Collège National des Cardiologues des Hôpitaux

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AOD ET CANCER: QUELS FAITS ET QUOI FAIRE?

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Avec le soutien institutionnel de

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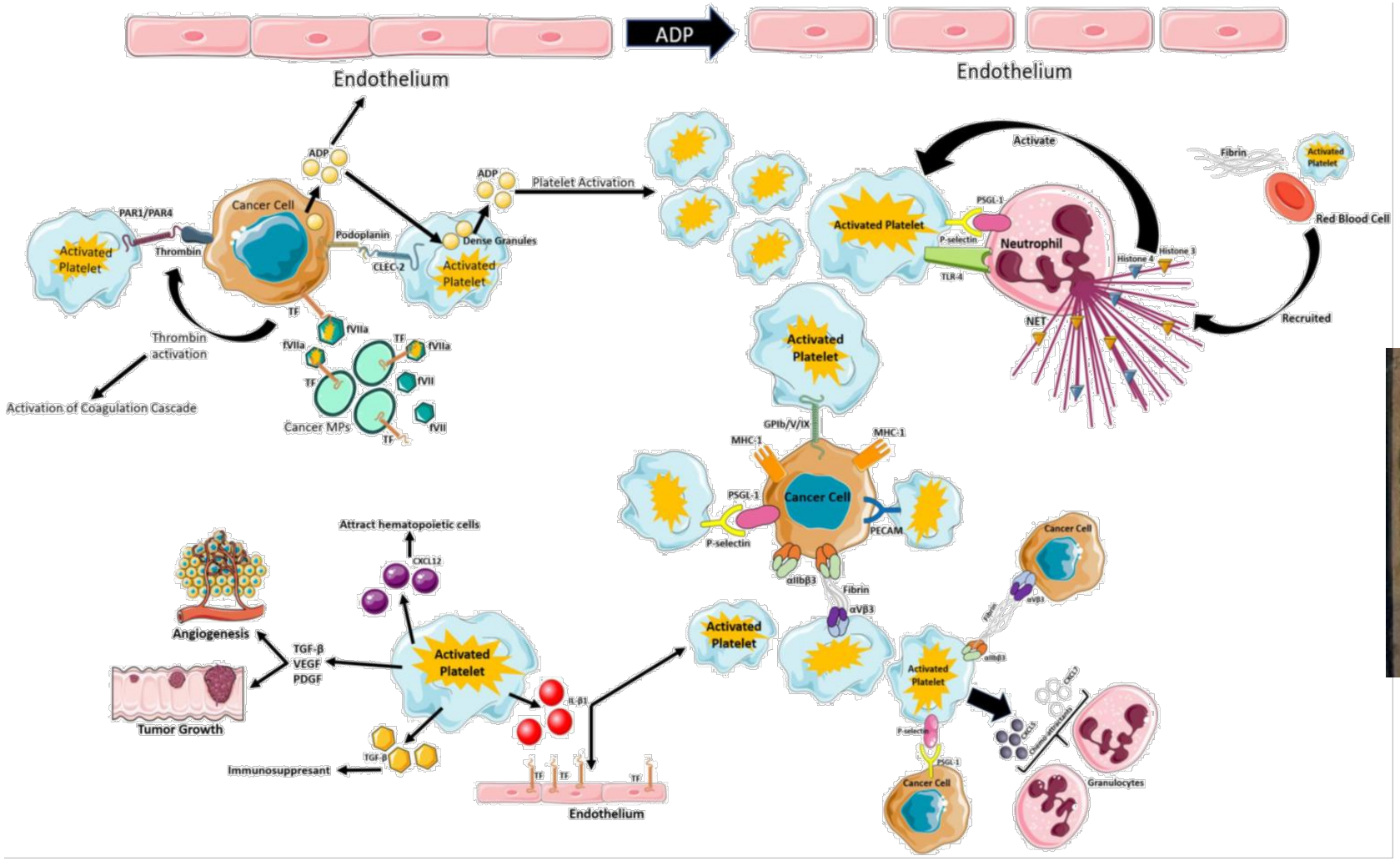
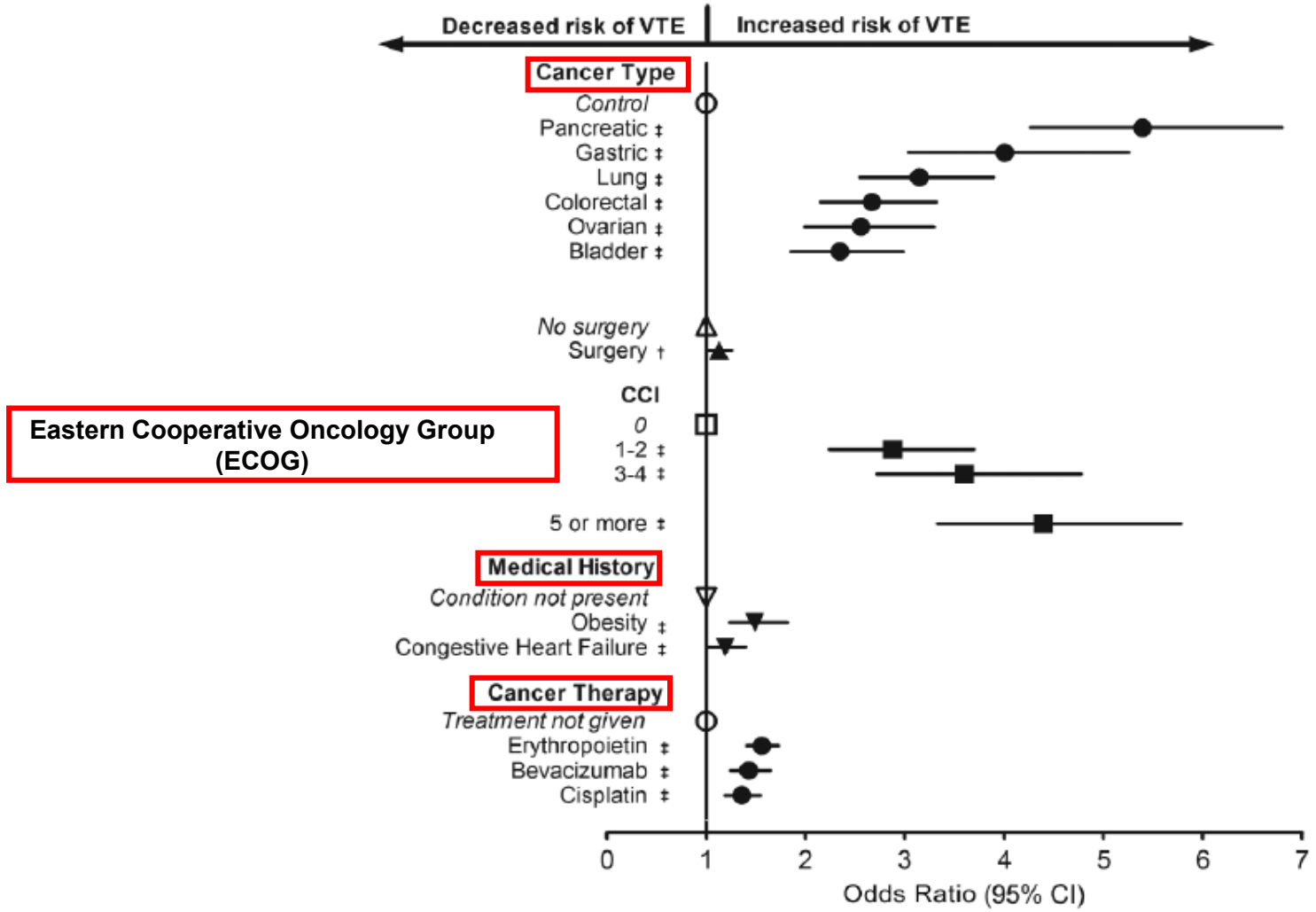
“Alliance” Cancer et Thrombose : Deux Faces d’un même “alien”



«JANUS – MALUS»

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

Les 4 Points Cardinaux du Cancer Associé à la Thrombose (CAT)



Eastern Cooperative Oncology Group (ECOG)

Khorana et al Cancer. 2013;119: 648-655

Facteurs de Risque Thrombotique liés aux Pts Avec Tumeur Solide

Variable	Odds ratio	Lower 95%CI	Upper 95%CI	*p* value
Female gender	1.10	1.04	1.16	0.001**
Chronic pulmonary disease	1.17	1.10	1.25	<0.001*
Liver disease	0.65	0.56	0.76	<0.001*
Obesity	1.37	1.24	1.51	<0.001*
Chronic kidney disease	0.54	0.49	0.59	<0.001*
End-stage renal disease	0.25	0.19	0.33	<0.001*
Age	1.00	0.99	1.00	0.58
Congestive heart failure	0.95	0.87	1.05	0.32
Diabetes	0.90	0.86	0.97	0.003

Kotecha et al Intern J Hematol 2020; 112:477–486

Facteurs de Risque Thrombotique liés aux Pts Sans Tumeur Solide

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	*p* value
Age	1.02	1.02	1.03	<0.001*
Female gender	0.77	0.73	0.82	<0.001*
Congestive heart failure	1.22	1.12	1.35	<0.001*
Uncomplicated diabetes	0.76	0.70	0.82	<0.001*
Chronic pulmonary disease	1.37	1.28	1.47	<0.001*
Obesity	2.63	2.43	2.84	<0.001*
End-stage renal disease	0.32	0.25	0.40	<0.001*
Iron deficiency anemia	1.00	0.93	1.08	0.99

Kotecha et al Intern J Hematol 2020; 112:477–486

CAT et Comorbidités

n = 11,950 RCC patients	DVT[b] (n = 990) HR (95% CI)	P-Value
Male sex	0.8 (0.7-0.9)	<0.001
Atherosclerosis	2.0 (1.7-2.3)	<0.001
Diabetes	1.2 (1.1-1.4)	0.004
Hypercholesterolemia	–	–
Kidney disease	1.9 (1.6-2.1)	<0.001
Varicose veins	2.2 (1.6-3.1)	<0.001
History of cancer diagnosis	–	–
History of VTE[c]	5.4 (4.4-6.4)	<0.001
Chemotherapy	1.8 (1.4-2.2)	<0.001
Central venous catheter[d]	0.4 (0.3-0.4)	<0.001
High-risk surgery[e]	0.4 (0.3-0.6)	<0.001
Stage		
Regional versus localized	2.5 (2.2-2.9)	<0.001
Distant versus localized	2.6 (2.2-3.0)	<0.001

Age > 65 yo
FU 12 months post-Dg 8,4% VTE
70% in the first 3 months
HR VTE : 2-4
HR recurrence : 5-19

Connelly-Frost et al. BMC Cancer 2013;13:209-219

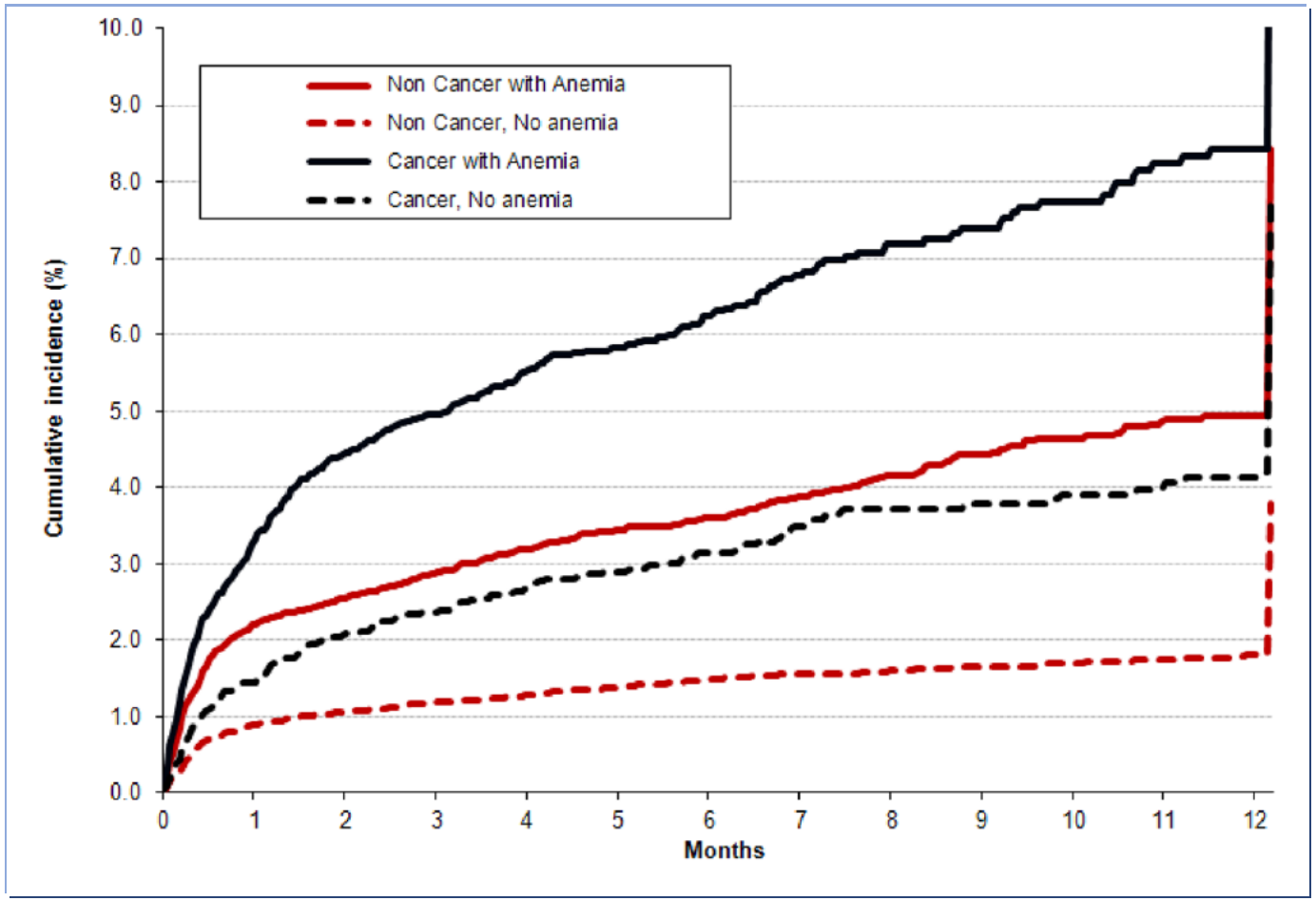
CAT et Comorbidités

	Patients with available values (*N*)	DVT cohort	PE cohort	Other patients[a]	Total
Patients (%)	72,107	33,150	35,745	3,212	72,107 (100%)
Disposition (inpatient vs. outpatient)	70,122	8,228 (25.5%)	10,872 (31.3%)	794 (25.4%)	19,894 (28.4%)
Demographics					
Male (%)	72,107	17,019 (51.3%)	16,668 (46.6%)	1,684 (52.4%)	35,371 (49.1%)
Age (y ± SD)	72,107	63.5 ± 18	67.3 ± 17	63.5 ± 15.4	65.4 ± 17.5
Body mass index (kg/m²)	50,118	27.6 ± 5.2	28.2 ± 5.7	27 ± 5.2‡	27.8 ± 5.5
Underlying conditions					
Chronic lung disease	72,107	2,800 (8.4%)	5,112 (14.3%)	326 (10.1%)	8,238 (11.4%)
Chronic heart failure	72,107	1,455 (4.4%)	3,263 (9.1%)	137 (4.3%)	4,855 (6.7%)
Diabetes	45,033	2,778 (14.8%)	3,693 (16%)	585 (18.7%)	7,056 (15.7%)
Hypertension	45,263	8,117 (43%)	11,869 (51%)	1,409 (44.9%)	21,395 (47.3%)
Prior myocardial infarction	45,002	1,224 (6.5%)	1,918 (8.3%)	176 (5.7%)	3,318 (7.4%)
Prior ischemic stroke	44,981	1,095 (5.8%)	1,800 (7.8%)	170 (5.5%)	3,065 (6.8%)
Recent major bleeding	72,107	678 (2%)	836 (2.3%)	125 (3.9%)	1,639 (2.3%)
Anaemia	72,107	11,883 (35.8%)	11,680 (32.7%)	1,410 (43.9%)	24,973 (34.6%)
Platelet count <150,000	71,990	885 (2.7%)	823 (2.3%)	144 (4.6%)	1,852 (2.6%)
Platelet count >450,000	71,990	1,113 (3.4%)	1,264 (3.5%)	155 (4.9%)	2,532 (3.5%)
Recent surgery	72,107	3,476 (10.5%)	4,241 (11.9%)	316 (9.8%)	8,033 (11.1%)
Recent immobility	72,107	7,530 (22.7%)	7,642 (21.4%)	464 (14.4%)	15,636 (21.7%)
Active cancer	72,107	7,655 (23.1%)	7,974 (22.3%)	1,612 (50.2%)	17,241 (23.9%)
Prior VTE	72,107	5,336 (16.1%)	5,258 (14.7%)	272 (8.5%)	10,866 (15.1%)
Pregnancy/Puerperium	72,107	561 (1.7%)	314 (0.9%)	31 (1%)	906 (1.3%)
Hormonal use	72,107	1,779 (5.4%)	1,916 (5.4%)	158 (4.9%)	3,853 (5.3%)

