Overview of Lecture Series

1. Cardiovascular System

Bits 'N' Pieces
Blood, Heart, Blood-Vessels

Keeping It Under Control
Heart Rate, Blood Pressure

When Things Go Wrong
Hypertension, Heart Failure, Arrhythmias

2. Hypertension

Aetiology Diagnosis

Treatment
Sympathoplegic Drugs, Diuretics, Vasodilators, Angiotensin Antagonists

3. Myocardial Ischemia

Aetiology Diagnosis

Treatment
Symptomatic: Nitrites, Calcium Channel Blockers, β-Blockers

Prophylactic: Lipid lowering, Anti-coagulant, Anti-platelet drugs

4. Heart Failure & Cardiac Arrhythmias

Aetiology Diagnosis

Treatment
Heart Failure: Nitrites, Calcium Channel Blockers, Diuretics, Angiotensin Antagonists, β-Blockers, b-Receptor Agonist, Cardiac Glycosides

Arrhythmias: Channel Blockers (Groups I – IV), Miscellaneous

Cardiovascular System & Its Diseases

Lecture #3 Myocardial Ischemia

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Myocardial Ischemia

Overview

1. Pathophysiology

- Stable Angina
- Unstable Angina
- Silent or Effort Ischemia
- Variant Angina
- Myocardial Infarction

2. Pharmacological Intervention

Symptomatic

- Nitrates
- Ca^{2+} Channel Blockers
- β-Blockers

Prophylactic

- Lipid Lowering Drugs
- Anti-Coagulants
- Fibrinolytic
- Anti-platelet

Major Drug Groups

Symptomatic

Nitrates
Ca^{2+} Channel Blockers
β-Blockers

Prophylactic

Lipid Lowering Drugs

1. Statins Inhibit cholesterol synthesis
2. Resins Block cholesterol reabsorption
3. Niacin Decreased VLDL secretion
4. Fibrates Lipoprotein lipase synthesis

Anti-Coagulants

1. Warfarin Vitamin K antagonist
2. Heparin Factor Xa & AT III

Fibrinolytic

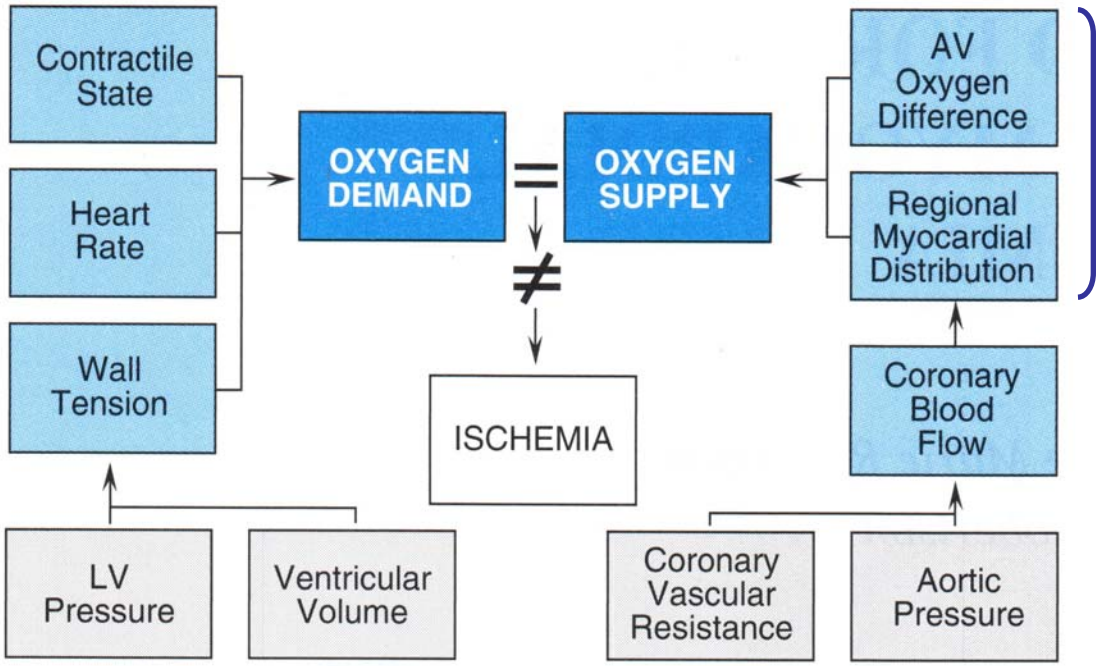
1. Streptokinase Plasmin activation
2. Tissue Plasminogen Activators Endogenous

Anti-platelet

1. Aspirin / Ibuporfen TXA_2 inhibition
2. Ticlopidine / Clopidogrel Adenosine-R block

Myocardial Ischemia

Pathophysiology: What Is It?



Imbalance in Oxygen Supply & Demand

Arteriovenous Oxygen Difference is near maximum in coronary circulation
Therefore, redistribution of **Regional Myocardial Flow** is of major importance

Myocardial Ischemia

Pathophysiology: Symptoms

Angina Pectoris: **(Chest Pain)** Primary symptom associated with ischaemic heart disease. Caused by transient episodes of myocardial ischaemia. Pain is due to accumulation of metabolites in muscle tissue.

Affects 6.4 Million Americans American Heart Association, 2001

Manifests in Different Forms:

Stable Angina (atherosclerotic block of coronary artery)

Unstable Angina (rupture of atherosclerotic plaque)

Silent / Effort Ischemia (Often induced by exercise)

Variant Angina (focal/diffuse coronary vasospasm)

Myocardial Infarction (Heart Attack, death of tissue)

Myocardial Ischemia

Pathophysiology: Aetiology

- **Atherosclerosis:**

  Deposition of Fatty Substances esp. cholesterol or fatty acids in arteries

  Risks Factors include:

  Hypertension

  Hyperlipidemia

  Obesity

  Carbon Monoaxide in Smoke

  Sedentary life-style

- **Coronary Artery Spasm:**

  Cause Unknown. May occur in patients with or without atherosclerosis

  Risks Factors include:

