# Antidoti per i farmaci anticoagulanti orali diretti

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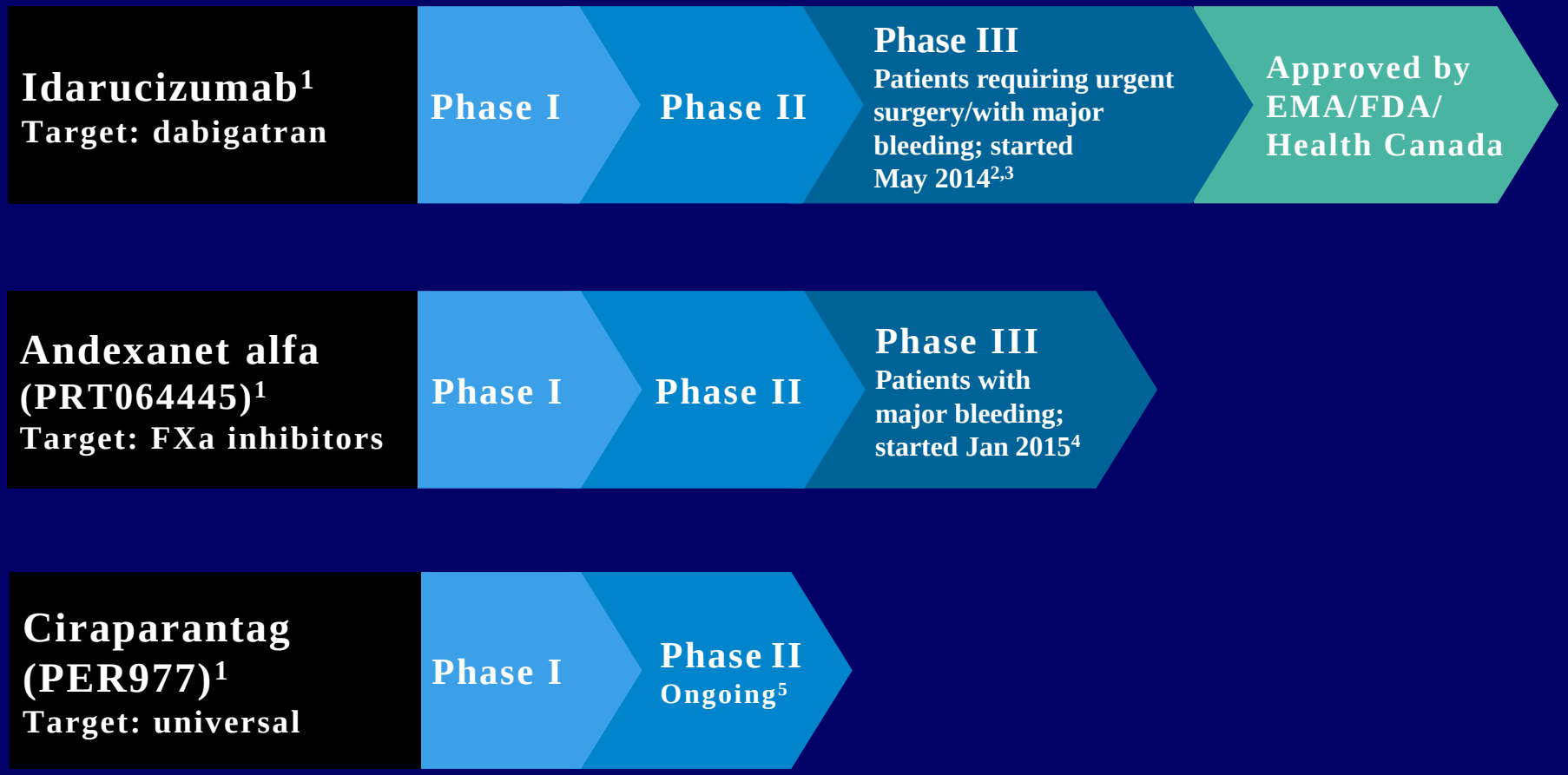
# Conflitti di interesse

- **Supporto alla ricerca: Bayer Healthcare, Boehringer Ingelheim**
- **Advisory Boards: Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, BMS-Pfizer, Italfarmaco, ONO**
- **Fees per letture a congressi: Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, BMS-Pfizer, Stago**

# DOAC reversal agents in development




**DOAC reversal agents are investigational compounds under development and have not been approved for use in the EU.**


1. Adapted from Greinacher A et al. Thromb Haemost 2015;113:931–42;
2. Clinicaltrials.gov: NCT02104947; 3. Pollack CV et al. Thromb Haemost. 2015;114:198–205;
4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

# Management strategies for the bleeding patient

- Inquire about last NOAC intake
- Blood sample to determine CrCl, haemoglobin, white blood cells
- Inquire with lab about possibility of rapid coagulation assessment

**Mild bleeding**

- Delay or discontinue next dose
- Reconsider concomitant medication

**Moderate/severe bleeding**

Supportive measures

- Mechanical compression
- Endoscopic haemostasis if GI bleed
- Surgical haemostasis
- Fluid replacement (colloids if needed)
- RBC transfusion if needed
- FFP (as plasma expander)
- Platelet transfusion (if platelet count $\leq 60 \times 10^9$/L)

For dabigatran-treated patients

- Idarucizumab 5 g IV (when available)
- Maintain adequate diuresis
- Consider haemodialysis

**Life-threatening bleeding**

For dabigatran-treated patients

- Idarucizumab 5 g IV (when available)

For all NOACs, consider:

- PCC 50 U/kg + 25 U/kg if indicated
- aPCC 50 U/kg; max 200 U/kg/day
- rFVIIa 90 µg/kg

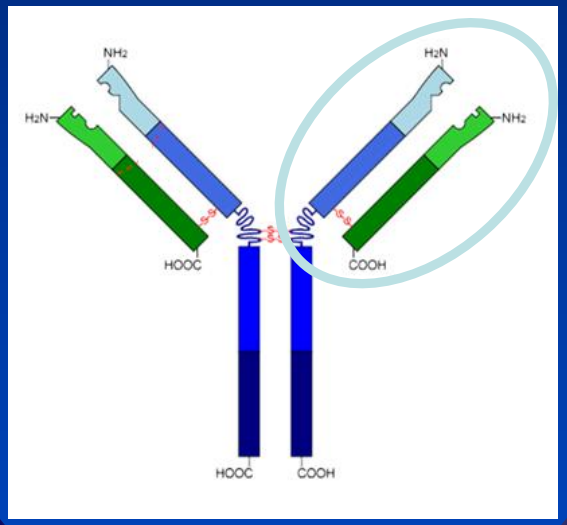
- FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; RBC, red blood cell; rFVIIa, activated Factor VII; Figure adapted from Heidbuchel et al. Europace 2015

