Antihyperlipidemic Drugs

Hyperlipidemias.

Hyperlipoproteinemias.

Hyperlipemia.

Hypercholestrolemia.

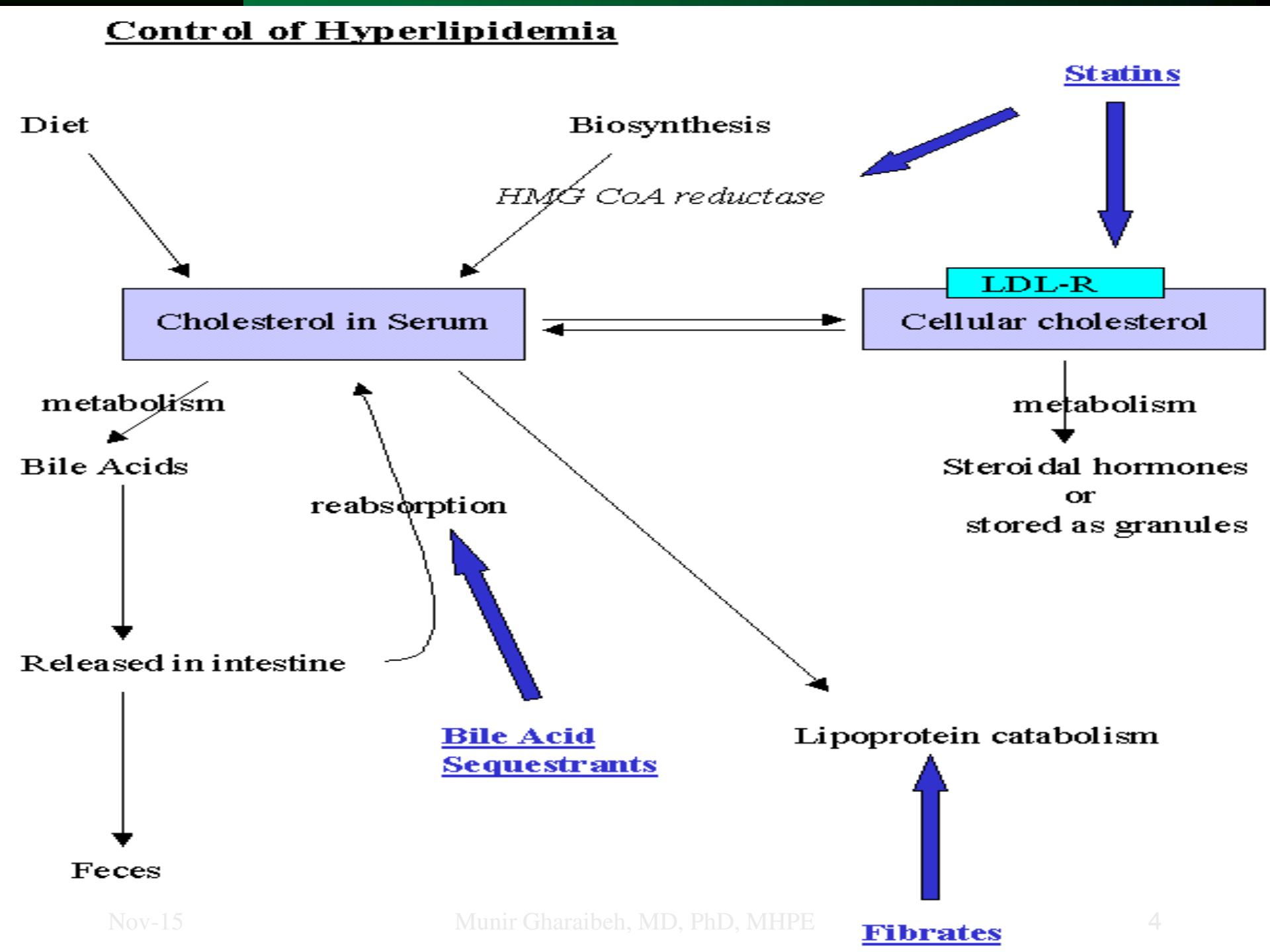
Direct relationship with acute pancreatitis and atherosclerosis.

