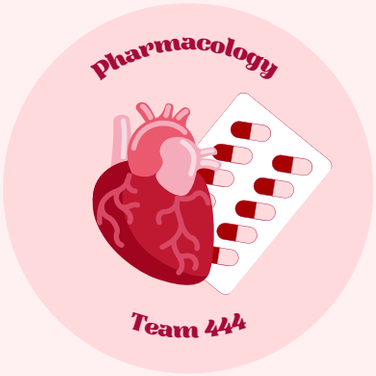
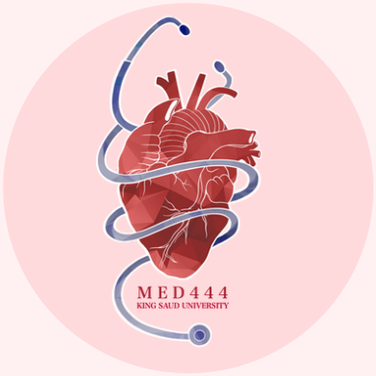




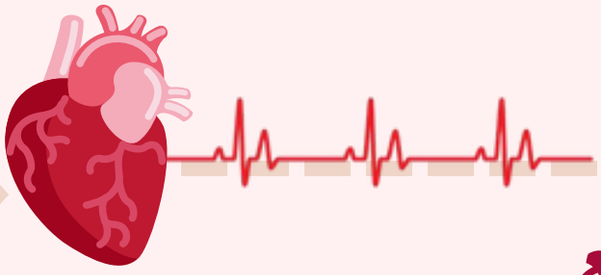
L7.

Drugs for hyperlipidemia [1]&[2]

EDITING FILE

COLOR INDEX :

- MAIN TEXT
- IMPORTANT
- GIRL'S SLIDES
- BOY'S SLIDES
- NOTES
- EXTRA

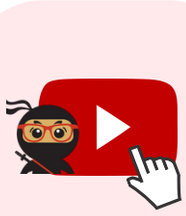


إذا زاد اللبد يا صاح إقنع
وغيّر أكلك وخفف ثريدك
وعندك أدويه كثرتها تفجع
ستاتن، رزن واللكشر يزيدك

✍️ علي العبدالعظيم

Objectives:

- Define hyperlipidemia vs normal lipid levels
- Discuss the non-pharmacological treatment of hyperlipidemia
- Classify lipid lowering agents targeting exogenous and endogenous pathways
- Expand on the pharmacology of drugs related to each group
- Hint on adjuvant drugs that can help in lipid lowering



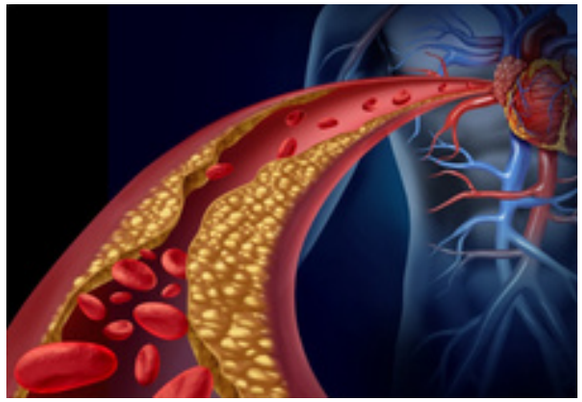
Video 1: introduction (slide 1-8)

Video 2: Drugs of hyperlipidemia

Definition of hyperlipidemia

- **Hyperlipidemia** is a major cause of atherosclerosis which may lead to Cardiovascular CAD diseases and ischemic cerebrovascular disease.
- Denotes abnormally ↑ levels of any or all Lipids and/or Lipoproteins [LP] in blood.

Lipids originate from 2 sources:



1

Endogenous lipids

Synthesized in the liver

2

Exogenous lipids

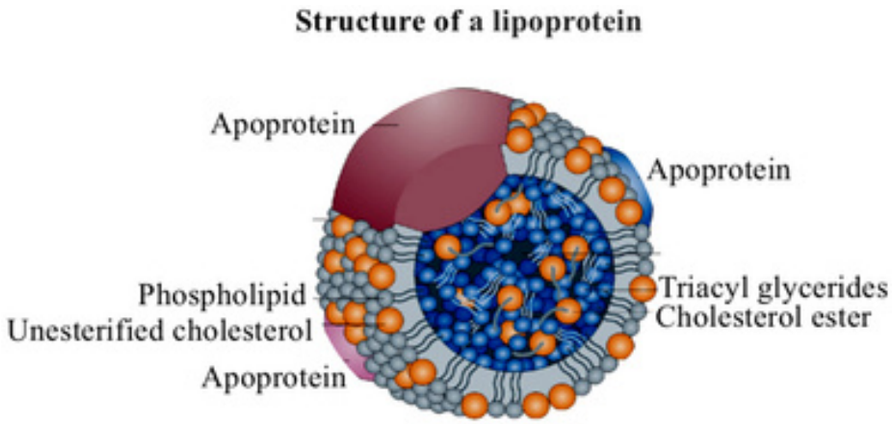
Ingested and processed in the intestine

from the Dite

The principle lipids in the blood are:

- Cholesterol (C)
- Triglycerides (TG) glycerol + 3 fatty acids
- Phospholipids (PL)
- Cholesterol esters (CE), it is cholesterol esterified with a fatty acid
- Non-estrified fatty acids (NEFA)

Definition of hyperlipidemia

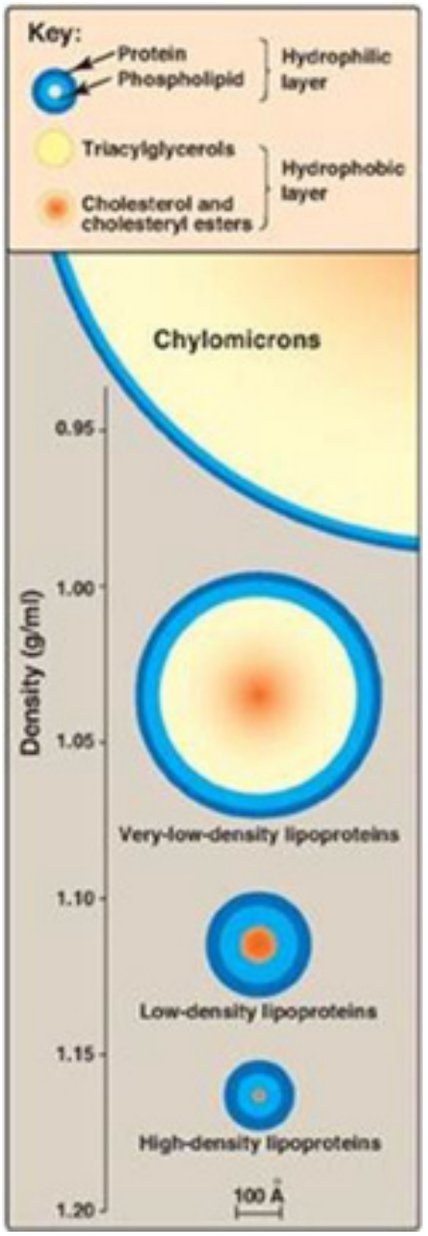


Lipoproteins:

- Endogenous molecules that contain both proteins and lipids in their structure.
- transport (carry) lipids to and from liver and peripheral tissues in the blood.
- All are Atherogenic Particles except HDL.

- Lipoproteins has different sizes
- Lipoproteins consist of TG, Cholesterol , CE, Phopholipid, Apoprotein
- **Chylomicron** has Large amounts of TG and CE
- **VLDL** has Large amounts of TG and CE, BUT less than Chylomicron
- **LDL** has TG and CE, BUT less than VLDL
- **HDL** mainly consists of protein and phospholipid

Types of lipoproteins:
1. **Chylomicrons**: Carry dietary TAG from intestinal mucosa to peripheral tissues
2. **VLDL**: Carry endogenous TAG from liver to peripheral tissue. (precursor of LDL)
3. **LDL**: " bad cholesterol" Synthesized in plasma from VLDL
4. **HDL**: "good cholesterol" Carry cholesterol from peripheral tissues to the liver



Lipoproteins differ in:

- lipid and protein composition
- Size
- Density
- Site of origin

☐Special thanks to Team443 ☐

Genetic Familial Hyperlipoproteinemia

LProteinemia		↑ LP	↑ Lipids	Risk
Type I	Familial hyperchylomicronemia	CM	TGs	-
Type IIa	Familial hyperchloesterolemia	**LDL**	**C**	↑
Type IIb	Familial combined hyperlipidemia	**VLDL & LDL**	**TGs & C**	↑
Type III	Familial dysbetalipoproteinemia	IDL	TGs & C	↑
Type IV	Familial hypertriglyceridemia	VLDL	TGs	↑
Type V	Familial mixed hypertriglyceridemia	VLDL & CM	TGs & C	-

High Risk of atherosclerosis and Cardiovascular Diseases

CM = chylomicron; VLDL = very–low-density lipoprotein
LDL = low-density lipoprotein; IDL = intermediate-density lipoprotein

Treatment of hyperlipidemia

Therapeutic strategies for treatment of hyperlipidemia

Therapeutic lifestyle changes

non-pharmacological

- Regular exercise
- Cessation of hazardous habits; smoking, alcohol, ...etc
- Losing weight
- Healthy diet; optimal quantitative & qualitative fat content:

1. Diet has < 30% of calories as fat, < 7% as saturated fat and <200mg cholesterol/day
2. Avoid trans-fatty acids and acute increase in C intake
3. Use vegetable oils rich in unsaturated fatty acids: oleic acid, linoleic acid & linolenic acids
4. Diet should also contain plant Stanols (interfere with the formation of micellar cholesterol) and soluble fibers
5. Eat food high in antioxidants vitamins

Can achieve a fall in LDL-C of 8-15%, but long-term compliance is a problem

(take long time to give the effect 'not enough alone without drugs')