# Idarucizumab

**Potente affinità di legame con dabigatran (~350 volte maggiore di quella di dabigatran con la trombina)**

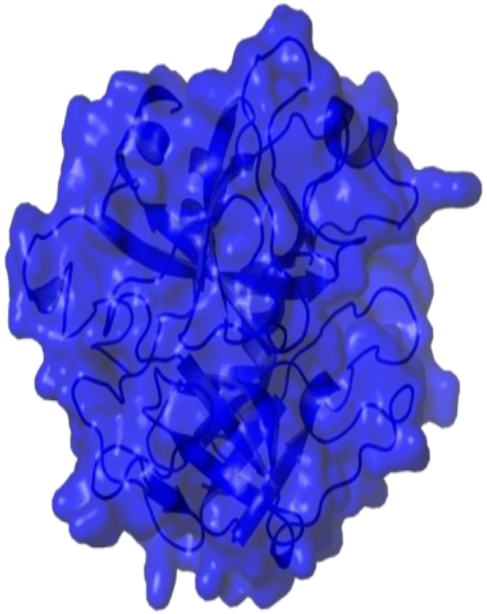
- **Somministrazione endovenosa**
  - **–Inizio di azione immediato**
  - **–Emivita breve (45 minuti circa)**
  - **–Eliminazione prevalentemente renale**
  - **–Privo di attività procoagulante o anticoagulante intrinseca**

**Humanized antibody fragment (Fab)**

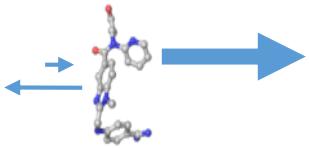



**Glund S et al. AHA 2013; abstract 17765; van Ryn J. AHA 2012; abstract 9928; van Ryn J et al. Circulation 2012;126:A9928**

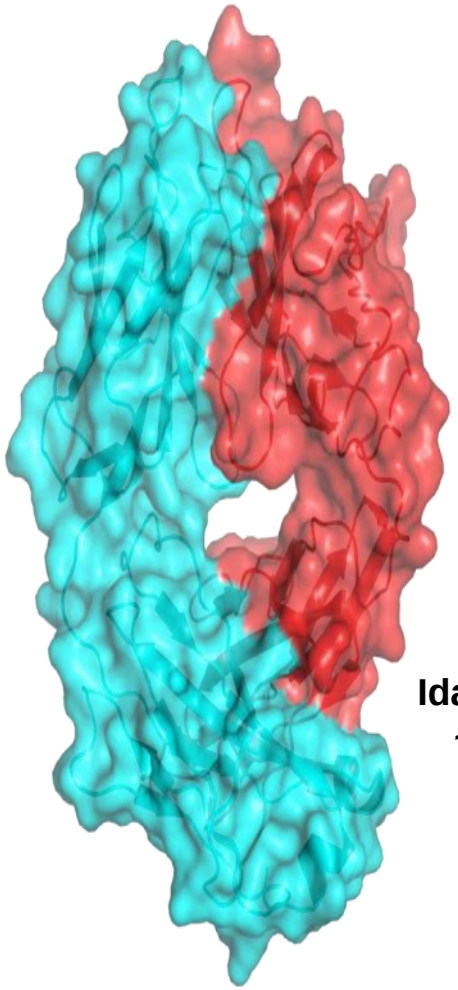
# Relative size and affinity of dabigatran, idarucizumab,and thrombin



