Medical Pharmacology

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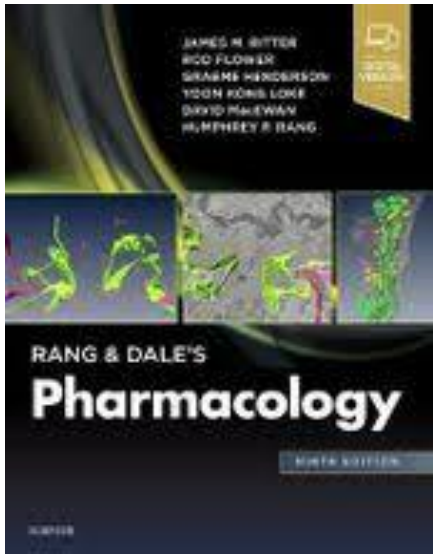
Celebrating 50 YEARS 1970 - 2020

Cardiovascular/Blood

Anticoagulants, antiplatelet drugs & thrombolytics



Rang & Dale's Pharmacology

10th ed 2020

Chap 22 and 25

Overview of antithrombotic drugs

3 groups

- anticoagulants
  - prevent coagulation, which often occurs around excessive platelet-platelet aggregation
  - also due to stasis / hypercoagulation states
- antiplatelet drugs
  - prevent platelet-platelet aggregation at the start of thrombus formation
- thrombolytics (aka fibrinolytics)
  - used after clots have formed to cause ischemia, MI or stroke, to breakdown clots and restore normal blood flow

Overview

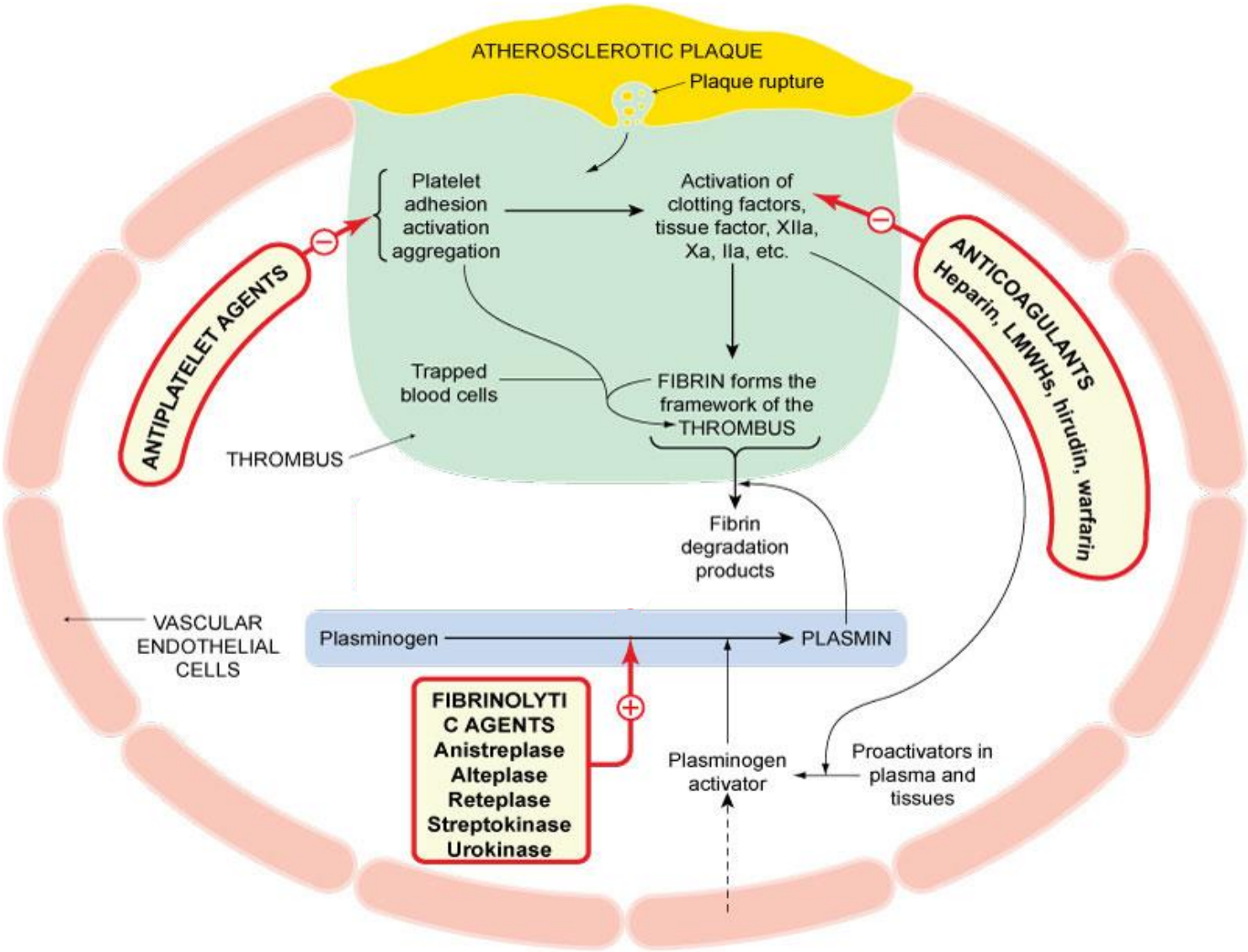


Fig. 24-10. **Fibrinolytic system.** The schematic shows interactions with coagulation and platelet pathways and sites of action of drugs that modify these systems. LMHs, low-molecular-weight heparins. For more details of platelet activation and the coagulation cascade, refer to Figures 24.1, 24.2 and 24.7.

Drugs acting on haemostasis and thrombosis

Drug class	subclass	exemplar	indication
Anticoagulants	Heparins	enoxaparin	ACS, VTE
	Direct thrombin inhibitors	dabigatran	VTE, AF
	Factor Xa inhibitors	rivaroxiban	VTE, AF
	Warfarin		VTE, stroke, AF
Antiplatelet drugs	Glycoprotein IIb/IIIa inhibitors	tirofiban	ACS
	P2Y12 antagonists	clopidogrel	stroke, TIA, ACS
	aspirin		stroke, TIA, ACS
Thrombolytics	tissue plasminogen activators	alteplase	ACS, VTE, stroke

Blood coagulation

- conversion of liquid blood to a gel or clot
- complex cascade
- converts soluble fibrinogen to insoluble strands of fibrin by thrombin (last step)

- accelerating enzyme cascade regulated by endogenous inhibitors, otherwise all the blood in the body would solidify within minutes of the initiation of haemostasis

