Perioperative Optimisation of Haemostasis & Coagulation

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Partial Curriculum Map (2010)

Basic	Intermediate	Higher
IO_BS_09	VS_IK_12	GU_HK_02
OB_BTC_C04	CT_IS_03	GU_HS_03
GU_BK_07	PC_IK_08	OB_HS_06
OB_BK_06	PB_IK_04	MA_HS_02
PB_BK_45	MT_IK_07	CT_HK_08
PB_BK_23	MT_IK_06	CT_HS_08
	MT_IS_04	CT_HK_09
	OR_IK_04	AD_HS_12
		MA_HK_08
		MA_HS_09

CCT in Anaesthetics 2010, The Royal College of Anaesthetists

Objectives

- List the components of an adequate haemostatic response
- Describe the pathophysiology of haemorrhagic shock
- Outline a management plan for haemorrhagic shock
- Diagnose DIC and list appropriate treatment options
- Describe risk factors and therapy for hyper-fibrinolysis
- Outline treatment of bleeding due to antiplatelet therapy
- Discuss the options to reverse effects of vitamin K antagonists

Clinical Scenarios

- Laparotomy for perforated viscus + septic shock
- Rib fractures & head injury in patient on warfarin
- Traumatic haemorrhagic shock

Scenario 1

67 year old female admitted with a 5 day history of severe abdominal pain, and vomiting. Anuria for 2 days. Hypotensive, peripherally shut-down, confused and lethargic in A&E. Chest x-ray shows air under the diaphragm. Scheduled for emergency laparotomy.

Hb 10.3 / WBC 29.8 / platelets 48
PT 24.6 / APTT 43 / Fibrinogen 0.95
Urea 21.8 / Creat 340

Q: How would you prepare this patient for theatre?
Q: How would you deal with intraoperative bleeding?

