Antihyperlipidemic Drugs

Hyperlipidemias.

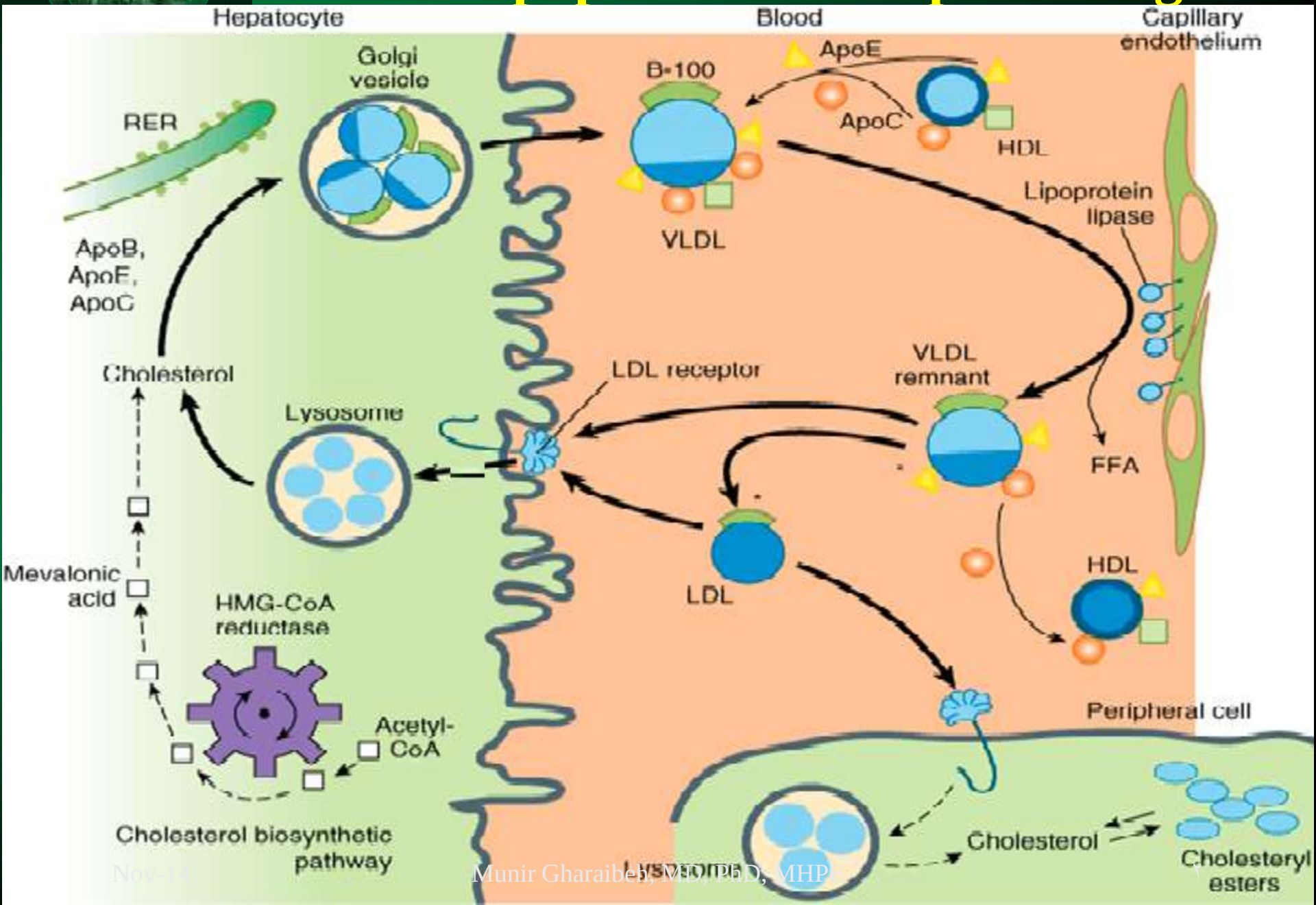
Hyperlipoproteinemias.

Hyperlipemia.

Hypercholestrolemia.

Direct relationship with acute pancreatitis and atherosclerosis.

Metabolism of Lipoproteins of Hepatic Origin



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	B100, E, CI, CII, CIII	Uptake: liver (apoB100 via LDL receptor)
HDL	Liver, intestine, and plasma	35% Phospholipid 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

APOLIPOPROTEIN	SITE OF SYNTHESIS	LIPOPROTEINS	FUNCTION
B48	Intestine	Chylomicrons and remnants	Structural protein for chylomicrons
B100	Liver	VLDL, IDL, LDL	Ligand for LDL receptor (LDL-R)
E	Liver Brain	Chylomicrons and remnants, VLDL, IDL, some HDL	Ligand for LDL-R and remnant receptor (LRP)
CI	Liver	Chylomicrons VLDL, IDL, LDL, HDL	Activates LCAT Modulates apoE activity Blocks uptake by LDL receptors. Small amounts on IDL and LDL. Function on HDL is unknown.
CII	Liver	Chylomicrons VLDL, IDL, LDL, HDL	Required cofactor for lipoprotein lipase (LPL). Blocks uptake by LDL receptors. Small amounts on IDL and LDL. Function on HDL unknown.
CIII	Liver	Chylomicrons VLDL, IDL, LDL, HDL	Inhibits LPL. Blocks uptake by LDL receptors. Small amounts on IDL and LDL. Function on HDL unknown.
AI	Liver Intestine	Chylomicrons HDL	Activates LCAT. Activates reverse cholesterol transport by SR-B1. Required for HDL structure. Inhibits apoE-receptor association
AII	Liver	HDL; small amounts on VLDL	May inhibit plasminogen → plasmin. Blocks catabolism by LDL receptors
apo(a)	Liver	Lp(a)	

The apoliprotein and lipid composition of the circulating lipoproteins

Lipoprotein	Major associated apolipoproteins	Cholesterol (%)	Triglyceride (%)
Chylomicrons	Apo A/apo C/apo B_{48}	3	90
VLDL	Apo C/apo B_{100}/apo E	20	50
LDL	Apo B_{100}	50	7
HDL	Apo A	40	6

Note: the balance of lipid content of the lipoprotein consists of phospholipids.

