CANCER AND FRAILTY IN ELDERLY PATIENTS

Hôpitaux Universitaires Est Parisien
Saint-Antoine • Rothschild
Trousseau La Roche-Guyon • Tenon

MÉDECINE SORBONNE UNIVERSITÉ

Inserm
La science pour la santé
From science to health

F-CRIN NETWORK
INNOVTE
INvestigation Network On Venous Thrombo-Embolism

Pr I. ELALAMY
Service d'Hématologie Biologique
HOPITAL TENON – INSERM UMR S938 UPMC PARIS

DISCLOSURES

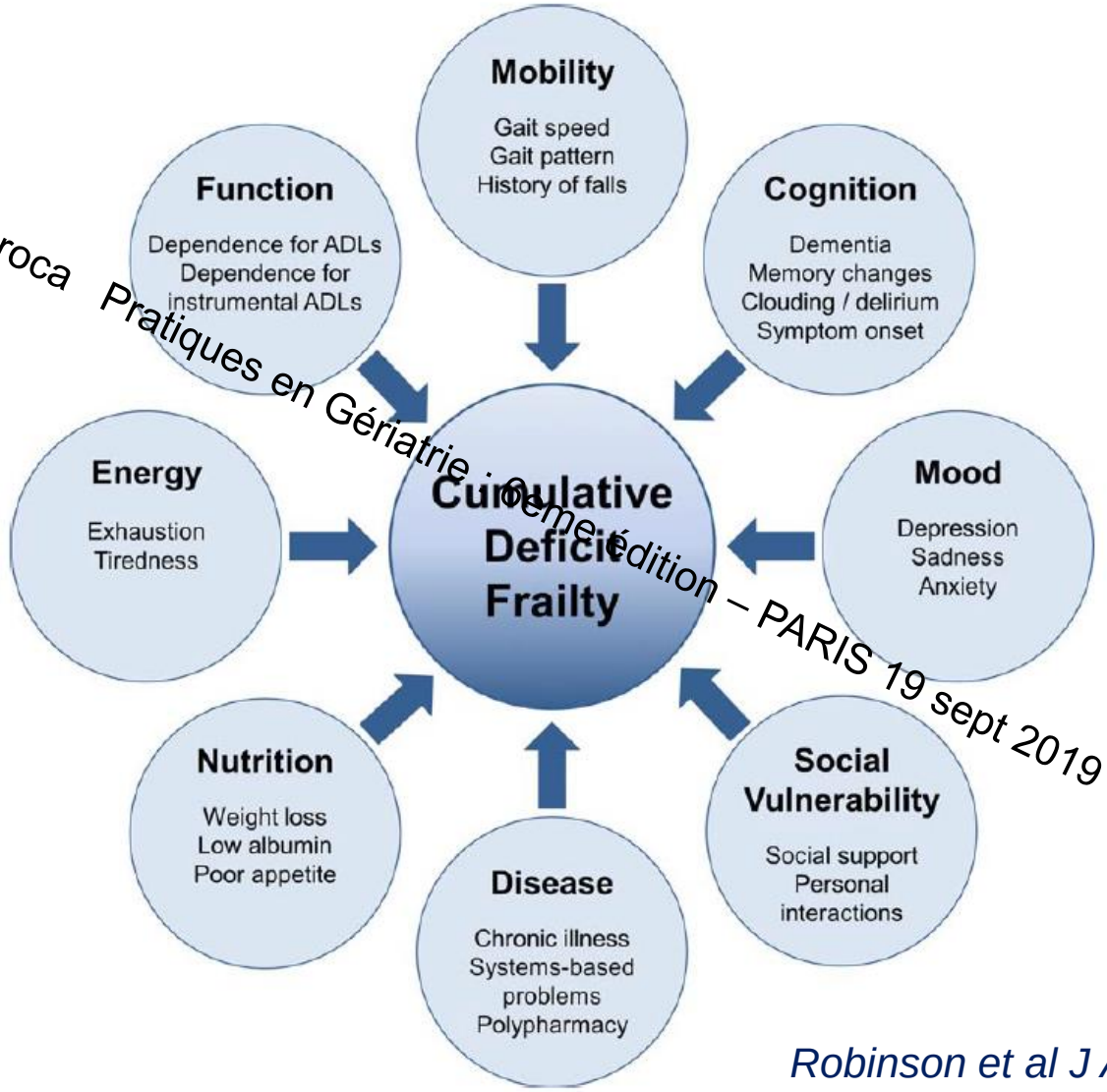
Aspen, Astra-Zeneca, Bayer Healthcare, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Leo-Pharma, Pfizer, Sanofi, Shire, Stago, Sysmex

