HYPERLIPIDEMIA

TREATMENT OF HYPERLIPIDEMIA

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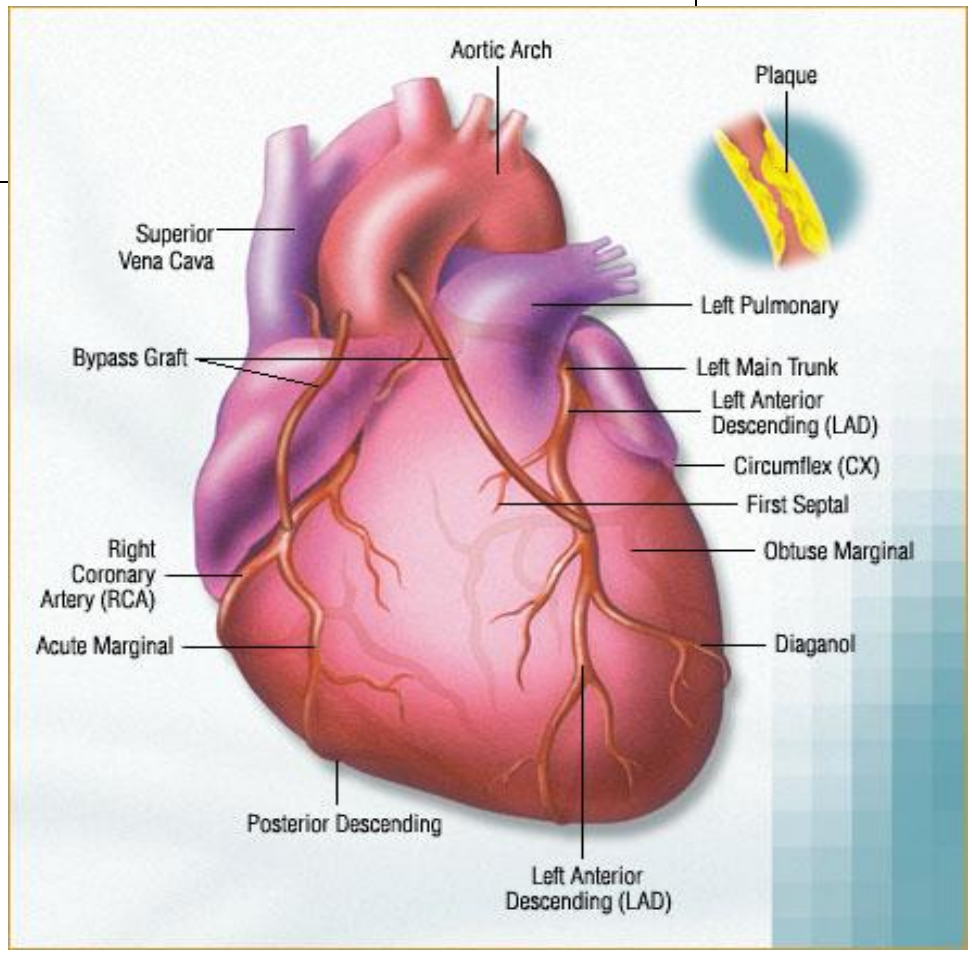


