Blood and Guts

Reversal of anticoagulation in GI Bleeding

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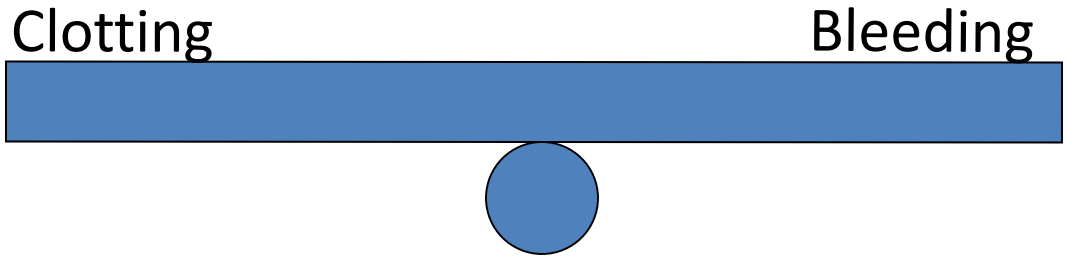
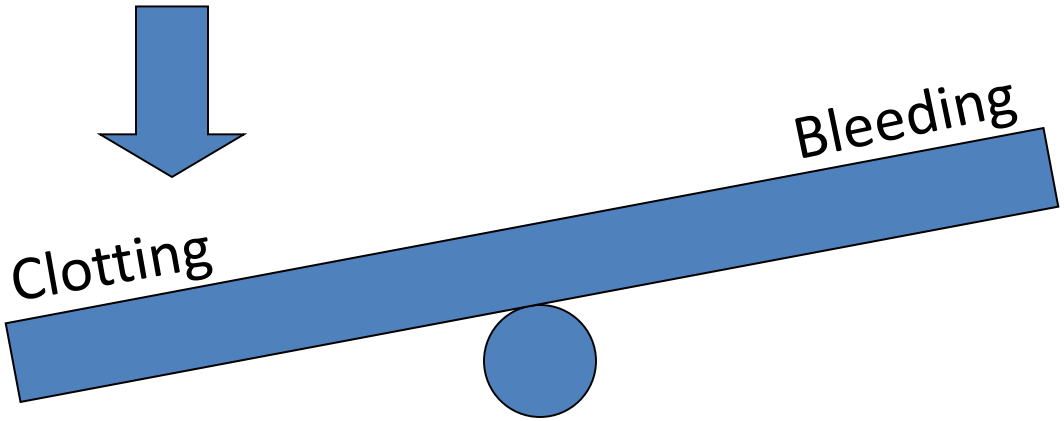
Healthy situation

Haemostatic seesaw in a happy balance



Clinical Thrombosis

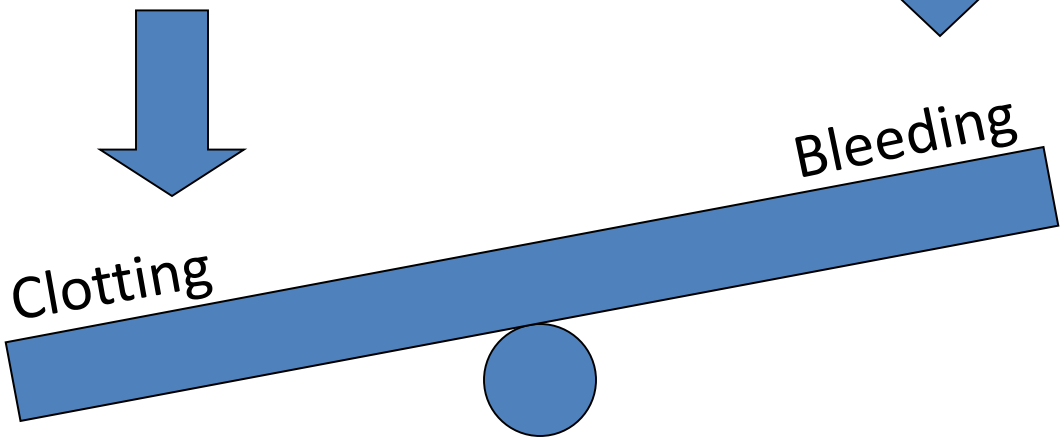
Atrial Fibrillation
Deep Vein Thrombosis
Pulmonary Embolus
Cerebral Sinus Thrombosis
Mesenteric Vein Thrombosis
Arterial Embolus or Thrombosis
Metallic Heart Valves
Ventricular Assist Devices
Antiphospholipid syndrome



Anticoagulation Therapy

Atrial Fibrillation
Deep Vein Thrombosis
Pulmonary Embolus
Cerebral Sinus Thrombosis
Mesenteric Vein Thrombosis
Arterial Embolus or Thrombosis
Metallic Heart Valves
Ventricular Assist Devices
Antiphospholipid syndrome

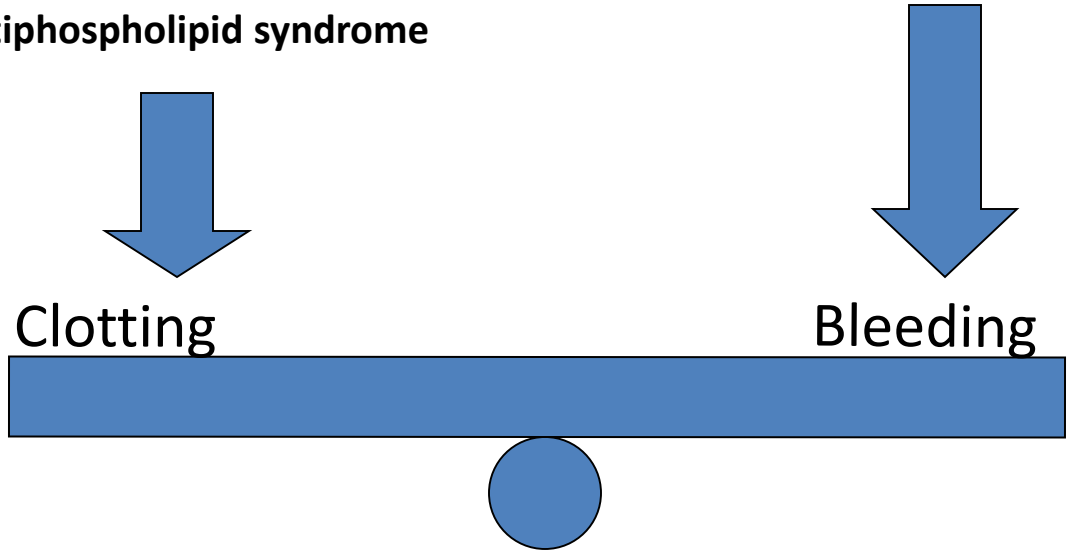
ANTICOAGULANT DRUG



Successful Anticoagulation

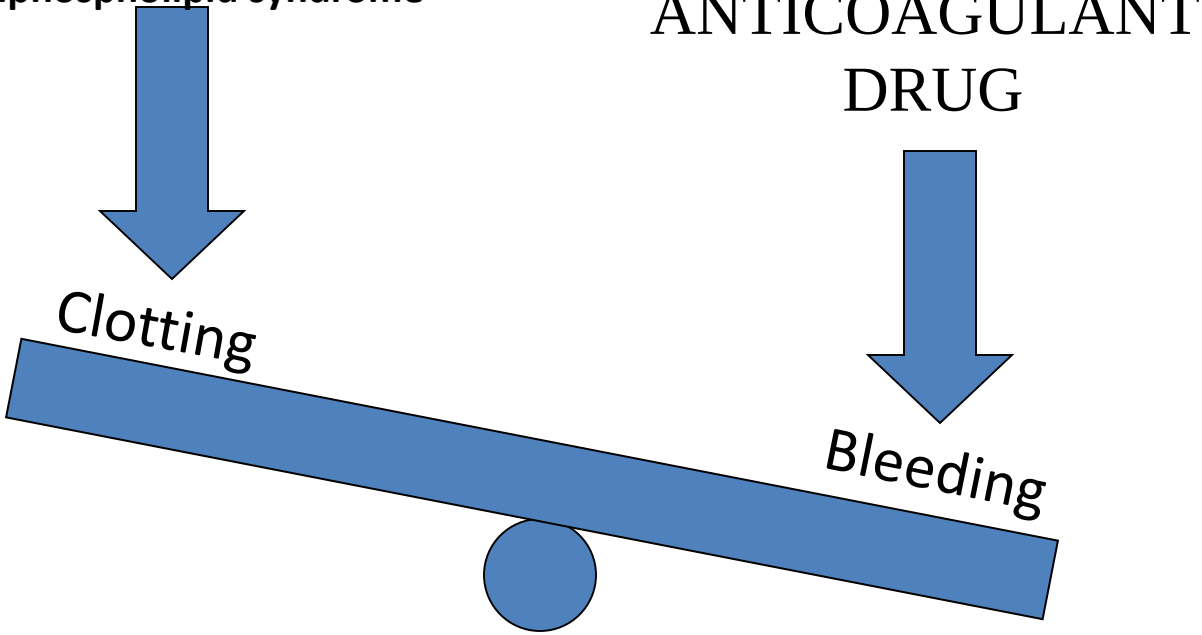
Atrial Fibrillation
Deep Vein Thrombosis
Pulmonary Embolus
Cerebral Sinus Thrombosis
Mesenteric Vein Thrombosis
Arterial Embolus or Thrombosis
Metallic Heart Valves
Ventricular Assist Devices
Antiphospholipid syndrome

