New Options for Anticoagulation Reversal:

A Practical Approach

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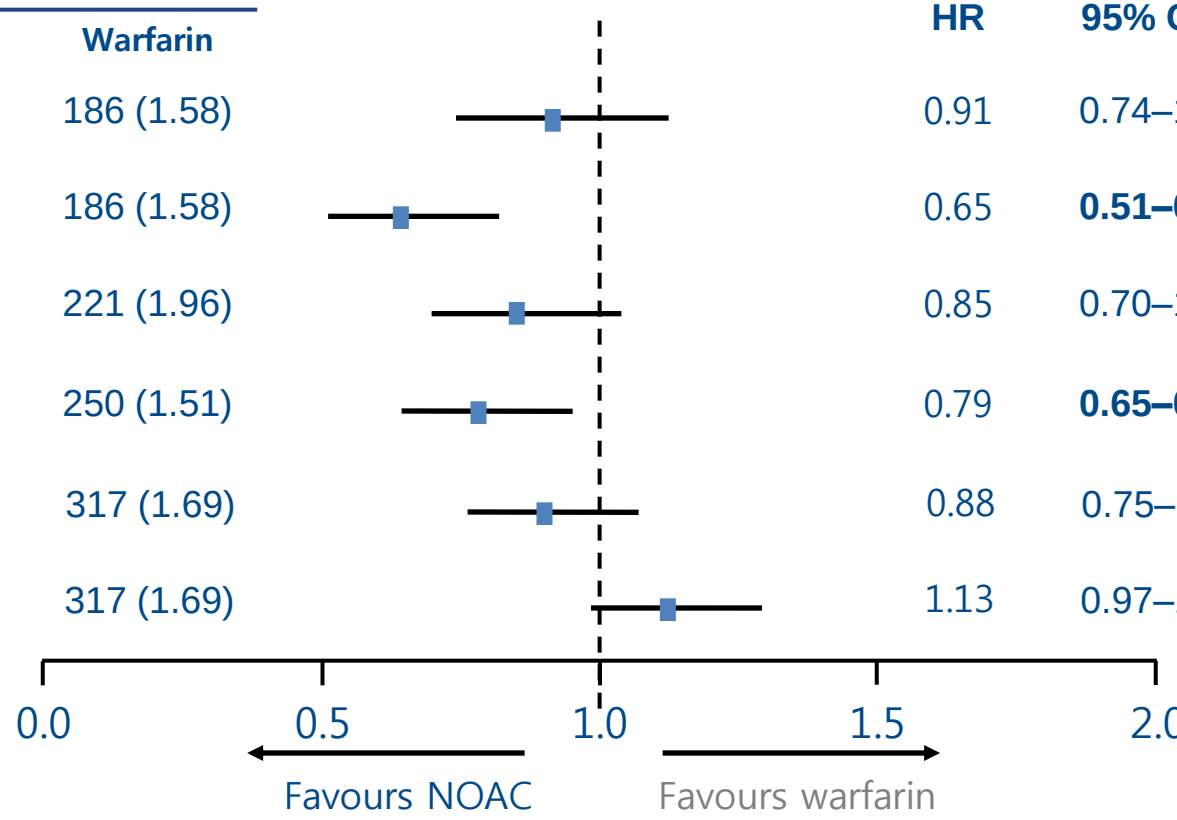
4 NOACs – Prevention of TE

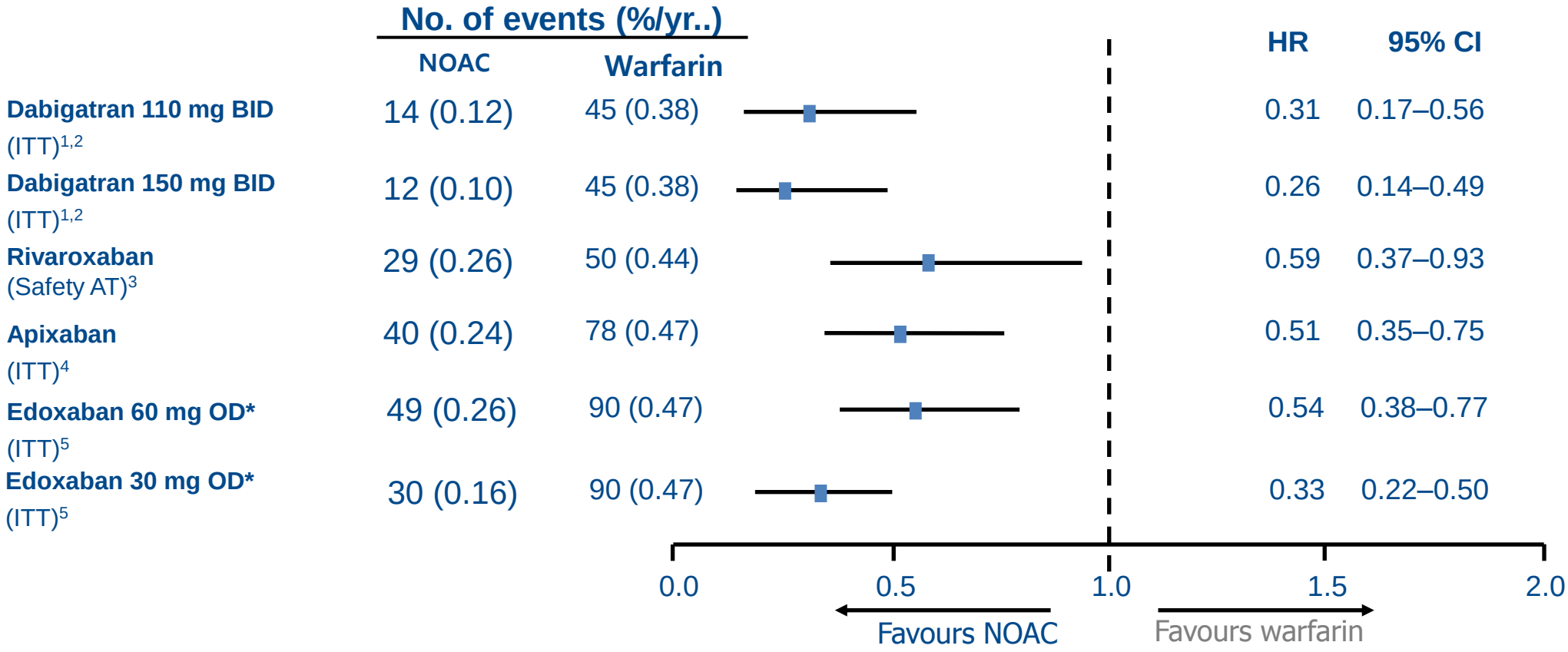
	No. of events (%/yr..)		HR	95% CI
	NOAC	Warfarin		
Dabigatran 110 mg BID (ITT)[1,2]	171 (1.44)	186 (1.58)	0.91	0.74–1.12
Dabigatran 150 mg BID (ITT)[1,2]	122 (1.01)	186 (1.58)	0.65	**0.51–0.81**
Rivaroxaban (Safety AT)	184 (1.65)	221 (1.96)	0.85	0.70–1.03
Apixaban (ITT)[4]	199 (1.19)	250 (1.51)	0.79	**0.65–0.95**
Edoxaban 60 mg OD* (ITT)[5]	281 (1.49)	317 (1.69)	0.88	0.75–1.03
Edoxaban 30 mg OD* (ITT)[5]	360 (1.91)	317 (1.69)	1.13	0.97–1.31



- Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5
- *Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weig ht <60kg, or concomitant verapamil, quinidine or dronedarone
- **AT = as treated**; BID = twice daily; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; **2.** Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; **4.** Granger C et al. N Engl J Med 2011;365:981–92;
5. Giugliano RP et al. N Engl J Med 2013; doi:10.1056/NEJMoa1310907

