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Anticoagulants oraux directs (AOD) et ”antidotes”

Charles Marc SAMAMA

Pôle Anesthésie Réanimations Thorax Explorations

GIHP Groupe d'intérêt en hémostase péri-opératoire

European Society of Anaesthesiology ESA

UNIVERSITÉ PARIS DESCARTES

Disclosures - Slides

Companies and products (DCI):

Aspen (fondaparinux – nadroparin) – Bayer (**rivaroxaban**) – BMS (**apixaban**)

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

Daïchi Sankyo (**edoxaban**) - LFB (**CCP** - fibrinogen) - Mitsubishi (argatroban) – Octapharma (**CCP**)

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

Rovi (bemiparine) - Sanofi-Aventis (enoxaparin, idrabiotaparinux, aspirine, clopidogrel)

Siemens (monitoring) - Stago (specific anti-Xa test)

Agencies, Societies and Guidelines:

American College of Chest Physicians (ACCP) : 8th, 9th and **10th (ongoing)** Guidelines

European Medicines Agency: efficacy working party (expert consultant)

INSERM : laboratory of experimental thrombosis (UMR 1140)

Slides – aknowledgements :

Pierre Albaladejo (Grenoble), Gilles Pernod (Grenoble), Pierre Sié (Toulouse),

Denise, 88 y.o.

- **Atrial Fibrillation treated with rivaroxaban 15mg o.d**
- Hypertension
- Transient Ischemic Attack 2 years ago
- Asymptomatic Angina
- Normal liver function. Creatinine clearance 40ml/min
- Aspirin, Simvastatin, Amiodarone
- CHA_2DS_2-VASC score: 6 (Hypertension, Age>75, TIA, woman) – thrombotic risk=9.8%/year

Last oral intake of Xarelto® 4 hrs ago
She just fell down at home 2 hrs ago: **hip fracture…**
????

When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

J Thromb Haemost 2016;
DOI: 10.1111/jth.13227.

J. H. LEVY,* W. AGENO,† N. C. CHAN,‡ M. CROWTHER,§ P. VERHAMME¶ and J. I. WEITZ,§ FOR THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION

*Duke University School of Medicine, Durham, NC, USA; †University of Insubria, Varese, Italy; ‡Monash University, Clayton, Vic., Australia; §McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada; and ¶University of Leuven, Leuven, Belgium

Table 1 Indications for use or non-use of the antidotes

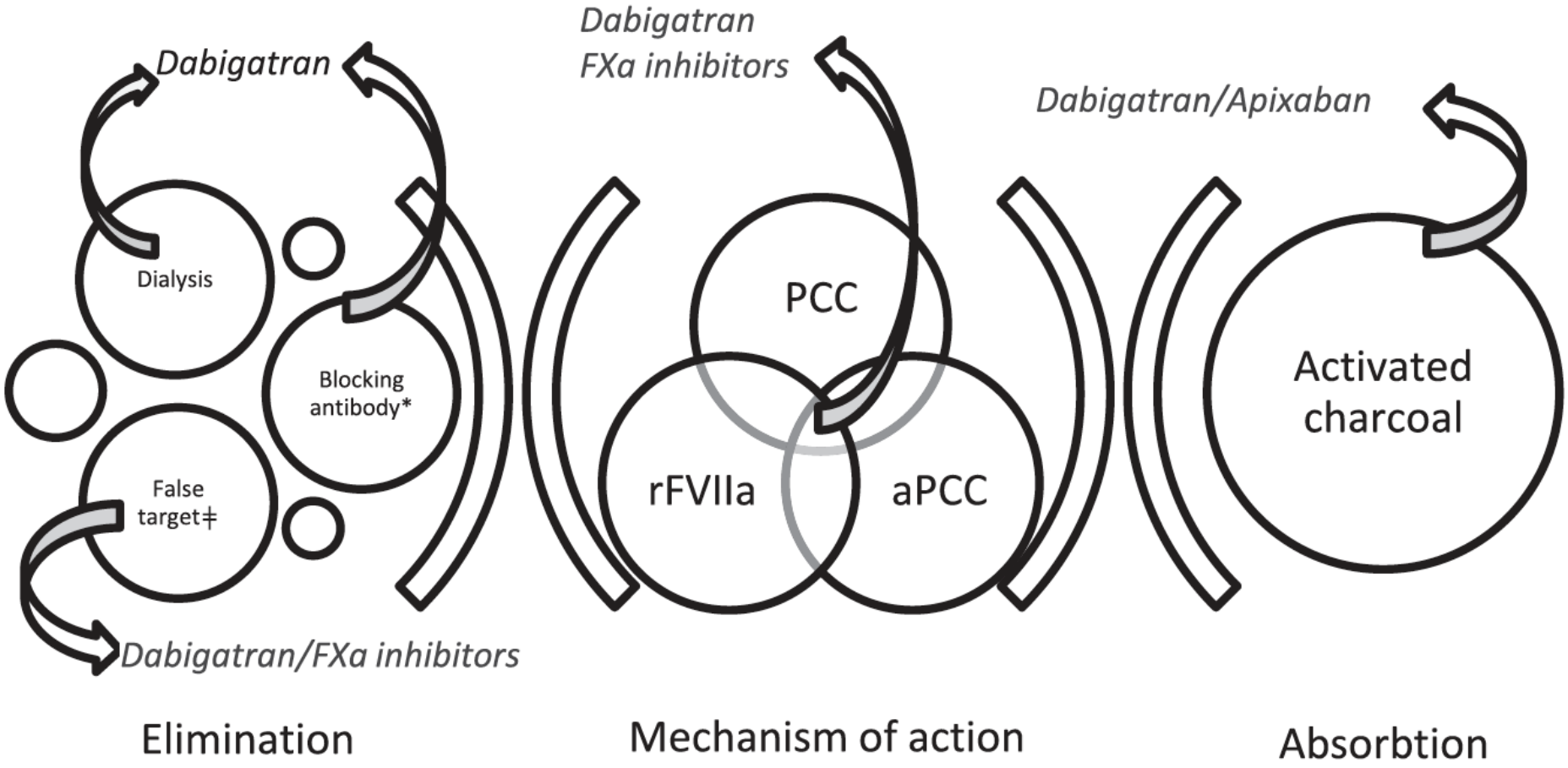
Indications for use	• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage • Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome • Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose • Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance • Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery
Potential indication for use	• Need for urgent surgery or intervention in patients with acute renal failure
Antidotes should not be used	• Elective surgery • Gastrointestinal bleeds that respond to supportive measures • High drug levels or excessive anticoagulation without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance

Antidotes for Novel Oral Anticoagulants

Current Status and Future Potential

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

Mark Crowther, Mark A. Crowther

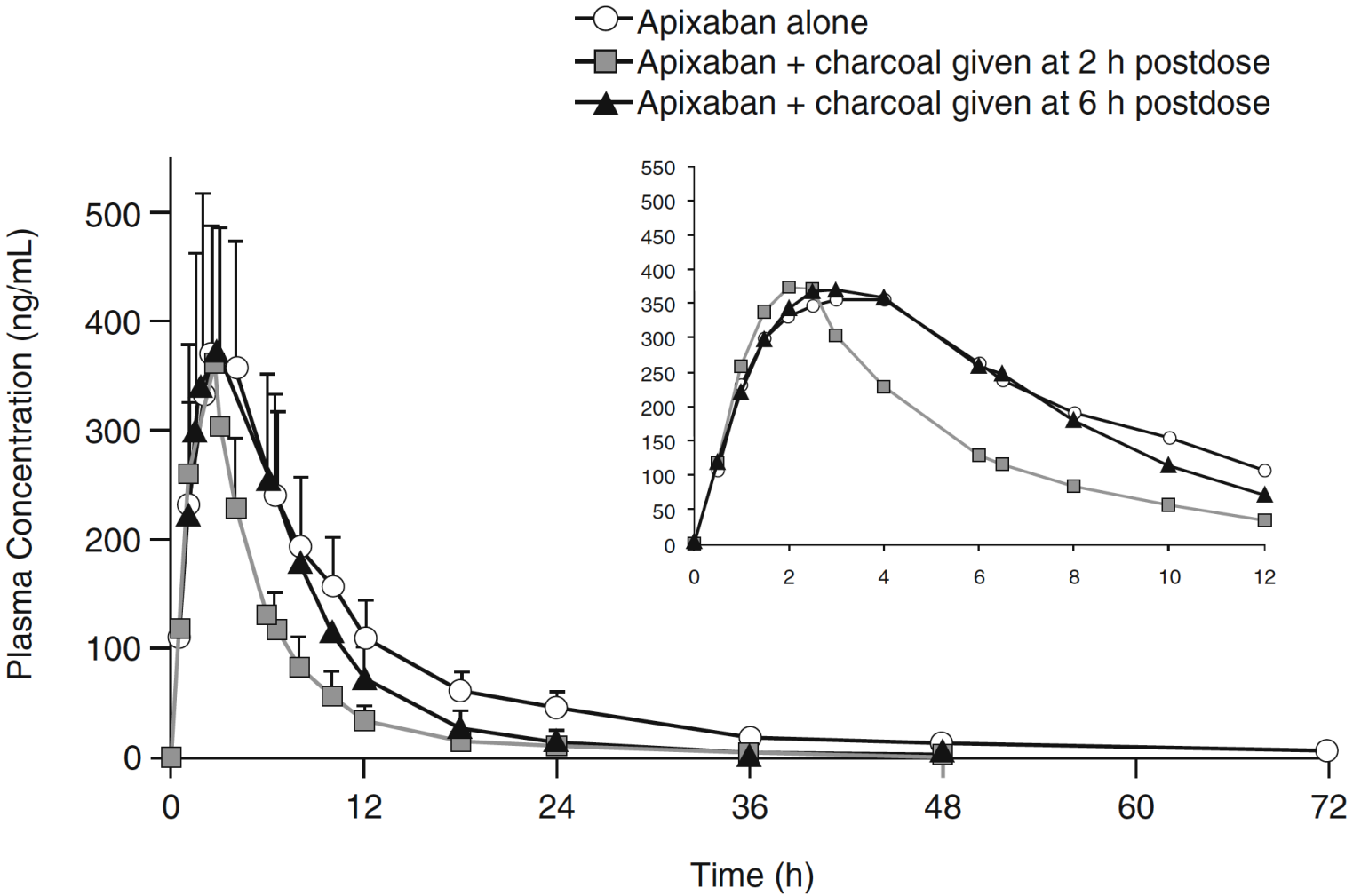


Non-specific « reversal » agents

Effect of Activated Charcoal on Apixaban Pharmacokinetics in Healthy Subjects

Am J Cardiovasc Drugs, 2013, Nov

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



The mean T for apixaban alone (13.4 h) decreased to 5 h when activated charcoal was administered at 2 or 6 h post-dose

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

Four hours of haemodialysis **removed 48.8% and 59.3% of total dabigatran** from the central compartment with 200 and 400 ml/minute targeted blood flow, respectively. The anticoagulant activity of dabigatran was linearly related to its plasma levels.There was a minor redistribution of dabigatran (<16%) after the end of the haemodialysis session.