RIETE REGISTRY DATA

Bikdeli et al. Thromb Haemost 2018;118:214-24

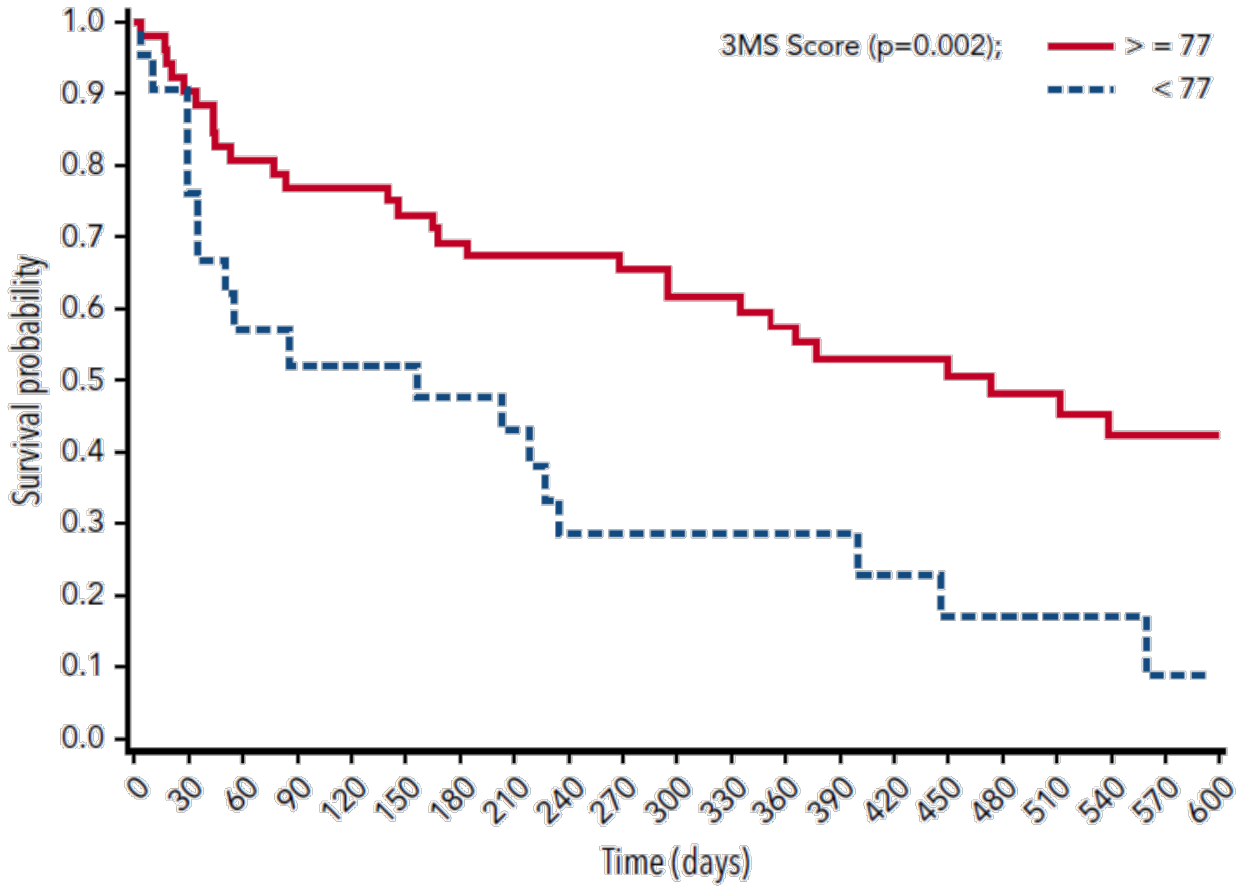
Risque de Récidive Thrombotique et d'Hémorragie si Cancer et Anémie



Kuperman A, et al. J Thromb Thrombolysis 2018Apr;45(3):360-368

Altération Cognitive et Vulnérabilité

Impaired cognitive function and physical performance are associated with worse survival for patients with AML



Abel & Klepin, Blood 2018; 131: 515-524

Caractéristiques des Patients Inclus dans les Etudes CAT

	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

Peterson & Lee. American College of Cardiology May 11, 2018
https://www.acc.org/latest-in cardiology/articles/2018/05/11/08/39/review-of-clot-and-catch-trials,

Caractéristiques des Patients CAT en Vie Réelle

Table 2. Cancer patients: Clinical characteristics according to long-term anticoagulant therapy.

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%)‡

Abbreviations: VKA, vitamin K antagonists; LMWH, low-molecular-weight heparin; SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis. Differences between patients staring VKA within the first week and the other groups

* p <0.05

† p <0.01

‡ p <0.001.

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

Anticoagulants et Pharmacocinétique/Pharmacodynamique

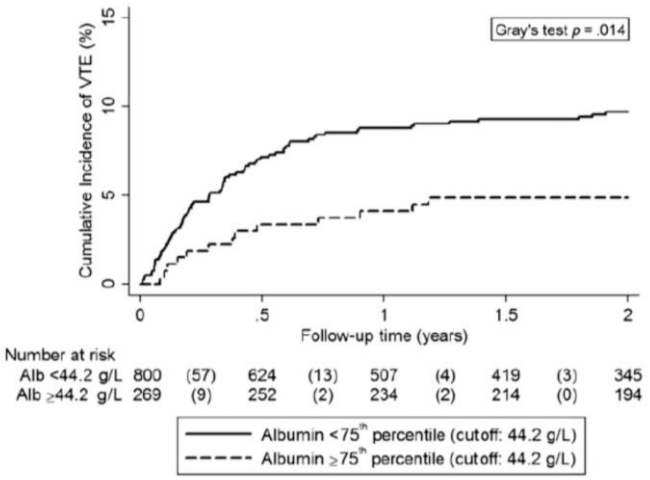
	Inhibition target	Bioavailability (%)	Protein binding (%)	Metabolism	Efflux protein	Elimination half-life (hours)	Elimination route
VKA							
Acenocoumarol	Vit K epoxy-reductase	60	>98	CYP2C9	P-gp	8-11	Renal: inactive metabolites
Fluindione		NA	>98	CYP2C9	P-gp	31	
Warfarin		90	>99	CYP3A4/3A5/2C9	BCRP	35-45	
LMWH	Anti-Xa/anti-IIa	87-92	-	Desulfation and depolymerisation	-	4.5-7	Renal
Fondaparinux	Anti-Xa	100	-	No	-	17-21	Renal
NOAC							
Dabigatran	Thrombin (IIa)	7	35	UGT: 20%	P-gp, BCRP	7-17	80% renal
Rivaroxaban	Anti-Xa	80-100	95	CYP3A4/3A5/2J2	P-gp, BCRP	7-11	36% renal
Apixaban	Anti-Xa	50	87	CYP3A4/3A5	P-gp, BCRP	8-15	35% renal
Edoxaban	Anti-Xa	62	42-59	CYP3A4 (<10%)	P-gp, BCRP	9-11	50% renal

Malnutrition et hypoalbuminémie?

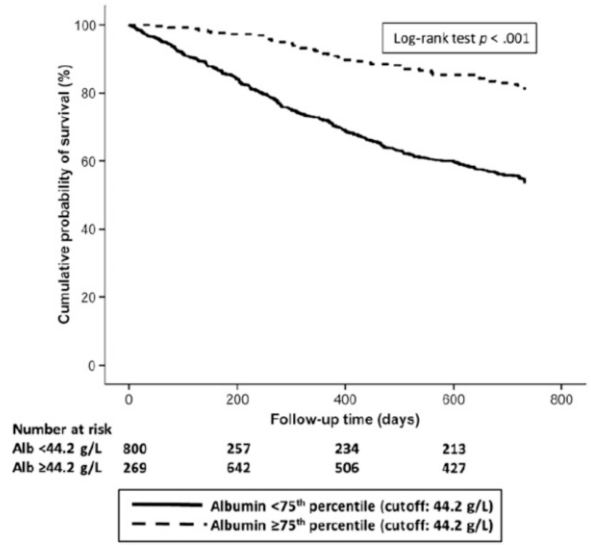
Bellesoeur et al. Crit Rev Oncol Hematol.2018;129:102-112

Hypoalbuminémie et Impact Pronostique

Vienna cohort prospective observational study (CATS) n=1070 pts with mean follow-up 723 d
VTE incidence 8.4%



HR 2.2 (95%CI 1.09–4.32), p=0.027



HR 2.3 (95%CI 1.68–3.20), p<0.001

Köningsbrüdgge et al. The Oncologist 2016;21:252-2574.

Study comparing the prognosis impact of hypoalbuminemia (< vs ≥ 35 g/L) in hospitalized pts with PE

Mortality at 30 d : **16,3% vs 3,6%**
Mortality at 90 d : **26,3% vs 6,2%**

Hoskin S, et al. Heart, Lung and Circulation 2019

Retrospective study in n=368 pts
Rivaroxaban-treated pts
albuminemia is significantly **lower** in bleeding pts (n=30)
Bleeding **x 4,4** if albuminemia decrease by 10 g/L

Wojakowski E, et al. J Thromb Thrombolysis 2020

Interactions Médicamenteuses : Problème Potentiel

- An Increasing Problem More Common in Cancer Patients

Studies on anticancer drugs **(26.7%)** contributed the most to published PBPK models, followed by cardiovascular (20.0%) and anti-infective (17.1%) drugs

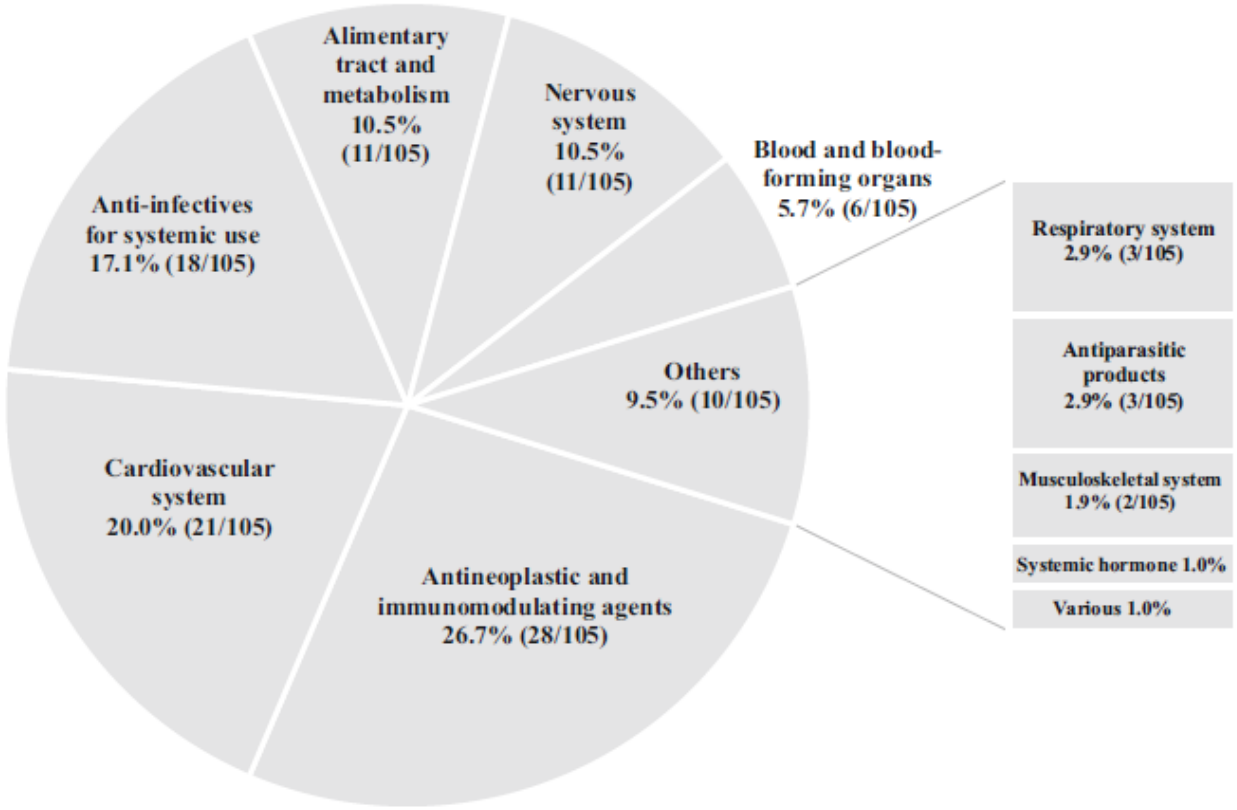
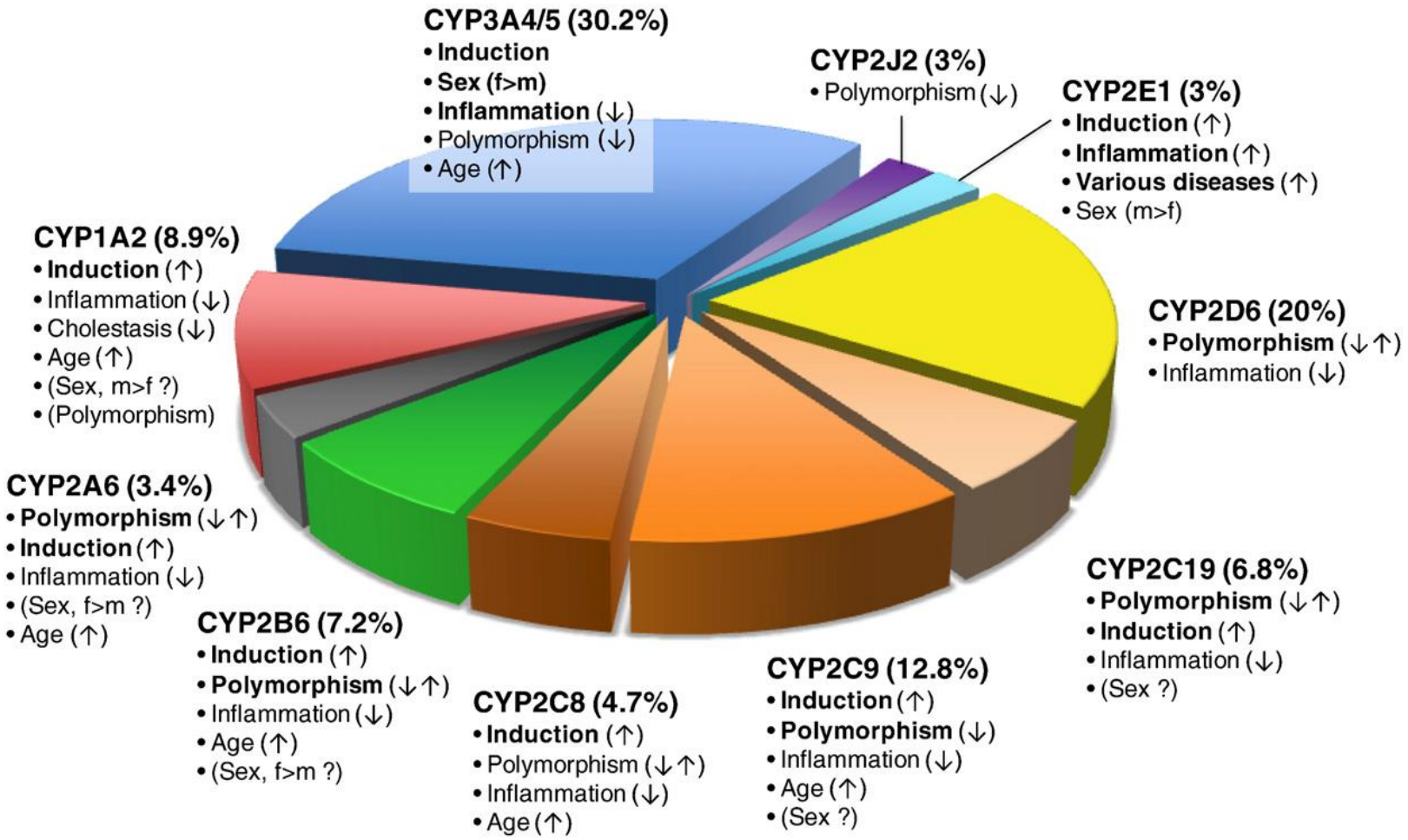


Fig. 2 Classification of 105 drugs selected in the DDI-related articles using PBPK modeling according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system, which groups drugs according to their main anatomical group, as developed by the World Health Organization (http://www.whocc.no/atcddd/)

Min et al Arch Pharm Res 2017; PBPK: physiologically based pharmacokinetic

Cytochromes : Variabilité Interindividuelle et Contextuelle



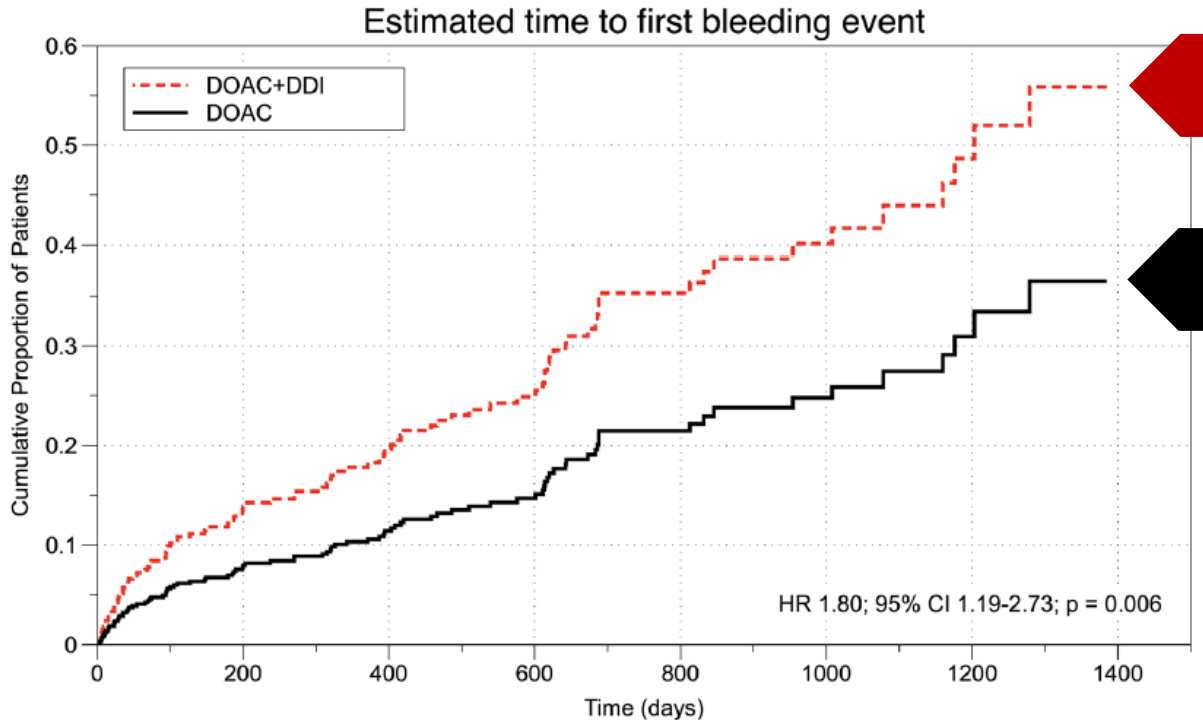
Zanger et al. Pharmacology and Therapeutics 2013

Association AOD et Inhibiteur Modéré de P-gp ou de CYP

Cohort retrospective study: concomitent use of Moderate Inhibitor of CYP3A4 and P-gp ≥ 3 months

N=226 pts DOAC + MI

N=400 pts DOAC alone (rivaroxaban or apixaban)



26.4% Bleeding with DOAC + MI

18.4% Bleeding with DOAC alone

Hanigan S et al. J Thromb Thrombolysis. 2020 49(4):636-643.

AOD et Traitements Anti-Tumoraux : Quelles Conséquences?

