84èmes Journées de l'APHO

29 et 30 mars 2018

Brest, Les ateliers des Capucins

"L'APHO, EN TOUTE TROMBE... OSE : CAP SUR LE CAILLOT !"

APHO

Antithrombotiques en populations particulières

Antithrombotiques du futur

Pr Karine LACUT

CHU Brest

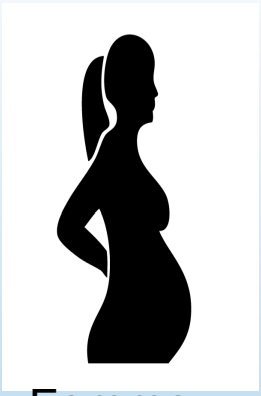
Déclarations Liens d'intérêts

- Participation en tant qu'investigateur aux essais pharmaceutiques évaluant les AOD sans rétribution à titre personnel
- Participation à des congrès internationaux soutenue par Bayer Health Care

Antithrombotiques en populations particulières

Sujet âgé

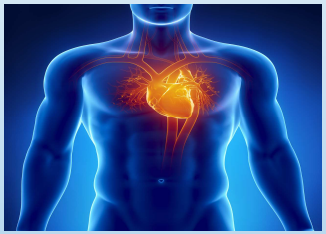
Insuffisance rénale



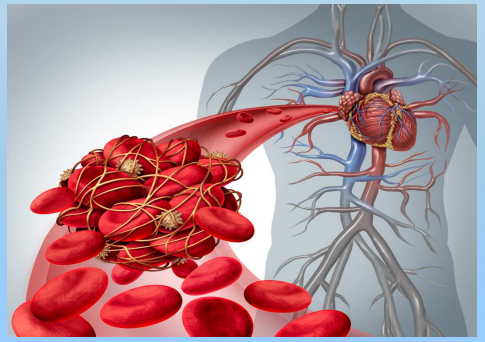
Femme enceinte

Enfant

Poids extrêmes



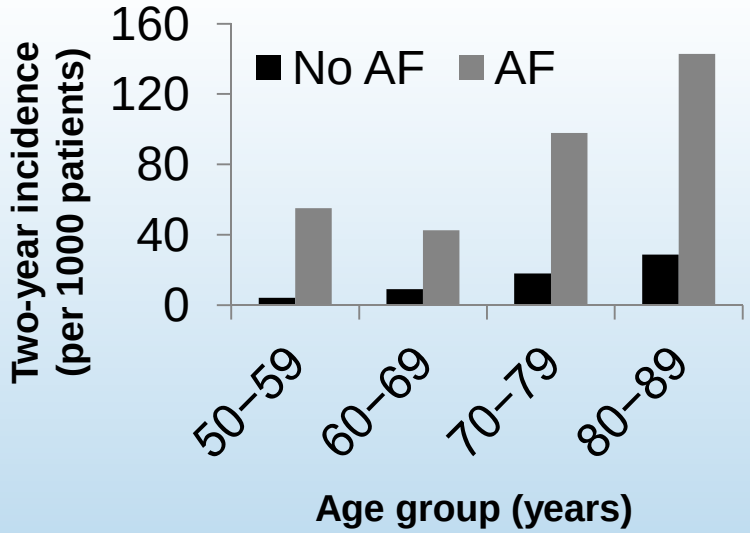
Anticoagulants et coronaires



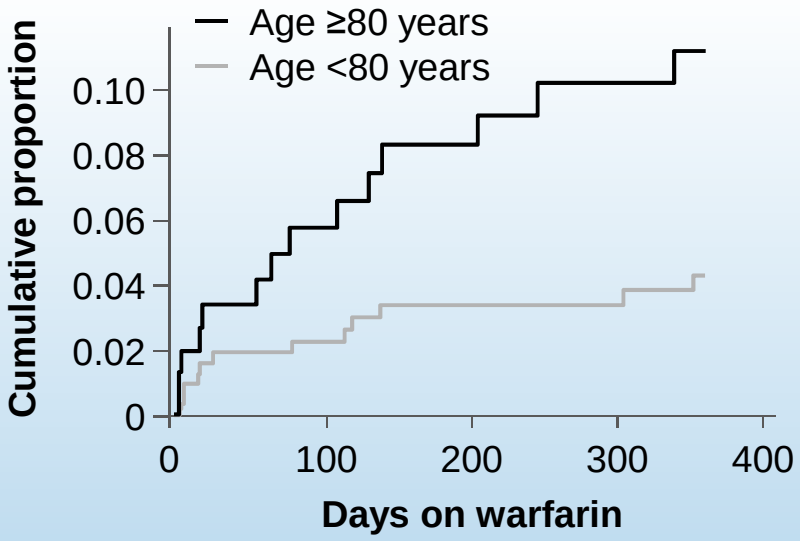
Thromboses atypiques et thrombophilies

Sujet âgé

AVC



Hémorragie majeure



Tous les patients de 75 ans et plus ayant une FA doivent recevoir un traitement anticoagulant, en tenant compte du risque hémorragique

Wolf PA et al. Arch Intern Med. 1987
Marinigh R et al. J Am Coll Cardiol. 2010
Sacco RL et al. Stroke 1997
Hart RG et al. Ann Intern Med. 2007
Hylek EM et al. Circulation 2007

Sujet âgé et AOD

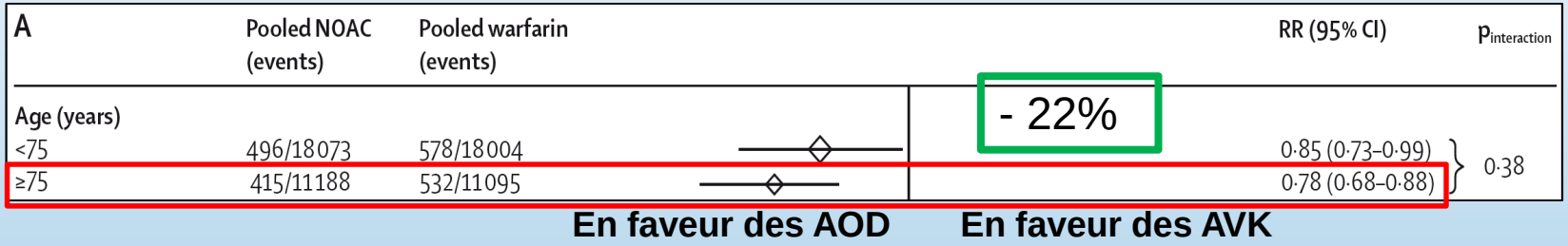
Dans les essais de FA

	Rely Dabigatran	**Rocket** Rivaroxaban	**Aristotle** Apixaban	**Engage** Edoxaban
n = 65 500	n = 18 113	n = 14 264	n = 18 201	n = 21 105
Age (moy)	71.5	73.1	70	72
> 75 ans	40%	43%	31%	39%
n = 29051	**n = 7245**	**n =6164**	**n = 5678**	**n =8231**

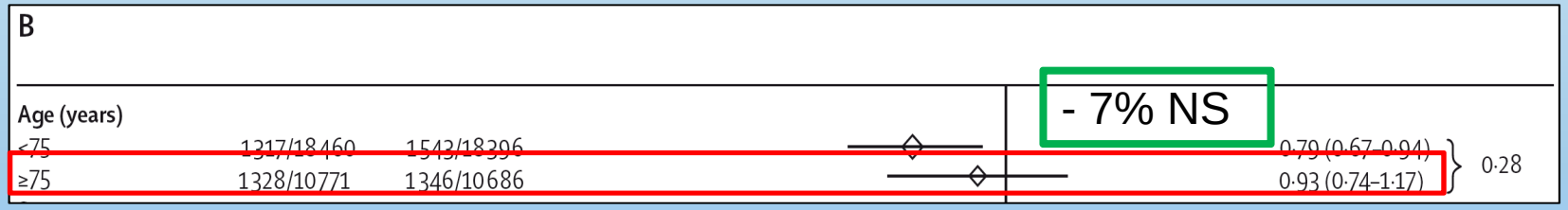
Sujet âgé et AOD

- Méta-analyse essais en FA
- 71 683 participants, dont **29 099 ≥ 75 ans**

Sous-groupe AVC, embolies systémiques



Sous-groupe hémorragies majeures



Ruff CT, Lancet 2014

Sujet âgé et AOD

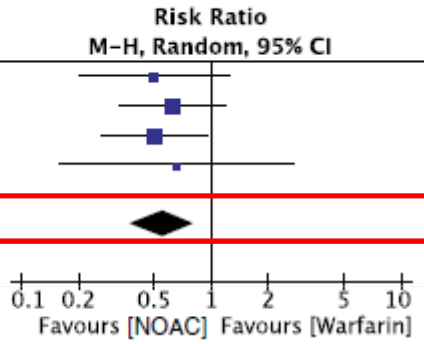
Essais FA	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 30	Edoxaban 60
AVC	↓	=	=	↓	=	=
H. Intra Cérébrale	↓	↓	↓	↓	↓	↓
H. graves	↑	=	=	↓	↓	↓