TYPE	ORIGIN	MAJOR LIPIDS	MAJOR APOLIPOPROTEINS	CATABOLISM
Chylomicrons	Intestine	85% Triglyceride	B48, AI, AIV, E, CI, CII, CIII	Hydrolysis of triglyceride (lipoprotein lipase)
Chylomicron remnants	From chylomicrons	40–60% Triglyceride	B48, AI, AIV, E, CI, CII, CIII	Uptake by liver (apoE via LDL receptor)
VLDL	Liver	20% Cholesterol 55% Triglyceride 20% Cholesterol	B100, E, CI, CII, CIII	Hydrolysis of triglyceride (lipoprotein lipase) to IDL; direct uptake by liver (apoE and B100 via LDL receptor)
IDL	From VLDL and liver	35% Cholesterol 25% Triglyceride	B100, E, CI, CII, CIII	→ LDL (hepatic lipase) → Liver (apoE and B100)
LDL	From IDL and liver	60% Cholesterol 5% Triglyceride 35% Phospholipid	B100, E, CI, CII, CIII	Uptake: liver (apoB100 via LDL receptor)
HDL	Liver, intestine, and plasma	20% Cholesterol 5% Triglyceride	AI, AII, CI, CII, CIII, E	1. Uptake of cholesterol ester by hepatocytes (SR-B1) 2. Transfer of cholesteryl ester (CETP) to LDL, IDL, and VLDL 3. Lipolysis of TG and CE by hepatic lipase and uptake by liver 4. Clearance of HDL particle by liver and kidney

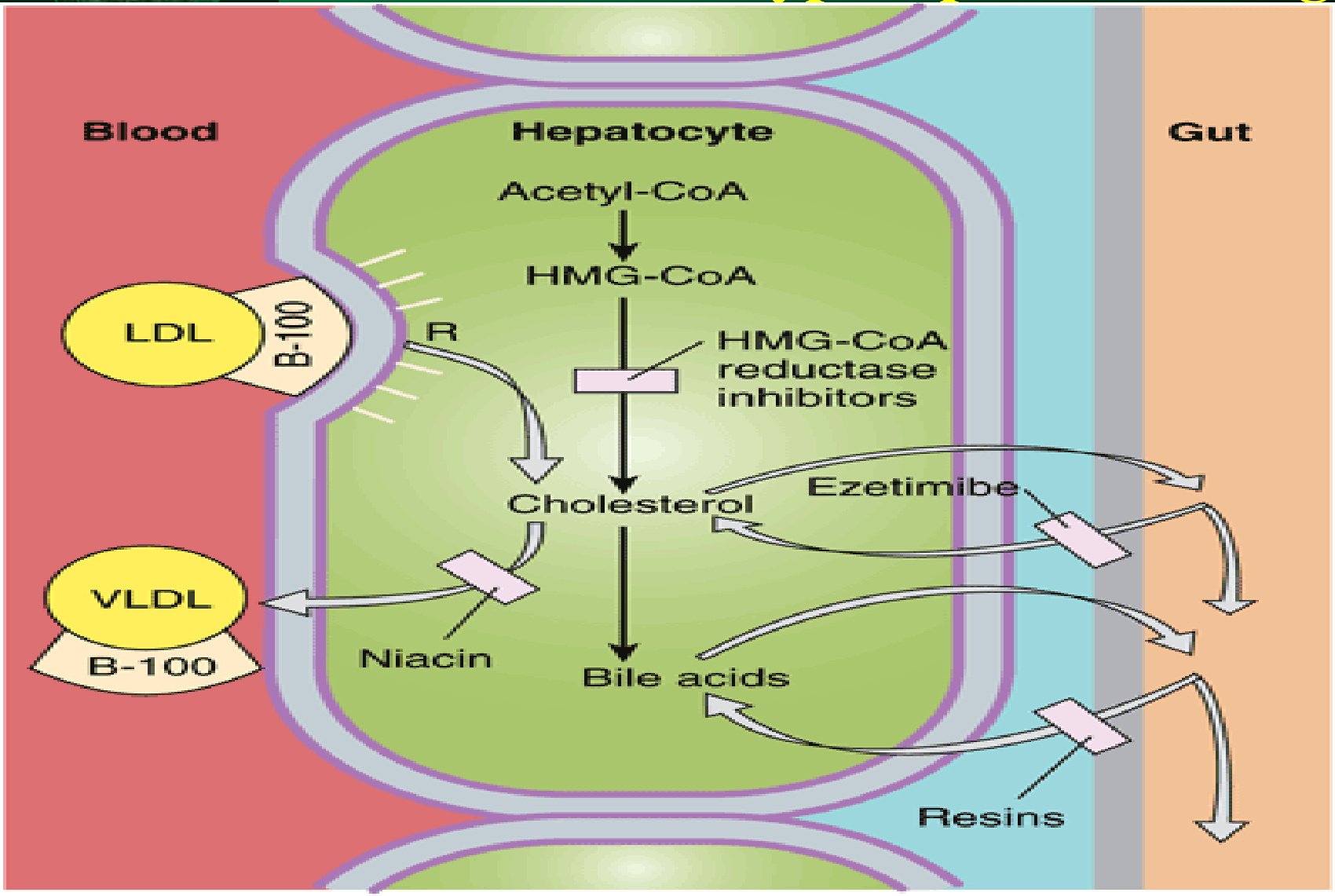
Table 35–3 Secondary Causes of Hyperlipoproteinemia.

