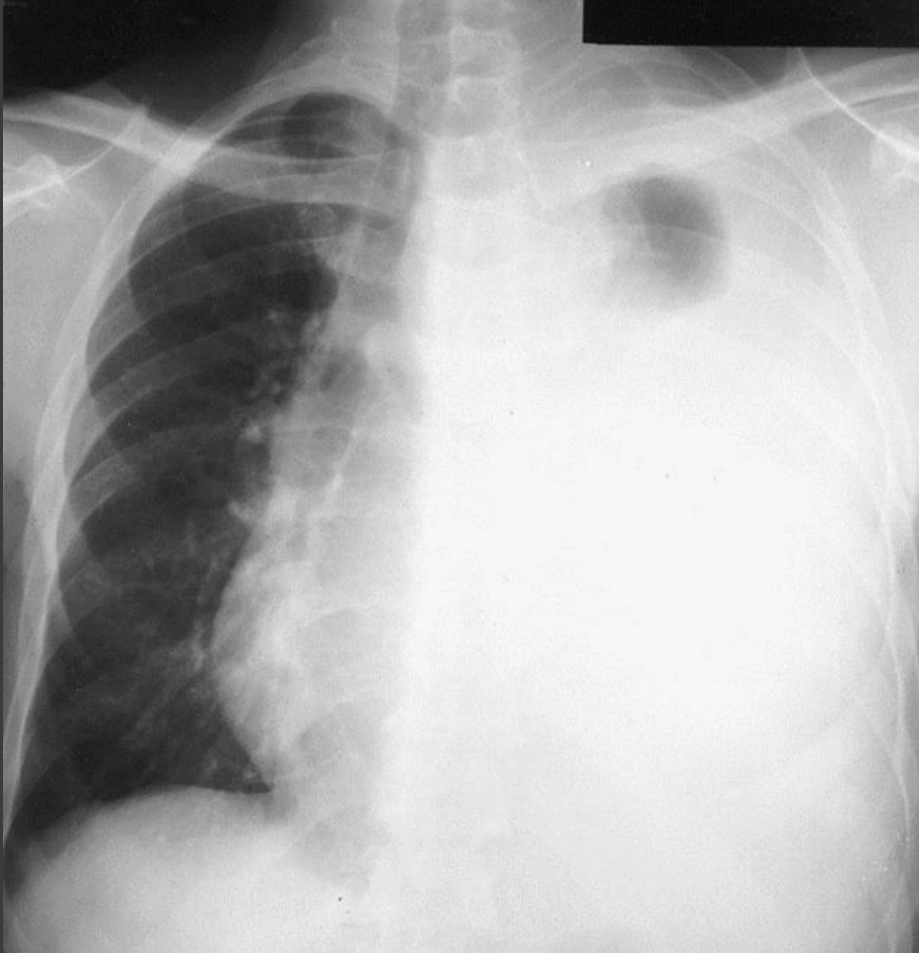
Characteristics	Cancer (n=164)	No cancer (n=1554)
Confirmed PE	54 (33%)	362 (23%)
Negative D-dimer test	18 (11%)	494 (32%)
Three-month follow-up		
– OAT for other indication than VTE	0	22
– Lost of follow-up	0	3
3-month thromboembolic risk		
No. of events in patients with negative D-dimer test and not receiving OAT	0 / 18	0 / 469
3-month thromboembolic risk (95% CI)	0% (0 to 18)	0% (0 to 0.8)
No. needed to test to rule out one PE	9.1	3.1

(Seuil = 500µg/L)

Tests Diagnostiques

- Probabilité(s) clinique(s)
- Scintigraphie pulmonaire
- D-dimères
- Echographie veineuse
- Angioscanner

Dyspnée et Cancer



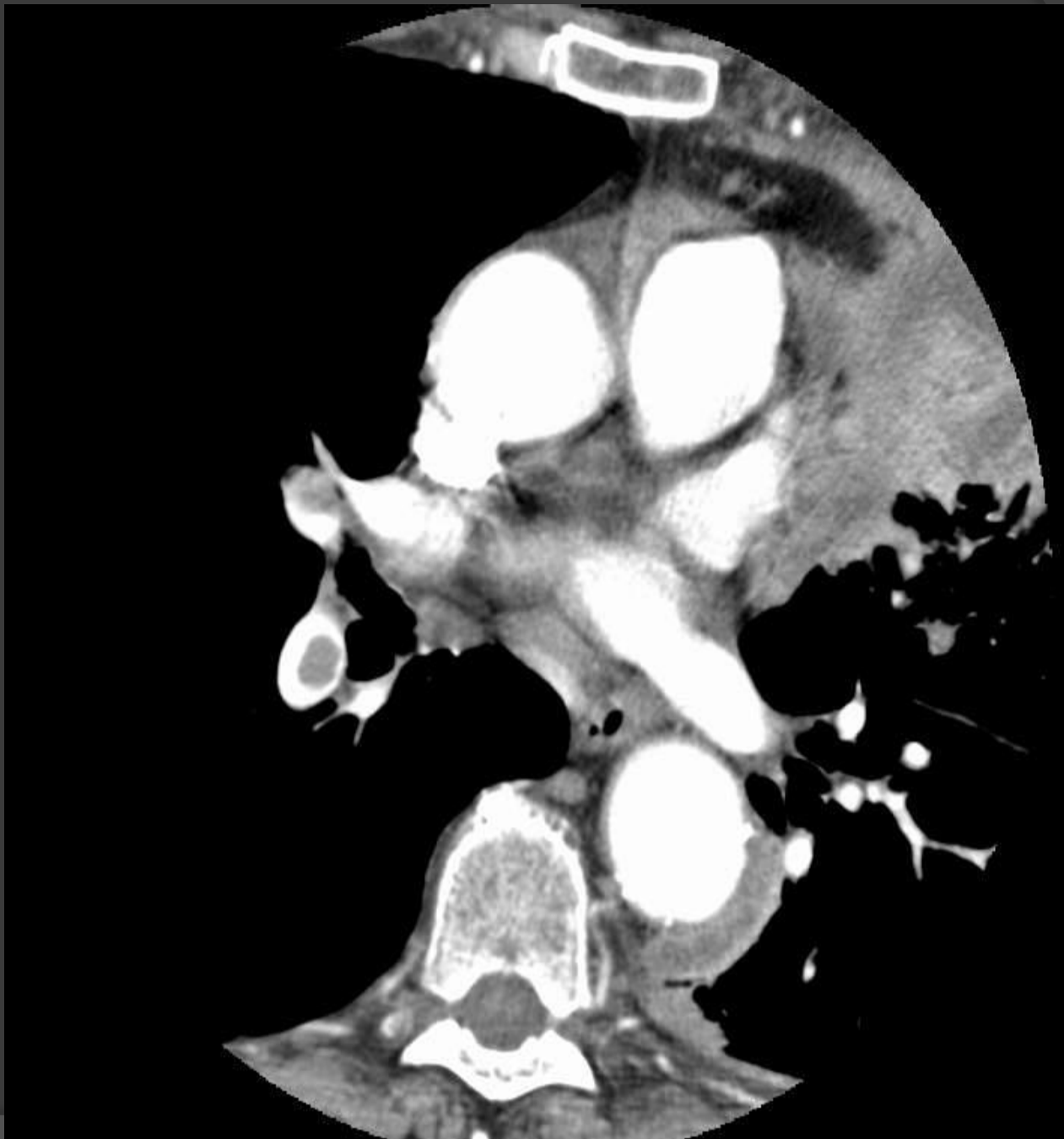
Les épanchements pleuraux
néoplasiques sont

