Anticoagulants et saignements

SSVQ 20 novembre 2015

OBJECTIFS

- Connaître l'épidémiologie des saignements
- Savoir gérer les saignements
- Connaître les antidotes et leur utilisation

Thrombosis Canada
Thrombose Canada

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Conflits d'intérêts potentiels 2014 - 2015

Comités aviseurs ou aviseur expert:

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

Fonds de recherche:

Astra-Zeneca et Bayer

Conférencier:

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

Risques d'hémorragies associées aux AVK

- **Hémorragie importante**
  - De 1,2 à 7,0 cas par 100 années-patients (études de cohortes)
  - De 0,5 à 4,2 % (essais cliniques)
- **Hémorragie légère**
  - De 2 à 24 cas par 100 années-patients
- **Hémorragie intracrânienne associée aux AVK**
  - Environ 13 000 cas par année aux États-Unis
  - ~ 70 % sont des hémorragies intracérébrales
  - ~ 30 % sont des hématomes sous-duraux

÷ 10 pour le Canada

- **Taux de mortalité lié aux hémorragies intracrâniennes : ~ 60 %**
  - Aggravation des saignements chez ~ 50 % des patients dans les 24 heures

Flaherty *et al. Neurology* 2007; 68:116–21; Libby et Garcia. *Arch Intern Med* 2002; 162: 1893–6; McMahan *et al. J Gen Intern Med* 1998; 13: 311–16; Schulman. *N Engl J Med* 2003; 349: 675–83

AOD vs AVK
Saignements majeurs

Study or Subgroup	TSOACs Events	TSOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Major Bleeding						
EINSTEIN-DVT, 2010	14	1718	20	1711	4.0%	0.70 [0.35, 1.38]
RE-MEDY, 2013	13	1430	25	1426	4.2%	0.52 [0.27, 1.01]
RE-COVER II, 2014	15	1279	22	1289	4.3%	0.69 [0.36, 1.32]
RE-COVER, 2009	20	1274	24	1265	5.0%	0.83 [0.46, 1.49]
AMPLIFY, 2013	15	2676	49	2689	5.1%	0.31 [0.17, 0.55]
J-ROCKET AF, 2012	26	639	30	639	5.9%	0.87 [0.52, 1.45]
EINSTEIN-PE, 2012	26	2412	52	2405	6.6%	0.50 [0.31, 0.80]
HOKUSAI-VTE, 2013	56	4118	66	4122	8.8%	0.85 [0.60, 1.21]
ARISTOTLE, 2011	327	9088	462	9052	13.8%	0.70 [0.61, 0.81]
ROCKET AF, 2011	395	7111	386	7125	13.8%	1.03 [0.89, 1.18]
RE-LY, 2009	741	12091	421	6022	14.2%	0.88 [0.78, 0.98]
ENGAGE-AF-TIMI-48, 2013	672	14014	524	7012	14.3%	0.64 [0.57, 0.72]
Subtotal (95% CI)		**57850**		**44757**	**100.0%**	**0.72 [0.62, 0.85]**
Total events	2320		2081			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 48.96$, df = 11 ($P < 0.00001$); $I^2 = 78\%$

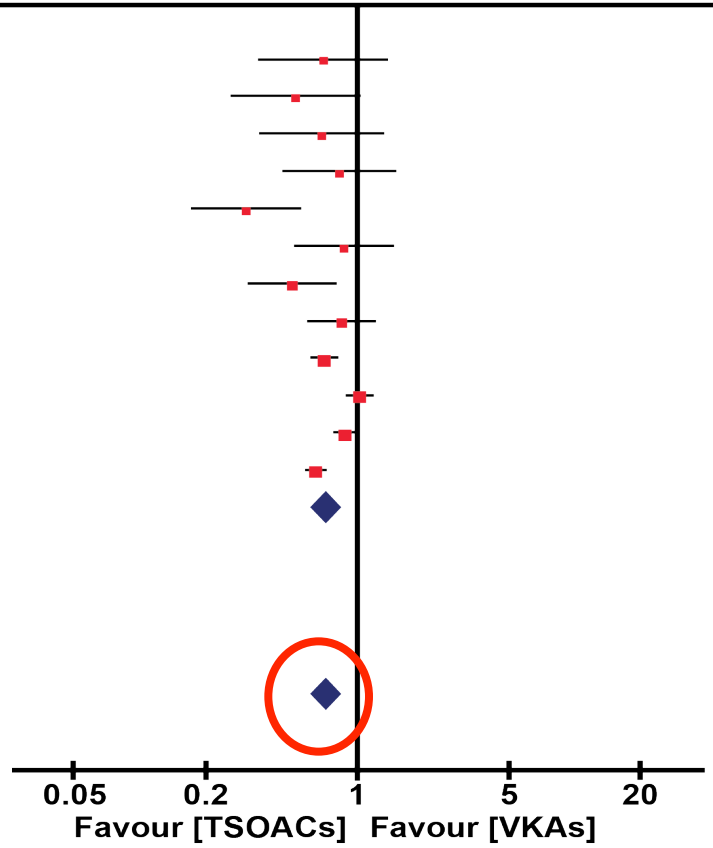
Test for overall effect: $Z = 3.98$ ($P < 0.0001$)

Total (95% CI)		**57850**		**44757**	**100.0%**	**0.72 [0.62, 0.85]**
Total events	2320		2081			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 48.96$, df = 11 ($P < 0.00001$); $I^2 = 78\%$

Test for overall effect: $Z = 3.98$ ($P < 0.0001$)

Test for subgroup differences: Not applicable



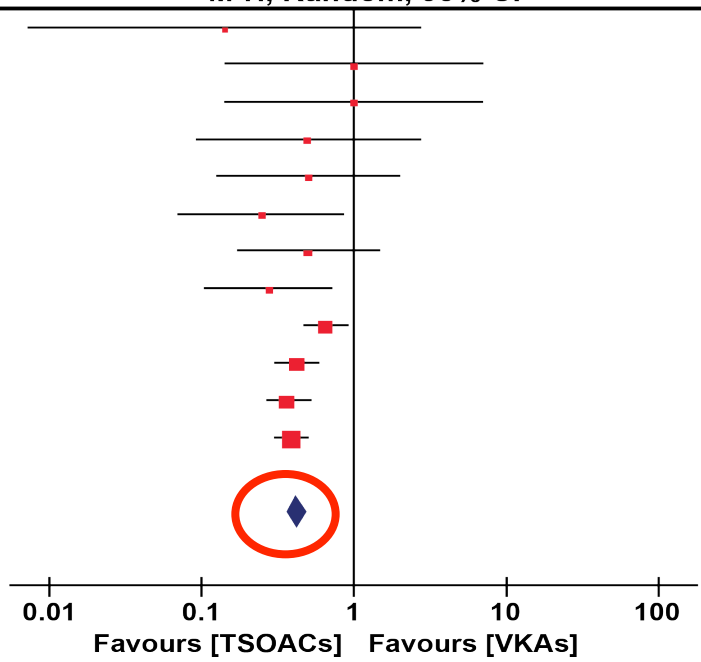
Chai-Adisaksopha C, et al. *Blood.* 2014;124(15):2450-2458.

AOD vs AVK
Hémorragies intra-crâniennes

Study or Subgroup	TSOACs Events	TSOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
RE-COVER, 2009	0	1274	3	1265	0.3%	0.14 [0.01, 2.74]
EINSTEIN-DVT, 2010	2	1718	2	1711	0.6%	1.00 [0.14, 7.06]
RE-COVER II, 2014	2	1279	2	1289	0.6%	1.01 [0.14, 7.14]
RE-MEDY, 2013	2	1430	4	1426	0.8%	0.50 [0.09, 2.72]
AMPLIFY, 2013	3	2676	6	2689	1.2%	0.50 [0.13, 2.01]
EINSTEIN-PE, 2012	3	2412	12	2405	1.4%	0.25 [0.07, 0.88]
J-ROCKET AF, 2012	5	639	10	639	2.0%	0.50 [0.17, 1.45]
HOKUSAI-VTE, 2013	5	4118	18	4122	2.3%	0.28 [0.10, 0.75]
ROCKET AF, 2011	55	7111	84	7125	18.6%	0.66 [0.47, 0.92]
ARISTOTLE, 2011	52	9088	122	9052	20.3%	0.42 [0.31, 0.59]
RE-LY, 2009	66	12091	90	6022	21.1%	0.37 [0.27, 0.50]
ENGAGE-AF-TIMI-48, 2013	102	14014	132	7012	31.0%	0.39 [0.30, 0.50]
Total (95% CI)		**57850**		**44757**	**100.0%**	**0.43 [0.37, 0.50]**
Total events	297		485			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.26$, df = 11 (P = 0.42); $I^2 = 2\%$

Total for overall effect: Z = 10.95 (P < 0.00001)



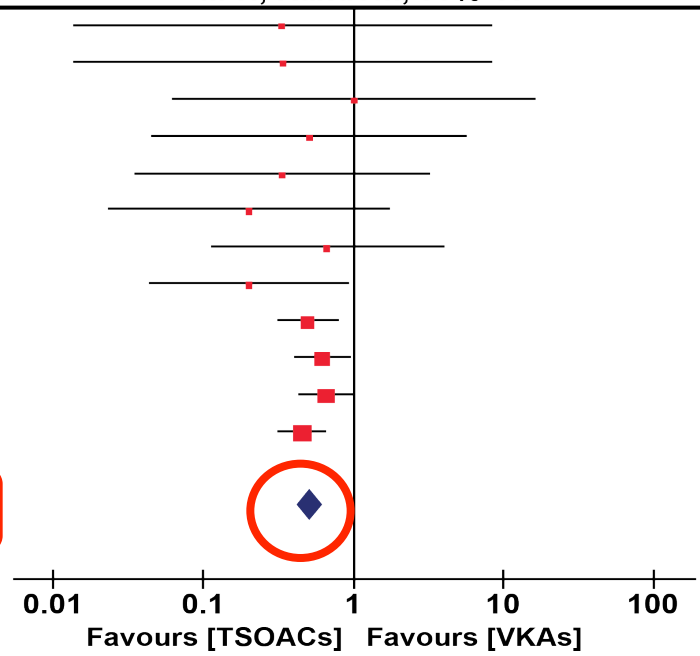
Chai-Adisaksopha C, et al. *Blood.* 2014;124(15):2450-2458.

