Antidotes for the direct oral anticoagulants: what news?

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Disclosures for Walter Ageno

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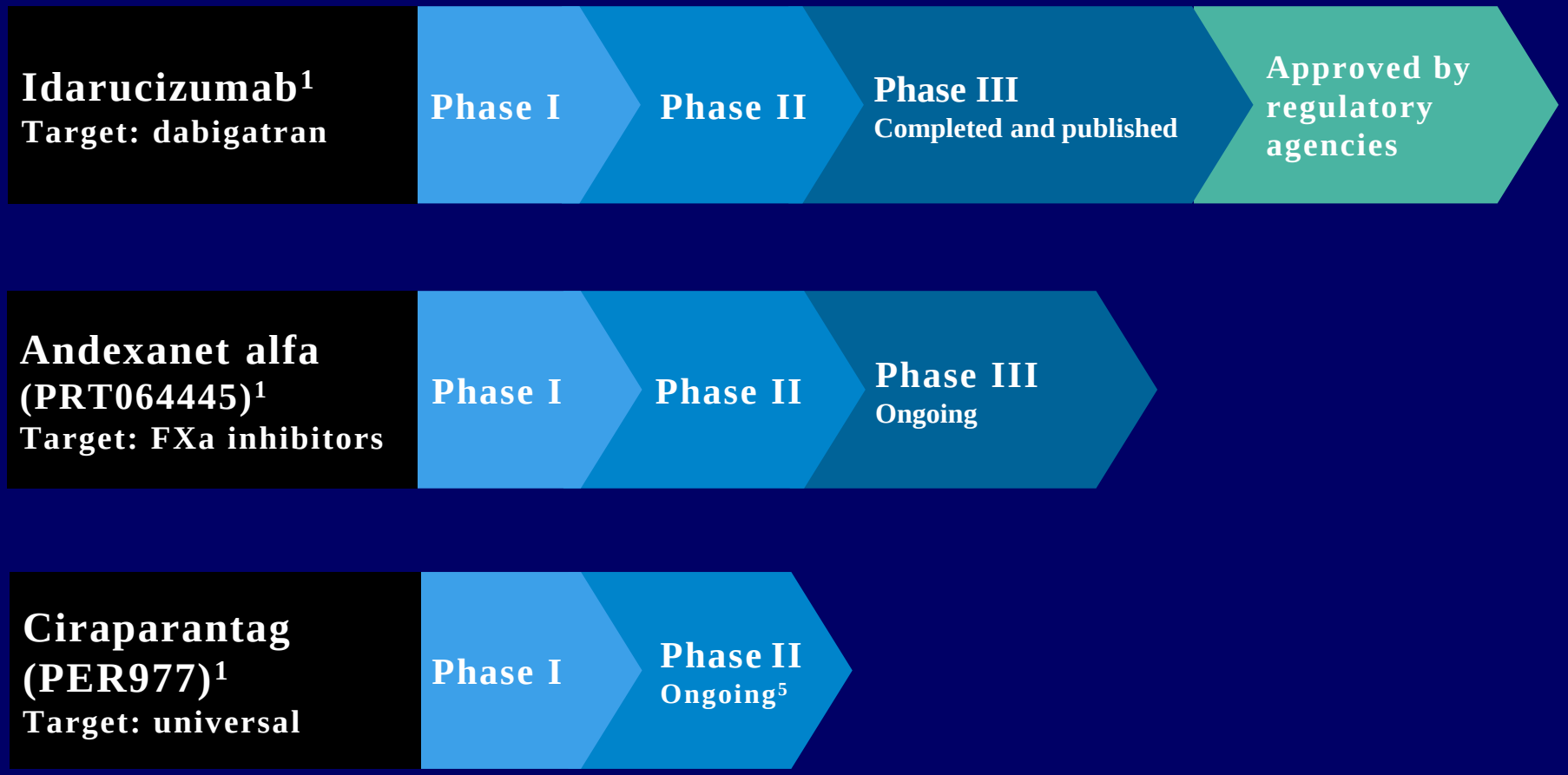
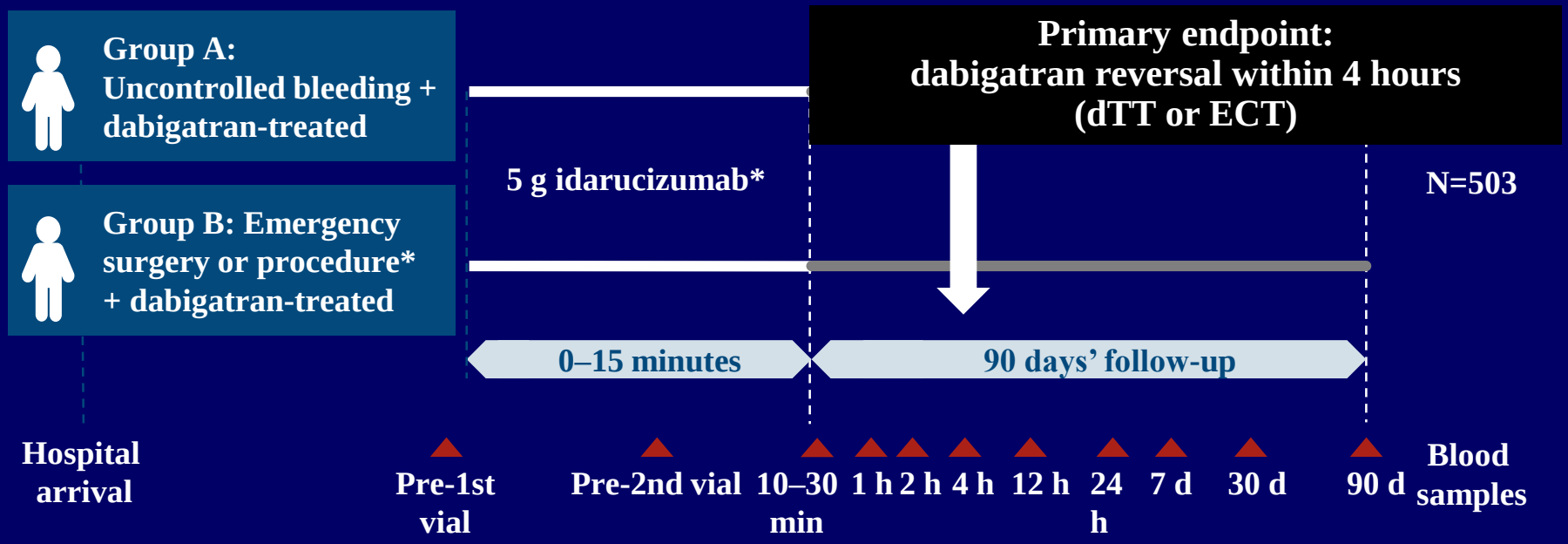
DOAC reversal agents in development



