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# Anticoagulants and antiplatelet drugs

## Classification

### Anticoagulants

#### Parenteral

Heparin	UFH LMWH	Enoxaparin Tinzaparin Dalteparin Certoparin
Heparinoids	Danaparoid	
Hirudins	Lepirudin Bivalirudin	
Pentasaccharide	Idraparinux Fondaparinux	

#### Oral

Warfarin Acenocoumarole (= nicoumalone) Phenindione		
Factor Xa inhibitors	Rivaroxaban	
Thrombin inhibitors	Ximelagatran (Exanta <sup>®</sup> ) Dabigatran (Pradaxa <sup>®</sup> )	

### Antiplatelet drugs

Aspirin Dipyridamole		
Thienopyridines		Clopidogrel Ticlopidine
GP IIb/IIIa antagonists		Abciximab Eptafibatide Tirofiban

### Thrombolytics

For acute arterial thromboembolism – see IHD.

#### Generally speaking!

- Anticoagulants
  - Esp. useful in prevention/treatment of venous occlusion
  - More effective
- Antiplatelet drugs
  - Esp. useful in arterial occlusions (?because arterial thrombi are platelet-rich)
  - Less likely to cause haemorrhage

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## Parenteral anticoagulants

### UFH

Naturally occurring mammalian mucopolysaccharides.  
Molecular weight ~30kD (mean 12kD)

## Indications

**Therapeutic** (because of rapid onset of action)

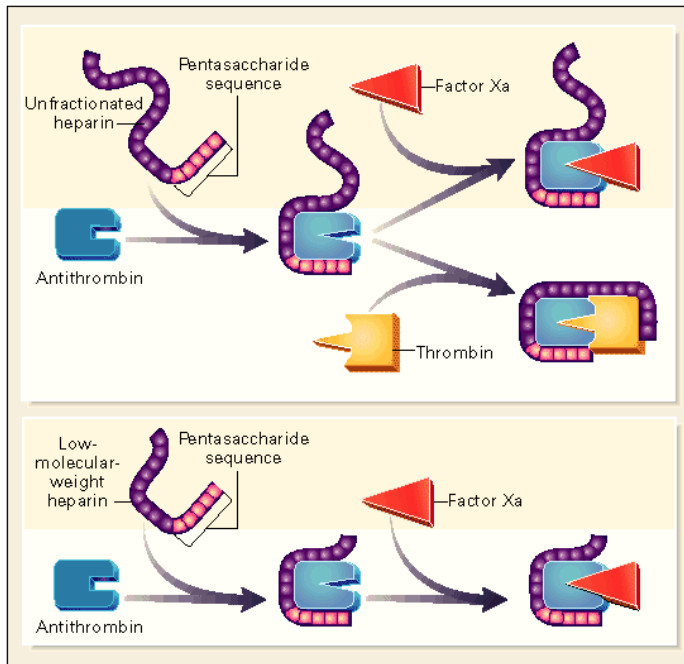
- DVT/PE
- ACS

## Prophylactic

- DVT/PE prophylaxis
  - Surgery, esp. orthopaedics
  - Immobile patients
- Extracorporeal circuits (cardiopulmonary bypass, haemodialysis)

## Mechanism of action

Pentasaccharide sequence: binds to natural antithrombin-III and accelerates breakdown of factor Xa 1000-fold.



