Drugs used in disorders of coagulation

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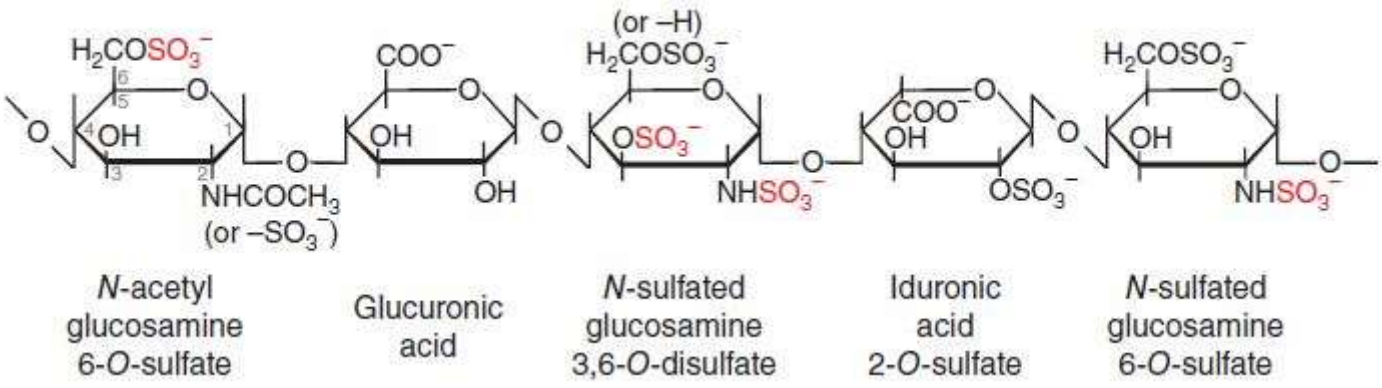
Classification

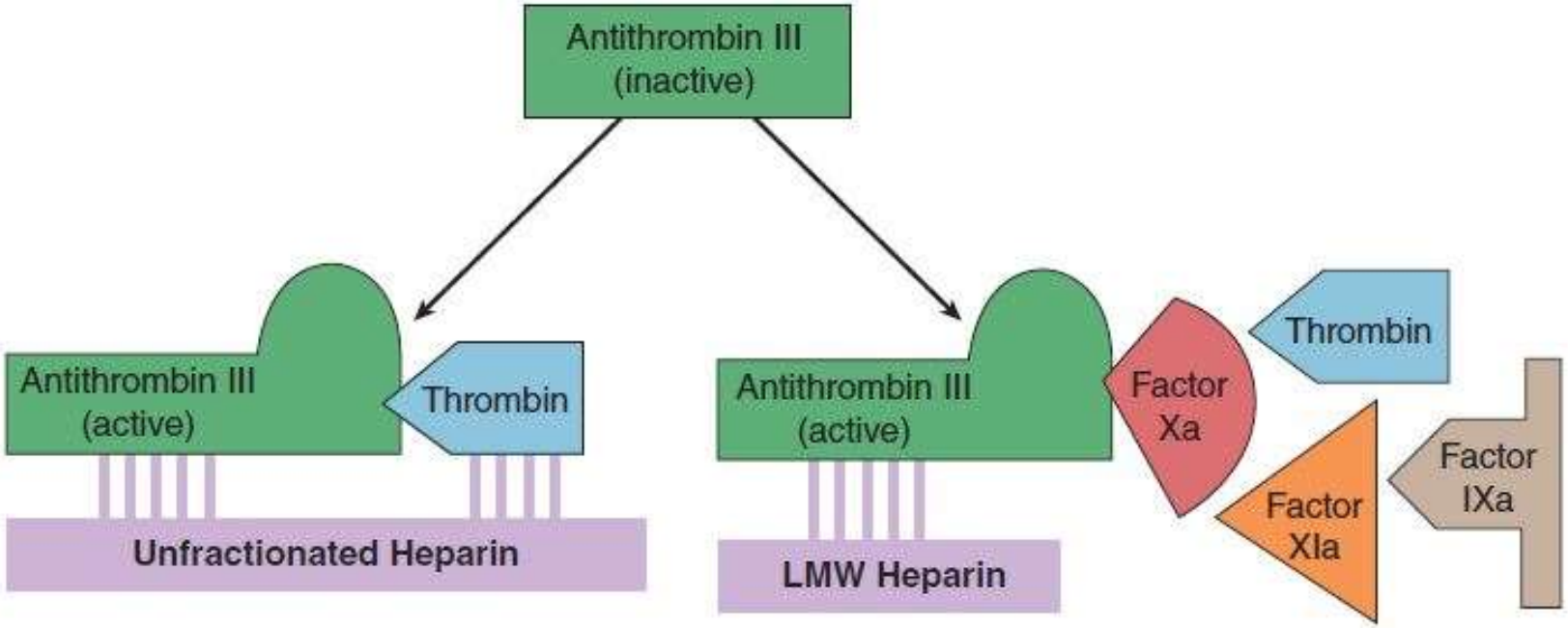
- **anticoagulants**
  - indirect thrombin inhibitors – e.g. heparin
  - vitamin K antagonists (coumarin derivatives)
  - direct anticoagulants
    - oral (DOAC / NOAC)
      - direct oral Xa inhibitors – e.g. rivaroxaban
      - direct oral thrombin inhibitor - dabigatran
    - parenteral – e.g. hirudin
- **fibrinolytics**
  - e.g. streptokinase, alteplase
- **thrombocyte aggregation inhibitors**
  - e.g. clopidogrel
- **drugs used in bleeding disorders**

