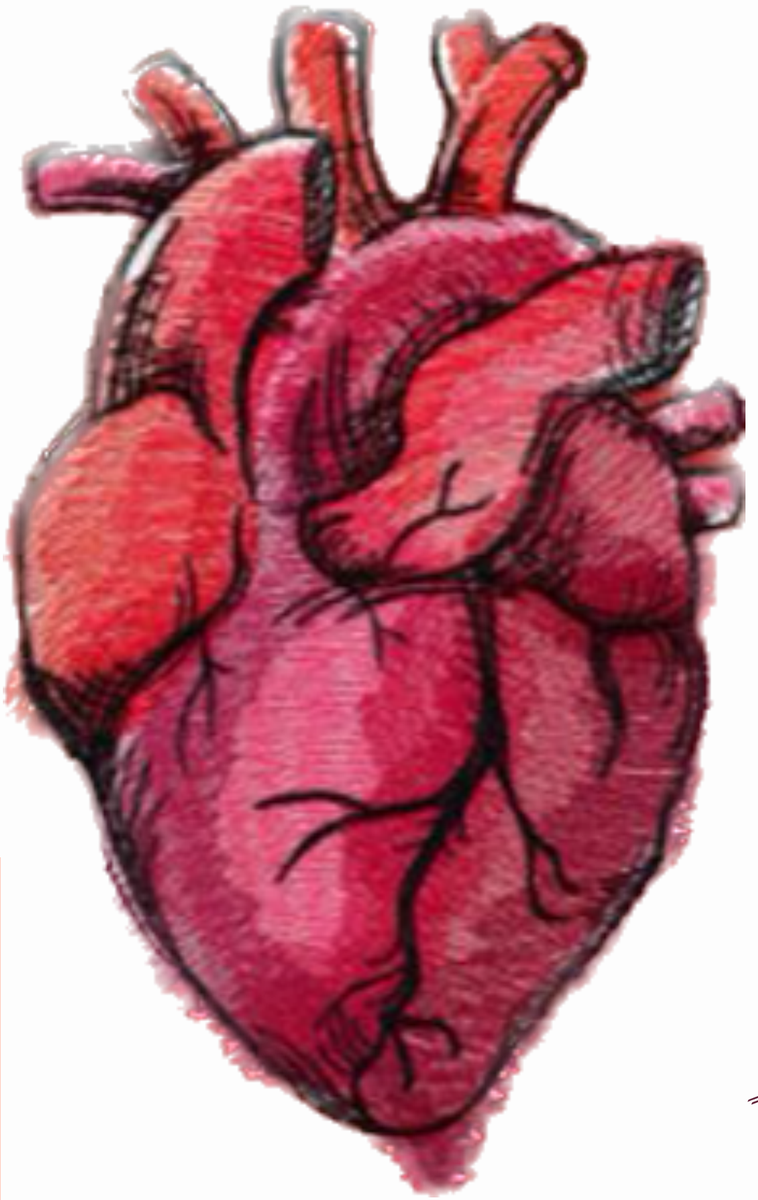


النادي الطبي

CARDIOVASCULAR SYSTEM

SUBJECT : Pharmacology

LEC NO. : Lecture 1

DONE BY : ATA 👀🫀

وَقُل رَّبِّ زِدْنِي عِلْمًا

SCAN ME!

التفريغ عن الريكورد تبع teams

المحاضره خفيفه لطيفه
الدكتوره شرحها ممتاز وفي حال ما فهمتوا عليها ارجعوا ع صفحة النادي حاطين مصادر للي حاب 😬

CVS- Pharmacolgy1

Drugs for hyperlipidemia

الدكتوره حكت بالعاده اسئلتها مش صعبه واللي دارس وباصم صح بجاوب وبضمن علاماتها واسئلتها من المحاضرة 🗿

Faculty of Medicine
The Hashemite University
Arwa Al Anber (MD, PhD)
Office: 1018

بسم الله نبدأ

Hyperlipidemias

ليش اعطيناها هذا الاسم ؟! لانها بتغير lipid profile لانه مش كل اشي عالي بجسم : - بالوضع الفيزيعي بنفضل HDL يكون عالي وال LDL يكون واطي بهيك الحالة ممكن يكون TAG و LDL Normal بهيك ال Range but HDL decrease

Hyperlipidemia(dyslipidemia) is excess lipid in the blood:

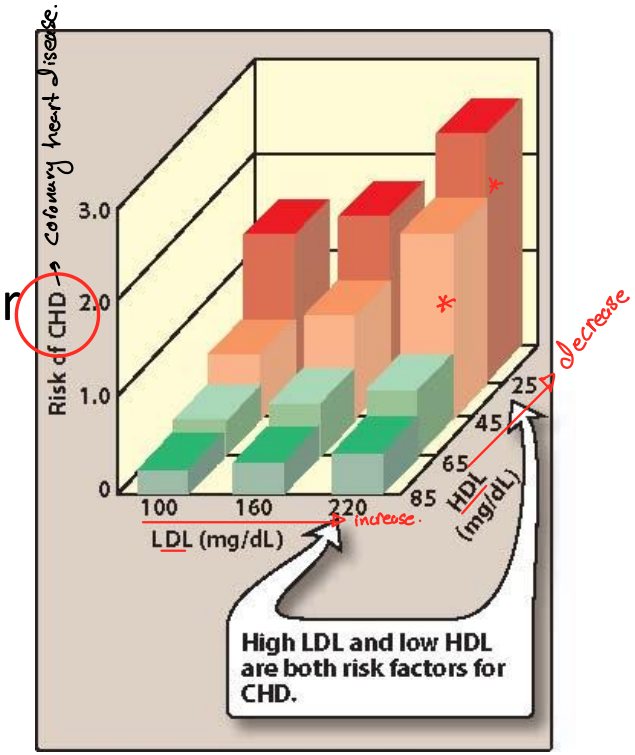
1. High level low-density lipoprotein cholesterol (LDL-C) ← Bad C
2. High level of triglycerides
3. Low level of high-density lipoprotein cholesterol (HDL-C) ← good C

- **Causes of Hyperlipidemias ?**

- Lifestyle factors (lack of exercise, diet containing excess saturated fats or smoking).
- An inherited defect in lipoprotein metabolism.
- A combination of genetic and lifestyle factors.
- Hypothyroidism. → تحول الى الغدة الدرقية
- Diabetes

High Risk for hyper lipidemia

High Risk for Coronary heart disease



Why we need to treat hyperlipidemia ?