Sujet âgé et AOD
MTEV

A) VTE recurrence in the subgroup age ≥75 years

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	7	389	13	360	18.3%	0.50 [0.20, 1.24]
EINSTEIN DVT & PE	15	656	23	627	36.7%	0.62 [0.33, 1.18]
HOKUSAI	14	560	27	544	37.5%	0.50 [0.27, 0.95]
RECOVER I & II	3	253	5	276	7.5%	0.65 [0.16, 2.71]
Total (95% CI)		**1858**		**1807**	**100.0%**	**0.55 [0.38, 0.82]**
Total events	39		68			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 3 (P = 0.96); $I^2 = 0\%$
Test for overall effect: Z = 2.98 (P = 0.003)

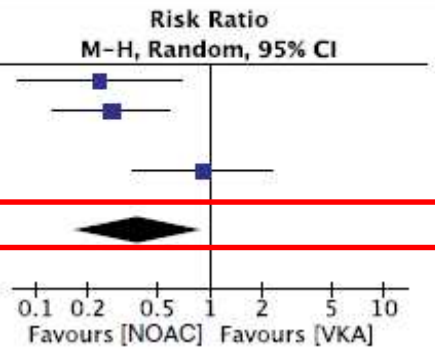


- 45%

C) Major bleeding in the subgroup age ≥75 years

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	4	398	16	370	28.8%	0.23 [0.08, 0.69]
EINSTEIN DVT & PE	8	655	28	624	37.6%	0.27 [0.13, 0.59]
HOKUSAI	0	0	0	0		Not estimable
RECOVER I & II	8	231	10	262	33.6%	0.91 [0.36, 2.26]
Total (95% CI)		**1284**		**1256**	**100.0%**	**0.39 [0.17, 0.90]**
Total events	20		54			

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 5.02$, df = 2 (P = 0.08); $I^2 = 60\%$
Test for overall effect: Z = 2.20 (P = 0.03)



- 61%

Geldhof, Thromb J 2014

Sujet âgé et AOD

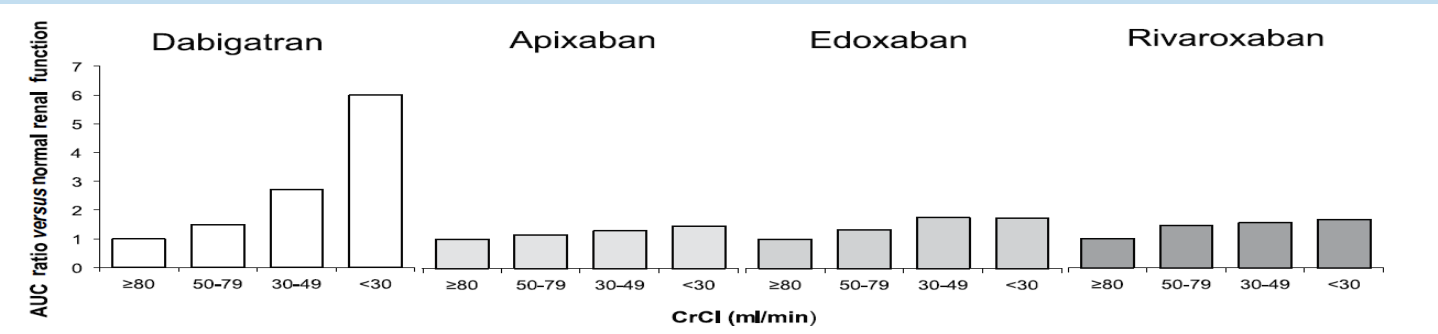
- **L'âge, seul, ne doit pas être un frein à la prescription d'AOD et n'impose pas d'adaptation des posologies (pas de dose réduite sauf dabigatran dans la FA)**
- **Dans les essais et données de « vraie » vie:**
  - **AOD>AVK pour l'efficacité**
  - **Avec Moins d'hémorragies cérébrales et moins de décès**
  - **Si les schémas thérapeutiques sont respectés**
- **Mais attention au rein….**

AOD et insuffisance rénale

Table 1. Pharmacokinetic/pharmacodynamic properties of the NOACs.

Characteristic	Dabigatran[4,8]	Apixaban[5,6]	Edoxaban[2,9]	Rivaroxaban[3,7]
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Dosing	BID	BID	OD	OD
Bioavailability, %	6.5	50	62	80–100*
Half-life, hours	12–14	8–15	9–11	5–13
Renal clearance (unchanged bioavailable drug)	85%	~27%	50%	~33%
Cmax, hours	1–2	3–4	1–2	2–4
Drug interactions	P-gp inhibitors	Strong inhibitors of CYP3A4 and P-gp	P-gp inhibitors	Strong inhibitors of CYP3A4 and P-gp

*When the 15 mg and 20 mg doses are taken with food. BID, twice daily; Cmax, maximum concentration; OD, once daily; P-gp, P-glycoprotein.



Turpie AGG, Ther Adv Cardiovasc Dis 2017

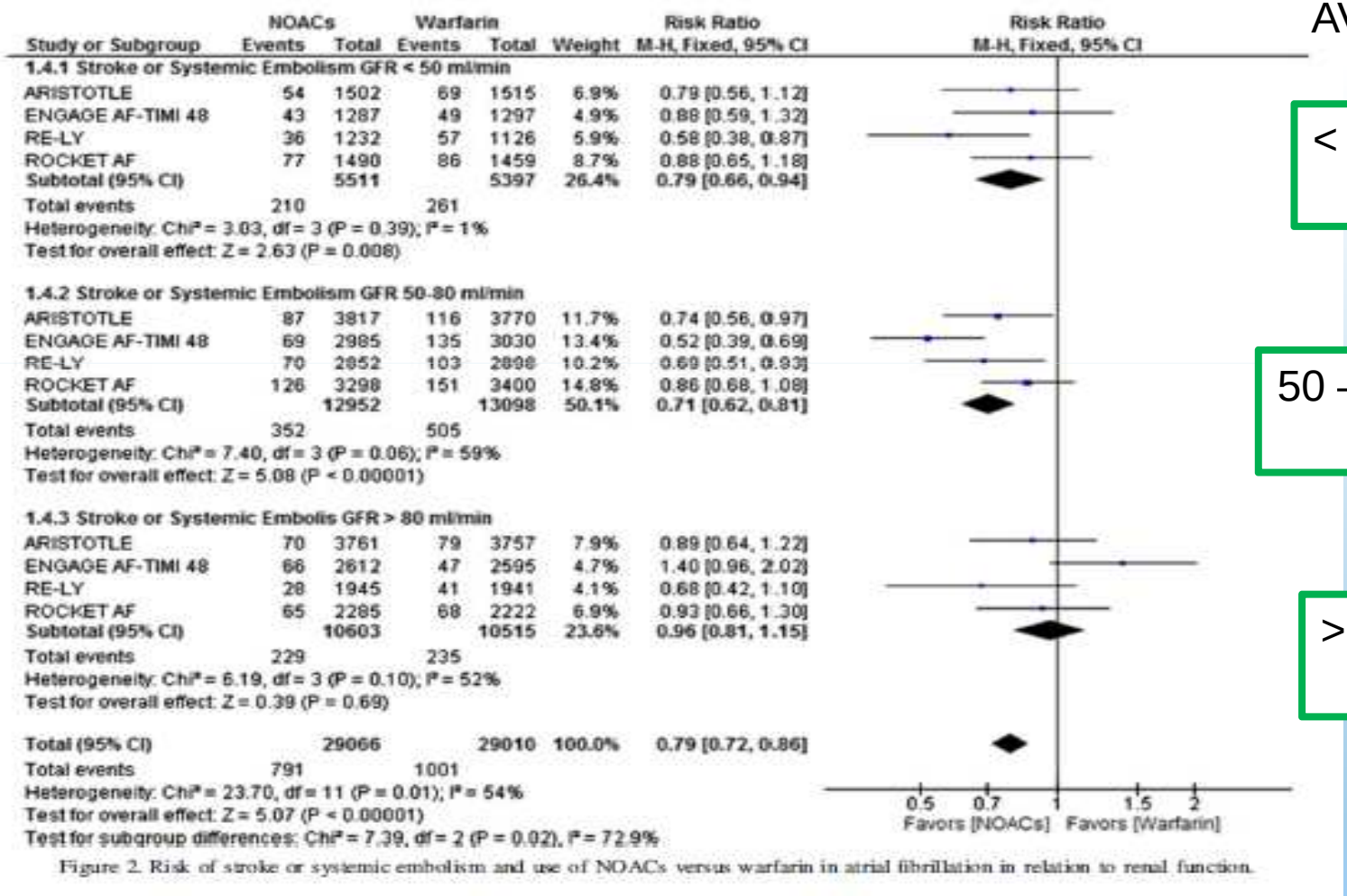
AOD et insuffisance rénale

Table 2. Clinical trial characteristics for patients with atrial fibrillation and moderate renal impairment.

