NOVITA' NEL REVERSAL DELLA ANTICOAGULAZIONE NELL'ERA DEI NUOVI FARMACI

DAVIDE IMBERTI

CENTRO EMOSTASI E TROMBOSI
MEDICINA INTERNA
DIPARTIMENTO DI MEDICINA GENERALE
OSPEDALE GUGLIELMO DA SALICETO
PIACENZA

Il sottoscritto ……IMBERTI DAVIDE ……..
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

x che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *ALFA WASSERMANN*
- *BAYER*
- *BMS-PFIZER*
- *BOHERINGER INGELHEIM*
- *DAIICHI-SANKYO*
- *IL*
- *KEDRION*
- *SANOFI AVENTIS*

AGENDA

- Complicanze emorragiche
- Procedure ed interventi chirurgici in urgenza
- Sovradosaggio

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DOACs e EMORRAGIE

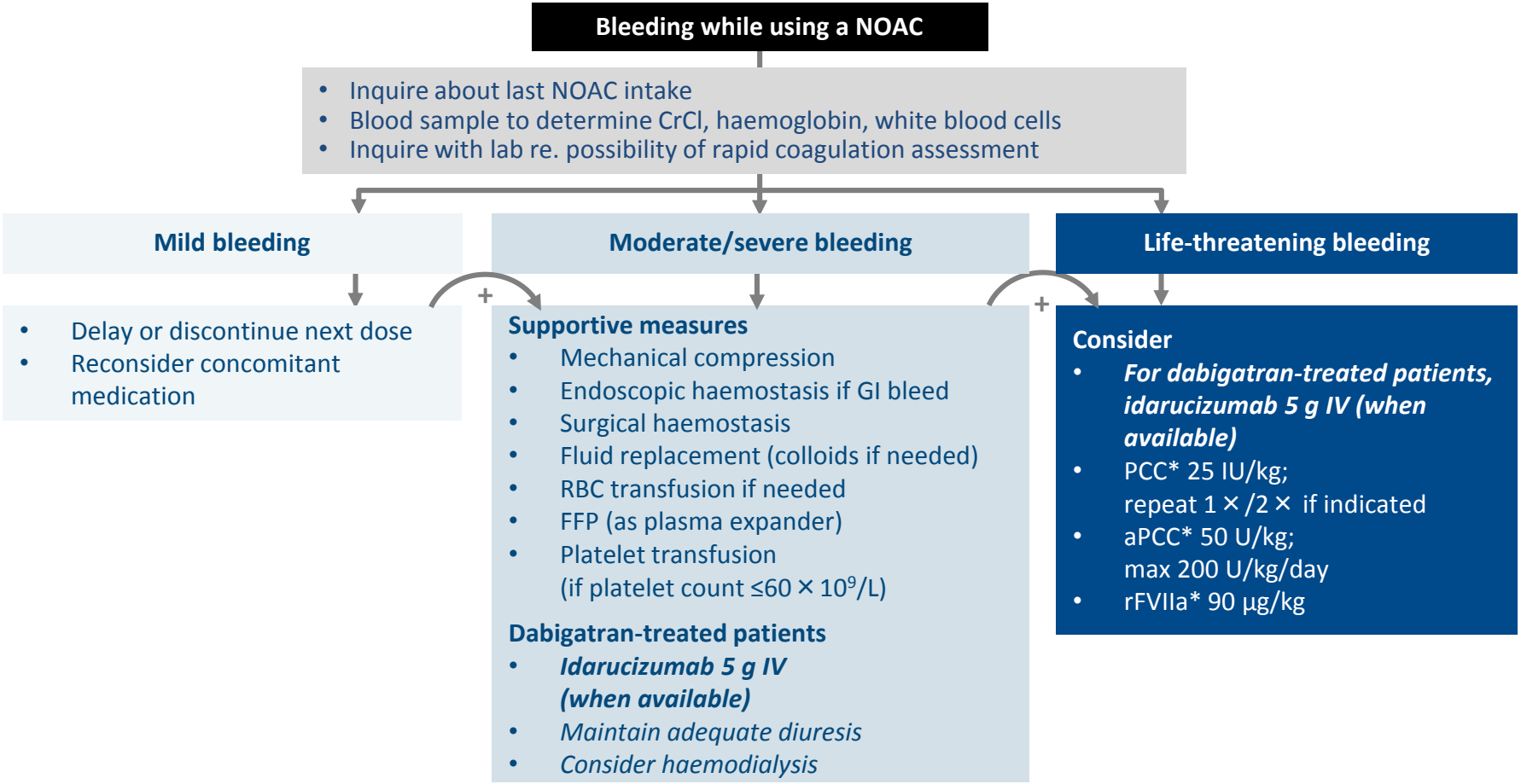
Informazioni cliniche importanti

- Tipo di farmaco
- Dose
- Ora dell'ultima assunzione
- Eventuale coesistenza di insufficienza renale
- Eventuali farmaci concomitanti

Emivita media dei farmaci attuali

- Warfarin: 36-42 ore
- Rivaroxaban: 7-11 ore
- Apixaban: 12 ore
- Dabigatran: 12-14 ore
- Edoxaban 6-12 ore
- EBPM: 3-6 ore
- Fondaparinux: 13-21 ore

EHRA 2015 guidelines: management of bleeding with new oral anticoagulants



Heidebuchel, EHRA Practical Guide, Europace, 2015

MISURAZIONE DELL'EFFETTO ANTICOAGULANTE DEI NUOVI ANTICOAGULANTI DIRETTI (NAO) DOCUMENTO RER

Raccomandazione

Il Gruppo di Lavoro raccomanda la misurazione dell'effetto anticoagulante dei NAO (Dabigratan, Rivaroxaban, Apixaban) nelle condizioni in cui è necessario conoscere la presenza dell'effetto anticoagulante per guidare l'attività medica in situazioni di emergenza.
In particolare in caso di:

- eventi avversi emorragici
- valutazione degli effetti dei trattamenti somministrati (reverse?)
- complicanze trombotiche
- preliminarmente a interventi chirurgici in emergenza
- preliminarmente a manovre invasive (diagnostiche o terapeutiche) in emergenza

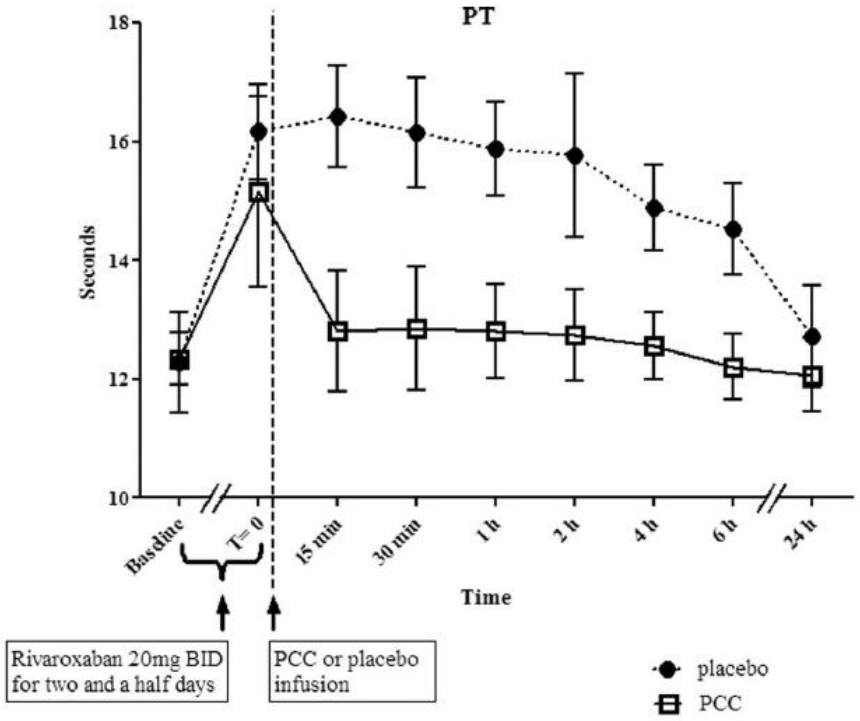
In queste situazioni il GdL raccomanda di utilizzare test specifici per la misurazione dell'effetto anticoagulante dei NAO:

- Tempo di Trombina diluito o il dosaggio cromogenico dell'attività anti-IIa per Dabigatran
- Dosaggio cromogenico dell'attività anti Xa per Rivaroxaban e Apixaban

Il GdL raccomanda che tali test siano disponibili in urgenza presso tutti i laboratori sui quali insista una struttura di Pronto Soccorso.

