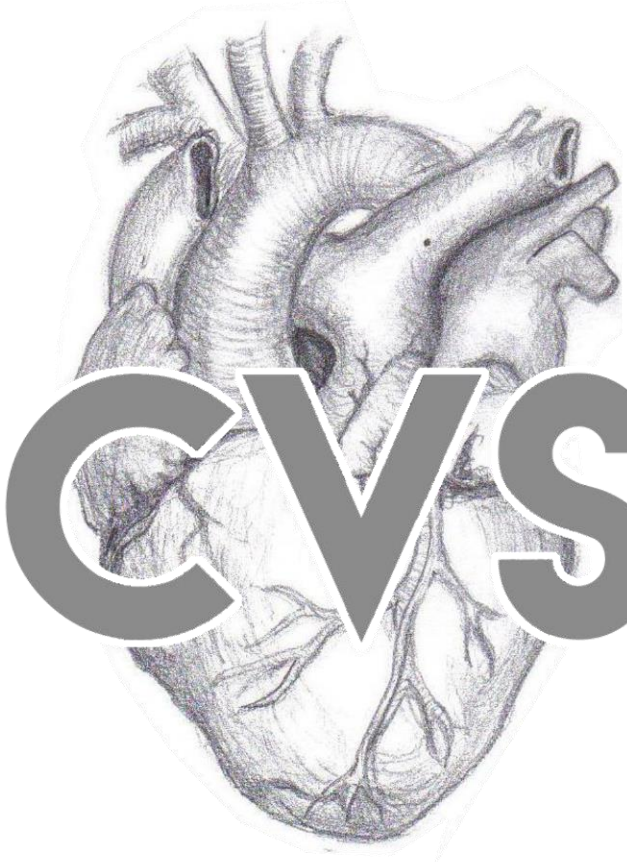


CVS

PHARMACOLOGY

✓Sheet ○Slide ○Handout

Number

11

Subject

Drugs Used in Hyperlipoproteinemias

Done By

Omar Saffar

Corrected by

.....

Doctor

Yacoub M. Irshaid

Date: 00/00/2016

Price:

بسم الله الرحمن الرحيم

- This sheet was written according to sec. 2 record
- Things written in *italic* were not mentioned by the doctor yet written in the slides! 👽💩
- The reference for anyone who is interested is:

McGraw Hill LANGE 13th edition chapter 35

"Be aggressive at treating hyperlipoproteinemia"

❁ Lipoproteins:

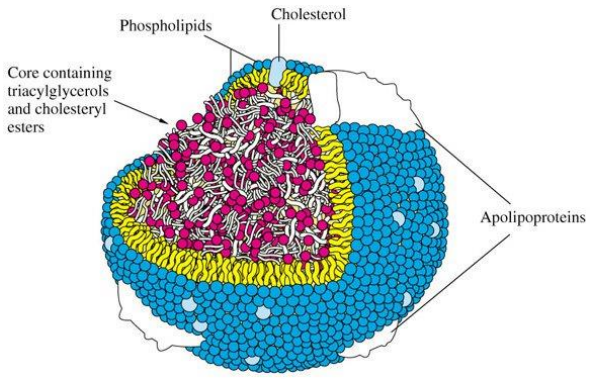
❖ Low-density (LDL), intermediate-density (IDL), very-low-density (VLDL) , and lipoprotein(a) (Lp[a]) are all risk factors for development of atherosclerosis.

❖ HDL cholesterol is protective, while low HDL levels is a risk factor,

❖ (HDL inhibits oxidation of of atherogenic lipoproteins + retrieval of cholesterol from arterial wall *"that's why treatment is reversible partially")*

❖ there are drugs that elevate HDL "you should memorize them"

*Lipoproteins Initiate atherosclerosis when they get oxidized!



WHAT IS THE MAJOR RISK FACTORS FOR ATHEROSCLESROSIS?

