Antihyperlipidemic Drugs

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Antihyperlipidemic Drugs

Hyperlipidemias.

Hyperlipoproteinemias.

Hyperlipemia.

Dyslipidemias

Hypercholestrolemia.

CHD Risk Factors ranking - PROCAM Study

Risk factor	Relative risk	P Value
Smoking	2.3	0.001
LDL cholesterol (mg%)		
> 100 but < 160	1.9	0.01
> 160	4.3	0.001
Hypertension (SBP > 140; DBP > 90)	1.8	0.001
HDL cholesterol (mg%)		
40 to 55	1.7	0.01
< 40	2.7	0.001
Triglycerides (mg%)		
105- 167	1.6	0.01
>167	2.6	0.001
Fasting blood glucose (mg%)		
110 - 126	1.4	0.05
> 126	1.9	0.01
Family history of MI	1.4	0.05

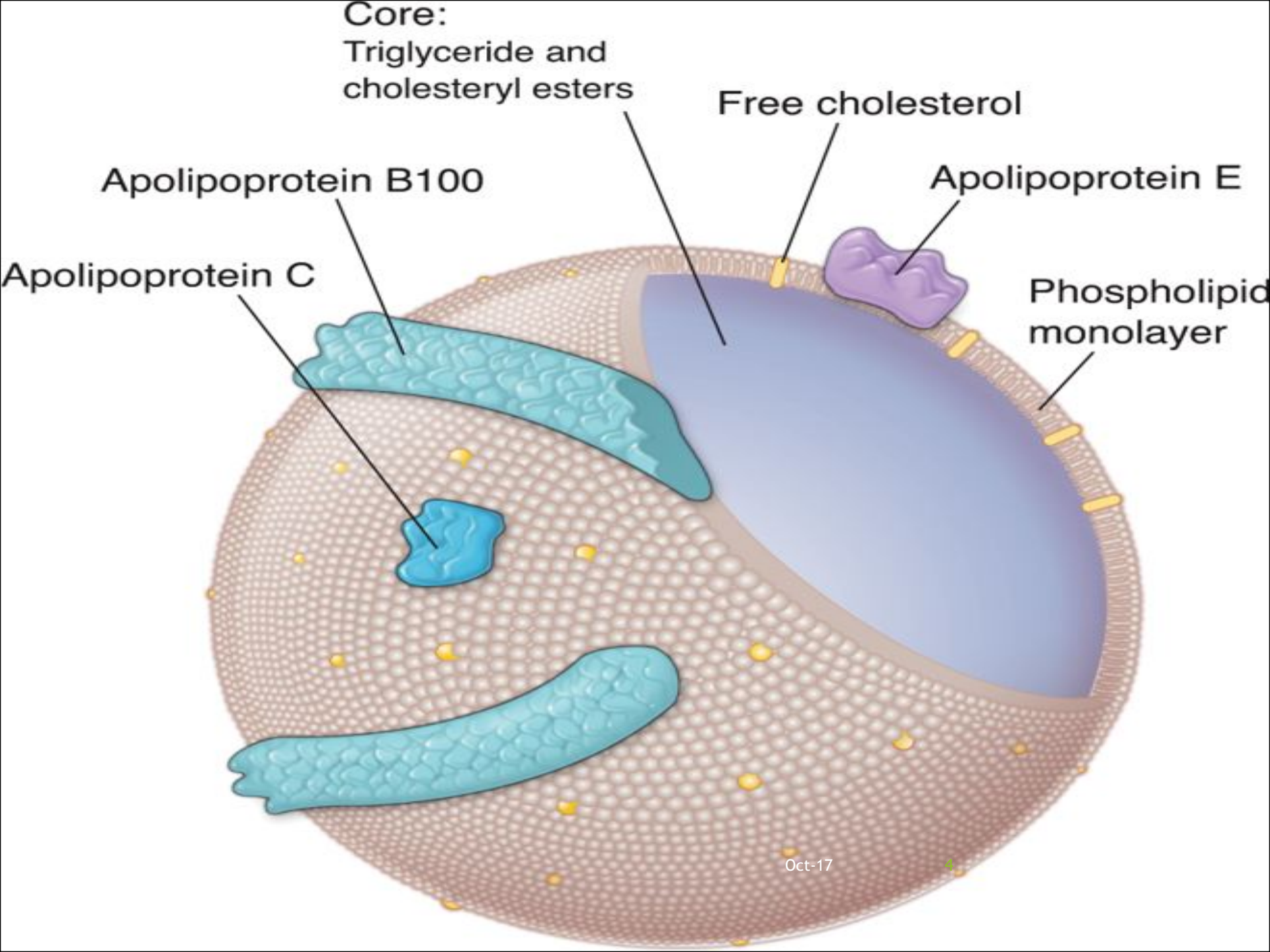

Core:
Triglyceride and
cholesteryl esters
Free cholesterol
Apolipoprotein B100
Apolipoprotein E
Apolipoprotein C
Phospholipid
monolayer

TABLE 35–1 National Cholesterol Education Program: Adult Treatment Guidelines (2001).

