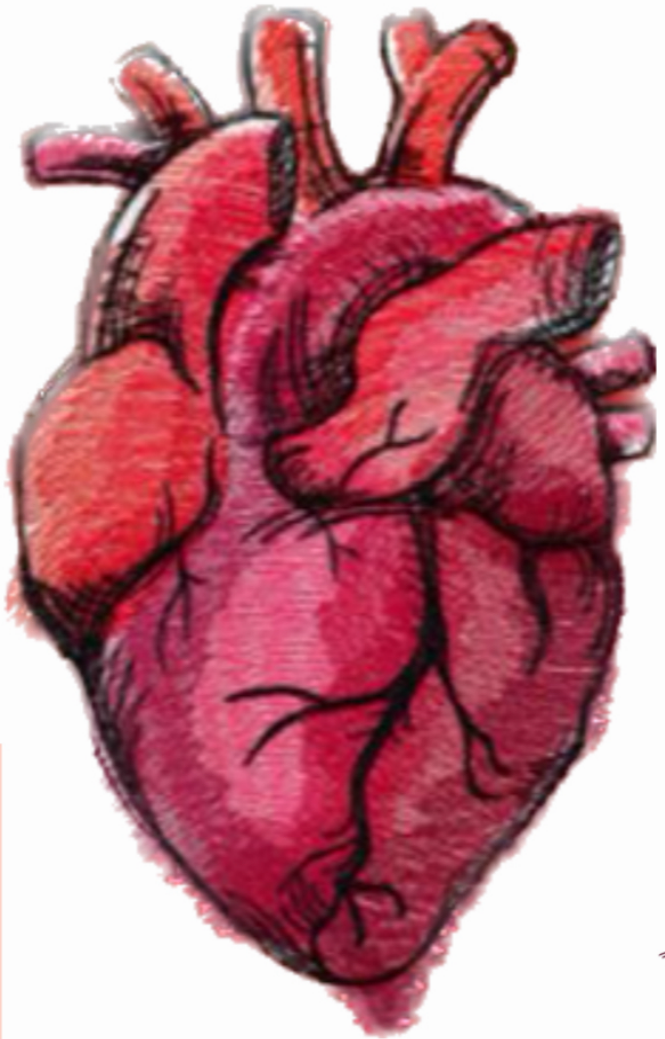


النادي الطبي

CARDIOVASCULAR SYSTEM

SUBJECT : _____

LEC NO. : 1

DONE BY Tabark Aldaboubi + Raneem azzam

وَقُل رَّبِّ زِدْنِي عِلْمًا

SCAN ME!

CVS- Pharmacolgy1

Drugs for hyperlipidemia

Faculty of Medicine

The Hashemite University

Arwa Al Anber (MD, PhD)

Office: 1018

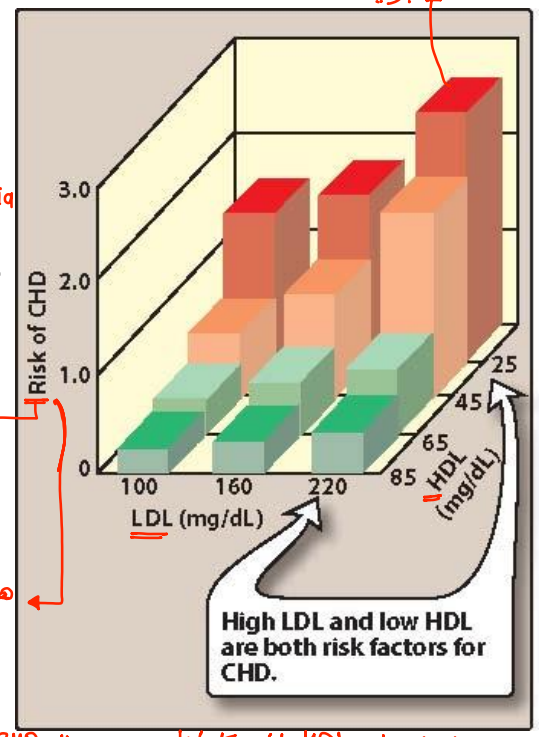
Hyperlipidemias

- **Hyperlipidemia(dyslipidemia) is excess lipid in the blood:**

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



Why we need to treat hyperlipidemia ?

" The fat speaks :

ما بتنذوب بالمي hydrophopic ⇐ Lipid الـ

With water, I say, Touch me not’s

To the tongue, I am tasteful; high amount of fat الشخص ما يتناول

give energy

Within limits, I am dutiful; بس كل اشي اذا زاد عن حده بنقلب ضده

Dangerous بصير

In excess, I am dangerous! "

Chemical Constituents of Life Ch 3

Why we need to treat hyperlipidemia ?

بعملهم Treatment لـ 2 resones ← مثلاً شخص عنده خطر CHD وعنده زيادة Cholestrol فلازم اقلل هذا الخطر فبعطي علاج

1. Reducing atherosclerotic cardiovascular disease (ASCVD)risk.

2. Reducing risk of pancreatitis

↑↑ TAG بتصير لهما بيكون

Goal of treatment

مش كل الناس بيلبش معهم العلاج زي بعض بيقف على انه قديش عندهم risk factor

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*
Coronary heart disease ↑ CHD or CHD risk equivalent (10-year risk >20 percent) diabetes و جلطات و Angina	<100 mg/dL(2.60 mmol/L)	≥100 mg/dL	≥130 mg/dL (at 100 to 129 mg/dL, drug optional)* mainly Statins
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 او 150
0 to 1 risk factor† healthy patient	<160 mg/dL (4.15 mmol/L) normal	≥160 mg/dL	≥190 mg/dL (at 160 to 189 mg/dL, LDL-lowering drug optional)

(TLC) اذا كان اكبر من 130 هعمل

*العريض ما استجاب drug therapy بلبش وحاد

* اذا كان العريض عنده قابلية انه يستجيب للـ (TLC) بلبش وقف حتى لو كان عالي خصوصًا اذا كان عمر العريض صغير

اذا صار اعلى من 160 لازم اعمل TLC اذا ما استجاب او كان عنده اكبر من 190 بلبش drug therapy

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.