4 NOACs – Prevention of hemorrhagic stroke



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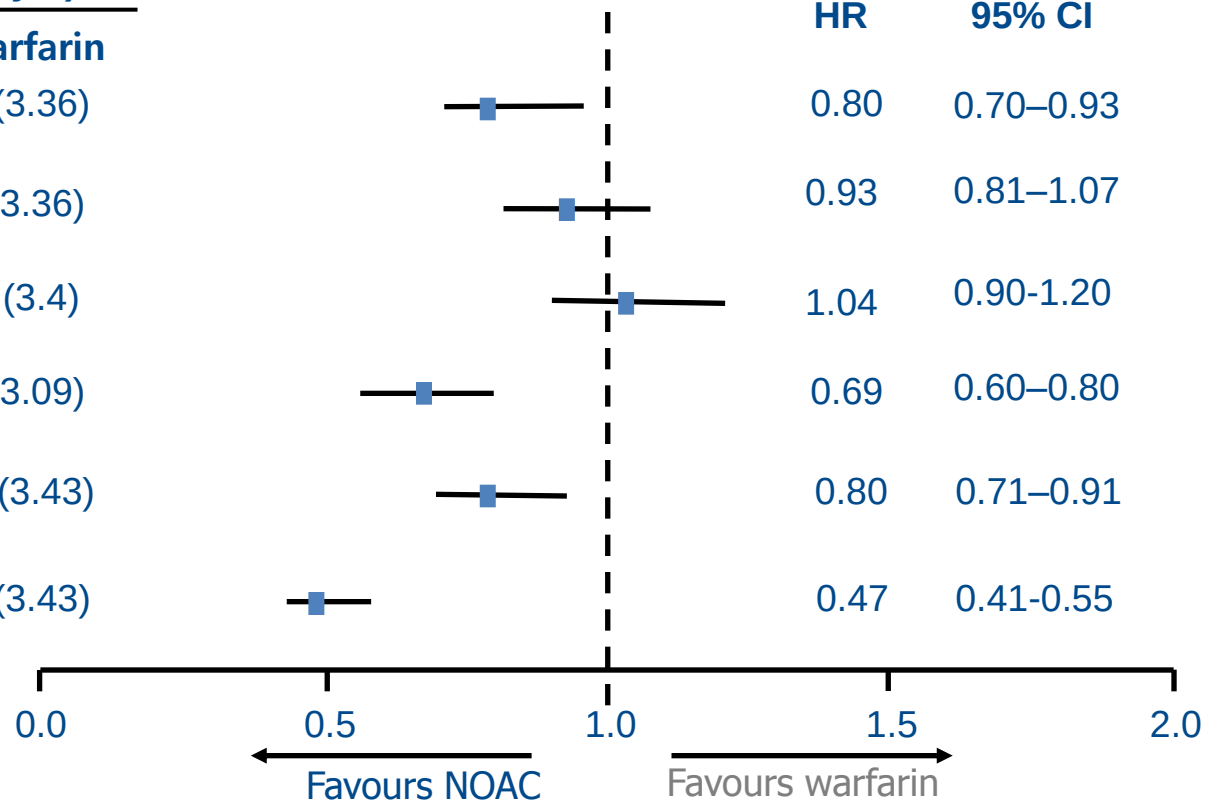
4 NOACs – Major bleedings

	No. of events (%/yr..)		HR	95% CI
	NOAC	Warfarin		
Dabigatran 110 mg BID (ITT)[1,2]	342 (2.71)	421 (3.36)	0.80	0.70–0.93
Dabigatran 150 mg BID (ITT)[1,2]	399 (3.11)	421 (3.36)	0.93	0.81–1.07
Rivaroxaban (Safety AT)[3]	395 (3.6)	386 (3.4)	1.04	0.90-1.20
Apixaban (ITT)[4]	327 (2.13)	462 (3.09)	0.69	0.60–0.80
Edoxaban 60 mg OD* (ITT)[5]	418 (2.75)	524 (3.43)	0.80	0.71–0.91
Edoxaban 30 mg OD* (ITT)[5]	254 (1.61)	524 (3.43)	0.47	0.41-0.55



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Limitations of NOACs

- Less clinical experience with NOACs

  - vs. 60 years of warfarin experience

- Measurement issues

  - Not widely available in clinical settings

    ECT, DTT - Dabigatran

    Anti-Factor Xa – Rivaroxaban or Apixaban

- No established reversal agents

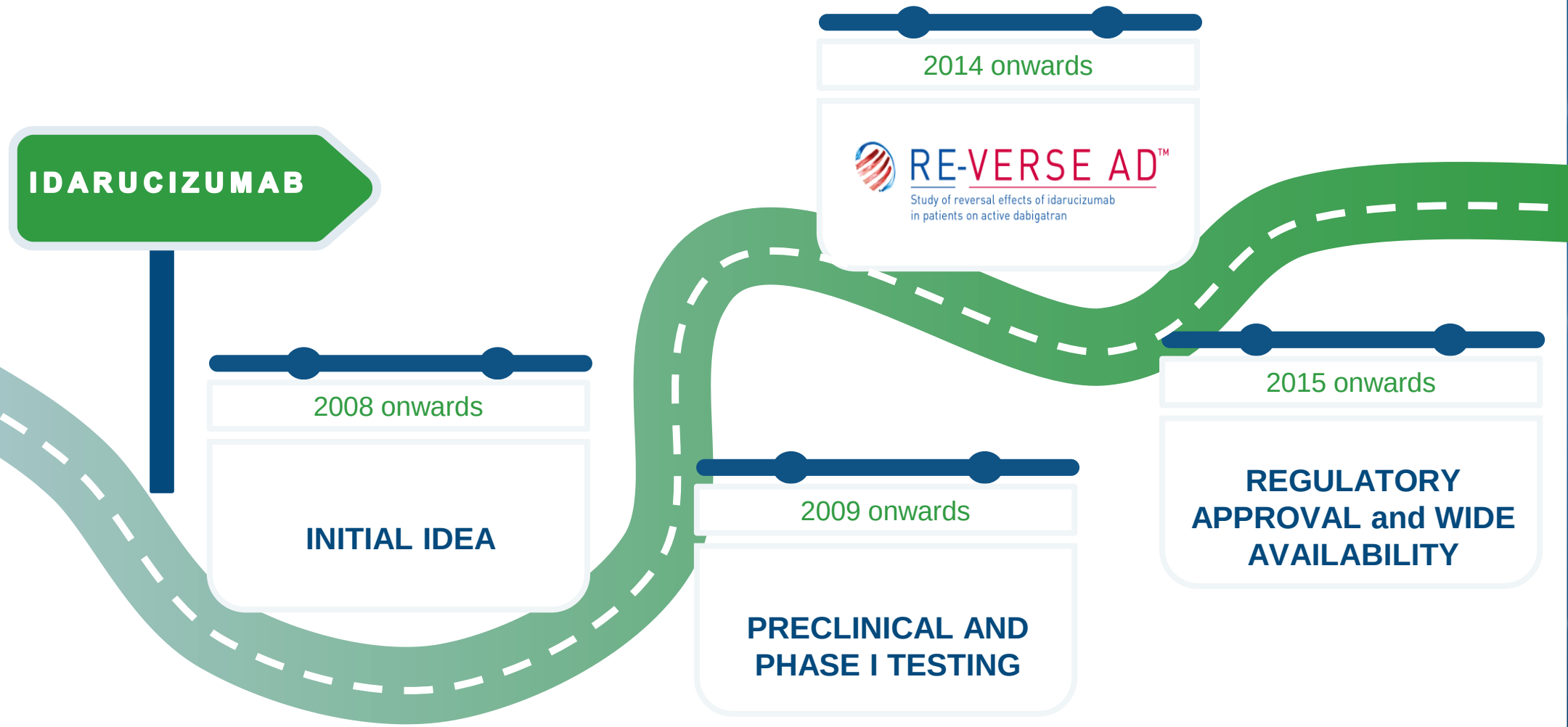
  - Lack of guidance in emergency surgery or major bleeding due to NOAC use

Candidates for reversal agents

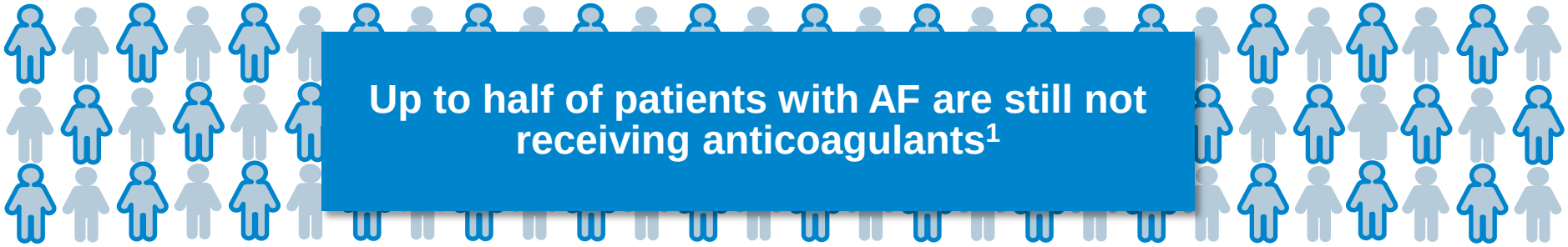
- Patients presenting with bleeding
  - Life-threating bleeding (eg, intracranial)
  - Critical organ or closed-space bleeding (eg, pericardial, retroperitoneal)
  - Ongoing bleeding despite measures to control bleeding