AOD vs AVK
Saignements mortels

Study or Subgroup	TSOACs Events	TSOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Random, 95% CI
RE-MEDY, 2013	0	1430	1	1426	0.4%	0.33 [0.01, 8.15]
RE-COVER II, 2014	0	1279	1	1289	0.4%	0.34 [0.01, 8.24]
RE-COVER, 2009	1	1274	1	1265	0.5%	0.99 [0.06, 15.86]
AMPLIFY, 2013	1	2676	2	2689	0.7%	0.50 [0.05, 5.54]
J-ROCKET AF, 2012	1	639	3	639	0.8%	0.33 [0.03, 3.20]
EINSTEIN-DVT, 2010	1	1718	5	1711	0.9%	0.20 [0.02, 1.70]
EINSTEIN-PE, 2012	2	2412	3	2405	1.3%	0.66 [0.11, 3.97]
HOKUSAI-VTE, 2013	2	4118	10	4122	1.7%	0.20 [0.04, 0.91]
ROCKET AF, 2011	27	7111	55	7125	19.0%	0.49 [0.31, 0.78]
ARISTOTLE, 2011	34	9088	55	9052	22.0%	0.62 [0.40, 0.94]
RE-LY, 2009	51	12091	39	6022	23.1%	0.65 [0.43, 0.99]
ENGAGE-AF-TIMI-48, 2013	53	14014	59	7012	29.3%	0.45 [0.31, 0.65]
Total (95% CI)		**57850**		**44757**	**100.0%**	**0.53 [0.43, 0.64]**
Total events	173		234			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.25$, df = 11 (P = 0.92); $I^2 = 0\%$

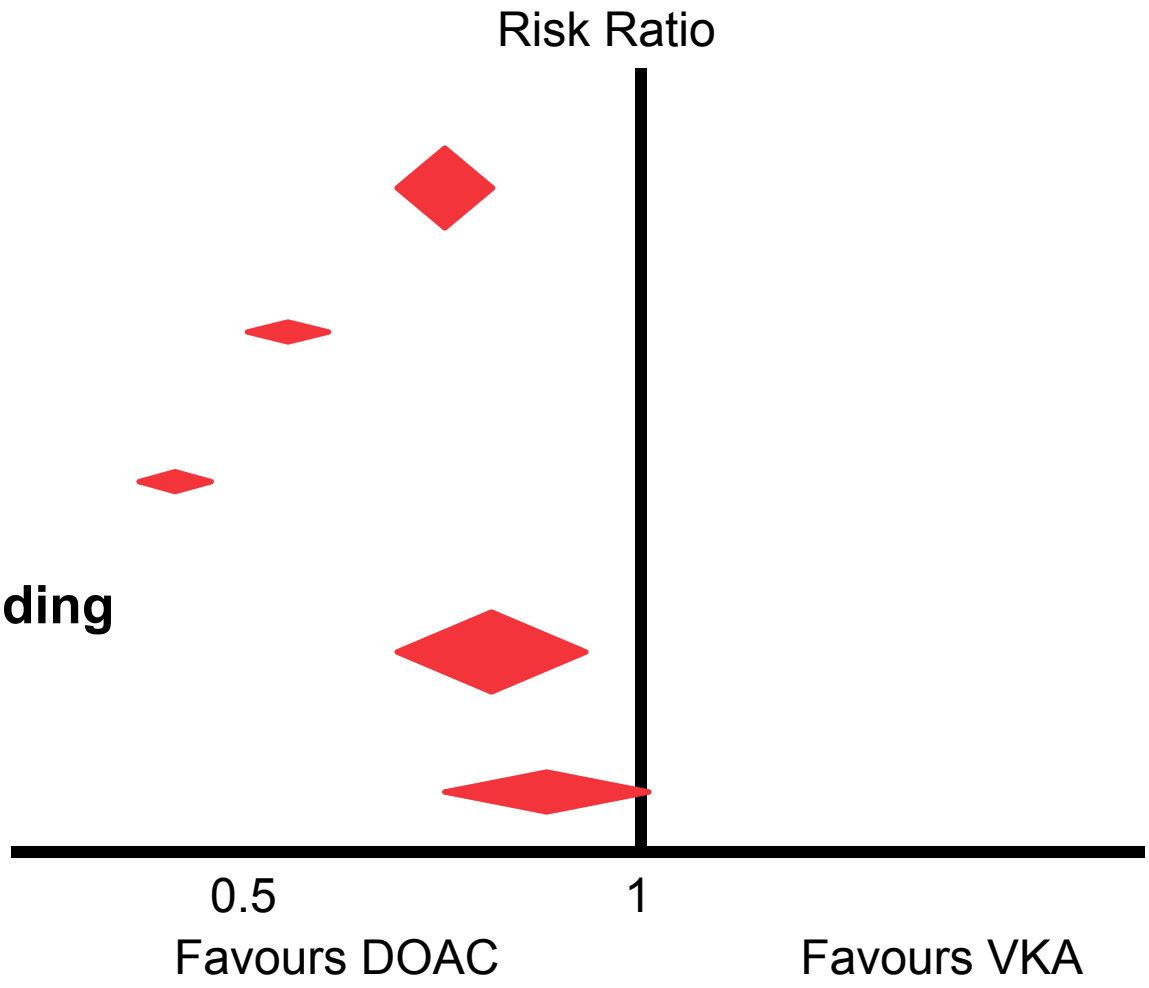
Test for overall effect: Z = 6.30 (P < 0.00001)



Chai-Adisaksopha C, et al. Blood. 2014;124(15):2450-2458.

AOD vs AVK
Saignements études Phase III

Major bleeding
0.72 (0.62-0.85)
Fatal bleeding
0.53 (0.43-0.64)
Intracranial bleeding
0.43 (0.37-0.50)
Clinically relevant non-major bleeding
0.78 (0.68-0.90)
Major GI bleeding
0.94 (0.75-1.19)



Chai-Adisaksopha C, et al. *Blood.* 2014;124(15):2450-2458.

Saignements majeurs pour la FA
Taux de mortalité AVK vs AOD

	Warfarine		AOD	
	N	%	N	%
ROCKET AF	55/386	14%	27/395	7%
Dabigatran revue systématique	53/407*	13%	57/627*	9%
ARISTOTLE	55/462	12%	34/327	10%
ENGAGE AF-TIMI 48	59/524	11%	32/418 21/254	8% 8%

Les saignements majeurs avec les AVK ont un haut taux de mortalité malgré les antidotes disponibles

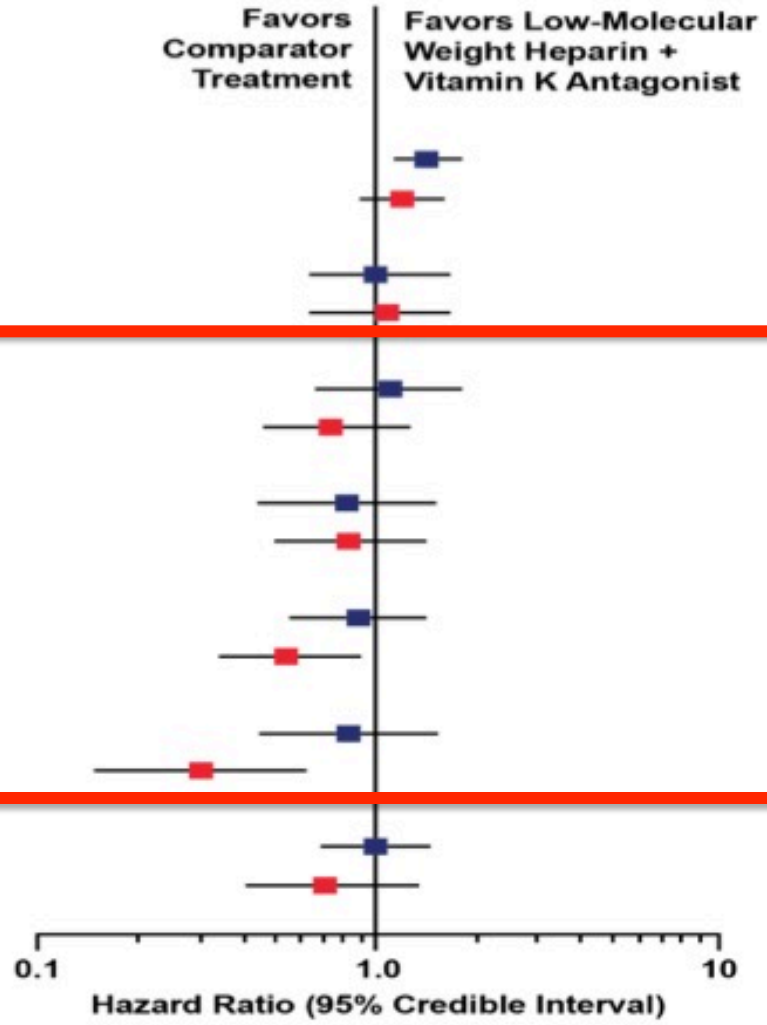
*estimé de la publication

Patel MR, et al. *N Engl J Med*. 2011;365(10):883-891;
Majeed A, et al. *Circulation*. 2013;128(21):2325-2332;
Granger CB, et al. *N Engl J Med*. 2011;365(11):981-992;
Giugliano RP, et al. *N Engl J Med*. 2013;369(22):2093-2104.

AOD vs HBPM-AVK pour TEV
Saignements majeurs

A. Recurrent venous thromboembolism and major bleeding

ComparatorTreatment	Hazard Ratio (95% Credible Interval)
Unfractionated heparin + vitamin K antagonist	
Recurrent VTE	1.42 (1.15-1.80)
Major bleeding	1.19 (0.90-1.58)
Fondaparinux + vitamin K antagonist	
Recurrent VTE	1.01 (0.65-1.62)
Major bleeding	1.07 (0.65-1.70)
Low-molecular-weight heparin + dabigatran	
Recurrent VTE	1.11 (0.67-1.80)
Major bleeding	0.74 (0.46-1.26)
Low-molecular-weight heparin + edoxaban	
Recurrent VTE	0.83 (0.46-1.49)
Major bleeding	0.84 (0.51-1.39)
Rivroxaban	
Recurrent VTE	0.90 (0.57-1.41)
Major bleeding	0.55 (0.35-0.89)
Apixaban	
Recurrent VTE	0.84 (0.46-1.51)
Major bleeding	0.31 (0.15-0.62)
Low-molecular-weight heparin alone	
Recurrent VTE	0.99 (0.70-1.42)
Major bleeding	0.71 (0.42-1.31)



Castellucci LA, et al. *JAMA*. 2014;312(11):1122-1135.

La réalité. FDA 2014: 134,414 patients

Dabigatran et Warfarine pour la FA 2010 à 2012

	Nombre d'événements		Incidence par 1000 pts-années		HR	P
	Dabi	W	Dabi	W		
AVC ischémiques	205	270	11.3	13.9	0.8	0.02
Saignements majeurs	777	851	42.7	43.9	0.97	0.5
Digestifs	623	513	34.2	26.5	1.28	<0.001
Intracrâniens	60	186	3.3	9.6	0.34	<0.001
Intracérébraux	44	142	2.4	7.3	0.44	<0.001
Infarctus du myocarde	285	327	15.7	16.9	0.92	0.29
Saignements nécessitant hospitalisation	1079	1139	59.3	58.8	1.00	0.97
Mortalité	603	744	32.6	37.8	0.86	0.006

Graham et al. Circulation 2014

Données de la "vraie vie"
AVK, dabigatran et rivaroxaban

	Types d'étude	AOD	Maladie	# de patients	F/U	Saignements majeurs taux
Beyer, 2014	Régistre prospectif	Rivaroxaban	VTE or AF	1776	2 ans	3.4%
Beyer, 2013	Régistre prospectif	Dabigatran	AF	303	14 mois	3.2%
Fontaine, 2014	Cohorte rétrospective	Dabigatran, rivaroxaban	AF	2579	2 ans	0.5%
Sorensen, 2103	Cohorte rétrospective	Dabigatran, warfarine	AF	52,366	4 mois	Tous saignements: 3.9%, dabigatran 110 mg: 1.4%
Larsen, 2013	Cohorte rétrospective	Dabigatran, warfarine	AF	13914	10.5 mois	Dabigatran: 2.2-2.5% Warfarine: 2.9-3.5%

Beyer-Westendorf, et al. *Blood.* 2014;124:955-962;
Beyer-Westendorf ,et al. *European Heart Journal.* 2013;34(suppl 1):P4871;
Fontaine GV, et al. *Clin Appl Thromb Hemost.* 2014;20(7):665-672;
Sorensen R, et al. *BMJ* Open. 2013; 3(5);
Larsen TB, et al. *J AM Coll Cardiol.* 2013;61(22):2264-2273.

