# Bleeding on DOACs and the Serenity Prayer

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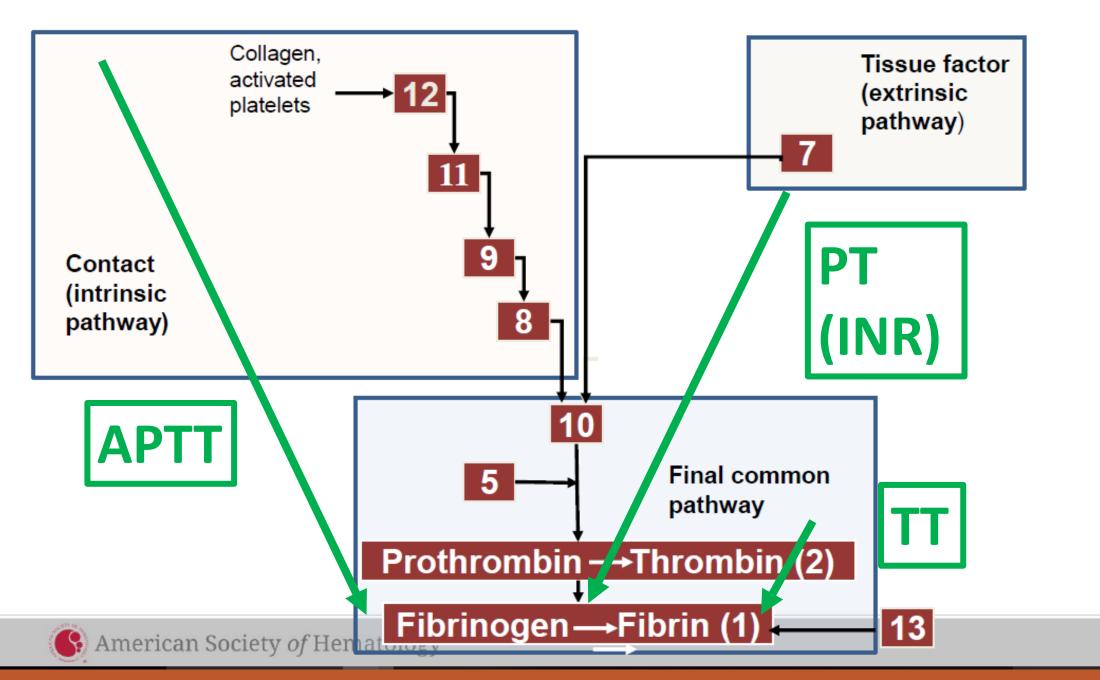
CLINICAL AND LABORATORY HAEMATOLOGIST

