

Thrombose associée au cancer

Gabriel Huard M.D.

Médecine interne générale et vasculaire

CIUSSS Saguenay-Lac-St-Jean Hôpital de Chicoutimi

Professeur d'enseignement clinique

Université de Sherbrooke

Centre intégré
universitaire de santé
et de services sociaux
du Saguenay-
Lac-Saint-Jean

Québec

UDS

Université de
Sherbrooke

CONFLITS D'INTÉRETS



Conférencier

Leo Pharma Pfizer Amgen
Bayer



Comité aviseur

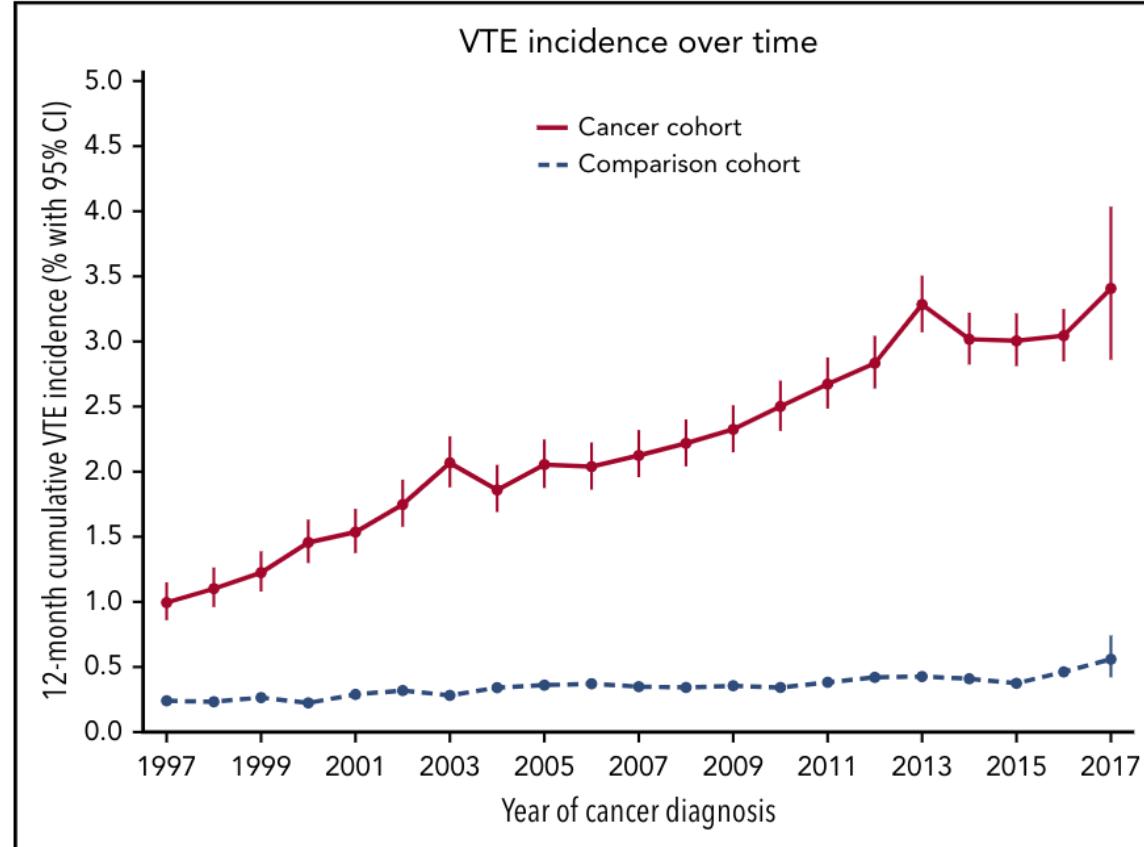
Pfizer

OBJECTIFS

- Identifier les facteurs de risques de MTEV chez les patients atteints de cancer;
- Référer les patients éligibles à une thromboprophylaxie primaire;
- Prendre en charge initialement le patient avec TAC.

THROMBOSE ET CANCER

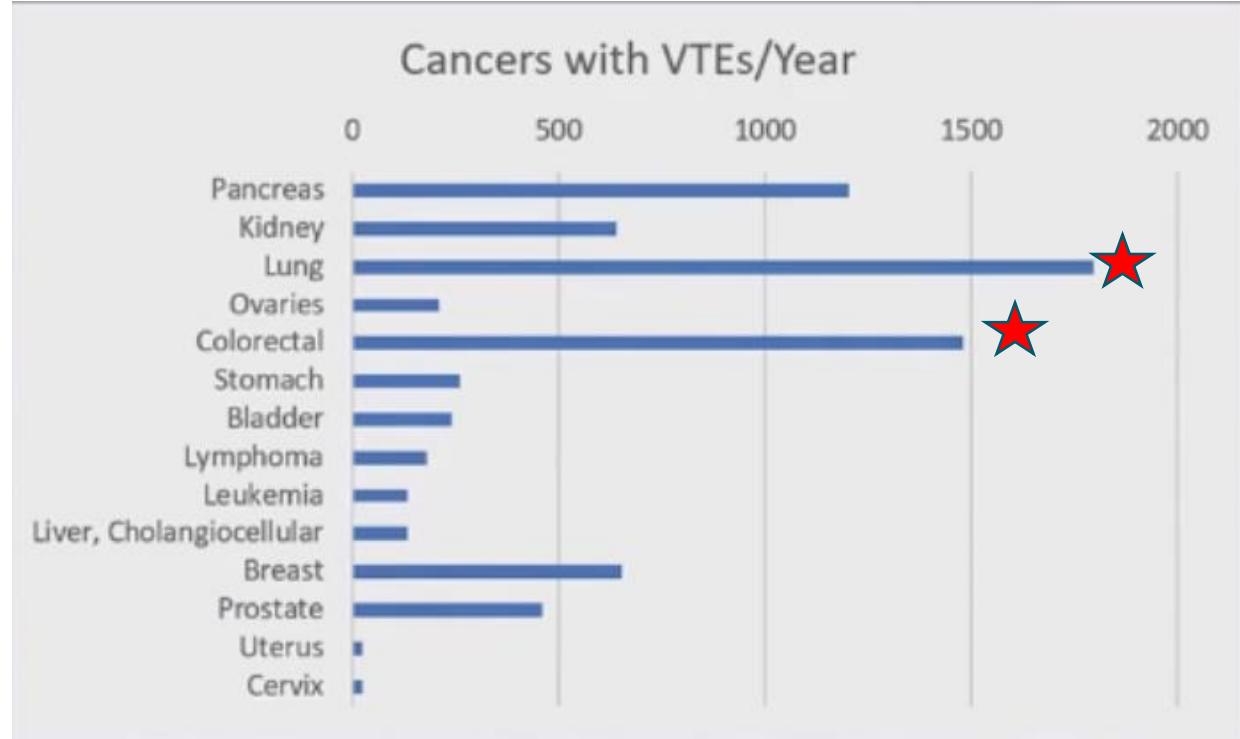
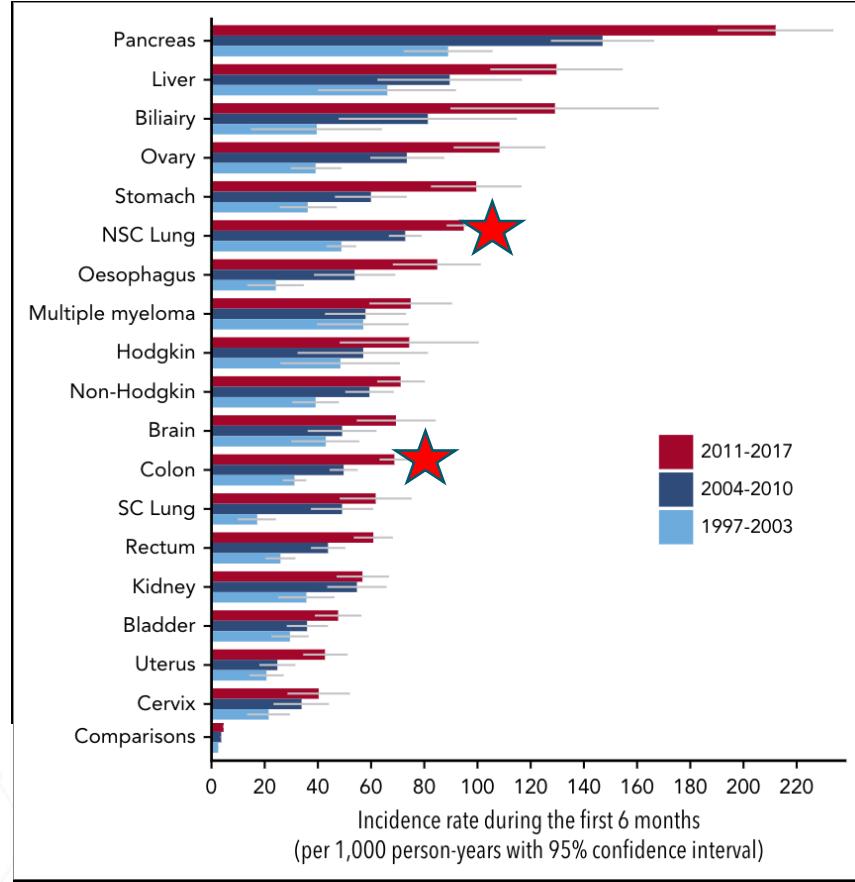
- UN PROBLÈME DE PLUS EN PLUS FRÉQUENT !



Venous thromboembolism in cancer patients: a population-based cohort study

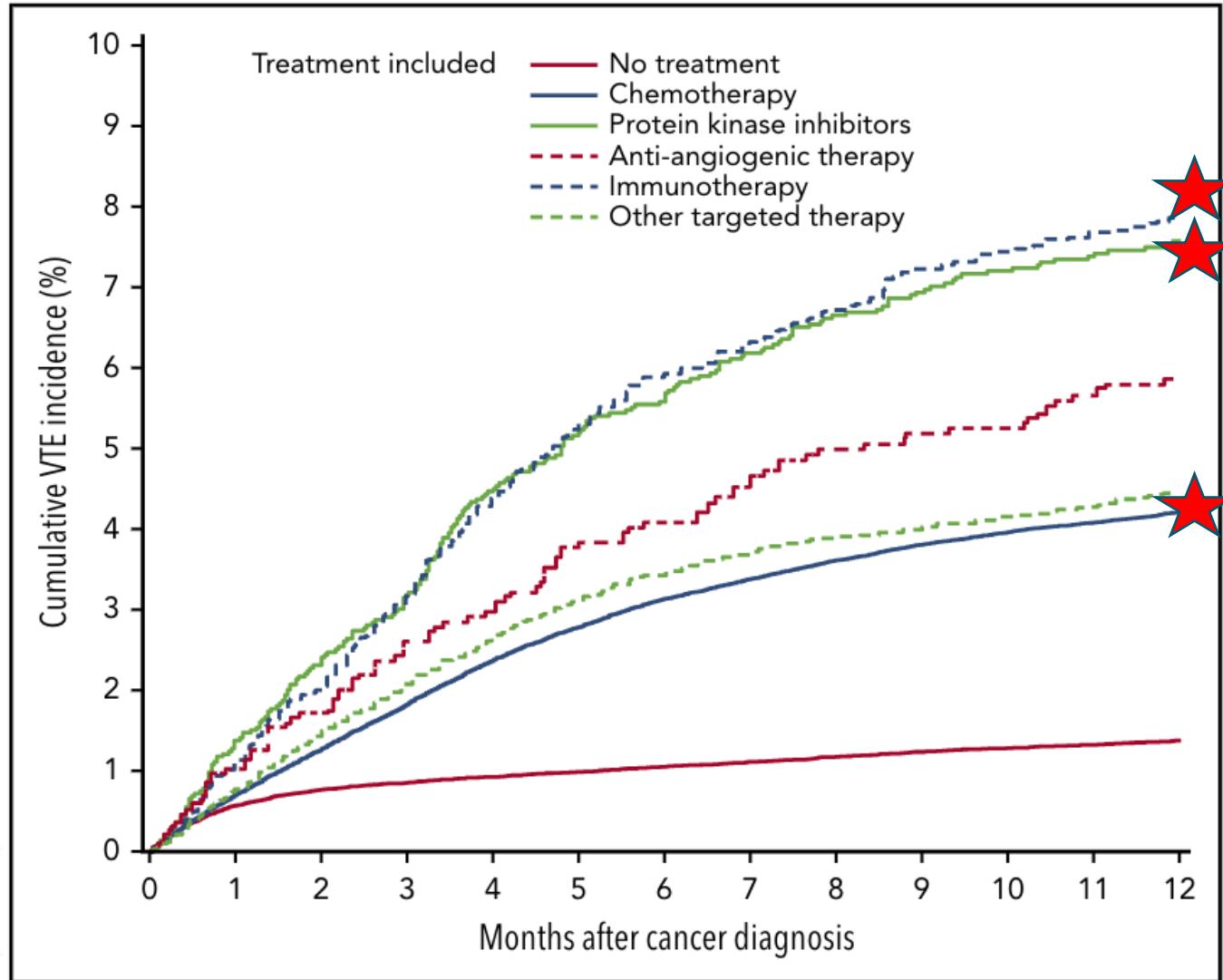
Plus de X 3 en 20 ans !
Et ça continue...