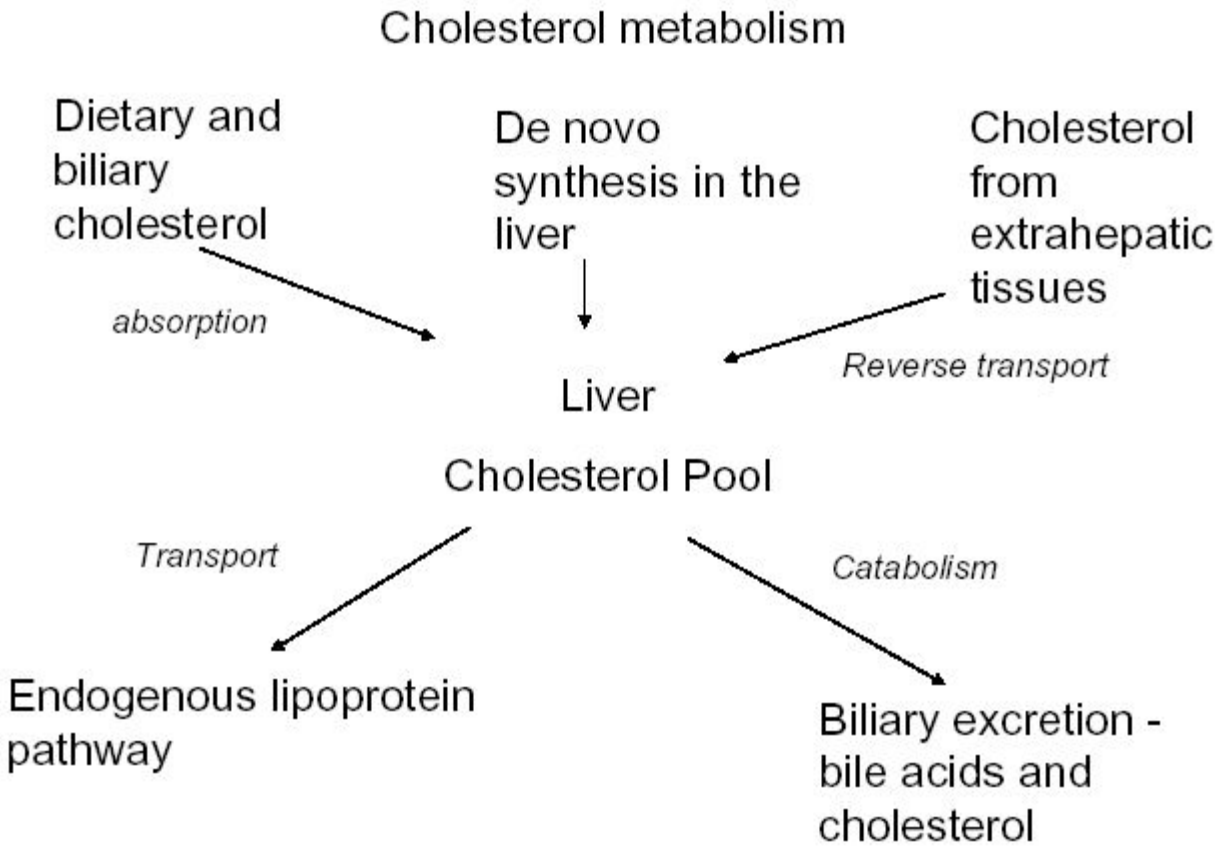
HYPERLIPIDEMIA

- **Hyperlipidemia is an elevation of lipids (fat) in the blood stream.**
- **According to World Health Organization (WHO)**

Most of the lipids in plasma are present as lipoproteins

- **Chylomicrons.**
- **Very low density lipoproteins (VLDL).**
- **Low density lipoproteins (LDL).**
- **High density lipoproteins (HDL).**

Metabolism of lipids


Cholesterol metabolism
Dietary and biliary cholesterol
De novo synthesis in the liver
Cholesterol from extrahepatic tissues
absorption
Reverse transport
Liver
Cholesterol Pool
Transport
Catabolism
Endogenous lipoprotein pathway
Biliary excretion - bile acids and cholesterol

Exogenous Pathway

Transport of dietary lipids from the intestine to the liver

Endogenous Pathway

Transport of lipoprotein synthesized in liver to peripheral tissues

Reverse cholesterol Transport

Cholesterol carried by HDL from peripheral tissues to the liver

Specific Lipoprotein Function

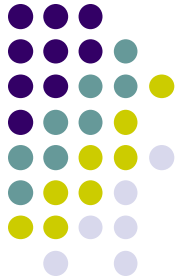
b. Very low density lipoproteins, VLDL, and chylomicrons are the richest in lipid and lowest in protein. They function primarily to deliver triglyceride (TG) to tissue.

c. High density lipoproteins, HDL, are the most dense (i.e. enriched in protein relative to lipid.) They are made by the liver and intestine. Their primary function is to remove cholesterol from peripheral tissues.

d. Chylomicrons are made in the intestines and deliver TG to peripheral tissues (mainly the adipose tissue). The action of lipoprotein lipase on the surface of the adipocyte and other peripheral tissues leads to the breakdown of TG to free fatty acids and glycerol, which are taken up by the cell.

e. IDL and LDL are intermediate in density. LDL is the major carrier of cholesterol to peripheral tissue.

