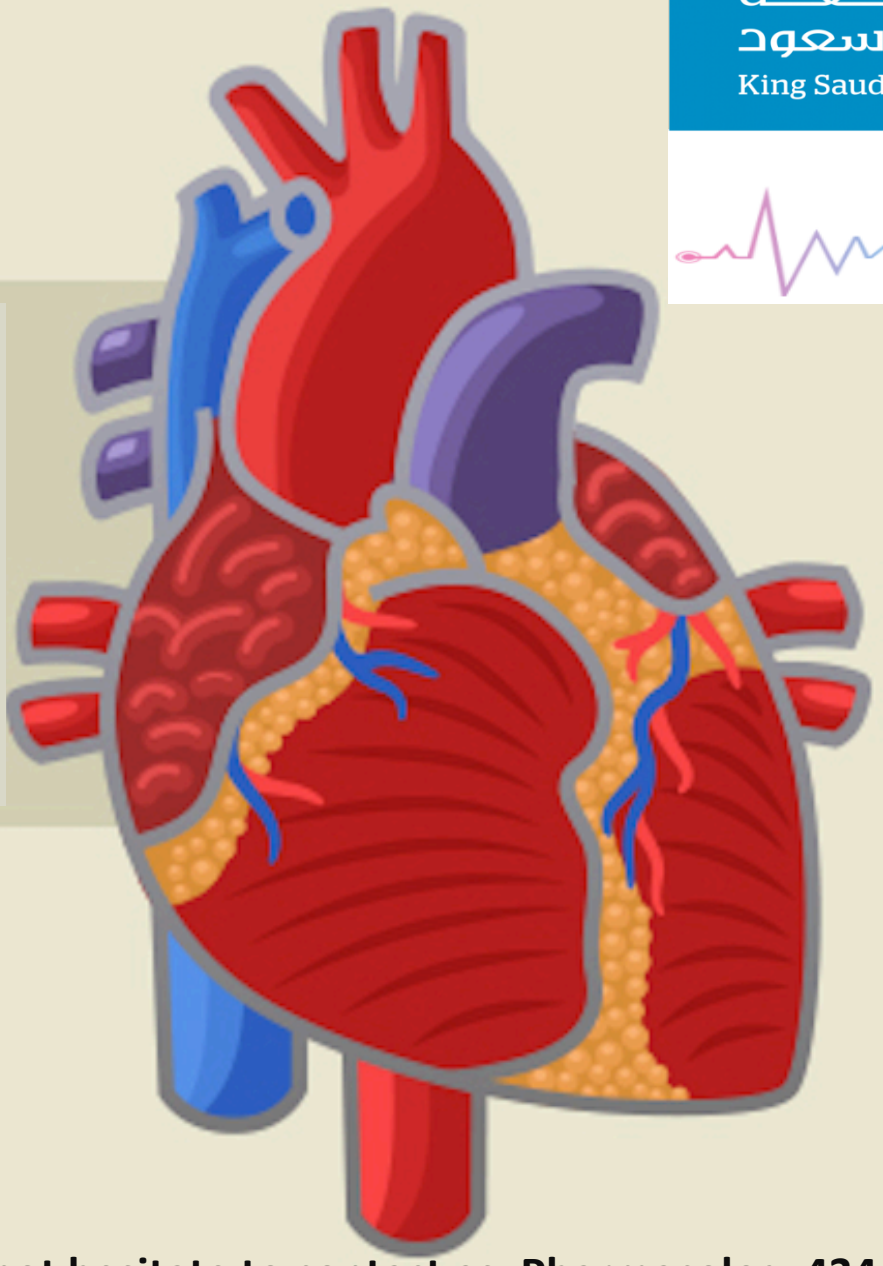
11&12

Antihyperlipidemic Drugs.