- The **Major** risk factor for atherosclerosis is LDL,

The other risk factors once again are:

- IDL and VLDL are also considered risk factors because they can transform into LDL, '*interchangeable (atherosclerotic)"*
- Low levels of HDL
- LP(A):

❖ LP(A) is a rare protein, elevated due to genetic abnormality, it's LDL linked with protein A by disulfide bridges
❖ LP(A) is homologus to plasminogen, but is not activated by tissue plasminogen activator ➔inhibits the work of plasminogen ➔ no thrombolysis, (anti-thrombolytic)
❖ Other use of Niacin is to reduce LPA (two benefits, will be discussed later) but its toxicity is severe!
❖ LPA can be reduced if LDL is reduced below 100mg/dL *"as does the administration of low dose aspirin"*

• Lp(a) can be found in atherosclerotic plaques and may contribute to coronary disease by inhibiting thrombolysis.

• Lp(a) can be secondarily elevated in patients with severe nephrosis and some inflammatory states.

• Niacin reduces levels of Lp(a) in many patients.

What conditions make HDL level low?

- Genetic disorders. *LCAT (lecithin:cholesterol acyltransferase) deficiency, and Familial hypoalphalipoproteinemia*
- Hypertriglyceridemia: due to the exchange of cholesteryl esters from HDL into triglyceride-rich lipoproteins. (if hypertriglyceridemia is corrected, HDL level is increased)
- Other causes…

How to raise HDL levels?

1. Niacin treatment.
2. Aggressive LDL reduction.(will elevate it but won't correct it)
3. Treatment of the hypertriglyceridemia.

More Risk factors of atherosclerosis:

- smoking ➔ damage to endothelial cells ➔ lowers HDL levels
  "Smoking is associated with reduced levels of HDL, impairment of cholesterol retrieval, cytotoxic effects on the endothelium, increased oxidation of lipoproteins, and stimulation of thrombogenesis."
- hyper-Homocystenemia

- NO is protective against atherosclerosis because it induces vasodilation(local vasodilator)
  "Nitric oxide, a local vasodilator released from endothelial cells, function is impaired by atherogenic lipoproteins. Reducing their levels restores endothelial function."

Hypertriglyceridemia is a risk factor for:

- Atherosclerosis: when VLDL level increases, LDL increases and causes atherosclerosis!
- also a risk factor for **acute pancreatitis** (which is very painful)

Treatment of secondary causes of hyperlipoproteinemia treats the condition itself

TABLE 35–3 Secondary causes of hyperlipoproteinemia.

Hypertriglyceridemia	Hypercholesterolemia
Diabetes mellitus	Hypothyroidism
Alcohol ingestion	Early nephrosis
Severe nephrosis	Resolving lipemia
Estrogens	Immunoglobulin-lipoprotein complex disorders
Uremia	Anorexia nervosa
Corticosteroid excess	Cholestasis
Myxedema	Hypopituitarism
Glycogen storage disease	Corticosteroid excess
Hypopituitarism	
Acromegaly	
Immunoglobulin-lipoprotein complex disorders	
Lipodystrophy	
Protease inhibitors	

Therapy:

☆ **Diet:** low in total fat, only 25% of calories from fat, saturated fat less than 7%, also complex carbohydrates not simple sugars (slower absorption > won't be converted to fat quickly), cholesterol less than 200 mg/day, cis **monounsaturated fat** should be predominate "olive oil"

(Saturated fat is animal fat or hydrogenated vegetable oil)

Cholesterol won't affect all people the same way!

"If you don't have genetic predisposition cholesterol won't be that bad for you(won't cause hypercholesterolemia)"

☆ **Omega3** FA found in fish not plants, activates PPAR-α "peroxisome proliferator-activated receptor-alpha", and can:

- Reduce triglycerides in some patients, why? Activation of PPAR-α induces lipolysis , remove FA from triglycerides, so reduces triglycerides
- also have anti-inflammatory & antiarrhythmic activities

- Omega 3 produces PGI3 not 2! Vasodilator and also inhibitor of platelet aggregation (antiplatelet)!

