Antihyperlipidemic drugs

- The clinically important lipoproteins are

  LDL low density lipoprotein, VLDL very low density lipoprotein, HDL high density lipoprotein.

- Hyperlipidemia may caused

  1. by individual lifestyle (lack of exercise and high consumption of fatty acid).

  2. single inherited gene defect in lipoprotein metabolism 3. more commonly, combination of genetics and lifestyle factors.

- The incidence of the heart failure is correlated with elevated levels of low density lipoproteins (LDL) cholesterol, and triglycerides with low level of high-density lipoprotein cholesterol (HDL).

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- Antihyperlipidimic drugs must be taken indefinitely, when terminated plasma levels return to pretreatments levels.

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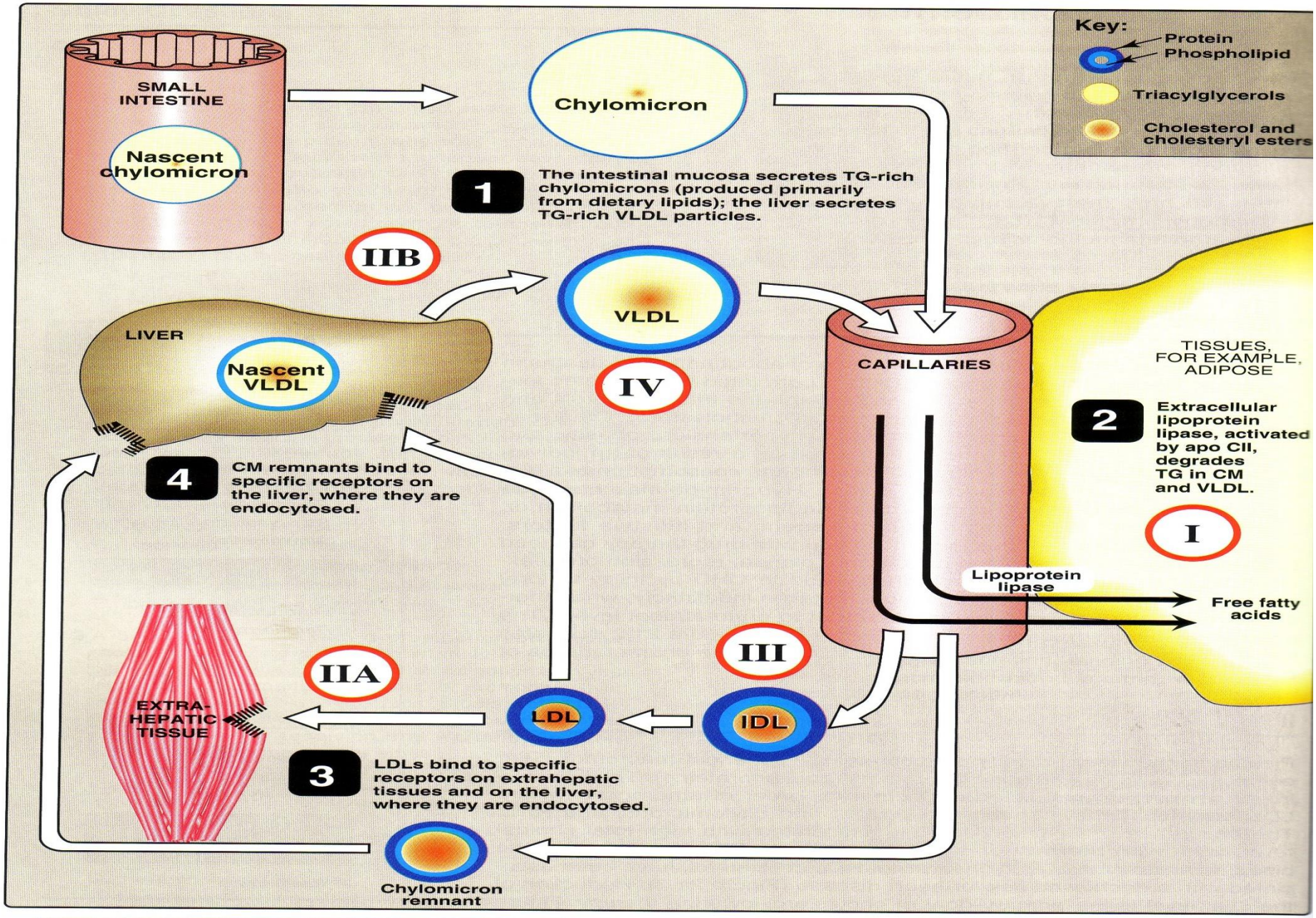


Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. The Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM=chylomicron, TG = triacylglycerol; VLDL=very-low density lipoprotein, LDL=low-density lipoprotein, IDL=intermediate-density lipoprotein, apo CII= apolipoprotein CII found in chylomicrons and VLDL.

