Lipid Lowering Drugs

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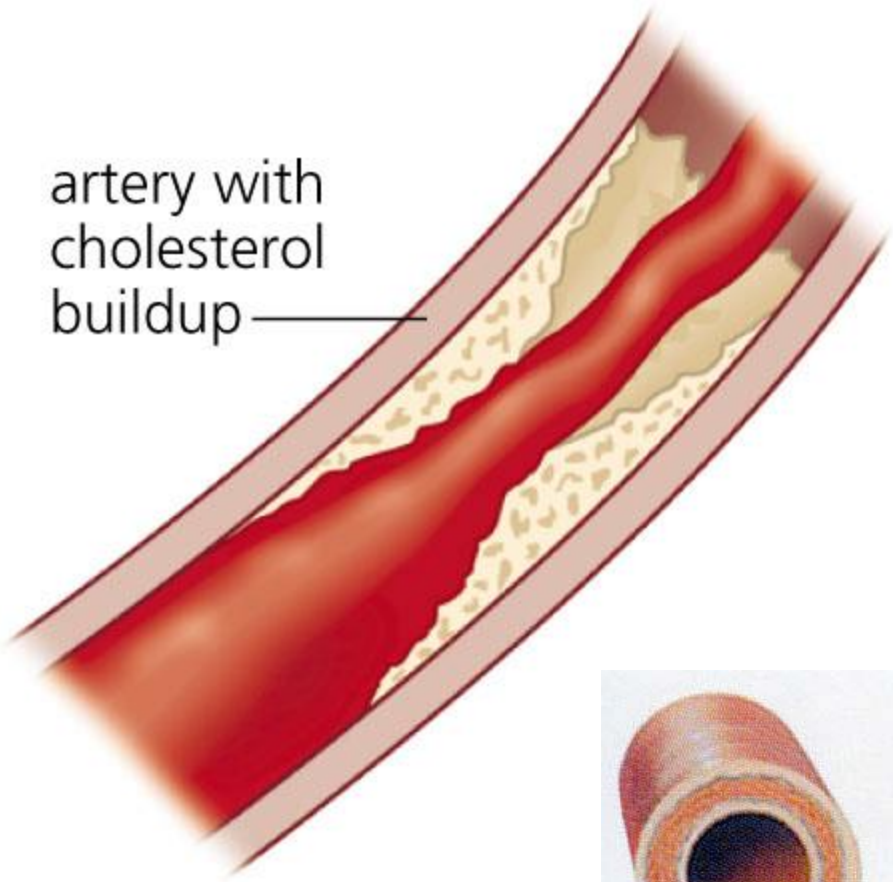
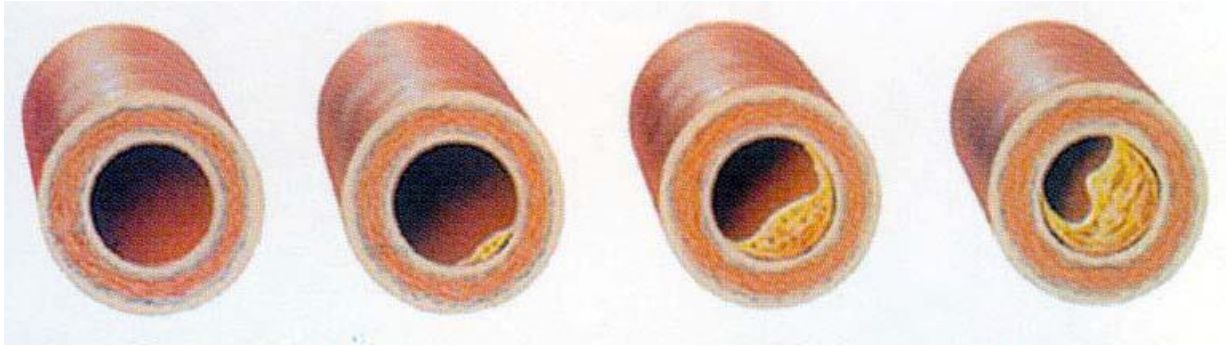
Atherosclerosis

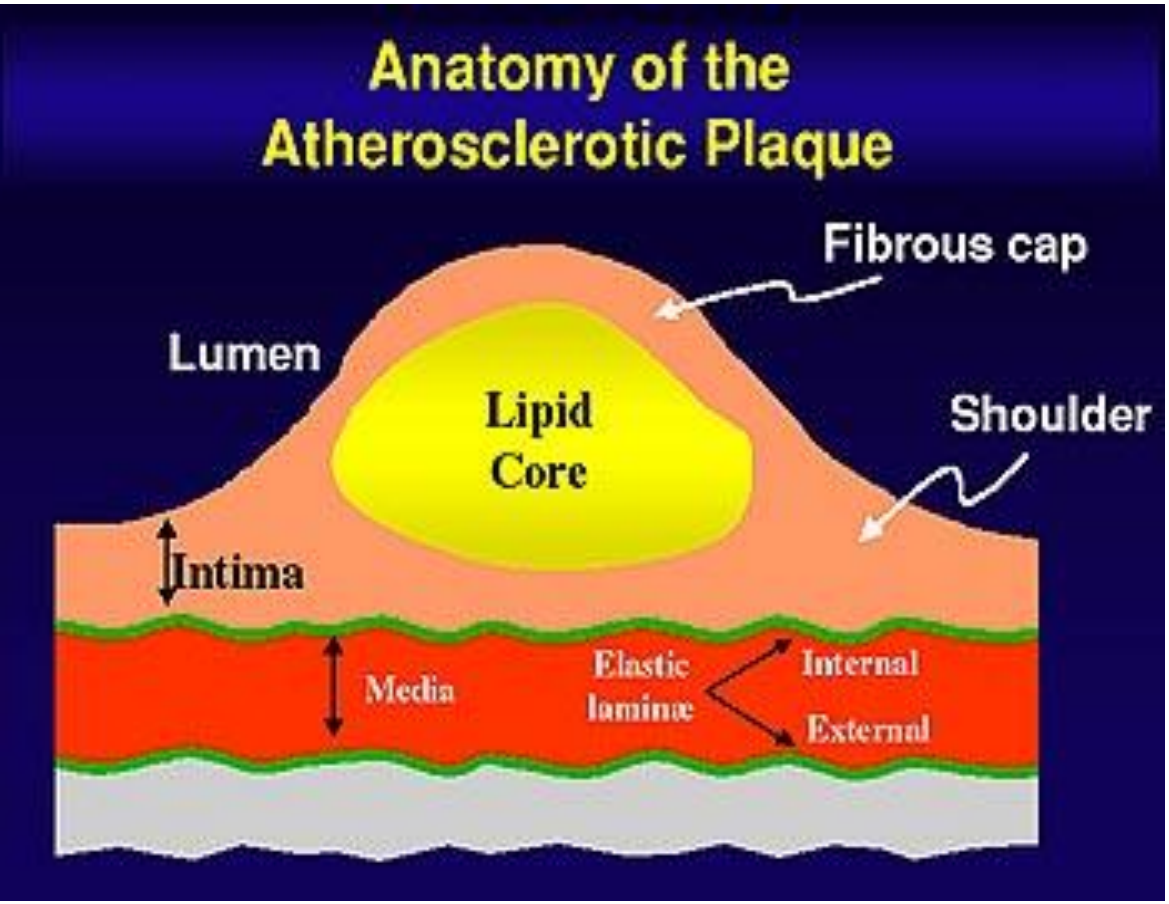
- A form of arteriosclerosis characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries.
- The nomenclature comes from the Greek words athero (meaning gruel or paste) and sclerosis (hardness).