Concentrati di Complesso Protrombinico (PCC)

- Rivaroxaban: significativo allungamento del PT
  - Allungamento revertito immediatamente e completamentre dal PCC
- Dabigatran: significativo allungamento dell'aPTT
  - Nessun effetto sull'aPTT del PCC
- Conclusioni
  - PCC reverte *in vivo* nell'uomo l'effetto anticoagulante di rivaroxaban



Eeremberg, Circulation, 2011

Reversing the NOACs with PCCs: what is the evidence ?

Study drug	Brand of PCC	Model	Results	
			Coagulation parameters	Bleeding
Dabigatran				
Non-activated PCCs				
Zhou et al., 2011 (29)	Beriplex®	Mouse intracerebral haemorrhage model	No data	↓
Pragst et al., 2012 (27)	Beriplex®	Kidney bleeding / coagulation rabbit	↓ PT and normalisation of V_{max} for thrombus formation but no change in aPTT	↓
Hoffman et al., 2012 (23)	Beriplex®	Cellular *in vitro* coagulation (human)	↑ rate, peak and total amount of thrombin generation	No data
van Ryn et al., 2011 (28)	Beriplex®/Octaplex®	Tail cut model / coagulation rat	No change in TT, aPTT or ECT, but PT reversed to baseline	↓
Herzog et al., 2013 (65)	Beriplex®	Arterial venous shunt / coagulation rabbit	↓ thrombin generation, but no change in PT or dPT	↓
Lambourne et al, 2012 (26)	Octaplex®	Tail clip bleeding / coagulation mouse	No change in TT or aPTT	No change
Eerenberg et al., 2011 (21)	Cofact®	Human volunteers / coagulation	No change in aPTT, ETP lag time, ECT or TT	No data
Marlu et al., 2012 (22)	Kanokad®	*Ex vivo* coagulation model (human)	↑ in EPT-AUC and thrombin peak, no change in lag time	No data
van Ryn et al., 2012 (30)	Profilnine®/Bebulin®	Tail cut model / coagulation rat	No change in aPTT, PT or ECT	↓
Activated PCC				
Marlu et al., 2012 (22)	FEIBA®	*Ex vivo* coagulation model (human)	↑ in EPT-AUC and thrombin peak, ↓ lag time	No data

Dickneite, Thromb Haemost, 2014

Reversing the NOACs with PCCs: what is the evidence ?

Study drug	Brand of PCC	Model	Results	
			Coagulation parameters	Bleeding
Rivaroxaban				
Non-activated PCCs				
Perzborn et al., 2013 (33)	Beriplex®	Mesenteric bleeding / coagulation, rats	↑ TAT; ↓ PT, but reversal was partial	↓
Zhou et al., 2013 (32)	Beriplex®	Mouse intracerebral haemorrhage model	No change in PT, but ↑ in plasma activity of FII, FIX, FX and proteins C and S	↓ (haematoma volume)
Godier et al., 2012 (34)	Kaskadil®	Hepatosplenic bleeding / coagulation, rabbits	↓ clot formation time (INTEM) and clotting time (EXTEM); moderate improvement in thrombin potential in TGA	No change
Eerenberg et al., 2012 (21)	Cofact®	Human volunteers / coagulation	↓ PT and EPT, both to normal levels	No data
Dinkelaar et al., 2013 (31)	Cofact®	*In vitro* coagulation model (human plasma and whole blood)	↓ PT (partial reversal), ↑ ETP-AUC and TG AUC (CAT plasma assay), normalisation of AUC (CAT whole blood assay), no change in lag time	No data
Marlu et al., 2012 (22)	Kanokad®	*Ex vivo* coagulation model (human)	↑ ETP-AUC and thrombin peak, slight ↓ in lag time, no change in TTP	No data
Activated PCC				
Marlu et al., 2012 (22)	FEIBA®	*Ex vivo* coagulation model (human)	↑ in EPT-AUC and thrombin peak, ↓ lag time and TTP	No data
Perzborn et al., 2013 (33)	FEIBA®	Mesenteric bleeding / coagulation, rats	↑ TAT and ↓ PT, but reversal was partial in both cases	↓
Perzborn et al., 2013 (33)	FEIBA®	Mesenteric bleeding / coagulation, baboons	↓ PT, but reversal was partial	↓ (not sustained post-infusion end)

Dickneite , Thromb Haemost, 2014

Reversing the NOACs with PCCs: what is the evidence ?

- Systematic review about NOACs (dabigatran, rivaroxaban, apixaban).

- PCCs (including activated PCCs) show promise for reversing the anticoagulant effects of the NOACs and may be considered a reasonable approach in dire clinical situations.

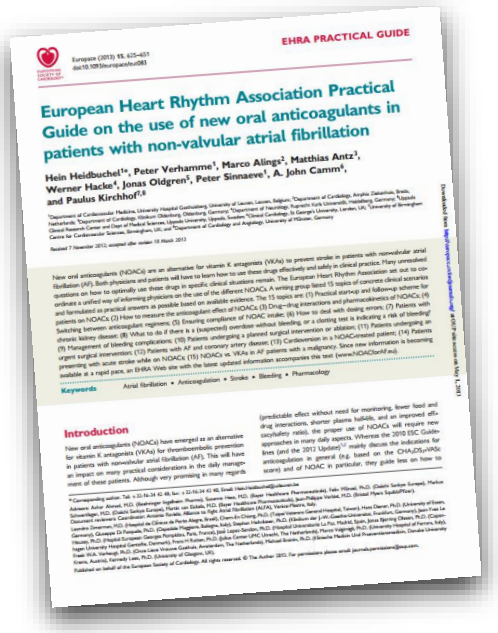
- Conventional laboratory assays do not correlate well with bleeding or reversal of anticoagulation in this setting; thrombin generation assays appear to have the best predictive value.

Dickneite , Thromb Haemost, 2014

EHRA: dosing recommendation for factor concentrates

In case of life-threatening bleeding:

- **PCC 25 U/kg**: may be repeated once or twice (no clinical evidence)
- **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 + expensive + thrombogenic
- Activated factor VII **(rFVIIa; 90 µg/kg)**: no data about additional benefit + expensive (only animal evidence)+ thrombogenic


EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1*], Peter Verhamme[2], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

Introduction

EHRA Practical Guide, Europace, 2013

Uso dei PCC nei pazienti con emorragia maggiore in corso di NAO

“Unsolved clinical problems”

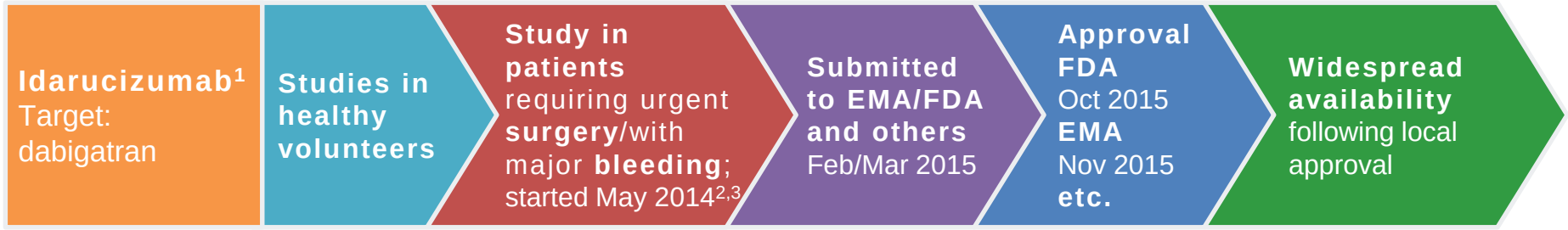
- Efficacia clinica
- Sicurezza
- Monitoraggio di laboratorio dell’effetto emostatico
- Posologia
- Preparati a 3 fattori oppure a 4 fattori
- Antidoti ?

