Agents used in dyslipidemia

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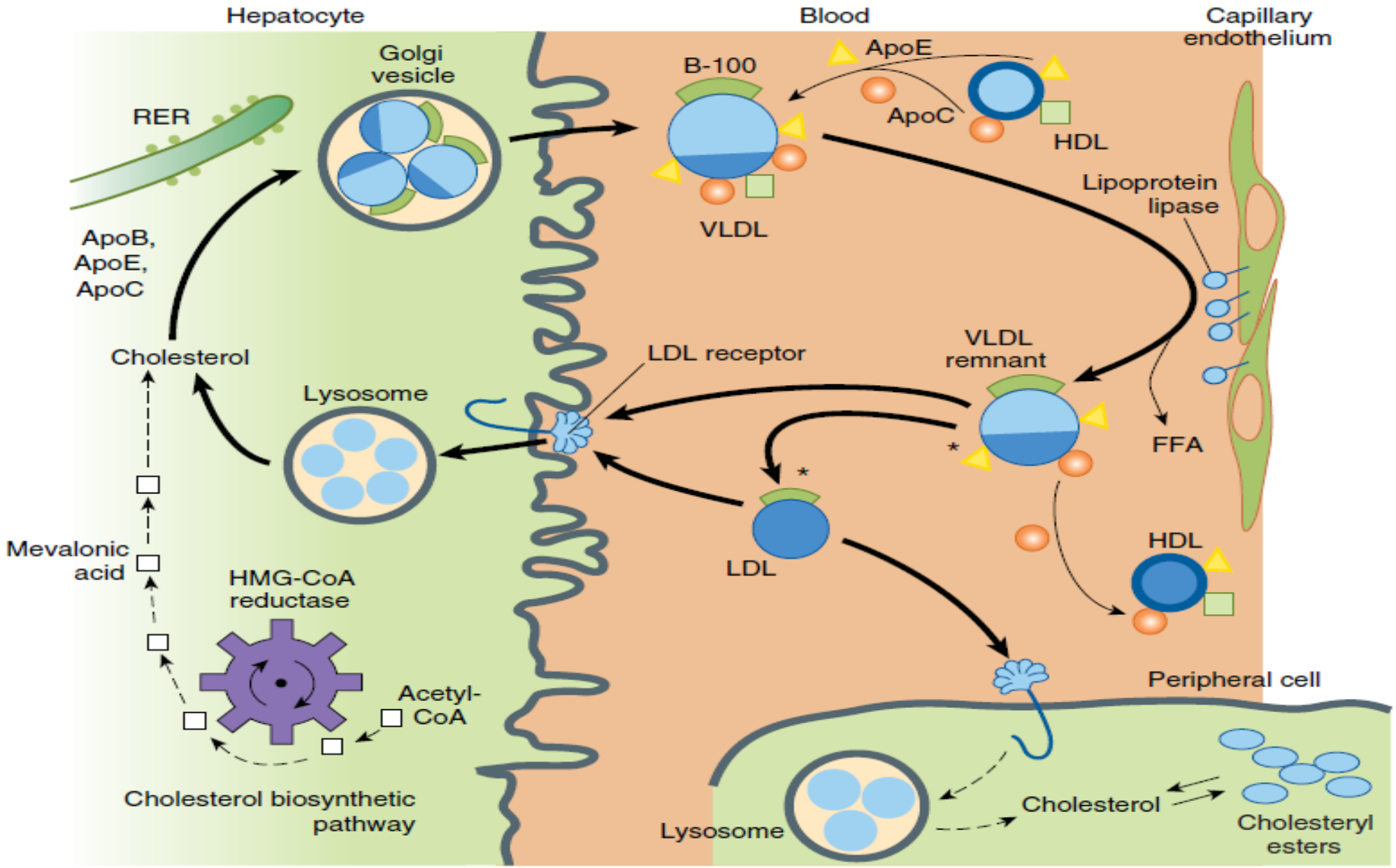
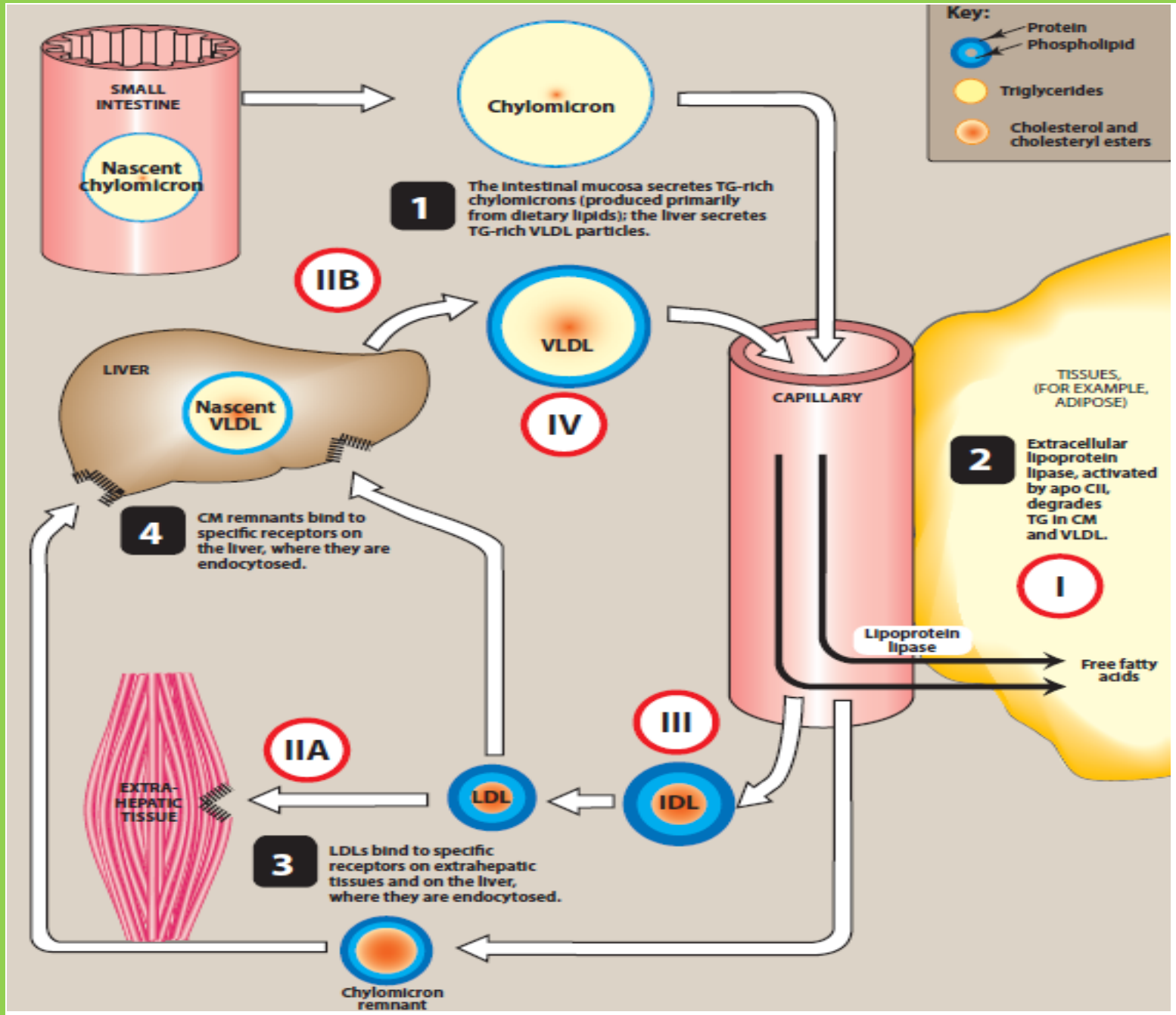
- Coronary heart disease (CHD) is the leading cause of death worldwide
- CHD is correlated with elevated levels of low-density lipoprotein cholesterol (LDL-C; "bad" cholesterol) and triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C; "good cholesterol")
- Other risk factors for CHD include cigarette smoking, hypertension, obesity, and diabetes
- Cholesterol levels may be elevated due to lifestyle factors (for example, lack of exercise or diet containing excess saturated fats).
- Hyperlipidemias can also result from an inherited defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors
- Appropriate lifestyle changes, along with drug therapy, can lead to a 30% to 40% reduction in CHD mortality
- Antihyperlipidemic drugs are often taken indefinitely to control plasma lipid levels

