AOD et saignements
Antidotes 2016

OBJECTIFS

- Discuter avec son patient des risques de saignements majeurs avec les AOD
- Comprendre le mécanisme d'action des nouvelles molécules qui serviront d'antidotes aux AOD
- Élaborer un plan d'action en cas de saignements sous AOD

Thrombosis Canada
Thrombose Canada

André Roussin MD
CHUM et ICM
Professeur agrégé
Université de Montréal

SSVQ
Société des sciences vasculaires du Québec

André Roussin MD, FRCP (C)

Conflits d'intérêts potentiels 2014 - 2016

Comités aviseurs ou aviseur expert:

Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Pfizer et Sanofi

Fonds de recherche:

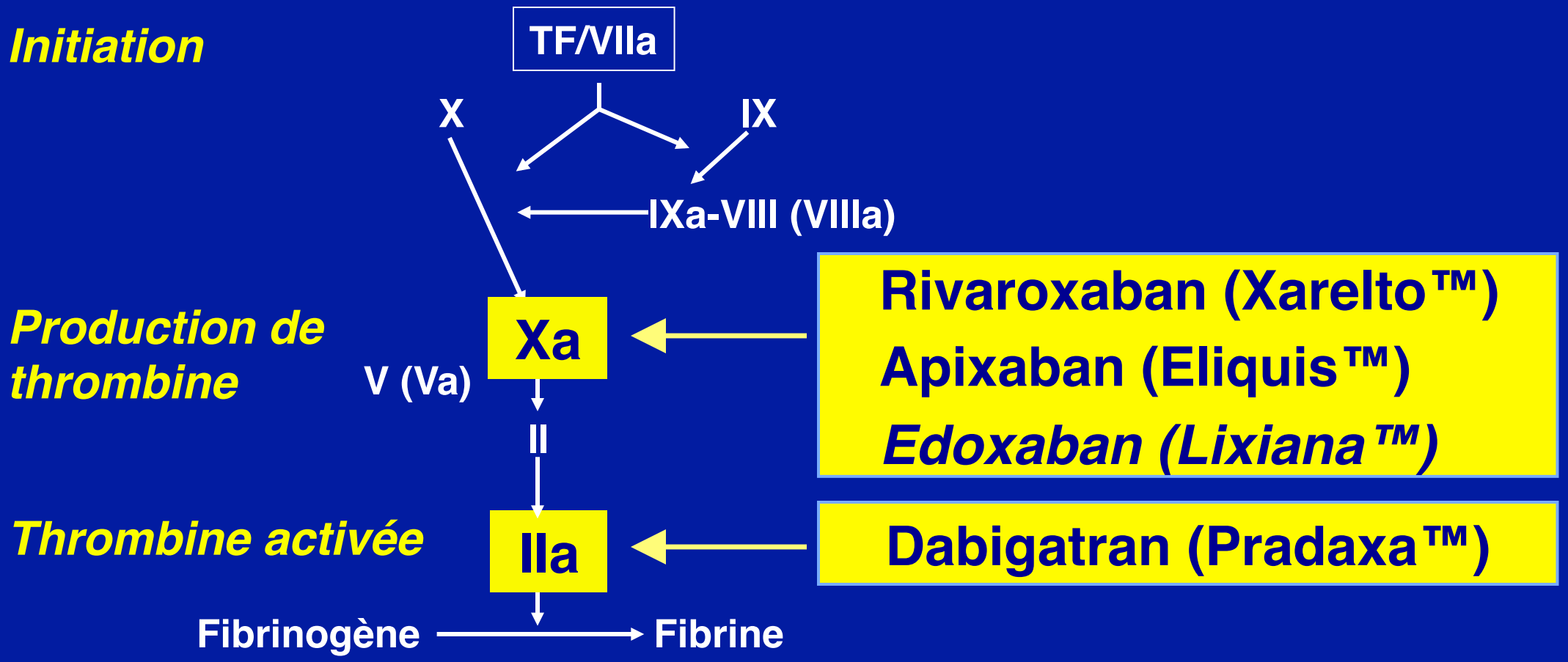
Astra-Zeneca et Bayer

Conférencier:

Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, LEO pharma, Pfizer et Sanofi

AOD 2016

Cascade de coagulation



AOD: Stratégies de renversement

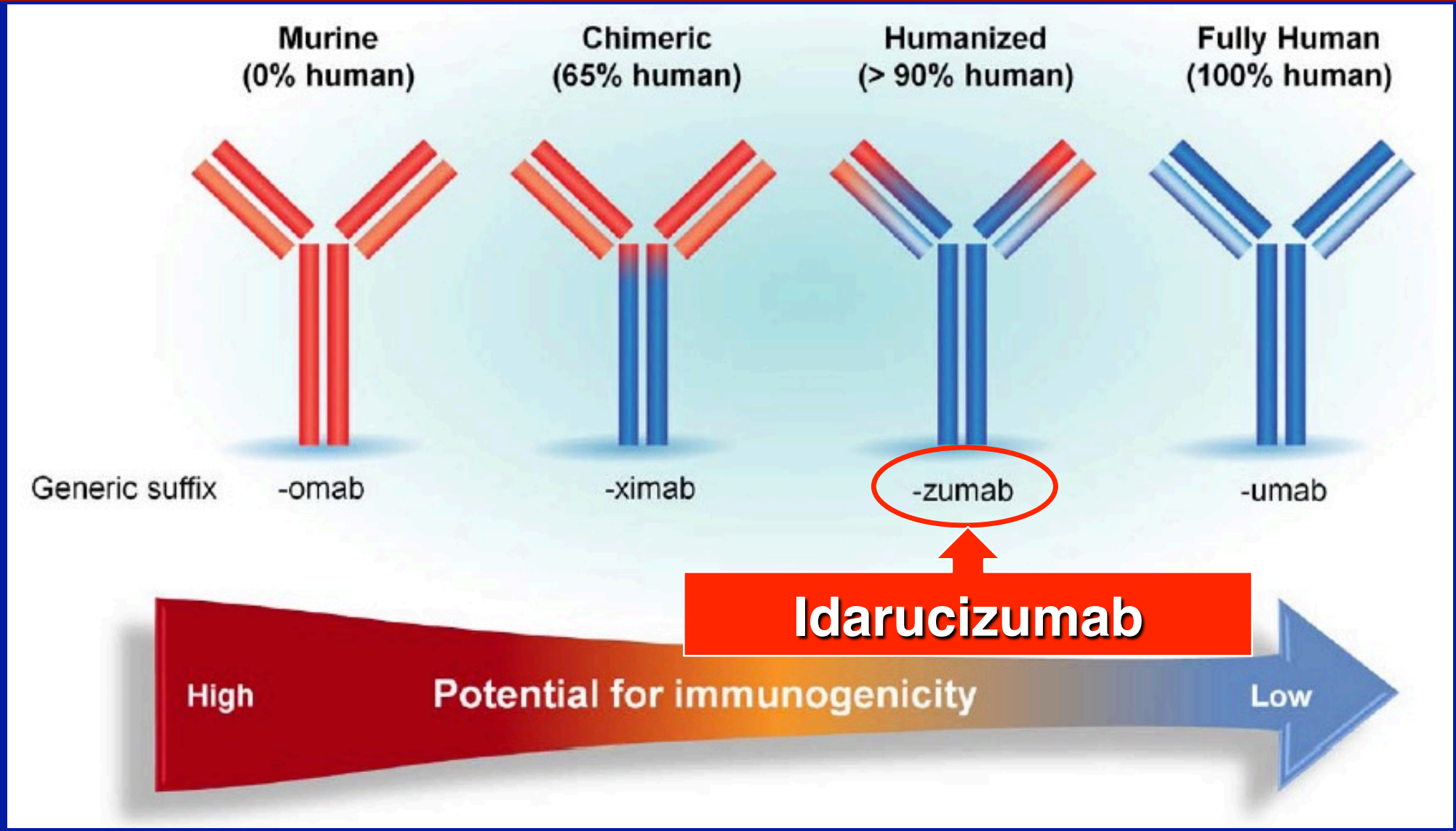
	Stratégie	Mécanisme
Non spécifique	Charbon activé	Décontamination si administré rapidement
	Hemodialyse	Élimination accélérée (dabigatran seulement)
	PCC (Beriplex™)	Remplacement des facteurs II, VII, IX, X
	rVIIa, aPCC (FEIBA™)	Facteurs de coagulation activés
	PER977	Blocage chimique de plusieurs AC
Spécifique	Idarucizumab	Ac monoclonal contre le dabigatran
	Andexanet	FXa recombinant inactif de haute affinité

Antidotes 2016
Pour les AOD

Compagnie	Produit	Antidotes pour:			Statut
		Inh. Xa	Inh. IIa	HBPM/ fondaparinux	
Portola Pharmaceuticals	Andexanet Alfa	Universel	Non	Oui	Phase III et IV: (apixaban/ rivaroxaban) ANNEXA A + R
Boehringer Ingelheim	PRAXBIND™ (idarucizumab) 2,250$ CAN	Non	Spécifique au dabigatran	Non	Approuvé FDA/EU/Canada
Perosphere, Inc.	(Aripazine ou Ciraparantag) PER977	Universel	Universel	Universel	Phase II en cours

