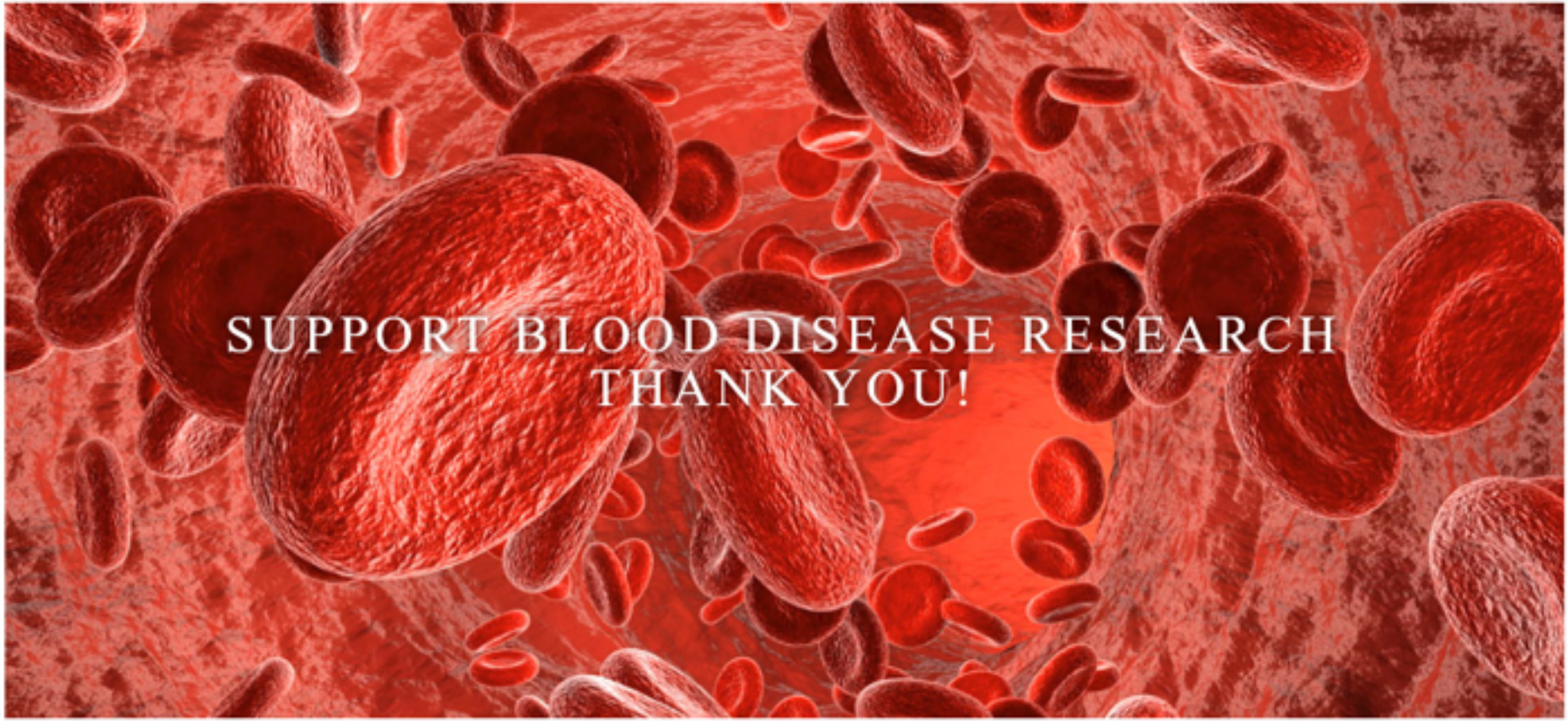
BLOOD DISEASE RESEARCH FOUNDATION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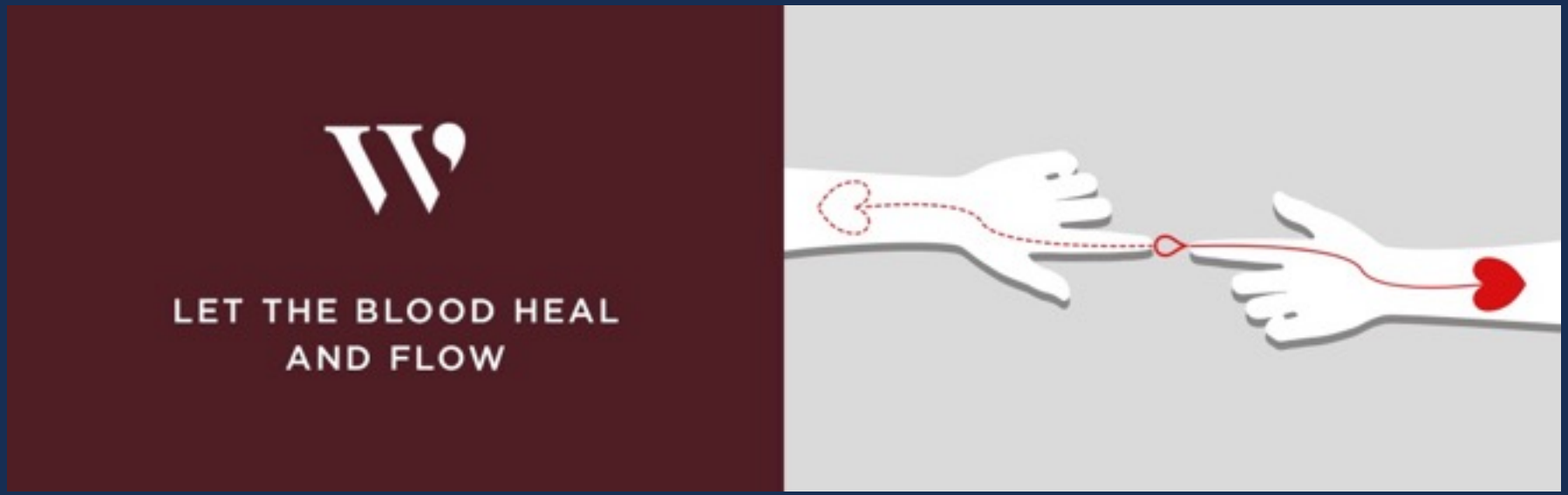
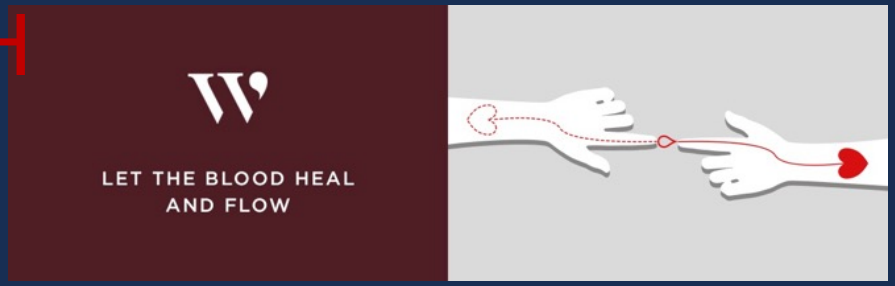
THANK YOU!

BLOOD DISEASE RESEARCH FOUNDATION

The mission of Blood Disease Research Foundation is to support hematological research, e.g. by donating grants for thesis work and abstract presentations in major hematological meetings



BLOOD DISEASE RESEARCH FOUNDATION WEBINAR



AGENDA 27.3.2018

4:00–4:10 pm
Riitta Lassila, the Finnish Blood Disease Research Foundation: Introduction

4:10–4:50 pm
Adam Cuker, Ass. Prof., hematologist: “Measurement and Reversal of the Direct Oral Anticoagulants”

4:50–5:30 pm
Questions and discussion

5:30–5:45 pm
Taru Kuittinen, Ass. Prof., hematologist: National experience on direct oral anticoagulants

5:45–6:00 pm
Conclusive remarks and closure

Measurement and Reversal of the Direct Oral Anticoagulants (DOACs)

Finnish Blood Disease Research Foundation
27 March 2018

Adam Cuker, MD, MS
University of Pennsylvania
Philadelphia, USA

FULL DISCLOSURES (Last 12 months)

Research support

- Alexion
- Bayer
- Bioverativ
- Novo Nordisk
- Pfizer
- Shire
- Spark Therapeutics
- Syntimune

Consultant/Advisory board

- Kedrion
- Novartis
- Stago
- Synergy

Off-label use

- Andexanet has not received regulatory approval

Outline and objectives

I. Laboratory Measurement	• List some potential indications for DOAC measurement • Name the best tests for measurement of the DOACs
II. Reversal	• Describe strategies for reversal in patients taking DOACs

Laboratory ~~Monitoring~~ Measurement

Case (1)

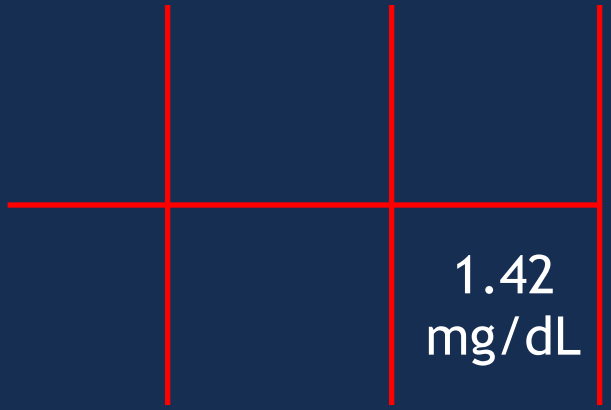
A 71-year old man is brought to the emergency department of the local hospital by his wife at 22:00 on Saturday night with headache, fever, and mental status changes. He has nuchal rigidity on exam.

Past Medical History: Non-valvular atrial fibrillation, Hypertension, Dyslipidemia, Stroke 1 year ago

Medications: Hydrochlorothiazide 25 mg daily, Atorvastatin 20 mg daily, Apixaban 5 mg twice daily

The patient and his wife are not able to report when he last took apixaban.

