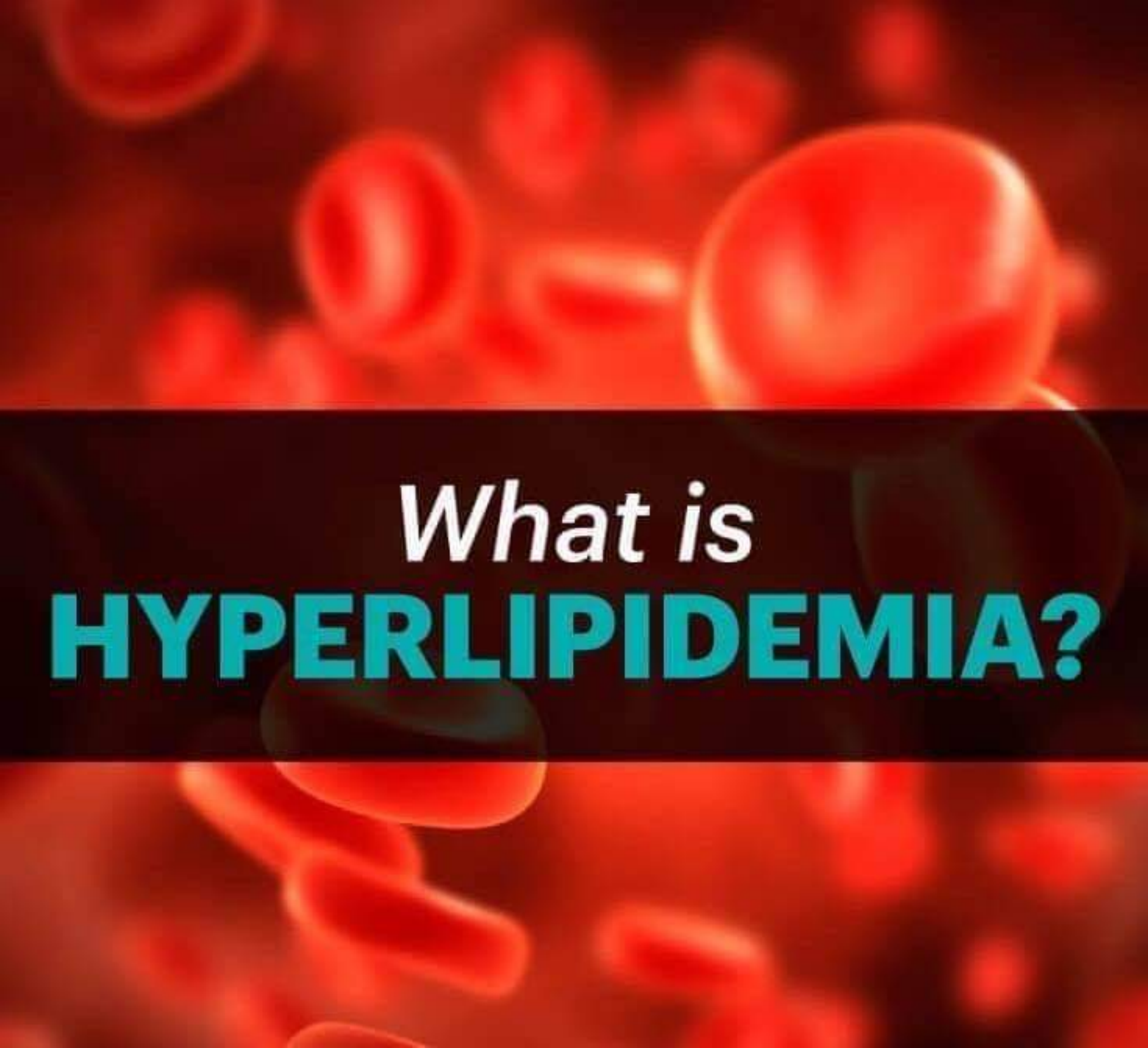

What is
HYPERLIPIDEMIA?

What is Hyperlipidemia?

Hyperlipidemia a broad term, also called hyperlipo-proteinemia, is a common disorder in developed countries and is the major cause of coronary heart disease.

It results from abnormalities in lipid metabolism or plasma lipid transport or a disorder in the synthesis and degradation of plasma lipoproteins

Causes of Hyperlipidemia

- Mostly hyperlipidemia is caused by lifestyle habits or treatable medical conditions.

- Obesity, not exercising, and smoking
- Diabetes, kidney disease, pregnancy, and an under active thyroid gland, Inherit hyperlipidemia

Lipoproteins are macromolecules consisting of lipoid substances (cholesterol, triglycerides) non-covalently bound with protein and carbohydrate.

These combinations solublize the lipids and prevent them from forming insoluble aggregates in the plasma.

Normal Level Of Lipid in Normal Human Body

- Total plasma cholesterol level < 200 mg/dL are considered desirable.
- Levels between 200 and 239 mg/dL are considered border line
- Levels > 240 mg/dL are considered high

Cholesterol Sources, Biosynthesis and Degradation

- **Diet**

  Only found in animal fat

- **Biosynthesis**

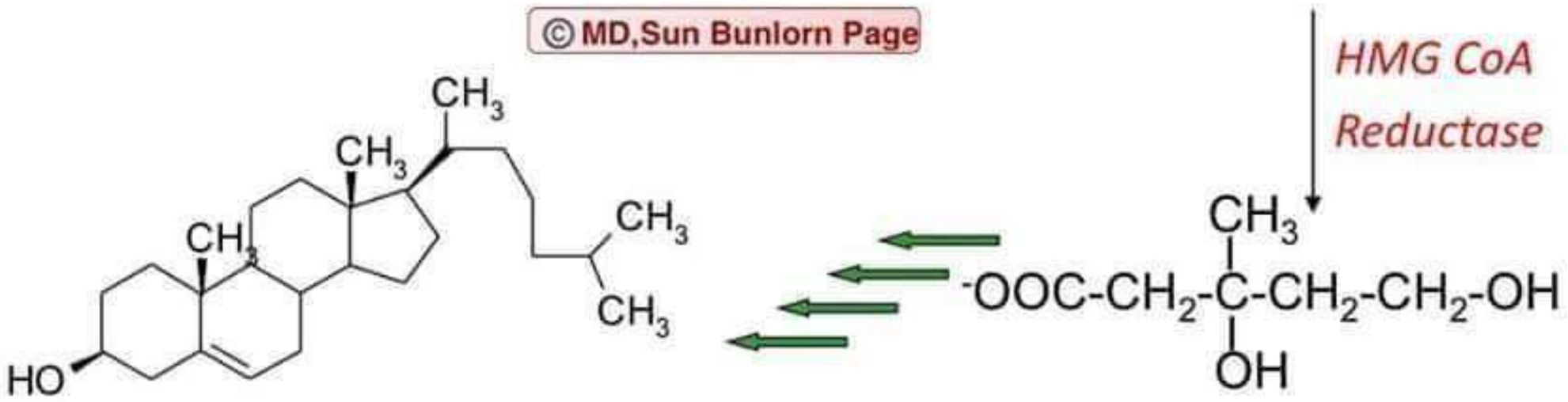
  Primarily synthesized in the liver from acetyl CoA

