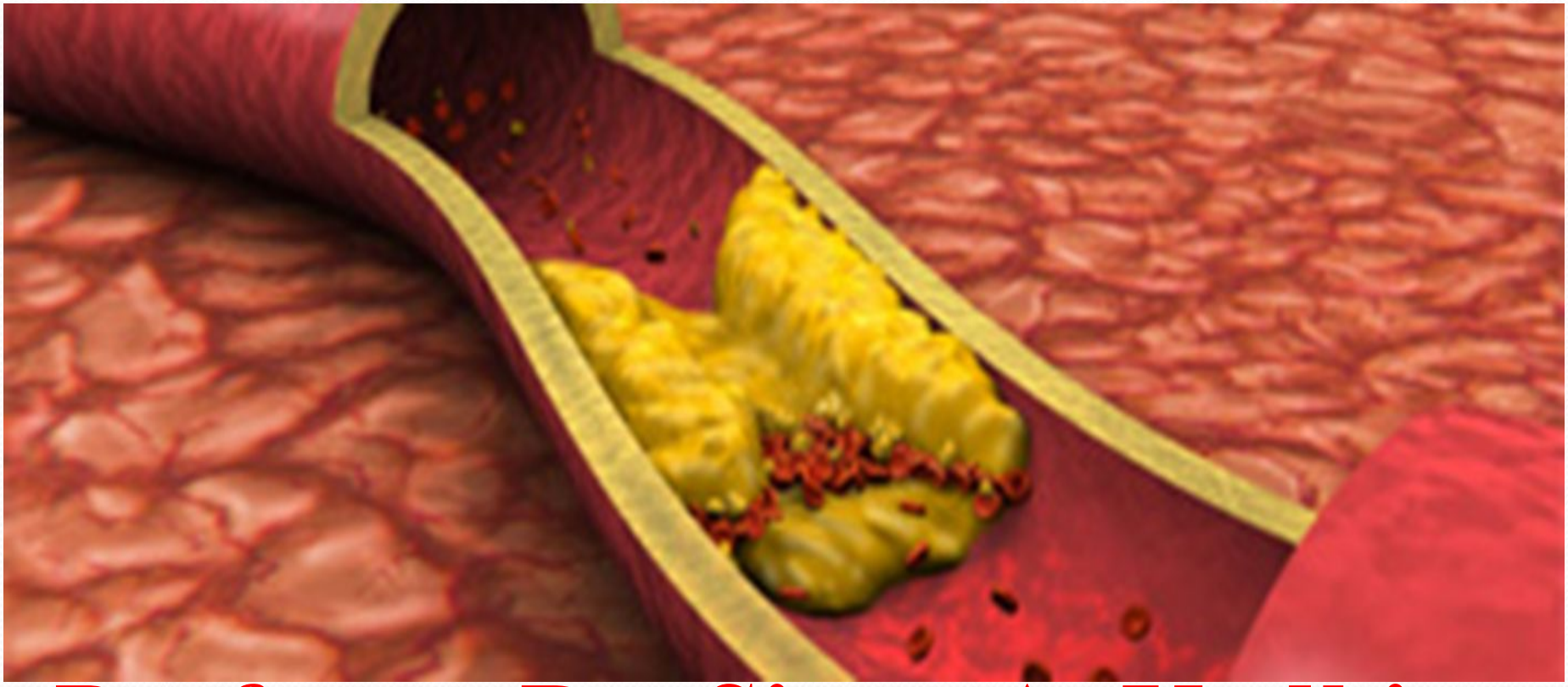
Therapy of hyperlipidemia (Lipid lowering drugs)



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.M.B.Ch.B, GP.Rad., M.Sc., Ph.D

:This lecture consist of 2 parts

1st part : pathophysiology, biochemistry & types

.2nd part : **objectives (important)**

:Objectives

know classes of drugs used in lipid lowering blood -1
.levels

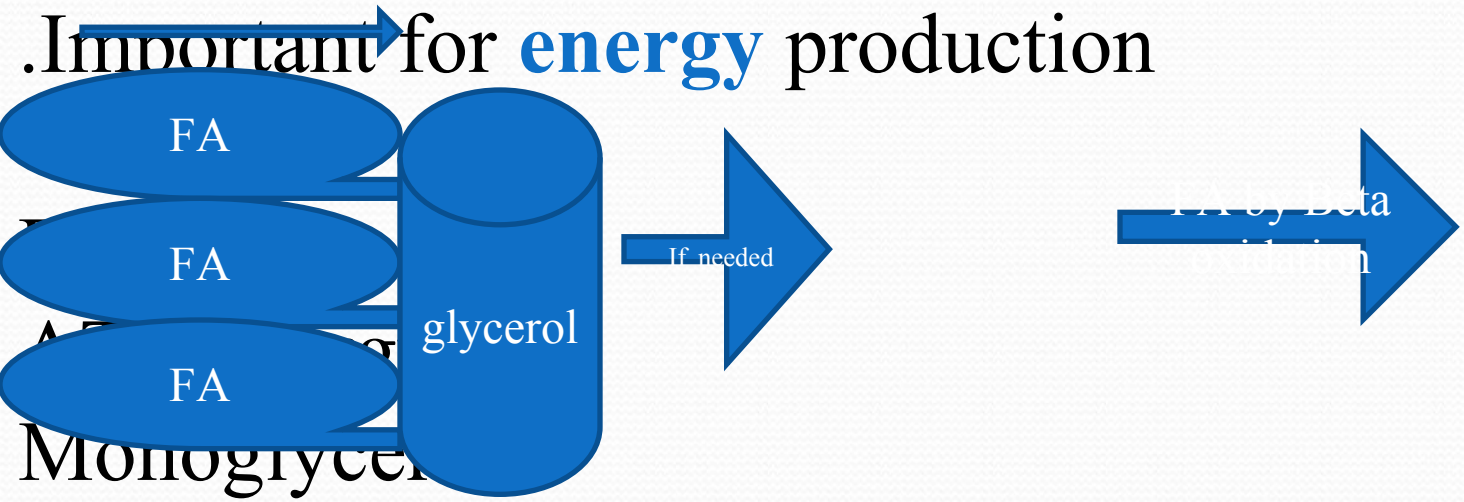
know MOA, kinetics, side effects, indications, -2
interaction and contraindications of drugs

Part 1

Hyperlipidemia refers to increased levels of **lipids** in the blood, the important lipids here are **cholesterol** (C) and **triglycerides(TG)**

,TG Consist of 3 fatty acids connected by glycerol*

.Important for **energy** production



Monoglycer

Cholesterol important in **biosynthesis** of many* substances like vit D, steroid hormone (**not for energy**)

