# Management of coagulation in anaesthesia and critical care

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## **Conflicts of interest**

Speaker honoraria:Boehringer Ingelheim, Bayer, BristolMyers Squibb, LEO Pharma, Pfizer

Advisory board:

Boehringer Ingelheim, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Pfizer

Support to attend

Scientific meeting:

Boehringer Ingelheim

## Case 1

- 54 year old male on ITU with severe chest infection following complex surgery. Ventilated
  - Tracheostomy required
  - Plts 102
  - INR 1.6, APTT 1.4, Fibrinogen 2.4g/l

Management of Haemostasis?

## Coagulopathy in critical care

- 30% of critically ill patients
- 50% of FFP is administered in ICU to non-bleeding patients
- Does FFP transfusion improve haemostasis?
- Is the INR predictive of bleeding?

## **TOPIC trial**

TRANSFUSION 2015;55:26-35, J Thromb Haemost 2015; 13:989-97

- 76 ICU patients requiring procedure with INR 1.5-3.0
- Randomised to 12ml/kg FFP vs no treatment

	FFP transfusion (n = 38)	No FFP transfusion (n = 38)
Fatal bleeding	0	0
Major bleeding	0	1
Minor bleeding	8	5
No bleeding	30	32

## Haemostatic balance: Hypo vs Hyper-coagulable



## Coagulation

**Tissue injury** 

Then a miracle occurs !!

A CLOT

## **TOPIC trial**

TRANSFUSION 2015;55:26-35, J Thromb Haemost 2015; 13:989-97

Median INR 1.8 (1.5-2.2)

FII 34% (26-46)

FV 48% (28-76)

FVII 25% (16-38)

AT 47% (35-78)

PC 33% (21-50)

PS 53% (32-75)

Thrombin generation 70% normal ROTEM virtually normal

### **Clotting factor increments with FFP**

British Journal of Haematology, 2004;125:69-73

Factor	3-4 units FFP	30ml/kg FFP
fibrinogen	0.4g/l	1.0g/l
Prothrombin	16u/dl	41u/dl
FV	10u/dl	28u/dl
FVII	10u/dl	38u/dl
FVIII	10u/dl	17u/dl
FIX	8u/dl	28u/dl
FX	15u/dl	37u/dl
FXI	9u/dl	23u/dl

### Case 2

- 76 year old female with carbomedics aortic valve requires elective hip replacement
- On warfarin with target INR 2.5

Management of peri-operative anticoagulation?

### Anticoagulation bridging: ORBIT-AF Circulation. 2015 Feb 3; 131: 488–494

- Prospective observational registry study
- 30% required anticoagulation interruption event
- 24% of these had heparin bridging
- Same CHADSVASc but more prior CVA and valve replacements in bridged patients
- Bleeding 5% vs 1.3% in non bridged
- MI, stroke and SE, major bleeding, hospitalisation or death 13% vs 6.3%
- Await BRIDGE and PERIOP-2 studies (LMWH vs no bridging)
- Continuation of anticoagulation with warfarin safer than stopping +/bridging for cardiac device implantation and catheter ablation





### Heparin production – New York Times



## Oral direct inhibitors (ODI's)



### EHRA PRACTICAL GUIDE (2013) 15, 625–651



~27%

**Bio-availability 50%** 

**Bio-availability 62%** 

~50%

### Case 3

- 75 year old male with AF and previous TIA
- Requires elective knee arthroplasty
- On Apixaban 5mg bd
- Advice on peri-operative anticoagulation management?

### How long to stop NOAC before surgery?

Adapted from EHRA practical guide for use of the new oral anticoagulants 2013

CrCl	Dabigatran		Rivaroxaban		Apixaban	
	Low risk	High risk	Low risk	High risk	Low risk	High risk
>80 ml/min	>24hr	>48 hr	>24 hr	>48hr	>24 hr	>48 hr
50-80 ml/mi	>36hr	>72 hr	>24 hr	>48hr	>24 hr	>48 hr
30-50 ml/mi	>48 hr	>96 hr	>24 hr	>48hr	>24 hr	>48 hr
15-30 ml/mi	Not indicated	Not indicated	>36 hr	>48 hr	>36 hr	>48 hr
<15 ml/min	PANIC					

### How to restart is the complicated bit!

### **APTT: increasing dabigatran concentration**



Dabigatran plasma concentration [ng/mL]

# Affect of Rivaroxaban on prothrombin time using different reagents



### From Mouse Monoclonal Antibody to Human Antibody Fragment (Fab):

A. Monoclonal antibodies were raised in mice immunized with dabigatran hapten coupled to carrier proteins.



B. Fc portion is removed (Fab)

- C. Constant regions are replaced with human amino acids (chimeric)
- D. Variable regions of Fab humanized



## The antidote issue

Lu et al Nature Medicine 19, 446-451 (2013)



thrombin and restore coagulation

## Guidelines

## Regional anaesthesia and patients with abnormalities of coagulation

The Association of Anaesthetists of Great Britain & Ireland The Obstetric Anaesthetists' Association

