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16-19 MARS 2023
PALAIS DES CONGRÈS DE PARIS
L'ACTIVITÉ PHYSIQUE
PAYS INVITÉ : LA SUISSE
Société Nationale Française de Gastro-Entérologie SNFGE
FMC HGE

GESTION DES ANTICOAGULANTS EN CAS DE CANCER DIGESTIF

Pr I. ELALAMY
Département d'Hématologie Biologique – Centre Thrombose & Hémostase
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LIENS D'INTERET

Afric-Phar, Amanys Pharma, Astra-Zeneca, Bayer Healthcare, Boehringer-Ingelheim, Bristol Myers Squibb, Gedeon Richter, Leo-Pharma, Pfizer, Sanofi, Stago, Viatris

Scientific Advisory Board

Symposia Speaker

Research Support

OBJECTIFS PEDAGOGIQUES

- Connaître la fréquence des pathologies thromboemboliques en cancérologie digestive
- Connaître les indications des anticoagulants à dose prophylactique
- Connaître les indications des anticoagulants à dose curative
- Connaître les modalités de surveillance et leurs interactions médicamenteuses

LES 4 POINTS CARDINAUX

1. **N**ATURE D'UNE ASSOCIATION INCENDIAIRE
2. **S**TRATIFICATION DU RISQUE VASCULAIRE
3. **E**LÉMENTS POUR UNE PRÉVENTION AVISÉE
4. **O**RIENTATIONS POUR UN TRAITEMENT ADAPTÉ

QUELLES SONT LES PROPOSITIONS JUSTES?

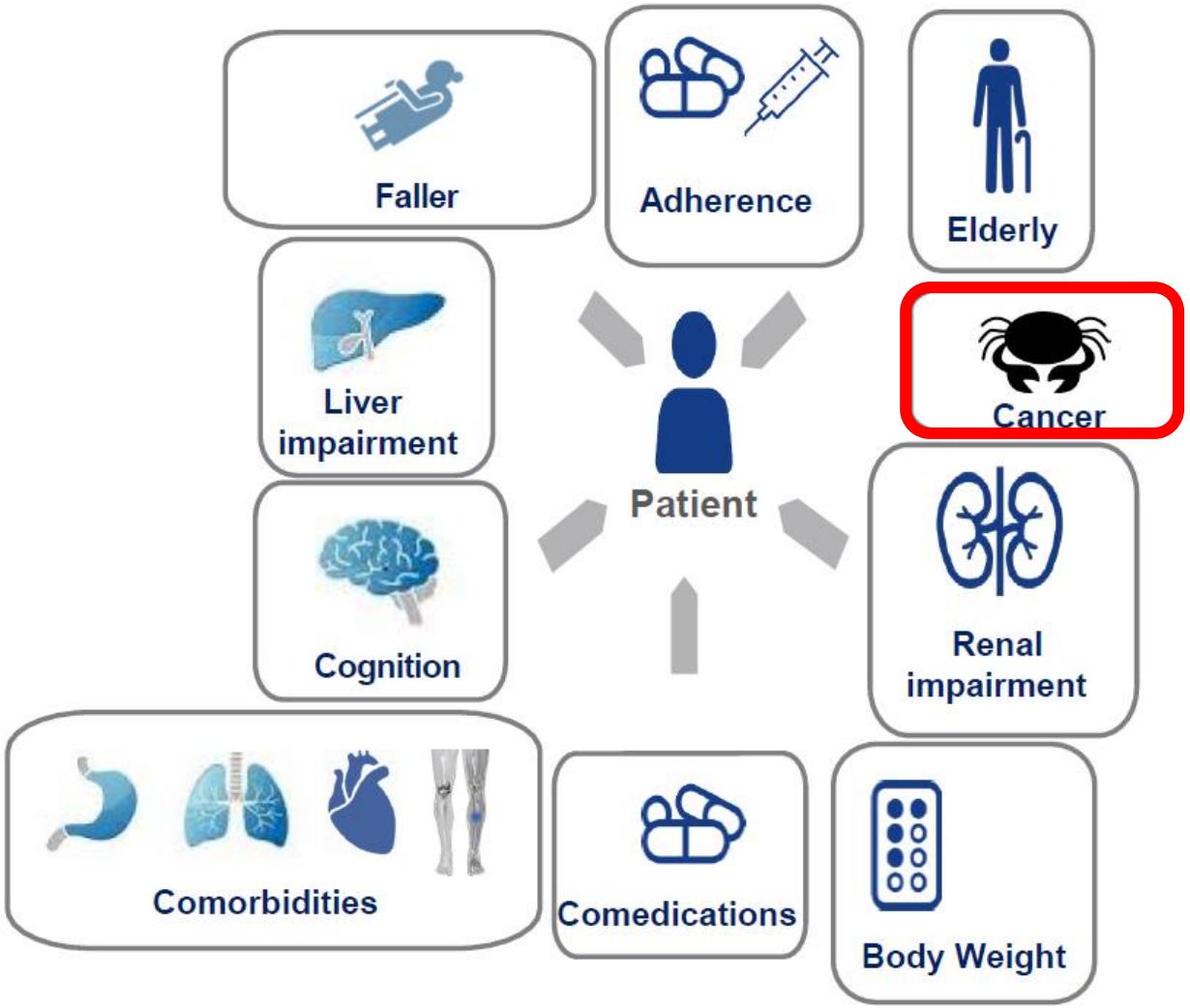
A. Chez le sujet atteint de cancer, le risque de MTEV est uniquement relatif au type de cancer et à son stade évolutif

B. La relation cancer et thrombose est bien connue des praticiens avec une évaluation plus systématique

C. Les cancers hématologiques type lymphomes ou leucémies sont aussi incendiaires que les cancers solides type pancréas ou estomac

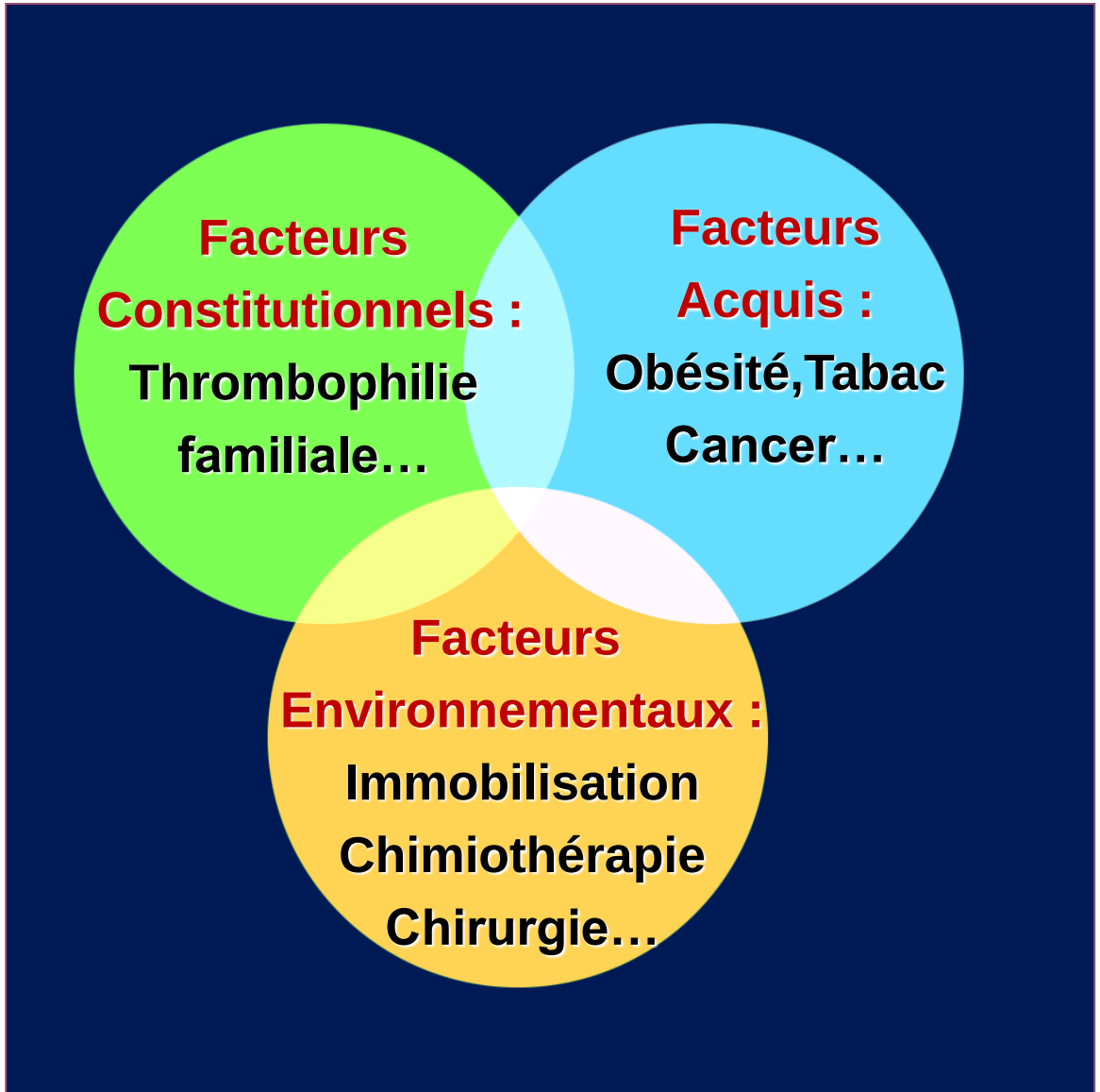
D. L'incidence de la thrombose associée au cancer est en constante progression et supérieure à celle de la population générale

UN MALHEUR NE VIENT JAMAIS SEUL…



Scotte, Elalamy et al Cancers 2019; 11(1): 48-62

THROMBOSE : ORIGINE MULTIFACTORIELLE EN 3D
« on ne thrombose pas par hasard »



TRIADE DE VIRCHOW ET CANCER

1. Stase sanguine

Accumulation des facteurs procoagulants
+
⇓ Elimination des facteurs activés

Immobilisation récente
Impotence fonctionnelle aiguë (paralysie)
Hyperviscosité sanguine
Déshydratation
Compression extrinsèque

2. Lésion endothéliale

Adhésivité accrue
+
⇓ thromborésistance

Traumatismes opératoires
Actes chirurgicaux
Cathéters veineux (surinfection++)
Produits intraveineux agressifs (chimiothérapie++)
Radiothérapie

3. Hypercoagulabilité

Potentiel prothrombotique
+
⇓ Potentiel antithrombotique

Acquise +++
RPCA, chimiothérapie...

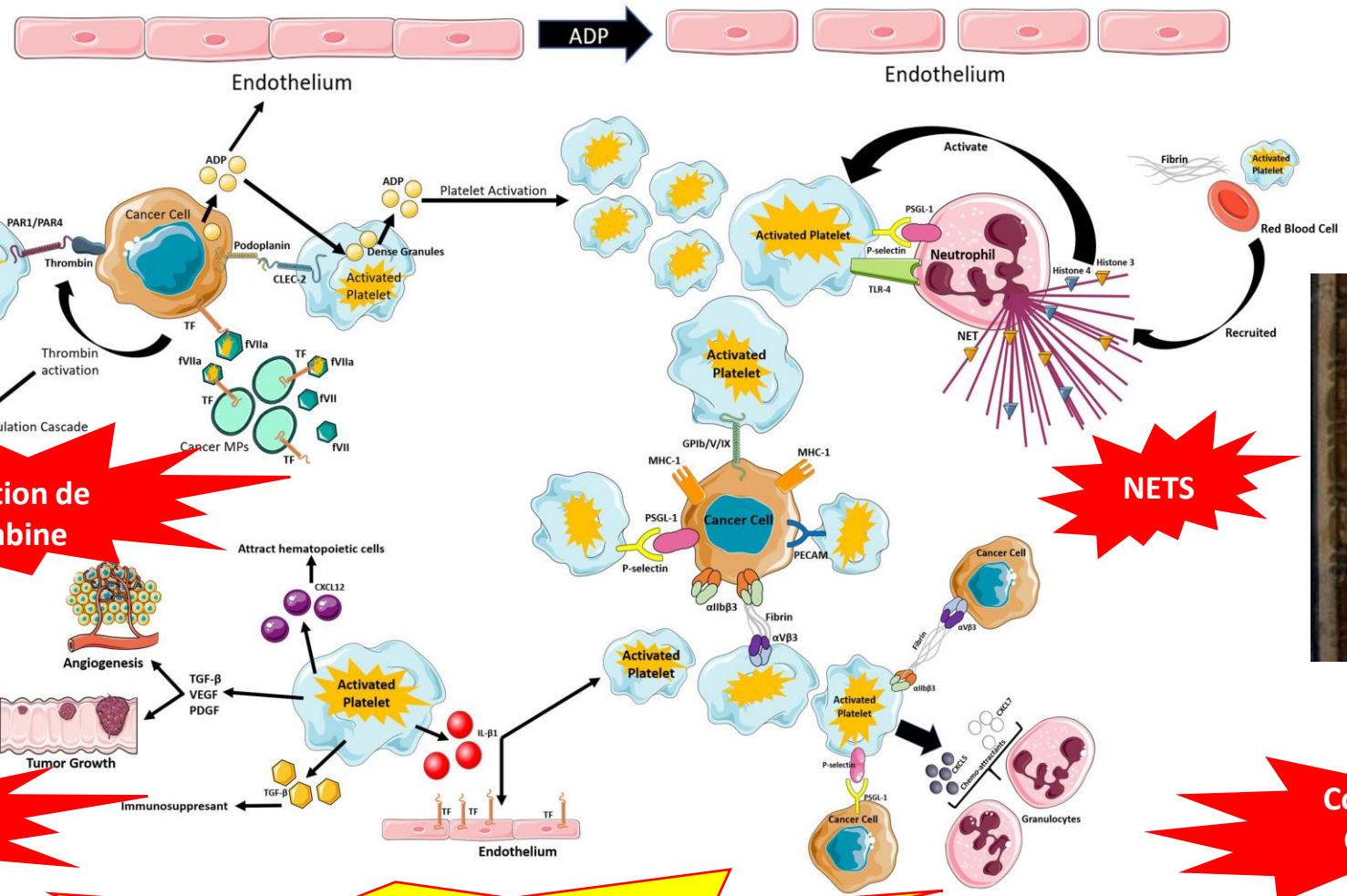
Elalamy et al Pathol Biol. 2008;56(4):184-94

THROMBOSE ET CANCER : RELATION RECONNUE

- Risque de TVP est ↑ x 4 à 7
- 15 à 20% TVP ± EP au cours d'un cancer
- Risque de récidive est ↑ x 3 si cancer
- Risque de TVP post-opératoire ↑ x 2 si cancer
- Risque de décès est ↑ x 4 si TVP et cancer
- MTEV chez 50% des autopsies de cancers
- MTEV 2ème cause de mortalité au cours du cancer

Donnellan & Khorana Oncologist. 2017;22(2):199-207
Ay et al Thromb Haemost. 2017;117(2):219-230.

THROMBOSE ET CANCER = UNE ALLIANCE
“2 FACES … DU MÊME ALIEN”



Facteur Tissulaire

Génération de Thrombine

Microparticules Procoagulantes

NETS

« JANUS – MALUS »

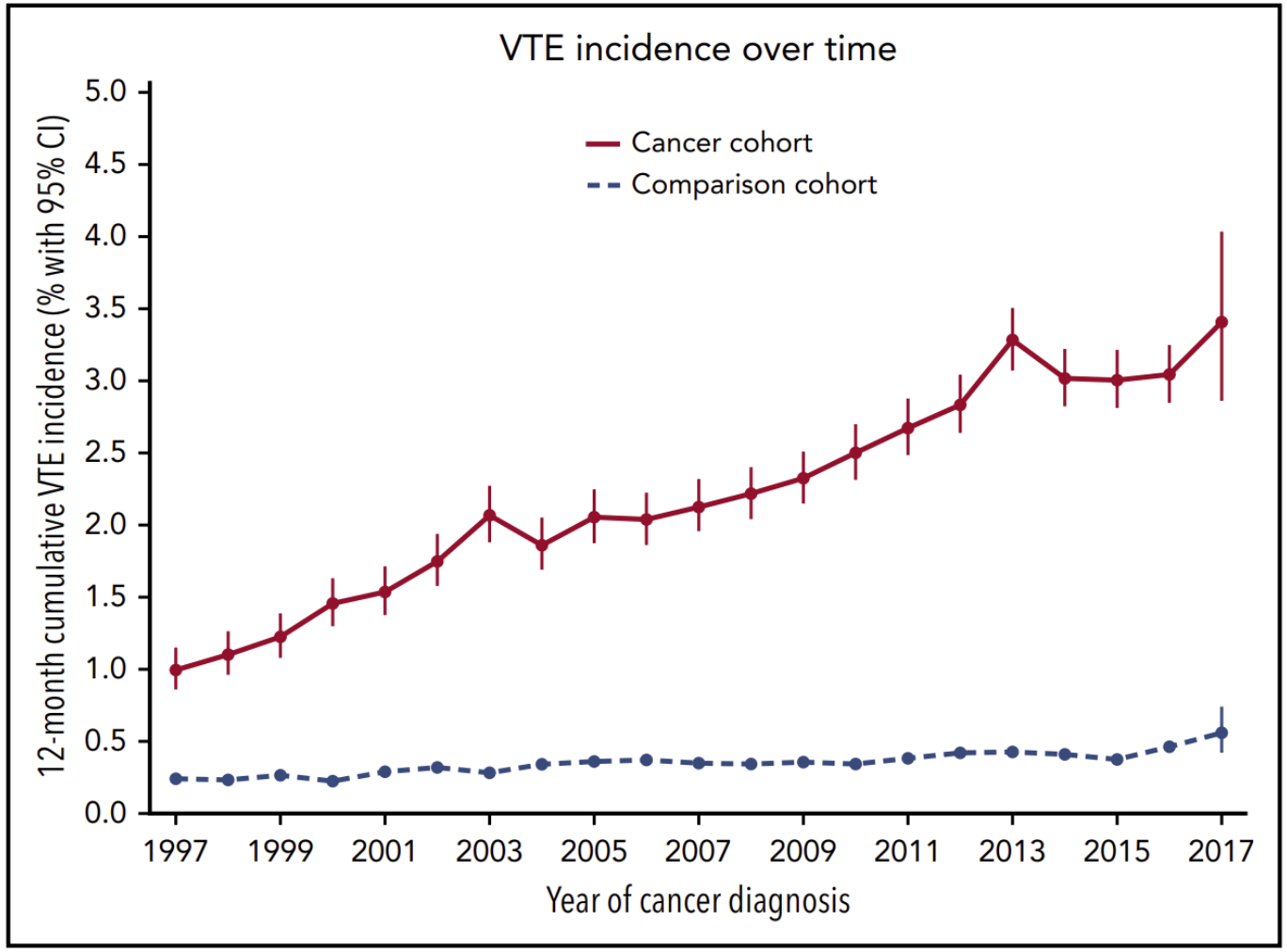
Coopération Cellulaire

Inflammation

Tumorogenèse ⇔ Thrombogenèse

Palacios-Acedo et al Front. Immunol. 2019; 10:1805-1811

LA TAC* EN PROGRESSION



12-month VTE incidence after Cancer Diagnosis
3% => 10 x general population incidence

12-month VTE incidence after Cancer Diagnosis
1% in 1997 => 3.4% in 2017

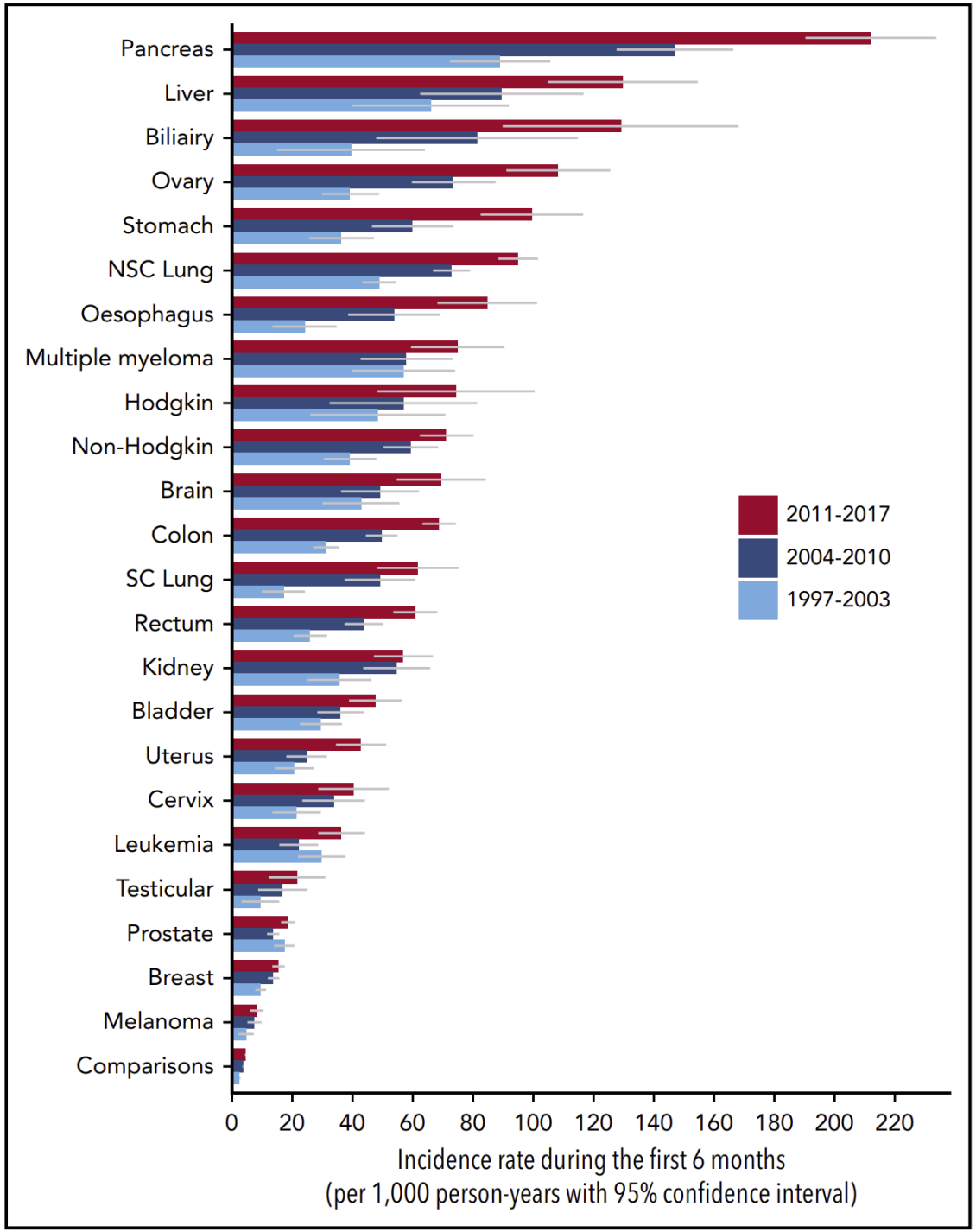
Important risk factors for CAT
- Prior VTE (SHR, 7.6; 95% CI, 7.2-8.0)
- Metastasis (SHR, 3.2; 95% CI, 2.9-3.4)
- Chemotherapy (SHR, 3.4; 95% CI, 3.1-3.7)
- PK inhibitors (SHR, 4.1; 95% CI, 3.4-4.9)
- Antiangiogenics (SHR, 4.4; 95% CI, 3.8-5.2)
- Immunotherapy (SHR, 3.6; 2.8-4.6)

Question Clé :
« Être ou Ne Pas Être Hypercoagulable?»

