PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Drugs for hyperlipidemia

Objectives:

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

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

helpful video

Editing file

Hyperlipidemia

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

Lipids originate from 2 sources

Endogenous

synthesized in the liver

Exogenous

ingested and processed in the intestine

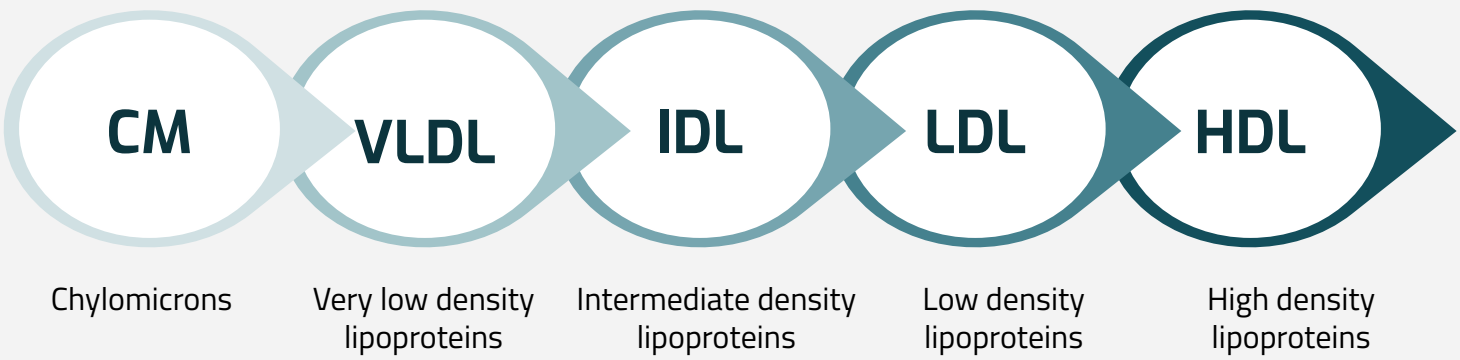
Principle lipids in the blood

- **Cholesterol (C)**
- Phospholipids (PL)
- Non-esterified fatty acids (NEFA)
- Cholesterol esters (CE)
- **Triglycerides (TG)**

Lipoproteins

- Endogenous molecules that contain both **proteins** and **lipids** in their structure
- transport (carry) lipids around the body in the blood

*All are Atherogenic Particles except HDL



Factors promoting elevated blood lipids

1. Family history of CAD
2. Hypertension
3. DM (increased generation of VLDL and free fatty acids presented to the liver)
4. Obesity
5. Inactivity/ lack of exercise
6. Alcohol intake (increases TGs)
7. Smoking (reduced levels of HDL, cytotoxic effects on the endothelium, increased oxidation of lipoproteins, and stimulation of thrombogenesis)

