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Gestion des gestes invasifs et hémorragiques sous anticoagulants oraux directs (AOD)

Charles Marc SAMAMA

Pôle Anesthésie Réanimations Thorax Explorations

GIHP Groupe d'intérêt en hémostase péri-opératoire

UNIVERSITÉ PARIS DESCARTES

European Society of Anaesthesiology ESA

Conflits d'intérêt - Diapositives

Firmes et produits (DCI):

Aspen (nadroparine – fondaparinux) – Bayer (rivaroxaban) – BMS (apixaban)

Boehringer-Ingelheim (dabigatran) - CSL Behring (CCP) – Covidien-Medtronic (CPI)

Daïchi Sankyo (edoxaban)- LFB (CCP - fibrinogène) - Octapharma (CCP)

Portola (betrixaban – andexanet) - Pfizer (daltéparine, apixaban) – Roche (POC)

Stago (tests specific anti-Xa)

Agences, societés et recommandations :

ACCP : 8th, 9th and **10th Guidelines**

ESA guidelines on VTE prophylaxis

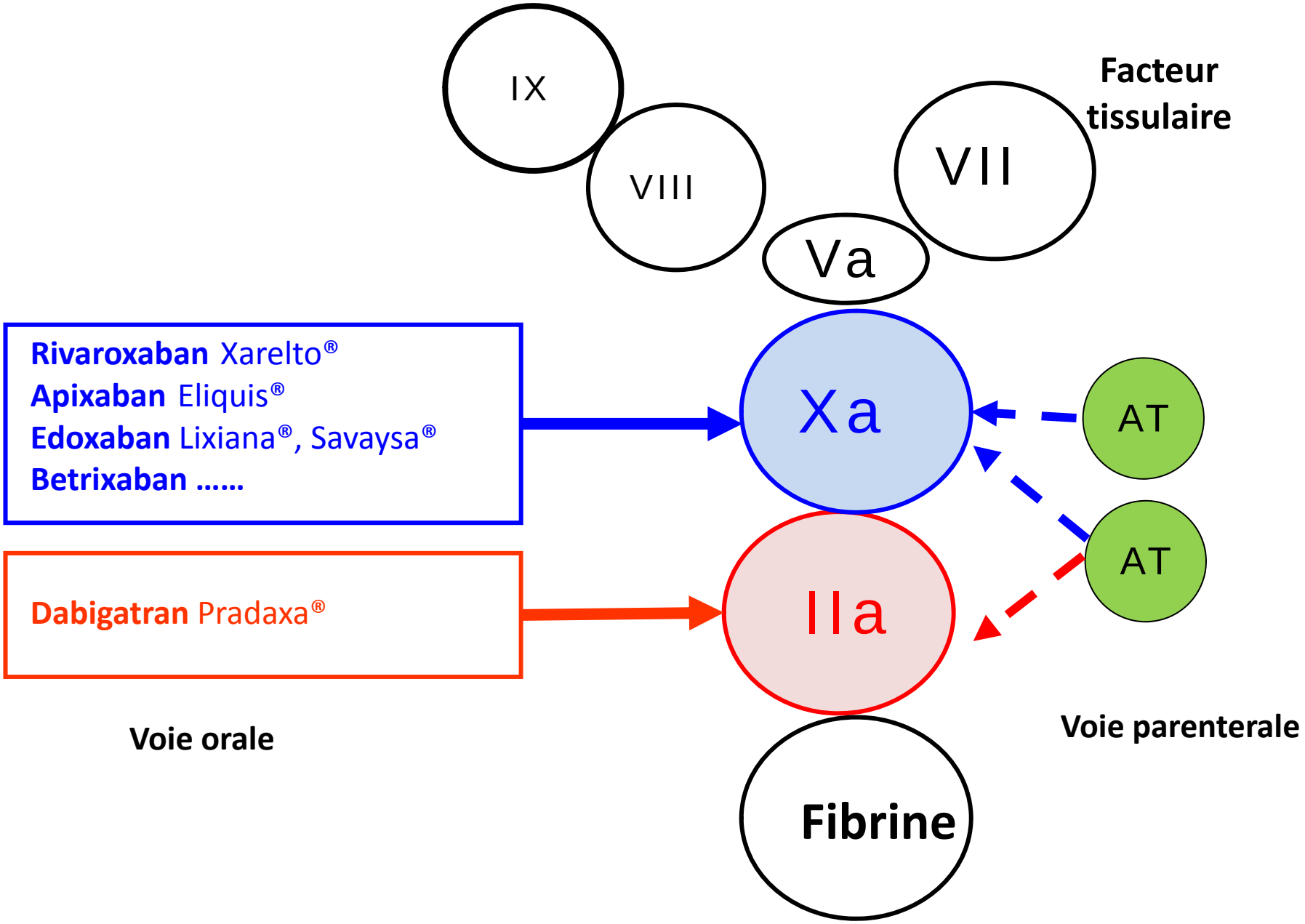
EMA : efficacy working party (expert consultant)

INSERM : Innovations Thérapeutiques en Hémostase (UMR_1140)

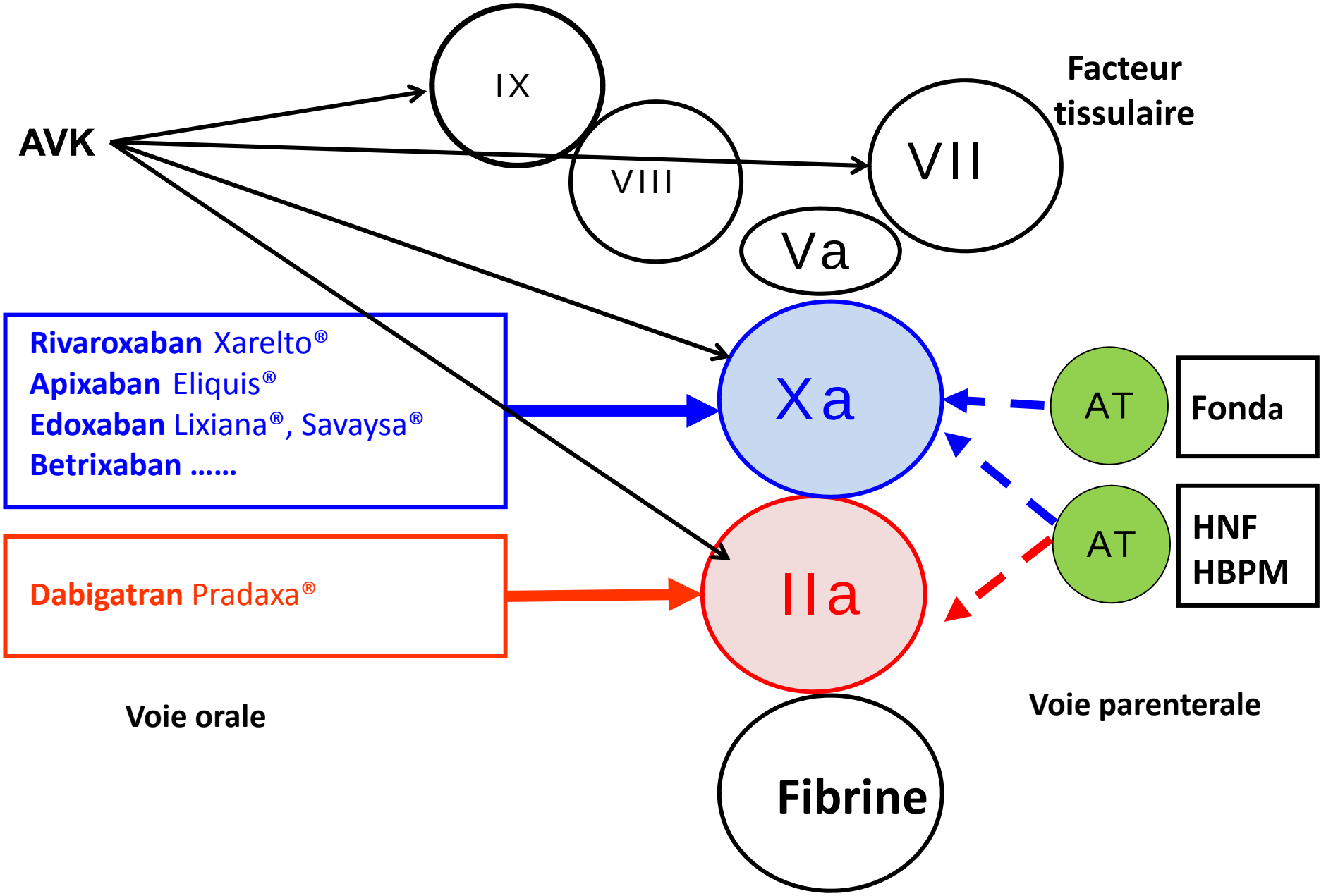
Diapos – remerciements :

Pierre Albaladejo (Grenoble), Jacqueline Conard (Paris), Ismael El-Alamy (Paris), Nadia Rosencher (Paris)

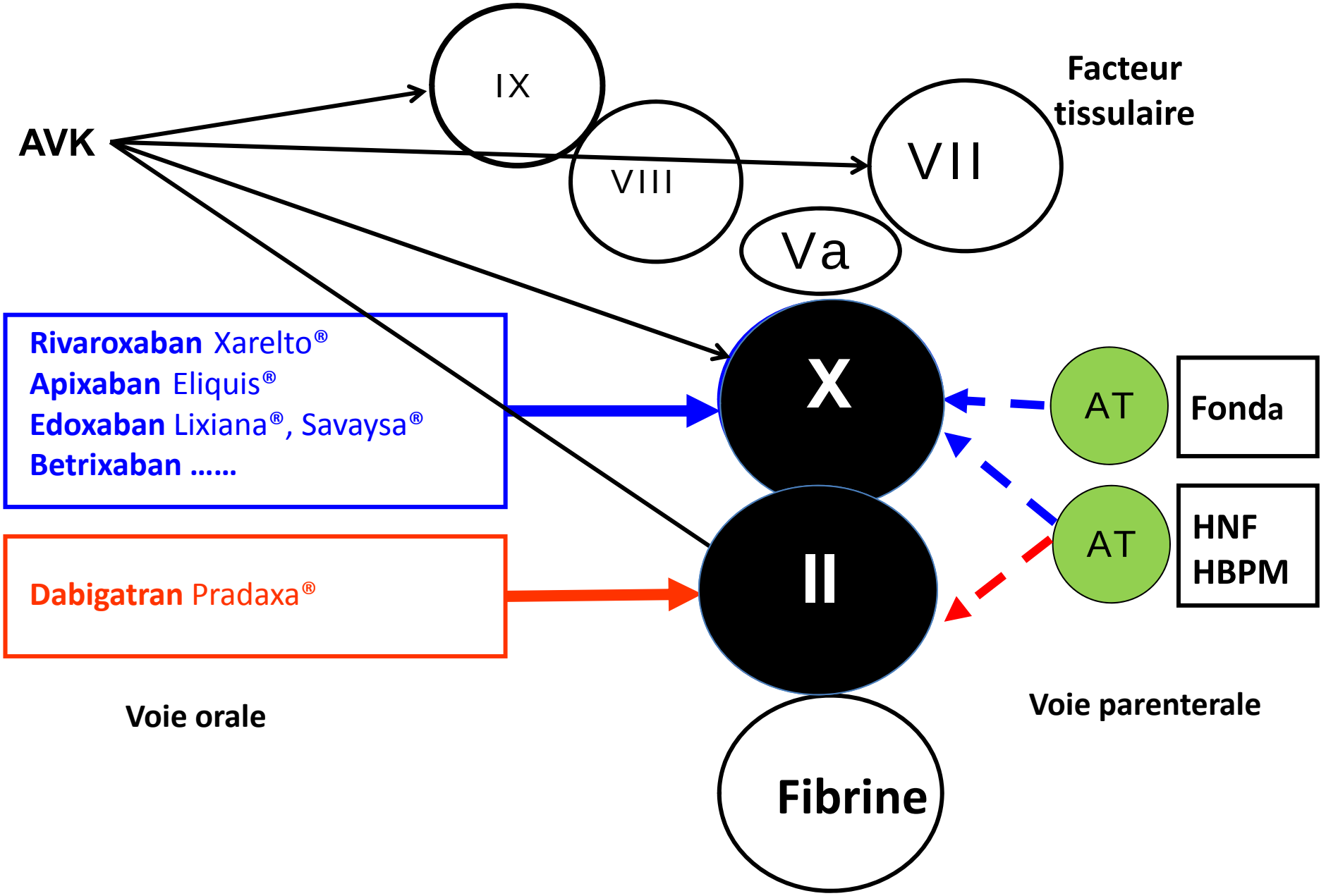
Les AOD ont une cible spécifique et unique



