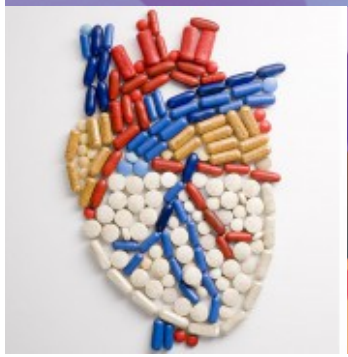
King Saud University
College of Medicine
1st Year, 4th Block

Drugs for Hyperlipidemia 9&10



Cardiovascular Block

Therapeutic strategies for treatment of hyperlipidemia

Antihyperlipidemic agents

1-Inhibits cholesterol (C) absorption in the intestine: Ezetimibe

2-Sequester bile acids in the intestine: Exchange resins

3-Inhibits synthesis of cholesterol: Inhibitors of hydroxymethylglutaryl coenzyme A reductase (HMG-COA Reductase)

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

Adjuvant agents :
Omega-3-Fatty Acids, Stanols

Therapeutic lifestyle changes

	Cholesetrol absorption inhibitor (Ezetimibe)
M.O.A	Inhibit absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
Pharmacological action	Lowers LDL 20%, TG 8%. Increase HDL 4%.
Pharmaco-kinetics	Metabolized in small intestine and liver by glucuronide conjugation. Half life 22h. prolong action of drug. Excreted in feces *Drug level ↑ with statins & ↓ with cholystyramine*.
Therapeutic uses	Primary prevention of low risk of CHD. Statin-intolerant patients. Can combination with statins or fibrates.
ADRs & Interactions Not common	GIT disturbance, headache, fatigue, Arthralgia & myalgia, seldom reversible impairment of hepatic function.
contraindication	Patient with severe hepatic insufficiency.

	BILE ACID SEQUESTRANTS ((Cholestyramine, Colestipol, Colesevelam	NICOTINIC ACID (Niacin, known as Vit B3)
M.O.A	Anion exchange resins that bind negatively charged bile acid in small intestine. The resin\bile acid complex is excreted in feces. Lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acid, resulting in decrease LDL, because the hepatocytes uptake the cholesterol from LDL.	Inhibit lipolysis in adipose tissue.
Pharmacological action	Lowers LDL up to 30%. Increase HDL ,TG &VLDL.	↓LDL 5-25%, TG, VLDL, LP(a), Fibrinogen. ↑HDL 30%, t-PA.
Therapeutic uses	✓ Drug of choice in hyperlipidemia if statin is contraindicated ✓ As combination; with statins in Type **IIa Hyperlipoproteinemia** ✓ Pruritus due to biliary stasis and Digitalis poisoning.	Type IIa and type IIb hypercholesterolemia & any combined hyperlipidemia Hyper-triglyceridemia, Hyper-chylomicronemia.
ADRs & Interactions	Dry flaking skin, GI effect. at high dose impair absorption of fat soluble vitamins (A,D,E, K). ↓absorption of some drugs; Digoxin, Thiazides, Frusemide, Propranolol, Warfarin. *These drugs must be taken 1 hr before or 4 hrs after sequestrantes*.	Cutaneous flush with feeling warmth (Aspirin prior to taking niacin decrease the flush), abdominal pain, nausea, hyperuricemia, hepatotoxicity, impaired glucose tolerance.
Contraindication	Biliary obstruction, Diverticulitis, Chronic constipation, Severe hypertriglyceridemia, Type IIb Hyperlipoproteinemia.	Gout, Peptic ulcer, Hepatotoxicity, Diabetes mellitus.