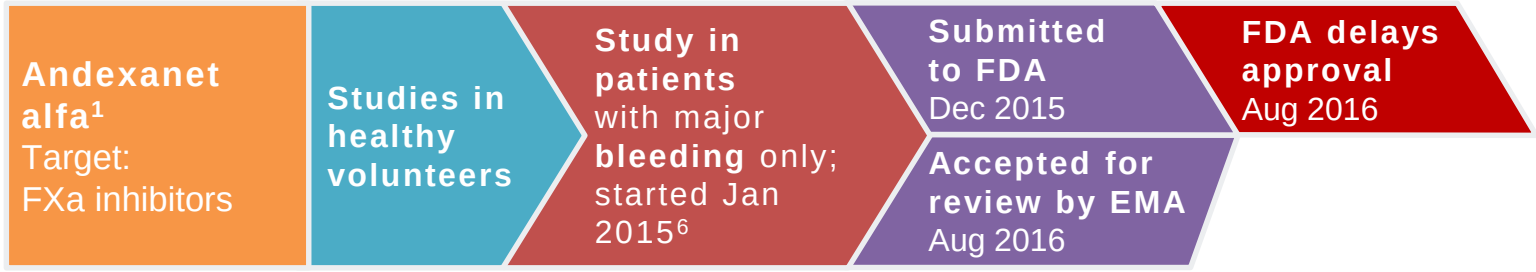
Monitoring and Antidotes

	Monitoring/Testing	Antidote
Warfarin	INR TTR	Vitamin K
Dabigatran	TT - Hemoclot®	Monoclonal Ab **(IDARUCIZUMAB)**
	ECT (aPTT)	
FXa Inhibitors	Factor Xa activity (PT)	Universal antidote (FX analogue) **(ANDEXANET ALFA)**
All	Hb concentrations HAS-BLED #	**ARIPAZINE** Fresh frozen plasma Prothrombin complex concentrate FEIBA rFVIIa

Weitz , Hematology Am Soc Educ Program, 2012 (mod)

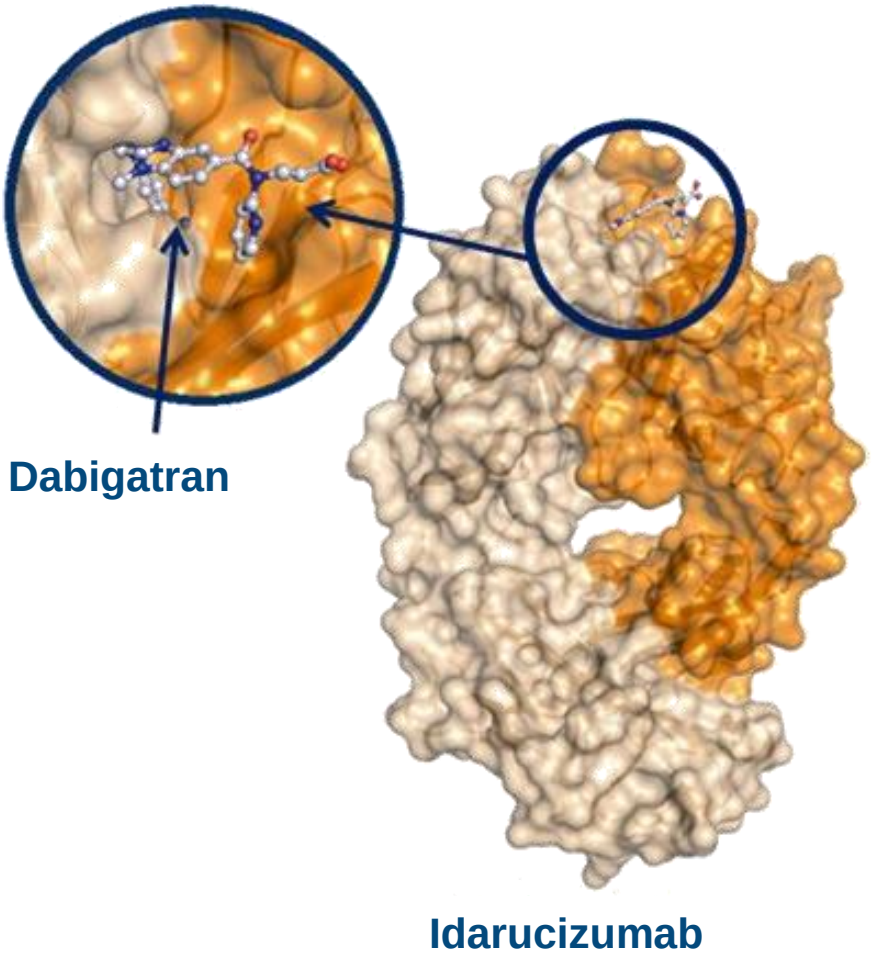
Antidotes


Idarucizumab[1]
Target:
dabigatran
Studies in healthy volunteers
Study in patients requiring urgent surgery/with major bleeding; started May 2014[2,3]
Submitted to EMA/FDA and others
Feb/Mar 2015
Approval
FDA
Oct 2015
EMA
Nov 2015
etc.
Widespread availability following local approval


Andexanet alfa[1]
Target:
FXa inhibitors
Studies in healthy volunteers
Study in patients with major bleeding only; started Jan 2015[6]
Submitted to FDA
Dec 2015
FDA delays approval
Aug 2016
Accepted for review by EMA
Aug 2016

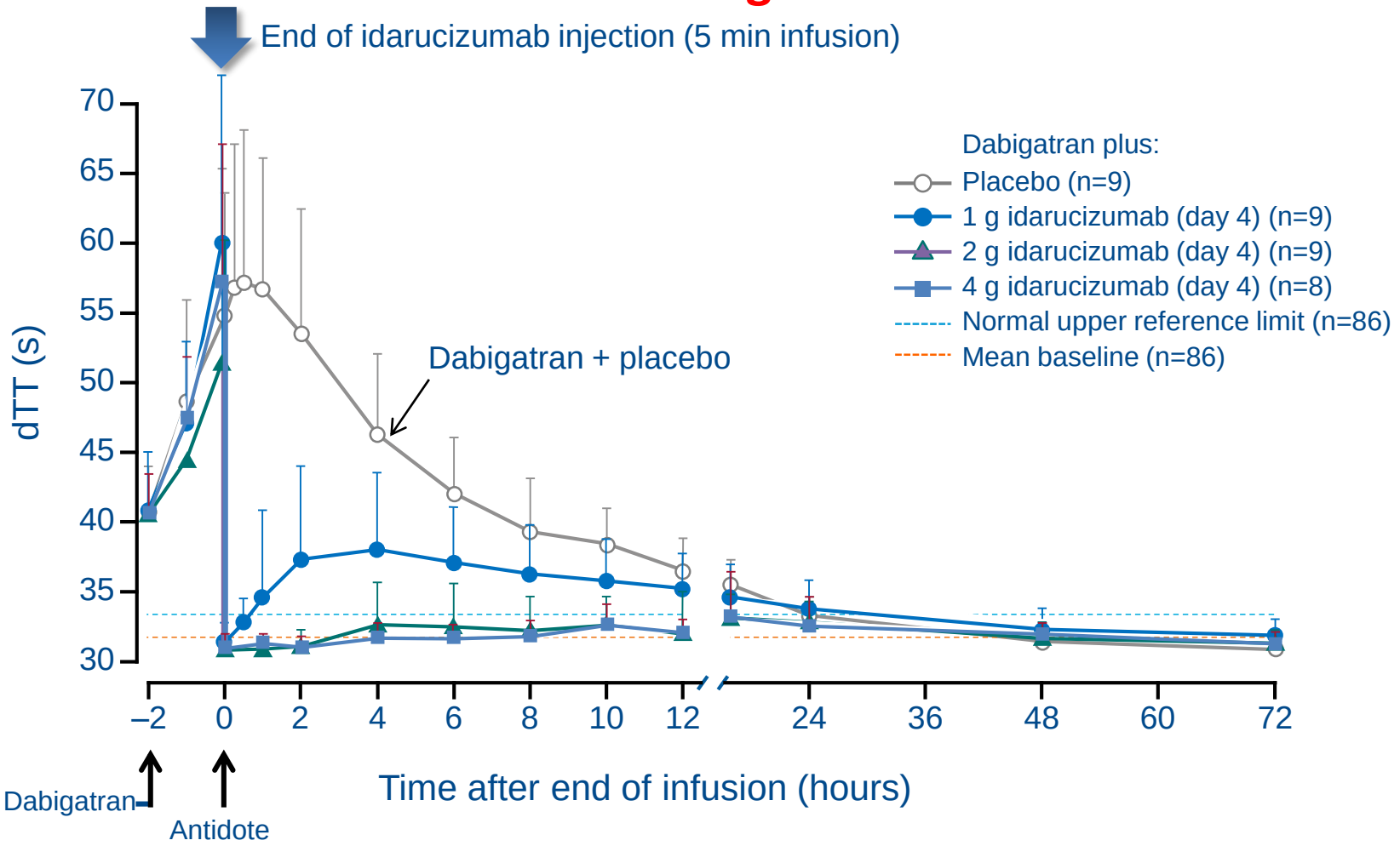

CIRAPARANTAG
(PER977)
Target: universal
Phase I
Phase II

Idarucizumab



- Humanized Fab fragment
- Binding affinity **~350 × higher** than dabigatran to thrombin
- No intrinsic procoagulant or anticoagulant activity
- IV bolus / rapid infusion; immediate onset of action
- Short half-life