**TAC : Thrombose Associée au Cancer*

Mulder et al Blood. 2021;137(14): 1959-1969

INCIDENCE DE LA TAC FONCTION DU CANCER



Mulder et al Blood. 2021;137(14): 1959-1969

Lésion endothéliale
Stase veineuse
Inflammation
Terrain et Type de chirurgie
MTEV HR x 2
EP fatale x 3
40% des ETE

Cytotoxicité plurielle
Hypercoagulabilité et Hyperadhésivité
↓ inhibiteurs ↑ facteurs procoagulants
MTEV HR x 6
Cisplatine >> Oxaliplatine
5FU, L-Asparaginase

Table 1. Risk factors for cancer-associated

Patient Characteristics	Tumour-Related Factors	Treatment Factors		
Increasing age	Site of tumour	Surgery	Thy	
Female sex	Tumour staging	Hospitalisation	strogen	Leucocyte count $\geq 11 \times 10^9$/L
Black ethnicity	Tumour histology	Chemotherapy	Oncogenes—K-RAS, p53	Elevated D-dimer
Comorbidities-heart failure, renal disease and infection		Radiotherapy	Oncoproteins—HPV E6	High expression of TF from cancer cells
Immobility		Central venous catheters		Elevated CRP
Previous VTE				Soluble *p*-selectin
BMI ≥ 35 kg/m^2				Prothrombin fragment 1.2

Abbreviations: VTE: venous thromboembolism, HPV: human papillomavirus, TF: tissue factor, CRP: C-reactive protein, BMI: body mass index.

Shah et al. Diseases 2021, 9, 34

SCORE DE CAPRINI

Each risk factor = 1 point

- Age 40-59 years
- Minor surgery planned
- BMI ≥ 30kg/m2
- History of prior major surgery (<1 month)
- Swollen legs (current)
- Varicose veins
- Sepsis (<1 month)
- Abnormal pulmonary function (COPD)
- Acute myocardial infarction (<1 month)
- Congestive heart failure (<1 month)
- History of IBD
- Medical patient currently at bed rest

For women only (1 point each)

- Pregnant of post-partum
- History of unexplained or recurrent spontaneous abortion
- Oral contraceptives or hormone replacement therapy

Each risk factor = 2 points

- Age 60 – 74 years
- Arthroscopic surgery
- Major open surgery (> 45 minutes)
- Laparoscopic surgery (> 45 minutes)
- Prior cancer (except non-melanoma skin cancer)
- Present cancer (except breast and thyroid)
- Confined to bed (>72 hours)
- Immobilizing plaster cast
- Central venous access

Caprini risk category based on total risk score

Total score	Category
0 - 4	Low
5 - 8	Moderate
≥ 9	High

Each risk factor = 3 points

- Age ≥ 75 years
- History of VTE
- Family history of VTE
- Present chemotherapy
- Positive Factor V Leiden
- Positive Prothrombin 20210A
- Positive Lupus anticoagulant
- Elevated anticardiolipin antibodies
- Elevated serum homocysteine
- Heparin-induced thrombocytopenia (HIT)
- Other congenital or acquired thrombophilias

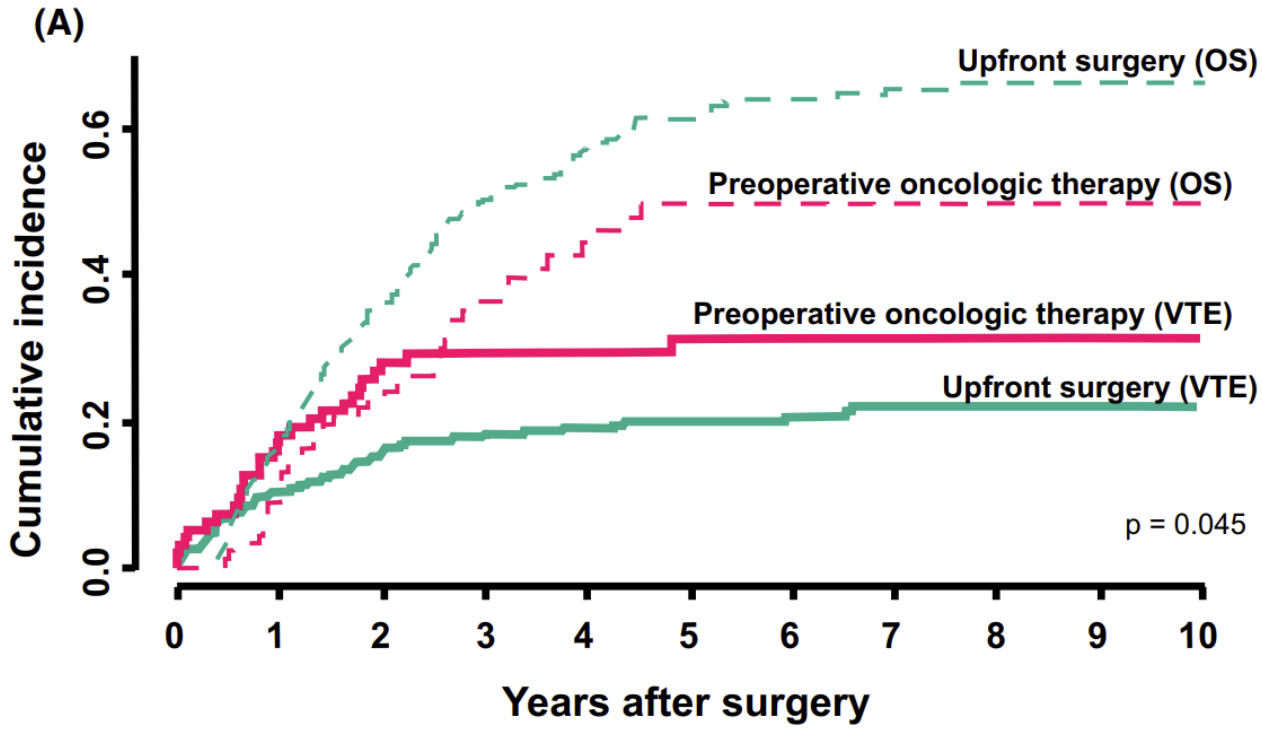
Each risk factor = 5 points

- Major surgery lasting > 6 hours
- Stroke (<1 month)
- Elective major lower extremity arthroplasty
- Hip, pelvis, leg fracture (< 1 month)
- Acute spinal cord fracture or paralysis (< 1 month)
- Multiple traumas (< 1 month)

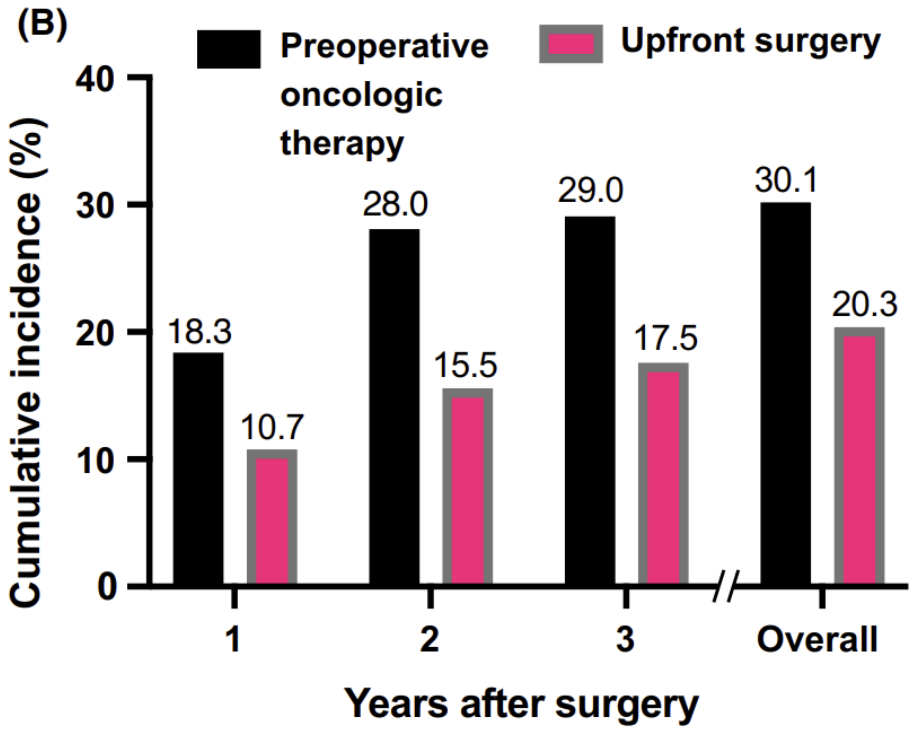
Sterbling at al Ann Thorac Surg 2018;105:879–85

PREOPERATIVE ONCOLOGIC THERAPY AND THE PROLONGED RISK OF VENOUS THROMBOEMBOLISM IN RESECTABLE PANCREATIC CANCER

patients surgically treated for pancreatic cancer at Helsinki University Hospital between 2000-2017
N=93 preoperative oncologic therapy (chemo-radiotherapy) and 291 initial surgery patients



Preoperative oncologic therapy increased thrombosis risk [HR] 1.61; 95%CI 1.03–2.53).



VTE incidence remained high > 2 years after surgery

Eurola et al Cancer Medicine. 2022;11:1605–1616

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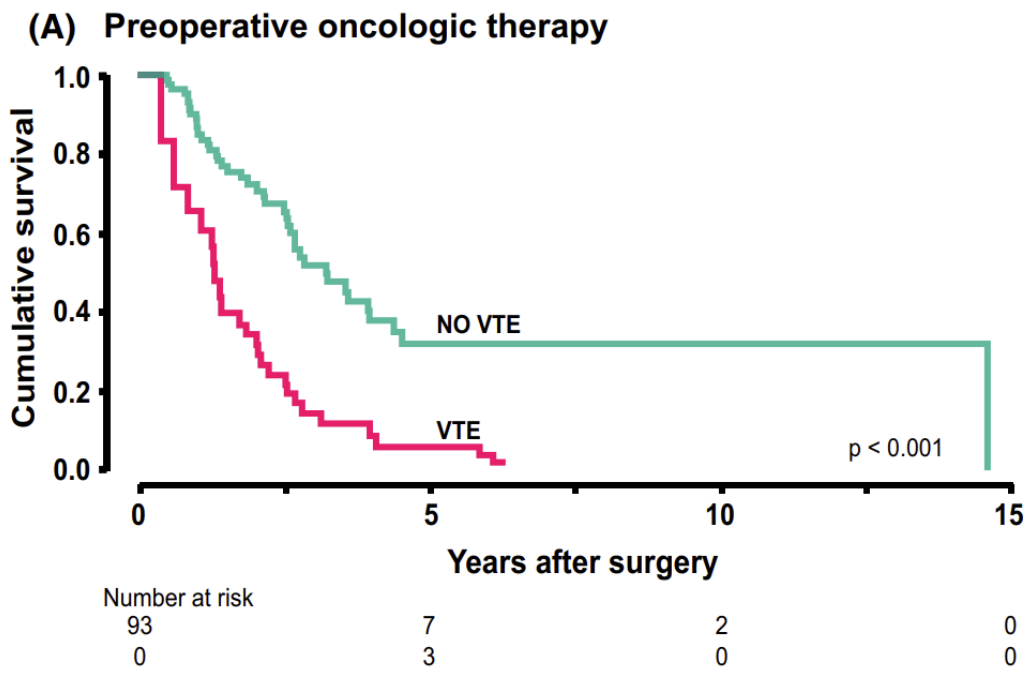
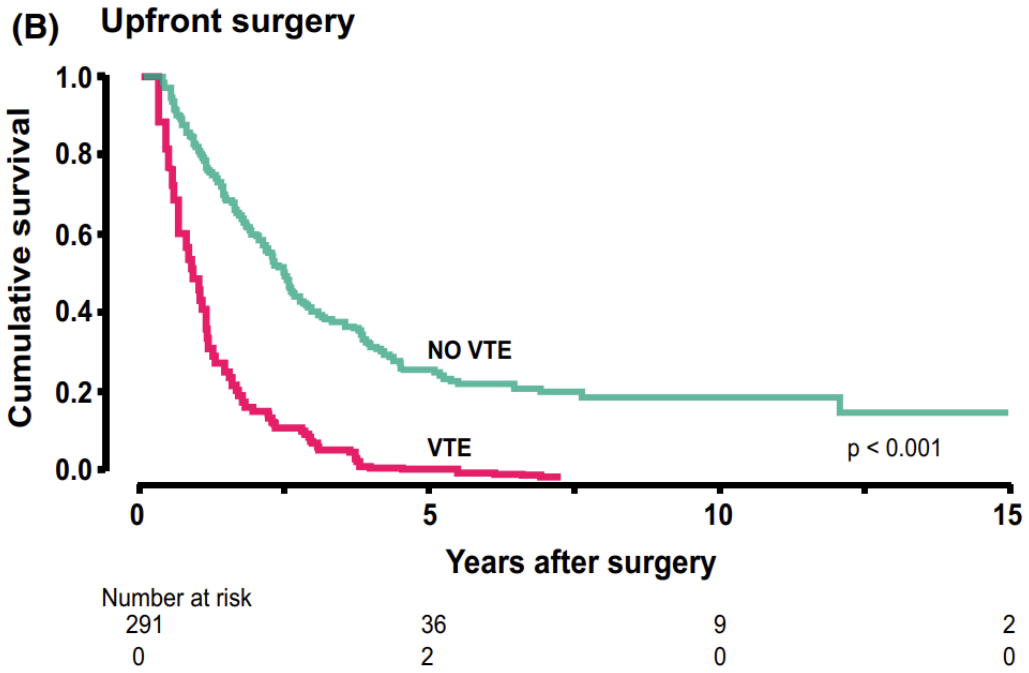




BMI ≥30 kg/m2, prior anticoagulation, and disease recurrence ($p < 0.05$) associated with VTE.
VTE associated with shorter overall survival (HR 3.25; 95% CI 2.36–4.44).
In 72% of patients, VTE was diagnosed after disease recurrence.

Eurola et al Cancer Medicine. 2022;11:1605–1616

Variation in the Association between Antineoplastic Therapies and Venous Thromboembolism in Patients with Active Cancer

UK Clinical Practice Research Datalink, data on 67,801 patients with first cancer diagnosis 2008-2016
CAT in 2.2% with a 1.2 y Follow-up

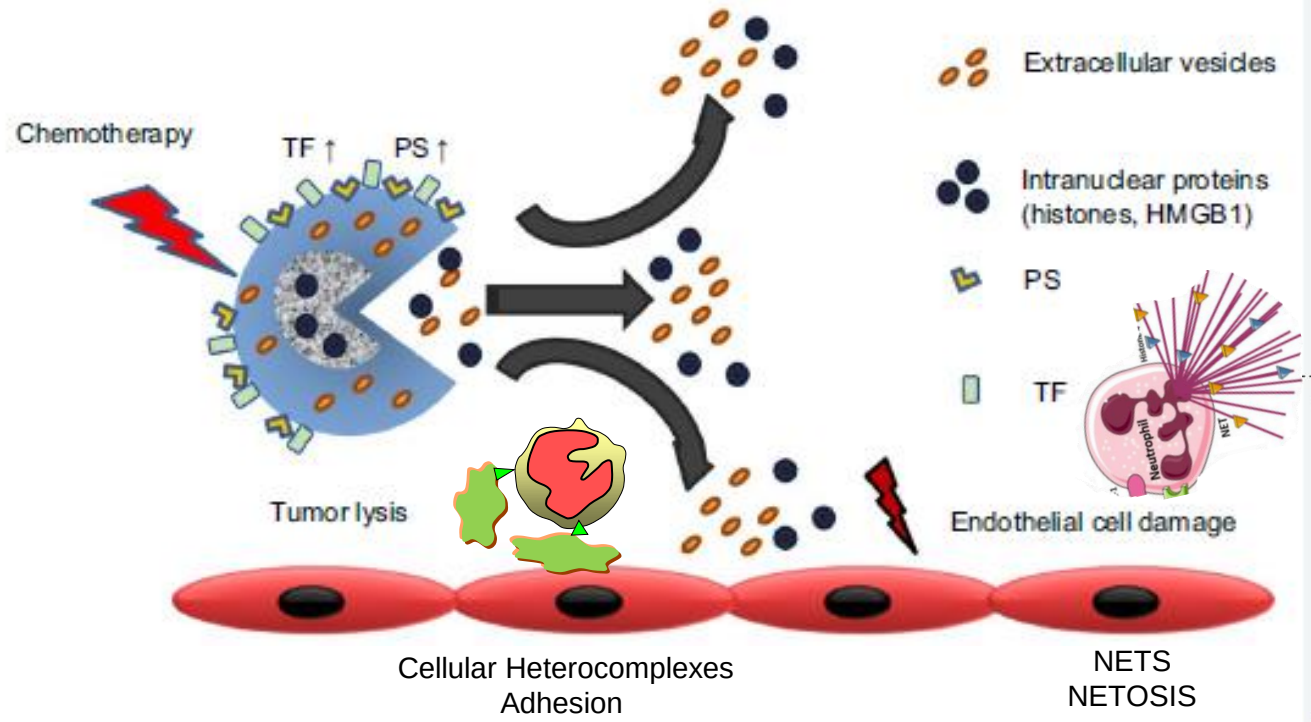
Type of anticancer treatment	VTE events	Person-years	Crude IR[f] (95% CI)
No current anticancer treatment	560	21,021	2.7 (2.4–2.9)
Chemotherapy only	620	10,865	5.7 (5.2–6.2)
Radiation only	38	2,275	1.7 (1.1–2.3)
Immunotherapy only	6	851	0.7 (0.2–1.6)
Hormonal therapy only (breast)[a]	76	18,827	0.4 (0.3–0.6)
Hormonal therapy only (prostate)[b]	61	7,433	0.8 (0.6–1.1)
Chemotherapy combination[c]	97	3,367	2.9 (2.3–3.6)
Radiation combination[d]	14	2,084	0.7 (0.3–1.2)
Immunotherapy combination[e]	<5	220	

Anticancer treatment[a]	All patients *n* (%)	Patients with VTE *n* (%)
Total	67,801	1,473
Yes	40,988 (60.5)	1,066 (72.4)
Chemotherapy	20,183 (49.2)	758 (71.1)
Hormonal	13,631 (33.3)	183 (17.2)
Radiation	12,189 (29.7)	187 (17.5)
Immunotherapy	1,019 (2.5)	15 (1.4)
No	26,813 (39.5)	407 (27.6)

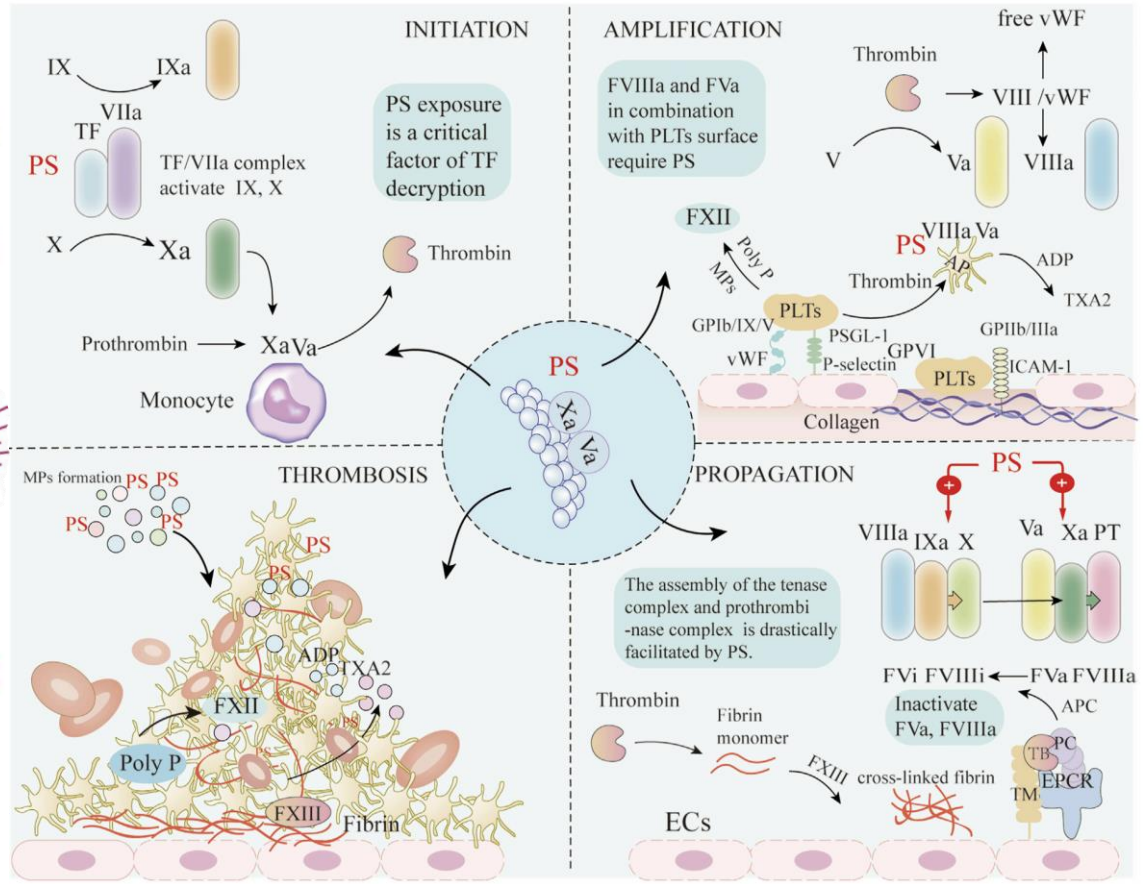
f Incidence rate of venous thromboembolism per 100 person-years.

