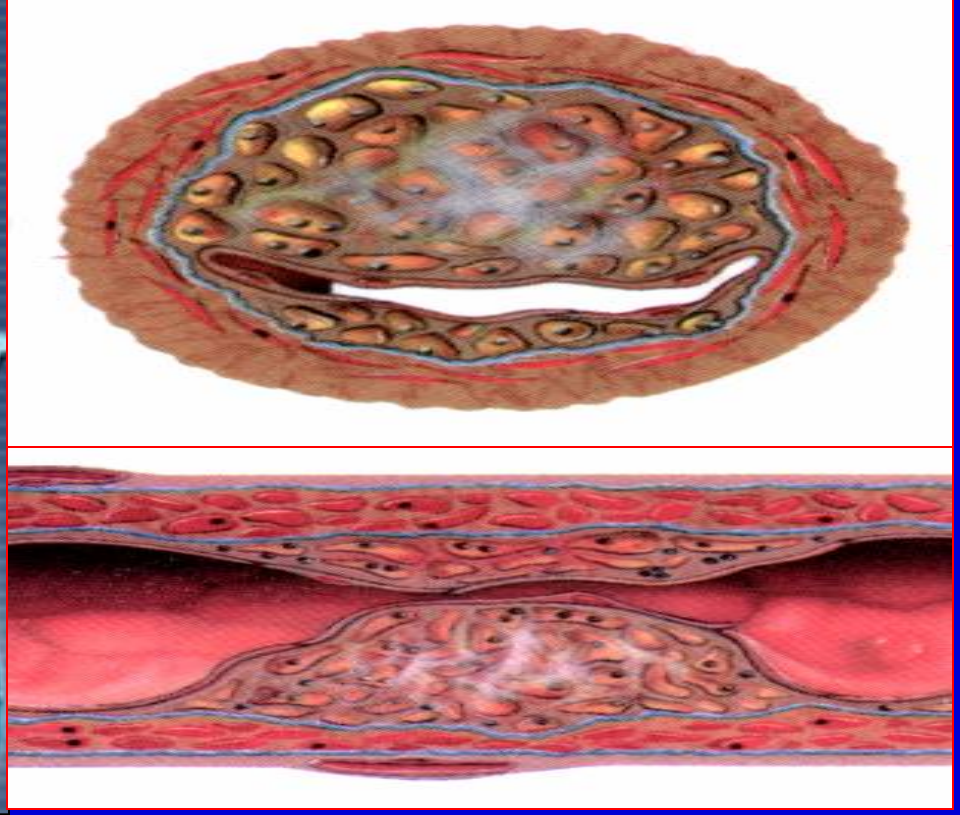


Drugs for hyperlipidemia

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

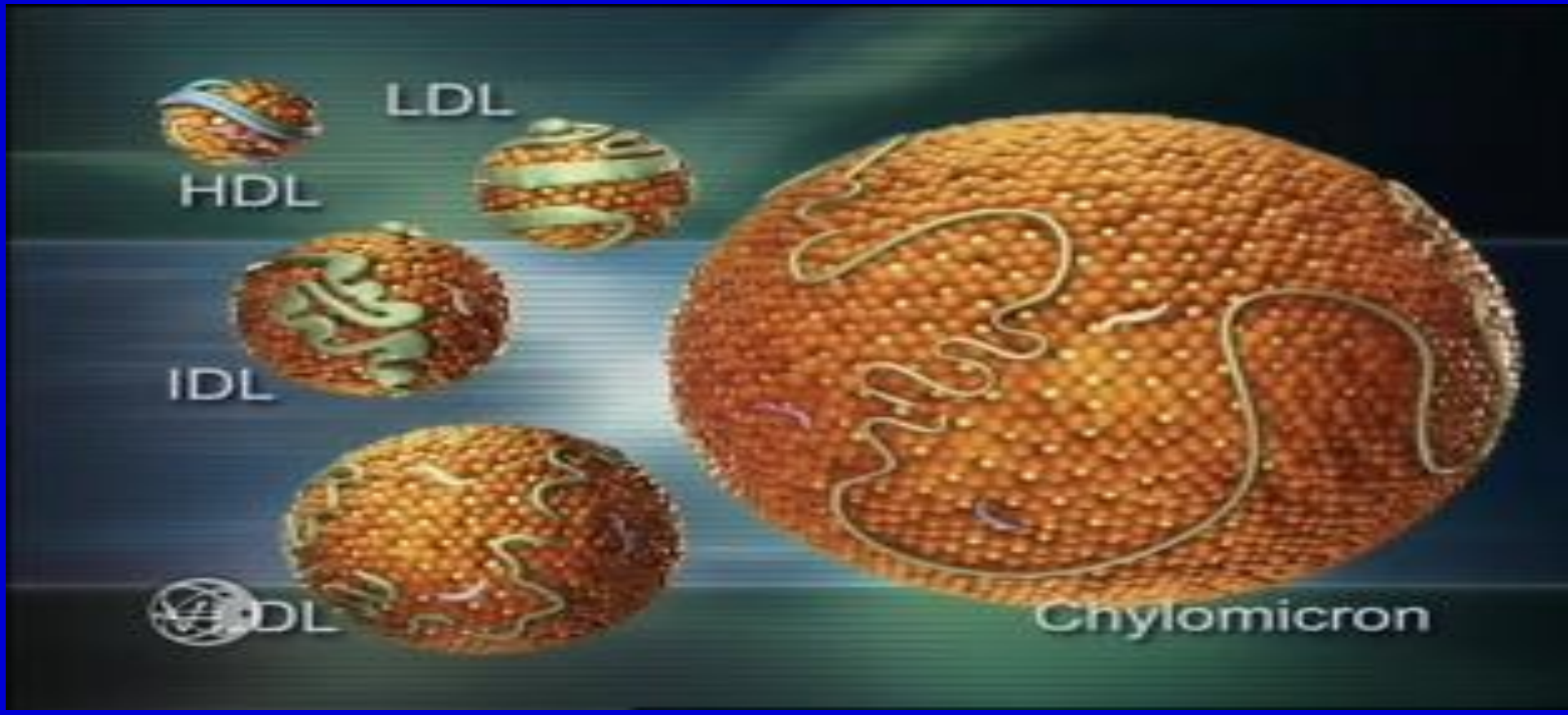
▸ Lipids originate from two sources:

