Hyperlipidemias

- CHD is correlated with elevated levels of LDL cholesterol and triacylglycerols and with low levels HDL

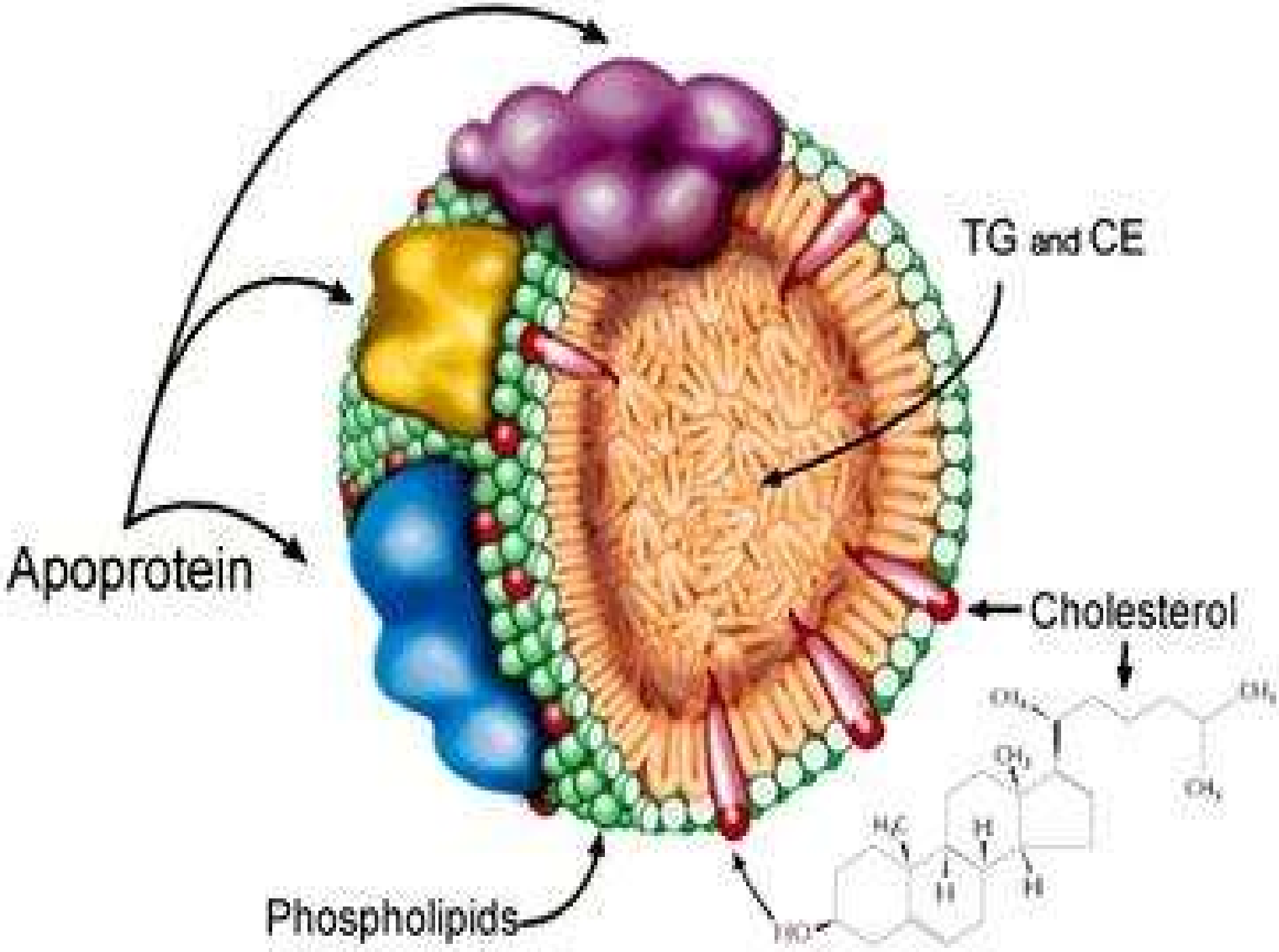
- Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids).

- Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30 to 40 percent.

Treatment Goals

- Plasma lipids consist mostly of lipoproteins spherical macromolecular complexes of lipids and specific proteins (apolipoproteins).