Giustozzi et al Thromb Haemost 2020;120:847–856..

CHIMIOTHÉRAPIE ET HYPERCOAGULABILITÉ



Sanfilippo Thromb Res 2020; 191S1: S74–S78

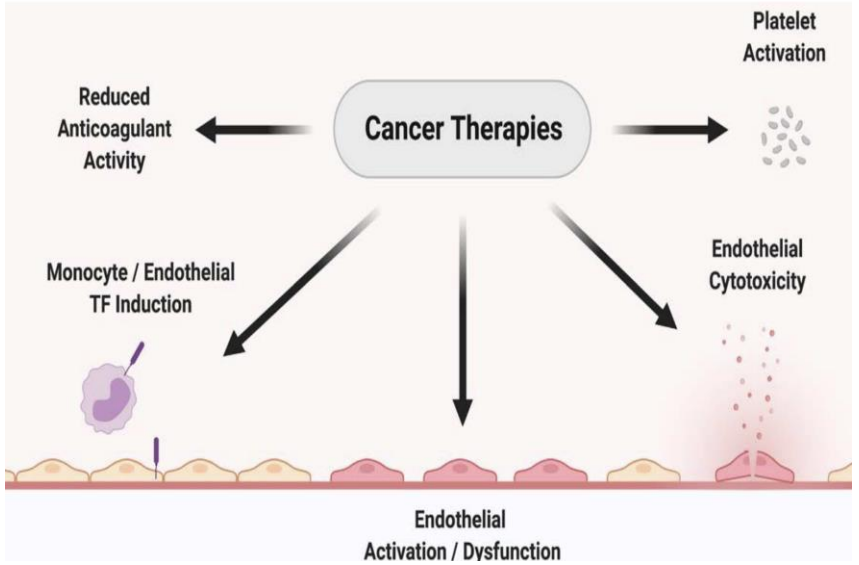


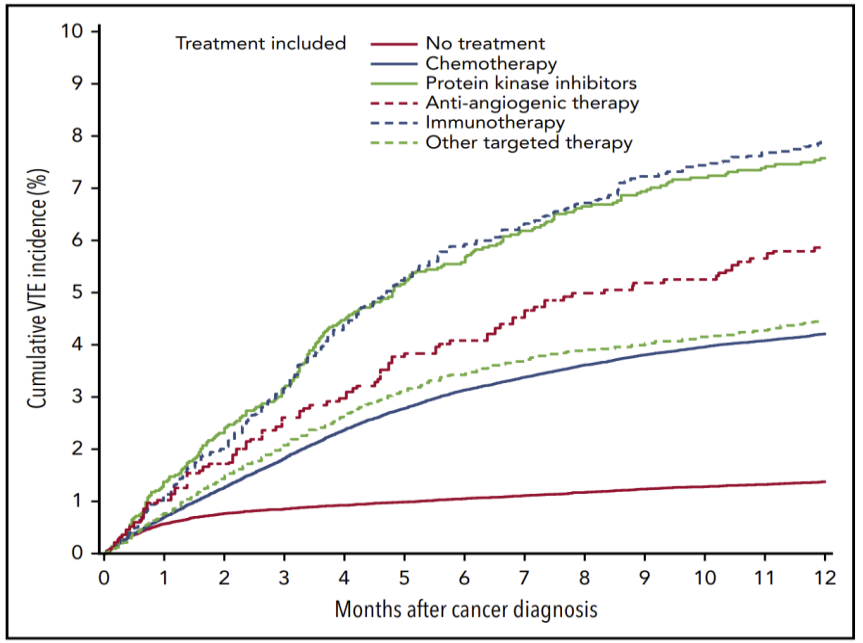
Jing et al. Front. Cell Dev. Biol. 2022; 9:792335

TTT ANTI-TUMORAL ET HYPERCOAGULABILITE

Agent	VTE
Platinum-based agents	
Cisplatin	++
Carboplatin	++
Oxaliplatin	+
Anthracyclines	
Doxorubicin	+
Daunorubicin	NR
Epirubicin	NR
Pyrimidine antagonists	
5-fluorouracil	–
Gemcitabine	–
L-asparaginase	NR
Tamoxifen	+
Immunomodulatory agents	
Thalidomide	++
Lenalidomide	++
Pomalidomide	+
Anti-EGFR antibodies	
Cetuximab	+
Panitumumab	+
Necitumumab	+
VEGF-targeted molecules	
Bevacizumab	–
Aflibercept	–
VEGFR RTKI	
Sunitinib	–
Sorafenib	–
Axitinib	–
Pazopanib	–
Vandetanib	–
Lenvatinib	NR
Cabozantinib	NR
BCR-ABL RTKI	
Imatinib	–
Dasatinib	++
Nilotinib	++
Ponatinib	++
Bosutinib	NR
CDK inhibitors	
Palbociclib	+
Abemaciclib	++
Ribociclib	+

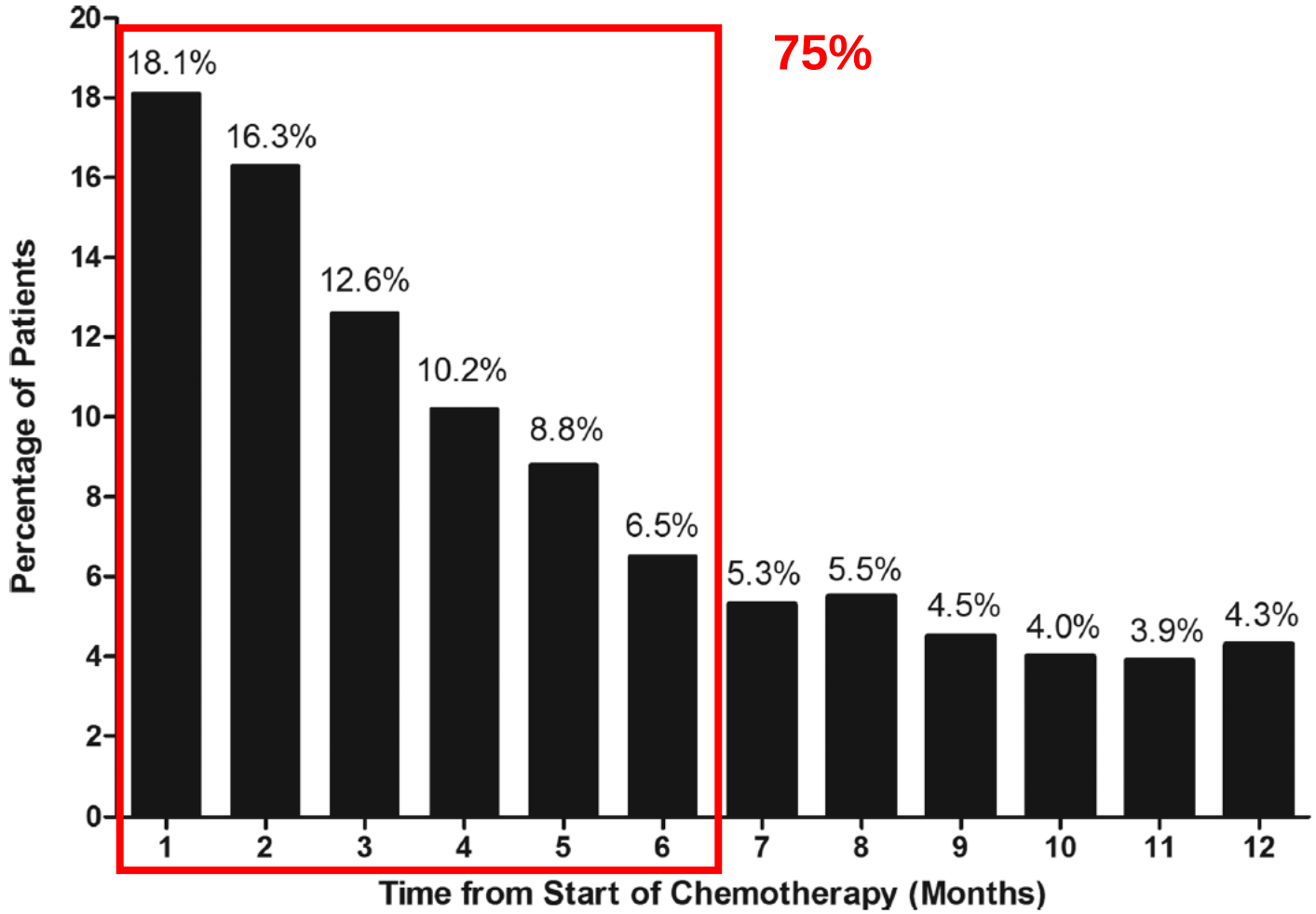
Grover et al Arterioscler Thromb Vasc Biol. 2021;41:1291





Mulder et al Blood. 2021;137(14): 1959-1969

TIMING DU RISQUE THROMBOTIQUE ET CHIMIOTHÉRAPIE



Khorana et al Cancer. 2013;119(3):648-55

LA TAC EN 4 DIMENSIONS

PATIENT-RELATED
Medical comorbidities (≥3)
Immobility
Elderly
Prior VTE
Hereditary Thrombophilia (FVL)
…

TUMOUR-RELATED
Site of cancer
Very high: stomach, pancreas, brain
High: lung, hematologic, gynaecologic, renal
Histological grade
Stage/Metastasis
Time since cancer diagnosis

Cancer-Associated VTE Risk

TREATMENT-RELATED
Platinum-based or other chemotherapy
Anti-angiogenesis agents
Hormonal therapy
Surgery
Radiotherapy
Central Venous Catheter
Blood transfusion

BIOMARKERS
Hematologic (Plts, Lcytes, Hb…)
D-Dimers
P-Selectin
Thrombin Generation Potential
Microparticle-Tissue Factor activity
C Reactive Protein

Sévérité? **V**ulnérabilité? **P**articularité?

Adapté de Ay et al . Thromb Haemost 2017;117(2):219-230.

QUELLES SONT LES PROPOSITIONS JUSTES?

A. Chez le sujet atteint de cancer, le risque de MTEV est uniquement relatif au type de cancer et à son stade évolutif

B. La relation cancer et thrombose est bien connue des praticiens avec une évaluation plus systématique

C. Les cancers hématologiques type lymphomes ou leucémies sont aussi incendiaires que les cancers solides type pancréas ou estomac

D. L'incidence de la thrombose associée au cancer est en constante progression et supérieure à celle de la population générale

QUELLES SONT LES PROPOSITIONS JUSTES?

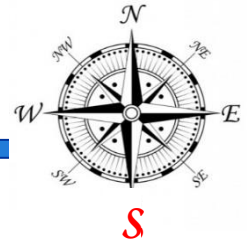
A. Il est recommandé de stratifier le risque thrombotique chez tout patient atteint de cancer hospitalisé ou ambulatoire

B. Le score de Khorana est validé pour tous les types de cancers

C. Le score de Khorana est simple et utile chez les patients atteints de cancer colorectal ou cancer de l'estomac

D. Le score de Khorana ne peut être utilisé qu'une seule fois en pré-chimiothérapie

RECOMMANDATIONS DE STRATIFICATION DU RISQUE



- MTEV est un facteur prédictif de **« mauvais pronostic ».**

- Même chez le **patient ambulatoire**, il faut évaluer le risque thrombotique en se basant sur un **score validé**

- Les patients atteints de cancer doivent être **évalués** à l'initiation du traitement anti-tumoral (chimiothérapie) et **périodiquement** ensuite.

- Le panel d'experts recommande que les oncologues informent leurs patients sur la MTEV (éducation), particulièrement dans des contextes favorisants comme la chirurgie majeure, l'hospitalisation, le traitement anti-néoplasique.

www.asco.org/guidelines/VTE last access Oct. 2021

SCORE KHORANA
PATIENT AMBULATOIRE ET PRÉ-CHIMIOTHÉRAPIE

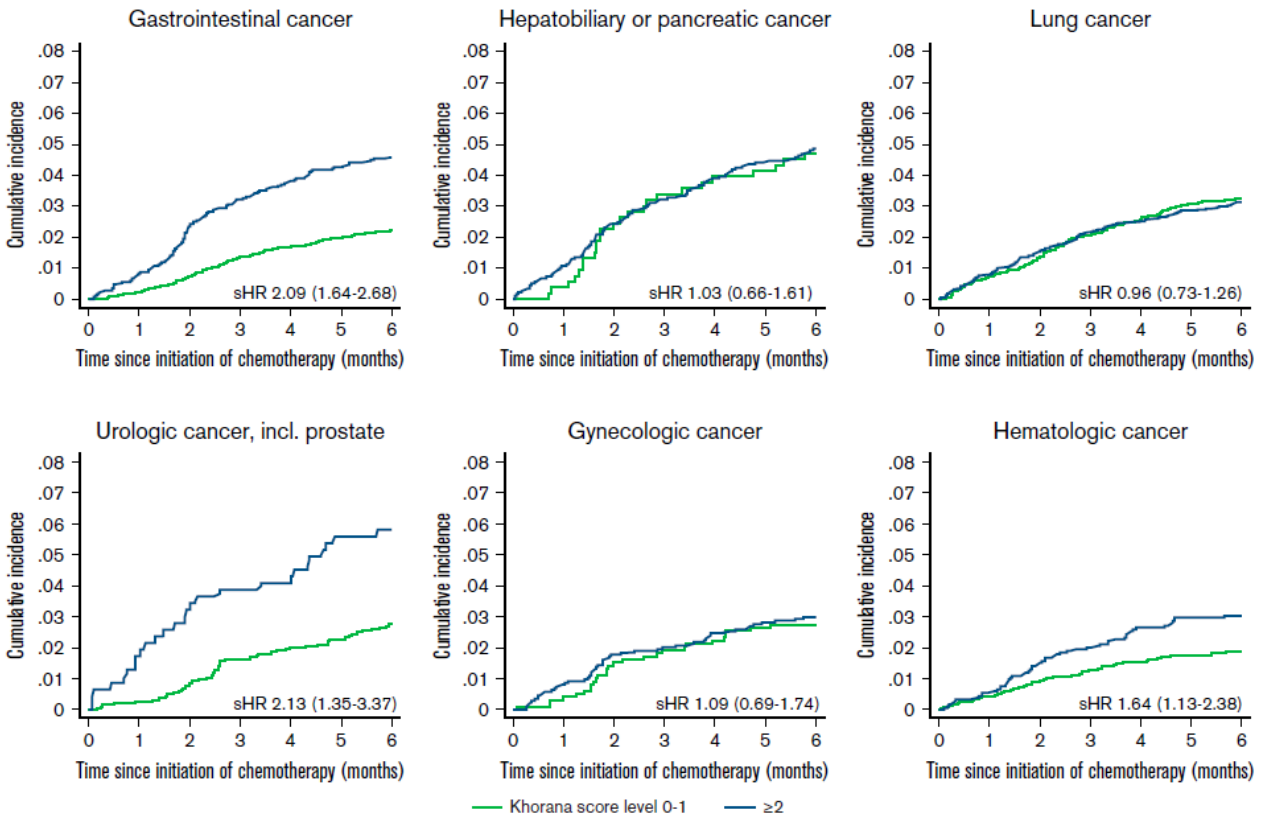
Patient Characteristic	Score
Site of Cancer Very high risk (stomach, pancreas) High risk (lung, lymphoma, gynecologic, GU excluding prostate)	 2 1
Platelet count $\geq$ 350 x 10^9/L	1
Hb < 100 g/L or use of ESA	1
Leukocyte count > 11 x 10^9/L	1
BMI $\geq$ 35 kg/m^2	1

Score=0 : Low-risk
Score=1 : Intermediate-risk
Score≥2 : High-risk

Score of ≥3 predicts higher VTE rate and 4-fold higher mortality rate

Khorana et al. Blood. 2008;111(10):4902-7. ; Sohal et al. Cancer. 2015;121(11):1779-84.

VALIDATION OF THE KHORANA SCORE FOR PREDICTING VTE IN 40 218 PATIENTS WITH CANCER INITIATING CHEMOTHERAPY



	Patients, n	Events, n	Cumulative incidence, % (95% CI)* at 6 months
Overall	40 218	1 000	2.5 (2.3-2.6)
Khorana risk category			
0: low risk	14 250	210	1.5 (1.3-1.7)
1-2: intermediate risk	21 565	610	2.8 (2.6-3.1)
≥3: high risk	4 403	180	4.1 (3.5-4.7)
Khorana score level			
1	12 856	318	2.5 (2.2-2.8)
2	8 709	291	3.3 (3.0-3.7)
3	3 623	141	3.9 (3.3-4.6)
4	717	34	4.7 (3.4-6.5)
5-6	63	5	7.9 (2.9-16.2)
Guideline threshold			
Score 0-1	27 106	529	2.0 (1.8-2.1)
Score ≥2	13 112	471	3.6 (3.3-3.9)

*Based on the cumulative incidence function considering death as competing risk.

Khorana score able to risk-stratify cancer pts only for some cancer types.

Absolute risk estimates were lower than previously reported in key randomized trials.

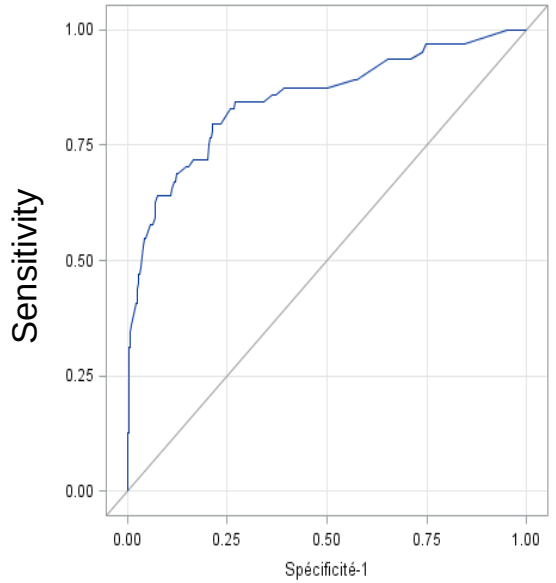
Overvad et al. Blood Adv 2022;6(10):2967-2976.