TABLE 22-3 Genetic Causes of Dyslipidemia

DISEASE	CHARACTERISTIC LIPID PROFILE	ESTIMATED PREVALENCE	ETIOLOGY
Primary Hypercholesterolemia			
Familial hypercholesterolemia	↑↑ LDL	1:500 (heterozygote) 1:1 million (homozygote)	↓/No functional LDL-R expression
Familial defective apoB100	↑ LDL	1:1,000	↓ Binding of apoB100 to LDL-R
Polygenic hypercholesterolemia	↑ Cholesterol	Common	Unknown. Variants in genes for lipid metabolism increasing susceptibility to diet
Primary Hypertriglyceridemia			
Familial hypertriglyceridemia	↑ TGs, ↑ VLDL, ↓ HDL	Common	Overproduction and impaired catabolism of triglyceride-rich VLDL
Familial lipoprotein lipase deficiency	↑↑ TGs	1:1 million	Defect in lipoprotein lipase
ApoCII deficiency	↑↑ TGs	1:1 million	Defect in apoCII
Mixed Hyperlipidemia			
Familial combined hyperlipidemia	↑ LDL, ↑TGs, sometimes ↓ HDL	1:100	Unknown. Dominant inheritance.
Familial dysbetalipoproteinemia	↑ Cholesterol, ↑ TGs, ↓ LDL, ↑ remnants	1:10,000	Inheritance of apoE2 isoform
Disorders of HDL Metabolism			
Polygenic low HDL	↓ HDL	Common	Overweight, diabetes, lack of exercise, high carbohydrate diet
Familial hypoalphalipoproteinemia	↓ HDL	1:400	Unknown. Dominant inheritance
Familial apoAI deficiency	↓ HDL	Rare	ApoAI
Tangier disease	↓↓ HDL	Rare	ABCA1 defect
LCAT deficiency	↓ HDL	Rare	LCAT
Fisheye disease	↓ HDL	Rare	Low activity of LCAT
CETP deficiency	↑ HDL	Rare	CETP

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	

Table 20-1. Classification of Hyperlipoproteinemias

Type	Lipoprotein increased	Main plasma lipids increased	Classification	Incidence	Relationship to increased CHD[1]
I	Chylomicrons	Triglyceride	Familial (exogenous) hypertriglyceridemia (lipoprotein lipase deficiency)	1:10	None
IIa	LDL	Cholesterol	Familial hypercholesterolemia (LDL receptor defects)	1:500	Positive
			Multifactorial hypercholesterolemia	1:4[2]	
IIb	LDL + VLDL	Cholesterol and triglyceride	Familial multiple-type or combined hyperlipoproteinemia	1:300	Positive
III	VLDL (IDL)	Cholesterol and triglyceride	Familial dysbetalipoproteinemia	?	Positive
IV	VLDL	Triglyceride	Familial (endogenous) hypertriglyceridemia	1:500	Questionable[3]
V	VLDL and chylomicrons	Triglyceride	Mixed hypertriglyceride	?	Questionable