Les AOD ont une cible spécifique et unique



Les AOD ont une cible spécifique et unique



Pharmacologie

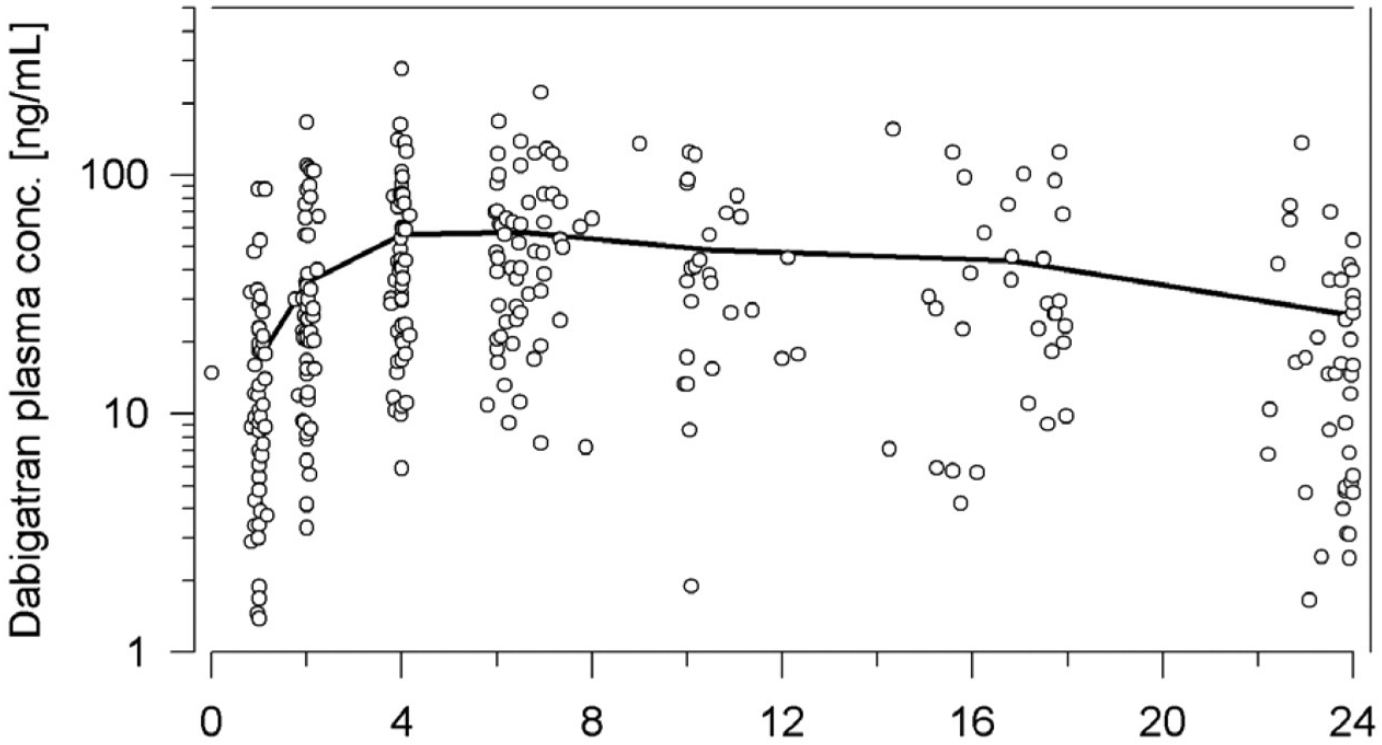
	Anti-IIa	Anti-Xa		
	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Bioavailability	3-7%	50%	62%	66% (w/o food) ~100% with food
Prodrug	yes	no	no	no
Clearance: non-renal/renal of adsorbed dose if normal renal function	20%/80%	73%/27%	50%/50%	65%/35%
Liver metabolism: CYP3A4	no	yes (elimination; minor CYP3A4)	minimal (<4% of elimination)	yes (elimination)
Absorption with food	no effect	no effect	6-22% more	+39%
Intake with food?	no	no	no official recommendation yet	mandatory
Absorption with H2B/PPI	plasma level -12 to -30%	no effect	no effect	no effect
Asian ethnicity	plasma level +25%	no effect	no effect	no effect
GI tolerability	dyspepsia 5-10%	no problem	no problem	no problem
Elimination half-life	12-17h	12h	9-11h	5-9h (young)/11-13h (elderly)

* not approved yet

Gestion périopératoire

Variabilité inter- et intra-individuelle

dabigatran 150 mg sd PTH (Bistro Ib)



Stangier 2005

CV (%) de la concentration plasmatique de dabigatran, 12 h après 150 mg:
PETRO-EX: 91 %, RELY: 81 % , BISTRO II: 87 %

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients in the RE-LY Trial.

Journal of the American College of Cardiology, 2013

Paul A. Reilly,[a *] PhD, Thorsten Lehr [b,c*] PhD, Sebastian Haertter,[b] PhD, Stuart J Connolly,[d] MD, FACC, Salim Yusuf,[d] MD, DPhil, FACC, John W. Eikelboom,[d] MBBS, Michael D. Ezekowitz,[e] MD, PhD, FACC, Gerhard Nehmiz [b] PhD, Susan Wang,[a] PhD, and Lars Wallentin,[f] MD, PhD on behalf of the RE-LY investigators.

Plasma concentrations of dabigatran were available from 9,183 and 8,449 patients for peak and trough measurements, respectively.

The geometric mean trough concentrations were 64.7 and 91.0 ng/mL for the Dabigatran 110mg b.i.d and Dabigatran 150 dg b.i.d doses, respectively, with 10th to 90th percentiles of 28.2 to 155 ng/mL for Dabigatran 110 and 39.8 to 215 ng/mL for Dabigatran 150, **a 5.2 to 5.5-fold range of variation**

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[#] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect* but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[**] (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[251]	No data yet	No effect	No effect[252]
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin[***]	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[247]

Continued

Exemples d'interactions médicamenteuses

Heidebuchel H et al. Recos ESC 2015. Europace. 2015;17:1467–507

Comparison of calibrated dilute thrombin time and aPTT tests with LC-MS/MS for the therapeutic monitoring of patients treated with dabigatran etexilate

Jonathan Douxfils[1]; Jean-Michel Dogné[1]; François Mullier[1, 2]; Bernard Chatelain[2]; Yuko Rönquist-Nii[3]; Rickard E. Malmström[3]; Paul Hjemdahl[3]

Thromb Haemost 2013; 110: 543–549

Temps de thrombine dilué (Hemoclot®)

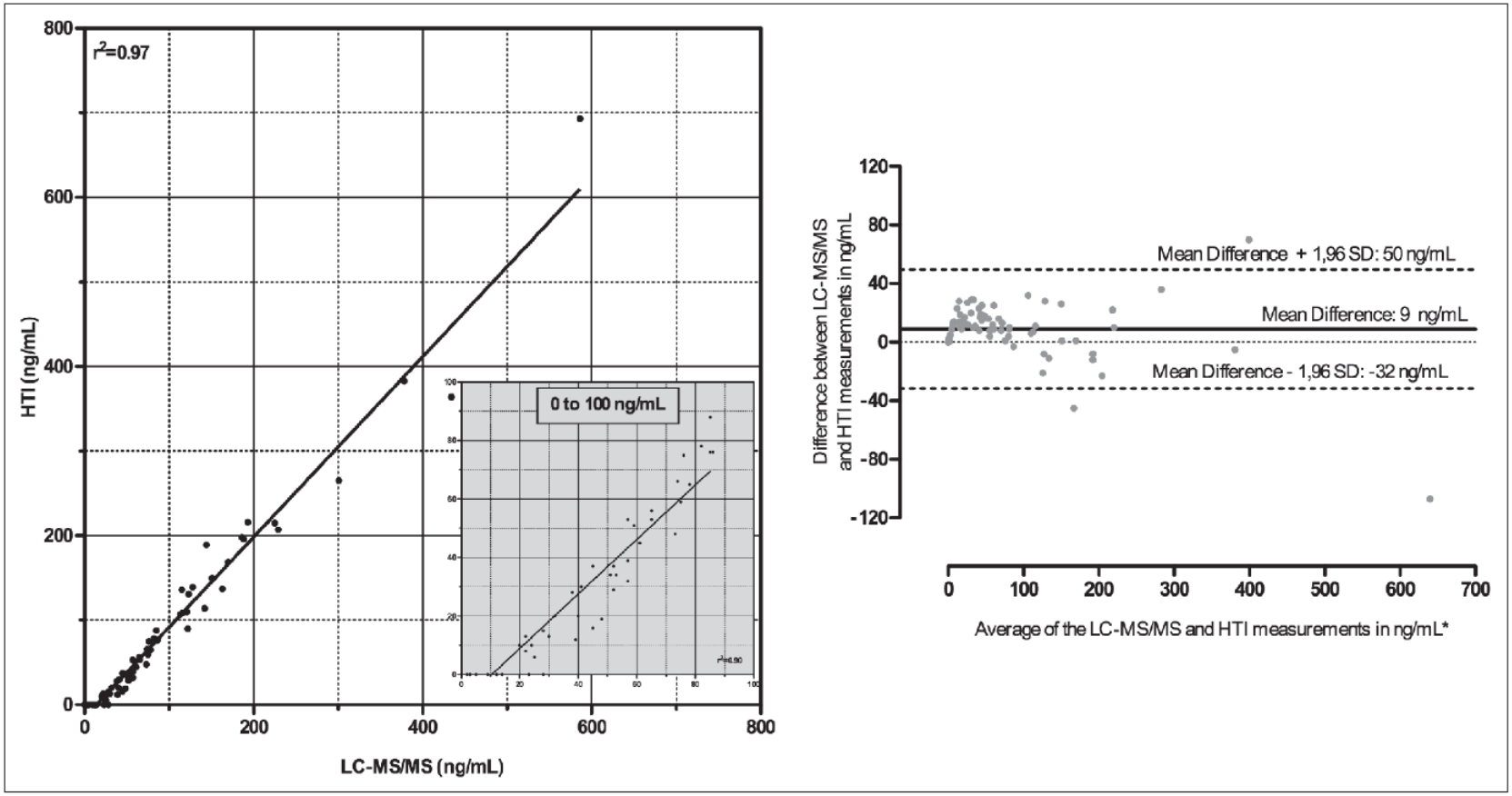
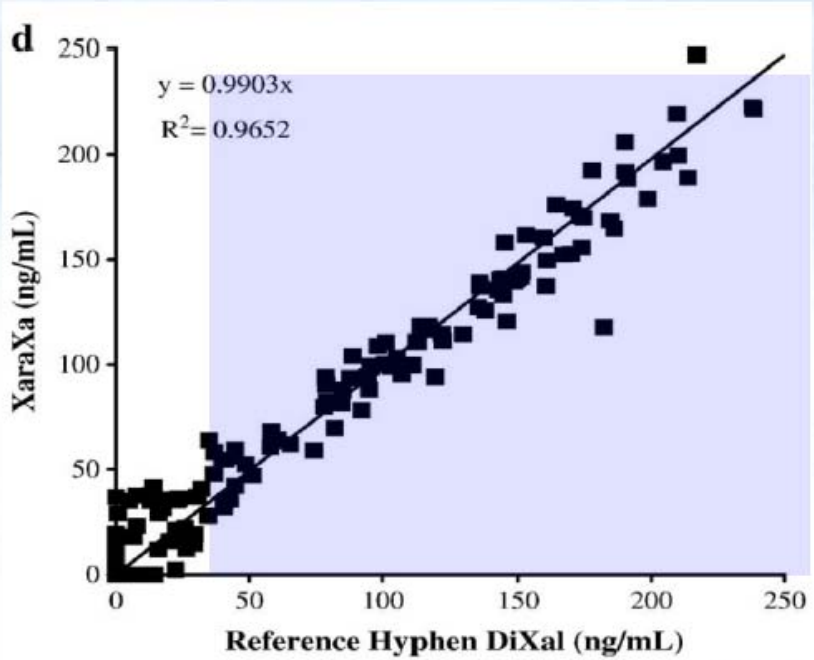


Figure 1: Correlation and Bland-Altman analysis between liquid chromatography-tandem mass spectrometry (LC-MS/MS) and the Hemoclot® Thrombin Inhibitors (HTI) assay for the measurement of dabigatran concentrations in patient plasma samples. The insert shows the relationship at dabigatran concentrations ≤100 ng/ml as determined by LC-MS/MS. Nine patients with HTI results of 0 ng/ml had measurable dabigatran concentrations by LC-MS/MS. (Highest concentration measured by LC-MS/MS giving 0 ng/ml with HTI is 28 ng/ml.) For the Bland-Altman analysis the difference is calculated as follow: [difference (A-B) vs average] where A is the result of the LC-MS/MS and B the result of HTI.

Concentration en rivaroxaban : Anti-Xa spécifique

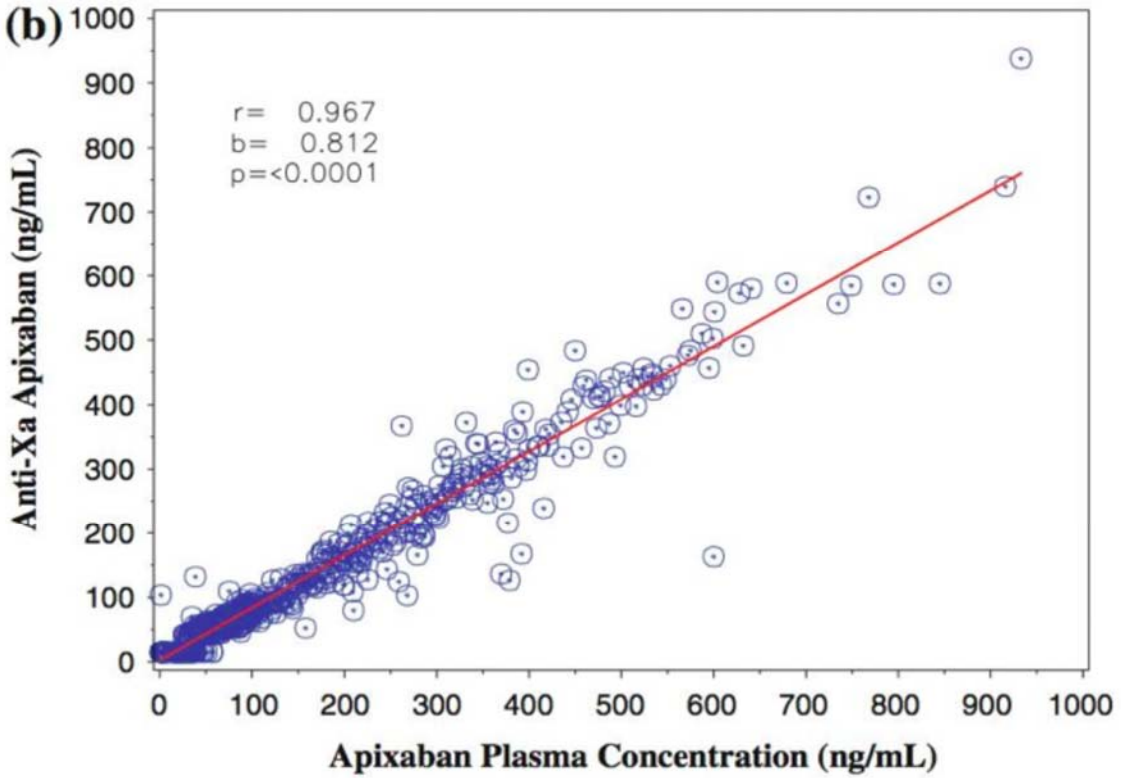


Freyburger G. Thrombosis Research 2011

Tests spécifiques :
Adaptation des tests de mesure de l'activité anti-Xa utilisés pour les héparines
calibration avec plasmas titrés en rivaroxaban

Enzyme -cible	méthode	Nom du test	Fournisseur
facteur Xa	chromogénique	Biophen DiXal®	Hyphen BioMed
facteur Xa	chromogénique	STA Liquid anti-Xa®	Diagnostica Stago

Anti-Xa spécifique et apixaban



Becker RC et al. J Thromb Thrombol 2011;32:183–7

Apixaban, TP et TCA

Assessment of apixaban plasma levels by laboratory tests: suitability of three anti-Xa assays

