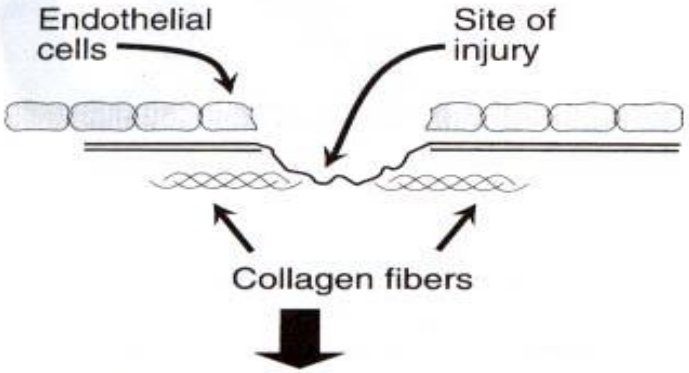
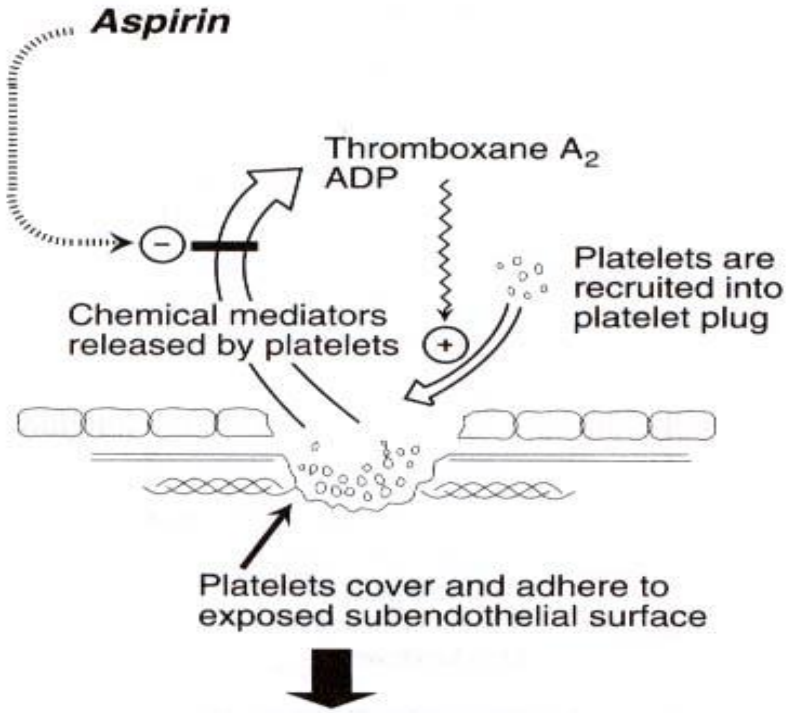
Drugs Used in Clotting Disorders

- **Reduce clotting**
  - **Antiplatelets**
  - **Anticoagulants**
  - **Thrombolytics**
- **Facilitate clotting**

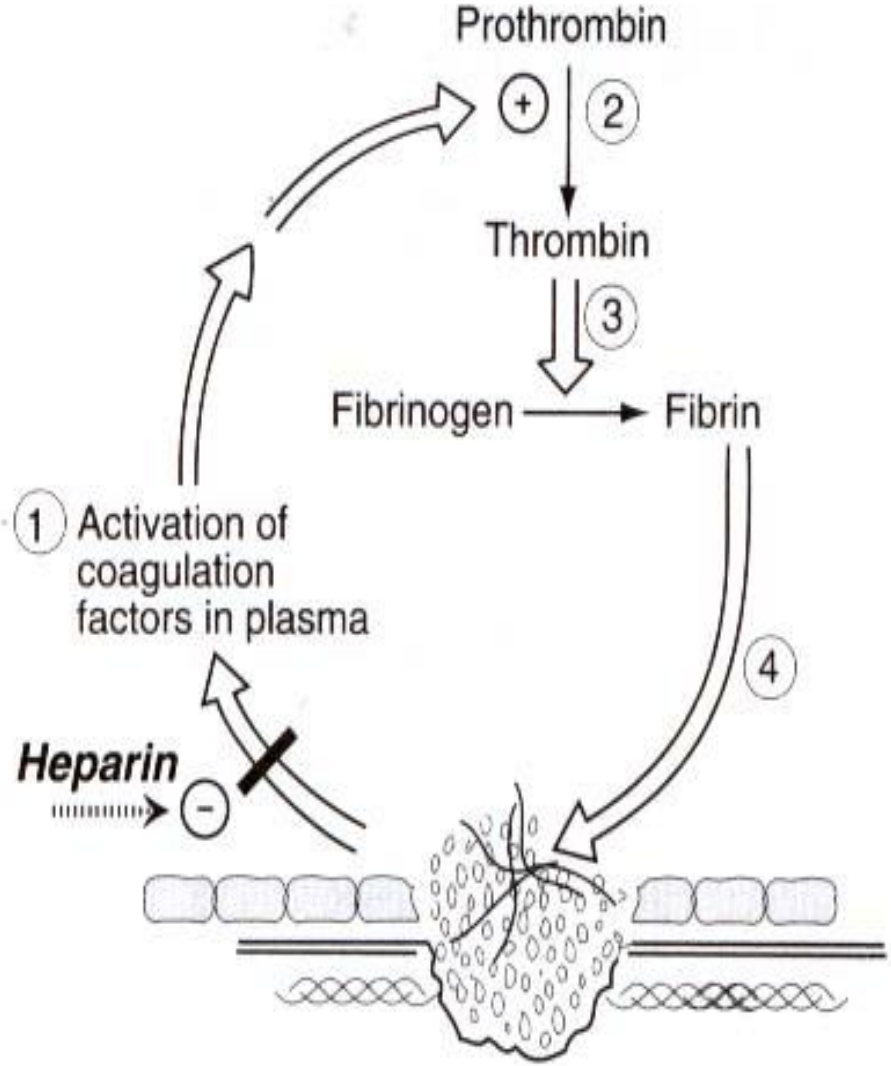
1 Damage to vessel exposes collagen of subendothelium



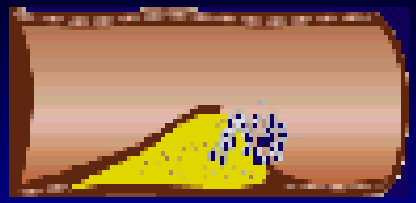
2 Platelet adhesion and release of granules



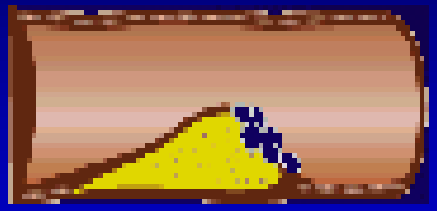
3 Platelet aggregation and formation of fibrin plug



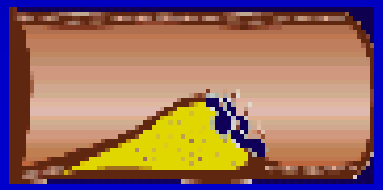
Unstable plaques activate platelets



Plaque Fissure or Rupture

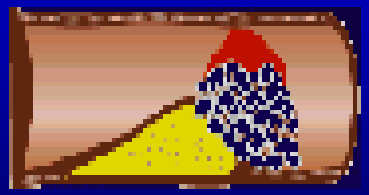


Platelet Adhesion



Platelet Activation

Platelet Aggregation



Thrombotic Occlusion

Platelet Inhibitors

- **These drugs prevent platelet activation.**

(1) Inhibition of prostaglandin synthesis (aspirin),

(2) Inhibition of ADP-induced platelet aggregation (*Ticlopidine, Clopidogrel, Prasugrel, Cangrelor, Ticagelor***),**

(3) blockade of glycoprotein IIb/IIIa receptors on platelets (abciximab, tirofiban, and eptifibatide).

(4) phosphodiesterase inhibitor (Dipyridamole ?? and cilostazol).

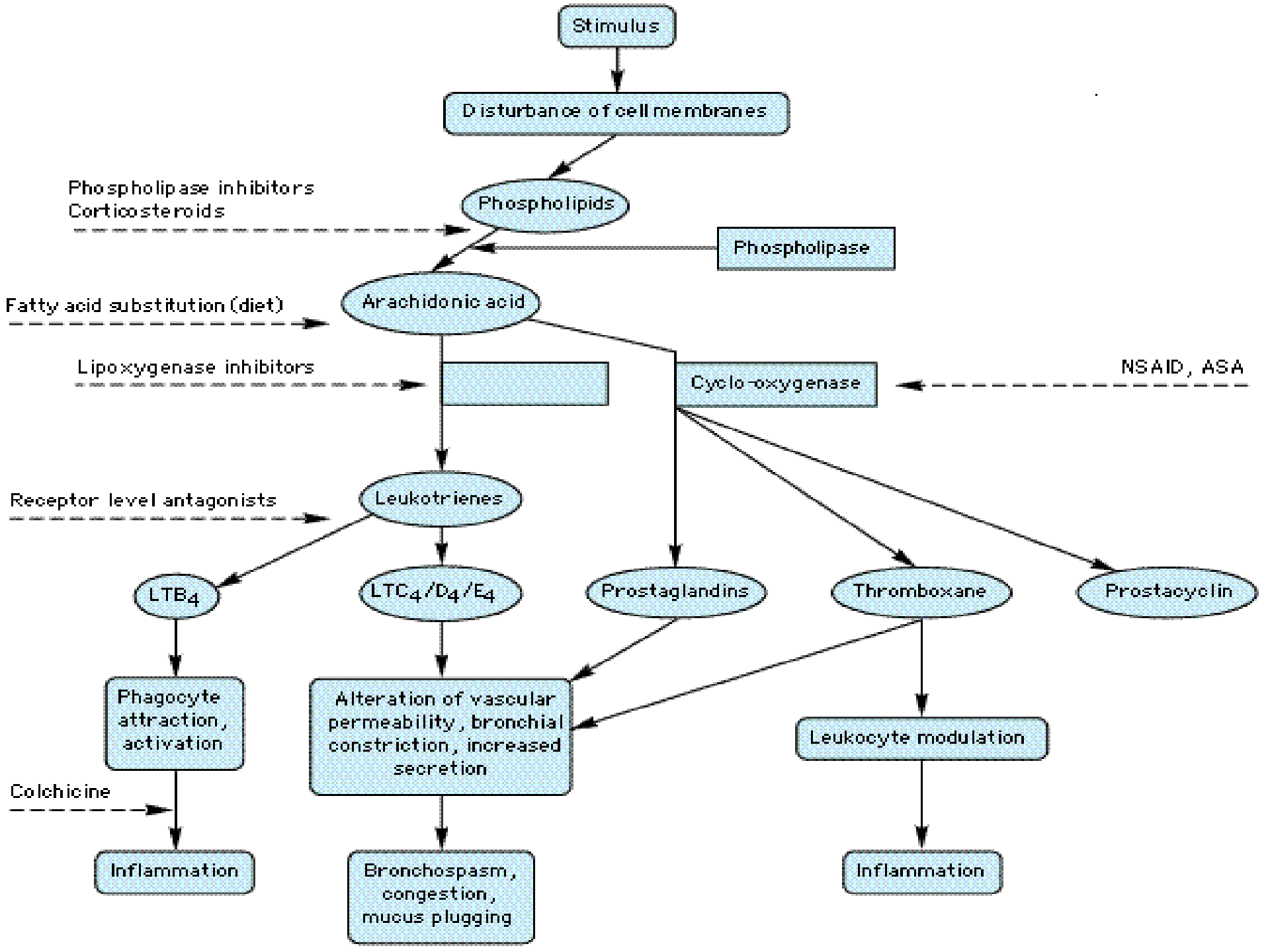
Aspirin

- **MOA: Blocks COX→ inhibits conversion of AA into TXA_2.**

- **Indications: -prophylactic in transient cerebral ischemia.**
  -to reduce recurrence of MI.
  -in angina.

