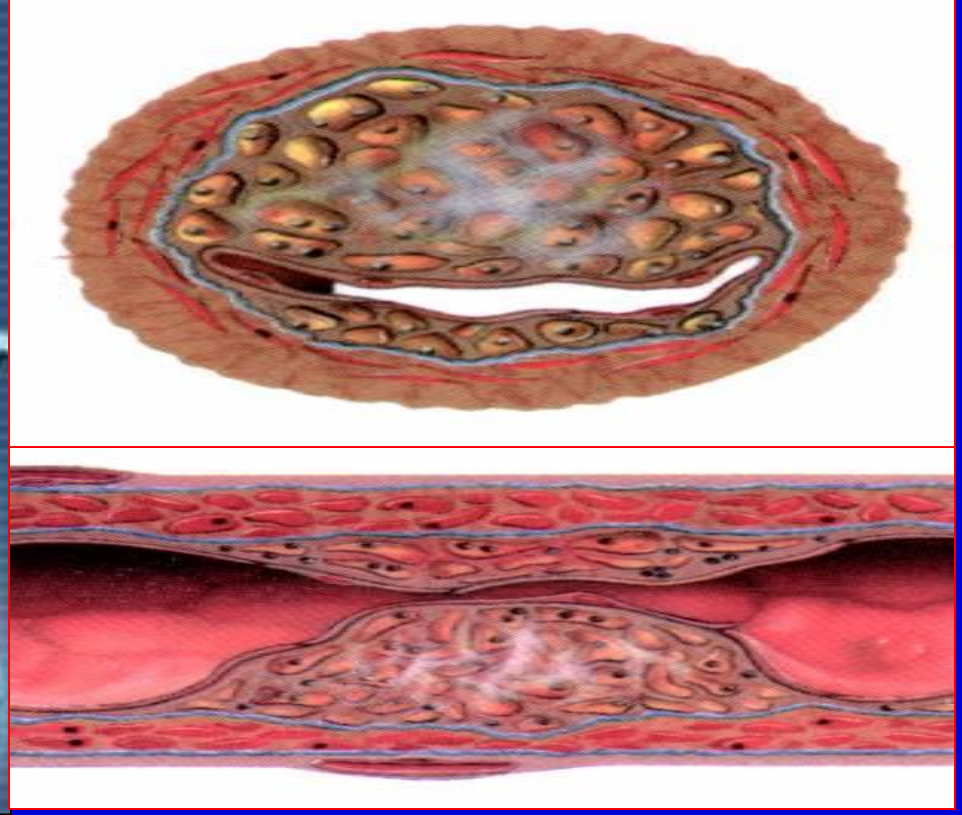


# Drugs for hyperlipidemia

**Prof. Yieldez Bassiouni**

# ILOs

By the end of those 2 lectures the student will be able to:

- Define hyperlipidemia vs normal lipid levels
- Discuss the non-pharmacological treatment of hyperlipidemia
- Classify lipid lowering agents targeting exogenous & endogenous pathways
- Expand on the pharmacology of drugs related to each group
- Hint on adjuvant drugs that can help in lipid lowering

# Hyperlipidemia

- Hyperlipidemia is a major cause of atherosclerosis which may lead to CAD and ischemic cerebrovascular disease
- Denotes abnormally ↑ levels of any or all Lipids and/or Lipoproteins [LP] in blood

▸ Lipids originate from two sources:

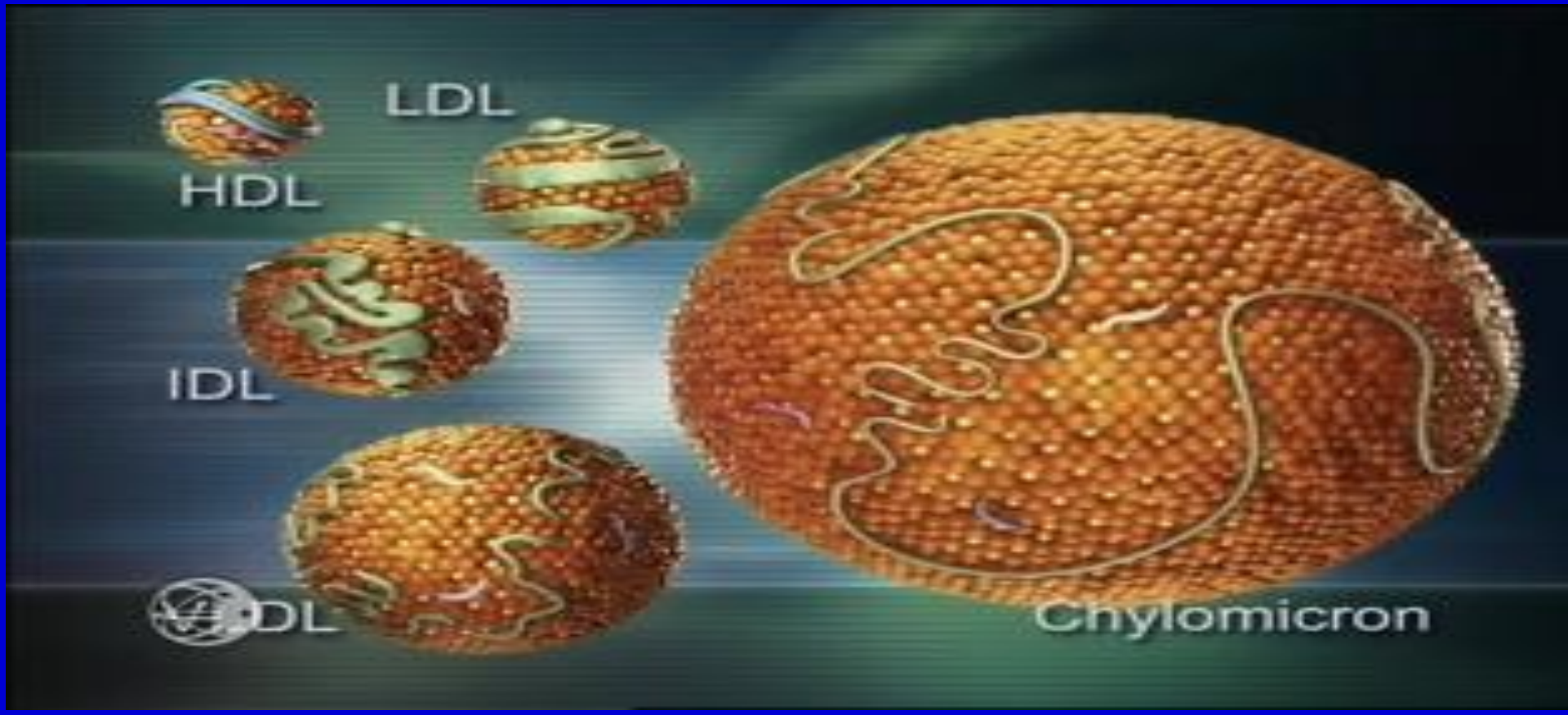
  ▸ endogenous lipids, synthesized in the liver

  ▸ exogenous lipids, ingested and processed in the intestine

- The principle lipids in the blood are:

  - Cholesterol (C)
  - Triglycerides (TG)
  - Phospholipids (PL)
  - Cholesterol esters (CE)
  - Non-estrified fatty acids (NEFA)

# Lipoprotein Classes




- Endogenous molecules that contain both proteins and lipids in their structure
- transport (carry) lipids around the body in the blood

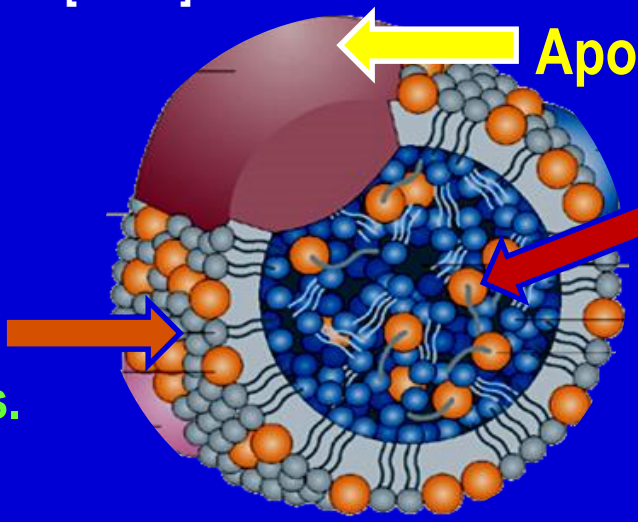
LP

Chylomicrons [CM]