A multicentre French GEHT study

Isabelle Gouin-Thibault[1,2]; Claire Flaujac[2]; Xavier Delavenne[3]; Sara Quenet[3]; Marie-Hélenè Horellou[2]; Silvy Laporte[3]; Virginie Siguret[4]; Thomas Lecompte[5]

doi:10.1160/TH13-06-0470
Thromb Haemost 2014; 111: 240–248

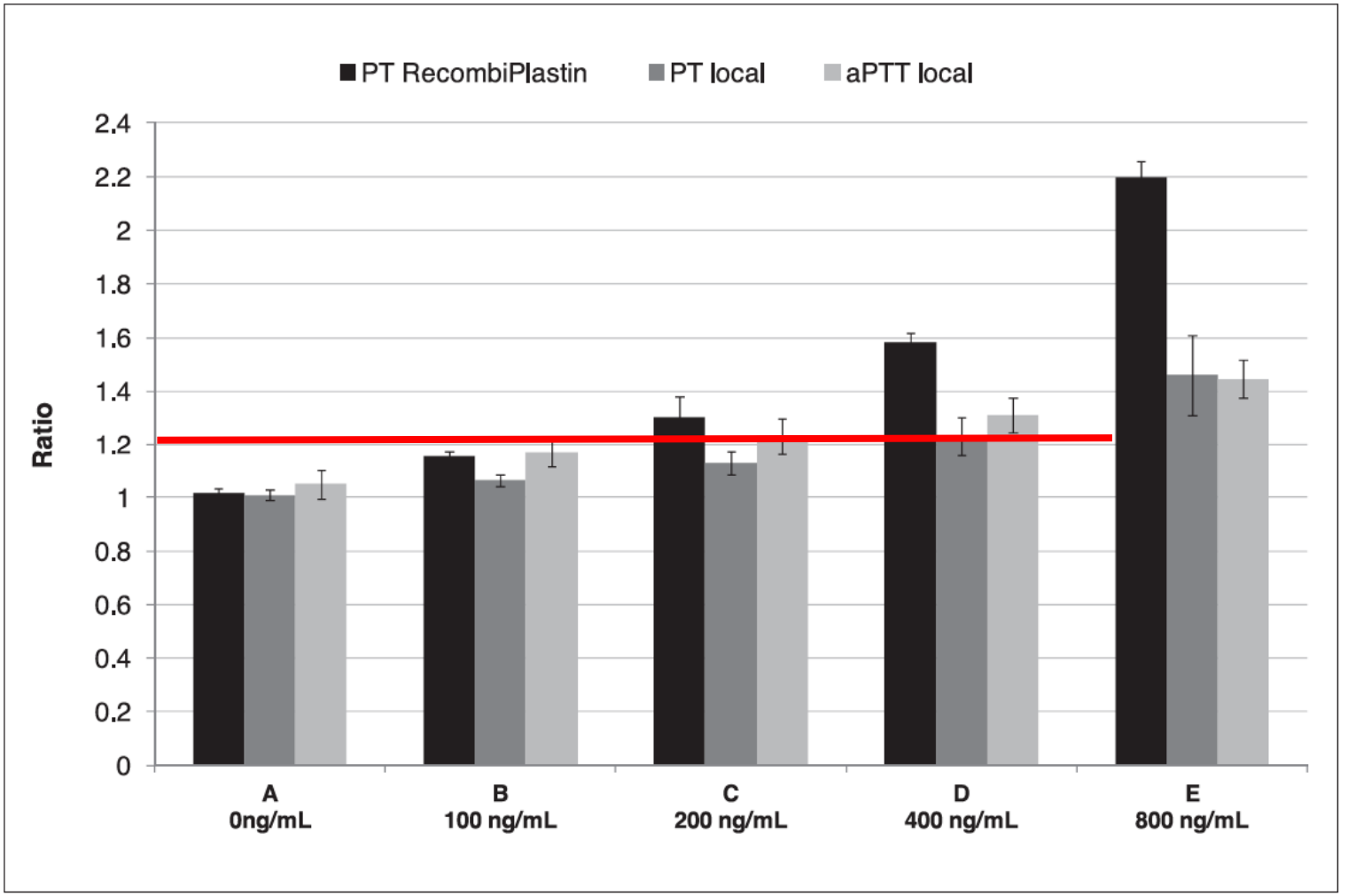


Figure 1: PT measurements with Recombi-Plastin 2G® or local reagents and APTT measurements with local reagents in plasmas A, B, C, D and E measured in the 13 laboratories.

Tests spécifiques

- **Rivaroxaban**
  - activité **anti-FXa spécifique**
  - TP et TCA modifiés selon le réactif (TP plus sensible)

- **Apixaban**
  - activité **anti-FXa spécifique**
  - TP et TCA peu ou pas allongés

- **Dabigatran**
  - Temps d'écarine, temps de thrombine dilué (**Haemoclot®)**
  - TP et TCA modifiés selon le réactif (TCA plus sensible)

MM Samama et al. *Clin Chem Lab Med* 2011;49:761

Dosages pré-op

Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study

Anne Godier[1,2]*, Anne-Sophie Dincq[3], Anne-Céline Martin[2,4], Adrian Radu[5], Isabelle Leblanc[6], Marion Antona[7], Marc Vasse[8,9], Jean-Louis Golmard[10], François Mullier[11], and Isabelle Gouin-Thibault[2,12,13]

European Heart Journal (2017) **38**, 2431–2439

- Etude prospective multicentrique, 422 patients traités par AOD nécessitant une procédure invasive
- **Mesure des concentrations pré-interventionnelles en AOD et des tests de routine d'hémostase**

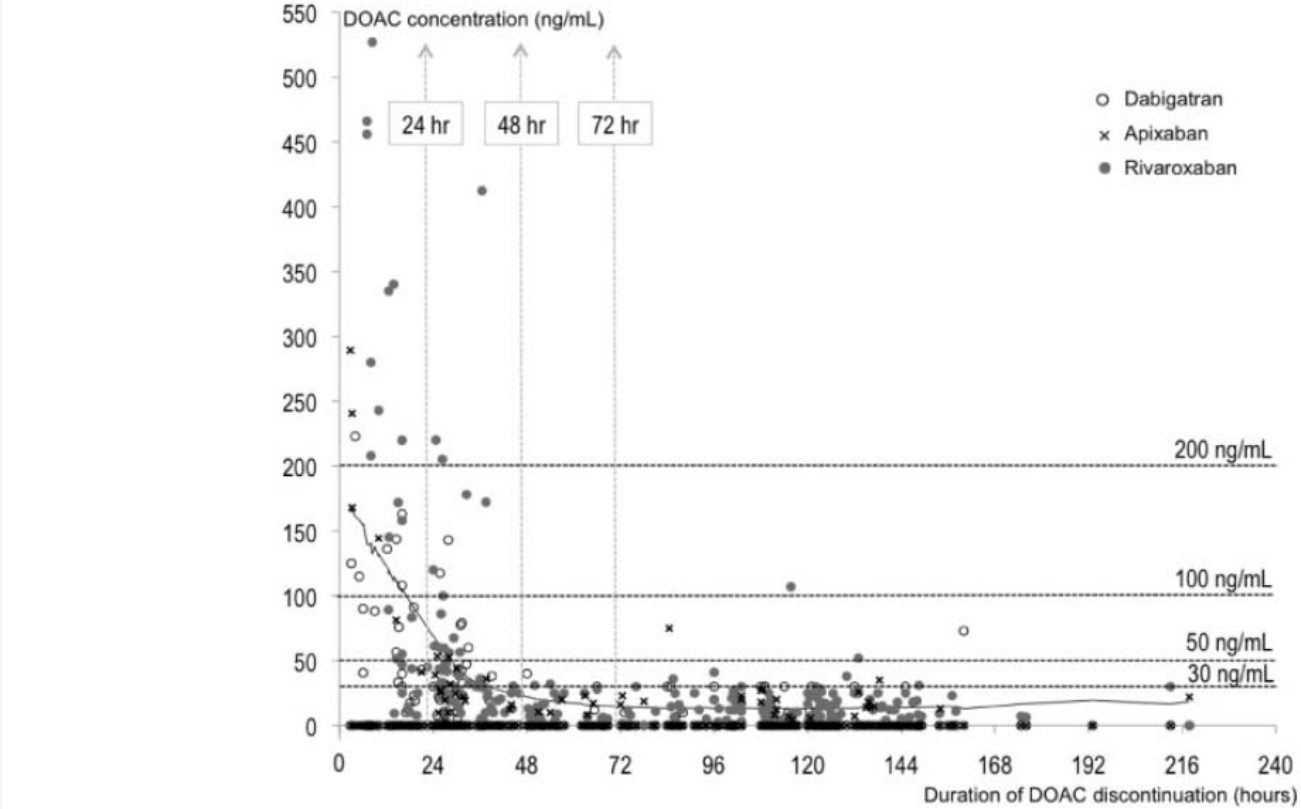


Figure 1 Fit plot of DOAC concentrations measured at the time of invasive procedure according to the duration of DOAC discontinuation. DOAC, direct oral anticoagulant.

Dosages pré-op

Après une interruption de 49–72-h de l'AOD, 95% des concentrations étaient inférieures à 30 ng/mL.

Une dernière prise à J-3 avant la procédure aboutissait à une concentration minimale d'AOD chez la grande majorité des patients

Les tests de routine (TP, TCA) n'étaient pas prédictifs de la concentration en AOD.
La clairance de la créatinine<50 mL/min, les antiplaquettaires et les procédure à haut risque hémorragique étaient prédictifs des complications hémorragiques.

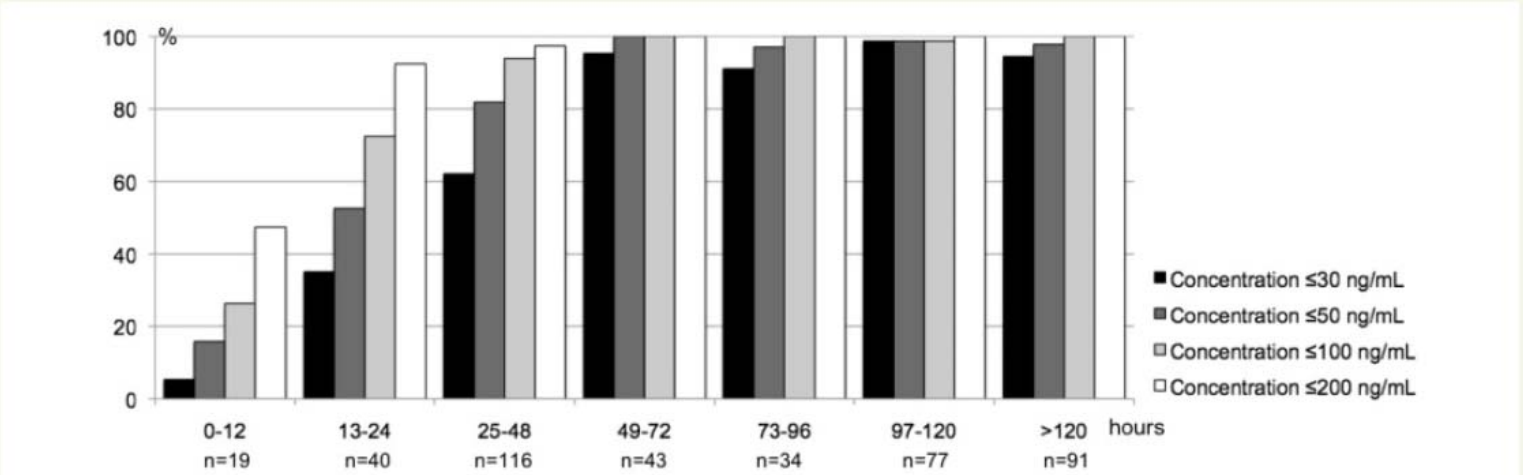


Figure 2 Proportion of patients with DOAC concentrations below various threshold values (30; 50; 100, and 200 ng/mL) at the time of the invasive procedure according to the duration of DOAC discontinuation. *n*: the number of patients with measured concentrations by duration of DOAC discontinuation. Each patient had a single blood sample taken in the operating room just before the beginning of the invasive procedure.

GIHP Groupe d'intérêt en hémostase péri-opératoire

Suggestions

Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure

Substudy of the RE-LY trial

James D. Douketis[1]; Jeff S. Healey[1,2]; Martina Brueckmann[3,4]; John W. Eikelboom[1,2]; Michael D. Ezekowitz[5]; Mandy Fraessdorf[3]; Herbert Noack[3]; Jonas Oldgren[6]; Paul Reilly[7]; Alex C. Spyropoulos[8]; Lars Wallentin[6]; Stuart J. Connolly[1,2]

Thromb Haemost 2015; 113: 625–632

Pas de relais !

Clinical outcome	Bridging status	Warfarin group (n = 1,415)		Dabigatran group (2,691)	
		% (N) patients with events /(N) patients assessed	OR (95 % CI): bridged vs not bridged‡	% (N) patients with events /(N) patients assessed	OR (95 % CI): bridged vs not bridged‡
Major bleeding	Bridged	6.8 (26/383)	4.62 (2.45–8.72),	6.5 (27/417)	3.68 (2.24–6.04),
	Not bridged	1.6 (16/1,032)	P <0.001	1.8 (42/2,274)	P <0.001
	Treatment interaction (warfarin vs. dabigatran) ¶	p = 0.577			
Stroke and systemic embolism	Bridged	0.5 (2/383)	2.70 (0.38–19.3),	0.5 (2/417)	1.82 (0.37–9.06),
	Not bridged	0.2 (2/1,032)	P = 0.321	0.3 (6/2,274)	P = 0.463
	Treatment interaction (warfarin vs. dabigatran) ¶	p = 0.760			
Any thrombo-embolism	Bridged	1.8 (7/383)	6.39 (1.64–24.8),	1.2 (13/417)	2.11 (0.75–5.95),
	Not bridged	0.3 (3/1,032)	P =0.007	0.6 (5/2,274)	P = 0.158
	Treatment interaction (warfarin vs. dabigatran) ¶	p = 0.204			

†27 patients (9 bridged, 18 not bridged) excluded from total sample (described in Table 1) due to missing creatinine clearance values to enable better comparison of univariate and multivariable logistic regression models; ‡odds ratios obtained from univariate logistic analysis within treatment groups; ¶p-value of interaction from logistic model with treatment, bridging and treatment by bridging interaction; OR, odds ratio; CI, confidence interval. ¥inclusion of 27 patients with missing creatinine clearance values did not significantly affect clinical outcome results in bridged and not bridged patients.

