Reversible anticoagulation. A new therapeutic standard in thromboembolism prevention

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Anticoagulants

- Warfarin: 1960

- Dabigatran (Pradaxa): june 2013
- Rivaroxaban (Xarelto): august 2013
- Apixaban (Eliquis): january 2014
- Edoxaban (Lixiana): september 2015

All anticoagulants can cause bleeding

Bleeding in VKA anticoagulated patients

- Is common
  - Major bleeding 1-5% per year in AF
  - Intracranial bleeding 1-1.2% per year in AF
- Associated with adverse outcomes
  - 3 to 5-fold increase in thrombotic events and death
- Rapid and timely control of bleeding is likely to improve clinical outcomes but the efficacy of anticoagulant reversal is unproven

Challenges in bleeding

- Management of bleeding
  - Prevention
  - Treatment (….antidotes)

Prevention of bleeding

- Anticoagulant selection
- Patient and dose selection

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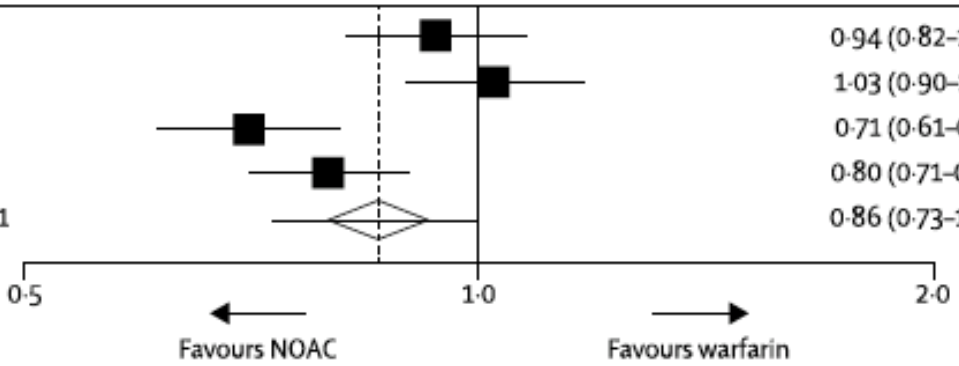
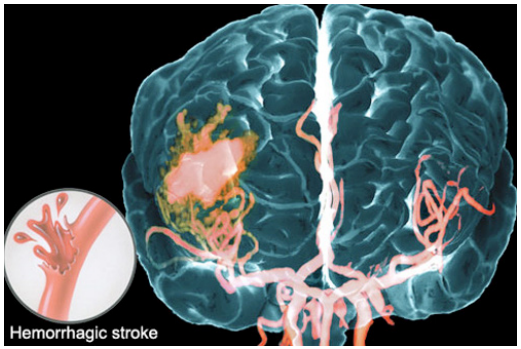
MAJOR BLEEDING

	NOAC (events)	Warfarin (events)	RR (95% CI)	p
RE-LY[5]*	375/6076	397/6022	0·94 (0·82–1·07)	0·34
ROCKET AF[6]†	395/7111	386/7125	1·03 (0·90–1·18)	0·72
ARISTOTLE[7]‡	327/9088	462/9052	0·71 (0·61–0·81)	<0·0001
ENGAGE AF–TIMI 48[8]§	444/7012	557/7012	0·80 (0·71–0·90)	0·0002
Combined (random)	1541/29 287	1802/29 211	0·86 (0·73–1·00)	0·06



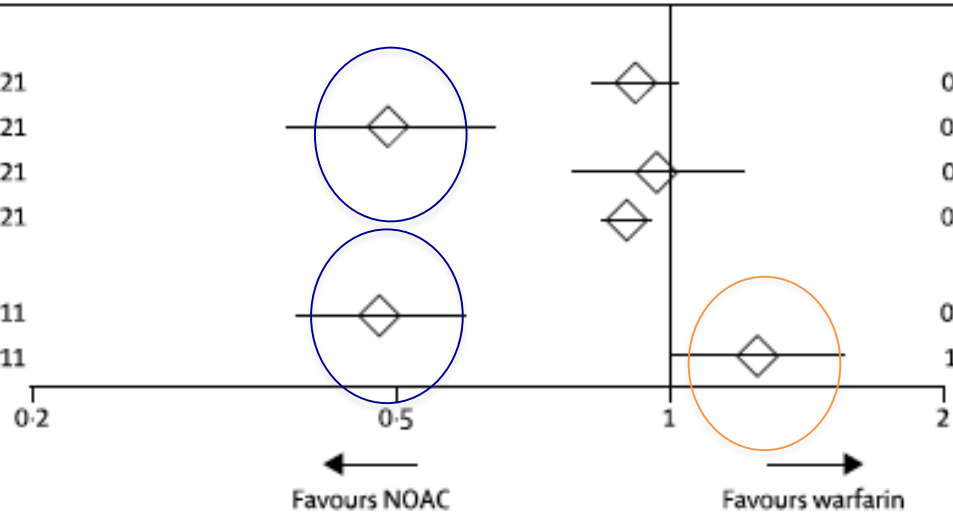


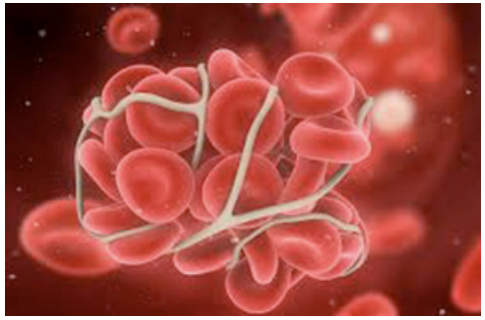
NOACs associated with a non significant RRR of 14% compared to Warfarin

Ruff CT, Lancet, December 4, 2013

EFFICACY AD SAFETY SECONDARY ENDPOINTS

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29 292	724/29 221	0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29 292	263/29 221	0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29 292	432/29 221	0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29 292	2245/29 221	0·90 (0·85–0·95)	0·0003
Safety				
Intracranial haemorrhage	204/29 287	425/29 211	0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29 287	591/29 211	1·25 (1·01–1·55)	0·043