Santini *et al. Exp Hematol Oncol* (2019) 8:22
https://doi.org/10.1186/s40164-019-0146-9

Experimental Hematology & Oncology

LETTER TO THE EDITOR Open Access

Cabozantinib and apixaban: an hitherto unreported interaction

Daniele Santini†, Fabrizio Citarella†, Bruno Vincenzi†, Marco Russano†, Giuseppe Tonini† and Marco Stellato*†

Abstract

The use of direct oral anticoagulant in cancer patients is an emerging issue, which seems to be an alternative to low molecular weight heparin. Every year several new drugs are approved as anticancer treatment with possible drug-drug interaction with other drugs such as oral anticoagulant. We describe, for the first time, a case of neutropenia and thrombocytopenia in a patient in treatment with cabozantinib, a novel anticancer treatment used in metastatic renal cell carcinoma, and apixaban with promptly resumption of the toxicity after the interruption of cabozantinib. This case suggest a possible interaction between these two pharmaceutical agents, which merit caution considering the spreading of the two drugs.

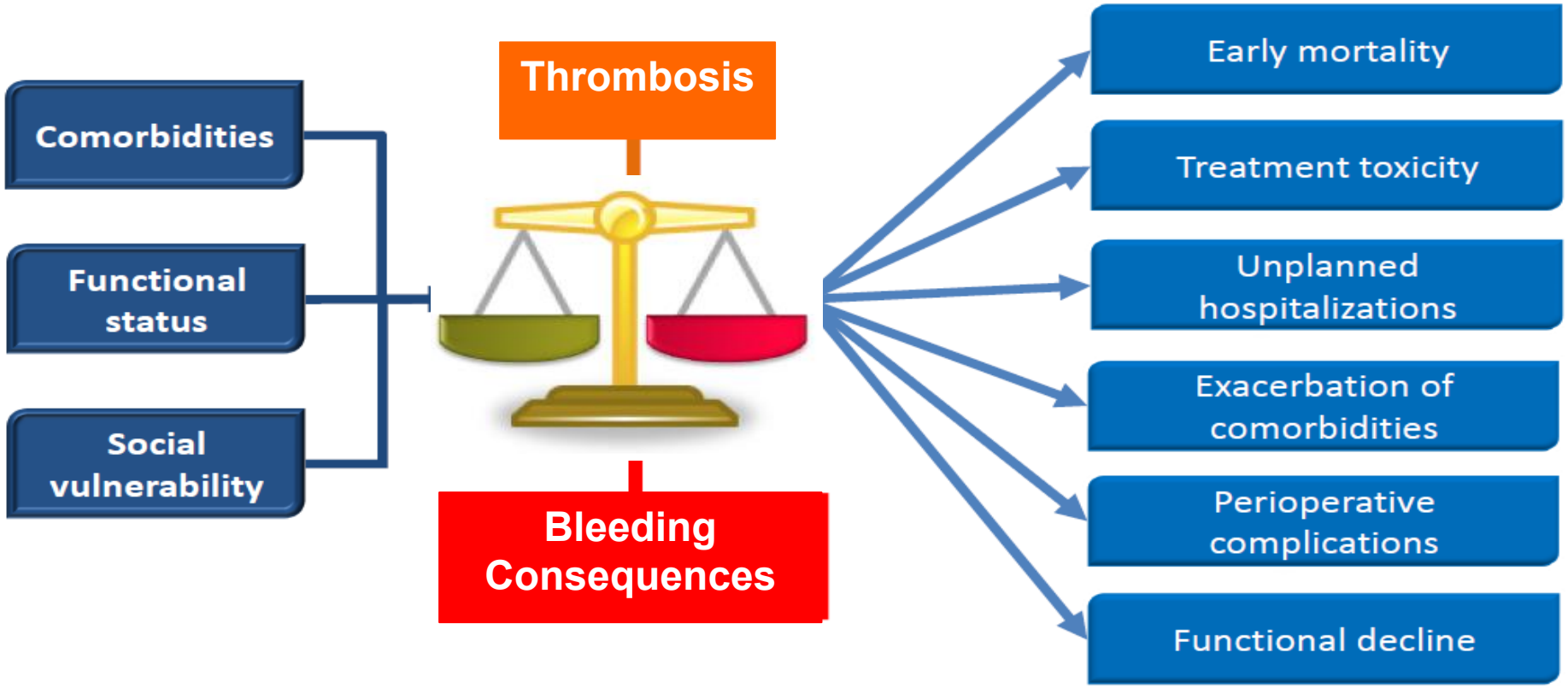
Keywords: Cabozantinib, Metastatic renal cell carcinoma (mRCC), Drug–drug interaction, Apixaban, Cytochrome P450 (CYP 450), P-glycoprotein (P-Gp)

Thrombose & Cancer… Thrombose & Co

- **Co-morbidités** *(Facteurs de Risque liés au Patient…)*
- **Co-médications** *(Interférences…)*
- **Co-ckcroft** *(Insuffisance Rénale…)*
- **Co-ntexte** *(Complexe…)*
- **Co-gnition** *(Compliance…)*
- **Co-rpulence** *(Plus ou moins…)*

Co-mplications

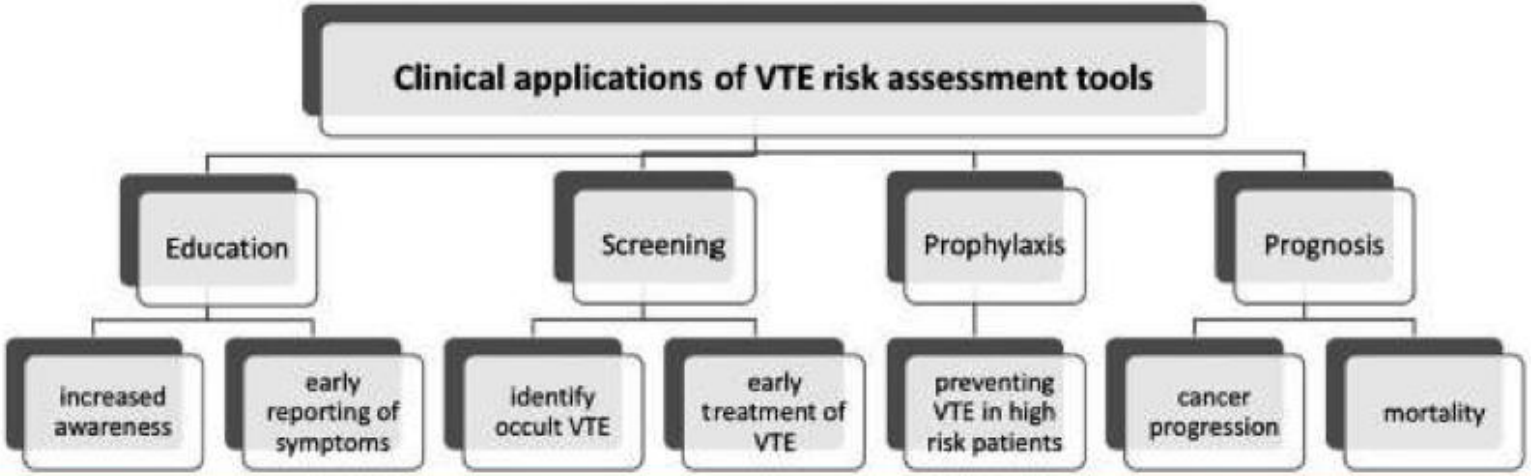
Challenge Difficile



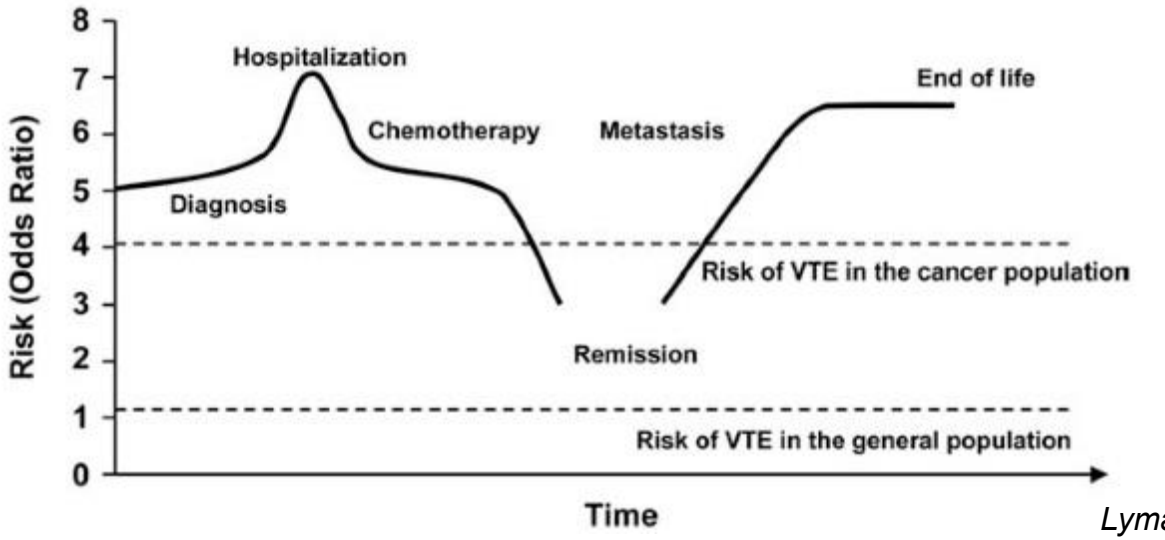
Adapted from Hamaker et al Lancet Oncol 2012;13(10): e437-e444

Evaluation Répétée Pour Identification Avisée

Emerging applications for risk assessment need to be clinically **integrated and repeated**



Angelini Semin Thromb Hemost. 2017; 43(5):469-478



Lyman et al. J Clin Oncol 2015 33:654-656

Stratifier le Risque chez le Patient Ambulatoire et Prophylaxer

Summary of Recommendations

CLINICAL QUESTION 2

Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all cancer outpatients. (Type: Evidence based; Evidence quality: intermediate to high; Strength of recommendation: Strong)

Recommendation 2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban or low-molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting. (Type: Evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: Moderate)

Recommendation 2.3. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients. (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong)

ASCO Guidelines

Key et al. J Oncol Pract. 2019.

Score de Khorana: pré-chimiothérapie et ambulatoire

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

High-risk: score ≥ 3
Intermediate risk: score =1-2
Low-risk: score =0

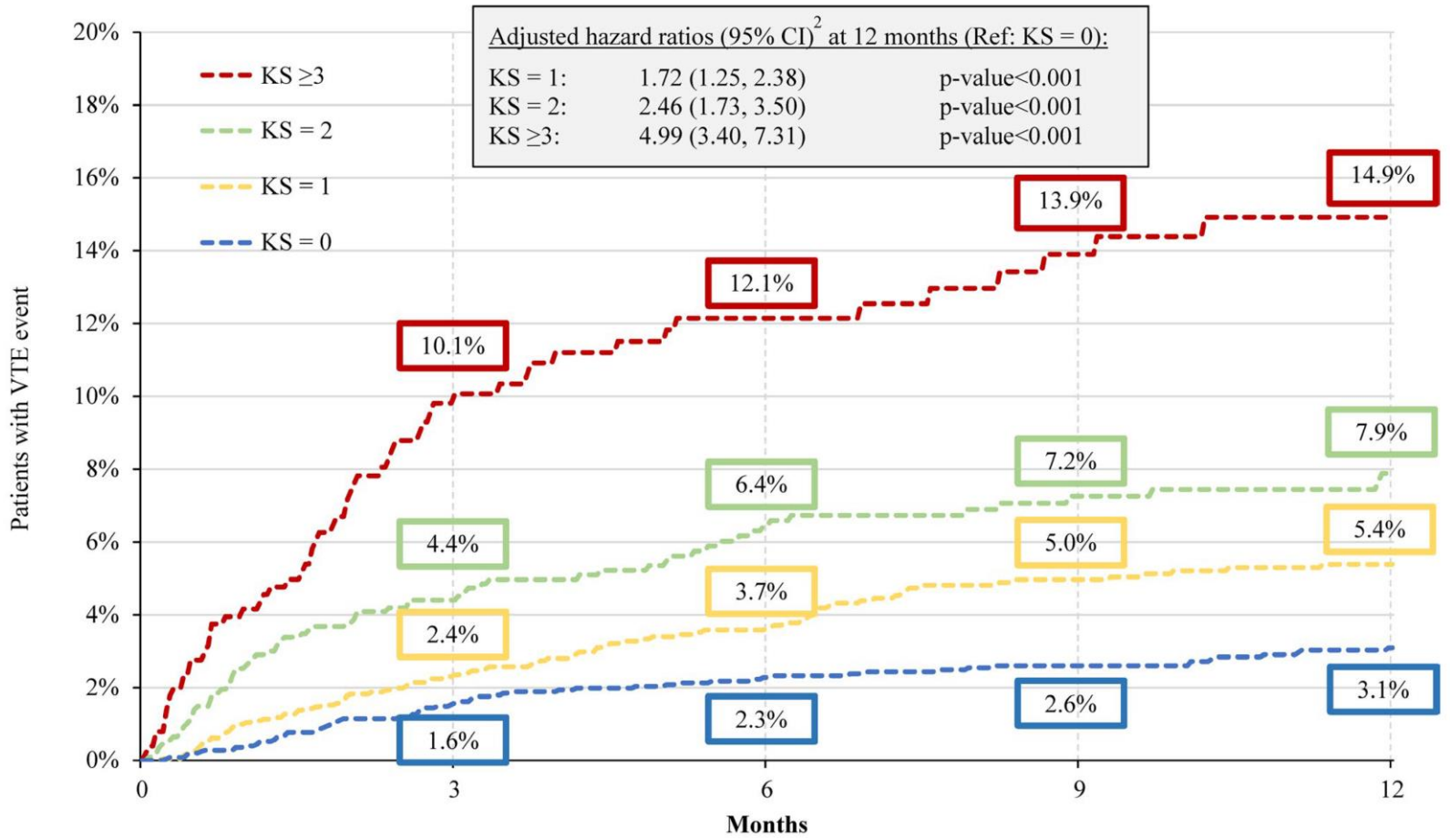
Score of ≥3 predicts higher VTE rate and 4-fold higher mortality rate

Khorana et al. Blood. 2008; Sohal et al. Cancer. 2015

Cancer et Risque Thrombotique Prolongé

KHORANA SCORE

n= 2488 in KS = 0
n= 2125 in KS = 1
n=1074 in KS = 2
n=507 in KS ≥ 3

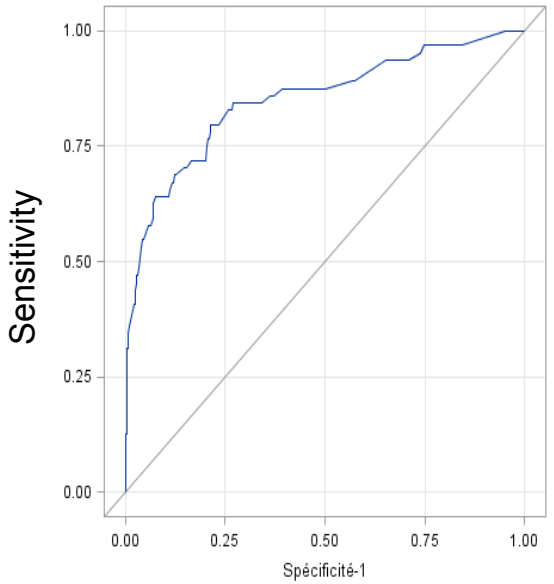


Khorana et al. Cancer Medicine. 2020;00:1–12

Score COMPASS-CAT: Ambulatoire, Hospitalisé, Traité… à Répéter

Predictors for VTE	Score
1. Cancer related risk factors	
a) Anti-hormonal therapy for women with hormone receptor-positive breast cancer or an anthracycline treatment	6
b) Time since cancer diagnosis ≤ 6 months	4
c) CVC	3
d) Advanced stage of cancer	2
2. Predisposing risk factors	
a)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
b) Recent hospitalization for acute medical illness	5
c) Personal history of VTE	1
3. Biomarkers	
a) Platelets count ≥ 35 X 10^9 / L	2

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



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

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

Score COMPASS-CAT: Validation Externe dans le Cancer Pulmonaire

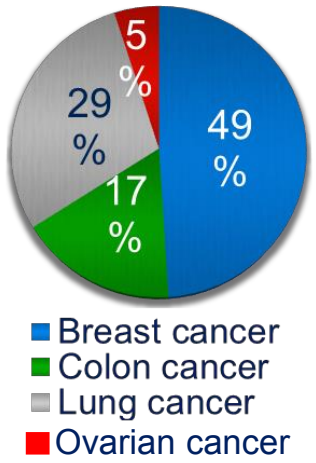
	Overall population $n=118$	VTE group during follow-up[a] $n=20$	Non-VTE group during follow-up[a] $n=98$
High KRS[b]	15 (13%)	2 (10%)	13 (13%)
High PROTECHT[c]	62 (52%)	11 (55%)	51 (52%)
High CONKO[d]	26 (22%)	4 (20%)	22 (22%)
High COMPASS[e]	84 (71%)	20 (100%)	64 (65%)

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 medical illness	0.02 (0.01–0.14)	0.001
Chronic kidney disease	4.24 (1.31–13.75)	0.017
Advanced disease	0.91 (0.29–2.84)	0.868

Rupa-Matysek et al Med Oncol 2018; 35: 63

COMPASS-CAT: Validation Externe avec mêmes types de cancers

Retrospective data-base analysis : n=3814 cancer patients
94% diagnosed <6 months prior to inclusion
46% on active therapy
52% localized disease
48% advanced stage disease
6% symptomatic VTE at 6-month follow-up



