CVS- Pharmacolgy1

Drugs for hyperlipidemia

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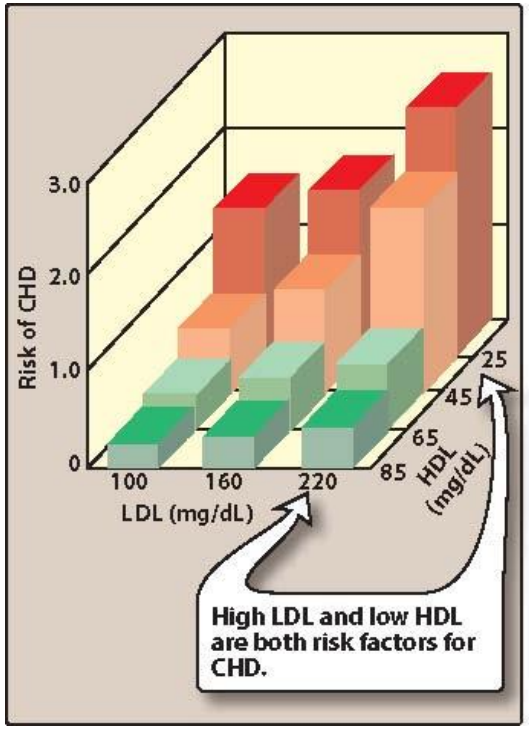
Hyperlipidemias

- **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 :

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

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)

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

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.

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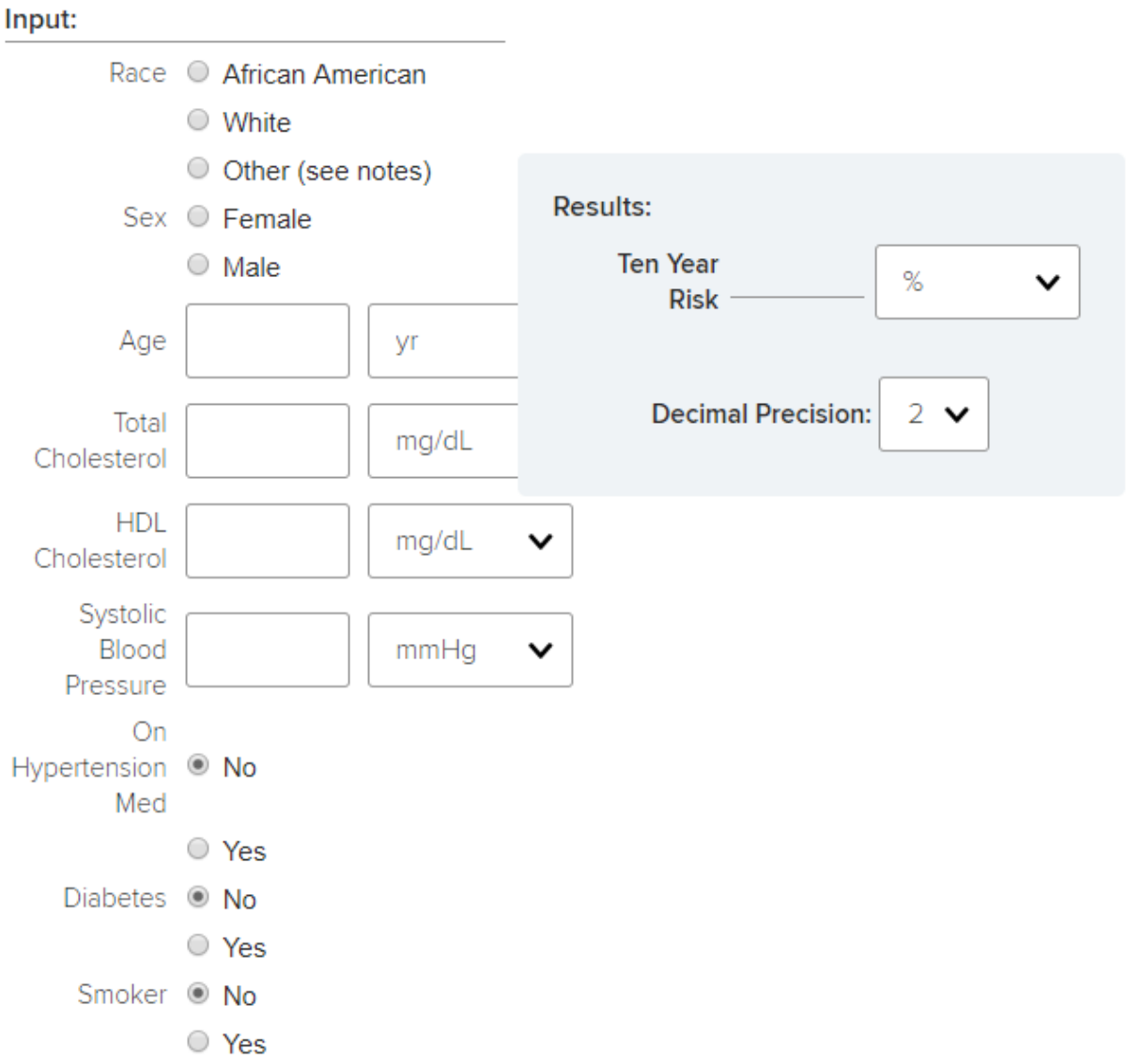
Clinical notes