Europace Advance Access published August 31, 2015

Europace doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Recos ESC 2015: interruption des AOD

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

Propositions GIHP 2016

<table>
<tr><th>GIHP Groupe d'intérêt en hémostase péri-opératoire</th><th>Risque hémorragique faible</th><th colspan="3">Risque hémorragique élevé</th></tr>
<tr><td rowspan="3">Avant le geste</td><td rowspan="3">Pas de prise la veille au soir ni le matin de l'acte invasif</td><td>rivaroxaban
apixaban
edoxaban</td><td>Cockcroft
≥ 30 ml/mn</td><td>Dernière prise à J-3</td></tr>
<tr><td rowspan="2">dabigatran</td><td>Cockcroft
≥ 50 ml/mn</td><td>Dernière prise à J-4</td></tr>
<tr><td>Cockcroft
30-49 ml/mn</td><td>Dernière prise à J-5</td></tr>
<tr><td colspan="4">Pas de relais
Pas de dosage</td></tr>
<tr><td rowspan="2">Après le geste</td><td rowspan="2">Reprise à l'heure habituelle et au moins 6 h après la fin de l'acte invasif</td><td colspan="3">Anticoagulant à dose « prophylactique »
au moins 6 heures après l'acte invasif, si une thromboprophylaxie veineuse est indiquée</td></tr>
<tr><td colspan="3">Anticoagulant à dose « curative »
dès que l'hémostase le permet
(à titre indicatif: entre 24 et 72 heures)</td></tr>
</table>

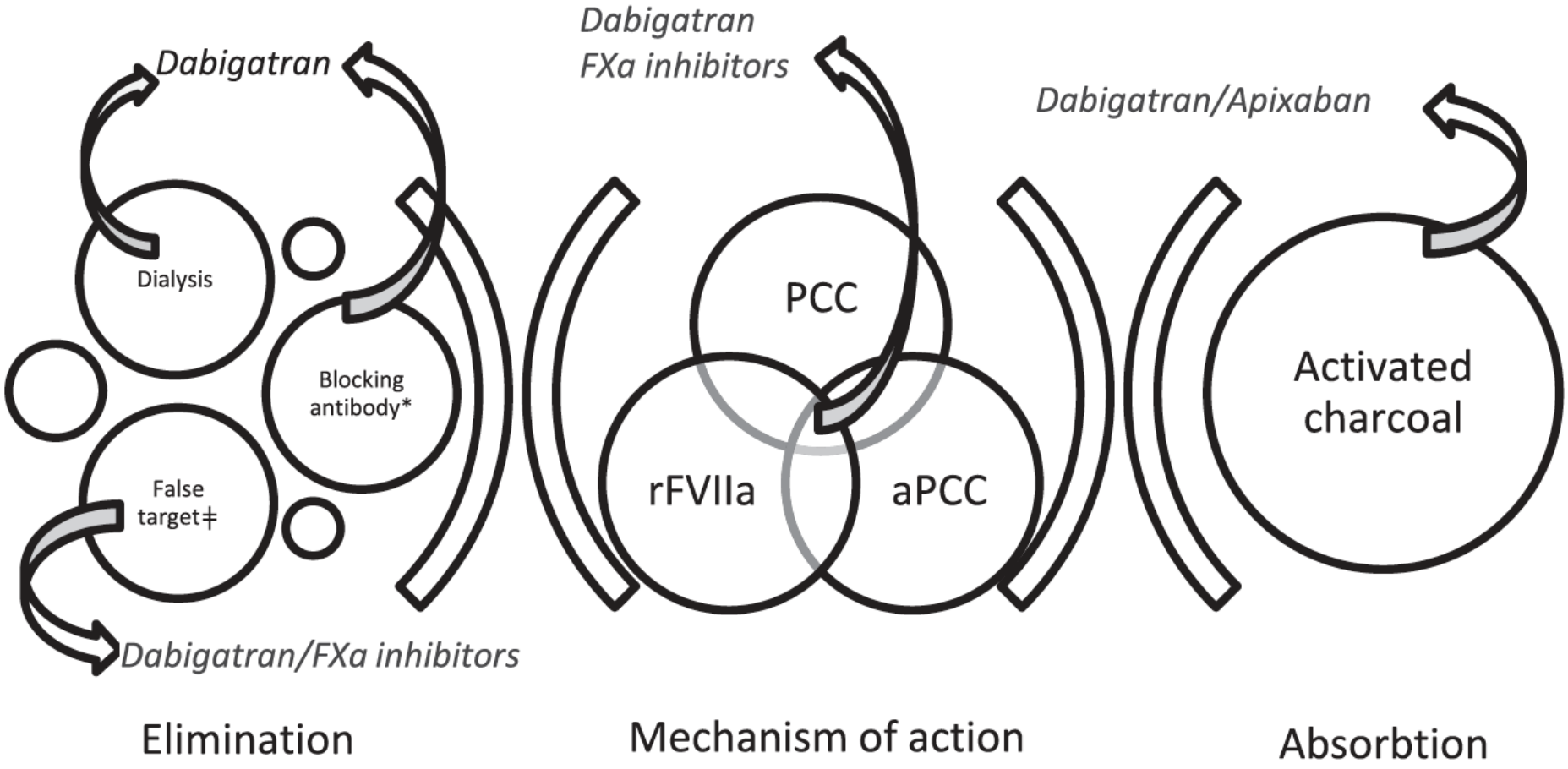
Procédures en urgence ou hémorragies ?

Antidotes for Novel Oral Anticoagulants
Current Status and Future Potential

Mark Crowther, Mark A. Crowther

Arterioscler Thromb Vasc Biol. 2015;35:1736-1745

Comment réverser ?



Agents de réversion non-spécifiques

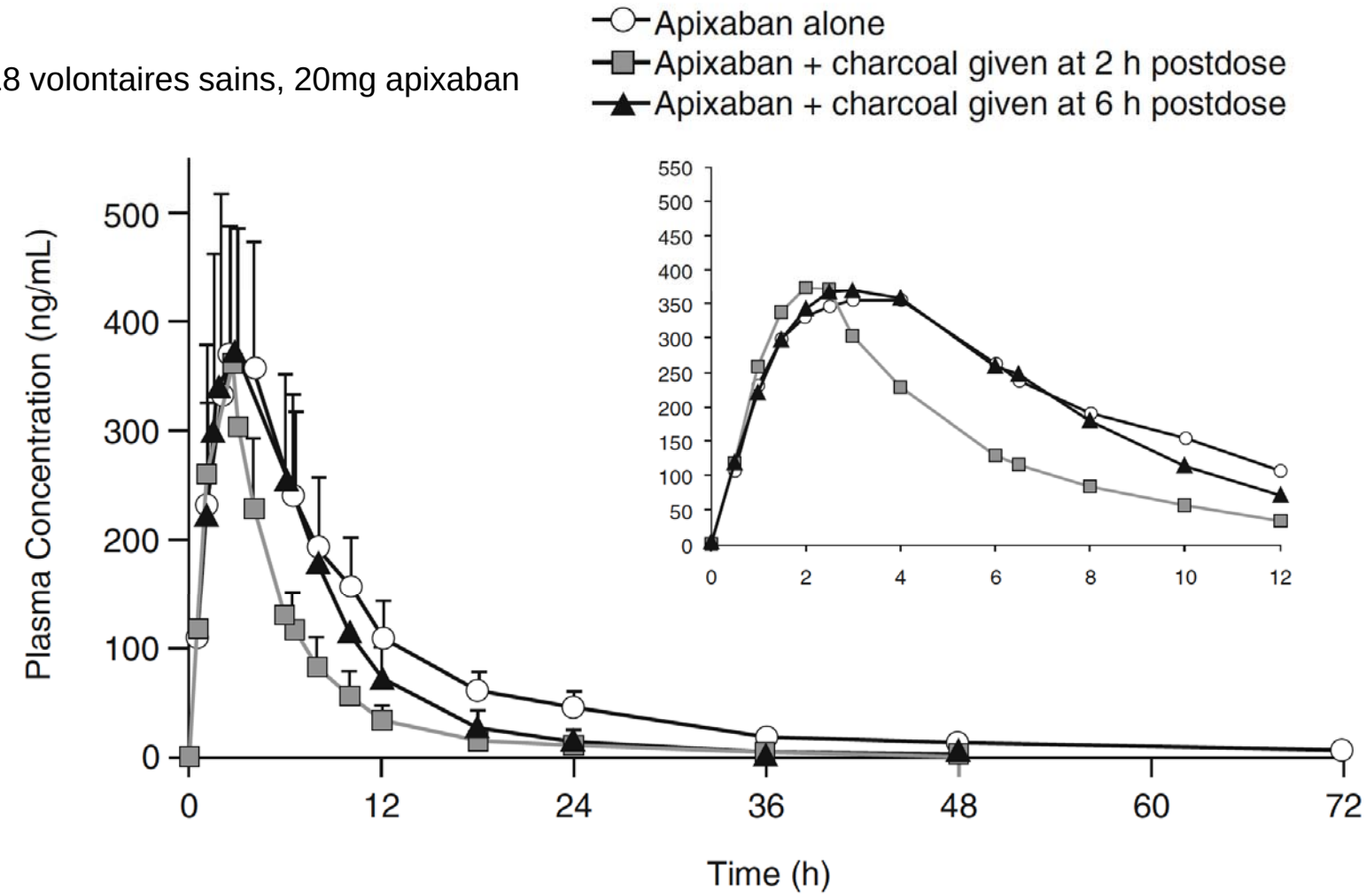
Effect of Activated Charcoal on Apixaban Pharmacokinetics in Healthy Subjects

Xiaoli Wang · Sabiha Mondal · Jessie Wang · Giridhar Tirucherai · Donglu Zhang · Rebecca A. Boyd · Charles Frost

Charbon actif

Am J Cardiovasc Drugs, 2013, Nov

18 volontaires sains, 20mg apixaban



La demi-vie de l'apixaban (13,4 h) était réduite à 5 h quand 50g de charbon actif était administré per os 2h ou 6h après la prise de l'AOD.

Effective elimination of dabigatran by haemodialysis

A phase I single-centre study in patients with end-stage renal disease

Dmytro Khadzhynov[1]*; Frank Wagner[2]*; Stephan Formella[3]; Erol Wiegert[2]; Viktoria Moschetti[3]; Torsten Slowinski[1]; Hans-H. Neumayer[1]; Karl-Heinz Liesenfeld[3]; Thorsten Lehr[3]; Sebastian Härtter[3]; Jeffrey Friedman[4]; Harm Peters[1#]; Andreas Clemens[3#]

[1]Department of Nephrology, Charité Universitätsmedizin Berlin, Charité Campus Mitte, Humboldt University, Berlin, Germany; [2]Charité Research Organisation GmbH, Berlin, Germany; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [4]Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Conneticut, USA

Hémodialyse

Quatre heures de dialyse **ont extrait du compartiment central 48.8% et 59.3% du dabigatran total** avec des débits respectifs de 200 et 400 ml/minute. L'activité anticoagulante du dabigatran était corrélée à sa concentration plasmatique. Redistribution mineure du dabigatran (<16%) après la fin de la session.

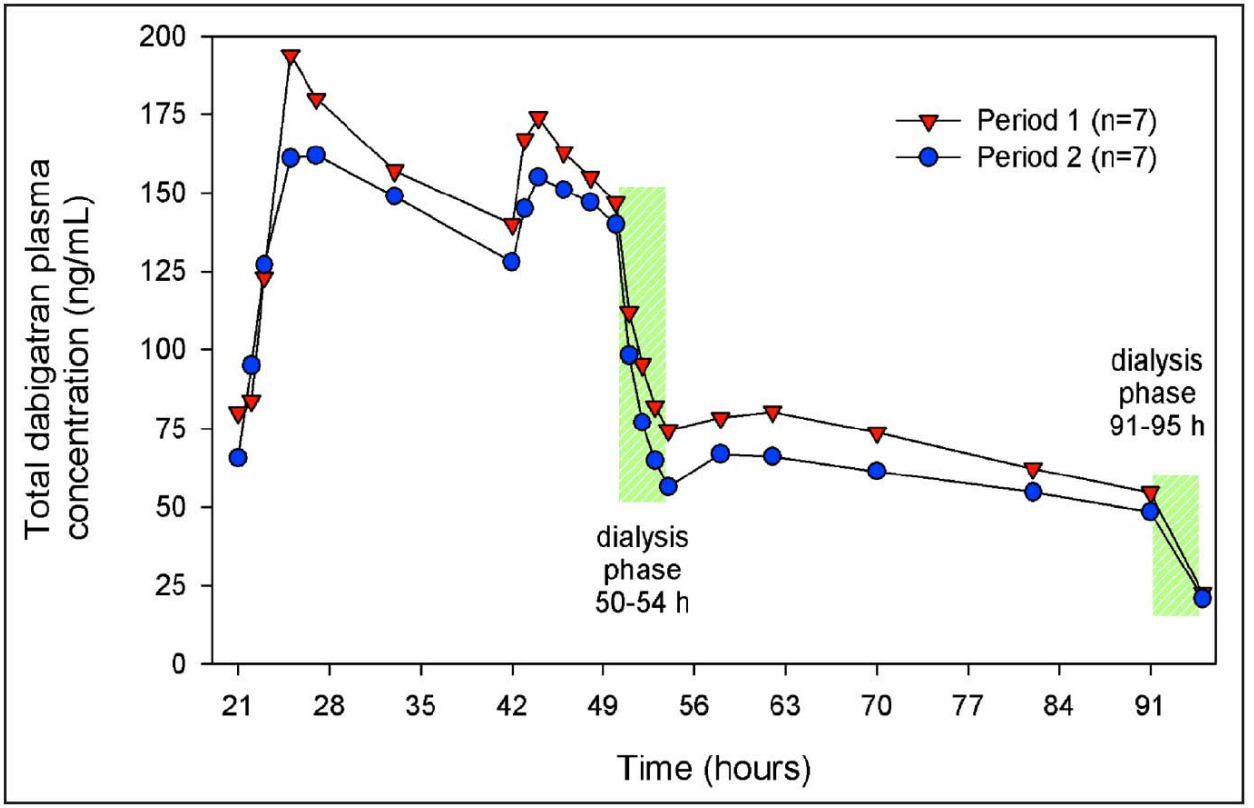


Figure 2: Geometrical mean plasma concentration-time profiles of total dabigatran in both treatment periods. Dabigatran was administered at 0, 21 and 42 h after the first dose; dialysis was performed from 50 to 54 and 91 to 95 h.