Goal of treatment

Major Risk Factors That Modify LDL Goals

Positive risk factors

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

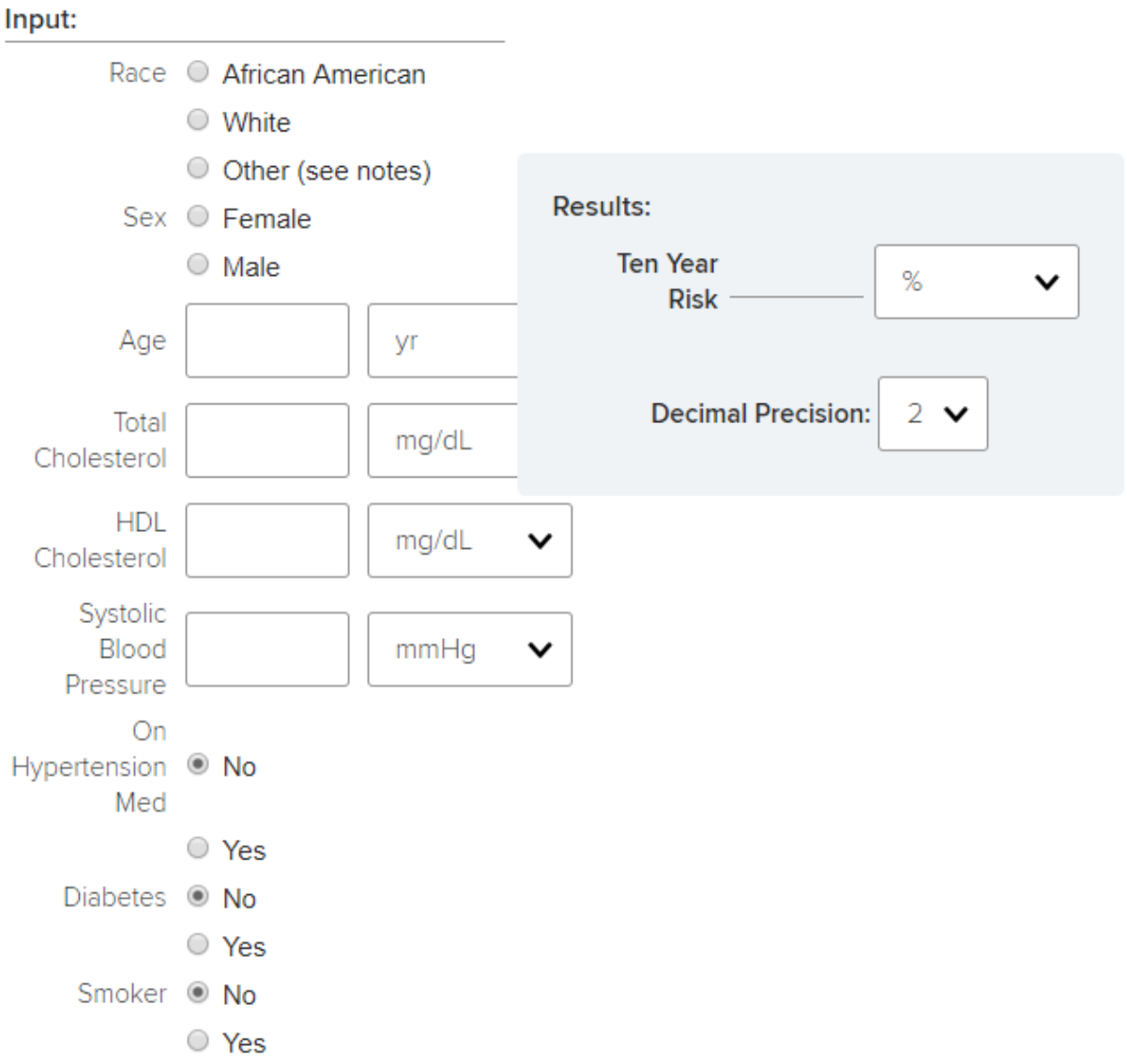
High HDL cholesterol (> 60 mg per dL [1.55 mmol per L]); presence of this risk factor removes one risk factor from the total count

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

* بندخل معلوماتن المريض وبعطينا قديش نسبة الـ risk



ACC/AHA 2013 Cardiovascular Risk Assessment

Drugs for Hyperlipidemia

1. Statins
2. Niacin
3. Fibrates
4. Bile acid sequestrants
5. Cholesterol absorption inhibitors
6. PCSK9 inhibitors

Statins
HMG CoA Reductase Inhibitors

Most potent and longer plasma half-life

اكثر اشي effective

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

توضيح خارجي

يتم تصنيع الكولسترول بالكبد و عشان اصنعه بحتاج ل precursors و هو HMG coA اللي حيتحول بالاخير ل mevalonic acid عن طريق انزيم اسمو HMG reductase فحيحول ال HMG coA الى مجموعة مركبات لاوصل لل mevalonic acid اللي بتحول ل cholesterol

بالتالي ال HMG reductase هو ال rate limiting step هو الاساس لانتاج الكوليسترول فلو عملتلو inhibition فأنا هيك وقفت كل ال pathway تاع تصنيع الكوليسترول بالكبد

Statins
HMG CoA Reductase Inhibitors

Denovo synthesis of cholestrol المسؤول عن ال inhibition بعمل

Mechanism of action

Inhibition of 3-Hydroxy-3-methylglutaryl coenzyme A (HMG) CoA reductase

(*de novo* cholesterol synthesis)

