CVS
PHARMACOLOGY

Modified NO:

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❖ The flow of information in this lecture:

1. Discussing Antihyperlipidemic drugs in general.
2. Discussing the Statins (first antihyperlipidemic drugs in this lecture).
3. Discussing the Niacin (second antihyperlipidemic drugs in this lecture).
4. Discussing the Fibrates (third antihyperlipidemic drugs in this lecture).

بسم الله نبدأ

Firstly, we will discuss antihyperlipidemic drugs in general 👌💊

Color code

- Slides
- Doctor
- Additional info
- Important

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).

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 of lipoproteins.

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

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

- Hyperlipidemia is closely linked to the cardiovascular system because many cardiovascular diseases, such as congestive heart failure, angina pectoris, and hypertension, are exacerbated by hyperlipidemia. This is primarily due to its strong association with atherosclerosis.

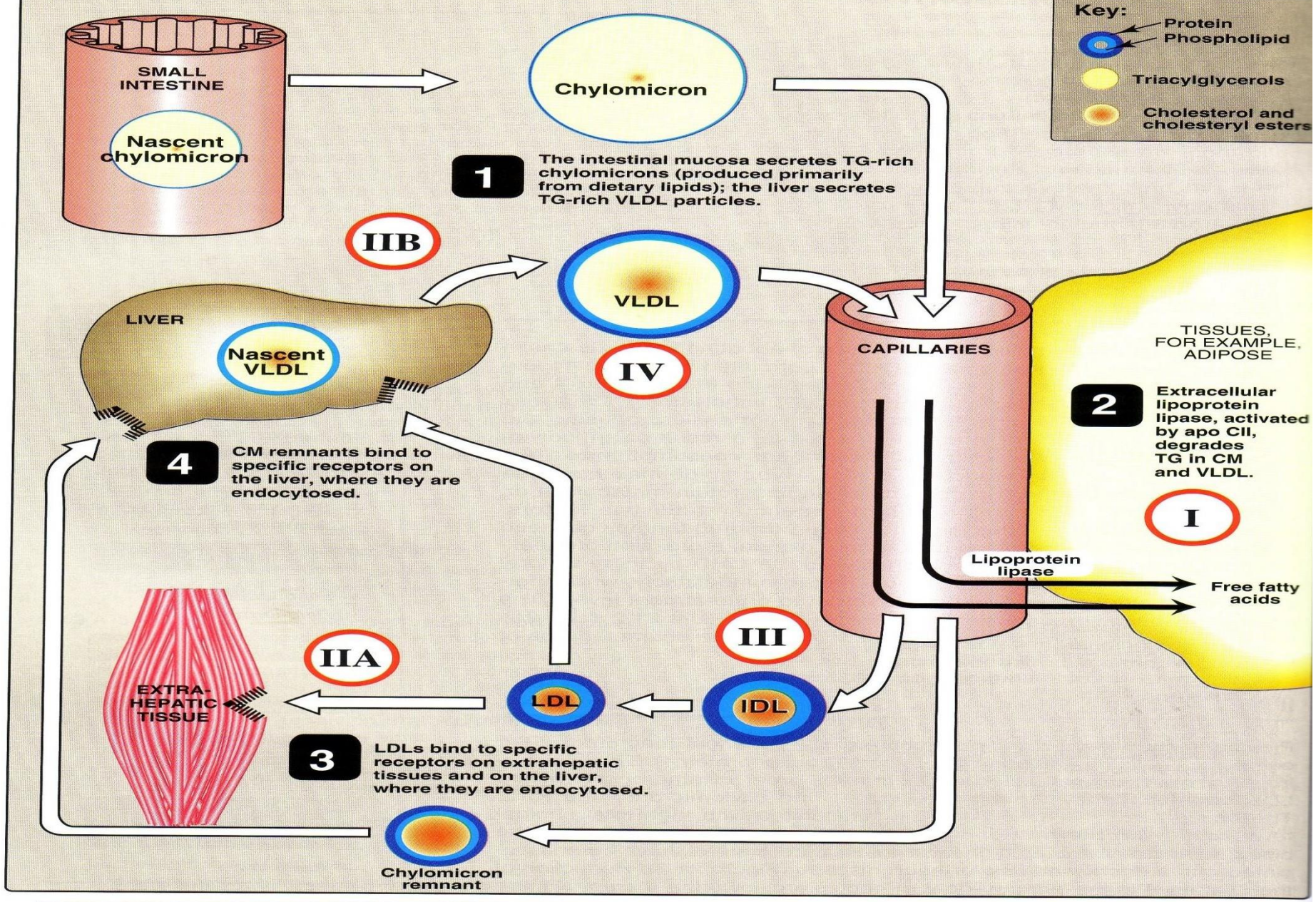


Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. The Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM=chylomicron, TG = triacylglycerol; VLDL=very-low density lipoprotein, LDL=low-density lipoprotein, IDL=intermediate-density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

- The lipids that we consume will go through the gastrointestinal (GI) tract, where their absorption relies on the presence of bile acids. Bile acids bind to fatty acids and cholesterol, forming micelles, which facilitate their absorption through the wall of the duodenum. During this process, a molecule called chylomicron is released.