- ▸ 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

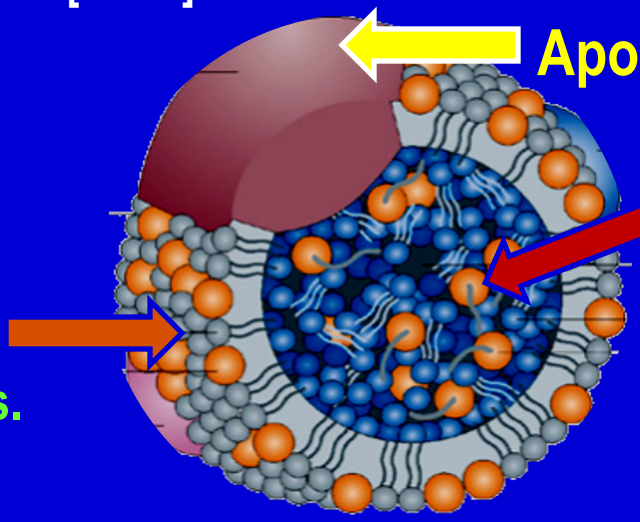
LP

Chylomicrons [CM]

Very low Density lipoprotein [VLDL]

Low Density lipoprotein [LDL]

High Density lipoproteins [HDL]

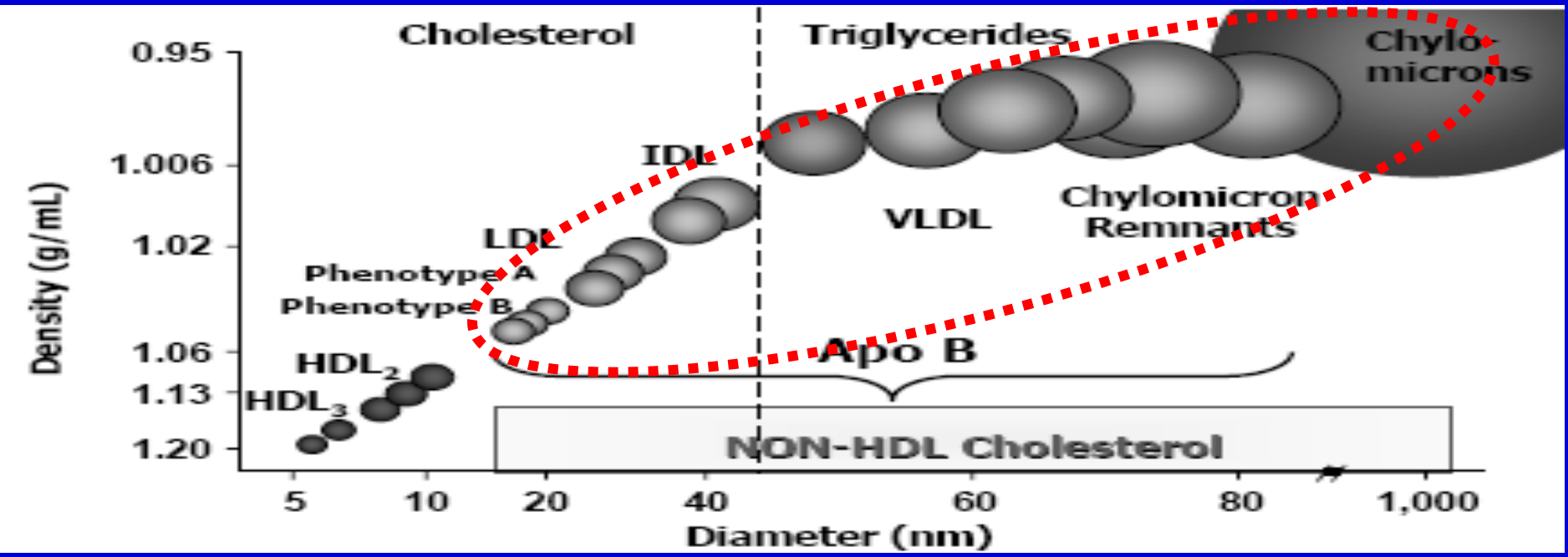


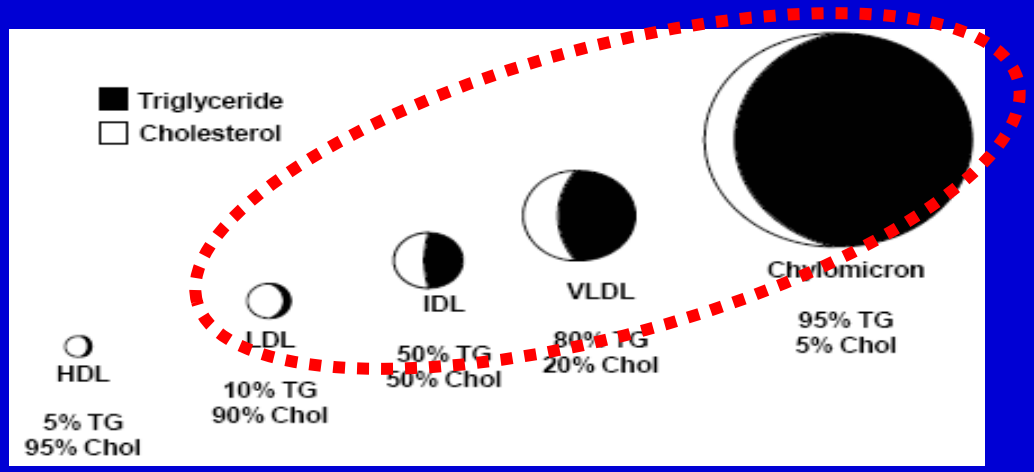
Outer Coat
Phospholipids
Cholesterol
Hydrophilic Gps.