Hypertriglyceridemia	Hypercholesterolemia
Diabetes mellitus	Hypothyroidism
Alcohol ingestion	Early nephrosis
Severe nephrosis	Resolving lipemia
Estrogens	Immunoglobulin-lipoprotein complex disorders
Uremia	Anorexia nervosa
Corticosteroid excess	Cholestasis
Myxedema	Hypopituitarism
Glycogen storage disease	Corticosteroid excess
Hypopituitarism	
Acromegaly	
Immunoglobulin-lipoprotein complex disorders	
Lipodystrophy	
Protease inhibitors	

Control of Hyperlipidemia



Sites of Action of Antihyperlipidemic Drugs



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Niacin

- Nicotinic Acid or Vitamin B3, is one of the oldest drugs.
- Water- soluble B-complex vitamin, functions only after conversion to NAD or NADP+ Nicotinamide.
- Niacin has hypolipidemic effects in large doses.
- 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:

- 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.

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

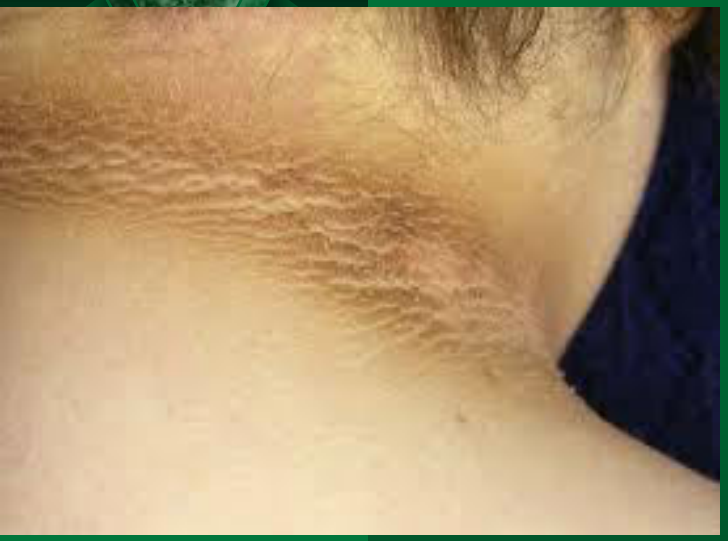
- Completely absorbed, peaks within 1hr, half-life is about 1 hr, so need to be given by twice or thrice daily administration.