Very low Density lipoprotein [VLDL]

Low Density lipoprotein [LDL]

High Density lipoproteins [HDL]

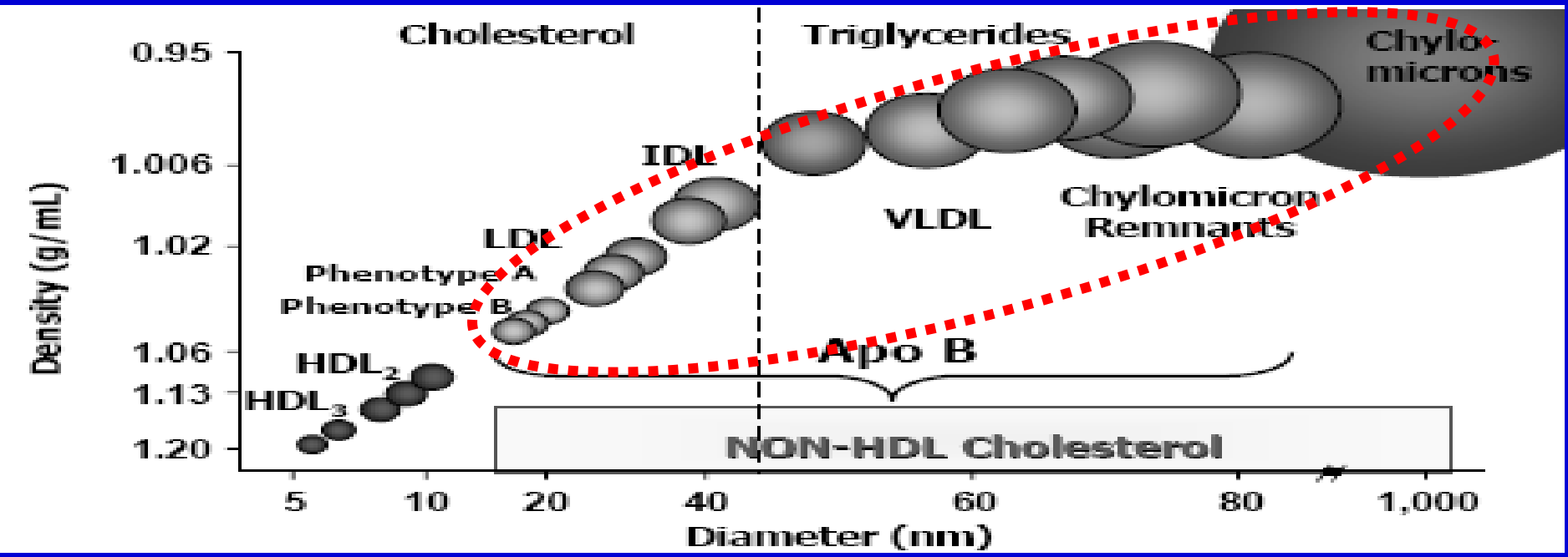


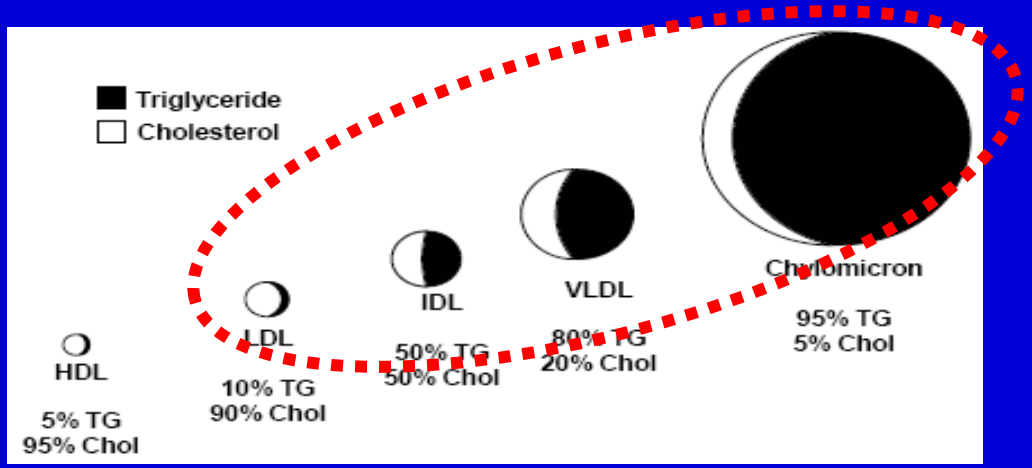

**Outer Coat**
Phospholipids
Cholesterol
Hydrophilic Gps.

**Inner Core**
Triglycerides
Cholesterol esters
Lipophylic Gps.

- Lipoproteins are classified into five major families which differ in the amounts of C, TG and types of apoproteins they contain
  - -Chylomicrons (CM)
  - -Very low density - lipoproteins (VLDL)
  - -Intermediate - density lipoproteins (IDL)
  - -Low density - lipoproteins (LDL)
  - -High density- lipoproteins (HDL)

# Atherogenic Particles



# Normal Lipid levels

- C < 200 mg/dl
- TGs < 220 mg/dl
- LDL < 130 mg/dl (Bad C)
- HDL > 50 mg/dl (Good C)

- Lipids levels are detected in serum after a 12-hour fast

# Factors promoting elevated blood lipids

- family history of CAD
- smoking (reduced levels of HDL, cytotoxic effects on the endothelium, increased oxidation of lipoproteins, and stimulation of thrombogenesis)
- hypertension
- obesity
- DM (increased generation of VLDL and free fatty acids presented to the liver)
- inactivity / lack of exercise
- alcohol intake ( increases TGs)

# Familial Hyperlipoproteinemia

| LProteinemia | ↑LP | ↑Lipids | Risk |
|---|---|---|---|
| Type I | CM | TGs | - |
| Type IIa | LDL | C | ↑ |
| Type IIb | VLDL & LDL | TG & C | ↑ |
| Type III | IDL | TGs & C | ↑ |
| Type IV | VLDL | TGs | ↑ |
| Type V | VLDL & CM | TGs & C | _ |

# Therapeutic strategies for treatment of hyperlipidemia

## Therapeutic lifestyle changes

## Antihyperlipidemic agents

**1. Healthy diet; optimal Quantitative & Qualitative fat content:**

- Diet has <30% of calories as fat, <7% as saturated fat and <200mg cholesterol/day
- Avoid trans-fatty acids & acute increase in C intake
- Use vegetable oils rich in unsaturated fatty acids: oleic acid, linoleic acid & linolenic acids. Diet should also contain plant stanols (interfere with the formation of micellar cholesterol) & soluble fibers
- Eat food high in antioxidants vitamins

**2. Regular exercise**

**3. Cessation of hazards habits; smoking, alcohol, …etc**

**4. Loss of weight**

- **Can achieve a fall in LDL-C of 8-15% … *but long-term compliance is a problem***

# Antihyperlipidemic agents

According to the mechanism of action:

1- Inhibits cholesterol absorption in the intestine
   Ezetimibe
2-Sequester bile acids in the intestine
   Exchange resins
3-Inhibits synthesis of cholesterol
   Inhibitors of hydroxymethylglutaryl coenzyme A reductase (Statins)
4-Alter relative levels & patterns of different plasma LPs
   Fibrates, Nicotinic acids

