Doctor.021

no. 8

CVS PHARMACOLOGY

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A small introduction for the lecture:

Antihyperlipidemic drugs are very important drugs, because they focus on the treatment of atherosclerosis, which is one of the main causes of most CVS morbidities and mortalities, this treatment is done via the following ways:-

1-↓LDL 2-↑HDL (questionable benefit) 3- ↓ VLDL

some notes regarding the metabolism and action of those 3, this is just so u can understand how some drugs work ,and what happens normally vs pathologically.

Small Intestines package dietary triglycerides and other lipids as chylomicrons and deliver them to adipose, cardiac, and skeletal muscle tissue , they turn into chylomicron remnants that are uptaken by receptor mediated endocytosis in the liver.

A small introduction for the lecture(Cont'd):

- Cholesterol is synthesized in the liver from acetyl-coa, when cholesterol is synthesized, it's transported via VLDL (very low density lipoprotein) , which is high in triglyceride content, and is delivered to the different tissues of the body.
- After the triglycerides are released from VLDL, it becomes IDL (intermediate density), then LDL (low density) , which is high in cholesterol content.

- if LDL cholesterol IS HIGH it increases the risk of atherosclerotic plaque formation and contributes directly in it's formation as we learned in pathology , by being ingested by the macrophages thus turning them into foam cells.

- LDL isn't always the reason , and its not always high , some people have some genetic diseases resulting in other problems with different mechanisms(we'll discuss later)
- So remember we need to target the LDL levels and the VLDL levels and lower them, and increase HDL cholesterol (good cholesterol, however very recently a beneficial effect of increasing HDL-C has been questioned).

Antihyperlipidemic drugs

- The clinically important lipoproteins are

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

- Hyperlipidemia may be 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 (and other complications of atherosclerotic CVS disease) is positively correlated with elevated levels of low density lipoproteins (LDL) cholesterol, and triglycerides with low level of high-density lipoprotein cholesterol (HDL).

Antihyperlipidemic drugs

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

- Antihyperlipidimic drugs target the problem with complimentary strategies, including:

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

  2. others increase the degradation or uptake of lipoproteins.

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

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

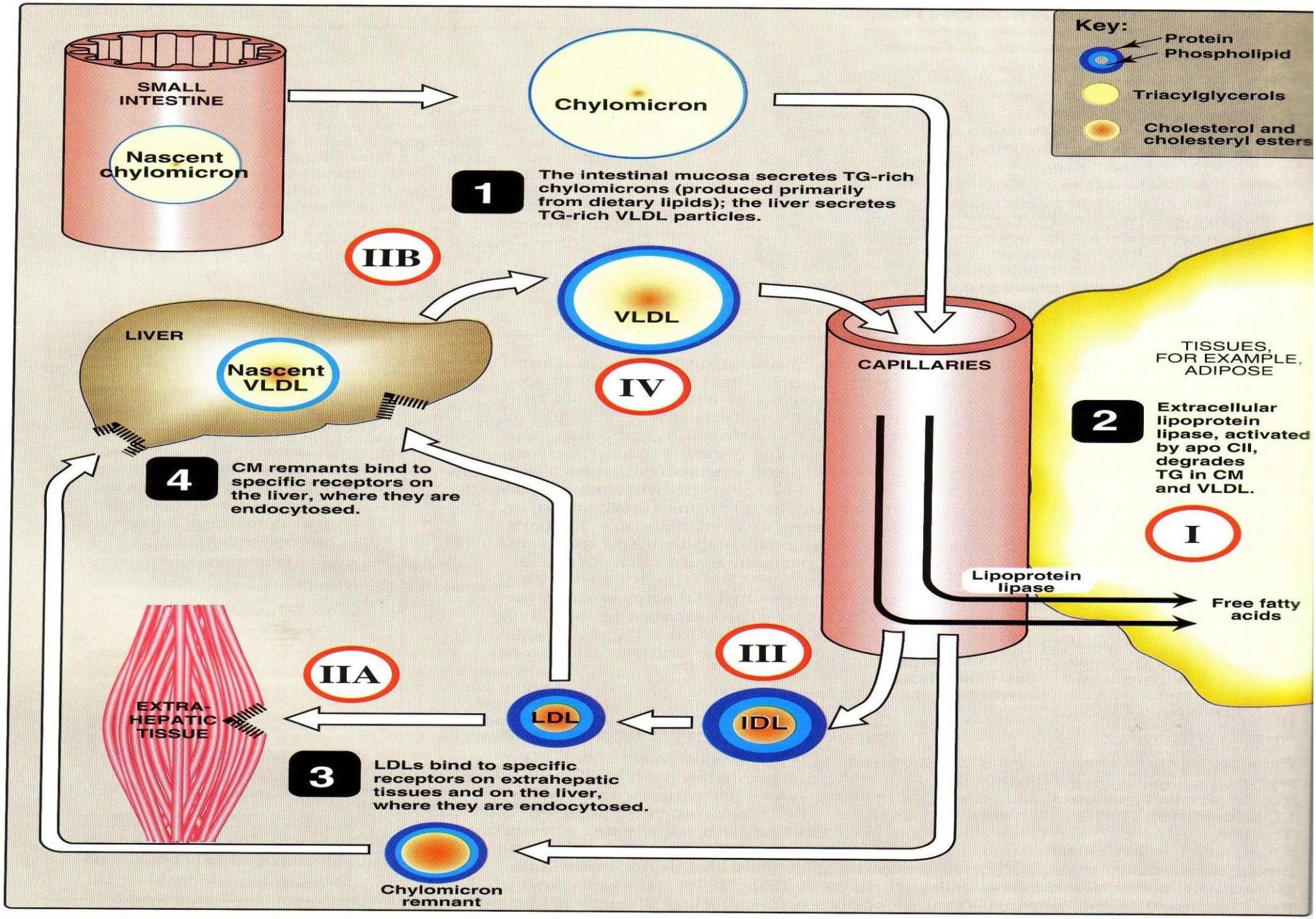


Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. The Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM=chylomicron, TG = triacylglycerol; VLDL=very-low density lipoprotein, LDL=low-density lipoprotein, IDL=intermediate-density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