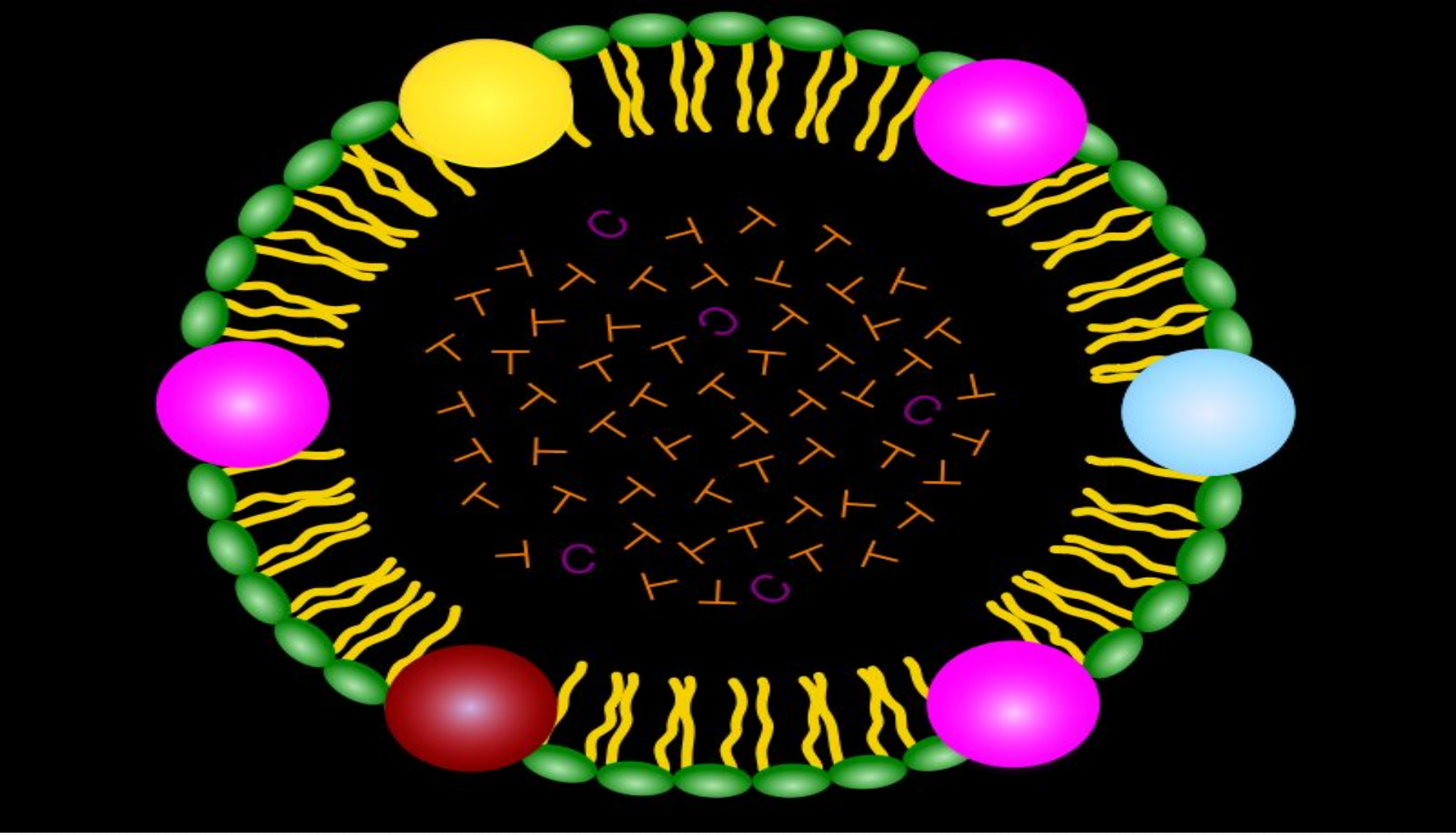
:Lipid metabolism and fate

When TG and Chol taking by food and enter intestine. TG is converted by activity of .**pancreatic lipase** to 2 FFA and monoglycerol

.Chol and TG **not** absorbed to enteric cells **unless** coated by **bile acid**

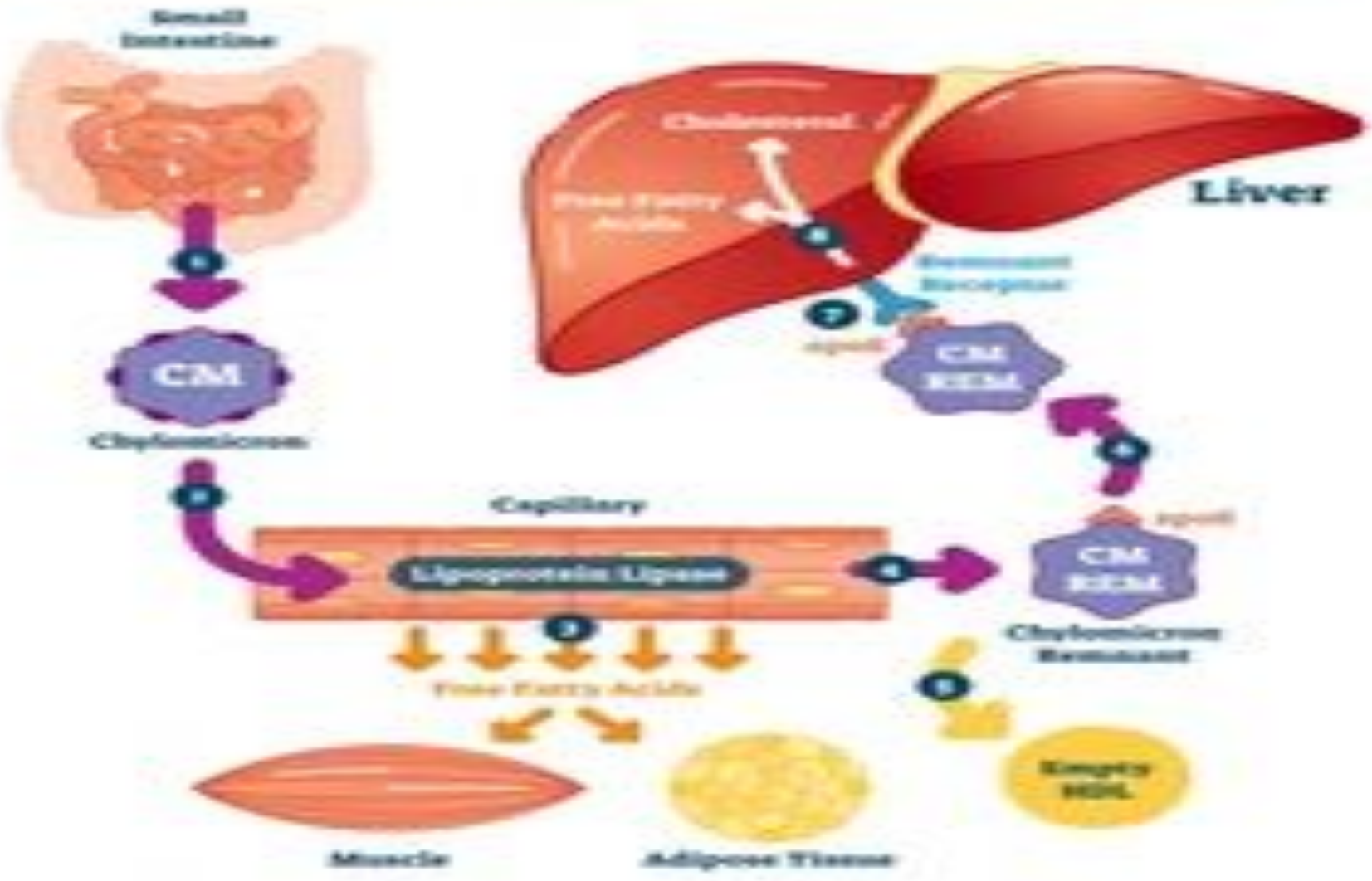
After absorption to enteric cell it will **coat** with **lipoprotein** layer ,here it is named as **lipoprotein**. Then it is sent to bl. Vess. (in form of **chylomicron** =containing large quantity of TG and small quantity of chol.)where in bl. there is **lipoproteinlipase** enzyme (enz. Secreted by endoth. cell of all bl. Vess.) started **destruction** of TG gradually (not degradate chol.) convert it to **FFA (then by beta oxidation to be used as** .(**energy)** till enter the liver as a **chylomicron reminantant**

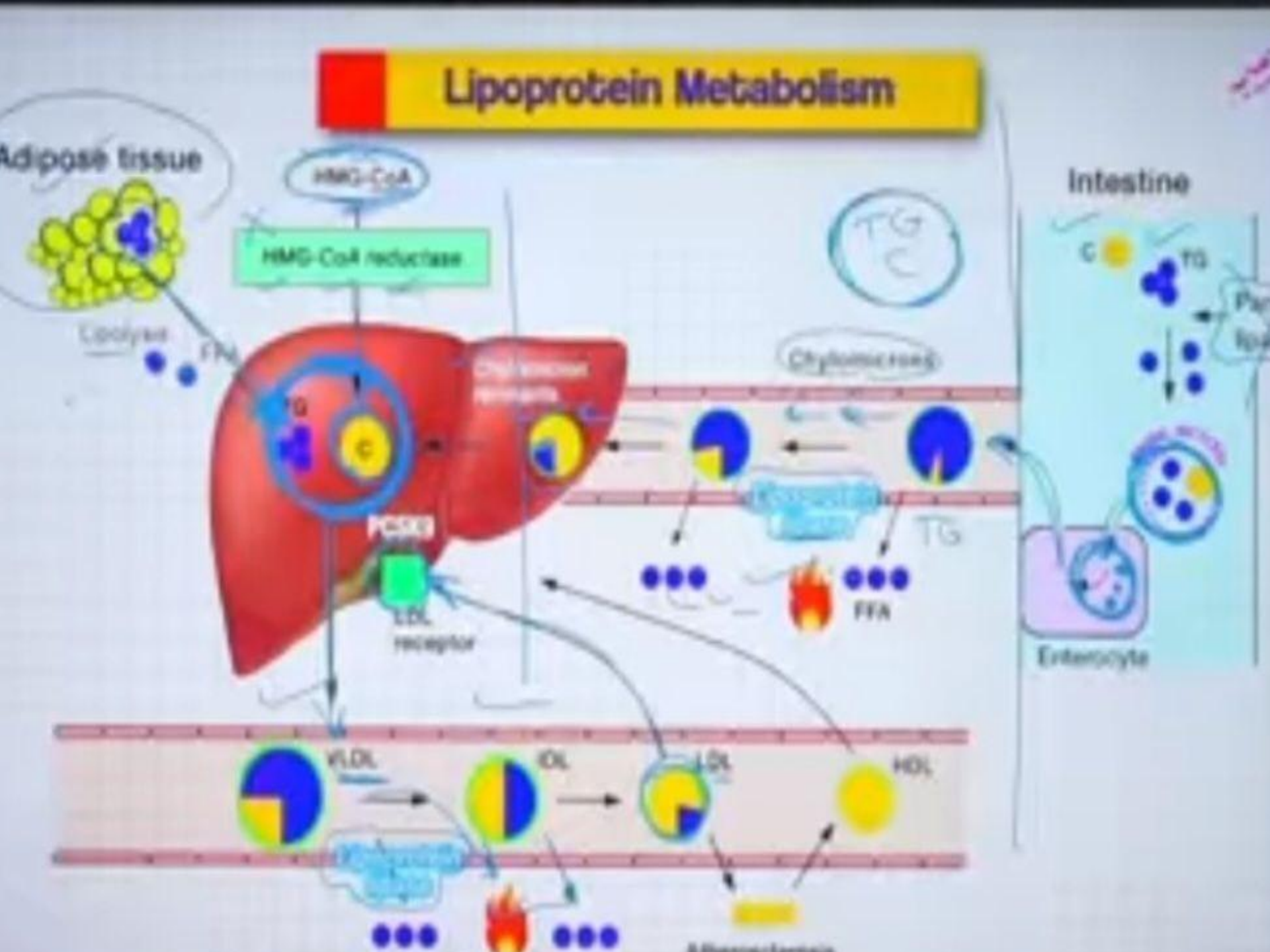
Liver **also** synthesis chol. By itself(de novo by HMG-COA), **also** liver receive TG from adipose tissue. All these 3 lipids in liver are mixed then to be released to bl in form of **VLDL** and.. in bl. Start conversion of VLDL to IDL then LDL (by **lipoprotein lipase activity**) to be sent to **LDL receptor** of liver in normal person and used in synthesis of bile and other process. But if the person have genetically no LDL receptor in liver then this LDL will **deposited in endoth** cell of bl. Vess. .Then **HDL-C (good chol.)** carry .lipid from blood vess. endoth Wall to blood then to liver where it will removed by liver



