

Praxbind-a novel anticoagulant reversal agent

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The Problem

- Venous Thrombosis is the third leading cause of vascular death.
- Incidence rates increase from 1 per 10,000 annually among persons less than 40 years of age to nearly 1% annually among persons 80 years of age or older.
- more than one third of cases occur in persons older than 60 years of age.

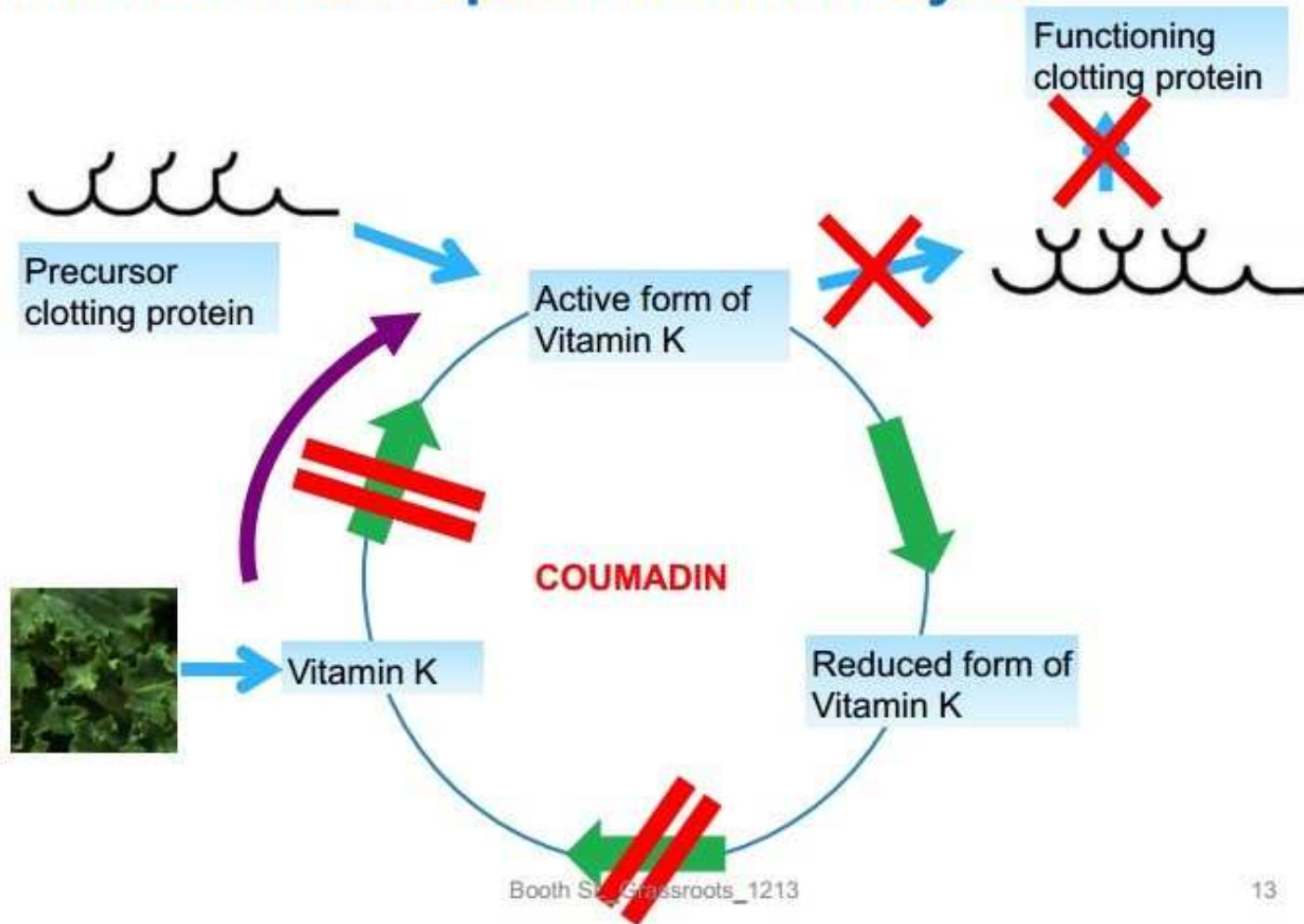
The Answer



Haemorrhagic Sweet Clover Disease



Warfarin Interrupts Vitamin K Cycle



The Problem with the Answer

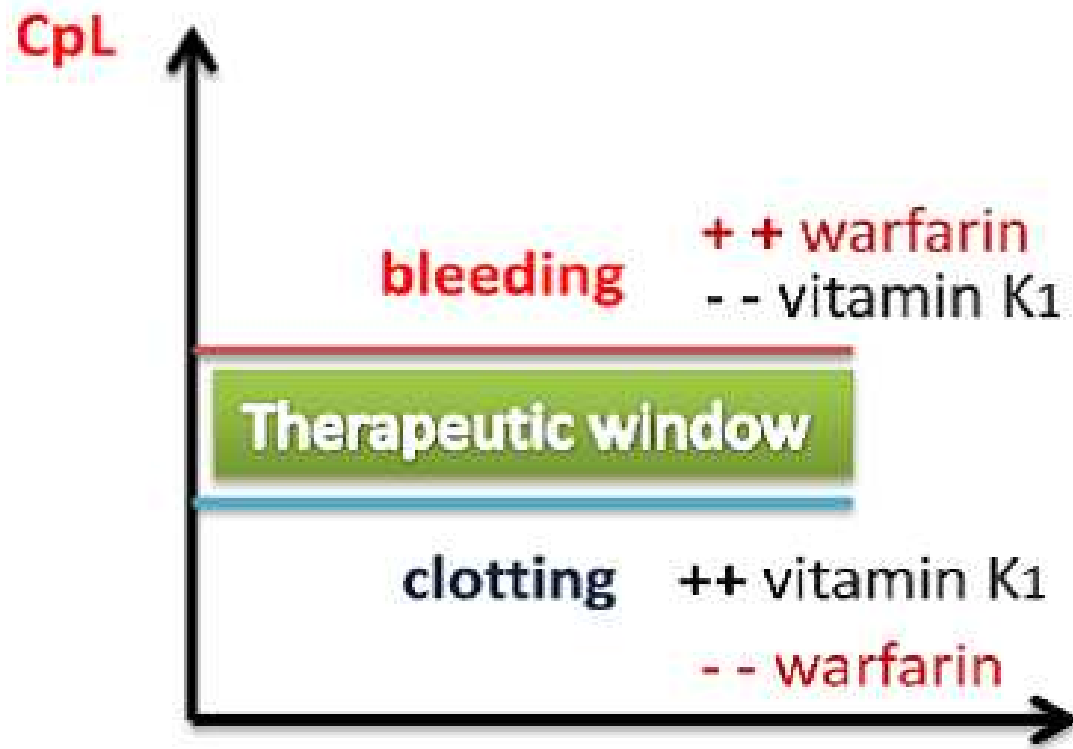
Table 2. Select Food, Drug, Herbal, and Dietary Supplement Interactions With Warfarin

Increase Anticoagulation Effect (↑ INR)	Decrease Anticoagulation Effect (↓ INR)
Amiodarone	Barbiturates
Azole antifungals	Carbamazepine
Capecitabine	Cholestyramine
Cimetidine	Estrogens
Dan shen	Ginseng
Fluoroquinolones	Green tea
Fluorouracil (5-FU)	Phenytoin
Garlic	St. John's wort
Ginkgo	Vitamin K
Levothyroxine	(e.g., leafy green vegetables
Macrolides	such as broccoli, brussels sprouts,
Metronidazole	cabbage, collard greens,
Omeprazole	kale, red leaf lettuce,
Trimethoprim/sulfamethoxazole	spinach)
Vitamin E	

