Drugs for hyperlipidemia

By

Anfal Bin Dayel, Ph.D

Assistant Professor

Department of Pharmacology and Toxicology

College of Pharmacy, KSU

Slides adopted from Dr. Osama Yousuf

College of Pharmacy, 2nd floor \ office 81, abindayel@ksu.edu.sa

Objectives

1.Define hyperlipidemia vs normal lipid levels

Discuss the non-pharmacological treatment of hyperlipidemia.

1.Classify lipid lowering agents targeting exogenous and endogenous pathways.

Expand on the pharmacology of drugs related to each group.

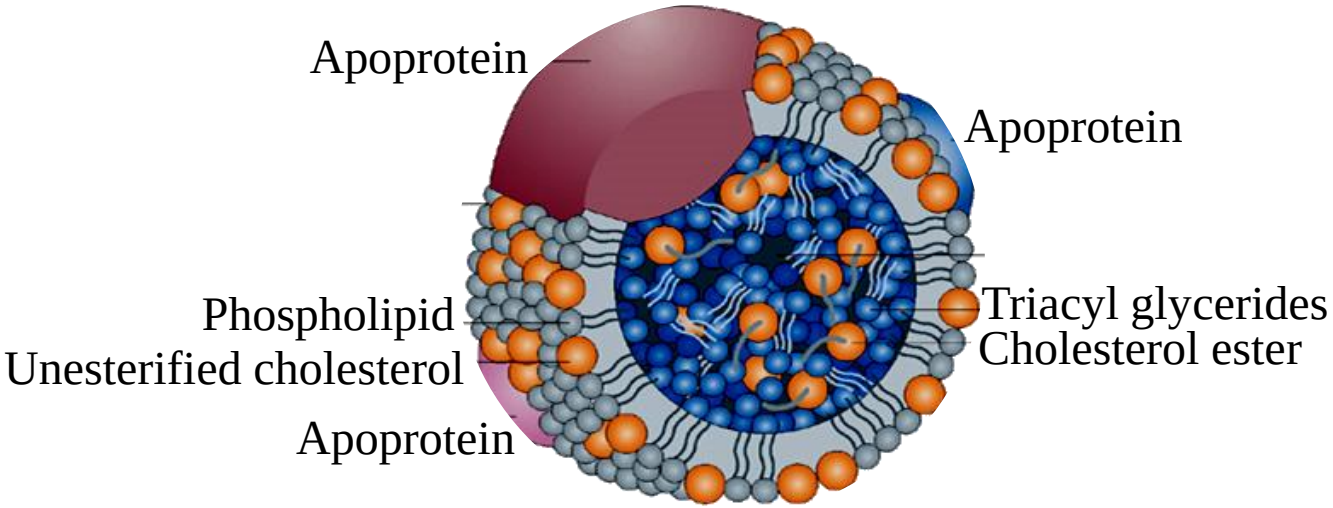
Hint on adjuvant drugs that can help in lipid lowering.

Definition

- Hyperlipidemia is a major cause of atherosclerosis which may lead to cardiovascular disease and ischemic cerebrovascular disease.
- Denotes abnormally ↑ levels of any or all Lipids and/or Lipoproteins [LP] in blood.
  - Lipids originate from two sources:
    - ➢ endogenous lipids, synthesized in the liver.
    - ➢ exogenous lipids, ingested and processed in the intestine.

Definition

Structure of a lipoprotein



Definition

The principle lipids in the blood are:

- **Cholesterol (C).**
- **Triglycerides (TG).**
- Phospholipids (PL).
- Cholesterol esters (CE).
- Non-estrified fatty acids (NEFA).

Familial Hyperlipoproteinemia

LProteinemia	↑LP	↑Lipids	Risk
Type I	CM	TGs	-
Type IIa	LDL	C	↑
Type IIb	VLDL & LDL	TG & C	↑
Type III	IDL	TGs & C	↑
Type IV	VLDL	TGs	↑
Type V	VLDL & CM	TGs & C	_

CM = chylomicron;VLDL = very–low-density lipoprotein; LDL = low-density lipoprotein; IDL = intermediate-density lipoprotein

Treatment of hyperlipidemia

Therapeutic strategies for treatment of hyperlipidemia:

- Therapeutic lifestyle changes.
- Antihyperlipidemic agents.

Therapeutic lifestyle changes

- **Healthy diet; optimal quantitative & qualitative fat content:**

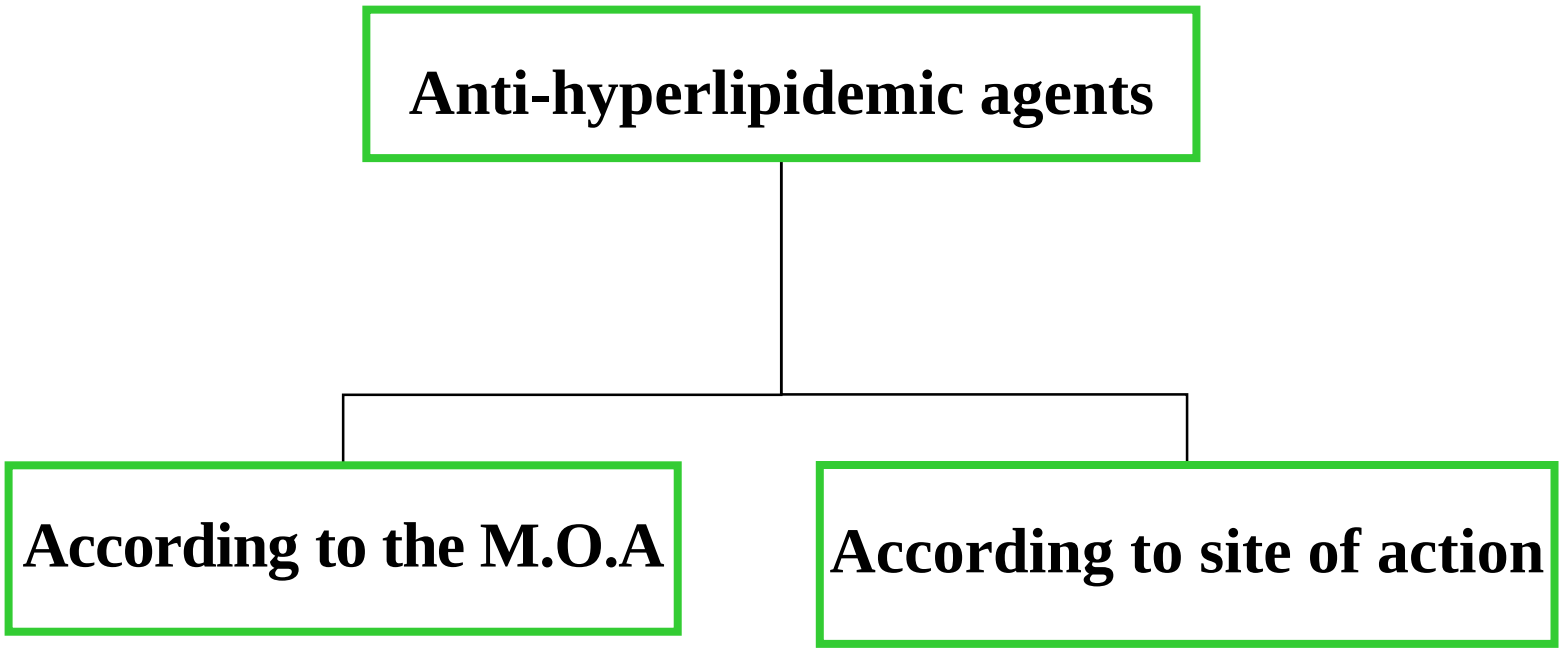
- Diet has < 30% of calories as fat, < 7% as saturated fat and <200mg cholesterol/day.
- Avoid trans-fatty acids and acute increase in C intake.
- Use vegetable oils rich in unsaturated fatty acids: oleic acid, linoleic acid and linolenic acids.
- Diet should also contain plant.
- Stanols (interfere with the formation of micellar cholesterol) and soluble fibers.
- Eat food high in antioxidants vitamins.

Therapeutic lifestyle changes

- **Regular exercise.**
- **Cessation of hazardous habits; smoking, alcohol, …etc.**
- **Losing weight.**

Can achieve a fall in LDL-C of 8-15% … *but long-term compliance is a problem.*

Anti-hyperlipidemic agents.



Antihyperlipidemic agents.

A-according to the M.O.A

- **Inhibits cholesterol absorption in the intestine :**
  - **-Ezetimibe.**
- **Sequester bile acids in the intestine:**
  - **- Exchange resins.**
- **Inhibits synthesis of cholesterol:**
  - **Inhibitors of hydroxy methyl glutaryl coenzyme A reductase (Statins).**
- **Alter relative levels & patterns of different plasma LPs:**
  - **-Fibrates.**
  - **- Nicotinic acids.**

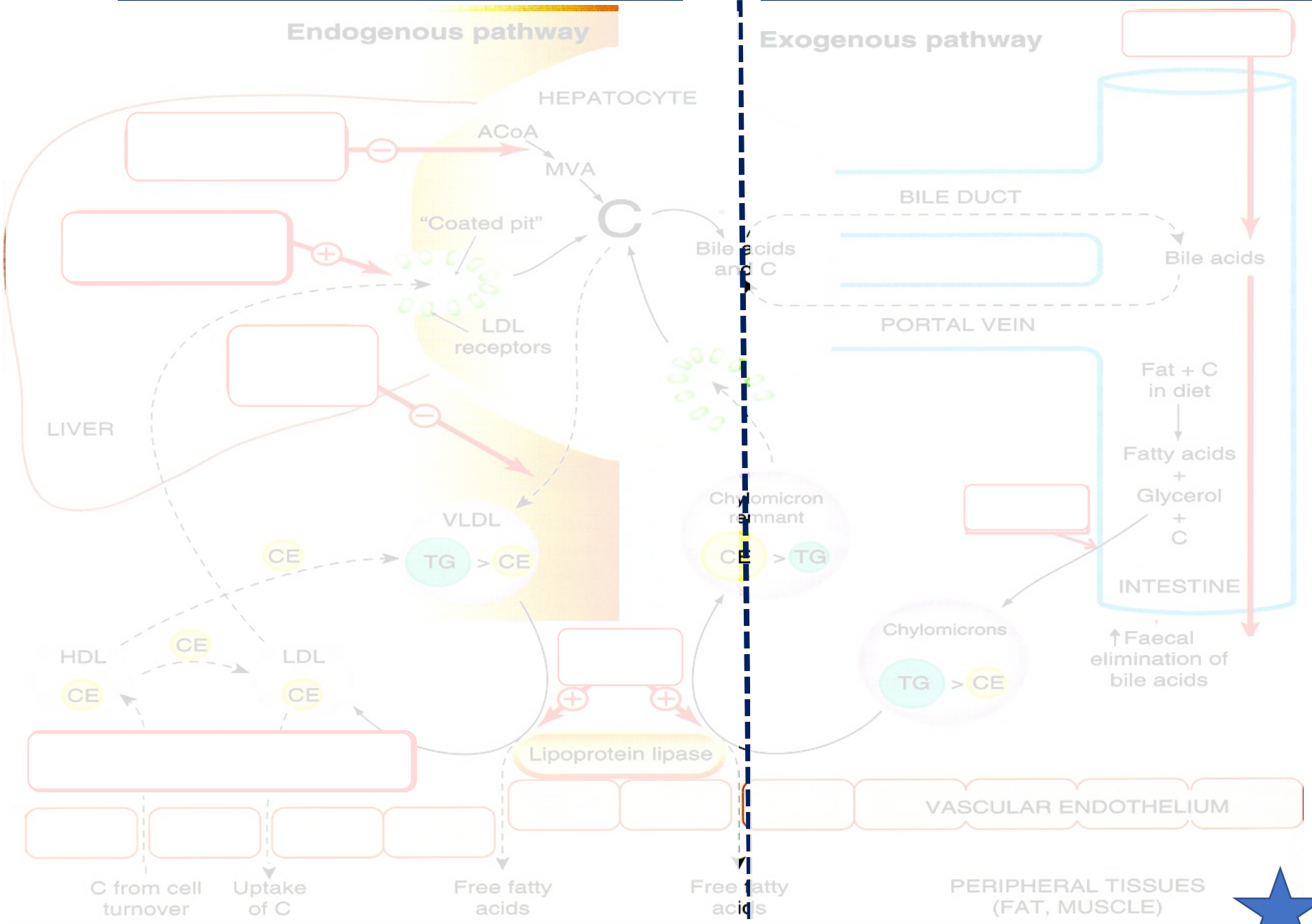
B-according to site of action

- **Agents targeting exogenous cholesterol:**
  - **-Ezetimibe.**
  - **-Colestipol.**
  - **-cholestyramine.**
- **•Agents targeting endogenous cholesterol:**
  - **• -Statins.**
  - **•- Fibrates.**
  - **•-Nicotinic acid.**

M.O.A: Mechanism of action

TARGETING ENDOGENOUS PATHWAYS

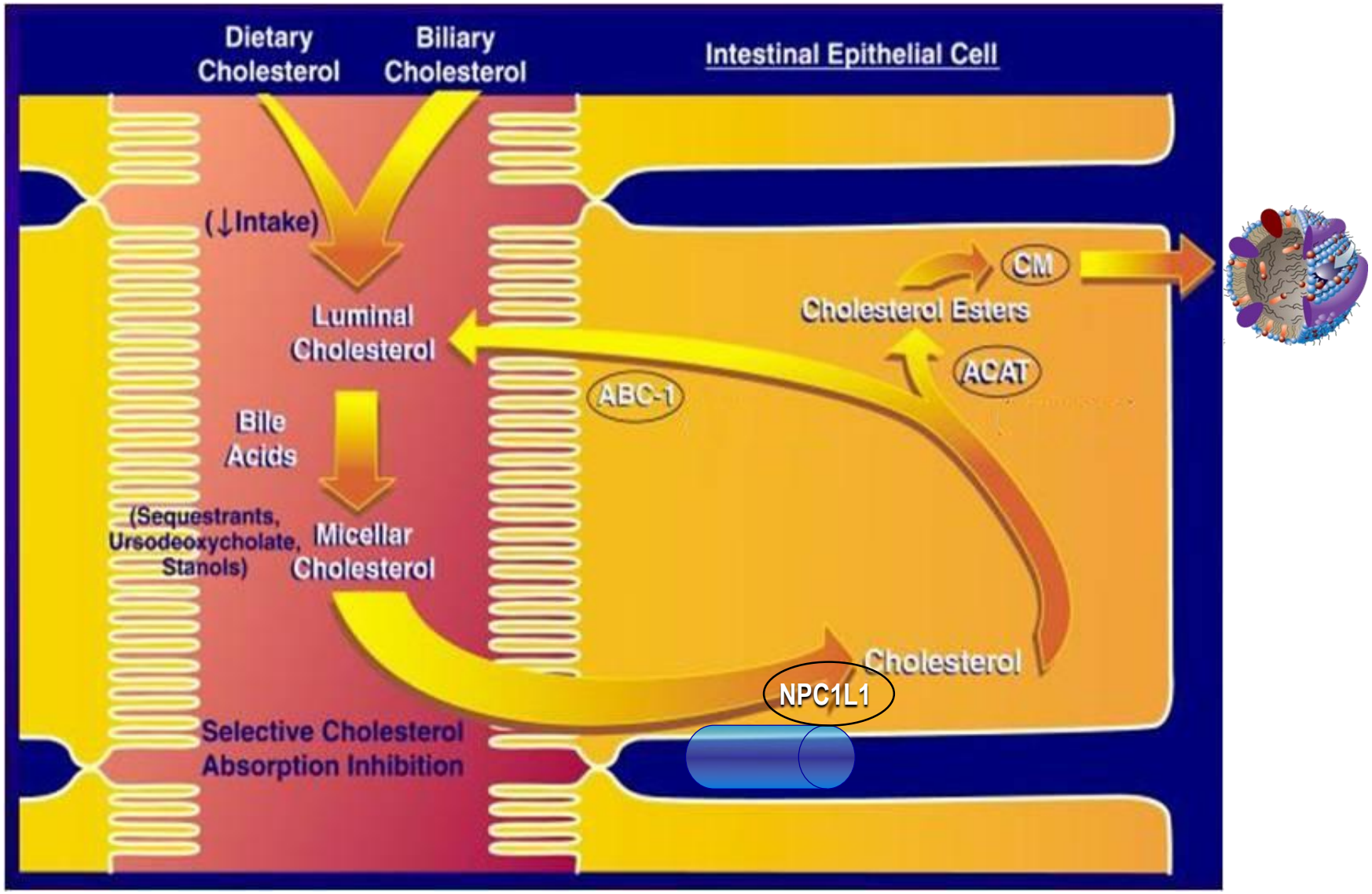
TARGETING EXOGENOUS PATHWAYS



Cholesterol Absorption Inhibitors

Ezetimibe

Ezetimibe: Mechanism of action



Ezetimibe: Mechanism of action

Mechanism of action:

Blocks C transporter located on brush border of small intestine ➜↓ pool of C available to the liver ➜ up regulate LDL receptor, trapping more LDL particles from blood.

Ezetimibe: Pharmacological action

Pharmacological action:

- ↓LDL 20%.
- ↓ TG 8%.
- **↑ HDL 1-4%.**
- No effect on steroids, lipid-soluble vitamins, bile acids.

Ezetimibe: Pharmacokinetics

Pharmacokinetics

- Absorbed and conjugated in intestine to active glucuronide.
- Reaches peak blood level in 12–14 hours.
- Undergoes enterohepatic circulation.
- Its half-life is 22 hours.
- Most of the drug is excreted in feces.

Ezetimibe: Indications

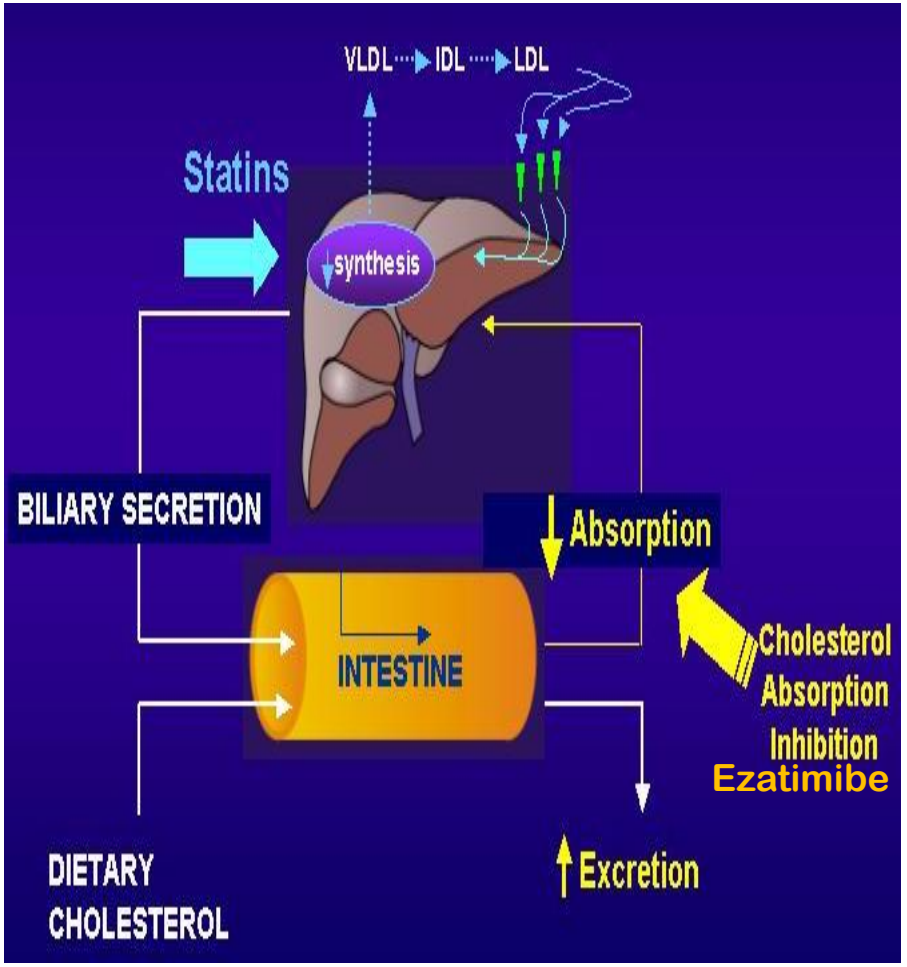
Indications

As Monotherapy:

Primary prevention of low risk of CHD which needs modest ↓LDL.

As Combination Therapy: (safe)

- **With statins**; synergistic in moderate/severe ↑ LDL.
- Or If must ↓ statins dose because of side effects.
- Or with other lipid lowering drugs; as **fibrates.**



Ezetimibe: Adverse effects

Adverse effects

- Not common.
- GIT disturbance, headache, fatigue, arthralgia and myalgia.

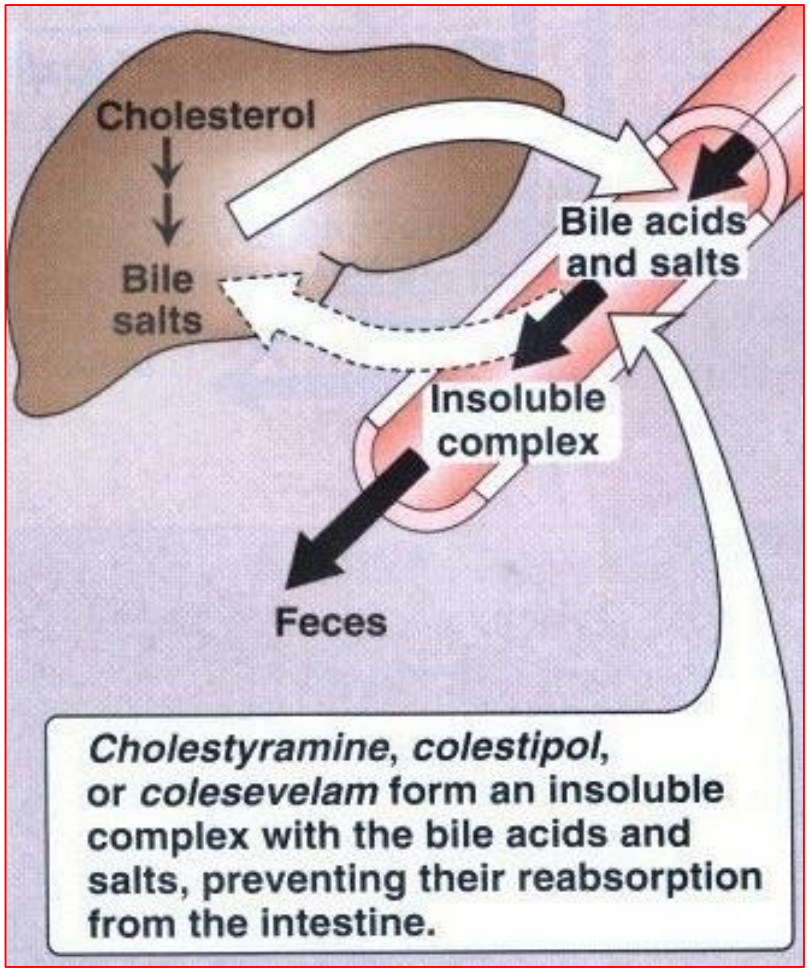
Exchange Resins Bile Acid Sequestrants

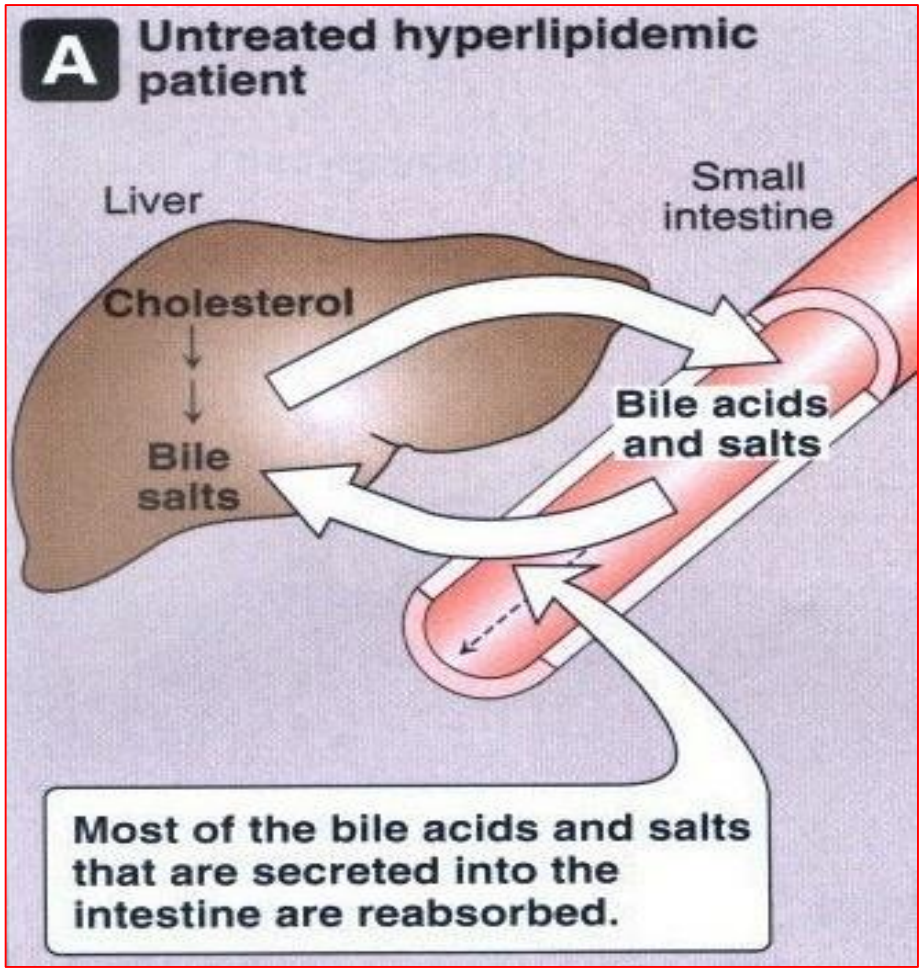
Cholestyramine

Colestipol

Colesevelam

Resins: Mechanism of Action





Bile Acid-Binding Resins

- Moderately effective with excellent safety record.
- Large MW polymers which bind to **bile acids** and the acid-resin complex is excreted so their fecal excretion ↑ 10 folds
  - **Prevents enterohepatic cycling of bile acids.**
  - **Obligates the liver to synthesize replacement bile acids from cholesterol.**

Bile Acid-Binding Resins

- The liver increases the number of LDL receptors to obtain more cholesterol.
- The levels of LDL-C in the serum are reduced as more cholesterol is delivered to the liver.
- Excellent choice for people that cannot tolerate other types of drugs.

Resins : Adverse Effects

- **Resins are** clinically safe as they are not systemically absorbed.
- **GIT upset:** abdominal discomfort, bloating, constipation.
- **Decreased absorption of:** fat soluble vitamins (Vitamin A, D, K).
- The concentration of HDL-C is unchanged.

Resins: Drugs interactions

Interfere with the absorption of:

- **Statins, Ezetimibe.**
- **Chlorothiazides, Digoxin, Warfarin.**

N.B. wait 1 hour before or 4 hrs. after administration of resins.

- **Colesevelam** has not been shown to interfere with the absorption of co-administered medications and is a better choice for patients on multiple drug regimens.

Resins: Contraindications

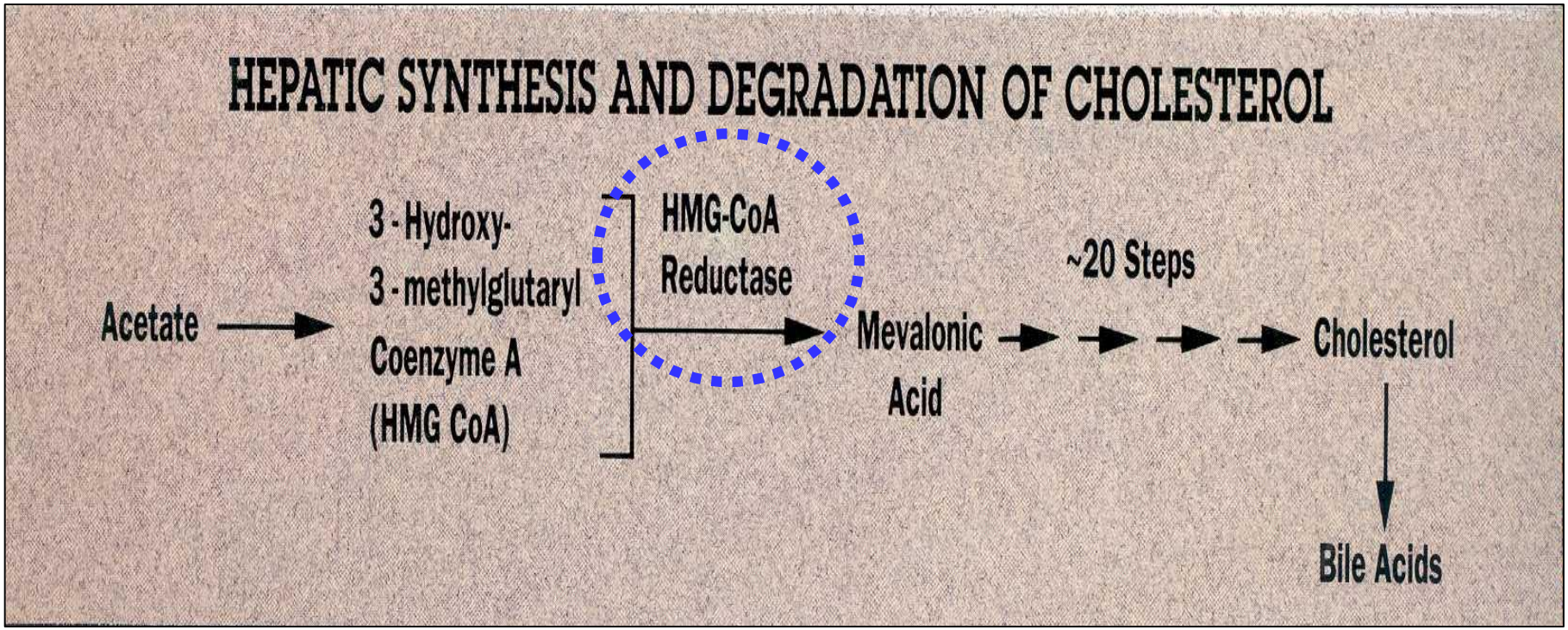
Contraindications

- **Complete biliary obstruction** (because bile is not secreted into the intestine).
- **Chronic constipation.**
- **Severe hypertriglyceridemia** (TG >400 mg/dL).

HMG-Co A Reductase Inhibitors

- **Hydroxy Methyl Glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors or Statins** are the most effective and best-tolerated agents for treating hyperlipidemia.
- Statins are considered as first-line drugs when LDL-lowering drugs are indicated.

Statins: Mechanism of Action



Statins are potent competitive inhibitors of (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in do-novo hepatic C synthesis. Thus, HMG-Co A is not converted to mevalonic acid

Statins: Preparations

- **Rosuvastatin.**
- **Atorvastatin.**
- **Simvastatin.**
- **Pravastatin.**
- **Lovastatin.**

Used alone or with other anti-hyperlipidemic drugs (Ezetimibe) for treatment of drug-resistant dyslipidemia.

Pleiotropic Antiatherogenic effects [> in Vessels]

- Improve endothelial function.
- ↓vascular inflammation.
- Stabilization of atherosclerotic plaque.
- ↓platelet aggregability .
- Antithrombotic actions.
- Enhanced fibrinolysis …etc.

Statins: Pharmacokinetics

- Most statins have a high first-pass clearance by the liver.
- Greater than 95% of most of these drugs are bound to plasma proteins with short half-life.
- Drug-drug interactions involve specific interactions with the cytochrome P-450 drug metabolizing system, especially CYP3A4.

Statins: Pharmacokinetics

- All statins are taken **orally at bedtime** because of hepatic C synthesis is maximal between midnight and 2:00 a.m. , except **atorvastatin** taken at any time because of its long half-life (14 hours).

Statins: Indications

As monotherapy;

2ndry Prevention; In all ischemic insults [stroke, AMI, …..etc.] So given from1st day of ischemic attack.

Pry Prevention;

1. Patients with hyperlipidemia and with other risks for ischemic insults.

2. Type IIa Hyperlipoprotinemia.

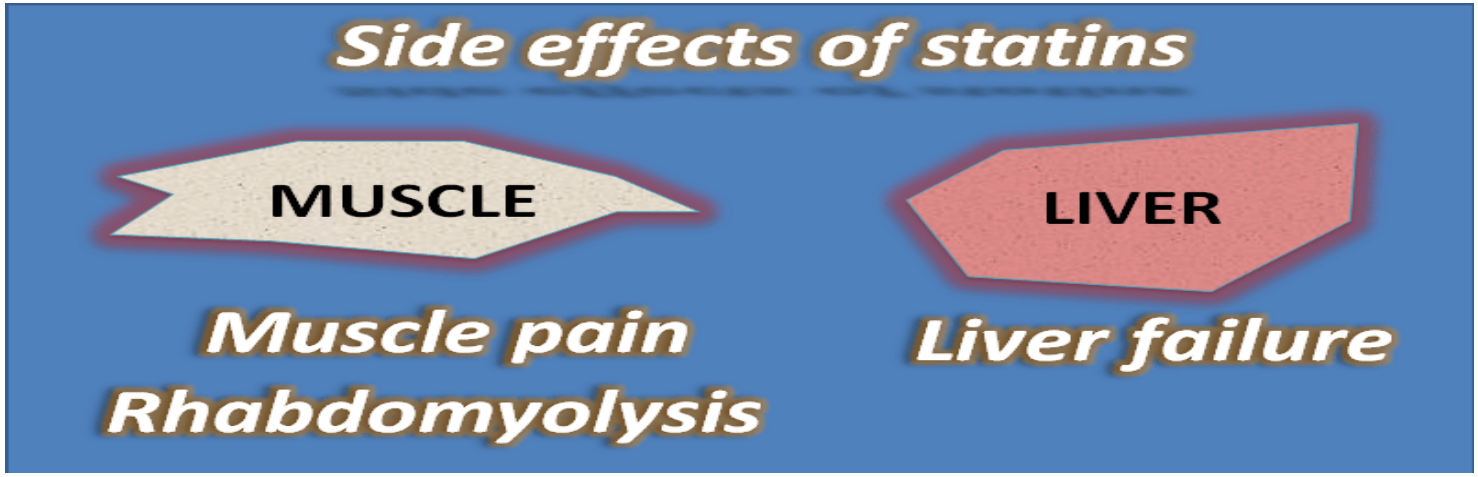
If no control ➔ combine (sequestrants / ezatimibe, niacin,..) to ↓ C.

As Combination therapy;

1. Mixed dyslipidaemias; added to fibrates or niacin if necessary.

2. In diabetics and patients with insulin resistance [metabolic syndrome] because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile.

Statins: Adverse Effects



Statins: Adverse Effects

- **Common side effects:** Headache , myalgia, fatigue, GI intolerance, and flu-like symptoms.
- **Hepatotoxicity,** raised concentrations of liver enzymes (serum aminotransferases).
- **Myopathy** (increased creatine kinase [CK] released from muscles)
- **Teratogenicity, statins should be avoided during pregnancy.**

Statins: Drug Interactions

- **Statins potentiate the action of oral anticoagulant and anti-diabetic drugs** (by displacement from plasma protein binding sites).
- **Drugs that increase the risk of statin-induced myopathy include:**

➢ Other antihyperlipidemics (fibrates).

➢ Drugs metabolized by 3A4 isoform of cytochrome P450: erythromycin, verapamil, cyclosporin, ketoconazole.

- **Pravastatin and fluvastatin** are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

Statin-induced myopathy

- **Muscle aches, soreness, or weakness associated with an elevation of creatine kinase (CK) , are the best indicator of statin-induced myopathy.**
- **Failure to recognize myopathy and to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis.**
- **↑serum transaminase** → can progress to evident hepatotoxicity.

  So lab investigations recommended every 6 month → if levels ↑ up

  to 3 folds at any time, statin must be stopped then dose adjusted.
- **↑ creatine kinase activity (index of muscle injury)** → Measured only if myalgia or myositis develops → if ↑ 3-5 folds → we↓ statin doses / omit combination with fibrates…..

Niacin (Nicotinic Acid)

Water soluble B-complex vitamin with multiple actions

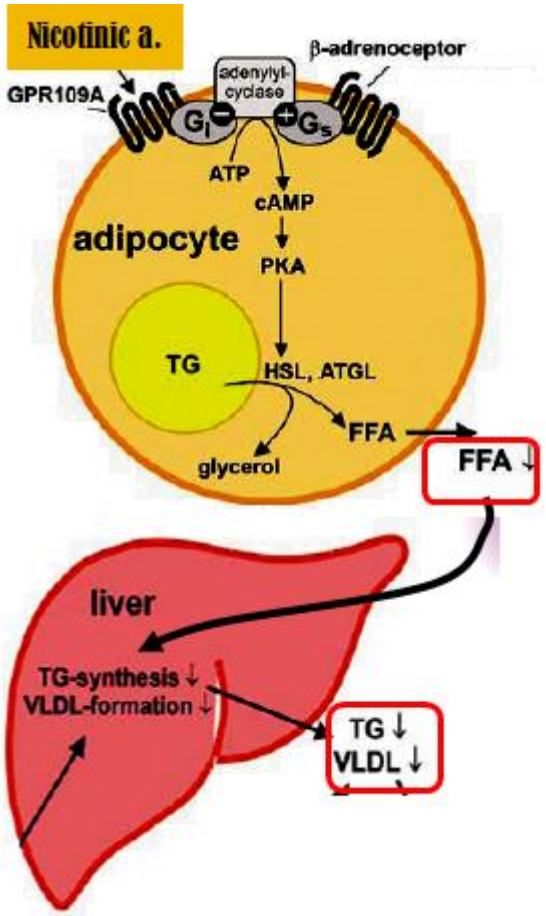
- Niacin is the most effective medication for increasing HDL cholesterol levels and it has positive effects on the complete lipid profile.
- It is useful for patients with mixed dyslipidemias.
- Niacin exerts greatest beneficial effects on wide range of lipoprotein abnormalities.

Niacin: Mechanism of action

1. **In adipose tissue**: it binds to adipocytes nicotinic acid receptors, this will lead to decrease in free fatty acids mobilization from adipocytes to the liver resulting in ↓ TG and thus VLDL synthesis.
2. **In liver:** niacin inhibits hepatocyte 2-diacylglycerol acyltransferase, a key enzyme for TG synthesis

➢ Thus, it decreases VLDL production (decreased TG synthesis and estrification)

3. **In plasma:** it increases LPL activity that increases clearance of VLDL & chylomicron



Niacin: Pharmacological of actions

- **Effect on VLDL: ↓ VLDL by:**

1) ↓ synthesis in liver.

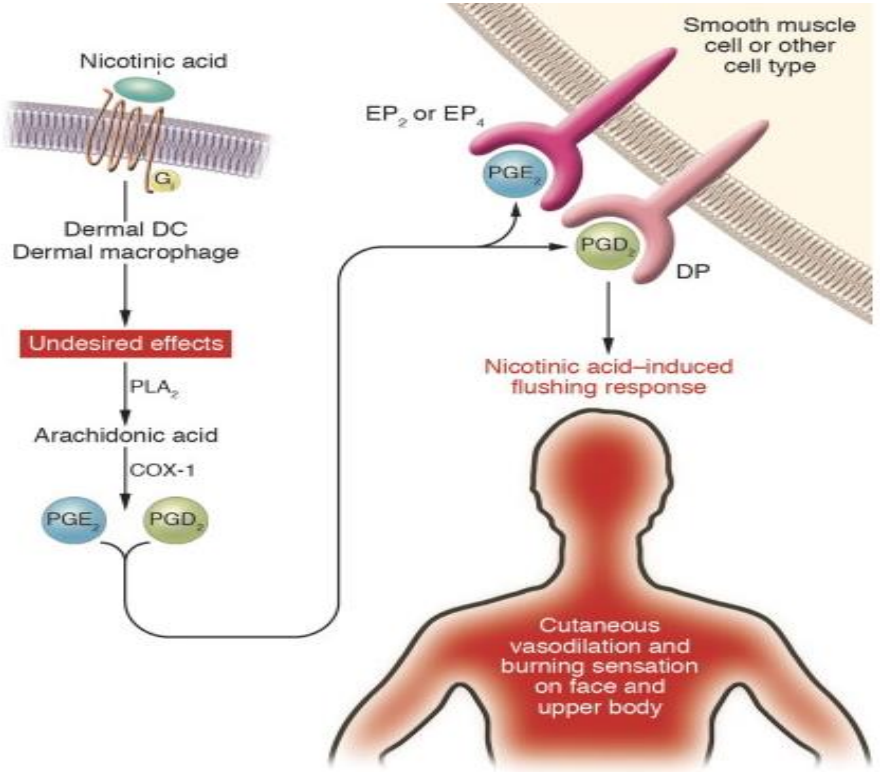
2) increased clearance in plasma.

3) ↓ mobilization of free fatty acids from adipose tissue.

- **Effect on LDL: ↓ LDL** due to reduction in its precursor (VLDL)
- **Effect on HDL:** Induces remarkable increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown).
- Niacin also promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL.

Niacin : Adverse Effects

- **The most common side effect is cutaneous flushing,** (which is prostaglandin -mediated , can be avoided by low dose aspirin ½ h before niacin).



Niacin : Adverse Effects

GIT disturbances: Dyspepsia , nausea , vomiting , reactivation of peptic ulcer (can be decreased if taken after meal).

- **High doses:**

♦ Reversible ↑ liver enzymes ➔hepatotoxicity.

♦ Impairment of glucose tolerance ➔ overt diabetes.

♦ ↑ uric acid.

Niacin : Indications

Monotherapy or in combination with fibrate, resin or statin

- Type IIa hypercholesterolemia.
- Type IIa, IIb hypercholesterolemia & any combined hyperlipidemia.
- Patient with hypertriglyceridemia & low HDL-C.

Niacin : Contraindications

- Gout.
- Peptic ulcer.
- Hepatotoxicity.
- Diabetes mellitus.

Fibric acid Derivatives (Fibrates)

- **Clofibrate.**
- **Gemfibrozil.**
- **Fenofibrate**

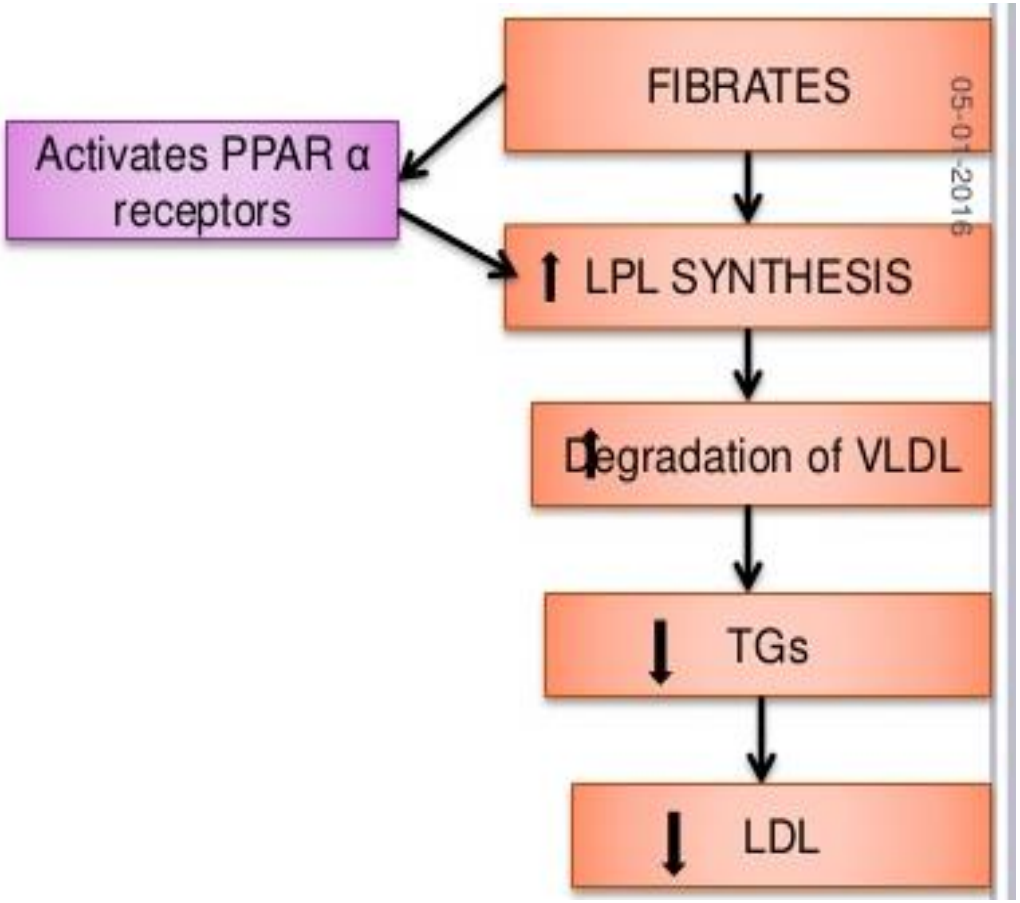
Fibrates :Mechanism of Action

- **Fibrates are agonists of peroxisome proliferator activated receptors (PPARα) which** are a class of intracellular receptors that modulate fat metabolism.
- **They increase genes transcription for lipoprotein lipase (LPL) leading to increased catabolism of TG in VLDL and chylomicrons.**

Fibrates: pharmacological effects

- ↑ LPL activity, which increases clearance of VLDL & chylomicron in plasma
- A marked **reduction in TG** (due to stimulation of catabolism of VLDL)
- ↑ FFA uptake by the liver
- ↑ LDL-C uptake by the liver
- ↑in **HDL-C** (by increasing the production of the apoprotein components of HDL).
- ↑ excretion of hepatic C in bile , thus endogenous hepatic C synthesis may be decreased.

Fibrates: pharmacological effects



Fibrates : Adverse Effects

GIT (indigestion, abdominal pain, diarrhea).

Myositis : can occur resulting in weakness and tenderness of muscles, use of fibrates with statins is generally inadvisable.

Gallstones: **Clofibrate** increases C content of bile, predisposes to gallstones, and its use is therefore limited to patients who have cholecystectomy.

Fibrates : Adverse Effects

- G.I.T upset, headache, fatigue, weight gain.
- Rash, urticaria, hair loss.
- Myalagia, Myositis, Rhabdomyolysis ➔ Acute renal failure ➔

  Occurs >

✓ In alcoholics,
✓ If combined with statins (each –ve metabolism of other).
✓ Or In impaired renal function.

- Fibrates should be used with caution in patients with biliary tract disease, as they increase the risk of cholesterol gallstones as a result of an increase in the cholesterol content of bile.

Fibrates: Indications

1st-line defense for:

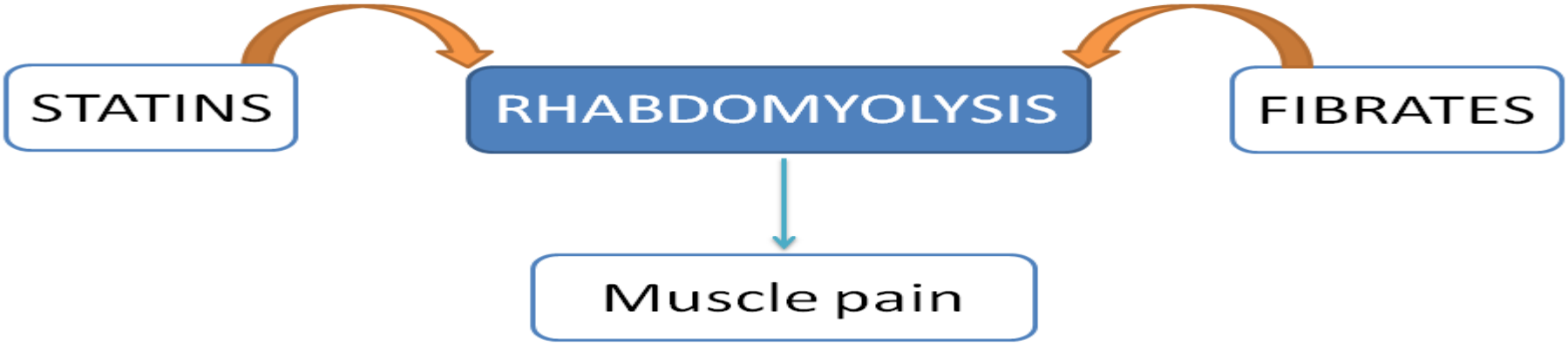
- **mixed dyslipidemia** (i.e. raised serum TG and C).
- **Patients with low HDL and high risk of atheromatous disease** (often type 2 diabetic patients).
- **Patients with severe treatment- resistant dyslipidemia** (combination with other lipid-lowering drugs).

Fibrates: Drug interactions

- Increased risk of myopathy when combined with statins.
- Displace drugs from plasma proteins (e.g. oral anticoagulants and oral hypoglycemic drugs).

Fibrates: Contraindications

- Patients with impaired renal functions
- Pregnant or nursing women
- Preexisting gall bladder disease



Adjuvants in hyperlipidemia

Omega -3-FA

β-Sitosterol

Omega -3-FA

found in fish oils containing highly unsaturated FA

Mechanism

- ↓ enzymes involved in TG synthesis
- ↑ beta-oxidation of FFA

Pharmacological Effects

↓ TGs

- ↓ platelet function
- Prolongation of bleeding time
- Anti-inflammatory effects

Some vascular protection

Indications

Approved as adjunctive for treatment of very high TGs

β-Sitosterol

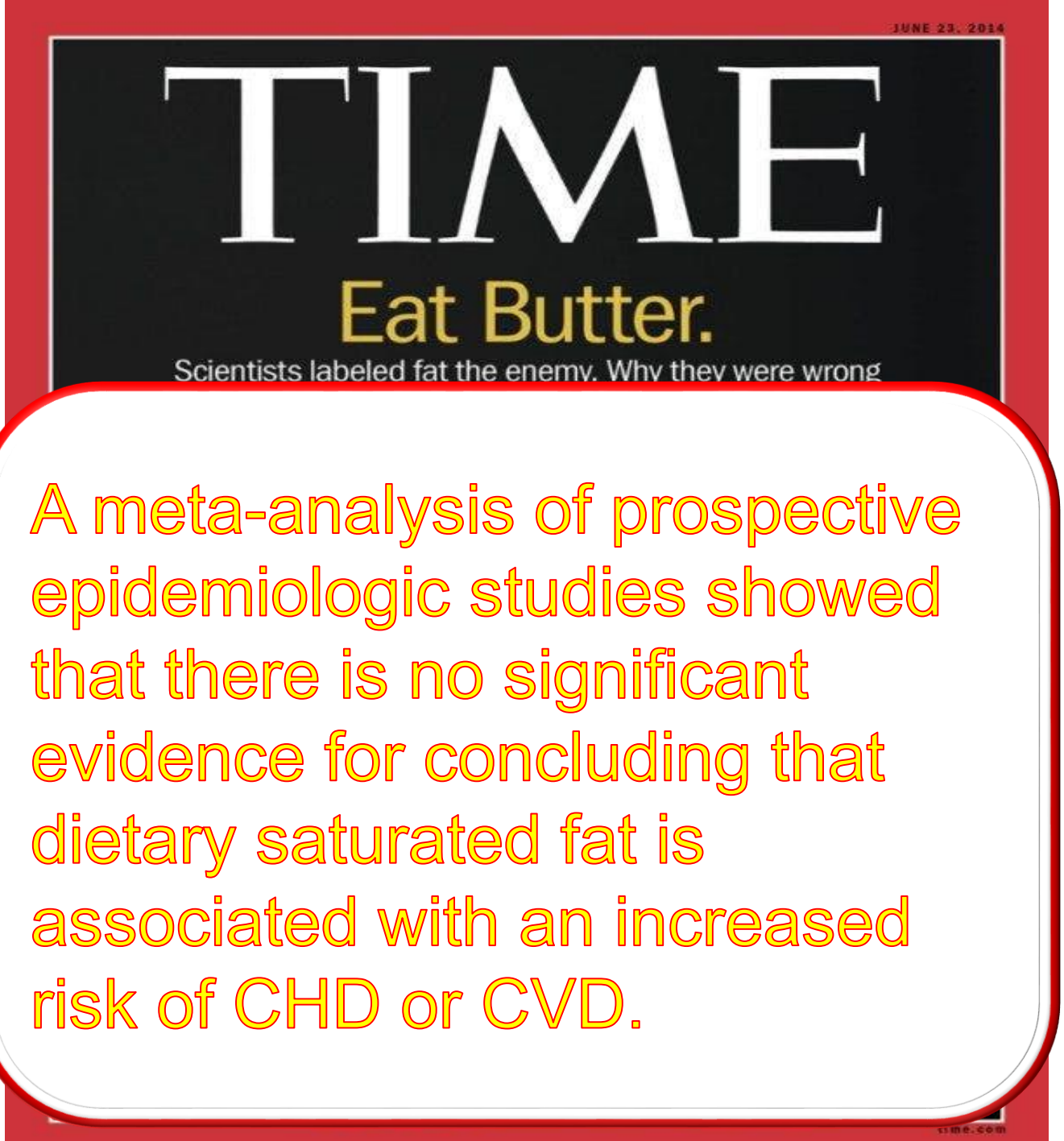
found in plants with structure similar to C

Mechanism &Pharmacological Effects

Compete with dietary & biliary C absorption→ ↓ levels LDL levels ±10%

Indications

Given as food supplement before meal in hypercholestrolemia



A meta-analysis of prospective epidemiologic studies showed that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD.


Pfizer
Lipitor® 40 mg
film-coated tablets
Atorvastatin
40 mg
28 film-coated tablets
Calendar pack
PRESS TO OPEN
VIAGRA®
50 mg
4 film-coated tablets
CHOLESTEROL
Erectile Dysfunction
Testosterone