

HÉMORRAGIES GASTRO-INTESTINALES SOUS AOD



Pr I. ELALAMY

Service d'Hématologie Biologique (DMU BioGeM)
Cancer, Hémostase et Angiogenèse - INSERM UMR S938
HOPITAL TENON (APHP) – PARIS

Déclaration de Relations Professionnelles et Liens d'Intérêt

Aspen, Bayer, Bristol Myers Squibb, Léo-Pharma, Pfizer, Sanofi,

AVK ... AVEC Assistance à Personne en Danger
AOD ... Anticoagulant aux Offices Demandés

Caractéristiques	AVK	AOD
Délai d'action	Lent	Rapide
Posologie	Variable	Fixe
Fenêtre Thérapeutique	Etroite	Large
Polymorphisme G ^{que}	Oui	Non
Interaction Aliment ^{res}	Oui	Non
Interactions Médic ^{ses}	Oui +++	Oui +
Surveillance biol ^{que}	Oui	Non
Demi-vie	Longue	Courte
Antidote	Non	Oui
Coût	Plus	Moins

CARACTÉRISTIQUES DES AOD

	Dabigatran ¹	Rivaroxaban ^{2,3}	Apixaban ⁴	Edoxaban ³	Warfarine
Cible	IIa	Xa	Xa	Xa	II VII IX X PC PS PZ
Bioadisponibilité, %	3–7	80-100	50	62	> 95%
PM Da	628/472	436	460	548	310
Tmax (h)	2-6	2-4	1-3	1-2	3 à 5 jours
Demi-vie, h	12–17	5–13	8-15	8–10	35-45 h
Clairance rénale, %	80/80*	33/66*	27/58*	35/50*	92% (inactive)
Transporteurs	P-gp	P-gp/BRCP	P-gp/BCRP	P-gp/BRCP	Pas P-gp/BRCP
Métabolisme CYP, %	Non	60% (3A4-2J2)	<35% (3A4)	<4%	100% CYP 2C9-3A4
Liaison Proteines , %	35	92–95	87	40–59	97% liaisons protéines
Prise Quotidienne	BID	BID/OD	BID	OD	OD

CYP, cytochrome P450;

P-gp, P-glycoprotein
administered/*absorbed dose

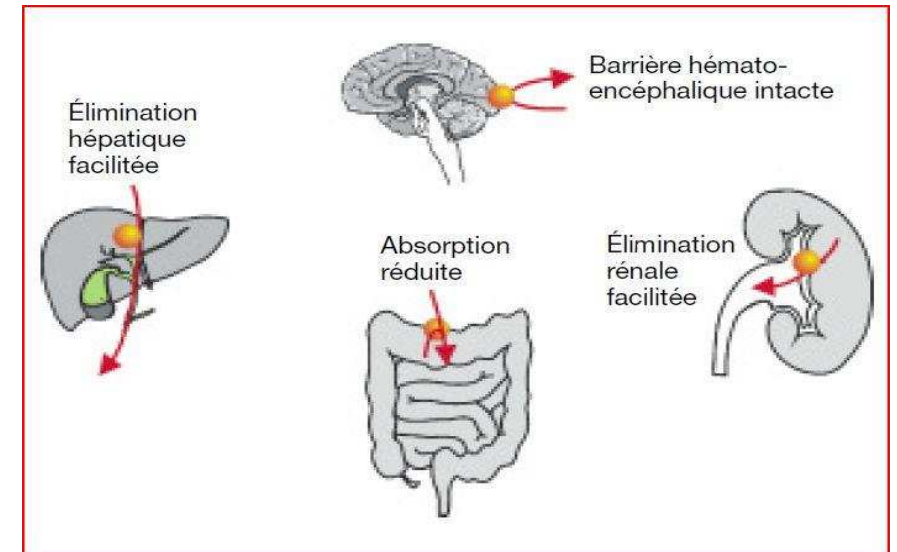
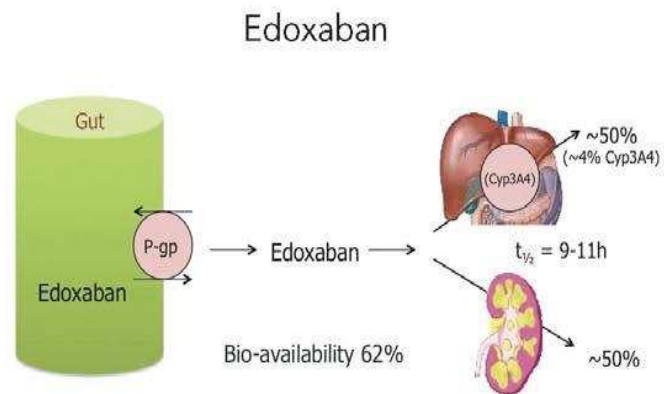
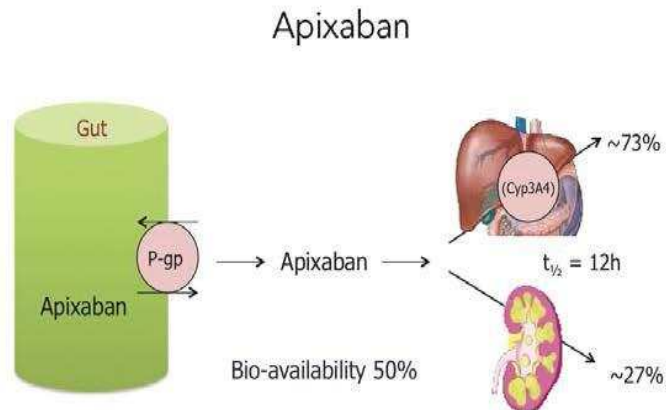
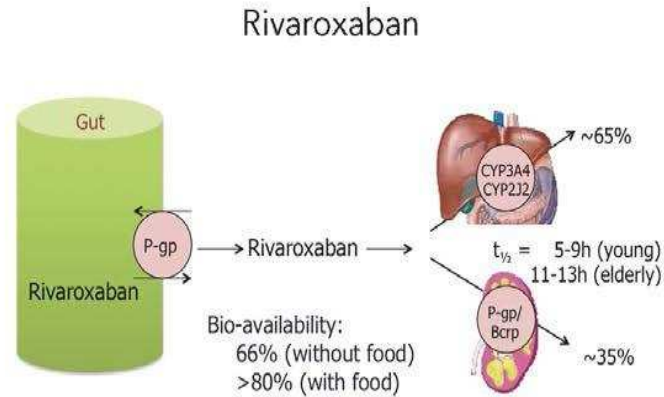
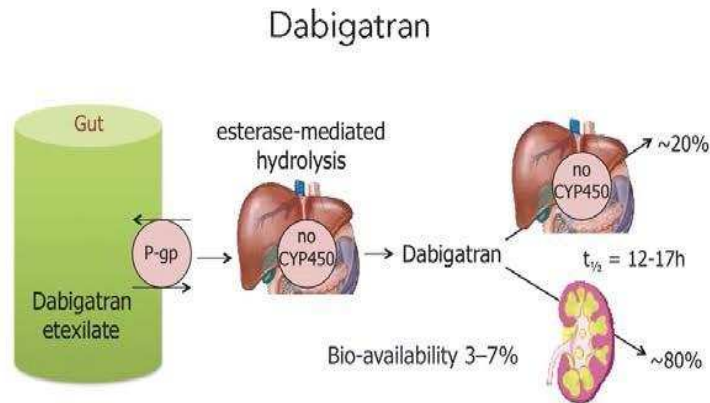
1. Pradaxa SmPC Boehringer Ingelheim Pharmaceuticals, Inc. 2013

2. Xarelto SmPC Janssen Pharmaceuticals, Inc. 2011

3. Weinz et al. Drug Dispos Metab 2009;37:1056–1064

4. ELIQUIS SmPC Bristol Myers Squibb/Pfizer EEIG, UK

Fonctions des Cytochromes et P-GlycoProtéines P-gp



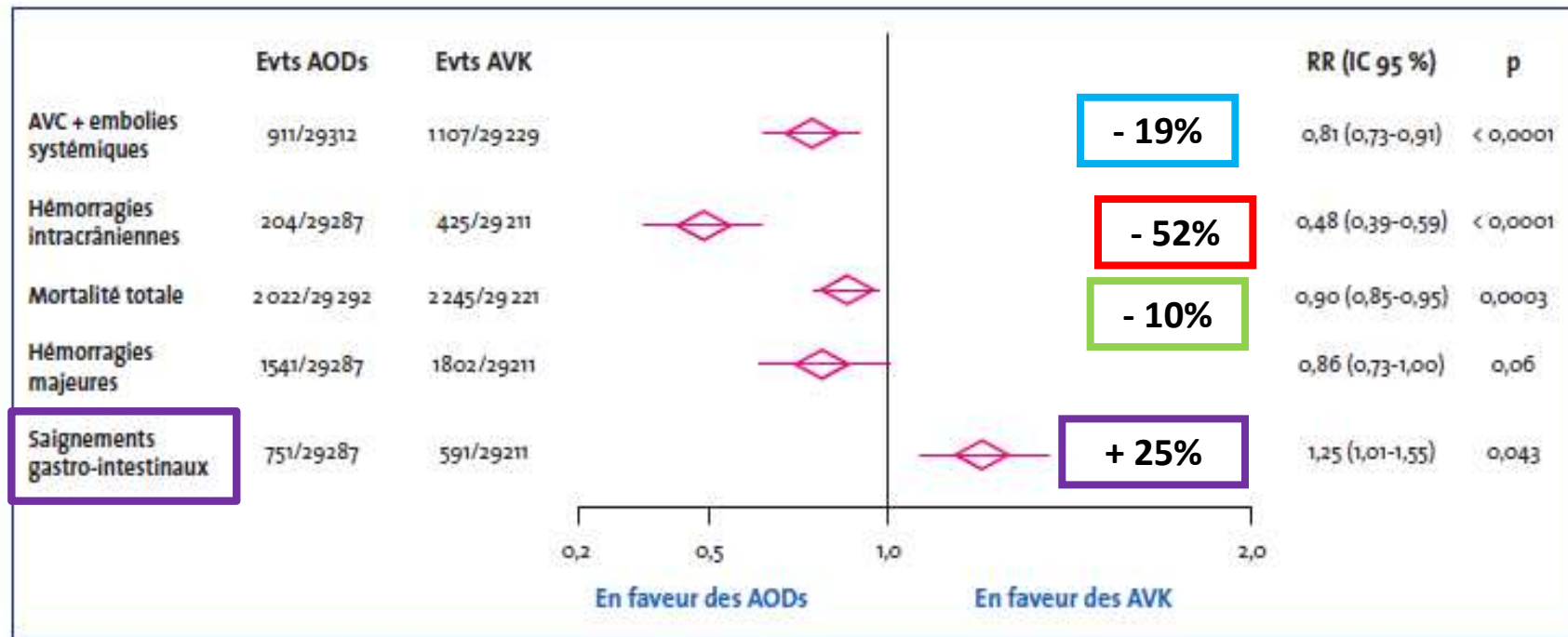
Si AOD Prescrit... Alors...

- A. Risque digestif hémorragique des AOD > AVK?**
- B. Risque digestif hémorragique de rivaroxaban > apixaban?**
- C. Hémorragie digestive sous AOD doit alors les contre-indiquer?**
- D. Il est conseillé de prescrire un IPP en prévention avec un AOD?**

Efficacité et Tolérance des AOD dans la FANV

Méta-analyse RE-LY, Rocket AF, ARISTOTLE et ENGAGE AF-TIMI 48 :

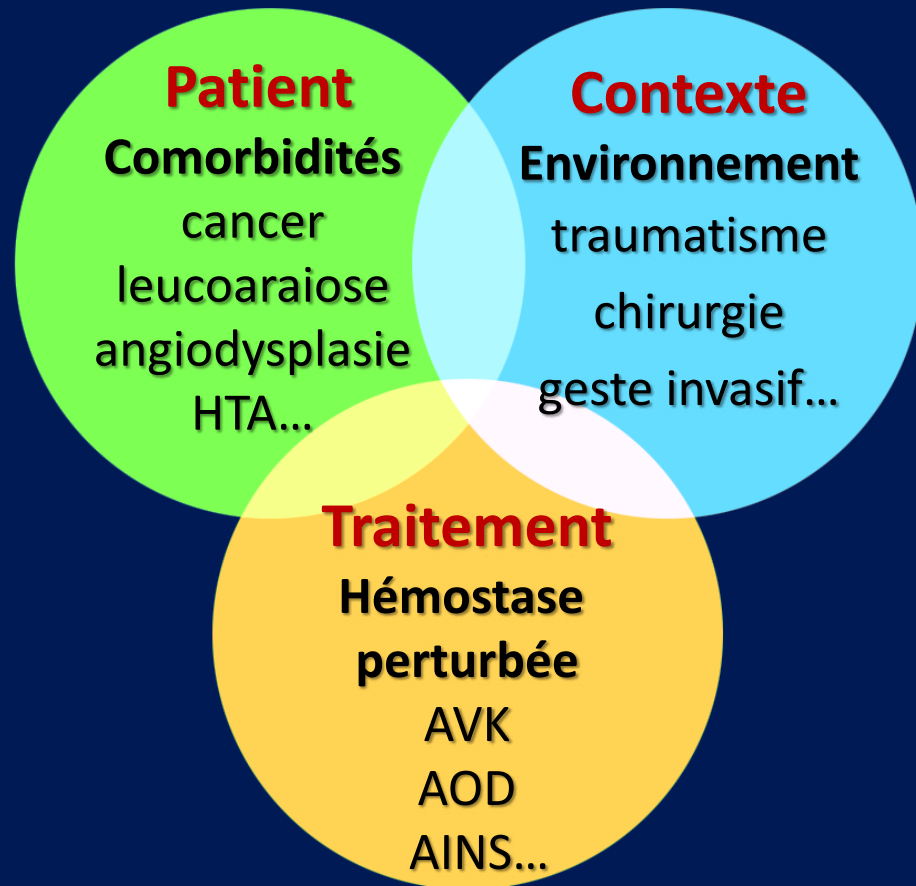
71 683 patients inclus (29 099 > 75 ans)



Efficacité et Tolérance des AOD dans la MTEV

Drug	Study	VTE recurrence active/control (%)	HR/RR (95%CI)	Major bleeding active/control (%)	HR/RR (95%CI)
Dabigatran	RE-COVER	2.4 / 2.1	1.10 (0.60–1.84)	1.6 / 1.9	0.82 (0.45–1.48)
Dabigatran	RE-COVER II	2.4 / 2.2	1.09 (0.65–1.81)	1.2 / 1.7	0.69 (0.66–1.33)
Rivaroxaban	EINSTEIN-DVT	2.1 / 3.0	0.68 (0.44–1.04)	0.8 / 1.2	0.65 (0.33–1.30)
Rivaroxaban	EINSTEIN-PE	2.1 / 1.8	1.12 (0.75–1.68)	1.1 / 2.2	0.49 (0.31–0.79)
Apixaban	AMPLIFY	2.3 / 2.7	0.84 (0.60–1.18)	0.6 / 1.8	0.31 (0.17–0.55)
Edoxaban	HOKUSAI	3.2 / 3.5	0.89 (0.70–1.13)	1.4 / 1.6	0.84 (0.59–1.21)

Hémorragie : Pathologie Multifactorielle



Lower GIB hospitalization rate 3.3-8,7/10 000
mortality rate 2.5-4% during hospitalization
rebleeding rate 13%-19% after 1 year

Upper GIB Incidence 6,1-7,8/10 000

>90 % of GI bleedings with DOAC not life-threatening

50% GIB unspecified with unknown source

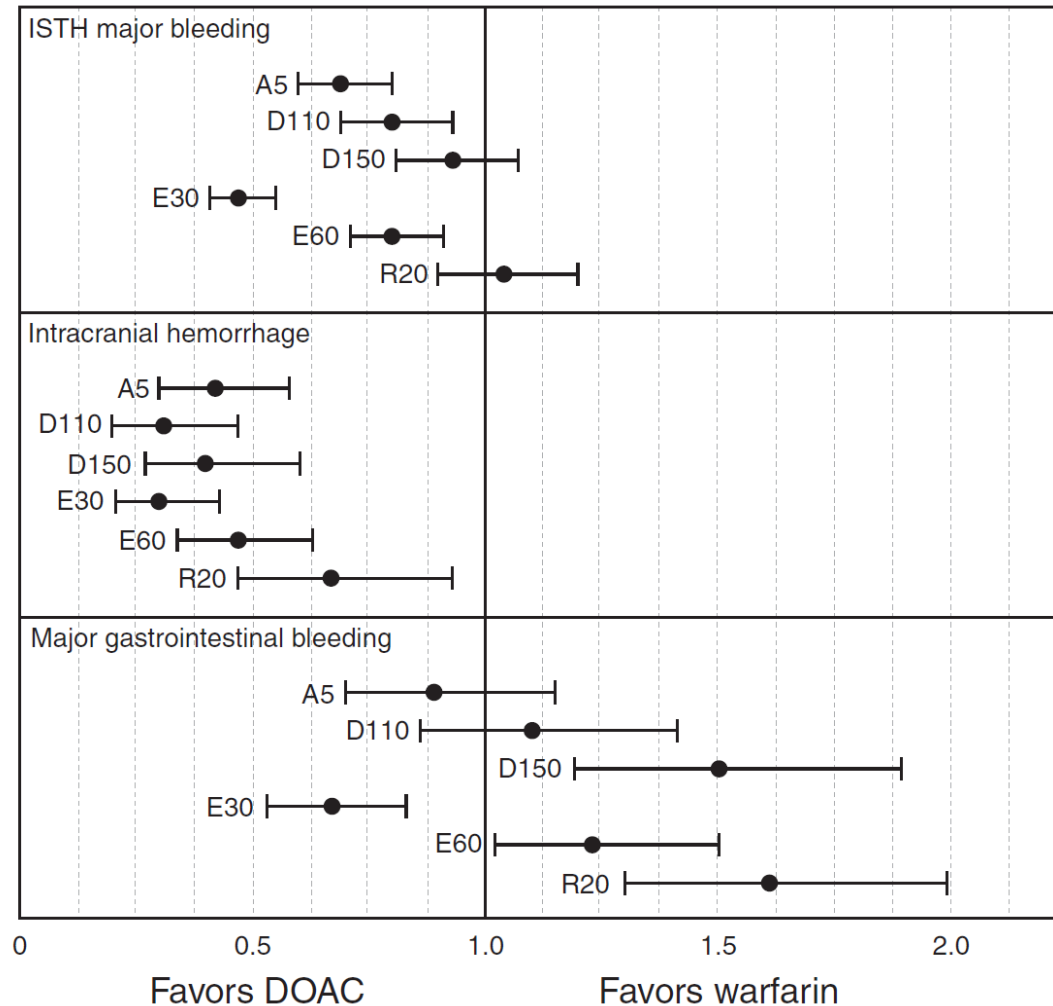
Risque d'Hémorragies Digestives: AOD vs. Warfarine