" The fat speaks :

With water, I say, Touch me not’s

To the tongue, I am tasteful;

Within limits, I am dutiful;

In excess, I am dangerous! "

Chemical Constituents of Life Ch 3

Why we need to treat hyperlipidemia ?

1. Reducing atherosclerotic cardiovascular disease (ASCVD)risk.

2. Reducing risk of pancreatitis

أكثر اشي تبهير لعايكون TAG أعلى اشي عالي

طبعًا انا ما بعالج كل الناس نفس الاشي بعقد عندي CVD عندهم Risk Factor

Goal of treatment

LDL Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk category	*LDL goal*	*LDL level at which to initiate TLC*	*LDL level at which to consider drug therapy*
CHD or CHD risk equivalent (10-year risk >20 percent)	<100 mg/dL(2.60 mmol/L)	≥ 100 mg/dL	≥ 130 mg/dL (at 100 to 129 mg/dL, drug optional)*
2 or more risk factors (10-year risk <20 percent)	<130 mg/dL (3.35 mmol/L)	≥ 130 mg/dL	≥ 130 mg/dL for 10-year risk of 10 to 20 percent; 160 mg/dL for 10-year risk of <10 percent
0 to 1 risk factor†	<160 mg/dL (4.15 mmol/L)	≥ 160 mg/dL	≥ 190 mg/dL (at 160 to 189 mg/dL, LDL-lowering drug optional)

DM.

ال risk أعلى أو طالستجاب لل TLC

لـ TLC أو طالستجاب لل

LDL = low-density lipoprotein; CHD = coronary heart disease; HDL = high-density lipoprotein.

**—If an LDL cholesterol level of <100 mg per dL cannot be achieved by therapeutic lifestyle changes, some authorities recommend use of LDL-lowering drugs in this category. Others prefer using drugs that primarily modify triglycerides and HDL (i.e., nicotinic acid or fibrate). Clinical judgment also may call for deferring drug therapy in this subcategory.*

†—*People with zero to one risk factor almost always have a 10-year risk <10 percent; thus, 10-year risk assessment is not necessary in this group.*

Adapted with permission from Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

هاي هي الـ guidline وهش ضروري الدكتور يلتزم فيها، بحيث الدكتور اللي بيعالج مريضا شاف انه فيه احتمالية هذا المريض بيعالج مع TLC لفترة اشهر وبشوف وضعه إذا تحسن تمام وإذا ما تحسن نضيف على دوا معين Drug therapy يعني يعطيه خرجة ومابيش مباشرة بالعلاج الدوائي

عادتنا نفضل خاصة لل young انه نضيفهم على TLC

* اهنا الخير عنا HDL وأقل ↑LDL
خلدم انا أقلل جا رفع HDL
* TAG حالها ماتأثر كثير على CVD تتأثر أعثر على البنكرياس.

Goal of treatment

Major Risk Factors That Modify LDL Goals

Positive risk factors → For coronary heart disease.

Age (men ≥ 45 years; women ≥ 55 years)

Low HDL cholesterol (<40 mg per dL [1.05 mmol per L])

Cigarette smoking

Hypertension (blood pressure >140/90 mm Hg or taking antihypertensive medication)

Family history of premature CHD (CHD in male first-degree relative <55 years;

CHD in female first-degree relative <65 years)

Negative risk factor → protective

High HDL cholesterol (> 60 mg per dL [1.55 mmol per L]); presence of this risk factor removes one risk factor from the total count

LDL = low-density lipoprotein; HDL = high-density lipoprotein; CHD = coronary heart disease.

Adapted with permission from Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2487.