Antihyperlipidemic Drugs

Important

1- Mechanism of action:

1- Inhibits cholesterol absorption in the intestine:
- Ezetimibe

2- Sequester (يعزل) bile acids in the intestine:
- Exchange resins

3- Inhibits synthesis of cholesterol:
- Inhibitors of hydroxy methyl glutaryl coenzyme A reductase (Statins)

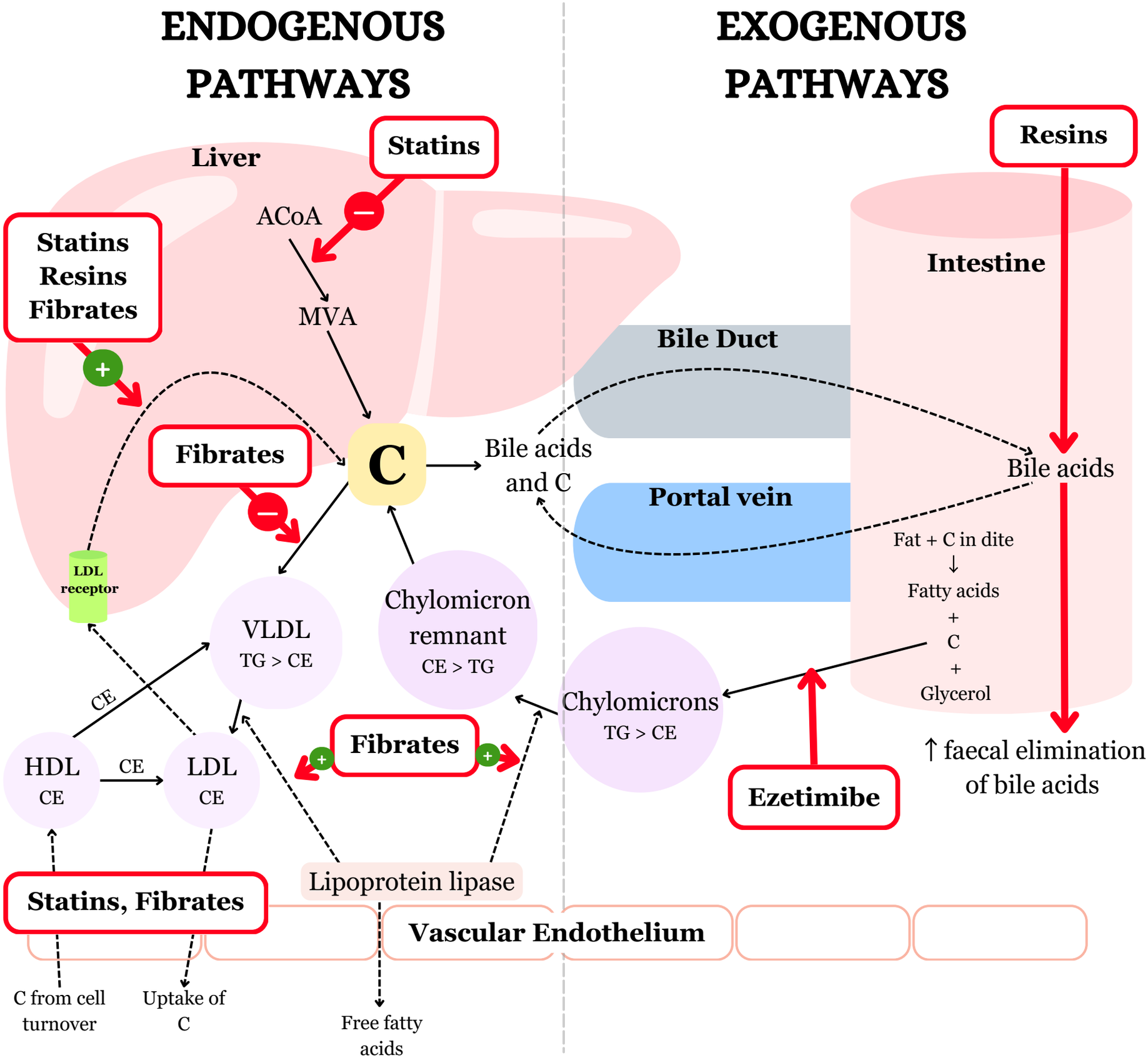
4- Alter relative levels & patterns of different plasma LPs:
- Fibrates
- Nicotinic acids

2- Site of action:

1- Agents targeting exogenous cholesterol:
- Colestipol & Cholestyramine (Resins)
- Ezetimibe

2- Agents targeting endogenous cholesterol:
- Statins
- Fibrates
- Nicotinic acid

3- Adjuvant agents:
- Omega-3-Fatty Acids
- Stanols



Doctors explanation on the next slide

Exogenous pathway

1. Ingested fat goes to intestine, bile acid helps to degrade the fat to → Cholesterol + fatty acids + glycerol
2. Bile acids facilitate digestion and absorption of lipids in the small intestine as well as regulate cholesterol homeostasis
3. Bile acid enters the enterohepatic cycle: (EHC) it is movement of bile acid molecules from the liver to the small intestine and back to the liver
4. Cholesterol packaged by large lipoprotein (chylomicron)
5. Cholesterol Transported by blood to the liver.