A daily dose of 100 mg.

Adverse effects: hemorrhagic stroke, GIT bleeding.


Stimulus
Disturbance of cell membranes
Phospholipase inhibitors
Corticosteroids
Phospholipids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Cyclo-oxygenase
NSAID, ASA
Receptor level antagonists
Leukotrienes
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucus plugging
Inflammation

Ticlopidine & Clopidogrel

- **Useful in patients who cannot tolerate aspirin or who failed aspirin.**

- **MOA: block ADP receptors on platelet.**

Indications:

-prevent vascular events in patients with transient ischemic attacks (TIA)

-unstable angina.

-prevent thrombotic stroke.

-to prevent thrombosis in patients undergoing placement of a coronary stent.

Ticlopidine & Clopidogrel

Adverse effects:

Ticlopidine

- **Hemorrhage**
- **Leucopenia: should monitoring WBCs during the first 3 months.**
- **Thrombotic thrombocytopenic purpura (TTP)**

Clopidogrel - fewer than with ticlopidine

- **Neutropenia.**
- **TTP**

Ticlopidine & Clopidogrel

- **Dose:**

-Ticlopidine: 250 mg BID orally.

-Clopidogrel: oral loading dose 300 mg, maintenance dose 75 mg once daily.

- **Because of less side effects & more convenient dosing with clopidogrel, it is preferred over ticlopidine**

($P2Y_{12}$)ADP receptors blockers

- Cangrelor (Kengreal) IV (not a prodrug)
- Clopidogrel (Plavix) Prodrug ??????
- Prasugrel (Effient) bleeding

  Hypertension (8%), hypotension (4%), atrial fibrillation (3%), bradycardia (3%),
- Ticagrelor (Brilinta) not a prodrug bleeding

  shortness of breath (dyspnoea)
- Ticlopidine (Ticlid) not any more (TTP)

Warning

- Clopidogrel was issued a black box warning from the FDA on 12 March 2010, as the estimated 2–14% of the US population who have low levels of the CYP2C19 liver enzyme needed to activate clopidogrel may not get the full effect. Tests are available to predict if a patient would be susceptible to this problem or not

Abciximab, eptifibatide, & tirofiban.

Glycoprotein IIb/IIIa inhibitors:

- **Abciximab** is a humanized monoclonal antibody directed against IIb/IIIa complex
- **Eptifibatide** & **Tirofiban** inhibit ligand binding to IIb/IIIa receptor by their occupancy of the receptor.

➔ All Inhibit bridging of platelet by fibrinogen.

- Approved for use in percutaneous coronary intervention (PCTA) & in ACSs.
- The three agents are administered parenterally

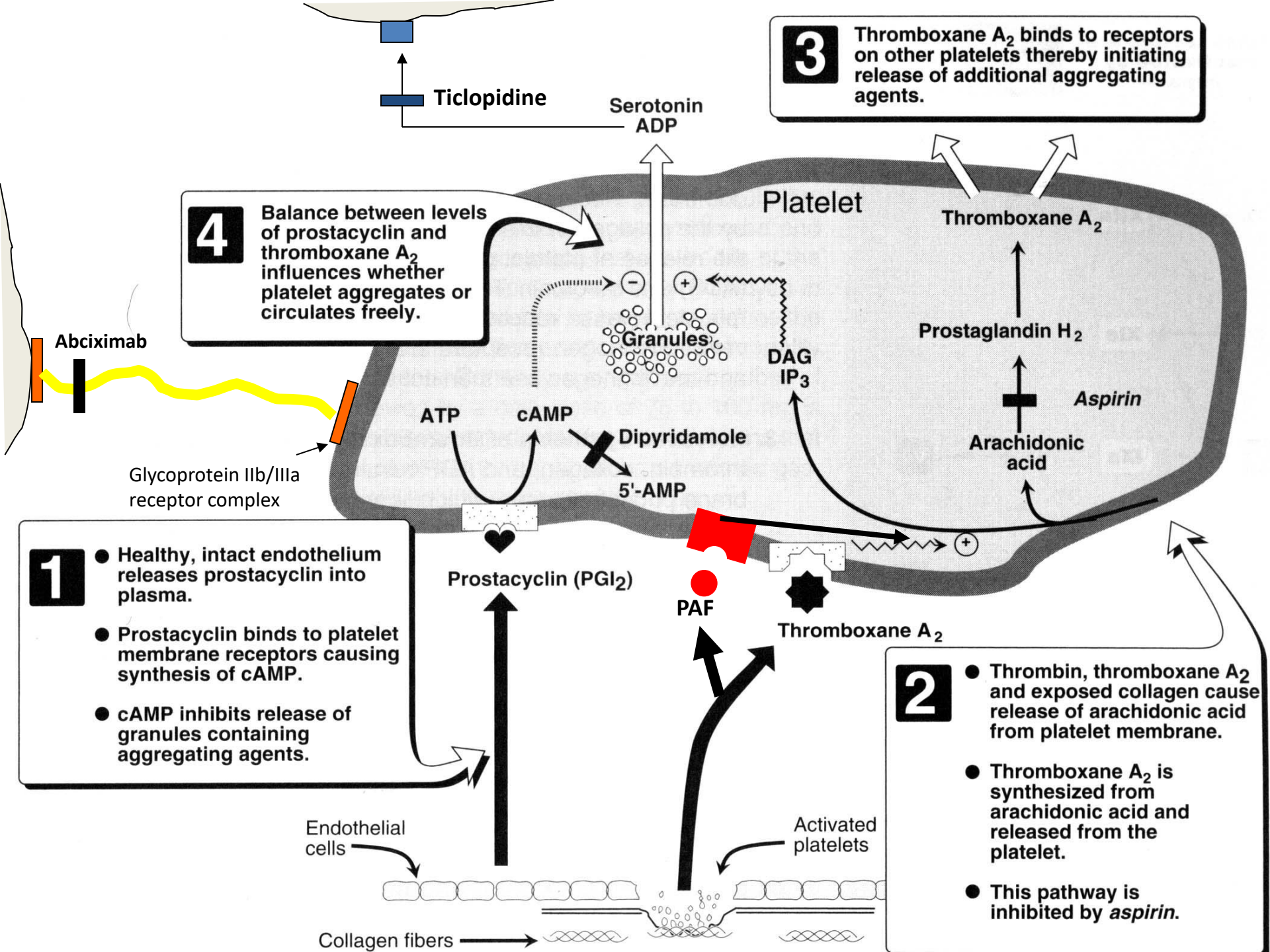
Dipyridamole:

- **MOA: -inhibits phosphodiesterase→ ↑ cAMP→ potentiates effects of prostacyclin→ platelet inhibition.**

  -dipyridamole is also a coronary vasodilator.

- **Indications:-with aspirin for prophylaxis in angina.**

  -with warfarin to inhibit embolization from prosthetic heart valves.