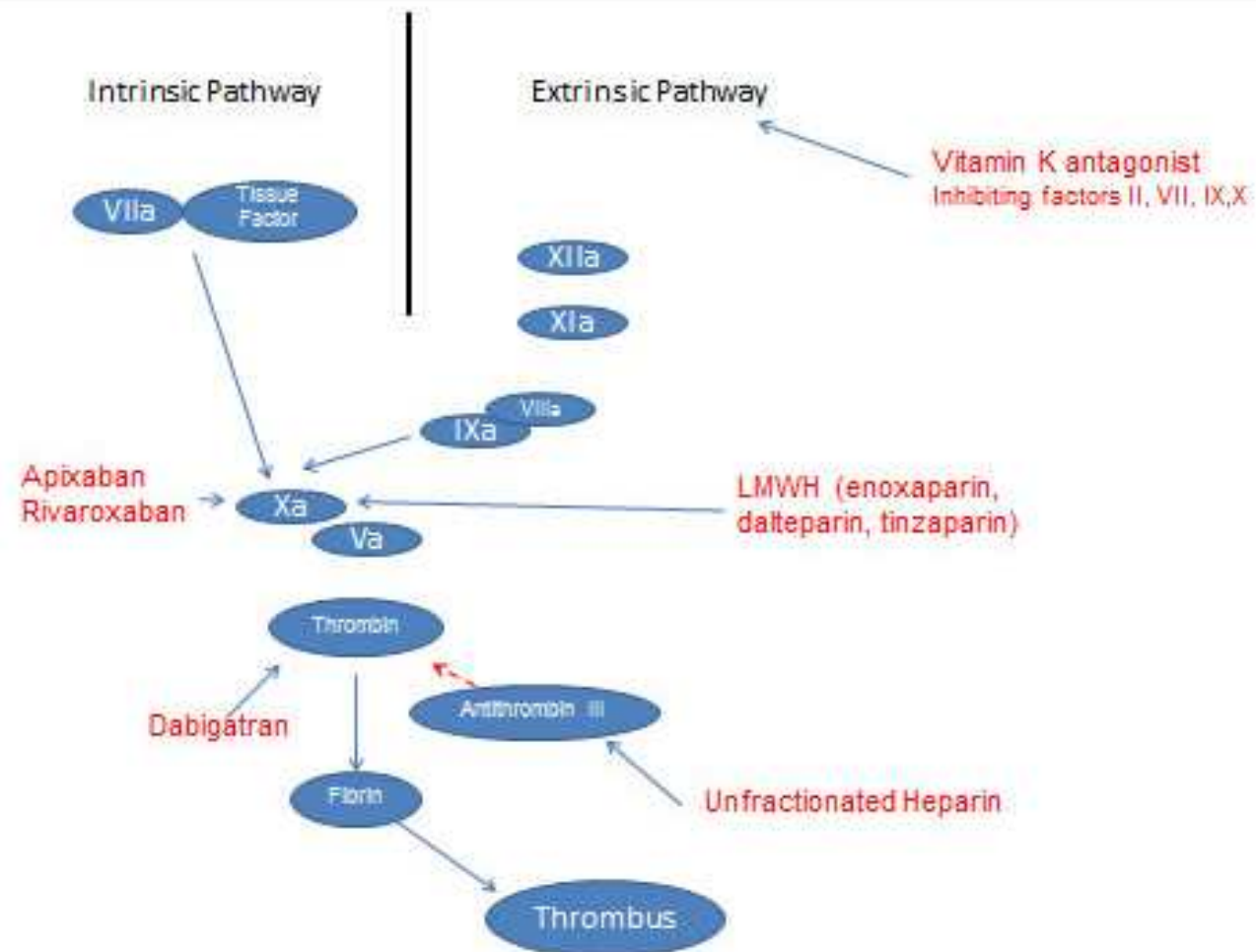
INR: international normalized ratio.

Sources: References 6, 8, 11. Please refer to these references for a complete list and description of interactions.