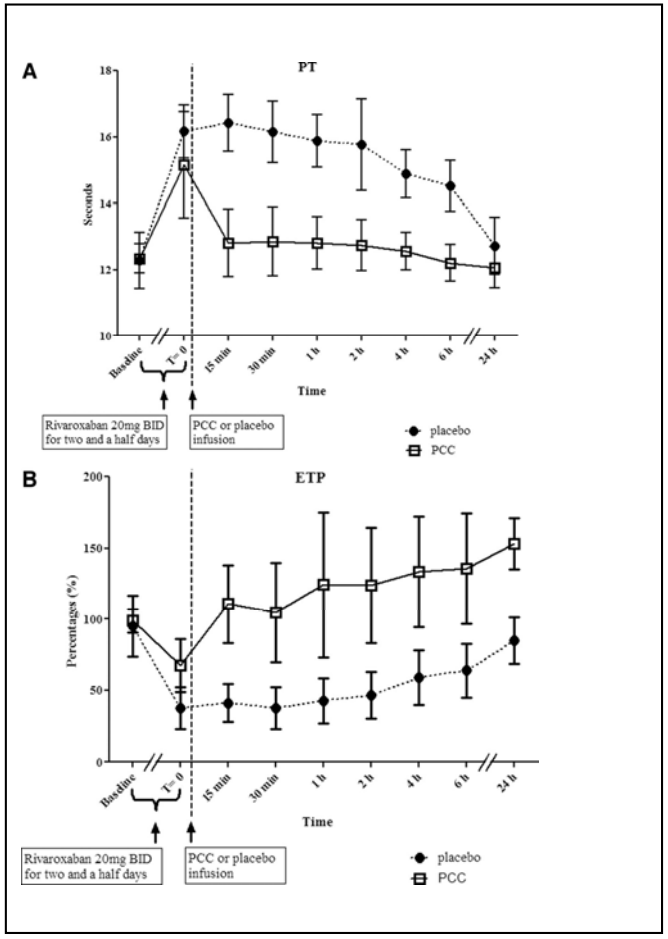
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

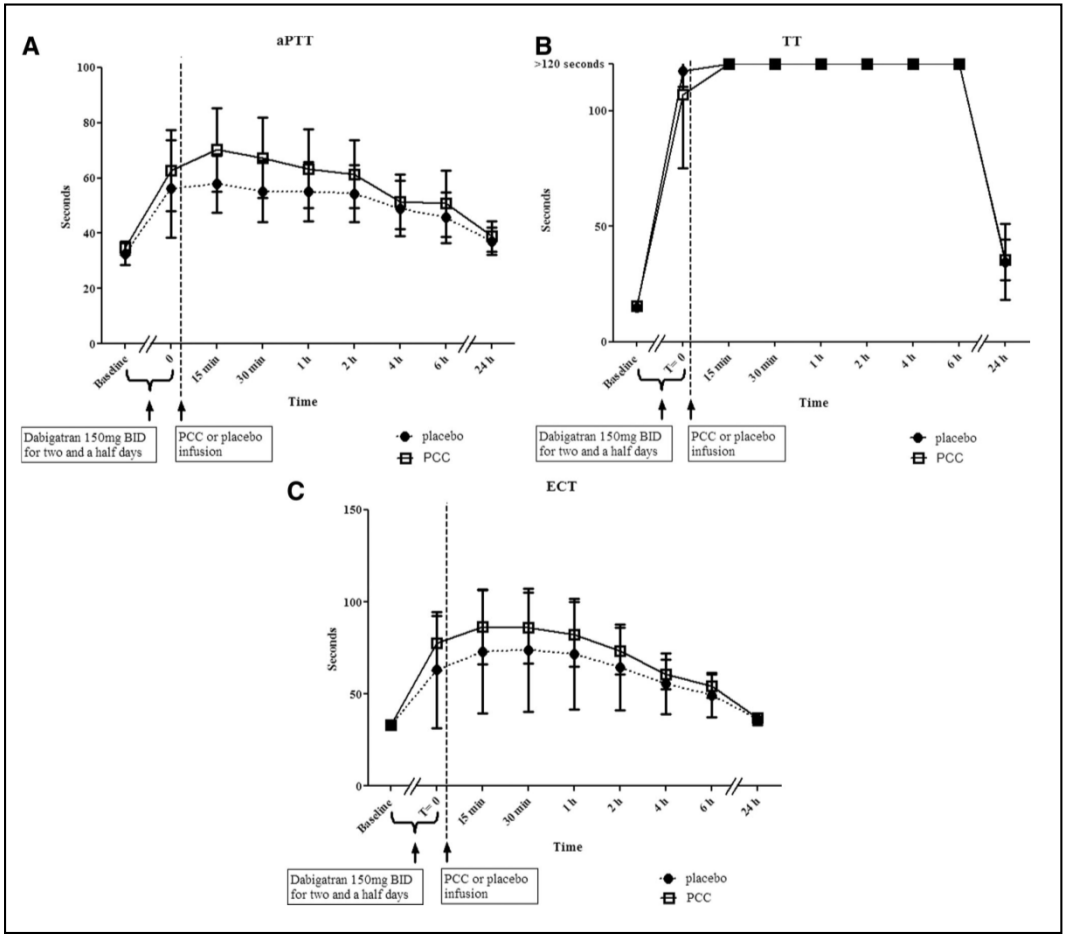
Circulation 2011; 124: 1573-1579

Concentrés de complexe prothrombinique (CCP) 50 UI/kg

Rivaroxaban (20 mg x 2)



Dabigatran (150 mg x 2)



Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

Ammar Majeed,[1-4] Anna Ågren,[1,3] Margareta Holmström,[1,3] Maria Bruzelius,[1,3] Roza Chaireti,[3,5,6] Jacob Odeberg,[1,3,7] Eva-Lotta Hempel,[1,3] Maria Magnusson,[6,8,9] Tony Frisk,[10] and Sam Schulman[11,12]

blood 2017;130(15):1706-1712

CCP et AOD en médecine

84 patients médicaux traités par des concentrés de complexe prothrombinique (CCP) pour réversion du rivaroxaban ou de l'apixaban après une hémorragie majeure.

CCP perfusés à la dose médiane de 2000 UI (IC 25-75% 1500-2000 IU) soit 26.7 UI/kg (21.4-29.9 UI/kg).

Hémorragies intra-craniennes les plus fréquentes (n = 59; 70.2%), suivies par des saignements gastro-intestinaux chez 13 patients (15.5%) .

Gestion des hémorragies : efficace chez 58 patients (69.1%) et inefficace chez 26 patients (30.9%). La plupart des patients du groupe « inefficace » avaient une hémorragie intra-cranienne (n =16; 61.5%).

Deux patients victimes d'un accident vasculaire cérébral, survenant 5 et 10 jours après le traitement par CCP.

L'administration de CCP pour le management des hémorragies majeures associées au rivaroxaban ou à l'apixaban est efficace dans la plupart des cas, et ne se complique que d'un faible nombre de thromboses.

Multimodal assessment of non-specific hemostatic agents for apixaban reversal

A.-C. MARTIN,*†‡ I. GOUIN-THIBAULT,*†§ V. SIGURET,*†¶ A. MORDOHAY,*†
C.-M. SAMAMA,*†** P. GAUSSEM,*†¶ B. LE BONNIEC*† and A. GODIER*†††

J Thromb Haemost 2015; **13**: 426–36.

FEIBA® (PCCa) ?

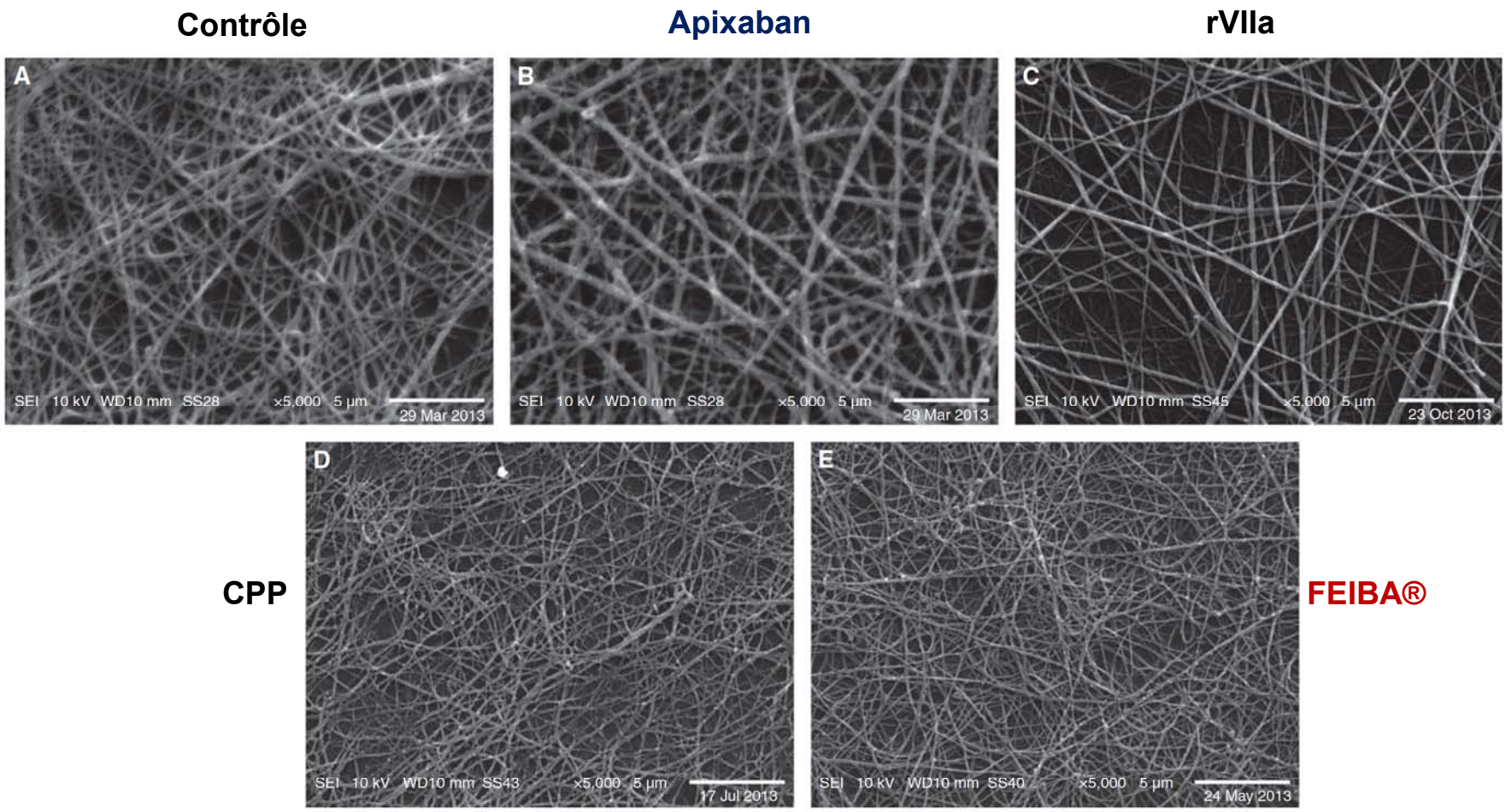


Fig. 2. Effects of the hemostatic agents on samples spiked with a supra-therapeutic apixaban concentration as assessed using scanning electron microscopy of the fibrin network structure in controls (A); blood spiked with apixaban only (B); and blood spiked with apixaban and rFVIIa (C), PCC (D) or aPCC (E). Same scale for all images (scale bar 5 µm). rFVIIa, recombinant activated factor VII; PCC, prothrombin complex concentrate; aPCC, activated PCC.

Management of Severe Bleeding in Patients Treated with Direct Oral Anticoagulants

An Observational Registry Analysis

Pierre Albaladejo, M.D., Ph.D., Charles-Marc Samama, M.D., Ph.D., F.C.C.P., Pierre Sié, M.D., Ph.D., Sophie Kauffmann, M.D., Vincent Mémier, M.D., Pierre Suchon, M.D., Ph.D., Alain Viallon, M.D., Ph.D., Jean Stéphane David, M.D., Ph.D., Yves Gruel, M.D., Ph.D., Lorenn Bellamy, M.D., Emmanuel de Maistre, M.D., Ph.D., Pauline Romegoux, B.Sc., Sophie Thoret, Ph.D., Gilles Pernod, M.D., Ph.D., Jean-Luc Bosson, M.D., Ph.D., on behalf of the GIHP-NACO Study Group*

GIHP-NACO registry – 732 patients

Anesthesiology. 2017;127:111–20

Table 4. Bleeding Management

	Dabigatran (n = 207)	Rivaroxaban (n = 472)	Apixaban (n = 53)	All (n = 732)
Transfusion, n (%)	94 (45)	150 (32)	17 (32)	261 (36)
Packed erythrocyte, n (%)	86 (42)	143 (30)	14 (26)	243 (33)
Platelets, n (%)	12 (5.8)	16 (3.4)	4 (7.5)	32 (4.4)
Fresh frozen plasma, n (%)	32 (16)	32 (6.8)	6 (11)	70 (9.6)
Fibrinogen concentrate, n (%)	5 (2.4)	6 (1.3)	—	11 (1.5)
PCC, n (%)	60 (29)	129 (27)	19 (36)	208 (28)
Total dose				
Median [25th–75th], U	3,000 [1,700–4,000]	3,000 [2,000–4,000]	3,000 [2,000–3,500]	3,000 [2,000–4,000]
Median [25th–75th], U/kg	40 [24–50]	44 [25–50]	42 [29–49]	43 [25–50]
Second dose, n (%)	5 (8.3)	20 (16)	2 (11)	27 (13)
aPCC, n (%)	26 (13)	41 (8.7)	6 (11)	73 (10)
Total dose				
Median [25th–75th], U	3,500 [2,500–4,000]	3,000 [2,500–3,575]	3,500 [3,000–4,000]	3,000 [2,500–4,000]
Median [25th–75th], U/kg	46 [40–52]	44 [37–50]	48 [46–48]	46 [38–50]
Second dose, n (%)	2 (7.7)	3 (7.3)	—	5 (6.8)
Recombinant factor VIIa	—	—	—	—
Tranexamic acid (%)	13 (6.3)	18 (3.8)	3 (5.8)	34 (4.7)
Hemodialysis (%)	7 (3.4)	2 (0.4)	—	9 (1.2)
Mechanical means (%)*	60 (29)	151 (32)	13 (25)	224 (31)
Intervention for hemostasis control (%)	48 (23)	119 (25)	8 (15)	175 (24)
Endoscopy (%)	26 (13)	64 (14)	7 (13)	97 (13)
Surgery (%)	4 (1.9)	17 (3.6)	1 (1.9)	22 (3)
Embolization (%)	18 (8.7)	38 (8.1)	—	56 (7.7)

*Compression, gauze packing.

aPCC = activated PCC; PCC = prothrombin complex concentrate.