- Antithrombin III neutralises all the serine proteases in the cascade

Coagulation cascade - drug targets

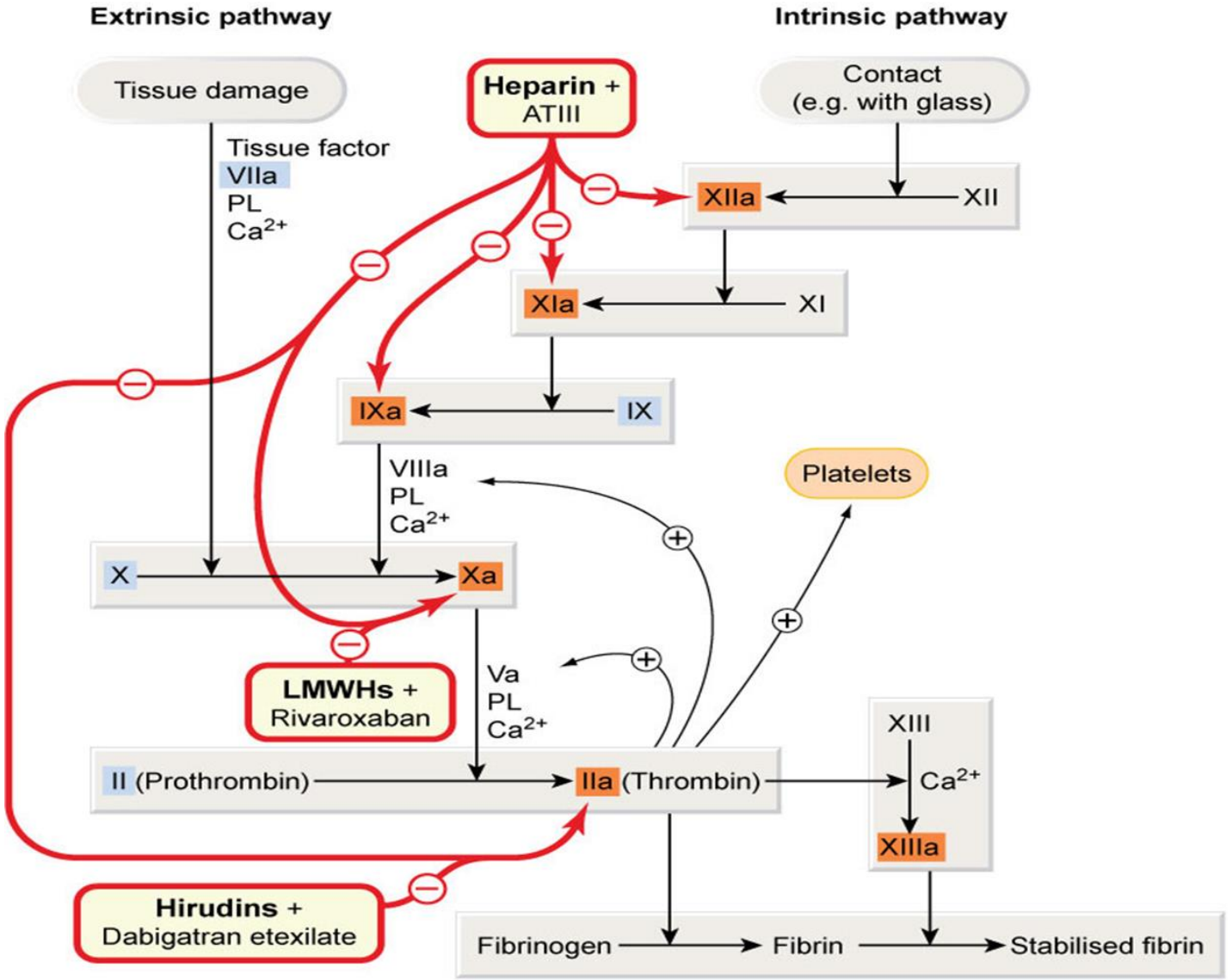


Fig. 24-2. **The coagulation cascade: sites of action of anticoagulant drugs.** Oral anticoagulants interfere with post-translational γ-carboxylation of factors II, VII, IX and X (shown in blue boxes). Heparins activate antithrombin III. ATIII, antithrombin III; LMWHs, low-molecular-weight heparins; PL, negatively charged phospholipid supplied by activated platelets.

Anti-coagulants

General Indications

- treatment of venous thromboembolism (VTE)
- prevention of venous thromboembolism
- ischaemic stroke and transient ischaemic attack
- acute coronary syndromes

Classes

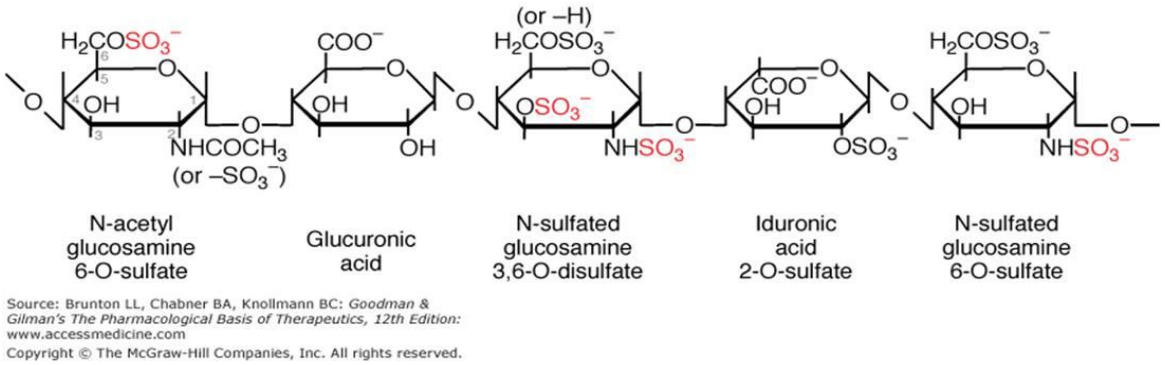
- Heparins } parenteral only
- Direct thrombin inhibitors } oral and parenteral
- Factor Xa inhibitors } oral and parenteral
- Warfarin (oral)

oral ones are called NOACs

Heparins

Exemplars

- heparin, LMW heparins (enoxaparin)
- Mucopolysaccharide in mast cells
- Mixture of different chain lengths (thus molecular weights varies between 5-30kDa)
- Strong acid (anion)



Low MW heparin (LMWH)

- MW 4,000-6,000 (4-6kDa)
- Differ in action and pharmacokinetics

Heparins

Exemplars

- heparin, LMW heparins (enoxaparin)

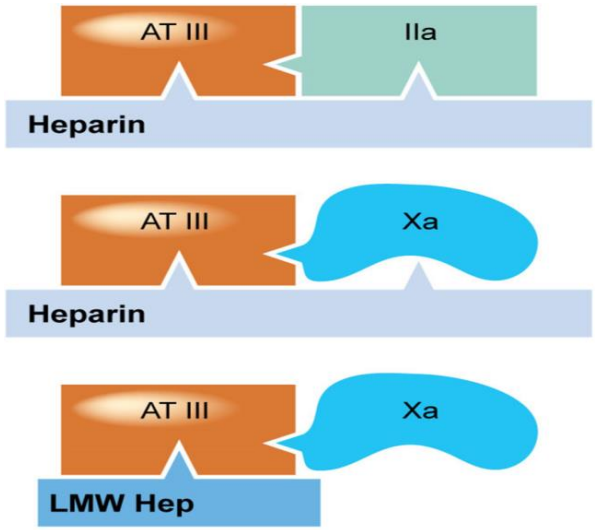
Mechanism of action

- Potentiates activity of antithrombin III
- Thrombin more sensitive to heparin-antithrombin III complex than factor X