	DOAC	Compared	n (DOAC/ comparator)	Indication	Mean CHADS2	Treatment duration (months)	Gastrointestinal bleeding RR (95% CI) or %
RE-LY	Dabigatran	VKA	6076 + 6015/6022	NVAF	2.1	24	1.5 (1.19–1.89)
RE-LY ABLE	Dabigatran 150 mg	Dabigatran 110 mg	2937 + 2914			27.6	0.99 (0.75–1.31)
ROCKET-AF	Rivaroxaban	VKA	7131/7133	NVAF	3.5	22	1.39 (1.19–1.61)
ARISTOTLE	Apixaban	VKA	9120/9081	NVAF	2.1	20	0.89 (0.70–1.15)
ENGAGE AF-TIMI48	Edoxaban	VKA	7035 + 7034/7036	NVAF	2.8	34	1.23 (1.02–1.50)
AMPLIFY	Apixaban	Enoxaparin/VKA	2691/2704	VTE	N/A	6	0.3% <i>versus</i> 0.7%
RE-COVER I	Dabigatran	UFH-LMWH/VKA	1274/1265	VTE	N/A	6	1.50 (0.99–2.29)
RE-COVER II	Dabigatran	UFH-LMWH/VKA	1279/1289	VTE	N/A	6	1.47 (0.95–2.27)
EINSTEIN-PE	Rivaroxaban	Enoxaparin/VKA	4151/4131	VTE (PE)	N/A	3–12	0.04% <i>versus</i> 0.08%
HOSUKAI	Edoxaban	Enoxaparin/VKA	4143/4149	VTE	N/A	12	1% <i>versus</i> 0.8%
Meta-analysis (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF TIMI 48)	DOAC	VKA	42411/29272	NVAF	2.6	26.4	1.25 (1.01–1.55)

Deutsh et al. Ther Adv Gastroenterol 2017; 10(6): 495-505

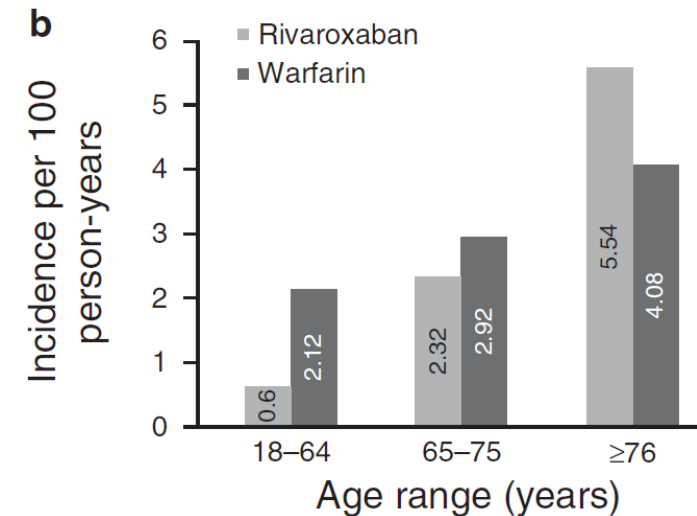
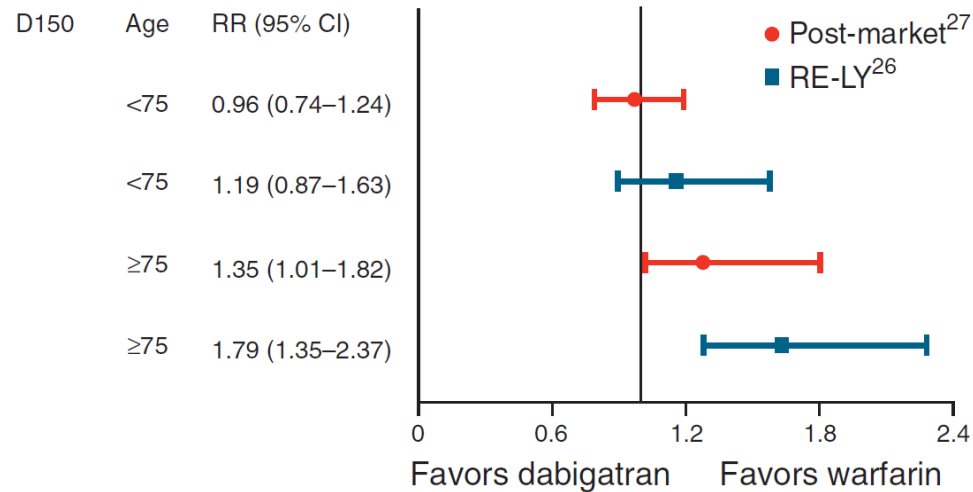
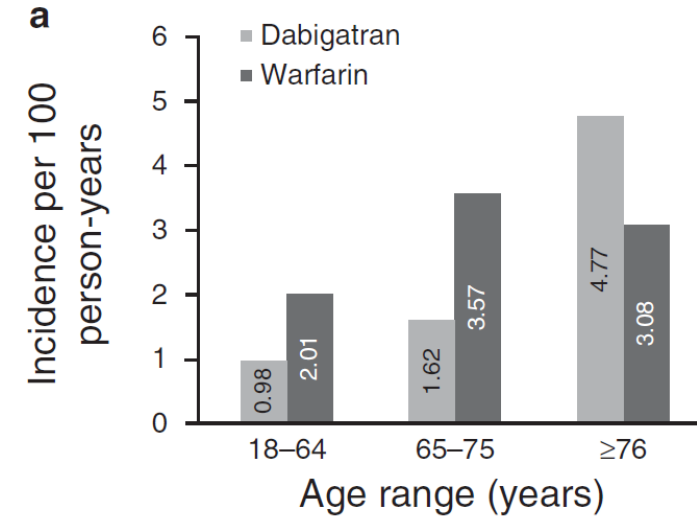
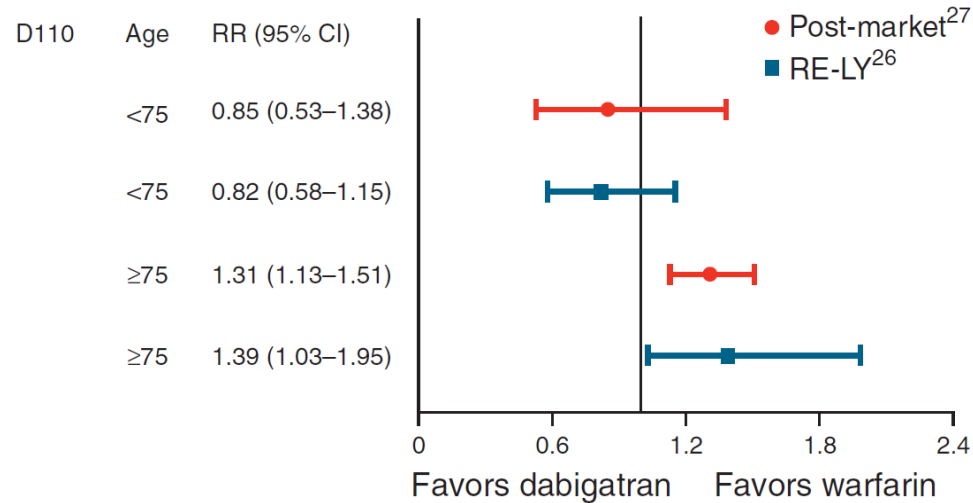
GI Bleeding Annual Risk 0.9%-1.2% for warfarin and 0.8%-2.0% for DOACs
 Fatal GI bleeds: warfarin 0.01/100 pt-y; Rivaroxaban 0.04/100 pt-y

Hémorragies et Anticoagulants au cours de la FANV: Essais Cliniques

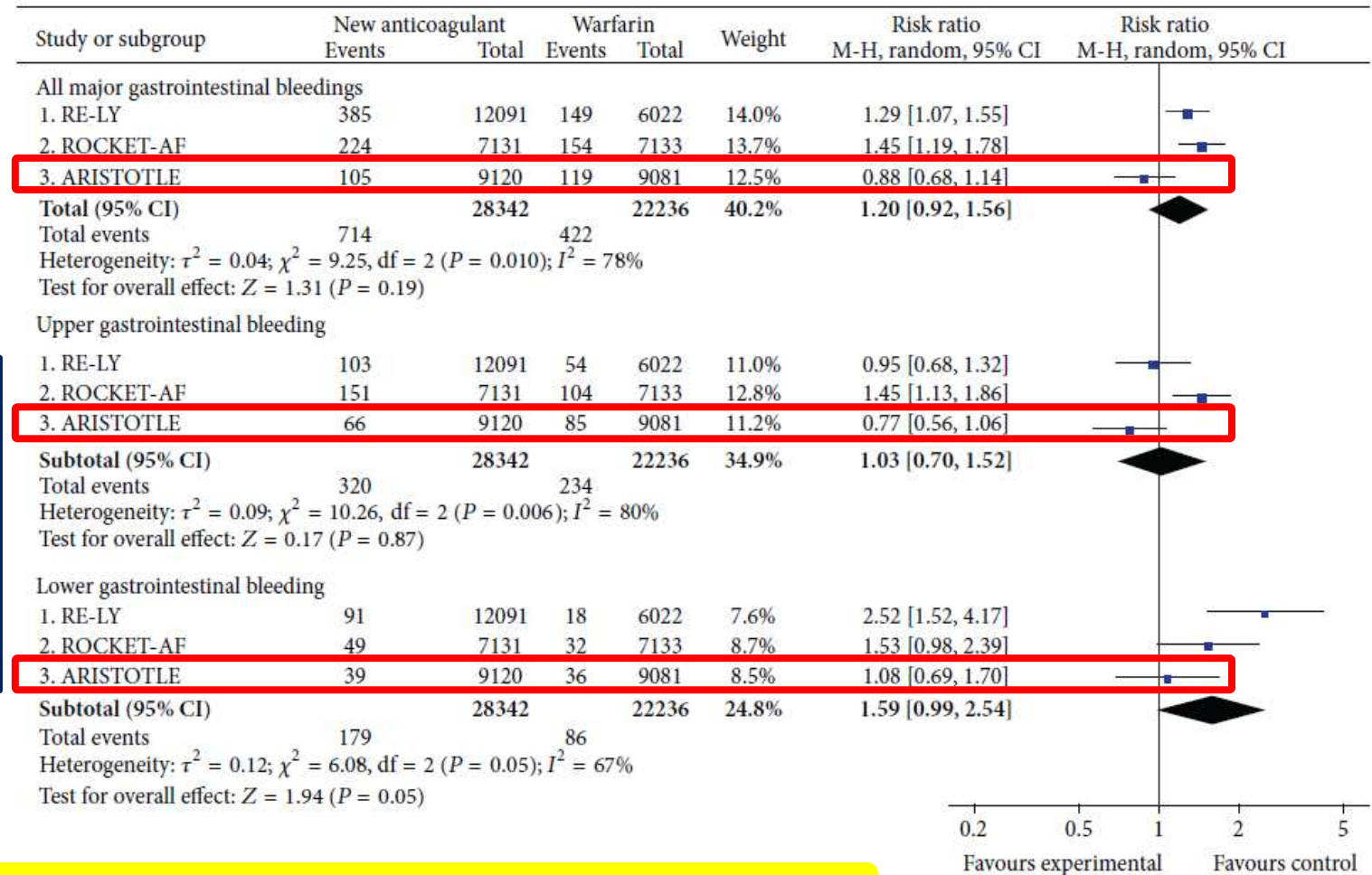


Lower GIB	Warfarin in 25%
	Dabigatran in 47%
	Rivaroxaban in 57%
Rectal B	Warfarin 29%
	Rivaroxaban 30%
Upper GIB	Warfarin in 47%
	Dabigatran in 43%
	Rivaroxaban in 48%

Hémorragies Digestives Majeures et FANV : Essais Cliniques et Vraie Vie



Sites des Hémorragies Digestives : AOD vs. Warfarine



There are no head-to-head randomised clinical trials comparing the NOACs.
Comparisons cannot be made between individual NOACs based on these data.

Gastro-Intestinal Bleeding and DOACs in Real Life

Retrospective cohort study based on medical and pharmacy claims data from OptumLabs Data Warehouse (includes private insurance and Medicare Advantage enrollees)

- 3 Matched cohorts (apixaban vs dabigatran, apixaban vs rivaroxaban, and rivaroxaban vs dabigatran) were generated via 1:1 propensity-score matching
- Following propensity-score matching, baseline sociodemographic, comorbidity, and pharmacologic-related risk factors were found to be similar
- Cox proportional hazards models, stratified by age, were used to estimate rates of total GI bleeding (18–64 years, 65–74 years, 75 years and older)
- Sensitivity analysis were conducted to examine for bias associated with secular trends in DOAC availability. Cox regression was performed limiting the cohort to those who had an index date between January 1, 2013 and February 28, 2015, the time corresponding to availability of all DOACs of interest. Patients at 6 months were censored to minimize potential impact of variable follow-up associated with each drug

Eligible patients*
n = 43,303

Apixaban
n = 6,576

Dabigatran
n = 17,426

Rivaroxaban
n = 19,301

* Eligible patients before propensity-score matching

Study population

- **Included:** Adult NVAF patients, 18 years of age or older, were identified by their index prescription of dabigatran, rivaroxaban, or apixaban between October 1, 2010 and February 28, 2015. The date of the first filled prescription was considered the index date and used to assign patients to a subcohort of exposure
- **Excluded:** Patients with any prior dispensed prescription for a DOAC during the 12 months before index date and those who lacked evidence of 12 months' continuous enrollment in the medical and pharmacy plan, which was defined as the baseline period. To be included, patients were required to have at least 1 inpatient or outpatient AF diagnostic code (ICD-9-CM code 427.31) at baseline. Patients with valvular heart disease, chronic hemodialysis, or peritoneal dialysis and kidney transplant were excluded
- **Follow-up:** Until end of study period, death, disenrollment, discontinuation, or switching
- **Dosing:** Study publication did not specify OAC dosage

Gastro-Intestinal Bleeding and DOACs in Real Life

Events, n	IR	Events, n	IR	HR (95% CI)	ARR (95% CI)	NNH
Rivaroxaban (n = 15,787)		Dabigatran (n = 15,787)		Rivaroxaban vs dabigatran (n = 31,574)		
222	2.74	215	2.02	1.20 (1.00 to 1.45)	0.72* (0.27 to 1.17)	139
Apixaban (n = 6,542)		Dabigatran (n = 6,542)		Apixaban vs dabigatran (n = 13,084)		
33	1.38	121	2.73	0.39* (0.27 to 0.58)	-1.35* (-2.0 to -0.67)	74
Apixaban (n = 6,565)		Rivaroxaban (n = 6,565)		Apixaban vs rivaroxaban (n = 13,130)		
32	1.34	116	3.54	0.33* (0.22 to 0.49)	-2.20* (-3.00 to -1.40)	45

Note: *p* value in the table is for interaction. **p* < 0.001 indicates significance for the HR.

**There are no adequate and well-controlled head-to-head RCTs comparing efficacy and safety of apixaban to any of the other DOACs.
Hence, the analysis presented does not imply a comparison of efficacy, safety, or product interchangeability.**

ARR: absolute risk reduction; CI: confidence interval; GI: gastrointestinal; HR: hazard ratio; IR: incidence rate per 100 person-years;

NNH: number needed to harm.

Abraham et al. *Gastroenterology*. 2017;152(5):1014-1022

Gastro-Intestinal Bleeding and DOACs in Real Life

Variable	Events, n	IR	Events, n	IR	HR (95% CI)	<i>p</i> for interaction
	Rivaroxaban (n = 15,787)		Dabigatran (n = 15,787)		Rivaroxaban vs dabigatran (n = 31,574)	
Age						
18–64 y	26	1.05	14	0.46	2.03* (1.06–3.90)	0.10
65–74 y	66	2.54	54	1.56	1.44* (1.00–2.06)	
≥ 75 y	130	4.29	147	3.54	1.06 (0.84–1.34)	
	Apixaban (n = 6,542)		Dabigatran (n = 6,542)		Apixaban vs dabigatran (n = 13,084)	
18–64 y	2	0.34	7	0.73	0.38 (0.08–1.84)	0.54
65–74 y	5	0.69	29	2.12	0.25** (0.10–0.65)	
≥ 75 y	26	2.43	85	4.06	0.45*** (0.29–0.71)	
	Apixaban (n = 6,565)		Rivaroxaban (n = 6,565)		Apixaban vs rivaroxaban (n = 13,130)	
18–64 y	2	0.34	6	0.81	0.38 (0.08–1.89)	0.36
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥ 75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

Note: p value in the table is for interaction.*p < 0.05; **p < 0.01; ***p < 0.001; indicates significance for the HR.

