THROMBOSE ET CANCER

- Antoine ACHKAR
- Service de Pneumologie
- CHES Hôpital Evreux-Vernon

G.I.T.A

AFMP BEUROUTH 2019

EURE SEINE HÔPITAL EVREUX-VERNON

Déclaration de Relations Professionnelles
Disclosure Statement of Financial Interest

J'ai actuellement, ou j'ai eu au cours des trois dernières années, une affiliation ou des intérêts financiers ou intérêts de tout ordre avec une société commerciale ou je reçois une rémunération ou des redevances ou des octrois de recherche d'une société commerciale :

I currently have, or have had over the last three years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company :

Affiliation/Financial Relationship

- Honoraires, invitations
- Consulting Fees/Honoraria

Company

- BMS-Pfizer, Boehringer Ingelheim, Elivie, Vivisol France, Aria, Isis Medical, Menarini, Novartis, AstraZeneca, ADIR Assistance, Roche

G.I.T.A

EURE SEINE
HÔPITAL EVREUX-VERNON

PREAMBULE

Patient avec thrombose et cancer

Raisons de la vulnérabilité

- **Patients avec thrombose et cancer : Caractéristiques**
- **Patients avec thrombose et cancer : Fragilité, vulnérabilité**

  Récidives et hémorragies sous traitement anticoagulant
- **Patients avec thrombose et cancer**

  Médicaments
- **Patients avec thrombose et cancer : vulnérabilité**

  Enjeu pour l'oncologue

  Besoin d'une collaboration oncologue/spécialiste thrombose

Patients avec thrombose et cancer

Les essais thérapeutiques

	CLOT Trial[8]	CATCH Trial[9]
Number of Patients	676	900
Study Design	Open-label, multicenter, RCT	Open-label, multicenter, RCT
LMWH Preparation*	Dalteparin	Tinzaparin
Mean Age	62 years dalteparin/63 years warfarin	59.7 years dalteparin/58.8 years warfarin
Tumor Types		
Breast	16%	9%
Colorectal	16%	13%
Lung	13%	12%
Genitourinary tract	13%	10%
Gynecologic system	10%	23%
Hematologic	10%	10%
Eastern Cooperative Oncology Group Score**		
0-1	63%	77%
2	36%	23%
Active Cancer Treatment***	78%	53%
Metastatic Disease	67%	55%
Time in Therapeutic Range (Warfarin Arm)	46%	47%

*Dalteparin 200 IU/kg x 1 month followed by 150 IU/kg for 5 months; tinzaparin 175 IU/kg x 6 months
**8 patients with ECOG 3 enrolled in CLOT trial prior to study amendment excluding these patients
***Including chemotherapy, radiation, or surgery

Lee A, et al. NEJM 2003
Lee A, et al. JAMA 2015

Copyrights apply

Patients avec thrombose et cancer:

RIETE Registry

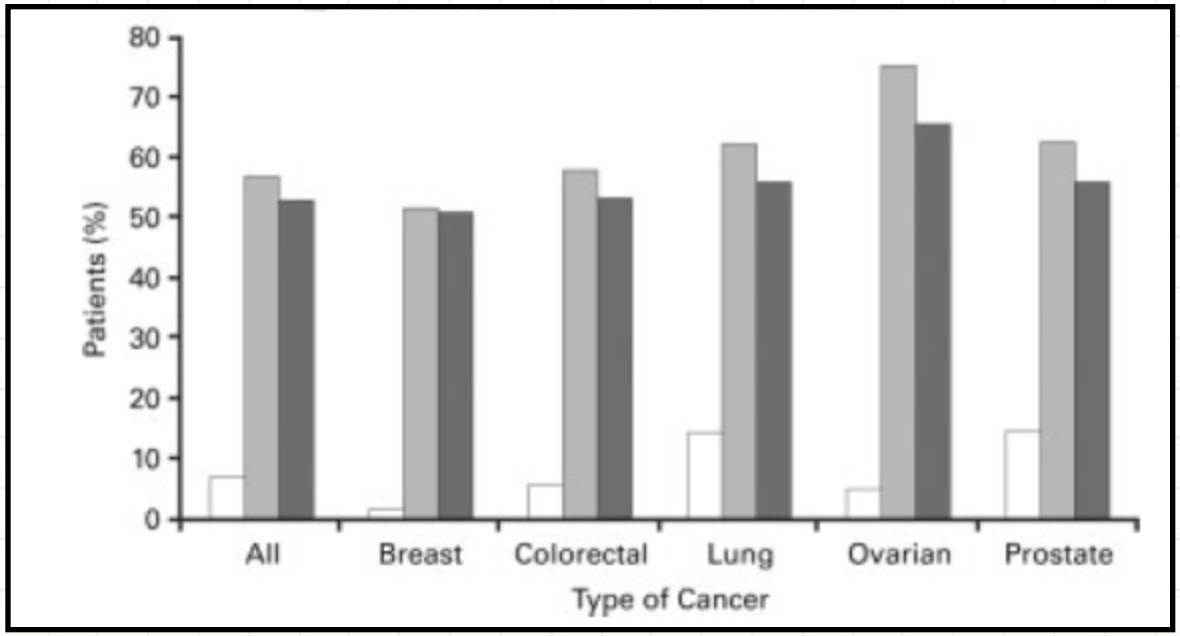
Patients		VKA start <7 days	VKA start >7 days	LMWH alone
	N	*1,516*	*619*	*4,210*
Clinical characteristics				
	Gender (males)	840 (55%)	350 (57%)	2,243 (53%)
	Mean age (years±SD)	70±12	67±13‡	66±13‡
	Age >75 years	632 (42%)	199 (32%)	1176 (28%)
	Body weight (kg±SD)	74±13	73±13	71±14‡
Underlying conditions				
	Chronic heart failure	87 (5.7%)	31 (5.0%)	152 (3.6%)‡
	Chronic lung disease	199 (13%)	70 (11%)	377 (9.0%)‡
	CrCl level 30–60 ml/min	575 (38%)	226 (37%)	1,454 (35%)
	CrCl levels <30 mL/min	87 (5.7%)	30 (4.8%)	253 (6.0%)
	Recent major bleeding	15 (1.0%)	18 (2.9%)†	95 (2.3%)†
	Anemia	757 (50%)	361 (58%)‡	2,926 (70%)‡
Cancer characteristics				
	Metastases	455 (30%)	200 (32%)	2,550 (61%)‡
Initial VTE presentation				
	Pulmonary embolism	791 (52%)	331 (54%)	2,060 (49%)*
	Proximal DVT alone	627 (41%)	246 (40%)	1,952 (46%)‡
	Bilateral DVT alone	27 (3.7%)	19 (6.6%)*	143 (6.7%)†
	Upper-extremity DVT	46 (6.3%)	32 (11%)*	395 (18%)‡