↓ intracellular cholestrol

Depletion of intracellular cholesterol

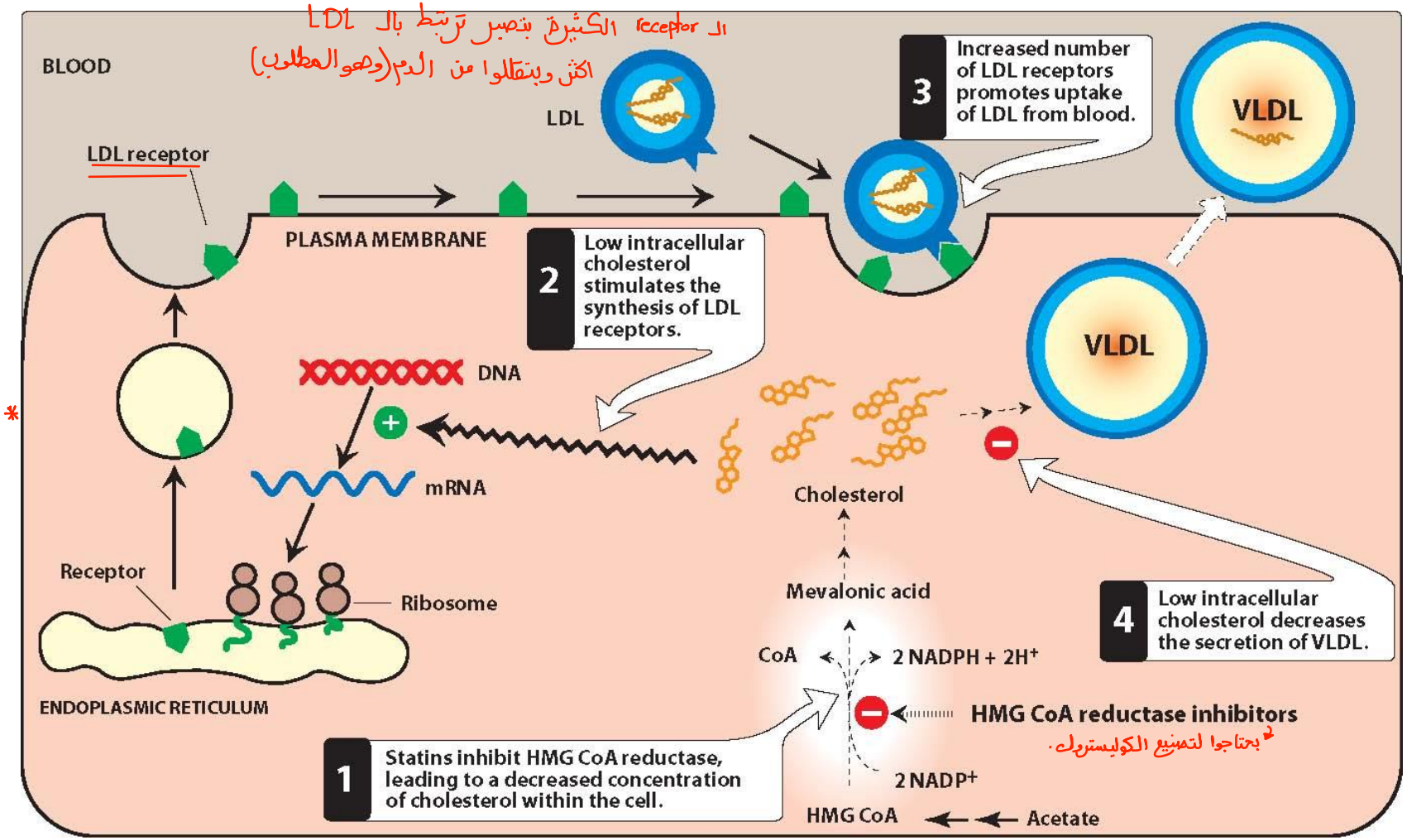
Increase the number of cell surface LDL receptors

موجودة جوا الخلايا بتصدها الخلايا الـ LDL receptor لما تطلع برا الخلايا بتقسل بالكوليسترول وبتفوتوا جوا الخلايا وبتعمل internalization