The Problem with the Answer



Newer Solutions



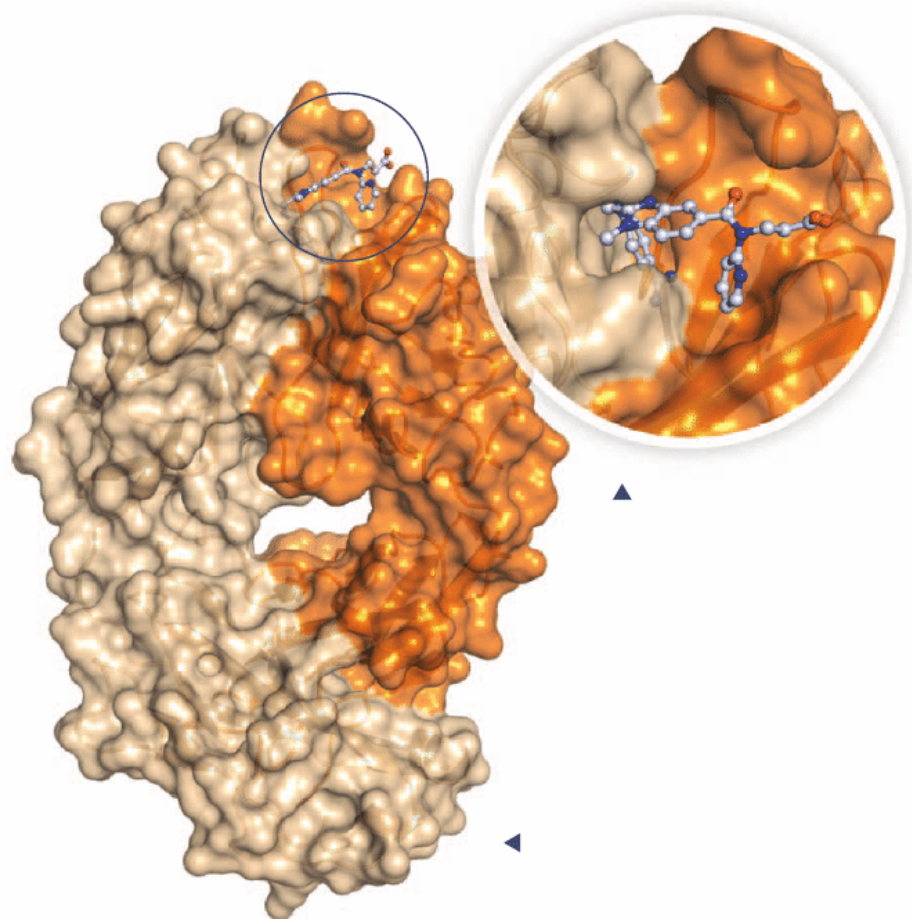
Dabigatran (Pradaxa)

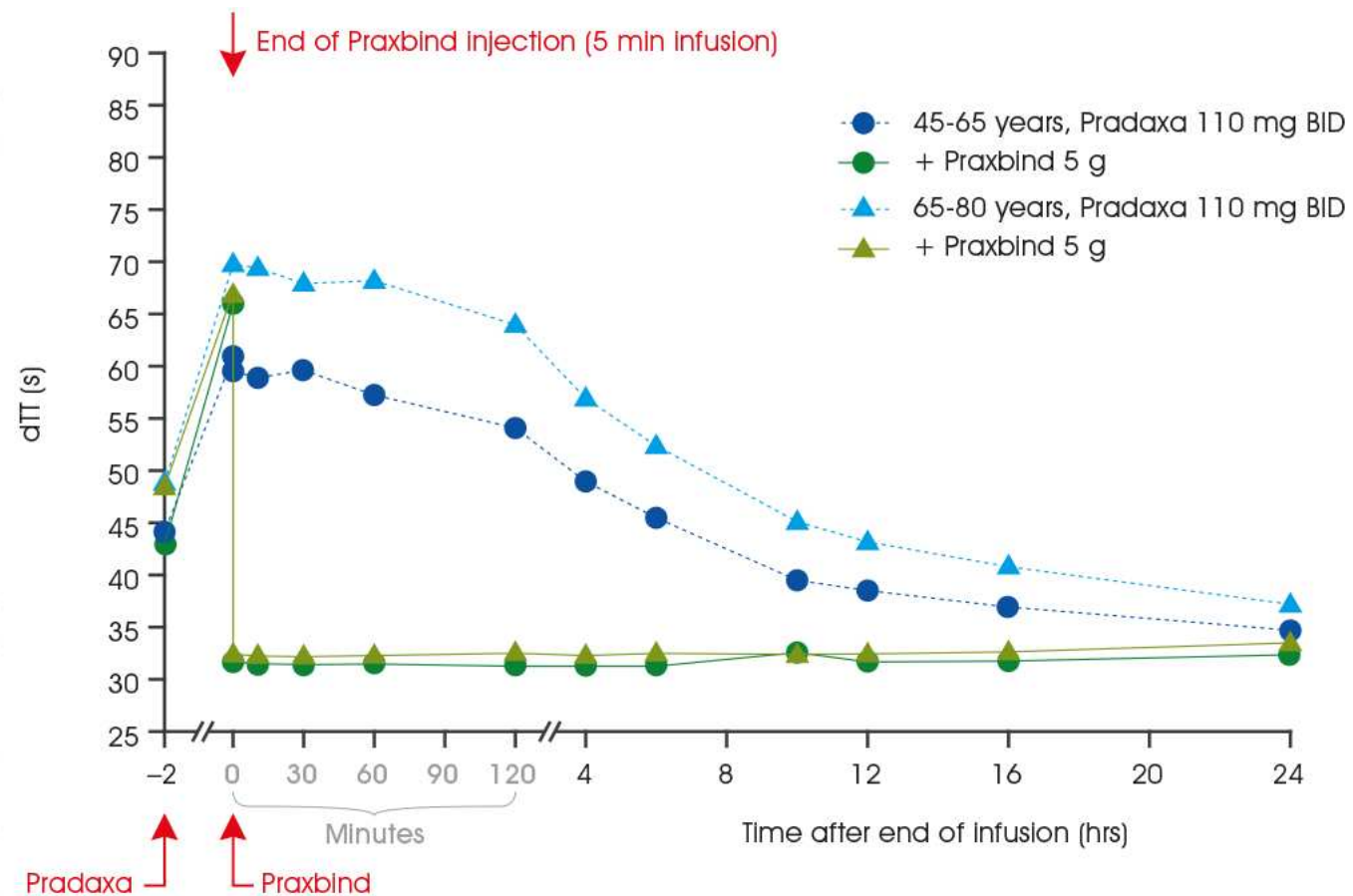
- Oral anticoagulant (DOAC)
- Direct Thrombin Inhibitor
- **No monitoring required**
- Used in AF/following orthopaedic procedures
- Not effective in pts with metallic heart valves
- Efficacy proven in large studies
- FDA (USA) approved 2010
- **No antidote at approval**