Atherosclerosis





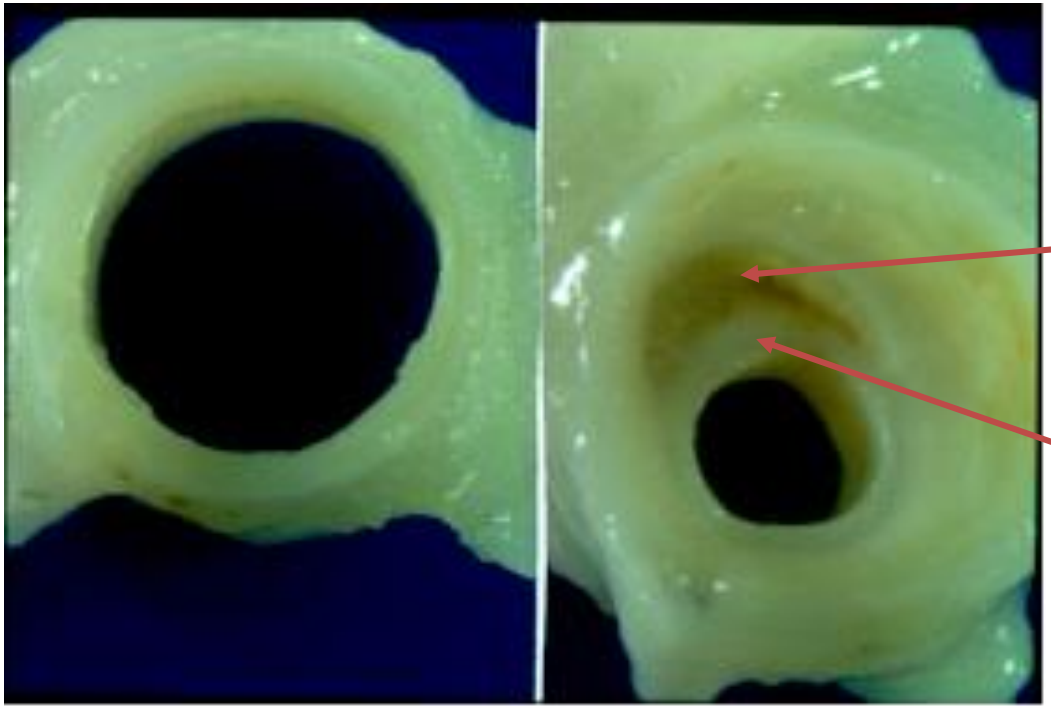
Atherosclerosis



Cell Types

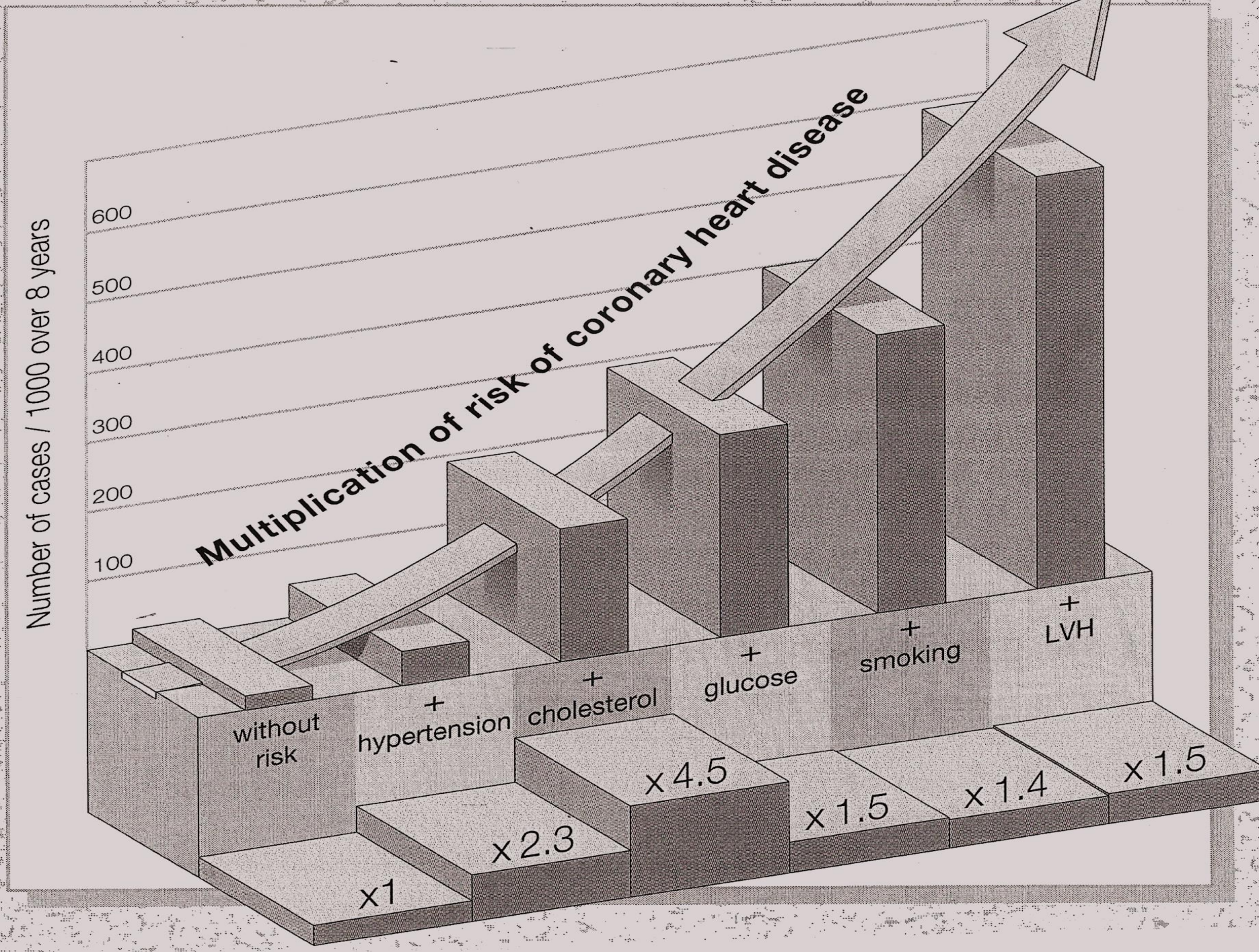
- Smooth muscle cell
- Endothelial cells
- Fibroblasts
- Macrophages
- “foam cells”
- T-lymphocytes
- Mast cells