- **Degradation**

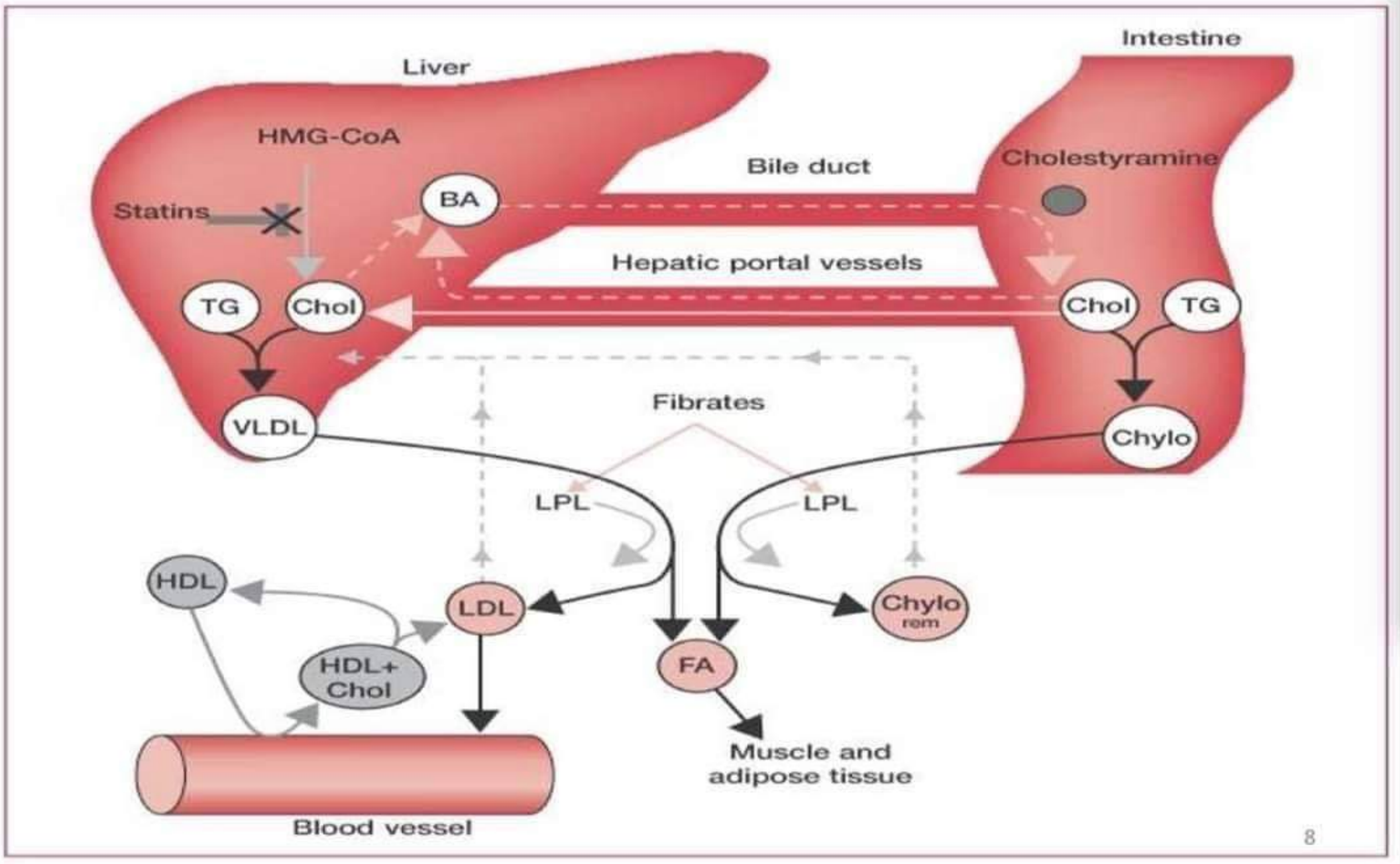
  Only occurs in the liver

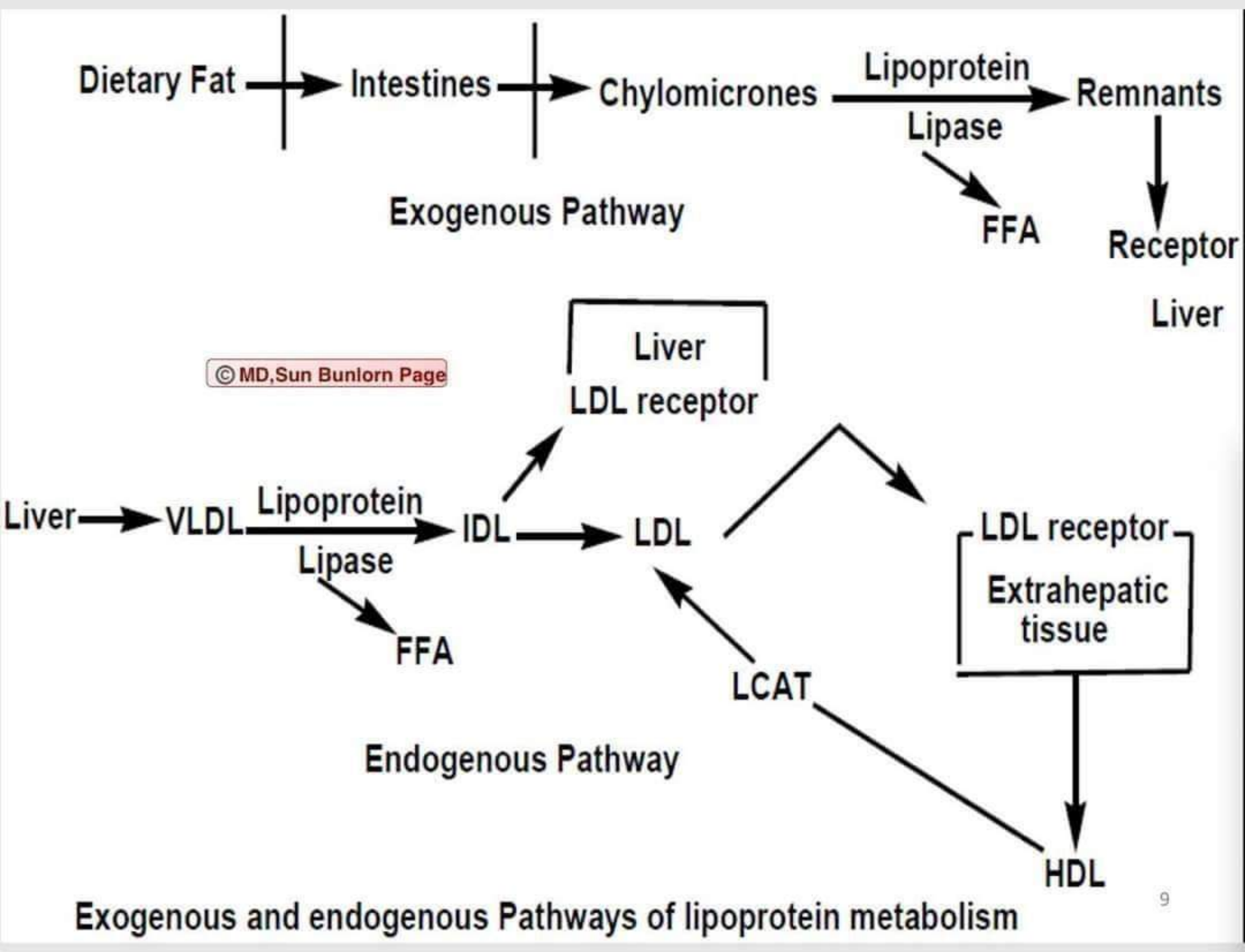
  Cholesterol is converted to bile acids