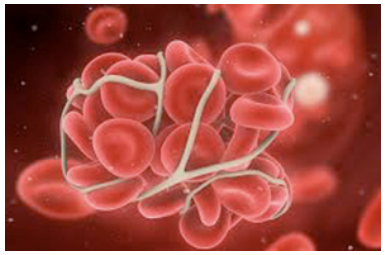




ICH NNT 141

Ruff CT, Lancet, December 4, 2013

Haemorrhagic stroke

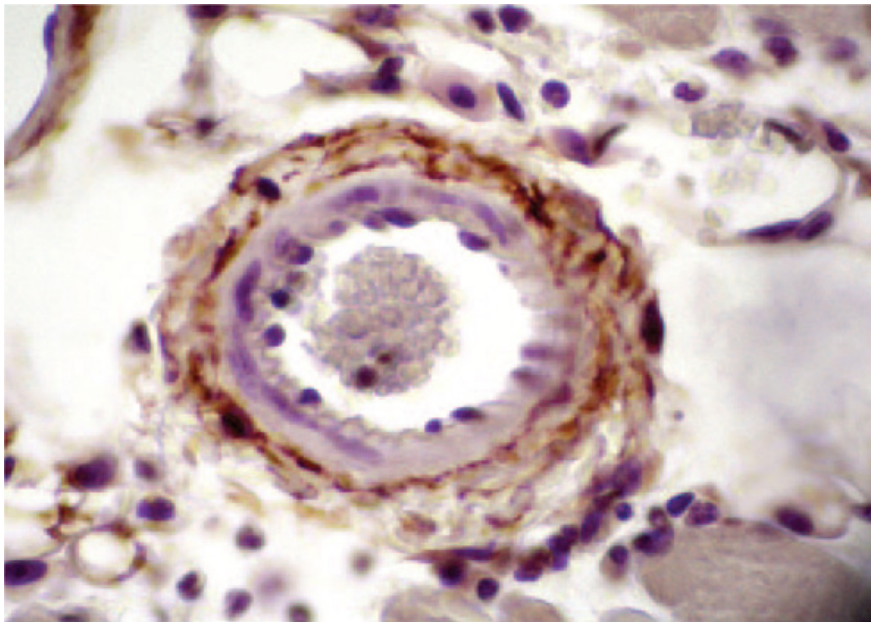


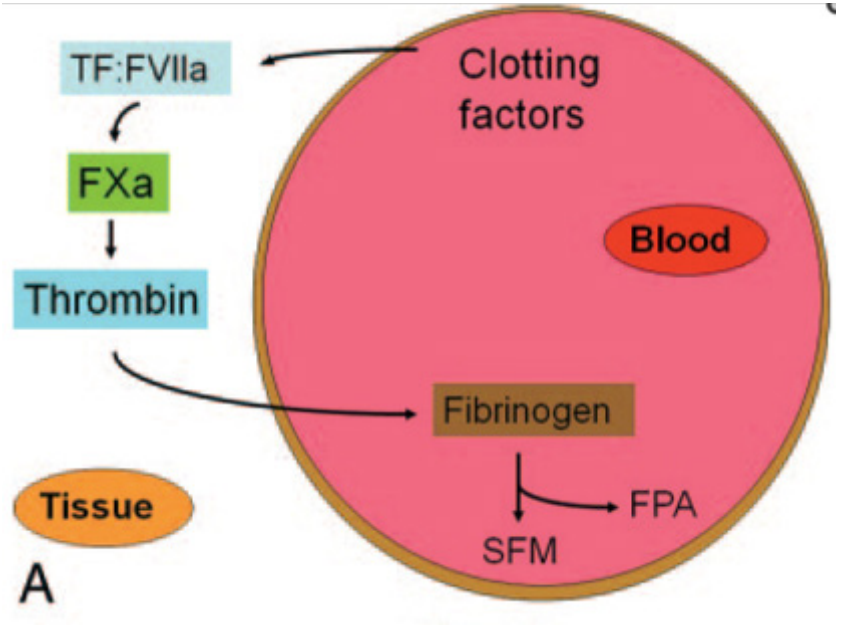
Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta analysis Daniel Caldeira et al. J Neurol 2014

"The unthinkable has become conceivable”

David Baltimore

Haemorrhagic stroke (TF receptor)





Mackmann, Anesth Analg. 2009 May; 108(5):1447-52
The role of tissue factor and factor VIIa in hemostasis.

Prevention of bleeding

- Anticoagulant selection
- Patient and dose selection

Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores

Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60%[a] in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatoy drugs[a,d]
Excess alcohol (≥8 drinks/week)[a,b]
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Age[e] (>65 years)[a] (≥75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[b]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin[e]
Growth differentiation factor-15[e]
Serum creatinine/estimated CrCl[e]

ESC Guidelines 2016

EHRA Guidelines (2015)
NOACs and their dosing in CKD

Table 8 Approved European labels for NOACs and their dosing in CKD

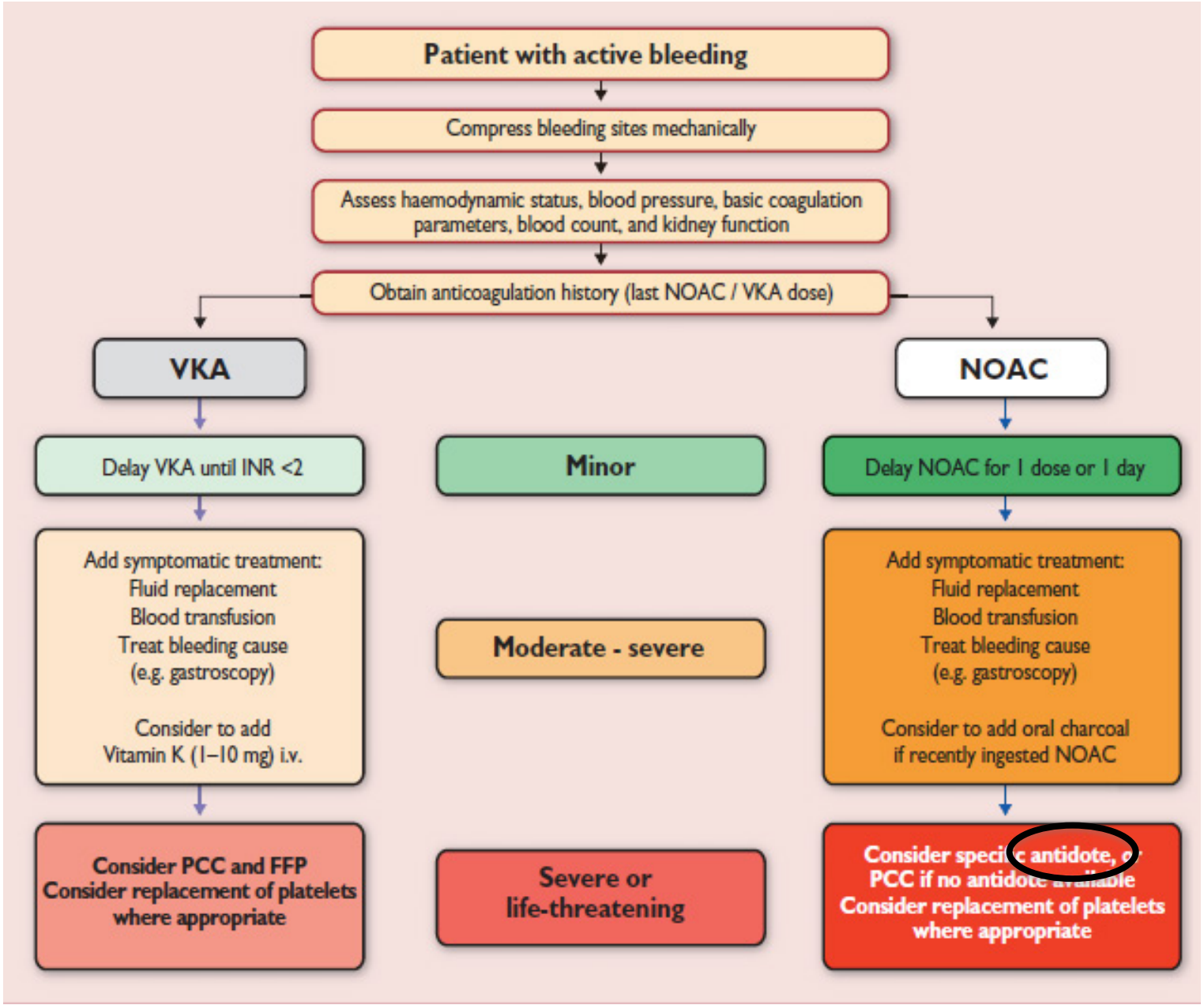
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Red: contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]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.
[b]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 CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