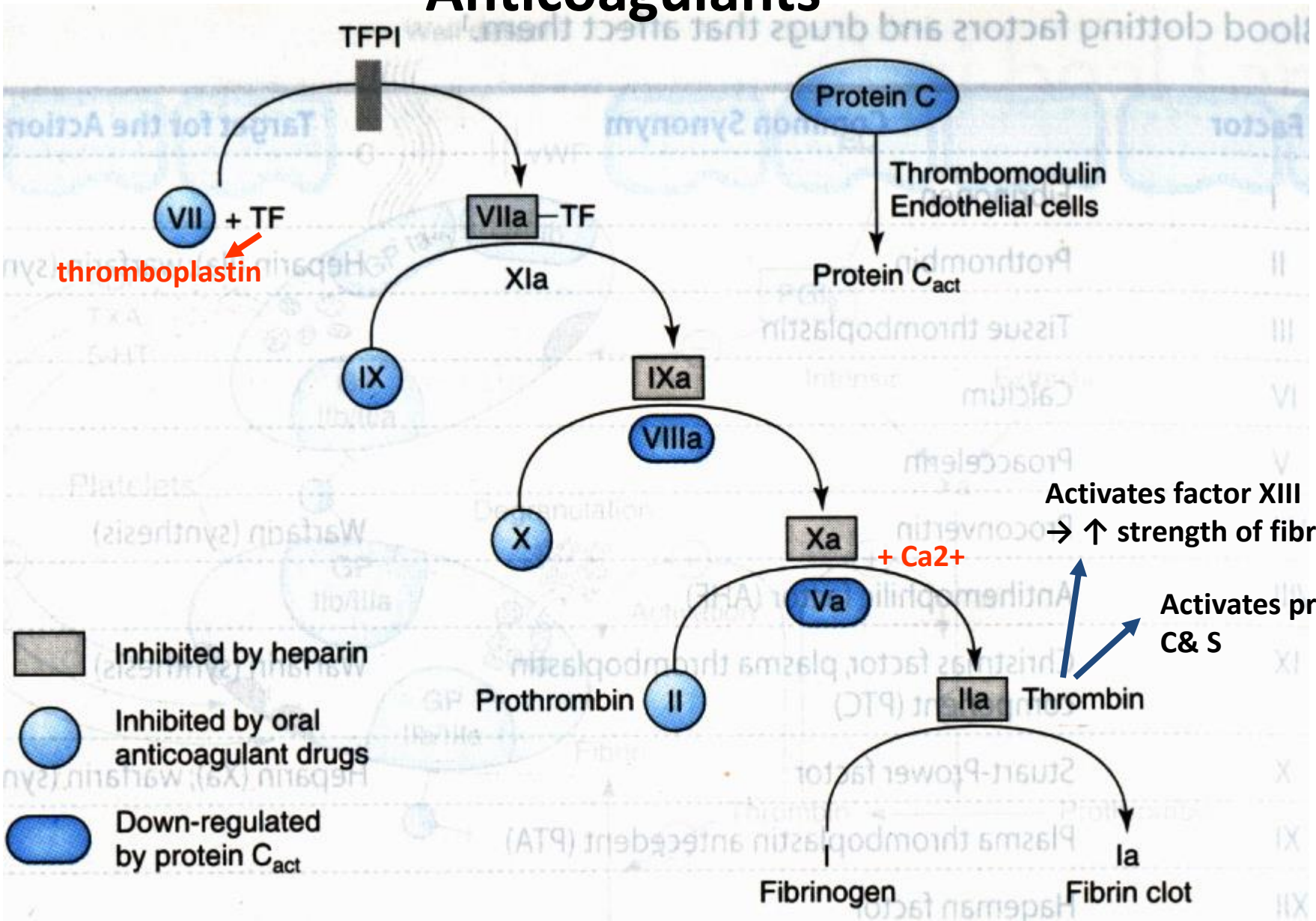

Ticlopidine
Serotonin
ADP
3
Thromboxane A_2 binds to receptors on other platelets thereby initiating release of additional aggregating agents.
4
Balance between levels of prostacyclin and thromboxane A_2 influences whether platelet aggregates or circulates freely.
Platelet
Thromboxane A_2
Prostaglandin H_2
Granules
DAG
IP_3
Aspirin
Arachidonic acid
Abciximab
ATP
cAMP
Dipyridamole
5'-AMP
Glycoprotein IIb/IIIa receptor complex
1
Healthy, intact endothelium releases prostacyclin into plasma.
Prostacyclin binds to platelet membrane receptors causing synthesis of cAMP.
cAMP inhibits release of granules containing aggregating agents.
Prostacyclin (PGI_2)
PAF
Thromboxane A_2
2
Thrombin, thromboxane A_2 and exposed collagen cause release of arachidonic acid from platelet membrane.
Thromboxane A_2 is synthesized from arachidonic acid and released from the platelet.
This pathway is inhibited by *aspirin*.
Endothelial cells
Activated platelets
Collagen fibers

Anticoagulants

Coagulation Cascade

- Series of steps
- Precursor proteins in plasma are activated by proteolysis
- Activated proteins activate other proteins
- Plasma contains protease inhibitors like Antithrombin III (ATIII), protein C, and S that rapidly inactivate coagulation proteins as they escape from site of vessel injury.

Anticoagulants



Anticoagulants

A) Heparin

B) Low-Molecular-Weight Heparins:

Enoxaparin, dalteparin, tenzaparin

C) Heparinoids:

Danaparoid**.**

D) Direct & specific thrombin inhibitors:

Hirudin (leech protein), lepiridun, bivalirudin, argatroban, melagatran.

E) Oral direct & specific thrombin inhibitors:

Ximelagatran and Dabigatran

F) Pentasacharide specific Xa inhibitors:

Fondaparinux, Rivaroxaban

F) Warfarin

Mechanism of unfractionated heparin UFH action

- Prevents further thrombus growth, allowing the body's own thrombolytic system to dissolve clot.

Activates plasma protease inhibitor **antithrombin III (AT III).**

- The complex inactivates factors:

XIIa, XIa, IXa, **Xa, & IIa** (thrombin)

For DVT & PE, heparin is given **for 5–7 days**.

Laboratory Monitoring for UFH

- Activated partial thromboplastin time **(aPTT**):
- Normal aPTT is 24-36 sec.
- An aPTT ratio (patient aPTT/control aPTT) of 2–2.5 should be achieved throughout infusion or 6 hours after intermittent administration.

UFH Toxicity

1. The major adverse effect is **bleeding**
2. Heparin is of animal origin & should be used cautiously in patients with **allergy.**
3. Increased loss of hair (reversible **alopecia**)
4. Long-term heparin therapy: **osteoporosis**
5. Hyperkalemia (decreases aldosterone)
6. **Heparin-induced thrombocytopenia (HIT**).

B) Low-Molecular Weight Heparins (LMWHs)

- **Enoxaparin**, **dalteparin, tenzaparin & ardeparin** are fragments of heparin.
- Similar to heparin, they possess a unique pentasaccharide sequence in order to bind to & catalyze ATIII.
- As opposed to heparin, this complex preferentially inactivates factor Xa & minimally affects thrombin.
- Since LMWHs minimally affect thrombin, they have minimal impact on the aPTT (which is most sensitive to thrombin).

B) Low-Molecular Weight Heparins (LMWHs)

- **Enoxaparin:** from same sources as regular heparin; doses are specified in milligrams.
- Eliminated renally.
- Higher costs for these agents may be outweighed by earlier discharge from hospital due to dosing convenience.
- Neutralization by protamine is incomplete.

Advantages of LMWHs over Heparin

- ↓ laboratory monitoring:

Blood conc determined only in renal failure, pregnancy, & obesity

- ↑ predictability of response
- Once-twice daily injections
- Ease of dosing and administration (SQ),
- ↓ requirement of hospitalization
- ↓ risk of thrombocytopenia
- ↓ risk of osteoporisis

ADR of LMWHs:

- Reactions at the injection site: irritation, pain, hematoma, bruising & redness
- bleeding.
- HIT: platelets should be measured at baseline & between days 3 and 5 of therapy.

Warfarin & Coumarin Anticoagulants

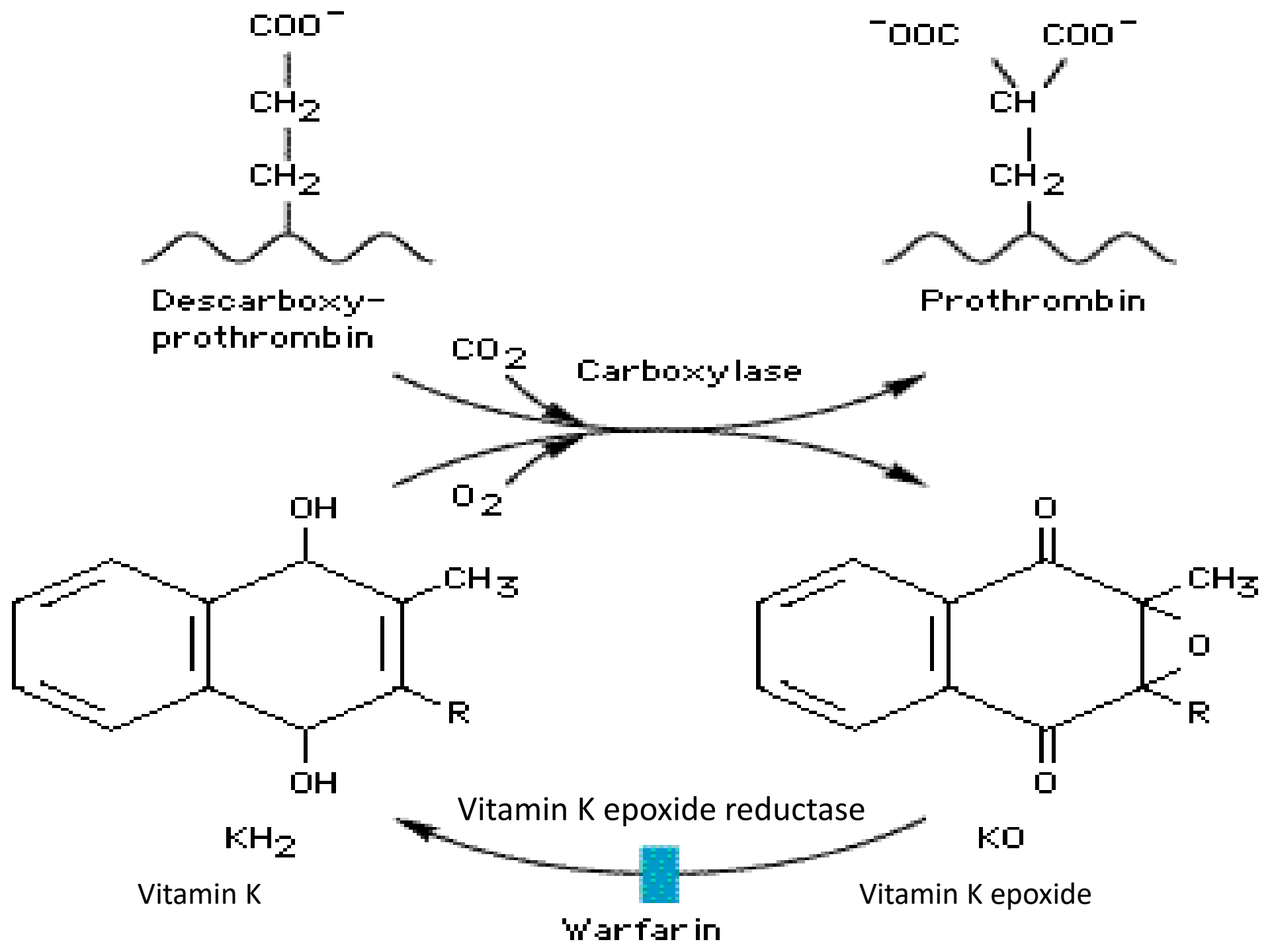
- is generally used as sodium salt & has 100% bioavailability.
- > 99% is bound to plasma albumin → small Vd, long half life.

Mechanism of Warfarin Action

- Blocks carboxylation of factors VII, IX, & X, & II as well as the proteins C and S.
- The blockade results in incomplete molecules that are biologically inactive in coagulation.
- This carboxylation is physiologically coupled with the oxidative deactivation of vitamin K.
- Warfarin prevents reductive metabolism of inactive vitamin K epoxide back to vitamin K.

- Full therapeutic effect is not achieved until existing factor II is cleared ($t_{1/2}$ of factor II is 60 hours).

- **heparin or enoxaparin must be overlapped** with warfarin & continued for 4–5 days until an **INR between 2.0 and 3.0** is reached.