Some notes regarding the previous table:-

- The previous table isn't really for memorizing, since we aren't studying pathology here, but u need to know that there are genetic problems that could result in different things, high LDL , or high VLDL ,or high chylomicrons, ….etc.
- we need to understand why we give our treatment, and where we direct it.
- Another note u need to understand that because we have genetic problems , this means that our therapy isn't only targeted for adults and old people , some children may also suffer from hyperlipidemic problems.
- We also have the usual(non-genetic) hyperlipidemia, which is the result from all the different reasons u read in the previous slides and in pathology, this most commonly represents Type IIa hyperlipidemia(↑LDL).

The ones in red have medium action and less potency than the ones in blue

Statins

Some of the most important drugs known to man, also most selling drugs ever

These agents include **Lovastatin, pravastatin, simvastatin, fluvastatin, Atorvastatin, rosuvastatin(strongest)**

Cerivastatin (withdrawn from the market because of high risk of fatal side effects such as rhabdomyolysis)

the doctor spoke alot about the therapeutics of those drugs , its not required but just understand that Atorvastatin and Rosuvastatin are the strongest, they are used for aggressive treatment in high risk patients , and the lower efficacy drugs that are in red sometimes cant give us the wanted effect.

- 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.

Continuation of the previous slide:

(3) After LDL binds to its receptors in the liver, the liver will now increase triglyceride packaging into VLDL ,but the low level of cholesterol has a negative effect on VLDL secretion, it decreases the rate of it's synthesis , so in the end , statins have depleted the LDL levels in the blood , and inhibited the VLDL secretion, so in the end there's decreased cholesterol level in the body.

(4) when the cholesterol levels in the liver are low , the HDL level increases as a feedback mechanism. (but as we said before it has been questioned)