	Desirable	Borderline to High[1]	High
Total cholesterol	< 200 (5.2)[2]	200–239 (5.2–6.2)[2]	> 240 (6.2)[2]
LDL cholesterol	< 130 (3.4)[3]	130–159 (3.4–4.1)	> 160 (4.1)
HDL cholesterol			> 60 (1.55)
Men	> 40 (1.04)		
Women	> 50 (1.30)		
Triglycerides	< 120 (1.4)	120–199 (1.4–2.3)	> 200 (2.3)

[1]Consider as high if coronary disease or more than two risk factors are present.

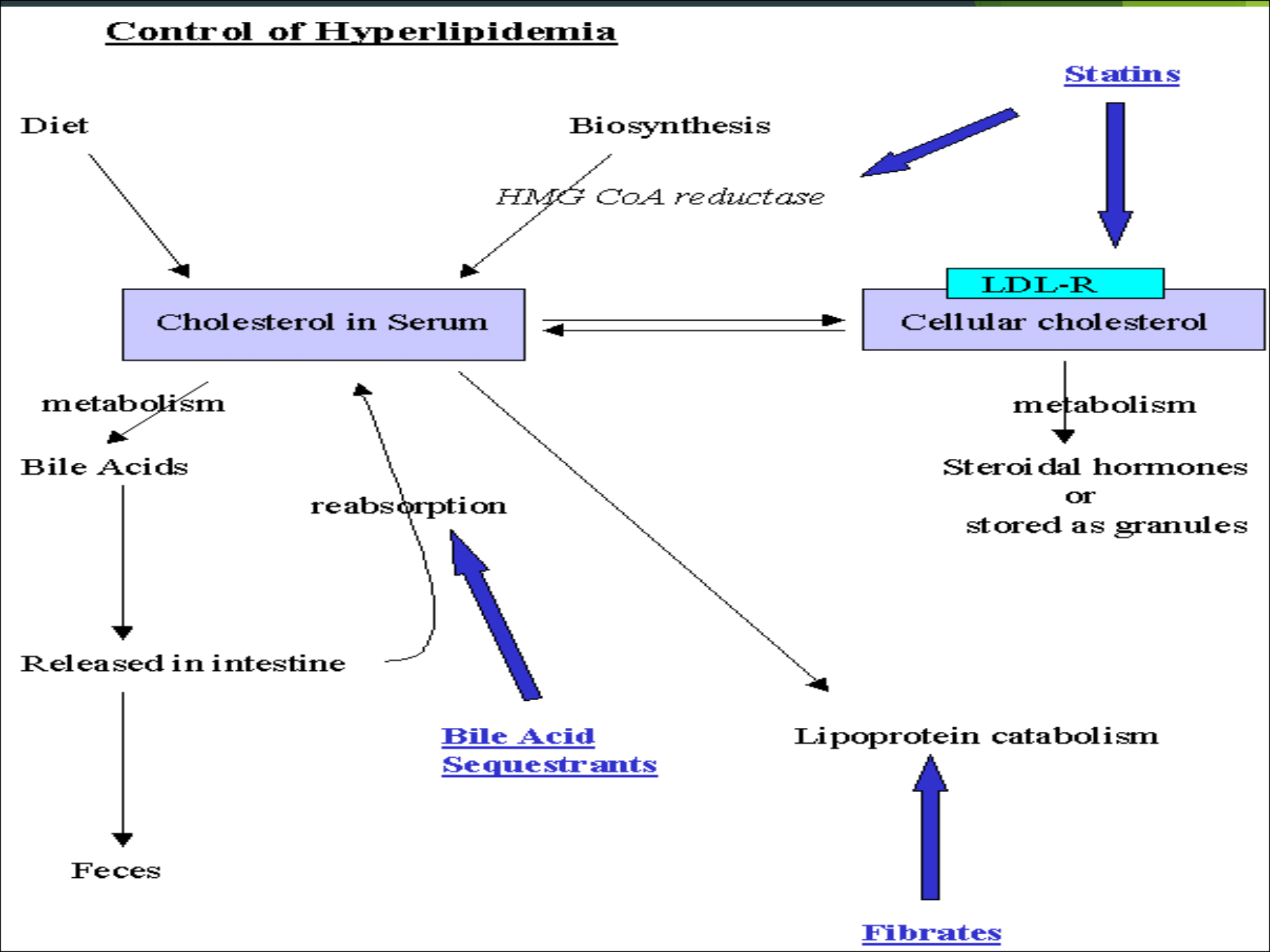
[2]mg/dL (mmol/L).