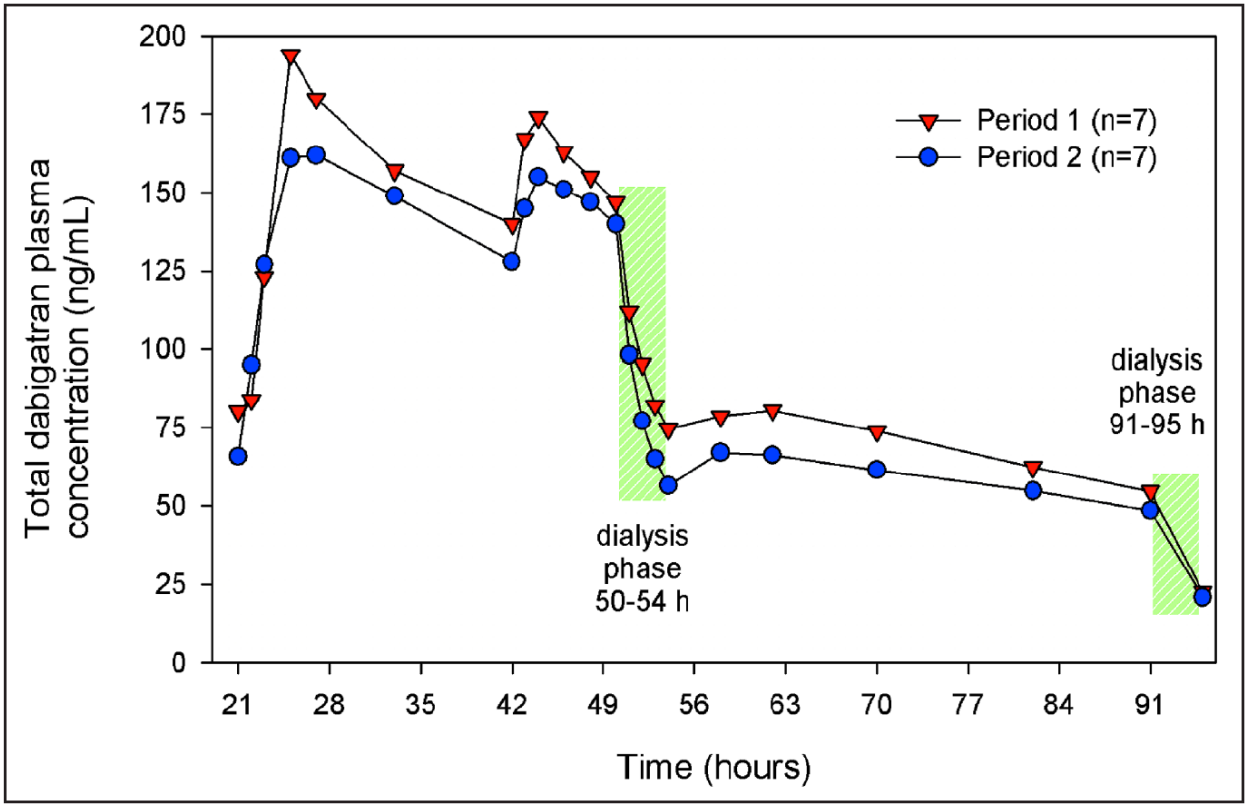


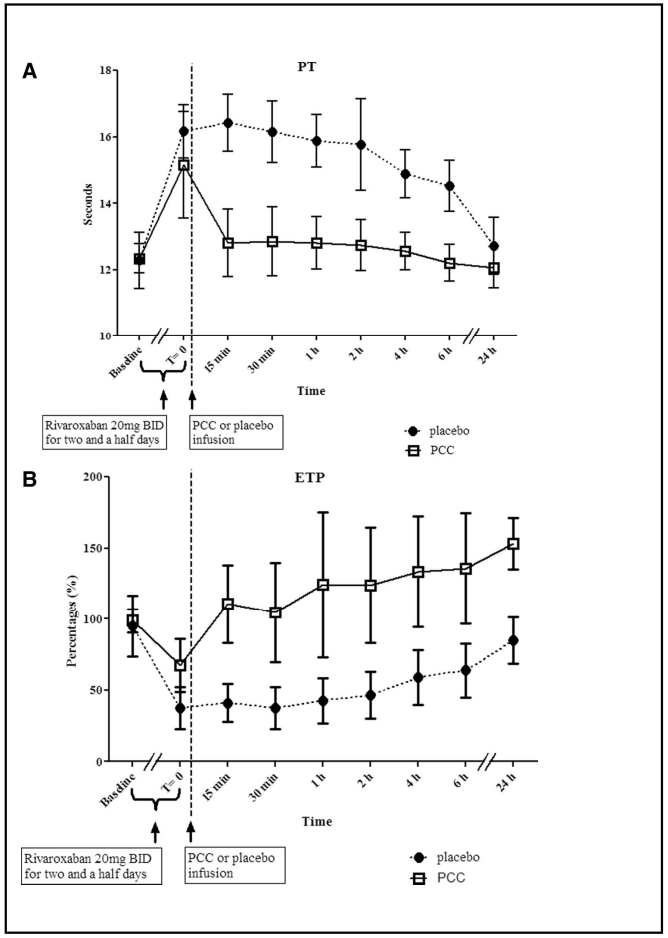
Figure 2: Geometrical mean plasma concentration-time profiles of total dabigatran in both treatment periods. Dabigatran was administered at 0, 21 and 42 h after the first dose; dialysis was performed from 50 to 54 and 91 to 95 h.

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

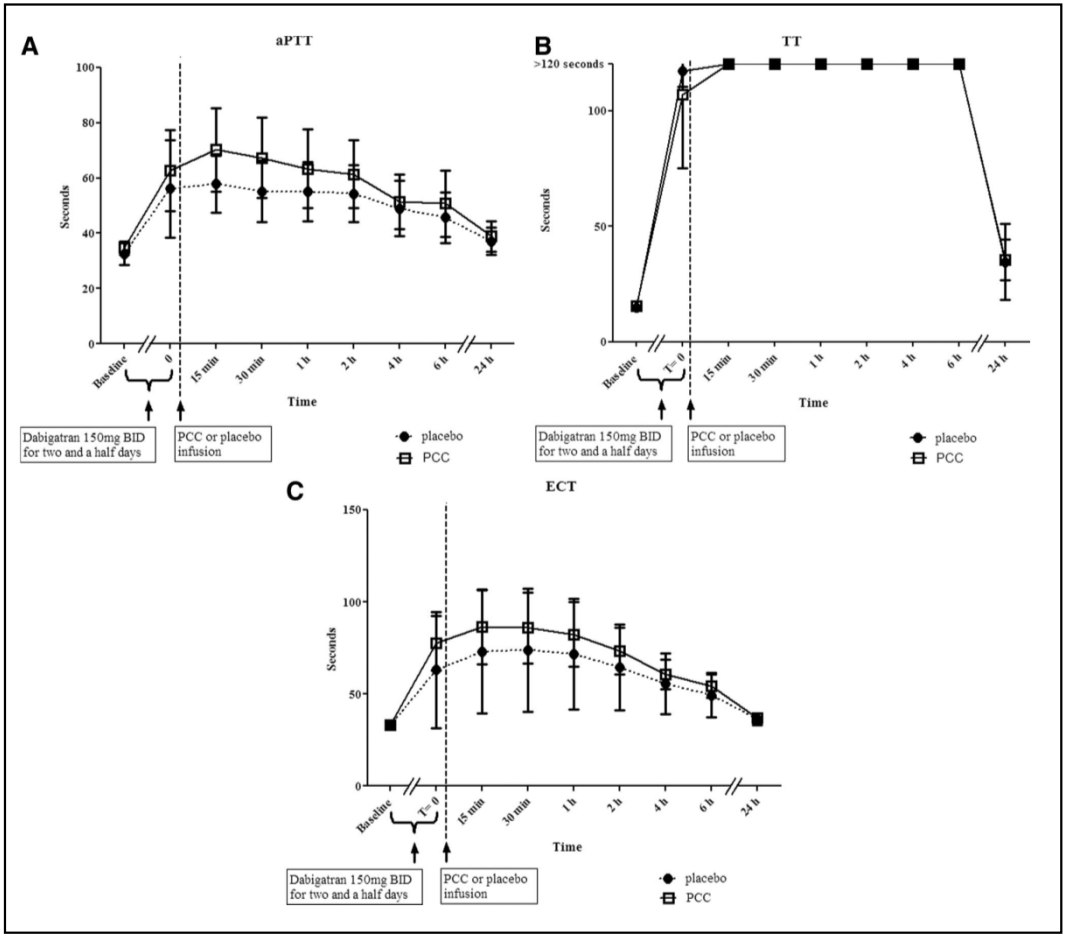
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

50IU/Kg

Rivaroxaban (20 mg bid)



Dabigatran (150 mg bid)



Circulation 2011; 124: 1573-1579

Evaluation of Prothrombin Complex Concentrate and Recombinant Activated Factor VII to Reverse Rivaroxaban in a Rabbit Model

Anesthesiology. 2012;116:94–102

Anne Godier, M.D., Ph.D.,* Anastasia Miclot, M.Sc.,† Bernard Le Bonniec, Ph.D.,‡
Marion Durand, M.D., Ph.D.,§ Anne-Marie Fischer, M.D., Ph.D.,# Joseph Emmerich, M.D., Ph.D.,‖
Catherine Marchand-Leroux, Ph.D.,** Thomas Lecompte, M.D., Ph.D.,††
Charles-Marc Samama, M.D., Ph.D., F.C.C.P.‡‡

rFVIIa and PCC partially improved laboratory parameters, **but did not reverse rivaroxaban induced-bleeding**

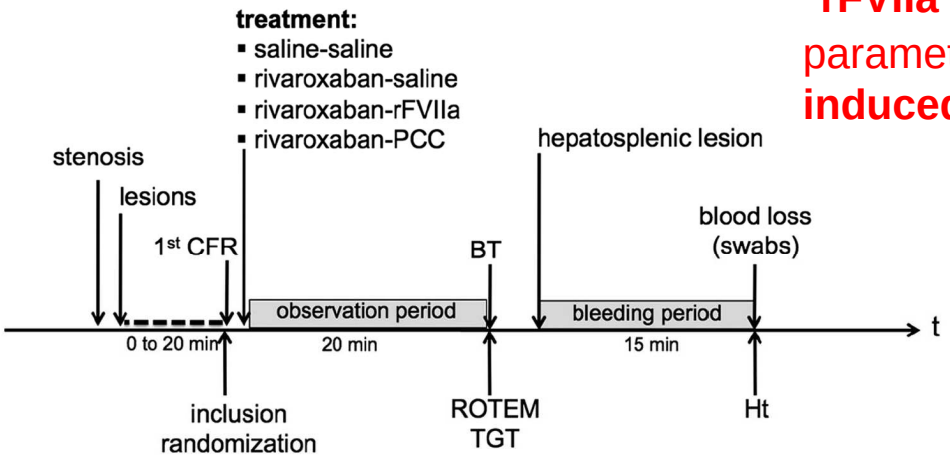


Fig. 1. Protocol design. BT = bleeding time; CFR = cyclic flow reductions; Ht = hematocrit; PCC = prothrombin complex concentrate; rFVIIa = recombinant activated factor VII; TGT = thrombin generation test.