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

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

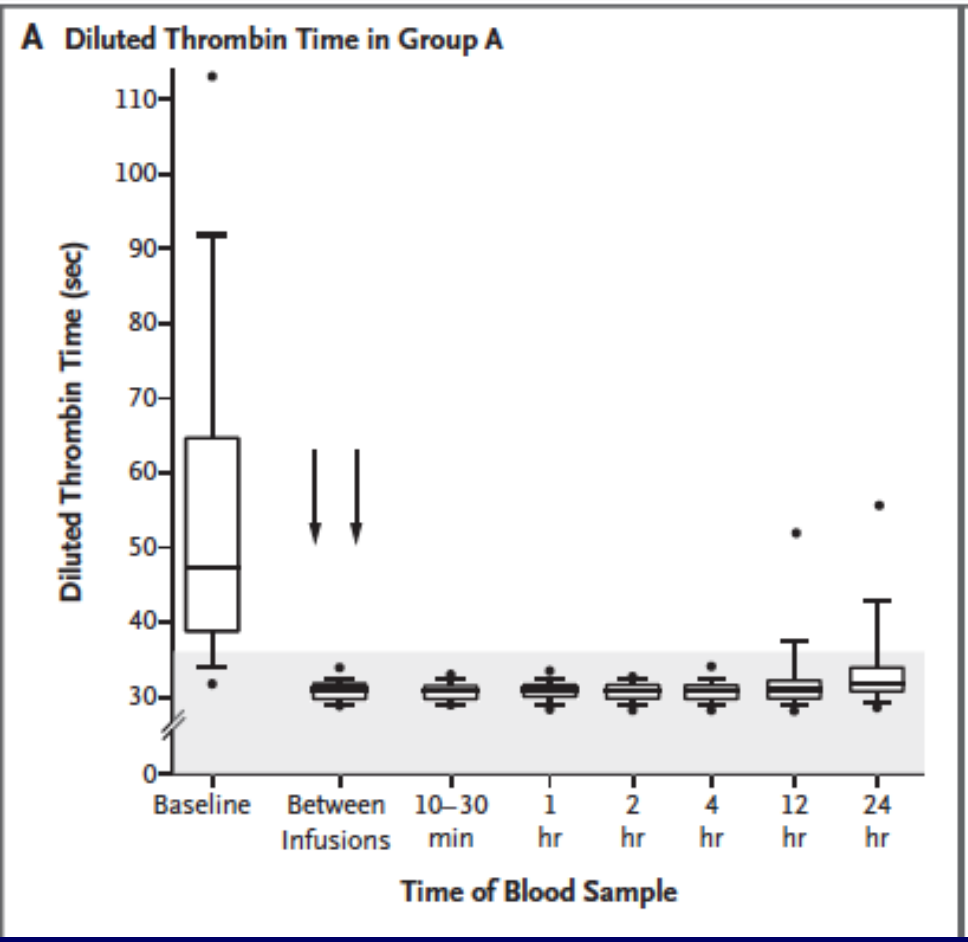
Pollack et al. N Engl J Med 2017

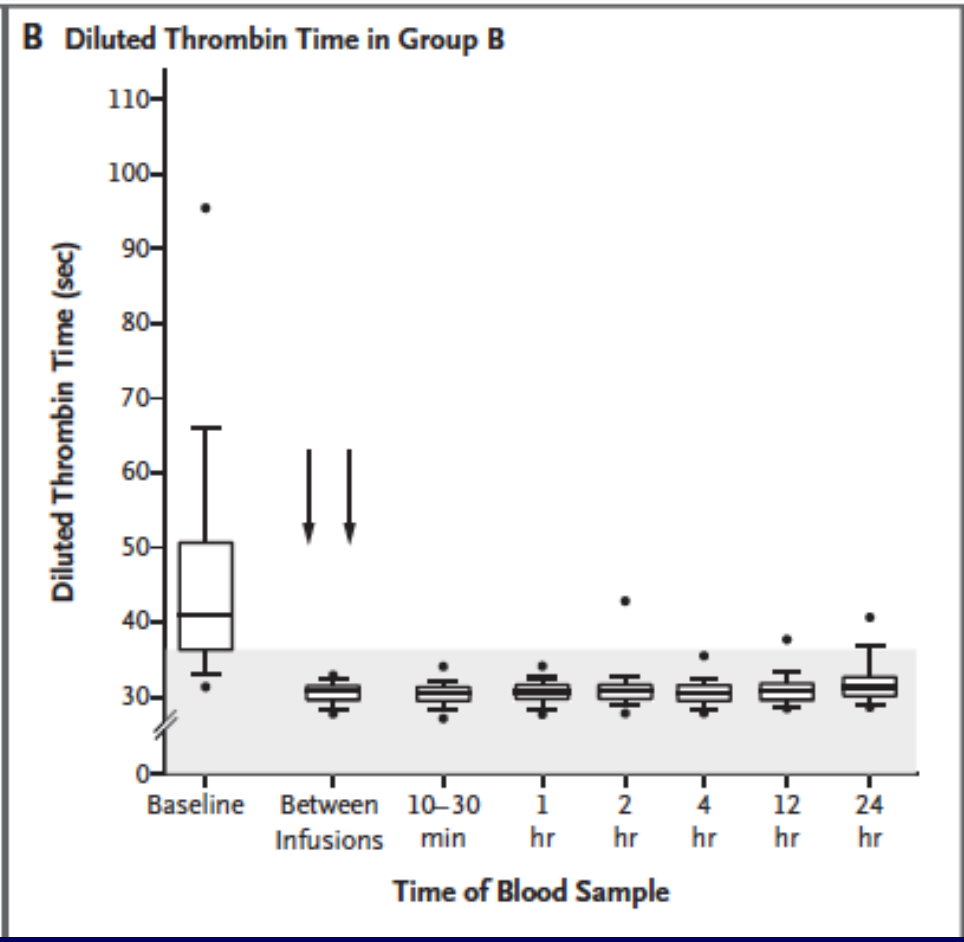
RE-VERSE AD: multicentre, single-arm, open-label Phase III study