Biosynthesis of Cholesterol



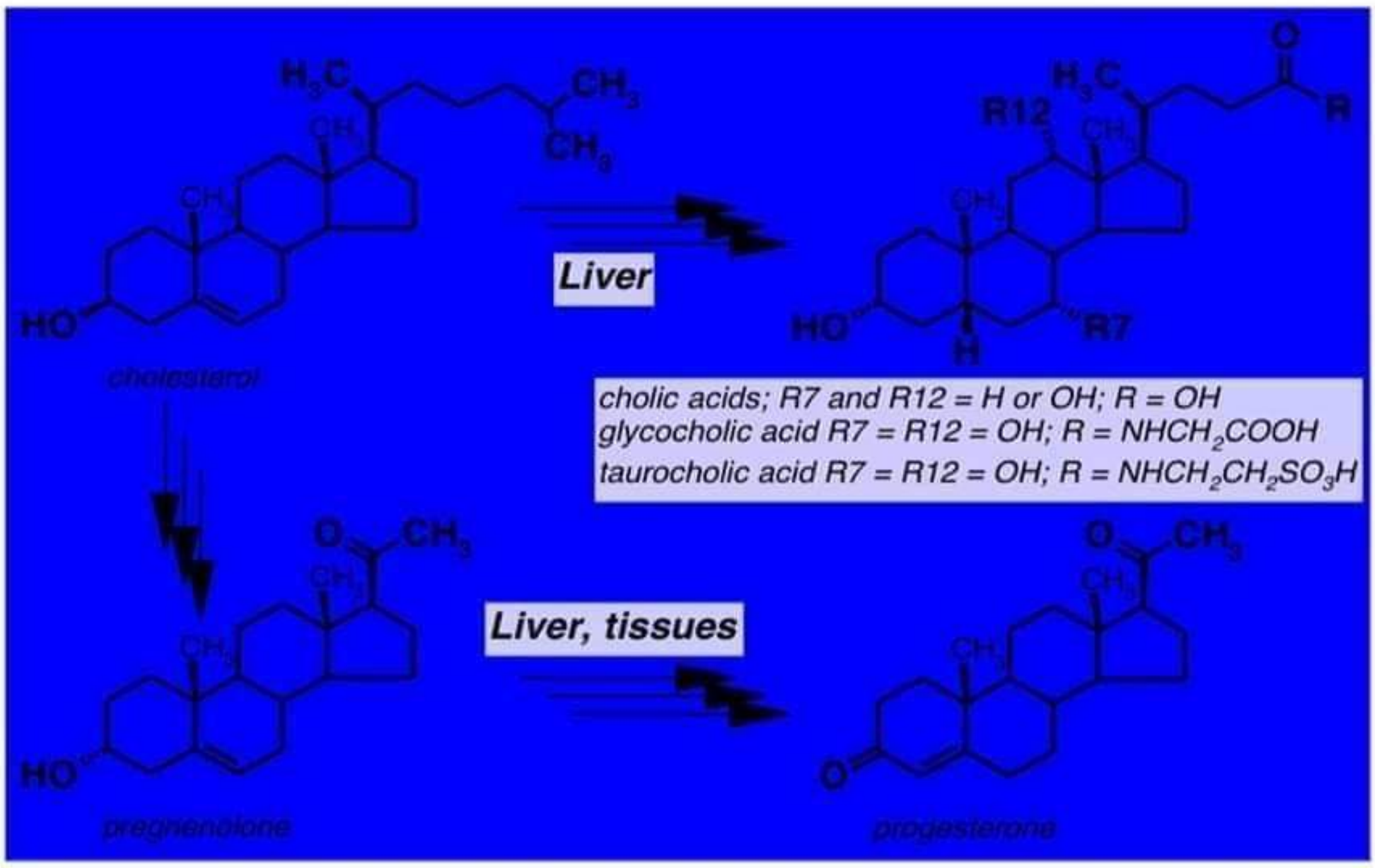
Metabolism





Exogenous and endogenous Pathways of lipoprotein metabolism

Metabolism of Cholesterol



Types of Hyperlipidemias

Types	I	IIa	IIb	III	IV	V
Lipids						
Cholesterol	N-⇧	⬆	⬆	N-⬆	N-⇧	N-⬆
Triglycerides	⬆	N	⬆	N-⬆	⬆	⬆
Lipoproteins						
Chylomicrons	⬆	N	N	N	N	⬆
VLDL	N-⇧	N-⬇	⬆	N-⇧	⬆	⬆
LDL	⬇	⬆	⬆	⬆	N-⇩	⬇
HDL	⬇	N	N	N	N-⇩	⬇

N = Normal, ⬆ = Increase; ⬇ = Decrease; ⇧ = Slight increase; ⇩ = Slight decrease

Types , Synonyms & their treatment

Hyperlipoproteinemia	Synonyms	Increased lipoprotein	Treatment
Type I (rare)	"Buerger-Gruetz syndrome", "Primary hyperlipoproteinaemia", or "Familial hyperchylomicronemia"	Chylomicrons	Diet control
Type IIa	"Polygenic hypercholesterolaemia" or "Familial hypercholesterolemia	LDL	Bile acid sequestrants, statins, niacin
Type IIb	"Combined hyperlipidemia"	LDL and VLDL	Statins, niacin, fibrate
Type III (rare)	"Familial dysbetalipoproteinemia"	IDL	Fibrates, statins
Type IV	"Familial hyperlipidemia"	VLDL	Fibrate, niacin], statins
Type V (rare)	"Endogenous hypertriglyceridemia	VLDL and Chylomicrons	Niacin, fibrate

Classification

A) Inhibitor of de novo cholesterol biosynthesis HMG CoA Reductase inhibitors (Statins)

B) Sequestering agents (Bile acids sequestrants)

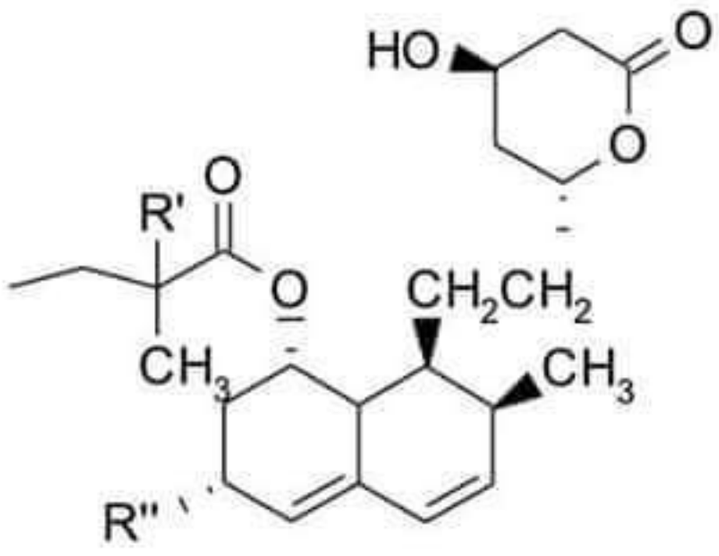
C) Alteration of cholesterol metabolism

D) Inhibition of cholesterol absorption

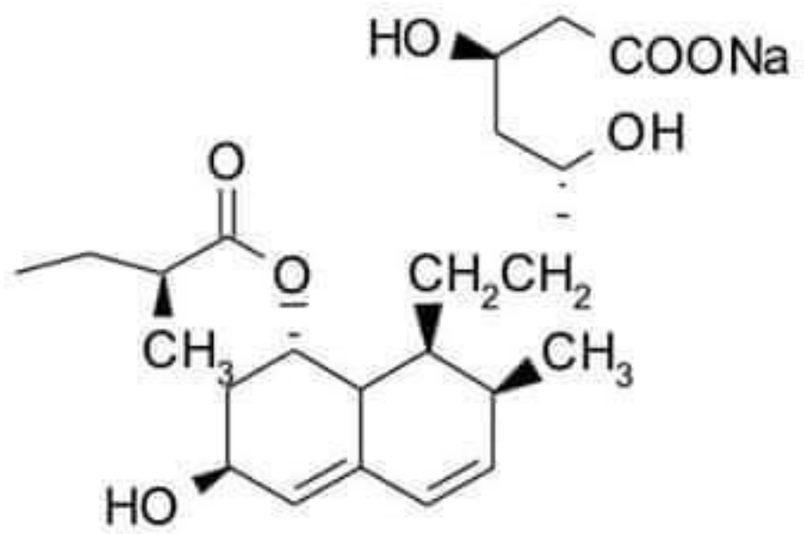
A) Inhibitor of de novo cholesterol biosynthesis HMG CoA Reductase inhibitors - Statins