Clinical notes

معادلة تطلع ال CHD ال Risk
وتقارنهم بال Goal اللي فوق

ACC/AHA 2013 Cardiovascular Risk Assessment

Drugs for Hyperlipidemia

Statins

Niacin

Fibrates

PCSK9 inhibitors

Cholesterol absorption inhibitors

Bile acid sequestrants

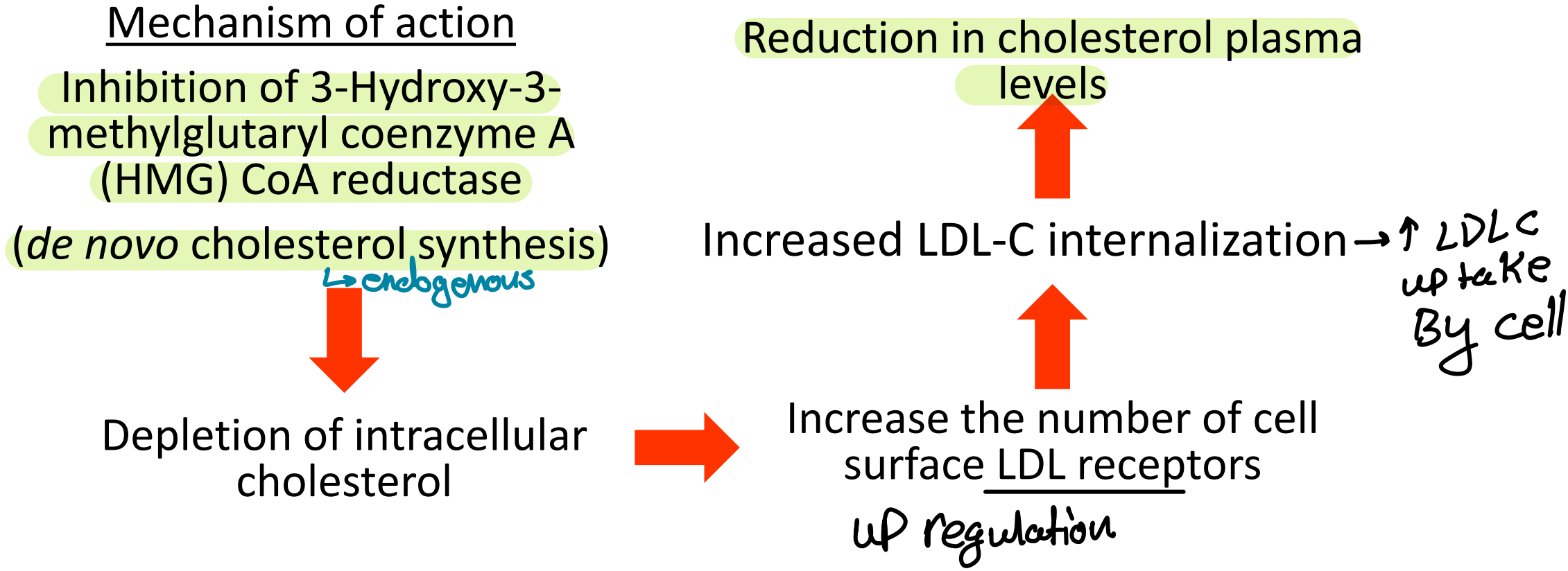
Statins
HMG CoA Reductase Inhibitors

* ملحوظة: - مش كل المرضى بنعطيهم نفس الدوا أو نفس Dose بتعتمد على حسب age مثلا على medical status للمريض. وعلى حسب severity وهيك

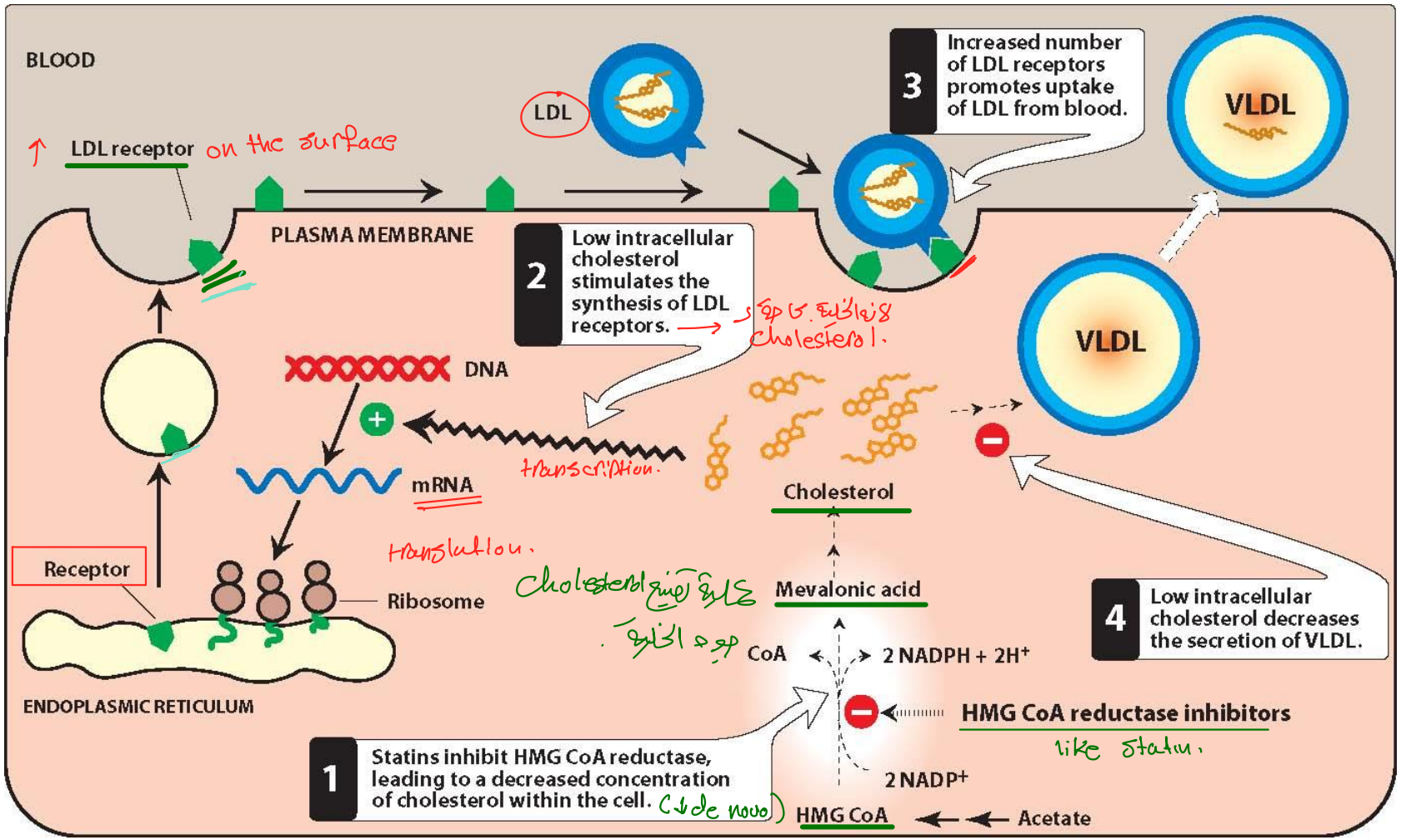
HMG CoA REDUCTASE INHIBITORS (STATINS)	
Atorvastatin	LIPITOR
Fluvastatin	LESCOL
Lovastatin	MEVACOR
Pitavastatin	LIVALO
Pravastatin	PRAVACHOL
Rosuvastatin	CRESTOR
Simvastatin	ZOCOR

