Drugs and Blood

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Medication & bleeding risk reduction

- Discontinuation of drugs that increase risk of bleeding
- Optimise patients haemoglobin pre-op
- Reducing blood loss peri-operatively

Discontinuation of drugs that increase bleeding risk

Drugs that increase the risk of bleeding

- Oral anticoagulants
- Antiplatelets
- NSAIDs
- Herbal medicines

Risk vs Benefit

Oral Anticoagulants

Main indications for warfarin:

- Stroke prevention in AF
- Stroke prevention in patients with prosthetic heart valves
- Treatment & prophylaxis of DVT & PE

Need to balance thrombotic risk of stopping with haemorrhagic risk of continuing

Risk of VTE vs bleeding depends on:

- Underlying reason for anticoagulation
- Risk of bleeding during surgery
- Period of post-op immobility
- Use of other methods of VTE prophylaxis (TEDS, foot pumps, early mobility)

Elective minor to moderate risk surgery (e.g. skin, dental):

- May not require dose adjustment or discontinuation of warfarin
- Safe to proceed when INR < 2.5

Elective major surgery & low risk of VTE:

- Omit warfarin 5 days pre-op
- Safe to proceed when INR <1.5
- LMWH post-op until warfarin restarted and INR > 2 for 2 days

High-risk patients:

- Prosthetic heart valves
- History of VTE within past 3 months
- AF with history of stroke/embolism
- Recurrent thrombosis
- Known hypercoagulable state

All patients should be discussed with relevant Consultant prior to admission

Elective major surgery & high-risk patient

- Omit warfarin 4 – 6 days pre-op
- Admit patient & start IV heparin
- Stop heparin 4 - 6 hrs pre-op
- Restart heparin 12 hrs post-op
- Restart warfarin ASAP at usual pre-op dose
- Continue heparin until INR > 2 for 2 days

Warfarin Bridging

Stop warfarin 5 days pre-op

Day 1 – no warfarin
Day 2 – no warfarin
Day 3 – high dose Fragmin
Day 4 – high dose Fragmin
Day 5 – low dose Fragmin (evening)
Day 6 – day of surgery