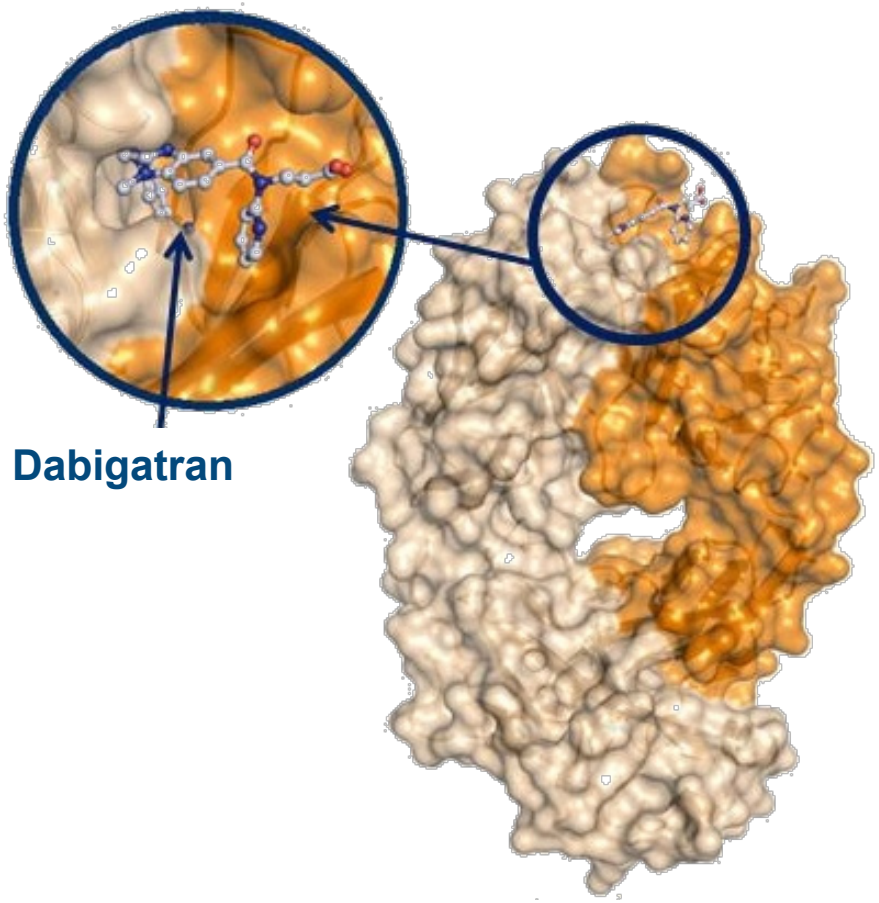
Challenges in bleeding

- Management of bleeding
  - Prevention
  - Treatment (….antidotes)

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS



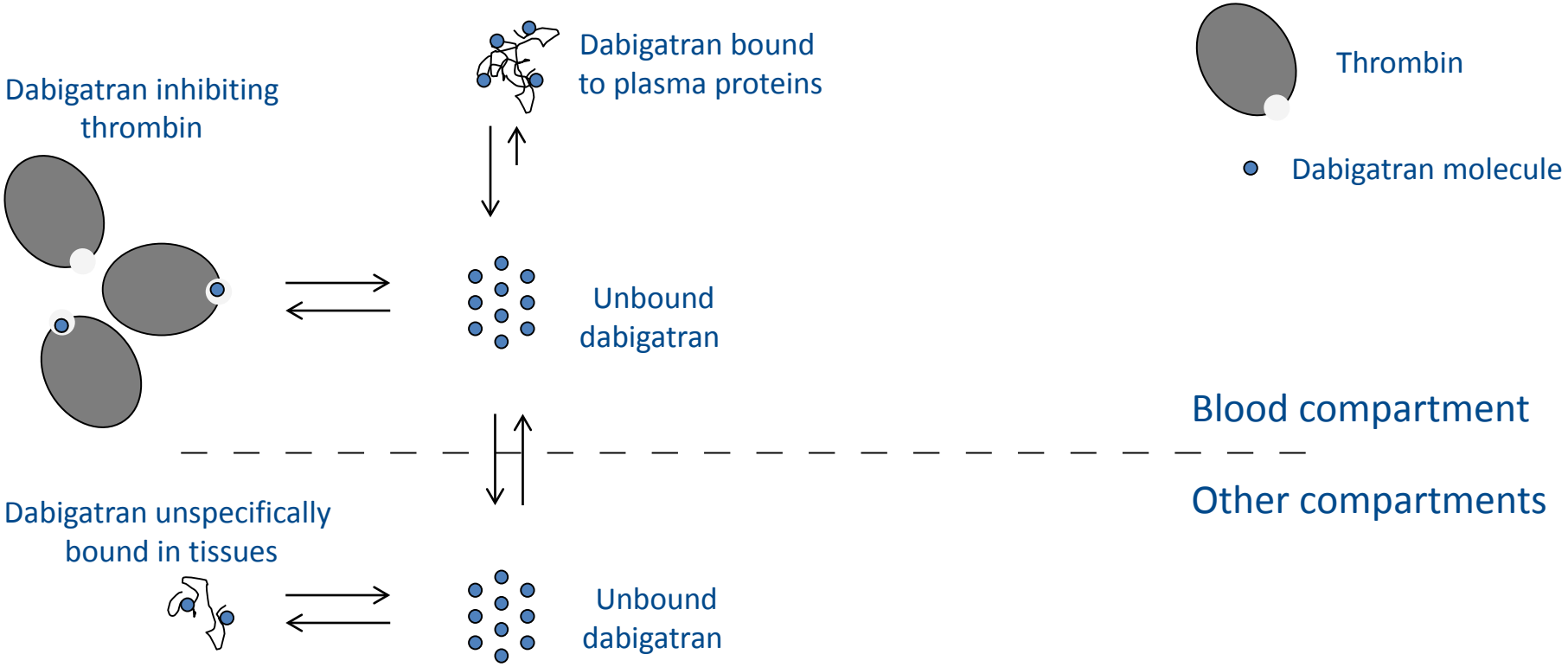
Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran



- Humanized Fab fragment
- Binding affinity for dabigatran **~350× higher** than dabigatran to thrombin
- IV administration, immediate onset of action
- Short half-life
- No intrinsic procoagulant or anticoagulant activity

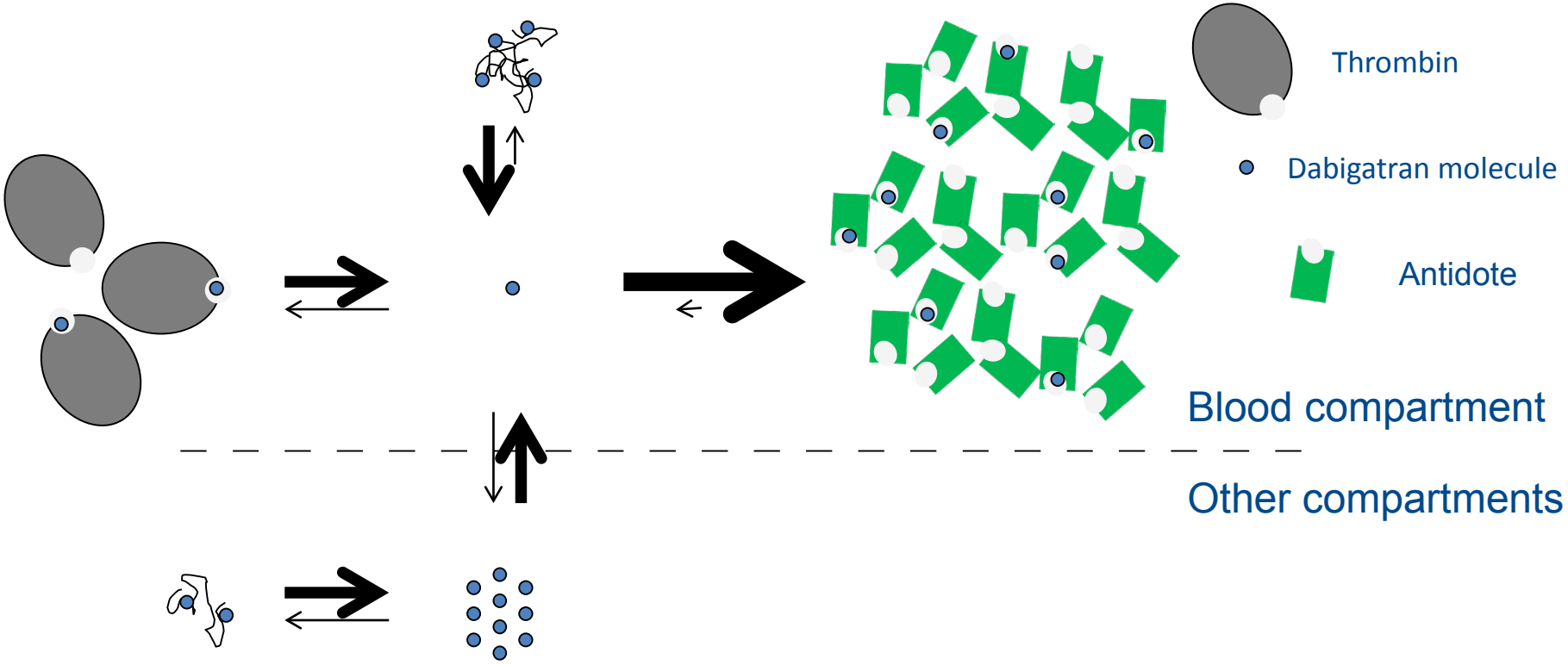
Adapted from Schiele F et al. Blood 2013; Stangier J et al. ISTH 2015, OR320