To inactivate IIa, hep needs to bind to both ATIII and IIa

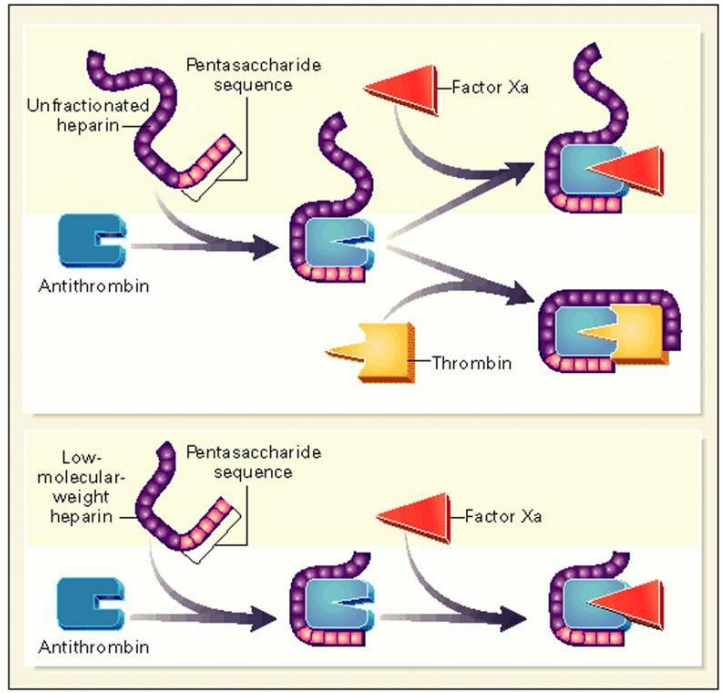
To inactivate Xa, hep needs to bind only to ATIII

LMWHs are small and can only bind to ATIII, not both ATIII and Xa, so they have a much greater effect on Xa than IIa



Modified from Hirsh J, Levine M 1992 Blood 79: 1–17.

Fig. 24-6. **Action of heparins.** The schematic shows interactions of heparins, antithrombin III (AT III) and clotting factors. To increase the inactivation of thrombin (IIa) by AT III, heparin needs to interact with both substances (top), but to speed up its effect on factor Xa it need only interact with AT III (middle). Low-molecular-weight heparins (LMW Hep) increase the action of AT III on factor Xa (bottom), but cannot increase the action of AT III on thrombin because they cannot bind both simultaneously.



Low Molecular Weight Heparins (LMWH)

Mechanism of action

- small heparin fragments
- ~4.5kDa (range 0.1 – 10kDa)
- have a much greater effect on factor Xa than on thrombin
- advantages over heparin
    - longer half-life, less bleeding risk, less monitoring
    - easier to self-administer

Precautions

- contraindicated in severe active bleeding / bleeding disorders states

Adverse effects

- bleeding from puncture sites, wounds, anaemia, heparin-induced thrombocytopenia (more details later)

Heparins

- **Pharmacokinetics**
  - Heparin not absorbed orally
    - Administered i.v. (bolus, infusion) or s.c. (with delayed onset → ~ 60min)
  - Unpredictable pharmacokinetics for unfractionated heparin
    - Binds to endothelial cells and others → saturable
    - $T_{½}$ (40-90min) increases with dose
    - Monitor response with aPTT (activated partial thromboplastin time) → assay is sensitive to factor IIa and aim for 2× prolongation (control aPTT=1)
  - LMWH (enoxaparin, dalteparin) – produced by digestion, fractionation and extraction of heparin
  - Heparinoid (danaparoid → chemically distinct from other LMWHs)

Heparins

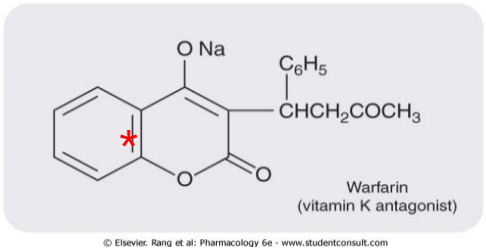
- **Pharmacokinetics**
  - Heparinoid (danaparoid → chemically distinct from other LMWHs)
    - Predictable pharmacokinetics → no binding to cells → linear (1st order) kinetics; response predictable
    - Longer $t_{½}$ ~ 3-6h
    - Do not prolong aPTT (do not affect factor IIa)
    - Monitoring not required
    - Suitable for outpatient, home use

Heparins

- **Adverse effects and Contraindications**
  - **Bleeding**
    - Contraindicated in ulcers, neurosurgery, uncontrolled hypertension…
    - No IM injection → increases haematoma risk (bleeding in muscle)
    - Can be reverse with protamine → a basic molecule, binds and forms a complex with heparin, prevents binding of heparin with ATIII (less effective for LMWH toxicity)
  - **Heparin-Induced Thrombocytopaenia (HIT) → bruise easily**
    - Generation of antibodies which complex with heparin and platelet factor
    - Complex binds platelet leading to platelet activation, aggregation and thrombosis
    - Monitor platelet count
    - LMWH *less likely* to initiate this
  - **Osteoporosis (chronic use → ≥ 6 months)**
    - Fractures
    - Mechanism unknown (inhibition of OPG and enhancement of osteoclast activity)
    - Lower risk with LMWH, fondaparinux (even shorter)

Warfarin

It's a coumarin analogue



(±) or R, S

- 1920s in USA
  - Cattle being fed clover silage → haemorrhage (due to coumarins)
- Active ingredient isolated by research scientists at Wisconsin Alumni Research Foundation (thus the name WARFarin)
  - Competitive inhibitors of vitamin K reductase
  - Prevent maturation/functionalisation of clotting factors (II, VII, IX and X) in liver

Also the active ingredient in rat poison!!