AOD vs AVK: mortalité

Revue systématique et méta-analyse

Study or Subgroup	DOACs Events	DOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
J-EINSTEIN DVT/PE, 2015	3	81	0	19	0.0%	1.71 [0.09, 31.74]
J-ROCKET AF, 2012	7	637	5	637	0.2%	1.40 [0.45, 4.39]
RE-MEDY, 2013	17	1430	19	1426	0.5%	0.89 [0.47, 1.71]
RE-COVER, 2009	21	1274	21	1265	0.6%	0.99 [0.55, 1.81]
RE-COVER II, 2014	25	1279	25	1289	0.7%	1.01 [0.58, 1.74]
EINSTEIN-DVT, 2010	38	1731	42	1718	1.1%	0.90 [0.58, 1.39]
AMPLIFY, 2013	41	2691	52	2704	1.3%	0.79 [0.53, 1.19]
EINSTEIN-PE, 2012	58	2419	50	2413	1.5%	1.16 [0.80, 1.68]
HOKUSAI-VTE, 2013	132	4118	126	4122	3.7%	1.05 [0.82, 1.33]
ROCKET AF, 2011	582	7081	632	7090	18.4%	0.92 [0.83, 1.03]
RE-LY, 2009	884	12091	487	6022	19.0%	0.90 [0.81, 1.01]
ARISTOTLE, 2011	603	9120	669	9081	19.0%	0.90 [0.81, 1.00]
ENGAGE-AF-TIMI-48, 2013	1510	14069	839	7036	33.9%	0.90 [0.83, 0.97]
Total (95% CI)		58021		44822	100.0%	0.91 [0.87, 0.96]
Total events	3921		2967			

Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 4.50$, d.f. = 12 ($P = 0.97$); $I^2 = 0\%$

Test for overall effect: $Z = 3.83$ ($P = 0.0001$)

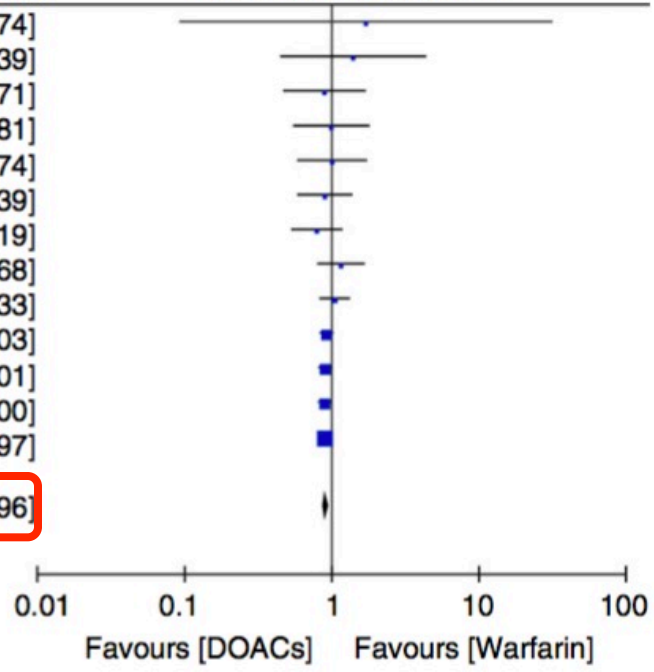


Fig. 3. All-cause mortality comparing direct oral anticoagulant vs. warfarin.

Conclusions

The use of DOACs compared with warfarin is associated with a lower rate of fatal bleeding, case-fatality rate of major bleeding, cardiovascular mortality and all-cause mortality.

Chai-Adisaksopha C et al. JTH 2015; 13: 2012-20

Gestion des saignements sous AVK

Minor

(e.g. subconjunctival hemorrhage, small bruising/ lacerations, dental bleeding, self-limited anterior epistaxis, hemorrhoids)

- Continue warfarin
- Check CBC and INR
- Assess co-medications that may contribute to bleeding (antiplatelet therapies, SSRIs, NSAIDs, fish oil)

Moderate

(e.g. hemodynamically stable GI bleeding, uncontrolled posterior epistaxis)

- Check CBC and INR
- Bleeding risk >> thrombosis risk → reverse warfarin if INR >1.5
  - Vitamin K 2-5 mg po **(action 12-24 hours)**
- Thrombosis risk >> bleeding risk → no reversal, monitor
- Local measures (e.g. compression, packing, splinting)

Severe/life-threatening

(e.g. ICH, critical site, hemodynamic compromise, hemoglobin decrease ≥20 g/L or of ≥2 units RBCs)

- Resuscitation and discontinue warfarin
- Local measures and referral for definitive treatment
- Reverse warfarin if INR >1.5
  - Vitamin K 10 mg IV **(action 6-12 hours)** and PCC as per INR and weight (kg)
- Transfuse to maintain Hb >70 g/L and plt count >50-100x10^9/L

Options québécoises pour l'inversion d'un AVK

Vitamine K

- Administration POS ou IV
- Produit accessible et abordable
- Réponse lente et imprévisible

Plasma humain (PFC)

- Contient des facteurs qui sont requis et d'autres qui ne le sont pas
- Risque de surcharge liquidienne et de transmission virale
- Administration plus longue en raison du temps de décongélation et de transfusion
- Perfusion nécessitant la surveillance du patient
- Inversion complète du traitement anticoagulant non garantie

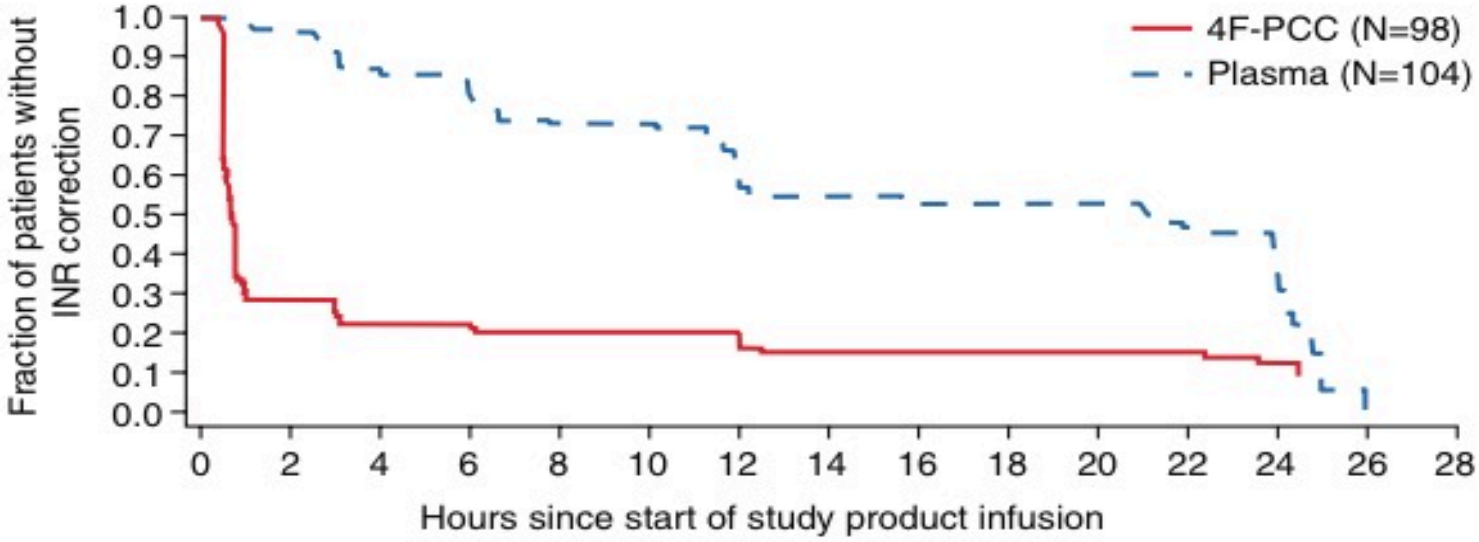
Concentrés de facteurs de coagulation (p. ex., Beriplex®)

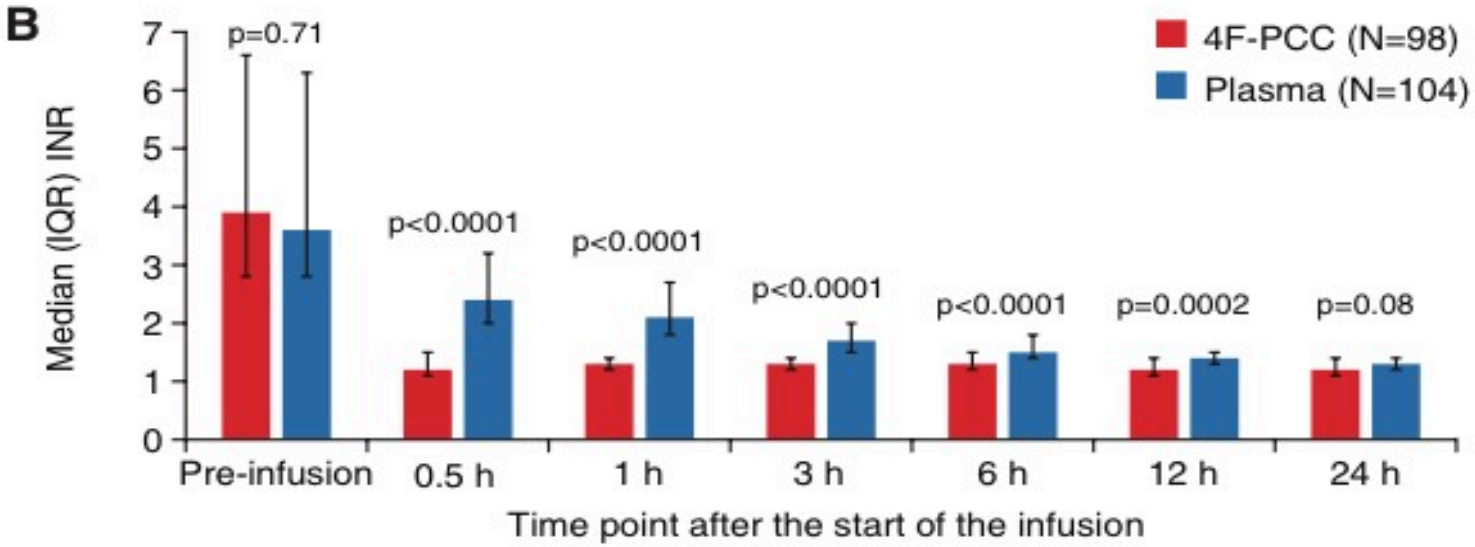
- Préparation concentrée contenant tous les facteurs de coagulation requis
- Possibilité d'une administration rapide
- Faible volume (20 mL)
- Effet prévisible et mesurable
  - Baisse rapide et démontrée du RNI à ≤ 1,3 dans les 30 minutes suivant l'administration de Beriplex®
- Avec Vitamine K

Adapté de : The Pharmacology and Management of Vitamin K Antagonists, *CHEST*, septembre 2004

Efficacité PCC chez patients saignant sous AVK

Étude Phase IIIb de non-infériorité, multi-centrique et ouverte





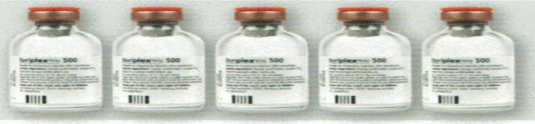
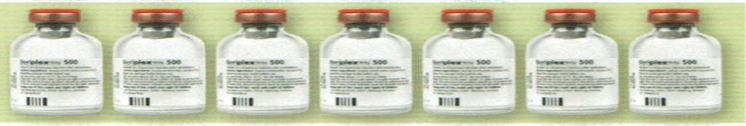
Sarode R et al. Circ 2013; 128: 1234-43

Dose de Beriplex™ pour un saignement
Selon le RNI pour un patient sous AVK

Dose requise :
La dose dépendra du rapport normalisé international (RNI) avant traitement et du RNI visé. Le tableau suivant indique les doses approximatives (en ml/kg de p.c. pour le produit reconstitué et en UI de facteur IX/kg de p.c.) requises afin de normaliser le RNI (p. ex., ≤ 1,3) en fonction de différentes valeurs initiales du RNI.

