Direct Oral Anticoagulants in clinical practice:

Guidance, Management, Interactions and reversal

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Declaration of interests

- The practice has received funding from: Abbott, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Dawn, INRStar, Medtronic, Oberoi Consulting, Pfizer, Roche, Sanofi-Aventis, Servier.
- An advisor to: Anticoagulation Europe, Arrhythmia Alliance, Heart Valve Voice, National Stroke Association, Syncope Trust
- A trustee of Thrombosis UK, AF Association

The perfect anticoagulant

- Effective
- Oral
- Fast onset of action
- Short half life
- Predictable pharmacokinetics
- No drug/food interactions
- Fully reversible

- Do the NOACs fulfill these criteria?

Indications and Dosing

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Prevention of VTE post THR/TKR	110mg bd	2.5mg bd		10mg od
Prevention of CVA in AF	150mg bd (110mg bd)	5mg bd (2.5mg bd)	60mg od	20mg od
Treatment of acute VTE	150mg bd	10mg bd for 7/7 5mg bd	60mg od	15mg bd for 3/52 20mg od

Renal function

Anticoagulant	Creatinine clearance (ml/min)		
	30-50	30-15	<15
Apixaban	5mg bd	2.5mg bd	AVOID
Dabigatran	150mg bd (110mg bd)	AVOID	
Edoxaban	60mg	30mg	AVOID
Rivaroxaban	15mg od	15mg od	AVOID

What do NOACs interact with?

Interaction Type	Outcome	Dabigatran	Rivaroxaban	Apixaban
Pharmaco kinetic	**Increase** of at least 50% in anticoagulant plasma concentration	Amiodarone Dronedarone Ketoconazole Quinidine Verapamil	Clarithromycin Itraconazole Ketoconazole Posaconazole Ritonavir Voriconazole	Itraconazole Ketoconazole Posaconazole Ritonavir Voriconazole
Pharmaco kinetic	**Decrease** of at least 50% in anticoagulant plasma concentration	Carbamazepine Rifampin St. Johns Wort	Carbamazepine Phenobarbital Phenytoin Rifampin St. John's Wort	Carbamazepine Phenobarbital Phenytoin Rifampin St. John's wort
Pharmaco dynamic	Increased risk of bleeding	ASA NSAIDs Platelet aggregation inhibitors Anticoagulants Thrombolytics	ASA NSAIDs Platelet aggregation inhibitors Anticoagulants Thrombolytics	ASA NSAIDs Platelet aggregation inhibitors Anticoagulants Thrombolytics

How do NOACs affect the coagulation screen?

Coagulation tests with Anticoagulant Drugs

Test	UFH	LMWH	Warfarin	Rivaroxaban	Apixaban	Dabigatran
PT	-	-	↑↑↑	↑/-	-/↑	-/↑
APTT	↑↑↑	-/↑	↑	-/↑	-/↑	↑↑↑
Fibrinogen	-	-	-	-	-	-
Thrombin Time	↑↑↑	↑	-	-	-	↑↑↑
Anti-Xa	↑	↑↑↑	-	↑↑↑	↑↑↑	-
Haemoclot	↑↑	↑	-	-	-	↑↑↑

Switching from one anticoagulant to another

Switching from warfarin to NOAC

- Apixaban
  - Wait till INR < 2.0
- Dabigatran
  - Wait till INR < 2.0
- Edoxaban
  - Wait till INR < 2.5
- Rivaroxaban
  - Wait till INR < 3.0 AF
  - Wait till INR < 2.5 DVT, PE

What to do if a dose of a NOAC is missed?