Hyperlipoproteinemia		Labs description
Type I	Familial hyperchylomicronemia	Elevated Chylomicrons and VLDL
Type IIa	Familial hypercholesterolemia	Elevated LDL only
Type IIb	Combined hyperlipidemia	Elevated LDL and VLDL and Triglycerides
Type III	Familial Dysbetalipoproteinemia	Increased IDL
Type IV	Familial Hyperlipemia	Increased VLDL
Type V	Endogenous Hypertriglyceridemia	Increased VLDL and Chylomicrons

Statins

These agents include **Lovastatin, pravastatin, simvastatin, fluvastatin, Atorvastatin, rosuvastatin**

Cerivastatin

- Mechanism of action

(1) They are 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA) inhibitors.

This enzyme facilitate rate-limiting-step in the cholesterol synthesis and inhibiting this step will stop cholesterol synthesis.

(2) Increase in LDL receptors: Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus the end result is a reduction in plasma cholesterol.

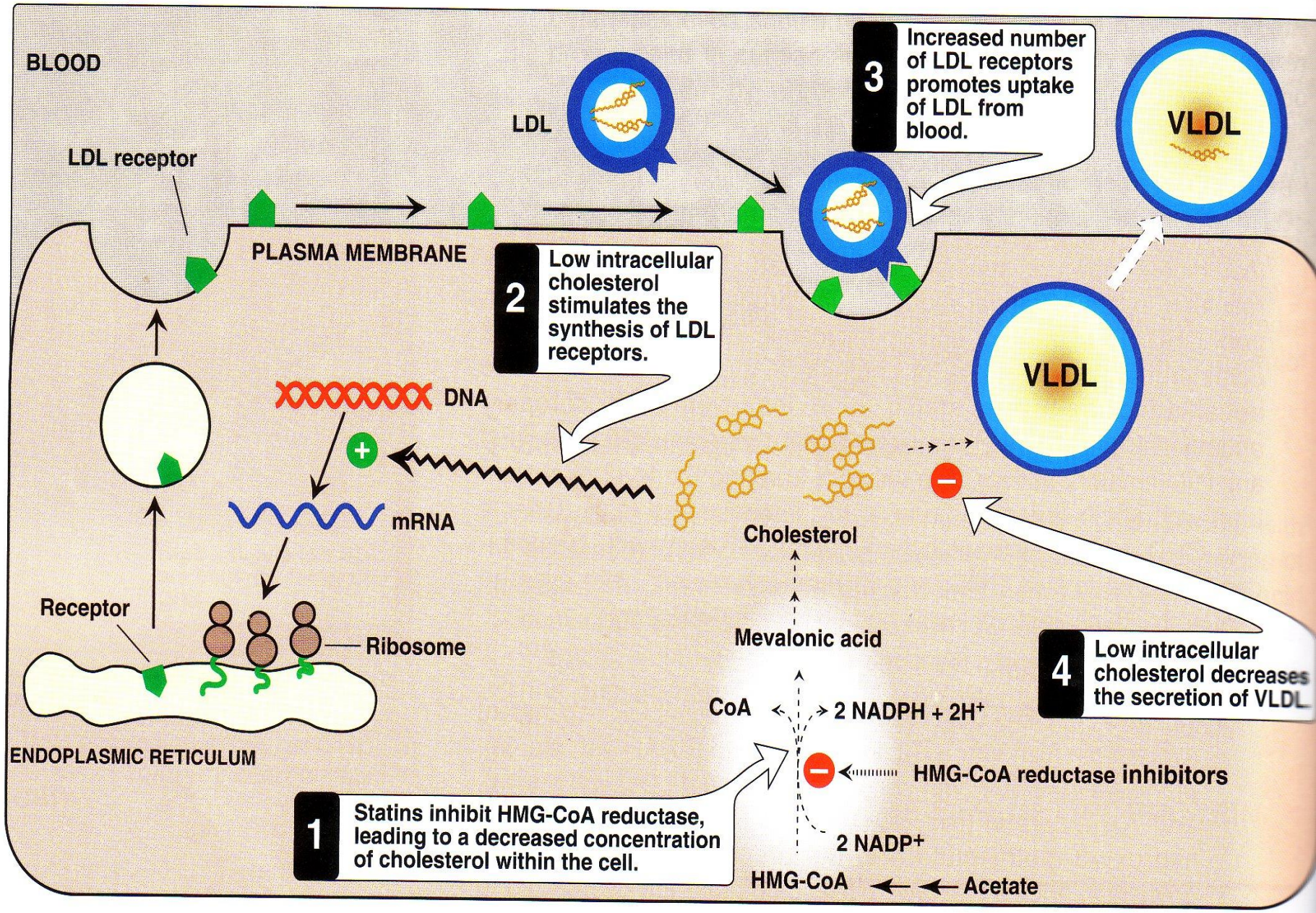


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG-CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Figure 21.14
Characteristics of hyperlipidemic drug families. HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl–coenzyme A; LDL = low-density lipoprotein.