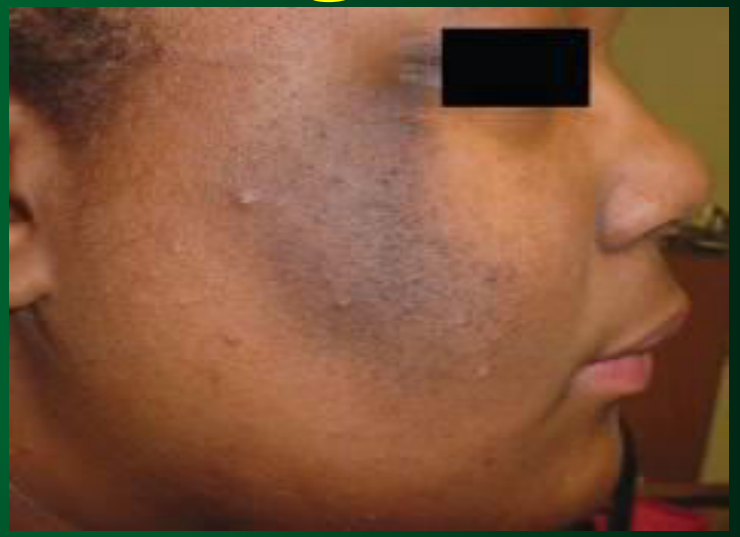
Niacin

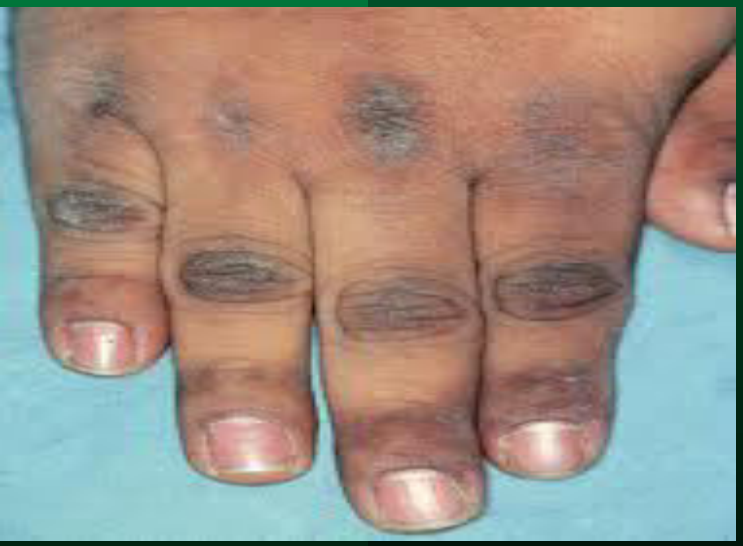
Toxicity:

- Harmless cutaneous vasodilation and sensation of warmth.
- Pruritus, rashes, dry skin or mucus membranes (*acanthosis nigricans*).
- Nausea, vomiting, abdominal discomfort, diarrhea.