Normal and atheromatous coronary artery



Normal coronary

Atherosclerotic coronary


Number of cases / 1000 over 8 years
600
500
400
300
200
100
Multiplication of risk of coronary heart disease
without risk
+ hypertension
+ cholesterol
+ glucose
+ smoking
+ LVH
x1
x 2.3
x 4.5
x 1.5
x 1.4
x 1.5

Non- Modifiable Risk Factors

Age

- Atherosclerosis begins in the young, but does not precipitate organ injury until later in life

Gender

- Men more prone than women, but by age 60- 70 about equal frequency

Family History

- Genetic differences

Modifiable Risk Factors (potentially controllable)

- Hyperlipidemia
- Hypertension
- Cigarette smoking
- Diabetes Mellitus
- Factors that affect hemostasis and thrombosis
- Infections: Herpes virus; Chlamydia pneumoniae
- Obesity, sedentary lifestyle, stress

- **Among all these factors, elevated serum cholesterol levels are unique in the ability to drive atherosclerosis in the absence of other risk factors**

Atherosclerosis

Genetics

- Familial hypercholesterolemia (FH) - Deficiency/mutation of LDL receptors

Atherosclerosis

What are the mechanisms leading to atherosclerosis lesions?

- Two major sources of cholesterol in the body
  - endogenous production (liver, 1g/day)
  - food (animal sources)

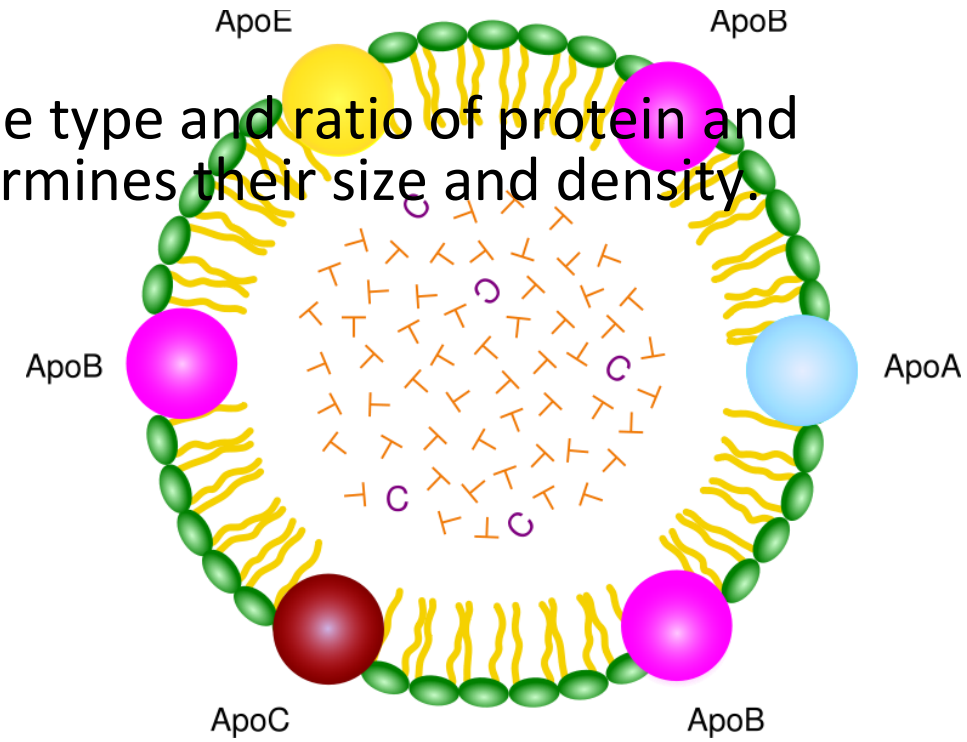
  LDL Cholesterol levels:
  - Less than 100 Optimal
  - 100 - 129 Near optimal/above optimal
  - 130 - 159 Borderline high
  - 160 - 189 High
  - 190 and above Very high