Indirect thrombin inhibitors

- heparin
  - non-fractionated heparin (UFH / HMWH)
  - low molecular weight heparin (LMWH)
    - enoxaparin, dalteparin, tinzaparin
- fondaparinux



Mechanism of action of indirect thrombin inhibitors



Pharmacokinetics

- parenteral administration – iv. / sc. – im. NEM
- monitoring
  - UFH – aPTT
  - LMWH – no routine monitoring
    - more predictable PK/PD
    - can be considered in: renal insufficiency (slower elimination), pregnancy, obesity, children
- does not cross placenta
  - in pregnancy only if absolutely necessary

Clinical indications

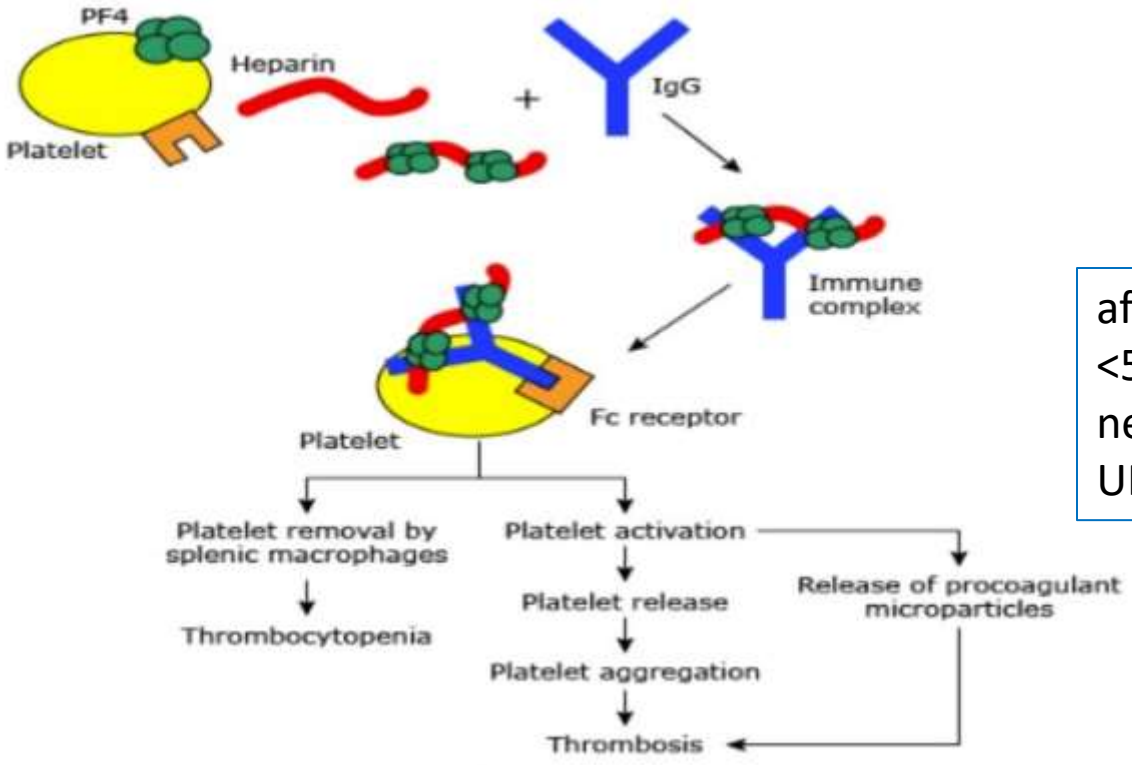
- **thrombosis prophylaxis**
- **deep vein thrombosis / pulmonary embolism**
- arterial embolisms
- unstable angina, AMI, DIC