5 à 10 fois

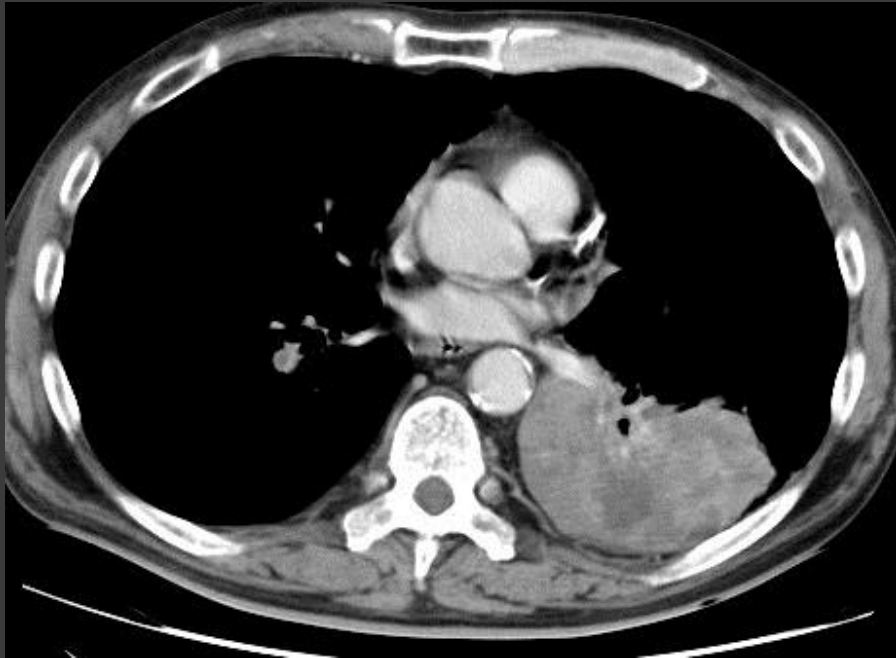
plus fréquents que l'EP !!!