  Smoking

  Stress

Myocardial Ischemia

Pathophysiology: Arteriosclerosis & Plaques

Blood Vessel Damage

↓

Plaque formation due to inflammation

↙ ↘

Two Types Of Plaque

Endothelium-Smooth Muscle Interface

Ruptured lesion in endothelium

↓

Narrowing of blood vessel lumen

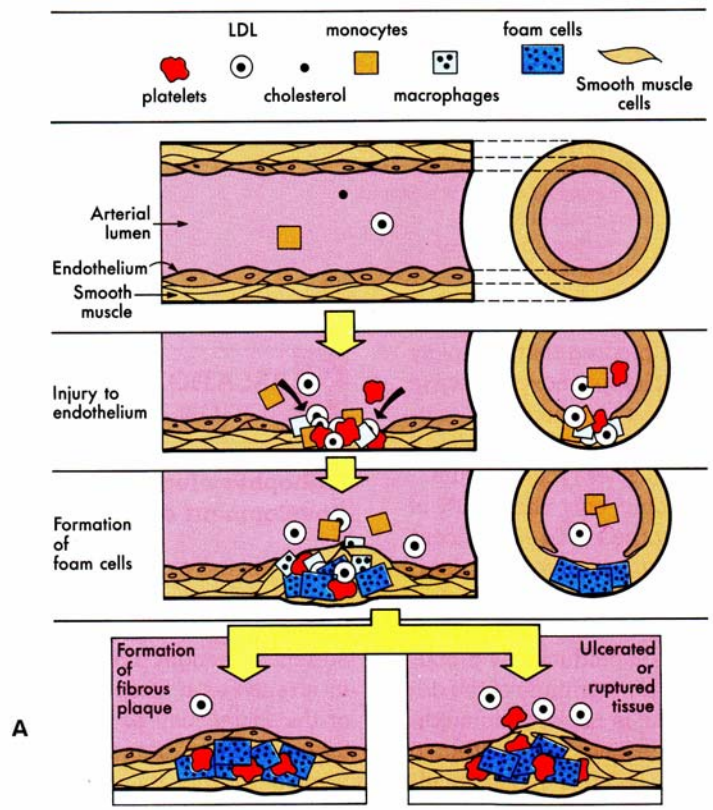
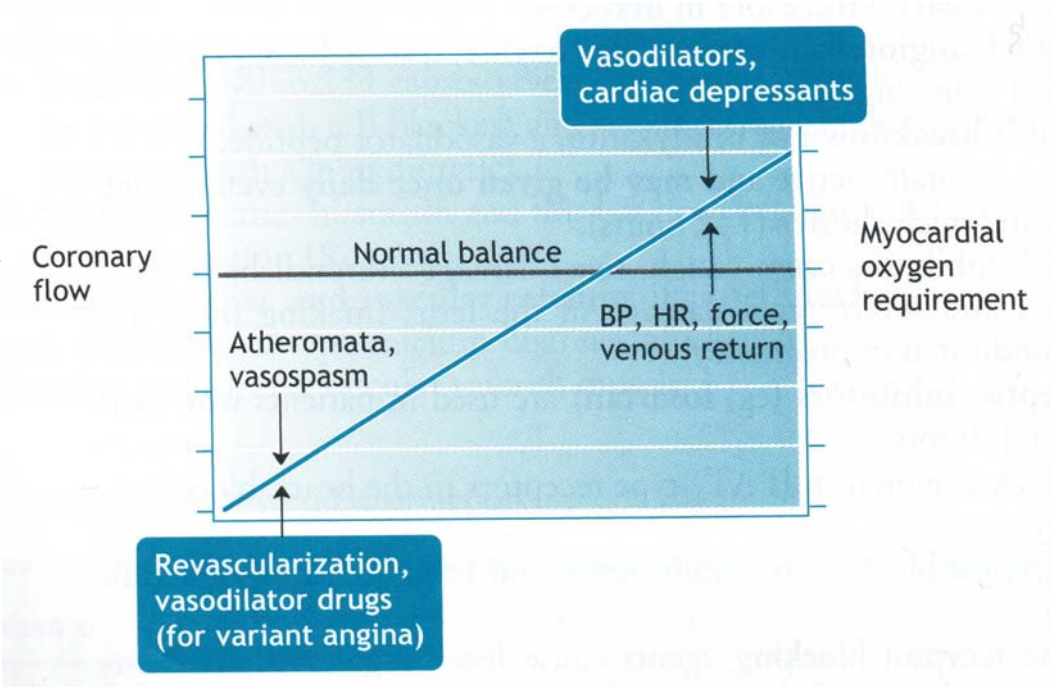


FIGURE 22-10 Development of an atheromatous plaque. An injury to the endothelial lining allows LDL particles, monocytes, and platelets to enter the smooth muscle tissue. Inflammation at the injury site triggers the conversion of monocytes to macrophages, which scavenge the LDL particles and cholesterol to form enlarged foam cells (xanthoma cells). Smooth muscle cells, foam cells, platelets, and LDL particles form fibrous plaques. The plaques form in two ways: **A,** at the interface between the endothelium and the smooth muscle tissue, leaving an elevation in the repaired endothelium, or **B,** as an ulcerated, or ruptured lesion in the endothelium that protrudes into the lumen. Both types of plaque narrow the lumen and restrict blood flow.

Myocardial Ischemia

Pharmacological Intervention: Possible Strategies



**** Must Match Supply & Demand ***

Several Possible Therapeutic Approaches:

1. Reduce Myocardial O_2 demand

2. Prophylactic Therapy

Myocardial Ischemia

Pharmacological Intervention: Drug Types

Drug Types Currently Used

1. Nitrates
2. Ca^{2+} Channel Blockers
3. β-Blockers

Reduce BP
Venous Return
Force/Rate of Heart

→ Reduce O_2 Demand and/or Improve Coronary Flow

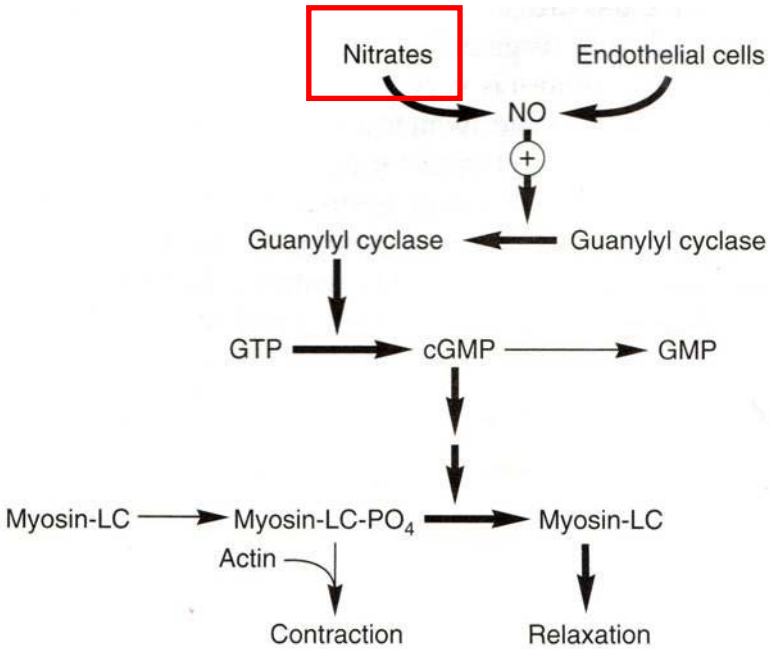
4. Lipid Lowering Drugs
5. Drugs Affecting Coagulation, Fibrinolysis & Platelet Aggregation

Targeted towards reducing plaque formation

→ Slower development of ischemia

Myocardial Ischemia

Symptomatic Intervention: Nitrates



- Drugs: *Nitroglycerin (synthesized 1846)
  Isosorbide Nitrate
- Indication: Effort Angina
  Variant Angina
  Acute Coronary Syndrome
- Mechanism: Reduce venous return, cardiac size & diastolic myocardial oxygen consumption
- Side-effects: Orthostatic hypotension
  Tachycardia reflex
  Headache

