Anticoagulants Oraux Directs

boite à outils

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Anticoagulants Oraux Directs

Agent Classe	½ vie	Tmax	Biodisponibilité	Elimination
Dabigatran anti-IIa	14-17h	0,5 à 2 h	6-8%	80% rein 20% foie
Rivaroxaban anti-Xa	7-13h	2-4h	>80%	33% rein (inchangée) 33% rein (metabolites inactifs) 33% foie
Apixaban anti-Xa	8-15h	3-4h	50-85%	25% rein 75% foie
Edoxaban anti-Xa	10-14h	1,5h	65%	35% rein

AOD dans la thromboprophylaxie en orthopédie majeure (PTH, PTG)

- **Dabigatran** (PRADAXA®)
  - 75 mg, puis 150 mg/j
  - 110 mg, puis 220 mg/j
- **Rivaroxaban** (XARELTO®)
  - 10 mg /j
- **Apixaban** (ELIQUIS®)
  - 2,5 mg x 2 mg /j
- **Edoxaban** (Lixiana®)

  (not EMA approved)

Fibrillation atriale-Traitement EP-TVP

- **Dabigatran (PRADAXA®)**
  - Fibrillation atriale
    - 110 mg x 2/j
    - 150 mg x 2/j
  - Traitement de la thrombose veineuse profonde
    - 150 mg x 2/j

(AC parentéral: qq jours)

- **Rivaroxaban (XARELTO®)**
  - Fibrillation atriale
    - 15 mg/j si Cockcroft entre 30 et 49 ml/min
    - 20 mg/j si Cockcroft > 50 ml/min
  - Traitement de la thrombose veineuse profonde
    - 15 mg x 2 pendant 3 semaines
    - Puis 15 ou 20 mg/j en fonction du Cockcroft

(AC parentéral: 0)

- **Apixaban (ELIQUIS®)**
  - Fibrillation atriale
    - 5 mg x 2/j
    - 2,5 mg x 2/j si 2 des trois facteurs de risque
  - Traitement de la thrombose veineuse profonde
    - 10 mg x 2/ j pendant 7 jours
    - 5 mg x 2/j

(AC parentéral: 0)

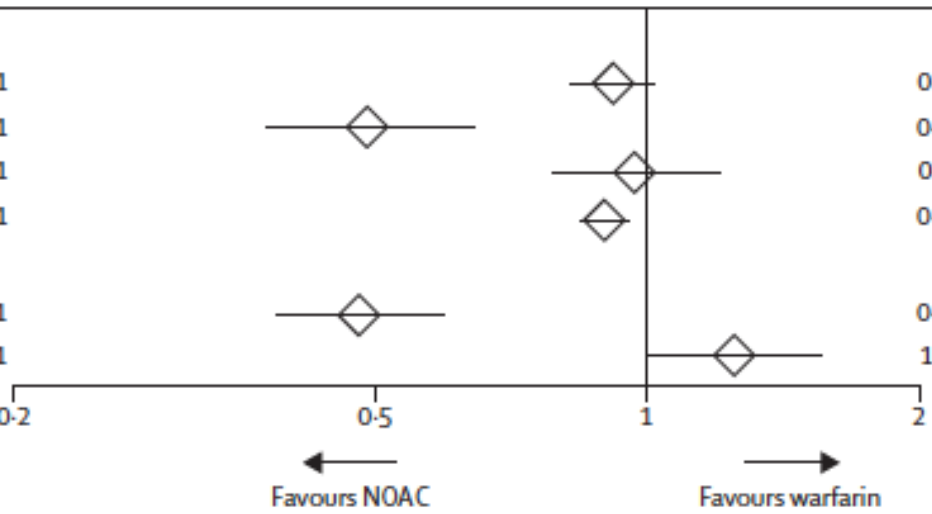
- **Edoxaban (Lixiana®)**
  - Fibrillation atriale
    - 60 mg
    - 30 mg
  - Traitement de la thrombose veineuse profonde
    - 60 mg
    - 30 mg

(AC parentéral: qq jours)

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29292	724/29221	0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29292	263/29221	0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29292	432/29221	0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29292	2245/29221	0·90 (0·85–0·95)	0·0003
Safety				
Intracranial haemorrhage	204/29287	425/29211	0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29287	591/29211	1·25 (1·01–1·55)	0·043



Efficacy and safety outcomes

CI, confidence interval; NOAC, newer oral anticoagulant; RR, relative risk

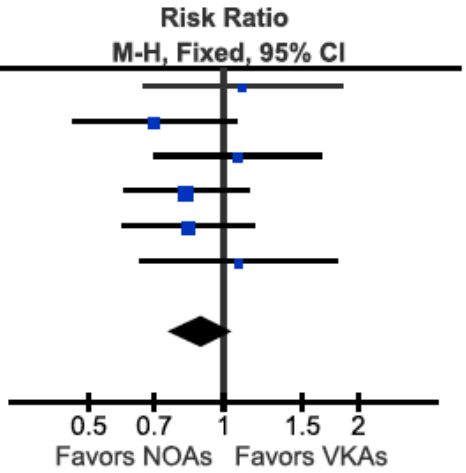
Ruff *et al. Lancet* 2014; **383**: 955–62

Recurrent symptomatic VTE

Study or Subgroup	NOAs Events	NOAs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-COVER	30	1274	27	1265	9.2%	1.10 [0.66, 1.84]	2009
EINSTEIN-DVT	36	1731	51	1718	17.3%	0.70 [0.46, 1.07]	2010
EINSTEIN-PE	42	2419	39	2413	13.2%	1.07 [0.70, 1.66]	2012
Hokusai-VTE	66	4118	80	4122	27.0%	0.83 [0.60, 1.14]	2013
AMPLIFY	59	2691	71	2704	23.9%	0.84 [0.59, 1.17]	2013
RE-COVER II	30	1279	28	1289	9.4%	1.08 [0.65, 1.80]	2014
Total (95% CI)		**13512**		**13511**	**100.0%**	**0.89 [0.75, 1.05]**	
Total events	263		296				

Heterogeneity: Chi² = 3.53, df = 5 (P = 0.62); I² = 0%

Test for overall effect: Z = 1.41 (P = 0.16)

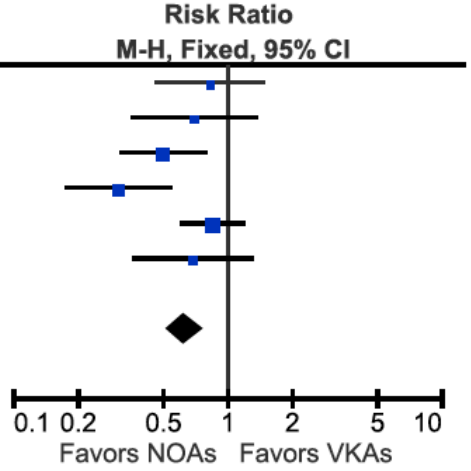


Major bleeding

Study or Subgroup	NOAs Events	NOAs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-COVER	20	1274	24	1265	10.3%	0.83 [0.46, 1.49]	2009
EINSTEIN-DVT	14	1718	20	1711	8.6%	0.70 [0.35, 1.38]	2010
EINSTEIN-PE	26	2412	52	2405	22.4%	0.50 [0.31, 0.80]	2012
AMPLIFY	15	2676	49	2689	21.0%	0.31 [0.17, 0.55]	2013
Hokusai-VTE	56	4118	66	4122	28.3%	0.85 [0.60, 1.21]	2013
RE-COVER II	15	1280	22	1288	9.4%	0.69 [0.36, 1.32]	2014
Total (95% CI)		**13478**		**13480**	**100.0%**	**0.63 [0.51, 0.77]**	
Total events	146		233				

Heterogeneity: Chi² = 10.65, df = 5 (P = 0.06); I² = 53%

Test for overall effect: Z = 4.46 (P < 0.00001)



Eur J Vasc Endovasc Surg 2014; 48: 565-575

	Dabigatran		Rivaroxaban	Apixaban
Insuffisance rénale				
ClCr normale (ClCr ≥ 80 mL/min)		$t_{1/2\ vie}$ 13,4h (11,0–21,6)		
Légère (50 ≤ ClCr < 80 mL/min)		$t_{1/2\ vie}$ 15,3h (11,7–34,1)	ASC + 40 %	ASC + 16 %
Modérée (30 ≤ ClCr < 50 mL/min)	ASC + 80–130 %	$t_{1/2\ vie}$ 18,4h (13,3–23,0)	ASC + 50 %	ASC + 29 %
Sévère (15 ≤ ClCr < 30 mL/min)	ASC + 500 %	$t_{1/2\ vie}$ 27,2h (21,6–35,0)	ASC + 60 %	ASC + 44 %
Sujets âgés (≥ 75–80 ans)				
ASC	ASC + 40–60 %		ASC + 50 %	ASC + 32 %
Cmax	C max + 25 %			Pas d'augmentation Cmax
Cmin	C min + 31 %			
Insuffisance hépatique				
Légère (stade A de Child et Pugh)	Pas d'influence. Non recommandé		ASC + 20 %	Prudence
Modérée (stade B de Child et Pugh)	Pas d'influence. Non recommandé		ASC + 130 %	Prudence
Sévère (stade C du Child et Pugh)	Contre-indiqué		Contre-indiqué si coagulopathie associée, y compris Child B et C	Non recommandé sauf si coagulopathie : contre-indiqué
Poids extrêmes			Incidence mineure	
> 100–120 kg	Cmin – 20 %			ASC – 30 %
< 50 kg	Augmentation ASC			ASC + 30 %
Femmes	Augmentation		Augmentation mineure	Augmentation mineure
ASC	ASC + 40–50 %			ASC + 18 %
Cmin	Cmin + 30–50 %			