PPV	**6.3%**
NPV	**97.7%**
Sensitivity	**95%**
Specificity	**12%**

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

ASCO recommendations

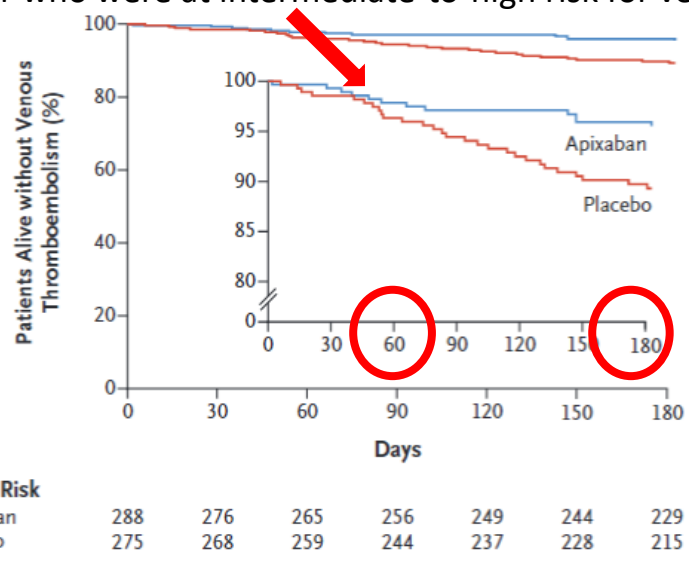
Key et al J Clin Oncol 2019

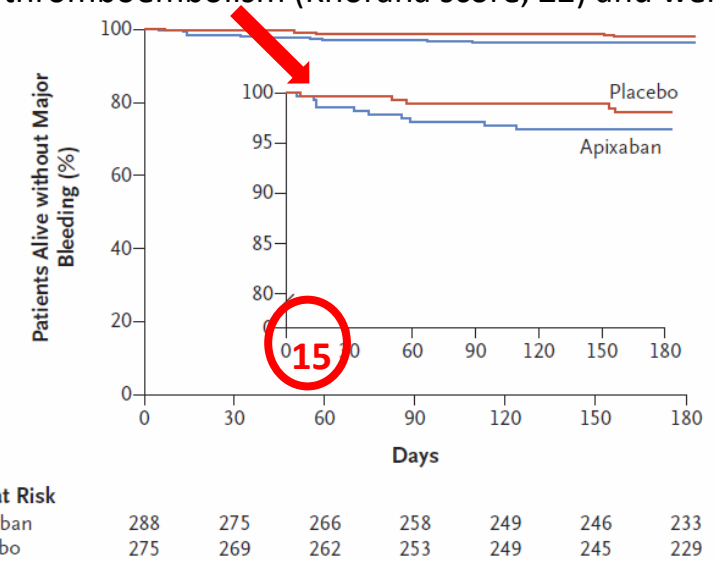
Spyropoulos et al The Oncologist 2020

Etude AVERT: Efficacité/Tolérance

36% 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





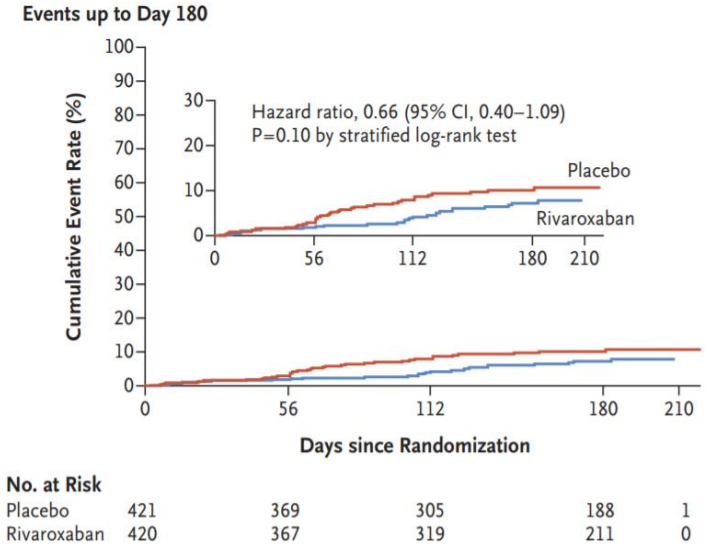
Cumulative Incidence	Apixaban	Placebo	HR (95% CI)	*P* Value	NNT/NNH
VTE (mITT), %	4.2	10.2	0.41 (0.26, 0.65)	< .001	NNT =17
Major bleeding (mITT), %	3.5	1.8	2.00 (1.01, 3.95)	.046	NNH = 59
Major bleeding (on treatment), %	2.1	1.1	1.89 (0.39, 9.24)	NS	NNH = 100

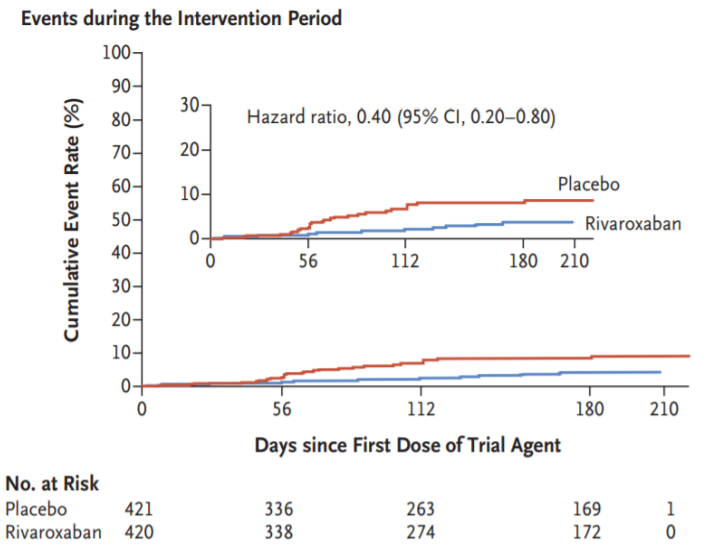
Carrier M et al. N Engl J Med. 2019

Etude CASSINI: Efficacité/Tolérance

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





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

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

DOACs for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH

1. We suggest the use of DOACs as primary thromboprophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥2 in patients with no drug-drug interactions and not at high risk for bleeding (such as patients with gastroesophageal cancers). A final treatment decision should be made after considering the risk of both VTE and bleeding, as well as patients' preference and values.

2. We suggest that if DOACs were to be used for primary thromboprophylaxis in ambulatory cancer patients, it is administered for up to 6 months after the initiation of chemotherapy. We recommend monitoring of platelet counts and risk of bleeding complications while on anticoagulation.

3. In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOAC (such as in patients with concern of drug interaction or high risk of gastrointestinal bleeding), we suggest using LWMH.

Wang et al J Thromb Haemost. 2019.

American Society of Hematology 2021 guidelines for management of venous thromboembolism in patients with cancer

- Primary prophylaxis for hospitalized medical patients with cancer… The ASH panel *suggests* using LMWH over UFH (no DOACS)

- For ambulatory patients at high risk for thrombosis receiving systemic therapy, (Khorana ≥2) the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis.

- Based on a validated risk assessment complemented by clinical judgment and experience. The panel noted that, even for patients at high risk for thrombosis, thromboprophylaxis should be used with caution for those at high risk for bleeding.

Lyman et al Blood Adv 2021; 5(4): 927-974

Etudes CAT et AOD : Critères d'Exclusion

• Hokusai

- PS 3-4
- Clairance < 30ml/min
- Cirrhosis, ALT-AST > 3N, Bili > 2N
- Uncontrolled hypertension
- NSAID
- P-gp Inhibitors

Mean age: 64 yo

• Select-D

- ECOG>2
- Hepatic disease
- Uncontrolled hypertension
- Antiplatelets
- Induc/Inhib CYP3A4
- Induc/Inhib P-gp

Mean age: 67 yo

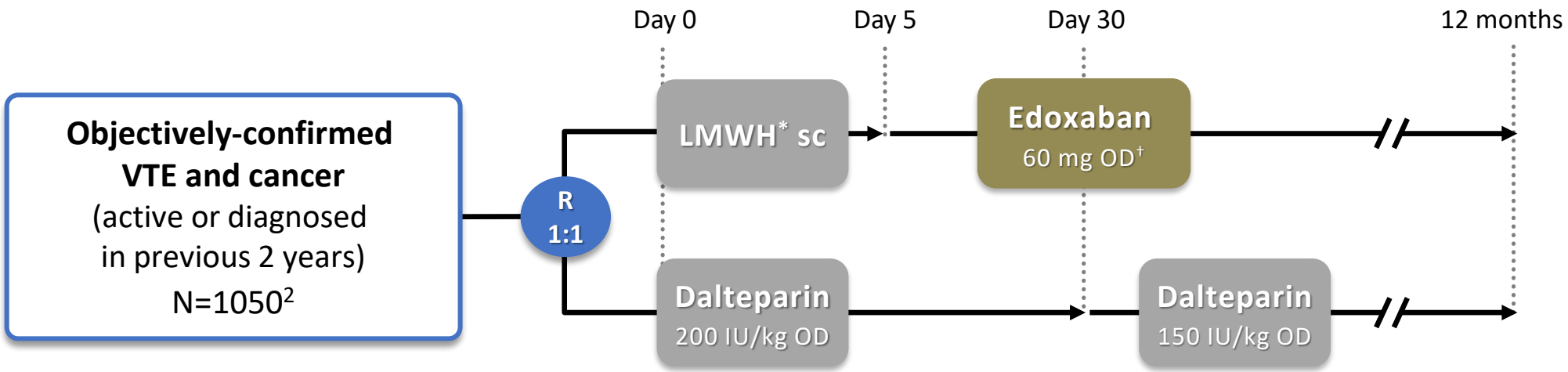
• Caravaggio

- ECOG 3-4
- Clairance < 30ml/min
- Cirrhosis, ALT-AST > 3N, Bili > 2N
- Uncontrolled hypertension
- Antiplatelets
- Induc/Inhib CYP3A4
- Anemia < 80g/L
- Platelets < 75G/L

Mean age: 67 yo

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.

Hokusai VTE cancer: Edoxaban vs Daltéparine



*≥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

1. Van Es N et al. Thromb Haemost 2015
2. Raskob GE et al. N Engl J Med 2018

Hokusai VTE cancer: Récidives thrombotiques

	Edoxaban (N=522)	Dalteparin (N=524)	HR (95% CI)
Recurrent VTE	41 (7.9%)	59 (11.3%)	0.71 (0.48, 1.06) P=0.093
Recurrent DVT	19 (7.9%)	35 (6.7%)	0.56 (0.32, 0.97)
Recurrent PE	27 (5.2%)	28 (5.3%)	1.00 (0.59, 1.69)
Confirmed fatal	0	0	
Unexplained death (PE not excluded)	6 (1.1%)	4 (0.8%)	

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

Hokusai VTE cancer: Hémorragies

	Edoxaban (N=522)	Dalteparin (N=524)	HR (95% CI)
Major	36 (6.9%)	21 (4.0%)	1.77 (1.03, 3.04) P=0.04
CRNM	76 (14.6%)	58 (11.1%)	1.38 (0.98, 1.94)
Major or CRNM	97 (18.6%)	73 (13.9%)	1.40 (1.03, 1.89)
Death from any cause	206 (39.5%)	192 (36.6)	1.12 (0.92, 1.37)

CRNM: Clinically Relevant Nonmajor

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

Hokusai VTE cancer: Hémorragies

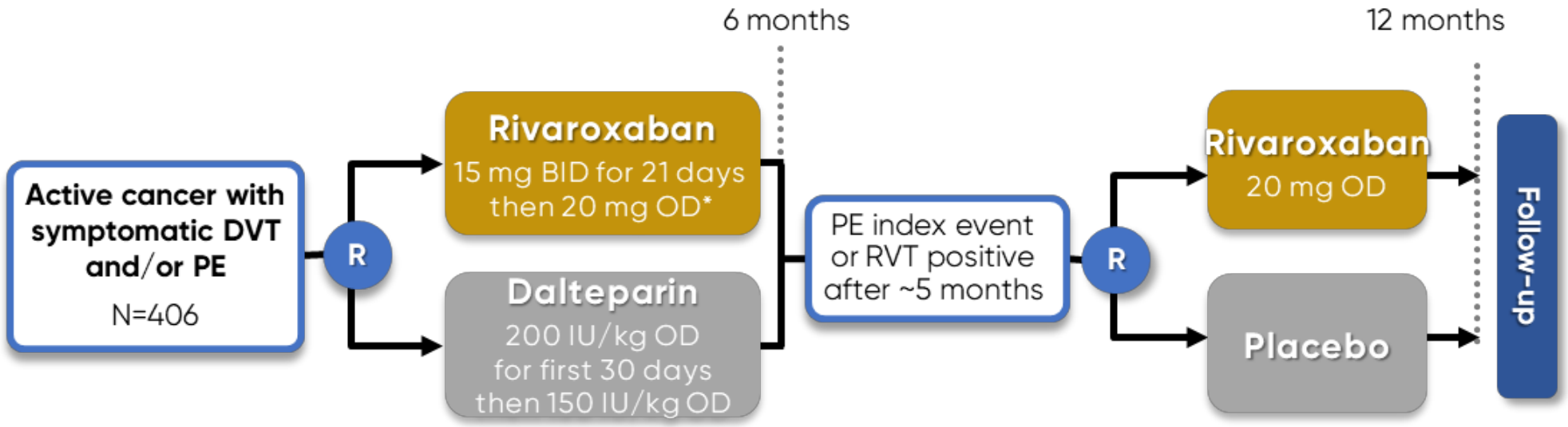
	Edoxaban	Dalteparin	
Major bleeding – no. (%)	33 (6.3)	17 (3.2)	x2
Fatal*	0	2 (0.4)	
Intracranial	2 (0.4)	4 (0.8)*	
Gastrointestinal	20 (3.8)	6 (1.1)	x3
Upper	17 (3.3)	3 (0.6)	
Lower	3 (0.6)	3 (0.6)	
Urogenital	5 (1.0)	0	x5

* 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 : Edoxaban vs Daltéparine

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



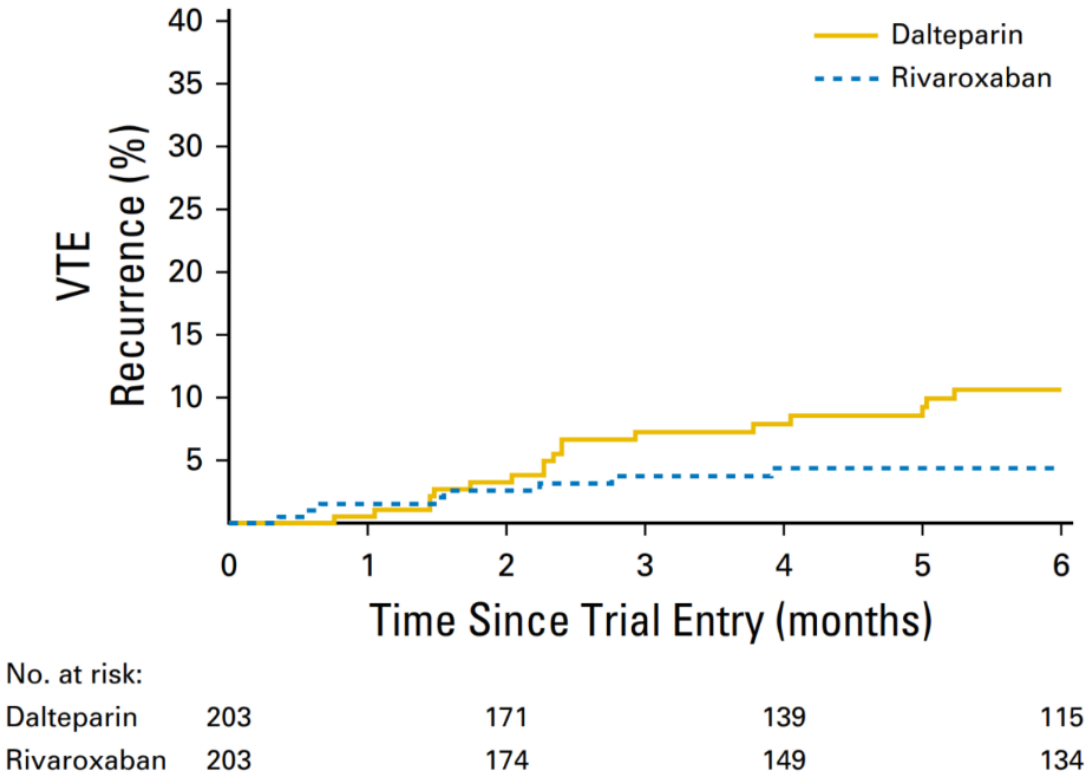
Efficacy (primary): Rate of VTE recurrence (symptomatic and incidental PE)
Secondary: Rate of major bleeding and CRNM bleeding (also assess survival, health economics)

*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.

SELECT-D : Récidives thrombotiques



	Dalteparin (n=203)	Rivaroxaban (n=203)
VTE recurrences within 6 months, n	18	8
DVT or PE	16	6
Other location	2	2
6-month VTE recurrence rate, % (95% CI)	11% (7-16%)	4% (2-9%)
6-month lower limb DVT or PE recurrence rate	9% (6-15%)	3% (1-7%)

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

SELECT-D : Hémorragies

	Dalteparin (n=203)	Rivaroxaban (n=203)	
Major*	6 (3%)	11 (5%)	x2
Clinically relevant non-major	6 (3%)	25 (12%)	x4
Total	12 (6%)	36 (17%)	x3

*1 fatal bleeding event in each arm

Most major bleeding events were gastrointestinal bleeding; no CNS bleeds

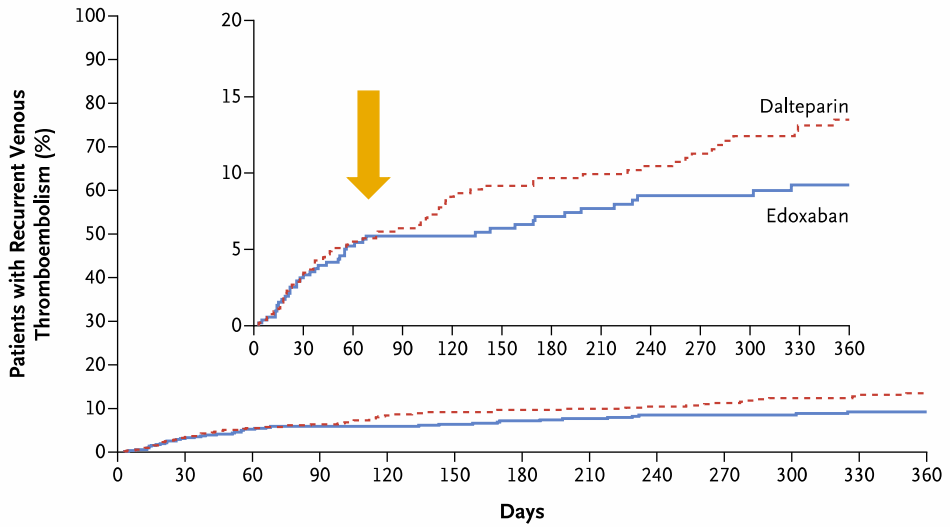
Most CRNMBs were gastrointestinal or urological

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

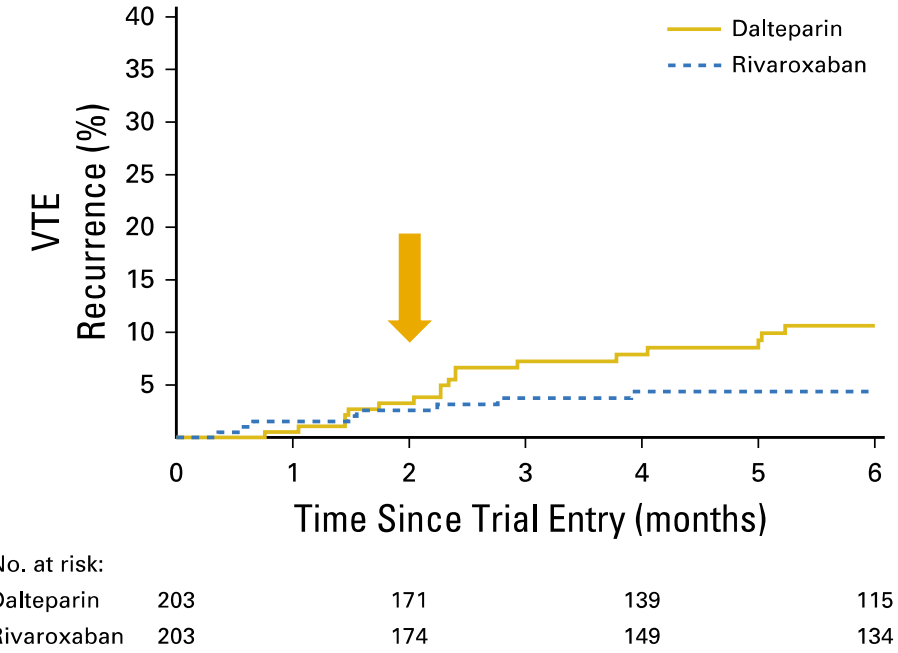
Young AM. J Clin Oncol. 2018 ;36(20):2017-2023.