- Chylomicrons do not enter the bloodstream directly with bile acids; instead, they are transported through the lymphatic system. They travel via the lymphatic circulation and eventually enter the bloodstream at the thoracic duct, then chylomicrons deliver lipids to extrahepatic tissues to itemize them through muscle tissues, the lipids are utilized to produce ATP, while in adipose tissues, fatty acids are stored. This process is facilitated by glycoprotein lipase, which breaks down triglycerides into fatty acids for uptake by tissues.

- The liver plays a significant role by producing very low-density lipoprotein (VLDL) and releasing it into the bloodstream. VLDL is essential as a source of fatty acids and cholesterol, which are used for the synthesis of hormones like testosterone, androgens, and estrogens. However, excess VLDL and chylomicrons are partially converted into remnants that return to the liver for further utilization. A portion of VLDL and chylomicrons is also converted into low-density lipoprotein (LDL).

- **LDL** (Bad cholesterol) plays a major risk because it can bind to receptors on macrophages, leading to the formation of **foam cells** by absorption of LDL and cholesterol . Foam cells accumulate beneath the endothelial lining, contributing to plaque formation in atherosclerosis. This makes reducing LDL levels critical, as LDL plays a central role in the development of atherosclerotic plaques.

- The primary targets in managing lipid levels are LDL and VLDL. Because elevated levels of these lipoproteins may result from a high-fat diet or familial lipid disorders, leading to an increased risk of atherosclerosis and cardiovascular complications.

foam cells

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

- Familial types(genetic):
- Type1 is a very rare disease
- Type IIb is typical Jordanian patients with a high fat diet (cheese, labneh, oil and mansaf) and smokers.
- If there is elevation in LDL there will be elevation in triglycerides.
- Type IIa in individuals who take a lot of cholesterol.
- Type IV in non-obese individuals with high VLDL level.

Now, we are going to discuss Statins 🧑

Their MOA and Side Effects 👉

1. 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.

- Statins are the kings 👑 👑 of anti-hyperlipidemia (six types), we will focus on **Atorvastatin and rosuvastatin**.

- Rosuvastatin 10mg, Atorvastatin 20mg, simvastatin 40mg, pravastatin 30mg, Lovastatin 40mg and fluvastatin 50 or 40mg. These drugs differ in the potency.

- The most potent is the least dose (the rosuvastatin).
- Rosuvastatin 10mg =20mg of Atorvastatin in potency not efficacy because all of them are equal in efficacy and reach the plateau. We concern with this concept because of the side effects.

- The difference between Potency and Efficacy (additional): 🤔

- Potency: refers to the amount of a drug needed to produce a desired effect. A more potent drug achieves the same effect at a lower dose. For example, rosuvastatin (10 mg) is as potent as atorvastatin (20 mg) because it achieves the same lipid-lowering effect at half the dose.

- Efficacy: refers to the maximum effect a drug can achieve, regardless of dose. In this case, all statins (e.g., rosuvastatin, atorvastatin, etc.) are equal in efficacy, meaning they all lower cholesterol effectively to the same extent once they reach their maximum potential (plateau).

Why Potency Matters: Potency is important to consider because drugs with higher potency require smaller doses, which may reduce the risk of side effects while still being effective. However, efficacy ensures the drug achieves the desired therapeutic outcome.