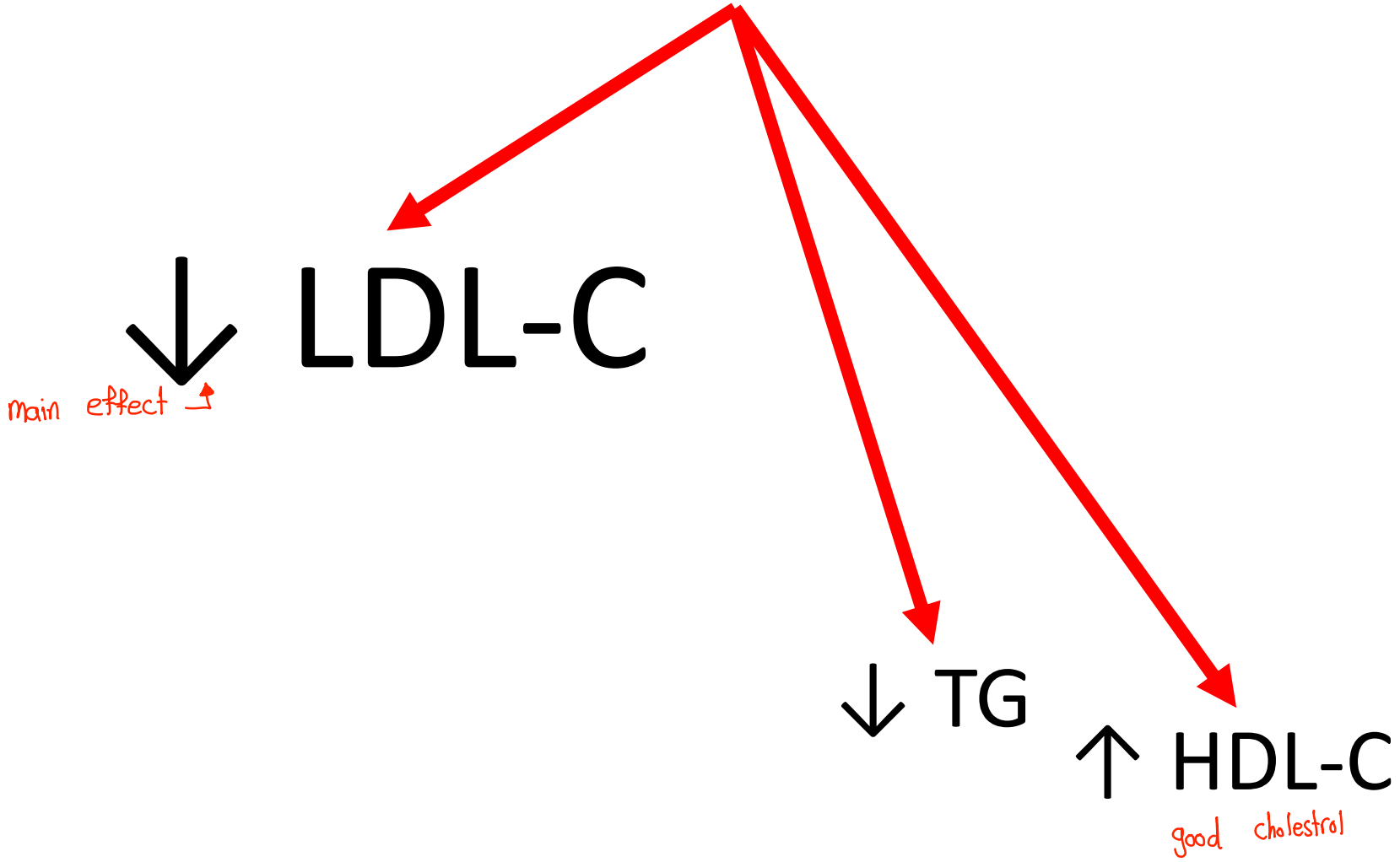
Increased LDL-C internalization

Reduction in cholesterol plasma levels

Statins
HMG CoA Reductase Inhibitors



Statins
HMG CoA Reductase Inhibitors



Statins
HMG CoA Reductase Inhibitors

Therapeutic uses

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

Familial hypelipidemia

Pharmacokinetics

drug - drug interaction ممكن يصير other drug بشتغل على

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

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

* اذا مريض عنده Liver disease
ممكن يكون Contraindecation الاعطاء
هلاوا لانو بزود الـ risk of liver Faliure