**Thrombin**
**~37000 daltons**



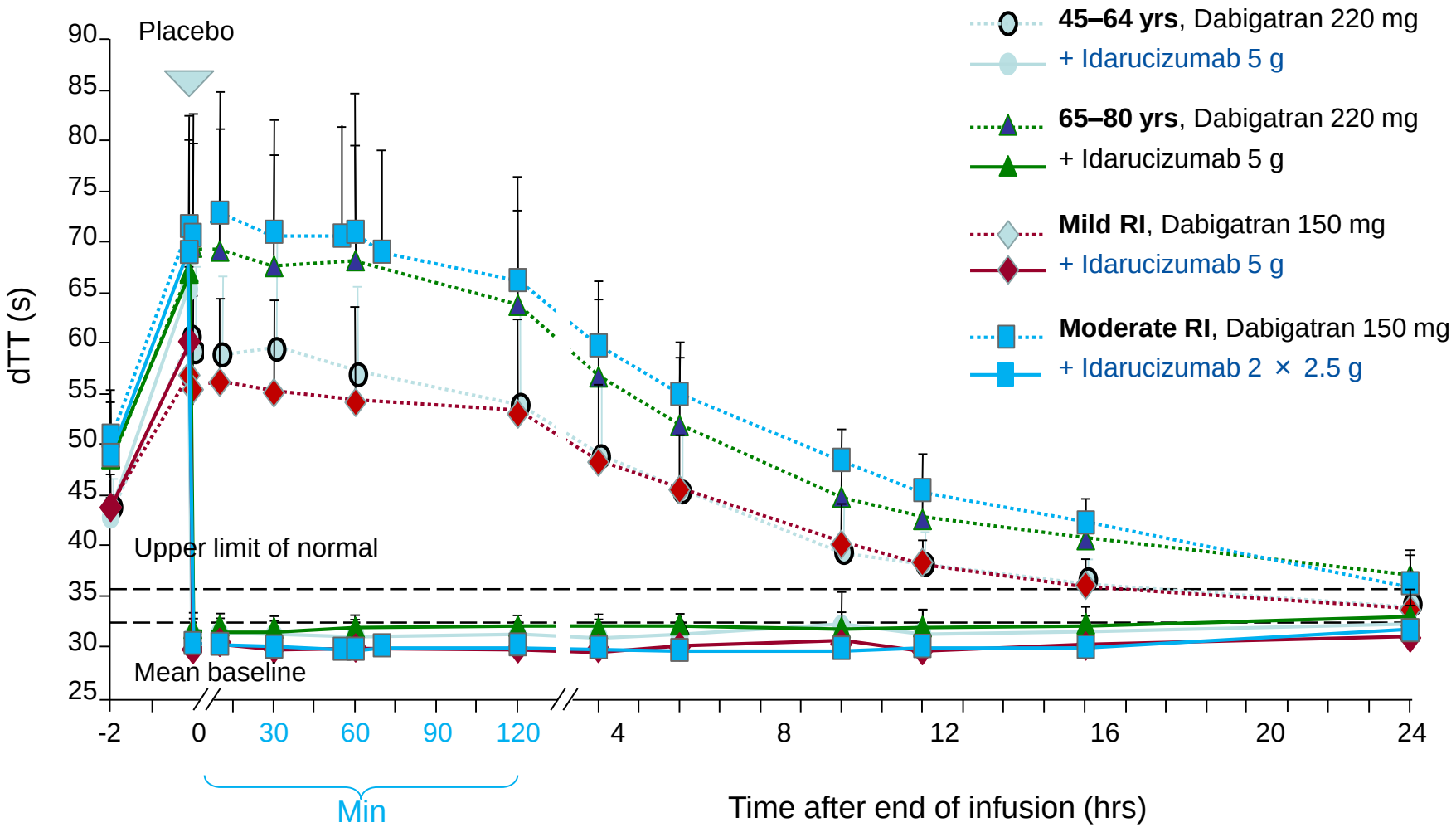
**Dabigatran**
**~500 daltons**



**Idarucizumab (Fab)**
**~47800 daltons**

Pollack et al. Thromb Haemost 2015

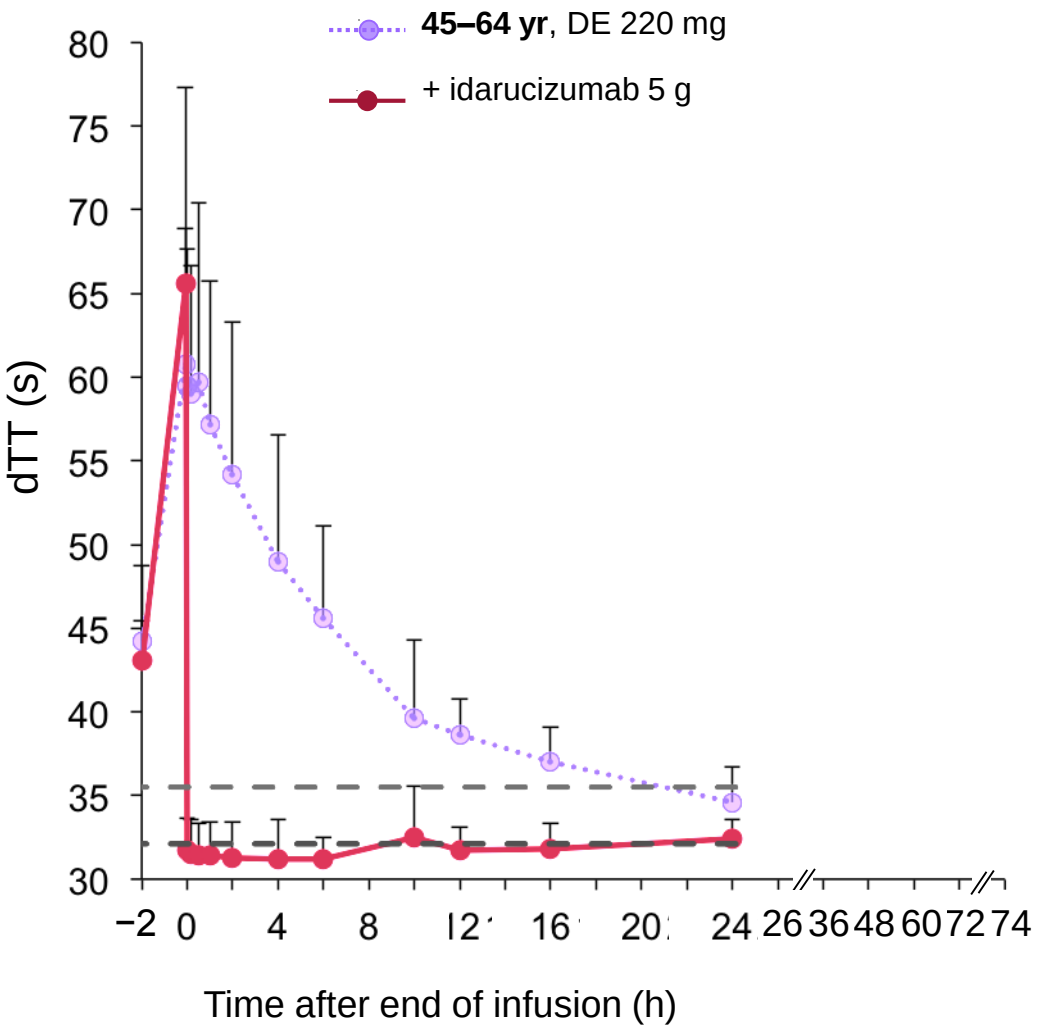
# Phase I study: effect of idarucizumab in elderly and renally impaired volunteers




dTT, diluted thrombin time; RI, renal impairment

Glund et al. Presented at ASH 2014

# Re-administration of dabigatran 24 h after idarucizumab




Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

N=6–8/group, mean ± SE

Glund et al. Blood 2014

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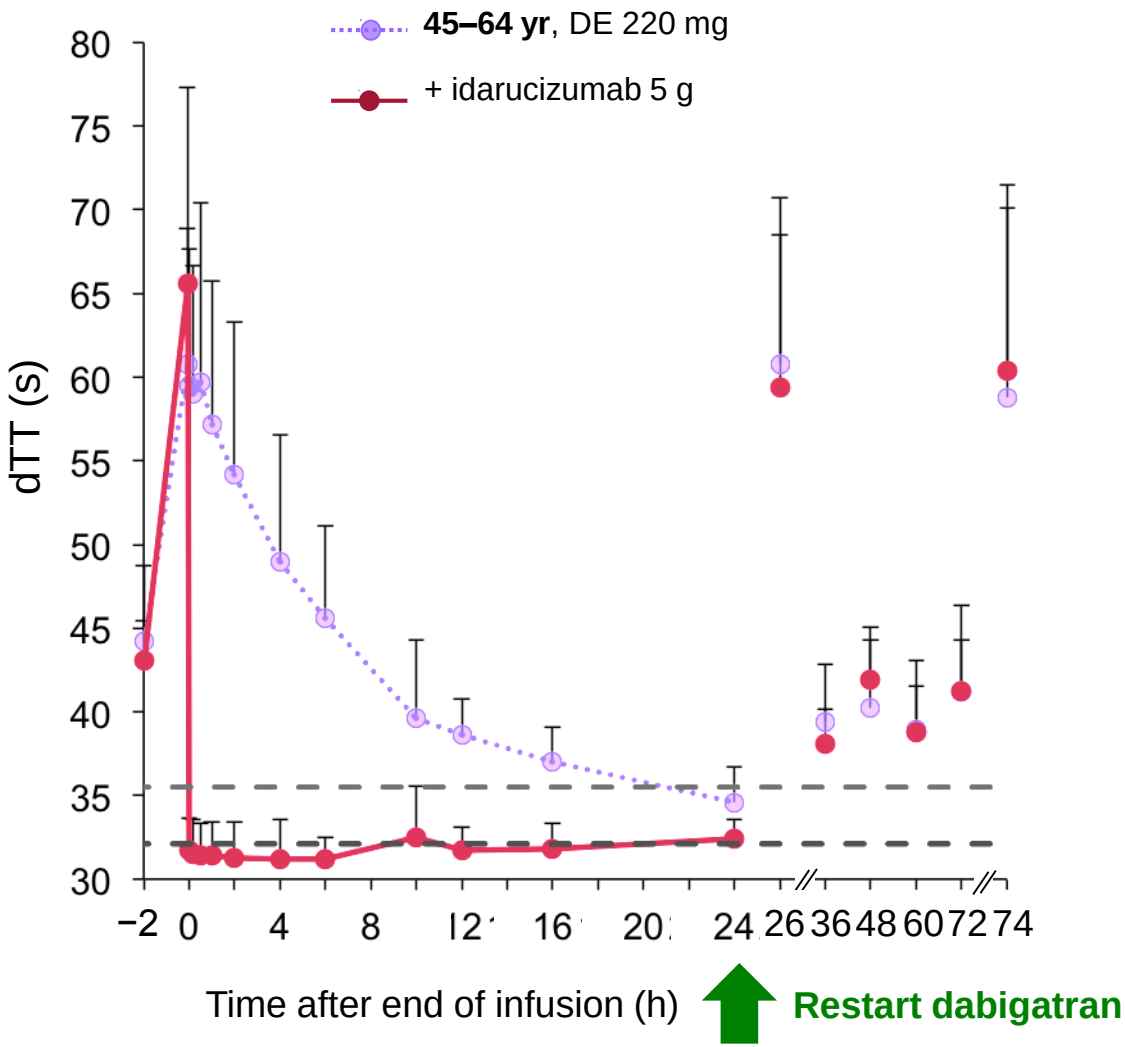


Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

24 hours later, dabigatran treatment was restarted

N=6–8/group, mean ± SE

Glund et al. Blood 2014

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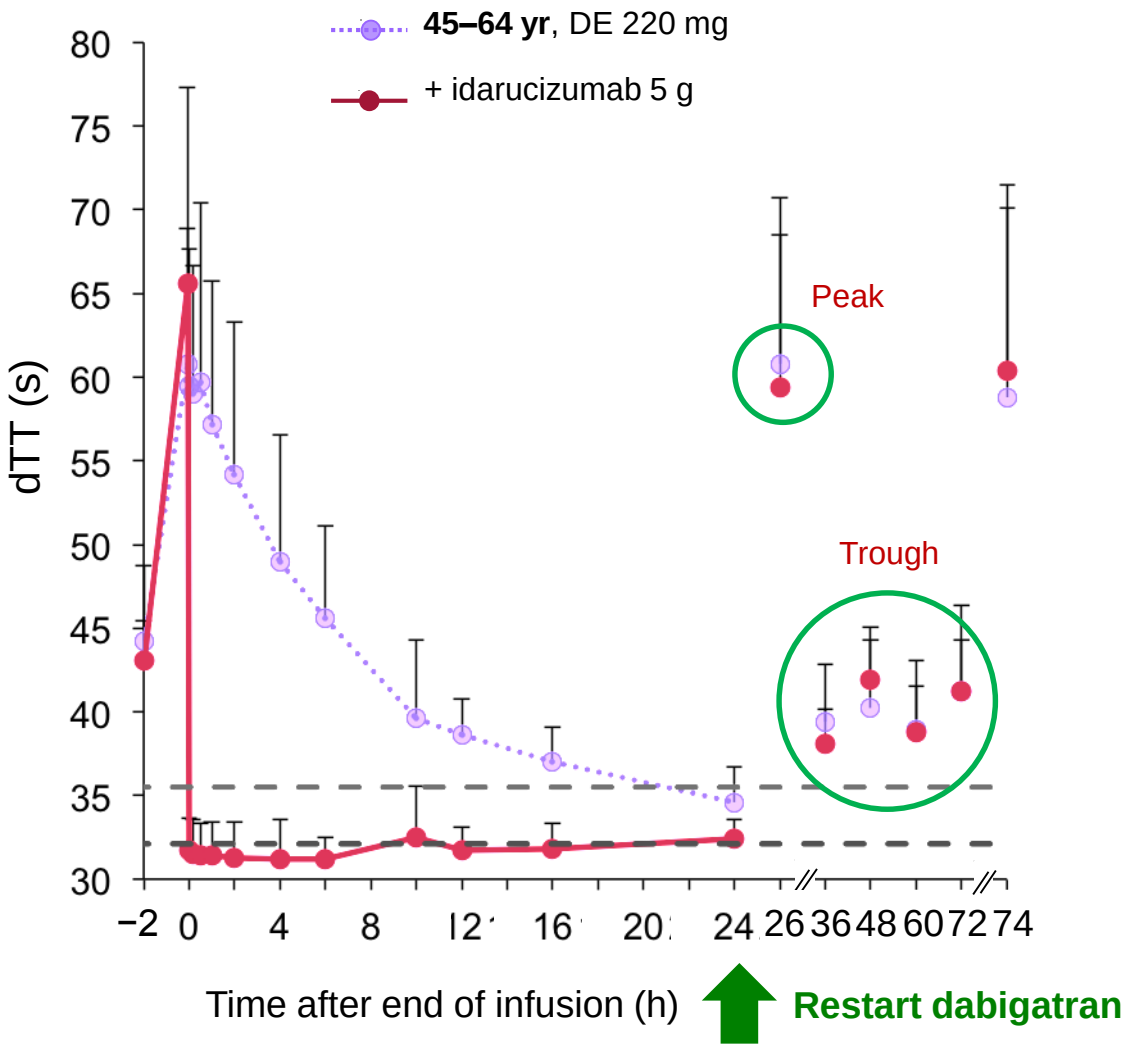



Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

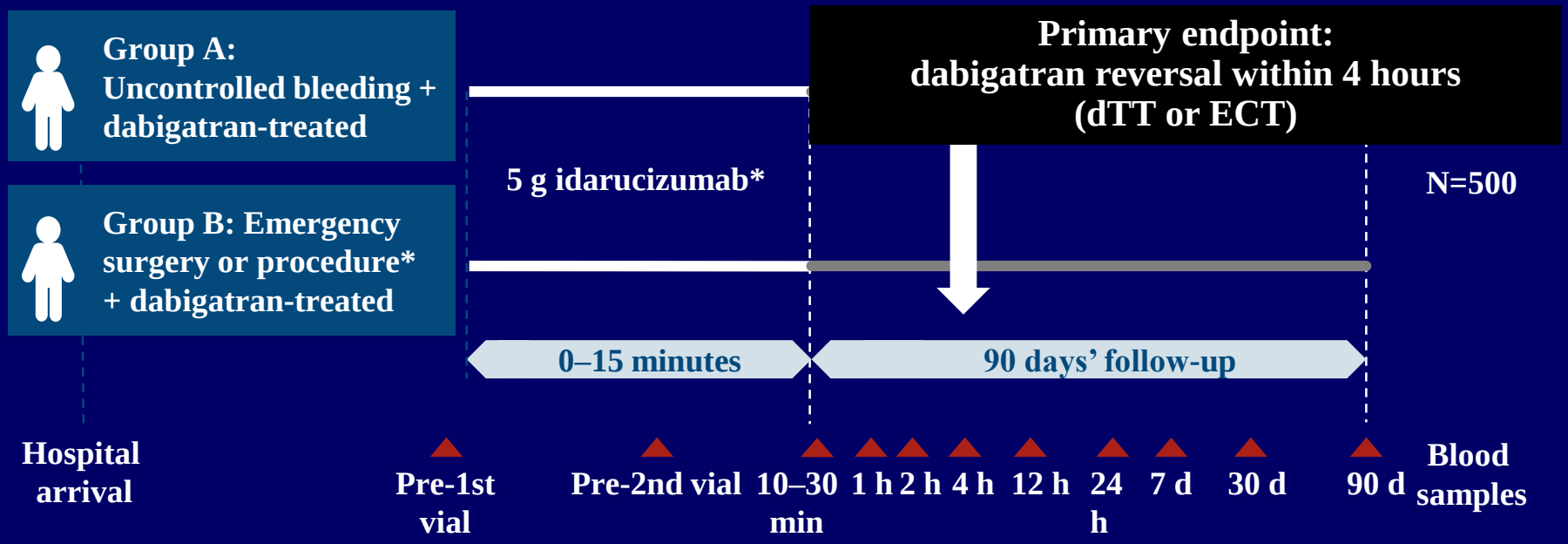
24 hours later, dabigatran treatment was restarted