Trial	Dabigatran[4,30]	Apixaban[5,31]	Edoxaban[2,9,32]	Rivaroxaban[3,29]
	RE-LY	ARISTOTLE	ENGAGE AF	ROCKET AF
Trial Design	Open label, blind to dabigatran dose	Double blind	Double blind	Double blind
Length of trial, years	2.0	1.8	2.8	1.9
Renal dose considerations	None; patients randomized to dabigatran dose	50% dose reduction (2.5 mg BID) if 2/3 criteria met: age ⩾ 80 weight ⩽ 60 kg creatinine ⩾ 133 µmol/l (1.5 mg/dl)	50% dose reduction (30 mg OD) if CrCl 30–49 ml/min	25% dose reduction (15 mg OD) if CrCl 30–49 ml/min
Number of patients in phase III clinical trial	18,113	18,201	21,105	14,264
Number of patients with CrCl <50 ml/min	3374	3017	2740*	2950$

Turpie AGG, Ther Adv Cardiovasc Dis 2017

AOD et insuffisance rénale



Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Stroke or Systemic Embolism GFR < 50 ml/min						
ARISTOTLE	54	1502	69	1515	6.9%	0.79 [0.56, 1.12]
ENGAGE AF-TIMI 48	43	1287	49	1297	4.9%	0.88 [0.59, 1.32]
RE-LY	36	1232	57	1126	5.9%	0.58 [0.38, 0.87]
ROCKET AF	77	1490	86	1459	8.7%	0.88 [0.65, 1.18]
Subtotal (95% CI)		**5511**		**5397**	**26.4%**	**0.79 [0.66, 0.94]**
Total events	210		261			
Heterogeneity: Chi² = 3.03, df = 3 (P = 0.39); I² = 1%						
Test for overall effect: Z = 2.63 (P = 0.008)						
1.4.2 Stroke or Systemic Embolism GFR 50-80 ml/min						
ARISTOTLE	87	3817	116	3770	11.7%	0.74 [0.56, 0.97]
ENGAGE AF-TIMI 48	69	2985	135	3030	13.4%	0.52 [0.39, 0.69]
RE-LY	70	2852	103	2898	10.2%	0.69 [0.51, 0.93]
ROCKET AF	126	3298	151	3400	14.8%	0.86 [0.68, 1.08]
Subtotal (95% CI)		**12952**		**13098**	**50.1%**	**0.71 [0.62, 0.81]**
Total events	352		505			
Heterogeneity: Chi² = 7.40, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 5.08 (P < 0.00001)						
1.4.3 Stroke or Systemic Embolis GFR > 80 ml/min						
ARISTOTLE	70	3761	79	3757	7.9%	0.89 [0.64, 1.22]
ENGAGE AF-TIMI 48	66	2612	47	2595	4.7%	1.40 [0.96, 2.02]
RE-LY	28	1945	41	1941	4.1%	0.68 [0.42, 1.10]
ROCKET AF	65	2285	68	2222	6.9%	0.93 [0.66, 1.30]
Subtotal (95% CI)		**10603**		**10515**	**23.6%**	**0.96 [0.81, 1.15]**
Total events	229		235			
Heterogeneity: Chi² = 6.19, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 0.39 (P = 0.69)						
Total (95% CI)		**29066**		**29010**	**100.0%**	**0.79 [0.72, 0.86]**
Total events	791		1001			
Heterogeneity: Chi² = 23.70, df = 11 (P = 0.01); I² = 54%						
Test for overall effect: Z = 5.07 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.39, df = 2 (P = 0.02), I² = 72.9%						

Risk Ratio M-H, Fixed, 95% CI

0.5 0.7 1 1.5 2

Favors [NOACs] Favors [Warfarin]

Figure 2. Risk of stroke or systemic embolism and use of NOACs versus warfarin in atrial fibrillation in relation to renal function.

AVC et ES

< 50ml/min - 21%

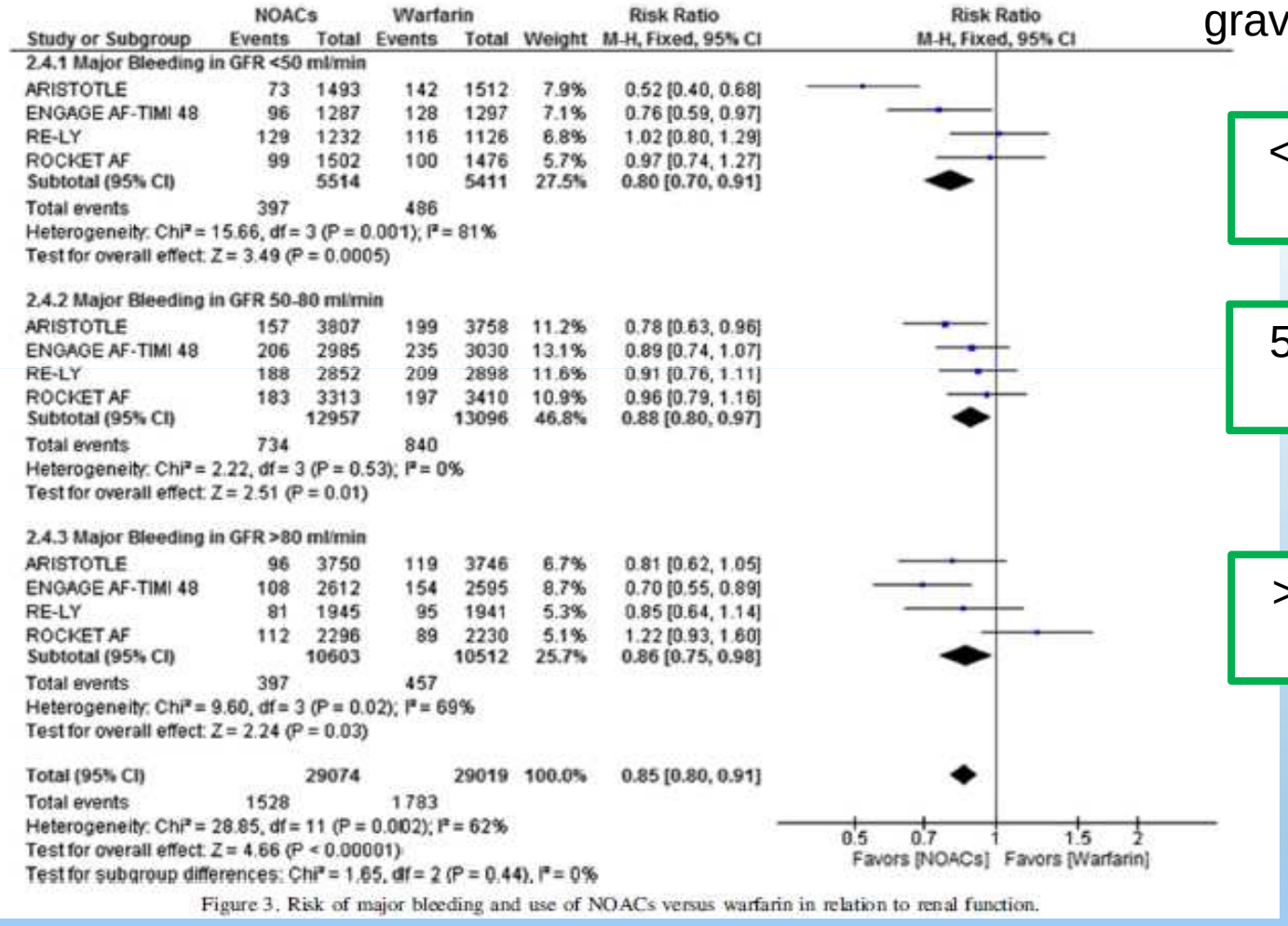
50 – 80 ml/min - 29%

> 80 ml/min ns

Del-Carpio Munoz F, Am J Cardiol 2016

AOD et insuffisance rénale

Hémorragies graves



Study or Subgroup	NOACs Events	Total	Warfarin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Major Bleeding in GFR <50 ml/min						
ARISTOTLE	73	1493	142	1512	7.9%	0.52 [0.40, 0.68]
ENGAGE AF-TIMI 48	96	1287	128	1297	7.1%	0.76 [0.59, 0.97]
RE-LY	129	1232	116	1126	6.8%	1.02 [0.80, 1.29]
ROCKET AF	99	1502	100	1476	5.7%	0.97 [0.74, 1.27]
Subtotal (95% CI)		**5514**		**5411**	**27.5%**	**0.80 [0.70, 0.91]**
Total events	397		486			
Heterogeneity: Chi² = 15.66, df = 3 (P = 0.001); I² = 81%						
Test for overall effect: Z = 3.49 (P = 0.0005)						
2.4.2 Major Bleeding in GFR 50-80 ml/min						
ARISTOTLE	157	3807	199	3758	11.2%	0.78 [0.63, 0.96]
ENGAGE AF-TIMI 48	206	2985	235	3030	13.1%	0.89 [0.74, 1.07]
RE-LY	188	2852	209	2898	11.6%	0.91 [0.76, 1.11]
ROCKET AF	183	3313	197	3410	10.9%	0.96 [0.79, 1.16]
Subtotal (95% CI)		**12957**		**13096**	**46.8%**	**0.88 [0.80, 0.97]**
Total events	734		840			
Heterogeneity: Chi² = 2.22, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 2.51 (P = 0.01)						
2.4.3 Major Bleeding in GFR >80 ml/min						
ARISTOTLE	96	3750	119	3746	6.7%	0.81 [0.62, 1.05]
ENGAGE AF-TIMI 48	108	2612	154	2595	8.7%	0.70 [0.55, 0.89]
RE-LY	81	1945	95	1941	5.3%	0.85 [0.64, 1.14]
ROCKET AF	112	2296	89	2230	5.1%	1.22 [0.93, 1.60]
Subtotal (95% CI)		**10603**		**10512**	**25.7%**	**0.86 [0.75, 0.98]**
Total events	397		457			
Heterogeneity: Chi² = 9.60, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 2.24 (P = 0.03)						
Total (95% CI)		**29074**		**29019**	**100.0%**	**0.85 [0.80, 0.91]**
Total events	1528		1783			
Heterogeneity: Chi² = 28.85, df = 11 (P = 0.002); I² = 62%						
Test for overall effect: Z = 4.66 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.65, df = 2 (P = 0.44), I² = 0%						

Figure 3. Risk of major bleeding and use of NOACs versus warfarin in relation to renal function.