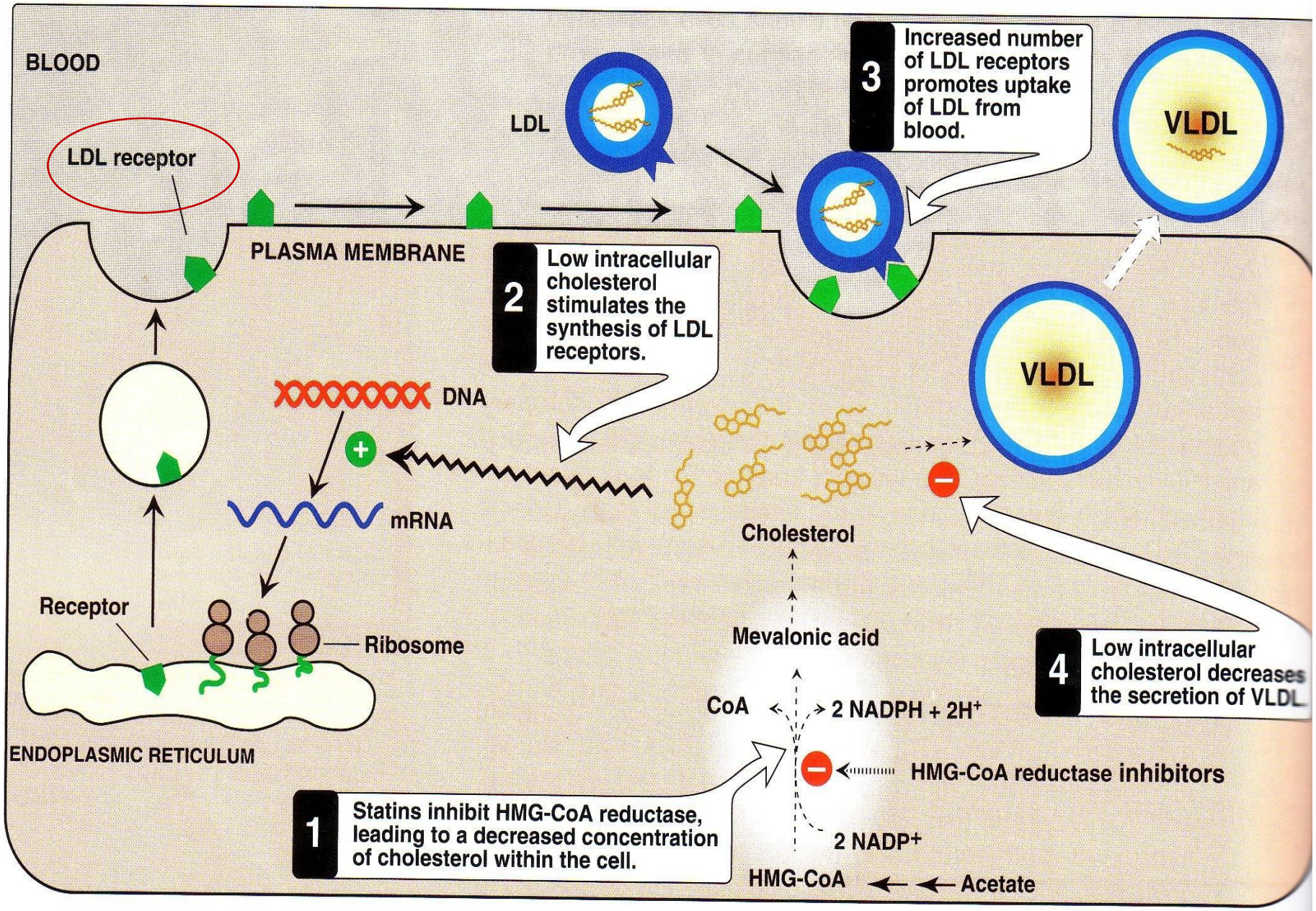


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

- HMG-CoA reductase inhibitors are naturally present in mushrooms.

- HMG-CoA reductase is a rate-limiting enzyme in the synthesis of mevalonic acid, which eventually leads to the production of cholesterol. Cholesterol is an essential compound synthesized in the liver. When the rate-limiting enzyme for cholesterol synthesis is inhibited, the body responds by increasing the transcription and translation of LDL receptors. These receptors bind to the hepatocyte surface and enhance the uptake of LDL (which is rich in cholesterol) from the bloodstream. This process leads to a reduction in LDL levels in the body and a depletion of cholesterol synthesis.

- VLDL contains cholesterol, fatty acids, and apolipoproteins. The fatty acids are absorbed by muscle cells and adipose tissue, while the remaining content is cholesterol.

- HDL is considered “good cholesterol” because it does not contain cholesterol when it is initially synthesized in the liver. Instead, HDL is secreted by the liver to collect cholesterol from foam cells (derived from plaques).

- Statins increase HDL levels, decrease LDL (“bad cholesterol”), and lower VLDL by decreasing its secretion from the liver.