Chylomicron structure
ApoA, ApoB, ApoC, ApoE(apolipoproteins); **T** (triacylglycerol); **C**(cholesterol); green (phospholipids)

Lipid Metabolism




Lipoprotein Metabolism
Adipose tissue
HMG-CoA
HMG-CoA reductase
Intestine
Lipolysis
FFA
TG
C
Chylomicrons
TG
FFA
LDL receptor
Enterocyte
VLDL
IDL
LDL
HDL

Although hyperlipidemia does **not cause symptoms**, it can significantly increase **risk** of developing **cardiovascular** disease, including disease of **blood vessels** supplying the **heart** (coronary artery disease), **brain** (cerebrovascular disease),and **limbs** (peripheral vascular .disease)

Cholesterol levels may be increase as a result :of

:An individuals **life style** like -1

a- Lack of **exercise**

b- **Diet** containing **excess** saturated **fats**

c- **Weight** gain

Inherited defect: like **gene defect** in lipoprotein metabolism or -2 .lack of **LDL receptor**

.**Combination** of 1 and 2 -3

:Thus

Life style changes + drug

lead to **reduce cholesterol** levels and

:**decline** in

Progression of coronary **plague** (decrease atherosclerosis)-1

.**Mortality** from CHD -2

however, lifestyle modifications do **not replace** the **need** for drug*

.therapy

Note: Normally LDL less than **130** mg/dl

Patient with **LDL** level more than **160mg/dl + one other risk** factors should **undergo drug** therapy.

Patients with **two** or **more** additional **risk** factors should be **treated aggressively**, with the **aim** of reducing their **LDL** level to less than **100 mg/dL** and, in some patients, to as low as **70 mg/dL**

A total cholesterol level of

.**Less** than **200** mg/dL is **normal**-
.mg/dL is **borderline high 239 - 200**-
Greater than or **equal** to **240** mg/dL is **high**-

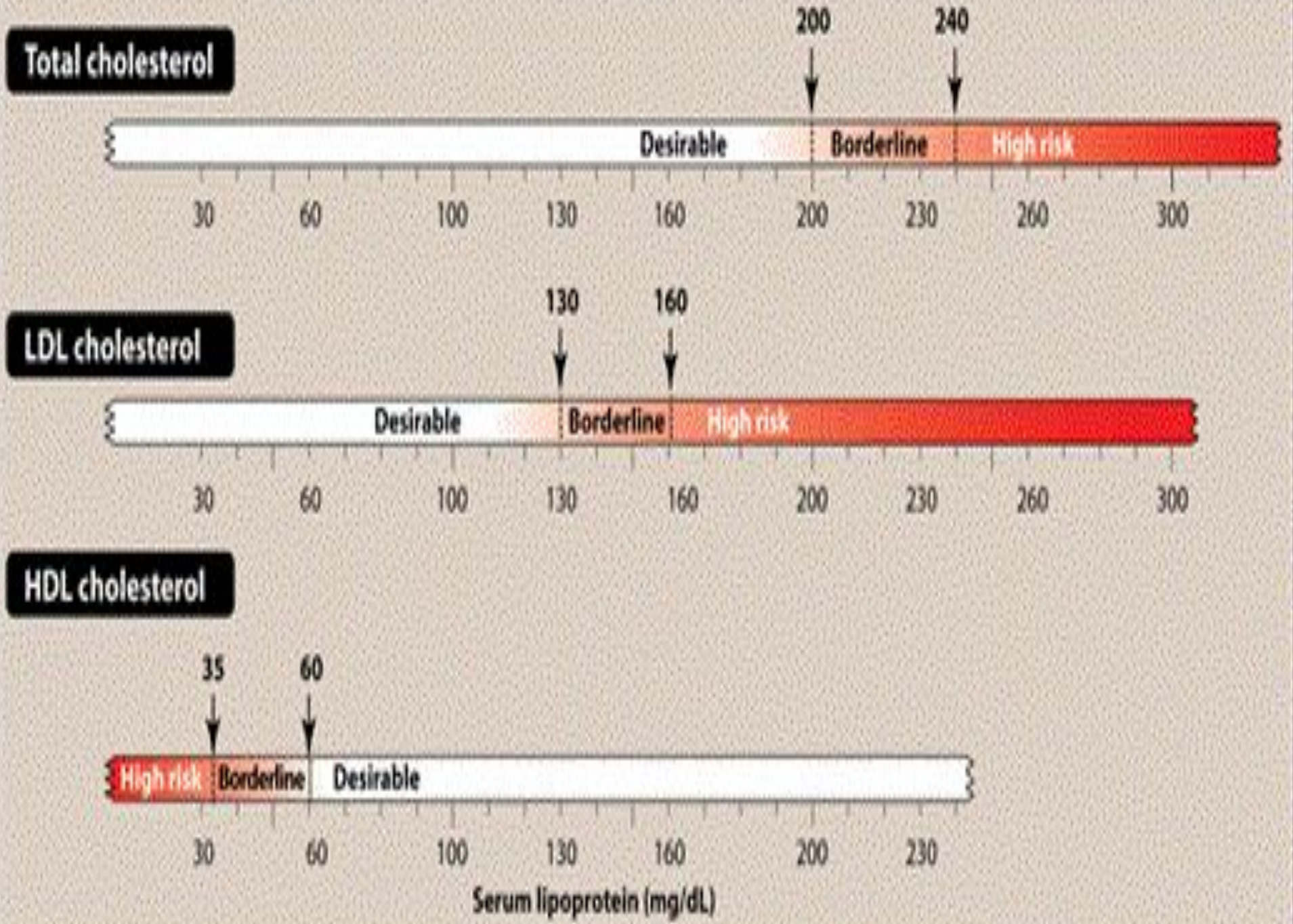
.**HDL normal** level = **more than 60 mg/dl**