- LMWH
  - simpler, more predictable, safer
  - slower onset of effect

Adverse effects

- **bleeding**
  - correlation with aPTT is not good
  - antidote: protamine sulfate (chemical antagonist)
- hypersensitivity
- **heparin-induced thrombocytopenia (HIT)**
  - type I. – clinically not important, transient, early
  - type II. – immune mechanism – IgG > PF4+heparin
- hair loss / osteoporosis / lipemia clearing

Heparin-induced thrombocytopenia



after 5-10 days thrombocytes <50% / <100 G/L
new **venous**/arterial thrombosis
UFH / females / surgery

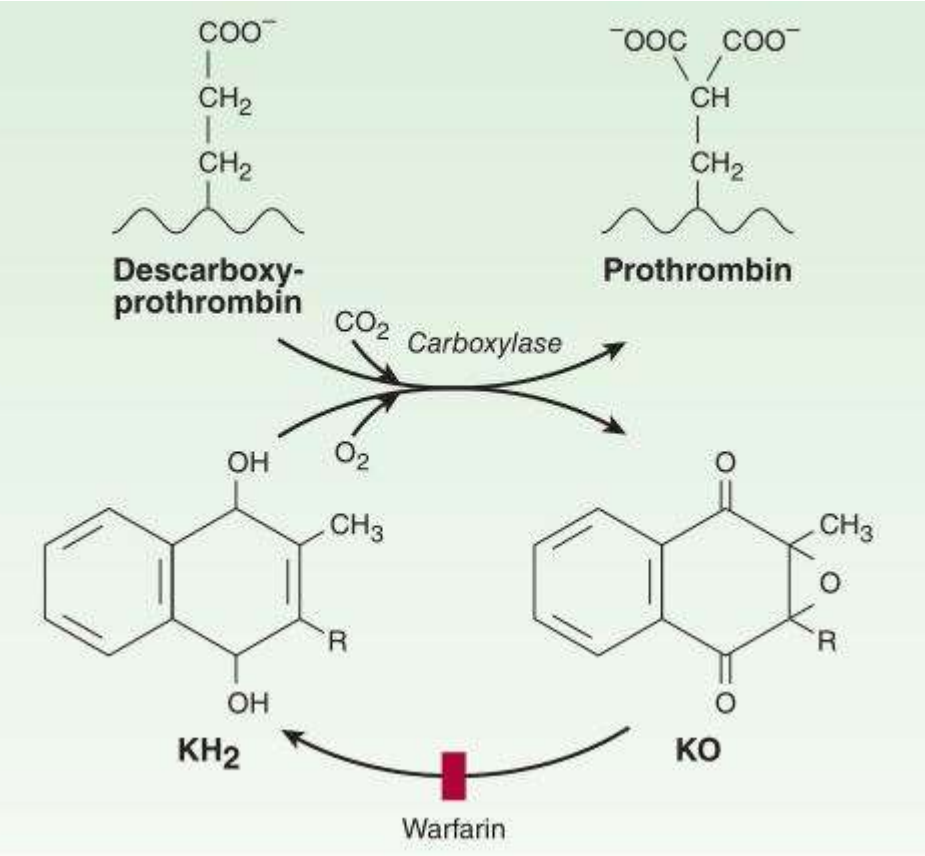
Therapy

- stop heparin / NO coumarin, thrombocyte transfusion
- alternative anticoagulant:
  - direct thrombin inhibitor (argatroban, bivalirudin)
  - fondaparinux

Vitamin K antagonists

(coumarin derivatives)