Scientific Advisory Board

Symposia Speaker

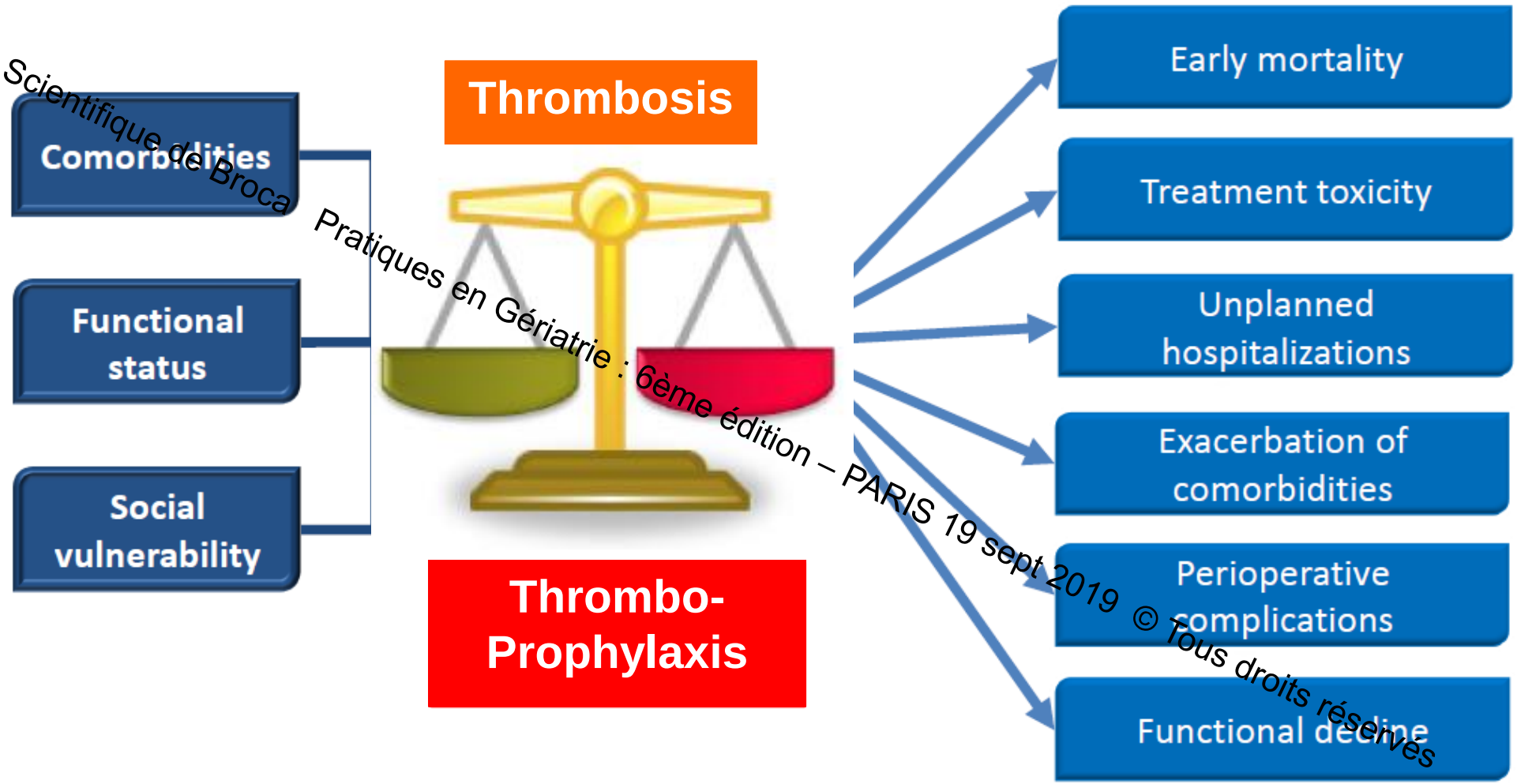
Research Support

CUMULATIVE DEFICIT MODEL OF FRAILTY



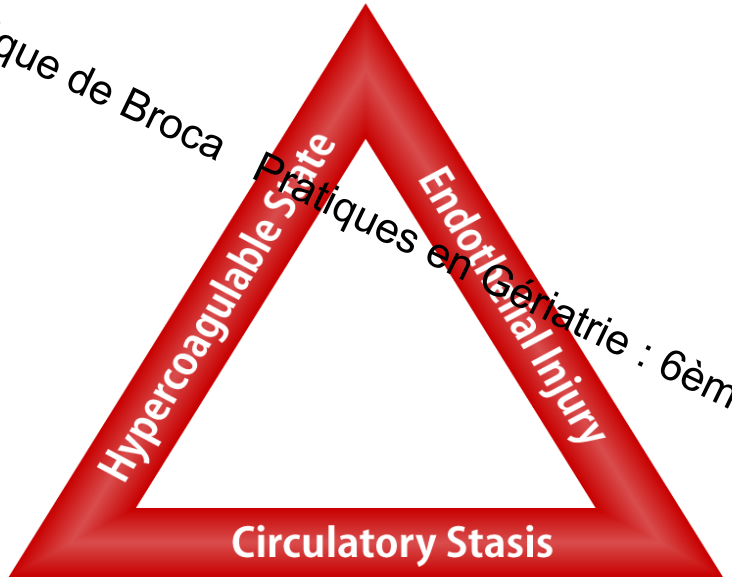
Robinson et al J Am Coll Surg. 2015;221:1083-1092

THERAPEUTIC CHALLENGE IN FRAIL CANCER PATIENTS

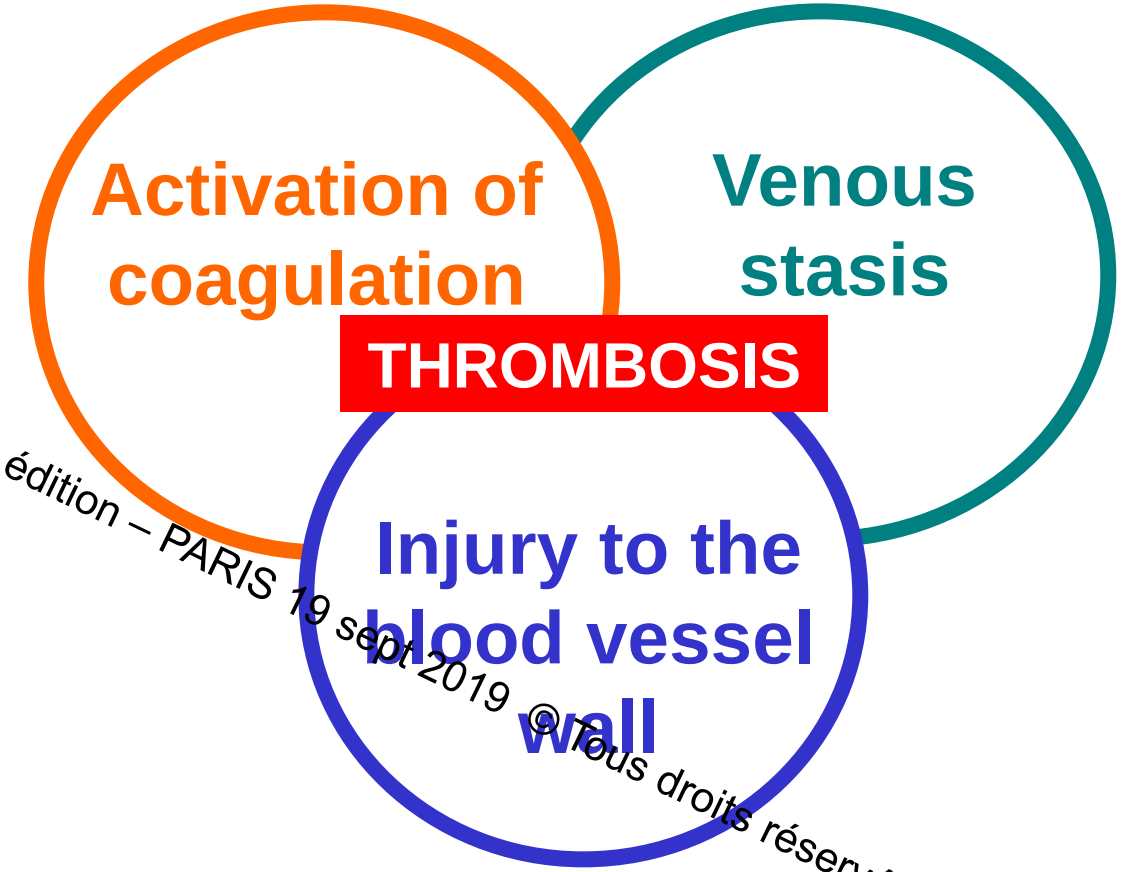


Adapted from Hamaker et al Lancet Oncol 2012;13(10): e437-e444

WHAT CAUSES THE BLOOD TO CLOT?