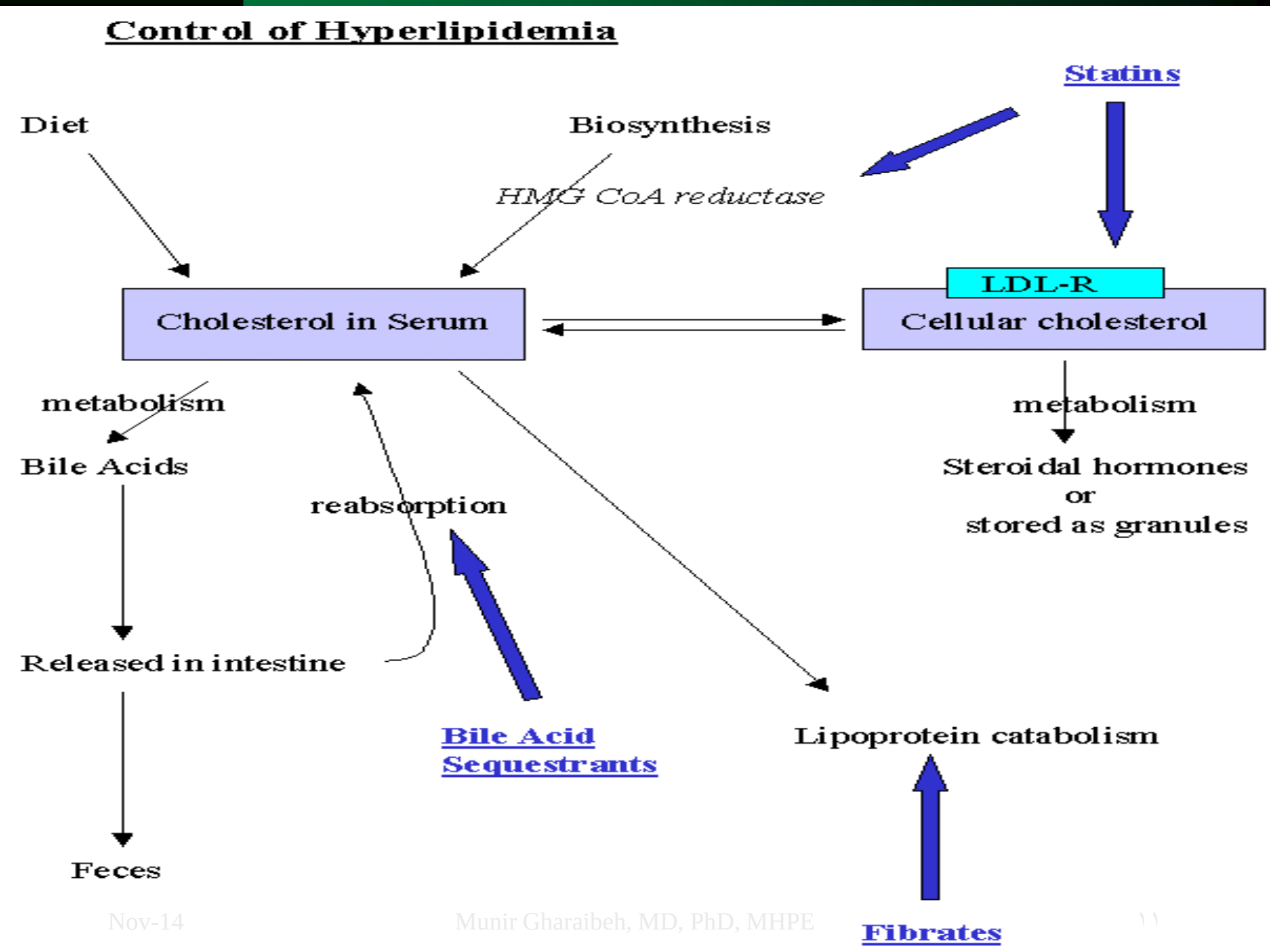
Table 31–5 Risk Factors for Coronary Heart Disease[a]
Age
Male >45 years of age or female >55 years of age
Family history of premature CHD
A first-degree relative (male <55 years of age or female <65 years of age when the first CHD clinical event occurs)
Current cigarette smoking
Defined as smoking within the preceding 30 days
Hypertension
Blood pressure ≥140/90 or use of antihypertensive medication, irrespective of blood pressure
Low HDL-C
<40 mg/dL (consider <50 mg/dL as "low" for women)
Obesity[b]
Body mass index >25 kg/m^2 and waist circumference >40 inches (men) or >35 inches (women)
Type 2 diabetes mellitus

TABLE 22-5 National Cholesterol Education Program Adult Treatment Panel III Guidelines

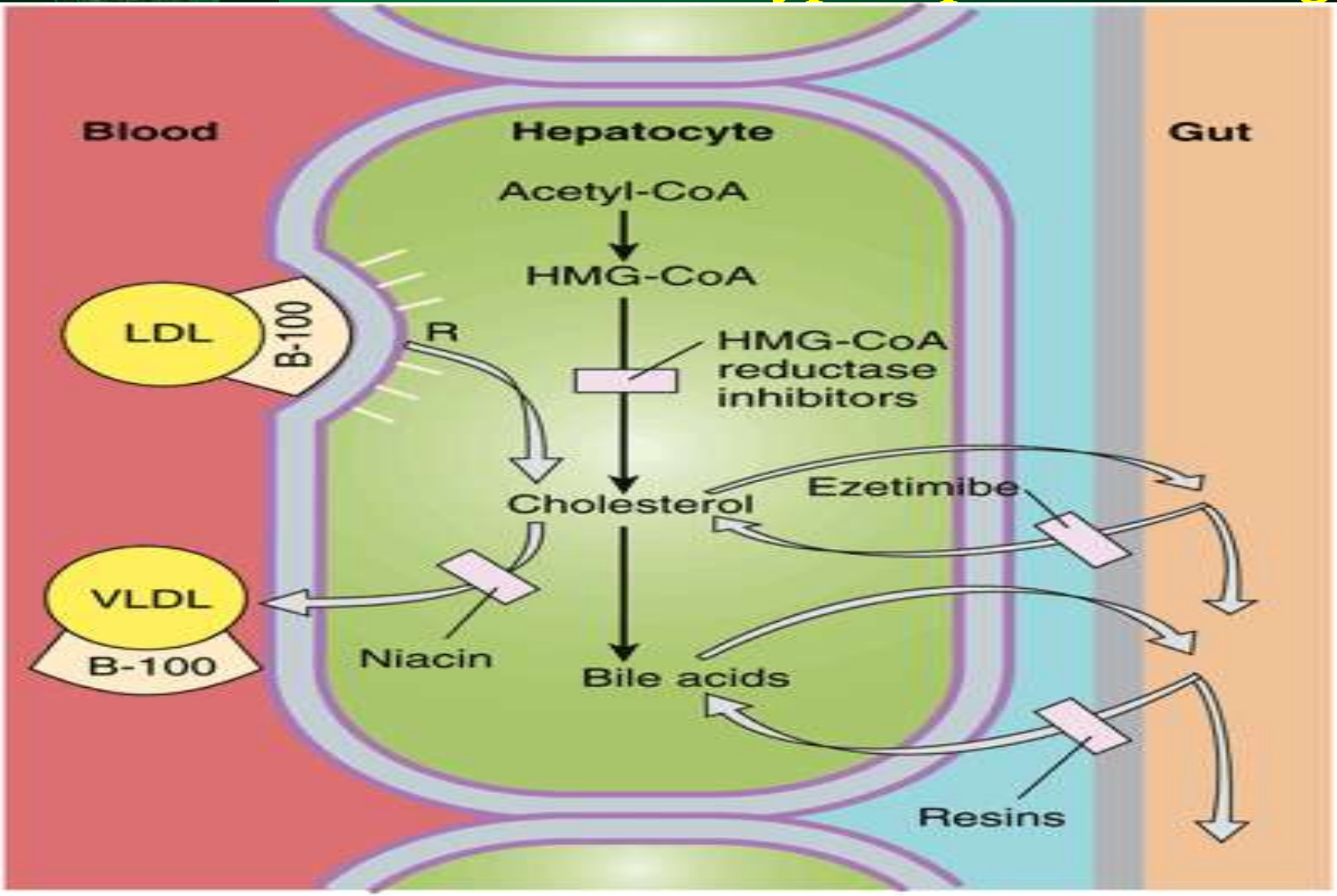
RISK CATEGORY	INITIATION LDL LEVEL FOR DRUG TREATMENT	LDL GOAL
High: CHD or CHD risk equivalents (10-year risk > 20%)	130 mg/dL (100 mg/dl optional)	<100 mg/dL
Moderate: 10-yr risk 10%–20%	130 mg/dL	<130 mg/dL
Moderate: 10-yr risk <10% and 2 or more risk factors	160 mg/dL	<130 mg/dL
Low: 0–1 risk factor	190 mg/dL (160 mg/dl optional)	<160 mg/dL