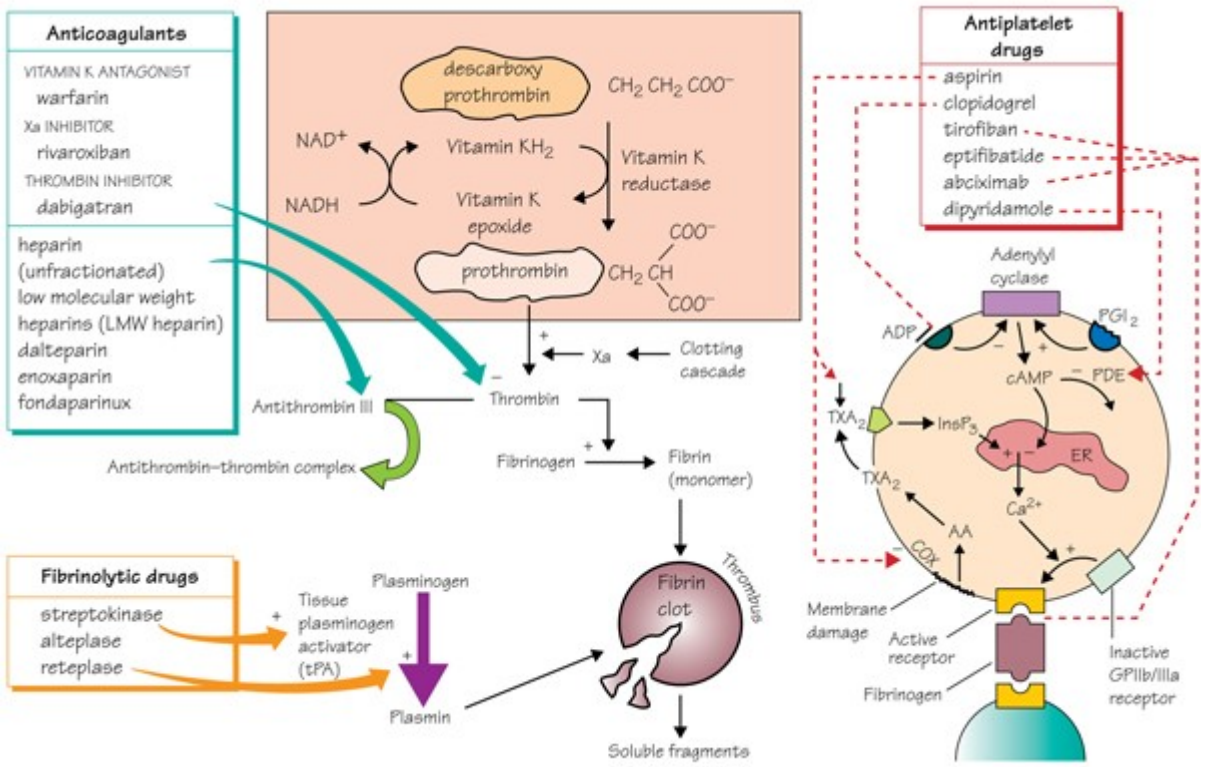
Emergency surgery

- Stop warfarin on admission
- Vitamin K (phytomenadione) lowers INR but may take 6 - 24 hours
  Dose: 0.5 – 5mg IV
  !Vit K $\Rightarrow$ warfarin resistance for 2-3 weeks
- FFP or clotting factors

New Oral Anticoagulants

- Dabigatran - Pradaxa▼
- Rivaroxaban - Xarelto▼
- Apixaban - Eliquis▼

Drugs used to affect blood coagulation



Antiplatelets

Antiplatelets

	When to stop pre-op
Aspirin	7 days
Clopidogrel	7 days
Dipyridamole	24 hours
Prasugrel	at least 7 days
Ticagrelor	7 days

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs

- Increased risk of bleeding due to antiplatelet effect
- Reversible effect restored with drug clearance (5 x half-life $t_{1/2}$)
- Stop pre-op to allow recovery of platelet function if significant risk of intra-op bleeding

NSAIDs

	$t_{1/2}$ (hrs)	No.days to stop pre-op
Ibuprofen	2-4	1
Diclofenac	2	1
Naproxen	12-15	3
Meloxicam	15-20	4
Piroxicam	45-50	10
Tenoxicam	60-75	16

Cyclo-Oxygenase 2 (COX-2) Inhibitors

- Celecoxib (Celebrex®)
- Etoricoxib (Arcoxia®)
- Lumiracoxib (Prexige®)

COX-2's do not inhibit platelet aggregation therefore may be continued pre-operatively

Herbal Medicines

Herbal Medicines

- Patients tend not to admit to taking herbal medicines
- Patients do not consider herbal medicines to be dangerous

Always ask patients about use of herbal medicines

Herbal Medicines

Increased risk of bleeding with:

- Garlic
- Ginkgo
- Ginseng
- Feverfew
- Chondroitin

Stop at least 2 weeks pre-op

Pre-operative Optimisation of Haemoglobin

Oral Iron Therapy

- Pre-op anaemia increases likelihood of blood transfusion
- Increasing initial Hb can allow larger expected blood loss without need for transfusion
- Pts scheduled for elective surgery should have FBC checked at least 4 weeks pre-op in order to identify & correct anaemia in time
- Evidence suggests 4 wks treatment with $FeSO_4$ led to improved post-op Hb’s

Oral Iron Therapy

Iron salt	Amount	Content of ferrous iron
Ferrous fumarate	200mg	65mg
Ferrous gluconate	300mg	35mg
Ferrous sulfate	300mg	60mg
Ferrous sulfate (dried)	200mg	65mg

Oral Iron Therapy

- Choice usually decided by incidence of side effects & cost
- Hb regeneration is little affected by type of salt used, provided sufficient iron is given
- Ferrous sulfate is first line choice
- Avoid EC & SR preparations (expensive)

Oral Iron Therapy

Dose

Iron deficiency need 100 – 200mg daily

$\Rightarrow$ Ferrous sulphate 200mg TDS

Hb should rise by 2g/dL over 3-4 weeks

Continue for at least 3 months once Hb normal to replenish iron stores

Oral Iron Therapy –Side Effects

- Epigastric pain
- Nausea & vomiting
- Constipation or diarrhoea
- Black stools (warn patient!)