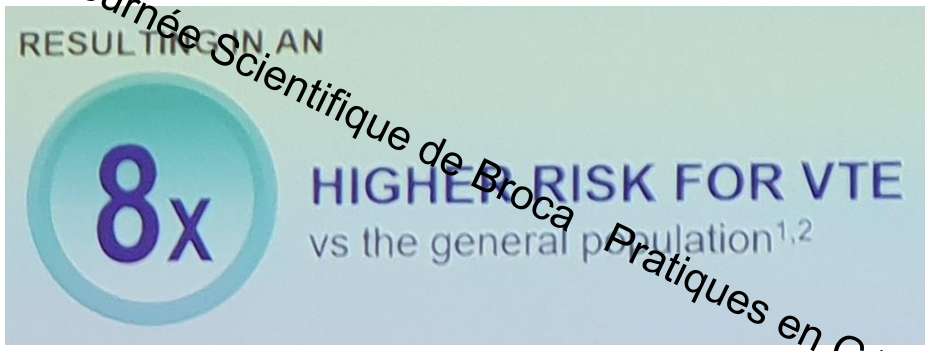
Virchow's Triad (1856)

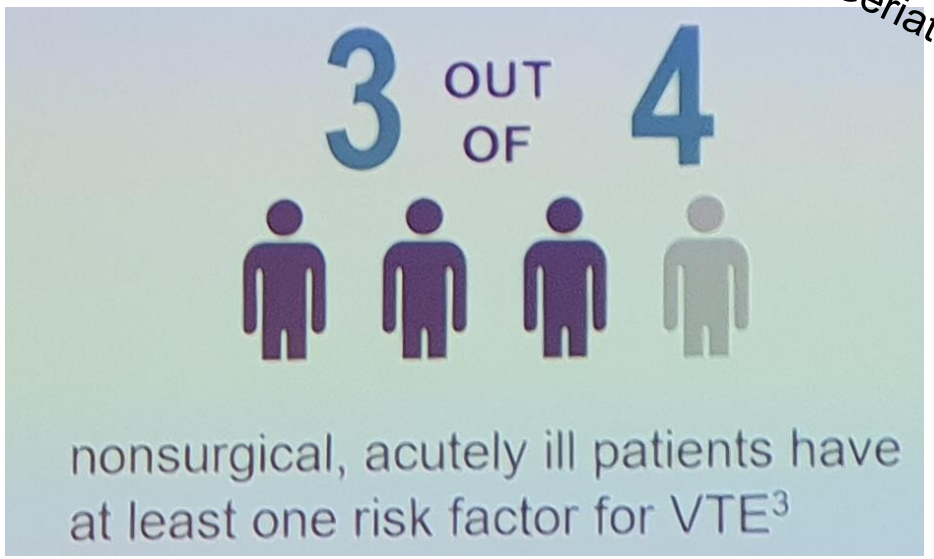


Adapted from Byrnes JR & Wolberg AS Hamostaseologie. 2017;37(1): 25–35

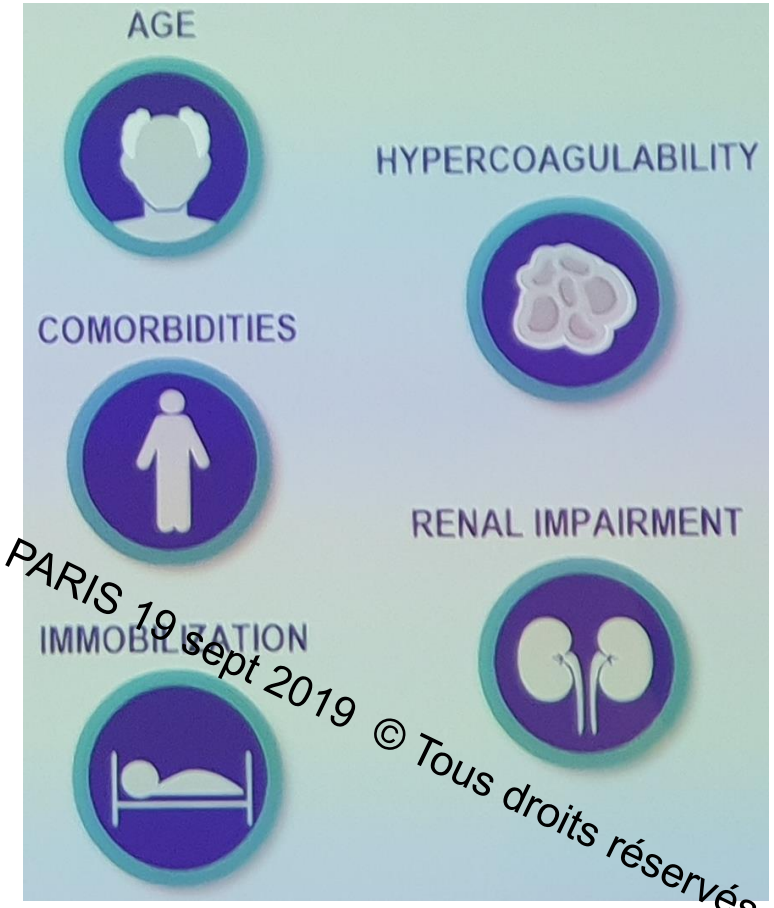
Hospitalized Nonsurgical Acutely Ill Pts are at Increased VTE Risk

Patients Hospitalized for Acute Medical Illness Cary Multiple Risk Factors





Key VTE Risk Factors in Hospitalized Nonsurgical Patients[2,4]



1- Khoury et al Thromb Haemost 2011; 106: 600-608
2- Khan et al Chest 2012; 141 (2 suppl): 195S-226S
3- Baser et al Am J Ther 2013; 20: 132-142
4- Ocak et al J Thromb Haemost 2013; 11: 627-633

SCANDINAVIAN THROMBOSIS AND CANCER COHORT

N=144,952 subjects aged 19–101 years without VTE or cancer.
Baseline information collected in 1993–1997
Validated VTE and cancer diagnoses registered up to 2007–2012.

VTE incidence1.4 per 1,000 person-years
0.3 per 1,000 PY aged 20–29 years
6.4 per 1,000 PY aged 80+ yo

51% VTE provoked : **cancer 19%**
immobilization 15% & surgery 15%.
acute medical condition 7%
trauma 6%
travel 3%

Jensvoll et al Clin Epidemiol 2015; 7: 401-410

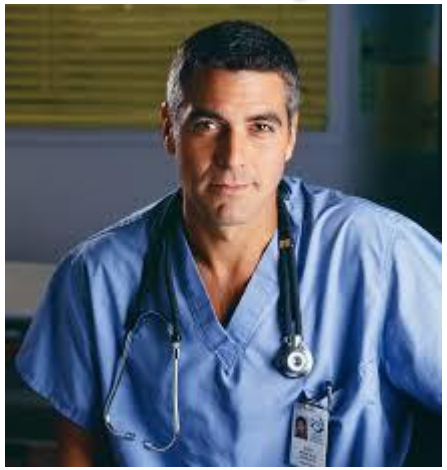
CANCER THROMBOSIS AND COMORBIDITIES

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

THROMBOSIS AND CANCER…
THROMBOSIS & CO…



- **Co-morbidities** *(Patient Risk Factors…)*
- **Co-medications** *(Chemotherapies…)*
- **Co-ckcroft** *(Renal Impairment)*
- **Co-ntext** *(Surgery, Bedridden…)*
- **Co-gnition** *(Compliance…)*