- Statins are the drugs that competitively inhibit HMG-CoA reductase, resulting a decrease in serum cholesterol levels .
- Till now there are seven statins available in pharmaceutical form. (*lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin*).
- Statins can be classified into naturally derived and chemically synthesized .
- The first statin identified was Mevastatin, which is not in use now

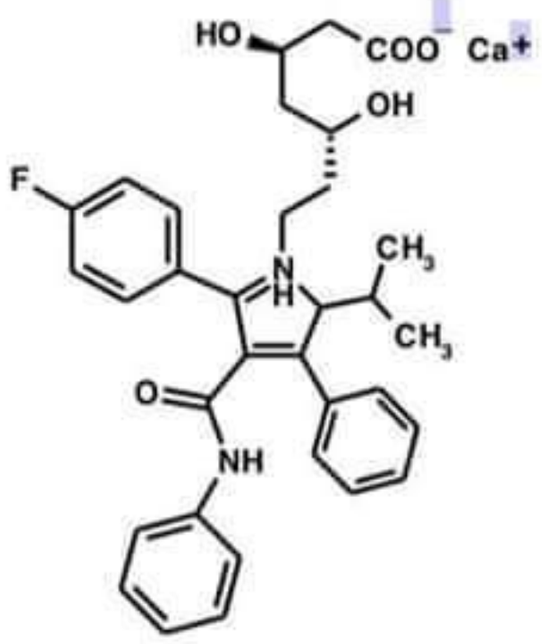
Drugs



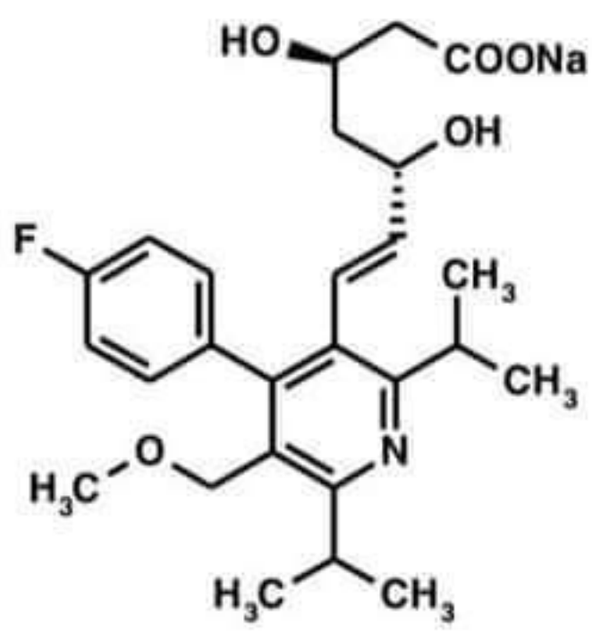
	R'	R''
Mevastatin	H	H
Lovastatin	H	CH_3
Simvastatin	CH_3	CH_3



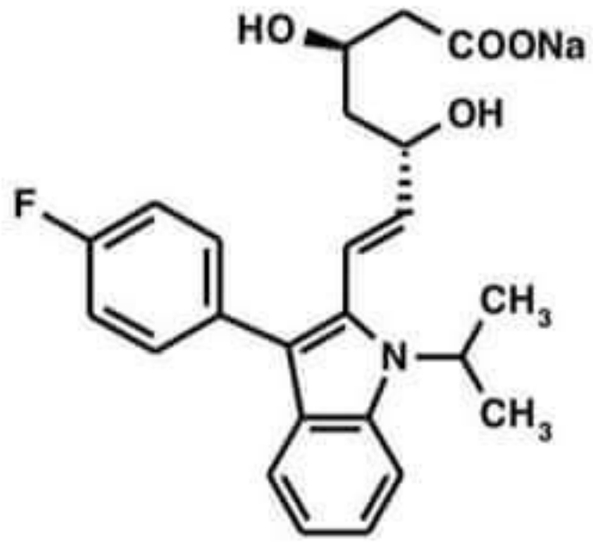
Pravastatin



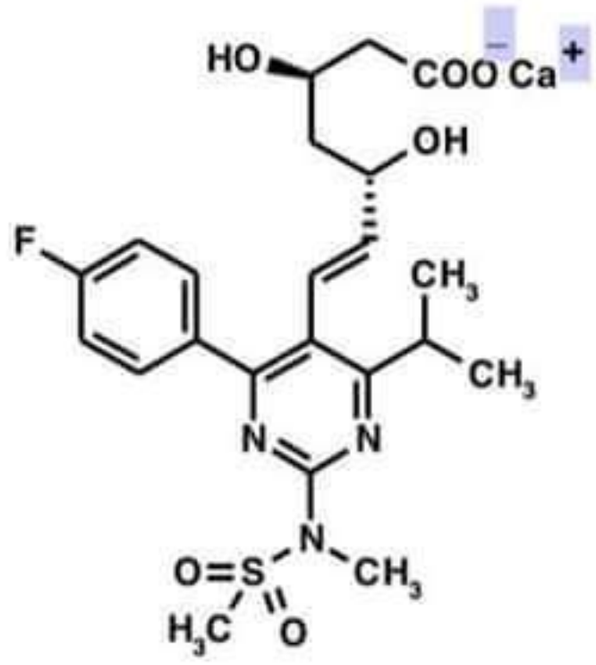
Atorvastatin



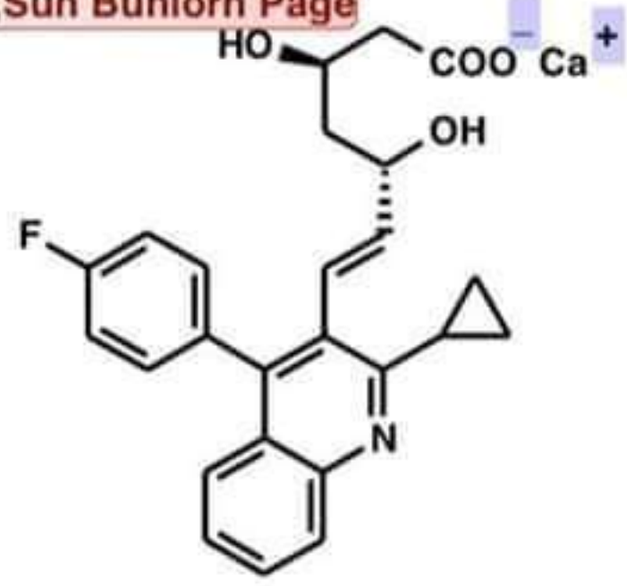
Cerivastatin



Fluvastatin



Rosuvastatin



Pitavastatin

SAR of HMG-CoA Reductase inhibitors

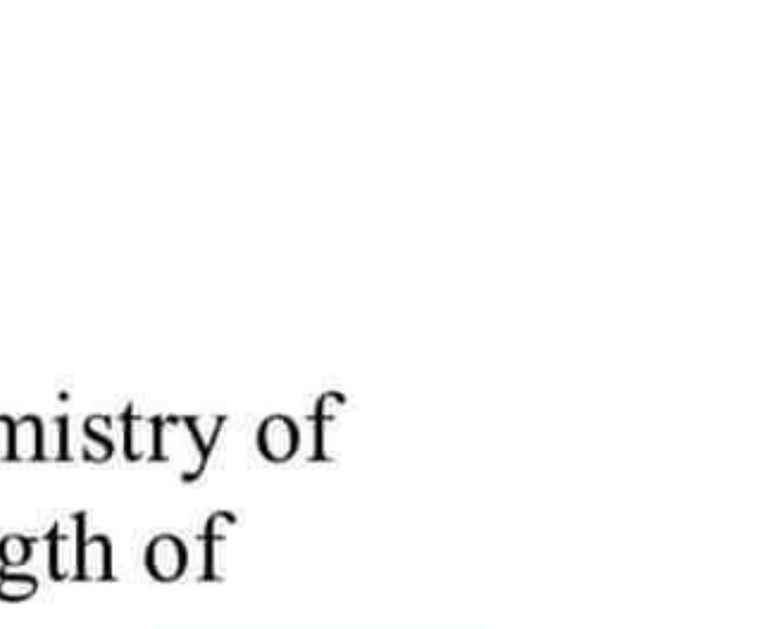
- Th 3,4-dihydroxycarboxylate is essential for inhibitory action
- Compound containing a lacton are prodrugs required in-vivo hydrolysis.
- Stereochemistry of 3- & 5- hydroxyl group same
- Alteration the 2 –C distance between C5 & the ring diminish activity
- Double bond between C6 & C7 ⇩ or ⇧ activity.
- Ethyl group provides optimal activity