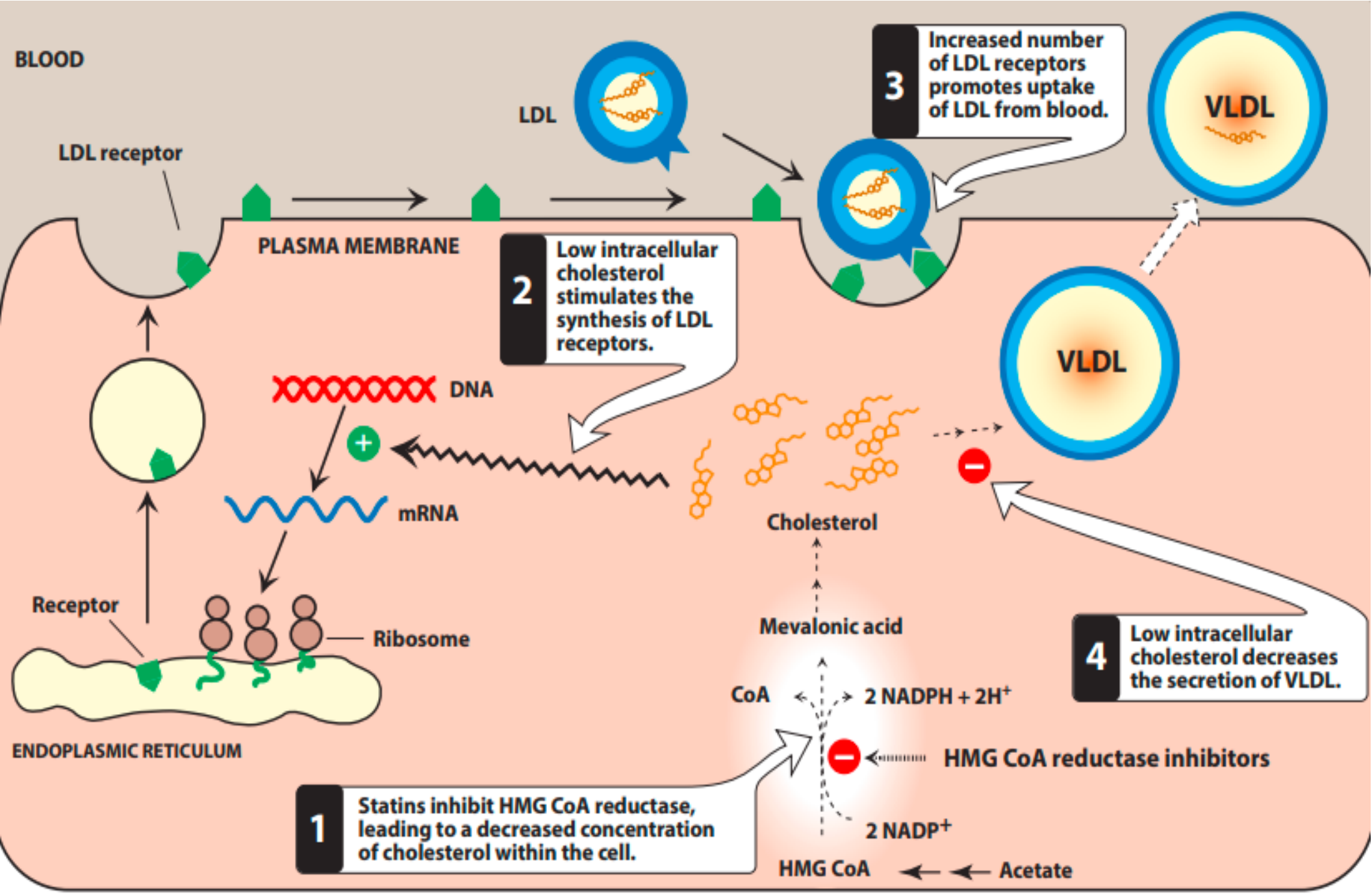
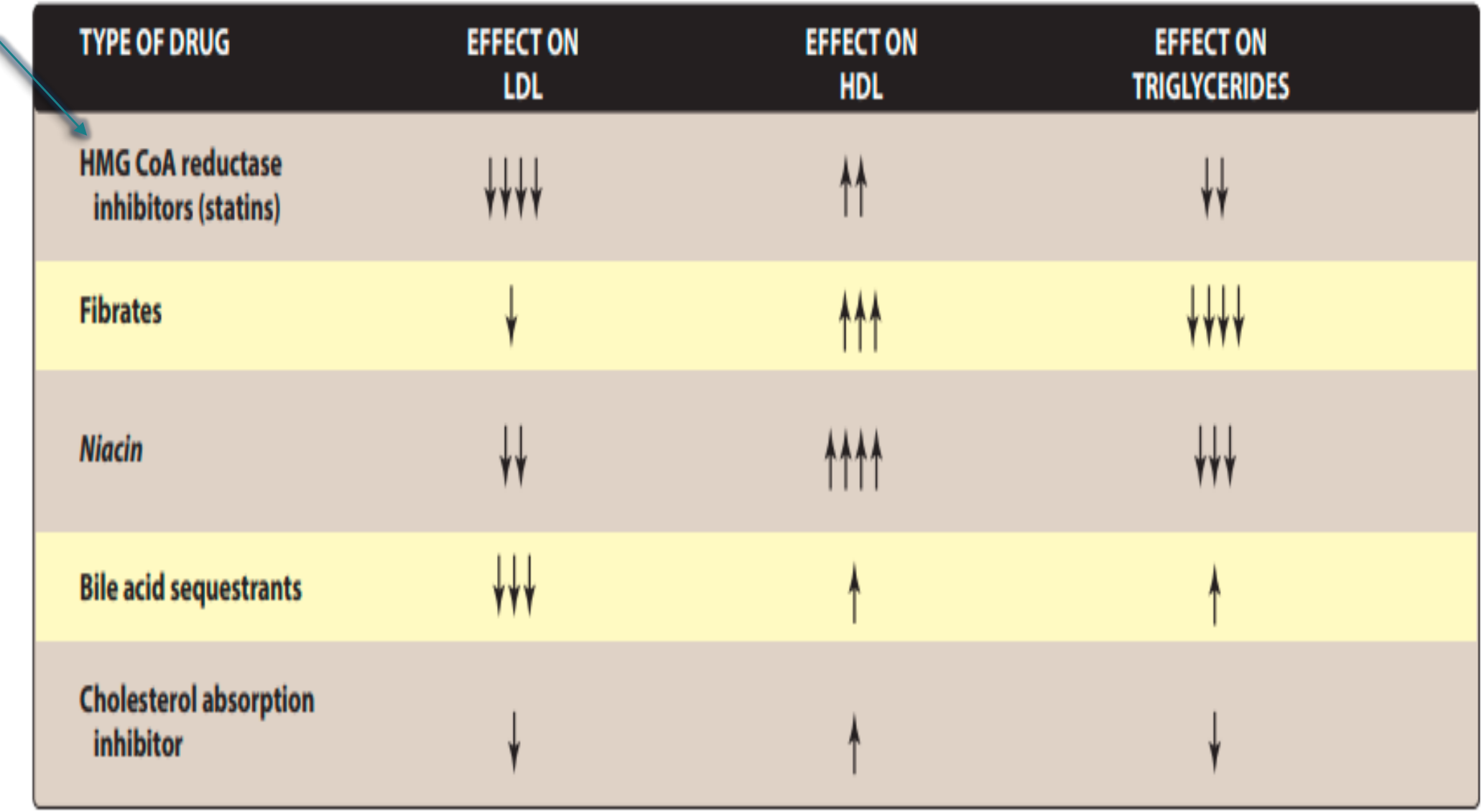


Figure 23.5

Inhibition of HMG CoA reductase by the statin drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; VLDL = very–low-density lipoprotein.



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	↓	↑	↓

Figure 23.12

Characteristics of antihyperlipidemic 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)(Elevated liver enzymes such as AST and ALT)

less in Lovastatin and fluvastatin

-Myopathy(15-30%)and rhabdomyolysis(0.6%)(disintegration or dissolution of muscle). Decreased synthesis of CoQ10 (Coenzyme Q or ubiquinone, which is very important in the electron transport chain), causing myopathy, and if it persists causes rhabdomyolysis, increasing level of myoglobin and Creatine kinase, which can cause nephrotoxicity.

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

we use them in some children with familiar hyperlipidemias, although they must be at least 8 years old.

Statins interaction

Grapefruit increases their efficacy , and increases the risk of myopathy.

- **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.**
- **Drugs that inhibit CYP450 such as protease inhibitors, increase the level of those drugs , thus increasing the risk of myopathy and other side effects**

- 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.

