CVS
PHARMACOLOGY

Modified NO: 8

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Welcome all to the world of Antihyperlipidemic drugs :)

Let's recap everything related to the Antihyperlipidemic drugs concept in our course:

1. Lecture 1 (Antihyperlipidemic drugs 1) > covered in modified (2)
2. Lecture 2 (Anti hyperlipidemc drugs 2) > will be covered in this modified
3. Lecture 3 (Lipid lowering agents) > will be covered in the next modified
4. Lectures 1 was held in person , while 2+3 are online
5. Kindly watch the first 6 min from the (anti arrhythmic drugs 1 lecture) , where the concept of Statins and Fibrates combination was explained, (I will summarize it in a minute)
6. Let's Go :)

- We have **5 main categories** of drugs when talking about **Antihyperlipidemic drugs** (the older ones in the market)

- 1. **Statins**
- 2. **Niacin**
- 3. **Fibrates**
- 4. **Bile acid-binding resins (or sequestrants)**
- 5. **Cholestrole absorption inhbitors (Ezetimibe)**
- The first 3 were explained in the previous lecture

- **Some notes about the previous lec :**
- Some patients have a partial response, or even no response toward **Statins** , so in many cases we need to **Add Drugs On** with Statins
- **Statins** and **Fibrates** may increase **myopathy and rhabdomyolysis**
- Nowadays Niacin is failing in treating hyperlipidemis , and is rarely prescribed
- The **Fibrates** mechanism of action is to lower the **VLDL and TAGs** , more than lowering LDL-C

- **The combination of Fibrates and Statins** :
- Firstly, you have to know that there is a slight difference between the Fibrates' subtypes (**Fenofibrate and Gemfibrozil)**
- Fibrates cause **Myositis**, however it is mild , and **can be worsen when giving Statins at the same time .**
- **Fenofibrates** cause **Myositis** and **Statins** cause **Myopathy**, so this will lead to a terrible situation regarding to muscles , However, in some cases we have to combine them together when both VLDL and LDL are elevated , as there is nothing better than **Fibrates** in decreasing **VLDL** , and nothing better than **Statins** in decreasing **LDL** .
- So How to overcome this obstacle?
- **Give them at 2 separate times a day** :
- **Statins at night** (as cholesterol synthesis occurs mostly during the night , remember that statins inhibit the cholesterol synthesis)
- **Fibrates during the day**
- What about **Gemfibrozil** ?
- Actually , **it's contraindicated to combine it with Statins** , bc Gemfibrozil **inhibit the CYP450** (which metabolises the Statins) , thus **Statins will accumulate** and this increases the risk of **Myopathy**
- So Do all Fibrates can't be given with Statins ? **No** , we **can** combine it with **Fenofibrates** (but at 2 different times in a day) . But for Gemfibrozil it's contraindicated.

- In this part of the modified we will review 2 groups of drugs that lower the LDL-C :

- 1. Bile acid-binding resins (sequestrants) > will bind to Bile acids within the GIT
- 2 . Cholestrole absorption inhbitors (Ezetimibe) > will bind to Cholesterol within the GIT

Let's start with Bile acid-binding resins (sequestrants) 

Bile acid-binding resins

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

- So they are not better than statins. They are less efficacious . However, we can add them to Statins in patients who do not really respond to the Statins .