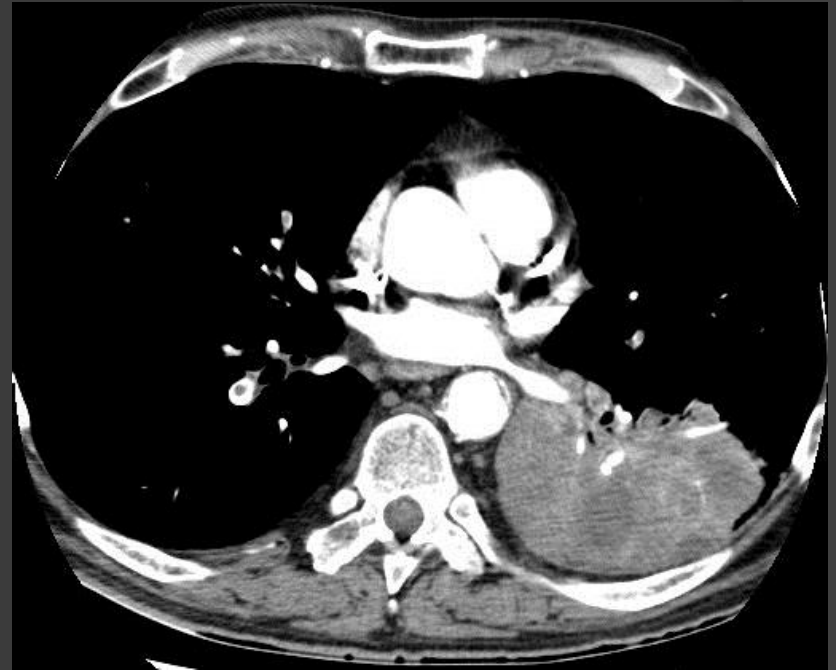
DFOV
1



Dyspnée et Cancer

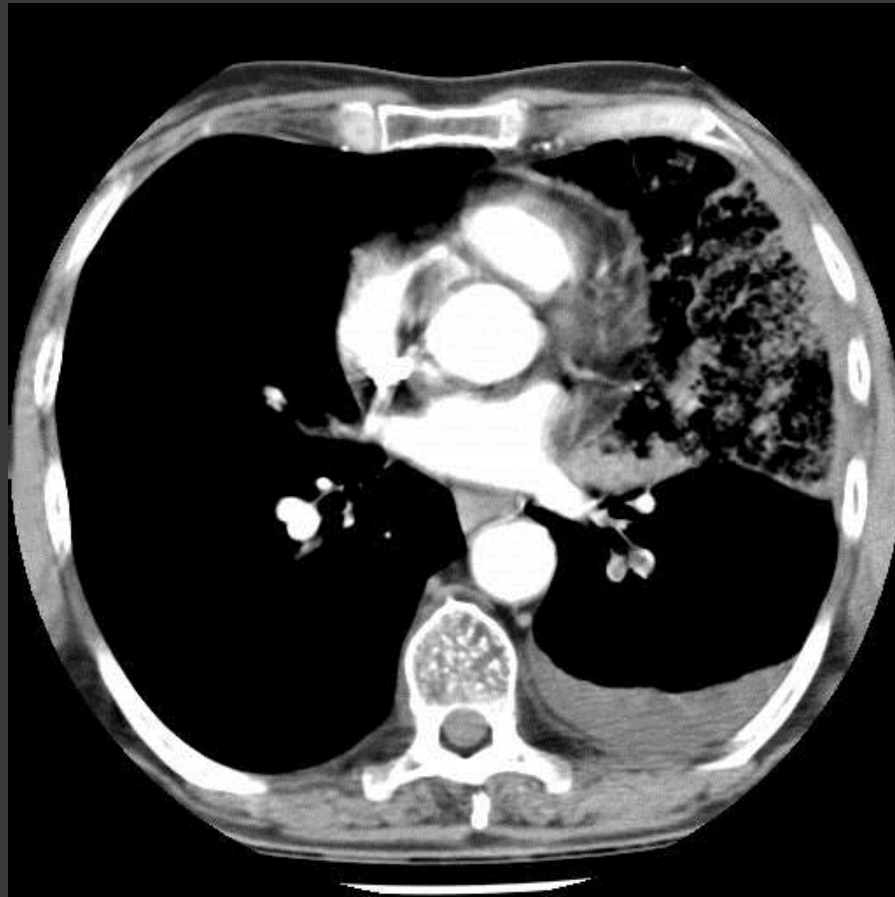


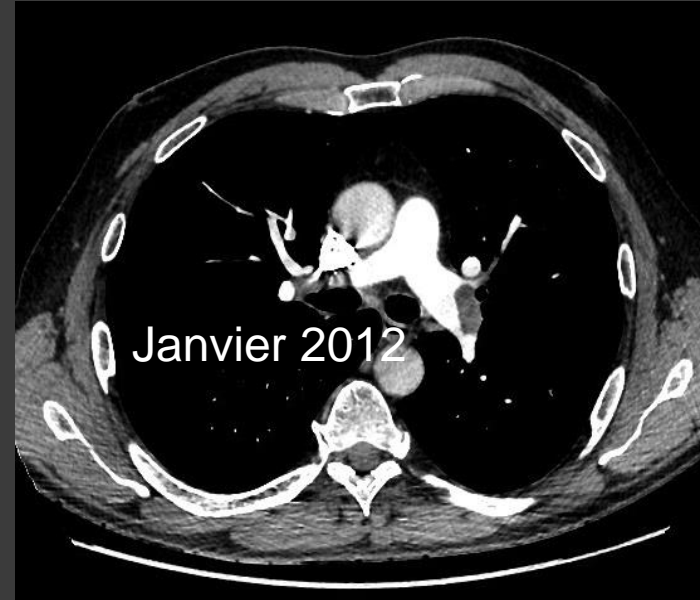
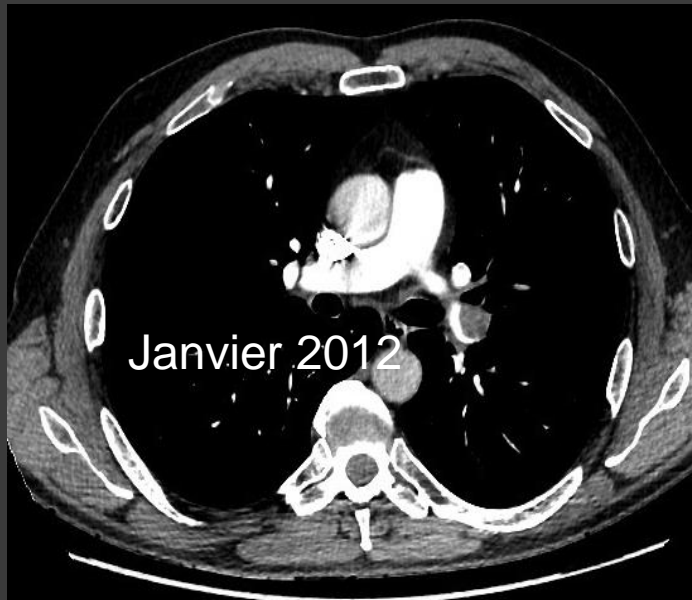
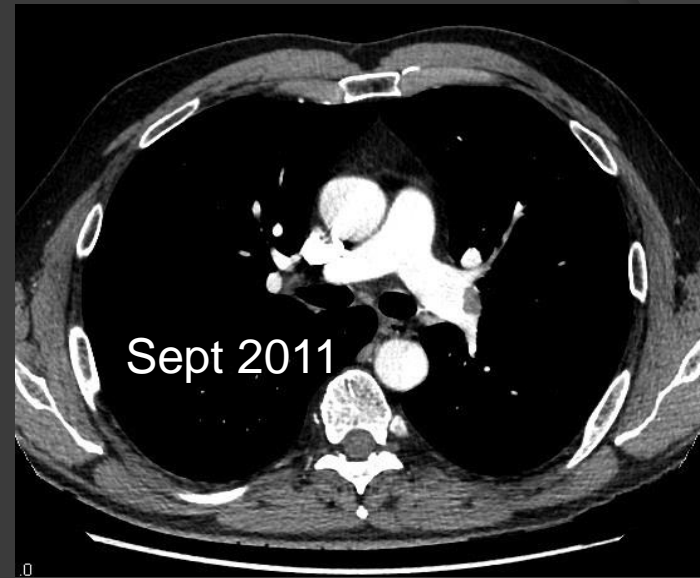
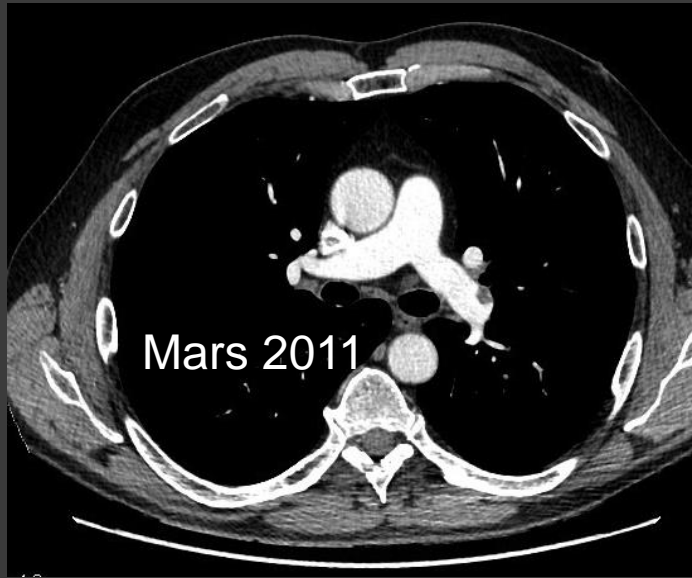
standard