Table 3. Bleeding

—	Control	Rivaroxaban	R + rFVIIa	R + PCC
Hepatosplenic blood loss (g)	7 (5–18)	17 (8–32)*	15 (10–25)*	19.5 (4–28)*
Ear immersion bleeding time (s)	77 (41–101)	140 (75–190)*	92 (65–115)*†	130 (55–165)*‡

Values are median (range).

* $P < 0.05$ *vs.* control. † $P < 0.02$ *vs.* rivaroxaban. ‡ $P < 0.006$ *vs.* rivaroxaban and recombinant activated factor VII.

PCC = prothrombin complex concentrate; R = rivaroxaban; rFVIIa = recombinant activated factor VII.

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International Journal of Cardiology xxx (2013) xxx–xxx
Contents lists available at SciVerse ScienceDirect
International Journal of Cardiology
journal homepage: www.elsevier.com/locate/ijcard

Evaluation of recombinant activated factor VII, prothrombin complex concentrate, and fibrinogen concentrate to reverse apixaban in a rabbit model of bleeding and thrombosis

Anne-Céline Martin [a,b,c], Bernard Le Bonniec [a,b], Anne-Marie Fischer [a,b,c], Catherine Marchand-Leroux [b,e], Pascale Gaussem [a,b,d], Charles-Marc Samama [a,b,f], Anne Godier [a,b,f,*]

Conclusion: rFVIIa, PCC, and Fibrinogen failed to reverse apixaban-induced bleeding. They only improved several laboratory parameters.

Table 2
Bleeding.

	Control (n = 12)	Apixaban (n = 14)	Apix-rFVIIa (n = 13)	Apix-PCC (n = 12)	Apix-Fib (n = 12)
Hepatosplenic blood loss (g)	8.3 ± 3	11.6 ± 3*	12.2 ± 7.5*	11.8 ± 5.1*	19.2 ± 6.3*†
BT (s)	70.8 ± 18.7	126.4 ± 33*	83.5 ± 20†	101.1 ± 37.5*	154.2 ± 40.2†
Hb (g dl^{-1})	7.7 ± 1.5	7.9 ± 1.3	7.8 ± 1.3	8.2 ± 1	6.4 ± 1.1*†

All values are means ± SD.
*p < 0.05 vs. control, † p < 0.05 vs. apixaban.

Table 3
Conventional laboratory parameters.

	Control (n = 12)	Apixaban (n = 14)	Apix-rFVIIa (n = 13)	Apix-PCC (n = 12)	Apix-Fib (n = 12)
PT (s)	13 ± 2	16.5 ± 1,7 *	11.2 ± 1.8*†	15.5 ± 4.6	17.9 ± 4.9*
aPTT (s)	105.4 ± 18.6	104.5 ± 21.3	52.2 ± 13.8 *†	77.4 ± 13.8*†	123.8 ± 24.2
Apix plasma concentration (ng ml^{-1})	0	90.8 ± 44.4*	113.2 ± 223.9*	60.3 ± 38.3 *	77.5 ± 64.4 *
Fibrinogen concentration (g l^{-1})	2.7 ± 0.9	2.5 ± 0.6	2.4 ± 0.5	3.2 ± 2.0	7.0 ± 0.9 *†

All values are means ± SD.
*p < 0.05 vs. control, † p < 0.05 vs. apixaban.

Favorable Outcome of Rivaroxaban-Associated Intracerebral Hemorrhage Reversed by 4-Factor Prothrombin Complex Concentrate: Impact on Thrombin Generation

Sophie Kauffmann, MD,* Russell Chabanne, MD,* Aurélien Coste, MD,† François Longeras, MD,* Thomas Sinegre, MD,‡ Jeannot Schmidt, MD, PhD,§ Charles-Marc Samama, MD, PhD,‖ Jean-Michel Constantin, MD, PhD,* and Aurélien Lebreton, MD, PhD‡

A&A Case Reports. 2015;4:151–4

Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors

Ramesh Grandhi[1], W. Christopher Newman[2], Xiaoran Zhang[3], Gillian Harrison[4], Colleen Moran[5], David O. Okonkwo[2], Andrew F. Ducruet[2]

World Neurosurg. (2015) 84, 6:1956-1961.

16 patients used rivaroxaban and 2 used apixaban.

8 patients traumatic ICH, 8 with hemorrhagic stroke, 1 with sub-arachnoid hemorrhage, and 1 patient with tumoral hemorrhage

In-hospital mortality: 6 patients (33.3%).

1 thromboembolic complication. Favorable outcomes at 90 days in 6 patients (33.3%).

Multimodal assessment of non-specific hemostatic agents for apixaban reversal

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

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

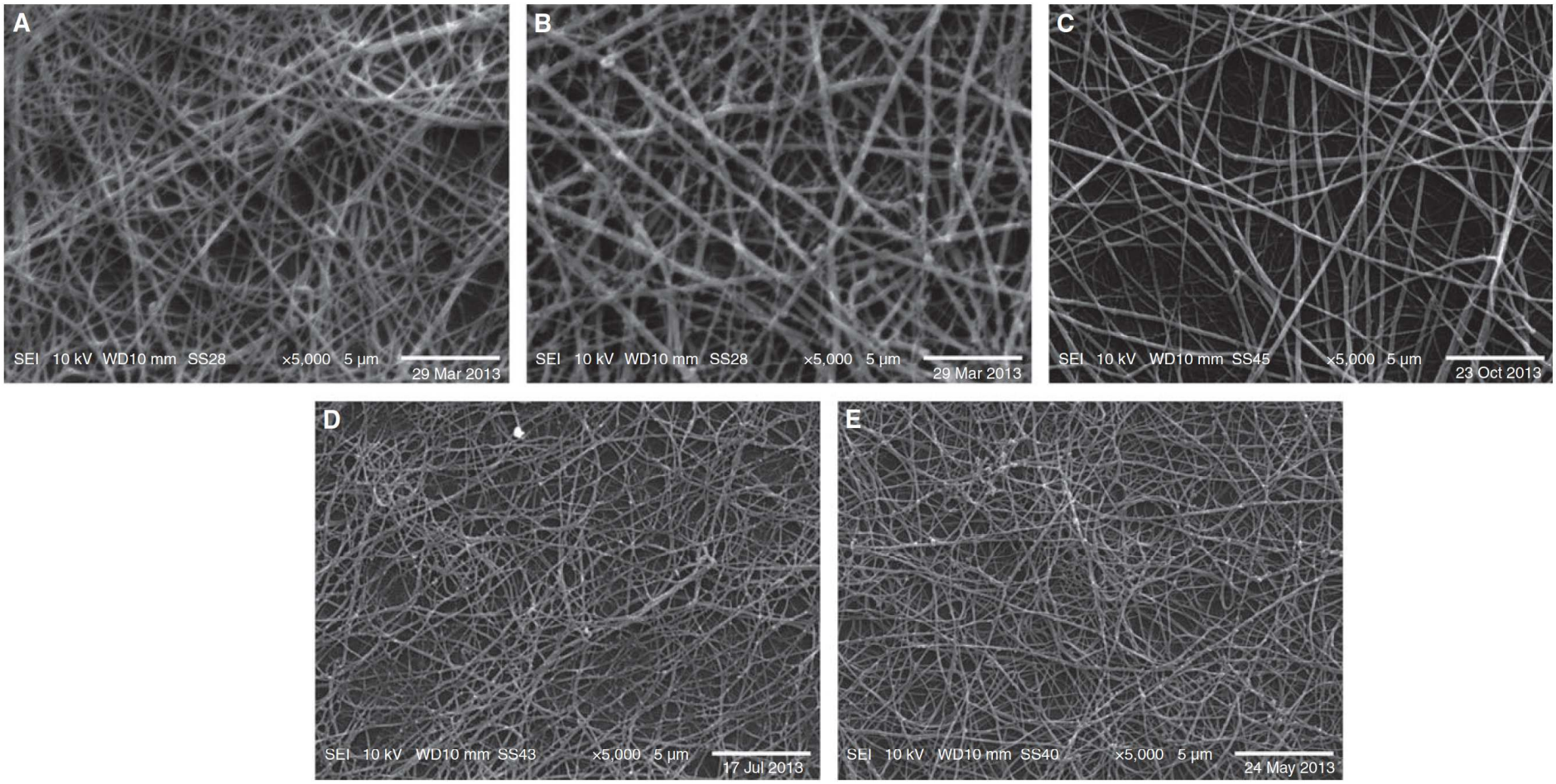


Fig. 2. Effects of the hemostatic agents on samples spiked with a supra-therapeutic apixaban concentration as assessed using scanning electron microscopy of the fibrin network structure in controls (A); blood spiked with apixaban only (B); and blood spiked with apixaban and rFVIIa (C), PCC (D) or aPCC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

GIHP

Groupe d'intérêt
en hémostase
péri-opératoire

Coagulation factor concentrate use

Clotting factors: 36.9%	Dabigatran (n=126)	Rivaroxaban (n=223)	All (n=349)
PCC, n (%)	33 (26.2)	60 (26.9)	93 (26.6)
aPCC, n (%)	17 (13.5)	19 (8.5)	36 (10.3)

Total dose	Dabigatran (n=126)	Rivaroxaban (n=223)	All (n=349)
PCC (median, range)			
Total dose, IU	2625 [1500–3500]	3000 [2000–4000]	3000 [2000–4000]
Total dose, IU/kg	36 [19–50]	45 [25–50]	40 [24–50]
aPCC (median, range)			
Total dose, IU	3500 [2500–4000]	3000 [2500–4000]	3200 [2500–4000]
Total dose, IU/kg	46 [40–52]	40 [31–47]	44 [35–50]

aPCC, activated prothrombin complex concentrate; PCC; prothrombin complex concentrate; SD, standard deviation; U, unit

(unpublished data, March 2015. GIHP working group)

Did the bleeding stop after administration of these clotting factors?