- warfarin, acenocoumarol



prothrombin, VII, IX, X, protein C: missing γ carboxylation

Pharmacokinetics

- oral administration – F ≈ 100%
- substantial plasma protein binding (>90%)
- liver metabolism
- significant individual variability
  - e.g. acenocoumarol $t_{1/2}$ ≈ 9-24 hours
- monitoring
  - INR (PT)
  - generally between 1.5-3
- crosses placenta
  - teratogenic, contraindicated in pregnancy

Clinical indications

- **thrombosis prophylaxis**
  - surgery, artificial heart valves, atrial fibrillation
- **deep vein thrombosis / pulmonary embolism**
  - after heparin

- variable dosing (acenocoumarol: 1-12 mg)
  - larger dose – higher risk of coumarin necrosis

Adverse effects

- **bleeding**
  - antidote: vitamin K, fresh frozen plasma
- teratogenicity
- **coumarin necrosis**
  - protein C (anticoagulant), shorter $t_{1/2}$
  - after 3-8 days, subcutaneous thrombosis
- allergy / gastrointestinal symptoms / hair loss

Interactions

- pharmacokinetic
  - primarily influencing the metabolism
    - inhibition → bleeding
      - e.g. cimetidine, amiodarone, NSAIDs, metronidazole, disulfiram
    - induction → thrombosis
      - e.g. rifampin, barbiturates
- pharmacodynamic
  - Vitamin K
    - diet
    - antibiotics
  - other anticoagulants, acetyl-salicylic acid

Direct oral anticoagulants (DOAC)

- oral direct Xa inhibitors
  - **rivaroxaban**, apixaban, edoxaban
- oral direct thrombin inhibitor
  - **dabigatran**

- similar effect / less adverse effects
- monitoring is not needed
- effect: rapid onset / short duration
- less interactions

Pharmacokinetics

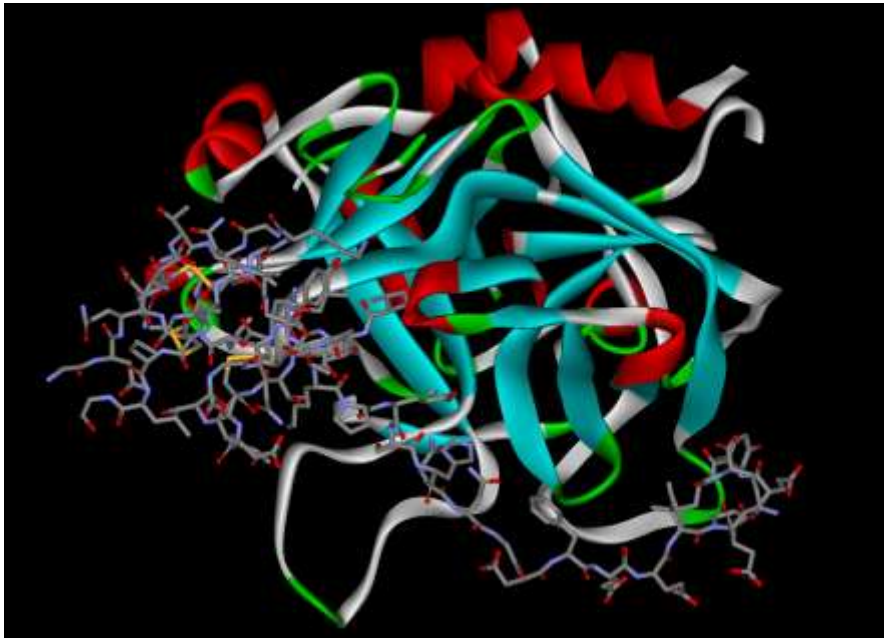
Generic name	Brand name	Enzyme target	Renal clearance	Half-life (h)
Dabigatran	*Pradaxa*	Thrombin	85%	12 -17
Rivaroxaban	*Xarelto*	Factor Xa	30%	7 - 11
Apixaban	*Eliquis*	Factor Xa	25%	12
Edoxaban	*Lixiana*	Factor Xa	35%	10 - 14