TYPES OF HYPERLIPIDEMIA



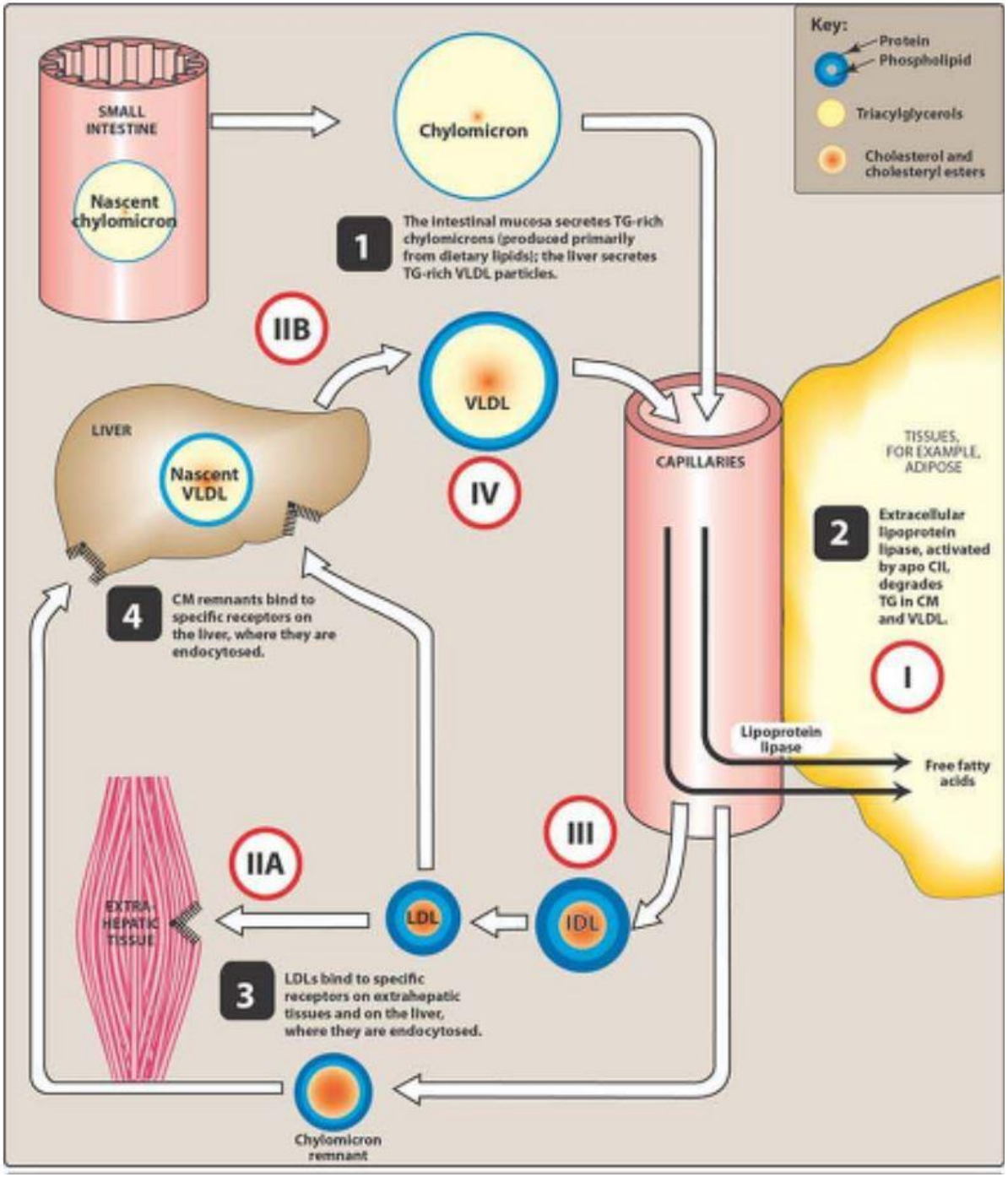
- **PRIMARY HYPERLIPIDEMIAS**

- **SECONDARY HYPERLIPIDEMIAS**

Types of Hyperlipidemia

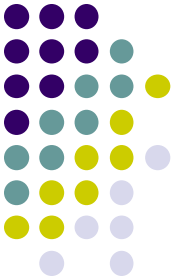
Type	Incidence	Lipoprotein	Lipid
1	Rare	Chylomicrons	TG
2a*	Common	LDL	CHOL
2b*	Common	VLDL + LDL	TG + CHOL
3*	Rare	IDL	TG + CHOL
4*	Common	VLDL	TG
5	Rare	VLDL + Chylomicrons	TG

*Increased risk for atherosclerosis


Key:
Protein
Phospholipid
Triacylglycerols
Cholesterol and cholesteryl esters
SMALL INTESTINE
Nascent chylomicron
Chylomicron
1
The intestinal mucosa secretes TG-rich chylomicrons (produced primarily from dietary lipids); the liver secretes TG-rich VLDL particles.
IIB
VLDL
IV
LIVER
Nascent VLDL
CAPILLARIES
TISSUES, FOR EXAMPLE, ADIPOSE
2
Extracellular lipoprotein lipase, activated by apo CII, degrades TG in CM and VLDL.
I
Lipoprotein lipase
Free fatty acids
4
CM remnants bind to specific receptors on the liver, where they are endocytosed.
III
IIA
EXTRA-HEPATIC TISSUE
LDL
IDL
3
LDLs bind to specific receptors on extrahepatic tissues and on the liver, where they are endocytosed.
Chylomicron remnant

