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Anticoagulants oraux directs (AOD)

Charles Marc SAMAMA

Pôle Anesthésie Réanimations Thorax Explorations

GIHP Groupe d'intérêt en hémostase péri-opératoire

UNIVERSITÉ PARIS DESCARTES

USPC Université Sorbonne Paris Cité

European Society of Anaesthesiology ESA

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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COCHIN BROCA HÔTEL-DIEU

Direct Oral Anticoagulants (DOACs) and bleeding

Charles Marc Samama

Professor and Chairman

Department of Anaesthesia and Intensive Care

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Paris, France

GIHP Groupe d'intérêt en hémostase péri-opératoire

UNIVERSITÉ PARIS DESCARTES

USPC Université Sorbonne Paris Cité

European Society of Anaesthesiology

ESA

Disclosures - Slides

Companies and products (DCI):

AstraZeneca (ximelagatran - ticagrelor) – Bayer (**rivaroxaban**) – BMS (**apixaban**)

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

Daïchi Sankyo (**edoxaban**) - GSK (fondaparinux – nadroparin)

LFB (**CCP** - fibrinogen) - Lilly+Daichii Sankyo (prasugrel) - Mitsubishi (argatroban) – Octapharma (**CCP**)

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

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

Stago (specific anti-Xa test)

Agencies, Societies and Guidelines:

ACCP : 8th and 9th Guidelines – SFAR : recos 2004 et 2011

EMA : efficacy working party (expert consultant)

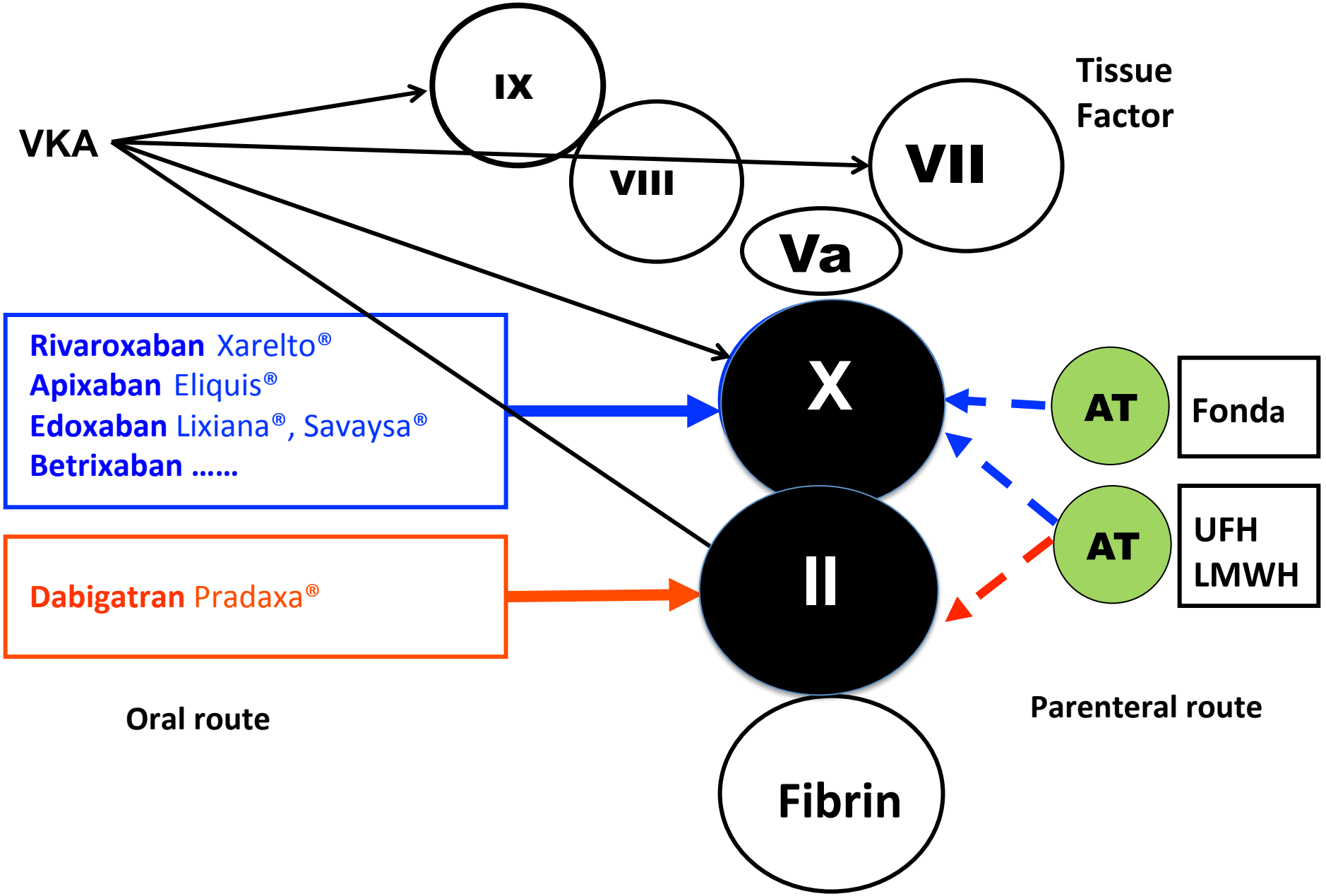
INSERM : laboratory of experimental thrombosis (UMR 1140)

Slides – aknowledgements :

Pierre Albaladejo (Grenoble), Anne Godier (Paris), Ismael El Alamy (Paris), Philippe de Moerloose (Genève), Patrick Mismetti (St Etienne), Gilles Pernod (Grenoble), Nadia Rosencher (Paris), Pierre Sié (Toulouse), and Michel Meyer Samama (Paris)

CAFE
FIGUE

New Oral Anticoagulants are Target-Specific



	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

Enoxaparin Versus Dabigatran or Rivaroxaban for Thromboprophylaxis After Hip or Knee Arthroplasty: Results of Separate Pooled Analyses of Phase III Multicenter Randomized Trials

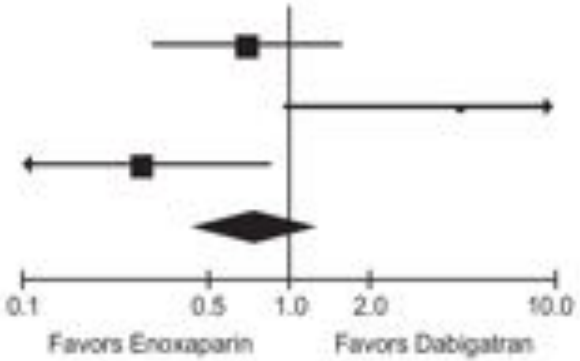
Menno V. Huisman, Daniel J. Quinlan, Ola E. Dahl and Sam Schulman

Circ Cardiovasc Qual Outcomes published online Oct 5, 2010;

A

Trial	n/N (%) Enoxaparin	n/N (%) Dabigatran	OR (95% CI)
RE-MOBILIZE	10/868 (1.2)	14/857 (1.6)	0.70 (0.31 - 1.59)
RE-MODEL	9/685 (1.3)	2/675 (0.3)	4·48 (0.96 - 20.81)
RE-NOVATE	4/1142 (0·4)	14/1137 (1.2)	0.28 (0.09 - 0.86)
Total	**23/2695 (0.9)**	**30/2669 (1.1)**	**0.76 (0.44 - 1.31)**

Test for heterogeneity: $I^2 = 76\%$, $P = .02$
Test for overall effect: $P = .32$



B

Trial	n/N (%) Enoxaparin	n/N (%) Dabigatran	OR (95% CI)
RE-MOBILIZE	33/868 (3.8)	28/857 (3.3)	1.17 (0.70 - 1.95)
RE-MODEL	46/694 (6.6)	50/679 (7.4)	0.89 (0.59 - 1.35)
RE-NOVATE	58/1154 (5.0)	71/1146 (6.2)	0.80 (0.56 - 1.14)
Total	**137/2716 (5.0)**	**149/2682 (5.6)**	**0.90 (0.71 - 1.15)**

Test for heterogeneity: $I^2 = 0\%$, $P = .49$
Test for overall effect: $P = .40$

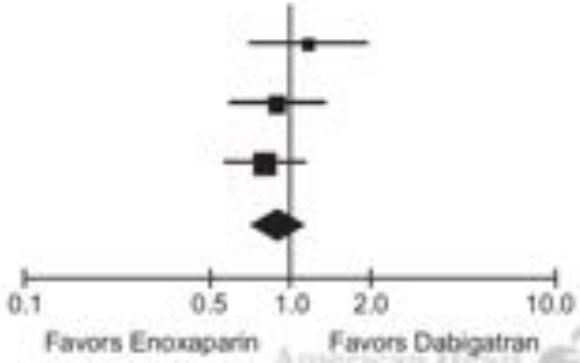


Figure 1. Enoxaparin versus dabigatran: A, Symptomatic VTE plus all-cause mortality; B, composite of major plus clinically relevant nonmajor bleeding. Vertical line indicates an OR of 1.0, equivalent to no difference between treatment groups. Size of the data markers

Enoxaparin Versus Dabigatran or Rivaroxaban for Thromboprophylaxis After Hip or Knee Arthroplasty: Results of Separate Pooled Analyses of Phase III Multicenter Randomized Trials

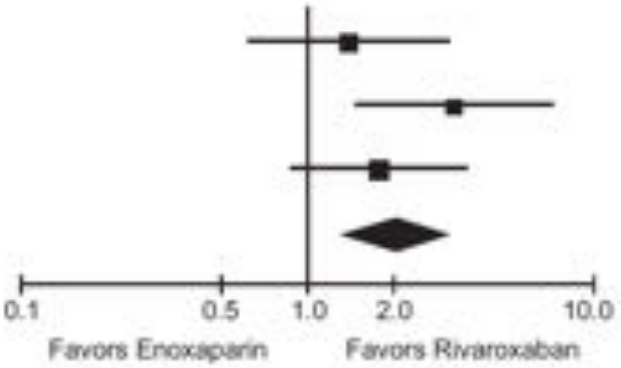
Menno V. Huisman, Daniel J. Quinlan, Ola E. Dahl and Sam Schulman

Circ Cardiovasc Qual Outcomes published online Oct 5, 2010;

A

Trial	n/N (%) Enoxaparin	n/N (%) Rivaroxaban	OR (95% CI)
RECORD1	14/2206 (0.6)	10/2193 (0.5)	1.39 (0.62 - 3.15)
RECORD3	26/1217 (2.1)	8/1201 (0.7)	3.26 (1.47 - 7.22)
RECORD4	21/1508 (1.4)	12/1526 (0.8)	1.78 (0.87 - 3.63)
Total	**61/4931 (1.2)**	**30/4920 (0.6)**	**2.04 (1.32 - 3.17)**

Test for heterogeneity: I^2 = 13%, P = .32
Test for overall effect: P = .001



B

Trial	n/N (%) Enoxaparin	n/N (%) Rivaroxaban	OR (95% CI)
RECORD1	56/2224 (2.5)	70/2209 (3.2)	0.79 (0.55 - 1.13)
RECORD3	34/1239 (2.7)	40/1220 (3.3)	0.83 (0.52 - 1.32)
RECORD4	34/1508 (2.3)	46/1526 (3.0)	0.74 (0.47 - 1.16)
Total	**124/4971 (2.5)**	**156/4955 (3.1)**	**0.79 (0.62 - 0.99)**

Test for heterogeneity: I^2 = 0%, P = .94
Test for overall effect: P = .049

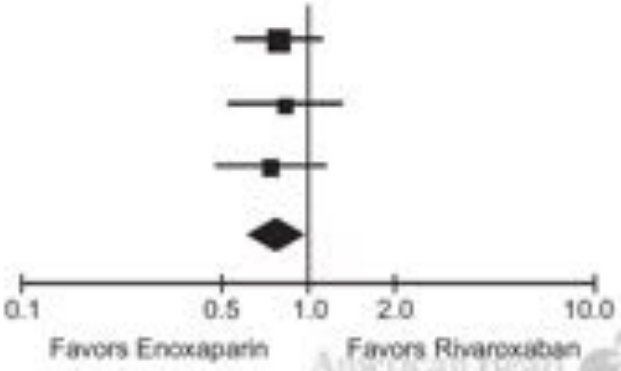


Figure 3. Enoxaparin versus rivaroxaban: A, Symptomatic VTE plus all-cause mortality; B, composite of major plus clinically relevant nonmajor bleeding.

Indirect Comparison
Network Meta-Analysis (Laporte S, in press)

Total Knee Replacement

- **Total VTE + death any cause**

  api vs riva: OR = **1.30** (0.71 – 2.40)

  api vs dabi 150: OR = **0.47** (0.28 – 0.81)

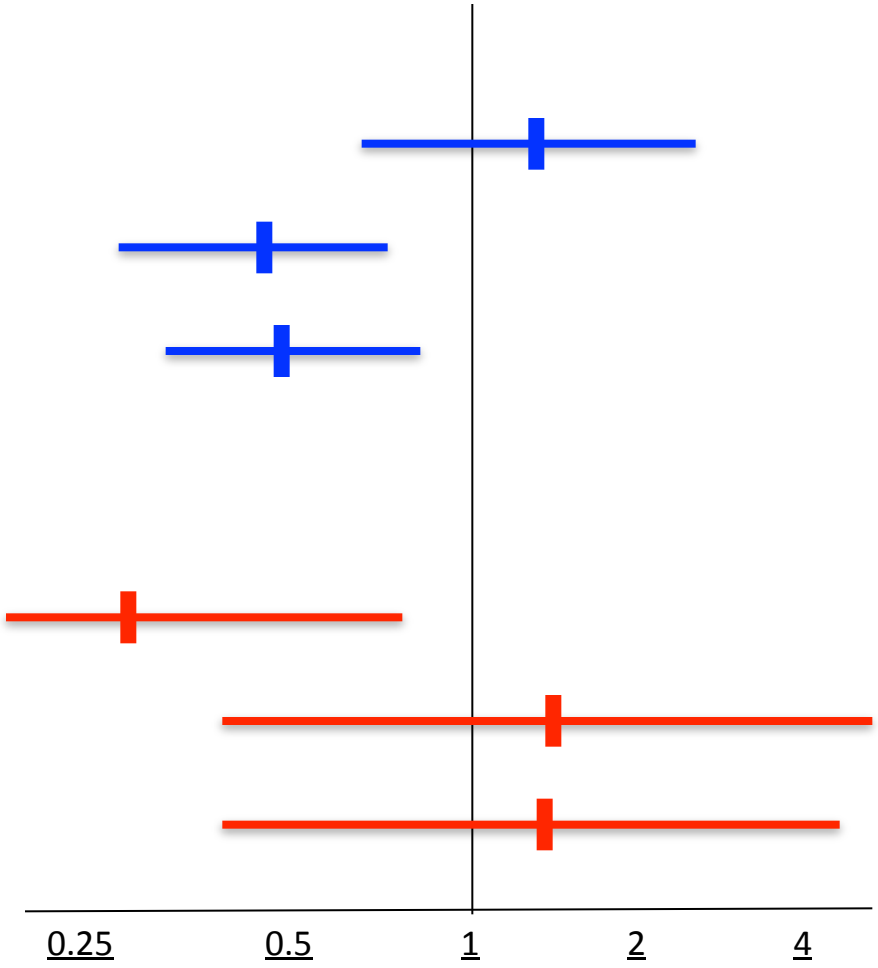
  api vs dabi 220: OR = **0.53** (0.31 – 0.92)

- **Major Bleeding**

  api vs riva: OR = **0.33** (0.13 – 0.86)

  api vs dabi 150: OR = **1.34** (0.40 – 4.47)

  api vs dabi 220: OR = **1.31** (0.41 – 4.19)



Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

N Engl J Med 2009;361:1139-51

RE-LY

18,113 patients who had atrial fibrillation and a risk of stroke received, in a blinded fashion, fixed doses of dabigatran— 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin.

Median duration of the follow-up period was **2.0 years**.

Primary outcome: stroke or systemic embolism:
1.69% per year in the warfarin group

1.53% per year 110 mg dabigatran b.i.d. (RR 0.91; P<0.001 for non inferiority).

1.11% per year 150 mg dabigatran b.i.d. (RR 0.66; P<0.001 for superiority).

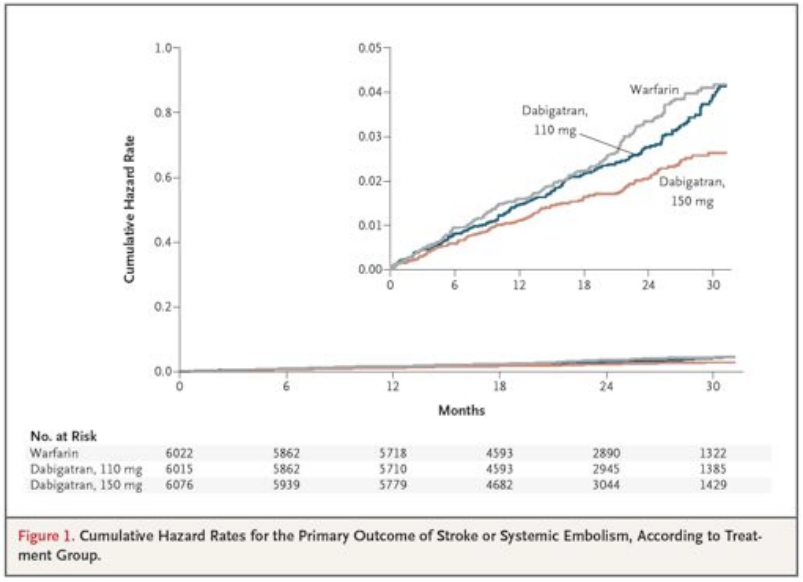


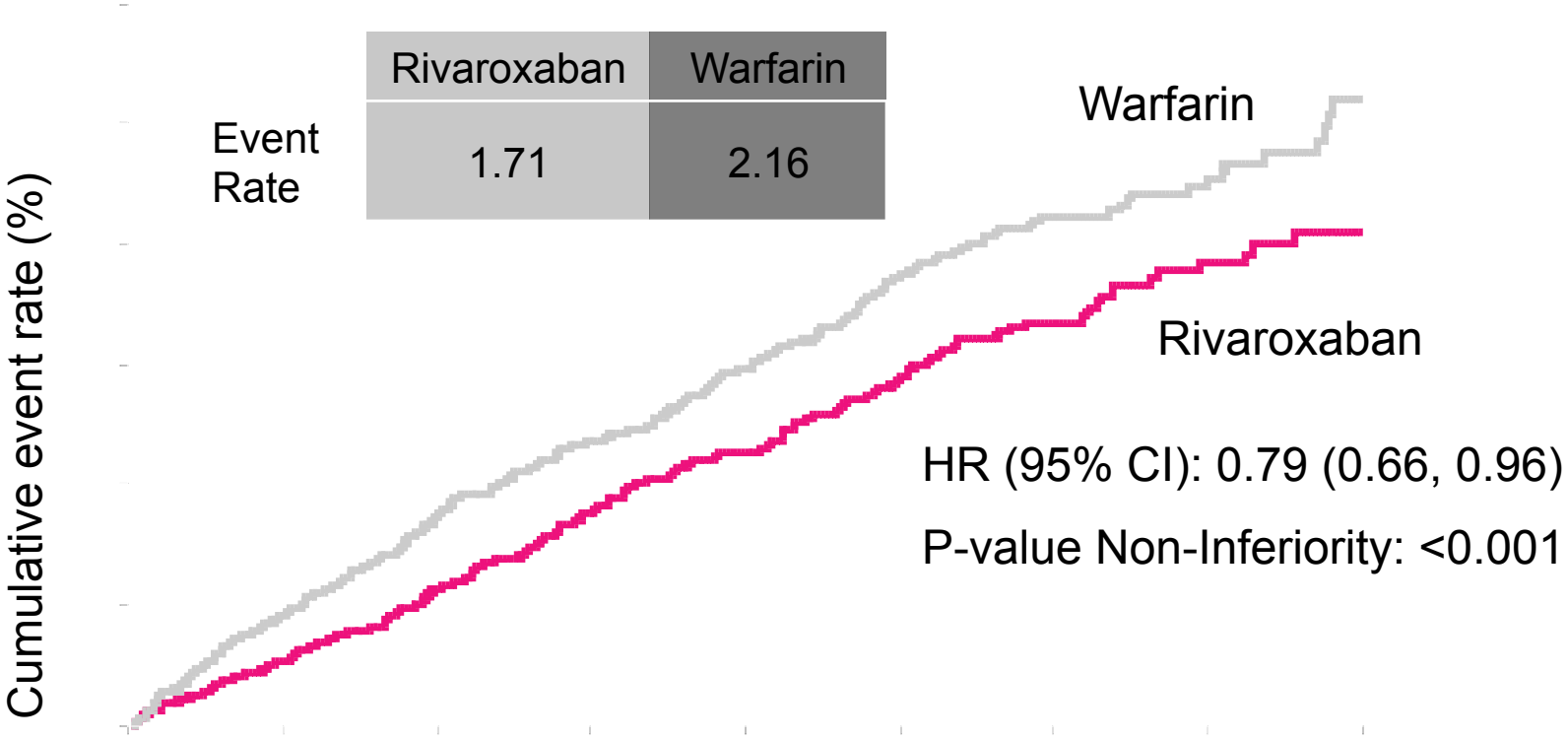
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Major bleeding: 3.36% per year (warfarin), 2.71% (110 mg dabigatran b.i.d. (P=0.003)) and 3.11% (150 mg of dabigatran b.i.d. (P=0.31)).

Hemorrhagic stroke: 0.38% per year warfarin) vs 0.12% (110 mg of dabigatran b.i.d. (P<0.001)) and 0.10% (150 mg dabigatran b.i.d. (P<0.001)).

ROCKET-AF
N Eng J Med 2011

Primary Efficacy Outcome
Stroke and non-CNS Embolism



Days from Randomization

No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Granger CB et al. **ARISTOTLE study**

N Engl J Med 2011.

Randomized, double-blind trial, apixaban (at a dose of 5 mg twice daily) vs warfarin (target INR, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke.

Primary outcome was1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio 0.79; P<0.001 for noninferiority; P = 0.01 for superiority).

Rates of death from any cause 3.52% and 3.94%, respectively (hazard ratio, 0.89; P = 0.047).

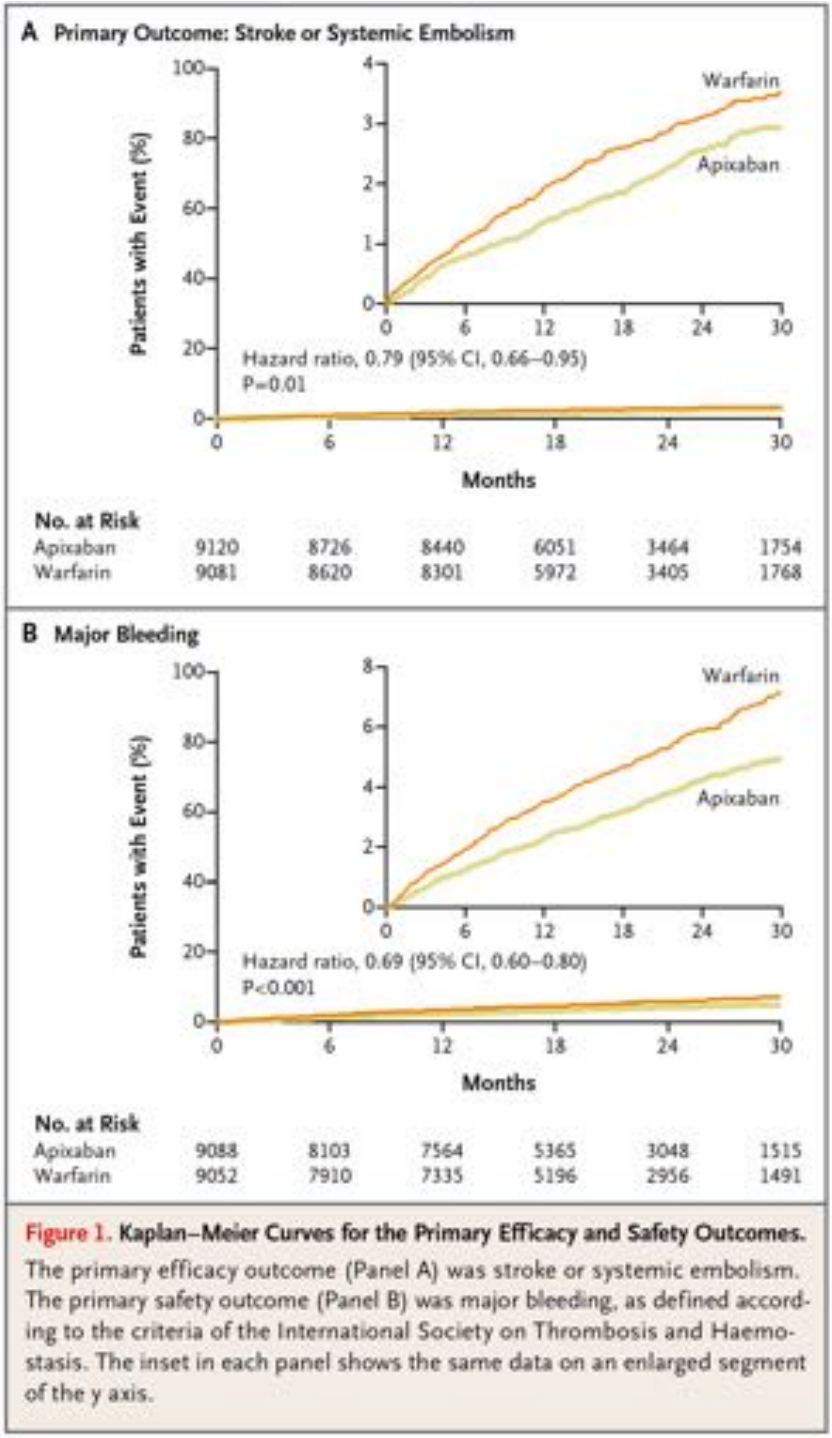
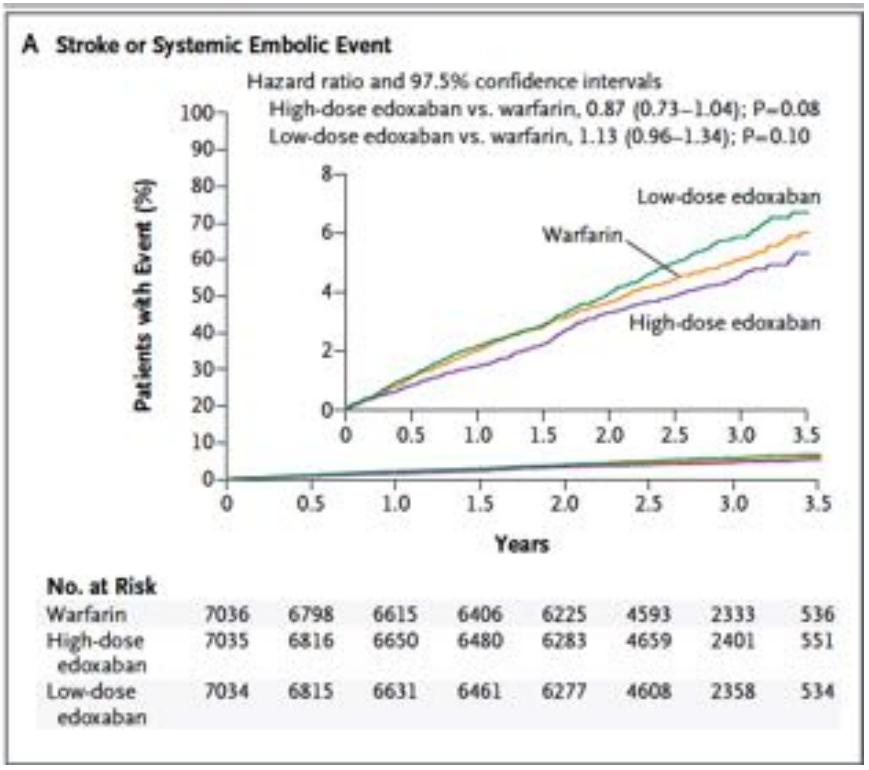


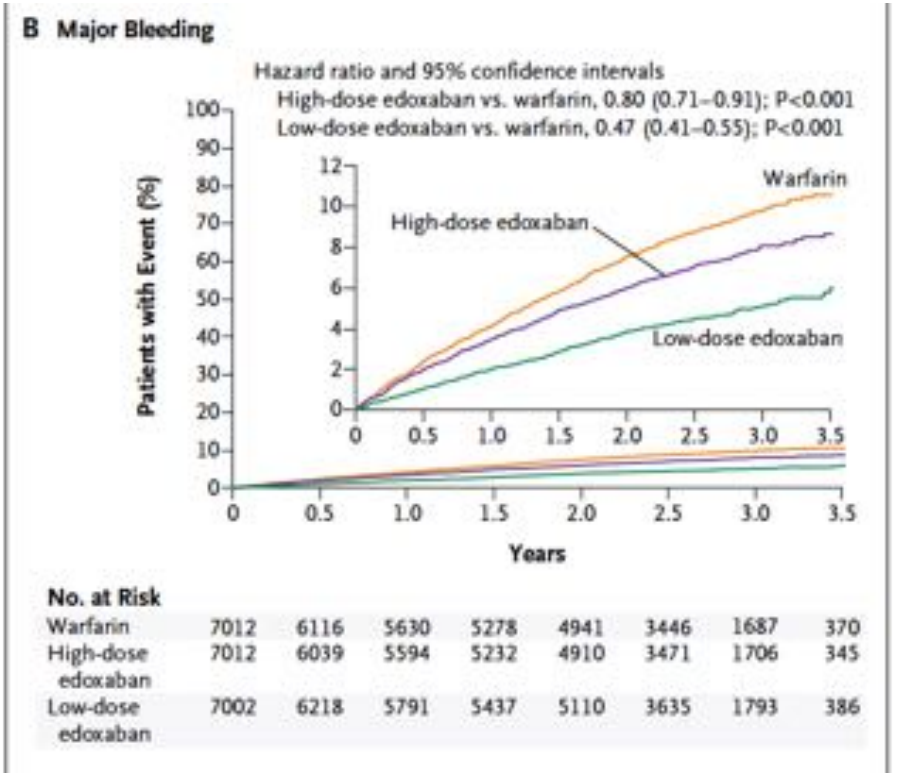
Figure 1. **Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.**
The primary efficacy outcome (Panel A) was stroke or systemic embolism. The primary safety outcome (Panel B) was major bleeding, as defined according to the criteria of the International Society on Thrombosis and Haemostasis. The inset in each panel shows the same data on an enlarged segment of the y axis.

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

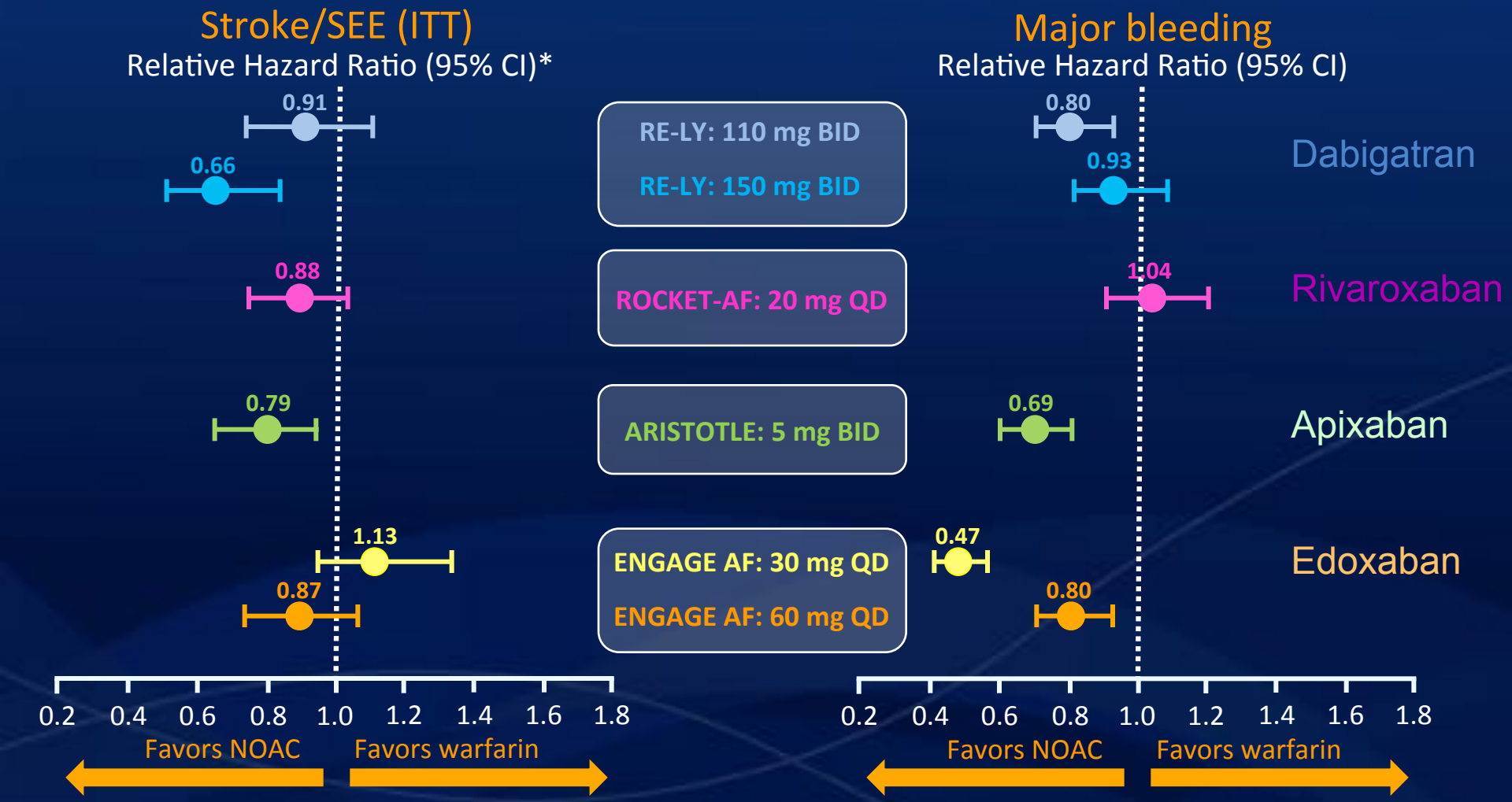
This article was published on November 19, 2013, at NEJM.org.





Randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban (60 and 30mg) with warfarin in 21,105 patients with moderate to-high-risk atrial fibrillation (median follow-up, 2.8 years).

