Hemorrhage Management and Antidote of NOAC

INNOVATION
EWHA

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COI Disclosure

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ICH is the most feared complication of antithrombotic therapy

- ICH
  - >10% of patients with ICH are on antithrombotic therapy
- Can be life-threatening
- Increased ICH risk* with traditional antithrombotics:
  - ~40% with ASA
  - ~200% with warfarin
    (INR 2.0–3.0; increases to 0.3–0.6%/year)

*Compared with placebo
ASA = acetyl salicylic acid; ICH = intracerebral haemorrhage; INR = international normalized ratio
Hart RG et al. Stroke 2005;36:1588–93

Longer times in therapeutic range may not improve the rate of ICH in patients on VKAs

cTTR (%)	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs warfarin		Dabigatran 150 mg vs warfarin	
	Rate per 100 person-yrs	Rate per 100 person-yrs	Rate per 100 person-yrs	HR (95% CI)	P value* (interaction)	HR (95% CI)	P value* (interaction)
<57.1	0.28	0.34	0.64	0.43 (0.19–1.00)		0.53 (0.25–1.15)	
57.1–65.5	0.30	0.42	0.93	0.31 (0.15–0.66)		0.45 (0.24–0.88)	
65.5–72.6	0.13	0.24	0.67	0.20 (0.07–0.58)		0.35 (0.15–0.82)	
>72.6	0.21	0.30	0.77	0.27 (0.11–0.66)	0.71	0.39 (0.18–0.84)	0.89

*Interaction P value evaluated by a multivariate approach with centre-based TTR as a continuous variable
cTTR = centre mean time in therapeutic range; HR = hazard ratio; ICH = intracranial haemorrhage; INR = international normalized ratio; TTR = time in therapeutic range; VKA = vitamin K antagonist
Wallentin L et al. Lancet 2010;376:975–83

Prognosis in VKA-associated ICH is poor despite reversal

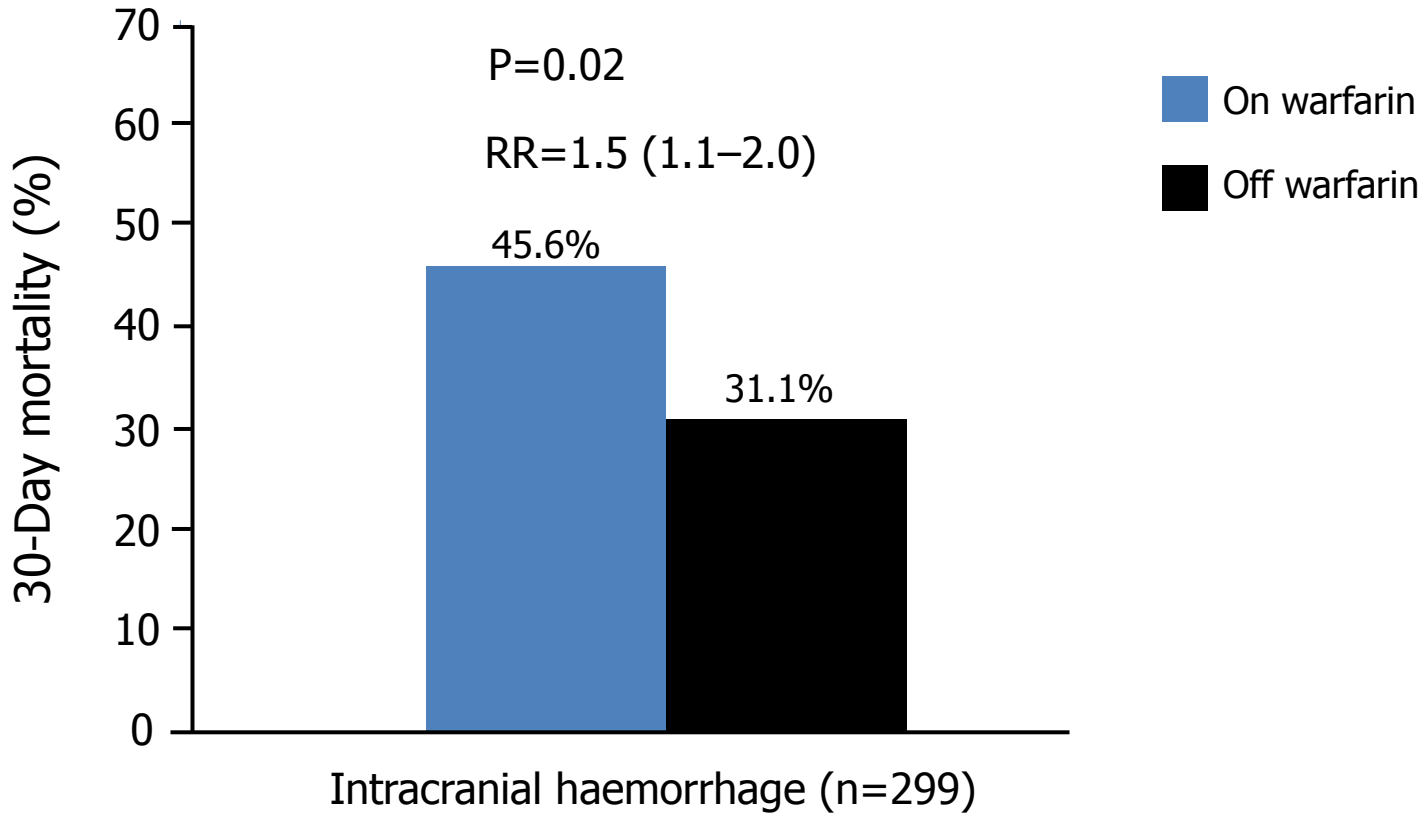
- Up to 60% of patients who suffer an ICH whilst receiving warfarin die[1]
- Prospective multicentre registry of patients with warfarin-associated ICH[2]
  - PCC reversed anticoagulation in 71.8% patients within 1 hour, yet outcomes remained poor

ICH type	n	In-hospital mortality* n (%)	Discharge mRS (Median IQR)†
Intraparenchymal	71	30 (42.3)	5 (3)‡
Subdural	61	21 (34.4)	3 (4)§
Epidural	1	0	3
Subarachnoid	8	1 (12.5)	3 (3)

*P=0.3; †P=0.012; ‡mRS missing in 9; §mRS missing in 2
ICH = intracranial haemorrhage; IQR = interquartile range; mRS = modified Rankin Scale;
PCC = prothrombin complex concentrate; VKA = vitamin K antagonist

1. Wiedermann CJ et al. Thrombosis Res 2008; 122(Suppl): S13–18;
2. Dowlatshahi WT et al. Stroke 2012;43:1812–17

VKAs can increase the likelihood of suffering an ICH, as well as the mortality associated with it



- ICH = intracerebral haemorrhage; RR = relative risk; VKA = vitamin K antagonist
- Fang MC et al. Stroke 2012;43:1795–9

Safe Anticoagulation Management

- Warfarin reversal
- Reversal agent of NOAC
- General managements
- Current guidance

ACCP Guidelines

- For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with
  - four-factor prothrombin complex concentrate (PCC) rather than with plasma (Grade 2C).