Familial Hyperlipoproteinemia

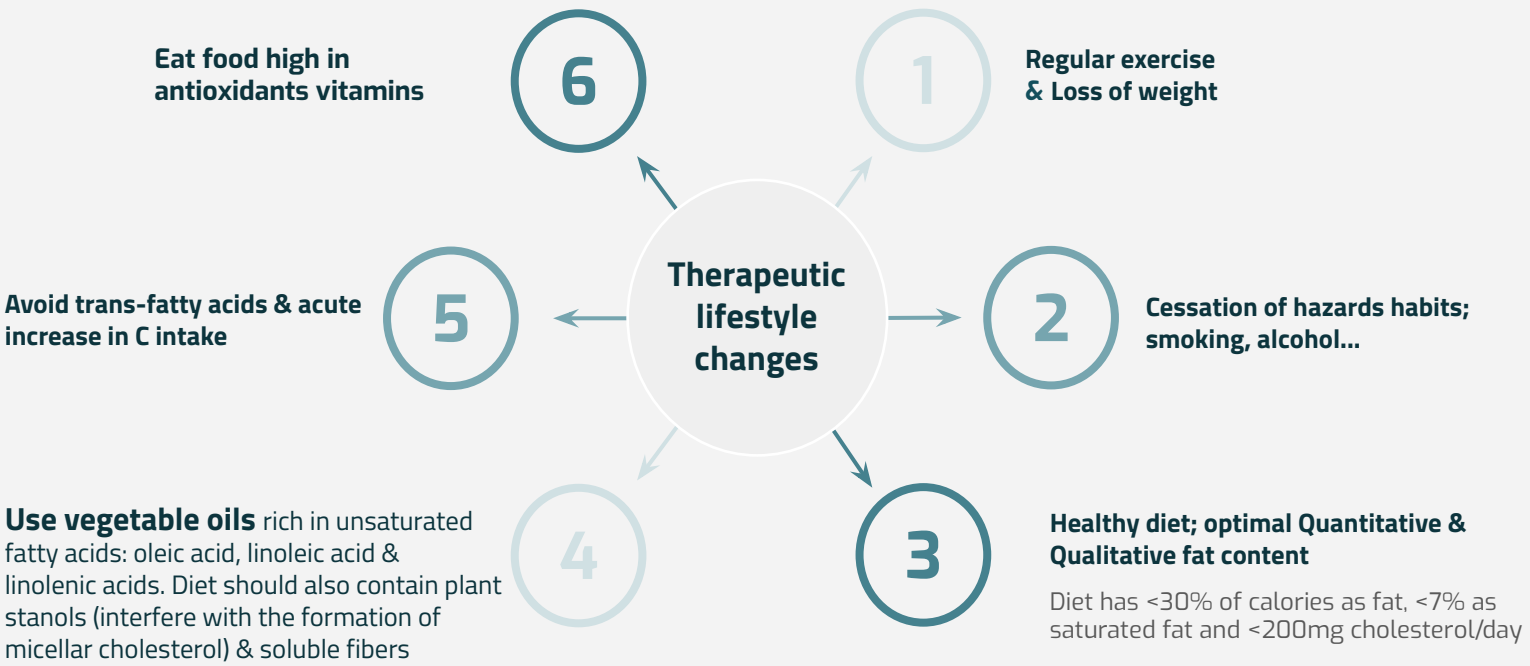
LProteinemia	↑ LipoProtein	↑ Lipids	Risk
Type I	CM	TGs	-
Type IIa	LDL	C	↑
Type IIb	VLDL & LDL	TG & C	↑
Type III	IDL	TGs & C	↑
Type IV	VLDL	TGs	↑
Type V	VLDL & CM	TGs & C	-

Normal lipid levels

Lipid levels are detected in serum after a 12-hour fast

C	<200 mg/dl
TGs	<220 mg/dl
LDL	<130 mg/dl (bad C)
HDL	>50 mg/dl (good C)

Therapeutic strategies for treatment of hyperlipidemia



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

Antihyperlipidemic Drugs

classified According to:

Site of action

I- Agents targeting *exo*genous cholesterol:
- Colestipol & cholestyramine
-Ezetimibe

II- Agents targeting *endo*genous cholesterol:
-Statins
-Fibrates
-Nicotinic acid

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

mechanism of action

1- Inhibits cholesterol absorption in the intestine:
Ezetimibe

2- Sequester bile acids in the intestine:
Exchange resins

3- Inhibits synthesis of cholesterol:
Inhibitors of HMG-CoA reductase (Statins)