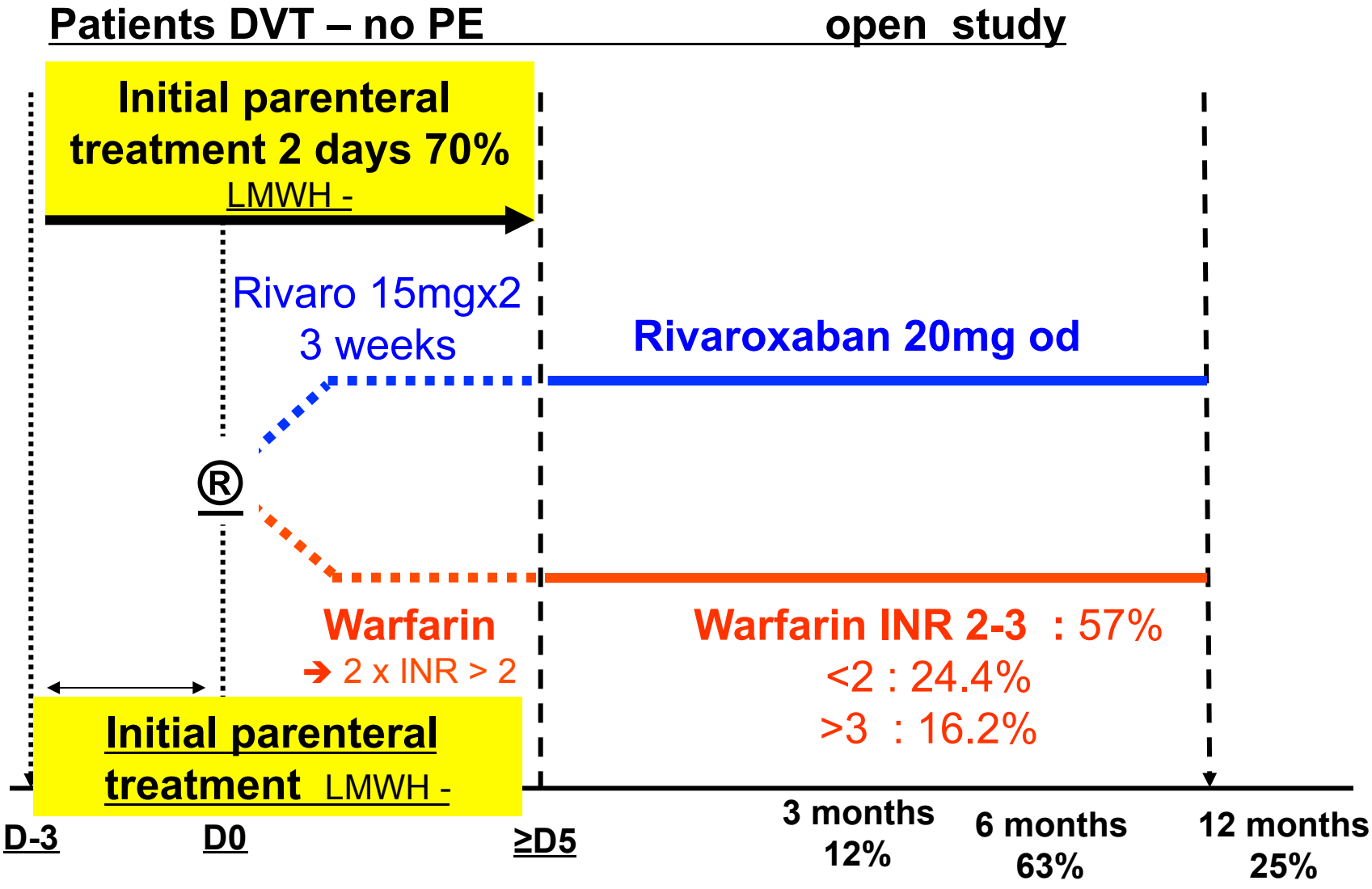
Atrial Fibrillation Trials: Summary Results



*97.5% CI for ENGAGE AF

1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Einstein DVT n= 3400 - Rivaroxaban



Harry Buller ESC 2010

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

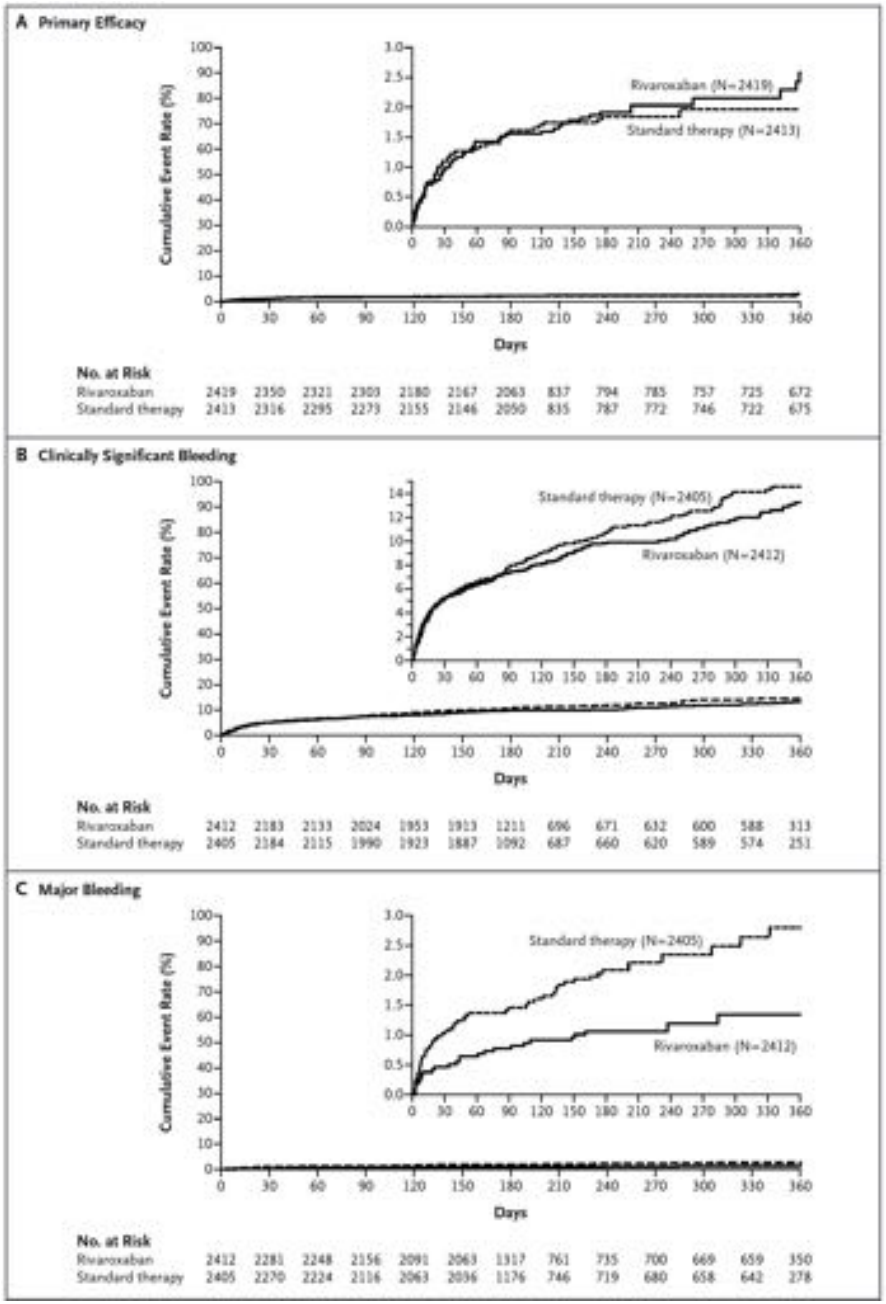
The EINSTEIN–PE Investigators*

N Engl J Med 2012;366:1287-97

Randomized, open-label, event-driven, noninferiority trial involving **4832 patients with acute symptomatic pulmonary embolism with or without deep-vein thrombosis**,

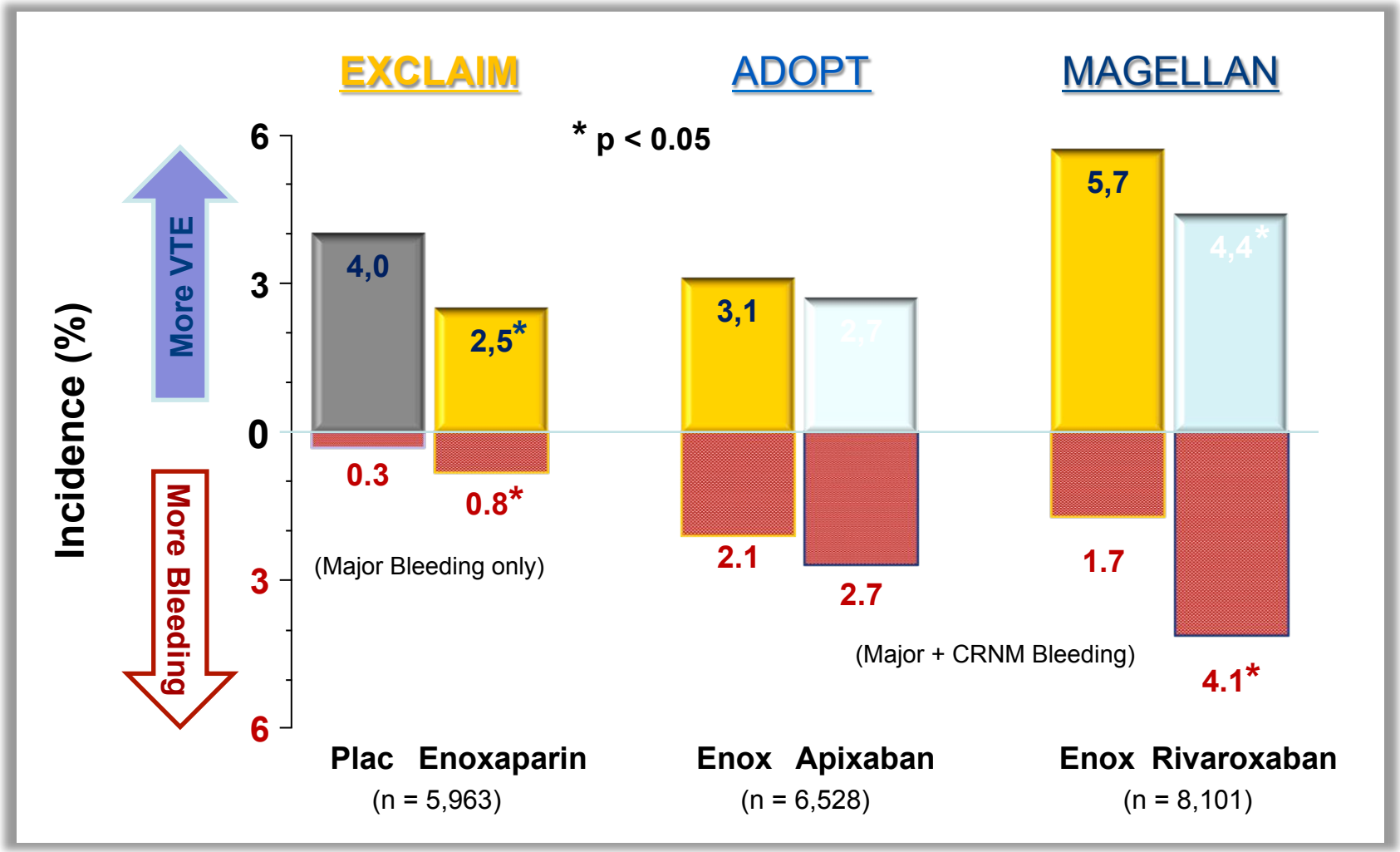
Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) compared with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months.

Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard - therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; P = 0.003).



Extended VTE Prophylaxis In Medical Patients

No Net Clinical Benefit for Factor Xa Inhibitors



Ann Intern Med 2010;153:8-18
NEJM 2013;368:513-23
N Engl J Med 2011; 365: 2167-2177

CRNM, Clinically Relevant Non-Major Bleeding

Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients

Alexander T. Cohen, M.D., Theodore E. Spiro, M.D., Harry R. Büller, M.D., Lloyd Haskell, M.D., Dayi Hu, M.D., Russell Hull, M.B., B.S., Alexandre Mebazaa, M.D., Geno Merli, M.D., Sebastian Schellong, M.D., Alex C. Spyropoulos, M.D., and Victor Tapson, M.D., for the MAGELLAN Investigators*

N Engl J Med 2013;368:513-23.

8101 patients - acute medical illness - ultrasound
SC enoxaparin, 40 mg QD, for 10±4 days and oral placebo for 35±4 days
or SC placebo for 10±4 days and oral rivaroxaban, 10 mg QD, for 35±4 days

Table 2. Rates of the Composite Primary Efficacy Outcome and Its Components.

Outcome	Day 10				Day 35			
	Rivaroxaban (N=2938)	Enoxaparin (N=2993)	Relative Risk (95% CI)*	P Value†	Rivaroxaban (N=2967)	Enoxaparin–Placebo (N=3057)	Relative Risk (95% CI)*	P Value†
	no. (%)				no. (%)			
Composite primary efficacy outcome	78 (2.7)	82 (2.7)	0.97 (0.71–1.31)	0.003	131 (4.4)	175 (5.7)	0.77 (0.62–0.96)	0.02
Asymptomatic proximal DVT	71 (2.4)	71 (2.4)	—	—	103 (3.5)	133 (4.4)	—	—
Symptomatic proximal or distal DVT	7 (0.2)	6 (0.2)	—	—	13 (0.4)	15 (0.5)	—	—
Symptomatic nonfatal pulmonary embolism	6 (0.2)	2 (<0.1)	—	—	10 (0.3)	14 (0.5)	—	—
VTE-related death	3 (0.1)	6 (0.2)	—	—	19 (0.6)	30 (1.0)	—	—

Principal **safety** outcome events: 111 of 3997 patients (2.8%) in the rivaroxaban group and 49 of 4001 patients (1.2%) in the enoxaparin group at **day 10** (P<0.001) and in 164 patients (4.1%) and 67 patients (1.7%) in the respective groups at **day 35** (P<0.001).

	VTE Prophylaxis	VTE Treatment	Atrial Fibrillation	ACS
Apixaban	Orthopaedic surgery **ADVANCE-1** **ADVANCE-2** **ADVANCE-3** Medical patients **ADOPT** Long term secondary prophylaxis **AMPLIFY-Ext**	**AMPLIFY**	**AVERROES** **ARISTOTLE**	(APPRAISE) **APPRAISE-2**
Da	Long term secondary prophylaxis RE-MEDY RE-SONATE			
Rivaroxaban	Orthopaedic surgery **RECORD I** **RECORD II** **RECORD III** **RECORD IV** Medical patients **MAGELLAN** Long term secondary prophylaxis **EINSTEIN-Ext**	**EINSTEIN-DVT** **EINSTEIN-PE**	**ROCKET-AF**	**ATLAS-TIMI 46** **ATLAS-TIMI 51**

Un progrès indiscutable…

Green : positive study
Red : negative study

	VTE Prophylaxis	VTE Treatment	Atrial Fibrillation	ACS
Apixaban	Orthopaedic surgery **ADVANCE-1** **ADVANCE-2** **ADVANCE-3** Medical patients **ADOPT** Long term secondary prophylaxis AMPLIFY-Ext NCT00633893	AMPLIFY NCT00643201	**AVERROES** **ARISTOTLE**	(APPRAISE) **APPRAISE-2**
D	Long term secondary prophylaxis RE-MEDY RE-SONATE			
Rivaroxaban	Orthopaedic surgery **RECORD I** **RECORD II** **RECORD III** **RECORD IV** Medical patients **MAGELLAN** Long term secondary prophylaxis **EINSTEIN-Ext**	**EINSTEIN-DVT** **EINSTEIN-PE**	**ROCKET-AF**	**ATLAS-TIMI 46** **ATLAS-TIMI 51**

A major step forward…

Green : positive study
Red : negative study

ESC AF Guidelines 2012: Recommendations for Anticoagulation in Patients with Nonvalvular AF

Recommendation	Class	Level
In patients with CHA_2DS_2-VASc score ≥ 2, OAC therapy with: • A dose-adjusted VKA (INR 2-3); or • A direct thrombin inhibitor (dabigatran); or • An oral factor Xa inhibitor (eg, rivaroxaban, apixaban*) ... is recommended unless contraindicated	I	A
In patients with CHA_2DS_2-VASc score of 1, OAC therapy with: • A dose-adjusted VKA (INR 2-3); or • A direct thrombin inhibitor (dabigatran); or • An oral factor Xa inhibitor (eg, rivaroxaban, apixaban*) ... should be considered, based upon an assessment of the risk for bleeding complications and patient preferences	IIa	A

*Pending approval

ESC = European Society of Cardiology; INR = international normalized ratio; OAC = oral anticoagulation

Adapted from Camm AJ, et al. *Eur Heart J*. 2012;33(21):2719-2747.

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]

« European guidelines have expressed a preference for NOACs over VKA in stroke prevention for AF patients, based on their over-all clinical benefit. »

Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

BID, twice a day; OD, once daily.

[a]See further tables and text for discussion on dose reduction considerations.

[b]110 mg BID not approved by FDA. 75 mg BID approved in USA only, if CrCl 15–30 mL/min or if CrCl 30–49 mL/min and other 'orange' factor as in *Table 6* (e.g. verapamil).

[c]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin

Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

Jeff S. Healey, MD, MSc; John Eikelboom, MD; James Douketis, MD; Lars Wallentin, MD, PhD; Jonas Oldgren, MD, PhD; Sean Yang, MSc; Ellison Themeles, BA; Hein Heidbuchel, MD; Alvaro Avezum, MD; Paul Reilly, PhD; Stuart J. Connolly, MD; Salim Yusuf, MD, DPhil; Michael Ezekowitz, MB, ChB, DPhil; on behalf of the RE-LY Investigators

Circulation. 2012;126:343-348

Mean follow-up of **2 years**, 4591 patients in the **RE-LY trial** had oral anticoagulant therapy interrupted at least once to have surgery or another

D'ores et déjà 30 000 à 45 000 patients par an en France

and 23.9% on warfarin. Mean age 72 y.o.

Most common surgeries and procedures:

pacemaker or defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%) and joint replacement (6.2%), with other types of surgery each accounting for a smaller proportion of cases

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Circulation. 2012;126:343-348

Mean follow-up of **2 years**, 4591 patients in the **RE-LY trial** had oral anticoagulant therapy interrupted at least once to have surgery or another invasive procedure.

Already 200 000 patients/year in the US

and 23.9% on warfarin. Mean age 72 y.o.

Most common surgeries and procedures:

pacemaker or defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%) and joint replacement (6.2%), with other types of surgery each accounting for a smaller proportion of cases

Outcomes of Temporary Interruption of Rivaroxaban Compared with Warfarin in Patients with Nonvalvular Atrial Fibrillation: Results from ROCKET AF

Matthew W. Sherwood, MD[1]; James D. Douketis, MD[2]; Manesh R. Patel, MD[1]; Jonathan P. Piccini, MD, MHS[1]; Anne S. Hellkamp, MS[1]; Yuliya Lokhnygina, PhD[1]; Alex C. Spyropoulos, MD[3]; Graeme J. Hankey, MD[4]; Daniel E. Singer, MD[5]; Christopher C. Nessel, MD[6]; Kenneth W. Mahaffey, MD[7]; Keith A. A. Fox, MB, ChB[8]; Robert M. Califf, MD[1]; Richard C. Becker, MD[1]
on behalf of the ROCKET AF Investigators

Management, and outcomes, including stroke, non-CNS systemic embolism, death, MI, and bleeding were reported in participants who experienced temporary interruptions (TI 3-30 days) for any reason.

14,236 participants who received at least one dose of study drug, 4692(**33%**) TI.
Median duration of TI was **5 (4,9) days**

D'ores et déjà 20 000 à 25 000 patients par an en France

40% experienced TI for a surgical or invasive procedure, while 25% of participants had TI for an adverse event unrelated to bleeding and 13% had TI due to an adverse bleeding event.
The remaining (12%) were attributed to subject error (majority), site error, and logistic difficulties.

DOI: 10.1161/CIRCULATIONAHA.113.005754

Issues with Direct Oral Anticoagulants (DOACs)?

- Scheduled surgery and invasive procedures
- Trauma and emergent surgery
- Bridging with a parenteral anticoagulant agent (ex: unavailability of oral route)
- **Ongoing bleeding**
- **Stroke with a proposed thrombolysis**
- Suicides…

Life-threatening bleeding in four patients with an unusual excessive response to dabigatran: Implications for emergency surgery and resuscitation

Agnès Lillo-Le Louët[1]; Martine Wolf[2]; Lilia Soufir[3]; Arnaud Galbois[4,5,6]; Anne-Sylvie Dumenil[2]; Georges Offenstadt[4,5,7]; Meyer-Michel Samama[8, 9]

Thromb Haemost 2012; 108: 583–585

Mrs X

- 72 y.o.
- Hypertension
- Creatinine clearance: 50 ml/min
- **Total hip replacement**
- **Dabigatran 220 mg**

Mrs X

At day 3 :

- Dyspnea
- Hypotension
- Tachycardia
- Oliguria
- Anemia (8 g/dL)

Mrs X

Day 3:

- 2 units of packed red blood cells (RBC)
- Pulmonary embolism (PE) was suspected. Therefore, dabigat- ran was replaced by enoxaparin (0.7 mg/ kg twice daily).

Day 4:

- One day later, an angio- scanner excluded PE, and enoxaparin was stopped.
- Hypovolemic shock and severe acute renal failure (creatinine clearance 14 ml/min), and a peritonitis was diagnosed. **Laparotomy was performed showing ischaemic lesions requiring bowel resection.**

Coagulation tests [units] (normal values)	Hours after Dabigatran withdrawal						
Case 1	**26 h**	**28 h**	**32 h**	**34 h**	**36 h**	**38 h**	**-**
Prothrombin time (12.6–14.6 sec)	> 60	> 60	31	58	20.9	24.3	N.A
aPTT ratio (0.9–1.2)	>4.5	>4.5	>4.5	>4.5	>4.5	>4.5	N.A
Fibrinogen [g/l] (2–4 g/L)	6.4	4.9	4.2	2.4	2.1	2.3	N.A
Platelets [G/l] (150–400)	124	92	80	105	36	11	N.A
Haemoglobin [g/dl] (12.0–16.0)	9.3	6.9	8	9.3	4.3	8.7	N.A
Dabigatran plasma concentration [µg/ml] (Ctrough 0.05 –0.15)	N.A.	N.A.	420–480	N.A.	N.A.	340–420	N.A

The patient received 22 units RBC, 26 units fresh frozen plasma (FFP), 40 units/kg of Kaskadil®, a prothrombin complex concentrate (PCC), 66 µg/kg of recombinant FVIIa (Novoseven®), 1.5 g of fibrinogen concentrate (Clottagen®) and tranexamic acid. Despite these treatments, PT and aPTT remained unmeasurable, haemoglobin fell to 4g/l and the patient died 2 hours (h) after the end of surgery.

The Use of Dabigatran in Elderly Patients

Matthieu Legrand, MD; Joaquim Mateo, MD; Alice Aribaud; Sixtine Ginisty, MD; Pirayeh Eftekhari, MD; Patrice Tran Ba Huy, MD, PhD; Ludovic Drouet, MD, PhD; Didier Payen, MD, PhD

Recent approval by the US Food and Drug Administration (FDA) of dabigatran etexilate, an oral direct thrombin inhibitor, for the prevention of stroke in patients with atrial fibrillation will likely extend its administration in elderly patients. The risk of major overdosage of dabigatran etexilate in this population is, however, much increased owing to frequent renal function impairment, low body weight, drug interactions that cannot be detected with a routine coagulation test, and no antagonist available. We report herein 2 clinical cases, including 1 fatal case, illustrating our concern regarding the risk of bleeding events in elderly patients.

Arch Intern Med. 2011;171(14):1285-1288

Dabigatran bleed risk with closed head injuries: are we prepared?

Clinical article

MICHAEL W. PARRA, M.D.,[1,2] LLOYD ZUCKER, M.D.,[1] ERIC S. JOHNSON, D.O.,[1,2]
DIANE GULLETT, R.N., B.S.N., M.P.H.,[1] CRISTINA AVILA, B.S.,[1,2]
ZACHARY A. WICHNER, D.O., M.P.H.,[1,2] AND CANDACE R. KOKARAM, M.S.N.[1]

[1]Delray Medical Center/Provisional Level I Trauma Center, Delray Beach; and [2]Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale–Davie, Florida

Fatal Association of Mechanical Valve Thrombosis With Dabigatran

A Report of Two Cases

Shaul Atar, MD; Alice Wishniak, MD; Alexander Shturman, MD; Sewaed Shtiwi, MD; and Marc Brezins, MD

Hemopericardium and Cardiac Tamponade Associated with Dabigatran Use

Eliza A Dy and Dane L Shiltz

Hemodialysis for the Treatment of Pulmonary Hemorrhage From Dabigatran Overdose

Betty C. Chen, MD,[1] Nijal R. Sheth, MD,[2] Kobena A. Dadzie, MD,[2] Silas W. Smith, MD,[1] Lewis S. Nelson, MD,[1] Robert S. Hoffman, MD,[1] and James F. Winchester, MD[2]

Wound Complications Following Rivaroxaban Administration

A Multicenter Comparison with Low-Molecular-Weight Heparins for Thromboprophylaxis in Lower Limb Arthroplasty

Simon S. Jameson, MRCS, Monika Rymaszewska, MRCS, Philip James, Ignacio Serrano-Pedraza, PhD, Scott D. Muller, MD, FRCS(Tr&Orth), Anthony C.W. Hui, MA, FRCSEd(Orth), and Mike R. Reed, MD, FRCS(Tr&Orth)

Management of Apixaban-Associated Subdural Hematoma: A Case Report on the Use of Factor Eight Inhibitor Bypassing Activity

Derrick R. Rinehart, PharmD[1]; Nicholas R. Lockhart, PharmD[1]; Leslie A. Hamilton, PharmD, BCPS[1]; J. Russell Langdon, MD[2]; A. Shaun Rowe, PharmD, BCPS[1]

Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants

Jan C. Purrucker, MD; Kirsten Haas, MPH, PhD; Timolaos Rizos, MD; Shujah Khan; Marcel Wolf, MD; Michael G. Hennerici, MD; Sven Poli, MD, MSc; Christoph Kleinschnitz, MD; Thorsten Steiner, MD, MME; Peter U. Heuschmann, MD, MPH; Roland Veltkamp, MD

JAMA Neurol. 2016;73(2):169-177. doi:10.1001/jamaneurol.2015.3682
Published online December 14, 2015.

38 stroke units across Germany (February 1, 2012, to December 31, 2014). The study included 61 consecutive patients with nontraumatic NOAC-associated ICH,

Mortality: 28% at 3 months, and 65% of survivors had an unfavorable outcome.

57% of the patients received prothrombin complex concentrate, with no statistically significant effect on the frequency of substantial hematoma expansion or on the occurrence of an unfavorable outcome

CONCLUSIONS AND RELEVANCE Non–vitamin K antagonist oral anticoagulant–associated ICH has a high mortality and an unfavorable outcome, and hematoma expansion is frequent.

Safety Alerts

21.3.2012

Bleeding Reports Prompt Pradaxa Label Changes in Canada

Health Canada
www.hc-sc.gc.ca

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Warnings and Alerting
Severe haemorrhages
in patients treated with Prazaxa

12.08.2011

FDA

7.12.2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/11/2011
European Medicines Agency updates on safety of Pradaxa

(Pradaxa®): Recommendation to use with caution in the elderly and renally impaired patients

Pharmac attacked for rushing drug

Australian Government
Department of Health and Ageing

03.11.2011
Alerts

Dabigatran (Pradaxa): risk of bleeding relating to use

Nov.2011
Reuters

Boehringer says about 260 deaths related to Pradaxa

An Observational Study of the Factor Xa Inhibitors Rivaroxaban and Apixaban as Reported to Eight Poison Centers

Henry A. Spiller, MS, DABAT*; James B. Mowry, PharmD, DABAT; Alfred Aleguas Jr, PharmD, DABAT; Jill R. K. Griffith, PharmD; Robert Goetz, PharmD, DABAT; Mark L. Ryan, PharmD; Stacey Bangh, PharmD, DABAT; Wendy Klein-Schwartz, PharmD, MPH; Scott Schaeffer, PharmD, DABAT; Marcel J. Casavant, MD

Conclusion: Bleeding after Xa inhibitor ingestion as a single agent is uncommon. Prothrombin time, partial thromboplastin time, or international normalized ratio may be elevated in a minority of cases but appears unreliable to measure risk of bleeding. Massive acute ingestion in suicide attempt may result in significant anticoagulation. Single exploratory ingestion by children was not associated with toxicity. [Ann Emerg Med. 2015;■:1-7.]

Massive human rivaroxaban overdose

Thomas Lehmann[1]; Katharina E. Hofer[2]; Michael Baumann[1]; Karin Hasler[3]; Alessandro Ceschi[2]; Hugo Kupferschmidt[2]; Gabriele Rohde[4]; Wolfgang Korte[1]

[1]Center of Laboratory Medicine and Hemostasis and Hemophilia Center St. Gallen, St. Gallen, Switzerland; [2]Swiss Toxicological Information Centre, Associated Institute of the Zurich University, Zurich, Switzerland; [3]Department of Emergency, Kantonsspital St. Gallen, Switzerland; [4]Bioanalytik, Bayer Pharma AG, Leverkusen, Germany

http://dx.doi.org/10.1160/TH14-02-0138
Thromb Haemost 2014; 112: 834–836

A 63-year-old Caucasian male with a history of coronary and hypertensive heart disease, chronic atrial fibrillation, idiopathic thrombocytopenia, and chronic vertigo with subsequent falls was brought to the emergency department 2.5 h after ingestion of 1960 mg Rivaroxaban (98 tablets of 20 mg.), 90 mg diazepam, 1 g quetiapine, and 50 mg zolpidem, with a suicidal intent.

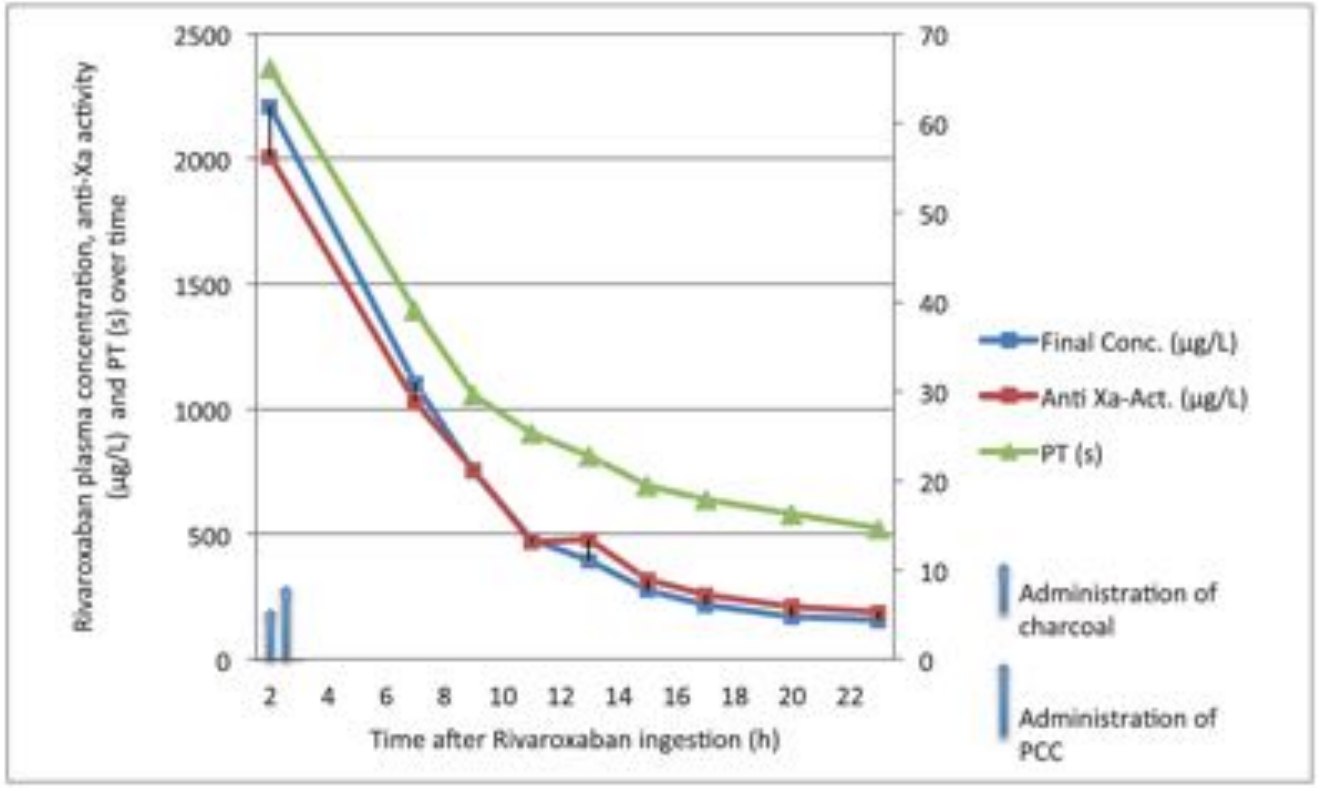


Figure 1: Course of rivaroxaban plasma concentration. Rivaroxaban plasma concentration measured by anti-FXa assay (red), by HPLC-MS/MS (blue) and prothrombin time (green) over 24 h after ingestion of an oral overdose. s = second, L = liter, h = hour.

UNIVERSITE JOSEPH FOURIER
GRENOBLE 1
SCIENCES. TECHNOLOGIE. MEDECINE

1160 patients included by the end of February 2016

CHU GRENOBLE

Reversal of direct oral anticoagulants in clinical practice: results from the French registry *GIHP-NACO*

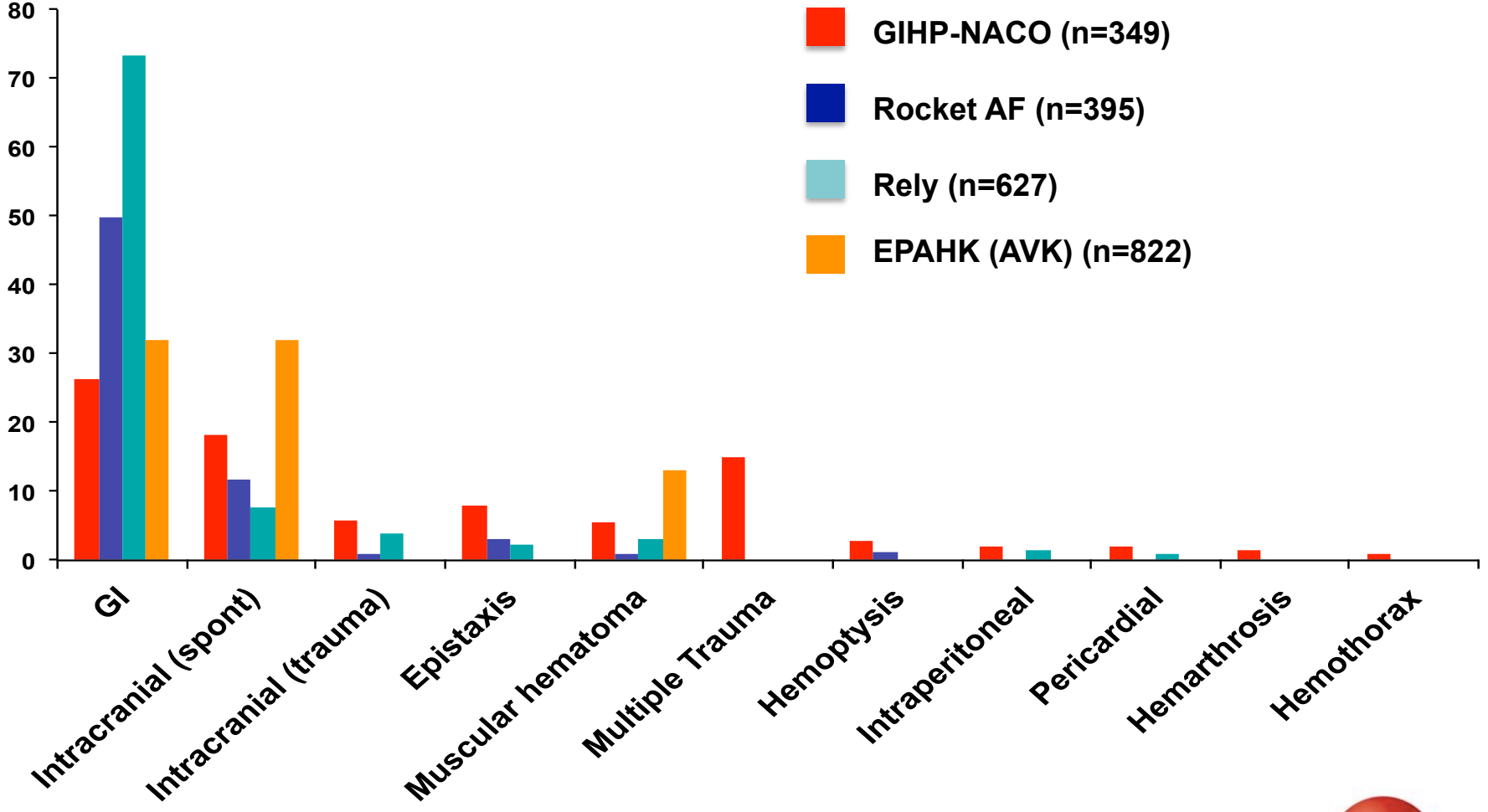
GIHP Groupe d'intérêt en hémostase péri-opératoire

Pierre Albaladejo, Pierre Sié, Charles Marc Samama, Gilles Pernod, Jean Luc Bosson

Major bleeding (ISTH)= 74.2%

GIHP-NACO Observatory

41 centres (included 1-60 patients) 349 Patients admitted and hospitalised for **major bleeding while on DOACs**



GIHP Groupe d'intérêt en hémostase péri-opératoire

(unpublished data, March 2015. GIHP working group)

Bleeding events reported to the FDA

Bleeding event	Warfarin	Dabigatran
Total bleeds (n)	590	2453
GI bleeds, n (%)	162 (27%)	1352 (55%)
Intracranial bleed, n (%)	69 (12%)	280 (11%)
Bleed fatalities, n (%)	47 (8%)	393 (16%)

McConeghy: the mean age of patients who had an adverse event with dabigatran reported to the FDA (75) was higher than those in the RE-LY trial (71), and more patients who had FDA reported events were female (48%) than included in RELY (36.7%).

"This suggests the drug is being used in a different profile of patients from that in the RE-LY trial," he said.

Of the 2453 dabigatran bleeding adverse events reported to the FDA, 393 (16%) were fatal, almost double the case fatality rate of patients who bled in the five phase 3 trials of the drug, he noted.

Le Monde
Vendredi 4 novembre 2011

Bénéfices et inconvénients des nouveaux médicaments pour prévenir les thromboses

De récents anticoagulants seraient plus sûrs et mieux tolérés que les traditionnels antivitamines K. Mais des précautions s'imposent

De nouveaux médicaments actifs par voie orale sont en train de transformer les modalités des traitements anticoagulants. Ils semblent plus sûrs et beaucoup plus simples d'emploi pour les nombreuses personnes qui ont besoin d'une anticoagulation afin d'empêcher la formation de caillots dans les veines ou dans le cœur, et les embolies qui en découlent.

Premiers à être commercialisés en France, le dabigatran (Pradaxa) inhibe directement la thrombine, tandis que le rivaroxaban (Xarelto) bloque un autre facteur de coagulation, le facteur Xa. Leur prescription est limitée actuellement à la prévention des accidents thromboemboliques qui peuvent survenir après la mise en place d'une prothèse de genou ou de hanche. Ils peuvent se substituer ainsi aux injections sous-cutanées d'héparine de bas poids moléculaire (HBPM), avec une efficacité équivalente, voire légèrement supérieure pour le rivaroxaban, sans augmentation du risque hémorragique.

Mais une évolution d'une bien plus grande ampleur se dessine avec l'extension prochaine des indications du dabigatran à la prévention des accidents emboliques chez les patients atteints de fibrillation auriculaire, sans maladie valvulaire. Actuellement, ces personnes sont généralement traitées par des antivitamines K (AVK), médicaments par voie orale, dont l'activité anticoagulante, fluctuante, doit être contrôlée par des prises de sang fréquentes pour adapter les doses.

En effet, les AVK sont soumis à de nombreuses interactions médicamenteuses et alimentaires, et la fenêtre thérapeutique est étroite entre les risques de thrombose (sous-dosage) et de saignements (surdosage). Près d'un million de personnes en France sont traitées par ces médicaments, qui représentent, de loin, la première cause de complications médicamenteuses graves.

Au contraire des AVK, le dabigatran a des concentrations sanguines très stables et des effets qui varient peu d'une personne à l'autre, ce qui lui donne le grand avantage de pouvoir être pris à dose fixe et sans surveillance biologique, comme n'importe quel médicament. Une grande étude a été menée auprès de 18 000 patients (Re-Ly). Elle indique que deux comprimés de 150 mg diminuent de 34 % le risque d'accident vasculaire cérébral à deux ans par rapport à un AVK, avec un risque global d'hémorragies majeures identique, et moins d'hémorragies cérébrales.

D'autres études ont montré les effets favorables, dans la même indication, du rivaroxaban et d'un nouvel anti Xa, l'apixaban, avec, dans ce dernier cas, une réduction de la mortalité totale (étude Aristotle). Pour Philippe Gabriel Steg, professeur de cardiologie à l'hôpital Bichat, « *c'est un progrès très net. Ces médicaments dont on pensait au départ qu'ils seraient simplement plus confortables que les AVK se révèlent aussi beaucoup plus sûrs et probablement plus efficaces* ».

Quelques réserves subsistent, qui doivent conduire à une certaine prudence. Contrairement aux AVK, ces nouveaux anticoagulants n'ont pas encore d'antidotes à administrer en cas d'hémorragie grave. Par ailleurs, le recul est encore assez limité, pour des traitements appelés à être pris à vie, le plus souvent par des personnes âgées. « *Les trois grandes études publiées incluaient 19 000 patients de plus de 75 ans, mais on a peu de données pour les personnes de plus de 80 ans* », confirme le professeur Olivier Hanon (hôpital Broca, Paris).

> Le dabigatran a des concentrations sanguines très stables et des effets qui varient peu d'une personne à l'autre

Des alertes lancées au Japon et en Australie, et deux cas de surdosage décrits en France, viennent rappeler que, même s'ils sont mieux tolérés, ces médicaments peuvent provoquer des accidents hémorragiques et imposent un respect strict des prises et des précautions d'emploi. Les accidents observés concernaient le plus souvent des personnes très âgées, souvent de faible poids. Le déclin de la fonction rénale avec l'âge peut en effet diminuer l'élimination du dabigatran et entraîner un risque de surdosage. « *L'intérêt de ces médicaments ne se discute pas, au regard du moindre risque d'accident vasculaire cérébral, mais il est indispensable de surveiller la fonction rénale pour réduire éventuellement les doses* », met en garde le professeur Hanon.

Enfin, lors d'un traitement par antivitamine K, la contrainte de la surveillance biologique, très inconfortable pour les patients, offre un moyen fiable de s'assurer que le traitement est pris convenablement. « *Cet inconvénient est aussi un avantage, qui n'existe pas actuellement avec les nouveaux anticoagulants*, remarque le professeur Steg. *Il est probable qu'avec la généralisation de l'emploi de ces médicaments, des tests seront développés qui permettront de vérifier de façon ponctuelle que le traitement est bien suivi et bien adapté. Tout un ensemble de questions demeurent à explorer en termes de surveillance, de respect des prescriptions et d'effets secondaires pouvant émerger quand il n'y aura plus 40 000 patients traités, mais 400 000 ou 4 millions.* »

Le coût de ces médicaments ne sera pas le moindre des problèmes à résoudre. Il explique probablement que la décision de remboursement du dabigatran dans la fibrillation auriculaire tarde en France, alors que la Commission européenne a accepté cette extension d'indication le 1er août. ■

CHANTAL GUÉNIOT

L'anticoagulant Pradaxa de Boehringer Ingelheim est lié à 260 décès "suspects"

LEMONDE.FR avec AFP | 14.11.11 | 22h38 • Mis à jour le 14.11.11 | 22h56

4 Partagez 0

Envoyer 53 personnes recommandent

Le laboratoire pharmaceutique Boehringer Ingelheim a enregistré au moins 260 décès *"suspects"* par hémorragie chez des patients traités avec son anti-coagulant Pradaxa, destiné à prévenir les attaques cérébrales, a-t-on appris lundi 14 novembre auprès du groupe allemand. Cela concerne 63 cas par an en moyenne et par tranche de 100 000 patients traités, a-t-il indiqué dans un communiqué. *"En plus, 80 cas ont été rapportés dans lesquels une grave hémorragie a été mêlée à d'autres causes de décès"*, a-t-il ajouté.