Myocardial Ischemia

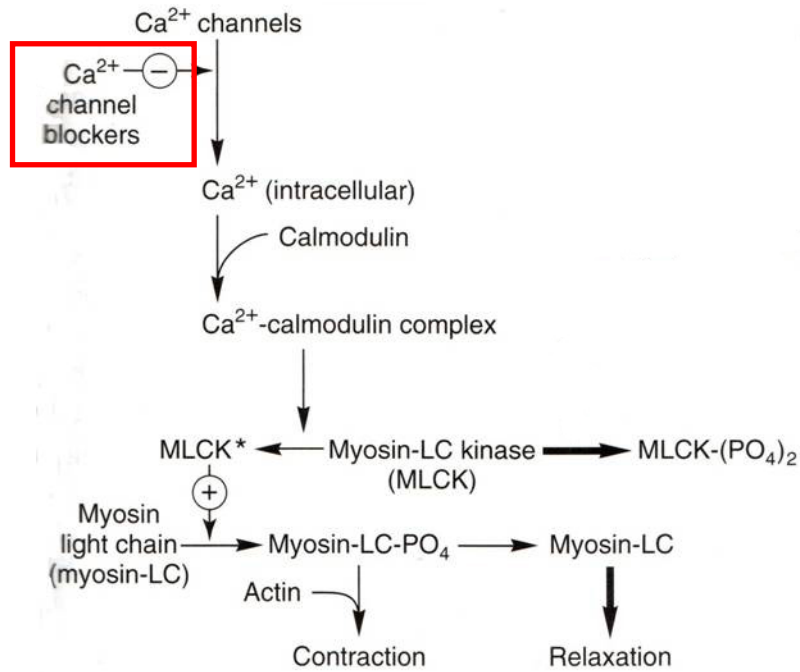
Symptomatic Intervention: Ca^{2+} Channel Blockers

- Drugs: * Verapamil
  * Nifedipine
  * Diltiazem

- Indication: Effort Angina (prophylactic)
  Variant Angina (prophylactic)

- Mechanism: Peripheral vasodilatation &
  Reduction of cardiac work

- Toxicity: Orthostatic hypotension
  AV Blockade
  Edema



Myocardial Ischemia

Symptomatic Intervention: β-Blockers

- Drugs: Propanolol
- Indication: Effort Angina (very important)
  Variant Angina (no benefit)
  Acute Coronary Syndrome (very important)
- Mechanism: Reduce blood pressure
  Reduce cardiac work
- Side-effects: Orthostatic hypotension
  Tachycardia
  Headache

Myocardial Ischemia

Symptomatic Intervention: Combination Therapy

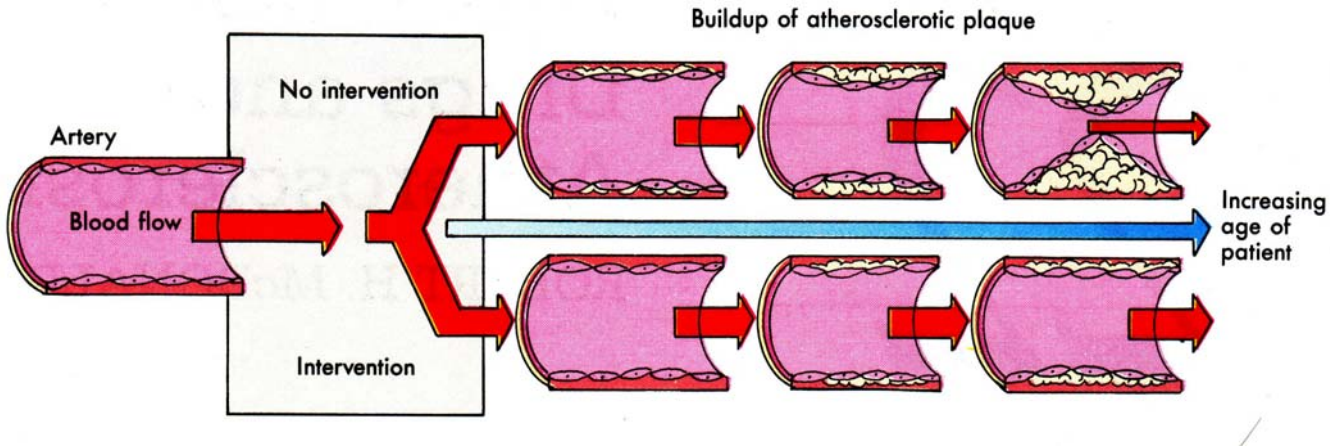
Variable	Nitrates Alone	β Blockers or Calcium Blockers Alone	Combined Nitrate and β Blocker or Calcium Blocker
Heart rate	*Reflex increase*	**Decrease**	**Decrease** or no effect
Arterial pressure	**Decrease**	**Decrease**	**Decrease**
End-diastolic pressure and fiber tension	**Decrease**	*Increase*	**Decrease**
Contractility	*Reflex increase*	**Decrease**	No effect or **decrease**
Ejection time	Reflex **decrease**	*Increase*	No effect

[1]Undesirable effects (effects that increase myocardial oxygen requirement) are shown in *italics*; beneficial effects are shown in **bold.**

Myocardial Ischemia

Prophylactic Intervention: Clinical Options

- Atherosclerosis: Deposition of Fatty Substances esp. cholesterol or fatty acids in arteries



- **Dietary changes to reduce cholesterol & lipids**
- **Cessation of Smoking**
- **Control of Blood Pressure**
- **Control of Diabetes**
- **Regular, moderate exercise**
- ***** Drugs to reduce plasma cholesterol *****

Myocardial Ischemia

Prophylactic Intervention: Overview of Lipid Lowering Drugs

THERAPEUTIC OVERVIEW	
GOAL	Prevent myocardial infarction and other atherosclerotic disorders such as stroke and peripheral vascular disease, prevent reinfarction (statins), and increase survival.
APPROACH	Prophylactic use to reduce formation of atherosclerotic plaque and subsequent narrowing of lumen in cardiac arteries.
PRIMARY RISK FACTORS	High blood concentrations of cholesterol and certain lipids. High blood pressure. Smoking. Obesity. Sedentary life-style.