Acanthosis Nigricans







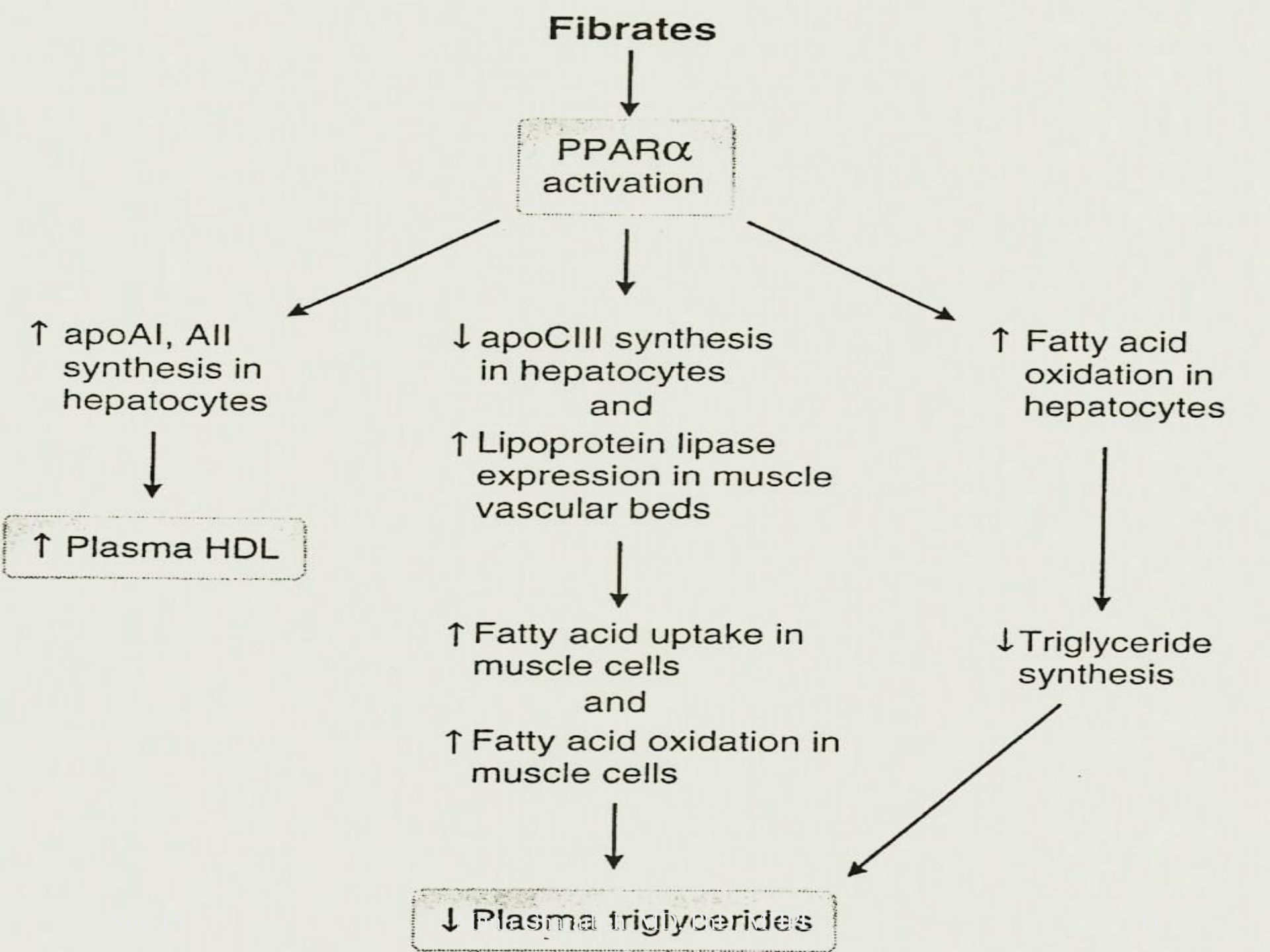
Fibrates or Fibric Acid Derivatives or "PPARs Activators"

- Clofibrate, 1962-1987.
- Gemfobrozil.
- Fenofibrate.
- Bezafibrate.

- Stimulate PPAR- α (Peroxisome Proliferator Activated Receptor- α) which stimulates fatty acid oxidation, increases LPL synthesis, and reduces expression of apo C-III, and increases apoA-I and apoA-II expression.

- 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.

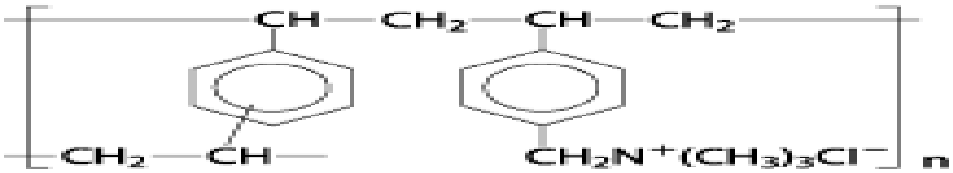
(Breakdown of muscle fibers resulting in the release of muscle fiber contents (myoglobin) into the blood stream).