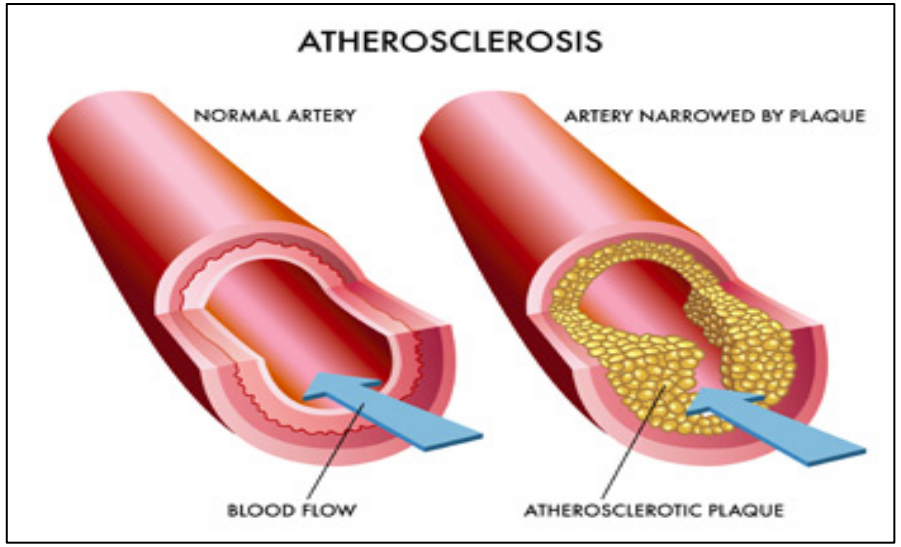
Cardiovascular Block.

Red = Important
MCQs & Summary Also Important

For any correction, suggestions or any useful information do not hesitate to contact as: Pharmacology434@gmail.com

Hyperlipidemia:

https://www.youtube.com/watch?v=6_pT_uL2b3E



- **Definition:** Hyperlipidemia or commonly called hypercholesterolemia, Is the most common form of dyslipidemia, it is high level of lipid in blood, which leads to atherosclerosis, atherosclerosis a major risk factor to development stroke, coronary heart disease, other vascular diseases

- **What is the Cause of hyperlipidemia?**

1- Primary : Caused by genetic defect or environmental factors

2- Secondary: result from other metabolic disorder such as diabetic, renal diseases .. etc.

- **Classification of antihyperlipidemic drugs: (in the table below)**

Classification of Drug	Mechanism of Action	Comment	Examples
Targeting Exogenous Pathways	**Ezetimibe**	Decrease bile and cholesterol absorption from the qut	-
	Bile Acid Sequestrants		Cholestyramine & Colestipol
Targeting Endogenous Pathways	**Nicotinic Acid**	Decrease secretion of hepatic VLDL	-
	FIBRATES	Increase peripheral clearance of lipoproteins	Fenofibrate & Gemfibrozil
	STATINS	Decrease hepatic cholesterol synthesis by inhibition of HMG reductase	Lovastatin, Simvastatin, Pravastatin, Fluvastatin & Atorvastatin
Adjuvants In Hyperlipidemia	**Omega -3-FA**	-	-
	β-Sitosterol	-	-

* Note: This section might have lots of information, but they are extra & are meant to help in understanding

Story of Lipid Metabolism

- Lipid metabolism may be broken down into two parts. We are going to start with dietary lipids & then move to lipid synthesis in our bodies.
- Concept: lipids are water insoluble, therefore, we need a protein to coat it for transport in the bloodstream "lipoprotein" such as chylomicrons, VLDL, LDL, HDL, IDL, etc.

• What happens after you eat a high fat meal?

- Intestinal juices breakdown the lipids into fatty acids & cholesterol
These are then shipped via chylomicrons into the blood stream

• **Lipoprotein lipase (LPL)** is found on adipose tissue & muscles. It takes the fatty acids from lipoproteins such as chylomicrons & VLDL (it does nothing to cholesterol)

