

Drugs for hyperlipidemia

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ILOs

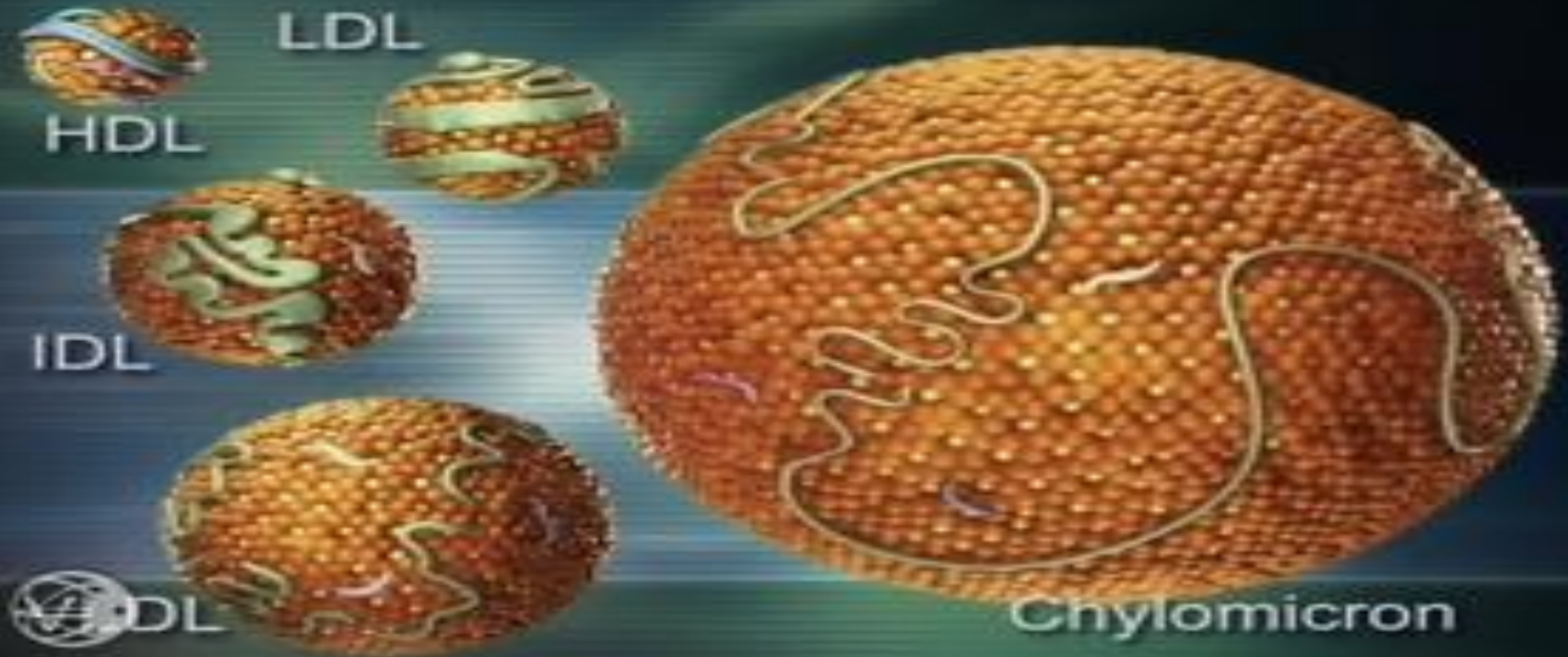
By the end of those 2 lectures the student will be able to:

- ✿ 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

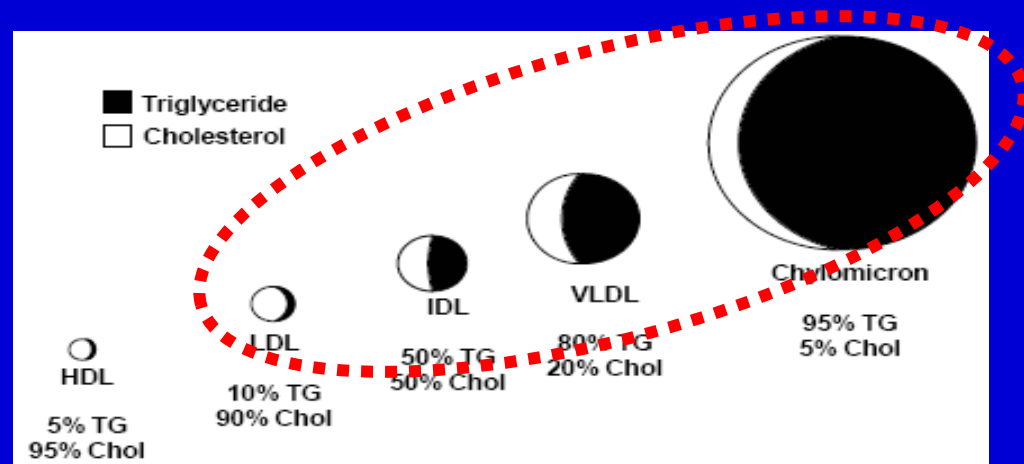
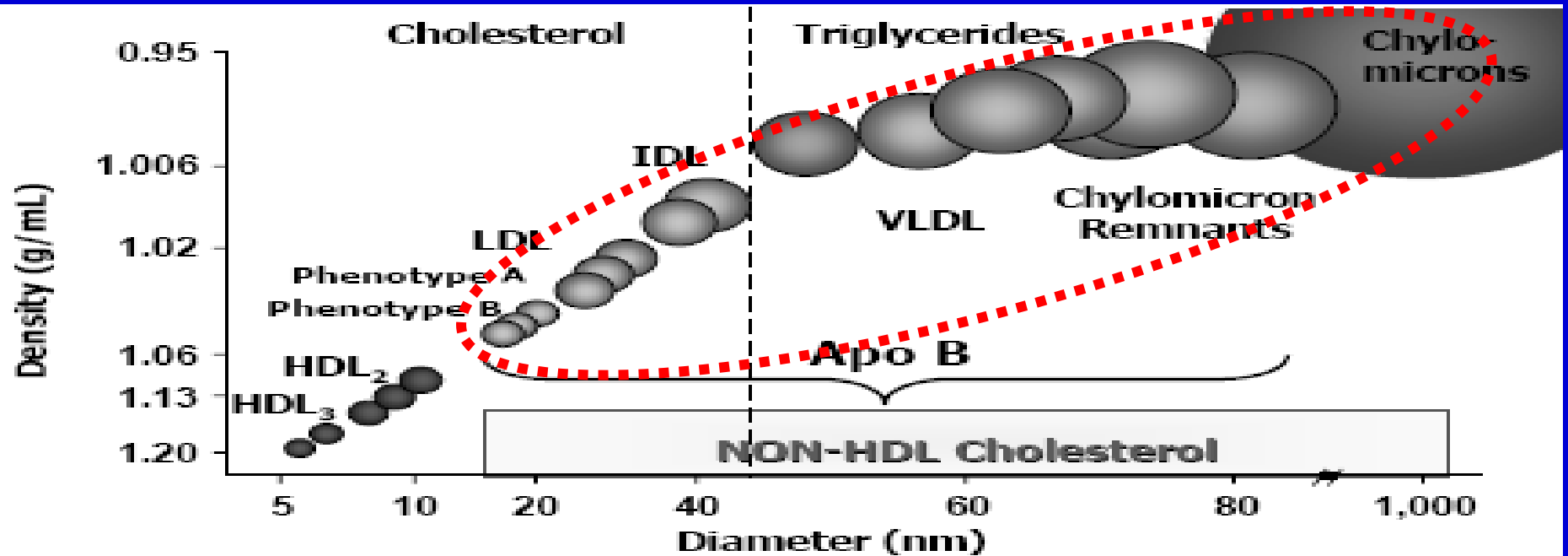
- Hyperlipidemia is a major cause of atherosclerosis which may lead to CAD and ischemic cerebrovascular disease
- Denotes abnormally ↑ levels of any or all **Lipids** and/or **Lipoproteins** [LP] in blood
- ▶ **Lipids** originate from two sources:
 - ▶ **endogenous** lipids, synthesized in the liver
 - ▶ **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

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)