Increased absorption on empty stomach and with ascorbic acid (vitamin C)

S/E’s directly related to amount of iron - take after food or change to salt containing less iron

Oral Iron Therapy - Interactions

Antacids, cholestyramine Tetracyclines, PPIs, H2RAs	→	Reduced iron absorption
Tetracyclines, quinolones, penicillamine, levodopa, Bisphosphonates	→	Reduced drug absorption

Dosages should be separated by at least 2 hrs

Parenteral Iron Therapy

Indications

- Genuine intolerance to oral iron
- Active IBD
- Malabsorption
- Clinical need for rapid replenishment of iron stores
- To optimise the effectiveness of epoetin

Parenteral Iron Therapy

- Venofer - Iron sucrose
- CosmoFer - Iron dextran
- Monofer▼ - Iron isomaltoside 1000
- Ferinject▼ - Ferric carboxymaltose

The Daily Telegraph

26th September 2004

Patient's liver 'saturated' with iron after hospital confusion over dosage

Parenteral Iron Therapy

Venofer® (iron sucrose) & CosmoFer® (iron dextran)

Dose - Determined by body wt and Hb deficit

100-200mg three times a week

Single dose infusion over 4-6 hrs (CosmoFer)

Hb rise of 2g/dL expected over 3 weeks

Parenteral Iron Therapy
Side Effects

- Anaphylaxis (CosmoFer, Venofer)

  - facilities for cardiopulmonary resuscitation (adrenaline, hydrocortisone, chlorphenamine) must be available

- Hypotension, nausea, headache, oedema, taste disturbance

Erythropoietins

‘Epo’ - Recombinant human erythropoietin

A hormone produced by the kidneys and controls

erythropoiesis

Epoetin Alfa - Eprex, Binocrit▼

“ Beta - NeoRecormon

“ Theta - Eporatio▼

“ Zeta - Retacrit ▼

Darbepoetin - Aranesp

Indications

- Tx of anaemia in chronic renal failure
- Tx of anaemia assoc'd with Ca chemo
- ↑ autologous blood yield in predonation
- Prior to ortho surgery to ↓ risk of blood transfusion

Dosing prior to ortho surgery (Eprex)

Aim to ↑ Hb at rate not > 2g/dL/month

- 300units/kg SC for 15 days beginning 10 days pre-op (~ £2,390/course/80kg)