ANTICOAGULANT DRUG



Unsuccessful Anticoagulation

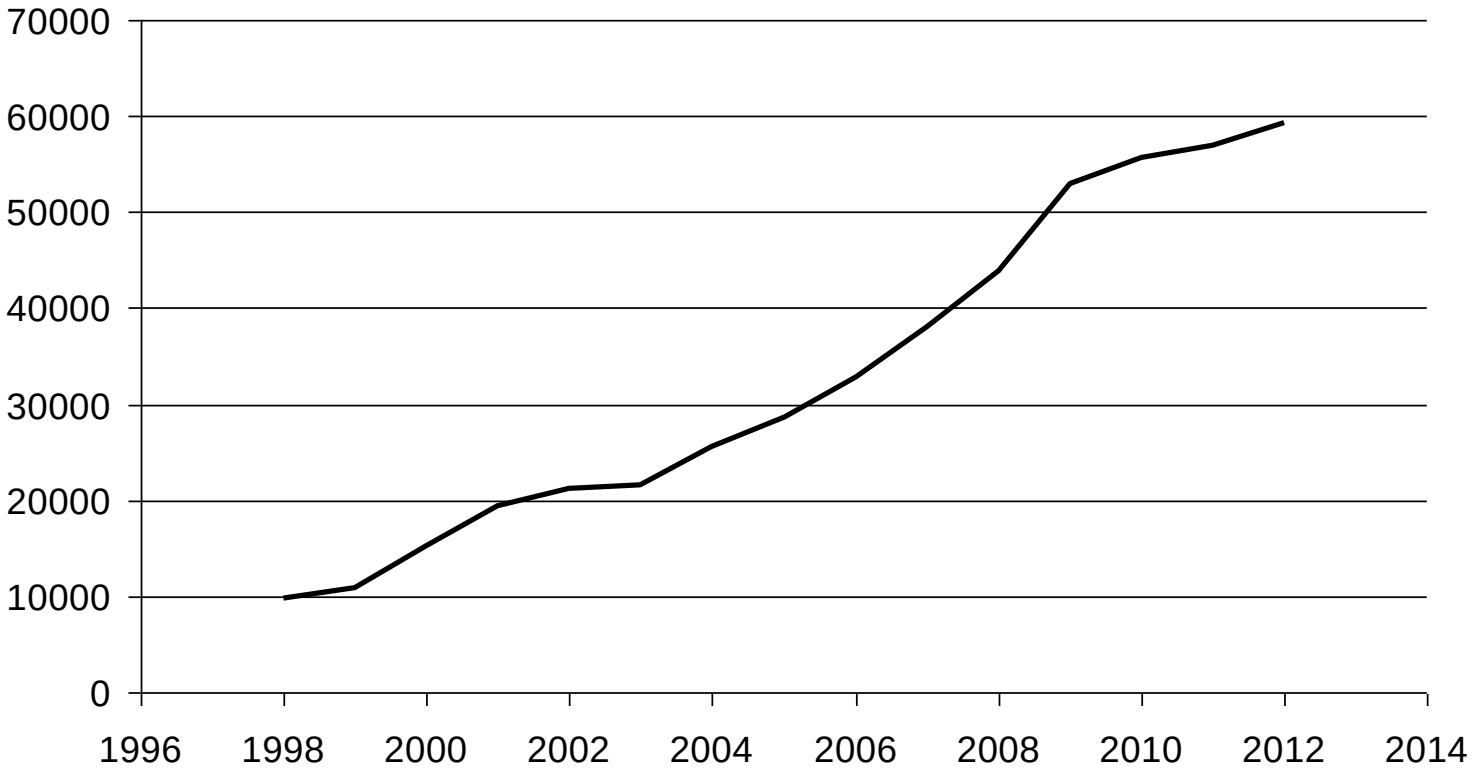
Atrial Fibrillation
Deep Vein Thrombosis
Pulmonary Embolus
Cerebral Sinus Thrombosis
Mesenteric Vein Thrombosis
Arterial Embolus or Thrombosis
Metallic Heart Valves
Ventricular Assist Devices
Antiphospholipid syndrome



Steady increase in numbers of patients receiving anticoagulation

≈1-2% of the UK population anti-coagulated

AF	70%
VTE	25%
Other	5%



Anticoagulants / Anti-platelets

Unfractionated Heparin	
Low Molecular Weight Heparin	
Warfarin	**Other Vit K antagonists**
Anti-Platelet Agents	**Aspirin** **Clopidogrel** **Others**
Xa Inhibitors	**Rivaroxaban** **Apixaban** **Edoxaban**
Thrombin Inhibitors	**Hirudin** **Dabigatran**

Anticoagulation 2017

Which is best?

Side-effect profile
GI bleeding

Who decides?

Clinical Trials

Real world experience

Clinician Bias

Patient choice

Anticoagulation 2017

Bleeding still a common clinical scenario

GI Bleeding probably commonest type of bleeding

50 YEAR OLD MAN

1999 Mechanical aortic valve replacement with aortic stent requiring anticoagulation

Ischaemic bowel post op; resection; ileostomy; reversed

2009 GI bleeding – melaena; capsule ? Bleeding near bowel anastomosis
On going iron deficiency anaemia ?on going slow bleeding

INR – target 3-4

50 YEAR OLD MAN

1999 Mechanical aortic valve replacement with aortic stent requiring anticoagulation

Ischaemic bowel post op; resection; ileostomy; reversed

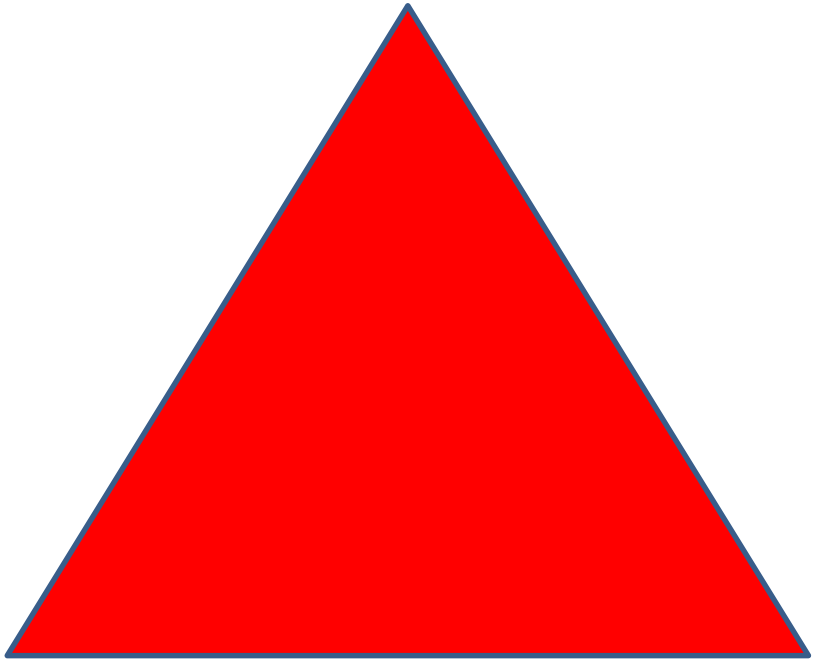
2009 GI bleeding – melaena; capsule ? Bleeding near bowel anastomosis
On going iron deficiency anaemia ?on going slow bleeding

INR – target 3-4

?Options

THE NATURAL ORDER

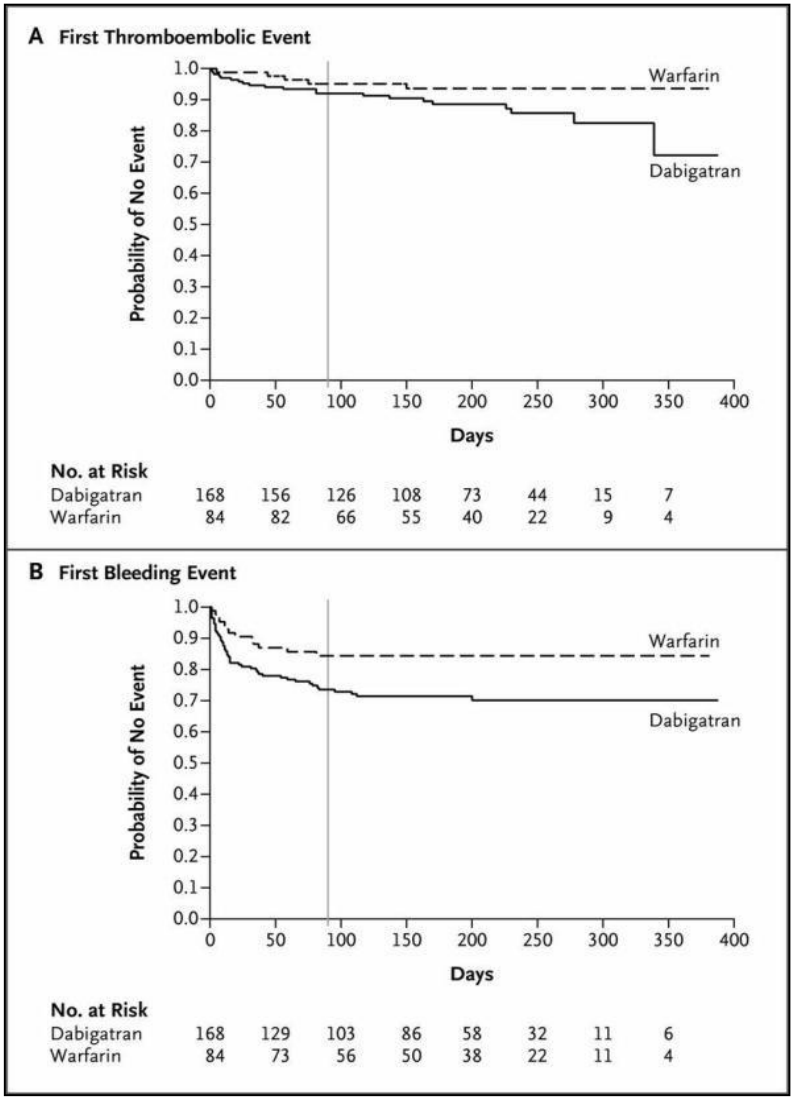
CARDIOLOGIST



GASTROENTEROLOGIST

HAEMATOLOGIST

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves
New England Journal of Medicine, 26 September 2013, p 1206–1214
J Eikelboom et al



“The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk”.