Récidives thrombotiques : AOD vs Daltéparine

HOKUSAI



SELECT-D

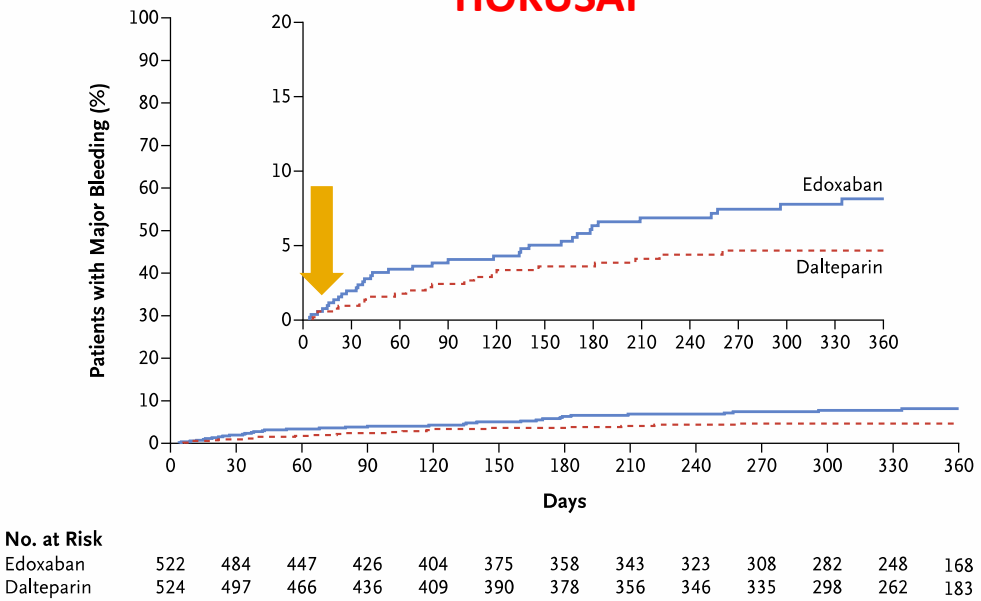


Dose reduction of dalteparin 25% after 4 weeks

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

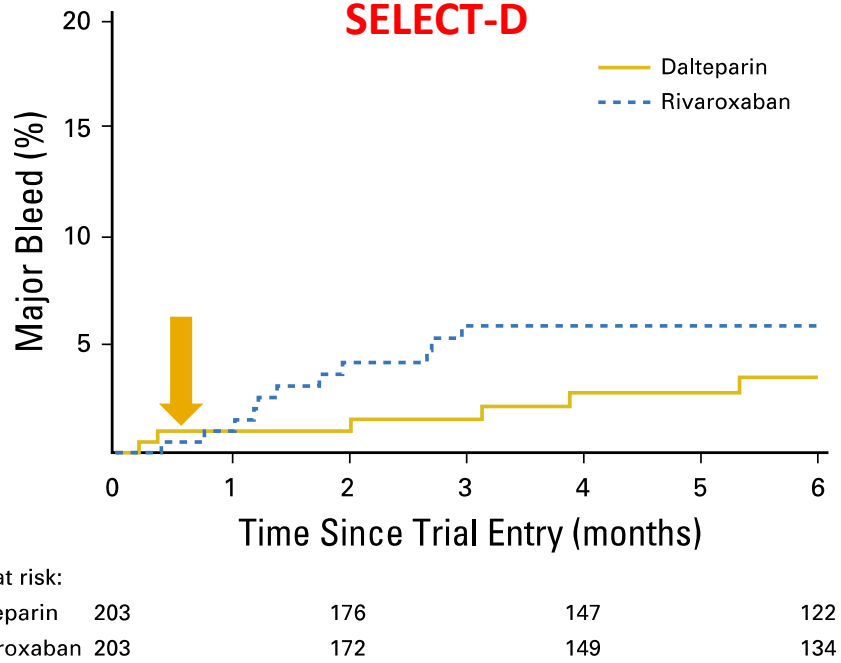
Hémorragies : AOD vs Daltéparine

HOKUSAI



Major bleeding: Edoxaban 6.9% vs. Dalteparin 4.0%; p = 0.04

SELECT-D



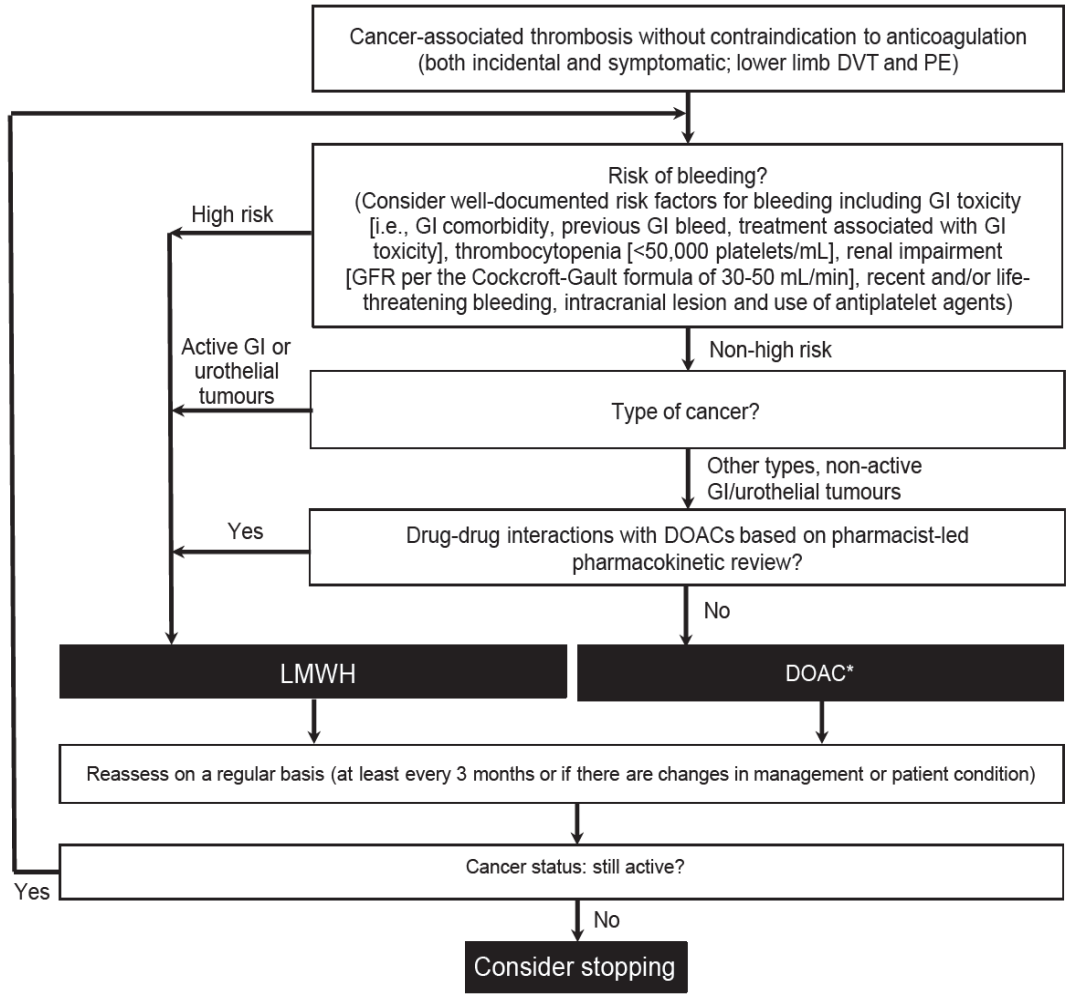
Major bleeding: Riva 6% vs. Dalte 4%; HR 1.83 (CI 95% 0.68 to 4.96)
CRNM bleeding: Riva 13% vs. Dalte 4%; HR 3.76 (CI 95% 1.63 to 8.69)
Total: 19% vs. 8%

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

Recommandations Canadiennes : CAT et Choix du Traitement

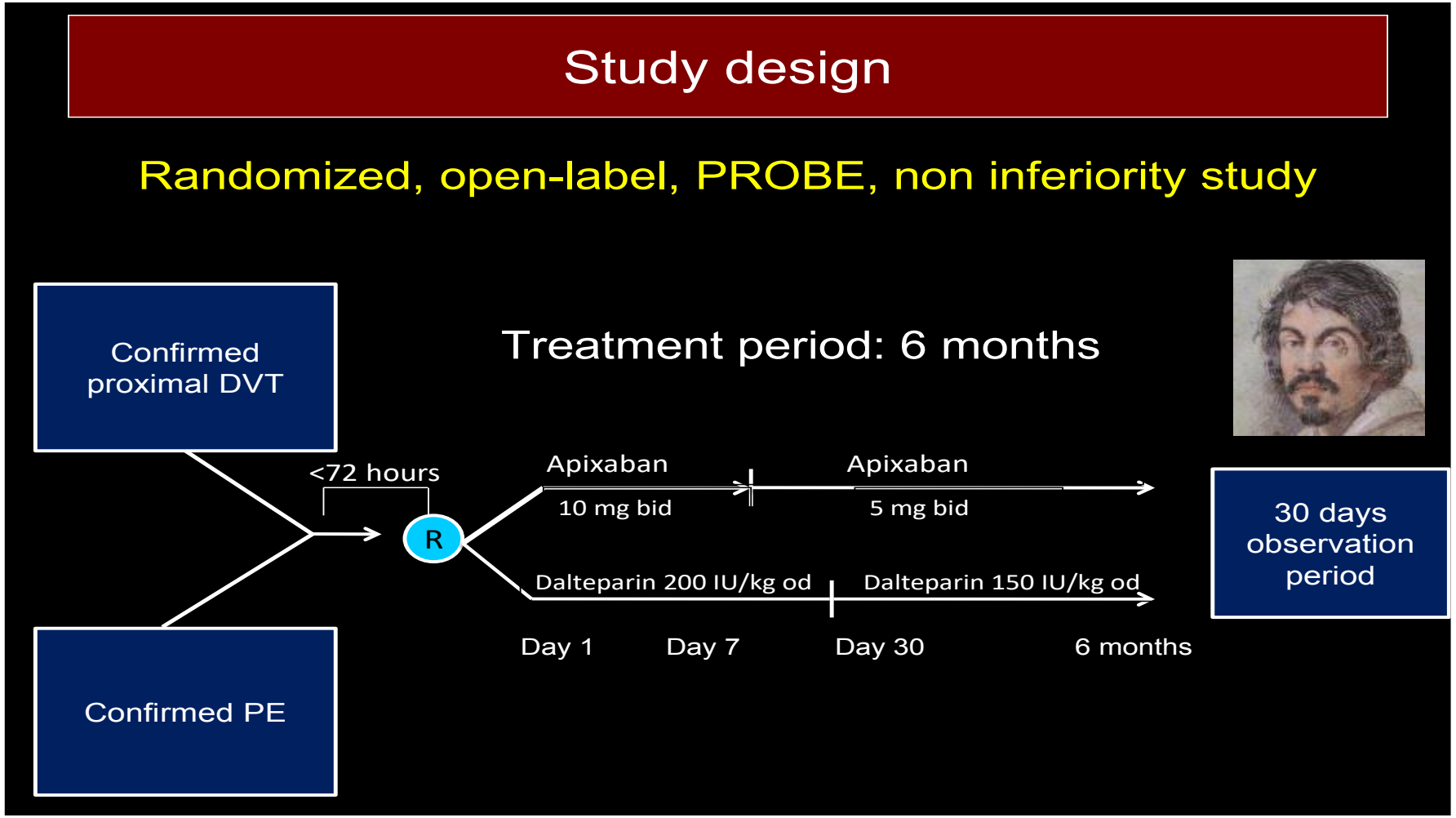
Risk factor	Major bleeding (%)		*p* Value
	Edoxaban	Dalteparin	
Urothelial cancer	13.2	0	NA
Creatinine clearance 30–50 mL/min	10.5	2.9	NA
Platelets 50–100×10^3/mL	12.5	4.3	NA
Use of antiplatelet agents	11.5	3.2	NA
3 Risk factors[a]	13.5	4.1	<0.05
4 Or more risk factors[a]	10.5	4.2	NA

Other factors to consider:
- Patient preference, after informing patient of risks and benefits
- Drug coverage
- Body weight (consider LMWH in patients with BMI >40 kg/m2 or weight >120 kg)
- Burden of cancer (e.g., recurrence or progression) and burden of VTE (consider LMWH for patients with severe symptoms, e.g., iliofemoral DVT, extensive PE, submassive PE, any thrombolysed patient)
- Renal impairment (consider LMWH for patients with GFR per the Cockcroft-Gault formula of 30-50 mL/min)
- Significant GI surgery or absorption disorders (consider LMWH for patients with impaired GI absorption)
- Pre-existing conditions and co-medication (e.g., ASA, other antiplatelet medications)



Carrier M et al. Curr Oncol 2018; 25: 329-337

Design de l'Etude CARAVAGGIO



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

Types de Cancers

	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%)

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

Caractéristiques des Patients

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)
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)

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2	109 (18.9)	132 (22.8)

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

Caractéristiques des Patients

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)
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)
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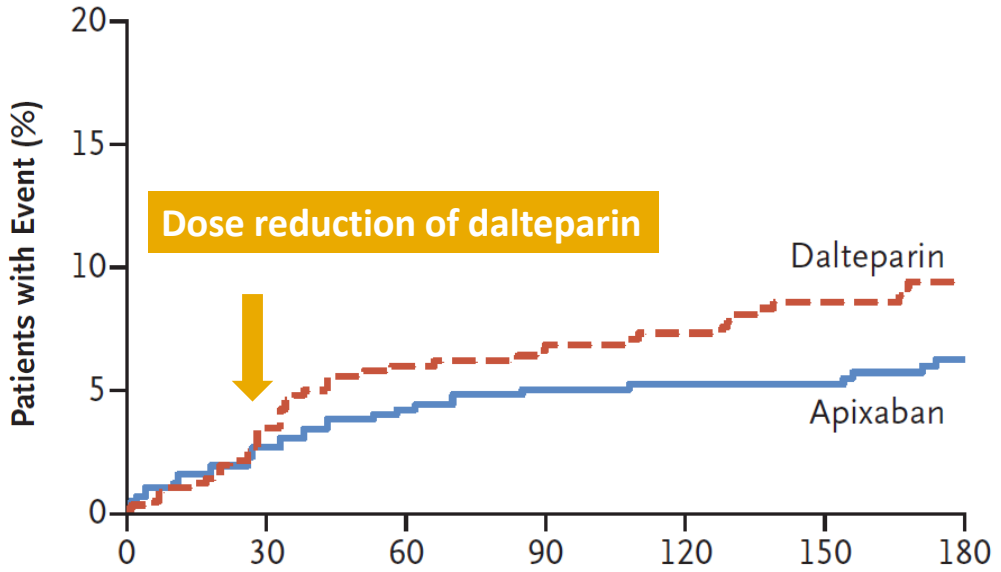
Résultats : Efficacité

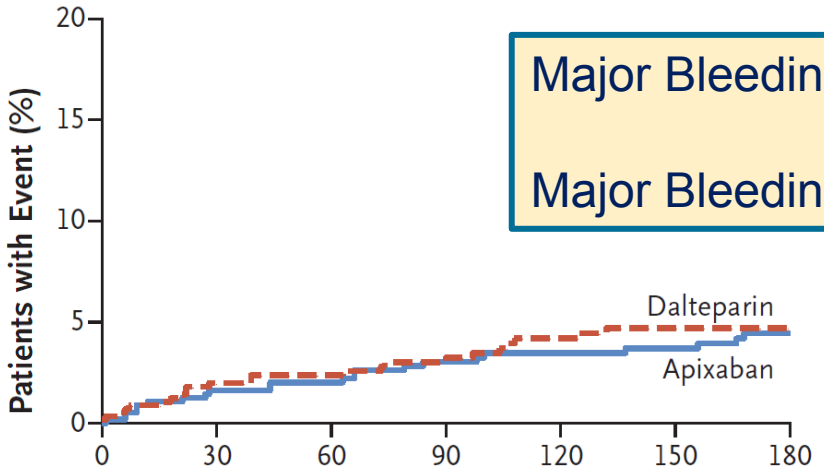
Outcome	Apixaban (N=576)	Dalteparin (N=579)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome — no. (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority; 0.09 for superiority
Recurrent deep-vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent 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.

Résultats : Sécurité

Primary safety outcome — no. (%)				
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

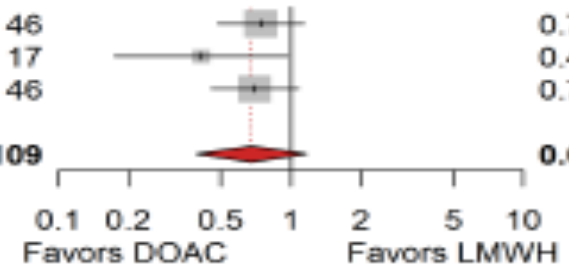
Agnelli et al N Engl J Med. 2020 ;382(17):1599-1607.

AOD et CAT : Méta-Analyse?