- We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

ACCP guideline : American College of Chest Physician Evidence-Based Clinical Practice Guidelines

Holbrook A. Chest. 2012 Feb;141(2 Suppl). PMID: 22315259

4 Factor PCC for Warfarin Related Bleeding

Table 5. Hemostatic Efficacy (Intention-to-Treat Efficacy Population)

	No. (%) of Patients [95% CI]		Difference 4F-PCC Minus Plasma, %
	4F-PCC	Plasma	

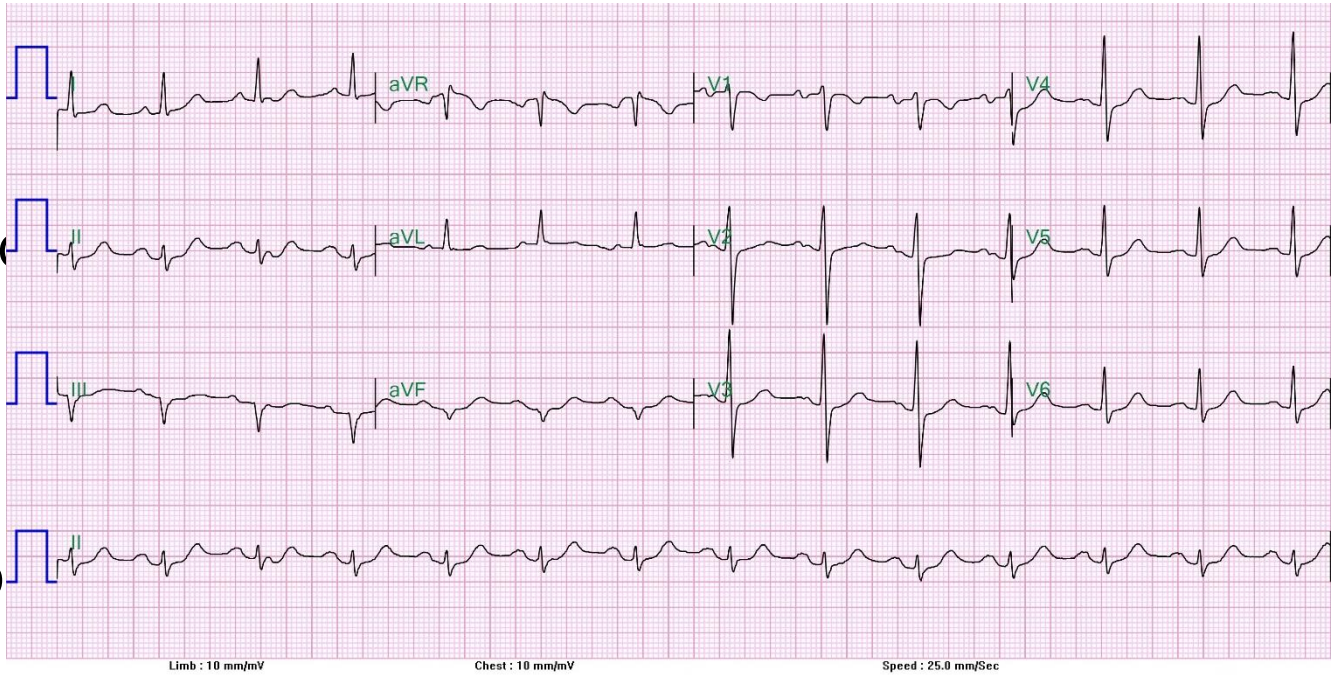
Table 7. Rapid INR Reduction (Intention-to-Treat Efficacy Population)

	No. (%) of Patients [95% CI]		
	4F-PCC (n=98)	Plasma (n=104)	Difference 4F-PCC Minus Plasma, % (95% CI)
Rapid INR reduction*	61 (62.2) [52.6 to 71.8]	10 (9.6) [3.9 to 15.3]	52.6† (39.4 to 65.9)