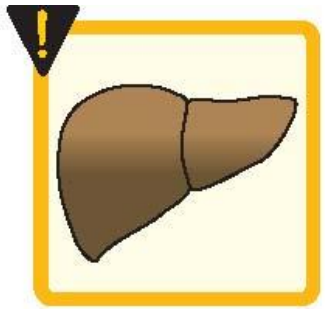
Statins
HMG CoA Reductase Inhibitors

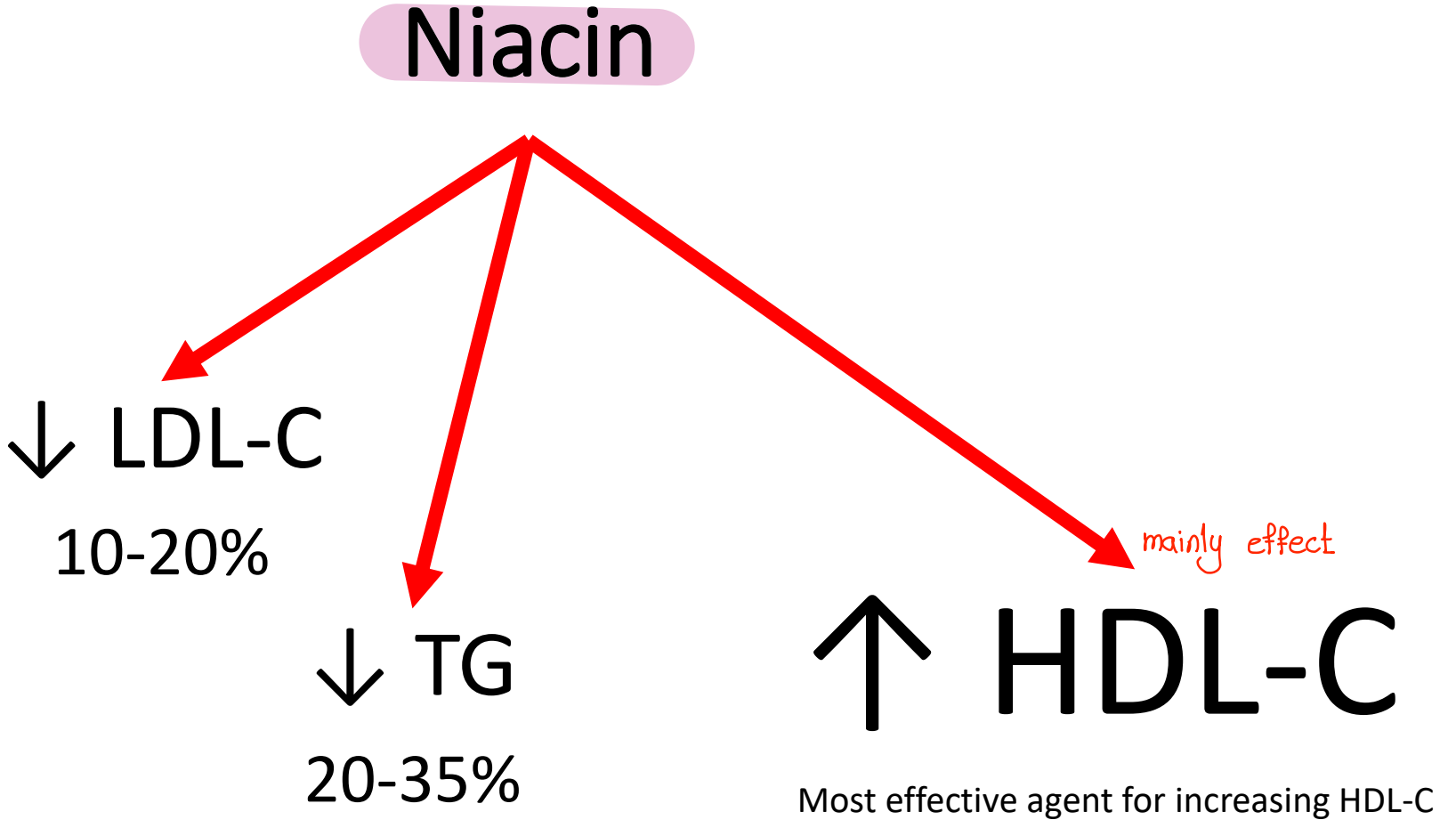
Adverse effects

- **↑ liver enzymes**

  Liver disease results in accumulation of statins

- **Myopathy and rhabdomyolysis**
- **Drug-drug interaction e.g., warfarin**
- **Contraindicated in pregnancy, lactation and active liver disease**





مريض عنده الـ LDL عالية والـ HDL نورمال
وعنده risk of CHD ستفيد من الـ Niacin !!
ممكن لأنه كلما كان الـ HDL لعلى بتعمل Protective

Niacin

Therapeutic uses

Treatment of familial hyperlipidemias and other severe hypercholesteremias

لتنهي غالبًا بيكونوا resistance

OFTEN IN COMBINATION WITH STATINS

e.g., niacin + lovastatin

e.g., niacin + simvastatin

مريض عنده الـ LDL عاليه والـ HDL نورمال وعنده

Niacin

قراءتها قراءة

Adverse effects

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

group 3

Fibrates

TG بشتغلو على

FIBRATES
Gemfibrozil LOPID
Fenofibrate TRICOR, LOFIBRA, TRIGLIDE

Fibrates

Mechanism of action

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

اختصاره

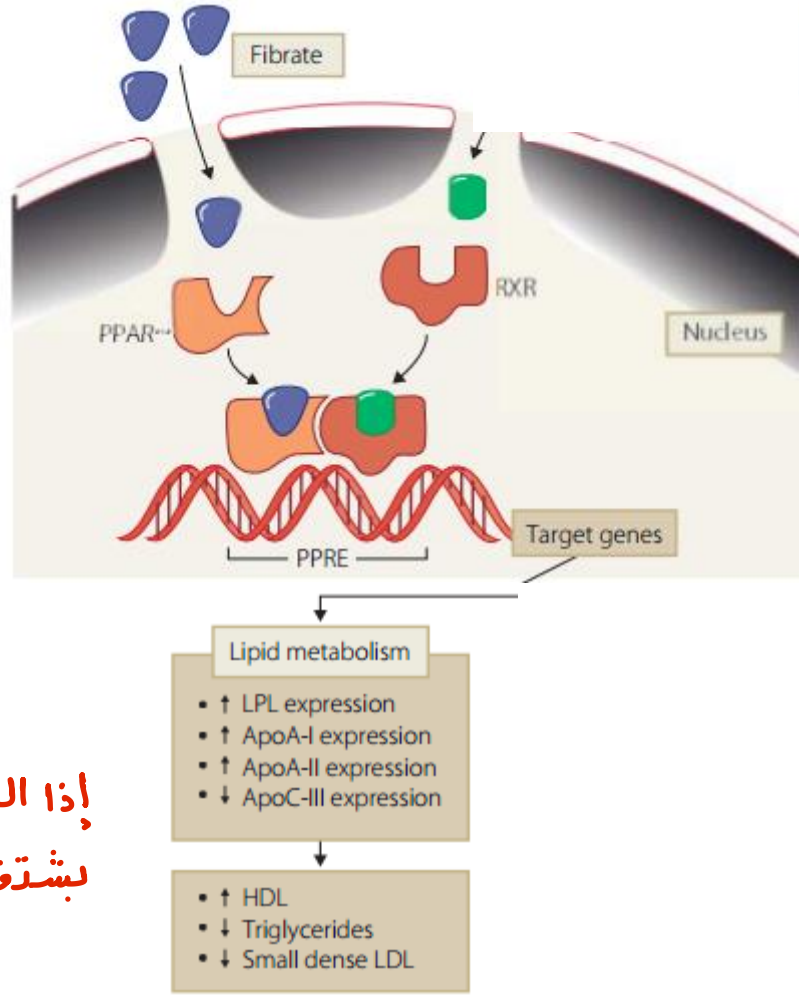
Increase the expression of lipoprotein lipase

↑↑ LPL expression

يؤدي إلى

↓ TG

إذا الـ fibrate بشتغل على TG mainly



في عندي chylomicron فيها كوليسترول وTG،وفيه lipoprotein lipase الي رح يخلي ال chylomicron بال TG الي فيها تتحول لل fatty acid بال fatty a adipose tissue ف
انا لما احفز ال LPL اكثر رح تتحول ال TG ورح يضل عددٍ قليل بالدم ما تحول