- Reduction of the LDL level is the primary goal of cholesterol-lowering therapy


TG and CE
Apoprotein
Cholesterol
Phospholipids

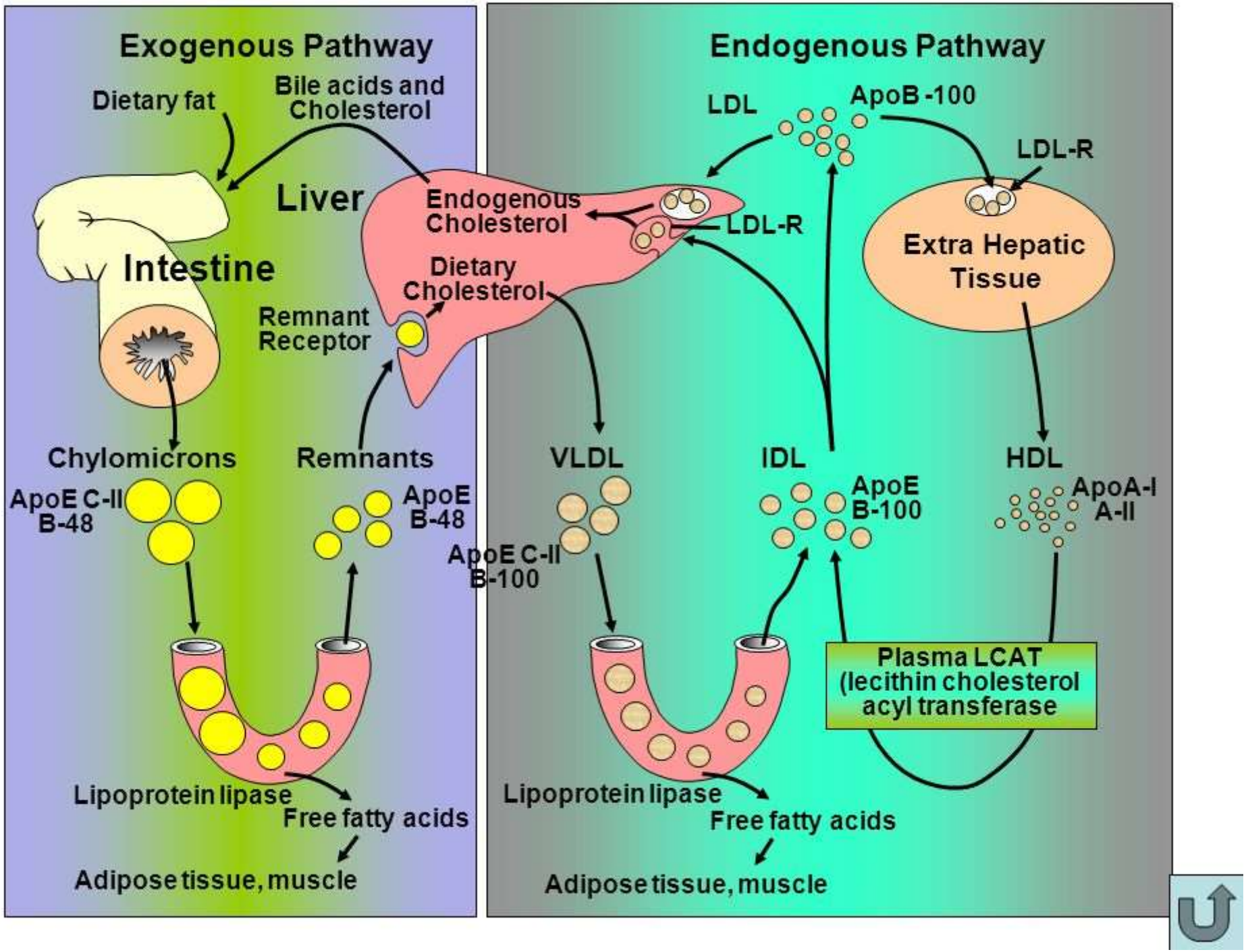
Treatment options for hypercholesterolemia