- Patients at high risk bleeding
  - Requiring emergent/urgent procedure
  - Expected long delay in spontaneous restoration of normal hemostasis (eg, over-anticoagulation, renal failure)

Key milestones



Reversal agents for NOACs may encourage appropriate stroke prevention in patients with AF



Cardiac Safety Research Consortium

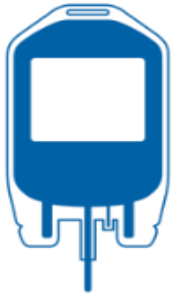
U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

'The availability of specific reversal agents for the NOACs would improve the confidence of clinicians and patients in these new agents and encourage an increase in appropriate stroke preventive therapy for patients with NVAF'[1]

1. Sarich TC et al. Am Heart J 2015

Rapid reversal of the anticoagulant effects of NOACs may be required in certain emergency situations

Emergency surgery

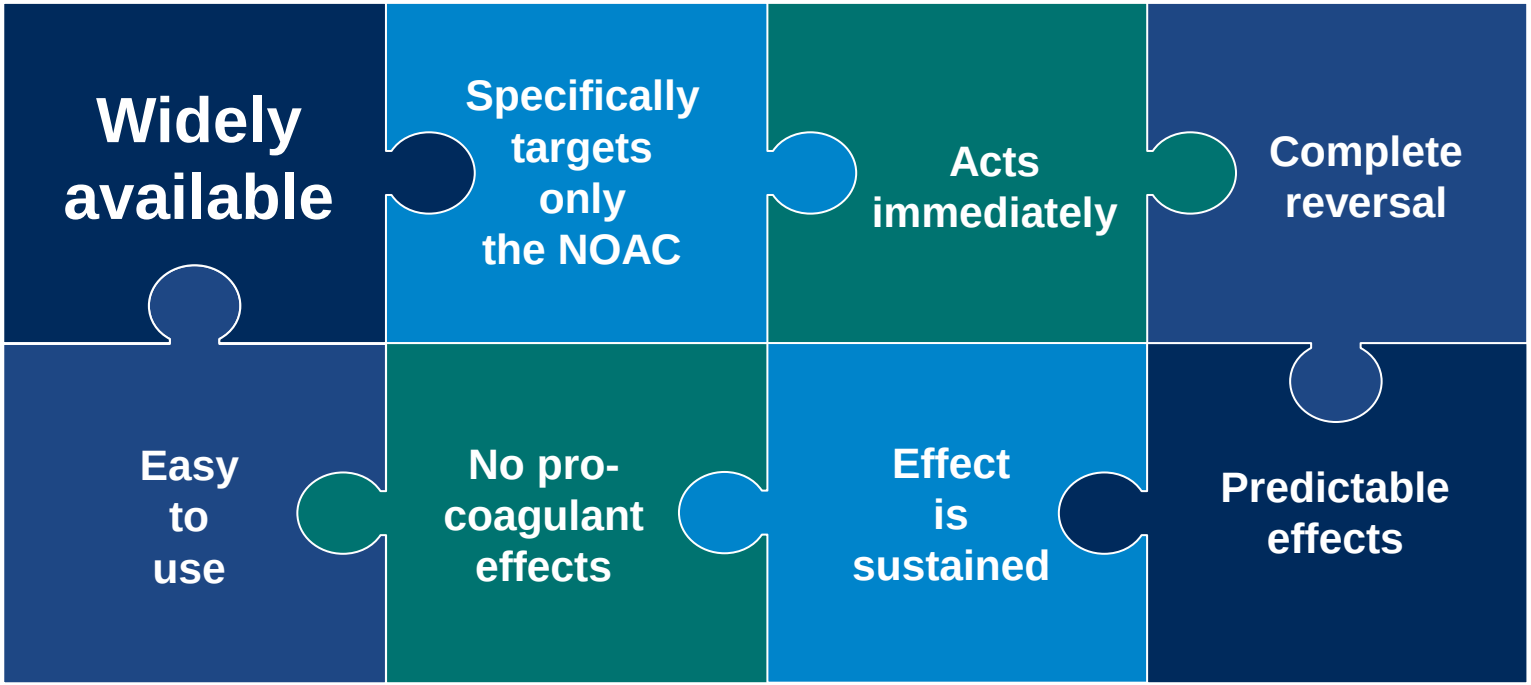


Uncontrolled bleeding

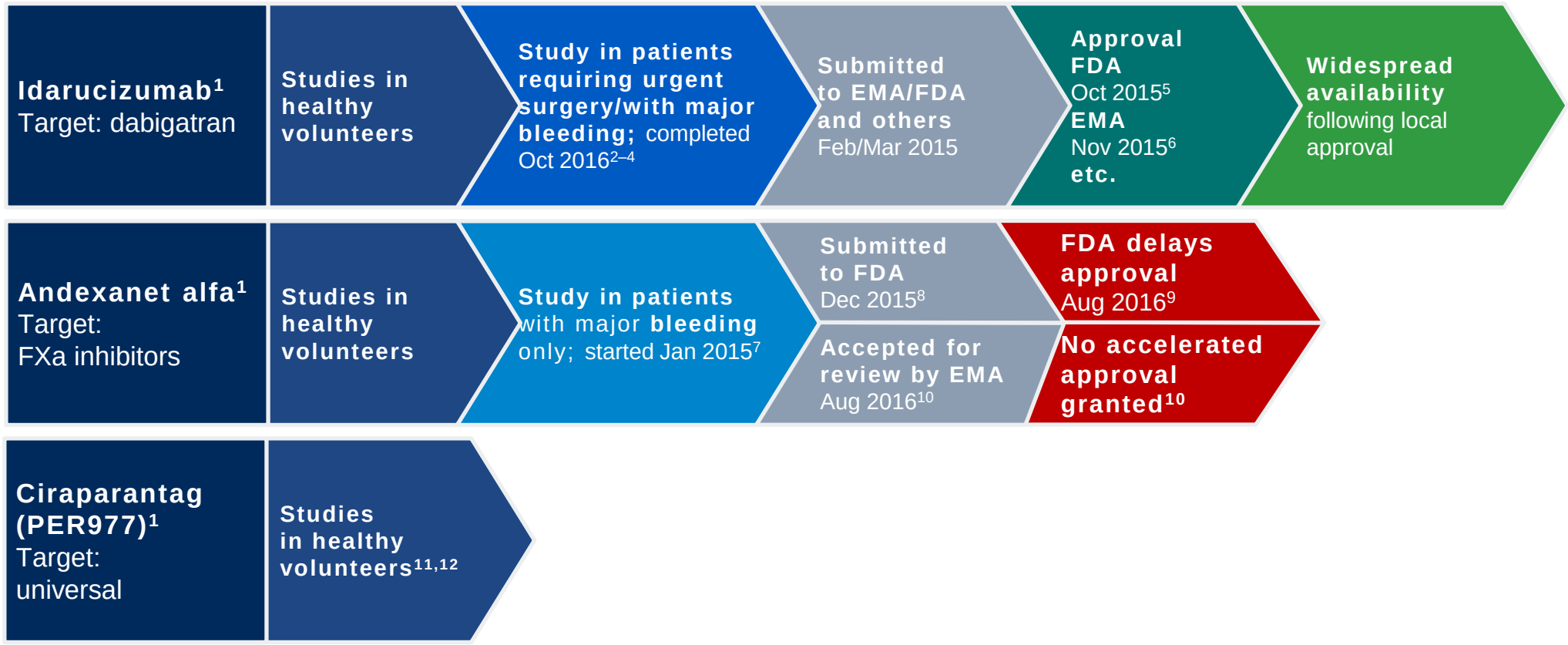
A specific reversal agent could take the NOAC out of the equation in these situations

While a specific reversal agent could remove the anticoagulant effect, other measures (e.g. surgery, fluid replacement) would still be required to correct the underlying cause of the bleed and its consequences

What are the characteristics of an ideal reversal agent?