Dabigatran distribution following administration of dabigatran etexilate



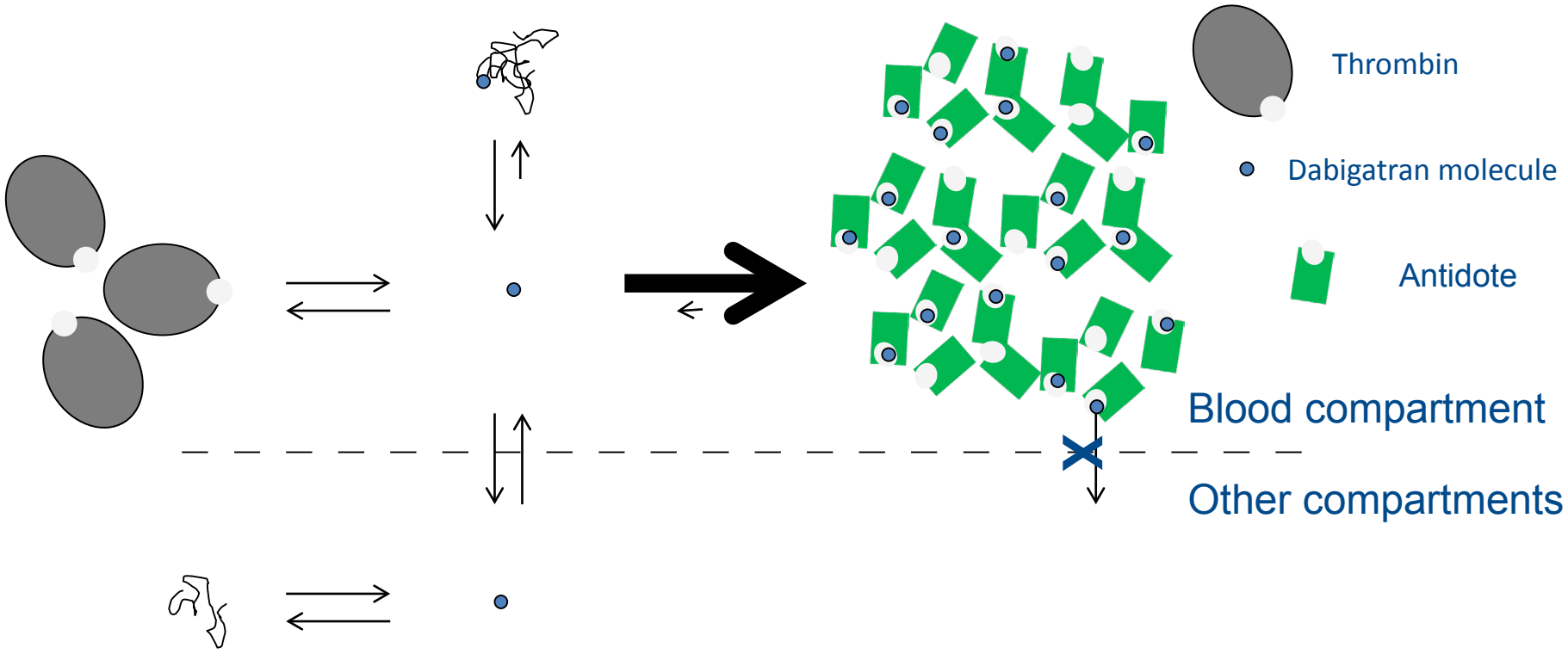
Glund S et al. Thromb Haemost 2015;19;113(5);
Glund S et al.SH 2014; abstr 344;
Schiele F et al. Blood 2013;121:3554–62;

Administration of the antidote



Glund S et al. Thromb Haemost 2015;19;113(5);
Glund S et al.SH 2014; abstr 344;
Schiele F et al. Blood 2013;121:3554–62;

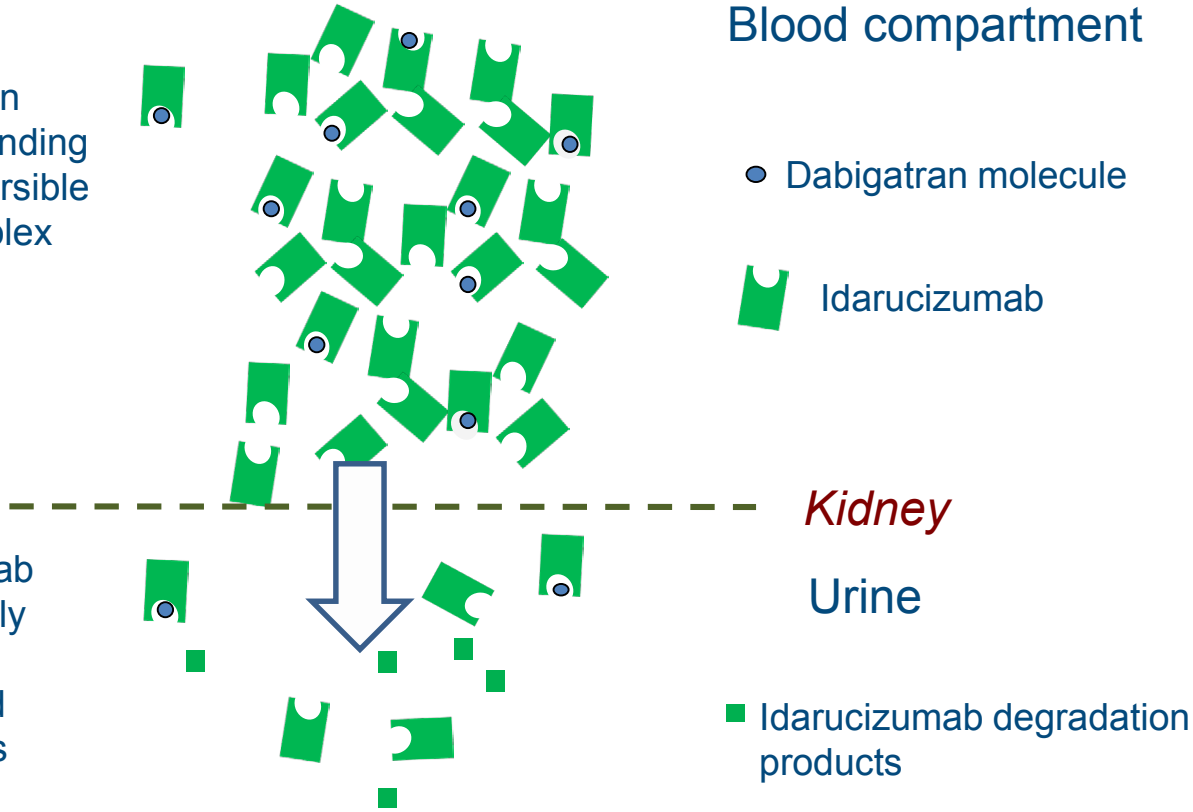
New equilibrium established



Glund S et al. Thromb Haemost 2015;19;113(5);
Glund S et al.SH 2014; abstr 344;
Schiele F et al. Blood 2013;121:3554–62;

Unbound idarucizumab and the idarucizumab–dabigatran complex are renally eliminated

The idarucizumab–dabigatran complex is very stable, i.e. the binding of dabigatran is essentially irreversible (half-life of the molecular complex ~260 hours)