## I-Agents targeting exogenous cholesterol

- Ezetimibe
- Colestipol & cholestyramine

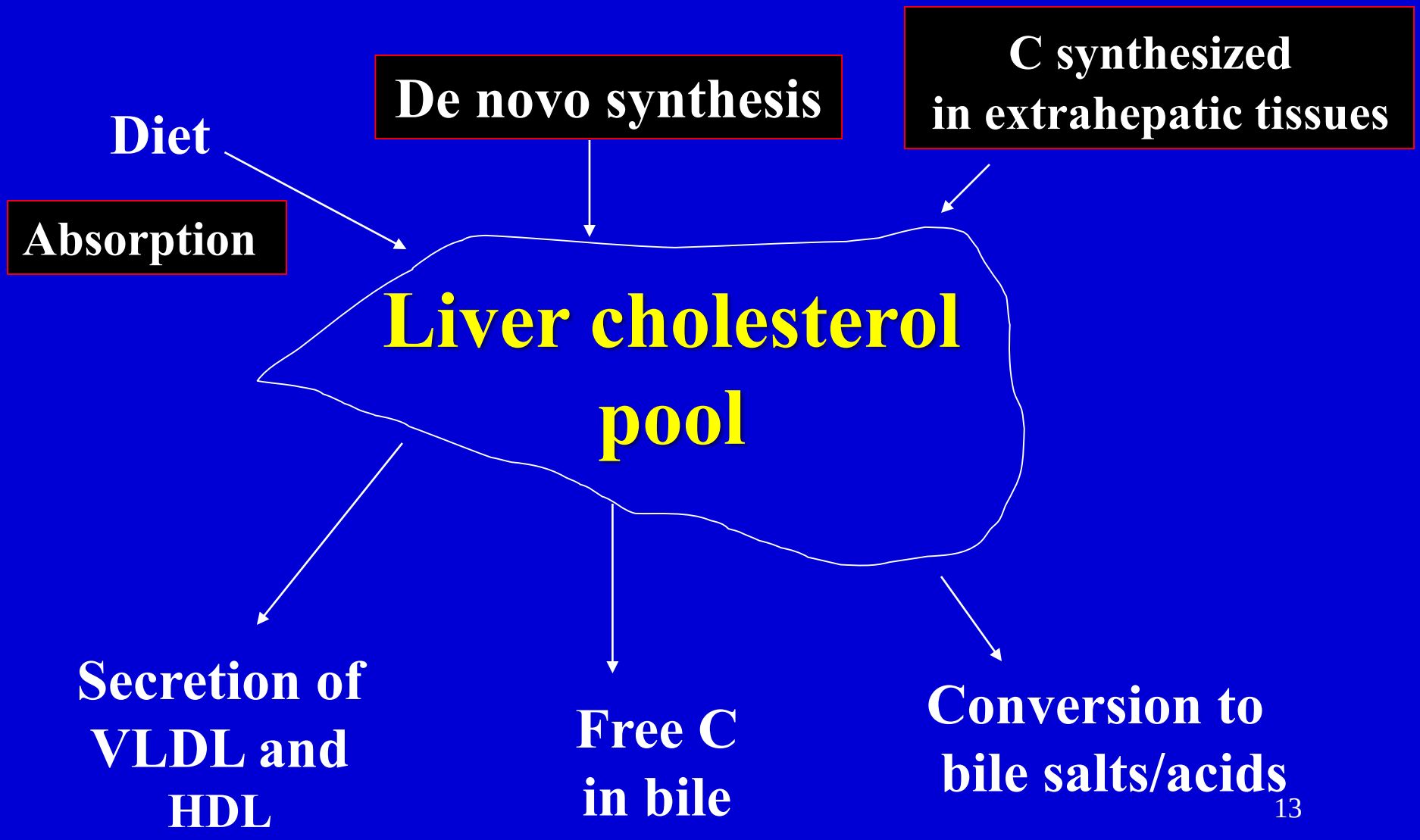
## II-Agents targeting endogenous cholesterol