COO⁻
CH2
CH2
Descarboxy-
prothrombin
⁻OOC
COO⁻
CH
CH2
Prothrombin
CO2
O2
Carboxylase
OH
CH3
R
OH
KH2
Vitamin K
O
CH3
O
R
O
KO
Vitamin K epoxide
Vitamin K epoxide reductase
Warfarin

Warfarin Drug Interactions

1. Pharmacokinetic mechanisms

- **enzyme induction,**
- **enzyme inhibition,**
- **↓ plasma protein binding.**

2. Pharmacodynamic mechanisms

- **synergism** (impaired hemostasis),
- **competitive antagonism** (vitamin K).

- Among the most dangerous are pharmacokinetic interactions with **azapropazone**:

-Azapropazone displaces warfarin from plasma protein & inhibits its metabolism

- The use of a drug that interacts with warfarin is not absolute contraindication to addition of warfarin.

I. Drugs that ↑ prothrombin time

↓ *warfarin metabolism*

Allopurinol Cimetidine Omeprazole Phenytoin (sometimes) Phenylbutazone Azapropazone Amiodarone	Ethanol (acute) Disulfiram Metronidazole Ketoconazole Fluconazole Miconazole	Erythromycin Azithromycin Ciprofloxacin Norfloxacin Sulfonamides

↑ *catabolism of clotting factors*

	Thyroid hormones	

↓ *synth. of clotting factors (↓ bacteria & direct inh. of epoxide reductase)*

Cefamandole Cefotetan	Cefmetazole Cefoperazone	

Unestablished mechanisms

Acetaminophen?	Fibrates Statins	Corticosteroids Androgens

II. Drugs that ↓ prothrombin time		
↑ synthesis of clotting factors		
Estrogens	Vitamin K	
↓ catabolism of clotting factors		
Methimazole	Propylthiouracil	
Induction of warfarin metabolism		
Carbamazepine Phenytoin (usually)	Barbiturates Ethanol (chronic)	Griseofulvin Rifampin
↓ absorption of warfarin		
Cholestyramine	Colestipol	Sucralfate
Unestablished mechanism		
Azathioprine	Cyclosporine	Cyclophosphamide
↑ risk of bleeding without effect on PT		
Aspirin NSAIDs	Ticlopidine Clopidogrel	SSRIs

Warfarin Toxicity

1. **Bleeding** – the most dangerous.

2. Warfarin crosses the placenta readily & can cause hemorrhagic disorders & abnormal bone formation **in the fetus**. Thus, warfarin should never be administered during pregnancy**.**

3. **Venous thrombosis** (due to ↓activity of protein C)

4. Purple toe syndrome (cholesterol microembolization → arterial obstruction)

Contraindications to warfarin:

<u>Absolute</u>:

- pregnancy
- others – see heparin

<u>Relative</u>:

- severe hepatic or renal disease
- vitamin K deficiency
- chronic alcoholism
- NSAIDs therapy

Dabigatran (Pradaxa)

Dabigatran

- MOA: direct thrombin inhibitor which inhibits:
  - Both free and fibrin-bound thrombin
  - Cleavage of fibrinogen to fibrin
  - Thrombin-induced platelet aggregation

Dabigatran

- Monitoring
  - PPT
- Onset: 1 hour, delayed by food
- Antidote: None
- ADRs
  - Bleeding (8% to 33%; major ≤ 6%)
  - Dyspepsia (11%)

Dabigatran

- Drug interactions
  - **Category X**: P-Gp inducers
  - **Category D**: Amiodarone, P-Gp inhibitors, quinidine, St. john's Wort, verapamil

Dabigatran

- FDA Bleeding Risk: **[12-7-2011]**

- Evaluating post-marketing reports of serious bleeding

- “Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies.”

Dabigatran

- FDA Drug Safety Communication: [**11-02-2012**]
  - "… FDA investigated the actual rates of gastrointestinal bleeding and intracranial hemorrhage for new users of [dabigatran] compared to new users of warfarin. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of [dabigatran] do not appear to be higher than bleeding rates associated with new use of warfarin …."

Dabigatran

- FDA Drug Safety Communication: [**12-19-2012**]
  - "A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because [dabigatran] users were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the [dabigatran] users than in the warfarin users [dabigatran] is not approved for patients with AF caused by heart valve problems. "

Thrombolytics (Fibrinolytics)

1. Streptokinase
2. Urokinase.
3. t-PA (tissue plasminogen activator), alteplase, tenecteplase, reteplase, &.

- Both protective hemostatic thrombi & target pathogenic thromboemboli are broken down.

Circulating fibrinogen will be degraded
➔ Bleeding can occur.

However, these drugs differ in their selectivity to plasminogen in clot & circulating plasminogen.

Thrombolytics (Fibrinolytics)

- **<u>Indications</u>:**

- IV for:

-Multiple pulmonary emboli

-Central deep venous thrombosis (eg, superior vena caval syndrome, ascending thrombophlebitis of iliofemoral vein).

-Acute myocardial infarction

-Acute ischemic stroke: tPA should be used within 3 hours after onset of symptoms.

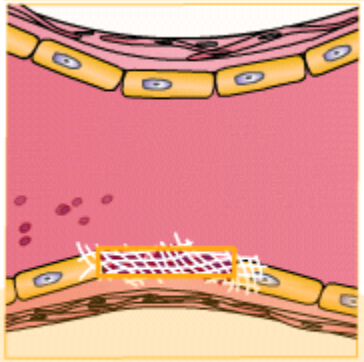
- Intra-arterially for:

-Peripheral vascular disease

Thrombolytic drugs – mechanism of action

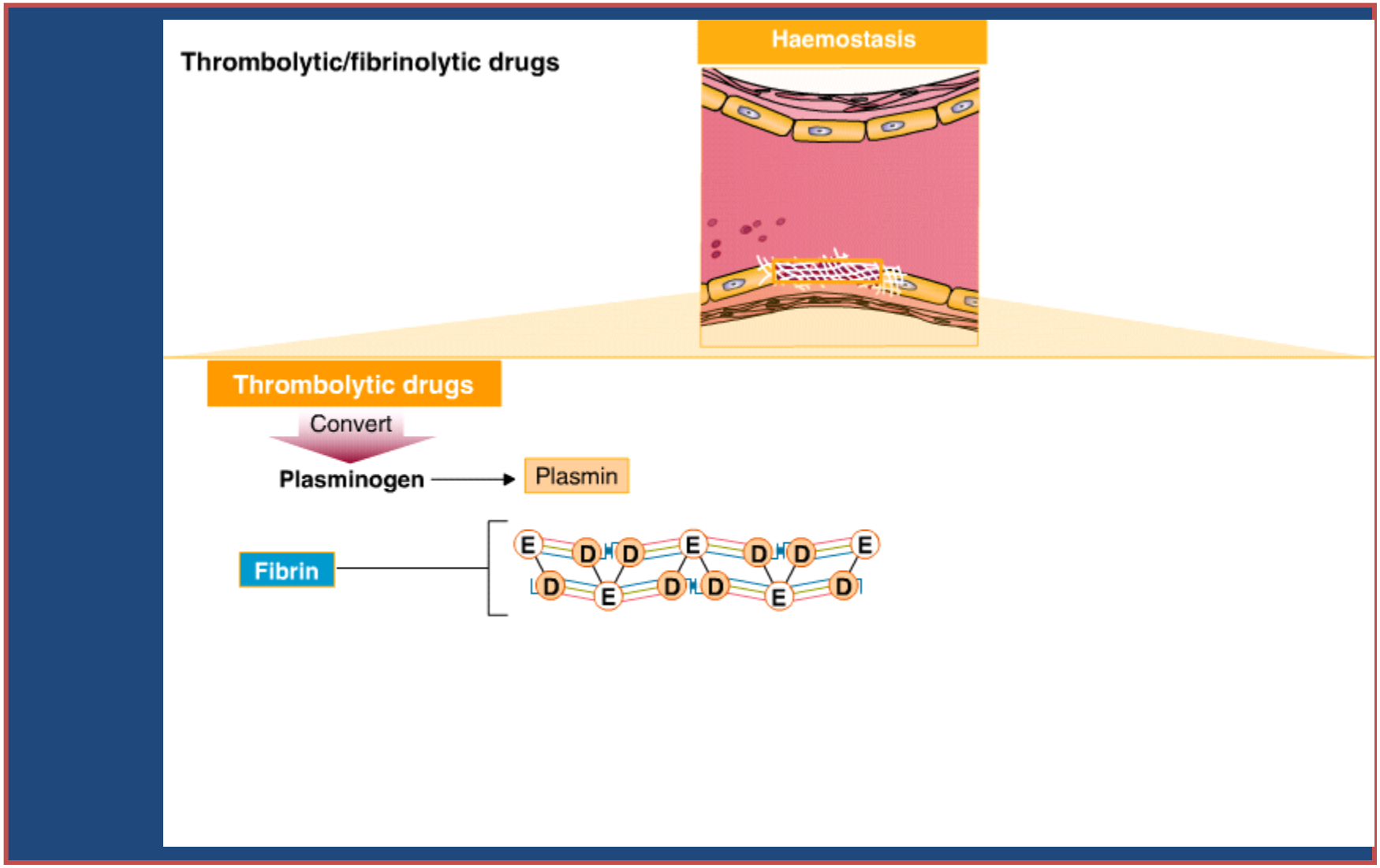
Thrombolytic/fibrinolytic drugs

Haemostasis

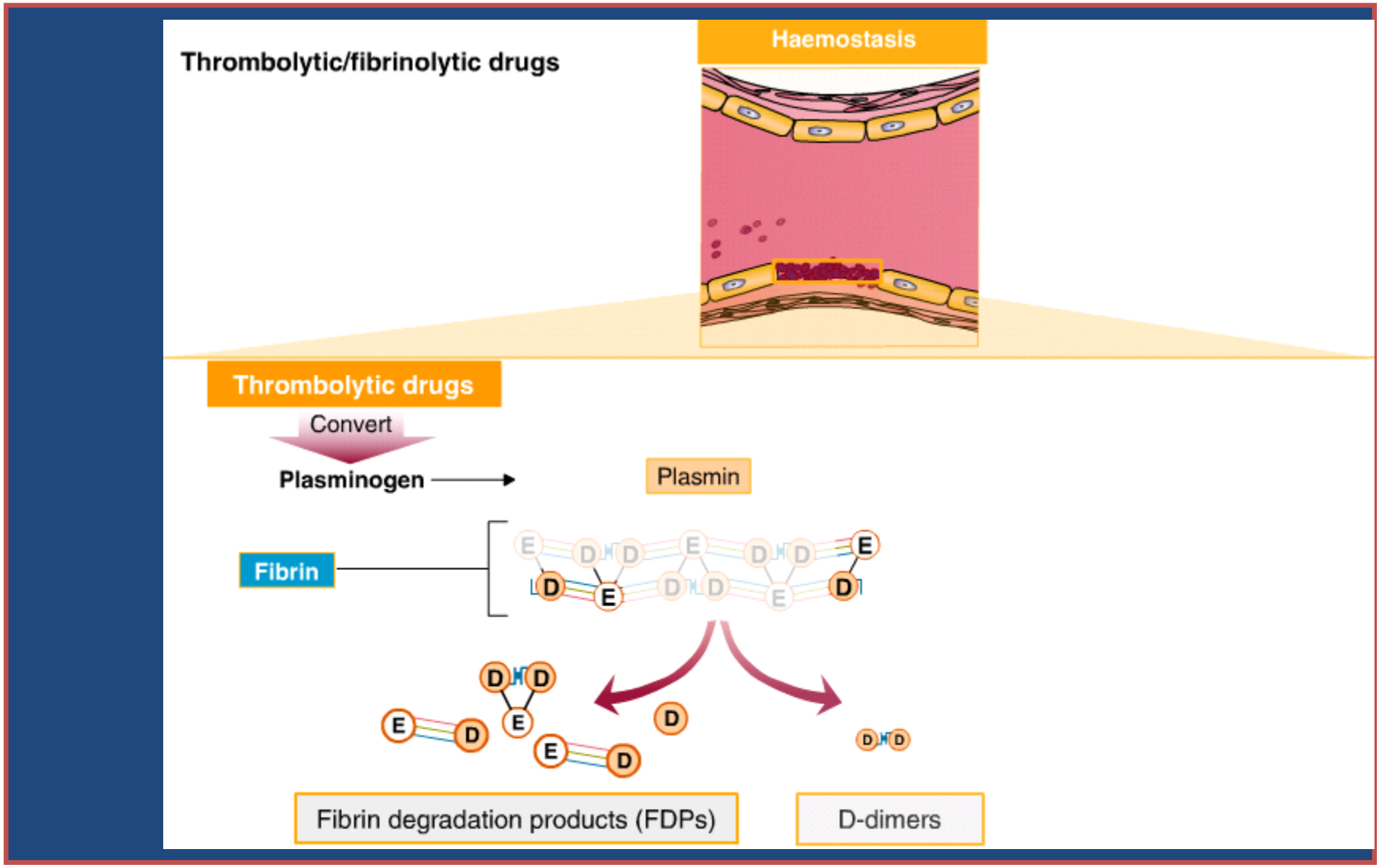


Thrombolytic drugs

Thrombolytic drugs – mechanism of action



Thrombolytic drugs – mechanism of action



MOA:

1-Streptokinase: combines with plasminogen. The complex cleaves another plasminogen molecule to plasmin

2-Anistreplase: an acetylated streptokinase-plasminogen complex that cleaves plasminogen to plasmin

3-Urokinase: directly cleaves plasminogen to plasmin

4-t-PA: an endogenous direct activator of plasminogen. It preferentially activates plasminogen that is bound to fibrin. This, in theory, confines fibrinolysis to formed thrombi

5-Alteplase: recombinant t-PA

6-Reteplase: genetically-modified recombinant.

-Less expensive than t-PA but less fibrin-selective

7-Tenecteplase: genetically-modified recombinant t-PA → long $t_{1/2}$

-Slightly more fibrin-selective than t-PA

- **Streptokinase** is formed by streptococci
- **Urokinase** is a human enzyme synthesized by kidney

- As the clot dissolves, concentration of thrombin ↑ locally→ ↑ platelet aggregation & ↑ formation of new thromi
- → Give an antiplatelet or anticoagulant to prevent thrombosis

- The earlier the thrombolytic is given the better.

- **<u>Side effects</u>:**

1) Bleeding: happens because these agents do not distinguish between the fibrin in an unwanted thrombus & fibrin in a beneficial hemostatic plug, or fibrinogen in the circulation.
2) Reperfusion arrhythmia.
3) Hypotension.

4) Hypersensitivity: with streptokinase & anistreplase (which includes streptokinase in its composition):

streptokinase is purified from culture broths of streptococci→ it is a foreign body & is, thus, antigenic.

Most people have had a streptococcal infection→ they may have circulating antibodies against streptokinase→ the streptokinase-antibody reaction can cause fever, hypersensitivity &/or failure of therapy (because the streptokinase molecules complexed with the antibody are pharmacologically inactive).

- Urokinase is nonantigenic because it exists normally in human urine→ it is used in patients hypersensitive to streptokinase.

Antihyperlipidemic drugs

- The clinically important lipoproteins are

  LDL low density lipoprotein, VLDL very low density lipoprotein, HDL high density lipoprotein.

- Hyperlipidemia may caused

  1. by individual lifestyle (lack of exercise and high consumption of fatty acid).

  2. single inherited gene defect in lipoprotein metabolism 3. more commonly, combination of genetics and lifestyle factors.

- The incidence of the heart failure is correlated with elevated levels of low density lipoproteins (LDL) cholesterol, and triglycerides with low level of high-density lipoprotein cholesterol (HDL).

Antihyperlipidemic drugs

- Antihyperlipidimic drugs must be taken indefinitely, when terminated plasma levels return to pretreatments levels.

- Antihyperlipidimic drugs target the problem with complimentary strategies, including:

  1. decrease production of the lipoproteins carriers of cholesterol and triglyceride.

  2. others increase the degradation of lipoproteins.

  3. decrease cholesterol absorption or directly increase cholesterol removal from the body.

- These agents may used as a singly or in combination.

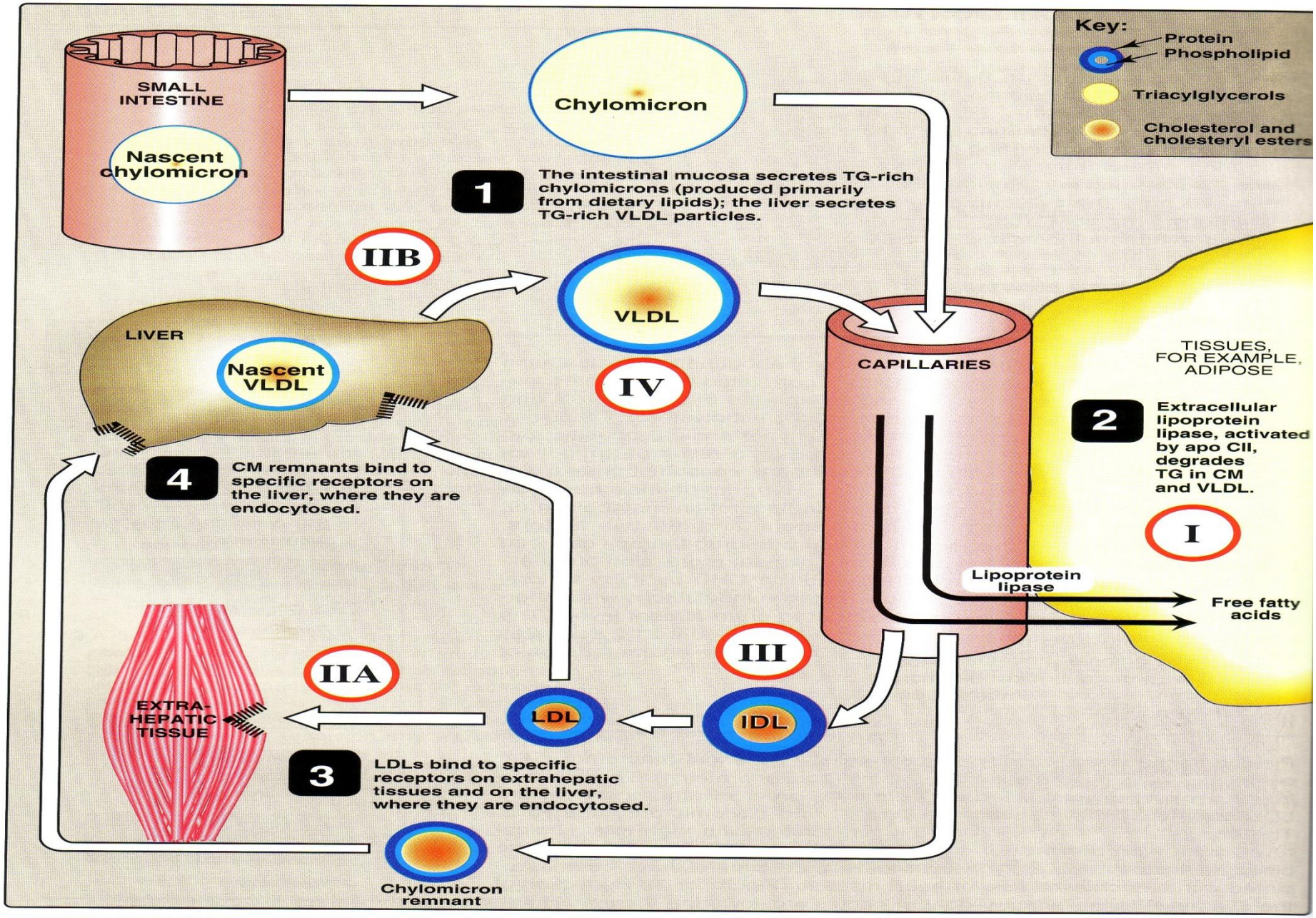


Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. The Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM=chylomicron, TG = triacylglycerol; VLDL=very-low density lipoprotein, LDL=low-density lipoprotein, IDL=intermediate-density lipoprotein, apo CII= apolipoprotein CII found in chylomicrons and VLDL.

Hyperlipoproteinemia		Labs description
Type I	Familial hyperchylomicronemia	Elevated Chylomicrons and VLDL
Type IIa	Familial hypercholesterolemia	Elevated LDL only
Type IIb	Combined hyperlipidemia	Elevated LDL and VLDL and Triglycerides
Type III	Familial Dysbetalipoproteinemia	Increased IDL
Type IV	Familial Hyperlipemia	Increased VLDL
Type V	Endogenous Hypertriglyceridemia	Increased VLDL and Chylomicrons

Statins

These agents include **Lovastatin, pravastatin, simvastatin, fluvastatin, Atorvastatin, rosuvastatin**

Cerivastatin

- Mechanism of action

(1) They are 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA) inhibitors.

This enzyme facilitate rate-limiting-step in the cholesterol synthesis and inhibiting this step will stop cholesterol synthesis.

(2) Increase in LDL receptors: Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus the end result is a reduction in plasma cholesterol.