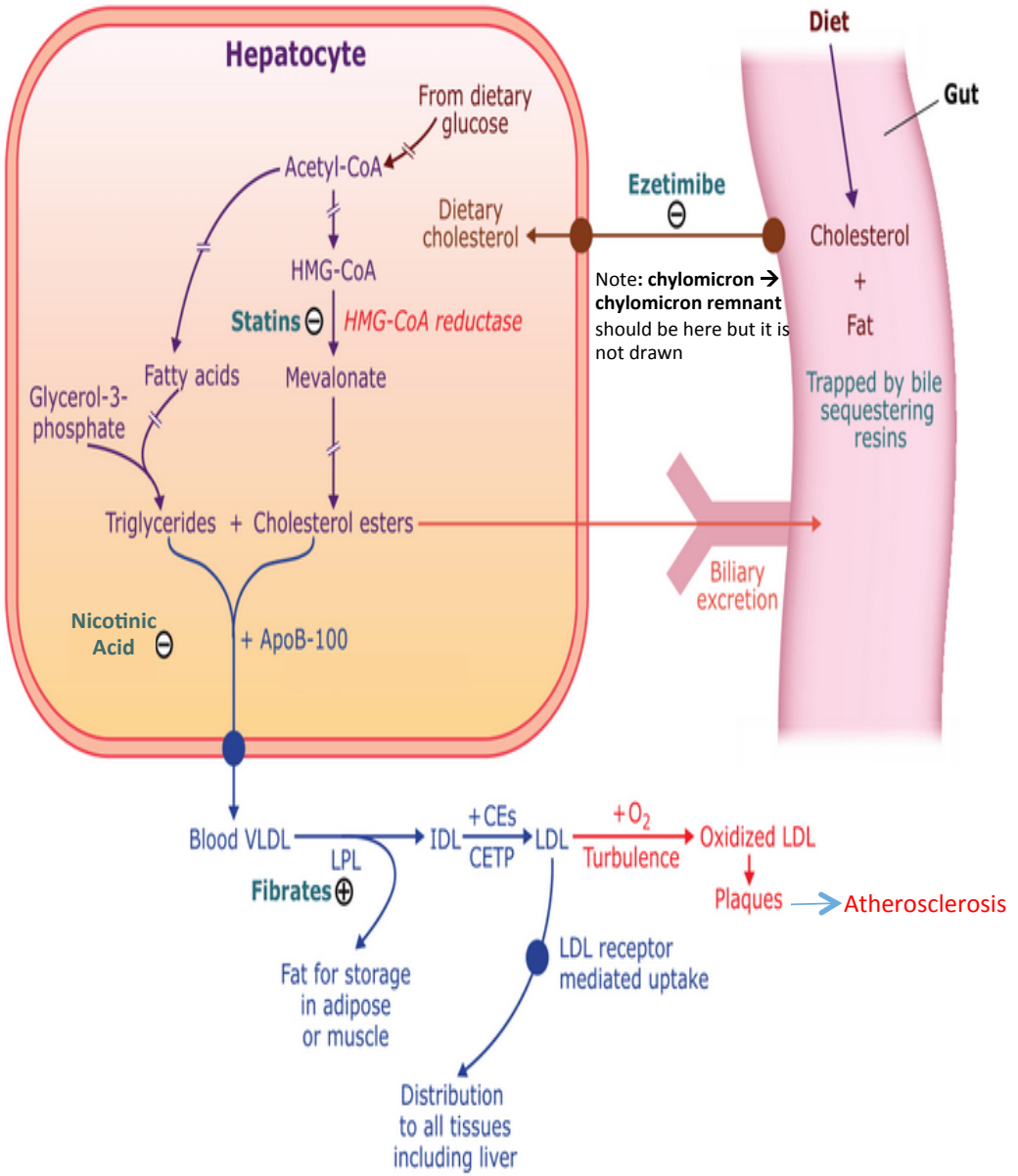
• What happens to chylomicron in the blood?

- It is digested by LPL on adipose & SKM. After that it is called: chylomicron remnant → which goes to the liver.
→The liver now gets the dietary fatty acids & cholesterol

• **The liver** makes its fatty acids & cholesterol from glucose.
Fatty acids (triglycerides) are not important for our disscussion, we will leave its biochemistry for now.

• What do you need to know about cholesterol synthesis?

- The rate limiting enzyme in cholesterol synthesis is HMG CoA reductase. If you block this enzyme (by using statins) the liver –and the whole body- can't make its own cholesterol
So, now the liver has got its cholesterol from the diet (chylomicron remnant) or by synthesizing cholesterol from glucose; what next?
- The liver ships its triglycerides (fatty acids) & cholesterol via VLDL Lipoprotein lipase (LPL) in adipose & muscles eat up the fatty acids (the same way they do with chylomicrons) & leave the cholesterol floating in the blood as LDL.
- This LDL plays a major role in the pathogenesis of atherosclerosis
- Take a look at the next picture & see if you can walk your way through it



▲Figure 10–3.2A Site of Action of Antihyperlipidemics

Ezetimibe

Mechanism of action	It Is a selective C absorption inhibitor : IT Blocks sterol transporter (NPC1L1) located on brush border of small intestine that is responsible for C translocation inside entrocytes to be esterified & incorporated in CMs ➔↓ pool of cholesterol available to the liver ➔upregulate LDL receptor, trapping more LDL particles from blood.
Pharmacological action	Decreases LDL 20%➔ 54% of intestinal cholesterol + phytosterol absorption are blocked . Decrease TG 8% & Increase HDL 1-4% no effect on steroids, lipid-soluble vitamins, bile a.
Pharmacokinetics	▪ Absorbed & conjugated in intestine to active glucuronide (> potent) ▪ Reaches peak blood level in 12–14 hours ▪ Its half-life is 22 hours ▪ Undergoes enterohepatic circulation (prolong action of drug) ▪ 80% of the drug is excreted in feces Note : Drug level in the blood increases with statins & decreases with cholystyramine
Indications	As Monotherapy; Primary prevention of low risk of CHD i.e. need modest↓LDL (used in modest increase of LDL) Statin-intolerant patients As Combination Therapy; Safe With statins; synergistic In moderate/severe ↑ LDL Or used with statin to decrease dose of statin because of its side effects -Or With other lipid lowering drugs; As fibrates,
ADV & interactions	Not common GIT disturbance, headache, fatigue, artheralgia & myalgia. Seldom reversible impairment of hepatic function