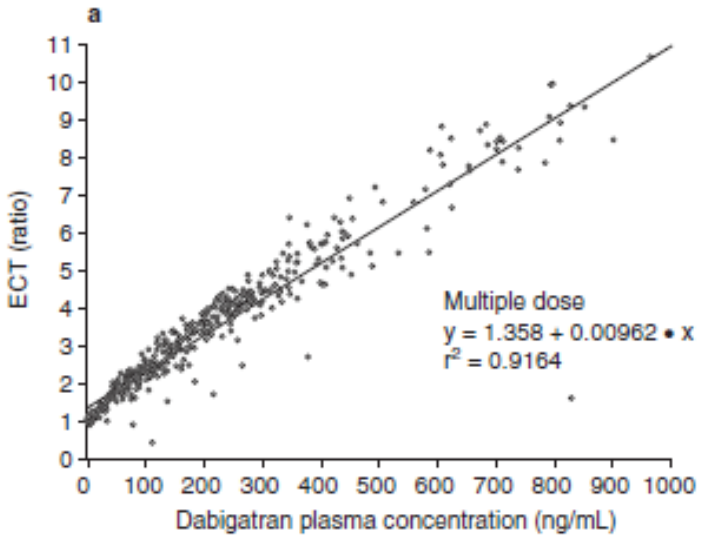
ANSM 2014

	Voie	Dabigatran	Rivaroxaban	Apixaban
Inhibiteurs de la protéase	Incidence sur P-gp et inhibition CYP3A4	Pas de donnée	ASC + 150 %	ASC + 100 %
Clarithromycine	Compétition P-gp et inhibition CYP3A4	ASC + 20 %	ASC + 50 % cliniquement non pertinent	
Erithromycine	Compétition P-gp et inhibition CYP3A4		ASC + 30 % cliniquement non pertinent	
Fluconazole	Inhibition modérée CYP3A4		ASC + 40 % cliniquement non pertinent	
Itraconazole	Compétition P-gp et BCRP et inhibition CYP3A4	ASC augmentée	ASC augmentée	ASC augmentée
Kétoconazole	Compétition P-gp et BCRP et inhibition CYP3A4	ASC + 140 à 150 %	ASC + 160 %	ASC + 100 %
Posaconazole	Compétition P-gp et BCRP et inhibition CYP3A4	ASC augmentée	ASC augmentée	ASC augmentée
Rifampicine	Inducteur P-gp, BCRP, CYP3A4 et CYP2J2	ASC – 66 %	ASC – 50 %	ASC – 54 %
Ciclosporine	Compétition P-gp	Pas de donnée		
Tacrolimus	Compétition P-gp	Pas de donnée		
Inhibiteurs pompe à protons		Pas d'effet	Pas d'effet	
Ranitidine		Pas d'effet		
Millepertuis	Inducteur P-gp, BCRP, CYP3A4 et CYP2J2	ASC diminuée	ASC diminuée	ASC diminuée
IRSNA		Risque hémorragique augmenté		
ISRS		Risque hémorragique augmenté		

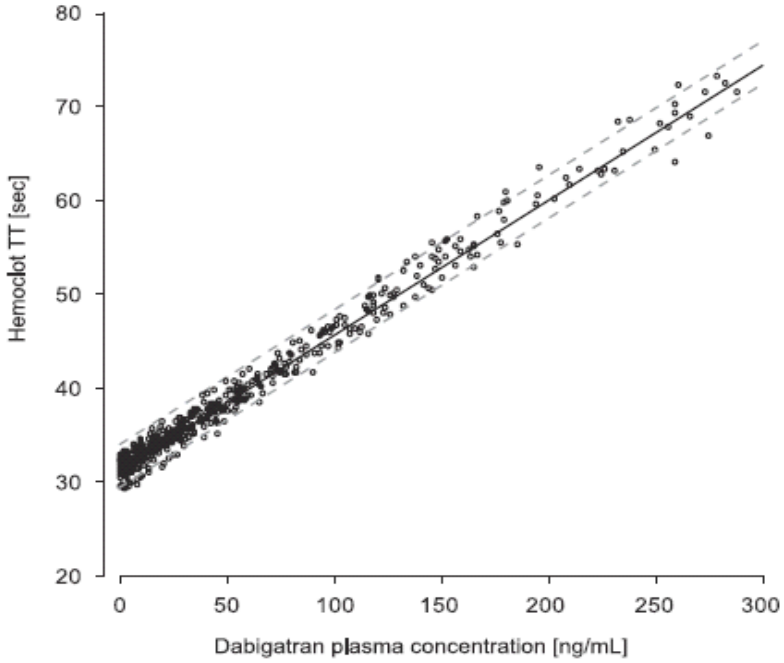
ANSM 2014

Dabigatran : tests spécifiques-activité anti-IIa

Test à l'écarine

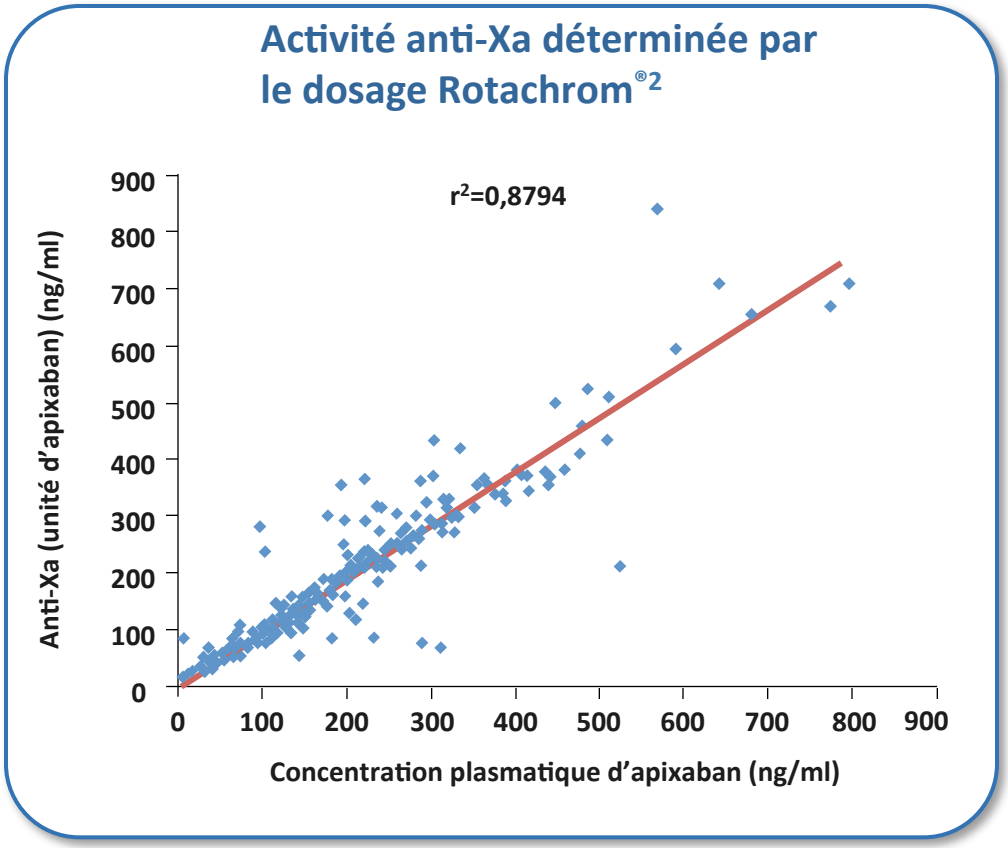


Temps de thrombine dilué (Hemoclot®)



Stangier, Clin Pharmacokinet, 2008
Van Ryn J, Thromb Haemost2010

Le dosage colorimétrique de l'anti-facteur Xa (Diagnostica Stago Rotachrom® Heparin) peut convenir pour le dosage de l'apixaban dans le plasma si nécessaire



Barrett *et al. Thromb Haemost* 2010;104:1263-71

Stratégies de réversion

Toujours:

- Traitements non spécifiques
  - Compression
  - chirurgie
  - Embolisation
  - Remplissage
  - Transfusion
  - Antifibrinolytiques
  - Facteurs de coagulation
    - PFC, Plaquettes
    - Fibrinogène

Stratégie de réversion

Options:

- Pharmacocinétique
  - Temps
  - Antidotes
  - Dialyse (dabigatran)
  - Charbon activé
- Agents hémostatiques
  - CCP
  - CCPa

CCP

AVK

Remplace des facteurs manquants

AODs

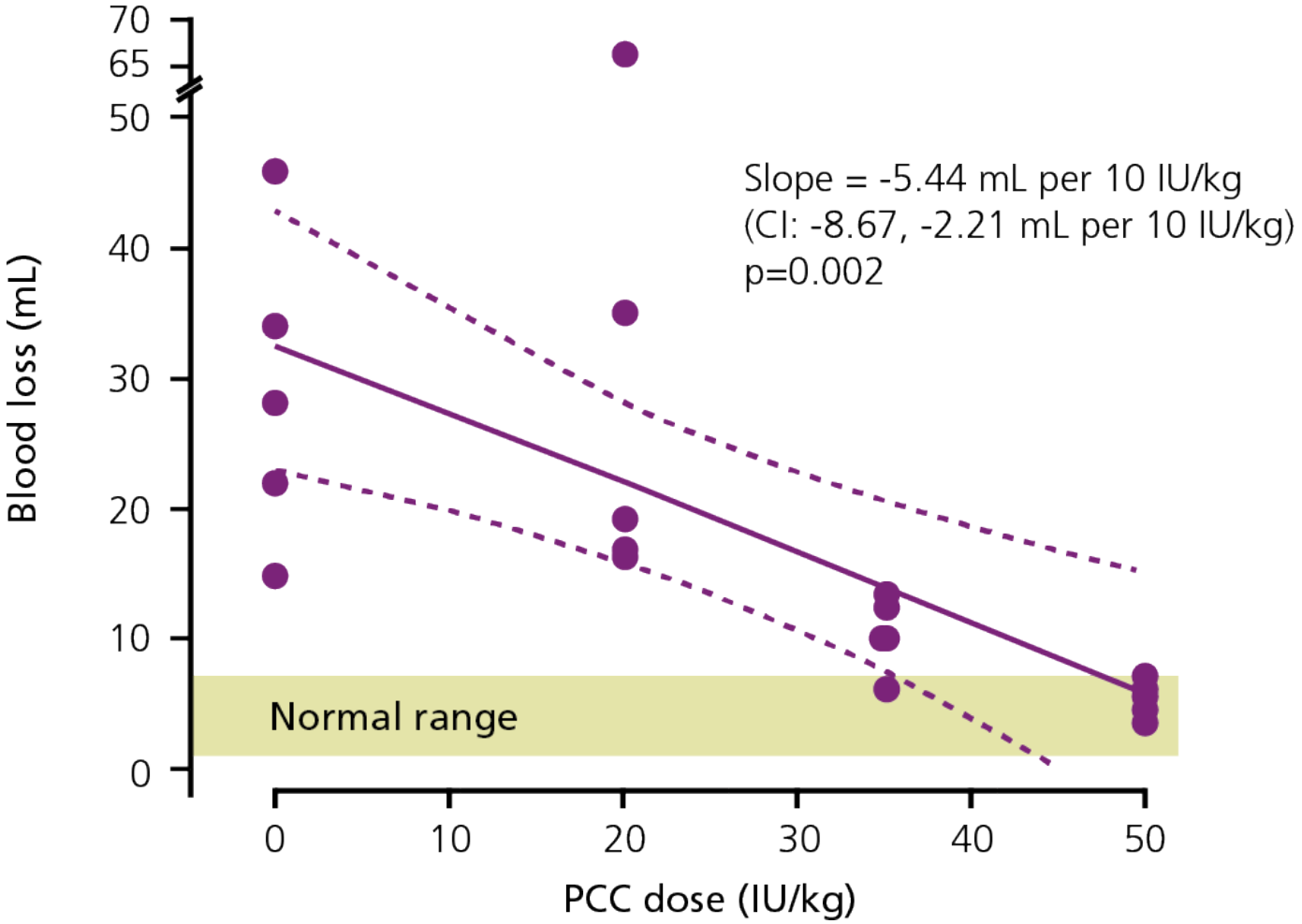
????