Case (2)



Prothrombin Time	12.9 s	(10.8-12.9)
International Normalized Ratio	1.1	
Activated Partial Thromboplastin Time	31.6 s	(21.6-32.5)
Anti-Xa apixaban level		Not available locally

Head CT scan: No acute abnormality

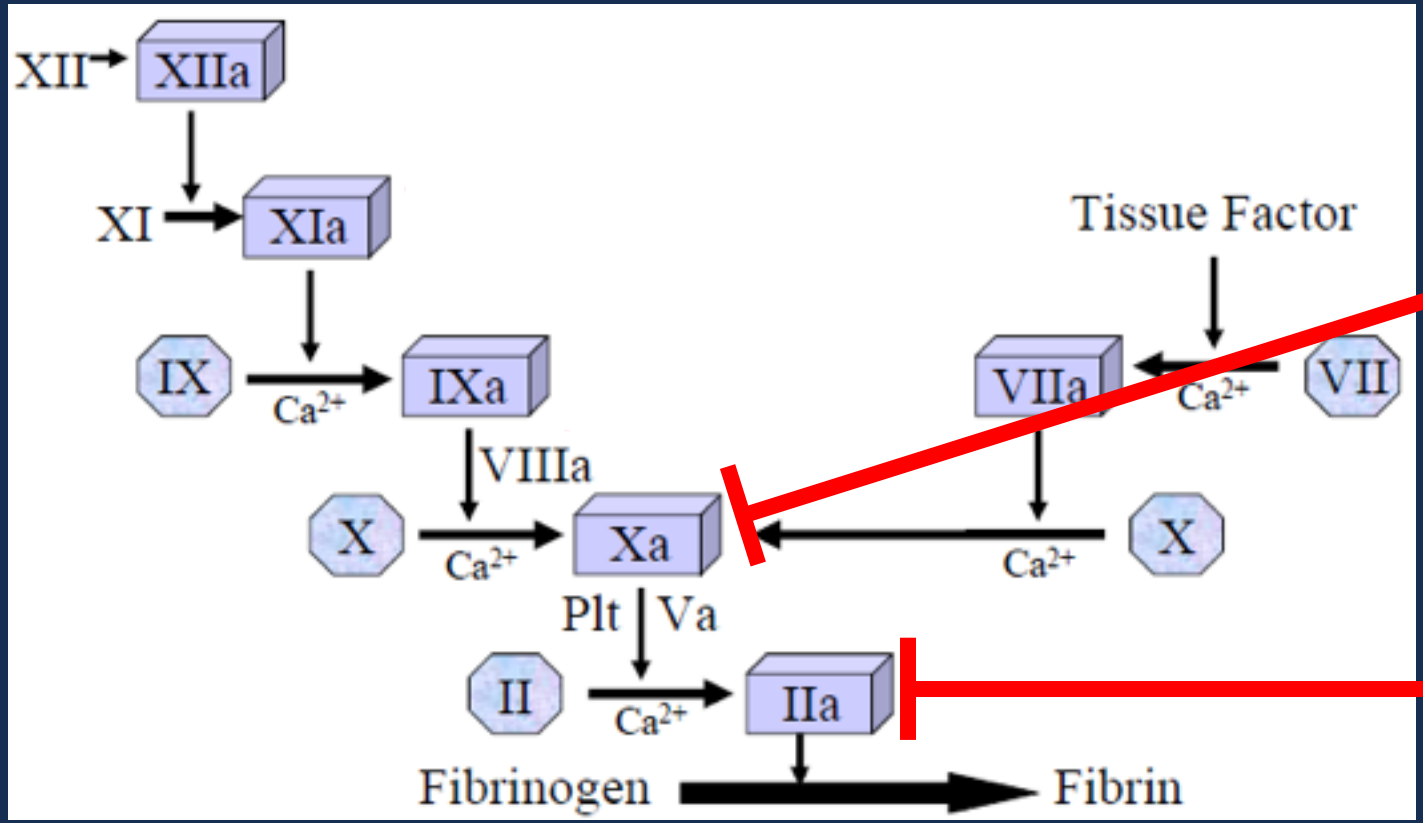
Case (3)

Infectious meningitis is suspected. The patient is initiated on empiric antibiotics. His condition deteriorates over the next 2 hours despite antibiotics. The infectious disease service recommends an urgent lumbar puncture.

What do you recommend?

a) PT and APTT are normal. Patient is cleared for lumbar puncture without anticoagulant reversal.
b) Treat patient empirically with a reversal agent, then perform procedure.

DOACs



Rivaroxaban
Apixaban
Edoxaban
Betrixaban

Dabigatran

Pharmacology

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	FXa	FXa	FXa
Peak activity	1-3 hr	2-3 hr	3-4 hr	1-2 hr
Half-life	12-14 hr	7-11 hr	12 hr	8-10 hr
Protein binding	35%	92-95%	84%	55%
Renal clearance	80%	36%	25%	35%
FDA-approved indications	NVAF, VTE, TKA/THA	NVAF, VTE, TKA/THA	NVAF, VTE, TKA/THA	NVAF, VTE

Eikelboom JW et al., Circulation 2010;121:1523; Samama MM et al., Clin Lab Med 2014;34:503

Reference standard

Liquid chromatography/tandem mass spectrometry

Plasma drug levels

Drug	Dose	Trough plasma level (ng/mL)		Peak plasma level (ng/mL)	
		Median	5th-95th percentile	Median	5th-95th percentile
Dabigatran	150 mg BID	90	31-225	184	64-443
Rivaroxaban	20 mg daily	26	6-87	270	189-419
Apixaban	5 mg BID	103	41-230	171	91-321
Edoxaban	60 mg daily	22	10-40[a]	170	120-250[a]

[a]Interquartile range

Ezekowitz MD et al., Am J Cardiol 2007;100:1419; Mueck W et al., Clin Pharmacokinet 2014;53:1;
Kowalski et al., J Pharmacokinet Pharmacodyn 2014;41(Supp 1):S19; Weitz JI et al., Thromb Haemost 2010;104:633

Variability in trough levels

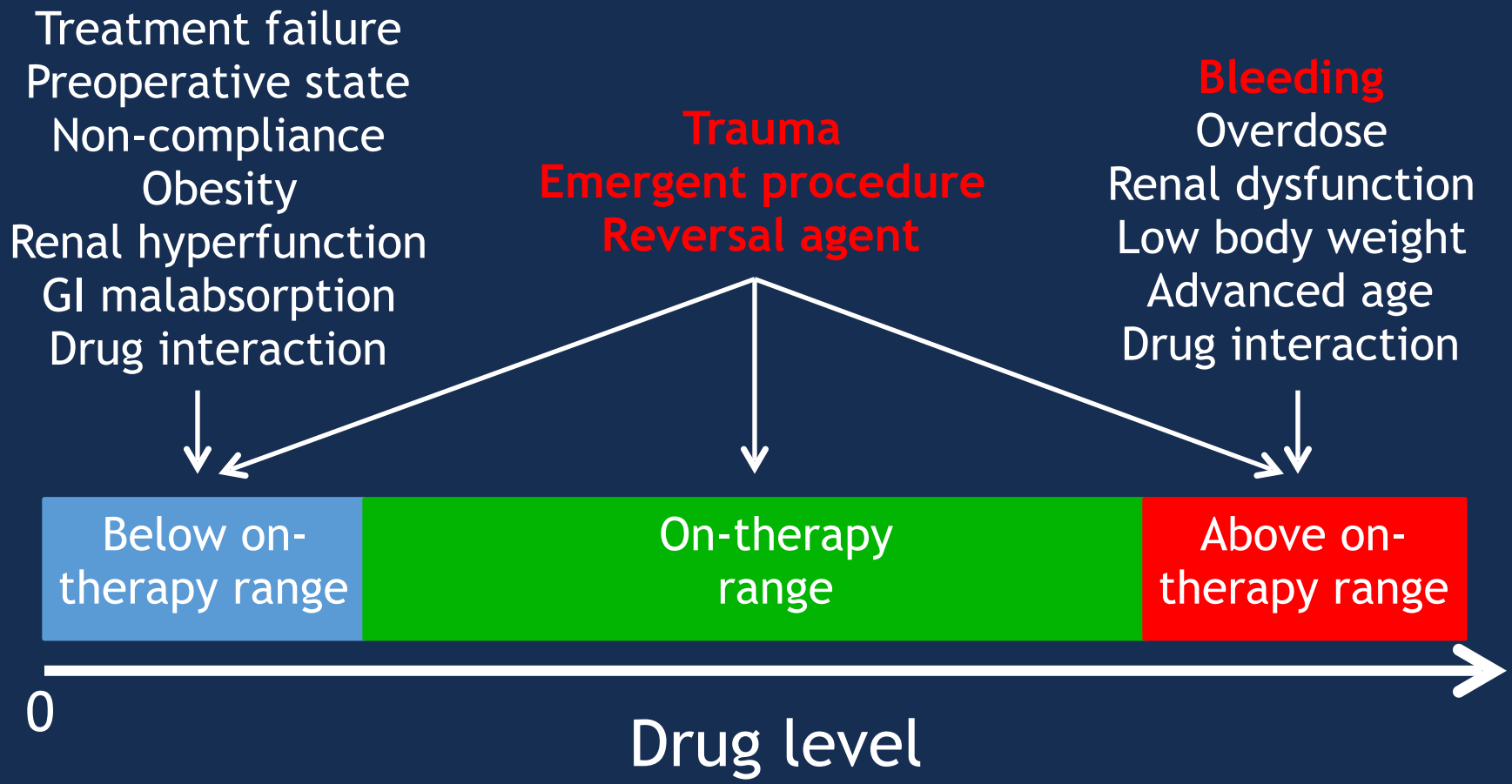
US adult male height:
5th percentile: 163 cm
95th percentile: 191 cm