- Statins
- Fibrates
- Nicotinic acid

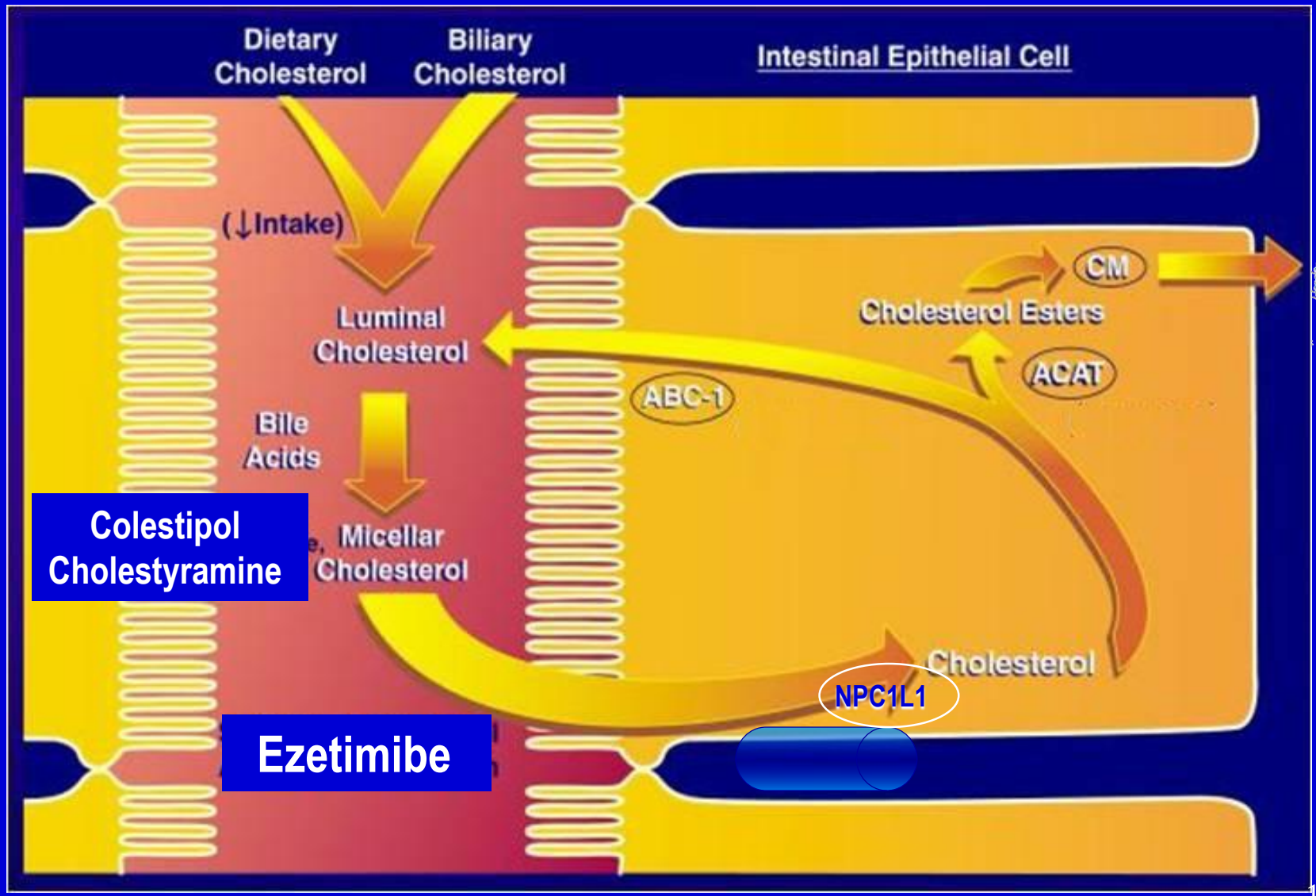
## III-Adjuvant agents

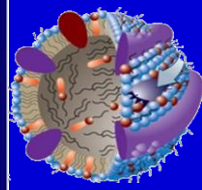
- Omega-3-Fatty Acids, Stanols

# Hepatic Cholesterol Metabolism



# I-Agents Targeting Exogenous Cholesterol



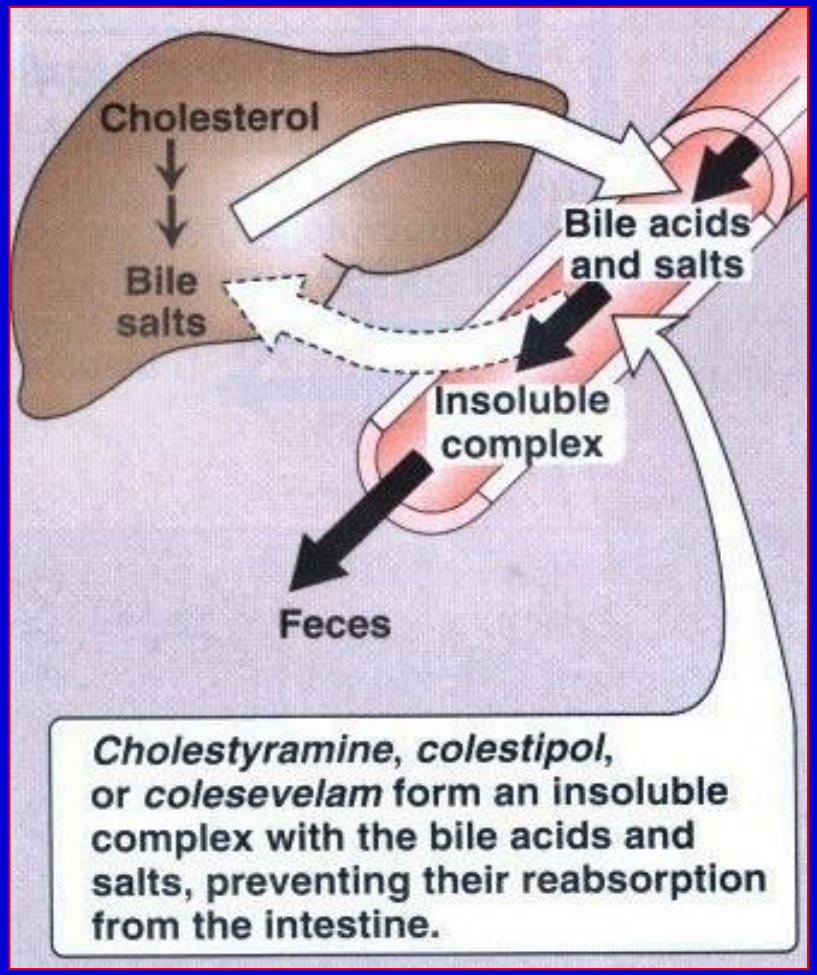



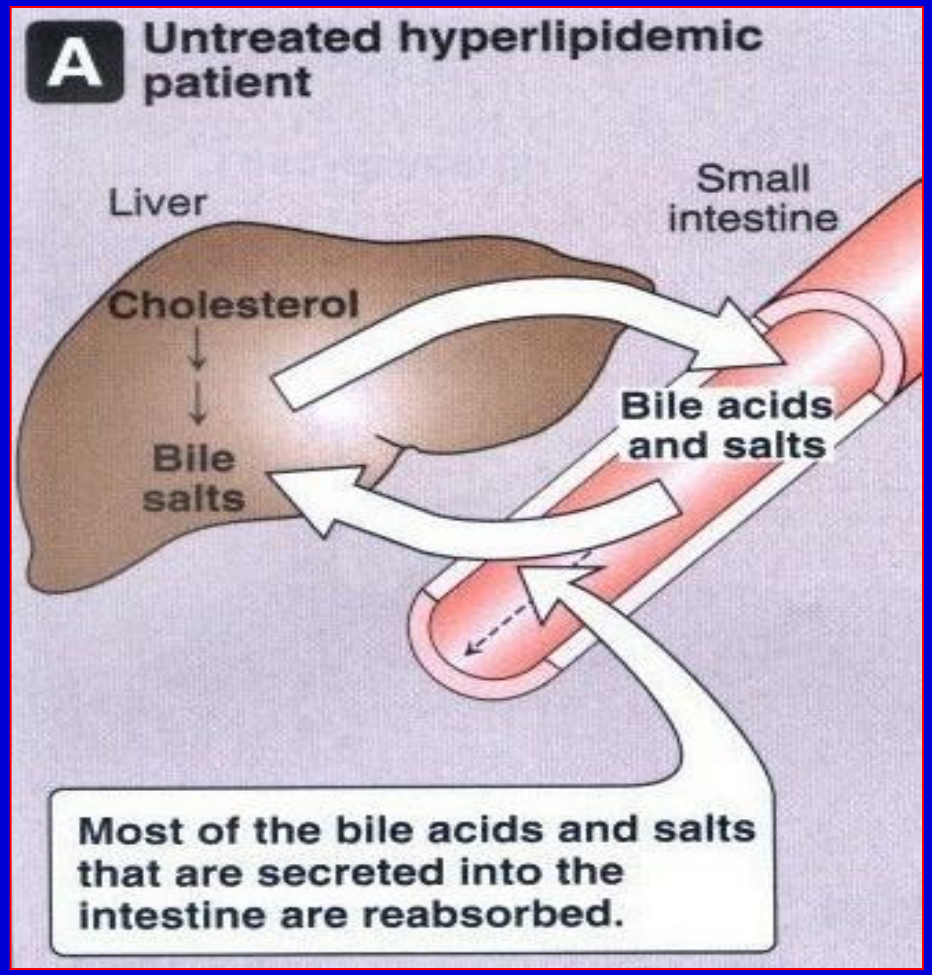
# Exchange resins
# Bile acid sequestrants

Cholestyramine &
Colestipol

Colesevelam

# Resins: Mechanism of Action




They disrupt the enterohepatic circulation of bile acids

# Bile Acid-Binding Resins

- Moderately effective with excellent safety record
- Large MW polymers which bind to bile acids and the acid-resin complex is excreted so their fecal excretion ▲ 10 folds
  - prevents enterohepatic cycling of bile acids
  - obligates the liver to synthesize replacement bile acids from cholesterol
- The liver increases the number of LDL receptors to obtain more cholesterol
- The levels of LDL-C in the serum are reduced as more cholesterol is delivered to the liver
- Excellent choice for people that cannot tolerate other types of drugs

# Resins : Adverse Effects

- **Resins are** clinically safe as they are not systemically absorbed
- **GIT upset:** abdominal discomfort, bloating, constipation
- **Decreased absorption of:** fat soluble vitamins (Vitamin A, D, K)
- The concentration of HDL-C is unchanged

# Resins: Drugs interactions

## Interfere with the absorption of:

- Statins, Ezetimibe
- Chlothiazides, Digoxin, Warfarin
- N.B. wait 1 hour before or 4 hrs after administration of resins

➢ Colesevelam has not been shown to interfere with the absorption of co-administered medications and is a better choice for patients on multiple drug regimens

# Contraindications of resins

1- Complete biliary obstruction ( because bile is not secreted into the intestine)