- **Resins** make insoluble complex with bile acid in the intestine to prevent its reabsorption back to the liver, then excreted by feces → no more bile acid available for fat ingestion in intestine, that forces the liver to use stored cholesterol to make new bile acids → ↓**Cholesterol** → ↑ expression of LDL receptors of hepatocyte → take more LDL from blood → ↓**LDL** in blood
- **Ezetimibe** blocks C transporters → prevents absorption of Cholesterol to the liver

Endogenous pathway

1. Cholesterol synthesized in the liver by HMG-CoA reductase
2. C in the liver used in synthesis of steroid hormones and bile acid

- **Statins** inhibit HMG-CoA from making MVA → decrease Cholesterol synthesis
- **Statins, resins** and **fibrates** increase uptake of LDL from blood → drop LDL levels in blood
- **Fibrates** decrease VLDL secretion from liver
- **Fibrates** enhance lipoprotein lipase activity → increase release of Free FAs
- **Statins** and **fibrates** improve the endothelial function

Agents Targeting Exogenous Cholesterol

1-Cholesterol Absorption Inhibitors

Ezetimibe

MOA

Blocks/inhibit Cholesterol transporter NPC1L1 located on brush border of small intestine

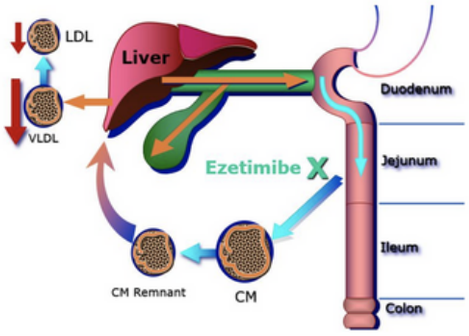
↓

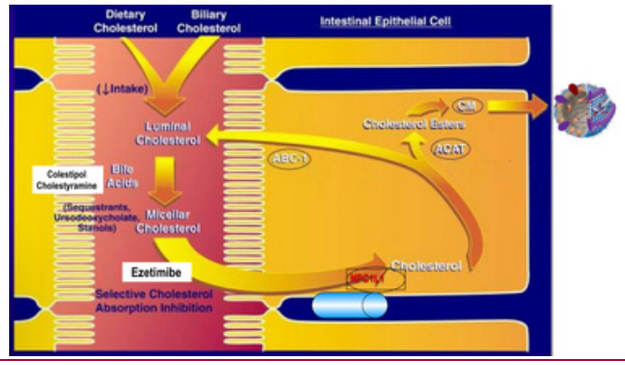
↓ pool of Cholesterol available to the liver

↓

upregulate LDL receptor, trapping more LDL particles from blood

(as a compensatory mechanism to elevate C, that lead to decrease LDL in blood)





Pharmacologic al action

↓ LDL 20%

↓ TG 8%

↑ HDL 1-4%

- No effect on steroids, lipid-soluble vitamins, bile acids

patients who take vitamins or steroids could use Ezetimibe

PK

- Absorbed and conjugated in intestine to active glucuronide
- Undergoes enterohepatic circulation
- Its half-life is 22 hours
- Reaches peak blood level in 12–14 hours
- Most of the drug is excreted in feces

Agents Targeting Exogenous Cholesterol

1-Cholesterol Absorption Inhibitors

Ezetimibe

indications

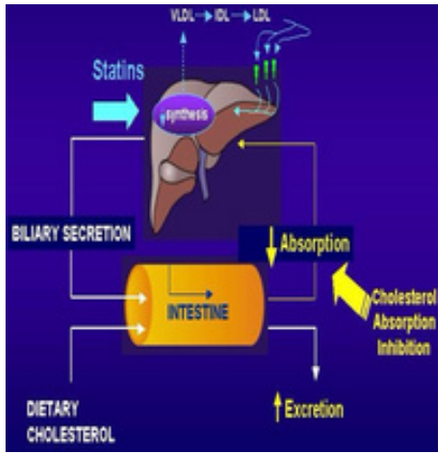
- **As Monotherapy:**

Primary prevention of low risk of CHD (coronary heart disease) which needs modest ↓ LDL, Type II hyperlipidemia

- **As Combination Therapy:**

Safe with:

1. Statins; synergistic (increase the effect of Statins if combined with Eztimibe) In moderate/severe ↑ LDL
2. Or If must ↓ statins dose because of severe side effects
3. Or with other lipid lowering drugs as fibrates



ADRs

- Not dangerous side effects; safe drug
- Not common
- GIT disturbance
- Headache, fatigue, arthralgia (pain in joint) and myalgia (pain in muscle)