THROMBOSE ET CANCER



Prévalence globale

THROMBOSE ET CANCER



THROMBOSE ET CANCER



Incidence of venous thromboembolism in cancer patients

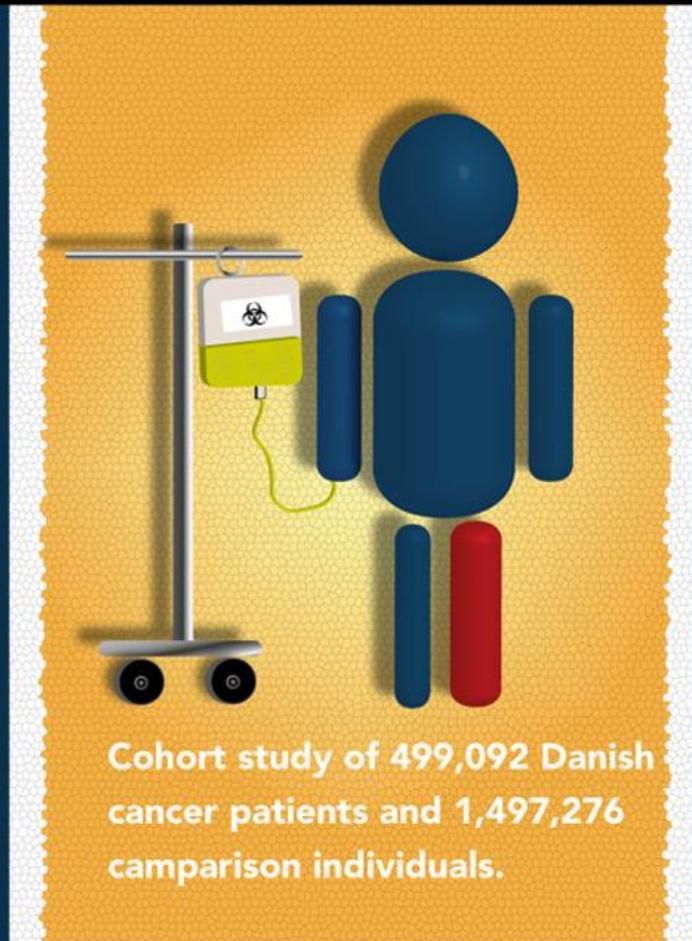
Compared to the general population, the contemporary 12-month VTE risk is increased in:

All cancer patients

- Cumulative incidence 3.0%
(95% CI, 2.9-3.1)
- Hazard ratio 9.1
(95% CI, 8.6-9.6)

Recipients chemotherapy or targeted therapy

- Cumulative incidence 5.3%
(95% CI, 5.1-5.5)
- Hazard ratio 20
(95% CI, 18-22)



Increased trend VTE 1997-2017:
- 3-fold increase all cancer patients
- 6-fold increase chemotherapy recipients.

Parallel increase:

Usage chemotherapy and targeted therapies

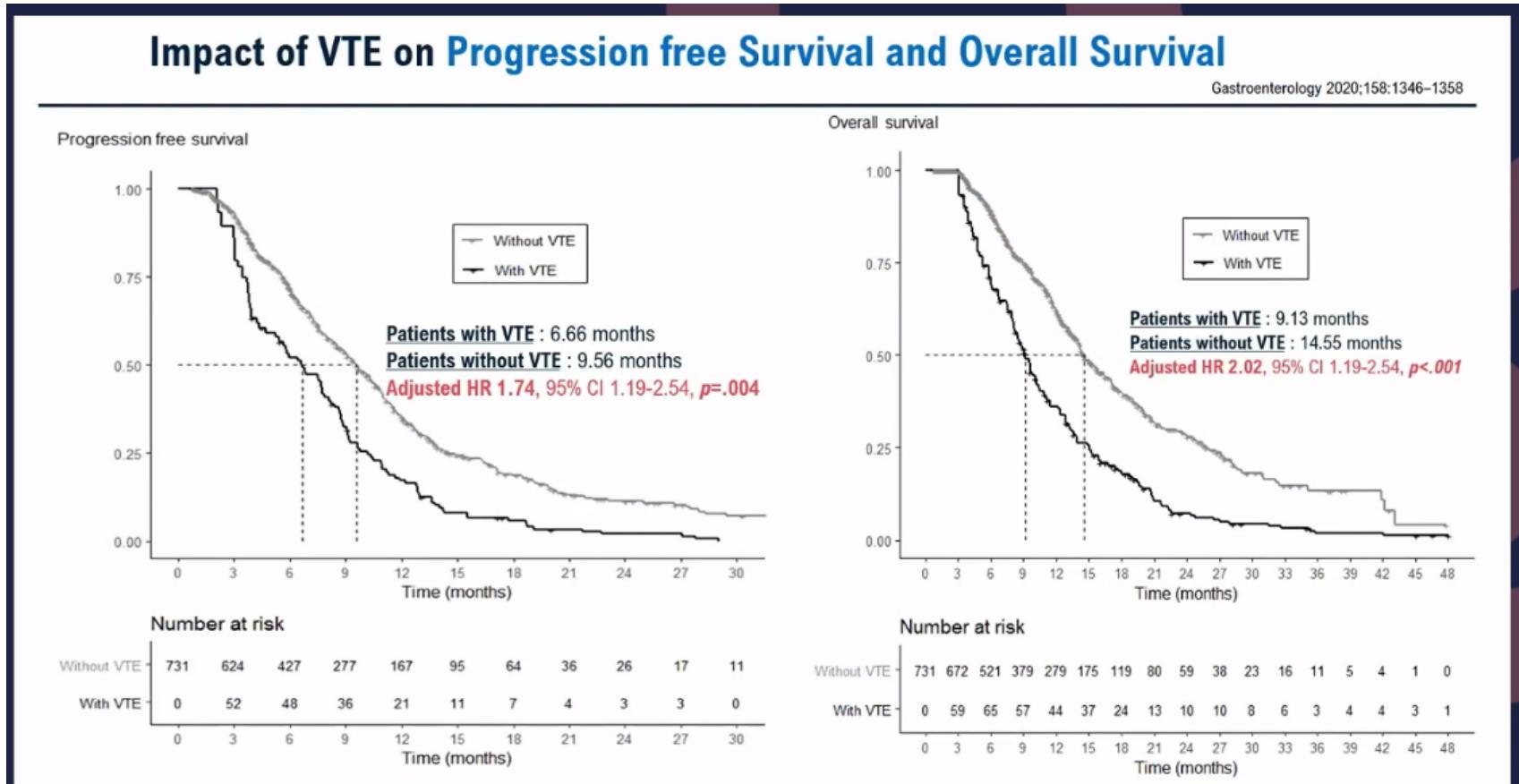


Usage CT-scanning

12-month survival



PFS et OS et thrombose - Pancréas

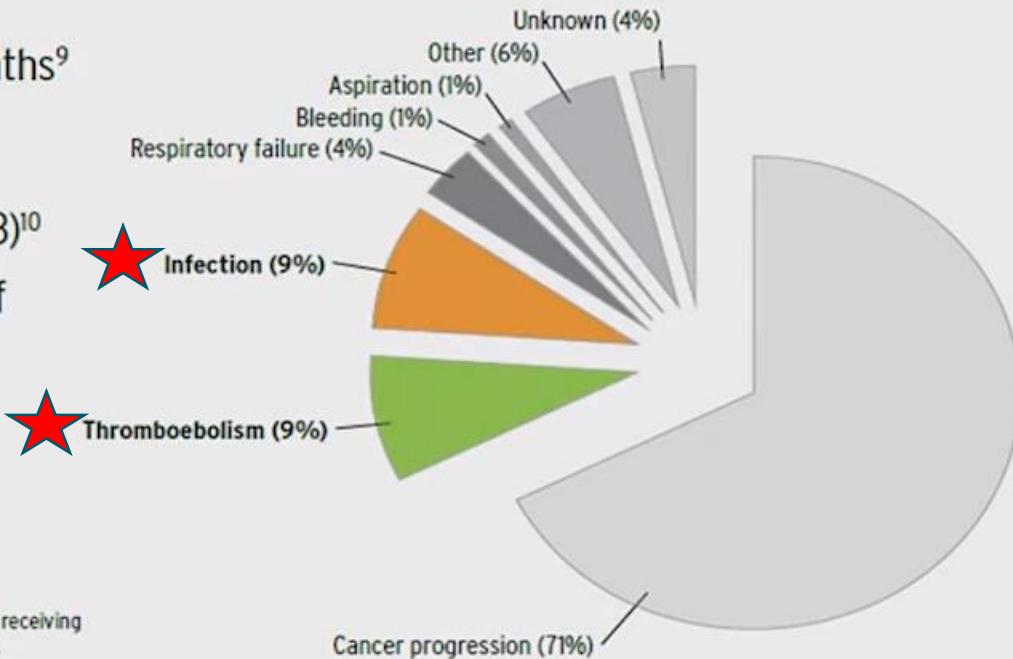


MORTALITÉ

Cancer and Death

- VTE is 2nd leading cause of death in cancer pts

- Accounts for 9% of deaths⁹
- Associated with early mortality during chemotherapy (HR=6.98)¹⁰
- 47-fold increased risk of mortality from VTE⁹



Adapted from Khorana AA, et al, 2007⁹.

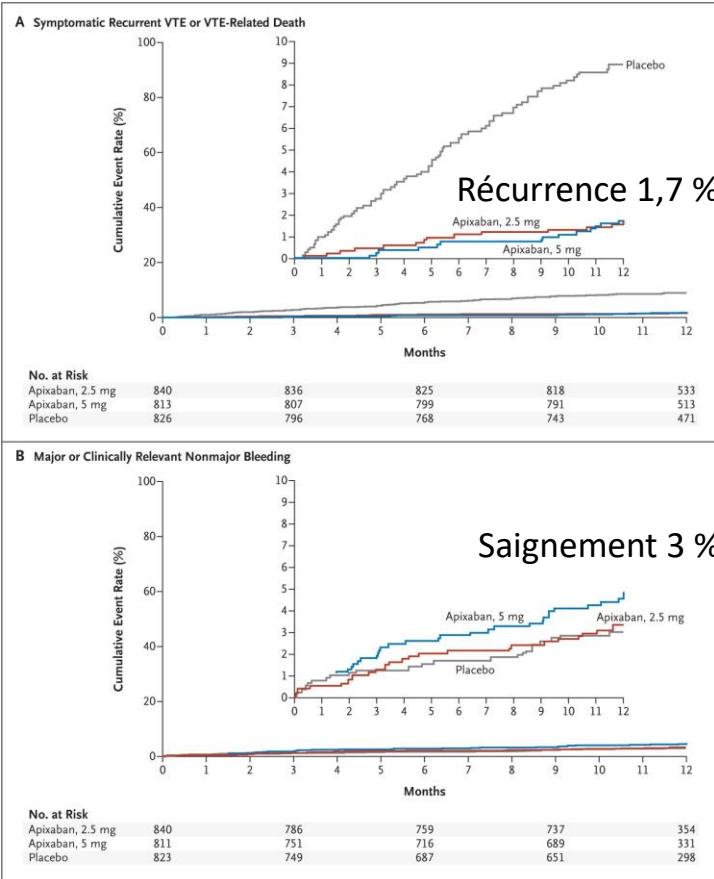
Analysis of causes of death in 4466 cancer patients receiving chemotherapy in a prospective observational study.

References

Khorana AA. JTH 2007.