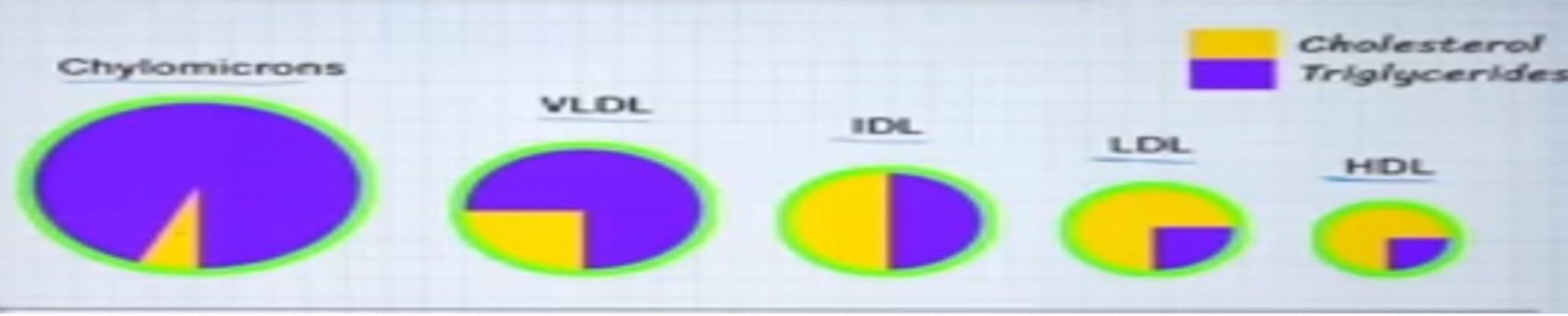
:Triglyceride levels are divided as follows

Normal – Less than 150 mg/dL●
Borderline high – 150 to 199 mg/dL●
High – 200 to 499 mg/dL●
Very high – Greater than 500 mg/dL●

Triglycerides should be **measured** after **fasting** for **12 to 14** hours

See the following picture


Total cholesterol
200
240
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
LDL cholesterol
130
160
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
HDL cholesterol
35
60
High risk
Borderline
Desirable
30
60
100
130
160
200
230
Serum lipoprotein (mg/dL)



Types of dyslipidemia

.Primary or genetic(=familial)lipoprotein disorders

The **types** and corresponding **lipoprotein elevations** include the :following

I (**chylomicrons**)= familial hyperchylomicronemia

IIa (**LDL**) = familial hypercholesterolemia

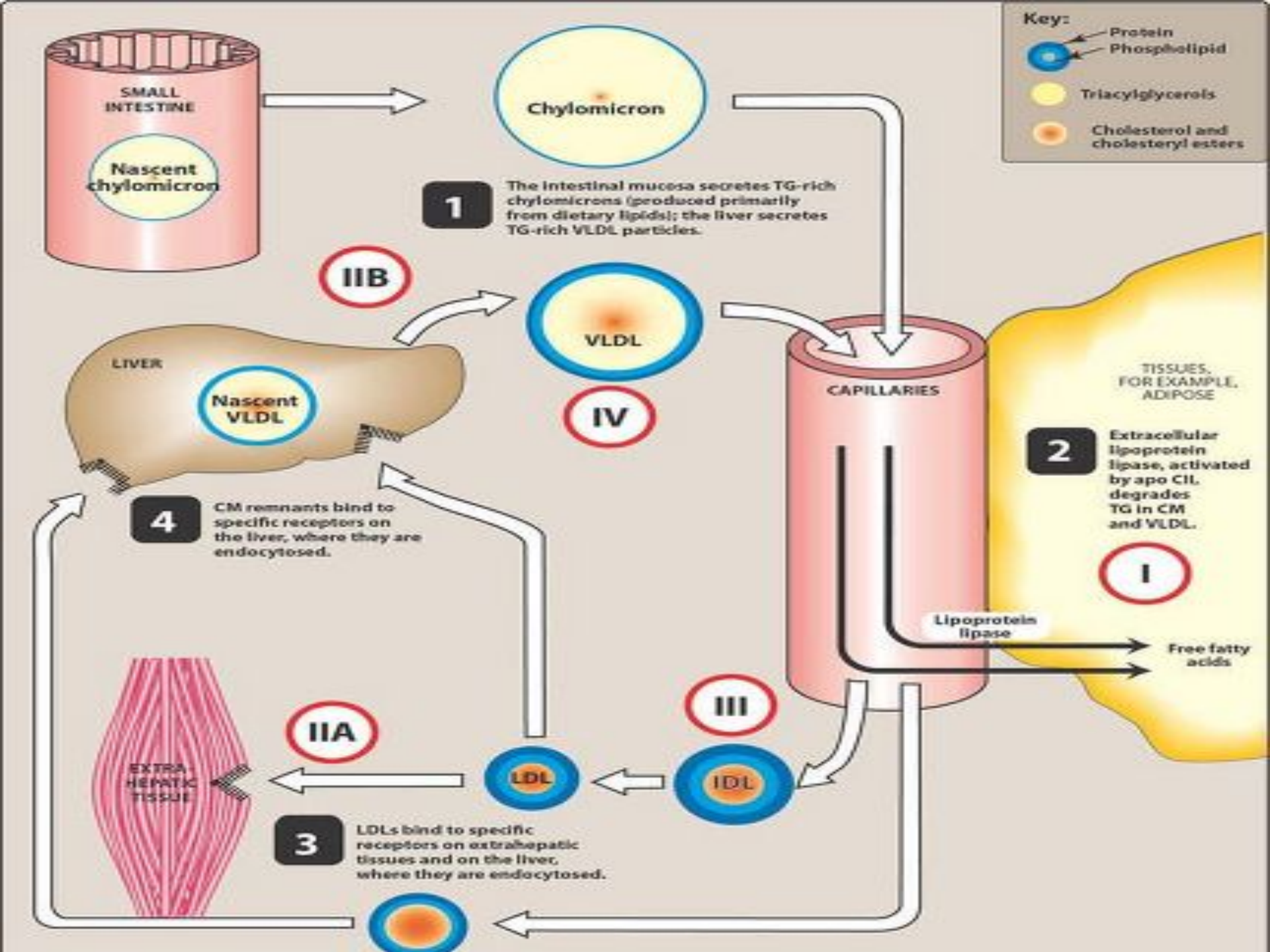
IIb (**LDL** + **VLDL**) =familial mixed (combined)hyperlipidemia

,III (**IDL**)= familial dys beta hyperlipoprotienemia

IV (**VLDL**) =familial hypertriglyceridemia

.V (**VLDL** + **chylomicrons**)= familial **mixed** hypertriglyceridemia

2. Secondary (acquired): In which several **drugs** may **elevate lipid** levels (e.g., progestins, thiazide diuretics, glucocorticoids, β-blockers,


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.

:Treatment lines

Patients should change their life style -1

A- Diet

B- Wt. reduction

C- Exercise

Drugs : includes lipid lowering -2 = (antihyperlipidemic)

: Part 2

Anti hyperlipidemic classes of drugs include:

1. **HMG COA reductase inhibitors (Statins)**
2. **Niacin(vitamin B 3)**
3. **Fibrates**
4. **Bile acid sequestrants.**
5. **cholesterol absorption inhibitor**
6. **Omega-3 fatty acids.**
7. **Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.**

These agents may be used **alone** or in **combination**.

HMG COA reductase inhibitors -1 :(Statins)

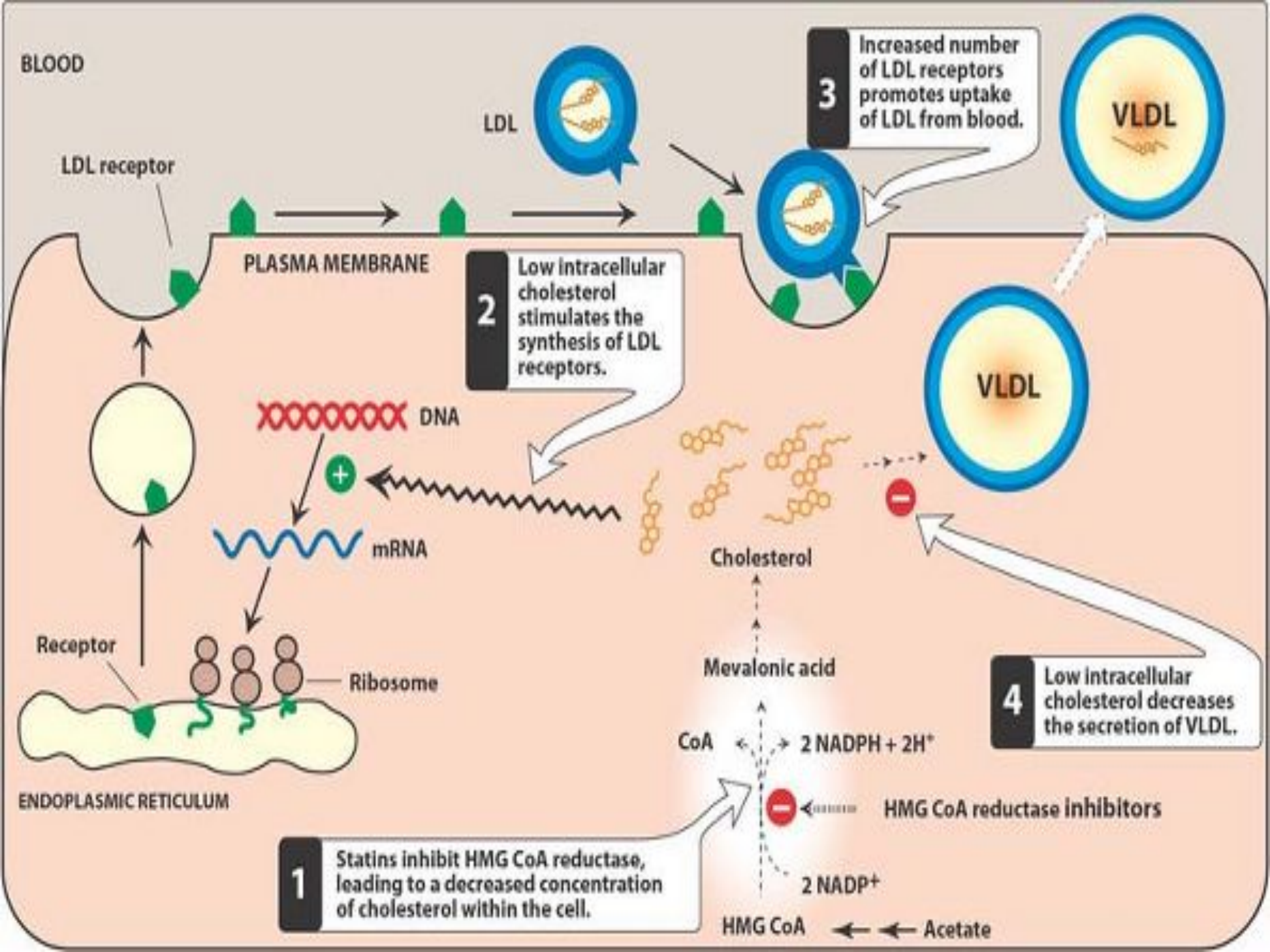
HMG COA=Hydroxyl methyl gluteryl COA enzyme