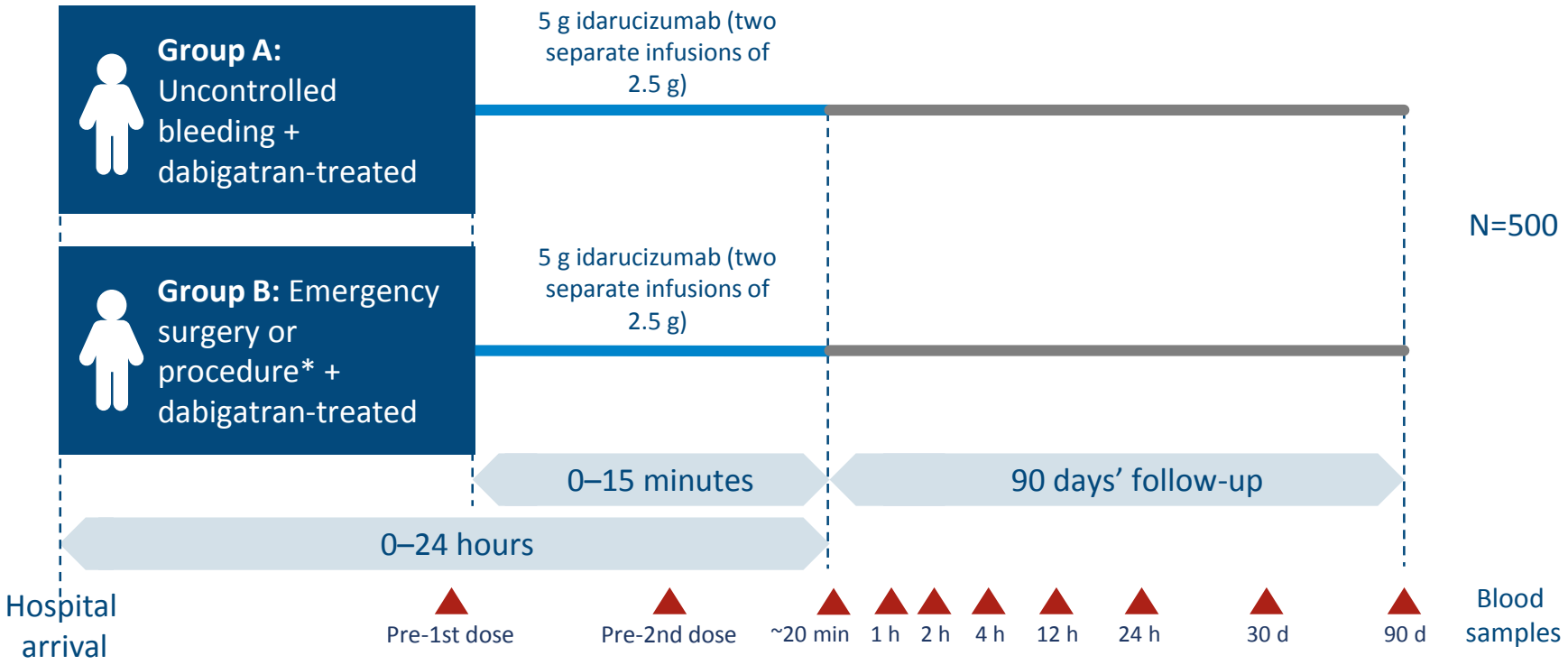
Healthy volunteer study: demonstrated potential of the antidote for immediate, complete and sustained reversal of dabigatran anticoagulation



Normal upper reference limit' refers to (mean+2SD) of 86 predose measurements from a total of 51 subjects

Glund, Circulation, 2013

Idarucizumab for Dabigatran Reversal
RE - VERSE AD STUDY



Interim analysis n = 90

Primary endpoint
Dabigatran reversal

Pollack, NEJM, 2015

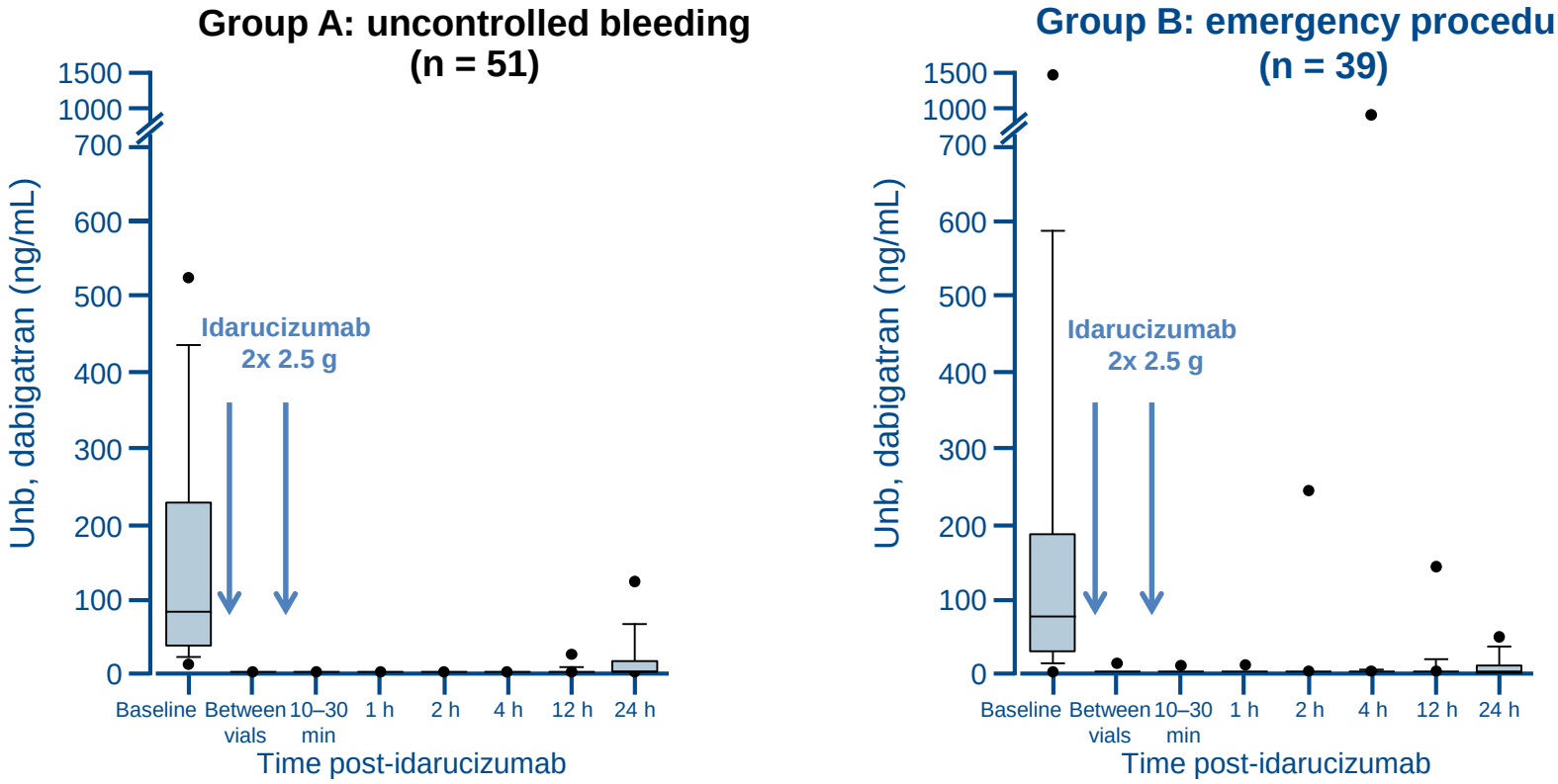
Idarucizumab for Dabigatran Reversal

Group A (n=51)	
Bleeding site	
Intracranial	18
Trauma	9
Gastrointestinal	20
Other*	11

Group B (n=39)	
Reason for surgery	
Aortic dissection	1
Pericardial tamponade	1
Peritonitis	1
Mesenteric ischaemia	2
Bone fractures	8
Acute cholecystitis	5
Nephrostomia	4
Appendicitis	3
Joint/wound infection	3
Abscess	2