- Once daily regimens
  - Take the forgotten dose up to 12hrs after time of usual intake
- Twice daily regimens
  - Take the forgotten dose up till 6hrs after time of usual intake

Bleeding

- Local measures
- Stop NOAC temporarily
- Tranexamic acid
- Coagulation screen
- Renal function
- Discuss with haematologist if ongoing issue

Elective minor (when warfarin would not be stopped)

	Dabigatran	Rivaroxaban	Apixaban
Minor dental work	12 hours post dose	18-24 hours post dose	>24 hours post dose
Major dental work	24 hours post dose Next dose > 4 hours post procedure	24 hours post dose Next dose > 4 hours post procedure	24-48 hours post dose Next dose > 4 hours post procedure
Upper/lower Endoscopy + simple biopsy Cataract removal Joint injection	24 hours post dose Next dose > 4 hours post procedure	24 hours post dose Next dose > 4 hours post procedure	24-48 hours post dose Next dose > 4 hours post procedure

NHS GGC Guidance based on SPC Dabigatran, Rivaroxaban, Apixaban

Emergency Surgery and Bleeding

Warfarin

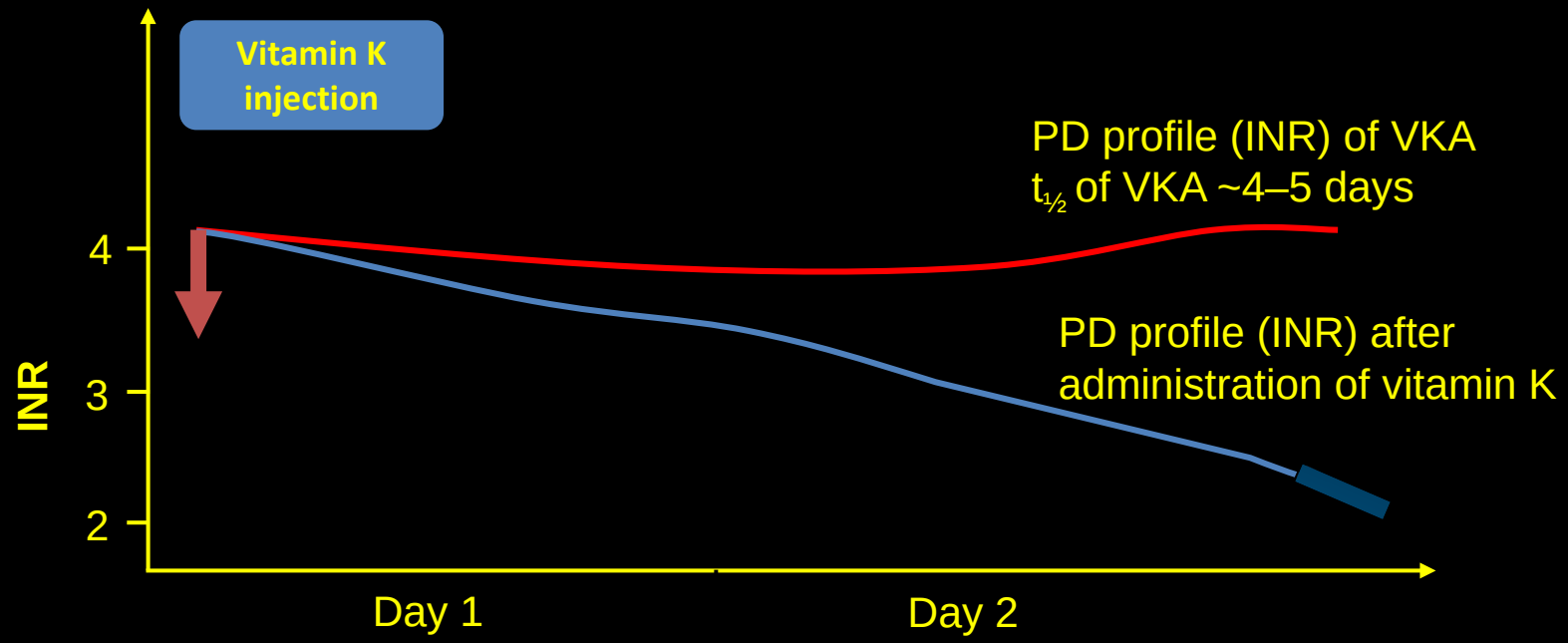
- Vitamin K
  - IV 6 hours
  - PO 24 hours
- Prothrombin complex concentrates (PCCs)
  - Factors II, VII, IX, X
  - Reversal within 30 minutes
- Can assess INR for effectiveness/safety