Warfarin

Indications

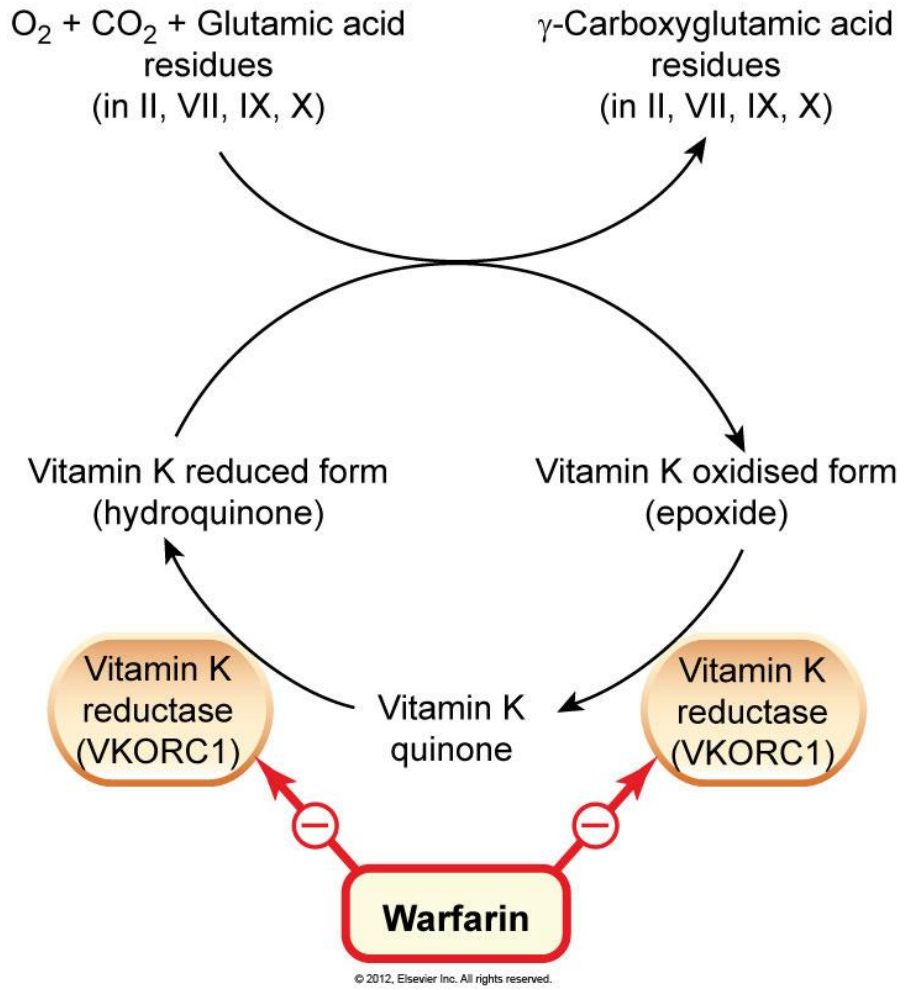
- prevention and treatment of VTE
- prevention of thromboembolism in patients with prosthetic heart valves
- prevention of stroke in patients with previous MI and increased embolic risk
- AF and a high risk of stroke or systemic embolism

- narrow therapeutic range
- effectiveness altered by many factors
    - eg diet, alcohol, body mass, other medications, co-existing disease, genetics
    - thus high degree of variability in response between patients

Warfarin

Mechanism of action

- Analogue of vitamin K
- Vitamin K = coenzyme in synthesis of prothrombin, factors II, VII, IX & X in liver
- Catalysed by epoxide reductase
- Warfarin competes with Vit K and inhibits vitamin K epoxide reductase complex subunit 1 (VKORC1)
- inhibits synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the antithrombotic factors protein C and protein S



Warfarin

Drug / diet / pharmacokinetic interactions

- racemic mixture of S (4x more potent) and R isomers
- S metabolised by CYP2C9 enzyme, R by CYP 3A4
- known to interact with > 250 different drugs
- eg antiarrhythmics, fibrates, H2 antagonists, some anticonvulsants, some diuretics, numerous antimicrobials, some NSAIDs, some antidepressants, corticosteroids etc
- fish oil, gingko biloba, St John's wort etc
- affected by alcohol, vitamin K, cranberry juice
- also genetic polymorphisms of CYP2C9 and VKORC1

Warfarin

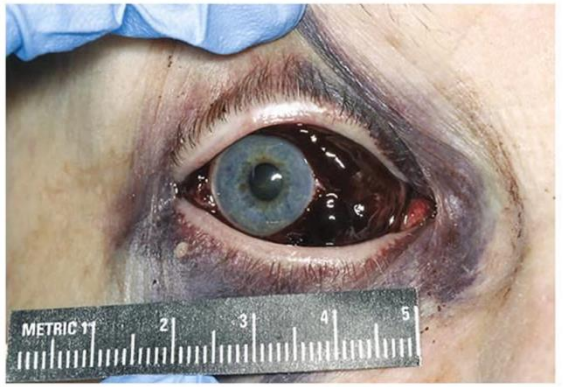
Drug / diet / pharmacokinetic interactions

- Highly bound to plasma albumin
  - Fraction of unbound drug, f_u=0.01 (i.e. 1% in circulation)
- Eliminated by metabolism (CYP450)
  - $T_{½}$ varies → 10-45h, depending on genetic, diet, other drugs coadministered.....
- S(-) isomer has 4× potency of R(+) isomer
  - Isomers being metabolised differently (warfarin is given as racemic mixture 50:50)
- Dose determined by trial in each patient → using INR to measure response
  - First dose → onset (12-16h); maximum effects (1-3d)
  - Usually take ~7 days to find suitable maintenance dose (1-10mg/d)

Warfarin

Adverse effects

- Severe bleeding, bleeding from the rectum or black stools
- Skin conditions such as hives, a rash or itching
- Swelling of the face, throat, mouth, legs, feet or hands
- Bruising
- Chest pain or pressure
- Nausea or vomiting
- Fever or flu-like symptoms
- Joint or muscle aches
- Diarrhoea



Warfarin

Precautions

- Alcoholism
- contraindicated in pregnancy (Cat D)
- contraindicated in severe active bleeding or disease states with an increased risk of severe bleeding
    - severe uncontrolled hypertension, severe hepatic disease, severe thrombocytopenia
- protein C or protein S deficiency—increases risk of skin necrosis
- use with care in patients with an increased risk of bleeding, eg frequent falls, severe renal impairment
- other drugs that can affect the clotting process may increase the risk of bleeding

Warfarin - patient management

- therapy requires regular monitoring
- "Prothrombin time" used as a measure of warfarin effect
- PT is a measurement of the extrinsic coagulation pathway
- measures activity of factors I (fibrinogen), II (prothrombin), V, VII, and X

- normally defined in terms of INR - International Normalised Ratio (standardises PT measurements)

- recommended INR for most indications = 2-3
- see detailed guidelines on LearnJCU

Direct thrombin inhibitors

Exemplar

- Dabigatran and bivalirudin

Indications

- moderate-to-high risk unstable angina
- non-ST-segment elevation MI (NSTEACS) undergoing early invasive management, including PCI

Mechanism of action

- serine protease inhibitor
- reversibly inhibit both free and fibrin-bound thrombin
- prevent conversion of fibrinogen to fibrin
- also inhibit thrombin-induced platelet aggregation

- monitor renal function

Factor Xa inhibitors

Exemplar

- Rivaroxaban and apixaban

Indications

- prevention of VTE after hip or knee replacement surgery
- treatment prevention of VTE
- AF

Mechanism of action

- Direct acting without involvement of ATIII – selective for factor Xa rather than thrombin
- thus block thrombin production, conversion of fibrinogen to fibrin and thrombus development