The structure should contains

a. lactone ring (sensitive to stereochemistry of it, ability of ring to hydrolyzed, length of bridge)

b. Bicyclic rings (could be replaced with other lipophlic rings, size and shape of it are important for activity)

c. Ethylene bridge between them is essntial



Pharmacokinetic properties of statins – case of cerivastatin

Drugs	Bioavailability	Dosage (mg)	Protein Binding	Metabolites
Atorvastatin	~14%	10 – 80	>98%	Active
Cerivastatin	~60%	0.2 – 0.3	>99%	Active
Fluvastatin	~24%	10 – 80	98%	Active
Lovastatin	~5%	10 – 80	>95%	
Pravastatin	~17%	10 – 40	~50%	
Simvastatin	~5%	10 - 80	~95%	

Typically all statins possess side effects. The most dominant side effect, cited in the withdrawal of cerivastatin, is rhabdomyolysis (lysis of rhabdomyose) or weakening of skeletal muscles.

Metabolic properties of statins

- Rapid first pass metabolism significantly reduces bioavailability
- Metabolism is complex
- Extensive conversion between the lactone and open-chain forms
- Glucuronidated forms as well
- Other than these three, many other lesser metabolites
- Inhibitors of cytochrome P450 increase bioavailability of statins
  ….. Greater incidences of myopathy ….. E.g., cyclosporin, gemfibrozil, erythromycin, itraconazole, etc.
- Rhabdomyolysis A rare complication of statin treatment. Characterized by breakdown of muscles

Release of myoglobin into blood, which travels to kidneys and stops working of its tubules

Also muscle breakdown increase K^+, which induces cardiac arrythmias and death

- **Adverse Effects of HMGRIs**

  Constipation, abdominal pain, diarrhea, nausea, vomiting, headache, elevated hepatic enzymes, myalgia, myopathy, muscle cramps, rhabdomyolysis, and chest pain

- **Uses**

  For primary hypercholesterolemia and familial combines hyperlipidemia (type II a, II b)
  In combination with bile acid sequestrants, ezetimibe, or niacin

Combination Products That Include an HMGRI

- HMGRI and antithrombotic

  Pravastatin/aspirin (Pravigard PAC)

- HMGRI and calcium channel blocker

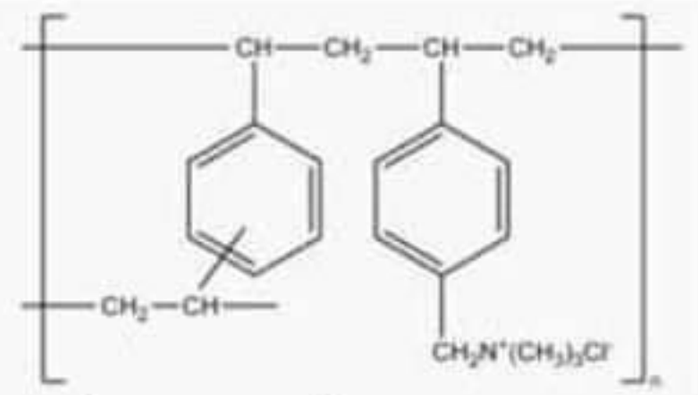
  Atrovastatin/amlodipine (Caduet)

- HMGRI and additional antihypercholesterolemic agent

  Lovastatin/niacin (Advicor)

  Simvastatin/ezetimibe (Vytorin)

Cholestyramine (Questran)



- Non-absorbed bile acid sequestrant that is used a therapy of hyperlipidemia
- It is Large & Highly positively charged anion exchange resin binds to bile acid
- The binding of bile acids to cholestyramine creates an insoluble compound that cannot be reabsorbed

- Cholestyramine and colestipol are basic anion exchange resins, which sequester bile acids in the intestine and prevent their re-absorption and their enterohepatic re-circulation.

- The result is a decreased in the absorption of exogenous cholesterol and increase in the metabolism of endogenous cholesterol into bile acids in the liver.

Generic	Brand
Atorvastatin	Lipitor
Fluvastatin	Lescol
Lovastatin	Mevacor
Pravastatin	Pravachol
Simvastatin	Zocor / vytorin
Rosvastatin	Crestor
Fenofibrate	Tricor
Gemfibrat	Lopid
Colstipol	Colestid
Chlolstyramine	Qstron
Ztimibe	zetia

Condition	Brand Name	Generic Drug
Angina	Coduet	Amolodipin + Atorvastatin
Diabetic (Type II)	Juvisync	Simvastatin + Sitagliptin
High B.P.	Caduet	Amolodipine + Atrovastatin
High cholestrol	Vytorin	Ztimib + Simvastatin
	Simcor	Niacin + Simvastatin
	Advicor	Lovastatin + Niacin
	Javisyne	Simvastatin + Sitagliptin
	Liptruzet	Atrovatatin + Eztimib
⬆ LDL	Simcor	Niacin + Simvastatin
	Advicor	Lovastatin + Niacin
Type IIa &IIb & ⬆ LDL &VLDL	Simcor	Niacin + simvastatin