[3]Optimal level is < 100 (2.6); if known atherosclerotic disease, goal is 60–70 mg/dL.

TABLE 35–2 The primary hyperlipoproteinemias and their treatment.

Disorder	Manifestations	Diet + Single Drug[1]	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase or cofactor deficiency; others)	Chylomicrons, VLDL increased	Dietary management (omega-3 fatty acids, niacin, or fibrate)	Niacin plus fibrate
Familial hypertriglyceridemia- Severe	VLDL, chylomicrons increased	Omega-3 fatty acids, niacin, or fibrate	Niacin plus fibrate
Moderate	VLDL increased; chylomicrons may be increased	Omega-3 fatty acids, niacin, or fibrate	Niacin plus fibrate
Familial combined hyperlipoproteinemia	VLDL predominantly increased	Omega-3 fatty acids, niacin, fibrate, or reductase inhibitor	Two or three of the individual drugs
	LDL predominantly increased	Niacin, reductase inhibitor, or ezetimibe	Two or three of the individual drugs
	VLDL, LDL increased	Omega-3 fatty acids, niacin, or reductase inhibitor	Niacin or fibrate plus reductase inhibitor[2]
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased	Omega-3 fatty acids, fibrate, or niacin	Fibrate plus niacin, or either plus reductase inhibitor
Familial hypercholesterolemia			
Heterozygous	LDL increased	Reductase inhibitor, resin, niacin, or ezetimibe	Two or three of the individual drugs
Homozygous	LDL increased	Niacin, atorvastatin, rosuvastatin, or ezetimibe	Niacin plus reductase inhibitor plus ezetimibe
Familial ligand-defective apo B	LDL increased	Niacin, reductase inhibitor, or ezetimibe	Niacin plus reductase inhibitor or ezetimibe
Lp(a) hyperlipoproteinemia	Lp(a) increased	Niacin	

[1]Single-drug therapy with marine omega-3 dietary supplement should be evaluated before drug combinations are used.


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

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 only 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.

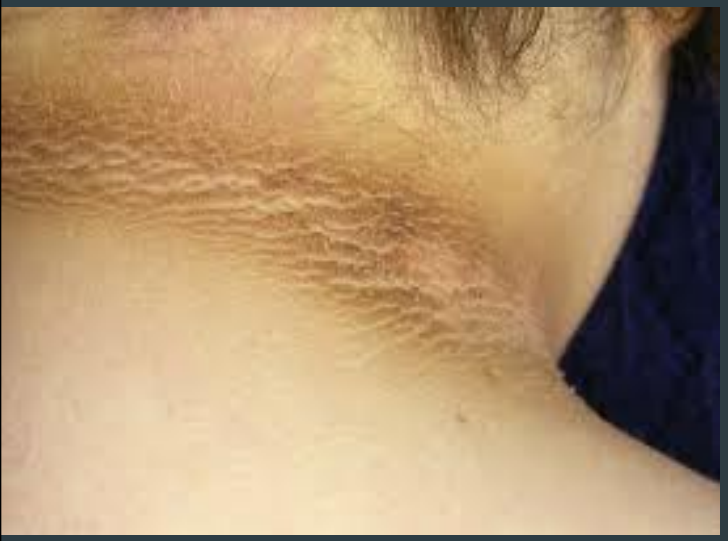
- Reduction of triglyceride synthesis reduces hepatic VLDL and consequently LDL.
- Inhibits intracellular lipase in adipose tissues leading to decreased FFA flux to the liver.
- Completely absorbed, peaks within 1hr, half-life is about 1 hr, so need to be given by twice or thrice daily administration.

