

Bleeding on DOACs and the Serenity Prayer

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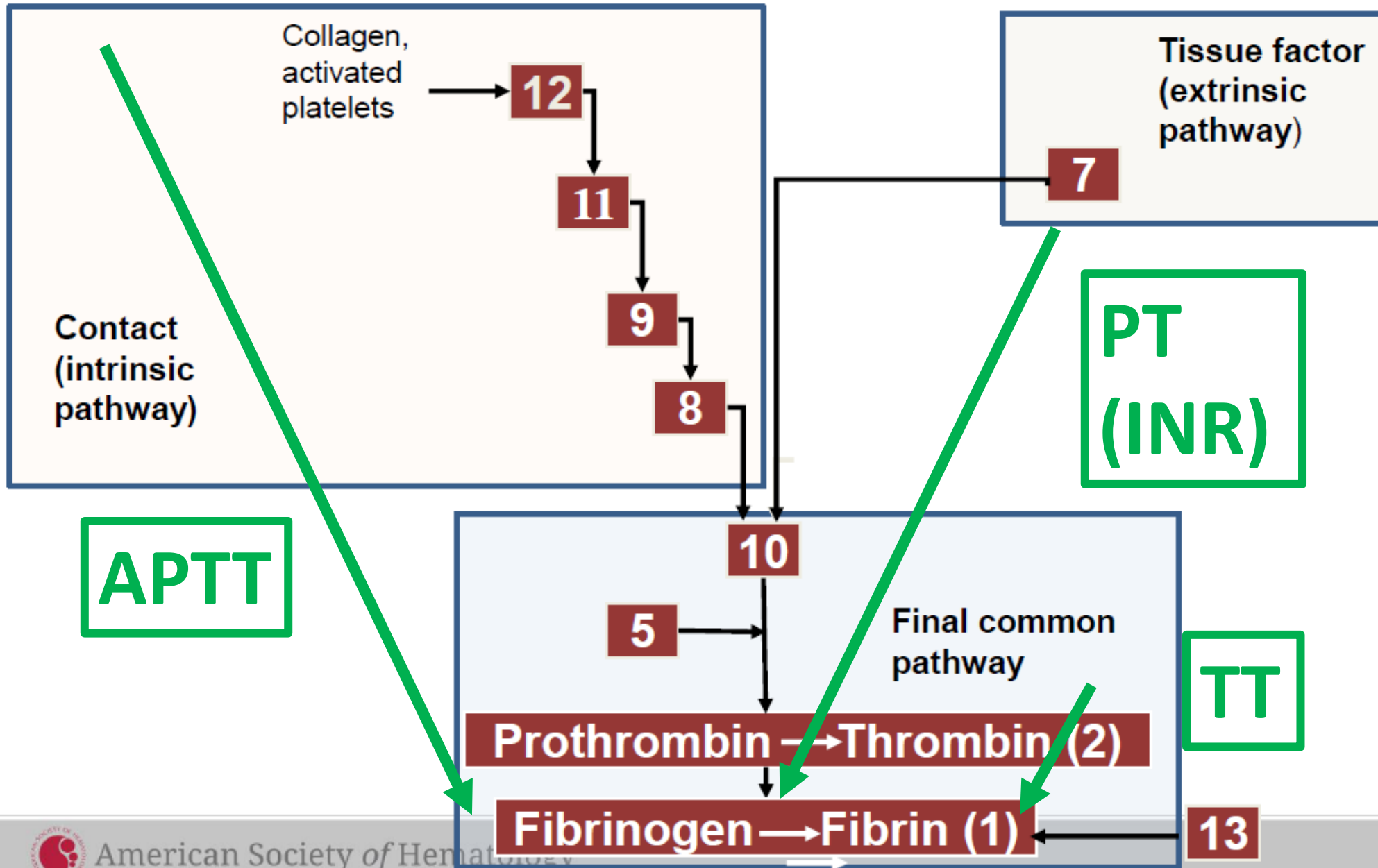
TRANSFUSION MEDICAL SPECIALIST