- Elevated transaminases or alkaline phosphatase.

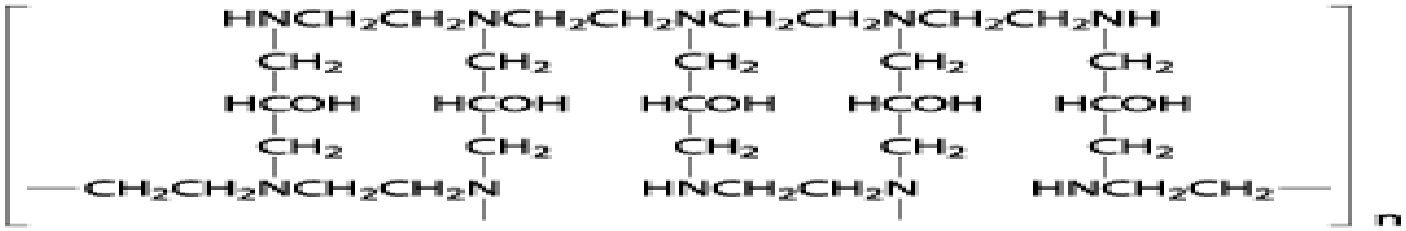
Bile Acid –Binding Resins

- **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.**
- **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-**

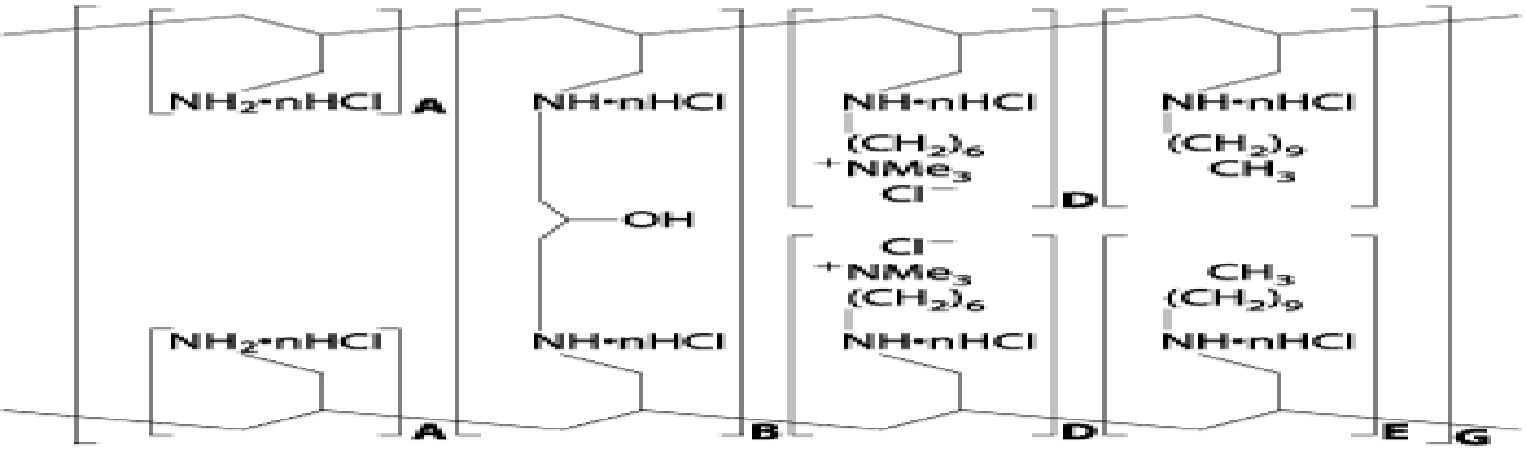
Cholestyramine



Colestipol



Colesevelam



A = Primary Amines
B = Cross-linked Amines
D = Quaternary Ammonium Alkylated Amines
E = Decyalkylated Amines
n = Fraction of Protonated Amines
G = Extended Polymeric Network

Bile Acid –Binding Resins

Idications:

- Lower LDL as much as 25%, but will cause GI side effects.
- Relieve pruritus in cholestasis.
- Digitalis toxicity, can bind digitoxin and enhance its excretion.