Recurrent VTE

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	34	524	46	0.74	[0.48; 1.14]	45.4%
SELECT-D	rivaroxaban	203	7	203	17	0.41	[0.17; 0.97]	11.2%
Caravaggio	apixaban	576	32	579	46	0.70	[0.45; 1.08]	43.4%
Random effects model		**1301**	**73**	**1306**	**109**	**0.68**	**[0.39; 1.17]**	**100.0%**

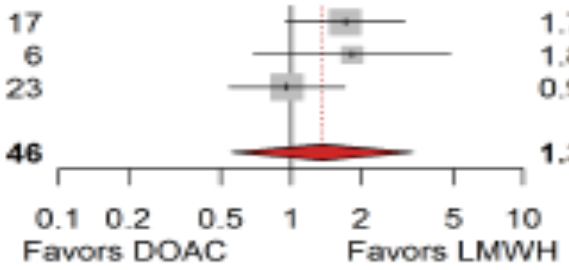
Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.0001$, $p = 0.48$



Major bleeding

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	29	524	17	1.71	[0.95; 3.08]	40.3%
SELECT-D	rivaroxaban	203	11	203	6	1.83	[0.69; 4.86]	18.0%
Caravaggio	apixaban	576	22	579	23	0.96	[0.54; 1.71]	41.7%
Random effects model		**1301**	**62**	**1306**	**46**	**1.36**	**[0.55; 3.35]**	**100.0%**

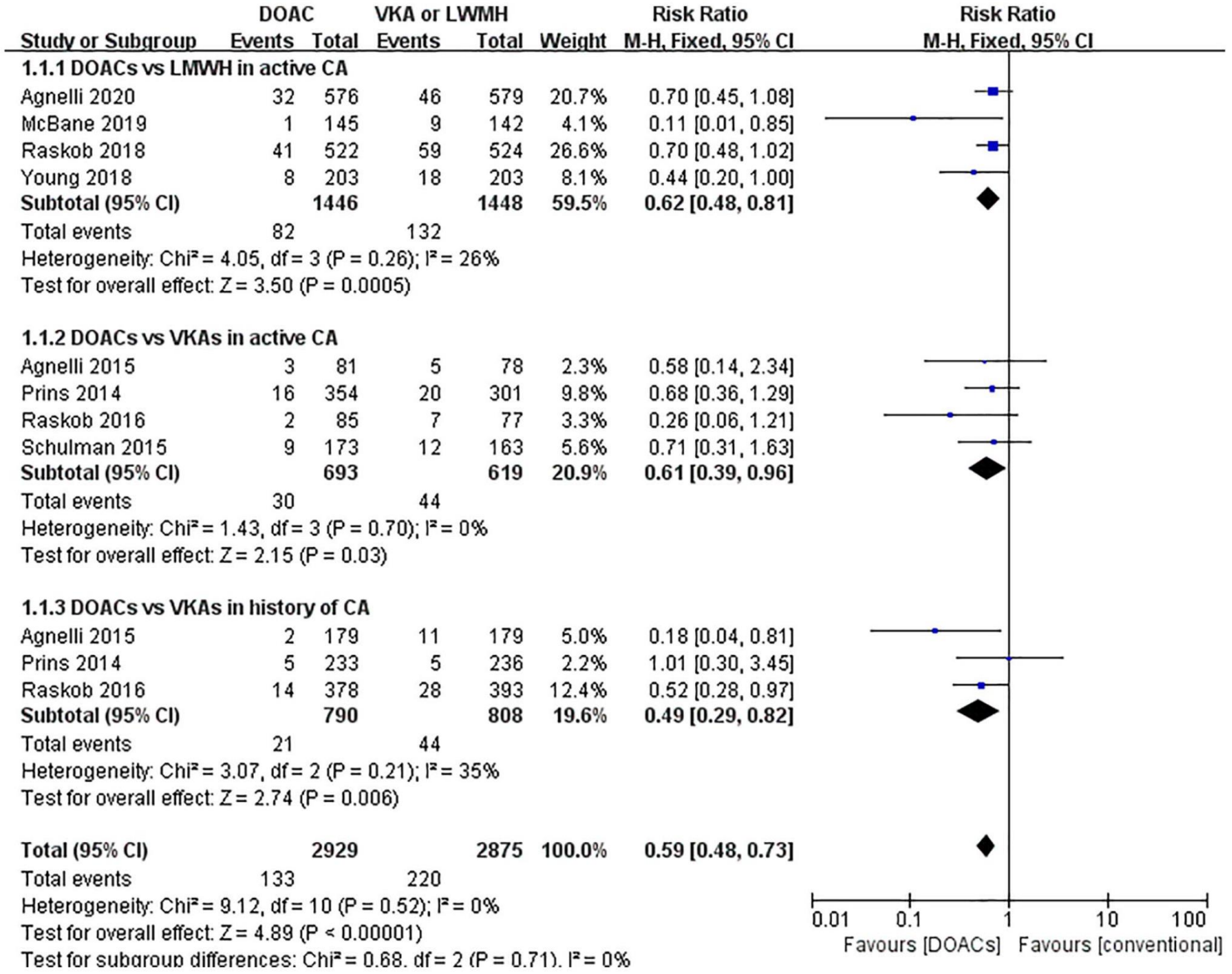
Heterogeneity: $I^2 = 15\%$, $\tau^2 = 0.0379$, $p = 0.31$



Mulder et al. Blood. 2020;136(12):1433-1441

AOD et CAT : Méta-Analyse?

Récidives Thrombotiques



Study or Subgroup	DOAC Events	Total	VKA or LWMH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 DOACs vs LMWH in active CA						
Agnelli 2020	32	576	46	579	20.7%	0.70 [0.45, 1.08]
McBane 2019	1	145	9	142	4.1%	0.11 [0.01, 0.85]
Raskob 2018	41	522	59	524	26.6%	0.70 [0.48, 1.02]
Young 2018	8	203	18	203	8.1%	0.44 [0.20, 1.00]
Subtotal (95% CI)		**1446**		**1448**	**59.5%**	**0.62 [0.48, 0.81]**
Total events	82		132			
Heterogeneity: Chi² = 4.05, df = 3 (P = 0.26); I² = 26%						
Test for overall effect: Z = 3.50 (P = 0.0005)						
1.1.2 DOACs vs VKAs in active CA						
Agnelli 2015	3	81	5	78	2.3%	0.58 [0.14, 2.34]
Prins 2014	16	354	20	301	9.8%	0.68 [0.36, 1.29]
Raskob 2016	2	85	7	77	3.3%	0.26 [0.06, 1.21]
Schulman 2015	9	173	12	163	5.6%	0.71 [0.31, 1.63]
Subtotal (95% CI)		**693**		**619**	**20.9%**	**0.61 [0.39, 0.96]**
Total events	30		44			
Heterogeneity: Chi² = 1.43, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.15 (P = 0.03)						
1.1.3 DOACs vs VKAs in history of CA						
Agnelli 2015	2	179	11	179	5.0%	0.18 [0.04, 0.81]
Prins 2014	5	233	5	236	2.2%	1.01 [0.30, 3.45]
Raskob 2016	14	378	28	393	12.4%	0.52 [0.28, 0.97]
Subtotal (95% CI)		**790**		**808**	**19.6%**	**0.49 [0.29, 0.82]**
Total events	21		44			
Heterogeneity: Chi² = 3.07, df = 2 (P = 0.21); I² = 35%						
Test for overall effect: Z = 2.74 (P = 0.006)						
Total (95% CI)		**2929**		**2875**	**100.0%**	**0.59 [0.48, 0.73]**
Total events	133		220			
Heterogeneity: Chi² = 9.12, df = 10 (P = 0.52); I² = 0%						
Test for overall effect: Z = 4.89 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.68, df = 2 (P = 0.71), I² = 0%						

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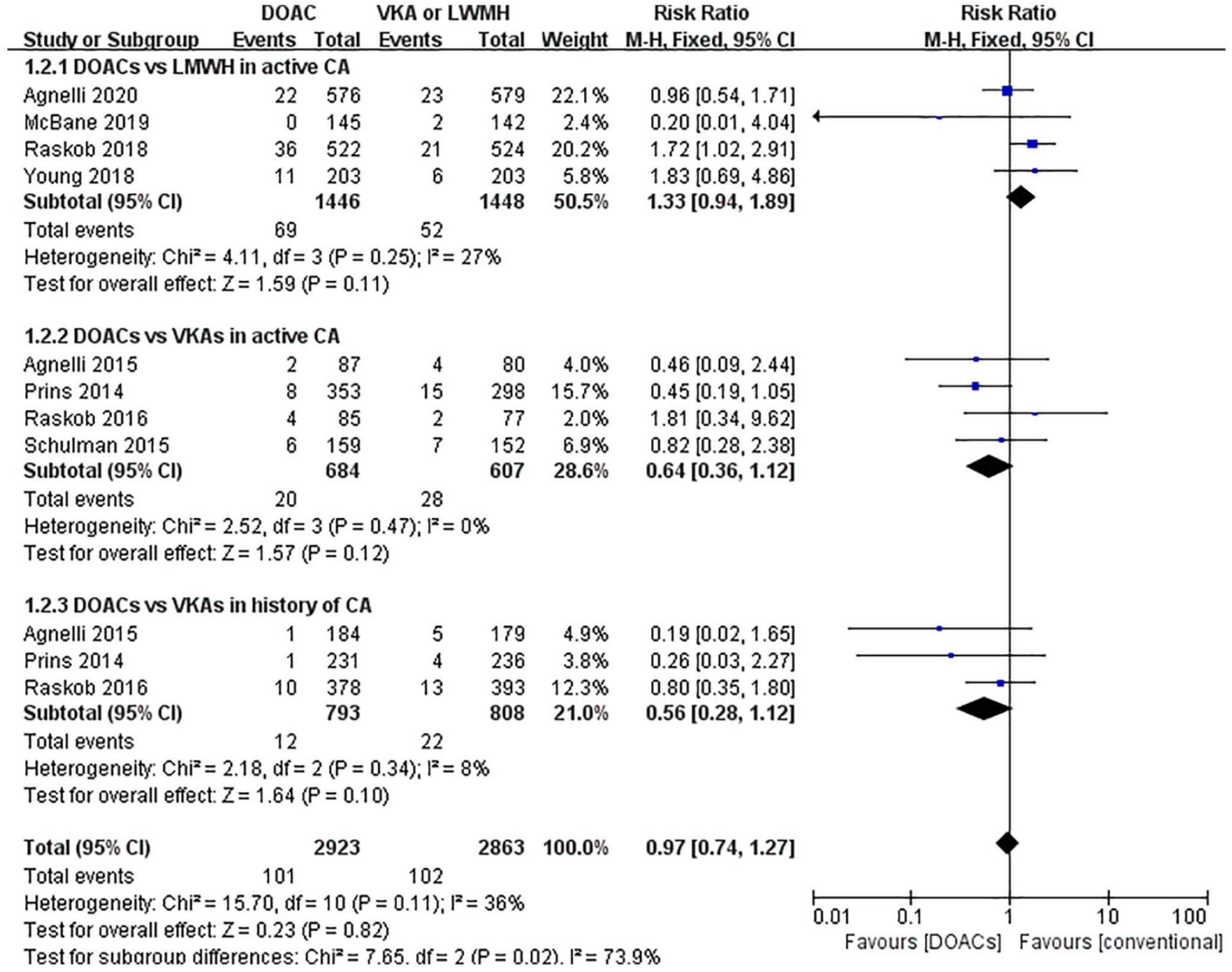
AOD et CAT : Méta-Analyse?

Hémorragies Majeures



Study or Subgroup	DOAC Events	DOAC Total	VKA or LWMH Events	VKA or LWMH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 DOACs vs LMWH in active CA						
Agnelli 2020	22	576	23	579	22.1%	0.96 [0.54, 1.71]
McBane 2019	0	145	2	142	2.4%	0.20 [0.01, 4.04]
Raskob 2018	36	522	21	524	20.2%	1.72 [1.02, 2.91]
Young 2018	11	203	6	203	5.8%	1.83 [0.69, 4.86]
Subtotal (95% CI)		**1446**		**1448**	**50.5%**	**1.33 [0.94, 1.89]**
Total events	69		52			
Heterogeneity: Chi² = 4.11, df = 3 (P = 0.25); I² = 27%						
Test for overall effect: Z = 1.59 (P = 0.11)						
1.2.2 DOACs vs VKAs in active CA						
Agnelli 2015	2	87	4	80	4.0%	0.46 [0.09, 2.44]
Prins 2014	8	353	15	298	15.7%	0.45 [0.19, 1.05]
Raskob 2016	4	85	2	77	2.0%	1.81 [0.34, 9.62]
Schulman 2015	6	159	7	152	6.9%	0.82 [0.28, 2.38]
Subtotal (95% CI)		**684**		**607**	**28.6%**	**0.64 [0.36, 1.12]**
Total events	20		28			
Heterogeneity: Chi² = 2.52, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.2.3 DOACs vs VKAs in history of CA						
Agnelli 2015	1	184	5	179	4.9%	0.19 [0.02, 1.65]
Prins 2014	1	231	4	236	3.8%	0.26 [0.03, 2.27]
Raskob 2016	10	378	13	393	12.3%	0.80 [0.35, 1.80]
Subtotal (95% CI)		**793**		**808**	**21.0%**	**0.56 [0.28, 1.12]**
Total events	12		22			
Heterogeneity: Chi² = 2.18, df = 2 (P = 0.34); I² = 8%						
Test for overall effect: Z = 1.64 (P = 0.10)						
Total (95% CI)		**2923**		**2863**	**100.0%**	**0.97 [0.74, 1.27]**
Total events	101		102			
Heterogeneity: Chi² = 15.70, df = 10 (P = 0.11); I² = 36%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Chi² = 7.65, df = 2 (P = 0.02), I² = 73.9%						

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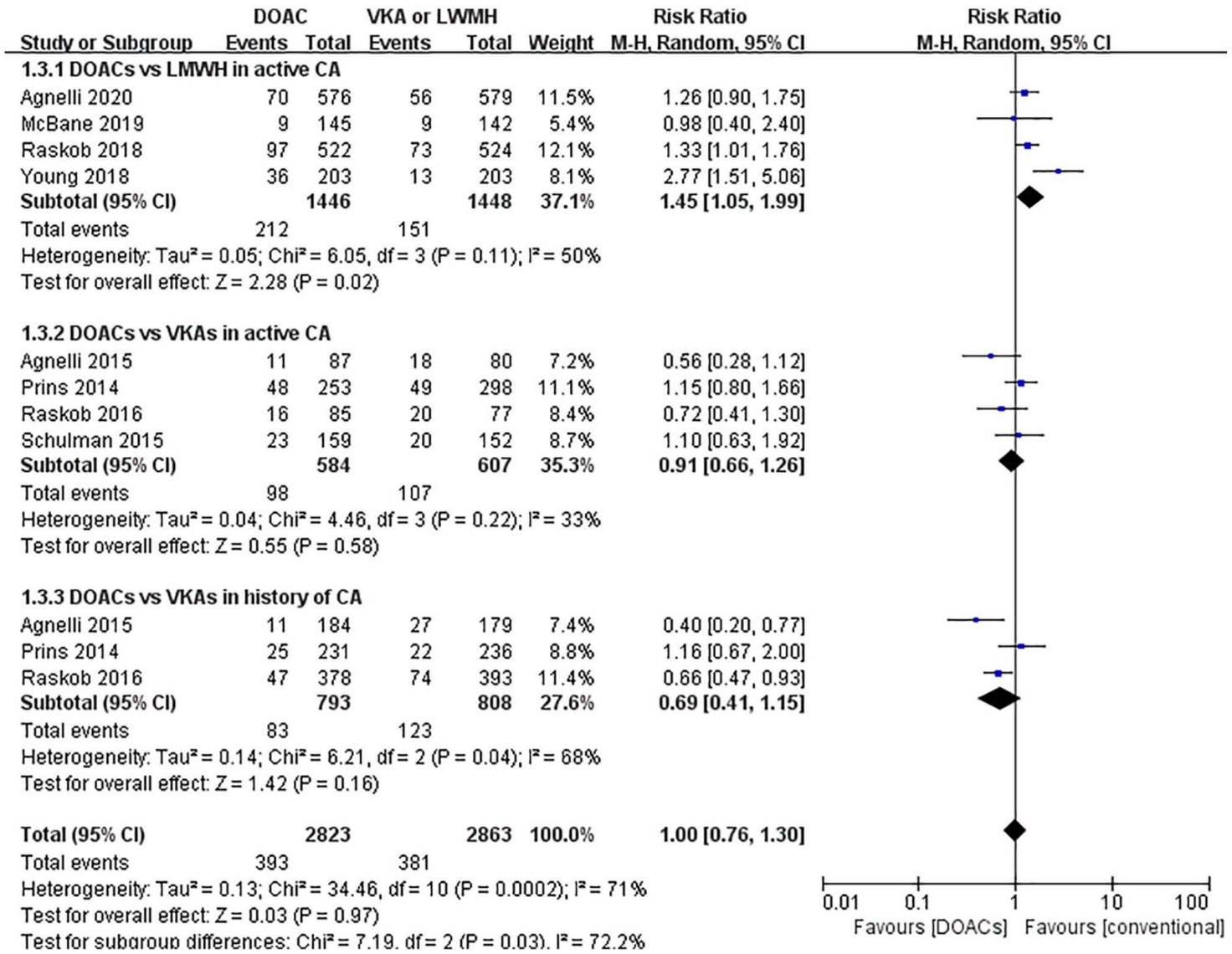
AOD et CAT : Méta-Analyse?