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

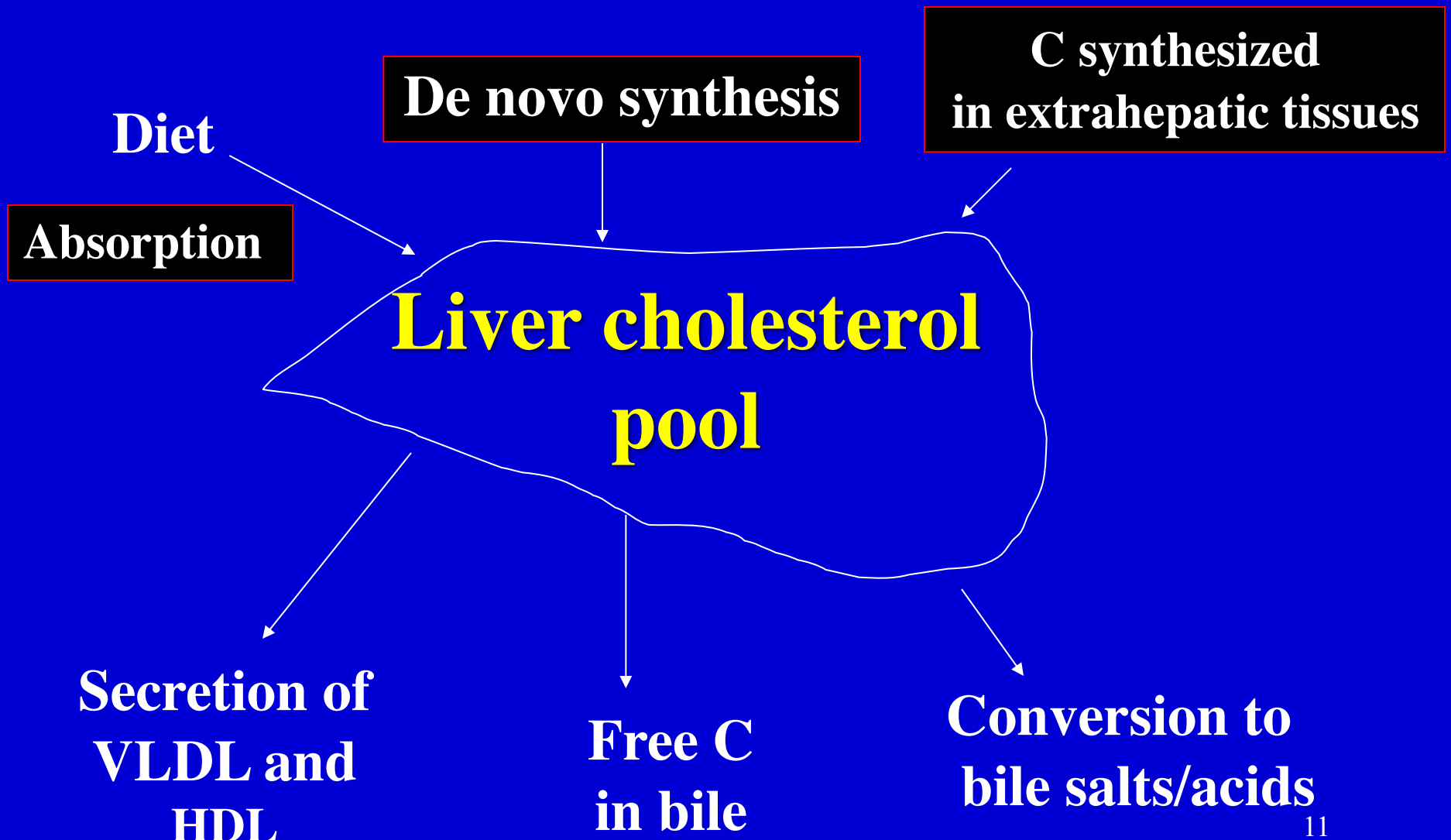
2. Regular exercise

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***

Hepatic Cholesterol Metabolism



Antihyperlipidemic agents

According to the mechanism of action:

1- Inhibition of cholesterol absorption in the intestine

Ezetimibe

2- Sequestering bile acids in the intestine

Bile acid sequestrants : Ion- exchange resins

3-Inhibition of cholesterol synthesis

Inhibitors of hydroxy-methyl-glutaryl coenzyme A reductase (Statins)