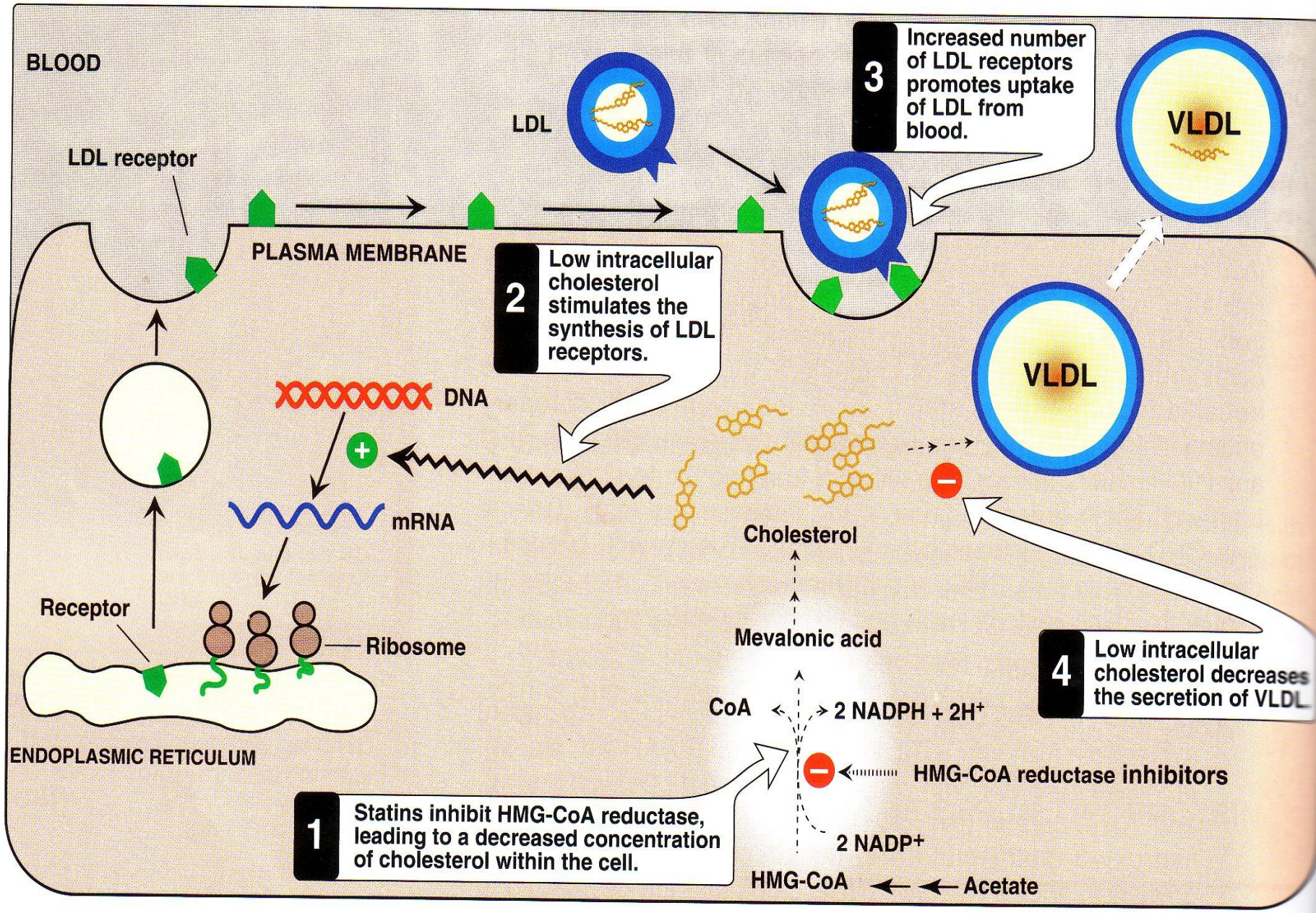


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG-CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Figure 21.14
Characteristics of hyperlipidemic drug families. HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl–coenzyme A; LDL = low-density lipoprotein.

Statins

- **Side effects:**

-Biochemical abnormalities in liver function (evaluate liver function is needed)

-Myopathy and rhabdomyolysis (disintegration or dissolution of muscle).

- **These agents are contraindicated during pregnancy and in nursing mothers. They also should not be used in children and teenagers.**

Statins interaction

- **the catabolism of lovastatin, simvastatin, and atorvastatin proceeds chiefly through CYP3A4,**
- **whereas that of fluvastatin and rosuvastatin is mediated by CYP2C9.**
- **Pravastatin is catabolized through other pathways, including sulfation.**
- **Concomitant use of reductase inhibitors with amiodarone or verapamil also causes an increased risk of myopathy.**
-

- The 3A4-dependent reductase inhibitors include the macrolide antibiotics, cyclosporine, ketoconazole and its congeners, HIVprotease inhibitors, tacrolimus, nefazodone, fibrates, and others.

- Conversely, drugs such as phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones increase expression of CYP3A4 and can reduce the plasma concentrations of the 3A4-dependent reductase inhibitors.

- Inhibitors of CYP2C9 such as ketoconazole and its congeners, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin.

- Plasma levels of lovastatin, simvastatin, and atorvastatin may be elevated in patients ingesting more than 1 liter of grapefruit juice daily.

Niacin (vitamin B_3)

Mechanism of Action: strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids,

both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered

- **Niacin is the most effective agent in increase the HDL (the good cholesterol carrier).**

- **it is used in type IIb and IV hyperlipoproteinemia, in which both VLDL and LDL are elevated. Also to treat other severe hypercholestrolemias**

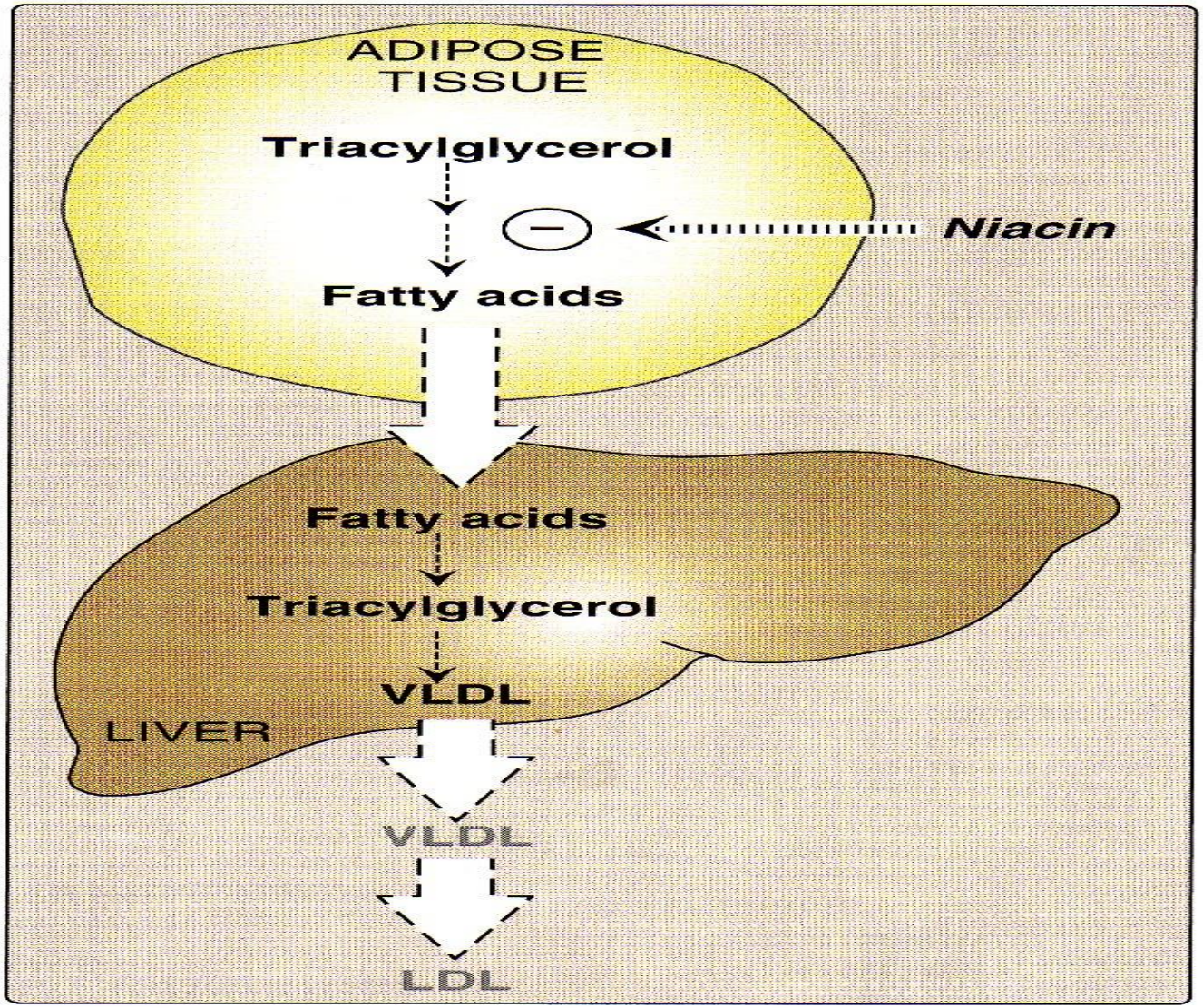


Figure 21.9
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.

Niacin

- **Adverse effects: Cutaneous flushing, burning and itching, GI irritation, nausea and vomiting.**

- **Peptic ulcer activation, elevation of liver enzymes, hyperglycemia and hyperuricemia.**

Fibrates

- **Fenofibrate and Gemfibrozil, Bezafibrate are derivatives of fibric acid lower serum level of LDL cholesterol, triglyceride and increase the HDL.**

MOA: Peroxisome proliferator activated receptors (PPARs) are a nuclear receptors that regulate lipid metabolism.

Fibrattriacylglyceroles binding to these receptors result in reduction of concentration by increasing the expression of lipoprotien lipase.