Myocardial Ischemia

Prophylactic Intervention: Sources Of Cholesterol

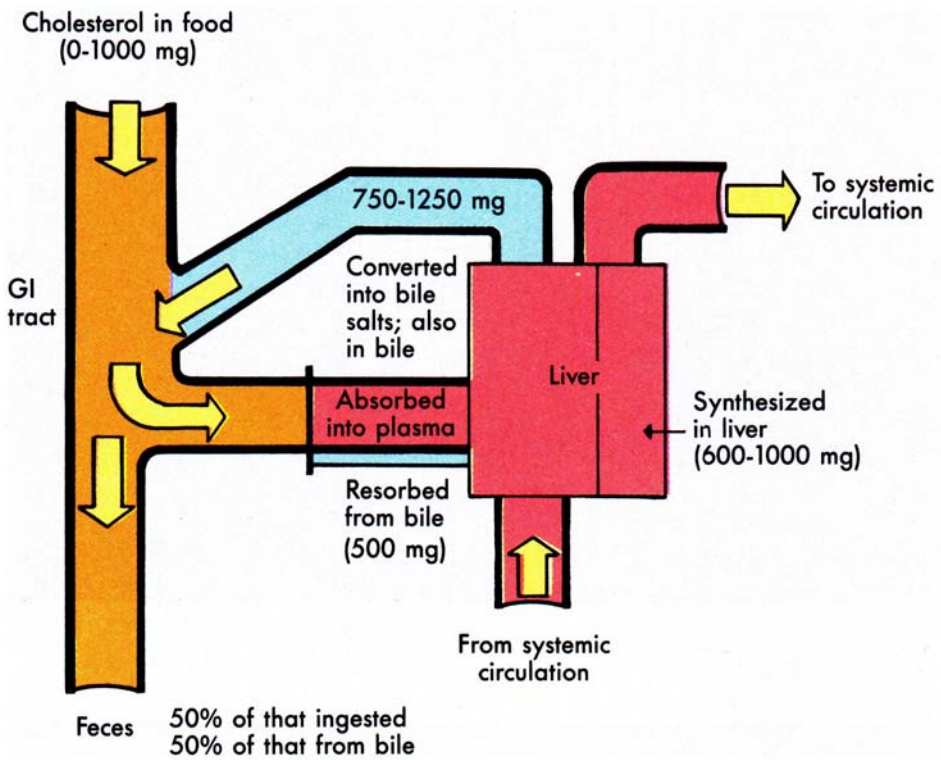


FIGURE 22-2 Total body balance of cholesterol, showing input by ingestion and liver synthesis, output by nonabsorption into feces, conversion into bile salts, delivery in bile salts to small intestine, partial reabsorption from bile, and delivery as lipoproteins into systemic circulation. Quantities shown are approximate daily amounts.

2 Possibilities:

Dietary (gut) or

***De Novo* Synthesis** (liver)

Myocardial Ischemia

Prophylactic Intervention: *De Novo* Synthesis Of Cholesterol liver

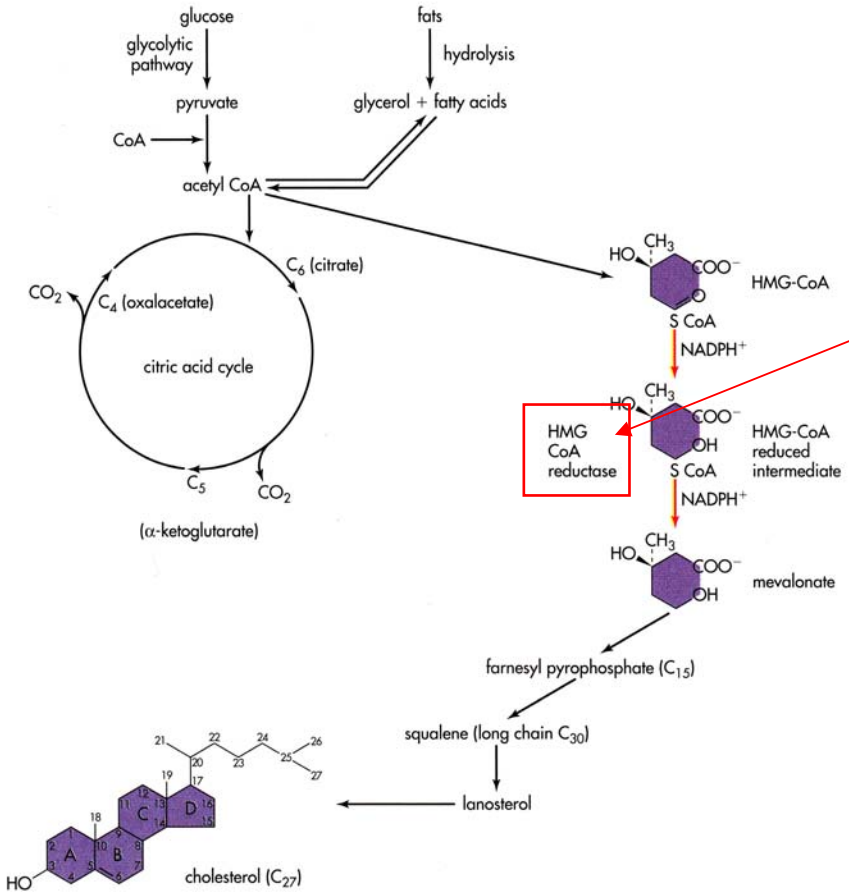


FIGURE 22-3 Sequence for *in vivo* synthesis of cholesterol. Note the similarity in structures of the reduced HMG-CoA and the statins, the HMG-CoA reductase inhibitors.

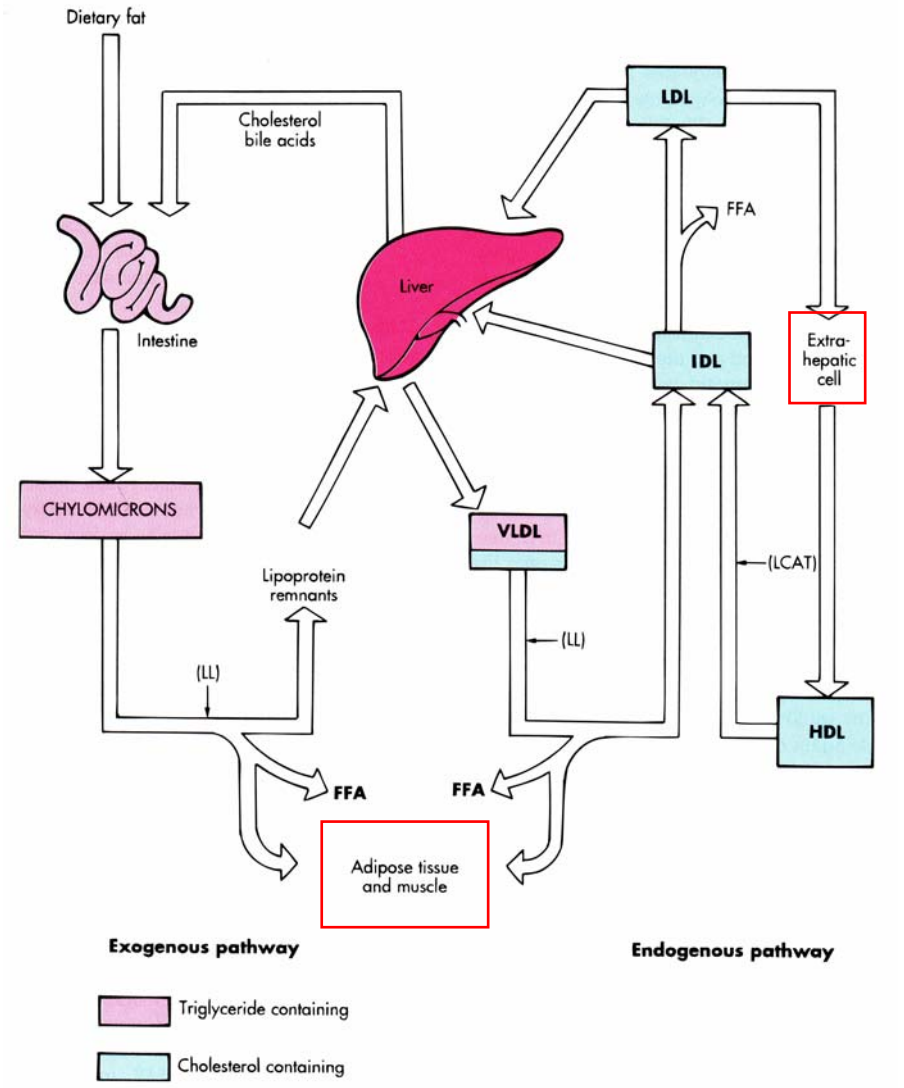
Targeted to reduce cholesterol synthesis