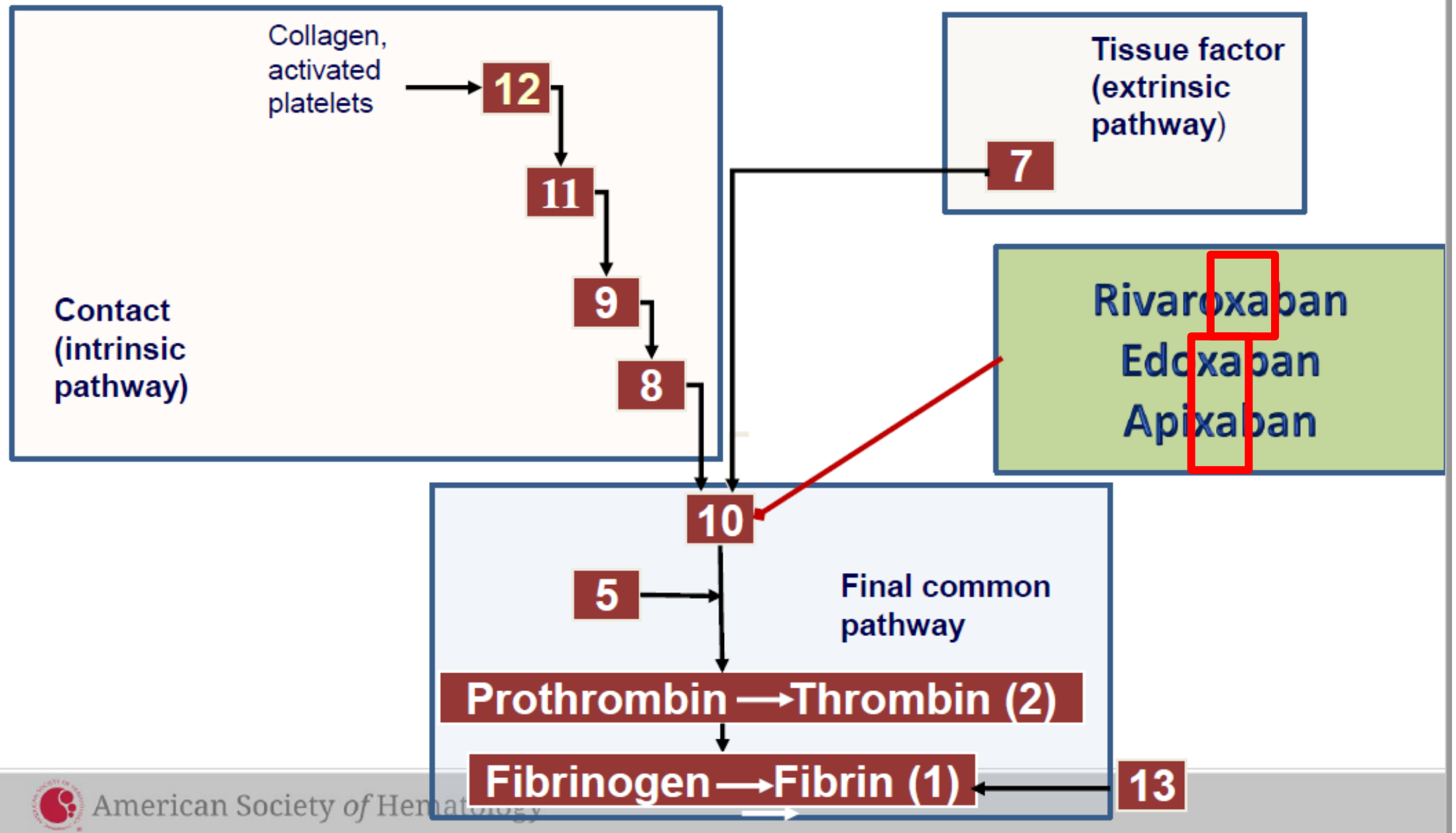


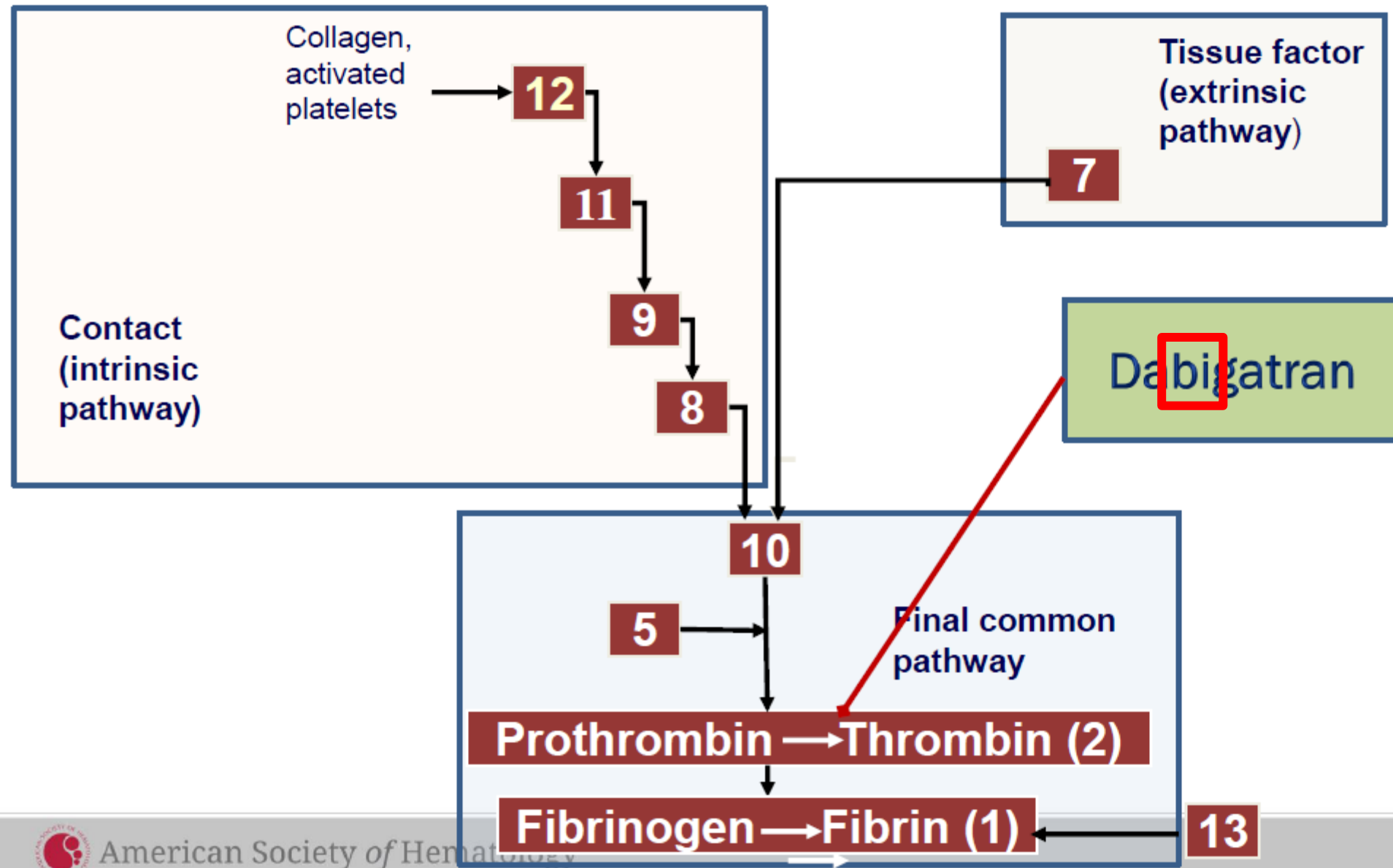
No disclosures

Outline

- Brief coagulation refresher
- Case 1: Dabigatran reversal
- Case 2: Rivaroxaban bleeding management
- The serenity prayer







Case 1:

70s woman

Presented with abdominal pain and vomiting, then PR bleeding

BP 80/40

Multiple IDC attempts with no urine output: bladder scan showed collapsed bladder

PMHx

1. Unprovoked PE 2012 – on Dabigatran
2. Rheumatoid arthritis- on methotrexate and hydrochloroquine
3. Cholecystectomy (laparoscopic)
4. Diverticulae – CT 2013
5. Shingles one month ago
6. Previous C-section
7. Hypertension

Case 1:

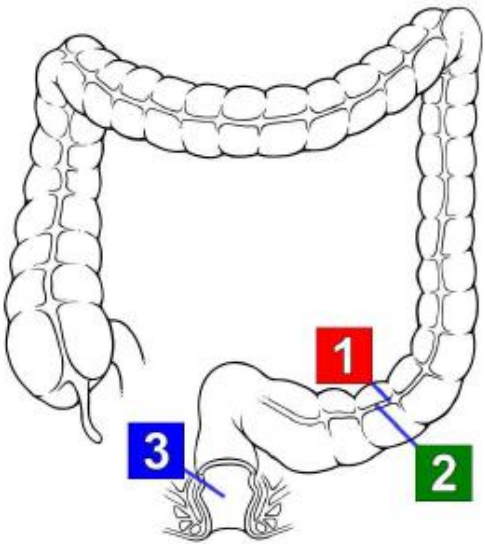
Admission bloods

- Hb 143
- Platelets 211
- Creatinine 122

Test Name	Result	Units	Ref. Range
Prothrombin Time	*> 100.0	seconds	10.0 - 13.0
INR	**> 10.0		0.8 - 1.2
A.P.T.T	**173	seconds	22 - 30
Thrombin Time:	*> 200.0	secs	< 21.0
Thrombin Time (protamine)	> 200	secs	
Fibrinogen	3.4	g/L	1.7 - 4.3

Case 1:

CT scan – possible ischaemic colitis



The Colon



1 Sigmoid Colon :
Abnormal mucosa



2 Sigmoid Colon : pale,
oedematous mucosa



3 Rectum: blood with
normal underlying
mucosa

Dabigatran (Pradaxa[®])

- Direct thrombin inhibitor (factor II)
- Oral
- Half life: 12-14 hours
- >80% renal excreted
- Lab test: Thrombin time (TT)
Dilute Thrombin Time (dTT)

Idarucizumab (Praxbind®)