Yes, completely	**42.7 %**
Yes, partially	**39.7%**
No	17.7%

GIHP Groupe d'intérêt en hémostase péri-opératoire

(unpublished data, May 2014. GIHP working group)

Outcome

	GIHP-NACO (30 days)	EHPAK (Crit Care 2014) (7 days	Major bleeding in dabigatran studies (Majeed, Circulation 2013)	Major bleeding in rivaroxaban studies (Piccini, Eur Heart J 2014)
Cardiovascular events	**9.1 %**			
Pulmonary oedema	**5.0 %**			
Cardiogenic shock	**1.8 %**			
Acute coronary syndrome	**1.8 %**			2.6
Stroke	**0.9 %**			4.7
VTE	**0.9 %**			
Mortality			(Hart et al, Stroke 2012) (Majeed et al Circulation 2013)	(Hankey, Stroke 2014) (Piccini et al Eur Heart J 2014)
All cause	**14.6 %**	**13 %**	D= **9.1 %** W = **13%**	R = **20.4 %** W = **26%**
Intracranial bleeding (Spont)	**31.8 %**	**33 %**	D = **37.5 %**	R= **49 %**
Intracranial bleeding (Trauma)	**12.5 %**		D = **27.3%**	

(unpublished data, May 2014. GIHP working group)

Specific antidotes

A specific antidote for dabigatran: functional and structural characterization

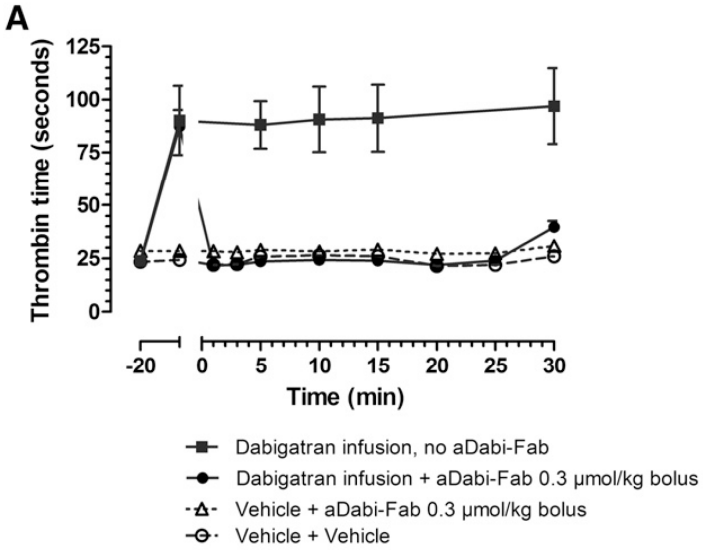
Felix Schiele,[1] Joanne van Ryn,[2] Keith Canada,[3] Corey Newsome,[3] Eliud Sepulveda,[3] John Park,[4] Herbert Nar,[1] and Tobias Litzenburger[4]

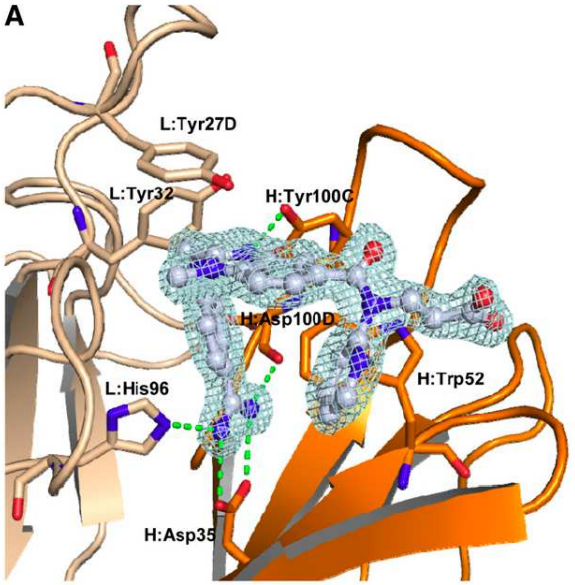
[1]Structural Research Group, and [2]CardioMetabolic Diseases Research, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany; [3]Biotherapeutics, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; and [4]New Biological Entity Discovery, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany

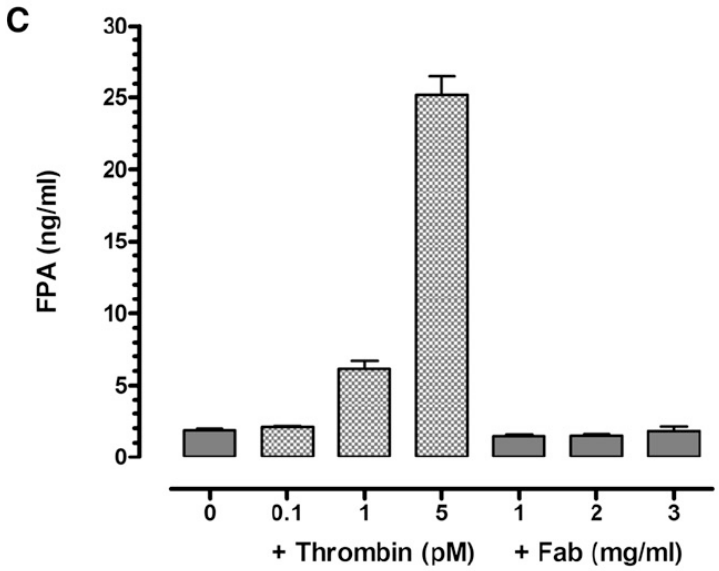
Blood. 2013;121(18):3554-3562

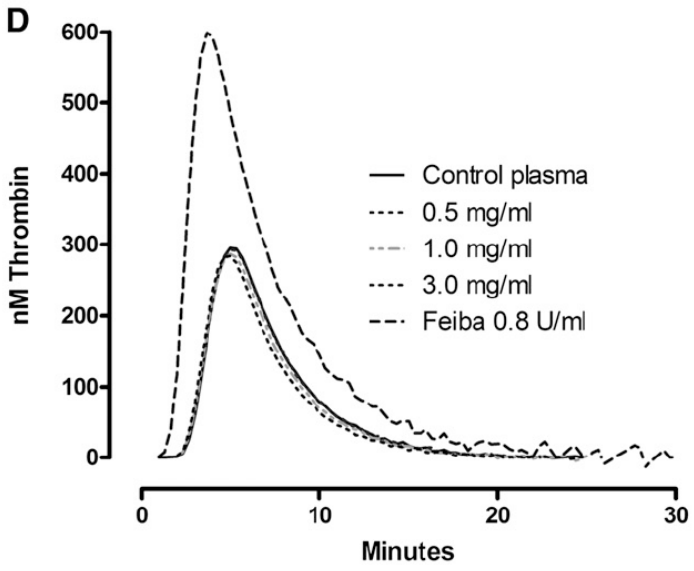
Idarucizumab: a fully humanised monoclonal antibody fragment

By a tighter network of interactions, the antidote achieves an affinity for dabigatran that is ~350 times stronger than its affinity for thrombin.









Idarucizumab Improves Outcome in Murine Brain Hemorrhage Related to Dabigatran

Shin-Young Na, PhD,[1]
Eva Mracsko, MD, PhD,[1]
Joanne van Ryn, PhD,[2] and
Roland Veltkamp, MD[1,3]

ANN NEUROL 2015;78:137–141

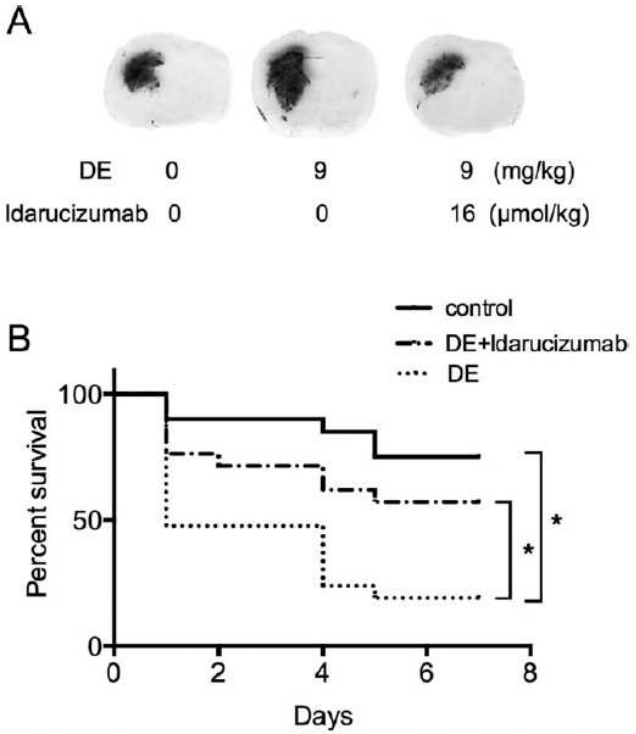
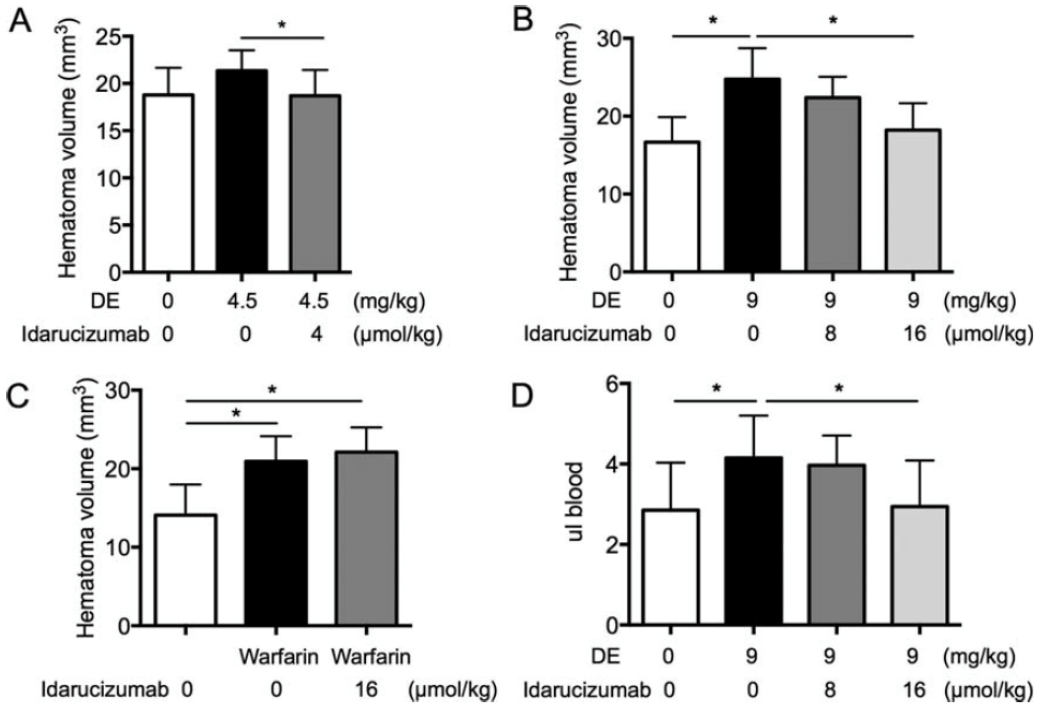


FIGURE 3: Administration of idarucizumab reduces 7 day mortality in intracerebral hemorrhage occurring during anticoagulation with dabigatran etexilate (DE). Intrastriatal injection of a higher dose of collagenase (0.06U) increased hematoma size in nonanticoagulated and anticoagulated mice. (A) Representative coronal sections. (B) Kaplan–Mayer survival curves during 7-day observation period ($p < 0.05$, n = 20/group, Mantel–Cox test).