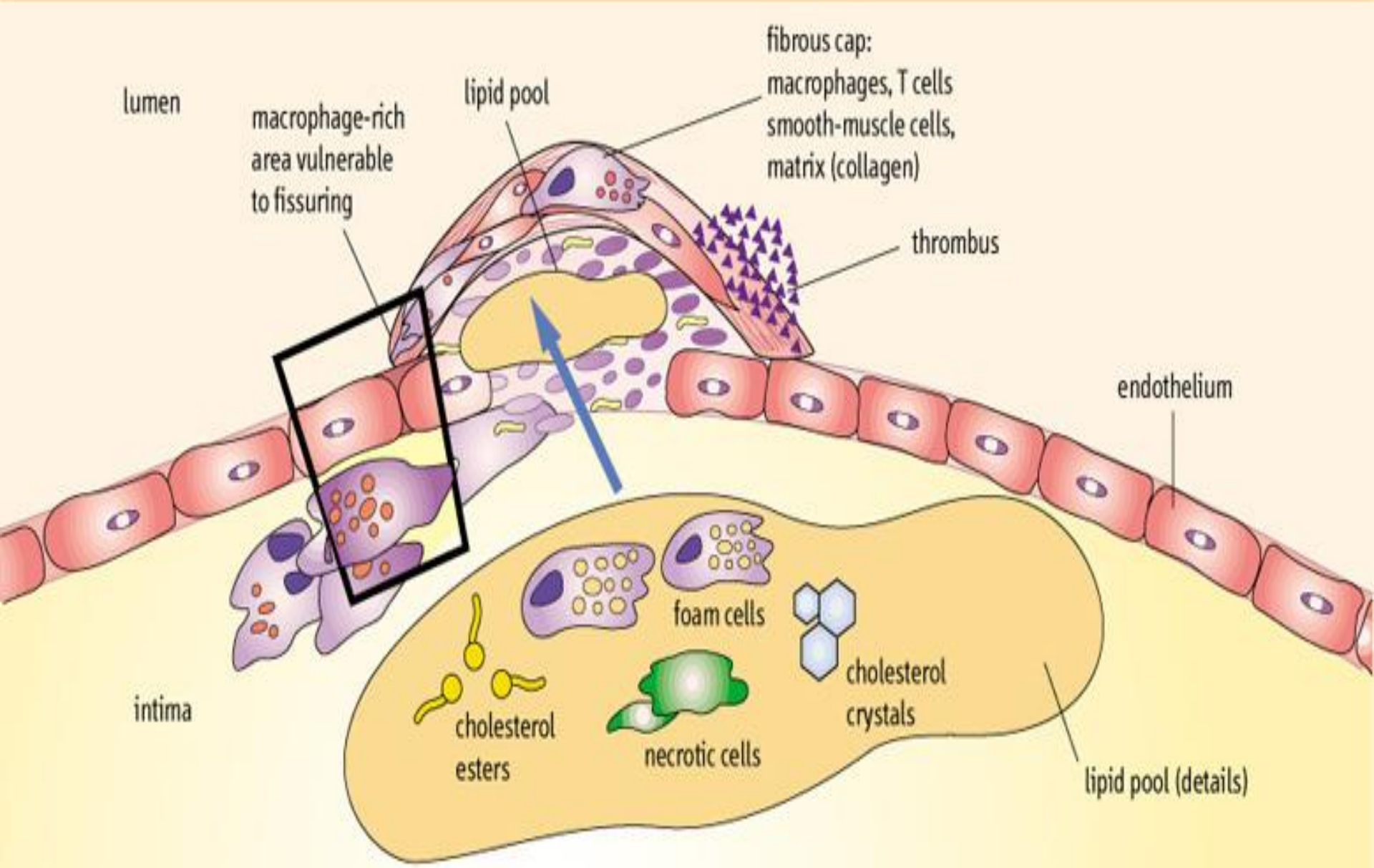
Hyperlipoproteinemia	Synonyms	Increased lipoprotein	Treatment
Type I (rare)	"Buerger-Gruetz syndrome", "Primary hyperlipoproteinaemia", or "Familial hyperchylomicronemia"	Chylomicrons	Diet control
Type IIa	"Polygenic hypercholesterolaemia" or "Familial hypercholesterolemia	LDL	Bile acid sequestrants, 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

SECONDARY HYPERLIPOPROTEINEMIAS



- Diabetes mellitus
- Alcohol ingestion
- Nephrotic syndrome
- Estrogens
- Uremia
- Drugs: Corticosteroid therapy
- Hypothyroidism

Atherosclerotic plaque



Non-drug Therapy for Hyperlipidemia

- Limit saturated fat and cholesterol in diet
- Weight control
- Smoking cessation
- Blood pressure control
- Treat contributory diseases

Dietary measures

Fats in the Diet

Dietary fats can be saturated or unsaturated.