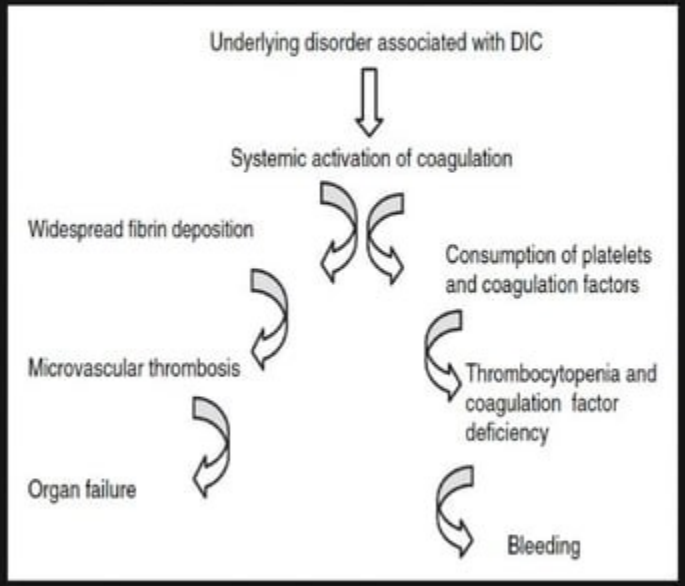
ISTH Scoring system for DIC

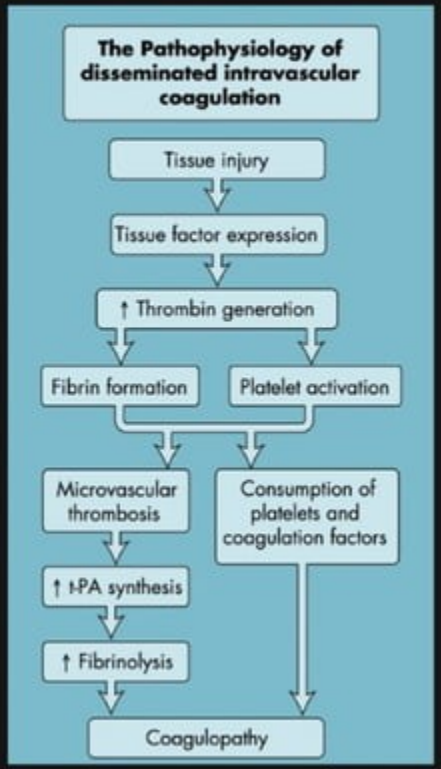
Test	Score
Platelet count	• > 100,000 = 0 • 51,000-100,000 = 1 • < 50,000 = 2
D-dimer or FDP	• No increase = 0 • Moderate increase = 1 • Strong increase = 2
Prolongation of PT	• < 3 seconds = 0 • > 3 but < 6 seconds = 1 • > 6 seconds = 2
Fibrinogen g/L	• ≥ 1 = 0 • < 1 = 1

Score ≥ 5 = overt DIC
Repeat daily if < 5

Taylor, F.B., Jr, , Toh, C.H., Hoots, W.K., Wada, H. & Levi, M. (2001) Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Journal of Thrombosis and Haemostasis., 86, 1327–1330.

Disseminated intravascular coagulation





DIC - Treatment

- Treat the underlying condition
- Platelets if < 50 and bleeding/high risk of bleeding
- FFP if bleeding or to cover procedure
- Factor concentrates e.g. PCC instead if volume overload
- If fibrinogen <1 g/L despite FFP treat with fibrinogen concentrate or cryoprecipitate
- Heparinise DIC with predominant thrombosis
- DVT prophylaxis if not bleeding
- Consider aPC in severe sepsis with DIC
- Consider tranexamic acid for DIC with primary hyper-fibrinolysis and severe bleeding

Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Brit J Haematol 2009; 145: 24-33.

Scenario 2

You are called to A&E to see a 78 year old male who has fallen of a ladder from a height of 6 feet. He was unconscious for around 10 minutes. He is now drowsy but responsive.
He has bruising and pain over his left chest. X-ray demonstrates at least 3 rib fractures and pleural fluid. There is no pneumothorax. CT brain shows a right frontal contusion with a small extradural.
He is in atrial fibrillation and takes warfarin.
PT 29 (INR 2.8), APTT 33, Platelets 145, HB 12.1

Q: How will you manage this man's coagulation?
Q: How will you deal with his pain?

Warfarin reversal

- Assuming bleeding or need for surgery in < 24 h
  - Prothrombin complex concentrate (PCC) ± Vitamin K
  - In absence of PCC can use FFP + Vitamin K, or rFVIIa*
- Vitamin K will reverse high INR within 24 hours
- INR < 5 will normalise over 4-5 days off warfarin
- What's in Octaplex?

* In urgent cases or where FFP is not available

PCC (Octaplex)

Name of ingredient	Octaplex Quantity per vial (20ml)	Octaplex Quantity per ml reconstituted solution
Total protein:		
Active substances		
Human coagulation factor II		
Human coagulation factor VII		
Human coagulation factor IX	500 IU	25 IU/ ml
Human coagulation factor X	360 - 600 IU	18 - 30 IU/ ml
Further active ingredients		
Protein C	140 - 620 IU	7 - 31 IU/ ml
Protein S	140 - 640 IU	7 - 32 IU/ ml

Factor	Half-life
II	48-60 hours
VII	1.5-6 hours
IX	20-24 hours
X	24-48 hours

The bleeding patient

Major/life threatening bleeding

- Intracranial
- Intraocular
- Compartment syndrome
- Pericardial
- Active bleeding and shock

Urgent clinical assessment
Check clotting screen
Contact Haematologist

- Stop warfarin
- Vitamin K 5mg (Konakion MM injection) by slow intravenous injection
- PCC (Beriplex®) 50units/kg IV

Check clotting screen 20 minutes post administration

- Adequate correction – recheck in 4 hours
- Inadequate correction – consider other causes, seek Haematological advice