- Vitesse de perfusion = 8 ml/min

$250 la fiole

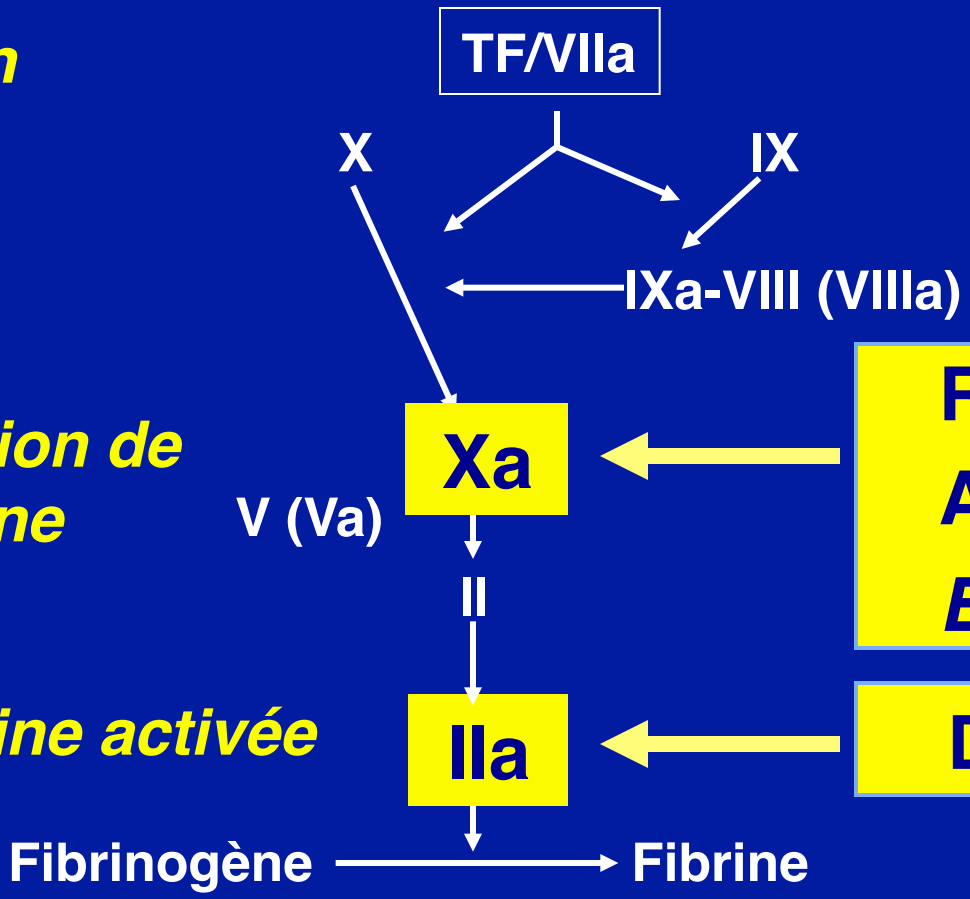
Les doses administrées sont établies en fonction d'une personne pesant 70 kg.				
RNI initial	Dose UI/kg	Dose requise pour une personne de 70 kg	Nbre de flacons correspondant (1 flacon = 500 UI de facteur IX)	Durée de la perfusion à 8 ml/min
2,0 – 3,9	25	1 750 UI		10 min
4,0 – 6,0	35	2 450 UI		12,5 min
> 6	50	3 500 UI		17,5 min

- Chez les patients pesant plus de 100 kg, le calcul de la dose doit être basé sur 100 kg de p.c.

Doses pour renverser un NACO ?

AOD 2015

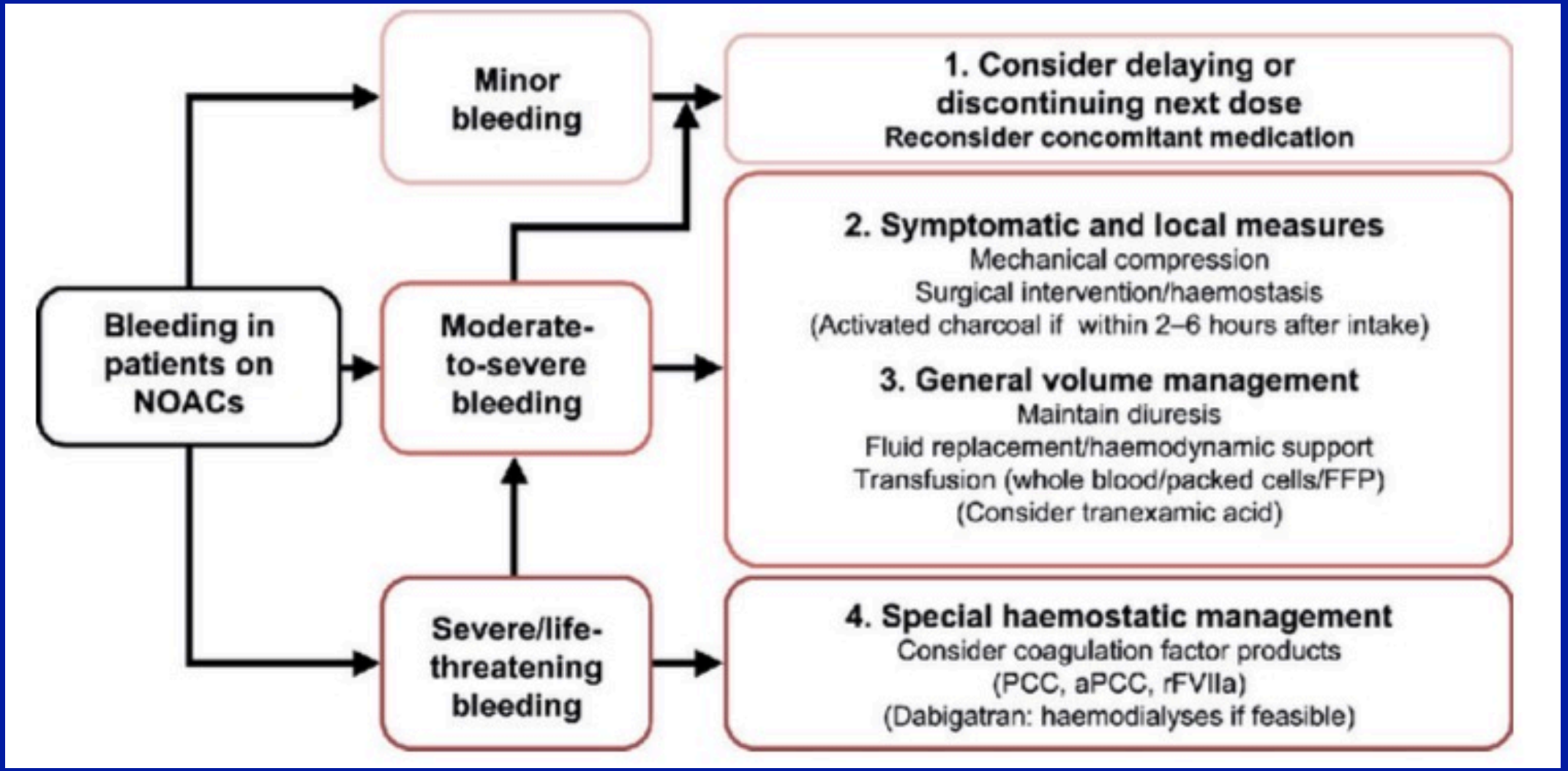
Cascade de coagulation



Rivaroxaban (Xarelto™)
Apixaban (Eliquis™)
Edoxaban (Savaysa™)

Dabigatran (Pradaxa™)

Renversement du dabigatran, rivaroxaban et apixaban
Stratification du risque de saignement et gestion 2015



Weitz JI, Pollack CV. Thrombosis Haemostasis 2015

A Roussin MD

AOD: Stratégies de renversement

	Strategy	Mechanism
Non-specific	Activated charcoal	Decontamination
	Hemodialysis	Accelerated elimination (only for dabigatran)
	PCC	Replacement of factors II, VII, IX, X
	rVIIa, aPCC (FEIBA)	Activated coagulation factors
	PER977	Small synthetic molecule
Specific	Idarucizumab	Monoclonal antibody against dabigatran
	Andexanet	Recombinant inactive FXa

In vitro Studies	Animal Studies	Healthy Volunteers
May not simulate in vivo biology	Animals may differ from humans	Healthy volunteers may differ from patients
Laboratory endpoints may not predict clinical outcomes	Artificial injury models may differ from clinical bleeding	Laboratory endpoints may not predict clinical outcomes

Antidotes
Pour les AOD

Company	Compound	Reversal for:			Status
		Factor Xa inhibitor	Factor IIa inhibitor	LMWH/ fondaparinux	
Portola Pharmaceuticals	ANNEXA™ ?, (andexanet alfa)	Universal	No	Yes	Phase III (apixaban/ rivaroxaban) planned (edoxaban): ANNEXA A + R
Boehringer Ingelheim	PRAXBIND™ 50mg/ml (idarucizumab) 3,500$ US	No	Specific for dabigatran	No	Phase III : RE-VERSE AD FDA approved
Perosphere, Inc.	(Ciraparantang, Aripazine) PER977	Universal	Universal	Universal	Phase II ongoing[6,7]

Antidotes pour les AOD

Études en cours

IDARUCIZUMAB
Praxbind™
Target: dabigatran

Phase I → **Phase II** → **Phase III**
Patients requiring urgent surgery/major bleeding: NEJM 2015
→ **Approved**
Oct 2015

Andexanet alfa
Target: FXa inhibitors

Phase I → **Phase II** → **Phase III**
Anti-Xa: NEJM 2015
Patients with bleeding: Jan 2015