angioscanner

Dyspnée et Cancer

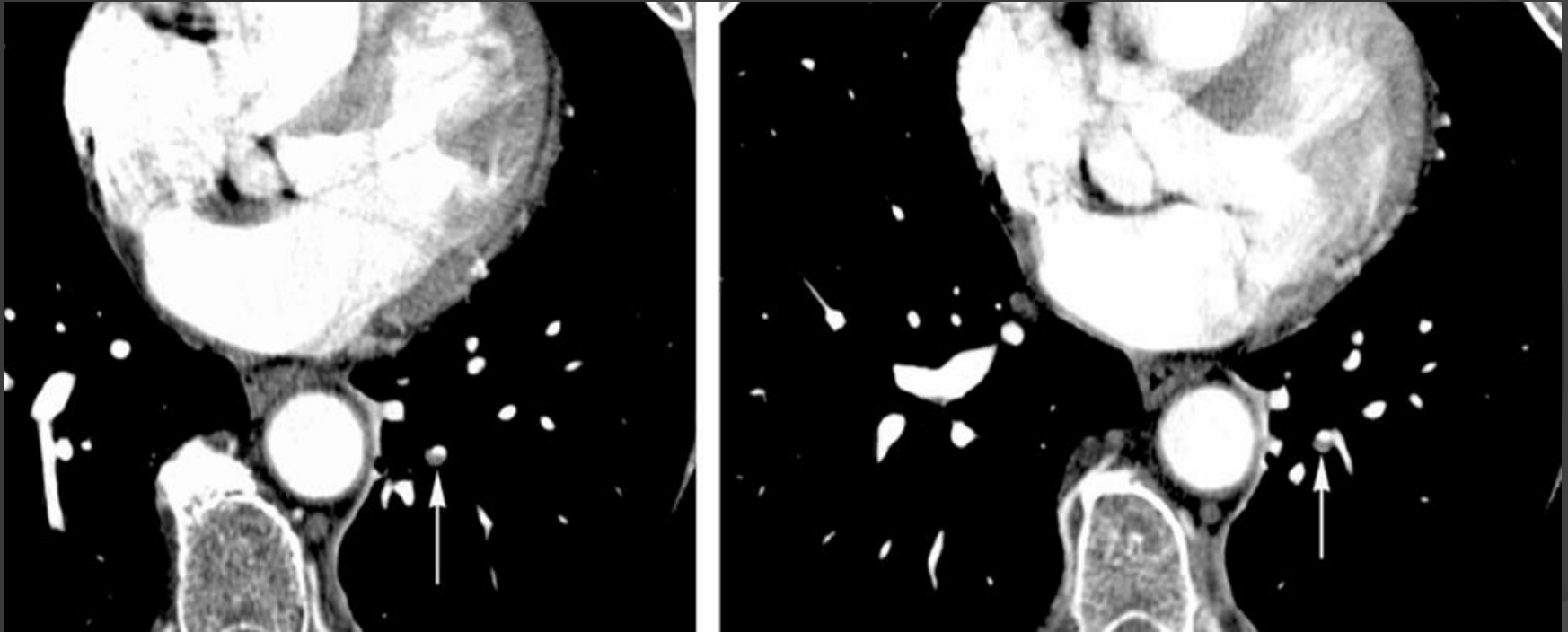




EP asymptomatiques

(« Unsuspected PEs »...)

- EP sous segmentaire isolée



Revel, Radiology 2005, 234:265-73

Risque de sur-traitement ?

Carrier, J Thromb Haemost 2010; 8: 1716-22

Angioscanner thoracique

BMJ

BMJ 2013;347:f3368 doi: 10.1136/bmj.f3368 (Published 2 July 2013)

Page 1 of 7

TOO MUCH MEDICINE

When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found

Renda Soylemez Wiener *assistant professor*^{1,2}, Lisa M Schwartz *professor*^{3,4}, Steven Woloshin *professor*^{3,4}

Risque de sur-traitement ?

Carrier, J Thromb Haemost 2010; 8: 1716-22

EP asymptomatiques

(« Unsuspected PEs »...)

	Ritchie, 2007	Farell, 2010
• Type de patients	hospitalisés	externes
• Nombre de scanners	487	440
- Cancer connu	340 (69.8%)	342 (77.7%)
• EP+	28 (5.7%)	10 (2.2%)
- Segm./ss-segm	18 (64%)	6 (60%)

Ritchie, Thorax 2007, 62:536–540

Farell, Clin Rad 2010, 65:1-5

Traiter les EP asymptomatiques ?

Rétrospectif 2004-2010:

51 pts EP asymptomatique + cancer
vs 144 pts EP symptomatique + cancer

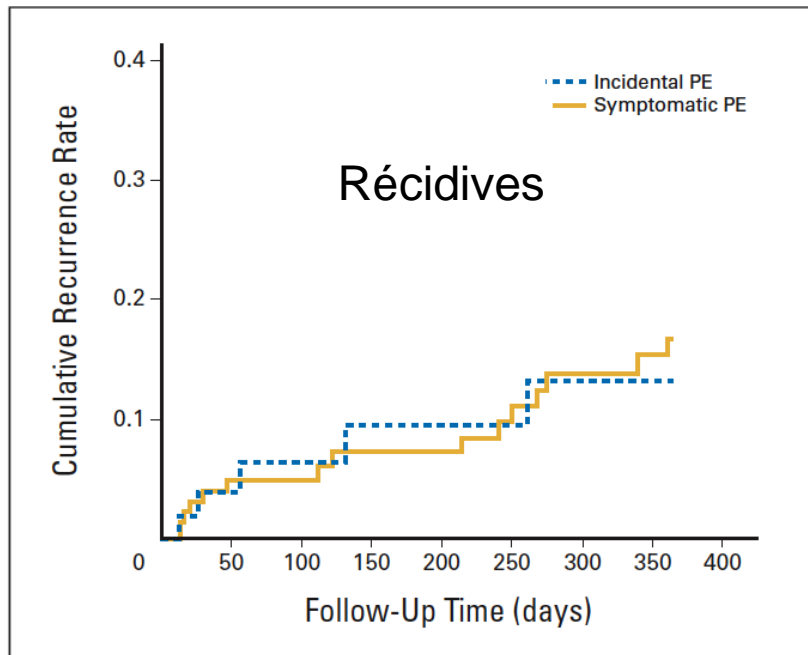


Fig 1. Cumulative risk of recurrent venous thromboembolism for patients with cancer with incidental versus symptomatic pulmonary embolism (PE; $P = .77$).