**There are no adequate and well-controlled head-to-head RCTs comparing efficacy and safety of apixaban to any of the other DOACs.
Hence, the analysis presented does not imply a comparison of efficacy, safety, or product interchangeability.**

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Hémorragies Digestives : Faire Mieux chez le Vieux?

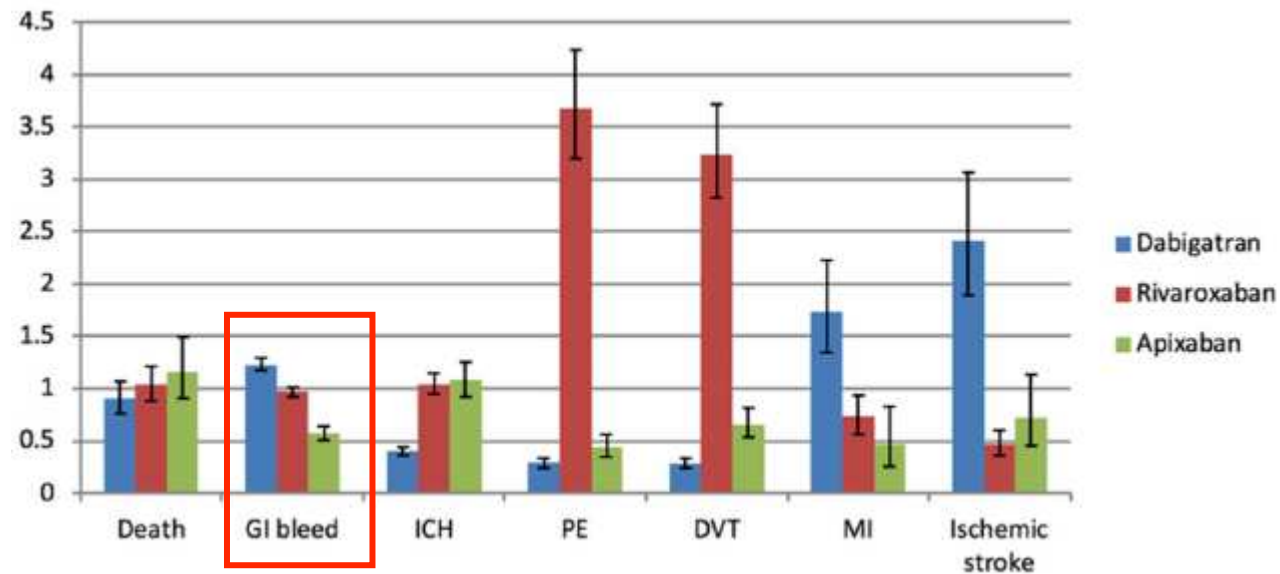
	riva 15 787	dabi 15 787	
pop totale	2.7 %	2.0 %	1.20 [1.0 – 1.5]
• >75ans	4.3 %	3.5 %	1.06 [0.8 – 1.3]

	apix 6 542	dabi 6 542	
pop totale	1.4 %	2.7 %	0.38 [0.1 – 0.6]
• >75ans	2.4 %	4.1 %	0.45 [0.3 – 0.7]

	apix 6 565	riva 6 565	
pop totale	1.3 %	3.5 %	0.38 [0.1 – 0.6]
• >75ans	2.3 %	5.1 %	0.39 [0.3 – 0.6]

A COMPARATIVE ANALYSIS OF THE SAFETY PROFILE OF DOACS USING THE FDA ADVERSE EVENT REPORTING SYSTEM

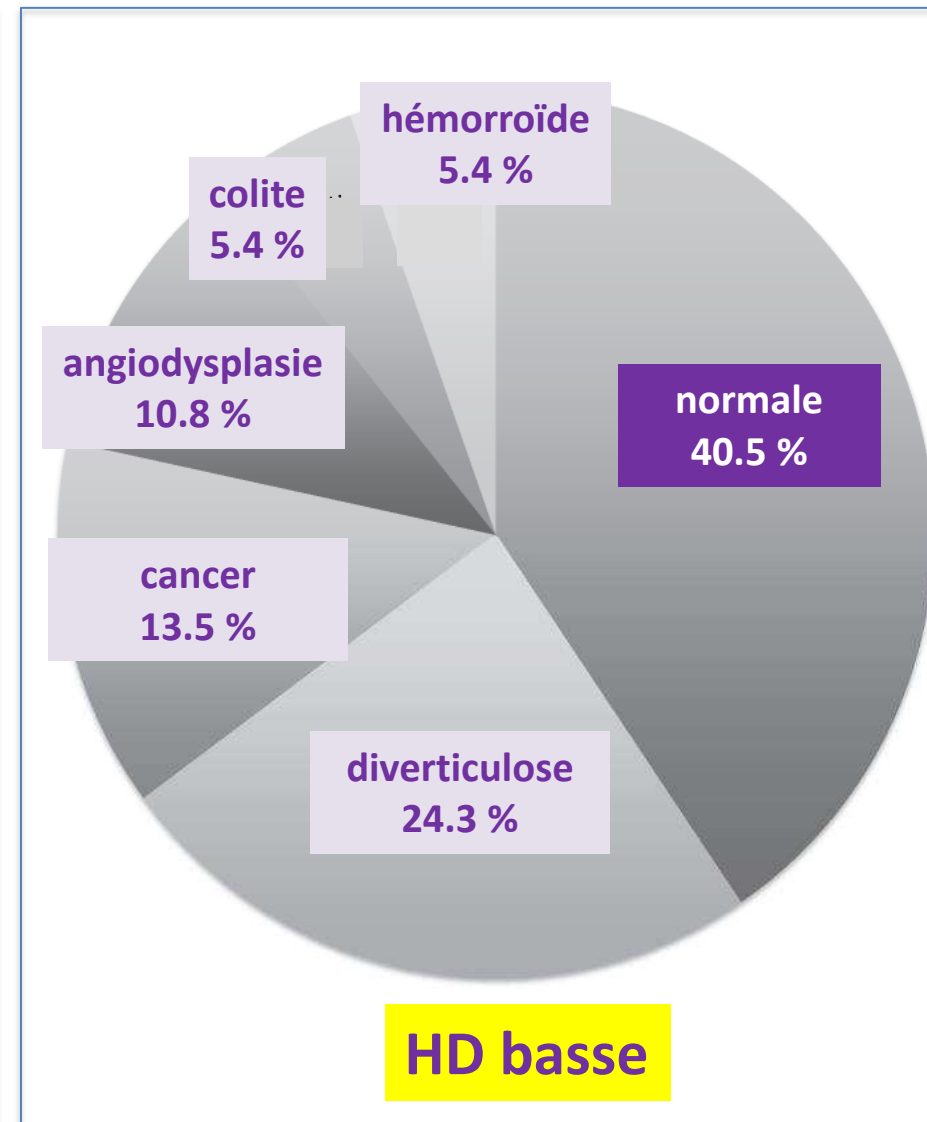
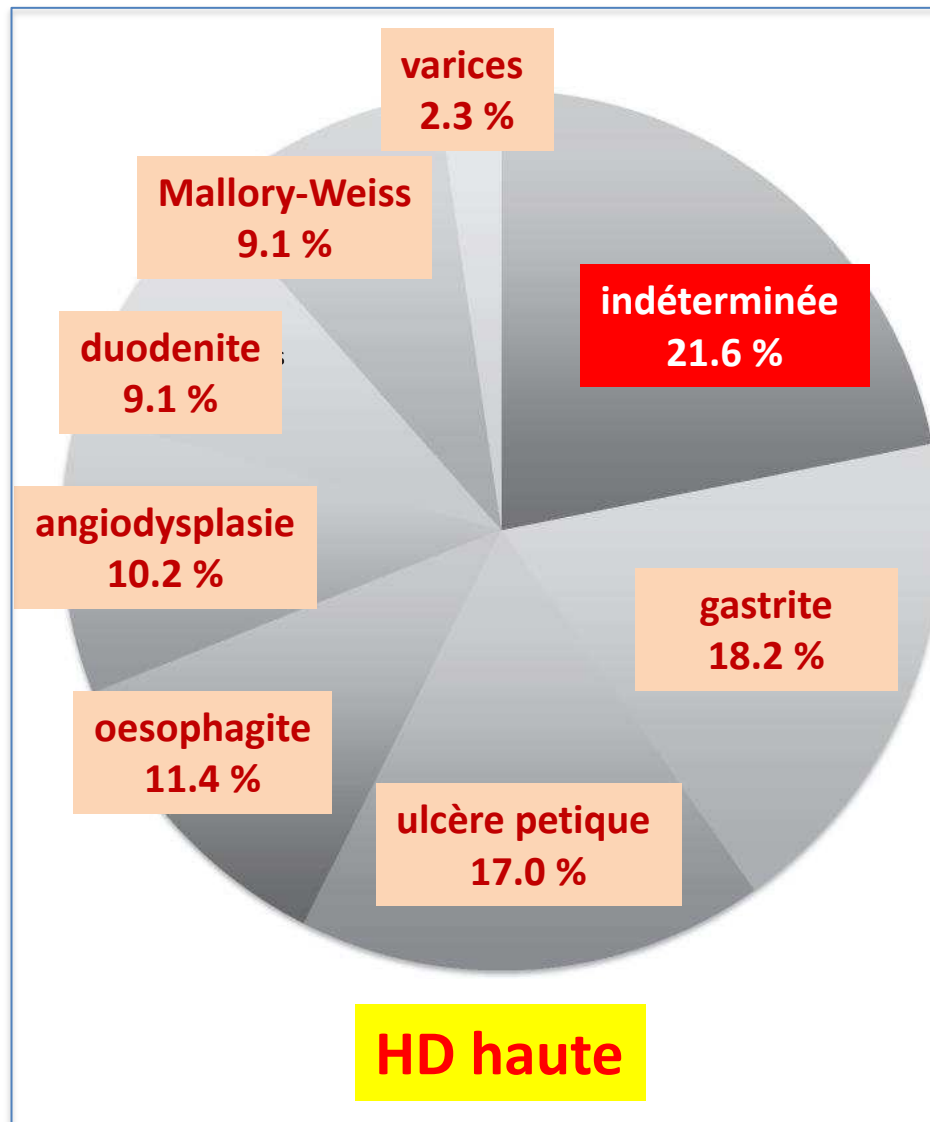
- FDA Adverse Event Reporting System (FAERS) supports FDA's post-marketing safety surveillance program
- Comparisons of total adverse events (n=42,964) per prescription from 2004–2015 for warfarin (n=10,909)
2010–2015 for dabigatran (n=10,850)
2012–2015 for rivaroxaban (n=17,962)
2014–2015 for apixaban (n=3243)



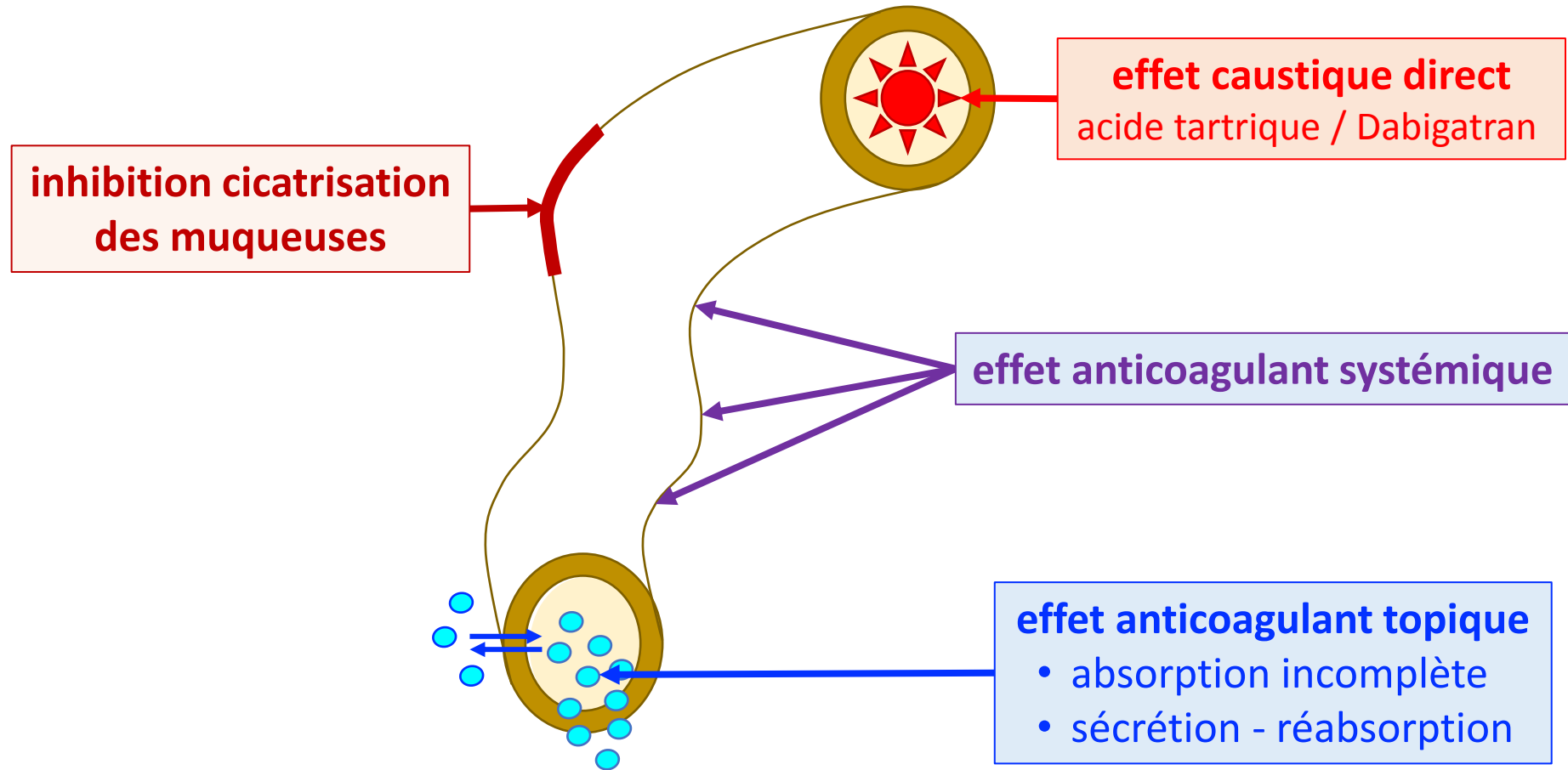
A COMPARATIVE ANALYSIS OF THE SAFETY PROFILE OF DOACS USING THE FDA ADVERSE EVENT REPORTING SYSTEM

	Warfarin	Dabigatran	PRR	Rivaroxaban	PRR	Apixaban	PRR
Cases	10909	10850	1,23	17962	1,04	3243	0,57
Prescriptions	323584946	13236206		11977071		4636173	
Death	135 (4.17×10^{-7})	183(1.38×10^{-5})	0.90 (0.76–1.07)	330(2.76×10^{-5})	1.04 (0.88–1.22)	67 (1.45×10^{-5})	1.16 (0.90–1.49)
GI bleed	1107 (3.42×10^{-6})	2036(1.54×10^{-4})	1.23 (1.17–1.30)	2910(2.43×10^{-4})	0.97 (0.92–1.02)	318 (6.86×10^{-5})	0.57 (0.51–0.64)
ICH	433 (1.34×10^{-6})	530(4.00×10^{-5})	0.40 (0.36–0.44)	941(7.86×10^{-5})	1.04 (0.95–1.15)	178 (3.84×10^{-5})	1.08 (0.92–1.25)
PE	202 (6.24×10^{-7})	169(1.28×10^{-5})	0.29 (0.25–0.34)	1084(9.05×10^{-5})	3.68 (3.20–4.24)	62 (1.34×10^{-5})	0.44 (0.34–0.57)
DVT	263 (8.13×10^{-7})	162(1.22×10^{-5})	0.28 (0.24–0.33)	1033(8.63×10^{-5})	3.24 (2.83–3.72)	88 (1.90×10^{-5})	0.65 (0.53–0.81)
MI	67 (2.07×10^{-7})	114(8.61×10^{-6})	1.73 (1.34–2.22)	117(9.77×10^{-6})	0.73 (0.57–0.94)	12 (2.59×10^{-6})	0.46 (0.26–0.82)
Ischemic stroke	20 (6.18×10^{-8})	148(1.12×10^{-5})	2.41 (1.90–3.06)	100(8.35×10^{-6})	0.47 (0.36–0.60)	20 (4.31×10^{-6})	0.72 (0.45–1.13)