The decision to initiate lipid-lowering therapy depends on the risk category for cardiovascular disease or equivalents (peripheral vascular disease, abdominal aortic aneurysm, cerebrovascular disease, or diabetes). A patient with documented cardiovascular disease or equivalent risk (>20% in 10 years) should have target LDL levels <100 mg/dL. A patient with two or more risk factors (cigarette smoking, hypertension, low HDL, positive family history of CAD, male >45 years, female >55 years) has moderate risk of mortality from cardiovascular disease, and LDL levels should be modified to <130 mg/dL. Subtract one risk factor when HDL is high (>60 mg/dL). Patients with 0–1 risk factors have a low risk of cardiovascular disease, and their LDL levels should be maintained at <160 mg/dL with either diet or drug therapy (drug therapy is indicated by an LDL level, after nonpharmacologic therapy of >190 mg/dL).

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, 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:

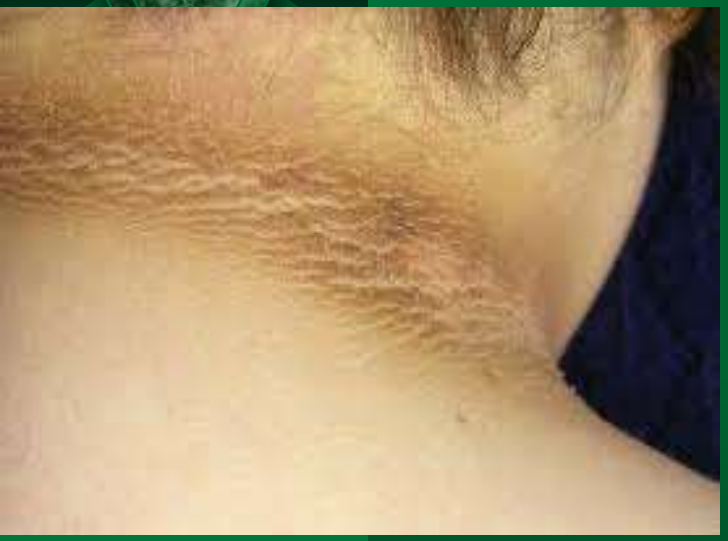
- In adipose tissue, inhibits the lipolysis of triglycerides by inhibiting adipocyte adenylyl cyclase, which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis.
- May also inhibit a rate –limiting enzyme of triglyceride synthesis, diacylglycerol acetyltransferase 2.
- 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.