Anticorps monoclonaux

Suffixes / terminologie

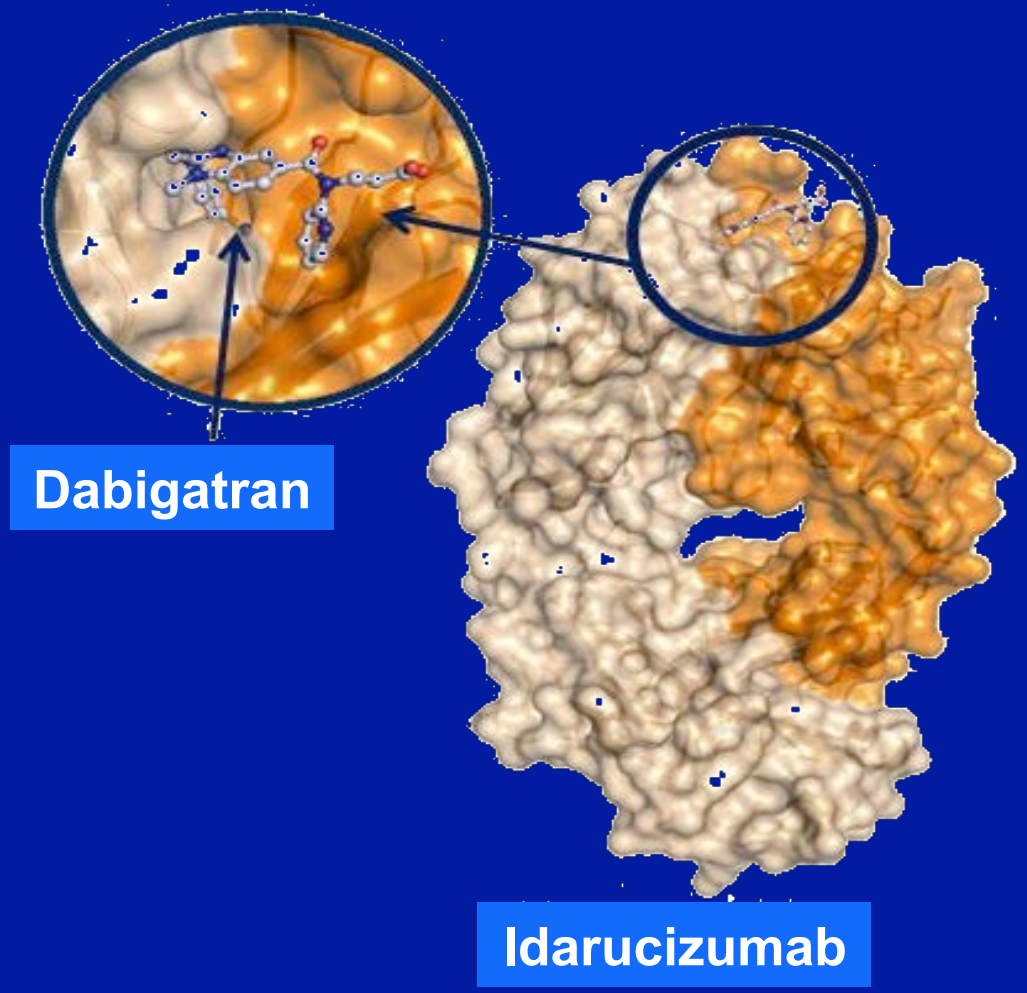


Foltz IN et al. Circulation 2013; 127: 2222-2230

A. Roussin

Antidote pour Dabigatran: Idarucizumab

Praxbind™



- Fregment Fab humanisé
- Affinité pour dabigatran ~300× plus que la thrombine
- Pas d'activité intrinsèque pro- ou anti-coagulante
- Administration IV bolus: début d'action immédiat
- **Demie-vie (4.5 – 9 hr)**

van Ryn J. Presented at the AHA Congress, Los Angeles, USA. 5 November 2012. Presentation 9928;
van Ryn J et al. Circulation 2012;126:A9928;
Glund S et al. Presented at AHA, Dallas, TX, USA, 16–20 November 2013; Abstract 17765
Schiele F et al. Blood 2013;121:3554–62

A. Roussin

Idarucizumab: Praxbind™

Administration IV par infusion ou injection

2 X 2.5 g

50 ml / fiole

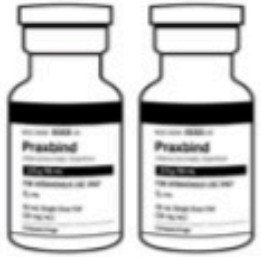


Figure 1 Recommended dose of PRAXBIND provided as two vials.

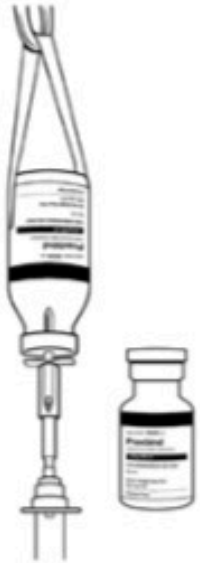


Figure 2 Two consecutive infusions by hanging vials.

Ou bien

Figure 3 Inject both vials consecutively via syringe.

Monographie de Praxbind™ USA

A. Roussin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

NEJM June 2015

RE-VERSE AD

Interim NEJM 2015 publication: premiers 90 patients

Incluant intracrânien, traumatique, gastrointestinal ou autre

Group A: saignement non contrôlé

- HIC n = 18
- Autres n = 33

51 patients

Group B: Chirurgie ou procédure urgente

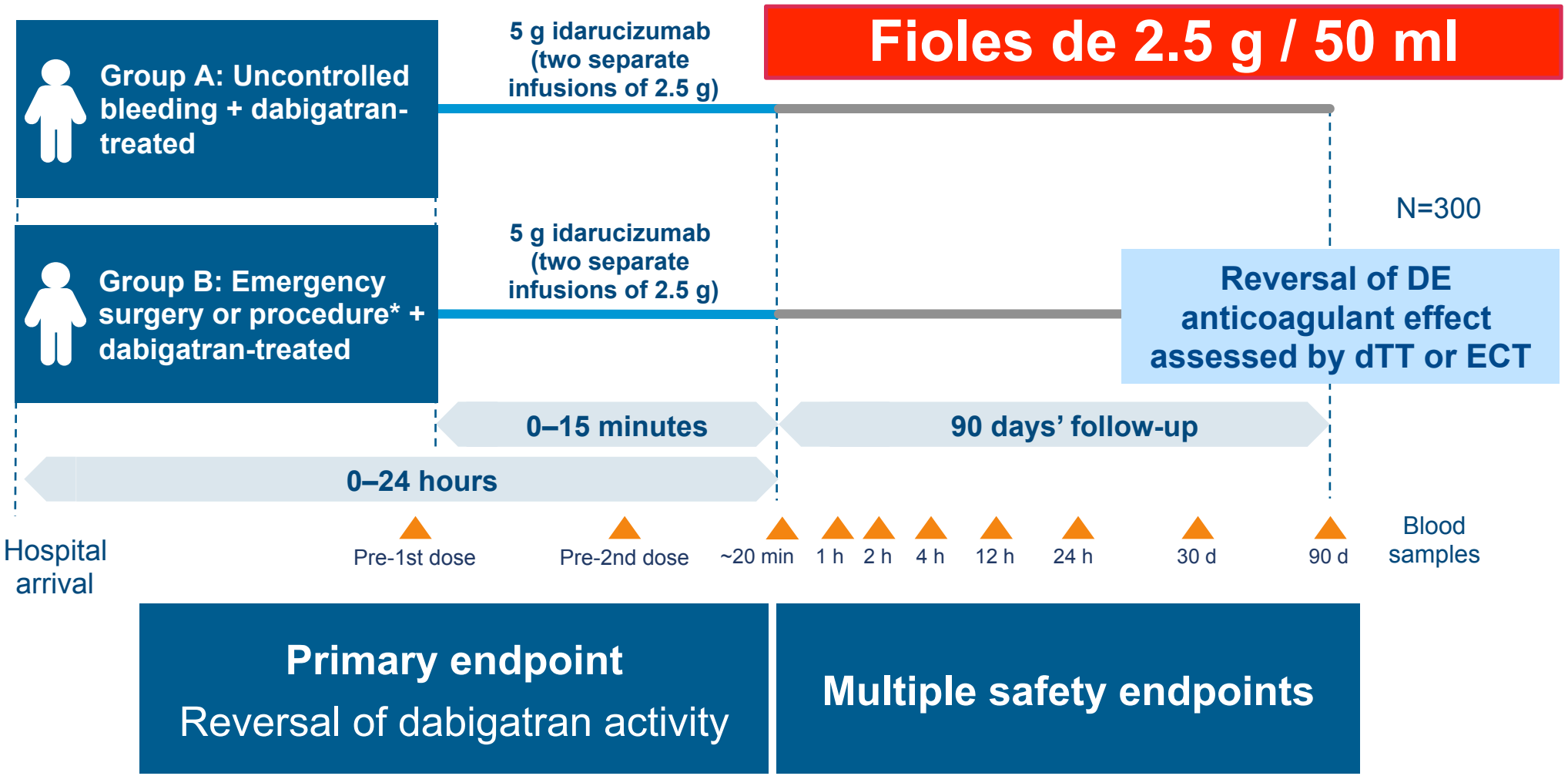
39 patients

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.