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

Hepatic Cholesterol Metabolism

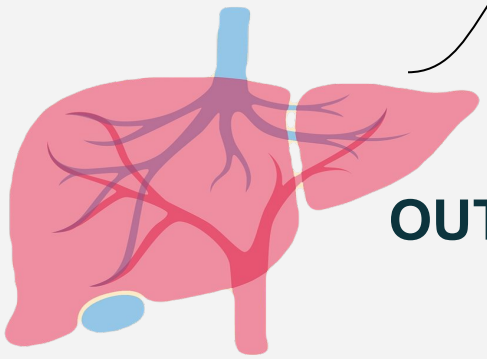
Liver Cholesterol pool

1. Absorption of dietary content

2. De novo synthesis

IN

3. C synthesized in extrahepatic tissues



1. VLDL and HDL

OUT

2. Free C in bile

3. Conversion to bile salts/acids

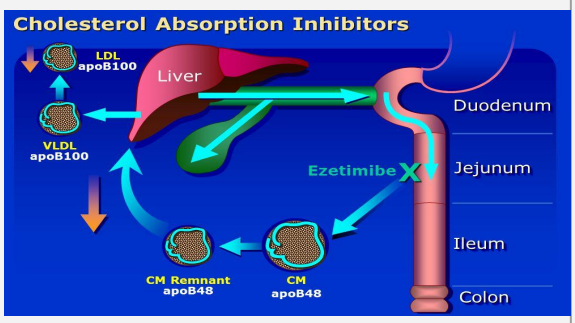
Agents Targeting Exogenous Cholesterol

1-Exchange Resins or Bile acid sequestrants

Drug	**Chol**estyramine	**Col**estipol	**Col**esevelam
Overview	• 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 folds - 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 thus: - 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	- Bind to bile acids and bile salts in the small intestine. - They form resin/bile acid (insoluble) complex which prevents their reabsorption from the intestine. - They disrupt the enterohepatic circulation of bile acids.		
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.**		
Contraindic-ations	• Complete Biliary obstruction (because bile is not secreted into the intestine). • Chronic constipation. • Severe hypertriglyceridemia (TG >400 mg/dL). ○ -The bile acid binding resins can raise triglycerides modestly (about 5%) and cannot be used if the triglycerides are elevated.		
Interactions	• Interfere with the absorption of: Statins, Ezetimibe, Chlorothiazide, Digoxin, Warfarin. Therefore, 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**		

Agents Targeting Exogenous Cholesterol

2-Cholesterol Absorption Inhibitors

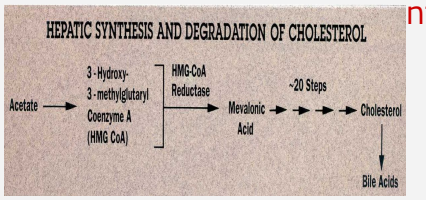
Drug	**Ezetimibe**
M.O.A	-Blocks C transporter located on brush border of small intestine→↓pool of C available to the liver→ upregulate LDL receptor, trapping more LDL particles from blood. -Ezetimibe reduces C absorption by blocking **Niemann-Pick C1-Like 1 transporter**. Therefore, ezetimibe reduces the flux of C from the intestine to the liver.  -Because this C is packaged and resecreted by the liver into the blood as VLDL (precursor of LDL in plasma), reduced flux of C to VLDL particles will lower LDL-C.
Pharmaco-logical actions	↓LDL 20% ↓TG 8% , ↑HDL 1-4% No effect on steroids, lipid-soluble vitamins, bile acids
P.k	- Absorbed & conjugated in intestine to active glucuronide - Undergoes enterohepatic circulation - Its half-life is 22 hours , and Reaches peak blood level in 12–14 hours. - Most of the drug is excreted in feces
Clinical Uses	**As Monotherapy:** Primary prevention of low risk of **CHD** which needs modest↓ LDL (if LDL is very high, statins should be used. Ezetimibe isn't used alone except in modest of LDL) **As Combination Therapy;**it's safe With: 1. **statins**; synergistic In moderate/severe ↑ LDL statins with ezetimibe is a good combination because ezetimibe will work in exogenous while statins in endogenous cholesterols 2. Or If must ↓ statin dose because of side effects 3. Or with other lipid lowering drugs As **fibrates**
ADRs	Not common • GIT disturbance(Dr: the main symptoms for most of antihyperlipidemics) • headache, fatigue, arthralgia and myalgia