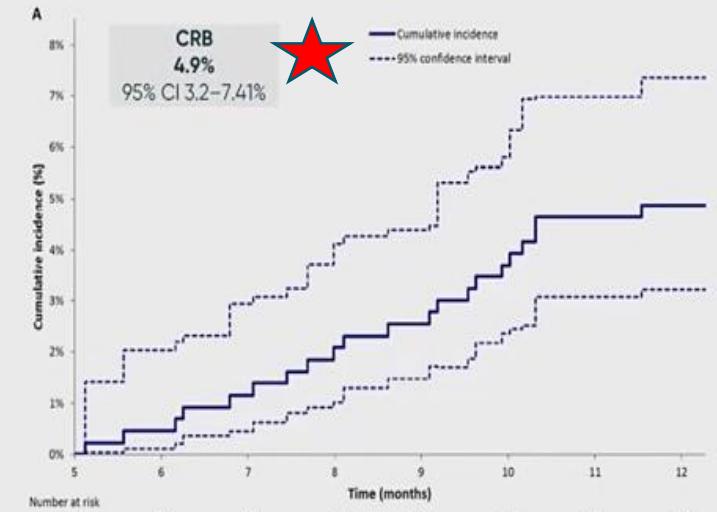
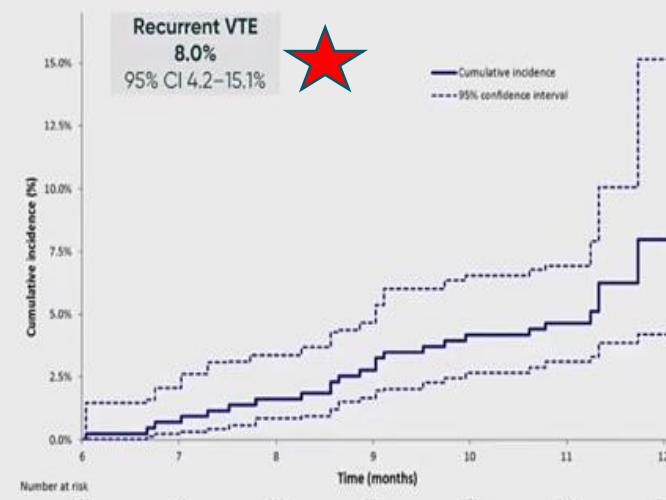
Récurrences et saignements, “Real life”

AMPLIFY EXT



USCAT

Long-term treatment of CAT beyond 6 months in medical practice



CANCER ET THROMBOSE

- INCIDENCE EN AUGMENTATION
 - X 3 CHEZ TOUS LES PATIENTS
 - X 6 CHEZ LES PATIENTS SOUS TRAITEMENT
- HAUT RISQUE CHEZ PATIENT SOUS TRAITEMENT
 - HR = 20 VERSUS POPULATION GÉNÉRALE
- IMPACT IMPORTANT
 - DIMINUE PFS ET OS
 - IMPACT DIRECT SUR LA MORTALITÉ
 - *** EN ÉGALITÉ AVEC INFECTION ***
- MALHEUREUSEMENT LES PATIENTS SONT MAL INFORMÉS

ÉTUDE – SONDAGE UK



Noble et al. 2015

Souliotis K. TH open. 2022

OBJECTIFS

**IDENTIFIER LES FACTEURS DE RISQUES DE MTEV CHEZ LES PATIENTS
ATTEINTS DE CANCER**



SCORE DE KHORANA

*Études en prévention primaire :
Score 2 et +

AVANTAGES :
SIMPLE,
UTILISÉ PAS ÉTUDES
PRÉVENTION 1'

DÉSAVANTAGE :
TROP SIMPLE

Patient characteristic	Risk Score
1. Site of cancer <ul style="list-style-type: none">▪ Very high risk (stomach, pancreas)▪ High risk (Lung, Lymphoma, Gynecologic, bladder, testicular)	2 1
2. Prechemotherapy platelet count $350 \times 10^9/L$ or more	1
3. Hemoglobin level less than 100 g/L or use of red cell growth factors	1
4. Prechemotherapy leukocyte count more than $11 \times 10^9 /L$	1
5. BMI: 35 kg/m^2 or more	1

Risk score (points)	Risk category	Rates of sVTE according to scores (%)
0	Low	0.3–0.8
1–2	Intermediate	1.8–2.0
≥ 3	High	6.7–7.1

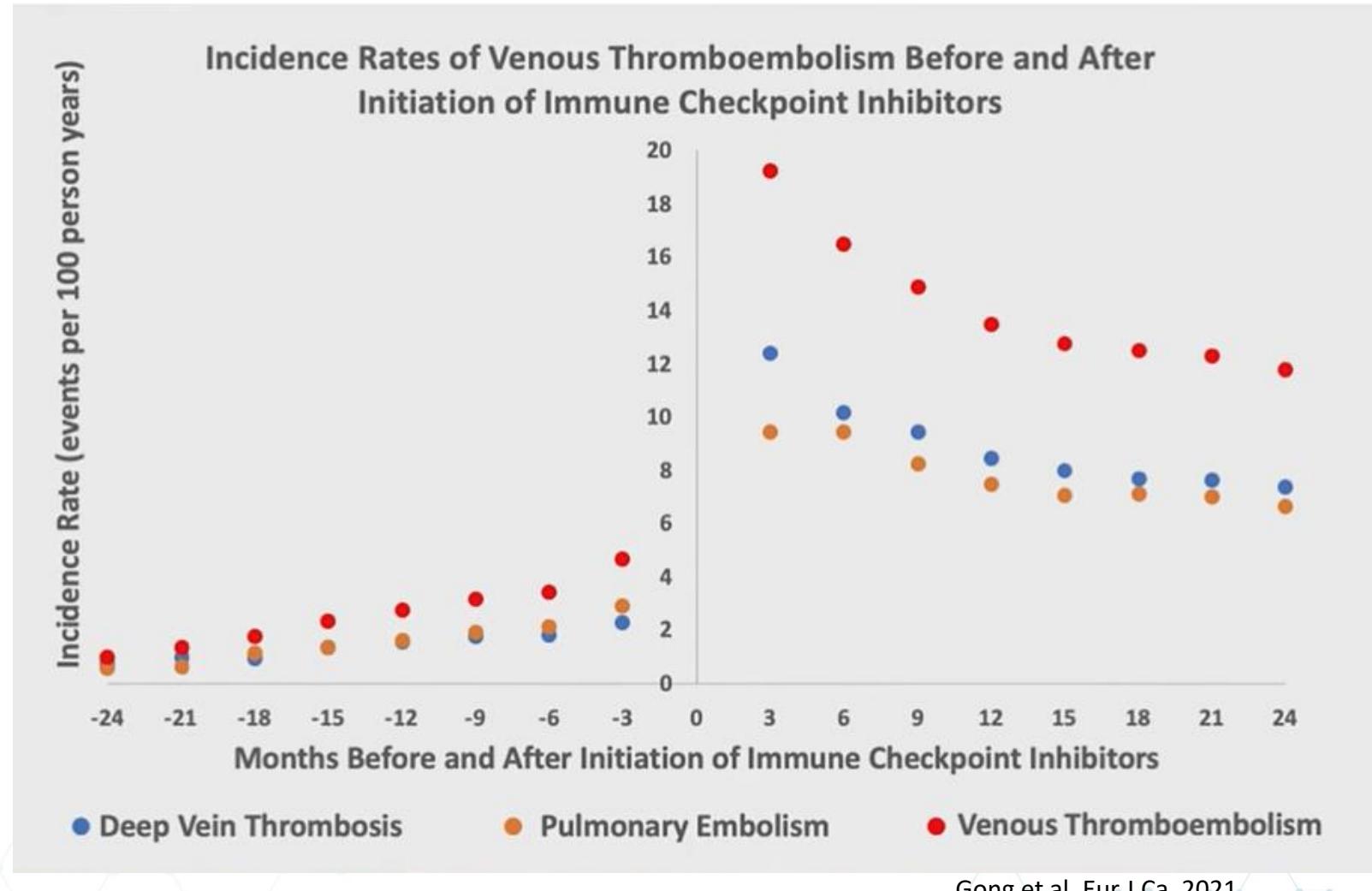
BMI body mass index, *sVTE* symptomatic VTE

RAFFINER LE RISQUE - IMMUNOTX

Risque absolu de MTEV

- 7,4% après 6 mois
- 13,8% après 1 An

HR 4,98



THÉRAPIES CIBLÉES



Anti-angiogenic therapies: VEGF & VEGFR1/2

Bevacizumab (Anti-VEGF-mAB)

Meta-analysis of 22 RCT (n=20,050, various cancers):
Bevacizumab vs control arms¹

VTE: RR 1.29 [1.12-1.47]
ATE: RR 1.37 [1.10-1.70]

Meta-analysis of 15 RCT (n=7,956, various cancers):
Bevacizumab vs control arms²

VTE: 11.9% vs 6.3%

Meta-analysis of 5 RCT (n=1,745, various cancers):
Bevacizumab vs control arms³

ATE 5.5 vs 3.1/100 PY

VEGFR-TKIs (sunitinib, sorafenib, pazopanib, cabozantinib, regorafenib, axitinib...)

Meta-analysis of 10 RCT (n=10,255, mostly RCC):
Sorafenib/Sunitinib vs control arms⁴

ATE: RR 3.03 [95%: 1.15-7.37]
Sorafenib: 1.7%, Sunitinib: 1.4%

Meta-analysis of 19 RCT (various cancers):
VEGFR-TKI vs control arms⁵

ATE: RR: 2.26 [1.38-3.68]

Meta-analysis of 14 RCT (various cancers):
VEGFR-TKI vs control arms⁶

VTE: RR 0.91 [95%: 0.62-1.35]

Totzeck et al. J Am Heart Assoc. 2017

Nalluri et al. JAMA. 2008

Scappaticci et al. J Natl Cancer Inst. 2007

Choueiri et al. JCO. 2010

Qi et al. Crit Rev Oncol Hematol. 2014

Qi et al. Int J Cancer. 2013

THÉRAPIES CIBLÉES



EGFR-targeted therapies

Anti-EGFR-mAB
(Cetuximab,
Panitumumab)

EGFR-TKI
(Gefitinib, Erlotinib,
Afatinib, Osimertinib)

Meta-analysis of 17 RCT (mostly colorectal, lung):
Cetuximab/panitumumab vs control arms¹

Meta-analysis of 13 RCT (various cancers):
**cetuximab, panitumumab, gefitinib, erlotinib
vs control arms²**

Severe VTE: RR 1.46 [95%: 1.26-1.69];
7.8%

VTE: RR: 1.32 [1.07-1.63]; 5.0% vs 3.7%

ATE: RR: 1.34 [0.94-1.90]; 4.5% vs 3.4%

Miroddi et al. Int J Cancer. 2013
Petrelli et al. Ann Oncol. 2012

THÉRAPIES CIBLÉES



BCR-ABL-TKIs

Meta-analysis of 10 RCT (n=3,043):
2nd generation BCR-ABL-TKIs vs
imatinib¹

Meta-analysis of 12 RCT:
2nd generation BCR-ABL-TKIs vs
imatinib²

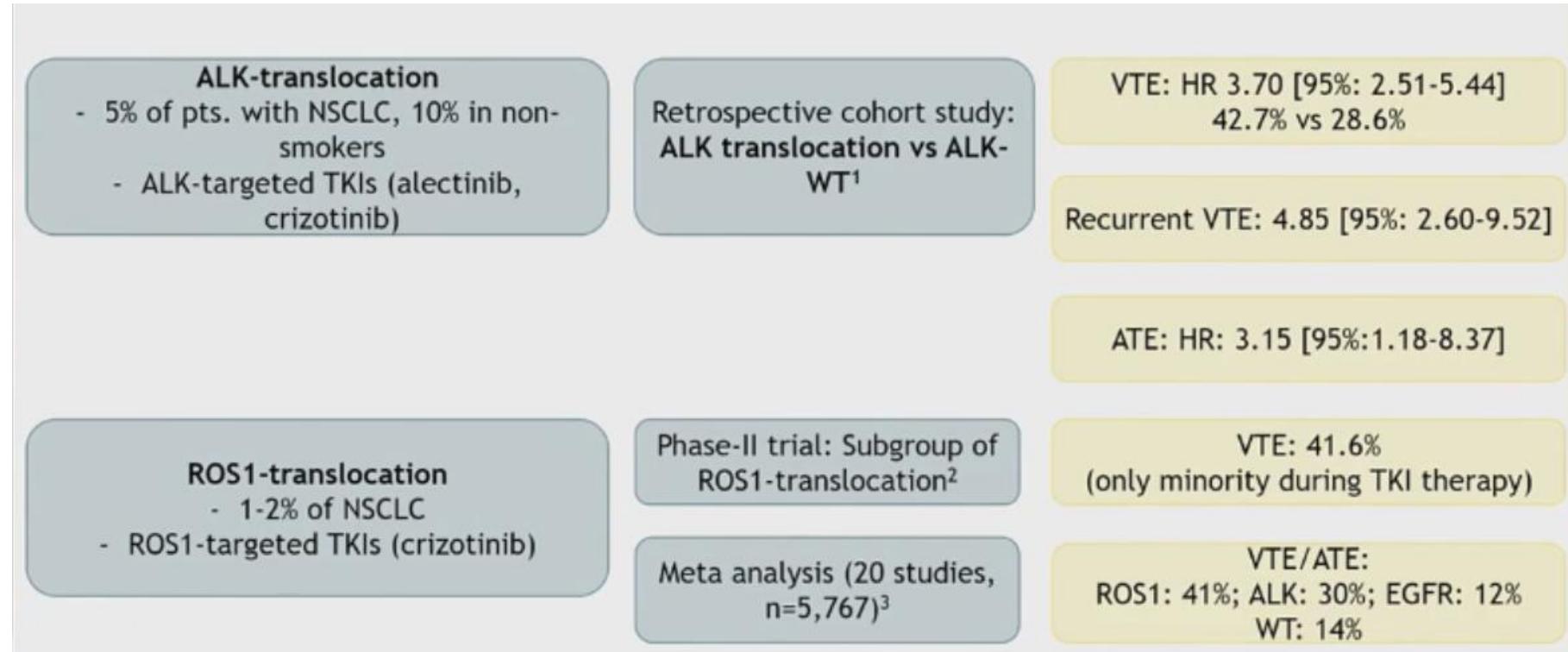
Risk of “vascular occlusive events”:
RR 3.45 [95%: 2.30-5.18]