Dabigatran-mediated anticoagulation was restored

N=6–8/group, mean ± SE

Glund et al. Blood 2014

# RE-VERSE AD: multicentre, ongoing, single-arm, open-label Phase III study




* Two 50-mL bolus infusions, no more than 15 minutes apart

*Other than bleeding. dTT, diluted thrombin time; ECT, ecarin clotting time

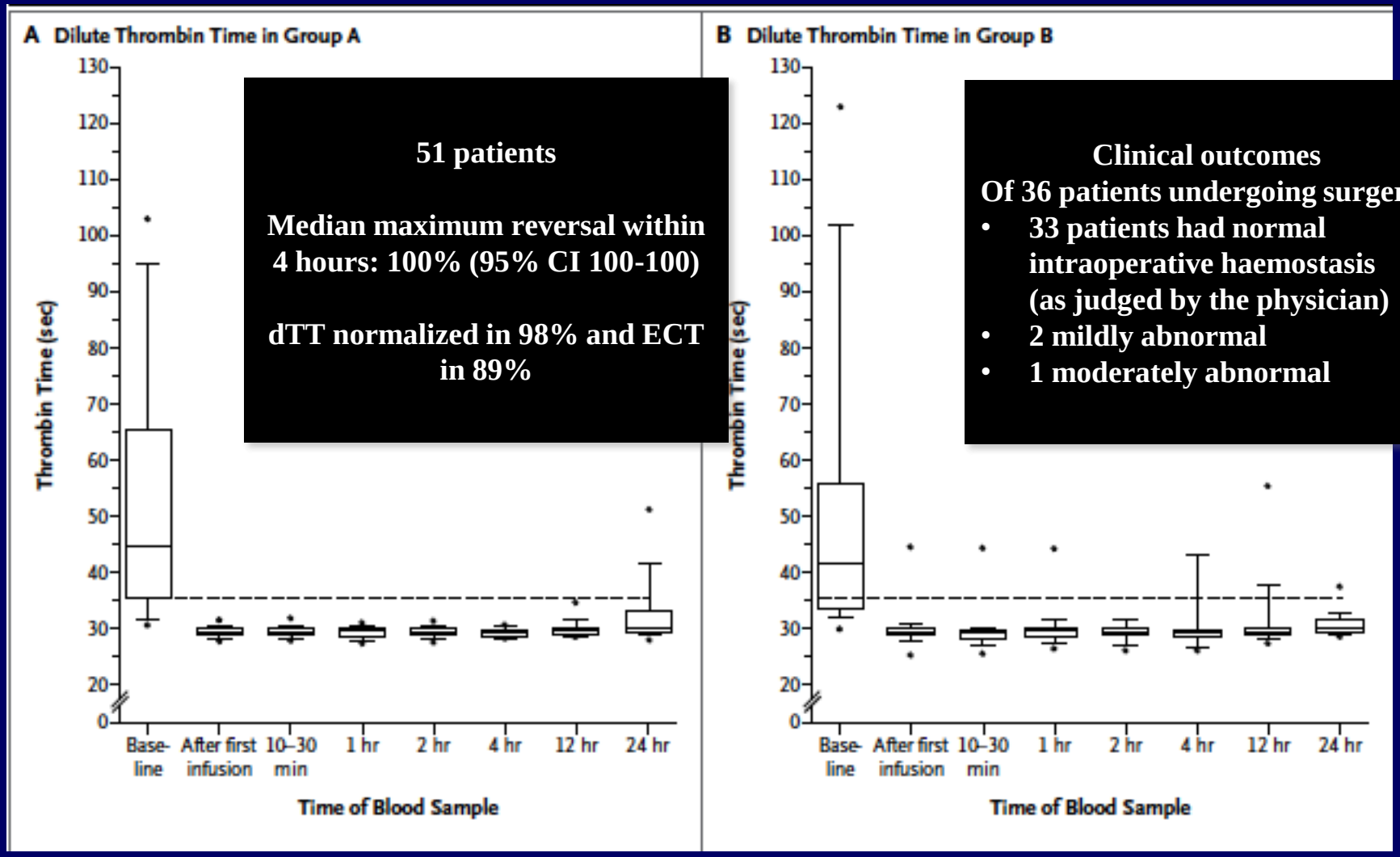
Pollack et al. N Engl J Med 2015

# RE-VERSE AD: multicentre, ongoing, single-arm, open-label Phase III study

| Characteristic | Group A | Group B |
|---|---|---|
| Number | 51 | 39 |
| Age (median) | 77 | 76 |
| CrCl <30 ml/min (n,%) | 5 (10) | 7 (18) |
| CrCl 30-50 ml/min (n,%) | 14 (27) | 6 (15) |
| Dabigatran 150 mg bid | 14 (27) | 15 (38) |
| Elevated dTT at baseline | 40 (78) | 28 (72) |
| Intracranial bleeding | 18 (35) | - |
| Trauma-related | 9 (18) | - |
| Gastrointestinal | 20 (39) | - |

**Pollack CV et al NEJM 2015**

# REVERSE-AD: dTT prima e dopo la somministrazione di idarucizumab



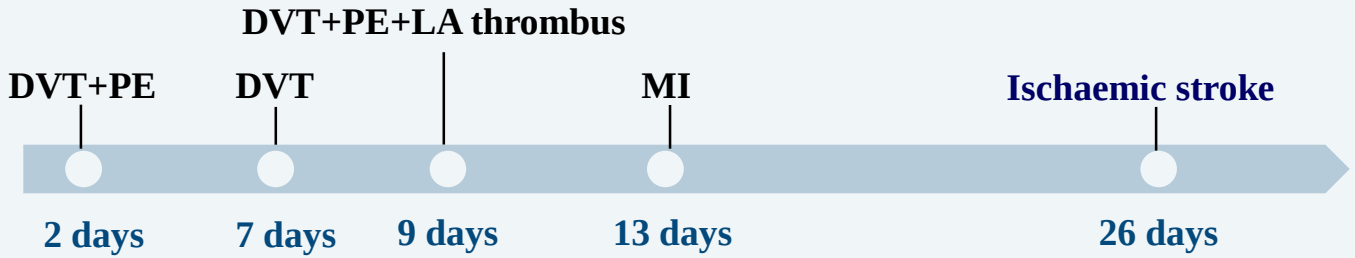

Pollack CV et al NEJM 2015

# RE-VERSE AD: Safety

## 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 et al; NEJM 2016

# Andexanet alfa

**Fattore Xa umano ricombinante**

- **Agisce come “esca” per gli inibitori del fattore Xa legandoli con affinità simile a quella del fattore Xa nativo.**