Atherosclerosis

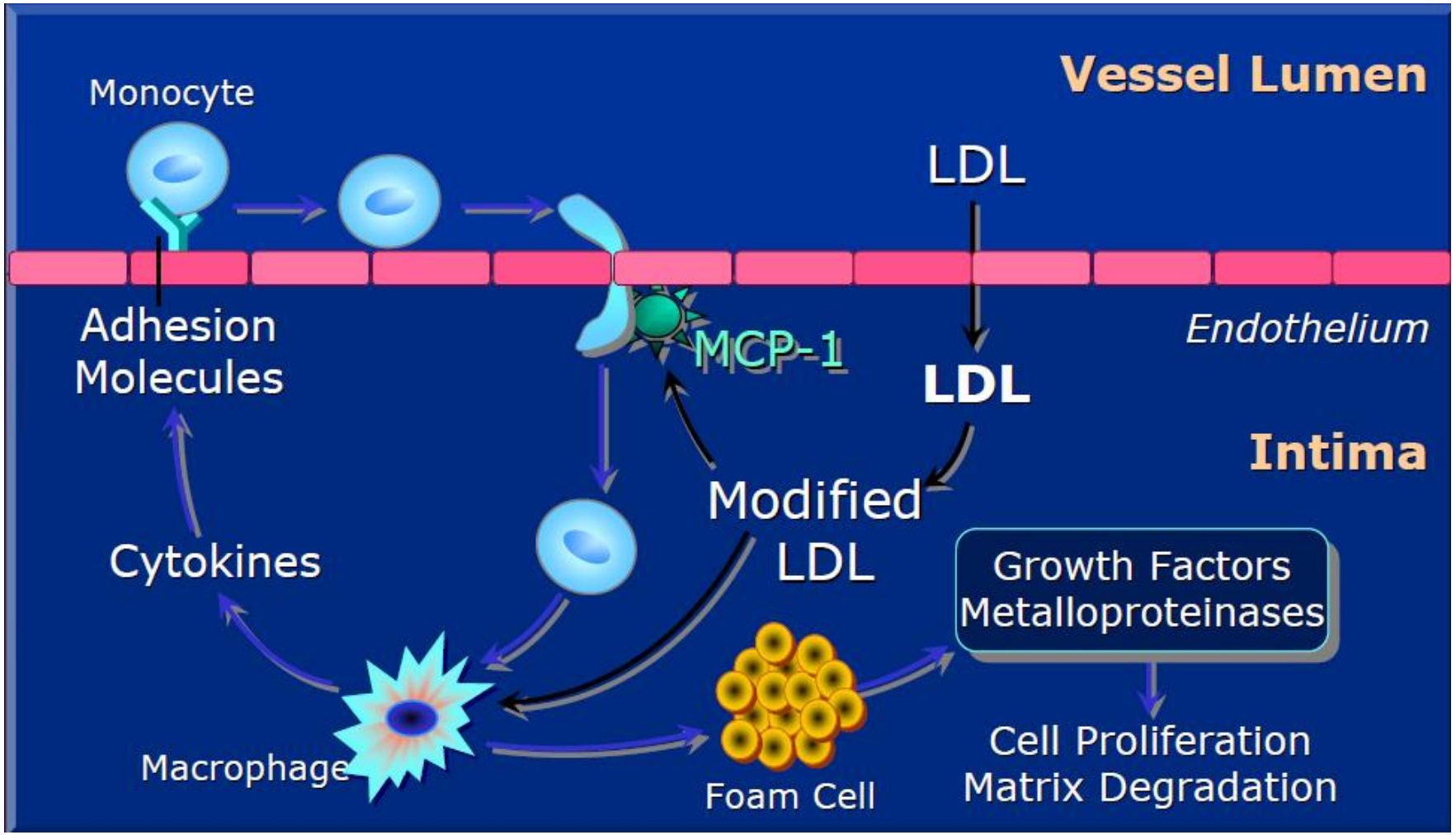
Mechanisms leading to atherosclerosis lesions?

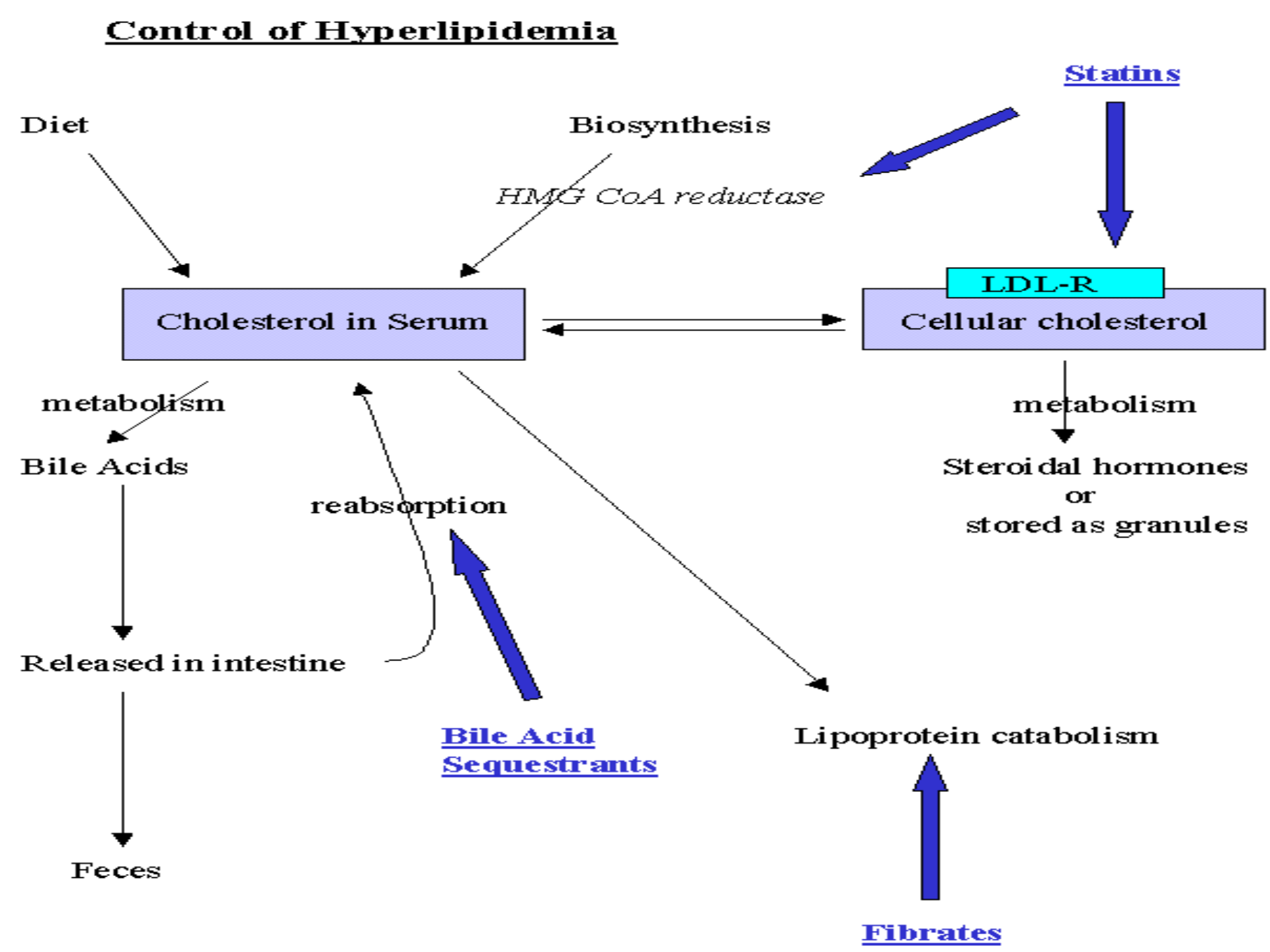
- Cholesterol and fats are poorly soluble in blood and therefore are transported via lipoproteins.