RE-VERSE AD

Multicentrique, ouverte, Phase III en cours



*Other than bleeding; Pollack et al. Thromb Haemost 2015

RE-VERSE AD
Population étudiée

	Group A (n=51) Bleeding	Group B (n=39) Procedure	Total (N=90)
Male, n (%)	32 (63)	18 (46)	50 (56)
Age (yrs), median (min, max)	77.0 (48, 93)	76.0 (56, 93)	76.5 (48, 93)
CrCl (Cockcroft-Gault), mL/min			
Median (min, max)	54 (16, 187)	60 (11, 171)	58 (11, 187)
<30	5	7	12
≥30–<50	14	6	20
≥50–<80	16	11	27
≥80	6	9	15
Missing	10	6	16
Elevated dTT at baseline	40	28	68
Elevated ECT at baseline	47	34	81

CrCl= Creatinine Clearance; dTT= Diluted Thrombin Time, ECT= Ecarin Clotting Time

Pollack et al. NEJM 2015

RE-VERSE AD: HIC vs sans HIC
Population étudiée (Groupe A)

	ICH (N = 18)	Non-ICH (N = 33)*
Time since last DE dose – hrs, median	17.4	15.1
Elevated dTT, n (%)	11 (61.1)	29 (87.9)
Elevated ECT, n (%)	15 (83.3)	32 (97.0)
Type of bleeding, n (%)†		
Intracranial	18 (100)	0
Trauma-related	6 (33.3)	3 (9.1)
Gastrointestinal	0	20 (60.6)
Other	0	11 (33.3)
SBP/DBP – mmHg, median	154/86	117/69
Unbound dabigatran concentration – ng/mL, median (range)	46.7 (9–218)	174.0 (3–641)
Type of ICH, n (%)†		
Subdural	8 (44.4)	0
Subarachnoid	4 (22.2)	0
Intracerebral	10 (55.6)	0
Deep	8 (80% of intracerebral)	0
Lobar	2 (20% of intracerebral)	0

; DE, dabigatran etexilate; dTT, diluted thrombin time; ECT, ecarin clotting time; ICH, intracranial hemorrhage;
*Two patients with missing location for bleeding are included in the non−ICH group. †Patients may appear in more than one category.

RE-VERSE AD
Médication préalable

	Group A (n=51) Bleeding	Group B (n=39) Procedure	Total (N=90)
Daily dose of dabigatran*, n			
75 mg BID	1	0	1
110 mg BID	34	24	58
150 mg BID	14	15	29
Time since last dabigatran intake, hrs			
Median	15.2	16.6	15.4
<12, n	17	15	32
12–<24, n	21	10	31
24–<48, n	12	10	22
>48, n	1	4	5
Dabigatran indicated for atrial fibrillation†, n	47	39	86
Plasma dabigatran concentration, ng/mL			
Unbound, median (min, max)	84.4 (3.3, 641)	76.4 (4.4, 2880)	–

*Two patients in Group A had 'other' daily dose; †In Group A, one patient was taking dabigatran for venous thromboembolism; three for 'other' indications

Pollack et al. NEJM 2015

RE-VERSE AD
Indications d'administration

	Group A (n=51)
Type of bleeding	
Intracranial	18
Trauma	9
Gastrointestinal	20
Other*	11

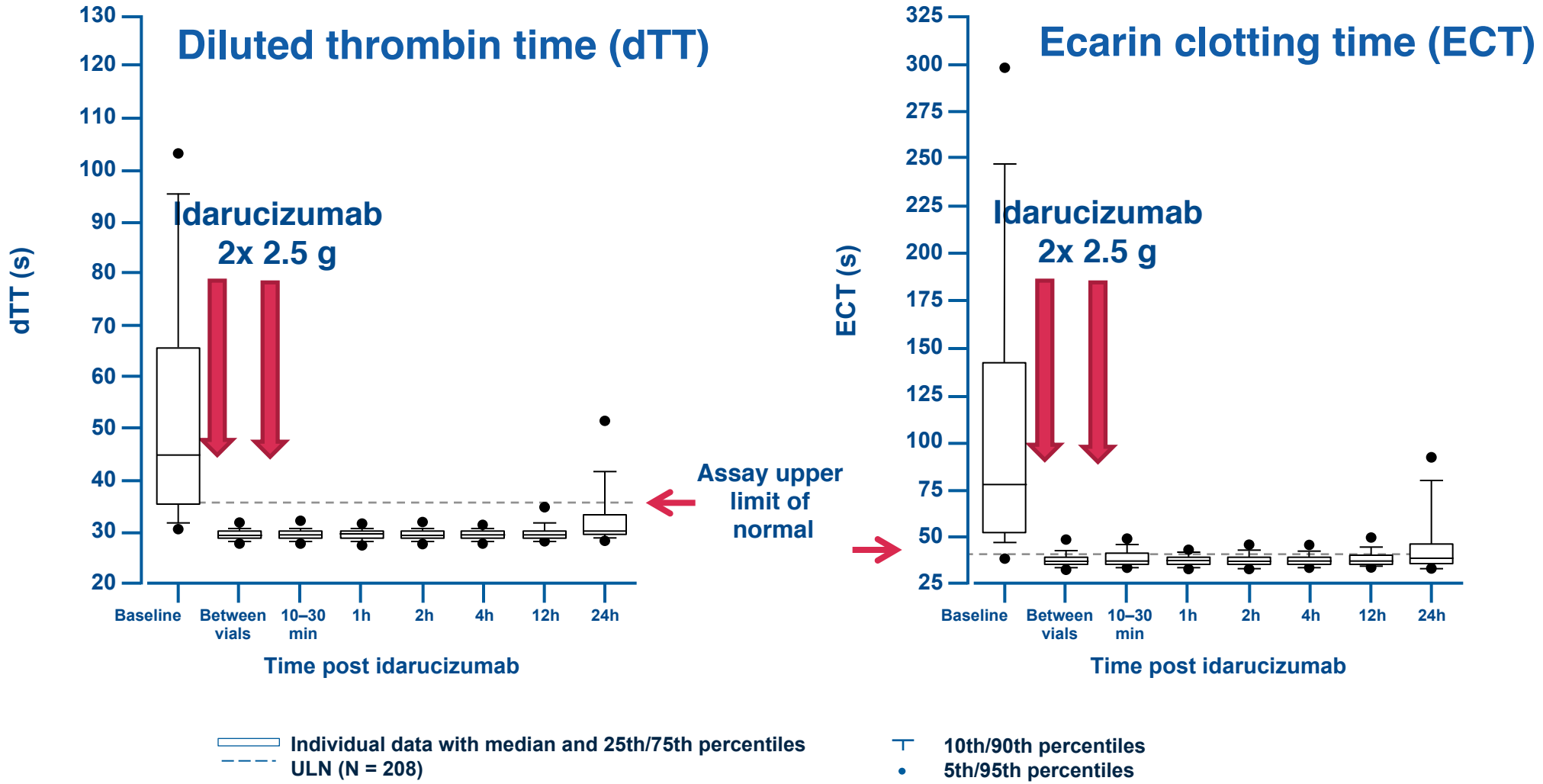
*'Other' bleeding types: urogenital, epistaxis, liver, aortic aneurism and aortic dissection

	Group B (n=39)
Reason for surgery†	
Aortic dissection	1
Pericardial tamponade	1
Peritonitis	1
Acute mesenteric ischaemia with sepsis	2
Bone fractures	8
Acute cholecystitis	5
Acute renal insuff., catheter placement	4
Acute appendicitis	3
Joint/wound infection	3
Abscess (suprapubic, scrotal)	2

†Other reasons for surgery (one patient each) were: acute deterioration of aortic valve; small bowel obstruction; pneumothorax; probable perforation of the viscera; incarcerated umbilical hernia; lumbar puncture; left leg gangrene; unstable angina, ureteral obstruction, and hydronephrosis