18+ saccharide sequence: also accelerates factor IIa breakdown by similar mechanism

LMWHs have shorter chain lengths and accelerate factor Xa breakdown more (ca. 3-fold)

## Dosing

### Prophylaxis

- Low dose e.g. 5,000 units SC 8 or 12 hourly
- Monitoring not required (APTT largely unaffected)

### Treatment

- High dose
  - Loading bolus (5,000U) plus continuous infusion (30,000-40,000U over 24 hours, or 25U/kg/h)
- Continue until fully anticoagulated with warfarin

### Monitoring

- APTT ratio (intrinsic + common systems) at 4-6h after starting
  - Repeat every 4-6h with dose adjustment until APTT ratio is 1.5-2.5 times control
  - If stopped, effect subsides in 2-3h

### Adverse effects

- Bleeding
  - Reversal: 1mg protamine for 100IU UFH if within 15min of heparin, less later
- HIT (2-3%)
  - Must monitor platelets from day 5
  - UFH >> LMWH
- Osteoporosis if more than 4 months treatment
  - Esp. in pregnant women who had to swap warfarin for heparin

## **Contraindications**

As NSAIDs, plus previous HIT

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## **LMWH**

LMWHs are produced by chemical (e.g. enoxaparin) or enzymatic (e.g. tinzaparin) depolymerisation of UFH  
Molecular weight 2-10kD (mean 5kD)

### **LMWH vs. UFH - theory**

The biological activity of heparins is related to fractional molecular weight:

- <5.4kD mainly anti-Xa activity
- >5.4kD both anti-Xa and anti-IIa activity

I.e. anti-IIa activity is dependent on chain length

### **Pros**

- Shorter chains cleared more slowly: UFH  $t_{1/2}$  = 2-3h, enoxaparin  $t_{1/2}$  = ca. 4h (this is a *con* in renal failure)
- Reduced binding to plasma proteins (which compete with and reduce inhibition of antithrombin)
- Not bound by PF4 from activated platelets
- Bioavailability of fractionated heparins from SC administration is considerably higher

→ more predictable anticoagulant activity for LMWHs; no need for IV infusion (more convenient for patient and saves on nursing time – but note prophylactic heparin can be given SC, too) and no need to monitor APTT (saves on lab time and costs)

- Lower incidence of HIT
- Lower incidence of osteoporosis
- Hope of lower incidence of bleeding at equivalent antithrombotic dose has not borne out

### **Cons**

- Cannot monitor APTT – need factor X ratio (expensive; no need if average body mass, n crea, short duration of use)
- Incompletely reversed by protamine (just 20%)
- Expensive (10x)

### **LMWH vs. UFH - practice**

Fractionated heparins are taking over from unfractionated heparins for most of the accepted indications.

Superior efficacy proven for

- Treatment of DVT/PE
- ACS (ESSENCE trial)
- Orthopaedic lower limb surgery

But also used in

- DVT/PE prophylaxis
- Extra-corporeal circuits (unlicensed indication)

*Note*

- The different methods of preparation of LMWHs mean that there are important differences in molecular weight distribution. It is not possible to extrapolate trial data between different preparations.
  - Only enoxaparin is now widely used
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## **Heparinoids**

Lower degree of sulfation

### **Possible indications**

Available on named-patient basis

- DVT prophylaxis in general and orthopaedic surgery

- Severe HIT if no evidence of cross-reactivity (rare: 10%)

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## Hirudins

Specific thrombin inhibitors

Factor IIa inhibitors

- Don't bind plasma proteins or PF4
- Don't rely on AT3
- No specific antidote

### Indication

Lepirudin: licensed for HIT type II

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## Pentasaccharides

New, hence still expensive and lack of experience.

Idraparinux given SC once a week; being evaluated in AF (AMADEUS trial)

Advantages

- Long  $t_{1/2}$  (15-20h) compared even to LMWH
- No HIT risk – does not bind PF4 or platelets

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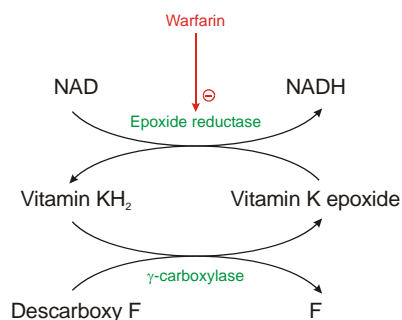
## Oral anticoagulants

### Warfarin

Wisconsin Alumni Research Foundation coumARIN (patent holder)

#### Mechanism of action

Structurally similar to vitamin K. Competitively inhibits vitamin K-dependent  $\gamma$ -carboxylation of factors II, VII, IX, X and proteins C/S.