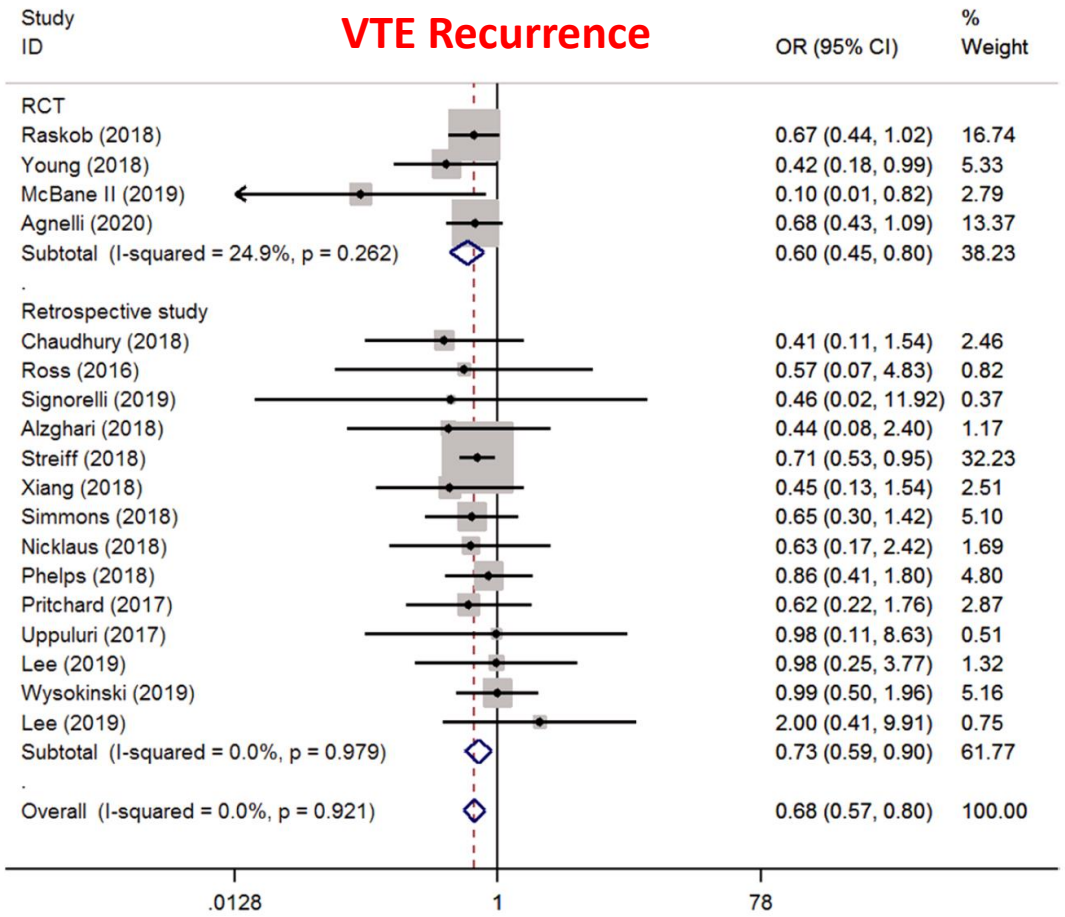
Hémorragies Majeures Et Cliniquement Pertinentes Non Majeures

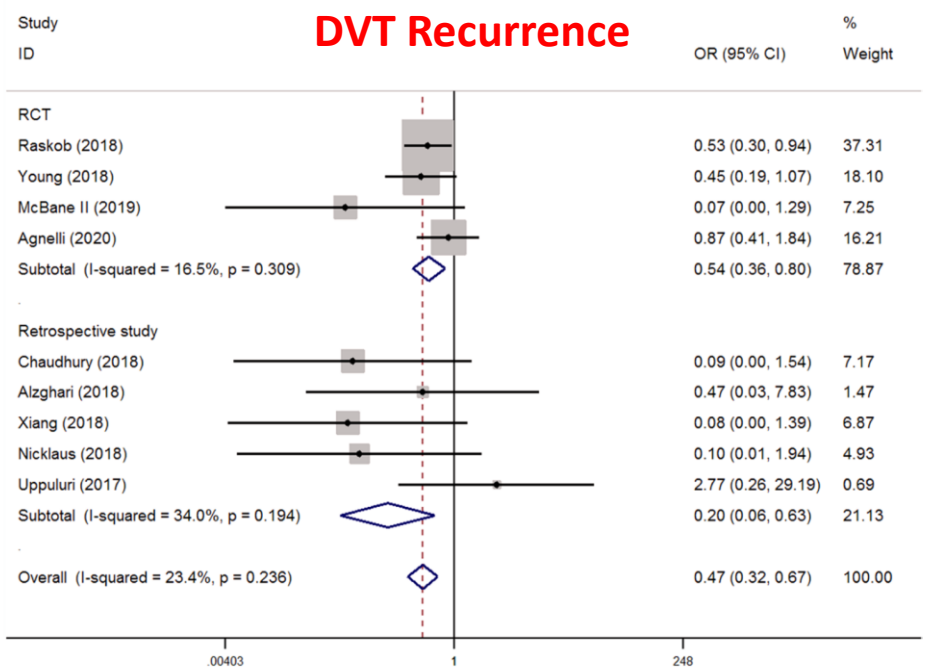


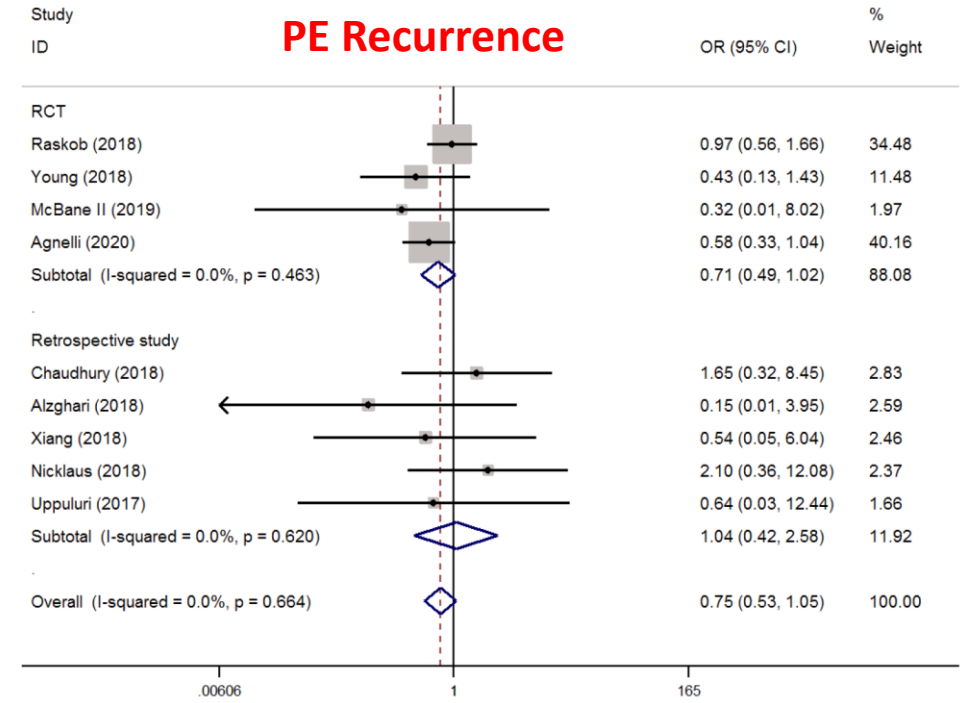
Study or Subgroup	DOAC Events	DOAC Total	VKA or LWMH Events	VKA or LWMH Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 DOACs vs LMWH in active CA						
Agnelli 2020	70	576	56	579	11.5%	1.26 [0.90, 1.75]
McBane 2019	9	145	9	142	5.4%	0.98 [0.40, 2.40]
Raskob 2018	97	522	73	524	12.1%	1.33 [1.01, 1.76]
Young 2018	36	203	13	203	8.1%	2.77 [1.51, 5.06]
Subtotal (95% CI)		**1446**		**1448**	**37.1%**	**1.45 [1.05, 1.99]**
Total events	212		151			
Heterogeneity: Tau² = 0.05; Chi² = 6.05, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 2.28 (P = 0.02)						
1.3.2 DOACs vs VKAs in active CA						
Agnelli 2015	11	87	18	80	7.2%	0.56 [0.28, 1.12]
Prins 2014	48	253	49	298	11.1%	1.15 [0.80, 1.66]
Raskob 2016	16	85	20	77	8.4%	0.72 [0.41, 1.30]
Schulman 2015	23	159	20	152	8.7%	1.10 [0.63, 1.92]
Subtotal (95% CI)		**584**		**607**	**35.3%**	**0.91 [0.66, 1.26]**
Total events	98		107			
Heterogeneity: Tau² = 0.04; Chi² = 4.46, df = 3 (P = 0.22); I² = 33%						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.3.3 DOACs vs VKAs in history of CA						
Agnelli 2015	11	184	27	179	7.4%	0.40 [0.20, 0.77]
Prins 2014	25	231	22	236	8.8%	1.16 [0.67, 2.00]
Raskob 2016	47	378	74	393	11.4%	0.66 [0.47, 0.93]
Subtotal (95% CI)		**793**		**808**	**27.6%**	**0.69 [0.41, 1.15]**
Total events	83		123			
Heterogeneity: Tau² = 0.14; Chi² = 6.21, df = 2 (P = 0.04); I² = 68%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Total (95% CI)		**2823**		**2863**	**100.0%**	**1.00 [0.76, 1.30]**
Total events	393		381			
Heterogeneity: Tau² = 0.13; Chi² = 34.46, df = 10 (P = 0.0002); I² = 71%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Test for subgroup differences: Chi² = 7.19, df = 2 (P = 0.03), I² = 72.2%						

Dong et al. Ann Pharmacother 2021;55(4): 430-439

AOD et CAT : Méta-Analyse?







Song et al. Ann Transl Med 2021;9(2):162-174

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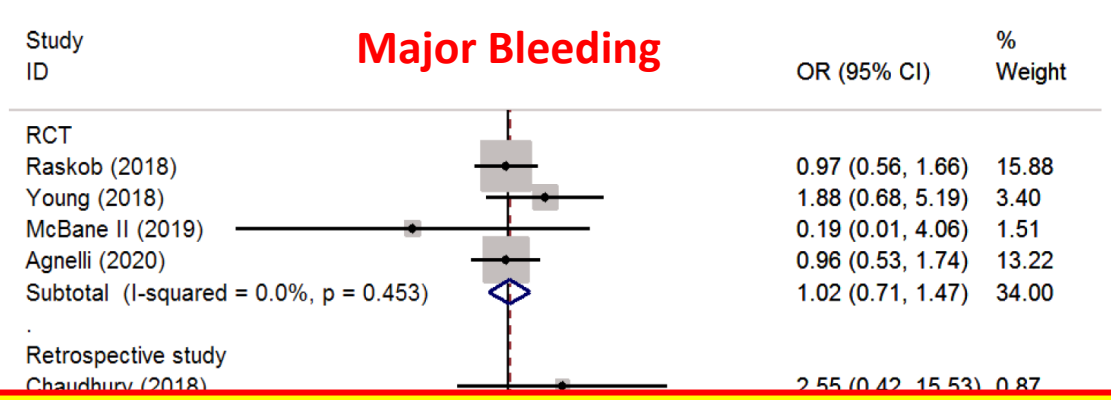
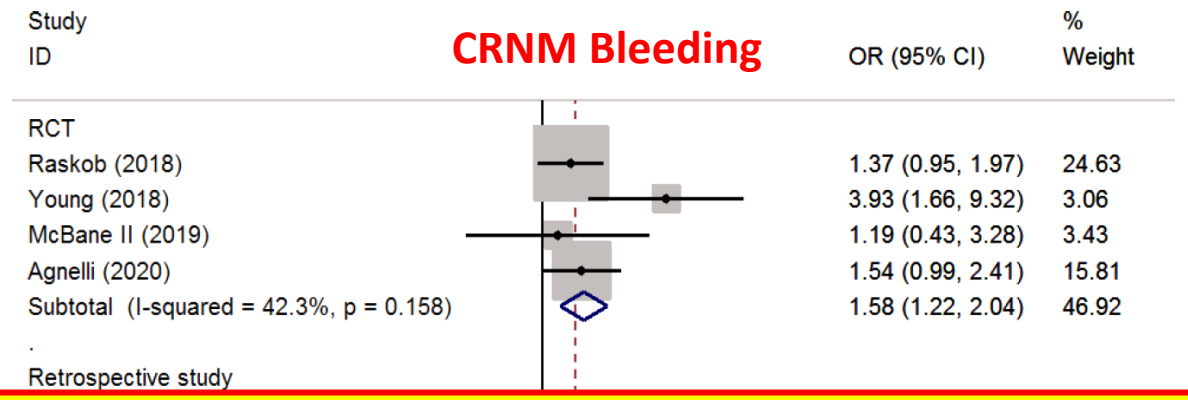
AOD et CAT : Méta-Analyse?





*"…The conclusions in this study still needed to be further confirmed by a **larger collection of data**… The number of RCTs for different DOACs is somewhat small, with **only 1 or 2 RCTs** being included in the meta-analysis. Multicenter RCTs with a large sample size are needed to further **investigate the efficacy and safety of specific DOACs**… The subgroups of different kinds of cancers were not analyzed, but influence the efficacy and safety of different DOACs **may vary depending on cancer type**… **Future studies** should focus on the effects of different DOACs on specific cancers so as **to help clinicians better determine the treatment strategy** for VTE in patients with different cancers…"*

Song et al. Ann Transl Med 2021;9(2):162-174

Situations Cliniques Fréquentes : Questions Pratiques en Attente…

1. Cancer at high bleeding risk?
2. Hematological malignancies or cerebral metastasis?
3. Comedications with potential or real interactions?
4. On-going chemotherapy?
5. Gastro-intestinal toxicity *(mucitis, vomiting diarrhea, malabsorption, ulcers…)?*
5. Surgical context?
6. *In situ* mucosal cancers?

7 Renal impairment with worsening (moderate to severe)?

7. Liver impairment?
8. Anemia and/or thrombocytopenia?
9. Extreme body weight?
10. Malnutrition? …

CAT Treatment: Patient Selection, Controversies and Caveats

Step 1: Assess Cancer-Related Variables

METABOLISM	SAFETY	DURATION
• Cancer drug interactions (p-gp, CYP3A4)	• Site of primary tumor (GI/GU) • Thrombocytopenia • Surgical/procedural interventions	• Minimum 6 months • Indefinite for metastatic CA

+

STEP 2: Assess Patient-Specific Variables

SAFETY	EFFICACY	DURATION
• Age • Renal Function • Comorbidities affecting bleeding risk • Other AC indications (mechanical valve, CAD)	• Oral intake • Compliance • Other AC indications (mechanical valve, CAD)	• Cost • Quality of life • Minor bleeding

⇒ **Practical Choice/Decision**

O'Connell et al The Oncologist 2021;26:e8–e16

CAT Treatment: Patient Selection, Controversies and Caveats

Panel 1: DOAC recommendations

Patients with cancer for whom DOAC is the preferred initial therapy for VTE

- Ambulatory patients with cancer with an intact upper gastrointestinal tract that can take oral medications
- Hospitalized patients with cancer for whom surgical intervention is not planned

DOACs not recommended for patients with

- Creatinine clearance <30 mL/min
- Luminal gastrointestinal lesion
- Luminal genitourinary lesion
- Recent (<3 months) history of peptic ulcer disease or other bleeding lesion
- Anticancer therapies that significantly affect P-glycoprotein, CYP3A4, or CYP2J2 pathways
- Severe hepatic impairment with coagulopathy
- Surgery or invasive procedure imminent

Panel 2: Patients with cancer for whom low-molecular-weight heparin is the preferred initial therapy for venous thromboembolism

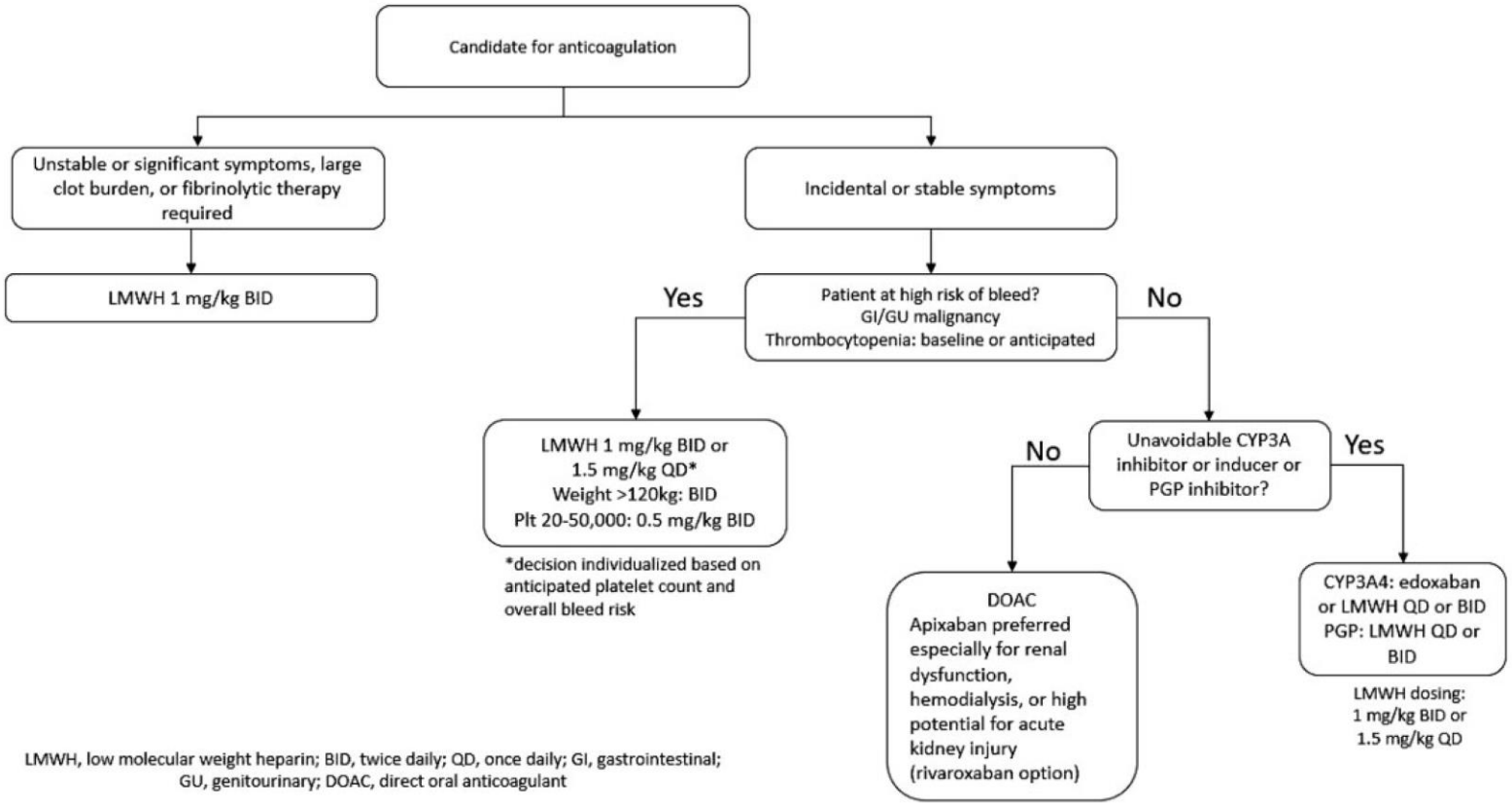
- Ambulatory patients who have gastrointestinal malignancies with luminal lesions
- Ambulatory patients who have genitourinary malignancies with luminal lesions
- Ambulatory patients who cannot take oral medications or lack an intact upper gastrointestinal tract
- Ambulatory or hospitalized patients whose anticancer therapy has significant drug interactions with DOACs
- Ambulatory or hospitalized patients who have thrombocytopenia >50,000 cells/L; dose reduction recommended for platelets 25,000–50,000 cells/L
- Hospitalized patients for whom surgical intervention is planned

Panel 3: Patients with cancer for whom warfarin is the preferred therapy for venous thromboembolism