- Primary disturbances in regulation occur in a number of genetic conditions involving mutations in apolipoproteins, their receptors, transport mechanisms, and lipid-metabolizing enzymes
- Secondary disturbancesare associated with a Western diet, many endocrine conditions,and diseases of the liver or kidneys
- Because alcohol raises triglyceride and very-low-density lipoprotein (VLDL) levels, it should be avoided by patients with hypertriglyceridemia

TABLE 35–2 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
HIV infection	Cholestasis
Myxedema	Hypopituitarism
Glycogen storage disease	Corticosteroid excess
Hypopituitarism	Androgen overdose
Acromegaly	
Immunoglobulin-lipoprotein complex disorders	
Lipodystrophy	
Protease inhibitors, tacrolimus, sirolimus, other drugs	


Hepatocyte
Blood
Capillary endothelium
Golgi vesicle
RER
B-100
ApoE
ApoC
HDL
VLDL
Lipoprotein lipase
ApoB, ApoE, ApoC
Cholesterol
LDL receptor
VLDL remnant
Lysosome
FFA
LDL
HDL
Mevalonic acid
HMG-CoA reductase
Acetyl-CoA
Peripheral cell
Cholesterol biosynthetic pathway
Lysosome
Cholesterol
Cholesteryl esters



Metabolism of plasma lipoproteins and related genetic diseases

Roman numerals in the *white circles* refer to specific genetic types of hyperlipidemias

CM = chylomicron

TG = triglyceride

VLDL = very–low-density Lipoprotein

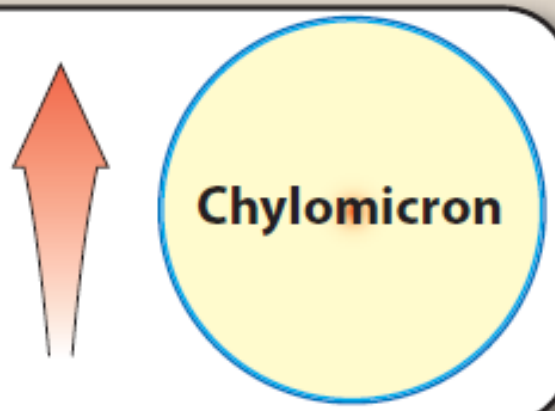
LDL = low-density lipoprotein

IDL = intermediate-density lipoprotein

apo CII = apolipoprotein CII found in chylomicrons and VLDL

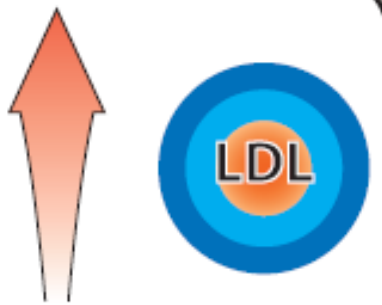
Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.



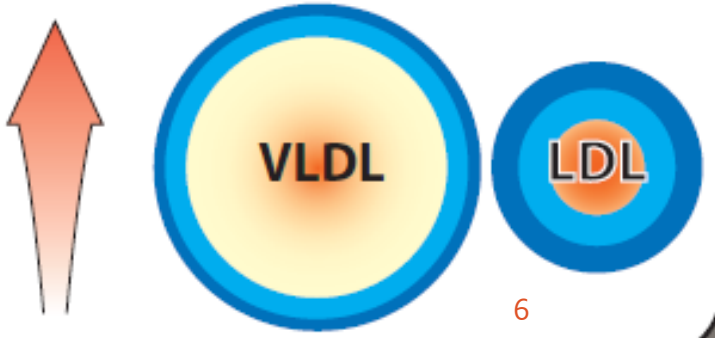
Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, or a statin.



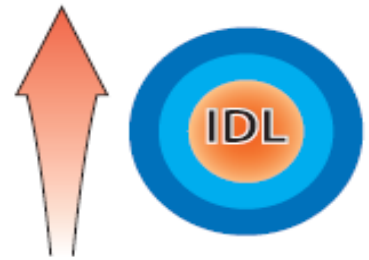
Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA .



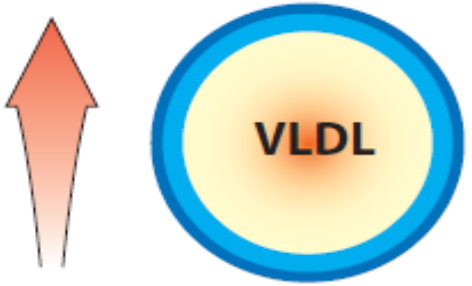
Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.



Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL and TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *niacin* and/or *fenofibrate*.



Type V (FAMILIAL MIXED HYPERTRIGLYCERIDEMIA)

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy includes *niacin*, and/or *fenofibrate*, or a statin.

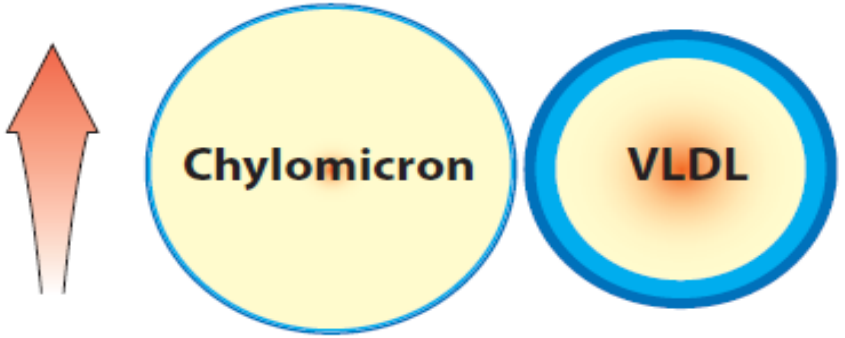


TABLE 35–1 The primary hyperlipoproteinemias and their treatment.

Disorder	Manifestations	Diet + Single Drug[1]	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase, cofactor deficiency; others)	Chylomicrons, VLDL increased	Dietary management; Omega-3 fatty acids, fibrate, or niacin (Apo C-III antisense)	Fibrate plus niacin
Familial hypertriglyceridemia	VLDL increased; chylomicrons may be increased	Dietary management; Omega-3 fatty acids, fibrate, or niacin	Fibrate plus niacin
Familial combined hyperlipoproteinemia	VLDL predominantly increased	Reductase inhibitor, Omega-3 fatty acids, fibrate, niacin	Two or three of the single agents[2]
	LDL predominantly increased	Reductase inhibitor, ezetimibe, or niacin	Two or three of the single agents
	VLDL, LDL increased	Reductase inhibitor, Omega-3 fatty acids, or niacin	Niacin or fibrate plus reductase inhibitor[2]
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased	Fibrate, reductase inhibitor, niacin, Omega 3 fatty acids	Reductase inhibitor plus fibrate or niacin
Familial hypercholesterolemia			
Heterozygous	LDL increased	Reductase inhibitor, resin, niacin, or ezetimibe	Two or three of the individual drugs
Homozygous	LDL increased	Atorvastatin, rosuvastatin, ezetimibe, mipomersen, lomitapide or PCSK9 MAB	Combinations of some of the single agents
Familial ligand-defective apo B-100	LDL increased	Reductase inhibitor, niacin, or ezetimibe	Two or three of the single agents
Lp(a) hyperlipoproteinemia	Lp(a) increased	Niacin	

[1]Single-drug therapy with marine omega-3 dietary supplement should be evaluated before drug combinations are used.