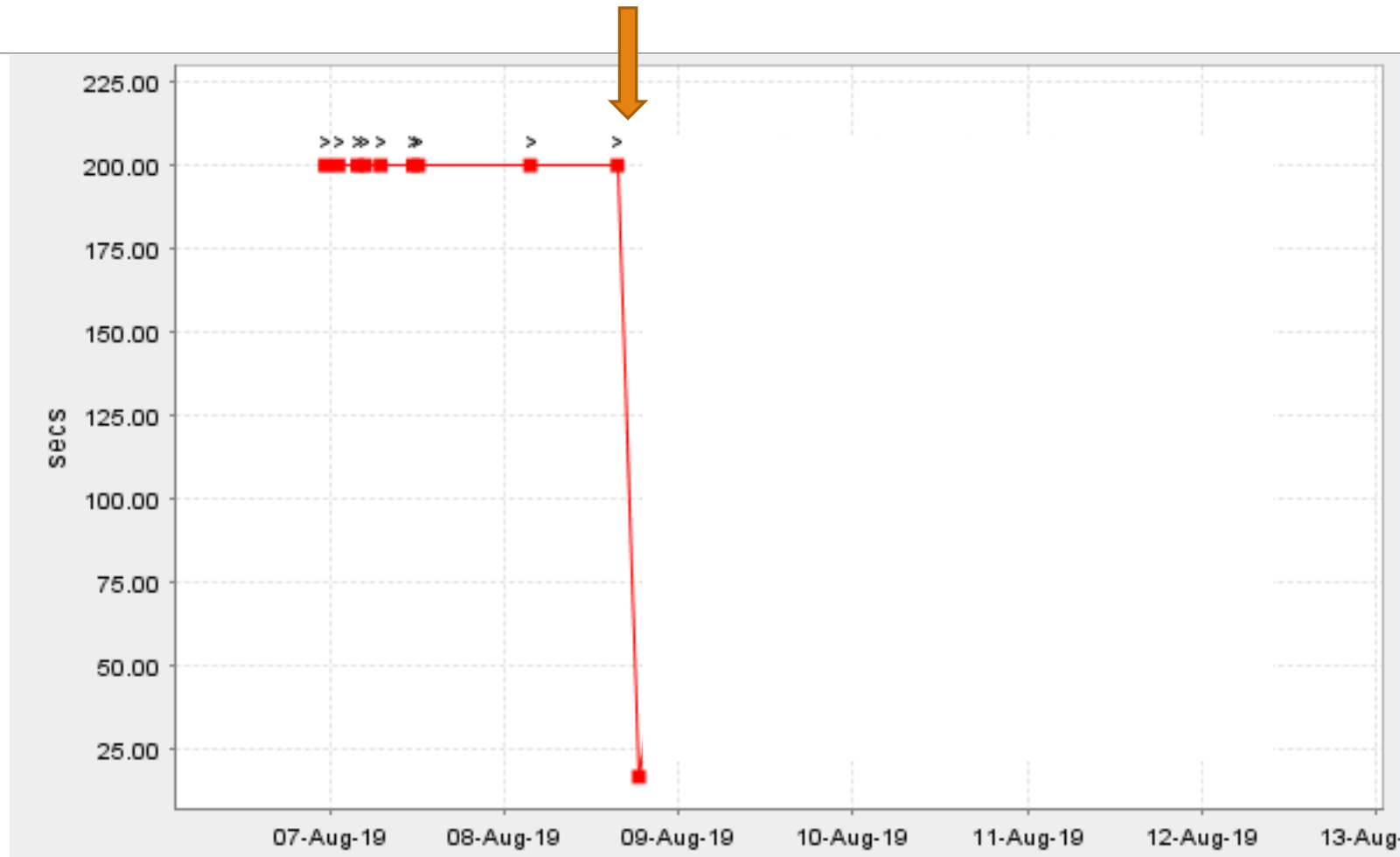
Humanised monoclonal antibody fragment

Binds Dabigatran with high affinity and specificity

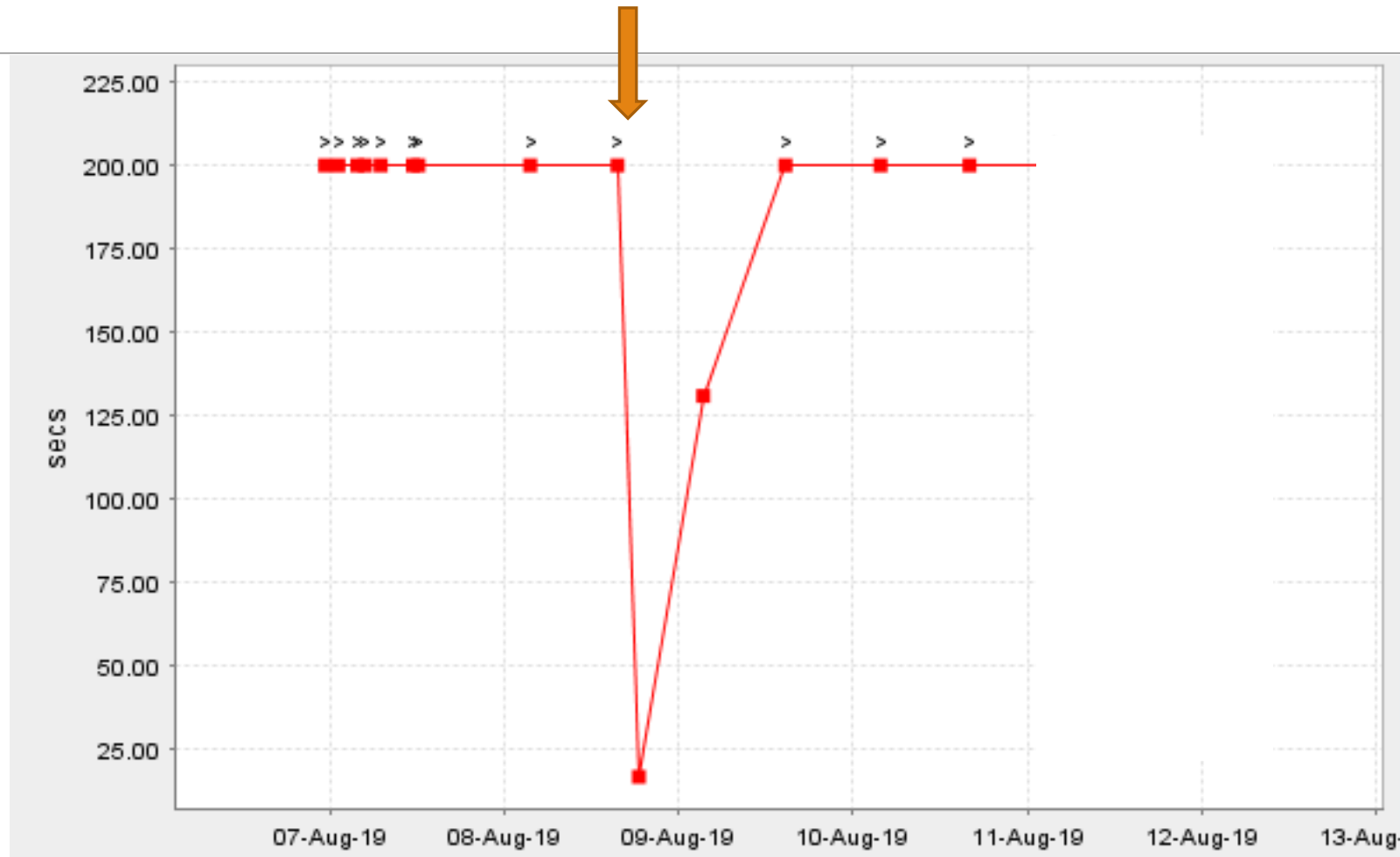
- Thrombin bound and free dabigatran
- >300x Stronger binding than Dabigatran to thrombin
- Clearance/Metabolism: not completely understood.
- No significant side effects
- Thrombotic risk from lack of anticoagulation