It lower **LDL -C, TG, and increase HDL**

:Mechanism of action

All are **competitive inhibiters of HMG COA reductase** -1 (the **rate limiting step** in cholesterol synthesis= any defect .in this point will block synthesis)

Increase in LDL receptors: Depletion of intracellular -2 chol. Causes the cells to increase number of LDL receptor that can bind to circulating LDL (**thus, the end result is a .reduction in plasma cholestrol**)


BLOOD
LDL
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
LDL receptor
PLASMA MEMBRANE
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+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Members of this group

Simvastatin
Atorvastatin
} the most common

Fluvastatin

Lovastatin

Pravastatin

Pitavastatin

Rosuvastatin

Cholesterol **synthesis** appears to occur mostly at* **night**, so statins with **short** **half-lives** are usually .**taken** at **night** to maximize their effect

:Uses

Lowering plasma **cholesterol** levels in **all types** of -1
hyperlipidemias, **However**, patients who are homozygous for
familial hypercholesterolemia lack LDL receptors and,
.therefore, **benefit** much **less** from treatment with these drugs

Combined hyperlipidemia (in combination with other drugs) -2

They are **first-line** treatment for patients with **elevated risk of**-3
.**atherosclerosis (it lowers atheros. Risk)**

:Therapeutic benefits include

.Atherosclerotic **plaque stabilization** -1
improvement of coronary **endothelial function** -2
.**inhibition** of platelet **thrombus** formation -3
.Vascular **anti-inflammatory** activity -4

Kinetics

Absorption is **variable** (30% to 85%) following **oral** -1 .administration1

.**Not** cross **BBB** **except** for **simvastatin** and **lovastatin** -2

Their **t1/2 differ**, ranging from **1-19 hrs** -3

The **longest** t ½ for **rosuvastatin** **(19 hrs)**

extensively metabolized by liver, CYP 450, **except pravastatin** -4

.Excreted by **kidney** -5

.**Lovastatin** and **simvastatin** are **hydrolyzed** to the **active** drug -6

Rosuvastatin and **atorvastatin** are the **most potent LDL-C** -7 lowering statins

Side effect: HMG COA Reductase=abbreviation

H : Hepatic dysfunction: Biochemical abnormalities in liver -1 function (increase liver transaminase), thus **monitoring** is needed .before and after Rx

M :**Myopathy** and **rhabdomyolysis in both sk. And cardiac** -2 **muscles:** (increase creatinine kinase (CK is an indicator of muscle damage….energy)

G: GIT: N&V -3

.COA : cataract middle age lenticular opacity -4

R : renal dysfunction (especialLy with **lovastatin**) -5

note:A clinical diagnosis of myopathy is made when there is muscle pain or weakness accompanied by a creatine kinase (CK) level more* than ten times the upper limit of normal. Rhabdomyolysis is a severe form of myopathy with muscle breakdown leading to .myoglobinuria, which may result in renal failure and death

:Interaction

Increase **warfarin** level (need monitoring)-

Simvastatin is metabolized by CYP450 3A4, and **inhibitors**-
.of this enzyme may **increase** the risk of rhabdomyolysis

:Contraindications

Pregnancy -1

Nursing mothers -2

Children or teenagers -3

Nicotinic acids (niacin= vit. B3) -2

vit. B3 contain 2 form either niacin (important In hyperlipidemia) or nicotinamide (not important in hyperlipidemia)

It Reduces **LDL-C** by (10% - 20%) and **TG** by (20% - 35%)

.It is the most **effective** agent for **increasing HDL-C**

Mechanism of action:

Niacin **strongly** **inhibit** **lipolysis** in **adipose** tissue (primary **producer** of circulating **FFA**) and the liver used this FFA in the **synthesis** of **TG**, thus decrease TG synthesis in the liver

Niacin → lipolysis → FFA → VLDL & LDL-C

Thus, niacin causes a **decrease** in liver **triacylglycerol** synthesis, which is **required** for **VLDL production,** .Thus decrease VLDL

LDL is **derived** from **VLDL** in the plasma. Therefore, a reduction in the VLDL concentration also results in a decreased plasma LDL concentration

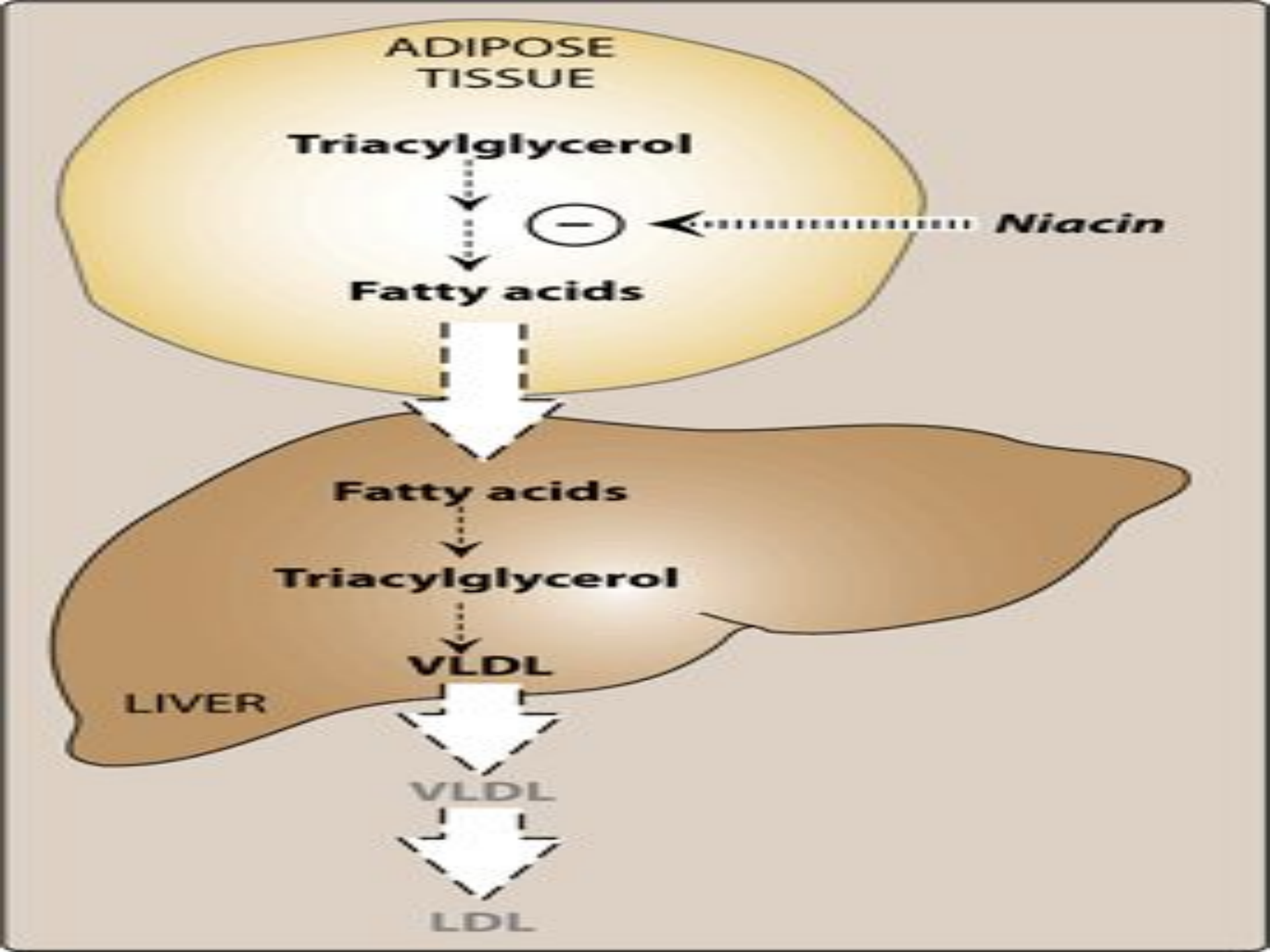
Kinetics

Given **orally**-1

.**Renal** excretion -2

Taken **once daily** at **bedtime** -3

Uses: in combination with other drugs for treatment of **all types** of hyperlipidemia **except type 1** which treated by **control of diet**