Antidotes spécifiques

A specific antidote for dabigatran: functional and structural characterization

Felix Schiele,[1] Joanne van Ryn,[2] Keith Canada,[3] Corey Newsome,[3] Eliud Sepulveda,[3] John Park,[4] Herbert Nar,[1] and Tobias Litzenburger[4]

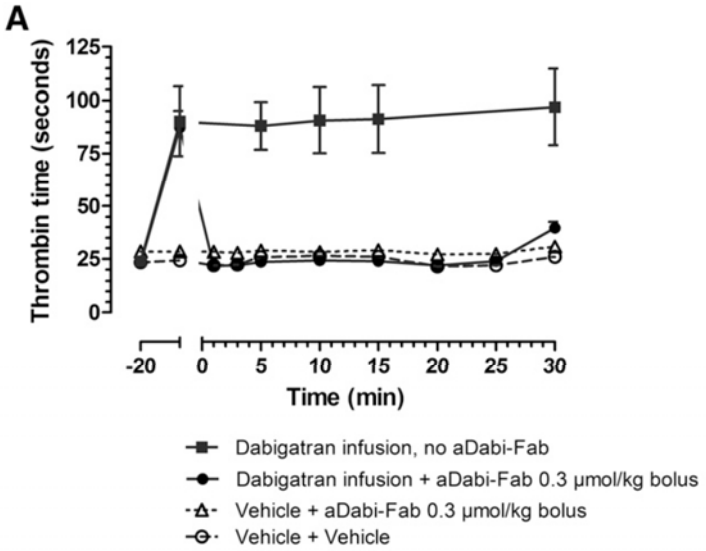
[1]Structural Research Group, and [2]CardioMetabolic Diseases Research, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany; [3]Biotherapeutics, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; and [4]New Biological Entity Discovery, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany

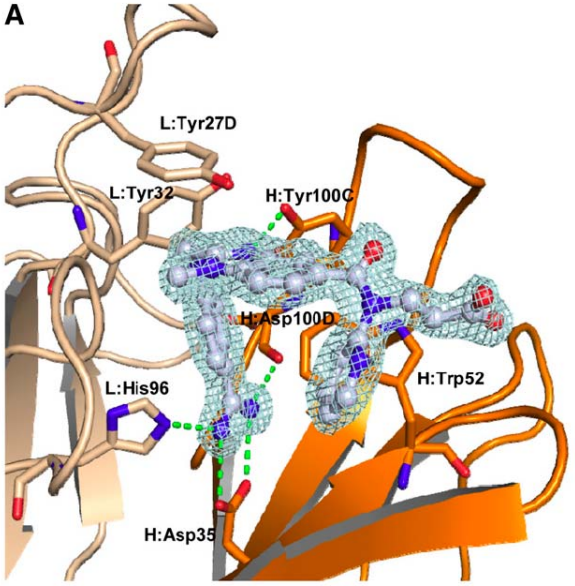
***Blood*. 2013;121(18):3554-3562**

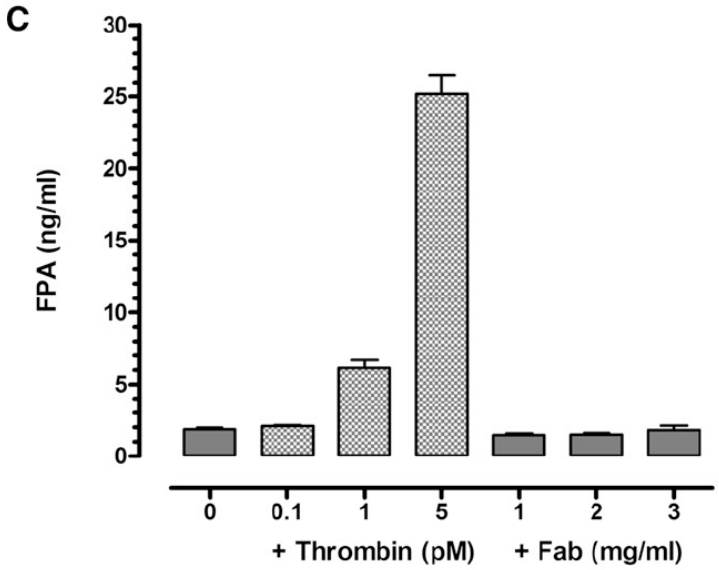
Idarucizumab

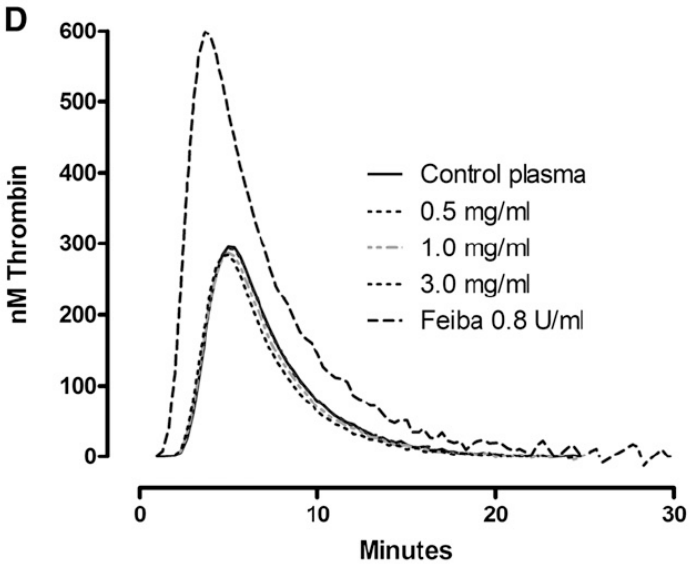
fragment Fab humanisé

Réseau dense d'interactions, affinité pour le dabigatran 350 fois plus forte que son affinité pour la thrombine.

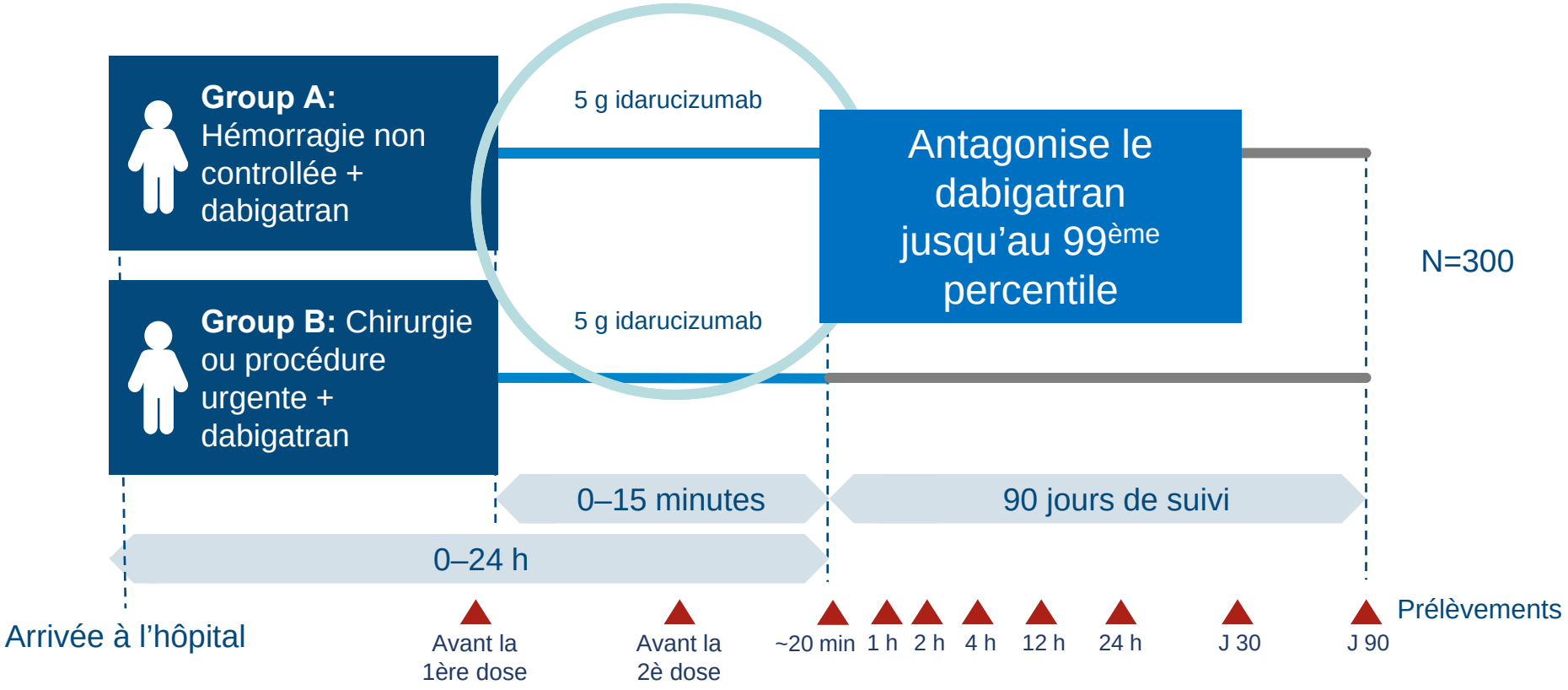








RE-VERSE AD™, étude ouverte, multicentrique, de phase III, un seul bras



Deux infusions IV de 2.5 g d'idarucizumab à moins de 15 minutes d'intervalle pour permettre un prélèvement après le premier flacon

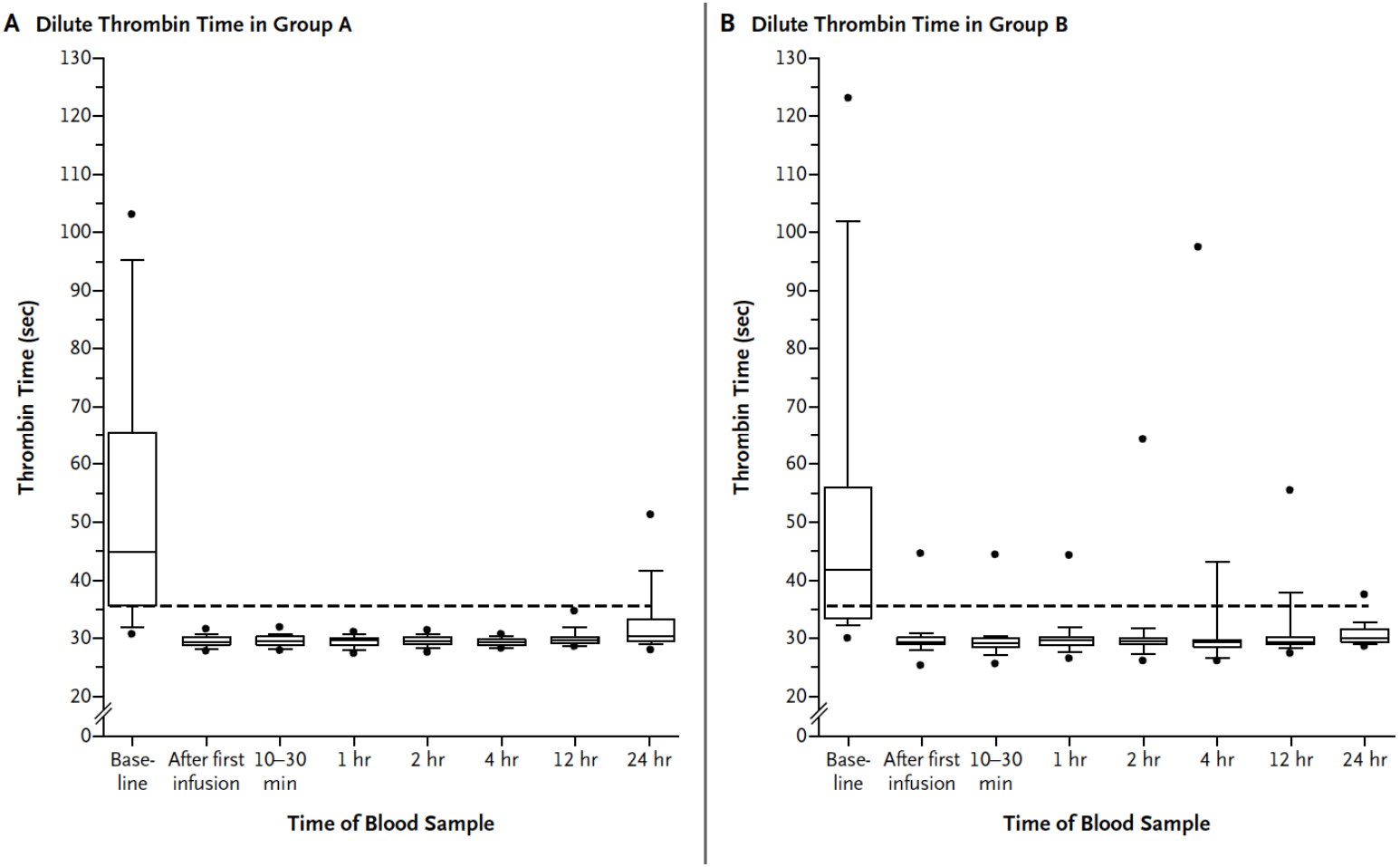
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Eng J Med. 2015;373:511–20

Prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure

Interim analysis: 90 patients (51 patients in group A and 39 in group B).



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/713107/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Praxbind

International non-proprietary name: idarucizumab

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D. Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Gordon Royle, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., Peter Verhamme, M.D., Bushi Wang, Ph.D., Laura Young, M.D., and Jeffrey I. Weitz, M.D.