Orally bioavailable but the onset of anticoagulation is delayed until  $\gamma$ -carboxylated clotting factors available in the circulation are depleted (about 72h); hence heparinise in acute situation.

Inactivated by hepatic metabolism.

#### Monitoring

By INR; can be monitored while on heparin

Issue National Anticoagulant Book, advice to show to all doctors and dentists

#### Target INR

- 2.5                      DVT/PE, AF, cardioversion, DCM, mural thrombus, rheumatic heart disease
- 3.5                      recurrent DVT/PE, mechanical heart valves, antiphospholipid syndrome

### Adverse effects

- Thrombosis, esp. if protein C/S deficient
- Bleeding, esp. gut and brain
- Pregnancy
  - Early pregnancy: fetal warfarin syndrome (phocomelia, chondrodysplasia)
  - At term: placental abruption, excessive haemorrhage, neonatal hypoprothrombinaemia
- Breastfeeding OK

### Management of bleeding/↑↑INR

Recommendations of British Society for Haematology

- Major bleeding Vitamin K 5mg slow IV, prothrombin complex concentrate (FII/VII/IX/X = Beriplex®) 50U/kg *or* FFP 15ml/kg if not available
- INR<6 Reduce dose or stop and restart when INR<5
- INR 6-8 Stop and restart when INR<5
- INR>8 Stop and restart when INR<5  
If other risk factors for bleeding: Vitamin K 0.5mg slow IV or 5mg PO, for partial reversal give 0.5-2.5mg of IV preparation PO

Vitamin K takes at least 6h to have any effect and can make subsequent re-warfarinisation unpredictable.

### FFP vs. PPC

- FFP contains insufficient factors to fully reverse warfarin
  - 70kg man would require 2.5l FFP to fully reverse
  - INR misrepresents degree of reversal
- PPC
  - Easier, faster, not group dependent, and even lower risk of viral transmission
  - Main risks: thrombosis, DIC
  - Also give vitamin K

### Interactions

If a drug is added that can affect warfarin action, more frequent monitoring is required

- Reduced absorption – cholestyramine or similar resins
- Reduced protein binding – hypoproteinaemic states e.g. nephrotic syndrome, drugs e.g. NSAIDs
- Altered clearance – P<sub>450</sub> induction/inhibition
- Altered vitamin K availability – altered food intake, antibiotic-induced reduction in gut-derived vitamin K, laxatives
- Altered levels of clotting factors – reduced in hypermetabolic states e.g. hyperthyroidism; increased in pregnancy
- Augmented bleeding tendency – in combination with antiplatelet agents e.g. NSAIDs

### Duration of treatment

- DVT/PE (akin to BTS guidelines)
  - Temporary risk factor 4-6w
  - First idiopathic 3-6m<sup>1</sup>
  - Recurrent May be lifelong
  - Associated with pro-thrombotic state e.g. protein C/S deficiency Lifelong
- AF Lifelong
- Cardioversion 1m prior and 1m after
- Large dilated heart/cardiac aneurysm Lifelong

### Surgery in patients receiving warfarin

- Withdraw 3-5 days pre-operatively; replace with low dose heparin
- Resume 1-3 days post-operatively

### Dental extractions

- Omit 1-2 days prior to surgery

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## Acenocoumarol, phenindione

<sup>1</sup> BTS multicentre trial ongoing

Use if warfarin intolerant.