ADIPOSE TISSUE
Triacylglycerol
Niacin
Fatty acids
Fatty acids
Triacylglycerol
VLDL
LIVER
VLDL
LDL

:Side effect

Intense cutaneous **flush and Pruritus** bs it enhance PG and -1 histamine released. Administration of **aspirin** prior to taking niacin decreases the flush (flush is **prostaglandin** mediated mainly and PG cause vasodilitation).(**CASE**)

Nausea & gastric irritation(bs histamine stimulate H2R) -2

3- **hyperuriceamia** and **gout** (bs Niacin **inhibits** tubular **secretion** of uric acid).(**CASE**)

.**Hyperglycemia** (bs decrease glucose metabolism) -4

hepatotoxicity -5

Should be **avoided** in active **hepatic disease** or in patient -6

.with an **active peptic ulcer**

:Fibrates-3

They lower TG and increase HDL-C

:Members of this group

Fenofibrate, Clofibrate Bezafibrate, Gemfibrozil

:Kinetics

Fenofibrate is a **prodrug**, its active metabolite is fenofibric-1 .acid

thanGemfibrozil 2-**Fenofibrate** is more **effective**

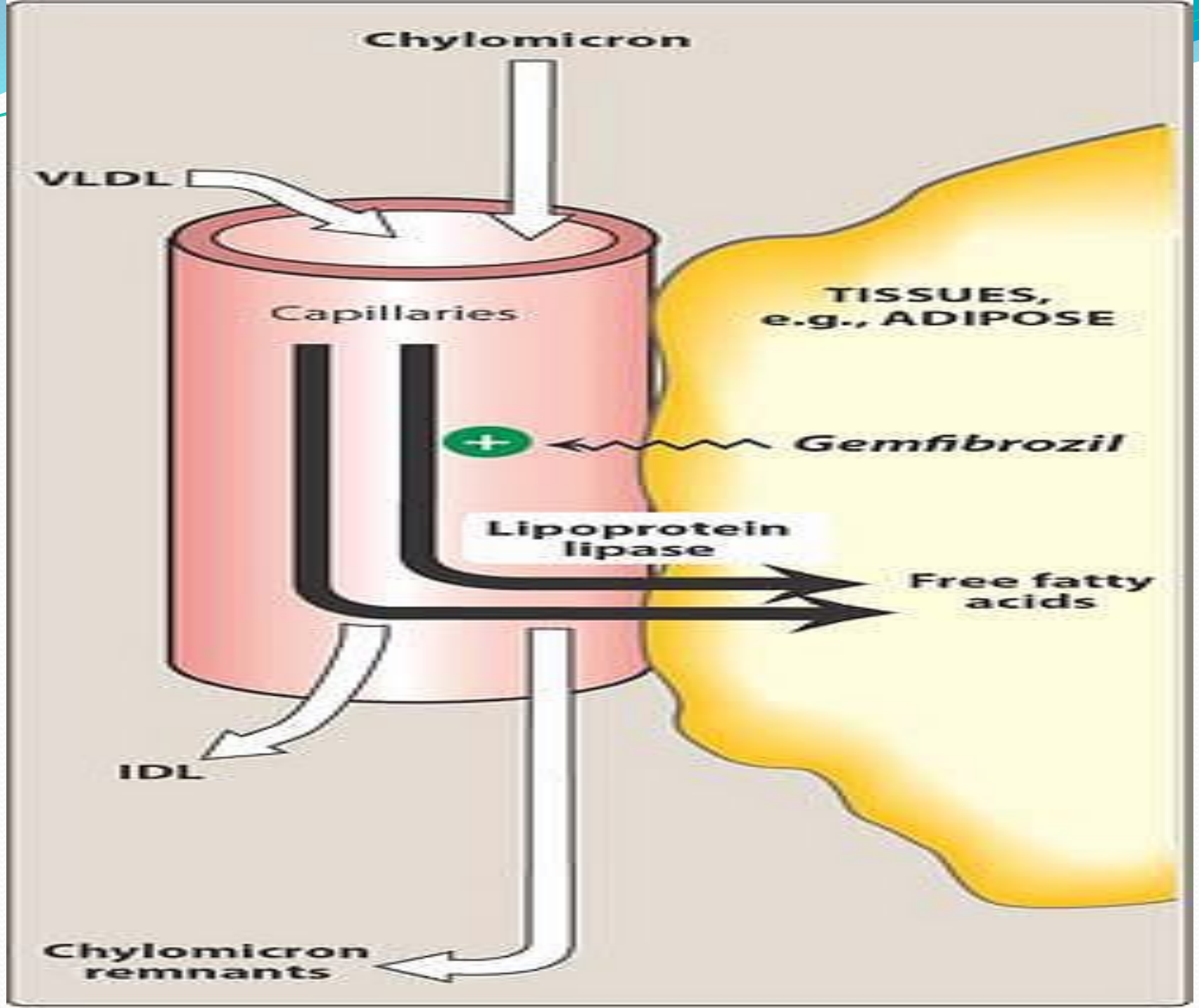
.Given **orally**-3

Absorption of Gemfibrozil is **improved** when taken with -4 .**food**

:Mechanism of action

Peroxisome proliferator- activated receptors (PPARs) are **nuclear receptors** that **regulates lipid metabolism**. They ,act as **transcription** factor

when **binding** to hypolipidemic drugs, the PPAR are activated, so they **regulate** the **expression** of **genes** that involved in **lipoprotein** structure and function thus, **Fibrate-mediated gene expression** ultimately leads to **decreased triacylglycerol** concentrations by increasing the **expression** of **lipoprotein lipase** (responsible for **lipid metabolism**) and decreased apolipoprotein (apo CII .concentration)


Chylomicron
VLDL
Capillaries
TISSUES,
e.g., ADIPOSE
Gemfibrozil
Lipoprotein
lipase
Free fatty
acids
IDL
Chylomicron
remnants

:Adverse effects

Mild gastrointestinal disturbances (most common) -1

Predisposition to form **gallstones** (**Because** these drugs-2 .**increase** biliary **cholesterol excretion**)

Myositis (inflammation of a voluntary muscle) -3

.Patients with **renal insufficiency** may be at **risk** -4

Myopathy and **rhabdomyolysis** if gemfibrozil and statins -5 **taking together (but not absolute contraindication)**

:Interact with

A-**Coumarin** anticoagulants (compete with anticoagulants for **binding** sites on plasma protein) **potentiate** anti coagulant .activity. (increase risk of warfarin)

B-**Sulfonylureas(oral antidiabetic)** compete with it for **binding** .sites on plasma protein

:Uses

.**Hypertriglyceridemia** (type IIb, III,IV,V) -1

Fenofibrate has **antidiuretic action** (bs it increase -2 renal sensitivity to antidiuretic hormone **ADH**)

Fenofibrite has mild **uricosuric action**(used in-3 gout)(case)

.Contraindications

Pregnancy -1

Lactating woman -2

Sever hepatic impairment-3

Renal failure-4

.Patients with preexisting gall bladder disease-5

Bile acids binding Resins(sequesterants)-4

LDL-C lowering effects (less than statin)

:**Family members include**

Cholestyramine (the **most commonly** used)