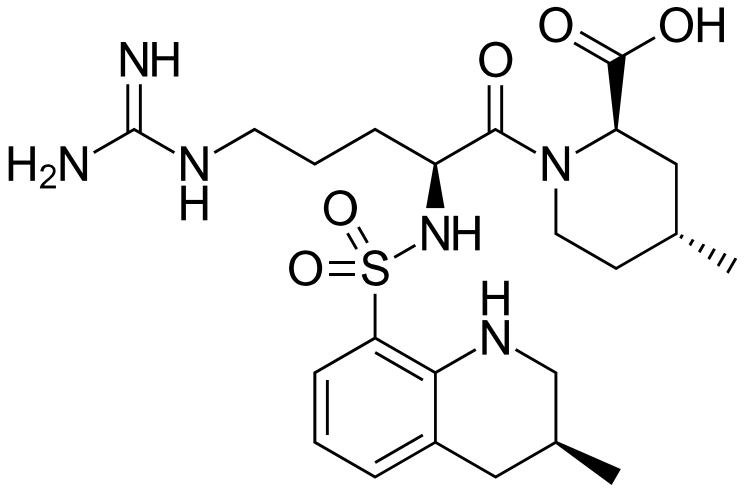
DOAC indications

- **thrombosis prophylaxis**
  - surgery, atrial fibrillation (stroke prevention)
- **deep vein thrombosis / pulmonary embolism**
  - after heparin too

Parenteral direct thrombin inhibitors

- hirudin / lepirudin / **bivalirudin**
- **argatroban** / melagatran



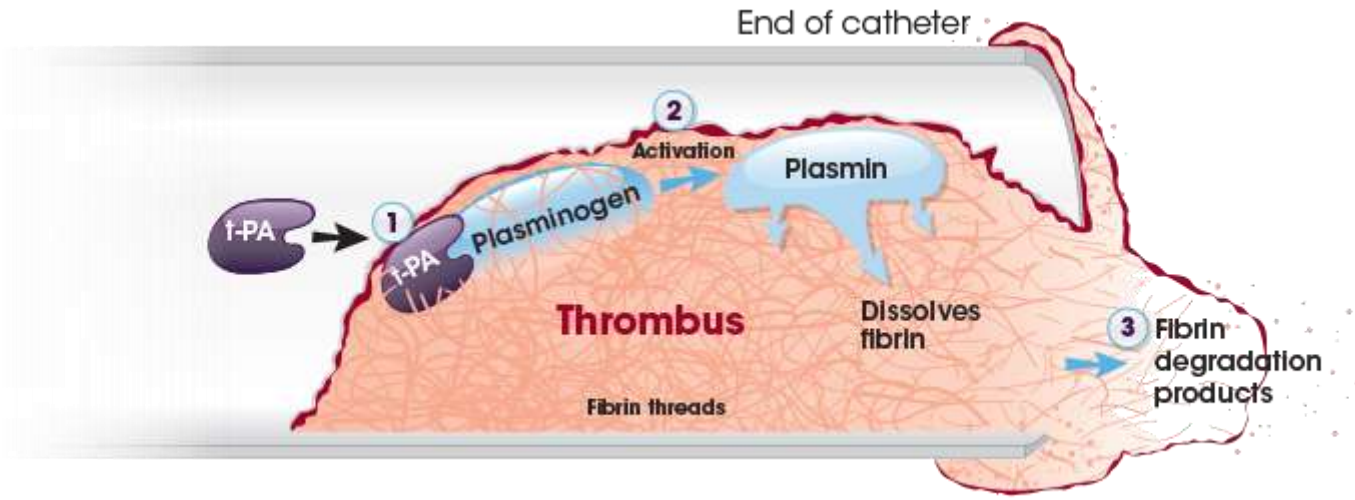


Parenteral direct thrombin inhibitors

- *Hirudo medicinalis* - hirudin
- bivalent thrombin inhibitor
  - peptide
  - lepirudin (recombinant) – withdrawn
  - **bivalirudin** – thrombocytes too (PCI)
- **argatroban** / melagatran
  - small molecules
- iv.
- **indication: HIT**

Fibrinolytics

- streptokinase
  - not an enzyme
  - plasminogen proactivator binding
- urokinase – human enzyme
- tissue plasminogen activators
  - alteplase, reteplase, tenecteplase