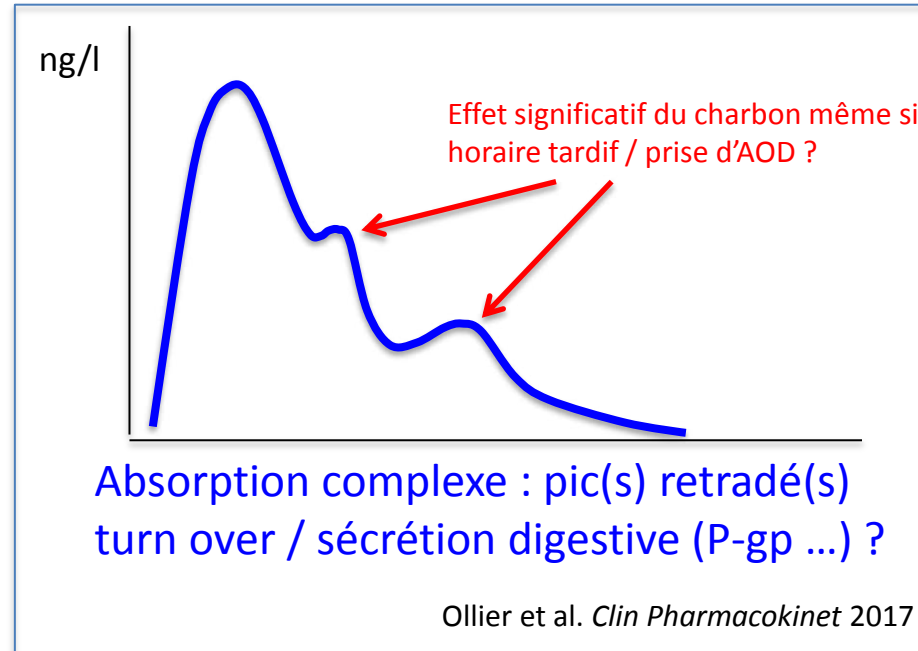
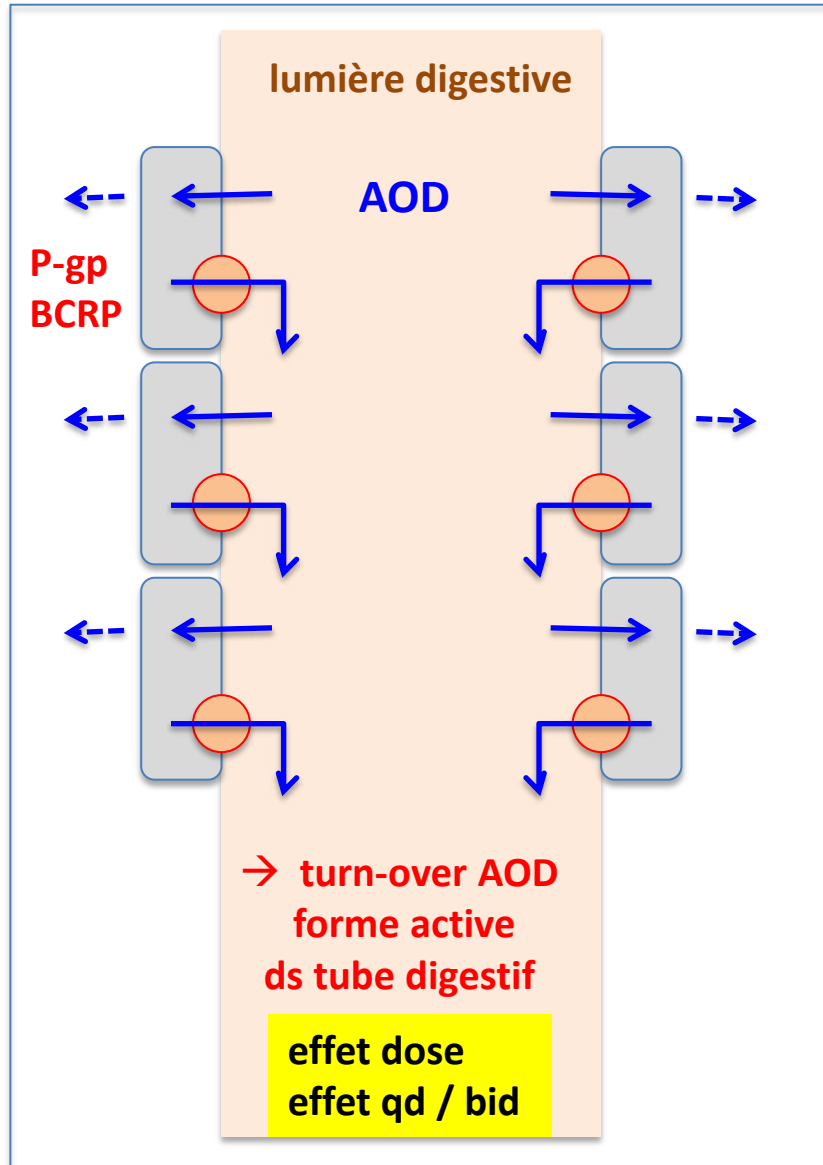
Hémorragies Digestives: Localisations Endoscopiques



Hémorragies Digestives: Hypothèses Physiopathogéniques



Hémorragies Digestives: Hypothèses Physiopathogéniques



vulnérabilité de la muqueuse intestinale et turn-over digestif des AOD

- érosions gastro-duodénales
→ 5 à 10 % des volontaires sains
- érosions intestin grêle
→ 10 à 15 % des volontaires sains

Desai et al. *Thromb Haemost* 2013

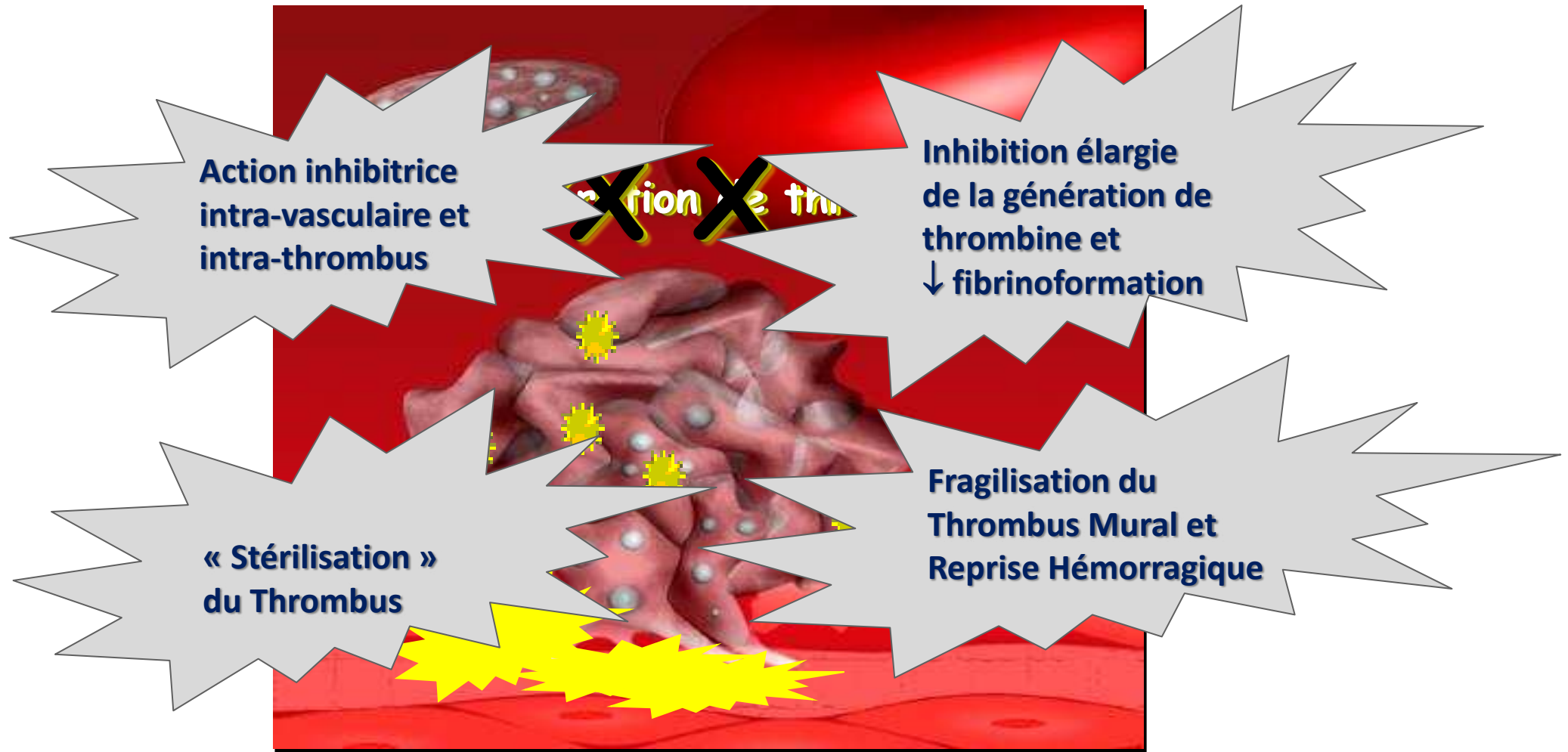
Constantes d'Association et Pharmacodynamique Apixaban et Rivaroxaban

AOD inhibiteurs spécifiques, réversibles et compétitifs des FXa ou FIIa
Caractérisés par des constantes d'inhibition (K_i) et d'association (K_{on})

	Apixaban	Rivaroxaban
K_{Iapp} (nM)	5.60 ± 0.20	3.55 ± 0.13
K_I (nM)	0.74 ± 0.03	0.47 ± 0.02
k_{obs} ($M^{-1}s^{-1}$)	$0.97 \pm 0.21 \cdot 10^6$	$0.38 \pm 0.08 \cdot 10^7$
k_{on} ($M^{-1}s^{-1}$)	$7.30 \pm 1.60 \cdot 10^6$	$2.90 \pm 0.60 \cdot 10^7$

- Affinité pour le FXa : Rivaroxaban > Apixaban (x1.5 plus grande)
- Neutralisation du FXa : Rivaroxaban > Apixaban (x4 plus rapide)
- Liaison aux protéines plasmatiques : Rivaroxaban > Apixaban

AOD Inhibiteur Intégral et Intime de la Thrombinoformation



Hémorragies Digestives: Facteurs Prédicatifs

14 236 pts – 684 M+CRNM HD - 4.8 %

→ 5.5 % sous Riva – 4.1 % sous AVK) ROCKET-AF

• anémie à l'inclusion	1.70 [1.4 – 2.0]	<0.001
• ATCD Hgie Digestive	2.11 [1.6 – 2.8]	<0.001
• ASA	1.47 [1.3 – 1.7]	<0.001
• Riva vs AVK	1.42 [1.2 – 1.7]	<0.001



**masculin, âgé, ATCD d'hémorragie digestive,
anémie, insuffisance rénale, antiplaquettaire**



• IPP inclusion	1.36 [1.1 – 1.7]	0.002
• ClCr (↗ ts les ↘ 5 unités <60)	1.06 [1.0 – 1.1]	0.015
• BPCO	1.30 [1.1 – 1.6]	0.016
• masculin	1.21 [1.0 – 1.4]	0.037
• AAP (autres que ASA)	1.50 [0.2 – 2.2]	0.039

Hémorragies Digestives: Prévention Primaire?

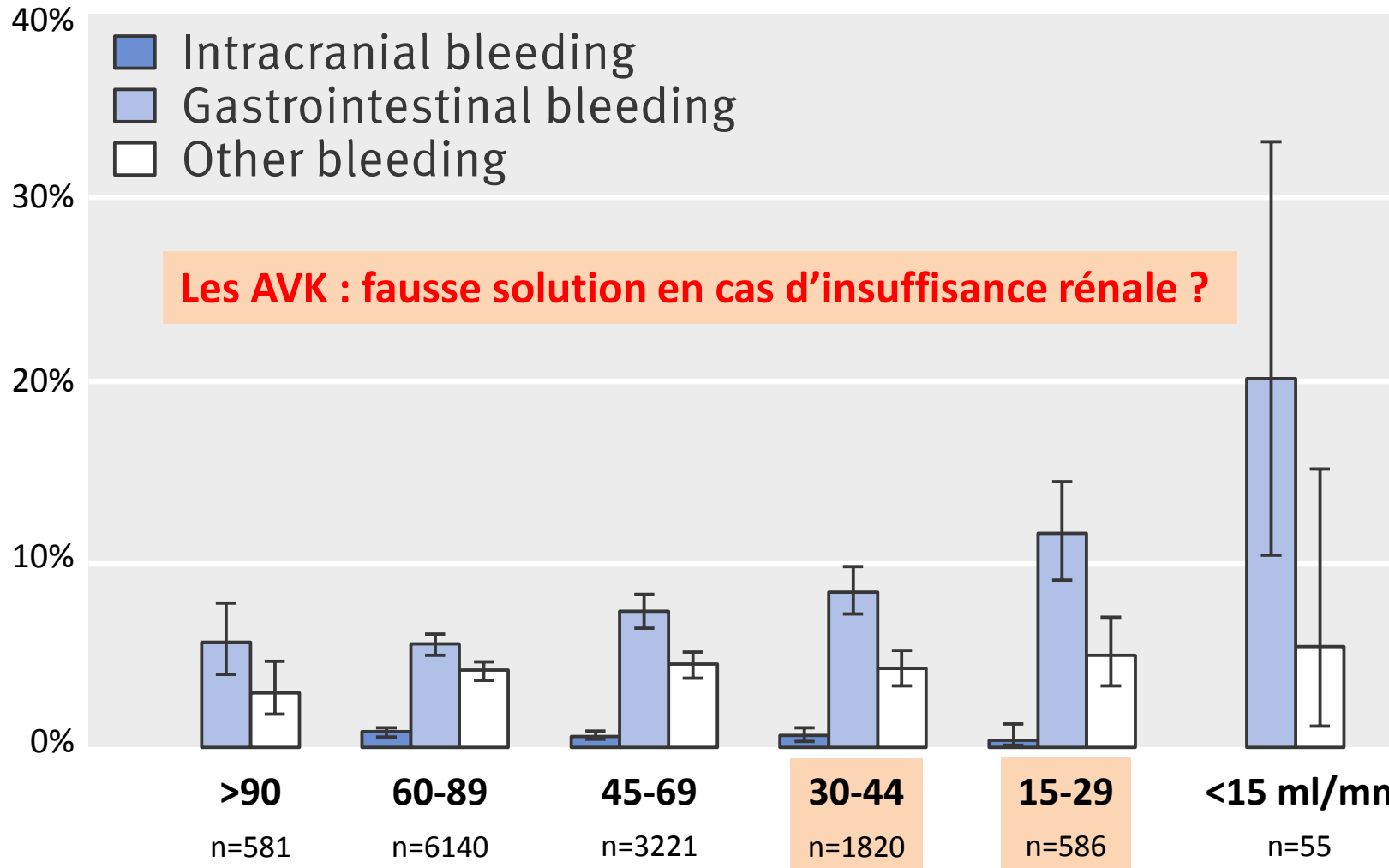
- Intérêt des IPP => *si HD Haute*
- Eradication Helicobacter Pylori => *si HD Haute*
- Bilan endoscopique (ATCD-anémie) => *si Lésion Evolutive ?*
- Discuter association AAP +++ => *Rapport Bénéfice/Risque?*
- Eviter antidépresseurs type ISRS => *Thrombopathie?*
- Discuter dose réduite AOD ou plutôt préférence apixaban
=> *Eviter AVK notamment si Ins. Rénale?*

MANAGEMENT OF GI BLEEDING

Recommendations	Class	Level
Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding.	IIa	B
When dabigatran is used, a reduced dose (110 mg twice daily) may be considered in patients >75 years to reduce the risk of bleeding.	IIb	B
In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.	IIa	B
Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC.	IIa	C
Genetic testing before the initiation of VKA therapy is not recommended.	III (no benefit)	B
Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke prevention interventions, improved management of factors that contributed to bleeding, and stroke risk.	IIa	B
In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the cause of bleeding is resolved.	I	C

Hémorragies Digestives: AVK si Insuffisance Rénale?