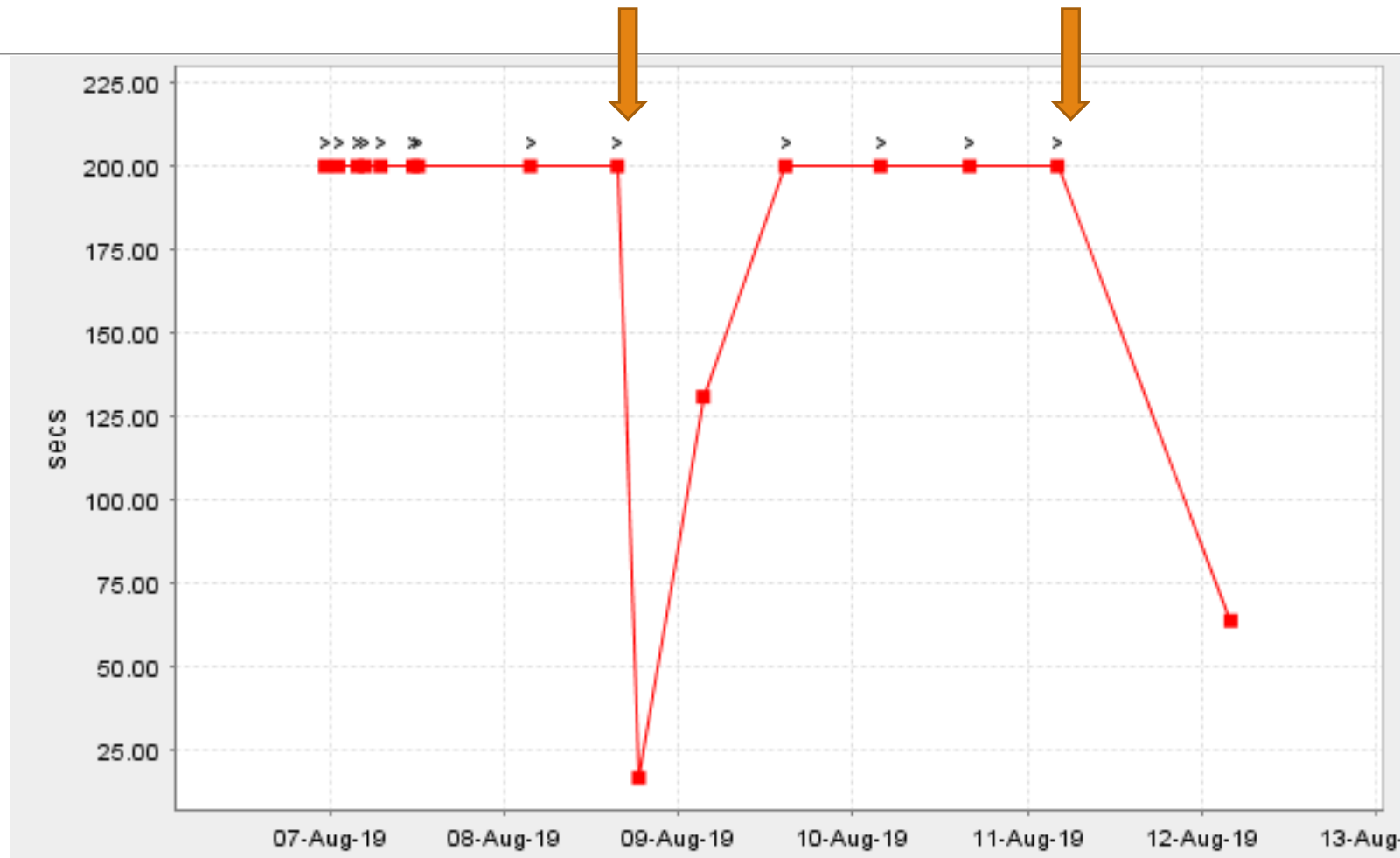
Thrombin time following Idarucizumab



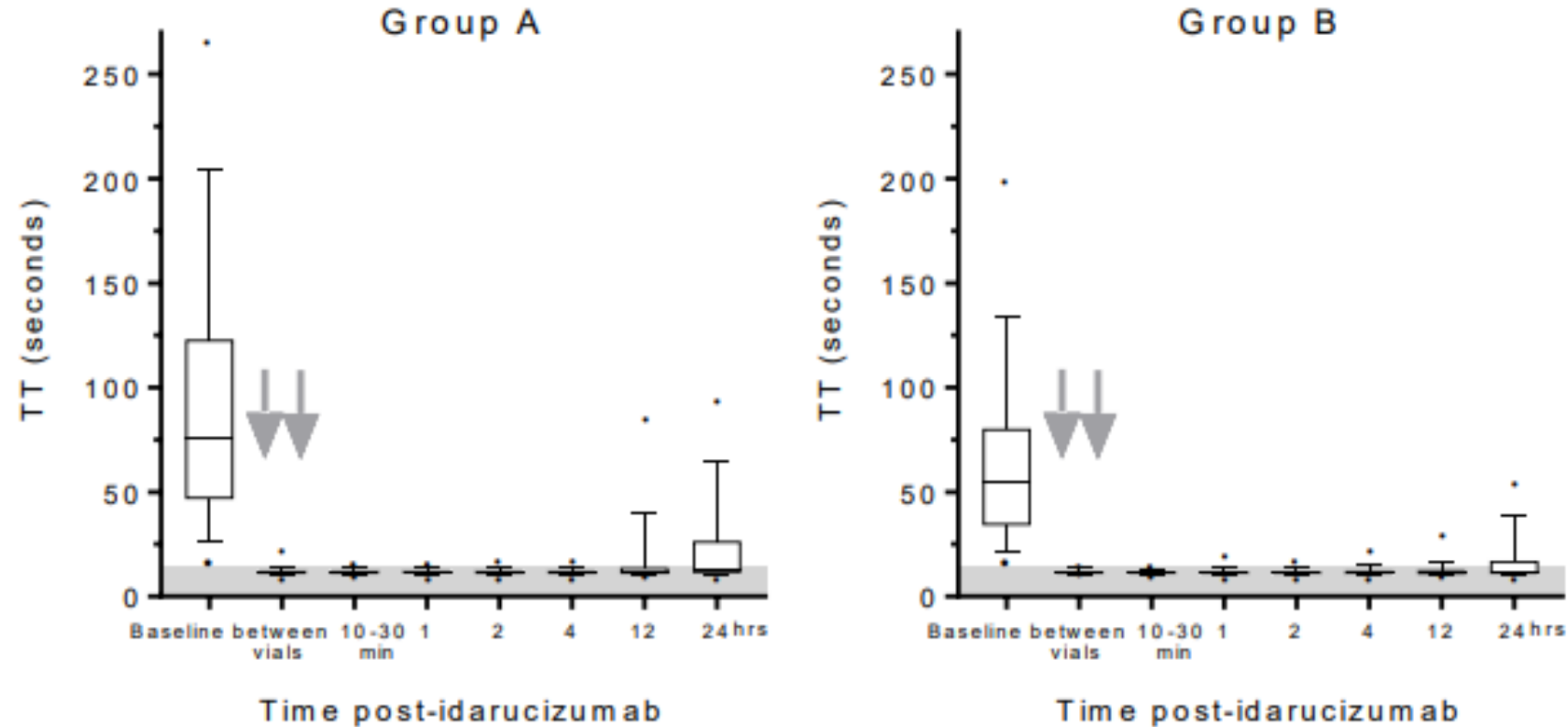
Thrombin time following Idarucizumab



Thrombin time following Idarucizumab



Thrombin Time with Idarucizumab