NOACs

- No specific reversal agent
- Well-adsorbed to activated charcoal
  - give within two hour of swallowing
- Dialysis
  - Dabigatran – yes
  - Rivaroxaban, apixaban – no
- General principles
  - Check coagulation screen
    - Assess effect
  - Check renal function
    - Assess half life
- Products
  - largely speculation/ based on non-clinical data
  - off-licence use; safety issues (thrombosis)

Vitamin K - no Immediate Effect on INR

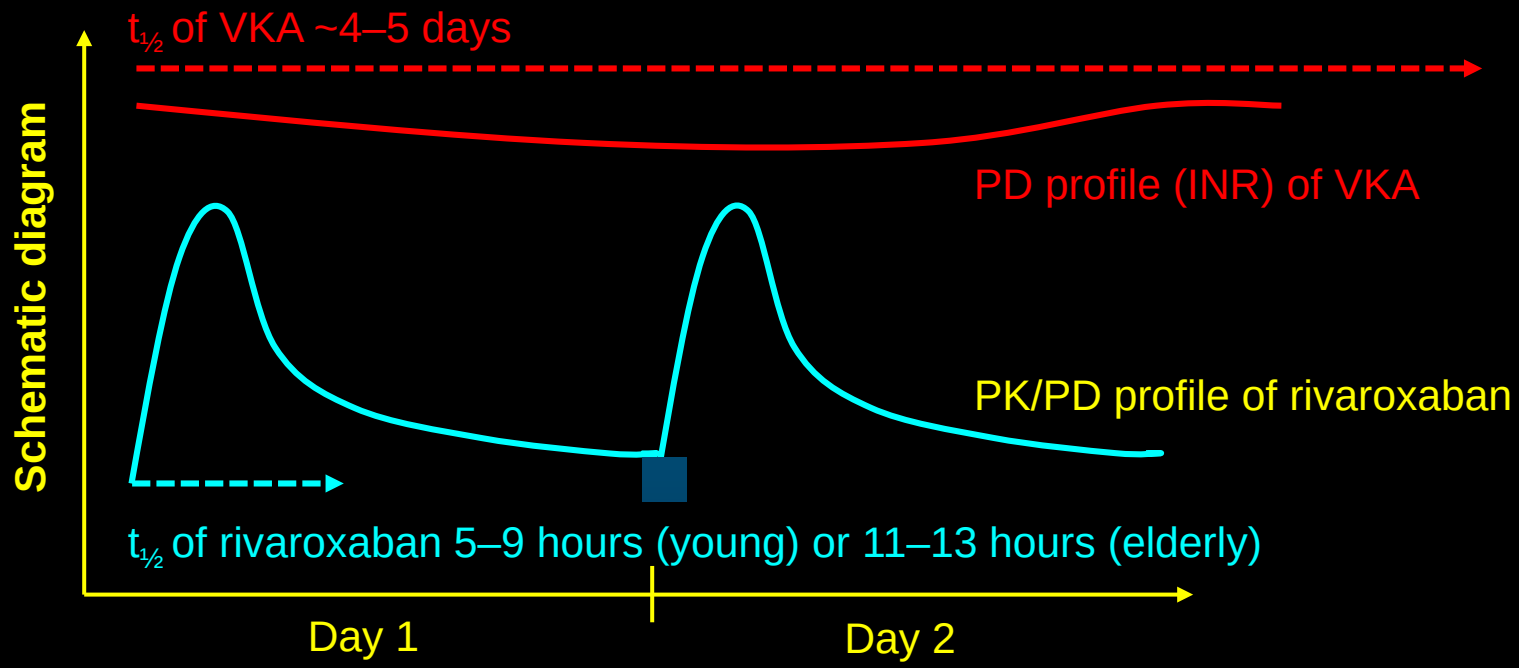
- **Schematic diagram showing effect of vitamin K on INR**
- **Vitamin K has a slow onset (>24 hours)[1]**
  - **Vitamin K supports generation of normal, functioning clotting factors in the liver**
  - **Effectivity of INR normalization depending on VKA used (different half-lifes; (from 9–11 hours for acenocoumarol, to 90–140 hours for phenprocoumon)[1,2]**