Significant bleeding without haemodynamic compromise

- Stop warfarin
- Vitamin K 2mg (Konakion MM injection) by slow intravenous injection
- Consider PCC (Beriplex®) 50units/kg IV
- Check clotting screen at 4 hours or sooner if clinical deterioration

Minor bleeding

- Stop warfarin
- Consider Vitamin K 2mg Oral (Konakion MM injection used orally) or 1mg slow intravenous injection (Konakion MM injection)
- Check clotting screen at 24 hours or sooner if clinical deterioration

INR too high, but not bleeding

INR > 3.0 and < 6.0 (target INR of 2.5)
INR > 4.0 and < 6.0 (target INR of 3.5)

- Reduce warfarin dose or stop
- Restart warfarin when INR < 5.0

INR > 6.0 and < 8.0

- Stop warfarin
- Restart warfarin when INR < 5.0

The warfarin patient and surgery

- Elective surgery – always plan in advance
- Decide on a 'safe' INR for the procedure
- If surgery is postponed, reassess coagulation

Full warfarin reversal

- Stop warfarin 4 days pre-op
- Check INR on admission or morning of operation

Rapid reversal necessary (urgent surgical procedure)

Reversal in 4 to 24 hours

- Vitamin K 2mg Oral (Konakion MM injection used orally) or 1mg slow intravenous injection (Konakion MM injection)

Reversal within 1 hour

- PCC (Beriplex®) 50units/kg

Scenario 3

47 year old crushed by forklift truck. Bilateral femoral shaft fractures and unstable pelvic fractures. Left rib fractures.
BP 75/30 HR 130 ABG Hb 7.6 lactate 5.9 pH 7.22
2 litres 0.9% saline and 4 units O negative in A&E, taken to theatre for pelvic and femur stabilisation.
Ongoing pelvic bleeding ++

Q: What factors are contributing to the bleeding?
Q: What do you tell the blood bank (and when)?
Q: How would you optimise haemostasis?

Predicting need for massive transfusion in trauma patients…

- **ABC Score:**
- One point for each of…
  - **Penetrating trauma**
  - **Positive FAST scan**
  - **Arrival SBP < 90 mmHg**
  - **Arrival HR > 120 bpm**
- Score $\geq$ 2 was 75-90% sensitive (67-88% specific) for need for MT (Area under ROC = 0.83-0.9)

Cotton BA, Dossett L, Haut E, *et al*. Multicentre validation of a simplified score to predict massive transfusion in trauma. J Trauma 2010; 69 (Suppl1): S33-39.

Massive transfusion protocols

- Issues
  - Activation and transport delays
  - Outdated approaches/missing latest literature
  - Requests for products too slow
  - Product delays (FFP/platelets)
  - Not (patho-)physiological
- Solutions
  - Products issued as massive transfusion packs
    - E.g. 4-6 PRBC + 4-6 FFP + 1 plts (achieves 1:2:2 RBC:FFP:plt)
  - Use factor concentrates instead (or as well?)



AAGBI SAFETY GUIDELINE

Blood Transfusion and the Anaesthetist

Management of Massive Haemorrhage

Traumatic coagulopathy

Systemic acquired coagulopathy

- "Conventional"
- Consumption, dilution, inhibition

Endogenous acute coagulopathy

- Present in 25% on arrival to hospital
- Related to systemic hypoperfusion/inflammation
- Associated with
  - Greater need for transfusion
  - Higher risk of MODS
  - Longer ICU stay & Higher mortality (4x)