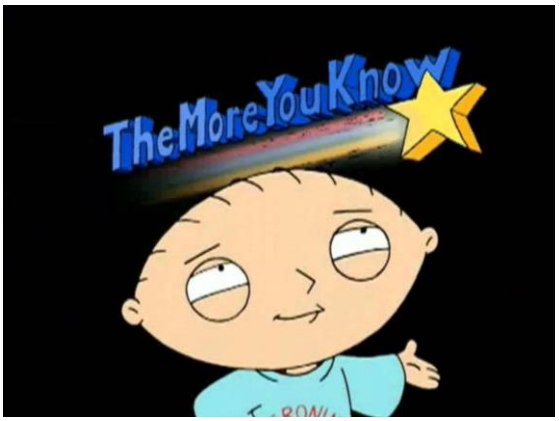
Hyperglycemia is associated with hyperlipidemia so PPAR-α is good for both "like thiazolin mono …" which increases sensitivity to insulin

Omega3 FA are:

DecosaHexanoic acid and **EicosaPentaenoic** acid

daily 3-4g of theses FAs to treat hypertriglyceridemia

Omega 3 is best found in fishes which live in cold water in the northern part of the globe like Salmon, Mackerel, Alaskan halibut, sardines, herring, albacore tuna and also Oyster



☆ **Hyper-Homocysteinemia** ➔risk factor for Atherosclerosis!!

Homocysteine is a Precursor of methionine, (homocysteine methylation by SAM ➔ methionine)

Deficiency in folic acid and B12 "failure of methylation" ⇨ Homocysteinemia

Homocysteine (Hyperhomocysteinemia) relation to atherosclerosis, and cardiovascular risk:

1. It increase proliferation of vascular smooth muscle cells.

2. It induces oxidative damage which participates in atherosclerosis.

3. It reduces the production of nitric oxide (a strong relaxing factor) by the endothelium.

4. It increases synthesis of collagen and deterioration of arterial wall elastic material.

5. It is capable of initiating an inflammatory response in vascular smooth muscle and endothelial cells.

6. It increases the activity of HMG-Co-A reductase which increases cholesterol synthesis.

7. Hyperhomocysteinemia is associated with a higher risk of venous thrombosis (it enhances platelet adhesion to endothelial cells and is associated with higher levels of prothrombotic factors).

- **Reduction of Homocysteine** (pro-atherogenic in endothelium) can be achieved by:

  1. Restriction of total protein intake to the amount required for amino acid replacement. "meat eaters have aggressive tendencies :O"

  2. Supplementation with folic acid and other B vitamins (B6, B12).

  3. Administration of **betaine** (methyl donor) necessary for folate-independent methylation of Homocysteine to methionine, in severe Homocysteinemia.

☆ Consumption of red meat should be minimized to reduce the production, by the intestinal biome "flora", of **tetra-methyl amine oxide**, a compound that can cause injury to arteries

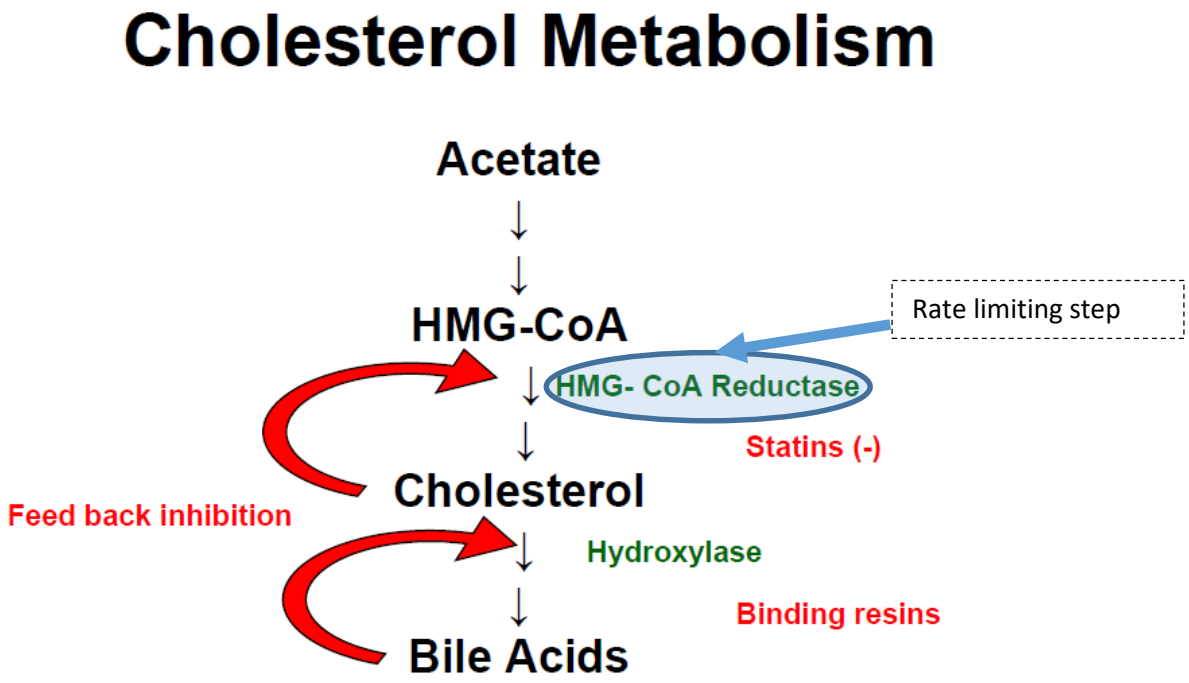
☆ Normalize body weight, and exercise.(it's hard I know) increases HDL