- **They are used in the treatment of hypertriglycerolemias, and also useful in treating type III hyperlipidemia.**

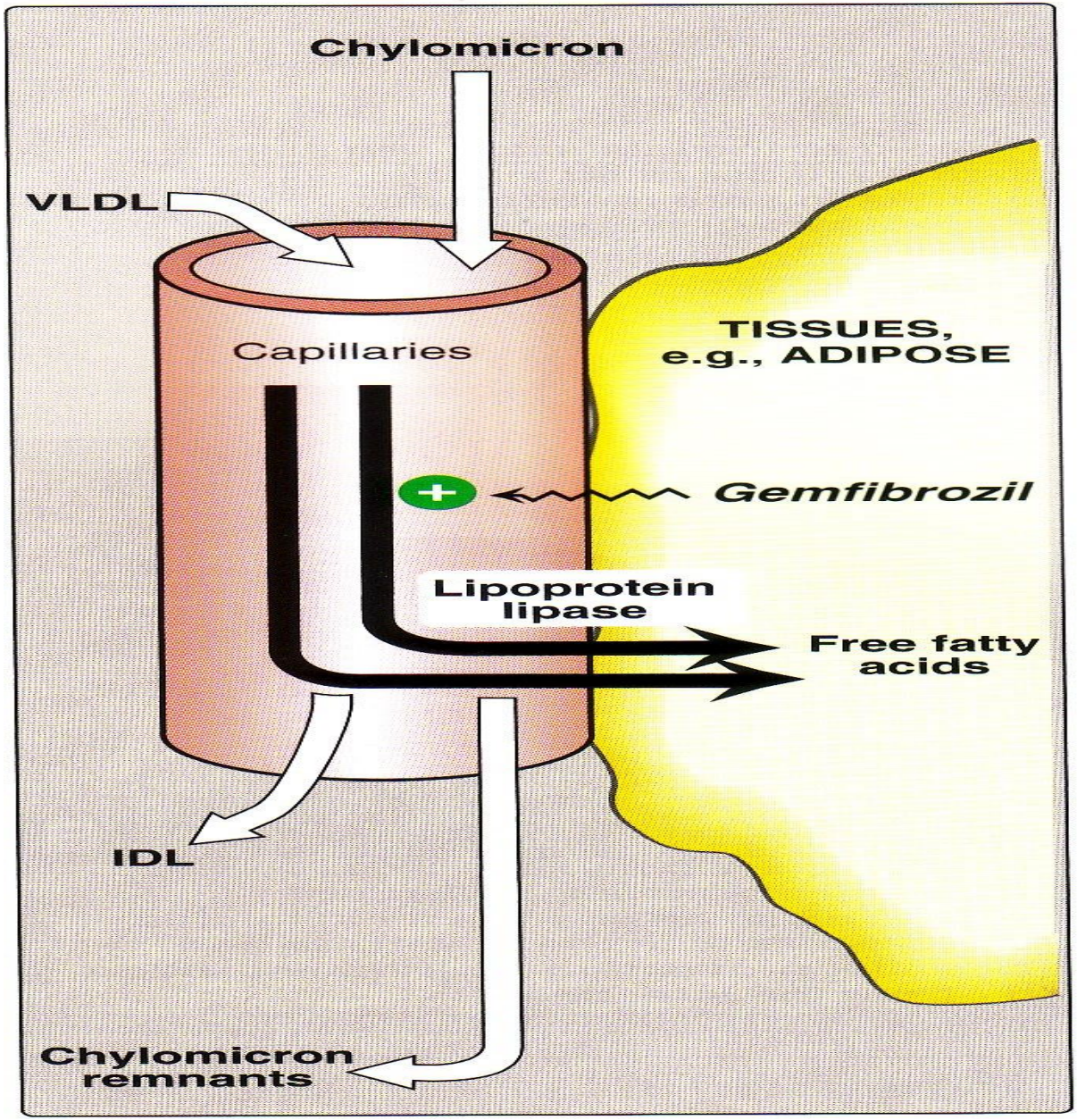


Figure 21.11
Activation of lipoprotein lipase by *gemfibrozil*.

Fibrates

Adverse effect

a. The most common adverse effects are mild gastrointestinal disturbances.

b. Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.

d. Myositis (inflammation of a voluntary muscle) can occur.

Fibrates compete with the coumarin anticoagulants for binding sites on plasma proteins.

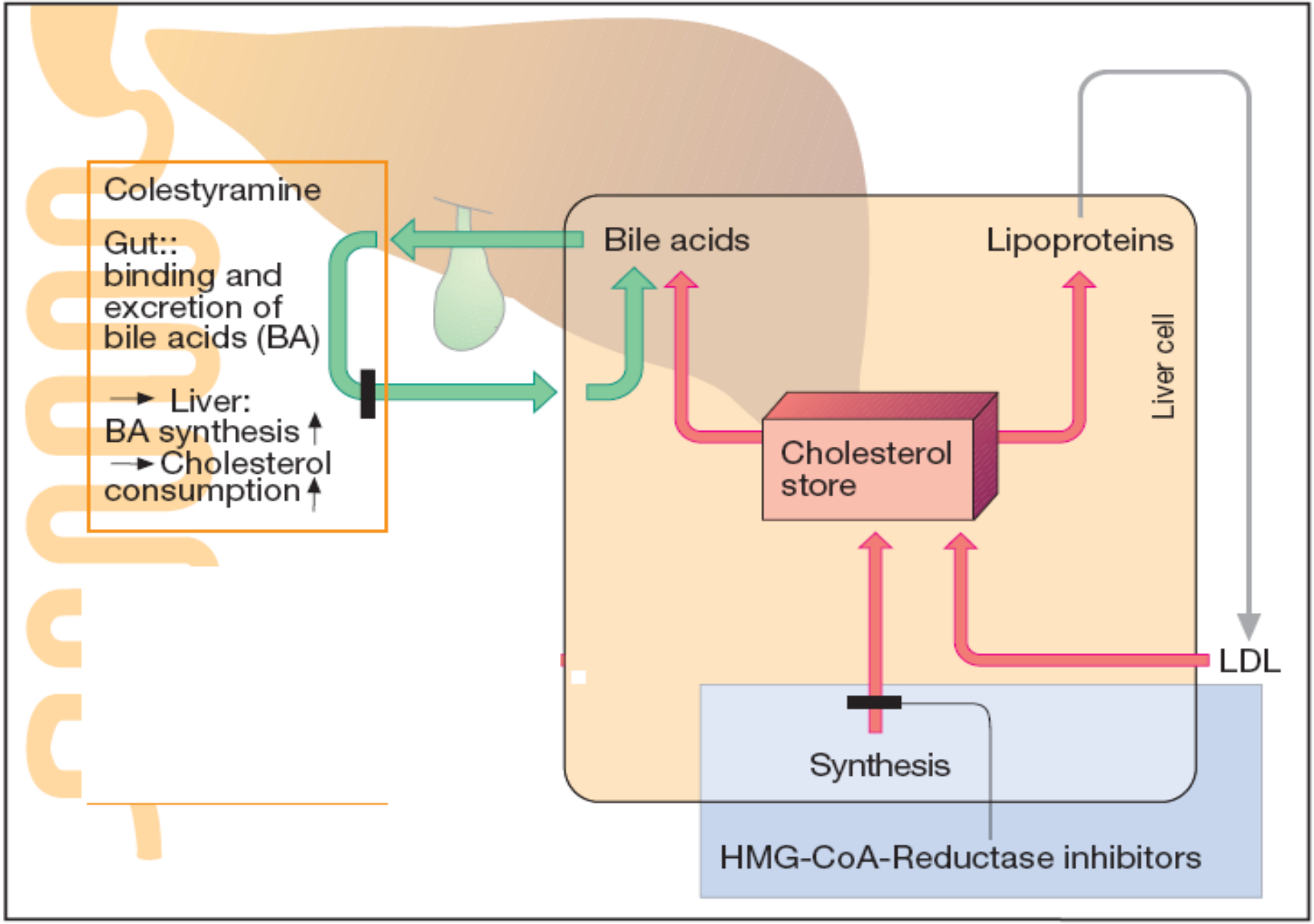
Bile acid-binding resins

- **Cholestyramine and colestipol have significant LDL cholesterol lowering effect, although the benefit is less than those observed with statins.**

- **These agents are resins that bind bile acid in the intestine, forming insoluble complexes that will excreted in the feces.**

- **Lowering bile acid level will trigger the conversion of cholesterol into bile acid and the end result will be a reduction in the cholesterol concentrations.**

Therapeutic uses: The bile acid binding resins are the drugs of choice (often in combination with diet or niacin) in treating Type lla.


Colestyramine
Gut::
binding and
excretion of
bile acids (BA)
→ Liver:
BA synthesis ↑
→ Cholesterol
consumption ↑
Bile acids
Lipoproteins
Liver cell
Cholesterol
store
LDL
Synthesis
HMG-CoA-Reductase inhibitors

Bile acid-binding resins

- **The most common side effect are gastrointestinal disturbances such as constipation and nausea.**
- **At high doses they impair the absorption of fat soluble vitamins (A,D,E, and K).**
- **These agents interact with the absorption of many drugs, for example, Tetracycline, Digoxin, Warfarin, Aspirin.**
- **Therefore, drugs should be taken at least 1 to 6 hr after.**

Cholestrole absorption inhbitors

Ezetimibe selectively inhibit intestinal absorption of dietary and biliary cholesterol in the small intestine, resulting in an increase in the clearance of cholesterol from the blood.

Common adverse are headache and/or diarrhea.