4-Altering the 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

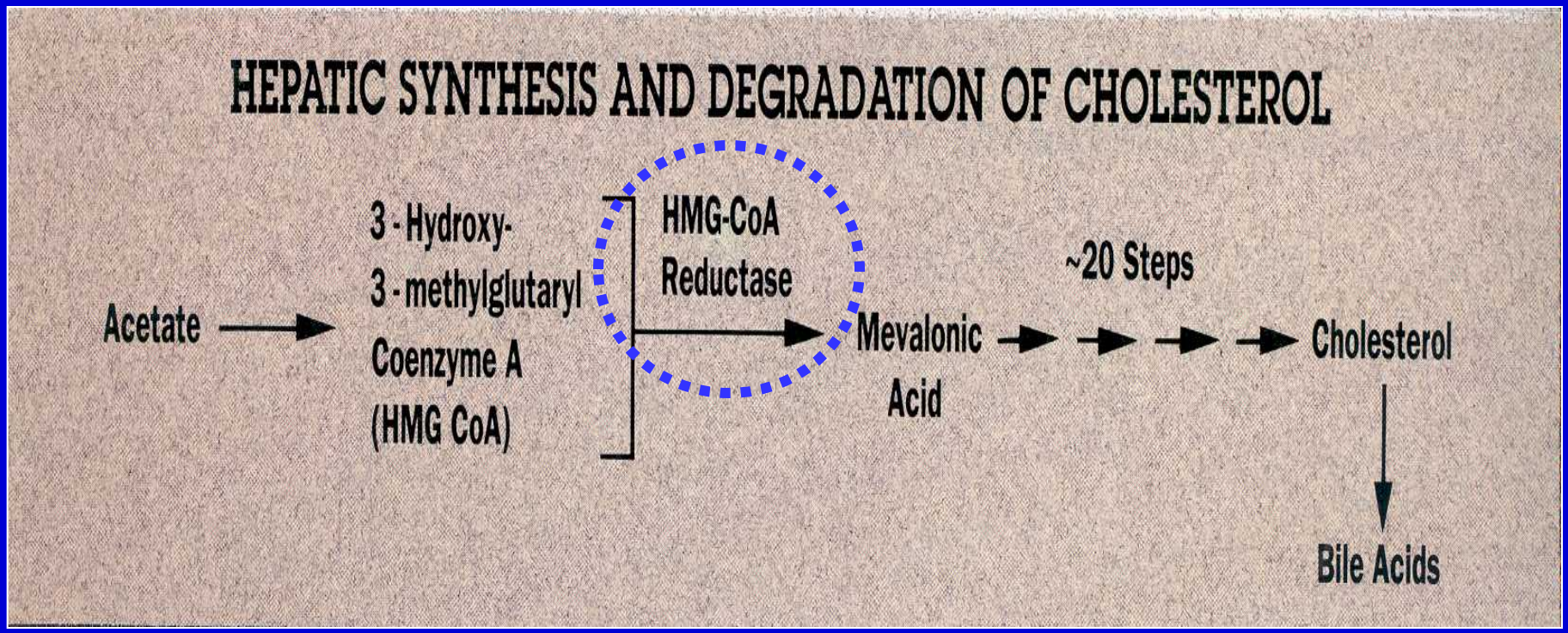
HMG-Co A Reductase Inhibitors

Statins

HMG-Co A Reductase Inhibitors

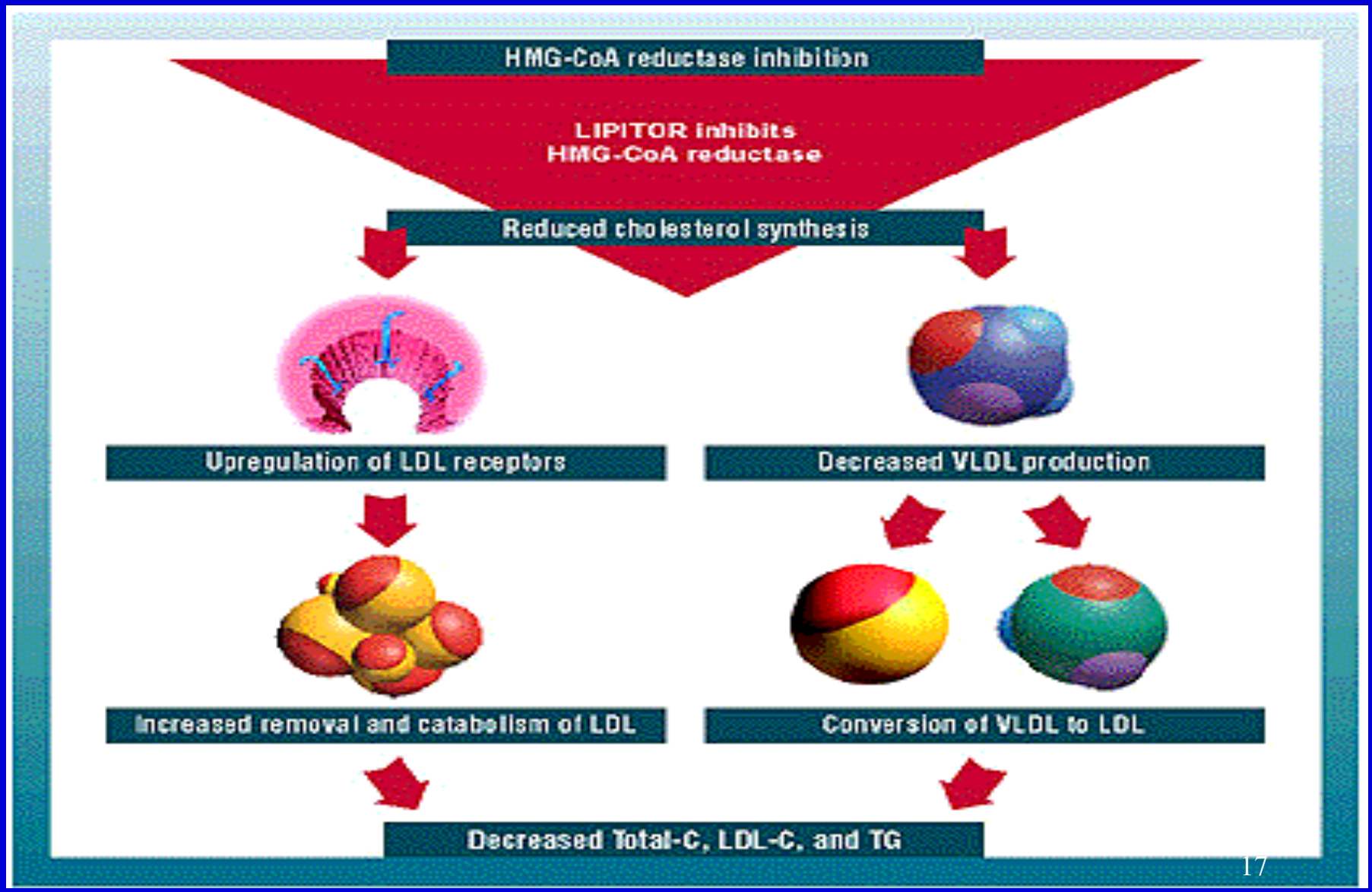
- Hydroxy-Methyl-Glutaryl-Coenzyme A reductase inhibitors or **statins** are the most effective and best-tolerated agents for treating hyperlipidemia
- Statins are considered as first-line drugs when LDL-lowering drugs are indicated

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 VLDL(the precursor of LDL-C) …… LDL-C ↓