Strategy for Controlling Hyperlipidemia

STATINS

Diet

Biosynthesis

HMG CoA reductase

Ezetimibe

Serum Cholesterol

LDL-R

Cellular Cholesterol

Bile Acids

Intestine

Feces

Re-absorption

BILE ACID SEQUESTRANTS

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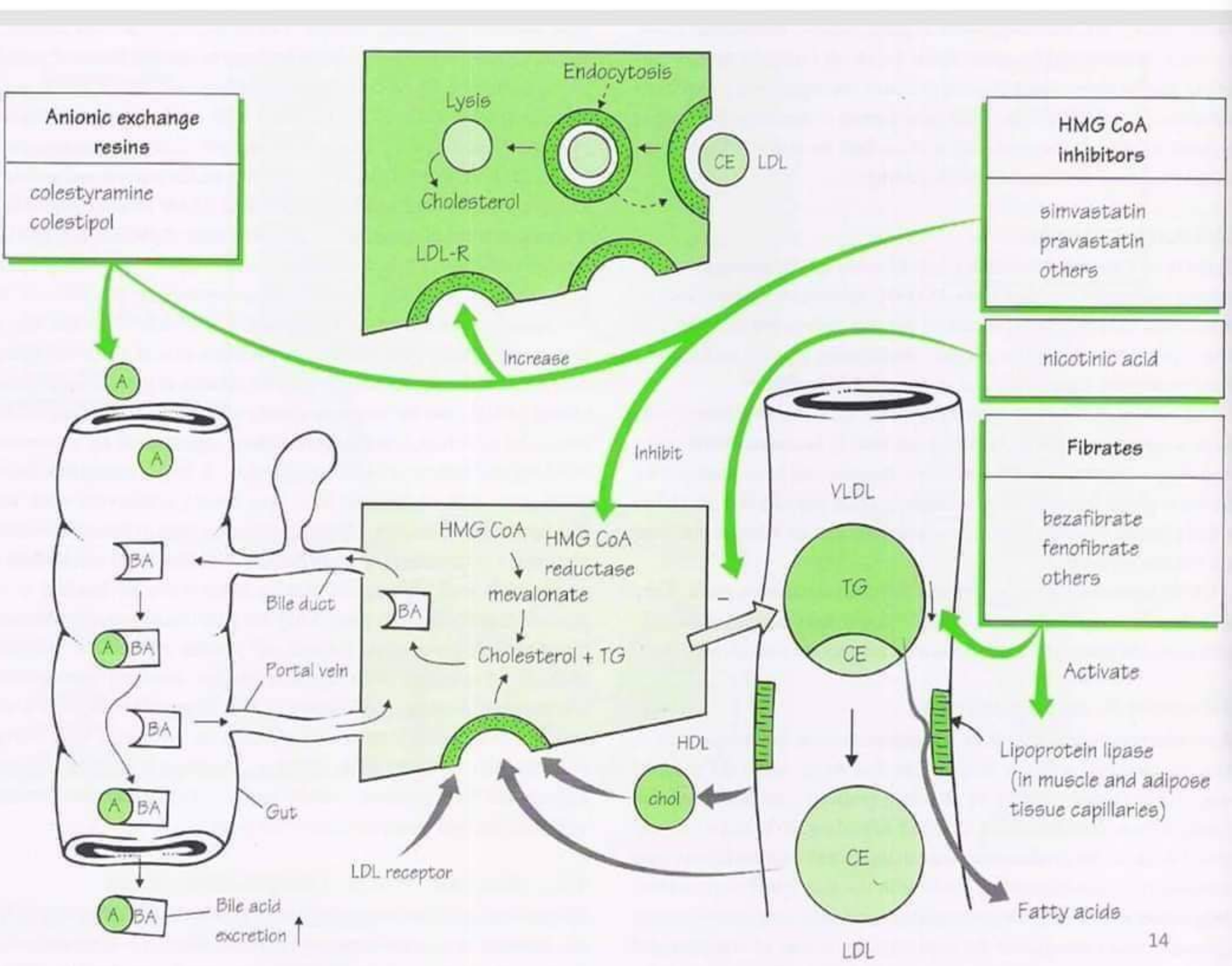
Lipoprotein catabolism

Conversion to hormones within cells or storage as granules

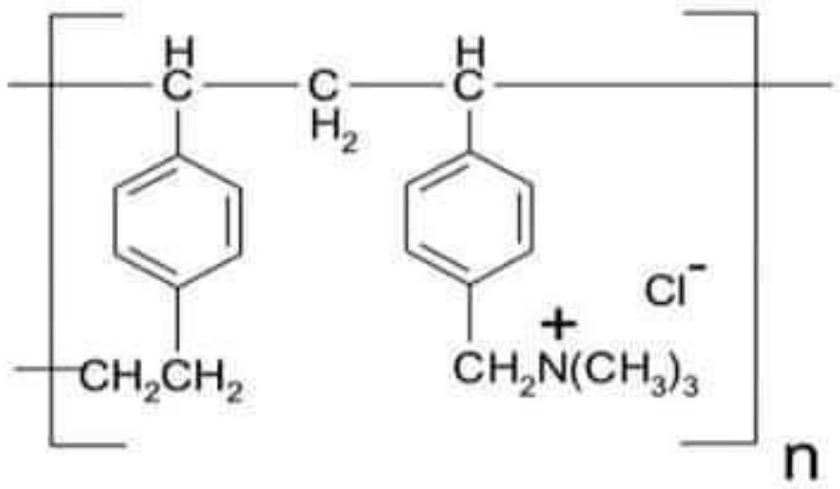
FIBRATES



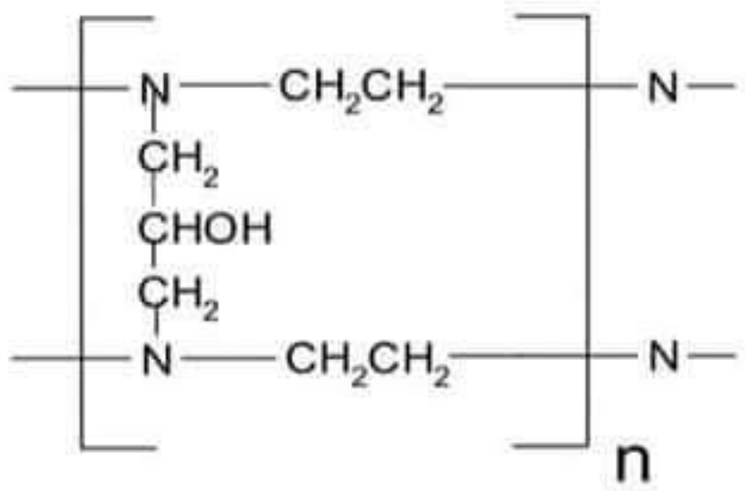
B) Bile Acid Sequestrants

- Anion exchange resins
- Water insoluble and inert to digestive enzymes
- Not absorbed through the GI tract
- Positively charged nitrogens sequester bile acid re-absorption
- Lower serum LDL levels
- Most useful in type IIa and IIb hyperlipidemias

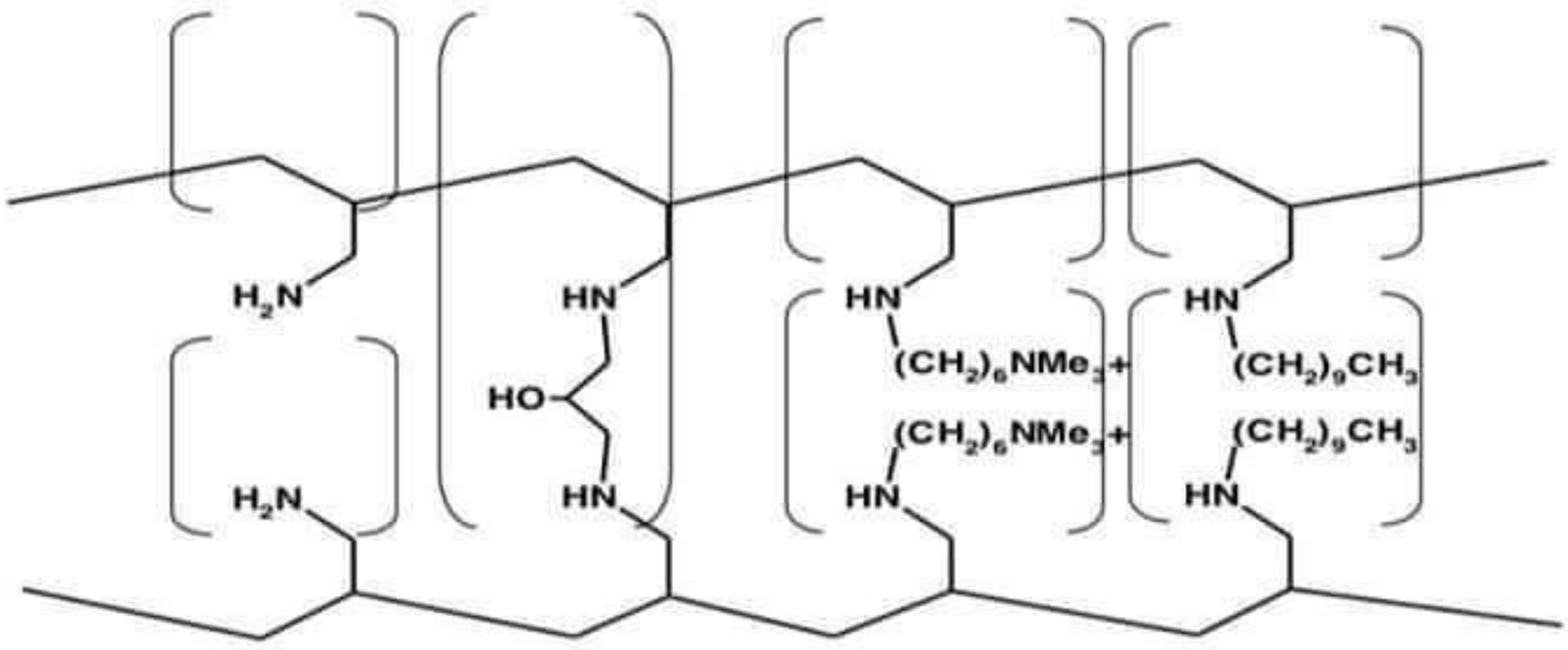
Sequestering agents (Bile acids sequestrants)