Statins

- **Side effects:**

-Biochemical abnormalities in liver function (evaluate liver function is needed)

-Myopathy and rhabdomyolysis (disintegration or dissolution of muscle).

- **These agents are contraindicated during pregnancy and in nursing mothers. They also should not be used in children and teenagers.**

Statins interaction

- **the catabolism of lovastatin, simvastatin, and atorvastatin proceeds chiefly through CYP3A4,**
- **whereas that of fluvastatin and rosuvastatin is mediated by CYP2C9.**
- **Pravastatin is catabolized through other pathways, including sulfation.**
- **Concomitant use of reductase inhibitors with amiodarone or verapamil also causes an increased risk of myopathy.**
-

- The 3A4-dependent reductase inhibitors include the macrolide antibiotics, cyclosporine, ketoconazole and its congeners, HIVprotease inhibitors, tacrolimus, nefazodone, fibrates, and others.

- Conversely, drugs such as phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones increase expression of CYP3A4 and can reduce the plasma concentrations of the 3A4-dependent reductase inhibitors.

- Inhibitors of CYP2C9 such as ketoconazole and its congeners, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin.

- Plasma levels of lovastatin, simvastatin, and atorvastatin may be elevated in patients ingesting more than 1 liter of grapefruit juice daily.

Niacin (vitamin B_3)

Mechanism of Action: strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids,

both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered

- **Niacin is the most effective agent in increase the HDL (the good cholesterol carrier).**

- **it is used in type IIb and IV hyperlipoproteinemia, in which both VLDL and LDL are elevated. Also to treat other severe hypercholestrolemias**