DOA reversal with PCC

DOA	Preclinical	Healthy volunteers	Patients
Dabigatran	Ø[1]; +/++[2–9]	Ø[17–19]; +/++[20–22]	Insufficient data
Rivaroxaban	+/++[10–13]	Ø[23]; +/++[19,20,24–27]	Insufficient data
Edoxaban	++[14,15]	++[15,28,29]	No data
Apixaban	Ø[16]	+/++[21,30,31]	No data

DOA, direct oral anticoagulant; PCC, prthrombin complex concentrate; Ø, no reversal; +, partial reversal; ++, complete reversal

1. Schaefer *et al. J Cereb Blood Flow Metab* 2014; **34**: 870–5; 2. Hoffman *et al. Anesthesiology* 2015; **122**: 353–62; 3. Zhou *et al. Stroke* 2011; **42**: 3594–9; 4. van Ryn *et al. Anesthesiology* 2014; **120**: 1429–40; 5. Herzog *et al. Thromb Res* 2014; **134**: 729–36; 6. Pragst *et al. J Thromb Haemost* 2012; **10**: 1841–8; 7. Grottke *et al. Crit Care* 2014; **18**: R27; 8. Honickel *et al. Thromb Haemost* 2015; **113** [Epub]; 9. Lambourne *et al. J Thromb Haemost* 2012; **10**: 1830–40; 10. Zhou *et al. Stroke* 2013; **44**: 771–8; 11. Perzborn *et al. Thromb Haemost* 2013; **110**: 162–72; 12. Herzog *et al. Thromb Res* 2015; **135**: 554–60; 13. Godier *et al. Anesthesiology* 2012; **116**: 94–102; 14. Herzog *et al. Anesthesiology* 2015; **122**: 387–98; 15. Fukuda *et al. Thromb Haemost* 2012; **107**: 253–9; 16. Martin *et al. Int J Cardiol* 2013; **168**: 4228–33; 17. Solbeck *et al. Int J Cardiol* 2014; **176**: 794–9; 18. Solbeck *et al. Scand J Clin Lab Invest* 2014; **74**: 591–8; 19. Eerenberg *et al. Circulation* 2011; **124**: 1573–9; 20. Marlu *et al. Thromb Haemost* 2012; **108**: 217–24; 21. Dinkelaar *et al. Clin Chem Lab Med* 2014; **52**: 1615–23; 22. Lindahl et al. Thromb Res 2015; 135: 544–7; 23. Korber *et al. Clin Appl Thromb Hemost* 2014; **20**: 735–40; 24. Perzborn *et al. Thromb Res* 2014; **133**: 671–81; 25. Escolar *et al. Circ J* 2015; **79**: 331–8; 26. Levi *et al. J Thromb Haemost* 2014; **12**: 1428–36; 27. Dinkelaar *et al. J Thromb Haemost* 2013; **11**: 1111–8; 28. Zahir *et al. Circulation* 2015; **131**: 82–90; 29. Halim *et al. Thromb Res* 2014; **134**: 909–13; 30. Escolar *et al. PloS one* 2013; **8**: e78696; 31. Martin *et al. J Thromb Haemost* 2015; **13**: 426–36; 32

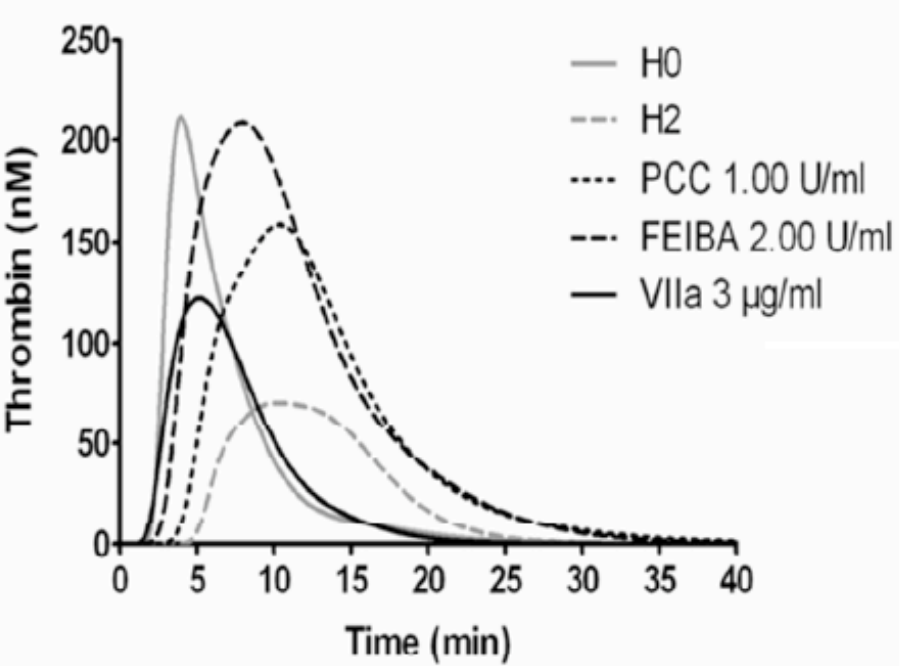


CI, confidence interval; ER, emergency room; IU, international unit; PCC, prothrombin complex concentrate

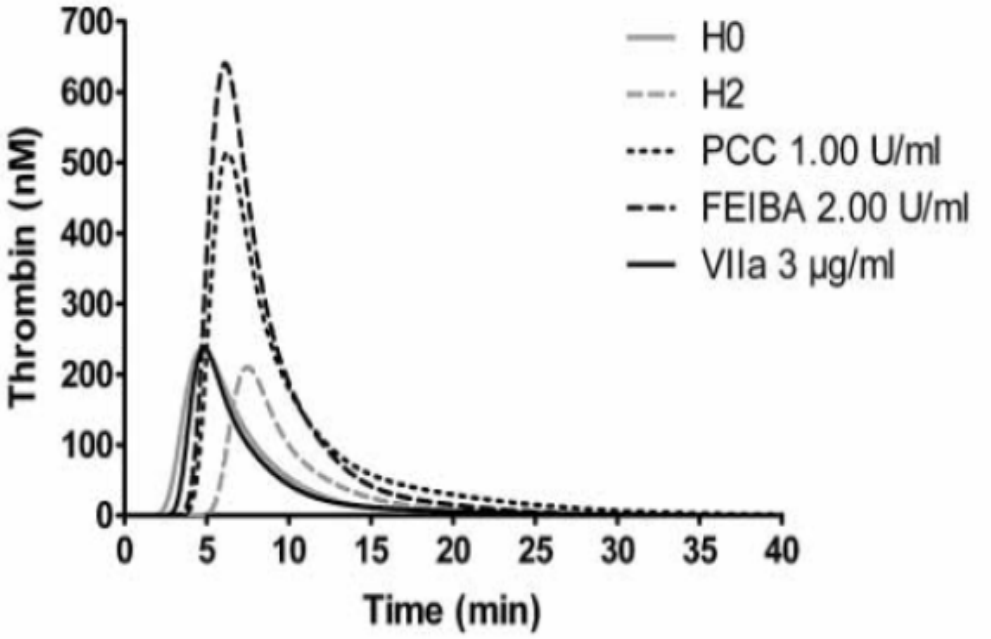
Pragst *et al. J Thromb Haemost* 2012; **10**: 1841–8

Effect of non-specific reversal agents on anticoagulant activity of Dabigatran and Rivaroxaban: a randomised crossover ex-vivo study in healthy volunteers

H0, traitement par du rivaroxaban 20 mg ou du dabigatran 150 mg
H2, temps de génération de thrombine
Ajout dans le tube de PPSB, FEIBA ou rFVIIa



