Doctor.021

no. 1, part2

CVS PHARMACOLOGY

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Just to recap, we have started talking about drugs that are used for lowering hyperlipidemia and we mentioned three drugs: statins, niacin and fibrates.

- Now, generally speaking in many cases that we face patients may not really have a good response toward statins or they may have a partial response toward them, so we sometimes need to add some drugs with statins.
- We mentioned that fibrates have a problem in increasing the rhabdomyolysis and myopathy incidence, also fibrates are directed towards VLDL and triglycerides rather than LDL cholesterol.
- As well as we mentioned that gemfibrozil is contraindicated with statins.
- Niacin is "falling out" of treatment of hyperlipidemia.

- So, we need other options in terms of lowering LDL, actually we have two groups of drugs that we will take about in this sheet: one of them binds to cholesterol within GIT and the other binds toward bile acid whitin GIT.

Bile acid-binding resins

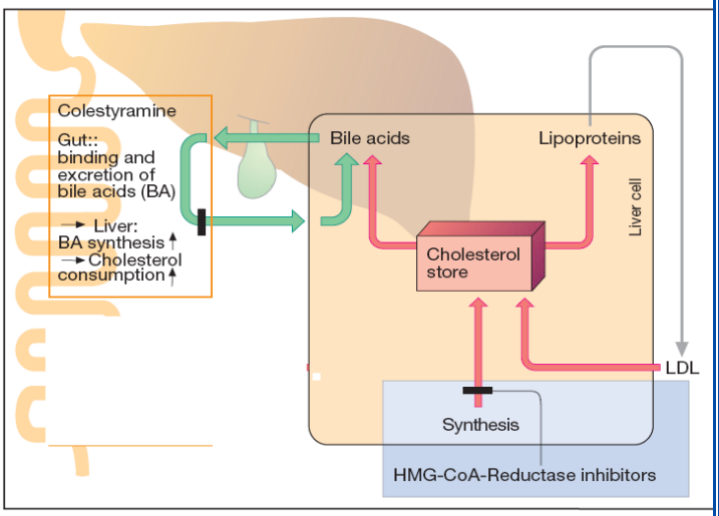
- These drugs bind toward bile acid within GIT and they increase its excretion through the feces, as a result more cholesterol is needed to synthesize new bile acid, so cholesterol level will be reduced.
- Resins, means something like glue, they bind to bile acids and excrete them out of the cells.
- **Cholestyramine and colestipol have significant LDL cholesterol lowering effect, although the benefit is less than those observed with statins (bile acid binding resins are less**

effective than statins). However, they are added with statins in patients who do not respond well to statins alone.

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

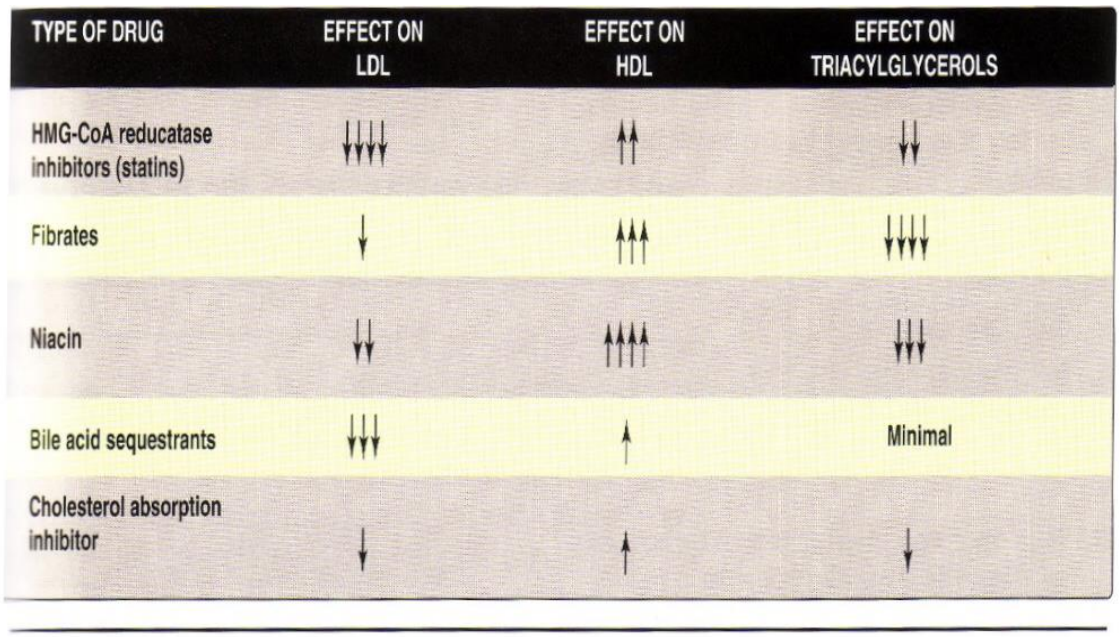
Therapeutic uses: The bile acid binding resins are the drugs of choice (often in combination with diet or niacin) in treating Type lla (high level of cholesterol).

- Again, MOA: Cholestyramine goes toward the gut, binds with bile acid and execrate it, which makes the liver responds and increases the synthesis of bile acid, this mechanism consumes cholesterol and reduces its level. As a result, LDL level will be reduced too.