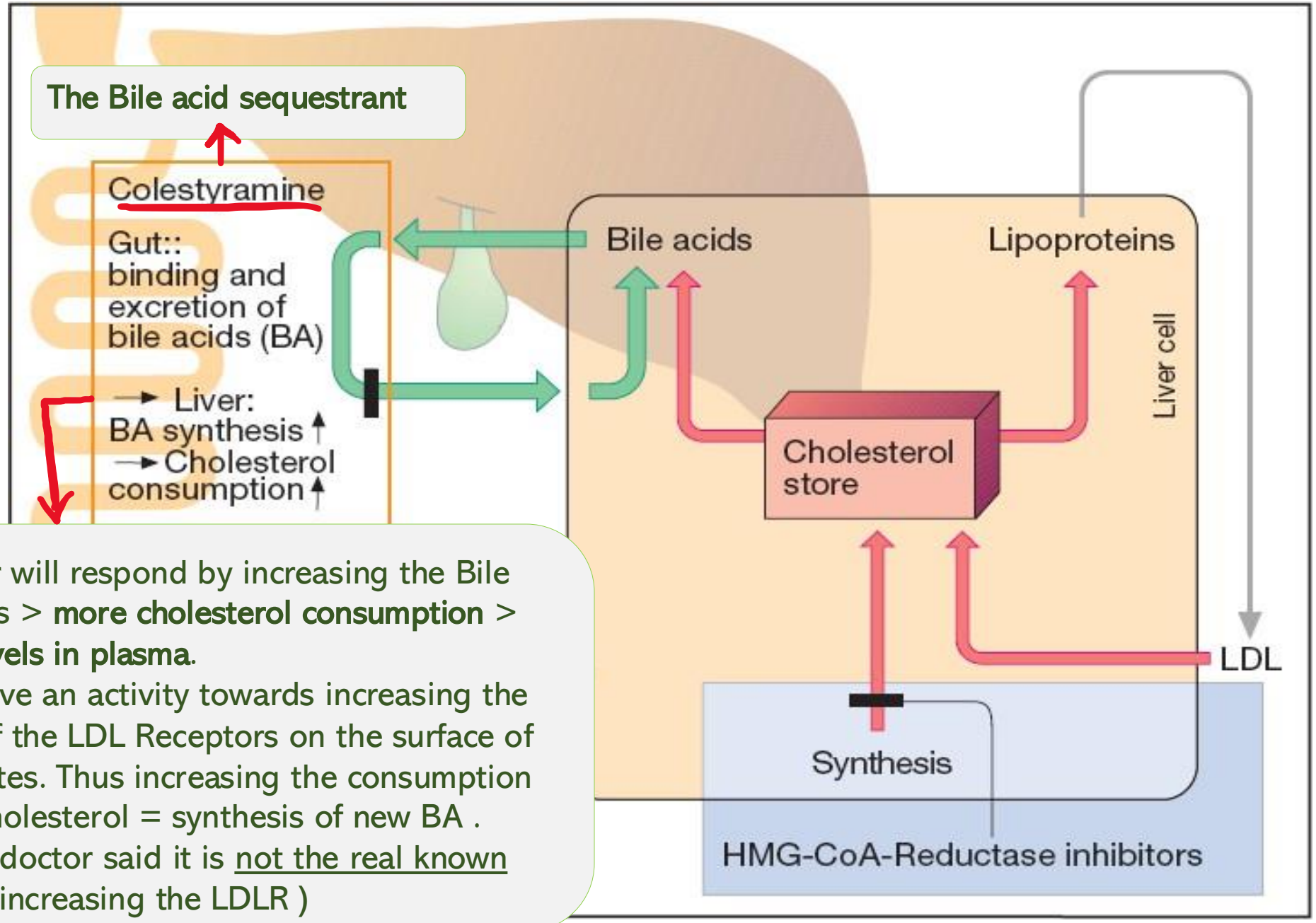
The mechanism of Action

Resin = صمغ
Stick to BA

- **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.**

- **Things you have to know to understand the mechanism of action :**
- Bile acids are **synthesized** in the **liver**, with **cholesterol** being a key **component**.
- Bile acids are secreted into the intestine, where they emulsify dietary fats and cholesterol, promoting their absorption
- When **bile acid levels decrease in the intestine** ,as part of the MOA of these drugs , **the liver compensates by producing more bile acids**, which involves **using cholesterol**. This process helps in **reducing cholesterol levels in the plasma** as the liver consumes it to maintain bile acid synthesis, ending up with **decreased LDL levels.**



Now the liver will respond by increasing the Bile acid synthesis > **more cholesterol consumption** > **lower LDL levels in plasma**.
(We **might** have an activity towards increasing the expression of the LDL Receptors on the surface of the hepatocytes. Thus increasing the consumption of the LDL cholesterol = synthesis of new BA .
However,the doctor said it is not the real known mechanism (increasing the LDLR)

Bile acid-binding resins

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

- Bile acids-binding resins should be taken with **food**, unlike statins, which are taken at night.
- *reminder : Type IIa is represented by high LDL

- Bile acids are released from the gallbladder into the intestines when food, especially fatty food, enters the digestive system. Taking bile acid sequestrants with meals ensures they are present in the GI tract at the same time as bile acids, optimizing their binding and effectiveness.