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

De novo synthesis

**C synthesized
in extrahepatic tissues**

Diet

Absorption

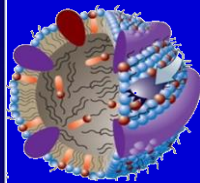
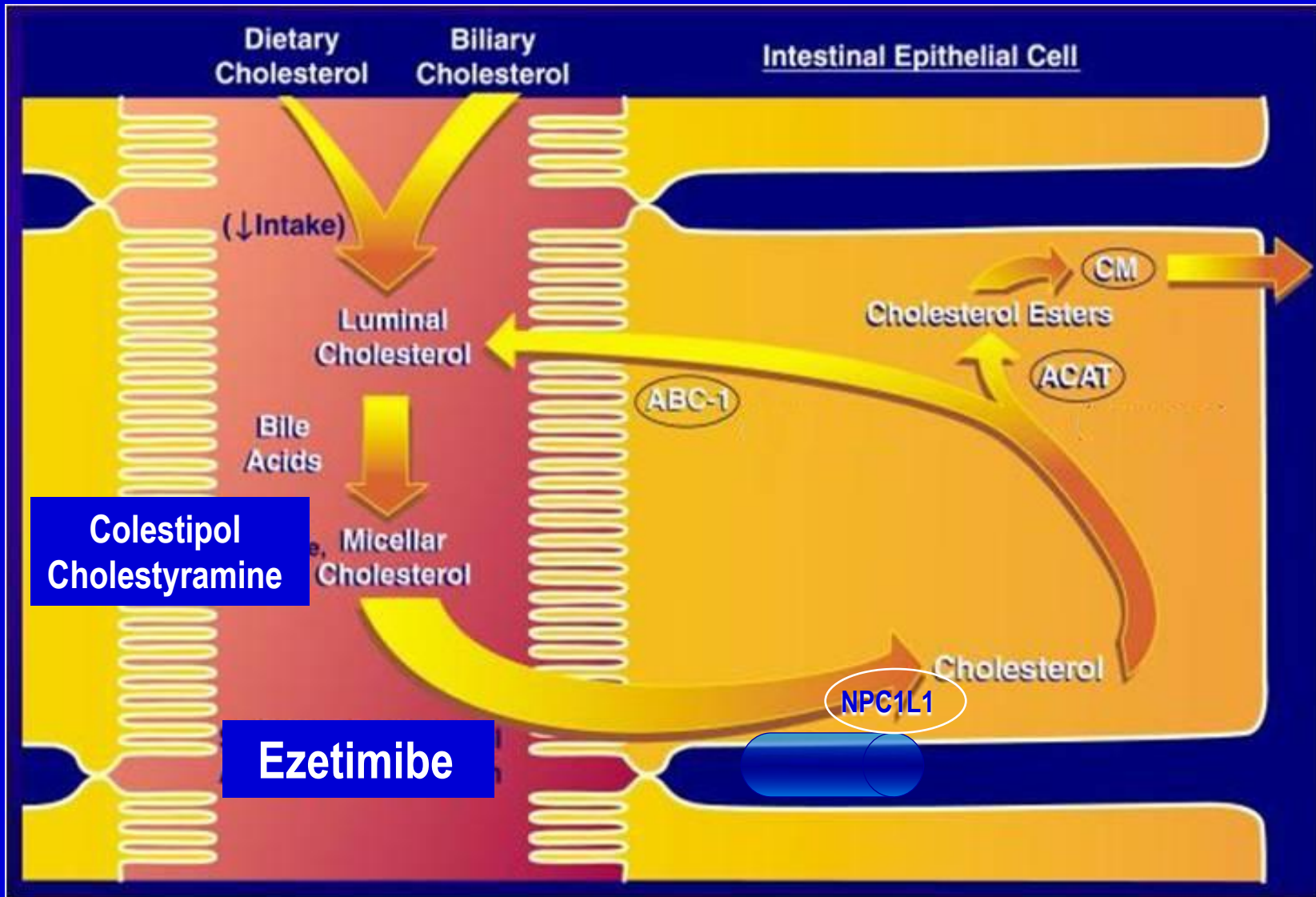
**Liver cholesterol
pool**