***Note: C = cholesterol**

Bile Acid Sequestrants (Resins)

Basic Information

Where does the liver get its cholesterol from?
a) From its LDL receptors (takes LDL from blood)
b) Endogenous synthesis of cholesterol by HMG CoA reductase (it can make its own cholesterol)
What does the liver do with its cholesterol ?
Cholesterol is used for cell membrane synthesis, bile acid synthesis, & steroid synthesis
If the liver has increased cholesterol, there will be down regulation of the LDL receptors (there will be a decrease in their number) & the opposite happens when there is decreased cholesterol in hepatocytes
Normally, a very small amount of cholesterol is used for bile acid synthesis. The reason is that bile acids are recycled "hepatoenteric recycling". This means that the bile acids go from the liver → intestine & from intestine → liver → intestine → liver … etc.

Drugs	Cholestyramine	Colestipol
Mechanism of Action	The aim of **bile acid sequestrants** is to make the bile acids leave the body with the feces. As a result, there will be decreased amount of bile acids. The liver now has to use a large amount of its cholesterol to synthesize bile acids → **The liver will increase the number of LDL receptors to get more cholesterol** → **The amount of LDL in the blood will decrease** It is important to note that bile acid sequestrants are non-selective for bile acids: **all lipid soluble vitamins or drugs will also be removed** by the resins	
Pharmacological Action	Decreased LDL, increased HDL, & a transient increase in triglycerides & VLDL However, there is a significant increase of triglycerides in type II b hyperlipoproteinemia patients	
Indications	1) Used for hyperlipidemias Ususally used in **combination with statins** to disable the liver from making its own cholestrol → synergistic effect 2) Since it decreases the absorbtion of lipid soluble drugs: we can use it in cases of drug poisoning. (Digoxin is lipid soluble) → **Used in digoxin poisoning**	
Side effects	Resins **increase** GIT diarrhea, bloating, constipation, dyspepsia ◆ ↓ absorption of fat soluble vitamins (A, D, E, K) - Dry flaking skin	
Contraindications	**It is contraindicated in type IIb hyperlipoproteinemia** (Extra info): this is because those patients have decreased LDL receptor (genetic deficiency) & therefore the whole idea of using the drug doesn't apply here Don't use in pts. with chronic constipation, severe hypertriglyceridemia (because these drugs increase triglycerides) Biliary obstruction. , Diverticulitis,,Chronic constipation Severe hypertriglyceridemia	
Interactions	↓ absorption of some drugs; Digoxin, Thiazides, Frusemide, Propranolol, L-thyroxin, Warfarin anticoagulant *N.B. So these drugs must be taken 1 hr before or 4 hrs after sequestrantes	

***Note: C = cholesterol**

Nicotinic Acid

Definition	- Is known as Vit B_3. - the Difference : Vit b3 has no lipid effect and Nicotinic Acid has lipid effect.
Mechanism	Bind to a specific receptors in adipose tissue (reverse effect of b-AR stimulation) → ↓ cAMP → ↓ PKA → -ve TGs breakdown → ↓FFA to liver → ↓TGs hepatic synthesis & VLDL formation This eventually ↓LDL & ↑ HDL In plasma: ↑ Lipoprotein Lipase activity → ↑ VLDL & CMs clearance
Pharmacological Actions	↓LDL 5-25% - ↑ HDL 15-30% (more drug elevate HDL) - ↓ TG & VLDL 20-50% - ↓ LP(a) - ↓ Fibrinogen (decrease coagulation). ↑Tissue plasminogen activator (increase clot dissolution).
Indication	- Mono or in combination with fibrate, resin or statin - Type llA hypercholestrolemia - Type llB hypercholesterolemia & any combined hyperlipidemia - Patient with hypertriglyceridemia & low HDL-C. - Hyperchylomicronemia.
Adverse effects	- Sensation of warmth & flushing due to prostaglandin induced → (can decrease by aspirin because it block prostaglandin). - N.B Slow release formulations → ↓incidence of flushing ! - Pruritus, rash, dry skin - Dyspepsia: nausea, vomiting, reactivation of peptic ulcer (↓ if taken after meal). - Reversible ↑ liver enzymes →hepatotoxicity. - Impairment of glucose tolerance → Hyperglycemia in diabetes patients (don't give to diabetes patient). - ↑ uric acid.
Contraindication	Gout - Peptic ulcer – Hepatotoxicity – Diabetes mellitus.