Le deuxième laboratoire pharmaceutique allemand dit publier ces chiffres *"face aux grandes inquiétudes"* existant dans le public quant à son médicament, mais

Dans l

L'autre fi ?

Une enq biberons

La sûret réacteur

Du plast

A nouve que la lu

Parmi vo

Roland Ber

Soyez rassu qu'anticipée

Réagiss

Article en Une

Chaque mois, la Rédaction publie des informations en accès libre.

Les 100 derniers : 1 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90

Tous les articles en Une

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- Les articles en Une depuis 2002

Dabigatran (Pradaxa®) : un anticoagulant à l'origine d'hémorragies graves parfois mortelles

Le dabigatran (Pradaxa®) est à utiliser avec beaucoup de précautions chez certains patients, en prenant en compte les situations majorant le risque hémorragique.

Les anticoagulants oraux utilisés pour éviter les caillots artériels ou veineux sont la première cause d'effets indésirables médicamenteux graves à l'origine d'hospitalisation (17 000 par an environ en France) et de morts (environ 5 000 par an en France). Commercialisés depuis des décennies, les antivitamine K sont très majoritairement en cause dans les études publiées.

Le Monde science&médecine

Fabriquer des organes Une technique qui permet de faire pousser un bourgeon de foie humain, transplanté chez la souris, illustre le foisonnement des recherches en bio-ingénierie. PAGE 2

Un échec russe en trompe-l'œil L'explosion de la fusée Proton est une mauvaise nouvelle pour l'industrie spatiale russe, mais ses concurrents savent qu'il faut compter avec elle. PAGE 3

Symphonie thyroïdienne La Galloise Barbara Demeneix, biologiste et violoniste, se passionne pour une hormone qui est le « chef d'orchestre » de nos métamorphoses. PAGE 7

Les trop belles promesses des nouveaux anticoagulants

Selon la Haute Autorité de santé, ces médicaments n'apportent pas de progrès global. De plus, ils pourraient induire un surcoût annuel de 150 millions d'euros pour l'Assurance-maladie. Enquête.

PAGES 4-5

La Sécu victime d'un hold-up de 400 millions d'euros

De nouveaux anticoagulants, pas plus efficaces que les anciens, envahissent le marché. Leur seul avantage : ils coûtent six fois plus cher. Et la Sécu paie.

COMMENT un nouveau médicament qui coûte plus cher que l'ancien mais ne soigne pas mieux, voire moins bien, peut-il être remboursé à 65 %, et creuser ainsi un peu plus le gouffre de la Sécu ? Ce miracle vient de se produire, de façon caricaturale, avec les trois molécules Pradaxa, Xarelto et Eliquis, toutes de la famille des nouveaux anticoagulants Naco, censés prendre la place des AVK, utilisés avec succès depuis des lustres.

Un progrès ? Dans un rapport remis, fin août, à la ministre de la Santé, Marisol Touraine, et au Parlement, la Caisse nationale d'assurance-maladie flingue sans pitié ces Naco : « *Il n'y a pas d'argument pour changer le traitement d'un patient stabilisé sous AVK.* » Avant ce constat, en forme de coup de grâce : « *Outre qu'ils sont très coûteux pour la collectivité – coût mensuel du traitement : 75,78 euros, à comparer à 12,50 euros* (pour les précédents) –, *leur profil de risque est mal connu, et des accidents hémorragiques graves ont été signalés.* » L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) en a remis une louche à la mi-septembre, en mettant en garde les toubibs contre les risques accrus d'hémorragie avec ces Naco.

Nacotrafiquants

Pourtant, sur le million de patients concernés par ces traitements, plus de la moitié avale aujourd'hui ces pilules miracles… pour les labos. Et la Sécu est obligée d'allonger gentiment 400 millions de plus par an. Comment expliquer cette dinguerie ? Par le parcours fléché, et semé de roses, qu'emprunte tout nouveau produit. Une vraie promenade de santé.

Première étape, l'autorisation de mise sur le marché. En France, l'ANSM étudie le dossier puis rend sa décision, fondée, pour l'essentiel, sur le rapport bénéfice-risque. Mais sa marge de manœuvre est étroite : la Commission européenne veille au grain. Et il suffit qu'un Etat de l'Union ait déjà donné son feu vert pour que les autres soient obligés de suivre. Sauf à présenter de solides arguments scientifiques, sous le contrôle de la Cour de justice de l'Union européenne, à Luxembourg. Par exemple, le Pradaxa a décroché une autorisation européenne de mise sur le marché dès 2008…

Deuxième étape, le médicament atterrit à la Haute Autorité de santé (HAS). Celle-ci se prononce d'abord sur le « service médical rendu ». Si elle considère que le remède est utile, elle donne son feu vert pour le remboursement par la Sécu, de 15 à 65 % selon son efficacité. Les anticoagulants étant très précieux, leur remboursement maximal est donc assuré. L'avis est « consultatif », mais très technique. Tout le monde y souscrit.

On arrête le progrès

Troisième étape : la HAS évalue ensuite l'« amélioration » du service médical rendu. En clair, y a-t-il progrès ou pas avec le nouveau produit ? En février 2012, pour Pradaxa et consorts, la Haute Autorité a clairement répondu : non, aucune amélioration du service médical rendu, les produits existants font parfaitement l'affaire ! Hélas, cette appréciation négative et sans appel n'a aucune incidence sur le taux de remboursement.

« *Ainsi va la réglementation en France* », soupire un juriste du ministère de la Santé. Et, si Marisol Touraine s'avisait de refuser de rembourser ces produits à 65 %, la riposte de l'industrie pharmaceutique serait immédiate : un recours devant le Conseil d'Etat. Puisqu'il s'agit de la même classe thérapeutique (en l'occurrence un anticoagulant), et d'efficacité comparable, les juges ne manqueraient pas de conclure qu'il doit être remboursé de la même façon.

Lors des Assises du médicament, en 2011, après l'affaire du Mediator, il avait été envisagé de ne rembourser les nouveautés qu'en cas de réel progrès thérapeutique. Les labos ont fait la danse du ventre, et cette idée diabolique a vite été abandonnée.

L'expérience des labos

Une fois les avis de la HAS rendus, le parcours touche à sa fin : la balle est dans le camp du ministre. Ou plutôt de son bras armé, le Comité économique des produits de santé, qui fixe le tarif. Et, là, le lobby des labos, qui participe aux réunions, pèse de tout son poids. Avec ces arguments classiques : il faut bien financer la recherche, et songer à préserver l'emploi… Il vaut mieux ne pas contrarier ces industriels méritants. Or la classe précédente d'anticoagulants, les fidèles et efficaces AVK, n'est plus rentable. Ils ont donné naissance à de nombreux génériques bon marché. Vive la nouvelle génération, six fois plus chère !

Il ne reste plus aux labos qu'à lancer d'énergiques campagnes de promotion en direction des médecins prescripteurs. Mission réussie : les nouveaux produits ont déjà conquis 57% des patients. Et, si tout va bien, quand les labos auront raflé tout le marché, sans aucun progrès pour la santé publique ni pour les malades, la facture de la Sécu ne sera pas loin du milliard d'euros.

Contre cette gabegie, personne n'a encore trouvé l'antidote…

Brigitte Rossigneux

The NEW ENGLAND JOURNAL of MEDICINE

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Pradaxa

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Pradaxa, Internal Bleeding, Hemorrhaging, Side Effects Lawsuit

Pradaxa Bleeding Hemorrhaging | Lawsuits, Lawyers | Side Effects: Unusual bruising or bleeding, Pink or brown urine, Red or black tarry stools, Coughing up blood, Vomiting that resembles blood or looks like coffee grounds, Bleeding from the gums, Frequent nosebleeds, Joint pain or swelling, Headaches, Dizziness, Weakness and swelling of the arms, hands, feet, ankles or lower legs, Death.

Have you or someone you care about suffered life-threatening internal bleeding or hemorrhaging side effects while taking Pradaxa? The defective drug lawyers at Parker Waichman Alonso LLP are currently investigating reports that some Pradaxa patients have experienced serious bleeding or hemorrhaging side effect episodes. In some instances, Pradaxa bleeding / hemorrhaging side effects was not discovered in a timely manner, leading to death.

If you or someone you know experienced serious internal bleeding / hemorrhaging that might be associated with Pradaxa, our defective drug lawyers want to hear from you today. We are currently offering free lawsuit consultations to all victims of Pradaxa bleeding / hemorrhaging side effects. To discuss your potential Pradaxa bleeding / hemorrhaging side effects lawsuit with an experienced defective drug lawyer, we urge you to contact us today.

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SEARCH

INFORMATION TRANSMISE SOUS L'AUTORITE DE L'ANSM

INFORMATIONS
SÉCURITÉ PATIENTS

Lettre aux professionnels de santé

Septembre 2013

Nouveaux anticoagulants oraux Eliquis®, Pradaxa®, Xarelto® :
Mises en garde sur les facteurs de risque hémorragiques – Il est recommandé de vérifier leur posologie, leurs contre-indications et leurs mises en garde et précautions d'emploi pour limiter le risque de saignement.

Information destinée aux anesthésistes, cardiologues, chirurgiens orthopédiques, chirurgiens cardiothoraciques, chirurgiens vasculaires, médecins généralistes, internistes, gériatres, urgentistes, neurologues, phlébologues, angéiologues, pneumologues hospitaliers, hématologues, pharmaciens d'officine et hospitaliers

Madame, Monsieur, Chère Consœur, Cher Confrère,

Eliquis® (apixaban), Pradaxa® (dabigatran étexilate) et Xarelto® (rivaroxaban) sont des anticoagulants oraux qui ont été autorisés au cours des dernières années dans des indications pour lesquelles les antagonistes de la vitamine K (warfarine, phenprocoumone et acénocoumarol) ou les héparines de bas poids moléculaire (HBPM) sont utilisés depuis des décennies. Contrairement aux antagonistes de la vitamine K, l'administration de ces nouveaux médicaments ne nécessite pas de surveillance biologique de l'activité anticoagulante en routine.

Cependant, les essais cliniques et l'expérience après la mise sur le marché ont démontré que les événements hémorragiques majeurs, y compris ceux ayant entrainé une issue fatale, ne concernent pas seulement les antagonistes de la vitamine K/ HBPM, mais sont aussi un risque important associés à l'utilisation des nouveaux anticoagulants oraux. Par ailleurs, les signalements rapportés après la mise sur le marché de ces spécialités indiquent que tous les prescripteurs ne sont pas suffisamment informés

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Depuis le bureau du Président

Paris, le 17/09/2013

Madame la ministre de la Santé,

Bien qu'ayant révolutionné le pronostic des accidents thrombo-emboliques et contribué à sauver de très nombreuses vies depuis leur introduction dans la pharmacopée occidentale, les Anti-Vitamine-K (AVK) pâtissent de la triste réputation d'être responsables d'environ 4000 décès par an en France (enquête AFSSAPS 1998). Ils occupent ainsi depuis des années la première place en matière de décès d'origine iatrogène.

Par ailleurs, si leur mode d'administration *per os* est tout à fait acceptable pour les patients, le contrôle au long cours de l'équilibre du traitement requiert des prises de sang régulières et contraignantes (équilibre parfois difficile à atteindre et de maintien précaire, astreignant à des adaptations posologiques répétées).

C'est dans ce contexte que les Nouveaux Anti-Coagulants Oraux (NACO) sont arrivés sur le marché. Les firmes pharmaceutiques les ont alors présentés comme des « *traitements anticoagulants révolutionnaires* ».

Libération

Un anticoagulant mis en cause après quatre décès

AFP 9 OCTOBRE 2013 À 07:37

Des gélules de Pradaxa du laboratoire allemand Boehringer Ingelheim (Photo Philippe Huguen. AFP)

Les proches de quatre personnes âgées ayant succombé à des hémorragies alors qu'elle prenaient du Pradaxa ont saisi la justice face au laboratoire allemand ayant développé le médicament.

Ancien Interne des hôpitaux de Paris
Et Chef de Clinique à la Faculté

Maladies du cœur et des Vaisseaux

Paris le,12/10/2012

8 JOURS AVANT L'INTERVENTION:

ARRETER ASPEGIC-KARDEGIC ET/OU PLAVIX-CLOPIDOGREL

4 JOURS AVANT L'INTERVENTION Commencer:

XARELTO 20mg
à LA DOSE DE:1 PAR JOUR, LE MATIN.

Le jour de l'intervention:
PAS DE XARELTO.

Le lendemain de l'intervention:

- SAUF interdiction par votre chirurgien ou anesthésiste...
- Reprendre durant 5 jours LE XARELTO aux doses habituelles.

ASSOCIE A ASPEGIC OU KARDEGIC ET/OU PLAVIX-CLOPIDOGREL
que l'on gardera.
ARRET DU XARELTO 5 JOURS APRES L'INTERVENION.

Paul Watzlawick

COMMENT RÉUSSIR A ÉCHOUER

Trouver l'ultrasolution

Seuil

Point sur l'utilisation des nouveaux anticoagulants oraux Pradaxa (dabigatran), Xarelto (rivaroxaban) et Eliquis (apixaban) - Communiqué

27/11/2013

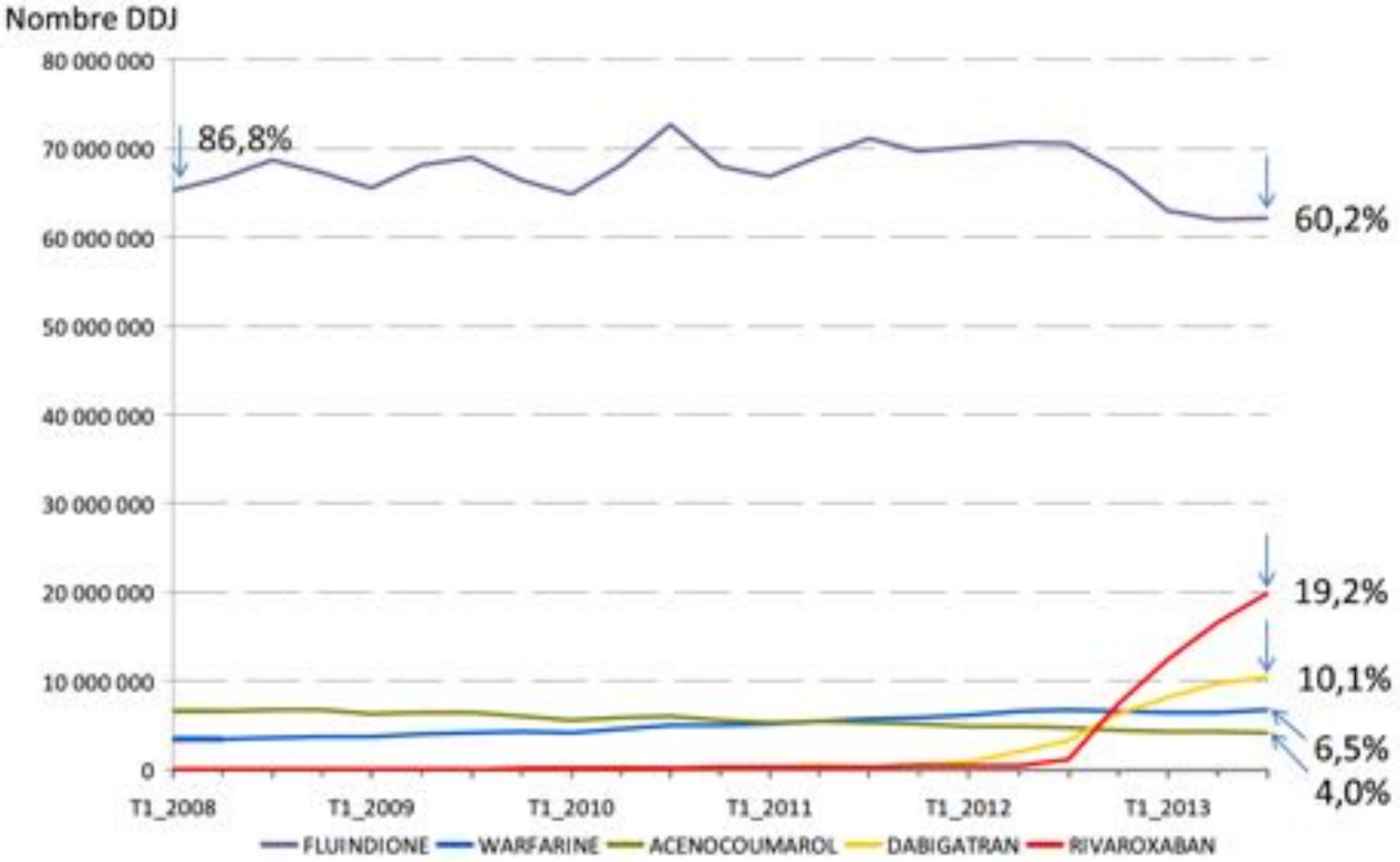
- AVK largement majoritaires (plus d'1 million de patients traités contre **265 000 pour les NACO**), mais large recours à ces nouveaux médicaments en initiation de traitement.

- Près de la moitié des patients débutant un traitement anticoagulant oral s'est vue prescrire un traitement par NACO. Les cardiologues libéraux prescrivent dans près de 3/4 des cas (73%) les NACO en 1ère intention, contre plus d'1/3 des cas (35%) pour les médecins généralistes libéraux. Les médecins hospitaliers se situent à un niveau intermédiaire : près de 44% de leurs prescriptions...

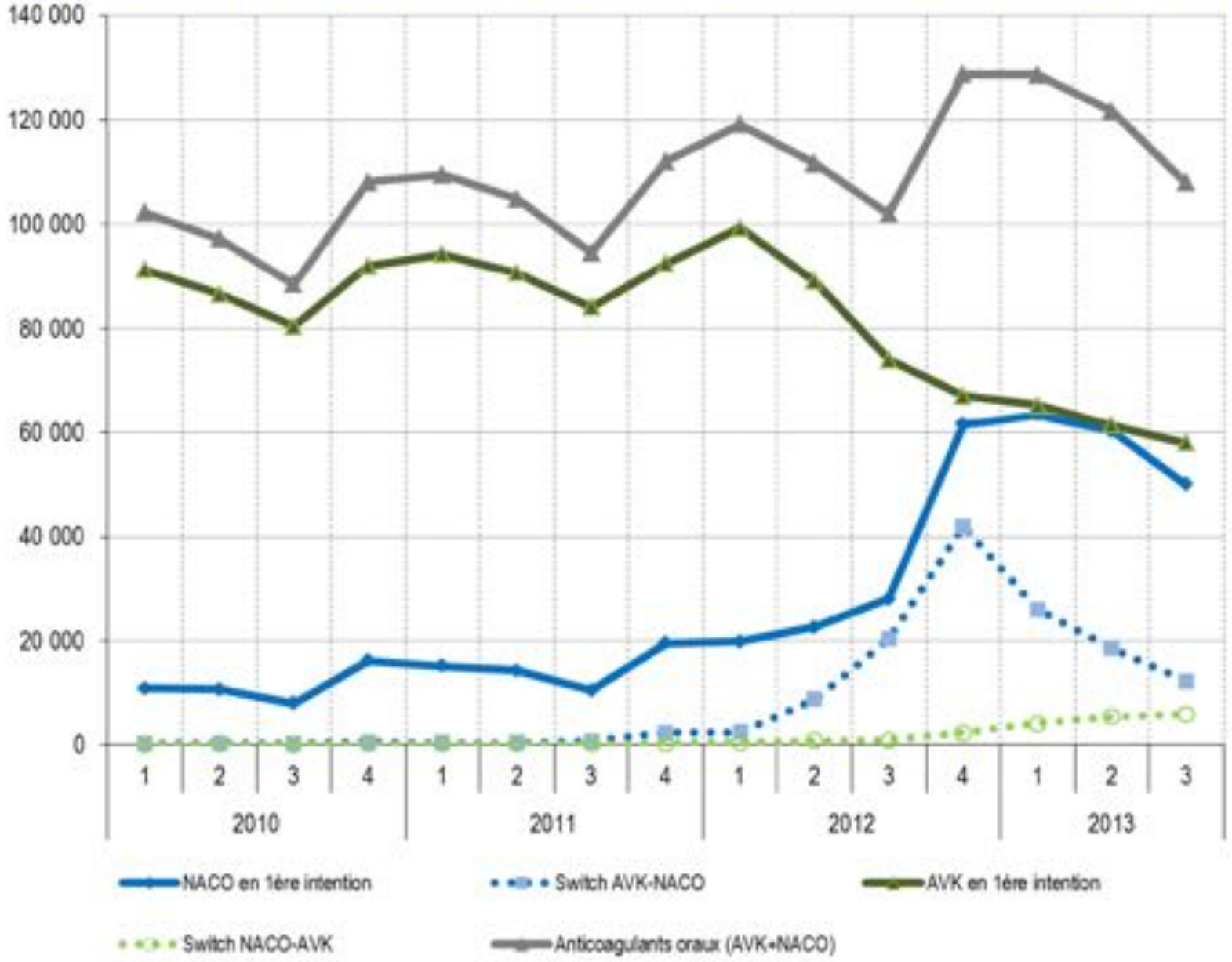
- Les changements de traitements AVK vers NACO ont représenté près de 100 000 patients sur la période observée.

- Selon les dernières données de ventes, 30 % des anticoagulants utilisés en 2013 sont des NACO

Figure 4. Evolution trimestrielle des ventes des anticoagulants oraux en fonction de leurs types (janvier 2008-septembre 2013), données Celtipharm



Evolution des effectifs de patients débutant un traitement par NACO ou AVK



Source : SNIIRAM, France entière, données Tous régimes

Point sur l'utilisation des nouveaux anticoagulants oraux Pradaxa (dabigatran), Xarelto (rivaroxaban) et Eliquis (apixaban) - Communiqué

27/11/2013

ansm – Agence nationale de sécurité du médicament et des produits de santé | Sécurité sociale – L'Assurance Maladie | HAS – Haute Autorité de Santé

Données de l'Assurance Maladie sur le dernier trimestre 2012 : une part des patients sous NACO prend de façon concomitante des médicaments majorant le risque hémorragique : 15% des patients suivent en parallèle un traitement par antiagrégants plaquettaires, 21% un traitement par amiodarone.

Près de 10% des patients débutant un traitement par NACO étaient des patients de 80 ans et plus sans surveillance de leur fonction rénale.

Une part des prescriptions de NACO estimée entre 5 et 10%, correspond à des indications non validées, éventuellement dangereuses : patients avec une insuffisance hépatique ou rénale, patients avec fibrillation auriculaire et atteints de valvulopathies.

Résultats globaux

Un profil de risque attendu avec des EI graves voire des décès chez des personnes âgées, fragilisées par leur pathologie sous jacente et polymédiquées

PRADAXA

- 1624 cas retenus
- 857 F, 755 H, 14 U
- âge moyen 77 ± 10 ans
- Indication conforme à AMM dans 97% des cas
- Effets attendus et listés
- Décès 175 cas (11% des cas) :
  - Indication FA dans 61% des décès
  - Hémorragies : 66% des décès
  - Thromboses : 12,5% des décès

XARELTO

- 1566 cas retenus
- 814 F, 748 H, 4 U
- âge moyen 72 ± 14 ans
- Indication conforme à AMM dans 95% des cas
- Effets attendus et listés
- Décès 127 cas (8% des cas) :
  - Indication FA dans 77% des décès
  - Hémorragies : 65% des décès
  - Thromboses : 19% des décès

Étude 'en vie réelle' du bénéfice/risque à court terme des nouveaux anticoagulants oraux (dabigatran, rivaroxaban) chez les patients débutant un traitement et non précédemment traités par des antivitamines K

Étude du projet NACORA (nouveaux anticoagulants oraux et risques associés)

Département des Études en Santé Publique,
Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS)

en collaboration avec le Pole Epidémiologie des Produits de Santé de l'Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM)

Rapport du 23 juin 2014

Original Investigation

Risk of Bleeding With Dabigatran in Atrial Fibrillation

Inmaculada Hernandez, PharmD; Seo Hyon Baik, PhD; Antonio Piñera, MD; Yuting Zhang, PhD

JAMA Intern Med. doi:10.1001/jamainternmed.2014.5398
Published online November 3, 2014.

Retrospective cohort study

Pharmacy and medical claims in 2010 to 2011 from a 5% random sample of Medicare beneficiaries.

Participants as those newly diagnosed as having **atrial fibrillation** from October 1, 2010, through October 31, 2011, and **who initiated dabigatran or warfarin treatment within 60 days of initial diagnosis.**

Table 2. Adjusted Incidence Rates of Bleeding Events by Treatment Group

Outcome	Incidence Rates, % (95% CI)[a]		P Value
	Warfarin (n = 8102)	Dabigatran (n = 1302)	
By severity			
Any	26.5 (24.3-28.6)	32.7 (29.9-35.4)	<.001
Major	5.9 (5.1-6.6)	9.0 (7.8-10.2)	<.001
Minor	23.6 (21.4-25.8)	28.6 (25.8-31.3)	<.001
By anatomical site			
Intracranial bleeding	1.8 (1.4-2.2)	0.6 (0.3-0.8)	<.001
Gastrointestinal bleeding	10.0 (9.0-11.0)	17.4 (15.7-19.2)	<.001
Hematuria	8.8 (6.9-10.7)	12.0 (9.3-14.7)	<.001
Vaginal bleeding	0.3 (0.2-0.4)	0.7 (0.4-0.9)	.003
Hemarthrosis	0.2 (0.1-0.3)	0.5 (0.3-0.7)	.007
Hemoptysis	1.4 (0.9-1.8)	2.0 (1.3-2.7)	.03
Epistaxis	3.1 (2.5-3.6)	2.0 (1.5 -2.5)	.002
NOS hemorrhage	5.9 (4.9-6.9)	4.4 (3.5-5.4)	.003

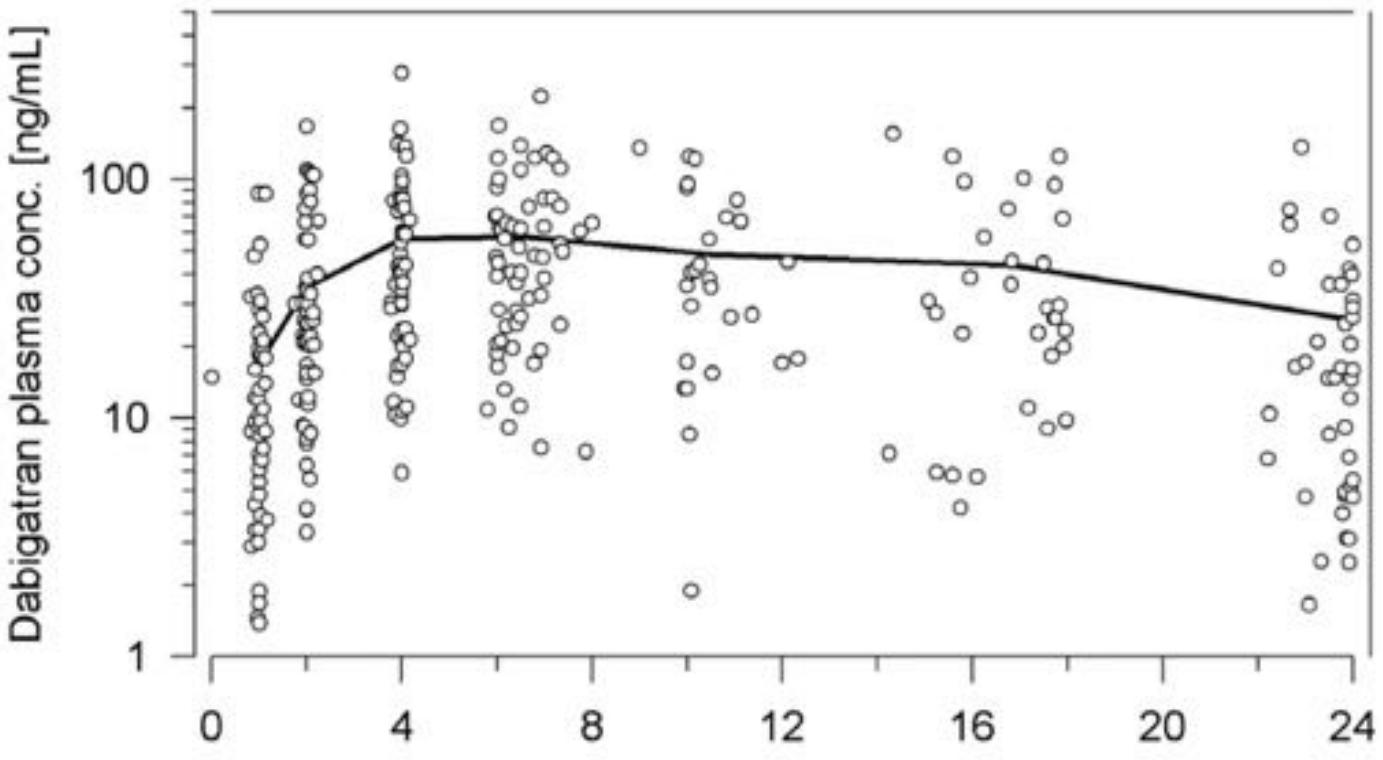
Gestion périopératoire : ce qu'on peut retenir

Quelle conduite à tenir dans les situations prévisibles suivantes, chez un sujet traité par un nouvel ACO:

- Chirurgie et actes invasifs programmés ?
- Trauma et chirurgie urgente ?
- Relais par un anticoagulant parentéral (ex: voie orale indisponible) ?
- Hémorragie active ?
- Surdosage (accidentel, volontaire ou criminel) ?

Antivitamines K	AOD
Antidotes disponibles (CCP, vit K)	Pas d'antidotes validés
Surveillance biologique simple (INR)	Pas de surveillance biologique simple
Importante variabilité phamacocinétique	Variabilité pharmacocinétique significative
Recommandations publiées	Peu de recommandations publiées
Large expérience clinique	Pas d'expérience clinique longue

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**

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.

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Paul A. Reilly,[a*] PhD, Thorsten Lehr[b,c*] PhD, Sebastian Haertter,[b] PhD, Stuart J Connolly,[a] 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.

A multiple logistic regression model showed that **the risk of ischemic events was inversely related to trough dabigatran concentrations** ($p=0.045$), with age and previous stroke (both $p< 0.0001$) as significant covariates.

Multiple logistic regression showed **major bleeding risk increased with dabigatran exposure** ($p<0.0001$), age ($p< 0.0001$), aspirin use ($p<0.0003$) and diabetes ($p= 0.018$) as significant covariates.

BMJ 2014;349:g4670 doi: 10.1136/bmj.g4670 (Published 23 July 2014)

FEATURE

ANTICOAGULANTS

Dabigatran: how the drug company withheld important analyses

In an investigation by *The BMJ* **Deborah Cohen** finds that recommendations for use of new generation oral anticoagulants may be flawed because regulators did not see evidence showing that monitoring drug plasma levels could improve safety

Deborah Cohen *investigations editor, The BMJ*

BMJ 2014;349:g4517 doi: 10.1136/bmj.g4517 (Published 23 July 2014)

ANALYSIS

Dabigatran, bleeding, and the regulators

Thomas J Moore and colleagues highlight the differences in how US and European regulators managed the safety problems of the new anticoagulant dabigatran and ask both to think again and mandate plasma monitoring of dabigatran

Thomas J Moore *senior scientist*[1], Michael R Cohen *president*[1], Donald R Mattison *chief medical officer*[2 3]

BMJ 2014;349:g4756 doi: 10.1136/bmj.g4756 (Published 24 July 2014)

NEWS

Boehringer Ingelheim withheld safety analyses on new anticoagulant, *The BMJ* investigation finds

Zosia Kmietowicz

The BMJ

BMJ 2014;349:g4747 doi: 10.1136/bmj.g4747 (Published 23 July 2014)

FEATURE

ANTICOAGULANTS

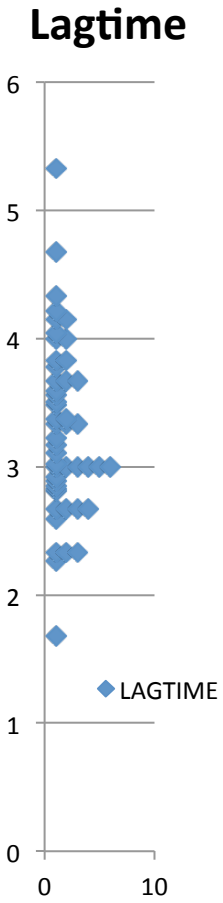
Concerns over data in key dabigatran trial

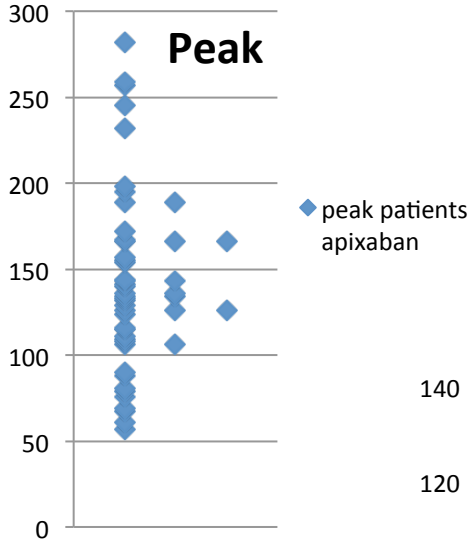
Deborah Cohen considers the evidence that there may be a higher risk of bleeding with dabigatran than has previously been reported

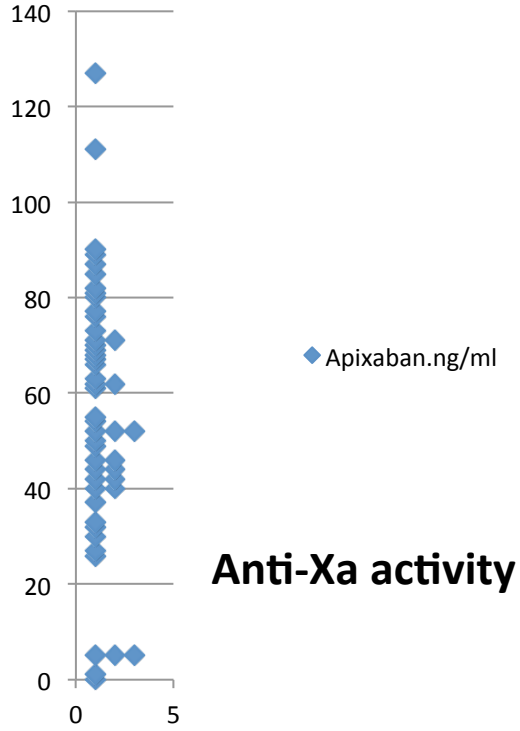
Deborah Cohen *investigations editor, The BMJ*

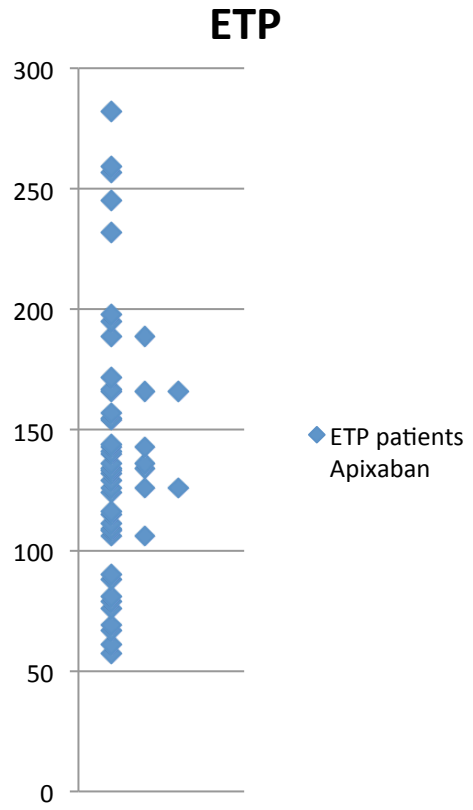
Apixaban treated patients
Total Hip Replacement
TGT and anti-Xa levels

Unpublished data MM SAMAMA









Influence of Renal Impairment on the Pharmacokinetics and Pharmacodynamics of Oral Dabigatran Etexilate

An Open-Label, Parallel-Group, Single-Centre Study

Joachim Stangier,[1] *Karin Rathgen,*[1] *Hildegard Stähle*[1] and *Dago Mazur*[2]

Clin Pharmacokinet 2010; 49 (4): 259-268

Dabigatran
150 mg x1 PO

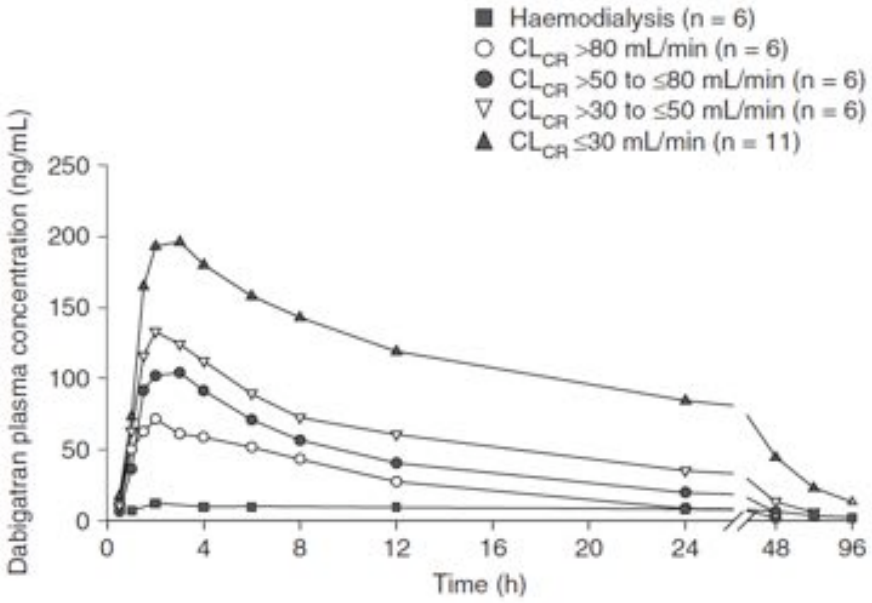


Fig. 1. Arithmetic mean dabigatran plasma concentration-time curves i subjects with normal and impaired renal function after oral administration c dabigatran etexilate (50 or 150 mg). **CL_{CR}** = creatinine clearance.