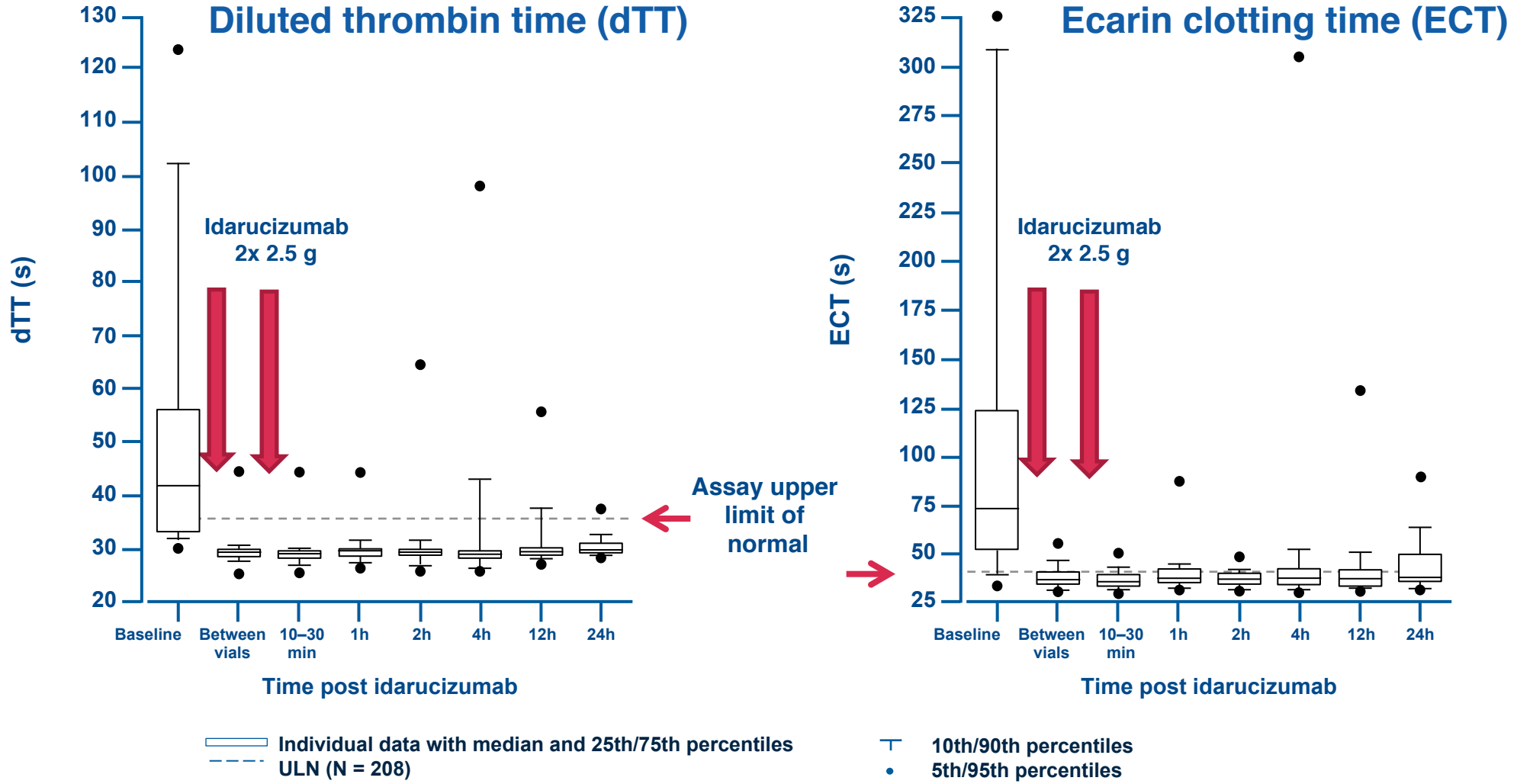
Pollack et al. NEJM 2015

Issue primaire Groupe A / Saignement
Selon dTT et ECT



Pollack et al. NEJM 2015

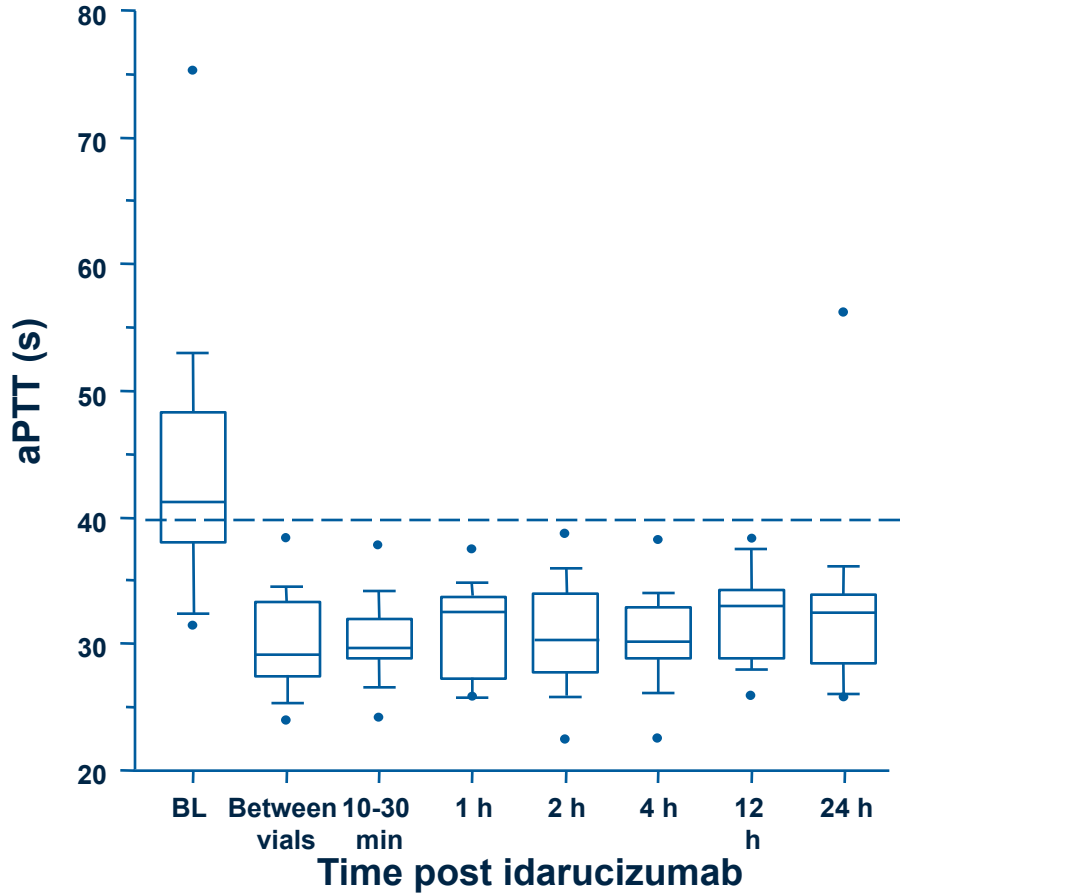
Issue primaire Groupe B / Procédures
Selon dTT and ECT



Pollack et al. NEJM 2015

Idarucizumab renverse le Dabigatran

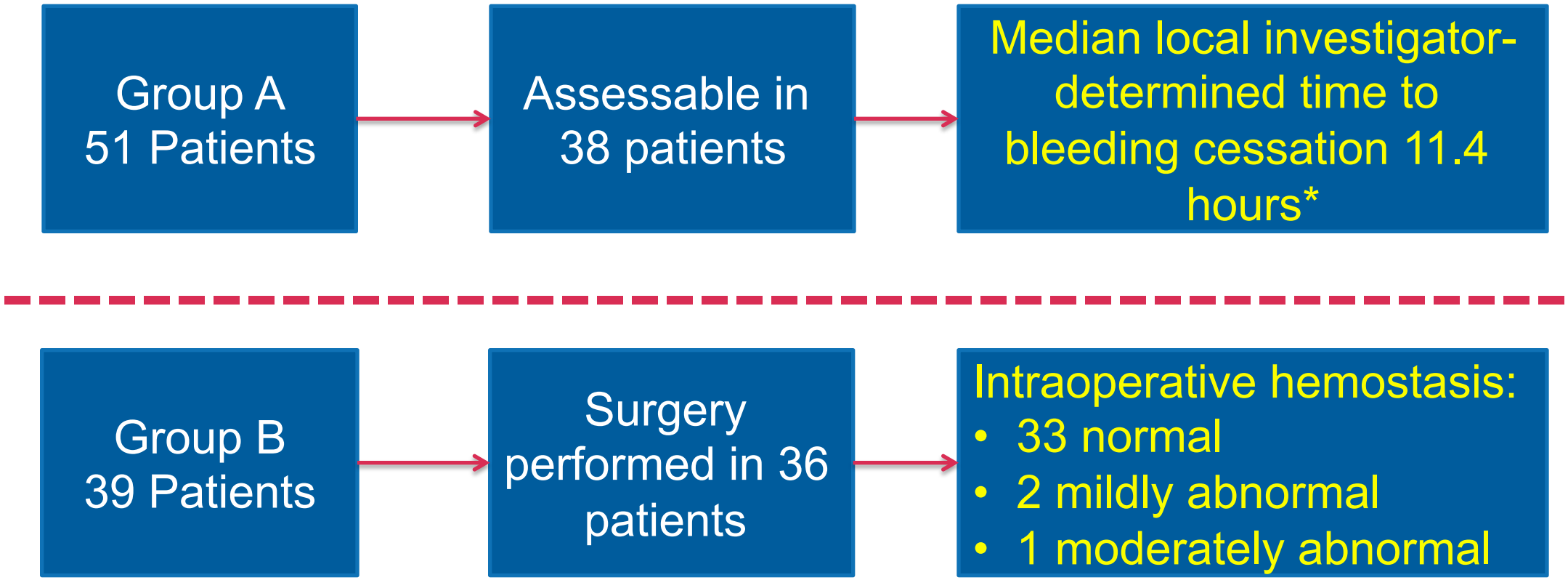
18 Patients avec HIC selon PTT



aPTT, activated partial thrombin time; BL, baseline; IC, intracranial; ULN, upper limit of normal.