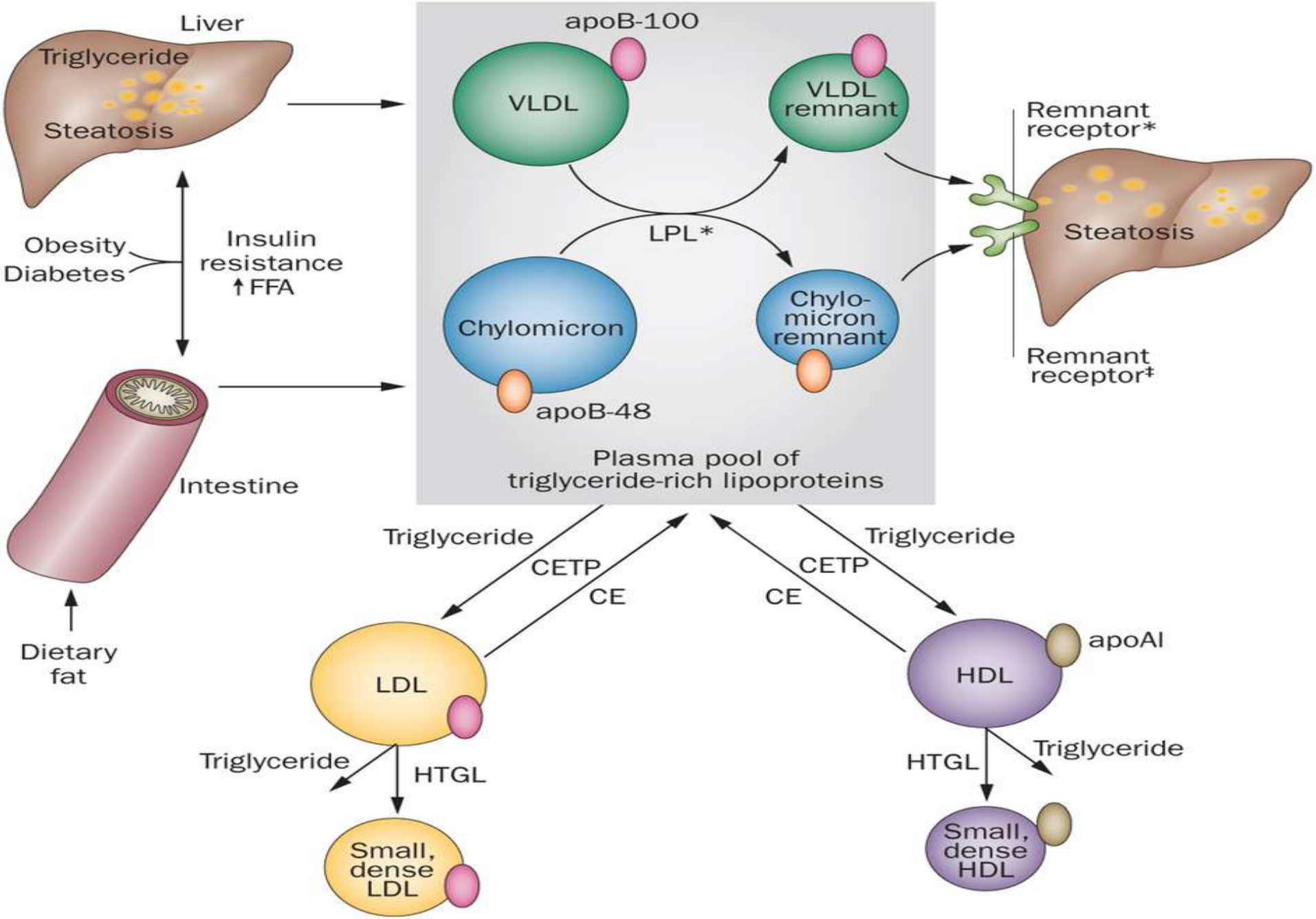
- In patients with moderate hyperlipidemia, lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL levels and increases in HDL levels.