Bile Acid –Binding Resins

Toxicity:

Probably the safest drugs, since they are not absorbed from the intestine because of their large size. Maximal doses are effective but cause side effects.

- **Gritty sensation is unpleasant but can be tolerated.**
- **Constipation and bloating.**
- **Heartburn.**
- **Malabsorption of Vitamin K.**
- **Gall stones.**
- **Impaired absorption of many drugs(digitalis, propranolol, thiazides, warfarin, folic acid, statins, aspirin….etc)..**

Competitive Inhibitors of HMG-CoA Reductase "Statins"

- Mevastatin
- Simvastatin
- Lovastatin
- Pravastatin
- Fluvastatin
- Atorvastatin.
- Rosuvastatin.

Competitive Inhibitors of HMG-CoA Reductase "Statins"

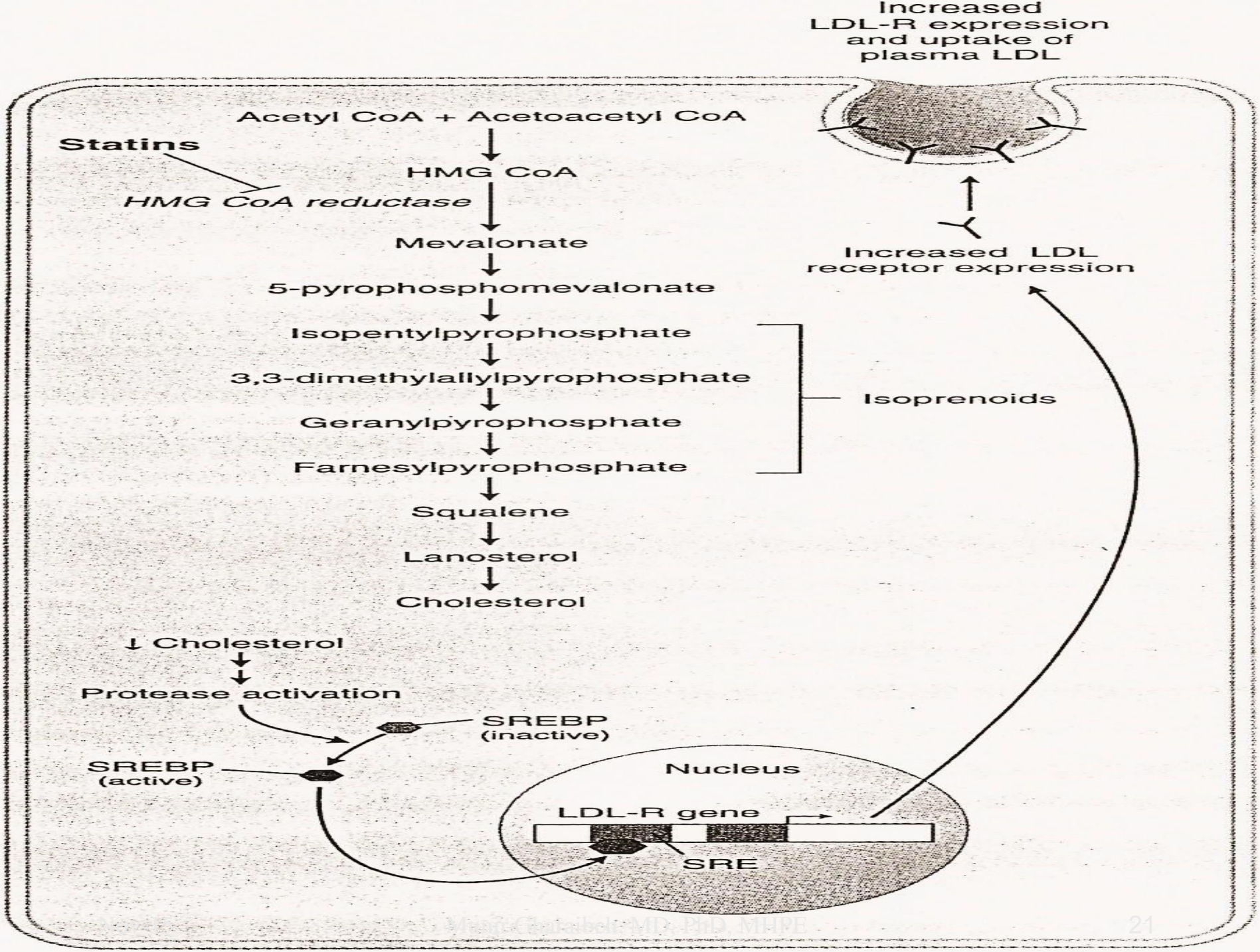
- Most commonly prescribed drugs worldwide.
- Isolated from a mold *Penicilliun citrinum*, 1976.
- Modified derivatives and distinct synthetic compounds.
- Most effective in lowering LDL.