If variation in height was equivalent to variation in rivaroxaban trough levels

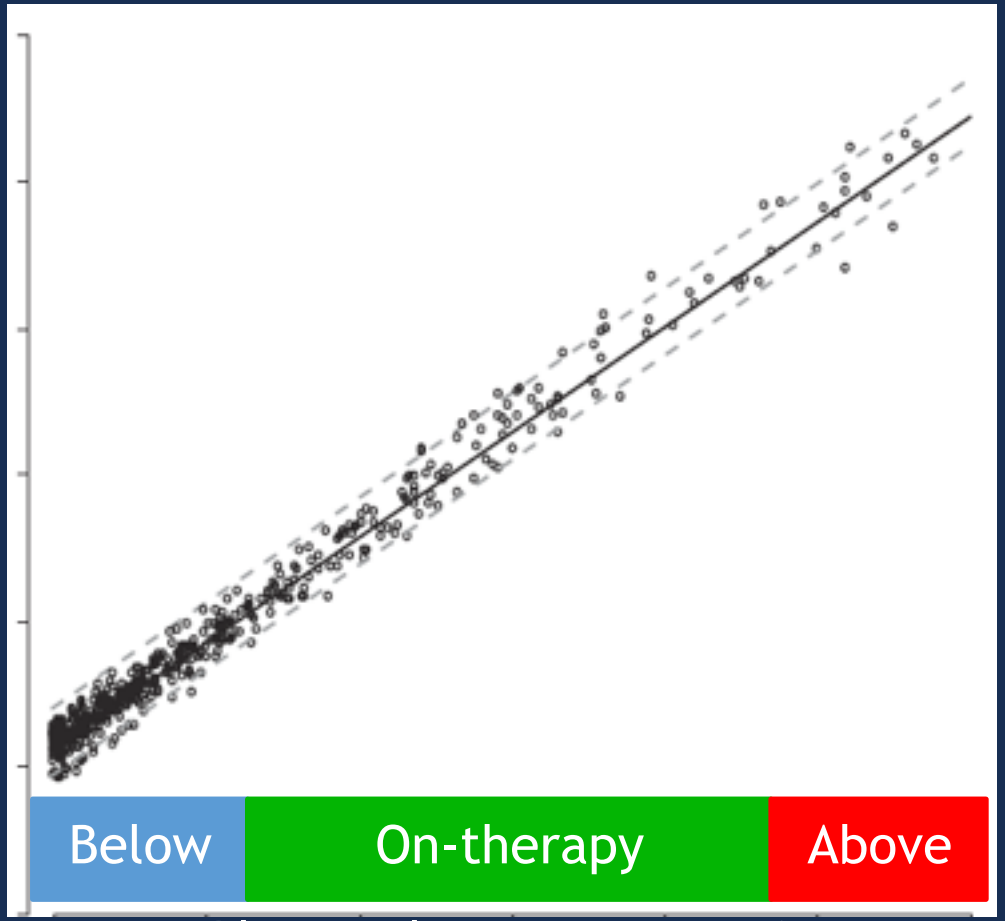
U.S. Census Bureau, Statistical Abstract of the United States: 2012

~~Therapeutic~~ On-therapy range

Why measure?


Treatment failure
Preoperative state
Non-compliance
Obesity
Renal hyperfunction
GI malabsorption
Drug interaction
Trauma
Emergent procedure
Reversal agent
Bleeding
Overdose
Renal dysfunction
Low body weight
Advanced age
Drug interaction
Below on-therapy range
On-therapy range
Above on-therapy range
0
Drug level

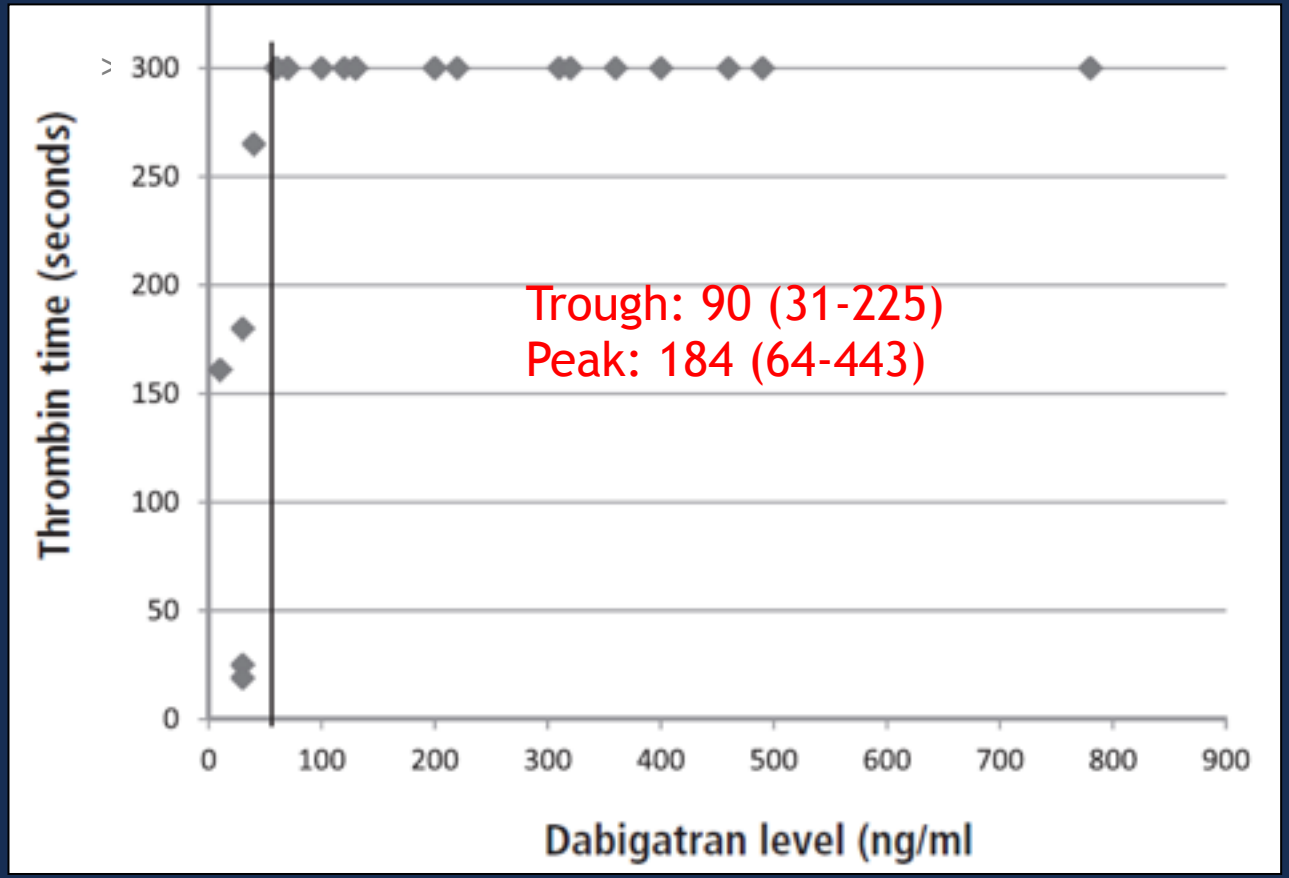
Attributes of an ideal assay



1. Linear correlation between assay result and drug levels
2. Across a broad range of drug levels
3. Sensitive
4. Specific
5. Available 24-7, short TAT

Dabigatran

Thrombin Time (TT)

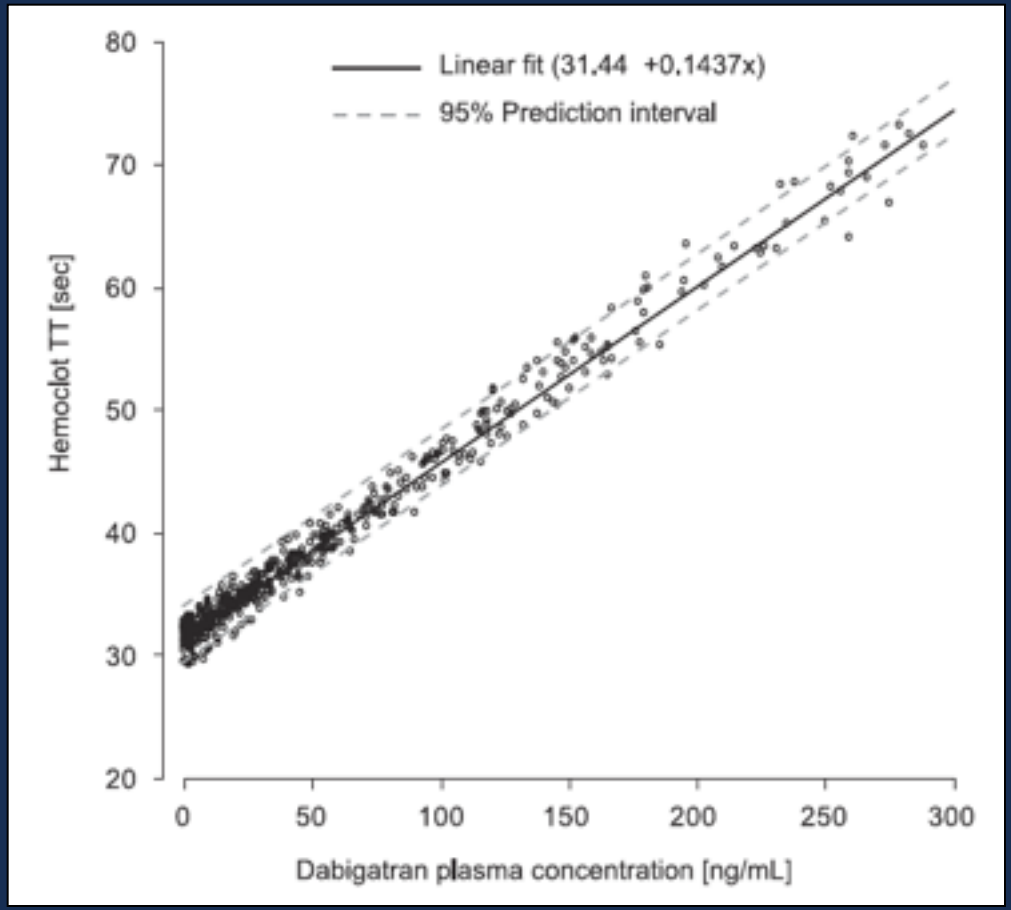


Problem: Too sensitive. Cannot be used to quantify drug.