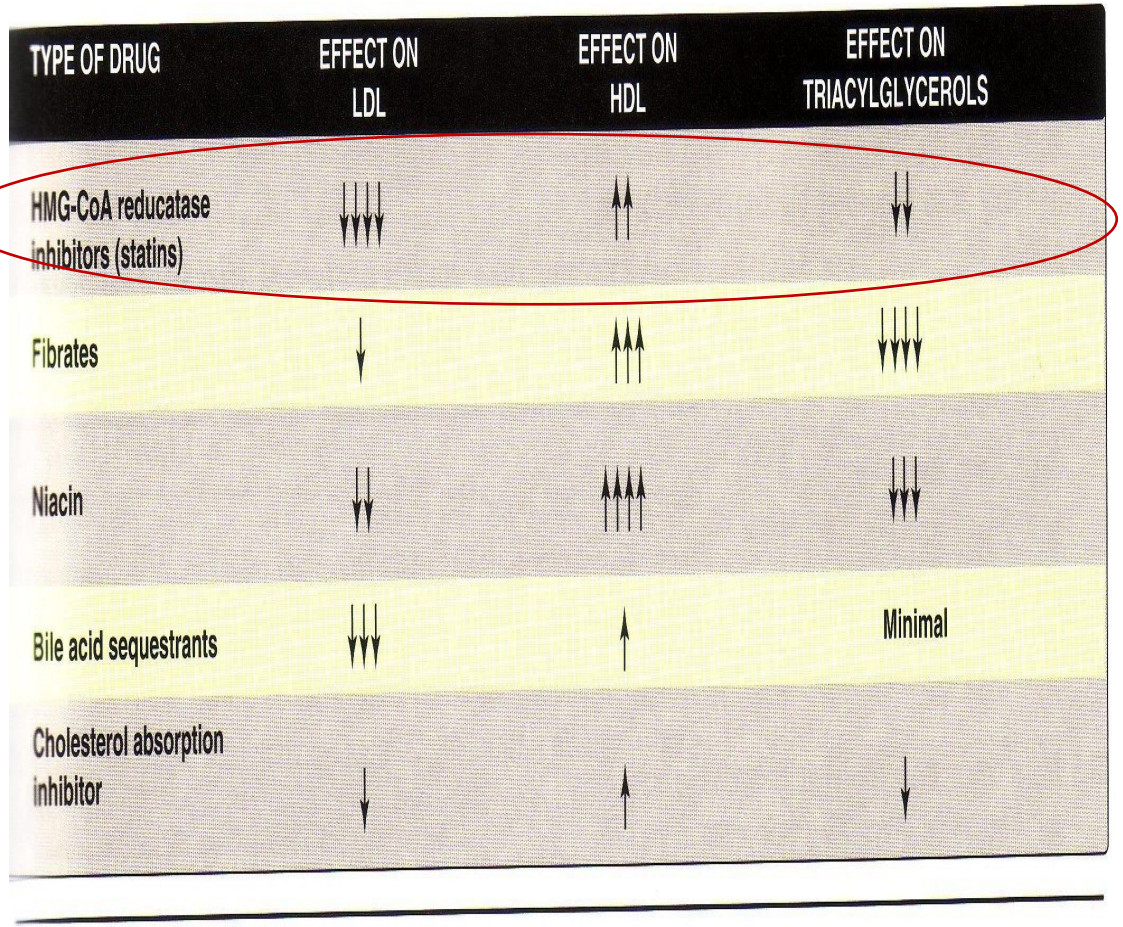


Figure 21.14
Characteristics of hyperlipidemic drug families. HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl–coenzyme A; LDL = low-density lipoprotein.

- Statin decreases the LDL by 4 arrows, triglycerides by 2 arrows, and increases the HDL by 2 arrows.
- The major side effect of statins is **myopathy.** A portion of the statin that does not reach the liver instead accumulates in the muscles, where it binds to CoQ10 (ubiquinone). CoQ10 is an essential component of the electron transport chain, responsible for utilizing oxygen to produce ATP. By inhibiting CoQ10, statins reduce ATP production, leading to muscle pain and weakness (myopathy).
- The liver is the primary site of cholesterol synthesis as it contains HMG-CoA reductase. If the amount of statin that reaches the liver decreases (due to reduced liver uptake, for example), the risk of developing myopathy increases due to higher concentrations of the drug in the muscles.

- The most potent statin, rosuvastatin, is often used to reduce the risk of myopathy by utilizing a lower concentration of the drug that reaches the muscles, thereby minimizing side effects. However, current treatment approaches favor aggressive therapy with the highest tolerated doses. For example, instead of prescribing 10 mg of rosuvastatin, 20 mg is now commonly used, and instead of 20 mg of atorvastatin, 40 mg is prescribed. This adjustment is because the lower doses (10 mg and 20 mg, respectively) are often insufficient to achieve the desired clinical outcomes worldwide.

- There is also a global trend to phase out the use of certain statins (such as lovastatin, pravastatin, simvastatin, and fluvastatin) due to their higher tolerated doses, which increase the risk of myopathy.

- Statins enter the liver through a transporter called SLCO1B1. If there is a polymorphism in this transporter, as seen in some Jordanian individuals, the risk of myopathy increases because more of the drug bypasses the liver and reaches the muscles. This risk remains significant even with potent drugs like rosuvastatin or atorvastatin.