Statins

- Competitively inhibit the early rate- limiting enzyme in *de novo* synthesis of cholesterol (*3-hydroxy-3methylglutaryl coenzyme A reductase*). This results in increased expression of the LDL receptor gene.
- Reduced free cholesterol in hepatocytes activates a protease which will cleave membrane- bound SREBPs which will be translocated to the nucleus to enhance trasncription of LDL receptors. Increased number of LDL receptors will increase removal of LDL-C from the blood thus lowering of LDL-C.

Statins

- Higher doses can reduce triglyceride levels caused by elevated VLDL levels.
- Some (simvastatin and rosuvastatin) can raise HDL-C levels.
- Decrease oxidative stress and vascular inflammation by enhancing NO production.
- Reduce platelet aggregation.


Increased LDL-R expression and uptake of plasma LDL
Acetyl CoA + Acetoacetyl CoA
Statins
HMG CoA
HMG CoA reductase
Mevalonate
5-pyrophosphomevalonate
Isopentylpyrophosphate
3,3-dimethylallylpyrophosphate
Geranylpyrophosphate
Farnesylpyrophosphate
Isoprenoids
Squalene
Lanosterol
Cholesterol
Increased LDL receptor expression
↓ Cholesterol
Protease activation
SREBP (inactive)
SREBP (active)
Nucleus
LDL-R gene
SRE

Statins

Toxicity:

Toxicity is dose-related, associated with advanced age, hepatic or renal dysfunction, small body size, associated diseases, hypothyroidism and concomitant drugs.

- **Elevation of transaminases, intermittent and not associated with strong evidence of liver failure.**
- **Elevation of creatine kinase (CK) activity.**
- **Rhabdomyolysis, causing myoglobinuria and renal injury and failure or even death. It is extremely rare (less than one in 10,000 people).**
- **Lupus-like disorder and peripheral neuropathy.**

Pharmacogenetics of Statins

- Statins are good example of the principles of pharmacogenetics. This is because they are metabolized by the CYP enzyme system, which is a subject to individual genetic differences. These differences will be exhibited for their:
- Therapeutic Response
- Side Effects.

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.
- Action is complementary to statins(60% reduction in LDL-C).
- Can cause allergic reactions, reversible impairment of liver function tests and myopathy.

Inhibitors of Cholesteryl Ester Transfer Protein

- Torcetrapib.
- JTT-705.

- CETP is a plasma glycoprotein synthesized by the liver that mediates the transfer of cholesteryl esters from the larger subfractions of HDL to triglyceride-rich lipoproteins and LDL in exchange for a molecule of triglyceride.
- Can increase HDL levels by 45-106% in humans.