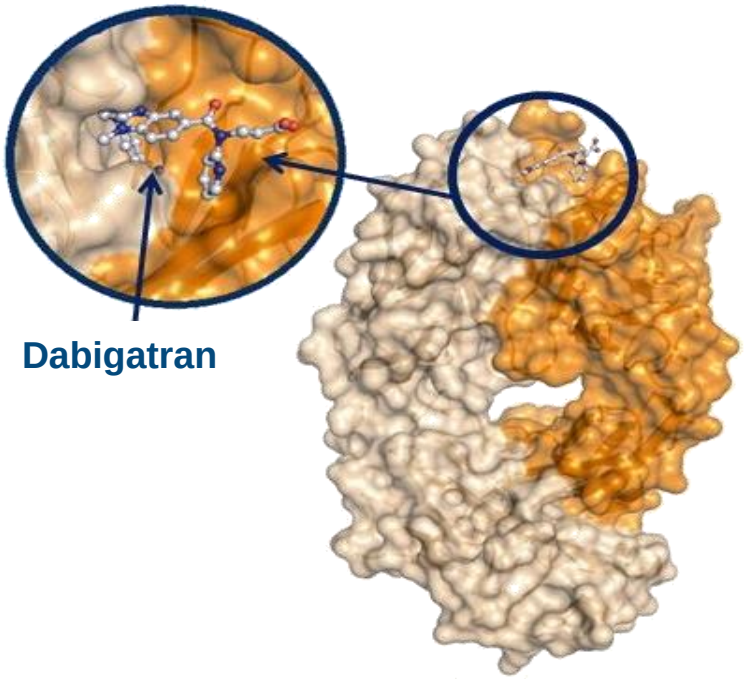


Idarucizumab is the only approved and widely available NOAC reversal agent



1. Greinacher A et al. Thromb Haemost 2015; 2. Pollack C et al. N Engl J Med 2015; 3. Pollack C et al. Thromb Haemost 2015; 4. Boehringer Ingelheim, data on file; 5. US FDA 2015 press release, 16 October 2015; 6. European Commission Community Register of Medicinal Products for Human Use 2015; 7. ClinicalTrials.gov Identifier: NCT02329327; 8. Portola Pharmaceuticals press release, 18 Dec 2015; 9. Portola Pharmaceuticals press release, 17 August 2016; 10. Portola Pharmaceuticals press release, 19 August 2016; 11. Ansell JE et al. N Engl J Med 2014; 12. Ansell JE et al. Thromb Res 2016

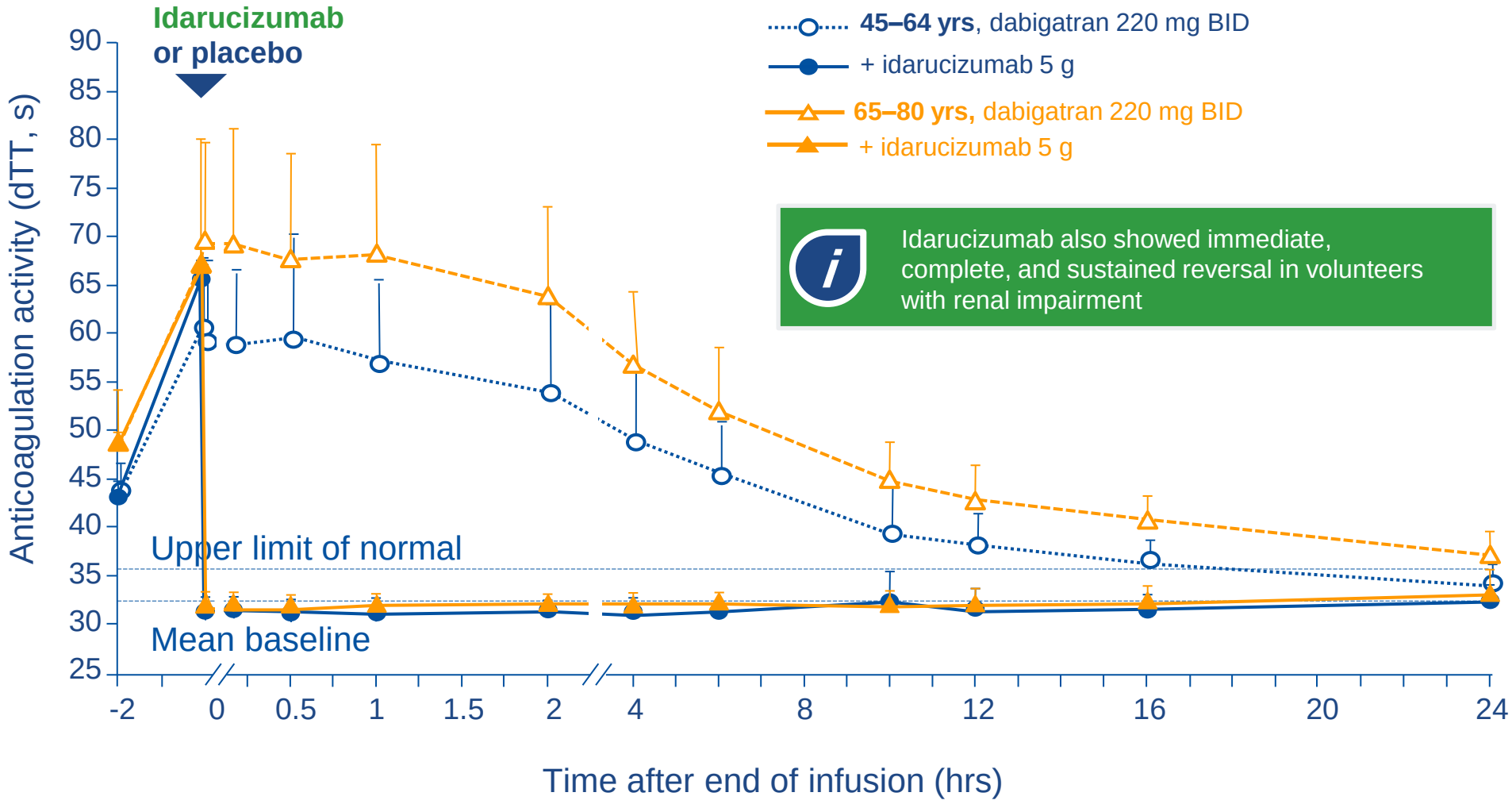
Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran



- Humanized antibody fragment (Fab)
- Binding affinity for dabigatran ~350× higher than dabigatran to thrombin, resulting in essentially irreversible binding
- Immediate onset of action
- No intrinsic procoagulant or anticoagulant activity
- Idarucizumab–dabigatran complex is eliminated in a few hours

Adapted from Schiele F et al. Blood 2013; Eikelboom J et al. Circulation 2015; Praxbind®: EU SPC, 2016; Schmohl M et al. Thromb Haemost 2016

Idarucizumab provided immediate, complete, and sustained reversal of dabigatran anticoagulation in volunteers