**Secretion of
VLDL and
HDL**

**Free C
in bile**

**Conversion to
bile salts/acids**

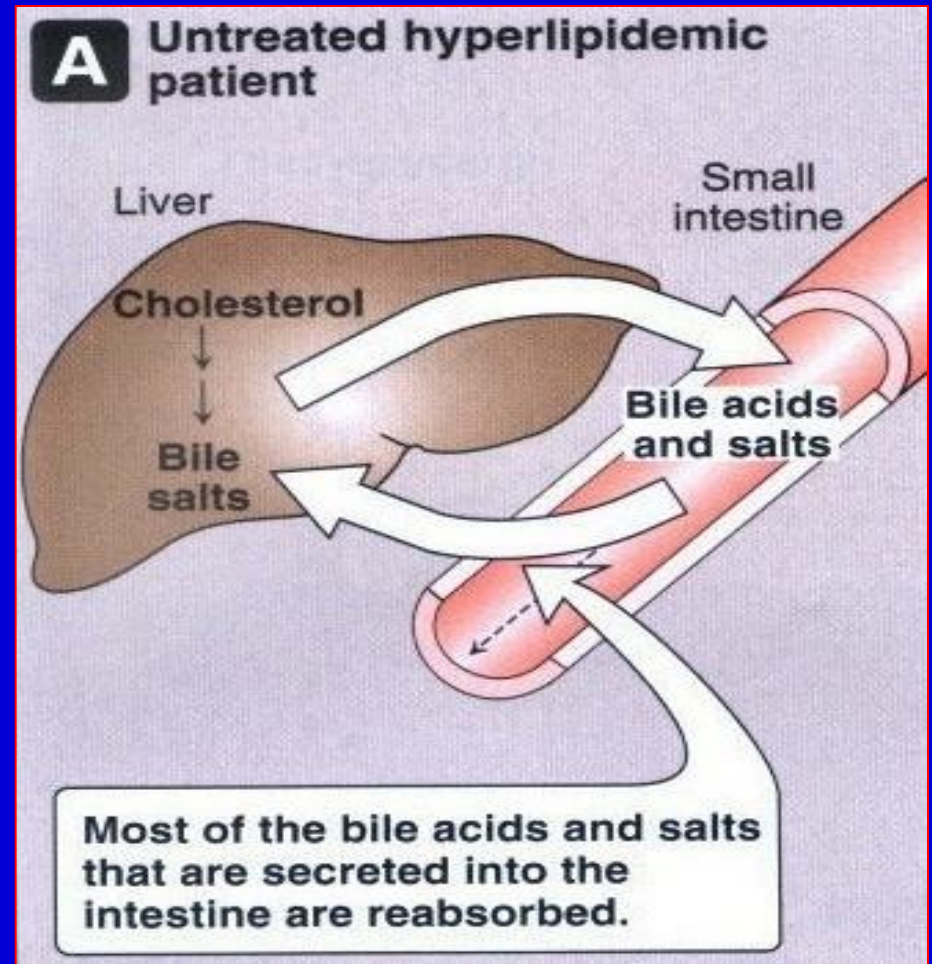
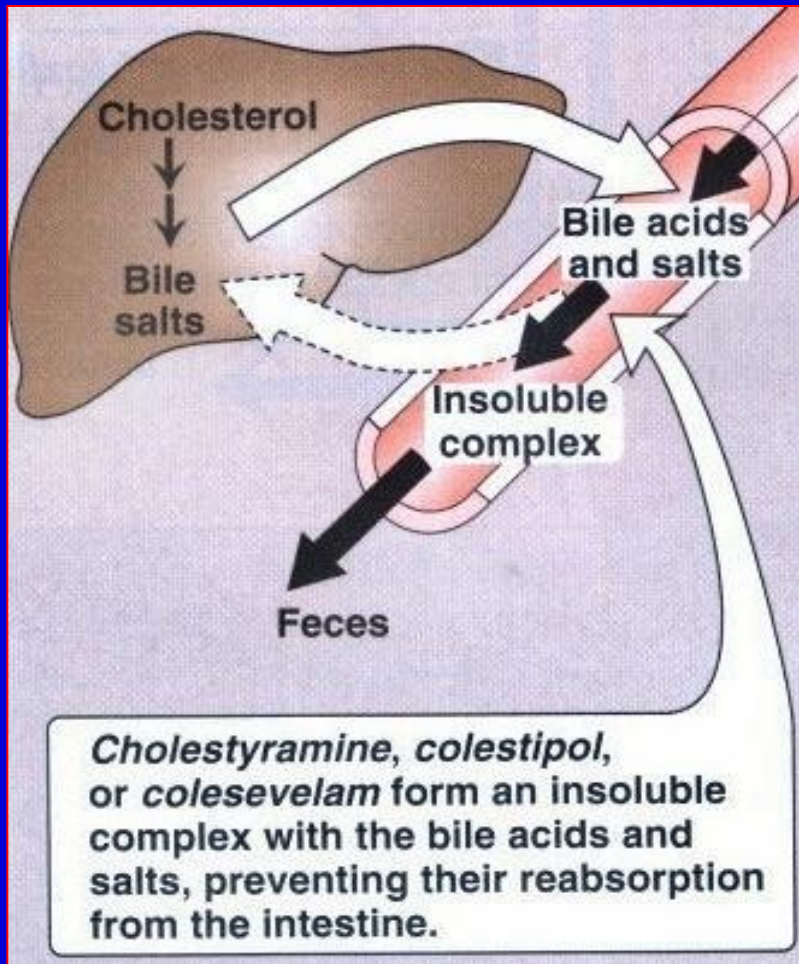
I-Agents Targeting Exogenous Cholesterol