Copyrights apply

Mahé I, Sterpu R, Bertoletti L, et al. Plos One 2015

Cancer et IR: association fréquente

- **Renal Insufficiency and Anticancer Medications (IRMA) study group (4684 pts)**
  - RI in 50–60 % of patients with solid tumours, whereas SCR were normal in most patients
  - Of the 7181 prescriptions : 80% received potentially nephrotoxic drugs
  - Nephrotoxicity of chemotherapeutic agents tends to increase with decreasing renal function

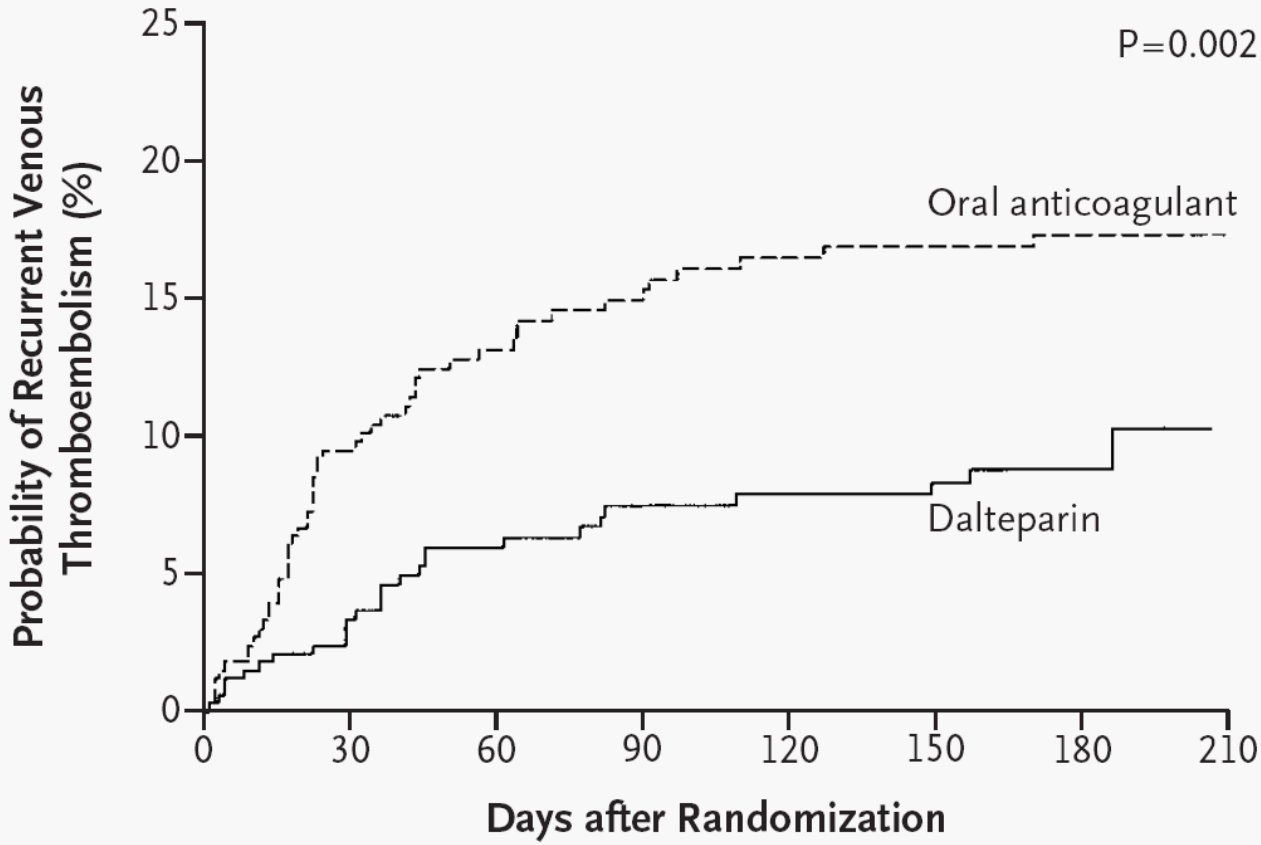


Serum Creatinine >110 mL/min
Creatinine Clearance <90 mL/min: Cockcroft-Gault
Creatinine Clearance <90 mL/min: aMDRD