Home INR monitoring

COAGUCHECK HOME MONITORING – WARFARIN ADJUSTMENT SCHEDULE

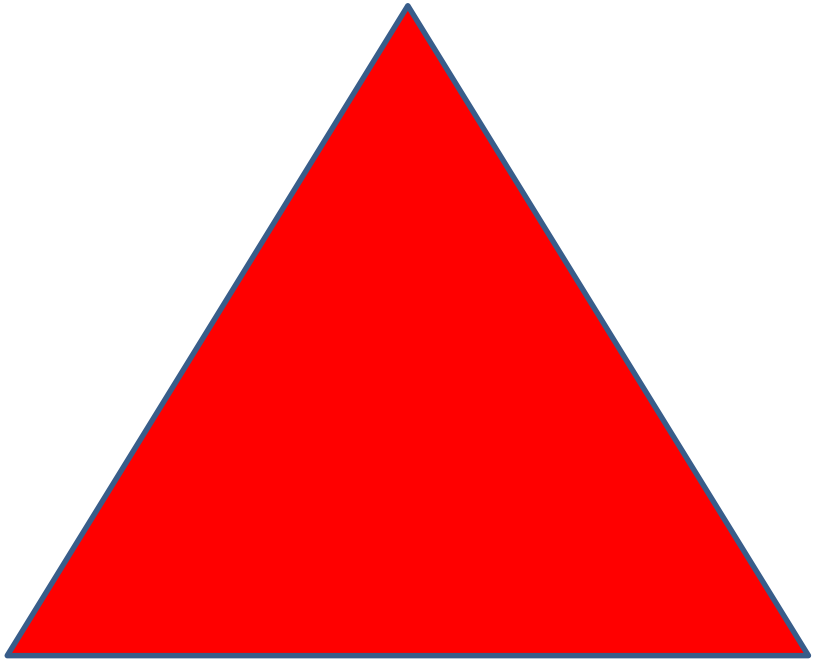
Name:
DOB:
Hospital Number:

Reason for warfarin therapy:	Aortic Valve Replacement / Stent GI Bleeding (?near bowel anastamosis) Consider vitamin K at lower INR than Standard protocol
Regular warfarin dose:	6 mg daily
INR Target Range:	2-2.5 (aiming for 2.5)

INR	
> 4	Phone for advice
3.0-4.0	Omit 1 dose; Re-test following day; if still > 3 phone for advice
2.5-3.0	Reduce to 5mg daily. Re-test in 2 days
2-2.5	Continue 6mg daily. Test in 1 week.
<2	Phone for advice (any of the numbers listed below)

THE NATURAL ORDER

CARDIOLOGIST – CAUSES GI BLEEDING



GASTROENTEROLOGIST
STOPS GI BLEEDING

HAEMATOLOGIST
TRYS TO BE HELPFUL

A Haematological Bias

Therapeutic monitoring is a good thing

A Haematological Bias

Therapeutic monitoring is a good thing

Unless you are a bog standard patient with bog standard risk

80 year old woman

Haematemesis

13 day hospital admission

Anaemia – iron deficient – on admission

OGD - severe oesophagitis – 3rd day of admission

Proximal L DVT (ileo-femoral) – 3rd day of admission

80 year old woman

Haematemesis

13 day hospital admission

Anaemia – iron deficient – on admission

OGD - severe oesophagitis – 3rd day of admission

Proximal L DVT (ileo-femoral) – 3rd day of admission

….decided to use rivaroxaban “to avoid the need for monitoring”

15mg bd

“GP to reduce the dose to 20mg od in 3 weeks (12/4) and complete a 6 month course”

…… 7/4

Readmitted with a brisk GI bleed

Initially shocked

Responded to resuscitation

	7/4	8/4	9/4
PT	31	25	15
APTT	42	37	30
Fibrinogen	3.2	4.2	3.8

V unstable for 48 hours

High dependency

7 units blood

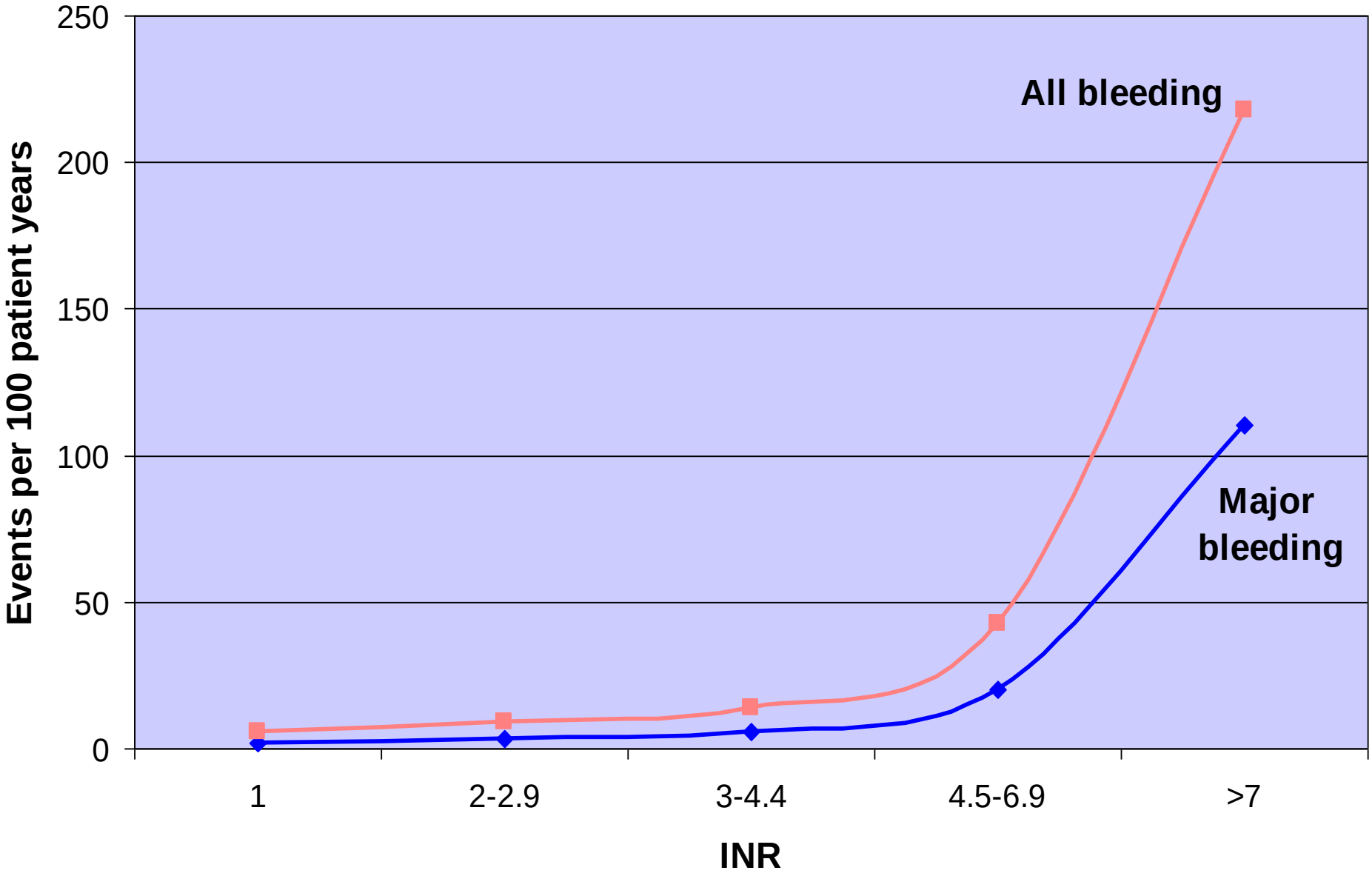
Anticoagulants / Anti-platelets

Unfractionated Heparin

Low Molecular Weight Heparin

Warfarin	**Other Vit K antagonists**
Anti-Platelet Agents	**Aspirin** **Clopidogrel** **Others**
Xa Inhibitors	**Rivaroxaban** **Apixaban** **Edoxaban**
Thrombin Inhibitors	**Hirudin** **Dabigatran**

INR and bleeding risk (Palareti et al 1996)



Reversal of over-warfarinisation

Options

Omit warfarin

Vitamin K - oral or SC or IV

Coagulation factor replacement

BALANCE IMMEDIATE BLEEDING RISK AGAINST THROMBOTIC COMPLICATIONS

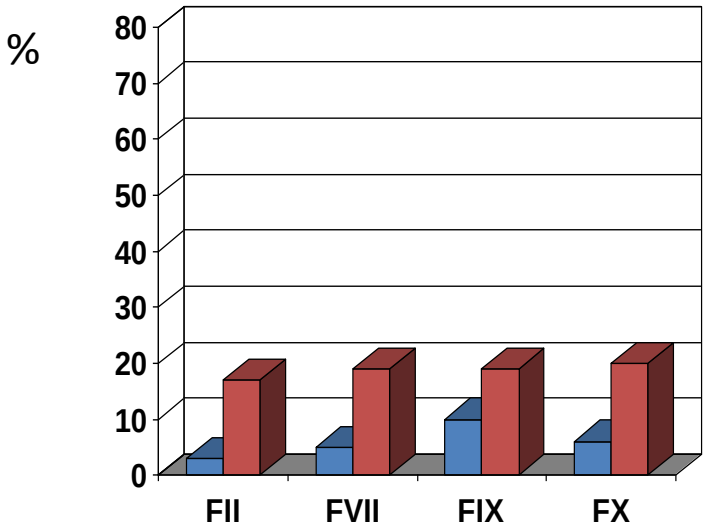
?indication for warfarin
?seriousness of bleeding
?speed of reversal required
?completeness of reversal required