**Nature Medicine 2013,19(4): 446-51**

# Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors

*Nature Medicine* (2013),19(4): 446-51

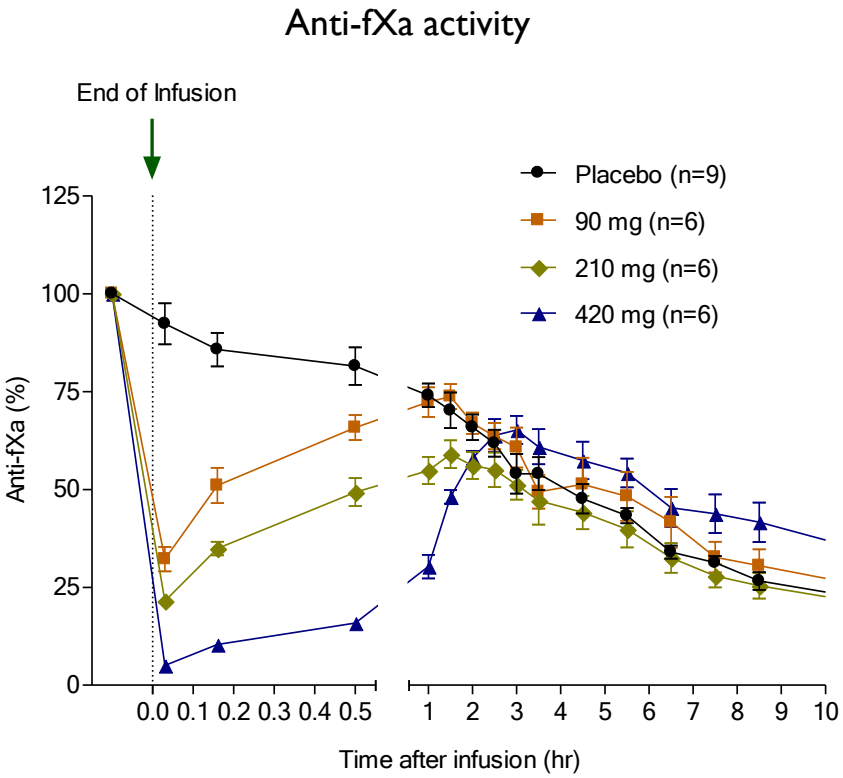
**Recombinant engineered version of human factor Xa produced in CHO cells**

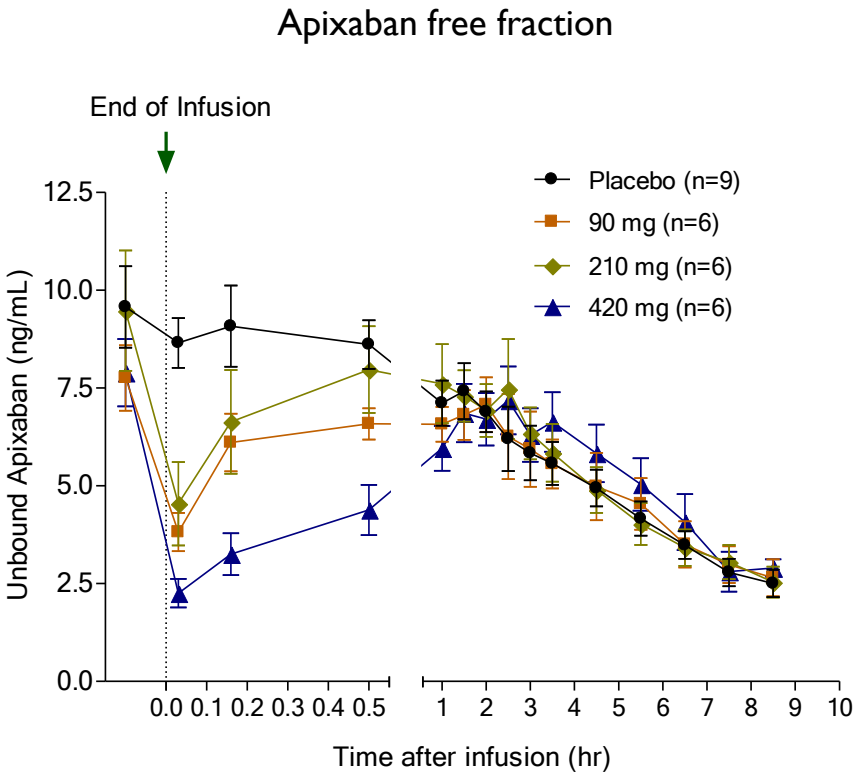
- **Acts as a fXa decoy and retains high affinity for all direct fXa inhibitors**
- **Change of Serine to Alanine to eliminate catalytic activity and prevent prothrombin cleavage**
- **GLA domain removed to prevent anticoagulant effect**


**Factor Xa** **PRT064445**

- **No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)**
- **No significant antibody signal found in development program to date**

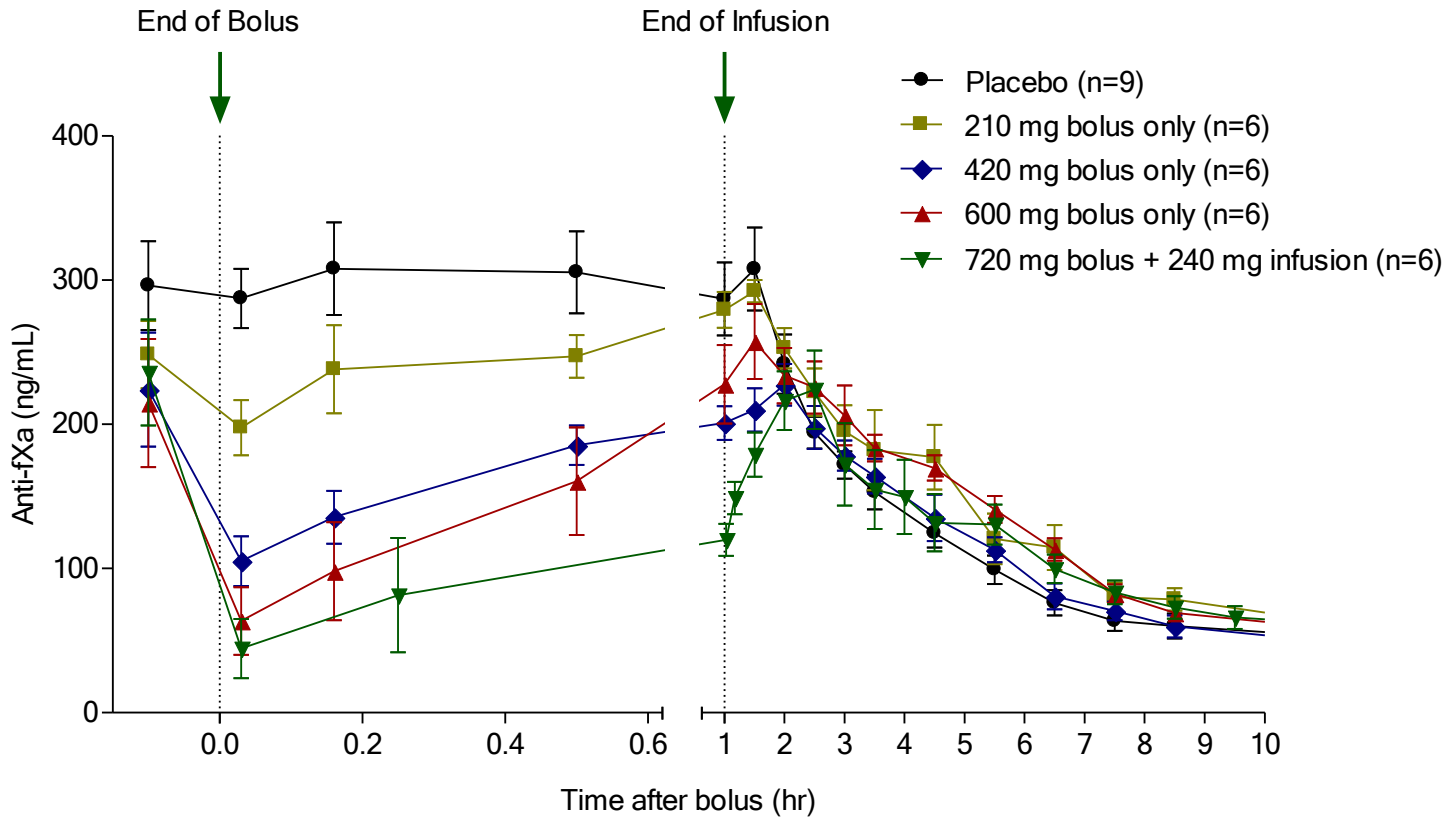
# Dose-Dependent Reversal of Apixaban-induced Anti-fXa Activity Correlates with Reduction in Apixaban Plasma Free Fraction