Use: Normal TT excludes clinically significant drug levels

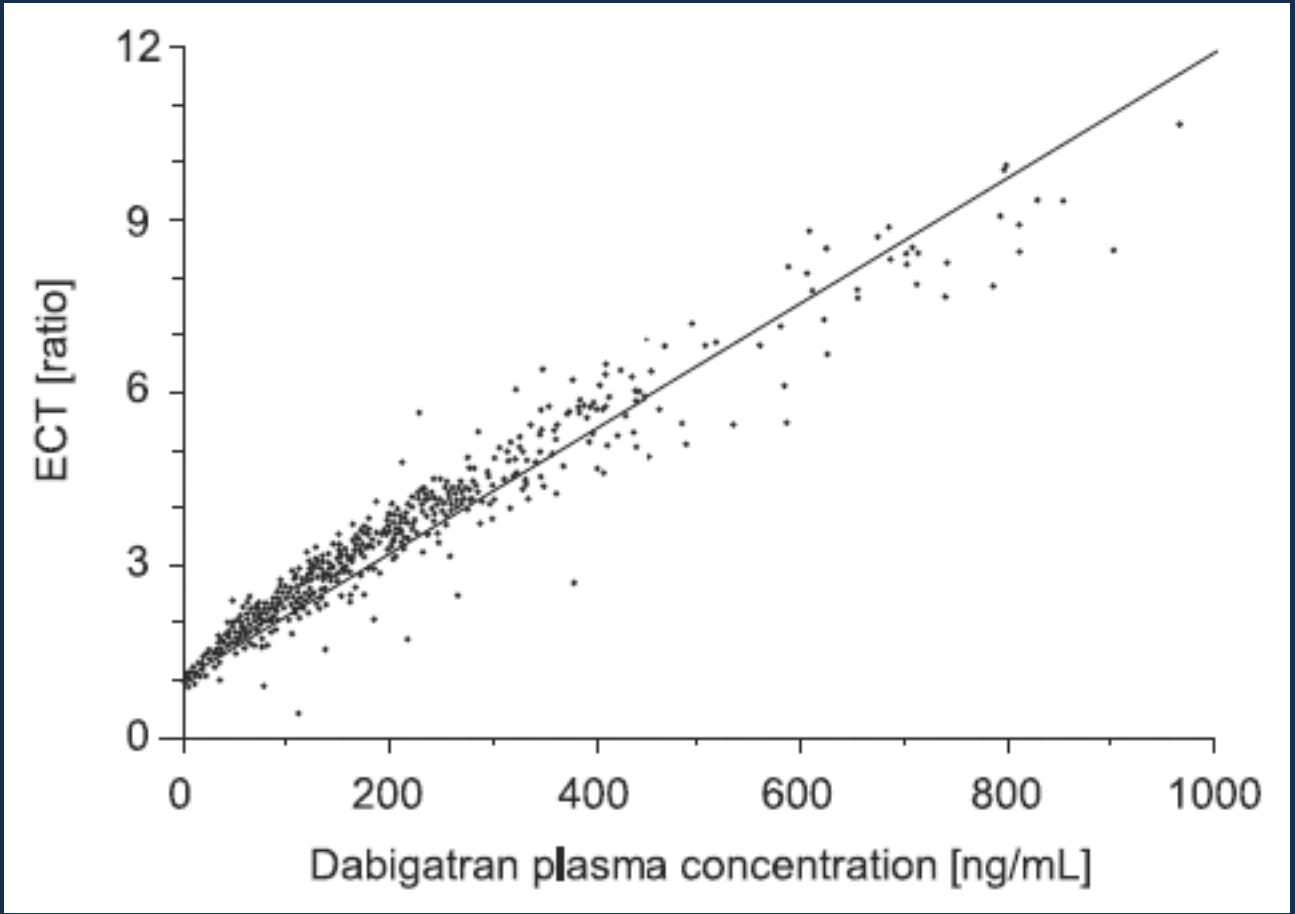
Hapgood et al., Thromb Haemost 2013;64:1128

Dilute Thrombin Time



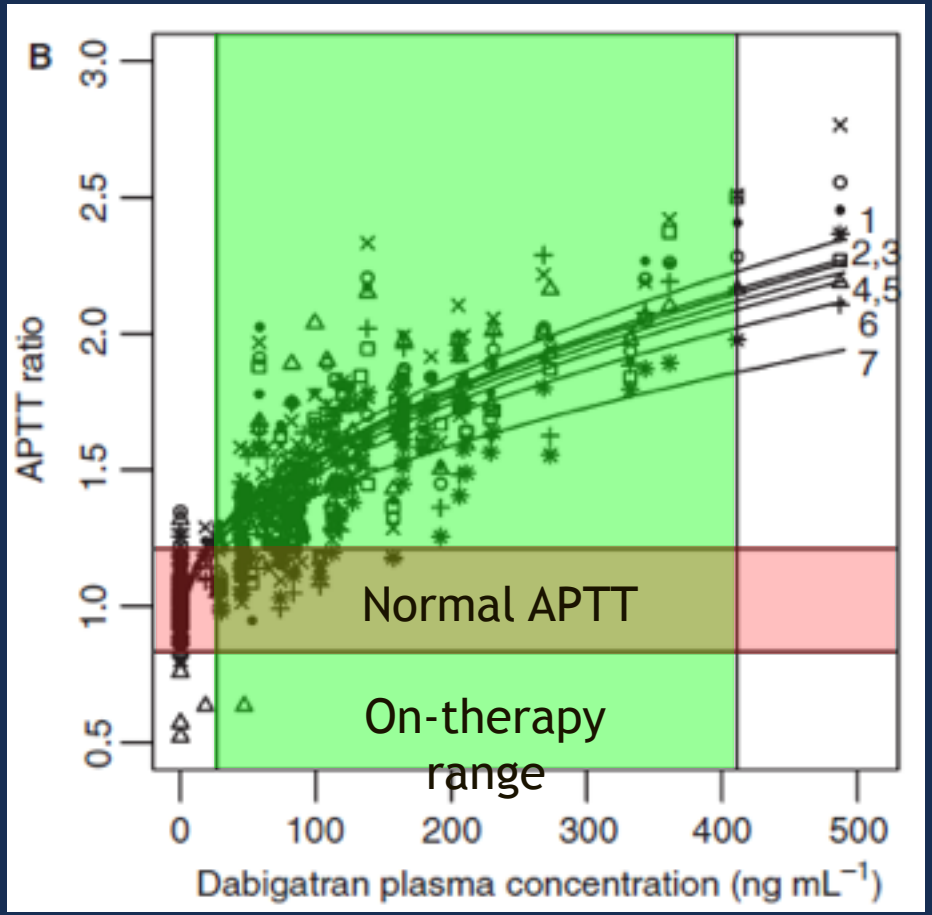
Cuker et al., J Am Coll Cardiol 2014;64:1128; van Ryn et al., Thromb Haemost 2010;103:1116

Ecarin-based assays



Cuker et al., J Am Coll Cardiol 2014;64:1128; van Ryn et al., Thromb Haemost 2010;103:1116

APTT



Peak and trough samples from patients taking dabigatran 150 mg BID (n=35)

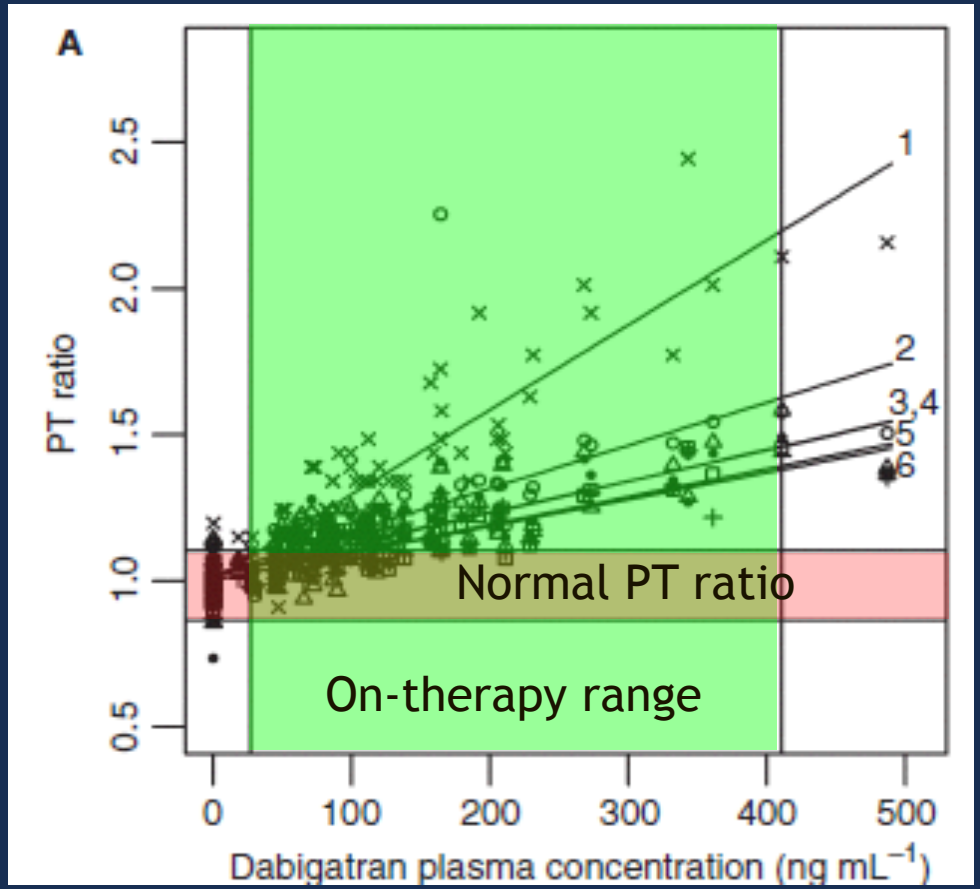
Curvilinear

18% of samples at trough had a normal APTT

Normal APTT does not necessarily rule out on-therapy levels

Hawes et al., J Thromb Haemost 2013;11:1493

PT/INR



Peak and trough samples from patients taking dabigatran 150 mg BID (n=35)