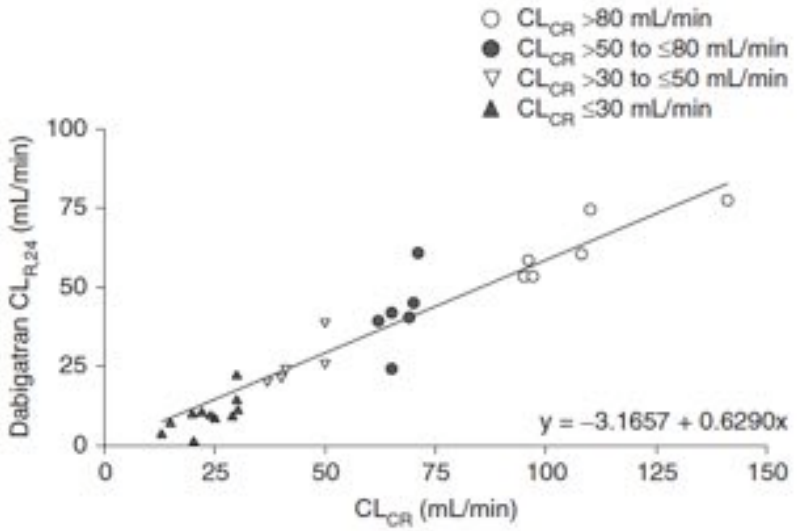


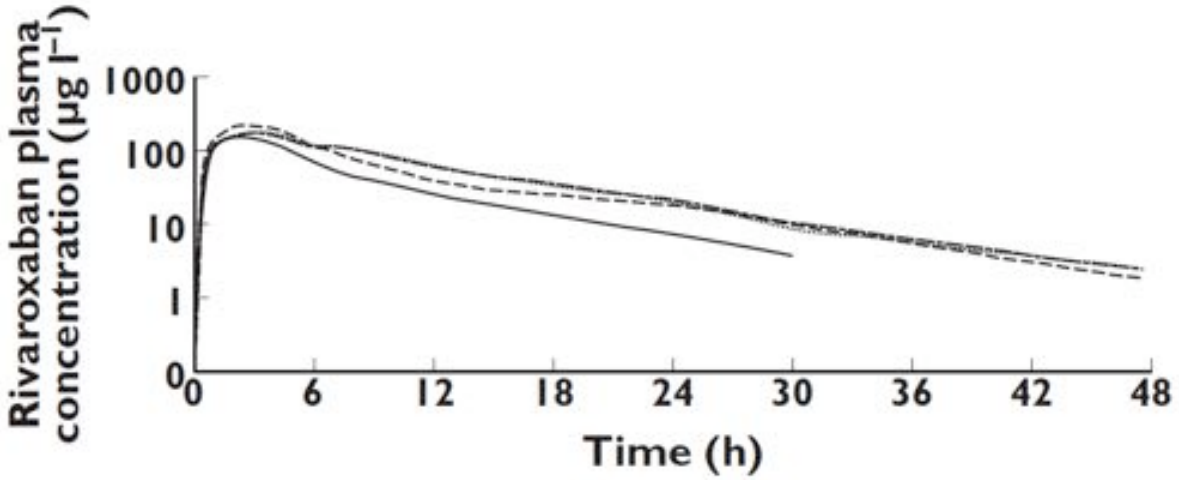
Fig. 3. Correlation between renal clearance over 24 hours ($CL_{R,24}$) of total dabigatran and renal function assessed by creatinine clearance (CL_{CR}) after oral administration of dabigatran etexilate. The datapoints indicate individual observations and the line indicates the estimated relationship based on linear regression analysis.

Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor

Dagmar Kubitza,[1] Michael Becka,[2] Wolfgang Mueck,[1] Atef Halabi,[3] Haidar Maatouk,[3] Norbert Klause,[4] Volkmar Lufft,[4] Dominic D. Wand,[5] Thomas Philipp[5] & Heike Bruck[5]

British Journal of Clinical Pharmacology 2010 Nov;70(5):703-12.

Rivaroxaban 10 mg x1 PO
One dose



	Healthy controls (n = 8)	Renally impaired groups: Mild impairment (n = 8)	Moderate impairment (n = 8)	Severe impairment (n = 8)
CL_O (ml min^{-1})	117.1 ± 29.3	66.5 ± 8.1	42.6 ± 5.0	22.2 ± 4.6
AUC (µg l^{-1} h)	1247 (49.3)	1 863 (30.9)	2 068 (33.1)	2 228 (37.0)
AUC_{norm} (g l^{-1} h)	9439 (49.6)	14 780 (31.6)	15 440 (28.1)	15 940 (48.5)
AUC ratio (90% CI) vs. healthy controls‡	–	1.44 (1.08, 1.91)	1.52 (1.15, 2.01)	1.64 (1.24, 2.17)
C_{max} ratio (90% CI) vs. healthy controls‡	–	1.28 (1.07, 1.55)	1.12 (0.93, 1.34)	1.26 (1.05, 1.51)

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%[18]	No PK data[a]	+40%[63, 64, 246]	Minor effect[a] (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[18]	+40%[63]	No data yet	Minor effect[a] (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[a] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 a 249]c	No data yet	+77%[248, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[18] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[246] (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[strong]	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[252]	minus 54%[208]	avoid if possible; minus 35%, but with compensatory increase of active metabolite[247]	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[249]c	No data yet	Up to +153%[247]

Continued

Table 6 Continued

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[347]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (UFH: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[#]	+87-95%[#] (reduce NOAC dose by 50%)	Up to +160%[347]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[334]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[41, 53, 58]	No effect[60]	No effect	No effect[340, 342]
Others					
Carbamazepine[#346]; Phenobarbital[#346]; Phenytoin[#346]; St John's wort[#346]	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[352]	minus 54%[SmPC]	minus 35%	Up to minus 50%
Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Red: contra-indicated/not recommended. **Orange**: reduce dose (from 150 to 110 mg BID for dabigatran; from 20 to 15 mg OD for rivaroxaban; from 5 to 2.5 mg BID for apixaban). **Yellow**: consider dose reduction if 2 or more 'yellow' factors are present. Hatching: no clinical or PK data available.

%: age had no significant effect after adjusting for weight and renal function.

BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI, proton pump inhibitor; P-gp, P-glycoprotein; GI, Gastrointestinal.

[346]Some interactions lead to reduced NOAC plasma levels in contrast to most interactions that lead to increased NOAC plasma levels. This may also constitute a contraindication for simultaneous use, and such cases are coloured **brown**. The label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which are deemed not clinically relevant (**blue**). Since not tested prospectively, however, such concomitant use should be used with caution, and avoided when possible.

[#]Based on in vitro investigations, comparing the IC_{50} for P-gp inhibition to maximal plasma levels at therapeutic dose, and/or on interaction analysis of efficacy and safety endpoints in the Phase III clinical trials.[82,83] No direct PK interaction data available.

[SmPC]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL.

Facteurs prédictibles d'exposition au médicament

- intrinséques
  - Fonctions physiologiques:
    - renale (dabigatran > rivaroxaban > apixaban),
    - hépatique (apixaban > rivaroxaban > dabigatran)
  - Age, sexe
  - Variables hématologiques: Ht, Albumine….
  - Poids
  - Race, polymorphismes génétiques?

Modélisation possible (PK des populations)

Adaptation aux populations "spéciales" si nécessaire

- extrinséque
  - Inhibiteurs ou inducteurs d'enzymes intervenant dans l'absorption, la secretion ou le métabolisme du médicament (P-gp, Cyp 3A4, ….)
  - différents selon le médicament

Mise en garde et précautions d'emploi

Niveau de complexité difficile pour l'application en routine

Messages
Photos
Musique
Appareil ph...
Notes
Meteo France
Calculette
Horloge
Liveradio
Réglages
Rappels
Bourse
Banque
Facebook
Google
Safari
UL FR-EN
Téléphone
Mail
Calendrier
Contacts

Jeux
Black Box
Dictation
Aquarelle
Amex FR
WeatherOnL...
Gymglish
Ultralingua
Le Gorafi
Road Bike
LeGeek New
Viber
PayPal
Cartoradio...
Thalys
Dabigatran
Téléphone
Mail
20
Calendrier
Contacts

Biological monitoring

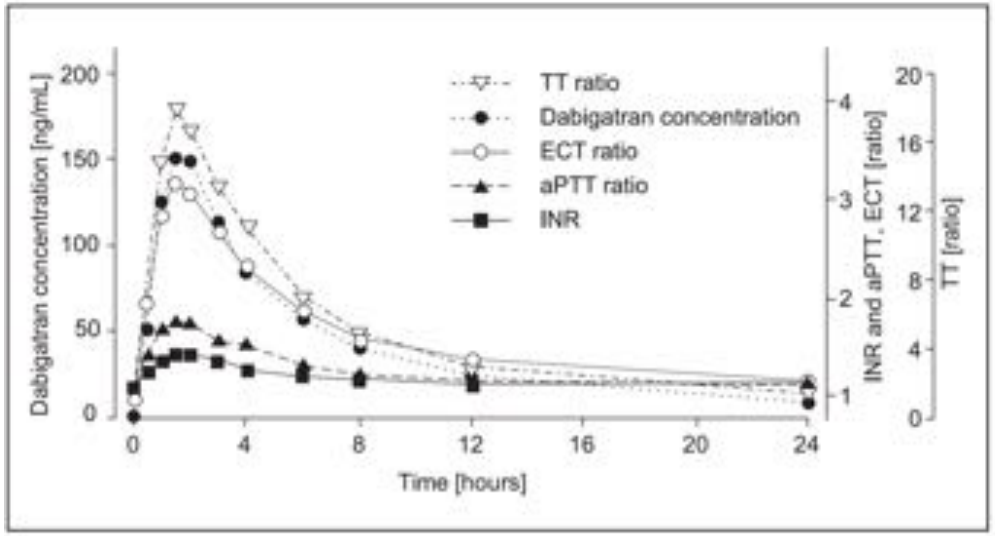


Figure 2: Geometric mean plots of aPTT prolongation, INR, TT and ECT together with plasma concentrations of dabigatran vs. time following a single dose oral dose of 200 mg dabigatran etexilate (N = 6) (14).

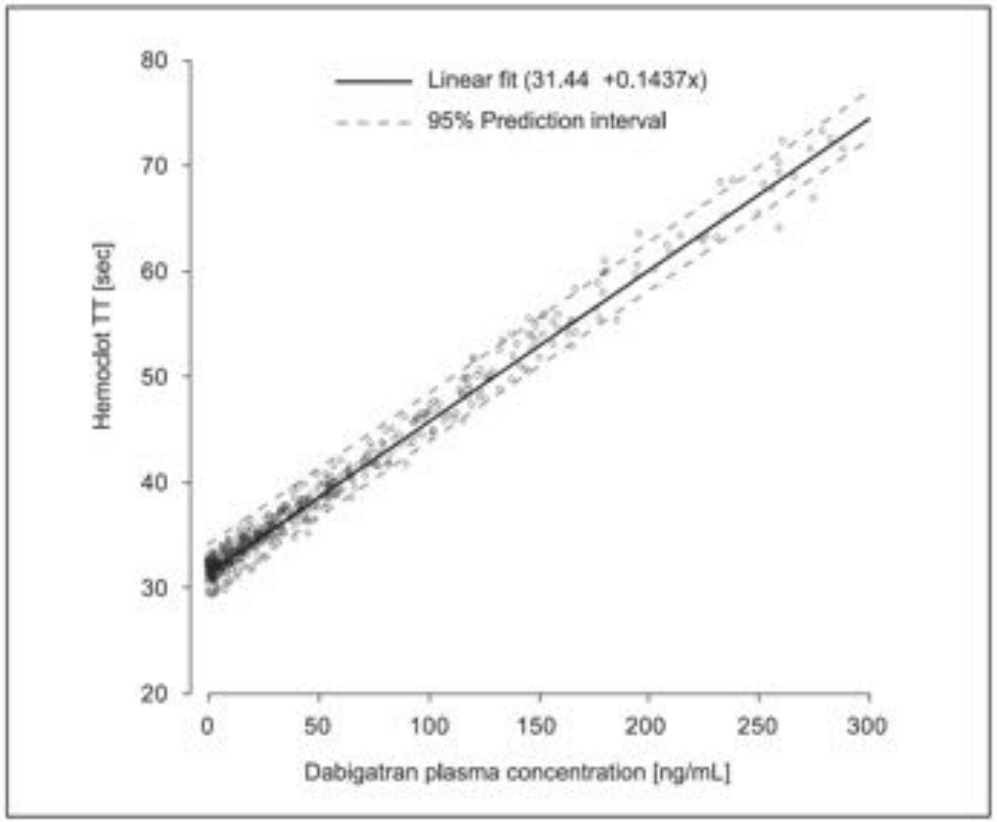


Figure 6: Linear relationship between Haemoclot® TT assay and dabigatran concentrations in samples from healthy volunteer subjects receiving dabigatran etexilate 220 mg (21).

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

Thromb Haemost 2013; 110: 543–549

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]

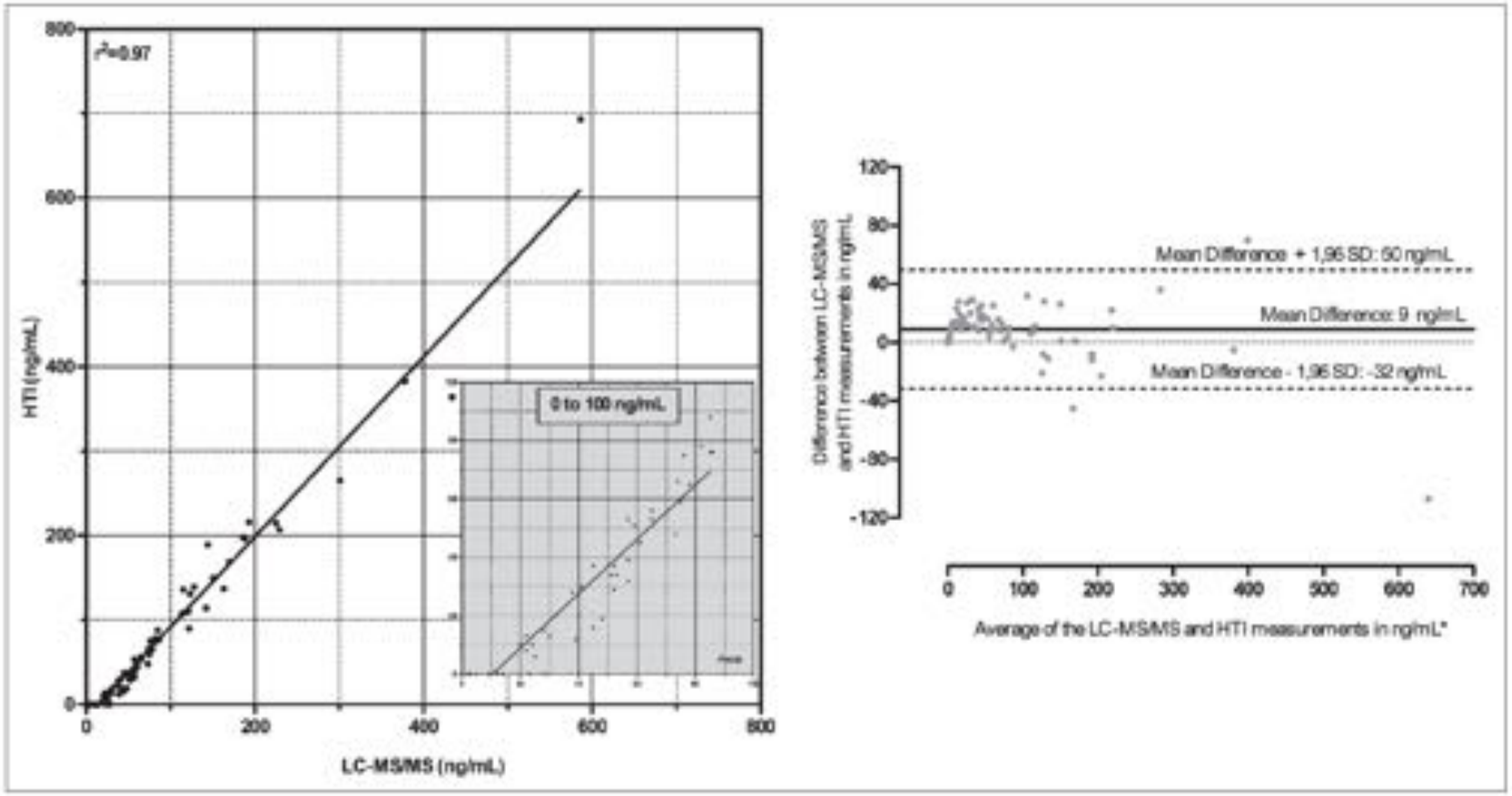


Figure 1: Correlation and Bland-Altman analysis between liquid chromatography-tandem mass spectrometry (LC-MS/MS) and the Hemoclot® Thrombin Inhibitors (HTI) assay for the measurement of dabigatran concentrations in patient plasma samples. The insert shows the relationship at dabigatran concentrations ≤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.

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

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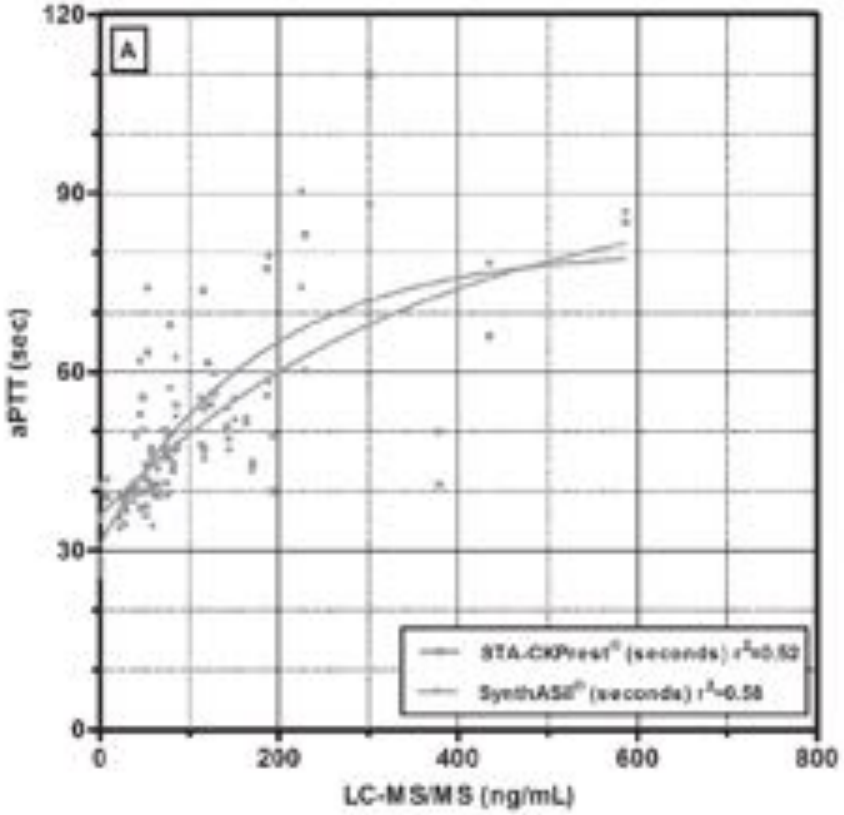
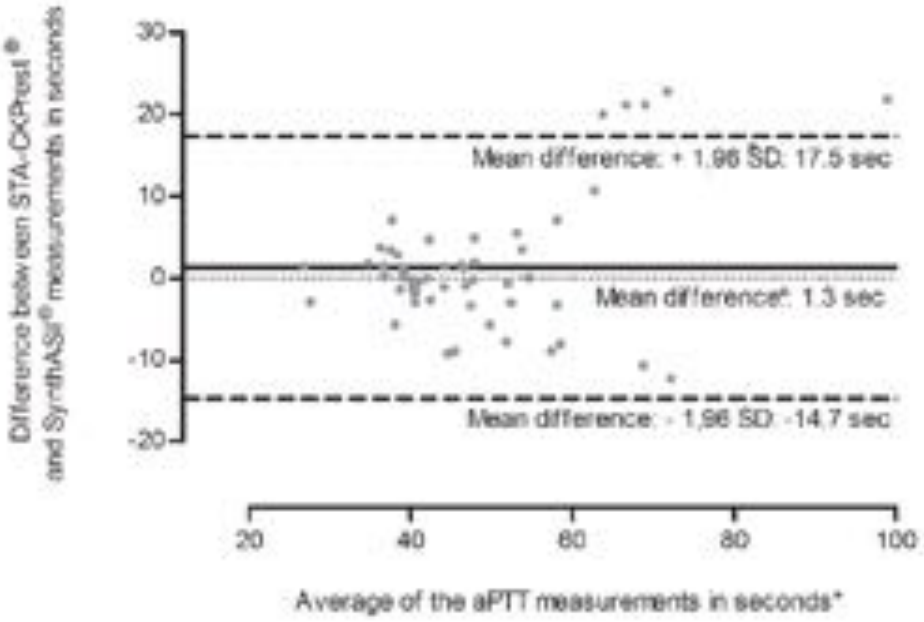




Comparison of calibrated dilute thrombin time and aPTT tests with LC-MS/MS for the therapeutic monitoring of patients treated with dabigatran etexilate

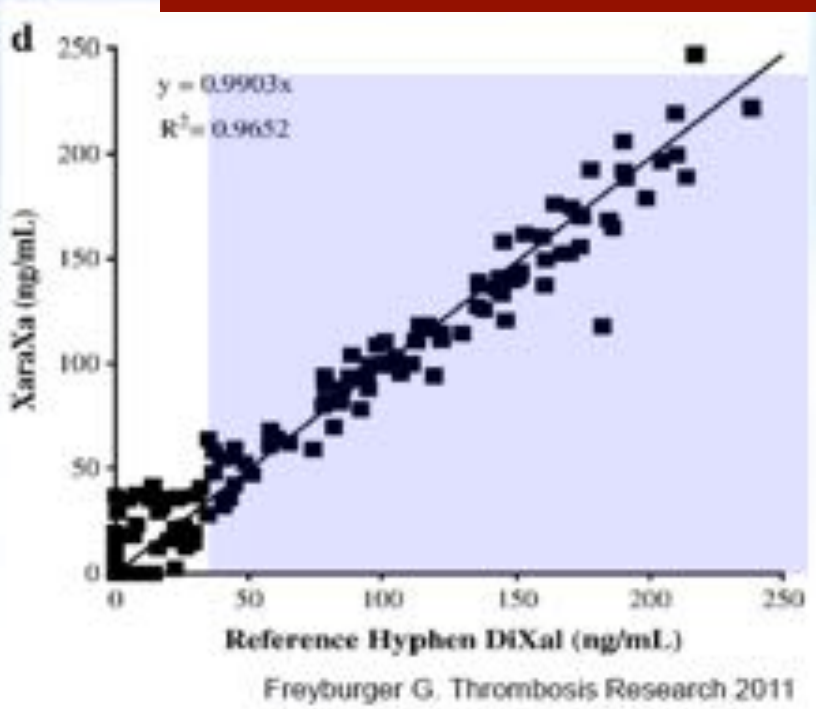
Thromb Haemost 2013; 110: 543–549

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]

There is a poor correlation between aPTT and the measured plasma dabigatran concentration. aPTT should not be used to estimate dabigatran concentrations in plasma and poorly reflects the intensity of anticoagulation due to dabigatran.

The Hemoclot® Thrombin Inhibitor assay correlates well with reference LC-MS/MS measurements for dabigatran concentration above 50 ng/ml.

Rivaroxaban concentration: Specific Anti-Xa



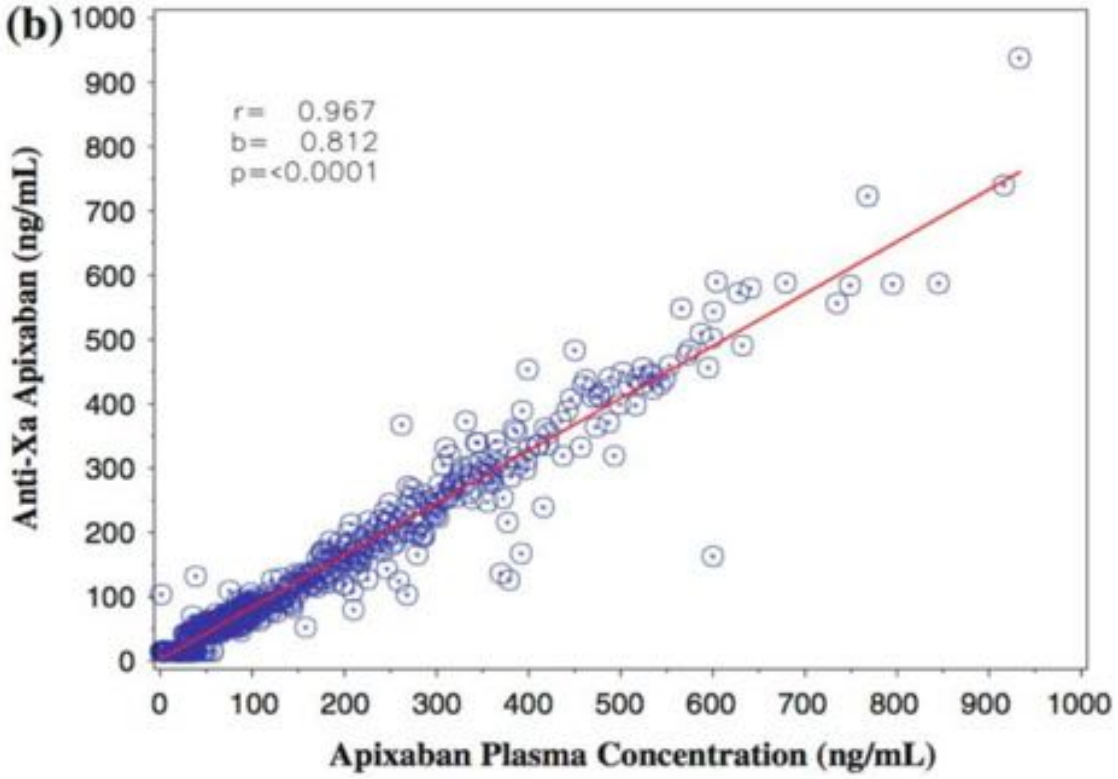
Freyburger G. Thrombosis Research 2011

Specific tests

Calibration with plasma titrated with rivaroxaban

Target	Method	Brand Name	Company
facteur Xa	chromogénique	Biophen DiXal®	Hyphen BioMed
facteur Xa	chromogénique	STA Liquid anti-Xa®	Diagnostica Stago

Specific Anti-Xa and Apixaban



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

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

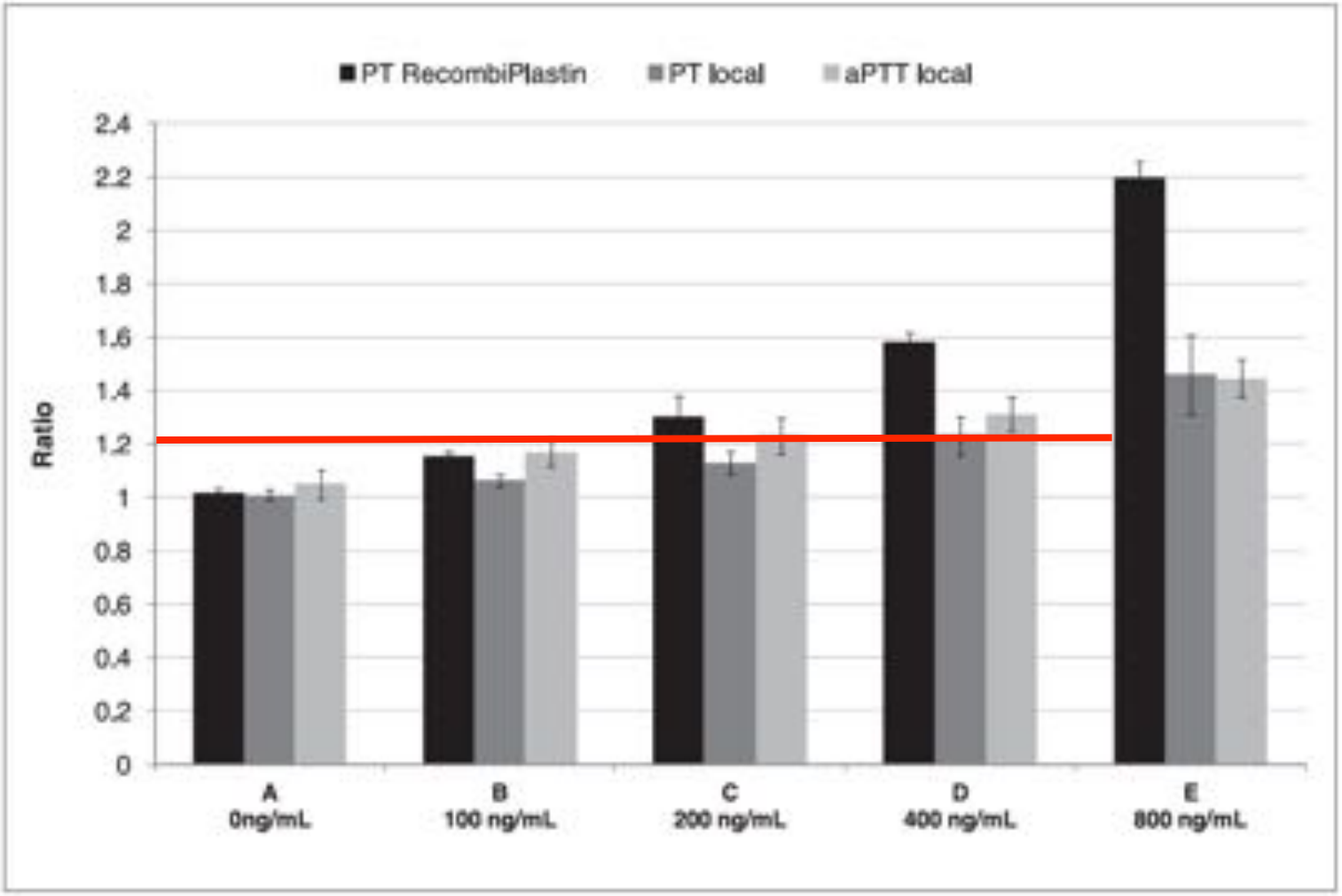


Figure 1: PT measurements with Recombi-Plastin 2G® or local reagents and APTT measurements with local reagents in plasmas A, B, C, D and E measured in the 13 laboratories.

ISTH Congress, Toronto, june 2015

PO352-MON

Monitoring novel anticoagulants dabigatran, rivaroxaban and apixaban using the new fully automated thrombelastography technique TEG®6S

Artang R[1], Galloway G[2], Amiral J[3] and Nielsen JD[4]

PO099-MON

Monitoring new oral anticoagulants (NOACS) using new-generation thrombelastography TEG®6S System

Bliden K[1], Muresan A[2], Raviv G[2], Cohen E[2], Zaman F[3], Saadin K[1], Mohammed N[1], Chaudhary R[1], Rafeedheen R[1], Tantry U[1] and Gurbel P[1]

PO078-TUE

Evaluating dabigatran and its specific reversal with idarucizumab using a fully automated thrombelastograph TEG®6s

Zaman F[1], Doubleday M[1], Grottke O[2] and Ryn JV[3]

PO365-MON

Impact of dabigatran, rivaroxaban and apixaban treatment on hemostasis point-of-care testing in patients with atrial fibrillation

Paniccia R[1], Marcucci R[1], Priora R[2], Poli D[2], Ahmed Y[1], Fanciullacci C[1], Liotta AA[2] and Abbate R[1]

PO370-TUE

Comparing reversal effect of factor X concentrate and by-passing agents on rivaroxaban in an *ex vivo* spiking study with rotem

Drebes A and Riddell A

PO416-WED

Detecting relevant rivaroxaban or dabigatran levels in clinical care by routine coagulation tests or thromboelastography in patients with atrial fibrillation

Henskens Y[1], van Oerle R[2,3], Wetzels R[3], Spronk H[4], Schalla S[5], Crijns H[5], Cate HT[2,6] and Cate-Hoek AT[4,6]

Specific Tests

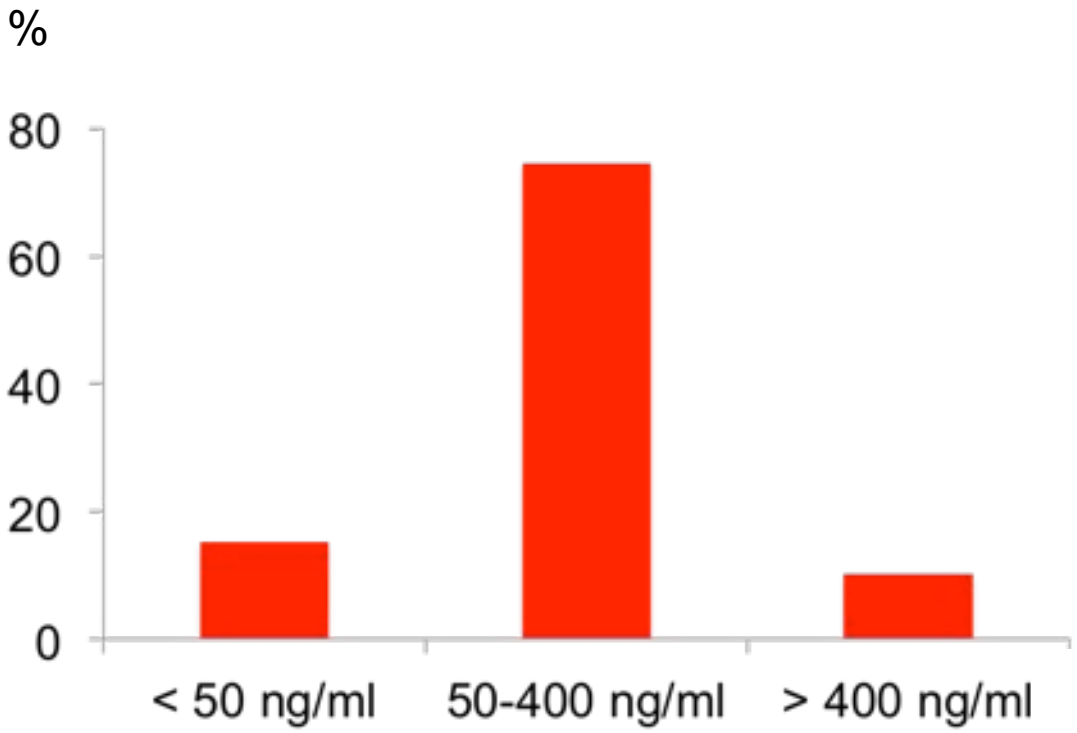
- **Rivaroxaban**
  - specific **anti-FXa activity**
  - PT and aPTT modified according to the reagent (PT more sensitive)

- **Apixaban**
  - specific **anti-FXa activity**
  - PT and aPTT not really prolonged

- **Dabigatran**
  - Ecarin clotting time, **Haemoclot** or anti-IIa
  - PT, aPTT and TT modified according to the reagent (aPTT more sensitive)

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

DOAC concentration determined in 42 % of the bleeding patients	
Dabigatran (n=54) median (range)	167 ng/ml (20-3500)
Rivaroxaban (n=100) median (range)	116 ng/ml (15-928)



GIHP Groupe d'intérêt en hémostase péri-opératoire

(unpublished data, May 2014. GIHP working group)

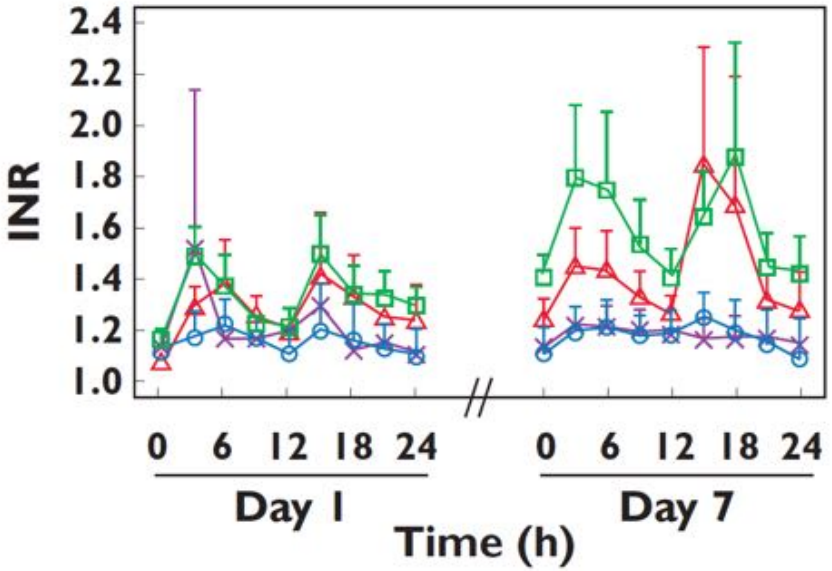
Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects

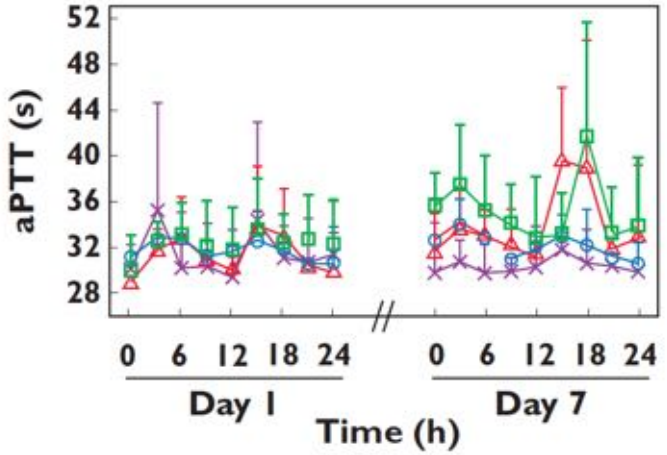
Charles Frost,[1] Sunil Nepal,[1] Jessie Wang,[1] Alan Schuster,[1] Wonkyung Byon,[2] Rebecca A. Boyd,[2] Zhigang Yu,[1] Andrew Shenker,[1*] Yu Chen Barrett,[1] Rogelio Mosqueda-Garcia[1†] & Frank LaCreta[1]

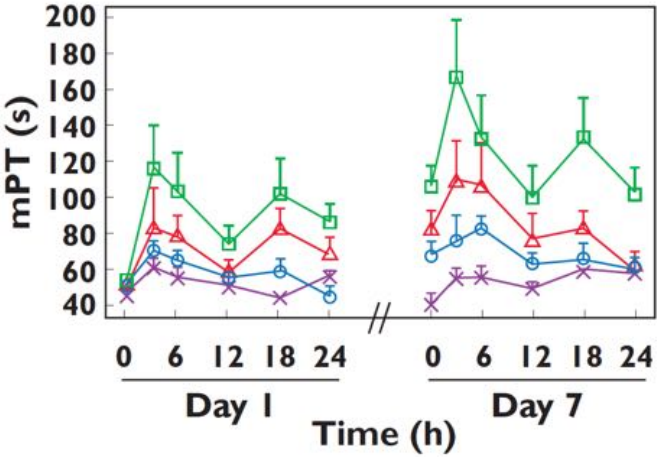
[1]Bristol-Myers Squibb, Princeton, NJ, USA and [2]Pfizer Inc, Groton, CT, USA

BJCP British Journal of Clinical Pharmacology

2013 ; 76:5 / 776–786







Mean international normalized ratio (INR), activated partial thromboplastin time (aPTT) and modified prothrombin time (mPT) values over time for day 1 to day 7. ×, 2.5 mg twice daily; ○, 5 mg twice daily; △, 10 mg twice daily; □, 25 mg twice daily; ▲, 10 mg once daily; ■, 20 mg once daily; ●, pooled placebo

Anaesthesist 2012
DOI 10.1007/s00101-012-2091-4
Received: 7 May 2012
Revised: 30 August 2012
Accepted: 7 September 2012
© Springer-Verlag Berlin Heidelberg 2012

M. Casutt · C. Konrad · G. Schuepfer
Department of Anaesthesiology and Intensive Care, Kantonsspital Lucerne, Lucerne 16

Effect of rivaroxaban on blood coagulation using the viscoelastic coagulation test ROTEM™

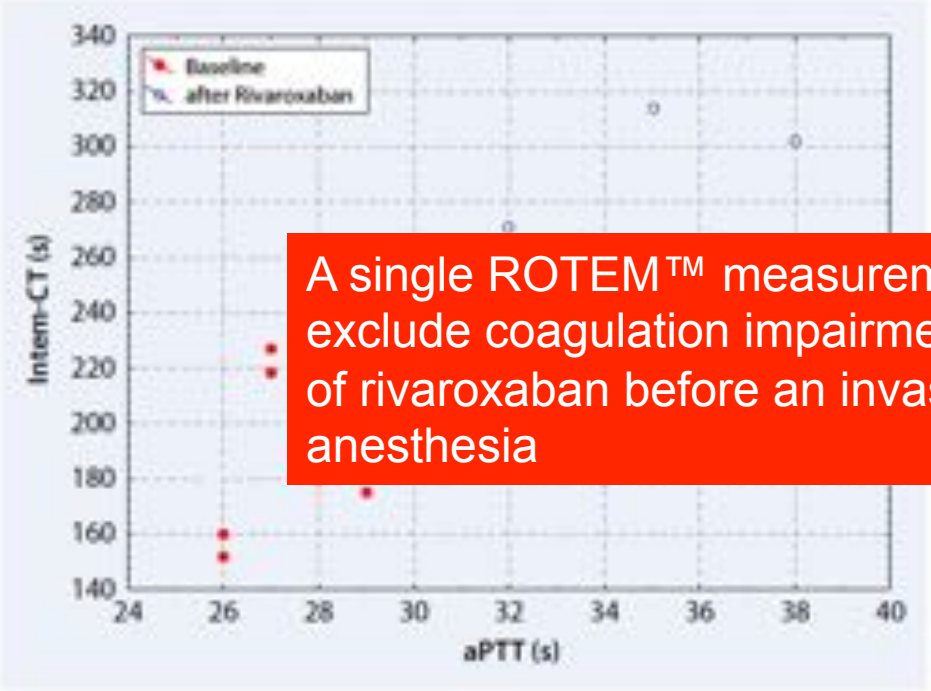


Fig. 1 ▲ Scatterplot of Intem-CT versus aPTT before (baseline) and 2.5 h after 10 mg rivaroxaban. Intem-CT before and after rivaroxaban: $p=0.02$; aPTT before and after Rivaroxaban: $p=0.01$. *aPTT* activated partial thromboplastin time, *CT* clotting time. There is an obvious difference of both clusters but the correlation of aPTT and Intem-CT are low in both pre-drug and post-drug groups. Using a cut off for aPTT (31 s) allows a perfect separation of pre-rivaroxaban and post-rivaroxaban values. In contrast, Intem-CT is not suitable for the differentiation of groups

A single ROTEM™ measurement is not sufficient to exclude coagulation impairment due to the administration of rivaroxaban before an invasive procedure or neuraxial anesthesia

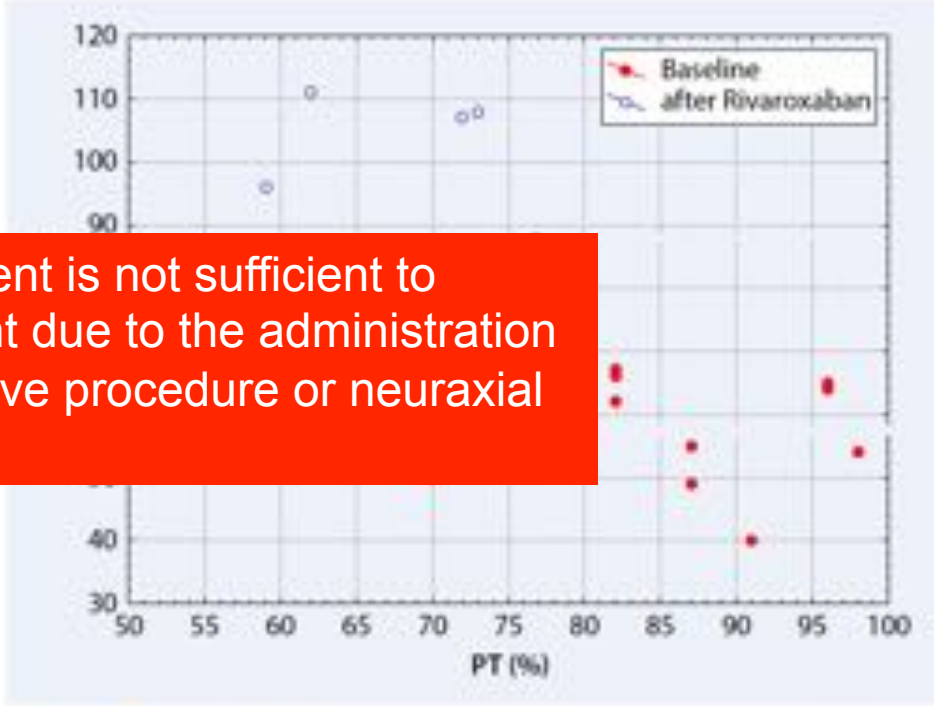


Fig. 2 ▲ Scatterplot of Extem-CT versus PT before (baseline) and 2.5 h after 10 mg rivaroxaban. Extem-CT before and after rivaroxaban: $p=0.01$; PT before and after Rivaroxaban: $p=0.01$. *CT* clotting time, *PT* Prothrombin time. There is an obvious difference of both clusters before but the correlation of PT and Extem-CT are low in both pre-drug and post-drug groups. There is no clear distinction between pre-rivaroxaban and post-rivaroxaban values and PT and Extem-CT are not suitable for the differentiation of groups

Thrombosis Research 134 (2014) 918–923

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journal homepage: www.elsevier.com/locate/thromres

Regular Article

Measuring the activity of apixaban and rivaroxaban with rotational thrombelastometry ☆

Dieter Adelmann [a], Marion Wiegele [a], Rudolf Karl Wohlgemuth [a], Stefan Koch [a], Sophie Frantal [b], Peter Quehenberger [c], Gisela Scharbert [a], Sibylle Kozek-Langenecker [d], Eva Schaden [a,*]

Conclusions: LowTF–ROTEM® could be a valuable diagnostic tool for rapid determination of the effect of apixaban and rivaroxaban at the point of care.