- A test (not currently available in Jordan) exists to evaluate the likelihood of myopathy. Women are particularly at higher risk because they express lower levels of β-glycoprotein than men, allowing more of the drug to enter their bodies. This results in increased efficacy but also a higher risk of side effects. Furthermore, women are more likely to report symptoms of myopathy, which contributes to a higher rate of discontinuation. Approximately 18–20% of patients experience myopathy, a significant proportion that leads to noncompliance, particularly among women.

- Global guidelines recommend using rosuvastatin 20 mg plus or atorvastatin 40 mg plus as the primary treatment. If simvastatin is prescribed, the dose is often 80 mg plus, but careful monitoring for myopathy is required.

Statins

- **Side effects:**

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

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

If the dose of statin is very high (abnormal dose), the muscle cells (myocytes) will damage = this condition is called rhabdomyolysis. Rhabdomyolysis is rare to happen, but it can cause acute renal failure. How? By increasing myoglobin level from damaged muscle cells that lead to Glomerular blockage => acute renal failure.

- هاد نادر الحدوث الا اذا كان الطبيب نايم في العسل او المريض بوخذ الدوا على كيفه

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

Mainly if the cause of hyperlipidemia is:
⬆️ LDL : the statins is best the best choice.
⬆️ VLDL: the fibrates is the best choice (will explained later in the lecture).

This slide and next slide are not required.
Read them for fun 😁.

Statins interaction

The statins are metabolized or catabolized by:
CYP3A4
CYP2C9
Sulfation

So any loss of function in these pathways can lead you to choose the suitable statin drug.

- **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.**

amiodarone or verapamil also causes an increased risk of myopathy.
Because they are inhibit the cytochrome P450

Not required

- 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.

Now, we are going to discuss Niacin 🤗

Its MOA and Side Effects 👉

2. Niacin (vitamin B_3)

- **Mechanism of Action:**

1. 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.

2. Niacin is the most effective agent in increasing 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**

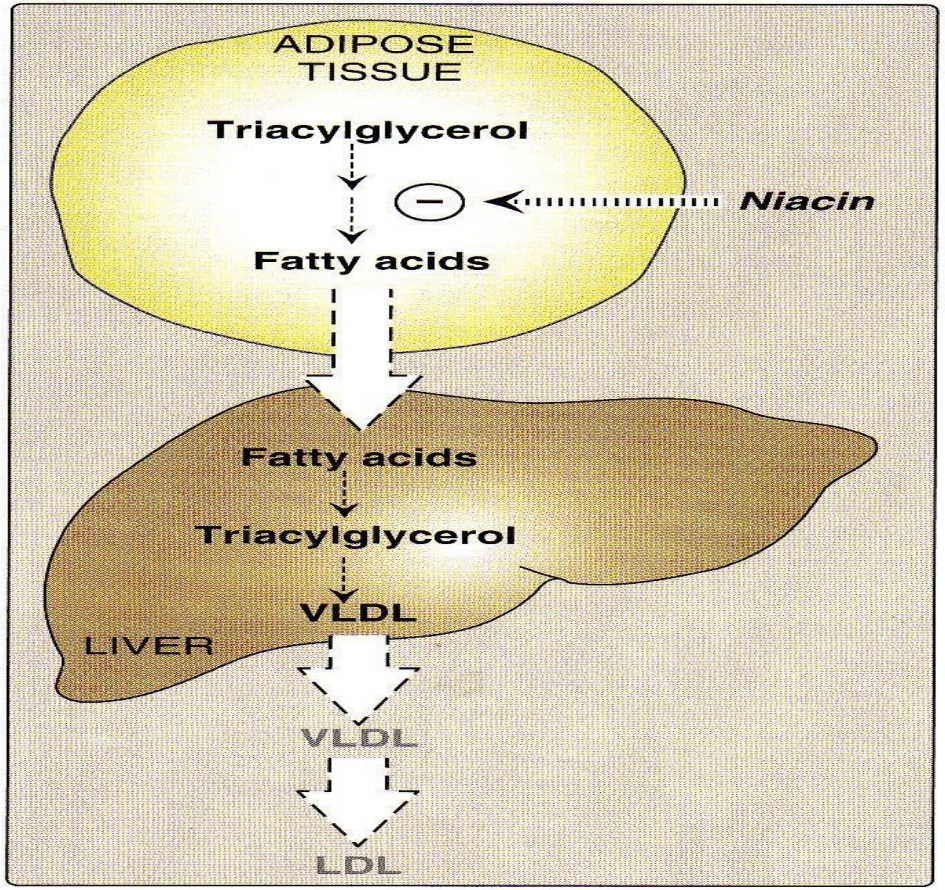


Figure 21.9
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.

The story of niacin(vit.B3):
In the past, the theory was focused on increasing the level of HDL could treat hyperlipidaemia and later on atherosclerosis and so decrease the mortality rate.