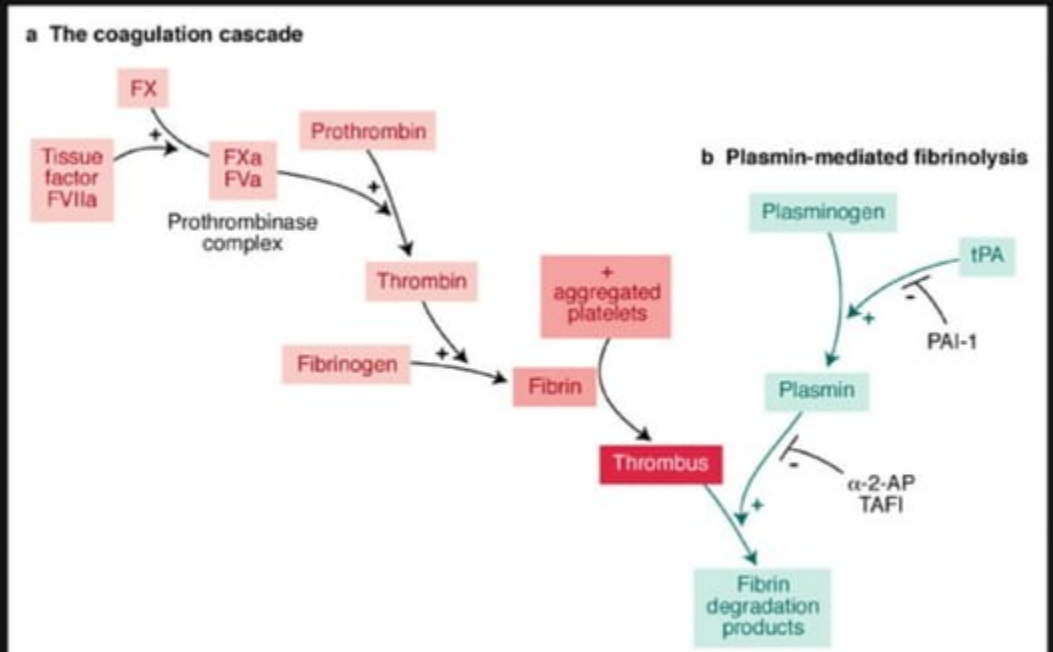
Mechanisms of Coagulopathy

- Loss of essential components
  - Absolute
    - *Consumption*
    - *Coagulation activation*
  - Relative
    - *Dilution*
- Inhibition of haemostatic system
  - Acidosis
  - Hypothermia

Hyperfibrinolysis

- Disinhibition of tPA
  - Consumption of PAI-1 by activated protein C
  - Direct release of tPA from damaged endothelium
- Settings
  - Cardiopulmonary bypass
  - Major trauma
  - Obstetrics
  - Major urological surgery
  - Major orthopaedic surgery

Coagulation and fibrinolysis



Summary of the coagulation and fibrinolysis cascades

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press

The “bloody vicious circle”…
The lethal triad…

- Acidosis
- Hypothermia
- Coagulopathy

Lier H, Krep H, Schroeder S, Stuber F. J Trauma. 2008;65:951–960

pH and coagulation

- pH < 7.4 - Altered platelet shape and structure
- pH 7.1
  - 50% reduction in thrombin formation
  - 35% reduction in fibrinogen
  - Reduced platelet count
  - Altered platelet receptor function
- Correction of acidosis
  - Effectiveness of bicarbonate unclear
  - THAM corrects thrombin and TEG values
- Aim to buffer to pH $\geq$ 7.25

Hypothermia and coagulation

- Greater blood loss in trauma when temp < 35°C
  - Reduced enzyme activity 10% per degree fall
  - Coagulopathy even without factor deficiency
  - Temp < 33°C as bad as a 50% fall in factor levels
  - Reduced platelet activation and altered platelet morphology
  - Platelet Ca^{2+} falls in hypothermia
- **Between 37 and 33°C main issue is platelets**
- **Below 33°C significant enzyme impairment**
- **Temperature should be maintained ≥ 35°C**

Calcium and coagulation

- Early ionised hypocalcemia in trauma

  Shock, ischaemia/reperfusion, colloids

- Ca^{2+} Actions
  - Protects fibrinogen from degradation
  - Essential for fibrin formation & stabilisation
  - Required for platelet function
  - Also required for activation of protein C
- **Maintain ionised calcium $\geq$ 0.9 mmol/L**
- **Remember citrate in blood products**