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

Most potent and longer plasma half-life

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

Statins
HMG CoA Reductase Inhibitors

<u>Mechanism of action</u>

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

(*de novo* cholesterol synthesis)

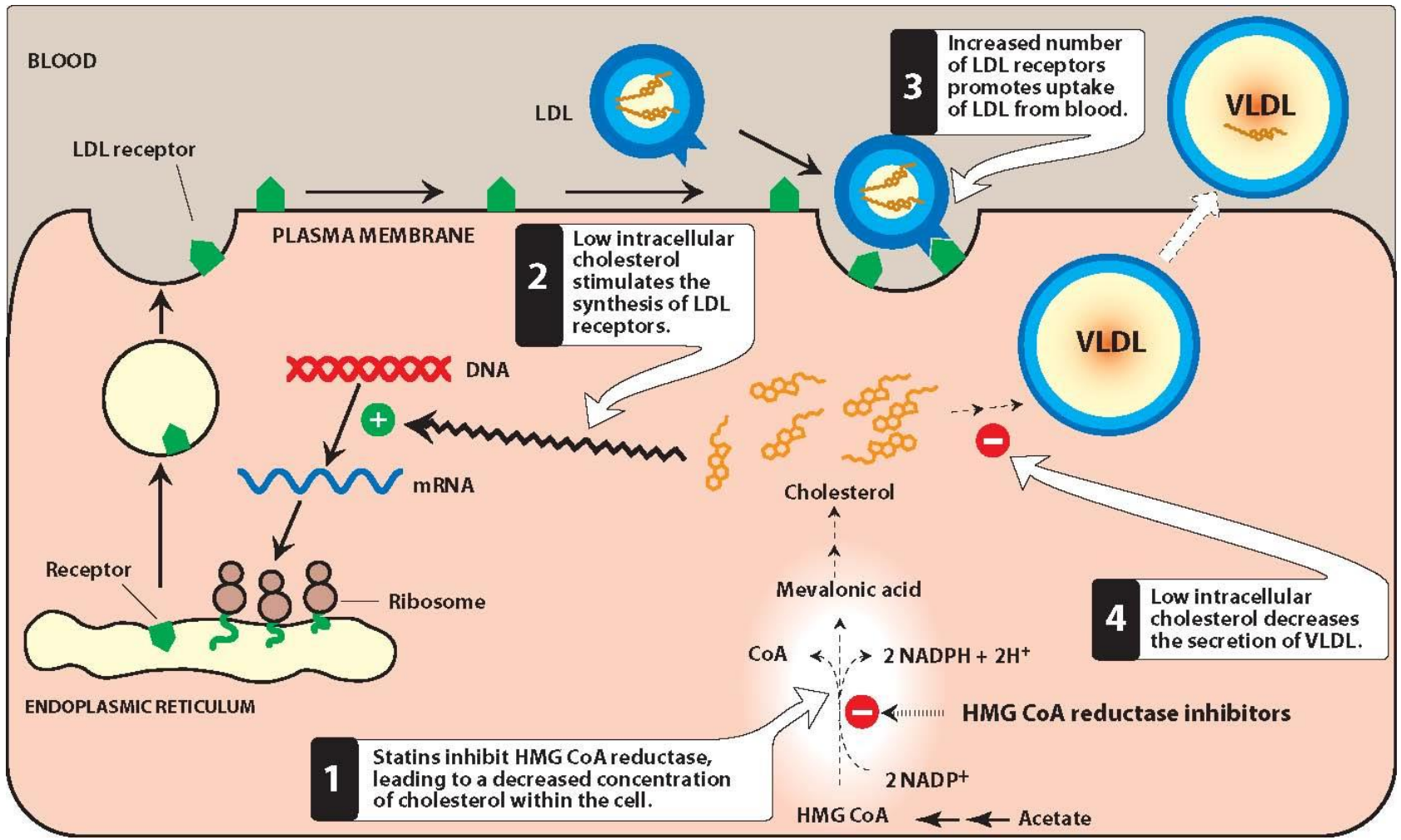
Depletion of intracellular cholesterol

Increase the number of cell surface LDL receptors

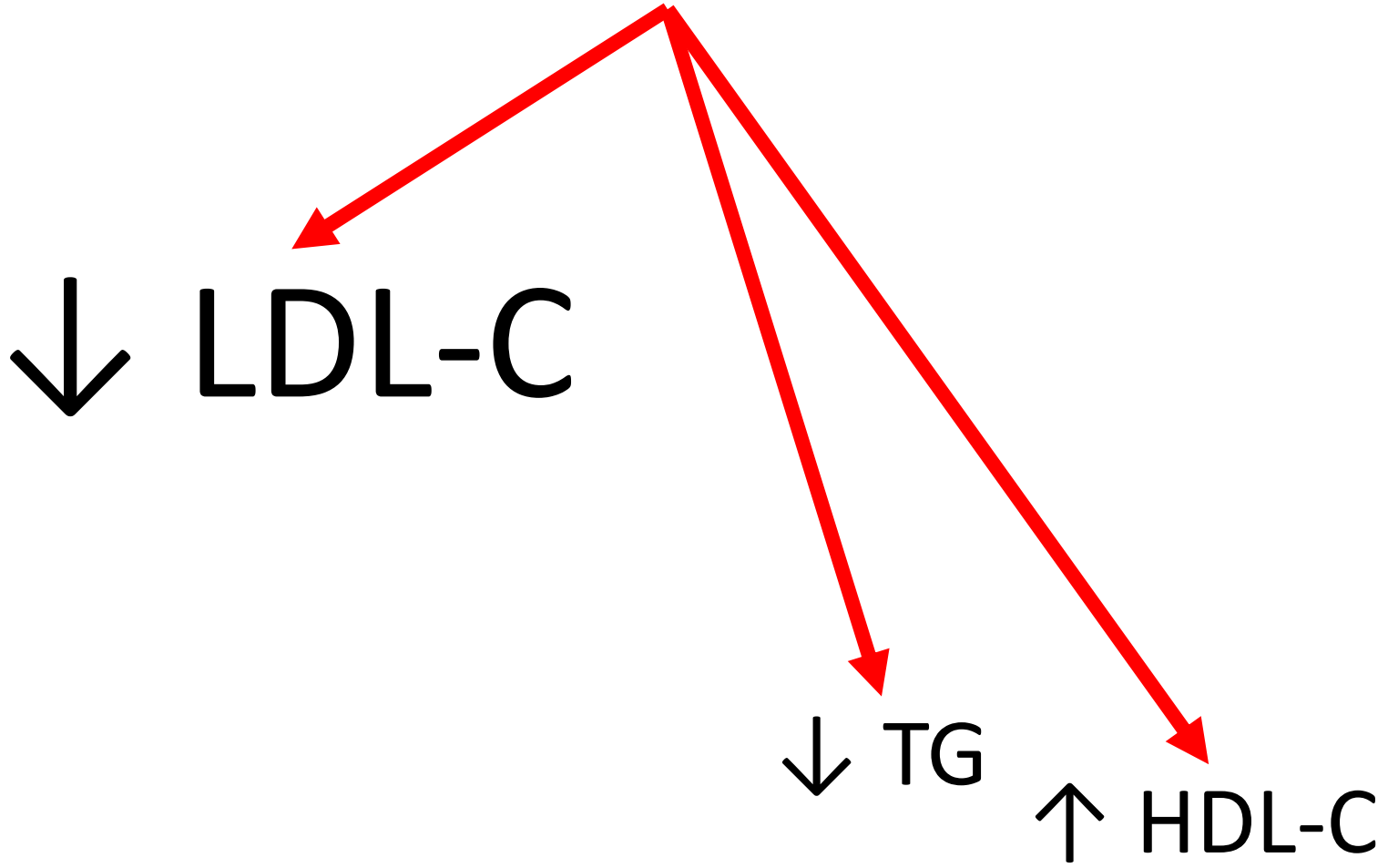
Increased LDL-C internalization

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.

Pharmacokinetics

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

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

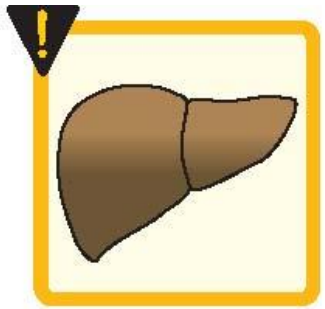
Statins
HMG CoA Reductase Inhibitors

Adverse effects

- **↑ liver enzymes**

  Liver disease results in accumulation of statins

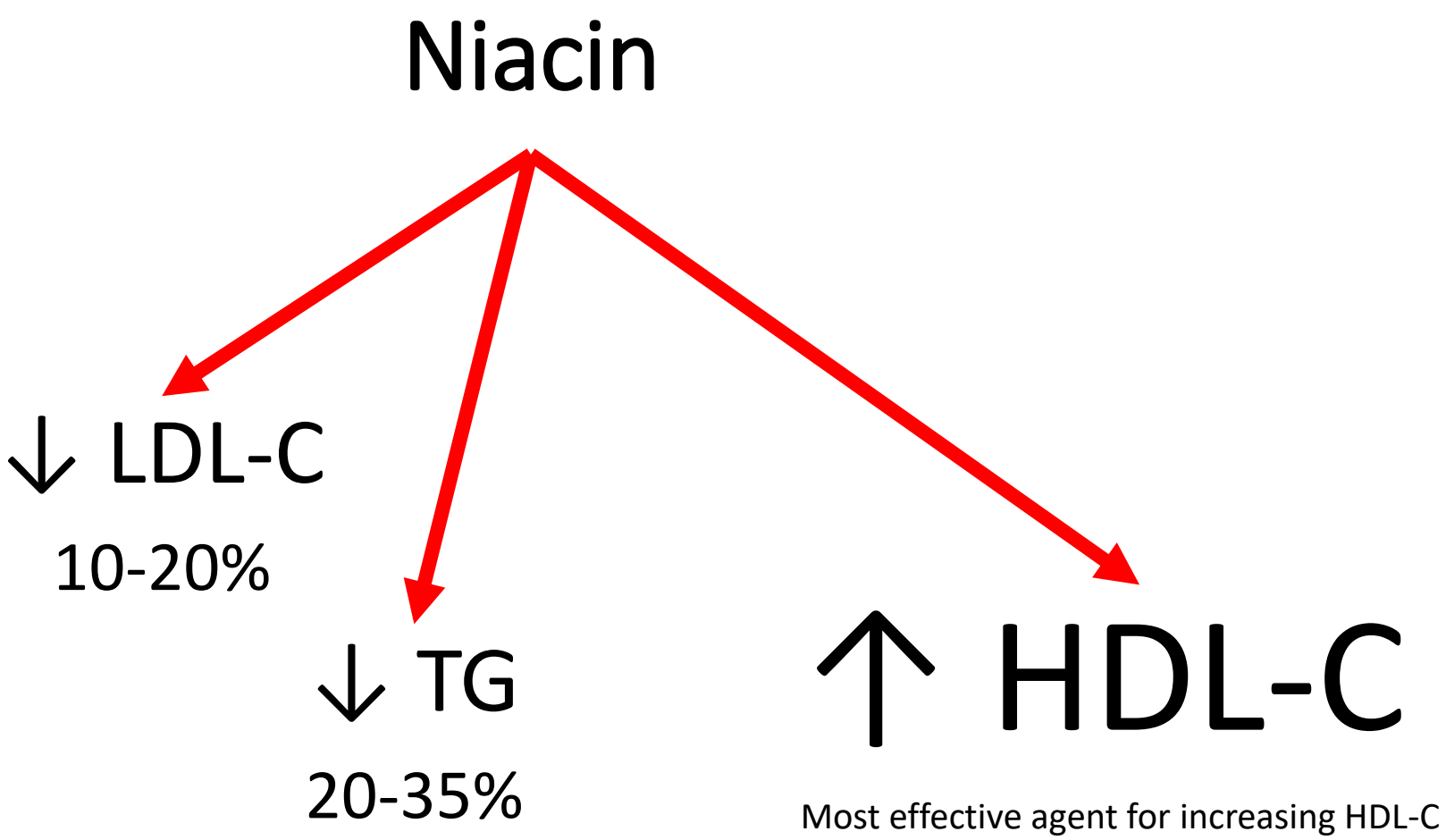
- **Myopathy and rhabdomyolysis**
- **Drug-drug interaction e.g., warfarin**
- **Contraindicated in pregnancy, lactation and active liver disease**



Liver failure

Myopathy

Contraindicated in pregnancy


Niacin
↓ LDL-C
10-20%
↓ TG
20-35%
↑ HDL-C
Most effective agent for increasing HDL-C

Niacin

Therapeutic uses

Treatment of familial hyperlipidemias and other severe hypercholesteremias

OFTEN IN COMBINATION WITH STATINS

e.g., niacin + lovastatin

e.g., niacin + simvastatin

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

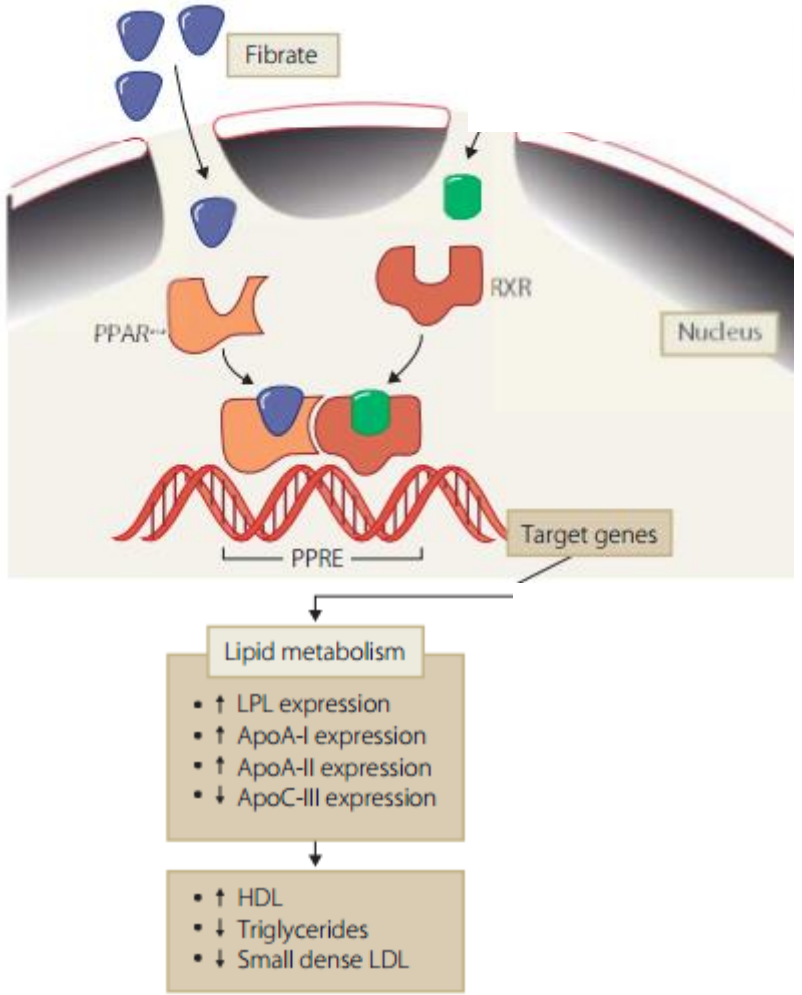
Fibrates

<u>Mechanism of action</u>

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

↓

Increase the expression of lipoprotein lipase → ↓ TG



Fibrates

Mechanism of action

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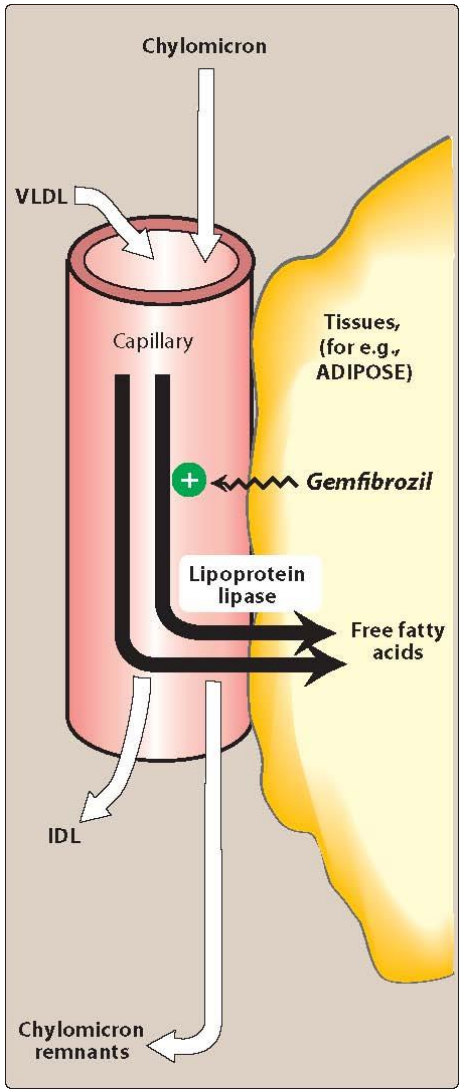
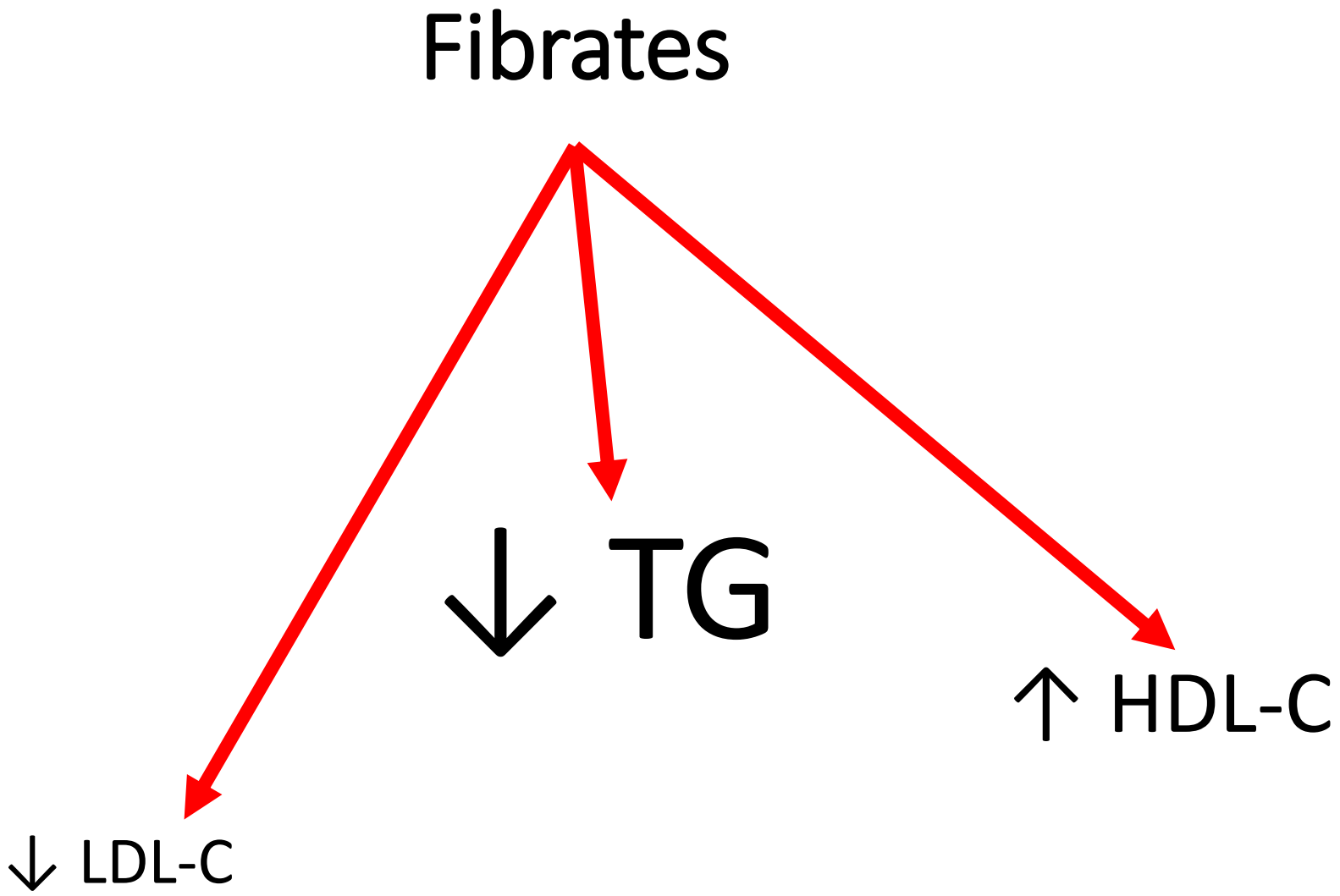



Fibrates
↓ TG
↑ HDL-C
↓ LDL-C

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).
  - 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

Bile acid sequestrants

<u>Mechanism of action</u>

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

↓

↑ excretion of bile acids in feces →

↓ bile acid concentration

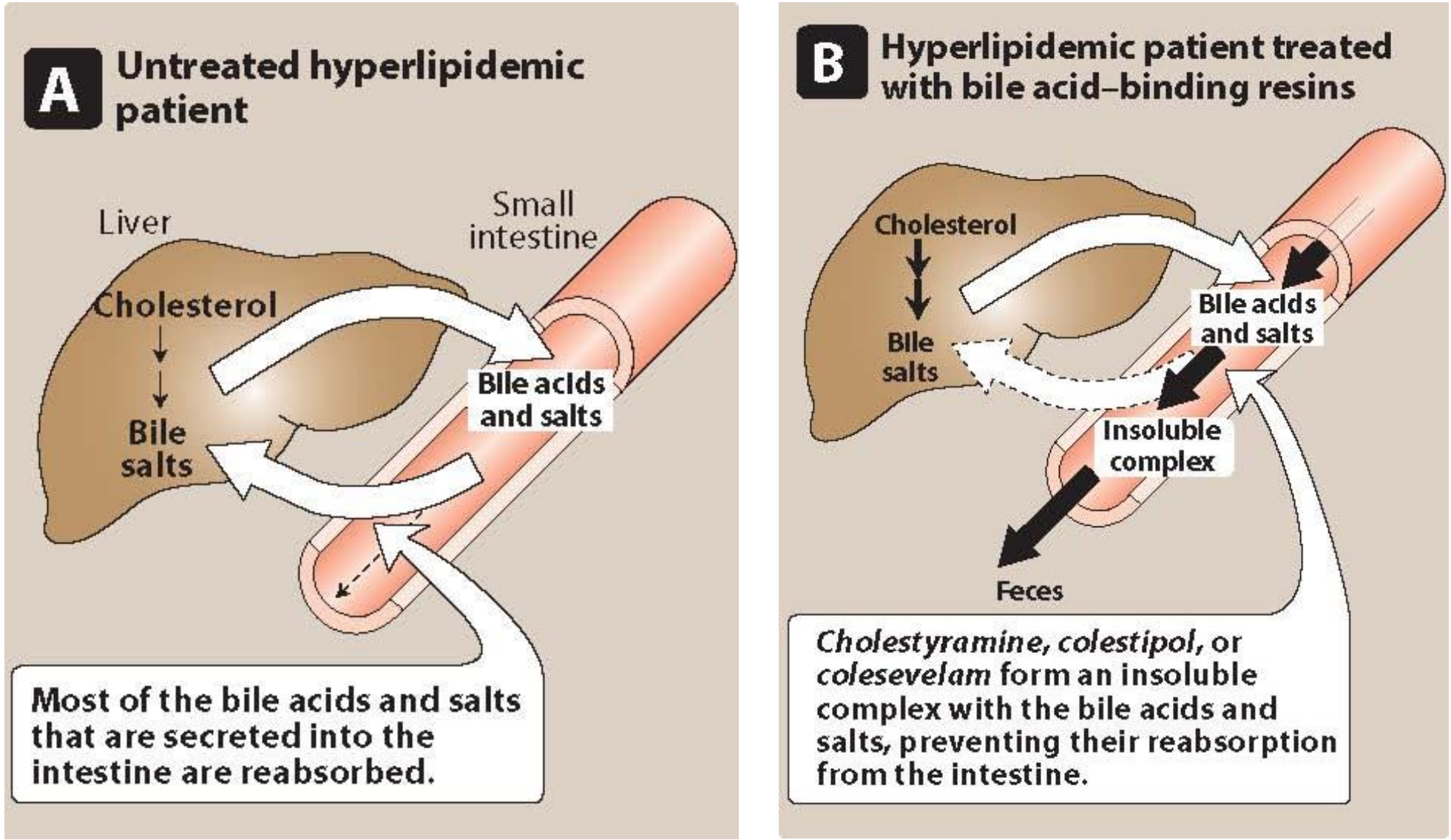
↑

↑ hepatocyte conversion of cholesterol to bile acids

↑

Depletion of intracellular cholesterol →

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


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

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

Alirocumab
Evolocumab

Proprotein Convertase Subtilisin kexin type 9 inhibitors (PCSK9 Inhibitors)

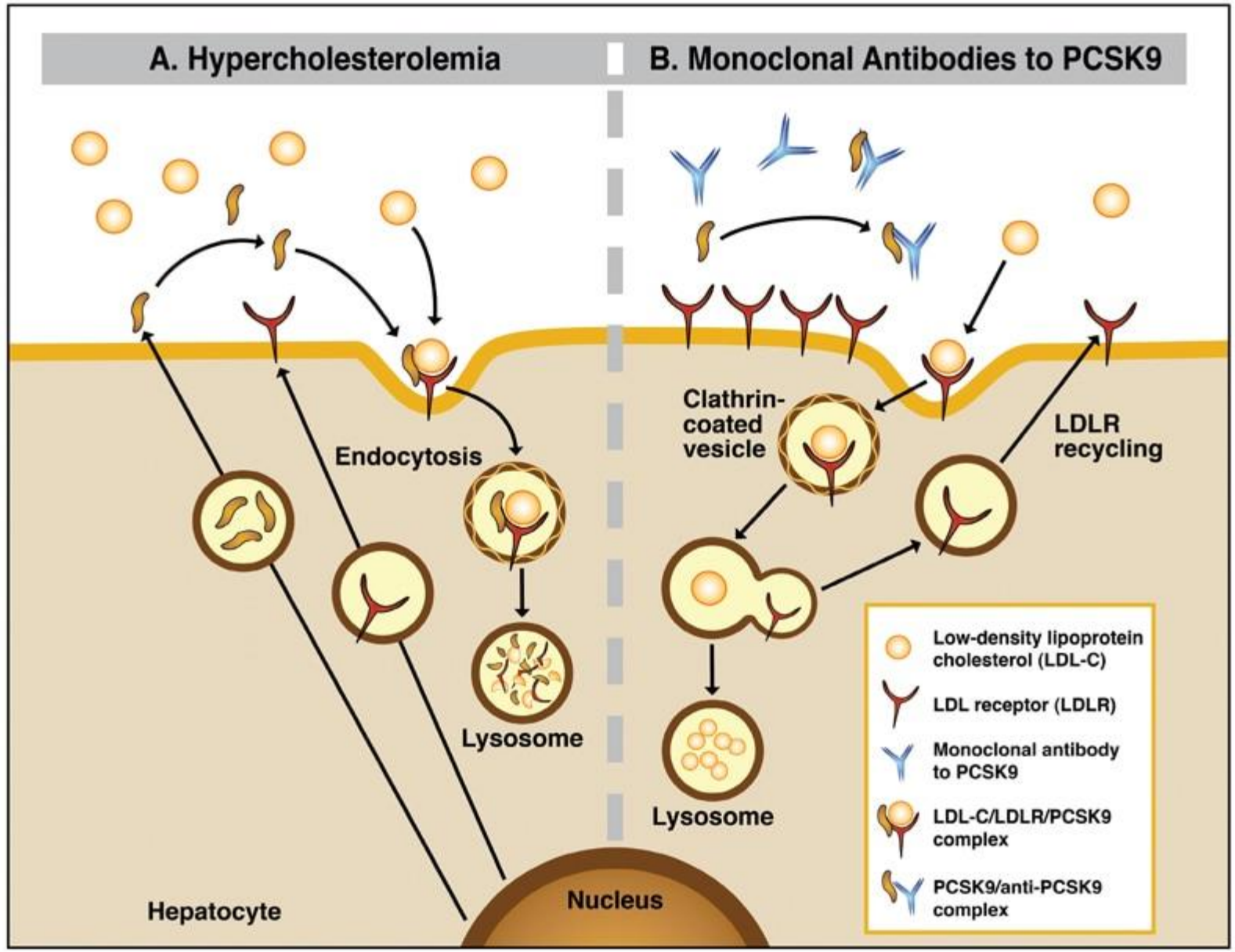
PCSK9

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

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


A. Hypercholesterolemia
B. Monoclonal Antibodies to PCSK9
Endocytosis
Lysosome
Clathrin-coated vesicle
LDLR recycling
Lysosome
Hepatocyte
Nucleus
Low-density lipoprotein cholesterol (LDL-C)
LDL receptor (LDLR)
Monoclonal antibody to PCSK9
LDL-C/LDLR/PCSK9 complex
PCSK9/anti-PCSK9 complex

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

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

❑Tuna, Halibut and Salmon

❑Avocado

Omega-3 Fatty Acids

DHA & EPA

EPA

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, various OTC preparations

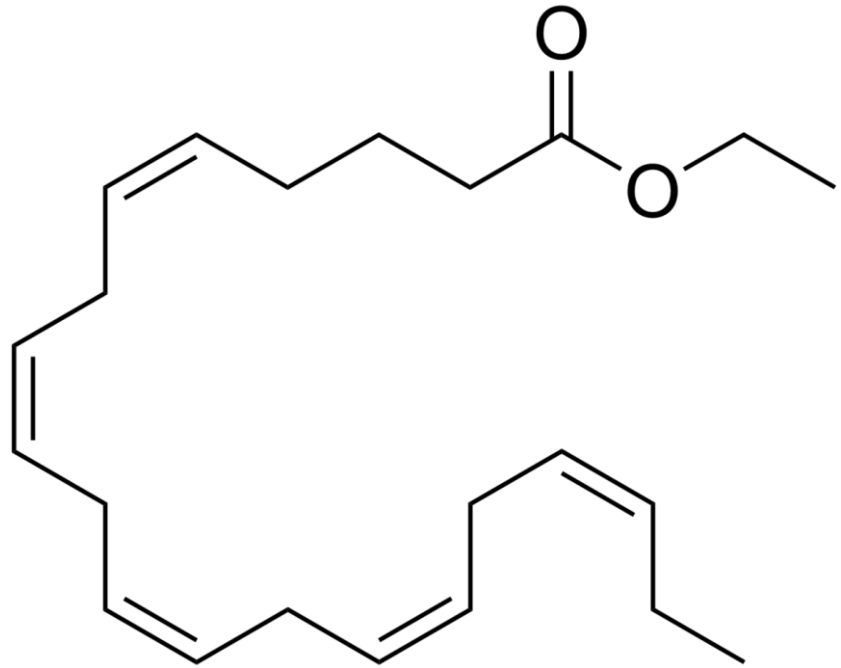
Icosapent ethyl VASCEPA

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

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

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*

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	**↓↓↓↓↓**	**↑↑**	**↓**