Differential sensitivity of reagents

29% of samples at trough had a normal PT

Normal PT does not rule out on-therapy levels

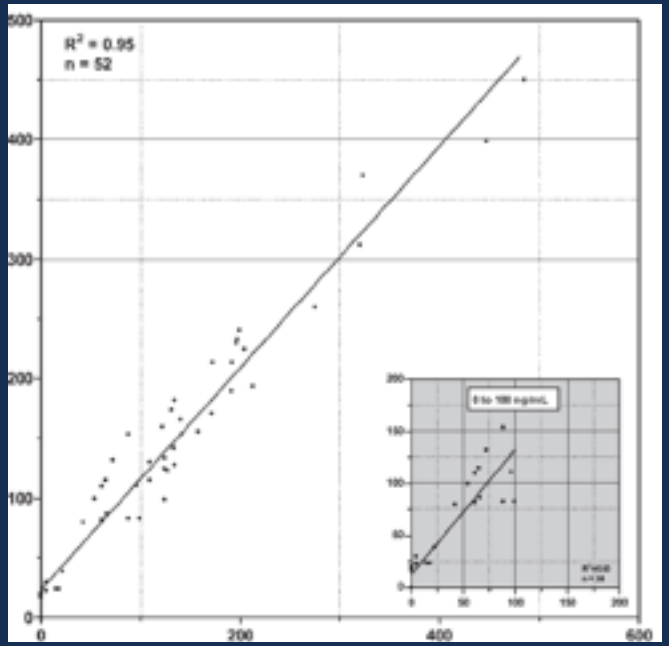
Hawes et al., J Thromb Haemost 2013;11:1493

Factor Xa inhibitors

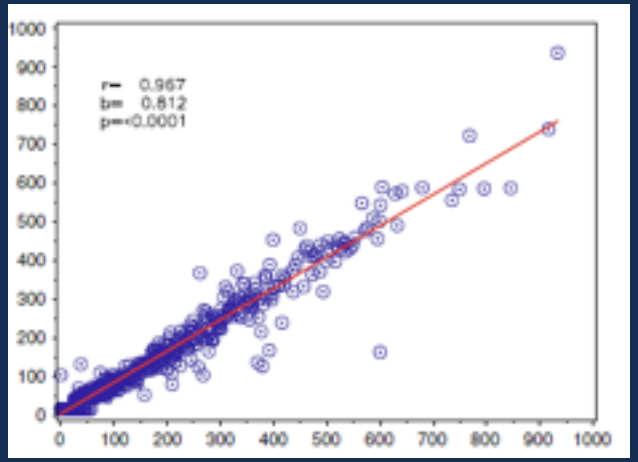
(apixaban, edoxaban, rivaroxaban)

Calibrated Anti-Xa activity

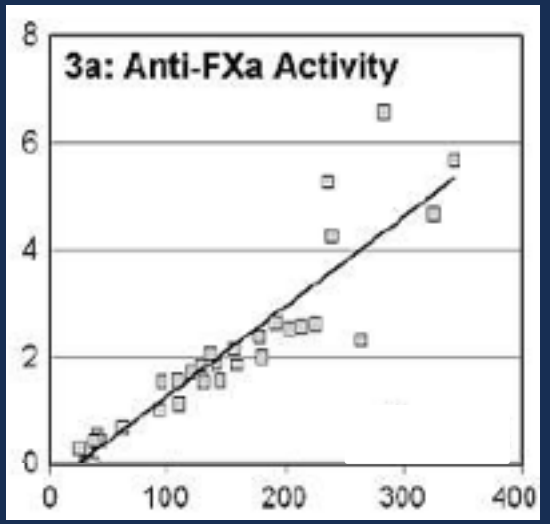
Rivaroxaban



Apixaban

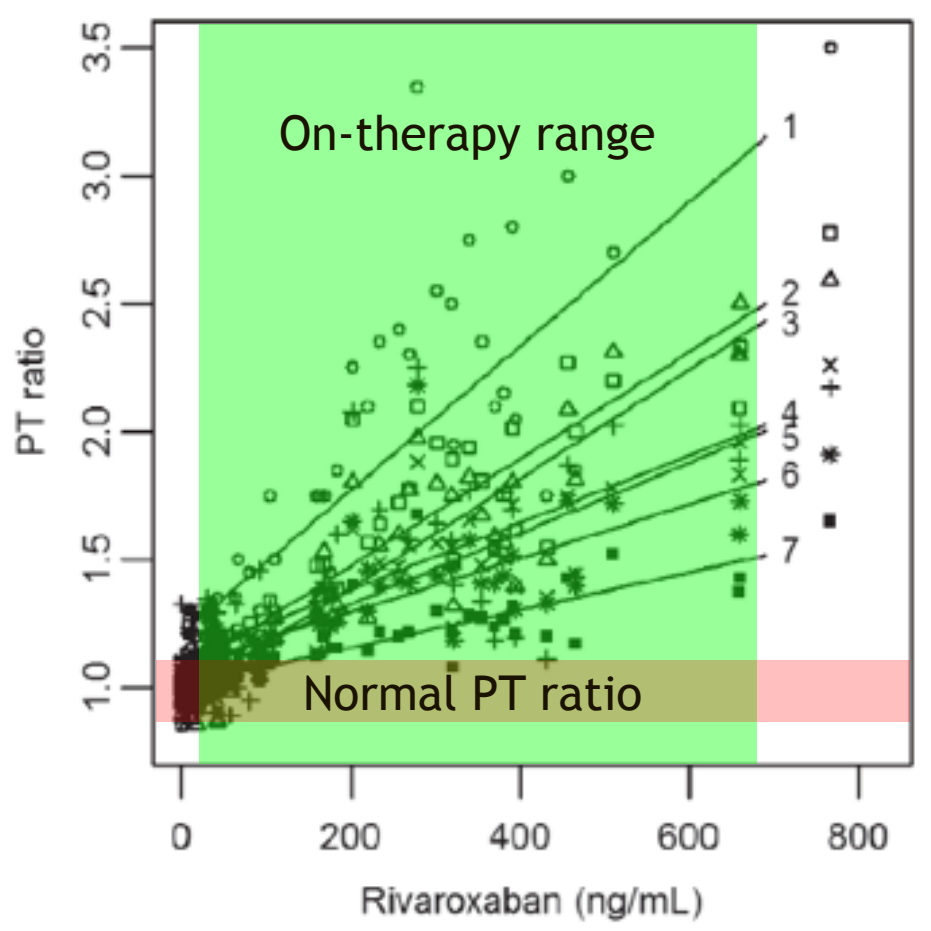


Edoxaban



Cuker et al., J Am Coll Cardiol 2014;64:1128; Cuker et al., J Thromb Thrombolysis 2015;39:288
Douxfils et al., Thromb Haemost 2013;110:723; Becker et al., J Thromb Thrombolysis 2011;32:183;
Zafar et al., Thromb Haemost 2007;98:883

Rivaroxaban: PT/INR



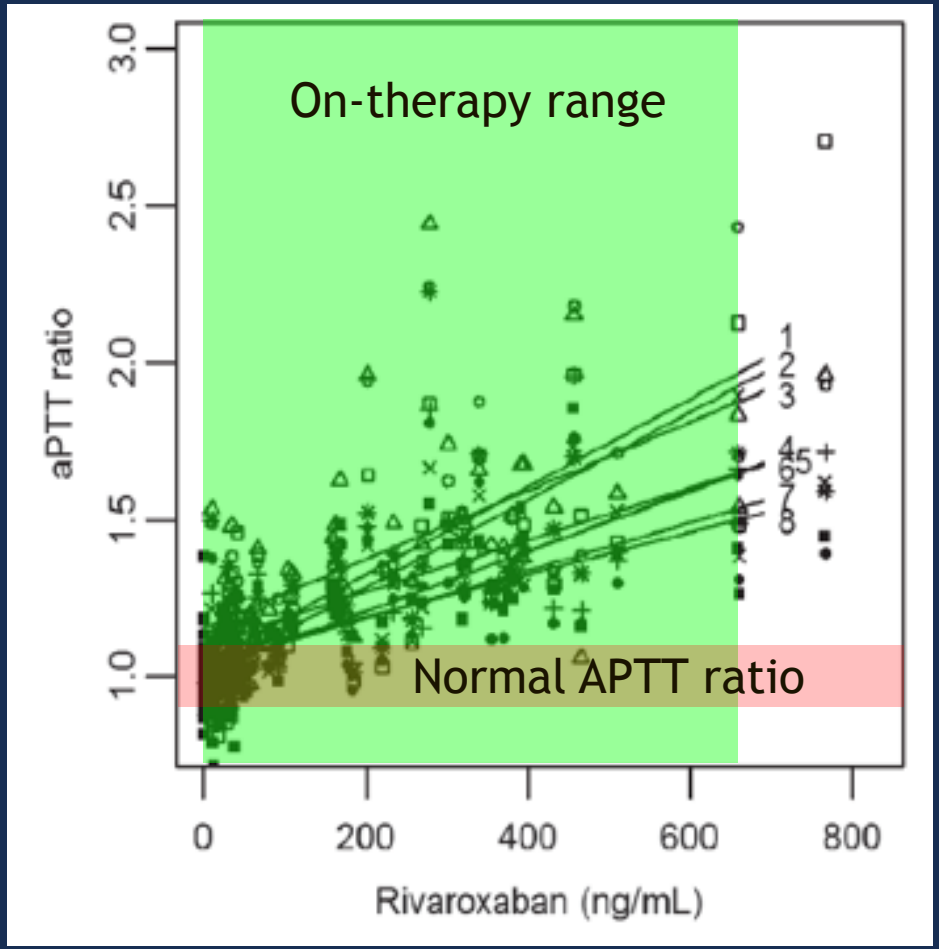
Peak and trough samples from patients taking rixaroxaban 20 mg QD (n=29)