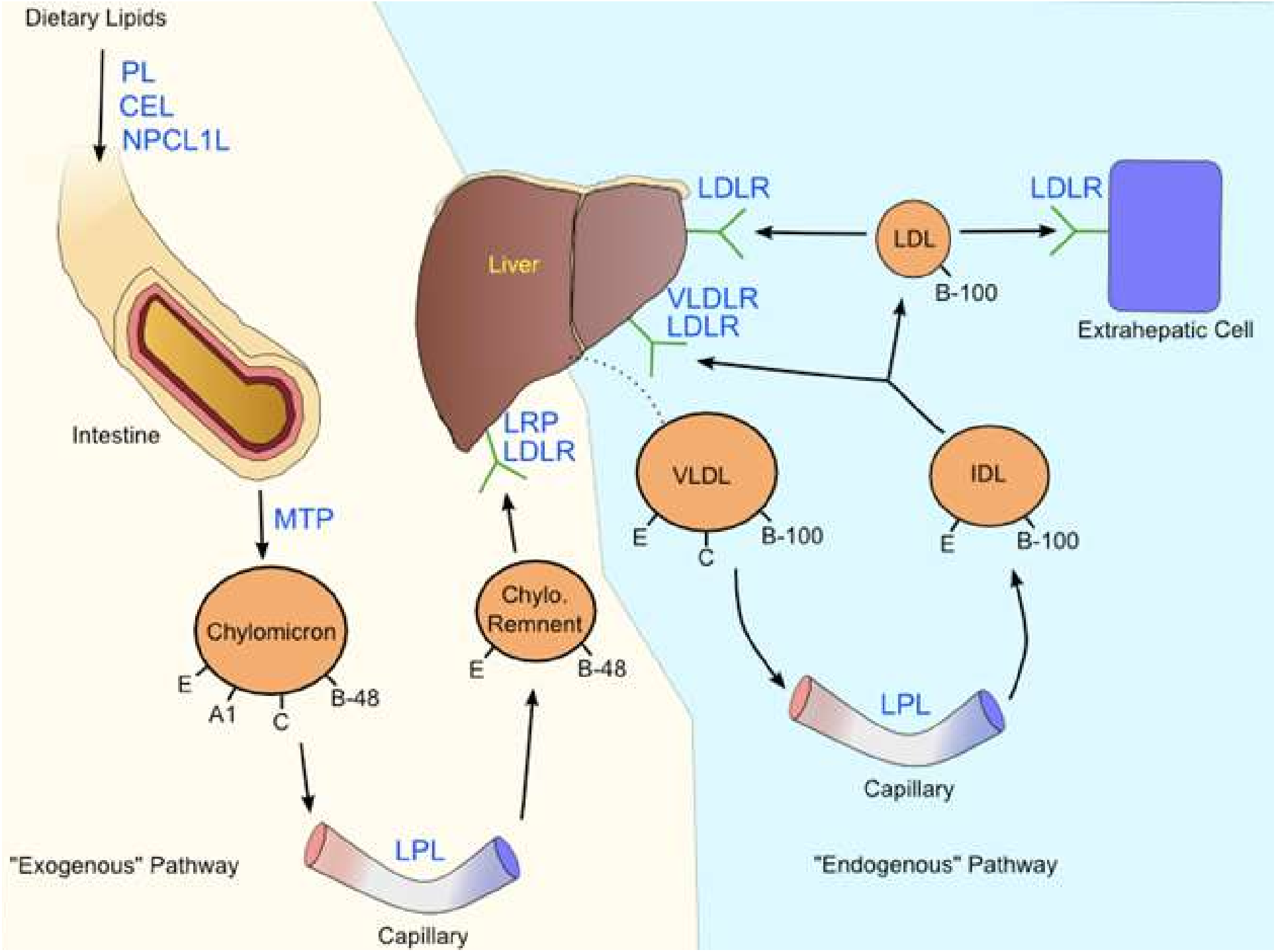
- aim of reducing their LDL level to less than 100 mg/dL and, in some patients, to as low as 70 mg/dL.