dTT, diluted thrombin time

Glund S et al. Clin Pharmacokinet 2016

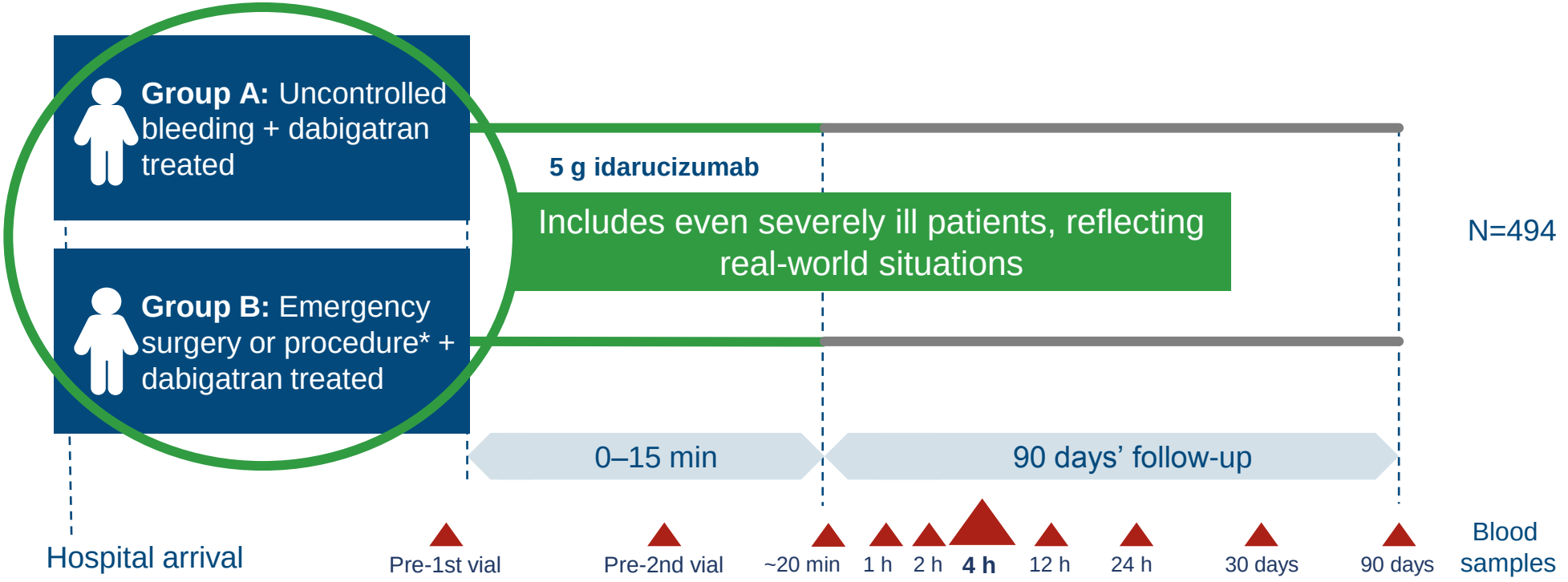
Idarucizumab was well tolerated across subject groups

- No drug-related AEs reported in total >200 volunteers
- No AEs indicative of immunogenic reactions
- AEs and local tolerability reactions similar for placebo and active treatment
- No relevant changes in any of the investigated safety parameters
- No procoagulant effects

Glund S et al. Lancet 2015; Glund S et al. Thromb Haemost 2015; Glund S et al. Clin Pharmacokinet 2016; Eikelboom J et al. Circulation 2015; Praxbind®: EU SPC, 2015

What clinical data are available for idarucizumab, and what are the implications for patients and physicians?

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

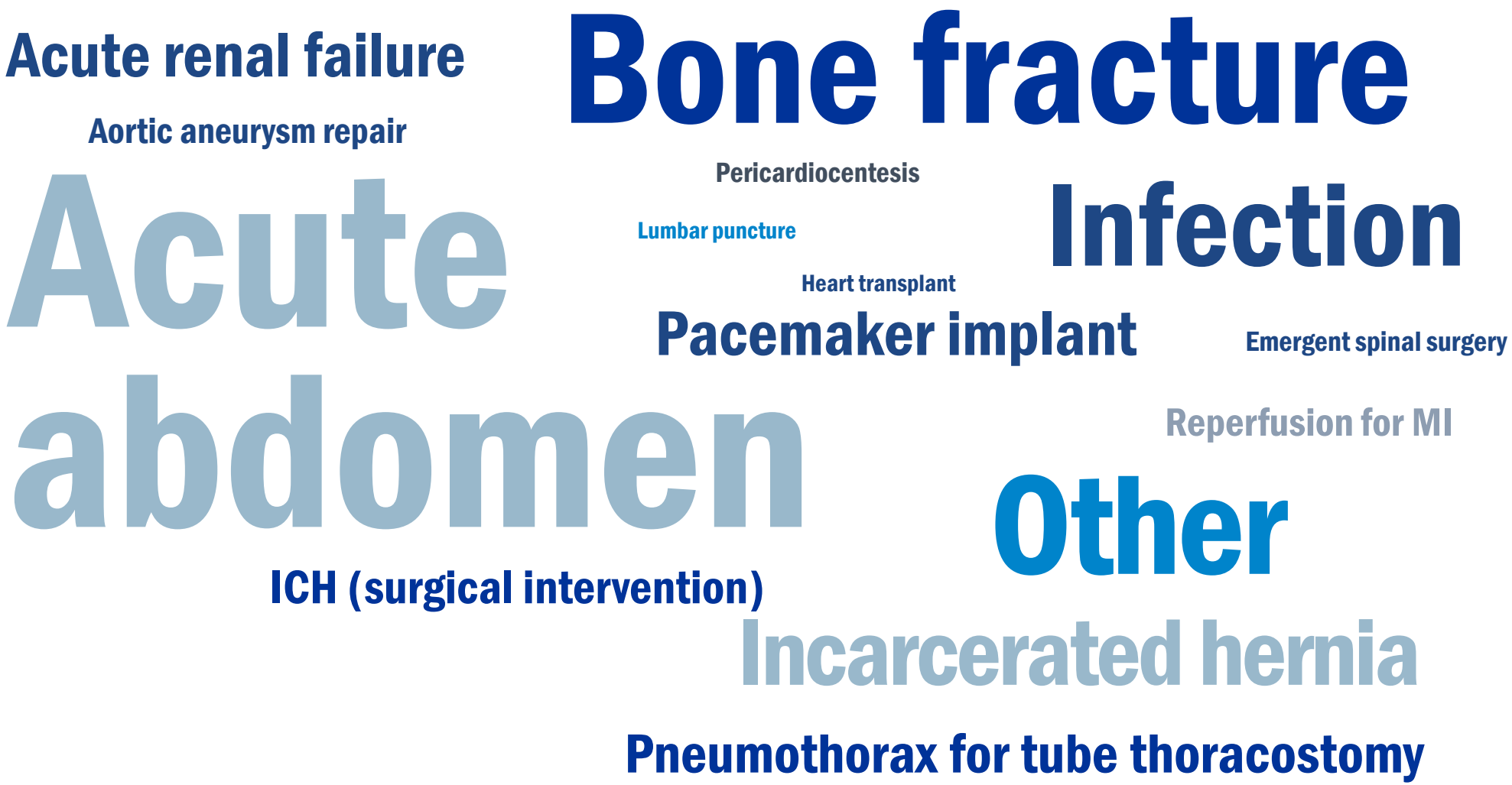


Patients were treated based on presenting condition, not coagulation tests

Primary endpoint: dabigatran reversal within 4 hours (dTT or ECT)

*Other than for bleeding.
dTT, diluted thrombin time; ECT, ecarin clotting time
Pollack C et al. AHA 2016; Pollack C et al. Thromb Haemost 2015