SCORE COMPASS-CAT

Predictors for VTE	Score
Cancer related risk factors	
Anti-hormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment	6
Time since cancer diagnosis ≤ 6 months	4
CVC	3
Advanced stage of cancer	2
Predisposing risk factors	
Cardiovascular risk factors (composed by at least 2 of the following predictors: personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)	5
Recent hospitalization for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelets count ≥ $350x10^9$/L	2

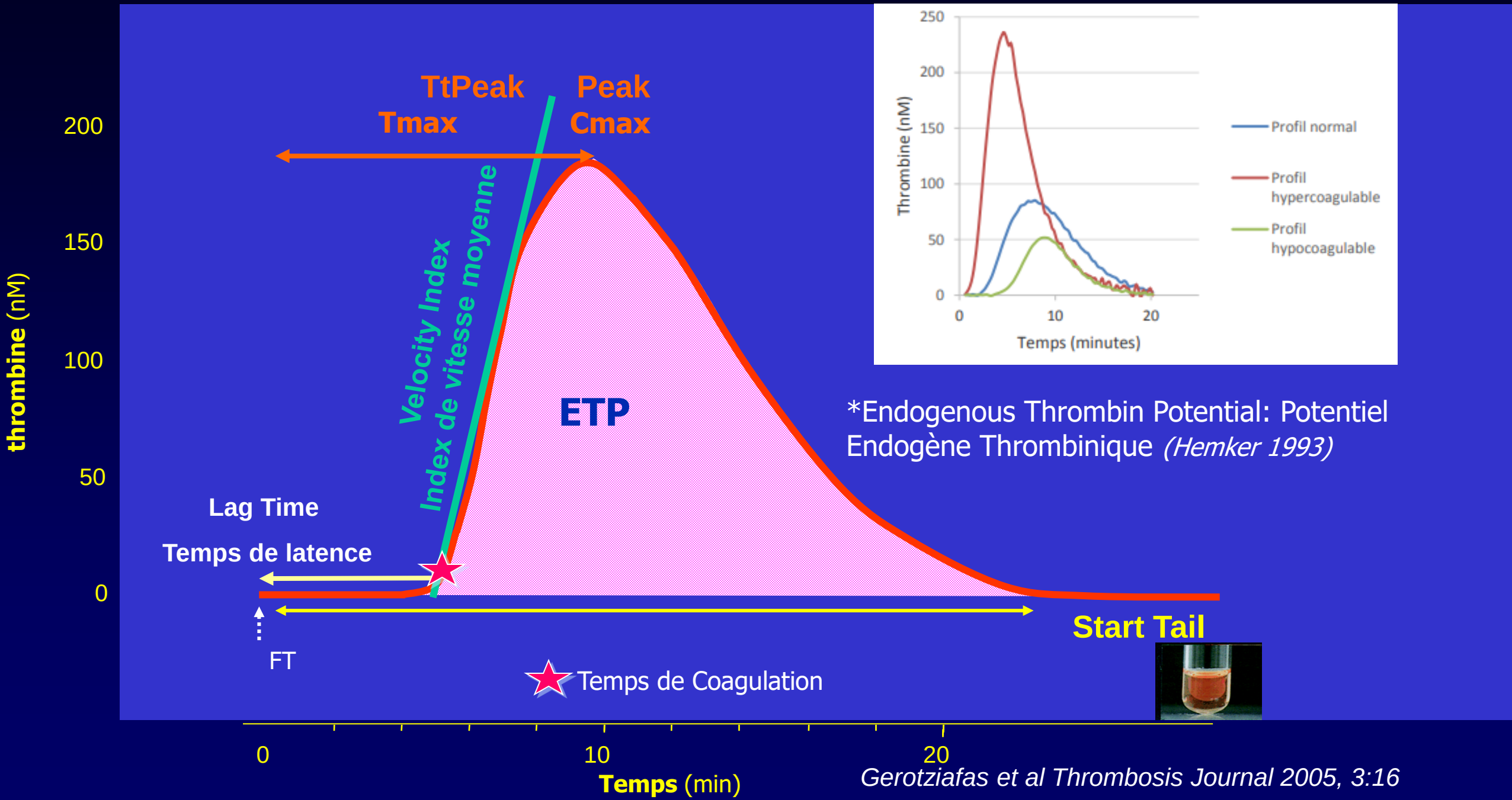
Gerotziafas et al. The Oncologist 2017; 22:1–10

VTE risk level	Ranges of COMPASS-CAT RAM (min-max)	Ranges of COMPASS-CAT Score (min-max)	Rate of VTE
Low (n=506)	≤ 4,7	0 to 6	1,7%
High (n=517)	≥ 4,8	≥ 7	13,3%



Specificity - 1

AUC: 0,85
NPV: 98%
Sensitivity: 88%
Specificity: 52%



*Endogenous Thrombin Potential: Potentiel Endogène Thrombinique *(Hemker 1993)*

Gerotziafas et al Thrombosis Journal 2005, 3:16

OPTIMISATION DU SCORE COMPASS-CAT

	COMPASS-CAT score	COMPASS-CAT and ROADMAP Biomarkers score*
Negative Predictive Value	97 %	97 %
Positive Predictive Value	13 % →	70 %
Sensitivity	83 %	88 %
Specificity	51 % →	70 %

*thrombin generation/Procoagulant-phospholipid dependent clotting time

Syrigos et al. Oncologist. 2018;23(11):1372-1381

EVALUATION DE LA PERFORMANCE DANS LE CANCER PULMONAIRE

	Overall population $n=118$	VTE group during follow-up[a] $n=20$	Non-VTE group during follow-up[a] $n=98$
High KRS[b]	15 (13%)	2 (10%)	13 (13%)
High PROTECHT[c]	62 (52%)	11 (55%)	51 (52%)
High CONKO[d]	26 (22%)	4 (20%)	22 (22%)
High COMPASS[e]	84 (71%)	20 (100%)	64 (65%)

Factor	Odds ratio (95% CI)	*P*
High COMPASS-CAT score	9.65 (1.24–75.24)	0.031
Gemcitabine chemotherapy	4.12 (1.09–10.39)	0.006
Atrial fibrillation	8.26 (2.40–28.41)	0.001
Recent hospitalization for acute	0.02 (0.01–0.14)	0.001

”In lung cancer, COMPASS-CAT best distinguished between patients at low or high risk of VTE”

ASCO recommendations

Key et al J Clin Oncol. 2020;38(5):496-520

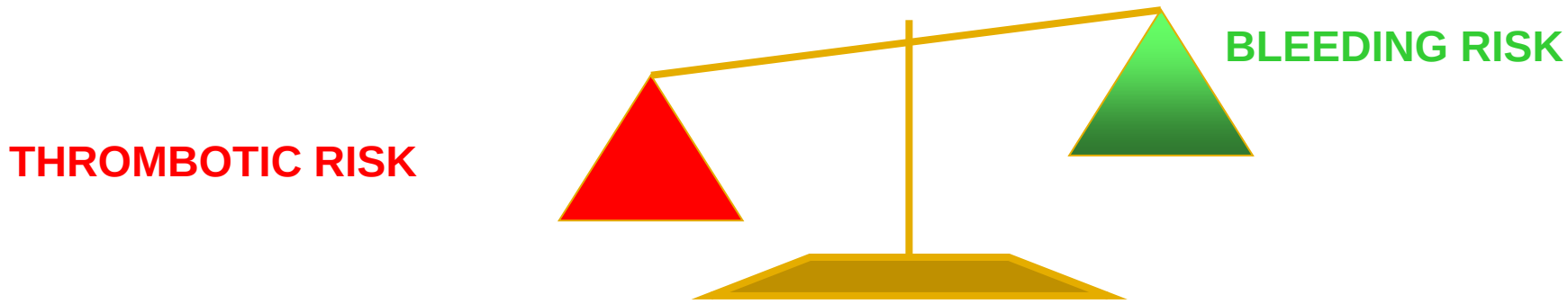
Rupa-Matysek et al. Med Oncol. 2018;35(5):63.

STRATIFICATION AVISÉE…
THROMBOPROPHYLAXIE ADAPTÉE…

PESER le RISQUE …

PRESCRIRE chez le HAUT RISQUE …

… PROSCRIRE chez le FAIBLE RISQUE!



QUELLES SONT LES PROPOSITIONS JUSTES?

A. Il est recommandé de stratifier le risque thrombotique chez tout patient atteint de cancer hospitalisé ou ambulatoire

B. Le score de Khorana est validé pour tous les types de cancers

C. Le score de Khorana est simple et utile chez les patients atteints de cancer colorectal ou cancer de l'estomac

D. Le score de Khorana ne peut être utilisé qu'une seule fois en pré-chimiothérapie

QUELLES SONT LES PROPOSITIONS JUSTES?

A. Il est recommandé de faire une thromboprophylaxie par HBPM chez les patients atteints de cancer et hospitalisés en situation aiguë

B. Il est suggéré de faire une thromboprophylaxie par HBPM chez les patients ambulatoires atteints de cancer et à haut risque thrombotique

C. Il est recommandé de faire une thromboprophylaxie par AOD chez les patients atteints de cancer et hospitalisés en situation aiguë

D. Il est suggéré de faire une thromboprophylaxie par AOD chez les patients ambulatoires atteints de cancer et à haut risque thrombotique

VTE PROPHYLAXIS IN CRITICALLY ILL ADULTS
A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Review 13 RCTs (n=9,619 patients).

Compared with control (no prophylaxis, placebo, or compression stockings only), ↓↓ DVT incidence

LMWH vs Control OR 0.59 [95% CI 0.33-0.90]

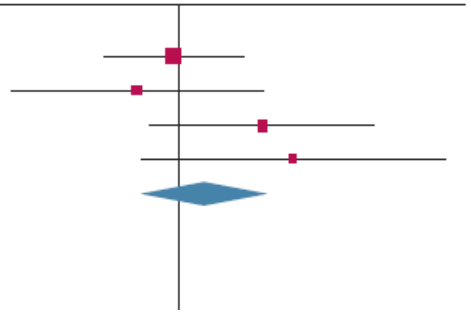
UFH vs Control OR 0.82 [95% CrI, 0.47-1.37]

LMWH vs UFH OR 0.72 [95% CrI, 0.46-0.98];

Major Bleeding

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	OR M-H, Random, 95% CI
2.1.1 LMWH vs UFH						
Cohn 1999	5	34	5	32	41.5%	0.93 [0.24-3.58]
De 2010	1	81	2	75	20.0%	0.46 [0.04-5.14]
Geerts 1996	5	171	1	173	23.6%	5.18 [0.60-44.81]
Olson 2015	4	216	0	220	14.8%	9.34 [0.50-174.51]
Subtotal (95% CI)		**502**		**500**	**100.0%**	**1.71 [0.49-5.95]**
Total events	15		8			

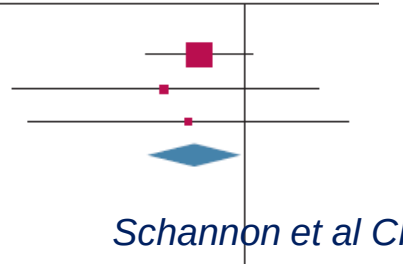
Heterogeneity: Tau² = 0.51; χ^2 = 4.33, *df* = 3 (*P* = .23); I^2 = 31%
Test for overall effect: *Z* = 0.84 (*P* = .40)



Heparin-Induced Thrombocytopenia

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	OR M-H, Random, 95% CI
1.1.1 LMWH vs UFH						
Cook 2011	5	1,873	12	1,873	81.7%	0.42 [0.15-1.18]
Geerts 1996	0	129	2	136	9.6%	0.21 [0.01-4.37]
Olson 2015	0	216	1	220	8.7%	0.34 [0.01-8.34]
Subtotal (95% CI)		**2,218**		**2,229**	**100.0%**	**0.38 [0.15-0.98]**
Total events	5		15			

Heterogeneity: Tau² = 0.00; χ^2 = 0.18, *df* = 2 (*P* = .91); I^2 = 0%
Test for overall effect: *Z* = 2.00 (*P* = .05)



Schannon et al CHEST 2022; 161(2):418-428

THROMBOPROPHYLAXIE CHEZ LES PATIENTS AVEC CANCER AMBULATOIRES & CHIMIOTHÉRAPIE

LMWH *versus* **no prophylaxis**: actualized meta-analysis

		Weighted Incidence [IC95%]			
		LMWH	**No LMWH**	RR [CI95%]	p
VTE Symptomatic	11 RCTs 5 284 pts	**3.9** % [3.2 - 4.6]	**7.7** % [6.7 - 8.8]	**0.56** [0.45 ; 0.69]	<0.0001
Major Bleeding	13 RCTs 6 356 pts	**2.0** % [1.6 - 2.5]	**1.5** % [1.0 - 1.9]	**1.44** [0.98 ; 2.11]	0.065

NNT = 26 **NNH = 200**

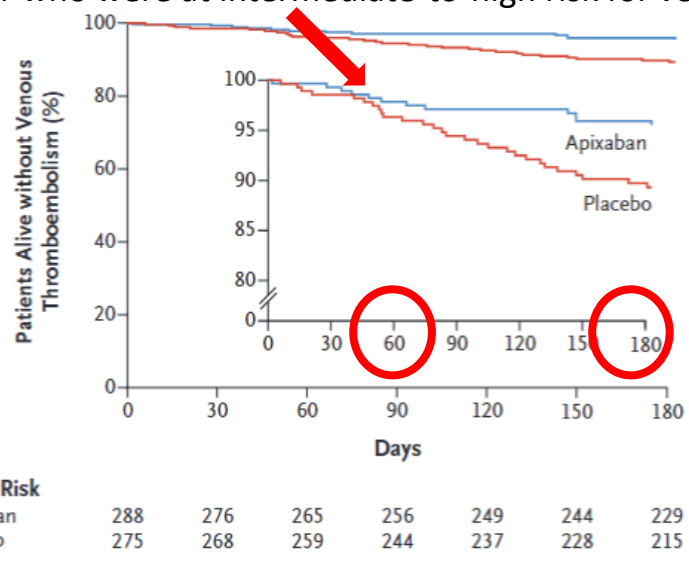
Mismetti et al. Oral Communication ICTHIC 2018
https://www.icthic.com/program/slides last access October 2019

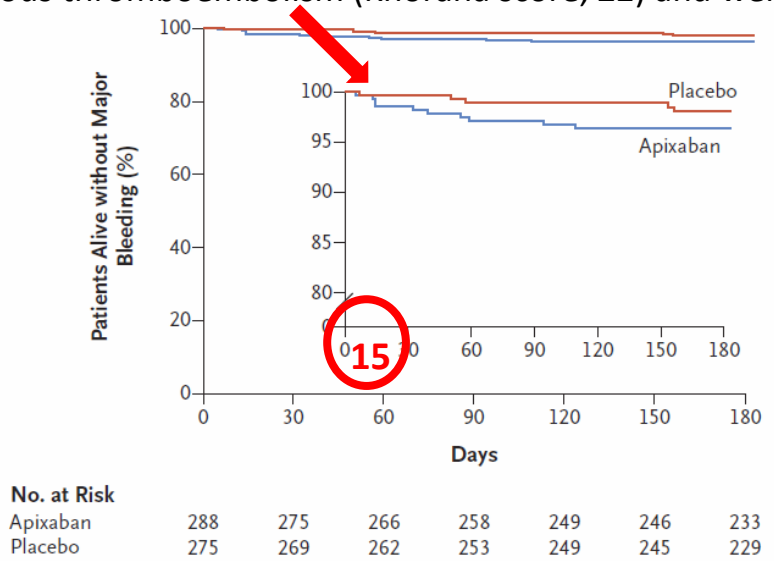
Courtesy P. Mismetti.

AVERT
EFFICACY/SAFETY

50% apixaban group
40% placebo group } ***have discontinued the trial regimen***

Randomized, placebo-controlled, double-blind clinical trial assessing the efficacy and safety of **apixaban (2.5 mg twice daily)** for thromboprophylaxis in ambulatory pts with cancer who were at intermediate-to-high risk for venous thromboembolism (Khorana score, ≥2) and were initiating chemotherapy



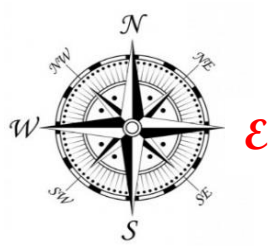


N=574

64% with KS=2

Pancreas	**13%**
Gastric	**9%**
Lung	**11%**
Gynecol	**26%**
Lymphoma	**26%**

Cumulative Incidence	Apixaban	Placebo	HR (95% CI)	*P* Value	NNT/NNH
VTE (mITT), %	4.2	10.2	0.41 (0.26, 0.65)	< .001	NNT =17
Major bleeding (mITT), %	3.5	1.8	2.00 (1.01, 3.95)	.046	NNH = 59
Major bleeding (on treatment), %	2.1	1.1	1.89 (0.39, 9.24)	NS	NNH = 100

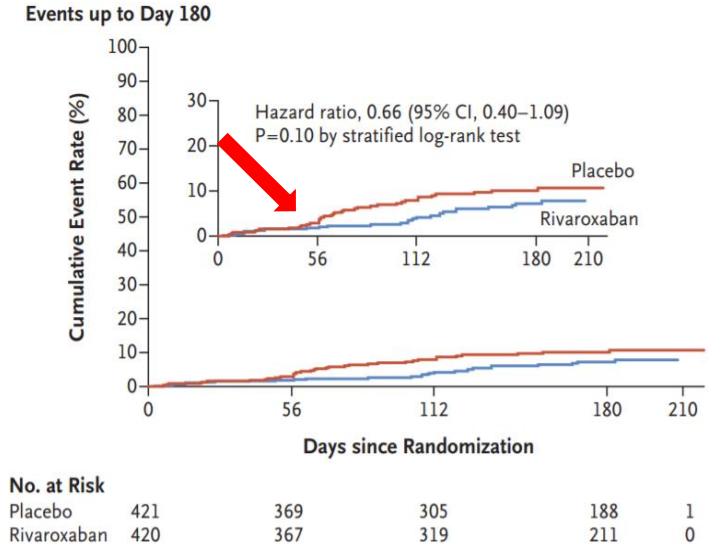


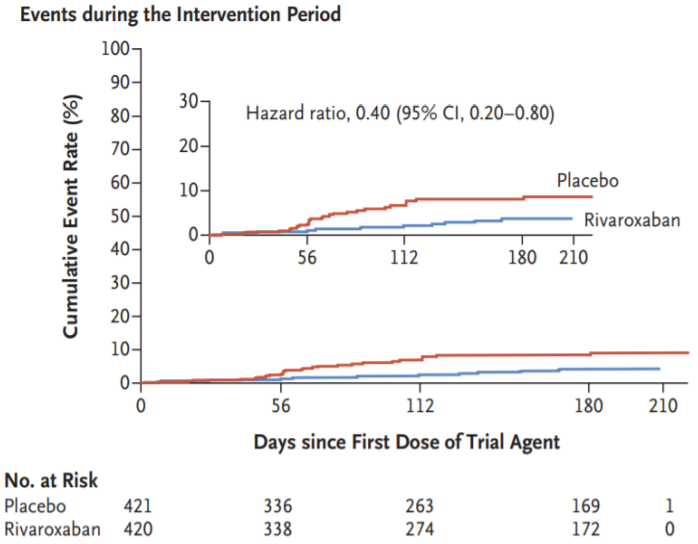
Carrier M et al. N Engl J Med. 2019;380(8):711-719.

CASSINI EFFICACY/SAFETY

44% rivaroxaban group
50% placebo group } ***have discontinued the trial regimen***

Double-blind, randomized trial involving high-risk ambulatory pts with cancer (Khorana score ≥2, on a scale from 0 to 6, with higher scores indicating a higher risk of VTE), pts without DVT at screening were assigned to receive **rivaroxaban (10 mg)** or placebo daily for up to 180 days, with screening every 8 weeks



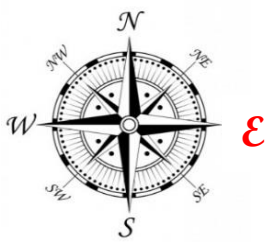


N=841

67% with KS=2

Pancreas	**32%**
Gastric	**23%**
Lung	**15%**
Gynecol	**10%**
Lymphoma	**8%**

Cumulative Incidence	Rivaroxaban	Placebo	HR (95% CI)	*P* Value
VTE, n, % (ITT)	25/420, 6.0	37/421, 8.8	0.66 (0.40, 1.09)	.10
VTE, n, % (during treatment)	11/420, 2.6	27/421, 6.4	0.40 (0.20, 0.80)	-
Major bleeding (ITT), n, %	8/405, 2.0	4/404, 1.0	1.96 (0.59, 6.49)	.26



Khorana AA et al. N Engl J Med. 2019;380(8):720-728.