Pollack, NEJM, 2015

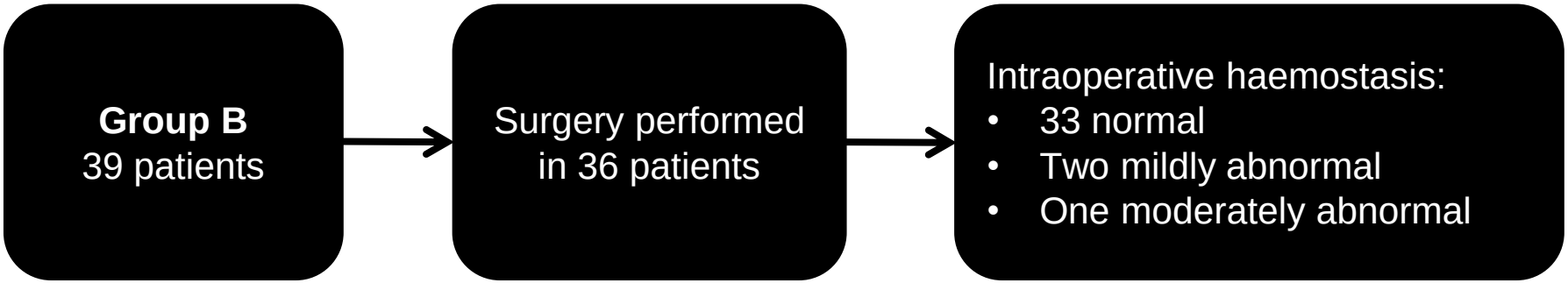
Dabigatran levels were reduced immediately after idarucizumab administration



Dabigatran levels were <20 ng/mL* in 89/90 patients after infusion of first vial, in 77/83 at 12 hours and 62/78 patients at 24 hours

Pollack, NEJM, 2015

Secondary clinical endpoints in Interim analysis RE-VERSE AD™ (Group B)



⇨ 92% of patients had normal intraoperative haemostasis, as judged by the physician

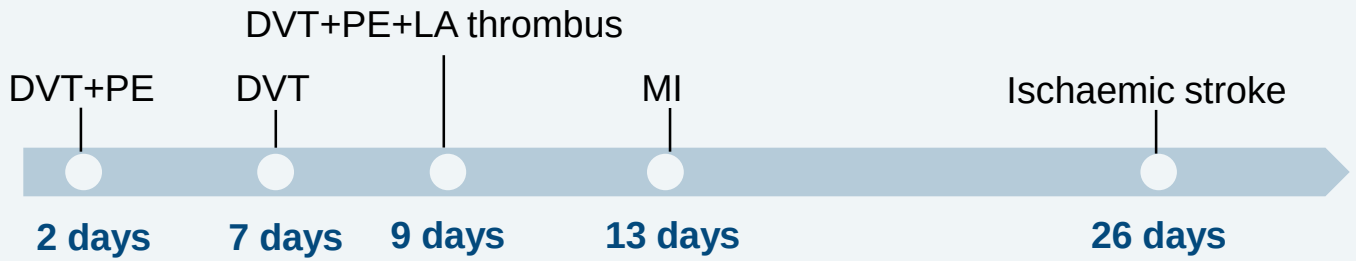
Pollack, NEJM, 2015

No safety concerns and no evidence of prothrombotic or immunogenic effect after idarucizumab administration

No cases of hypersensitivity observed

5 thrombotic events

- 1 early event (DVT+PE) 2 days after idarucizumab administration
- 4 events after >6 days of idarucizumab administration



- None of these 5 patients were receiving any antithrombotic therapy when the events occurred

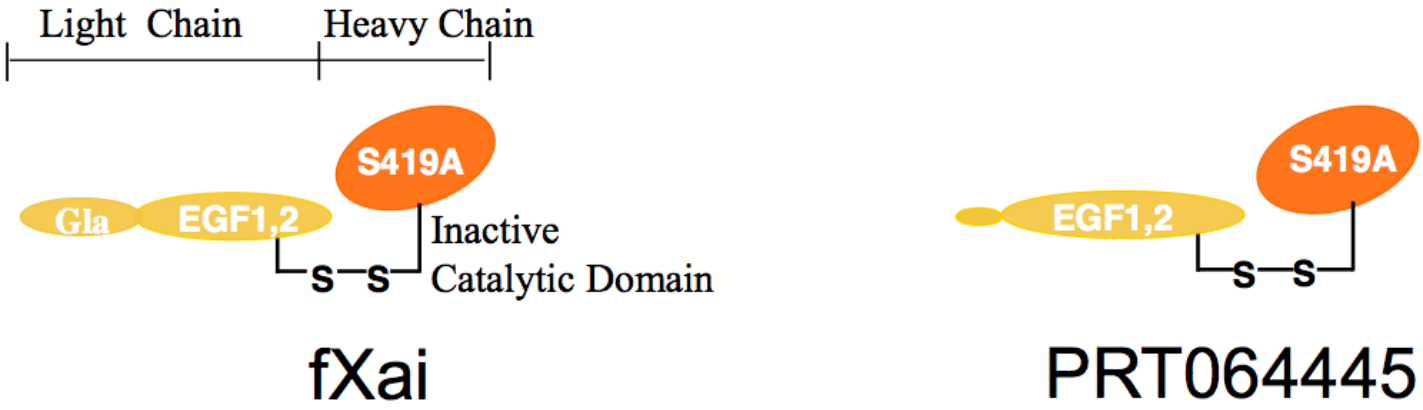
18 deaths (9 in each Group)

- RE-VERSE AD™ allows even severely ill patients into the study
- All deaths related to presenting index event and comorbidities