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## Ximelagatran (Exanta®)

Oral thrombin inhibitor with predictable pharmacokinetics. Taken bd, metabolised to melagatran.  
May be a useful alternative to warfarin (SPORTIF trials showed similar efficacy in AF)

Removed from sale in 2006 due to hepatotoxicity

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## Antiplatelet drugs

Clinical indications include

- CNS
  - Prophylaxis of CVA/TIA
    - Warfarin preferred if AF/LA dilatation/mitral valve disease/LV dysfunction
  - Acute ischaemic CVA/TIA
- Heart
  - Prophylaxis of coronary artery disease
  - ACS
  - Following PTCA/stenting/CABG
  - AF
- Peripheries
  - Peripheral vascular disease

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## Aspirin

### Mechanism of action

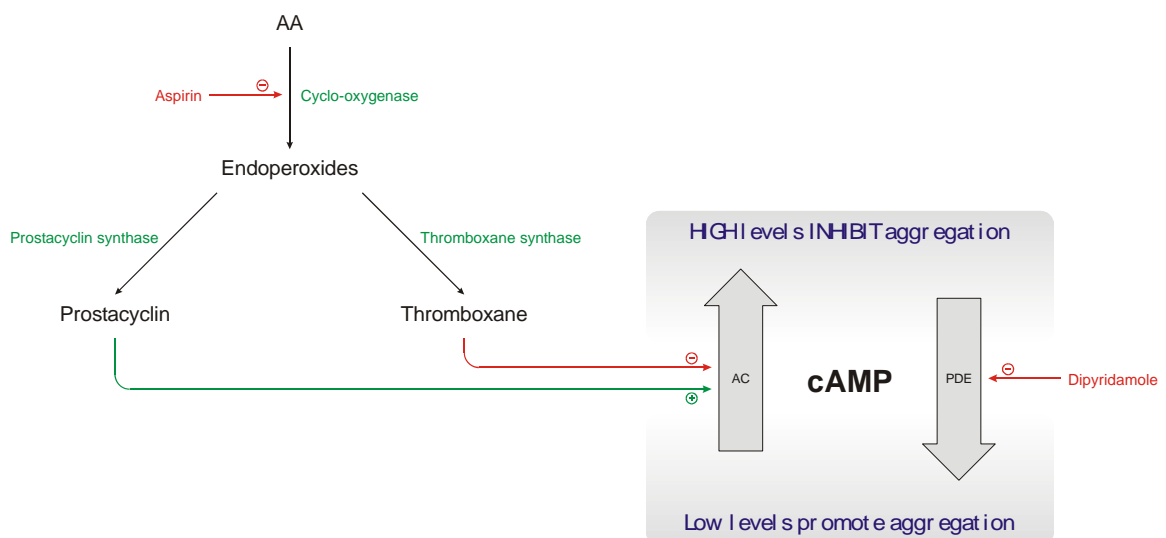
cAMP plays important role in platelet aggregation (high levels inhibit and low levels promote)

[cAMP] determined by;

- Adenylate cyclase activity (production)
  - Stimulated by prostacyclin (PGI<sub>2</sub>) from endothelium
  - Inhibited by thromboxane (TXA<sub>2</sub>) from platelets
- PDE activity (degradation)

Inhibits cyclo-oxygenase by enzyme acetylation, irreversible and thus lasts life of platelet (~10 days)

Thus blocks formation of prostacyclin and thromboxane



Ideally want to block thromboxane formation but not prostacyclin; this occurs at a low dose of aspirin. Why?

- Endothelium has synthetic capacity, platelets don't (anucleate)
- Extensive pre-systemic hydrolysis

The lower the dose, the greater the differential effect

Low-dose aspirin still affects bleeding time

<100mg takes several days for effect, hence 300mg loading dose in acute conditions

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## Dipyridamole

### **Mechanism**

Reversible inhibition of platelet PDE

Effect is potentiated by aspirin

### **Indications**

Infrequently used

- Adjunct to PO anticoagulation for thromboembolic prophylaxis in prosthetic heart valves
- MR preparation licensed for secondary prevention in ischaemic CVA/TIA
  - European Stroke Prevention Study 2 (1996): low dose aspirin (25mg bd) plus dipyridamole (200mg bd) more effective than either agent alone for secondary prevention of stroke (end point stroke/death)
  - Risk reduction of 36% for stroke or death for combination compared to placebo
  - This combination is now available Asasantin retard
  - Used in high risk stroke patients