Bound and unbound idarucizumab is eliminated by the kidney (partly catabolized) and is also catabolized to amino acids and reabsorbed; 90% of the dose is eliminated within 5 hours

Idarucizumab is eliminated renally
Renal impairment did not impact the reversal effect of idarucizumab

Glund S et al. Thromb Haemost 2015;19;113(5);
Glund S et al.SH 2014; abstr 344;
Schiele F et al. Blood 2013;121:3554–62;

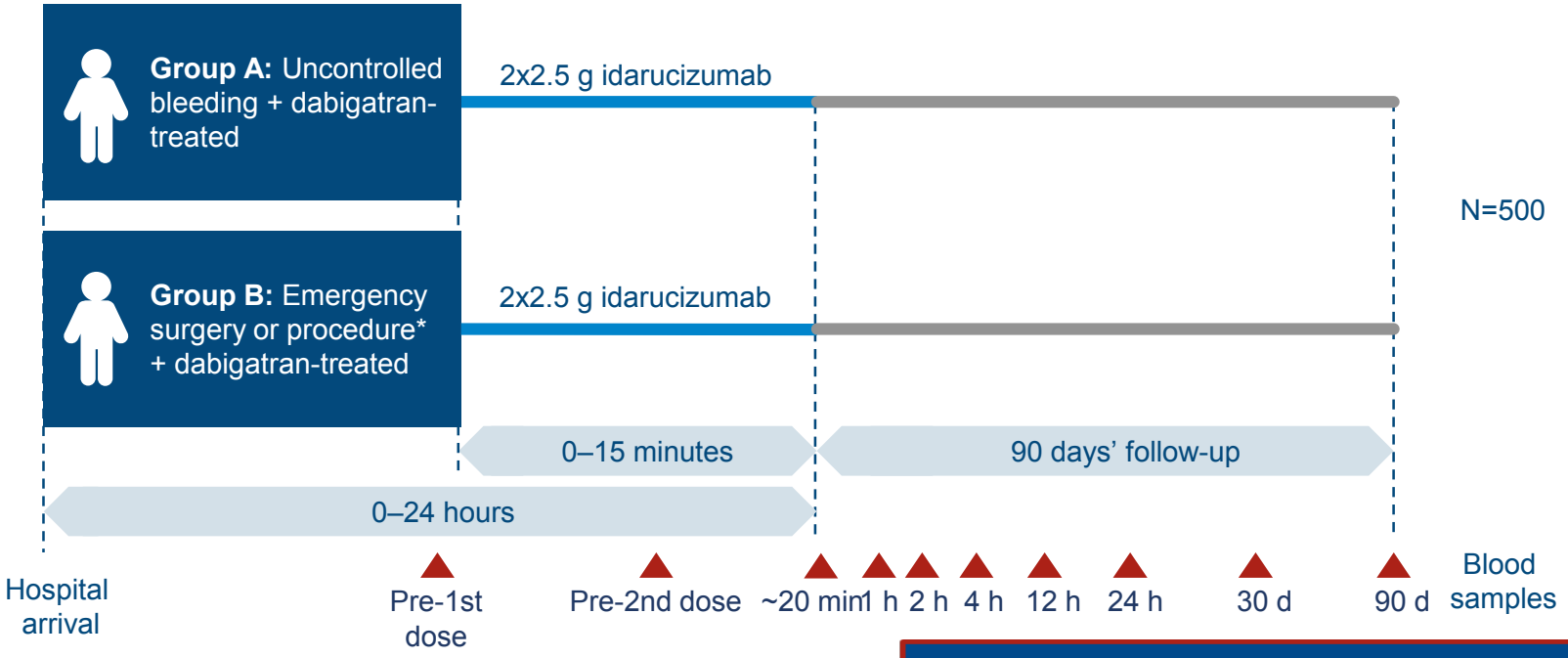
RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

Setting:
>400 sites in up to 38 countries

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

is the first patient study of a NOAC-specific reversal agent



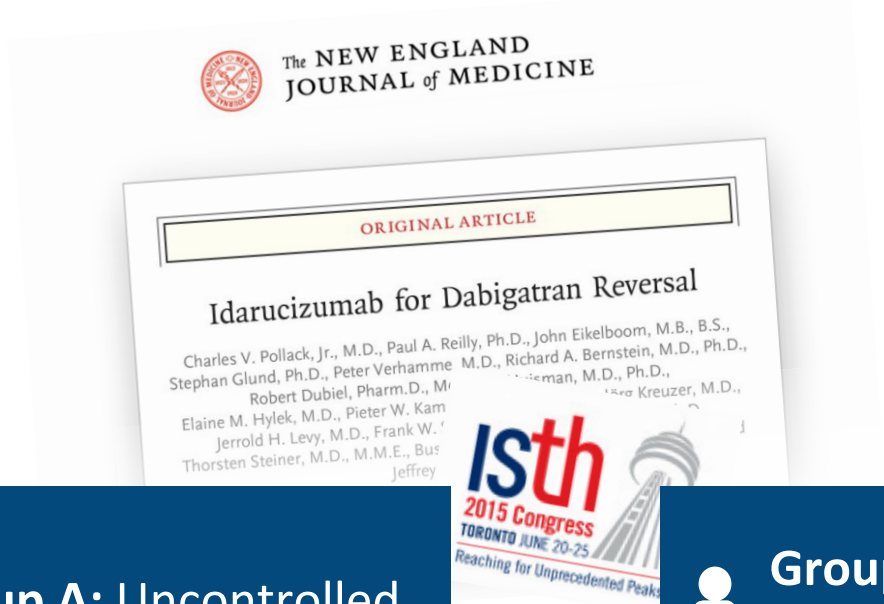
Safety endpoints
- Adverse events
- Formation of antidrug antibodies
- Patient status (BP, haemoglobin, haematocrit)
- Mortality and thrombotic events (ischaemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, systemic embolism)

Efficacy Endpoint

•Maximum reversal of dabigatran's activity, based on central laboratory measurements of dTT or ECT from end of first infusion up to 4 hours after completion of last infusion

Pollack et al. Thromb Haemost 2015

RE-VERSE AD™: interim results from the first 90 patients have been presented and published