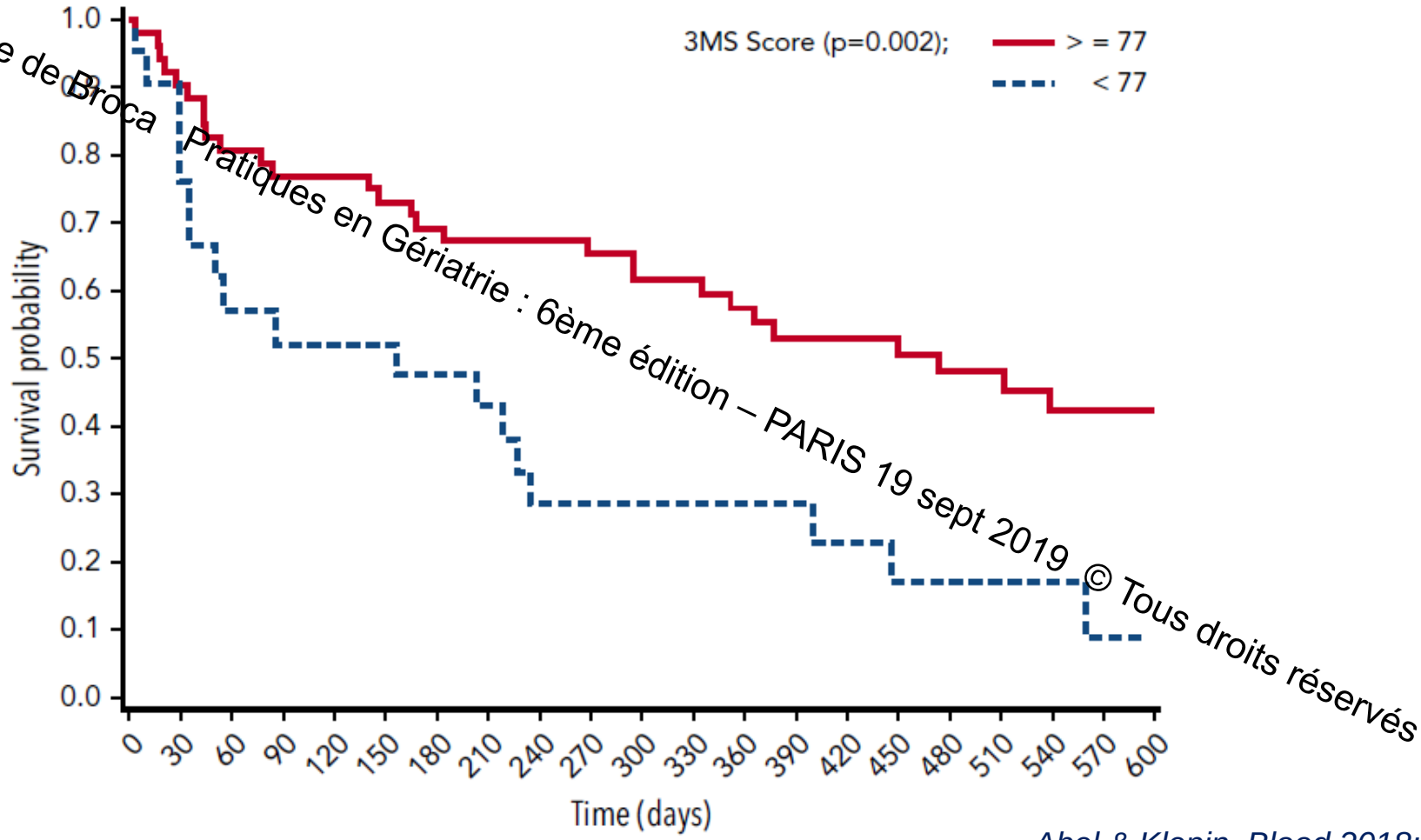
Co-mplications

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

Cognition

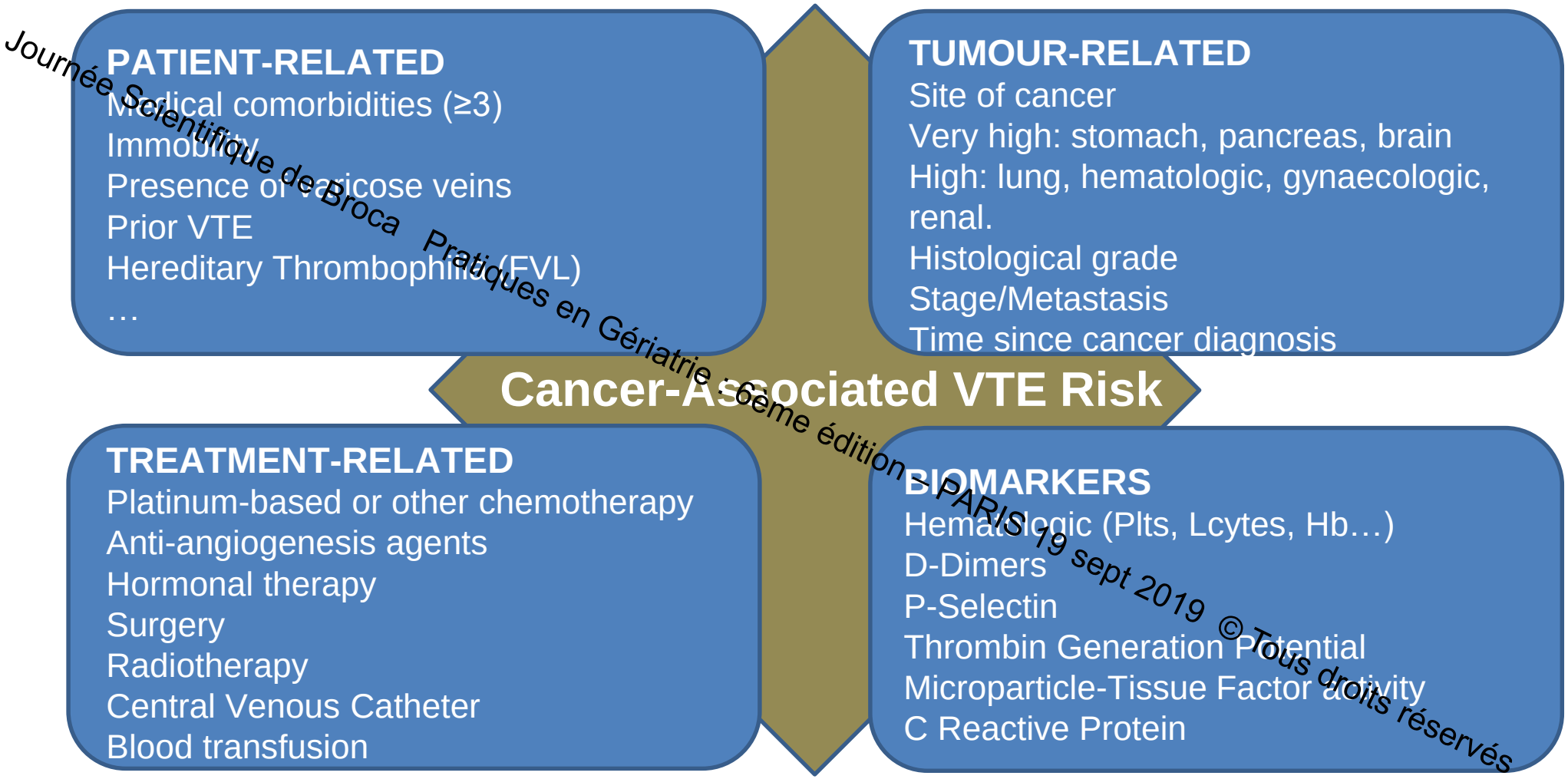
COGNITIVE IMPAIRMENT AND FRAILTY

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



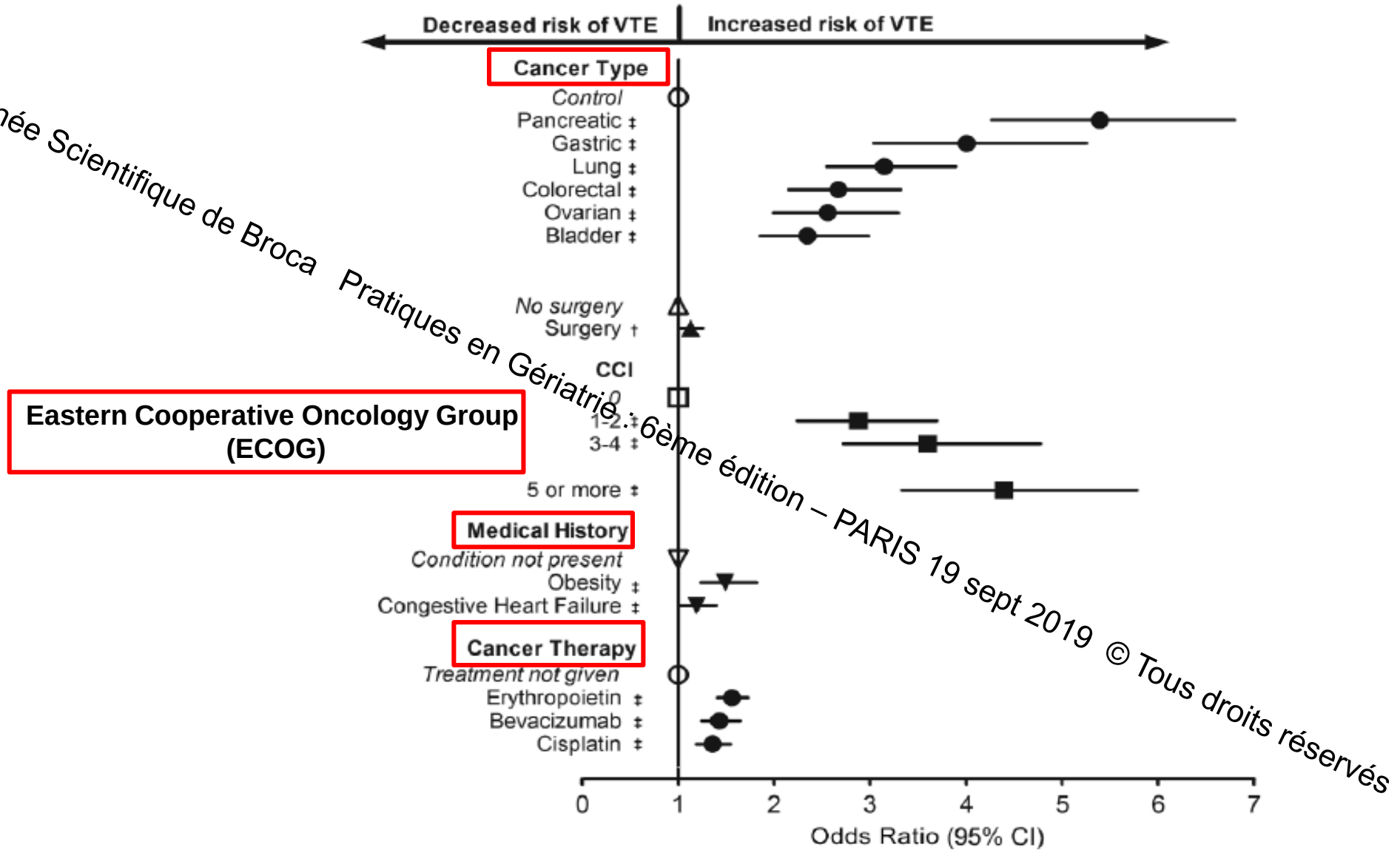
Abel & Klepin, Blood 2018; 131: 515-524

THE 4 DIMENSIONS OF CAT RISK



Adapted from Ay et al Thromb Haemost 2017; 117: 219-230

CAT AND COEXISTENCE OF RISK FACTORS



Eastern Cooperative Oncology Group (ECOG)

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

CAT AND CLINICAL TRIALS

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

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