Characteristic	Group A	Group B
Number	301	202
Age (median)	79	77
CrCl <30 ml/min (n,%)	53 (17.6)	38 (18.8)
CrCl 30<50 ml/min (n,%)	86 (28.6)	41 (20.3)
Dabigatran 150 mg bid	94 (31.2)	57 (28.2)
Elevated dTT at baseline	244 (81.1)	152 (75.2)
Time since last dose hrs	14.6	18.0
Intracranial bleeding	98 (25.9)	-
Trauma-related	78 (18)	-
Gastrointestinal	137 (45.5)	-

Pollack CV et al NEJM 2017

REVERSE-AD: dTT before and after the administration of idarucizumab





Pollack CV et al NEJM 2017

RE-VERSE AD: Safety

- 3 cases of hypersensitivity observed (rash, vomiting and loss of consciousness, hypotension reported as anaphylactic reaction)

- 24 thrombotic events (4.8%) within 30 days
  - 14 in group A
  - 10 in group B
- 34 thrombotic events (6.8%) within 90 days
  - 19 in group A
  - 15 in group B

- Deaths within 5 days: 19 (6.3%) in group A and 16 (7.9%) in group B
- 30-day mortality rate: 13.5% in group A and 12.6% in group B

Pollack et al; NEJM 2017

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

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

Post-marketing data?

Case reports and case series published on patients treated with idarucizumab

280 citations after first NEJM paper 2015

47 case reports or case series (last access April 12th 2018): 109 cases

- **43 major bleeding events**
- **41 patients with acute ischemic stroke prior to thrombolytic treatment**
- **4 undergoing emergent cardiac surgery**
- **12 undergoing other surgical/invasive procedures**
- **2 overdoses (1 was a child)**

Case reports and case series published on patients treated with idarucizumab

2 cases of CANCER patients with major bleeding (1 ICH and 1 hemopericardium) associated to excessively high dabigatran levels (due to drug-drug interactions?) successfully managed with idarucizumab