Group A: Uncontrolled bleeding

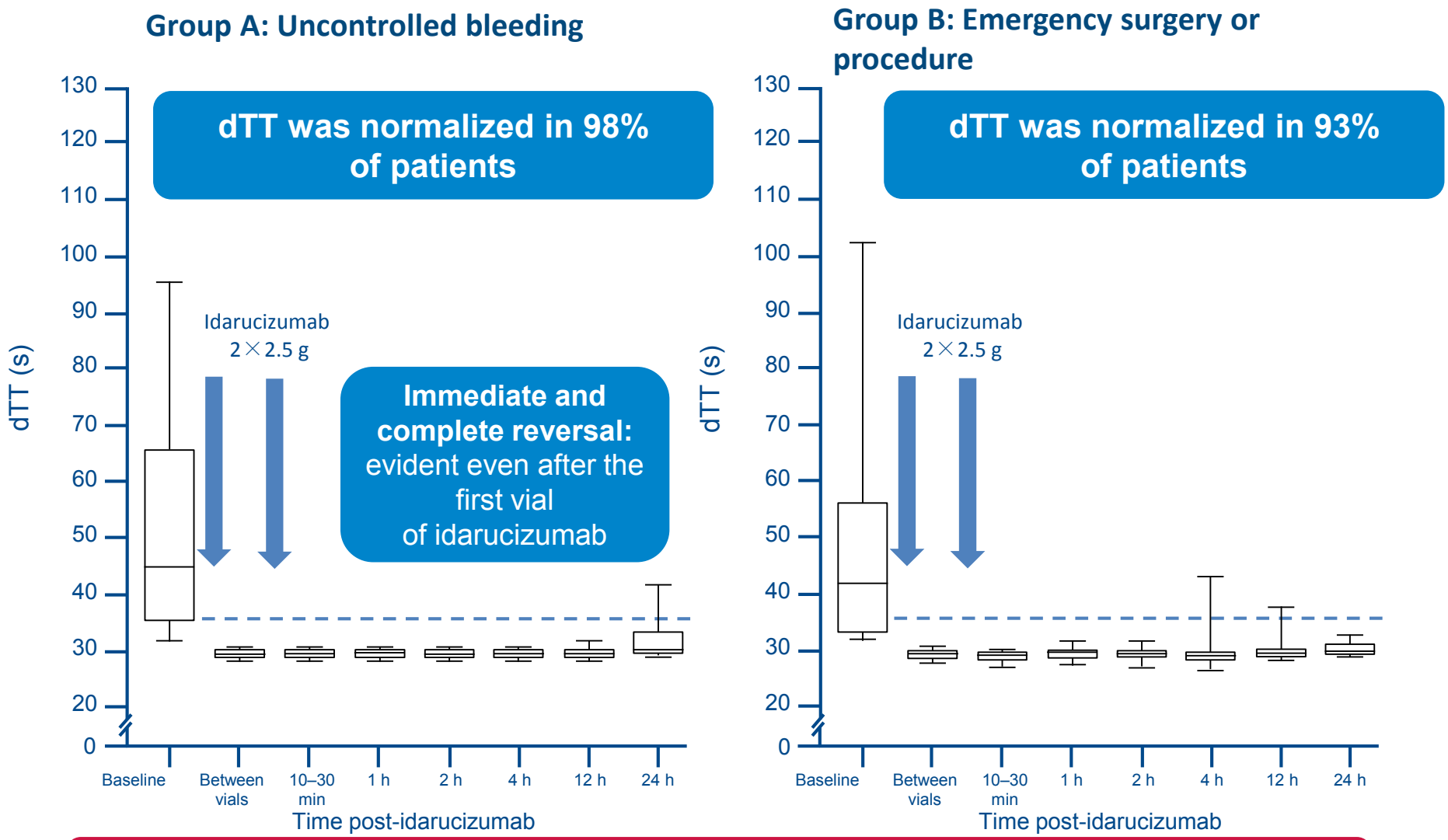
51 patients

Group B: Emergency surgery or procedure

39 patients

- Pollack et al. Presented at ISTH 2015; Pollack et al. N Engl J Med 2015

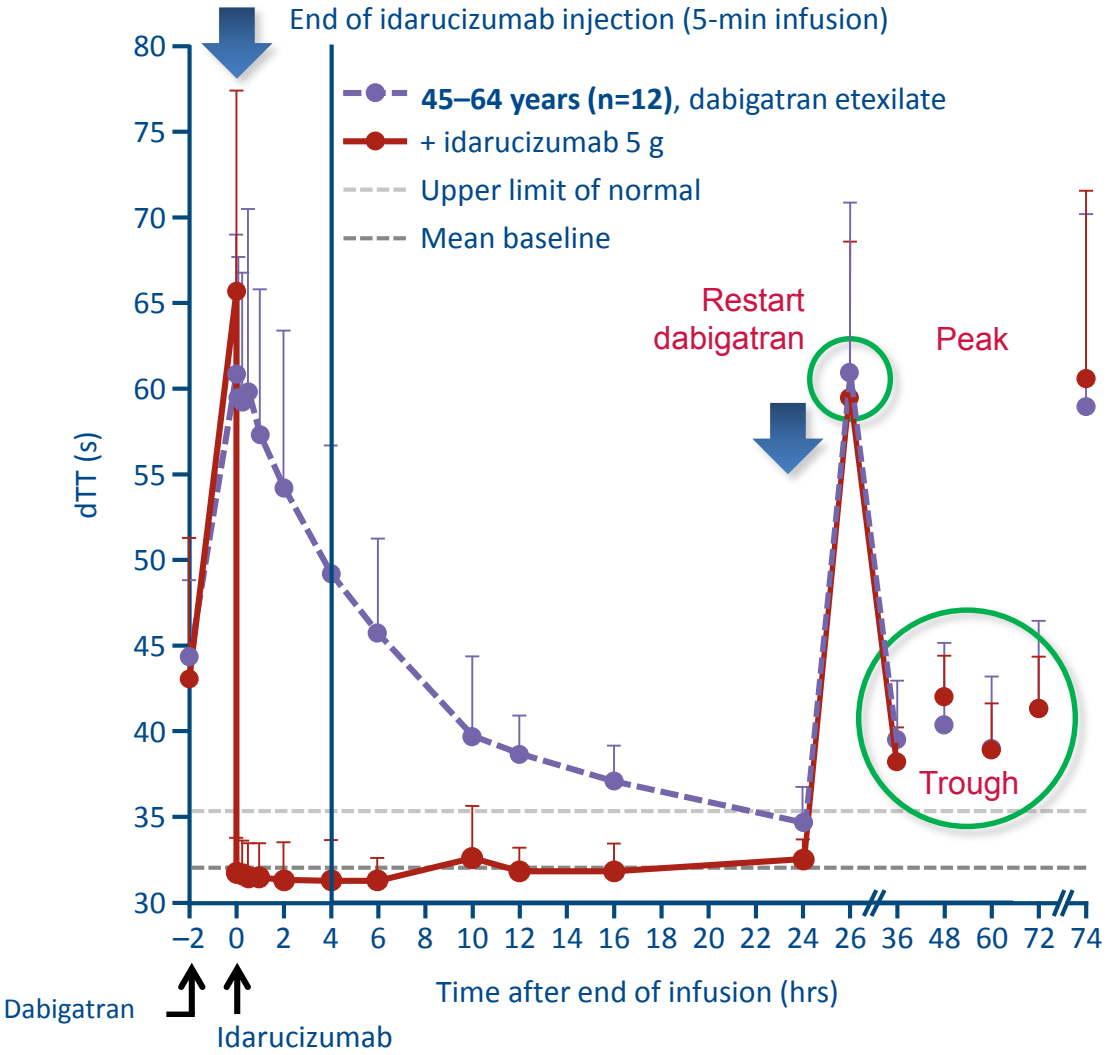
RE-VERSE AD™ interim results (Primary Outcome)



Similar results were also demonstrated with ECT, aPTT

Pollack CV et al. N Engl J Med 2015

Re-administration of dabigatran 24 hours after idarucizumab restores anticoagulation



Idarucizumab effect does not last >24 hours

Glund S et al. ASH 2014

All deaths in RE-VERSE AD™ related to the presenting index event and comorbidities

18 deaths occurred (nine in each group)

- RE-VERSE AD™ allows even severely ill patients into the study

Age/ Gender	Treatment Group	SAE that led to death	Days from treatment to Death	Index event
82/F	B	Cardiac arrest	<1	Malignant pericardial tamponade
93/M	B	Circulatory collapse	<1	Acute mesenteric ischemia
88/F	B	Hemodynamic collapse	<1	Acute mesenteric ischemia
87/F	B	Septic shock	1	Peritonitis
60/M	B	Sepsis and shock, GI bleed	1	Acute renal failure (NSAID induced)
60 /M	A	Respiratory failure progression	1	GI bleed
77/M	A	Intracranial hemorrhage new	1	Aortic root dissection Type A
69/M	A	Intracranial hemorrhage progression	2	Intracranial hemorrhage
87/M	B	Multi-organ failure	2	Acute renal failure
69/M	A	Intracranial hemorrhage regression	4	Intracranial hemorrhage
83/F	A	Pulmonary edema	11	Intracranial hemorrhage
78/F	B	Cardiac arrest	21	Acute renal failure and sepsis
72/F	B	Ischemic stroke	26	Infected left knee joint
73 /M	A	Congestive heart failure	30	GI bleed
80/M	A	Parkinson's disease	43	GI bleed
83/M	A	General health deterioration	42	Intracranial hemorrhage
86/F	A	Pneumonia	94	Intracranial hemorrhage
80/M	B	Progression of malignancy	101	Scrotal abscess