Launay Vacher V, et al. Cancer 2007

Copyrig

The CLOT Study

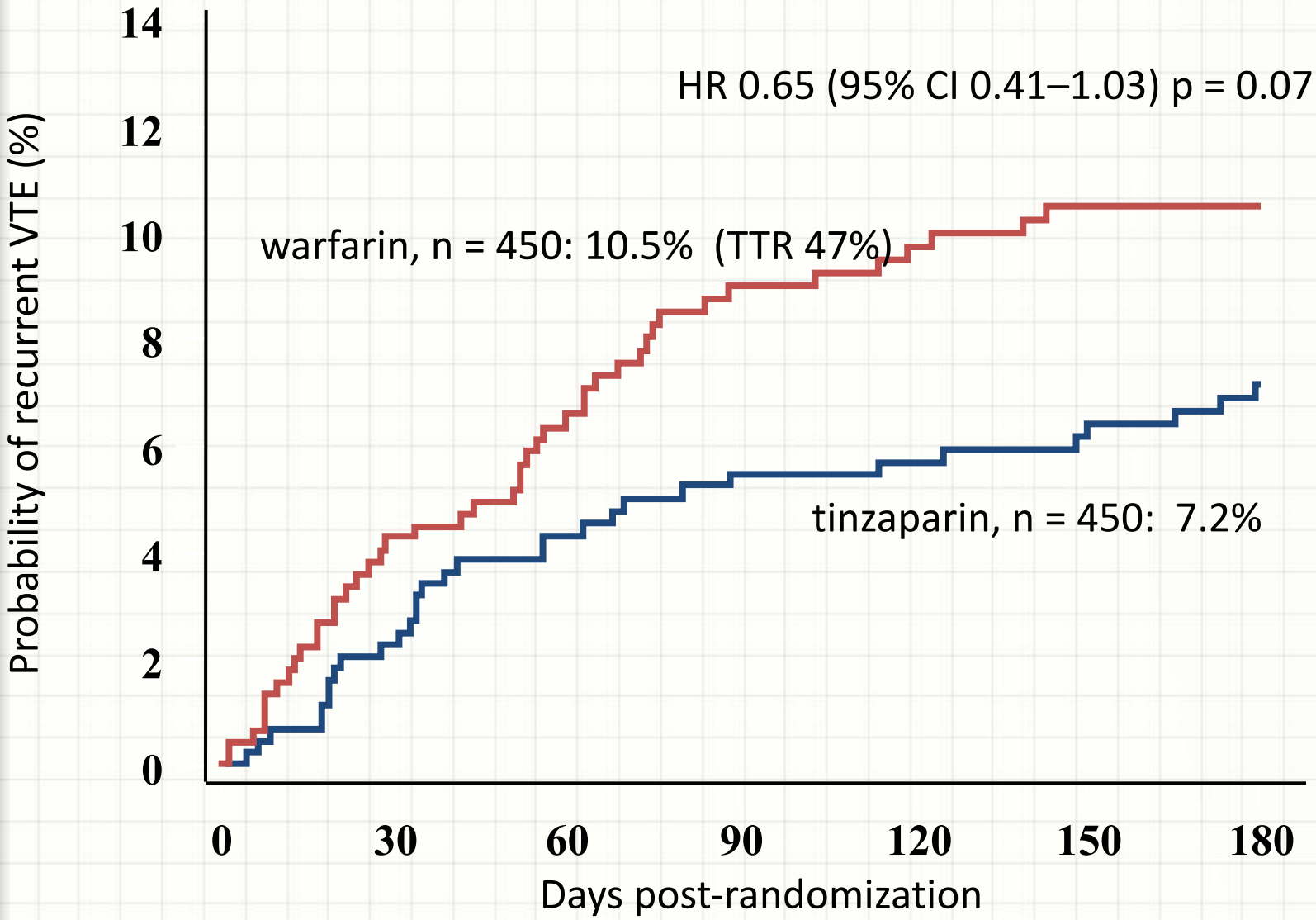


No. at Risk

Dalteparin	336	301	264	235	227	210	164
Oral anticoagulant	336	280	242	221	200	194	154

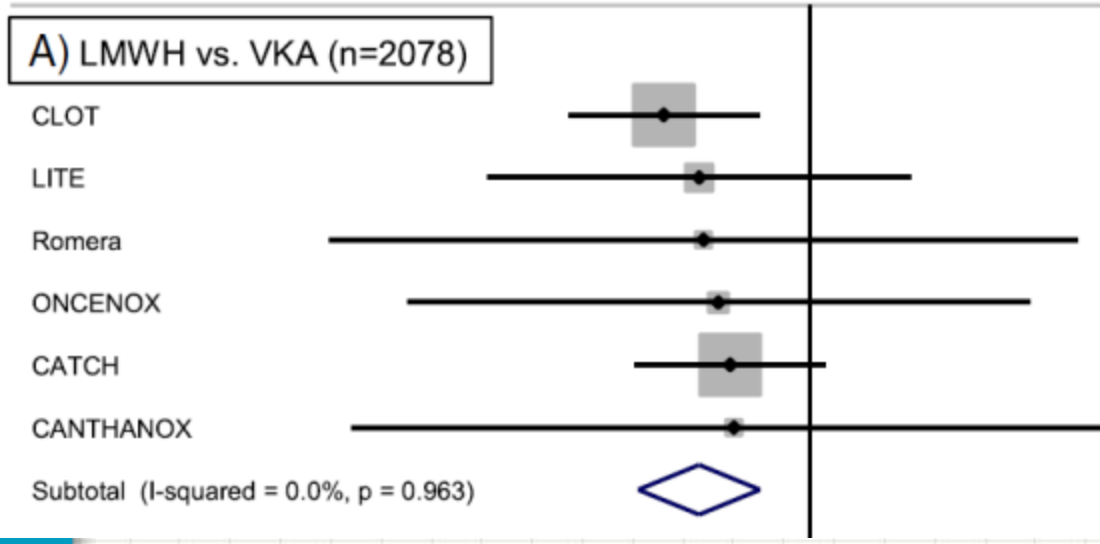
Lee A. et al. *N Engl J Med* 2003; 349: 146-153

CATCH. Récidives thromboemboliques



Lee A. et al. *JAMA* 2015; 314: 677-86

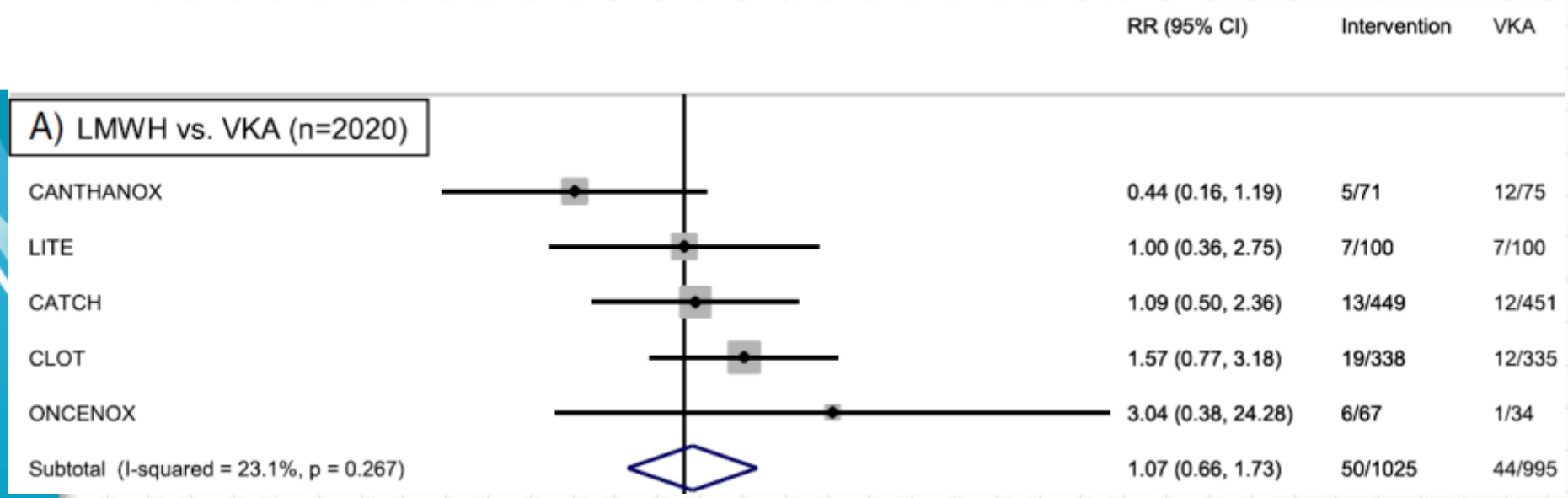
HBPM vs AVK après CATCH: efficacité



	RR (95% CI)	Events, Intervention	Events, VKA
CLOT	0.51 (0.33, 0.79)	27/336	53/336
LITE	0.60 (0.23, 1.59)	6/100	10/100
Romera	0.61 (0.11, 3.43)	2/36	3/33
ONCENOX	0.66 (0.16, 2.74)	4/61	3/30
CATCH	0.69 (0.45, 1.07)	31/449	45/451
CANTHANOX	0.70 (0.12, 4.09)	2/71	3/75
Subtotal (I-squared = 0.0%, p = 0.963)	0.60 (0.45, 0.79)	72/1053	117/1025

Posh F. et al. *Thromb Res* 2015;136: 582-89.

HBPM vs AVK après CATCH: sécurité



Posh F. et al. *Thromb Res* 2015;136: 582-89.