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

CAT PATIENTS AND RIETE REGISTRY

Patients	N	VKA start <7 days 1,516	VKA start >7 days 619	LMWH alone 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%)	2,066 (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%)‡

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

COCKCROFT : BLEEDING MARKER?

- Age
- Renal Impairment
- Low Body Weight

Cockcroft & Gault Formula

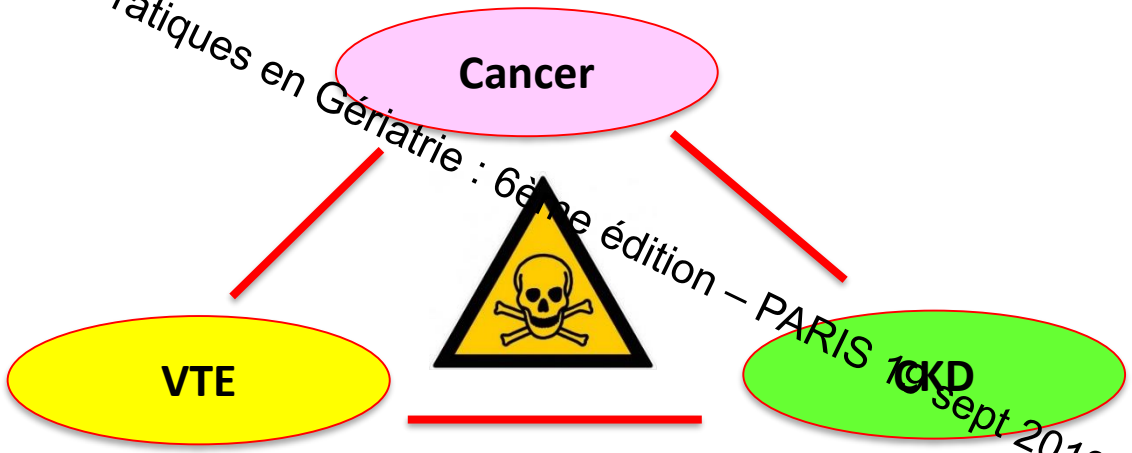
$$\text{Men} = \frac{1.23 \times \text{body weight (kg)} \times (140 - \text{age})}{\text{creatinin (micromols/l)}}$$

Cockcroft & Gault : ***New BMI?***
Bleeding Meaning Index?