HMG-CoA

Hydroxy-3-methyl-glutaryl-coenzyme-A

Myocardial Ischemia

Prophylactic Intervention: Lipoprotein-transport system



VLDL transports cholesterol & triglycerides

↓

VLDL deposited in adipose tissue & muscle
After lipolysis by lipoprotein lipase **(LL)**

↓

Resultant **IDL** goes to hepatocytes
or becomes **LDL**

LDL: low-density lipoprotein

VLDL: very low-density lipoprotein

IDL: intermediate-density-lipoprotein

Myocardial Ischemia

Prophylactic Intervention: Strategy For Lipid Lowering Drugs

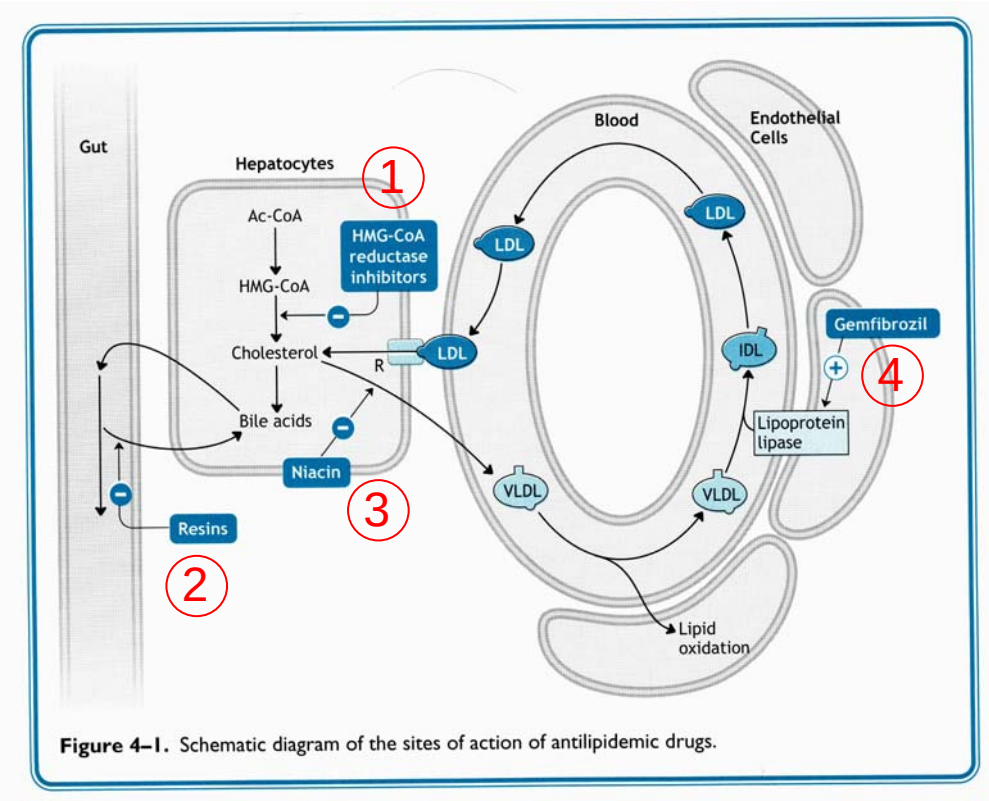


Figure 4–1. Schematic diagram of the sites of action of antilipidemic drugs.

1. Inhibition of Cholesterol Synthesis

(HMG-CoA Reductase Inhibitors, e.g. Statins)

2. Prevention of Cholesterol Reabsorption

(e.g. Resins)

3. Reduction of VLDL Secretion

(e.g. Niacin)

4. Increased Synthesis of Lipoprotein Lipase

(e.g. Fibrates)

Myocardial Ischemia

Symptomatic Intervention: Inhibition of Cholesterol Synthesis

- Drugs: Statins (e.g. *lovastatin, atorvastatin)
- Mechanism: Inhibit HMG-Co-A reductase that blocks the *de novo* synthesis of cholesterol
- Side-effects: May damage skeletal muscle or liver
  Interference with myelination of infants
  (contraindicated in pregnancy)

Myocardial Ischemia

Symptomatic Intervention: Preventing Cholesterol Reabsorption

- Drugs: Resins (e.g. * cholestyramine, colestipol)
- Mechanism: Non-absorbable macromolecules that bind cholesterol preventing reabsorption from gut
- Side-effects: Unpleasant gritty taste
  GI tract discomfort
  Interference of vitamin or drug absorption

Myocardial Ischemia

Symptomatic Intervention: Reduction of VLDL Secretion

- Drugs: * Niacin (nicotinic acid, vitamin B_3)

- Mechanism: Action not well understood though decrease in secretion of VLDL particles from liver

- Side-effects: Occasional flush with itching reduced with aspirin
  Rarely causes glucose intolerance

Myocardial Ischemia

Symptomatic Intervention: Increased Synthesis of Lipoprotein Lipase

- Drugs: Fibrates (e.g. * gemfibrozil, fenofibrate)
- Mechanism: Activate peroxisome proliferation-activated receptor-α which increases lipoprotein lipase synthesis
- Side-effects: Nausea
  Skin Rash
  Occasional increase risk of gallstones