< 50ml/min
- 20%

50 – 80 ml/min
- 12%

> 80 ml/min
- 14%

Del-Carpio Munoz F, Am J Cardiol 2016

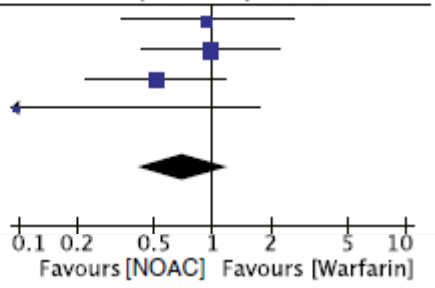
AOD et insuffisance rénale

B) VTE recurrence in the subgroup CrCl ≤50 ml/min

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	7	169	7	158	24.7%	0.93 [0.34, 2.61]
EINSTEIN DVT & PE	11	332	11	322	36.3%	0.97 [0.43, 2.21]
HOKUSAI	8	268	16	273	35.5%	0.51 [0.22, 1.17]
RECOVER I & II	0	129	5	138	3.4%	0.10 [0.01, 1.74]
Total (95% CI)		**898**		**891**	**100.0%**	**0.71 [0.41, 1.21]**
Total events	26		39			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.35$, df = 3 (P = 0.34); $I^2 = 10\%$

Test for overall effect: Z = 1.26 (P = 0.21)

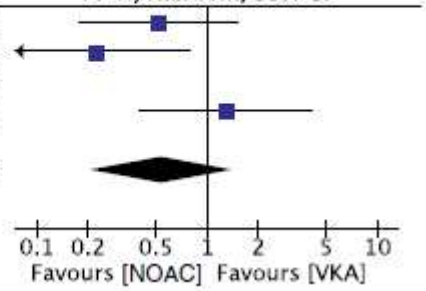


D) Major bleeding in the subgroup CrCl ≤50 ml/min

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	5	175	9	163	35.8%	0.52 [0.18, 1.51]
EINSTEIN DVT & PE	3	329	13	320	30.9%	0.22 [0.06, 0.78]
HOKUSAI	0	0	0	0		Not estimable
RECOVER I & II	6	106	5	114	33.3%	1.29 [0.41, 4.10]
Total (95% CI)		**610**		**597**	**100.0%**	**0.54 [0.21, 1.42]**
Total events	14		27			

Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 4.13$, df = 2 (P = 0.13); $I^2 = 52\%$

Test for overall effect: Z = 1.25 (P = 0.21)



Geldhof, Thromb J 2014

AOD et insuffisance rénale

Dans la FA

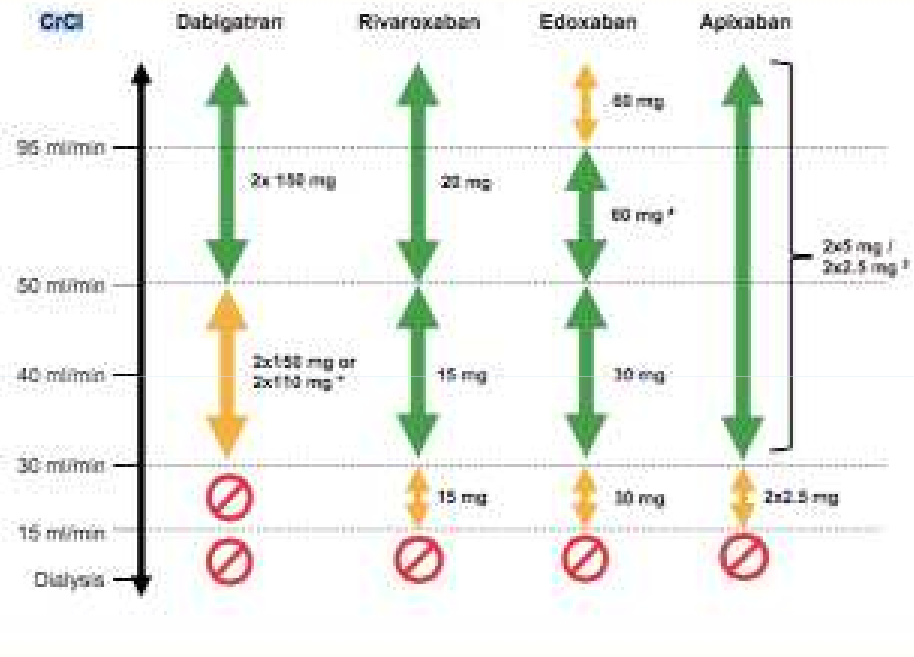


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPC). †Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). ‡2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 μmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Dans la MTEV: pas d'ajustement posologique en cas d'insuffisance rénale

Surveillance régulière de la fonction rénale

Insuffisance rénale sévère

Les AOD sont déconseillés, et contre-indiqués si Cl Cr < 15 ml/min

Dans la FA: traitement par AVK d'emblée

Dans la MTEV: AVK au long cours

- à la phase initiale:
  - si Cl Cr < 15 ml/min: HNF
  - si Cl Cr > 15 ml/min: HBPM enoxaparine en 1 injection ou tinzaparine en 1 injection ?

Poids extrêmes

- Petits poids (< 50-60 kg): ↑ risque de saignement?
- Obésité (BMI > 30): ↓ efficacité?

Petits poids

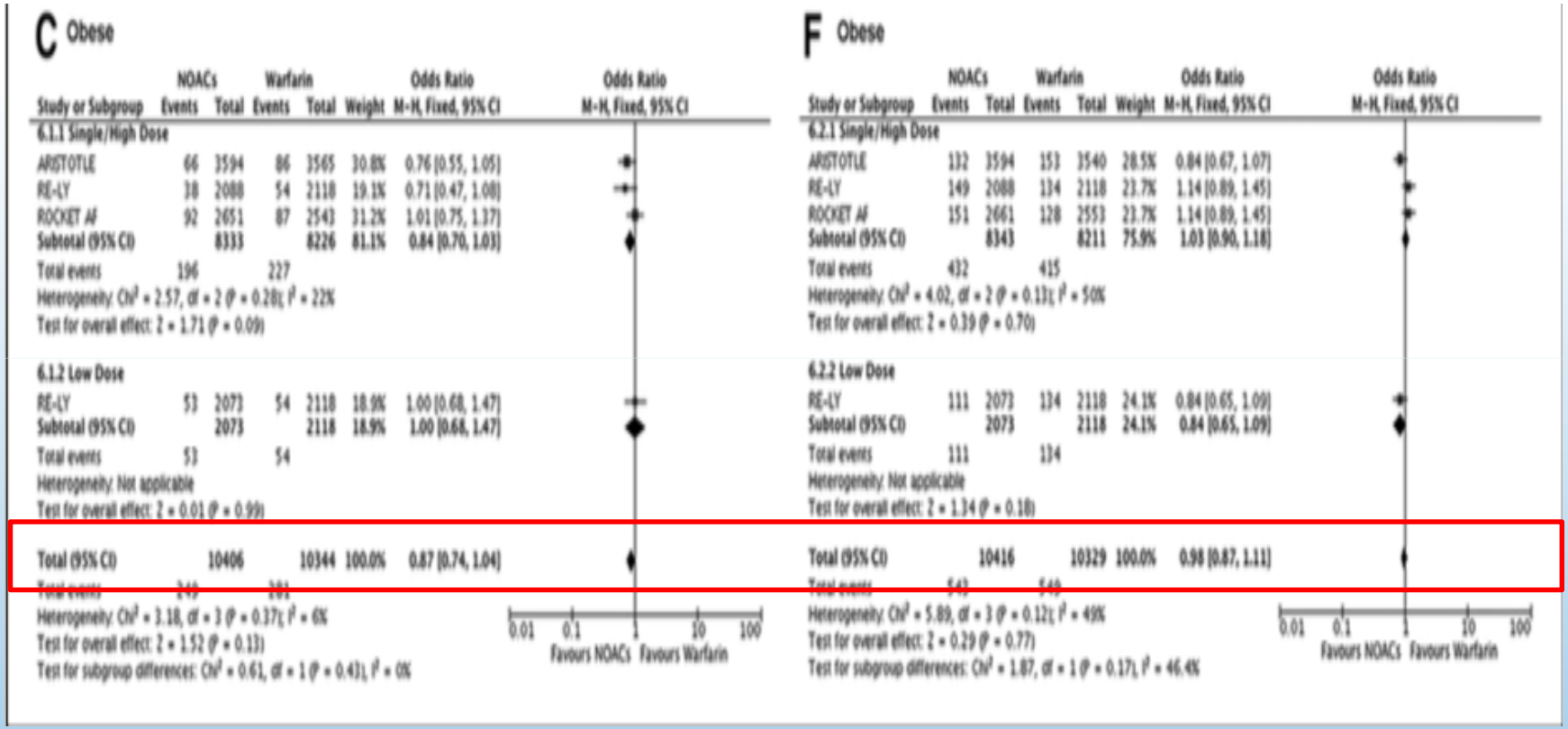
- Dabigatran: résultats des essais ≈ vraie vie. Possible ↑ des saignements
- Rivaroxaban: 167 patients < 50 kg; pas de corrélation entre poids et saignement
- Apixaban: < 60 kg = critère de dose réduite (avec 1 autre). Pas de différence par rapport aux poids normaux
- Edoxaban: < 60 kg = critère de dose réduite. Pas de différence par rapport aux poids normaux

De Caterina R, Clin Res Cardiol, 2017
Di Nisio M, Thromb Haemost 2016

Obésité

AVC et ES

Saignements majeurs



Pas de perte d'efficacité chez les patients obèses en FA

Et pour la chirurgie bariatrique?