Agents Targeting Exogenous Cholesterol

2-Exchange Resins or Bile Acid Sequestrants

Drugs	Cholestyramin	Colestipol	Colesevelam

Overview

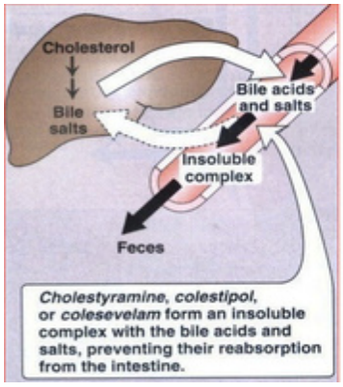
Bile acid-binding resins:

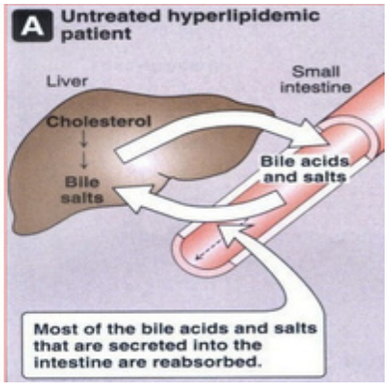
- Moderately effective with **excellent safety record**
- Large MW polymers which bind to bile acids and the acid-resin complex is excreted so their fecal excretion ↑ 10 fold
  - -Prevents enterohepatic cycling of bile acids
  - -Obligates the liver to synthesize replacement bile acids from cholesterol
- The liver increases the number of LDL receptors to obtain more cholesterol.
- The levels of LDL-C in the serum are reduced as more cholesterol is delivered to the liver.
- Excellent choice for people that cannot tolerate other types of drugs.

M.O.A

Very Important

Form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.





ADRs

They are clinically safe as they are not systemically absorbed.

- -**GIT upset**: abdominal discomfort, bloating, constipation.
- -Decreased absorption of fat soluble vitamins (A, D, K).
- -The concentration of **HDL-C is unchanged**. (Advantage)

Agents Targeting Exogenous Cholesterol

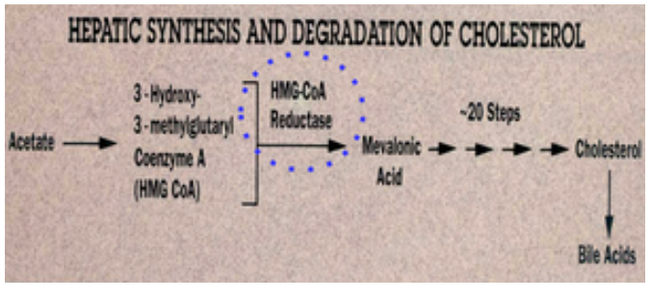
2-Exchange Resins or Bile Acid Sequestrants

Drugs	Cholestyramin	Colestipol	Colesevelam
Contraindications	-**Complete biliary obstruction** (because bile is not secreted into the intestine). -**Chronic constipation**. -**Severe hypertriglyceridemia** (TG >400 mg/dL). Because Resins can raise TGs		
Drug Interactions	Interfere with the absorption of: -**Statins, Ezetimibe,** Chlorothiazide, Digoxin, Warfarin. N.B: These drugs should be taken at least 1 hour before, or 4 hours after taking Resins. Colesevelam has not been shown to interfere with the absorption of co-administered medications and is a **better** choice for patients on **multiple drug regimens** We have 2 possible ways to avoid the interactions; either by separating between the time of administration of drugs or by giving Colesevelam (which is more preferred)		

Agents Targeting Endogenous Cholesterol

1-HMG-CoA Reductase inhibitors

- **Hydroxy MethylGlutaryl-Coenzyme (HMG-CoA) A reductase inhibitors or statins are the most effective and best-tolerated agents for treating hyperlipidemia.**
- **Statins are considered as first-line drugs when LDL-lowering drugs are indicated.**

Drug	Statins (first line)
MOA	Statins are potent competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in do-novo hepatic Cholesterol synthesis. Thus, HMG-CoA is not converted to mevalonic acid. 
P.K	• Most statins have a high first-pass clearance by the liver. • Greater than 95% of most of these drugs are bound to plasma proteins with short half-life. • Drug-drug interactions involve specific interactions with the cytochrome P-450 drug metabolizing system, especially CYP3A4. • All statins are taken orally at bedtime because of hepatic C synthesis is maximal between midnight and 2:00 a.m. , except atorvastatin taken at any time because of its long half-life (14 hours).

Agents Targeting Endogenous Cholesterol

Drug	Statin (first line)
Preparations	• Rosuvastatin • Atorvastatin long duration of action • Simvastatin • Pravastatin & Fluvastatin safe to use with drugs metabolized through CYP3A4 • Lovastatin Used alone or with other anti-hyperlipidemic drugs (ezetimibe) for treatment of drug-resistant dyslipidaemia.
Pleiotropic Anti-atherogenic effects **[> in Vessels]**	• ↓ vascular Inflammation • Improve endothelial function • Stabilization of atherosclerotic plaques • Anti-thrombotic actions • Enhanced fibrinolysis • ↓ platelet aggregability • Has anticancer effect
ADRs	• Common side effects: Headache, myalgia, fatigue, GI intolerance, and flu-like symptoms. • Hepatotoxicity, raised concentrations of liver enzymes (serum aminotransferases). • Myopathy (increased creatine kinase [CK] released from muscles) • Teratogenicity, statins should be avoided during pregnancy.