Etude rétrospective : 12 403 pts en FA sous AVK de 2003 – 2010 – estimation CLCr / CKD-EPI
suivi médian 2 ans



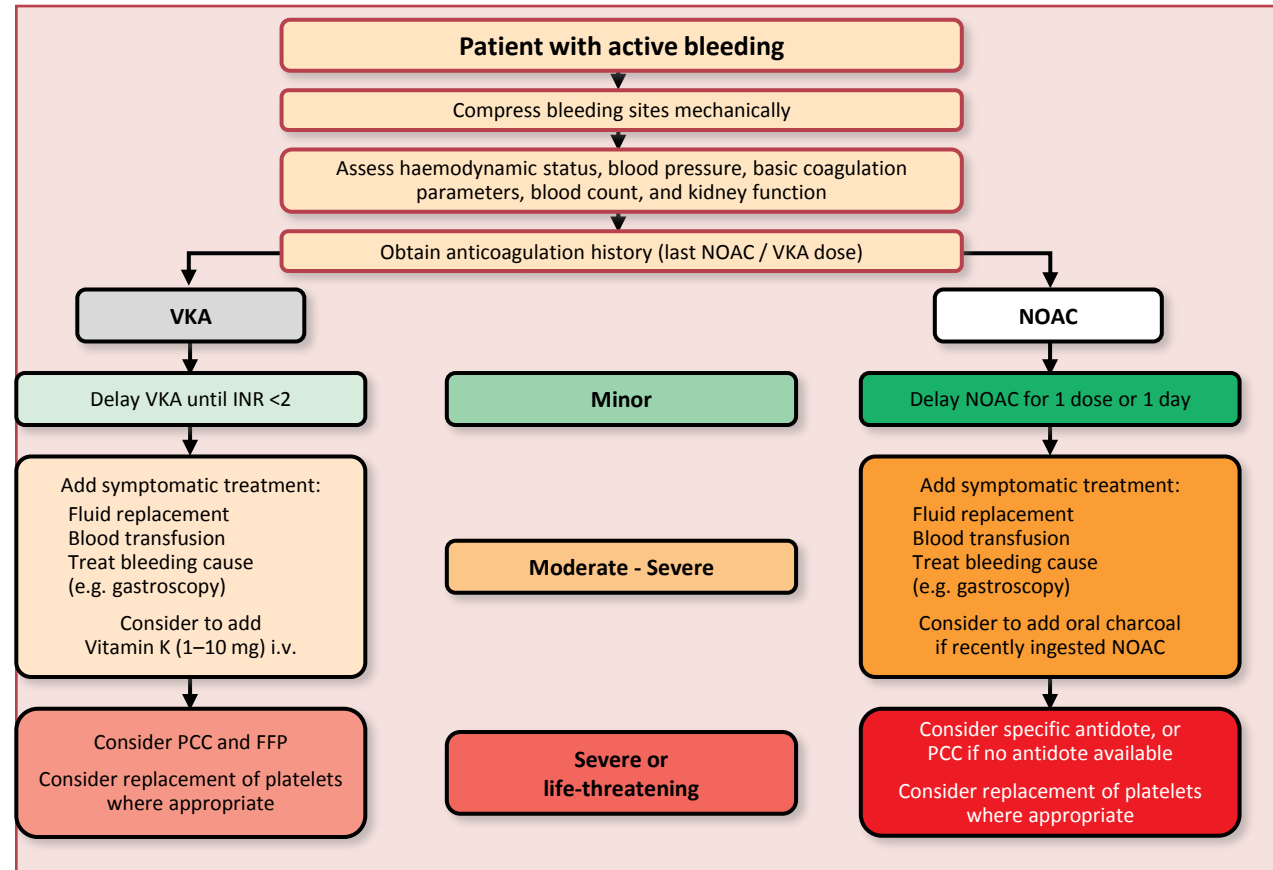
Gestion des Hémorragies

Comprendre... Colmater... Corriger... Compenser... Contrôler...

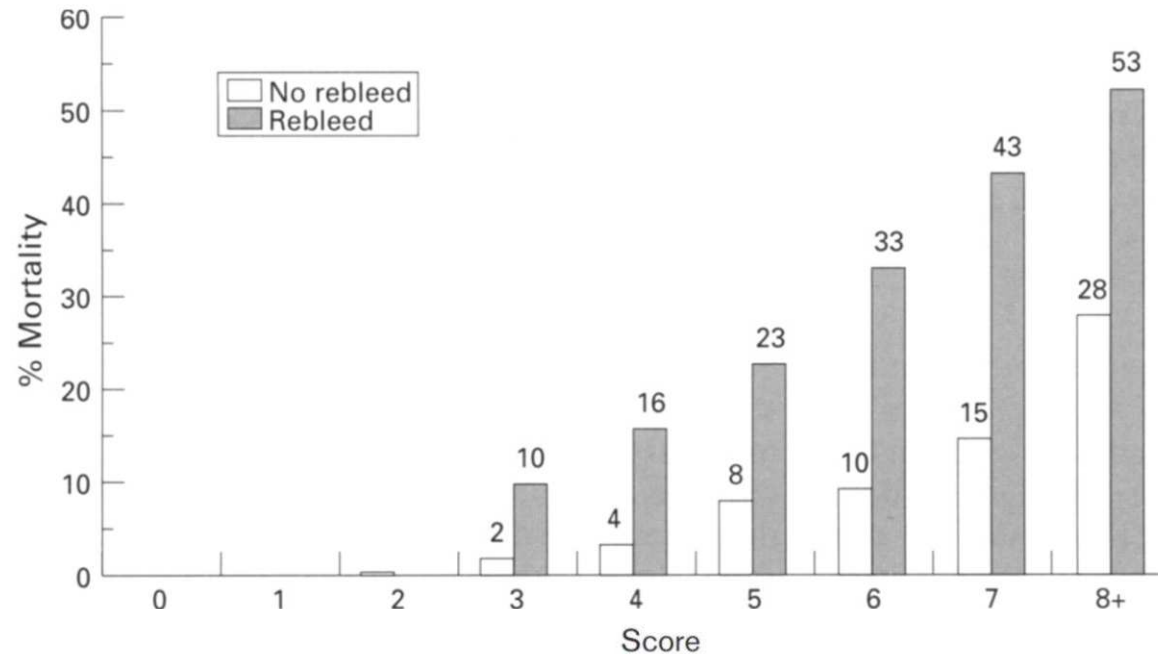
Profil patient
Délai apparition de l'Hgie?
Délai dernière prise AOD?
Fonction rénale?
Anémie <80g/L?
Comorbidités?

Si HD haute
Score de Risque?
Endoscopie et clip?

Si HD basse
Score sévérité?
Coloscopie différée?



Hémorragie Digestive Haute : ROCKALL Score



Component	0	1	2	3
Age (years)	< 60	60 – 79	≥ 80	
Pulse rate (beat/min)	< 100	≥ 100		
SBP (mmHg)	≥ 100	≥ 100	< 100	
Comorbidity	None	None	IHD, cardiac failure, any other major comorbidity	Renal failure, liver failure or disseminated malignancy
Diagnosis	Mallory – Weiss lesions or no lesion, no SRH	All other diagnoses	Malignant lesions of the upper-gastrointestinal tract	
Stigmata of recent haemorrhage	No stigmata or dark spot in ulcer base		Any other signs	

Elimination des AOD et Fonction Rénale

CrCl (ml/min)	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
> 80	14	8	7 - 8	8 – 9
50 - 79	17	9	7 - 8	8 – 9
30 - 49	19	9	17 - 18	9 – 10
15 - 29	28	10	17 - 18	17
< 15	NA	NA	NA	NA

Burnett et al J Thromb Thrombolysis 2016; 41: 206-232.

Dabigatran

- Estimate normalization of plasma levels:
 - Normal renal function: 12–24 h
 - CrCl 50–80 mL/min: 24–36 h
 - CrCl 30–50 mL/min: 36–48 h
 - CrCl <30 mL/min: ≥48 h
- Maintain diuresis

Anti-Xa DOACs

- Normalization of plasma levels: 12–24 h

Steffel et al Eur Heart J 2018; 39: 1330-1393.

AOD et Intérêt des Tests de Coagulation

	Dabigatran	Rivaroxaban	Apixaban
■ ↗ TQ	+	++	±
■ ↗ TCA	++	+	±
■ ↗ TT	+++	-	-
■ Anti-Xa	-	++	++
■ Anti-IIa	++	-	-

Finie la Prise de Test...?

Activité Anticoagulante Ciblée mais sans Cibles

Drug	Dose	Peak concentration (ng/mL)		Trough concentration (ng/mL)	
		Median	5th to 95th percentile	Median	5th to 95th percentile
Dabigatran [2]	150 mg BID	184	64–443 ^a	90	31–225 ^a
Rivaroxaban [3]	20 mg daily	270	189–419 ^b	26	6–87 ^b
Apixaban [4]	5 mg BID	171	91–321 ^b	103	41–230 ^b
Edoxaban [5]	60 mg daily	170	120–250 ^{b,c}	22	10–40 ^{b,c}

^a Based on direct measurement of clinical samples

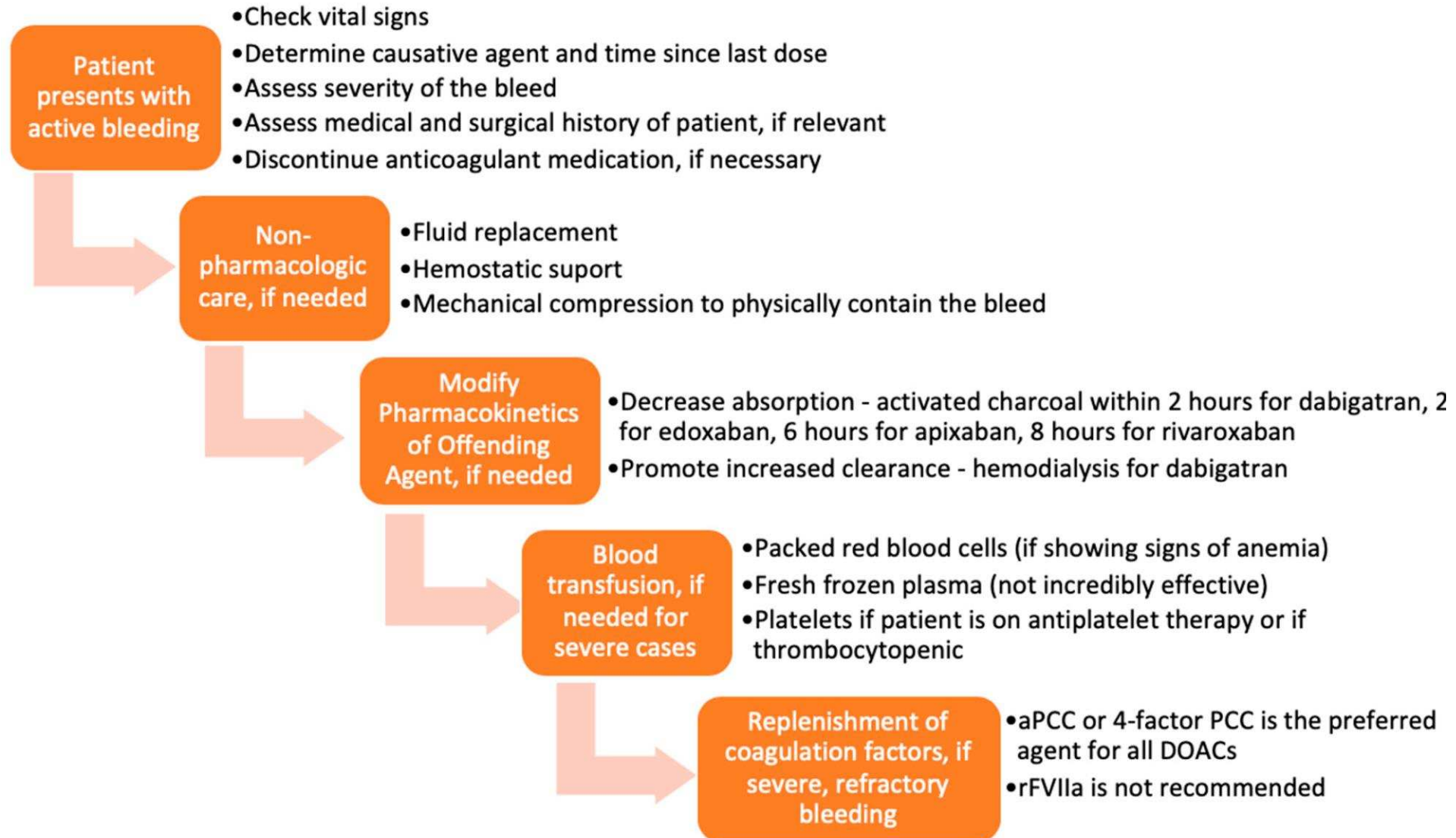
^b Based on pharmacokinetic modeling

^c Interquartile range

On-therapy levels

Cuker J Thromb Thrombolysis 2016

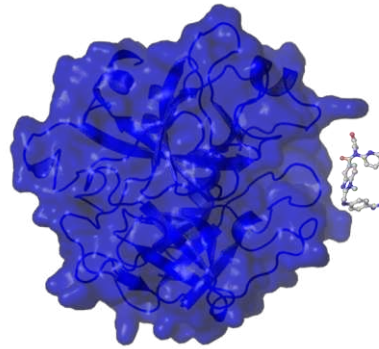
Bleeding Management in Absence of Antidotes



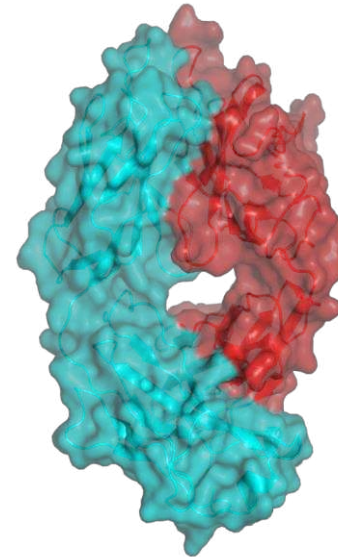
Dabigatran et Idarucizumab : Antidote par Détournement d'Inhibiteur



Fragment d'anticorps murin humanisé (Fab)



Thrombin
~37000 daltons



**Idarucizumab
(Fab)**
~47800 daltons

Affinité 350 x grande que celle du Dabigatran pour la Thrombine

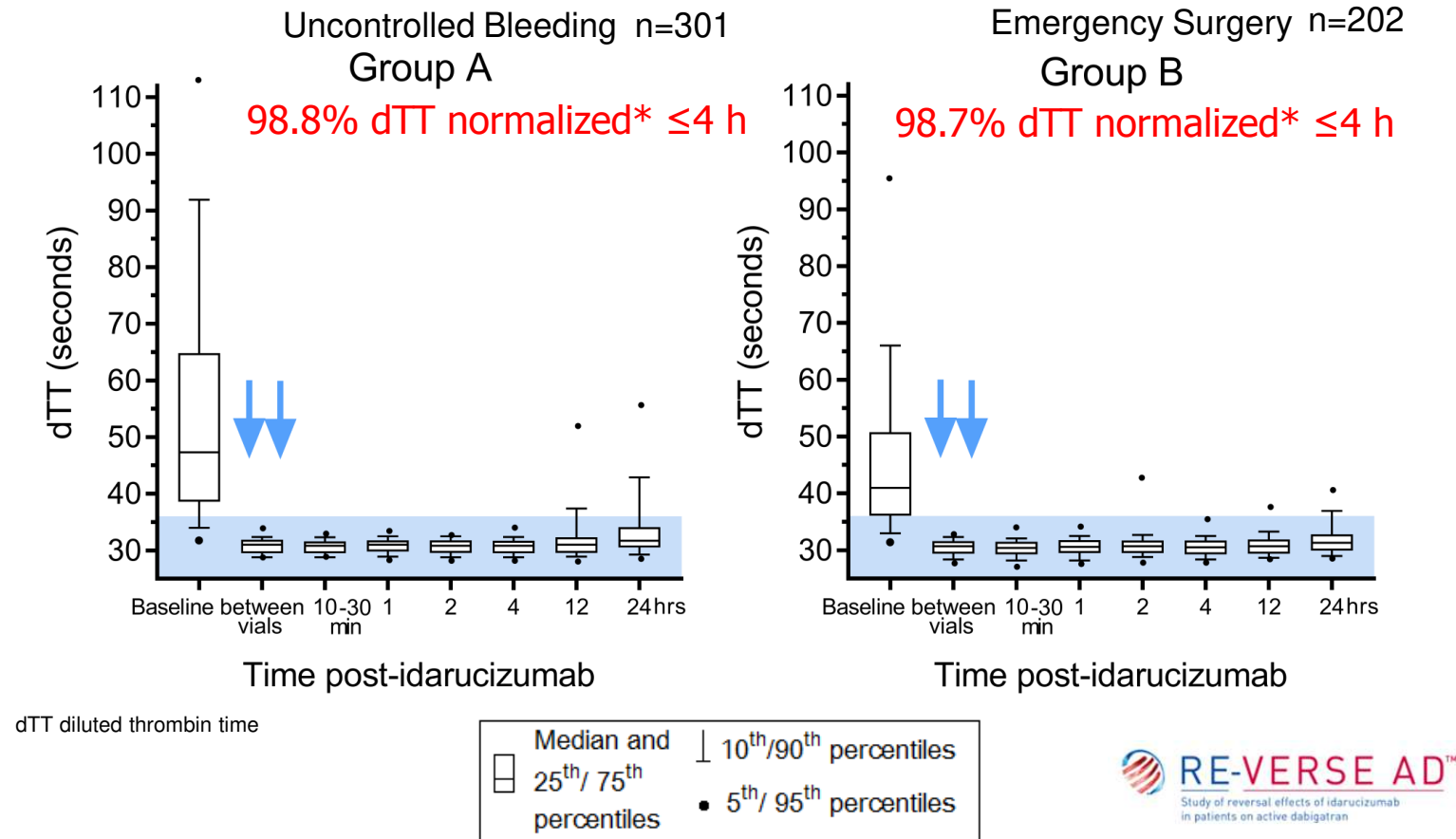
Demi-vie 45 min

Catabolisme protéique puis élimination rénale

Schiele F et al. Blood 2013

Pollack et al. Thromb Haemost 2015

Résultats : Normalisation du Temps de Thrombine Diluée par Inhibition Immédiate et Durable



Groupe A: Arrêt du Saignement en 2.5 h chez les Patients ayant une Hémorragie Extra-Crânienne

301 patients with bleeding type classed as:



Assessable non-ICH (n=198)
ICH (non-assessable)* (n=98)
Non-assessable non-ICH (n=5)

The 198 assessable non-ICH bleeds[†] were:



GI (n=120)
Non-GI (n=78)

With a median time to bleeding cessation[‡] of:



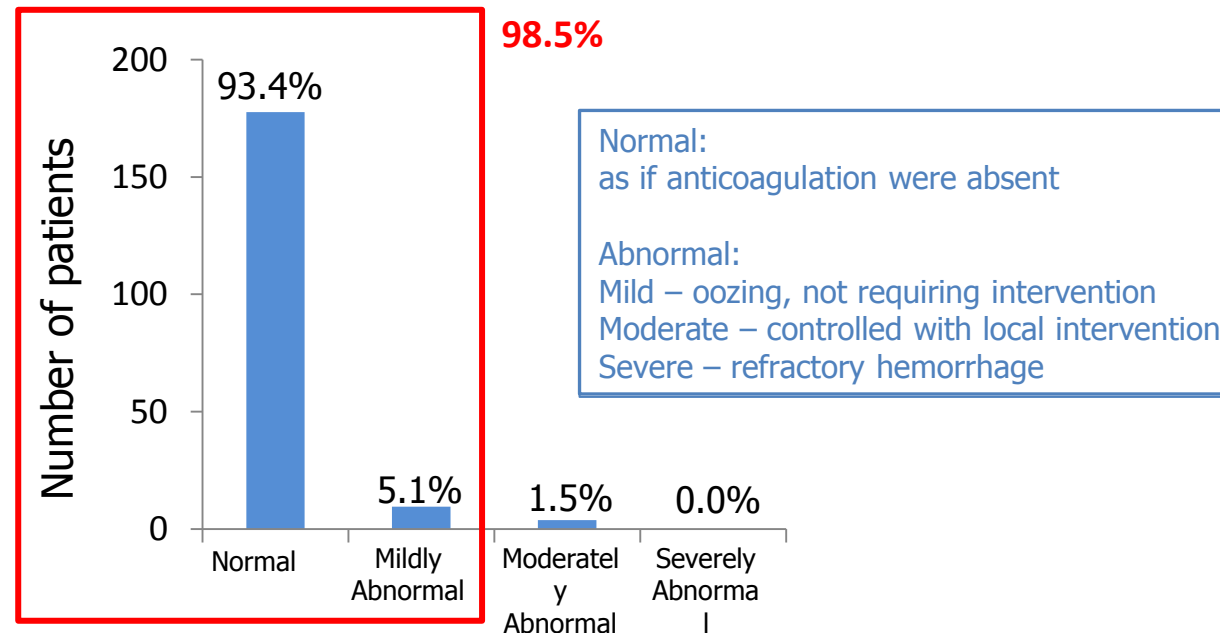
2.5 hrs

*Serial CT scans were not mandated by the protocol; [†]Cessation confirmed within 24 hours in 134/198 – bleeding stopped before treatment in two patients and could not be determined in 67 patients; [‡]Local investigator-determined time to bleeding cessation. Pollack et al. N Engl J Med 2017; Pollack et al. Presented at ISTH 2017

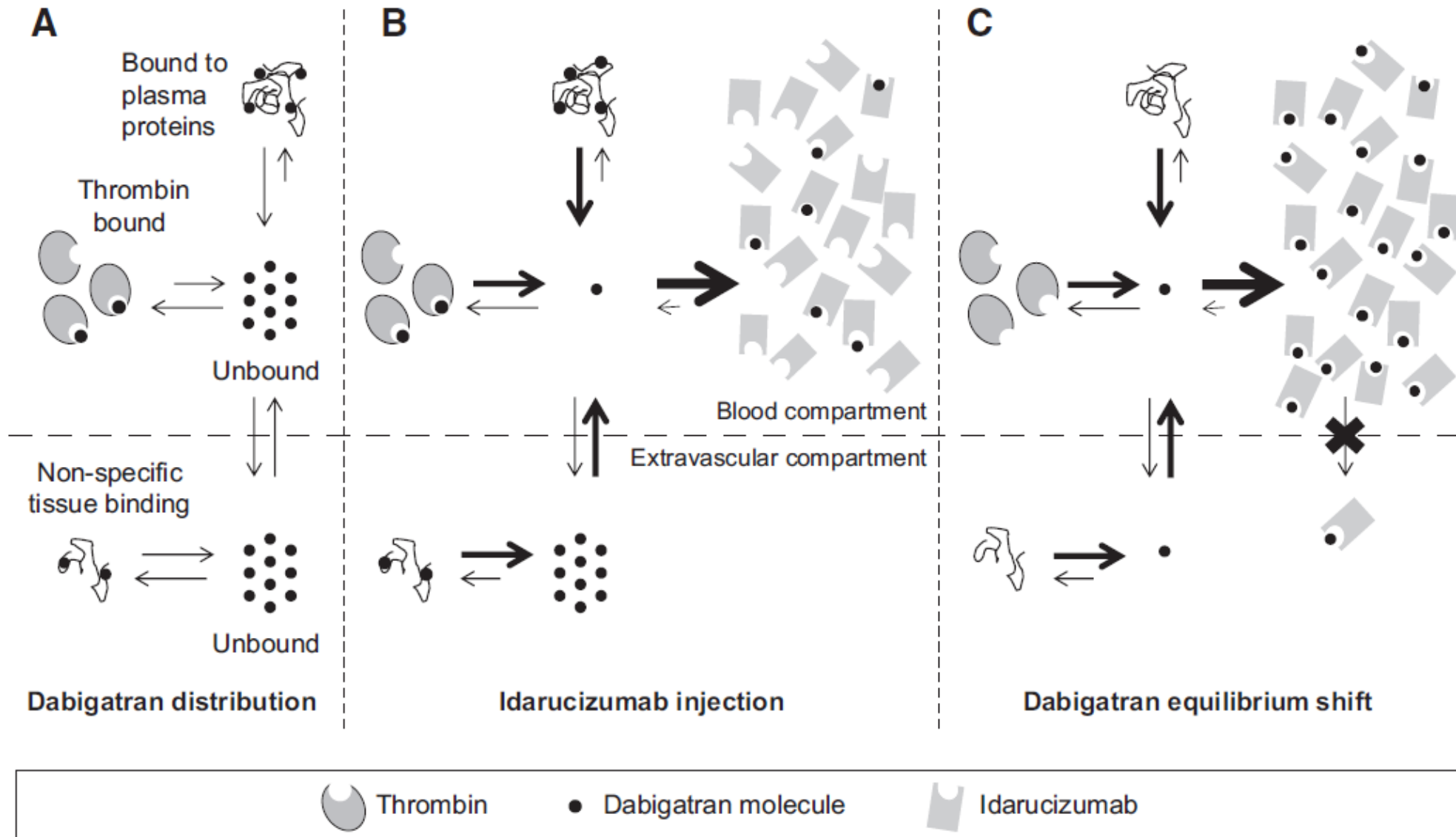
27

Groupe B: Hémostase Péri-Opératoire

- 197 of 202 (97.5%) patients underwent anticipated surgery/procedures
- Median time from administration of first vial to procedure was **1.6 hours**
- Adequacy of hemostasis during surgery determined locally



Dabigatran : Volume de Distribution et Recirculation



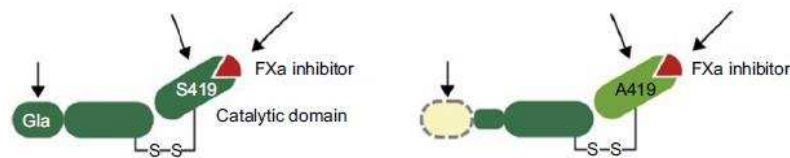
Attention si Recirculation de Dabigatran => 2^{ème} Neutralisation

« Increase of dTT at 12-24h (**114 pts**) unbound Dabigatran redistribution
From Extra- to Intra-vascular compartment but with bleeding in only **10 pts** »

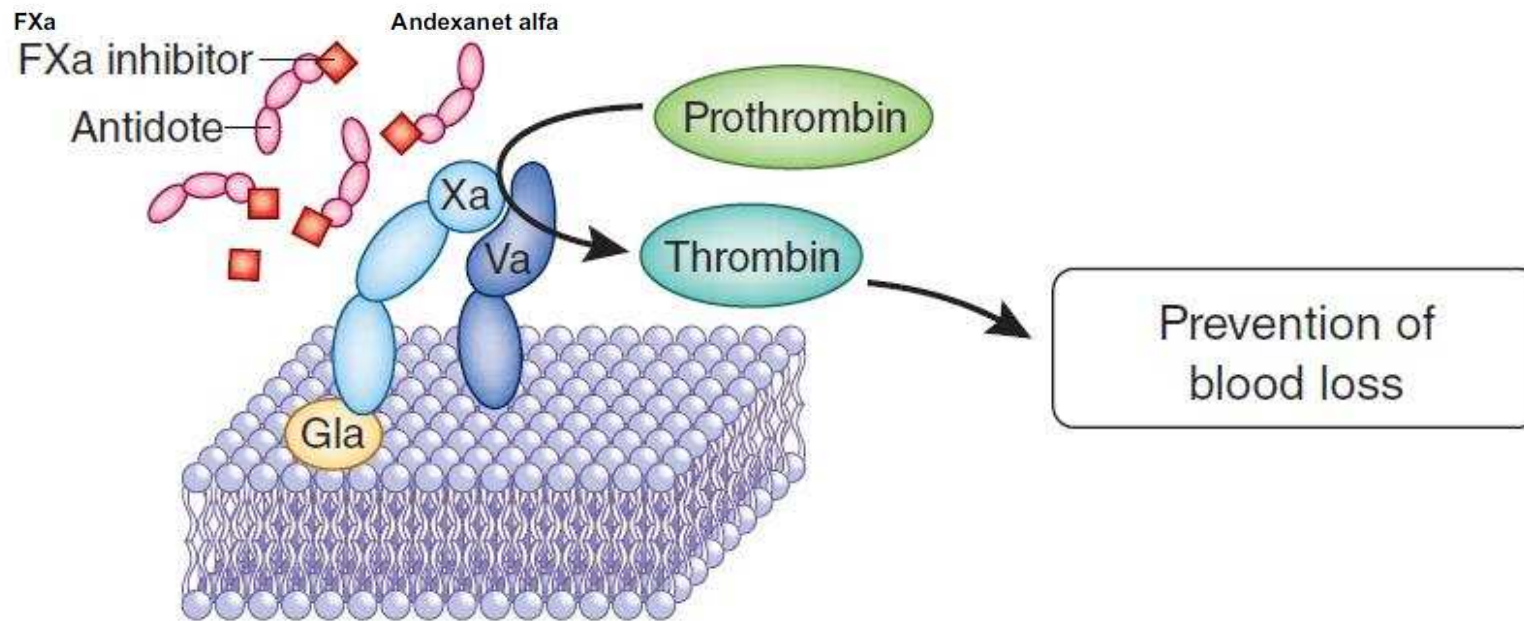
- 9 patients* received a second dose (1.8%)
- 4 in Group A due to re-bleeding ≥ 24 hours post first-dose of idarucizumab
- 4 in Group B due to post-operative bleeding or requiring a new procedure ≥ 12 hours post first-dose of idarucizumab

Group	Age/ Gender	Dose of Dabigatran (bid)	Index event	Unbound dabigatran (ng/mL)	Creatinine Clearance (mL/min)	Approximate Time to Additional dose	Reason for additional dose
A	60 M	110	Gastrointestinal bleed	955	25.7	48 hr	Recurrent bleeding
	79 M	110	Gastrointestinal bleed	325	43.4	36 hr	Recurrent bleeding
	76 M	110	Hematuria	1360	15.2	24 hr	Recurrent bleeding
	73 M	110	Gastrointestinal bleed	329	29.0	24 hr	Recurrent bleeding
B	85 F	75	Intestinal occlusion	51	31.2	5 days	New procedure
	73 F	150	Ischemic large bowel	1630	34.0	12 hr	Postoperative bleeding
	82 F	110	Catheter placement for dialysis	271	8.0	6 days	Postoperative bleeding
	70 M	110	Catheter placement for dialysis	240	18.6	3 days (dose 2) 8 days (dose 3)	Postoperative bleeding and new procedure

Andexanet-Alpha : Antidote des Anti-Xa



FXa Recombinant Humain servant de LEURRE
Pas d'activité catalytique (Ser 419=> Ala 419)
Pas de domaine Gla : sans activité procoagulante

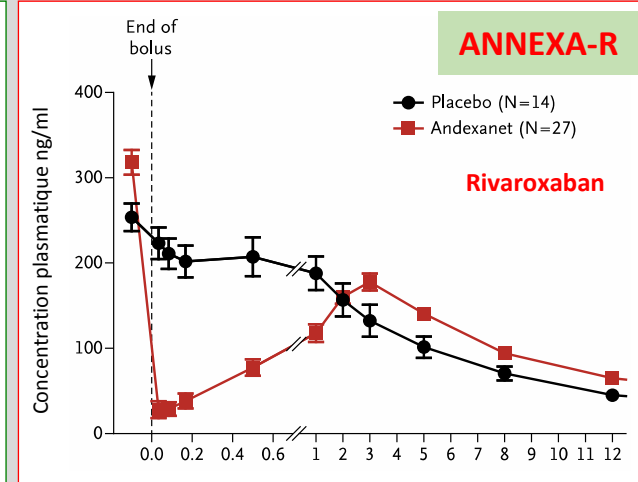
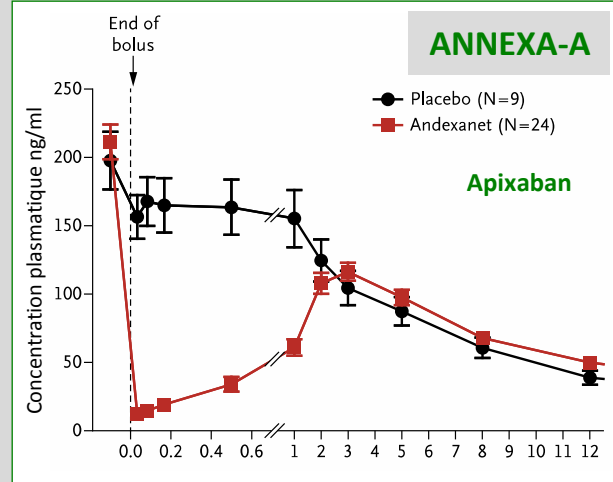


Antidote binds free
FXa inhibitor and allows activated
FX to convert prothrombin to
thrombin and restore coagulation

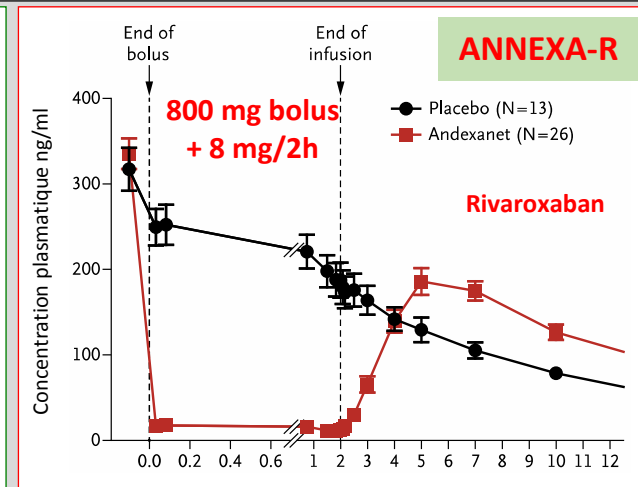
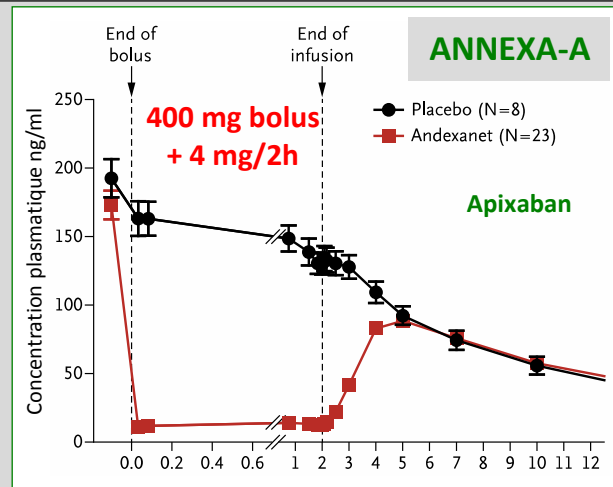
Ansell J Nature Medicine 2013

Andexanet-Alpha : Antidote des Anti-Xa

BOLUS andexanet



BOLUS + PERFUSION andexanet



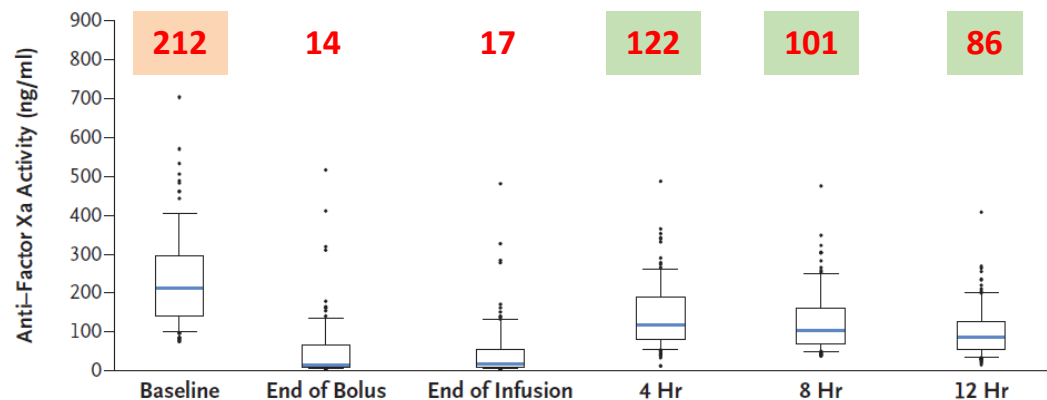
Efficacité d'Andexanet-Alpha : Etude Annexa-4

N = 254 (Efficacy) - 77 ans FA (80%) → GIB = 24% - HIC = 67% - autres = 9% andexanet à 5h ± 2 / admission