Proietti M, Stroke 2017
MartinK, J Thromb Haemost 2016

Poids extrêmes

Dans la FA

AOD	Limite inférieure de poids (RCP)	Limite supérieure de poids (RCP)	Ajustement de dose
Dabigatran	50 kg	110 kg	Non
Rivaroxaban	Aucune	Aucune	Non
Apixaban	Aucune	Aucune	Si < 60 kg avec un autre facteur: creat > 133 µmol/l ou > 80 ans
Edoxaban	Aucune	Aucune	Si < 60 kg: 30 mg

AOD chez les coronariens

- Anti-agrégant plaquettaire + anticoagulant = hémorragie
- Pour le Coronarien stable (> 1 an) + FA
  - Anticoagulation seule
  - Anticoagulation + anti-agrégant si haut risque coronarien. Alors, si AOD, dose réduite

EHRA Pratical Guide 2015 & 2018
Windeker S Eur Heart J 2014
Lamberts M, Circulation 2012

AOD chez les coronariens

- Dans les études en FA:
  - 30% ATCD coronarien, 15-20% IDM
  - 30 à 40% d'aspirine
  - Pas d'interaction avec ATCD d'IDM
- Méta-analyse des essais:
  - 22000 patients avec Aspirine à l'inclusion
  - AOD vs AVK: ↓ 20% AVC et ES, ↓15% décès CV, ↓ 60% d'HIC, ↑16% d'IDM

Si association :
AOD + aspirine > AVK + aspirine

Bennaghmouch N, Circulation 2018

Thromboses atypiques

- **<u>Thromboses du Membre supérieur:</u>**
  - Majorité de cancer et/ou cathéter veineux
  - Pour les autres : AOD ?
- **<u>Thrombophlébites cérébrales:</u>**
  - Pour les AOD: risque réduit d'HIC
  - Après la phase aigue
- **<u>Thromboses digestives</u>**:
  - Contre les AOD: risque hémorragique majoré dont 80% d'hémorragies digestives, Insuffisance hépato-cellulaire avec impact sur la PK

« Thrombophilies »

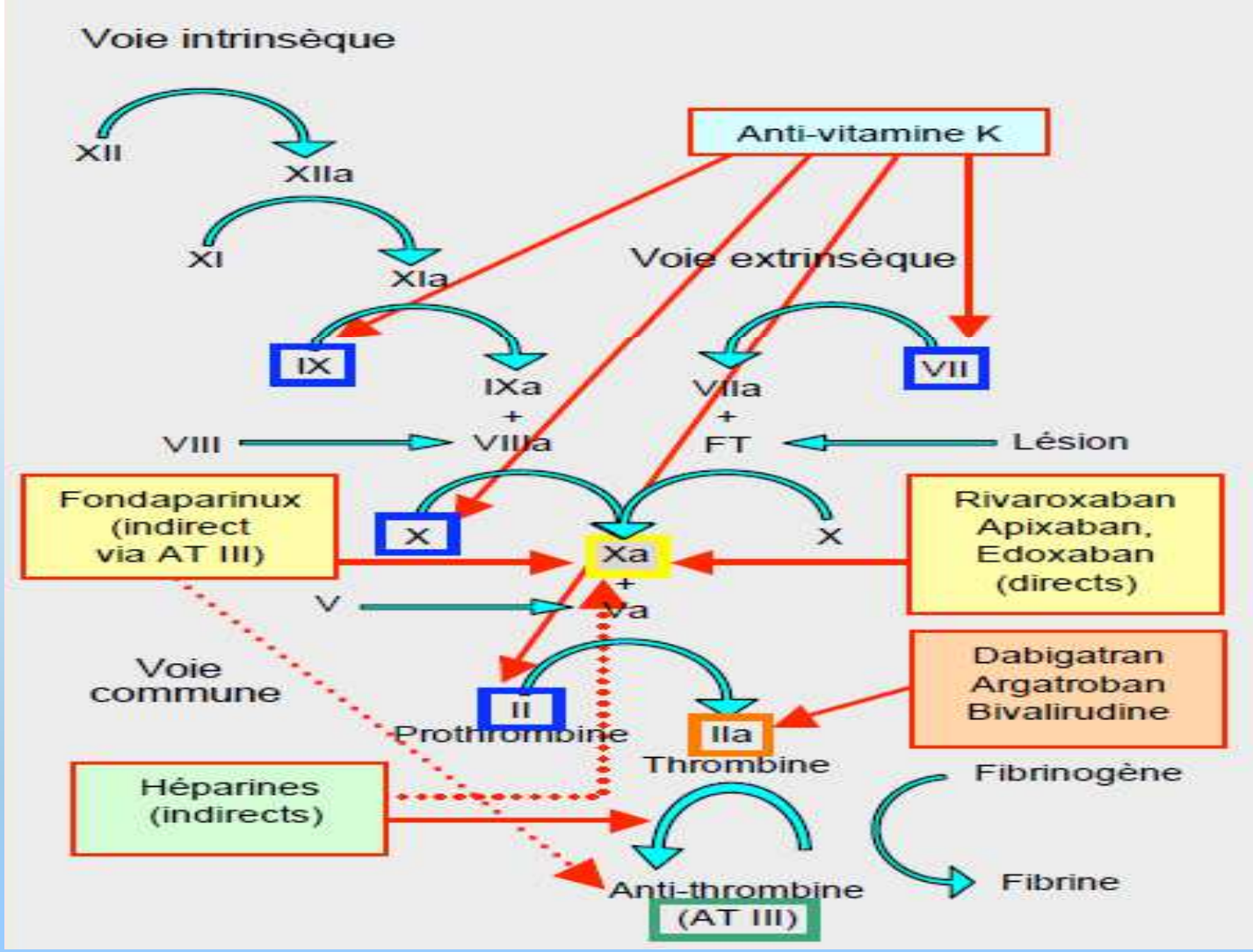
- Pour les AOD:
  - Pas d'individualisation des thrombophilies biologiques dans les essais de MTEV
  - Mécanismes d'action + favorables pour déficit en PC et PS, et antithrombine

- Contre les AOD: le SAPL
  - Description de syndromes catastrophiques au switch AVK- AOD
  - Echec de l'essai RAPS