Warfarin Reversal - Options

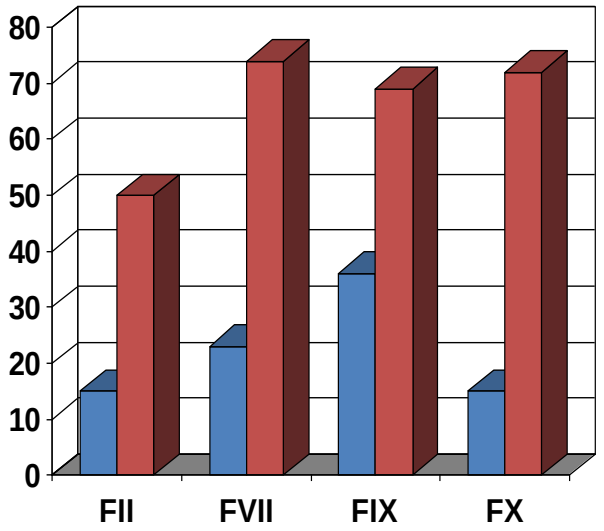
Rapid	10 mins	PCC
Fast (Partial)	1-2 hrs FFP	
Prompt	4-6hrs	IV vitamin K
Slow	24 hrs	Oral vitamin K
Ultra-slow	2-4 days	Omit warfarin (No vitamin K)

Emergency reversal of oral anticoagulation: FFP vs PCC

FFP



PCC (25-50u FIX / kg)



Makris M et al. Thromb Haemost 1997

British Guidelines On Warfarin reversal

Makris *et al*. Br J Haematol 2013;160:34

- All hospitals managing patients on warfarin should stock a Prothrombin Complex Concentrate
- In emergency reversal use 25-50u/kg PCC and 5mg iv vitamin K
- rFVIIa is not recommended
- FFP produces suboptimal correction and should only be used if PCC is not available

NORTHERN REGION HAEMATOLOGISTS GROUP GUIDE TO WARFARIN REVERSAL

NB All bleeding in a patient on warfarin should be taken seriously. Bleeding may occur when the INR is therapeutic. If the INR is sub-therapeutic e.g. <1.5 bleeding may be due to factors other than warfarin and reversal may not be appropriate.
If in doubt discuss with haematologist.

BLEEDING

Life / Limb /Sight Threatening

CONTACT HAEMATOLOGIST

- Intracranial (CT or MRI)

Patients with rapid onset neurological signs while on warfarin do URGENT INR and CT scan (within 1 hour). If INR>4.5, consider urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately

- Retroperitoneal (CT or MRI)
- Intra-ocular (NOT conjunctival)
- Spontaneous muscle bleed with compartment syndrome
- Pericardial
- Active bleeding from any orifice plus either BP ≤ 90 mmHg systolic, oliguria or 2 g fall in haemoglobin

↓

Vitamin K 5 mg IV[1] and Prothrombin complex concentrate IV (Beriplex P)[2] 30 units/kg

↓

Check INR & APTT Immediately

↓ Adequate correction

Repeat INR & APTT in 4-6 hours

↓ Inadequate correction

Consider other factors contributing to prolonged coagulation tests eg DIC, Congenital coagulation factor deficiency, Liver disease, Inadequate replacement.

Significant bleeding[3] without haemodynamic compromise

↓

2mg Vitamin K IV

↓

Check INR & APTT at 4-6 hours or sooner if clinical deterioration

Minor

↓

Vitamin K 2mg PO[4]

Oral vitamin K is safe and adequate treatment for the majority of patients. There may be some clinical circumstances when 1-2 mg IV vitamin K should be considered e.g. gross over-anticoagulation or unsteady patients

↓

Check INR at 24 hours or sooner if clinical deterioration

NO BLEEDING

INR >8

↓

Vitamin K 1mg PO[4]

Remember to document any reason for high INR

↓

Check INR at 24 hours or sooner if clinical deterioration

INR 4.5-7.9[5]

↓

Omit or reduce dose or Vitamin K 1mg PO[4] if considered "High Risk" of bleeding

[1]Oral vitamin K - there are marked differences between formulations of vitamin K. The most effective preparation is IV Konakion (Roche) given orally. The vial contains 10 mg/ml -dilute appropriate dose in small amount of juice/water after drawing up in 1 ml insulin syringe. Alternatively the Konakion MM paediatric formulation may be used

[2]Vitamin K IV may rarely cause anaphylaxis. Give by slow IV bolus

[3]Prothrombin complex concentrate (PCC) may induce a prothrombotic state. Use with caution in patients with DIC or decompensated liver disease

[4]In serious but non-life-threatening bleeding (e.g. GI bleeding or epistaxis without haemodynamic compromise) prompt reversal with IV vitamin K is indicated

The use of FFP for warfarin reversal is no longer recommended

NORTHERN REGION HAEMATOLOGISTS GROUP GUIDE TO WARFARIN REVERSAL

BLEEDING

Life / Limb /Sight Threatening

CONTACT HAEMATOLOGIST

- Intracranial (CT or MRI)
- Retroperitoneal (CT or MRI)
- Intra-ocular (NOT conjunctival)
- Spontaneous muscle bleed with compartment syndrome
- Pericardial
- Active bleeding from any orifice plus either BP $\leq$ 90 mmHg systolic, oliguria or 2 g fall in haemoglobin

↓

Vitamin K 5 mg IV and
Prothrombin complex concentrate IV
(Beriplex P) 30 units/kg

↓

Check INR & APTT
Immediately

↓

Adequate correction

↓

Repeat INR & APTT
in 4-6 hours

Inadequate correction

↓

Consider other factors contributing to prolonged coagulation tests eg DIC, Congenital coagulation factor deficiency, Liver disease, Inadequate replacement. **Seek haematological advice**

Significant bleeding[3] without haemodynamic compromise

↓

2mg Vitamin K IV

↓

Check INR & APTT
at 4-6 hours or sooner
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NORTHERN REGION HAEMATOLOGISTS GROUP GUIDE TO WARFARIN REVERSAL

BLEEDING

Life / Limb /Sight Threatening

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Significant bleeding[3] without haemodynamic compromise

↓

2mg Vitamin K IV

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Check INR & APTT
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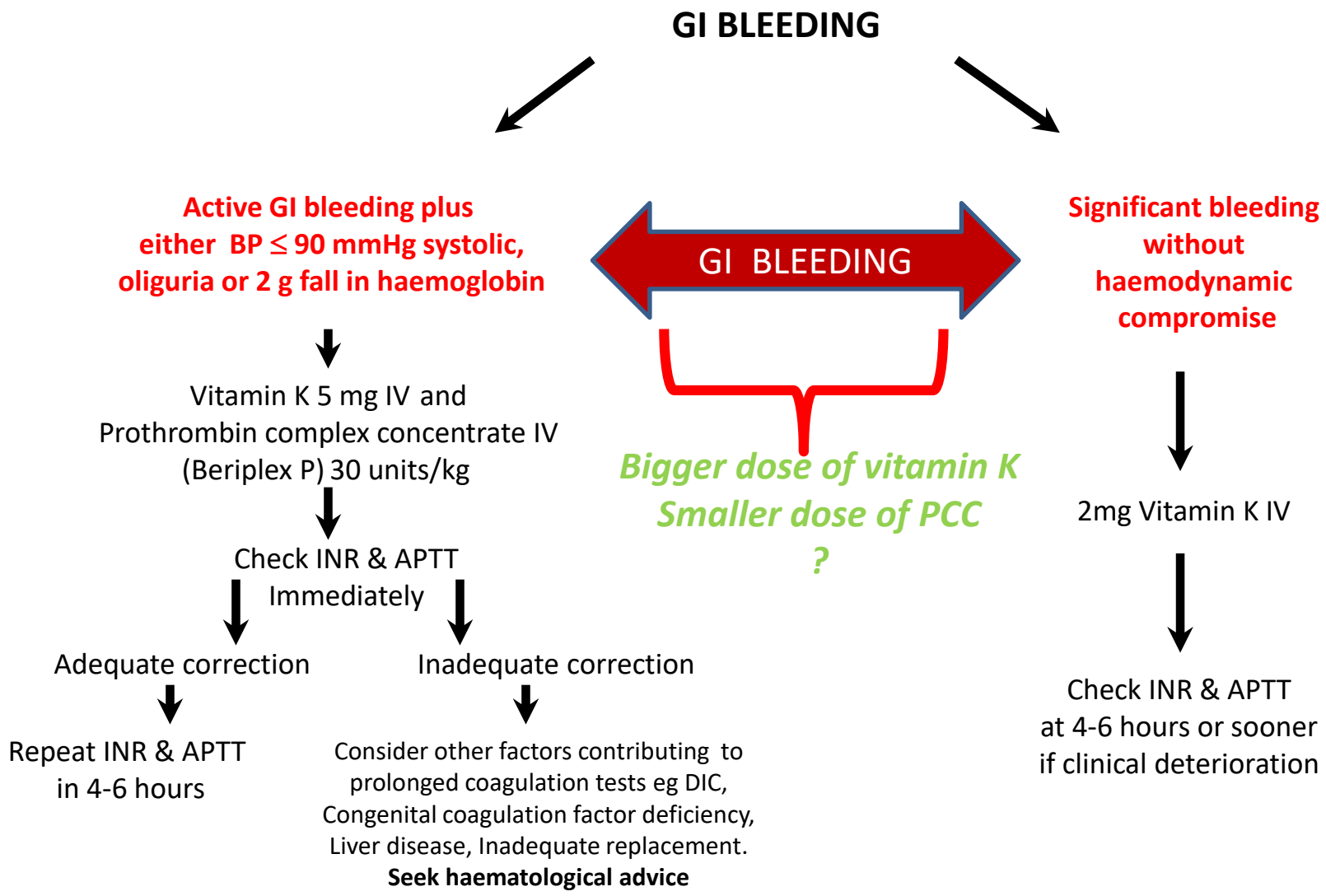
if clinical deterioration