- monitor renal function

Coagulation cascade - drug targets

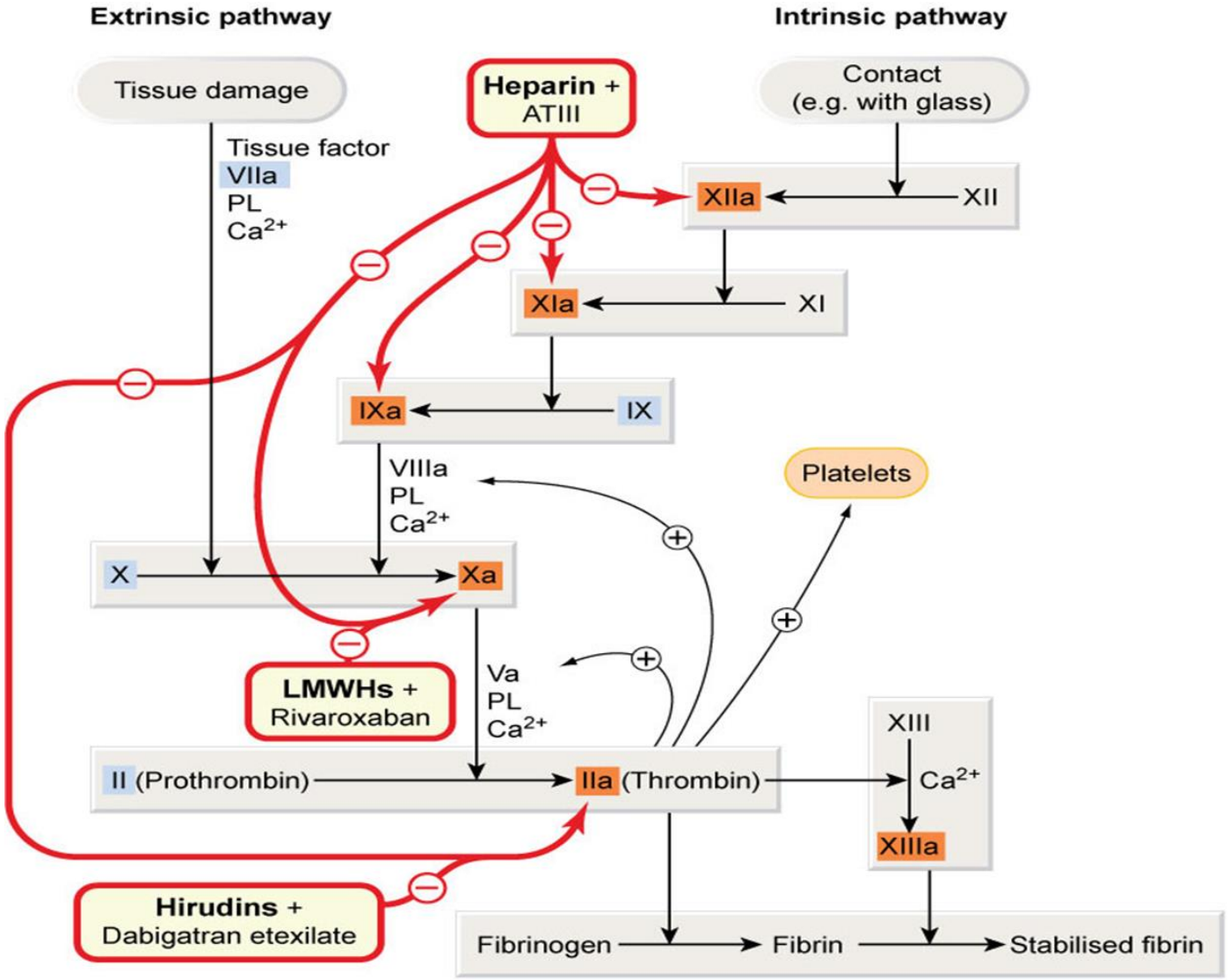
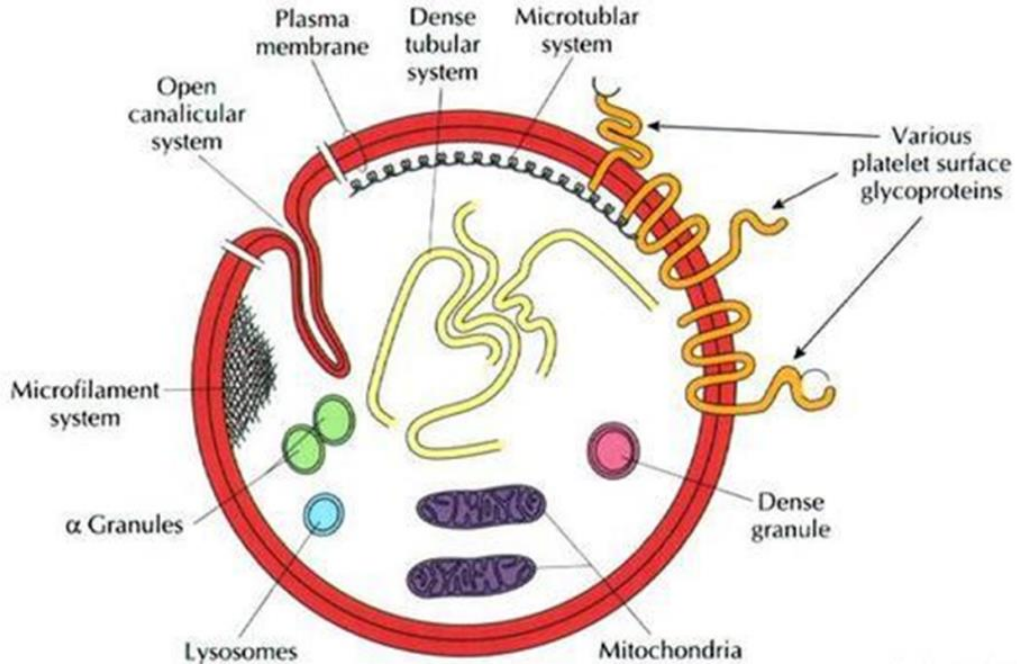


Fig. 24-2. **The coagulation cascade: sites of action of anticoagulant drugs.** Oral anticoagulants interfere with post-translational γ-carboxylation of factors II, VII, IX and X (shown in blue boxes). Heparins activate antithrombin III. ATIII, antithrombin III; LMWHs, low-molecular-weight heparins; PL, negatively charged phospholipid supplied by activated platelets.

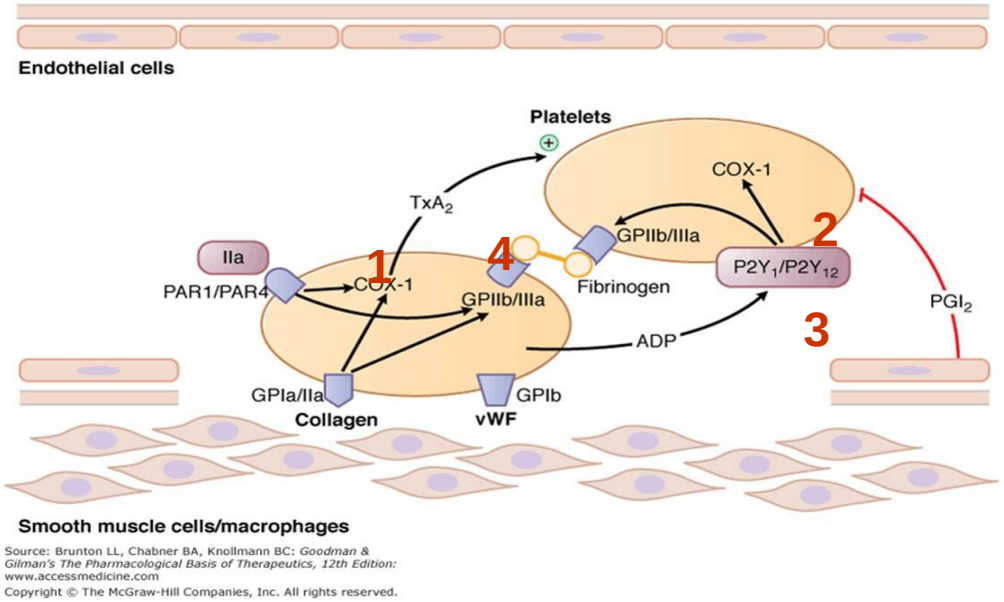
Anti-Platelet Drugs

- inhibit platelet aggregation



- Key steps in process
- endothelial damage exposes collagen etc to which platelets bind
- bound platelets release pro-clotting & activating factors
- Arachidonic acid - TXA2 (COX-1)
- ADP
- GP IIb/IIIa receptors expression
- GP IIb/IIIa receptor binds to fibrinogen - aggregation