- **limit saturated fats. Saturated fats are found mainly in meats and dairy products made with whole milk.**
- **Unsaturated fats (polyunsaturated and monounsaturated) are found mostly in plants.**

Drug Therapy for Hyperlipidemia

- Bile acid sequestrants
- HMG CoA reductase inhibitors
- Gemfibrozil
- Niacin
- Cholestrol absorption inhibitor ezitmibe
- PCSK9 inhibitors

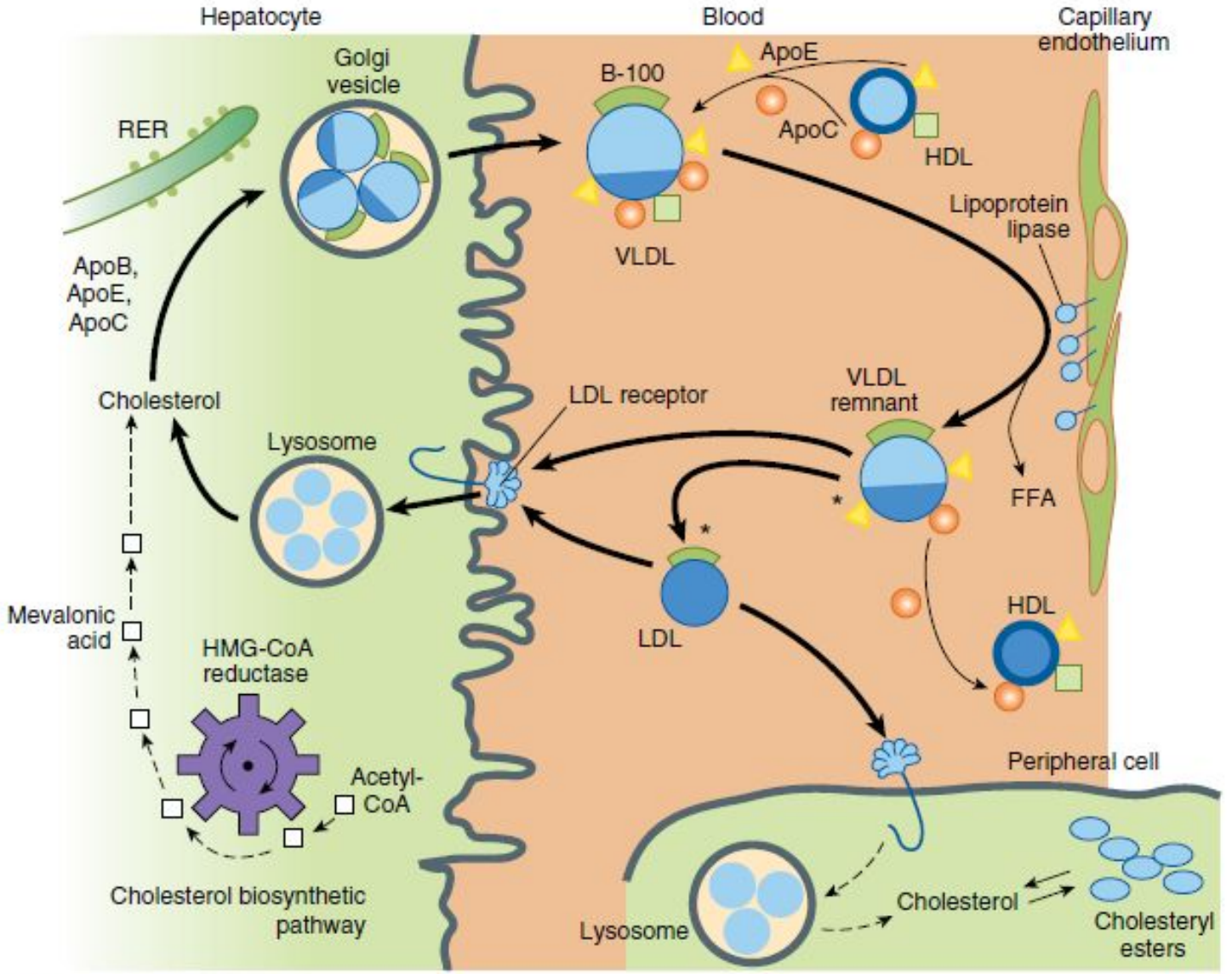


FIGURE 35–1 Metabolism of lipoproteins of hepatic origin. The heavy arrows show the primary pathways. Nascent VLDL are secreted via the Golgi apparatus. They acquire additional apo C lipoproteins and apo E from HDL. Very-low-density lipoproteins (VLDL) are converted to VLDL remnants (IDL) by lipolysis via lipoprotein lipase in the vessels of peripheral tissues. In the process, C apolipoproteins and a portion of the apo E are given back to high-density lipoproteins (HDL). Some of the VLDL remnants are converted to LDL by further loss of triglycerides and loss of apo E. A major pathway for LDL degradation involves the endocytosis of LDL by LDL receptors in the liver and the peripheral tissues, for