ATE: OR 3.32 [95%: 2.29-4.81]
4.8% vs 1.0%

VTE: OR: 2.17 [95%: 0.90-5.25]
0.7% vs 0.3%

Douxflis et al. JAMA Oncol 2016.
Haguet et al. Expert Opinion on Drug Safety. 2017

STATUT MUTATIONNEL



Autres : *KRAS* (HR, 1.34), *STK11* (HR, 2.12); *KEAP1* (HR, 1.84), *CTNNB1* (HR, 1.73); *CDKN2B* (HR, 1.45) and *MET* (HR, 1.83)

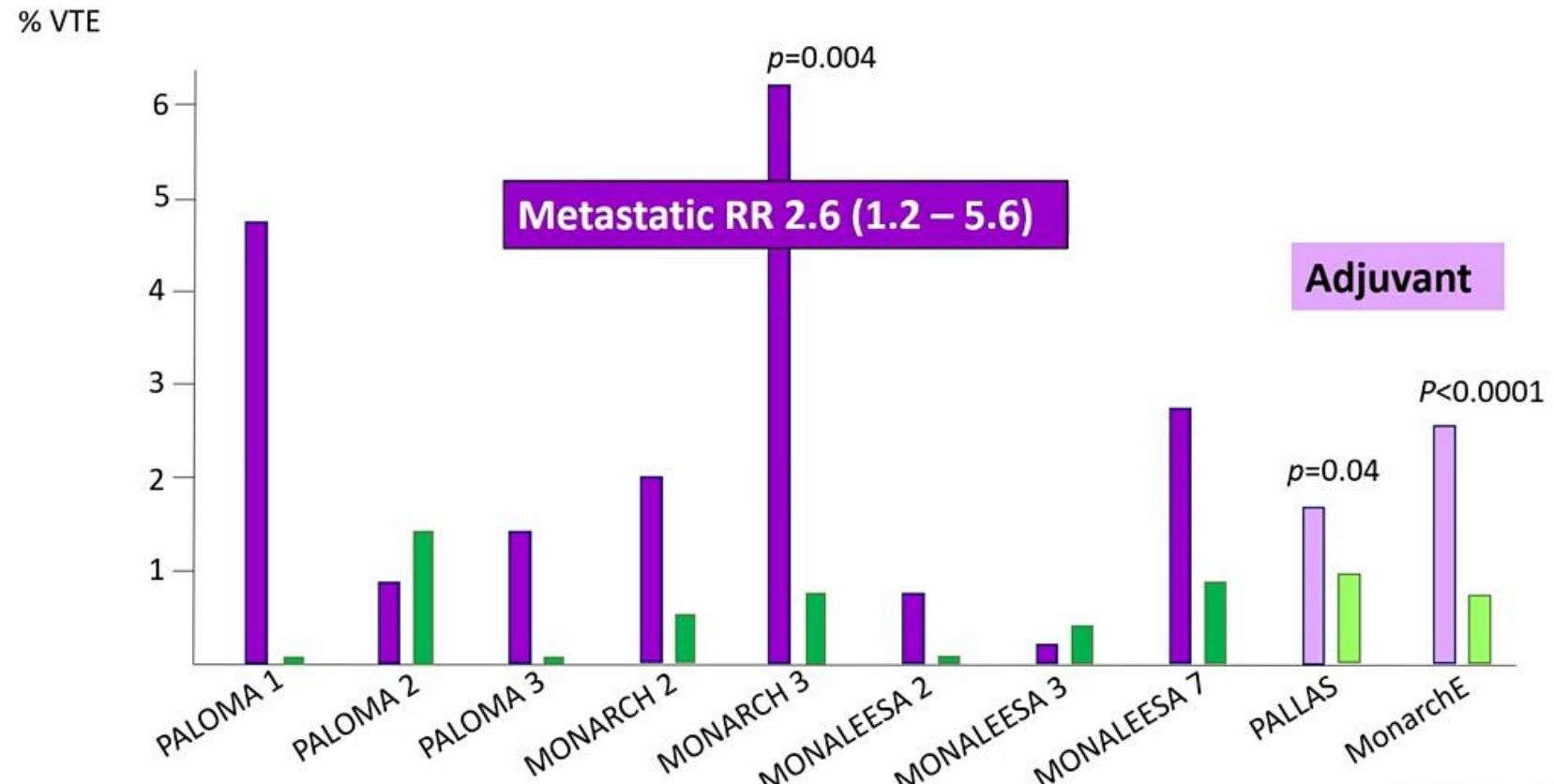
Al-Samkari et al. J Thorac Oncol. 2021
Chiari et al. Clin Lung Cancer. 2020
Liu et al. Transl Lung Cancer Res. 2021

CANCER DU SEIN - TAMOXIFEN

	Tamoxifen	AI	p
TEAM (n=9779), Exemestane	2%	1%	<0.001
ATAC (n=9366), Anastrazole	4.5%	2.8%	0.004
BIG-1 (n=8010), Letrozole	3.5%	1.5%	<0.001
Pooled analysis	2.8%	1.6%	OR 0.55

CANCER DU SEIN – INHIBITEURS CDK4/6

Systemic therapy and Breast CAT: CDK4/6 inhibitors



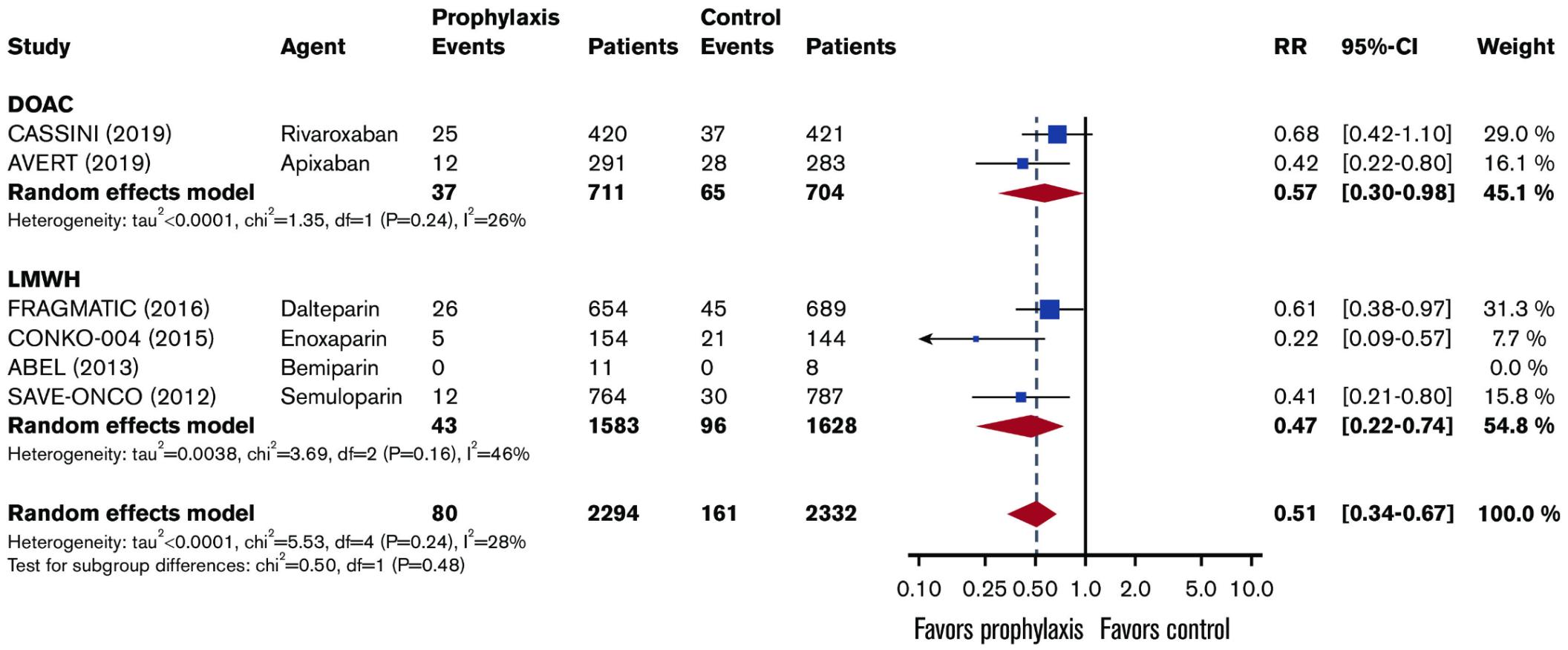


STRATIFICATION

- PAS DE MODÈLE PARFAIT
- DIFFICILE DE SUIVRE LA CLINIQUE...