GI BLEEDING

Pragmatic interpretation of the protocol



Key Question to Ask

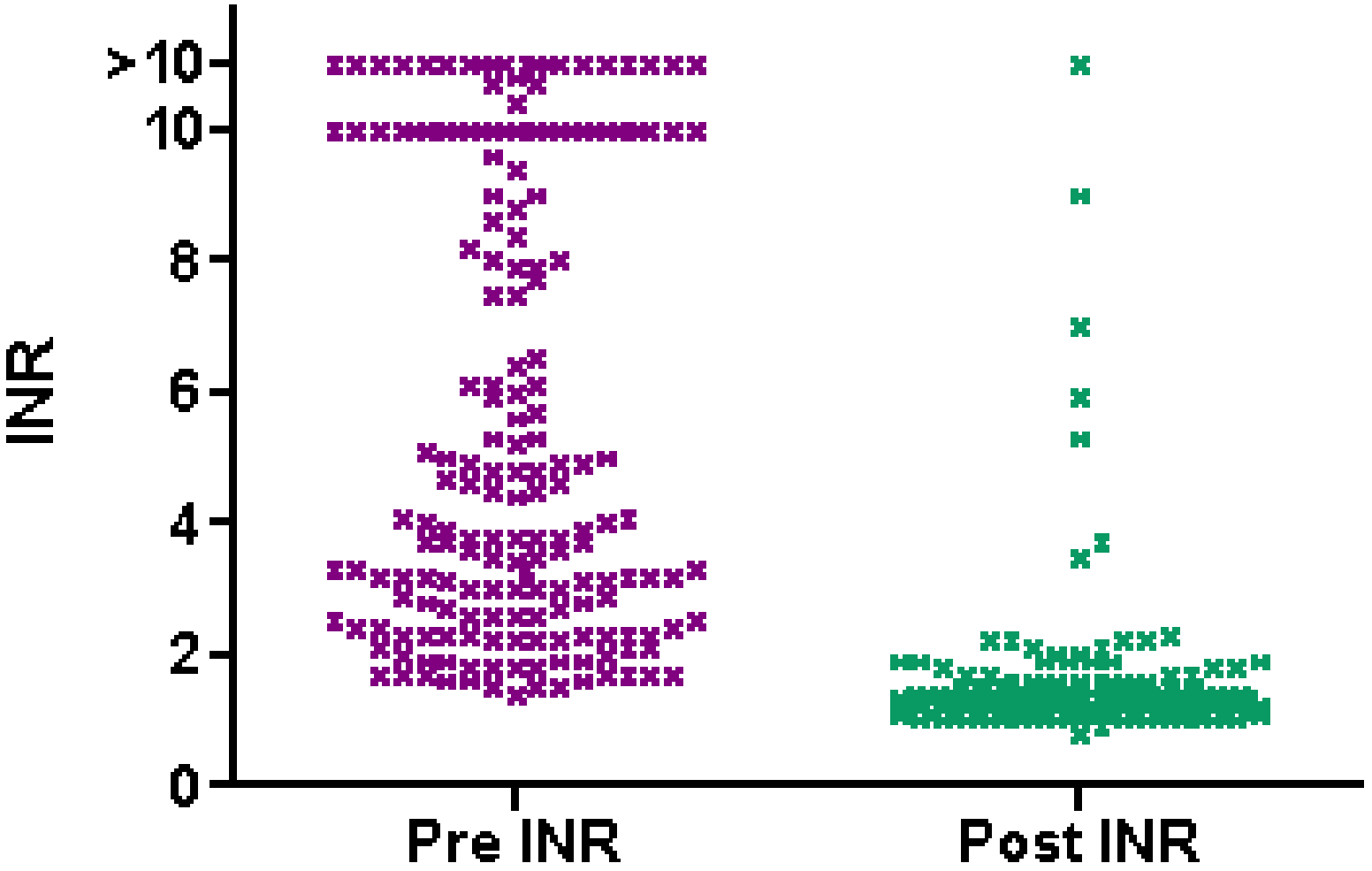
In a patient with “stable” warfarin-associated GI bleeding

Give Vitamin K promptly

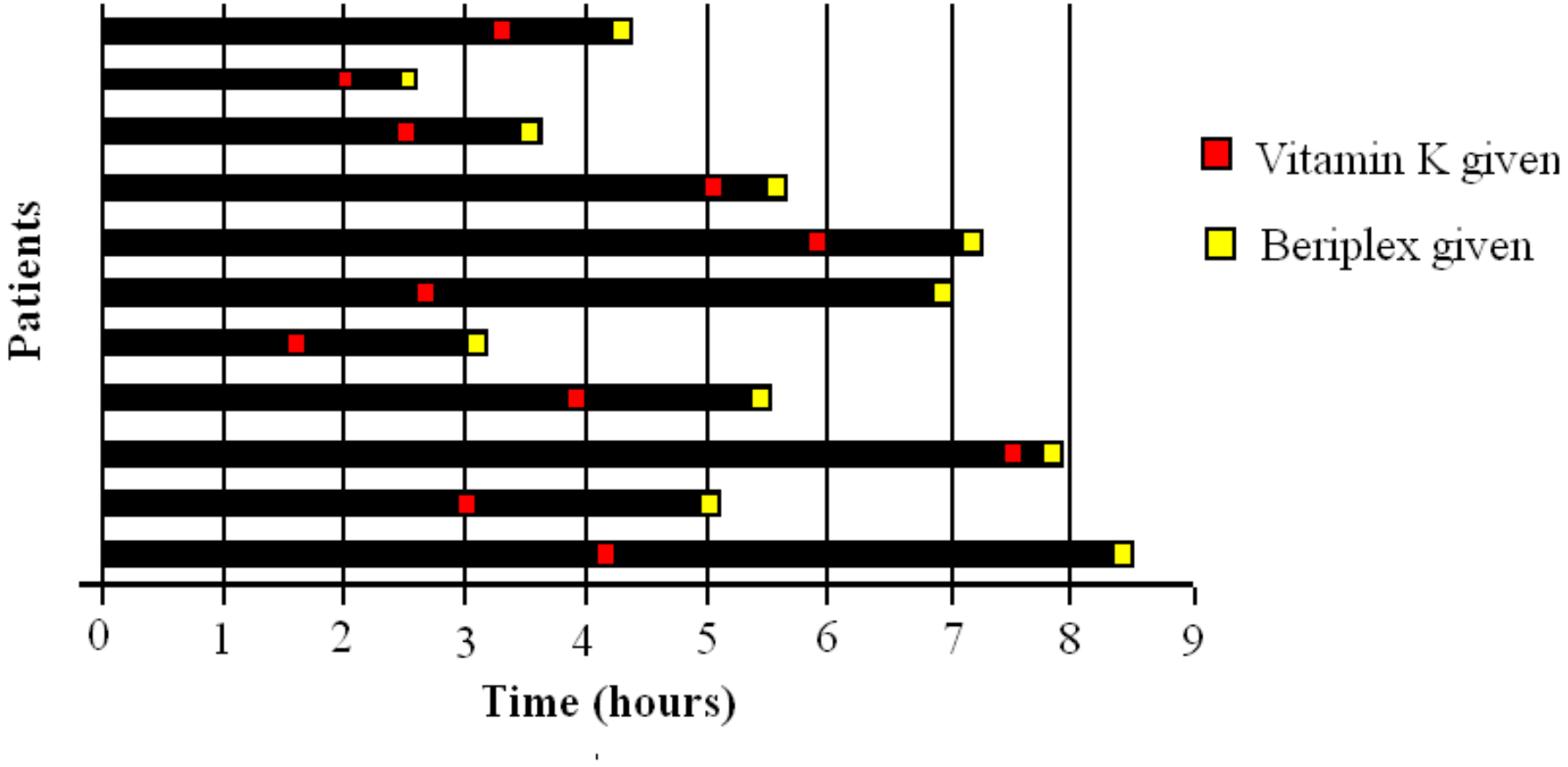
What are the consequences for the patient if less “stable” over the next 4 hours

If bad – give PCC

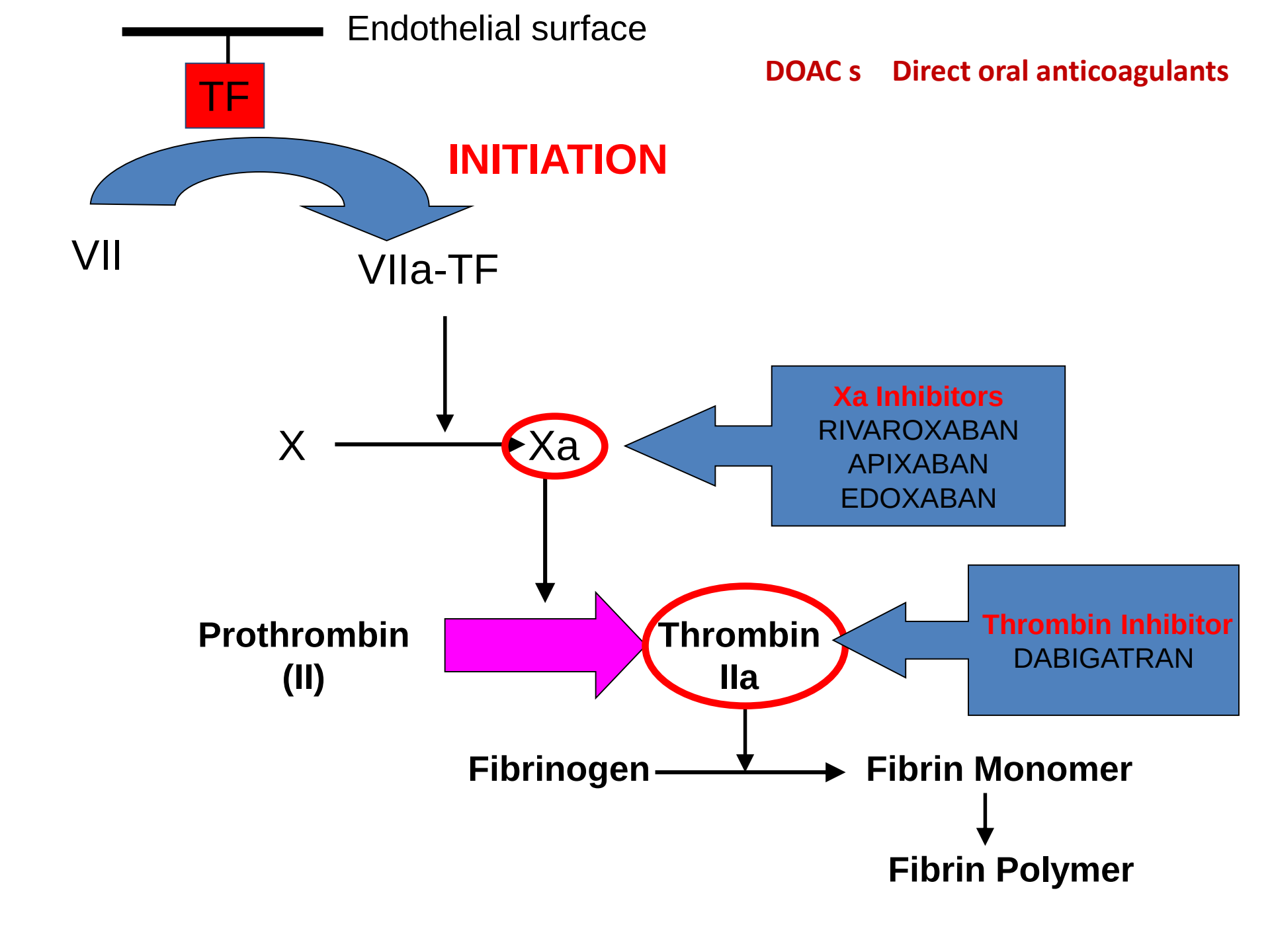
Massively over-anticoagulated
30 units/kg may not be enough



TIME FROM ADMISSION TO VITAMIN K AND BERIPLEX ADMINISTRATION IN PATIENTS WITH INTRACRANIAL HAEMORRHAGE



GIVE THE VITAMIN K ASAP IN GI BLEEDING!!