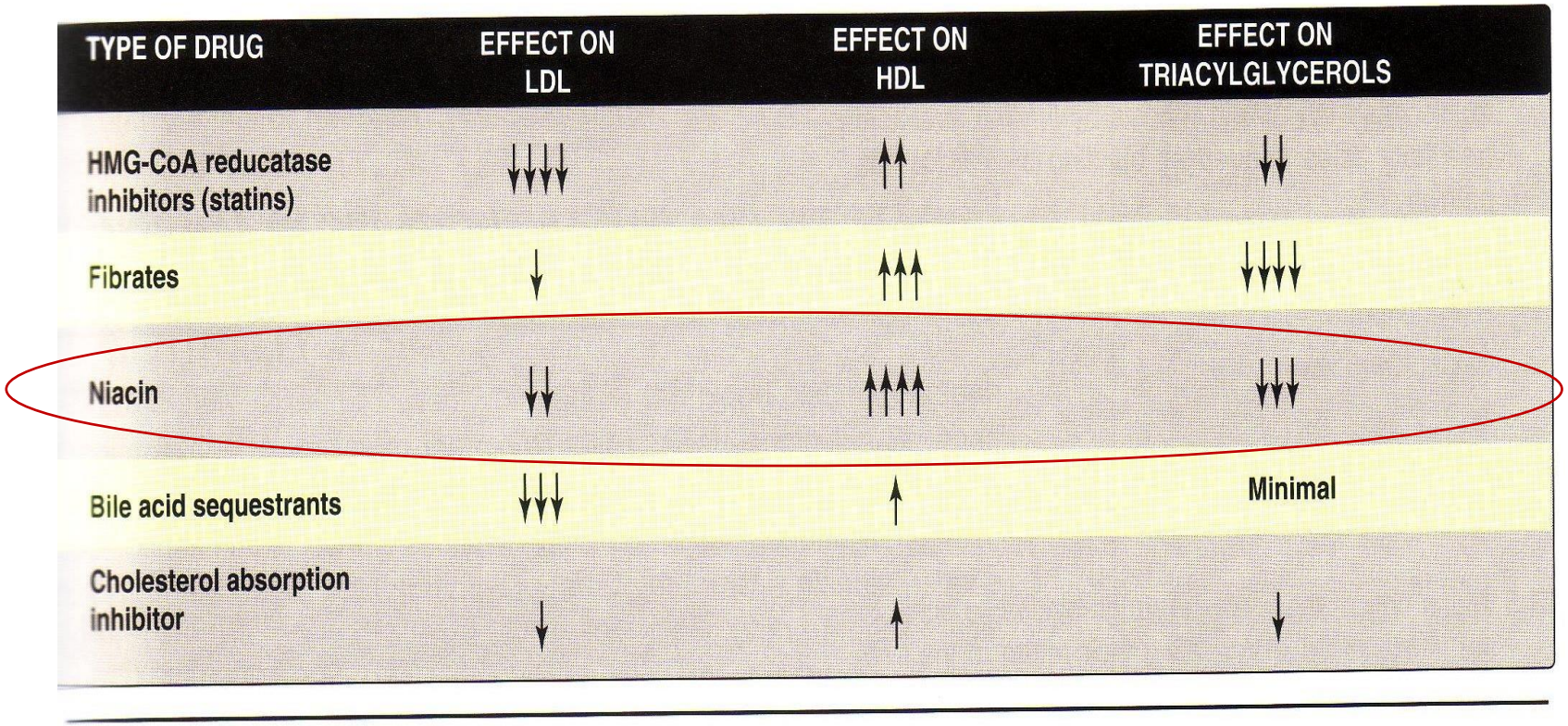
But as a result ,the experience showed no effective effects even if you give niacin only or if you augmented it with a statin.

The mechanism of ⬆️HDL is unknown.

So, it doesn't do any thing and we don't use it anymore.

The mechanism of ⬇️VLDL and ⬇️LDL is w-known:
niacin (vitamin B3) inhibits hormone-sensitive lipase (HSL), which is a key enzyme involved in the breakdown of triglycerides in adipose tissue to fatty acids that will decrease the fatty acidin liver ,decrease VLDL, decrease LDL.
See the image in next slide.

But this function is not special to niacin, it is more effective in increasing 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.

Niacin

Also prostaglandin and interleukin effect on histamine release lead-in to burning and itching.

- Adverse effects: Cutaneous flushing [Because of the niacin structure, it can go to liver and increase the arachidonic acid that will increase prostaglandin and interleukin, which they increase the skin permeability = causing Cutaneous flushing], burning and itching, GI irritation, nausea and vomiting, Peptic ulcer activation, elevation of liver enzymes, hyperglycemia (Inhibit insulin release from islets of Langerhans of pancrease) and hyperuricemia (Inhibit the excretion of uric acid) so it is contraindicated in gout pateints.