Cohen H, Lancet Haematol 2016

ANTITHROMBOTIQUES DU FUTUR

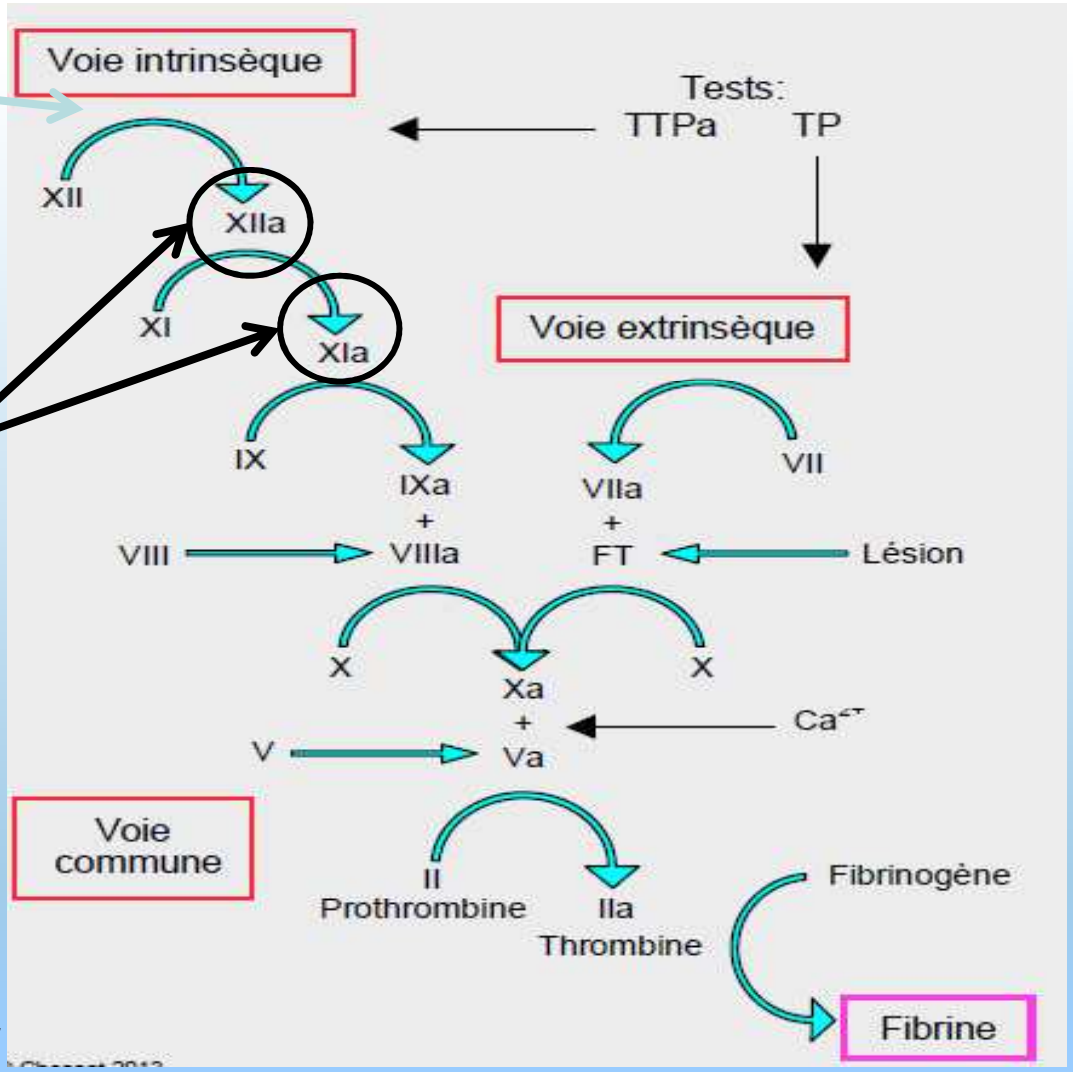
Cibles des anticoagulants actuels



Nouvelles cibles: FXI, FXII

Phase « contact »: Stents, valves, catheter…

Antisense oligonucleotide (ASO)
Aptamers
Antibodies
Small molecules



Weitz JI, Thromb Haemost 2017
Schulman S, Thromb Haemost 2017

Anti- FXI

Comparison of the Characteristics of the Various Factor XI Directed Anticoagulant Therapies.

Characteristic	ASO [27,29,39,42,43]	Antibodies [25,30]	Small Molecules [32-36]
Mechanism	Reduces hepatic synthesis of factor XI	Bind factor XI and blocks its activation or bind factor XIa and block its activity	Reversible active site inhibition
Delivery	Subcutaneous	Intravenous or subcutaneous	Oral
Onset of action	Slow	Rapid	Rapid
Offset of action	Slow	Slow	Rapid
Indications	Chronic	Acute or chronic	Acute or chronic

Weitz JI, Thromb Res 2016

FXI - ASO

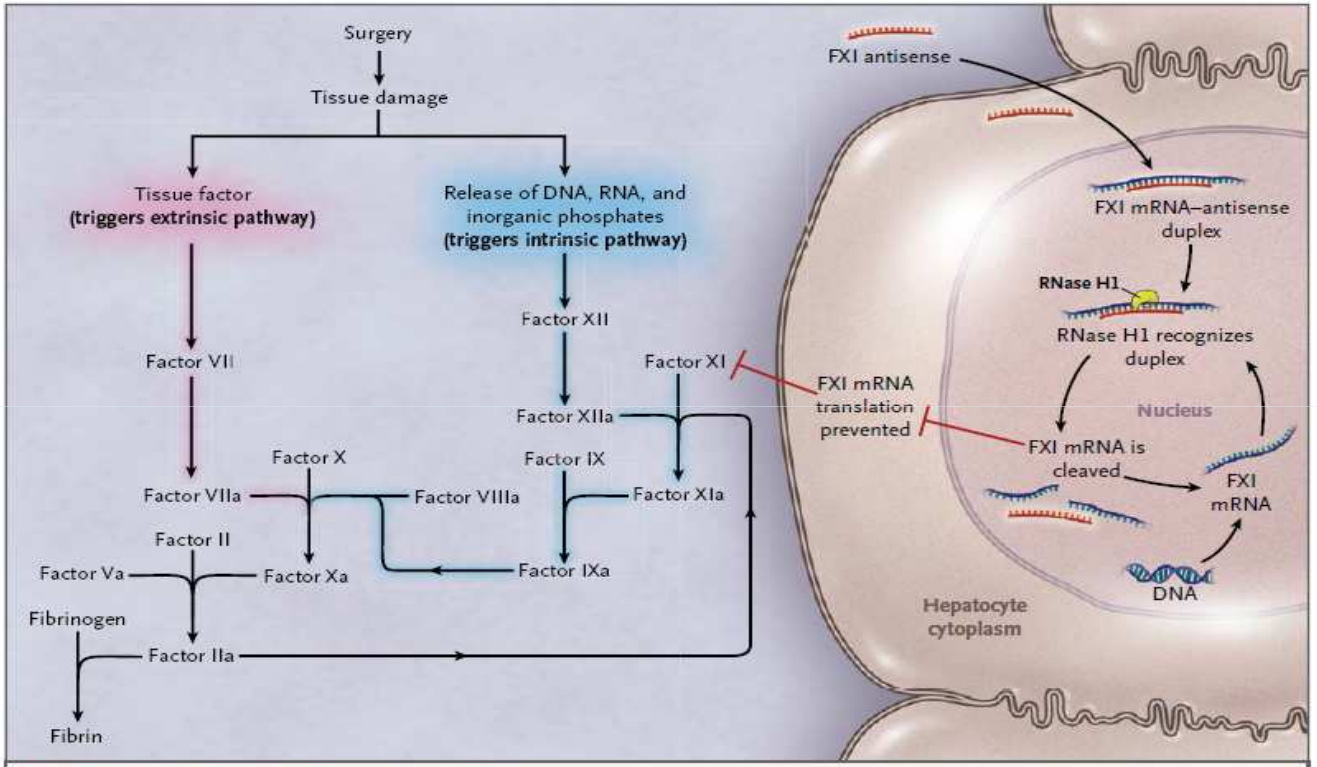
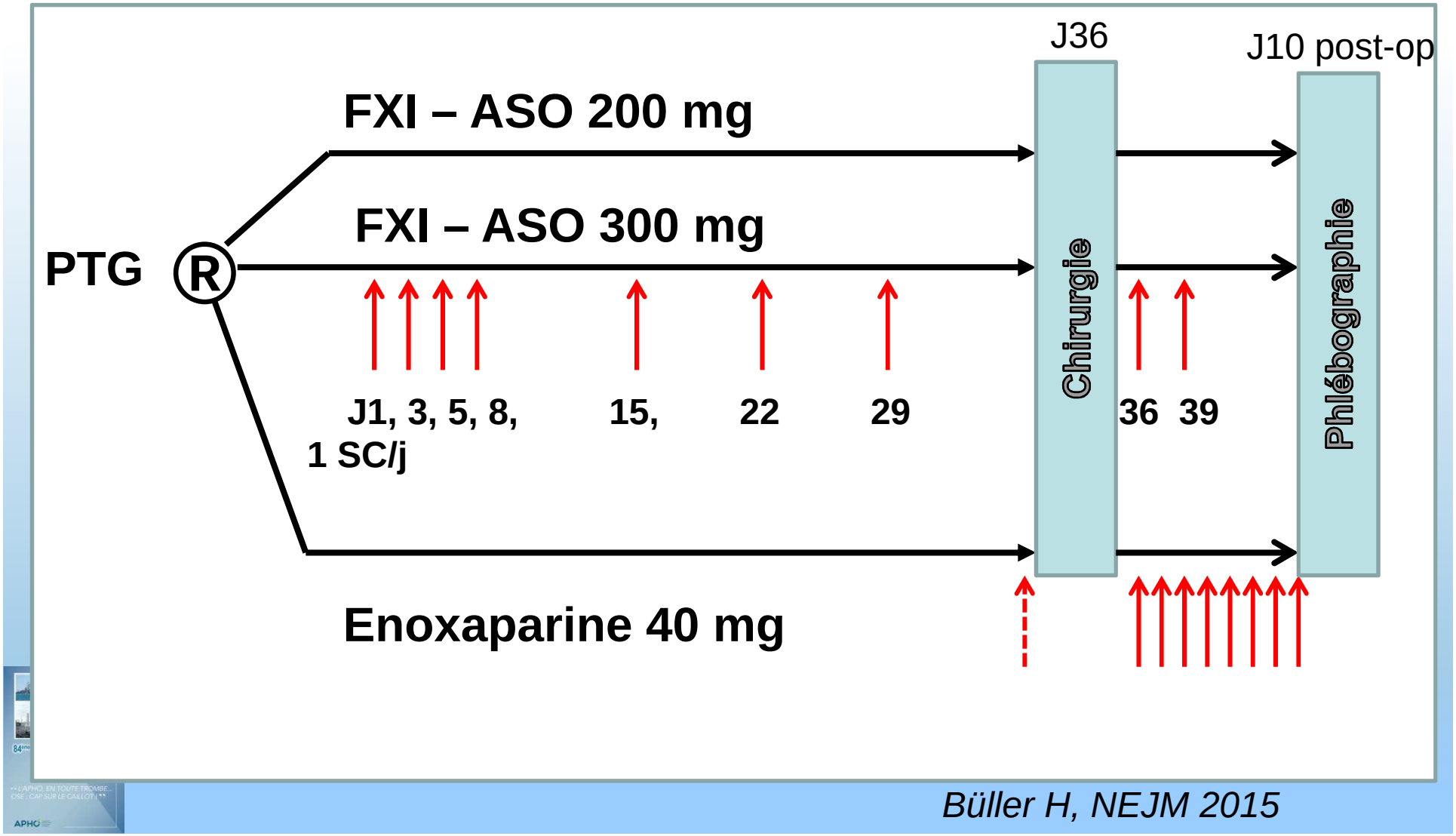


Figure 1. Effect of FXI-ASO on the Coagulation System.