Rivaroxaban

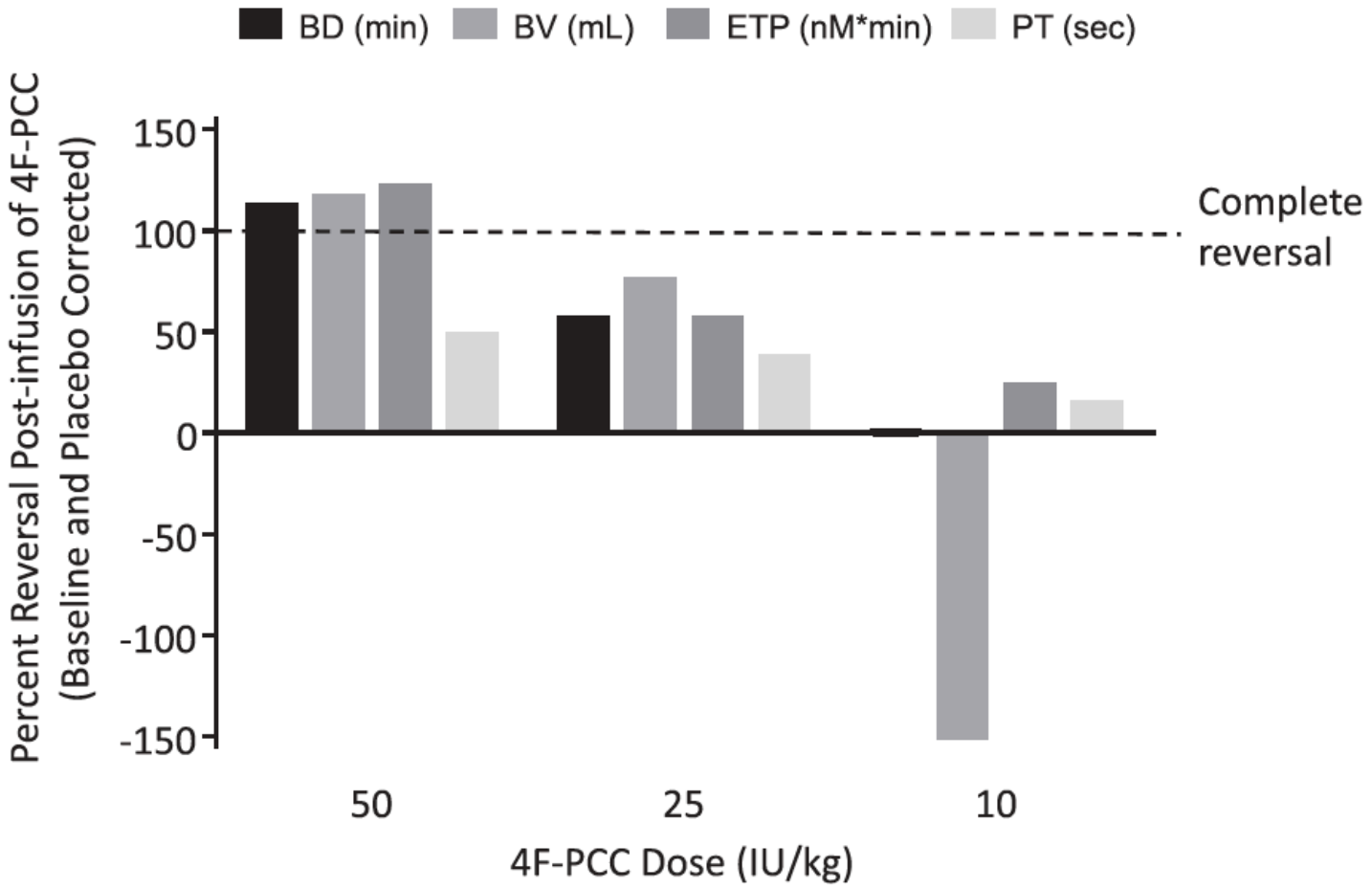


Dabigatran

Marlu et al, Thromb Haemostasis 2012

Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor Prothrombin Complex Concentrate

Hamim Zahir, PhD*; Karen S. Brown, PhD*; Alexander G. Vandell, PharmD, PhD; Madhuri Desai, MS; Jen-Fue Maa, PhD; Victor Dishy, MD; Barbara Lomeli, MD; Annette Feussner; Wenqin Feng, PhD; Ling He, PhD; Michael A. Grosso, MD; Hans J. Lanz, MD; Elliott M. Antman, MD



Zahir et al, Circulation 2015; 131: 81-90

Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin k antagonists

A meta-analysis

Table 2: Rate of complications.

	Rate (95% CI)
TE events	1.4% (0.8–2.1)
Death for all causes	10.6% (5.9–16.6)
TE events in pts treated for bleeding	1.9% (1.0–3.1)
TE events in pts treated before urgent surgery or invasive procedures	0.8% (0.1–2.0)
TE events in pts treated with 4-factor PCCs	1.8% (1.0–3.0)
TE events in pts treated with 3-factor PCCs	0.7% (0.0–2.4)
TE events in high quality studies	2.3% (0.5–5.4)

CI, confidence interval; PCC, prothrombin complex concentrate; pts, patients; TE, thromboembolic