I Elalamy et al J Blood Disorders Transf 2014;5: 4-8

ANOTHER TRIAD… TO MANAGE

- VTE & Cancer : worse prognosis and reduced survival
- CKD & Cancer : worse prognosis and reduced survival
- VTE & CKD : worse prognosis and reduced survival



TRIAD
=
MAFIA

Arora et al Sem Thromb Haemost 2014; 40: 313-318

I Elalamy et al J Blood Disorders Transf 2014;5: 4-8

ANTITHROMBOTICS AND PHARMACOKINETICS

	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		99	>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

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

LMWH ACCUMULATION IN CASE OF RENAL IMPAIRMENT

LMWH	Mean molecular weight (Da) [13, 47]	Accumulation therapeutic	Accumulation prophylactic
Bemiparin	3600	CrCl<30 ml/min [38]	CrCl<30 ml/min [38]
Certoparin	3800	CrCl<30 ml/min [48]	CrCl<30 ml/min [39]
Nadroparin	4300	Yes[a] [20]	No conclusion[b]
Enoxaparin	4500	CrCl<30 ml/min [21–24]	CrCl<30 ml/min 4 days [37] and 20–50 ml/min 8 days [35]
Dalteparin	6000	CrCl<30 ml/min after 6 days [32], but not after 3 [43]	No[c] [31–34]
Tinzaparin	6500	No[d] [25, 26]	No[d] [35]

CrCl creatinine clearance
a Only correlation GFR/anti-Xa activity reported, no specific accumulation limit
b Only one multiple dose study in six patients with CrCl above 30 ml/min and one single intravenous dose study
c Largest study no lower limit for CrCl33
d CrCl>20 ml/min

Atiq et al. Eur J Clin Pharmacol 2015;71(8):921-9

ANTITHROMBOTICS AND PHARMACOKINETICS

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Fondaparinux	Anti-Xa	100	-	No	-	17-21	Renal
NOAC							
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Bellesoeur et al. Crit Rev Oncol Hematol.2018;129:102-112

6. NOACs in patients with chronic kidney or advanced liver disease

Calculation of the Child-Pugh score and use of NOACs in hepatic insufficiency

Parameter	1 point	2 points	3 points
Encephalopathy	No	Grade 1-2 (suppressed with medication)	Grade 3-4 (refractory / chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate-severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2-3 mg/dL	>3 mg/dL
	<34 µmol/L	34-50 µmol/L	>50 µmol/L
Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
	>35 g/L	28-35 g/L	<28 g/dL
INR	<1.7	1.71-2.30	>2.30

Child-Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5-6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7-9 points)	Use with caution	Use with caution	Use with caution	DO NOT USE
C (10-15 points)	DO NOT USE	DO NOT USE	DO NOT USE	DO NOT USE

Steffel et al., EHRA Practical Guide, European Heart Journal 2018

DRUG INTERACTIONS IN MEDICAL PATIENTS

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

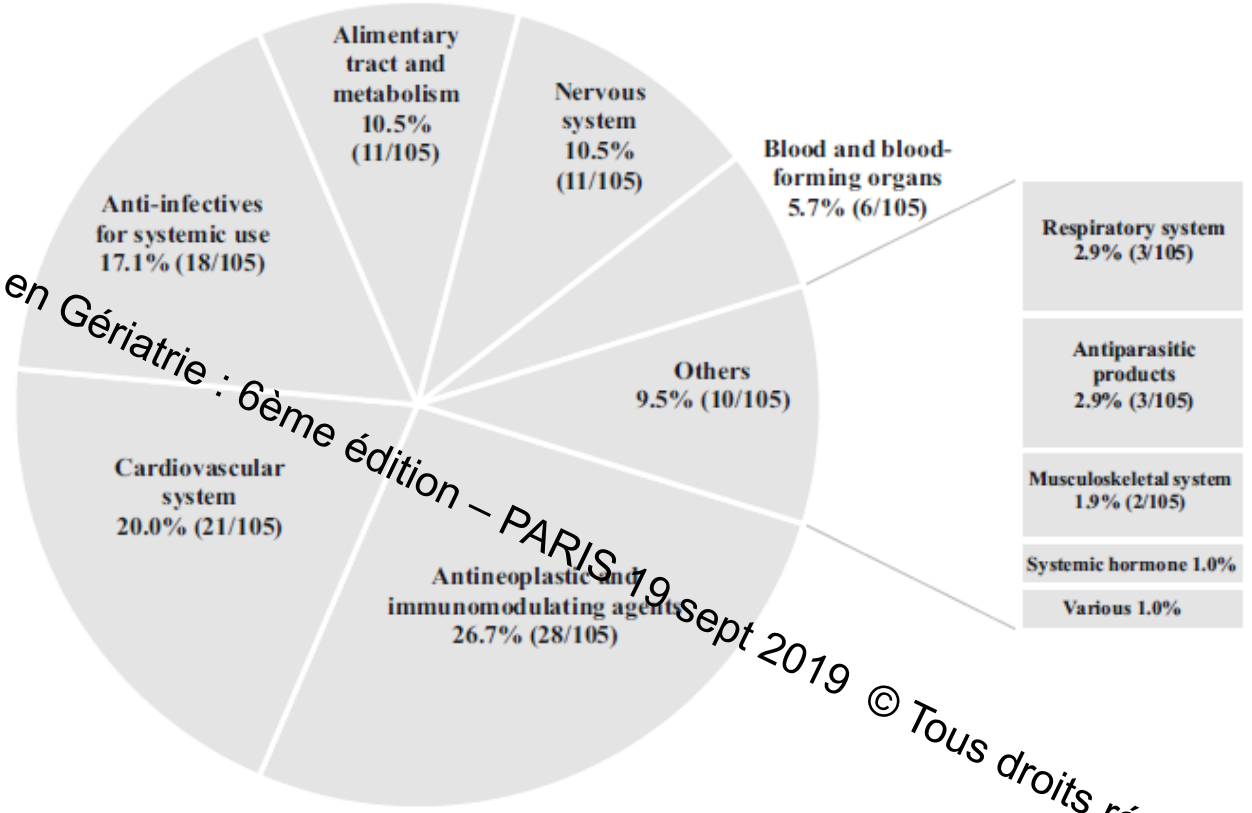


Fig. 2 Classification of 105 drugs selected in the DDI-related articles using PBPK modeling according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system, which groups drugs according to their main anatomical group, as developed by the World Health Organization (http://www.whocc.no/atcddd/)

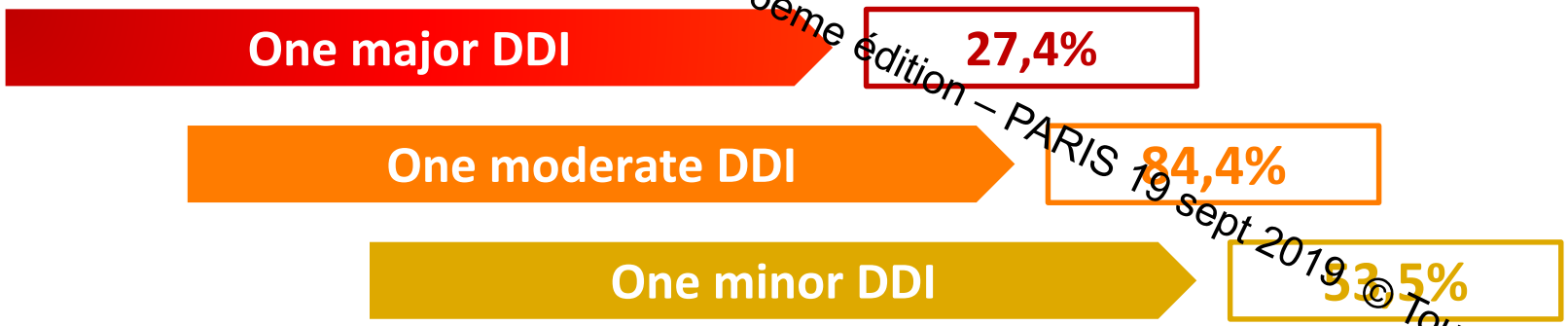
Min et al Arch Pharm Res 2017; PBPK: physiologically based pharmacokinetic