Mean ± SEM

# Rivaroxaban – Reversal of anti-Xa effect



ORIGINAL ARTICLE

# Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

| | |
|---|---|
| **ANDEXANET DOSES** | **Bolus followed by 2-hour infusion:**<br>**Apixaban or rivaroxaban >7 h: 400 mg b + 480 mg infusion**<br>**Enoxa/edoxaban or riva <7 h: 800 mg b + 960 mg infusion** |
| **PRIMARY ENDPOINT** | **Percent change in the anti–factor Xa activity** |
| **COPRIMARY ENDPOINT** | **The rate of excellent or good hemostatic efficacy 12 hours after the andexanet infusion.** |

**Connolly et al; NEJM 2016**

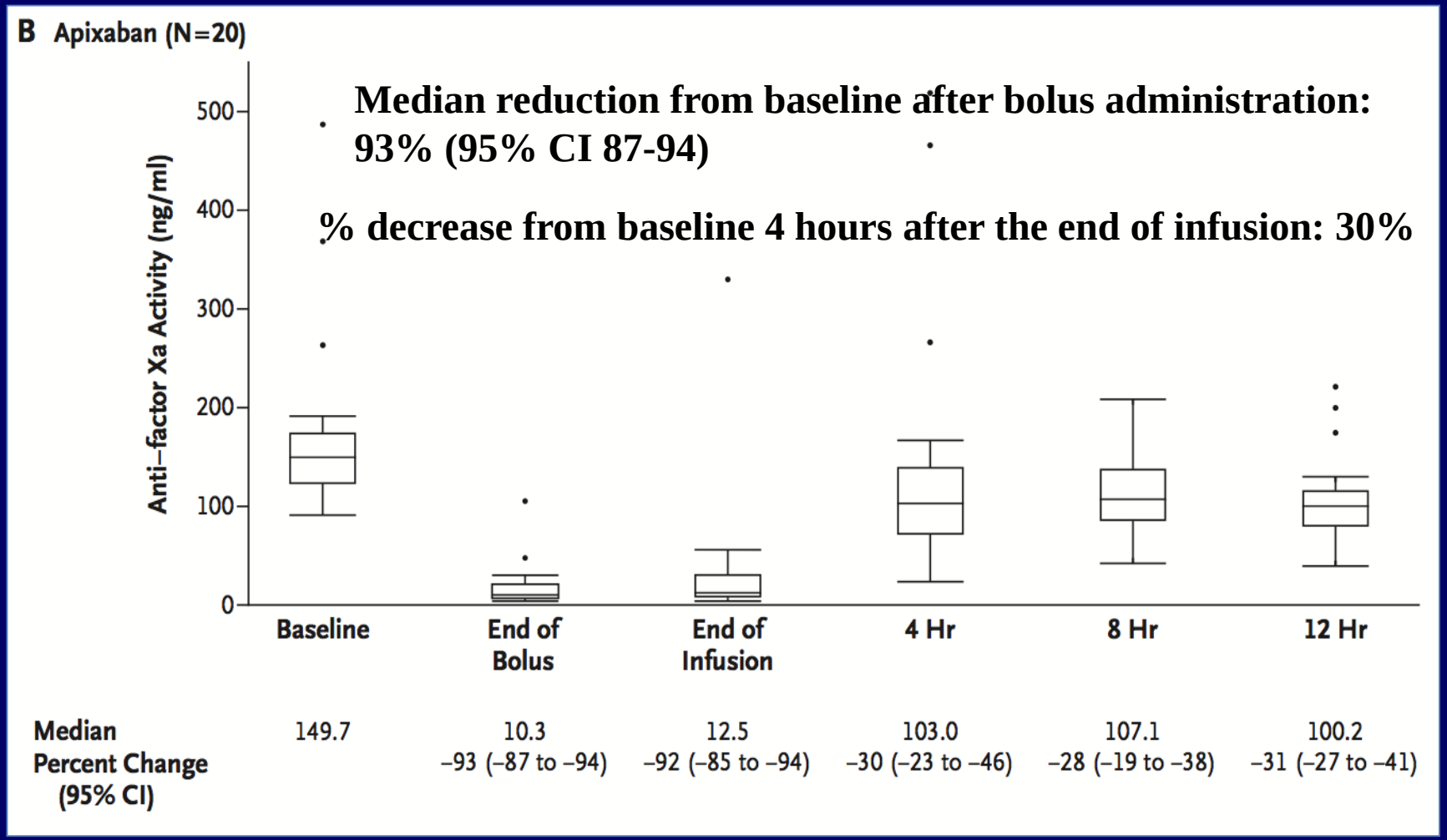
ORIGINAL ARTICLE

# Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

| Characteristic | Safety population |
|---|---|
| Number | 67 |
| Age (median) | 77 |
| CrCl <30 ml/min (n,%) | 6 (9) |
| CrCl 30-60 ml/min (n,%) | 31 (46) |
| Rivaroxaban | 32 |
| Apixaban | 31 |
| Enoxaparin | 4 |
| Intracranial bleeding | 28 (42) |
| Gastrointestinal | 33 (49) |