Idarucizumab prevents excess intracerebral hematoma formation in mice anticoagulated with dabigatran and reduces mortality.

Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healt male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial

Stephan Glund, Joachim Stangier, Michael Schmohl, Dietmar Gansser, Stephen Norris, Joanne van Ryn, Benjamin Lang, Steven Ramael, Viktoria Moschetti, Fredrik Gruenenfelder, Paul Reilly, Jörg Kreuzer

Published **Online**
June 16, 2015
http://dx.doi.org/10.1016/
S0140-6736(15)60732-2

47 participants received **oral dabigatran etexilate 220 mg twice daily** for 3 days and a final dose on day 4.

Idarucizumab (1g, 2g, or 4g 5-min infusion, or 5 g plus 2.5 g in two 5-min infusions given 1h apart) was administered about 2 h after the final dabigatran etexilate dose.

Primary endpoint: incidence of **drug-related adverse events**, analysed in all randomly assigned participants who received at least one dose of dabigatran etexilate.

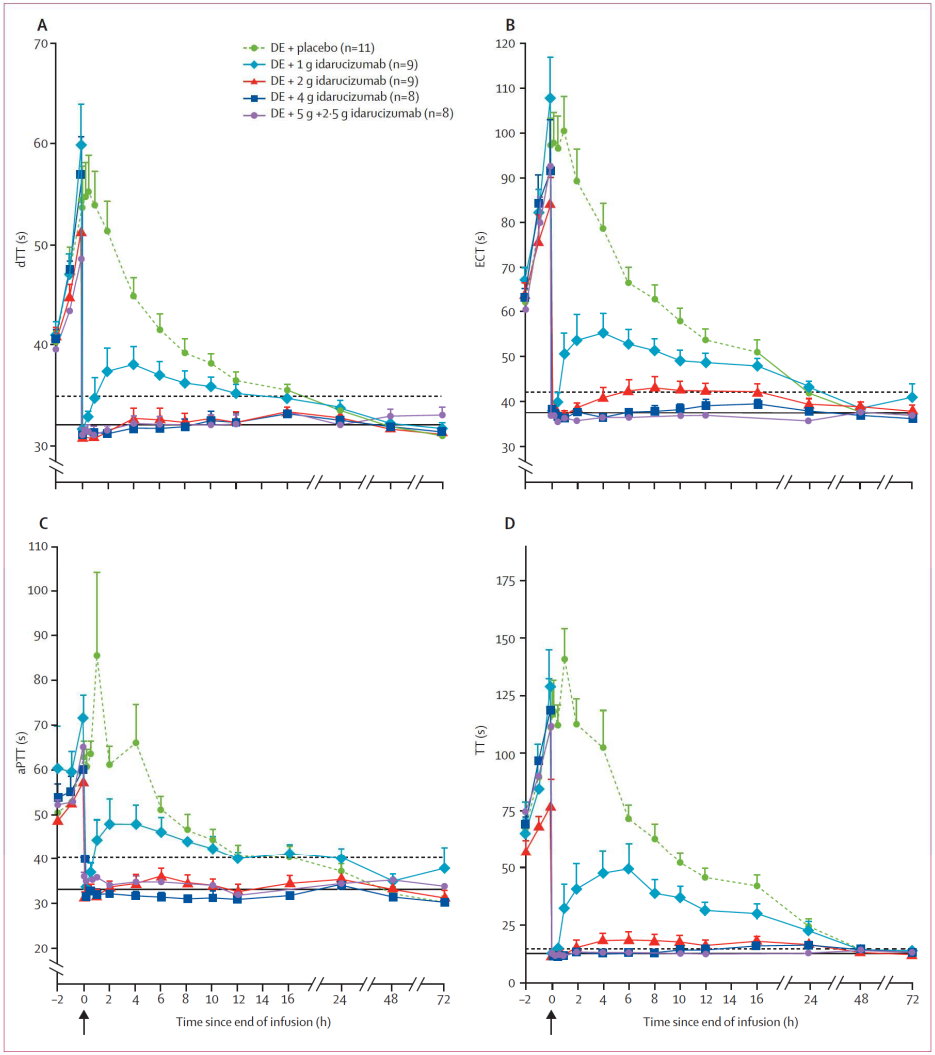
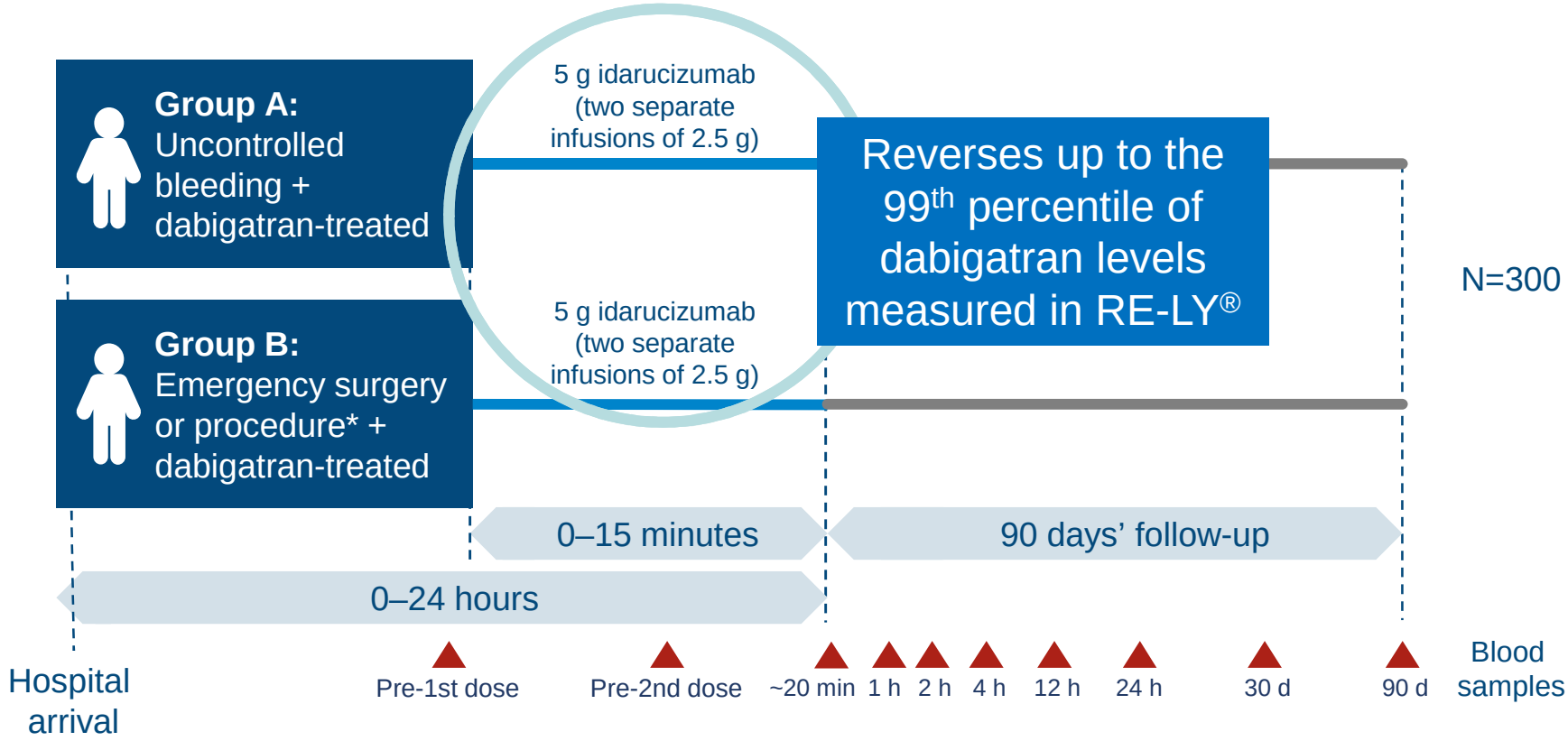


Figure 2: **Effect of idarucizumab or placebo infusion on coagulation variables, by dose group**
Effect of idarucizumab (1 g, 2 g, 4 g, or 5 g plus 2·5 g) and placebo on (A) diluted thrombin time (dTT), (B) ecarin clotting time (ECT), (C) activated partial thromboplastin time (aPTT), and (D) thrombin time (TT). Dotted horizontal lines show upper limit of normal. 0 h and the arrows on x-axes show when the idarucizumab or placebo infusion ended. Solid horizontal lines show the mean baseline measurement. Datapoints show mean; error bars show SE. DE=dabigatran etexilate.