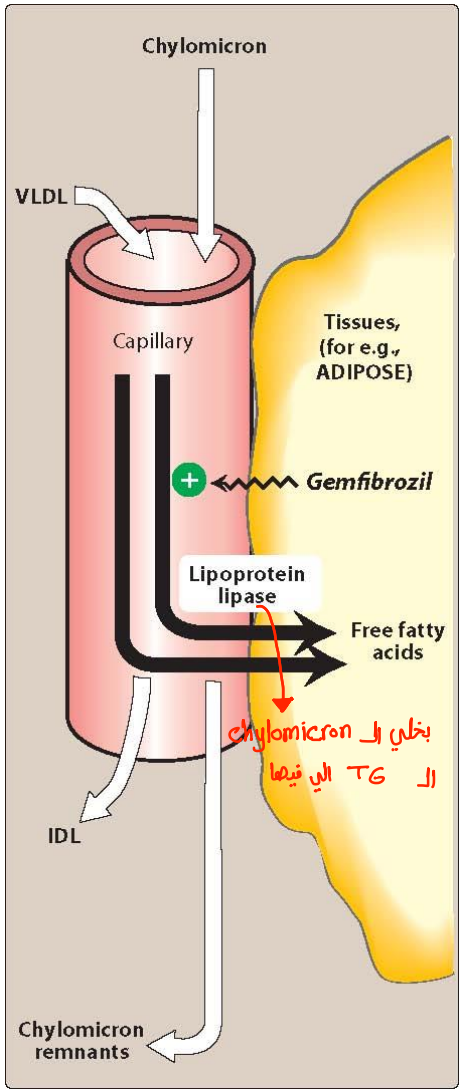
Fibrates

Mechanism of action

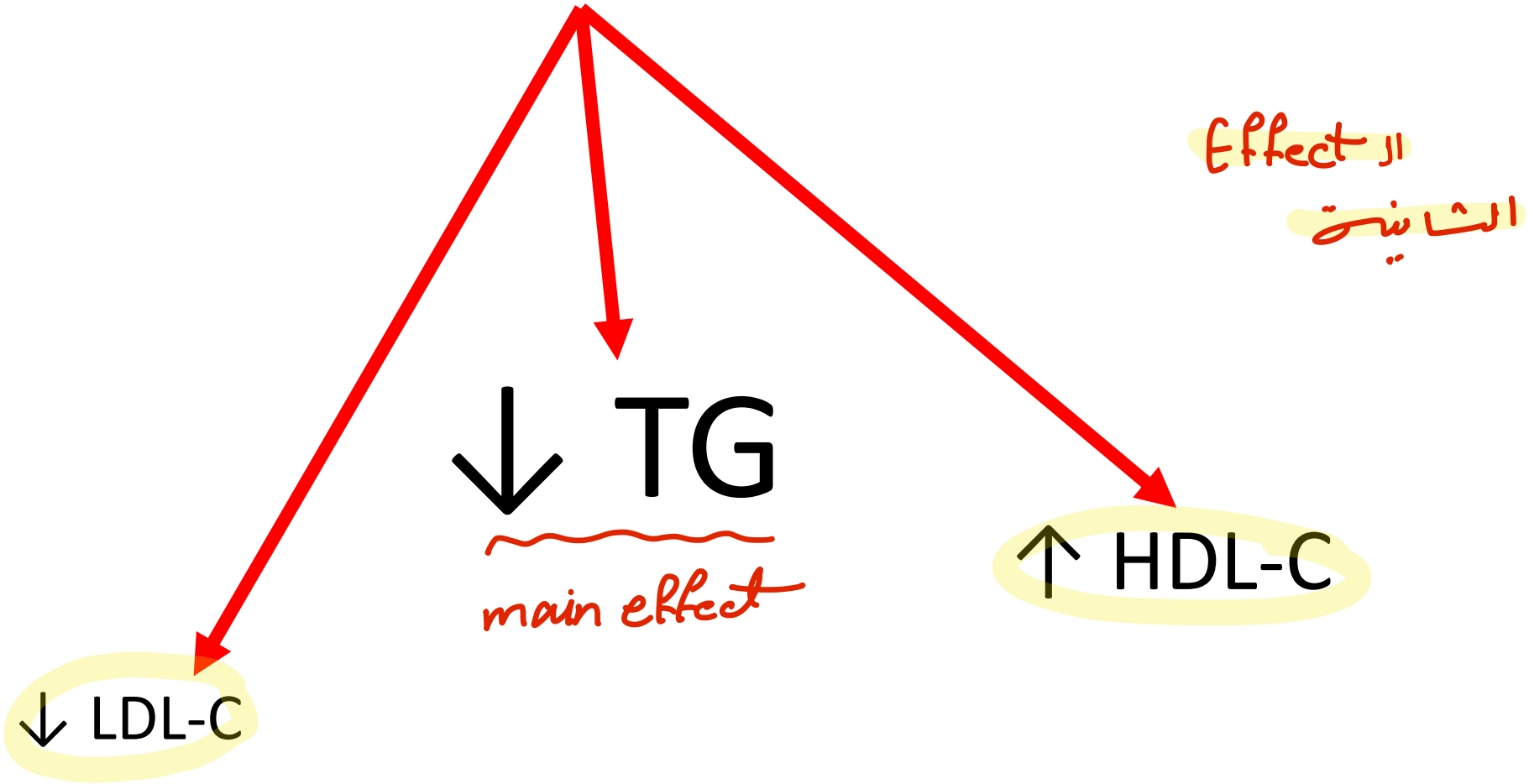
Activators of (peroxisome proliferator-activated receptors), especially PPARα

↓

Increase the expression of lipoprotein lipase → ↓ TG



Fibrates



Fibrates

Therapeutic uses

Treatment of hypertriglyceridemia

Fibrates

* حكتهم حكي كلهم بخ

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).
  - It is **CONTRAINDICATED** in hepatic or renal insufficiency
  - Drug-drug interaction e.g., warfarin

Bile acid sequestrants

group 4

BILE ACID SEQUESTRANTS	
Colesevelam	WELCHOL
Colestipol	COLESTID
Cholestyramine	QUESTRAN, PREVALITE

most common

هسا ال bile acid موجود في ال small intestine
وبعدين بصيرتهم reabsorption in liver،،هما موجودين
بالعادة نيجتف شارج باجي بعطيهم sequestrant بعملو
bind مع هاي النيجاتف ويعملو insoluble compound
هاد المركب بدل ما يصيرله re absorption زي دائما ،رح
يصيرله excretion in faeces