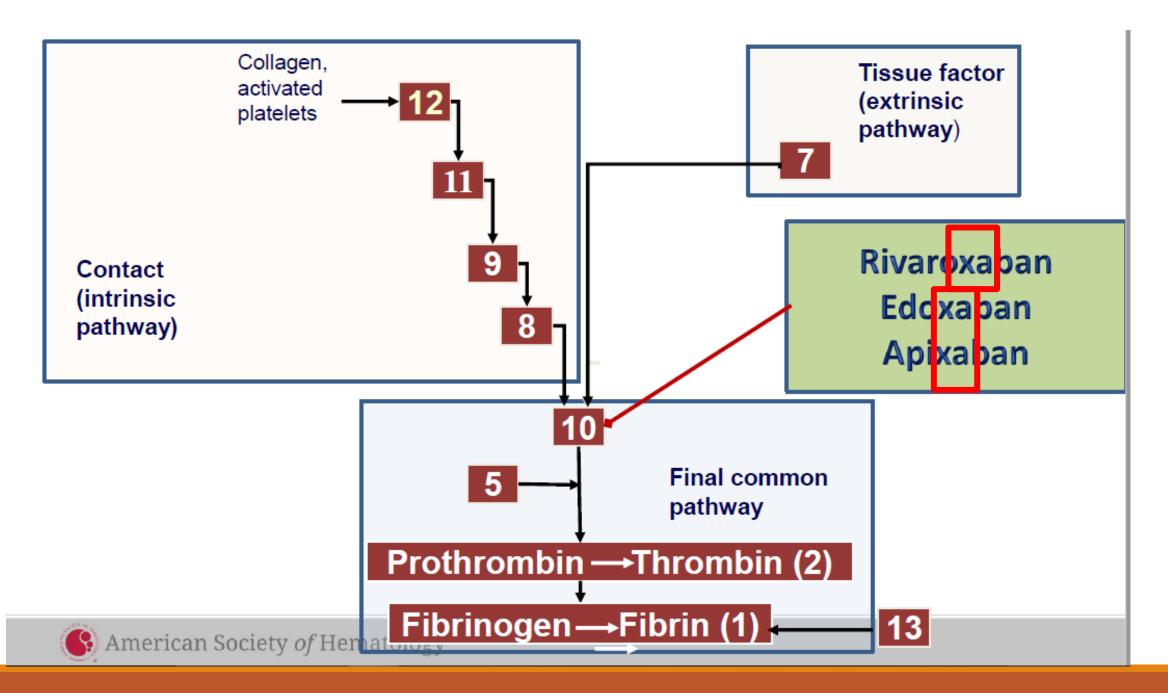
TRANSFUSION MEDICAL SPECIALIST

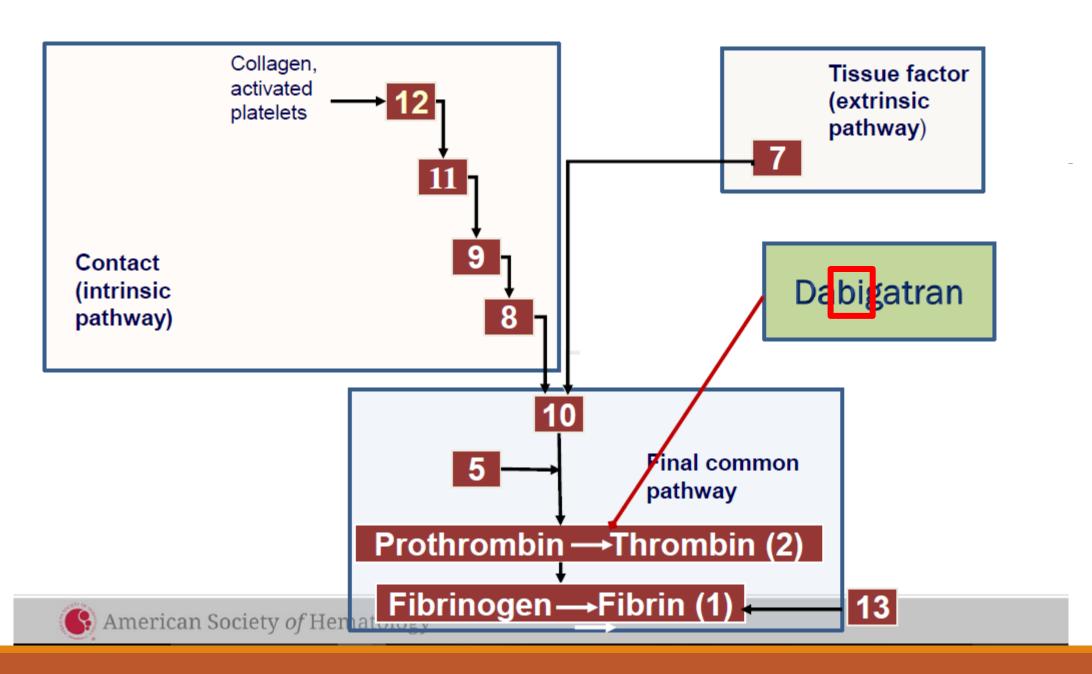
# No disclosures

## 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:

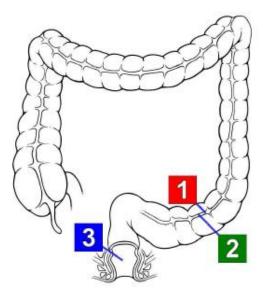
#### Admission bloods

- Hb 143
- Platelets 211
- Creatinine 122

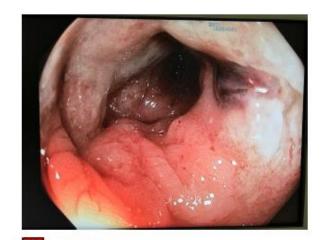
Test Name	Result	Units	Ref. Range
Prothrombin Time	*> 100.0	seconds	10.0 - 13.0
INR	**> 10.0		0.8 - 1.2
A.P.T.T	**173	seconds	22 - 30
Thrombin Time:	*> 200.0	secs	< 21.0
Thrombin Time (protamine)	> 200	secs	
Fibrinogen	3.4	g/L	1.7 - 4.3