RE-VERSE AD™ is a multicentre, open-label, single-arm Phase III trial



Two separate infusions of 2.5 g idarucizumab are administered intravenously <15 minutes apart to allow for blood sampling after the first vial

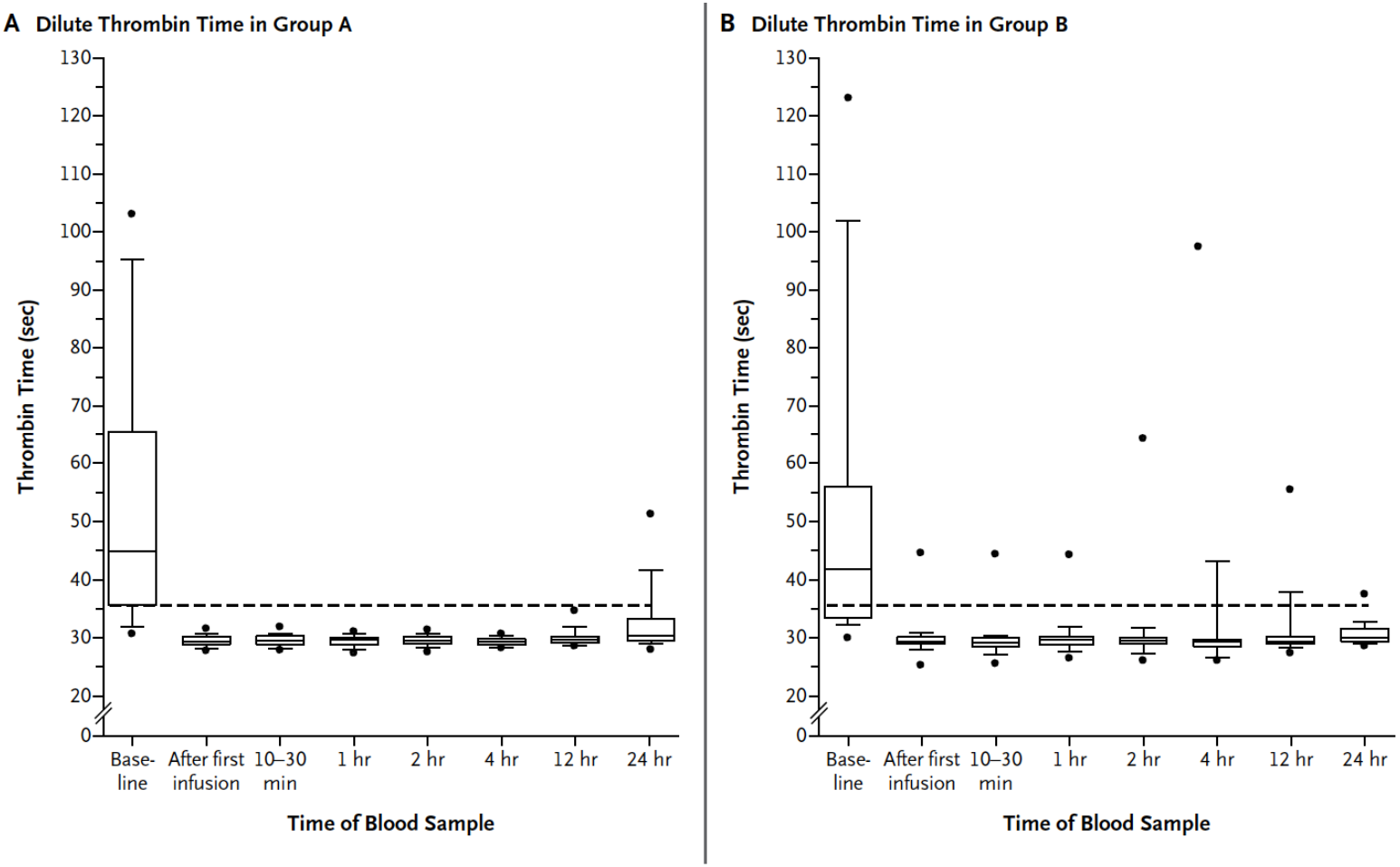
Idarucizumab for Dabigatran Reversal

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).



RE-VERSE AD™: safety

There were no safety concerns in the 90 patients in this study

18 deaths occurred (9 in each group)/90 patients

= 20% mortality

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

There were 26 deaths in the 123 patients included in this analysis, 13 in Group A and 13 in Group B. Thirteen of the deaths occurred in the first 5 days of the study, 6 in Group A and 7 in Group B, while the remaining 13 deaths occurred 6 or more days after treatment, with 7 in Group A and 6 in group B.

= 21% mortality

Pollack et al. NEJM 2015

Dabigatran-Reversal Agent Fast, Effective in RE-VERSE AD, but Now What?

Steve Stiles

November 17, 2016 New Orleans, American Heart Association

Adjudicated Thrombotic Events After Idarucizumab in RE-VERSE AD

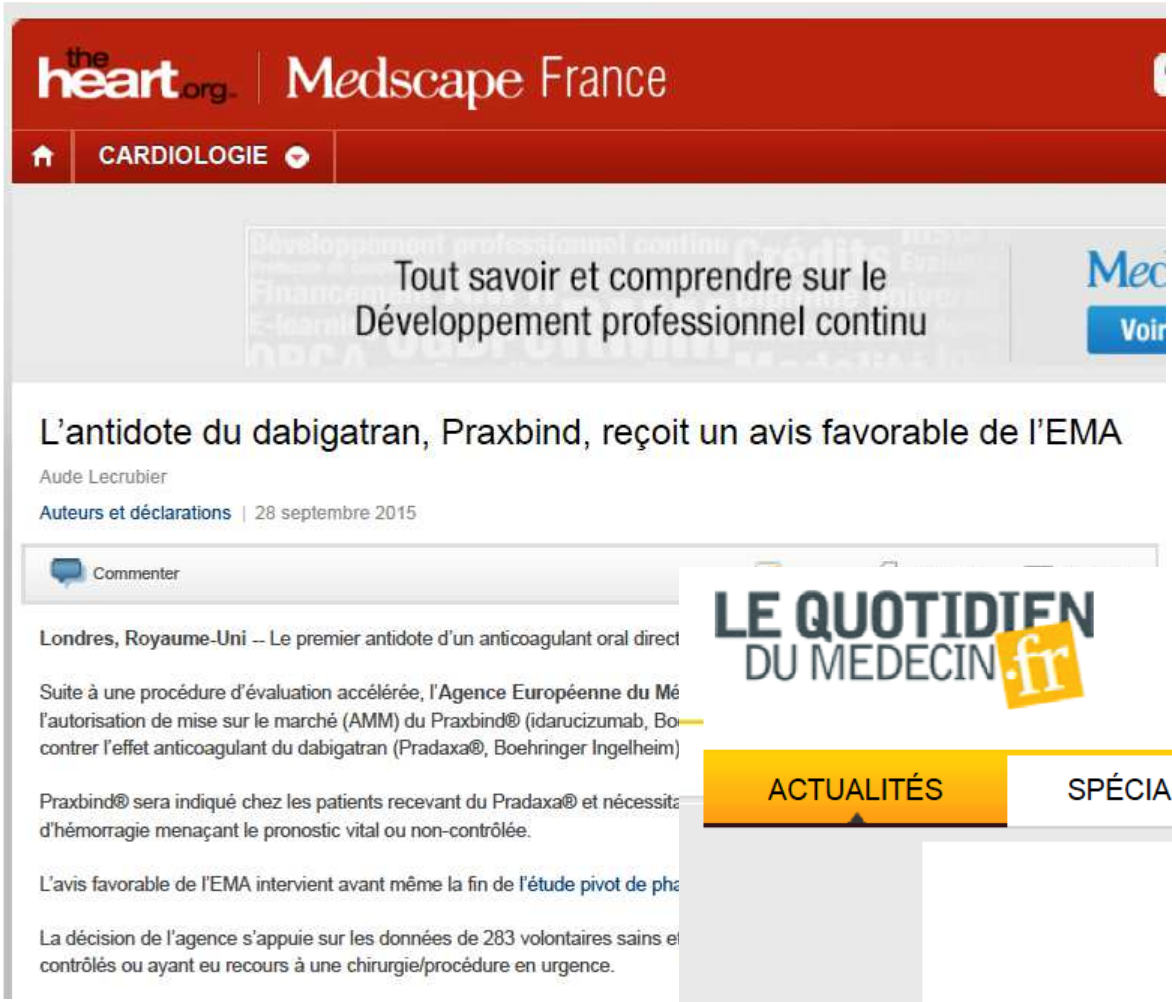
End points	Group A, n=298 (%)	Group B, n=196 (%)
Thrombotic events		
30 d	4.4	4.6
90 d	6.0	6.6
Mortality		
30 d	12.3	12.4
90 d	18.7	18.5

Group A=uncontrolled bleeding

Group B=Emergency surgery

Clinical Characteristics of Patients from spontaneous reports in French pharmacovigilance database and in RE-VERSE AD trial, group A (serious bleeding).

	French Database n= 1051	French Database: Subgroup of patients treated with PCC (activated or not) n = 97	RE-VERSE AD Group A n=51
Age (year), Median (Range)	82 (34-90)	82 (54-95)	77 (48-93)
Male sex (%)	50.4	51.5	63
Weight (Kg), Median (Range)	72 (37-170)	74.8 (40-135)	70.5 (42.4-127.5)
Creatinine clearance (ml/min) Mean Median (range)	 59.9 56 (4-162)	 56.3 55 (4-126)	 59 ± 33 54 (16-187)
Dose of Dabigatran (%) 150 bid 110 bid 75 bid other	 9 80.2 0.3 11	 19 70 0 11	 27 67 2 4
Indication for Dabigatran (%) AF VTE Orthopedic surgery Other	 82.8 0.9 16.3	 89 0 11	 92 2 6
Type of Bleeding (%) Intracranial Trauma related Gastro-intestinal Other	 19 2 48 31	 18 2 48 32	 35 18 39 22
Fatality Rate (%)	16.7 *95% CI [14.4; 19]* (n=176/1051)	18,6 *95% CI [10.9; 26.3]* (n=18/97)	17.6 *95% CI [7.1; 28.1]* (n=9/51)


theheart.org | Medscape France
CARDIOLOGIE
Tout savoir et comprendre sur le
Développement professionnel continu
L'antidote du dabigatran, Praxbind, reçoit un avis favorable de l'EMA
Aude Lecrubier
Auteurs et déclarations | 28 septembre 2015
Commenter
Londres, Royaume-Uni -- Le premier antidote d'un anticoagulant oral direct
Suite à une procédure d'évaluation accélérée, l'Agence Européenne du Mé
l'autorisation de mise sur le marché (AMM) du Praxbind® (idarucizumab, Bo
contrer l'effet anticoagulant du dabigatran (Pradaxa®, Boehringer Ingelheim)
Praxbind® sera indiqué chez les patients recevant du Pradaxa® et nécessita
d'hémorragie menaçant le pronostic vital ou non-contrôlée.
L'avis favorable de l'EMA intervient avant même la fin de l'étude pivot de pha
La décision de l'agence s'appuie sur les données de 283 volontaires sains e
contrôlés ou ayant eu recours à une chirurgie/procédure en urgence.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ACTUALITÉS
SPÉCIALITÉS
FMC - MOOC
Accueil / Actualités / La FDA autorise l...
La FDA autorise l'antidote du Pradaxa
21.10.2015
Commenter
Partager
L'Agence américaine a accordé, à la fin de la semaine dernière, une autorisation de mise sur le marché (AMM) à l'idarucizumab (Praxbind), dans les situations d'urgence chez les patients sous dabigatran (Pradaxa).