HMG-Co A Reductase inhibitors

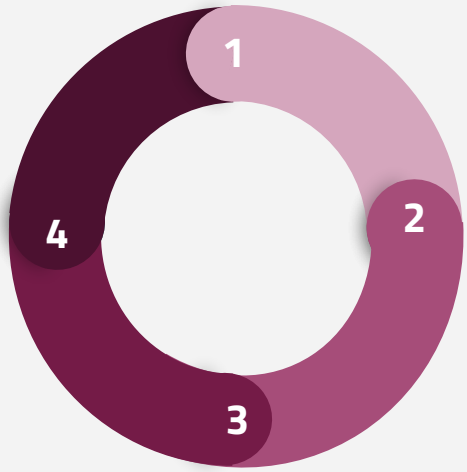
- Hydroxy MethylGlutaryl-Coenzyme A reductase inhibitors or statins are the most effective and best tolerated agents for treating hyperlipidemia.
- Statins are considered as first line drugs when LDL-lowering drugs are indicated.
- Statins cause modest decrease in plasma TG and slight increased in HDL-C

Statins: Mechanism of action

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 C nthesis. Thus, HMG-Co A is not converted to mevalonic acid



Statins lower blood C levels by inhibiting de novo hepatic C synthesis



Because C is required for the synthesis of (the precursor of LDL-C) production of VLDL ↓

The liver compensates by ↑ the number of LDL receptors on the surface of hepatocytes (upregulation of LDL- R)

This results in ↑removal of LDL from the blood and lowering of serum LDL- C levels

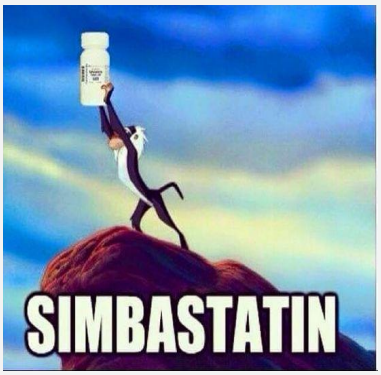
Statins: Preparation

Rosuva**statin** Atrova**statin** Lova**statin** Prava**statin** Simva**statin**

Used alone or with other anti-hyperlipidemic drugs (ezetimibe) for treatment of drug resistant dyslipidemia.

Pleiotropic effects of statins (additional effects other than lowering C)

- Enhanced fibrinolysis
- Improve endothelial function
- Enhancing the stability of atherosclerotic plaques
- Decreasing oxidative stress and inflammation (antioxidant)
- Antithrombotic actions
- Decrease vascular Inflammation
- Decrease platelet aggregability
- Extrahepatic effects on immune system, CNS and bone



Agents Targeting Endogenous Cholesterol

1-HMG-Co A Reductase inhibitors

Drug	**Statins**
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 P450 drug metabolizing system especially **CYP3A4**. "drug with same mechanism or CYP3A4 have more chance to develop drug drug interactions" • All statins are taken orally at bedtime because of hepatic C synthesis is maximal between midnight and 2:00 am except atorvastatin taken at any time because of its long half-life (14 hours).
Indication	**As monotherapy:** • Secondary Prevention: In all ischemic insults [stroke, AMI ...etc] So given from 1st day of ischemic attack. • Primary Prevention: 1. Patients with hyperlipidemia and with other risks for ischemic insults (e.g. smoker). 2. Type IIa Hyperlipoproteinemia , If no control → combine (sequestrants ezetimibe, niacin) to decrease C. **As Combination therapy:** • Mixed dyslipidaemias added to fibrates or niacin if necessary. • 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.
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
Interactions	Statins potentiate the action of oral anticoagulant and antidiabetic drugs (by displacement from plasma protein binding sites). "The effect of drug will increase because it's become free" • Drugs that increase the risk of statin induced myopathy include 1. Other antihyperlipidemics (fibrates). 2. Drugs metabolized by 3A4 isoform of cytochrome P450: erythromycin, verapamil ,cyclosporine, ketoconazole. • **Pravastatin** and **fluvastatin** are the statin 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