RE-VERSE AD

Issue secondaire: impact clinique



Additional information on clinical outcomes will be provided by the full study data set following recruitment of the planned 300 patients

***Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding**

Pollack et al. NEJM 2015

Algorithme proposé pour le dabigatran advenent un saignement ou une intervention urgente

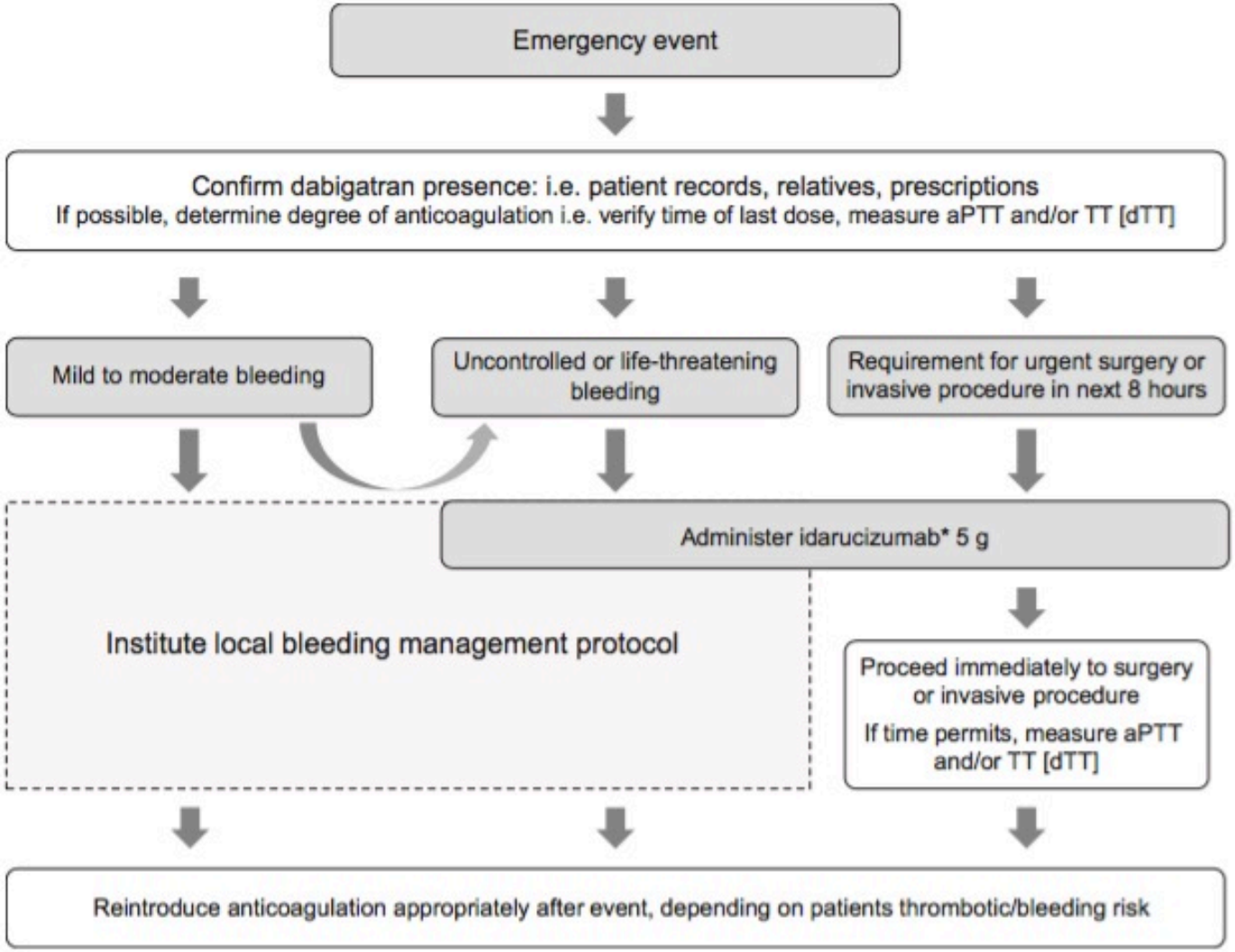


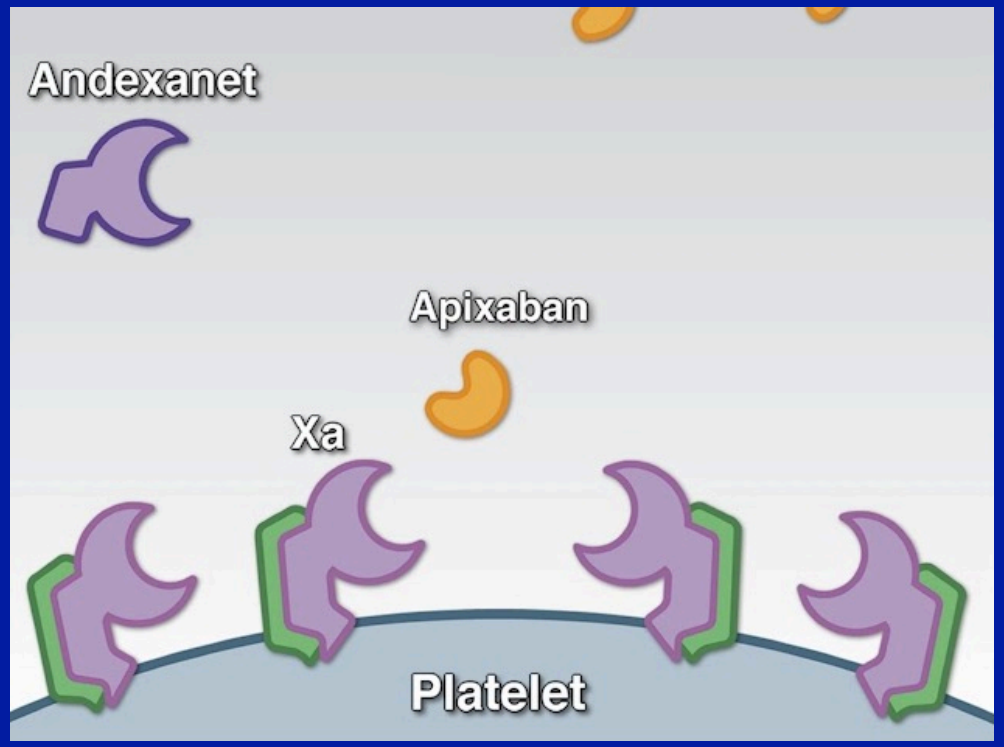
Figure 7. Proposed algorithm for management of patients treated with dabigatran who present with bleeding episodes or require urgent surgery/invasive procedures. *Administer two 50-mL vials of idarucizumab (each containing 2.5 g) intravenously. In rare cases when dabigatran anticoagulation remains present after idarucizumab and bleeding continues in the patient, a second 5-g dose of idarucizumab may be considered. aPTT indicates activated partial thromboplastin time; dTT, diluted thrombin time; and TT, thrombin time.

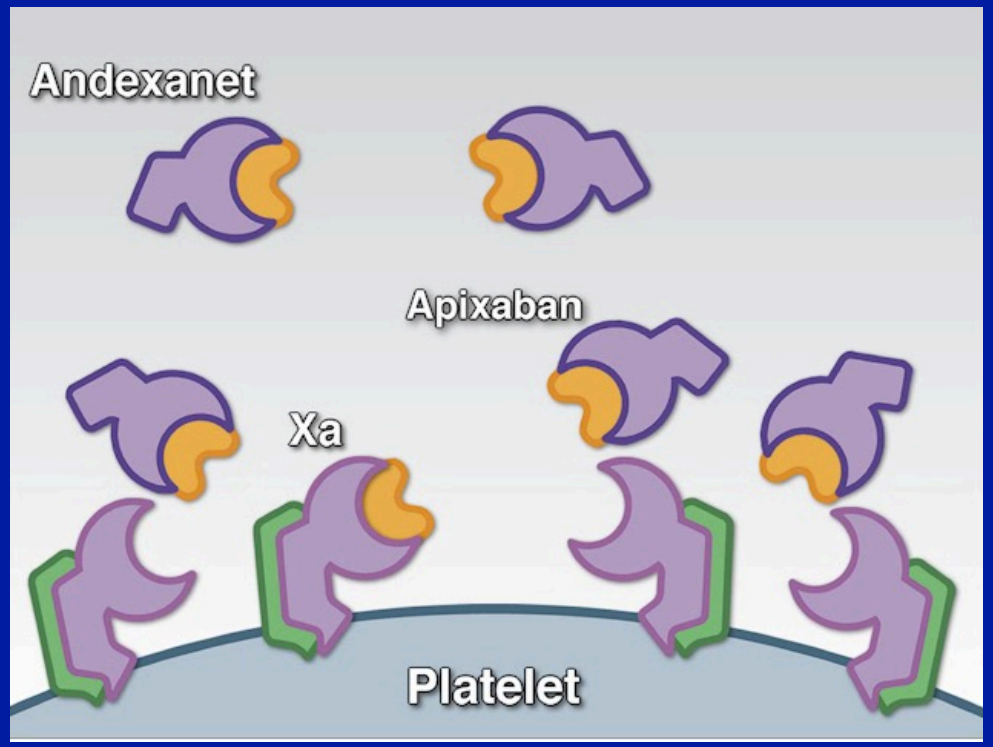
Eikelboom JW et al. Circulation 2015; 132: 2412-2422

Andexanet alfa
Renversement des AOD bloquant le facteur Xa

The Andexanet alfa antidote is a recombinant, modified version of human FXa:

- It acts as a FXa decoy and has high affinity for all direct FXa inhibitors





Siegal D et al. NEJM 2015;