Myocardial Ischemia

Prophylactic Intervention: Drugs Affecting Plaque Formation

3 Main Types:

THERAPEUTIC OVERVIEW

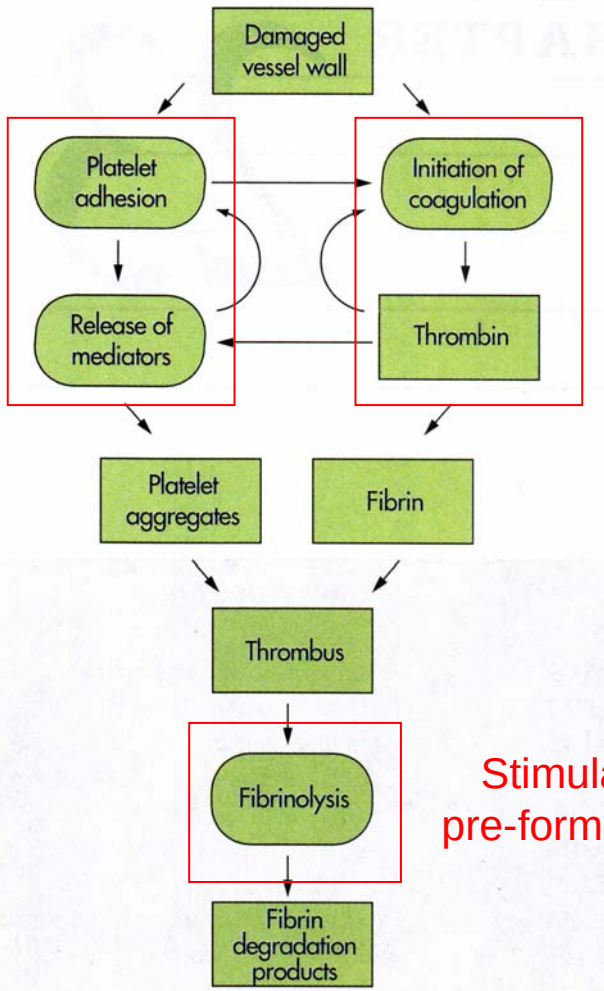
ANTICOAGULATION	
Heparin, coumarins	Arterial thrombosis Atrial fibrillation Cardiomyopathy Cerebral emboli Hip surgery Vascular prostheses Heart valve disease Venous thromboembolism
FIBRINOLYSIS	
Streptokinase, urokinase, tissue plasminogen activator	Acute myocardial infarction Deep vein thrombosis Pulmonary embolism
PLATELET AGGREGATION INHIBITION	
Aspirin	Cerebrovascular accident, stroke After coronary artery bypass surgery Restenosis after angioplasty or thrombolysis Myocardial infarction Transient ischemic attack
Ticlopidine	Cerebrovascular accident, stroke

Myocardial Ischemia

Prophylactic Intervention: Strategies Of Drug Therapy

Inhibition of platelet function

Inhibition of blood coagulation



Stimulate lysis of pre-formed thrombus

FIGURE 23-1 Involvement of thrombin and platelets and their interaction in thrombosis.

Myocardial Ischemia

Prophylactic Intervention: Inhibition Of Blood Coagulation

- Drugs: * Warfarin $_{\text{rat poison}}$ and * Heparin

- Mechanism: Blocks reactivation of Vitamin K epoxide **Warfarin**
  Binds coagulation factor Xa and antithrombin III **Heparin**

- Indications: Prevention & treatment of venous clotting
  (especially deep vein thrombosis)

- Side-effects: Teratogenic Warfarin, contraindicated during pregnancy
  Bleeding Both

Myocardial Ischemia

Prophylactic Intervention: Inhibition Of Blood Coagulation

Warfarin binds coagulation factors:

II, VII, IX and X

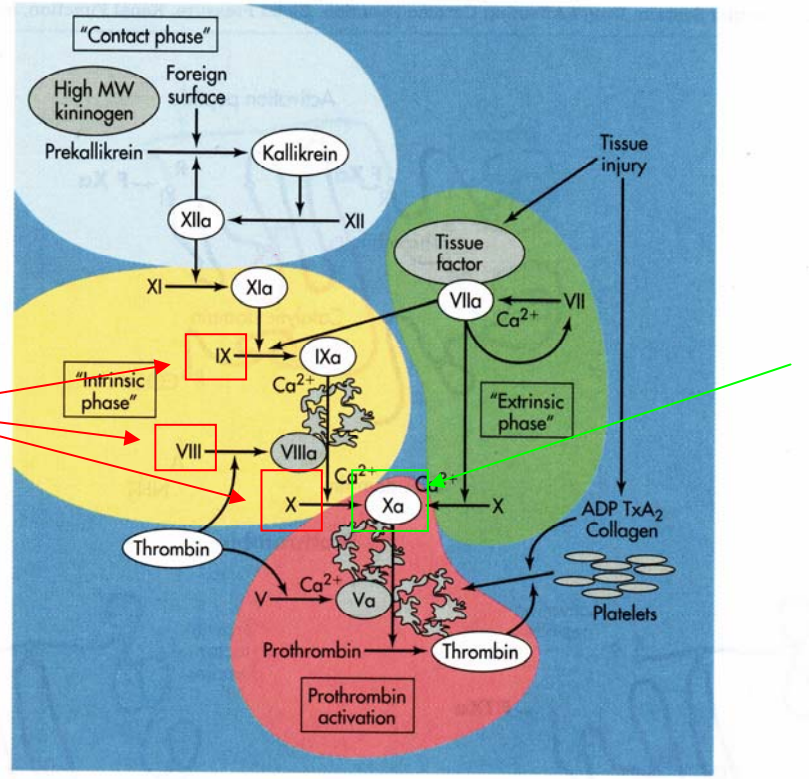


FIGURE 23-2 A simplified model of thrombin generation. Reactions fall into four phases, which occur preferentially on surfaces. Activated platelets provide the surface for two of these phases; nonvascular tissue provides the surface for the extrinsic phase, and foreign surfaces such as glass and collagen activate the contact phase. In each, a multicomponent complex is assembled, comprising an enzyme, its substrate (a proenzyme), and a cofactor. This complex affects conversion of proenzyme to its active form at a rate thousands of times faster than that of the enzyme alone.

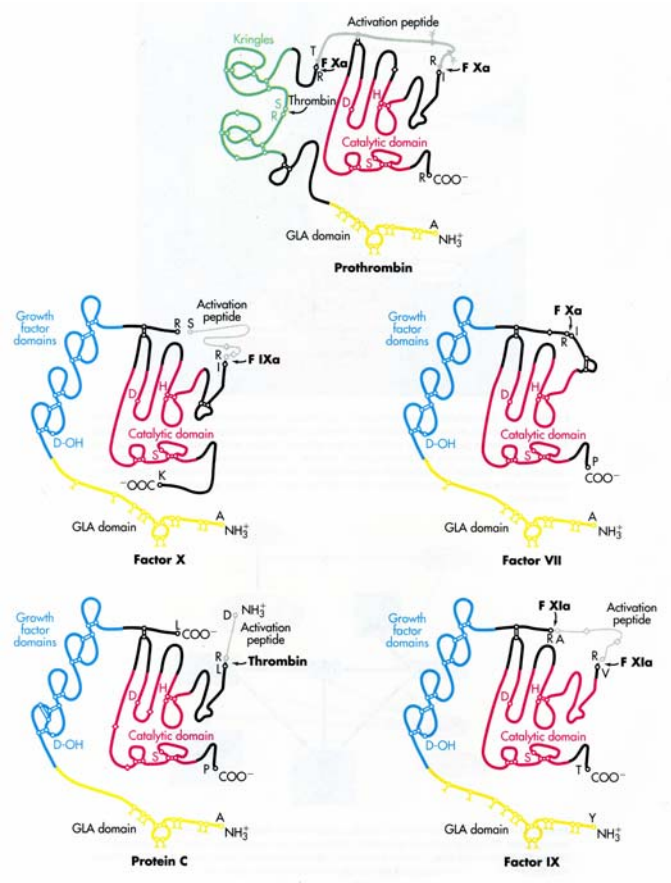
Heparin binds:

Coagulation factor Xa
&
Antithrombin III

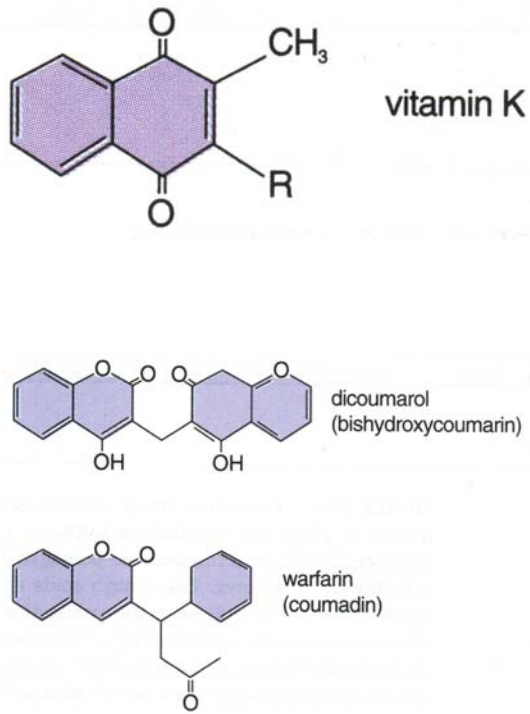
Myocardial Ischemia

Prophylactic Intervention: Vitamin K Antagonists

Structural Similarity Amongst Vitamin K Dependent Proenzymes



Similarity Amongst Vitamin K & Its Antagonists



Myocardial Ischemia

Prophylactic Intervention: Vitamin K Antagonists

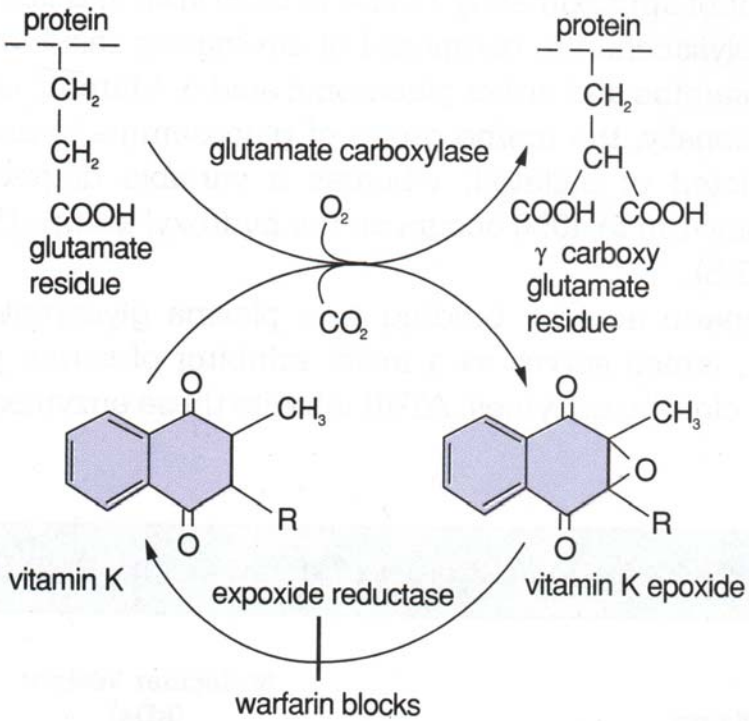


FIGURE 23-8 The role of vitamin K in the conversion of glutamate residues in certain plasma proteins to γ-carboxyglutamate *(GLA)* residues in the liver. Warfarin and other coumarin derivatives block the reduction of vitamin K epoxide formed in this reaction to its active form.

Warfarin effects vary significantly amongst patients therefore effect is monitored with **prothrombin time test**

Myocardial Ischemia

Prophylactic Intervention: Heparin

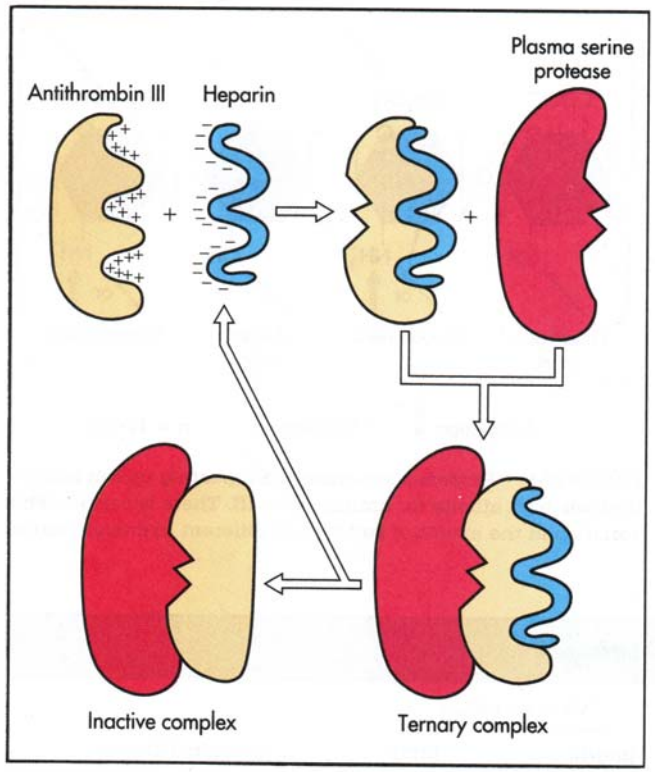


FIGURE 23-6 Heparin binds to a positively charged region of antithrombin III *(AT-III)* and greatly increases the rate at which AT-III interacts with plasma serine proteases. Heparin then dissociates from the ternary complex and can interact with more AT-III. This gives heparin the quality of a nonprotein enzyme. AT-III can inactivate thrombin and factors X_a, VII_a, and IX_a.