☆ Treat aggravating factors:

Diabetes mellitus, alcoholism, nephrotic syndrome, obesity, smoking, hypothyroidism, corticosteroids, ..

1. **Statins**: lovastatin, simvastatin, atorvastatin, rosuvastatin, .. most important one
2. **Bile acid binding resins**: cholestyramine, colestipol, colesevelam.
3. **Nicotinic acid (Niacin).**
4. **Fibric acid derivatives**: gemfebrozil, fenofibrate.
5. **Inhibitors of intestinal sterol absorption**: ezetimibe
6. Others.

All these drugs can be used <u>with **statin**</u>



- **Binding resins** will bind to bile acids in the intestines preventing them from being reabsorbed which will make the liver synthesize more bile acids decreasing cholesterol in the body.

  Yet resins are not comfortable to take, because they taste like sand particles in the mouth, also they cause bloating in the abdomen ☹

- HMG-CoA Reductase Inhibitors "**Statins**"

  Atorvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Rosuvastatin, Pitavastatin ..

  - **Pharmacokinetics:**

  • Lovastatin and simvastatin are prodrugs.

  • Lovastatin, simvastatin, and atorvastatin undergo extensive first-pass effect "metabolized" by **CYP3A4**, bioavailability varies from 40-75%.

  Their metabolism is inhibited by grapefruit juice, *macrolide antibiotics, cyclosporine, ketoconazole some HIV protease inhibitors, tacrolimus, nefazodone, fibrates, paroxetine, venlafaxine, and others.*

  Keep in mind 

  Grapefruit juice inhibit CYP3A4 and also P-glycoprotein!

  • Metabolism of fluvastatin and rosuvastatin, and to a lesser extent pitavastatin, is mediated by **CYP2C9**

  • **Pravastatin** *is metabolized through other pathways, including sulfation*.

  • Absorption generally (with the exception of pravastatin and pitavastatin) is enhanced by **food**.

  • t½ varies from 1-3 hours for many, ~ 14 hours for atorvastatin and ~ 19 hours for rosuvastatin, and 12 hours for pitavastatin.

  "cholesterol synthesis occurs at night, so we have to give these drugs at night" t½ 2h means in 8h the drug is all gone, if we took the drug at 6 am at 2 pm will be gone, so it should be taken at night (single dose), but drugs with long t½ like 12h we can give them anytime, (more flexibility with higher t½)"

- **Pharmacodynamics:**

• They inhibit the rate-limiting step in cholesterol biosynthesis, the 3-hydroxy-3-methylglutaryl CoA reductase. (HMG-CoA)

• The reduced cholesterol content of hepatocytes increase LDL receptor

Synthesis → an increase in catabolic rate of LDL and the liver's extraction of LDL precursors (VLDL remnants) from the blood, thus reducing LDL.