Statins
HMG – CoA Reductase Inhibitors

Structural analogues of HMG-CoA

Compactin

- Lovastatin
- Simvastatin
- Cerivastatin.
- Pravastatin
- Fluvastatin
- Atorvastatin

Prodrugs ---- GIT---active B-hydroxyl derivatives

Pharmacokinetics

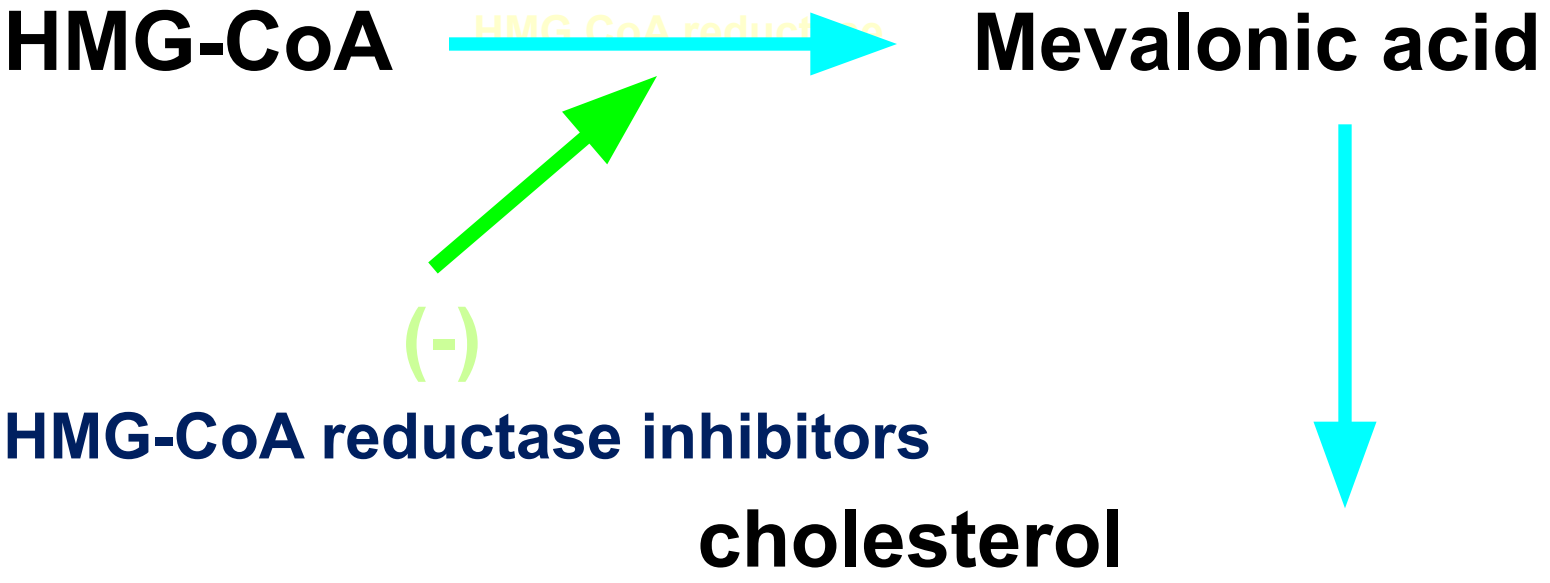
- Pro drugs (L;S)
- Fluvasatin (absorption complete , least efficacious)

- Most effective (R,S,A)

- High first pass metabolism

HMG-CoA Reductase Inhibitors

- **Mechanism of action**



Consequences of inhibition of hepatic HMGCoA reductase

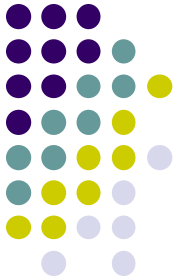
- Decrease in hepatic cholesterol concentration
- Increase in LDL receptor activity
- Decrease in LDL cholesterol concentration

Mechanism other than lipoproteins metabolism

Adverse effects

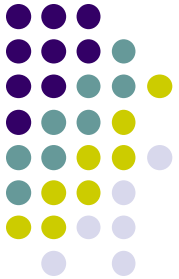
- Abnormalities in liver function (LFTs)
- Muscle pain
- Weakness
- Myopathy (rare)
- Rhabdomyolysis (rare) ---- myoglobinuria ------renal shutdown
- Hypersensitivity syndrome

Contraindication



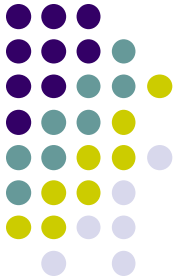
- **Pregnancy**
- **Nursing Mothers**
- **Children**

Bile Acid Binding Resins



- **Cholestyramine**
- **Colestipol**
- **Colesvelem**

Mechanism of Action



- **Form an insoluble complex with the bile acids and salts preventing their reabsorbtion from the intestine into liver.**