19-93% of samples at trough had a normal PT depending on the reagent

Normal PT/INR does not rule out on-therapy levels

Francart et al., Thromb Haemost 2014;111:1133

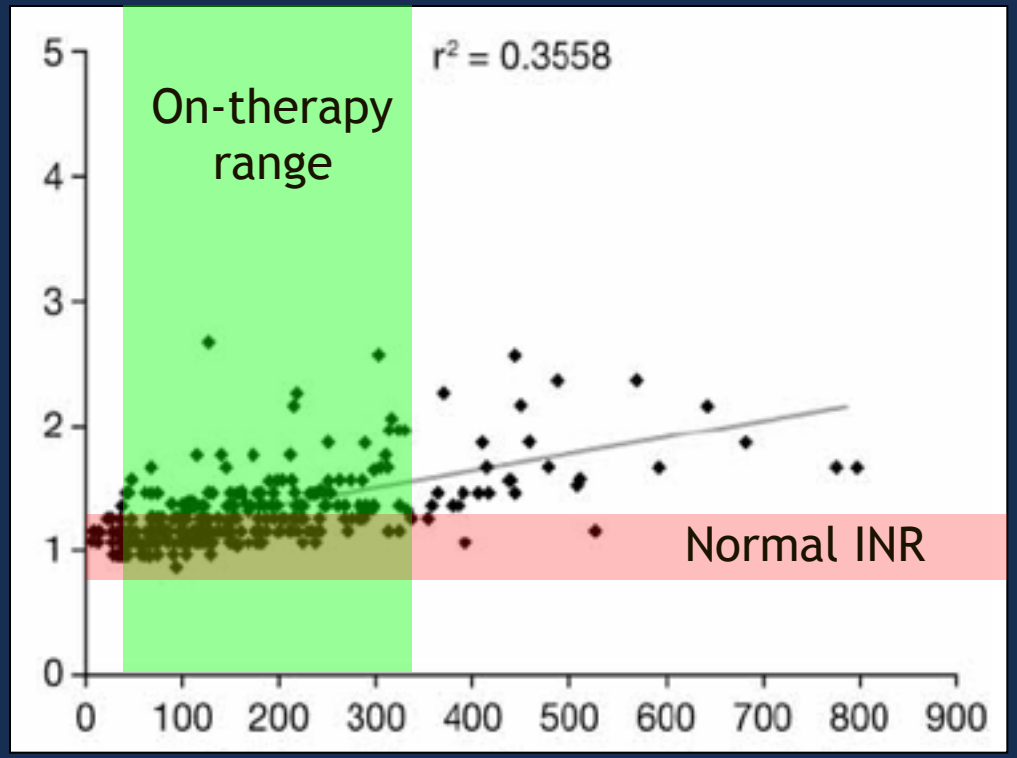
Rivaroxaban: APTT



- Peak and trough samples from patients taking rivaroxaban 20 mg QD (n=29)
- 56-89% of samples at trough had a normal APTT depending on the reagent
- Normal APTT does not rule out on-therapy levels

Francart et al., Thromb Haemost 2014;111:1133

Apixaban: PT/INR



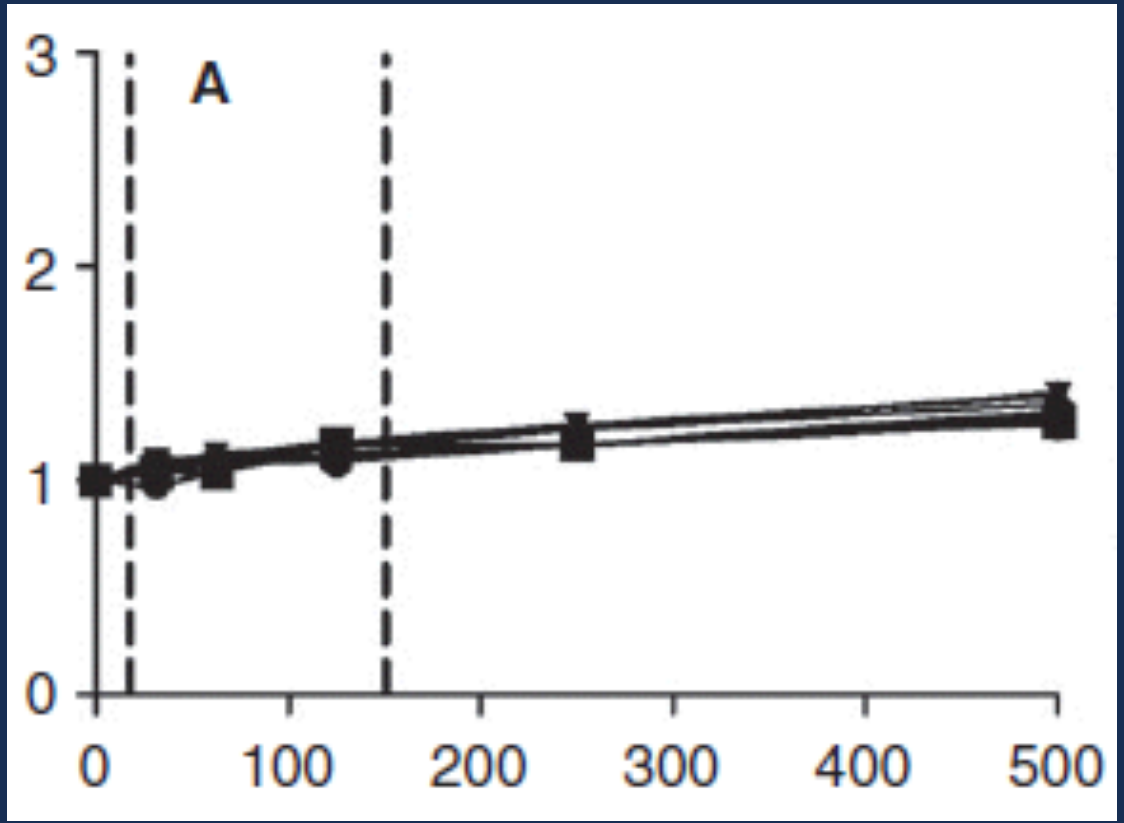
Trough: 103 (41-230)
Peak: 171 (91-321)

A normal PT does not exclude on-therapy levels of apixaban

A normal PT may not exclude above on-therapy levels of apixaban

Barrett et al., Thromb Haemost 2010;104:1263

Apixaban: APTT



Trough: 103 (41-230)
Peak: 171 (91-321)

Dale et al., J Thromb Haemost 2014;12:1810

My recommendations for laboratory assessment of DOACs

Choice of assay depends on:

1. Which DOAC the patient is on
2. Which assays are available
3. Goal of assessment
   - -Measure drug level
   - -Exclude “clinically relevant” drug level

If the goal is to measure DOAC levels…

Drug	Assay
Dabigatran	Dilute thrombin time Ecarin clotting time Ecarin chromogenic assay Chromogenic anti-IIa assay* Dilute Russell Viper venom time*
Factor Xa inhibitors	Calibrated anti-Xa

If the goal is to exclude clinically relevant DOAC level and a specialized assay is not available…

Drug	Assay
Dabigatran	Thrombin time ? APTT
Factor Xa inhibitors	UFH or LMWH anti-Xa ? PT (rivaroxaban and edoxaban only)

Back to the case…

Infectious meningitis is suspected. The patient is initiated on empiric antibiotics. His condition deteriorates over the next 2 hours despite antibiotics. The infectious disease service recommends an urgent lumbar puncture.

What do you recommend?

a) PT and APTT are normal. Patient is cleared for lumbar puncture without anticoagulant reversal.

b) Treat patient empirically with a reversal agent, then perform procedure.

Back to the case…

You decide to treat the patient with a reversal agent. Which reversal agent do you recommend?

a) Idarucizumab
b) Recombinant FVIIa
c) Prothrombin complex concentrate
d) Andexanet alfa

Reversal

Potential reversal strategies

For serious bleeding: Maximal supportive care (e.g. stopping DOAC, local hemostatic measures, volume resuscitation, transfusion support)

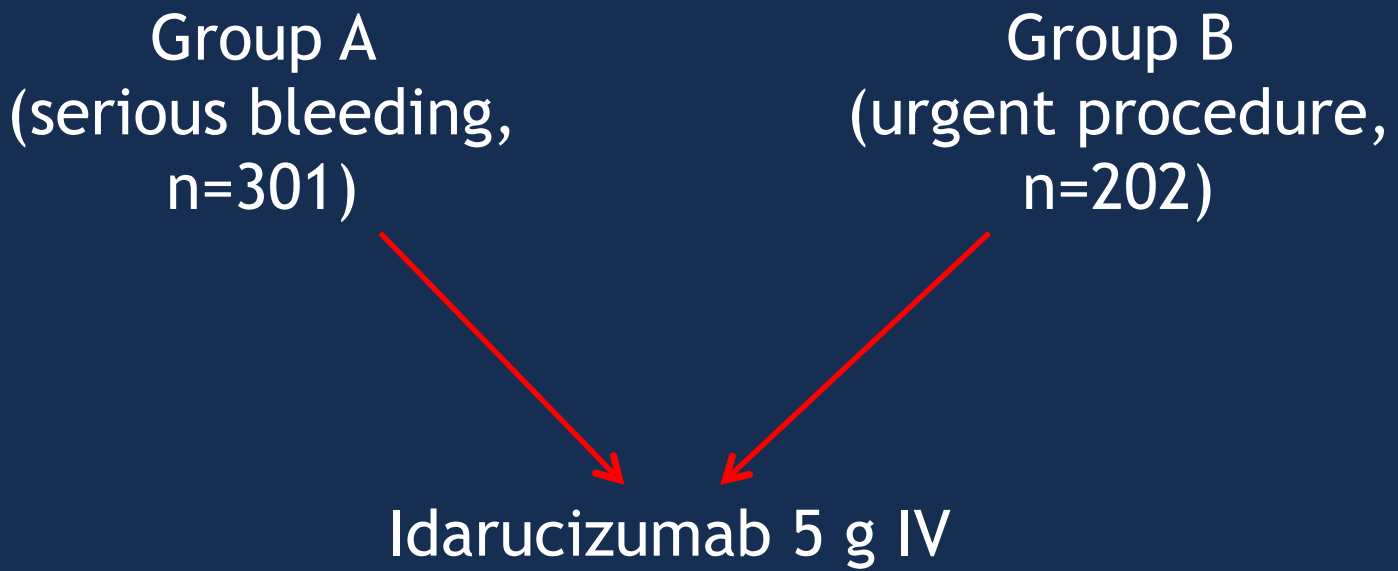
Strategy	Example
Removal	Activated charcoal Hemodialysis (dabigatran only)
Bypassing	Prothrombin complex concentrate (PCC) Activated PCC rFVIIa
Sequestration	Idarucizumab (dabigatran) Andexanet alfa (FXa inhibitors)

Idarucizumab (Praxbind ®)

- Monoclonal antibody fragment
- Dabigatran has 350-fold greater affinity for idarucizumab than thrombin
- EMA approval: November 2015 based on the REVERSE-AD study