- The question is what can I give the patient to release this side effects?

Aspirin or prophine

Now, we are going to discuss Fibrates 🥳

Their MOA and Side Effects 👉

3. Fibrates

As we said before, fibrates are special to patients with high VLDL.

- **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.**

Fibrat 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, and also useful in treating type III hyperlipidemia.**

The explain in the next slide

Fibrates bind to Peroxisome proliferator activated receptors (PPARs). What are Peroxisome proliferator activated receptors (PPARs) ?
They are Nuclear receptors [genetic regulators that control various processes in our body, such as glucose and fat metabolism, by increasing or decreasing the expression of specific genes] 😊 .

Ok, what will happen From this binding ?

1. Increase the expression of lipoprotein lipase gene expression.
2. Then increase the utilization of fatty acids to adipose tissue and muscle.
3. Then decrease VLDL directly and LDL indirectly .

For more understanding this biochemical mechanism, go back to the first image in this file with its explain

This drugs is most suitable for type IV patient and type I.

Statins are more suitable for type IIb patient or we can use a combination drug of it with fibrates.

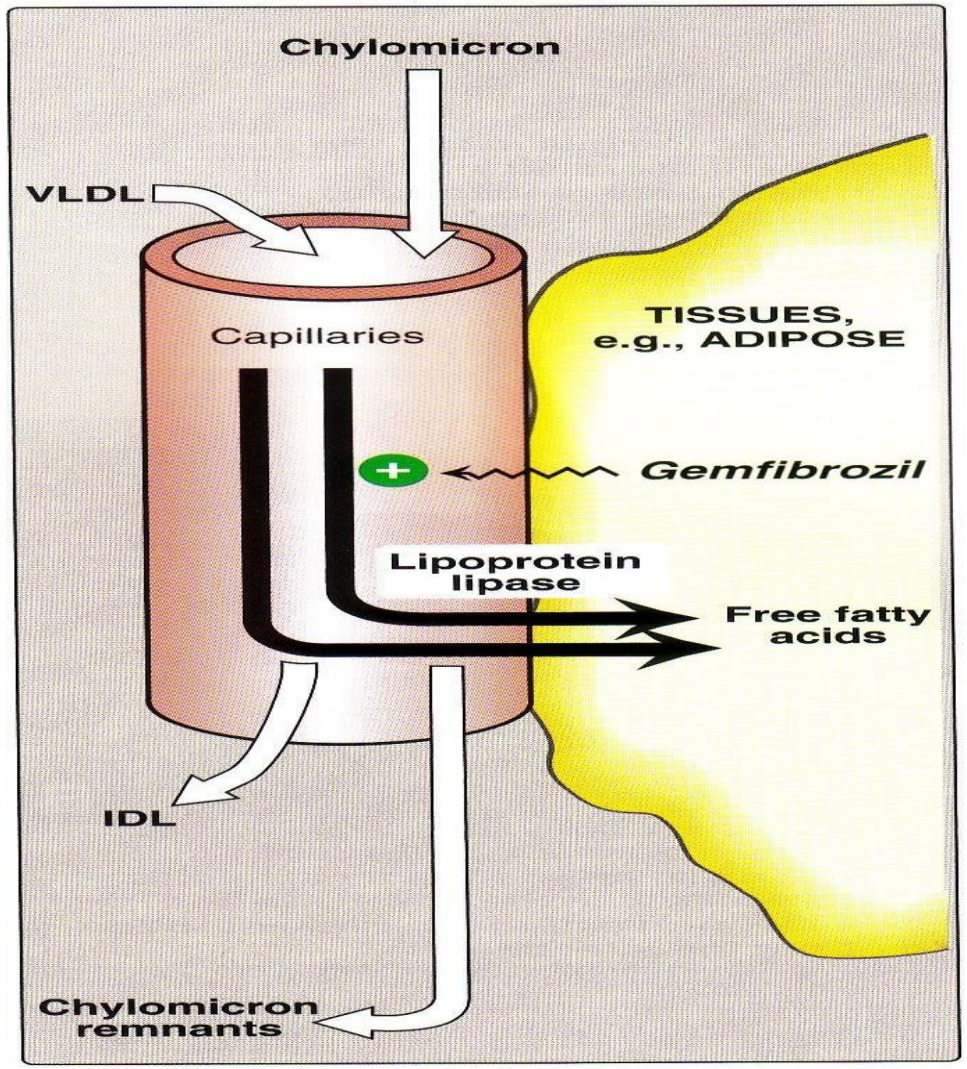


Figure 21.11
Activation of lipoprotein lipase by *gemfibrozil*.

Fibrates

Adverse effect

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

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

Fibrates inhibit alph hydroxylase, which is responsible to metabolize the bile acid.
That lead to increase the bile acid concentration the chance for binding it with cholesterol = gallstones.