- Failure to recognize myopathy and to discontinue drug therapy can lead to:
  - rhabdomyolysis
  - myoglobinuria
  - acute renal necrosis
- ↑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.
- ↑ creatine kinase activity (index of muscle injury)
  - measured only if myalgia or myositis develops
  - if it is up to3-5 folds □ we deacrease statin doses
  - omit combination with fibrates

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

Agents Targeting Endogenous Cholesterol

2-Niacin (Nicotinic Acid)

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 **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
Pharmaco-logical actions	**Effect on ↓VLDL by:** 1. ↓synthesis in liver 2. increased clearance in plasma 3. ↓mobilization of free fatty acids from adipose tissue **Effect on↓ LDL:** ● due to reduction of its precursor (VLDL). **Effects on ↑HDL by :** ● 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 apoAI production and slows hepatic clearance of apoA-I and HDL. → Q: How niacin increase HDL ?
Clinical Uses	**As monotherapy or in combination with fibrate, resin or statin.** ● 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. -Impairment of glucose tolerance → overt diabetes -↑ uric acid → gout
Contra-indications	● Gout ● Peptic ulcer ● Hepatotoxicity ● Diabetes mellitus (used with caution) helpful video

Agents Targeting Endogenous Cholesterol

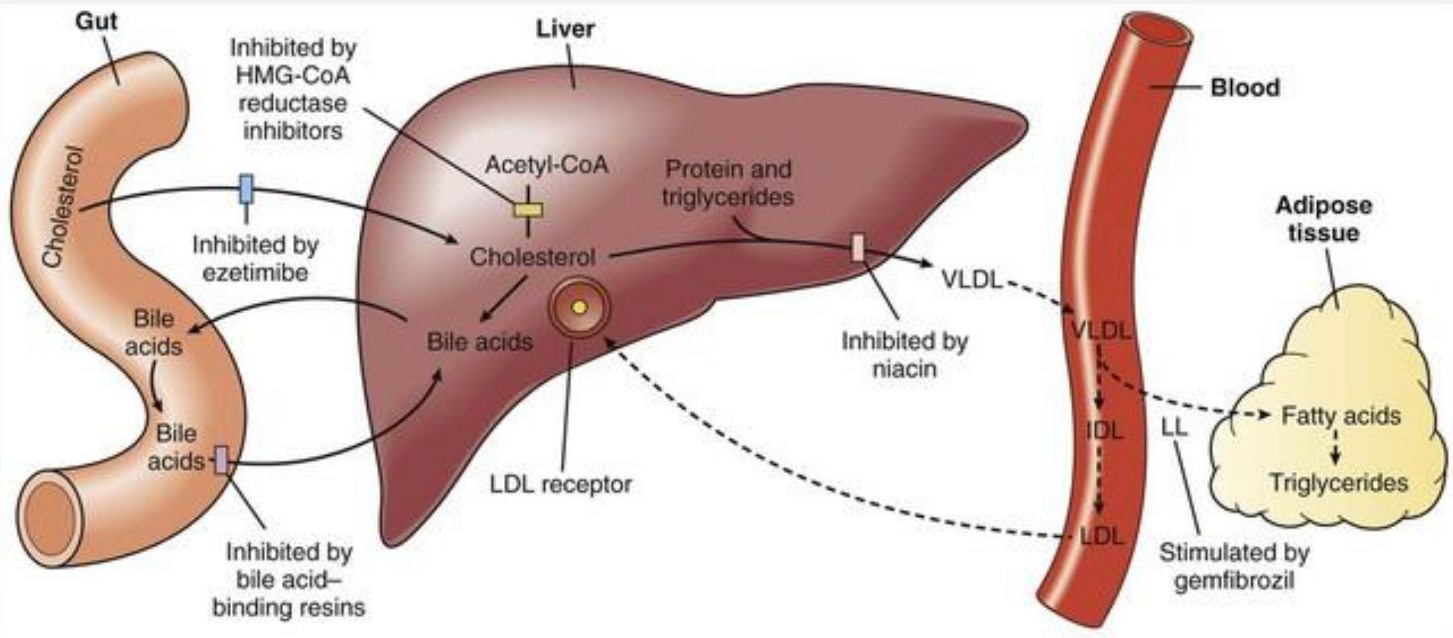
3-Fibrates

Drugs	**Clofibrate** (carcinogenic and cause gallbladder stones)	**Gemfibrozil**	**Fenofibrate**
M.O.A	● They are agonist of peroxidase proliferator activated receptors (PPARα) which is intracellular receptor "Nuclear receptor" that modulate fat metabolism. ● So, they increase gene transcription of **lipoprotein lipase (LPL)** leading to increased catabolism of TG in VLDL and chylomicrons.		
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 C in bile, thus endogenous hepatic C synthesis may be decreased.		
Clinical Uses	**1st-line defense for:** ● mixed dyslipidemia (i.e. raised serum TG and C). ● 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).		