• Prenylation of Rho and Rab proteins, and thus, reduction of activation of **Rho kinase**. This might explain the reduction in new coronary events before improving morphology of arterial atherosclerotic plaques. (Induces vasodilation)

Remember:
Rho kinase induces vasoconstriction

And that's why ⇨ "We should give statins irrespectively to the level of cholesterol in the patients with ischemic heart disease"

• They also modestly reduce triglycerides and slightly increase HDL.

• *Rosuvastatin is the most efficacious.*

• *Because cholesterol synthesis occurs predominantly at night, these drugs should be given in the evening if a single daily dose is prescribed (except atorvastatin, rosuvastatin, and pitavastatin) (why??).*

Other actions:

• They reduce oxidative stress and vascular inflammation, stabilize atherosclerotic lesions and improve the microcirculation.

• *They also inhibit proliferation of arterial wall smooth muscle and improve endothelial cell function.*

• *They are indicated after acute coronary syndromes irrespective of cholesterol level in the plasma*

Therapeutic Uses:

• Useful alone or with other drugs in **reducing levels of LDL.**

• Women who are a. **pregnant** (teratogenic), b. **lactating**(traverse through milk) "produces toxicity in baby", or c. **likely to become pregnant** should not be given statins.!!

• Use in children under 16 is restricted to selected patients with familial hypercholesterolemia or familial combined hyperlipidemia.

(because baby is small )

Adverse effects:

CK is a muscle enzyme

Trauma may increase it…

1. Elevated CK activity, statins are toxic to muscles

2. Generalized discomfort or weakness in skeletal muscles. ache in muscles (especially in shoulders)

"all patients have this symptom when starting using statins"

3. Myopathy "more important" → **Rhabdomyolysis** "damage to muscle fibers, just like hemolysis in RBC" → Myoglobinuria "large particles"→ renal shutdown. "Obstruct tubules" acute renal failure, which May lead to death!

It is reversible upon cessation of therapy.

• Genetic variation in an anion transporter (OATP1B1) is associated with statin induced Rhabdomyolysis and induced severe myopathy.

OATP1B1:

Make statins enter the liver, if inhibited ⇨ no entry, so concentration is increased and drug become toxic!

☆ All drugs that metabolized by/ or inhibit CYP3A4 or CYP2C9 can increase the conc. Of their substrate "which is statins here" an that will increase the severity of myopathy."

These drugs are:

• *Nicotinic acid, fibrates, ketoconazole, cyclosporine, erythromycin, verapamil, cimetidine, metronidazole, amiodarone, grapefruit juice and protease inhibitors (anti HIV).*

• *Inhibitors of CYP2C9, ketoconazole, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin.*

In contrary:

• Phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones **induce** CYP3A4 and can reduce the plasma levels of the 3A4-dependent reductase inhibitors, so they won't increase myopathy. "reduce effect of statins and toxicity!!"

• **Pravastatin and Rosuvastatin** are the statins of choice for use with verapamil, ketoconazole, macrolides, and cyclosporine. "They can be given with drugs that are substrates of CYP3A4" or CYP2C9

Rosuvastatin conc. is increased when coadminstered with inhibitors of CYP2C9 yet the doctor said that it can be given with drugs that are substrates of CYP2C9! And that it is not metabolized by it!

4. **Teratogenicity**: contraindicated in pregnancy (and lactation).

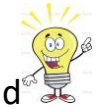
5. GIT upset, headache, skin rash.

6. Elevated **hepatic enzymes** (in asymptomatic patients, stop drug if elevated ➔ three times more than normal limit). If it's less than "three times" there's no need to worry,

7. Hepatic toxicity **(malaise, anorexia,** and precipitous **decreases in LDL** ➔ stop drug immediately). Excess intake of alcohol tends to aggravate hepatotoxic effects of statins.

8. Small but significant increase in the incidence of type 2 diabetes in statin treated patients, most of them were prediabetic before treatment.

Malaise and Anorexia are clinically important as they indicate liver toxicity!

So if you see anorexic patient this should raise a light bulb above your head 

And the doctor here said that we read the rest…

So these are copied from the slides and "required"

9. Peripheral neuropathy.

10.Lupus-like syndrome.