Drugs inhibiting platelet activation



1. Cyclooxygenase-1 (COX-1) inhibition
2. Phosphodiesterase inhibitors
3. ADP (adenosine diphosphate) receptor antagonists
4. Glycoprotein IIb/IIIa receptor antagonists

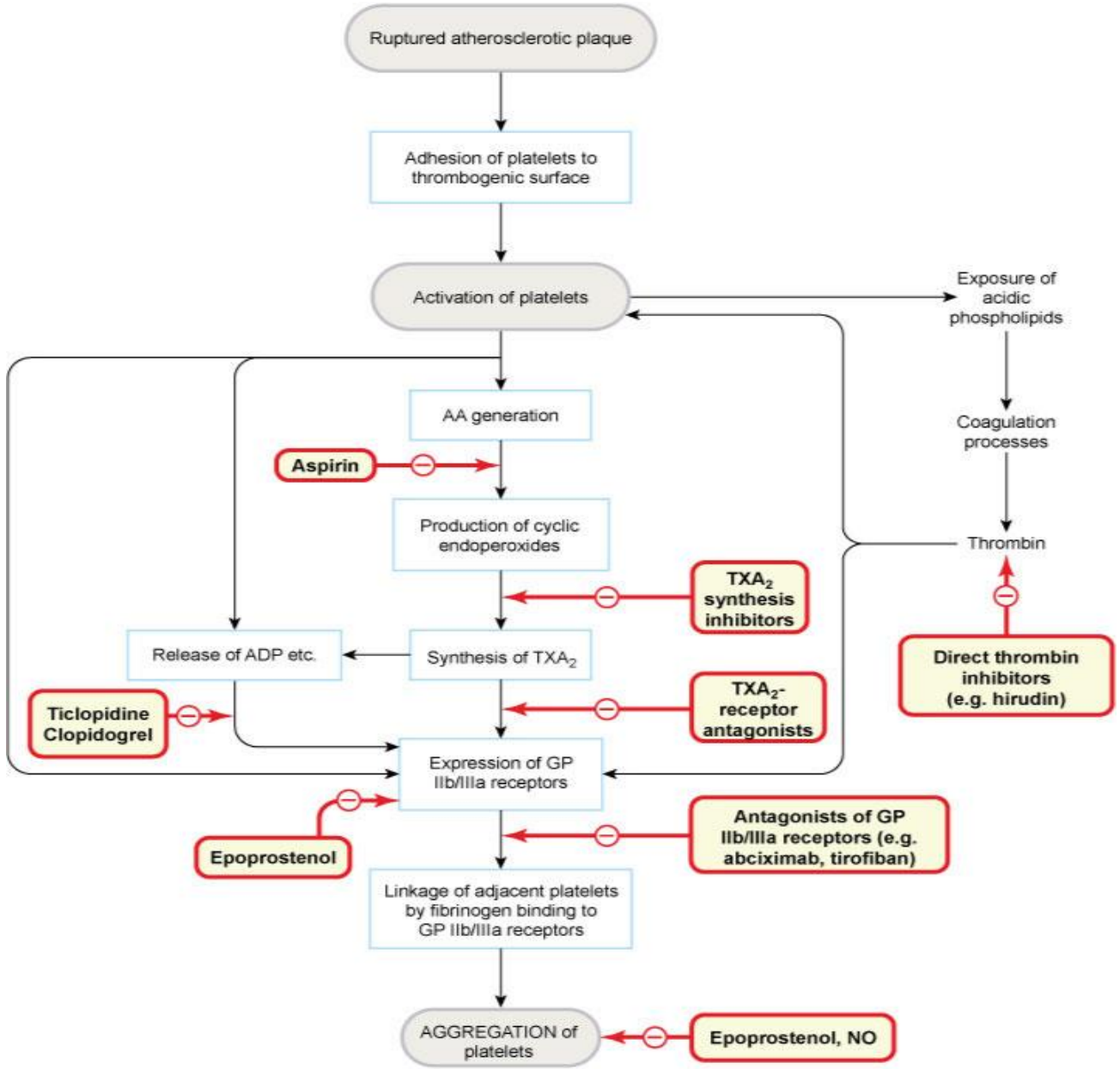


Fig. 24-7. **Platelet activation.** Events involved in platelet adhesion and aggregation are shown, with the sites of action of drugs and endogenous mediators. AA, arachidonic acid; ADP, adenosine bisphosphate; GP, glycoprotein; NO, nitric oxide; TXA_2, thromboxane A_2.

Anti-Platelet Drugs

General Indications

- used in managing arterial thrombosis
- not useful in venous thromboembolism (VTE)
- reduce the incidence of vascular events
- may be more effective when used in conjunction but increases risk of bleeding

Classes

- aspirin
- P2Y12 antagonists
- glycoprotein IIb/IIIa inhibitors

Aspirin - NSAID

Indications

- prevention of MI, unstable angina (ACS), ischemic stroke, TIA

Mechanism of action

- irreversible inhibitor of cyclo-oxygenase
- prevents thromboxane (TXA2) formation
  - remains low for 7 days (platelet lifespan)
- thus inhibits platelet aggregation
- reduces participation of platelets in thrombus formation
- reduce incidental thrombus formation
- low doses used have selective effect on platelets
- precautions – allergy, aspirin-sensitive asthma
- adverse effects - GI