Sarode R. Circulation. 2013 Sep 10;128(11): 1234-43

Case in current practice

- CC: syncope and
- F/63
- Symptomatic par
  - CHA2DS2VASc=2
  - HASBLED = 1



- ➢ Medication : Dab
- ➢ EKG : NSR

- ➢ Brain CT
  - ➢ Acute SAH at Rt parietal sulci, Acute SDH in the falx

Reversal Agents in NOAC

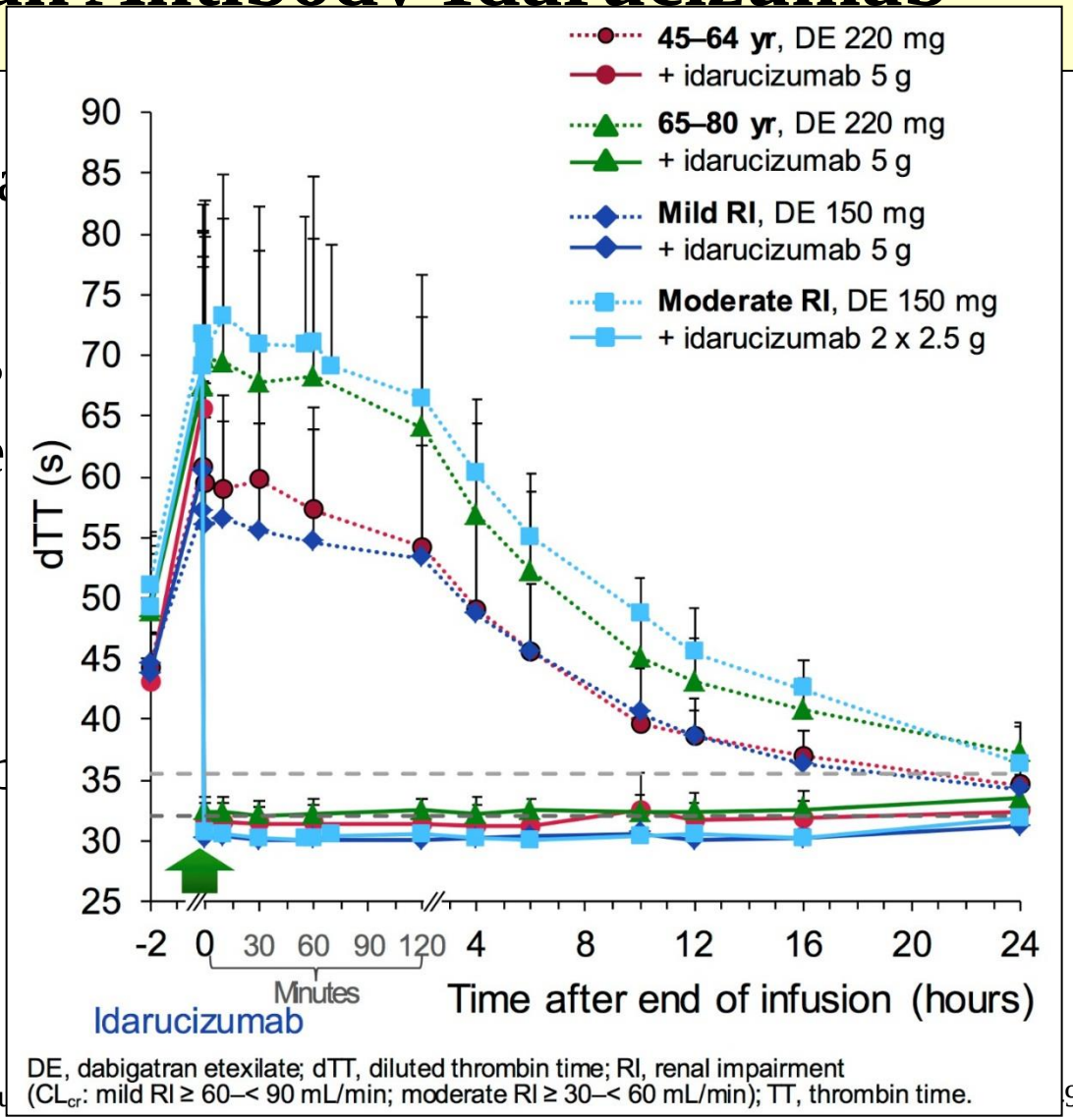
Company	Agent	Target
Boehringer-Ingelheim	**Idarucizumab:** Fully humanized Fab	Dabigatran only
Portola Pharmaceuticals, Inc.	**Andexanet alfa:** Recombinant, modified human Factor Xa	Factor Xa Inhibitors (Riva; Apix; Edox)
Perosphere Inc.	**Aripazine:** Di-arginine piperazine	All NOACs (Dabi; Riva; Apix; Edox) UFH, LMWH, fondaparinux

FDA Approval & Availability (Idarucizumab)

- Approved by the FDA in October 2015
- FDA labeling:
  - **Reversal of dabigatran** for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding
- Supplied as 2.5g vials (5g total dose)

Dabigatran Antibody Idarucizumab

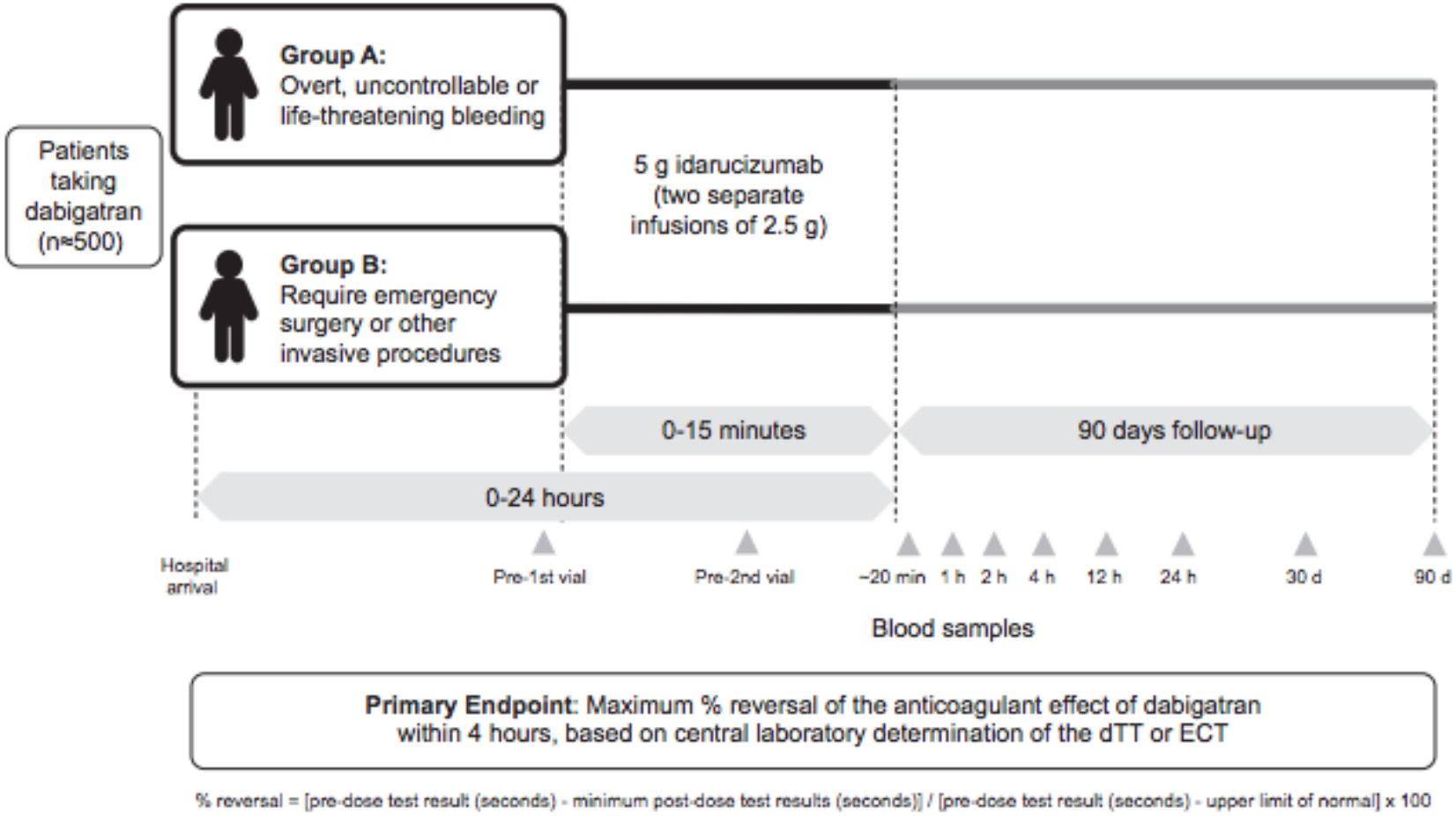
- 46 male and female pa
- Dabigatran for 4 days
- Idarucizumab 2 hours
- 5 mg completed corre
  - Dilute thrombin time
  - Ecarin clotting time
  - aPTT
- Well tolerated and dab
  anticoagulation effect



DE, dabigatran etexilate; dTT, diluted thrombin time; RI, renal impairment (CL_{cr}: mild RI ≥ 60–< 90 mL/min; moderate RI ≥ 30–< 60 mL/min); TT, thrombin time.