Pollack, NEJM, 2015

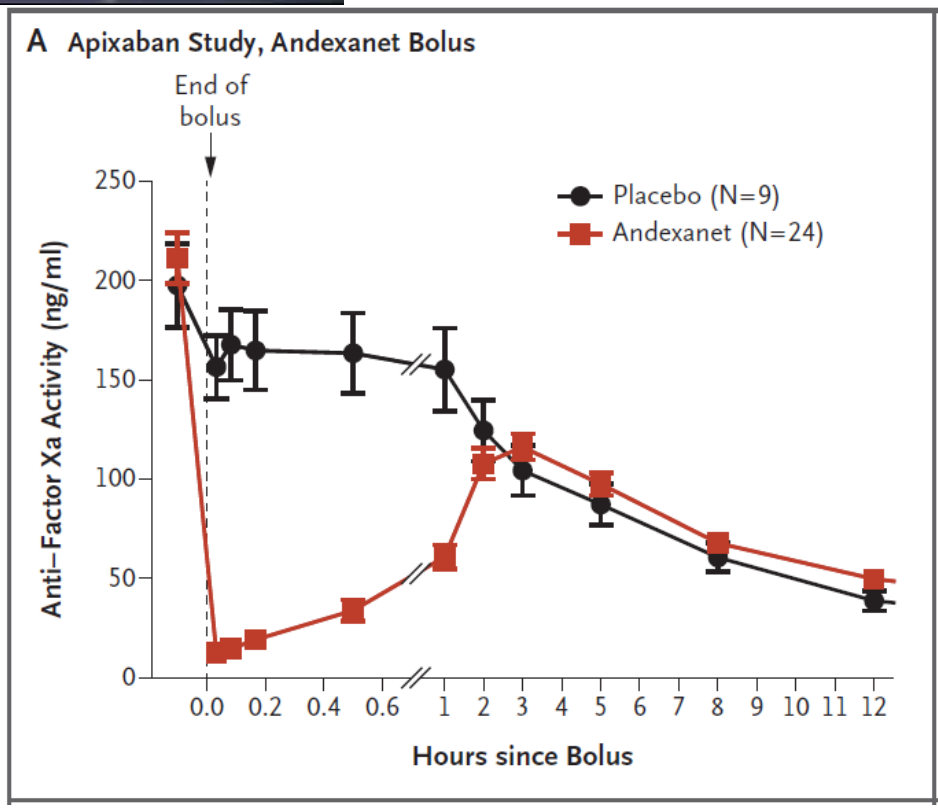
Andexanet alfa

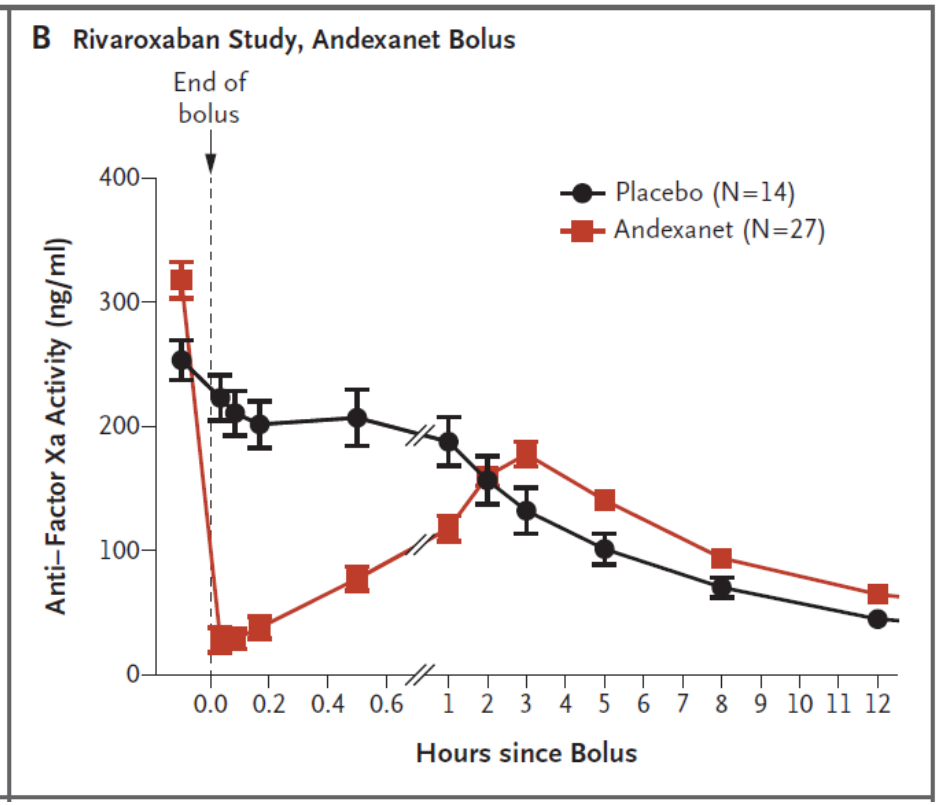
- Recombinant modified human factor xa decoy protein
  - it binds factor Xa inhibitors (rivaroxaban, apixaban, betrixaban, etc) with high affinity
  - It binds and sequesters factor Xa inhibitors within the vascular space



ORIGINAL ARTICLE

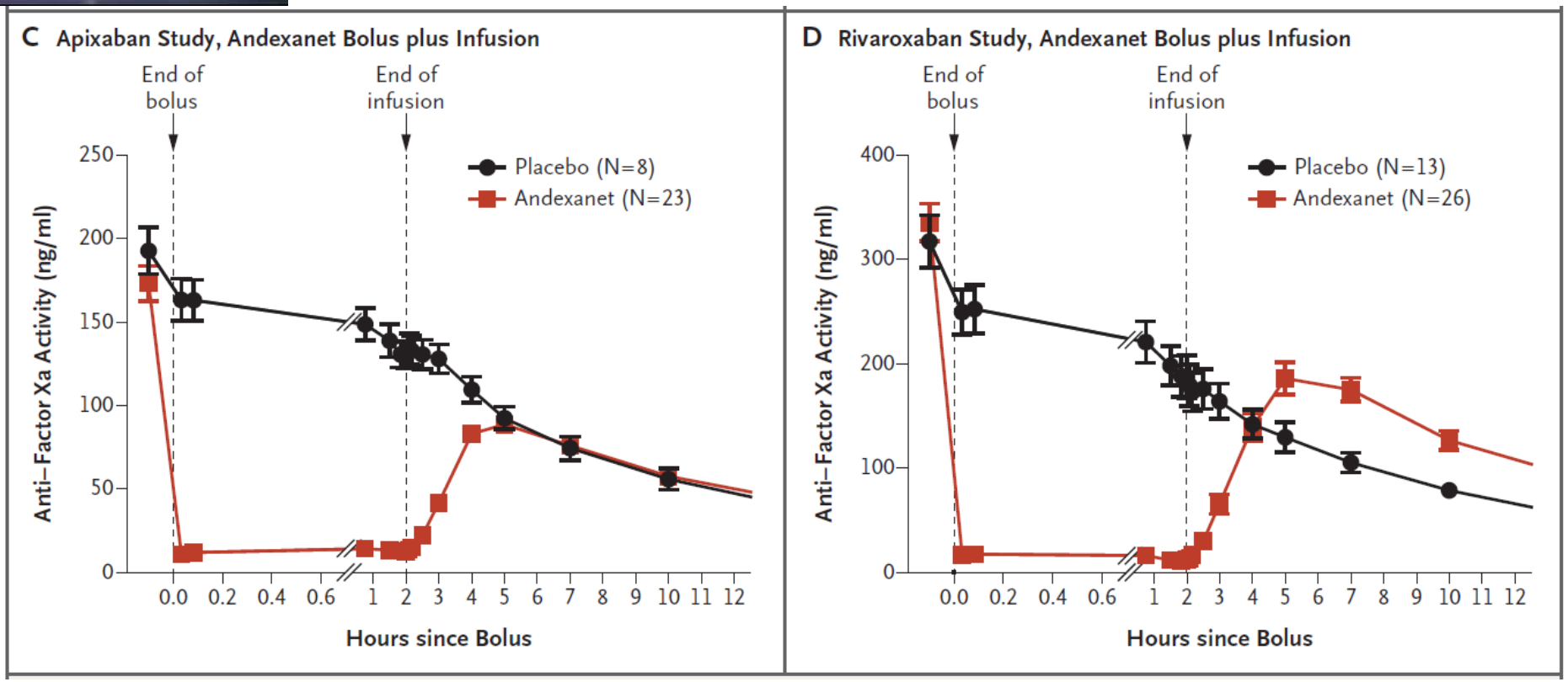
Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity





Siegal, NEJM, 2015

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity



Siegal, NEJM, 2015

Annexa A/R: adverse events

- Assessed on days 15, 36, and 43 after andexanet
- No serious or severe adverse events
- No thrombotic events

Table 1. Drug-Related Adverse Events.*

Event	Apixaban		Rivaroxaban		Placebo (N = 44)
	Bolus (N = 24)	Bolus + Infusion (N = 24)	Bolus (N = 27)	Bolus + Infusion (N = 26)	
	number of events				
Gastrointestinal disorders	2	2	0	0	0
Constipation	0	2	0	0	0
Dysgeusia	2	0	0	0	0
General disorders and administration-site conditions	3	4	2	0	1
Feeling hot	1	2	0	0	1
Flushing	2	2	2	0	0
Immune system disorders	0	1	1	0	0
Urticaria	0	1	1	0	0

Siegal, NEJM, 2015

Annexa A/R: antibody formation

- Antibodies to FX / FXa (through day 43) → not detected
- Antibodies to andexanet:
  - Neutralizing → **not detected**
  - Non-neutralizing → 2% placebo vs 17% andexanet
  - Antibodies tended to appear within 15 to 30 days

Andexanet has little immunogenicity after a single intravenous exposure

Siegal, NEJM, 2015

Andexanet alfa for acute major bleeding associated with factors Xa inhibitors

- 67 patients with acute MB receiving apixaban or rivaroxaban (anti factor Xa activity ≥ 75 ng/ml; efficacy population = 47)
- Bolus + infusion 120' (1/2 life = 1 h)*
- Age mean = 77 yrs, women = 48%
- 30-days follow-up
- Primary end point: rivaroxaban and apixaban reversal

*** 400 mg for patients who had taken DOACs > 7 hours before administration of andexanet or 800 mg (≤ 7 hours or at unknown time), followed by 480 or 960 mg**

Siegal, NEJM, 2015

Andexanet alfa for acute major bleeding associated with factors Xa inhibitors

Site of bleeding

Table 2. Characteristics of Acute Major Bleeding Episodes and Clinical Outcomes.*