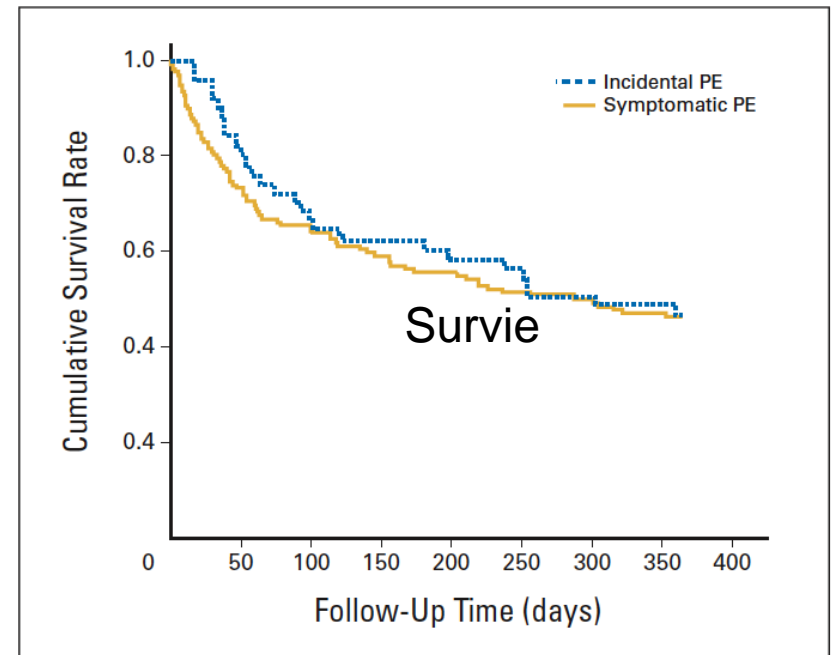


Fig 2. Kaplan-Meier cumulative survival curve until overall death for patients with cancer with incidental versus symptomatic pulmonary embolism (PE; $P = .70$).

EP asymptomatiques

(« Unsuspected PEs »...)

5.1.6. In patients who are unexpectedly found to have asymptomatic PE, we recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 1C).

Kearon, ACCP guidelines, Chest 2008;133:454S-545S

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B).

Kearon, ACCP guidelines, Chest 2012;141:e419S-e494S

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Traitement TVP/EP (J0-J90)

- AMM traitement initial EP (janvier 2015)
 - HNF (IVSE, dose adaptée TCA, ou SC 250UI/kg/12h)
 - Tinzaparine (Innohep®, 175UI/kg/24h)
 - Enoxaparine (Lovenox®, 100UI/kg/12h)
 - Fondaparinux (Arixtra®, 7,5mg/24h pour 50-100 kg)
 - Anticoagulants Oraux Directs (AOD)



puis
AVK
INR 2-3

Traitement EP : Cancer

Recommendations.

1 LMWHs are preferred over VKA for the early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) of VTE in cancer patients [Grade 1A].

Values and preferences: daily subcutaneous injection may represent a burden for patients.

HBPM > AVK

For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3–6 months.

IIa

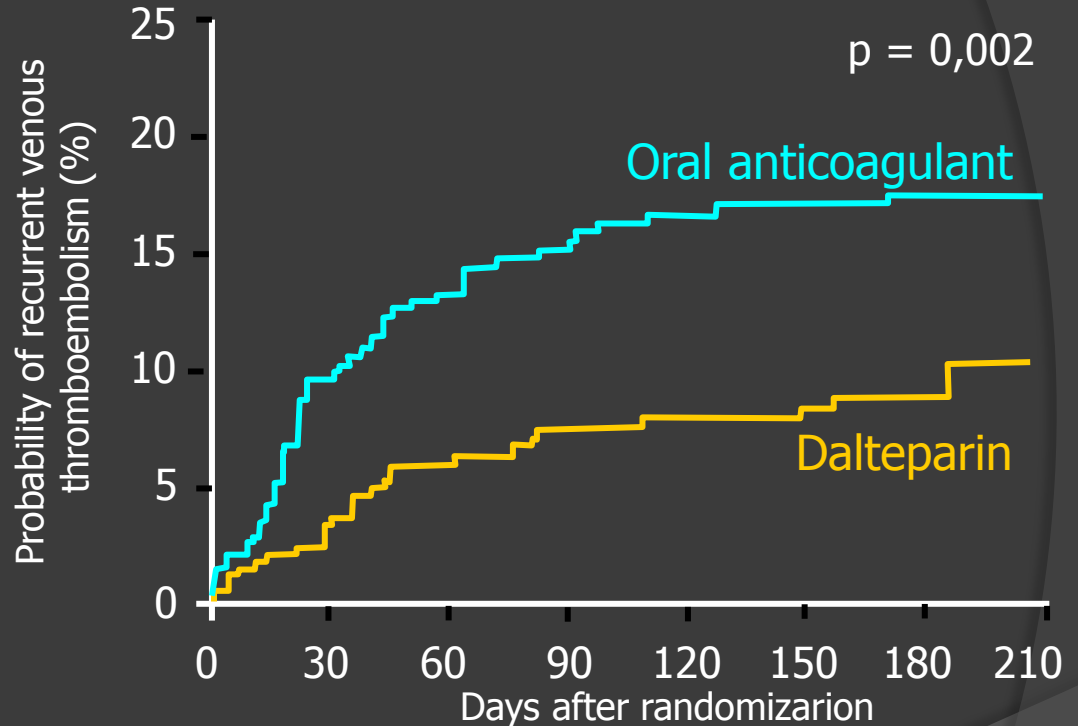
B

TVP et EP en cancérologie

CLOT
672 patients

HBPM
dalteparine 200 UI/kg/j
X 5 sem. puis 150 UI/kg/j
versus
AVK (INR 2-3)

x 6 mois



N° at Risk	0	30	60	90	120	150	180	210
Dalteparin	336	301	264	235	227	210	164	
Oral anticoagulant	336	280	242	221	200	194	154	



AMM en France:

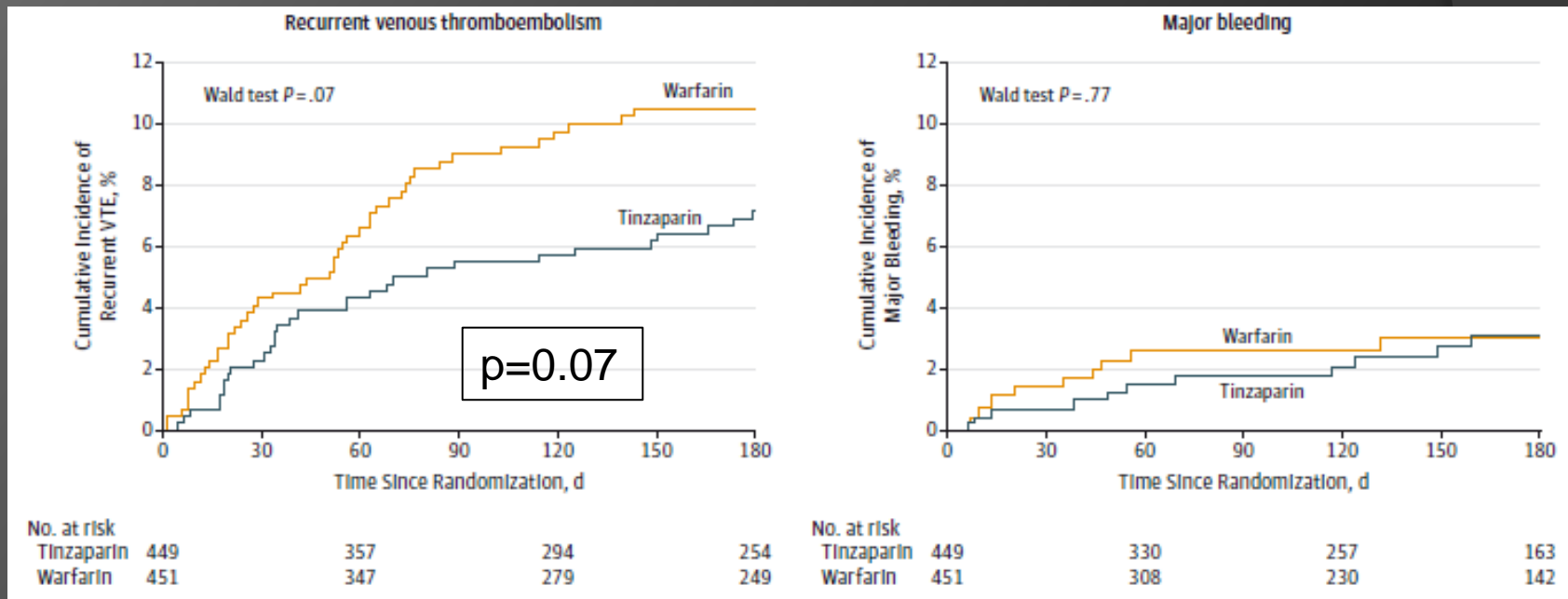
- Dalteparine 200 puis 150U/kg/j
- Tinzaparine 175 U/kg/j

TVP/EP et cancer: CATCH

- 900 patients, cancer « actif » + TVP/EP

« Active cancer » = malignancy + any of the following features:

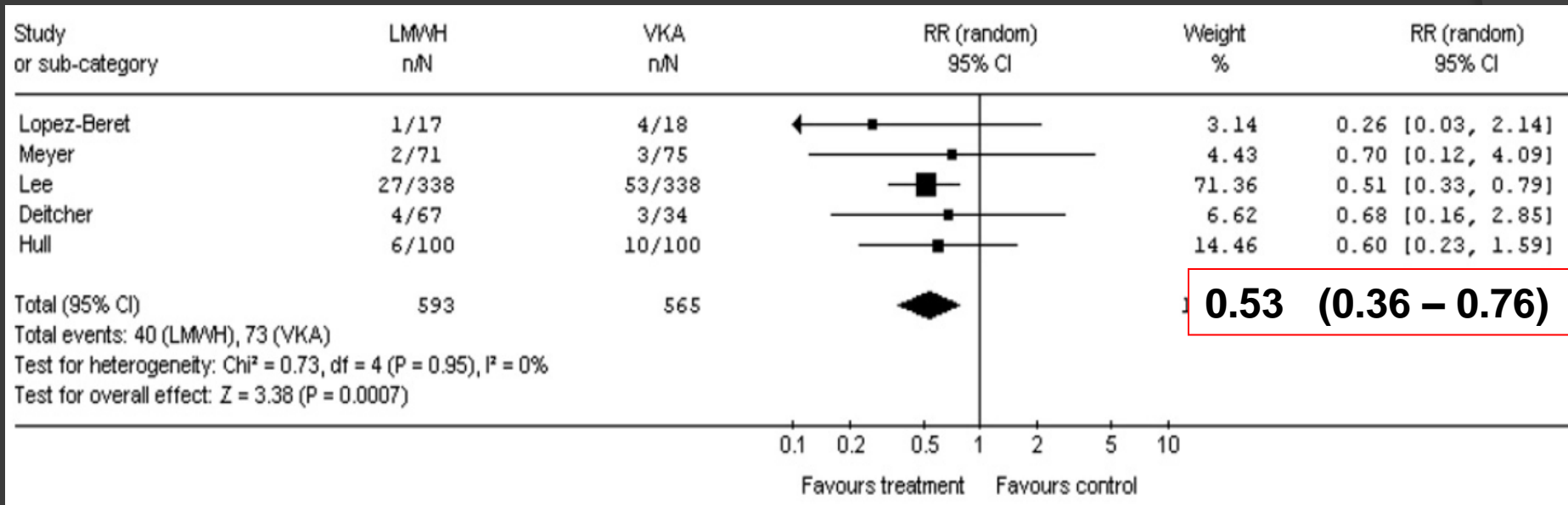
- cancer diagnosis within the previous 6 months;
- recurrent, regionally advanced, or metastatic disease;
- treatment for cancer during the previous 6 months;...



Cancer et EP/TVP:

HBPM vs AVK

- Récidives

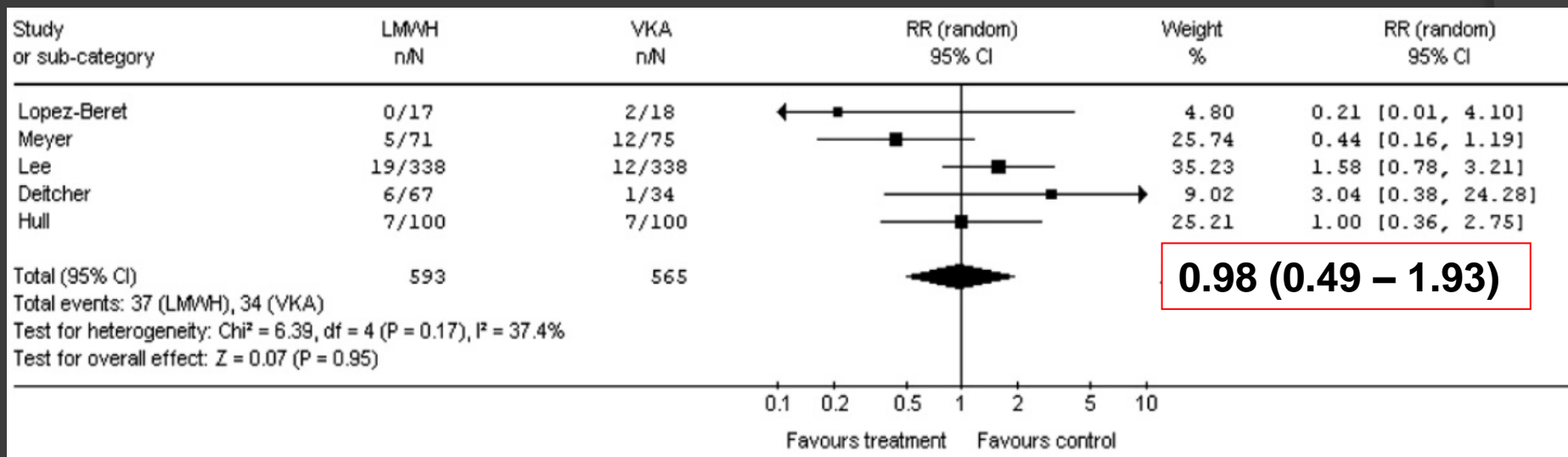


Louzada M et al. *Thromb Res* 2009; 123: 837-844
(Laporte, *Thromb Res* 2012, 130:853–858)

Cancer et EP/TVP:

HBPM vs AVK

- Hémorragies



Plaquettes ?

Surveillance

- Héparine 2 fois/semaine x 3 semaines
- HBPM **pas de surveillance**

Thrombopénie

- >50.000 pas de modif. traitement
- 20-50.000 ½ dose ?
- <20.000 arrêt (ou doses préventives??)

Lyman, ASCO guidelines, JCO 2013

<http://afssaps.fr>

MTEV et Cancer: Durée du traitement ?

6.4. In patients with PE and **active cancer**, if the risk of bleeding is not high (Table 2), we recommend **extended anticoagulant therapy** over 3 months of therapy (Grade 1B), and if there is a

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.

IIa

C

Kearon, ACCP Guidelines, Chest 2012

Konstantinides, ESC guidelines, Eur Heart J 2014

- Après 3-6 mois:
- poursuite HBPM ?
 - AVK ?
 - AOD ??

MTEV et cancer : après 3-6 mois ?

“Anticoagulation with LMWH or VKAs beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy”

[evidence: insufficient; strength: informal consensus, weak to moderate]

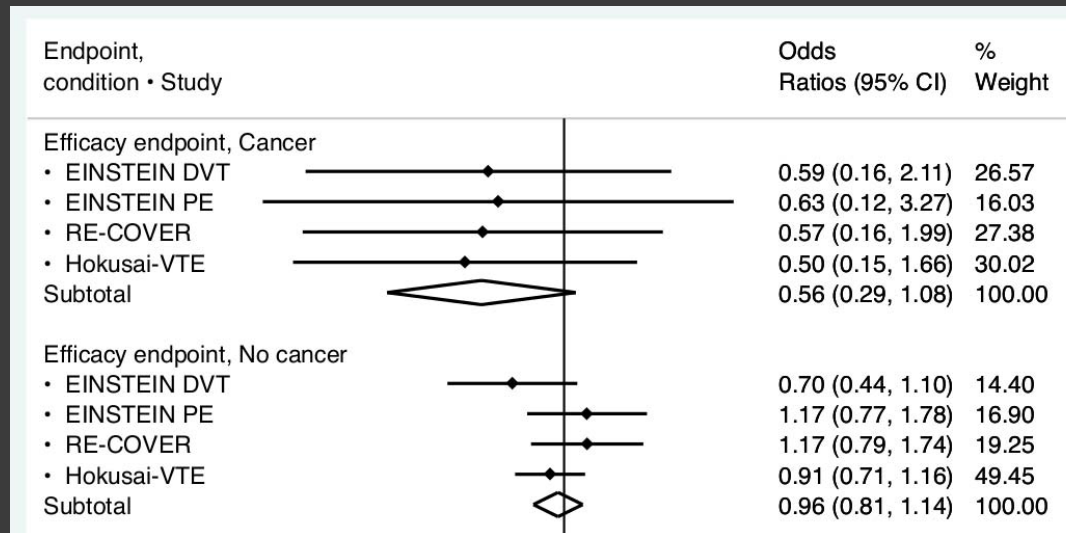
Lyman, ASCO guidelines, J Clin Oncol 2013; 31: 2189-204

“After 3–6 months, termination or continuation of anticoagulation (LMWH or VKA) should be based on individual evaluation of the benefit-risk ratio, tolerability, patients preference and cancer activity”

[Best clinical practice, in the absence of data]

Farge, ISTH guidelines, J Thromb Haemost 2013; 11: 56–70.

AOD et cancer ? ≥ 5 méta-analyses...



Larsen, *PLOS One* 2014,9(12): e114445

MAIS:

- 2-5% de cancer dans ces études (vs 15-20% dans la « vraie vie »)
- Peu de détails sur le type de cancer et son « activité »
- Pas de comparaison AOD vs HBPM