2015-FDA approve dabigatran antidote

- Praxbind (Idarucizumab)-effective antidote to dabigatran
- Dabigatran is almost completely covered making it unable to interact with thrombin.
- Praxbind potently and rapidly binds to with a high affinity (350-fold more potent than the binding affinity of dabigatran for thrombin).

Praxbind binding to dabigatran





dTT: diluted thrombin time

Review of uses 2016

- June-November 2016
- Praxbind issued on 4 occasions (for 4 patients)

HWPH

- Held in Bloodbank
- 4 cases

Frimley

- Held in pharmacy
- Never used

4 patients

4 patients-overview

Request Source	Indication for Dabigatran	Reason for reversal	Dabigatran dose	Clotting response	outcome
ED	AF	Collapse Intra-cerebral bleed	150mg BD	complete	survived
ED	AF (liver cirrhosis)	GI bleed	150mg BD	complete	RIP D0
ED	AF	GI bleed	110mg BD	complete	RIP D+7
ED	AF (colostomy)	# femur	110mg BD	95%	Survived

Patient 1

- 72 yr old woman-AF on dabigatran 150mg BD
- Collapse at home
- Low Glasgow Coma Scale
- CT scan: extensive haemorrhage
- APTT ratio 1.53
- Recovering on Stroke Unit

[A]



Patient 2

- 74 yr old man on dabigatran 150mg BD (AF)
- Liver cirrhosis/aortic Stenosis/Ischaemic heart disease
- On warfarin previously ? Non-tolerant
- Recent admission with fall/kidney injury
- Admitted with massive PR bleed
- APTT ratio 5.5
- Received Vit K/RBC transfusion
- Died on evening of admission

Patient 3

- 89 yr old man with AF previously on warfarin
- June 2016-spontaneous retroperitoneal bleed
- Anticoagulation halted for two weeks
- Cardiology advice: start dabigatran 110mg BD
- October 2016-Upper GI bleed
- Mesenteric artery embolisation-? Pancreatic mass
- Patient died on ITU

Se:610
Im:50

[H]

[R]