9 of the reported cases were defined as unsuccessful

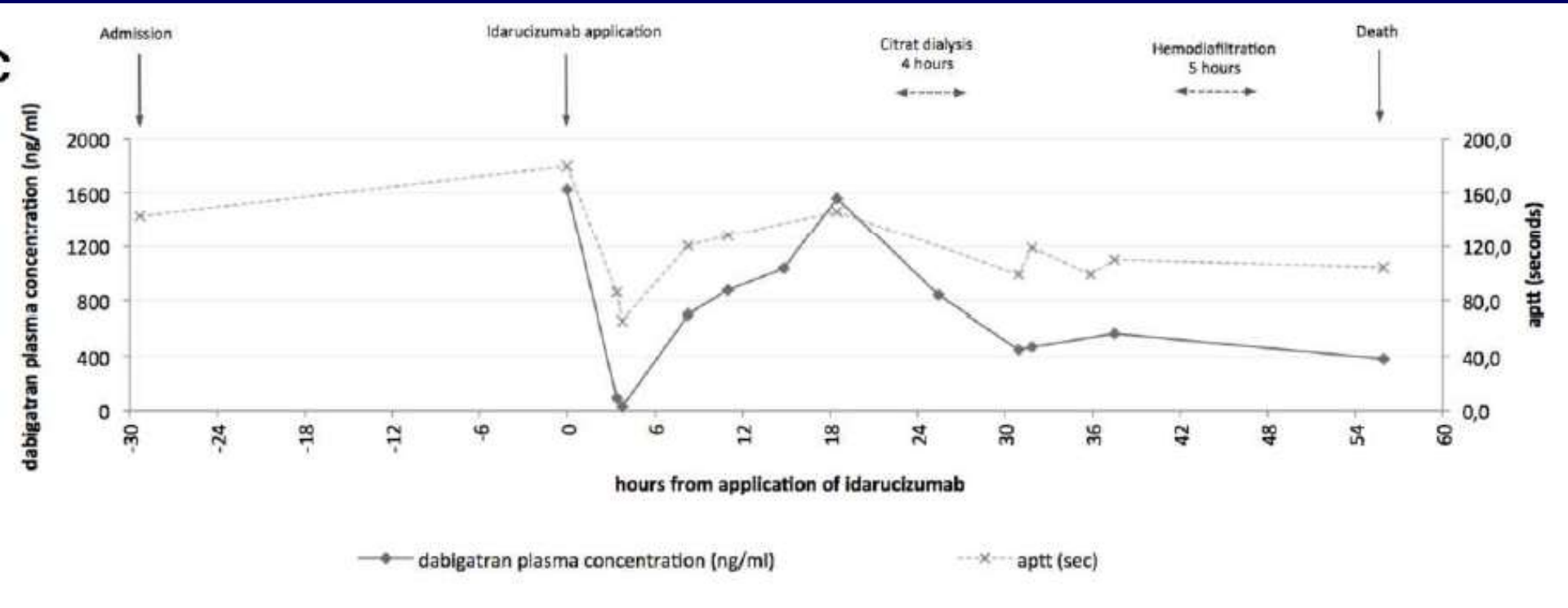
1 case of anaphylaxis

Recommended dose of idarucizumab may not always be sufficient for sustained reversal of dabigatran

Variable	On admission	Before idarucizumab	Reference ranges
Hemoglobin	13.8 g/dL	9.8 g/dL	13.5-18.0
Platelets	289 G/l	22 G/l	150-350
INR	1.6	3.1	1.0
aPTT	143 seconds	>180 seconds	27-41