Mechanisms of Trauma-induced Coagulopathy

- Tissue damage
  - Release of tissue factor
  - Vessel damage
  - Initial hypercoagulation
- Hypoperfusion
  - Endothelial release of tPA => fibrinolysis
  - Initial excessive thrombin burst
  - Increased thrombomodulin and activation of PC
  - Inactivation of Va, VIIIa, and PAI-1
  - Loss of regulation of tPA
  - Plasmin-mediated hyperfibrinolysis

Mechanisms of Trauma-induced Coagulopathy

- Acidosis
  - Reduced thrombin generation (50% by pH 7.2)
  - Decreased fibrinogen and platelet levels
  - Decreased clot quality and increased formation time
- Volume replacement (e.g. 30% dilution)
  - Decreased clot quality (HES/gelatins etc.)
  - Decreased II, VII, VIII, XI, XIII and fibrinogen
  - Thrombin generation maintained
  - Corrected by fibrinogen concentrate

Other issues - platelet margination

- At normal Hct:
  - platelets flow near vessel walls
  - RBCs in centre of vessel
- Exposed to greatest shear force
  - Important in partial activation
  - Important in interaction with vWF on vessel wall
- As anaemia progresses, more mixing occurs
- Anaemia reduces platelet/endothelium contact

Key components in haemostasis…

- **Platelets**
- **Fibrinogen**

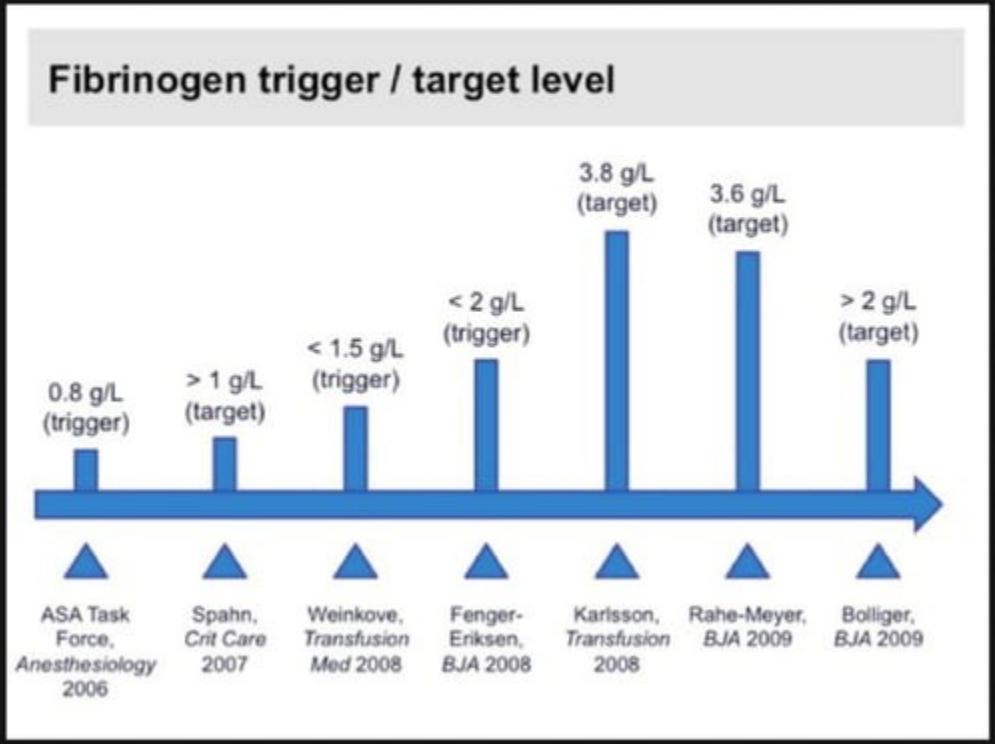
- Factor XIII (?) – when levels below 60%

Innerhofer P, Kienast J. Principles of perioperative coagulopathy. Best Pract Res Anesthesiol 2010; 24: 1-14.