Patient 4

- 78yr old man AF on dabigatran 110mg BD
- AKI stage 2/bilateral hip replacements
- Aortic artery aneurysm (stented)
- October 2010-fall-#pelvis
- Confused
- Pre-theatre request for Praxbind

Se:601
Im:33

[R]

[H]

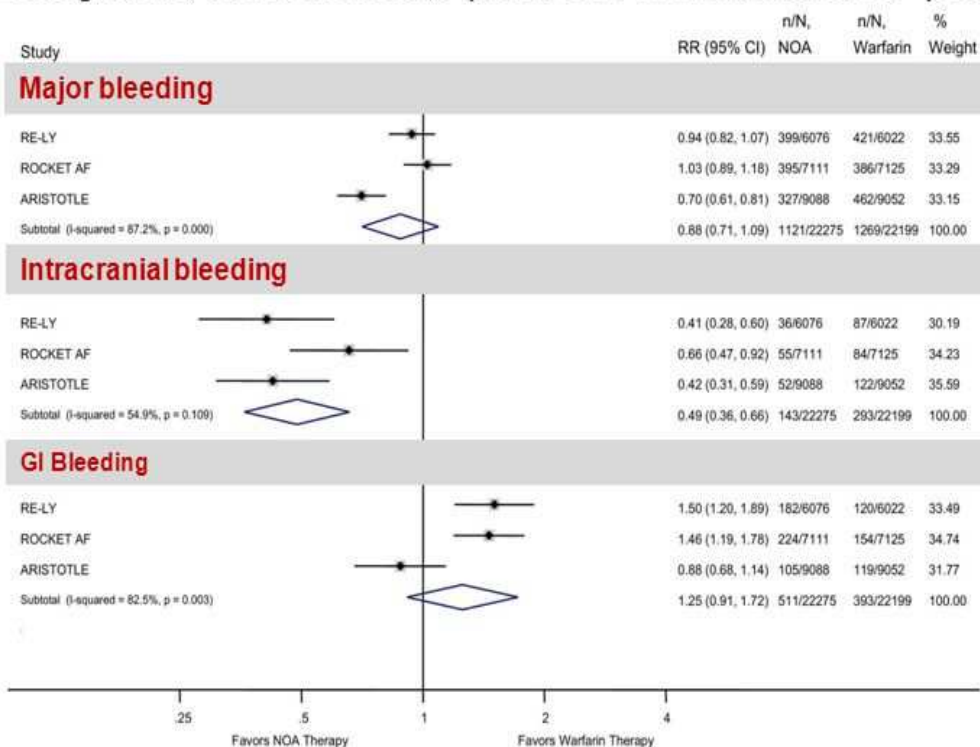


Risk-assessment?

- High BP
- Abnormal renal function
- Stroke
- Bleeding condition
- Labile INR
- Elderly (over 65 yrs)
- Drug associated with bleeding

Meta-analysis of Efficacy and Safety of New Oral Anticoagulants

Dabigatran, Rivaroxaban, Apixaban vs. Warfarin in AF patients



Should Praxbind be issued by Transfusion?

Pros

- Control by Haematologist
- Its not a blood product but neither is Novo VII or Beriplex