Dentali *et al. Thromb Haemost* 2011; **106**: 429–38

Dabigatran

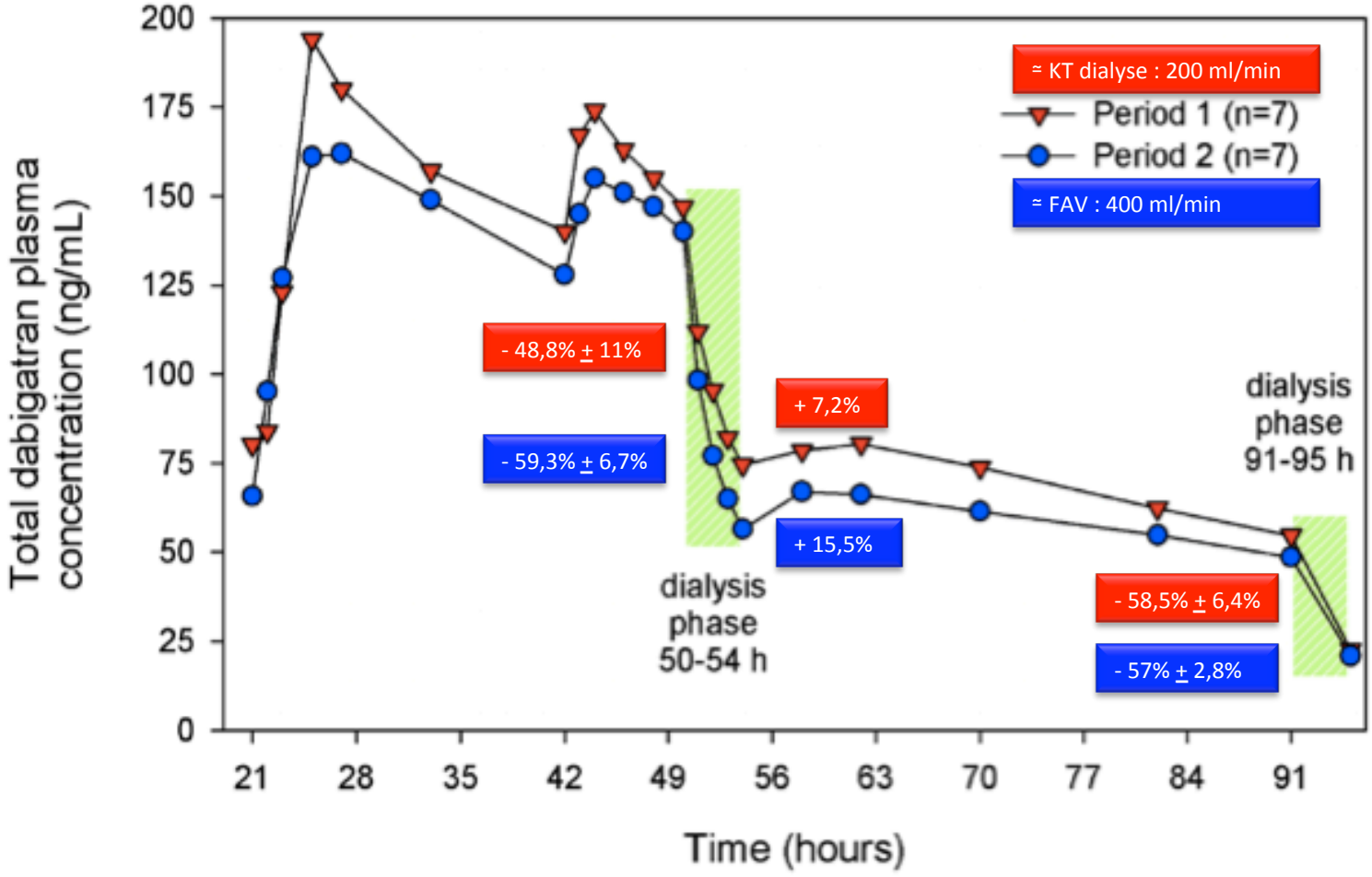
35% de liaison protéique

Soluble dans l'eau, petite 630 kDa

Volume de distribution : 60-70 l

Effective elimination of dabigatran by haemodialysis

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

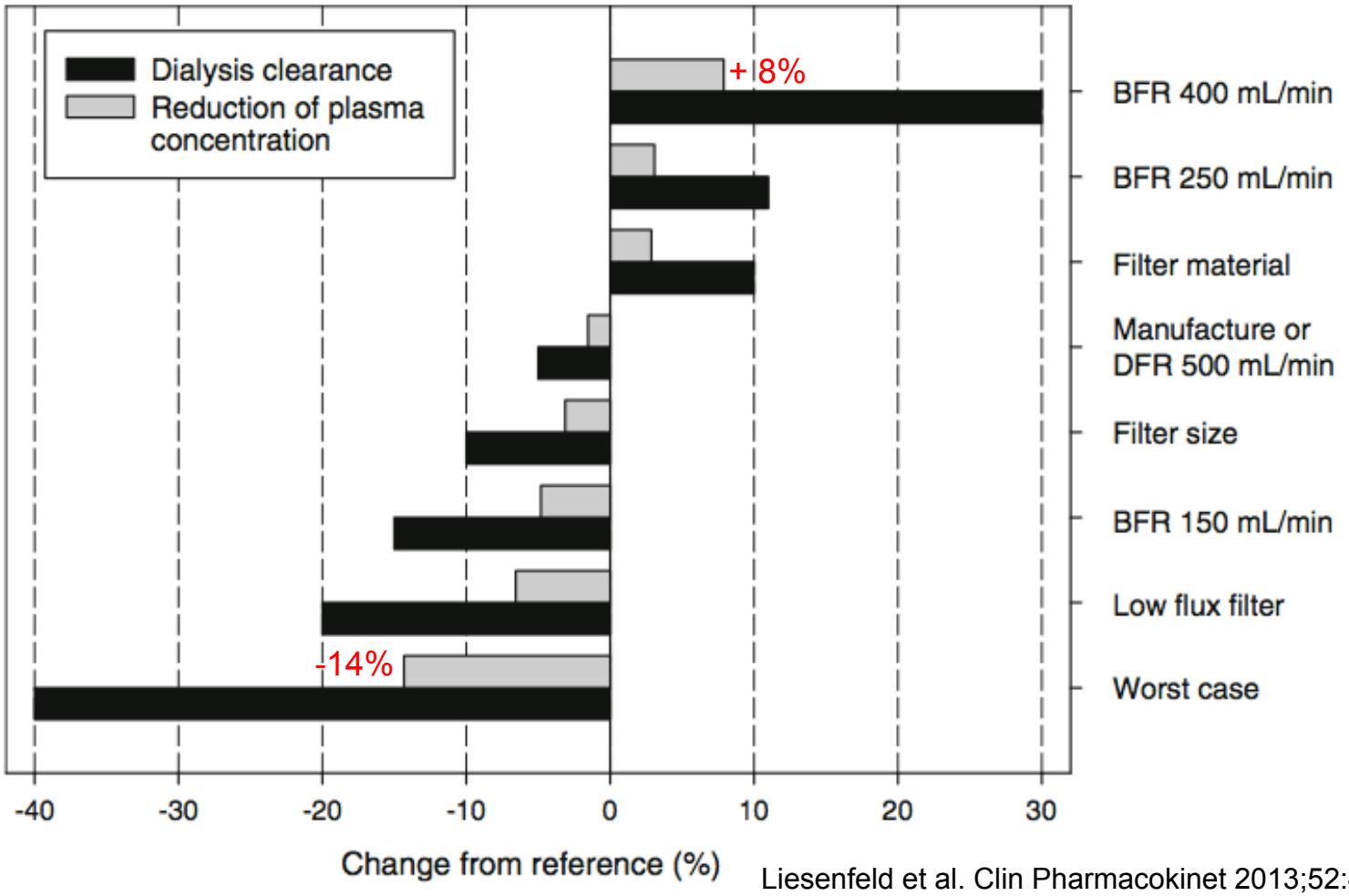


Khadzhynov et al. Thromb Haemost 2013; 109: 596–605

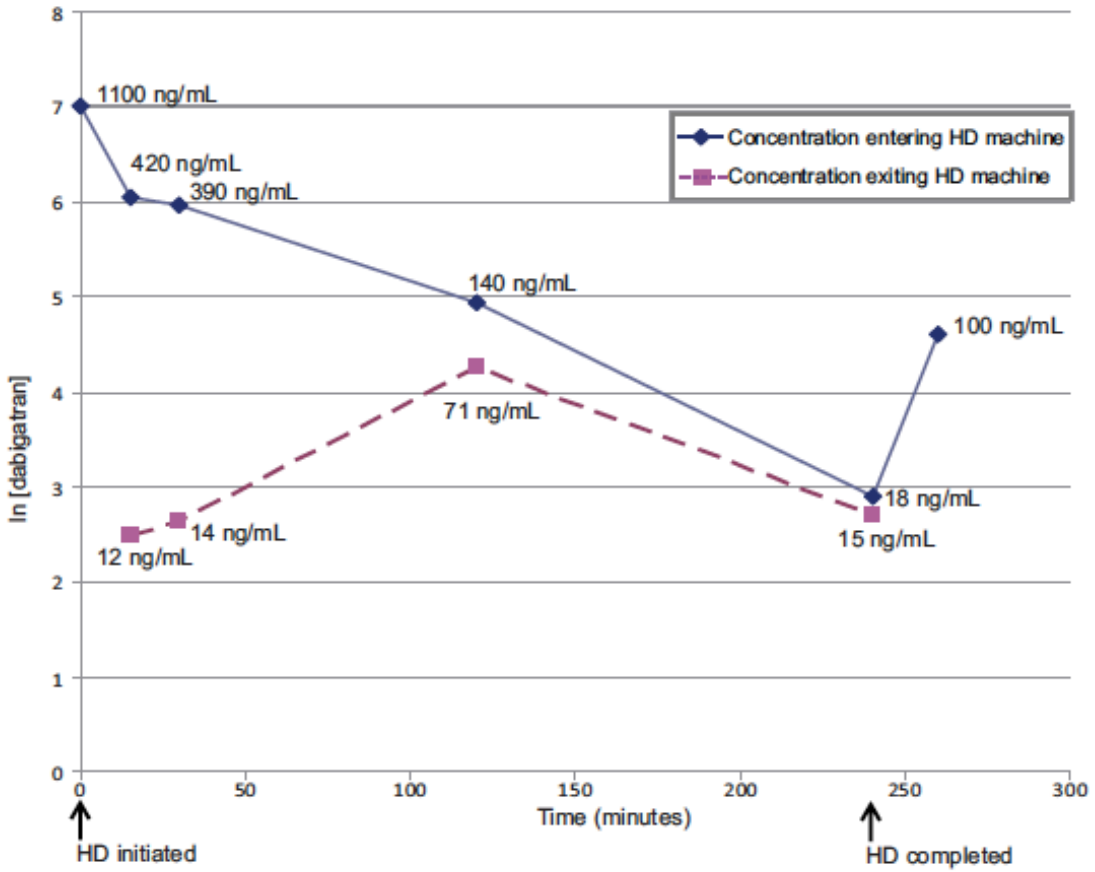
Pharmacometric Characterization of Dabigatran Hemodialysis

Conditions de dialyse

Situation de référence :
- blood flow rate : 200 ml/min
- dialysat flow rate : 700 ml/min
- membrane haut flux, grande surface 2,1m^2
- dialyse 4h



Liesenfeld et al. Clin Pharmacokinet 2013;52:453–62

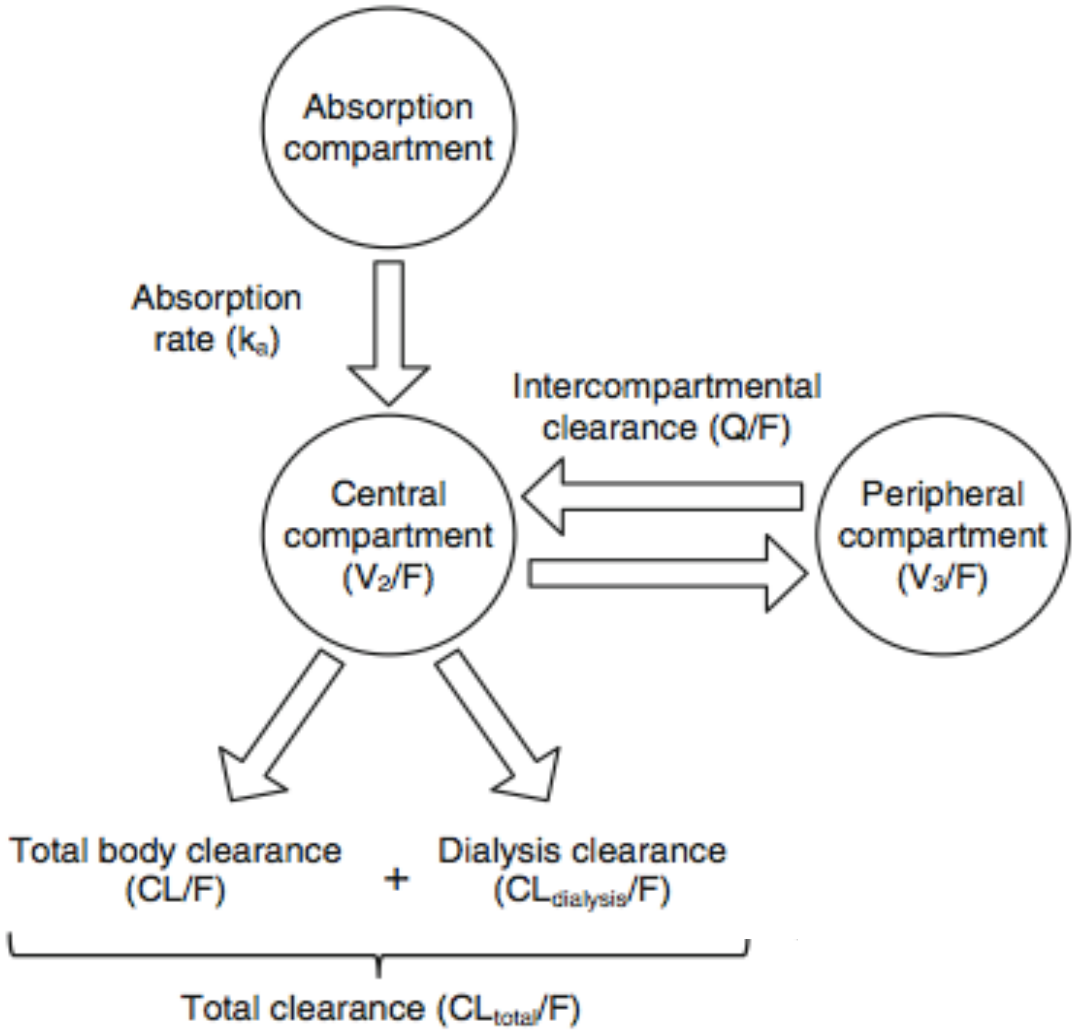


	0 min[a]	15 min	30 min	120 min	240 min[b]	260 min[c]
Dabigatran concentration						
Entering HD machine (ng/mL)	1,100	420	390	140	18	100
Exiting HD machine (ng/mL)	—	12	14	71	15	—
Blood flow rate (mL/min)	—	300	300	300	300	—
Extraction ratio	—	0.97	0.96	0.49	0.17	—
Dabigatran blood clearance (mL/min)	—	291	288	147	51	—

Chen et al, Am J Kidney Dis 2013

Débit sang= 300 ml/mn
Membrane= 1,8 m^2

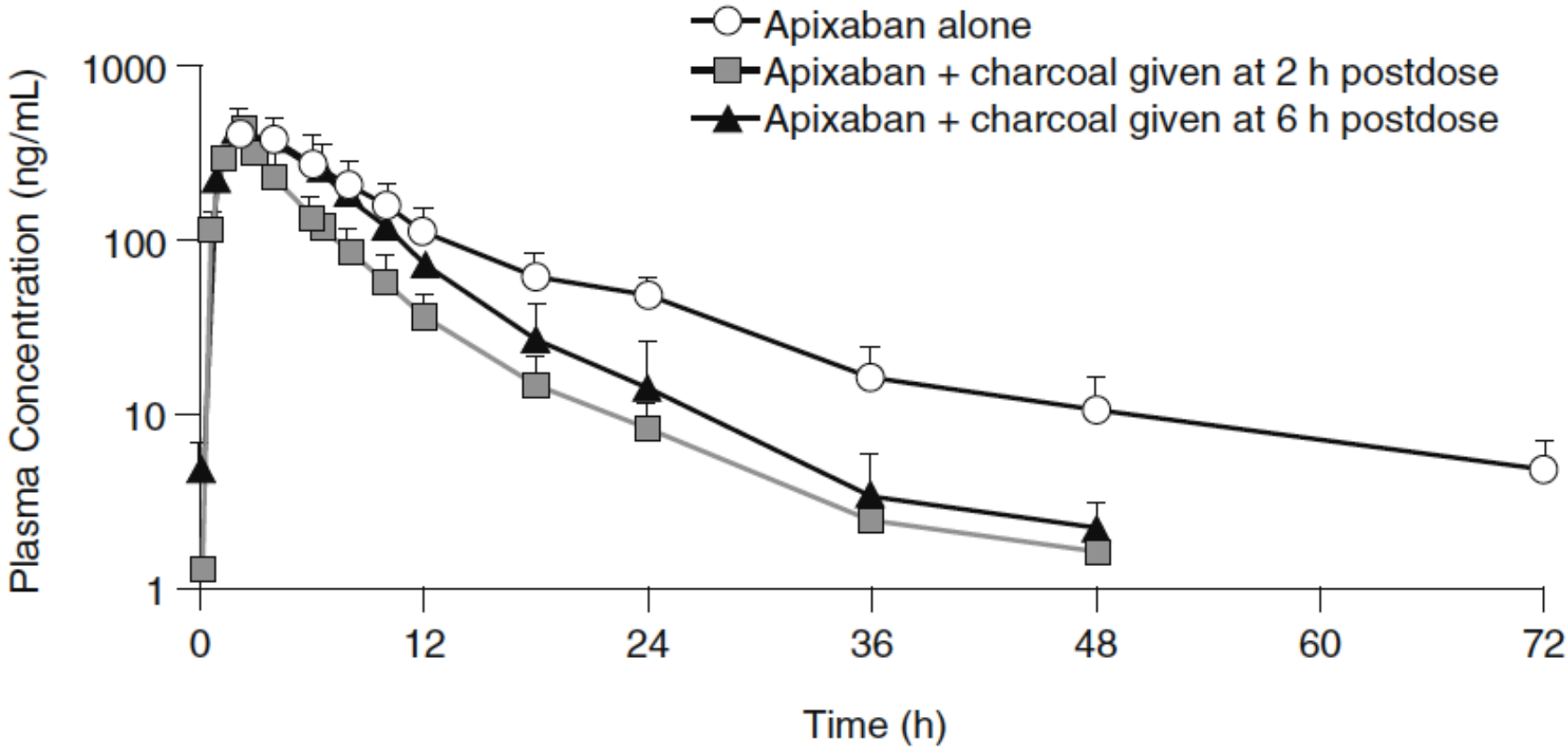
Pharmacometric Characterization of Dabigatran Hemodialysis