1. Heidbuchel et al, 2013; 2. Scharf et al, 2009

Emergencies in Anticoagulated Patients

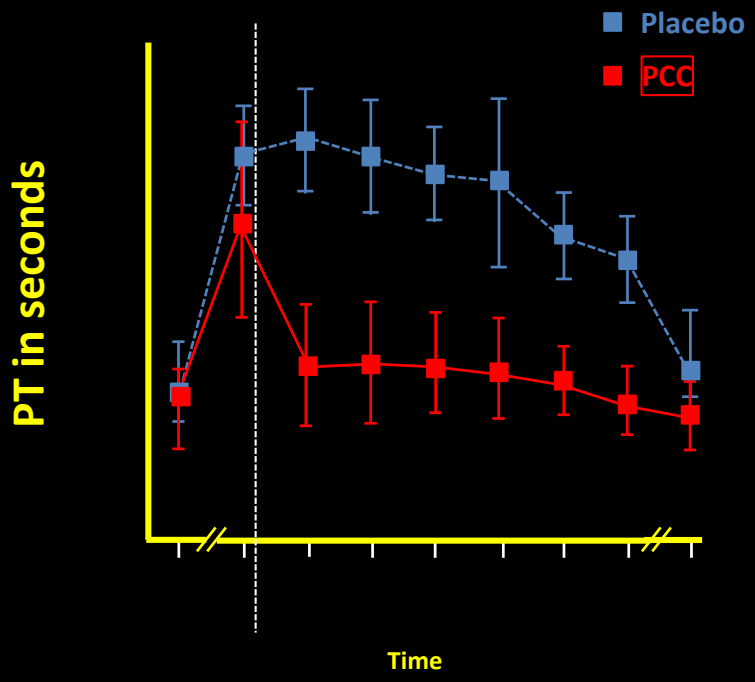
- Schematic diagram showing PK/PD characteristics of VKA and rivaroxaban
  - Reversal strategies may be required if action of drug is long and needs to be antagonized in emergency situations



PD, pharmacodynamic; PK, pharmacokinetic; $t_{½}$, half-life

1. Makris *et al*, 2012; 2. Kubitza *et al*, 2005; 3. Kubitza *et al*, 2008

Rivaroxaban-Induced Anticoagulation Reversal with PCC



- 20 mg rivaroxaban was administered bid for 2.5 days followed by PCC (Prothrombin Complex Concentrate - Cofact®, 50 U/kg body weight)
- Prolongation of PT was reversed completely by PCC
- ETP was reversed by PCC with an overshoot in effects
- Limitation
  - PT agent used showed low sensitivity to rivaroxaban
  - Prolongation of PT in this study was approximately 4 seconds at maximum