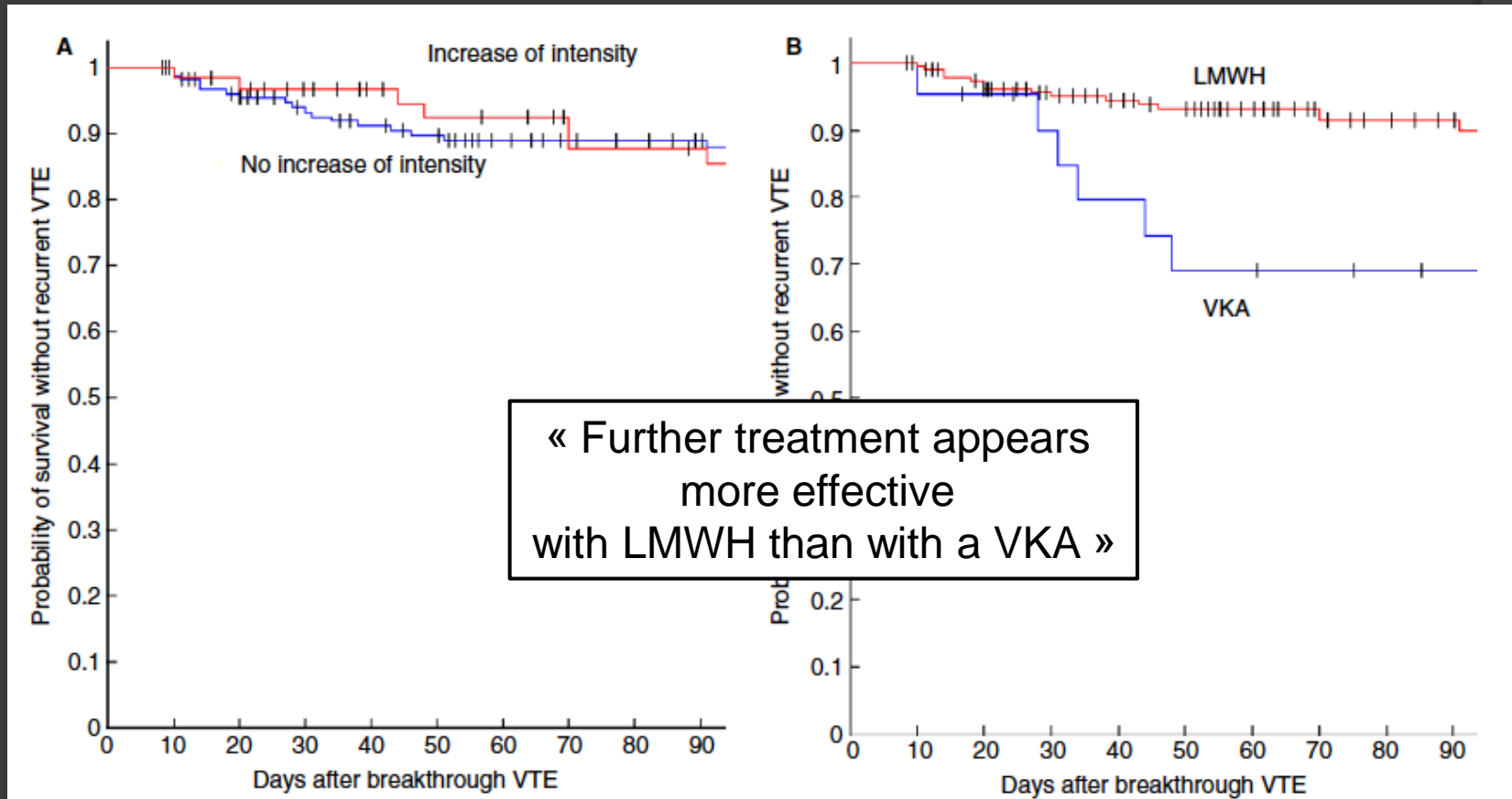
DONC: Pas d'AOD dans le cancer...pour l'instant.

Récidive EP/TVP ?

1. Vérifier le diagnostic de récurrence +++
2. Vérifier la qualité du traitement (dose, compliance...)
3. Patients sous AVK ?
 - passer aux HBPM
4. Patients sous HBPM ?
 - augmenter dose (+20%?), 2 inj./j.?...
 - (activité anti-Xa, HNF-IV...)
5. (Discuter filtre cave ??)(seulement si TVP proximale)

Récidive EP/TVP ?

Registre 212 patients cancer et **récidive** MTEV sous anticoagulants



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MTEV « non provoquée »: faut-il chercher un cancer?

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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*

MTEV « non provoquée »: faut-il chercher un cancer?

Stratégie de « screening limitée »

- Interrogatoire,
- Examen clinique complet
- Bilan biologique standard (NFS, bilan hépatique, fonction rénale)
- Radiographie pulmonaire
- Mammographie et frottis cervical
- Toucher rectal et dosage des PSA

Scanner abdominopelvien

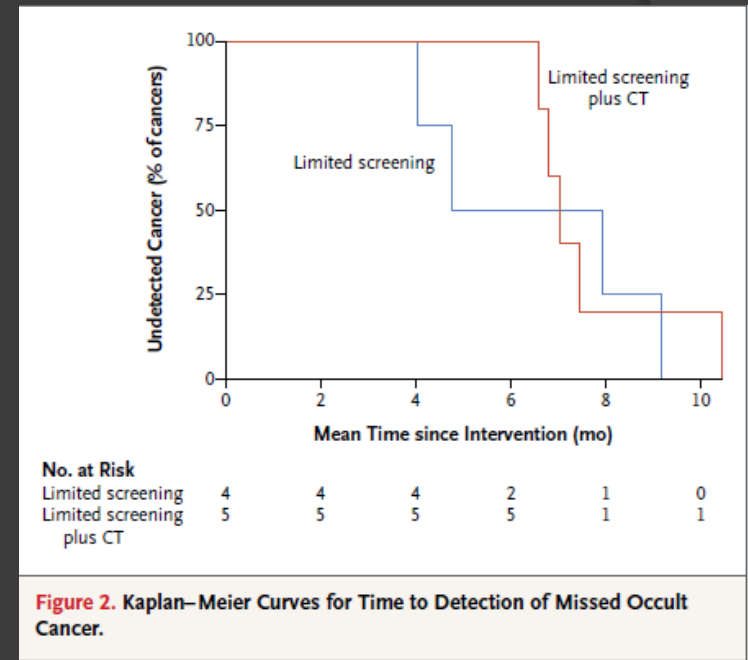
- 1^{er} temps type colo scanner et gastroscopie virtuelle
- Injection de produit de contraste

MTEV « non provoquée »: faut-il chercher un cancer?

854 patients randomisés

33 (3.9%) had a new diagnosis of occult cancer between randomization and the 1-year follow-up:

- 14 of the 431 patients (3.2%) in the limited-screening
 - 19 of the 423 patients (4.5%) in the limited-screening-plus-CT group
- ($P = 0.28$).



“Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit”

MTEV « non provoquée »: faut-il chercher un cancer?

Messages

- Pas de screening extensif
(pas de TEP, scanner abdominal...)
- points d'appel cliniques+++
- dépistage routine lié à l'âge/sexe
(sein, prostate, colon...)

MTEV et Cancer: Conclusions

- **MTEV et cancer**: association fréquente et grave
- **Diagnostic**: le plus rigoureux possible ++++
- **Prévention**: mieux cibler les populations à risque
- **Traitement**: HBPM > AVK (3-6 premiers mois)
- **Durée du traitement**: tant que le cancer est « actif »
- **Qualité des soins**: « RCP thrombose » ?...