Dose d'andexanet < 7 h post-dose AOD : bolus **800 mg** + perf /2H **960 mg**

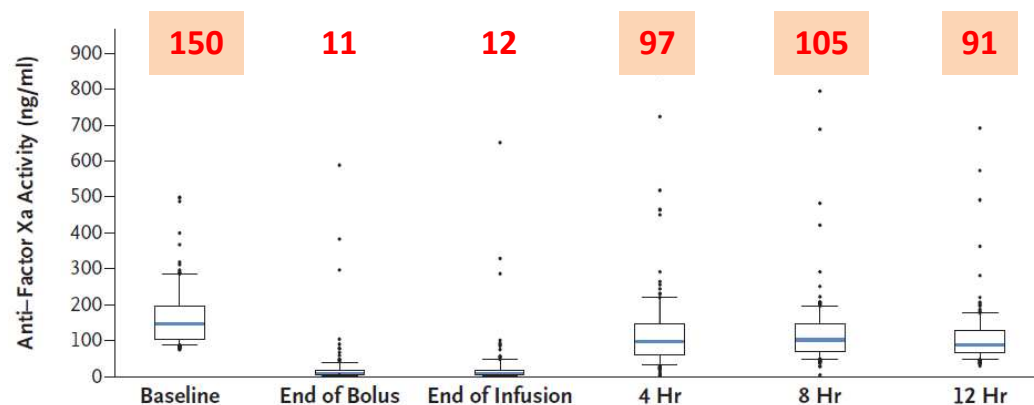
> 7 h post-dose AOD : bolus **400 mg** + perf /2H **480 mg**

Rivaroxaban : n = 100



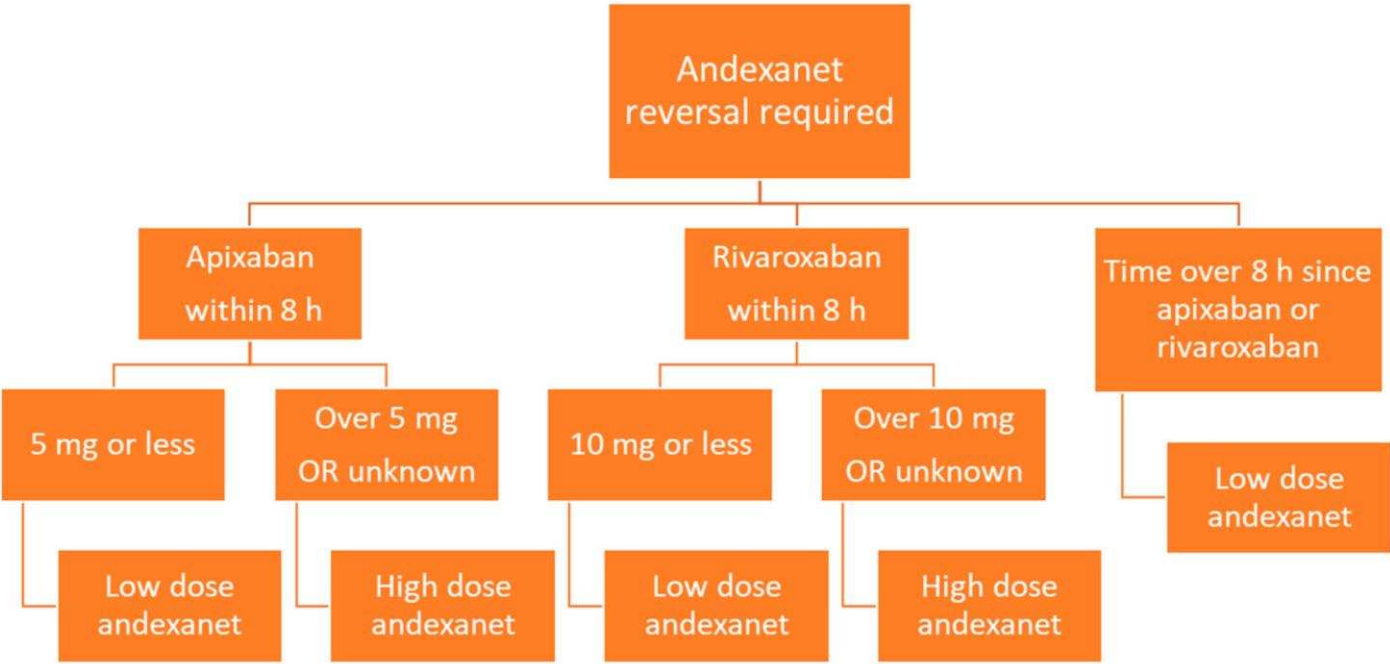
Efficacité clinique
bonne/excellente
80 % [IC95% 72-88]

Apixaban : n = 134



Efficacité clinique
bonne/excellente
83 % [IC95% 77-90]

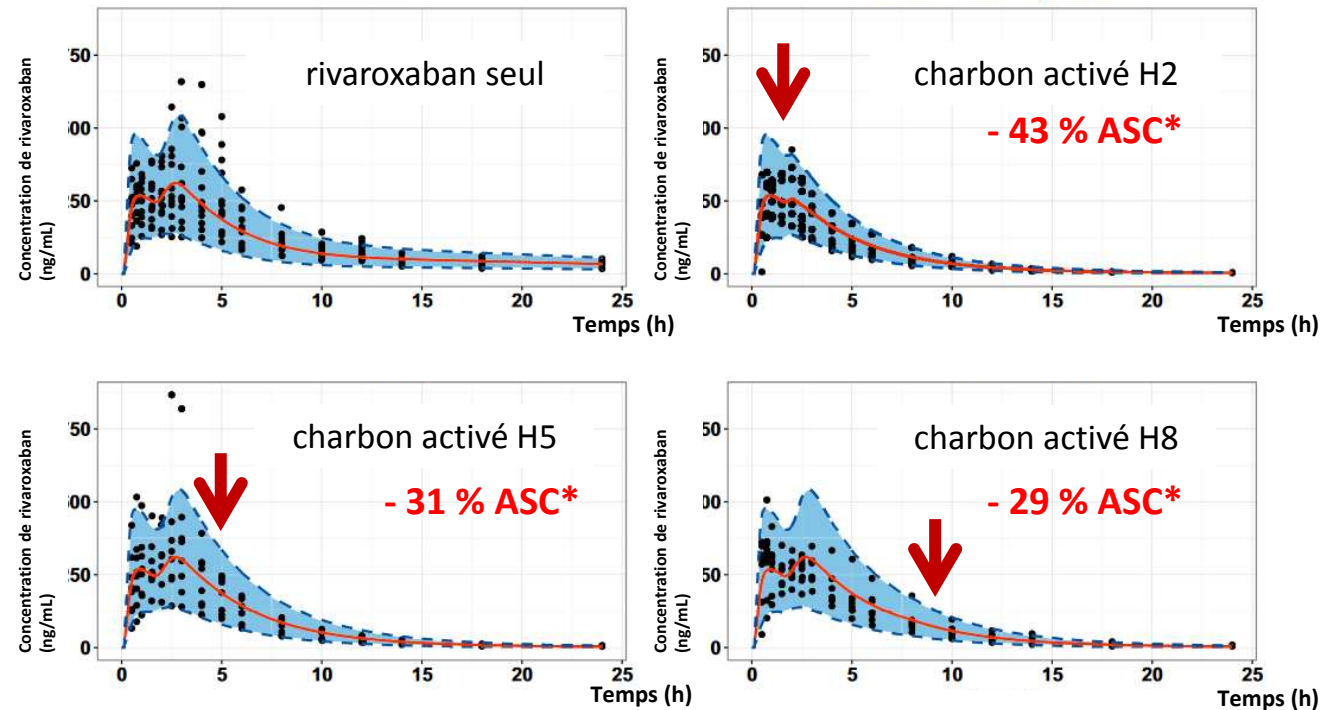
Bleeding Management with Andexanet Alpha



Administration	Low Dose	High Dose
Bolus	400 mg at 30 mg/min	800 mg at 30 mg/min
Infusion	4 mg/min for 120 mins	8 mg/min for 120 mins
Number of vials	Bolus = 400 mg → 4 vials Infusion = 480 mg → 5 vials Total = 9 vials of 100 mg	Bolus = 800 mg → 8 vials Infusion = 960 mg → 10 vials Total = 18 vials of 100 mg OR 9 vials of 200 mg

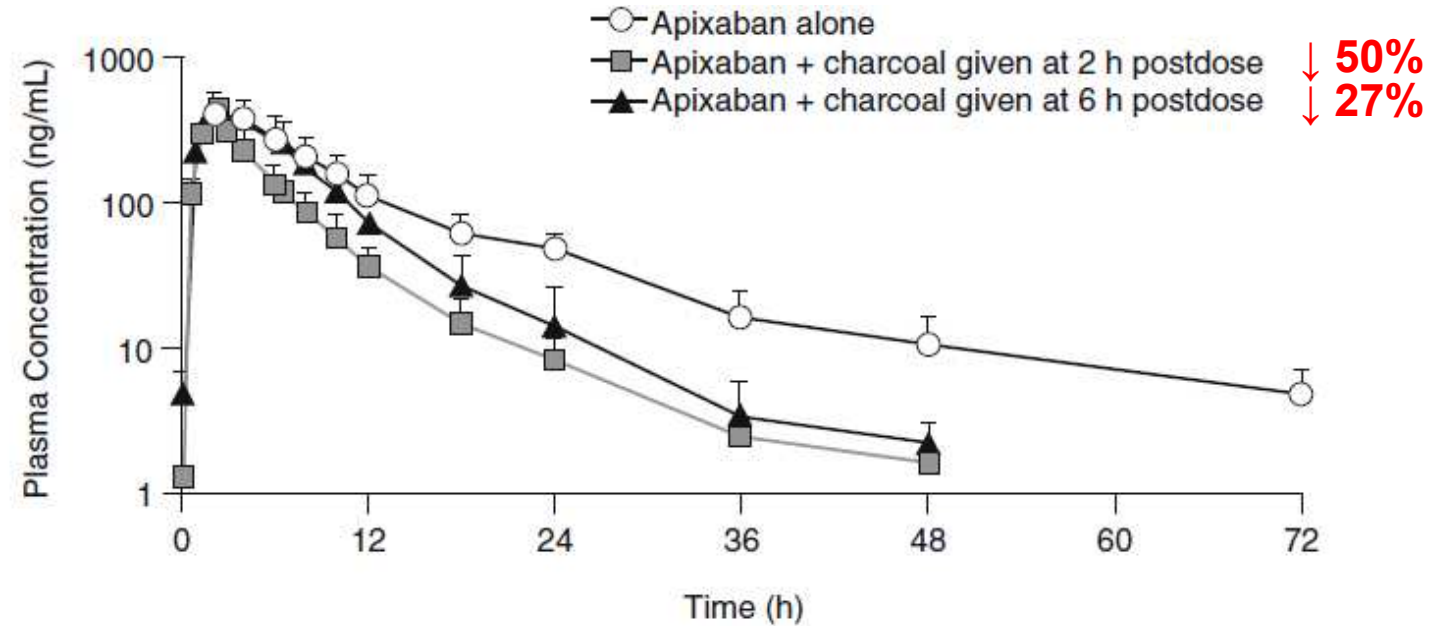
Effet du Charbon Activé

- ✓ Volontaires sains, **âge médian 26 ans** (20 – 30), **poids moyen 71 kg** (62 – 88), **créatinine 88 μM** (67 – 104)
- ✓ Etude pharmacocinétique du rivaroxaban (40 mg, prise unique *PO*) +/- charbon activé



*ASC : aire sous la courbe

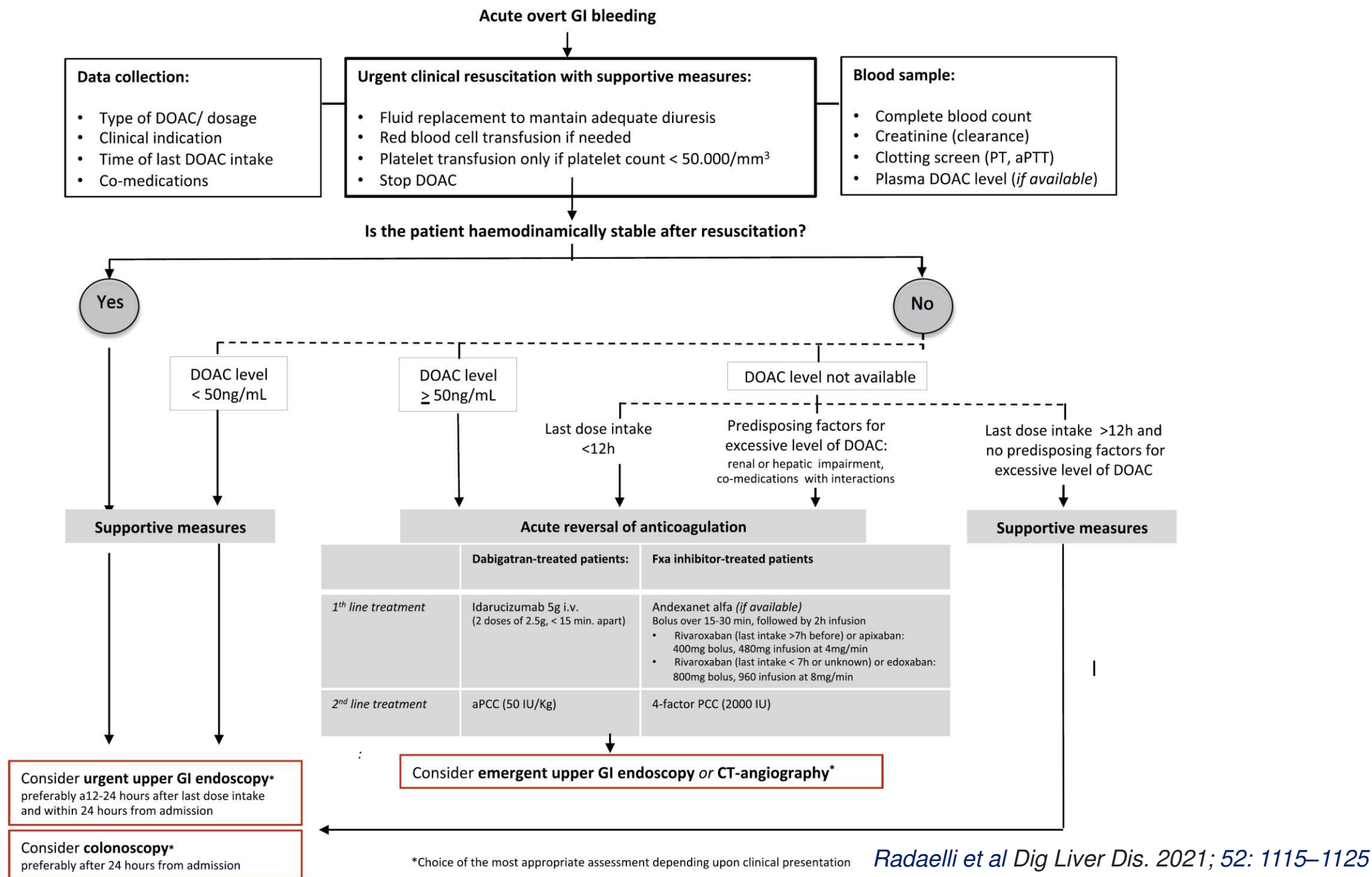
Effet du Charbon Activé



Wang et al Am J Cardiovasc Drugs 2014

	General measures	Specific reversal agent	Charcoal after ingestion	Haemodialysis
Dabigatran	Yes	Idarucizumab	Yes within 2 h	Yes
Rivaroxaban	Yes	No in Europe Yes in USA: Andexanet alpha	Yes, can be considered	No
Apixaban	Yes		Yes within 2 – 6 hours	No
Edoxaban	Yes		Yes, can be considered	No

Steffel et al Eur Heart J 2018; 39: 1330-1393.