- Heparin available in high molecular weight (**HMW**) and low molecular weight (**LMW**) form
- **HMW** Heparin binds coagulation factor Xa and antithrombin III

  Effect must be monitored
- **LMW** heparins inhibit factor Xa but less effect on antithrombin III

  Predictable response, not monitored

Myocardial Ischemia

Prophylactic Intervention: Fibrinolytic Drugs

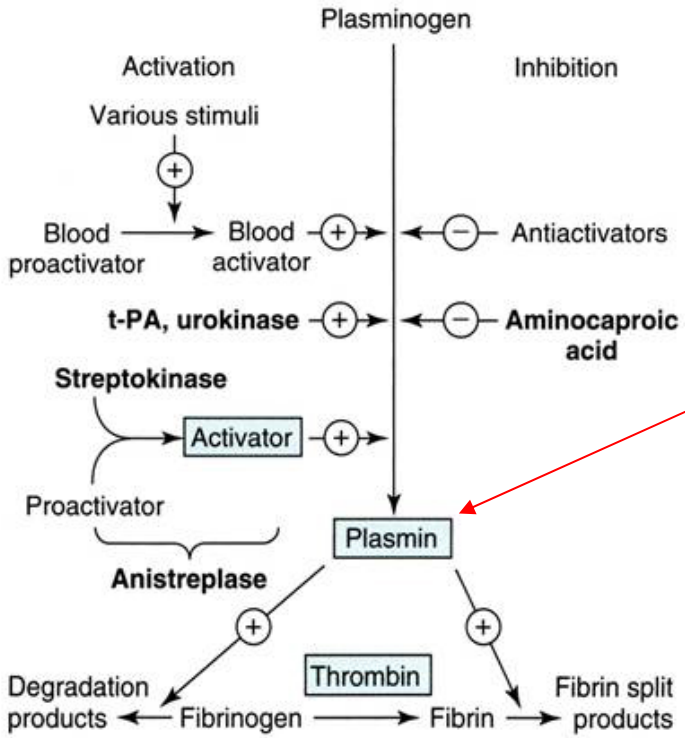


Figure 34–3. Schematic representation of the fibrinolytic system. Plasmin is the active fibrinolytic enzyme. Several clinically useful activators are shown on the left in bold. Anistreplase is a combination of streptokinase and the proactivator plasminogen. Aminocaproic acid (right) inhibits the activation of plasminogen to plasmin and is useful in some bleeding disorders.

Activate endogenous plasminogen to plasmin
An enzyme that breaks down fibrin
dissolving blood clots

Myocardial Ischemia

Prophylactic Intervention: Fibrinolytic Drugs

- Drugs: * Streptokinase bacterial culture & * Tissue Plasminogen Activators (tPA) recombinant

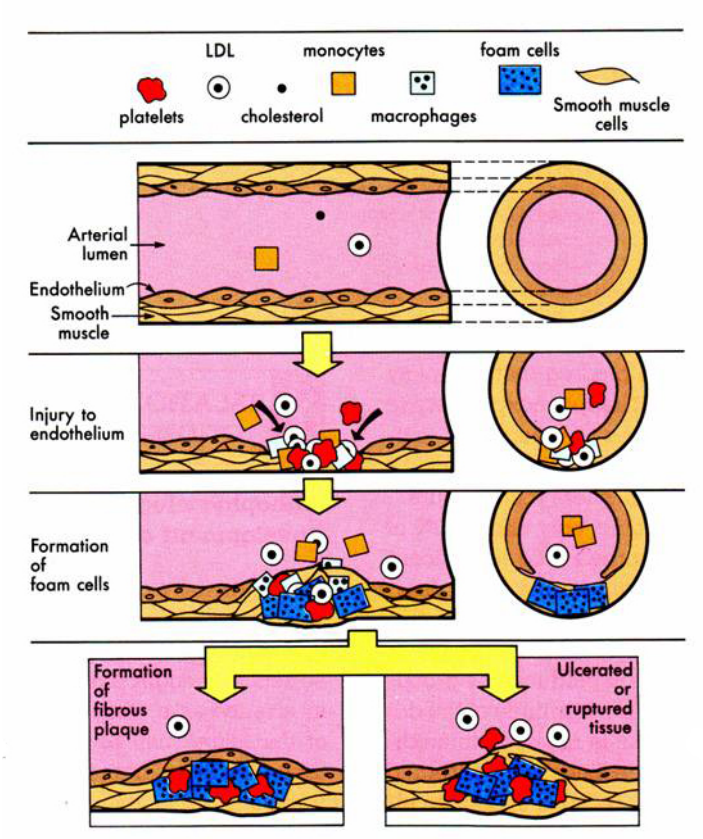
- Mechanism: Conversion of plasminogen to plasmin **Streptokinase, cost-effective**
  Activation of plasminogen bound to fibrin **tPA, expensive**

- Indications: Pulmonary embolism & Myocardial infarction

- Side-effects: Allergic response Streptokinae
  Bleeding Both

Myocardial Ischemia

Prophylactic Intervention: Anti-platelet Drugs



Collagen Wall activates platelets

↓

1. Release of thromboxane A_2 (from archidonic acid)
2. Secretion of adenosine diphosphate (ADP)

↓

Thromboxane A_2 is potent aggregating agent & vasoconstrictor

↓

Thromboxane A_2 & ADP stimulates appearance of fibrinogen binding sites on platelet membrane

(platelet aggregation)

Myocardial Ischemia

Prophylactic Intervention: Cyclooxygenase inhibitors

- Drugs: * Aspirin $_{\text{irreversible}}$ & * Ibuprofen $_{\text{competitive}}$
- Mechanism: Inhibits platelet cyclooxygenase
  blocking the synthesis of thromboxane A_2
- Indications: Transient ischemic attacks & Myocardial infarction
- Side-effects: Bleeding
  GI ulceration $_{\text{aspirin}}$

Myocardial Ischemia

Prophylactic Intervention: Adenosine receptor blockers

- Drugs: * Ticlopidine & Clopidogrel

- Mechanism: Alternative to Aspirin;
  Inhibits platelet response to secreted ADP
  at adenosine receptors

- Indications: Transient ischemic attacks & Myocardial infarction

- Side-effects: Bleeding
  Skin rashes

Major Drug Groups

Symptomatic

Nitrates
Ca^{2+} Channel Blockers
β-Blockers

Prophylactic

Lipid Lowering Drugs

1. Statins Inhibit cholesterol synthesis
2. Resins Block cholesterol reabsorption
3. Niacin Decreased VLDL secretion
4. Fibrates Lipoprotein lipase synthesis

Anti-Coagulants

1. Warfarin Vitamin K antagonist
2. Heparin Factor Xa & AT III

Fibrinolytic

1. Streptokinase Plasmin activation
2. Tissue Plasminogen Activators Endogenous

Anti-platelet

1. Aspirin / Ibuporfen TXA_2 inhibition
2. Ticlopidine / Clopidogrel Adenosine-R block

Mystery Case

ELEMENTARY, DR. WATSON...

Myocardial Ischemia

Case Study

A 63-year-old man complains of sudden onset of numbness of his right hand plus a "funny feeling" on the right side of his face. This lasted for an hour but had resolved by the time he reached your office. On examination there are no neurological deficits and he looks well. The vital signs reveal BP 150/75 mmHg, pulse 110 beats/min and irregularly irregular, respiration 14/min and temperature of 37°C.

Has the patient had a stroke?

No; most probably, a transient ischemic attack

Affecting the left middle cerebral artery

Myocardial Ischemia

Case Study

What could account for the episode of transient ischemia?

Occlusion by small embolus

Where did the embolus come from?

From inefficiently contracting left atrium

He has atrial fibrillation

Myocardial Ischemia

Case Study

What is the most appropriate treatment for this patient?

Asymptomatic atrial fibrillation; prophylactic anticoagulent for life

Warfarin or Aspirin (though less effective)

Myocardial Ischemia

What Have We Learned?

1. Different Types Of Ischemia

2. Different Types of Drug Therapy

Symptomatic and/or Prophylactic