Drugs Used in Hyperlipoproteinemias

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

13th edition, Chapter 35.

Office hours until 17/11/2016

Sunday, Tuesday 11-12

Thursday 10-11

Drugs Used in Hyperlipoproteinemias

- **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 is a risk factor.**
- **HDL participates in retrieval of cholesterol from the artery wall and inhibits the oxidation of atherogenic lipoproteins.**

Drugs Used in Hyperlipoproteinemias

Some causes of low HDL:

1. Some genetic disorders: LCAT (lecithin:cholesterol acyltransferase) deficiency, and Familial hypoalphalipoproteinemia.
2. Hypertriglyceridemia: because of exchange of cholesteryl esters from HDL into triglyceride-rich lipoproteins.

Drugs Used in Hyperlipoproteinemias

HDL can be elevated by:

1. **Niacin treatment.**
2. **Aggressive LDL reduction.**
3. **Treatment of the hypertriglyceridemia.**

- **Cigarette smoking is a major risk factor for coronary disease.**

Drugs Used in Hyperlipoproteinemias

- 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.
- Nitric oxide, a local vasodilator released from endothelial cells, function is impaired by atherogenic lipoproteins. Reducing their levels restores endothelial function.

Drugs Used in Hyperlipoproteinemias

- **Lp(a) lipoprotein is formed from LDL and the (a) protein, linked by a disulfide bridge.**
- **It is highly homologous with plasminogen but is <u>not activated</u> by tissue plasminogen activator.**
- **Its level is variable (nil to over 2000 nM/L) and is determined chiefly by genetic factors.**

Drugs Used in Hyperlipoproteinemias

- 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.

Drugs Used in Hyperlipoproteinemias

- Reduction of levels of LDL-C below 100 mg/dL decreases the risk attributable to Lp(a), as does the administration of low dose aspirin.

- Hypertriglyceridemia is a risk factor for acute pancreatitis.

Drugs Used in Hyperlipoproteinemias

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	

Drugs Used in Hyperlipoproteinemias

Principles of therapy:

- **Diet low in total fat (20–25% of daily caloric intake), saturated fats to less than 7%, and cholesterol to less than 200 mg/day). *cis-* monounsaturated fats should predominate.**
- **Use of complex carbohydrates and fiber is recommended.**

Drugs Used in Hyperlipoproteinemias

- **Omega-3 fatty acids found in fish oils, but not those from plant sources, activate peroxisome proliferator-activated receptor-alpha (PPAR-α) and can reduce triglycerides in some patients. They also have antiinflammatory and antiarrhythmic activities.**
- **3 – 4 g of docosahexaenoic acid and eicosapentaenoic acid daily.**

Drugs Used in Hyperlipoproteinemias

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).**

Drugs Used in Hyperlipoproteinemias

- **Reduction of homocysteine (proatherogenic in endothelium) can be achieved by:**

1. **Restriction of total protein intake to the amount required for amino acid replacement.**
2. **Supplementation with folic acid and other B vitamins (B_6, B_{12}).**

Drugs Used in Hyperlipoproteinemias

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, of tetramethyl amine oxide, a compound that can cause injury to arteries.

Drugs Used in Hyperlipoproteinemias

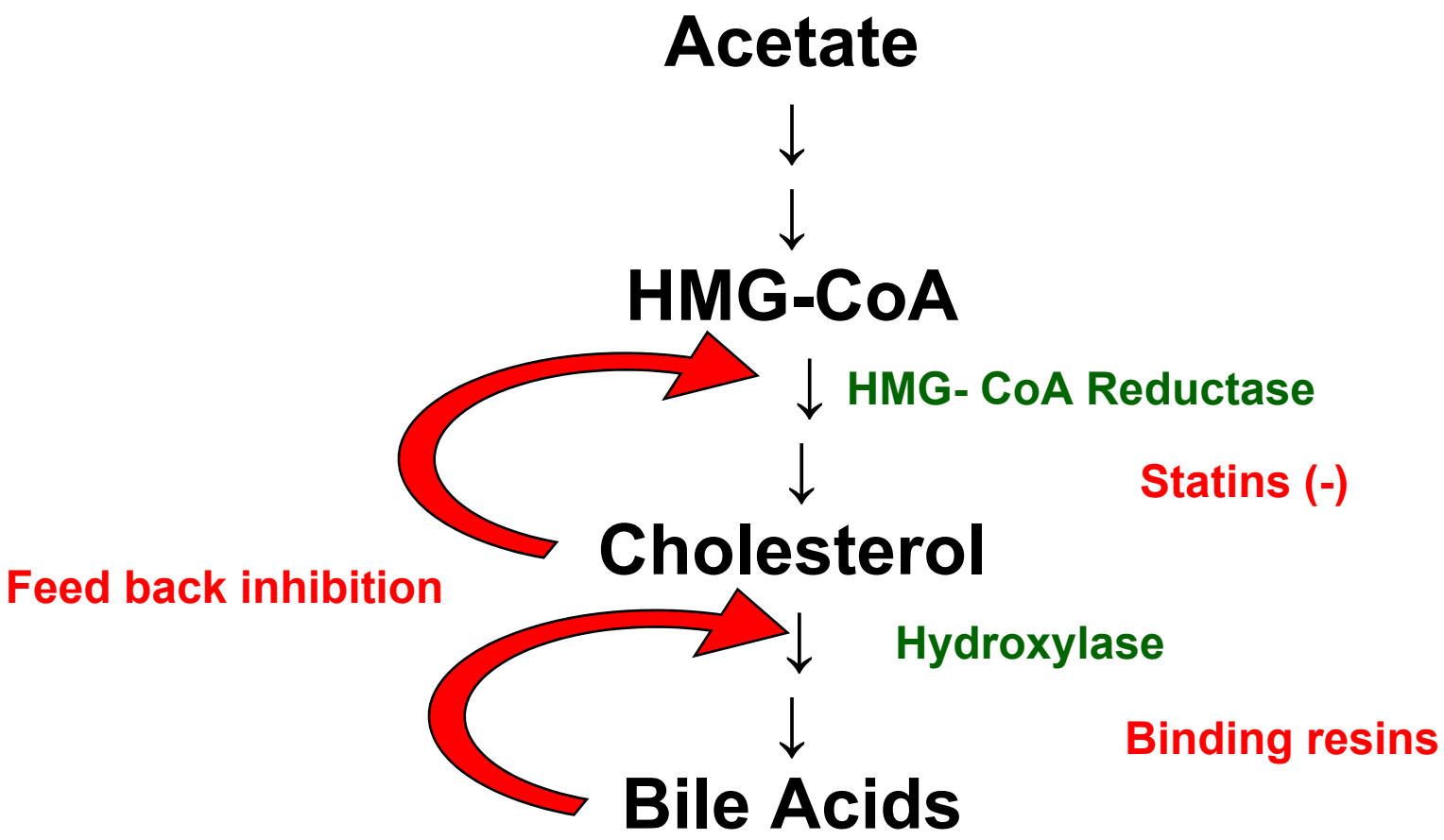
- **Normalize body weight, and exercise.**
- **Treat aggravating factors:**

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

Drugs Used in Hyperlipoproteinemias

1. Statins: lovastatin, simvastatin, atorvastatin, rosuvastatin, ..
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.

Cholesterol Metabolism



HMG-CoA Reductase Inhibitors

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

Pharmacokinetics:

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

HMG-CoA Reductase Inhibitors

- Their metabolism is inhibited by grapefruit juice, macrolide antibiotics, cyclosporine, ketoconazole some HIV protease inhibitors, tacrolimus, nefazodone, fibrates, paroxetine, venlafaxine, and others.
- Metabolism of fluvastatin and rosuvastatin, and to a lesser extent pitavastatin, is mediated by CYP2C9.

HMG-CoA Reductase Inhibitors

- Pravastatin is metabolized through other pathways, including sulfation.
- Absorption generally (with the exception of pravastatin and pitavastatin) is enhanced by food.
- $t_{1/2}$ varies from 1-3 hours for many, ~ 14 hours for atorvastatin and ~ 19 hours for rosuvastatin, and 12 hours for pitavastatin.

HMG-CoA Reductase Inhibitors

Pharmacodynamics:

- They inhibit the rate-limiting step in cholesterol biosynthesis, the 3-hydroxy- 3-glutaryl CoA reductase.
- 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.

HMG-CoA Reductase Inhibitors

- **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.**
- **They also modestly reduce triglycerides and slightly increase HDL.**

HMG-CoA Reductase Inhibitors

- **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??).**

HMG-CoA Reductase Inhibitors

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.**

HMG-CoA Reductase Inhibitors

Therapeutic Uses:

- **Useful alone or with other drugs in reducing levels of LDL.**
- **Women who are pregnant, lactating, or likely to become pregnant should not be given statins.**
- **Use in children is restricted to selected patients with familial hypercholesterolemia or familial combined hyperlipidemia.**

HMG-CoA Reductase Inhibitors

Adverse effects:

1. **Elevated CK activity.**
2. **Generalized discomfort or weakness in skeletal muscles.**
3. **Myopathy → rhabdomyolysis → myoglobinuria → renal shutdown. It is reversible upon cessation of therapy.**

- **Genetic variation in an anion transporter (OATP1B1) is associated with statin-induced severe rhabdomyolysis and myopathy.**

HMG-CoA Reductase Inhibitors

- Increases in severity if coadministered with nicotinic acid, fibrates, ketoconazole, cyclosporine, erythromycin, verapamil, cimetidine, metronidazole, amiodarone, grapefruit juice and protease inhibitors (anti HIV).
- Phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones induce CYP3A4 and can reduce the plasma levels of the 3A4-dependent reductase inhibitors, so do not increase myopathy.

HMG-CoA Reductase Inhibitors

- **Inhibitors of CYP2C9, ketoconazole, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin.**
- **Pravastatin and rosuvastatin are the statins of choice for use with verapamil, ketoconazole, macrolides, and cyclosporine.**

HMG-CoA Reductase Inhibitors

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 the upper limit of normal).

HMG-CoA Reductase Inhibitors

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 prediabetes before treatment.

HMG-CoA Reductase Inhibitors

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.
- $t_{1/2}$ ~ 1.5 hours.

Fibric Acid Derivatives

- **Fenofibrate is mainly metabolized, and metabolites are excreted in urine and feces.**
- **$t_{1/2}$ ~ 20 hours.**

Fibric Acid Derivatives

Mechanism of Action:

- **They bind to the nuclear transcription receptor, peroxisome proliferator-activated receptor-α (PPAR-α), and up-regulate 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. → →**

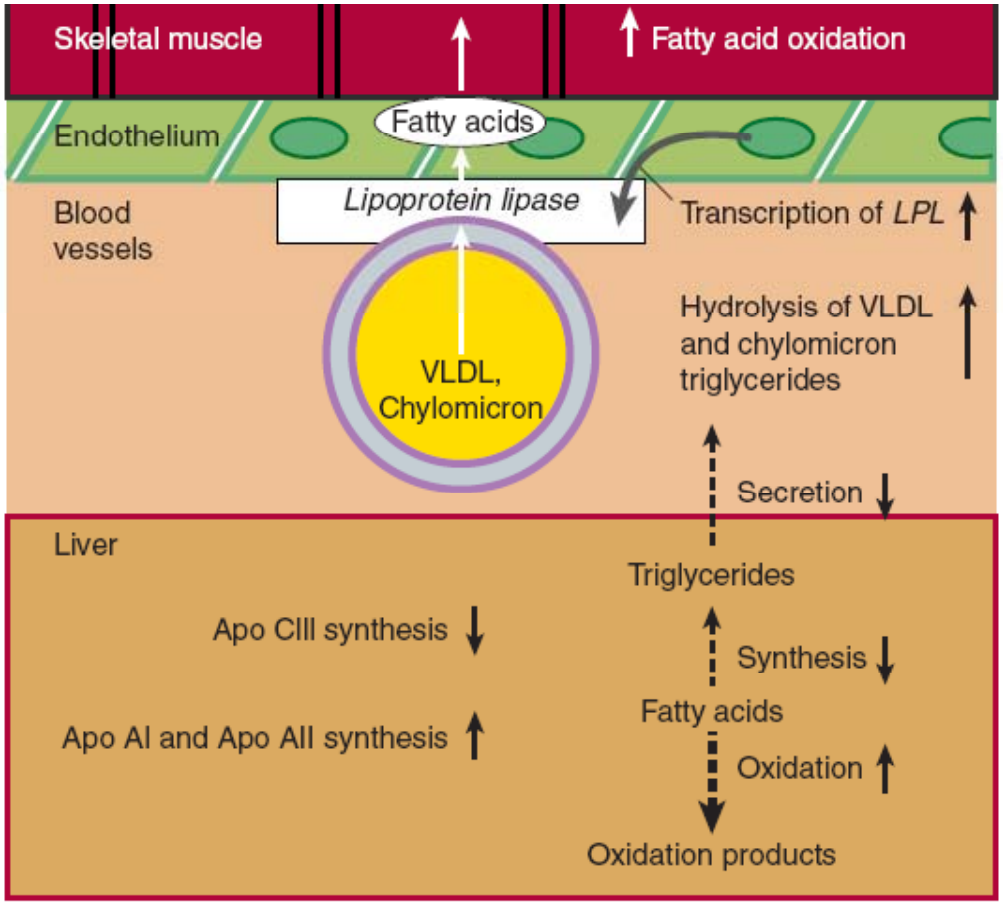


FIGURE 35–4 Hepatic and peripheral effects of fibrates. These effects are mediated by activation of peroxisome proliferator-activated receptor-α, which modulates the expression of several proteins. LPL, lipoprotein lipase; VLDL, very-low-density lipoproteins.

Fibric Acid Derivatives

- 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).

Fibric Acid Derivatives

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.**

Fibric Acid Derivatives

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 B_3)

- 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.

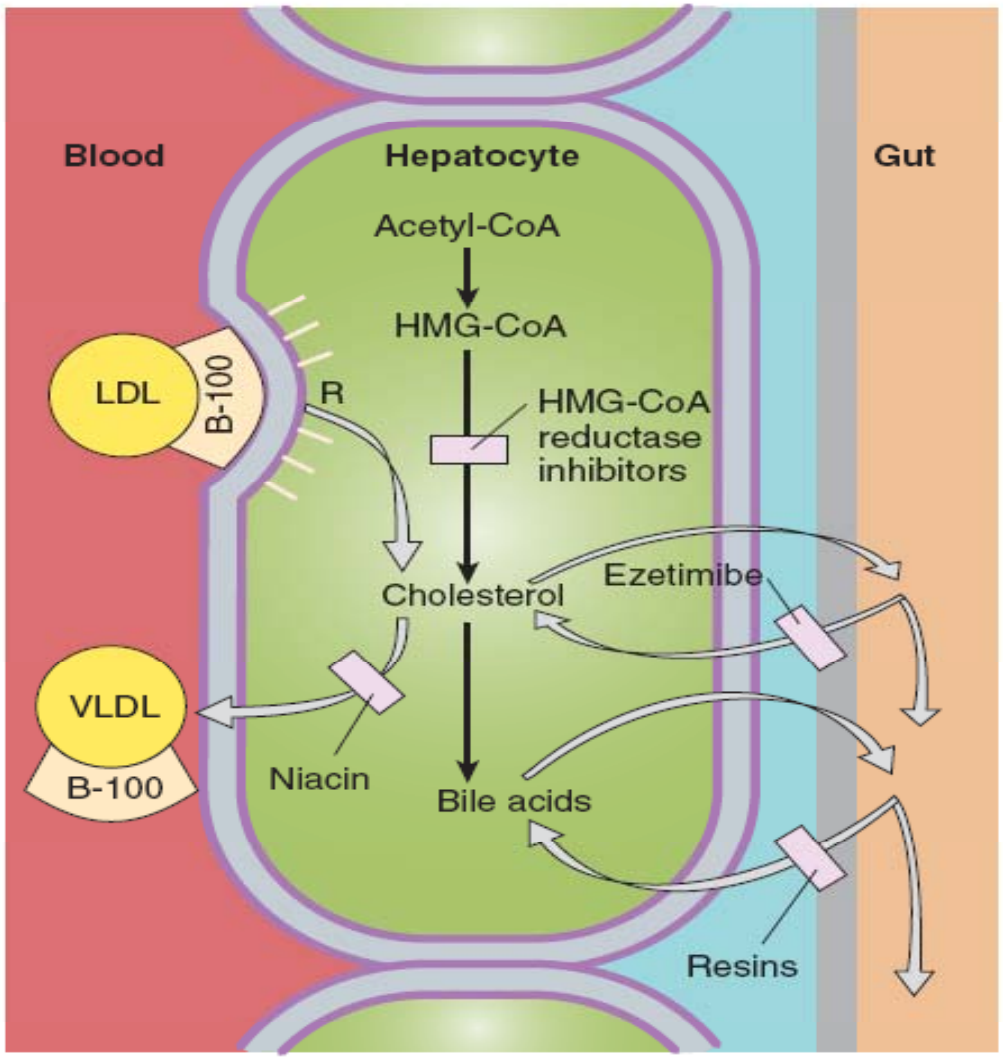


FIGURE 35–2 Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. Low-density lipoprotein (LDL) receptors are increased by treatment with resins and HMG-CoA reductase inhibitors. VLDL, very-low-density lipoproteins; R, LDL receptor.

Nicotinic Acid (Niacin, Vitamin B_3)

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.

Nicotinic Acid

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.**

Nicotinic Acid

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.

Nicotinic Acid

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.**

Bile Acid Binding Resins

- 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.

Bile Acid Binding Resins

- 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.

Bile Acid Binding Resins

- 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.

Bile Acid Binding Resins

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 <u>not</u> 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.

Ezetimibe

- It undergoes enterohepatic circulation, $t^{1}/_{2}$ ~ 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.