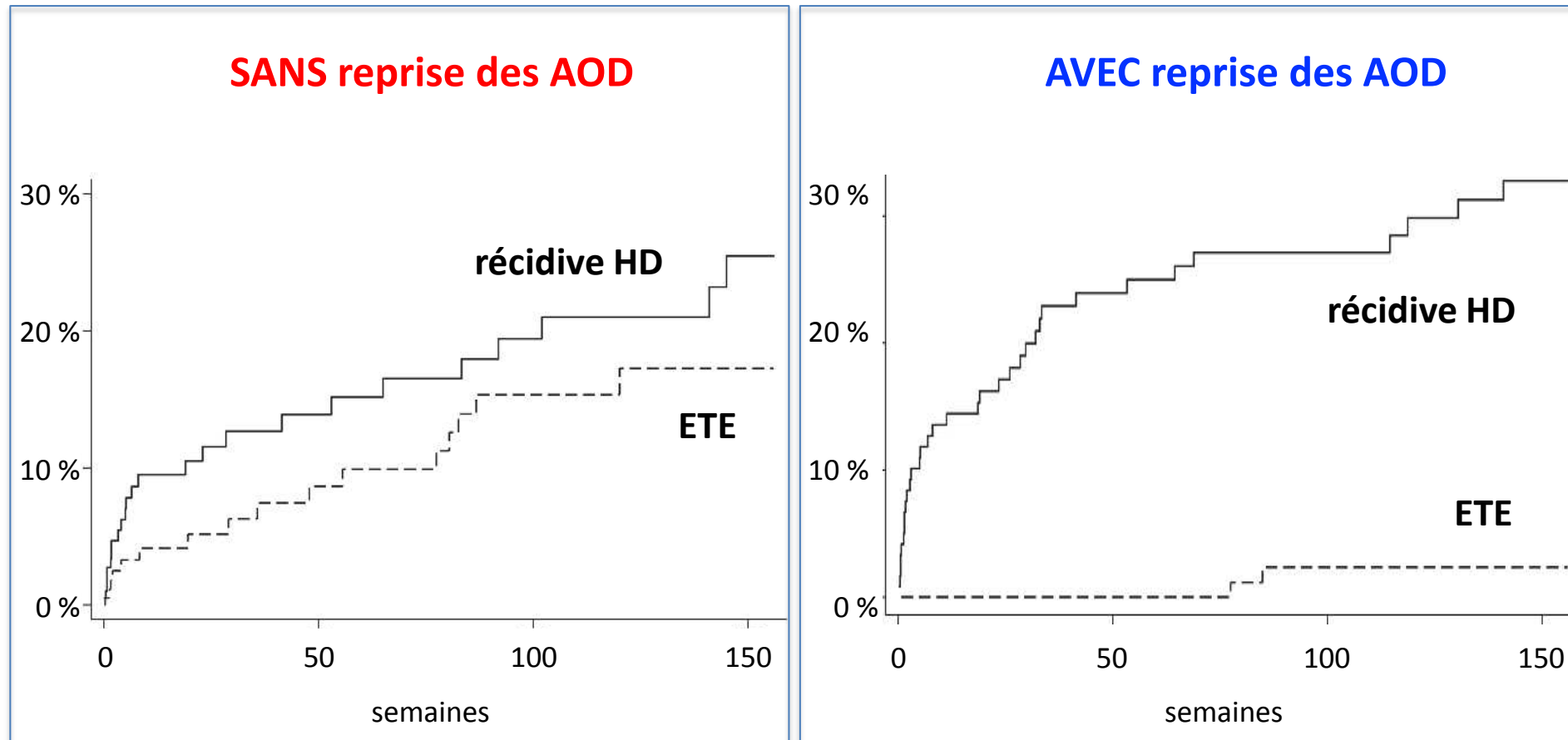


Clinical Benefits of Specific Reversion

Trial	Reversal agent	Anticoagulant	Number of patients		Hemostatic Efficacy (95% CI)	Thrombotic event rate at 30 days (%)	Mortality at 30 days (%)
			Total	% ICH			
ANNEXA-4 (2019)	Andexanet	FXa inhibitors (enoxaparin, apixaban, edoxaban, rivaroxaban)	352	64	82% (77–87)	10	14
RE-VERSE AD (2017)	Idarucizumab	Dabigatran	301	32.6	67.7% ^a	4.8	12
Sarode (2013)	4F-PCC	Warfarin	98	12	72% (64–81)	7.8 ^b	5.8
	Plasma		104	12	65% (56–75)	6.4 ^b	4.6

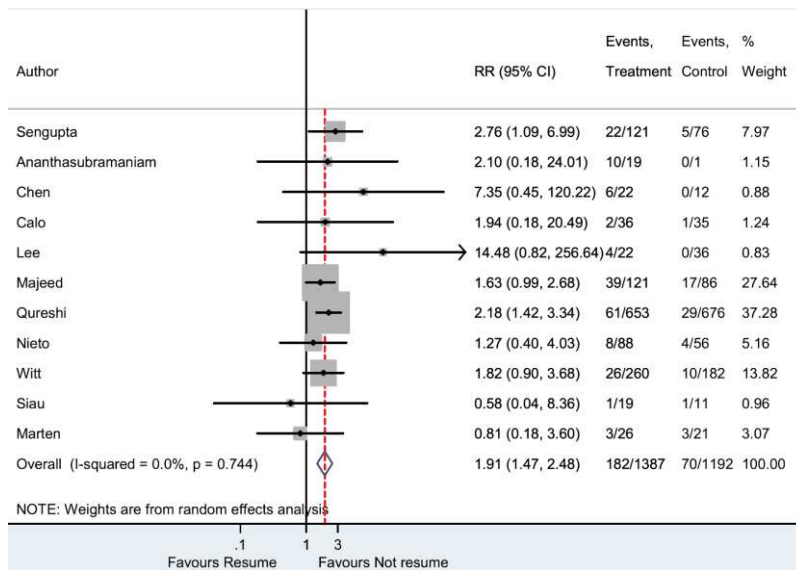
Hémorragies Digestives: Conséquences Cliniques

Suède 2004-2010 : 207 pts avec HD sous AVK dont 121 avec reprise post-HD
50% des patients restent **sans AC** après une Hémorragie Digestive



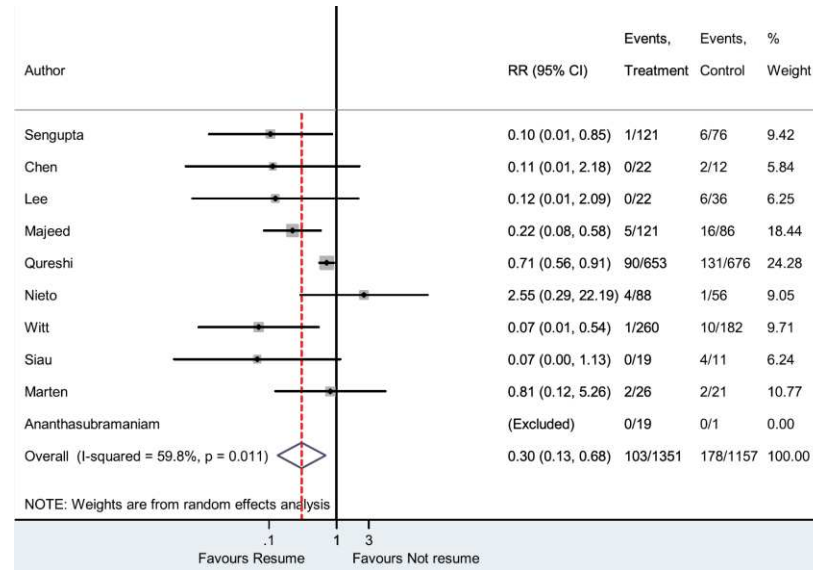
Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: meta-analysis

12 observational studies N=3098 pts



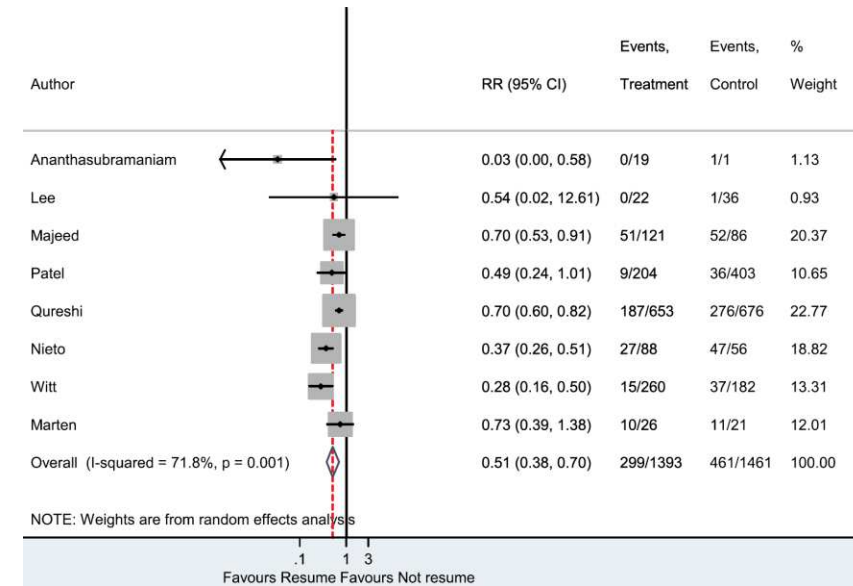
Recurrent GI Bleeding

RR 1.91, 95% CI 1.47–2.48



Recurrent Thromboembolism

RR 0.30, 95% CI 0.13–0.68



Mortality

RR 0.51, 95% CI 0.38–0.70

Hémorragies Digestives: Délai Optimal de Reprise de l'AVK

N=1,329 pts with major GIB (mean age 76 years, women 45%). Warfarin restarted n=653 (49.1%).

	< 7 j	7 - 15 j	> 30 j	arrêt
HR* décès 1 mois	0.56 [0.3 ; 0.9] 0.03	0.56 [0.3 ; 1.0] 0.04	ref -	1.26 [1.0 ; 1.6] 0.04
HR* ETE 12 mois	0.76 [0.4 ; 1.6] 0.47	0.48 [0.2 ; 1.2] 0.09	ref -	1.35 [1.0 ; 1.9] 0.07
HR* GIB 3 mois	3.27 [1.8 ; 5.9] 0.03	1.03 [0.5 ; 2.4] 0.93	ref -	1.27 [0.8 ; 2.1] 0.37

*HR ajusté sur âge, sexe, race, Charlson, nbre CGR,
INR admission, CHADS₂, HASBLED.

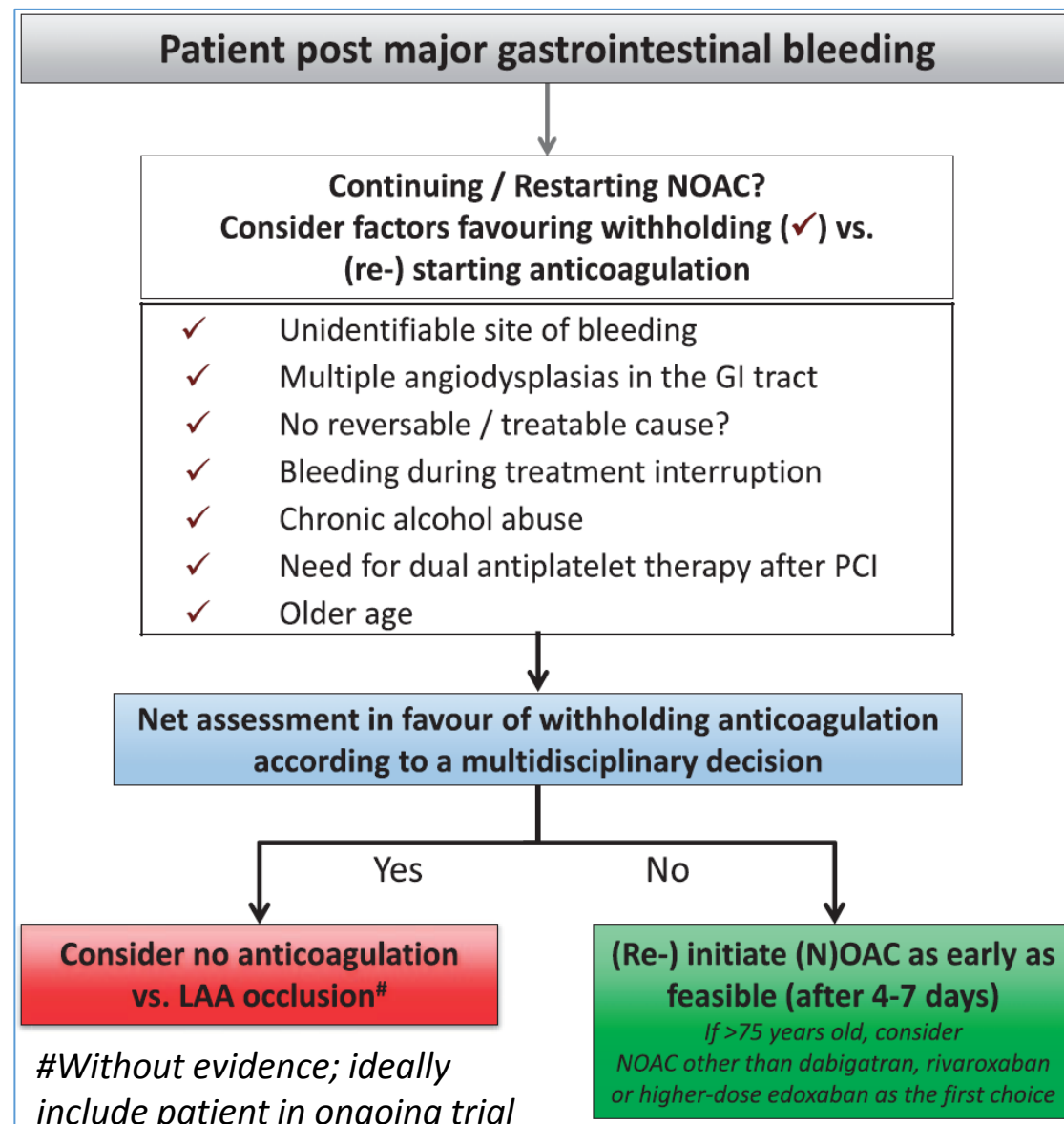
Qureshi et al. Am J Cardiol 2014;113:662-668.

Management of Bleeding Complications (EHRA 2018*)

(Re-) initiation of anticoagulation post gastrointestinal bleeding.

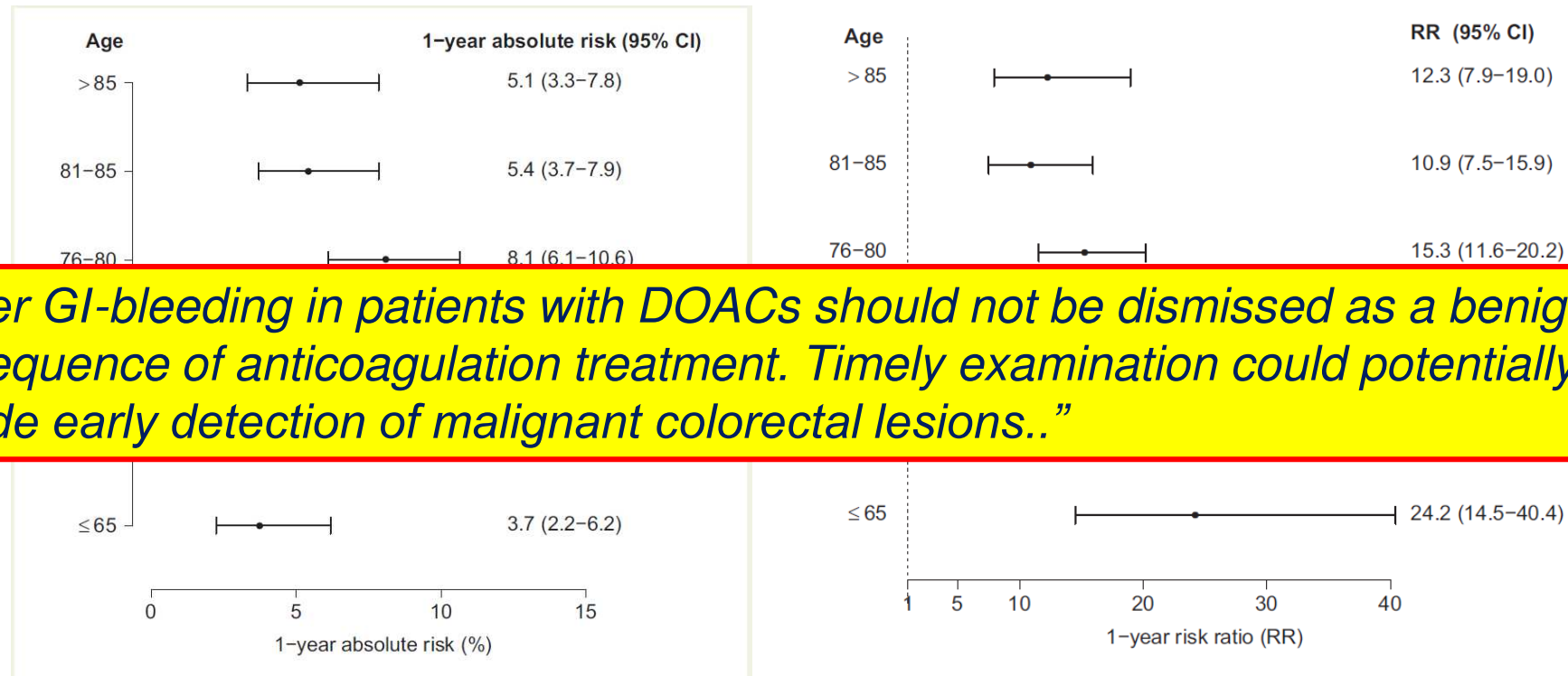
Temporary CI:

- active bleeding or active ulcers,
- hemorrhagic angiodysplasia with recurrent bleeding requiring iterative transfusions.
- Inaccessible gastrointestinal lesions to endoscopic or surgical treatments
- patients with Child-Pugh C cirrhosis



Gastrointestinal bleeding and the risk of colorectal cancer in anticoagulated patients with atrial fibrillation

N=125 418 Danish AF pts with OAC therapy (Danish administrative registers) and with 3 years of follow-up,
N=2576 patients with lower GI-bleeding and N=140 patients diagnosed with colorectal cancer within the first year



“Lower GI-bleeding in patients with DOACs should not be dismissed as a benign consequence of anticoagulation treatment. Timely examination could potentially provide early detection of malignant colorectal lesions..”

Risk of Colorectal K in Lower GIB pts

Risk Ratio of Colorectal K between pts
with and without Lower GIB

Conclusions

- AOD : Optimisation Thérapeutique avec Simplicité
- Meilleur Rapport Bénéfice Clinique/Tolérance Hémorragique
- Particularités et Posologies des AOD selon Profils des Patients
- Risque Digestif et Muqueux Potentiel
- Stratifier et Surveiller les Profils à Risque Hémorragique
- Protocoles de Prise en Charge en cas d'Hémorragie $\pm$ Antidotes
- Réparer la Lésion Tissulaire et Reprendre la Protection Vasculaire
- « AOD : Pris par la Bouche mais ne restent pas Tous sur l'Estomac! »