Liesenfeld et al. Clin Pharmacokinet 2013;52:453–62

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



Am J Cardiovasc Drugs
DOI 10.1007/s40256-013-0055-y

In the case of potential dabigatran overdose

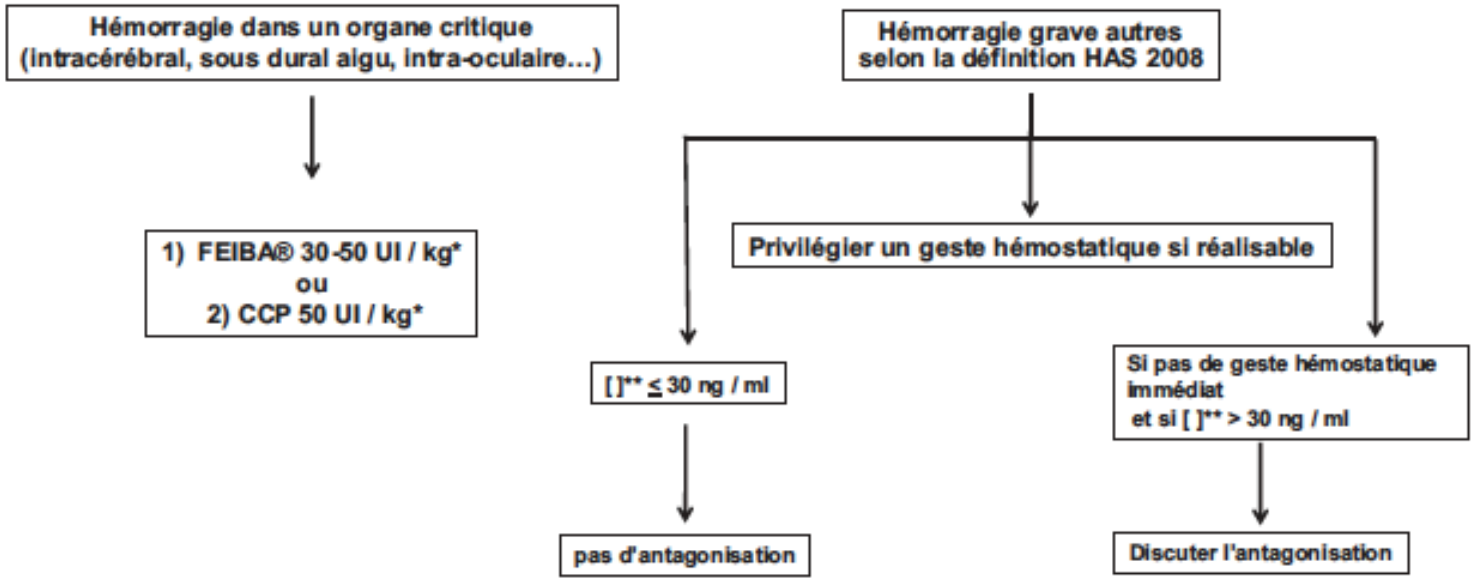
Since dabigatran etexilate is a lipophilic molecule (log P=3.8) adsorption by activated charcoal is expected. The use of activated charcoal to reduce absorption and avoid intoxication following potential overdose of dabigatran etexilate has been investigated *in vitro* using two models (32). In the first study, binding of dabigatran etexilate to activated charcoal in water was used to simulate recent ingestion (2–3 h) of large amounts of dabigatran etexilate in the stomach fluid. Activated charcoal suspension (Ultracarbon®,

Prise en charge des complications hémorragiques graves et de la chirurgie en urgence chez les patients recevant un anticoagulant oral anti-IIa ou anti-Xa direct. Propositions du Groupe d'intérêt en Hémostase Périopératoire (GIHP) - mars 2013☆

G. Pernod [a,b], P. Albaladejo [b,c,*], A. Godier [d], C.M. Samama [d], S. Susen [e], Y. Gruel [f], N. Blais [g], P. Fontana [h], A. Cohen [i], J.V. Llau [j], N. Rosencher [k], J.F. Schved [l], E. de Maistre [m], M.M. Samama [n], P. Mismetti [o], P. Sié [p]

Hémorragie et Dabigatran (Pradaxa®) ou Rivaroxaban (Xarelto®)

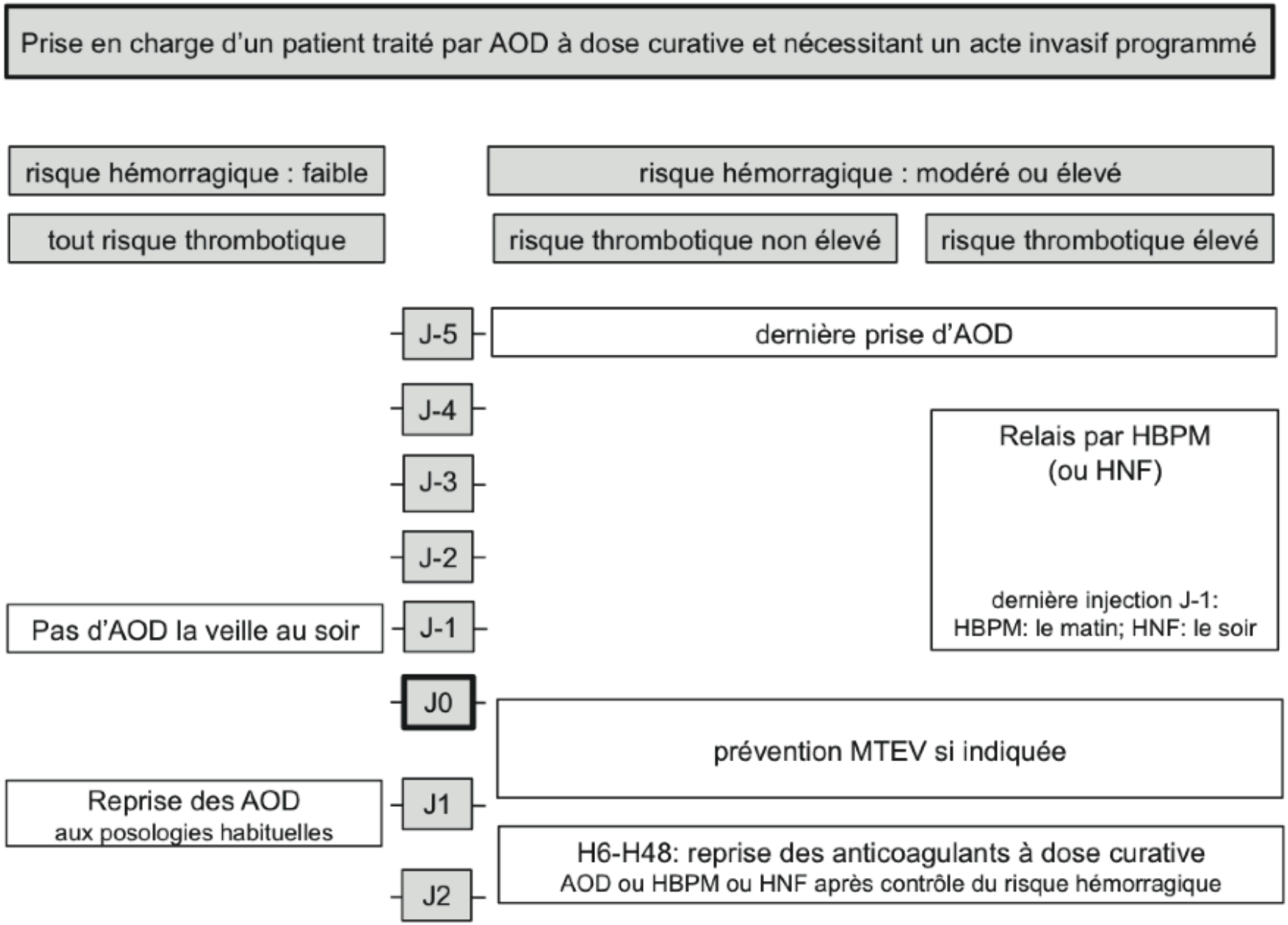
Votre établissement dispose d'un dosage spécifique de dabigatran (Pradaxa®) ou rivaroxaban (Xarelto®)



* Fonction de la disponibilité. Pas de données disponibles sur le risque thrombotique des fortes doses de CCP ou de FEIBA, chez ces patients
** [ ] signifie concentration
*** CCP=25-50 UI/kg ou FEIBA=30-50 UI/Kg
Le rFVIIa n'est pas envisagé en première intention

Ann Fr Anesth Reanim (2013), http://dx.doi.org/10.1016/j.annfar.2013.04.016

GIHP Groupe d'intérêt en hémostase péri-opératoire



GIHP AFAR 2011

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.

[a]No EMA approval yet. Needs update after finalisation of SmPC.

[b]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 (15 mg QD).

Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.

CrCl, creatinine clearance.