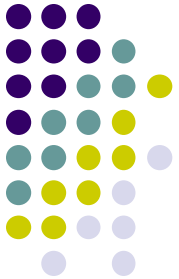
- **The resin/bile acid complex is excreted in the faeces.**

Consequences of interfering with the enterohepatic circulation of bile acids

- Promotes bile acid synthesis
- Decreases hepatic cholesterol pool
  - Increases the expression of LDL receptor
  - In some subjects increases VLDL secretion by stimulating cholesterol biosynthesis

- Improve glucose intolerance
- Role in triglyceride conc.(FXR receptor)

Therapeutic Uses



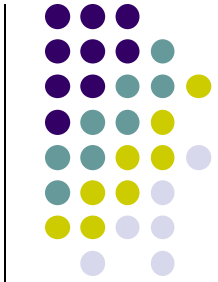
- **Type IIa hyperlipidemia**
- **Type IIb hyperlipidemia**
- **Pruritis (Cholestyramine)**
- **Digoxin toxicity (not colesvelam)**

Adverse Effects

- **G.I – Constipation, Nausea,Flatulence, steatorrhea**

- **Impairment of absorption of fat soluble vitamins (A, D, E &K), Folic Acid, Ascorbic acid.**
- **Gall stones**

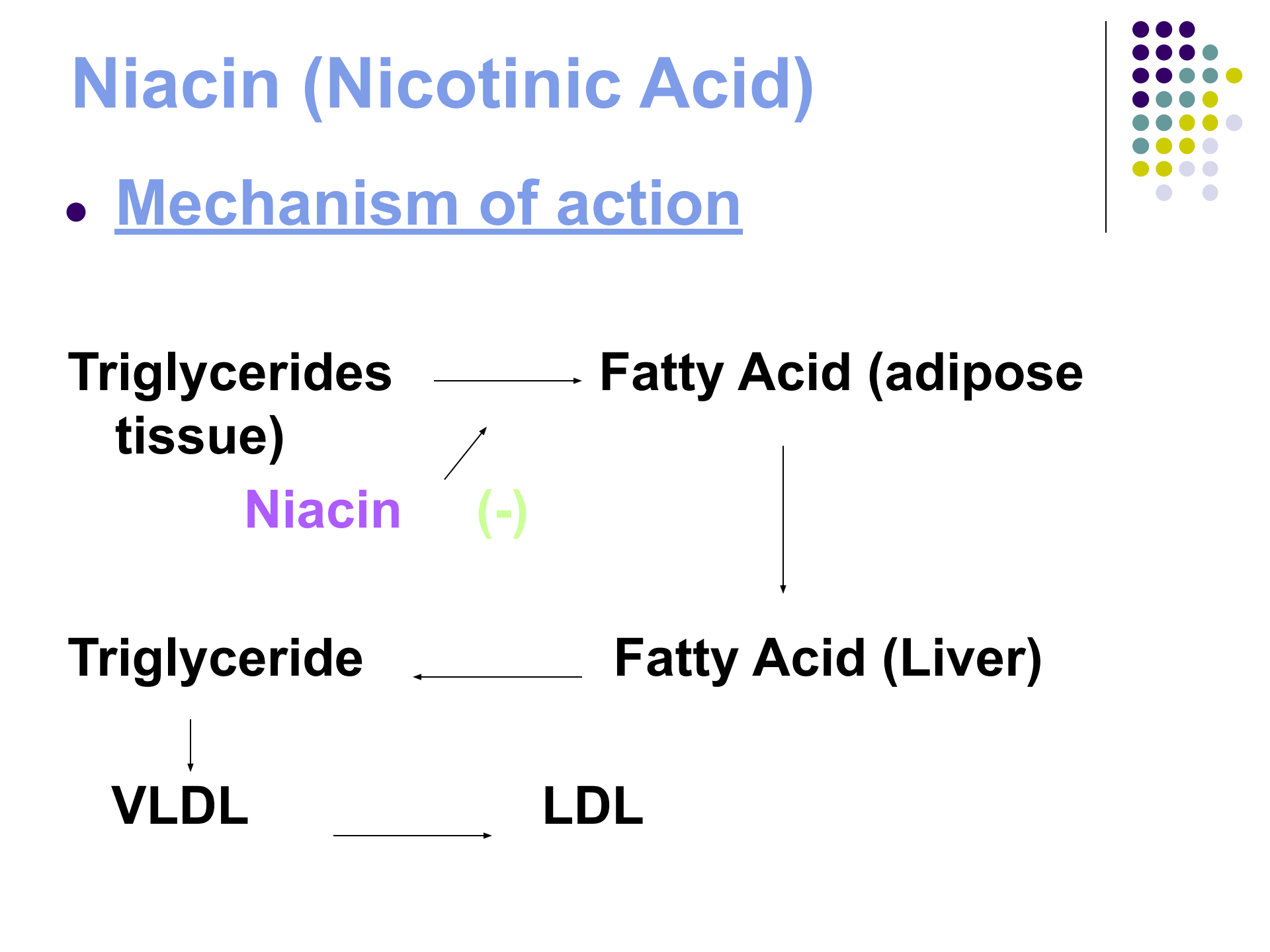
Niacin
Nicotinic Acid



- **Water soluble vitamin (B3**
- **Converted in the body to amide which is incorporated into nicotinamide adenine dinucleotide (NAD)**