Exchange resins
Bile acid sequestrants

**Cholestyramine &
Colestipol
Colesevelam**

Resins: Mechanism of Action



They disrupt the enterohepatic circulation of bile acids 16

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

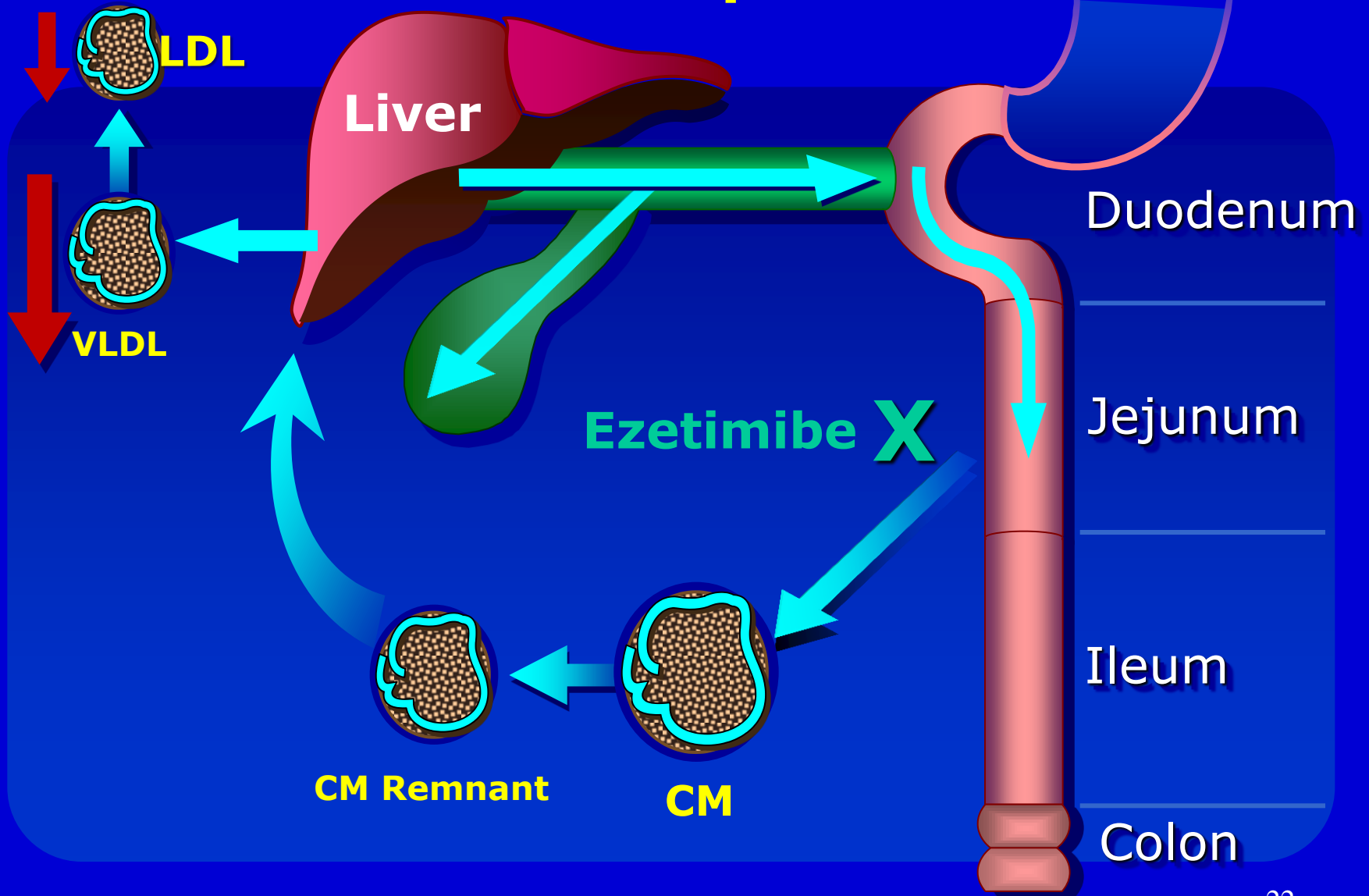
3- Severe hypertriglyceridemia (TG >400 mg/dL) ??

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.
- This mechanism is distinct from that of statins, which promote the clearance of LDL principally in the liver.

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:

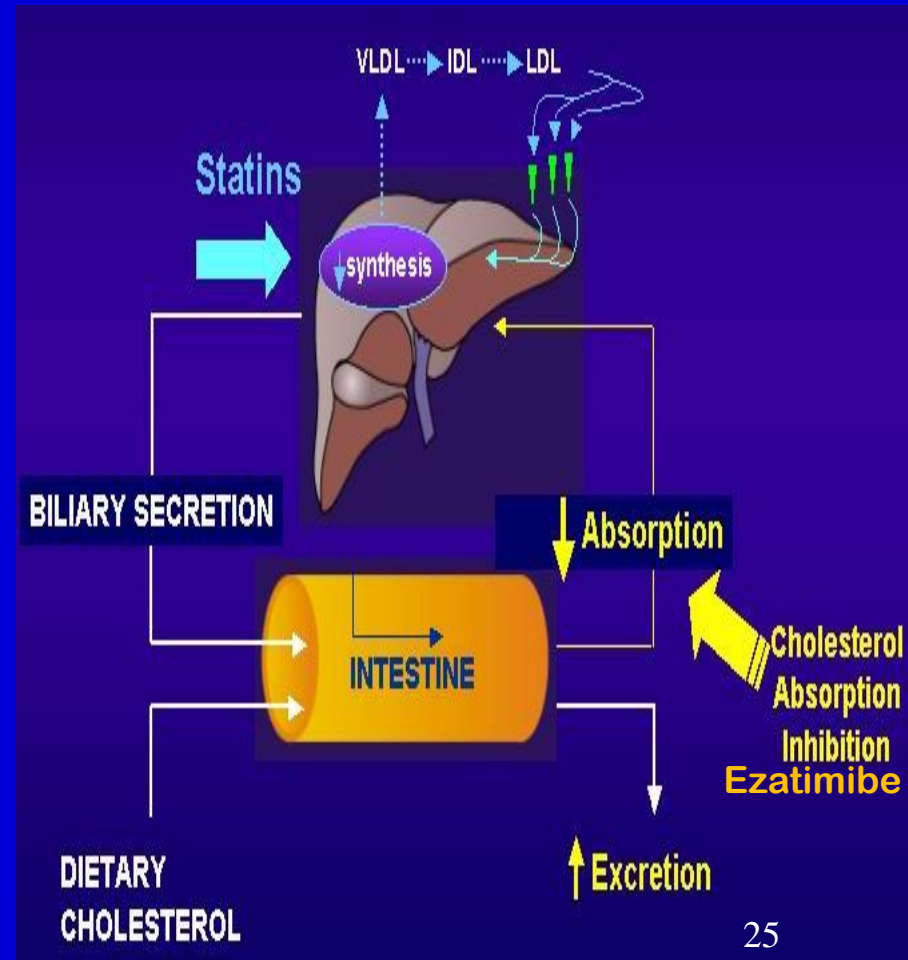
Primary prevention of low risk of CHD which needs modest ↓ LDL