The doctor said don't memorize those drugs , you need to understand generally what are those drug-drug interactions, and why they increase or decrease the levels of Statins. (just remember some main names of them that we already took before)

Those drugs were heavily used before , since they were thought to be very good , but now they are much less used, almost to the point of no use at all.

Niacin (vitamin B_3)

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

It inhibits the HSL (hormone sensitive lipase) which will result in inhibition of lipolysis.

It inhibits degradation of HDL by the liver , and it decreases the catabolism of HDL by the scavenger receptors (receptors on the surface of phagocytes) and the foam cells.

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**

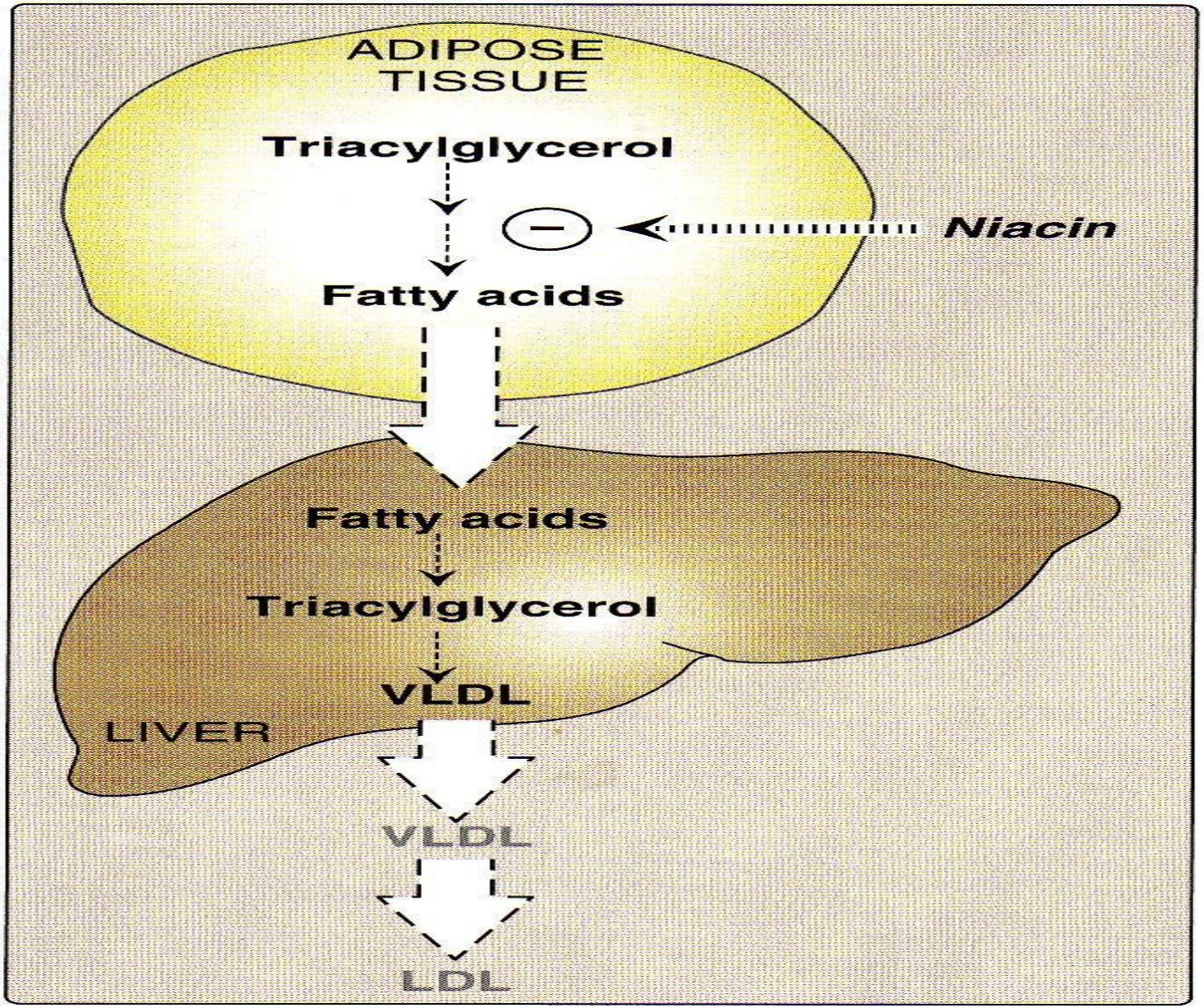


Figure 21.9
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.