Les médecins ne suivent pas les recommandations

	VKA
Imberti (Italy); n = 424	64%
Gussoni (RIETE) n = 5483	32%
Spirk (Switzeland) n = 315	51%
Belhadj Chaidi (France) n = 145	23%
Kleinjan (International)* n = 141	18%

* Survey on 141 doctors

Imberti D. *et al. Haematologica* 2008 ; 93: 273-278.
Gussoni G. *et al. Thromb Res* 2013; 131: 24-30
Spirk D. et al. *Thromb Haemost* 2011; 105: 962–967
Belhadj Chaidi et al. *J Mal Vasc* 2013; 38: 185-92
Kleinjan A. et al. *Thromb Haemost* 2013 August 15

Problèmes liés au traitement prolongé par HBPM

- Injections
- Plaquettes
- Coût: 8.60 euros to 16.90 euros
- Infirmière
- Hématomes
- Récidives: 7%
- Hémorragies: 3-7%

Patients atteints de cancer dans les essais de phase III AOD

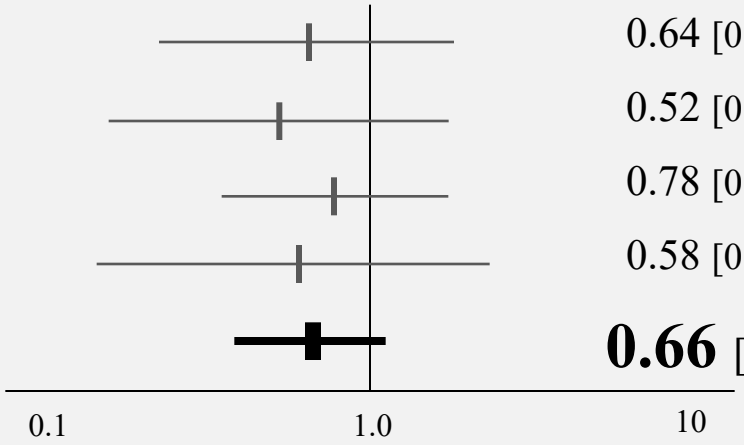
Essai	HBPM-AVK	AOD
Einstein (DVT-PE)	198	232
RECOVER-I-II	107	114
Amplify	77	66
Hokusai	99	100

Prins M. et al. *Thromb Journal* 2013; 11: 21
Schulman S. et al. *Circulation* 2013; Dec 16
Agnelli G. et al. *N Engl J Med* 2013; 369:799-808
Buller H. et al. *N Engl J Med 2013*; 369:1406-15

AOD MTEV et cancer : méta-analyse

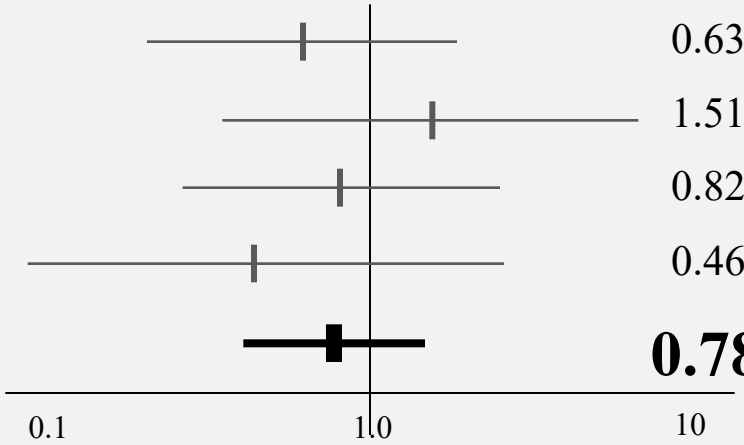
Rec ETE

	AOD	enox/AVK	RR [CI95%]
EINSTEIN	6/232	8/198	0.64 [0.23 ; 1.81]
HOKUSAI	4/109	7/99	0.52 [0.16 ; 1.72]
RECOVER	10/173	12/102	0.78 [0.35 ; 1.76]
AMPLIFY	3/81	5/78	0.58 [0.14 ; 2.34]
total	25/595	32/537	**0.66** [0.39 ; 1.11]



Hgie majeure

	AOD	enox/VKA	
EINSTEIN	6/232	8/196	0.63 [0.22 ; 1.79]
HOKUSAI	5/109	3/99	1.51 [0.37 ; 6.17]
RECOVER	6/159	7/152	0.82 [0.28 ; 2.36]
AMPLIFY	2/87	4/80	0.46 [0.09 ; 2.44]
total	19/587	22/527	**0.78** [0.42 ; 1.44]



Carrier M. et al. *Thromb Res* 2014;134:1214-9.

Einstein, Hokusai, Amplify CLOT, CATCH

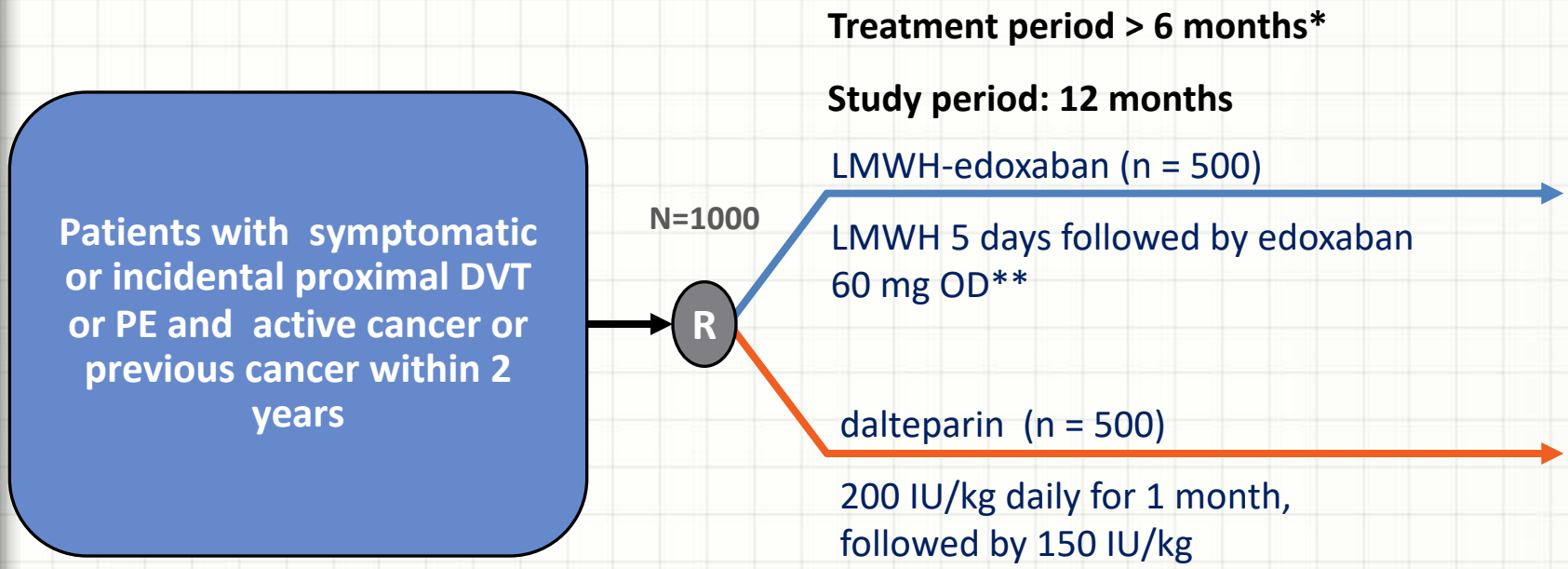
	Einstein (n = 655)	Hokusai (n = 208)	Amplify (n = 169)	CLOT (n = 672)	CATCH (n = 900)
Cancer récidivant ou métastatique	22%	20.7%	Approx 1/3	67.3%	54.7%
TT anticancéreux	13%*	30.8%	NA	77.7%**	42.4%***
% INR 2-3	57%-59%	63%%	57.5%	46%	47%