***Note: C = cholesterol *FFA: Free fatty acid**

FIBRATES

Peroxisome Proliferator Activator Receptor [PPARa] Agonist			
Mechanism	Bind & activate PPARa R. Dimerize with RXR. EXPRESS (Gene Transcription). REPRESS (Shut Gene Transcription). mRNA Translation. Protein Formation. Responsible For: ↓ TGs ↓ VLDL by liver, ↑ HDL ↑ RCT repress C synthetic pathways & ↓ LDL.		
Drugs	Clofibrate ↑ Gall stones/ Cancer	Fenofibrate(F)	Gemfibrozil(G)
Pharmacological actions	-	• ↓ LDL 5-20%. • ↑ HDL 10-20% > (G). • ↓ TG & VLDL 20-50%. • ↓ Fibrinogen • ↓ Vascular inflammation > (G) • Improve glucose tolerance > (F) N.B. Fenofibrate → uricosuric action → > if gout or in metabolic syndrome	
Protein binding	-	99%	95%, passes to placenta
Metabolism	-	Glucuronidation	Hepatic (CYP3A4)

***Note: C = cholesterol**

FIBRATES

Drugs	Fenofibrate(F)	Gemfibrozil(G)
Indications	As monotherapy: Hypertriglcyredemia; Type IV lipoproteinemia > (G). As combined therapy with statins: > (F) 1.Mixed dyslipidaemia; i.e type IIb & III lipoproteinemia. 2. In ↓ HDL, ↑ TGs ± [~LDL] + ↑ risk of atherothrombosis [Type 2 diabetes]. As combined therapy with other lipid lowering drugs: in severe treatment-resistant dyslipidaemia. N.B. (F) used >(G) with statin (specially lipophylic) to ↓ interaction on CYT P450 that leads to toxicity (myositis & rhabdomyolysis). Also (F) used > uricosuric action in insulin resistance [metabolic syndrome]	
Adverse effect	1.G.I.T upset, headache, fatigue, weight gain. 2.Rash, urticaria, hair loss. 3.Myalagia, Myositis, Rhabdomyolysis → Acute renal failure → Occurs > In alcoholics. If combined with lipophylic statins (each –ve metabolism of other) Or In impaired renal function	
Contrindications	•Pregnant or nursing women. •Renal or hepatic impairment. •Gall-bladder disease & morbid obesity. •In hypoalbuminaemia •In alcoholics	
Interactions	•They displace warfarin from their protein binding sites → ↑ bleeding tendency → anticoagulant dose must be adjusted. •They ↓ metabolism of lipophylic not hydrophilic statins → toxicity → myalgia, myositis, Rhabdomyolysis. Give lower doses	
Excretion	**Renal 60%**	**Renal 94% >**
t ½	**20 hrs**	**1.5 hours**

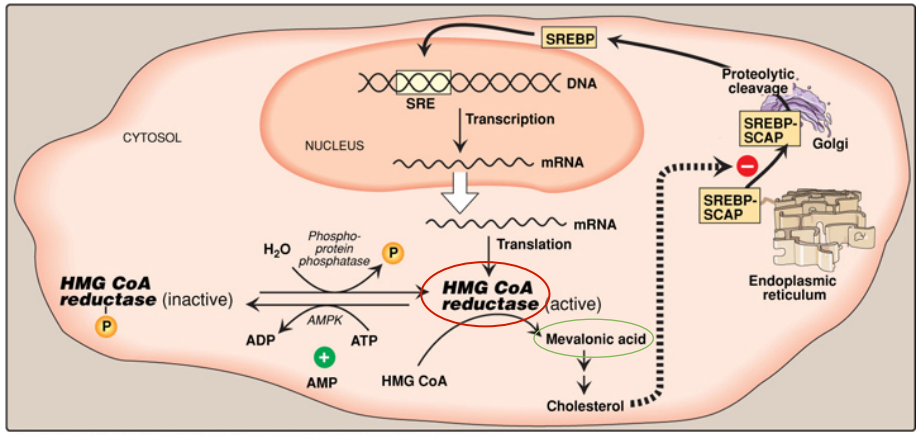
***Note: C = cholesterol**

STATINS

https://youtu.be/dgHqMhegMvk

MECHANISM OF ACTION

They are specific , reversible and competitive **HMG-CoA Reductase** INHIBITORS , which is one of the enzymes in cholesterol synthetic pathway that controls the rate limiting step of conversion to Mevalonate