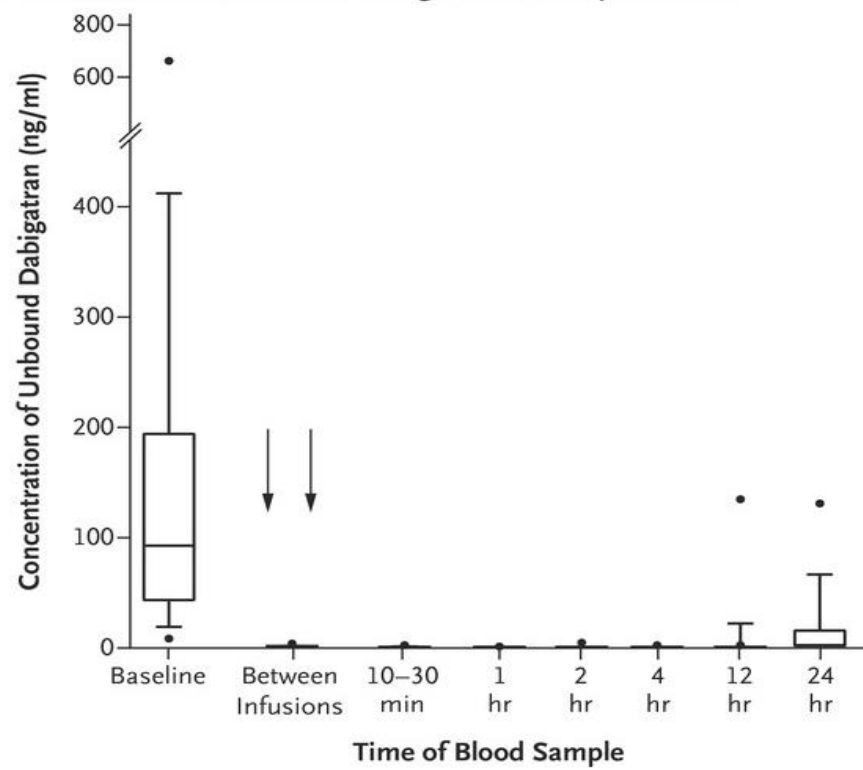
RE-VERSE AD study

- Uncontrolled bleeding (Group A n=301)
- Urgent procedure (Group B n=202)

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N Engl J Med 2017; 377:431-441