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Jan Beyer-Westendorf[1]*, Vera Gelbricht[1], Kati Förster[1], Franziska Ebertz[1], Christina Köhler[1], Sebastian Werth[1], Eberhard Kuhlisch[2], Thoralf Stange[2], Christoph Thieme[1], Katharina Daschkow[1], and Norbert Weiss[1]

Table 5 **Uni- and multivariate analyses of potential risk factors for cardiovascular events**

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Dabigatran vs. rivaroxaban	7.4	0.7–82.2	0.101	–	–	–
Arterial hypertension	n.a.	0–∞	0.996	–	–	–
Diabetes	14.9	1.9–119.9	**0.011**	13.2	1.6–107.3	**0.016**
TIA/stroke in history	1.8	0.4–8.8	0.467	–	–	–
Coronary artery disease	2.0	0.5–8.0	0.337	–	–	–
Impaired renal function (GFR < 50 mL/min)	n.a.	0–∞	0.996	–	–	–
Major vs. non-major procedure	7.4	2.0–28.2	**0.003**	7.3	1.9–28.5	**0.004**
Age >65 years vs. <65 years	1.7	0.2–13.7	0.616	–	–	–
Pre-procedural NOAC interruption >24 h vs. <24 h	0.6	0.2–2.7	0.545	–	–	–
Heparin bridging vs. no bridging	1.9	0.5–7.1	0.341	–	–	–

Bold indicates statistical significance ($P < 0.05$).
Of note, some ORs could not be determined (n.a.) due to the low absolute number of events and zero events in some subgroups.
OR, odds ratios; GFR, glomerular filtration rate; NOACs, novel oral anticoagulants; TIA, transient ischaemic attack; CI, confidence interval.

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CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

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Table 6 Uni- and multivariate analyses of potential risk factors for major bleeding events

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Arterial hypertension	n.a.	0–∞	0.996	–	–	–
Diabetes	1.2	0.3–4.3	0.763	–	–	–
TIA/stroke in history	0.7	0.1–5.5	0.728	–	–	–
Coronary artery disease	2.7	0.7–9.5	0.133	–	–	–
Impaired renal function (GFR < 50 mL/min)	0.67	0.1–5.2	0.687	–	–	–
Major vs. non-major procedure	22.5	5.7–88.9	**<0.001**	16.8	3.8–78.9	**<0.001**
Age >65 years vs. <65 years	0.8	0.2–4.0	0.847	–	–	–
Pre-procedural NOAC interruption >24 h vs. <24 h	n.a.	0–∞	0.955	–	–	–
Heparin bridging vs. no bridging	5.6	1.4–21.9	**0.013**	5.0	1.2–20.4	0.023
HAS-BLED ≥ 3 vs. <3	1.5	0.4–5.7	0.589	–	–	–

Bold indicates statistical significance ($P < 0.05$).
Of note, some odds ratios (OR) could not be determined (n.a.) due to the low absolute number of events and zero events in some subgroups.
OR, odds ratios; GFR, glomerular filtration rate; NOACs, novel oral anticoagulants; TIA, transient ischaemic attack; CI, confidence interval.

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists

Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Deborah Siegal, MD, MSc; Jovana Yudin, MD, BSc; Scott Kaatz, DO, MSc; James D. Douketis, MD, FRCPC; Wendy Lim, MD, MSc, FRCPC; Alex C. Spyropoulos, MD, FCCP, FRCPC

	Bridging		No bridging			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Daniels et al., 2009	36	342	18	213	9.8%	1.27 [0.70, 2.31]
Dotan et al., 2002	2	20	1	20	3.7%	2.11 [0.18, 25.35]
Ercan et al., 2010	11	44	21	1421	9.0%	22.22 [9.92, 49.81]
Garcia et al., 2008	14	108	9	1185	8.8%	19.46 [8.21, 46.14]
Ghanbari et al., 2010	6	29	3	74	6.5%	6.17 [1.43, 26.68]
Jaffer et al., 2010	24	229	7	263	8.8%	4.28 [1.81, 10.14]
Marquie et al., 2006	21	114	2	114	6.4%	12.65 [2.89, 55.34]
McBane et al., 2010	34	514	5	261	8.4%	3.63 [1.40, 9.39]
Robinson et al., 2009	20	113	3	35	7.2%	2.29 [0.64, 8.24]
Tischenko et al., 2009	9	38	5	117	7.6%	6.95 [2.16, 22.33]
Tompkins et al., 2010	23	155	15	513	9.5%	5.78 [2.94, 11.40]
Varkarakis et al., 2005	2	25	7	762	5.9%	9.38 [1.85, 47.64]
Wysokinski et al., 2008	15	204	6	182	8.4%	2.33 [0.88, 6.13]
Total (95% CI)		**1935**		**5160**	**100.0%**	**5.40 [3.00, 9.74]**
Total events	217		102			

Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 52.47$, $df = 12$ ($P < 0.00001$); $I^2 = 77\%$

Test for overall effect: $Z = 5.61$ ($P < 0.00001$)

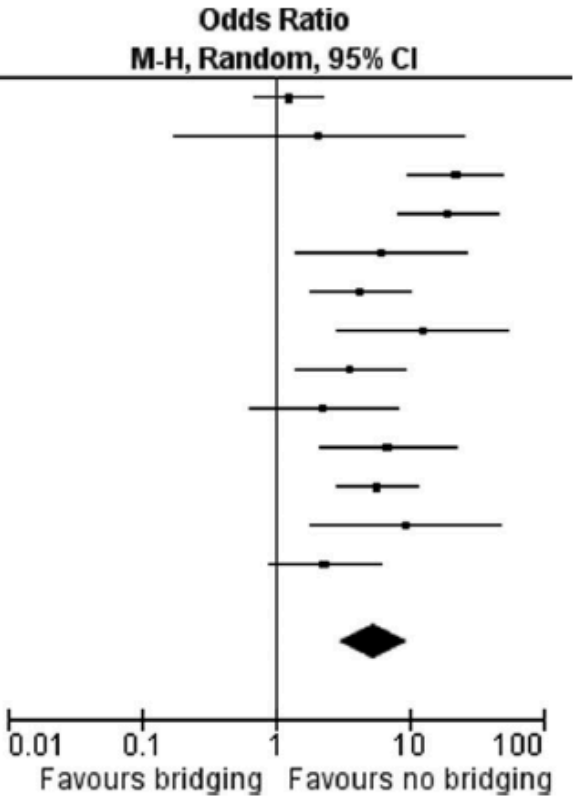

Figure 3. Forest plot of overall bleeding events. M-H indicates Mantel-Haenszel; CI, confidence interval.

***Circulation*. 2012;126:1630-1639**

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists

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Study or Subgroup	Bridging Events	Bridging Total	No bridging Events	No bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	4	342	1	213	8.8%	2.51 [0.28, 22.60]
Garcia et al., 2008	0	108	7	1185	5.2%	0.72 [0.04, 12.76]
Jaffer et al., 2010	1	229	3	263	8.2%	0.38 [0.04, 3.68]
Marquie et al., 2006	0	114	2	114	4.6%	0.20 [0.01, 4.14]
McBane et al., 2010	10	514	6	261	40.5%	0.84 [0.30, 2.35]
Tompkins et al., 2010	1	155	6	513	9.4%	0.55 [0.07, 4.59]
Varkarakis et al., 2005	0	25	3	762	4.7%	4.25 [0.21, 84.56]
Wysokinski et al., 2008	3	204	4	182	18.6%	0.66 [0.15, 3.01]
Total (95% CI)		**1691**		**3493**	**100.0%**	**0.80 [0.42, 1.54]**
Total events	19		32			

Heterogeneity: Tau² = 0.00; Chi² = 3.68, df = 7 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)

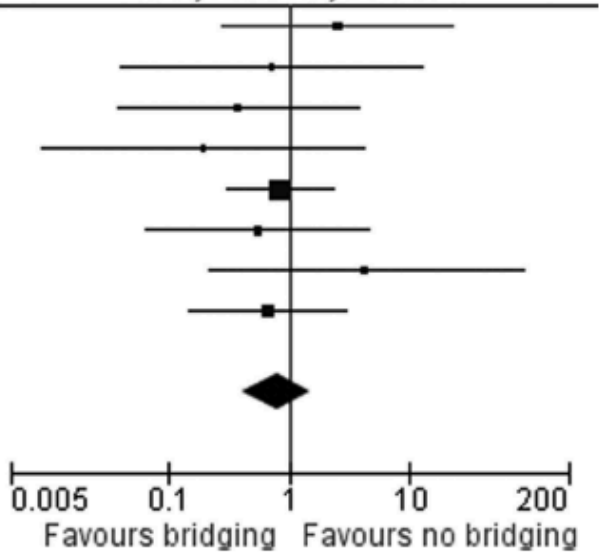


Figure 2. Forest plot of thromboembolic events. M-H indicates Mantel-Haenszel; CI, confidence interval.