Blood 2013;121:3554; Thromb Haemost 2015;113:943; Lancet 2015;386:680

REVERSE-AD Trial



Primary endpoint: Correction of coagulation assays

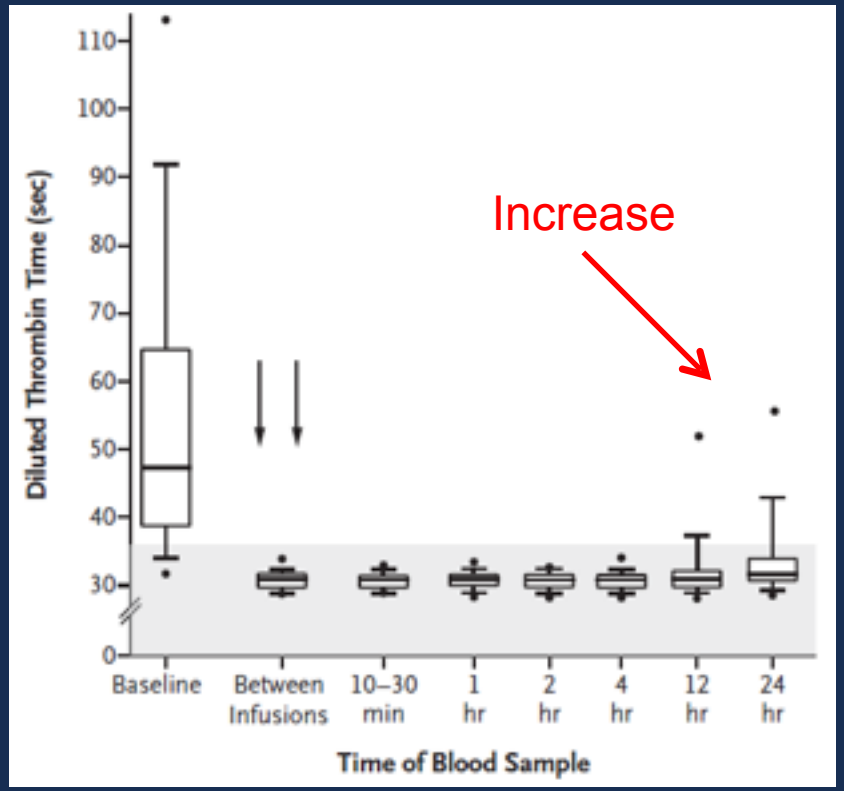
Pollack et al., N Engl J Med 2017;377:431

Patient characteristics

	Bleeding Group (n=301)	Procedure Group (n=202)	Overall (n=503)
Median age	79	77	78
NVAF (%)	96	94	95
Normal dTT (%)	19	25	21

Pollack et al., N Engl J Med 2017;377:431

Normalization of coagulation parameters

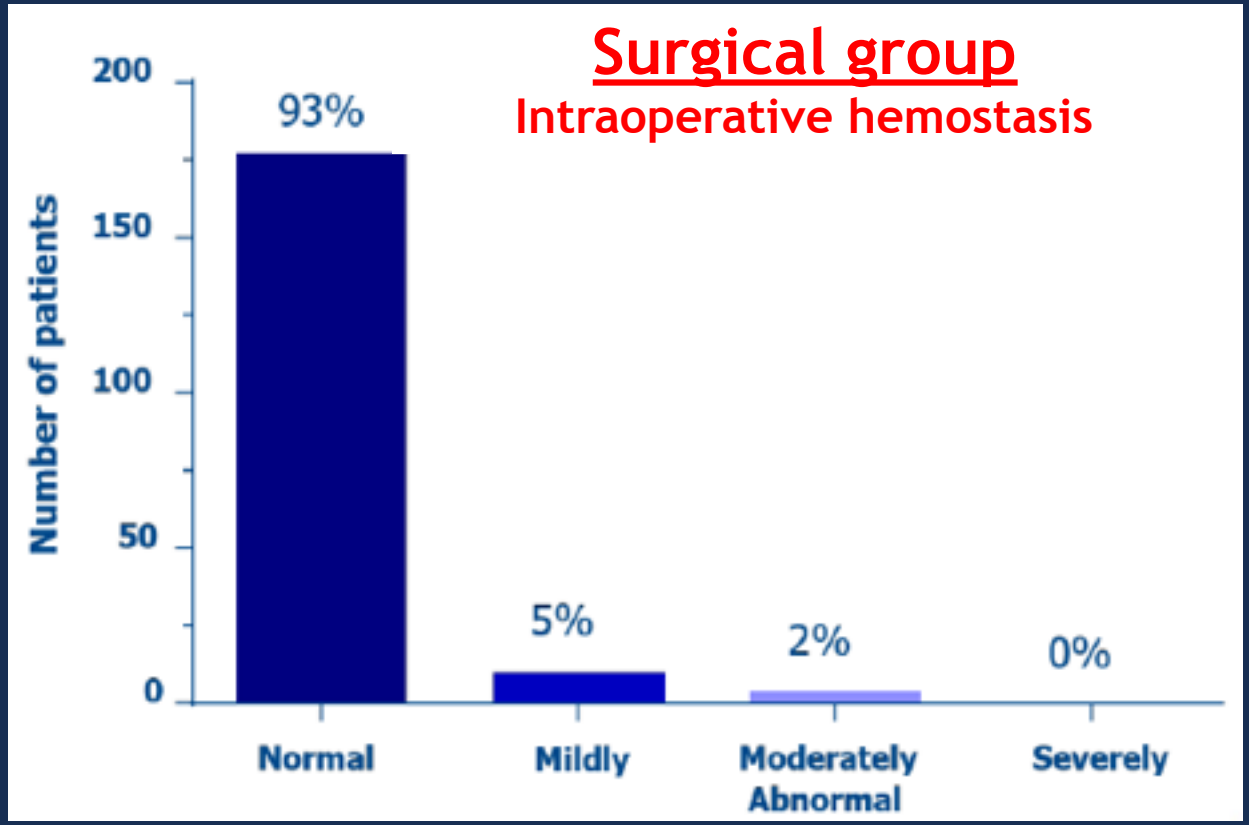


Pollack et al., N Engl J Med 2017;377:431

Clinical outcomes

Bleeding group

Median time to cessation of bleeding was 2.5 hrs



Pollack et al., N Engl J Med 2017;377:431

Safety

- Anti-idarucizumab antibodies (5.6%)
- Thromboembolic events occurred in 24 of 503 patients (4.8%) within 30 days
  - 6 MI, 7 CVA, 10 VTE, 1 systemic embolism
  - 15 (63%) occurred off antithrombotic therapy
  - 12 (50%) occurred within 5 days

Pollack et al., N Engl J Med 2017;377:431

Idarucizumab: conclusions & questions

Rapidly corrects coagulation tests in patients taking dabigatran

Appears to be safe and well-tolerated

How should patients be selected to receive idarucizumab (up to 21% had insignificant dabigatran levels at study entry)?

What is the significance of increased dabigatran levels at 12 and 24 hrs? Are these patients at risk for rebleeding? Should they be re-dosed?

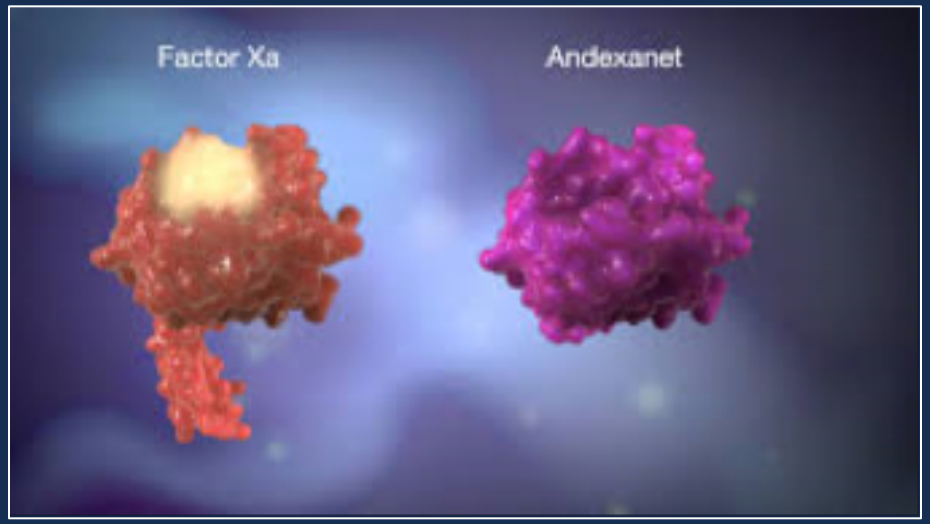
Andexanet alfa

Modified recombinant FXa

Lacks catalytic and membrane-binding activity

Retains the ability to bind FXa inhibitors

Not approved (PDUFA date 4 May 2018)



Lu et al., Nat Med 2013;19:446; Crowther et al., Circulation 2014;130:2116; Siegal et al., N Engl J Med 2015;373:2413