Strategy for Controlling Hyperlipidemia

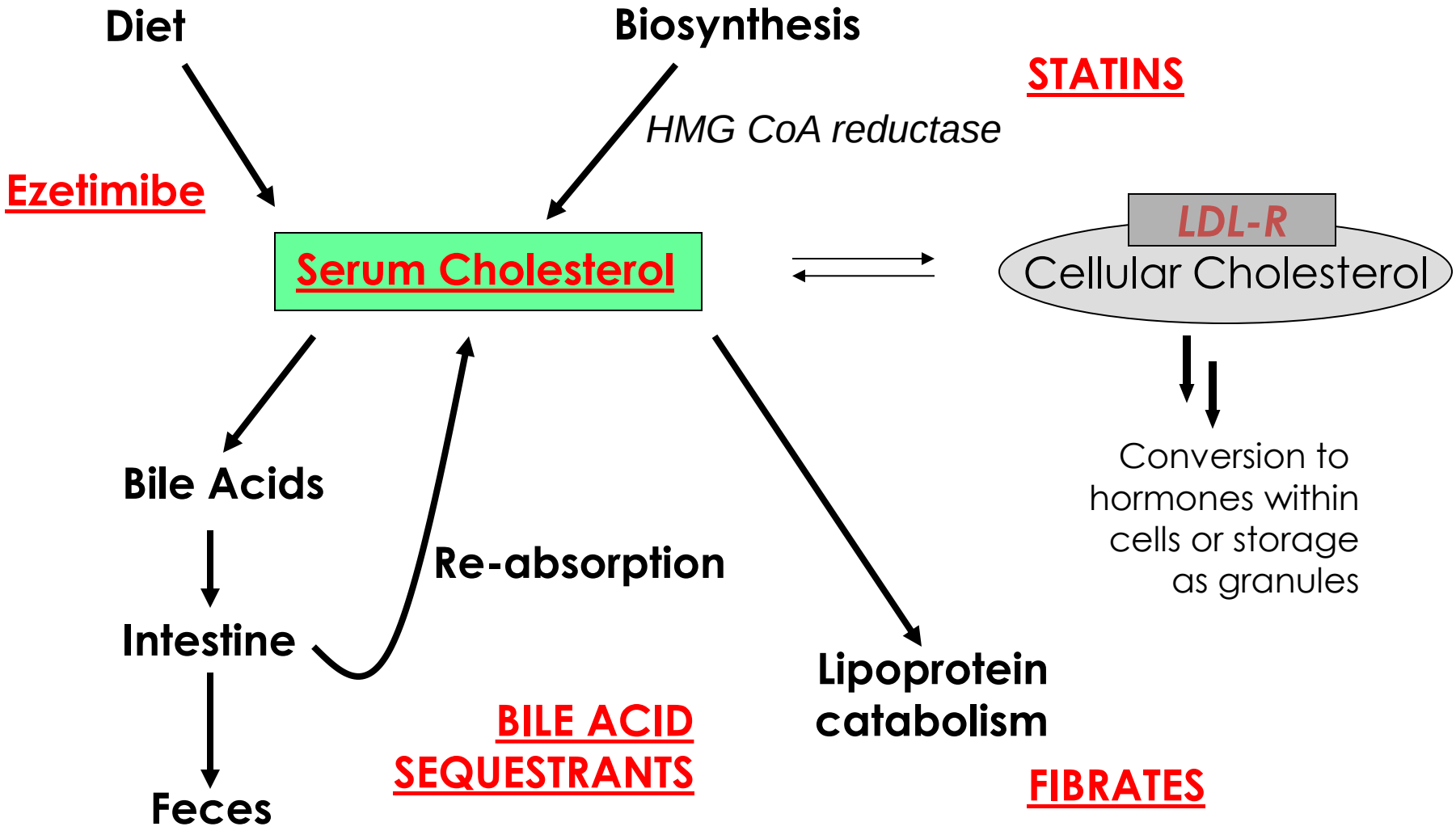


Table 35–3. Lipid-modifying effects of antihyperlipidemic drugs.*

Drug	LDL Cholesterol	HDL Cholesterol	Triglyceride
Atorvastatin	–25% to –40%	+5% to –10%	↓↓
Fluvastatin[1]	–20% to –30%	+5% to –10%	↓
Lovastatin[2]	–25% to –40%	+5% to –10%	↓
Cholestyramine, colestipol	–15% to –25%	+5%	±
Gemfibrozil	–10% to –15%	+15% to –20%	↓↓
Niacin	–15% to –40%	+25% to –35%	↓↓

*Modified, with permission, from Tierney LM, McPhee SJ, Papadakis MA (editors): *Current Medical Diagnosis & Treatment,* 40th ed. McGraw-Hill, 2001.

[1]Cerivastatin has effects similar to those of fluvastatin.

[2]Pravastatin and simvastatin have effects similar to those of lovastatin.

± = variable, if any.

Antihyperlipidemic drugs

- The clinically important lipoproteins are

  LDL low density lipoprotein, VLDL very low density lipoprotein, HDL high density lipoprotein.

- Hyperlipidemia may caused

  1. by individual lifestyle (lack of exercise and high consumption of fatty acid).

  2. single inherited gene defect in lipoprotein metabolism 3. more commonly, combination of genetics and lifestyle factors.

- The incidence of the heart failure is correlated with elevated levels of low density lipoproteins (LDL) cholesterol, and triglycerides with low level of high-density lipoprotein cholesterol (HDL).

Antihyperlipidemic drugs

- Antihyperlipidimic drugs must be taken indefinitely, when terminated plasma levels return to pretreatments levels.

- Antihyperlipidimic drugs target the problem with complimentary strategies, including:

  1. decrease production of the lipoproteins carriers of cholesterol and triglyceride.

  2. others increase the degradation of lipoproteins.

  3. decrease cholesterol absorption or directly increase cholesterol removal from the body.

- These agents may used as a singly or in combination.

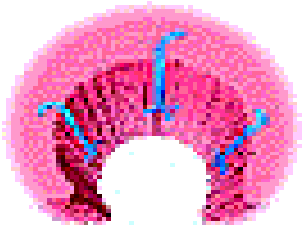
Statins

- These agents include **Lovastatin, Simvistatin, Pravastatin, and Fluvastatin.**
- They are 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA) inhibitors.
- This enzyme facilitate rate-limiting-step in the cholesterol synthesis and inhibiting this step will stop cholesterol synthesis.
- Statins reduce serum level of LDL cholesterol, VLDL cholesterol and triglycerides.
- Statins resulting in reduction in coronary events and death from Heart failure.

HMG-CoA reductase inhibition

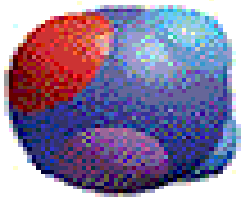
LIPITOR inhibits
HMG-CoA reductase

Reduced cholesterol synthesis

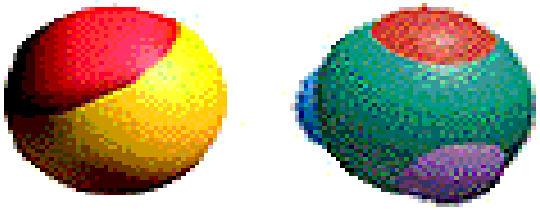


Upregulation of LDL receptors

Increased removal and catabolism of LDL



Decreased VLDL production



Conversion of VLDL to LDL

Decreased Total-C, LDL-C, and TG

Adverse effects

1. Hepatotoxicity (increased serum transaminase).
2. Myopathy (increased creatine kinase) especially when combined with:
   - other lipid lowering drugs: i)Fibrates. ii) Niacin.
3. G.I.T upset.
4. Headache.

N.B : liver transaminases and CK must be regularly measured during therapy with statins

Statins

- They do interact with Warfarin and resulting in elevation of Warfarin.

- These agents are contraindicated during pregnancy and in nursing mothers. They should not be used in children and teenagers.

Fibrates and Niacin

Preparations: Gemfibrozil , fenofibrate , clofibrate .

Mechanism of action:

Ligand for the nuclear transcription regulator, peroxisome proliferator-activated receptor-α (PPAR- α) in the liver, heart, kidney, & skeletal muscle. *N.B The PPAR-a are a class of intracellular receptors that modulate fat metabolism. It is through PPAR-a that fibrates lead to:*

- Increased LPL activity, which increases clearance of VLDL & chylomicron in plasma.

- They are used in the treatment of hypertriglycerolemias, an also useful in treating hyperlipidemia.

Adverse effects

- G.I.T upset,rash, urticaria
- Myopathy
- Since fibrates increase the cholesterol content of bile, they increase the risk for gallstones.

Adverse effects

- G.I.T upset,rash, urticaria
- Myopathy
- Since fibrates increase the cholesterol content of bile, they increase the risk for gallstones.

Steps to Minimize the Risk of Muscle Toxicity with Fibrate–Statin Combination Therapy

- Use statin alone for non-HDL-C goals
- Use fish oils or niacin rather than fibrates
- Keep the doses of the statin and fibrate low
- Dose the fibrate in the AM and the statin in the PM
- Avoid (or cautiously use) combo in renal impairment
- Assure no interactions
- Teach the patient to recognize muscle symptoms
- Discontinue therapy if muscle symptoms are present and CK is >10 times the upper limit of normal

Niacin

- reduce the LDL and is the most effective agent in increase the HDL (the good cholesterol carrier). Can be used with statins.
- Used in the treatment of hyperlipidemia and hypertriglycerolemias.
- Niacin inhibits the lipolysis in adipose tissue, the primary producer of free fatty acid.

Pharmacological actions

- **Effect on VLDL:** Decreased VLDL by:

1) decreased synthesis in liver;
2) increased clearance in plasma.

- **Effect on LDL:** Decreased LDL due to reduction in its precursor (VLDL).

- **Effect on HDL:** Induces modest increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown).

Adverse effects

1. Pruritus, flushing The niacin flush results from the stimulation of prostaglandins D(2) and E(2). This flush is avoided by low dose aspirin 325 mg ½ h before niacin.

2. Reactivation of peptic ulcer (because it stimulates histamine release resulting in increased gastric motility and acid production .
3. Hepatotoxicity.

1. Hyperglycemia which is believed to be caused by an increase in insulin resistance.
2. Increased uric acid level(due to decreased uric acid excretion).

Contraindications

1. Gout.
2. Peptic ulcer.
3. Hepatotoxicity.
4. Diabetes mellitus.

Bile acid-binding resins

- Cholestyramine and colestipol have significant LDL cholesterol lowering effect, although the benefit is less than those observed with statins.

- These agents are resins that bind bile acid in the intestine, forming insoluble complexes that will excreted in the feces.

- Lowering bile acid level will trigger the conversion of cholesterol in to bile acid and the end result will be a reduction in the cholesterol concentrations.

- The most common side effect are gastrointestinal disturbances such as constipation and nausea.

Bile acid-binding resins

- At high doses they impair the absorption of fat soluble vitamins (A,D,E, and K).
- These agents interact with the absorption of many drugs, for example, Tetracycline, Digoxin, Warfarin, Aspirin.
- Therefore, drugs should be taken at least one to six hr after.

Ezetimibe

Mechanism of action:

- Impairs dietary and biliary cholesterol absorption at the brush border of the intestines without affecting fat-soluble vitamins.

- Reducing the pool of cholesterol absorbed from the diet results in a reduced pool of cholesterol available to the liver.

-The liver in turn will upregulate the LDL receptor, trapping more LDL particles from the blood and result in a fall in measured LDL cholesterol .

- **CLASSIFICATION- based on the pattern of lipoprotein on electrophoresis or ltracentrifugation.**
- **Familial Chylomicronemia (I)**:increased Chylomicrons due to deficiency of lipoprotein lipase or its cofactor
- **Familial Hypercholesterolemia (IIA):** levels of LDL tend to increase with normal VLDL.
- **Familial Combined (mixed)Hyperlipidemiaa (IIB):** elevated levels of VLDL, LDL.
- **Familial Dysbetalipoproteinemia (III):** Increased IDL resulting increased TG and cholesterol levels.
- **Familial Hypertriglyceridemia (VI):** Increase VLDL production with normal or decreased LDL.
- **Familial mixed hypertriglyceridemia (V):** Serum VLDL and chvlomicrons are increased