Bile acid sequestrants

Mechanism of action

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

↓

↑ excretion of bile acids in feces

→ ↓ bile acid concentration

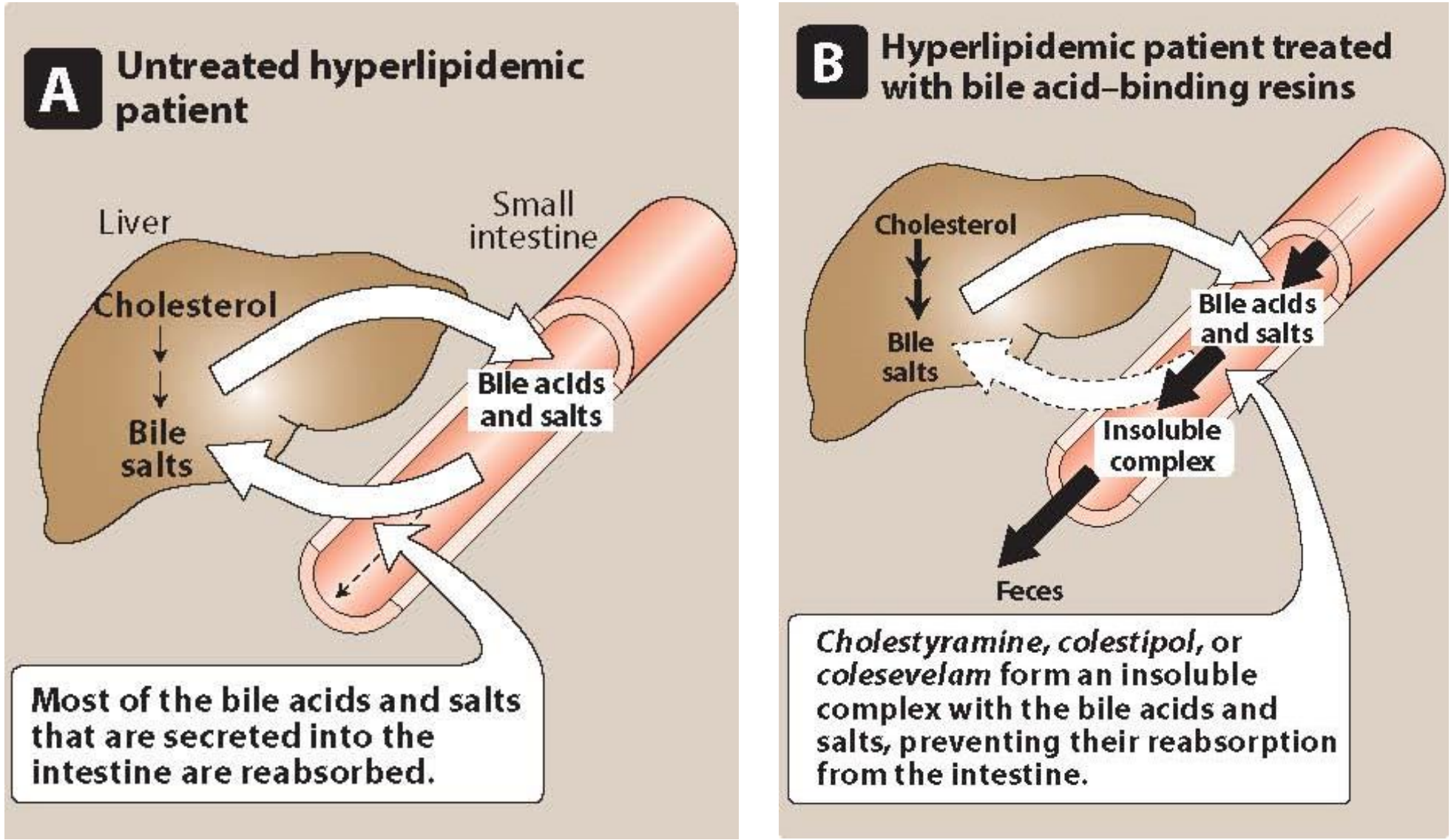
↑ hepatocyte conversion of cholesterol to bile acids

↑

Depletion of intracellular cholesterol

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

طب هذيك الي بالامعاء طلعتها والي بالكبد؟رح يقل تركيزها لانو ما صار re absorption
طب لمًا تقل انا ك كبد شو رح اعمل لاني بحاجتها ؟رح احول الكوليسترول ل bile acid
بالتالي رح يقل ال intercellular cholesterol بالتالي رح يزيد ال uptake of
cholesterol in plasma


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.

Cholesterol Absorption Inhibitors

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
- Adverse effects: uncommon

* أدوية اخرى

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

احفظوهاد

مثال ١ → Alirocumab

مثال ٢ → Evolocumab

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

PCSK9 : شو هو هلا؟

- Is a hepatic enzyme
- Binds to LDL receptors
- Causes the degradation of LDL receptors