PRÉVENTION PRIMAIRE

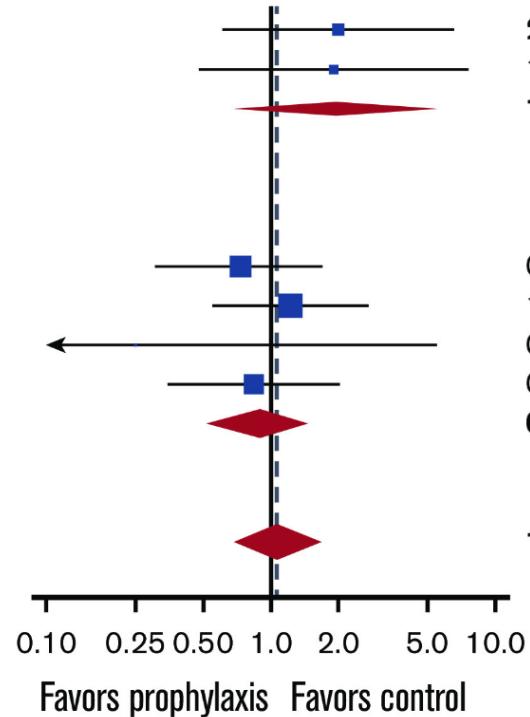
A Venous thromboembolism



PRÉVENTION PRIMAIRE

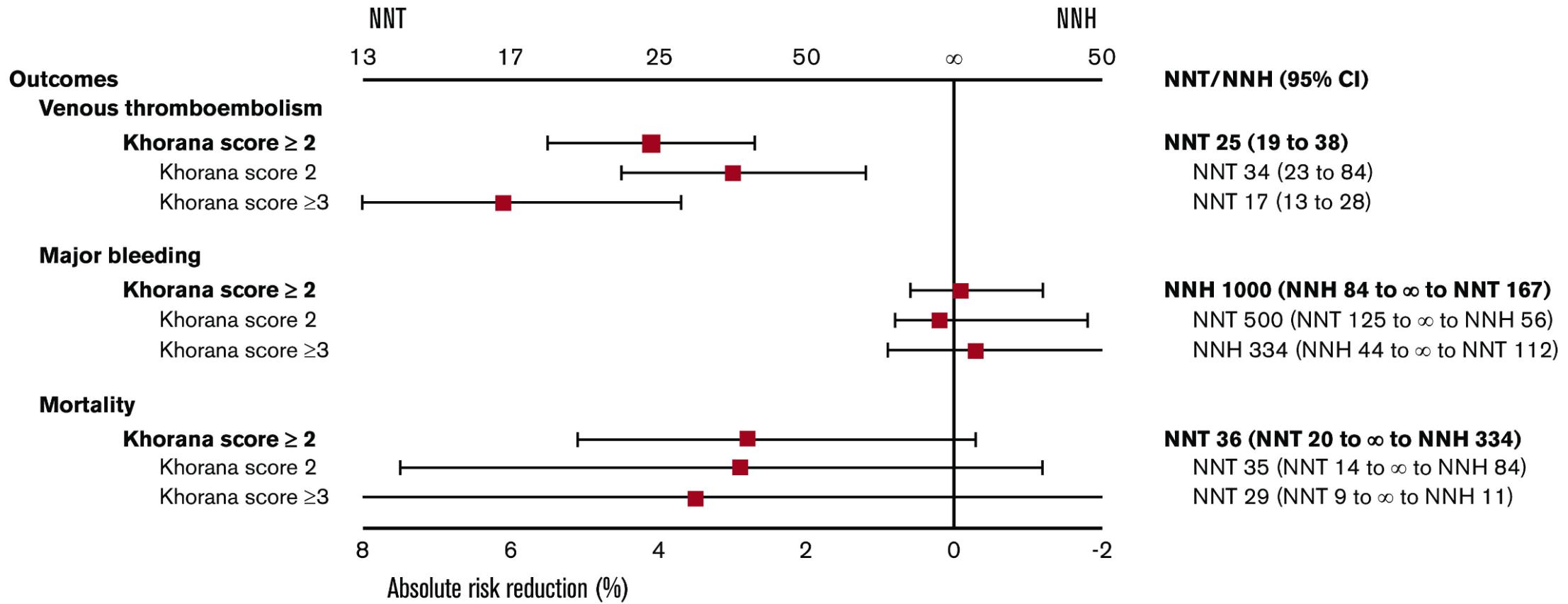
B Major bleeding

Study	Agent	Prophylaxis		Control		RR	95%-CI	Weight
		Events	Patients	Events	Patients			
DOAC								
CASSINI (2019)	Rivaroxaban	8	405	4	404	2.00	[0.61-6.57]	12.5 %
AVERT (2019)	Apixaban	6	288	3	275	1.91	[0.48-7.56]	9.4 %
Random effects model		14	693	7	679	1.96	[0.69-5.50]	21.9 %
Heterogeneity: $\tau^2=0$, $\chi^2=0.00$, $df=1$ ($P=0.96$), $I^2=0\%$								
LMWH								
FRAGMATIC (2016)	Dalteparin	9	654	13	689	0.73	[0.31-1.69]	24.9 %
CONKO-004 (2015)	Enoxaparin	13	154	10	144	1.22	[0.55-2.69]	28.2 %
ABEL (2013)	Bemiparin	0	11	1	8	0.25	[0.01-5.45]	1.9 %
SAVE-ONCO (2012)	Semuloparin	9	764	11	787	0.84	[0.35-2.02]	23.1 %
Random effects model		31	1583	35	1628	0.89	[0.52-1.45]	78.1 %
Heterogeneity: $\tau^2=0$, $\chi^2=1.49$, $df=3$ ($P=0.68$), $I^2=0\%$								
Random effects model		45	2276	42	2307	1.06	[0.69-1.67]	100.0 %
Heterogeneity: $\tau^2=0$, $\chi^2=3.78$, $df=5$ ($P=0.58$), $I^2=0\%$								
Test for subgroup differences: $\chi^2=2.29$, $df=1$ ($P=0.13$)								



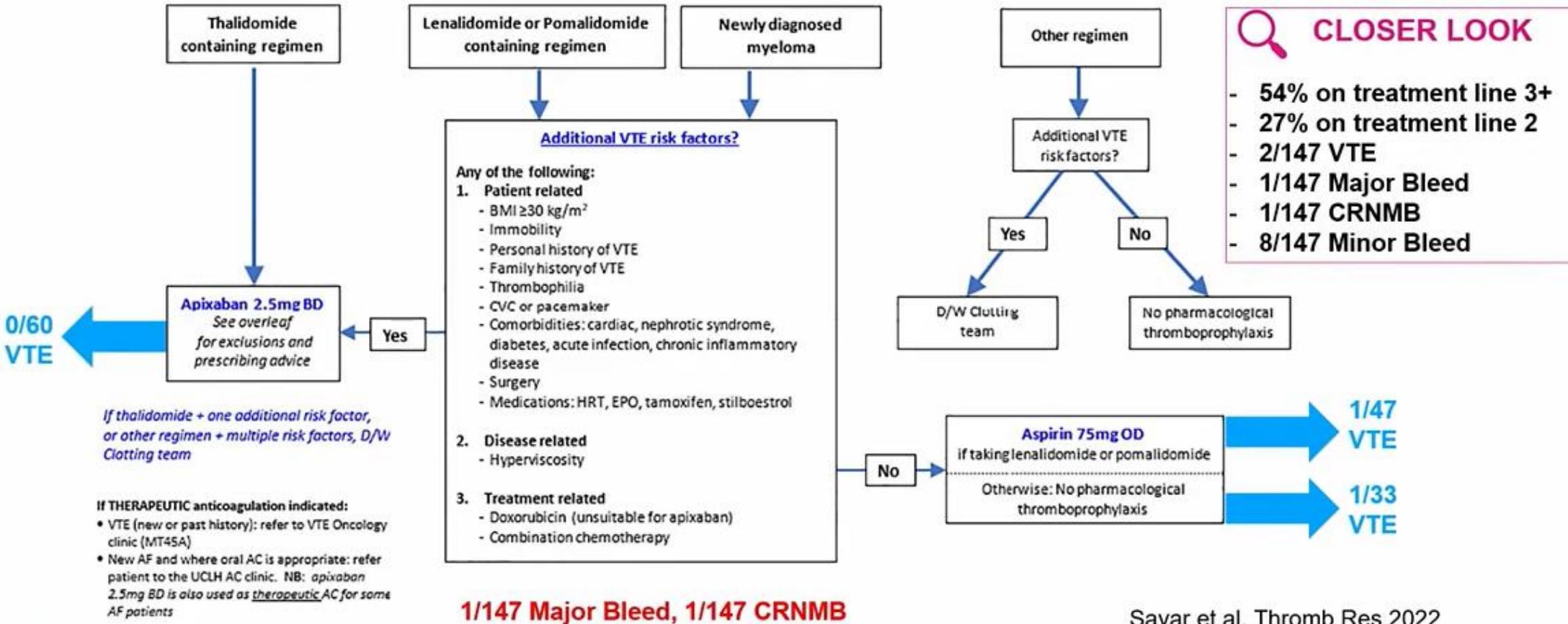
Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis

PRÉVENTION PRIMAIRE



Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis

MYÉLOME



Sayar et al. Thromb Res 2022

RECOMMENDATION ASH

In **ambulatory patients with cancer at high risk of thrombosis** receiving systemic therapy, the ASH guideline panel suggests **thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis**

Outcomes (Quality of Evidence)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no thromboprophylaxis	Risk difference with DOAC thromboprophylaxis
Mortality	RR 0.94 (0.64 to 1.38)	185 per 1,000	11 fewer deaths per 1,000 (67 fewer to 70 more)
PE	RR 0.24 (0.12 to 0.47)	60 per 1,000	46 fewer PEs per 1,000 (53 fewer to 32 fewer)
Symptomatic DVT	RR 0.61 (0.31 to 1.21)	95 per 1,000	37 fewer DVTs per 1,000 (66 fewer to 20 more)
Major bleeding	RR 1.65 (0.72 to 3.80)	14 per 1,000	9 more bleeds per 1,000 (4 fewer to 40 more)

PRÉVENTION PRIMAIRE – TUMEUR SOLIDE

- Score de Khorana ≥ 3 = thromboprophylaxie pour la plupart
 - *PANCRÉAS*
- Score de Khorana ≥ 2
 - Tumeurs à haut risque (pancréas, GI haut, GBM) = OUI
 - Thérapeutique à haut risque = OUI
 - ATCD TVP non provoquée = OUI
 - ATCD TVP multiples provoquées = OUI
 - ATCD TVS liée au cancer = OUI
 - Faible risque de saignement = OUI

PRÉVENTION PRIMAIRE – TUMEUR HÉMATO

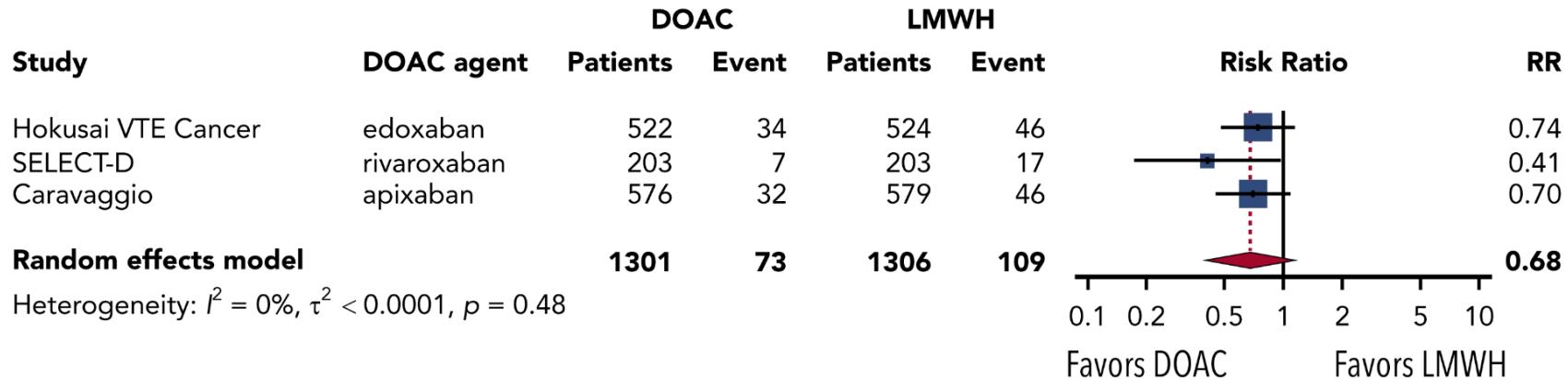
- Lymphome = Score de Khorana ≥ 2
- Myélome multiple = IMPEDE avec utilisation des AOD

STRATIFICATION

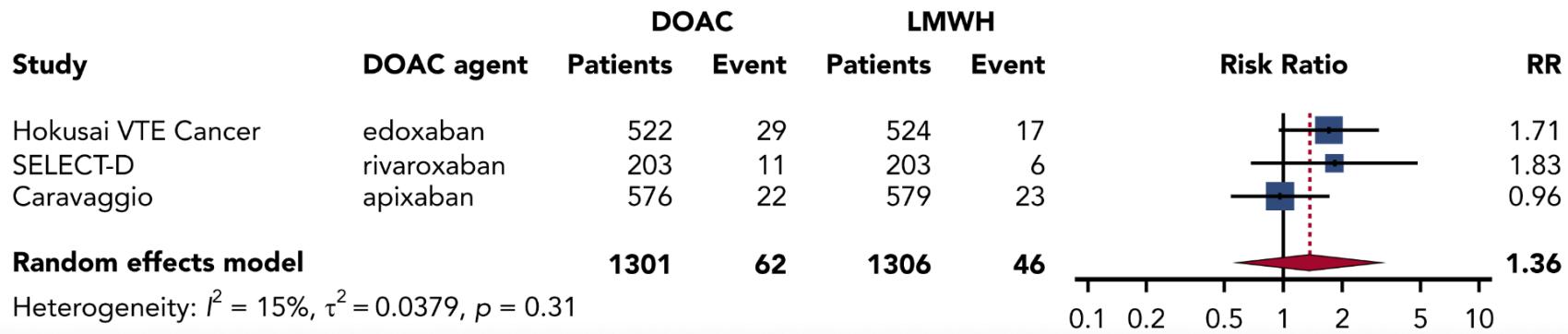
- PAS DE MODÈLE PARFAIT
- DIFFICILE DE SUIVRE LA CLINIQUE...
- PRENDRE COMPTE DE L'ÉVOLUTION
 - AUGMENTATION DE L'INCIDENCE
 - AUGMENTATION DE LA SURVIE ET DE LA DURÉE DES TRAITEMENTS
 - AUGMENTATION DE LA PRÉVALENCE
 - SI ON A UNE INTERVENTION EFFICACE, LES BÉNÉFICES AUGMENTENT

PRÉVENTION SECONDAIRE

Recurrent VTE



Major bleeding



RISQUE DE THROMBOSE

Risk Factors for Developing VTE in Cancer Patients

Tumour-related risk factors

- ◆ Site of cancer:
 - Very high: stomach, brain, pancreas,
 - High: lung, haematological, gynaecological, renal, bladder
- ◆ Histological grade of a tumour
- ◆ Stage of cancer/metastases
- ◆ Time since cancer diagnosis

Patient-related risk factors

- ◆ Medical comorbidities (CCI ≥ 3)
- ◆ Presence of varicose veins
- ◆ Prior VTE
- ◆ Coagulation risk factors (e.g., factor V Leiden)

Treatment-related risk factors

- ◆ Platinum-based and other chemotherapy
- ◆ Anti-angiogenesis agents
- ◆ Surgery
- ◆ Radiotherapy
- ◆ Blood transfusion
- ◆ Central venous catheters
- ◆ Immobility and hospitalization

Biomarkers

- ◆ Haematological biomarkers (e.g. platelets, haemoglobin, leukocyte counts)
- ◆ D-dimer, P-selectin,
- ◆ ...