- Lipoproteins- classified by the type and ratio of protein and fats they contain which determines their size and density.
  - Chylomicrons
  - VLDL
  - IDL
  - ***LDL***
  - ***HDL***



How does high cholesterol lead to atherosclerosis?

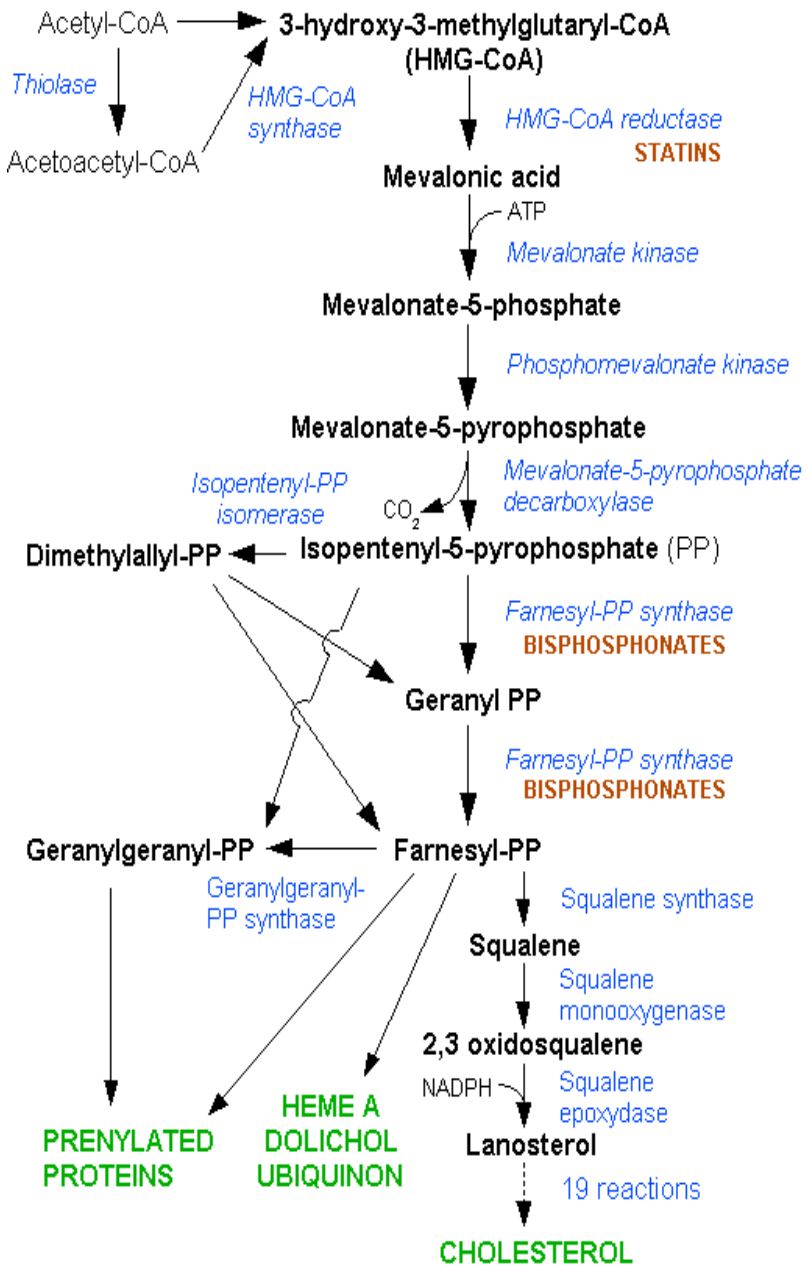



Control of Hyperlipidemia
Statins
Diet
Biosynthesis
HMG CoA reductase
LDL-R
Cholesterol in Serum
Cellular cholesterol
metabolism
metabolism
Bile Acids
Steroidal hormones
or
stored as granules
reabsorption
Released in intestine
Bile Acid
Sequestrants
Lipoprotein catabolism
Feces
Fibrates

Treatment

Drugs which lower Cholesterol

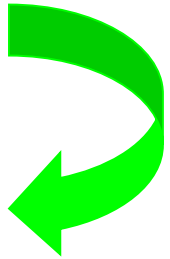
- Statins (simvastatin, atorvostatin, pravastatin) **Decrease LDL by 30-50%.**
- **Block HMG CoA reductase.**
- Increase expression of LDL receptor in the liver, further decreasing circulating LDL.



LIPID-LOWERING DRUGS: Statins

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors. The reductase catalyses the conversion of **HMG-CoA** to **mevalonic acid; blocks the synthesis of CHO in the liver:**

decrease hepatic CHO synthesis: lowers total and LDL



increase in synthesis of CHO receptors

+ increased clearance of LDL

Several studies demonstrated positive effects on morbidity and mortality.

Relatively few side-effects...

However, *adverse effects*: myopathy (incr in pts given combined therapy with nicotinic acid or fibrates. Should not be given during pregnancy.