EFFECTS

- LIPID LOWERING effects [In Liver]
  - ↓hepatic **C** synthesis →↓ hepatic intracellular **C**
  - 1. ↑synthesis of LDL receptors →↑ clearance of LDL
  - 2. ↓ secretion of VLDL & ↑uptake of non-HDL-C
  - Because STATINS Decrease C Synthesis & Blocks Signaling Molecules ,So STATINS Are Drugs of Choice in all Atherogenic Hyper-lipidemia
- PLEIOTROPIC (multiple) ANTIATHEROGENIC effects [> in Vessels]
  - Because it blocks cholesterol synthetic pathway it is also blocks signaling molecules responsible for progress of inflammation, vulnerability & athrothrombosis occuring 2ndry to excess C accumulation in periphery
    - Improve endothelial function
    - ↓vascular inflammation
    - Stabilization of atherosclerotic plaque
    - ↓platelet aggregability
    - Antithrombotic actions
    - Enhanced fibrinolysis
    - …etc

***Note: C = cholesterol**

STATINS

Classification	ProDrugs		Active Drugs			
Drugs	Simvastatin	Lovastatin	Fluvastatin	Atrovastatin	Pravastatin	Rosuvastatin
	Lipophilic				Hydrophilic	Partial
Fluorine containing	-	-	Weak	Strong	-	Super / Mega
Pharmacokinetics	Absorption varies (40-70%) , Fluvastatin almost completely Absorption enhanced if taken with food, except Pravastatin All have high first-pass extraction by the liver, except Pravastatin Excreted in bile & 5–20% is excreted in urine, except Pravastatin 80-90% urine					
Half-life	Short 1-3 Hours (taken only in evening , because Cholesterol Synthesis > at night)			14 Hours (taken any time)	-	19 Hours (taken any time)
Metabolized by	CYP3A4		CYP2C9	CYP3A4	Sulphonation	CYP2C9
Interactions	↓ Efficacy with INDUCERS (Phenytoin, rifampin, barbiturates , TZDs) ↑ Toxicity with INHIBITORS (Macrolides, cyclosporine, ketoconazole….)		↑ Toxicity with INHIBITORS (metronidazole , amiodarone , cimetidine)	Same as Simvastatin	-	Same as Fluvastatin

*Note: C = cholesterol

STATINS

Indications

Monotherapy

Secondary Prevention

In all ischemic insults : [stroke, ACSs up to AMI, …..etc.]

So given from 1st day of ischemic attack → stabilize plaques + help to limit ischemic zone & to salvage preferential tissues

Primary Prevention

1. Patients with hyperlipidemia and with other risks for ischemic insults.
2. Type IIa Hyperlipoprotinemia.

If no control → combine (sequestrants / ezatimibe, niacine,..) to ↓ C.

Combination therapy

Mixed dyslipidemias

Added to fenofibrates or niacine if necessary

In diabetics and patients with insulin resistance [Metabolic Syndrom]

Even if only hypertriglyceridemia & low HDL without ↑ in LDL , because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile.
SO MUST TAKE STATINS

Contraindications

In pregnancy and cautiously under age of 18 years

You can read more about statins in these websites

MedLine Plus – WebMD - Mayoclinic

***Note: C = cholesterol**

ADVERSE EFFECTS

↑**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 ↑ 3-5 folds → we ↓ statin doses / change to hydrophilic statin / omit combination with fibrates.
If severe elevation + blood in urine → this is **Rhabdomyolysis** → **Renal failure** could be fatal → dialysis is needed
Others: ↑ lenticular opacity, insomnia, rash, GIT disturbance

Adjuvants in Hyperlipidemia

The adjuvant	**Omega -3-FA** found in fish oils containing highly unsaturated FA	**β-Sitosterol** found in plants with structure similar to C
Mechanism of action and pharmacological effect	◆↓ enzymes involved in TG synthesis ◆↑ beta-oxidation of FFA So decreases TG ◆↓ platelet function ◆ Prolongation of bleeding time ◆ Reduction of plasma fibrinogen ◆ Anti-inflammatory effects So gives Some vascular protection	Compete with dietary & biliary C absorption→ decrease LDL levels ±10%
Indication	Approved as adjunctive for treatment of very high TGs	Given as food supplement before meal in hypercholesterolemia