© VASC | 2021

RISQUE DE SAIGNEMENT

Risk Factors for Developing Bleeding in Cancer Patients

Tumour-related risk factors

- ◆ Site of cancer:
 - Very high: stomach, brain, GI
 - High: haematological, gynaecological, renal, bladder
- ◆ Histological grade of a tumour
- ◆ Stage of cancer/metastases
- ◆ Time since cancer diagnosis

Patient-related risk factors

- ◆ Medical comorbidities (CCI ≥ 3)
- ◆ Presence of mucosal abnormalities, ulcer
- ◆ Prior Bleeding
- ◆ Coagulation risk factors (e.g., acquired vWD)

Treatment-related risk factors

- ◆ Type of anticoagulant
- ◆ Platinum-based and other chemotherapy
- ◆ Anti-angiogenesis agents
- ◆ Surgery
- ◆ Radiotherapy
- ◆ Blood transfusion
- ◆ Mucositis, thrombocytopenia
- ◆ DDI

Biomarkers

- ◆ Haematological biomarkers (e.g. platelets, haemoglobin, creatinine)

THÉRAPIES CIBLÉES



Bleeding outcomes

	VEGFR TKIs + all anti-Xa inhibitors vs anti-Xa inhibitors (N=86)	VEGFR TKIs + LMWH vs LMWH (N=84)	VEGFR TKIs + DOAC vs DOAC (N=20)
First bleeding within 6 months	HR 3.64 95% CI: 1.48-8.96 [P = 0.005]	HR 2.8 95% CI: 1.12-7.0 [P = 0.03]	HR 4.15 95% CI: 0.38-45.0 [P = 0.24]

MOLÉCULES

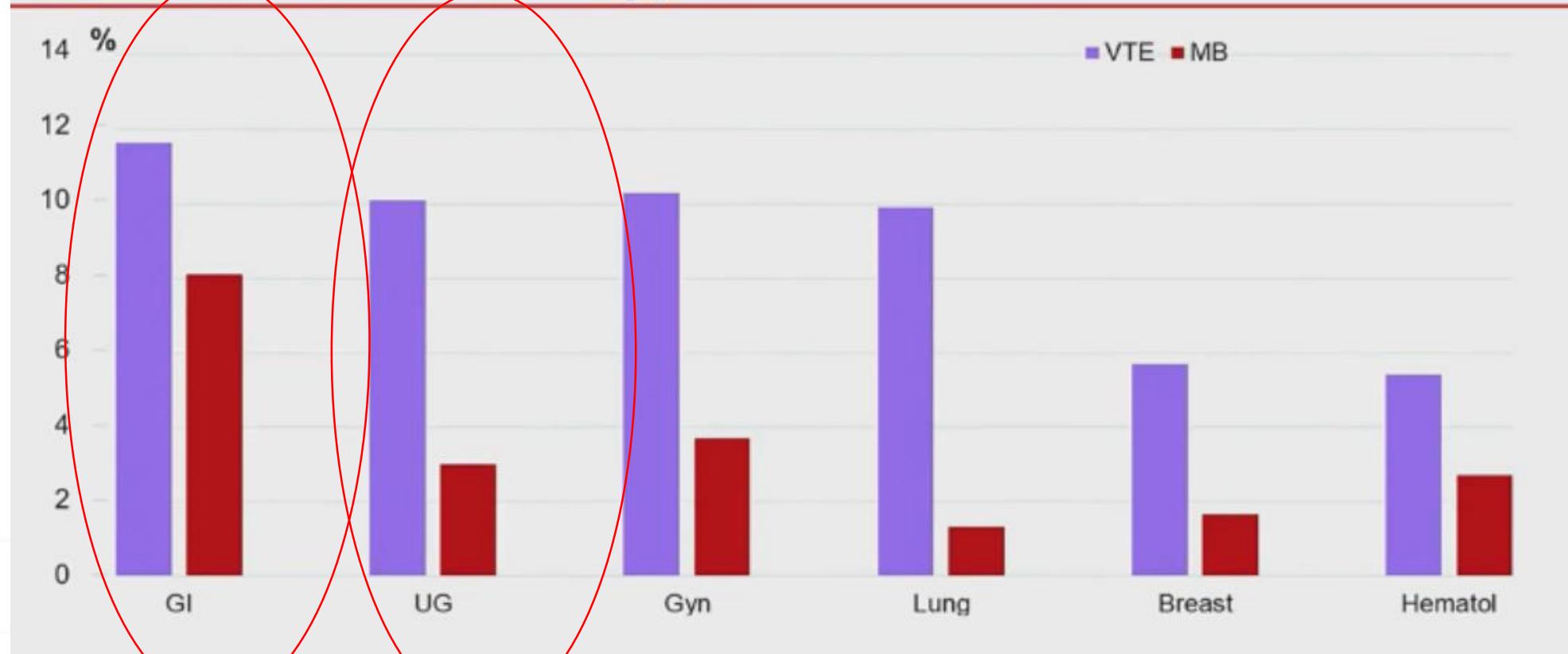
DOACs vs LMWH in CAT: Meta-Analysis

Outcomes	DOACs % (95% CI)	Dalteparin % (95% CI)	RR	95% CI	I^2
Major bleeding	4.3% (3.4-5.5)	3.3% (2.5-4.4)	1.31	0.83-2.08	23%
CRNMB	10.4% (8.9-12.1)	6.4% (5.2-7.7)	1.65	1.19-2.28	29%
Fatal bleeding*	0.2% (0.07-0.6)	0.3% (0.2-0.8)	0.37	0.07-2.00	0%

Outcomes	DOACs % (n/N)	Dalteparin % (n/N)	RR	95% CI	I^2
GI-Bleeding	2.7% (39 /1,446)	1.4% (20 /1,448)	1.91	0.96-3.82	35%
genitourinary	0.7% (10/1,446)	0.01% (1/1,448)	4.99	1.08-23.08	0%
ICH	0.1% (2/1,446)	0.5% (7/1,448)	0.37	0.10-1.49	0%

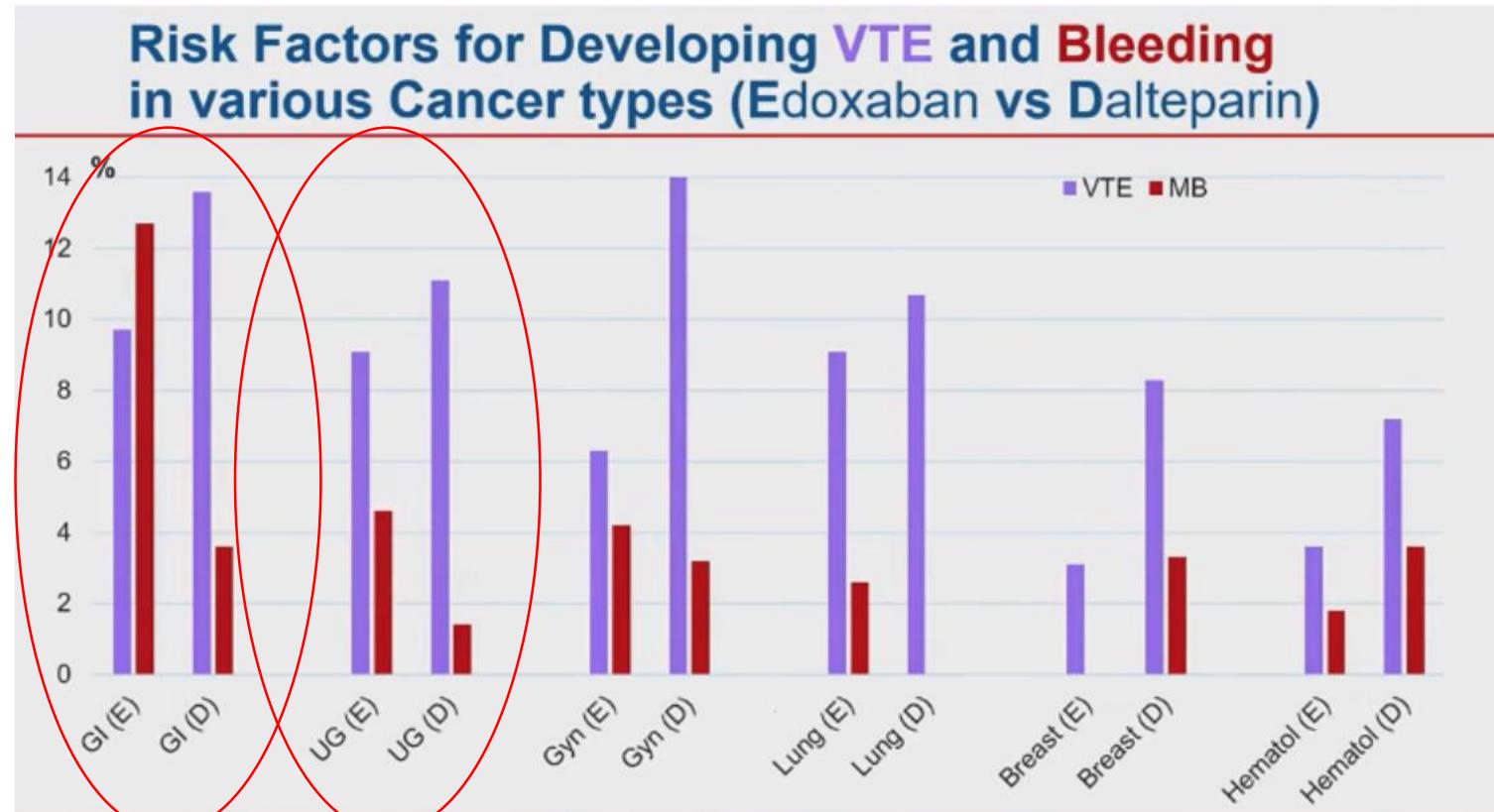
SELON LE TYPE DE CANCER

Risk Factors for Developing VTE and Bleeding in various Cancer types



Mulder FI et al. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: Results from the Hokusai VTE Cancer study. Thromb Res. 2020

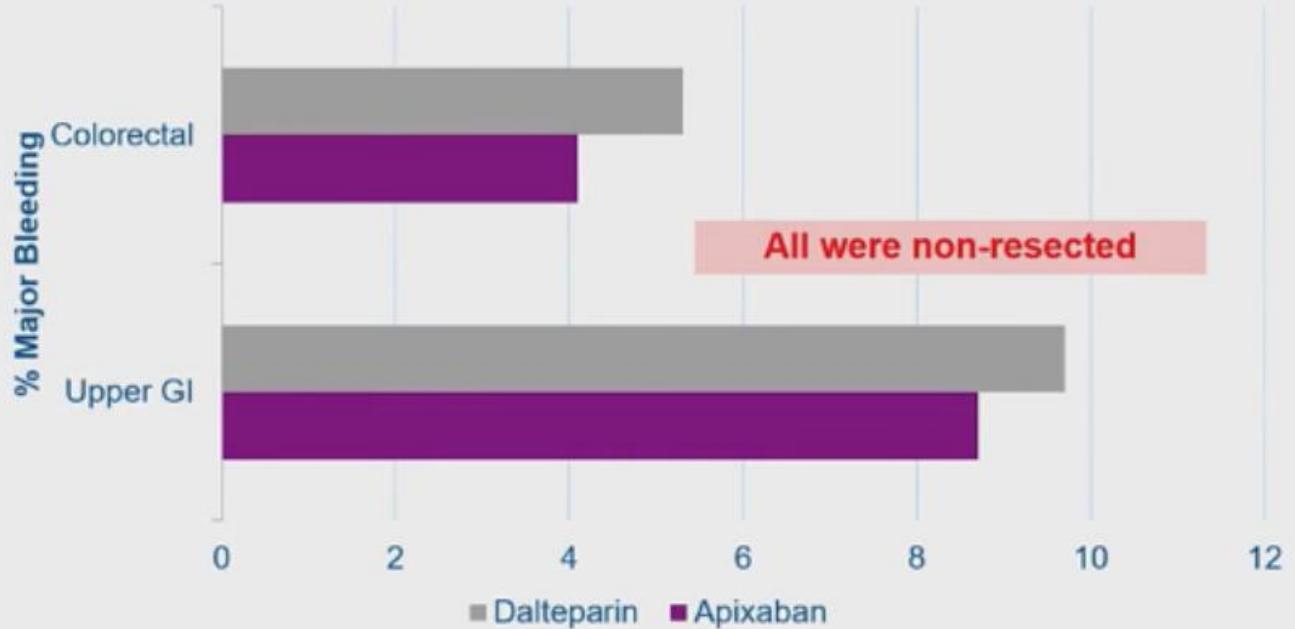
SELON TYPE ET TRAITEMENT



Mulder FI et al. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: Results from the Hokusai VTE Cancer study. Thromb Res. 2020