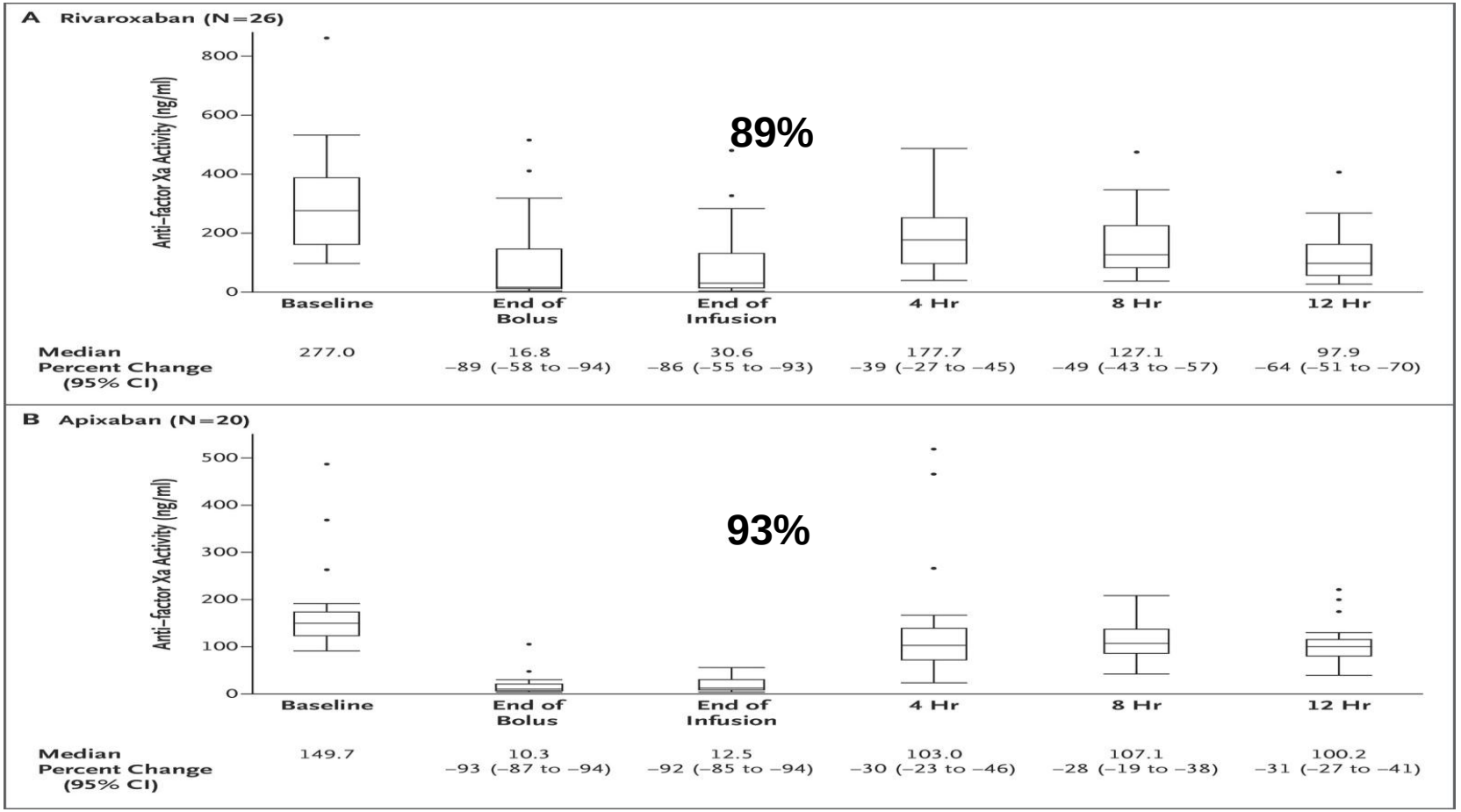
Characteristic	Safety Population (N = 67)	Efficacy Population (N = 47)
Gastrointestinal bleeding — no./total no. (%)	33/67 (49)	25/47 (53)
Patients receiving rivaroxaban	20/33 (61)	16/25 (64)
Patients receiving apixaban	11/33 (33)	8/25 (32)
Site of bleeding		
Upper gastrointestinal tract	9/33 (27)	7/25 (28)
Lower gastrointestinal tract	10/33 (30)	8/25 (32)
Unknown	14/33 (42)	10/25 (40)
Baseline hemoglobin ≤10 g/dl	20/33 (61)	16/25 (64)
Pretreatment red-cell transfusion	21/33 (64)	19/25 (76)
Intracranial bleeding — no./total no. (%)	28/67 (42)	20/47 (43)
Patients receiving rivaroxaban — no./total no. (%)	10/28 (36)	8/20 (40)
Patients receiving apixaban — no./total no. (%)	17/28 (61)	12/20 (60)
Baseline score on Glasgow Coma Scale†	14.1±1.7	14.1±1.7
Intracerebral site — no./total no. (%)	14/28 (50)	12/20 (60)
Baseline score on modified Rankin scale‡	3.0±1.8	2.8±1.9
Hematoma volume — no./total no. (%)		
≤10 ml	8/14 (57)	8/12 (67)
11 to 60 ml	6/14 (43)	4/12 (33)
Subdural site — no./total no. (%)	11/28 (39)	7/20 (35)
Baseline score on modified Rankin scale	2.1±1.6	1.4±1.5
Maximal thickness — no./total no. (%)		
≤10 mm	8/11 (73)	5/7 (71)
>10 mm	3/11 (27)	2/7 (29)
Subarachnoid site — no./total no. (%)	3/28 (11)	1/20 (5)
Other bleeding site — no./total no. (%)	6/67 (9)	2/47 (4)
Patients receiving rivaroxaban	2/6 (33)	2/2 (100)
Patients receiving apixaban	4/6 (67)	0
Site of bleeding		
Nasal	1/6 (17)	0
Pericardial, pleural, or retroperitoneal	3/6 (50)	1/2 (50)
Genital or urinary	1/6 (17)	1/2 (50)
Articular	1/6 (17)	0
Pretreatment red-cell transfusion	3/6 (50)	1/2 (50)
Clinical outcome — no./total no. (%)		
Death	10/67 (15)	7/47 (15)
Thromboembolic event	12/67 (18)	7/47 (15)

* Plus–minus values are means ±SD.
† Scores on the Glasgow Coma Scale range from 15 (normal) to 3 (deep coma).
‡ Scores on the modified Rankin scale for global disability and handicap range from 0 (no symptoms or disability) to 6 (death).

Bleeding was predominantly gastrointestinal (53%) or intracranial (43%)

Connolly, NEJM, 2016

Andexanet alfa for acute major bleeding associated with factors Xa inhibitors

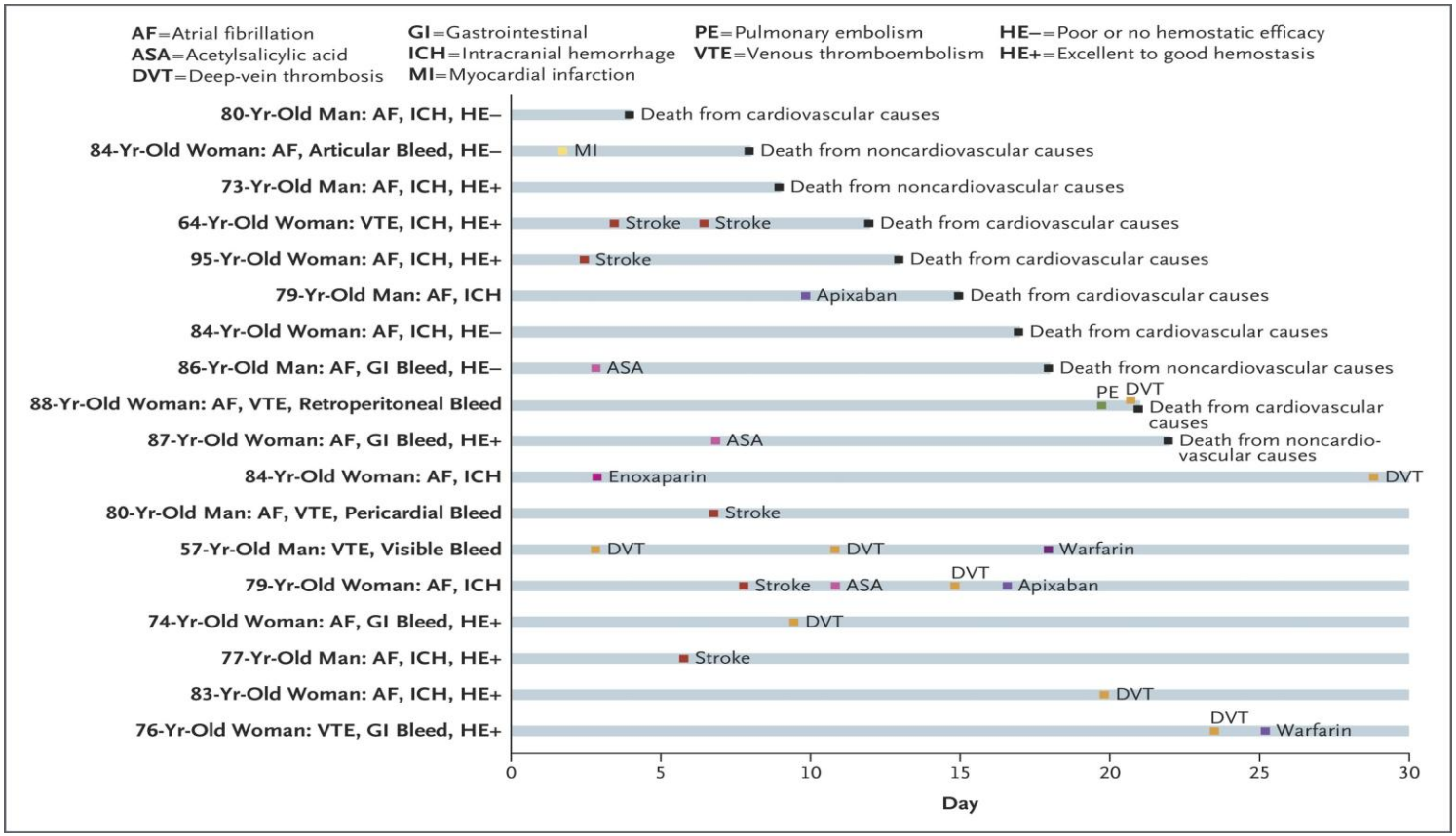


Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population)