Mnemonic
H: hepatic dysfunction
M: myopathy
G : GIT upset
Co-A : cataract (lenticular Opacity) عتامه العين
R eductase : Renal dysfunction

Agents Targeting Endogenous Cholesterol

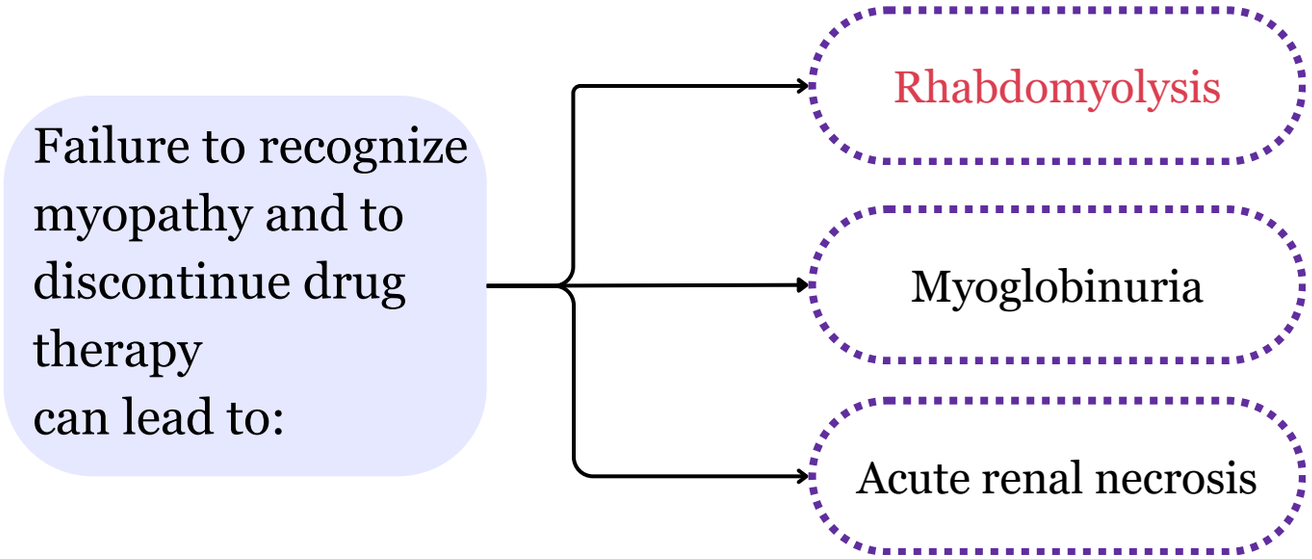
Drug	Statin (first line)
Indications	**As monotherapy:** • **Primary Prevention;** 1. Patients with hyperlipidemia and with other risks for ischemic insults. 2. Type IIa Hyperlipoproteinemia • If no control → combine (sequestrants/ ezetimibe, niacin) to decrease Cholesterol . • **2nd primary Prevention;** In all ischemic insults [stroke, AMI, ...etc.] So given from 1st day of ischemic attack. • **As Combination therapy;** 1. Mixed dyslipidaemias; added to fibrates or niacin if necessary 2. In diabetics and patients with insulin resistance [metabolic syndrome] because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile.

Agents Targeting Endogenous Cholesterol

Drug	Statin (first line)
Interactions	• **Statins potentiate the action of oral anticoagulant and anti-diabetic drugs** (by displacement from plasma protein binding sites). • **Drugs that increase the risk of statin-induced myopathy include:** • Other antihyperlipidemics (fibrates) • Drugs metabolized by 3A4 isoform of cytochrome P450: Erythromycin, verapamil, cyclosporin, ketoconazole. • **Pravastatin and fluvastatin** are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

Statin induced myopathy

- Muscle aches, soreness, or weakness associated with an elevation of creatine kinase (CK) , are the best indicator of statin-induced myopathy.



Statin induced myopathy (continued)

1. ↑ **serum transaminase:** can progress to evident hepatotoxicity so lab investigations recommended every 6 month:

- if levels ↑ up to 3 folds at any time, statin must be stopped then dose adjusted.

2. ↑ **creatine kinase activity** **(index of muscle injury):** measured only if myalgia or myositis develops.

- if it is up to 3-5 folds, we decrease statin doses omit combination with fibrates.

Agents Targeting Endogenous Cholesterol

2- Niacin (Nicotinic Acid)

● Water soluble B-complex vitamin with multiple actions.

● The most effective medication for increasing HDL cholesterol levels and it has positive effects on the complete lipid profile.

● It is useful for patients with mixed dyslipidemias.

● Niacin exerts greatest beneficial effects on wide range of lipoprotein abnormalities.