A. Roussin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

CONCLUSIONS

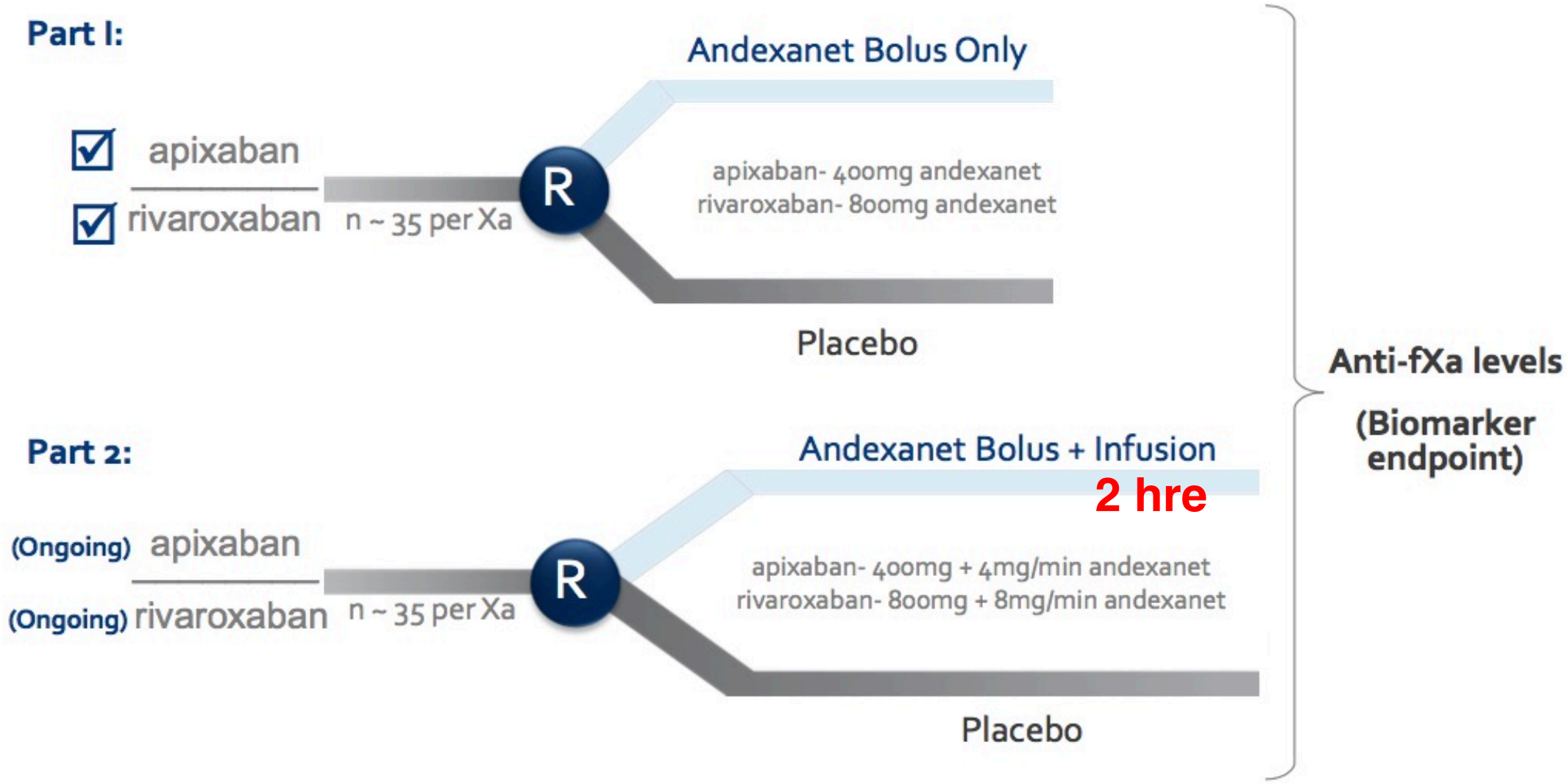
Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects

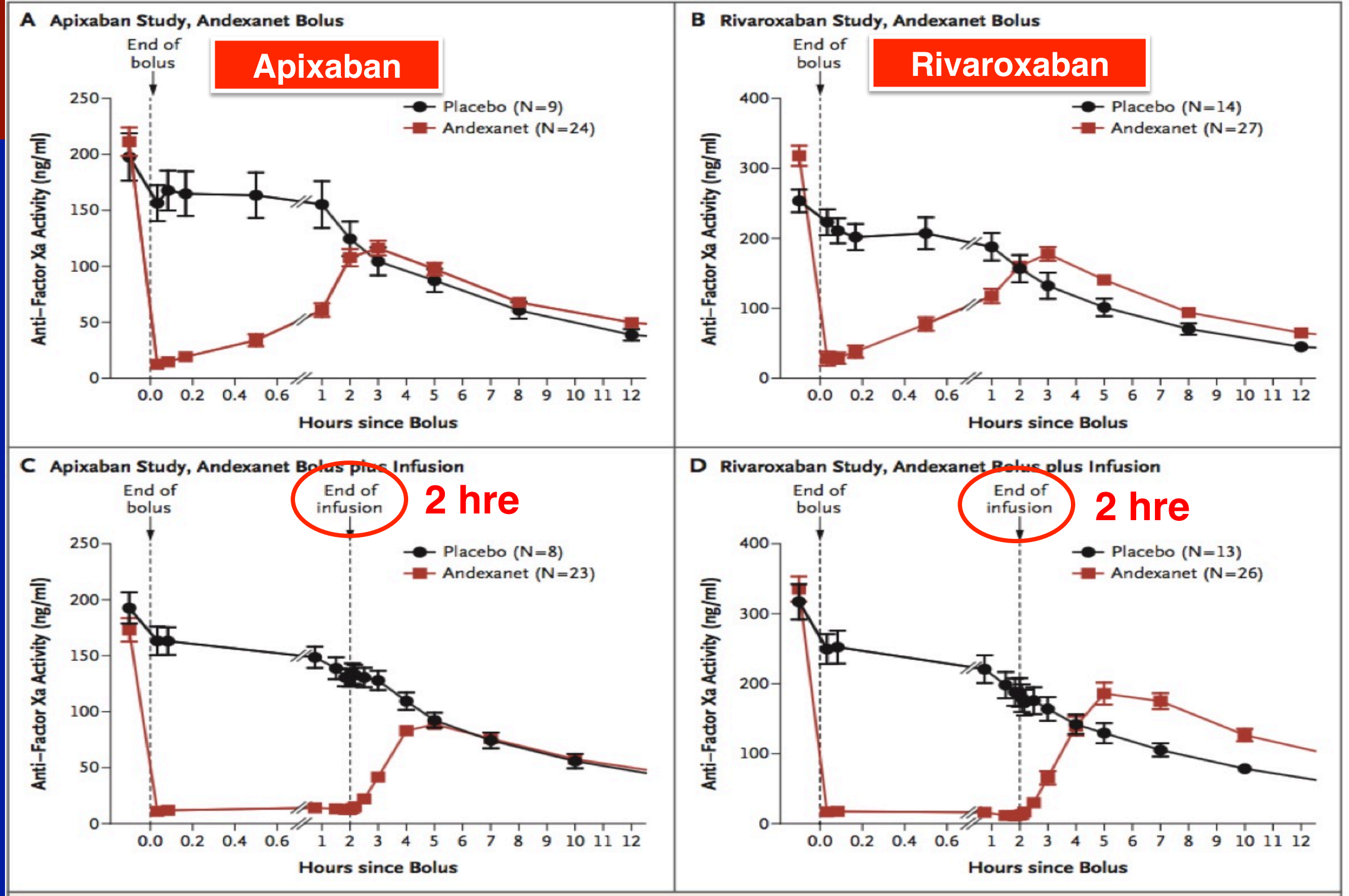
NEJM Novembre 2015

A. Roussin

Andexanet Alfa: ANNEXA™ Registration-Enabling Studies

Accelerated Approval Phase 3 Design for Apixaban and Rivaroxaban




A Apixaban Study, Andexanet Bolus
Apixaban
End of bolus
Placebo (N=9)
Andexanet (N=24)
Anti–Factor Xa Activity (ng/ml)
Hours since Bolus
B Rivaroxaban Study, Andexanet Bolus
Rivaroxaban
End of bolus
Placebo (N=14)
Andexanet (N=27)
Anti–Factor Xa Activity (ng/ml)
Hours since Bolus
C Apixaban Study, Andexanet Bolus plus Infusion
End of bolus
End of infusion
2 hre
Placebo (N=8)
Andexanet (N=23)
Anti–Factor Xa Activity (ng/ml)
Hours since Bolus
D Rivaroxaban Study, Andexanet Bolus plus Infusion
End of bolus
End of infusion
2 hre
Placebo (N=13)
Andexanet (N=26)
Anti–Factor Xa Activity (ng/ml)
Hours since Bolus

Phase 4 Outcomes Study in Bleeding Patients: ANNEXA™-4 on Apixaban, Rivaroxaban and Enoxaparin