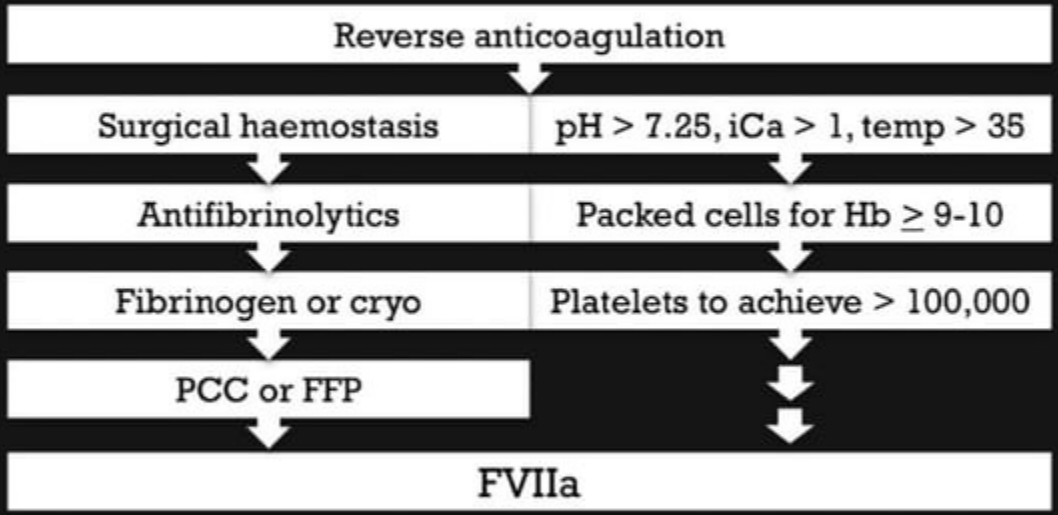
Fibrinogen levels must be protected

- "Conventional" targets outdated & inaccurate
  - Fibrinogen levels fall earlier than previously appreciated
  - Traditional target of > 1 g/L is too low
  - Bleeding risk increased when levels are < 2g/L
- Effect of fluid replacement
  - Fibrinogen levels 1st to fall in conventional fluid resuscitation
  - This effect also occurs with HES 130/0.4 and impairs clotting
- Fibrinogen strengthens clot & tolerance of low platelets
- **Low fibrinogen main cause of coagulopathy in PPH**

Evolution of fibrinogen targets…



Potential Interventions



Fresh Frozen Plasma

- Acellular portion of donor blood
  - Frozen to -30°C with 8 hours of donation
  - Contains near-normal levels of plasma proteins
  - Also lipids, carbohydrates, minerals, anticoagulant components
  - INR of FFP often at upper normal level
- Quality control is based on Factor VIII levels in Europe
- Indicated for multiple-factor deficiencies
  - NOT for isolated deficiency (use factor concentrate)
  - Still used too much in USA to correct high INR
  - NOT indicated for fibrinogen replacement alone
- Viral transmission risk (inactivation lowers factor content)

FFP in massive transfusion

- Modern recommendations FFP:RBC 1:1-1:2
- Coagulopathy begins after as few as 3 PRBCs
- Dose = 30 ml/kg
  - “Traditional” recommendation 10-15 ml/kg FFP insufficient
- Complications
  - Febrile reaction
  - Allergic reaction (1-1.5% per unit, rarely severe)
  - Transfusion associated circulatory overload (TACO!)
  - TRALI