- inhibits lipolysis

M.O.A

• In adipose tissue:

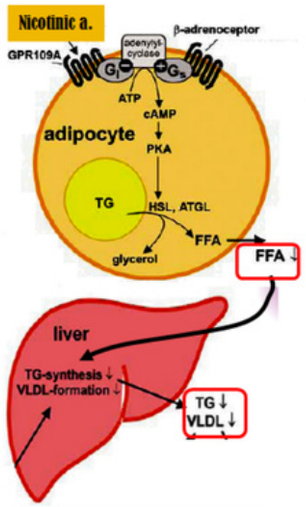
- It binds to adipocytes nicotinic acid receptors, this will lead to decrease in free fatty acids mobilization from adipocytes to the liver resulting in ↓TG and thus ↓VLDL synthesis.

• In liver:

- Niacin inhibits hepatocyte 2-diacylglycerol acyltransferase, a key enzyme for TG synthesis.
- Thus it decreases VLDL production (decreased TG synthesis and esterification).

• In plasma:

- It increases Lipoprotein lipase (LPL) activity that increases clearance of VLDL & chylomicrons



Pharmacological actions

Effect on VLDL: ↓VLDL by

- ↓synthesis in liver.
- increased clearance in plasma .
- ↓mobilization of free fatty acids from adipose tissue.

Effect on LDL: ↓ LDL

- due to reduction of its precursor (VLDL).

Effects on HDL: ↑HDL

- Induces modest increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown).
- Niacin also promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL.

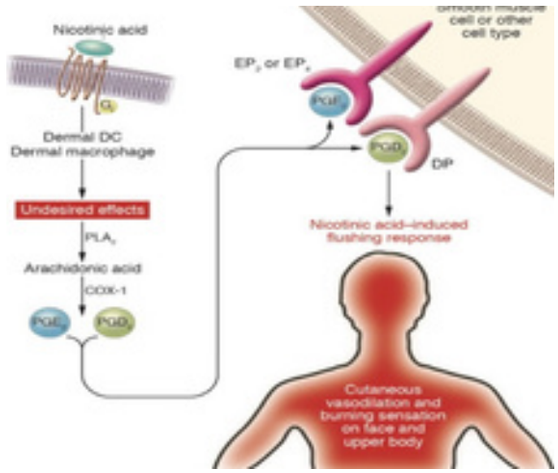
Indications

Monotherapy or in combination with fibrate, resin or statin

- Type IIa hypercholesterolemia.
- Type IIa, IIb hypercholesterolemia & any combined hyperlipidemia.
- Patient with hypertriglyceridemia & low HDL-C.

ADRs

● **The most common side effect is cutaneous flushing** (which is prostaglandin-mediated, can be avoided by low dose Aspirin ½ hour before niacin).
● GIT disturbances: Dyspepsia, nausea, vomiting, reactivation of peptic ulcer (can be
decreased if taken after meal)
● High doses:
- Reversible ↑ in liver enzymes → hepatotoxicity.
- Not used in diabetic patients because it has Impairment of glucose tolerance → overt diabetes
- ↑ uric acid → gout

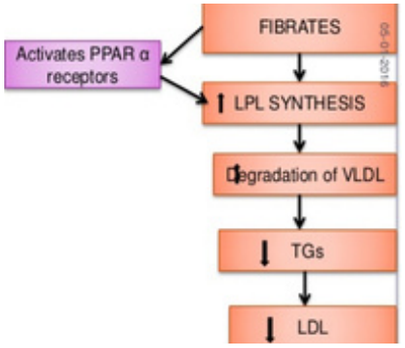
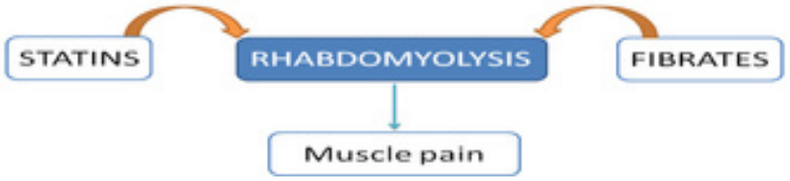


Contra-indications

● Gout ● Hepatotoxicity.
● Peptic ulcer ● Diabetes mellitus.
From female Dr.
If patient have diabetes and hyperlipidemia the best choice of drug?
Statins

Agents Targeting Endogenous Cholesterol

3- Fibric Acid Derivatives (Fibrates)

Drug	Clofibrate	Gemfibrozil	Fenofibrate
M.O.A	• Fibrates are agonists of peroxisome proliferator activated receptors (PPARα) which are a class of intracellular receptors that modulate fat metabolism . • They increase genes transcription for lipoprotein lipase (LPL) leading to increased catabolism of TG in VLDL and chylomicron		
Pharmaco logical actions	• ↑ LPL activity which increases clearance of VLDL & chylomicron in plasma • A marked reduction in TG (due to stimulation of catabolism of VLDL). • ↑ FFA uptake by the liver • ↑ LDL-C uptake by the liver • ↑ in HDL-C (by increasing the production of the apoprotein components of HDL). • ↑ excretion of hepatic cholesterol in bile, thus endogenous hepatic cholesterol synthesis may be decreased.		
Indications	**1st-line defense for:** **- Mixed dyslipidemia** (i.e. raised serum TG and Cholesterol). **- Patients with low HDL and high risk of atheromatous disease** (often type 2 diabetic patients) **- Patients with severe treatment-resistant dyslipidemia** (combination with other lipid-lowering drugs)		
Contra-indications	- Patients with impaired renal functions - Pregnant or nursing women - Preexisting gallbladder disease		