## Case 1:

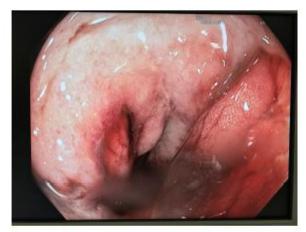
#### CT scan – possible ischaemic colitis



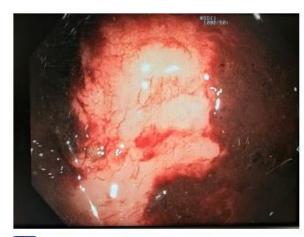
The Colon



Sigmoid Colon :
Abnormal mucosa



2 Sigmoid Colon : pale, oedematous mucosa



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®)

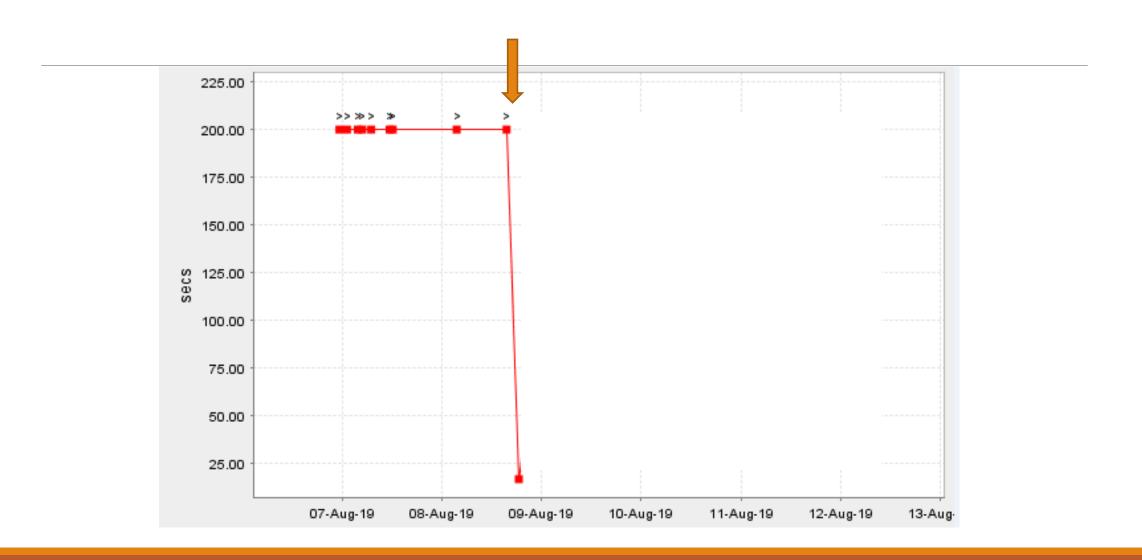
Humanised monoclonal antibody fragment

Binds Dabigatran with high affinity and specificity

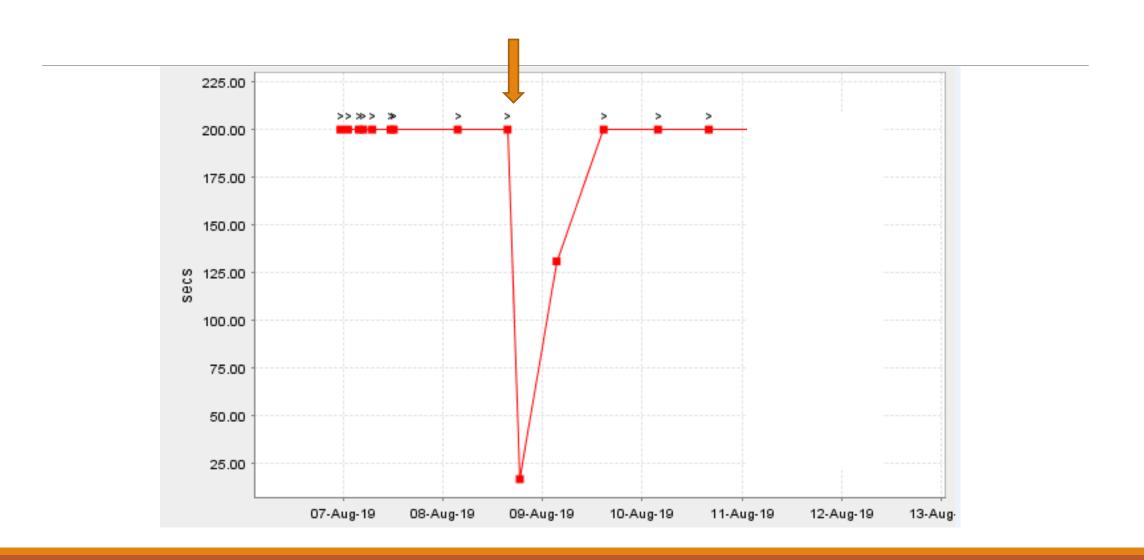
- Thrombin bound and free dabigatran
- >300x Stronger binding than Dabigatran to thrombin
- Clearance/Metabolism: not completely understood.
- No significant side effects
- Thrombotic risk from lack of anticoagulation