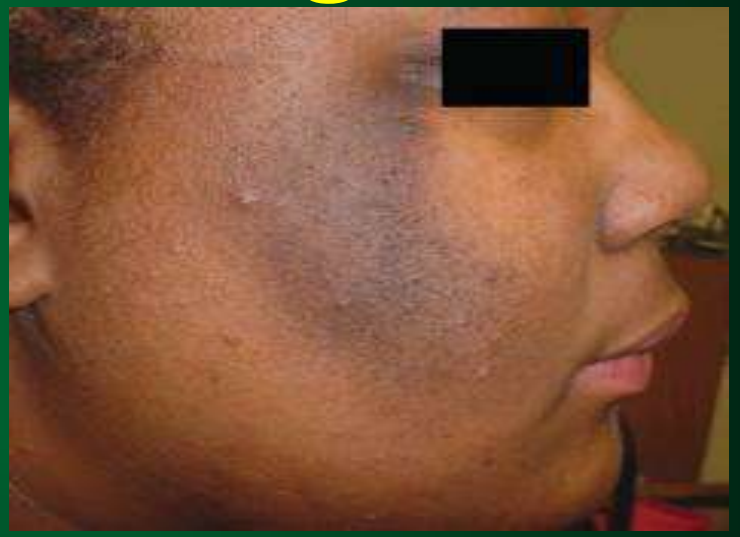
Niacin

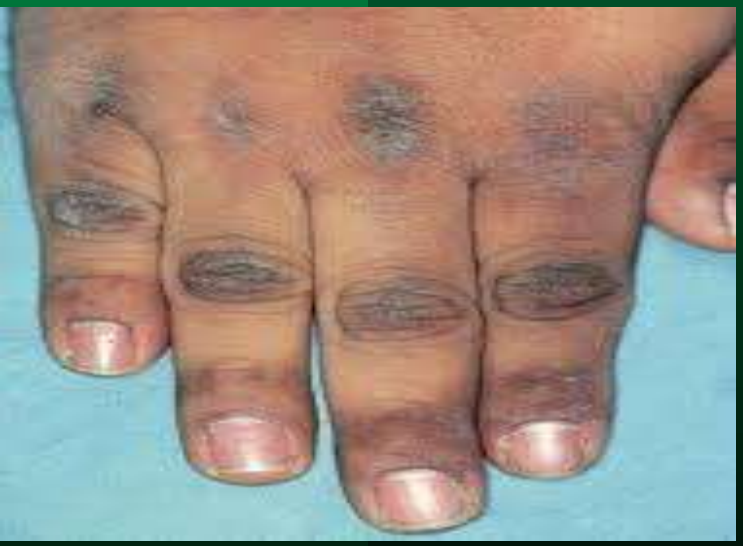
Toxicity:

- Harmless cutaneous vasodilation and sensation of warmth.
- 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

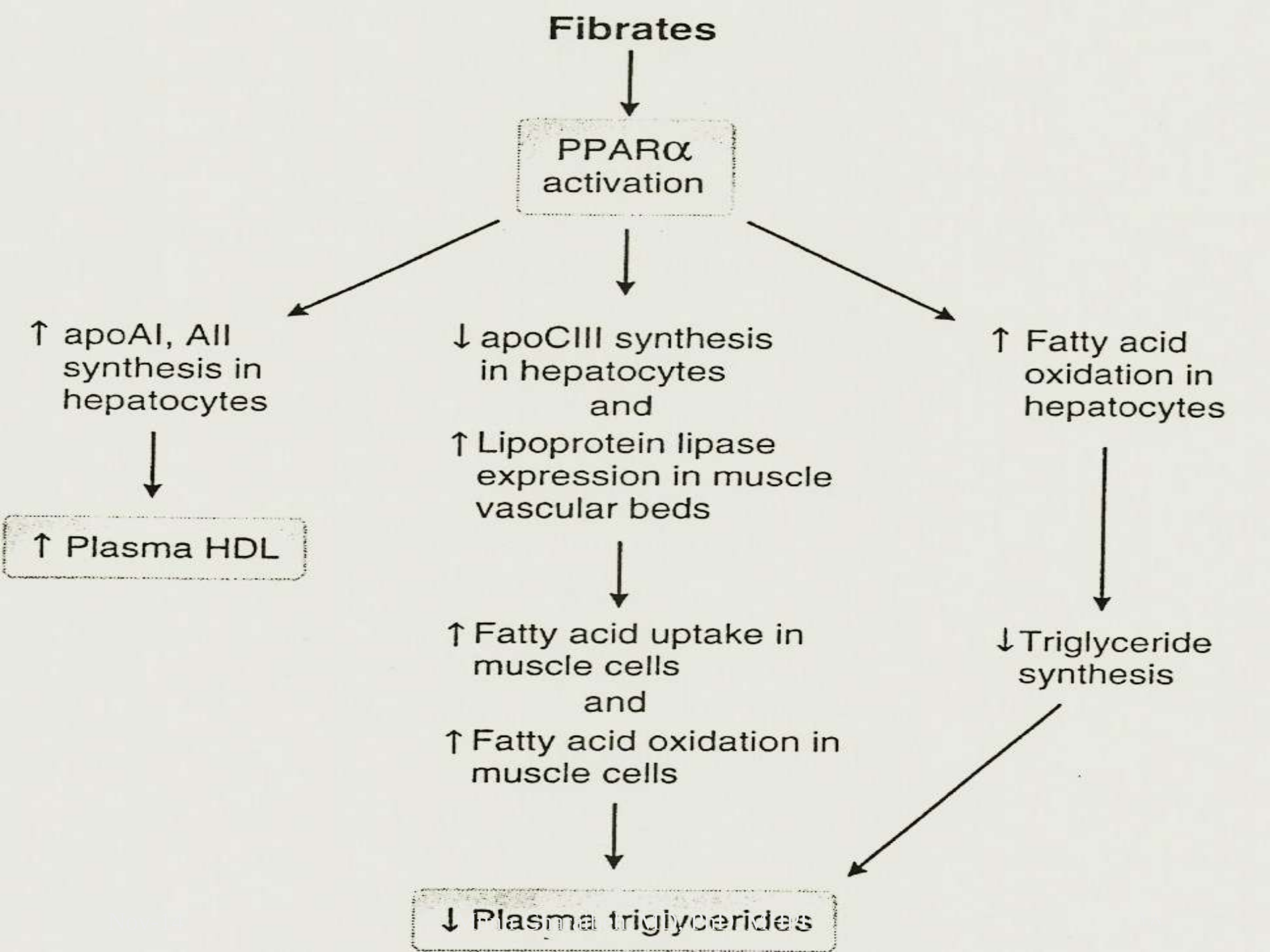




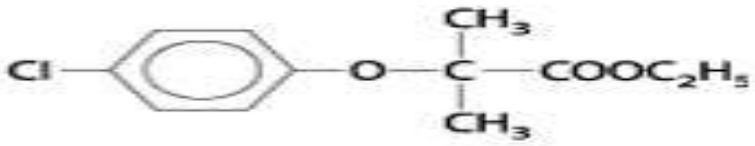


Fibrates or Fibric Acid Derivatives or "PPARs Activators"