GIHP Groupe d'intérêt en hémostase péri-opératoire

Suggestions…

RECOMMANDATIONS PROFESSIONNELLES

Prise en charge des surdosages en antivitamines K, des situations à risque hémorragique et des accidents hémorragiques chez les patients traités par antivitamines K en ville et en milieu hospitalier

RECOMMANDATIONS

GEHT

HAS

Agence Française de Sécurité Sanitaire des Produits de Santé
Association Pédagogique Nationale des Enseignants de Thérapeutique
Groupe d'Etudes sur l'Hémostase et la Thrombose (demandeur et promoteur)
Collège National des Généralistes Enseignants
Société Française d'Anesthésie et Réanimation
Société Française de Cardiologie
Société Française de Chirurgie Thoracique et Cardiaque
Société Française d'Endoscopie Digestive
Société Française de Médecine Interne
Société Française de Médecine d'Urgence
Société Française de Médecine Vasculaire
Société Française de Rhumatologie
Société de Réanimation de Langue Française

HAS
HAUTE AUTORITÉ DE SANTÉ

CHIRURGIE ET ACTES INVASIFS

Actes responsables de saignements de faible intensité et aisément contrôlés, pouvant être réalisés sans interrompre les AVK

Conditions :

- INR compris entre 2 et 3, à contrôler avant le geste
- absence de risque médical associé (prise d'un autre médicament ou comorbidité interférant avec l'hémostase ou avec l'équilibre du traitement anticoagulant).

Actes :

- chirurgie cutanée
- chirurgie de la cataracte
- actes de rhumatologie à faible risque hémorragique*
- certains actes de chirurgie bucco-dentaire**
- certains actes d'endoscopie digestive***

(sites consultables : * www.rhumatologie.asso.fr ; ** www.societechirbuc.com ; *** www.sfed.org)

HAUTE AUTORITÉ DE SANTÉ

Actes programmés nécessitant l'interruption des AVK

(objectif : INR au moment de l'intervention < 1,5 ou < 1,2 si neurochirurgie)

■ ACFA sans antécédent embolique
■ MTEV à risque modéré

- Arrêt des AVK sans relais préopératoire par héparine.
- Reprise des AVK dans les 24 - 48 h ou, si elle n'est pas possible, héparine à dose curative si le risque hémorragique est contrôlé**.

■ Valves mécaniques (tout type)
■ ACFA avec antécédent embolique
■ MTEV à haut risque*

- Arrêt des AVK et relais préopératoire par héparine à dose curative.
- Reprise des AVK dans les 24 – 48 h ou, si elle n'est pas possible, héparine à dose curative si le risque hémorragique est contrôlé**.

* i.e. TVP proximale et/ou EP < 3 mois, MTEV récidivante idiopathique (n ≥ 2, au moins un accident sans facteur déclenchant). La mise en place d'un filtre cave en préopératoire est discutée au cas par cas.

** L'héparinothérapie à dose curative ne doit pas être reprise avant la 6e heure postopératoire. Si le traitement par héparine à dose curative n'est pas repris à la 6e heure, dans les situations où elle est indiquée, la prévention postopératoire précoce de la MTEV doit être réalisée selon les modalités habituelles.

(MTEV : maladie thrombo-embolique veineuse ; TVP : thrombose veineuse profonde ; EP : embolie pulmonaire ; ACFA : arythmie complète par fibrillation auriculaire)

Modalités du relais, si relais…

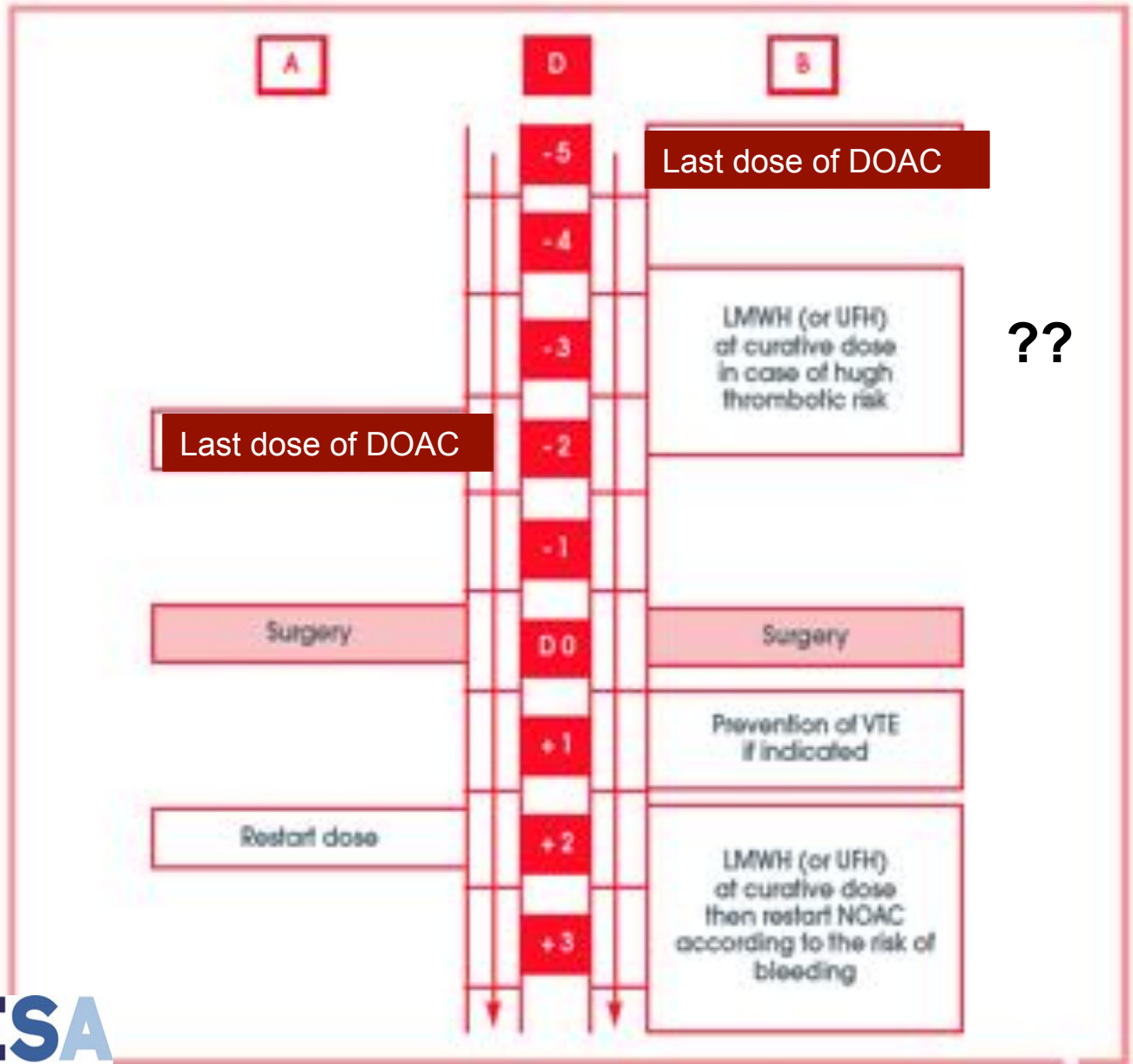
- J-5: dernière prise ~~fluindione, warfarine~~ **dabigatran, rivaroxaban, apixaban**
- J-4: pas d'héparine ni d'**ACO**
- J-3 première dose d'HBPM curatif ou d'HNF, 48h après dernière prise d'**ACO**
- J-2: HBPM X2 ou HNF sc X2 ou X3
- J-1: hospitalisation,
  - HBPM curatif matin J-1
  - HNF sc soir J-1
- **J0 : chirurgie**

  Il est souhaitable que les interventions aient lieu le matin.

[1] l'aspirine ne modifie pas le schéma

surgery or an invasive procedure with a low risk of bleeding

surgery or an invasive procedure with a **moderate** or **high risk of bleeding**



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European Society of Anaesthesiology ESA

GIHP Groupe d'intérêt en hémostase péri-opératoire

Annales Françaises d'Anesthésie et de Réanimation 30 (2011) 645–650

Disponible en ligne sur ScienceDirect www.sciencedirect.com

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Article spécial

Chirurgies et actes invasifs chez les patients traités au long cours par un anticoagulant oral anti-IIa ou anti-Xa direct
Propositions du Groupe d'intérêt en hémostase périopératoire (GIHP) et du Groupe d'études sur l'hémostase et la thrombose (GEHT)☆,☆☆

Surgery and invasive procedures in patients on long-term treatment with oral direct thrombin or factor Xa inhibitors

P. Sié [a], C.-M. Samama [b], A. Godier [b], N. Rosencher [c], A. Steib [d], J.-V. Llau [e], P. van der Linden [f], G. Pernod [g], T. Lecompte [h], I. Gouin-Thibault [i], P. Albaladejo [j]

[a] *Laboratoire d'hématologie, hôpital Rangueil, CHU de Toulouse, 1, avenue du Pr-Jean-Poulhès, TSA 50032, 31059 Toulouse cedex, France*
[b] *Service d'anesthésie-réanimation, Hôtel-Dieu, AP–HP, 1, place du Parvis-Notre-Dame, 75181 Paris cedex 04, France*
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[e] *Service d'anesthésie-réanimation, Valence, Espagne*
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[g] *Médecine vasculaire, CHU de Grenoble, BP 217, 38043 Grenoble cedex 09, France*
[h] *Laboratoire d'hématologie biologique, hôpital central, 29, avenue du Maréchal-de-Lattre-de-Tassigny, 54035 Nancy cedex, France*
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[j] *Pôle anesthésie-réanimation, CHU de Grenoble, BP 217, 38043 Grenoble cedex 09, France*

Archives of Cardiovascular Disease (2011) 104, 669–676

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GUIDELINES

Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis

EJA

Eur J Anaesthesiol 2013; **30:**

GUIDELINES

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Sibylle A. Kozek-Langenecker, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa Alvarez Santullano, Edoardo De Robertis, Daniela C. Filipescu, Dietmar Fries, Klaus Görlinger, Thorsten Haas, Georgina Imberger, Matthias Jacob, Marcus Lancé, Juan Llau, Sue Mallett, Jens Meier, Niels Rahe-Meyer, Charles Marc Samama, Andrew Smith, Cristina Solomon, Philippe Van der Linden, Anne Juul Wikkelsø, Patrick Wouters and Piet Wyffels

Table 3 Comparison of new oral antithrombotic agents

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran Etexilate
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Brand name	Xarelto	Eliquis	Lixiana	Pradaxa
Route of administration	Oral	Oral	Oral	Oral
Bioavailability	80%	51–85%	60%	6–8%
T_{max}	2–4 h	3 h	1–3 h	2 h
Half-life	9–13 h	9–14 h	5–11 h	14–17 h
Frequency of administration	Once-daily	Twice-daily	Once-daily	Once- or twice-daily
Renal excretion	66% (half inactive)	25%	36–45%	80%
Antidote	No	No	No	No

Management of Antithrombotic Therapy in Patients Undergoing Invasive Procedures

N Engl J Med 2013;368:2113-24.

Todd H. Baron, M.D., Patrick S. Kamath, M.D., and Robert D. McBane, M.D.

Dabigatran (Pradaxa, Boehringer Ingelheim)	Oral	Direct thrombin inhibitor	1 or 2 days with creatinine clearance rate of ≥50 ml/min; 3–5 days with creatinine clearance rate of <50 ml/min
Rivaroxaban (Xarelto, Bayer HealthCare)	Oral	Direct factor Xa inhibitor	≥1 day when renal function is normal; 2 days with creatinine clearance rate of 60–90 ml/min; 3 days with creatinine clearance rate of 30–59 ml/min; and 4 days with creatinine clearance rate of 15–29 ml/min[52]
Apixaban (Eliquis, Bristol-Myers Squibb)	Oral	Direct factor Xa inhibitor	1 or 2 days with creatinine clearance rate of >60 ml/min; 3 days with creatinine clearance rate of 50–59 ml/min; and 5 days with creatinine clearance rate of <30–49 ml/min

The recommended durations are taken from package inserts, if the information is provided, or are derived from guidelines and drug pharmacokinetics**. However, because of the lack of available reversal agents, we prefer to take a more conservative approach, withholding these agents for slightly longer periods than those based on package inserts, guidelines, or pharmacokinetic data (i.e., 1 to 2 days longer than the specifications outlined in the table).**

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

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 (19/1,032)	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 (5/417)	2.11 (0.75–5.95)
	Not bridged	0.3 (3/1,032)	P = 0.007	0.6 (15/2,274)	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. ¥exclusion of 27 patients with missing creatinine clearance values did not significantly affect clinical outcome results in bridged and not bridged patients.

Outcomes of Temporary Interruption of Rivaroxaban Compared with Warfarin in Patients with Nonvalvular Atrial Fibrillation: Results from ROCKET AF

Matthew W. Sherwood, MD[1]; James D. Douketis, MD[2]; Manesh R. Patel, MD[1]; Jonathan P. Piccini, MD, MHS[1]; Anne S. Hellkamp, MS[1]; Yuliya Lokhnygina, PhD[1]; Alex C. Spyropoulos, MD[3]; Graeme J. Hankey, MD[4]; Daniel E. Singer, MD[5]; Christopher C. Nessel, MD[6]; Kenneth W. Mahaffey, MD[7]; Keith A. A. Fox, MB, ChB[8]; Robert M. Califf, MD[1]; Richard C. Becker, MD[1]
on behalf of the ROCKET AF Investigators

Risk of major bleeding during the at-risk period was similar in rivaroxaban-treated and warfarin-treated participants (0.99% vs. 0.79% per 30 days; HR(CI) = 1.26 (0.80, 2.00), P=0.32

Stroke/SE rates during TIs with bridging compared with those without bridging were not different.

Rates of major bleeding were similar between bridged and non-bridged TIs, while rates of major/non major clinically relevant bleeding appeared numerically higher in patients receiving bridging therapy (4.83% vs. 3.02%).

Table 7. Outcomes during TIs with and without bridging therapy

Events	Bridging therapy (N=483 TIs)		No bridging therapy (N=7072 TIs)	
	Number of events	Event rate per 30 days	Number of events	Event rate per 30 days
Stroke/Systemic Embolism	1	0.17%	31	0.37%
Death	2	0.33%	14	0.17%
MI	4	0.69%	25	0.30%
Stroke/SE/MI/Death	5	0.86%	67	0.82%
Major/NMCR Bleeding	22	4.83%	184	3.02%
Major Bleeding	5	0.91%	69	0.88%

MI = Myocardial Infarction; SE = Systemic embolism; NMCR = Non-major clinically relevant; Stroke/SE/MI/Death as a composite does not include multiple events in the same patient

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]

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).

GIHP Groupe d'intérêt en hémostase péri-opératoire

Suggestions…deux ans plus tard

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

<table>
<tr><th>GIHP Groupe d'intérêt en hémostase péri-opératoire</th><th colspan="3">Low bleeding risk</th><th colspan="3">Moderate and high bleeding risk</th></tr>
<tr><td rowspan="3">Before</td><td colspan="3" rowspan="2">No oral intake the day before,
or the morning of the procedure</td><td>rivaroxaban
apixaban
edoxaban</td><td>Cockcroft
≥ 30 ml/mn</td><td>Last intake at D-3</td></tr>
<tr><td rowspan="2">dabigatran</td><td>Cockcroft
≥ 50 ml/mn</td><td>Last intake at D-4</td></tr>
<tr><td colspan="3">No bridging
No biology</td><td>Cockcroft
30-49 ml/mn</td><td>Last intake at D-5</td></tr>
<tr><td>After</td><td colspan="3">Restart oral intake at least 6 hours after the end of the procedure</td><td colspan="3">Anticoagulant: « prophylactic dose »
At least 6 hours after the procedure, if venous thromboembolism prophylaxis is required</td></tr>
<tr><td colspan="3"></td><td colspan="3">Anticoagulant: « therapeutic dose »
when surgical haemostasis is completed
(between 24 and 72 hours)</td></tr>
</table>

Emergent cases or bleeding?

Procédures en urgence ou hémorragies ?

Denise, 88 y.o.

- **Atrial Fibrillation treated with dabigatran 110mg b.i.d.**
- Hypertension
- Transient Ischemic Attack 2 years ago
- Asymptomatic Angina
- Normal liver function. Creatinine clearance 40ml/min
- Aspirin, Simvastatin, Verapamil
- CHA_2DS_2-VASC score: 6 (Hypertension, Age>75, TIA, woman) – thrombotic risk=9.8%/year

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

RECOMMENDATIONS AND GUIDELINES

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

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

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

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

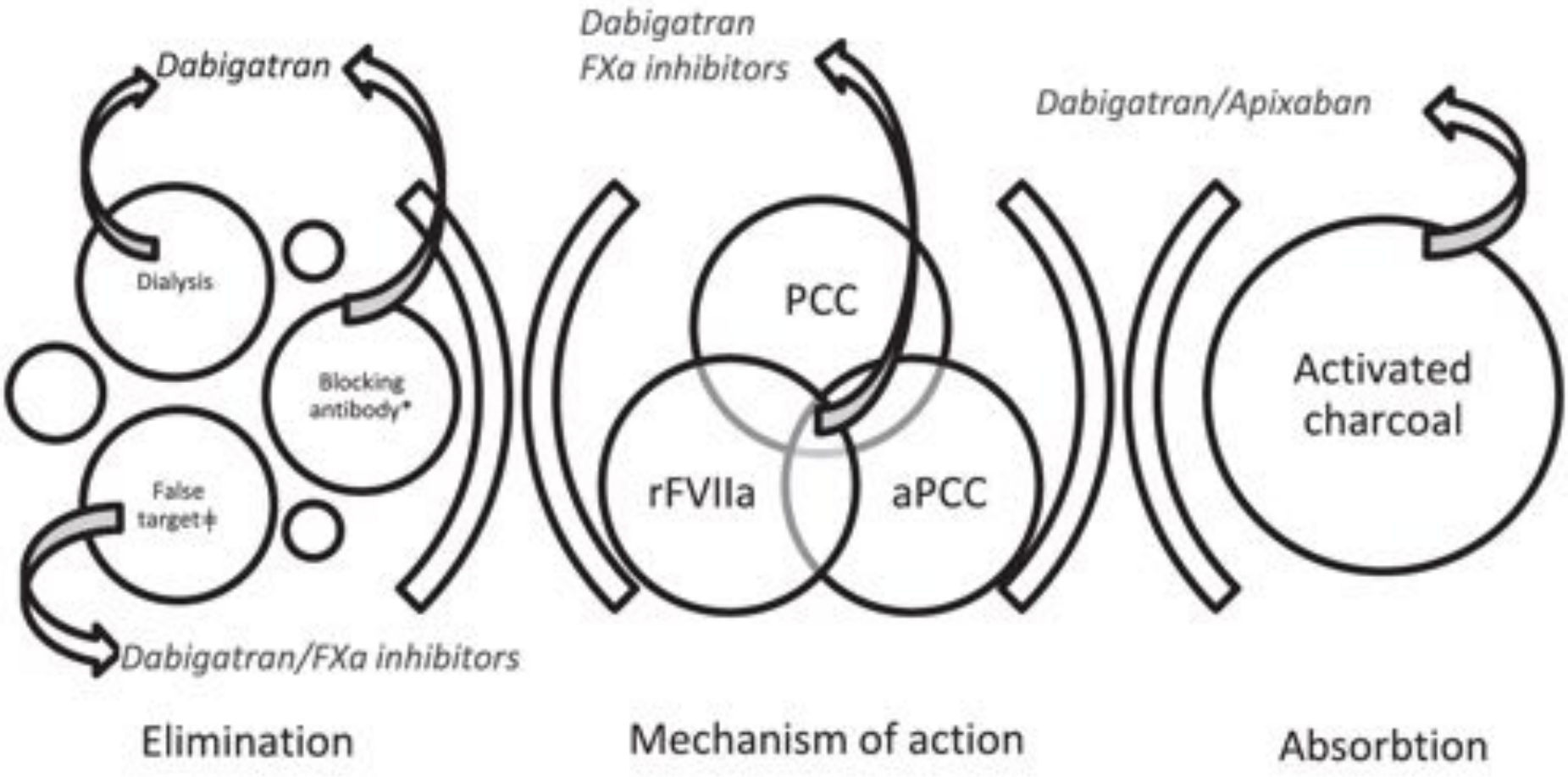
Indications for use	• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage • Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome • 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

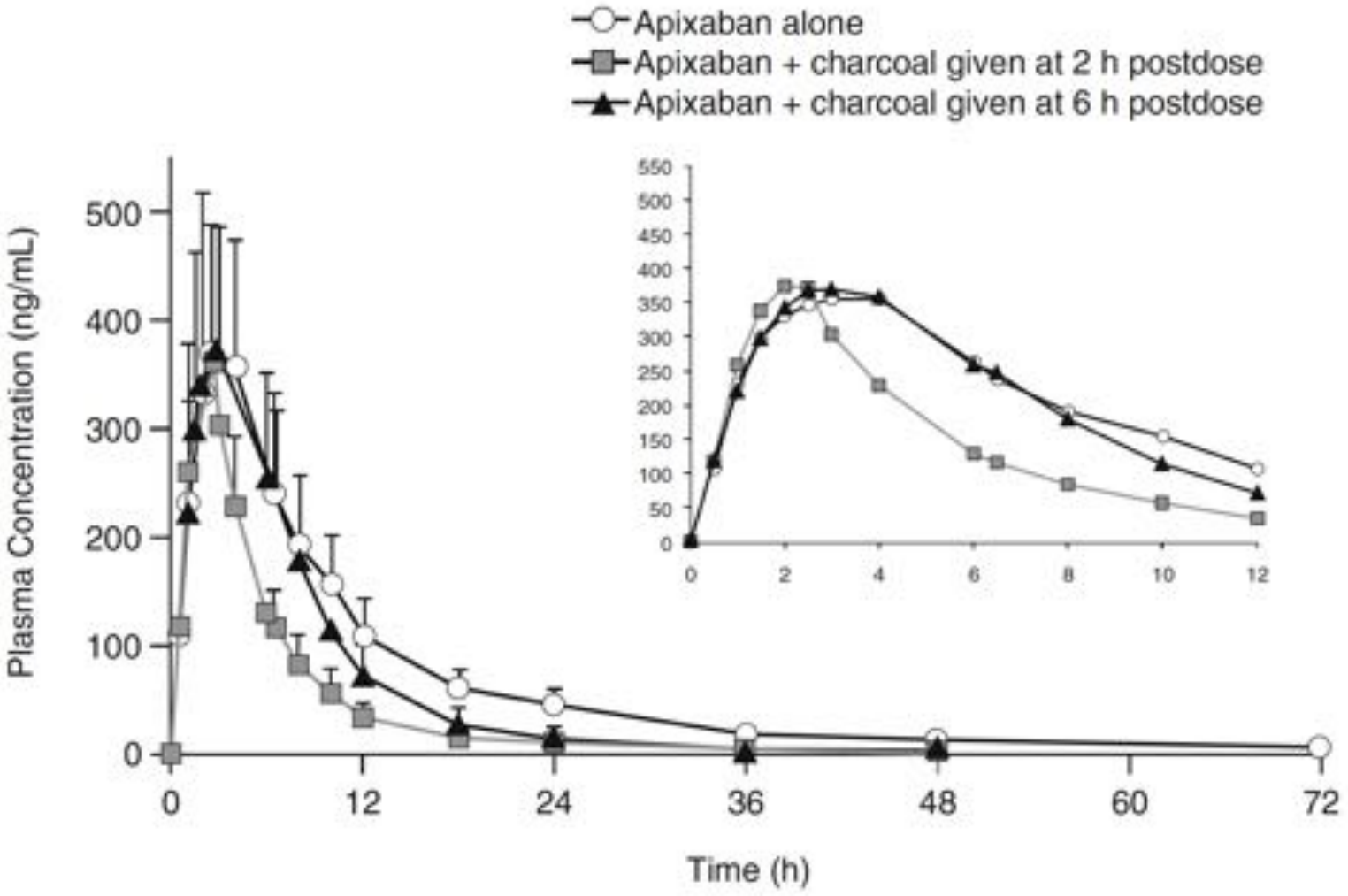


Non-specific « reversal » agents

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

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

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.

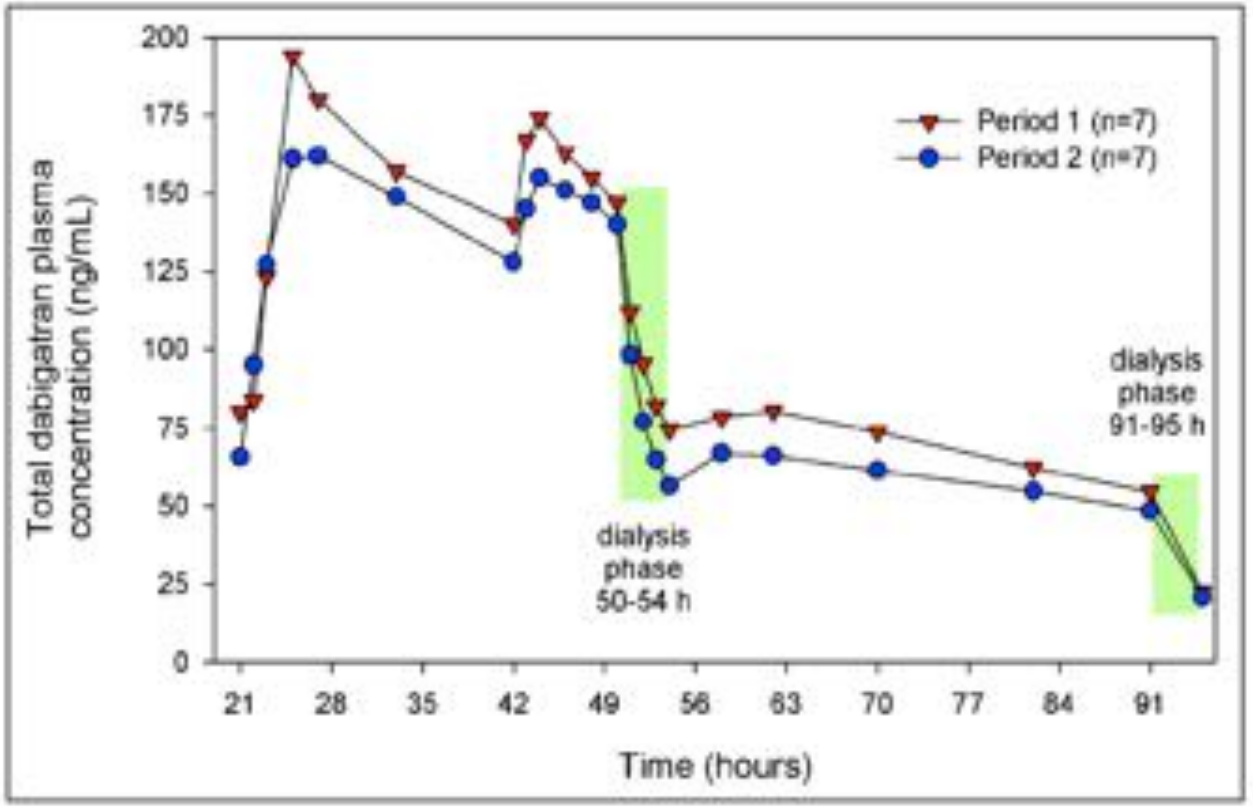


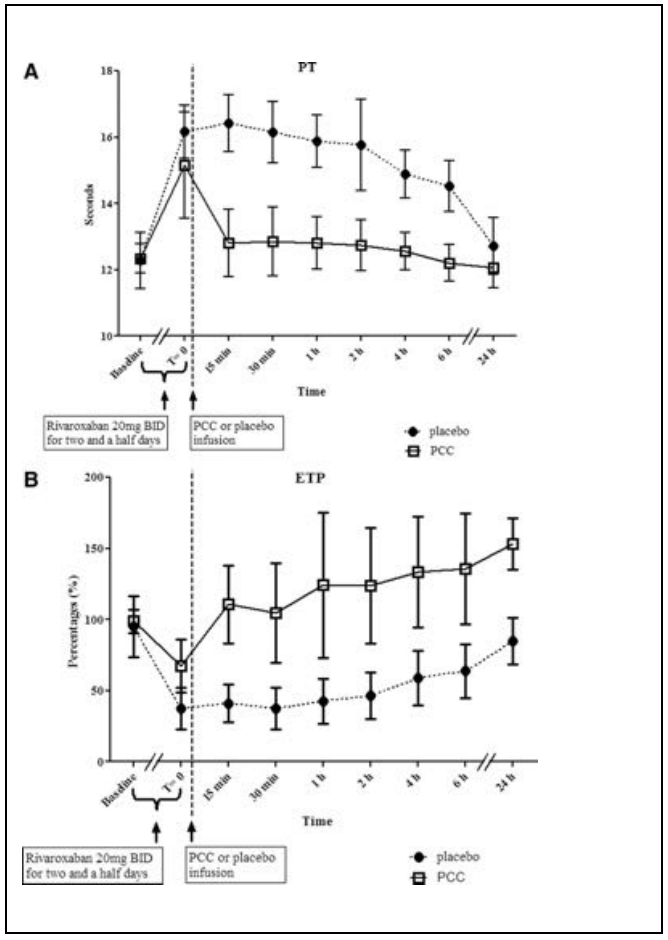
Figure 2: Geometrical mean plasma concentration-time profiles of total dabigatran in both treatment periods. Dabigatran was administered at 0, 21 and 42 h after the first dose; dialysis was performed from 50 to 54 and 91 to 95 h.

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

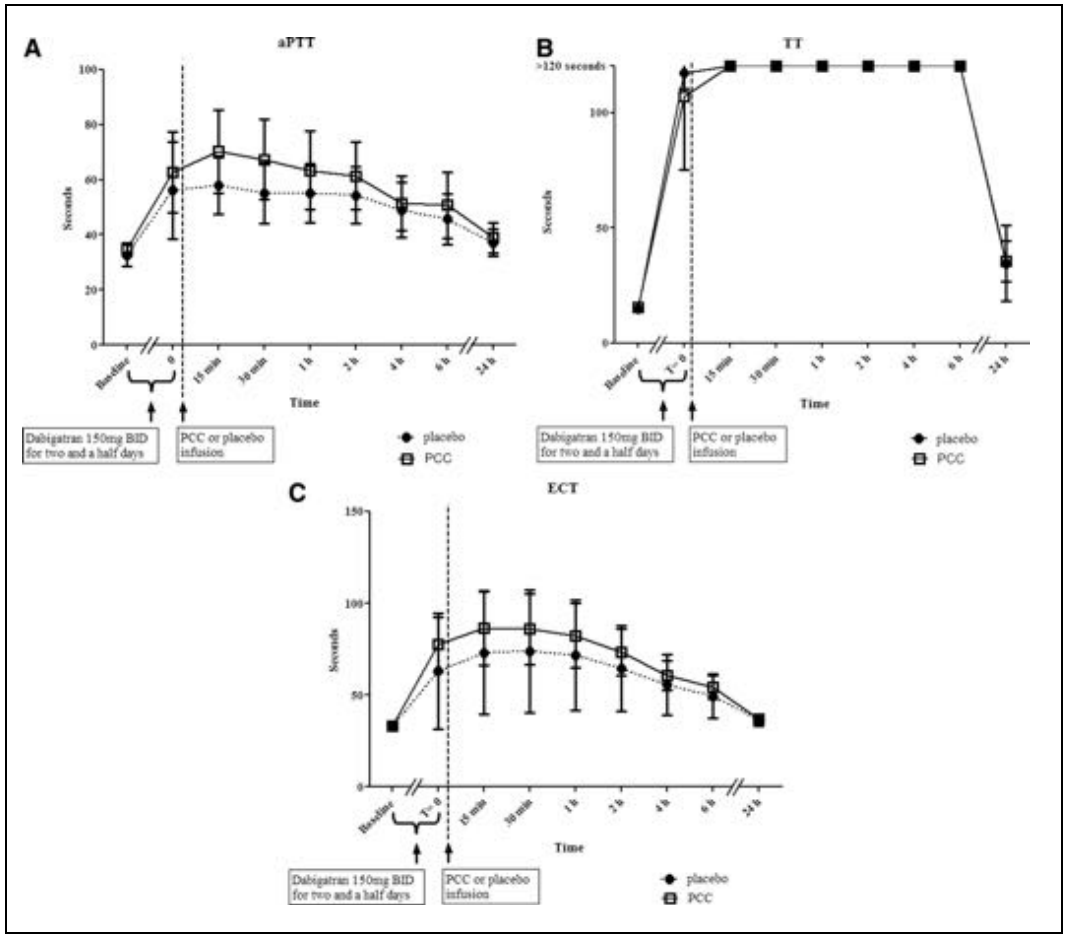
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

PCC 50 UI/kg

Rivaroxaban (20 mg bid)



Dabigatran (150 mg bid)



Circulation 2011; 124: 1573-1579

In vivo reversal of the anticoagulant effect of rivaroxaban with four-factor prothrombin complex concentrate

Stefano Barco,[1,2,*] Y. Whitney Cheung,[1,*] Michiel Coppens,[1] Barbara A. Hutten,[3] Joost C. M. Meijers[4,5] and Saskia Middeldorp[1]

British Journal of Haematology, 2016, **172,** 255–261

Double-blind, crossover, placebo-controlled study, comparing PCC 37.5 IU/kg, PCC 25IU/kg, and placebo on thrombin generation and prothrombin time in 6 healthy subjects receiving twice-daily rivaroxaban 15 mg for 2.5 days.