Glu 960.html

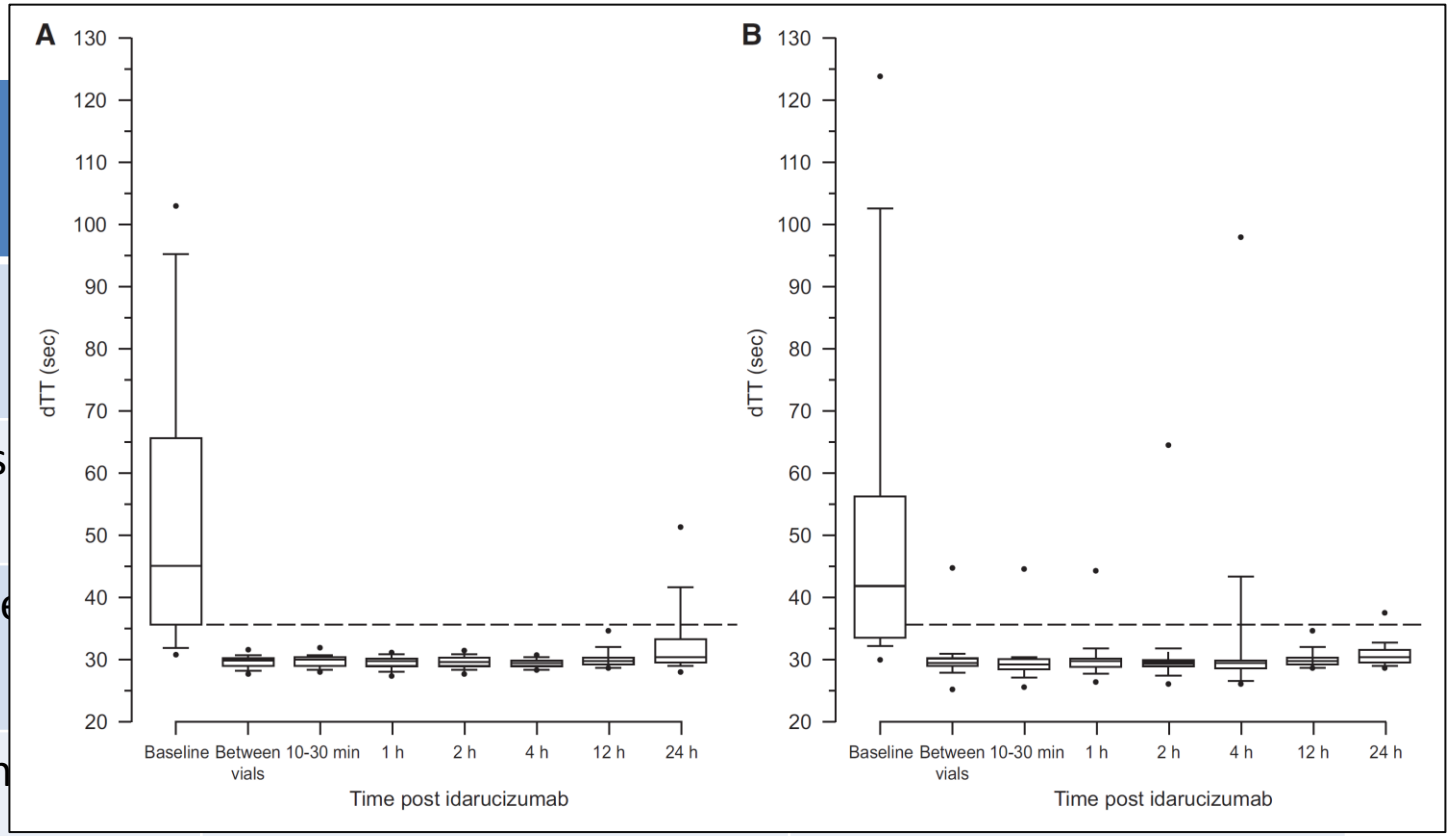
REVERSE-AD



Circulation. 2015;132:2412-2422.