Bile acid-binding resins Side effects :

- **The most common side effects are gastrointestinal disturbances such as constipation and nausea.**

- **At high doses they impair the absorption of fat soluble vitamins (A,D,E, and K)**

  - Because these fat soluble vitamins' absorption is dependent on bile acids , thus their absorption will be impaired. So we should monitor these vitamins while using this drug , some doctors prescribe vitamin supplements with the drug.

Bile acid-binding resins Side effects :

- **These agents interact with the absorption of many fat soluble drugs, for example, Tetracycline, Digoxin, Warfarin, Aspirin.**

- **Therefore, The above drugs should be taken at least 1 to 6 hr after administration of bile acid sequestrants .**

- Bile acid sequestrants are well-known and generally well-tolerated drugs. Although they may cause some side effects, these are typically mild and mainly involve gastrointestinal disturbances or interference with the absorption of other medications.

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	↓	↑	↓

- In conclusion, Bile acid sequestrants are **good reducers of LDL** , Same as Statins which also reduce LDL significantly, so we usually use **Statins with Bile acid sequestrants** .

- The second group in this lecture :
- Cholestrole absorption inhibitors (Ezetimibe) 

Cholestrole absorption inhbitors

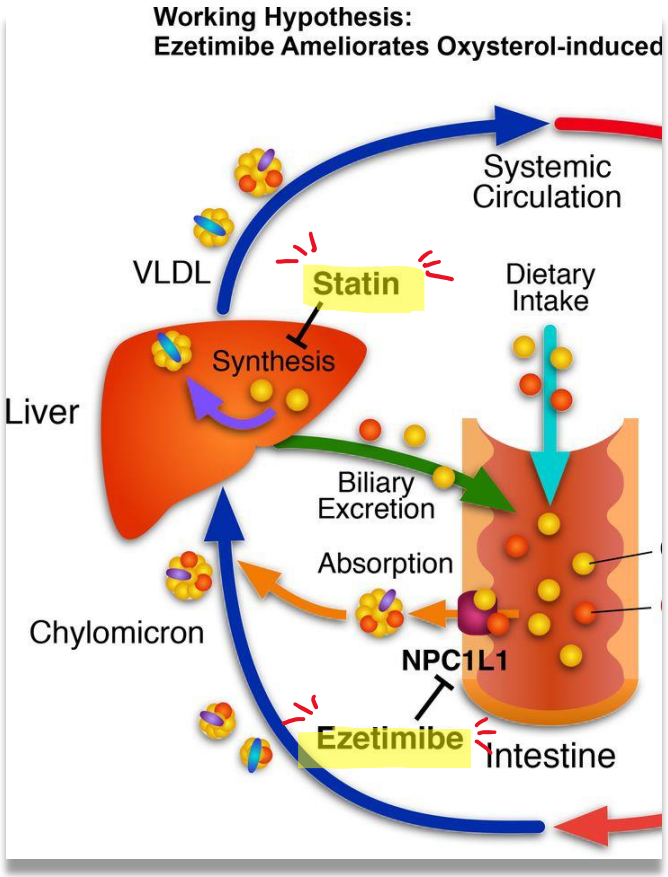
- Unlike the Bile acid sequestrants which bind to " Bile Acids in intestine " , **Ezetimibe will selectively bind to the "Cholesterol itself "inhibiting intestinal absorption of dietary and biliary cholesterol in the small intestine**, resulting in an **increase in the clearance of cholesterol from the blood.**
- **Issues to know about Ezetimibe :**
- It has **very minimal side effects** such as headache or diarrhea.
- It has **very limited activity when it is used alone**.
- however It is found that **when combined with Statins**, it will provide a **synergistic effect** towards the **reduction of LDL cholesterol** reducing the plasma cholesterol more and more.
- Statins+ Ezetimibe = synergism
- They are sometimes used with **Niacin**.