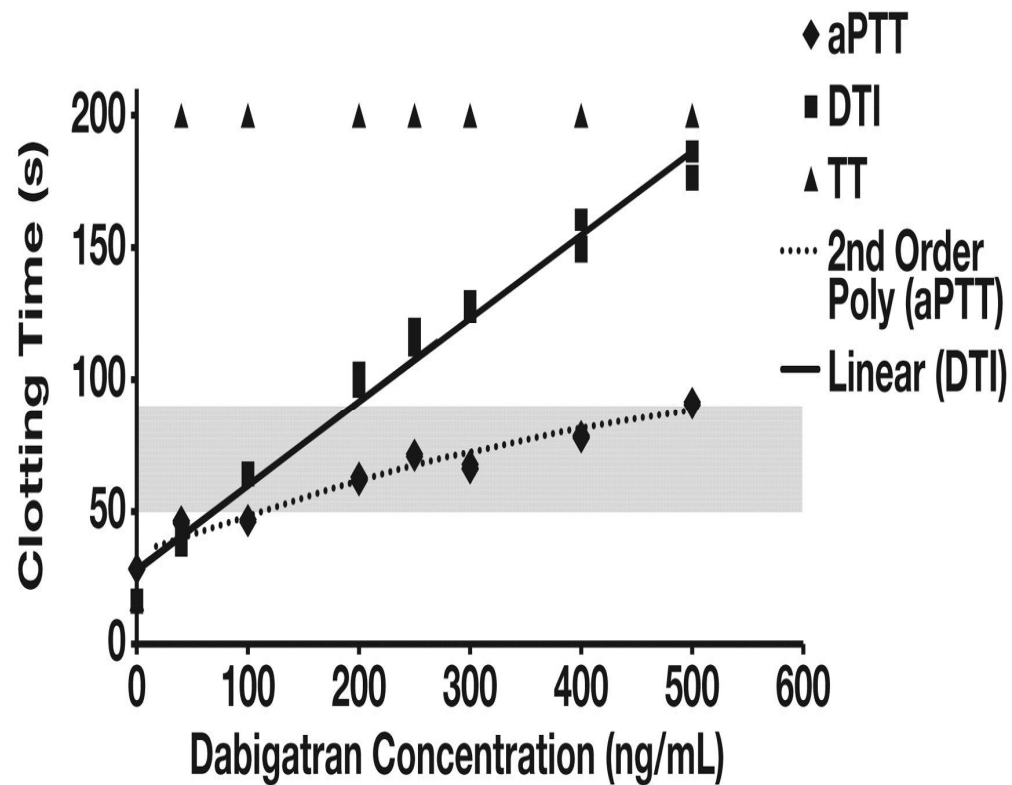
Cons

- First in a line of NOAC antidotes
- This is a drug not a blood product

Measuring dabigatran effect

Dilute Thrombin time

ECT ecarin clotting time



Questions

- Are we using the DOACs appropriately?
- Who should hold the reversal agent?
- How do we assess response?
- Are there any better ways of anticoagulating patients?

Summary

- Newer anticoagulants safer, but not risk-free
- Search still on for ideal anticoagulant
- We are gaining experience with newer agents.

Anticoag tomorrow

Margaret Gomes	70Kg	18499Q	4.6.16/	ED	AF, on dabigatran	Collapse, Large Intracerebral bleed	150mg	04/06/2016 02:10	5g (100ml)	No		No	18.4/1.2 (23:55)	49/1.53	NA	33.5/1.05	Survived: On ASU
Peter Charles		34732N	19/10/2016	ED	AF, on dabigatran, previously on Warfarin but patient choose to stop Cirrhosis, CAD	Massive PR bleed	150mg prior admission, 110mg as inpatient	19/10/2016, 19:05	5g (100ml)	Yes 2 RBC	Vit k 10mg IV	3.9.16-fall, 24.6.16-ascities	77.8/4.8 (17:47)	189.3/5.92 (17:47)	N/A	N/A	RIP: 19/10/2016 22:50 cause GI haemorrhage
Peter LEE	72.2Kg	21928H	02/07/2016	ED	AF, on dabigatran, started 2 days ago, previously on warfarin	Vomiting, abdo pain, PR bleeding, ITU notes state secondary to malignancy	110mg	2.7.16, 13:00	5g (100ml)	Yes 2 RED CELLS		14.6.16 Retroperitoneal bleed secondary to warfarin	18.2 40.5/1.27	N/A	N/A	Surgery at Frimlry on 7.7.16: Mesenteric embolisation. Transferred back to WXP W11 then to ITU, developed bowel Ischaemia due as consequence of procedure MH: 9RBC, 3FFP, 1Cryo, 1Plt. RIP 9.7.16	
David WEBB			24/05/2016	ED	AF, AAA stents, Stoma	Fall FNOF	110mg	27.5.16, 11:10	5g (100ml)				30.5/2.0 (15:39) 25.9/1.7 (02:58 25.5.16) 20.3/1.3 (26.5.16 09:54) 16.9/1.1 (27.5.16 10:57)	87.5/2.73 (25.5.16 10:16) 74.7/2.33 (26.5.16 09:54), 60.7/1.9 27/5/2016	42.7/1.33 28.5.16,	14.4 00:07	Survived