ANNEXA-4 Trial

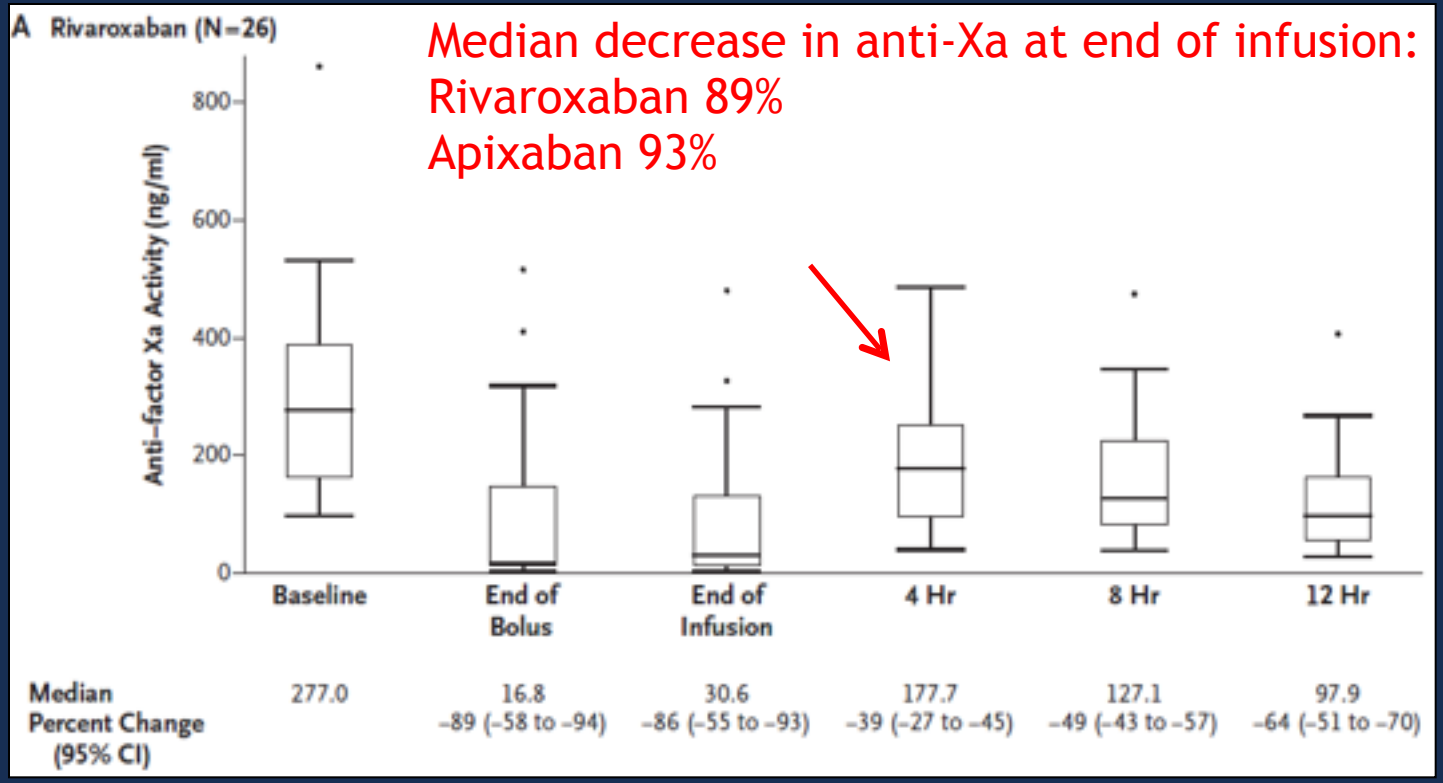
Acute major bleeding on
apixaban (n=31), edoxaban (n=0),
rivaroxaban (n=32), enoxaparin (n=4)

Andexanet bolus
f/b 2 hour infusion

1° Endpoints:
Reduction in anti-Xa activity
Hemostatic efficacy at 12 hours

Connolly SJ et al., N Engl J Med 2016; 375:1131

Efficacy

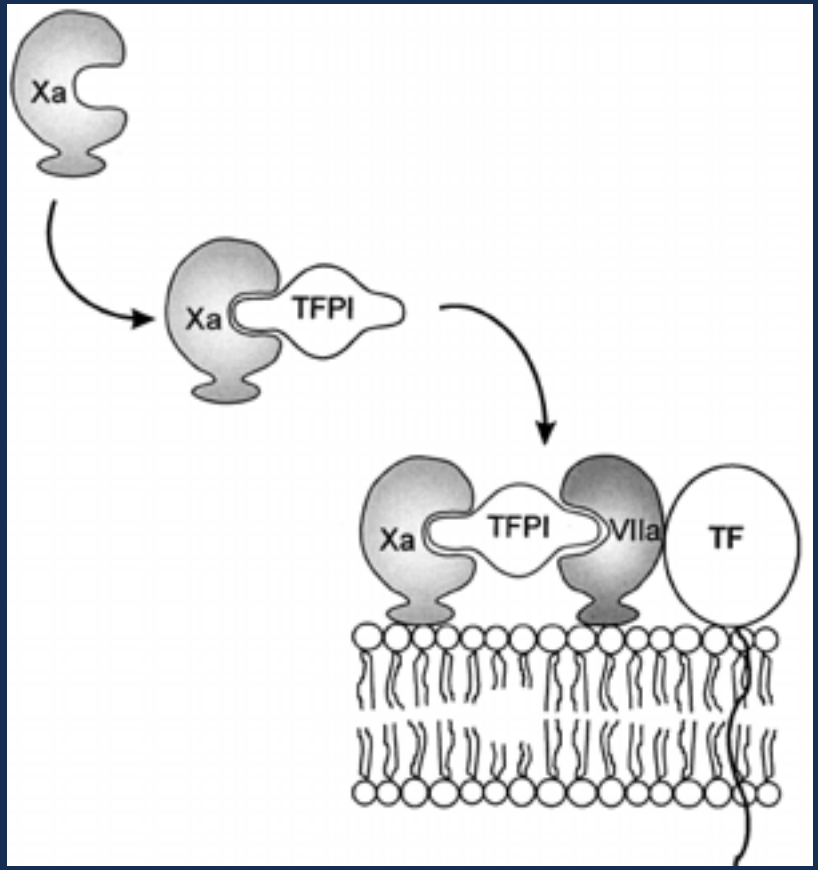


79% of subjects adjudicated as excellent or good hemostasis at 12 hrs

Connolly SJ et al., N Engl J Med 2016; 375:1131

Safety

- No infusion reactions or neutralizing antibodies
- 16 thrombotic events in 12 patients (17.9%) at 30 days
  - 1 MI, 6 CVA, 9 VTE
  - 14 occurred off AC
  - 4 occurred within 3 days of andexanet



Connolly SJ et al., N Engl J Med 2016; 375:1131

Andexanet: conclusions and questions

Rapidly corrects coagulation tests in patients taking FXa inhibitors

How long does the continuous infusion need to be given? Is 2 hours enough?

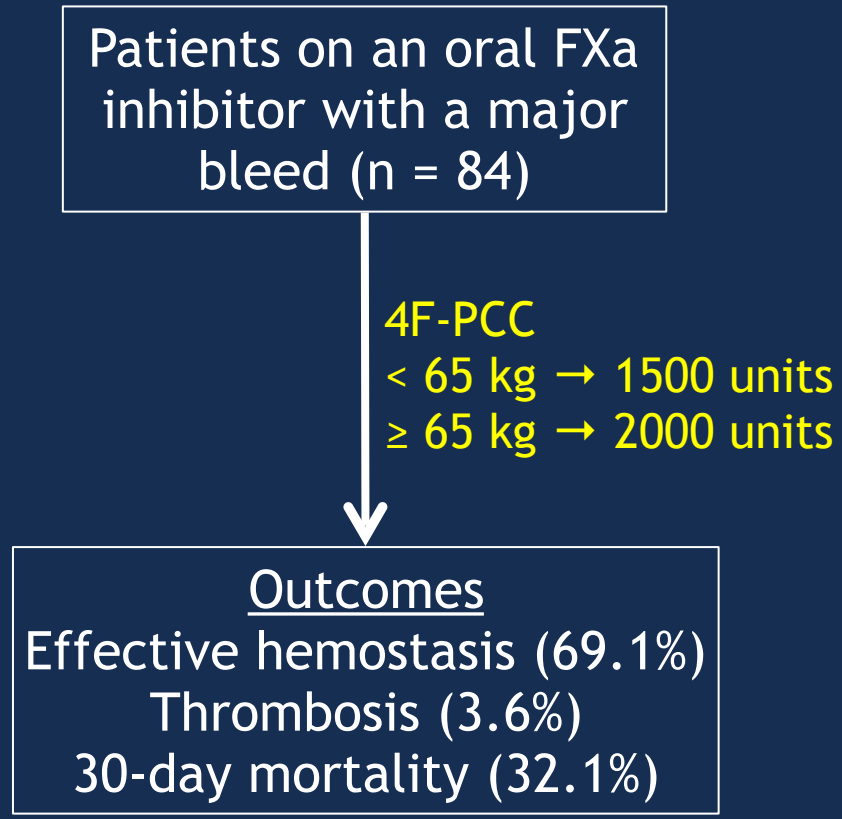
Does andexanet improve clinical outcomes in bleeding patients?

- Ongoing ANNEXA-4 phase 3b-4 study (target enrollment 350)

Is andexanet prothrombotic?

Will the manufacturer be able to make enough?

Prothrombin complex concentrate (PCC)

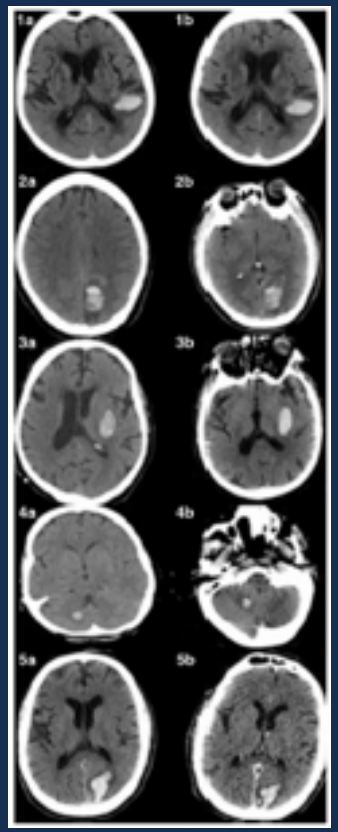


Majeed A et al., Blood 2017;130:1706

Activated PCC

Age	DOAC
49	Rivaroxaban
81	Rivaroxaban
81	Rivaroxaban
83	Apixaban
69	Dabigatran

B/L 6 hrs



No patients had ICH expansion

No thrombotic complications

Dibu et al., Neurocrit Care 2016;24:413

Back to the case…

You decide to treat the patient with a reversal agent. Which reversal agent do you recommend?

a) Idarucizumab
b) Recombinant FVIIa
c) Prothrombin complex concentrate
d) Andexanet alfa

Take-home points

- DOAC levels vary widely within and between patients.
- Laboratory measurement may be desirable in special circumstances.
- The best assays for quantification are not widely available.
- The most widely available assays (i.e. PT, APTT) are not suitable for quantitation and may have insufficient sensitivity to exclude clinically relevant DOAC levels.
- The dawn of specific reversal agents is upon us.
- These agents correct coagulation test abnormalities within minutes of infusion
- More data are needed to define their safety and efficacy

Kiitos