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

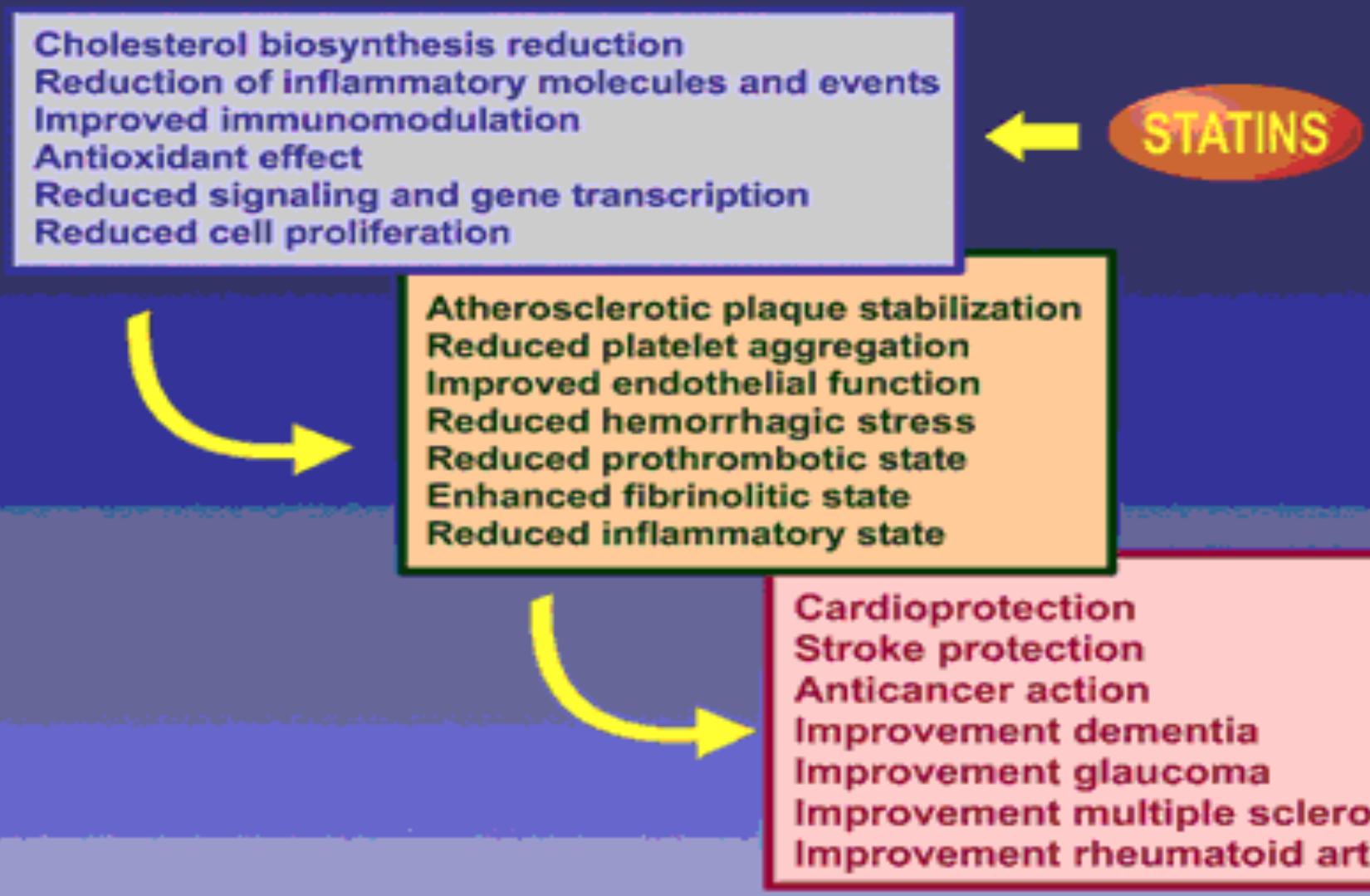
➢ enhancing the stability of atherosclerotic plaques

➢ decreasing oxidative stress and inflammation

➢ inhibiting the thrombogenic response

➢ Furthermore, statins have beneficial extra-hepatic 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

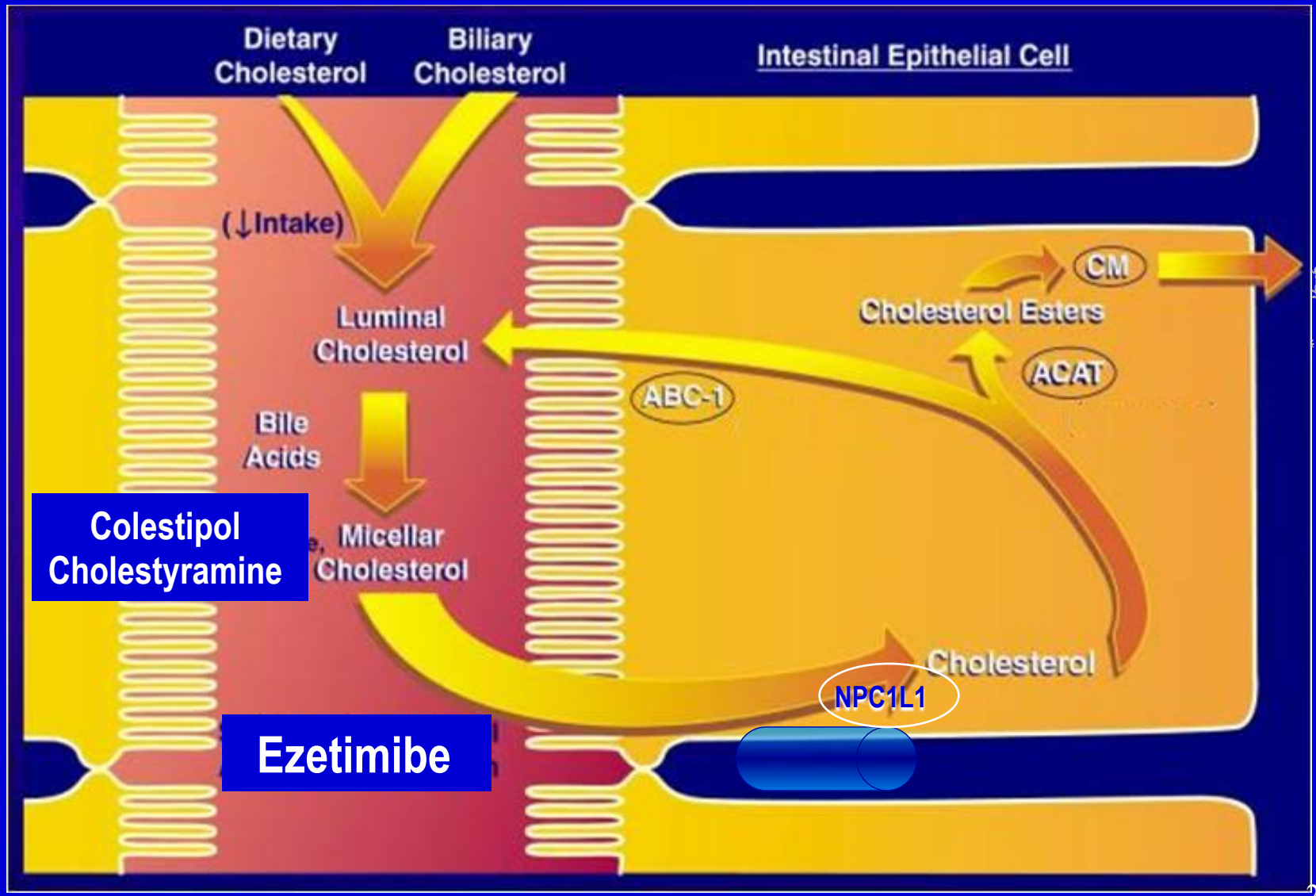
- **Pravastatin and fluvastatin** are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system