P2Y12 antagonists

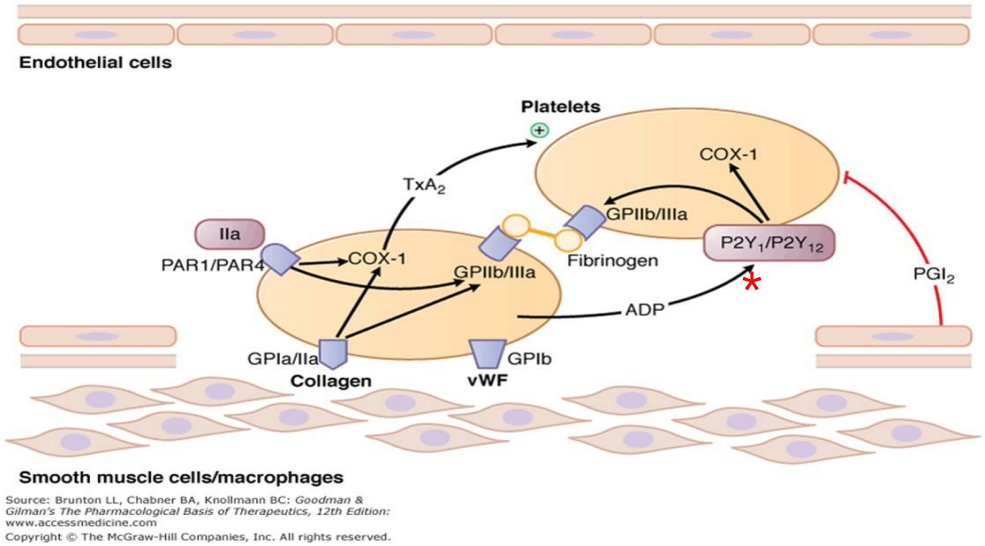
Exemplar

- Clopidogrel, ticagrelor and prasugrel

Indications

- prevention of ACS, ischemic stroke, TIA
- with / instead of aspirin (combination therapy)

Mechanism of action



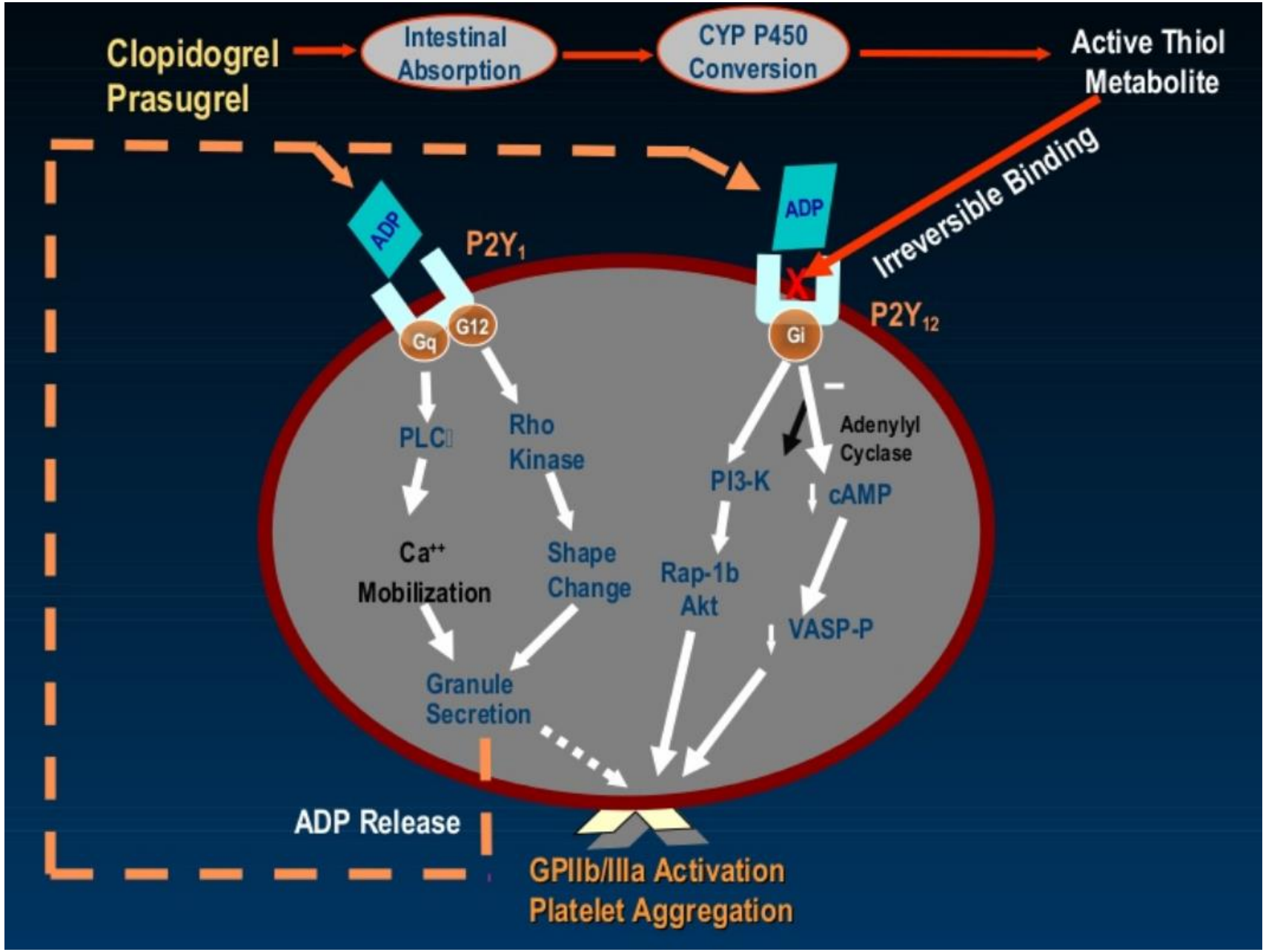
- ADP P2Y12 receptor antagonist
- receptors found on platelets
- Prevents ADP-mediated activation of glycoprotein receptor IIb – IIIa
- No direct interaction with GPIIb/IIIa receptors
- reduces cross-linking of platelets
- reduces incidental thrombus formation

P2Y12 antagonists

Pharmacokinetics

- Clopidogrel and prasugrel must be metabolised by cytochrome P450 isozymes to be active
- thus wide patient variability in response
- metabolised by CYP2C19
- caution when using with drugs that inhibit CYP2C19 (eg some PPIs) or patients lacking CYP2C19 activity
  - may decrease effectiveness of clopidogrel

ADRs - diarrhoea, thrombocytopenia (rare)


Clopidogrel
Prasugrel
Intestinal Absorption
CYP P450 Conversion
Active Thiol Metabolite
Irreversible Binding
ADP
P2Y1
Gq
G12
PLC
Rho Kinase
Ca++ Mobilization
Shape Change
Granule Secretion
ADP Release
ADP
P2Y12
Gi
Adenylyl Cyclase
PI3-K
cAMP
Rap-1b Akt
VASP-P
GPIIb/IIIa Activation
Platelet Aggregation