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, arthralgia & myalgia



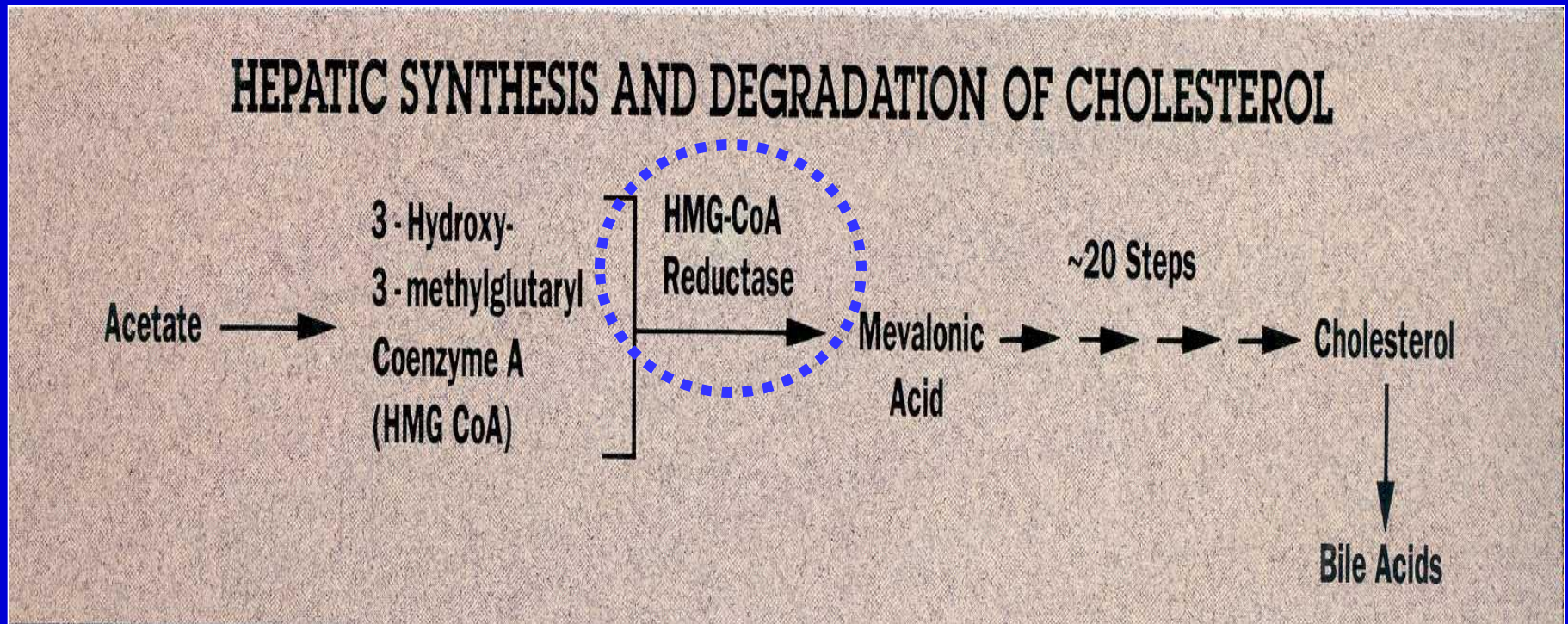
HMG-Co A Reductase Inhibitors

Statins

HMG-Co A Reductase Inhibitors

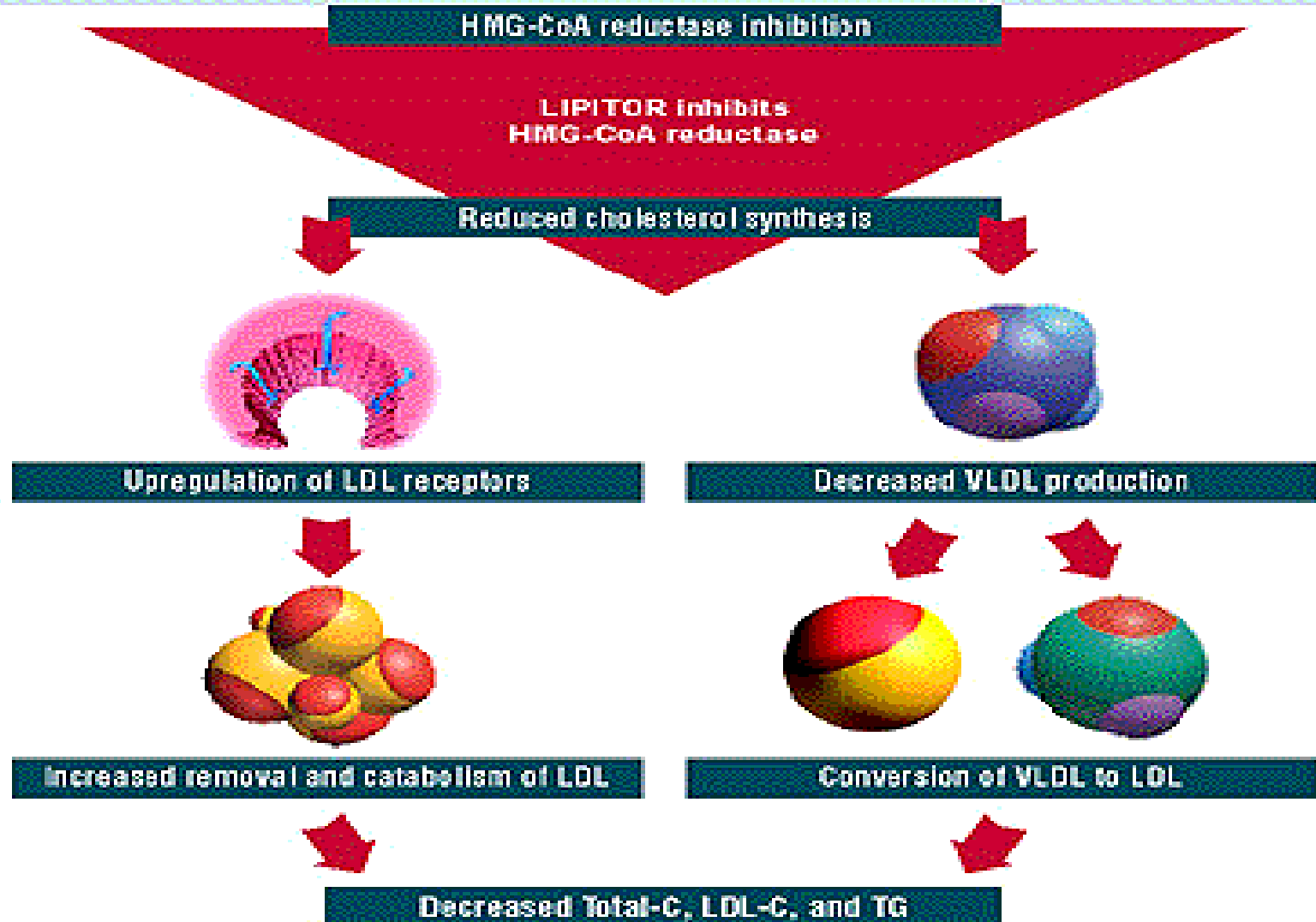
- Hydroxy MethylGlutaryl-Coenzyme A reductase inhibitors or **statins** are the most effective and best-tolerated agents for treating hyperlipidemia
- **Statins** are considered as first-line drugs when LDL-lowering drugs are indicated






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

Cholesterol biosynthesis reduction
Reduction of inflammatory molecules and events
Improved immunomodulation
Antioxidant effect
Reduced signaling and gene transcription
Reduced cell proliferation

STATINS

Atherosclerotic plaque stabilization
Reduced platelet aggregation
Improved endothelial function
Reduced hemorrhagic stress
Reduced prothrombotic state
Enhanced fibrinolytic state
Reduced inflammatory state

Cardioprotection
Stroke protection
Anticancer action
Improvement dementia
Improvement glaucoma
Improvement multiple sclerosis
Improvement rheumatoid arthritis

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 Ila Hyperlipoproteinemia.