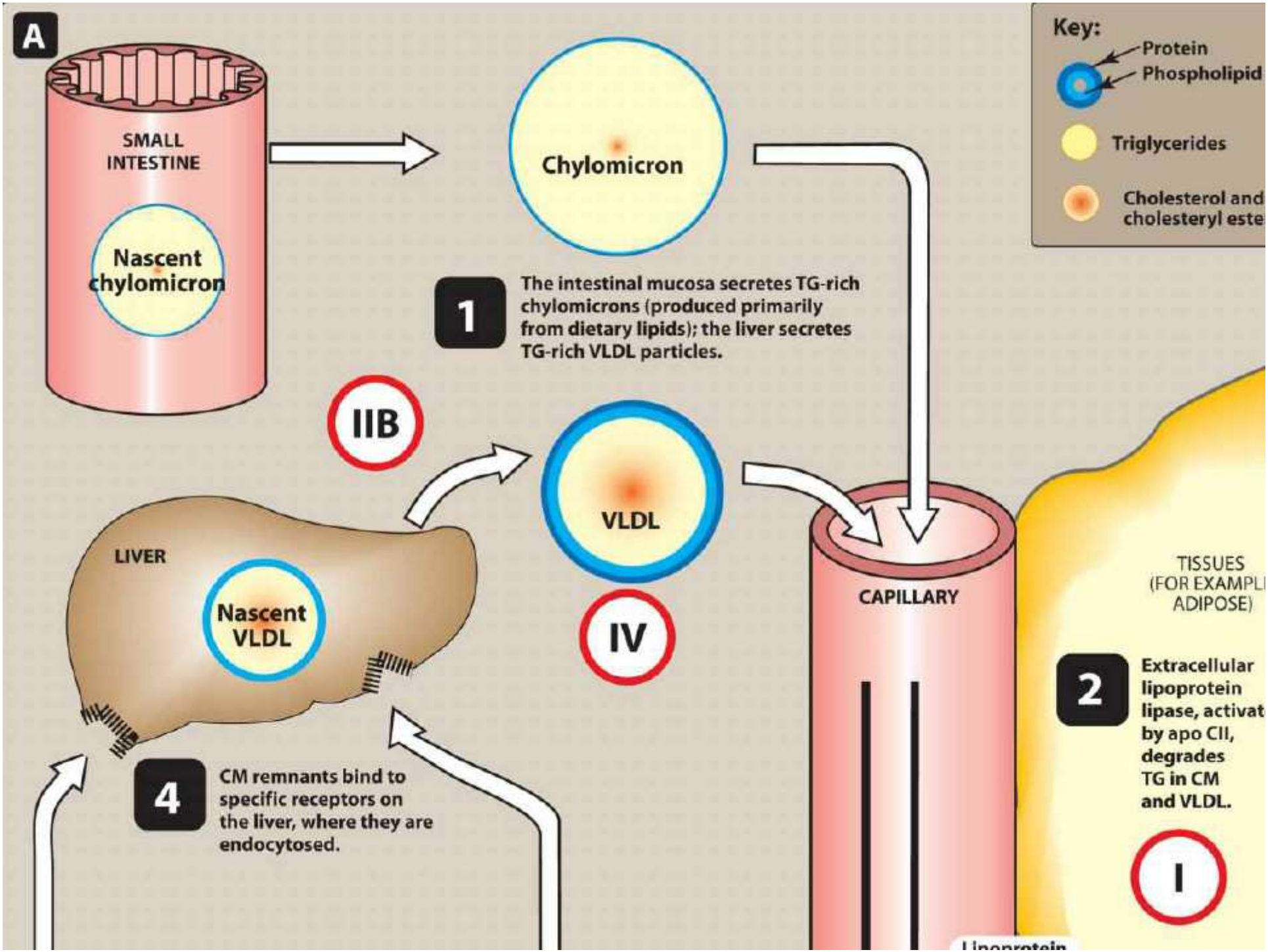
Treatment options for hypertriacylglycerolemia

- Elevated triacylglycerol (triglyceride) levels are independently associated with increased risk of CHD.
- Diet and exercise are the primary modes of treating hypertriacylglycerolemia.
-
- The major lipid component of VLDL is composed of triacylglycerol.


Exogenous Pathway
Dietary fat
Bile acids and Cholesterol
Liver
Intestine
Endogenous Cholesterol
Dietary Cholesterol
Remnant Receptor
Chylomicrons
ApoE C-II B-48
Remnants
ApoE B-48
Lipoprotein lipase
Free fatty acids
Adipose tissue, muscle
Endogenous Pathway
LDL
ApoB -100
LDL-R
LDL-R
Extra Hepatic Tissue
VLDL
ApoE C-II B-100
IDL
ApoE B-100
HDL
ApoA-I A-II
Plasma LCAT (lecithin cholesterol acyl transferase
Lipoprotein lipase
Free fatty acids
Adipose tissue, muscle