FXI-ASO (ISIS 416858) is a factor XI (FXI)–targeted second-generation antisense oligonucleotide. Tissue damage after surgery exposes tissue factor and results in the release of DNA, RNA, and inorganic polyphosphate from damaged cells and from activated platelets and neutrophils. Tissue factor binds factor VIIa and initiates the extrinsic pathway of coagulation, whereas DNA, RNA, and polyphosphate activate factor XII and initiate the intrinsic pathway of coagulation. Factor XI–targeted antisense oligonucleotide attenuates the intrinsic pathway by binding to factor XI messenger RNA (mRNA) in the liver, which results in ribonuclease H1 (RNase H1)–mediated degradation of FXI messenger RNA, thereby preventing protein synthesis and reducing circulating FXI levels.

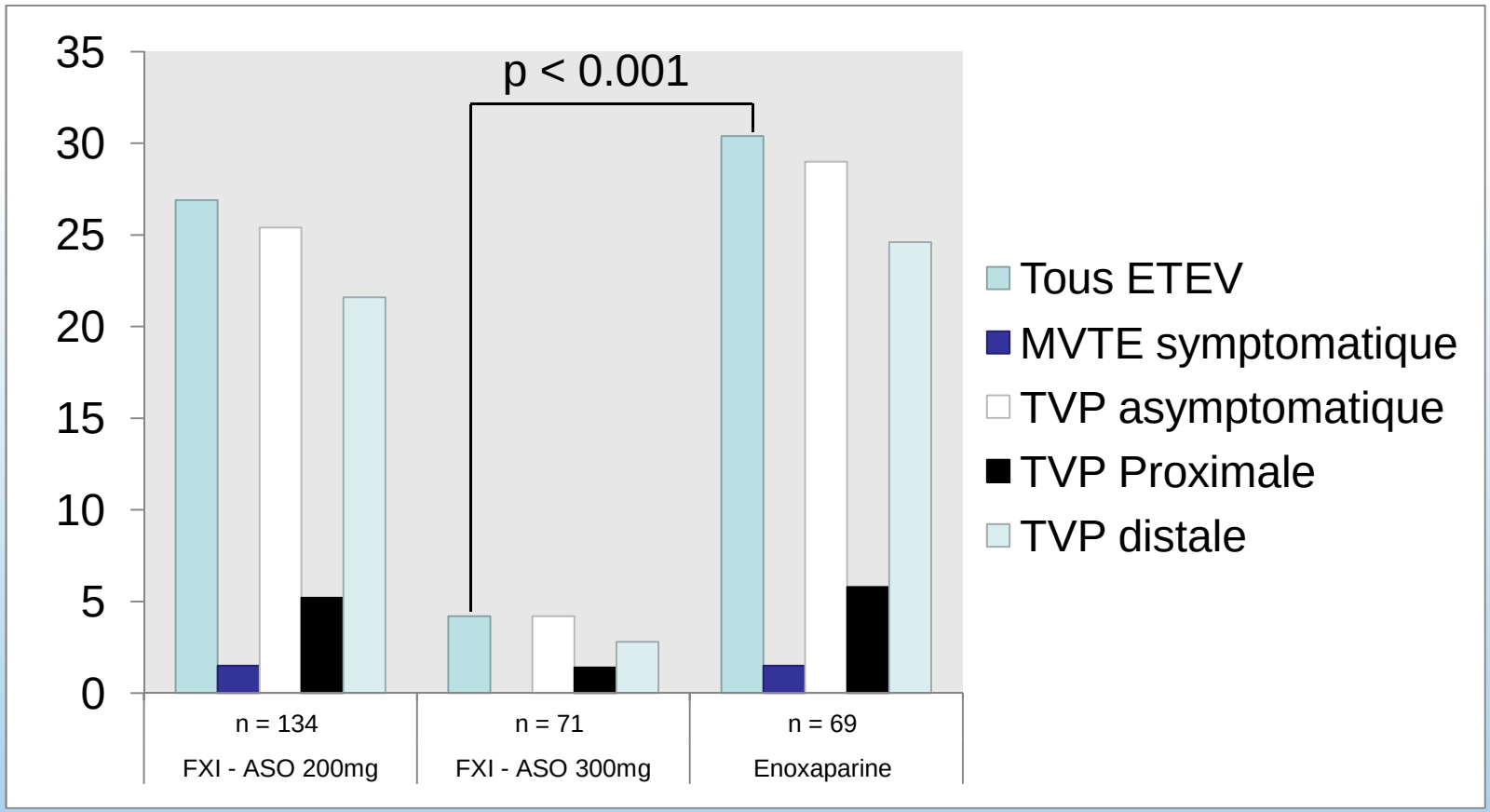
Büller H, NEJM 2015

FXI - ASO



Büller H, NEJM 2015

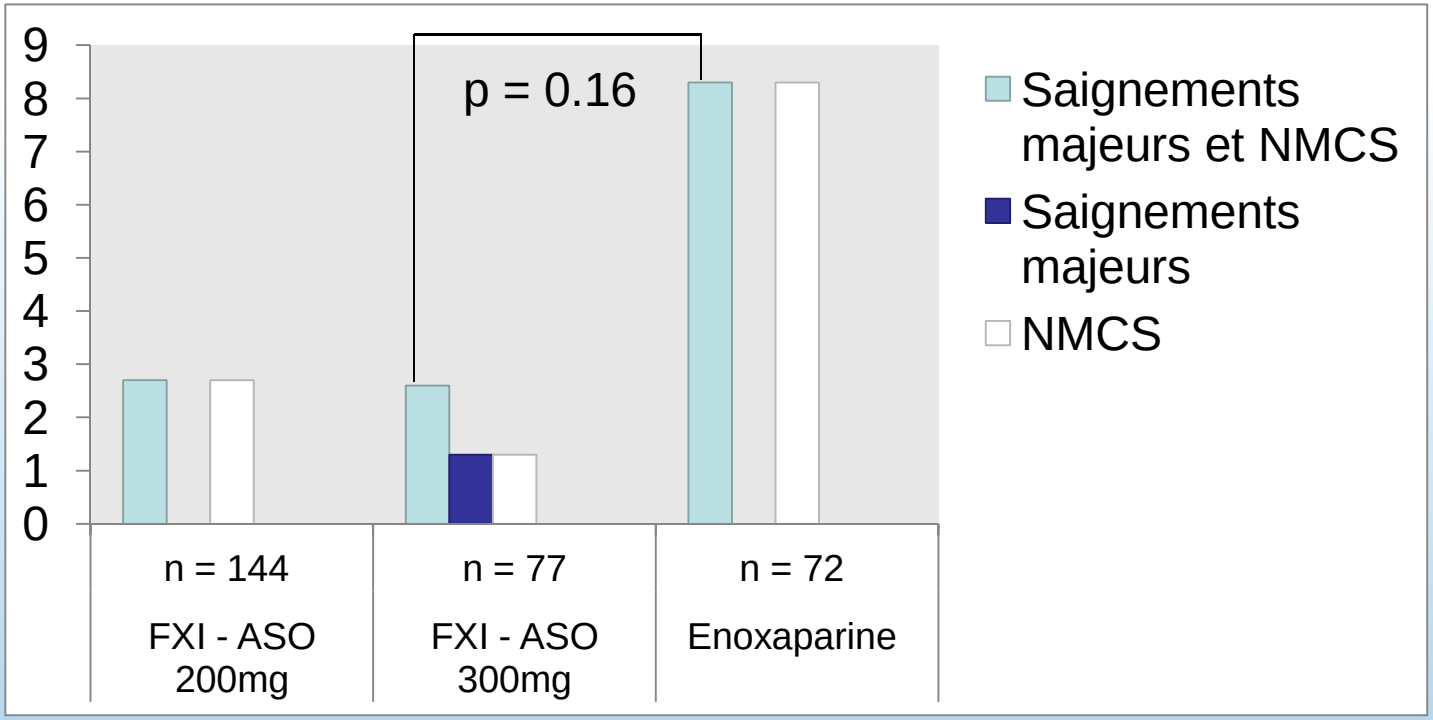
FXI - ASO



Tous ETEV: **4 %** FXI- ASO 300mg vs **30%** Enoxaparine, p de supériorité <0.001