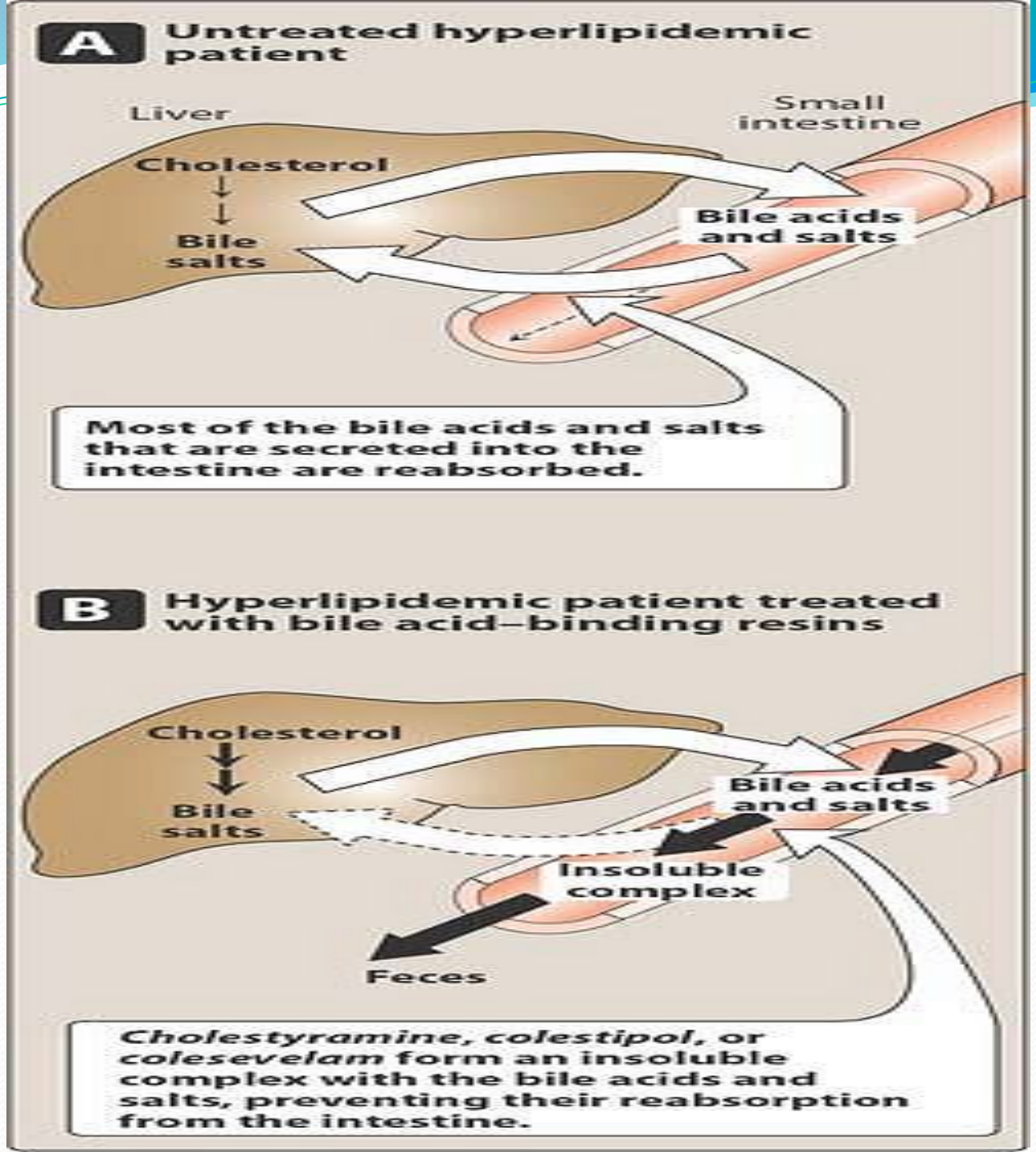
Colestipol

Colesevelam

Mechanism of action

binds with bile acids and salts small intestine to form a **complex excreted** with the **feces** , thus, **Preventing** the bile acids from **returning** to the **liver** and converted to cholesterol. Lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds, which are essential components of the bile

Consequently, the **intracellular cholesterol** concentration **decreases**, which activates an **increased hepatic uptake** of cholesterol-containing **LDL** particles, leading to a **fall** in **plasma LDL**


A
Untreated hyperlipidemic patient
Liver
Small intestine
Cholesterol
Bile salts
Bile acids and salts
Most of the bile acids and salts that are secreted into the intestine are reabsorbed.
B
Hyperlipidemic patient treated with bile acid–binding resins
Cholesterol
Bile salts
Bile acids and salts
Insoluble complex
Feces
Cholestyramine, *colestipol*, or *colesevelam* form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.

Adverse effect

GIT disturbances : **N&V,** constipation and flatulance, -1
.**steatorrhea** (due to decrease fat absorption)

At **high doses**, cholestyramine and colestipol -2 (but **not colesevelam**) **impair** the **absorption** of the **fat-soluble vitamins** (A, D, E, and K) and some .**drugs** (warfarin, digoxin,…)

:Uses

Hypercholestrolemia (type IIa) (reduce plasma chol. By -1 **10-20%**)

.**Diarrhea** bs bile acid malabsorption -2

.**Pruritis** due to obstructive jaundice -3

Cholesterol absorption-5 inhibitors:

Ezetimibe

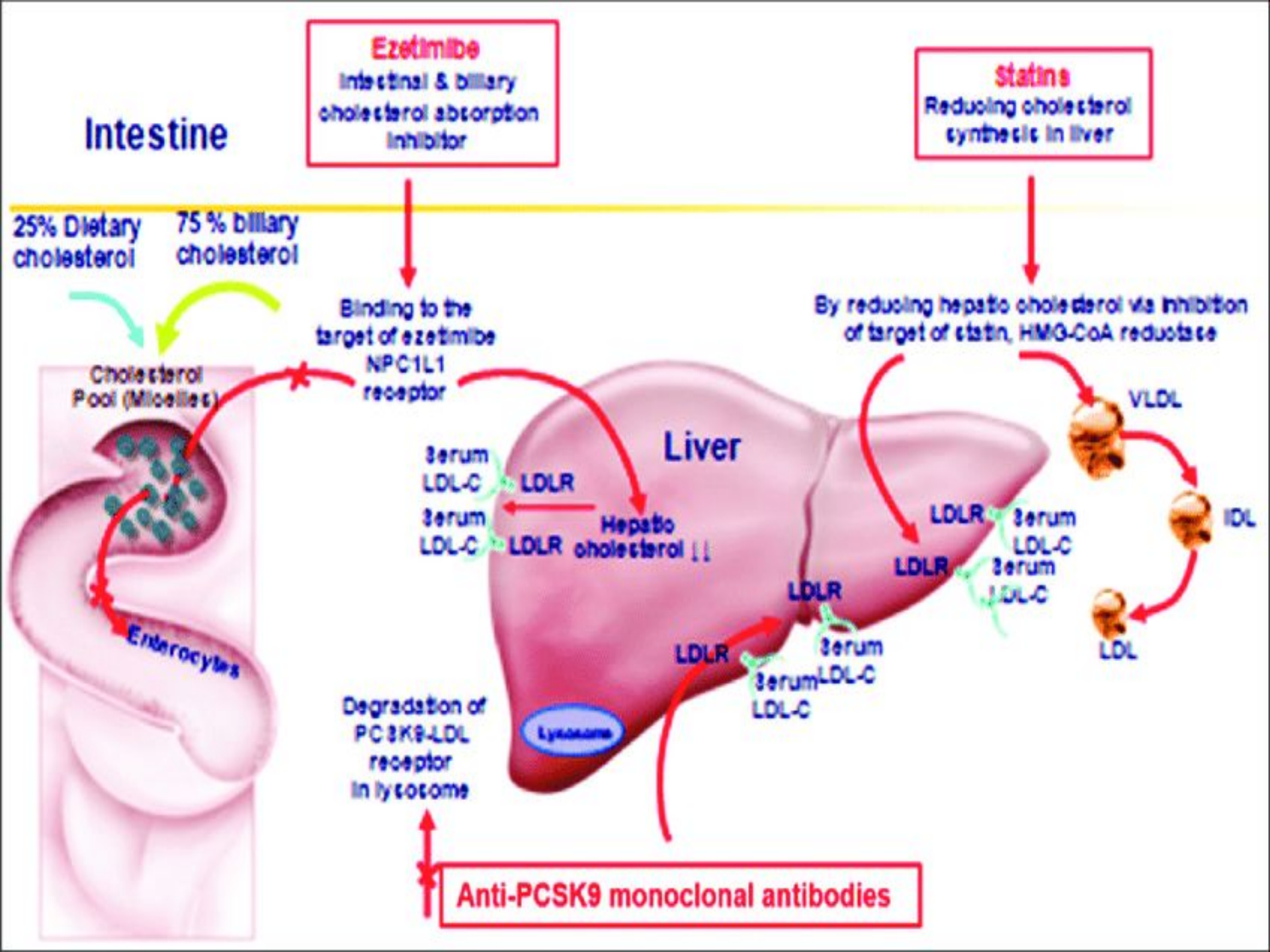
Inhibit intestinal **absorption** of dietary and biliary **cholesterol** (in the small intestine) leading to decrease in the delivery of .intestinal cholesterol to the liver