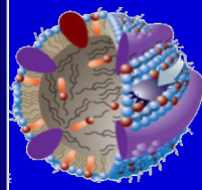
Statin-induced myopathy

- 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 if myalgia or myositis develops → if ↑ 3-5 folds → we ↓ statin doses / omit combination with fibrates…..

Agents Targeting Exogenous Cholesterol



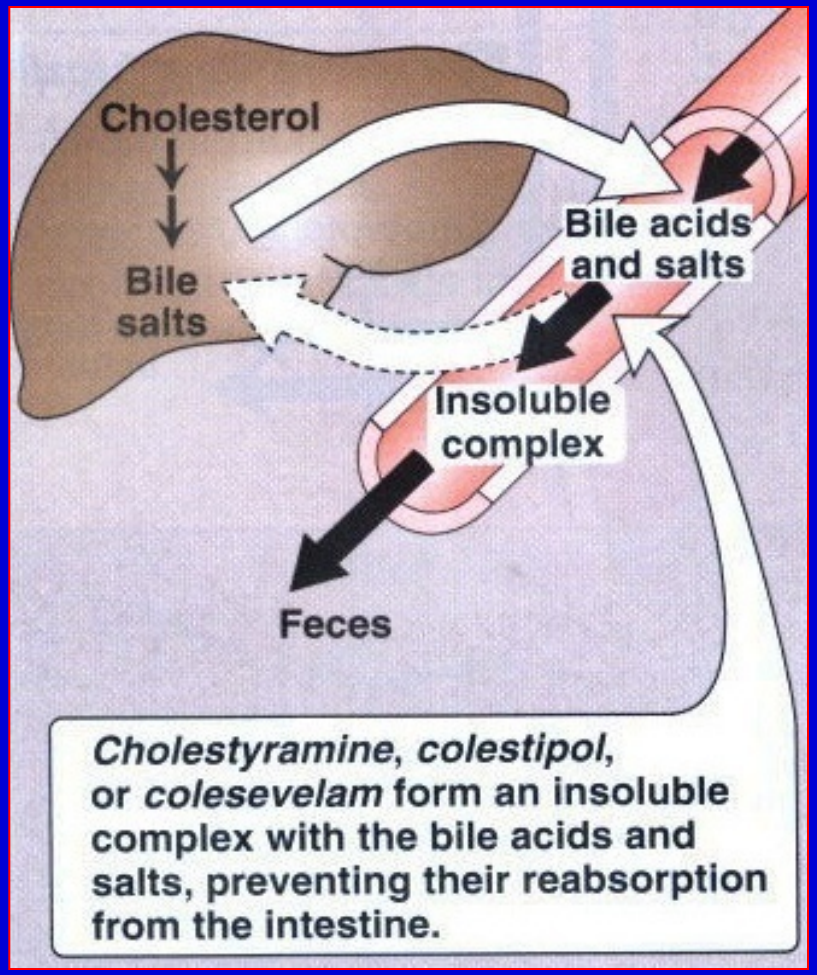


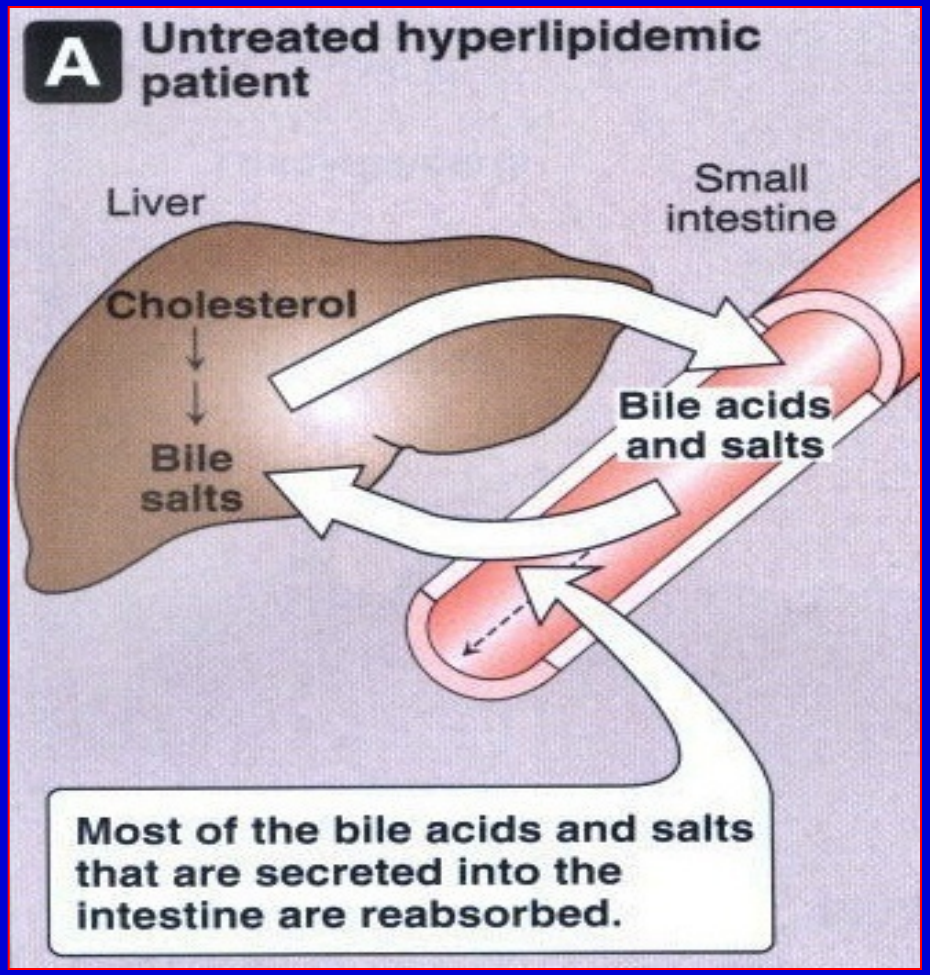