Most potent and longer plasma half-life and most effective one

Statins
HMG CoA Reductase Inhibitors

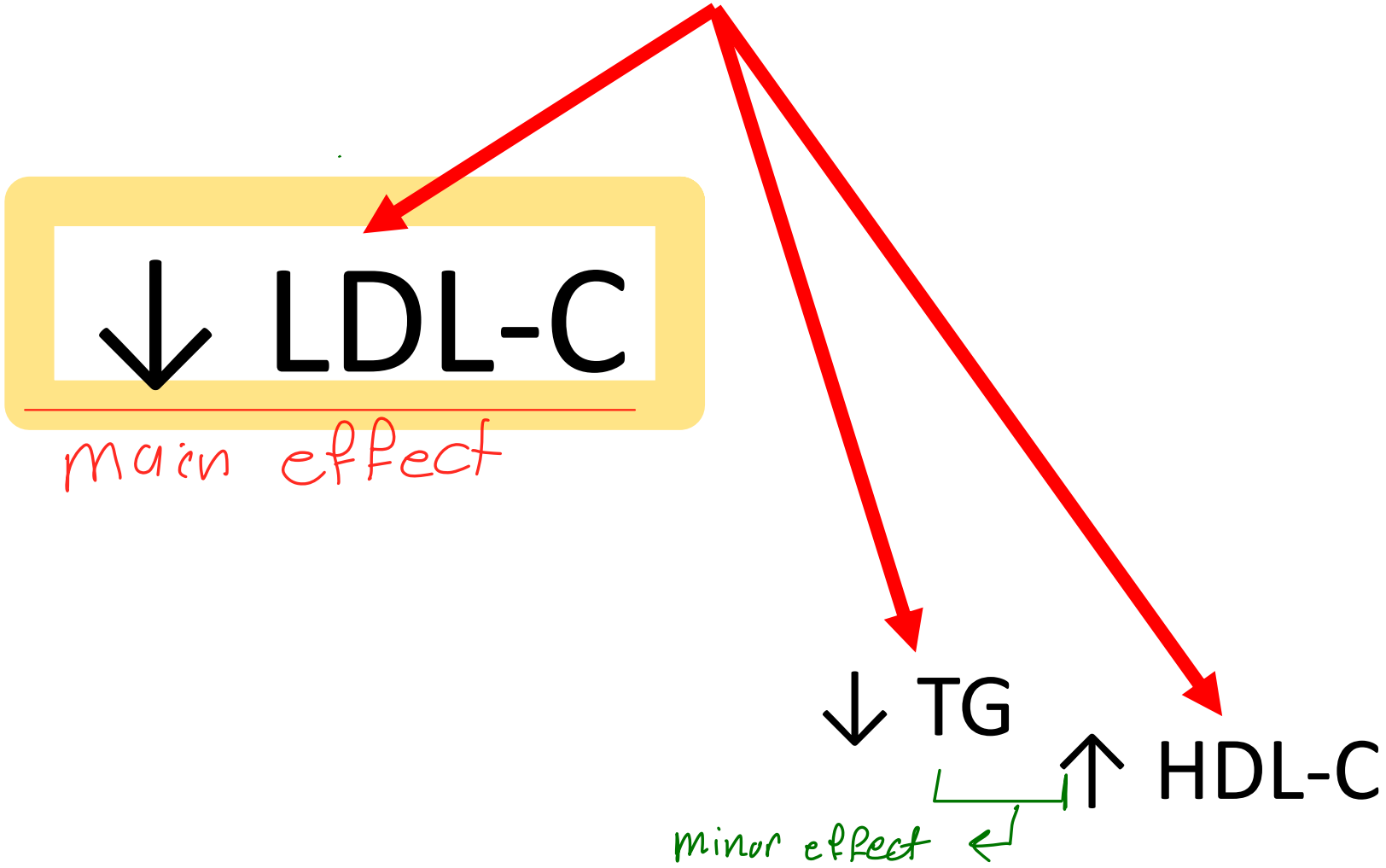


Statins
HMG CoA Reductase Inhibitors



Statins
HMG CoA Reductase Inhibitors

يعدل ال lipid profile



Statins
HMG CoA Reductase Inhibitors

Therapeutic uses

First line drugs to lower LDL-C and to lower the risk of atherosclerotic cardiovascular disease. or Familial hyperlipidemia

Pharmacokinetics

Drug-Drug interaction وهيك زاد عنا Drug وذي ما نعرف هذا enzyme يشتغل عليك أكثر من

All statins metabolized by cytochrome p450(CYP450)in the **liver**

Excretion mainly through **bile and feces** with some urinary elimination

Risk of liver Failure لانه ع يزود Contra indication ⇐ Statin liver Disease عنده بيكون ∴ لهيك هذا

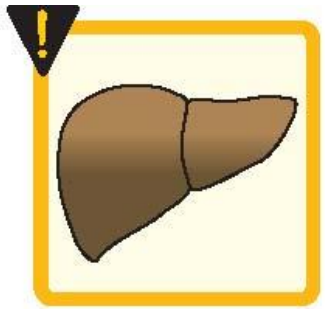
Statins
HMG CoA Reductase Inhibitors

Adverse effects

- **↑ liver enzymes** (liver Failure)

  Liver disease results in accumulation of statins

- **Myopathy and rhabdomyolysis** especially patient with history of muscle disease.
- **Drug-drug interaction e.g., warfarin**
- **Contraindicated in pregnancy, lactation and active liver disease** → teratogenicity effect



Liver failure

Myopathy

Contraindicated in pregnancy

Niacin

↓ LDL-C

10-20%

minor effect

↓ TG

20-35%

↑ HDL-C mainly.