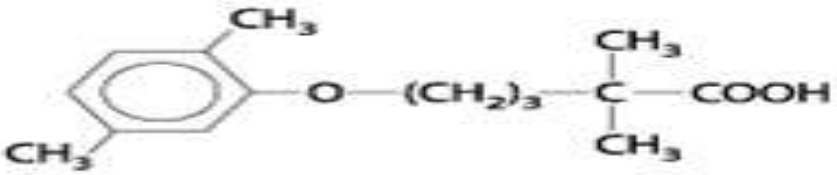
- Clofibrate, 1962-1987.
- Gemfobrozil.
- Fenofibrate.
- Bezafibrate.
- Work on PPAR- α (Peroxisome Proliferator Activated Receptor- α) which stimulates fatty acid oxidation, increases LPL synthesis, and reduces expression of apo C-III, and increases apoA-I and apoA-II expression.
- Increase lipolysis 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
↑ 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

CLOFIBRATE

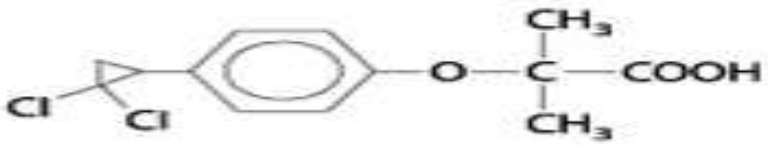


GEMFIBROZIL

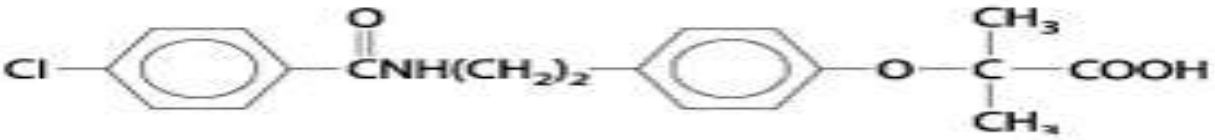


FENOFIBRATE

CIPROFIBRATE



BEZAFIBRATE



Fibrates

Toxicity:

- Rashes, urticaria, hair loss, headache, GIT symptoms, impotence, and anemia.
- **Myalgia, fatigue, myopathy and rhabdomyolysis.**

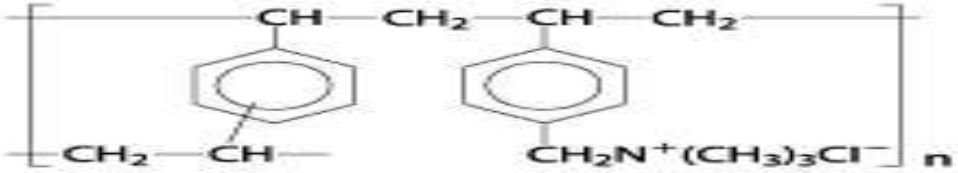
(Breakdown of muscle fibers resulting in the release of muscle fiber contents (myoglobin) into the blood stream).

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

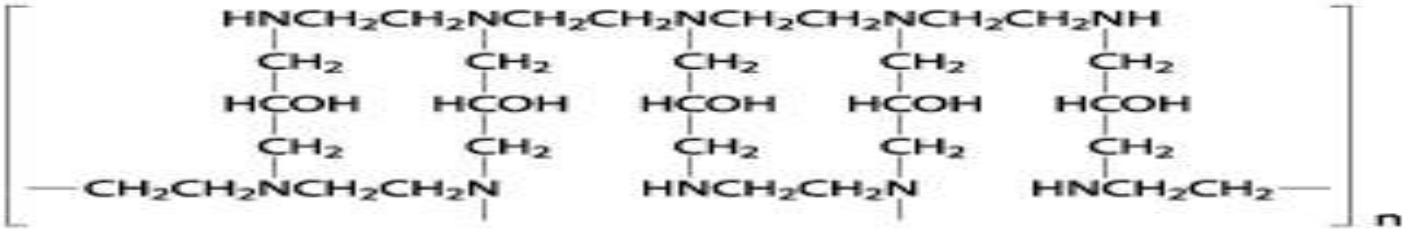
Bile Acid –Binding Resins

- 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-CoA reductase.
- May increase triglyceride levels.