*: chimiothérapie,
**: tous traitements,
***: traitement systémique(chimio thérapeutique ciblée ou hormonothérapie)

Lee A. et al. *N Engl J Med* 2003; 349: 146-153
Prins M H. et al. *Lancet Haematol*. 2014; 1: e37–46
Lee A. et al. *JAMA* 2015; 314: 677-86
Agnelli G. et al. *J Thromb Haemost* 2015; 13: 2187–91

AOD vs HBPM: HOKUSAI CANCER

Prospective, randomised, open-label, multicentre study comparing dalteparin with LMWH-edoxaban for 12 months



Primary outcome: Recurrent VTE (symptomatic VTE, incidental VTE or death due to PE) or Major bleeding

* Intention is to treat patients for 12 months with the study treatment, but continuation of anticoagulation beyond six months will be based on the risk-benefit assessment of the treating physician and/or the patient preference

**Dose adjustment to 30 mg od in patients with body weight ≤ 60 kg, creatinin clearance between 30 and 50 ml/min or concomitant use of P-glycoprotein inhibitors

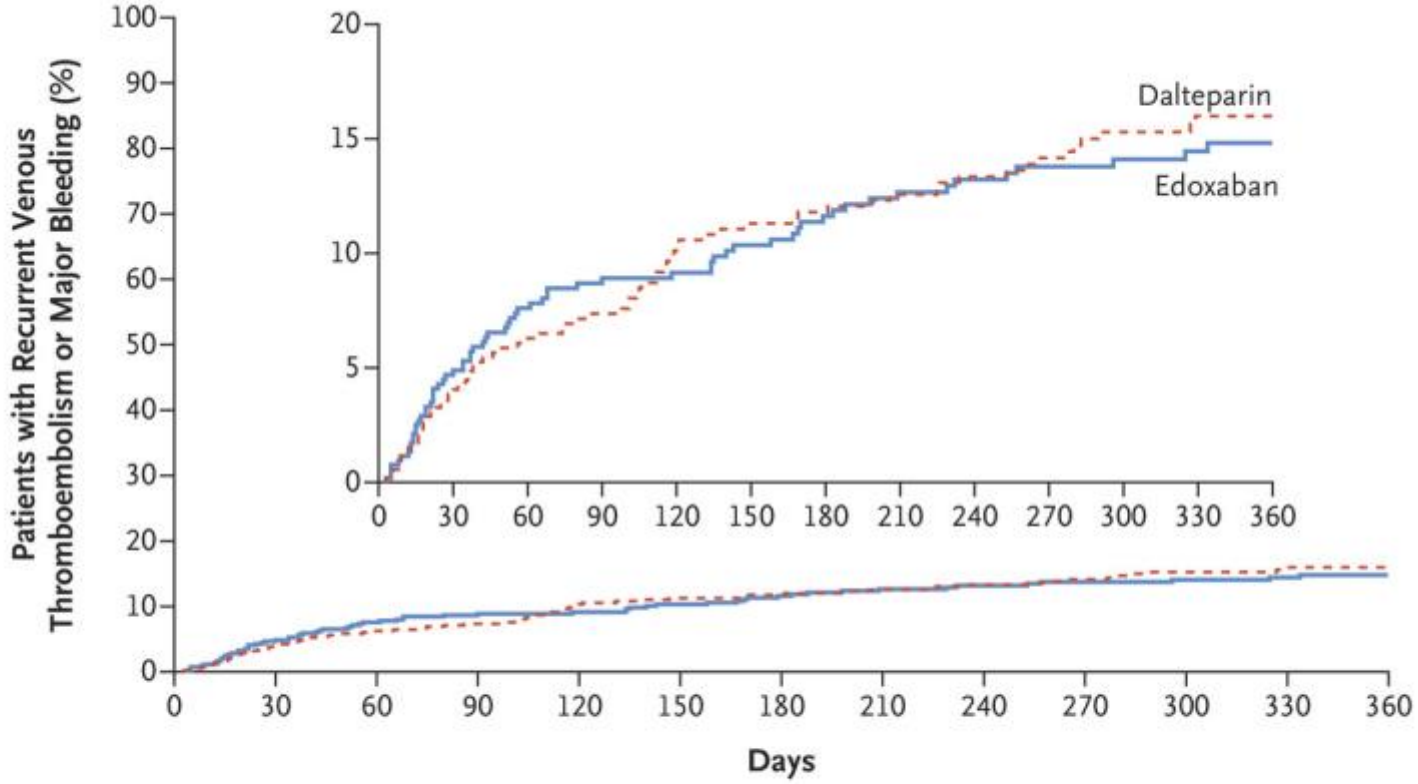
Van Es N. et al. *Thromb Haemost* 2015; 114: 1268-76

AOD vs HBPM: HOKUSAI CANCER

	Edoxaban N = 522	Dalteparin N = 524
Age	64.3±11.0	63.7±11.7
Pulmonary Embolism	328 (62.8)	329 (62.8)
Active cancer	513 (98.3)	511 (97.5)
Metastasis	274 (52.5)	280 (53.4)
ECOG 2	123 (23.6)	124 (23.7)