Büller H, NEJM 2015

FXI - ASO



Saignements majeurs et non majeurs cliniquement significatifs:
2.6 % FXI- ASO 300 mg vs **8.3%** Enoxaparine, p <0.16

Büller H, NEJM 2015

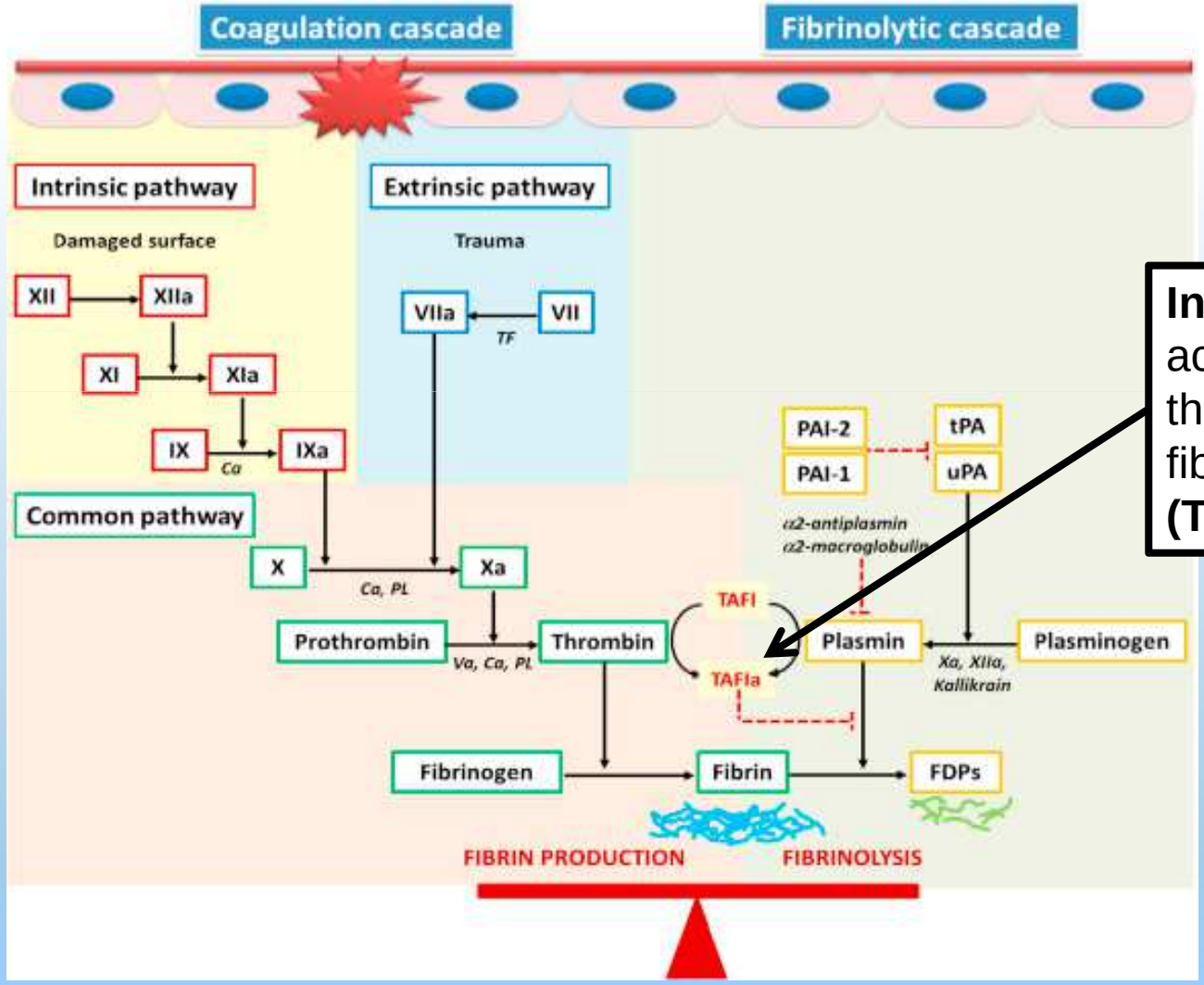
Anti FXI – Anti FXII

Potential Clinical Indications and Rationale for Factor XII or Factor XI Directed Anticoagulants.

Indication	Rationale
Elective knee arthroplasty	Provides proof-of-principle and permits head-to-head comparison of factor XII and factor XI directed therapies
Secondary prevention of venous thromboembolism	May be safer than current therapies and once or twice monthly injections with antibodies or ASO may be more convenient than daily oral therapy
Stroke prevention in atrial fibrillation patients with end stage renal disease on dialysis	Unmet medical need because of high risk of stroke, myocardial infarction and bleeding; lack of clear benefit of warfarin and NOACs contraindicated; factor XII or XI directed therapies may have a superior benefit-risk profile compared with aspirin or warfarin and may enable dialysis without heparin
Extracorporeal membrane oxygenation, left ventricular assist devices or mechanical heart valves	May be better than heparin at preventing clotting on extracorporeal membrane oxygenation circuits and may be safer than warfarin in patients with left ventricular assist devices or mechanical heart valves

Weitz JI, Thromb Res 2016
Weitz JI, ATVB 2018

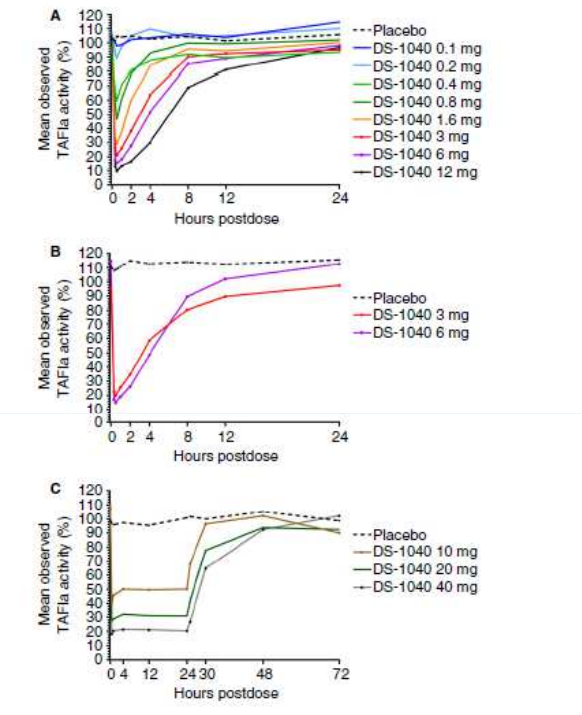
Nouvelles cibles: TAFIa

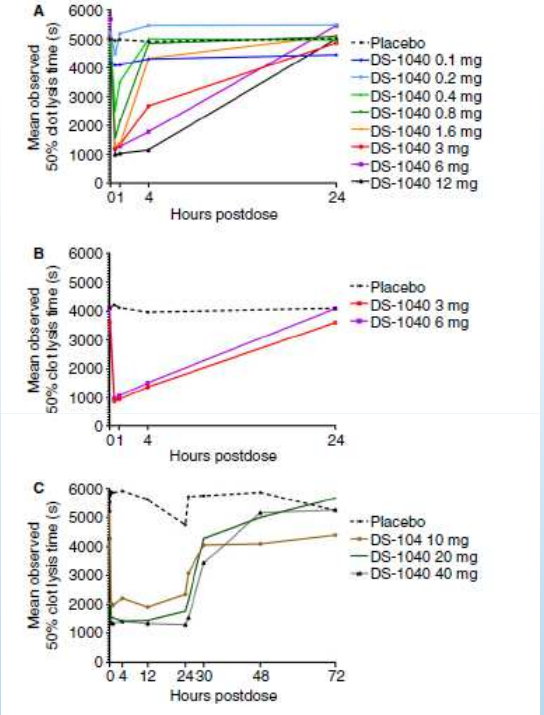


Inhibitor of the activated form of thrombin activatable fibrinolysis inhibitor **(TAFIa) (DS-1040)**

Noguchi K, J Thromb Haemost 2015

L’anti - TAFIa DS-1040





Profil PK-PD favorable
Profil de sécurité favorable

Noguchi K, J Thromb Haemost 2015

DS-1040: anti - TAFIa

- **Etudes en cours:**

NIH U.S. National Library of Medicine
ClinicalTrials.gov

  - Phase 1b/2, double-blind (Principal Investigators and study subjects blinded, Sponsor unblinded), placebo-controlled, randomized, single-ascending dose, multi-center study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of DS-1040b in **subjects with Acute Ischemic Stroke (AIS).**

  - A Phase I, Single Blind, Placebo-controlled, Randomized Study to Assess the Safety of DS-1040b in **Subjects With Thrombectomy Treated Acute Ischemic Stroke**

  - A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Single Ascending Dose Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of DS-1040b When Added to Standard of Care Anticoagulation Therapy in **Subjects With Acute Submassive Pulmonary Embolism**