OR

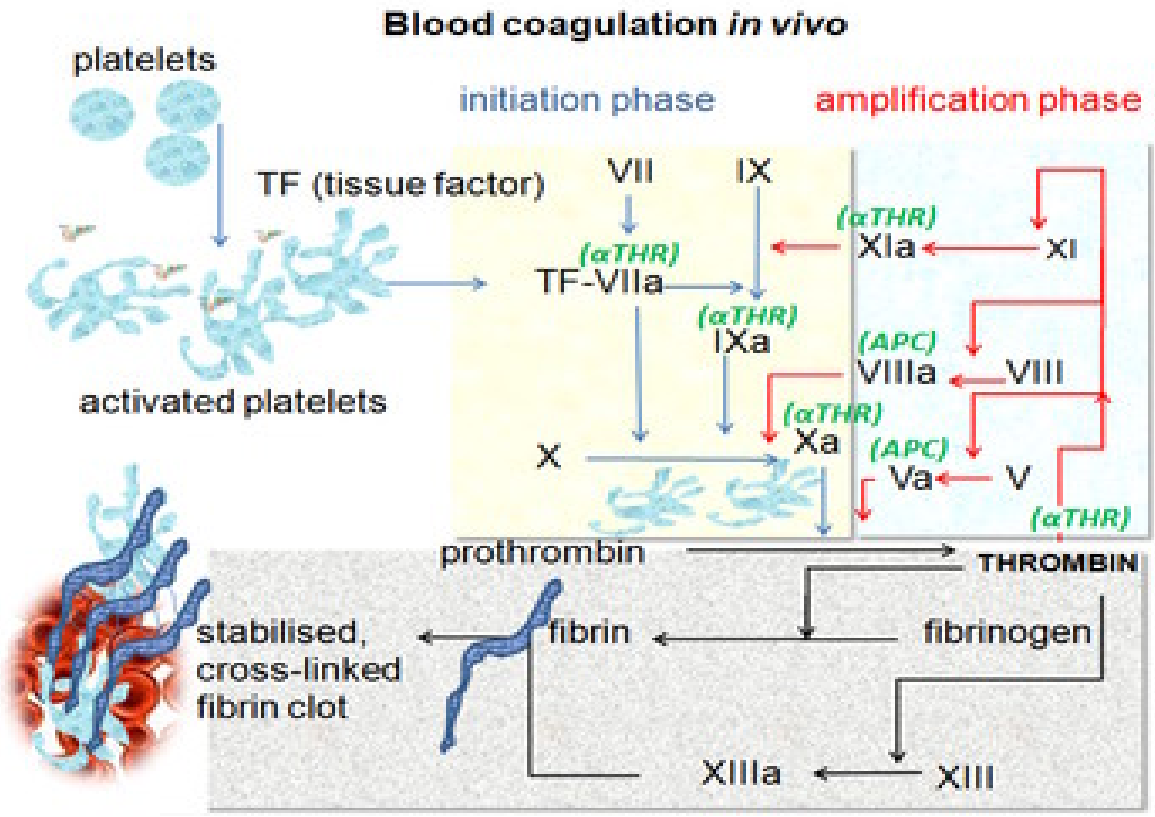
- 600units/kg SC three times a week for 3 weeks pre-op (~ £3,405/course/80kg)

Side Effects

- Flu-like symptoms
- Hypertension (dose-dependent)
- Iron deficiency (give iron supplements)
- ↑ thrombosis risk
- Pure red cell aplasia

Reducing Blood Loss Peri-Operatively

Clotting cascade



Antifibrinolytic Drugs

- Tranexamic acid
- Epsilon aminocaproic acid
- Questions raised about safety recently
- Aprotinin withdrawn May 2008 due to concerns re cardiac complications and death
- ADR’s – vascular occlusion, renal dysfunction, death

Tranexamic Acid

Uses

- Prophylaxis & treatment of post-op bleeding assoc'd with prostatectomy, menorrhagia & dental extractions in haemophiliacs or Jehova's Witnesses
- May also be effective at reducing blood loss following trauma

Mechanism of action

Inhibits the activation of plasminogen to plasmin thereby preventing the break-up of fibrin and maintaining clot stability

Tranexamic Acid

Dose

Oral 15 – 25mg/kg TDS

IV injection 500mg – 1g TDS

IV infusion 25 – 50mg/kg/24hrs

* Dose reduction required in renal impairment

Side effects

- Nausea, vomiting, diarrhoea (reduce dose)
- Colour visual disturbances (discontinue)
- Thromboembolic events (rare)
- Dizziness &/or hypotension on rapid IV inj^{n}

Aprotinin (Trasylol®)

Action - Antifibrinolytic agent

Uses - To reduce blood loss during cardiac surgery

Dose – See SPC

Side effects – anaphylactic/hypersensitivity
- transient deterioration in RF
- thrombosis

Withdrawn 2008 due to safety concerns

Desmopressin (DDAVP®)

Uses

- Mild to moderate haemophilia
- von Willebrands disease

A reduction in use of blood & blood products has been shown in patients on aspirin who are given desmopressin peri-operatively.

Fibrin sealant

Biological “glue” or fibrin tissue adhesive

e.g. FloSeal, Tisseel, Evicel, Vitagel, Crosseal

Complications

- Impair wound healing/infection
- Anaphylaxis
- Transmission of disease
- Vascular thrombosis

Fibrin Sealant

Choice of agent

- Amount & location of bleeding
- Availability
- Cost
- Surgeon preference