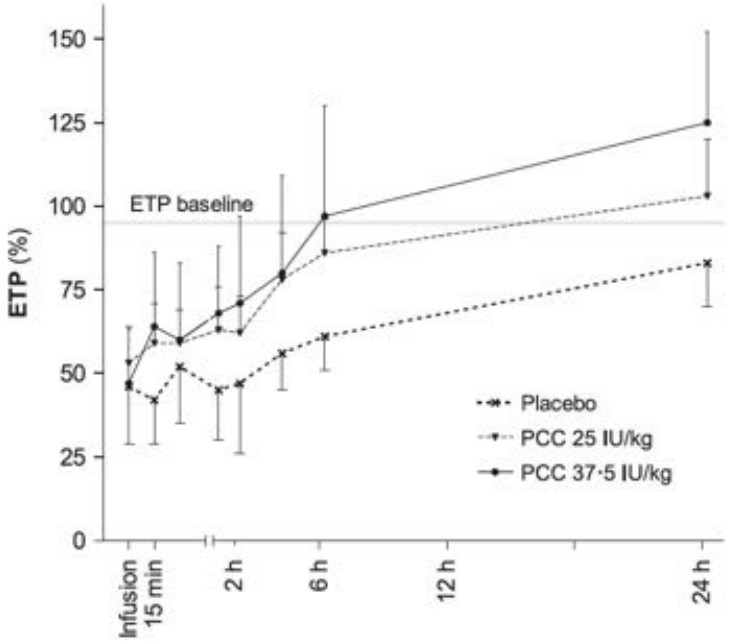


Fig 2. Effect of rivaroxaban followed by two dosages of four-factor PCC or placebo on the ETP (%). Immediate effect outcome: differences between $T = 0$ min (pre-PCC) and $T = 15$ min. PCC, prothrombin complex concentrate; ETP, endogenous thrombin potential. ETP baseline (pre-rivaroxaban ETP): mean ETP value before rivaroxaban administration.

PCC 37.5 iu/kg may be insufficient for immediate full reversal of peak therapeutic rivaroxaban levels.

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**

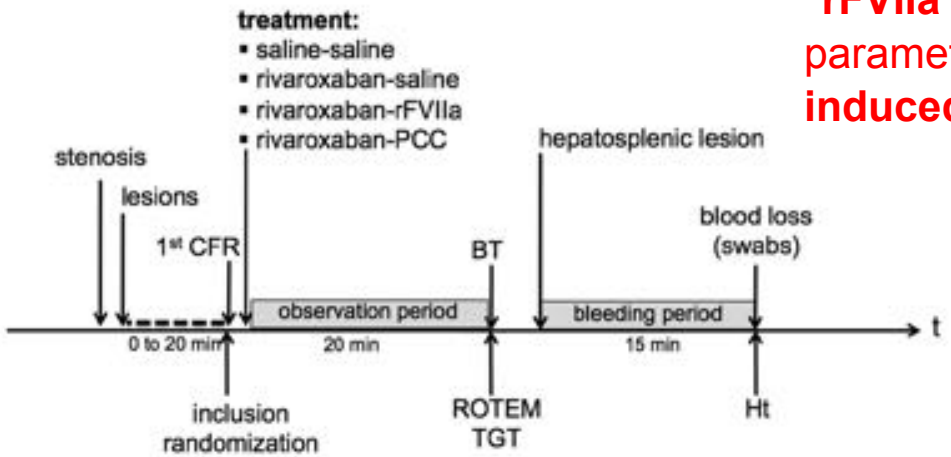


Fig. 1. Protocol design. BT = bleeding time; CFR = cyclic flow reductions; Ht = hematocrit; PCC = prothrombin complex concentrate; rFVIIa = recombinant activated factor VII; TGT = thrombin generation test.

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
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.

Four-factor prothrombin complex concentrate reverses apixaban-associated bleeding in a rabbit model of acute hemorrhage

J Thromb Haemost 2015; **13**: 2220–6.

E. HERZOG, F. KASPEREIT, W. KREGE, J. MUELLER-COHRS, B. DOERR, P. NIEBL and G. DICKNEITE

Research, CSL Behring GmbH, Marburg, Germany

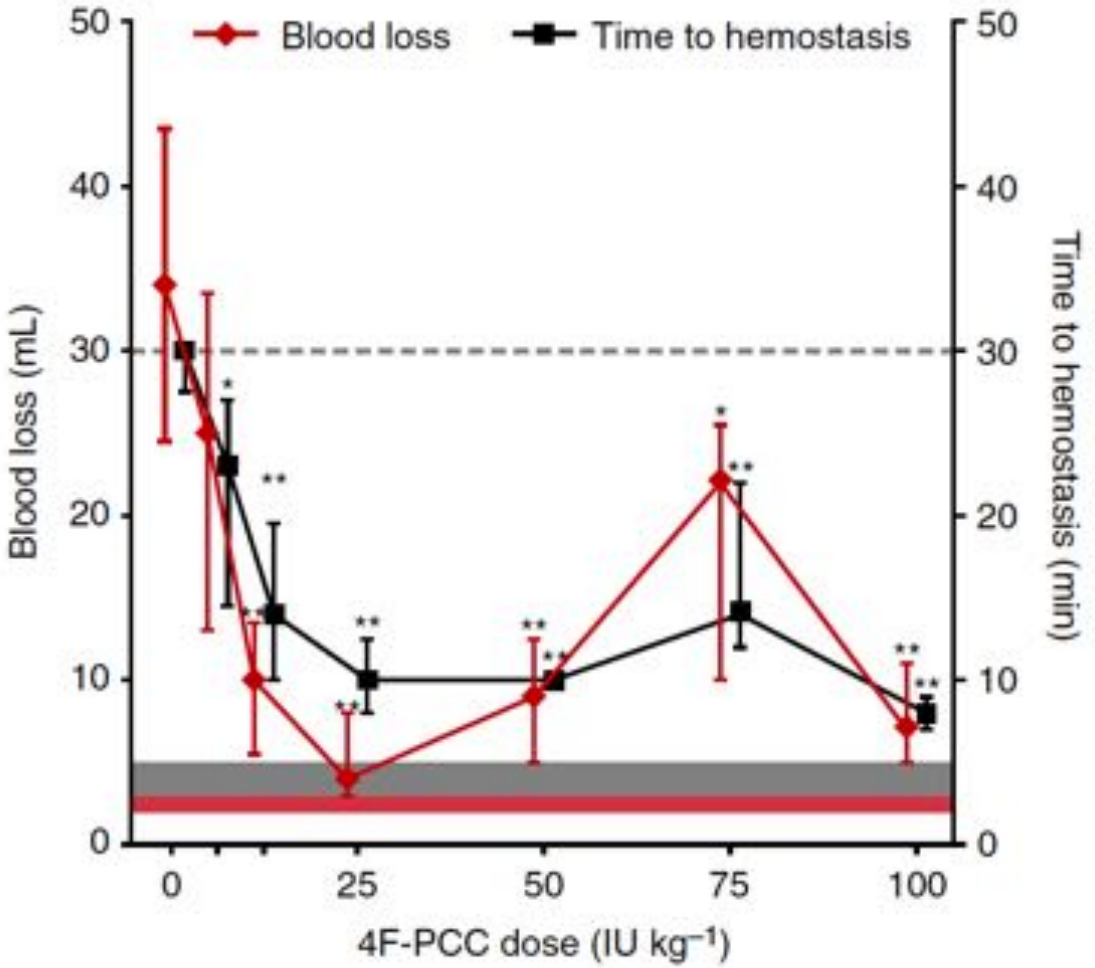


Fig. 2. Reversal of apixaban (1200 μg kg^{-1}) effects on time to hemostasis and blood loss with 4F-PCC. Data are median ± IQR.

Journal of Thrombosis and Haemostasis, 10: 1830–1840 DOI: 10.1111/j.1538-7836.2012.04863.x

ORIGINAL ARTICLE

Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate

M. D. LAMBOURNE,* L. J. ELTRINGHAM-SMITH,† S. GATAIANCE,† D. M. ARNOLD,*‡ M. A. CROWTHER‡ and W. P. SHEFFIELD*†

*Canadian Blood Services, Research and Development; †Department of Pathology and Molecular Medicine; and ‡Department of Medicine, McMaster University, Hamilton, Ontario, Canada

To cite this article: Lambourne MD, Eltringham-Smith LJ, Gataiance S, Arnold DM, Crowther MA, Sheffield WP. Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate. *J Thromb Haemost* 2012; 10: 1830–40.

Summary. *Background:* Both established oral anticoagulants such as warfarin and newer agents such as dabigatran etexilate (DE) effectively prevent thromboembolic disease, but may provoke bleeding. Limited clinical data exist linking oral anticoagulant reversal and bleeding tendency, as opposed to surrogate laboratory markers. *Objective:* To quantify bleeding in warfarin-anticoagulated and DE-anticoagulated mice by tail transection with or without pretreatment with potential reversal agents: prothrombin complex concentrate (PCC); activated PCC (APCC); recombinant factor VIIa (rFVIIa); or murine fresh-frozen plasma (FFP). *Methods:* CD1 mice were given warfarin or DE by gavage, and the effects on *in vitro* coagulation assays, volume of blood loss and the bleeding time following tail transection injury were evaluated with different reversal agents. *Results:* PCC (14.3 IU kg^{-1}), but not rFVIIa

Keywords: bleeding, dabigatran etexilate, fresh-frozen plasma (FFP), prothrombin complex concentrates (PCCs), warfarin.

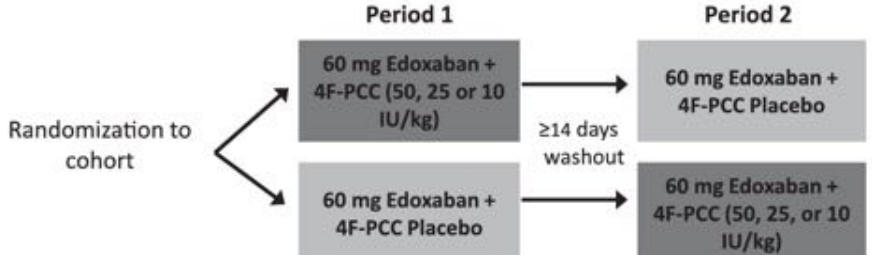
Introduction

Patients at risk for thromboembolic events, such as those with atrial fibrillation, prosthetic heart valves, and a history of deep vein thrombosis, have been effectively treated with oral anticoagulation therapy (OAT) for many years [1–4]. Until recently, OAT has relied on vitamin K antagonists (VKAs) such as warfarin, phenprocoumon, or acenocoumarol, which reduce the activities of the vitamin K-dependent coagulation factors II, VII, IX and X by interfering with γ-carboxylation, an obligatory post-translational modification of these factors [5,6]. VKA treatment requires dose adjustment and laboratory

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

Circulation. 2015;131:82-90



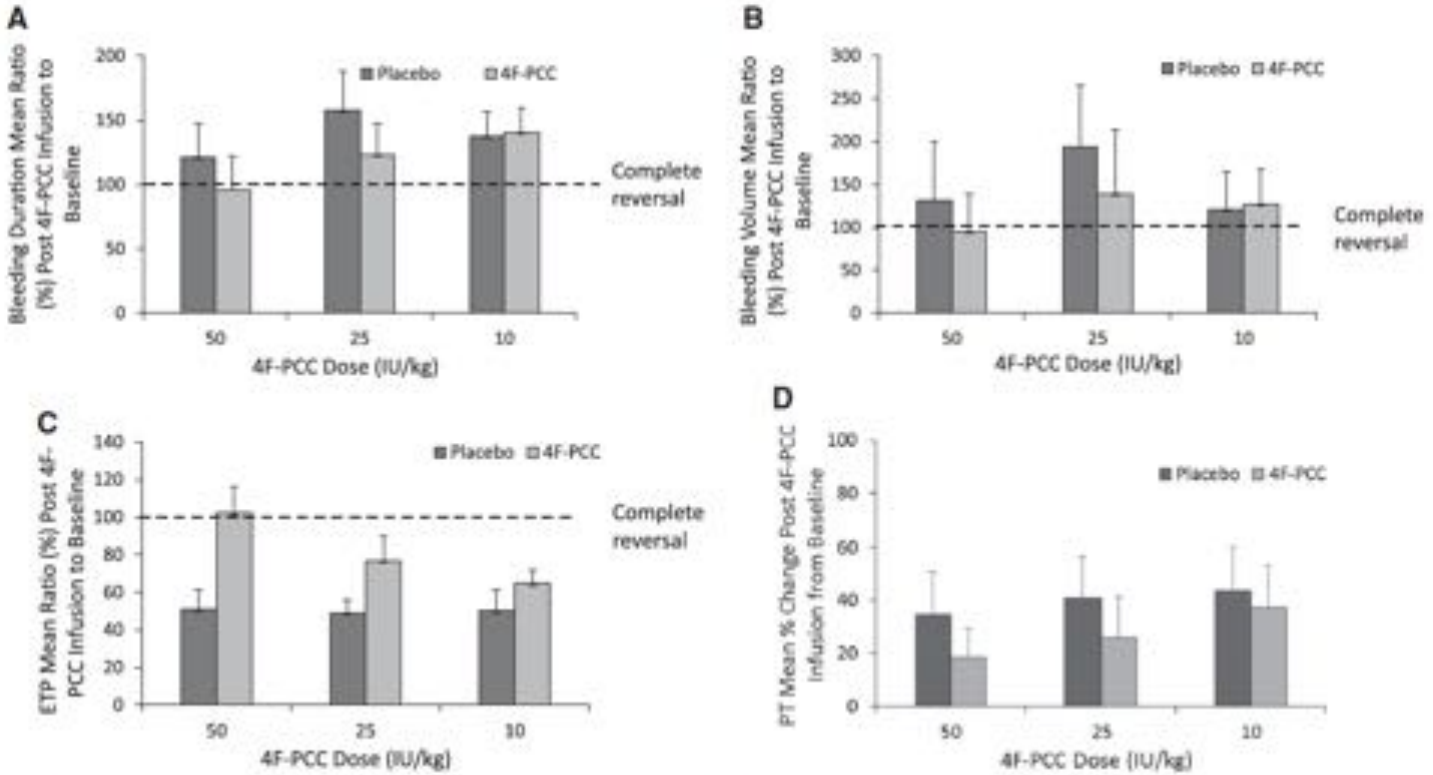


Figure 3. Effect of treatment with 4F-PCC or placebo on the mean ratio post–4F-PCC infusion to baseline from bleeding duration (minutes) (**A**), baseline bleeding volume (mL) (**B**), ETP (nM×min) (**C**), and for mean percent change in PT (seconds) (**D**). Error bars represent upper limit of the 95% CI. CI indicates confidence interval; ETP, endogenous thrombin potential; 4F-PCC, 4-factor prothrombin complex concentrate; and PT, prothrombin time.

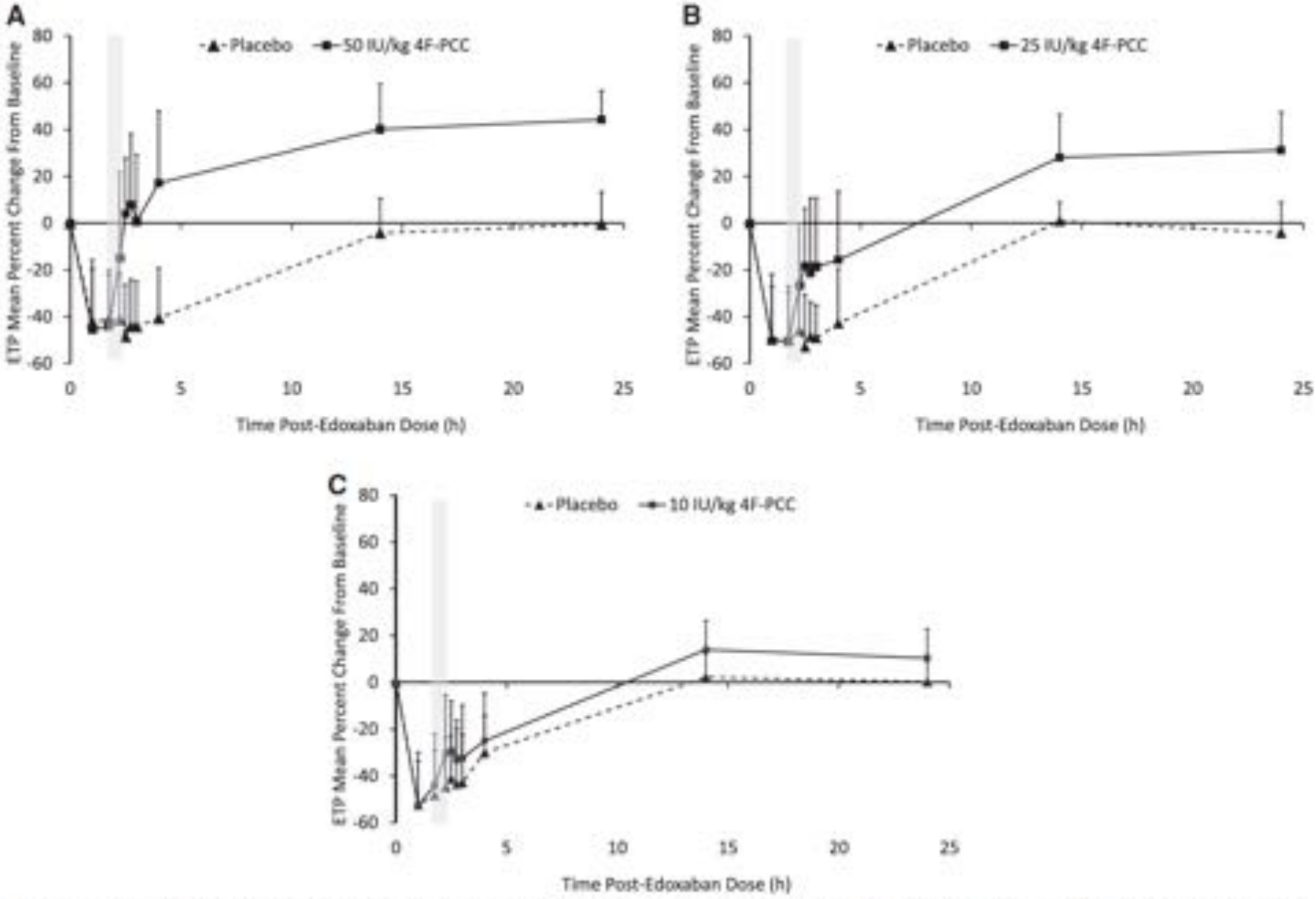


Figure 4. Time course of ETP on mean percent change from baseline for treatment with 50 IU/kg (**A**), 25 IU/kg (**B**), or 10 IU/kg 4F-PCC or placebo (**C**). Error bars represent standard deviation. Shaded bar indicates 4F-PCC infusion. ETP indicates endogenous thrombin potential; and 4F-PCC, 4-factor prothrombin complex concentrate.

Journal of Thrombosis and Haemostasis, **10**: 1841–1848 DOI: 10.1111/j.153

ORIGINAL ARTICLE

Reversal of dabigatran anticoagulation by prothrombin concentrate (Beriplex P/N) in a rabbit model

I. PRAGST,* S. H. ZEITLER,* B. DOERR,* F. J. KASPEREIT,* E. HERZOG,* G. DICKNEITE and J. VAN RYN†
*CSL Behring GmbH, Marburg; and †Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany

Anesthetized rabbits were treated with 0.4 mg/kg dabigatran followed by PCC doses of 20, 35 or 50 IU.kg^{-1} or placebo. After a standardized kidney incision, volume of blood loss and time to hemostasis were determined.

From an initial mean of 29 mL, blood loss progressively declined by 5.44 mL with a 95% confidence interval (CI) of 2.21–8.67 mL per 10 IU/kg increment in PCC dose (P = 0.002).

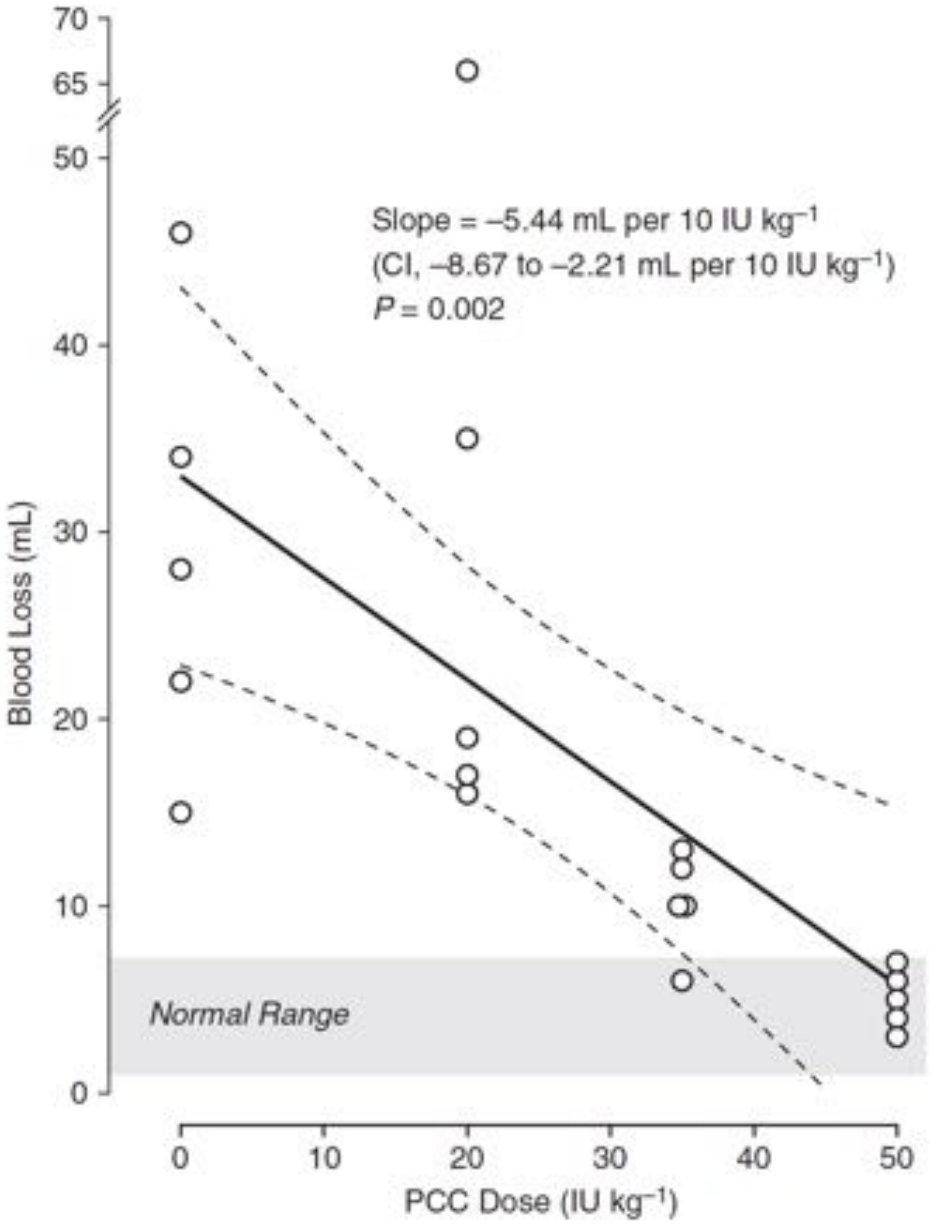


Fig. 4. Blood loss after kidney incision in dabigatran-treated rabbits receiving PCC doses in the range of 0–50 IU kg^{-1}. Graphic conventions as in Fig. 3. CI, 95% confidence interval; PCC, prothrombin complex concentrate.

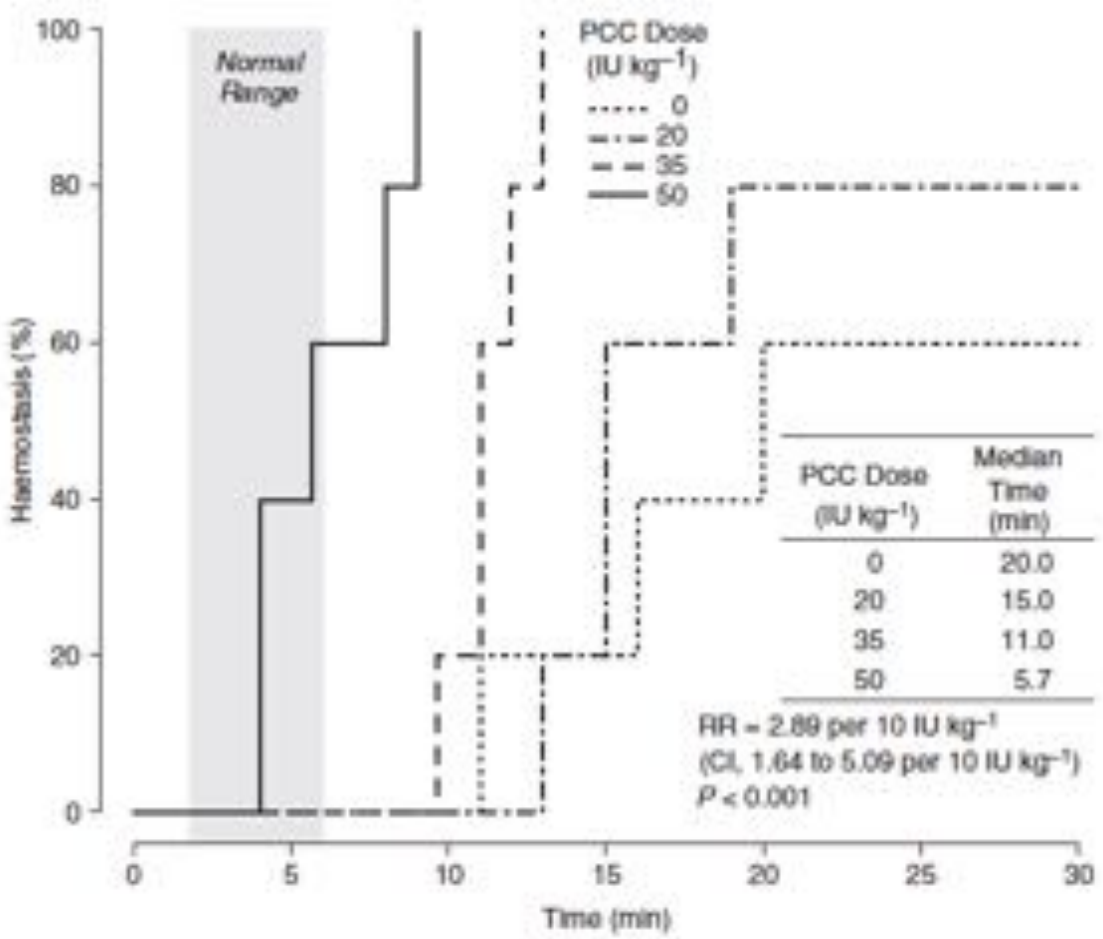


Fig. 5. Time to hemostasis after kidney incision in dabigatran-treated rabbits receiving 0–50 IU kg^{-1} PCC. Normal range spans the minimum and maximum measured times to hemostasis in the negative control group. RR for hemostasis computed by Cox regression. CI, 95% confidence interval; PCC, prothrombin complex concentrate; RR, rate ratio.

At a PCC dose of 50 IU/kg blood loss was fully normalized.

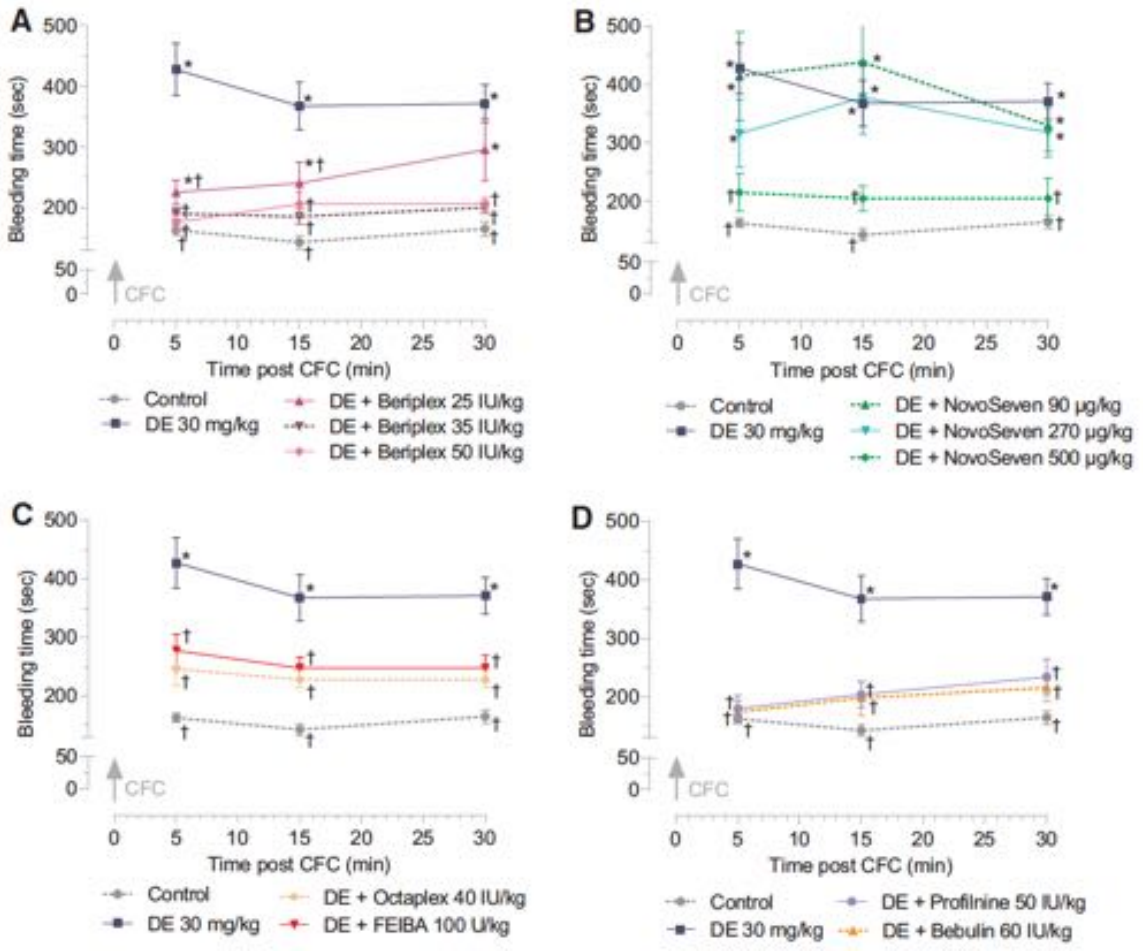
Increasing PCC doses shortened the median time to hemostasis from 20.0 to 5.7 min (P < 0.001).

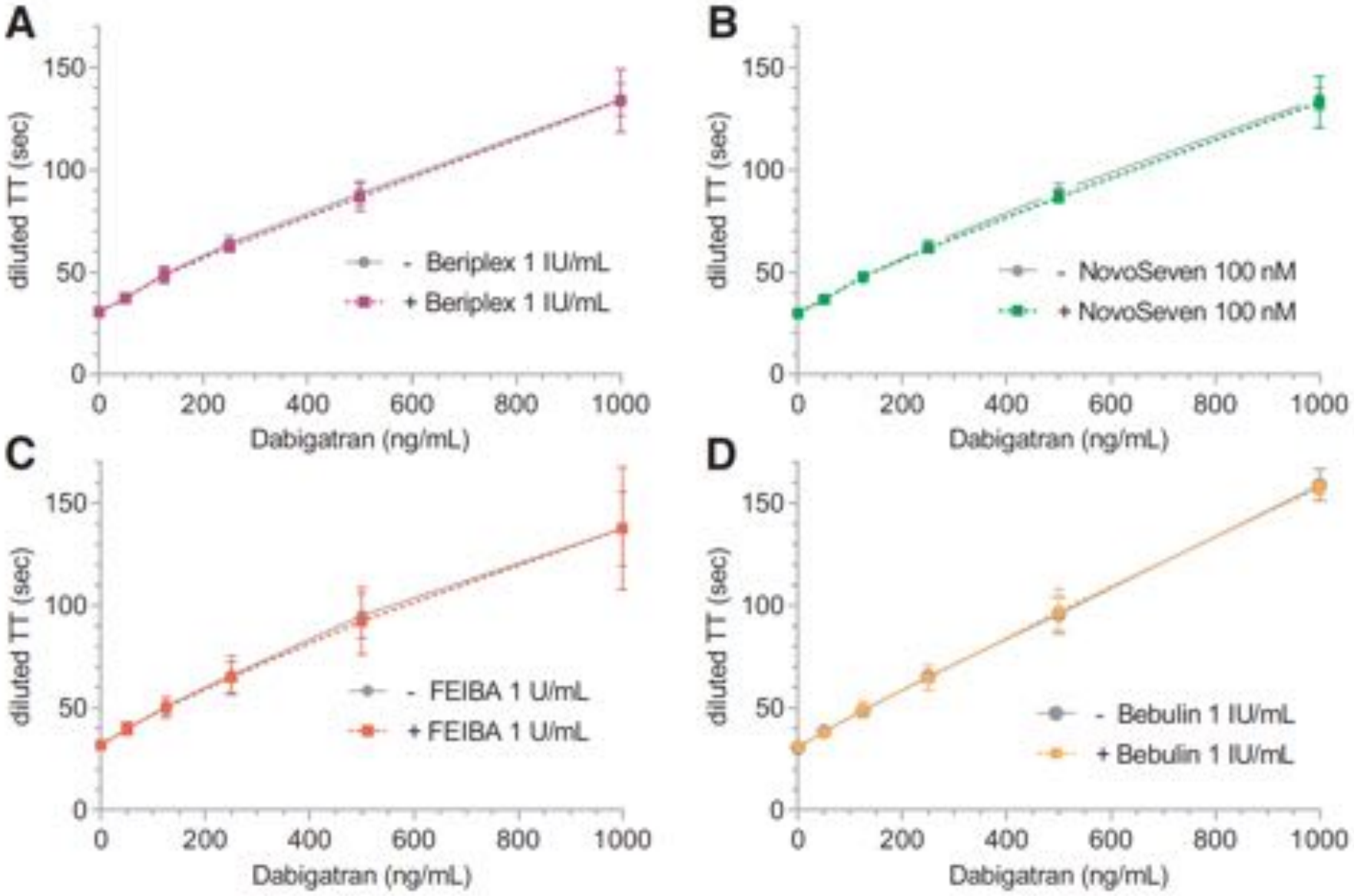
Reversal of Dabigatran-induced Bleeding by Coagulation Factor Concentrates in a Rat-tail Bleeding Model and Lack of Effect on Assays of Coagulation

ANESTHESIOLOGY 2014; 120:1429-40

Joanne van Ryn, Ph.D., Johanna Schurer, Monika Kink-Eiband, Andreas Clemens, M.D.

6 coagulation factor concentrates (CFCs) - **oral dabigatran etexilate (30 mg/kg)** - **Rat-tail bleeding model**: 3-factor (Profilnine, Bebulin) and 4-factor prothrombin complex concentrates (Beriplex, Octaplex), activated prothrombin complex concentrate (Factor Eight Inhibitor Bypassing Activity), and recombinant factor VIIa (NovoSeven).

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Dabigatran (ng/mL)
- Bebulin 1 IU/mL
+ Bebulin 1 IU/mL

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%).

haematologica 2013; 98:e143

M Quintana Díaz (1,2), AM Borobia (1,3), MA Rivera Núñez (1), AM Martínez Virto (1), S Fabra (1), JA García-Erce (4), CM Samama (5)

Use of prothrombin complex concentrates for urgent reversal of dabigatran in the Emergency Department

Table 1. Demographic and clinical characteristics, bleeding complications.

ID	Age (years)	Gender	Weight (kg)	HAS-BLED Score	Creatinine clearance (mL/min)	Bleeding complications	Hours from last dose to admission	PCC Dose (IU)	Dose/ weight (IU/kg)	Vitamin K	RBC (N. of units)	Time from admission to bleeding cessation	Death
1	83	Male	57	3	36.5	rectal bleeding	1.5	1000	17	No	No	<6 hours	No
2	82	Male	67	3	73.3	melena	1	1000	15	Yes	Yes (2)	–	No
3	88	Male	51	5	53.7	rectal bleeding	1.1	1000	20	No	Yes (2)	<12 hours	Yes
4	76	Male	54	5	113	rectal bleeding	2	1000	19	No	Yes (1)	<12 hours	No
5	82	Female	60	4	35.5	rectal bleeding	2	1500	25	No	No	<6 hours	No

RBC: red blood cell transfusion.

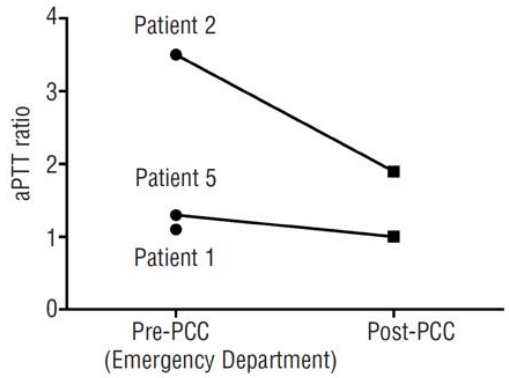


Figure 1. Coagulation tests before and after the bleeding episode. Activated partial thromboplastin (aPTT) ratio at the emergency department during the bleeding episode (before PCC administration) and after the treatment of the hemorrhage (post-PCC administration).

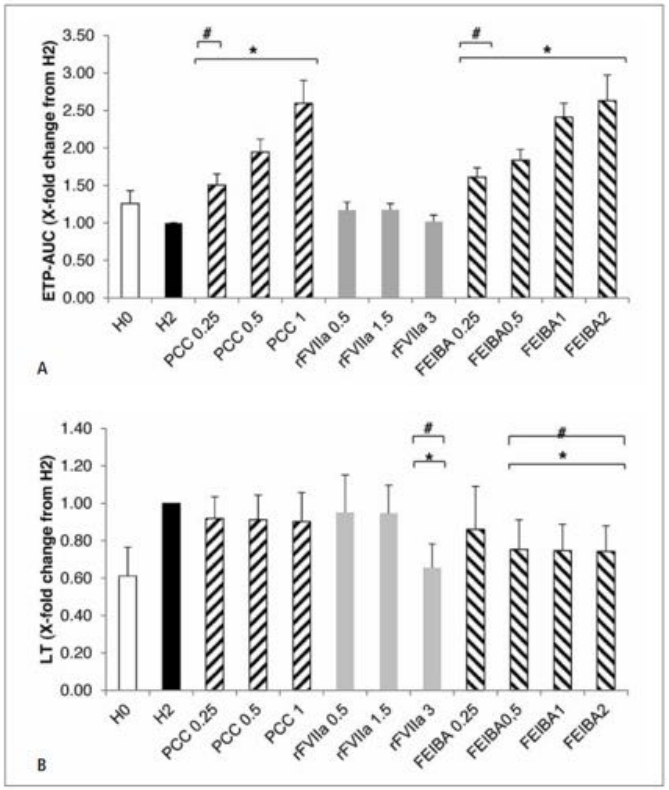
Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban

A randomised crossover *ex vivo* study in healthy volunteers

Raphael Marlu[1]; Enkelejda Hodaj[2]; Adeline Paris[2]; Pierre Albaladejo[3,5]; Jean Luc Crackowski[2]; Gilles Pernod[4,5]

[1]Haemostasis Unit, University Hospital Grenoble, France; [2]Clinical Research Centre, INSERM CIC03, University Hospital Grenoble, France; [3]Department of Anaesthesiology, University Hospital Grenoble, France; [4]Vascular Medical Unit, University Hospital Grenoble, France; [5]Joseph Fourier Grenoble 1 University / CNRS TIMC-IMAG UMR 5525 / THemas, Grenoble, France

Thromb Haemost 2012; 108:217-24

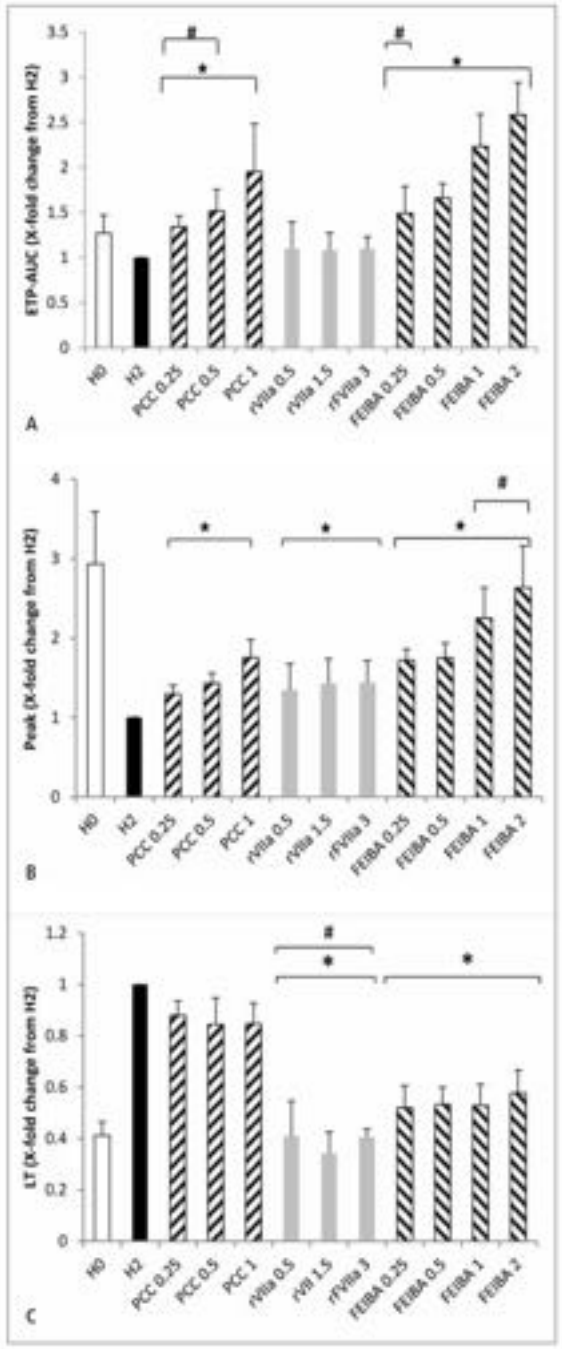


dabigatran

Ex-vivo study, 10 healthy white male subjects were randomised to receive rivaroxaban (20 mg) or dabigatran (150 mg) in one oral administration

thrombin generation tests.