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.

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

Case Rep Neurol 2016;8:140–144

Waldemar Kafke Peter Kraft

Department of Neurology, University Hospital Würzburg, Würzburg, Germany

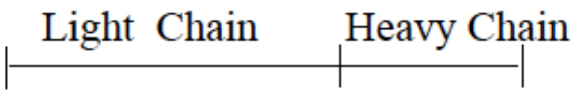
75-year-old female patient with nonvalvular atrial fibrillation who presented with acute ischemic stroke during treatment with dabigatran 2 × 110 mg per day.

Idarucizumab and intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (off-label use).

An intracerebral hemorrhage was excluded after systemic thrombolysis.

Despite the IVT, the patient's clinical condition deteriorated and she developed an ischemic lesion in the right pons, the right thalamus and right cerebellum.

r-Antidote: a recombinant human fXa variant lacking the membrane binding Gla-domain and active site serine



A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa

Genmin Lu[1], Francis R DeGuzman[2], Stanley J Hollenbach[2], Mark J Karbarz[1], Keith Abe[2], Gail Lee[2], Peng Luan[1], Athiwat Hutchaleelaha[3], Mayuko Inagaki[3], Pamela B Conley[1], David R Phillips[1] & Uma Sinha[1]

PRT064445 (r-Antidote)

- **Unable to assemble into the prothrombinase complex and cleave prothrombin**
- **Retained binding ability for all fXa inhibitors**

PORTOLA PHARMACEUTICALS

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.

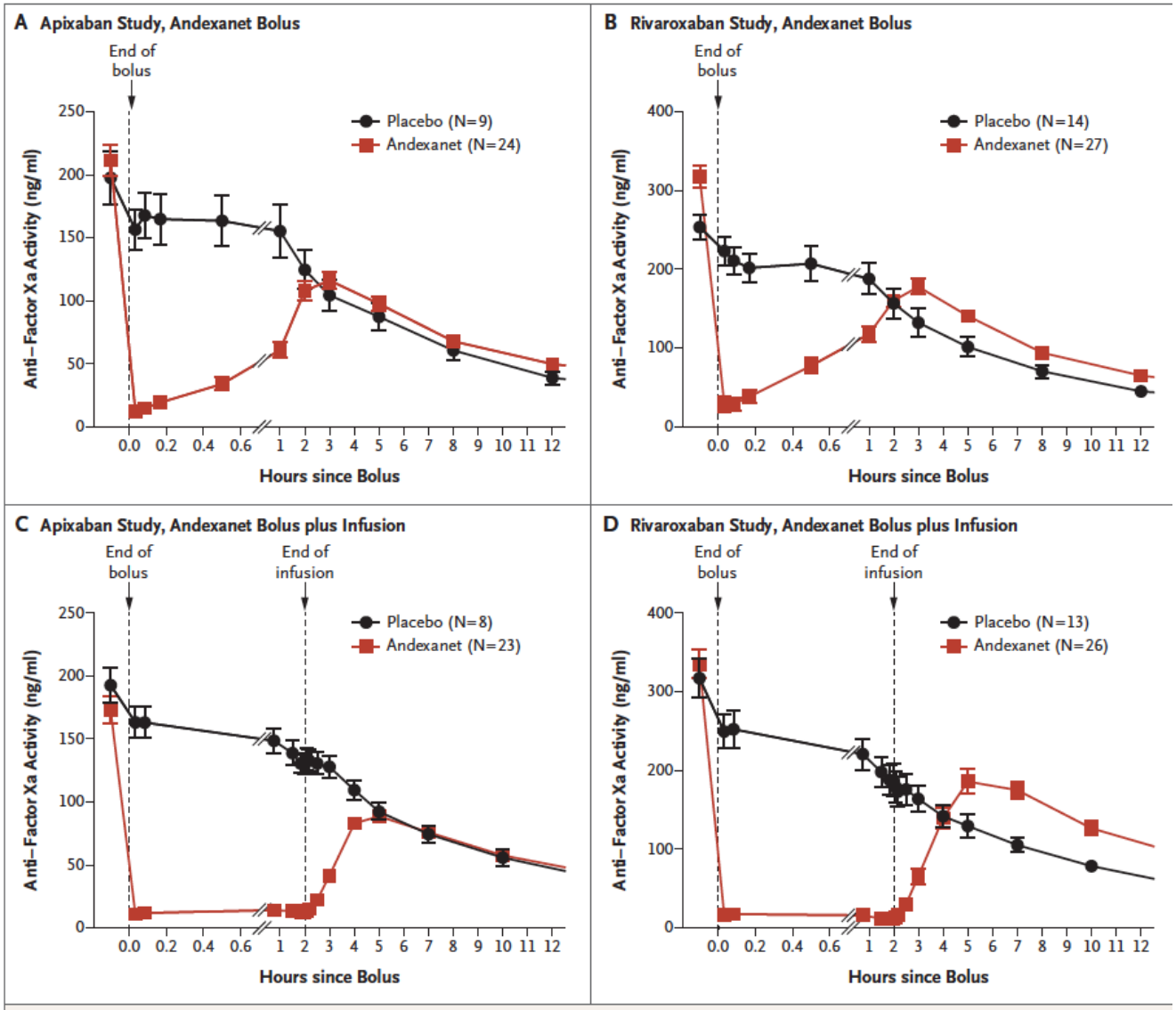


Figure 1. Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.

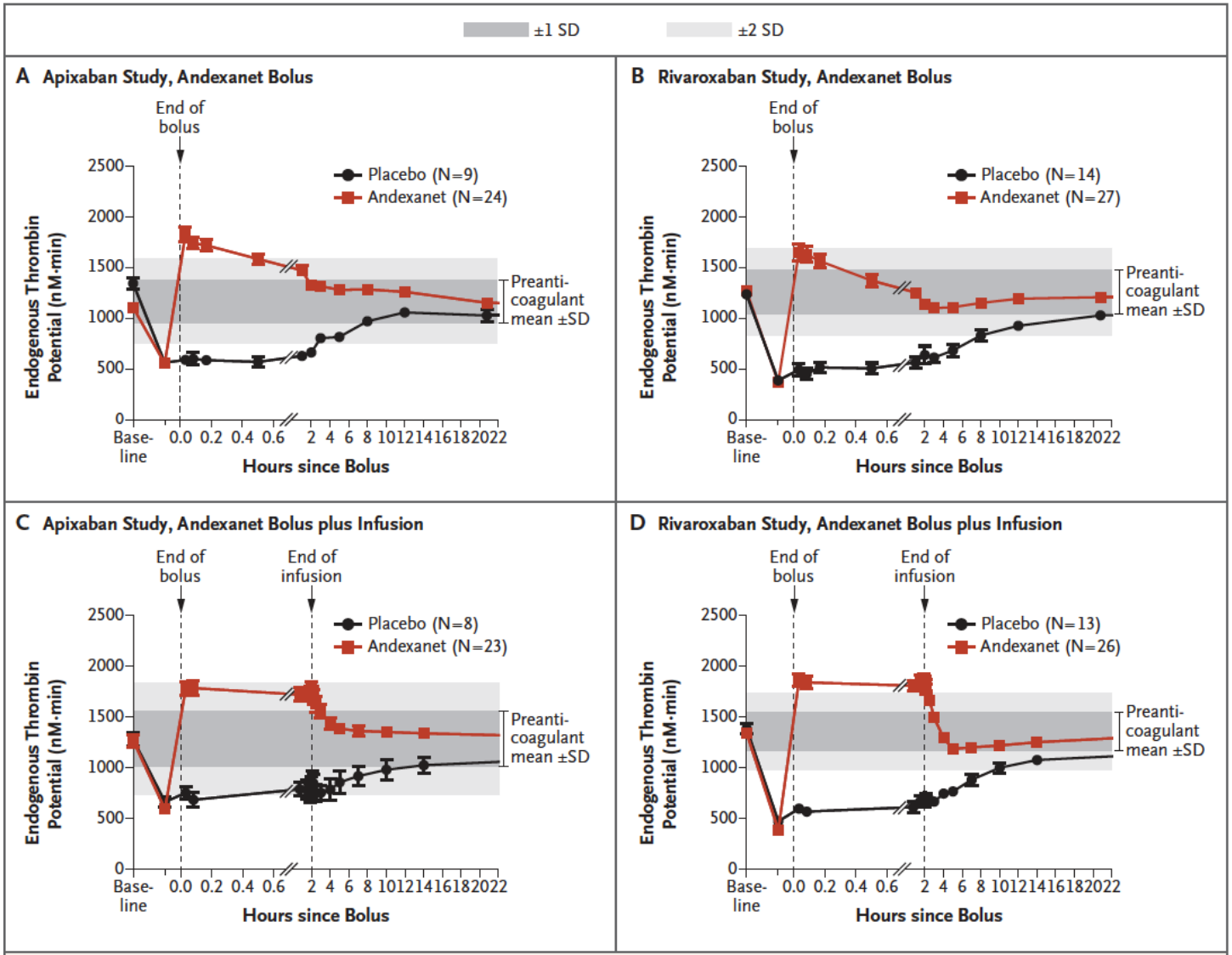


Figure 2. Time Courses of Thrombin Generation before and after the Administration of Andexanet.

In a subgroup of participants, transient increases in levels of D-dimer and prothrombin fragments 1 and 2 were observed, which resolved within 24 to 72 hours. No serious adverse or thrombotic events were reported.