Pollack NEJM 2015

Thrombotic events reported in only five patients over a period of 90 days of follow-up

- One early event (DVT + PE) 2 days after idarucizumab administration
- Four events 7–26 days after idarucizumab administration
  - DVT: 7 days
  - DVT + PE + left atrial thrombus: 9 days
  - MI: 13 days
  - Ischaemic stroke: 26 days

None of these five patients was receiving any antithrombotic therapy when the events occurred

These events reflect the underlying thromboembolic potential of these patients when not on anticoagulation therapy

DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism

Pollack NEJM 2015

REVERSE-AD conclusions

- Idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 93% to 98% of patients

- There were no safety concerns

- The major limitation is the lack of a control group

Specific Antidotes for NOACs

Table 1. Pharmacologic and Pharmacokinetic Properties of Specific Antidotes for TSOACs[12,–16]

Agents	Target	Structure	Route	MOA
Idarucizumab	Dabigatran	Humanized monoclonal antibody fragment	IV	Binds to dabigatran with a high affinity (~350 times greater affinity than thrombin) No binding to thrombin substrates (no procoagulant activity)
Andexanet alfa	Direct and indirect FXa inhibitors	Modified recombinant form of FXa	IV	Binds to FXa inhibitors with affinity similar to that of native FXa
Aripazine	Universal (oral FXa and FIIa inhibitors, UFH, LMWH, and fondaparinux	Small synthetic molecule	IV	Binds to TSOACs and heparin and reverses the anticoagulant effects

Yoonsun Mo, Felix K. Yam. Pharmacotherapy 2015;35(2):198–207

The NEW ENGLAND JOURNAL of MEDICINE

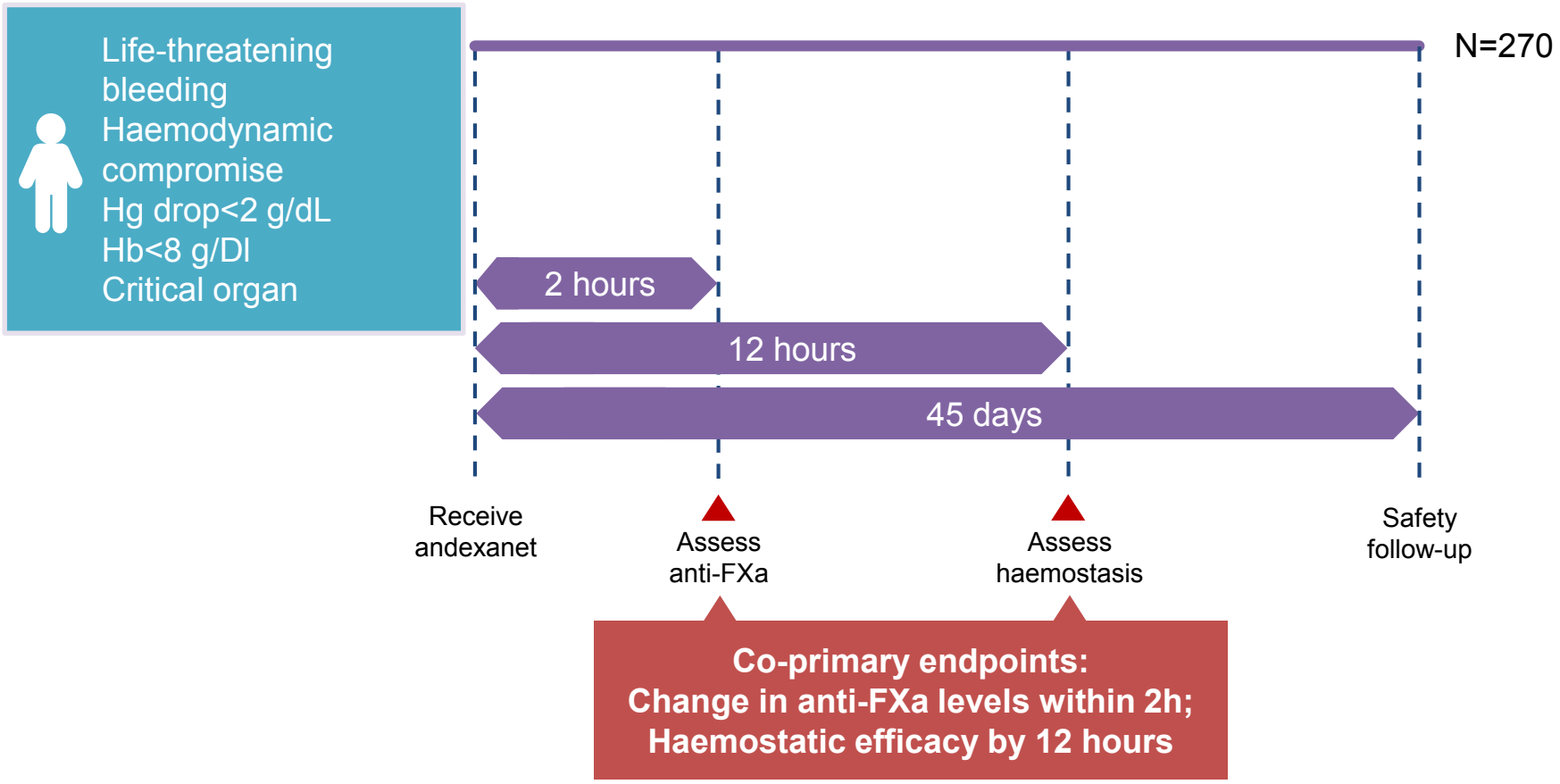
ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

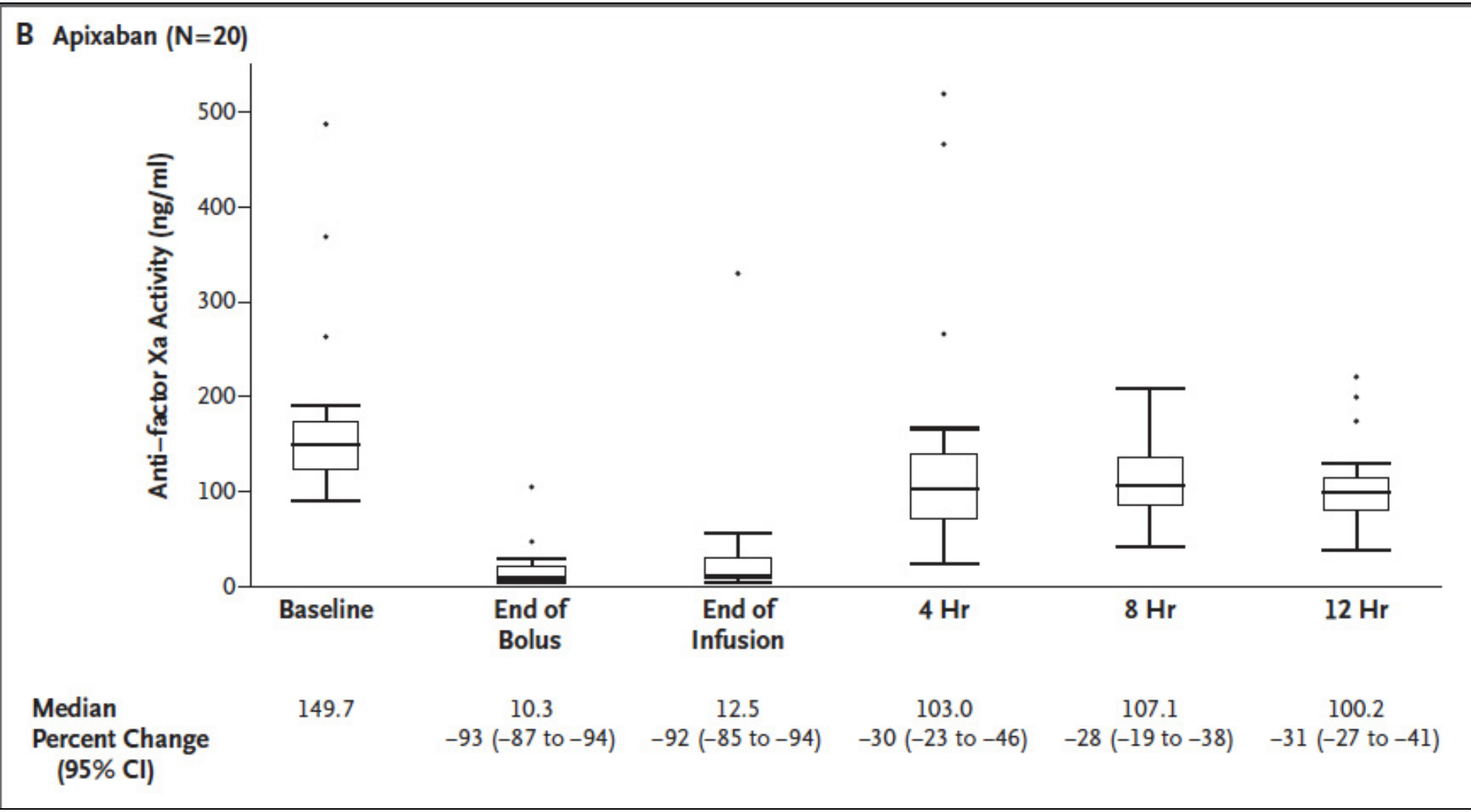
Connolly SJ et al. NEJM; August 30, 2016