REVERSE-AD: Results (Primary Outcome)
* Dilute Thrombin Time (dTT) *

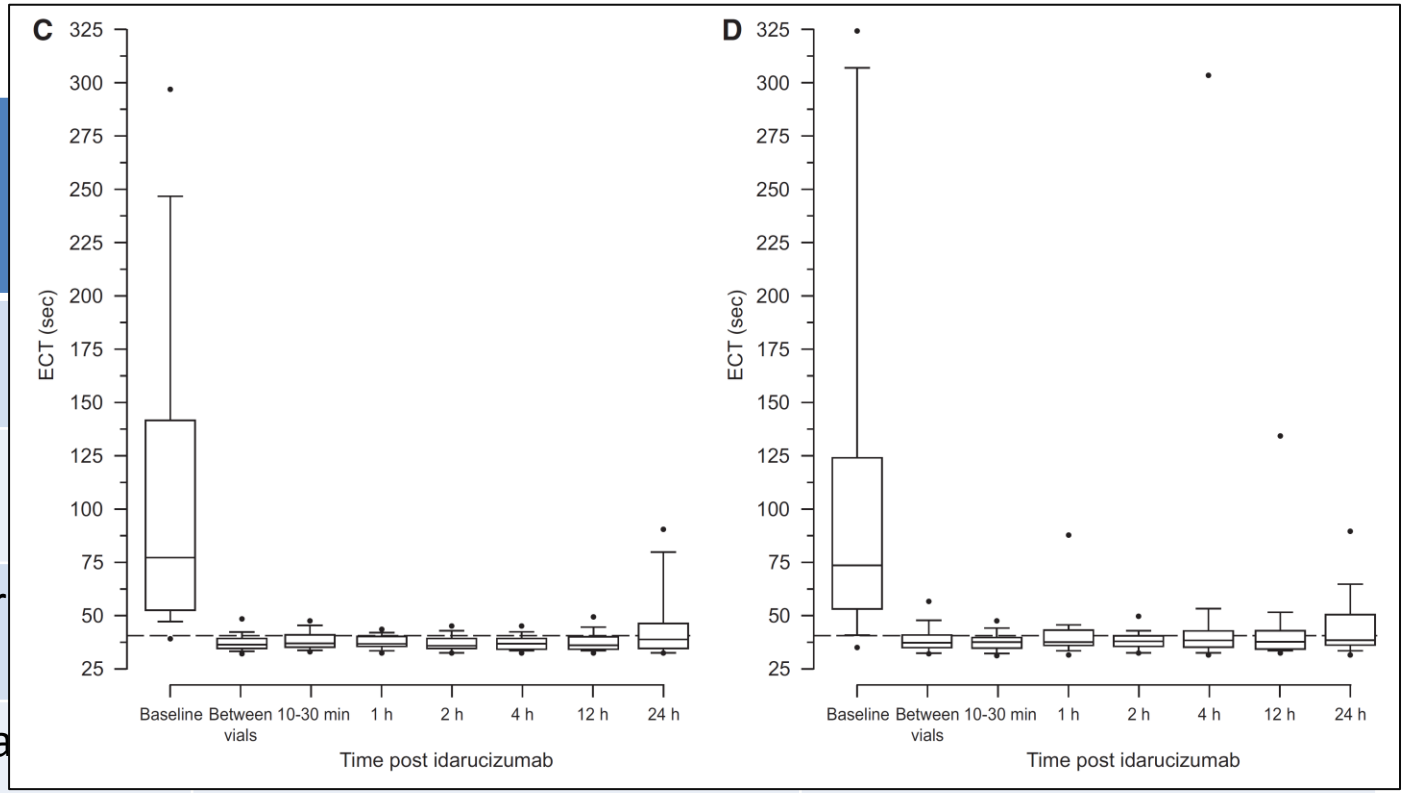
Mean dTT at baseline
Mean dTT between vials
Mean dTT 10-30 min afte second vial
Mean dTT 4 h +/- 30 min second vial



N Engl J Med, 2015, 373: 511-520

REVERSE-AD: Results (Primary Outcome)
* Ecarin Clotting Time (ECT) *

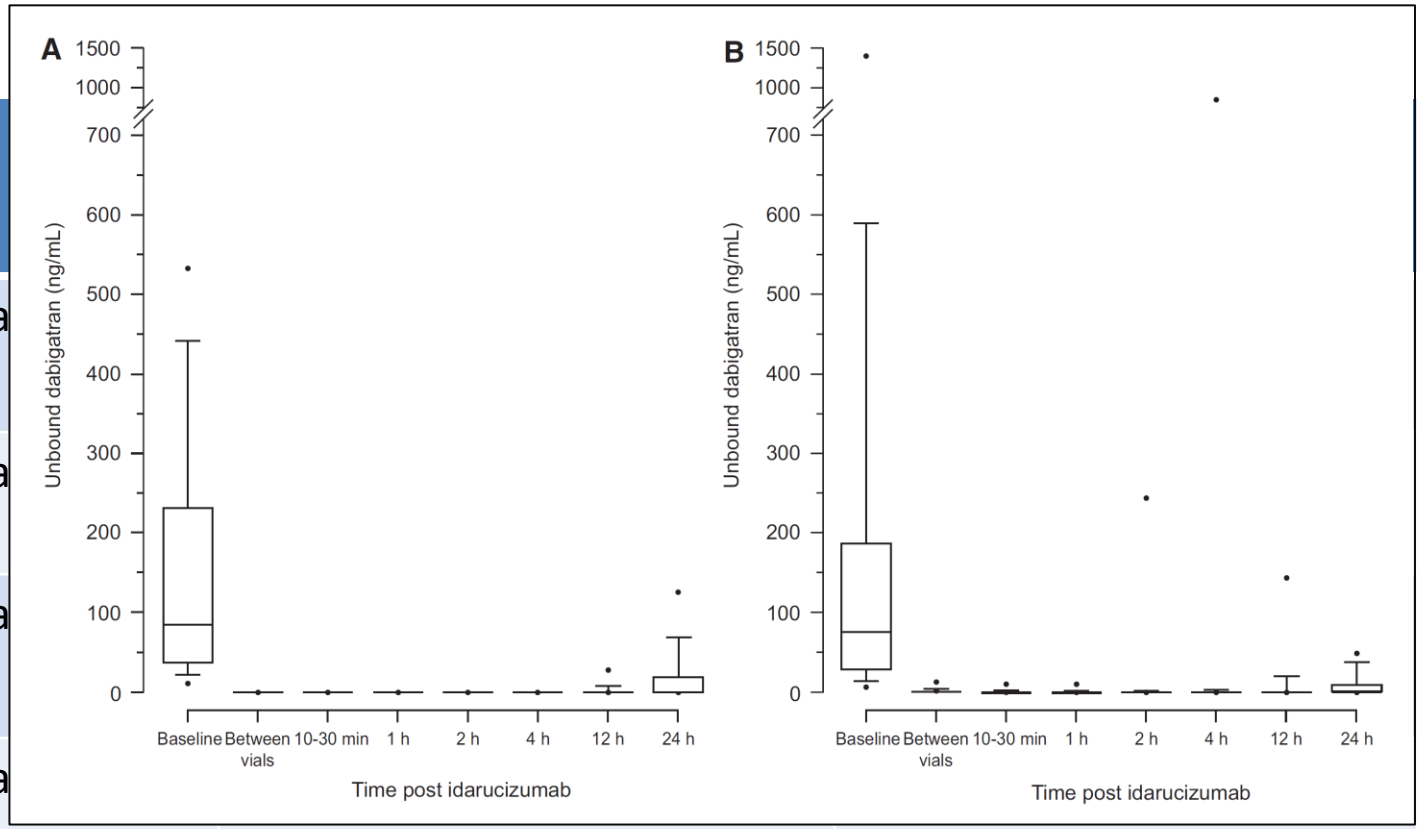
Mean ECT at baseline
Mean ECT between vials
Mean ECT 10-30 min after vial
Mean ECT 4 h +/- 30 min a second vial



N Engl J Med, 2015, 373: 511-520

REVERSE-AD: Results (Secondary Outcome)
* Unbound (free) dabigatran [ng/mL] *

Mean unbound dabigatra baseline
Mean unbound dabigatra between vials
Mean unbound dabigatra min after second vial
Mean unbound dabigatra 30 min after second vial