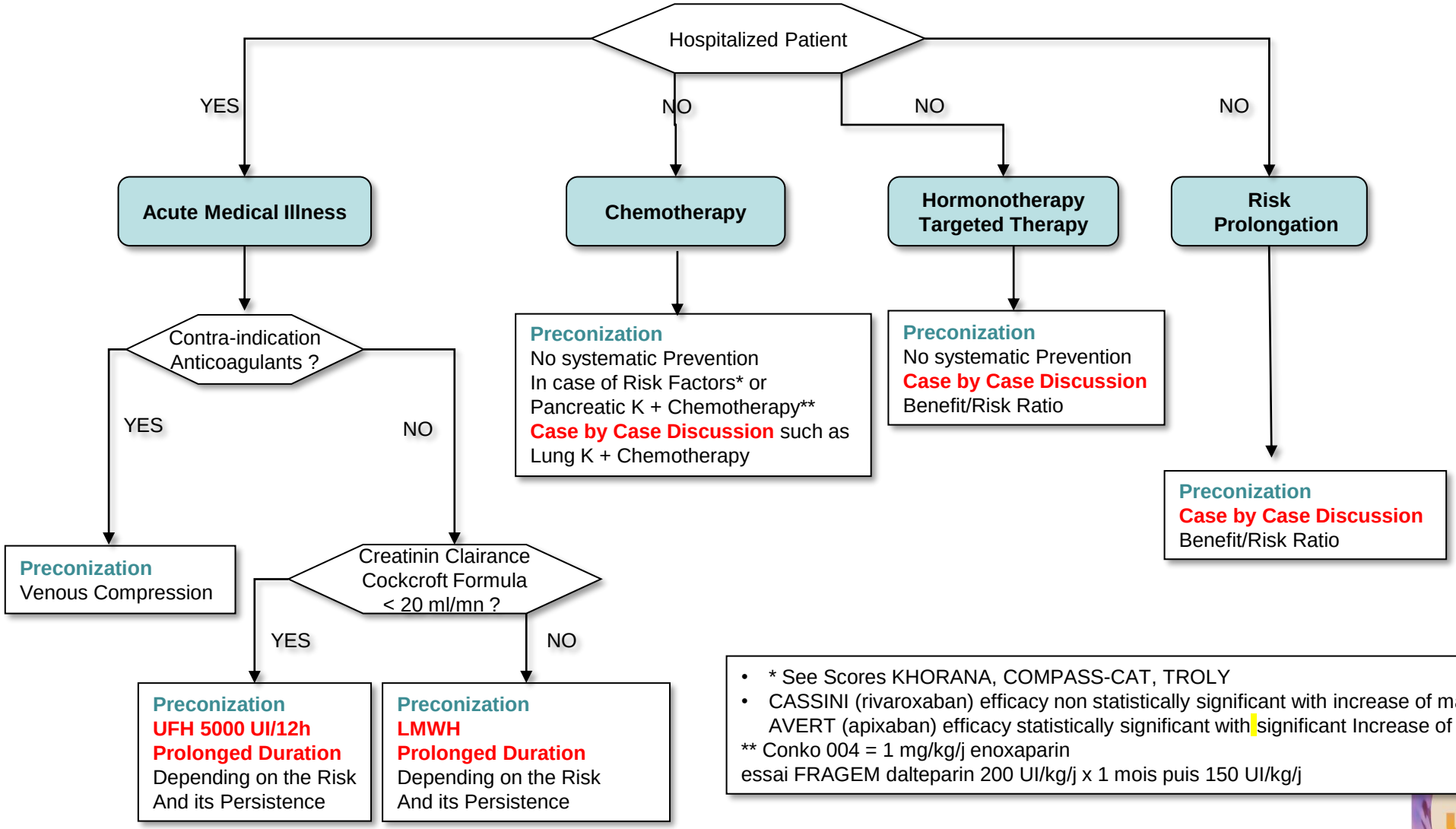
LMWH IN PRIMARY PREVENTION IN CANCER PATIENTS

Clinical trial	Efficacy – VTE Primary efficacy endpoint	Safety –Major bleeding
SAVE ONCO Semuloparin (S) vs. Placebo (P)	✓ S 1.2% vs P 3.4%; P<0.001	✓ S 2.8% vs P 2.0% Clinically relevant bleeding (major and nonmajor) Main safety outcome
PROTECHT Nadroparin (N) vs. Placebo (P)	✓ N 2.0% vs. P 3.9%; p=0.02 Composite of symptomatic venous or arterial thromboembolic events	✓ Major bleeding N 0.7% vs. P 0.0%; p=0.18 Minor bleeding N 7.4% vs. P 7.9%
CONKO-004 Enoxaparin (E) vs. Observation (O)	✓ E 2/160 vs. O 15/152 HR 0.12 (95% CI, 0.03-0.52); p=0.001 symptomatic VTE at 3 months	✓ Major bleeding E 7/160 vs. O 5/152 HR 1.4 (95% CI 0.35-3.72); p=1.0
FRAGEM-UK Dalteparin (D) vs. Observation (O)	✓ D 3.4% vs O 23.0%; p=0.002 VTE during the treatment period	✓ D 3.4% vs O 3.2%; p=NS ISTH 'Severe'
CASSINI Rivaroxaban (R) vs. Placebo(P)	✗ R 6.0% vs P 8.8%; p=0.10 ITT analysis	✗ 2.0% vs P 1.0%; HR 1.96; 95% CI, 0.59-6.49; p=0.26 Major bleeding
AVERT Apixaban (A) vs. Placebo(P)	✓ A 4.2% vs P 10.2%; p<0.001 ITT analysis	✗ R 3.5% vs P 1.8%; HR 2.00; 95% CI, 1.01-3.95; p=0.046 Major bleeding

« AVERT pour AVERTI» … « CASSINI pour ce Cas C'est Ni Ni : Ni efficacy Ni safety »

AFSOS 2021

Primary Prevention in Cancer Patient In Medical Seetings



- * See Scores KHORANA, COMPASS-CAT, TROLY
- CASSINI (rivaroxaban) efficacy non statistically significant with increase of major bleeding
  AVERT (apixaban) efficacy statistically significant with significant Increase of major bleeding

** Conko 004 = 1 mg/kg/j enoxaparin
essai FRAGEM dalteparin 200 UI/kg/j x 1 mois puis 150 UI/kg/j

https://www.afsos.org/referentiels-recommandations/decouvrir-tous-les-referentiels/

RECOMMANDATIONS ITAC & ESC 2022

Prophylaxis of VTE in surgically-treated patients with cancer

International Advisory Panel ranking: 8·62 out of 9·00

1 Use of low-molecular-weight-heparin (LMWH) once per day (when creatinine clearance is ≥30 mL/min) or low-dose unfractionated heparin three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 2–12 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another (grade 1A). Values and preferences: LMWH once per day is more convenient.

2 There is insufficient evidence to support fondaparinux (grade 2C) or direct oral anticoagulants (grade 2B) as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer. Values and preferences: as per the first recommendation.

3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A).

4 Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major abdominal or pelvic surgery (either laparotomy or laparoscopy) is recommended in patients with cancer who do not have a high risk of bleeding (grade 1A). Values and preferences: longer duration of injections.

5 Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated (grade 2A). Values and preferences: no injection.

6 Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A).

Prophylaxis of VTE in medically-treated patients with cancer

International Advisory Panel ranking: 8·44 out of 9·00

1 We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance is ≥30 mL/min, or with unfractionated heparin in medically-treated patients with cancer and reduced mobility who are admitted to hospital (grade 1B). In this setting, direct oral anticoagulants are not recommended routinely (guidance). Values and preferences: subcutaneous injections. Costs: in some countries, price differences between LMWH, unfractionated heparin, or fondaparinux might affect the choice.

2 Primary pharmacological prophylaxis of VTE with LMWH (grade 1A) or with direct oral anticoagulants (rivaroxaban or apixaban; grade 1B) is indicated in ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low risk of bleeding. Values and preferences: subcutaneous injections.

3 Primary pharmacological prophylaxis of VTE with LMWH is not recommended outside of a clinical trial for patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy, including patients who have a low risk of bleeding (guidance).

4 Primary prophylaxis with direct oral anticoagulant (rivaroxaban or apixaban) is recommended in ambulatory patients who are receiving systemic anticancer therapy and are at intermediate-to-high-risk of VTE, identified by a validated risk assessment model (ie, a Khorana score ≥2), and not actively bleeding or not at a high risk for bleeding (grade 1B).

Recommendation	Class[a]	Level[b]
Extended prophylaxis with LMWH for 4 weeks post-operatively is recommended for patients with cancer undergoing major open or laparoscopic abdominal or pelvic surgery with low bleeding risk and high VTE risk.[c,298,299,595]	I	B
Prophylactic LMWH for the primary prevention of VTE is indicated in hospitalized patients with cancer or those with prolonged bedrest or reduced mobility in the absence of bleeding or other contraindications.[298,299,592,594]	I	B
For ambulatory patients with cancer at high risk of thrombosis receiving systemic therapy,[d] primary thromboprophylaxis with a NOAC (apixaban or rivaroxaban) or LMWH may be considered, provided there are no significant contraindications.[e,298,593,594,601,602]	IIb	B
A discussion with the patient about the relative benefits and harms, cancer prognosis, drug cost, and duration of treatment is recommended prior to prophylactic anticoagulation for the primary prevention of VTE.	I	C

Farge et al. 2022 Lancet Oncol 2022;23:e334-e347.

Lyon et al Eur Heart J. 2022;ehac244:1-133.

QUELLES SONT LES PROPOSITIONS JUSTES?

A. Il est recommandé de faire une thromboprophylaxie par HBPM chez les patients atteints de cancer et hospitalisés en situation aiguë

B. Il est suggéré de faire une thromboprophylaxie par HBPM chez les patients ambulatoires atteints de cancer et à haut risque thrombotique

C. Il est recommandé de faire une thromboprophylaxie par AOD chez les patients atteints de cancer et hospitalisés en situation aiguë

D. Il est suggéré de faire une thromboprophylaxie par AOD chez les patients ambulatoires atteints de cancer et à haut risque thrombotique

QUELLES SONT LES PROPOSITIONS JUSTES?

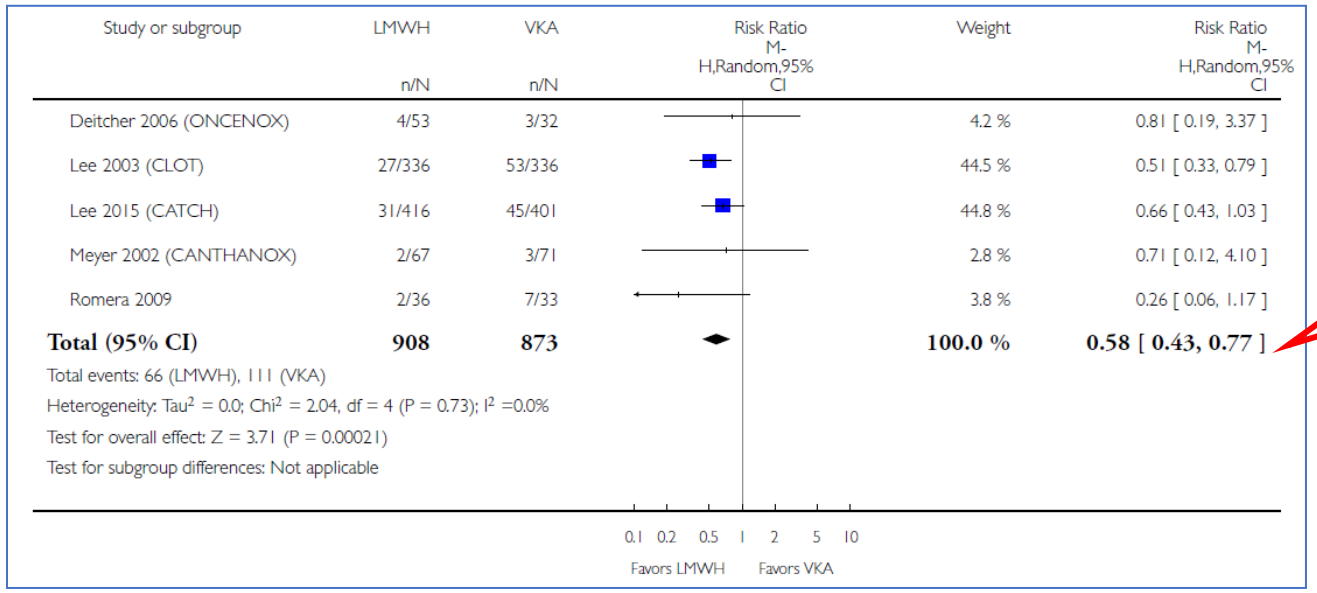
A. Il est suggéré de traiter par AVK une MTEV chez les patients atteints de cancer en cas d'insuffisance rénale sévère (Clcr < 30 ml/min)

B. Il est recommandé de traiter par HBPM une MTEV chez les patients atteints de cancer en cas thrombopénie modérée (Plaquettes ≥ 50 G/L)

C. Il est recommandé traiter par AOD une MTEV récidivante sous HBPM chez les patients atteints de cancer en l'absence d'interaction médicamenteuse sur les voies des Pgp et des cytochromes.

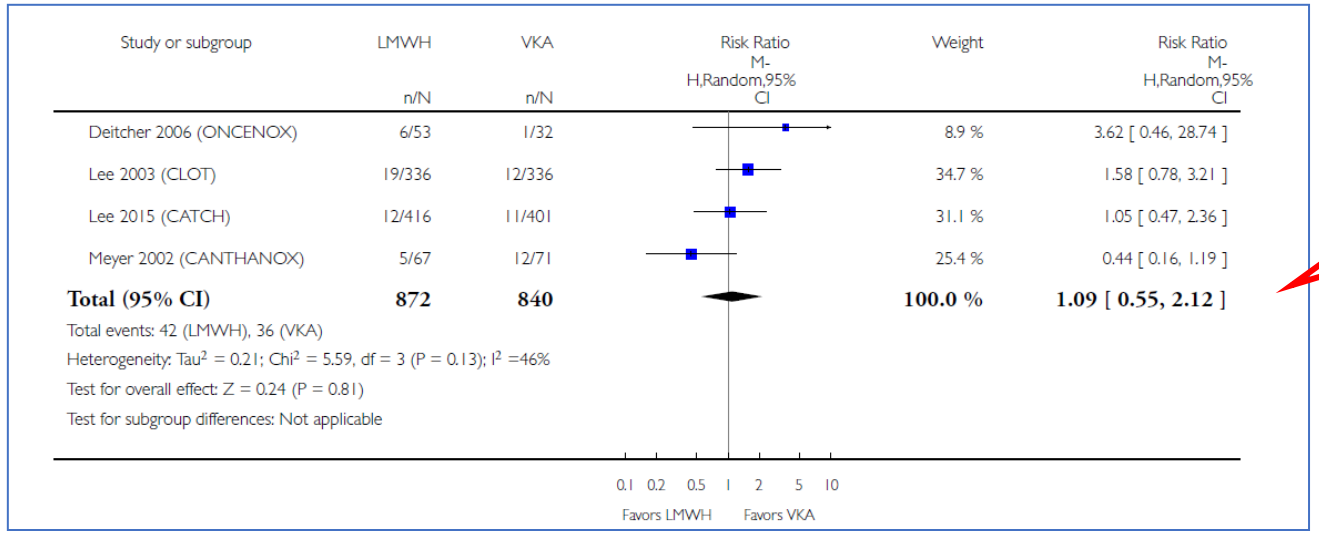
D. Il est suggéré de maintenir un traitement par AOD d'une MTEV au-delà des 6 mois de traitement chez les patients ambulatoires ayant un cancer actif

LMWH VS VKA: META-ANALYSIS IN CAT TREATMENT



Recurrent venous thromboembolism (up to 6 months)

0.58 (CI: 0.43-0.77)

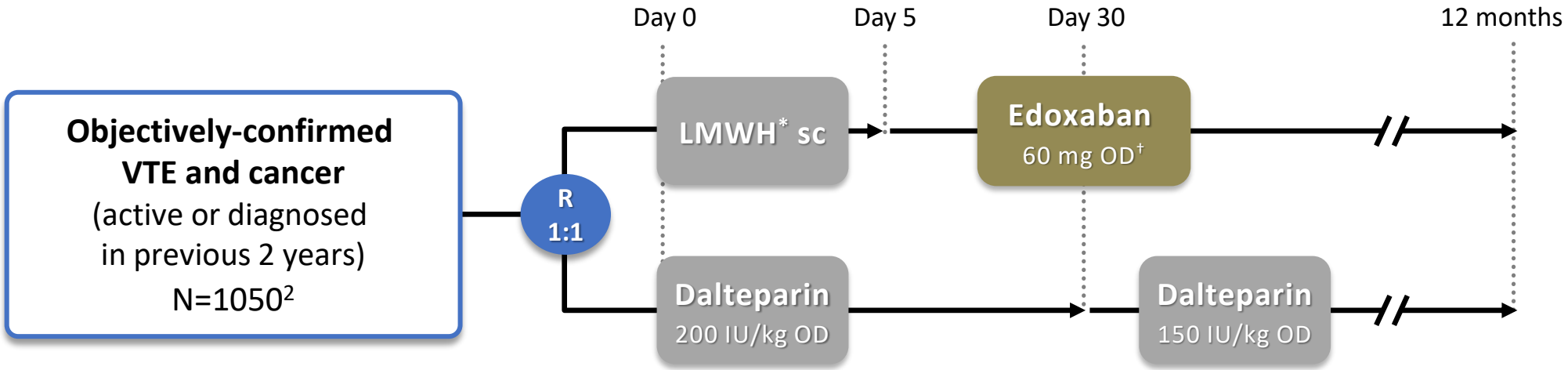


Major bleeding (6-12 months)

1.09 (CI: 0.55-2.12)

Kahale et al. Cochrane Database Syst Rev. 2018;6(6):CD006650.

HOKUSAI VTE CANCER: EDOXABAN VS HBPM



Primary endpoint: Composite of recurrent VTE or major bleeding

Key secondary endpoints: Recurrent VTE, major bleeding

*≥5 days of LMWH. Choice of LMWH type and lead-in duration were left to treating physician
†Edoxaban 30 mg OD for patients requiring dose adjustment for CrCl 30–50 mL/min, body weight ≤60 kg and/or concomitant P–gp inhibitor use

CrCl: creatinine clearance; LMWH: low-molecular-weight heparin; OD: once daily; P-gp: P-glycoprotein;
PROBE: Prospective Randomised Open Blinded End-Point; sc: subcutaneous; VTE: venous thromboembolism

Raskob GE et al. N Engl J Med 2018 ;378(7):615-624.

HOKUSAI VTE-CANCER RESULTS

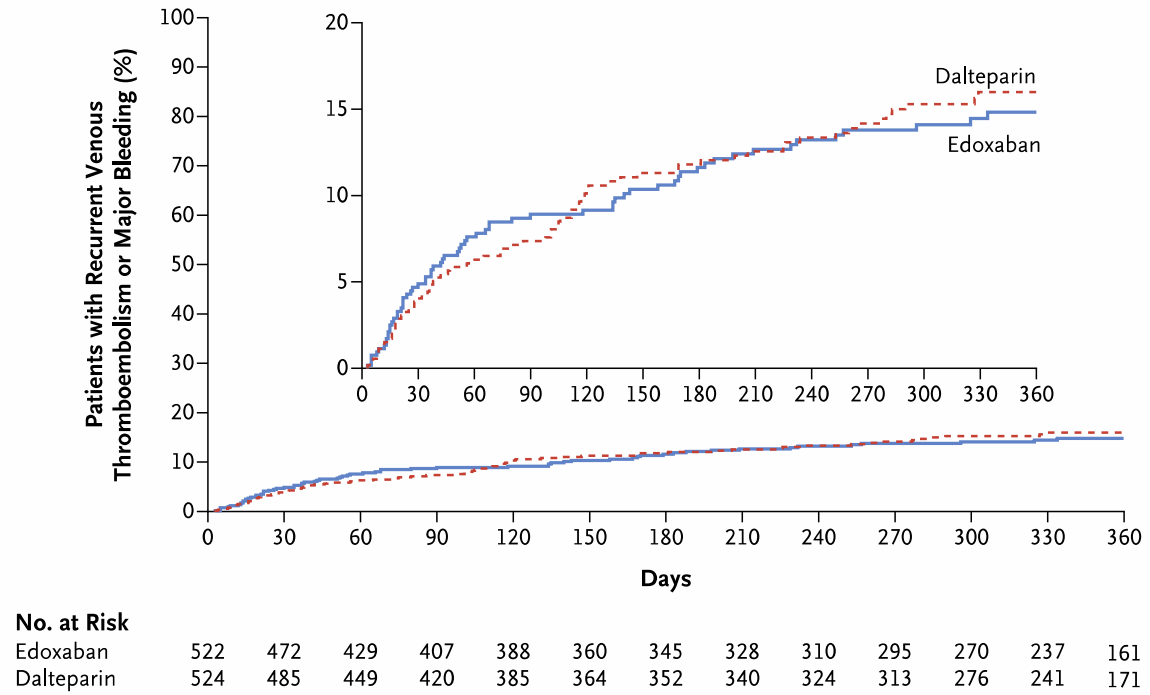


Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.

The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority

Raskob GE et al. N Engl J Med 2018 ;378(7):615-624.

HOKUSAI VTE CANCER: BLEEDING

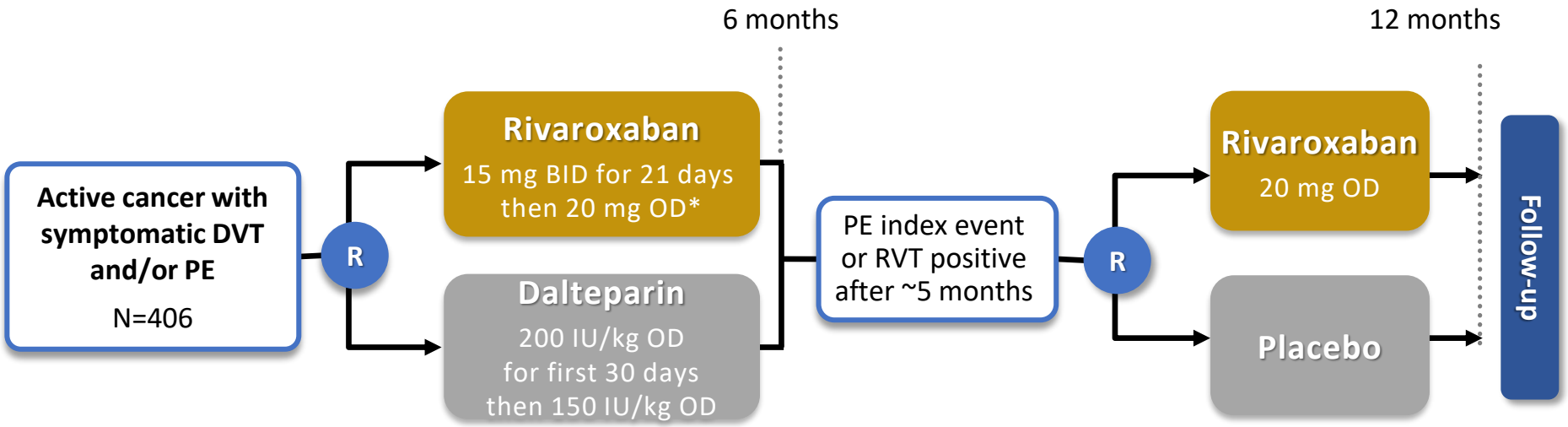
	Edoxaban	Dalteparin	
Major bleeding – no. (%)	33 (6.3)	17 (3.2)	x2
Fatal*	0	2 (0.4)	
Intracranial	2 (0.4)	4 (0.8)*	
Gastrointestinal	20 (3.8)	6 (1.1)	x3
Upper	17 (3.3)	3 (0.6)	
Lower	3 (0.6)	3 (0.6)	
Urogenital	5 (1.0)	0	x5

* The site of fatal bleeding was intracranial in one patient and lower gastrointestinal in one patient.

Raskob GE et al. N Engl J Med 2018 ;378(7):615-624.