ADRs	• GIT (indigestion, abdominal pain, diarrhea). GIT upset, headache, fatigue, weight gain, myalgia • Rash, urticaria, hair loss. • Gallstones: Clofibrate increases Cholesterol content of bile, predisposes to gallstones, and its use is therefore limited to patients who have cholecystectomy. • Myositis: can occur resulting in weakness and tenderness of muscles (if left untreated may lead to Rhabdomyolysis, Myalagia→ Acute renal failure), this occurs in: - If combined with statins (each –ve metabolism of other). The use of fibrates with statins is generally inadvisable. - In alcoholics - In impaired renal function. ➔ Fibrates should be used with caution in patients with biliary tract disease, as they increase the risk of cholesterol gallstones as a result of an increase in the cholesterol content of bile.
Interactions	• Increased risk of myopathies when used with statins. • They displace drugs from plasma proteins (oral anticoagulant like warfarin, oral hypoglycemic drugs).

Adjuvant Therapy in Hyperlipidemia

Drug	**Omega 3 FA**	**β-sitosterol**
MOA and Pharmaco - logical actions	• **↓ (TG) by:** 1. ↓ the enzymes involved in TG synthesis. 2. ↑ beta oxidation of FFA • **provide some vascular protection by:** 1. ↓ platelet function 2. Prolongation of bleeding time. 3. Anti-inflammatory effect.	Compete with dietary and logical biliary Cholesterol absorption → ↓ LDL levels +10%

Indications	Approved as adjunctive for treatment of very high TGs.	Given as food supplement before meal in hypercholesterolemia
Found in	Fish oil containing highly unsaturated Fatty acids.	in plants with structure similar to Cholesterol .

MALE SLIDES

A meta analysis of prospective epidemiological studies showed that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD

Important

- One of the effects of statins that it decrease cholesterol in the body → decreasing testosterone levels → erectile dysfunction
- The solutionis adding sildenafil (phosphodiesterase inhibitor) while continuing statins
- Sildenafil have vasodilator action

“ study smarter , not harder “

Active recall

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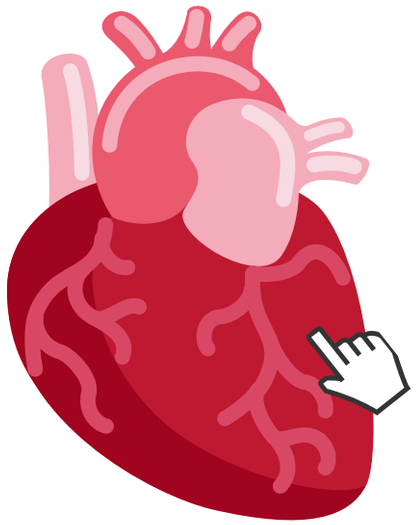
summary



MCQs

1 A patient with hyperlipidemia is prescribed ezetimibe. Which of the following substances is not affected by ezetimibe?

A HDL
B Vitamin A
C LDL
D Triglycerides

2 Which of the following drugs is combined with Statins to treat severe increases in LDL levels?

A Fibrate
B Aspirin
C Ezetimibe
D Erythromycin

3 Patient take vitamins and suffer hyperlipidemia recommend him this drug.

A Ezetimibe
B colestipol
C colesevlam
D A+B

4 What drug can affect the liver and muscle enzymes?

A Niacin
B Colestipol
C Lovastatin
D Gemfibrozil

1)B 2)C 3)A 4)C

MCQs

5 Which drug should pregnant women has hyperlipidemia avoid

A Ezetimibe
B Colesevelam
C Cholestyramin
D Fenofibrate

6 Which drug is combined with statin to treat severe hyperlipidemia?

A Ezetimibe
B Gemfubrozil
C Erythromycin
D Clofibrate

7 A diabetic patient presented to the doctor with hyperlipidemia. Which drug is contraindicated in his case?

A Niacin
B Ezetimibe
C Clofibrate
D Gemfubrozil

8 What is the MOA of gemfibrozil?

A inhibits hepatocyte 2-diacylglycerol acyltransferase
B increase genes transcription for lipoprotein lipase (LPL)
C Inhibit HMG-CoA reductase
D Inhibit cholesterol absorption in the intestine

5)D 6)A 7) A 8)B

SAQs

1 **What is the classification of antihyperlipidemic drugs (according of MOA)? give examples of each one**

Slide 6

2 **mention 1 indecation of Statin .**

slide 17

3 **Mention 2 Therapeutic lifestyle changes for treatment of hyperlipidemia?**

1- Regular exercise & Loss of weight 2- Eat food high in antioxidants vitamins.

4 **Mention 2side effect of Gemfibrozil**

Slide22

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