ADRs	● GIT (indigestion, abdominal pain, diarrhea). GIT upset, headache, fatigue, weight gain, myalgia ● Rash, urticaria, hair loss. ● Gallstones: Clofibrate increases C content of bile, predisposes to gallstones and its use is therefore limited to patients who have cholecystectomy OR biliary tract disease ● Myositis: can occur resulting in weakness and tenderness of muscles (if left untreated may lead to Rhabdomyolysis → Acute renal failure), this occurs in: - If combined with statins (use of fibrates with statins if generally inadvisable) (each –ve metabolism of other) - In alcoholics - In impaired renal function.		
Inter-actions	● Increased risk of myopathies when used with statins,They ↓ metabolism of statins → toxicity myalgia, myositis,...etc. so we give lower doses ● They displace drugs from plasma proteins (oral anticoagulant like warfarin, oral hypoglycemic drugs). ● They displace warfarin from their protein binding sites which↑ bleeding tendency and anticoagulant dose must be adjusted		
Contra-indications	- Impaired renal function. - Pregnant or nursing women. - Preexisting gallbladder disease.		

Medications for Hyperlipidemia

Drug class	Agents	Effects (% change)	Side Effects
Bile acid sequestrants	Cholestyramine Colestipol Colesevelam	↓LDL ↑HDL **↑triglycerides**	GI distress constipation, decreased absorption of other drugs
Cholesterol Absorption Inhibitors	Ezetimibe	↓LDL(14-18) ↑HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
HMG-Co A Reductase Inhibitors	Lovastatin Pravastatin	**↓LDL (18-55)** ↑HDL (5-15) ↓Triglycerides (7-30)	Myopathy, increased liver enzymes
Niacin (Nicotinic Acid)		**↓LDL (15-30)** **↑HDL (15-35)** **↓Triglyceride (20-50)**	Flushing, Hyperglycemia, Hyperuricemia, GI distress , hepatotoxicity
(Fibrates)	Gemfibrozil Fenofibrate	↓LDL (5-20) ↑HDL (10-20) **↓Triglyceride (20-50)**	Dyspepsia, gallstones, myopathy

Sites and mechanism of drugs for hyperlipidemia



Which drug increases HDL ? Niacin
Which class of drug causing gallstones ? Fibrates
Which is better to diabetic patient statin or fibrate ? statin due to pleiotropic effects

Anti hyperlipidemic combinations:

Indications

1. Severe hypertriglyceridemia or hypercholesterolemia
2. To take lower doses of each drug
3. High LDL or VLDL not normalized with a single drug.