TUMEUR ENDOLUMINALE

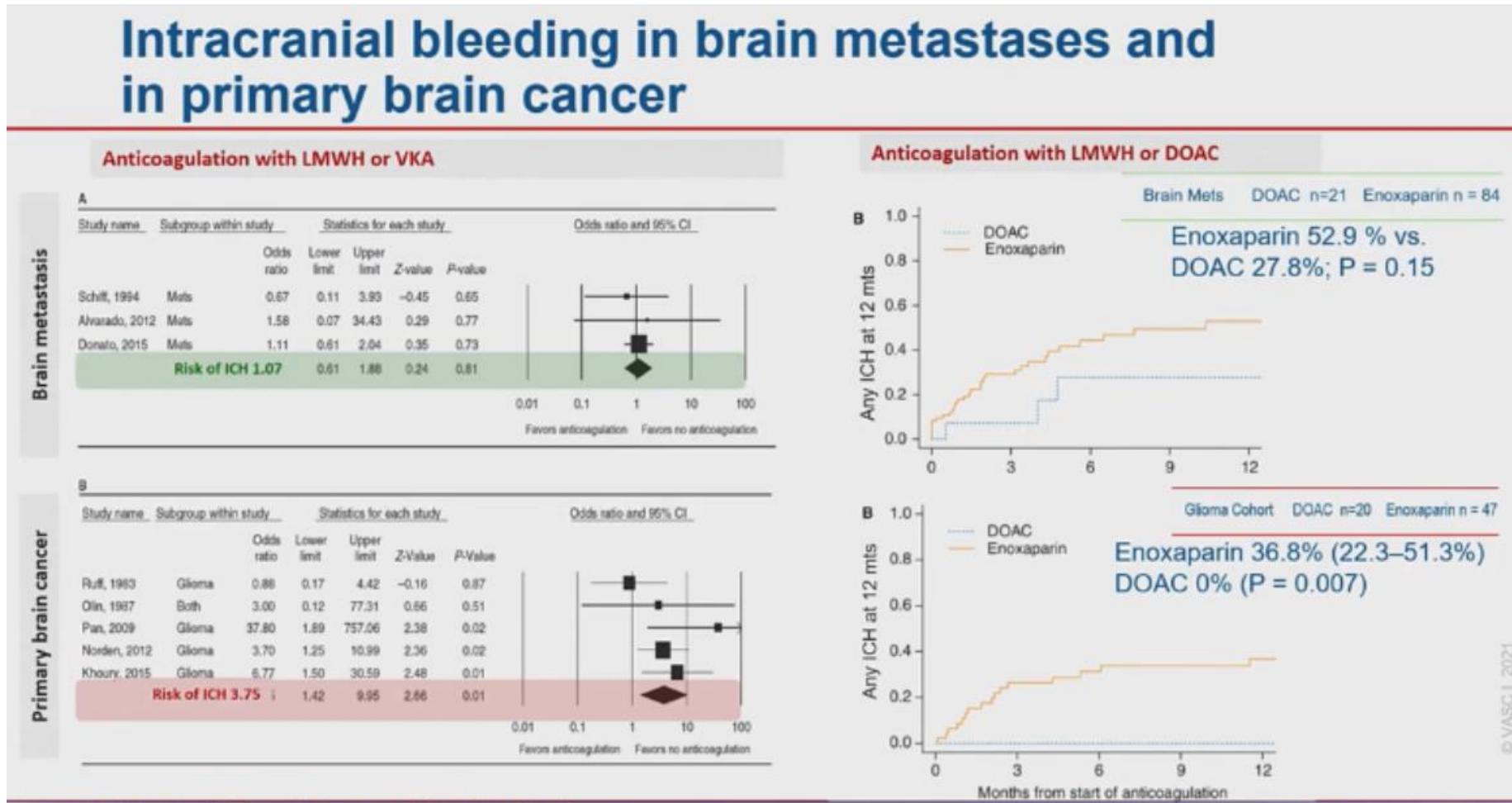
Caravaggio: GI-bleeding according to resection status



Ageno et al. Thromb Haemost.2021.

ATTEINTE SNC

Intracranial bleeding in brain metastases and in primary brain cancer



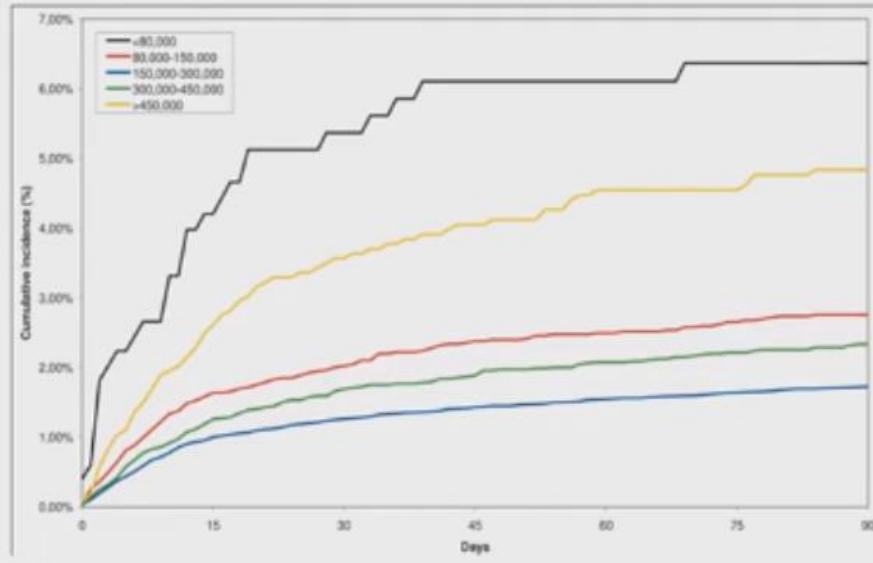
Zwicker et al. J Thromb Haemost. 2019.

THROMBOPÉNIE



Thrombocytopenia and Major Bleeding

- › RIETE: n= 43,078 patients, 9,452 Cancer, 2.1 % major Bleeding
- › (54% LMWH, 7.1% UFH, 30% VKA)
- › Multivariable analysis for major Bleeding in Cancer Patients



Platelet count at baseline	
<80,000	2.69 (1.14-6.35)
80,000-150,000	2.29 (1.41-3.73)
150,000-300,000	1 (Ref.)
300,000-450,000	1.13 (0.63-2.01)
>450,000	2.71 (1.41-5.20)
Initial therapy	
Thrombolytics	10.4 (2.54-42.5)

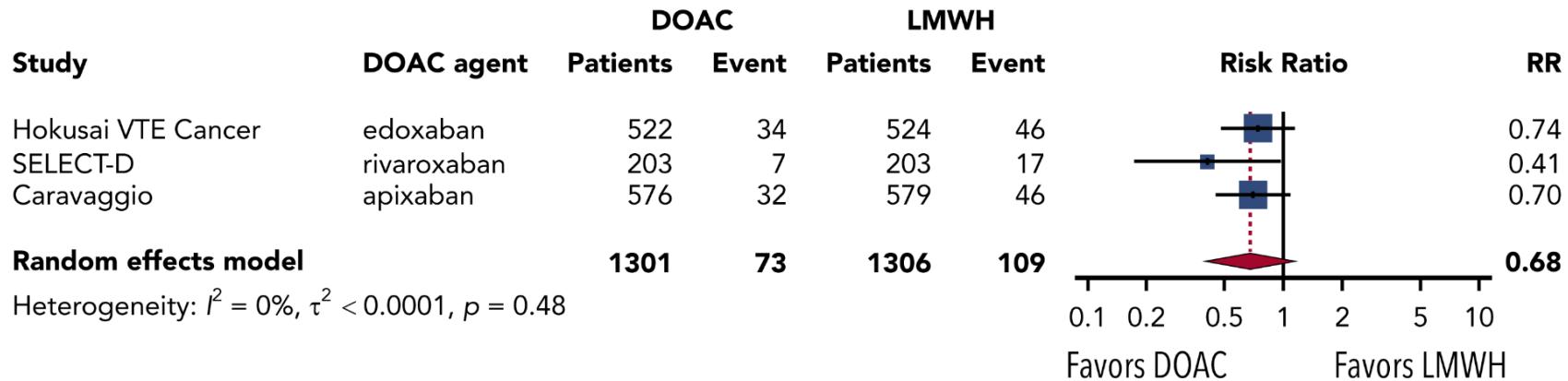
Di Micco et al. Platelet count and outcome in patients with acute venous thromboembolism. Thromb Haemost. 2013

RISQUE DE SAIGNEMENT

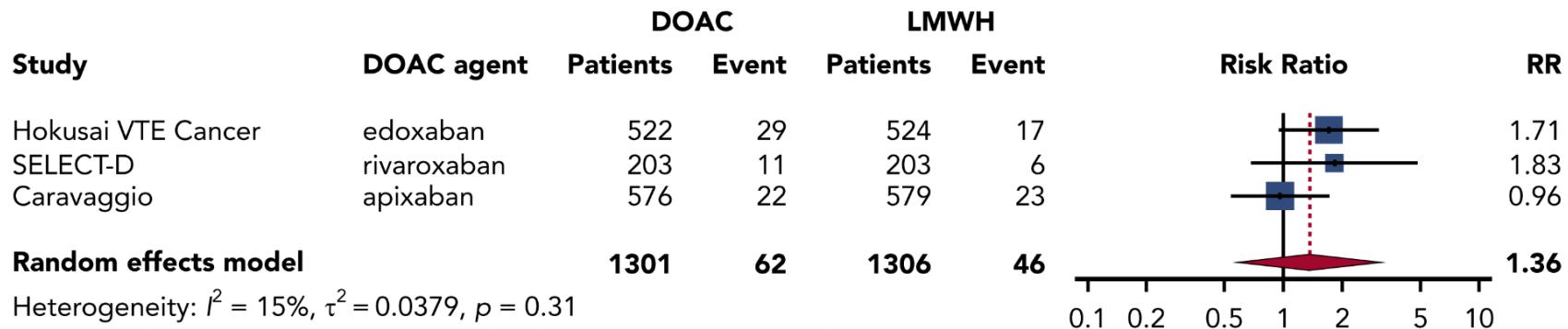
- **Sites tumoraux importants selon ANTICOAGULANT utilisé**
 - Types de cancer
 - GI HAUT > BAS, GU, PRIMAIRE et m+ SNC
 - Tumeur intraluminale non réséquée
- Néoplasie avancée, IRC, Anémie préexistante, THÉRAPIE
- Saignement GI haut plus sévère