*Note: C = cholesterol

SUMMARY

Drug	Action	Uses	S.E
Ezetimibe	↓LDL 20% TG 8% ↑HDL 1-4%	• Pry prevention of low risk of CHD • With statins; synergistic In moderate/ severe↑LDL	Seldom reversible impairment of hepatic function GIT disturbance, Headache, Artheralgia
Cholestyramine, Colestipol, Colesevelam	↓LDL 15-30% HDL 3-5% ↑TG &VLDL	• In Hyperlipidemia, Seldom • with statins in Type IIa Hyperlipoproteinemia • Pruritus	↑ GIT bloating, diarrhea, constipation, dyspepsia ↓ absorption of fat soluble vitamins (A, D, E, K) Dry flaking skin
NICOTINIC ACID	↓LDL 5-25% ↑ HDL 15-30% ↓TG, VLDL 20-50% ↓ LP(a) ↓ Fibrinogen	Type IIa hypercholestrolemia Type IIb hypercholesterolemia hypertriglyceridemia & low HDL-C. Hyperchylomicronemia	Sensation of warmth & flushing Pruritus, rash, dry skin Dyspepsia, ↑ liver enzymes Impairment of glucose tolerance, ↑ uric acid
Fenofibrate	Improve glucose tolerance	With statins in Mixed dyslipidaemia ↓ HDL, ↑ TGs + [~LDL] ↑ risk of atherothrombosis	• G.I.T upset, headache, fatigue, weight gain • Rash, urticaria, Myalgia, Myositis, Rhabdomyolysis
Gemfibrozil	↓ Vascular inflammation ↑ HDL 10-20%	As monotherapy; > (G) Hypertriglcyredemia; Type IV lipoproteinemia	• G.I.T upset, headache, fatigue, weight gain • Rash, urticaria,Myalgia, Myositis, Rhabdomyolysis
STATINS	• ↓hepatic intracell-C • ↑LDL clearance •↑non-HDL-C uptake	-In all ischemic insults (2ndry) -Patients with hyperlipidemia (1pry) -Type IIa Hyperlipoprotinemia. (1pry) -With dyslipidaemias in diabetics and patients with insulin resistance	No in pregnancy Carefully for <18
Omega -3-FA	↓TGs Some vascular protection	adjunctive for treatment of very high TGs	

MCQs

- 1- Patient diagnosed with Type IIb hypercholesterolemia, Which of the following drugs have the most effect in this patient?

A) Nicotinic acid B) Cholestyramine

C) Ezetimibe D) Statins

- 2- Patient went to the hospital to check his blood cholesterol level and he had an increase in LDL, The doctor prescribes one of the anti hyperlipidemia drugs with vitamins supplement, What is the most likely drug the doctor prescribed?

A) Ezetimibe B) Nicotinic acid

C) Colestipol D) statins

- 3- Which drug of the following cause Hyperglycemia and contraindication in diabetes patients?

A) Cholestyramine B) Nicitonic acid

C) Fenofibrate D) Ezetimibe

- 4- Patient with hypercholesterolemia taking one of the anti hyperlipidemic drugs, After 4 days the patient complaining of myalagia. Which drugs did this patient use?

A) Fenofibrate B) Cholestyramine

C) Ezetimibe D) niacin

- 5- ONE of the side effect of Atorvastatin is?

A) hepatotoxicity B) Sensation of warmth & flushing

C) decrese creatine kinase activity D) urticaria

- 6- Which of the following is one of the mechanism of action of stastin drugs ?

A) Improve endothelial function because they have pleiotropic antiatherogenic effects

B) PPARa agonist

C) Bind to a specific receptors in adipose tissue

D) Cause sodium and water loss

- 7- Diabetic patient taking Atrovastatin with fenofibrate as an anti hyperlipidimic drugs, from the history it is shown that this patient is taking one of the macrolides (Clarithromycin) What do suspect the interaction betweeen these two drugs?

A) ↓ efficacy of Atrovastin

B) ↑ the toxicity of the macrolide

C) Decrease serum transaminase

D) Acute renal failure

- 8- Patient with High TGs in the blood he had been treated with anti hyperlipidemic drugs, What is the drug that can be used as an adjunct treatment ?