ANNEXA-4 study design



Connolly SJ et al. NEJM; August 30, 2016

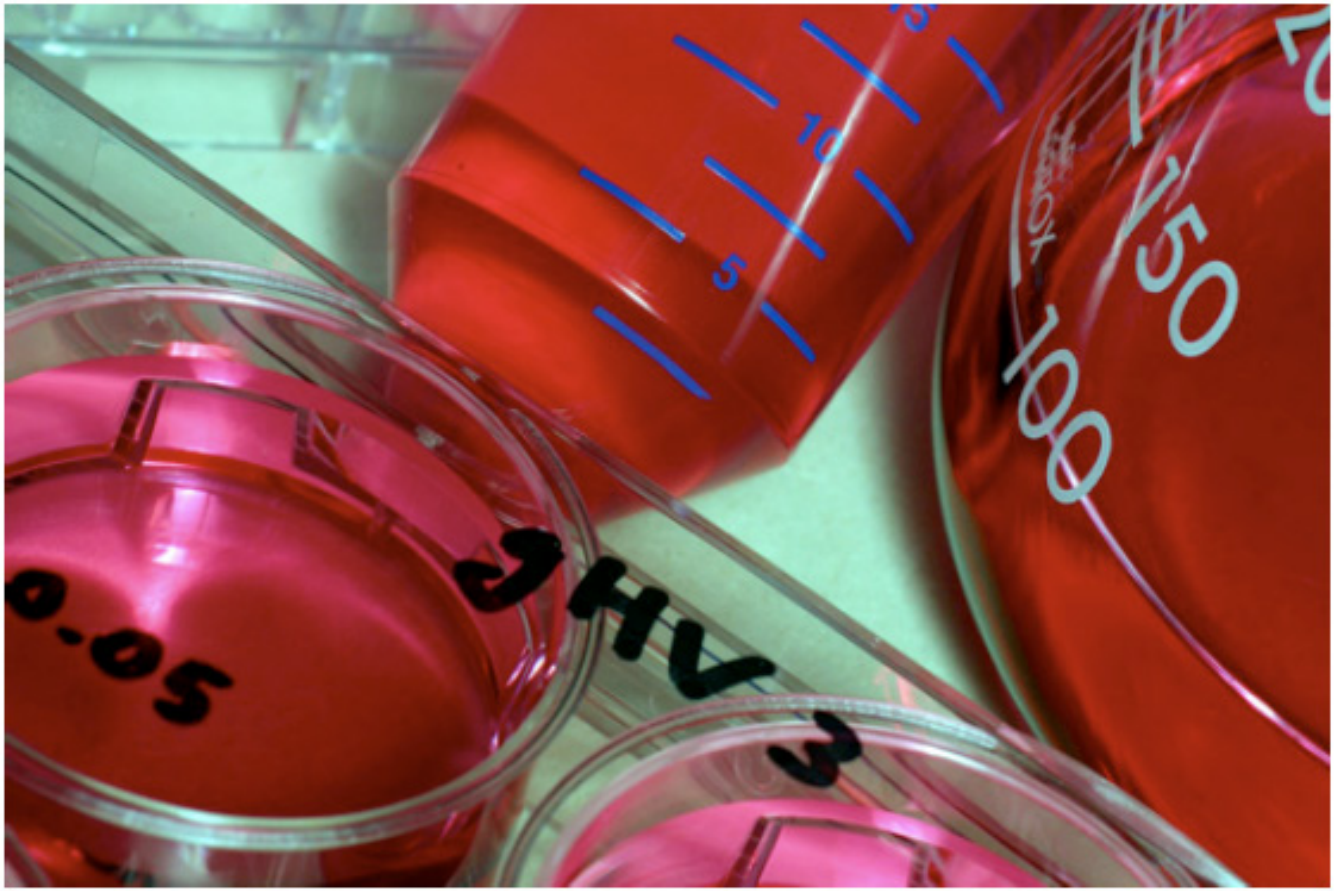
Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban



Connolly SJ et al. NEJM; August 30, 2016

PHARMASTAR
il Giornale on-line sui Farmaci

Fda nega l'ok all'antidoto agli anticoagulanti che agiscono sul fattore Xa



18 agosto 2016

http://www.pharmastar.it/index.html?cat=search&id=22160

18 agosto 2016

Portola Pharmaceuticals ha annunciato di aver ricevuto una lettera di risposta completa (CRL) dall'Fda per quanto riguarda la sua Biologics License Application (BLA) per AndexXa (andexanet alfa). In sostanza, almeno per ora, l'agenzia americana ha negato l'approvazione al farmaco.

Andexanet alfa è in fase di sviluppo per i pazienti trattati con un inibitore diretto del fattore Xa (apixaban, rivaroxaban, o edoxaban) o indiretto (enoxaparina) quando è necessaria un'inversione dell'azione anticoagulante a causa di un sanguinamento a potenziale pericolo di vita o di un sanguinamento incontrollato. Attualmente, non esiste un antidoto approvato dalla Fda per gli inibitori del fattore Xa.

Nella CRL per andexanet alfa, l'Fda ha chiesto che Portola fornisca ulteriori informazioni relative alla produzione del farmaco. Essendo andexanet alfa una proteina complessa, la sua produzione richiede un elevato livello di sofisticazione tecnica.

La domanda di registrazione di andexanet è stato presentata basandosi in gran parte su dati di Fase 2 raccolti in volontari sani. L'Fda aveva concesso l'approvazione accelerata visto l'elevato "unmet medical need".
La società non ha quindi avuto a disposizione il tempo necessario per perfezionare il metodo di produzione di andexanet come sarebbe successo nel corso della più tipica fase 3 di sperimentazione clinica che di solito viene richiesta per l'approvazione di un farmaco.

L'Fda ha anche fatto sapere che in assenza di nuovi dati non potrà approvare l'impiego di andexanet per contrastare l'effetto anticoagulante di edoxaban e dell'enoxaparina. I due farmaci non sono stati oggetto dello studio di Fase II.

Nella migliore delle ipotesi, l'approvazione di andexanet alfanon arriverà che alla fine dell'anno. Un grave danno per l'azienda che ha sviluppato l'antidoto (Portola ha perso oltre il 20% del valore delle proprie azioni).

http://www.pharmastar.it/index.html?cat=search&id=22160

Conclusioni

- Antidoto: novità scientifica e gestionale
- Prescrizione NAO basata sulle caratteristiche paziente e farmaco
- Pazienti in triplice o duplice terapia
- Pazienti con HASBLED>4 non modificabile
- Pregressa emorragia maggiore