DRUG-DRUG INTERACTIONS IN GERIATRICS : IPOP STUDY

89.5%

of the patients had at least one DDI

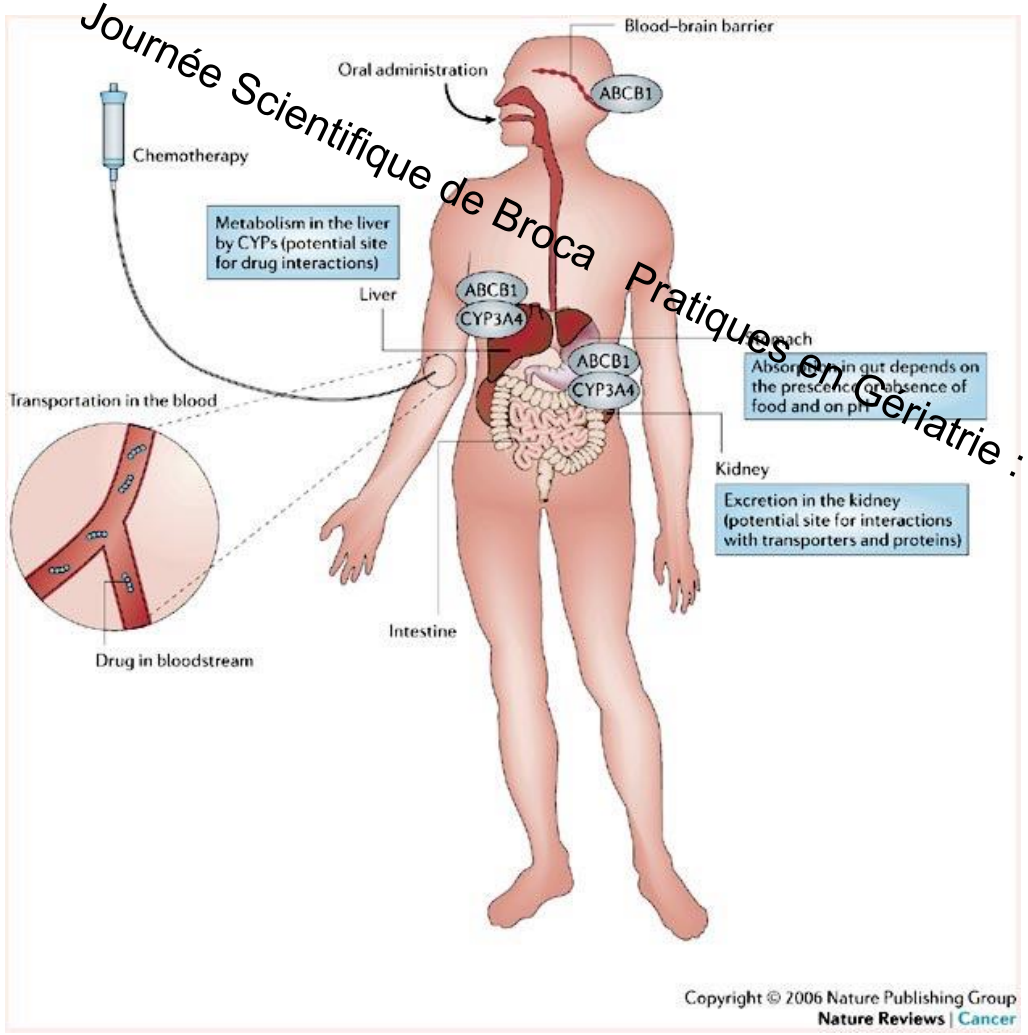
Patients with at least:



Major DDI: highly clinically significant; avoid combinations; the risk of the interaction outweighs the benefit; **Moderate DDI:** moderately clinically significant; usually avoid combinations; use it only under special circumstances; **Minor DDI:** minimally clinically significant; minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

Lechat et al La Lettre du Pharmacol 2016. IPOP Study;

VARIATION FACTORS FOR PHARMACOKINETICS



Absorption
- Previous surgery, radiation or chemotherapy
- Nausea and/or vomiting
- Patient compliance
- Diet
- Genetic differences in intestinal drug-metabolizing and drug-transport systems
- Concomitant medications

Distribution
- Amount of body fat
- Presence of extravascular fluid collections (for example, PLEURAL EFFUSION)
- Hypoalbuminaemia
- Concomitant medications

Metabolism
- Hepatic dysfunction
- Altered hepatic blood flow (age-related changes)
- Genetic differences in hepatic drug-metabolizing and drug-transport systems
- Concomitant medications

Excretion
- Hepatic dysfunction
- Renal insufficiency
- Urinary pH
- Genetic differences in drug-elimination pathways
- Concomitant medications

« ADMET »

Undevia et al. Nature Reviews Cancer 2005

POTENTIAL INTERACTIONS WITH ANTI-TUMORAL TREATMENT

Cytotoxic chemotherapy							Colour codes
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							

Zanger et al. Pharmacology and Therapeutics 2013

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

POTENTIAL INTERACTIONS WITH DOACS

CYP Interactions

- **Ginkgo Biloba**
  - inhibition CYP3A4 et CYP2C19
- **Ginseng**
  - inhibition CYP3A4
- **Echinacea**
  - induction CYP3A4
- **Kava Kava**
  - induction CYP3A4
  - Liver toxicity ++
- **St John's Wort (Millepertuis)**
  - induction numerous CYP

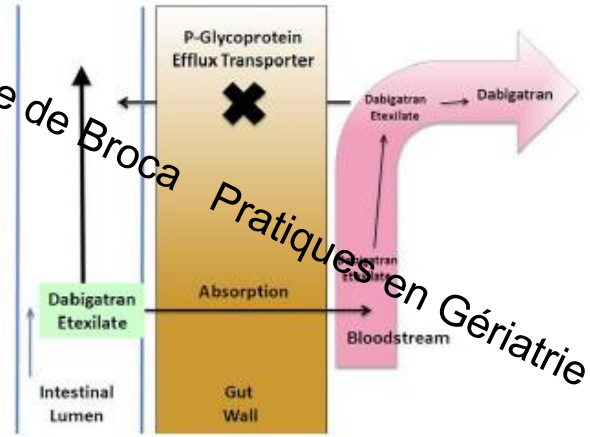
Chassenet/BSIP/Science Photo Library

Principaux sites pour informations

OCCAM (Office of Cancer Complementary and Alternative Medicine) http://cam.cancer.gov/cam/
NCCAM (National Center for Complementary and Alternative Medicine): http://nccam.nih.gov/
NCI (National Cancer institute) http://www.cancer.gov/cancertopics/cam
MSKCC (Memorial Sloan Kettering Cancer Center)

POTENTIAL INTERACTIONS WITH DOACS

P-Glycoprotein



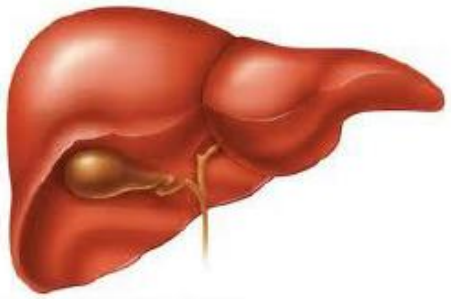
DOAC Metabolism and Drug Interactions

Thrombotic Risk

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

Bleeding Risk

CYP3A4/5 Metabolism



Except Dabigatran

Thrombotic Risk

- Strong inducers of CYP3A4/5 decrease exposure of drug

- CYP3A4 Inhibitors increase blood concentrations drug

Bleeding Risk

Shih & Crowther, ASH Hematology 2016

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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 and hypoalbuminemia?