Uses: Hypercholesterolemia (decrease chol. level By 18%)

:**S.E**

Reversible liver dysfunction (liver function should be checked regularly)

GIT: stomach pain, diarrhea


Intestine
Ezetimibe
Intestinal & biliary cholesterol absorption inhibitor
Statins
Reducing cholesterol synthesis in liver
25% Dietary cholesterol
75 % biliary cholesterol
Binding to the target of ezetimibe NPC1L1 receptor
By reducing hepatic cholesterol via inhibition of target of statin, HMG-CoA reductase
Cholesterol Pool (Micelles)
Enterocytes
Liver
Serum LDL-C
LDLR
Hepatic cholesterol ↓↓
VLDL
IDL
LDL
Degradation of PCSK9-LDL receptor in lysosome
Lysosome
Anti-PCSK9 monoclonal antibodies

:Kinetics

Slowly eliminated from plasma -1

.**Half-life** of about **22 hours** -2

Ezetimibe has **no** meaningful effect on the plasma -3

,level of the **fat-soluble vitamins** A, D

.and E

Orlistate :is a **lipase enz. inhibitor** (**reversibly** inhibiting the gastric and pancreatic enzyme (enzyme that secreted from pancreas and **responsible** the **digestion of dietary fat**. They work by breaking down the **triglycerides into absorbable free fatty acids** and monoglycerides for fat digestion)

:Side effect of orlistat

. Gas (flatulence)

.Fatty/oily stools

.Increased defecation

.Fecal incontinence/inability to control bowel movements

.Urgent bowel movements

.Loose stools

.Diarrhea

Omega-3 fatty acid -6

: poly unsaturated FA (PUFAs)includes 3

α-linolenic acid : (found in plant oils)

eicosapentaenoic acid (EPA) and **docosahexaenoic acid** (DHA) are found in marine sources such as tuna and salmon.

Approximately **4 g** of marine-derived omega-3 PUFAs **daily decreases serum triglyceride** concentrations by 25% to 30%, with **small increases in LDL-C and HDL-C**

: Uses

an adjunct to other lipid-lowering therapies -1

.in very high blood TG

.**supplements**, but in **lower** doses **-2**

Icosapent ethyl is a product that contains **only EPA** and **DHA** ,**unlike other fish oil** supplements, does **not** .significantly **raise LDL-C**

it **decreases** **C-reactive protein**, **interleukin 6** and **TNF .alpha**

Side effects

GIT upset (abdominal pain nausea and diarrhea) -1

Fishy aftertaste -2

3- **Bleeding** risk in those who are concomitantly taking .anticoagulants or antiplatelet agents

PCSK9 Inhibitors -7

PCSK9 inhibitors are **monoclonal antibodies**, a type of biological drug. They are **inactivating** a protein called .**proprotein convertase subtilisin kexin 9**

This protein reduces the number of LDL receptors on the liver by **binds to the LDL receptor** on the surface of hepatocytes, **leading to** the **degradation of LDL receptors**). When PCSK9 is deactivated, there are more receptors available to **eliminate LDL -C** .**%** from the blood by **50 -70**

:Uses

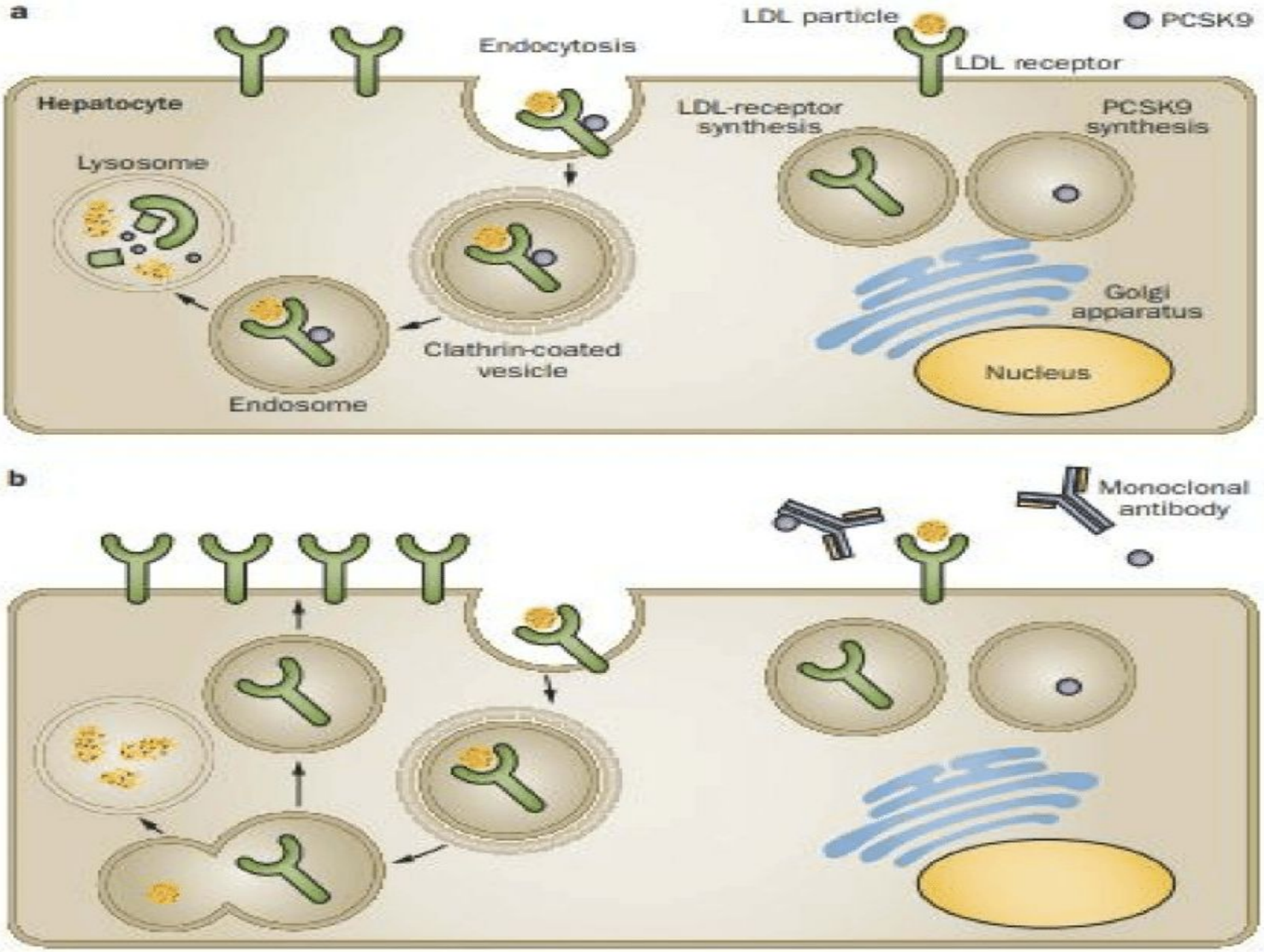
familial (primary) **hypercholestrolenemia**-1

Atheroseclortic coronary events in **combination** with -2 **statin** 3- statins **intolerance**

:They include

Alirocumab

Evolocumab


a
LDL particle
PCSK9
Endocytosis
LDL receptor
Hepatocyte
LDL-receptor synthesis
PCSK9 synthesis
Lysosome
Golgi apparatus
Clathrin-coated vesicle
Nucleus
Endosome
b
Monoclonal antibody

:Kinetics

Only available as **subcutaneous** injections -1

.they are **administered every 2 – 4 weeks** -2

are **not eliminated** by the **kidneys** (and have been -3

used in dialysis patients or those with severe renal

.impairment)

: Side effects

:They are **well tolerated,** The most common are

,Injection site reactions

,immunologic or allergic reactions

.flu like illness

.

:Case

A 67 yr. old male patient , aknown case of increase hyperlipidemia, he was on niacin treatment, he presented to Medical Consultant .Unite with intense cutaneous flash and pruritis

?Explain why this happened

?How you can treat it

.Note : summary in the the following slide***

Lipid lowering drug	LDL -C	TG
Cholysteramine and ezitimibe	↓ ↓ ↓	
HMG CoA reductase inhibitor	↓ ↓ ↓	
Fibrate		↓ ↓ ↓
Niacin	↓	↓ ↓
Omega		↓ ↓
Pcsk 9	↓ ↓ ↓	


Thank You!