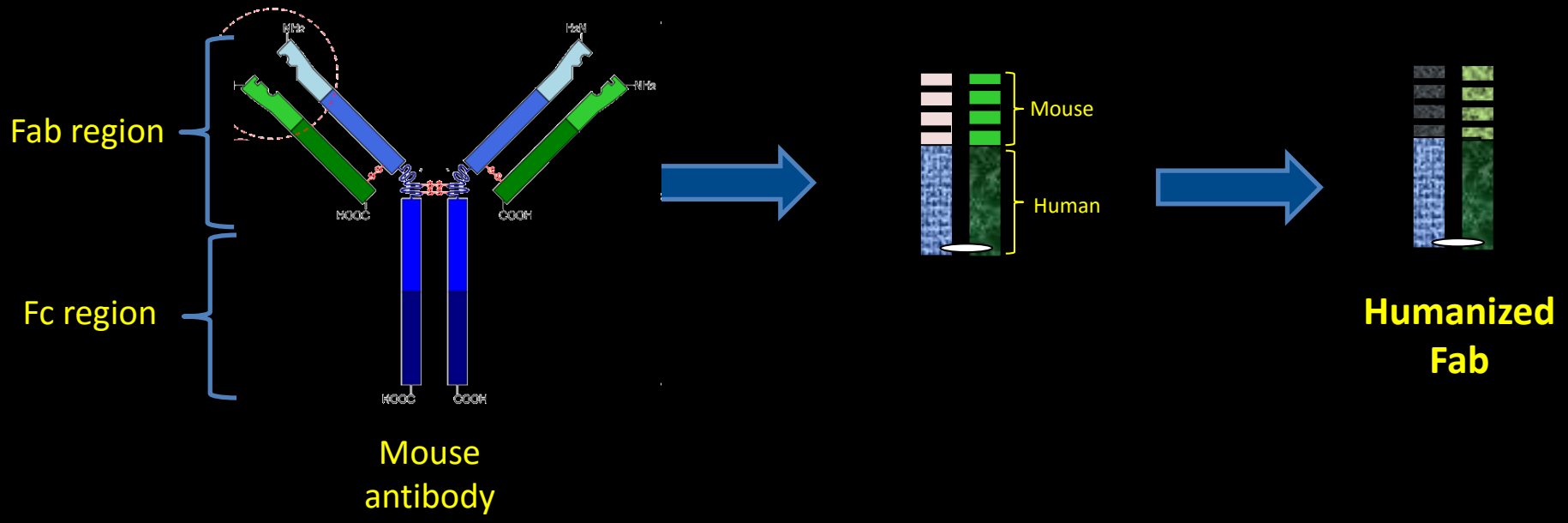
Eerenberg et al. Circulation 2011;124:1573–1579

Specific Reversal Agents for Non-VKA Oral Anticoagulants

Company	Compound	Reversal for:			Status
		Factor Xa inhibitor	Factor IIa inhibitor	LMWH/ fondaparinux	
Portola Pharma-ceuticals	**PRT064445/ (andexanet alfa)**	Universal	No	Yes (antithrombin-mediated Factor Xa inhibition)	Phase II completed One phase III with apixaban completed; rivaroxaban and edoxaban - onngoing
Boehringer Ingelheim	**BI 655075 (idarucizumab)**	No	Specific for dabigatran	No	Phase I completed;[3] phase III started[4]
Perosphere, Inc.	**PER977** (aripazine)	Universal	Universal	Universal	Phase I completed[5]

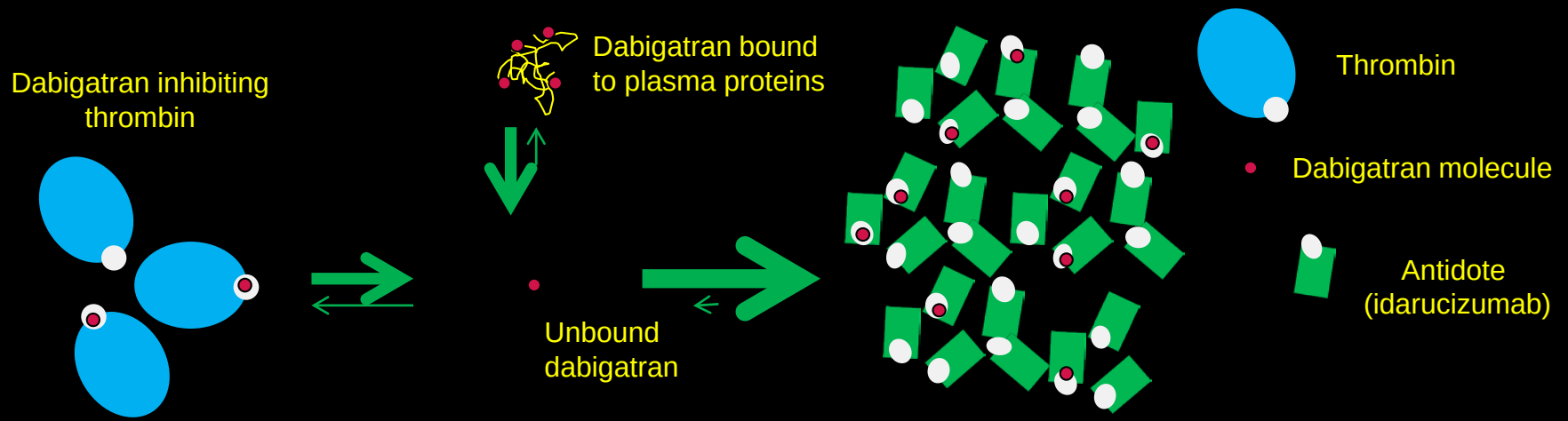
Idarucizumab development process

- Monoclonal mouse antibody developed with high dabigatran binding affinity
- Monoclonal antibody was then humanized and directly expressed as a Fab fragment in mammalian cells