Most effective agent for increasing HDL-C

* مريض عنده LDL-C عالي حال HDL-C صنعت Normal Range وعنده High Risk For CHD هل ح يستخدم من ١٢ Niacin
على حسب؟ هسا ال HDL زي ماشرحنا protective فانا بدي اياه يزيد خلو مثلا" مشيت هذا العلاج حال statin ونزلي ال LDLc بس مش لدرجة optimum
بس انا بدي اقلل Risk واقلل كمان LDLc وارفع HDL ← فانا هيك بطيح Niacin

Niacin

Therapeutic uses

Treatment of familial hyperlipidemias and other severe hypercholesteremias

OFTEN IN COMBINATION WITH STATINS

e.g., niacin + lovastatin

e.g., niacin + simvastatin

Familial hyperlipidemia
usually resistant
لازم يكونوا

Niacin

Adverse effects

- Intense cutaneous flush + warmth/pruritis
- Hepatotoxicity/chemical hepatitis
- Nausea, abdominal pain
- Hyperuricemia/gout
- **Contraindicated in liver disease and active peptic ulcer**

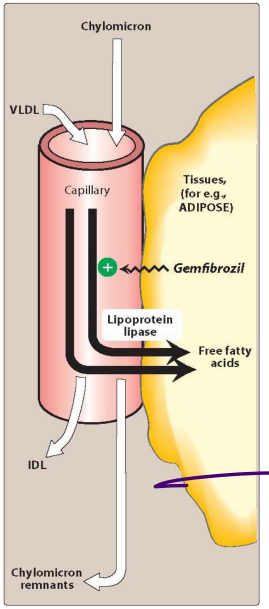
Fibrates

FIBRATES	
Gemfibrozil	LOPID
Fenofibrate	TRICOR, LOFIBRA, TRIGLIDE

Fibrates mainly affect on TAG.