Raskob, GE. et al. *N Engl J Med* 2018; 378:615-624

AOD vs HBPM: HOKUSAI CANCER



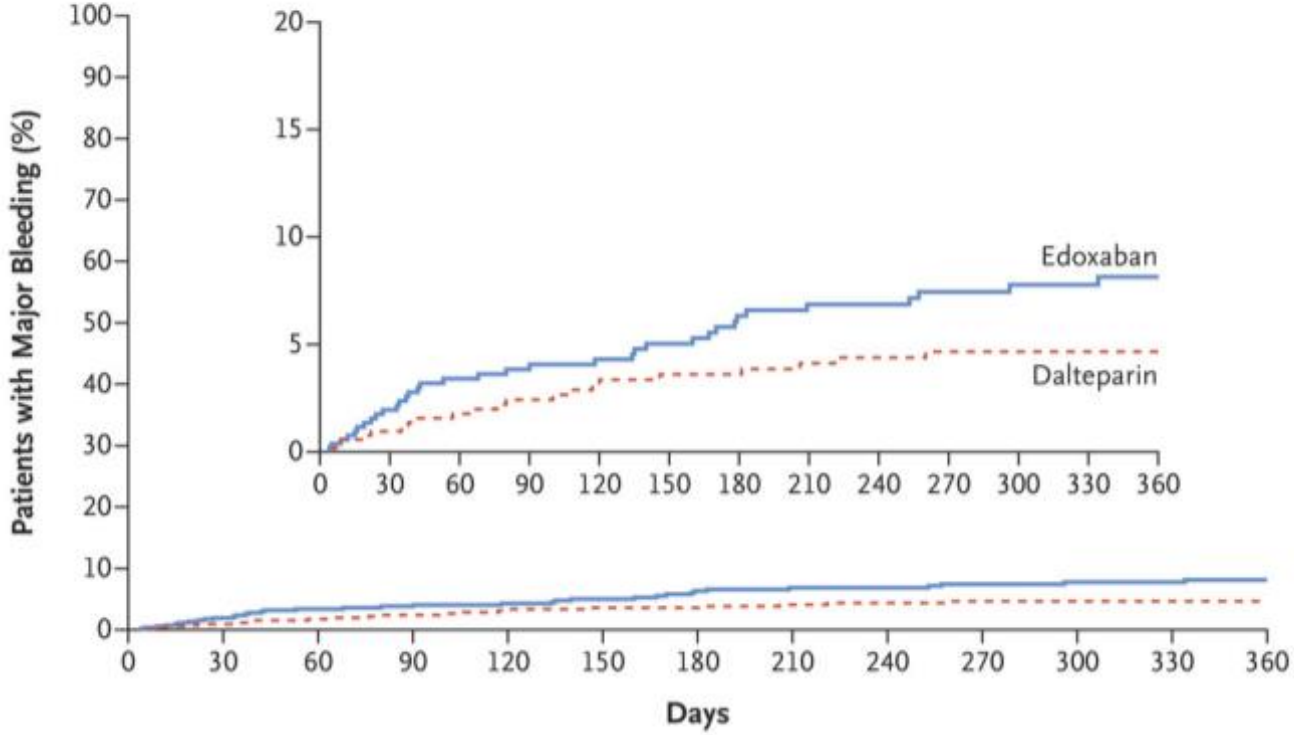
No. at Risk													
Edoxaban	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin	524	485	449	420	385	364	352	340	324	313	276	241	171

Raskob, GE. et al. *N Engl J Med* 2018; 378:615-624

AOD vs HBPM: HOKUSAI CANCER

A

B



No. at Risk													
Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

Raskob, GE. et al. *N Engl J Med* 2018; 378:615-624

AOD vs HBPM: HOKUSAI CANCER

	Edoxaban N = 522	Dalteparin N = 524	Hazard Ratio
Recurrent DVT	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)
Recurrent PE	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)
Major bleeding	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)
CRNMB	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)
Mortality	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)

Raskob, GE. et al. *N Engl J Med* 2018; 378:615-624

AOD vs HBPM: HOKUSAI CANCER

Quelques éléments supplémentaires

- Durée de traitement plus longue avec l'edoxaban (211 vs 184 j)
- Première cause d'arrêt (apres le déces): inconvénient du mode d'administration (dalteparine > edoxaban)
- La différence dans le taux de saignement majeur est liée aux saignements digestifs
- La différence dans le taux de saignements est marquée dans les cancers digestifs

Raskob, GE. et al. *N Engl J Med* 2018; 378:615-624

AOD vs HBPM: HOKUSAI CANCER

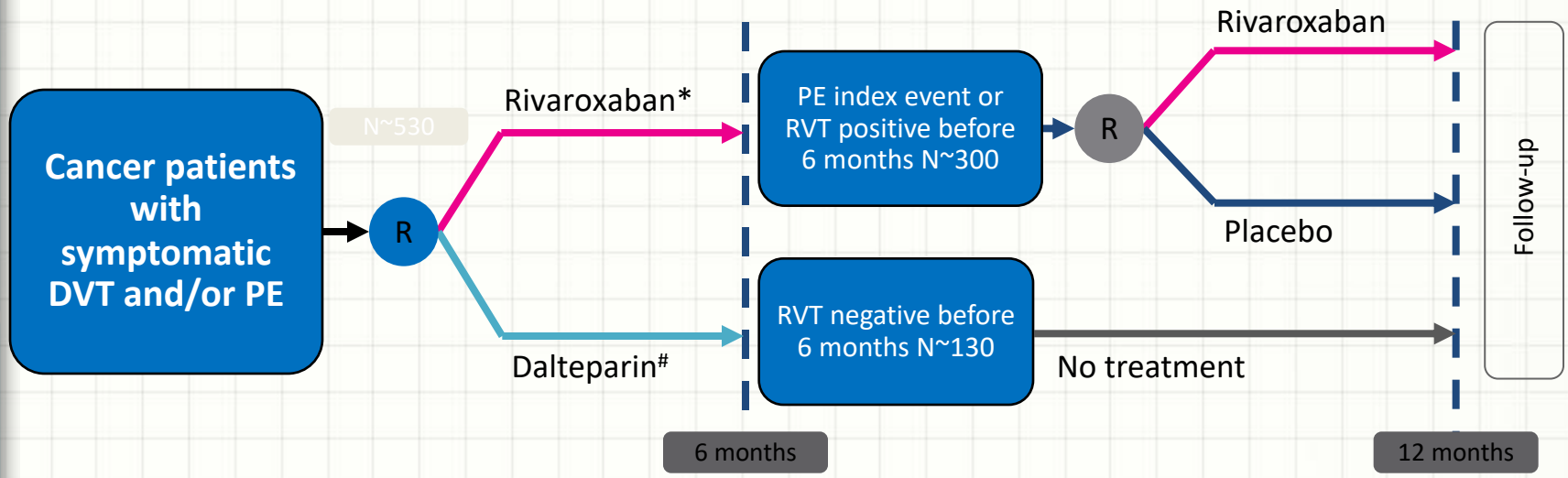
Données à six mois

	Edoxaban	Dalteparine	Hazard Ratio
Composite	10.5	10.7	1.01 (0.69-1.46)
Récidives TE	6.5	8.8	0.75 (0.48-1.17)
Saignements majeurs	5.6	3.2	1.74 (0.95-3.18)
Saignements majeurs et cliniquement significatifs	15.9	10.7	1.54 (1.10-2.16)