Endothelial surface
TF
DOAC s Direct oral anticoagulants
INITIATION
VII
VIIa-TF
X
Xa
Xa Inhibitors
RIVAROXABAN
APIXABAN
EDOXABAN
Prothrombin
(II)
Thrombin
IIa
Thrombin Inhibitor
DABIGATRAN
Fibrinogen
Fibrin Monomer
Fibrin Polymer

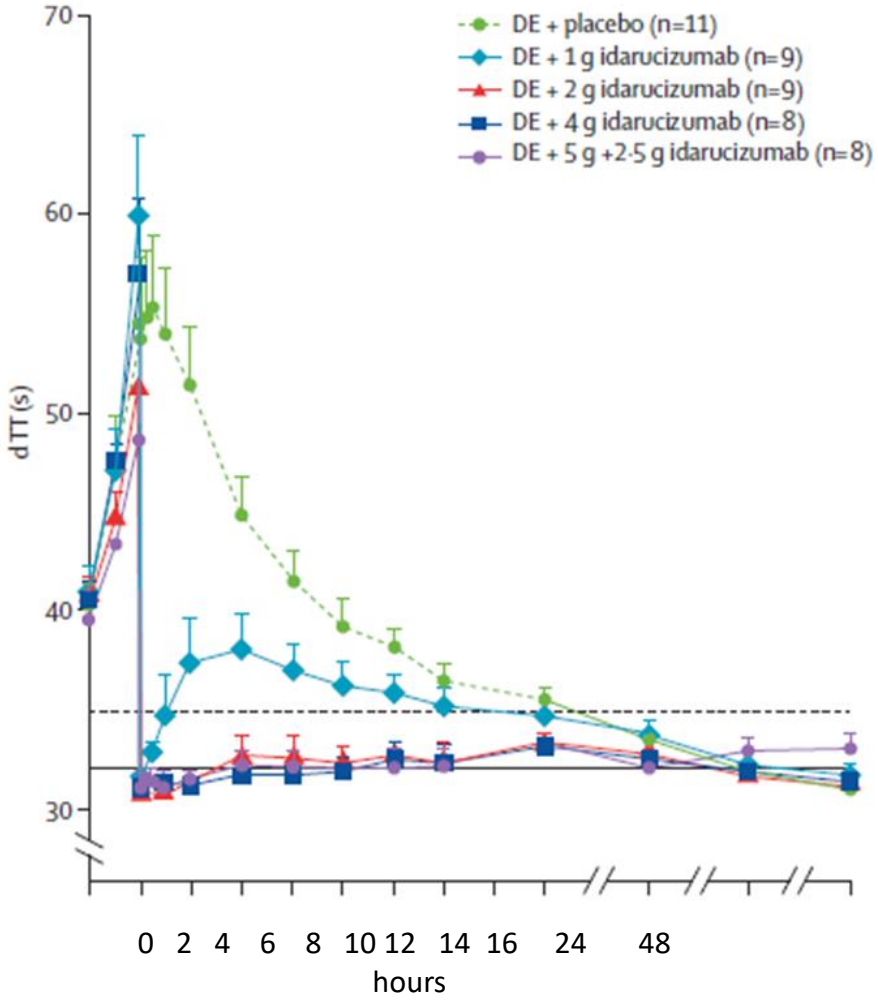
GI bleeding on DOACs

- Establish which drug the patient is taking
- Establish when the last dose was taken
- PT/APTT/TT may be helpful in Xa inhibitors and dabigatran
- Specific drug levels if available
- Wait 1 – 2 half lives if possible
- General supportive measures
- IV Tranexamic Acid
- Activated charcoal (if recent ingestion)
- Do not use non specific haemostatic agents prophylactically as effectiveness unproven & thrombotic risk – consider if life/limb threatening bleeding

Management of bleeding on DOACs: specific reversal agents

- Dabigatran
  - Idarucizumab: Humanised monoclonal antibody fragment

Dabigatran reversal with iv Idarucizumab in healthy volunteers



Glund et al. Lancet 2015; 386:680-690

Dabigatran reversal with Idarucizumab
Clinical endpoints

- Interim analysis of first 90 patients of 300 patient study
- Recruiting in 400 centres in 38 countries
- Group A: Major bleeding, Group B: Emergency surgery
- All got 5g of Idarucizumab over 15 min (2x 2.5g doses)

- Group A: Cessation of bleeding in 11.4 hours
- Group B: Normal haemostasis in 92%

- One thrombosis within 72hrs and four other after this time

- Pollack CV et al. NEJM 2015; 373:511-520

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Pollack et al NEJM 2017 Volume 377(5):431-441

503 patients

Group A	Uncontrolled Bleeding	301
Group B	Required Urgent Surgery	201

Idarucizumab was 100% effective in reversing the anticoagulant effect of dabigatran

Indications for Dabigatran Reversal (Group A)

	n	%
GI Bleeding	**137**	**45.5**
Intracranial	98	32.6
Trauma-related	78	25.9
Other	52	17.3
IM/Retroperitoneal	19	6.3
Pericardial	7	2.3
Intraarticular	5	1.7
Intraocular	1	0.3
Unknown	4	1.3

Pollack et al NEJM 2017 Volume 377(5):431-441

Patients Who Received More Than One Dose of Idarucizumab.

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

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

Pollack et al NEJM 2017 Volume 377(5):431-441

GUIDE TO THE MANAGEMENT OF BLEEDING AND URGENT SURGEY IN PATIENTS TAKING DABIGATRAN (A DIRECT THROMBIN INHIBITOR)

Major bleed

Dabigatran

Consider time since last oral dose + dosing regimen, concomitant medications

Measure FBC, U+E, eGFR, PT/aPTT/fibrinogen, thrombin time (TT)

Dabigatran assay* if TT is abnormal

- **Consider oral activated charcoal (<2 hours since ingestion)**
- **Local haemostatic measures (**mechanical compression, surgical/endoscopic/radiological intervention)
- **Blood product replacement therapy and optimisation of pH and body temperature as per major haemorrhage protocol**
- **Tranexamic acid (1g IV)**
- **<u>If reversal is necessary, administer Idarucizumab (Praxbind®)</u>****

Limb / Life-threatening bleed

<u>Administer Idarucizumab (Praxbind®)</u>**

(Dialysis is an alternative means of removing dabigatran from the circulation if Idarucizumab is not available)

*__Measurement of dabigatran level__ may be appropriate, particularly if there is concern about impaired renal function as dabigatran is 80% renally excreted. **This is not necessary if the thrombin time is normal as the thrombin time is very sensitive to dabigatran.**

- Dabigatran assay: test available in the RVI laboratory

A level of 200-400 ng/mL at 2-4 hours post-dose reflects therapeutic anticoagulation. A level of 50-150 ng/mL is considered a trough level. A level of <30 ng/mL should reflect negligible anticoagulant effect

Please discuss with a haematologist prior to requesting measurement of drug levels

**A standard dose of 5g IV idarucizumab is administered. This is given as two boluses of 2.5g not more than 15 minutes apart. It is obtained from the RVI EAU antidote cupboard or RVI/FRH emergency drug cupboard.

Please discuss with a haematologist prior to using Idarucizumab (Praxbind®)

Send a coagulation sample 15 mins after administration and continue to monitor any other factors that are contributing to bleeding

GUIDE TO THE MANAGEMENT OF BLEEDING AND URGENT SURGEY IN PATIENTS TAKING A FACTOR Xa ANTAGONIST

Major bleed

FXa inhibitor
(rivaroxaban, apixaban, edoxaban, betrixaban)

Consider time since last oral dose + dosing regimen, concomitant medications

Measure FBC, U+E, eGFR, PT/aPTT/fibrinogen

Drug-specific assay*

- **Consider oral activated charcoal (<2 hours since ingestion)**
- **Local haemostatic measures (**mechanical compression, surgical/endoscopic/radiological intervention)
- **Blood product replacement therapy and optimisation of pH and body temperature as per major haemorrhage protocol**
- **Tranexamic acid (1g IV)**

Limb / Life-threatening bleed

Consider: Prothrombin complex concentrate (PCC)
Activated PCC (FEIBA) rFVIIa (NovoSeven)**

No specific reversal agent exists for this class of anticoagulant. Treatment is largely supportive while waiting for the drug to be cleared

*__Measurement of drug level__ may be appropriate, particularly if there is concern about impaired renal function as the FXa inhibitors are 25-35% renally excreted

- FXa inhibitor assay: test available in the RVI laboratory

A level of 200-400 ng/mL at 2-4 hours post-dose reflects therapeutic anticoagulation. A level of 50-150 ng/mL is considered a trough level. A level of <30 ng/mL should reflect negligible anticoagulant effect

Please discuss with a haematologist prior to requesting measurement of drug levels

There is no published evidence to support the **use of haemostatic agents (PCC/aPCC/rFVIIa) in the setting of haemorrhage or urgent surgery in patients taking a factor Xa antagonist

Please discuss with a haematologist prior to use

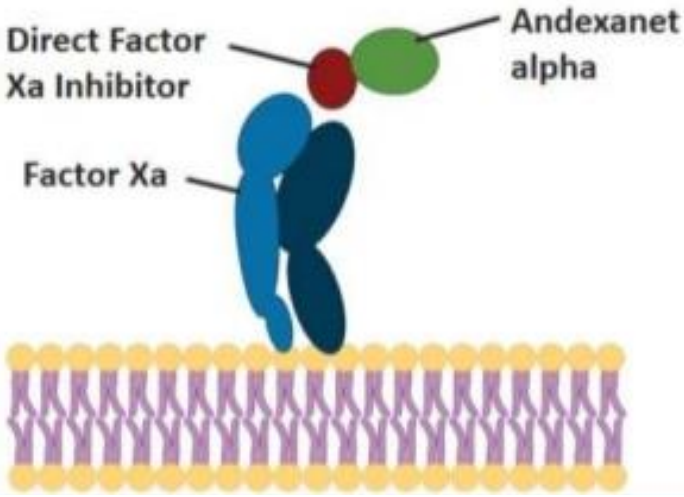
More antidotes are coming …….