Niacin

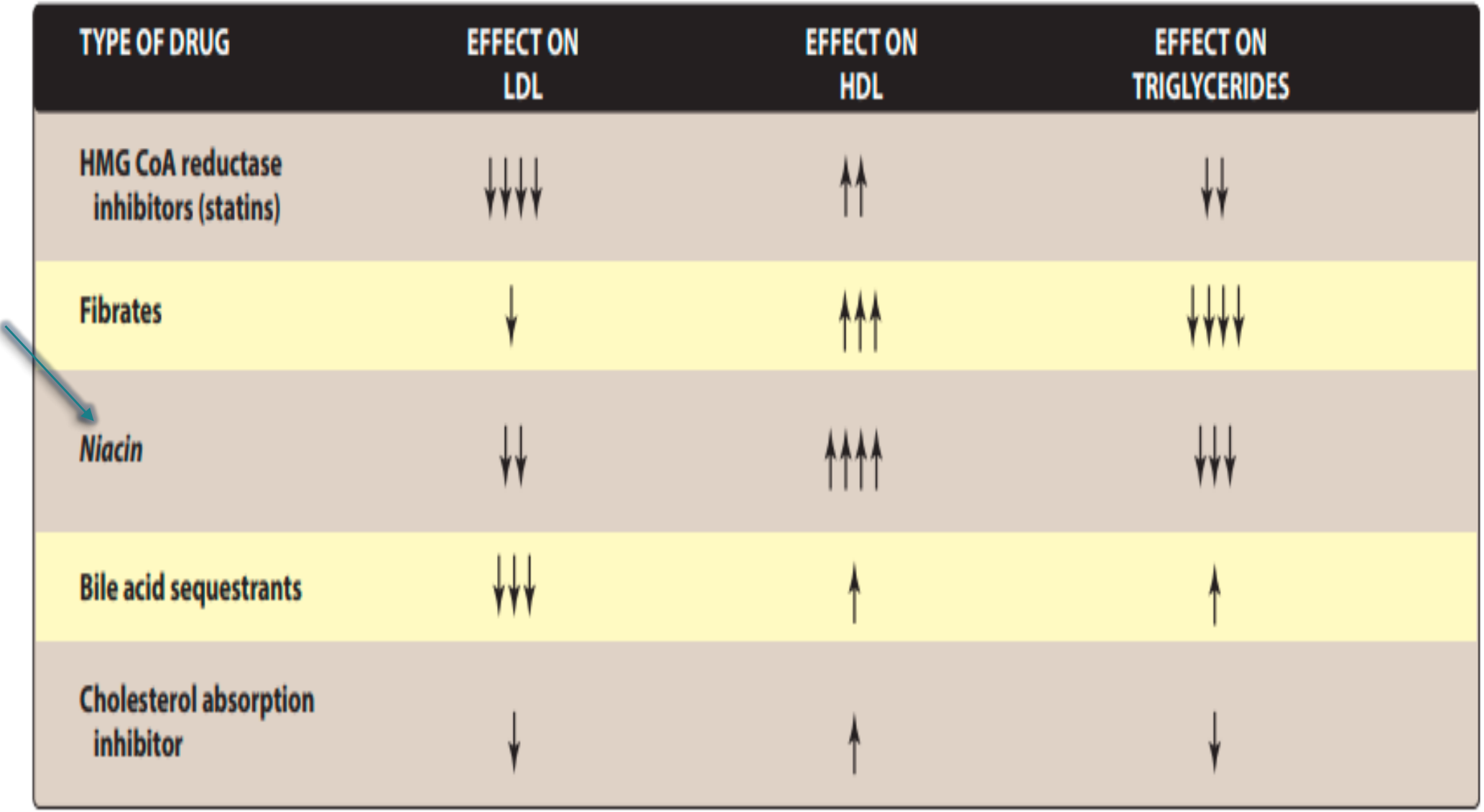
- **Adverse effects: Cutaneous flushing , burning and itching, GI irritation, nausea and vomiting.**

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

SOME NOTES ON THE PREVIOUS SLIDE:-

This slide is just to explain the mechanism of some of the previous side effects and talk about some ways to manage them :-

- Cutaneous flushing happens because Niacin increases the production of prostaglandins (PG), we can administer aspirin or ibuprofen before niacin to reduce PG levels.
- GI irritation could be stopped via gradual escalation of the dose of the drug.
- Peptic ulcer activation happens because of the decreased platelet count which will result in increased bleeding.
- Hyperglycemia occurs due to insulin resistance.
- Hyperuricemia's mechanism is similar to that of the thiazide and loop diuretics, and that is inhibition of the proximal tubular excretion of uric acid.



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Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

Figure 23.12

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

Fibrates

Fenofibrate can be used with statins, Gemfibrozil can't be used with statins because it inhibits cyp450, only statin that can be used with it is Pravastatin, because its metabolized by sulfation.

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

MOA: Peroxisome proliferator activated receptors (PPARs)

are a nuclear receptors that regulate lipid metabolism.

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

- **They are used in the treatment of hypertriglycerolemias.**

The increased LPL causes decreased levels of triglycerides and VLDL, the decreased levels of LDL are due to 2 reasons: increased clearance of LDL , and the drug also decreases the synthesis of VLDL which in turn will cause decreased LDL