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 esterification)
- 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 1/2 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 hypercholesterolemia
- 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 (PPAR α) 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. Myalgia, Myositis, Rhabdomyolysis → Acute renal failure → **Occurs >**
 - In alcoholics,
 - If combined with statins (each –ve metabolism of other)
 - 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

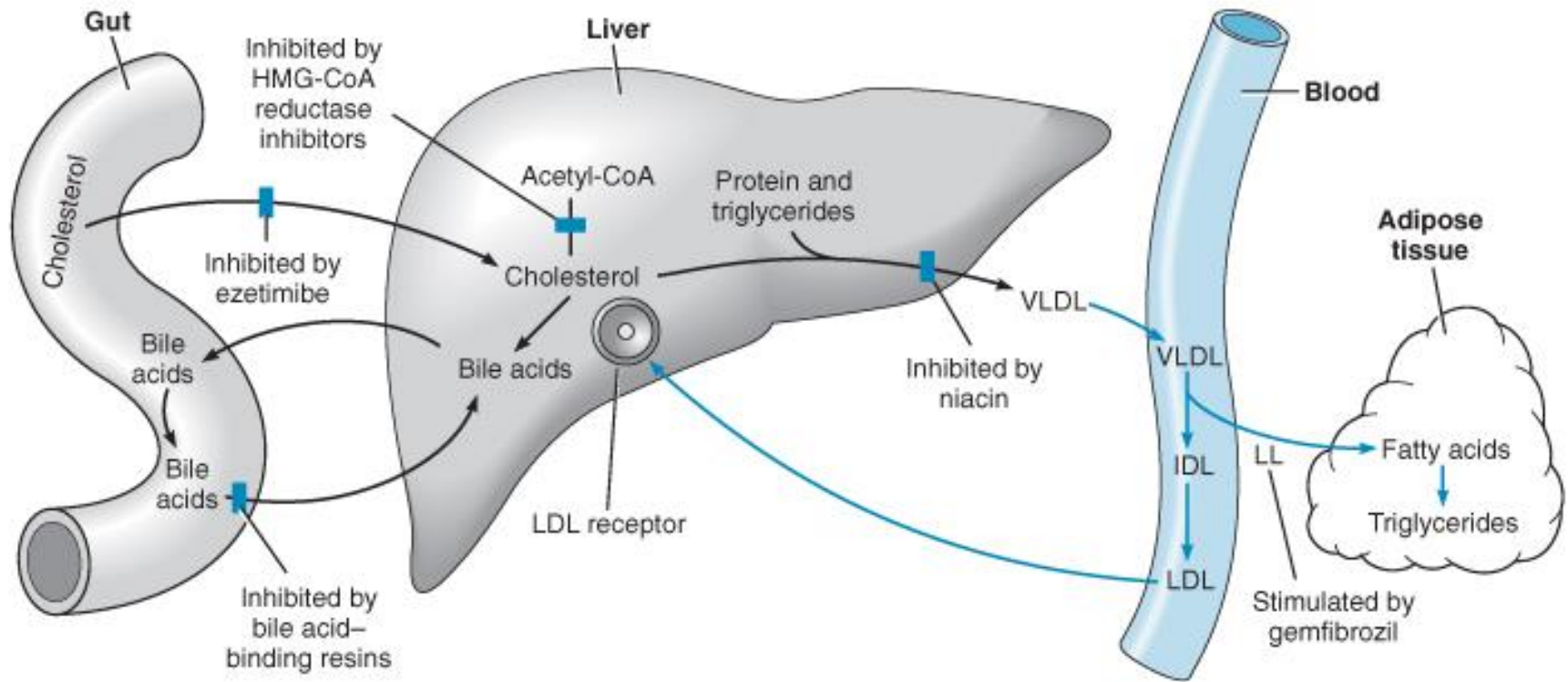
Drug interactions

- **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



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Medications for Hyperlipidemia

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Lovastatin Pravastatin	↓LDL (18-55), ↑ HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↓ ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid		↓LDL (15-30), ↑ HDL (15-35) ↓ Triglyceride (20-50)	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL No change in 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 exogenous cholesterol

Statins & Fibrates

- Contraindicated (in full dose) because the incidence of myopathy may increase
- So, use not more than $\frac{1}{4}$ 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
- ◆ ↓ platelet function
- ◆ Prolongation of bleeding time
- ◆ Anti-inflammatory effects

Pharmacological Effects

↓ TGs

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 $\pm 10\%$

Indications Given as food supplement before meal in hypercholesterolemia