Raskob, GE. et al. *N Engl J Med* 2018; 378:615-624

select-d (IIR): Study Design

- **Rationale:** To assess the efficacy and safety of rivaroxaban versus dalteparin for the treatment of VTE in patients with cancer



Short design: Prospective, randomized, open-label, multicentre pilot phase III study

Indication: VTE treatment in patients with cancer

FPFV: Q4-13
LPLV: Q2-17

*15 mg bid for 21 days followed by 20 mg od; for patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; #200 IU/kg od for the first 30 days of treatment followed by 150 IU/kg od

Young A *et al*, *Thromb Res* 2016;140 Suppl 1:S172–173: Abstract OC-11; EudraCT number: 2012-005589-37; Bach M *et al*, *Thromb Haemost* 2016;116:S24–S32

select-d (IIR)

Données à six mois

	Rivaroxaban	Dalteparine	Hazard Ratio
Composite	10	15	1.01 (0.69-1.46)
Récidives TE	4	11	0.75 (0.48-1.17)
Saignements majeurs	6	4	1.74 (0.95-3.18)
Saignements non majeurs et cliniquement significatifs (GI)	13	4	1.54 (1.10-2.16)

Young A. et al. *J Clin Oncol* May 10, 2018

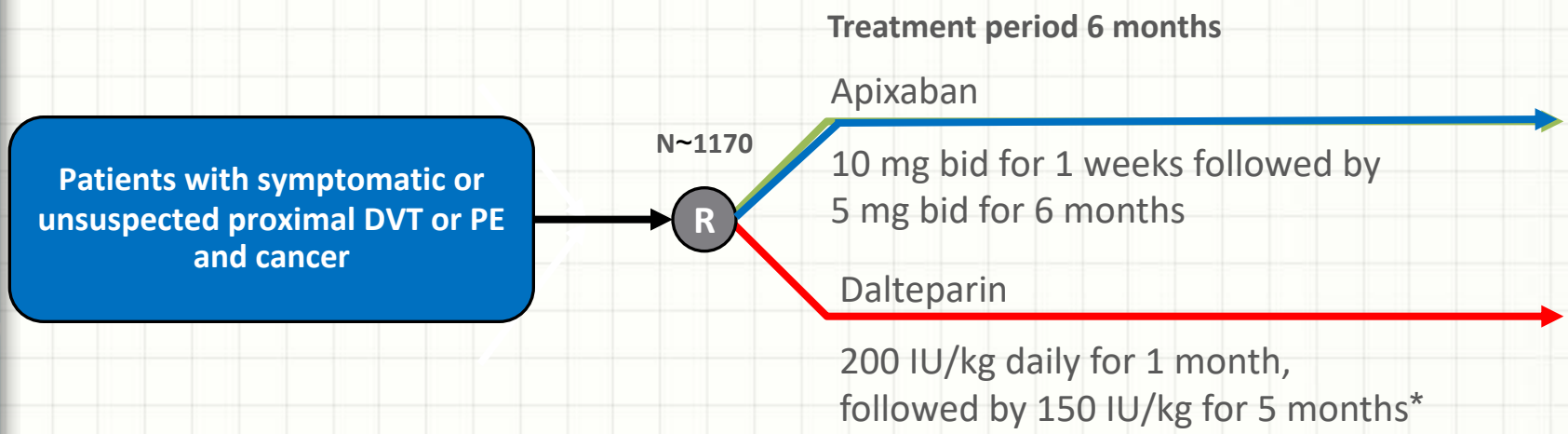
select-d (IIR)

- Etude pilote
- Plus grande efficacité du rivaroxaban
- Evenements adjudiqués secondairement
- Taux élevé de récidive sous dalteparine (11%)
- Augmentation non-significative des hémorragies majeures
- Augmentation significative des hémorragies majeures et cliniquement significatives

Young A. et al. *J Clin Oncol* May 10, 2018

CARAVAGGIO– Study Design

- Prospective, randomized, open-label, multicentre pilot study comparing dalteparin with apixaban for 6 months



- Primary outcome: objectively confirmed recurrent VTE occurring during the study period, defined as the composite of: proximal DVT of the lower limbs (symptomatic or unsuspected), DVT of the upper limb (symptomatic), PE (symptomatic or unsuspected)

https://clinicaltrials.gov/ct2/show/NCT03045406 [accessed 27 June 20]

Pulmonary embolism severity index scores: Full and simplified

Pulmonary embolism severity index (PESI) – Full		
Clinical feature		**Points**
Age		x (eg, 65)
Male gender		10
History of cancer		30
Heart failure		10
Chronic lung disease		10
Pulse ≥110/min		20
Systolic blood pressure <100 mmHg		30
Respiratory rate ≥30/min		20
Temperature <36° Celcius		20
Altered mental status		60
Arterial oxygen saturation <90 percent		20
Class I	Low risk	<66
Class II		66 to 85
Class III	High risk	86 to 105
Class IV		106 to 125
Class V		>125

Simplified pulmonary embolism severity index (sPESI)	
Clinical feature	**Points**
Age >80 years	1
History of cancer	1
Chronic cardiopulmonary disease	1
Pulse ≥110/min	1
Systolic blood pressure <100 mmHg	1
Arterial oxygen saturation <90 percent	1
Low risk	0
High risk	≥1

The full PESI score is rarely calculated in clinical practice since it is generally considered cumbersome. In contrast, sPESI is brief, contains a limited number of easily accessible parameters, and is therefore, much more practical.

Adapted from:

1. *Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005; 172:1041.*
2. *Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010; 170:1383.*

UpToDate®

Issues to be considered when making decisions concerning the use or non-use of anticoagulation in patients with malignancy

Overall treatment plan and prognosis
Therapeutic goal (eg, palliation of symptoms related to VTE, planned oncologic intervention, immediate prognosis, Hospice care)
Planned chemotherapy
Stage of the malignancy, overall prognosis
Other causes for hypercoagulability (eg, bed ridden, pathologic fracture, recent surgery or invasive procedures, use of hormonal agents or other medications with a high incidence of thrombotic side-effects, presence of a central venous access line)
Patient preferences, logistic, and financial issues
Inpatient or outpatient care planned
Who will supervise medication's use and required monitoring, if any?
Patient preferences (eg, oral versus injectable agent, need for frequent monitoring of coagulation status)
Food and Drug Administration approval of agent chosen
Treatment costs. Will the patient's insurance pay for the medication?
Relative contraindications to anticoagulation
Presence of central nervous system involvement
- Central nervous system primary or metastases
- Prior intracerebral hemorrhage
Thrombocytopenia or bleeding diathesis present?
Are risk factors for bleeding after use of warfarin present? (eg, impaired liver function, hepatic metastases, concomitant medication, poor nutrition)
Technical issues
Selection of appropriate dosing (eg, impaired renal function, obesity, advanced age)
Need for monitoring of treatment (eg, INR for treatment with warfarin)
Ability or inability to reverse anticoagulation if bleeding occurs