Dabigatran	n.a.	1630 ng/mL	<200 (through)
Fibrinogen	574 mg/dL	380 mg/dL	200-400
C-reactive protein	4.58 mg/dL	19.78 mg/dL	<0.5
Creatinine	4.13 mg/dL	3.63 mg/dL	0.70-1.20
GFR-MDRD	14.10	16.37	>90

Simon et al JTH 2017

Recommended dose of idarucizumab may not always be sufficient for sustained reversal of dabigatran



Simon et al JTH 2017

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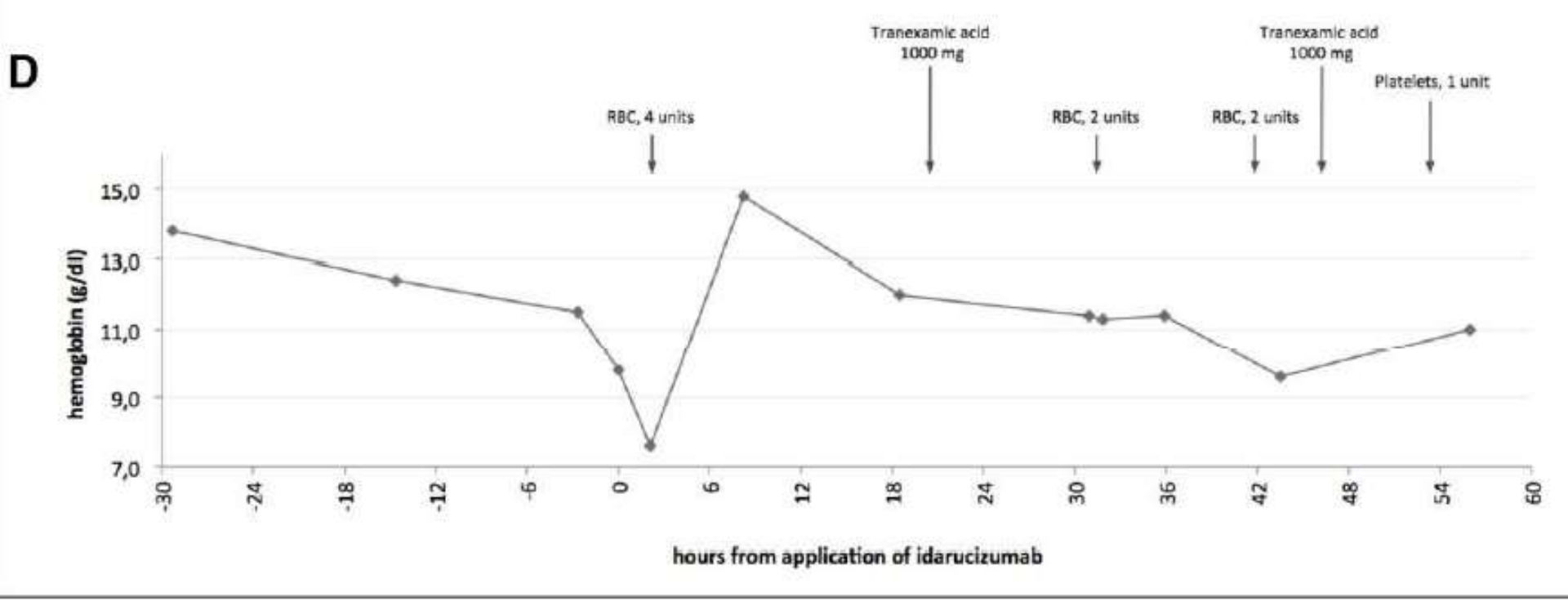