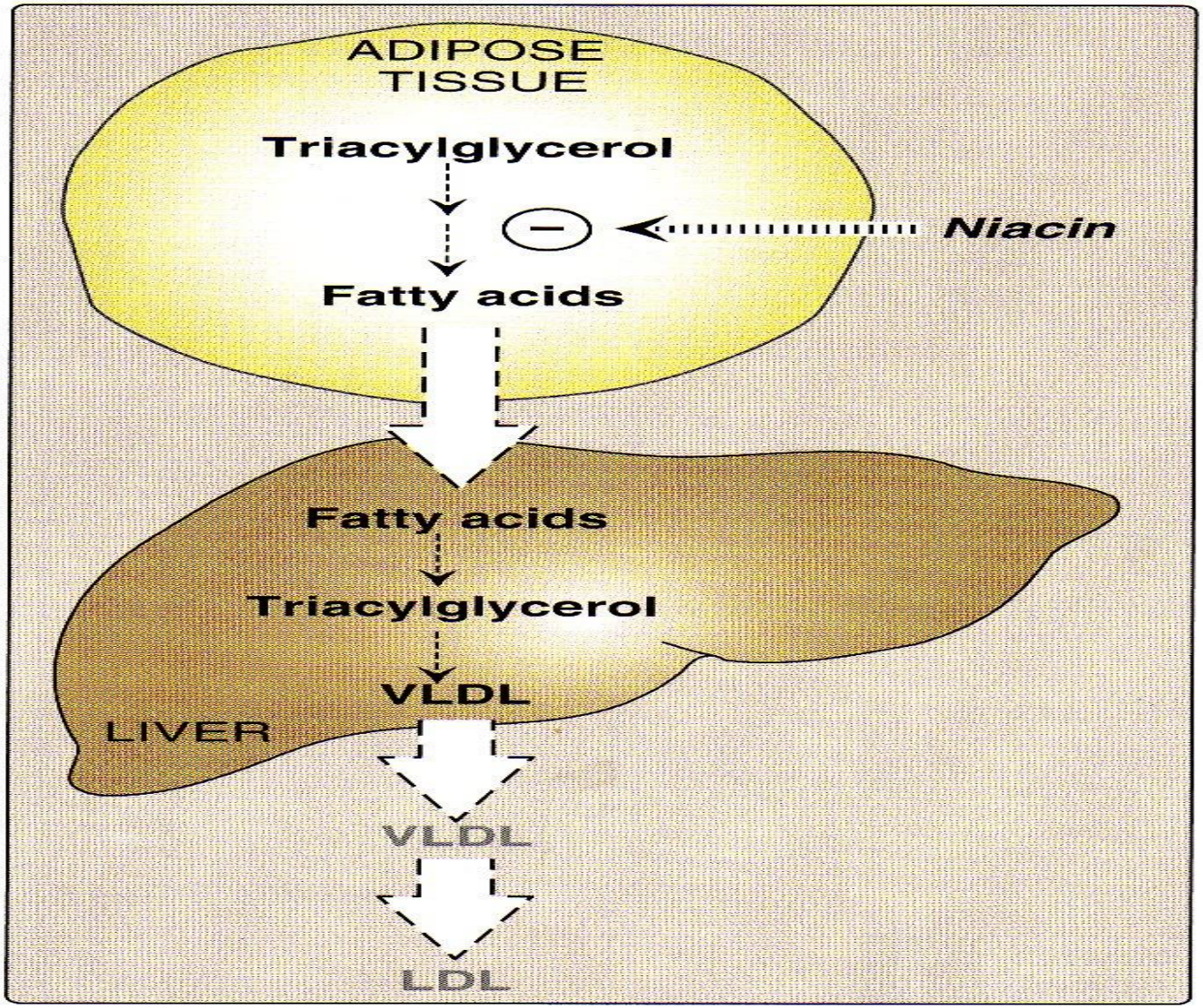


Figure 21.9
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.

Niacin

- **Adverse effects: Cutaneous flushing, burning and itching, GI irritation, nausea and vomiting.**

- **Peptic ulcer activation, elevation of liver enzymes, hyperglycemia and hyperuricemia.**

Fibrates

- **Fenofibrate and Gemfibrozil, Bezafibrate are derivatives of fibric acid lower serum level of LDL cholesterol, triglyceride and increase the HDL.**

MOA: Peroxisome proliferator activated receptors (PPARs) are a nuclear receptors that regulate lipid metabolism.

Fibrattriacylglyceroles binding to these receptors result in reduction of concentration by increasing the expression of lipoprotien lipase.

- **They are used in the treatment of hypertriglycerolemias, and also useful in treating type III hyperlipidemia.**

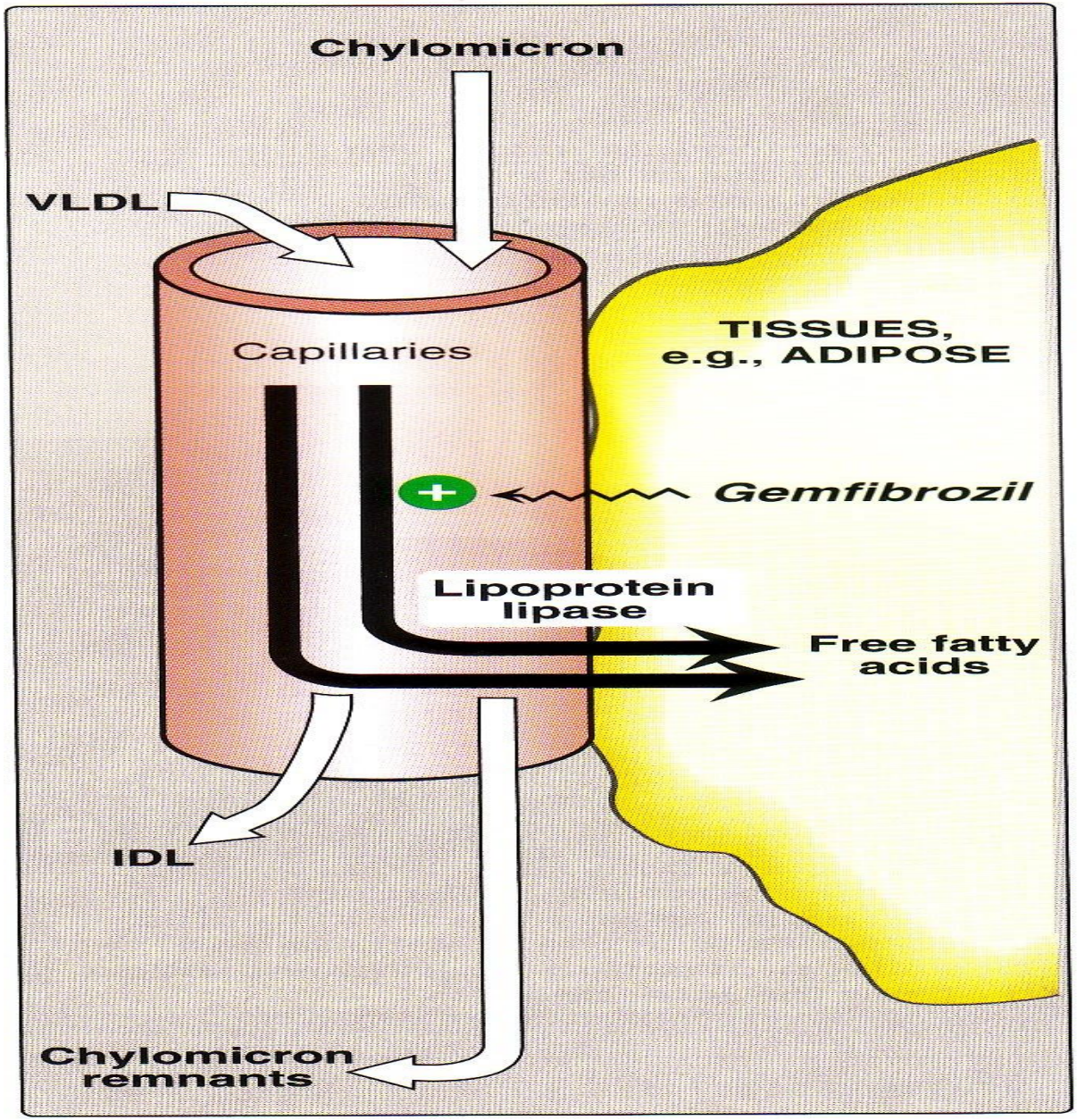


Figure 21.11
Activation of lipoprotein lipase by *gemfibrozil*.

Fibrates

Adverse effect

a. The most common adverse effects are mild gastrointestinal disturbances.

b. Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.

d. Myositis (inflammation of a voluntary muscle) can occur.

Fibrates compete with the coumarin anticoagulants for binding sites on plasma proteins.

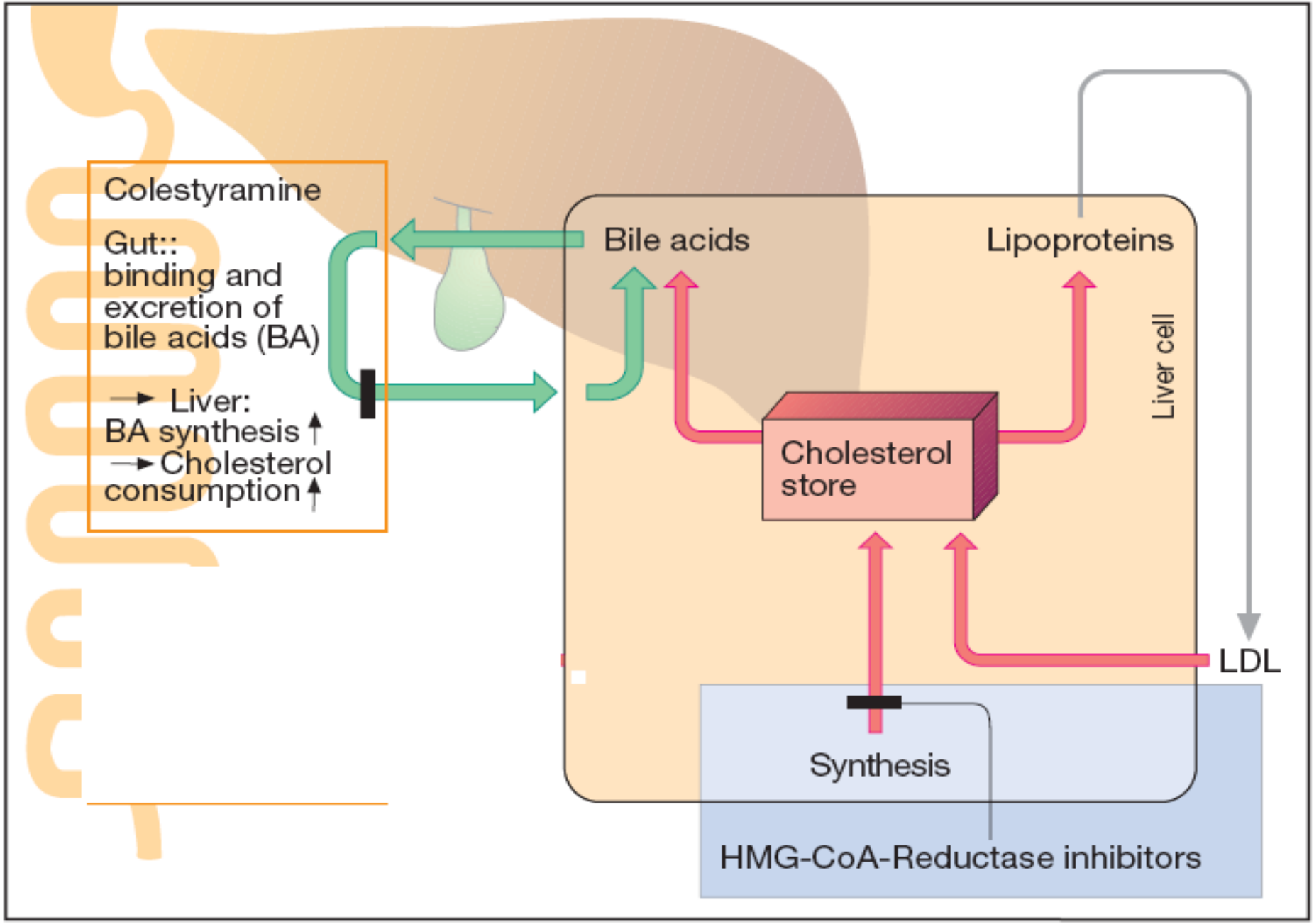
Bile acid-binding resins

- **Cholestyramine and colestipol have significant LDL cholesterol lowering effect, although the benefit is less than those observed with statins.**

- **These agents are resins that bind bile acid in the intestine, forming insoluble complexes that will excreted in the feces.**

- **Lowering bile acid level will trigger the conversion of cholesterol into bile acid and the end result will be a reduction in the cholesterol concentrations.**

Therapeutic uses: The bile acid binding resins are the drugs of choice (often in combination with diet or niacin) in treating Type lla.


Colestyramine
Gut::
binding and
excretion of
bile acids (BA)
→ Liver:
BA synthesis ↑
→ Cholesterol
consumption ↑
Bile acids
Lipoproteins
Liver cell
Cholesterol
store
LDL
Synthesis
HMG-CoA-Reductase inhibitors

Bile acid-binding resins

- **The most common side effect are gastrointestinal disturbances such as constipation and nausea.**
- **At high doses they impair the absorption of fat soluble vitamins (A,D,E, and K).**
- **These agents interact with the absorption of many drugs, for example, Tetracycline, Digoxin, Warfarin, Aspirin.**
- **Therefore, drugs should be taken at least 1 to 6 hr after.**

Cholestrole absorption inhbitors

Ezetimibe selectively inhibit intestinal absorption of dietary and biliary cholesterol in the small intestine, resulting in an increase in the clearance of cholesterol from the blood.

Common adverse are headache and/or diarrhea.

Strategy for Controlling Hyperlipidemia

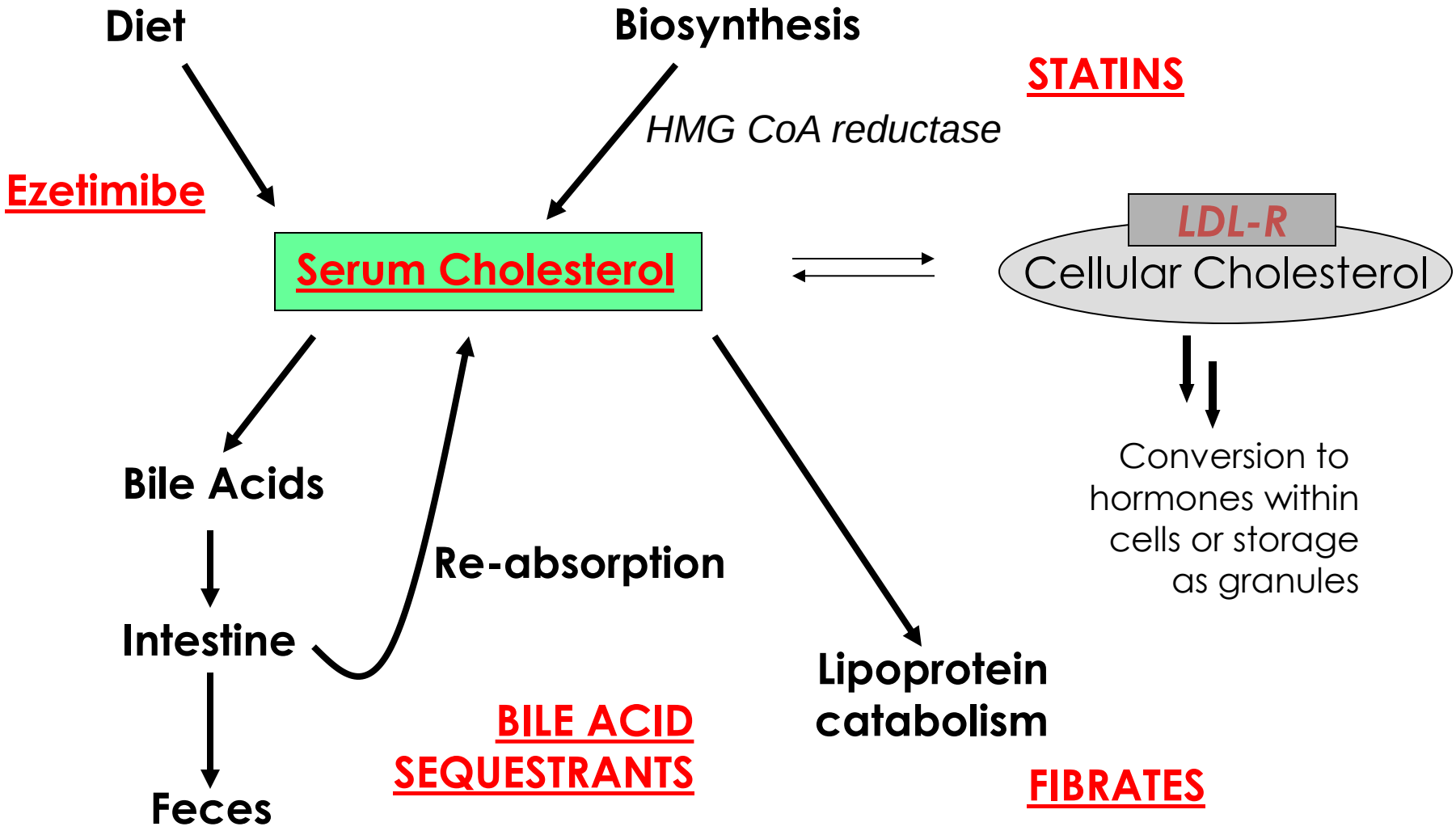


Table 35–3. Lipid-modifying effects of antihyperlipidemic drugs.*

Drug	LDL Cholesterol	HDL Cholesterol	Triglyceride
Atorvastatin	–25% to –40%	+5% to –10%	↓↓
Fluvastatin[1]	–20% to –30%	+5% to –10%	↓
Lovastatin[2]	–25% to –40%	+5% to –10%	↓
Cholestyramine, colestipol	–15% to –25%	+5%	±
Gemfibrozil	–10% to –15%	+15% to –20%	↓↓
Niacin	–15% to –40%	+25% to –35%	↓↓

*Modified, with permission, from Tierney LM, McPhee SJ, Papadakis MA (editors): *Current Medical Diagnosis & Treatment,* 40th ed. McGraw-Hill, 2001.

[1]Cerivastatin has effects similar to those of fluvastatin.

[2]Pravastatin and simvastatin have effects similar to those of lovastatin.

± = variable, if any.

Antihyperlipidemic drugs

- The clinically important lipoproteins are

  LDL low density lipoprotein, VLDL very low density lipoprotein, HDL high density lipoprotein.

- Hyperlipidemia may caused

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- The incidence of the heart failure is correlated with elevated levels of low density lipoproteins (LDL) cholesterol, and triglycerides with low level of high-density lipoprotein cholesterol (HDL).

Antihyperlipidemic drugs

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  1. decrease production of the lipoproteins carriers of cholesterol and triglyceride.

  2. others increase the degradation of lipoproteins.

  3. decrease cholesterol absorption or directly increase cholesterol removal from the body.

- These agents may used as a singly or in combination.

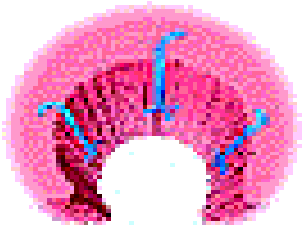
Statins

- These agents include **Lovastatin, Simvistatin, Pravastatin, and Fluvastatin.**
- They are 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA) inhibitors.
- This enzyme facilitate rate-limiting-step in the cholesterol synthesis and inhibiting this step will stop cholesterol synthesis.
- Statins reduce serum level of LDL cholesterol, VLDL cholesterol and triglycerides.
- Statins resulting in reduction in coronary events and death from Heart failure.

HMG-CoA reductase inhibition

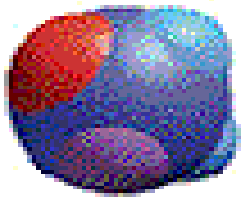
LIPITOR inhibits
HMG-CoA reductase

Reduced cholesterol synthesis

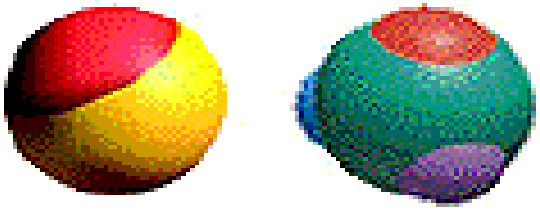


Upregulation of LDL receptors

Increased removal and catabolism of LDL



Decreased VLDL production



Conversion of VLDL to LDL

Decreased Total-C, LDL-C, and TG

Adverse effects

1. Hepatotoxicity (increased serum transaminase).
2. Myopathy (increased creatine kinase) especially when combined with:
   - other lipid lowering drugs: i)Fibrates. ii) Niacin.
3. G.I.T upset.
4. Headache.

N.B : liver transaminases and CK must be regularly measured during therapy with statins

Statins

- They do interact with Warfarin and resulting in elevation of Warfarin.

- These agents are contraindicated during pregnancy and in nursing mothers. They should not be used in children and teenagers.

Fibrates and Niacin

Preparations: Gemfibrozil , fenofibrate , clofibrate .

Mechanism of action:

Ligand for the nuclear transcription regulator, peroxisome proliferator-activated receptor-α (PPAR- α) in the liver, heart, kidney, & skeletal muscle. *N.B The PPAR-a are a class of intracellular receptors that modulate fat metabolism. It is through PPAR-a that fibrates lead to:*

- Increased LPL activity, which increases clearance of VLDL & chylomicron in plasma.

- They are used in the treatment of hypertriglycerolemias, an also useful in treating hyperlipidemia.

Adverse effects

- G.I.T upset,rash, urticaria
- Myopathy
- Since fibrates increase the cholesterol content of bile, they increase the risk for gallstones.

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Steps to Minimize the Risk of Muscle Toxicity with Fibrate–Statin Combination Therapy

- Use statin alone for non-HDL-C goals
- Use fish oils or niacin rather than fibrates
- Keep the doses of the statin and fibrate low
- Dose the fibrate in the AM and the statin in the PM
- Avoid (or cautiously use) combo in renal impairment
- Assure no interactions
- Teach the patient to recognize muscle symptoms
- Discontinue therapy if muscle symptoms are present and CK is >10 times the upper limit of normal

Niacin

- reduce the LDL and is the most effective agent in increase the HDL (the good cholesterol carrier). Can be used with statins.
- Used in the treatment of hyperlipidemia and hypertriglycerolemias.
- Niacin inhibits the lipolysis in adipose tissue, the primary producer of free fatty acid.

Pharmacological actions

- **Effect on VLDL:** Decreased VLDL by:

1) decreased synthesis in liver;
2) increased clearance in plasma.

- **Effect on LDL:** Decreased LDL due to reduction in its precursor (VLDL).

- **Effect on HDL:** Induces modest increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown).

Adverse effects

1. Pruritus, flushing The niacin flush results from the stimulation of prostaglandins D(2) and E(2). This flush is avoided by low dose aspirin 325 mg ½ h before niacin.

2. Reactivation of peptic ulcer (because it stimulates histamine release resulting in increased gastric motility and acid production .
3. Hepatotoxicity.

1. Hyperglycemia which is believed to be caused by an increase in insulin resistance.
2. Increased uric acid level(due to decreased uric acid excretion).

Contraindications

1. Gout.
2. Peptic ulcer.
3. Hepatotoxicity.
4. Diabetes mellitus.

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- These agents interact with the absorption of many drugs, for example, Tetracycline, Digoxin, Warfarin, Aspirin.
- Therefore, drugs should be taken at least one to six hr after.

Ezetimibe

Mechanism of action:

- Impairs dietary and biliary cholesterol absorption at the brush border of the intestines without affecting fat-soluble vitamins.

- Reducing the pool of cholesterol absorbed from the diet results in a reduced pool of cholesterol available to the liver.

-The liver in turn will upregulate the LDL receptor, trapping more LDL particles from the blood and result in a fall in measured LDL cholesterol .

- **CLASSIFICATION- based on the pattern of lipoprotein on electrophoresis or ltracentrifugation.**
- **Familial Chylomicronemia (I)**:increased Chylomicrons due to deficiency of lipoprotein lipase or its cofactor
- **Familial Hypercholesterolemia (IIA):** levels of LDL tend to increase with normal VLDL.
- **Familial Combined (mixed)Hyperlipidemiaa (IIB):** elevated levels of VLDL, LDL.
- **Familial Dysbetalipoproteinemia (III):** Increased IDL resulting increased TG and cholesterol levels.
- **Familial Hypertriglyceridemia (VI):** Increase VLDL production with normal or decreased LDL.
- **Familial mixed hypertriglyceridemia (V):** Serum VLDL and chvlomicrons are increased