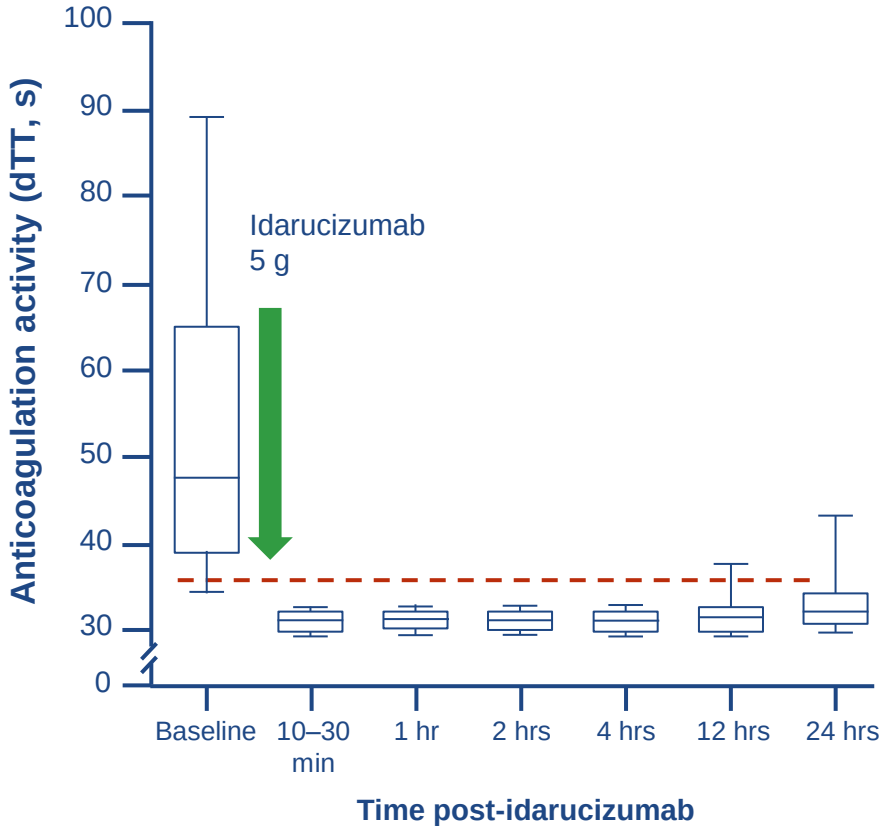
Group B results: reasons for surgery



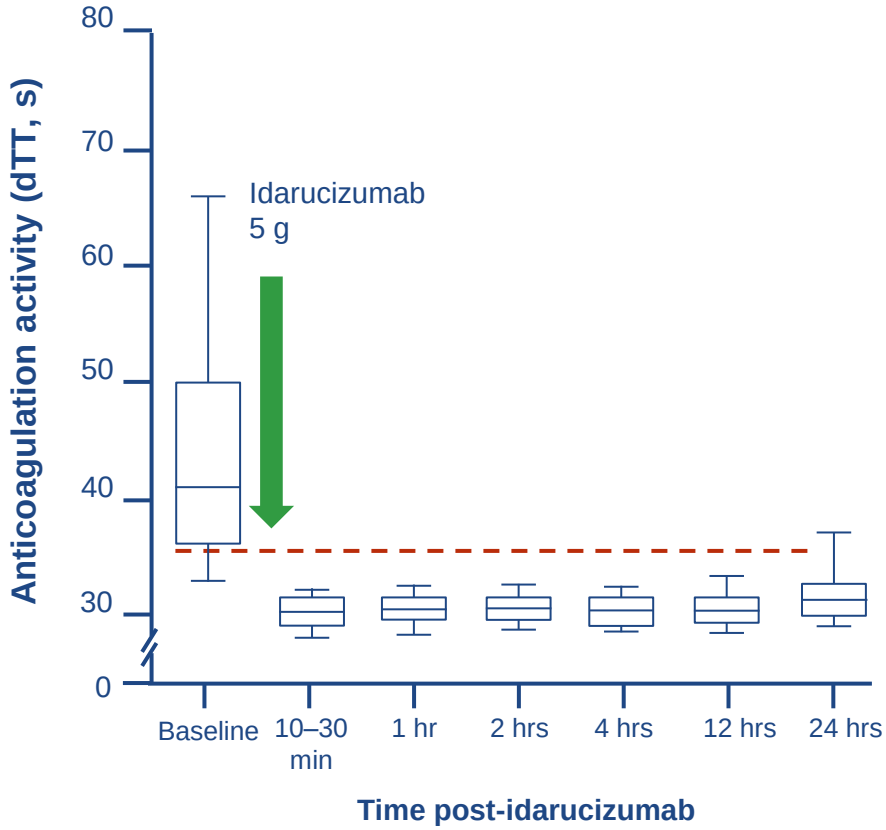
Pollack C et al. AHA 2016

RE-VERSE AD™: reversal of dabigatran anticoagulation in Group A and B, based on dTT

Group A: uncontrolled bleeding (N=298)



Group B: emergency surgery or procedure (N=196)



Median and 25th/75th percentiles 10th/90th percentiles Assay upper limit of normal

dTT, diluted thrombin time

Adapted from Pollack C et al. AHA 2016

RE-VERSE AD™: primary endpoint showed immediate reversal of dabigatran-mediated anticoagulation in the majority of patients

Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI: 100–100)

dTT normalized within 4 hours in 235/238 patients (98.7%) in group A and 141/143 patients (98.6%) in group B*

Similar results with ECT and central laboratory aPTT

*Calculated for patients with elevated levels at baseline (efficacy population)
aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time
Pollack C et al. AHA 2016

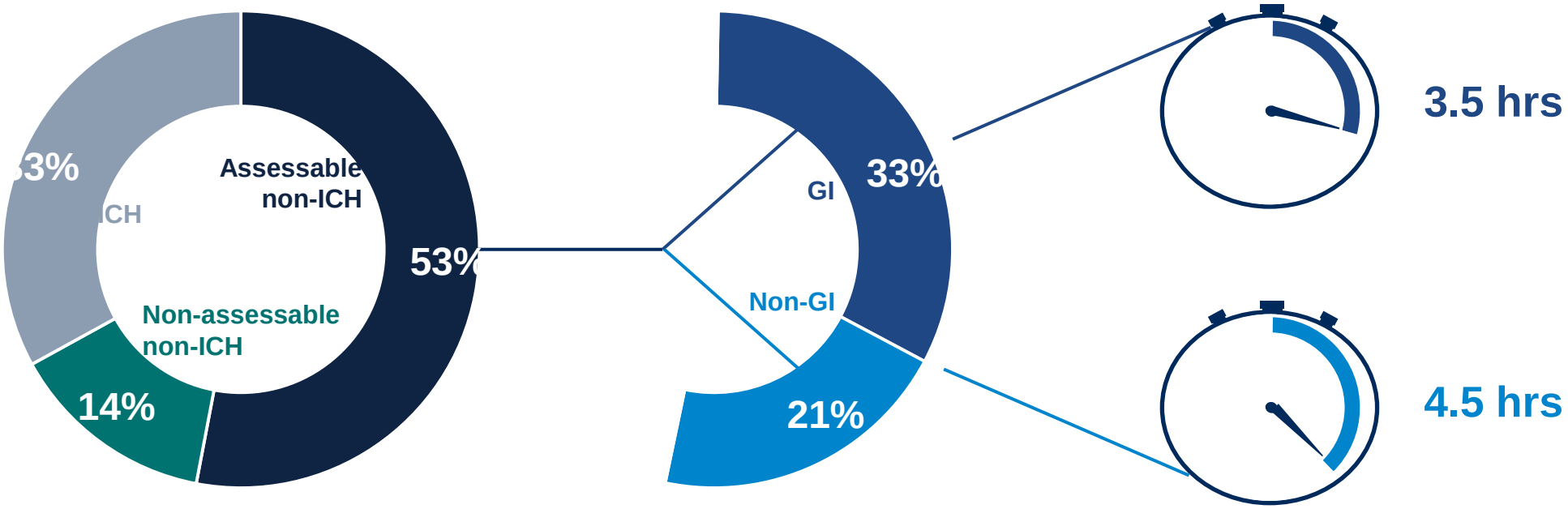
Clinical results indicate rapid cessation of extracranial bleeding in Group A

Group A

298 patients with bleeding type classed as:

The 158 assessable non-ICH bleeds were:

With a median time to bleeding cessation of:

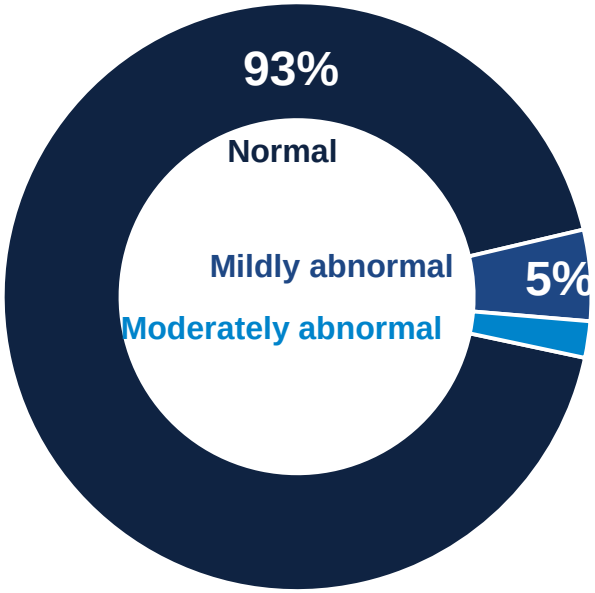


Pollack C et al. AHA 2016

Clinical results indicate mostly normal haemostasis during surgery in Group B

Group B

191 of 196 (97.4%) patients underwent surgery/procedure with periprocedural haemostasis classed as:



1%

0%
Severely abnormal

Overall median time from first vial to procedure:

1.6 hrs

Pollack C et al. AHA 2016

Idarucizumab is easy to use and has no contraindications

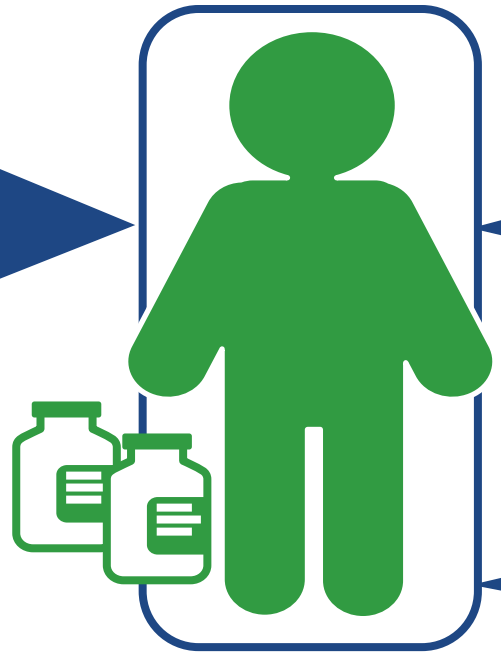
Idarucizumab is indicated when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures or in life-threatening bleeding

Praxbind®: EU SPC, 2015

Idarucizumab can be used alongside other supportive therapy, and allows for anticoagulation to be resumed soon after administration

Allows protection against thrombotic risk to be resumed as soon as the need for surgery or the bleeding event has been addressed

Other antithrombotic treatment (e.g. heparin) can be initiated at any time after administration of idarucizumab*



Can be used alongside other supportive therapy (e.g. PCC, FFP)

Dabigatran can be re-started 24 hours after administration*

FFP, fresh frozen plasma; PCC, prothrombin complex concentrate
*If the patient is clinically stable and adequate haemostasis has been achieved
Praxbind®: EU SPC, 2015

South Korea case – CNUH experience

- 84yr-old male patient
  - He has Hypertension, Presence of pacemaker, AF and liver Cirrhosis
  - Pradaxa 110mg BID for AF
  - Gum bleeding (uncontrolled bleeding)

South Korea case – CNUH experience

CBC

WBC	6700 /mm^3
Hgb	5.6 g/dL
PLT	212 x10^3 /mm^3

LFT

AST	11 U/L
ALT	<6 U/L

RFT and Electrolyte

Cr	2.5 mg/dL
Na/K	136/4.9/104 mEq/L

Coagulation profile

PT	57.0/10.3/4.84 sec/%/INR
aPTT: No coagulation (>180 sec)	

Cardiac enzymes

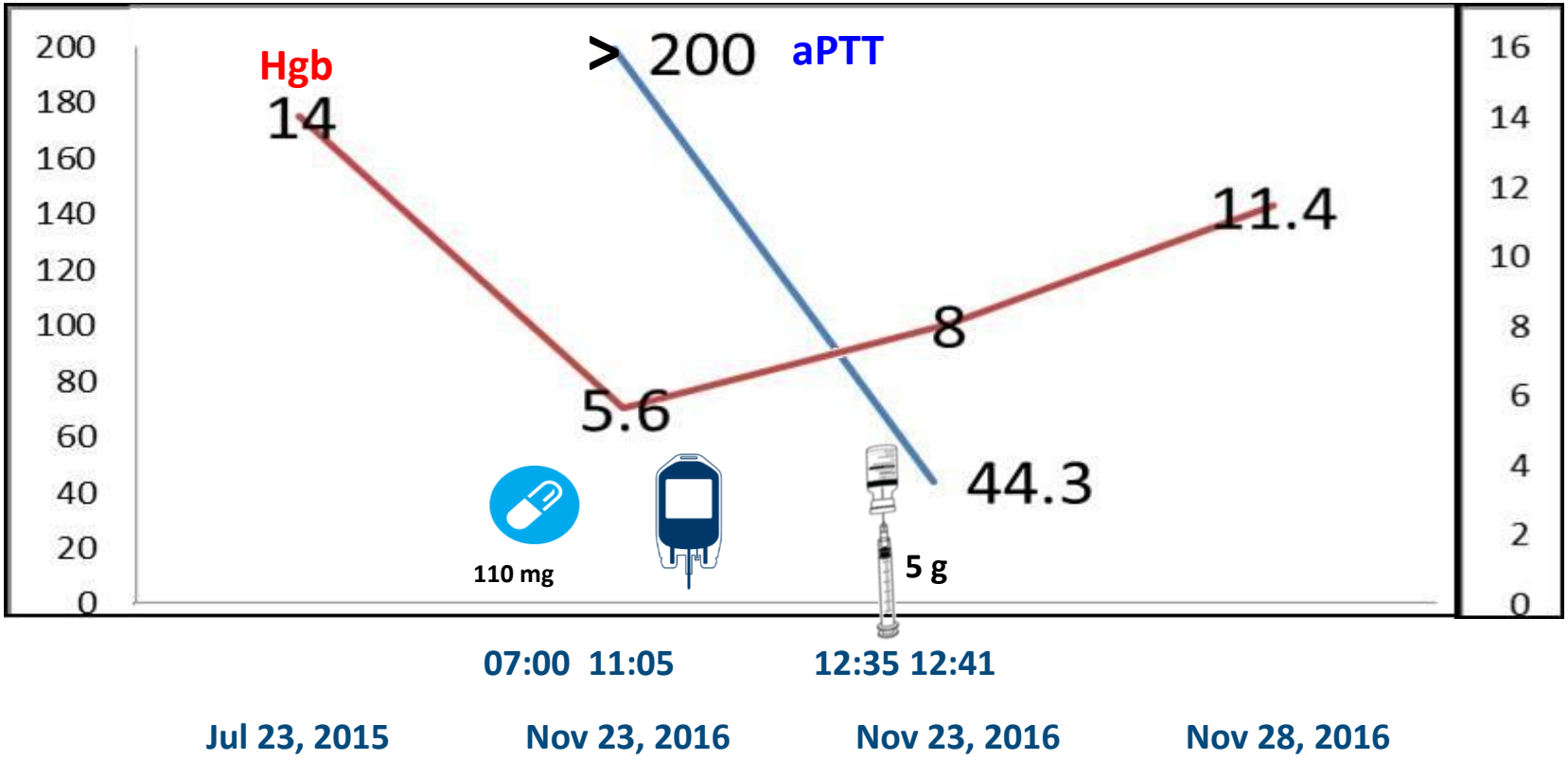
TnT	0.045	ng/mL

South Korea case – CNUH experience

Major Bleeding in Non-Surgical Patients

1. Fatal bleeding.
2. Symptomatic bleeding in a critical area or organ, such as **intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial,** or intramuscular with **compartment syndrome**.
3. Bleeding causing a **fall in hemoglobin level of 2 g/dL** (1.24 mmol/L) or more, or leading to transfusion of **two or more units of whole blood or red cells.**