Exchange resins
Bile acid sequestrants

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

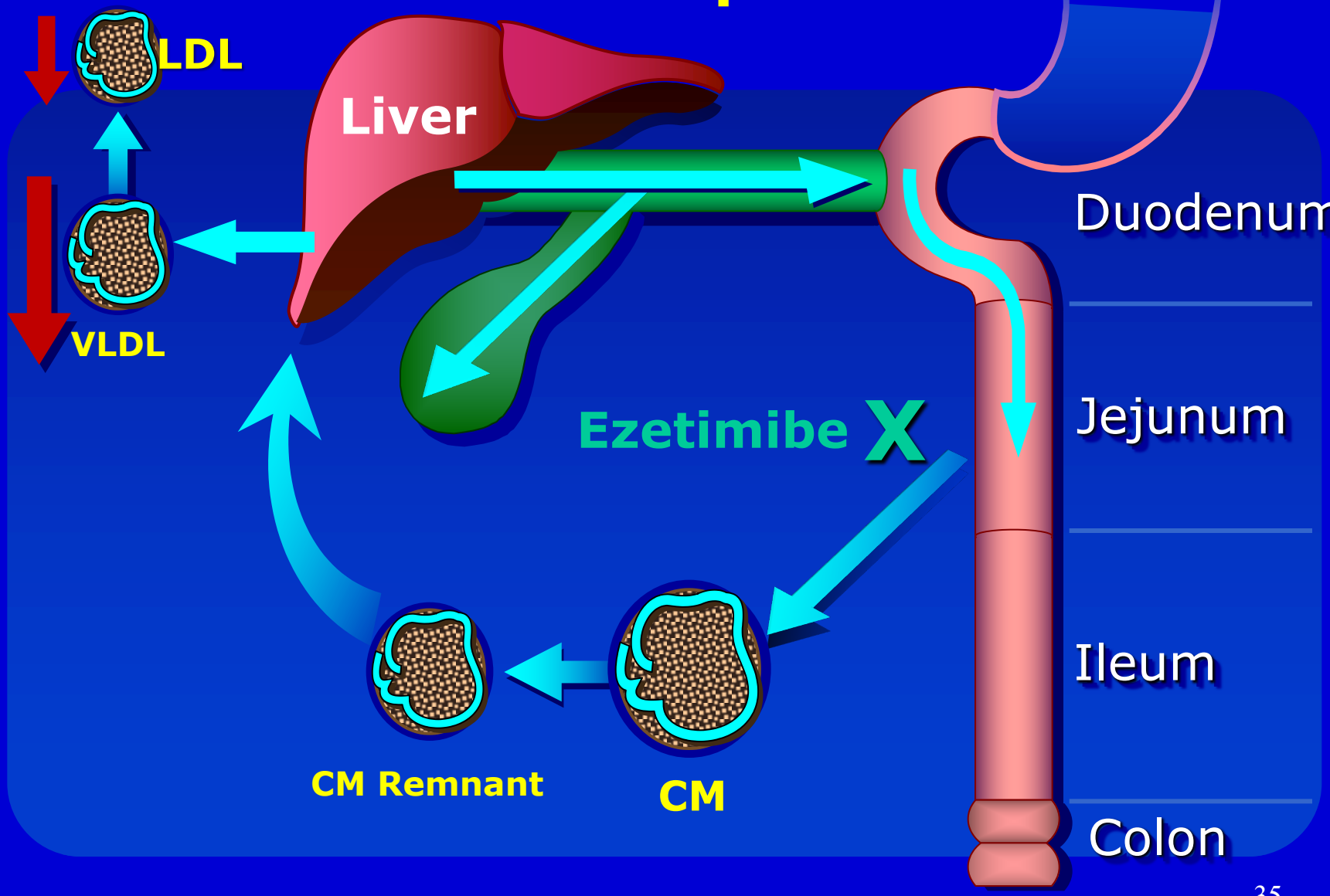
3-Severe hypertriglyceridemia (TG >400 mg/dL) ??

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 by blocking Niemann-Pick C1-Like 1 transporter. 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;