11. Statins may potentiate the effects of warfarin.

• Reductase inhibitors may be discontinued in serious illness, trauma, or major surgery to minimize the potential for liver and muscle toxicity.

Fibric Acid Derivatives

Gemfibrozil, Fenofibrate, & Bezafibrate

Pharmacokinetics:

• Absorption of gemfibrozil is improved when the drug is taken with food.

• Gemfibrozil is tightly bound to plasma proteins, undergoes enterohepatic cycling, and readily crosses the placenta.

70% is eliminated by the kidney mostly unchanged.

t½ ~ 1.5 hours.

• Fenofibrate is mainly metabolized, and metabolites are excreted in urine and feces.

t½ ~ 20 hours.

Mechanism of Action:

• They bind to the nuclear transcription receptor, peroxisome proliferatoractivated receptor-α (PPAR-α), and upregulate LPL, apo AI and apo AII, and down-regulate apo CIII, an inhibitor of lipolysis. A major effect is an increase in oxidation of fatty acids in liver and striated muscle.

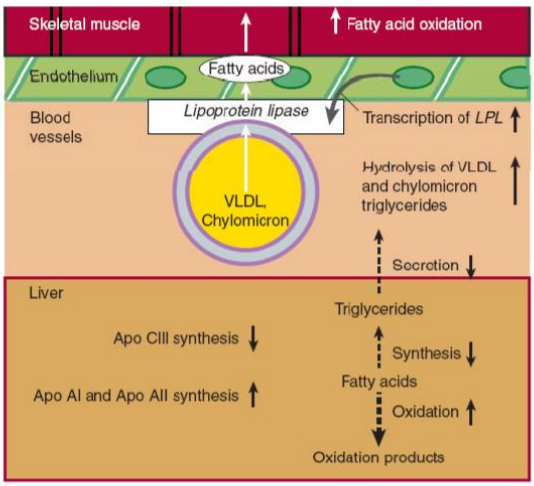


FIGURE 35–4 Hepatic and peripheral effects of fibrates. These effects are mediated by activation of peroxisome proliferator-activated receptor-α, which modulates the expression of several proteins. LPL, lipoprotein lipase; VLDL, very-low-density lipoproteins.

• Reduction of VLDL.

• Modest decrease in LDL.

• Elevation of HDL, partly due to lower triglyceride in plasma, resulting in reduction in the exchange of triglycerides into HDL in place of cholesteryl esters.

• They may increase LDL in patients with hypertriglyceridemia as triglycerides are reduced).

Therapeutic uses:

• Hypertriglyceridemias.

Adverse Effects:

1. Myopathy → rhabdomyolysis. Risk increases if given with statins.

2. Increase bile lithogenicity → cholesterol gall stones, due to an increase in the cholesterol content of bile.

3. Reduce platelet activity→ potentiate actions of anticoagulants.

4. Hypokalemia and cardiac arrhythmias.

5. GIT upset and rashes.

6. Elevation of liver enzymes (aminotransferases and alkaline phosphatase).

7. Reduce WBCs and hematocrit.

• Avoid in hepatic or renal dysfunction.

Nicotinic Acid (Niacin, Vitamin B3)

• It is reduced in the body to the amide which is incorporated into NAD energy metabolism.

Pharmacodynamics:

1. It inhibits VLDL secretion from the liver and thus LDL production. It reduces LDL, triglycerides and VLDL. Increased clearance of VLDL via the LPL pathway contributes to reduction of triglycerides triglycerides