SELECT-D : RIVAROXABAN VS HBPM

Prospective, randomised, open-label, multicentre pilot phase III study



Efficacy (primary): Rate of VTE recurrence (symptomatic and incidental PE)
Secondary: Rate of major bleeding and CRNM bleeding (also assess survival, health economics)

*Dose reduction or discontinuation specified for different levels of renal impairment. If a patient's platelet counts falls to <50,000/mm^3, rivaroxaban should be discontinued until the platelet count recovers to above 50,000/mm^3

BID: twice daily; CRNM: clinically-relevant nonmajor; PE: pulmonary embolism; RVT: residual vein thrombosis

Young AM. J Clin Oncol. 2018 ;36(20):2017-2023.

BLEEDING N (%)

Category	Dalteparin (n=203)	Rivaroxaban (n=203)
Major*	6 (3%)	11 (5%)
Clinically relevant non-major	6 (3%)	25 (12%)
Total	12 (6%)	36 (17%)

x2

x 4

*1 fatal bleeding event in each arm

Most major bleeding events were gastrointestinal bleeding; no CNS bleeds

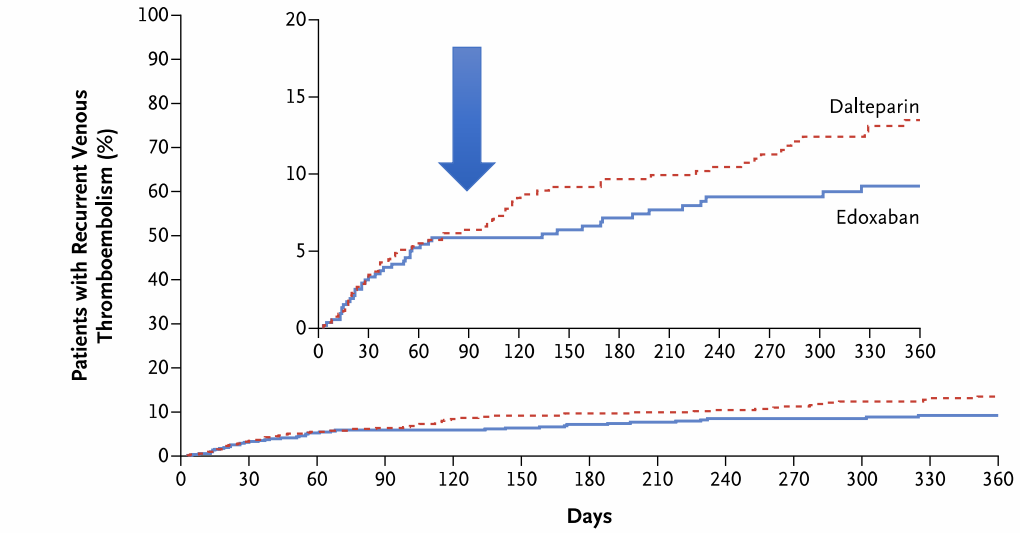
Most CRNMBs were gastrointestinal or urological

SELECT-D: STOP recruitment gastro-oesophageal cancer due to bleeding 36% Riva vs 11% Dalté

Young AM. J Clin Oncol. 2018 ;36(20):2017-2023.

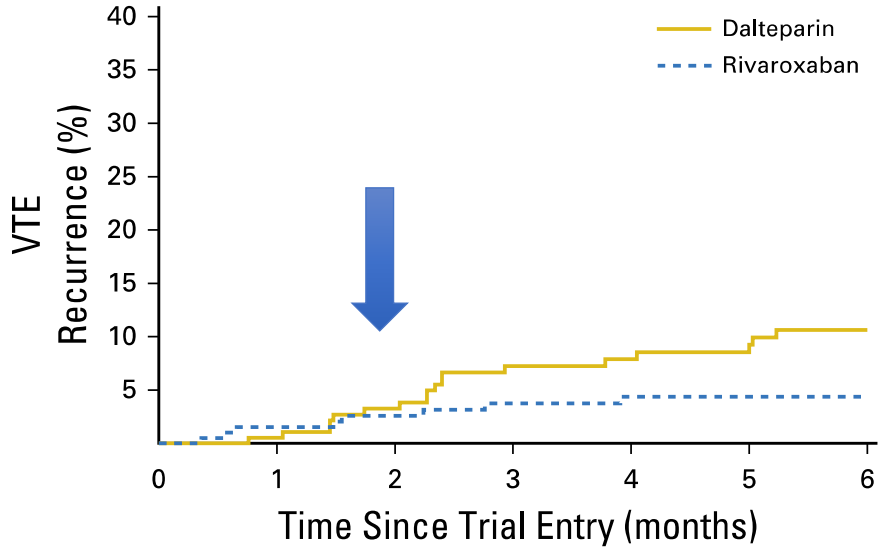
THROMBOTIC RECURRENCES

HOKUSAI



No. at Risk													
Edoxaban	522	480	437	415	395	370	356	340	320	307	281	245	168
Dalteparin	524	488	452	423	389	370	358	348	333	321	282	246	174

SELECT-D



No. at risk:				
Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

Dose reduction of dalteparin 25% after 4 weeks

Raskob GE et al. N Engl J Med 2018 ;378(7):615-624

Young AM. J Clin Oncol. 2018 ;36(20):2017-2023.

CARAVAGGIO : APIXABAN VS DALTEPARIN

Study design

Randomized, open-label, PROBE, non inferiority study

Treatment period: 6 months

Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

CARAVAGGIO : TYPES OF CANCER

	Apixaban (N=576)	Dalteparin (N=579)
Solid tumor – no.(%)		
Colorectal	121 (21.0%)	113 (19.5%)
Lung	105 (18.2%)	95 (16.4%)
Breast	79 (13.7%)	76 (13.1%)
Genitourinary	66 (11.5%)	73 (12.6%)
Gynecological	60 (10.4%)	59 (10.2%)
Pancreatic or hepatobiliary	44 (7.6%)	43 (7.4%)
Upper gastrointestinal	23 (4.0%)	31 (5.4%)
Head and neck	14 (2.4%)	8 (1.4%)
Bone/Soft tissue	11 (1.9%)	7 (1.2%)
Skin - Melanoma	4 (0.7%)	7 (1.2%)
Other	16 (2.8%)	15 (2.6%)
Hematological malignancy – no. (%)	33 (5.7%)	52 (9.0%)

Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

CARAVAGGIO : PATIENT CHARACTERISTICS

Characteristic	(N=576)	(N=579)
Age — yr	67.2±11.3	67.2±10.9
Male sex — no. (%)	292 (50.7)	276 (47.7)
Weight — kg	75.7±16.1	76.1±16.7
Platelet count <100,000 per mm^3 — no. (%)	21 (3.6)	22 (3.8)
Creatinine clearance ≤50 ml per min — no. (%)	51 (8.9)	61 (10.5)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without deep-vein thrombosis	304 (52.8)	334 (57.7)
Deep-vein thrombosis only	272 (47.2)	245 (42.3)
Symptomatic deep-vein thrombosis or pulmonary embolism	460 (79.9)	465 (80.3)
Incidental deep-vein thrombosis or pulmonary embolism†	116 (20.1)	114 (19.7)
History of venous thromboembolism before index event — no. (%)	45 (7.8)	61 (10.5)
Type of cancer — no. (%)		
Active	559 (97.0)	565 (97.6)
Recurrent locally advanced or metastatic	389 (67.5)	396 (68.4)
Cancer treatment — no. (%)‡		
At enrollment	350 (60.8)	367 (63.4)
Within previous 6 mo	143 (24.8)	129 (22.3)
During trial period	344 (59.7)	346 (59.8)
ECOG performance-status score — no. (%)§		
0	186 (32.3)	170 (29.4)
1	281 (48.8)	277 (47.8)
2	109 (18.9)	132 (22.8)

Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

CARAVAGGIO : PATIENT CHARACTERISTICS

Characteristic	Apixaban (N=576)	Dalteparin (N=579)
Age — yr	67.2±11.3	67.2±10.9
Male sex — no. (%)	292 (50.7)	276 (47.7)
Weight — kg	75.7±16.1	76.1±16.7
Platelet count <100,000 per mm^3 — no. (%)	21 (3.6)	22 (3.8)
Creatinine clearance ≤50 ml per min — no. (%)	51 (8.9)	61 (10.5)
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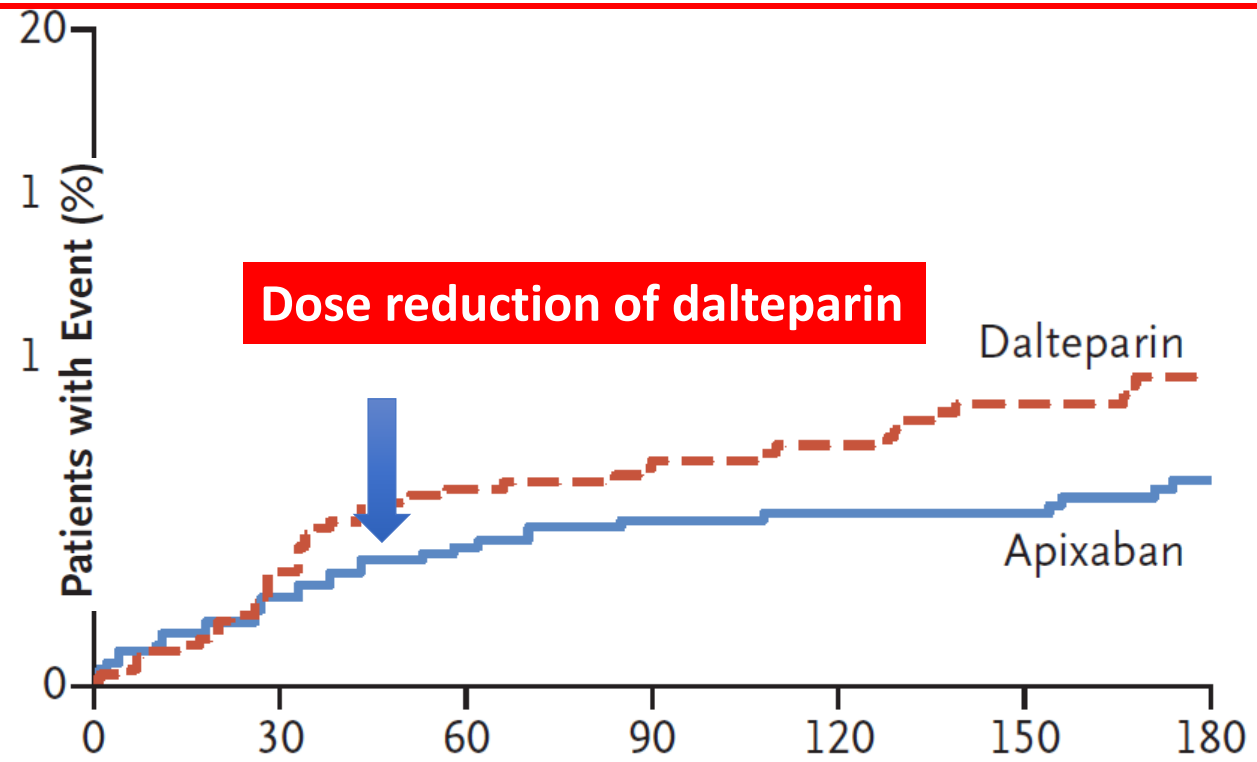
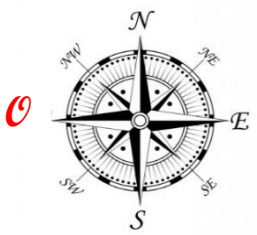
Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

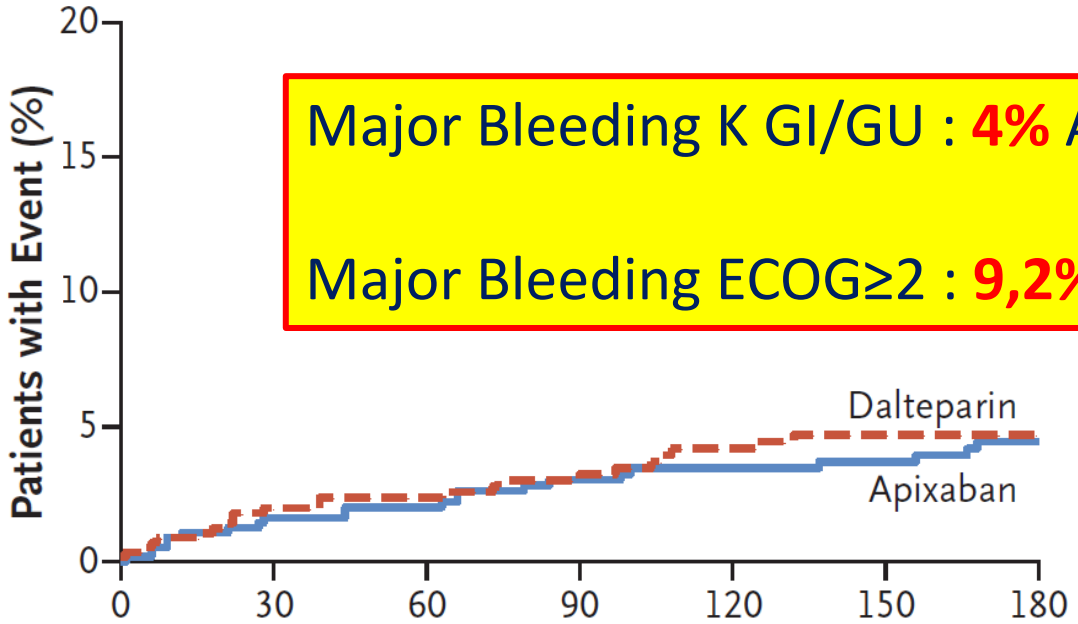
Outcome	Apixaban (N=576)	Dalteparin (N=579)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome — no. (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for nonin-feriority; 0.09 for superiority
Recurrent deep-vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent pulmonary embolism	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal pulmonary embolism¶	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	





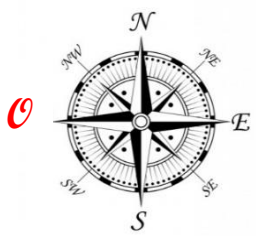
Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

Primary safety outcome — no. (%)	Apixaban	Dalteparin	Hazard Ratio	P Value
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	
Secondary outcomes — no. (%)				
Recurrent venous thromboembolism or major bleeding	51 (8.9)	66 (11.4)	0.70 (0.45–1.07)	
Clinically relevant nonmajor bleeding	52 (9.0)	35 (6.0)	1.42 (0.88–2.30)	
Major or clinically relevant nonmajor bleeding‖	70 (12.2)	56 (9.7)	1.16 (0.77–1.75)	
Death from any cause**	135 (23.4)	153 (26.4)	0.82 (0.62–1.09)	
Event-free survival††	422 (73.3)	397 (68.6)	1.36 (1.05–1.76)	



Major Bleeding K GI/GU : **4%** Apixaban vs **1%** Dalteparin

Major Bleeding ECOG≥2 : **9,2%** Apixaban vs **3,8%** Dalteparin



Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

ESSAIS CLINIQUES AOD ET CAT

- **Hokusai**

Critères d'exclusion:

- PS3-4
- Clairance < 30ml/min
- Cirrhose, ALT-AST > 3N, Bili > 2N
- HTA non contrôlée
- AINS
- **Inhibiteurs P-gp**

Age médian : 64 ans

- **Select-D**

Critères d'exclusion

- ECOG>2
- Pathologie hépatique
- HTA non contrôlée
- Antiplaquettaires
- **Induc/Inhib CYP3A4**
- **Induc/Inhib P-gp**

Age médian : 67 ans

- **Caravaggio**

Critères d'exclusion

- ECOG 3-4
- Clairance < 30ml/min
- Cirrhose, ALT-AST > 3N, Bili > 2N
- HTA non contrôlée
- AIntiplaquetaires
- **Induc/Inhib CYP3A4**
- Anémie <80g/L
- Plaquettes < 75G/L

Age médian : 67 ans

Pas d'analyse concernant la conséquence sur le traitement anti-tumoral

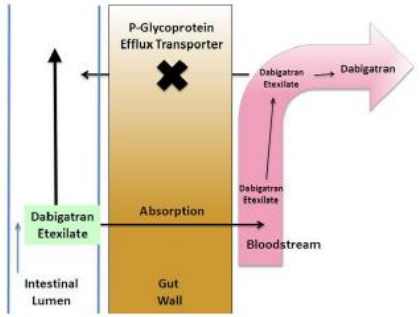
Raskob GE et al. N Engl J Med 2018 ;378(7):615-624.
Young AM. J Clin Oncol. 2018 ;36(20):2017-2023.
Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

INTERACTIONS POTENTIELLES

Table 5
Drug-drug interactions with antineoplastic therapies and direct oral anticoagulants or low-molecular-weight heparin (LMWH).

	Metabolic pathway	R	A	E	D	References	LMWH[1]	Colour codes
Cytotoxic chemotherapy								
cyclophosphamide	CYP3A4 induction	*	*			(Boddy and Yule, 2000)		Moderate to major increase in anticoagulant AUC (> 50%)
docetaxel	CYP3A4 induction	*	*			(Nallani et al., 2004)		
ifosfamide	CYP3A4 induction					(Hamberg et al., 2010)		Minor increase in anticoagulant AUC (< 2fold)
mitotane	CYP3A4 induction					(van Erp et al., 2011)		
paclitaxel	CYP3A4 induction	*	*			(Kostrubsky et al., 1998)		* Potential increase in anticoagulant AUC according to *in vitro* data
Oral targeted therapy								
axitinib	inhibition Pgp	*	*	*	*	axitinib SPC		Moderate to major decrease in anticoagulant AUC (> 50%)
crizotinib	inhibition of P-gp and CYP3A4	*	*	*	*	crizotinib SPC		
dabrafenib	CYP3A4 induction					dabrafenib SPC		Minor decrease in anticoagulant AUC (<50%)
dasatinib	CYP3A4 inhibition					dasatinib SPC		
erlotinib	CYP3A4 inhibition	*	*			erlotinib SPC		* Potential decrease in anticoagulant AUC according to *in vitro* data
idelalisib	CYP3A4 inhibition					idelalisib SPC		
imatinib	CYP3A4 inhibition					(Filppula et al., 2012)		No effect
lapatinib	inhibition of P-gp and CYP3A4					(Koch et al., 2015)		
nilotinib	CYP3A4 inhibition					(Zhang et al., 2015)		
pazopanib	CYP3A4 inhibition					(Goh et al., 2010)		
sunitinib	inhibition P-gp	*	*	*	*	sunitinib SPC		
vandetanib	inhibition P-gp	*	*	*	*	(Johansson et al., 2014)		
vemurafenib	CYP3A4 induction and P-gp inhibition					vemurafenib SPC		
Hormonal agents								
anastrozole	CYP3A4 inhibition	*	*			(Grimm and Dyroff, 1997)		
bicalutamide	CYP3A4 inhibition					(Cockshott, 2004)		
enzalutamide	CYP3A4 induction					(Gibbons et al., 2015)		
tamoxifène	CYP3A4 induction					(Dowsett et al., 1999)		
Supportive care								
aprepitant	CYP3A4 inhibition					(Majumdar et al., 2003)		
dexamethasone	CYP3A4 induction					(McCune et al., 2000)		

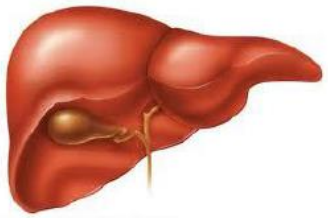
P-Glycoprotein



DOAC Metabolism and Drug Interactions

- P-gp inducers reduces drug level
- P-gp inhibitors increases drug level

CYP3A4/5 Metabolism



Except Dabigatran

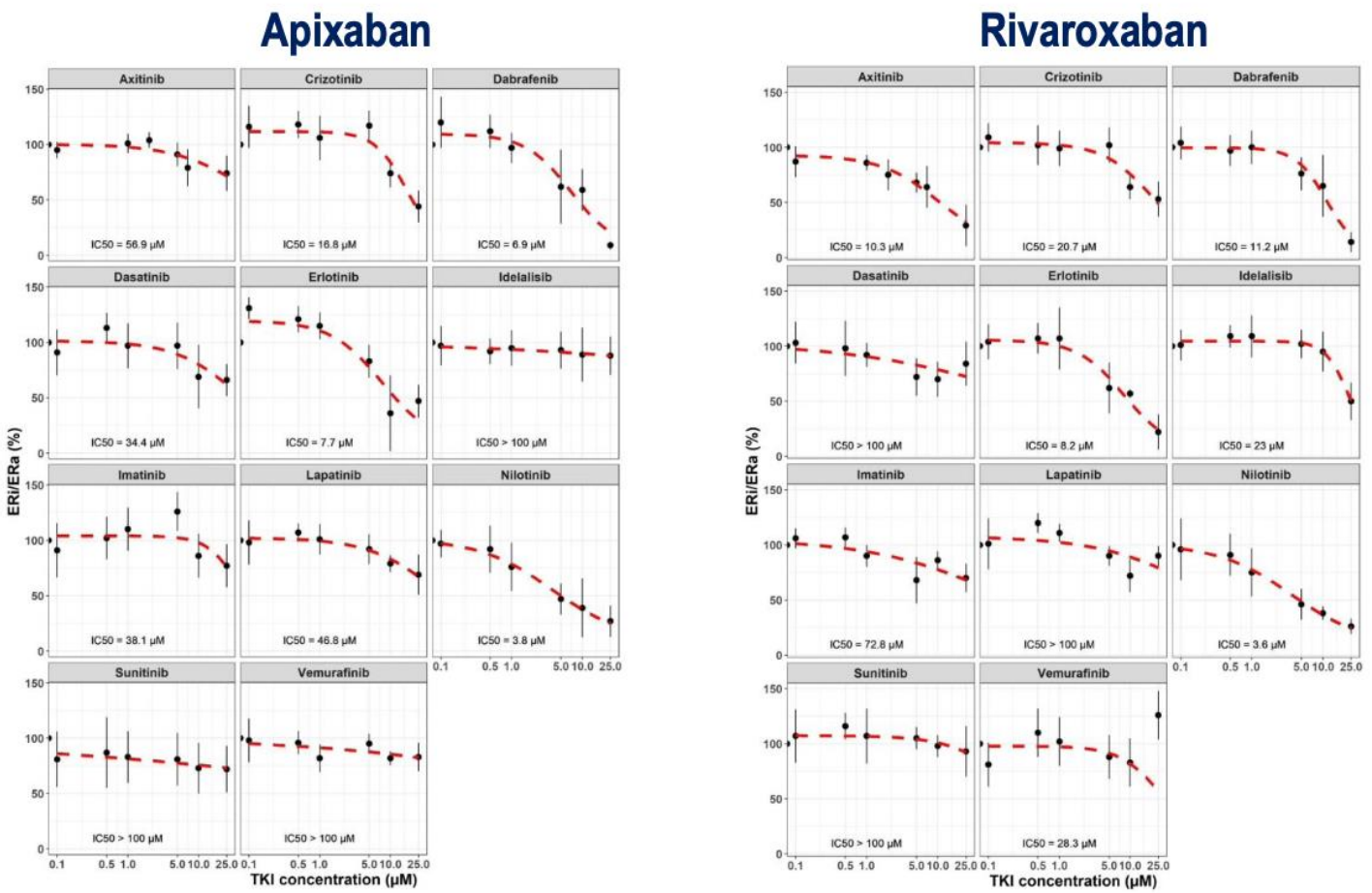
- Strong inducers of CYP3A4/5 decrease exposure of drug
- CYP3A4 Inhibitors increase blood concentrations drug