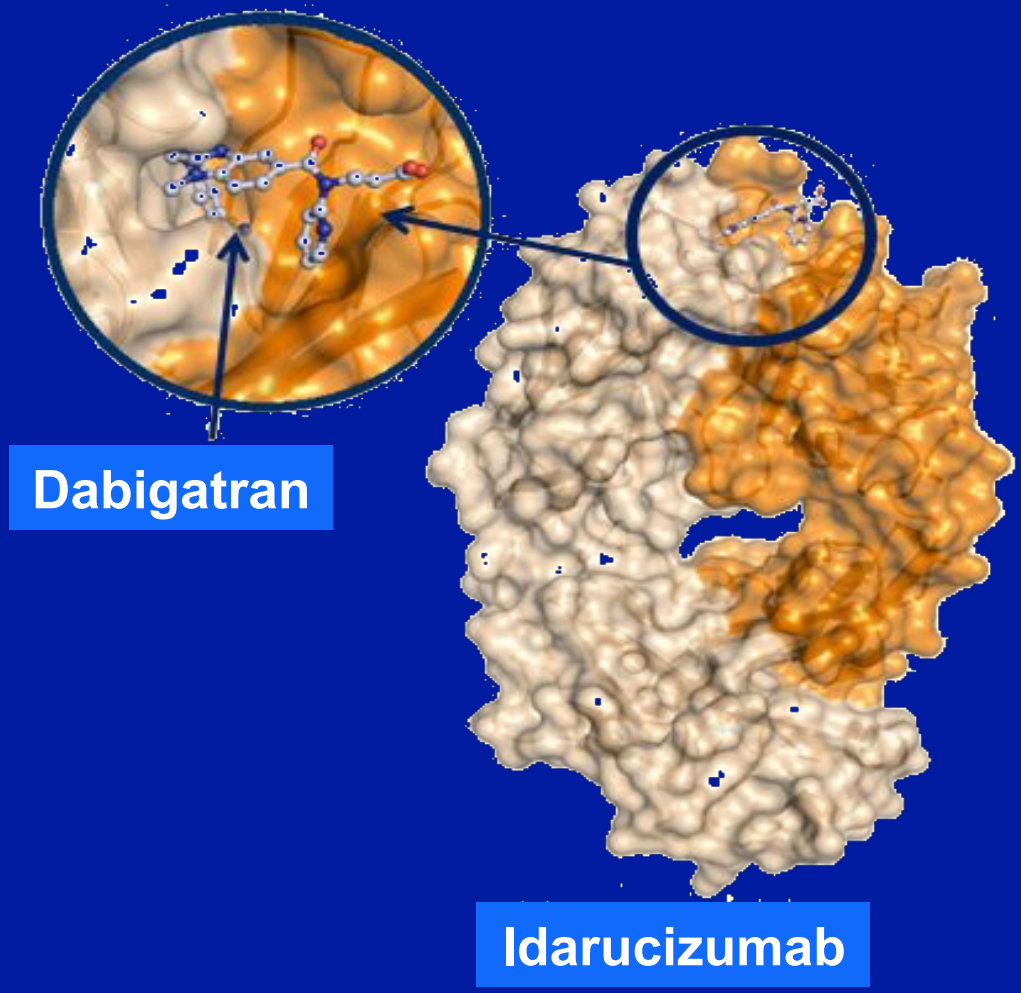
Ciraparantag/Aripazine
(PER977)
Target: universal

Phase I → **Phase II**
Ongoing[5]

A. Roussin

Antidote pour Dabigatran (Idarucizumab)

Praxbind™

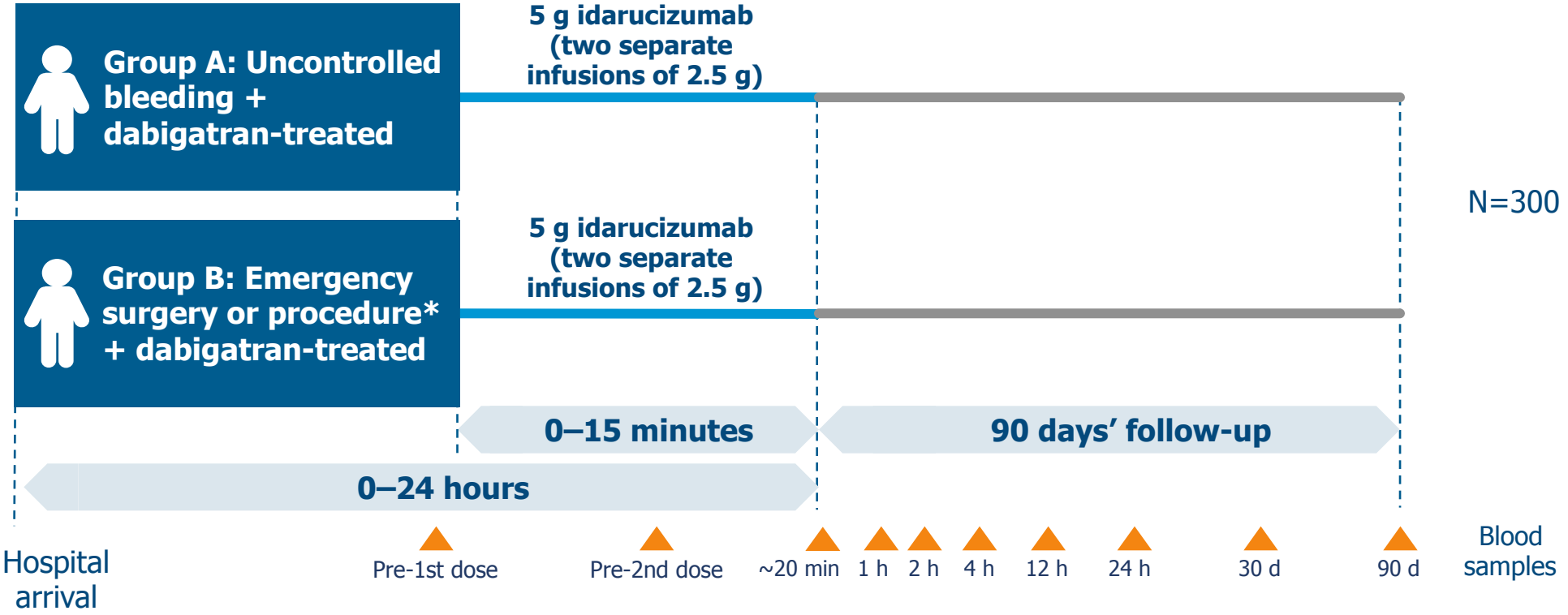


- Humanized Fab fragment
- Binding affinity to dabigatran ~350× higher than thrombin
- No intrinsic procoagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion; immediate onset of action
- Half-life (4.5 – 9 hr)

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

RE-VERSE AD™

Multicentre, open-label, single-arm Phase III trial



Primary endpoint
Reversal of dabigatran activity

Multiple safety endpoints

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

RE-VERSE AD™

Interim NEJM 2015 publication: first 90 patients

Group A: Uncontrolled bleeding

51 patients

Group B: Emergency surgery or procedure

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™
Baseline patient characteristics

	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™

Baseline patient drug characteristics

	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™

Types of Bleeding in Group A and Reasons for Surgery in Group B

	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

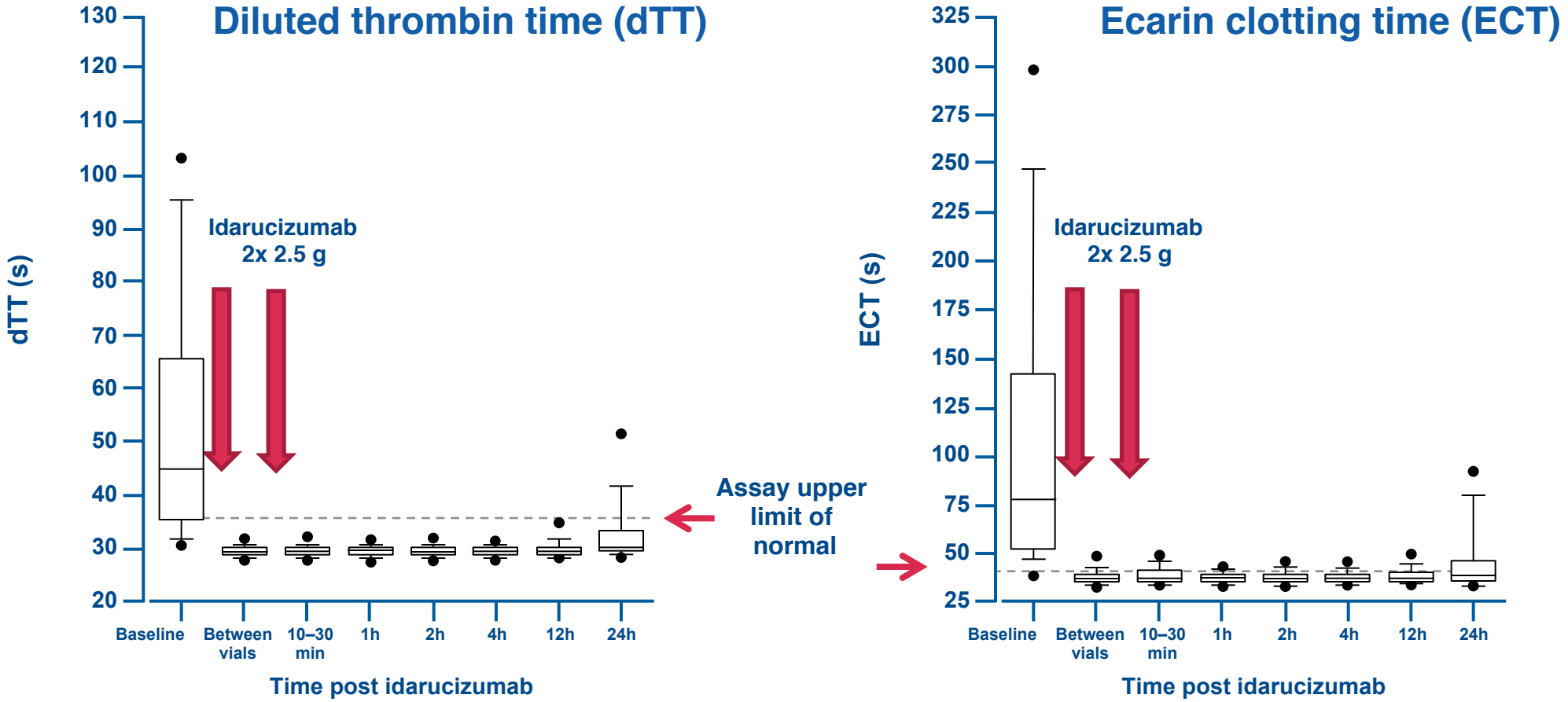
	Group B (n=39)
Reason for surgery†	
Aortic dissection	1
Pericardial tamponade	1
Peritonitis	1
Acute mesenteric ischaemia with sepsis	2
Bone fractures	8
Acute cholecystitis	5
Acute renal insuff., catheter placement	4
Acute appendicitis	3
Joint/wound infection	3
Abscess (suprapubic, scrotal)	2