Andexanet alfa

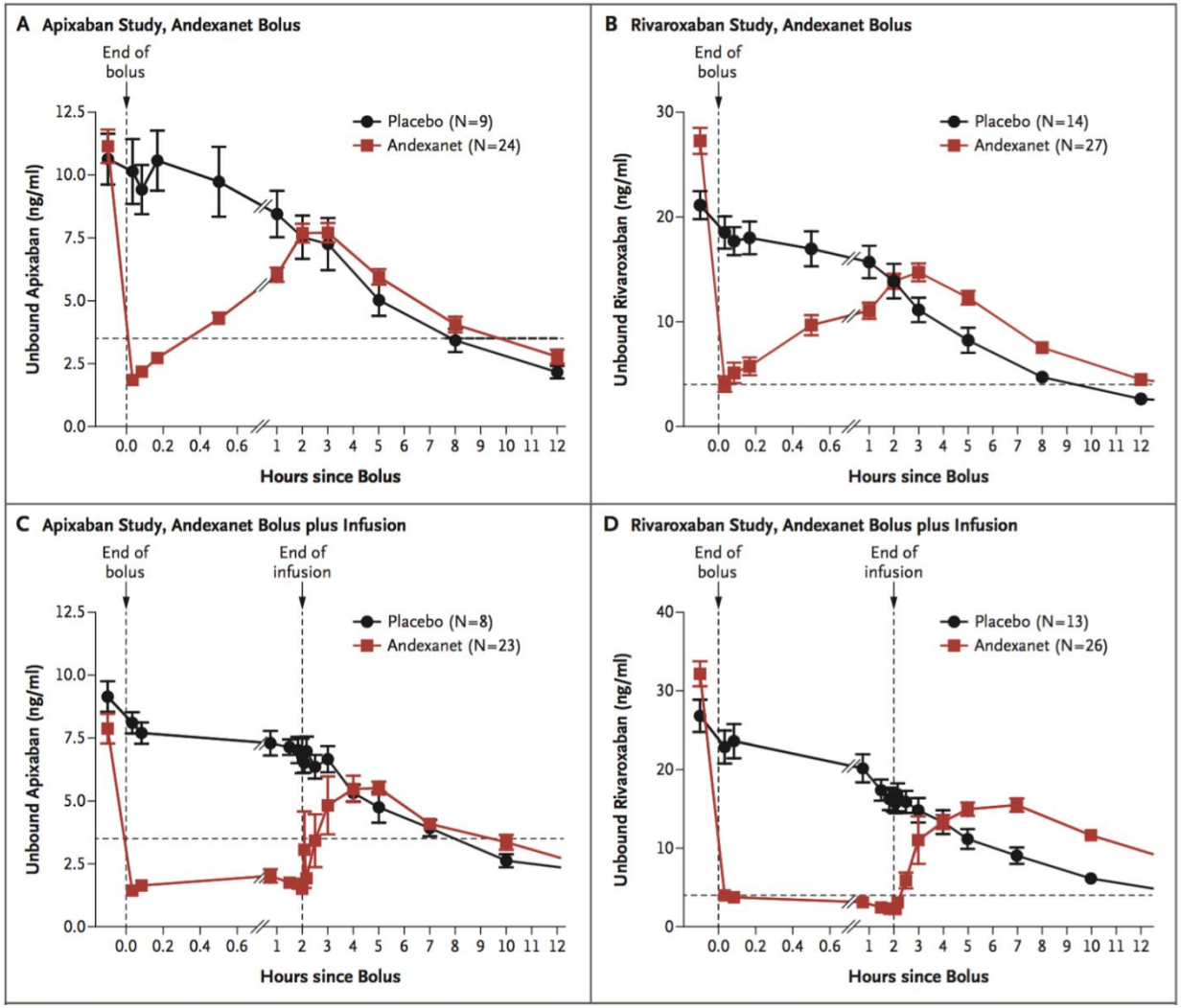
Antidote for Factor Xa Inhibitors

Properties

- An engineered version of human FXa, lacking the direct catalytic activity of the native protein[a]
- Acts as a Factor Xa decoy. Binds with high-affinity, blocking inhibition of FXa[a]



Andexanet Reverses Apixaban and Rivaroxaban in Healthy Volunteers



Siegal D et al NEJM 2015

Andexanet Alfa for Acute Major Bleeding Associated With Factor Xa Inhibitors

Connolly et al NEJM, 2016

67 patients with acute bleeding

20 were found subsequently to have v little anti-Xa inhibition on board (<75 ng/ml)

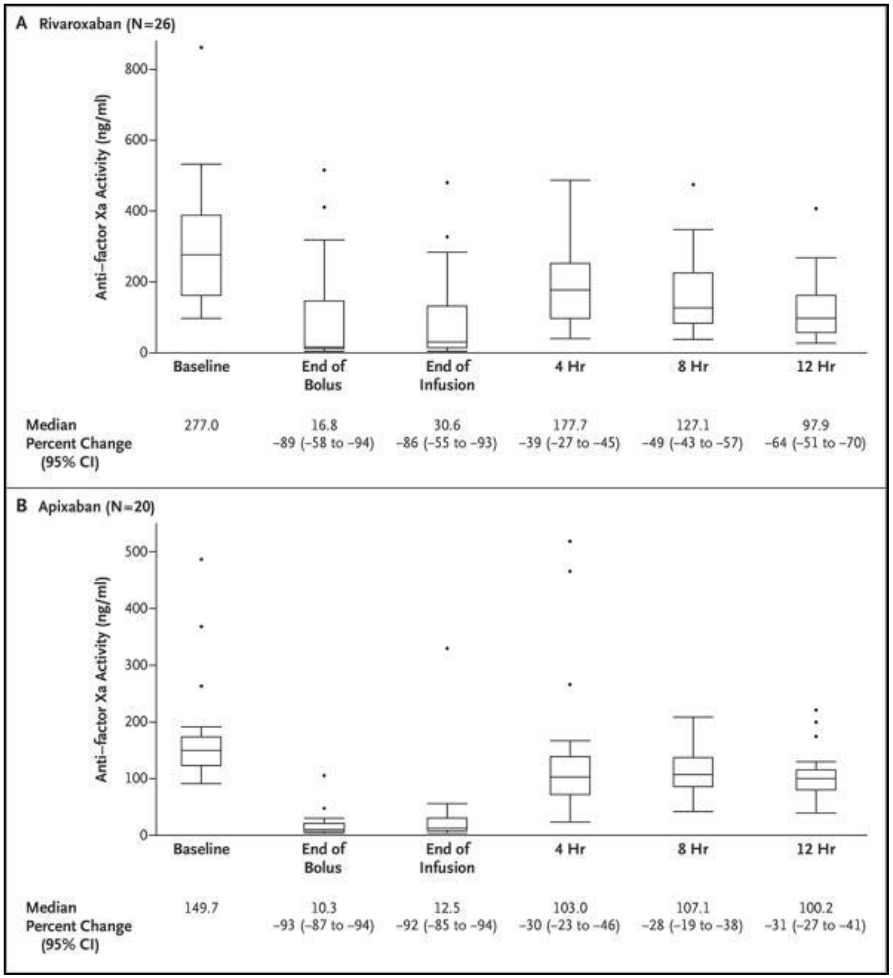
49% GI Bleeding

Rivaroxaban / Apixaban

Andexanet bolus then 2 hour infusion; dose depended on time since most recent dose of Xa inhibitor