For both anticoagulants, lower doses of **FEIBA**, corresponding to a quarter to half the dose usually used, have potential reversal profile of interest



rivaroxaban

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*†††

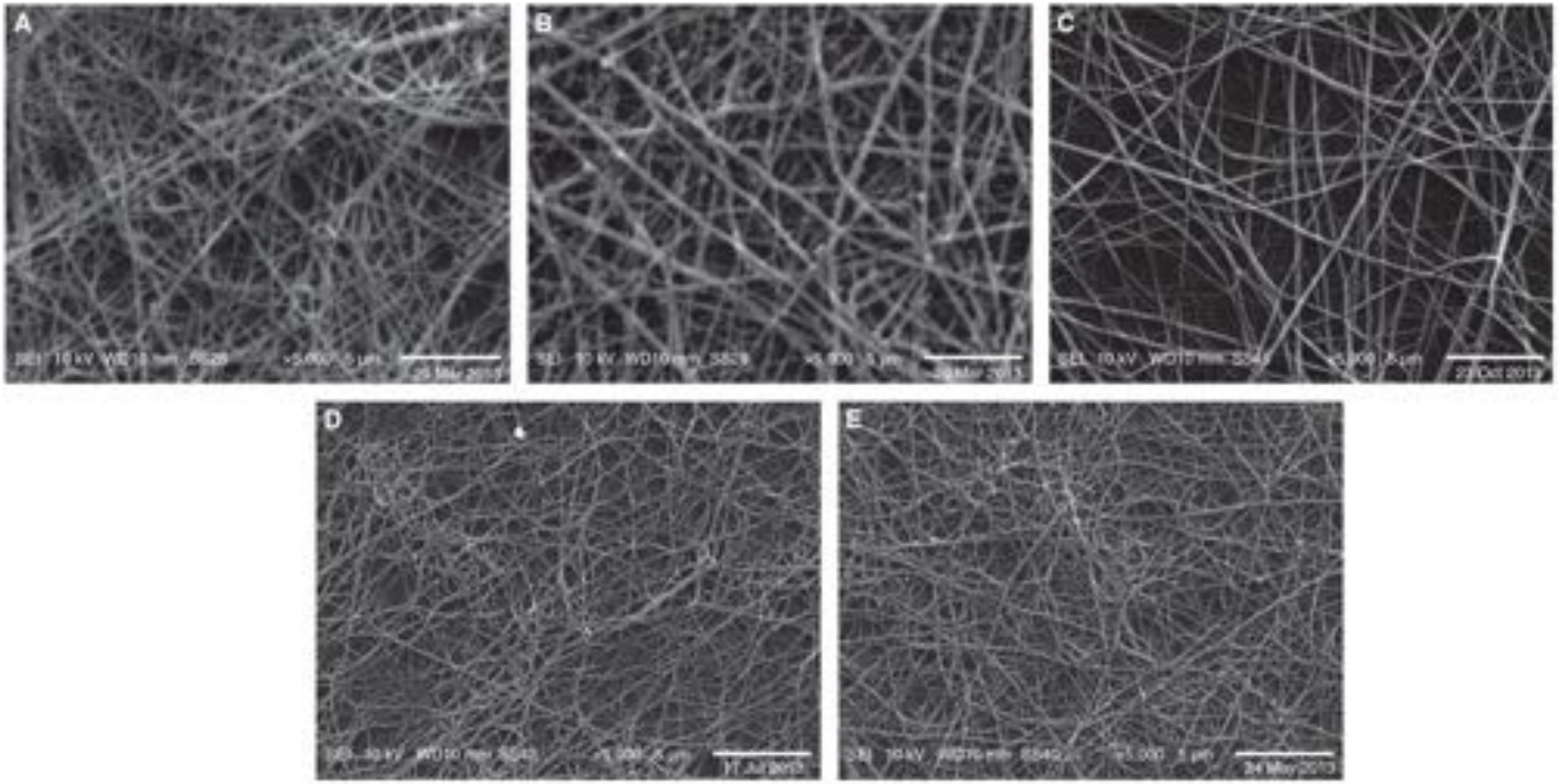


Fig. 2. Effects of the hemostatic agents on samples spiked with a supra-therapeutic apixaban concentration as assessed using scanning electron microscopy of the fibrin network structure in controls (A); blood spiked with apixaban only (B); and blood spiked with apixaban and rFVIIa (C), PCC (D) or aPCC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

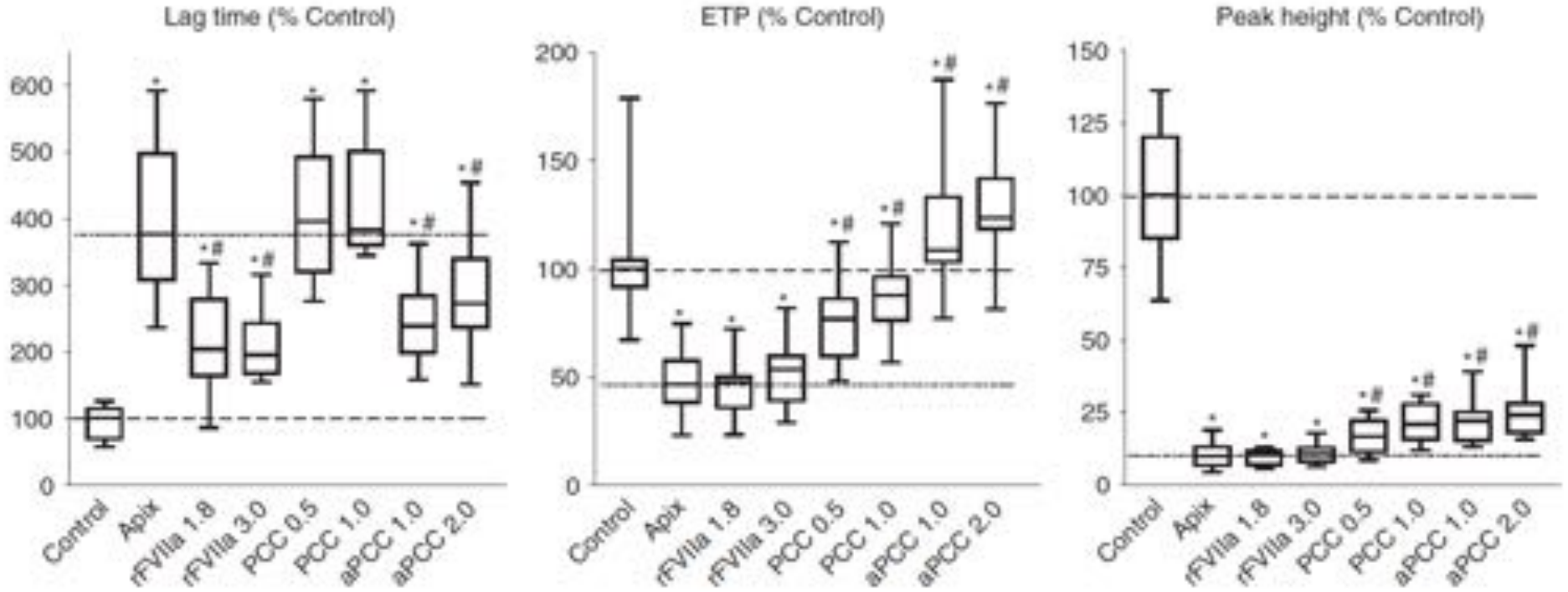


Fig. 3. Effects of the hemostatic agents with a supra-therapeutic apixaban concentration as assessed using thrombin generation assay. Box-and-whisker plots showing median, 25% and 75% percentiles, and minimum and maximum. The results are expressed as the percentage of the control value. *P<0.05 vs. control, #P<0.05 vs. apixaban. ETP, endogenous thrombin potential; others: same as in Fig. 2.

aPCC was more effective than PCC or rFVIIa in reversing in vitro the effects of apixaban.

aPCC rapidly triggered the development of an apparently normal fibrin network and corrected latency and quantitative parameters, whereas PCC or rFVIIa had only a partial effect.

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]

GIHP Groupe d'intérêt en hémostase péri-opératoire

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

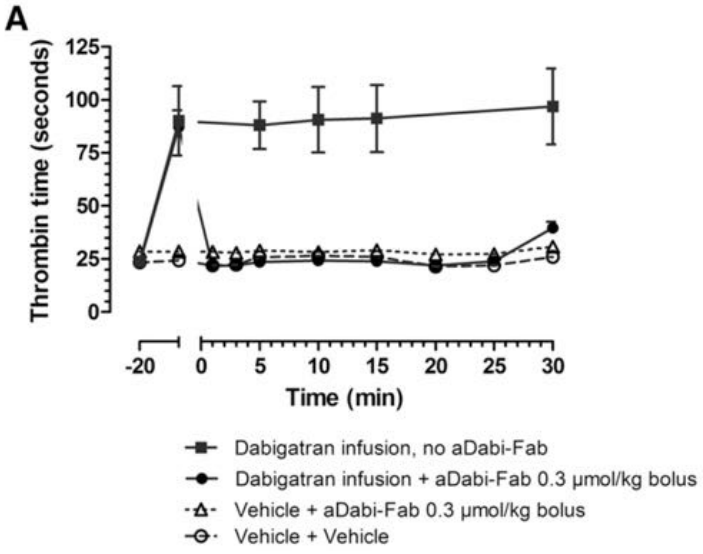
Blood. 2013;121(18):3554-3562

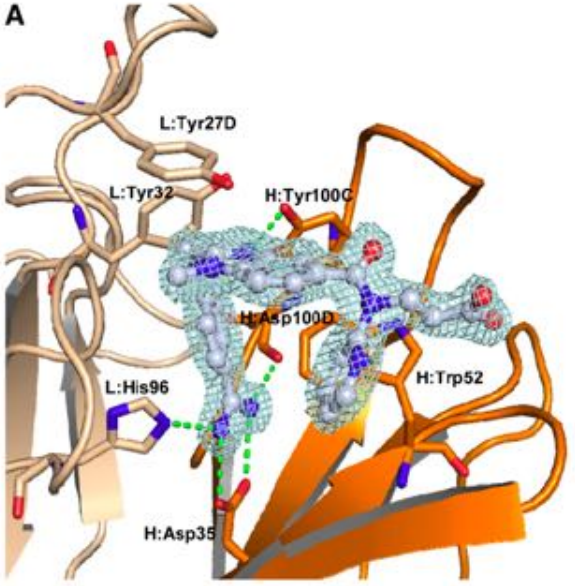
Felix Schiele,[1] Joanne van Ryn,[2] Keith Canada,[3] Corey Newsome,[3] Eliud Sepulveda,[3] John Park,[4] Herbert Nar,[1] and Tobias Litzenburger[4]

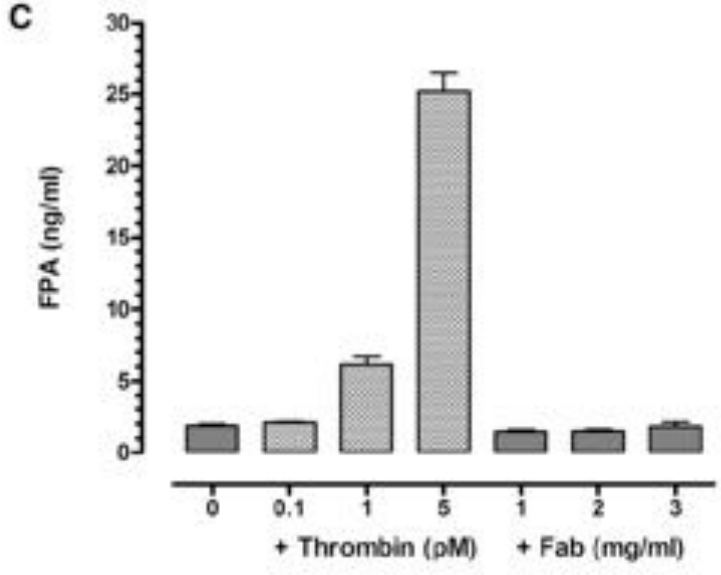
[1]Structural Research Group, and [2]CardioMetabolic Diseases Research, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany; [3]Biotherapeutics, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; and [4]New Biological Entity Discovery, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany

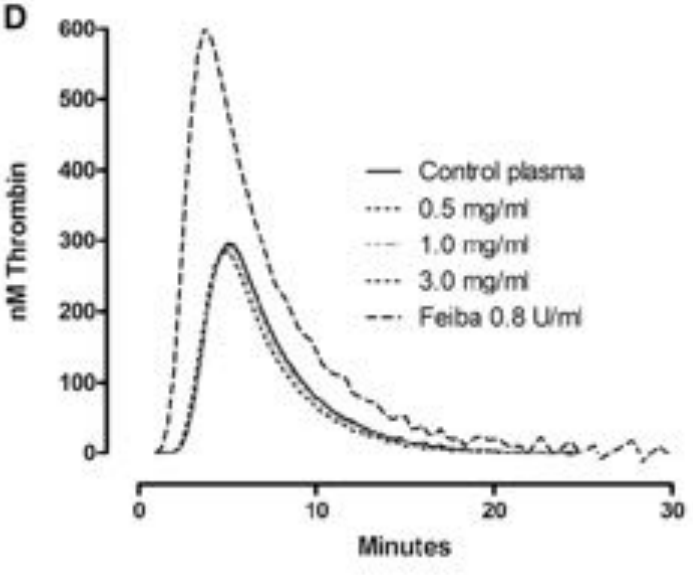
Idarucizumab: a fully humanised monoclonal antibody fragment

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

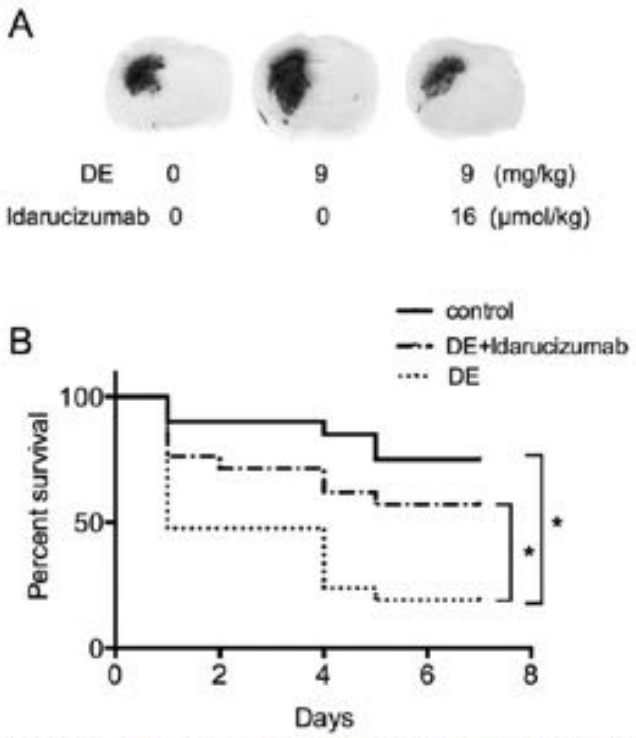
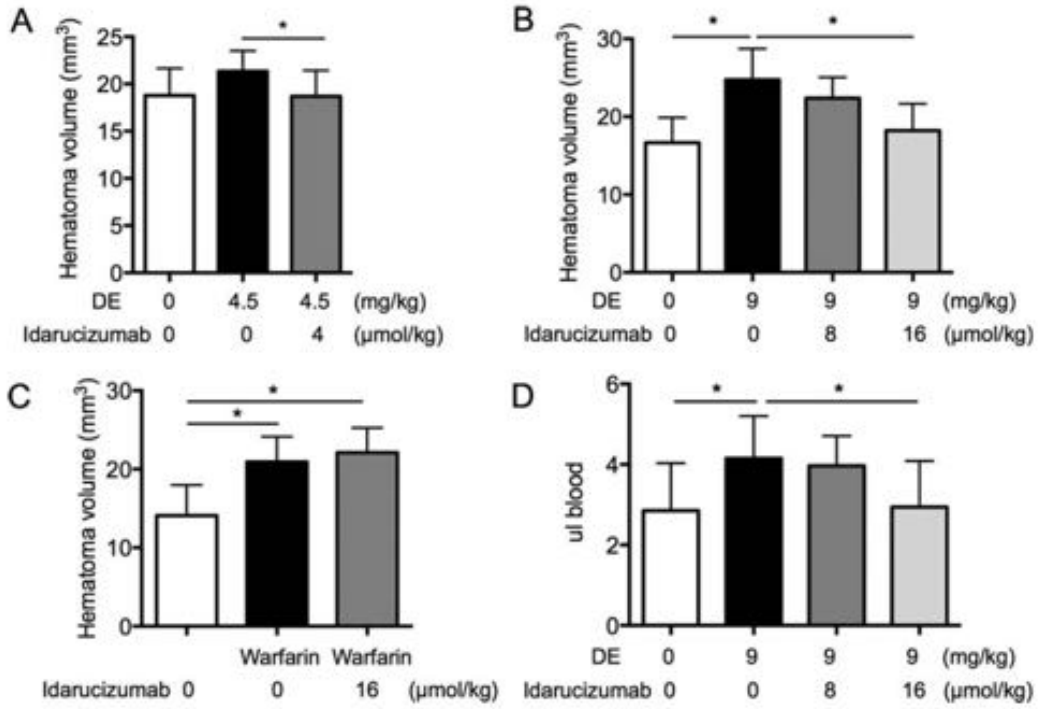


FIGURE 3: Administration of idarucizumab reduces 7 day mortality in intracerebral hemorrhage occurring during anticoagulation with dabigatran etexilate (DE). Intrastriatal injection of a higher dose of collagenase (0.06U) increased hematoma size in nonanticoagulated and anticoagulated mice. (A) Representative 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.

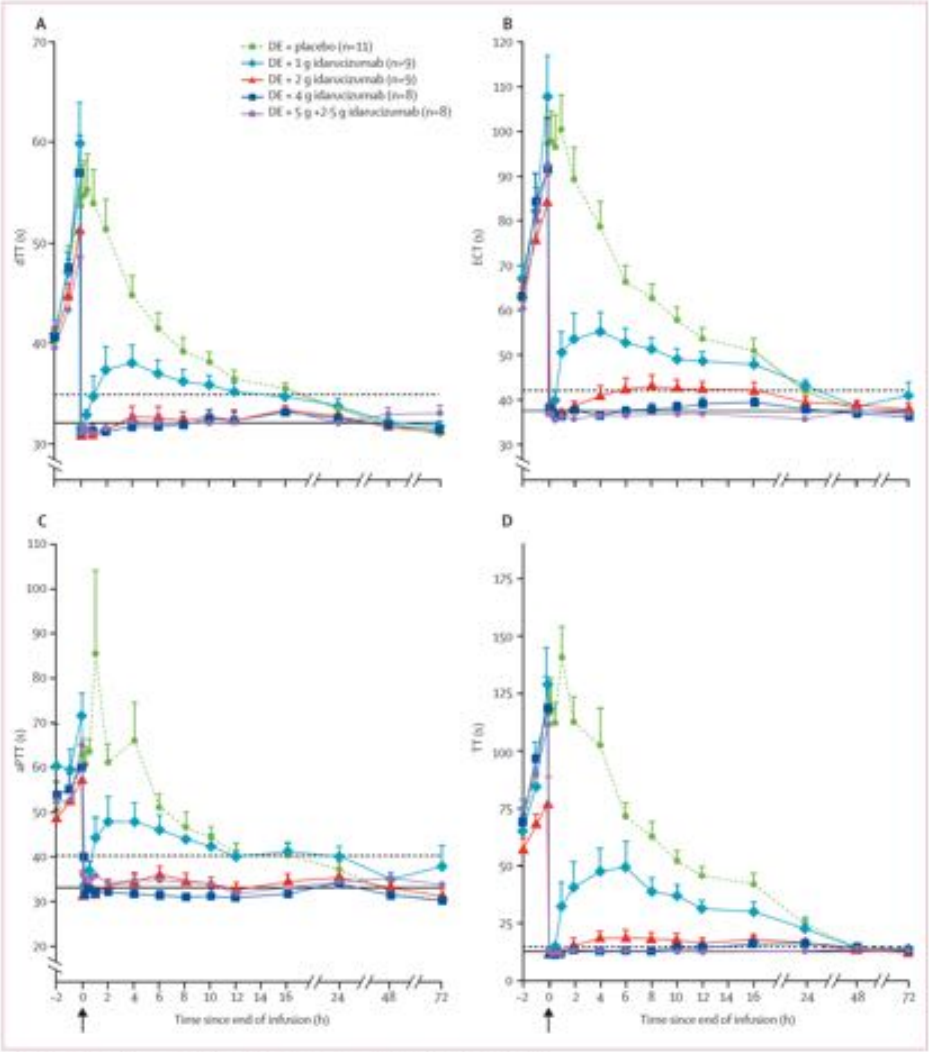
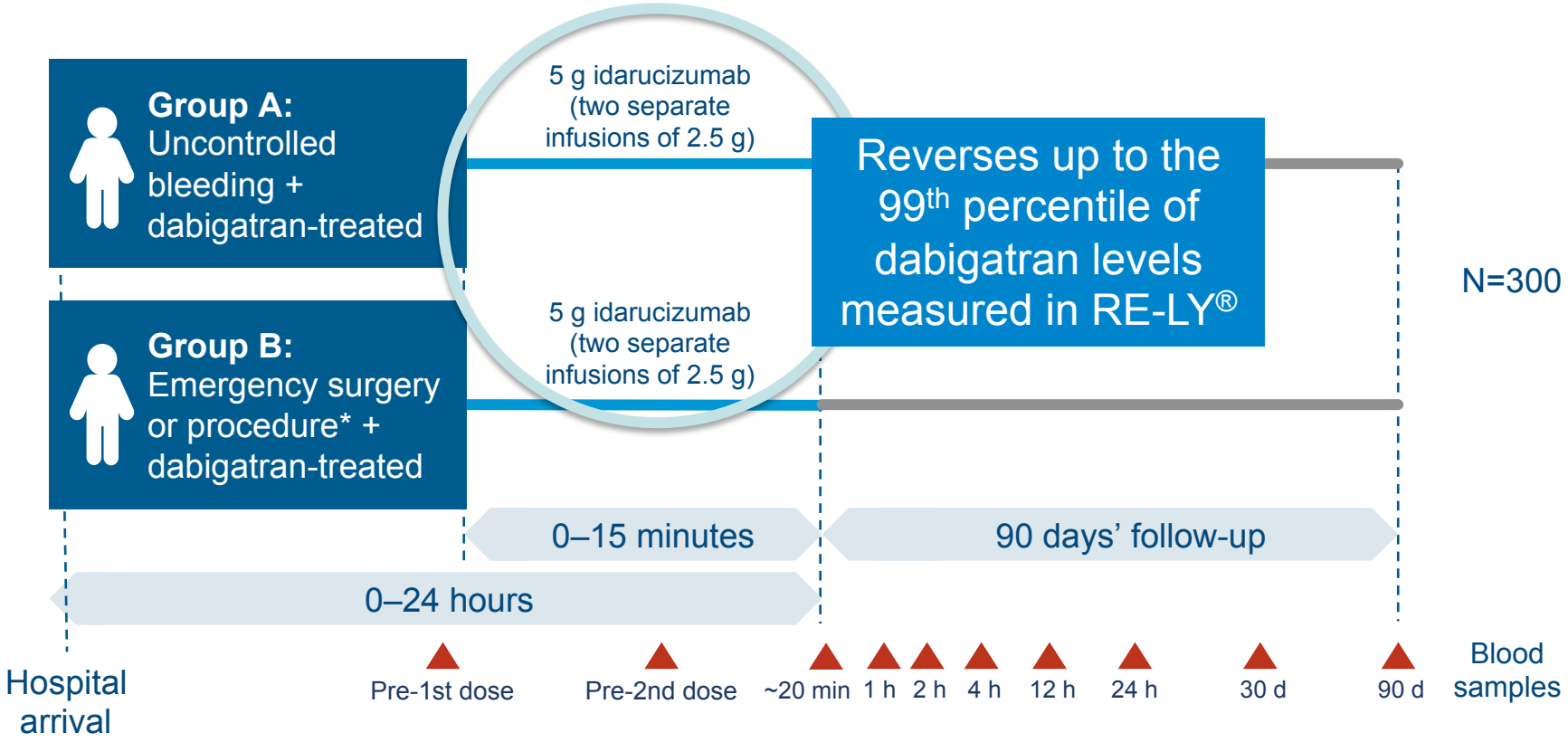


Figure 2: Effect of idarucizumab or placebo infusion on coagulation variables, by dose group
Effect of idarucizumab (1 g, 2 g, 4 g, or 5 g plus 2·5 g) and placebo on (A) diluted thrombin time (dTT), (B) ecarin clotting time (ECT), (C) activated partial thromboplastin time (aPTT), and (D) thrombin time (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

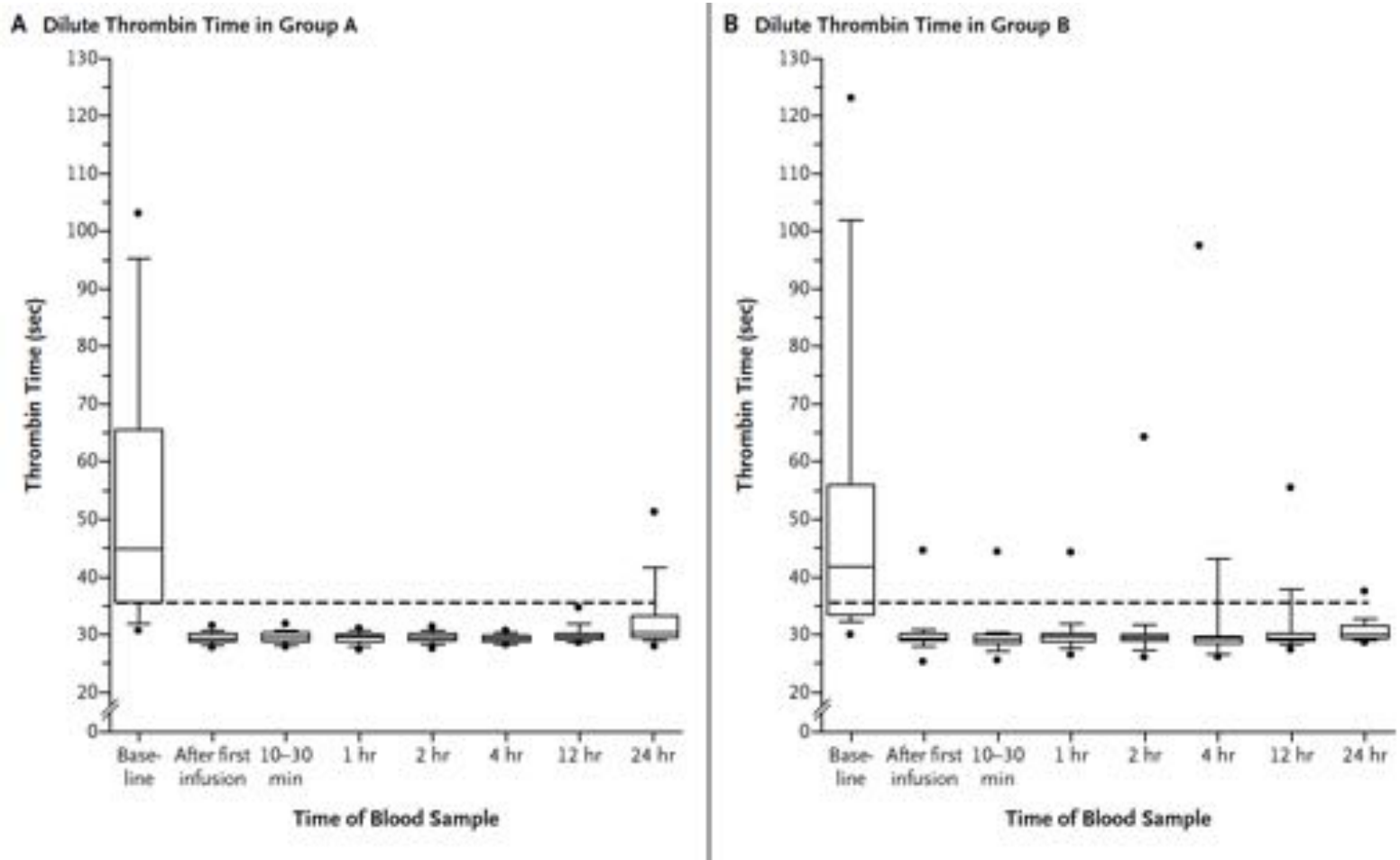
Idarucizumab for Dabigatran Reversal

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

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)

16/66=19,7%

FDA Approves *Praxbind* to Reverse Anticoagulant *Pradaxa*

Caroline Cassels

Disclosures | October 16, 2015

Print Email

EDITORS' RECOMMENDATIONS

EMA Recommends Approval of Dabigatran-Specific Antidote

Idarucizumab May Reverse Anticoagulation Before Emergency Surgery

Reversing New Oral Anticoagulants: New Agents on the Horizon

The US Food and Drug Administration (FDA) has granted accelerated approval to *Praxbind* (idarucizumab, Boehringer Ingelheim) to rapidly reverse the blood-thinning effects of the anticoagulant *Pradaxa* (dabigatran, Boehringer Ingelheim).

"The anticoagulant effects of Pradaxa are important and life-saving for some patients, but there are situations where reversal of the drug's effects is medically necessary," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research.

"Today's approval offers the medical community an important tool for managing patients taking Pradaxa in emergency or life-threatening situations when bleeding can't be controlled," he added.

Tout savoir et comprendre sur le
Développement professionnel continu

Mec
Voir

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 et
contrôlés ou ayant eu recours à une chirurgie/procédure en urgence.

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.

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

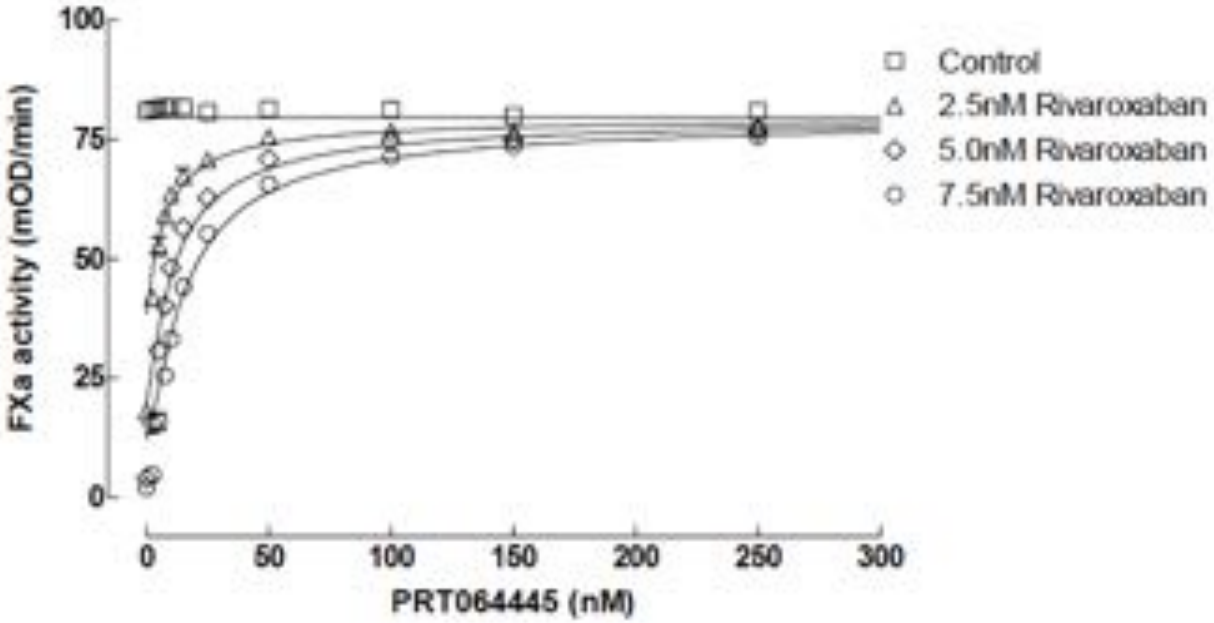
Genmin Lu[1], Francis R DeGuzman[2], Stanley J Hollenbach[2], Mark J Karbarz[1], Keith Abe[2], Gail Lee[2], Peng Luan[1], Athiwat Hutchaleelaha[3], Mayuko Inagaki[3], Pamela B Conley[1], David R Phillips[1] & Uma Sinha[1]

PRT064445 (r-Antidote)

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

PORTOLA

r-Antidote has a high affinity for fXa inhibitors



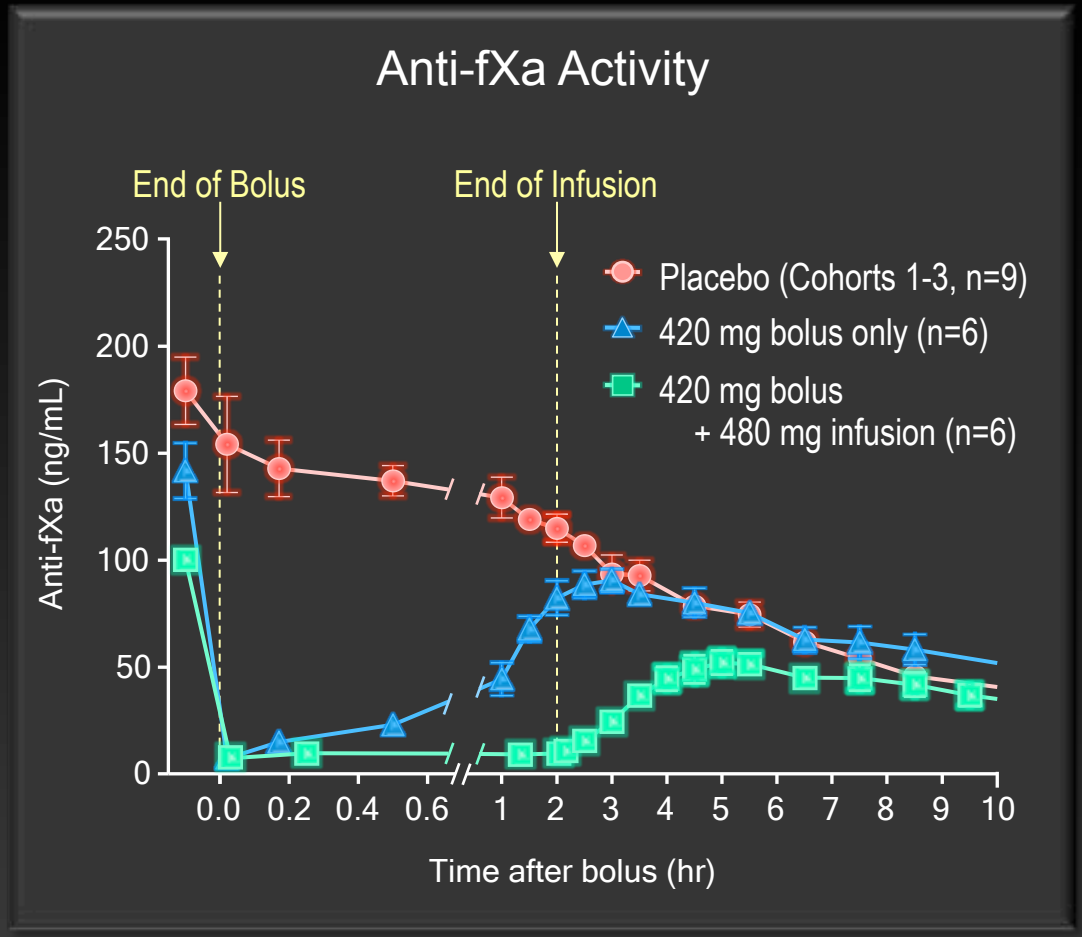
Inhibitor	r-Antidote Kd (nM)	fXa Ki (nM)
Rivaroxaban	1.53	0.40*
Apixaban	0.58	0.08*
Betrixaban	0.53	0.12

*Perzborn at al J Thromb Haemost 2005;3:514,
Pinto et al J Med Chem 2007; 50:5339

PORTOLA

Andexanet Alfa: Apixaban Phase 2

- Apixaban 5 mg b.i.d. x 6 d prior to andexanet/placebo bolus
- 420 mg bolus + 4 mg per minute infusion over 2 hours:
  - >90% reversal at 2 minutes
  - >90% reversal at 2 hours
  - Highly statistically significant
- Reversal sustained throughout andexanet infusion
  - Anti-fXa activity returns to normal decay curve after termination of infusion
- Well tolerated; no thrombotic events or serious adverse events reported
- No antibodies to fXa or fX detected



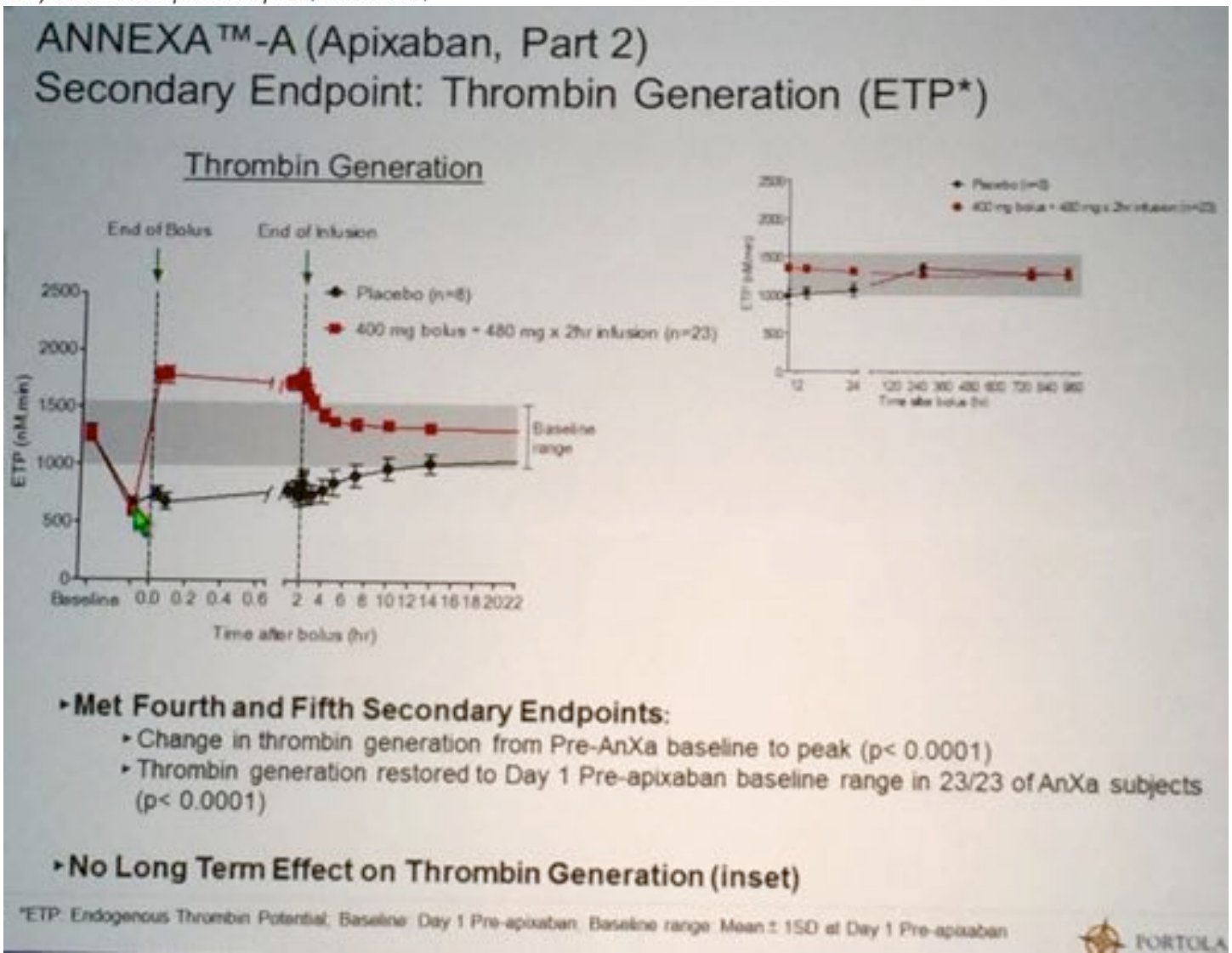
Crowther, M.A., *et al.* 2013. *J Thromb Haemost.* (abstract); 11: AS20.1

ANNEXA™-A PART 2: A phase 3 randomized, double-blind, placebo-controlled trial demonstrating sustained reversal of apixaban-induced anticoagulation in older subjects by andexanet ALFA (PRT064445), a universal antidote for factor XA (FXA) inhibitors

Crowther M[1], Gold A[2], Lu G[2], Leeds JM[2], Wiens BL[2], Mathur V[3], Castillo J[2], Conley PB[2], Connolly S[4] and Curnutte JT[2]

[1]*McMaster University and St Joseph's Hospital, Hamilton,*

ISTH Congress, Toronto, june 2015
Breaking News Session



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.