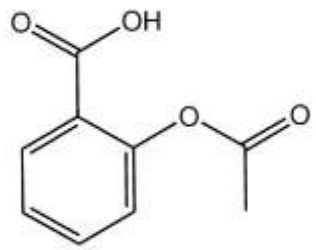


Clinical indications

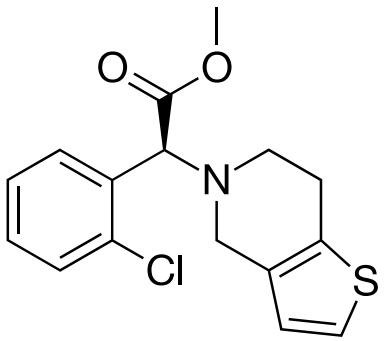
- pulmonary embolism with hemodynamic instability
- severe deep vein thrombosis
- peripheral vascular disease
  - arterial administration
- acute myocardial infarction (AMI)
  - **not common** nowadays (if PCI is not available)
- acute ischemic stroke (rec. tPA, in 3 hours)
  - tenecteplase longer duration

Thrombocyte aggregation inhibitors

- acetylsalicylic acid (Aspirin®)
- thienopyridines (ADP $P2Y_{12}$ antagonists)
  - ticlopidin, clopidogrel, prasugrel
- glycoprotein IIb/IIIa receptor antagonists
  - abciximab, eptifibatide, tirofiban