2- Chronic constipation

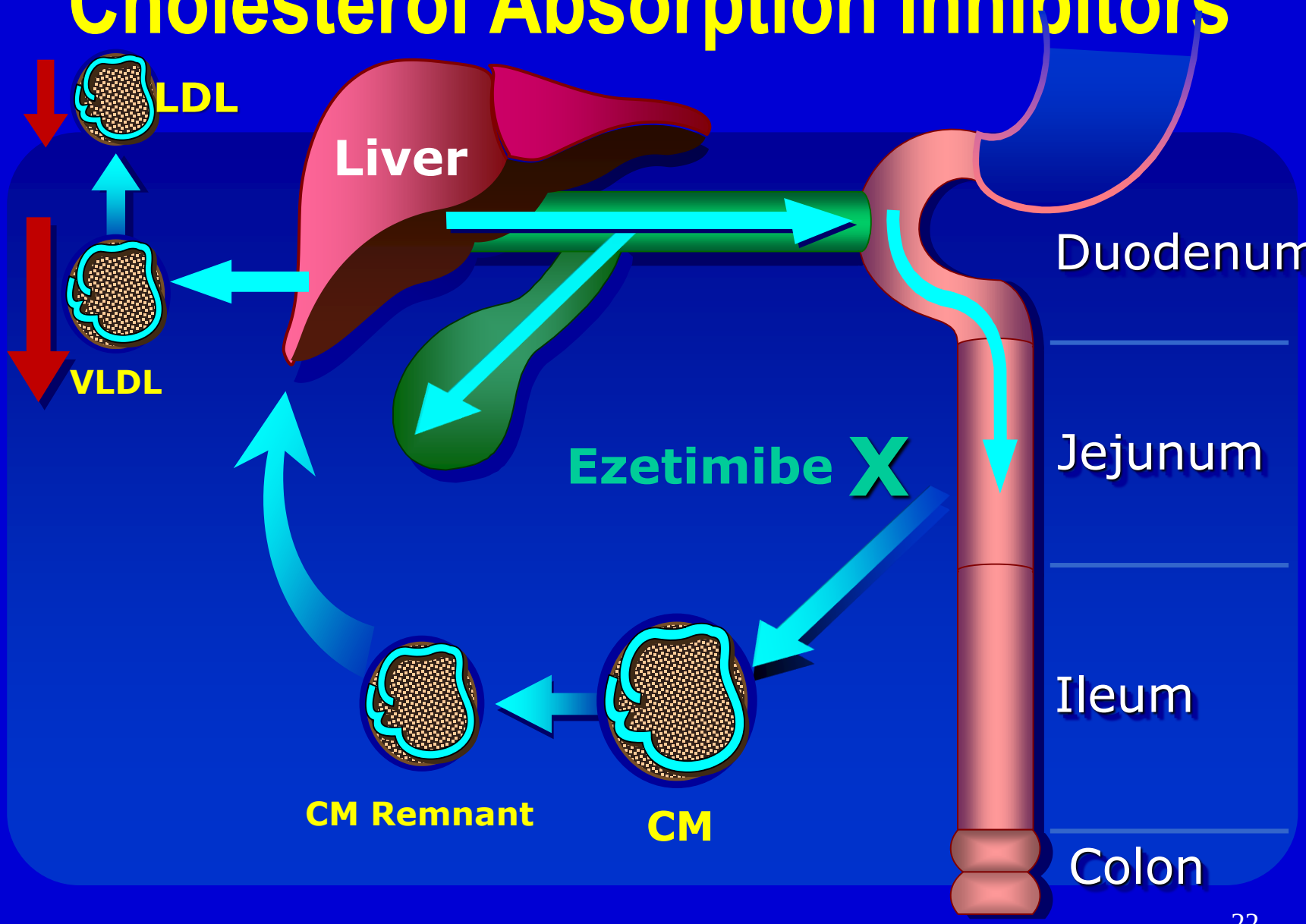
3-Severe hypertriglyceridemia (TG >400 mg/dL) ??

The bile acid binding resins can raise triglycerides modestly ( about 5%) and cannot be used if the triglycerides are elevated.

# Cholesterol Absorption Inhibitors

## Ezetimibe

# Cholesterol Absorption Inhibitors



# Mechanism of action of Ezetimibe

- Ezetimibe reduces C absorption. Therefore, ezetimibe reduces the flux of C from the intestine to the liver.
- Because this C is packaged and resecreted by the liver into the blood as VLDL (precursor of LDL in plasma), reduced flux of C to VLDL particles will lower LDL-C.

# Pharmacological action

↓LDL 20%  ↓ TG 8% , ↑ HDL 1-4%

No effect on steroids, lipid-soluble vitamins, bile acids.

# Pharmacokinetics

- Absorbed & conjugated in intestine to active glucuronide
- Reaches peak blood level in 12–14 hours
- Undergoes enterohepatic circulation
- Its half-life is 22 hours
- Most of the drug is excreted in feces

## Indications

**As Monotherapy;**

Primary prevention of low risk of CHD which needs modest ↓ LDL

**As Combination Therapy: safe**

-With statins; synergistic in moderate/severe ↑ LDL

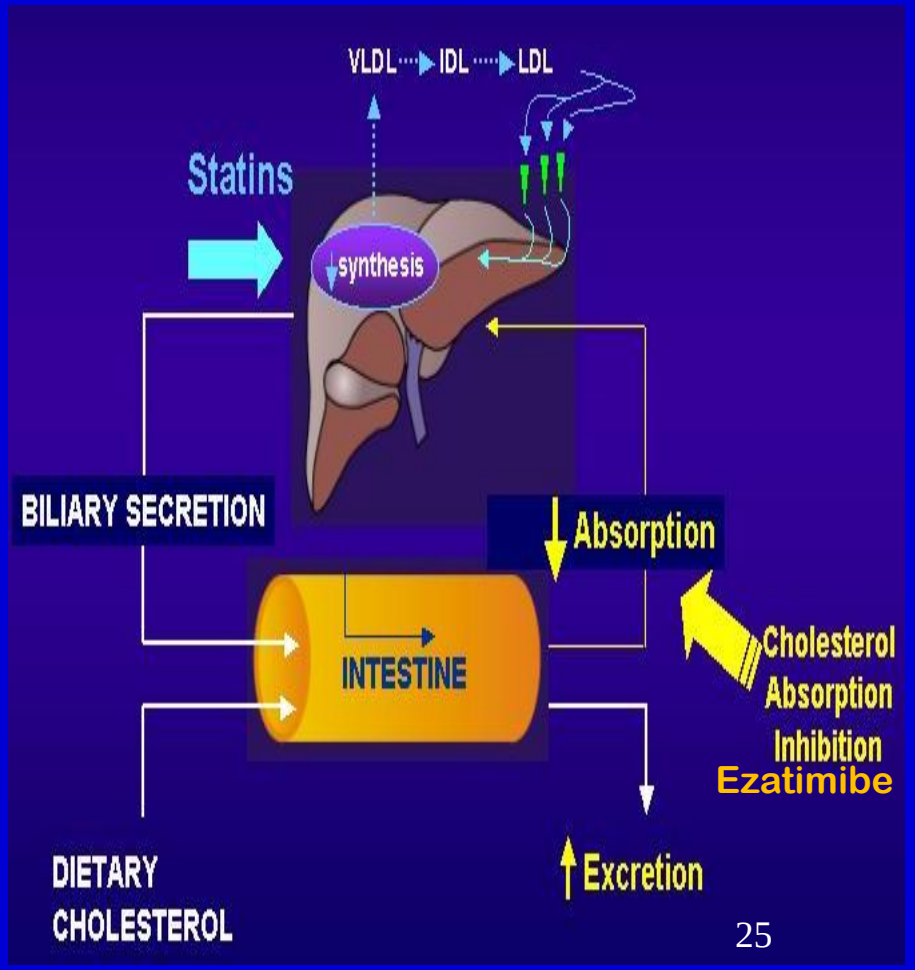
-Or If must ↓ statin dose because of side effects