C Concentration of Unbound Dabigatran in Groups A and B



Group A and B

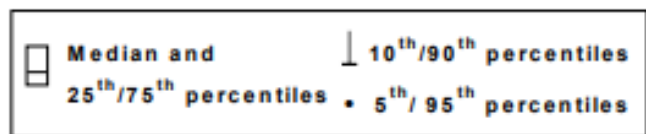
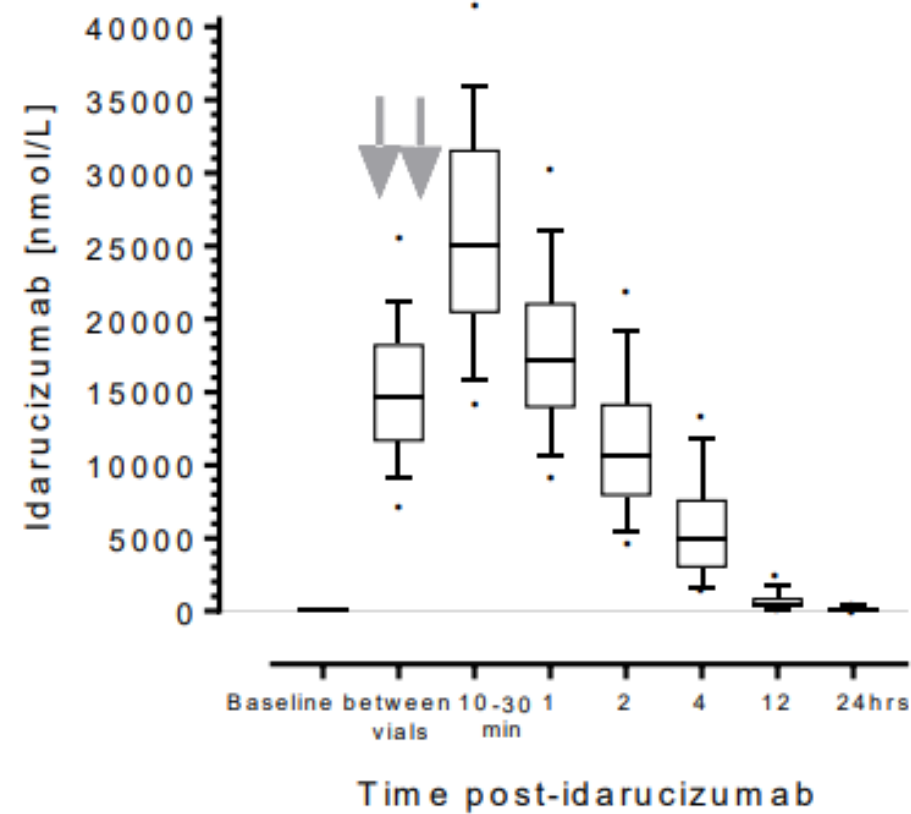


Table 3. Patients Who Received More Than One Dose of Idarucizumab.*

Patient No.	Age yr	Sex	Previous Dose of Dabigatran mg twice daily	Index Event	Baseline Level of Unbound Dabigatran ng/ml	Creatinine Clearance ml/min	Approximate Time to Additional Dose	Reason for Additional Dose
Group A								
1	60	Male	110	Gastrointestinal bleeding	955	25.7	48 hr	Recurrent bleeding
2	79	Male	110	Gastrointestinal bleeding	325	43.4	36 hr	Recurrent bleeding
3	76	Male	110	Hematuria	1360	15.2	24 hr	Recurrent bleeding
4	73	Male	110	Gastrointestinal bleeding	329	29.0	24 hr	Recurrent bleeding
Group B								
5	85	Female	75	Intestinal occlusion	51	31.2	5 days	New procedure
6	73	Female	150	Ischemic large bowel	1630	34.0	12 hr	Postoperative bleeding
7	82	Female	110	Catheter placement for dialysis	271	8.0	6 days	Postoperative bleeding
8	70	Male	110	Catheter placement for dialysis	240	18.6	3 days (dose 2); 8 days (dose 3)	Postoperative bleeding and new procedure

* One patient who received two doses in error is not included in the table.

Case 1: take home

Idarucizumab

1. Reversal maintained only for 24 hours

- 1.b Only rarely associated with bleeding

2. A second dose is indicated if prolonged clotting times PLUS:

- Bleeding
- Second procedure

Rivaroxaban

Direct Factor Xa inhibitor

Highly protein bound 95%

Half life 9-13 hrs

57% metabolised via Cytochrome P450

33% renal excretion

Blood test: anti-Xa (rivaroxaban specific)

Rivaroxaban



Case 2:

Male 60yr

PMHx: A. fib On Rivaroxaban

IHD

CVD

PVD

Hypertension

Diabetes

Mild chronic renal impairment

Previous alcohol dependence

Presentation: PR bleeding

Last dose >24 hours

Haemodynamically stable

Bloods: Hb 118 g/L ----- 88 g/L (6hrs)