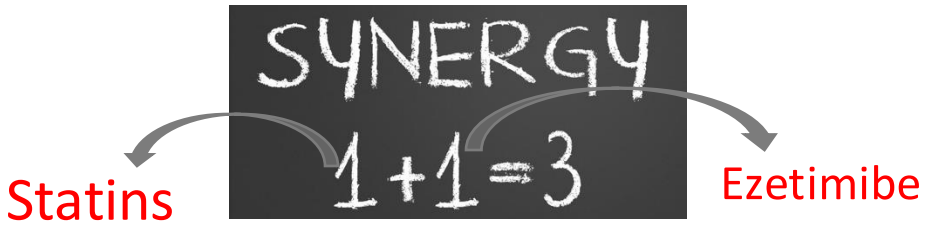
- To understand the synergistic effect :

- Statins and ezetimibe have a **synergistic effect** in **lowering LDL cholesterol** levels by targeting different pathways of cholesterol metabolism. **Statins inhibit HMG-CoA reductase,** reducing cholesterol synthesis in the liver, which increases LDL receptor activity and enhances LDL clearance from the blood. **Ezetimibe**, on the other hand, **blocks cholesterol absorption** in the small intestine, reducing the amount of dietary and biliary cholesterol entering the bloodstream. When used together, these drugs provide a more substantial LDL reduction than either agent alone, making this combination effective for patients needing intensive lipid-lowering therapy.

In other words: Statins inhibit cholesterol synthesis, and as part of the compensatory effect, the body activates a **feedback mechanism** that **increases cholesterol absorption.** Here, **ezetimibe plays its role by reducing cholesterol absorption.**

This way, we decrease both synthesis and absorption, resulting in a synergistic effect!!





Cholestrole absorption inhbitors

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.

Common adverse are headache and/or diarrhea.

- Explained previously

- Explained previously

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 .

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
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Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

- Emphasizing on what we have said previously , **Ezetimibe** has a very mild and limited activity when used alone (lowering VLDL , LDL by **one arrow**) .

- This is a diagram summarizes the 5 drug categories
- Everything is explained in the previous slides