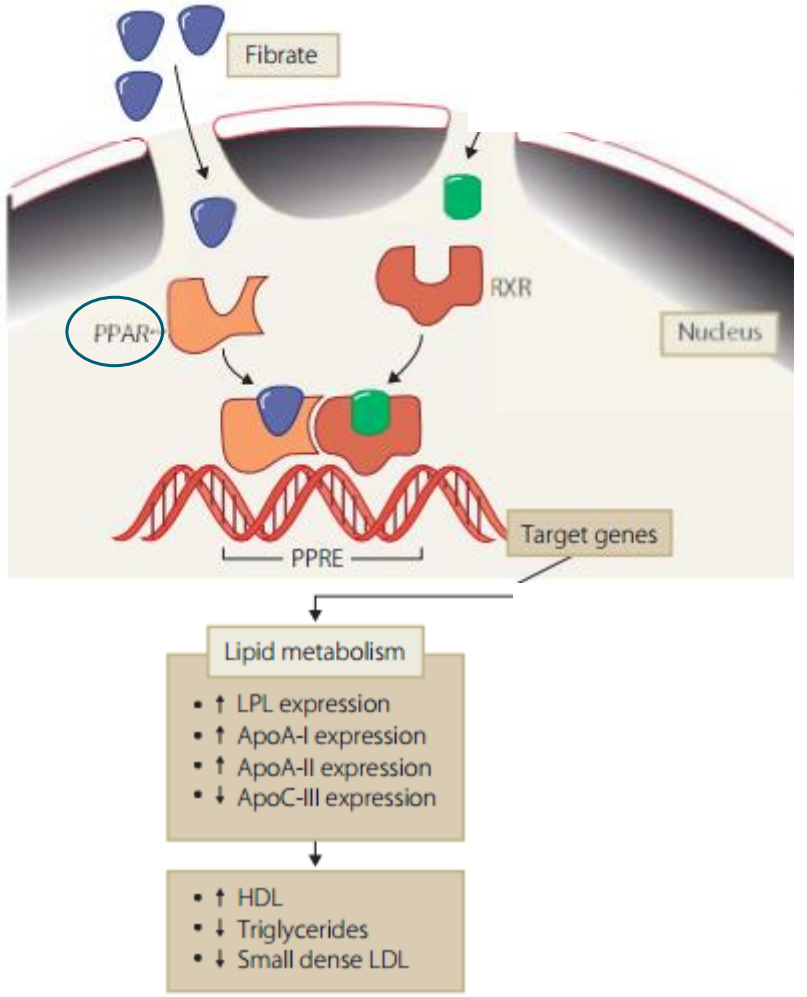
Mechanism of action

Activators of (peroxisome proliferator-activated receptors), especially PPARα

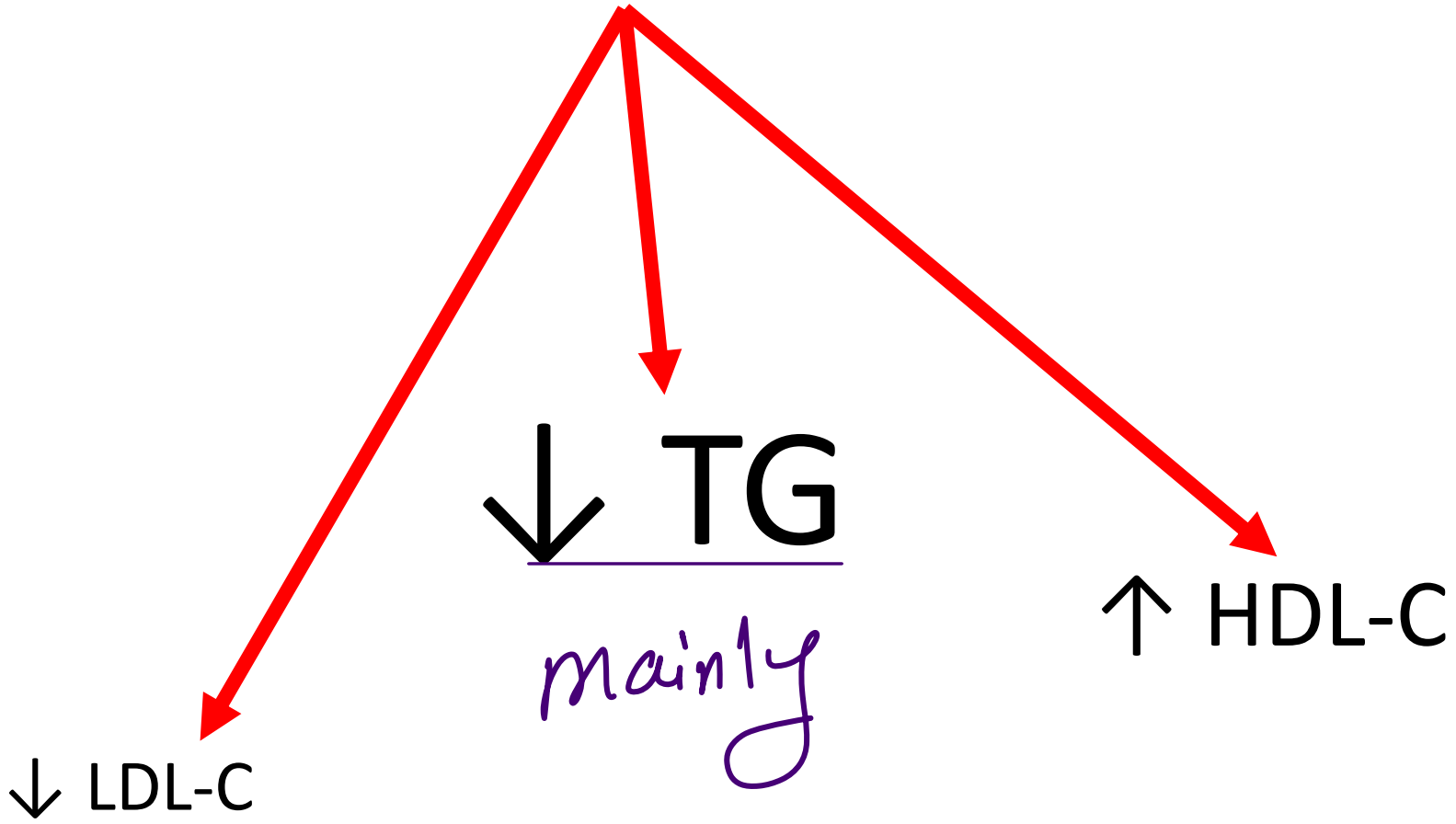


محاضرات البيوكم معرضة هنا الحكي.

Increase the expression of lipoprotein lipase → ↓ TG



Fibrates



Fibrates

Therapeutic uses

Treatment of hypertriglyceridemia

Fibrates

Adverse effects

- **Mild GI disturbance (most common)**
- **Increased risk of gallstone formation**
- **Myositis**
- **Cautions:**
  - The use of Gemfibrozil is **CONTRAINDICATED** with simvastatin (or other statins). ↑ Risk of **Myopathy and rhabdomyolysis**
  - It is **CONTRAINDICATED** in hepatic or renal insufficiency
  - Drug-drug interaction e.g., warfarin

Bile acid sequestrants

BILE ACID SEQUESTRANTS	
Colesevelam	WELCHOL
Colestipol	COLESTID
Cholestyramine	QUESTRAN, PREVALITE

→ most common.

*Bile Acid in intestine reabsorped to liver.

Bile acid sequestrants

Bile هو صفراء يستخدم لتهضيم الدهون

Mechanism of action

Bind negatively-charged bile acids and salts in the small intestines

↓

↑ excretion of bile acids in feces

→

↓ bile acid concentration

↑

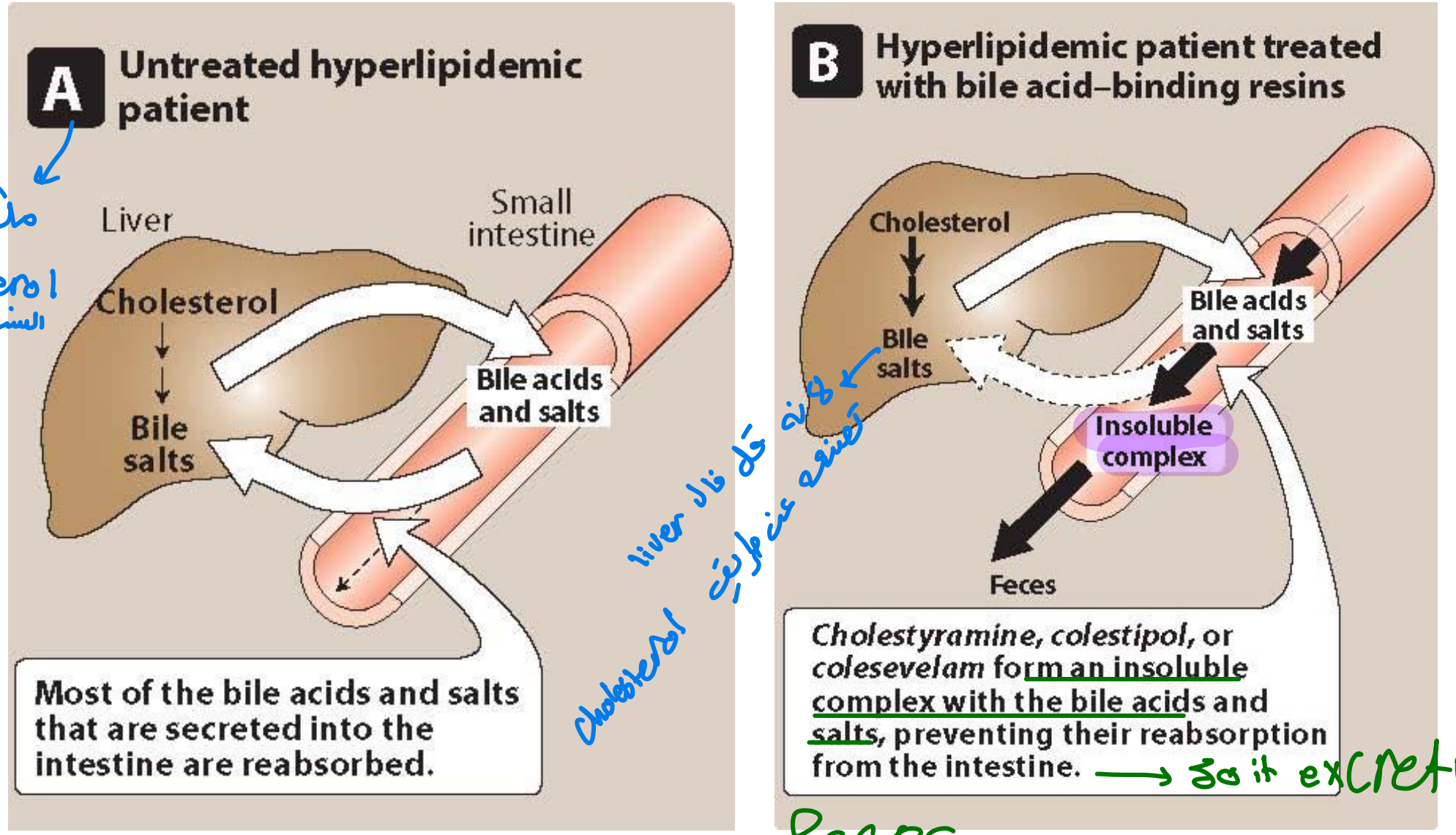
↑ hepatocyte conversion of cholesterol to bile acids