Competitive Inhibitors of HMG-CoA Reductase "Statins"

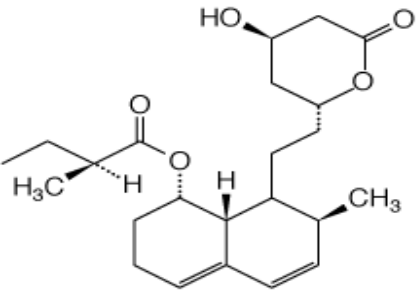
High-, Moderate-, and Low-Intensity Statin Therapy*

Table 3

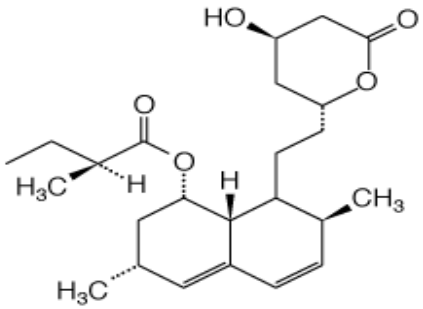
	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering†	≥50%	30% to 49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 (40 mg)**	**Atorvastatin 10 mg (20 mg)** **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	–	**Pravastatin 40 mg (80 mg)** **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

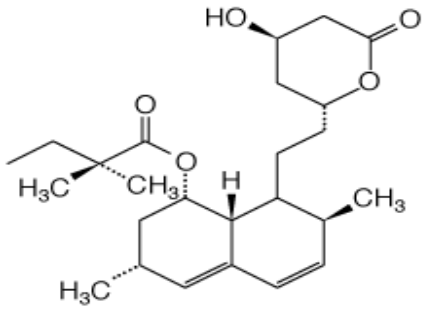
MEVASTATIN



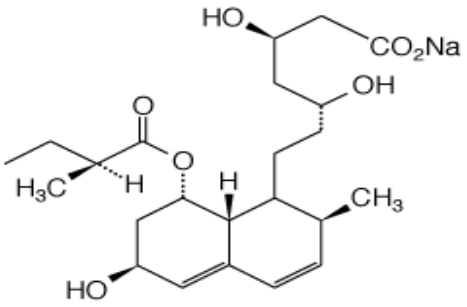
LOVASTATIN



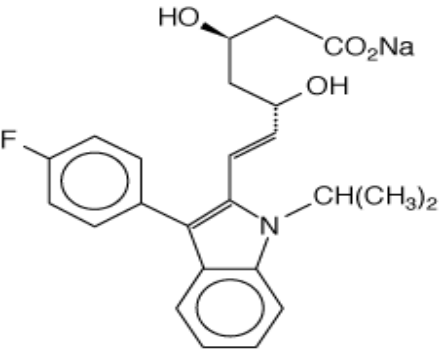
SIMVASTATIN



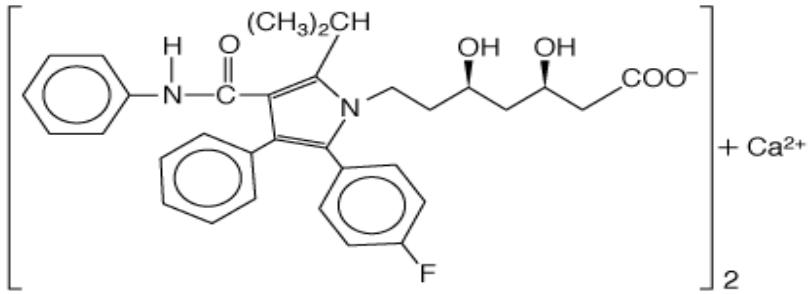
PRAVASTATIN



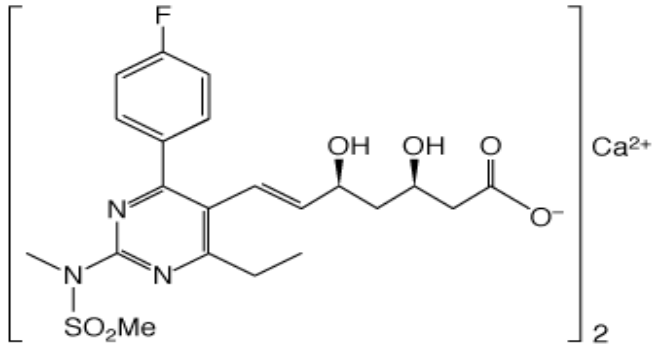
FLUVASTATIN



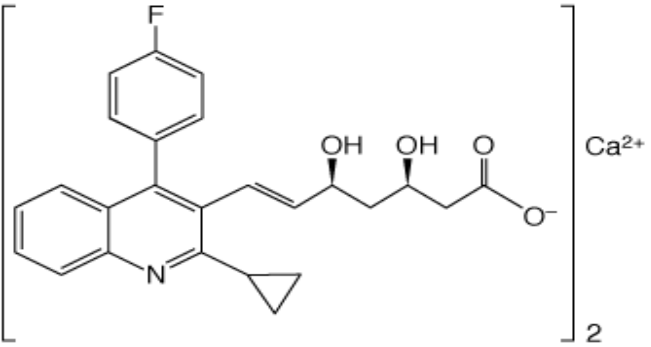
ATORVASTATIN



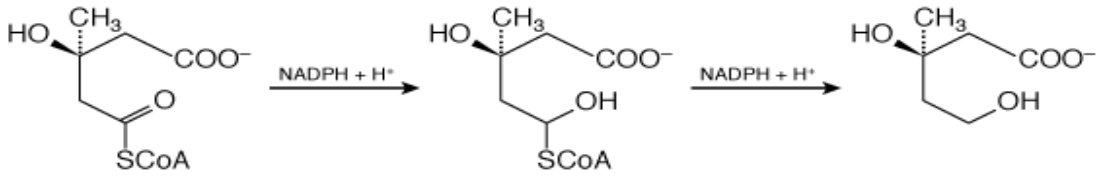
ROSUVASTATIN



PITAVASTATIN



Reaction Catalyzed by HMG-CoA Reductase



HMG-CoA intermediate MEVALONATE

Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

LIPID-LOWERING DRUGS: Statins

Promising pharmacodynamic actions:

- improved endothelial function
- reduced vascular inflammation and platelet aggregability
- antithrombotic action
- stabilisation of atherosclerotic plaques
- increased neovascularisation of ischaemic tissue
- enhanced fibrinolysis
- immune suppression
- osteoclast apoptosis and increased synthetic activity in osteoblasts

LIPID-LOWERING DRUGS: Statins

Pharmacokinetics

- well absorbed when given orally
- extracted by the liver (target tissue), undergo extensive presystemic biotransformation

Simvastatin is an inactive pro-drug

LIPID-LOWERING DRUGS: Statins

Clinical uses

- **Secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease** (angina, transient ischemic attacks) **following acute myocardial infarction or stroke**
- **Primary prevention of arterial disease in patients who are at high risk because of elevated serum CHO concentration, especially it there are other risk factors for atherosclerosis**
- **Atorvastatin lowers serum CHO in patients with homozygous familiar hypercholesterolemia**

LIPID-LOWERING DRUGS: Statins

- Pleiotropic actions.