UpToDate®

Risk factors for recurrent venous thromboembolism and bleeding in patients with malignancy

Recurrent VTE	Bleeding
General factors	
Poor adherence to medication	Older age (>65 years)
Inadequate dosing	Higher intensity anticoagulation
Presence of HIT	Prior gastrointestinal bleeding
Inherited thrombophilia disorders	Thrombocytopenia
Acquired factors (eg, presence of venous catheter, recent surgery)	Overdosing
Interruption of therapy for procedures	Bleeding diathesis (eg, elevated INR in cirrhosis)
Drugs (eg, tamoxifen bevacizumab)	
Prolonged immobilization	
Heart failure	
Smoking	
Inflammatory bowel disease	
Patient-related factors[1]	
Younger patients (<65 years)	Immobilization
PE at study entry	Presence of metastases
Newly diagnosed cancer (<3 months)	Creatinine clearance <30 mL/min

VTE: venous thromboembolism; HIT: heparin-induced thrombocytopenia; INR: international normalized ratio; PE: pulmonary embolism.

Reference:

1. *Trujillo-Santos J, Nieto JA, Tiberio G, et al. Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost 2008; 100:435.*

UpToDate®

Factors that influence agent selection for anticoagulation in patients with acute venous thromboembolism

Factor	Preferred anticoagulant	Qualifying remarks
Cancer	LMWH	More so if: Just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	DOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	DOACs and LMWH contraindicated with severe renal impairment. Dosing of DOACs with levels of renal impairment differ with the DOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other DOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a DOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy.
Reversal agent needed	VKA, UFH, dabigatran	Reversal agents for dabigatran may not be universally readily available.
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta.
Cost, coverage, licensing	Varies among regions and with individual circumstances	

LMWH: low molecular weight heparin; VTE: venous thromboembolism; VKA: vitamin K-dependent antagonist; DOACs: direct oral anticoagulants; INR: international normalized ratio; GI: gastrointestinal; UFH: unfractionated heparin.

Original figure modified for this publication. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016; 149:315. Table used with the permission of Elsevier Inc. *All rights reserved.*

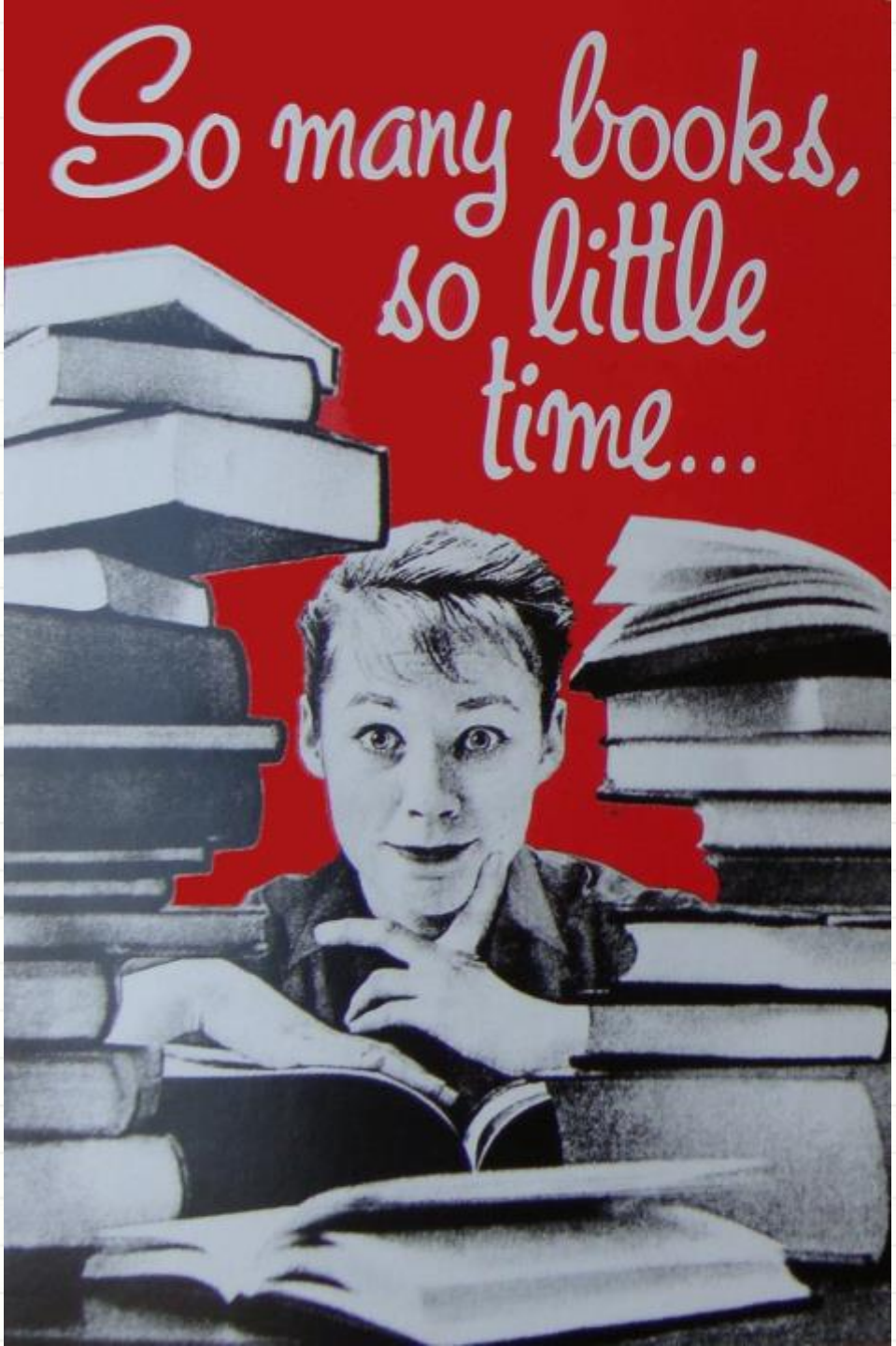
UpToDate®

Recommandations

	Tt préférence	Alternative	Grade
Cancer sans IR	HBPM	AOD	2 C
Cancer avec IR	HNF	HBPM / anti Xa	2 B
Cancer sans IR Durée	HBPM	AVK	2 B
Cancer sans IR au long cours Si saignement GI	 AVK	AOD Apixaban	

Conclusion (?)

- Les premiers essais semblent indiquer un profil des AOD différent de celui des HBPM: meilleure efficacité (?) mais risque de saignement accru
- Vraisemblablement pas pour les cancers digestifs
- Vers une personnalisation du traitement en fonction du risque hémorragique et du risque de récidive? (mais manque d'outils)
- Attention, les données ne sont peut-être pas généralisables à tous les AOD


So many books,
so little
time...