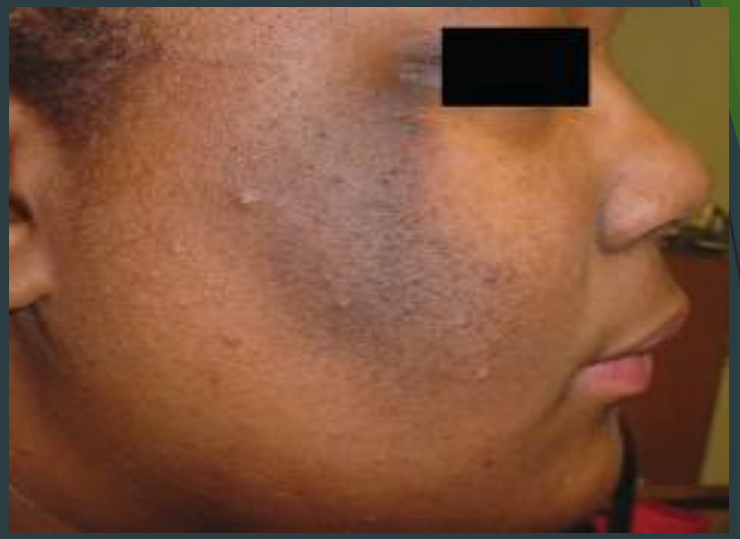
Niacin

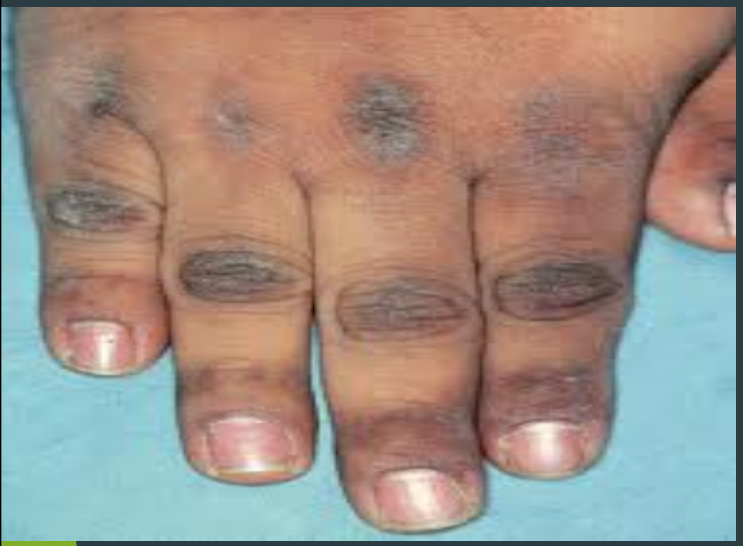
Toxicity:

- Harmless cutaneous vasodilation and sensation of warmth, can be prevented by NSAIDS.
- Pruritus, rashes, dry skin or mucus membranes (*acanthosis nigricans*).
- 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