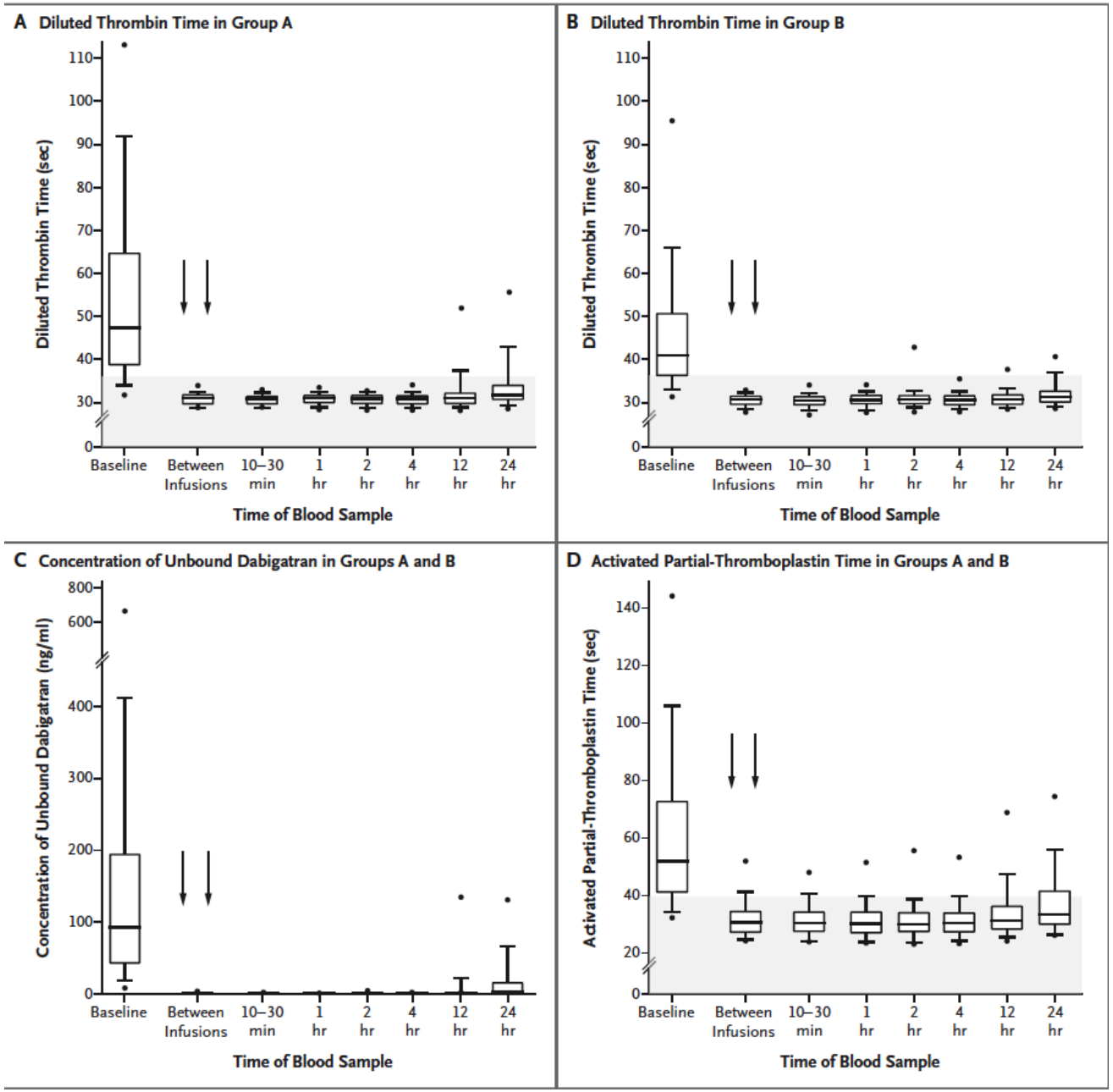
N Engl J Med 2017;377:431-41.
DOI: 10.1056/NEJMoa1707278

RE-VERSE AD : résultats

Characteristic	Group A (N=301)	Group B (N=202)	Total (N=503)
Time since last intake of dabigatran — hr‡			
Median	14.6	18.0	15.6
Range	1.5–90.4	2.6–105.8	1.5–105.8
Elevated ecarin clotting time at baseline — no. (%)	276 (91.7)	185 (91.6)	461 (91.7)
Elevated diluted thrombin time at baseline — no. (%)	244 (81.1)	152 (75.2)	396 (78.7)
Elevated ecarin clotting time or diluted thrombin time at baseline — no. (%)	276 (91.7)	185 (91.6)	461 (91.7)

* Group A included patients who had uncontrolled bleeding, and group B included patients who required urgent surgery or intervention.
† Race or ethnic group was reported by the patient.
‡ Data were available for 501 patients (299 in group A, and 202 in group B).

RE-VERSE AD biologie



REVERSE-AD : résultats cliniques

- Groupe A (hémorragies) : 137 patients (45.5%) ont développé un saignement gastro-intestinal, et 98 (32.6%) une hémorragie intra-cranienne.
- **La durée médiane pour l'arrêt du saignement était de 2.5 heures**

- Groupe B (procédure urgente) : durée médiane pour le début de l'intervention 1.6 heures.

- **Evaluation de l'hémostase périopératoire comme normale pour 93.4% des patients**, un peu anormale chez 5.1%, and modérément anormale pour 1.5%.

- **A 90 jours, évènements thrombotiques chez 6.3% des patients du groupe A et 7.4% du groupe B**
- **Mortalité: 18.8% (A) et 18.9% (B)**

Praxbind - the first specific reversal agent

Pradaxa is the first non vitamin K antagonist oral anticoagulant (NOAC) with a specific reversal agent.[1] Together, Pradaxa and Praxbind set a new standard in anticoagulation care.

Idarucizumab et thrombose

Intravenous Thrombolysis after Reversal of Dabigatran by Idarucizumab: A Case Report

Waldemar Kafke Peter Kraft

Department of Neurology, University Hospital Würzburg, Würzburg, Germany

Case Rep Neurol 2016;8:140–144

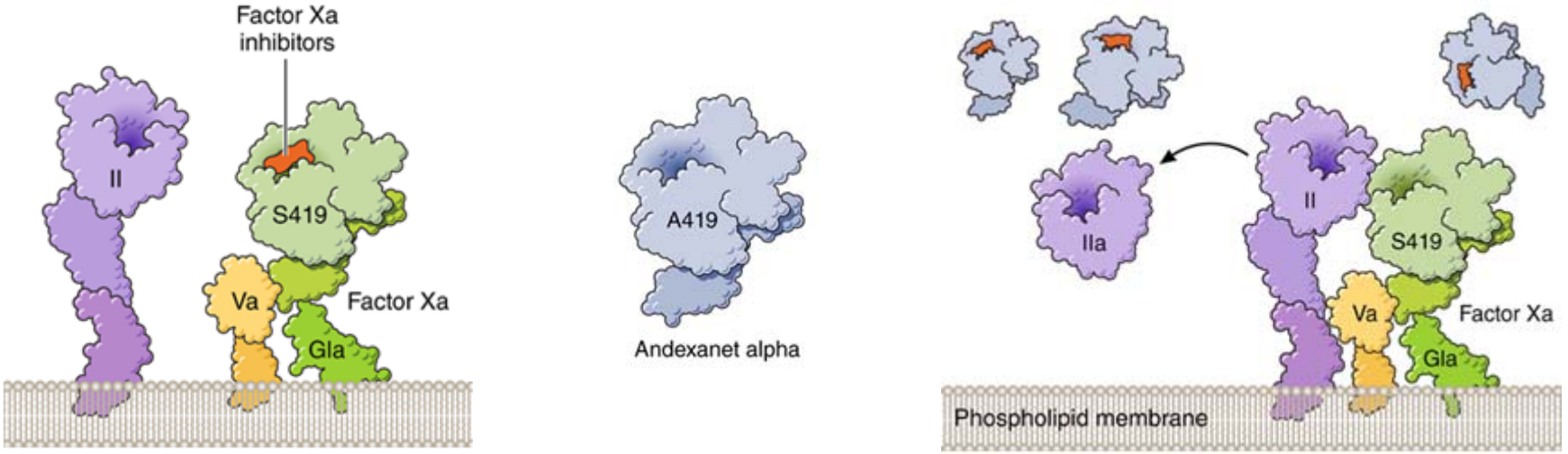
Patiente de 75 ans, fibrillation atriale et accident vasculaire cérébral alors qu'elle était traitée par dabigatran 110mg x 2 par jour.

Idarucizumab et thrombolyse intra-veineuse avec du tPA.

Pas d'hémorragie intra-cranienne secondaire à la lyse.

Malgré la thrombolyse, aggravation clinique avec lésions ischémiques pontines, thalamiques et cérebelleuses à droite.

Andexanet alfa et AOD anti-Xa



- Factor Xa recombinant
  - Pas de domaine Gla
  - Activité catalytique
- Inhibition des anti-Xa directs et indirects
- Efficacité immédiate en 2-5 min ; Demi-vie : 1h
- Résultats très préliminaires, peu de recul
- Risque thrombotique
- Pas d'autorisation pour l'instant

Lu *et al*. Nat Med 2013
Greinacher *et al*. Thromb Haemost 2015
Siegal *et al*. N Engl J Med 2015
Ruff *et al*. Circulation 2016
Connolly *et al. N* Eng J Med 2016

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

This article was published on November 11, 2015, at NEJM.org.

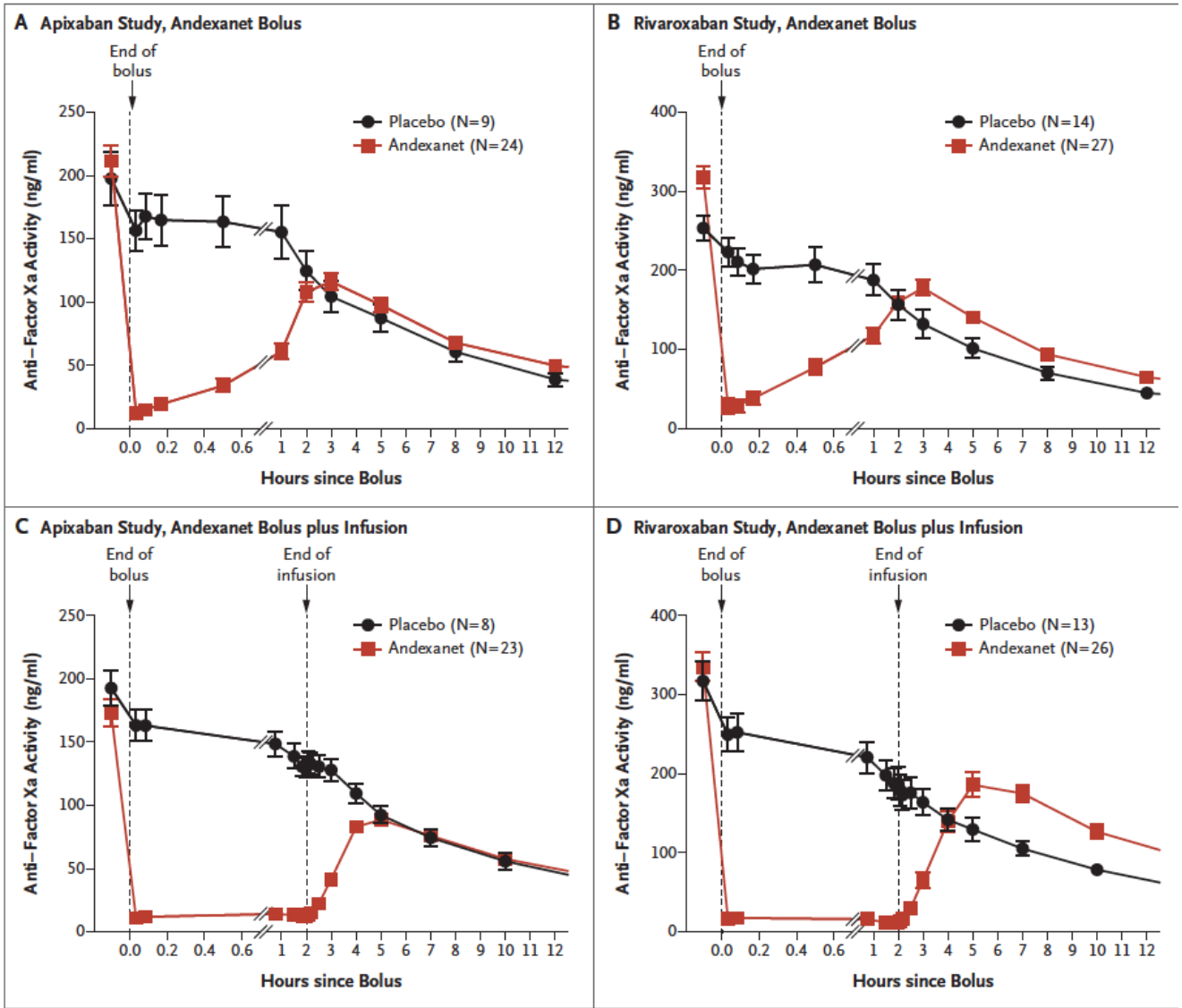


Figure 1. Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

N Engl J Med 2016;375:1131-41

Multicenter, prospective, open-label, single-group study.
67 patients whith acute major bleeding within 18 hours after the administration of a factor Xa inhibitor.

Bolus of andexanet (400 or 800mg) followed by a 2-hour infusion of the drug (480 or 960mg).

Efficacy population: 47 patients with a baseline value for anti–factor Xa activity of at least 75 ng/mL and had confirmed bleeding severity at adjudication.