van Ryn J. Presented at the AHA Congress, Los Angeles, USA. 5 November 2012. Presentation 9928; van Ryn J et al. Circulation 2012;126:A9928

Idarucizumab mode of action



Idarucizumab alters the equilibrium – dabigatran dissociates from thrombin

Idarucizumab rapidly binds to dabigatran in the plasma

Guideline for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on rivaroxaban

Rivaroxaban is an oral factor Xa inhibitor with a half life of 7-11 hours and mostly renal 66% excretion.
There is no licensed reversal agent for rivaroxaban.

Rivaroxaban-related bleeding
Or requirement for urgent reversal in case of need for emergency surgery

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STOP rivaroxaban

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- Assess clinical bleeding [1,2] and resuscitate patient as appropriate. May need to act before lab results are back in emergency.
- Check: FBC, G&S, U&E and Clotting screen, PT, APTT, TT, Fibrinogen, d-dimer
- Rivaroxaban prolongs PT – if PT is normal rivaroxaban levels are low.
- Consider rivaroxaban plasma level
- Indicate time of last rivaroxaban dose when requesting test and considering management options.

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Mild bleeding

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Delay next dose or discontinue treatment as appropriate.

With normal renal function level of riavaroxaban reduces rapidly in 24 hours

Monitor clotting screen and PT

Moderate-Severe bleeding

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Discuss with haematologist on call

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Activate massive haemorrhage pathway

- Symptomatic treatment
- Consider tranexamic acid (avoid in DIC)
- Mechanical compression
- Surgical intervention
- Activated charcoal (if rivaroxaban ingestion < 2 hours before
- Fluid replacement and haemodynamic support- ensure good diuresis
- Consider Prothrombin complex concentrate (Octaplex) (50 units/Kg), max 3000 units, IV infusion at 10ml/min
- blood product support as indicated
- consider role for interventional vascular radiology

Life-threatening or site critical bleeding

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Discuss with haematologist on call

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- Manage as for Moderate-Severe bleeding
- Give Prothrombin complex concentrate (Octaplex) (50 units/Kg), max 3000 units, IV infusion at 10ml/min

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Reassess clinically
Repeat FBC, U&E, Clotting. PT and rivaroxaban level to be monitored

[1] **Moderate to Severe bleeding: -** reduction in Hb ≥ 2gd/L, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area (i.e. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).

[2] **Life-threatening bleeding:** – symptomatic intracranial bleed, reduction in Hb ≥ 5gd/L, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

Practical Considerations

Starting a patient on a NOAC

- Check patient is not taking interacting drugs
- Counsel patient: it is an anticoagulant
  - Head injury, trauma, melaena, significant GI bleed, prolonged epistaxis, large ecchymoses/ haematoma
- Compliance- important to take as advised (od Rivaroxaban, bd Apixaban, bd Dabigatran)
- Baseline FBC, renal and liver function

Summary of use of NOACs

- Benefits of novel anticoagulants
  - Non inferior/superior to warfarin
  - More stable anticoagulation (in patients poorly controlled on warfarin)
  - Shorter half life
  - No requirement for anticoagulant monitoring
  - Fewer drug-drug interactions
  - No food-drug interactions
  - Less intracranial bleeding
- But
  - Limited reversal options
  - Increased drug costs compared to warfarin
  - Current lack of familiarity

Bleeding

- Local measures
- Stop NOAC temporarily
- Tranexamic acid
- Coagulation screen
- Renal function
- Discuss with haematologist if ongoing issue

Monitoring of Anticoagulants

Thank you for your attention

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