A) EZETIMIBE B) Omega -3-FA

C) Losartan D) β-Sitosterol

- 9- Which of the following class of the stastins has short t½ and can only be used in evening ?

A) Atorvastatin B) Rosuvastatin

C) Simvastatin D) thiazides

- 10- What is the routine investegations of a person take statins ?

A) Serum transaminase B)creatine kinase activity

C) Both (A&B) C) None of them

1- A 2-C 3-B 4-A 5-A 6-A 7- B 8-B 9-C 10-C

https://www.youtube.com/watch?v=Pa_IbndwNHg

Long video but it is helpful

GOOD LUCK!

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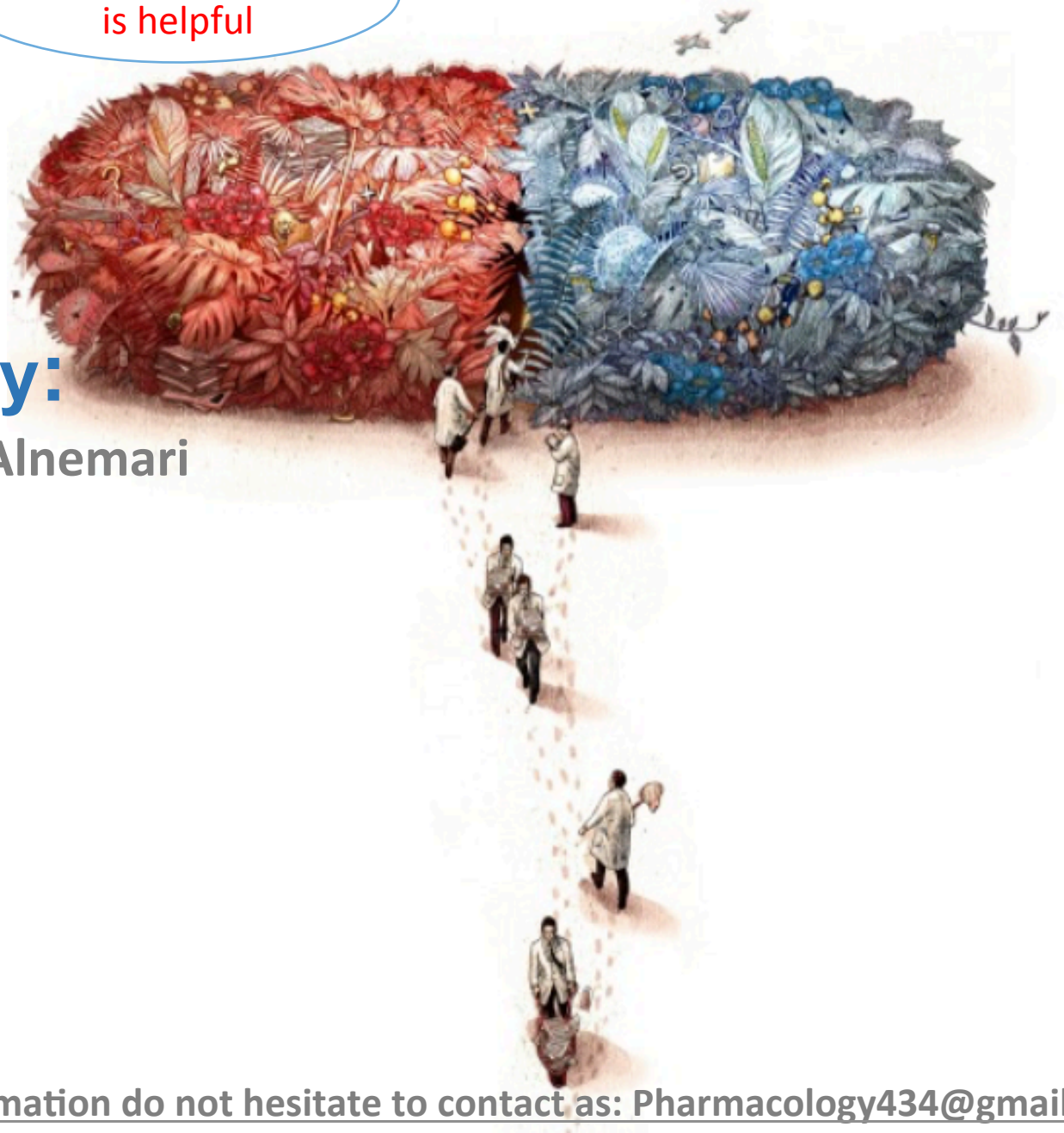

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