Liver
Triglyceride
Steatosis
Obesity
Diabetes
Insulin resistance
↑ FFA
Intestine
Dietary fat
apoB-100
VLDL
VLDL remnant
LPL*
Chylomicron
Chylo-micron remnant
apoB-48
Plasma pool of triglyceride-rich lipoproteins
Remnant receptor*
Steatosis
Remnant receptor‡
Triglyceride
CETP
CE
Triglyceride
CETP
CE
LDL
HDL
apoAI
Triglyceride
HTGL
HTGL
Triglyceride
Small, dense LDL
Small, dense HDL

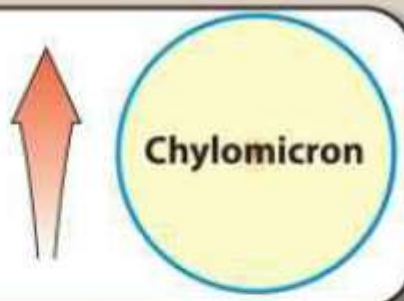

Dietary Lipids
PL
CEL
NPCL1L
Intestine
MTP
Chylomicron
E
A1
C
B-48
Capillary
LPL
"Exogenous" Pathway
Liver
LDLR
VLDLR
LDLR
LRP
LDLR
Chylo.
Remnent
E
B-48
LDL
B-100
LDLR
Extrahepatic Cell
VLDL
E
C
B-100
IDL
E
B-100
LPL
Capillary
"Endogenous" Pathway


A
SMALL INTESTINE
Nascent chylomicron
Chylomicron
Key:
Protein
Phospholipid
Triglycerides
Cholesterol and cholesteryl este
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
CAPILLARY
TISSUES (FOR EXAMPL ADIPOSE)
2
Extracellular lipoprotein lipase, activat by apo CII, degrades TG in CM and VLDL.
I
4
CM remnants bind to specific receptors on the liver, where they are endocytosed.

B

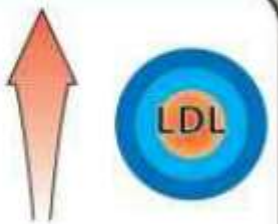
Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.



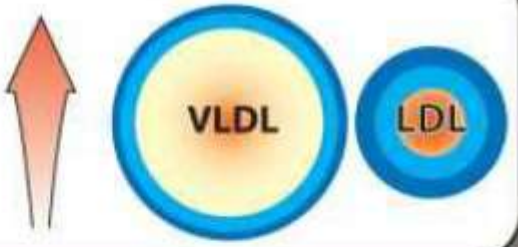
Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, a statin, or a statin and a PCSK9 inhibitor.



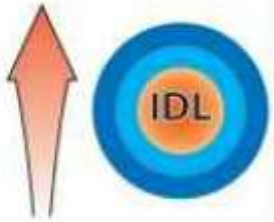
Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA.



Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.



Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in

Drugs that Lower the Serum Lipoprotein Concentration

(1) Some of these agents decrease production of the lipoprotein carriers of cholesterol and triglyceride,

(2) others increase the degradation of lipoprotein.

(3) others decrease cholesterol absorption

(4) directly increase cholesterol removal from the body.

These drugs may be used singly or in combination.