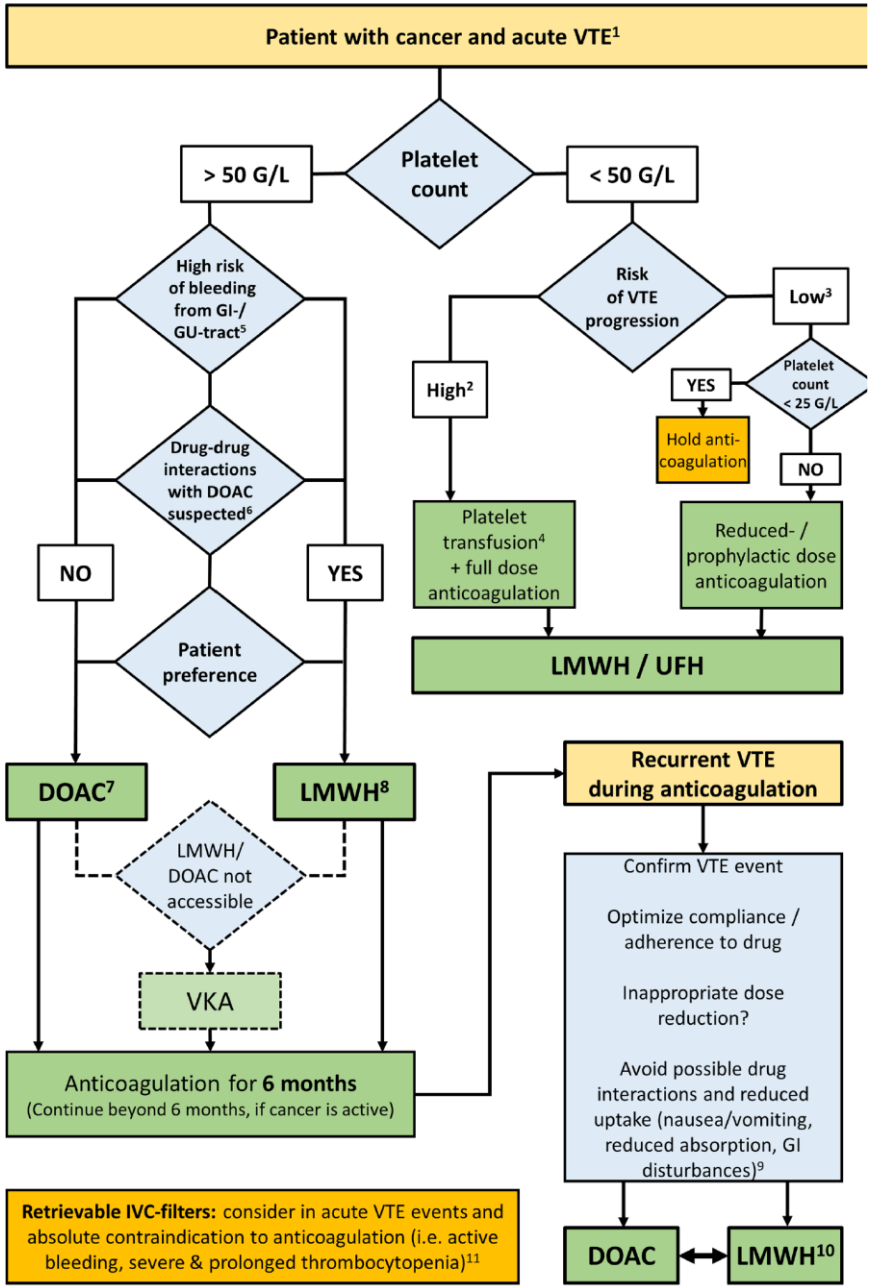
- Patients who have a contraindication to DOACs and cannot or will not use LMWH
- Patients who have end-stage renal disease nearing or on hemodialysis

O'Connell et al The Oncologist 2021;26:e8–e16

Algorithmes d'aide à la prescription

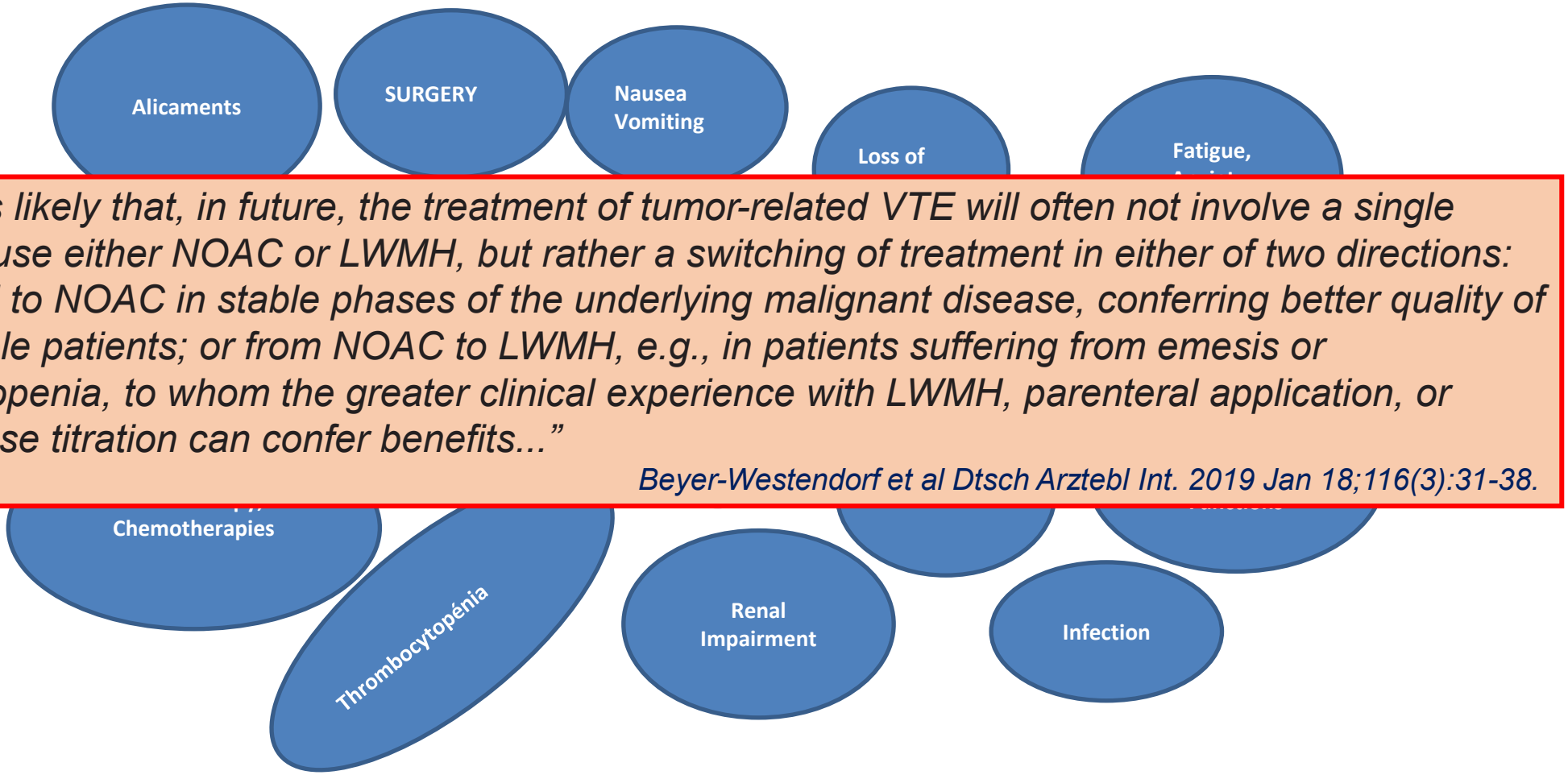


Nachar & Schepers J Oncol Pharm Practice 2021; 0(0): 1–15



Moik F, et al. ESMO Open 2020;4:e000610

Patient CAT : Patient Complexe A Traiter



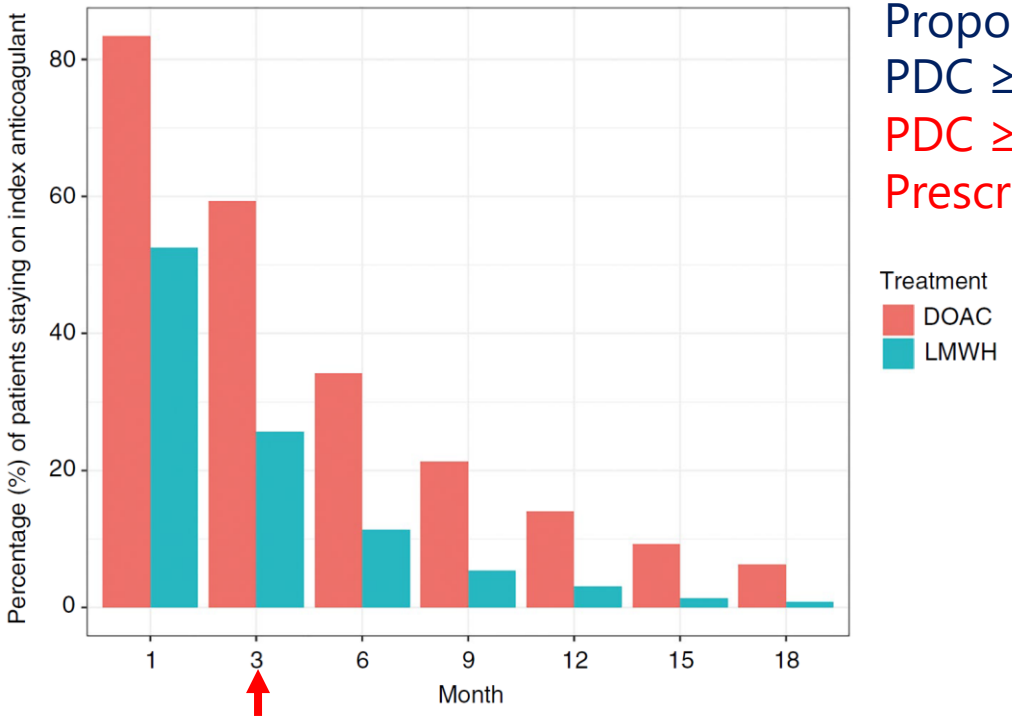
"… It seems likely that, in future, the treatment of tumor-related VTE will often not involve a single decision to use either NOAC or LWMH, but rather a switching of treatment in either of two directions: from LWMH to NOAC in stable phases of the underlying malignant disease, conferring better quality of life to suitable patients; or from NOAC to LWMH, e.g., in patients suffering from emesis or thrombocytopenia, to whom the greater clinical experience with LWMH, parenteral application, or stepwise dose titration can confer benefits..."

Beyer-Westendorf et al Dtsch Arztebl Int. 2019 Jan 18;116(3):31-38.

Voigtländer M. and LangerF. Hamostaseologie. 2017;37(4):241-255.

Anticoagulant medication adherence for cancer-associated thrombosis: A comparison of LMWH to DOACs

Optum's de-identified Clinformatics® Data Mart Database of Cancer pts (Jan 2009 – Jun 2016)
Comparison of 2 propensity score–matched groups of 1128 patients on DOACs and LMWH
Median FU 72 days (interquartile range [IQR]: 30–170 days).
Pts remained on DOACs median 116 days (IQR: 57–231 days) vs 34 days for LMWH (IQR: 30–92 days;

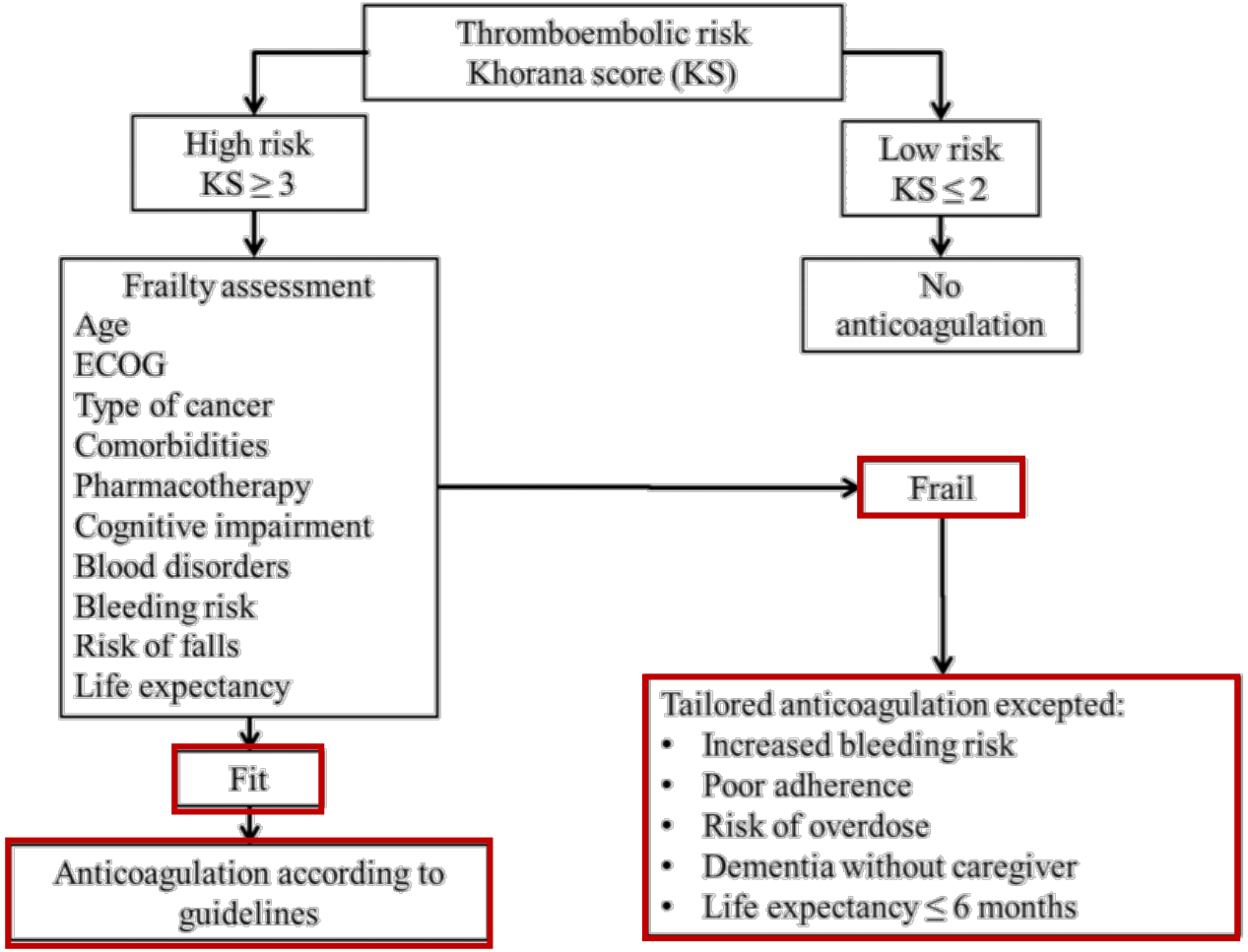


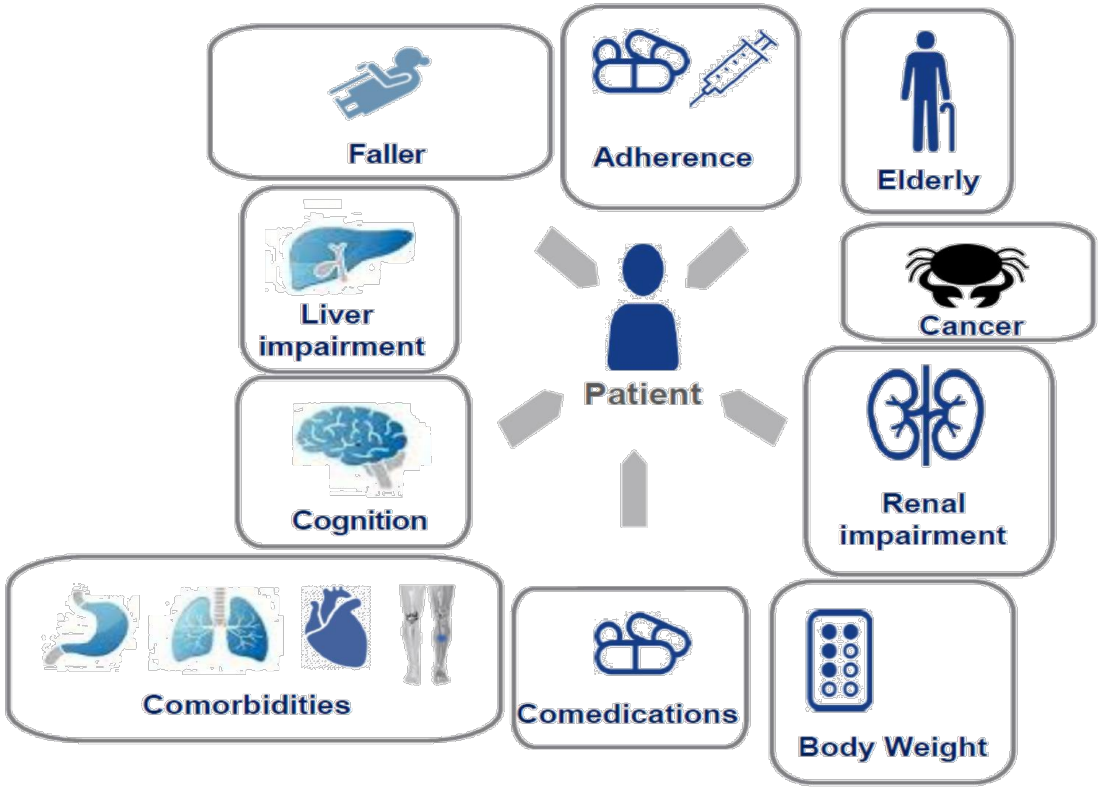
Proportion of Days Covered (PDC): date of AC prescription =>stop or switch
PDC ≥ 80% : adherence with DOACs 95.6% vs 94.6% LMWH, *P* = .33).
PDC ≥ 95% : adherence with DOACS 73% vs 81% LMWH (*P* < .001).
Prescription copayments LMWH >> DOACS (x5)

… high proportion of cancer patients are adherent to the anticoagulant class prescribed by their physician, which highlights the importance of choosing the best anticoagulation agent for an individual patient for the management of CAT, not necessarily the most convenient…
Adherence** does not differ between DOACs and LMWH… with more striking difference in medication **persistence…

Schaefer et al J Thromb Haemost. 2021;19:212–220

Audit du Patient pour un Choix Adapté





Scotte & Elalamy et al Cancers (Basel). 2019 Jan 7;11(1):48.

Elaborated by author.

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