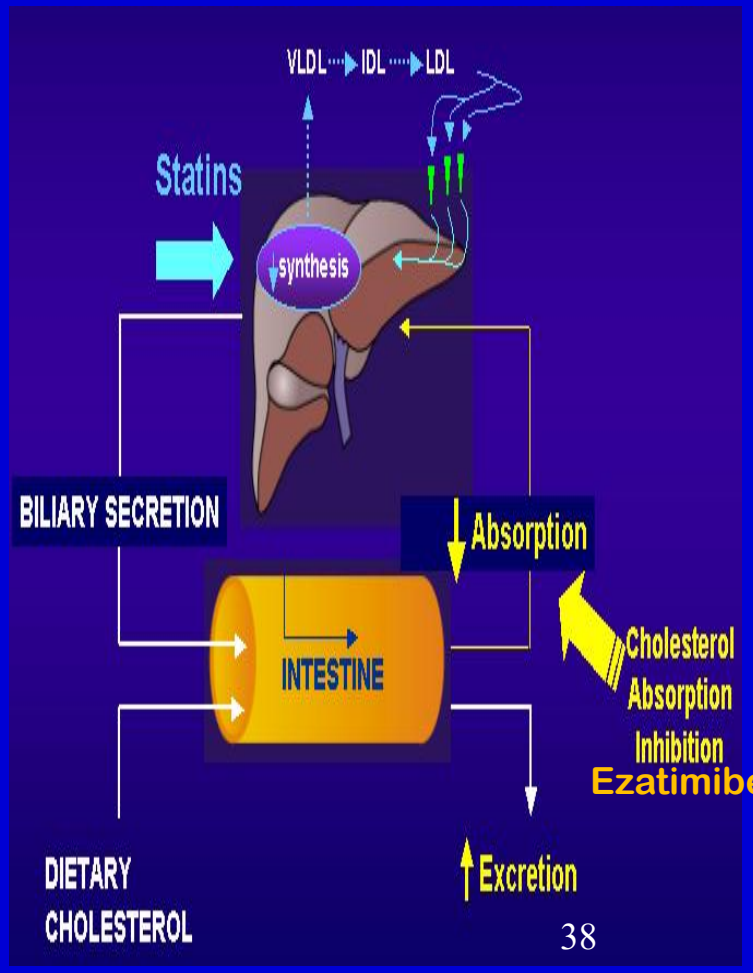
Primary prevention of low risk of CHD which needs modest ↓ LDL

As Combination Therapy; safe

-With statins; synergistic in moderate/severe ↑ LDL

-to ↓ statin dose because of side effects

-Or with other lipid lowering drugs; as fibrates



ADRs

Not common

GIT disturbance, headache, fatigue, artheralgia & myalgia

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 (the major protein component of HDL-C) 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

- 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.

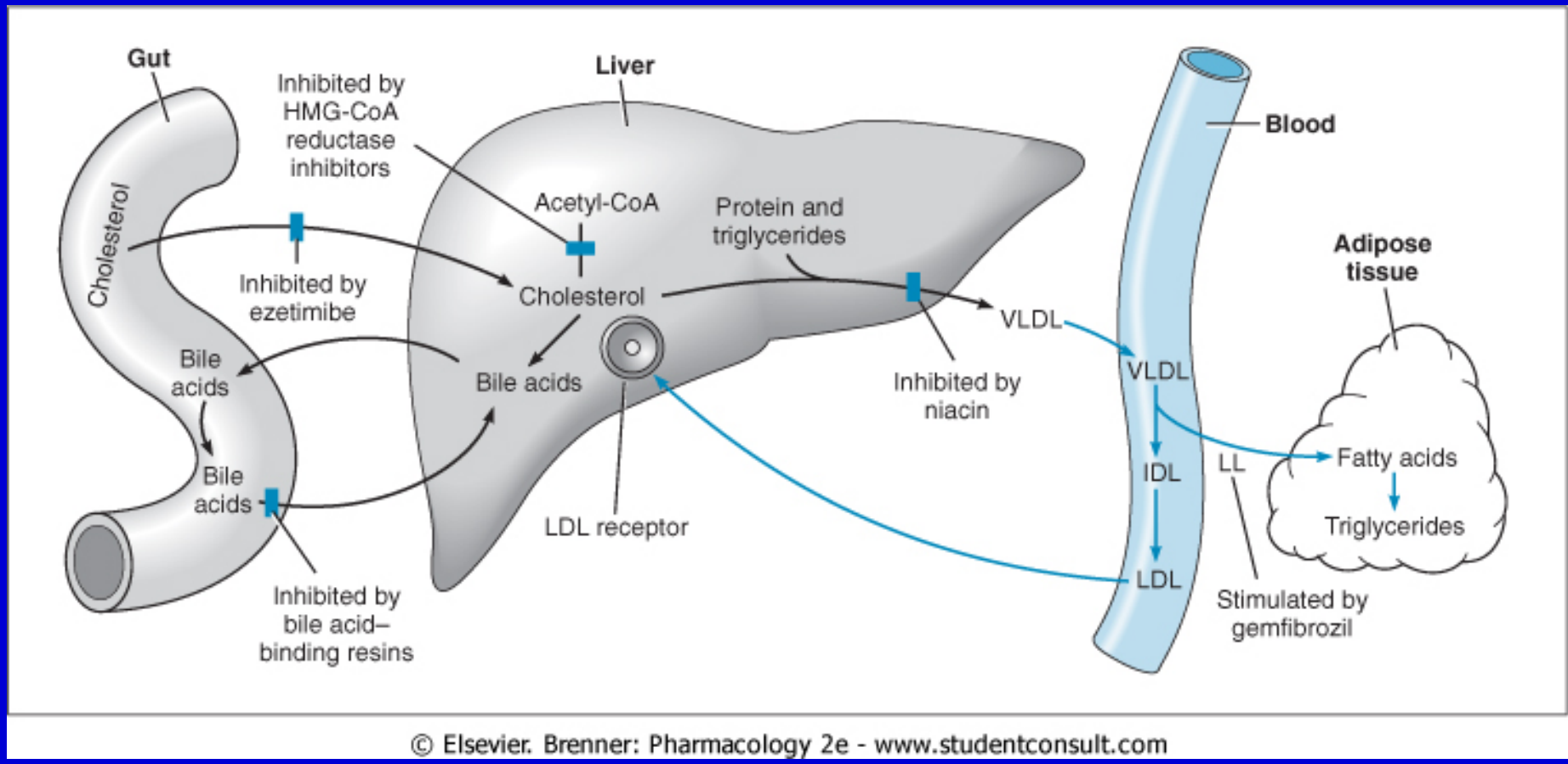
Drug interactions

- Increased risk of myopathy when combined with statins.
- ↓ metabolism of statins → toxicity → myalgia, myositis, …….etc. Give lower doses
- Displace drugs from plasma proteins (e.g. oral anticoagulants and oral hypoglycemic drugs)
- Fibrates displace warfarin from their protein binding sites → ↑bleeding tendency → anticoagulant dose must be adjusted

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 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, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) **↓Triglyceride (20-50)**	Dyspepsia, **gallstones,** **myopathy**
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL **↑ 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