انا بدي اعمل inh لهاد الأنزيم حتى يبطل يعمل degradation

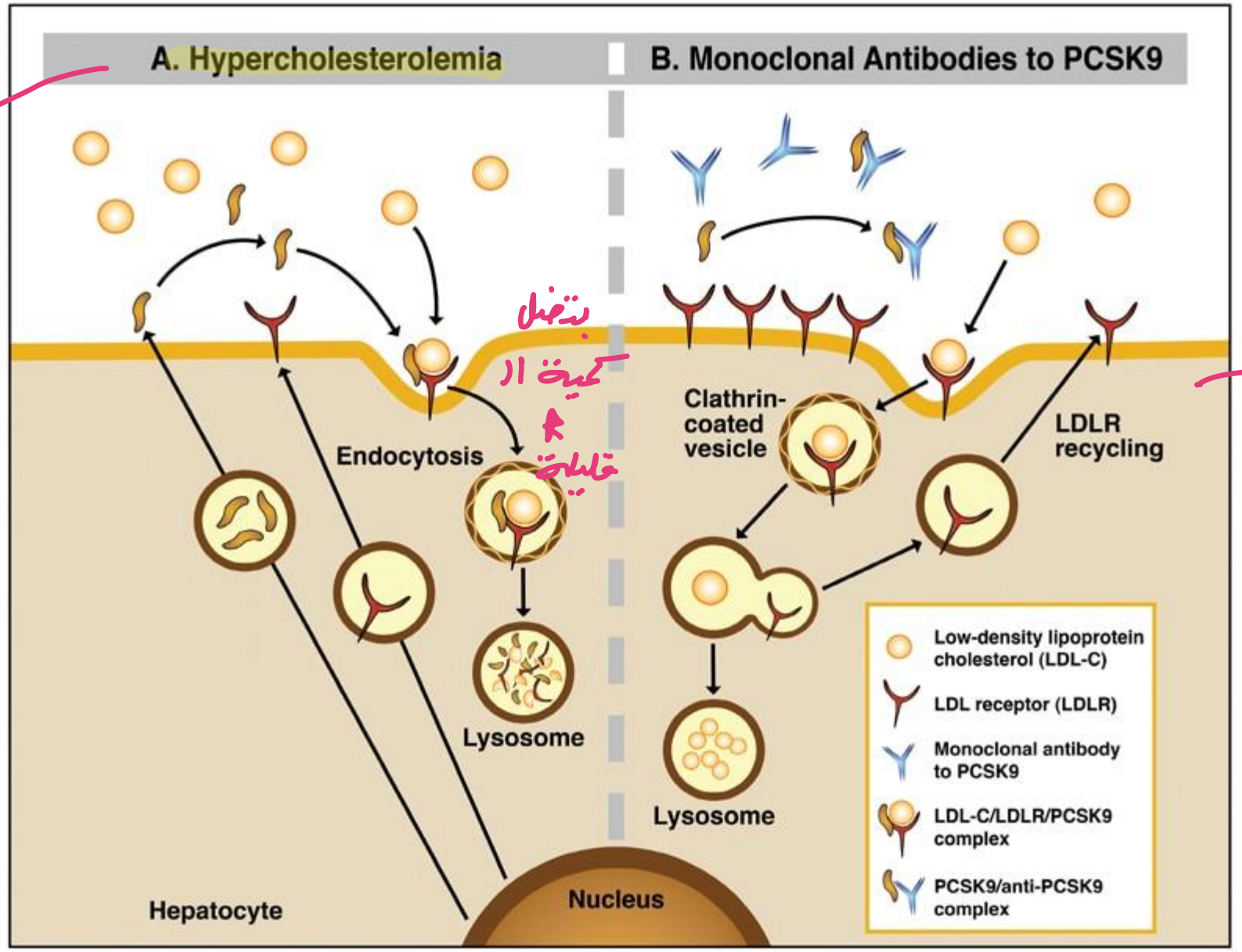
Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

PCSK9 inhibitors

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

لسا ما أخذ دوا

حتى لو بنتج ك بضل عدد هم قليل عشان بتكسروا



قللت ال LDL

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

- Adverse effects: allergic reactions, respiratory tract infections

Omega-3 Fatty Acids

بتحسن هاي الاكلات ال lipid profile زي ال sea food وتقليل الred meat

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

❑Tuna, Halibut and Salmon

❑Avocado

اكثر انواع السمك احتواء

حصه نباتي

Omega-3 Fatty Acids

حفظ الاختصارين

DHA & EPA

EPA

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, various OTC preparations

Icosapent ethyl VASCEPA

DHA → بس الو هاد effect

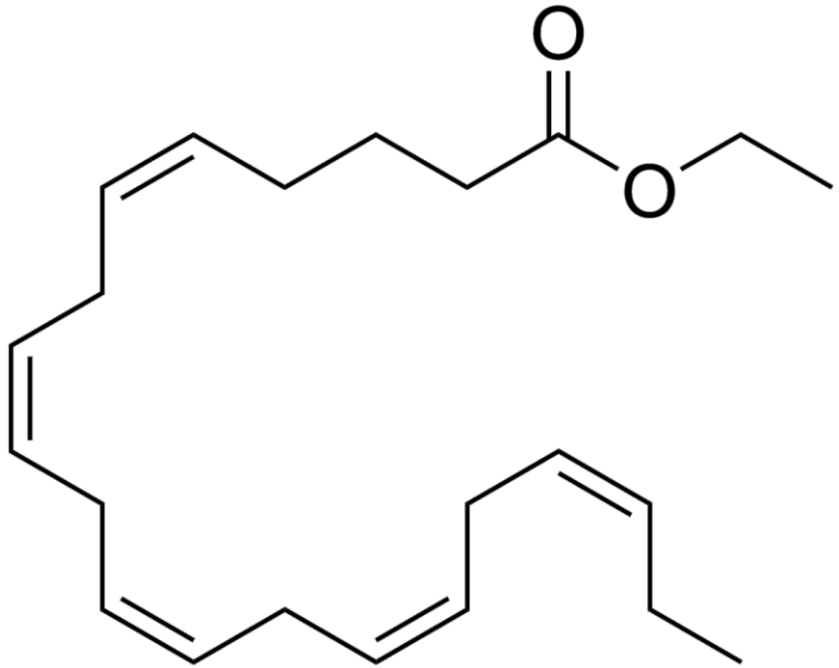
One problem with most supplements is that they might elevate LDL-C slightly

Omega-3 Fatty Acids

Icosapent ethyl EPA

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

ممكن يكون حامل
جزء من diet
علاج



eicosapentaenoic acid (EPA)

Omega-3 Fatty Acids

Main therapeutic use of omega-3 Fatty Acids:

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

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

* معلومات الـ patho فوق
بتساعدك في حل أسئلة
الامتحان

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	**↓↓↓↓↓**	**↑↑**	**↓**