South Korea case – CNUH experience



Andexanet Alfa

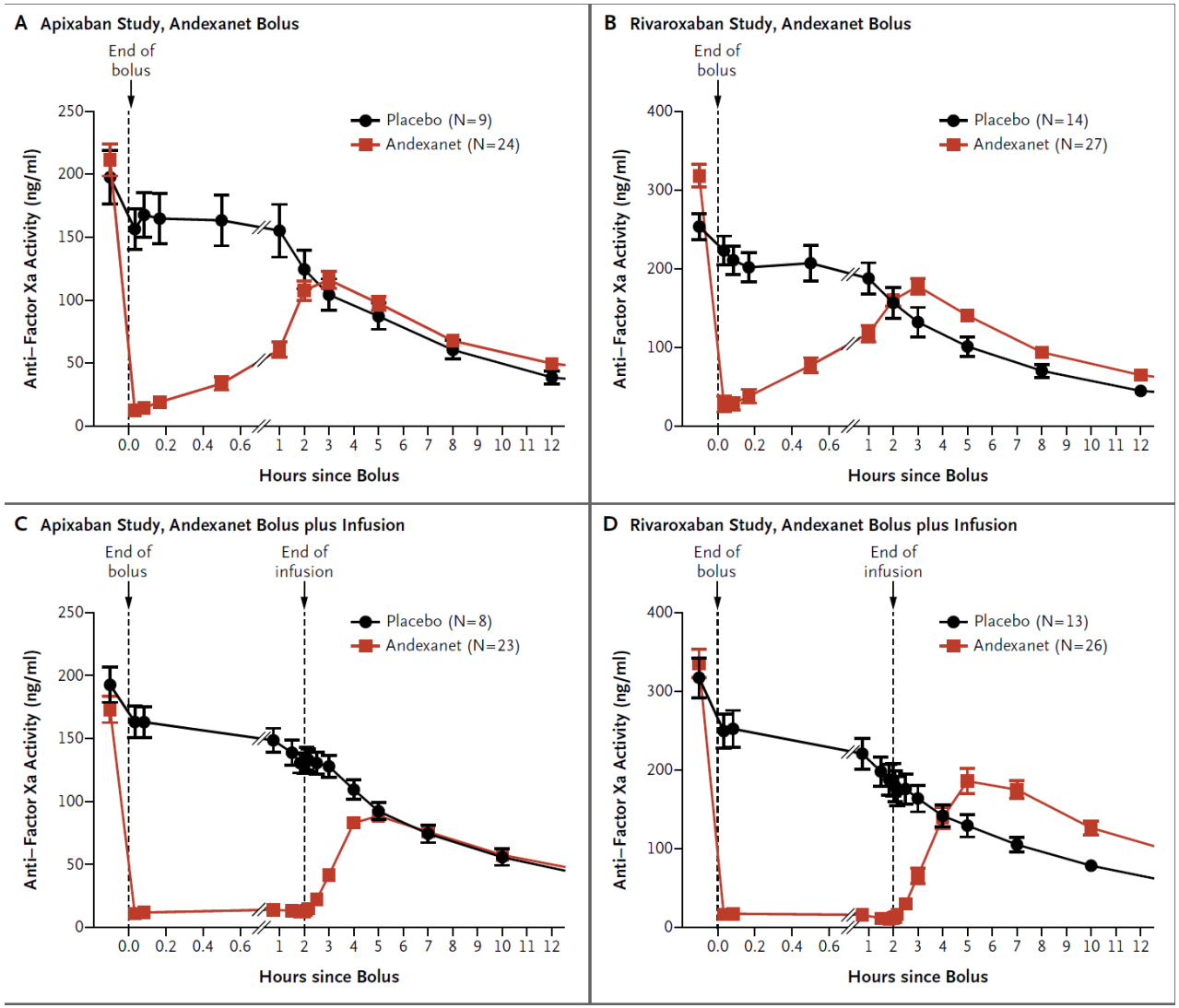
- Recombinant modified human Factor Xa decoy protein
- Catalytically inactive
- Binds to Factor Xa inhibitors in their active site
- Enhances the activity of endogenous factor Xa and attenuates le vels of anticoagulant activity
- Half life; - 1 hr

Andexanet Alfa; ANNEXA-A and ANNEXA-R

- Anticoagulant effects of Fxa inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R)
  - 2 parallel trials

- Study objective;
  - To determine the efficacy and safety of andexanet alfa for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers

Andexanet Alfa; ANNEXA-A and ANNEXA-R



Siegal DM, et al. N Engl J Med 2015;373:2413-24

ANNEXA-4; Inclusion/Exclusion criteria

Prospective, Open-Label Study of Andexanet Alfa in patients receiving a Factor Xa inhibitor who have acute major bleeding

•Acute major bleeding that is
- Potentially life-threatening

or
- Assoicated with a fall in Hb of ≥ 2 g/dL or
- Associated with Hb of ≤ 8 g/dL or
- In a critical area or organ

- Demonstrated ICH by MRI/CT
- Received factor Xa inhibitor within prior 18 hours

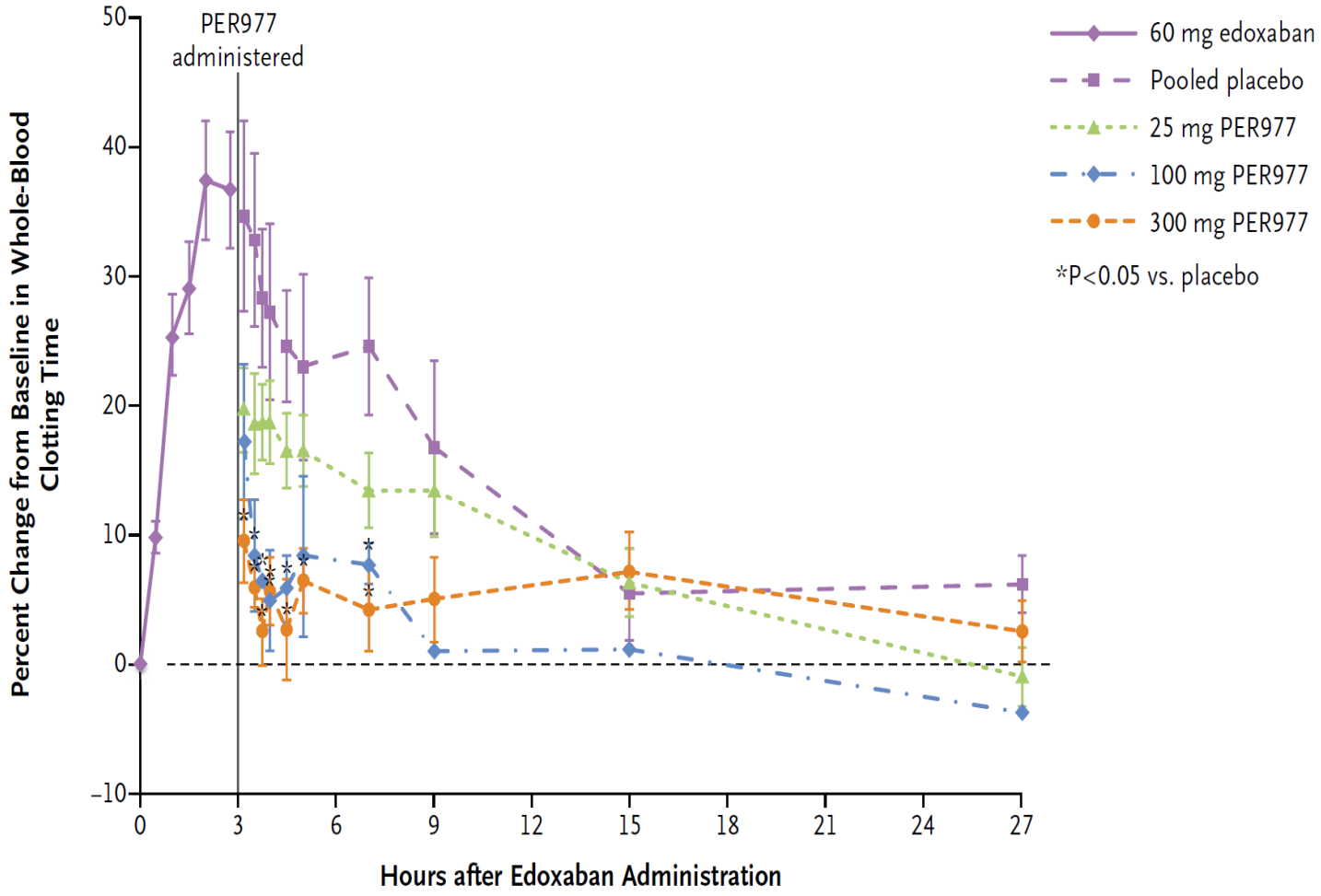
•Surgery expected in < 12 hr, except minimally invasive procedures
•Intracerebral hemorrhage with
- Glasgow coma score < 7 or
- Intracerebral hematoma > 60 cc

Expected history (within 2 자) of thrombotic event
Severe sepsis or septic shock
Received
- VKA, dabigatran, PCC, rfVIIa, whole blood, or plasma fractions

Ciraparantag/Aripazine

Structure	Synthetic small molecule
Target	Direct Xa inhibitors, DTIs, UFH, LMWH (universal antidote)
Mechanism	Noncovalent hydrogen bind (exact mechanism unsure)
Current status	Phase 2 study ongoing

Ciraparantag/Aripazine; reversal of edoxaban activity



Jack AE. N Engl J Med 2014;371:2141-2

Summary I

1. **A specific reversal agent for dabigatran is now widely available in Europe, the USA, and other countries**

2. **Idarucizumab immediately reverses the anticoagulant activity of dabigatran and is easy to use**

3. **The availability of a specific reversal agent for dabigatran adds more control and is an important factor in NOAC choice**

Summary II

- Need for reversal agents expected in increase with
  - Aging population (increased risk of AF and VTE)
  - Increase in uptake of NOACs
- Reversal agents
  - Idarucizumab currently available
  - Andexanet alfa in late stage development
  - Ciranparantag/aripazine in early stage development
- Available of reversal agents
  - Reassures clinicians of starting OACs in high-risk patients