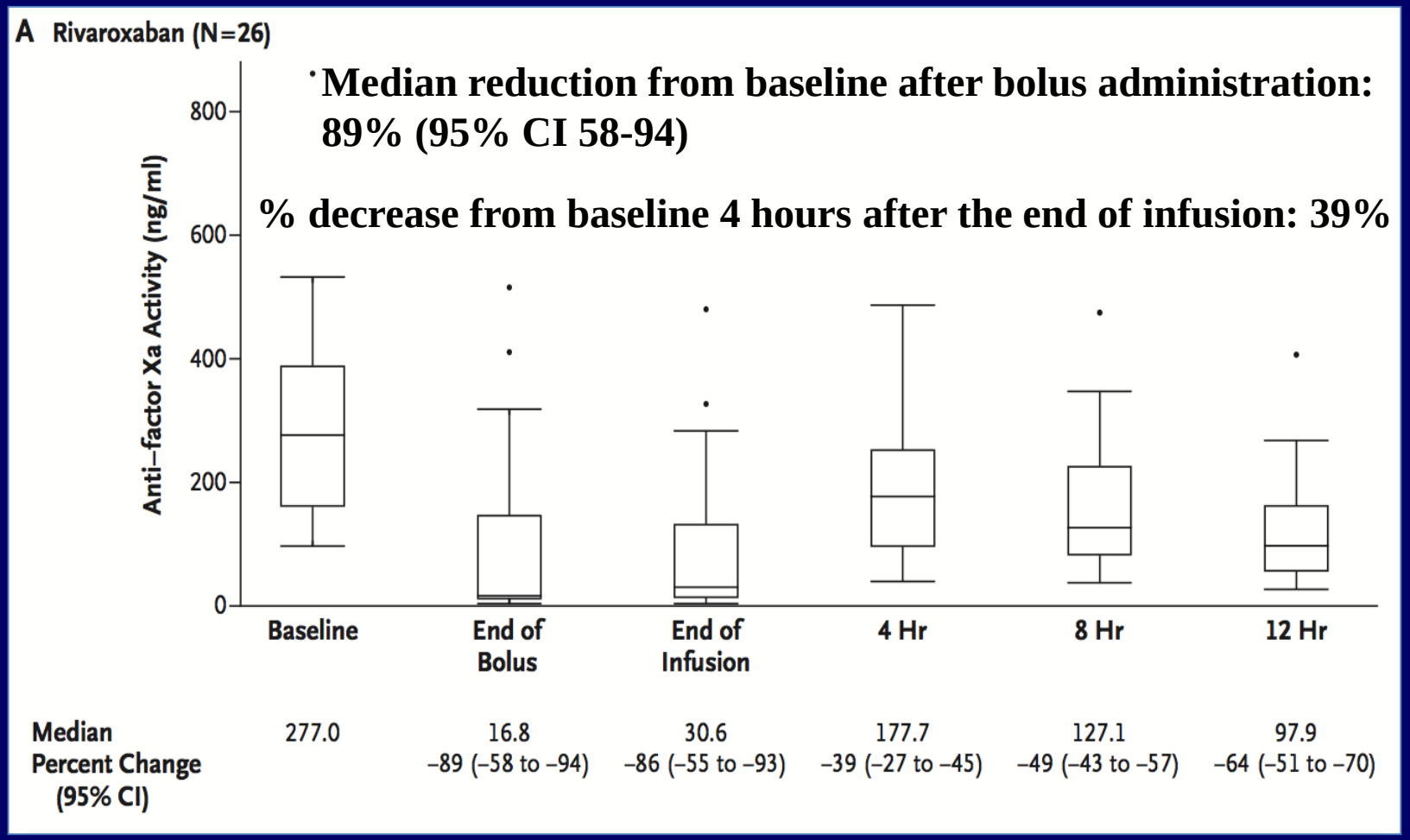
**Connolly et al; NEJM 2016**

# Anti–Factor Xa Activity: apixaban




Connolly et al; NEJM 2016

# Anti–Factor Xa Activity: rivaroxaban




Connolly et al; NEJM 2016

# ANNEXA-4: secondary outcomes

- **Clinical haemostasis 12 hours after infusion adjudicated as excellent or good: 79% (95% CI 64-89)**
- **Thrombotic events at 30 days: 12 (18%)**
- **Mortality: 10 (15%), 6 CV, 4 non CV**

**Connolly et al; NEJM 2016**

*Journal of Thrombosis and Haemostasis*, **14**: 623–627 DOI: 10.1111/jth.13227

RECOMMENDATIONS AND GUIDELINES

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

J. H. LEVY,* W. AGENO,† N. C. CHAN,‡ M. CROWTHER,§ P. VERHAMME¶ and J. I. WEITZ,§ FOR THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION

| Clinical situation | Definite need for a reversal agent |
|---|---|
| Life-threatening bleeding | YES |
| Bleeding in a closed space or critical organ | YES |
| Persistent major bleeding despite local haemostatic measures or delayed DOAC clearance or DOAC overdose | YES |
| Need for urgent intervention with high risk of bleeding and that cannot be delayed | YES |
| Emergency surgery or intervention and high risk for procedural bleeding | YES |
| Urgent surgery or intervention and acute renal failure | POSSIBLE |

**Levy J et al J Thromb Haemost 2016**

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- **Delaying antidote administration until coagulation test results are available may be detrimental in DOAC-treated patients with life-threatening bleeding or in those requiring emergency surgery for life-threatening conditions (e.g. ruptured aortic aneurysm)**

**Levy J et al J Thromb Haemost 2016**

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- **With the exception of these patients, the decision can be guided by:**
  - **Time since the last intake of the DOAC**
  - **Determination of the creatinine clearance**
  - **Results of laboratory tests (also useful to assess the extent of reversal)**

**Levy J et al J Thromb Haemost 2016**

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- **A drug concentration >50 ng/mL$^{-1}$ is likely sufficiently high in a patient with serious bleeding to warrant antidote administration**

- **A drug concentration >30 ng/mL$^{-1}$ should mandate antidote administration in patients requiring urgent procedures associated with a high risk of bleeding**

**Levy J et al J Thromb Haemost 2016**

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- **Andexanet and idarucizumab require refrigeration**
- **Idarucizumab is supplied in two glass vials (2.5 g), no mixing required**
- **These agents should be stored in the pharmacy or blood bank, but storage in a locked refrigerator in the ED may provide more rapid access**

**Levy J et al J Thromb Haemost 2016**

# Managing reversal of direct oral anticoagulants in emergency situations

## Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

**A broad range of medical professional societies, patient groups, healthcare providers invited to nominate physicians and lay members with interest and expertise in anticoagulation and reversal agents**

- **Meeting funded by Boehringer Ingelheim**

**Thrombosis and Haemostasis 116.5/2016**

# Who should control access to reversal agents?

- Is there a hospital bleeding management protocol?
- Has the reversal agent been incorporated in the hospital formulary?
- Redraft policy and flow charts on the management of bleeding related to DOACs
- Discuss where the reversal agent should be stored
- All appropriate hospital staff members should be made aware of the availability of the reversal agent
- Maintain a log on the use of the reversal agent and consider joining a local, national or international registry of post-marketing experience with the reversal agent

# Idarucizumab: indicazioni da scheda tecnica

- **Interventi chirurgici d'emergenza/procedure urgenti**
- **Sanguinamento potenzialmente fatale o non controllato**

- **Dose raccomandata 5 g (2x2,5 g/50 mL) per via endovenosa, tramite due infusioni consecutive di 5-10 minuti ciascuna o tramite iniezione in bolo**

# Idarucizumab: indicazioni da scheda tecnica

- La somministrazione di una seconda dose di 5 g può essere presa in considerazione:
  - In presenza di recidiva di sanguinamento clinicamente rilevante con tempi di coagulazione prolungati*
  - Se la potenziale ricomparsa del sanguinamento dovesse essere pericolosa per la vita e se si dovessero osservare tempi di coagulazione prolungati*
  - Se i pazienti dovessero avere necessità di un secondo intervento chirurgico di emergenza/una seconda procedura d'urgenza e presentare tempi di coagulazione prolungati*

* aPTT, dTT, ECT

# Idarucizumab: indicazioni da scheda tecnica

- Non sono necessari aggiustamenti della dose per:
  - Pazienti con compromissione renale
  - Pazienti con compromissione epatica
  - Anziani

  - Sicurezza ed efficacia nella popolazione pediatrica non sono stabilite