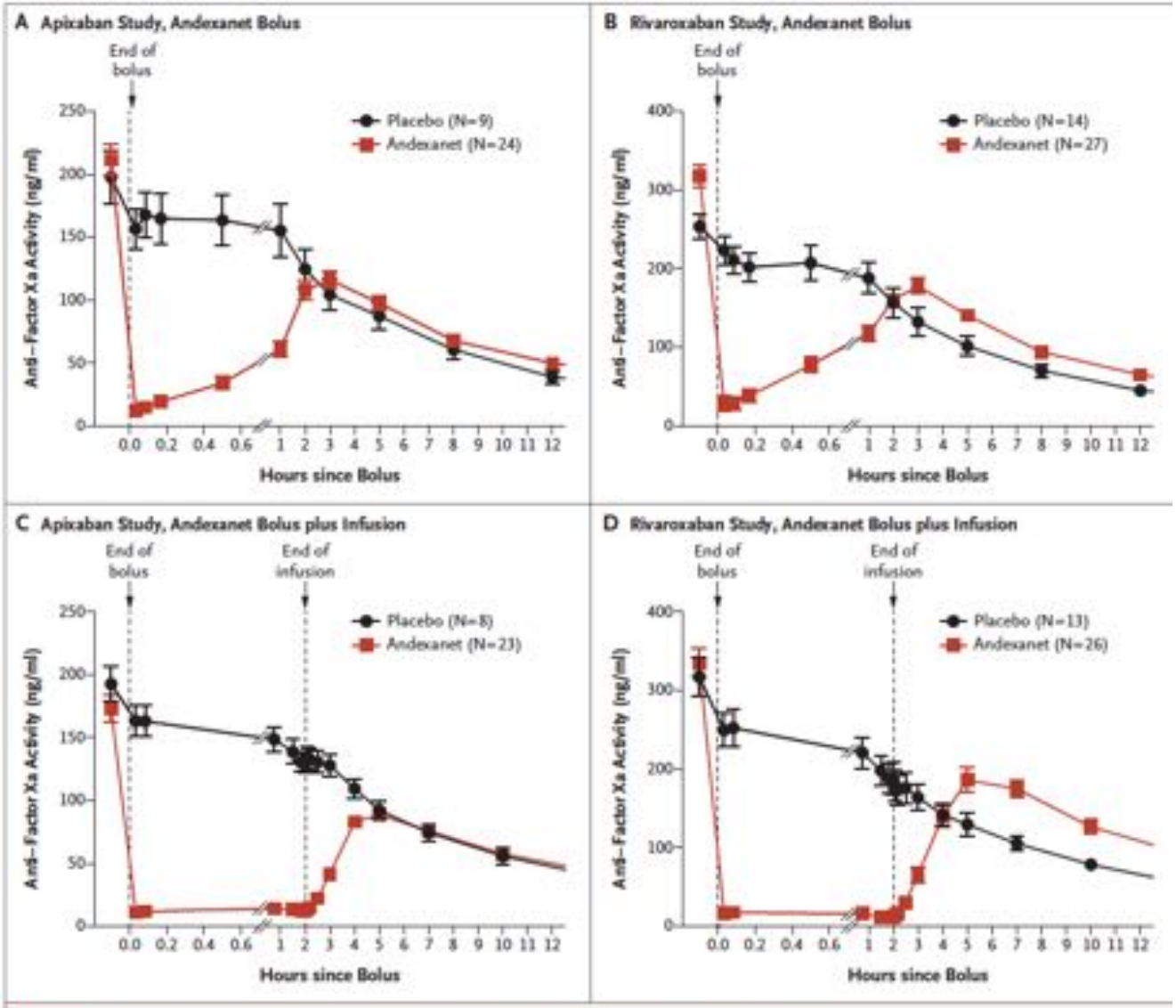


Figure 1. Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.

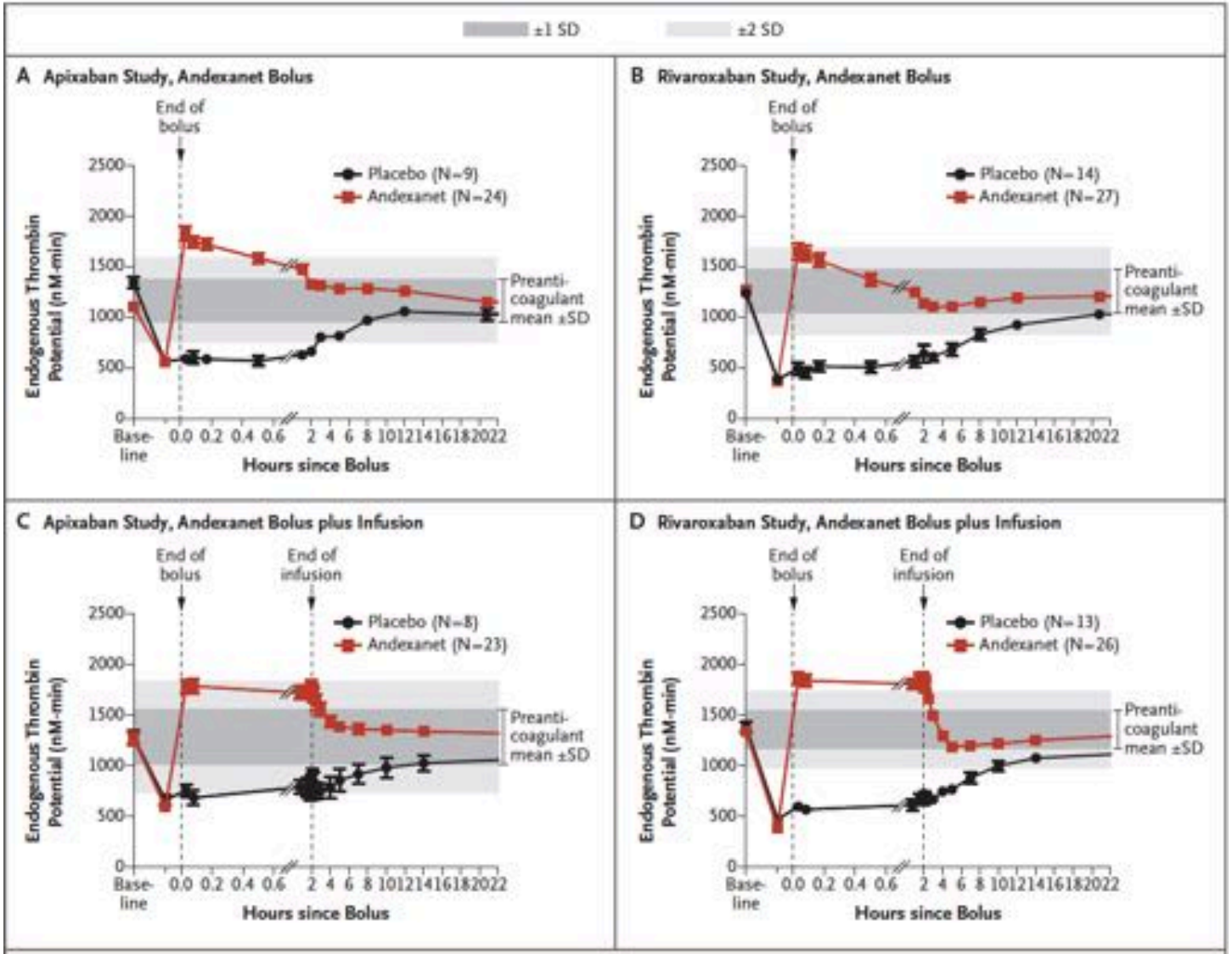


Figure 2. Time Courses of Thrombin Generation before and after the Administration of Andexanet.

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

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**.

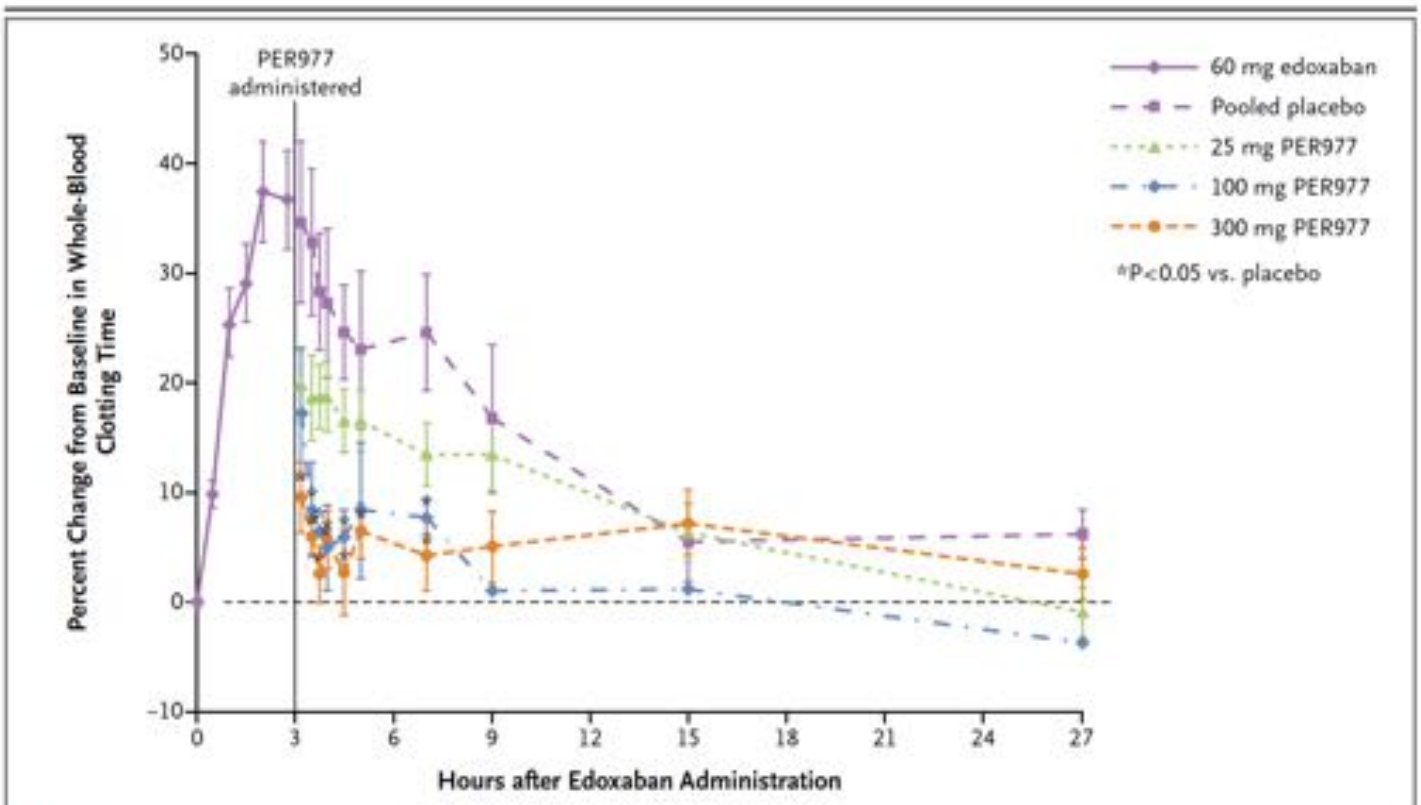


Figure 1. Effect of PER977 on Whole-Blood Clotting Time.
Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

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Sasha H. Bakhru, Ph.D.
Bryan E. Laulicht, Ph.D.
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Michael Grosso, M.D.
Karen Brown, Ph.D.
Victor Dishy, M.D.
Daiichi Sankyo Pharma Development
Edison, NJ
Robert J. Noveck, M.D.
Duke University Medical Center
Durham, NC

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

EMERGENCY SURGERY and DABIGATRAN (PRADAXA®)

Your center has a specific assay for DABIGATRAN (Pradaxa®)

[Dabigatran] ≤ 30 ng /ml	• Operate
30 ng/ml < [Dabigatran] ≤ 200 ng/ml	• Wait up to12 hrs* then re-test** **or** (if the emergency cannot wait) • Operate, if abnormal bleeding: reverse the anticoagulant effect***
200 ng/ml < [Dabigatran] ≤ 400 ng/ml	• Wait 12 – 24 hrs then re-test** **or** (if the emergency cannot wait) • Postpone surgery as long as possible • Consider dialysis, especially if Cockcroft < 50 ml/min • Operate, if abnormal bleeding: reverse***
[Dabigatran] > 400 ng/ml	• Overdose – Risk of severe bleeding • Consider dialysis prior to surgery

In severe renal impairment the half-life of dabigatran is much longer

*The time to reach the 30 ng/ml cutoff cannot be precisely determined, hence the phrase « up to 12 hrs »
**This second assay can give an estimate of the time needed to reach the 30 ng/ml cutoff
***This proposal applies mainly to emergency situations that cannot wait:

PCC=25-50 IU/kg or FEIBA=30-50 IU/kg depending on availability
No data available on thrombotic risk of high doses of PCC or FEIBA in these patients
Reversal with PCC or FEIBA does not completely correct coagulation test abnormalities
First-line rFVIIa is not considered

Version 1.0 , 27_11_2012

BLEEDING and DABIGATRAN (Pradaxa®) or RIVAROXABAN (Xarelto®)

Your center has a specific assay for DABIGATRAN (Pradaxa®) 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

Version 1.0 , 27_11_2012

Annales Françaises d'Anesthésie et de Réanimation xxx (2013) xxx–xxx

SFAR
Société Française d'Anesthésie et de Réanimation

Article spécial

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]

Dans tous les cas:

- Noter : âge, poids, nom du médicament, dose, nombre de prises par jour, heure de la dernière prise, indication

- Prélever :
  - créatininémie (calculer une clairance selon Cockcroft)
  - dosage spécifique:
    - temps de thrombine modifié pour dabigatran
    - activité antiXa spécifique pour le rivaroxaban

- Contacter le laboratoire d'hémostase pour informer du niveau d'urgence et discuter des examens et prélèvements à effectuer

- Interrompre le traitement

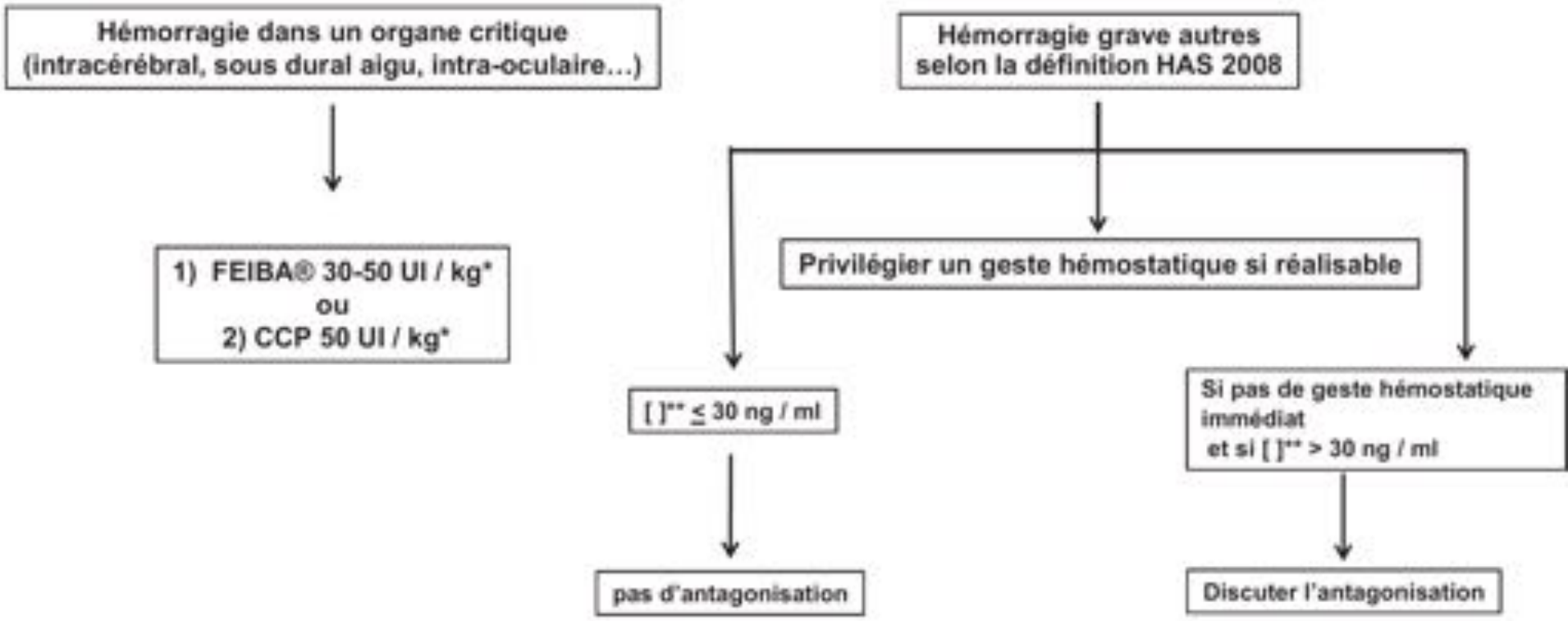
Une comédication par de l'aspirine ne change rien au raisonnement

La surveillance postopératoire doit être prolongée

GIHP Groupe d'intérêt en hémostase péri-opératoire

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

Table 9 Possible measures to take in case of bleeding

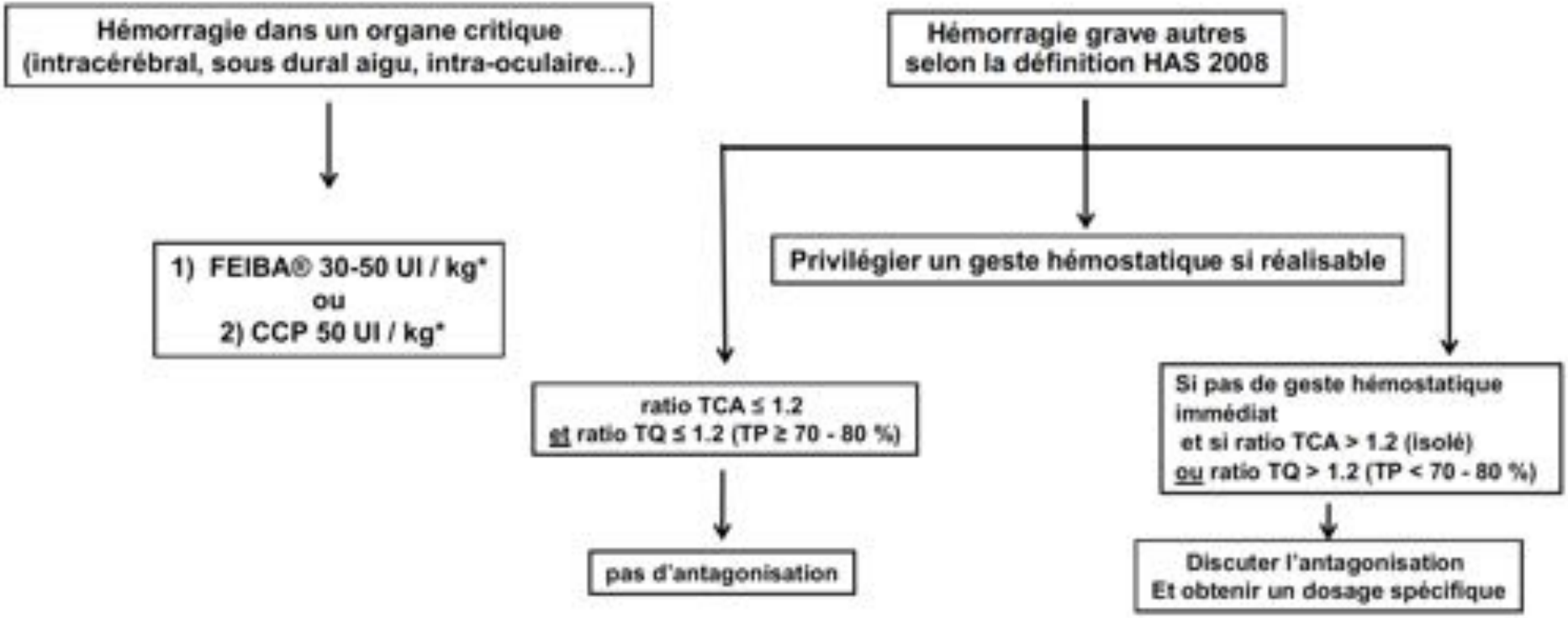
	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: ≥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.

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

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

Il s'agit d'une solution dégradée en cas d'indisponibilité immédiate de dosage spécifique



* Fonction de la disponibilité. Pas de données disponibles sur le risque thrombotique des fortes doses de CCP ou de FEIBA, chez ces patients

** CCP=25-50 UI/kg ou FEIBA=30-50 UI/Kg

Le rFVIIa n'est pas envisagé en première intention

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Acta Anaesthesiol Scand. 2014 Mar 6. doi: 10.1111/aas.12303. [Epub ahead of print]

Dabigatran anticoagulation and Stanford type A aortic dissection: lethal coincidence: Case report with literature review.

Stein P[1], Boeshart M, Brand B, Schlicker A, Spahn DR, Bettex D.

Author information

Abstract

BACKGROUND: Novel oral anticoagulants are now encountered in patients needing emergency surgery. Knowledge and treatment options are limited.

METHODS AND RESULT: We present the case of a 76-year-old patient who suffered from an acute Stanford type A aortic dissection, needing emergency surgical aortic repair. He was anticoagulated with dabigatran due to past atrial fibrillation. Despite haemodiafiltration, surgical revision and massive transfusion of packed red blood cells, fresh frozen plasma, platelets, coagulation factors, and recombinant factor VIIa, the patient died from intractable bleeding with sustained therapeutic levels of dabigatran.

CONCLUSION: After reviewing the literature, we summarize the limited treatment options and show possible approaches for patients treated with dabigatran needing emergency surgery.

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UNIVERSITE JOSEPH FOURIER
SCIENCES TECHNOLOGIE MEDECINE
GRENOBLE 1

CHU GRENOBLE

842 patients inclus
au 5 mars 2015

Observatoire

des Gestes Invasifs et des Hémorragies chez les Patients

traités par les Nouveaux AntiCoagulants Oraux

GIHP-NACO

GIHP Groupe d'intérêt en hémostase péri-opératoire

Pierre Albaladejo, Pierre Sié, Charles Marc Samama, Gilles Pernod, Jean Luc Bosson

Patient demographics and clinical characteristics

- 41 centres (included 1-60 patients)
- 18 months
- 349 patients admitted and hospitalised for major bleeding while on DOAs

	Dabigatran (n=126)	Rivaroxaban (n=223)	All (n=349)
Age, years (median [IQR])	81 [75–87]	77 [69–82]	79 [72–84]
Sex, female (%)	42.1%	39.9%	40.7%
BMI (median [IQR])	25.1 [22.9–28.0]	26.2 [23.6–29.3]	25.8 [23.4–29.2]
Creatinine clearance, n (%) (Cockcroft-Gault)			
>60 mL/min	27.0	37.7	33.8
30–59 mL/min	49.2	51.6	50.7
15–29 mL/min	19.4	9.4	13.2
<15 mL/min	4.0	1.3	2.3

DOA, direct oral anticoagulant; IQR, interquartile range; LVEF, left ventricular ejection fraction; PAOD, peripheral arterial occlusive disease; TIA, transient ischaemic attack

(unpublished data, March 2015. GIHP working group)

Medication taken within 3 days before admission

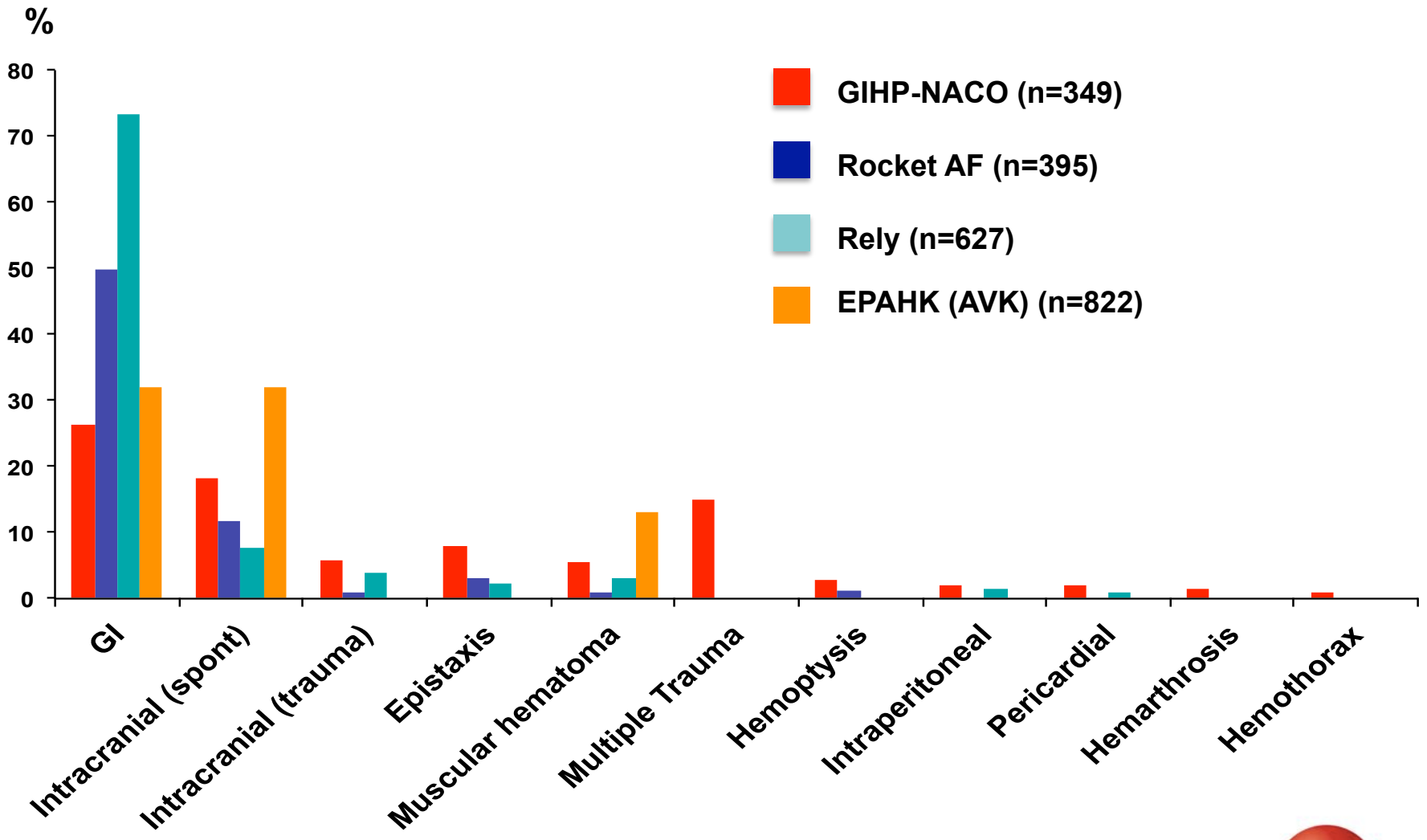
	Dabigatran (n=126)	Rivaroxaban (n=223)	All (n=349)
Total	30.2%	22.9%	25.6%
NSAIDs	4.8%	2.7%	3.4%
Aspirin	16.7%	14.3%	15.2%
Clopidogrel	5.6%	2.7%	3.7%
VKA	1.6%	0.4%	0.9%
LMWH	1.6%	0.4%	0.9%
UFH	0	0.4%	0.3%

DOA, direct oral anticoagulant; IQR, interquartile range; LVEF, left ventricular ejection fraction; PAOD, peripheral arterial occlusive disease; TIA, transient ischaemic attack

(unpublished data, March 2015. GIHP working group)

Major bleeding (ISTH)= 74.2%

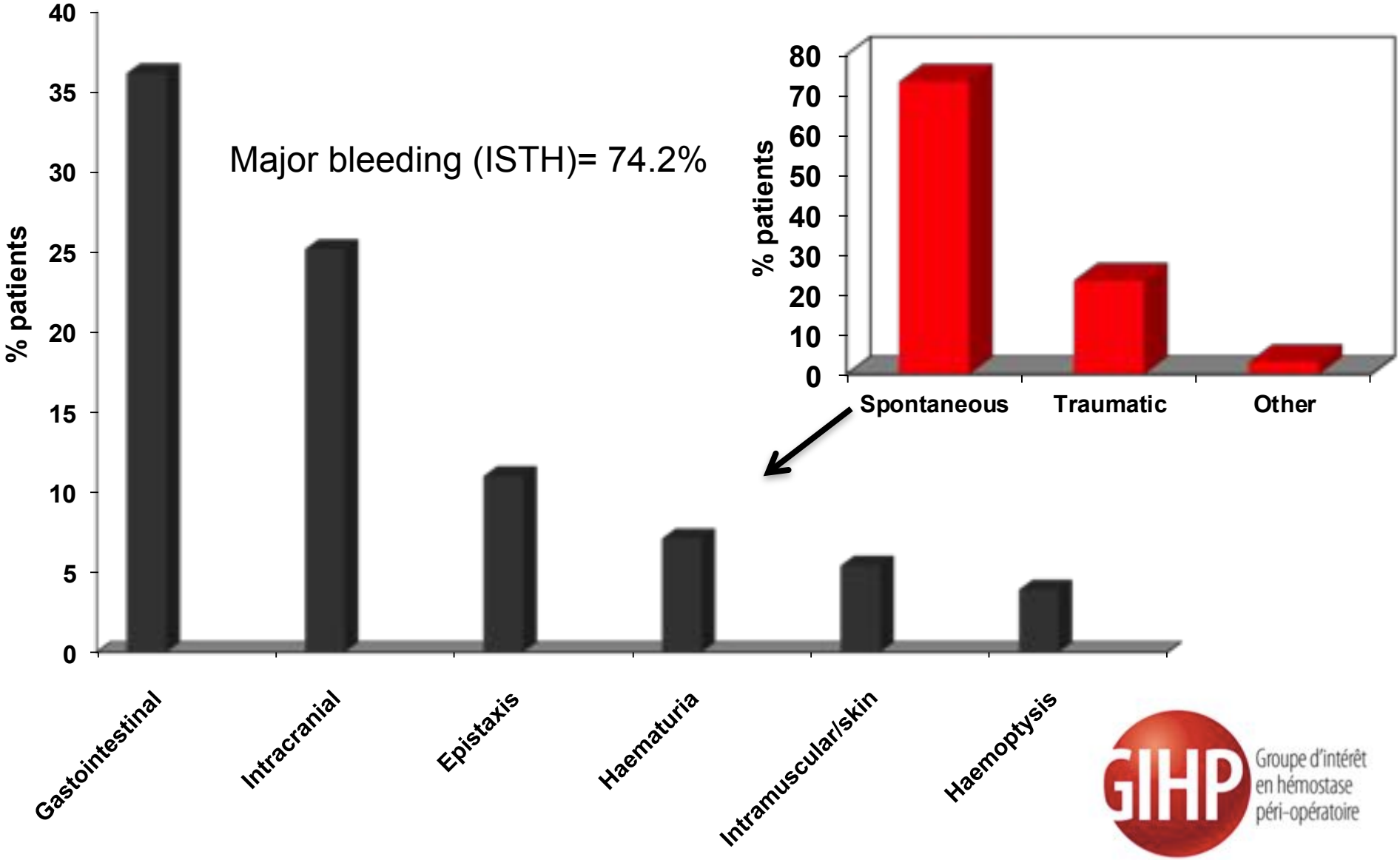
GIHP-NACO Observatory



GIHP Groupe d'intérêt en hémostase péri-opératoire

(unpublished data, March 2015. GIHP working group)

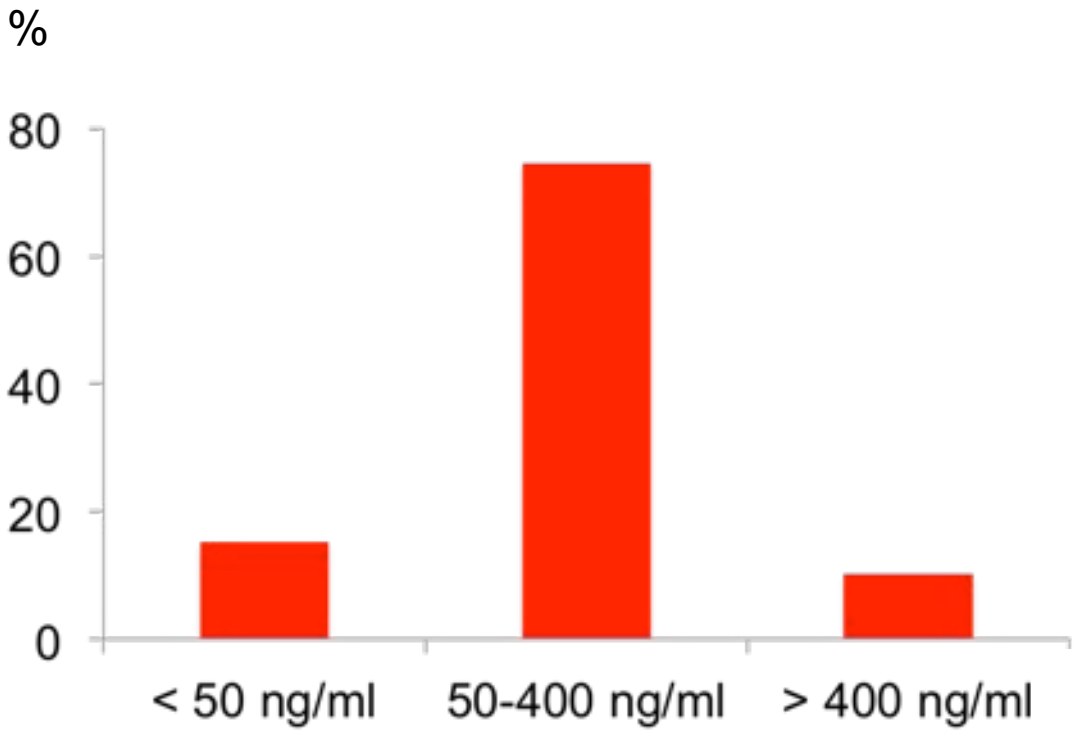
Bleeding types and location



Groupe d'intérêt en hémostase péri-opératoire

(unpublished data, March 2015. GIHP working group)

DOA concentration determined in 42 %	
Dabigatran (n=54) median (range)	167 ng/ml (20-3500)
Rivaroxaban (n=100) median (range)	116 ng/ml (15-928)



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(unpublished data, May 2014. GIHP working group)

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]

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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%

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(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%**	

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(unpublished data, May 2014. GIHP working group)

European Society of Anaesthesiology ESA

Take Home Messages

- **A huge educational challenge. Trade off efficacy/bleeding risk**
- **We have to foresee an upcoming major health issue…**
- **Scheduled procedure: 3-4 or** 5 days wash-out could be optimal, pending the increasing number of agents, the variability, the drug interactions, etc, etc…
- **Monitoring is becoming available: anti-Xa (rivaroxaban-apixaban-edoxaban) – diluted thrombin time (dabigatran) but…**
- **Emergency procedure: PCC? FEIBA?? Dose? Haemodialysis (dabi only)… Arch Cardiovasc Dis. 2013; 106: 382-93**
- **Antidotes have to be better evaluated**

GIHP Groupe d'intérêt en hémostase péri-opératoire

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
- Idarucizumab (Praxbind®) pour le dabigatran (Pradaxa®) ?

PUBLICITÉ

FA : moins de 50% d'observance des anticoagulants à un an, les AOD un peu mieux que les AVK

Vincent Richeux, Pam Harrison

Auteurs et déclarations | 15 mars 2016

Commenter Imprimer Envoyer

Washington, Etats-Unis -- Moins de la moitié des patients en fibrillation auriculaire (FA) non valvulaire prend correctement son traitement par anticoagulant, selon une étude américaine portant sur près de 65 000 patients, pour une période médiane de 1,1 an. L'observance est toutefois légèrement améliorée dans le cas des anticoagulants oraux directs (AOD), par rapport à la warfarine.

Philippe Geluck, Le Monde, 2014