Alternatives to FFP…

- **FP24 (USA)**
  - Plasma frozen to < -18°C within 24 hrs of donation
  - Factor VIII levels 16-24% less than FFP
- **Thawed plasma**
  - FFP/FP24 stored at 1-6°C for up to 5 days
  - Factor VIII at 5 days 35-41% lower than FFP
- **Prothrombin complex concentrates**
  - Variable amounts of factors II, VII, IX, X
- **Recombinant FVIIa**
  - Increasingly controversial
  - Poor evidence and high cost
- **Fibrinogen concentrate (Riastap)**
  - Dose (mg/kg) = (target – actual fibrinogen)/0.017

Cryoprecipitate

- Higher fibrinogen concentration than FFP
- Fibrinogen concentration is variable
  - 75% of units must have at least 140mg fibrinogen
- Lower volume
- Withdrawn from many countries
  - Still available UK and USA
- No studies looking at perioperative efficacy
- Viral infection risk as FFP

Infection risks

- FFP
  - HIV: 1 in 10 million
  - Hepatitis C: 1 in 50 million
  - Hepatitis B: 1 in 1.2 million
  - vCJD ?
  - West Nile virus (USA) very rare now
- Cryoprecipitate
  - Prepared from untreated FFP
  - Similar infection risks
  - Viral inactivation decreases fibrinogen by 16-41%