### **Adverse effects**

Provokes myocardial ischaemia (used in chemical stress testing) → CI in IHD

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## Thienopyridines

Prodrugs – activated in vivo

ADP antagonists at P2Y receptors

ADP is released by platelets when they adhere to collagen and provokes aggregation

### **Clopidogrel**

Expensive, but more effective than aspirin

Cost implications potentially huge (>£1 vs. 1p per tablet), may cost >£100k to prevent an event

### **Indications**

- Aspirin intolerance
- ACS/acute MI
  - NSTEMI: CURE<sup>2</sup> (clopidogrel and aspirin vs. aspirin alone)
    - More effective at event reduction (9.3% vs. 11.4% reached end-point, p<0.001)
    - Higher risk of major bleed (3.7 vs. 2.7%, p=0.001), but no significant difference in risk of life-threatening bleed (2.1% vs. 1.8%, p=0.13)
  - STEMI: CLARITY-TIMI 28<sup>3</sup>
- Recent MI/CVA, symptomatic PVD: CAPRIE<sup>4</sup> (clopidogrel vs. aspirin)
  - More effective at event reduction (absolute risk reduction 3.8%)
  - Most benefit in PVD group
- Recent TIA/CVA (and additional cardiovascular risk factor): MATCH

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<sup>2</sup> YUSUF, S. ET AL. (2001): Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *NEJM* **345**:494-502.

<sup>3</sup> SABATINE, M. ET AL. (2005): Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *NEJM* **352**:1179-89.

<sup>4</sup> No authors listed (1996): A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* **348**:1329-39.

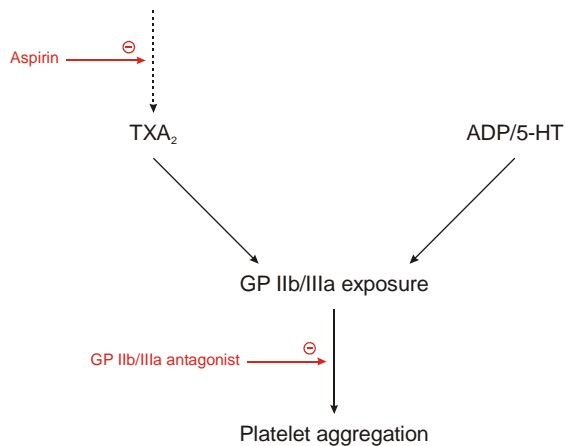
## **Ticlopidine**

Now rarely used due to adverse effects: neutropenia (1%, reversible), TTP (<0.02% but 50% mortality), diarrhoea (20%), intrahepatic cholestasis

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## **GP IIb/IIIa antagonists**

Central role of GP IIb/IIIa (integrin)



All given IV; should be used by specialists only

### **Indications (NICE guidance)**

- PTCA
  - In unstable angina and NSTEMI, if PTCA indicated but delayed
  - In diabetics
  - Complex procedure

Eptafibatide/tirofiban given early on; only abciximab is licensed as an adjunct to PTCA

3 distinct chemical groups:

### **Monoclonal antibody (abciximab)**

- Slow dissociation from the receptor (antiplatelet effect last for ~10s hrs after administration) and immunogenic
- Beneficial in
  - Unstable angina (EPILOG-Stent) if not responding to normal Rx and scheduled for PTCA
  - High-risk angioplasty (EPIC)
- Low risk of thrombocytopenic haemorrhage – can reverse by platelet administration
- Use only once

### **Peptide antagonist (eptafibatide)**

- Rapid receptor binding/dissociation and high systemic clearance

### **Non-peptide antagonists (tirofiban)**

- Developed with a view to PO administration, but have failed to show clinical efficacy by this route