Haemostasis was clinically adjudicated excellent or good in 79% of the patients (CI 64 to 89)

Connolly, NEJM, 2016

Thrombotic events or Death during the 30-Day Study Period

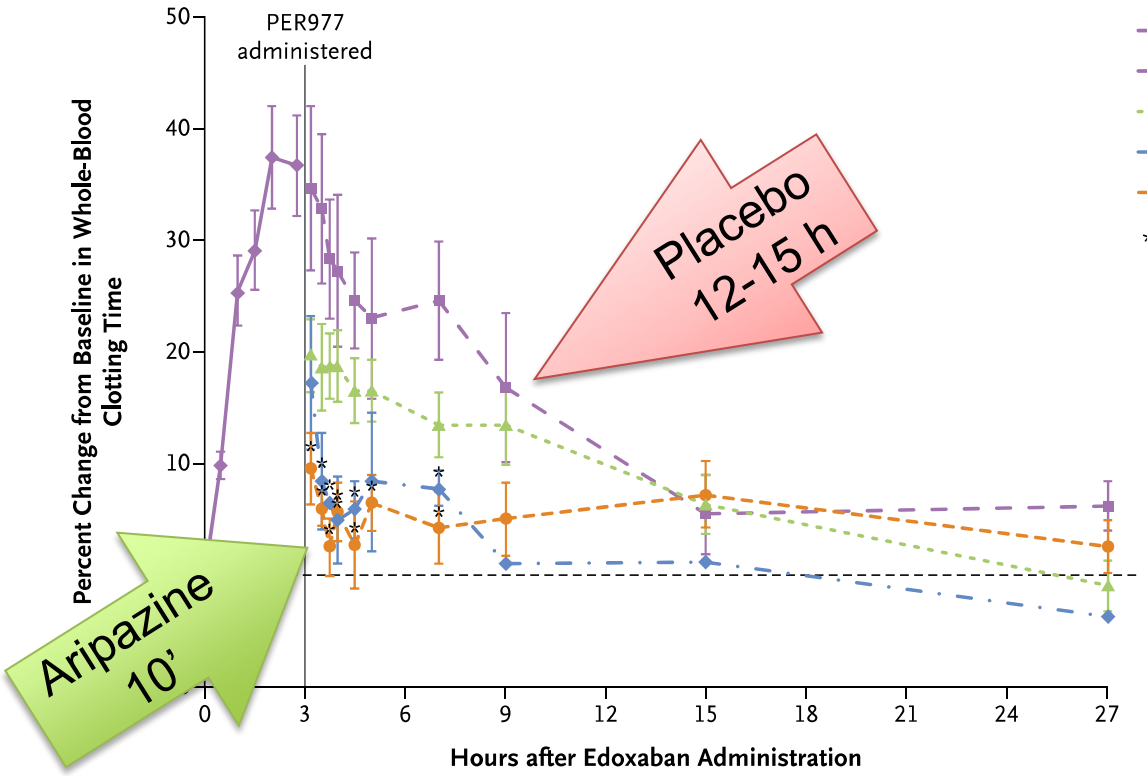


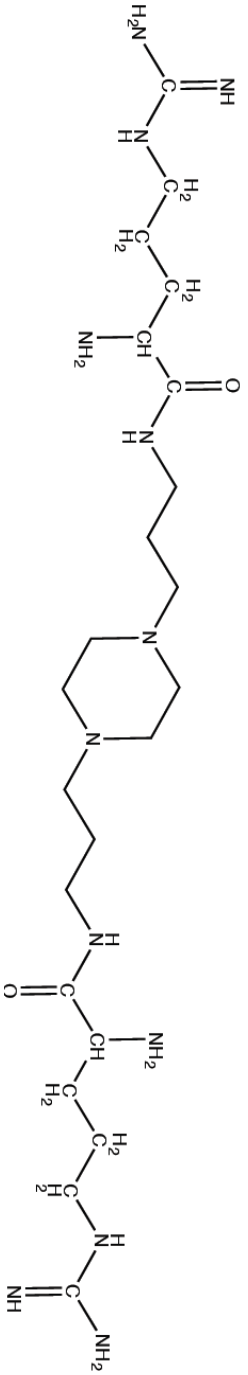
Thrombotic events: 12 of 67 patients (18%)

Siegal, NEJM, 2015

Ciraparantang

- 80 volunteers treated with Edoxaban 60 mg
- Single dose IV (25, 100, 300 mg)
- Double-blind, placebo controlled





Ansell, NEJM, 2014

Indications for Use or non-Use of the antidotes Guidance from the SSC of the ISTH

Indication for USE:	Potential Indication for use	Antidotes should NOT be used
Life-threatening bleeding: • Intracranial hemorrhage • Syntomatic or expanding extradural hemorr or uncontrollable hemorrage **Bleeding in a closed space or critical organ**: • Intracranial/intraspinal/itraocular/pericardial/pulmonary/retroperitoneal/intramuscolar with compartment syndrome **Persistent major bleeding** despite local hemostatic measure, 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 pts at high risk for procedural bleeding:** Neurosurgery/lumbar puncture/cardiac or vascular surgery/hepatic or othr major organ surgery	**Need for urgent surgery or intervention in patients with acute renale failure**	**Elective surgery** **Gastrointestinal bleeds that responde 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**

Levy, JTH, 2016

Antidoti: quesiti per il futuro

- Profilo di sicurezza ed efficacia clinica degli antidoti (hard endpoints vs. endpoint surrogati quali TT, ECT, anti-Xa, whole blood clotting time)
- Rilevanza clinica ed interpretazione dei test coagulativi di monitoraggio
- Rischio di uso improprio
- Costi

AGENDA

- Complicanze emorragiche
- Procedure ed interventi chirurgici in urgenza
- Sovradosaggio

11. Patients undergoing an urgent surgical intervention

- Discontinue NOAC.
- Try to defer surgery at least 12 h and ideally 24 h after last dose.
- Urgent surgery associated with much higher rates of bleeding than elective procedures, but lower than VKA-treated patients. [1]
- Coagulation tests can be considered (classical test or specific tests) but strategy based on these results has never been evaluated. Therefore such strategy cannot be recommended and should not be used routinely.

1. Healey et al, Circulation 2012:126;343-8 (Re-LY)

EHRA Practical Guide, Europace, 2015

MISURAZIONE DELL'EFFETTO ANTICOAGULANTE DEI NUOVI ANTICOAGULANTI DIRETTI (NAO)

Raccomandazione

Il Gruppo di Lavoro raccomanda la misurazione dell'effetto anticoagulante dei NAO (Dabigratan, Rivaroxaban, Apixaban) nelle condizioni in cui è necessario conoscere la presenza dell'effetto anticoagulante per guidare l'attività medica in situazioni di emergenza. In particolare in caso di:

- eventi avversi emorragici
- valutazione degli effetti dei trattamenti somministrati (reverse?)
- complicanze trombotiche
- preliminarmente a interventi chirurgici in emergenza
- preliminarmente a manovre invasive (diagnostiche o terapeutiche) in emergenza

In queste situazioni il GdL raccomanda di utilizzare test specifici per la misurazione dell'effetto anticoagulante dei NAO:

- Tempo di Trombina diluito o il dosaggio cromogenico dell'attività anti-IIa per Dabigatran
- Dosaggio cromogenico dell'attività anti Xa per Rivaroxaban e Apixaban

Il GdL raccomanda che tali test siano disponibili in urgenza presso tutti i laboratori sui quali insista una struttura di Pronto Soccorso.

Patients undergoing an urgent surgical intervention

Emergency surgery in patients receiving NOACs

- Surgeons should assess the urgency of the surgery against the risk of bleeding complications, and an individualised clinical judgement is essential.

- When the procedure cannot be postponed and residual anticoagulant activity of NOACs is detected, in patients at high risk of bleeding the prophylactic use of **an antidote** of haemostatic blood products such **as prothrombin complex concentrate (PCC)** for reversal of the effects of NOACs should be considered.

- However, in case of severe bleeding, antidote or PCC should be used.

Imberti, Clin Appl Thromb Haemost, 2013 (mod)