↑

Depletion of intracellular cholesterol

→

↑ hepatic uptake of cholesterol leading to ↓ plasma LDL-C



ملخ تغير على Cholesterol السبة ثابتة.

liver هاد خل فال Cholesterol تصنعه عن طريق

→ so it excretion in feces.

Cholesterol Absorption Inhibitors

mechanism of Action . تعرف من اسمه

CHOLESTEROL ABSORPTION INHIBITOR
Ezetimibe ZETIA

treatment of * hyper-lipidemia

we use it as preventive for CVD or Decrease risk of CVD

Cholesterol Absorption Inhibitors

- Mechanism of action: Ezetimibe selectively inhibits absorption of dietary and biliary cholesterol
- Actions: Ezetimibe lowers LDL-C by 18-23% (modest)
- Therapeutic uses:: in adjunct (combination) with statins in patients with high ASCVD risk like familial hypercholesteremia.
- Adverse effects: uncommon

مثلاً مريض عنده high risk of CHD ومشي على statin وعلى TLC ولسه اموره ماتحسنت فانا بدي اضيفله هنا الدوا

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

Alirocumab
Evolocumab

Monoclonal antibody

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

PCSK9

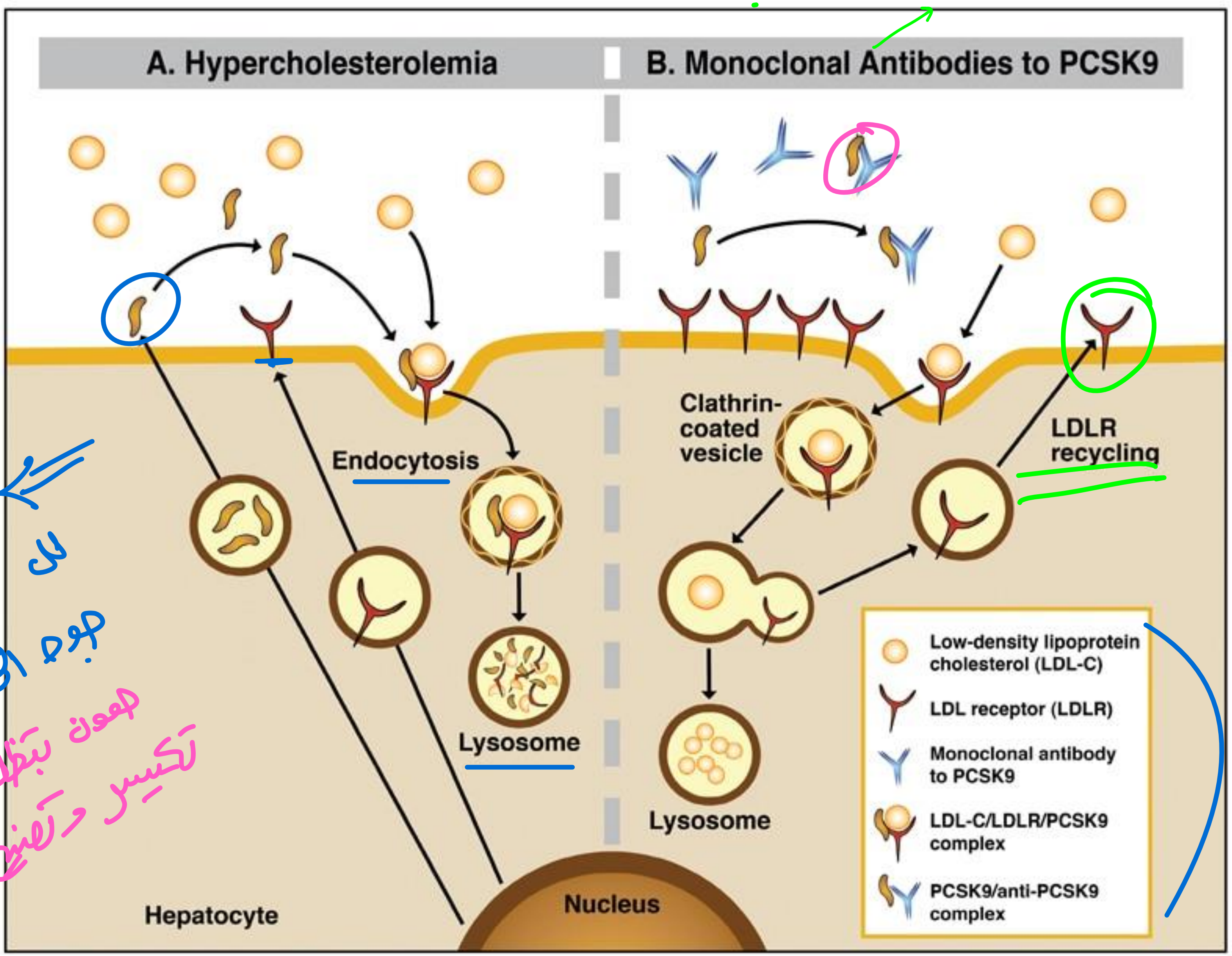
- Is a hepatic enzyme
- Binds to LDL receptors
- Causes the degradation of LDL receptors → so this will ↑ LDL in Blood.