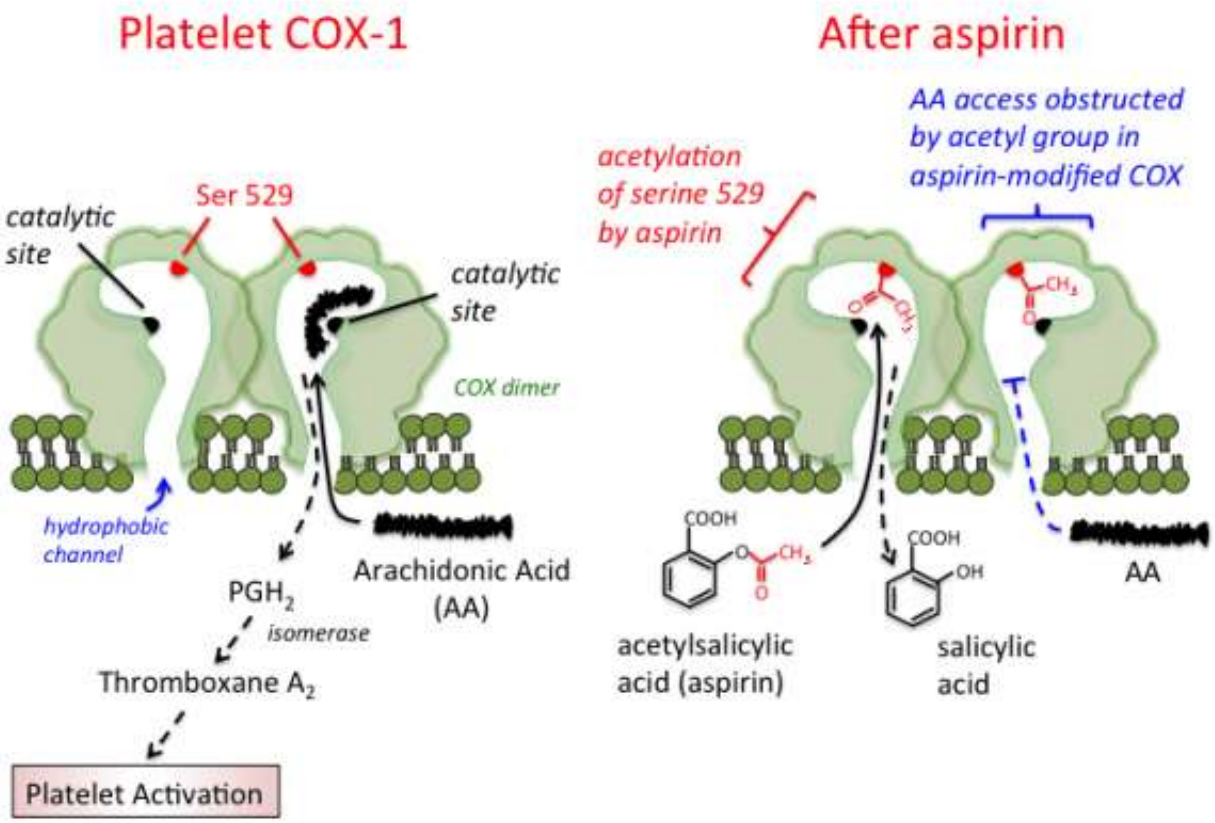
acetylsalicylic acid



clopidogrel

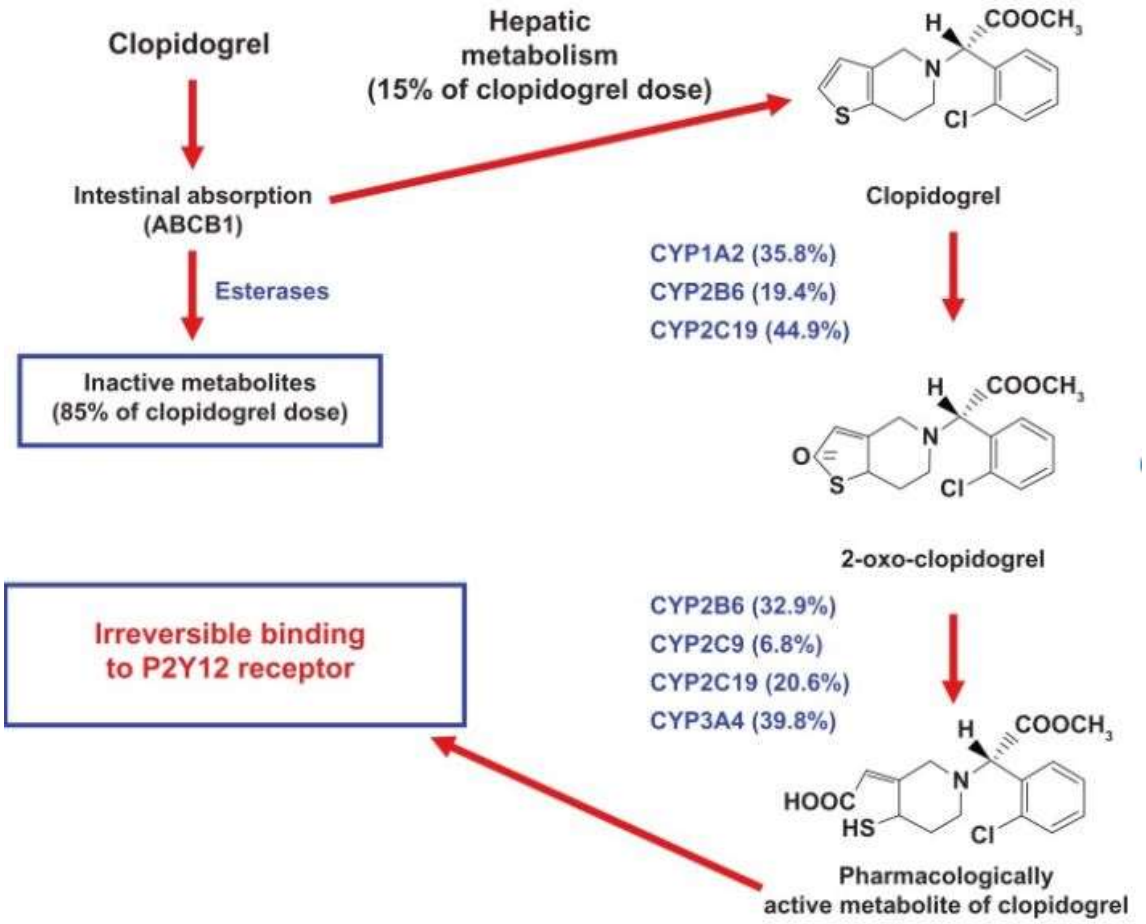
abciximab

Acetylsalicylic acid (Aspirin®)



not for primary prophylaxis, secondary prophylaxis: yes
low dose (≈ 100 mg daily)

Mechanism of action of clopidogrel



indication: common after coronary stents
CYP2C19 poor metabolizers – alternative needed ? / see omeprazole interaction

Ticlopidine

- stroke prevention
  - TIA, secondary (post-stroke)
- with Aspirin® after coronary stent

- non-spec. gastrointestinal AEs, bleeding
- **leukopenia**
  - maybe dose dependent (<500 mg daily ?)
  - administer carefully