FIBRATES

-Nuclear Transcription Factors , Peroxisome Proliferator Activator Receptor [PPARa]

Mechanism:	1-Bind and activate PPARa receptor 2-Dimerize with RXR so, EXPRESS (Gene Transcription) 3-mRNA Translation and Protein Formation and Responsible: ↑ RCT)-(↓ TGs-↓ VLDL by liver -↑ HDL *REPRESS (Shut Gene Transcription) is responsible for cholesetrol Synthetic pathways	
FIBRATES	**Pharmacological actions**	**Indication**
1-clofibrate (X) **-not used-** **(↑gall stones-cancer)** **2-Fenofibrate (F)** **3 Bezafibrate** **4-Gemfibrozil (G)**	◆ **↓LDL (5-20%) , TG & VLDL (20-50%), Fibrinogen, Vascular inflammation > (G)** ◆ **↑ HDL 10-20% > (G)** ◆ **Improve glucose tolerance > (F)** N.B. : Fenofibrate → uricosuric action → if gout or in metabolic syndrome	As monotherapy; > (G) Hypertriglcyredemia; Type IV lipoproteinemia As Combined therapy with statins ; > **(F)** 1. Mixed dyslipidaemia; i.e type IIb & III lipoproteinemia 2. In ↓ HDL, ↑ TGs + ↑ risk of atherothrombosis [Type 2 diabetes] As Combined therapy with other lipid lowering drugs ; in severe treatment-resistant dyslipidaemia.

Adverse effect	Contrindications
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 Or impaired renal function	-Renal or hepatic impairment. -Pregnant or nursing women. -Gall-bladder disease. -morbid obesity. -hypoalbuminaemia. -alcoholics.

Interactions

-displace warfarin from their protein binding sites ➔ ↑bleeding ➔ anticoagulant dose must be adjusted.

-↓metabolism of lipophylic not hydrophilic statins ➔ toxicity ➔ myalgia, myositis ➔ Give lower doses.

Pharmacokinetics	Gemfibrozil	Fenofibrate
Protein binding	95%, passes to placenta	99%
Metabolism	Hepatic (CYP3A4)	Glucuronidation
t ½	1.5 hours	20 hrs
Excretion	Renal 94% >	Renal 60%

STATINS

MOA

HMG-coA reductase inhibitor (specific, reversible, competitive)

1. 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.

2. Pleiotropic 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.

*Because STATINS -ve C Synthesis & Blocks Signaling Molecules they are drug of choice in all Atherogenic Hyper-lipidemia

Effect of STATINS:

↓LDL 18-55%

↑ HDL 5-10%

↓ TG & VLDL 10-30%

Its also:

- ✓ Improve endothelial function.
- ✓ ↓vascular inflammation.
- ✓ Stabilization of atherosclerotic plaque.
- ✓ ↓platelet aggregability.
- ✓ Antithrombotic actions .
- ✓ Enhanced fibrinolysis …etc.

Classification of STATINS:

Simvastatin	Lovastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pravastatin
Prodrugs		Active drugs			
Lipophylic				Partial	Hydrophilic
		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
- ✓ Metabolized variably;
  - By CYP3A4 → Simvastatin, Lovastatin, Atorvastatin
  - By CYP2C9 → Fluvastatin, Rosuvastatin
  - By sulphonation → Pravastatin
- ✓ Excreted in bile & 5–20% is excreted in urine, except pravastatin 80-90% urine
- ✓ t½ → Short 1-3 hrs → Simvastatin, Lovastatin, Fluvastatin → Taken only in evening
  - → 14 hrs → Atorvastatin
  - → 19 hrs → Rosuvastatin

} Taken any time

indication

As monotherapy:

Secondary Prevention; In all ischemic insults.
So given from1st 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.

As Combination therapy:

1. Mixed dyslipidaemias; added to fenofibrates or niacine if necessary

2. In diabetics and patients with insulin resistance [metabolic syndrome]

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

ADRs:

*↑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

Drug interaction:

*Those metabolized by CYP3A4 [Simvastatin, Atrovastatin] show

↓ efficacy with INDUCERS (Phenytoin, rifampin, barbiturates, TZDs ….)

↑ toxicity with INHIBITORS (Macrolides, cyclosporine, ketoconazole….)

*Those metabolized by CYP2C9 [Fluvastatin & Rosuvastatin] show

↑ toxicity with INHIBITORS (metronidazole, amiodarone, cimetidine…)

Adjuvants in hyperlipidemia

	Omega -3-FA	β-Sitosterol
Mechanism	found in fish oils containing highly unsaturated FA ↓ TGs	found in plants with structure similar to C Compete with dietary & biliary C absorption→ ