Therapy of Dyslipidemias

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Therapy of Dyslipidemias

- **Hypercholesterolemia, elevated low-density lipoprotein (LDL), low high-density lipoprotein (HDL) and elevated lipoprotein(a) Lp(a) are linked to increased risk for coronary heart disease, peripheral vascular disease, and cerebrovascular disease (both morbidity and mortality).**
- **Hypertriglyceridemia is associated with the development of acute pancreatitis. VLDL also increase the risk of vascular diseases.**

Therapy of Dyslipidemias

- **Initial therapy of lipoprotein disorder is life-style modification with restricted intake of total and saturated fat and cholesterol, and a modest increase in unsaturated fat intake (specially mono-unsaturated fat), in addition to regular exercise, smoking cessation and weight reduction.**

Therapy of Dyslipidemias

- **A Statin is the drugs of choice for patients with hypercholesterolemia.**
- **Patients NOT responding to statin monotherapy may be treated with combination therapy for hypercholesterolemia, but should be monitored closely because of an increased risk for adverse effects and drug interactions.**

Therapy of Dyslipidemias

- **Hypertriglyceridemia usually responds well to niacin, and fibrates (gemfibrozil, fenofibrate).**
- **Low HDL-C needs life-style modifications such as smoking cessation, and exercise; and drug therapy with niacin and fibrates which can significantly increase HDL-cholesterol.**

Therapy of Dyslipidemias

- Lp(a) is formed from LDL and apolipoprotein (a).
- It is homologous with plasminogen but is NOT activated by tissue plasminogen activator.
- Its level is variable (nil to over 2000 nM/L).
- It may be found in atherosclerotic plaques and may contribute to coronary disease by inhibiting thrombolysis.
- It can be secondarily elevated in patients with severe nephrosis and some inflammatory states.
- Niacin reduces levels of Lp(a) in many patients.

Therapy of Dyslipidemias

- **Hypertriglyceridemia (diabetes mellitus, nephrotic syndrome, and chronic renal disease) is also associated with increased cardiovascular risk.**
- **VLDL carries about 10 - 15% of serum cholesterol and most of the triglycerides in the fasting state.**
- **VLDL is a precursor for LDL, and VLDL remnants may be atherogenic.**
- **It is a risk factor for developing acute pancreatitis.**
- **Chylomicrons are triglyceride-rich particles formed from dietary fat solubilized by bile salts.**

Secondary Causes of Lipoprotein Abnormalities

A. **Hypercholesterolemia:**

1) **Hypothyroidism.**
2) **Obstructive liver disease.**
3) **Nephrotic syndrome.**
4) **Anorexia nervosa.**
5) **Acute intermittent porphyria.**
6) **Drugs: progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, sirolimus, mirtazapine (Tetra-CA).**

Secondary Causes of Lipoprotein Abnormalities

B. Hypertriglyceridemia:

1. Obesity
2. Diabetes mellitus
3. Lipodystrophy
4. Glycogen storage disease
5. Ileal bypass surgery
6. Sepsis
7. Pregnancy
8. Acute hepatitis
9. Systemic lupus erythematous
10. Monoclonal gammopathy: multiple myeloma, lymphoma.

Secondary Causes of Lipoprotein Abnormalities

12. **Drugs:** Alcohol, estrogens, isotretinoin, thiazides β-blockers, glucocorticoids, bile-acid binding resins, asparaginase, interferons, azole antifungals, bexarotene, mirtazapine, anabolic steroids, sirolimus.

C. Low HDL:

- Malnutrition, **obesity**, sedentary life-style.
- **Drugs:** non-ISA β-blockers, anabolic steroids, probucol, isotretinoin, progestins.

Therapy of Dyslipidemias

Desired Outcomes:

- **The ultimate goals of therapy are to reduce the risk of MI, angina, heart failure, ischemic stroke, and peripheral arterial disease (carotid stenosis, abdominal aortic aneurysm, ..).**

Therapy of Dyslipidemias

Nonpharmacologic Therapy:

Therapeutic life-style modification should be implemented in all patients prior to considering drug therapy:

- **Reduced intakes of saturated fats, cholesterol and total fat.**
- **The use of dietary options to reduce LDL-C such as plant phytosterols and increased soluble fiber intake, in addition to, weight reduction and increased physical activity.**

Therapy of Dyslipidemias

- **Plant phytosterols are structurally similar to cholesterol, and compete for its intestinal absorption.**
- **They also reduce bile acid absorption, thus, cholesterol is degraded into bile acids.**
- **Thus, they have an LDL-lowering effect.**

Therapy of Dyslipidemias

Food sources of phytosterols:

1) Cereals (oat, wheat, brown rice).
2) Legumes (peas, beans, lentils).
3) Nuts and Seeds (peanuts, almonds, sunflower seeds, pumpkin seeds, sesame seeds).
4) Fruits and vegetables (broccoli, cauliflower, apples, avocados, tomato, blueberries).

Therapy of Dyslipidemias

- **Physical activity of moderate intensity 30 minutes per day for most days of the week.**
- **Patients with known CAD or at high risk should be evaluated before undertaking vigorous exercise.**
- **Weight reduction should be attempted in persons who are overweight.**

Therapy of Dyslipidemias

- **Patients should stop smoking and have their hypertension controlled.**
- **Weight control plus increased physical activity raises HDL and reduces non-HDL cholesterol.**
- **Increased intake of soluble fiber in the form of oat bran, pectins, certain gums, and psyllium products can result in useful adjunctive reductions in total and LDL cholesterol.**

Drugs Used in Hyperlipoproteinemias

- **Omega-3 fatty acids found in fish oils (eicosapentaenoic acid and docosahexaenoic acid), activate peroxisome proliferator-activated receptor-alpha (PPAR-α) and can reduce triglycerides in VLDL in some patients.**
- **Fish oil causes also alterations in the synthesis of prostanoids → synthesis of vasodilator prostaglandins and inhibitors of platelet aggregation.**

Therapy of Dyslipidemias

Other effects of omega-3 fatty acids:

a) **changes in immune function and cellular proliferation.**
b) **antioxidative effects.**
c) **antiinflammatory actions.**
d) **antiarrhythmic activities.**

- **Potential complications: thrombocytopenia and bleeding disorders, especially with high doses (eicosapentaenoic acid 15 to 30 g/d).**

Therapy of Dyslipidemias

Pharmacologic Therapy:

- **Many effective lipid-lowering drugs exist, but none is useful for all lipoprotein disorders.**
- **In addition, all agents are associated with adverse effects and drug-drug interactions.**

Therapy of Dyslipidemias

Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia:

Type	Lipoprotein Elevation
I	Chylomicrons
IIa	LDL
IIb	LDL + VLDL
III	IDL
IV	VLDL
V	VLDL + Chylomicrons

Lipoprotein Phenotype and Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	--
IIa	Statins Cholestyramine or colestipol Niacin	Niacin or bile acid resins (BAR) Statins or niacin Statins or BAR **Ezetimibe** Mipomersen, lomitapide
IIb	Statins Fibrates Niacin	BAR or Fibrates or niacin Statins or niacin or BAR[a] Statins or Fibrates **Ezetimibe**
III	Fibrates Niacin	Statins or niacin Statins or Fibrates **Ezetimibe**
IV	Fibrates Niacin	Niacin Fibrates
V	Fibrates Niacin	Niacin Fish oils

[a]BAR are not used as first-line therapy if triglycerides are elevated at baseline since hypertriglyceridemia may be worsen with BAR alone.

[b]Mipomersen and lomitapide are used in combinations with other lipid lowering therapy, in particular, statins for patients with familial hypercholestermia (homozygotes or heterzygotes) and in patient who cannot be managed adequately with maximally tolerated statin therapy.

Therapy of Dyslipidemias

- **Treatment of type I hyperlipoproteinemia (↑ Chylomicrons) is directed toward reduction of chylomicrons derived from dietary fat with the subsequent reduction in plasma triglycerides.**
- **Total daily fat intake should be reduced.**
- **Look for secondary causes of hypertriglyceridemia and treat them appropriately, if present.**

Therapy of Dyslipidemias

- **Type V hyperlipoproteinemia (↑ VLDL and chylomicrons) also requires reduction of total fat intake.**
- **In addition, drug therapy (fibrates and niacin) is indicated if the response to diet alone is inadequate.**
- **Omega-3 fatty acids may be useful in lipoprotein lipase (LPL) deficiency in some patients.**

Therapy of Dyslipidemias

- **Type III hyperlipoproteinemia may be treated with fibric acid derivatives or niacin.**

Niacin (Nicotinic Acid, 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.

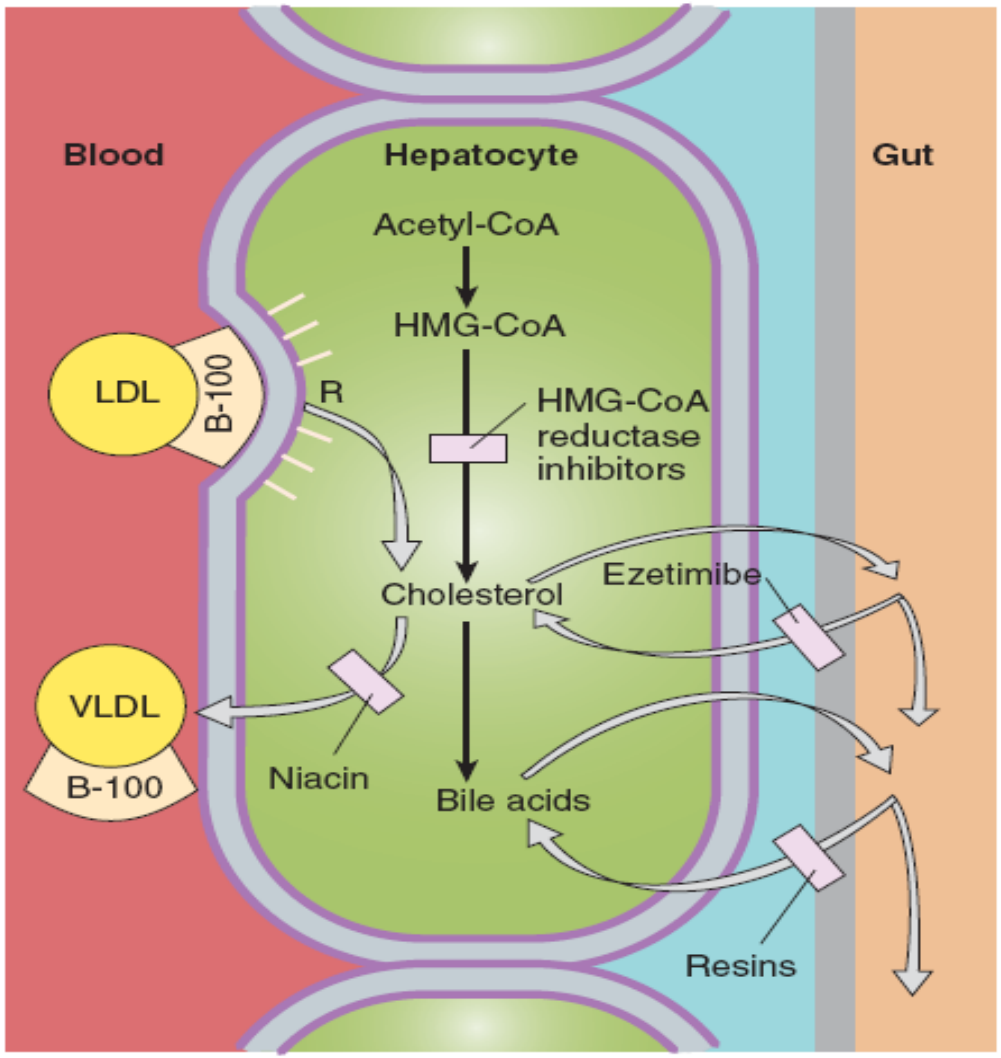


FIGURE 35–2 Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. Low-density lipoprotein (LDL) receptors are increased by treatment with resins and HMG-CoA reductase inhibitors. VLDL, very-low-density lipoproteins; R, LDL receptor.

Niacin

2. It raises HDL cholesterol by decreasing its catabolism (most effective agent).
3. It reduces the level of $LP_{(a)}$.
4. It reduces fibrinogen levels.
5. It increases tissue plasminogen activator.

Niacin

- **The principal use of niacin is for mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia.**
- **It is also considered to be the first-line agent or an alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.**
- **Used for low HDL not responsive to life-style modification.**

Niacin

Adverse reactions:

1. **Cutaneous flushing and itching: prostaglandin-mediated and can be reduced by aspirin 325 mg given shortly before niacin ingestion.**
- **Laropiprant is a selective antagonist of the prostaglandin D receptor subtype 1 (DP1), which may mediate niacin-induced vasodilation, can be co-administred with extended-release (ER) niacin to lower flushing symptoms.**
2. **Acanthosis nigricans, darkening of the skin in skin-folds. (external marker of insulin resistance).**

Niacin

3. **Elevation liver function tests (more common with sustained-release preparations). It is contraindicated in patients with active liver disease.**
4. **Hyperuricemia, and hyperglycemia.**

- **Preexisting gout and diabetes may be exacerbated by niacin.**

5. **Increases risk of myopathy when given with statins.**

- **Concomitant alcohol and hot drinks may magnify flushing and pruritus with niacin and they should be avoided at the time of ingestion.**

Fibric Acid Derivatives

Mechanism of Action:

- They bind to the nuclear transcription factor 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.

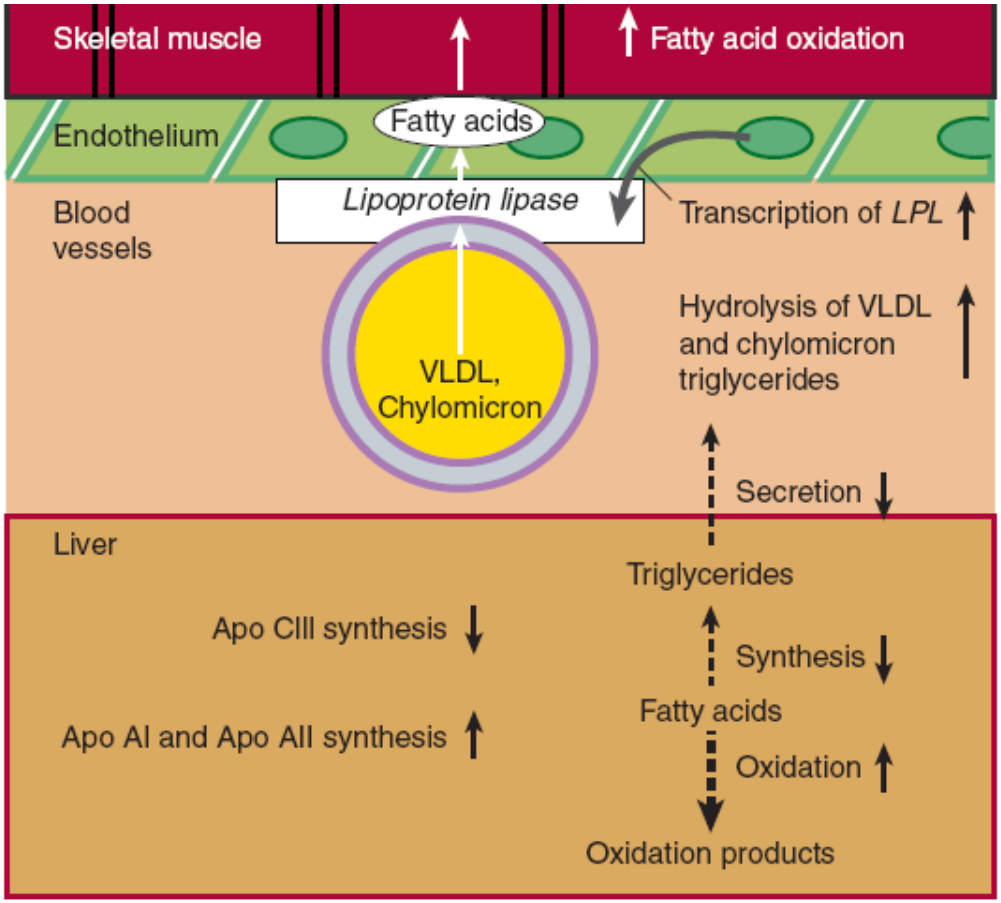


FIGURE 35–4 Hepatic and peripheral effects of fibrates. These effects are mediated by activation of peroxisome proliferator-activated receptor-α, which modulates the expression of several proteins. LPL, lipoprotein lipase; VLDL, very-low-density lipoproteins.

Fibric Acid Derivatives

- **A major effect is an increase in oxidation of fatty acids in liver and striated muscle. → →**

1. **Reduction of VLDL.**
2. **Modest decrease in LDL.**
3. **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.**
4. **They may increase LDL in patients with hypertriglyceridemia as triglycerides are reduced.**

Fibric Acid Derivatives

Adverse effects:

1. **Gastrointestinal symptoms.**
2. **Skin rash.**
3. **Gallstones due to an increase in the lithogenicity of bile.**
4. **May potentiate the effects of oral anticoagulants and the (INR) should be monitored with this combination.**
5. **Reduce platelet activity→ potentiate actions of anticoagulants.**

Fibric Acid Derivatives

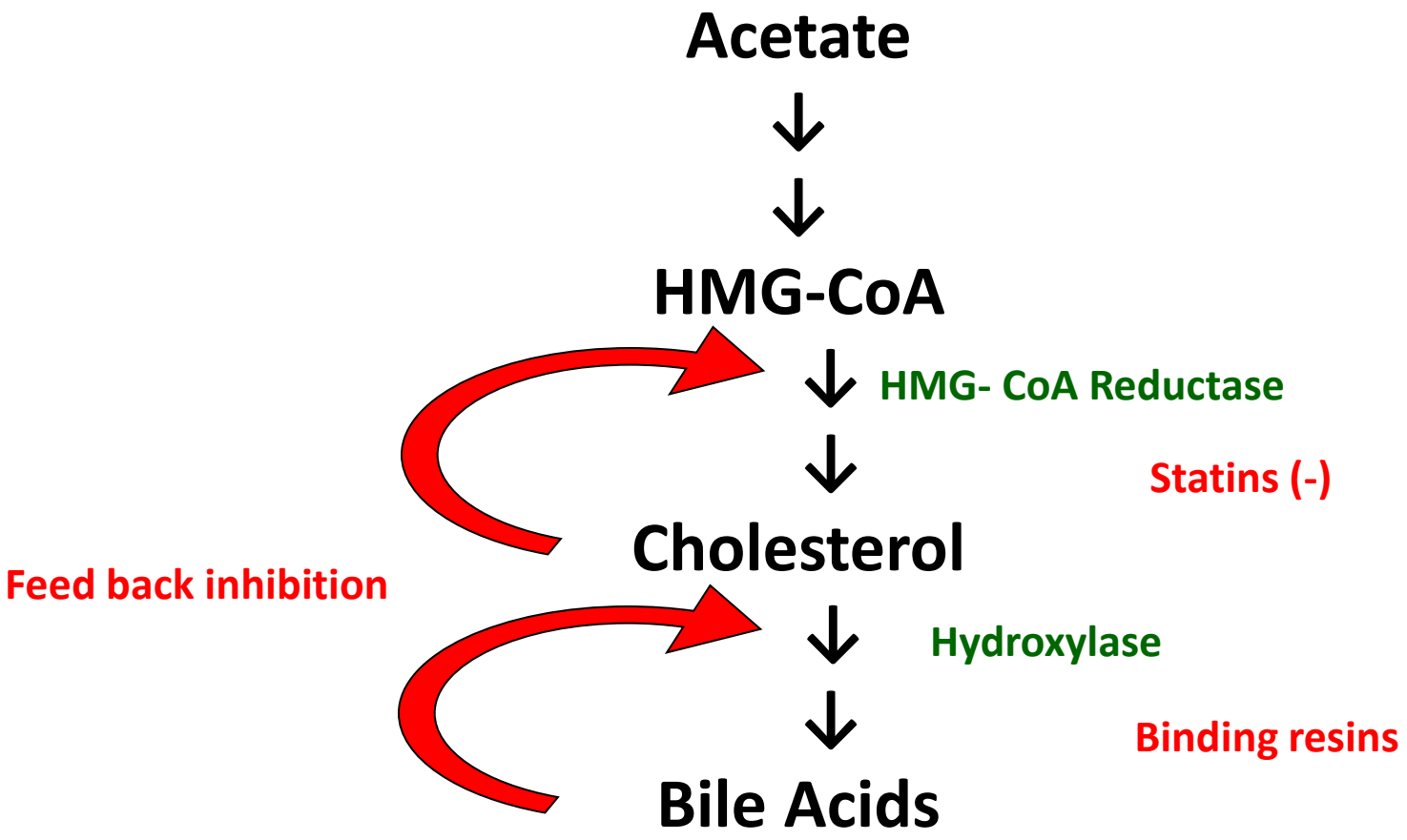
5. **A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatine phosphokinase, especially in patients with renal insufficiency.**
6. **Hypokalemia and cardiac arrhythmias.**
7. **Elevation of liver enzymes (aminotransferases and alkaline phosphatase).**
8. **Reduce WBCs and hematocrit.**

- **Avoid in hepatic or renal dysfunction.**

Therapy of Dyslipidemias

- **Primary hypercholesterolemia (familial hypercholesterolemia, familial combined hyperlipidemia, and type IIa hyperlipoproteinemia) may be treated with bile acid resins (colestipol, cholestyramine, & colesevelam), HMG Co-A reductase inhibitors (statins), niacin or ezetimibe.**
- **Of these, statins are the first choice.**

Cholesterol Metabolism



Statins (HMG-CoA reductase inhibitors)

- **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 LDL precursors (VLDL remnants) from the blood, thus reducing LDL.**

Statins (HMG-CoA reductase inhibitors)

Other actions:

a) reduce oxidative stress.
b) reduce vascular inflammation.
c) stabilize atherosclerotic lesions.
d) improve the microcirculation.
e) inhibit proliferation of arterial wall smooth muscle and improve endothelial cell function.

Statins (HMG-CoA reductase inhibitors)

- **Available products include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, and pitvastatin.**

Statins (HMG-CoA reductase inhibitors)

- **Combination therapy with bile acid sequestrants and statins is rational as LDL receptor numbers are increased, leading to greater degradation of LDL-C; inhibition of intracellular synthesis of cholesterol, and interruption of the enterohepatic recycling of bile acids.**
- **Combination therapy with a statin plus ezetimibe is also rational since ezetimibe inhibits cholesterol absorption through the gut.**

Statins (HMG-CoA reductase inhibitors)

Adverse effects:

1. **Elevation of serum alanine aminotransferase.**
2. **Serious muscle toxicity (myopathy), elevated serum CK, rhabdomyolysis , myoglobinuria , renal shutdown.**
3. **Teratogenicity: contraindicated in pregnancy (and lactation).**

Statins (HMG-CoA reductase inhibitors)

Drug interactions:

- **Myopathy increases in severity if coadministered with nicotinic acid, fibrates, ketoconazole, cyclosporine, erythromycin, verapamil, cimetidine, metronidazole, amiodarone, grapefruit juice and protease inhibitors (anti HIV).**

Bile Acid Binding Resins

- **Include cholestyramine, colestipol, and colesevelam.**
- **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 combined hyperlipidemia (hypertriglyceridemia and hypercholesterolemia), VLDL may be increased during treatment with the resins.**
- **Thus, they are useful only for isolated increases in LDL.**

Bile Acid Binding Resins

Adverse effects:

1. **Gastrointestinal complaints of gritty taste, constipation, bloating, epigastric fullness, nausea, and flatulence, GIT obstruction.**
- **Patients may discontinue therapy because of these adverse effects.**
2. **Impaired absorption of fat-soluble vitamins A, D, E, and K.**
3. **Hypernatremia and Hyperchloremic metabolic acidosis.**

Bile Acid Binding Resins

Drug interaction:

- **Reduced bioavailability of many drugs such as coumarin anticoagulants, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron, ….**
- **Drug interactions may be avoided by spacing administration by 6 hours between the bile acid resin and other drugs.**

Bile Acid Binding Resins

- **Both the statins and the resins are NOT effective in patients lacking LDL receptors. (familial homozygous hypercholesterolemia).**
- **Severe forms of hypercholesterolemia (familial hypercholesterolemia, familial defective apolipoprotein B-100, severe polygenic hypercholesterolemia, familial combined hyperlipidemia, and familial dysbetalipoproteinemia (type III) may require more intensive combination therapy.**

Inhibitors of Intestinal Sterol Absorption

Ezetimibe:

- **It inhibits intestinal cholesterol and phytosterol absorption → reduces LDL.**
- **It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in bile.**
- **It could be used in combination therapy in Type IIb, synergistic with statins. [unlike BARs]**
- **Plasma concentration is increased when coadministered with fibrates and reduced when given with the resins.**
- **May produce reversible hepatic impairment.**
- **Myositis is rare.**

Therapy of Dyslipidemias

- **Combined hyperlipoproteinemia (type IIb) may be treated with statins, niacin, or gemfibrozil combinations to lower LDL cholesterol without elevating VLDL and triglycerides.**
- **Bile acid resins monotherapy may elevate VLDL and triglycerides, and should be avoided.**
- **Fibric acid (gemfibrozil, fenofibrate) monotherapy is effective in reducing VLDL, but may increase LDL.**

Therapy of Dyslipidemias

Low HDL Cholesterol (< 40 mg/dL ???):

- **It may be a consequence of insulin resistance, physical inactivity, type 2 diabetes, cigarette smoking, very high carbohydrate intake, and certain drugs (non-ISA beta blockers, anabolic steroids, probucol, isotretinoin, progestins).**
- **Weight reduction, increased physical activity, and smoking cessation should be emphasized.**
- **Niacin or fibric acid derivatives are the drugs of choice.**

Therapy of Dyslipidemias

Hypertriglyceridemia:

- **It is important to remember that lipoprotein pattern types I, III, IV, and V are associated with hypertriglyceridemia.**
- **High serum triglycerides should be treated by achieving desirable body weight, consumption of a low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol.**

Therapy of Dyslipidemias

Diabetic Dyslipidemia:

- **Diabetic dyslipidemia is characterized by hypertriglyceridemia, low HDL, and minimal elevation of LDL.**
- **Most patients will require therapeutic life-style modification and drug therapy.**
- **When LDL-C is high, intensify glycemic control and add fibric acid derivatives or niacin, and intensify LDL-C-lowering therapy using statins.**

Therapy of Dyslipidemias, Special Considerations

The Elderly:

- **Changes in body composition, renal function, and other physiologic changes of aging may make older patients more susceptible to adverse effects of lipid-lowering drug therapy.**
- **They are more likely to have constipation (bile acid resins), skin and eye changes (niacin), gout (niacin), gallstones (fibric acid derivatives), and bone/joint disorders (fibric acid derivatives, statins).**
- **Therapy should be started with lower doses and titrated up slowly to minimize adverse effects.**

Therapy of Dyslipidemias, Special Considerations

Women:

- **HDL may be a more important predictor of disease in women.**
- **Cholesterol and triglyceride levels rise progressively throughout pregnancy.**
- **Drug therapy is NOT instituted and it should NOT be continued during pregnancy.**
- **Dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet.**
- **If their is a very high risk, a bile acid resin may considered.**
- **Statins are category X and are contraindicated.**
- **Ezetimibe might be an alternative (Category C drug).**

Therapy of Dyslipidemias, Special Considerations

Children:

- **Drug therapy in children is NOT recommended until the age of 8 years or older.**
- **Younger children are generally managed with therapeutic life-style changes until after the age of 2 years.**
- **Statins may be safe and are effective in children.**
- **Severe forms of hypercholesterolemia (familial hypercholesterolemia) may require more aggressive treatment.**

Mipomersen

- It is an antisense oligonucleotide that specifically binds to the apolipoprotein B-100 mRNA, blocking translation of the gene product.
- The reduction in production of apo B-100 results in reduced hepatic production of the atherogenic lipoproteins VLDL, IDL, LDL, and lipoprotein(a).
- It is indicated in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other lipid-lowering medications.
- It is hepatotoxic (hepatic steatosis), and its use is restricted.

Lomitapide

- **Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), which is responsible for absorbing dietary lipids and transferring triglycerides onto apolipoprotein B (apo-B) in the assembly of VLDL.**
- **Thus, transfer of lipid to apo-B is blocked, leading to apo-B destruction and inhibition of lipoprotein secretion.**
- **It also inhibits CYP3A4 and P-Glycoprotein.**
- **It is used for familial hypercholesterolemia.**

Adverse effects:

- **Elevation of serum aminotransferase.**
- **Increased hepatic fat (steatohepatitis) and hepatic fibrosis.**

Alirocumab

- **PCSK9 binds to LDLRs on hepatocytes → LDLR degradation, thus, elevating LDL-C blood levels.**
- **Alirocumab inhibits the binding of PCSK9 to LDLR → reduces LDL-C levels.**
- **Given by SC injection.**
- **Used as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia.**
- **Evolocumab is similar.**

Classification of Total-, LDL-, HDL-Cholesterol and Triglycerides in Adults

Total Cholesterol	
<200 mg/dL	Desirable
200-239 mg/dL	Borderline high
≥240 mg/dL	High
LDL Cholesterol	
<100 mg/dL	Optimal
100-129 mg/dL	Near or above optimal
130-159 mg/dL	Borderline high
160-189 mg/dL	High
≥190 mg/dL	Very high
HDL Cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High
Triglycerides	
<150 mg/dL	Normal
150-199 mg/dL	Borderline high
200-499 mg/dL	High
≥500 mg/dL	Very high

Cut Points for Total Cholesterol and LDL Concentrations in Children and Adolescents:

Category	Total Cholesterol, mg/dL	LDL Cholesterol, mg/dL
Acceptable	<170	<110
Borderline	170-199	110-129
Elevated	>200	>130

Lipoprotein Disorders

Disorder	Lipoproteins		Clinical signs
	Elevated	Phenotype	
Isolated Hypercholesterolemia			
Familial hypercholesterolemia (Hetero- and homo-zygous)	LDL	IIa	Usually develop xanthomas in adulthood and vascular disease at 30-50 years
Familial defective apo B100	LDL	IIa	
Polygenic hypercholesterolemia	LDL	IIa	Usually asymptomatic until vascular disease develops; no xanthomas

Isolated Hypertriglyceridemia			
Familial hypertriglyceridemia	VLDL	IV	Asymptomatic; maybe associated with increased risk of vascular disease
Familial LPL* deficiency	Chylomicrons, VLDL	I, V	May be asymptomatic; may be associated with pancreatitits, abdominal pain, hepatosplenomegaly
Familial apo CII deficiency	Chylomicrons, VLDL	I, V	May be asymptomatic; may be associated with pancreatitits, abdominal pain, hepatosplenomegaly

*LPL, lipoprotein lipase.

Hypertriglyceridemia and Hypercholesterolemia			
Combined hyperlipidemia	VLDL, LDL	IIb	Usually asymptomatic until vascular disease develops; familial form may also present as isolated high TG or an isolated high LDL cholesterol
Dysbetalipoproteinemia	VLDL, IDL; LDL normal	III	Usually asymptomatic until vascular disease develops; may have palmar or tuboeruptive xanthomas

Effects of Drug Therapy on Lipids and Lipoproteins

Drugs	Mechanism of action	Effects on lipids	Effects on Lipoproteins	Comments
Cholestyramine, colestipol and colesevelam	↑ LDL catabolism ↓ Cholesterol absorption	↓ Cholesterol	↓ LDL ↑ VLDL	Problem with compliance; binds many co-administered acidic drugs
Niacin	↓ LDL and VLDL ↓ synthesis	↓ Triglyceride And ↓ cholesterol	↓ VLDL, ↓ LDL, ↑ HDL	Problems with patient acceptance; good in combination with bile acid resins; extended release niacin causes less flushing and is less hepatotoxic than sustained release

Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride and cholesterol	↓ VLDL, ↓LDL, ↑ HDL	Clofibrate causes cholesterol gall stones; modest LDL-lowering; raises HDL; gemfibrozil inhibits glucuronidation of simvastatin, lovastatin and atorvastatin
Lovastatin, Pravastatin, Simvastatin, Fluvastatin, Atorvastatin Rosuvastatin	↑ LDL catabolism; inhibit LDL synthesis	↓ Cholesterol	↓ LDL	Highly effective in heterozygous familial hypercholesterolemia and in combination with other agents

Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	↓ LDL	Few adverse effects; effects additive to other drugs
Mipomerson	Inhibitor of Apolipoprotein B-100	↓ Cholesterol	↓ LDL, non-HDL	Increase in transaminases, risk of hepatosteatosis and hepatotoxicity; must be given by SQ injection. Only indicated for familial hypercholesterolemia. To be used along with other lipid lowering therapies (statins)

Lomitapide	Microsomal triglyceride transfer protein inhibitor	↓ Cholesterol	↓ LDL, non-HDL	Hepatotoxicity must be monitored. Only indicated for familial hypercholesterolemia. To be used along with other lipid lowering therapies (statins)
Alirocumab, Evolocumab	PCSK9 inhibitor	↓ Cholesterol, ↓ Lpa	↓Cholesterol and LDL	Given by SQ injection, injection site pain, low risk of hepatoxicity