[2]Select pharmacologically compatible reductase inhibitor (see text).

Treatment goals

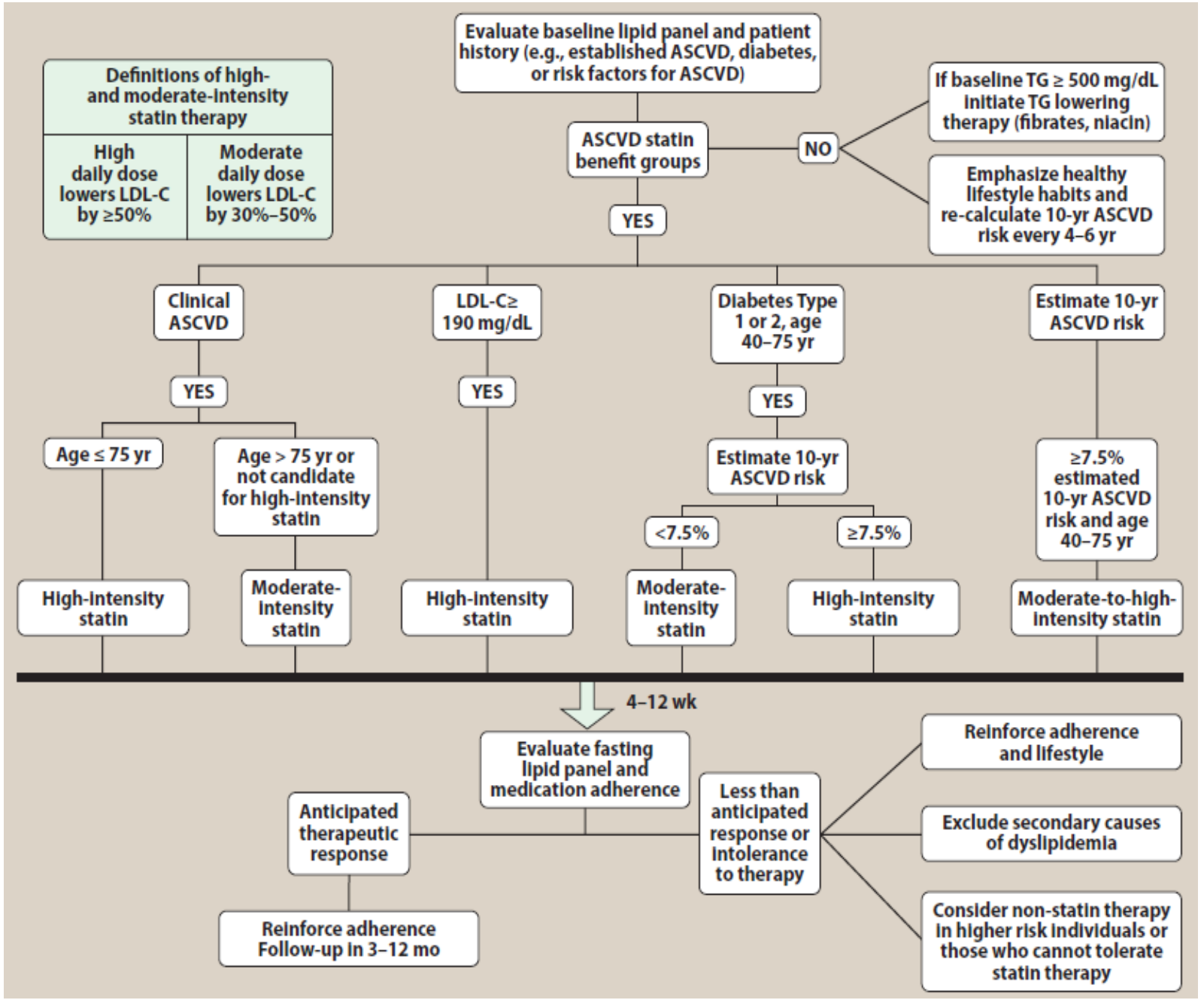
- Plasma lipids consist mostly of lipoproteins, which are spherical complexes of lipids and specific proteins (apolipoproteins)
- The clinically important lipoproteins, listed in decreasing order of atherogenicity, are
  - LDL, very–lowdensity lipoprotein (VLDL) and chylomicrons, and HDL
- The occurrence of CHD is positively associated with high total cholesterol and more strongly with elevated LDL-C
  - [Note: Total cholesterol is the sum of LDL-C, VLDL-C, and HDL-C.]
- In contrast to LDL-C, high levels of HDL-C have been associated with a decreased risk for heart disease
- Reduction of LDL-C is the primary goal of cholesterol-lowering therapy

Treatment options for hypercholesterolemia

- Lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL-C and increases in HDL-C
- However, most patients are unable to achieve significant LDL-C reductions with lifestyle modifications alone, and drug therapy may be required.
- Treatment with HMG CoA reductase inhibitors (statins) is the primary treatment option for hypercholesterolemia

Treatment options for hypertriglyceridemia

- Elevated triglycerides are independently associated with increased risk of CHD
- Diet and exercise are the primary modes of treating hypertriglyceridemia
- If indicated, *niacin* and fibric acid derivatives are the most efficacious in lowering triglycerides
- Omega-3 fatty acids (fish oil) in adequate doses may also be beneficial
- Triglyceride reduction is a secondary benefit of the statins, with the primary benefit being reduction of LDL-C.


Definitions of high- and moderate-intensity statin therapy
High daily dose lowers LDL-C by ≥50%
Moderate daily dose lowers LDL-C by 30%–50%
Evaluate baseline lipid panel and patient history (e.g., established ASCVD, diabetes, or risk factors for ASCVD)
ASCVD statin benefit groups
NO
If baseline TG ≥ 500 mg/dL initiate TG lowering therapy (fibrates, niacin)
Emphasize healthy lifestyle habits and re-calculate 10-yr ASCVD risk every 4–6 yr
YES
Clinical ASCVD
LDL-C≥ 190 mg/dL
Diabetes Type 1 or 2, age 40–75 yr
Estimate 10-yr ASCVD risk
YES
YES
YES
Age ≤ 75 yr
Age > 75 yr or not candidate for high-intensity statin
Estimate 10-yr ASCVD risk
≥7.5% estimated 10-yr ASCVD risk and age 40–75 yr
<7.5%
≥7.5%
High-intensity statin
Moderate-intensity statin
High-intensity statin
Moderate-intensity statin
High-intensity statin
Moderate-to-high-intensity statin
4–12 wk
Evaluate fasting lipid panel and medication adherence
Anticipated therapeutic response
Reinforce adherence Follow-up in 3–12 mo
Less than anticipated response or intolerance to therapy
Reinforce adherence and lifestyle
Exclude secondary causes of dyslipidemia
Consider non-statin therapy in higher risk individuals or those who cannot tolerate statin therapy