Clopidogrel

- unstable angina, NSTEMI
- STEMI
- stroke
- peripheral vascular disease

+ Aspirin®

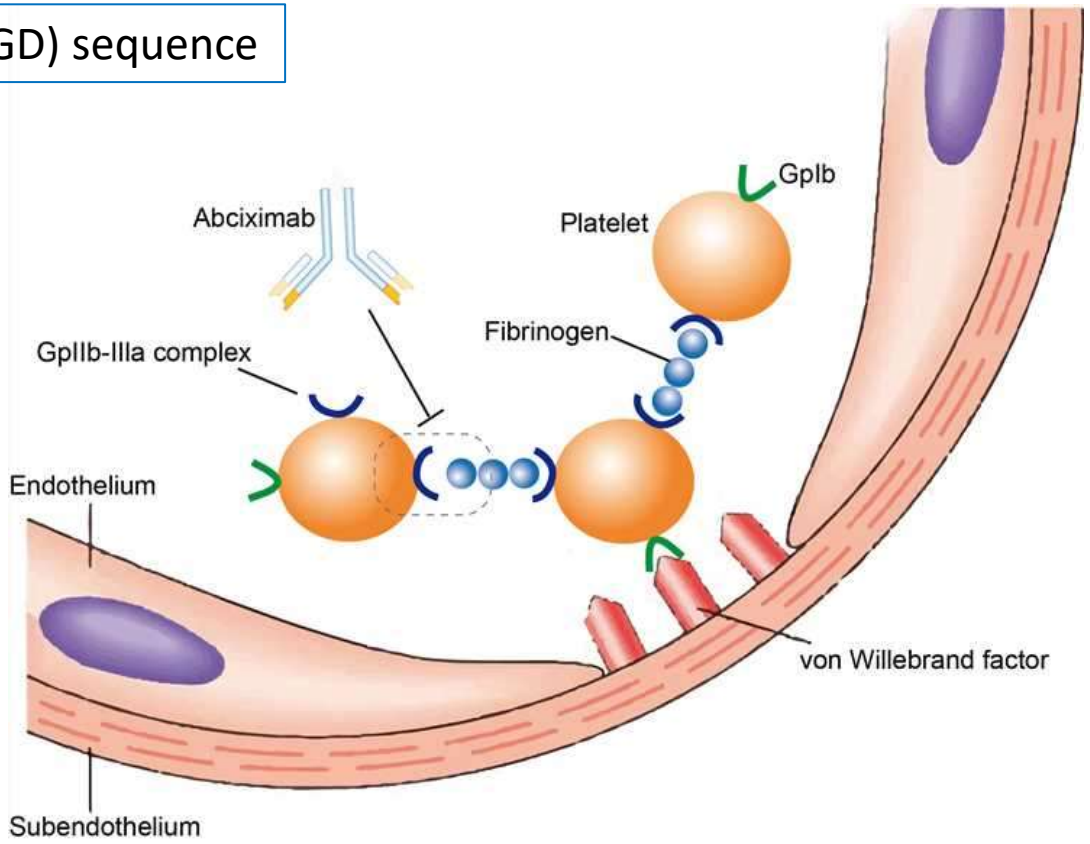
- better AE profile

- **prasugrel** similar
  - no influence of CYP status
  - greater bleeding risk?

Mechanism of action of GP IIb/IIIa antagonists

ligand: Arg-Gly-Asp (RGD) sequence

- abcixi**mab**
- eptifibatide
  - cyclic peptide
- tirofiban



- primarily after coronary stent (PCI)
- iv. infusion (short half life)

Drugs used in bleeding disorders

- topical
  - protein denaturing
    - e.g. iron(III)chloride
    - hydrogen peroxide
  - large molecules
    - collagen, gelatin
    - fibrin foam
  - vasoconstrictors
    - adrenalin, noradrenalin
- systemic
  - clotting factors
  - thrombocyte concentrates
  - **fibrinolysis inhibitors**
    - ε-aminocaproic acid
    - tranexamic acid

ε-aminocaproic acid / tranexamic acid

PD/PK

- chemically similar to lysine
- inhibits plasminogen activation
- good oral absorption / iv. too

Ind.

- bleeding with fibrinolytic therapy
- secondary prophylaxis of intracranial aneurysm bleeding
- adjuvant in hemophilia

AEs

- intravascular thrombosis, hypotension
- DIC / kidney, ureter bleeding: contraindicated