-Or with other lipid lowering drugs; as fibrates

## ADRs

Not common

GIT disturbance, headache, fatigue, artheralgia & myalgia



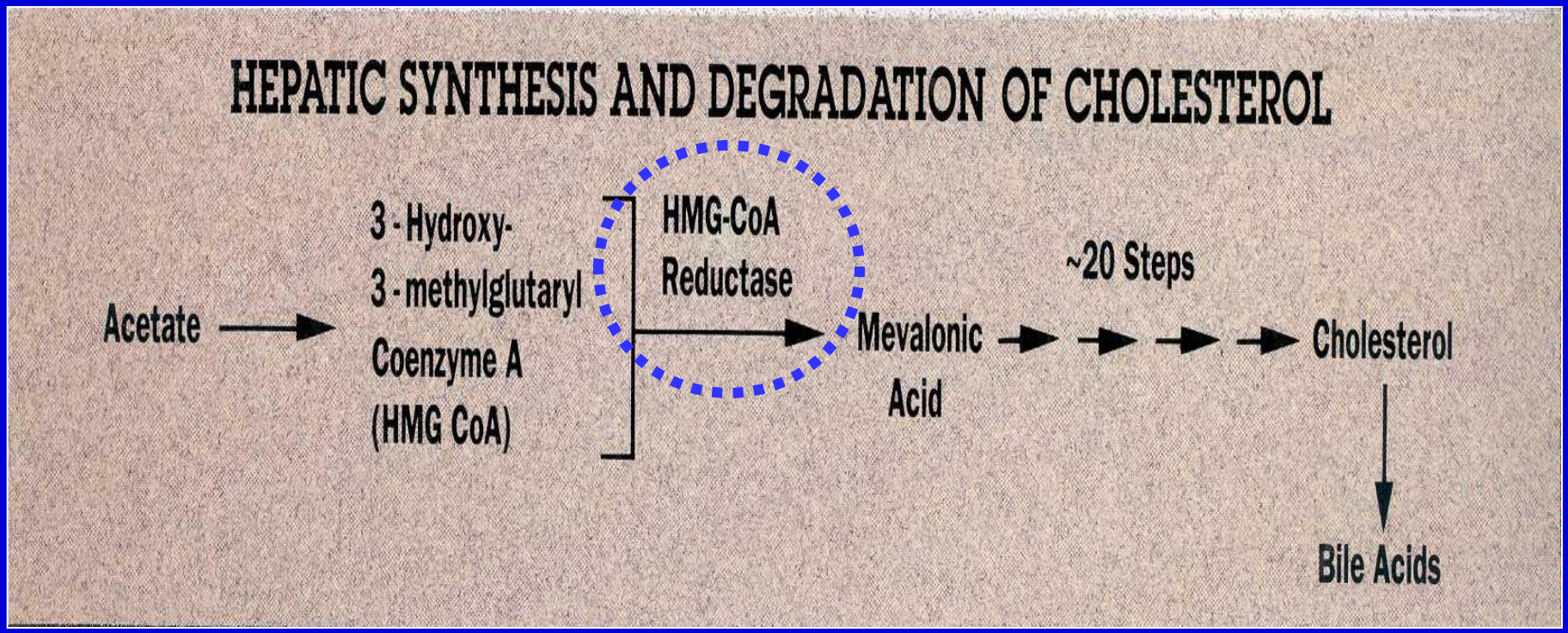
# HMG-Co A Reductase Inhibitors

## Statins

# HMG-Co A Reductase Inhibitors

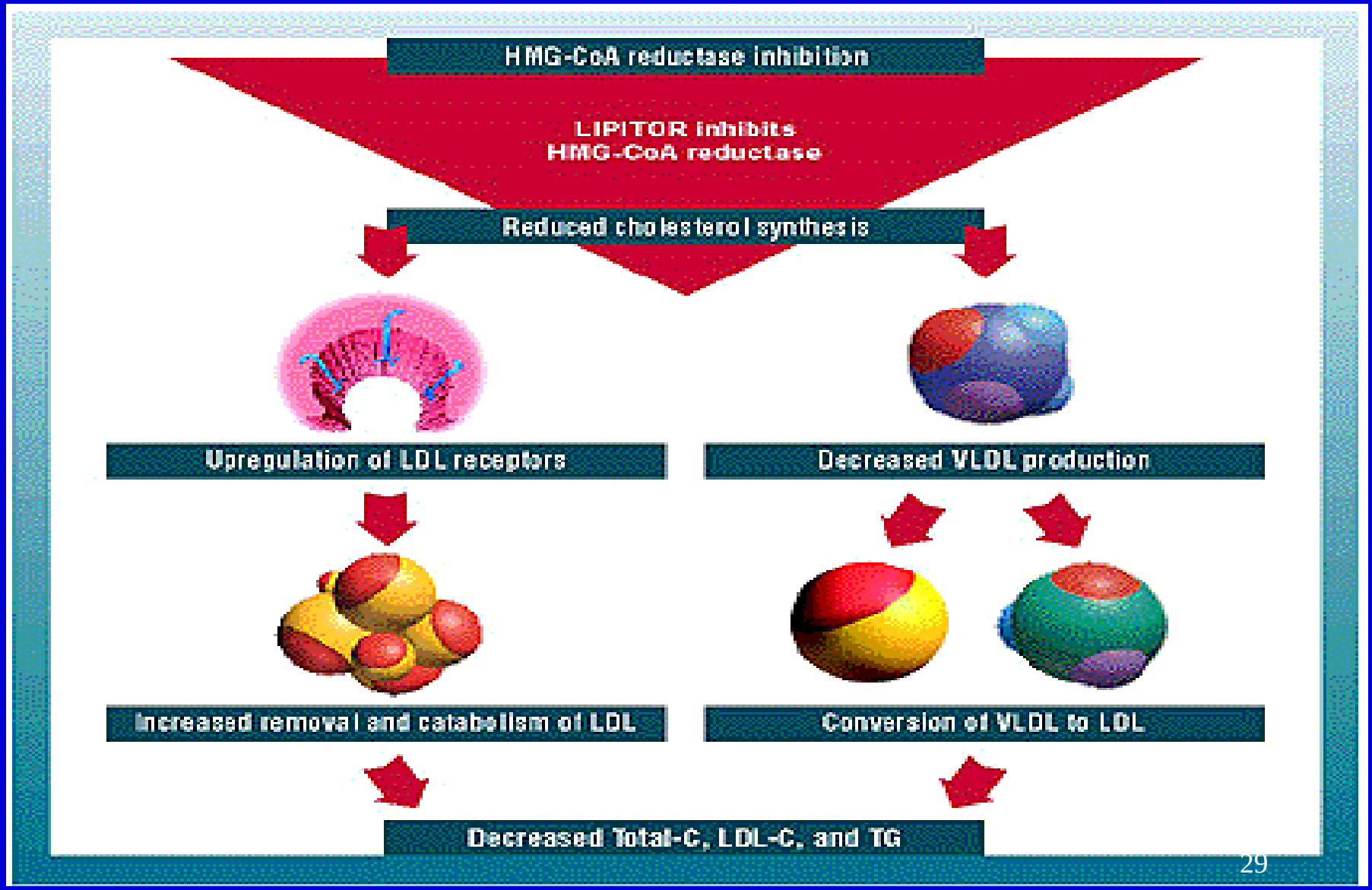
- Hydroxy MethylGlutaryl-Coenzyme A reductase inhibitors or **statins** are the most effective and best-tolerated agents for treating hyperlipidemia
- Statins are considered as first-line drugs when LDL-lowering drugs are indicated

# Statins: Mechanism of Action




**Statins are potent competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in do-novo hepatic C synthesis. Thus, HMG-Co A is not converted to mevalonic acid**

# Statins: Mechanism of Action



1- Statins lower blood C levels by inhibiting de-novo hepatic C synthesis

2- The liver compensates by ↑ the number of LDL receptors on the surface of hepatocytes (upregulation of LDL- R)

3- This results in ↑ removal of LDL from the blood and lowering of serum LDL- C levels

4- Because C is required for the synthesis of (the precursor of LDL-C), production of VLDL ↓

5- Statins cause modest ↓ in plasma TG and slight ↑ in HDL-C

# PLEIOTROPIC EFFECTS OF STATINS

- **Beyond cholesterol lowering , recent studies indicate that some of the cholesterol-independent or "pleiotropic" effects of statins involve:**