N Engl J Med, 2015, 373: 511-520

REVERSE-AD: Results (Secondary Outcomes)

**** Time to cessation of bleeding (for Group A only)**

•Median investigator-reported time to the cessation of bleeding for patients was 11.4 hours

Occurrence of major bleeding (for group B only) intraoperatively and up to 24 hours post-surgery

•Of the 36 patients who received a procedure:

- Normal intraoperative hemostasis was reported in 33 (92%) patients
- Mildly abnormal hemostasis during the procedure was reported in 2 patients
- Moderately abnormal hemostasis reported in 1 patient

N Engl J Med, 2015, 373: 511-520

REVERSE-AD: Results (Adverse Events)

Deaths

- 18 total (9 in each group)
- 10 due to vascular causes (5 fatal bleeds)
- 9 deaths occurred > 96 hours after treatment and appear related to index event

Thrombotic Events

Occurred in five patients overall (none were on any anti-thrombotic agents at the time of these events)

Table 2. Serious Adverse Events Leading to Death.

Event	Characteristics of the Patients		Study Group*	Time from Treatment to Death
	Age	Sex		
	yr			*days*
Cardiac arrest	82	Female	B	<1
Circulatory collapse	93	Male	B	<1
Hemodynamic collapse	88	Female	B	<1
Septic shock	87	Female	B	1
Sepsis, shock, and gastrointestinal bleeding	60	Male	B	1
Progression of respiratory failure	60	Male	A	1
New intracranial hemorrhage	77	Male	A	1
Progression of intracranial hemorrhage	69	Male	A	2
Multiorgan failure	87	Male	B	2
Progression of intracranial hemorrhage	69	Male	A	4
Pulmonary edema	83	Female	A	11
Cardiac arrest	78	Female	B	21
Ischemic stroke	72	Female	B	26
Congestive heart failure	73	Male	A	30
Parkinson's disease	80	Male	A	43
General health deterioration	83	Male	A	42
Pneumonia	86	Female	A	94
Progression of cancer	80	Male	B	101

N Engl J Med, 2015, 373: 511-520

When and How, use reverse agent?

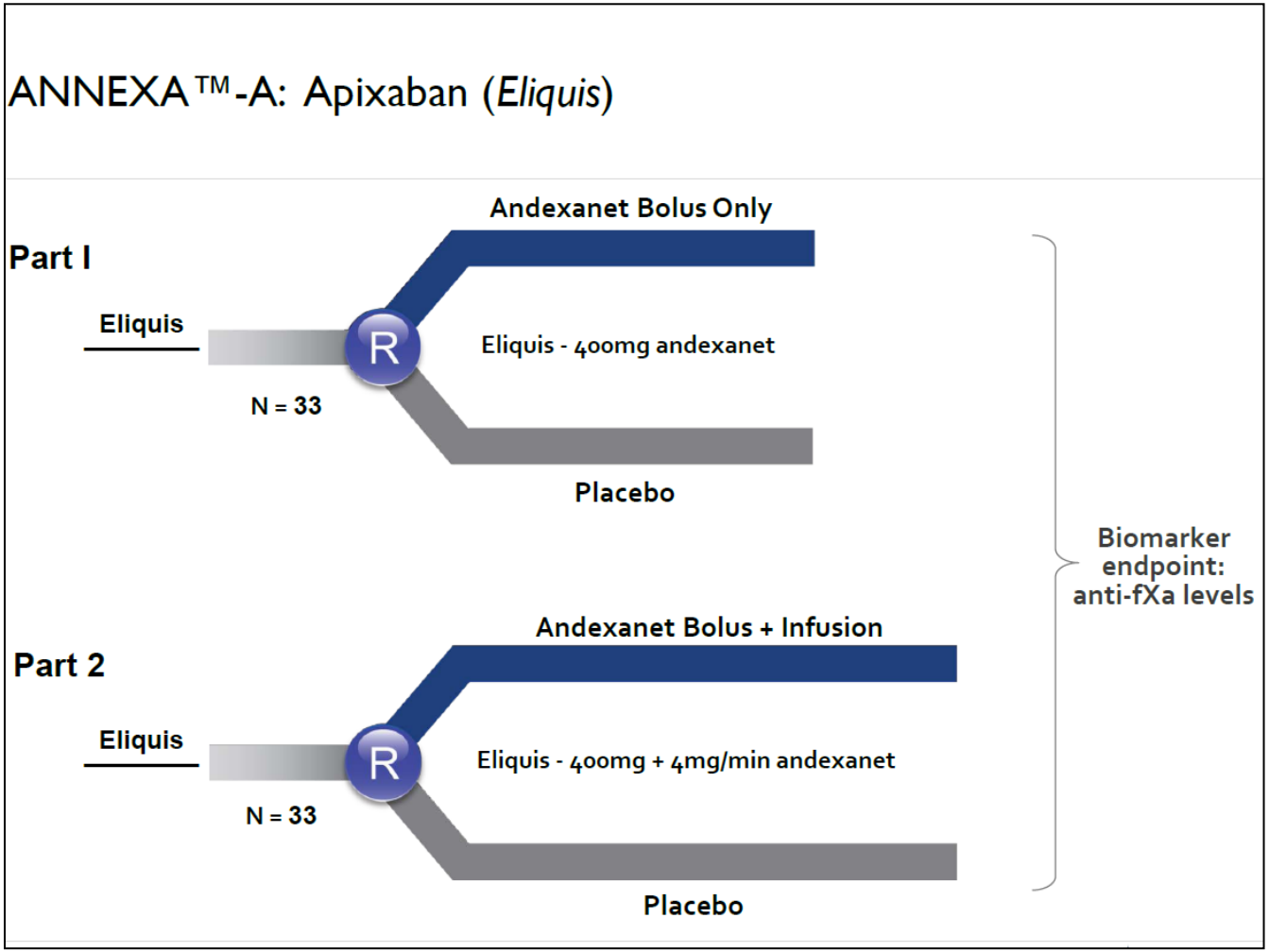
- Demonstrated that idarucizumab safely and efficaciously reverses anticoagulation induced by dabigatran administration

- Standardization of laboratory testing and monitoring will be necessary on an institution-to-institution basis
  - **dTT** vs. **ECT** vs. **TT** vs. **aPTT**

- Consideration must be given to time of last dabigatran dose and native renal function when deciding whether idarucizumab is appropriate
  - $T^{1/2}$: 12-17 hours; **Elderly**: 14-17 hours; **Mild/moderate**: 15-18 hours; **Severe**: 28 hours