Glycoprotein IIb/IIIa inhibitors

Exemplar

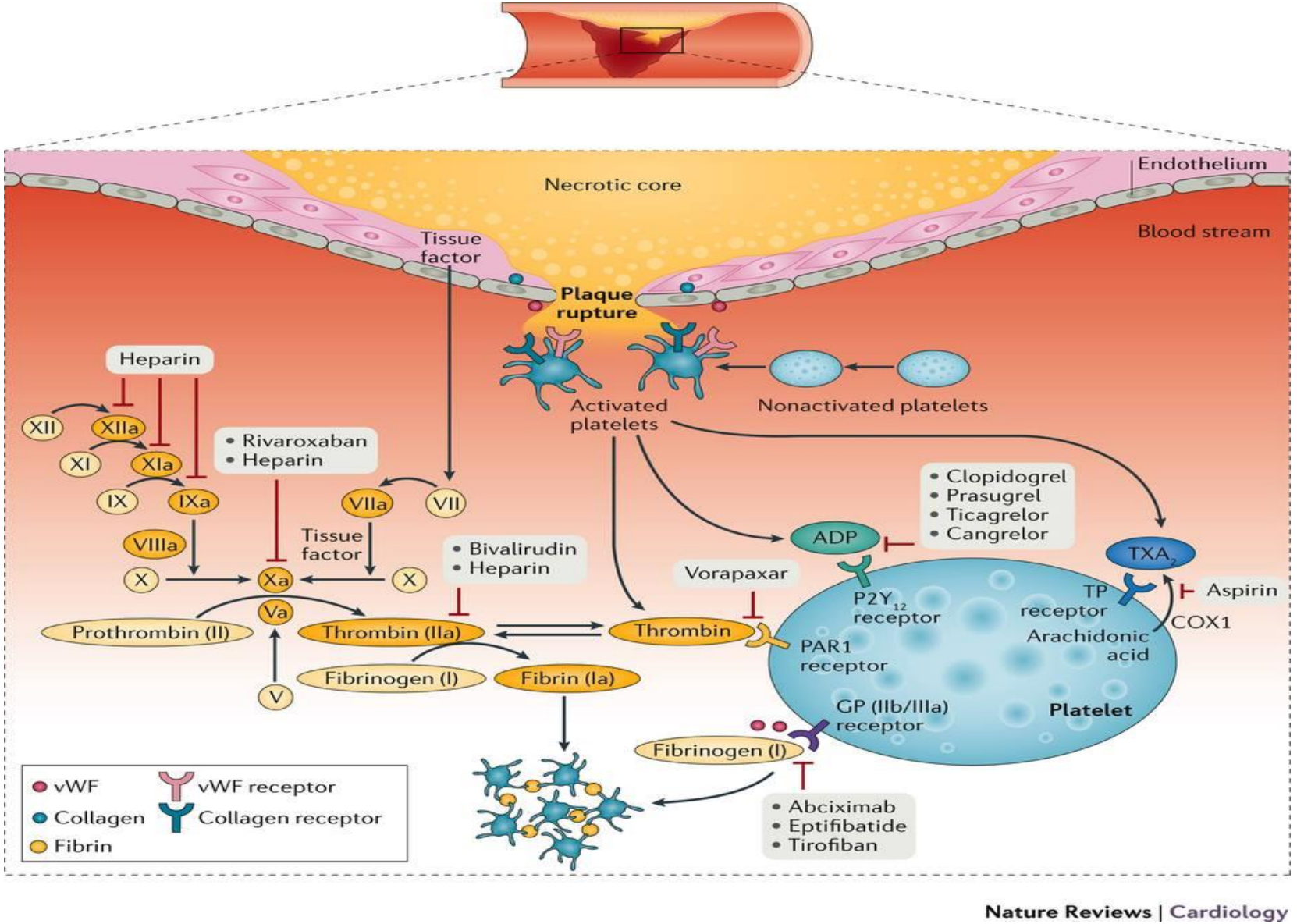
- Abciximab (peptide), eptifibatide (cyclic heptapeptide), tirofiban (non-peptide)

Mechanism of action of tirofiban

- glycoprotein IIb/IIIa receptor antagonist
- occupies glycoprotein IIb/IIIa receptor
- inhibits binding of fibrinogen to platelet
- thus blocks platelet aggregation

- Administered IV

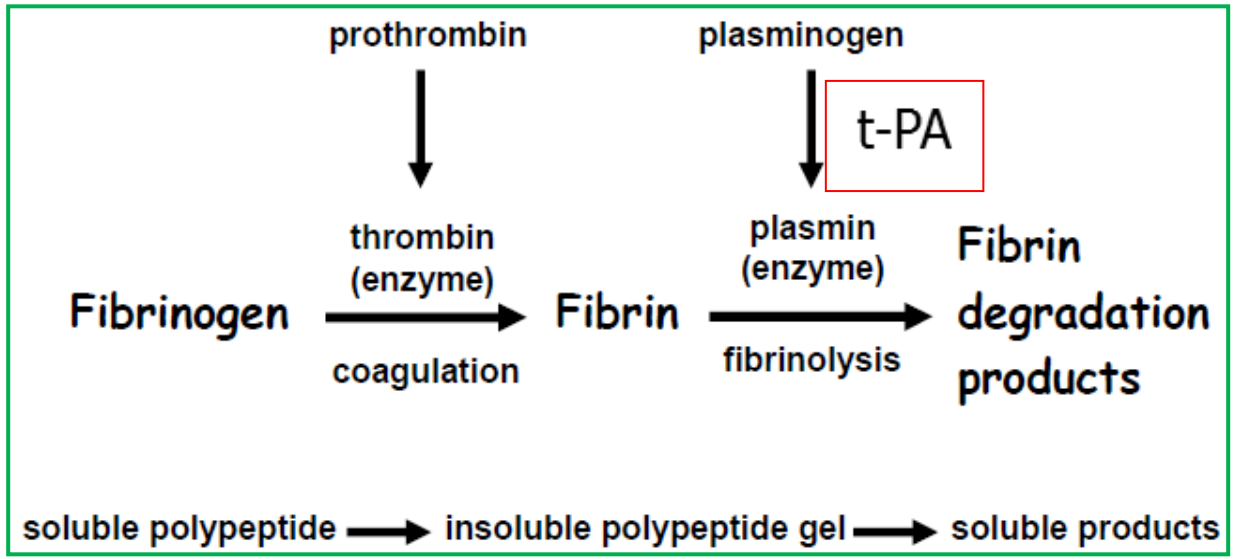
Anticoagulants, Antiplatelets



Thrombolytics (fibrinolytics)

- plasmin - endogenous fibrinolytic enzyme that rapidly degrades clots by splitting fibrin
- drugs act as 'tissue plasminogen activators'
- convert plasminogen to plasmin, which then catalyses breakdown of fibrin

  - plasmin itself can not be used because naturally occurring inhibitors in plasma prevent effects
- clot-specific, causing fewer haemorrhages
- more active on fibrin-bound plasminogen than on plasma plasminogen



Thrombolytics (fibrinolytics)

- Tissue Plasminogen Activators (tPA)
  - Synthetic tPA (alteplase [aka rt-PA], reteplase, tenecteplase)
    - Clot-selective
    - Bind fibrin-bound plasminogen → convert plasminogen to plasmin
  - Streptokinase
    - Protein extracted from haemolytic bacteria Streptococci
    - Binds plasminogen to form an active complex
    - Active complex converts plasminogen to plasmin
    - Use limited due to generation of antibodies (→ anaphylaxis and loss of effect)
  - Use with aspirin to break down blood/platelet clots

Thrombolytics (fibrinolytics)

Indications

- acute STEMI, acute ischemic stroke
- acute massive VTE in haemodynamically unstable patients
- peripheral arterial thromboembolism
- clear thrombosed shunts and cannulae

Precautions

- bleeding disorders
- pregnancy

Adverse effects

- bleeding, transient hypotension, allergic reaction