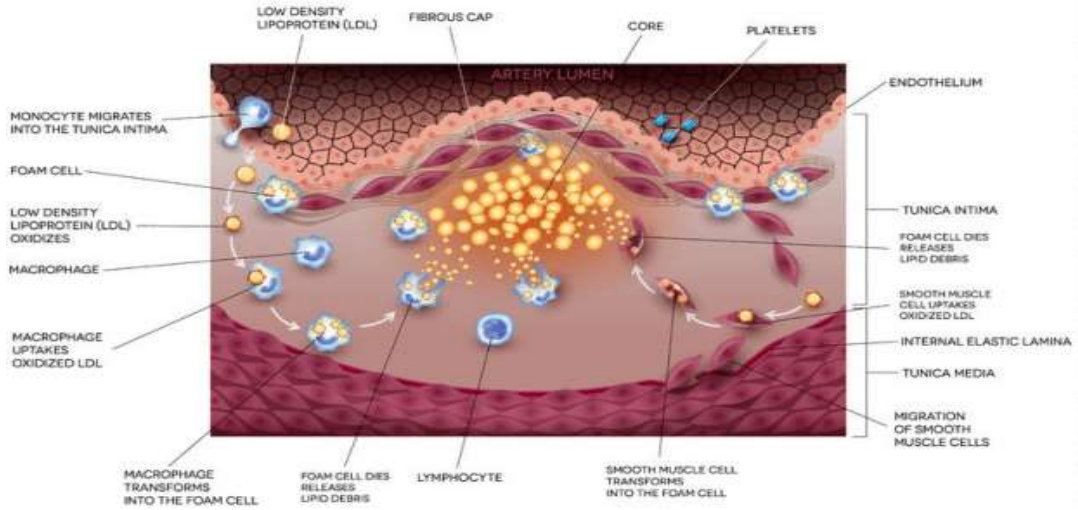
HMG CoA reductase inhibitors

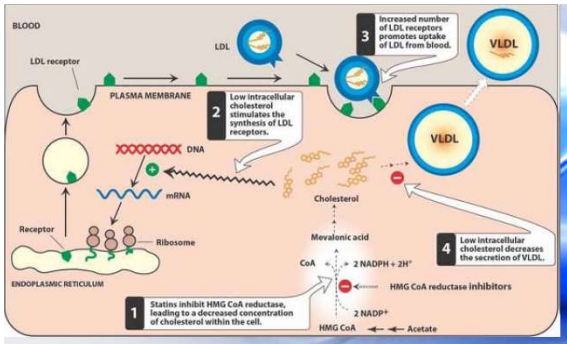
- 3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (COA) reductase inhibitors (commonly known as **statins**)

HMG CoA REDUCTASE INHIBITORS (STATINS)
Atorvastatin LIPITOR
Fluvastatin LESCOL
Lovastatin ALTOPREV
Pitavastatin LIVALO
Pravastatin PRAVACHOL
Rosuvastatin CRESTOR
Simvastatin ZOCOR

HMG CoA reductase inhibitors

- lower elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from CHD.




BLOOD
LDL
LDL receptor
PLASMA MEMBRANE
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
HMG CoA reductase inhibitors
ENDOPLASMIC RETICULUM
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Mechanism of action:

1-Inhibition of HMG CoA reductase:

- HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol.

2-Increase in LDL receptors: Depletion of intracellular cholesterol causes the cell to increase the number of LDL receptors that can bind and internalize circulating LDLs..

Therapeutic uses:

- These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias,

- These drugs are often given in combination with other antihyperlipidemic drugs

Adverse effects:

- **Liver:** Biochemical abnormalities.Therefore, it is prudent to evaluate liver function and measure serum transaminase levels periodically. These return to normal on suspension of the drug.
- **Muscle**: Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) have been reported only rarely.

Niacin (nicotinic acid)

- Niacin can reduce LDL levels by 10 to 20 percent and is the most effective agent for increasing levels. Niacin can be used in combination with statins,

Mechanism of action:

- niacin strongly inhibits lipolysis in adipose tissue the primary producer of circulating free fatty acids. The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis.

Niacin (nicotinic acid)

- niacin causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production.
- since LDL is derived from VLDL in the plasma. Therefore, a reduction in the VLDL concentration also results in a decreased plasma LDL concentration

Adverse effects

- an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus.

- Impaired glucose tolerance and hepatotoxicity have also been reported.

The fibrates: Fenofibrate and gemfibrozil
lower serum triacylglycerols and increase HDL levels

- The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family that regulate lipid metabolism.

- PPARs function as ligand-activated transcription factors.upon binding to their natural ligands
- Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII.