†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

Primary Endpoint in Group A / Bleeding

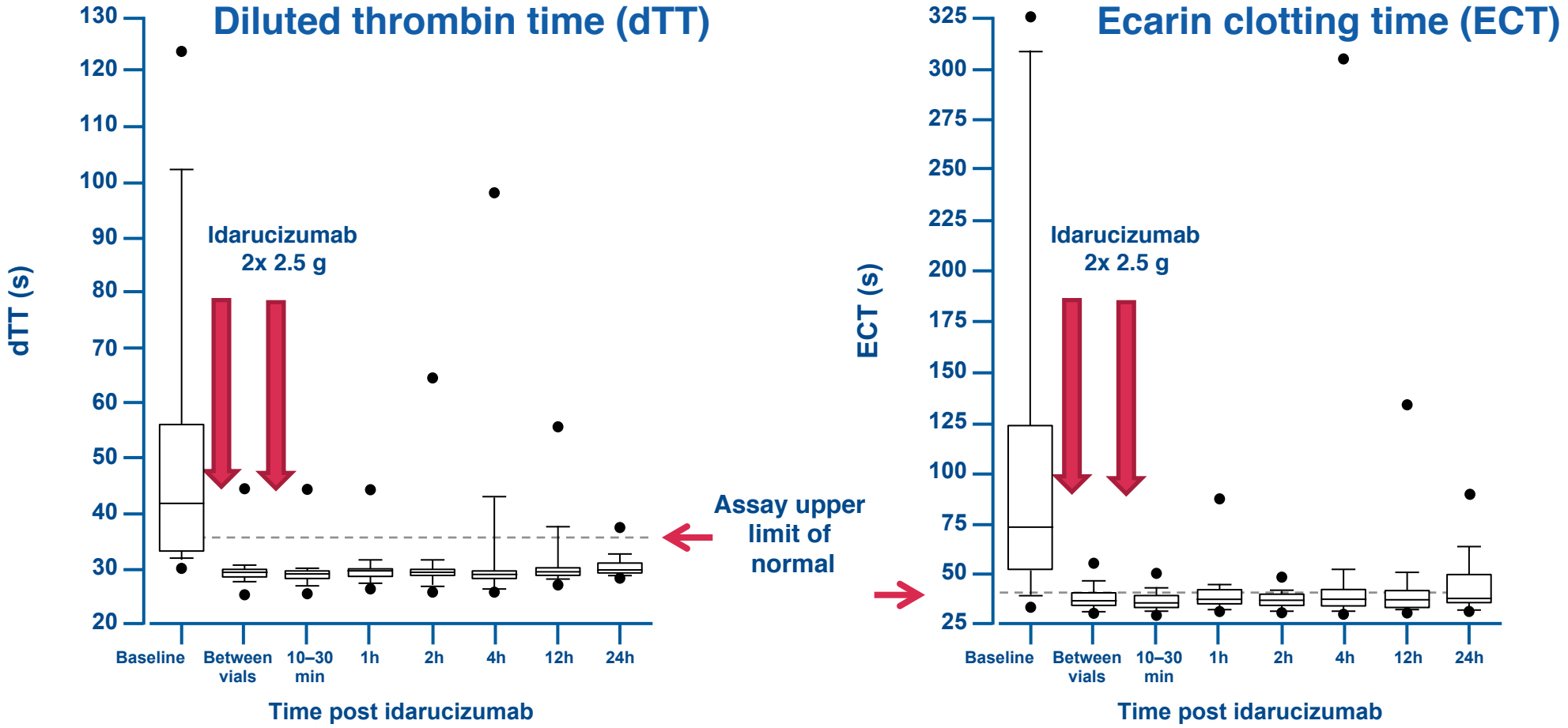
Reversal of Dabigatran with Idarucizumab based on dTT and ECT



Pollack et al. NEJM 2015

Primary Endpoint in Group B / Procedure

Reversal of Dabigatran with Idarucizumab based on dTT and ECT



Pollack et al. NEJM 2015

RE-VERSE AD

Secondary Endpoint: Clinical Outcomes

Group A
51 Patients → Assessable in 38 patients → Median local investigator-determined time to bleeding cessation 11.4 hours*

Group B
39 Patients → Surgery performed in 36 patients → Intraoperative hemostasis:
- 33 normal
- 2 mildly abnormal
- 1 moderately abnormal

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

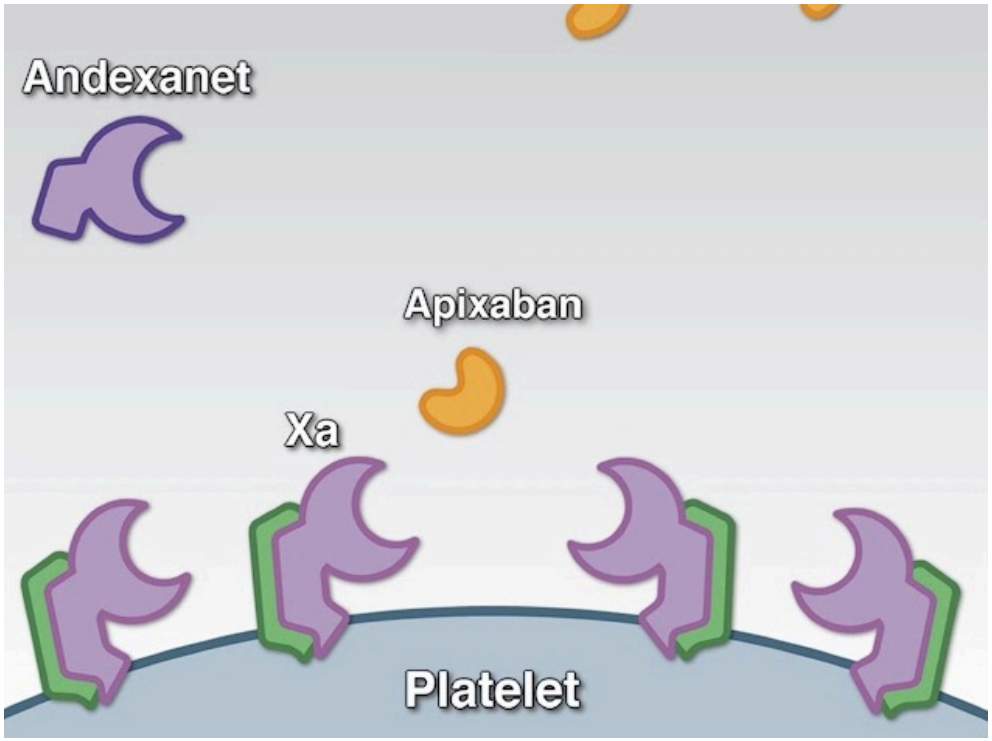
***Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding**

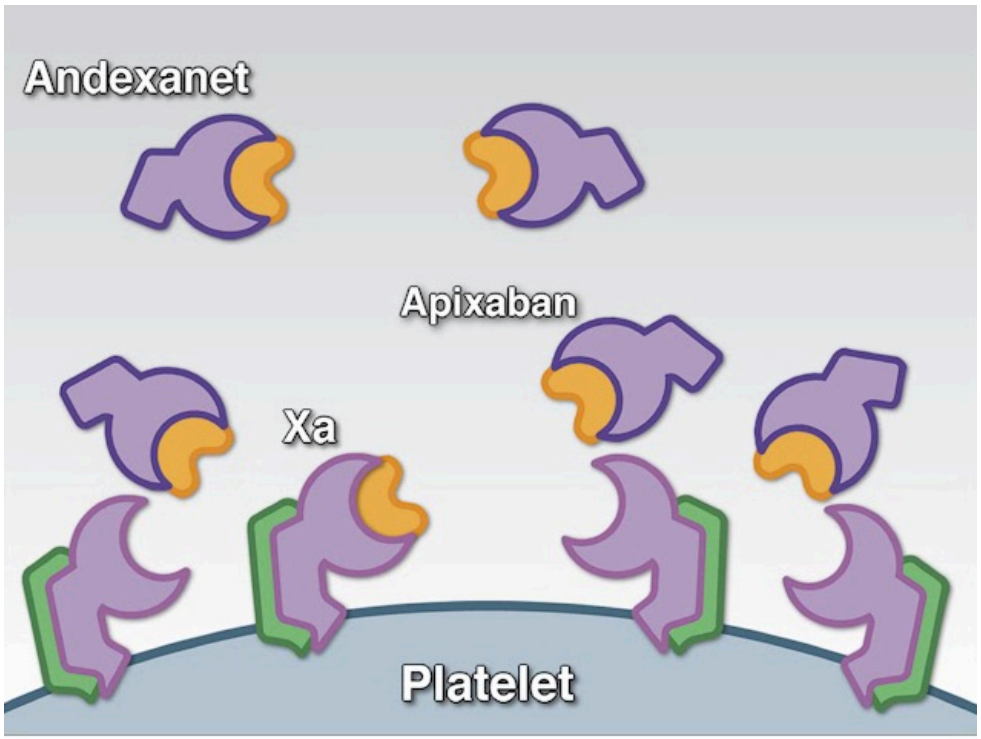
Pollack et al. NEJM 2015

Andexanet alfa
Designed to reverse activity of FXa Inhibitors

The Andexanet alfa antidote is a recombinant, modified version of human FXa [1]:

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

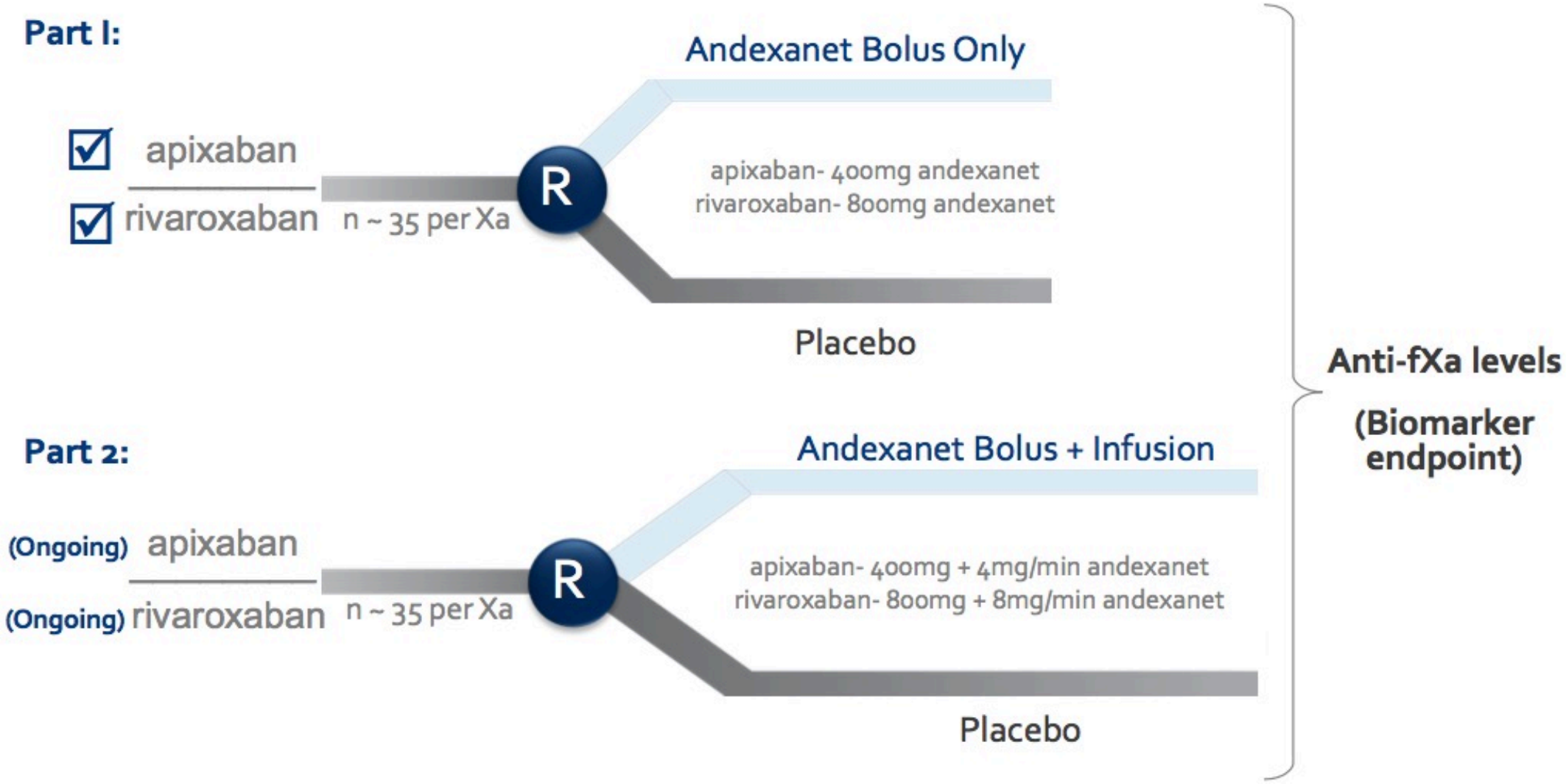


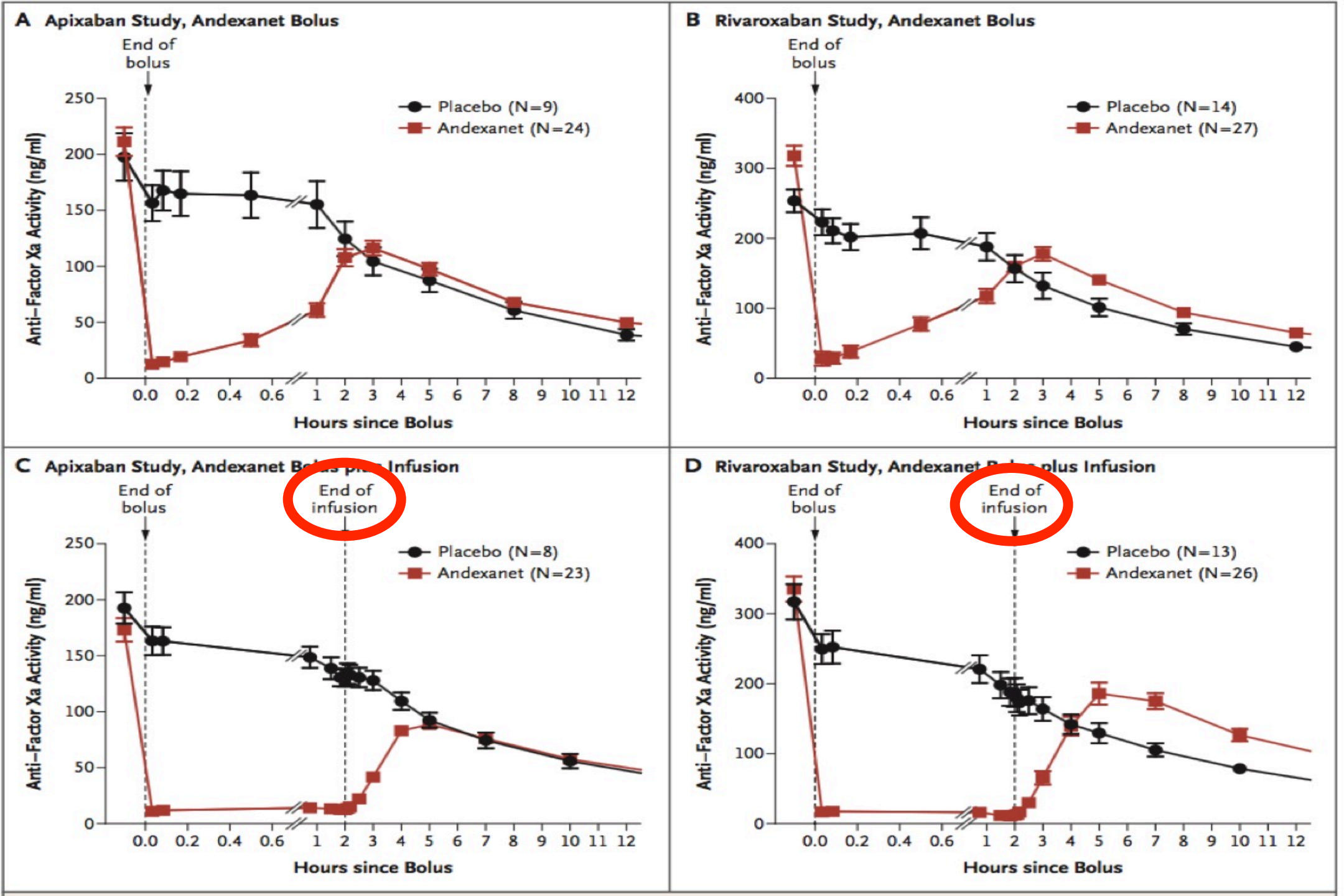


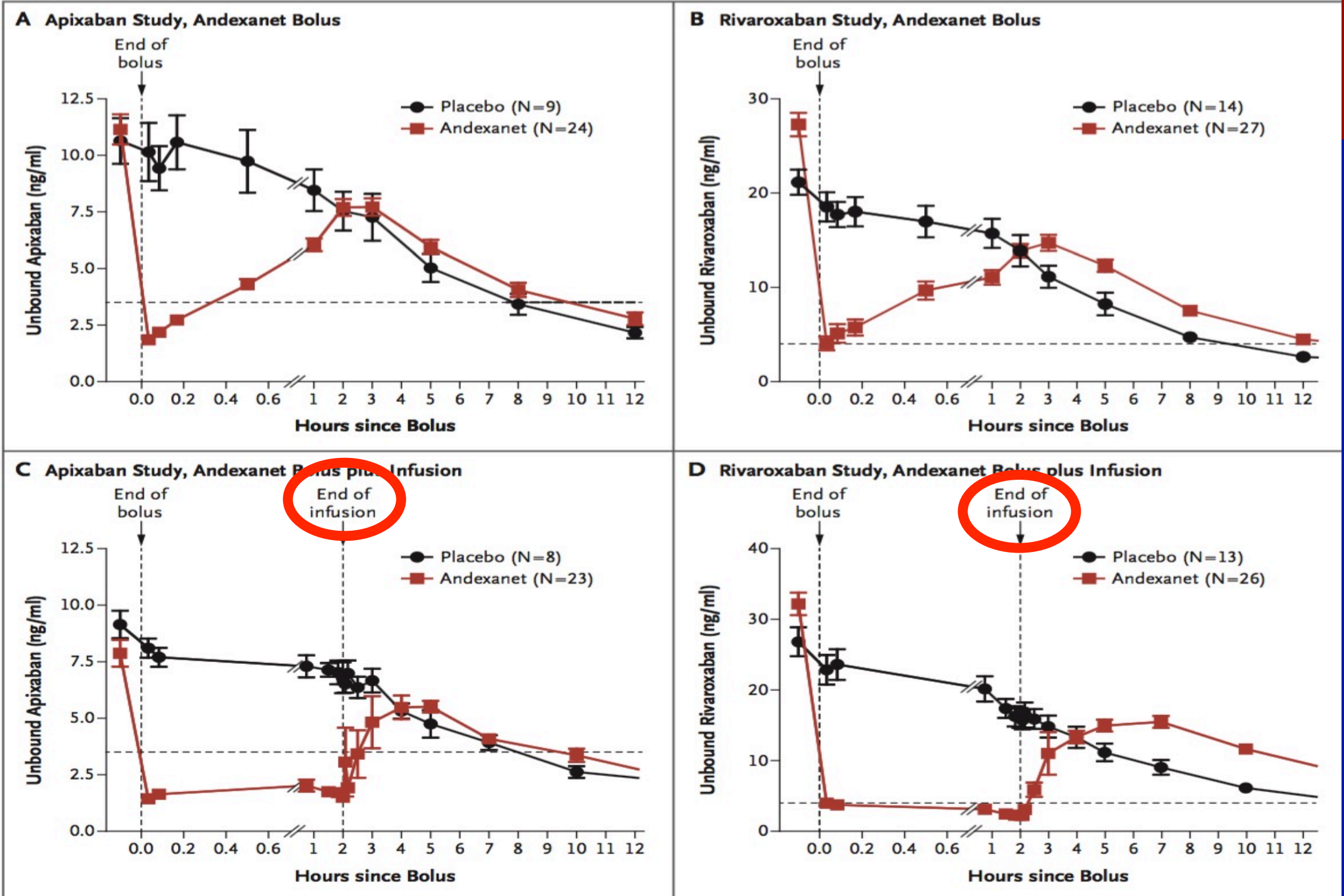
Siegal D et al. NEJM 2015;

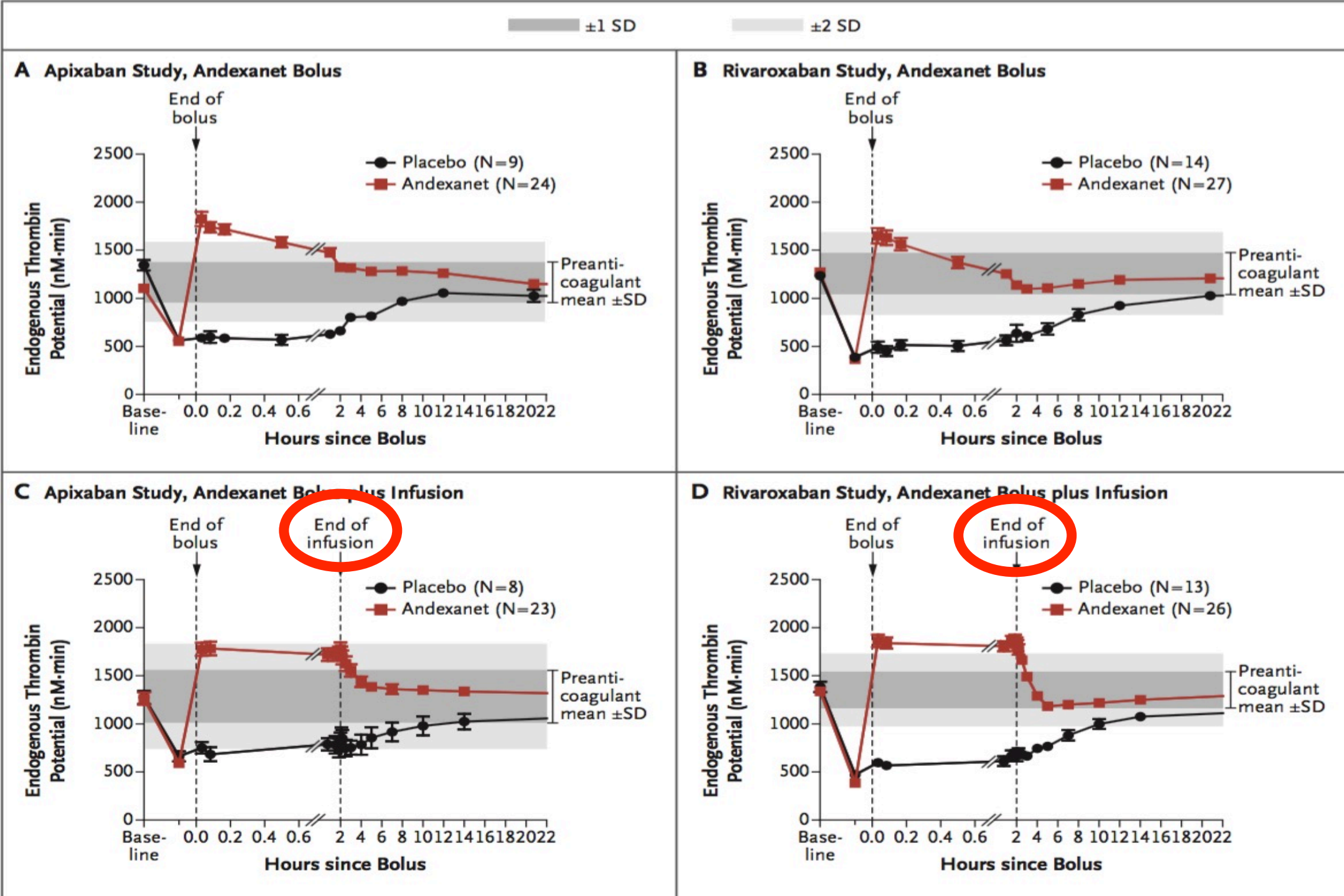
Andexanet Alfa: ANNEXA™ Registration-Enabling Studies

Accelerated Approval Phase 3 Design for Apixaban and Rivaroxaban




A Apixaban Study, Andexanet Bolus
End of bolus
Placebo (N=9)
Andexanet (N=24)
Anti–Factor Xa Activity (ng/ml)
Hours since Bolus
B Rivaroxaban Study, Andexanet Bolus
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
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
Placebo (N=13)
Andexanet (N=26)
Anti–Factor Xa Activity (ng/ml)
Hours since Bolus