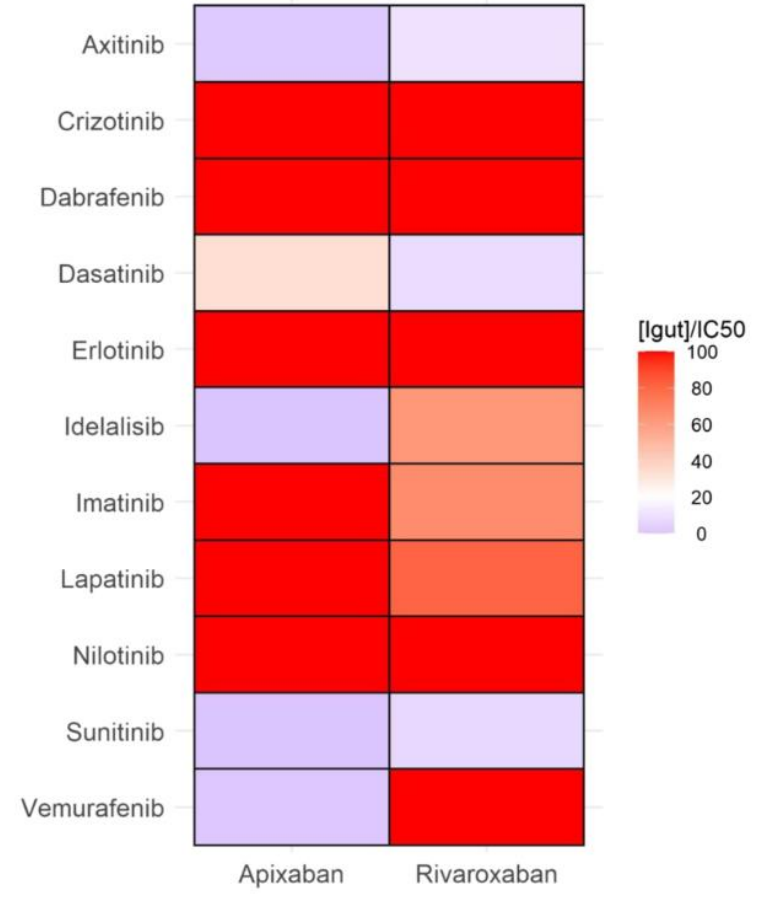
- **Inducers => ↑Thrombotic Risk**
- **Inhibitors => ↑ Bleeding Risk**

Shih & Crowther, Hematology Am Soc Hematol Educ Program;2016

Bellesoeur et al. Crit Rev Oncol Hematol 2018; 129:102-112

INTERACTIONS MÉDICAMENTEUSES EN ONCOLOGIE



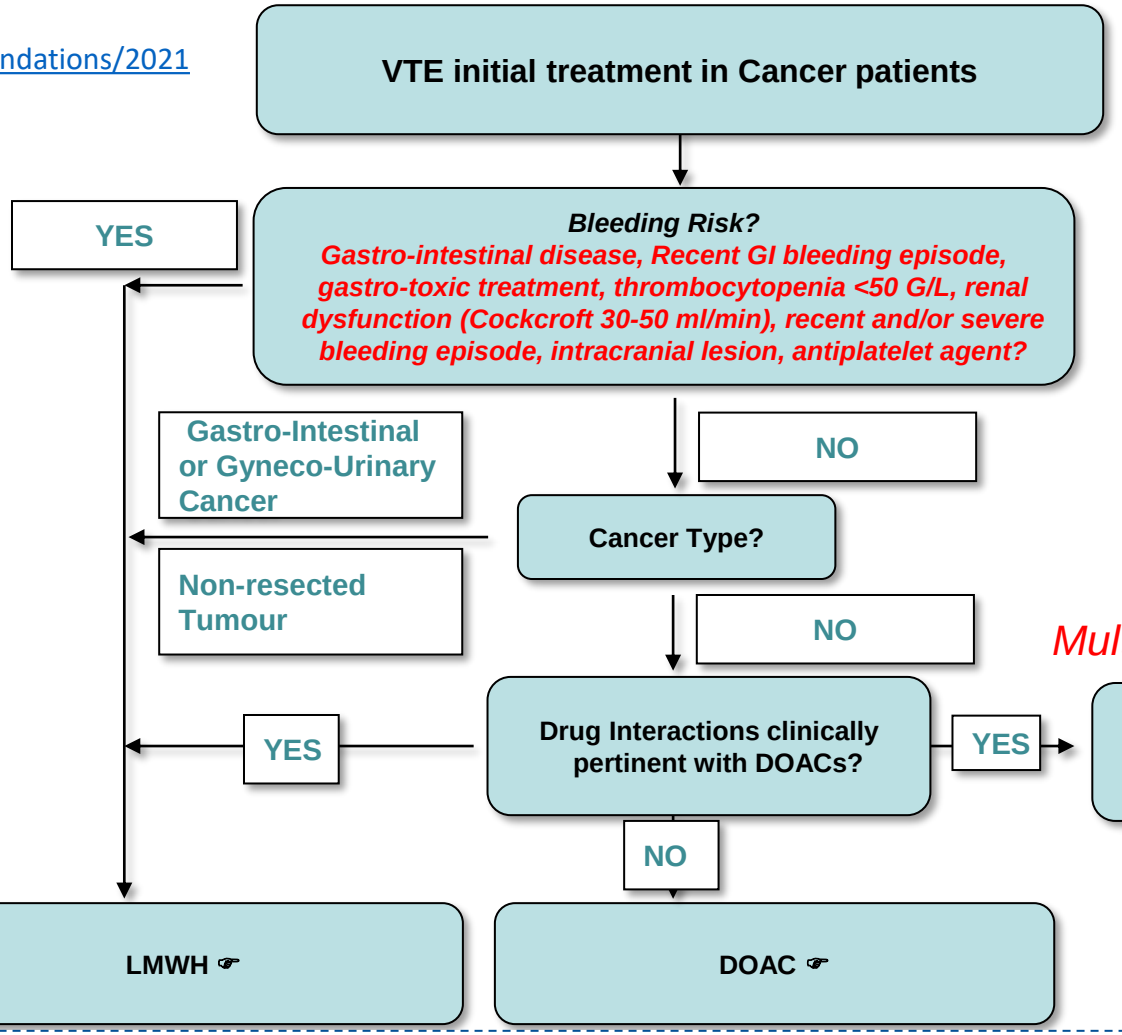


Diapo A. Bellesoeur

Lafaie L et al. Clin Pharmacol. 2022 Feb 16.

https://www.afsos.org/referentiels-recommandations/2021

AFSOS 2021

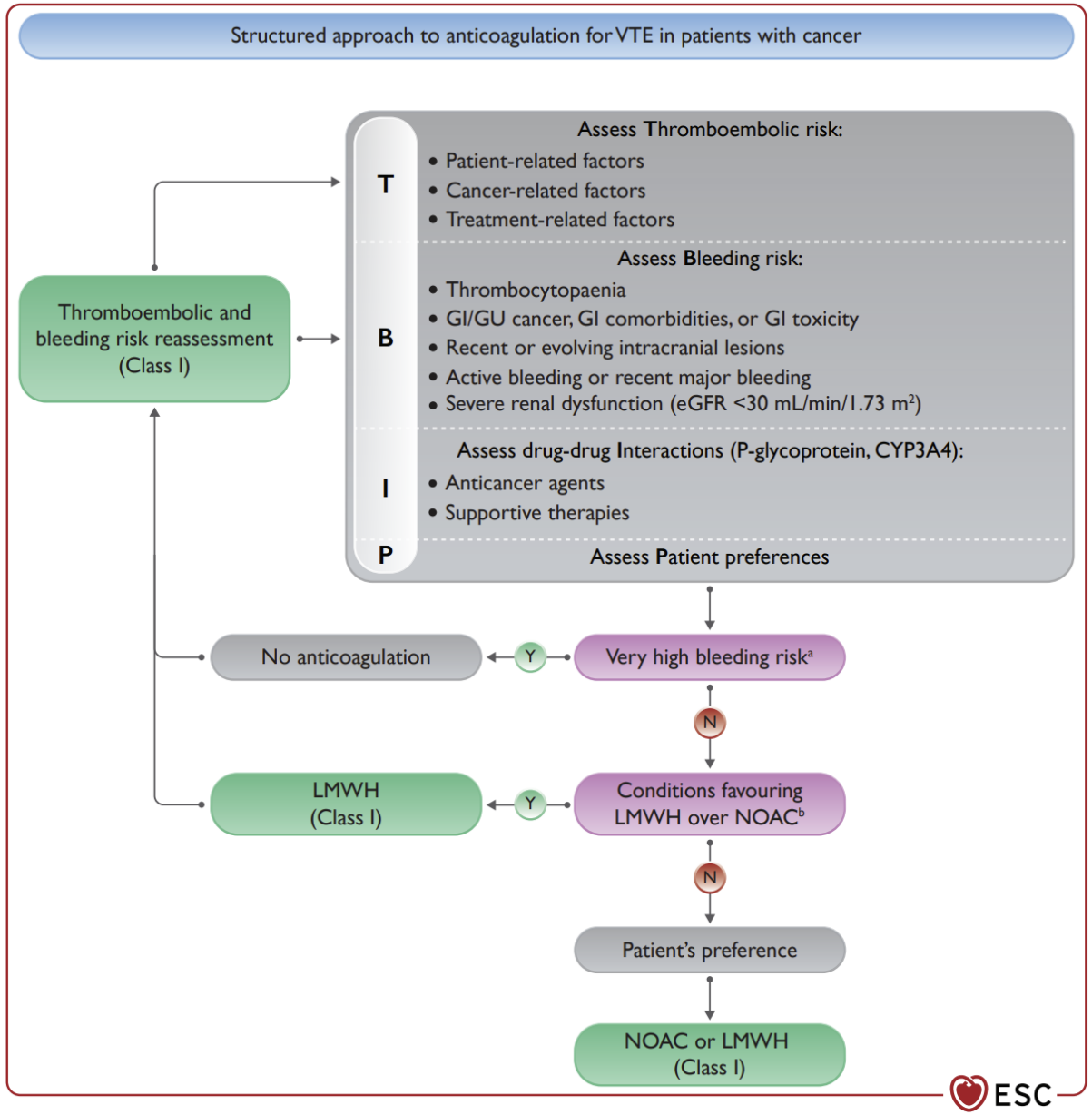


Multidisciplinary Consultation Meeting

Other factors to consider

Patient preference, after information on the Benefits / Risks report
BMI (prefer LMWH if BMI> 40 kg / m^2 or weight> 120 kg
Stage of cancer, severity of thrombotic event (prefer LMWH in patients with severe events)
Renal function (prefer LMWH in patients with Cockcroft clearance between 20 and 50 ml / min)
Recent history of gastrointestinal surgery or malabsorption: prefer LMWH
Possible drug interactions (Cytochrome P450, P-gp, etc.)

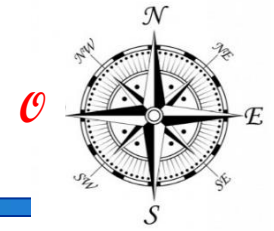
CAT TREATMENT AND RECOMMENDATIONS 2022



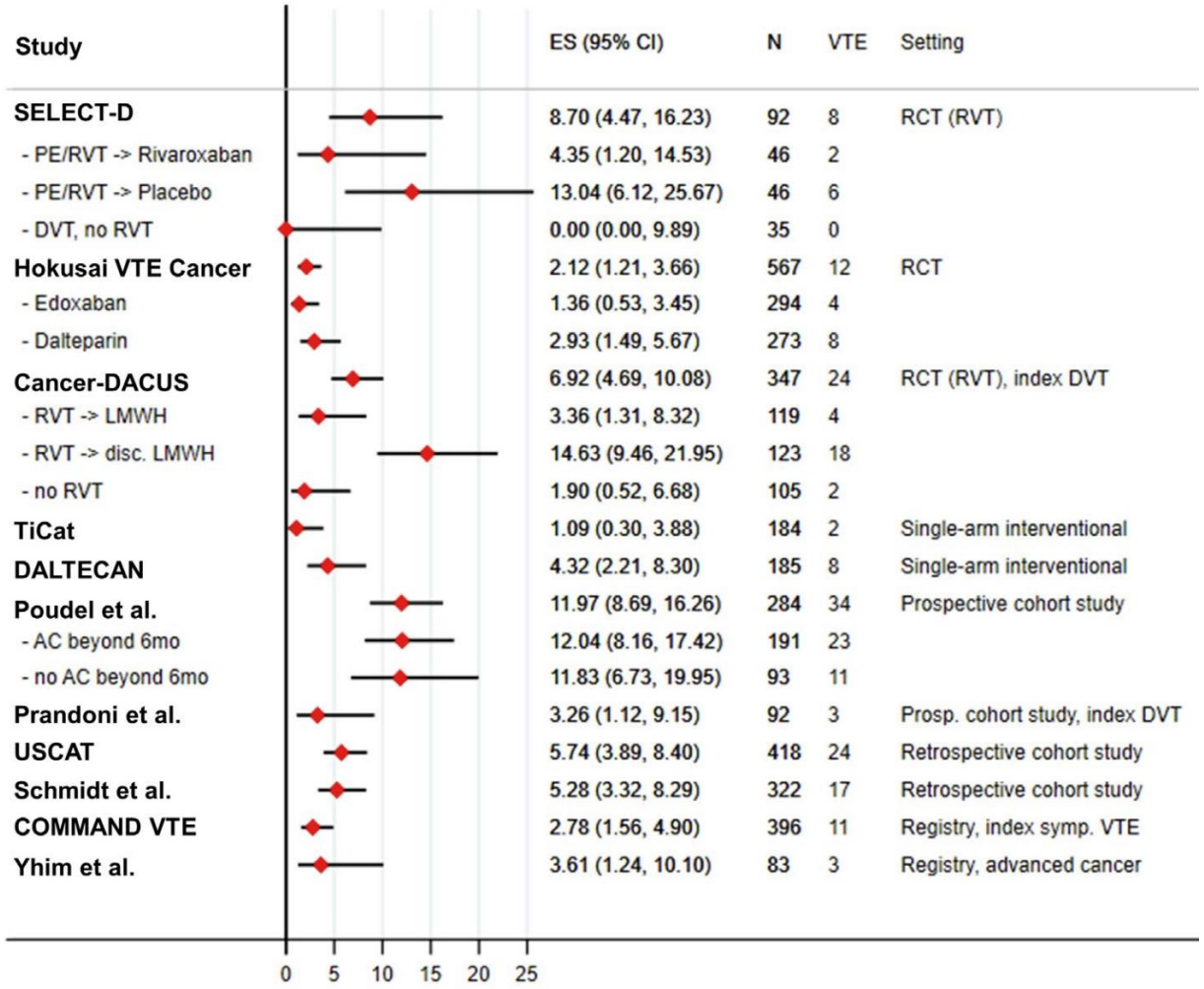
Recommendations	Class[a]	Level[b]
Apixaban, edoxaban, or rivaroxaban[c] are recommended for the treatment of symptomatic or incidental VTE in patients with cancer *without* contraindications.[d,578–581,584,585]	I	A
LMWH are recommended for the treatment of symptomatic or incidental VTE in patients with cancer with platelet count >50 000/μL.[298,299,578–581,584,585]	I	A
In patients with cancer with platelet counts of 25 000–50 000/μL, anticoagulation with half-dose LMWH may be considered after a multidisciplinary discussion.[591]	IIb	C
Prolongation of anticoagulation therapy beyond 6 months should be considered in selected patients with active cancer[e] including metastatic disease.[589,590]	IIa	A
Catheter-associated VTE		
Duration of anticoagulation in patients with cancer with a catheter-associated VTE is recommended for a minimum of 3 months and continuing longer if the catheter remains *in situ*.	I	C

Lyon et al Eur Heart J. 2022:ehac244.

EXTENDED ANTICOAGULATION TREATMENT FOR CAT: RECURRENCE AND BLEEDING BEYOND 6 MONTHS

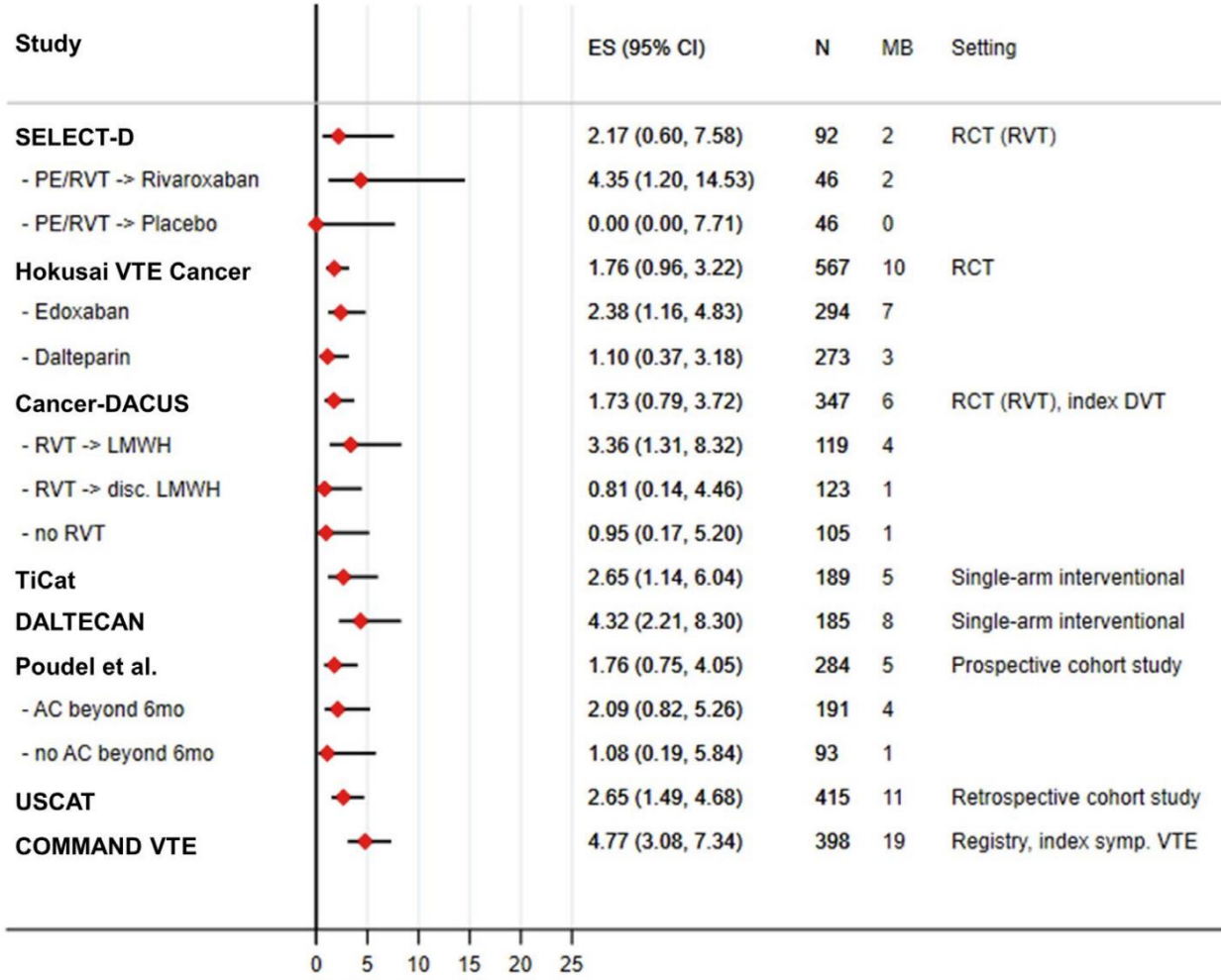


Study	ES (95% CI)	N	VTE	Setting
SELECT-D	8.70 (4.47, 16.23)	92	8	RCT (RVT)
- PE/RVT -> Rivaroxaban	4.35 (1.20, 14.53)	46	2	
- PE/RVT -> Placebo	13.04 (6.12, 25.67)	46	6	
- DVT, no RVT	0.00 (0.00, 9.89)	35	0	
Hokusai VTE Cancer	2.12 (1.21, 3.66)	567	12	RCT
- Edoxaban	1.36 (0.53, 3.45)	294	4	
- Dalteparin	2.93 (1.49, 5.67)	273	8	
Cancer-DACUS	6.92 (4.69, 10.08)	347	24	RCT (RVT), index DVT
- RVT -> LMWH	3.36 (1.31, 8.32)	119	4	
- RVT -> disc. LMWH	14.63 (9.46, 21.95)	123	18	
- no RVT	1.90 (0.52, 6.68)	105	2	
TiCat	1.09 (0.30, 3.88)	184	2	Single-arm interventional
DALTECAN	4.32 (2.21, 8.30)	185	8	Single-arm interventional
Poudel et al.	11.97 (8.69, 16.26)	284	34	Prospective cohort study
- AC beyond 6mo	12.04 (8.16, 17.42)	191	23	
- no AC beyond 6mo	11.83 (6.73, 19.95)	93	11	
Prandoni et al.	3.26 (1.12, 9.15)	92	3	Prosp. cohort study, index DVT
USCAT	5.74 (3.89, 8.40)	418	24	Retrospective cohort study
Schmidt et al.	5.28 (3.32, 8.29)	322	17	Retrospective cohort study
COMMAND VTE	2.78 (1.56, 4.90)	396	11	Registry, index symp. VTE
Yhim et al.	3.61 (1.24, 10.10)	83	3	Registry, advanced cancer