Improve endothelial function, upregulate eNOS.
Anti-inflammatory, reduce odds of plaque rupture.

Statins as an antiplatelet drug

Statins act by

- inhibiting NADPH oxidase–mediated isoprostane formation,
- modulating phospholipase A2 (PLA2)–mediated thromboxane A2 (TXA2) formation, and
- upregulating endothelial nitric oxide synthase (eNOS)

LIPID-LOWERING DRUGS: Statins

A d v e r s e e f f e c t s:

- **mild gastrointestinal disturbances**

- **increased plasma activities in liver enzymes**

- **severe myositis (rhabdomyolysis)** and **angioedema (rare)**

Niacin

- **Nicotinic Acid or Vitamin B3, one of the oldest drugs.**
- **Water- soluble B-complex vitamin, functions only after conversion to NAD or NADP+ Nicotinamide.**
- **Affects all lipid parameters:**
  - **Best agent to increase HDL-C(35-40%).**
  - **Lowers triglycerides (35-45%).**
  - **Decreases LDL-C production(20-30%).**
- **Reduces fibrinogen levels.**
- **Increases plasminogen activator,**

Niacin

Mechanism of Action:

1. In adipose tissue: inhibits the lipolysis of triglycerides by inhibiting adipocyte adenylyl cyclase, which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis.

2. May also inhibit a rate –limiting enzyme of triglyceride synthesis, diacylglycerol acetyltransferase -2.

- Reduction of triglyceride synthesis reduces hepatic VLDL and consequently LDL.

3. Inhibits intracellular lipase in adipose tissues leading to decreased FFA flux to the liver.

- **Completely absorbed, peaks within 1hr, half-life is about 1 hr, so need to be given by twice or thrice daily administration.**

Niacin

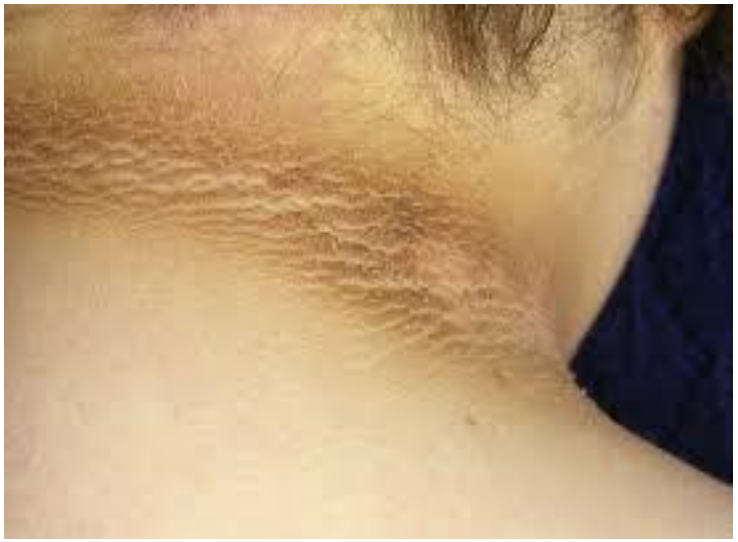
- **Completely absorbed**
- **peaks within 1hr**
- **half-life is about 1 hr, so need to be given by twice or thrice daily administration.**

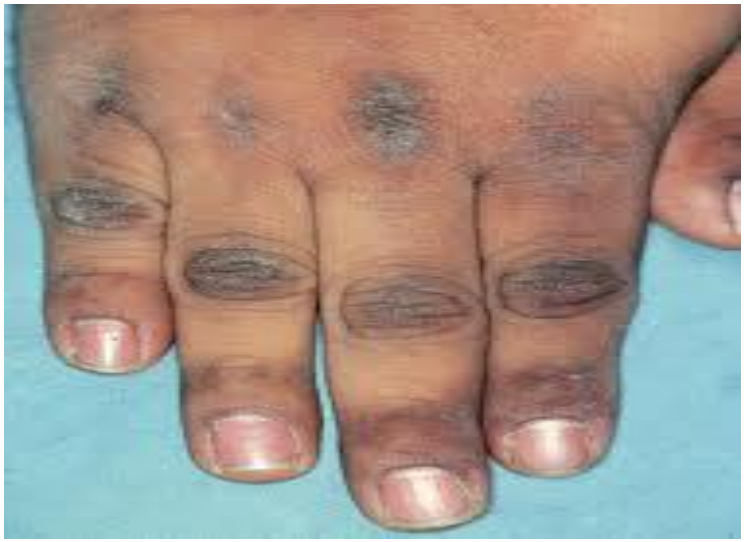
Niacin

Toxicity:

- **Harmless cutaneous vasodilation and sensation of warmth.**
- **Pruritus, rashes, dry skin or mucus membranes**
- **Acanthosis Nigricans:a skin condition that causes a dark discoloration in body folds and creases.**
- **Nausea, vomiting, abdominal discomfort, diarrhea.**
- **Elevations in transaminases and possible hepatotoxicity.**
- **Insulin resistance and hyperglycemia.**
- **Hyperuricemia and gout.**
- **Cardiac arrhythmias.**
- **Amblyopia, blurring of vision.**