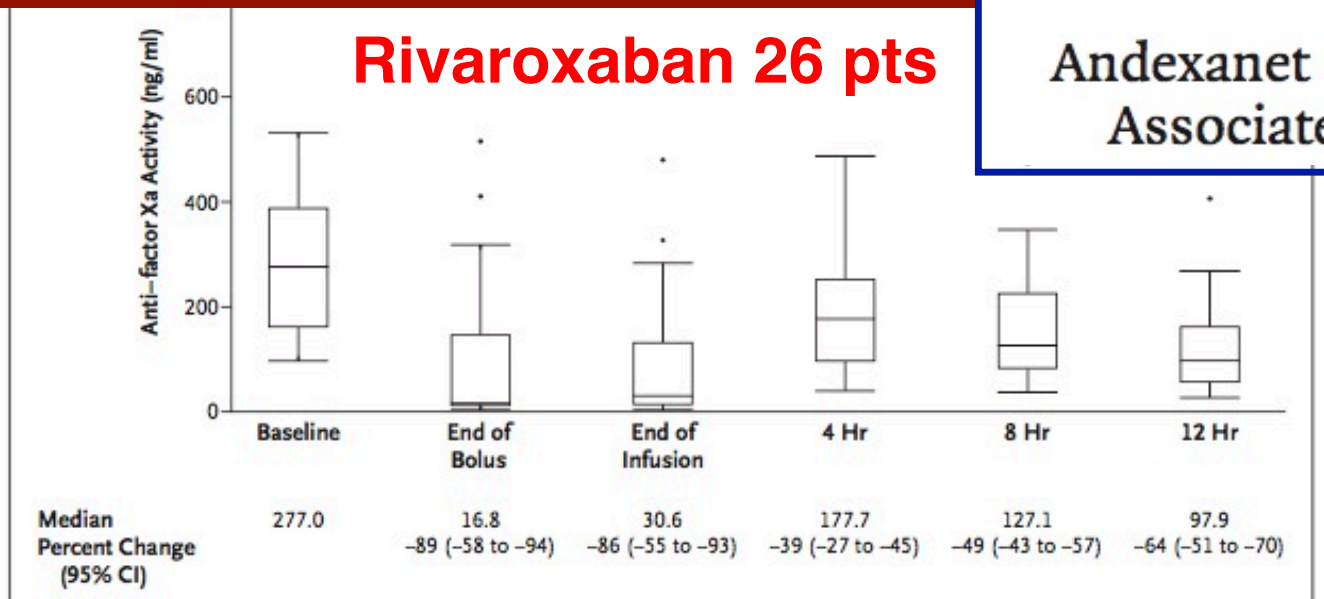
- **An open-label, multinational study in patients receiving fXa inhibitors presenting with acute major bleeding**
  - Two Primary Endpoints
    - First primary: Percent change from baseline in anti-fXa activity
    - Second primary: Occurrence of patients achieving "effective hemostasis" as adjudicated by an Independent Endpoint Adjudication Committee
- **Study is ongoing; to be conducted at over 50 sites in North America and Europe**
- **Plan to add edoxaban to study by mid-2015**

ANNEXA-4

ORIGINAL ARTICLE

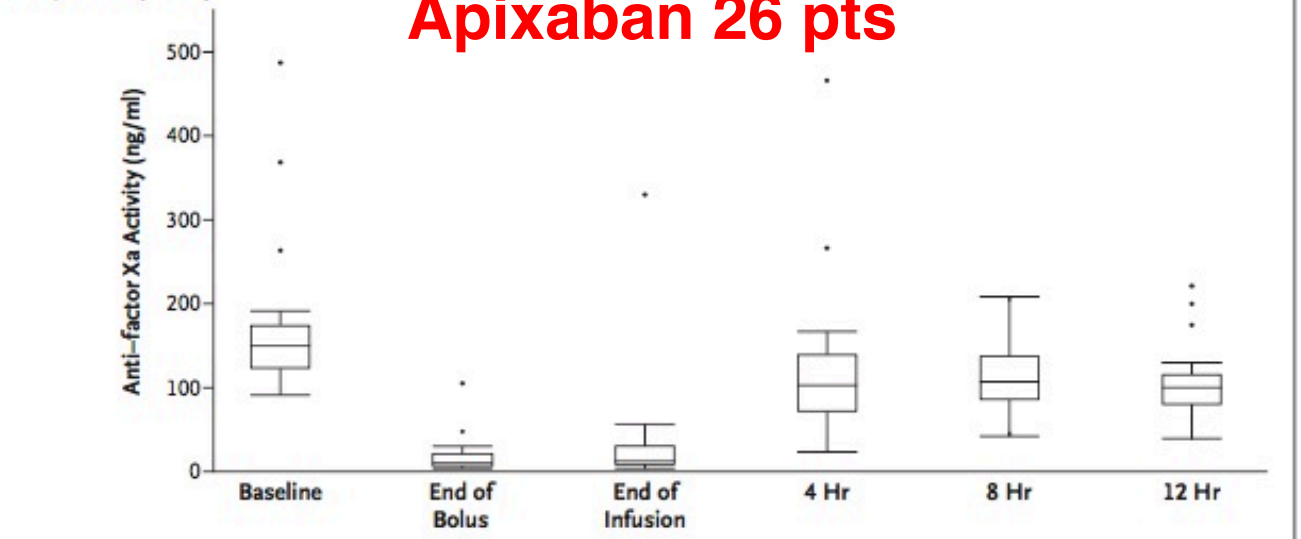
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Rivaroxaban 26 pts



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median Percent Change (95% CI)	277.0	16.8 –89 (–58 to –94)	30.6 –86 (–55 to –93)	177.7 –39 (–27 to –45)	127.1 –49 (–43 to –57)	97.9 –64 (–51 to –70)

Apixaban 26 pts



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median Percent Change (95% CI)	149.7	10.3 –93 (–87 to –94)	12.5 –92 (–85 to –94)	103.0 –30 (–23 to –46)	107.1 –28 (–19 to –38)	100.2 –31 (–27 to –41)

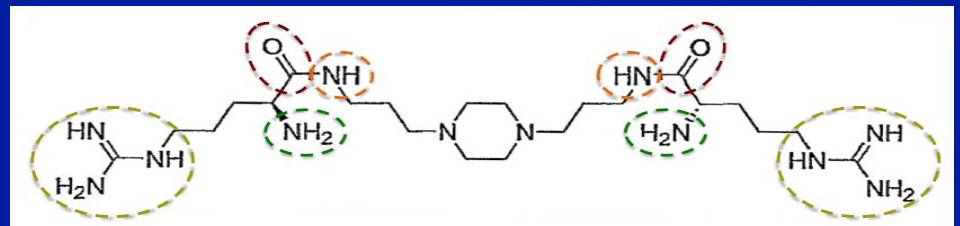
"On the basis of a descriptive preliminary analysis, an initial bolus and subsequent **2-hour infusion** of andexanet substantially reduced anti–factor Xa activity in patients with acute major bleeding associated with factor Xa inhibitors, **with effective hemostasis occurring in 79%**"

Connoly SJ et al. NEJM 2016; 375: 1131-41

PER977 (Aripazine)

- **Inhibiteur universel**: HBPM, HNF, rivaroxaban, apixaban, dabigatran, edoxaban

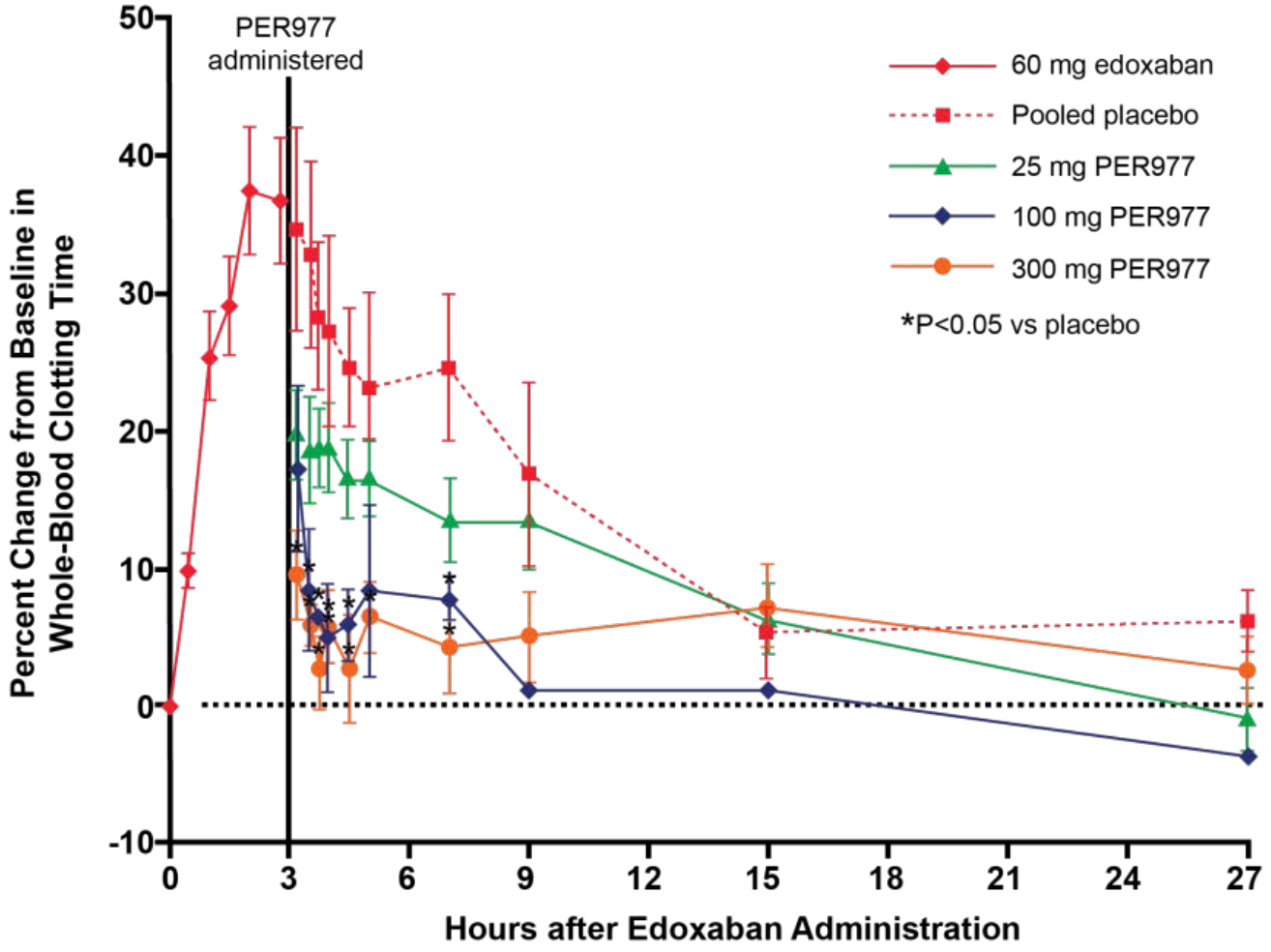
- **Mécanisme d'action:**
  - Petite molécule (~500 daltons), chargée positivement
  - Se lie aux molécules chargées négativement (héparine)
  - Se lie aux molécules neutres par liens hydrogènes
  - Non immunogène et non pro-coagulant