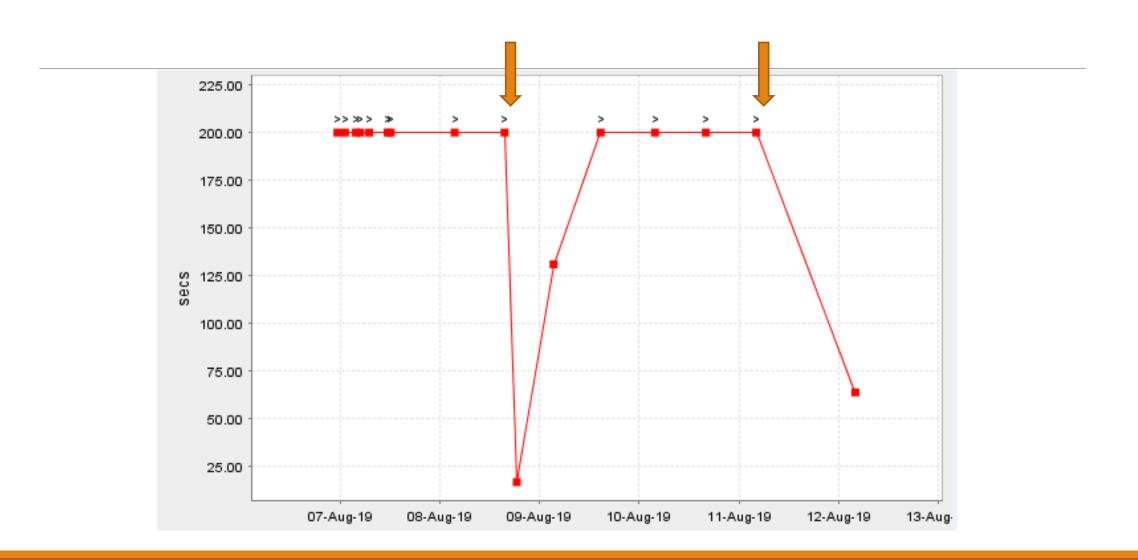
# Thrombin time following Idarucizumab



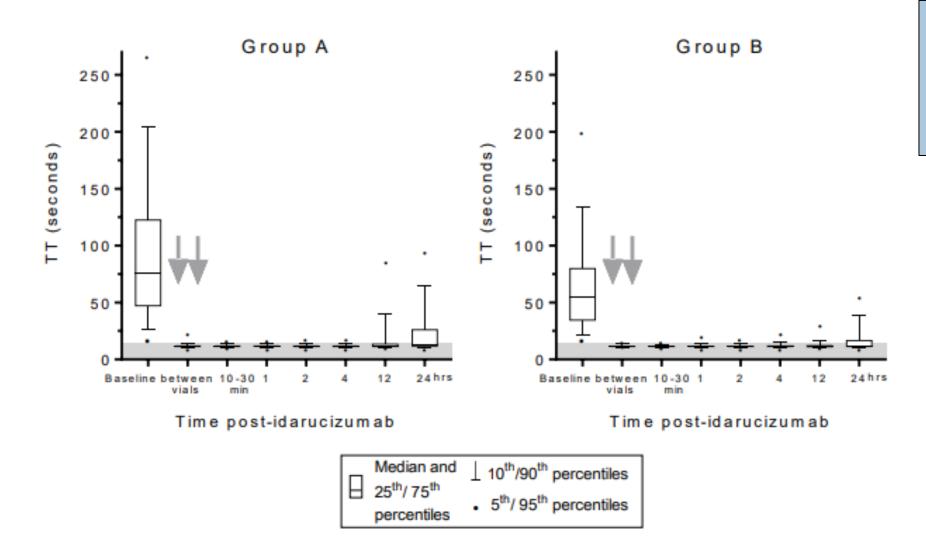
# Thrombin time following Idarucizumab



# Thrombin time following Idarucizumab



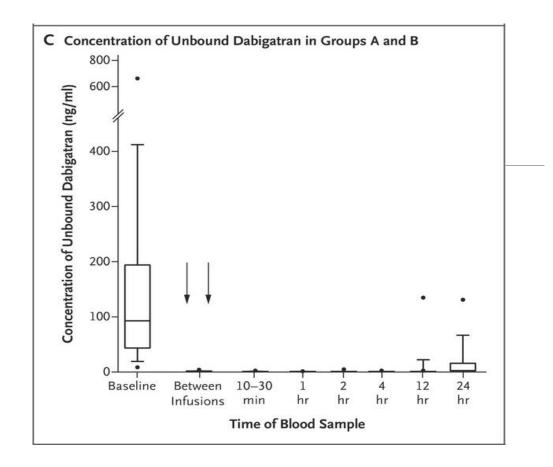
#### **Thrombin Time with Idarucizumab**



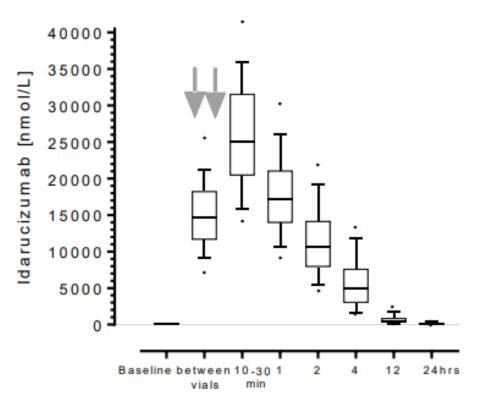
#### **RE-VERSE AD study**

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

August 3, 2017 N Engl J Med 2017; 377:431-441



#### Group A and B



Time post-idarucizumab



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

Patient No.	Age	Sex	Previous Dose of Dabigatran	Index Event	Baseline Level of Unbound Dabigatran	Creatinine Clearance	Approximate Time to Additional Dose	Reason for Additional Dose
	yr		mg twice daily		ng/ml	ml/min		
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

<sup>\*</sup> 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 Initiate standard resuscitation measures STOP RIVAROXABAN Blood tests • Check FBC, liver and renal function, electrolytes, group and hold . Check coagulation screen including (indicate time of last rivaroxaban dose when ordering test): Activated partial thromboplastin time (APTT) (TO) Anti-Xa level Clinically significant bleedingb Mild bleeding Seek Haematology advice

- Local haemostatic measures