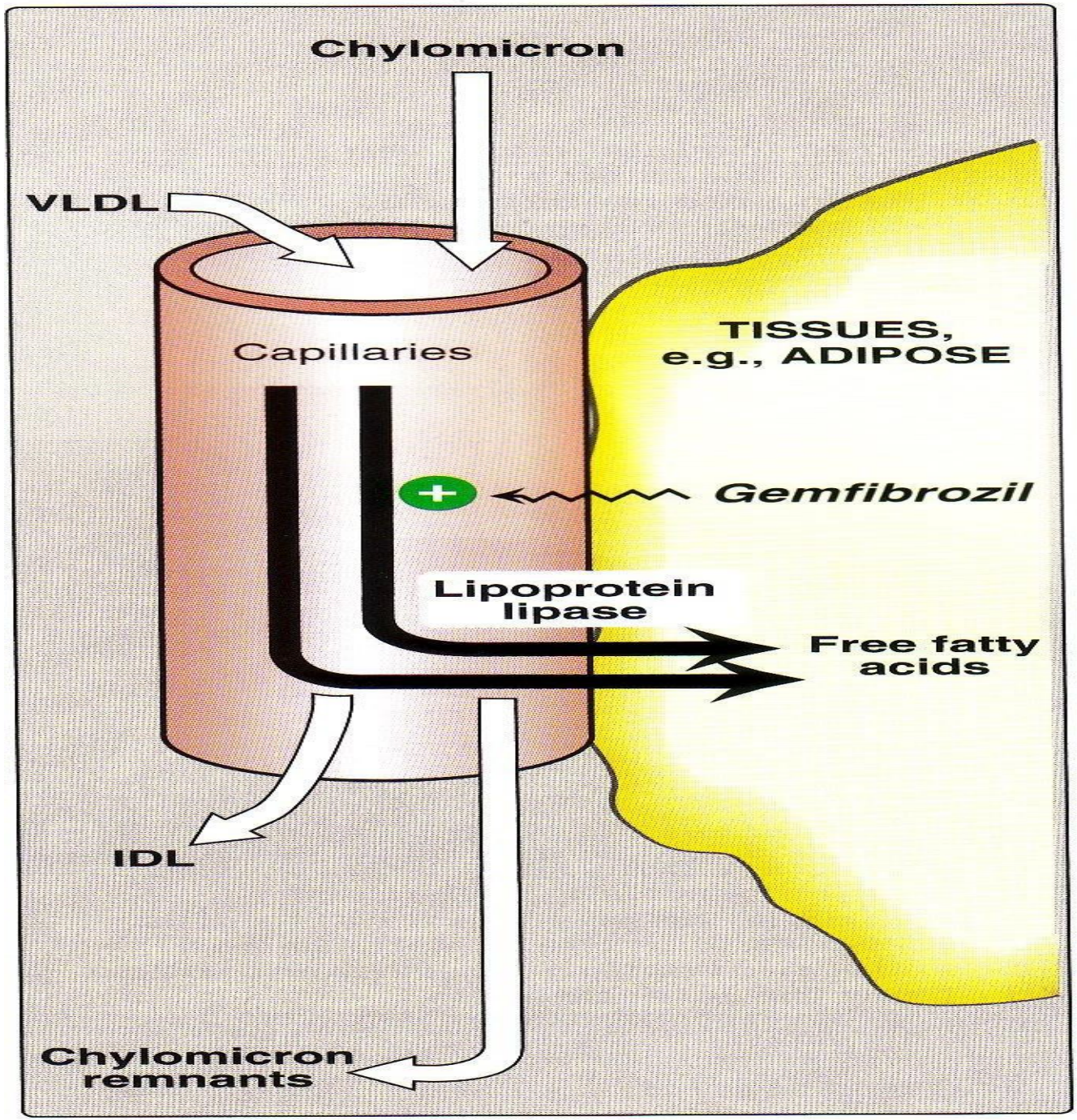


Figure 21.11
Activation of lipoprotein lipase by *gemfibrozil*.

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. They increase biliary excretion of cholesterol. They also decrease bile acid synthesis, so the bile is now supersaturated with cholesterol

d. Myositis (inflammation of a voluntary muscle) can occur. Contraindicated with Statins because they inhibit cyp450,so it will increase the risk of myopathy and rhabdomyolysis induced by the statin.

Fibrates compete with the coumarin anticoagulants (such as WARFARIN) for binding sites on plasma proteins.
Therefore they increase warfarin's effect on INR (PT).

Bile acid-binding resins

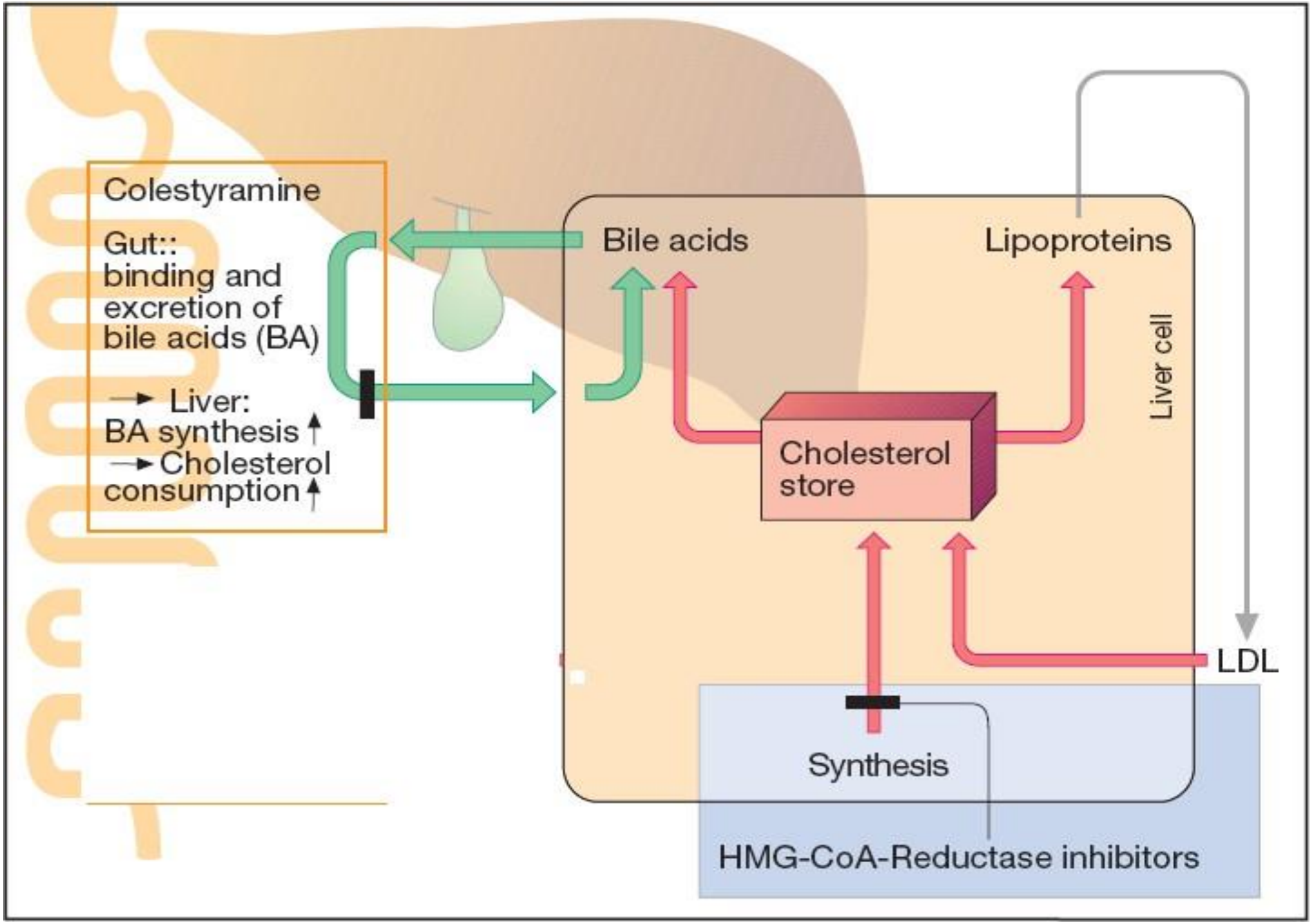
Giving statins for some patients isn't enough to lower the LDL to our target , so we give those with them. Or for a patient that cant tolerate statin