RECURRENT VTE %

Study	ES (95% CI)	N	MB	Setting
SELECT-D	2.17 (0.60, 7.58)	92	2	RCT (RVT)
- PE/RVT -> Rivaroxaban	4.35 (1.20, 14.53)	46	2	
- PE/RVT -> Placebo	0.00 (0.00, 7.71)	46	0	
Hokusai VTE Cancer	1.76 (0.96, 3.22)	567	10	RCT
- Edoxaban	2.38 (1.16, 4.83)	294	7	
- Dalteparin	1.10 (0.37, 3.18)	273	3	
Cancer-DACUS	1.73 (0.79, 3.72)	347	6	RCT (RVT), index DVT
- RVT -> LMWH	3.36 (1.31, 8.32)	119	4	
- RVT -> disc. LMWH	0.81 (0.14, 4.46)	123	1	
- no RVT	0.95 (0.17, 5.20)	105	1	
TiCat	2.65 (1.14, 6.04)	189	5	Single-arm interventional
DALTECAN	4.32 (2.21, 8.30)	185	8	Single-arm interventional
Poudel et al.	1.76 (0.75, 4.05)	284	5	Prospective cohort study
- AC beyond 6mo	2.09 (0.82, 5.26)	191	4	
- no AC beyond 6mo	1.08 (0.19, 5.84)	93	1	
USCAT	2.65 (1.49, 4.68)	415	11	Retrospective cohort study
COMMAND VTE	4.77 (3.08, 7.34)	398	19	Registry, index symp. VTE



MAJOR BLEEDING %

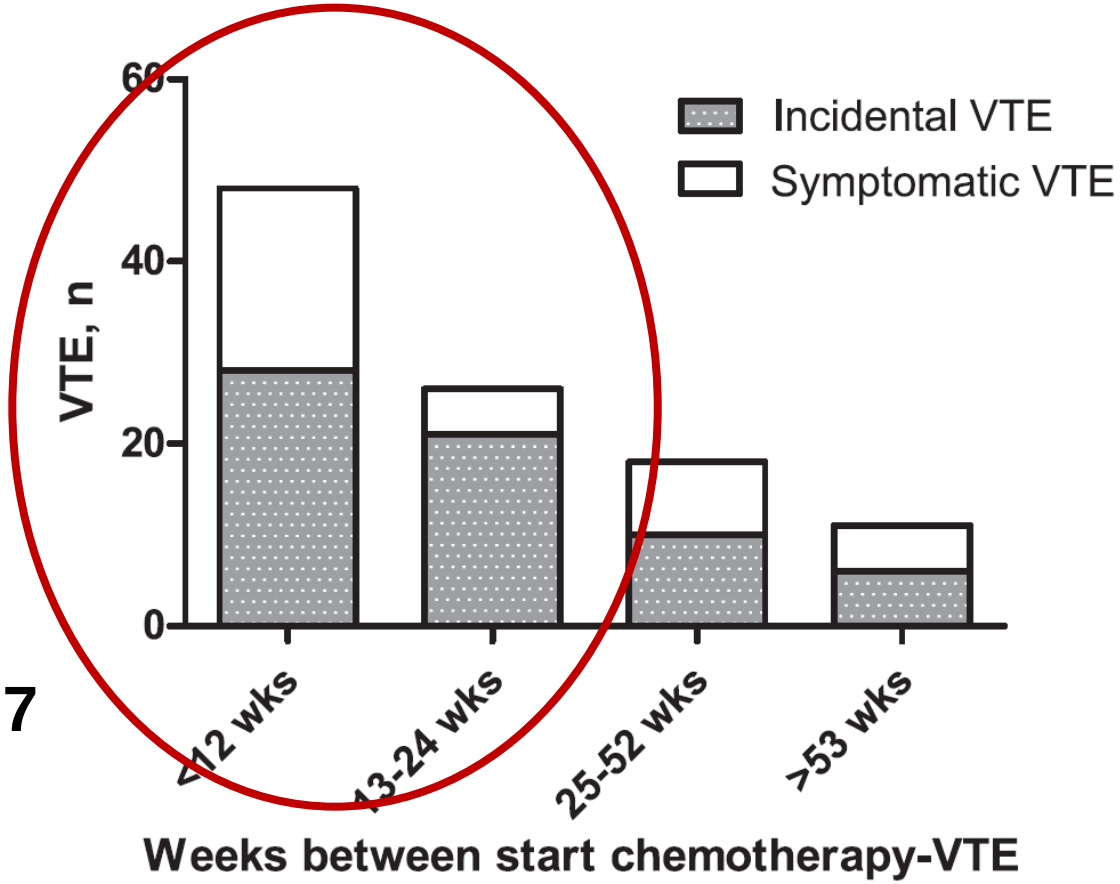
Moik et al. J Thromb Haemost. 2022;20:619–634.

« INCIDENTAL THROMBOSIS »
THROMBOSE DE DÉCOUVERTE FORTUITE

>2/3 avant le 6ème mois

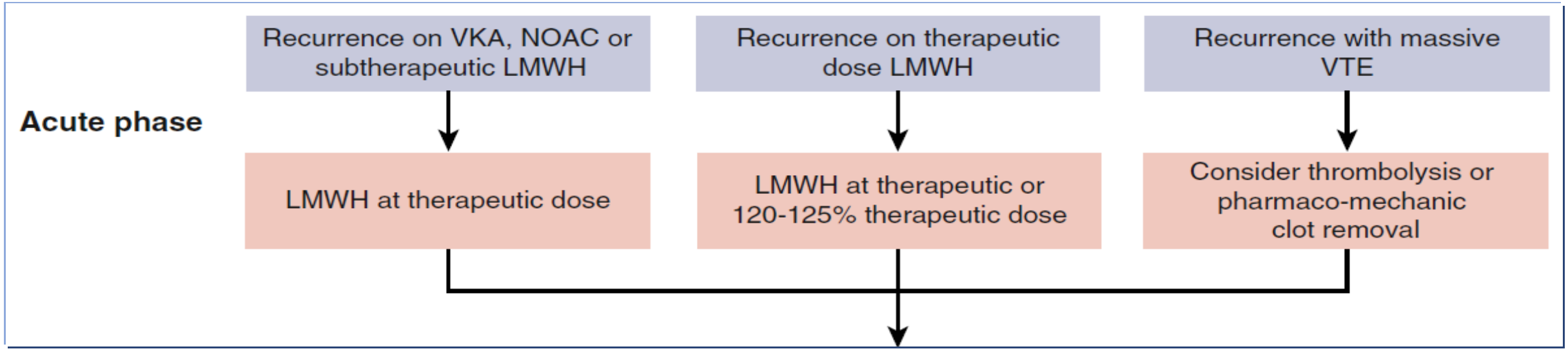
Risque x 3 :
Métastases
↑Leucocytes
Cisplatine

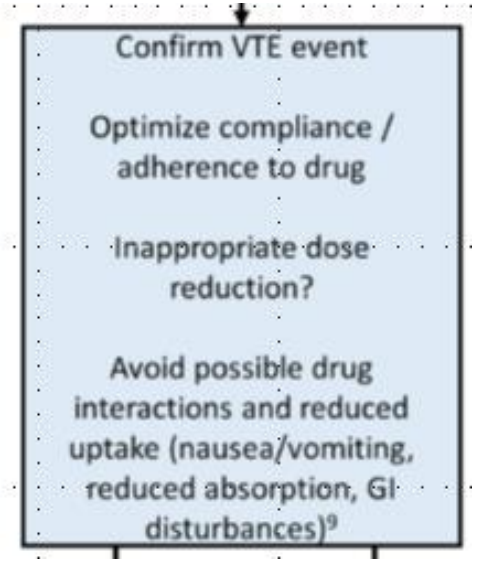
Incidence croissante
Mêmes risques qu'EP ∑que
Etude en cours NCT01727427
(30 centres)



D'après Di Nisio et al Thromb Haemost. 2010;104(5):1049-54.
D'après Van Es et al Thromb Res. 2014;133 Suppl 2:S172-8.

EN CAS DE RÉCIDIVE THROMBOTIQUE SOUS TRAITEMENT





Confirmed event

Compliant patient

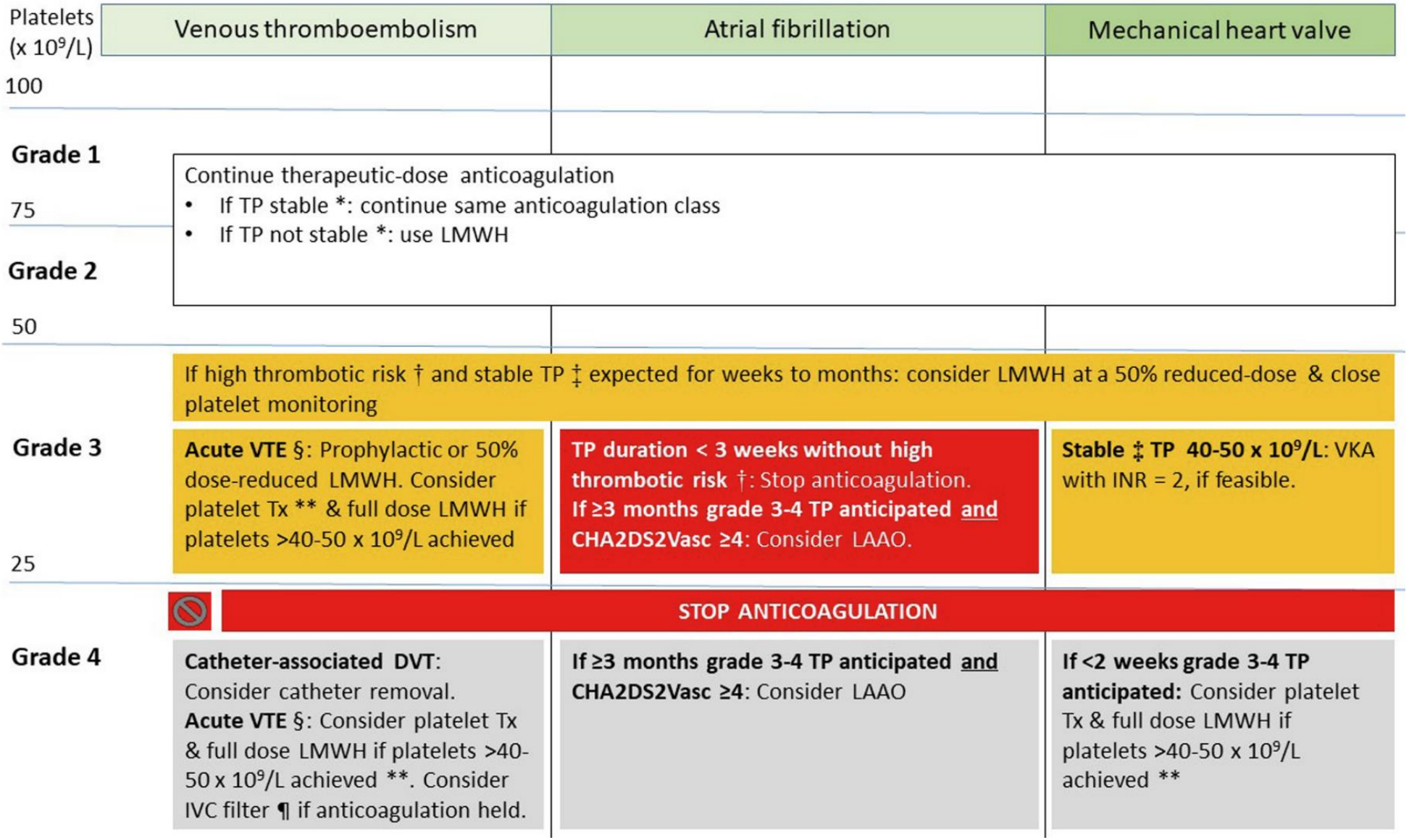
Convenient dose

Compromising drug

Comorbidities

Schulman S Blood. 2017 Jun 22;129(25):3285-3293.

EN CAS DE THROMBOPÉNIE SOUS TRAITEMENT



Falanga, Elalamy et al. HemaSphere 2022; 6:8(e750). 1-25

QUELLES SONT LES PROPOSITIONS JUSTES?

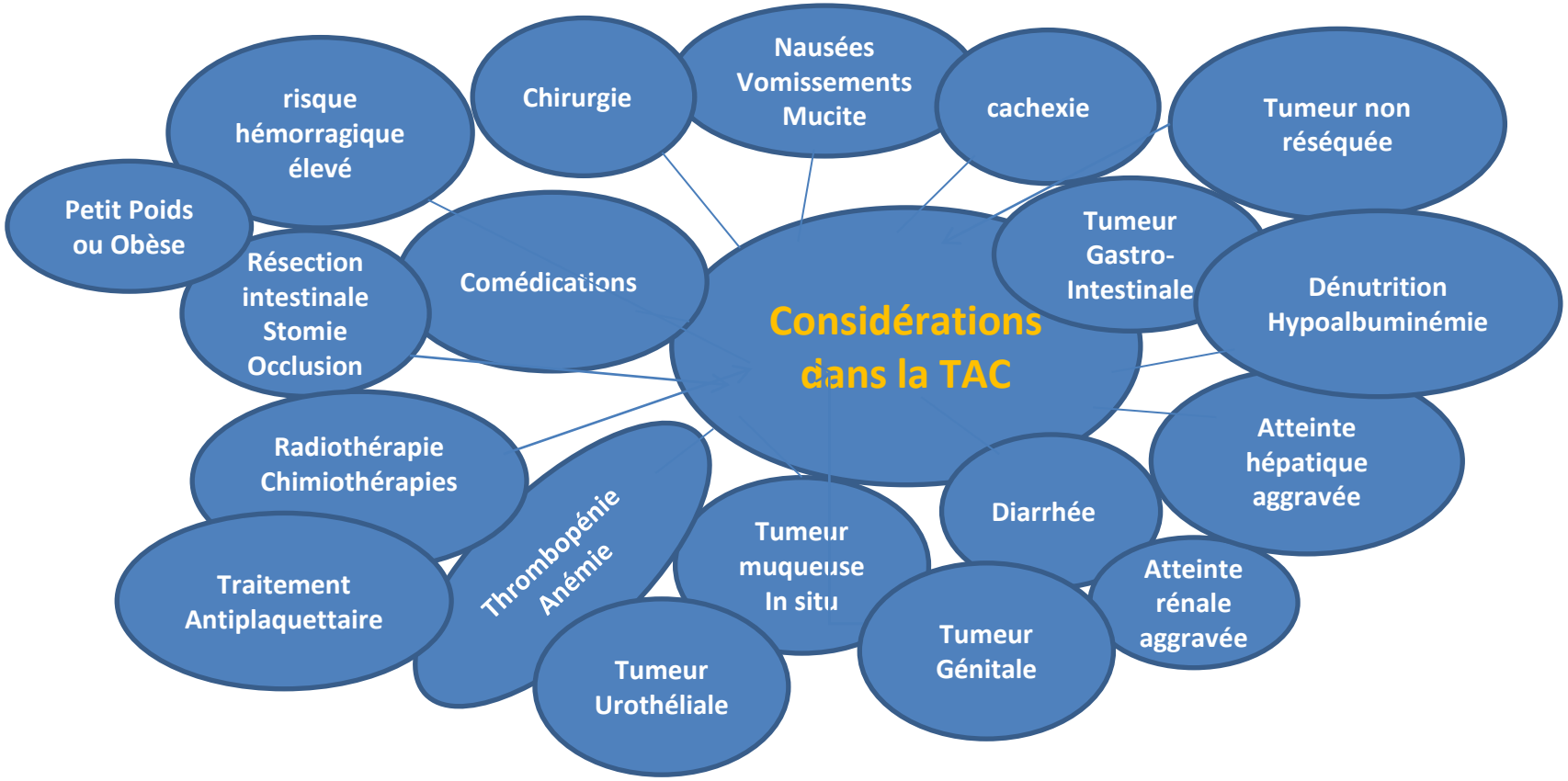
A. Il est suggéré de traiter par AVK une MTEV chez les patients atteints de cancer en cas d'insuffisance rénale sévère (Clcr < 30 ml/min)

B. Il est recommandé de traiter par HBPM une MTEV chez les patients atteints de cancer en cas thrombopénie modérée (Plaquettes ≥ 50 G/L)

C. Il est recommandé traiter par AOD une MTEV récidivante sous HBPM chez les patients atteints de cancer en l'absence d'interaction médicamenteuse sur les voies des Pgp et des cytochromes.

D. Il est suggéré de maintenir un traitement par AOD d'une MTEV au-delà des 6 mois de traitement chez les patients ambulatoires ayant un cancer actif

PATIENT, CANCER ET THROMBOSE
COMPLEXITÉS ET LIMITES



Adapted from Voigtländer et al Hamostaseologie. 2017 ;37(4):241-255.

POUR LA TAC… CHOIX DE L'ARSENAL : PARENTÉRAL OU ORAL?

HBPM préférable	AOD préférable
Hospitalisé, Chirugie Récente, Gastrectomie…	Ambulatoire sans Troubles Digestifs
Troubles Digestifs (vomissements, glossites…)	Absence de Tumeur Digestive ou Génito-Urinaire
Patient Vulnérable => injectable…	Patient Subnormal => oral…
Cancer Muqueux ou Intraluminal (Gastro-Intestinal/Génito-Urinaire)	Pas d'Interférence des Voies CYP +/- P-gp
Petit Poids, Dénutrition, Hypoalbuminémie	Problème de Compliance +/- Tolérance des Injections
Thrombopénie < 50G/L, Anémie < 85 g/L	Bon Etat Général, < 65-75 ans
Chimiothérapie, Thérapie Ciblée	Pas d'Atteinte Hépatique (stades B,C), Pas d'atteinte Rénale Sévère (Clcr≤30 ml/min)
Inhibiteurs/Inducteurs de CYP +/- P-gp	Traitement Prolongé Requis (FA, Cancer Actif…)

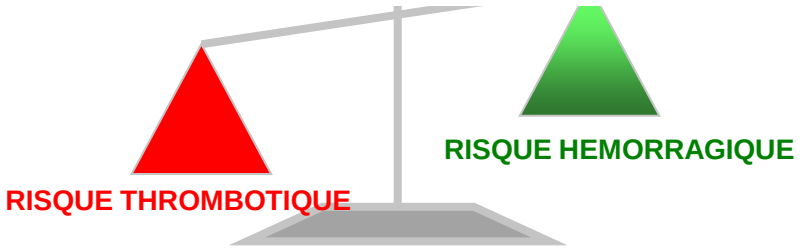
Tous les AOD n'ont pas le même Rapport Bénéfice/Risque
Les Patients Atteints de Cancer ne sont pas Tous Eligibles aux AOD

D'après O'Connell et al Oncologist. 2021 Jan;26(1):e8-e16

VOIR PLUS LARGEMENT… AGIR JUDICIEUSEMENT

Situations Complexes + Profils Multirisques
Hospitalisé avec pathologie aiguë +++
Ambulatoire avec stratification du Risque +++

PESER le RISQUE …
PRESCRIRE chez le FORT …
… PROSCRIRE chez le FAIBLE!



“Vision 3D : Drogue, Dose, Durée”

« HBPM »
Héparine Bénéfique si Prolifération Maligne

« AOD »
Anticoagulant Optionnel à Discuter

QUELLES SONT LES PROPOSITIONS JUSTES?

A. Chez le sujet atteint de cancer, le risque de MTEV et hémorragique sont plus élevés

B. Les HBPM contrairement aux AOD ne sont pas influencés par la chimiothérapie

C. Les AOD sont préférables aux HBPM chez le sujet atteint de cancer pour la prophylaxie antithrombotique

D. Le bénéfice clinique net des AOD est supérieurs aux HBPM chez le sujet atteint de cancer pour le traitement de la MTEV

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POINTS FORTS

- L’incidence de la thrombose associée au cancer est en augmentation constante.
- Les cancers digestifs les plus fréquemment associés au risque thrombo-embolique veineux sont les cancers du pancréas, du foie, des voies biliaires et de l’estomac
- Une thromboprophylaxie (HBPM ou AOD) est indiquée chez les patients en cours de chimiothérapie pour un cancer localement avancé ou métastatique du pancréas
- Il est recommandé de traiter une thrombose associée au cancer pendant au moins 6 mois.
- Le choix de l’anticoagulant doit tenir compte de ses interactions potentielles avec le traitement anti-tumoral