  - · Mechanical compression
- Delay next dose of rivaroxaban or discontinue treatment if appropriate
- Local measures
  - Mechanical compression
  - · Consider surgical intervention or wound packing or radiological intervention to identify and treat bleeding source
- Fluid replacement
  - Maintain adequate hydration to aid drug clearance
- Blood product transfusion
  - Red cell transfusion as indicated by haemoglobin.
  - · Consider platelet transfusion if platelets <50 x 10 9/L or patient on antiplatelet medication.
  - Use FFP if concerned about dilutional coagulopathy.
- Administer oral charcoal if rivaroxaban ingested <8 hours ago
- Consider pro-haemostatic agent<sup>d</sup> (e.g., Prothombinex -VF, FEIBA) only if bleeding persists and becomes life-threatening. Consult Haematologist.

#### Life-threatening bleeding<sup>c</sup>

#### Seek Haematology advice

- Implement measures for clinically significant bleeding (see left).
- · Consider use of one of the following agents<sup>d</sup> (constitute match pist):
  - Prothombinex-VF 25-50 IU/kg
  - Activated PCC (FEIBA) 50 IU/kg
  - Tranexamic acid 15-30 mg/kg IV +/infusion for mucosal bleeding

Note: pro-haemostatic agents are unlikely to improve outcome in patients on rivaroxaban with a normal PT.

## 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