Cholestyramine Resin



Colestipol hydrochloride



Colesevelam

Adverse effects

•Beceause they are not orally absorbed, they produce minimal systemic side effects

•Constipation, Heartburn, nausea, bloating

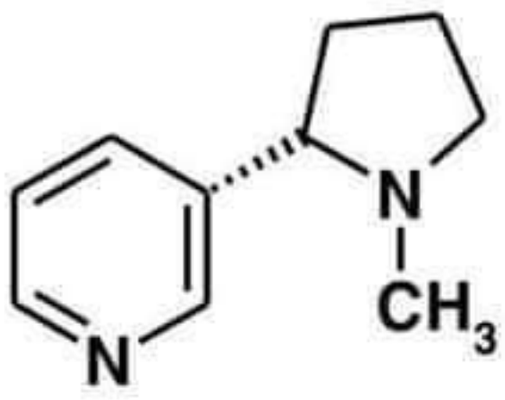
– These adverse effects tend to disappear over time

C) Alteration of cholesterol metabolism
Fibrates

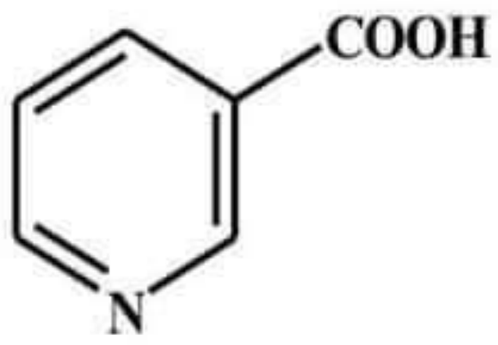
- Older generation drugs; introduced in 1981
- Second most useful anti-hyperlipidemic drugs
- Primarily decrease serum triglycerides
- Increase lipoprotein catabolism; increase TG usage by the body
- activate PPAR-a (peroxisome proliferator-activated receptor a)
- Most used in Type III, IV and V hyperlipidemias

Nicotinic Acid

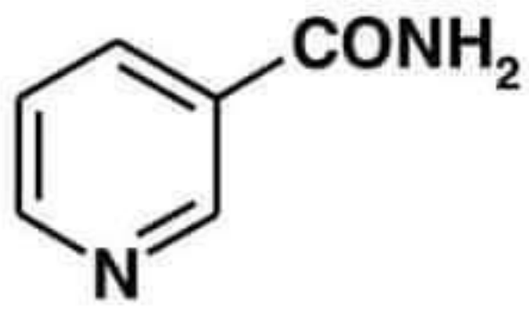
- Administered in large doses (0.5 to 6 grams daily)
- Reduces triglycerides and total cholesterol
- Increases biliary secretion of cholesterol, but not bile acids
- Useful in Type IIa, IIb, III, IV and V hyperlipidemias



NICOTINE



NICOTINIC ACID (NIACIN)



NICOTINAMIDE

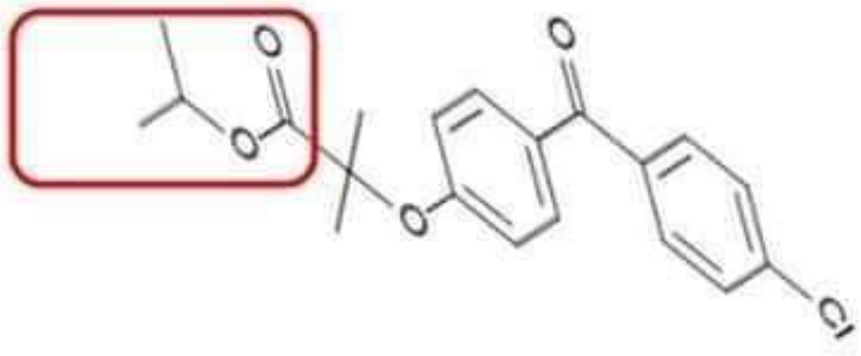
- **Mechanism of action**

Increases activity of lipase, which breaks down lipids
Reduces the metabolism of cholesterol and triglycerides

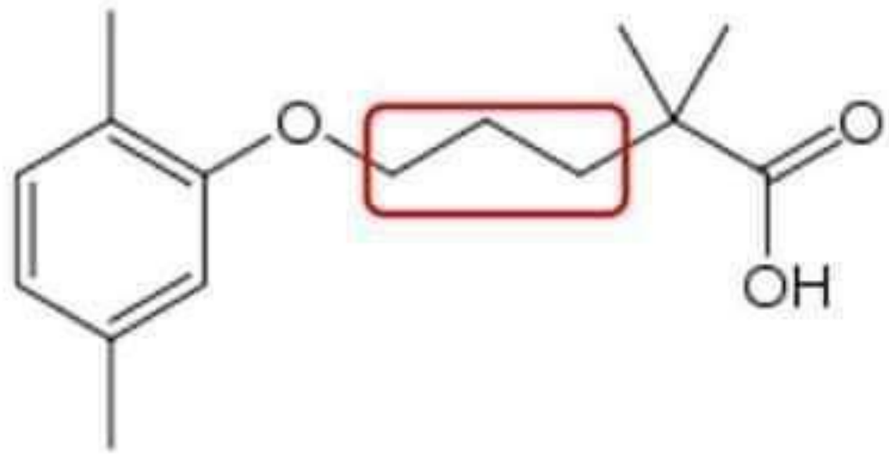
- **Adverse Effects of Niacin**

Flushing, headache, nausea, vomiting, diarrhea, hepatic dysfunction, jaundice, hyperglycemia,

hyperuricemia, blurred vision, and tachycardia



Fenofibrate



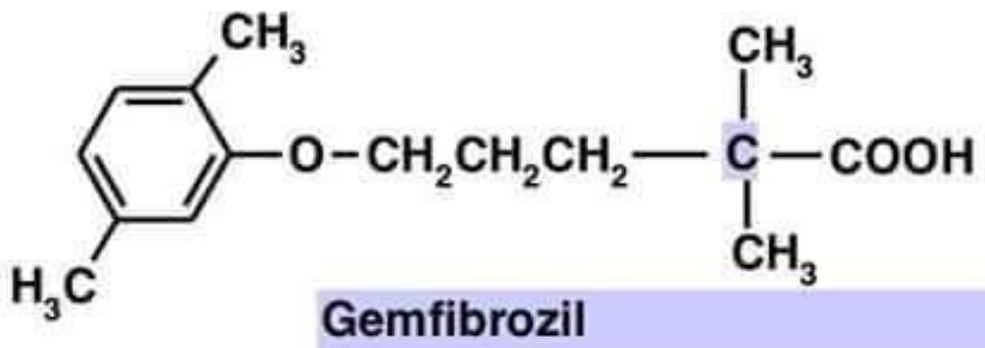
gemfibrozil

2) Fenofibrate contain ester (prodrug) and requires for in vivo hydrolysis.
3) Para-subtitution with Cl or Cl containing isopropyl ring increase half-lives.
4) A phenoxy isobutyric acid, the addition of an n-propyl spacer, as seen in gemfibrozil , results in an active drug.