PRÉVENTION SECONDAIRE

Recurrent VTE



Major bleeding

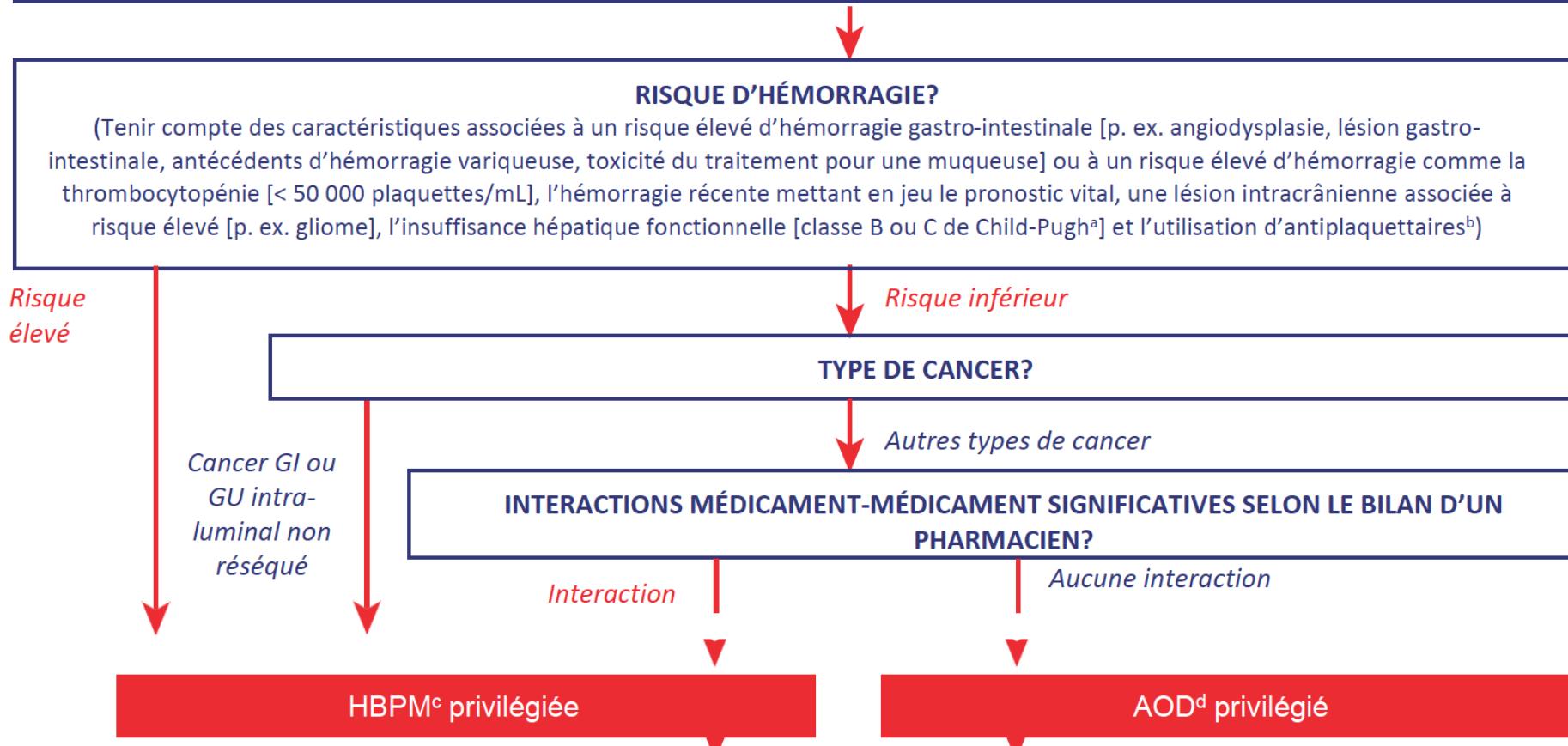


BÉMOLS

Exclusion Criteria		Exclusion Criteria	
HOKUSAI VTE Cancer	SELECT-D	ADAM-VTE	CARAVAGGIO
ECOG 3-4	ECOG 3-4	ECOG 3-4	ECOG 3-4
Previous DVT	Previous DVT	VTE <6 Mo prior	Previous DVT allowed
RR >100/170 mmHg	RR >110/180 mmHg	Not found	RR >100/180 mmHg
PltLts <50.000/ μ l	PltLts <100.000/ μ l	PltLts <50.000/ μ l	PltLts <75.000/ μ l
Severe liver disease	Severe liver disease	Severe liver disease (Child B, C)	Severe liver disease
LFT > 3x ULN	LFT > 3x ULN	LFT > 3x ULN	LFT > 3x ULN
Bili > 2x ULN	Bili not listed	Bili not listed	Bili > 2x ULN
CreaCl <30 ml/min	CreaCl <30 ml/min	CreaCl < 30 ml/min	CreaCl <30 ml/min
ASS >100 mg/d or DAT	ASS >75 mg/d or DAT	Not found	ASS >165 mg/d or DAT
Life expect <3 months	Gastroesophageal CA	Life expect <2 months	Life expect <6 months

ALGORITHME CANADIEN

THROMBOSES ASSOCIÉES AU CANCER SANS CONTRE-INDICATION À L'ANTICOAGULATION (TVP et EP des membres supérieurs et inférieurs, décelées de manière fortuite et symptomatiques)



ALGORITHME CANADIEN



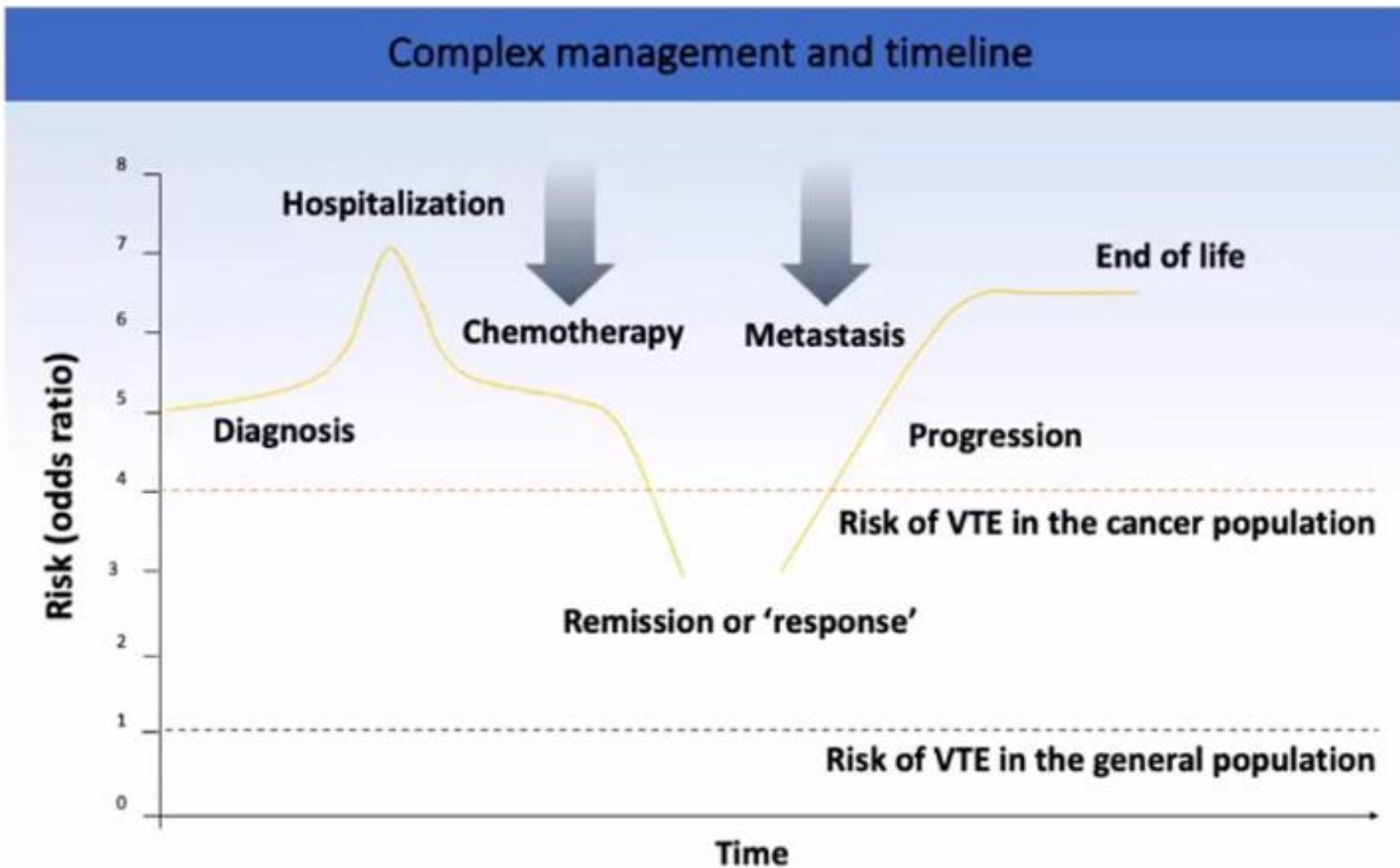
AUTRES FACTEURS À PRENDRE EN COMPTE

- Préférences du patient et du clinicien, après discussion des risques et des avantages
- Coût du médicament
- Poids corporel (envisager une HBPM chez les patients pesant > 150 kg, et un agent dont la posologie est basée sur le poids chez les patients pesant < 50 kg)
- Fardeau du cancer (p. ex. récidive ou progression) et fardeau de la TEV (envisager une HBPM pour les patients présentant des symptômes graves tels qu'une TVP iliofémorale, une EP étendue ou une EP submassive, et chez tout patient ayant subi une thrombolyse)
- Saignement utérin anormal (envisager une HBPM pour les patientes ayant des antécédents de saignement utérin anormal secondaire à un AOD)
- Chirurgie gastro-intestinale lourde ou troubles de l'absorption (envisager une HBPM pour les patients présentant des syndromes de malabsorption gastro-intestinale)

CONCLUSION

- PRÉVENTION PRIMAIRE EFFICACE ET SÉCURITAIRE
 - UTILISATION DU SCORE DE KHORANA
- PATIENTS COMPLEXES ET QUI CONTINUENT DE SE COMPLEXIFIER
 - PRENDRE COMPTE DE L'ÉVOLUTION
 - AUGMENTATION DE L'INCIDENCE
 - AUGMENTATION DE LA SURVIE ET DE LA DURÉE DES TRAITEMENTS
 - AUGMENTATION DE LA PRÉVALENCE
 - SI ON A UNE INTERVENTION EFFICACE, LES BÉNÉFICES AUGMENTENT !

RISQUE CHANGE DANS LE TEMPS

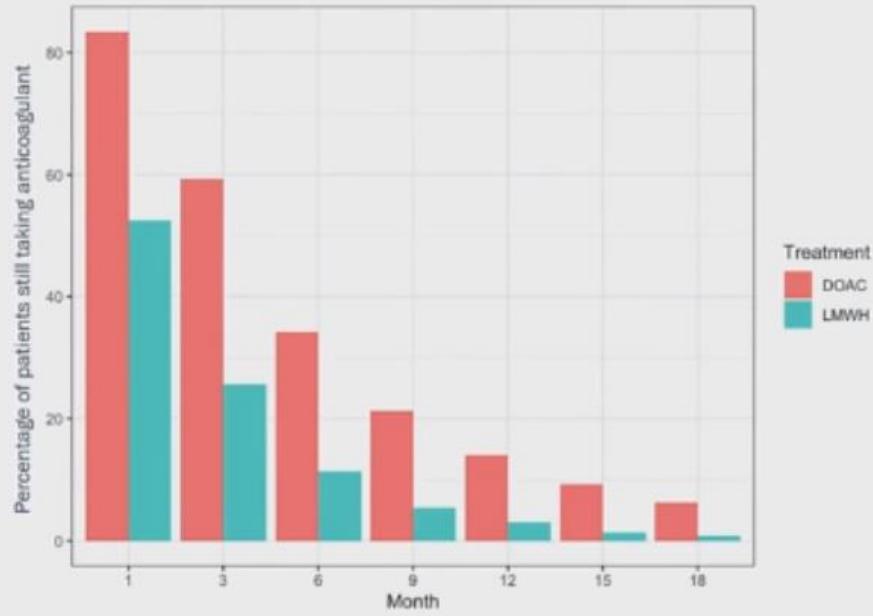


QUI RÉFÉRER

- TOUS !
- PRÉVENTION PRIMAIRE
 - RÉFÉRENCE, SENSIBILISER LE PATIENT
- PRÉVENTION SECONDAIRE– THROMBOSE AIGUE
 - THROMBOSE CANADA, TRÈS UTILE
 - EN AIGU, L'HBPM TOUJOURS UN BON CHOIX EN ATTENDANT ÉVALUATION

VÉRIFIER LA COMPLIANCE

'Drugs don't work in patients who don't take them'
(C. Everett Koop, MD, US Surgeon General, 1985)



Schaefer JK, et al. J Thromb Haemost. 2021;19(1):212-220. doi:10.1111/jth.15153.
Overhage JM, Agrawal A. NEJM Catalyst. July 29, 2021. DOI: 10.1056/CAT.21.0162

MERCI !