Niacin (Nicotinic Acid)

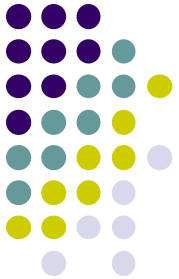
- Mechanism of action



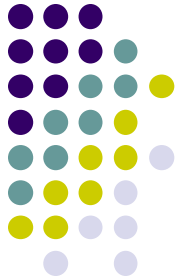
Therapeutic Uses

- **Type IIb hyperlipidemia (↑ VLDL, LDL)**
- **Type IV hyperlipidemia (↑ VLDL, LDL)**
- **Familial dysbetalipoproteinemia.**
- **Most potent antihyperlipidemic agent for raising HDL Levels.**

Adverse Effects

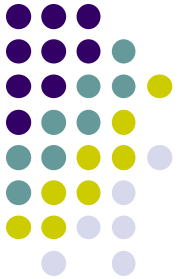


- Intense cutaneous flush (prostaglandin mediated)
- Uncomfortable feeling of Warmth.
- Pruritis, Skin rash. Dry skin.
- Nausea, Abdominal Pain.
- Hyperuricemia, Gout (inhibits tubular secretion of Uric acid)



- **Impaired glucose tolerance.**
- **Hepatotoxicity**
- Atrial arrhythmias
- Macular edema
- Birth defects

Fibric acid derivatives



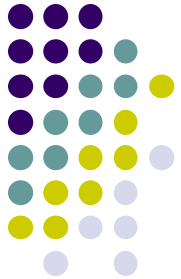
- **Clofibrate**

  Gemfibrozil (congener)

- **Fenofibrate (congener) Most effective..less AE….pro drug**

Mechanism of action

- Ligand for PPAR- α (Peroxisome proliferator - activated receptor alpha)---
- Stimulates lipoprotein lipase (LPL) activity.
- Increasing hydrolysis of TG in chylomicrons and VLDL particles
- Liberates free Fatty acids for storage in fat or for metabolism in striated muscles



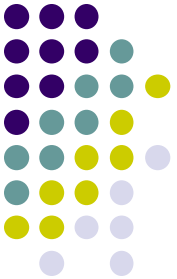
- Intracellular lipolysis in adipose tissue is decreased
- Reduce hepatic VLDL production
- Increase hepatic LDL uptake
- Increase in HDL production

Therapeutic Uses

Hypertriglyceridemia in which VLDL predominates

- **Type III Hyperlipidemia**
- **Type IV Hyperlipidemia**
- **Type V Hyperlipidemia**

Adverse Effects



- Gastro intestinal- Diarrhea
- Gall stones
- Myositis
- Myopathy & Rhabdomyolysis
- Increased LFTs
- Skin rash

Contraindications

- Renal and hepatic insufficiency
- Pregnancy
- Pts taking anticoagulants, biliary tract disease

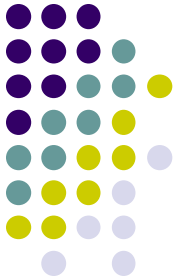
Ezitimibe

- Cholesterol absorption inhibitor (dietary, bile)
- Decrease LDL
- NPC1L1
- Well tolerated caution in pts with liver disease

New drugs

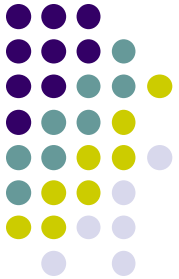
- PCSK9 inhibitors…. Evolcumab
- Antisense Inhibition of apoB100…mipomersen
- Cyclodextrins
- AMP kinase activation

Combination therapy



- Fibrates + resins…Gall stones
- Statins+ resins…not for VLDL
- Niacin +resins.. LDL+VLDL
- Niacin +statins…LDL
- Statin +ezetimibe
- Statin+fibrates…hepatic ,myo toxicity

IMPORTANT POINTS



- Drugs that raise HDL
- Drugs that decrease LDL
- Drugs that decrease TAGs
- Drugs that increase TAGs

Adverse effects😑

- Gall stones,(FR)
- glucose intolerance, gout ,Cutaneous flush (Niacin)
- hepatotoxicity, myotoxicity(SF)
- Improve glucose intolerance