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

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

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).

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:

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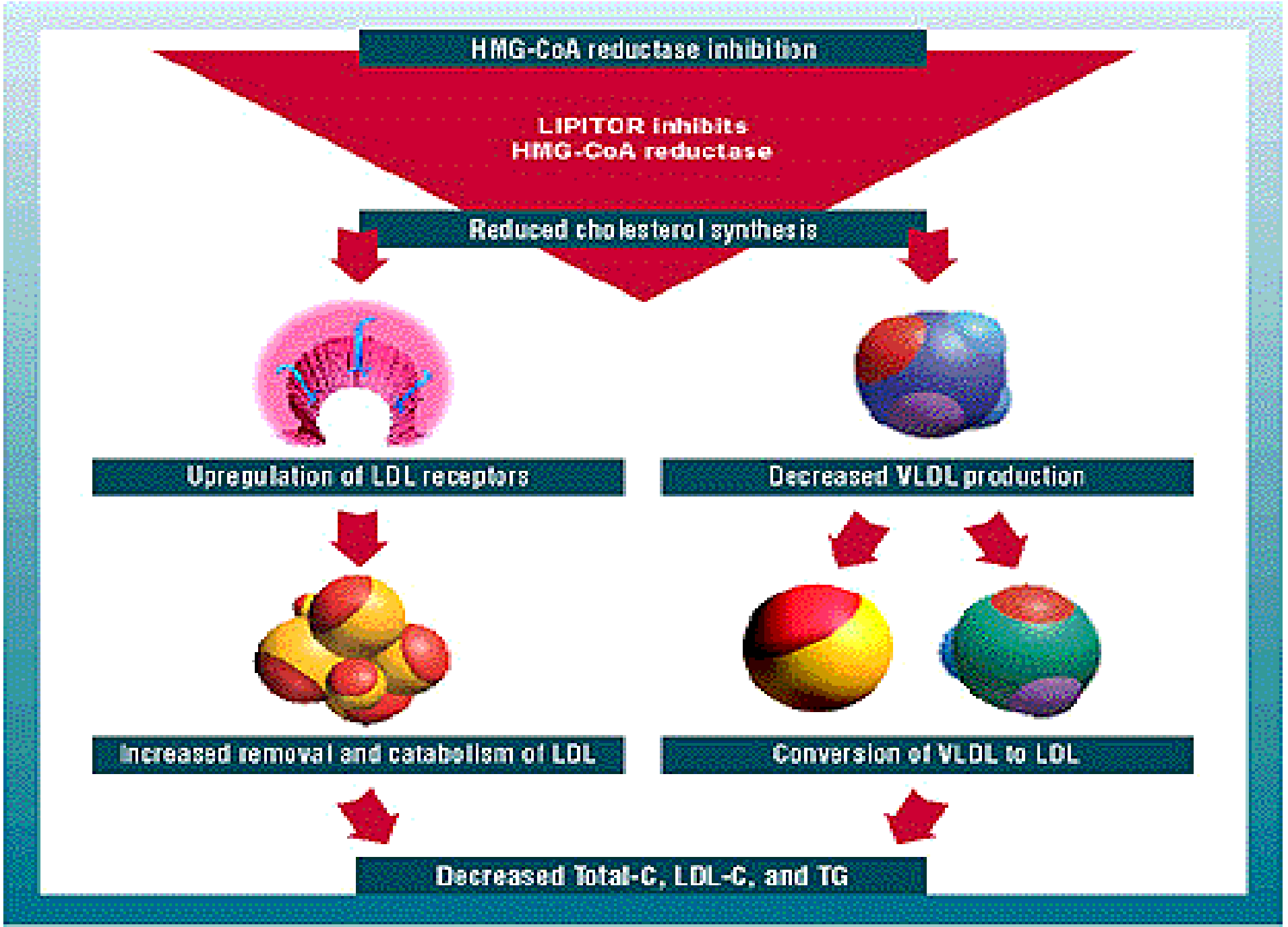
- These agents may used as a singly or in combination.

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
Decreased VLDL production
Increased removal and catabolism of LDL
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 increas
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Adverse effects

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  the risk for gallstones.

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.

- **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 chylomicrons are increased

وليس هوايَ نازعًا عن ثنائه
لعلّي بهِ في جنَّة الخلدِ أخلدُ
مع المصطفى أرجو بذاك جوارهُ
وفي نيل ذاك اليوم أسعى وأجهدُ
وفي نيلِ ذاك اليوم أسعى وأجهدُ...

Additional sources
https://youtu.be/-VwH33qYjPw?si=nQ2xRllbEnj1ka68

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	v2	تم إضافة عدد من السلايدات	من سلايد رقم 30 الى نهاية الملف
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!