➢ improving endothelial function,

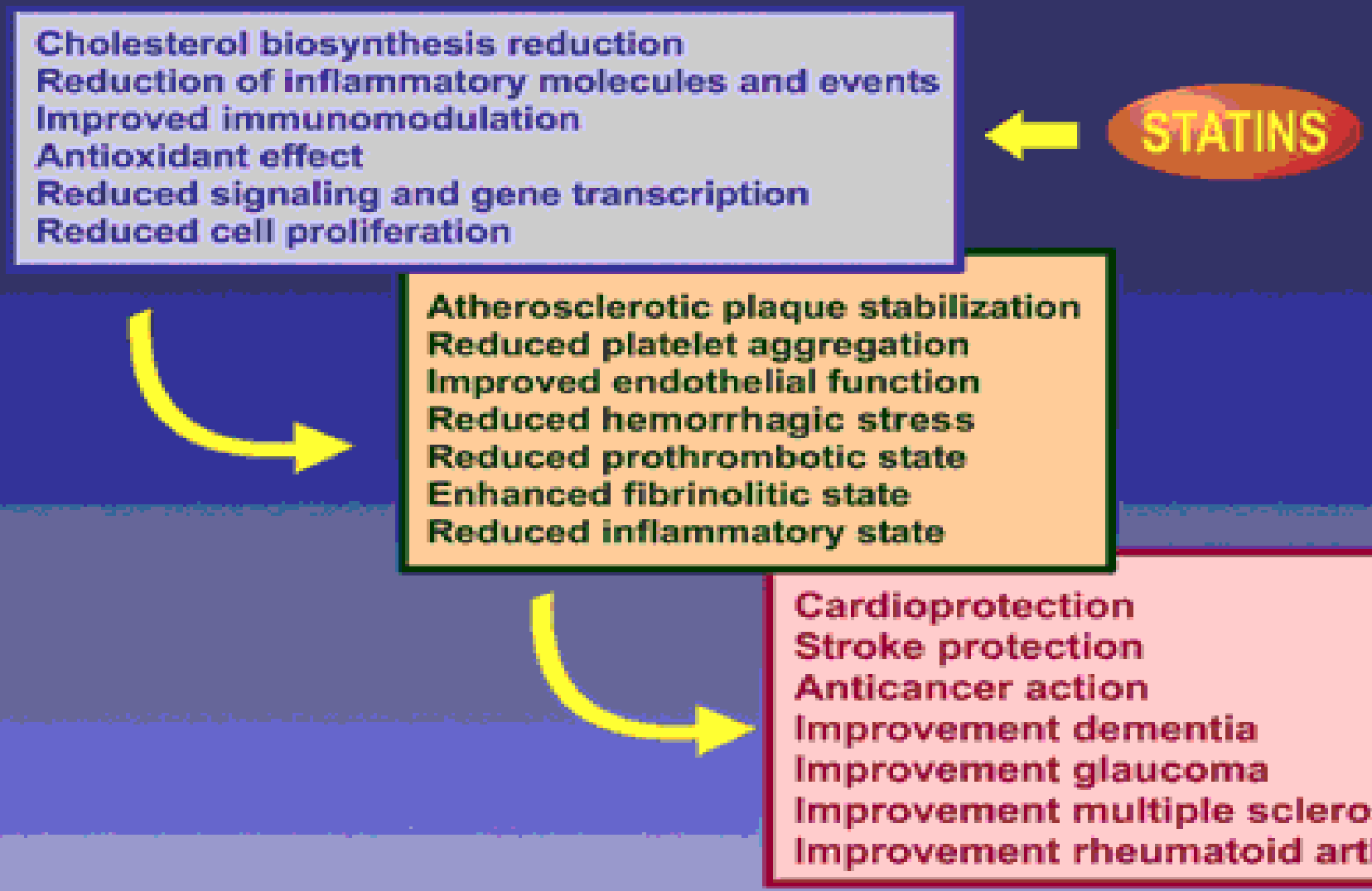
➢ enhancing the stability of atherosclerotic plaques,

➢ decreasing oxidative stress and inflammation,

➢ inhibiting the thrombogenic response.

➢ Furthermore, statins have beneficial extrahepatic effects on the immune system, CNS, and bone.

# PLEIOTROPIC EFFECTS OF STATINS



# Statins: Preparations

- Rosuvastatin (Crestor)
- Atorvastatin (Lipitor)
- Simvastatin (Zocor)
- Pravastatin (Pravachol)
- Lovastatin (Mevacor)

- Used alone or with other anti-hyperlipidemic drugs ( ezetimibe ) for treatment of drug-resistant dyslipidaemia

# Statins: Pharmacokinetics

- Most statins have a high first-pass clearance by the liver
- Greater than 95% of most of these drugs are bound to plasma proteins with short half-life
- Drug-drug interactions involve specific interactions with the cytochrome P-450 drug metabolizing system, especially CYP3A4
- All statins are taken orally at bedtime because of hepatic C synthesis is maximal between midnight and 2:00 a.m. , except atorvastatin taken at any time because of its long half-life (14 hours)

# Indications

## As monotherapy;

**2nd ry Prevention;** In all ischemic insults [stroke, AMI, …..etc.]

So given from the 1st day of ischemic attack

## Pry Prevention;

1. Patients with hyperlipidemia and with other risks for ischemic insults.
2. Type IIa Hyperlipoprotinemia.

If no control → combine (sequestrants / ezetimibe, niacin,.. ) to ↓ C

## As Combination therapy;

1. Mixed dyslipidaemias; added to fibrates or niacin if necessary
2. In diabetics and patients with insulin resistance [metabolic syndrome] because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile

# Statins: Adverse Effects

- **Common side effects:** Headache , myalgia, fatigue, GI intolerance, and flu-like symptoms
- **Hepatotoxicity,** raised concentrations of liver enzymes (serum aminotransferases)
- **Myopathy** (increased creatine kinase [CK] released from muscles)
- **Teratogenicity, statins should be avoided during pregnancy**

# Statins: Drug Interactions

- Statins potentiate the action of oral anticoagulant and anti-diabetic drugs (by displacement from plasma protein binding sites)
- **Drugs that increase the risk of statin-induced myopathy include:**
  - Other antihyperlipidemics ( fibrates )
  - Drugs metabolized by **3A4 isoform of cytochrome P450**: erythromycin, verapamil, cyclosporin, ketoconazole
- **Pravastatin and fluvastatin** are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

# Statin-induced myopathy

- Muscle aches, soreness, or weakness associated with an elevation of creatine kinase (CK) , are the best indicator of statin-induced myopathy.
- Failure to recognize myopathy and to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis.

- ↑serum transaminase → can progress to evident hepatotoxicity
  So lab investigations recommended every 6 month → if levels ↑ up to 3 folds at any time, statin must be stopped then dose adjusted.
- ↑ creatine kinase activity (index of muscle injury) →
  Measured only if myalgia or myositis develops → if ↑ 3-5 folds → we ↓ statin doses / omit combination with fibrates…..

# Niacin (Nicotinic Acid)

# Niacin (Nicotinic Acid)

**Water soluble B-complex vitamin with multiple actions**

- **Niacin is the most effective medication for increasing HDL cholesterol levels and it has positive effects on the complete lipid profile**
- **It is useful for patients with mixed dyslipidemias**
- **Niacin exerts greatest beneficial effects on wide range of lipoprotein abnormalities**

# Mechanism of action:

1. **In adipose tissue**: it binds to adipose **nicotinic acid receptors, this will lead to** decrease in free fatty acids mobilization from adipocytes to the liver resulting in **↓ TG and thus VLDL synthesis**
2. **In liver:** niacin inhibits hepatocyte diacylglycerol acyltransferase-2, a key enzyme **for TG synthesis**

➢ Thus, it decreases VLDL production (decreased TG synthesis and estrification)

**3. In plasma:** it increases LPL activity that increases clearance of VLDL & chylomicron

Niacin also promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL

# Pharmacological actions

- **Effect on VLDL:** ↓ VLDL by:

1) ↓ synthesis in liver

2) increased clearance in plasma

3) ↓ mobilization of free fatty acids from adipose tissue

- **Effect on LDL:** ↓ LDL due to reduction in its precursor (VLDL)
- **Effect on HDL:** Induces modest increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown)
- Niacin also promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL

# Niacin : Adverse Effects

- **The most common side effect is cutaneous flushing,** (which is prostaglandin -mediated , can be avoided by low dose aspirin ½ h before niacin)
- **GIT disturbances:** Dyspepsia , nausea , vomiting , reactivation of peptic ulcer ( can be decreased if taken after meal)
- **High doses:**

♦ Reversible ↑ liver enzymes → hepatotoxicity.
♦ Impairment of glucose tolerance → overt diabetes
♦ ↑ uric acid

# Indications

**Monotherapy or in combination with fibrate, resin or statin**

- Type IIa, IIb hypercholesterolemia & any combined hyperlipidemia
- Patient with hypertriglyceridemia & low HDL-C

# Contraindications

- Gout
- Peptic ulcer
- Hepatotoxicity
- Diabetes mellitus

# Fibric acid Derivatives (Fibrates)

# Fibrates :Mechanism of Action

- Fibrates are agonists of peroxisome proliferator activated receptors (PPARα) which are a class of intracellular receptors that modulate fat metabolism
- They increase genes transcription for lipoprotein lipase (LPL) leading to increased catabolism of TG in VLDL and chylomicrons
- Examples: Clofibrate & Gemfibrozil & Fenofibrate

# Fibrates: pharmacological effects

- ↑ LPL activity, which increases clearance of VLDL & chylomicron in plasma
- A marked reduction in TG (due to stimulation of catabolism of VLDL)
- ↑ FFA uptake by the liver
- ↑ LDL-C uptake by the liver
- ↑in HDL-C (by increasing the production of the apoprotein components of HDL)
- ↑ excretion of hepatic C in bile , thus endogenous hepatic C synthesis may be decreased

# Fibrates : Adverse Effects

- **GIT** (indigestion, abdominal pain, diarrhea)
- **Myositis** : can occur resulting in weakness and tenderness of muscles, use of fibrates with statins is generally inadvisable
- **Gallstones:** Clofibrate increases C content of bile, predisposes to gallstones, and its use is therefore limited to patients who have cholecystectomy

## Indication of Fibrates

1st-line defense for:

*mixed dyslipidemia (i.e. raised serum TG and C)

* Patients with low HDL and high risk of atheromatous disease (often type 2 diabetic patients)

* Patients with severe treatment- resistant dyslipidemia (combination with other lipid-lowering drugs).