Bleeding was predominantly gastrointestinal or intracranial. **For intracerebral hemorrhage, an increase in volume of 20% or less from baseline at both 1 hour and 12 hours after infusion was considered to be excellent hemostasis, whereas an increase in volume of 35% or less from baseline at 12 hours was considered to be good.**

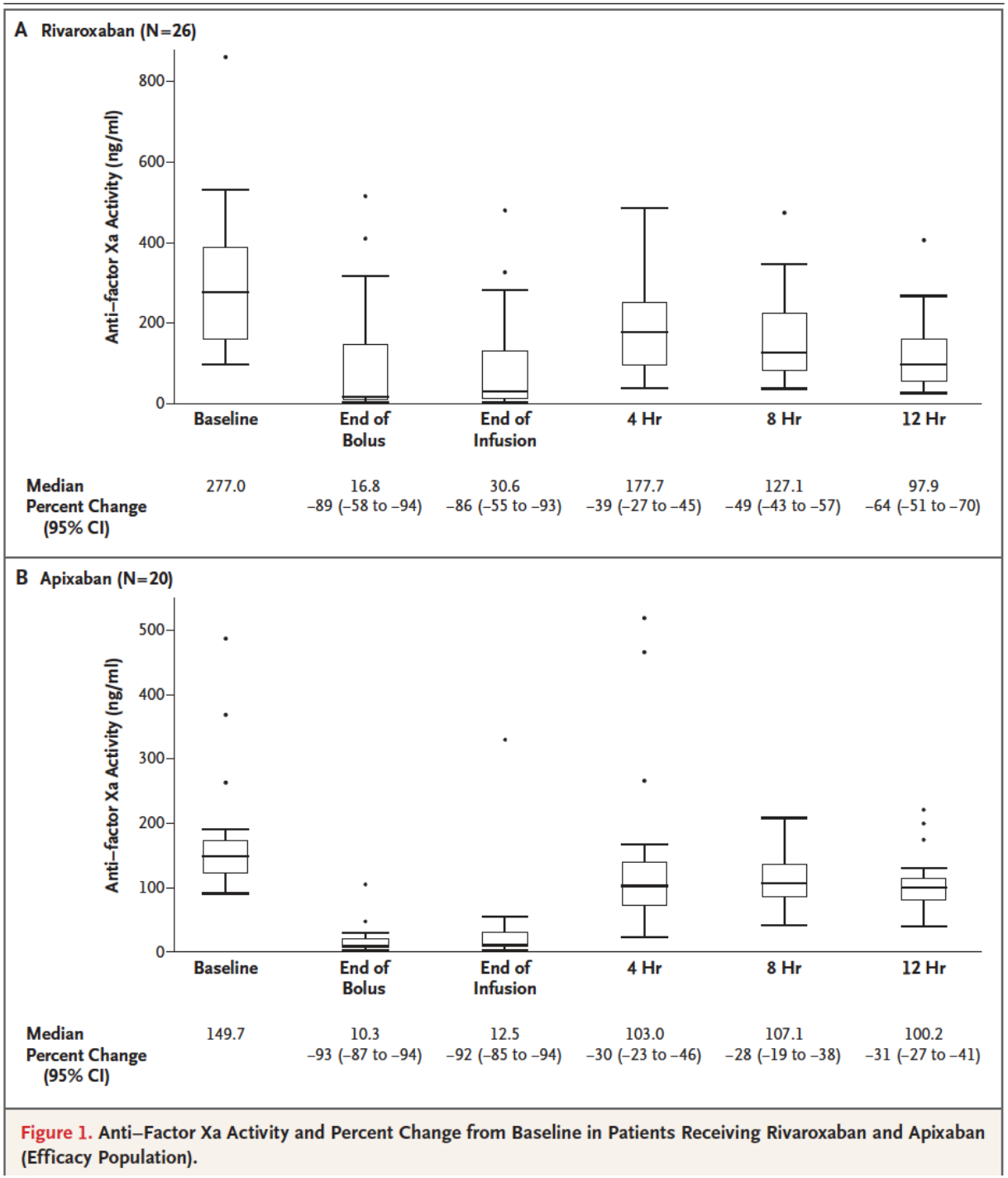


Figure 1. Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

After the bolus administration, the median anti–factor Xa activity decreased by 89% from baseline among patients receiving rivaroxaban and by 93% among patients receiving apixaban.

12 hrs after the andexanet infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%)

Thrombotic events occurred in 12 of 67 patients **(18%)** during the 30-day follow-up.

Deaths: 15% in efficacy and safety populations

Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban

The New England Journal of Medicine
DOI: 10.1056/NEJMc1411800

Small, synthetic, water-soluble, cationic molecule that is designed to bind specifically to **unfractionated heparin and low-molecular-weight heparin** through noncovalent hydrogen bonding and charge–charge interactions.
It binds in a similar way to **edoxaban, rivaroxaban, apixaban**, and to **dabigatran**.

Jack E. Ansell, M.D.
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Sasha H. Bakhru, Ph.D.
Bryan E. Laulicht, Ph.D.

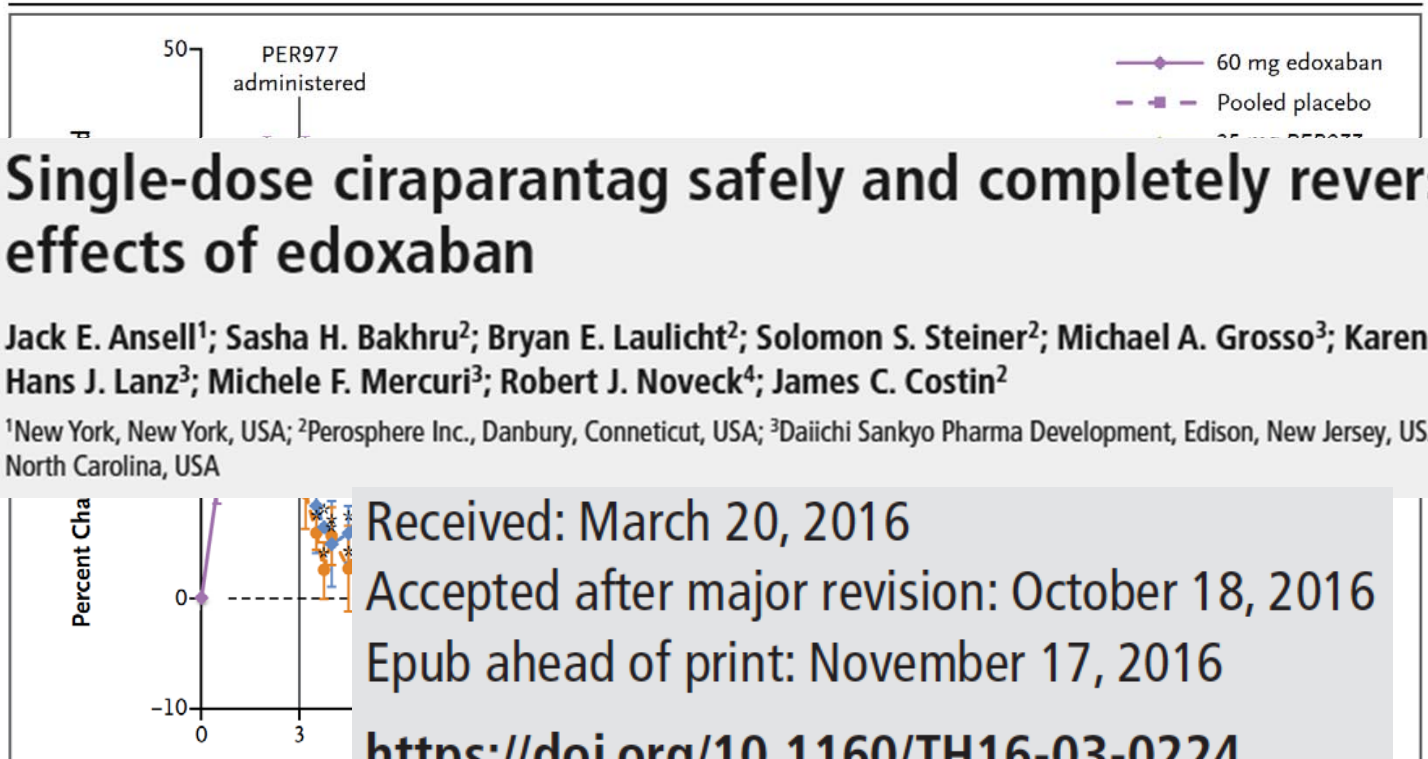


Figure 1. Effect of PER977 c
Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban

Jack E. Ansell[1]; Sasha H. Bakhru[2]; Bryan E. Laulicht[2]; Solomon S. Steiner[2]; Michael A. Grosso[3]; Karen Brown[3]; Victor Dishy[3]; Hans J. Lanz[3]; Michele F. Mercuri[3]; Robert J. Noveck[4]; James C. Costin[2]

[1]New York, New York, USA; [2]Perosphere Inc., Danbury, Conneticut, USA; [3]Daiichi Sankyo Pharma Development, Edison, New Jersey, USA; [4]Duke University Medical Center, Durham, North Carolina, USA

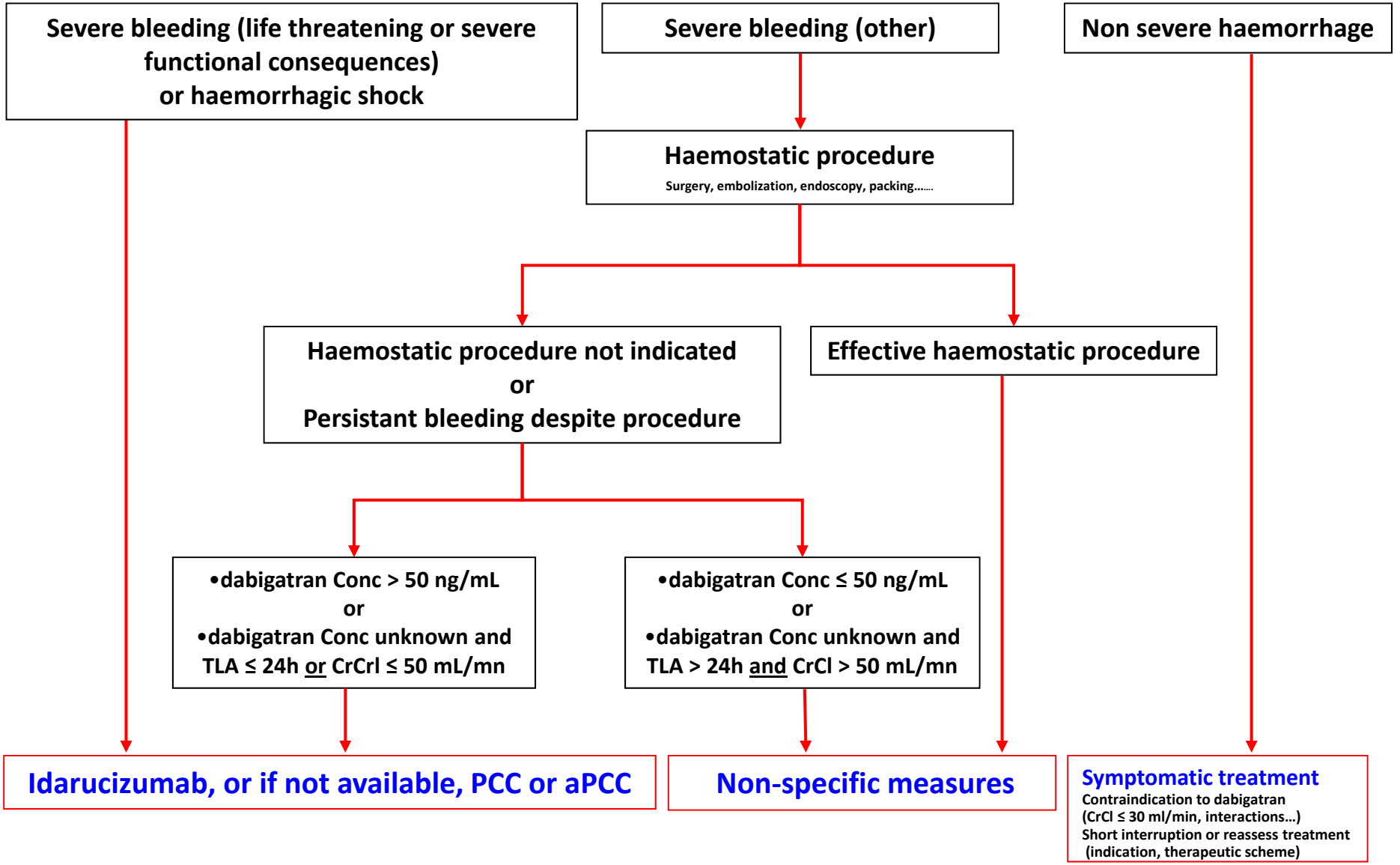
Received: March 20, 2016
Accepted after major revision: October 18, 2016
Epub ahead of print: November 17, 2016

https://doi.org/10.1160/TH16-03-0224
Thromb Haemost 2017; 117: 238–245

Edoxaban significantly reduced the mean fibrin-fiber diameted which was restored to normal 30 minutes after administration of PER977

www.gihp.org

Bleeding in a patient treated with dabigatran



(TLA: Time since Last Administration; CrCl: Creatinine Clearance (Cockcroft et Gault); Conc: Plasmatic concentration)

Groupe d'intérêt en hémostase péri-opératoire

BLEEDING and APIXABAN (Eliquis®) or RIVAROXABAN (Xarelto®)

Your center has a specific assay for APIXABAN (Eliquis®) or RIVAROXABAN (Xarelto®)

Bleeding into critical organs
(intracerebral, acute subdural, intra-ocular…)

1) FEIBA® 30-50 IU/kg*
or
2) PCC 50 IU/kg*

Severe hemorrhage as per HAS 2008
(apart from above case)

- **If [ ]** ≤ 30 ng/ml: no reversal**
- **Prefer hemostatic intervention if feasible**
- **If no immediate hemostatic intervention and if [ ]** > 30 ng/ml**

► **Consider reversal*** ** (not always necessary)

* **Depending on availability. No data available on thrombotic risk of high doses of PCC or FEIBA in these patients**
** **[ ] means concentration**
*** **PCC=25-50 IU/kg or FEIBA=30-50 IU/kg**
First-line rFVIIa is not considered

En pratique…

- Les AOD représentent un vrai progrès, mais aussi un vrai challenge
- Procédure réglée : arrêt des traitements (dernière prise) à J-3 pour les anti-Xa et J-4 ou J-5 pour le dabigatran (selon la fonction rénale)
- Monitorage disponible (temps de thrombine dilué et anti-Xa spécifiques)
- Urgences hémorragiques : recommandations GIHP, essayer d'attendre deux 1/2 vies. Doser.
- CCP ou FEIBA ? Idarucizumab pour peu de patients. Pas de NovoSeven®
- Charbon (tous) - Dialyse (dabigatran)
- Déclarations à la Pharmacovigilance

NEUROLOGIA I NEUROCHIRURGIA POLSKA 50 (2016) 200–202

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journal homepage: http://www.elsevier.com/locate/pjnns

Case report

Fatal consequences of climbing a ladder under apixaban and drunken

Claudia Stöllberger *, *Josef Finsterer*

Krankenanstalt Rudolfstiftung, Wien, Austria

ARTICLE INFO

Article history:
Received 22 November 2015
Accepted 25 January 2016
Available online 5 February 2016

Keywords:
Anticoagulation
Apixaban
Atrial fibrillation
Cerebral hemorrhage

ABSTRACT

Background: Apixaban, a factor-Xa-inhibitor, is one of the non-vitamin-K-antagonist oral anticoagulants (NOACs) which are increasingly used in atrial fibrillation (AF). In real life even patients with contraindications to vitamin K antagonists (VKAs) receive NOAC because NOAC are considered as "safer" than VKAs.

Case description: In a 61-years-old man with hypertension, heart failure and paroxysmal AF apixaban was started. Despite advices from his physicians, he continued alcohol abuse and suffered from recurrent falls. After 9 months he fell from a ladder and suffered from extensive subarachnoidal and intraparenchymal hemorrhages, subdural hematoma, brain edema with midline shift and a left-sided skull fracture. Because of the inability to reverse the anticoagulant therapy, no neurosurgical intervention was carried out and the patient died without regaining consciousness.

Conclusions: Patients with recurrent falls or chronic alcohol abuse should not be considered as candidates for NOACs. If anticoagulation is deemed necessary, VKA with its potential for prompt reversibility should be favored.