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

- These agents are anion exchange resins that bind negatively charged bile acid in the intestine, forming insoluble complexes that will be excreted in the feces.

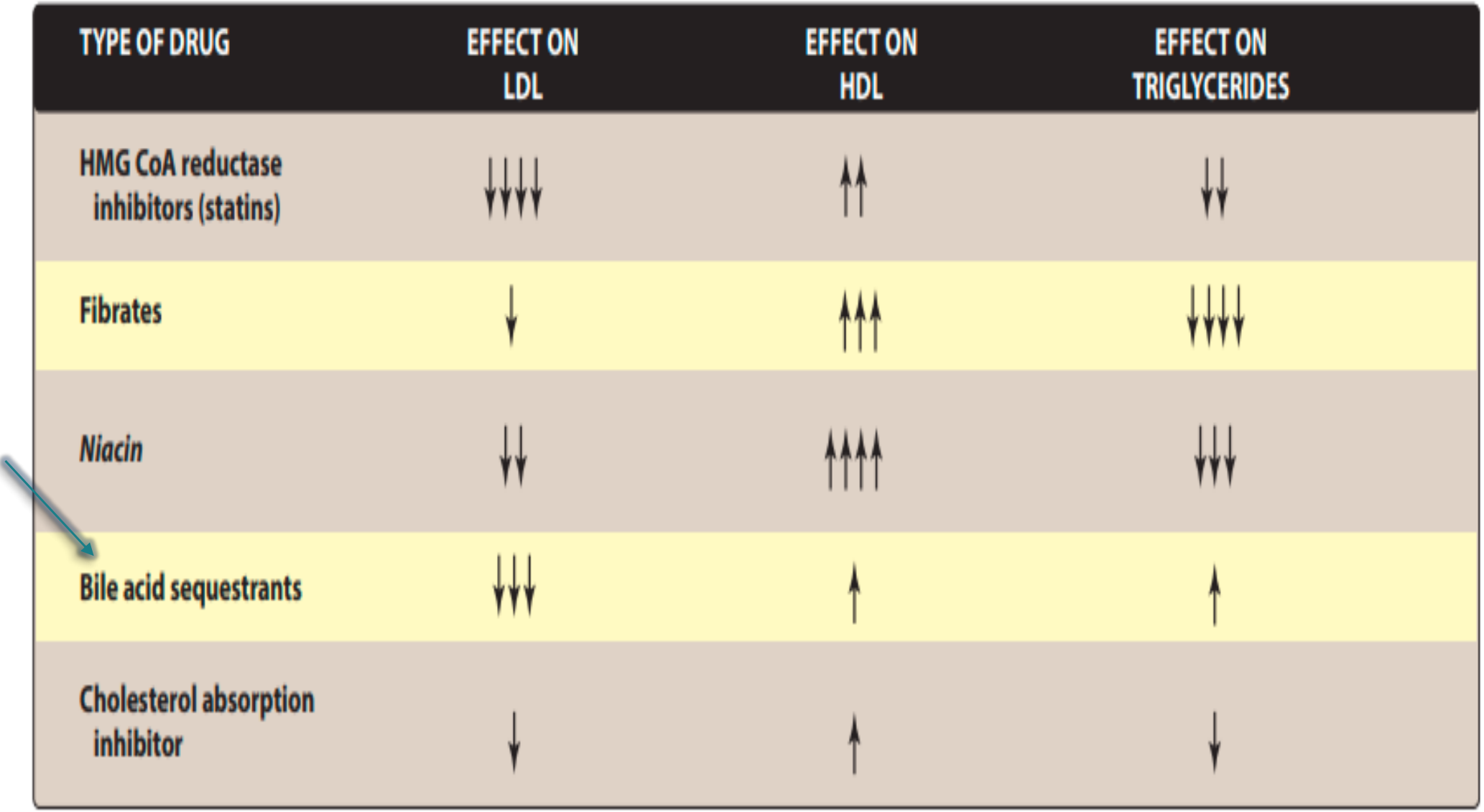
- Lowering bile acid level will increase the conversion of cholesterol into bile acid in the liver and the end result will be a reduction in the intracellular cholesterol concentrations. What happens here is the same thing that happened with statins, decreased cholesterol levels means increased LDL receptors , meaning we deplete the LDL in the circulation , and we decrease the VLDL.