Drugs for hyperlipidemia

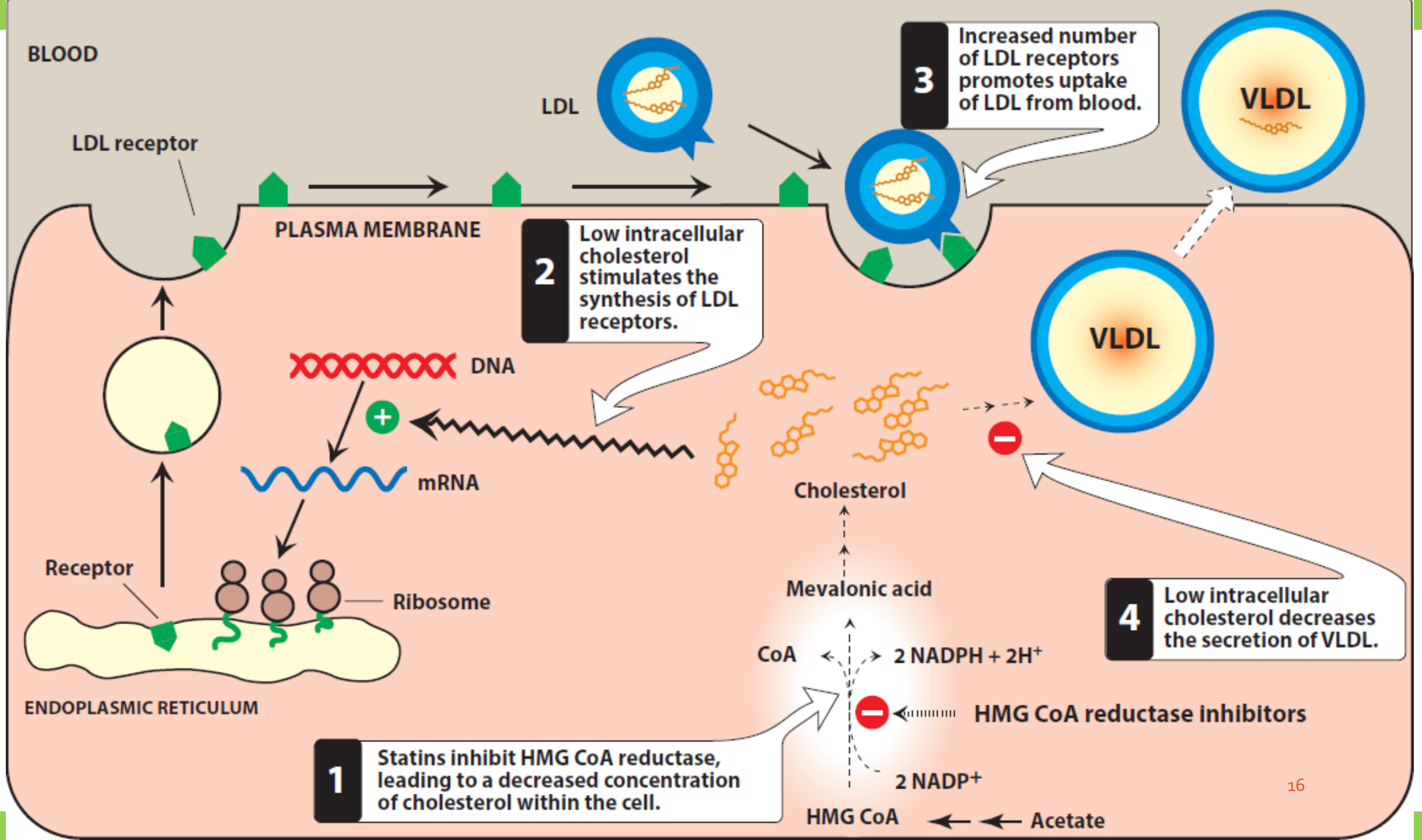
- Antihyperlipidemic drugs include
- statins, *niacin*, fibrates, bile acid–binding resins, a cholesterol absorption inhibitor, and omega-3 fatty acids
- These agents may be used alone or in combination
- However, drug therapy should always be accompanied by lifestyle modifications, such as exercise and a diet low in saturated fats

HMG CoA reductase inhibitors

- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors
  - (commonly known as statins) lower elevated LDL-C
  - resulting in a substantial reduction in coronary events and death from CHD
- They are considered first-line treatment for patients with elevated risk of ASCVD
- Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity

Mechanism of action of HMG CoA reductase inhibitors

- *Lovastatin*, *simvastatin*, *pravastatin*, *atorvastatin*, *fluvastatin*, *pitavastatin* and *rosuvastatin*
  - are competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis
  - By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol
  - Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs
  - Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism.
- *Pitavastatin*, *rosuvastatin*, and *atorvastatin* are the most potent LDL cholesterol–lowering statins, followed by *simvastatin*, *pravastatin*, and then *lovastatin* and *fluvastatin*.
- [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.]
- The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL cholesterol levels in some patients.


BLOOD
LDL
LDL receptor
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
PLASMA MEMBRANE
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
HMG CoA reductase inhibitors
ENDOPLASMIC RETICULUM
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Therapeutic uses of HMG CoA reductase inhibitors

- These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias

- However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.

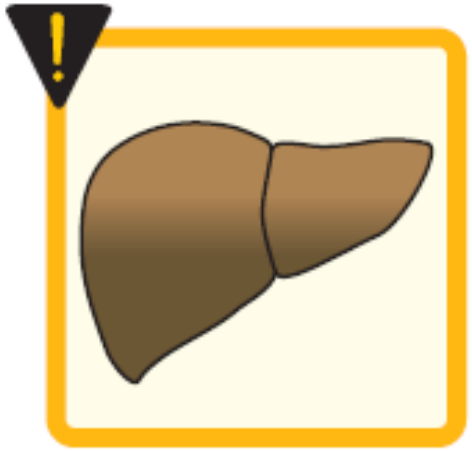
Pharmacokinetics of HMG CoA reductase inhibitors

- *Lovastatin* and *simvastatin* are lactones that are hydrolyzed to the active drug
- The remaining statins are all administered in their active form
- Absorption of the statins is variable (30% to 85%) following oral administration.
- All statins are metabolized in the liver, with some metabolites retaining activity.
- Excretion takes place principally through bile and feces, but some urinary elimination also occurs
- Their half-lives are variable

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (h)	14	1–2	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	15	20	10	13

Adverse effects of HMG CoA reductase inhibitors

- Elevated liver enzymes may occur with statin therapy
  - Therefore, liver function should be evaluated prior to starting therapy and if a patient has symptoms consistent with liver dysfunction. [Note: Hepatic insufficiency can cause drug accumulation.]
- Myopathy and rhabdomyolysis (disintegration of skeletal muscle; rare) have been reported
  - In most of these cases, patients usually had renal insufficiency or were taking drugs such as *erythromycin*, *gemfibrozil*, or *niacin*
  - *Simvastatin* is metabolized by cytochrome P450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis
  - Plasma creatine kinase levels should be determined in patients with muscle complaints
- The HMG CoA reductase inhibitors may also increase the effect of *warfarin*
  - it is important to evaluate international normalized ratio (INR) frequently
- These drugs are contraindicated during pregnancy and lactation