Andexanet Has Demonstrated Deep and Rapid Reversal of Biomarkers of Anticoagulation for Four fXa Inhibitors to Date

- **Multiple Phase 2 Proof-of-Concept Studies**
  - ☑ Apixaban 5 mg PO Q12 – *completed; successful*
  - ☑ Rivaroxaban 20 mg PO QD - *completed; successful*
  - ☑ Enoxaparin 40 mg SQ QD – *completed; successful*
  - ☑ Edoxaban 60 mg PO QD – *ongoing; successful with the cohorts completed to date*
  - ☐ Betrixaban 80 mg PO QD – *planned for 2015*

- **Phase 3 and Confirmatory Registration-enabling Studies**
  - ☑ Phase 3 studies: older healthy subjects – *ongoing*
  - ☑ Phase 4 "Confirmatory study" with bleeding patients – *ongoing*

Enrolling bleeding patients with rivaroxaban, apixaban, edoxaban and enoxaparin

PORTOLA

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.**

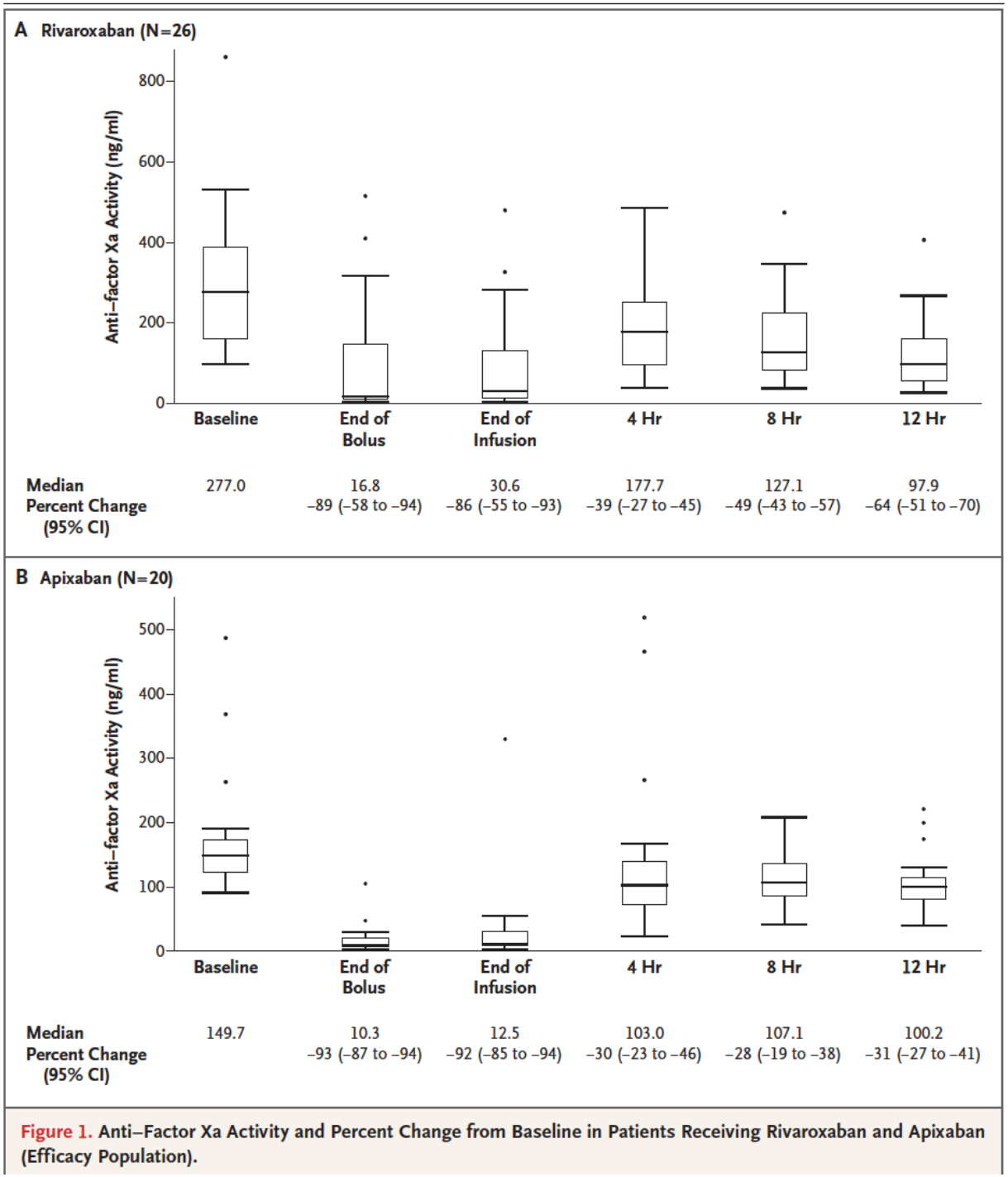


Figure 1. Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

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**.

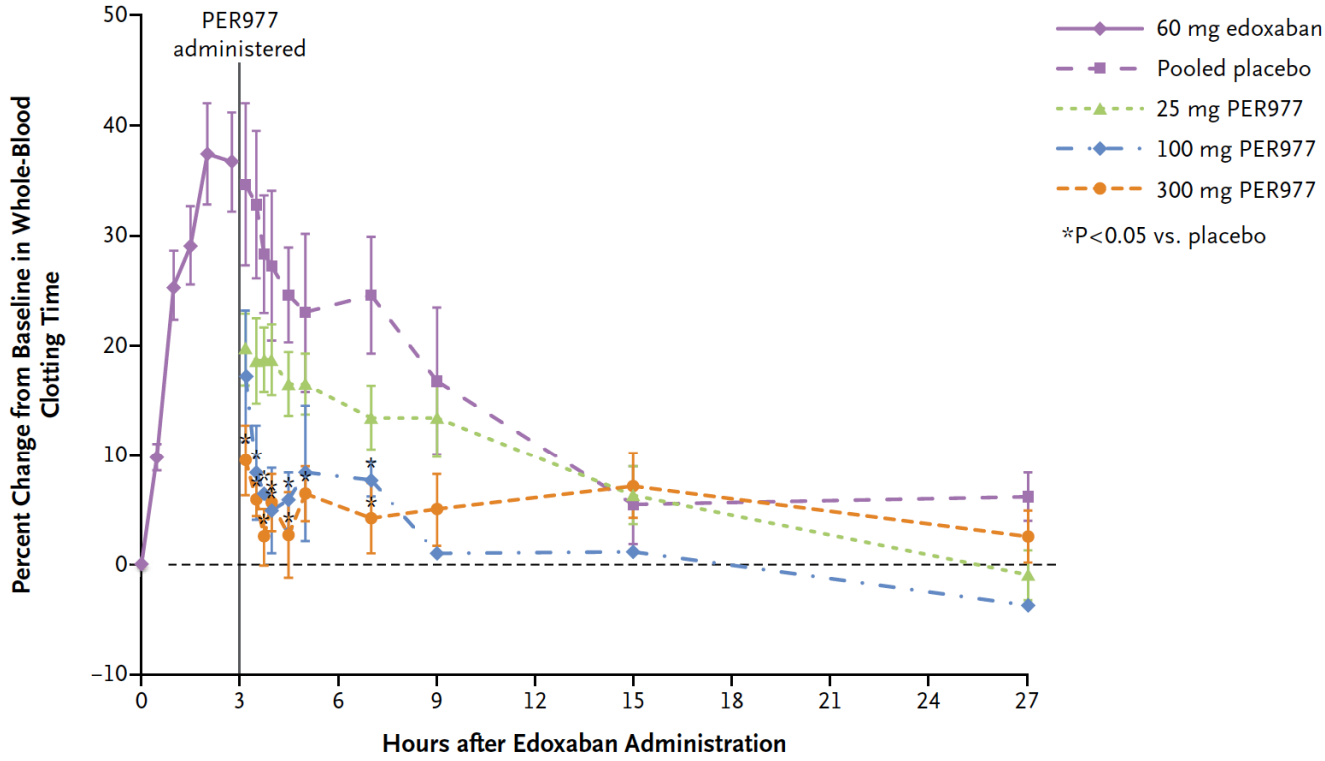


Figure 1. Effect of PER977 on Whole-Blood Clotting Time.
Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

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Victor Dishy, M.D.
Daiichi Sankyo Pharma Development
Edison, NJ
Robert J. Noveck, M.D.
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Edoxaban significantly reduced the mean fibrin-fiber diameted which was restored to normal 30 minutes after administration of PER977

Suggestions…

Hémorragie chez un patient traité par dabigatran (PRADAXA®)

Hémorragie menaçant le pronostic vital ou fonctionnel et ne pouvant être rapidement contrôlée par les mesures standards
(comme par exemple: Hémorragie dans un organe critique (HIC, intramédullaire, rétinienne) ou un choc hémorragique)

Idarucizumab ou si indisponible, CCP ou FEIBA

Hémorragie grave ne menaçant pas le pronostic vital ou fonctionnel

Geste hémostatique
chirurgie, endoscopie, embolisation, tamponnement....

Geste hémostatique non indiqué ou saignement persistant

et une des conditions suivantes

- DDP < 24h
- Cockcroft < 50 ml/mn
- Concentration > 50 ng/ml

Geste hémostatique efficace

ou

< 50 ng/ml

ou

DDP > 24 h et Cockcroft > 50 ml/mn

Mesures non spécifiques
(si doute discuter CCP)

Hémorragie non grave

Pas de réversion
Traitement symptomatique
Rechercher CI AOD, notamment:
Cockcroft< 30 ml/min
Interactions médicamenteuses
Discuter un saut de prise

Geste invasif urgent sous DABIGATRAN (PRADAXA®)

Risque hémorragique très élevé
(hémostase incontrôlable: ex: neurochir, hépatique)

et une des conditions suivantes

- Concentration > 30 ng/ml
- Concentration inconnue

Risque hémorragique élevé
(hémostase contrôlable: ex: péritonite, orthopédie)

et une des conditions suivantes

- DDP < 24h
- Cockcroft < 50 ml/mn
- Concentration > 50 ng/ml

Risque hémorragique faible

ou

Risque hémorragique élevé
(hémostase contrôlable: ex: péritonite, orthopédie)
et une des conditions suivantes
- DDP > 24 h et Cockcroft > 50 ml/mn
- Concentration < 50 ng/ml

ou

Risque hémorragique très élevé
(hémostase incontrôlable: ex: neurochir, hépatique)
et Concentration < 30 ng/ml

Risque très élevé		Risque élevé		Risque faible ou élevé ou très élevé
PEC < 8 heures ou geste d'hémostase	PEC > 8 heures	PEC < 8 heures	PEC > 8 heures	
	Reporter et Mesure de la concentration		Reporter et Si besoin, mesure de la concentration	
	ou		ou	
Idarucizumab ou si indisponible, CCP ou FEIBA puis Réaliser le geste		Réaliser le geste et si saignement per/postop attribuable à l'AOD: Idarucizumab ou si indisponible, CCP ou FEIBA		Réaliser le geste

Saignement imputable à l'AOD

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

Table 9 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: ≥48 h Maintain diuresis. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4 h).[122] Charcoal haemoperfusion can be considered (based on preclinical data)	Inquire last intake + dosing regimen. Normalisation of haemostasis: 12–24 h Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata). Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence) Idarucizumab 5 g IV (approval waiting)	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data) Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.

En pratique…

AOD: un vrai progrès, c'est indiscutable

…mais il est inacceptable de la part de Big Pharma :

- de systématiquement nier les complications attendues des AOD
- d'avoir volontairement « oublié » de développer le monitorage
- de proposer des antidotes **7 ans** après la première AMM et …de brûler à présent les étapes
- Irresponsabilité des agences (ANSM, EMA…) qui cèdent à la peur

En attendant :

- Facilitons la disponibilité du monitorage
- Utilisons les CCP dans l'attente du développement normal des antidotes
- **Cadre strict pour idarucizumab** (PV AP-HP) et bientôt pour l'Andexanet

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*

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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.