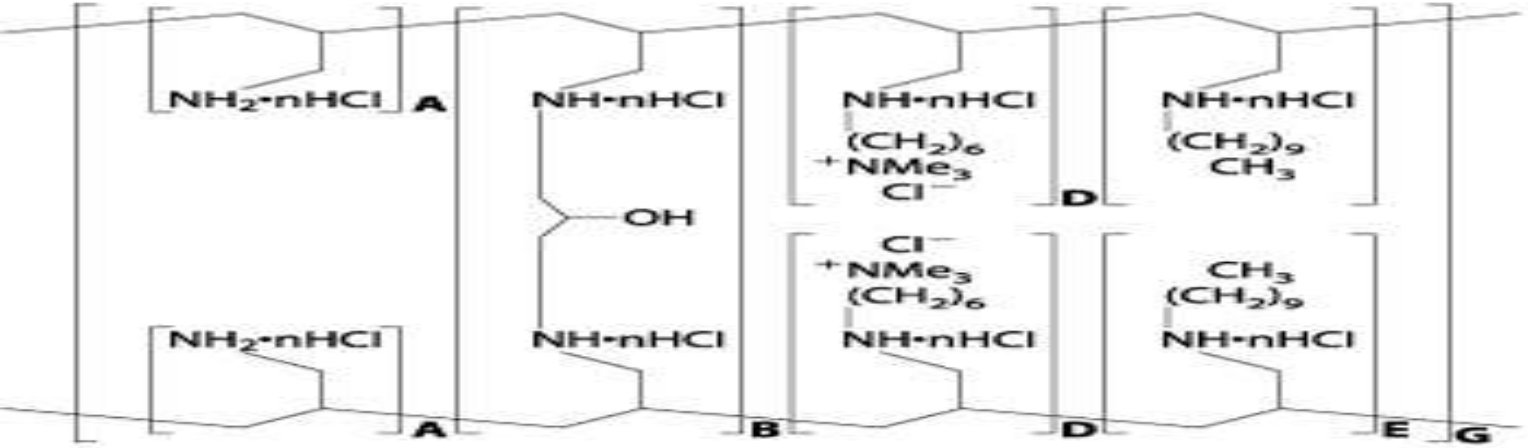
Cholestyramine



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:

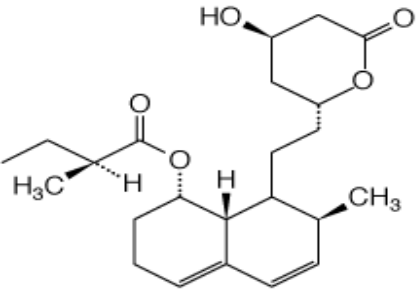
Probably the safest drugs, since they are not absorbed from the intestine because of their large size. Maximal doses are effective but cause side effects.

- 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)..

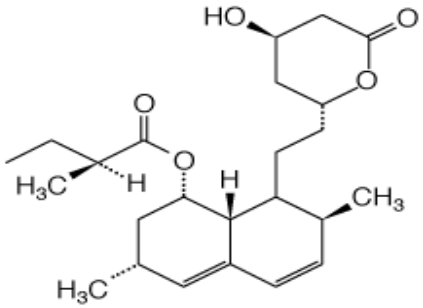
Competitive Inhibitors of HMG-CoA Reductase "Statins"