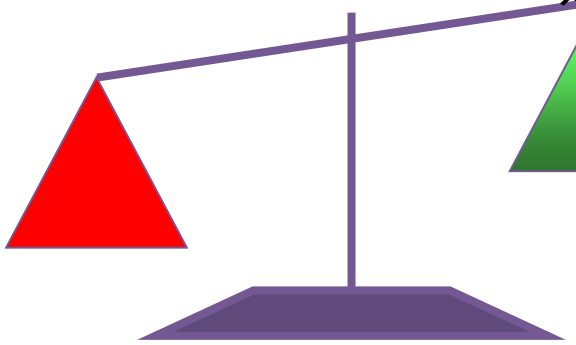
Bellesoeur et al. Crit Rev Oncol Hematol.2018;129:102-112

CANCER AND THROMBOPROPHYLAXIS: A COMPLEX RELATIONSHIP TO AUDIT

PROFILE THE RISK…

PRESCRIBE IN THE HIGH RISK?…

… PROSCRIBE IN THE LOW RISK!



THROMBOTIC RISK

BLEEDING RISK

ASH RECOMMENDATIONS 2018

Recommendations 1, 2, and 3. In acutely ill medical patients, we suggest using UFH, LMWH, or fondaparinux rather than no parenteral anticoagulant… the panel suggests using LMWH rather than UFH…

Recommendations 4 and 5. In critically ill medical patients, we recommend using UFH or LMWH over no UFH or LMWH and we suggest using LMWH over UFH…

Recommendation 6. In acutely or critically ill medical patients, we suggest using pharmacological VTE prophylaxis over mechanical VTE prophylaxis…

Recommendation 7. In acutely or critically ill medical patients who do not receive pharmacological VTE prophylaxis, we suggest using mechanical VTE prophylaxis over no VTE prophylaxis…

Recommendation 8 and 9. In acutely or critically ill medical patients, we suggest pharmacological or mechanical VTE prophylaxis alone over mechanical combined with pharmacological VTE prophylaxis

Recommendation 10. In acutely or critically ill medical patients who are receiving mechanical VTE prophylaxis, we suggest using pneumatic compression devices or graduated compression stockings for VTE prophylaxis

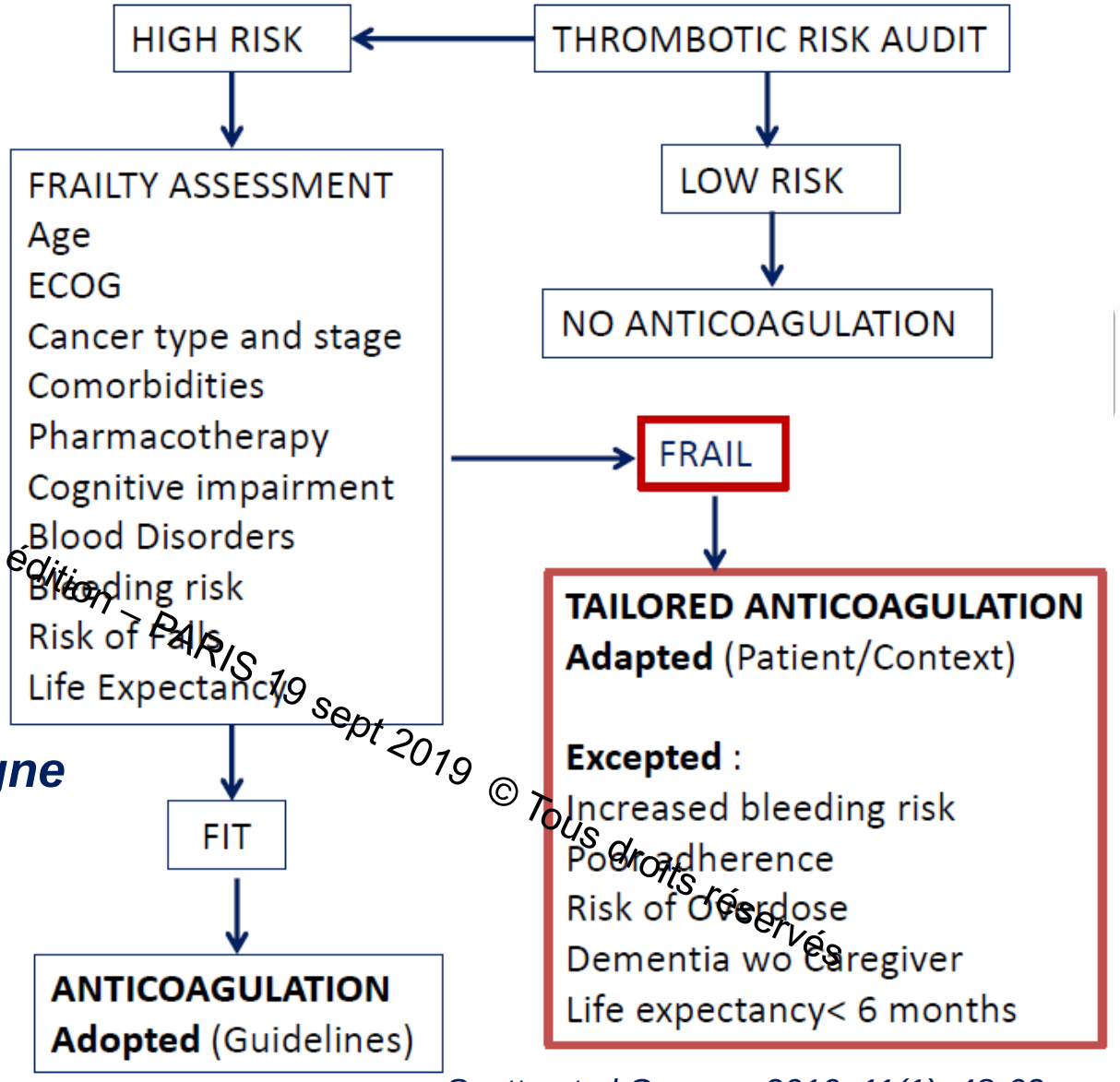
Recommendation 11 and 12. In acutely ill hospitalized medical patients, **we recommend** using LMWH over DOACs for VTE prophylaxis and inpatient VTE prophylaxis with LMWH only, rather than inpatient and extended duration outpatient VTE prophylaxis with DOACs…

Schunemann et al Blood Advances 2018; 22: 3198–3225

THROMBOPROPHYLAXIS CHALLENGE IN CANCER

« HBPM »
Hypocoagulation Bénéfique si Prolifération Maligne

« AOD »
Attention Ô Doute



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