# ADRs

1. G.I.T upset, headache, fatigue, weight gain
2. Rash, urticaria, hair loss
3. Myalagia, Myositis, Rhabdomyolysis ➔ Acute renal failure ➔ Occurs >
   -In alcoholics,
   -If combined with statins
   -Or In impaired renal function
4. fibrates should be used with caution in patients with biliary tract disease, as they increase the risk of cholesterol gallstones as a result of an increase in the cholesterol content of bile.

# Interactions

- They displace warfarin from their protein binding sites ➔ ↑ bleeding tendency ➔ anticoagulant dose must be adjusted

- They ↓ metabolism of statins ➔ toxicity ➔ myalgia, myositis, …….etc. Give lower doses

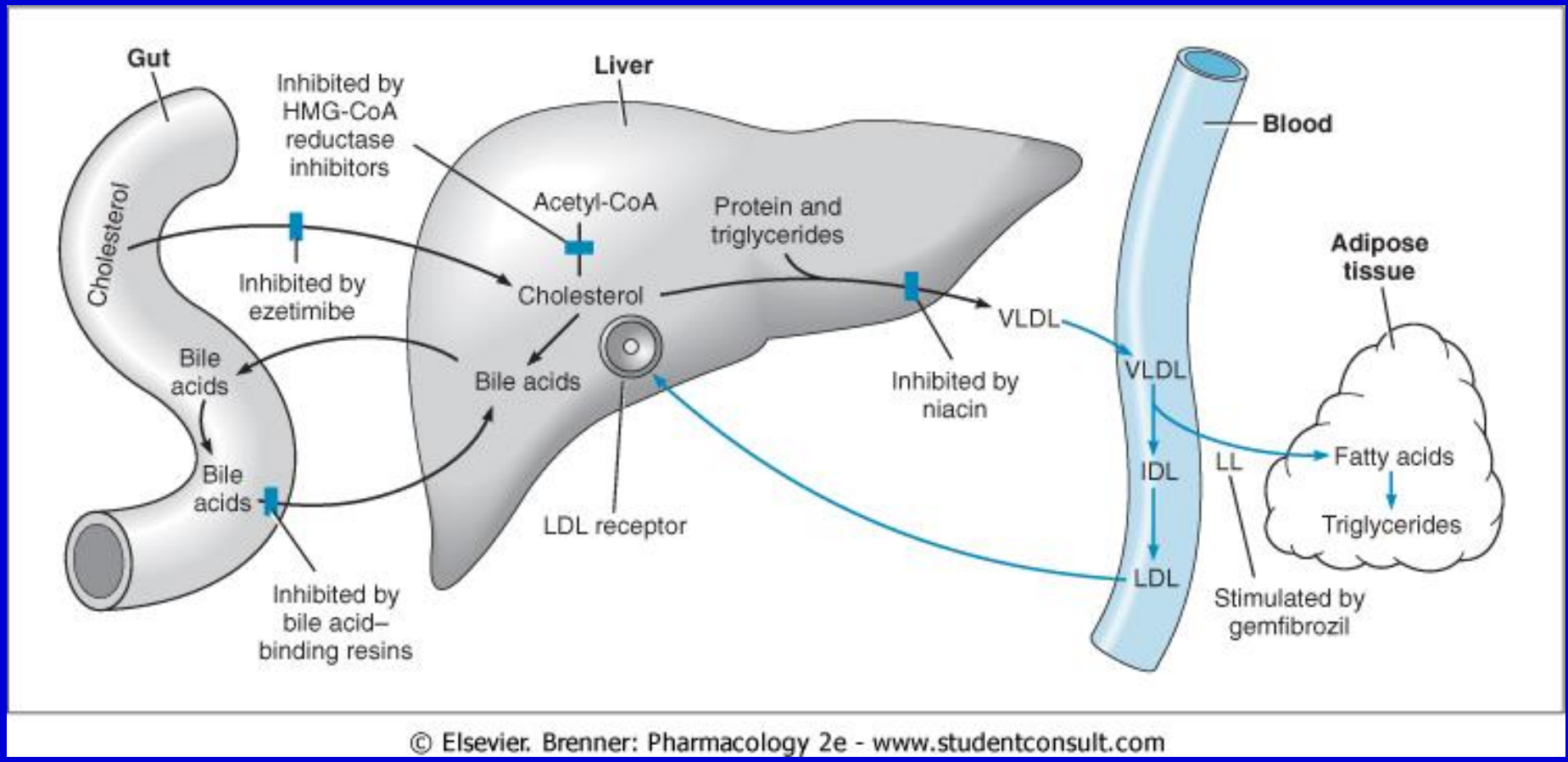
## Drug interactions

- Increased risk of myopathy when combined with statins.
- Displace drugs from plasma proteins (e.g. oral anticoagulants and oral hypoglycemic drugs)

## Contraindications

- Patients with impaired renal functions
- Pregnant or nursing women
- Preexisting gall bladder disease

# Sites and mechanism of drugs for hyperlipidemia



# Medications for Hyperlipidemia

| Drug Class | Agents | Effects (% change) | Side Effects |
|---|---|---|---|
| **HMG CoA reductase inhibitors** | Lovastatin<br>Pravastatin | **↓LDL (18-55),**<br>↑ HDL (5-15)<br>↓ Triglycerides (7-30) | Myopathy, increased liver enzymes |
| **Cholesterol absorption inhibitor** | Ezetimibe | ↓ LDL( 14-18),<br>↓ ↑ HDL (1-3)<br>↓Triglyceride (2) | Headache, GI distress |
| **Nicotinic Acid** | | **↓LDL (15-30),**<br>**↑ HDL (15-35)**<br>**↓ Triglyceride (20-50)** | Flushing,<br>Hyperglycemia,<br>Hyperuricemia, GI distress, hepatotoxicity |
| **Fibric Acids** | Gemfibrozil<br>Fenofibrate | ↓LDL (5-20),<br>↑HDL (10-20)<br>**↓Triglyceride (20-50)** | Dyspepsia, gallstones, myopathy |
| **Bile Acid sequestrants** | Cholestyramine | ↓ LDL<br>↑ HDL<br>**↑ triglycerides** | GI distress, constipation, decreased absorption of other drugs |

# Antihyperlipedemic combinations

**Indications:**

1. Severe hypertriglycerdemia or severe hypercholesterolemia
2. To take lower doses of each drug
3. High LDL or VLDL not normalized with a single drug.

**Resins:** decreases the absorption of statins and ezetimibe ??

**Statin & ezetimibe** (synergistic combination)

Statin blocks synthesis of endogenous cholesterol while ezetimibe blocks absorption of exogenous cholesterol

**Statins & Fibrates**

- Contraindicated (in full dose) because the incidence of myopathy may increase
- So, use not more than ¼ maximum dose of statin and use pravastatin

# Adjuvants in hyperlipidemia

## Omega -3-FA

found in fish oils containing highly unsaturated FA

**Mechanism**

- ↓ enzymes involved in TG synthesis
- ↑ beta-oxidation of FFA

**Pharmacological Effects**

↓ TGs

- ↓ platelet function
- Prolongation of bleeding time
- Anti-inflammatory effects

Some vascular protection

**Indications** Approved as adjunctive for treatment of very high TGs

## β-Sitosterol

found in plants with structure similar to C

**Mechanism & Pharmacological Effects**

Compete with dietary & biliary C absorption → ↓ levels LDL levels ±10%

**Indications** Given as food supplement before meal in hypercholestrolemia