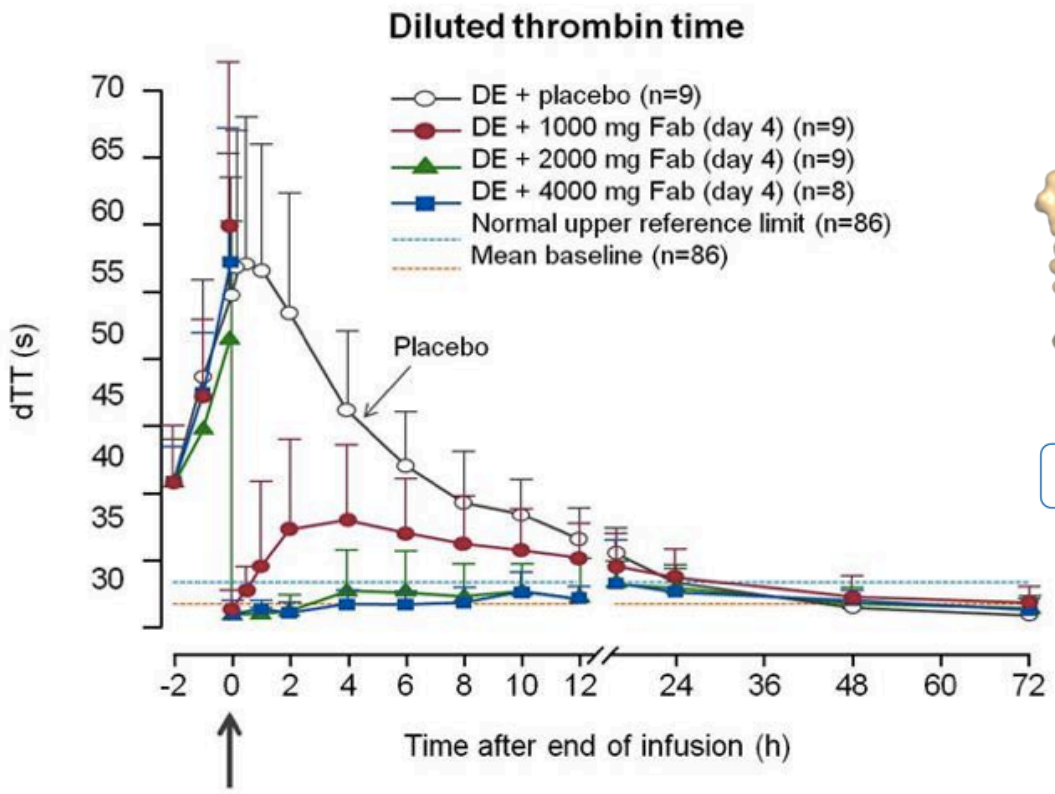
***Circulation*. 2012;126:1630-1639**

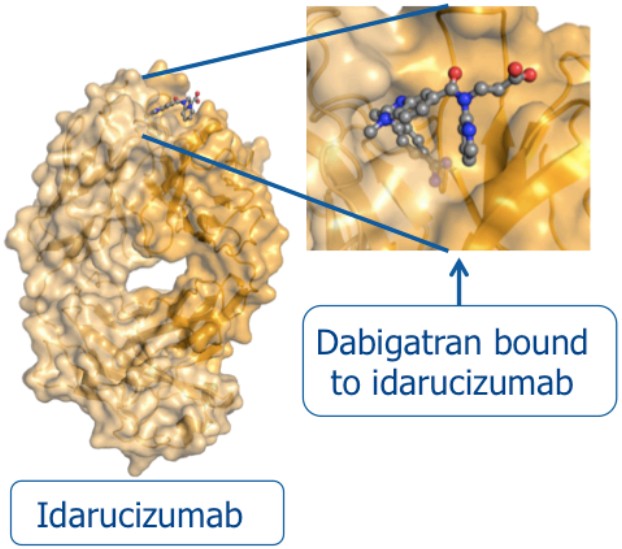
Antidotes

NOAC reversal agent	Target	Mechanism of action	Investigation status
Idarucizumab[1]	Dabigatran	Humanized Fab: specifically binds dabigatran with high affinity[2]	Phase III study in patients requiring urgent surgery/ procedure or with uncontrolled bleeding ongoing[3,4]
Andexanet alfa (PRT064445)[1]	Factor Xa inhibitors	Recombinant modified activated FX: competitive affinity for direct FXa inhibitors[5]	Phase III study in bleeding patients ongoing[6]
Aripazine (PER977)[1]	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)[7]	Phase II ongoing[8]

Idarucizumab: PRAXBIND®

Reversal of dabigatran-induced anticoagulation with antibody fragment (Fab), measured using Diluted thrombin time (dTT)





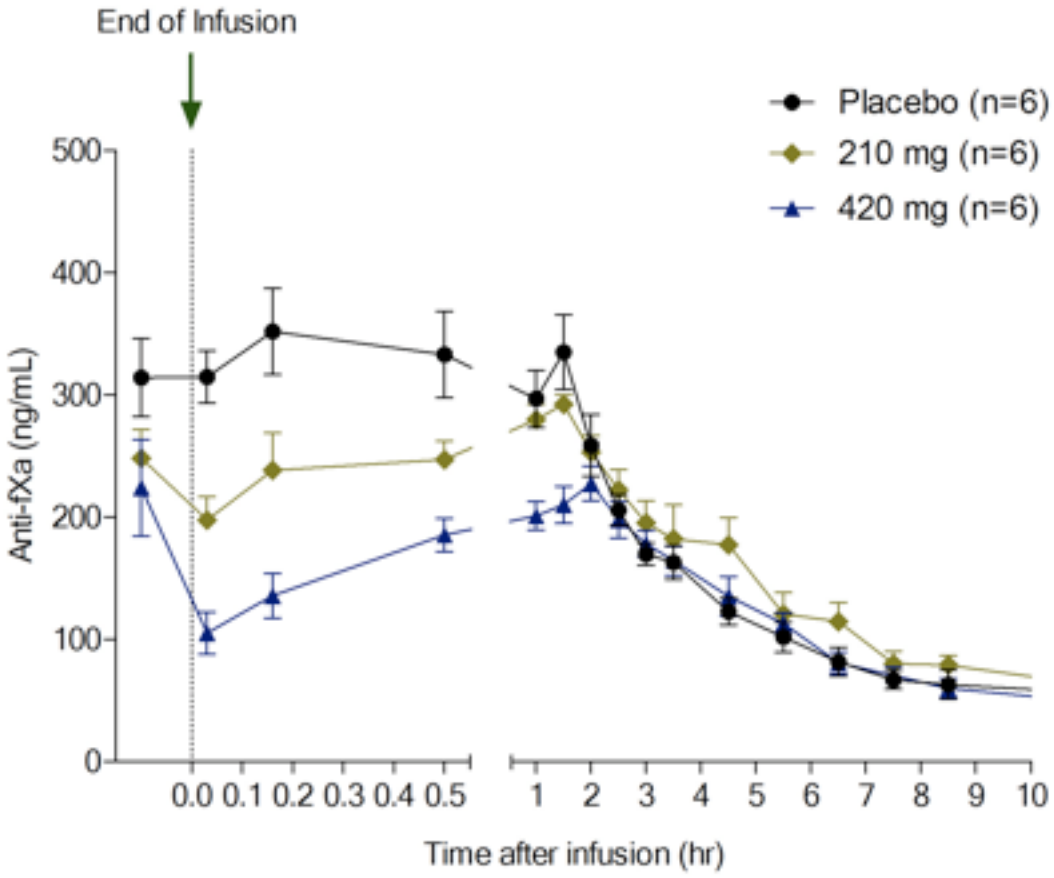
Glund S, *et al.* A Specific Antidote for Dabigatran: Immediate, Complete and Sustained Reversal of Dabigatran Induced Anticoagulation in Healthy Male Volunteers. Oral presentation #17765 on Monday 18 November 2013 at the American Heart Association's Scientific Sessions, Dallas, Texas, USA.

3636 A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial Demonstrating Reversal Of Rivaroxaban-Induced Anticoagulation In Healthy Subjects By Andexanet Alfa (PRT064445), An Antidote For Fxa Inhibitors

Program: Oral and Poster Abstracts
Session: 332. Antithrombotic Therapy: Poster III

Monday, December 9, 2013, 6:00 PM-8:00 PM
Hall E (Ernest N. Morial Convention Center)

Crowther Mark, MD[1*], *Mathur Vandana, MD*[2*], *Kitt Michael, MD*[3*], *Lu Genmin, PhD*[4*], *Pamela B. Conley, Ph.D.*[5], *Hollenbach Stanley, JD*[4*], *Janice Castillo*[6*], *Athiwat Hutchaleelaha, Ph.D.*[7*], *Mark Karbarz, Ph.D.*[6*], *Joyce P Lin*[8*], *Lee Barron, PhD*[6*], *Sandra Russell, R.N*[6*], *Gallia G. Levy, MD, PhD*[6], *Stuart Connolly, M.D.*[9*] *and John T. Curnutte, MD, PhD*[6]



Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban

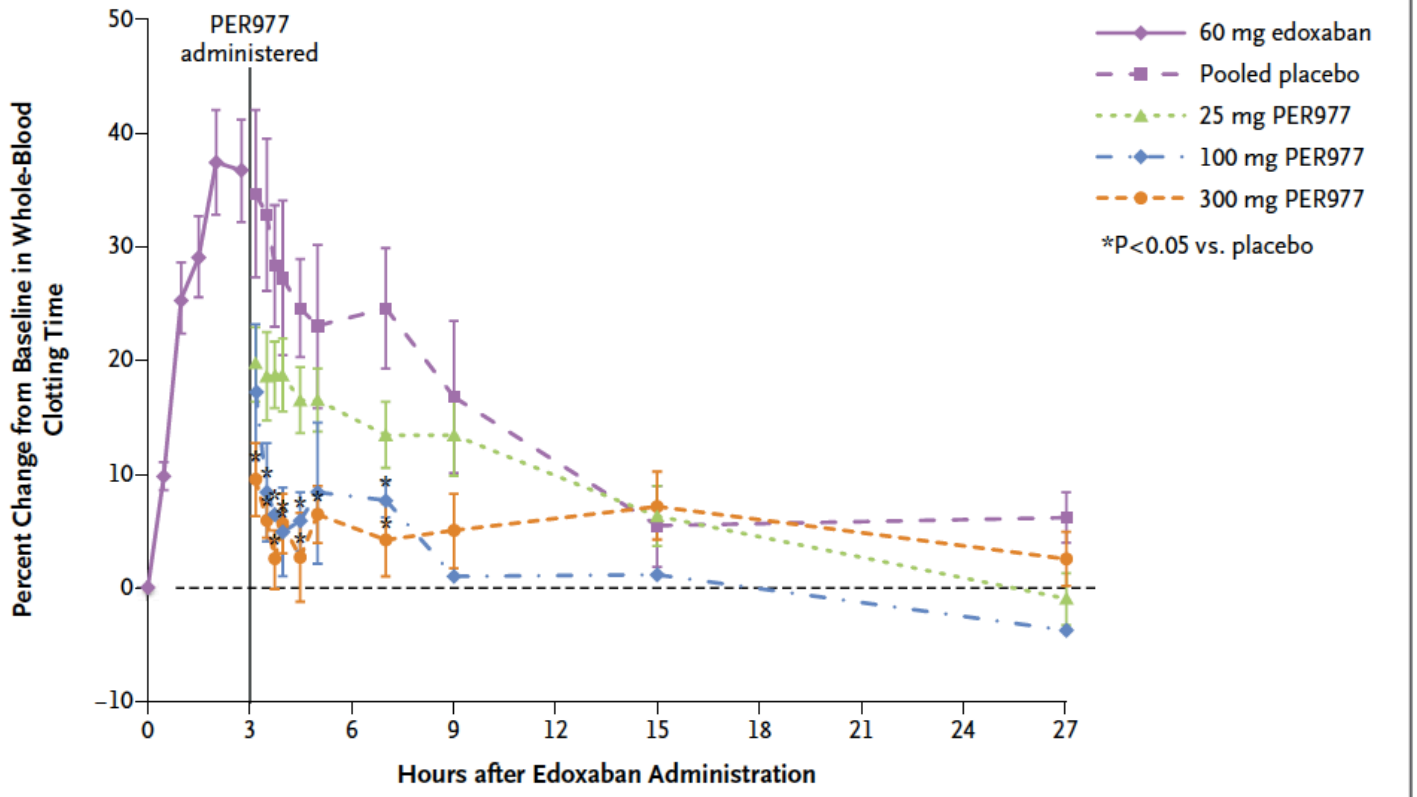


Figure 1. Effect of PER977 on Whole-Blood Clotting Time.

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.

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Merci de votre attention !!!