Simon et al JTH 2017

Andexanet alfa?

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

ANDEXANET DOSES	**Bolus followed by 2-hour infusion:** **Apixaban or rivaroxaban >7 h: 400 mg b + 480 mg infusion** **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

FDA delays BLA review for Andexanet Alfa as Anticoagulation Reversal Agent (Thursday Feb 1st)

The FDA extended by 90 days its review of the biologics license application (BLA) for andexanet alfa for the second time, from Feb 3 to May 4, 2018.

The drug's manufacturer recently submitted additional data requested by the FDA for the ongoing ANNEXA-4 study, and the agency moved the action date to evaluate the new information

Andexanet alfa in Factor Xa Inhibitor-Associated Acute Major Bleeding

- 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., Michele D. Bronson, Ph.D., Patrick Yue, M.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., Andrew Demchuk, M.D., Shelly Goodman, B.S.N., Janet Leeds, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, M.Sc., Juliet Nakamya, Ph.D., Balakumar Swaminathan, M.Sc., Mark Crowther, M.D.
- on behalf of the ANNEXA-4 investigators

Baseline Characteristics

	Safety population (n:227)	Efficacy population* (n:137)
Age, mean	77 years	77 years
Male	52%	51%
Time from presentation to Andexanet	4.7 hrs	5.0 hrs
Creatinine clearance <30 mL/min	9%	10%
Indication for AC		
AF	78%	76%
VTE	23%	28%
AF and VTE	4%	4%

*Excludes patients with baseline anti-fXa activity <75 ng/mL, 0.25 IU/mL for enoxaparin

Connolly et al ACC 2018

Site of initial bleeding

	Safety population (n:227)	Efficacy population (n:137)
Gastrointestinal	27%	31%
Intracranial	61%	57%
Intracerebral	52%	54%
Subdural	32%	30%
Subarachnoid	16%	16%
Other bleeding site	13%	12%

Connolly et al ACC 2018

Percent change in anti-factor Xa activity

	End of bolus	End of infusion	4 Hr	8 Hr	12 Hr
Rivaroxaban N: 75	**-88%**	**-87%**	**-42%**	**-49%**	**-60%**
Apixaban N: 105	**-91%**	**-91%**	**-36%**	**-30%**	**-35%**
Enoxaparin N: 16	**-75%**	**-73%**	**-44%**	**-44%**	**-52%**

Connolly et al ACC 2018

Clinical hemostatic efficacy at 12 hours

Number of major bleeds adjudicated	Number of patients with excellent or good hemostasis	Percent of patients with excellent or good hemostasis	Binomial exact 95% confidence interval
132	109	83%	75%-89%

Connolly et al ACC 2018

Safety assessment

Anticoagulation re-started in 57% of patients by 30 days

Thrombosis within 3 days of andexanet: 2.6%

Thrombosis within 30 days of andexanet: 11%

(only 9 of 24 patients restarted anticoagulation)

Deaths by 30 days: 12%

Deaths after ICH 12%

Connolly et al ACC 2018

Conclusions

- **Reversal agents for the DOACs may reduce concerns regarding the use of DOACs by facilitating ready control of bleeding in emergency situations**

- **Certain situations (e. g. life-threatening or persistent bleeding, bleeding into a closed space, and urgent interventions) warrant prompt use of reversal agents; other situations should be decided on a case-by-case basis**

Conclusions 2

- **Rapid reversal of anticoagulation per se will never solve bleeding until the source of bleeding has been appropriately managed and treated**

- **Entry of these agents into clinical practice requires consideration of access and operationalization that must be clearly elucidated on an institutional level to prevent over- and misuse of reversal agents**