- **The most common side effects** (they do not have real side effects) **are gastrointestinal disturbances such as constipation and nausea** caused by the absorption of them in the GIT.
- Those drugs should be taken with food because they react toward food and the activity of bile acid through the absorption of drugs, so bile acid will be execrated more at the time of food intake (it is better to take them with food because at that time the level of bile acids will be elevated).

- Bile acids binding resins are better to be taken with food, unlike statins which are better to be taken at night because they work on inhibiting the cholesterol synthesis which primarily happens at night (fasting, low metabolic time).
- **At high doses they impair the absorption of fat soluble vitamins (A, D, E, and K), bile acid is very important to absorb many molecules, so these drugs may impair their absorption.**
- **These agents interact with the absorption of many drugs** (fat soluble drugs)**, for example, Tetracycline, Digoxin, Warfarin, Aspirin.** (Which is problematic especially for the first drugs.)
- **Therefore, drugs should be taken at least 1 to 6 hr <u>after</u> bile acid sequestrants.**
- The end results of these bile acid sequestrants is a good reduction of LDL level in the blood, and they add on the activity of the HMG-CoA reductase inhibitors (statins) as we said before, and we may need to use them with niacin sometimes to reduce LDL and increase HDL.



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.

Cholesterol absorption inhibitors

Ezetimibe selectively inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine, resulting in an increase in the clearance of cholesterol from the blood. (their activity is mild towards lowering LDL, see the pic above)

- Ezetimibe is the drug that inhibits the intestinal absorption of cholesterol from the blood SELECTIVELY, so it does not bind to bile acid.
- This drug is a good combiner with statins. As ezetimibe has a very limited activity if it is used alone (not a real effect only reducing LDL and VLDL and increasing HDL a little), but when used with statins, they exert a **synergistic activity** toward reducing the LDL and cholesterol levels. (And a drug that combines Ezetimibe and statins within the same bill is available)
- The reason why that combination is powerful is because when the synthesis of cholesterol is inhibited within the liver and its levels will be low (by statins), cholesterol will be absorbed more from GIT as a compensatory mechanism towards the statin effect (and this absorption will be impaired by the use of cholesterol absorption inhibitors), as well as that will call the LDL to increase its expression and it will collect the cholesterol from the blood.
- Another mechanism may take place, that increasing the absorption of cholesterol toward the portal vein and so toward the blood, so when ezetimibe is added to statins it will exert a good synergistic response and inhibit that absorption.

Common adverse effects are headache and/or diarrhea. (very little side effects)

Ezetimibe (like bile acid binding resins) is better to be taken with food, while statins are taken before bed, and doesn't matter when fibrates are taken (directed towards VLDL).

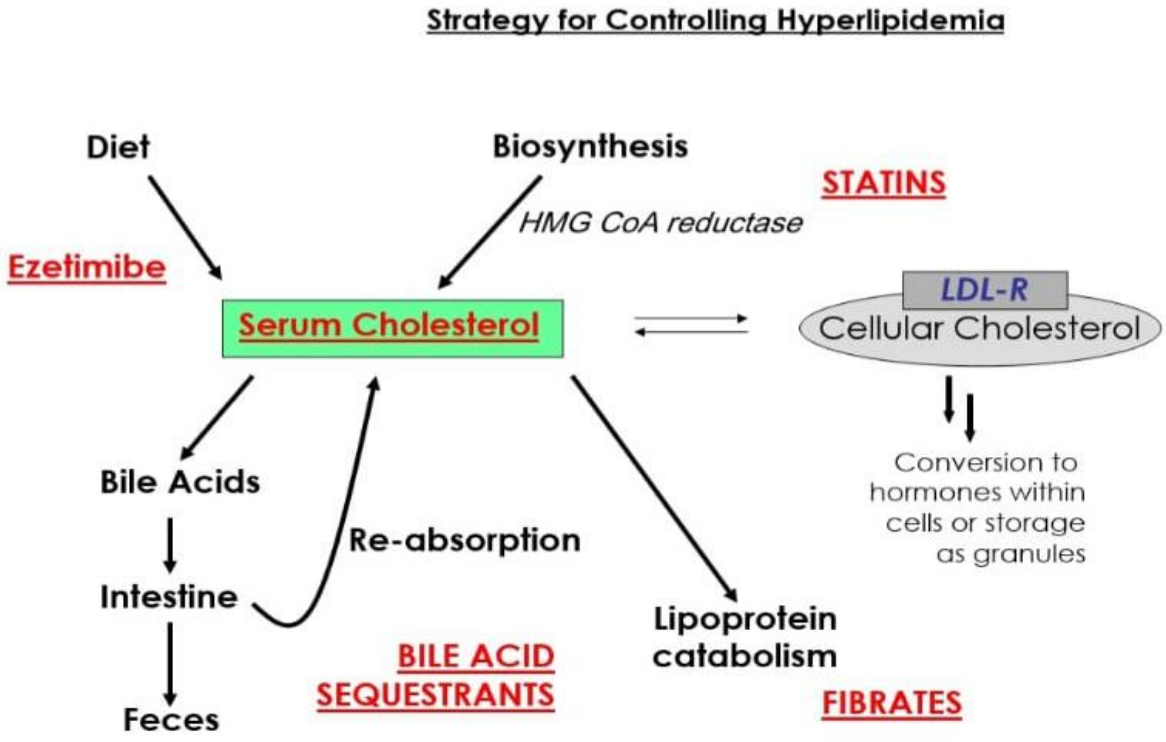


Table 35–3. Lipid-modifying effects of antihyperlipidemic drugs.*

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.