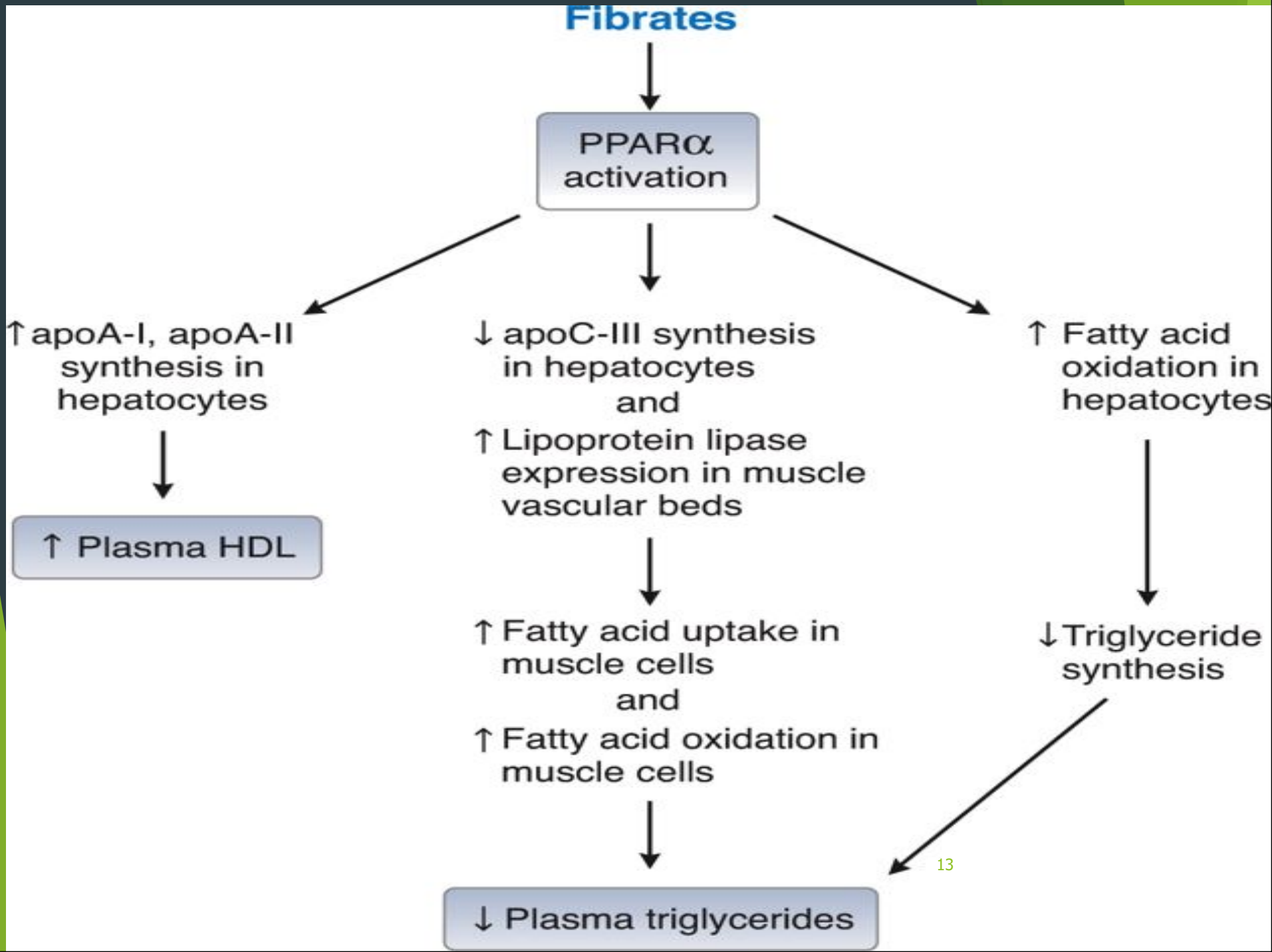






Fibrates or Fibric Acid Derivatives or "PPARs Activators"

- Clofibrate, 1962-1987.
- Gemfobrozil.
- Fenofibrate.
- Bezafibrate.
- Activate PPAR- α (Peroxisome Proliferator Activated Receptor- α) which stimulates fatty acid oxidation, increase LPL synthesis, and reduce expression of apoC-III, and increase apoA-I and apoA-II expression.
- Increase lipolysis of lipoprotein triglyceride via LPL.
- Decrease levels of VLDL and LDL.
- Moderately increase HDL.
- Also have anticoagulant and fibrinolytic activities.
- Drugs of choice in severe hypertriglyceridemia.


Fibrates
PPARα activation
↑ apoA-I, apoA-II synthesis in hepatocytes
↓ apoC-III synthesis in hepatocytes and ↑ Lipoprotein lipase expression in muscle vascular beds
↑ Fatty acid oxidation in hepatocytes
↑ Plasma HDL
↑ Fatty acid uptake in muscle cells and ↑ Fatty acid oxidation in muscle cells
↓ 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.
- Interact with statins, levels of both drugs will increase.
- Used with caution in renal failure.
- 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 lowered 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.

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"