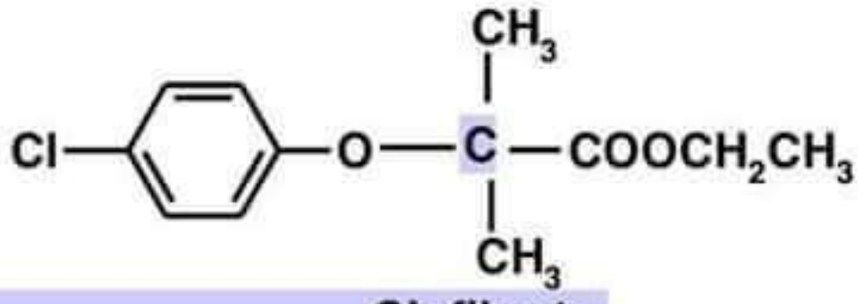
Adverse Effects

Abdominal pain, nausea, vomiting, diarrhea, constipation, cholestasis, jaundice, cholelithiasis, pancreatitis,
headache, dizziness, drowsiness, blurred vision, mental depression, impotence, myopathy, myositis, anemia, leukopenia, eosinophilia, pruritus, and rash

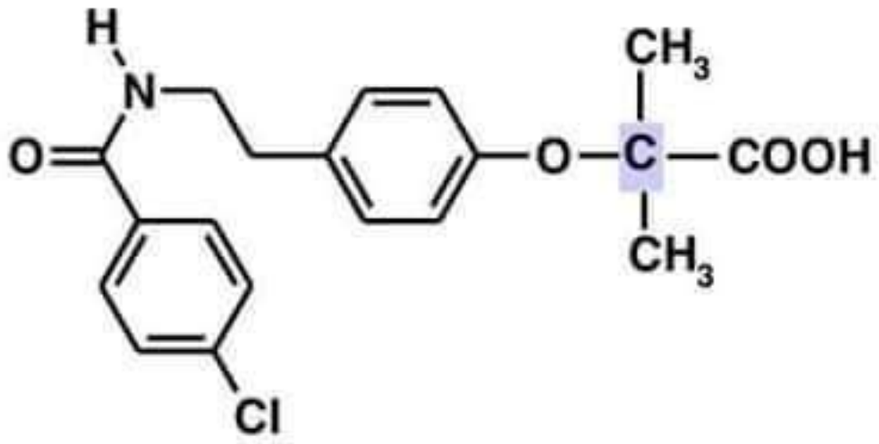
Drugs - Fibrates



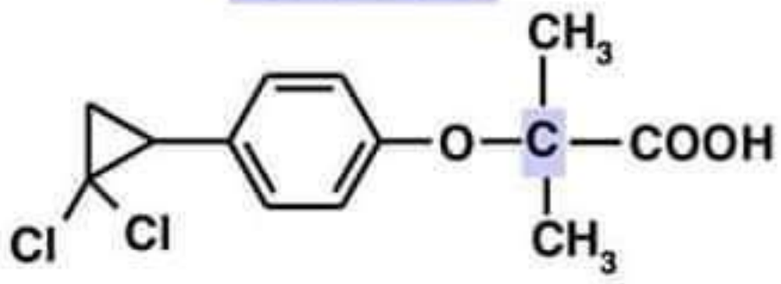
Gemfibrozil



Clofibrate



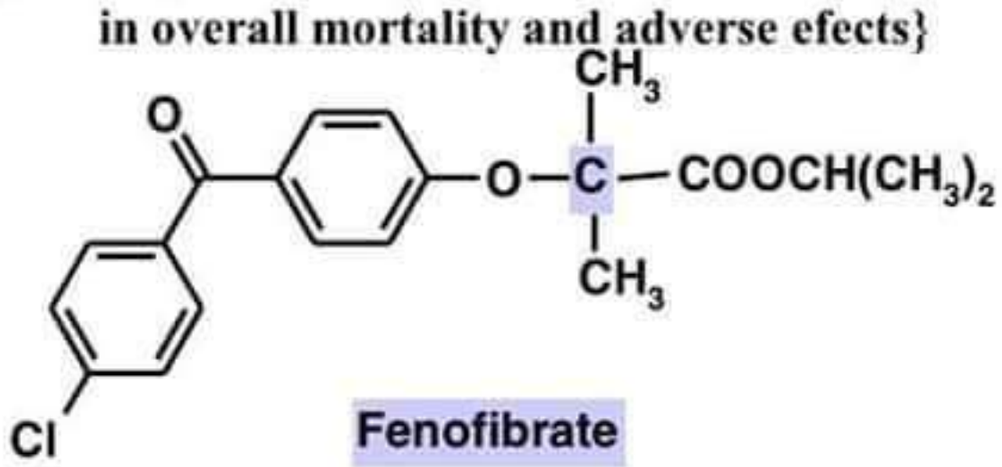
Bezafibrate



Ciprofibrate

{rhabdomyolysis ... highest PPAR-α affinity
→ clinical trials stopped in the US}

{No longer recommended because of an increase in overall mortality and adverse efects}

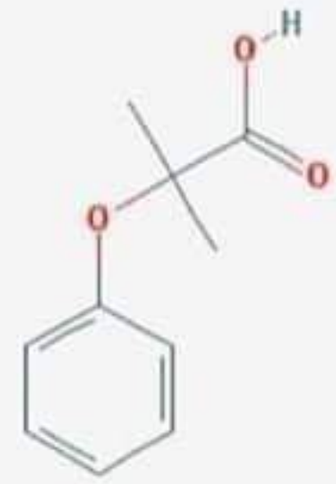


Fenofibrate

SAR of Fabric acid derivatives

[aromatic ring]-O-[spacer group]-$C(CH_3)_2$-CO-OH

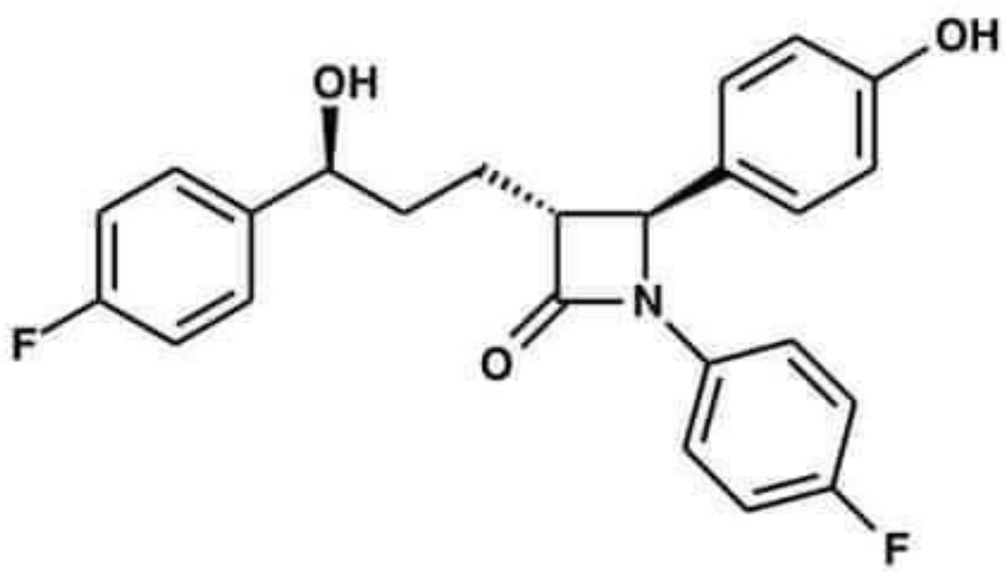
1) They are classified as analogues of isobutyric acid derivatives (essential for activity)



Fabric acid

D) A Cholesterol Absorption Inhibitor– Ezetimibe

- Approved in October 2002
- Reduces serum LDL, TC, and TG and increases HDL
- Prevents the absorption of cholesterol from diet
- Useful in Type IIa, IIb, III, IV and V hyperlipidemias



Ezetimibe

- **Mechanism of action**

Is a drug that lowers plasma cholesterol levels. It acts by decreasing cholesterol absorption in the intestine

- **Adverse Effects of Ezetimibe**

Abdominal pain, diarrhea, arthralgia, back pain, cough, pharyngitis, sinusitis, fatigue, and viral infection