Combinations

Resins: decreases the absorption of statins and ezetimibe

Statin & ezetimibe (synergistic combination): Statin blocks synthesis of endogenous cholesterol while ezetimibe blocks absorption of exogenous cholesterol

Statins & Fibrates: Contraindicated (in full dose) because the incidence of myopathy may increase. So, use not more than ¼ maximum dose of statin and use pravastatin

Adjuvant Therapy in Hyperlipidemia:

Drug	Omega 3 FA	β-Sitosterol
Pharmaco-logical actions	▪ ↓ **(TG) by:** - ↓ the enzymes involved in TG synthesis. - ↑ beta oxidation of FFA ▪ **provide some vascular protection by:** - ↓ platelet function. - Prolongation of bleeding time. - Anti-inflammatory effect.	Compete with dietary and biliary C absorption → ↓ LDL levels 10%
Indication	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 similar structure as Cholesterol (C).

MCQ

Patient comes into the ER with gallstones, after further investigations You find out that he is on drugs to treat his hyperlipidemia. Which of the following drugs could have caused his gall stones?			
A- Niacin	B- Colesevelam	C-Fenofibrate	D-Ezetimibe

2-A 72-year-old female who is treated for hyperlipidemia with Pravastatin for the past 6 months.. Her physician wishes to add an additional agent to block absorption of exogenous cholesterol. Which of the following choices is the best option?			
A-Niacin	B-Gemfibrozil	C-Ezetimibe	D-Colesevelam

3-Patient with diabetes has hyperlipidemia, Which drug of the following can not be used in his case due the risk of development of Hyperglycemia?			
A-Statins	B-Niacin	C-Ezetimibe	D-Colestipol

4-Facial flushing is the most common adverse effect of this drug			
A-Lovastatin	B-Cholestyramine	C-Ezetimibe	D-Niacin

5-A 42-year-old man who was started on niacin sustained-release tablets 2 weeks ago for elevated triglycerides and low HDL levels. He is complaining of an uncomfortable flushing and itchy feeling that he thinks is related to the niacin. Which of the following options can help him manage this adverse effect of niacin therapy?			
A-Administer aspirin 30 minutes prior to taking niacin.	B-Administer aspirin 30 minutes after taking niacin.	C-Increase the dose of niacin to 1000 mg	D-Change the sustained-release niacin to immediate-release niacin.

6-A 62-year-old female with hyperlipidemia and hypothyroidism. Her current medications include cholestyramine and levothyroxine (thyroid hormone). What advice would you give to her to avoid a drug interaction between her cholestyramine and levothyroxine?			
A-Stop taking the levothyroxine as it can interact with cholestyramine.	B-Take levothyroxine 1 hour before cholestyramine on an empty stomach.	C-Switch cholestyramine to colestipol as this will eliminate the interaction.	D-Take levothyroxine and cholestyramine at the same time to minimize the interaction.

Answers

1	2	3	4	5	6
C	C	B	D	A	B

SAQ

A 72-year-old male who is treated for hyperlipidemia with high-dose atorvastatin for the past 6 months. He also has a history of renal insufficiency. His most recent lipid panel shows an LDL cholesterol level of 131 mg/dL, triglycerides of 510 mg/dL, and HDL cholesterol of 30 mg/dL.

Q1: What is the mechanism of action of Atorvastatin ?

Q2: What are the most serious side effect of statin group, that we have to be aware of them by frequent lab investigation ?

Q3: if his physician wishes to add an additional agent for his hyperlipidemia. Which of choices is the best option in his case ? why ?

Q4: why we can not use any drug from Resins group in this case ?

Q5: why we can not use any drug from Fibrate group in this case ?

A1) potent competitive inhibitors of (HMG-CoA) reductase which is an important enzyme in cholesterol synthesis in the liver.

A2) Hepatotoxicity, Myopathy

A3) Niacin (nicotinic acid), because it is the most effective medication for increasing HDL cholesterol levels and it has positive effects on the complete lipid profile. So it is useful for patients with mixed dyslipidemias

A4) Because he has high level of TG and The bile acid binding resins can raise triglycerides more and more which will worse his situation

A5) He has a history of renal insufficiency so we can not combine the fibrate with statin because the incidence of myopathy may increase, he also may develop Rhabdomyolysis.

GOOD LUCK!

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