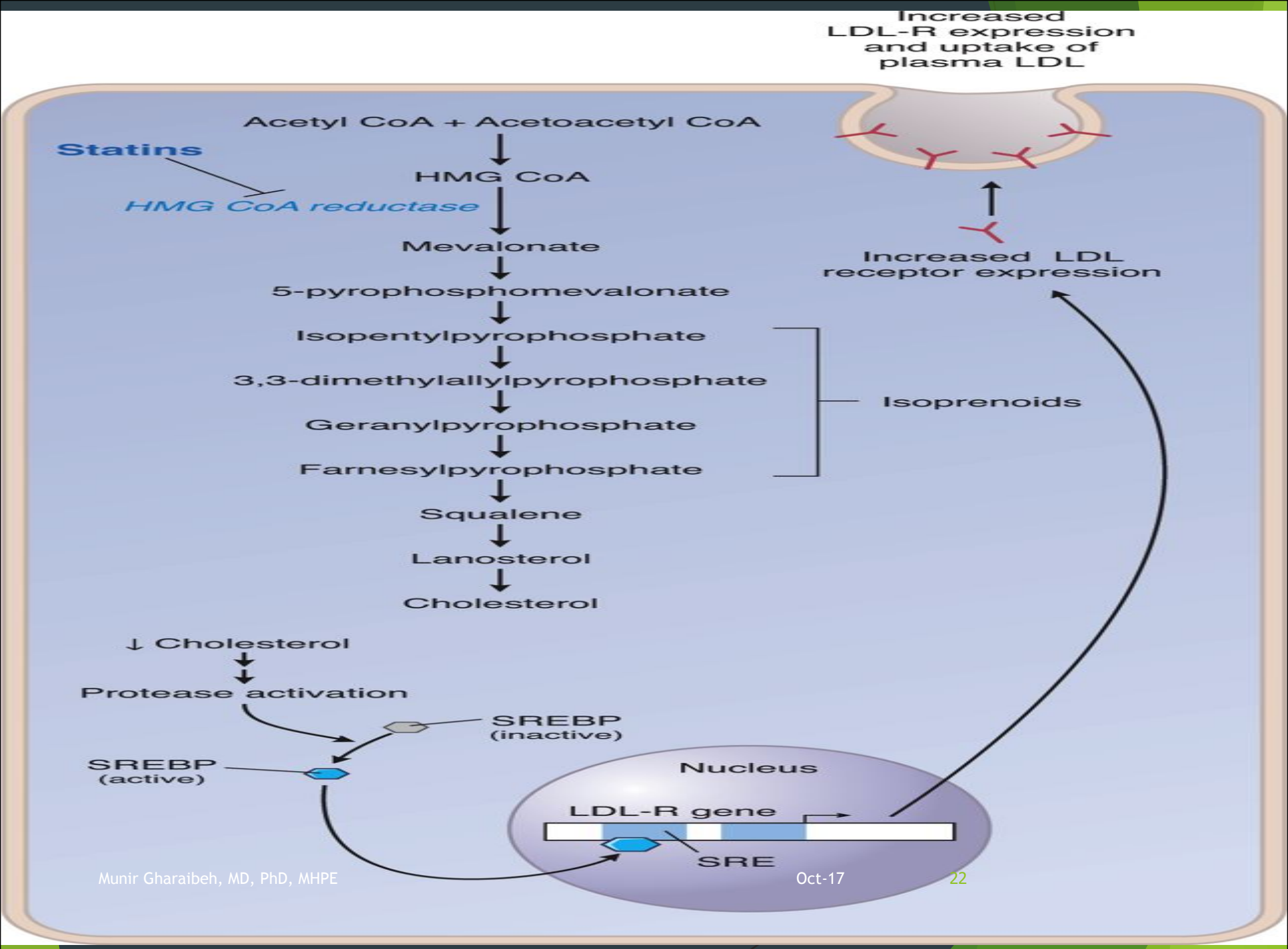
- Most commonly prescribed drugs worldwide.
- Isolated from a mold *Penicillium citrinum*, in 1976.
- Most effective drugs in lowering LDL.

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.
- Also can reduce LDL levels by enhancing the removal of LDL precursors (VLDL and IDL) and by decreasing hepatic VLDL production.

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, this is 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.

Less Important Side Effects to Statins

- Headache
- Difficulty sleeping
- Flushing of the skin
- Muscle aches, tenderness, or weakness (myalgia)
- Drowsiness
- Dizziness
- Nausea and/or vomiting
- Abdominal cramping and/or pain
- Bloating and/or gas
- Diarrhea
- Constipation
- Rash
- Statins also carry warnings that memory loss, mental confusion, high blood sugar, and type 2 diabetes are possible side effects. It is important to remember that statins may also interact with other medications.

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

- **Ezetimib:**
- Can reduce LDL.
- Inhibitor of NPC1L1, a specific transport process in jejunal brush border.
- Reduces cholesterol absorption and reabsorption by 54%, precipitating a compensatory increase in cholesterol synthesis.
- Reduces cholesterol 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%).
- Action is complementary to statins(60% reuction in LDL-C)..
- Can cause allergic reactions, reversible impairment of liver function tests and myopathy.

Inhibitors of Cholesteryl Ester Transfer Protein

- **Torcetrapib:** withdrawn
- **Anacetrapib.**
- **Dalcetrapib**

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