2. It raises HDL cholesterol by decreasing its catabolism (most effective agent).

3. It reduces the level of LP(a) (only agent).

4. It reduces fibrinogen levels.

5. It increases tissue plasminogen activator.

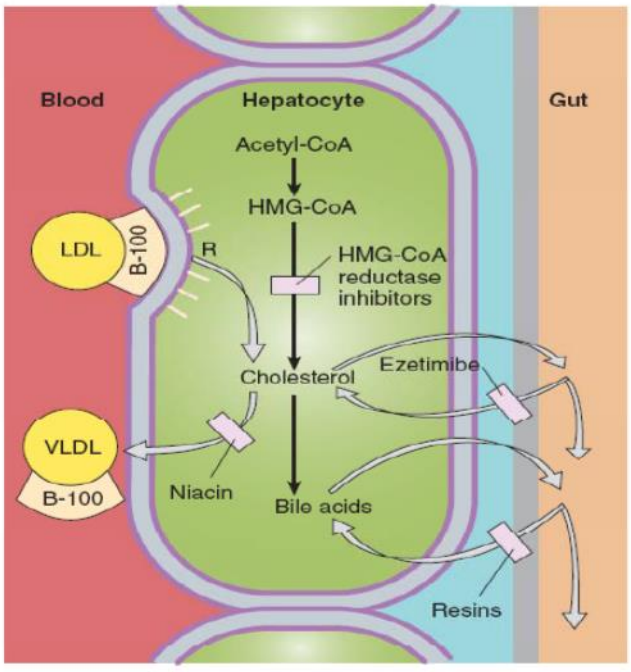


FIGURE 35–2 Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. Low-density lipoprotein (LDL) receptors are increased by treatment with resins and HMG-CoA reductase inhibitors. VLDL, very-low-density lipoproteins; R, LDL receptor.

Adverse Effects:

Occur in > 50% of patients.

1. Flushing, feeling of warmth, postural hypotension, headache (reduced by aspirin or ibuprofen, why?).

Tachyphylaxis to flushing usually occurs within a few days.

2. Pruritus, rashes, dry skin or mucous membranes.

3. Acanthosis nigricans (AN). AN requires discontinuance of niacin because of its association with insulin resistance and hyperglycemia.

4. Nausea and abdominal discomfort.

5. Elevation of liver enzymes and hepatic dysfunction.

6. Myopathy.

7. Peptic ulceration.

8. Hyperuricemia gout.

9. Cardiac arrhythmias, atrial.

10. Macular edema blurring of distance vision.

11. Platelet deficiency.

Bile Acid Binding Resins

Cholestyramine, Colestipol, Colesevelam

• Non-systemic agents.

• They are large polymeric cation-exchange resins that are insoluble in water.

• Bind bile acids in the intestine and prevent their absorption. The resin itself is not absorbed.

• They exchange Cl- for the negatively charged bile acids, thus, preventing the negative feedback on the hydroxylase → enhancing of cholesterol breakdown

• Reduction of hepatic cholesterol increases LDL receptors which accelerates cholesterol removal from plasma Increased uptake of LDL and IDL from plasma.

• Loss of bile acids also reduces fat and cholesterol absorption from GIT.

• In patients with hypertriglyceridemia and hypercholesterolemia, VLDL may be increased during treatment with the resins.

• Thus, they are useful only for isolated increases in LDL.

• They may be helpful in pruritus due to cholestasis and bile salt accumulation.

• They should be taken with meals. They lack effect if taken between meals.

Adverse Effects:

1. Sandy or gritty taste.

2. Bloating, abdominal discomfort, fecal impaction and constipation, and should be avoided in patients with diverticulitis.

3. Steatorrhea due to reduced fat absorption.

4. Decreased absorption of fat-soluble vitamins (A, D, E, K) and others.

5. Hyperchloremic acidosis.

6. Decrease absorption of many drugs:

digitalis glycosides, thiazides, warfarin, tetracycline, thyroxine, iron salts, pravastatin, fluvastatin, ezetimibe, folic acid, phenylbutazone, aspirin, and ascorbic acid, among others. What to do? (1, 2-4??). Colesevelan does not bind digoxin, warfarin or statins!

Both the statins and the resins are not effective in patients lacking LDL receptors. (familial homozygous hypercholesterolemia)

Inhibitors of Intestinal Sterol Absorption

Ezetimibe

• It inhibits intestinal cholesterol and phytosterol absorption → reduces LDL.

• A transport protein, NPC1L1, is the target of the drug.

• Minimal increase in HDL cholesterol.

• It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in bile.

• It undergoes enterohepatic circulation, t½ ~ 22 hours, excreted in feces.

• Plasma concentration is increased when coadministered with fibrates and reduced when given with the resins.

• Effect is synergistic with statins.

• May produce reversible hepatic impairment.

• Myositis has been reported rarely.

Le Fin.

Omar Saffar