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place <sup>1</sup>	Acceptable time after block performance or catheter removal for next drug dose
Heparins					
UFH sc prophylaxis	< 30 min	1–2 h	4 h or normal APTTR	Caution	1 h
UFH iv treatment	< 5 min	1–2 h	4 h or normal APTTR	Caution <sup>2</sup>	4 h
LMWH sc prophylaxis	3-4 h	3–7 h	12 h	Caution <sup>3</sup>	4 h <sup>3</sup>
LMWH sc treatment	3–4 h	3–7 h	24 h	Not recommended	4 h <sup>4</sup>
Heneric alternatives					
Danaparoid prophylaxis	4-5 h	24 h	Avoid (consider anti-Xa levels)	Not recommended	6 h
Danaparoid treatment	4-5 h	24 h	Avoid (consider anti-Xa levels)	Not recommended	6 b
Bivalinudin	5 min	25 min	10 b or normal APTTR	Not recommended	6 b
Argatrobag	< 30 min	30-35 min	4 h or normal APTTR	Not recommended	6 b
Fondanarin ur, prophylaxis <sup>5</sup>	1-2 h	17-20 h	36-42 b (mosider anti-Xa levels)	Not recommended	6-12 h
Fondaparin ux treatment <sup>5</sup>	1-2 h	17-20 h	Avoid (consider anti-Xa levels)	Not recommended	12 h
			,		
Antiplatelet drugs		4.45.6	No	No. and Philament	Mar and distances i
NDAIDS	1-12 n	1-12 h	No additional precautions	No additional	No additional
• t t	12.241		No della terra terra secolaria a	precautions	precautions
Aspirin	12-24 h	Not relevant;	No additional precautions	No additional	No additional
Closed door of	12.245	irreversible	7 days	Net recommended	e la
Ciopidogrei	12-24 h	effect	7 days	Not recommended	on ch
Teneralar	15-30 minj	0.43 k	/ days	Not recommended	on ch
Tagreior	2 n	0-12 n	5 days	Not recommended	on ch
Fred Mills and July	< 5 min	4-8 n	an	Not recommended	on ch
eptimoatide	< o min	4-8 n	a n	Not recommended	on ch
Abciximab	< 5 min	24-48 h	48 n	Not recommended	6 h
Dipyridamole	/5 min	10 h	No additional precautions	No additional	6 h
				precautions	
Oral anticoagulants					
Warfarin	3–5 days	4–5 days	INR ≤ 1.4	Not recommended	After catheter removal
Rivaroxaban prophylaxis <sup>5</sup> (CrCl > 30 ml.min <sup>-1</sup> )	3 h	7–9 h	18 h	Not recommended	6 h
Rivaroxaban treatment <sup>5</sup>	3 h	7–11 h	48 h	Not recommended	6 h
(CrCl > 30 ml.min <sup>-1</sup> )					
Dabigatran prophylaxis or tr	eatment <sup>7</sup>				
(CrCl > 80 ml.min <sup>-1</sup> )	0.5-2.0 h	12–17 h	48 h	Not recommended	6 h
(CrCl 50-80 ml.min <sup>-1</sup> )	0.5-2.0 h	15 h	72 h	Not recommended	6 h
(CrCl 30-50 ml.min <sup>-1</sup> )	0.5-2.0 h	18 h	96 h	Not recommended	6 h
Apixaban prophylaxis	3-4 h	12 h	24-48 h	Not recommended	6 h
Thrombolutic decor					
Altenlare anistranlare	< 5 min	4-24 min	10 day	Not recommended	10 days
reteplase, streptokinase	< <b>3</b> mm		To days	Not recommended	io udys

### Antifibrinolytics – Tranexamic acid









- Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml)
- Consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in complex cardiac and vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery)

#### **Patient information**

- Provide verbal and written information to patients who may have or who have had a transfusion, and their family members or carers (as appropriate), explaining:
  - the reason for the transfusion
  - the risks and benefits
  - the transfusion process
  - any transfusion needs specific to them
  - any alternatives that are available, and how they might reduce their need for a transfusion
  - the implications of having a transfusion, such as no longer being able to donate blood
  - that they are encouraged to ask questions

- Offer oral iron before and after surgery to patients with irondeficiency anaemia
- Consider intravenous iron before and after surgery for patients with iron-deficiency anaemia who:
  - cannot tolerate or absorb oral iron
  - are diagnosed with functional iron deficiency
  - are diagnosed with iron-deficiency anaemia and the interval to surgery is considered short
  - are unable to adhere to oral iron treatment

### **Red cells**

- Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not have major haemorrhage or acute coronary syndrome.
- When using a restrictive red blood cell transfusion threshold, consider a threshold of 70 g/l and a haemoglobin concentration target of 70–90 g/l after transfusion.
- Consider a red blood cell transfusion threshold of 80 g/l and a haemoglobin concentration target of 80–100 g/l after transfusion for patients with acute coronary syndrome.
- Consider single-unit red blood cell transfusions for adults who do not have active bleeding

### Platelets

Patients who are having invasive procedures or surgery:

- Consider prophylactic platelet transfusions to raise the platelet count above 50x10<sup>9</sup>/L in patients who are having invasive procedures or surgery
- Do not routinely give more than a single dose of platelets in a transfusion

## Case 4

- Patient admitted for TKR
- Anaesthetist rings for advice (from theatre)
  Bouting pro on EBC a work earlier
  - Routine pre-op FBC a week earlier
    - Hb 120g/l
    - WCC 6.8
    - Plt 72

## Rate of complications in hip and knee surgery in English Hospitals 2012; 90 day VTE readmission, infection and bleeding rate



### 90 day VTE readmission rate: Elective Hip surgery







90-day VTE deaths

### 90 day VTE readmission rate: Elective Knee surgery



### 90 day VTE death: Elective hip surgery



90-day VTE deaths

admidate (Year)

#### 90 day VTE readmission rate: Hip and lower limb fracture



90-day VTE readmission rate (%)

### 90 day VTE death: hip and lower limb fracture



### Haemorrhage and Haematoma: trend 2002-2012



### 90 day infections: trend 2002-2012