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

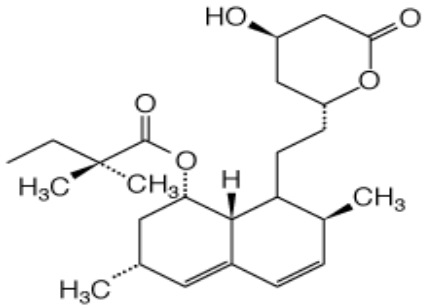
MEVASTATIN



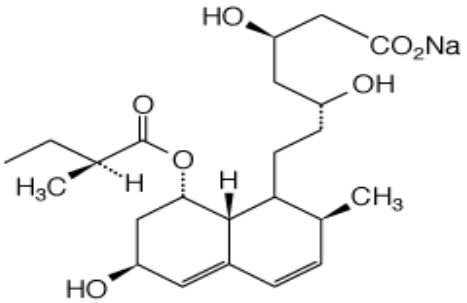
LOVASTATIN



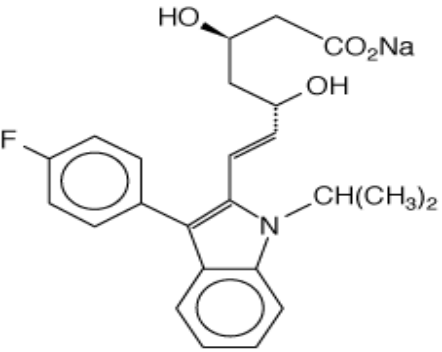
SIMVASTATIN



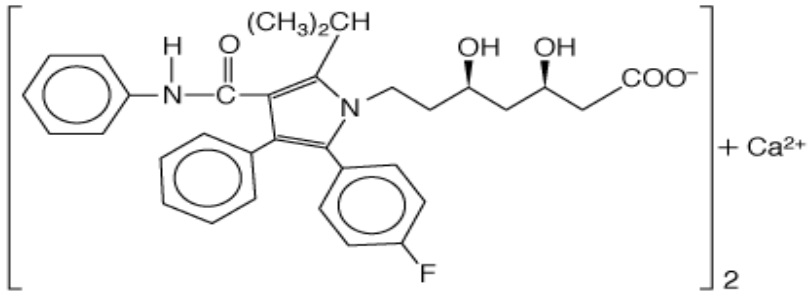
PRAVASTATIN



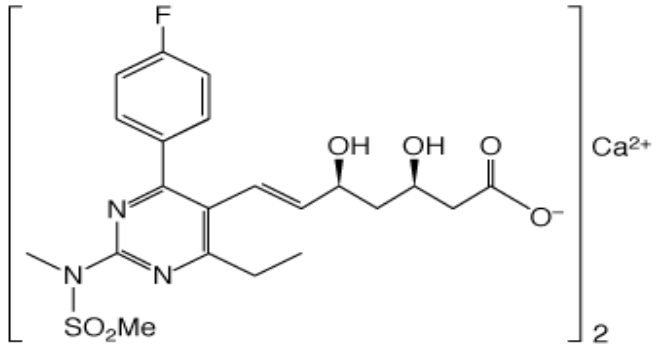
FLUVASTATIN



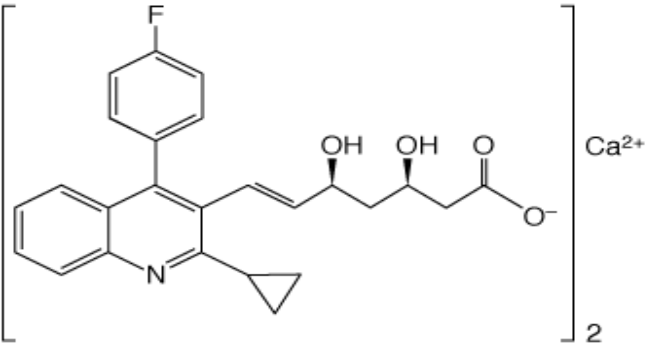
ATORVASTATIN



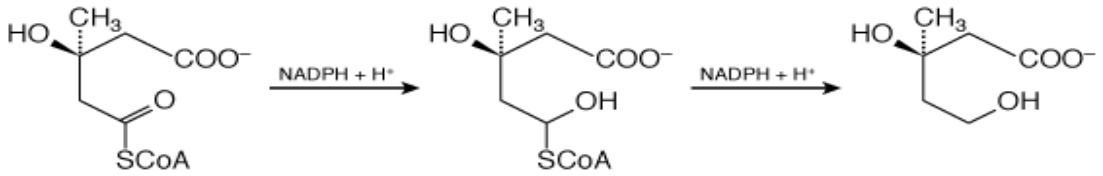
ROSUVASTATIN



PITAVASTATIN



Reaction Catalyzed by HMG-CoA Reductase



HMG-CoA intermediate MEVALONATE

Competitive Inhibitors of HMG-CoA Reductase "Statins"

- Originally isolated from a mold *Penicilliun citrinum*, 1976.
- Modified derivatives and distinct synthetic compounds.
- Most effective in lowering LDL.

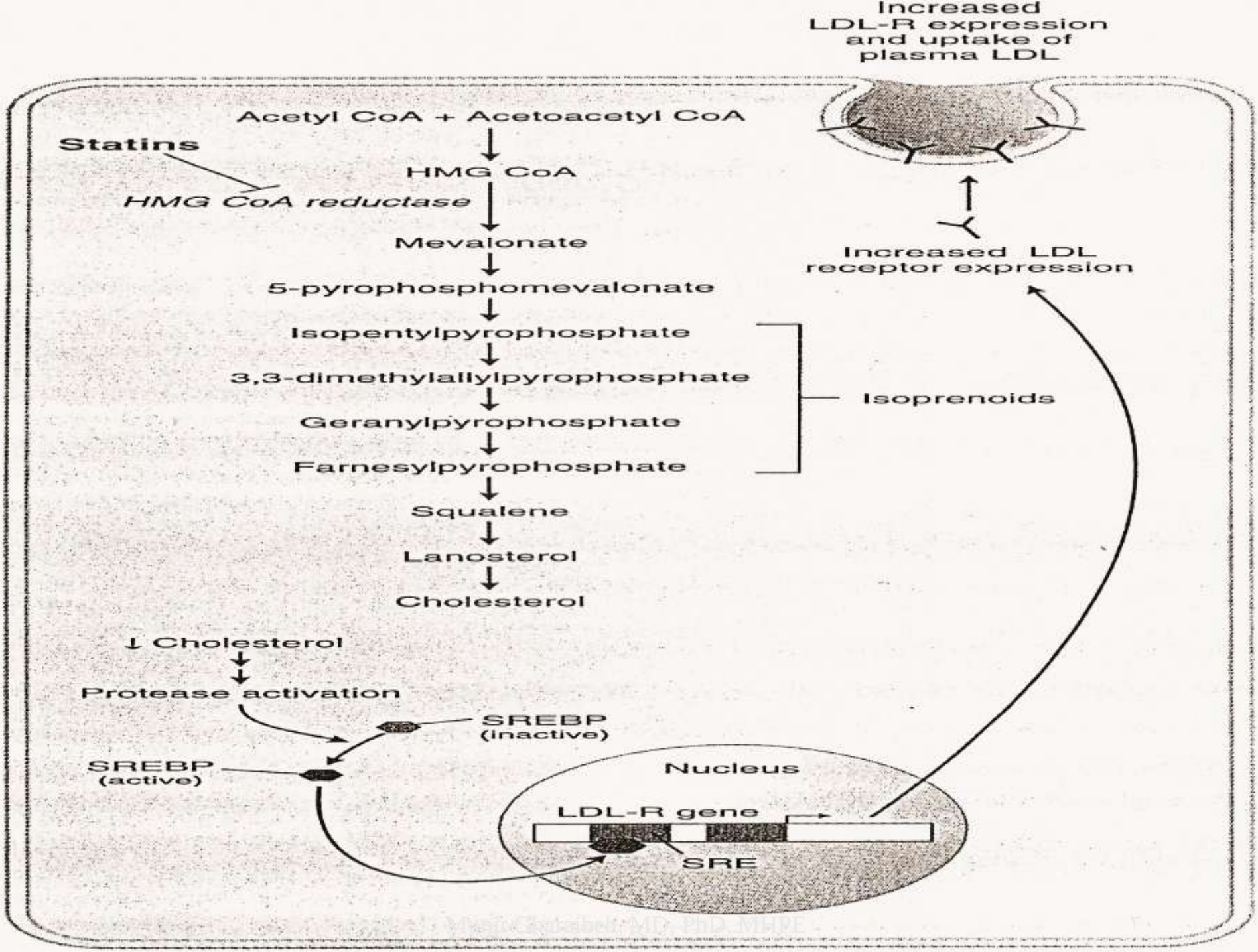
Statins

- 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.

- 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, 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.**

Common 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's important to remember that statins may also interact with other medications you take.

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.

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.