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


±1 SD
±2 SD
A Apixaban Study, Andexanet Bolus
End of bolus
Placebo (N=9)
Andexanet (N=24)
Endogenous Thrombin Potential (nM·min)
Preanti-coagulant mean ±SD
Base-line
Hours since Bolus
B Rivaroxaban Study, Andexanet Bolus
Placebo (N=14)
Andexanet (N=27)
C Apixaban Study, Andexanet Bolus plus Infusion
End of infusion
Placebo (N=8)
Andexanet (N=23)
D Rivaroxaban Study, Andexanet Bolus plus Infusion
Placebo (N=13)
Andexanet (N=26)

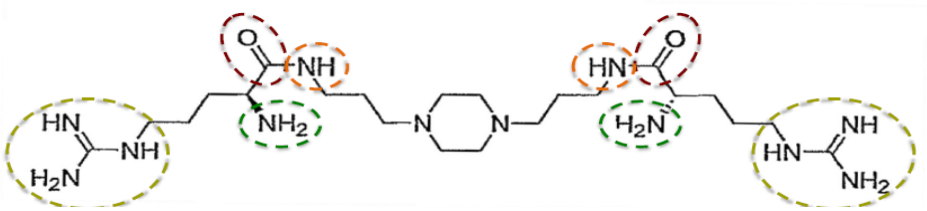
Phase 4 Outcomes Study in Bleeding Patients: ANNEXA™-4 on Apixaban, Rivaroxaban and Enoxaparin

- **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**

PER977 (Aripazine)

- **Universal inhibitor**: low molecular weight heparin, unfractionated heparin, rivaroxaban, apixaban, dabigatran, edoxaban

- **Mechanism of action**:
  - Small molecule (~500 daltons), highly positively charged
  - Binds to negatively charged molecules (heparin)
  - Binds to neutrally charged molecules by hydrogen bonding (ratio of inhibitor 6:1 PER977:inhibitor)
  - Non immunogenic and non pro-coagulant

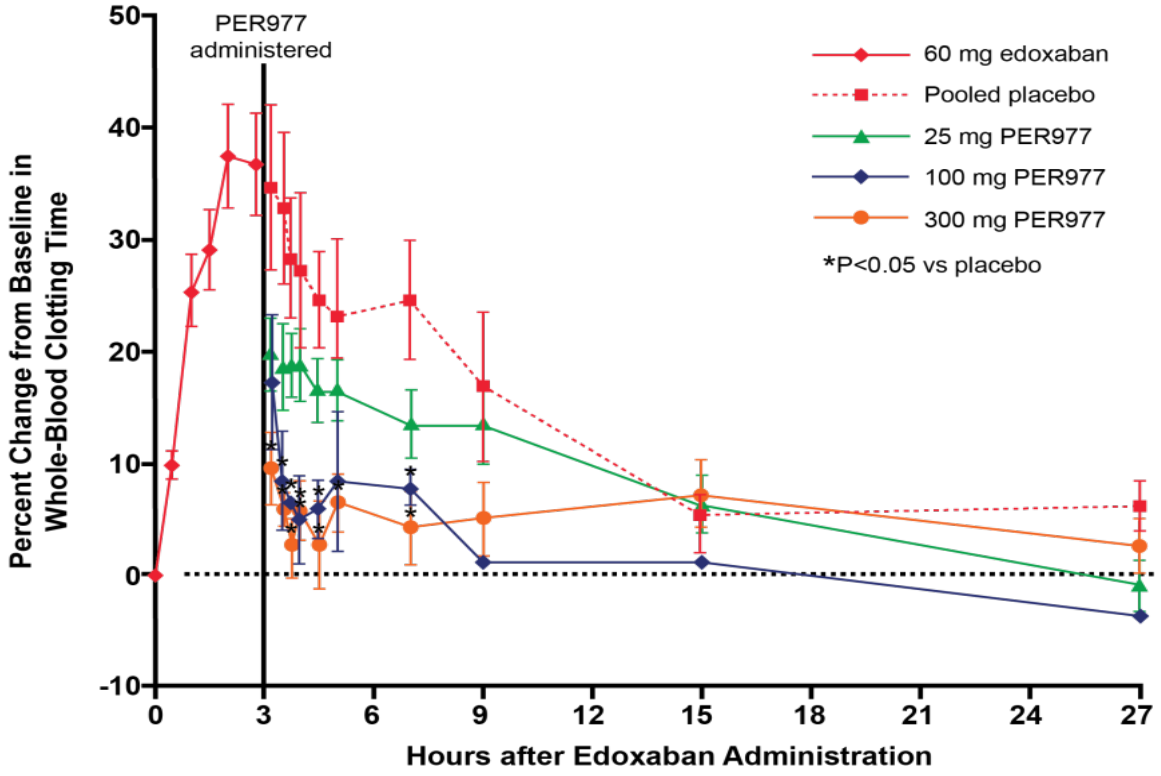


- H-bonds edoxaban, dabigatran, rivaroxaban and heparins
- H-bonds dabigatran, rivaroxaban, apixaban, argatroban, and heparins
- H-Bonds dabigatran, rivaroxaban and heparins
- H-bonds edoxaban and apixaban

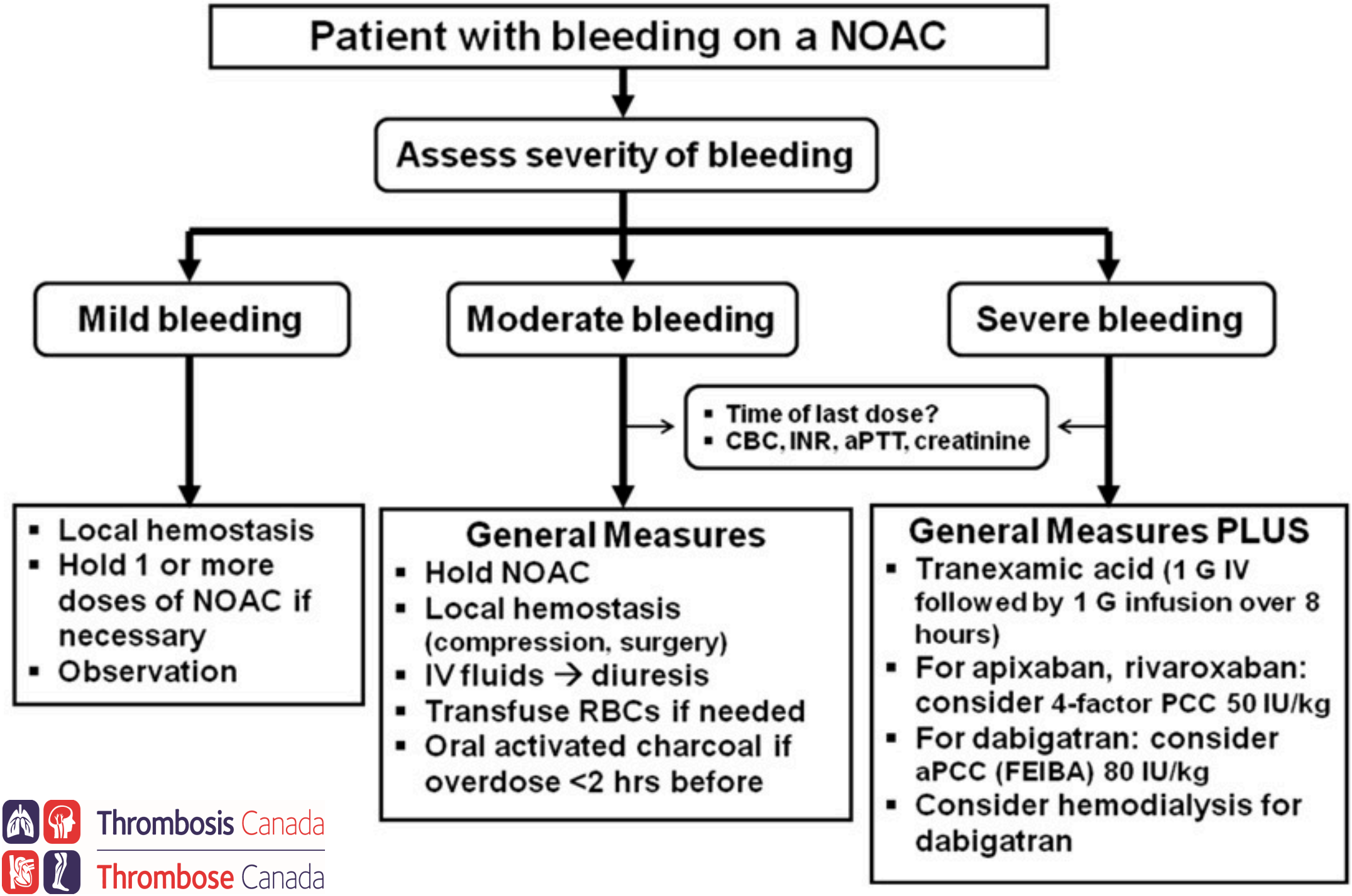
Bahkru et al. AHA Nov 2013, www.perosphere.com

PER977 (ciraparantag)

- Small synthetic molecule (~500 daltons)
- Positively charged
- Binds to a variety of anticoagulants (non-covalent, charge-charge)



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


Patient with bleeding on a NOAC
Assess severity of bleeding
Mild bleeding
Moderate bleeding
Severe bleeding
Time of last dose?
CBC, INR, aPTT, creatinine
Local hemostasis
Hold 1 or more doses of NOAC if necessary
Observation
General Measures
Hold NOAC
Local hemostasis (compression, surgery)
IV fluids → diuresis
Transfuse RBCs if needed
Oral activated charcoal if overdose <2 hrs before
General Measures PLUS
Tranexamic acid (1 G IV followed by 1 G infusion over 8 hours)
For apixaban, rivaroxaban: consider 4-factor PCC 50 IU/kg
For dabigatran: consider aPCC (FEIBA) 80 IU/kg
Consider hemodialysis for dabigatran
Thrombosis Canada
Thrombose Canada

Références: "App" de *THROMBOSE CANADA*

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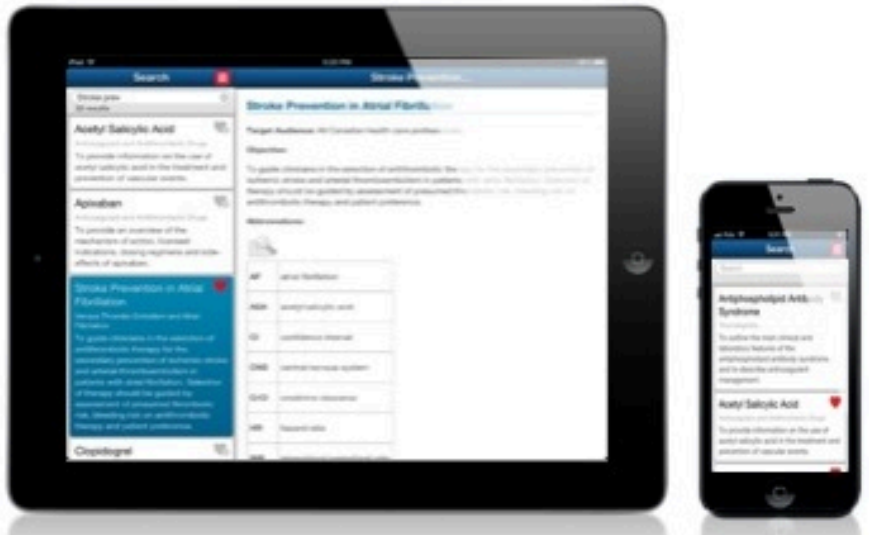

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