Other haemostasis options



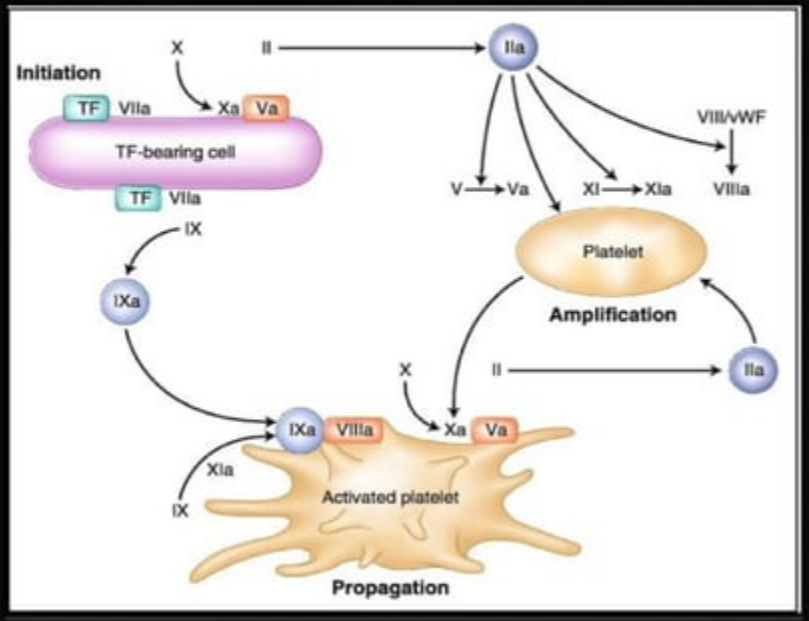






The cell-based coagulation system

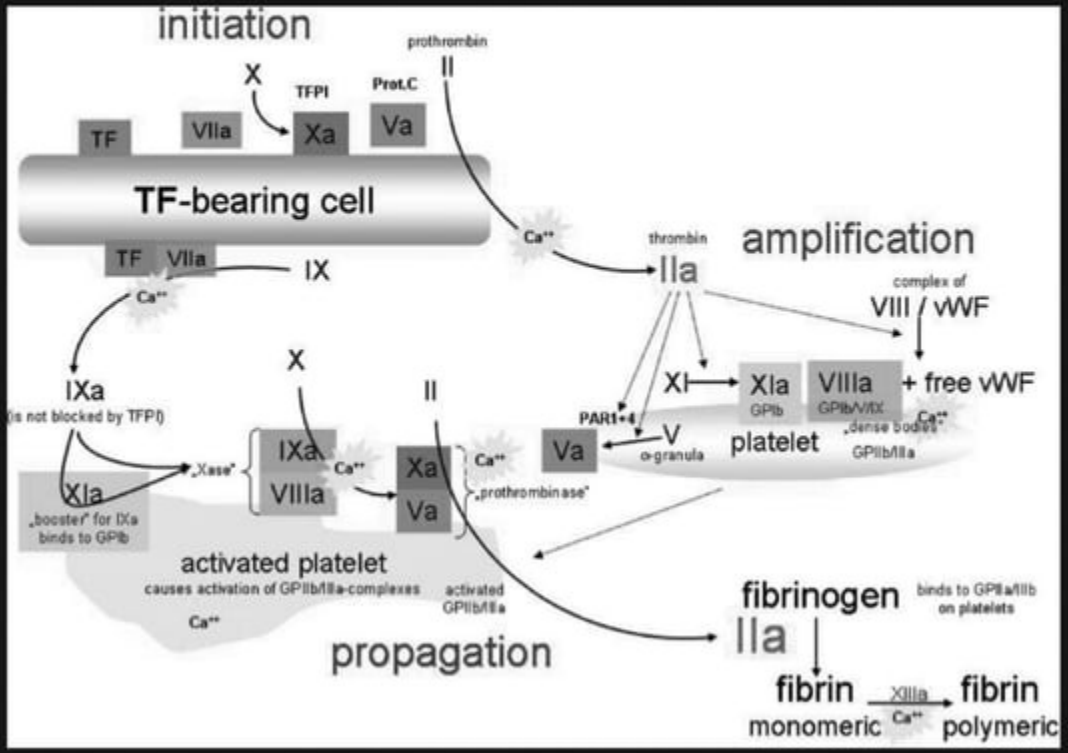
Haemostatic response – cell-based



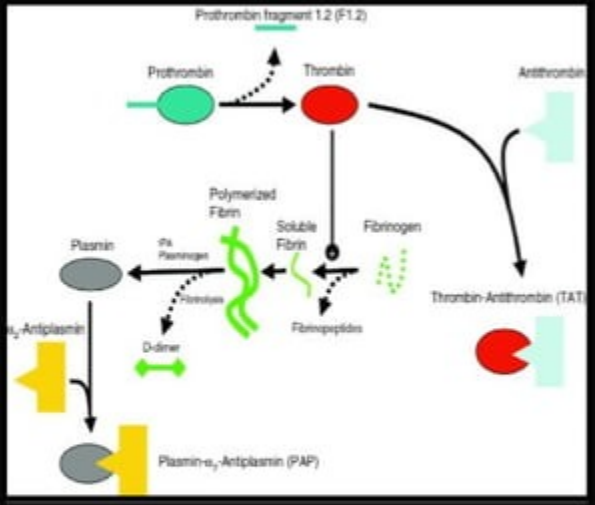
Clot formation

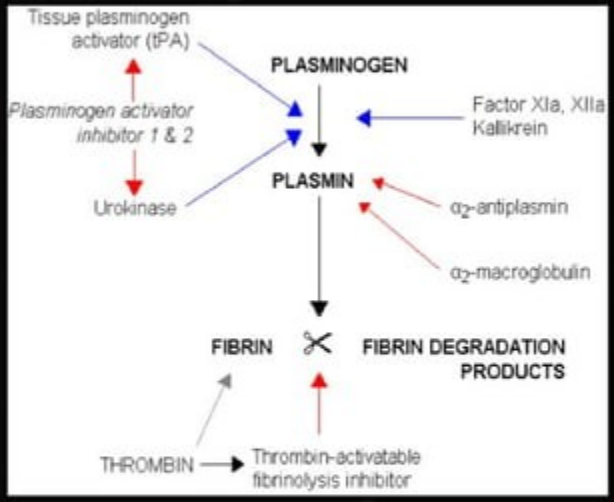
- Clotting factors incl. **fibrinogen**
- **Platelets**
- Endothelium
- Cofactors
  - Ca^{2+}/Vitamin K

Haemostatic response – cell-based



Regulation of clot formation





Protein C, Protein S, Antithrombin III, tPA, TAFI, TFPI, PAI-1

Questions?