Platelets 164

Creatinine 96 umol/L

PT 21.4 sec

APTT 41 sec

TT 27 sec

Fib 2.0 g/L

Rivaroxaban and bleeding management

Prospective cohort studies: x2

Several small non-randomised, single arm case series

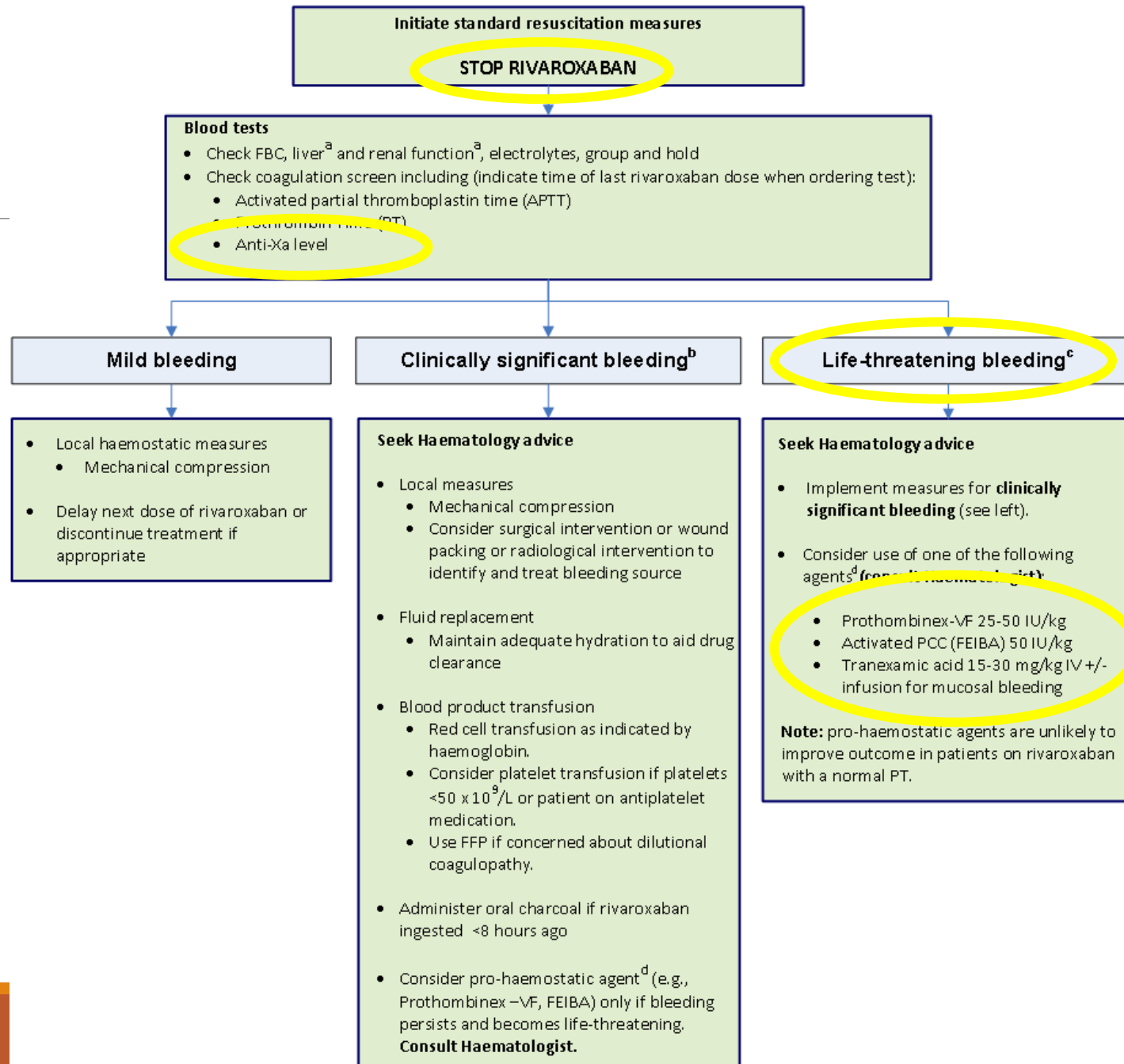
Studies on healthy volunteers

Animal models

Ex vivo patient plasma samples

Pro-haemostatic agents: only in life threatening bleeding

Rivaroxaban associated bleeding



Andexanet alfa

Factor Xa inhibitor reversal agent

Decoy factor X – binds and sequesters Rivaroxaban and apixaban

Bolus, followed by 2 hour infusion.

Short lived effect: 1-3 hours following infusion

~\$60,000 NZD

Overcorrection of Thrombin generation --- prothrombotic

Prothrombin complex concentrate (PCC)

- Does not stop the Rivaroxaban inhibiting factor Xa
- Does not affect drug levels
- Assists with stopping bleeding by increasing levels of Factor X
 - Therefore risk: prothrombotic
- In NZ : ProthrombineX-VF[®]: Unactivated 3 factor PCC (II, IX, X)
- Trials: Unactivated 4 PCC (II, VII, IX, X)

Case 2:

- Rivaroxaban held

Plan reassessed: life threatening bleeding

- Vitamin K
- Prothrombin X: 25iu/kg
- FFP 1:1 RBC
- Rivaroxaban anti-Xa assay 138.8 ng/mL
(c.f. No significant drug: <30ng/mL)
- Cause treated.

Case 2: CTA



Rivaroxaban: future

- VmX-COO1: Factor X- xymogen without Riva binding site

Abstract ISTH 2022

- Blood purification devices



Rivaroxaban: take home points

1. No reversal agent available in NZ
2. Pro-Haemostatic agents in life threatening bleeding only
3. Treating the cause stopped the bleeding

Anticoagulants and bleeding

We can reverse some:

Heparin, warfarin, Dabigatran

We cannot reverse others:

Enoxaparin, Rivaroxaban

DOAC bleeding and the Serenity Prayer

Grant me the serenity to accept the things I cannot change
Courage to change the things I can
And the wisdom to know the difference

Reinhold Niebuhr 1951