- Must be vigilant about perioperative NOAC use
  - **CrCl ≥ 50 mL/min** = 1-2 days | **CrCl < 50 mL/min** = 3-5 days
  - i.e. discontinuation at the appropriate time depending on renal function

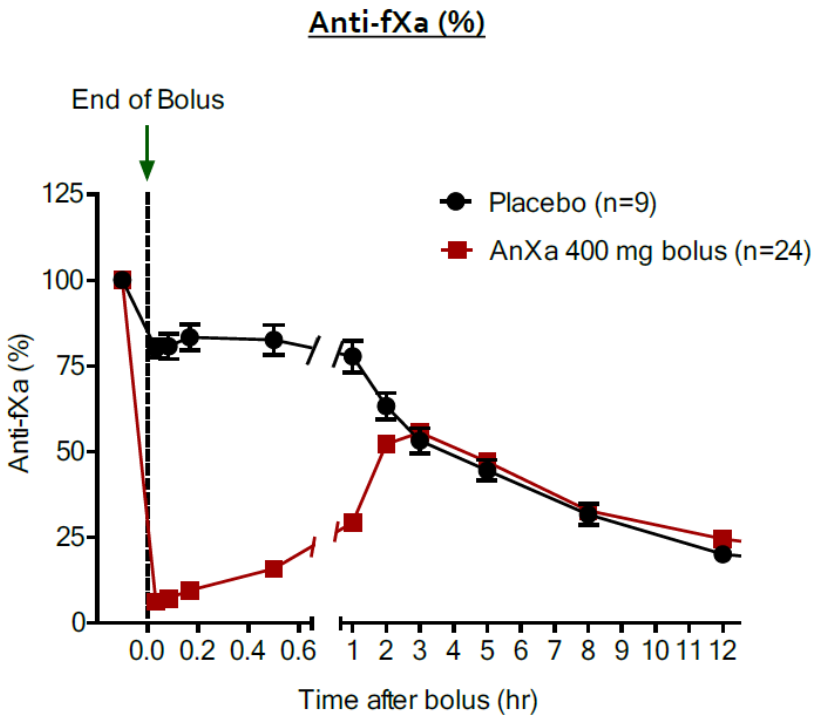
Andexanet Alpha



https://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469639.pdf

Andexanet Alpha

ANNEXA™-A (Apixaban, Part I)
Primary Endpoint: Anti-fXa



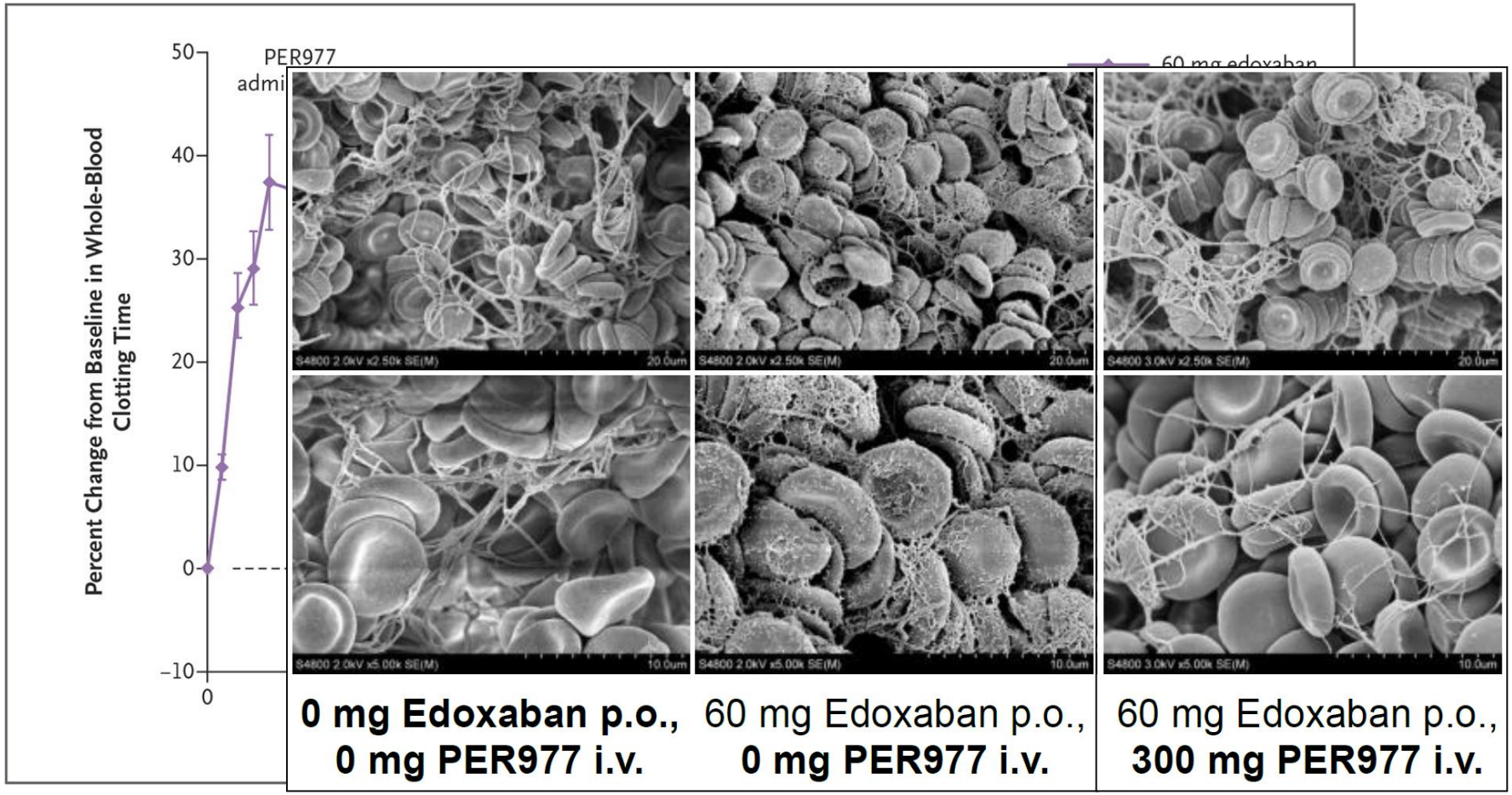
- **Met Primary Endpoint:**
  - Percent change anti-fXa from baseline to nadir (= 94%)
    - p< 0.0001
- **Met first Secondary Endpoint:**
  - Number of subjects with > 80% reversal: andexanet (100%) *vs.* placebo (0%)
    - p< 0.0001
  - All andexanet subjects achieved ≥ 90% reversal

https://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469639.pdf

Looking Ahead…….