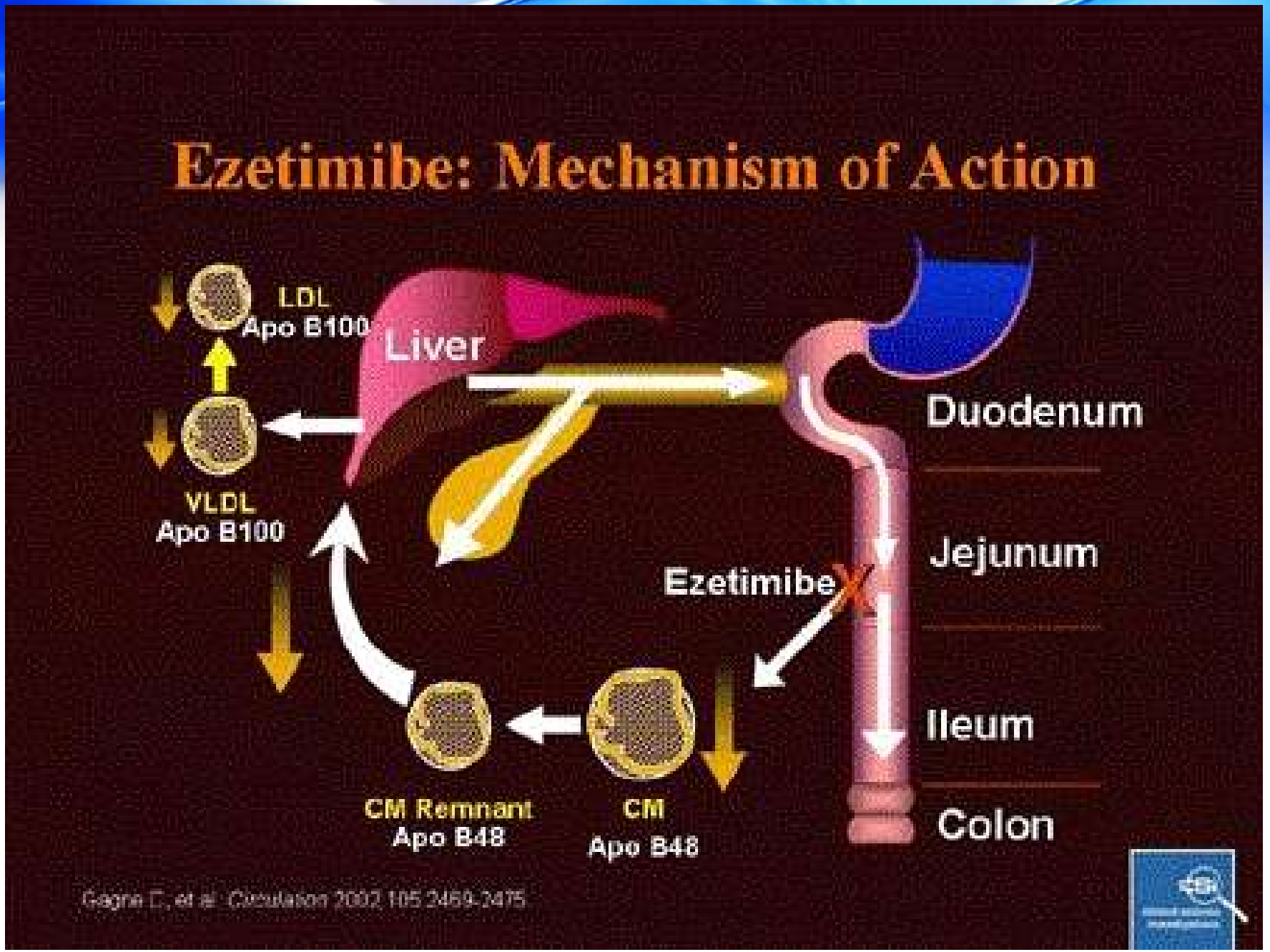
Adverse effects

- mild gastrointestinal disturbances.
- Because these drugs increase biliary cholesterol excretion, there is a predisposition to form gallstones.
- Fibrates should not be used in patients with severe hepatic or renal dysfunction, in patients with preexisting gallbladder disease or biliary cirrhosis.

Therapeutic uses

- treating type IIA and type IIB hyperlipidemias.
- Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis.
- Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects.

Ezetimibe: Mechanism of Action



Gagne C., et al. Circulation 2002;105:2469-2475

Omega-3 fatty acids

- Omega-3 polyunsaturated fatty acids are essential fatty acids that are predominately used for triglyceride lowering.
- Inhibit VLDL and triglyceride synthesis in the liver.
- Icosapent ethyl is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C.
- GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk

Proprotein convertase subtilisin kexin type 9 inhibitors(PCSK9)

- PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to the degradation of LDL receptors
- Alirocumab and evolocumab are PCSK9 inhibitors, which are fully humanized monoclonal antibodies.
- .
- The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.