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


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.**



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

The doctor didn't mention all the following slides , enjoy☺

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

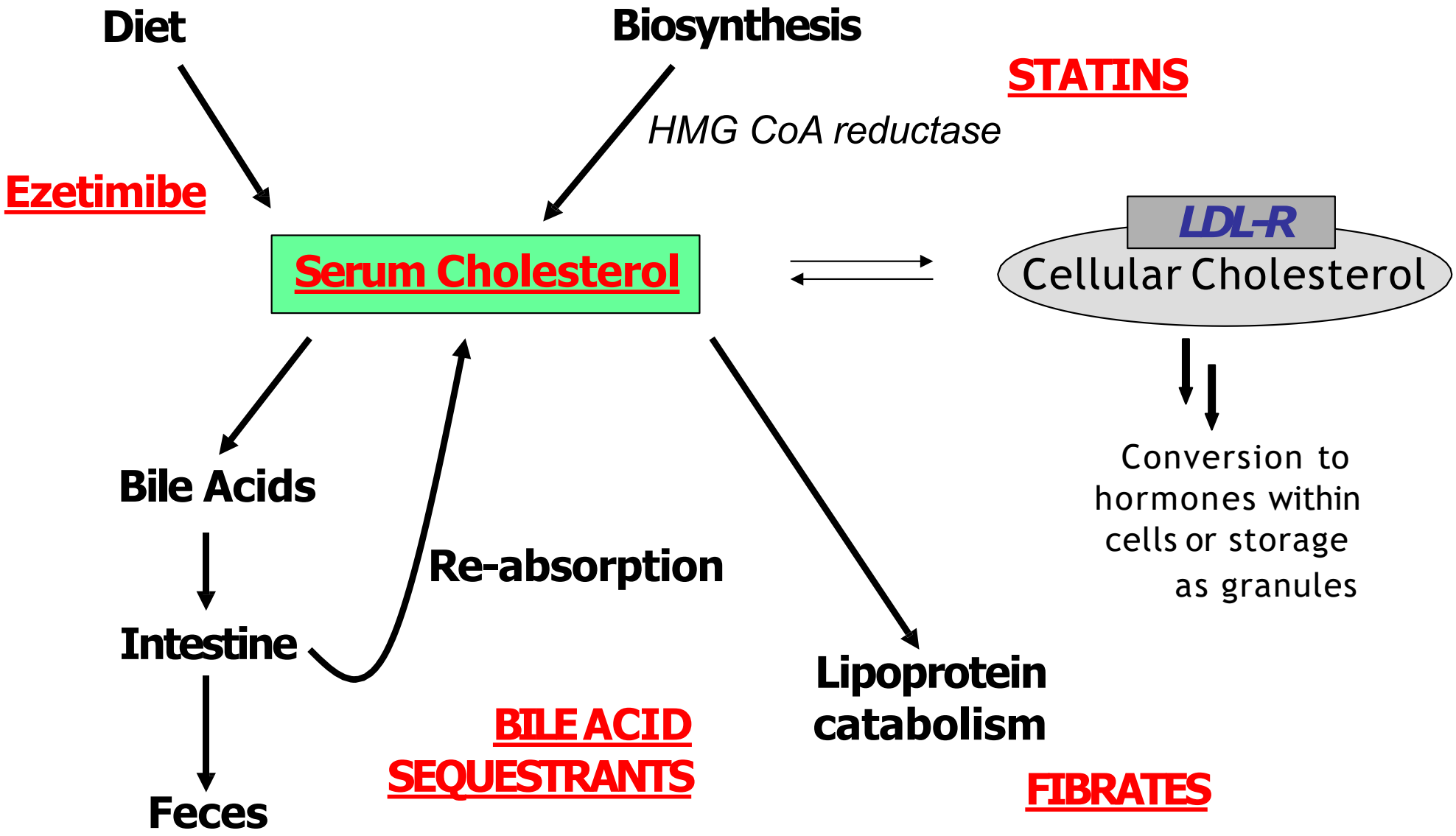

Table 35-3. Lipid-modifying effects of antihyperlipidemic drugs.*

Drug	LDL Cholesterol	HDL Cholesterol	Triglyceride
AtoNastatin	-25%to-40%	+5% to-10%	j,j,
Fluvastatin[1]	-20% to-30%	+5°/o to-10%	j,
Lovastatin[2]	-25%to-40%	+5% to-10%	j,
Cholestyramine, colestipol	-15 /o to-25%	+5%	±
Gemfibrozil	-10% to-15%	+15% to-20%	j,j,
Niacin	-15% to-40%	+25% to-35%	j,j,

*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 *lova* statin.

±=variable, if any.

اللهم ارزق إخواننا في فلسطين الصمود والقوة في وجه الطغيان وانصرهم.

اللهم ارحم أهلنا في غزة و ادلب و جميع بلاد المسلمين يا رب

Thank You

V2:slide 21 , the MOA of fibrates was changed a bit, it had some misinformation regarding the levels of LDL.

v3: added some notes in green , additional notes that the doctor mentioned in the other sections

v4: Added a note on how fibrates cause lithiasis