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

PCSK9 inhibitors

- Humanized monoclonal antibodies
- Inhibit PCSK9 enzyme
- Result in more LDL receptors available to bind LDL-C from serum

نسبة هان Receptor أكثر فال cholesterol الموجود رح يفوت لجوه الخلية ونسبة LDLC بالدم رح تقل



لهان يمنع Destruction لل LDLC وال Receptor جوه الخلية

لهون بتطلعها كمية ال Receptor محدودة الإنتاجية (تكييس وتصنع ال Receptor).

سؤال خطر عندالكل: -

هسا بما انه الخلية رح تفوت LDL مش رح تأثر على الخلية ويعمل مثلاً Fatty liver ؟!

بس لازم نعرف انه الخلية بتقدر تصنع cholesterol فلما يزيد عندها LDL فتعمل protective mechanism and decrease de novo LDL C synthesis.

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

- Actions: lower LDL-C levels (potent)

- Therapeutic uses::
  1. in adjunct (combination) with statins in patients with high ASCVD risk
  2. In adjunct to statins to treat familial hypercholesterolemia

TLC بحيث مارظ ههههم

- Adverse effects: allergic reactions, respiratory tract infections

Omega-3 Fatty Acids

لـ مدة تكون هذي من TLC بحيث ينصحوا العضل تقللوا
اللحمة ويكللوا السمك ١-٢ يوم بالاسبوع. لانه السمك يحسن lipid profile

- Polyunsaturated fatty acids
- Main actions: lower VLDL and TGs synthesis in the liver
- Dietary sources:

❑ Tuna, Halibut and Salmon

❑ Avocado

as treatment أو supplement ممكن العريف يوخذهم multi vit ممكن تكون من *

Omega-3 Fatty Acids

DHA & EPA

EPA

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, various OTC preparations

Icosapent ethyl VASCEPA

الأعلى من فيتامين الطويلة
افضل الاختيار

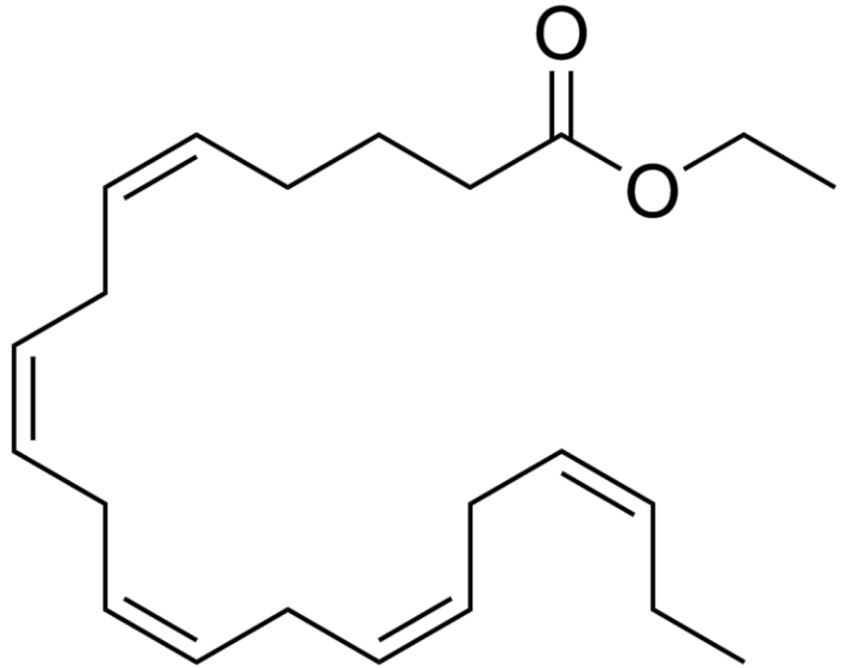
One problem with most supplements is that they might elevate LDL-C slightly (DHA)

أقل بـ EPA

Omega-3 Fatty Acids

Icosapent ethyl

- Prescription product
- Contains only eicosapentaenoic acid (EPA)
- Unlike other preparations→ DOES NOT elevate LDL-C



eicosapentaenoic acid (EPA)

Omega-3 Fatty Acids

Risk of Bleeding ← ما بعطيه لحدا بيزود

Main therapeutic use of omega-3 Fatty Acids:

Adjunct to other lipid-lowering therapies for individuals with high triglycerides > 500 mg/dL

↑ Risk of pancreatitis عند ليفل ← TAG

*** omega-3 fatty acids can increase the risk of bleeding with concomitant use of anticoagulants* or antiplatelets*

* ← ما بعطيهم لناس بتوخذ أو عندها genetic Factor deficiency that lead to bleeding.

Summary

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓
PCSK9 inhibitors	**↓↓↓↓↓**	**↑↑**	**↓**