- **Aripazine (PER977)** - universal reversal agent for oral direct thrombin and factor XA inhibitors, injectable UFH, LMWH, and fondaparinux
  - Synthetic molecule
  - IV administration
  - Stored at room temp
  - Currently only phase II trials underway

Effect of PER977 on Whole-Blood Clotting Time



PER977 (Perosphere) is a small, synthetic, water-soluble, cationic molecule that is designed to bind specifically to unfractionated heparin and low-molecular-weight heparin through noncovalent hydrogen bonding and charge–charge interactions

Ansell JE. N Engl J Med. 2014 Nov 27;371(22):2141-2

General managements

- Charcoal absorption
- Dialysis
- Prothrombotic agents

Activated Charcoal

- Dabigatran
  - Not mentioned
- **Rivaroxaban**
  - The use of **activated charcoal** to reduce absorption in case of XARELTO overdose may be considered.
- **Apixaban**
  - In healthy subjects, administration of activated **charcoal 2 and 6 hours after ingestion of a 20-mg** dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively.
  - Mean apparent half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban, indicating that charcoal blocked the continued absorption of apixaban from the gut.
  - Thus, administration of **activated charcoal** may be useful in the management of apixaban overdose or accidental ingestion by leading to a more rapid fall in apixaban blood levels.
- Edoxan
  - Not mentioned

Pradaxa.com, Xarelto.com, Eliquis.com, Savaysa.com

Dialysis

- **Dabigatran**
  - Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%.
  - **Hemodialysis** can remove dabigatran; however, data supporting this approach are limited.
  - Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics.
  - Measurement of aPTT or ECT may help guide therapy

- Rivaroxaban
  - Because of high plasma protein binding, rivaroxaban is **not expected** to be dialyzable

- Apixaban
  - Because of high plasma protein binding, apixaban is **not expected** to be dialyzable

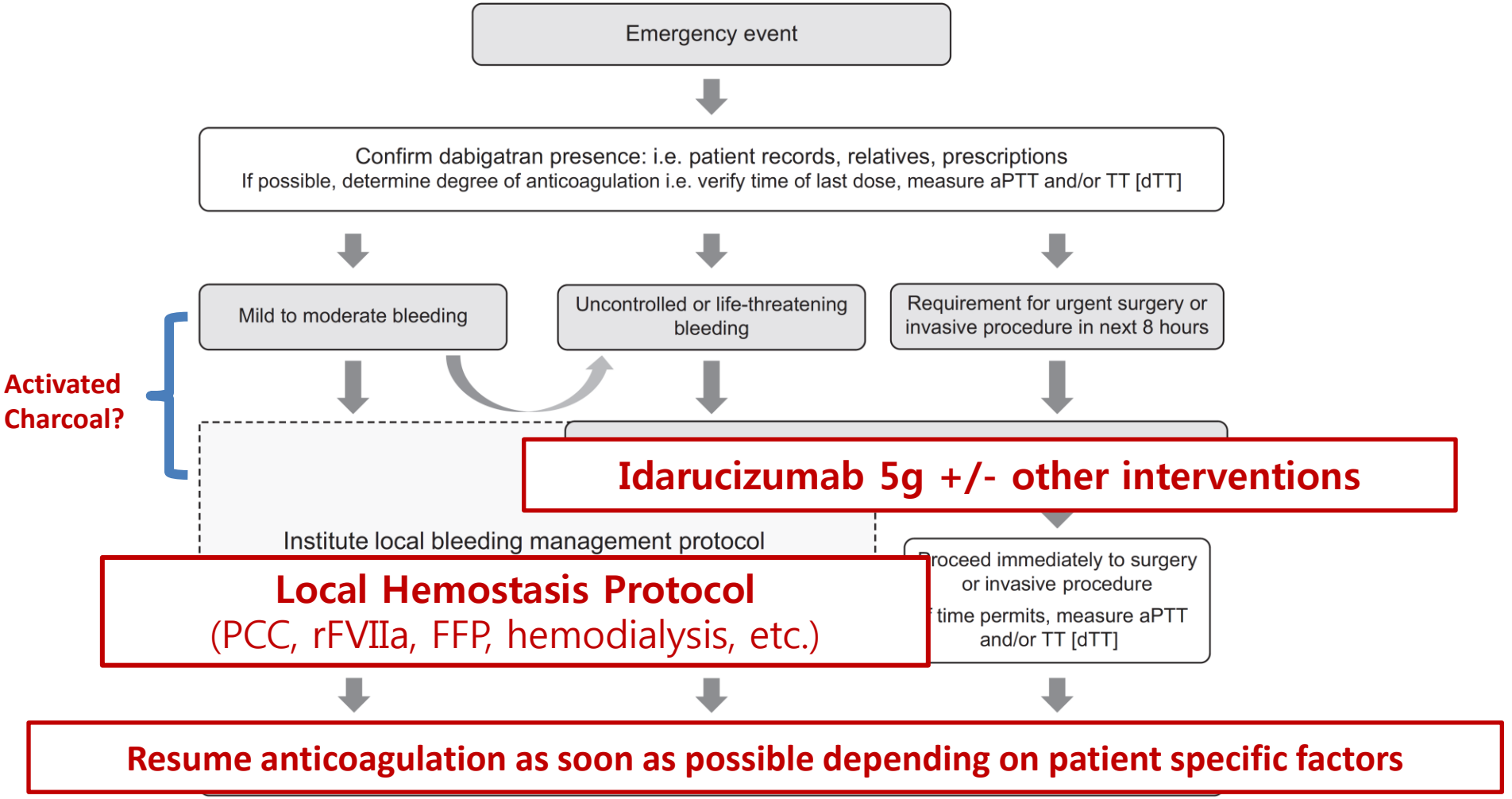
- Edoxaban
  - Hemodialysis does **not** significantly contribute to edoxaban clearance

Pradaxa.com, Xarelto.com, Eliquis.com, Savaysa.com

Prothrombotic agents
-FDA Labeling

- Dabigatran
  - Activated prothrombin complex concentrates (aPCCs, e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered but their use has not been evaluated in clinical trials.
- Rivaroxaban
  - Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.
- Apixaban
  - Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies.
- Edoxaban
  - A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of SAVAYSA.

Final guidance



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Circulation. 2015;132:2412-2422.

Ewha. Light of healing

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