Strategy for Controlling Hyperlipidemia

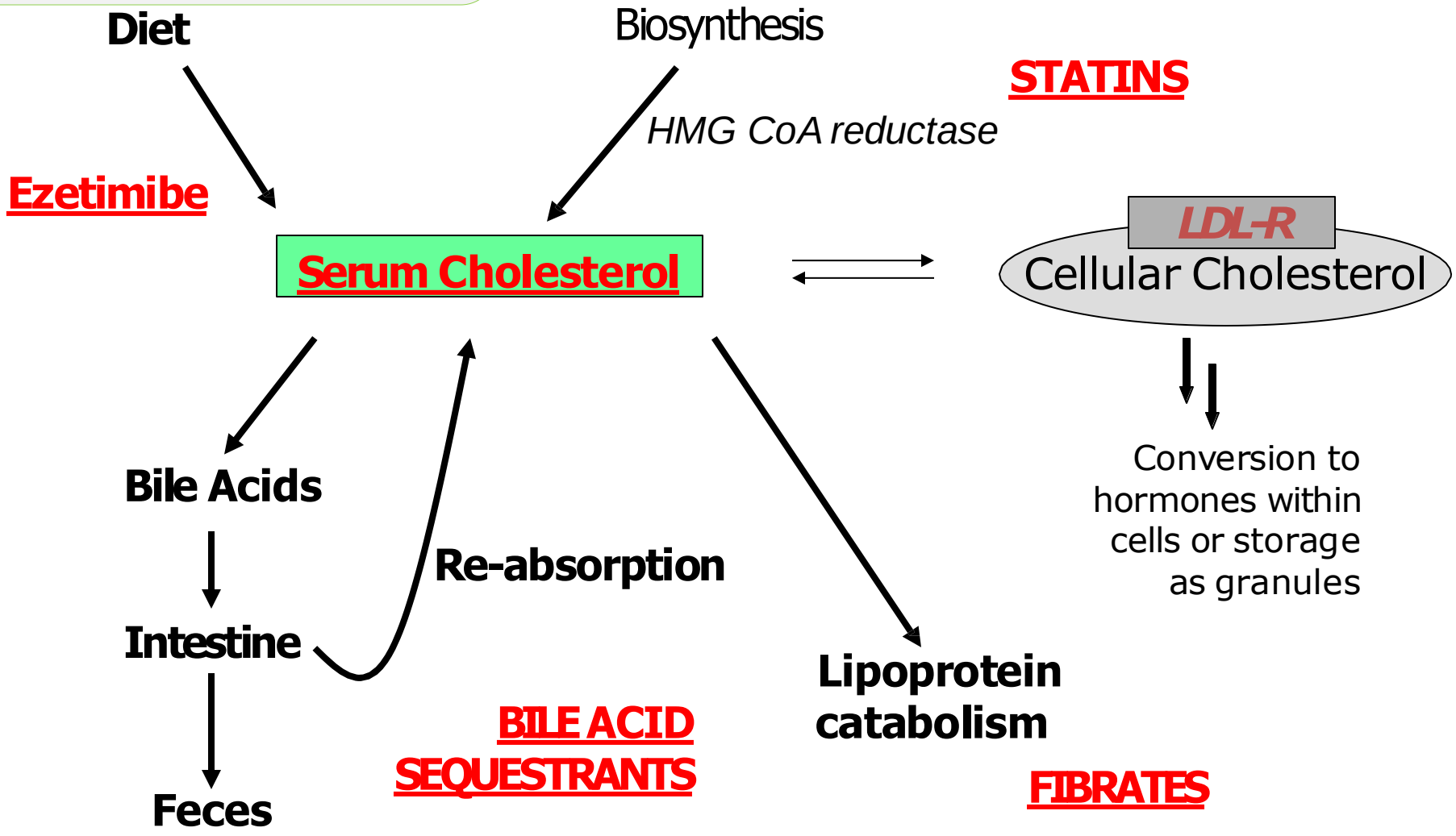

Table 35–3. Lipid-modifying effects of antihyperlipidemic drugs.*

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.

To recap:

Antihyperlipidemic drugs:

1- statins

2- Niacin

3- Fibrates

4- Bile Acid – binding resins (sequestrants)

Ex: Cholestyramine and colestipol

MOA: bind to bile acid in the intestine —> triggering the conversion of cholesterol into bile acid —> reduction cholesterol concentration

Side affects: 1) gastrointestinal disturbances (constipation + nausea)

2) Impair fat soluble vitamins absorption (A,D,E, and K)

3) Impair fat soluble drugs absorption (Tetracycline, Digoxin, Warfarin, Aspirin)

"Added On" with Statins

Taken with food

5- Cholestrol absorption inhbitors

Ex: Ezetimibe

MOA: Selectively inhibit absorption of cholestrol

Very minimal side effects (headache + diarrhea)

Very limited activity (one arrow)

Provide synergistic affect with statins (1+1=3)

Both have minimal effects compared to statins

قال ابن القيّم :

" فإنّه القلبُ ، كلّما كانت حياتُهُ أتمّ

كان غضبه لله و رسوله أقوى

و انتصارُهُ للدّين أكملُ "

فأينَ أنت مِن هذا ؟

Additional sourcesl :

. 1.Fouda :

https://youtu.be/815ebVbCWrE?si=SGQCn0EtZ5wMY4zc

2. https://youtu.be/-VwH33qYjPw?si=DCqYXnzebEd_NRGC

3. Ninja nerd :

https://youtu.be/t5BODWgysAY?si=wZzk5suMaB5BEWpC

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!