Liver failure

Contraindicated in pregnancy

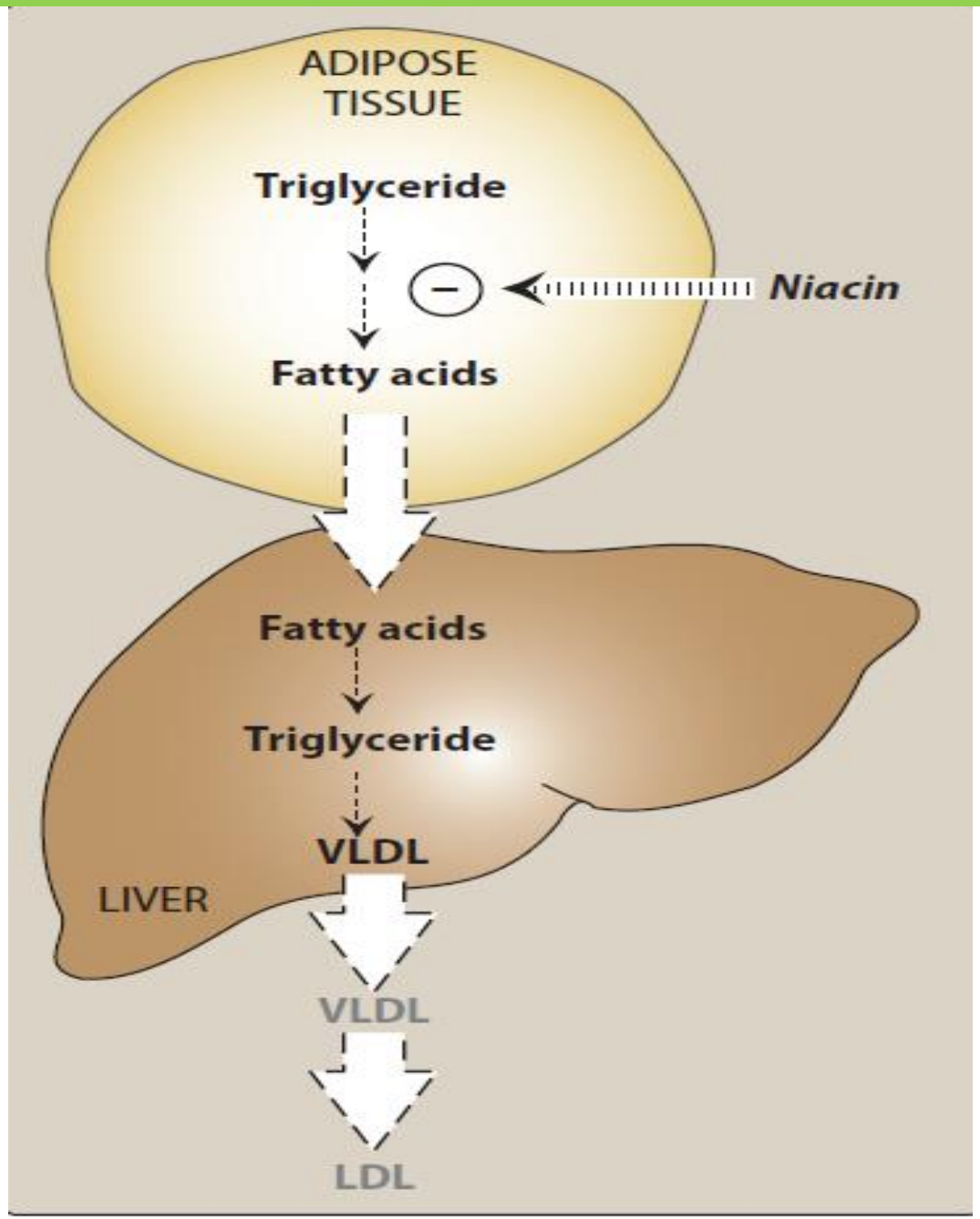
Myopathy

Niacin (nicotinic acid)

- *Niacin* can reduce LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C
- It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 grams/day
- *Niacin* can be used in combination with statins, and a fixed-dose combination of *lovastatin* and long-acting *niacin* is available.

Mechanism of action of Niacin

- At gram doses, *niacin* strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids
- The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis
- Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations
- Increased clearance of VLDL by the lipoprotein lipase associated with capillary endothelial cells accounts for the reduction in plasma triglyceride concentrations
- reduces the catabolic rate for HDL


ADIPOSE TISSUE
Triglyceride
Niacin
Fatty acids
Fatty acids
Triglyceride
VLDL
LIVER
VLDL
LDL

Therapeutic uses of Niacin

- Since *niacin* lowers plasma levels of both cholesterol and triglycerides, it is useful in the treatment of familial hyperlipidemias
- It is also used to treat other severe hypercholesterolemias, often in combination with other agents

Pharmacokinetics uses of Niacin

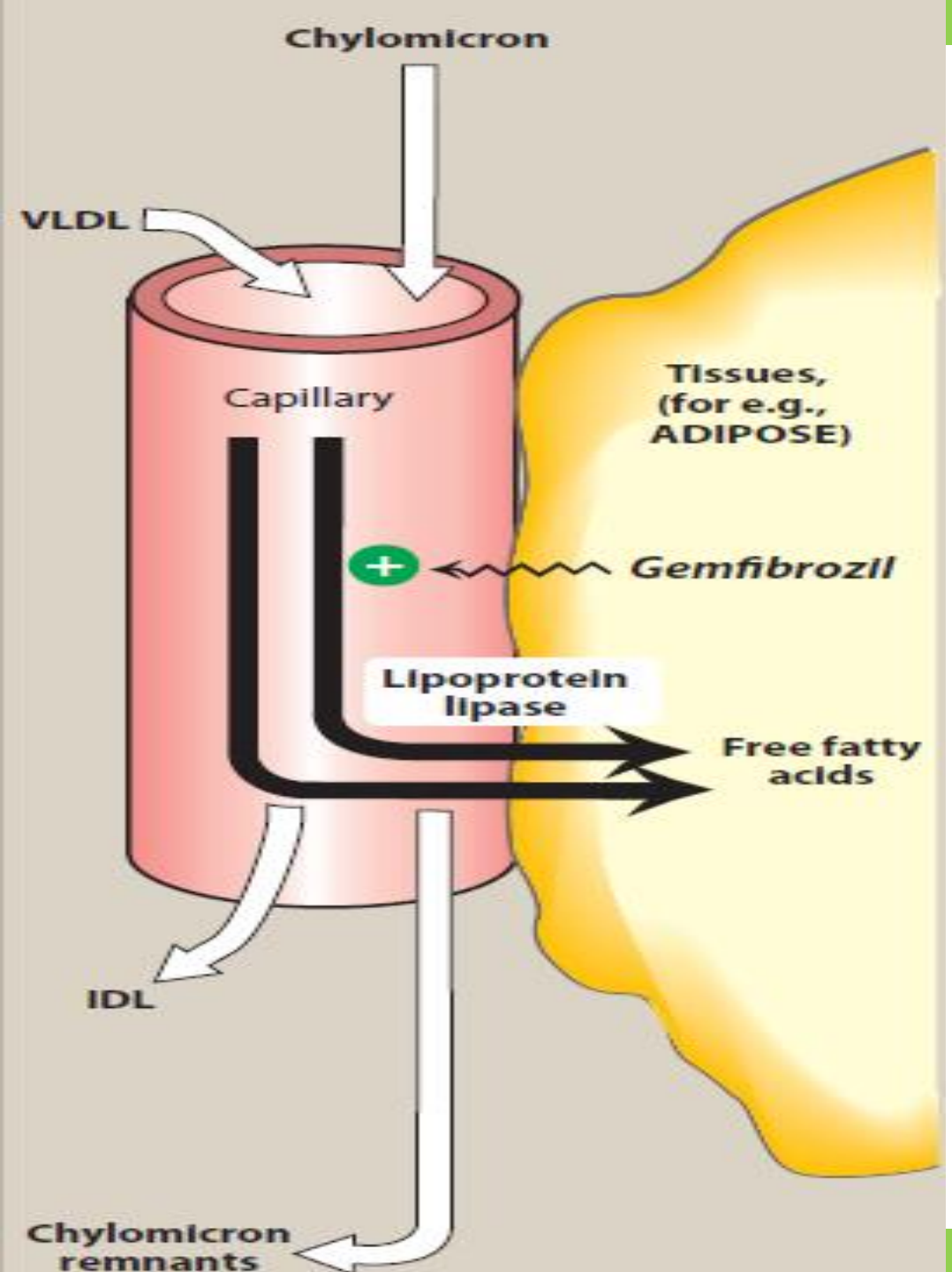
- *Niacin* is administered orally
  - It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD_+)
  - *Niacin*, its nicotinamide derivative, and other metabolites are excreted in the urine
- Note: Nicotinamide alone does not decrease plasma lipid levels
- For treatment of heterozygous familial hypercholesterolemia, 2–6 g of niacin daily is usually required; more than this should not be given
- For other types of hypercholesterolemia and for hypertriglyceridemia, 1.5–3.5 g daily is often sufficient
- Crystalline niacin should be given in divided doses with meals, starting with 100 mg two or three times daily and increasing gradually
- Niacin may potentiate the action of antihypertensive agents, requiring adjustment of their dosages

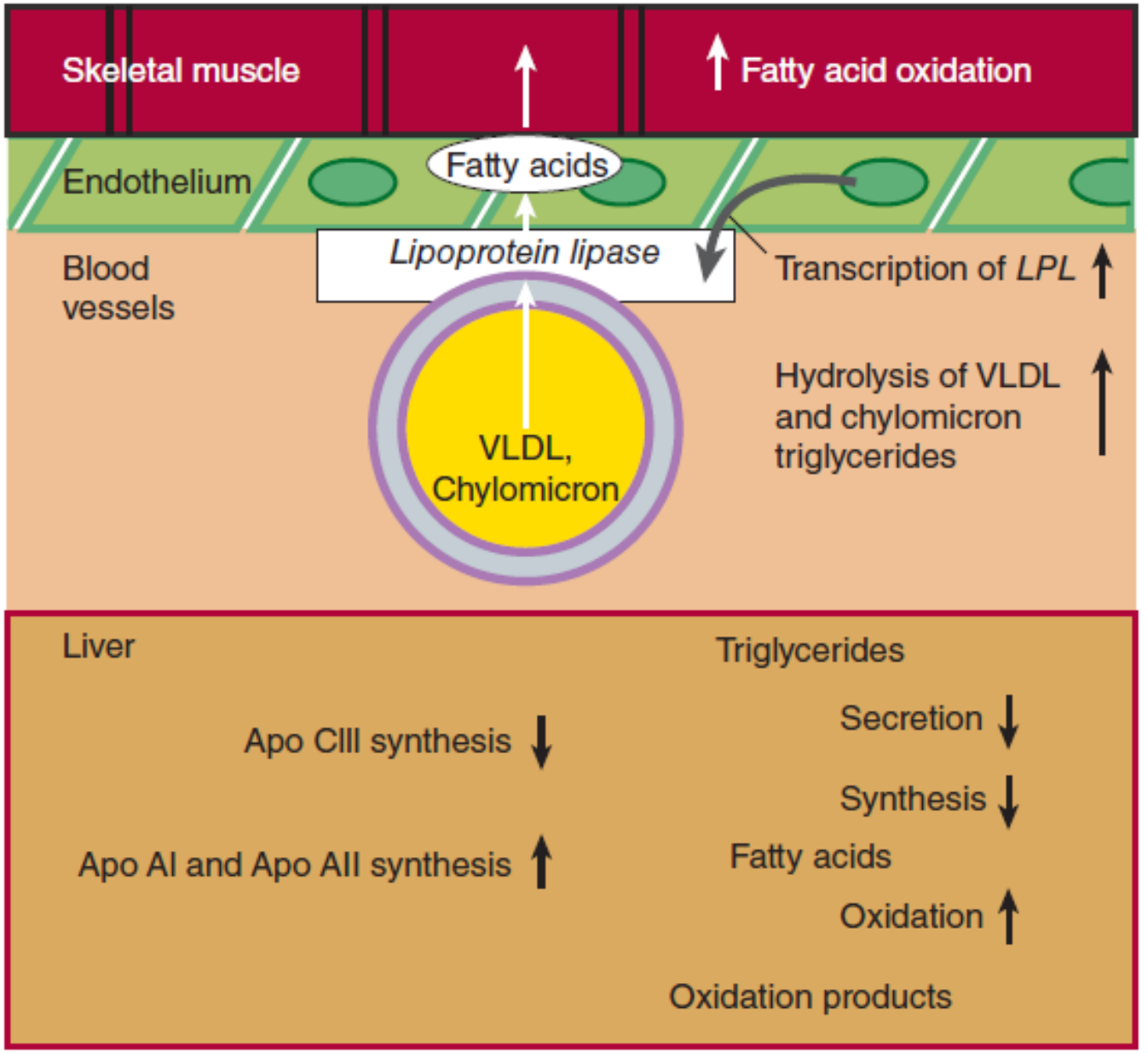
Adverse effects of Niacin

- The most common side effects of *niacin* are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus
  - Administration of aspirin or other NSAIDs prior to taking *niacin* decreases the flush, which is prostaglandin mediated.
- Some patients also experience nausea and abdominal pain
  - Niacin should be avoided in patients with significant peptic disease
- Slow titration of the dosage or usage of the sustained-release formulation of *niacin* reduces bothersome initial adverse effects
- *Niacin* inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout
  - Allopurinol can be given with niacin if needed
- Impaired glucose tolerance and hepatotoxicity have also been reported
- The drug should be avoided in hepatic disease
- Patients should be instructed to report blurring of distance vision as incidence of macular edema

Fibrates

- *Fenofibrate* and *gemfibrozil* are derivatives of fibric acid that lower serum triglycerides and increase HDL levels
- The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism
  - PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated.
  - They then bind to peroxisome proliferator response elements, which ultimately leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase and decreasing apolipoprotein (apo) CII concentration
- *Fenofibrate* is more effective than *gemfibrozil* in lowering triglyceride levels
- Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII


Chylomicron
VLDL
Capillary
Tissues, (for e.g., ADIPOSE)
Gemfibrozil
Lipoprotein lipase
Free fatty acids
IDL
Chylomicron remnants


Skeletal muscle
Fatty acid oxidation
Fatty acids
Endothelium
Lipoprotein lipase
Blood vessels
Transcription of LPL
Hydrolysis of VLDL and chylomicron triglycerides
VLDL, Chylomicron
Liver
Triglycerides
Apo CIII synthesis
Secretion
Synthesis
Apo AI and Apo AII synthesis
Fatty acids
Oxidation
Oxidation products

Therapeutic uses of Fibrates

- The fibrates are used in the treatment of hypertriglyceridemias
- They are particularly useful in treating type III hyperlipidemia (dysbetalipoproteinemia)
  - in which intermediate density lipoprotein particles accumulate
- They also may be of benefit in treating the hypertriglyceridemia that results from treatment with antiviral protease inhibitors
- In most patients, fibrates have little or no effect on LDL concentrations
  - However, fibrates can increase LDL cholesterol in patients with a genetic condition called familial combined hyperlipoproteinemia, which is associated with a combined increase in VLDL and LDL

Pharmacokinetics of Fibrates

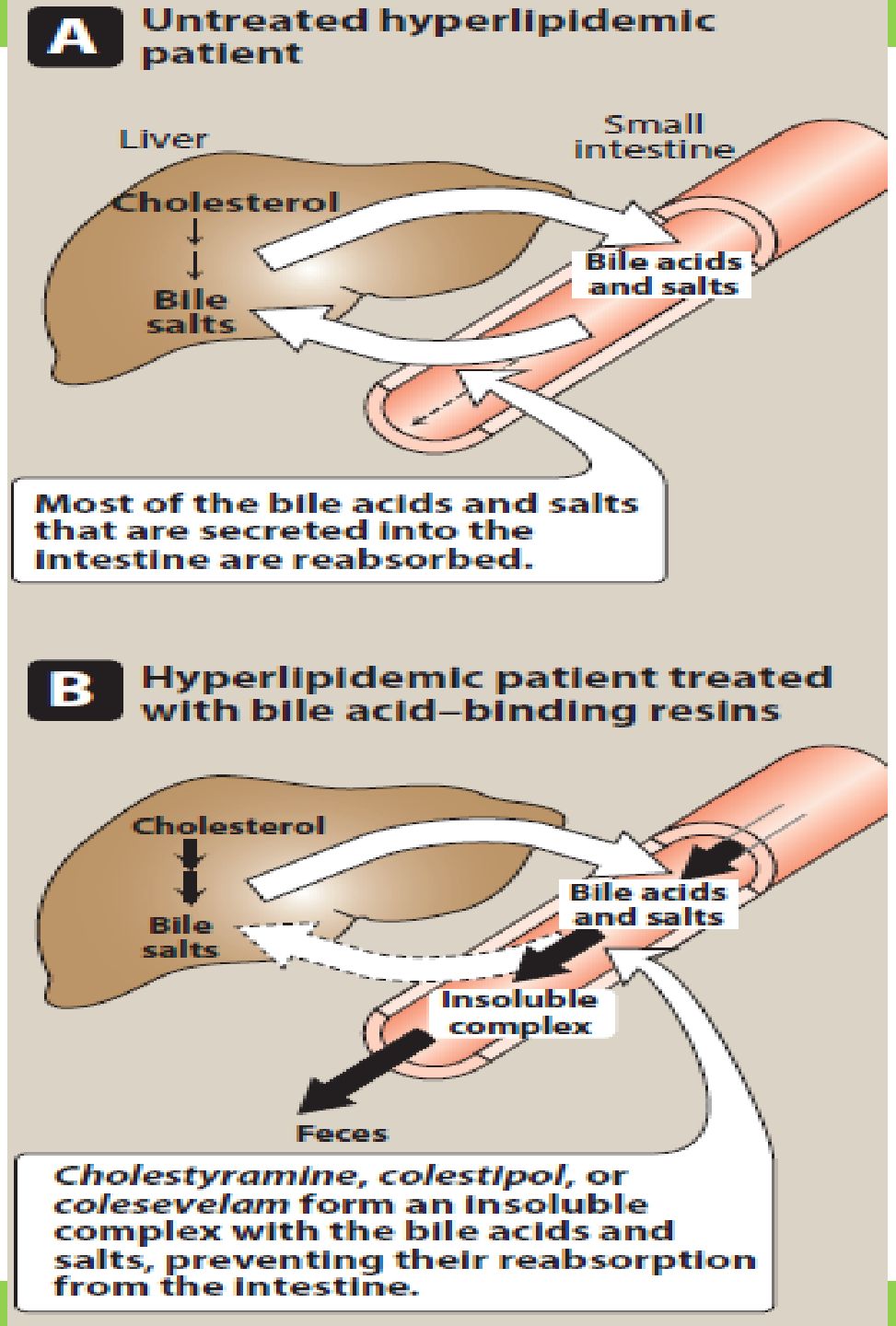
- *Gemfibrozil* and *fenofibrate* are completely absorbed after oral administration and distribute widely, bound to albumin
- *Fenofibrate* is a prodrug, which is converted to the active moiety fenofibric acid
- Both drugs undergo extensive biotransformation and are excreted in the urine as glucuronide conjugates
- The usual dose of gemfibrozil is 600 mg orally once or twice daily.
- The dosage of fenofibrate as Tricor is one to three 48-mg tablets (or a single 145-mg tablet) daily
  - Dosages of other preparations vary
- Absorption of gemfibrozil is improved when the drug is taken with food

Adverse effects of Fibrates

- The most common adverse effects are mild gastrointestinal (GI) disturbances specially Nausea
  - These lessen as the therapy progresses
- Skin rashes are common with gemfibrozil
- A few patients show decreases in white blood count or hematocrit
- Because these drugs increase biliary cholesterol excretion, there is a predisposition to form gallstones
- Myositis (inflammation of a voluntary muscle) can occur, and muscle weakness or tenderness should be evaluated
  - Patients with renal insufficiency may be at risk
- Myopathy and rhabdomyolysis have been reported in patients taking *gemfibrozil* and statins together
  - Fenofibrate is the fibrate of choice for use in combination with a statin
  - The use of *gemfibrozil* is contraindicated with *simvastatin*
- Both fibrates may increase the effects of *warfarin*
  - INR should, therefore, be monitored more frequently when a patient is taking both drugs.
- Fibrates should not be used in patients with severe hepatic or renal dysfunction or in patients with preexisting gallbladder disease

Bile acid–binding resins (resins)

- significant LDL cholesterol–lowering effects, although the benefits are less than statins
- Normally, over 90% of bile acids, metabolites of cholesterol, are reabsorbed in the gastrointestinal tract and returned to the liver for reuse
- *Cholestyramine*, *colestipol*, and *colesevelam* are anion-exchange large nonabsorbable polymers that bind negatively charged bile acids and bile salts in the small intestine
  - The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration.
  - causes hepatocytes to increase conversion of cholesterol to bile acids
  - intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL particles by an up-regulation of cell surface LDL receptors, leading to a fall in plasma LDL-C


A
Untreated hyperlipidemic patient
Liver
Small intestine
Cholesterol
Bile salts
Bile acids and salts
Most of the bile acids and salts that are secreted into the intestine are reabsorbed.
B
Hyperlipidemic patient treated with bile acid–binding resins
Cholesterol
Bile salts
Bile acids and salts
Insoluble complex
Feces
Cholestyramine, colestipol, or colesevelam form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.

Therapeutic uses of resins

- The bile acid–binding resins are useful (often in combination with diet or *niacin*) for treating type IIA and type IIB hyperlipidemias
- [Note: In those rare individuals who are homozygous for type IIA and functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.]
- *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis
- *Colesevelam* is also indicated for type 2 diabetes due to its glucose-lowering effects.
- In some patients with a genetic condition that predisposes them to hypertriglyceridemia and hypercholesterolemia (familial combined hyperlipidemia), resins increase triglycerides and VLDL

Pharmacokinetics of resins

- Bile acid sequestrants are insoluble in water and have large molecular weights
- After oral administration, they are neither absorbed nor metabolically altered by the intestine.
- Instead, they are totally excreted in feces
- Colestipol and cholestyramine are available as granular preparations.
  - A gradual increase of dosage of granules from 4 or 5 g/d to 20 g/d is recommended
  - Total dosages of 30–32 g/d may be needed for maximum effect
  - The usual dosage for a child is 10–20 g/d
  - Granular resins are mixed with juice or water and allowed to hydrate for 1 minute

Adverse effects of resins

- The most common side effects are GI disturbances, such as constipation, nausea, and flatulence (usually relieved by increasing dietary fiber) and an unpleasant gritty taste
- *Colesevelam* has fewer GI side effects than other bile acid sequestrants
- These agents may impair the absorption of the fat-soluble vitamins (A, D, E, and K), and they interfere with the absorption of many drugs (for example, *digoxin*, *warfarin*, and thyroid hormone).
  - Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid–binding resins
  - Prothrombin time should be measured frequently in patients who are taking resins and anticoagulants.
- These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL) and also patients with diverticulitis

Cholesterol absorption inhibitor

- *Ezetimibe* selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver
  - This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood
- *Ezetimibe* lowers LDL cholesterol by approximately 17%
  - Due its modest LDL-lowering effects, often used as an adjunct to statin therapy or in statin-intolerant patients
  - It is also effective in patients with phytosterolemia
- metabolized in the small intestine & liver via glucuronide conjugation, with subsequent biliary and renal excretion
- Patients with moderate to severe hepatic insufficiency should not be treated with *ezetimibe*
- a daily dose of 10 mg is used
- Adverse effects are uncommon with use of *ezetimibe*

Omega-3 fatty acids

- Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering
- Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver
- The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon.
  - Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C
  - Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources al
- *Icosapent ethyl* is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C
- considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL)
  - The most common side effects include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste
  - Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets.

Inhibition of Microsomal Triglyceride Transfer Protein (MTP)

- MTP plays an essential role in the addition of triglycerides to nascent VLDL in liver, and to chylomicrons in the intestine
  - Its inhibition decreases VLDL secretion and consequently the accumulation of LDL in plasma
- An MTP inhibitor, lomitapide, is available but is currently restricted to patients with homozygous familial hypercholesterolemia
  - It causes accumulation of triglycerides in the liver in some individuals
  - Elevations in transaminases can occur
  - Patients must maintain a low fat diet to avoid steatorrhea and should take steps to minimize deficiency of essential fat-soluble nutrients
- given orally in gradually increasing doses of 5- to 60-mg capsules once daily 2 hours after the evening meal
- available only through a restricted (REMS) program for patients with homozygous familial hypercholesterolemia

Antisense Inhibition of Apo B-100 Synthesis

- **Mipomersen** is an antisense oligonucleotide that targets apo B-100, mainly in the liver
  - It is important to note that the apo B-100 gene is also transcribed in the retina and in cardiomyocytes
- Subcutaneous injections of mipomersen reduce levels of LDL and Lp(a)
- Mild to moderate injection site reactions and flu-like symptoms can occur
- The drug is available only for use in homozygous familial hypercholesterolemia through a restricted (REMS) program

PCSK9 Inhibition

- Development of inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) followed on the observation that loss of function mutations result in very low levels of LDL and no apparent morbidity
  - humanized antibodies to PCSK9 (**evolocumab, alirocumab**).
- LDL reductions up to 70%, Triglycerides and apo B-100 are reduced, and Lp(a) levels decrease about 25%
- Rarely, hypersensitivity reactions, local reactions at the injection site, upper respiratory and flu-like symptoms
- restricted to patients who have familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional reduction of LDL
- They are given with diet and maximal tolerated statin and/or ezetimibe
- Studies of PCSK9 inhibition should be approached with caution because of its established role in normal cell biology
- These agents are very expensive

Combination drug therapy

- Combined drug therapy is useful
  - (1) when VLDL levels are significantly increased during treatment of hypercholesterolemia with a resin
  - (2) when LDL and VLDL levels are both elevated initially;
  - (3) when LDL or VLDL levels are not normalized with a single agent
  - (4) when an elevated level of Lp(a) or an HDL deficiency coexists with other hyperlipidemias
- The lowest effective doses should be used in combination therapy and the patient should be monitored more closely for evidence of toxicity
- In combinations that include resins, the other agent (with the exception of niacin) should be separated temporally to ensure absorption
- The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has been shown to be very useful in lowering LDL-C levels

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

SUMMARY Drugs Used in Dyslipidemia

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
STATINS				
• Atorvastatin, simvastatin, rosuvastatin, pitavastatin	Inhibit HMG-CoA reductase	Reduce cholesterol synthesis and upregulate low-density lipoprotein (LDL) receptors on hepatocytes • modest reduction in triglycerides	Atherosclerotic vascular disease (primary and secondary prevention) • acute coronary syndromes	Oral • duration 12–24 h • *Toxicity:* Myopathy, hepatic dysfunction • *Interactions:* CYP-dependent metabolism (3A4, 2C9) interacts with CYP inhibitors/competitors
• *Fluvastatin, pravastatin, lovastatin: Similar but somewhat less efficacious*				
FIBRATES				
• Fenofibrate, gemfibrozil	Peroxisome proliferator-activated receptor-alpha (PPAR-α) agonists	Decrease secretion of very-low-density lipoproteins (VLDL) • increase lipoprotein lipase activity • increase high-density lipoproteins (HDL)	Hypertriglyceridemia, low HDL	Oral • duration 3–24 h • *Toxicity:* Myopathy, hepatic dysfunction

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
BILE ACID SEQUESTRANTS				
• Colestipol	Binds bile acids in gut • prevents reabsorption • increases cholesterol catabolism • upregulates LDL receptors	Decreases LDL	Elevated LDL, digitalis toxicity, pruritus	Oral • taken with meals • not absorbed • *Toxicity:* Constipation, bloating • interferes with absorption of some drugs and vitamins
• *Cholestyramine, colesevelam: Similar to colestipol*				
STEROL ABSORPTION INHIBITOR				
• Ezetimibe	Blocks sterol transporter NPC1L1 in intestine brush border	Inhibits reabsorption of cholesterol excreted in bile • decreases LDL and phytosterols	Elevated LDL, phytosterolemia	Oral • duration 24 h • *Toxicity:* Low incidence of hepatic dysfunction, myositis
NIACIN				
	Decreases catabolism of apo AI • reduces VLDL secretion from liver	Increases HDL • decreases lipoprotein(a) [Lp(a)], LDL	Low HDL • elevated VLDL, Lp(a); elevated LDL in statin-unresponsive or intolerant patients	Oral • large doses • *Toxicity:* Gastric irritation, flushing, low incidence of hepatic toxicity • may reduce glucose tolerance
• *Extended-release niacin: Similar to regular niacin*				
• *Sustained-release niacin (not the same as extended-release product): Should be avoided*				
PCSK9 HUMANIZED MONOCLONAL ANTIBODIES				
Evolocumab	Complexes PCSK9	Inhibits catabolism of LDL receptor	Familial hypercholesterolemia not responsive to oral therapy	Parenteral • Cost ~ $14,000/year • *Toxicity*: injection site reactions, nasopharyngitis, flu-like symptoms, rarely myalgia, neurocognitive and ophthalmologic events
• *Alirocumab Similar to evolucumab*				

HMG CoA REDUCTASE INHIBITORS (STATINS)

Atorvastatin LIPITOR
Fluvastatin LESCOL
Lovastatin MEVACOR
Pitavastatin LIVALO
Pravastatin PRAVACHOL
Rosuvastatin CRESTOR
Simvastatin ZOCOR

NIACIN

Niacin NIASPAN, SLO-NIACIN

FIBRATES

Gemfibrozil LOPID
Fenofibrate TRICOR, LOFIBRA, TRIGLIDE

BILE ACID SEQUESTRANTS

Colesevelam WELCHOL
Colestipol COLESTID
Cholestyramine QUESTRAN, PREVALITE

CHOLESTEROL ABSORPTION INHIBITOR

Ezetimibe ZETIA

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, various OTC preparations
Icosapent ethyl VASCEPA