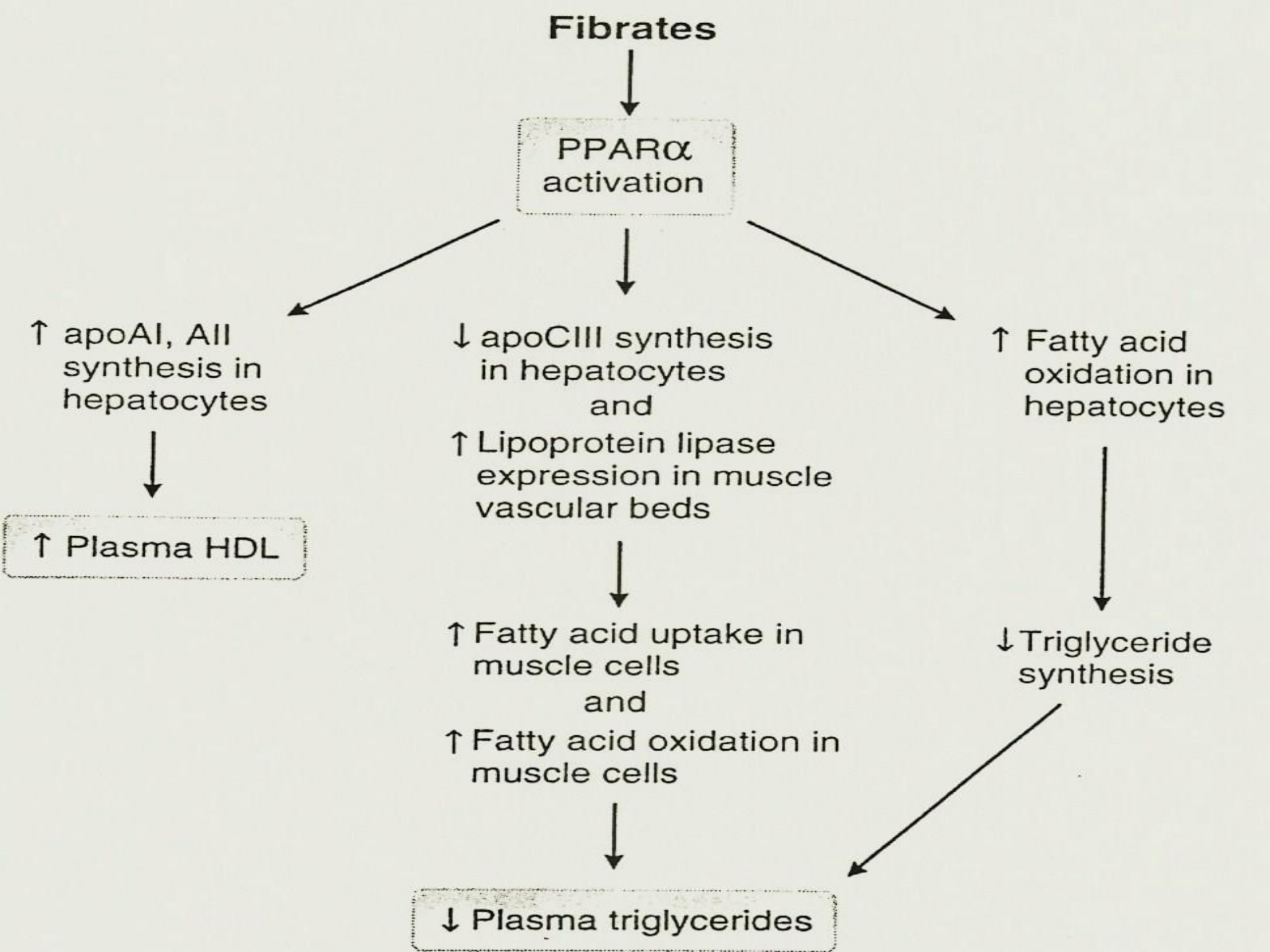
Acanthosis Nigricans





Fibrates or Fibric Acid Derivatives or "PPARs Activators"

- **Clofibrate, 1962-1987.**
- **Gemfobrozil.**
- **Fenofibrate.**
- **Bezafibrate.**
- **Work on PPAR- α (Peroxisome Proliferator Activated Receptor- α) which stimulates fatty acid oxidation, increases LPL synthesis**
- **reduces expression of apo C-III, and increases apoA-I and apoA-II expression.**
- **Increase lipolysis of lipoprotein triglyceride via LPL**
- **Leading to decrease TG.**
- **Decrease levels of VLDL and LDL.**
- **Moderately increase HDL.**
- **Also have anticoagulant and fibrinolytic activities.**
- **Drugs of choice in severe hypertriglyceridemia.**


Fibrates
PPARα activation
↑ apoAI, AII synthesis in hepatocytes
↑ Plasma HDL
↓ apoCIII synthesis in hepatocytes
and
↑ Lipoprotein lipase expression in muscle vascular beds
↑ Fatty acid uptake in muscle cells
and
↑ Fatty acid oxidation in muscle cells
↑ Fatty acid oxidation in hepatocytes
↓ Triglyceride synthesis
↓ Plasma triglycerides

Fibrates

Toxicity:

- **Rashes, urticaria, hair loss, headache, GIT symptoms, impotence, and anemia.**

- **Myalgia, fatigue, myopathy and rhabdomyolysis.**

(Breakdown of muscle fibers resulting in the release of muscle fiber contents (myoglobin) into the blood stream).

- **Risk of cholesterol gallstones.**
- **Interacts with statins, levels of both drugs will increase.**
- **Used with caution in renal failure.**
- **Elevated transaminases or alkaline phosphatase.**

- **Combination of statins and fibrates increases risk of rhabdomyolysis by 10+ fold. Can improve insulin resistance**

Bile Acid –Binding Resins

- **Colestipol.**
- **Chlestyramine.**
- **Colesevelam.**
- **These are large polymeric anionic- exchange resins, insoluble in water, which bind the negatively charged bile acids in the intestinal lumen and prevent their reabsorption leading to depletion of bile acid pool and increased hepatic synthesis.**

Bile Acid –Binding Resins

- **Consequently, hepatic cholesterol content is decreased, stimulating the production of LDL receptors. This leads to increased LDL clearance and lowers LDL-C levels.**
- **However, this effect is partially offset by the enhanced cholesterol synthesis caused by upregulation of HMG-CoA reductase.**
- **May increase triglyceride levels.**

Inhibitors of Sterol Absorption

Ezetimibe:

- **Can reduce LDL.**
- **Inhibitor of a specific transport process in jejunal enterocytes, which takes up cholesterol from the lumen (NPC1L1).**
- **Can reduce cholesterol absorption by 54%, precipitating a compensatory increase in cholesterol synthesis.**
- **Reduces incorporation of cholesterol into chylomicrons, thereby reducing delivery to the liver by the chylomicron remnants. This will stimulate the expression of the hepatic genes regulating the LDL receptor expression leading to enhanced LDL-C clearance from the plasma(15-20%).**
- **Does not affect triglyceride absorption.**
- **Action is complementary to statins(60% reuction in LDL-C)..**

- **Can cause allergic reactions, reversible impairment of liver function tests and myopathy.**