Andexanet Alfa for Acute Major Bleeding Associated With Factor Xa Inhibitors

Connolly et al NEJM, 2016



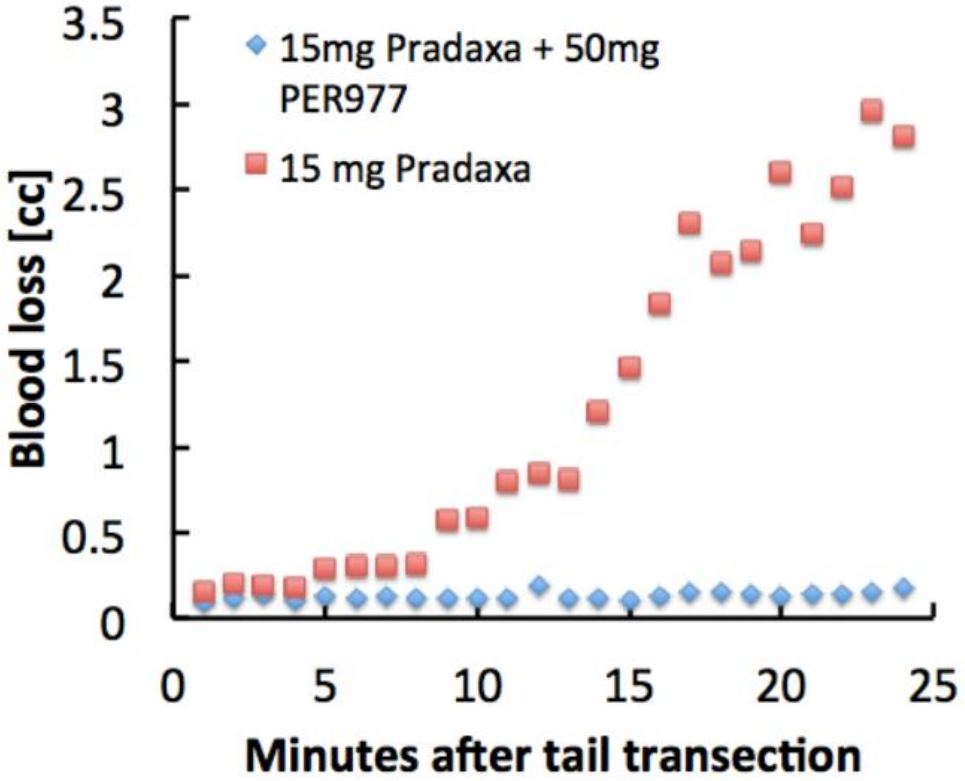
Effective Haemostasis in 79%

Thrombotic events in 18%

Aripazine - Universal DOAC antidote

- PER977 (Aripazine) from Perosphere Inc
- Synthetic small molecule (512Da)
- Binds all DOACs plus UFH and LMWH
- Action: Binding by charge-charge interaction (non-covalent) preventing the anticoagulant from binding to target

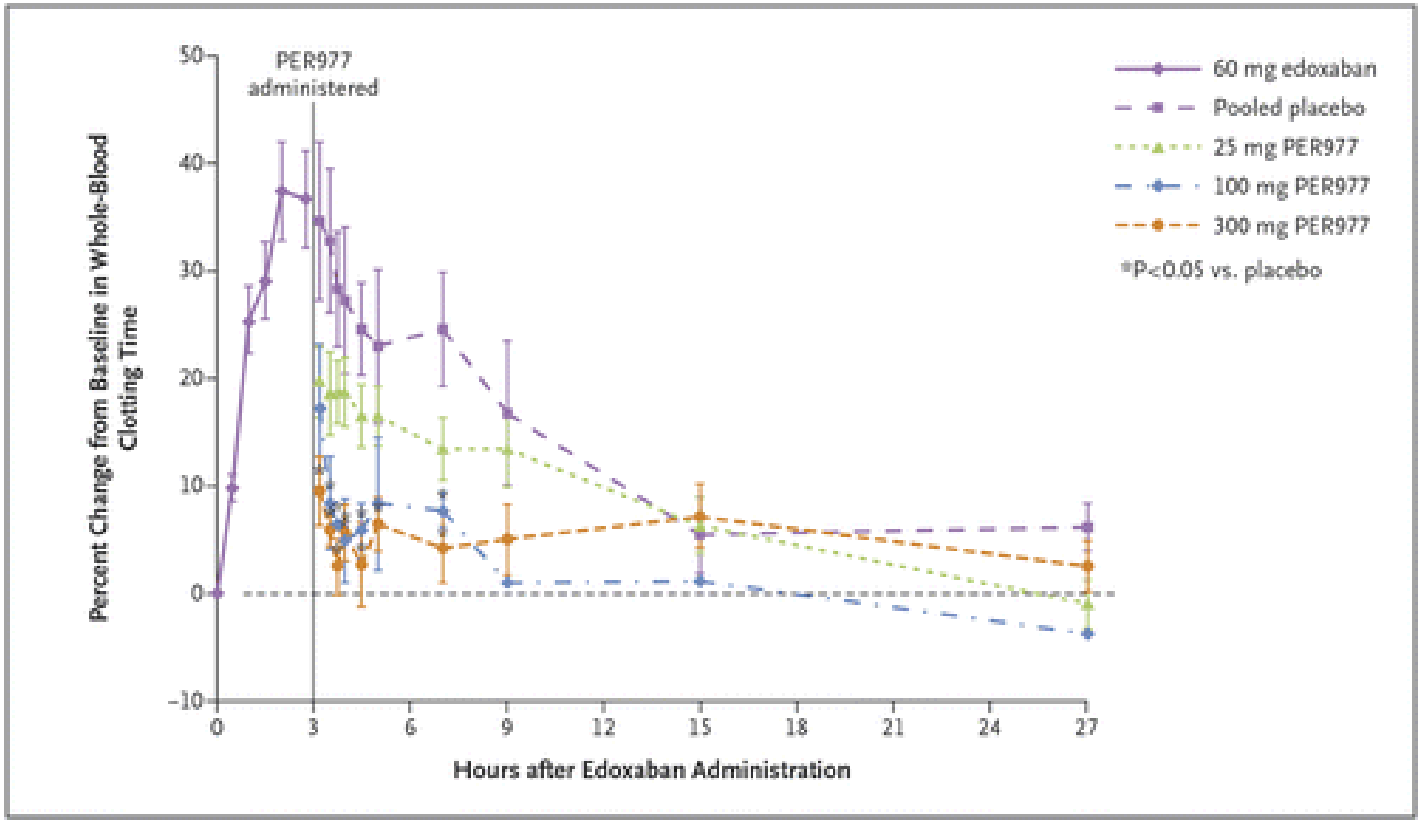
PER977 reverses ~100x overdose of dabigatran etexilate (15mg p.o.) in a rat tail transection model



No PER977 50mg PER977

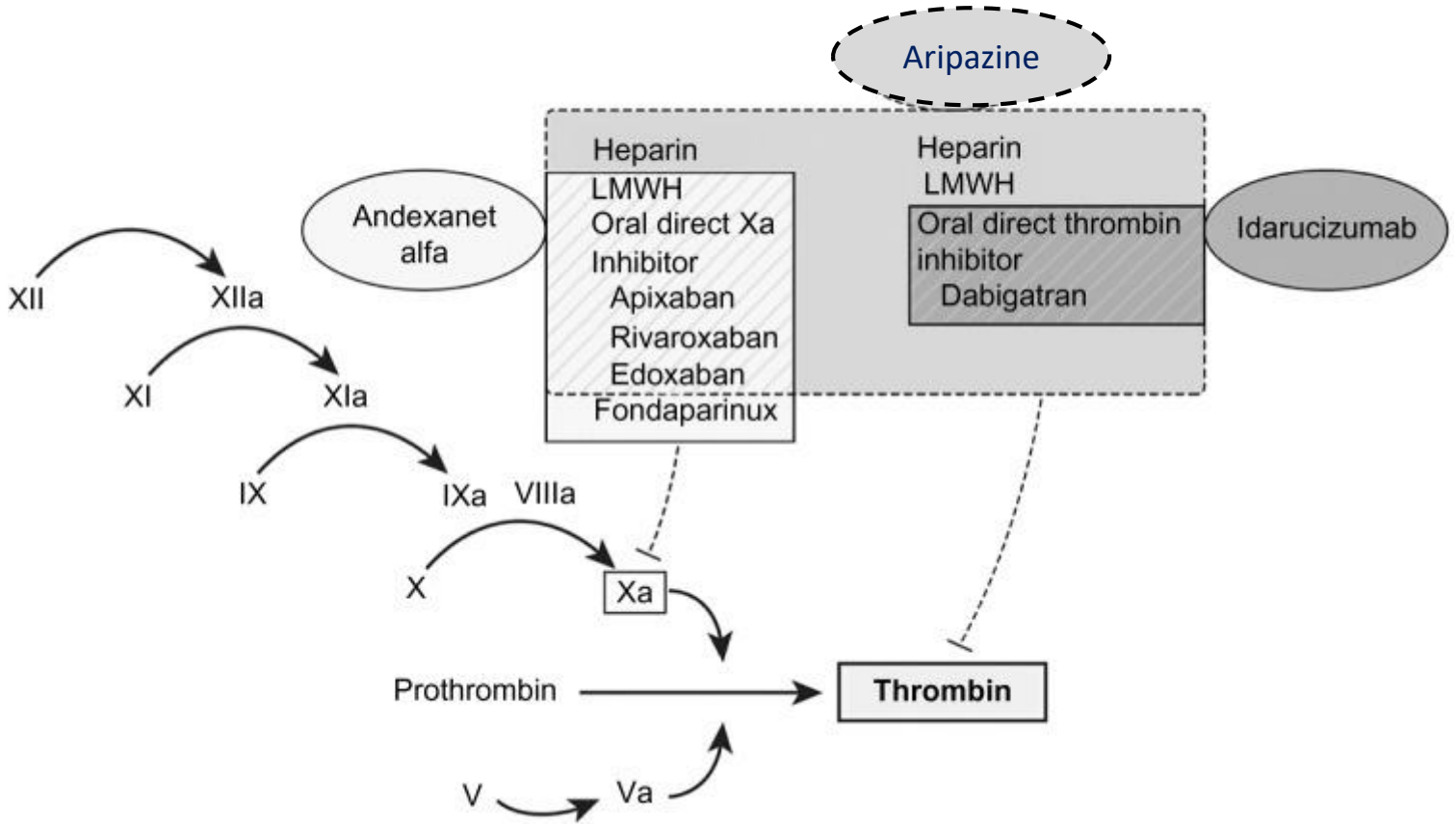
AHA 2012 meeting presentation

Aripazine reverses Apixaban effect



Ansell JE et al. NEJM 2014

DOACS AND THEIR REVERSAL AGENTS – THE FUTURE



Summary

- GI bleeding in anticoagulated patients remains challenging
- For warfarin the antidotes are vitamin K and PCC
- Current DOAC bleeding management is with supportive care, waiting for effect to wear off
- Idaricuzimab is licensed and available for Dabigatran reversal
- Andexanet not yet licensed but likely to be available within 1-2 years
- Aripazine may be a universal antidote for Thrombin and Xa inhbitors

- When/If to re-start anticoagulation?

When/If to re-start anticoagulation after GI Bleeding

Most studies have shown an net benefit of restarting anticoagulation

Overcome reluctance to re-start

Individualise decision – type and intensity of anticoagulation