- H-bonds edoxaban, dabigatran, rivaroxaban and heparins
- H-bonds dabigatran, rivaroxaban, apixaban, argatroban, and heparins
- H-Bonds dabigatran, rivaroxaban and heparins
- H-bonds edoxaban and apixaban

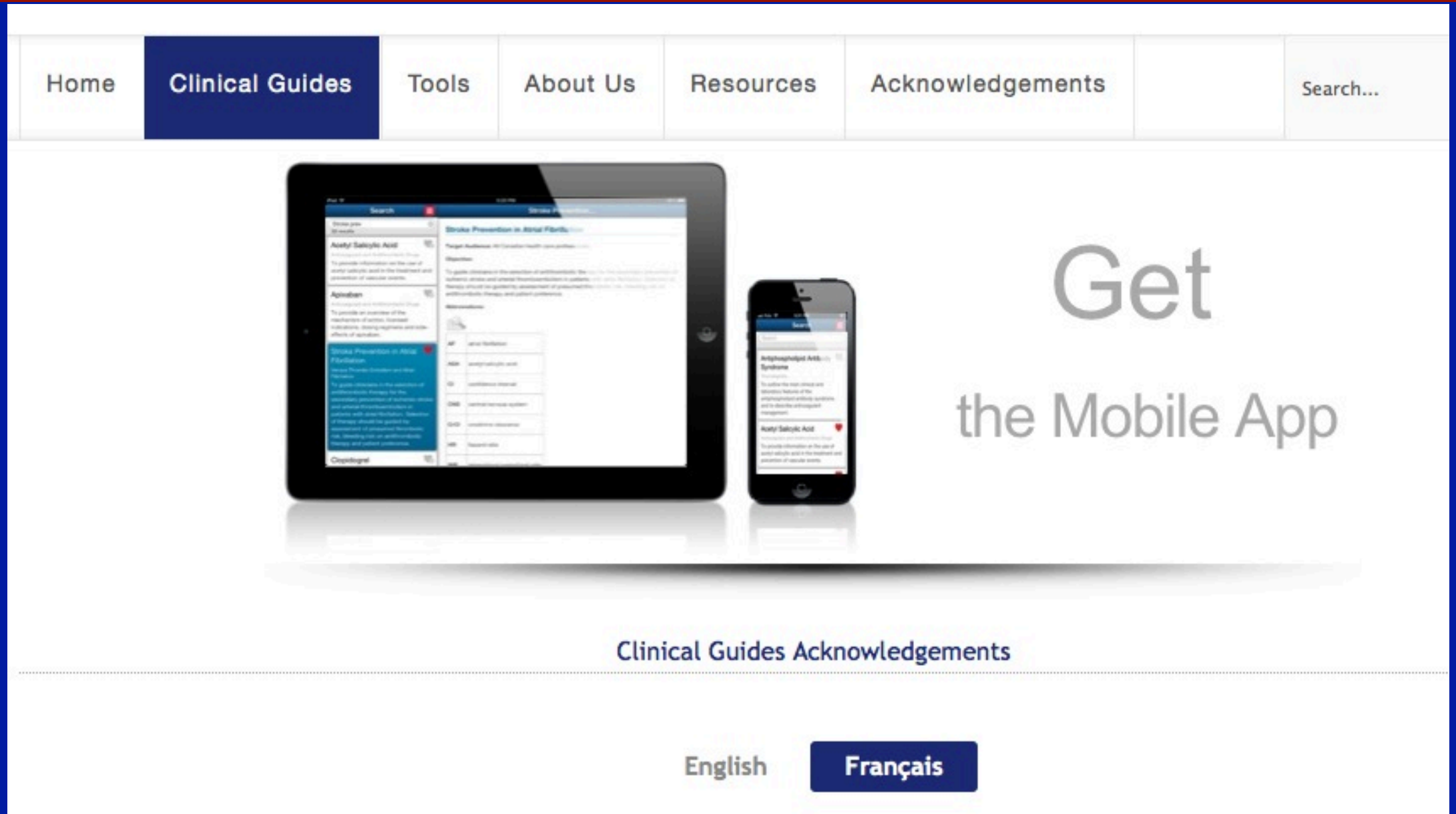
Bahkru et al. AHA Nov 2013, www.perosphere.com

PER977 (Aripazine)
Effet sur l'edoxaban



Ansell JE, et al *N Engl J Med*. 2014;371(22):2141-2142.

Guides de *THROMBOSE CANADA*



Outils de *THROMBOSE CANADA*

TOOLS

Bleed Management

What type of bleeding does the patient have?

- ◯ Minor bleeding (e.g. subconjunctival hemorrhage, small bruising/lacerations, dental bleeding, anterior epistaxis, hemorrhoidal bleeding)
- ◯ Moderate bleeding (e.g. hemodynamically stable gastrointestinal bleeding, uncontrolled posterior epistaxis)
- ◯ Severe/Life-threatening bleeding
  - Intracranial hemorrhage
  - Critical site (e.g. retroperitoneal, intra-spinal, intra-ocular, intra-articular)
  - Actual or impending hemodynamic compromise (e.g. massive GI bleed)

"App" de *THROMBOSE CANADA*

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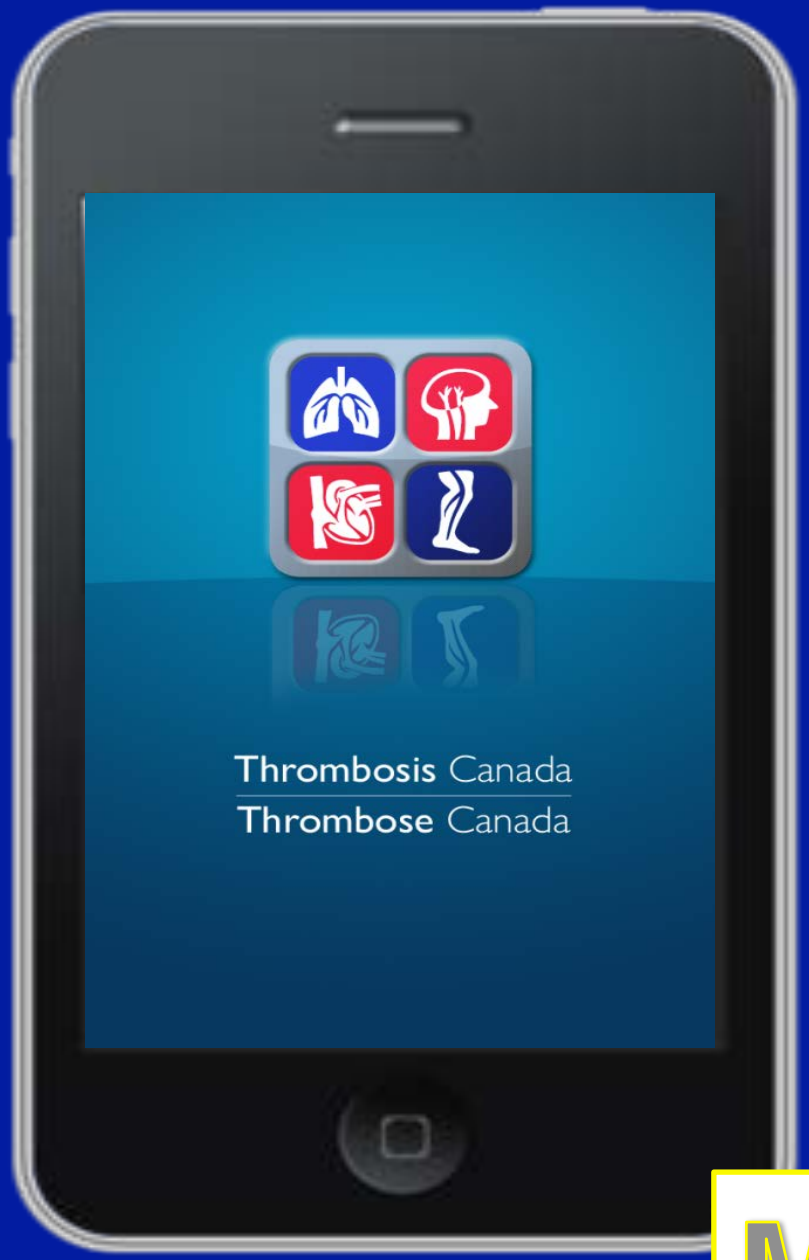
Thrombose Canada

ANDROID APP ON Google play

Download on the App Store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Merci!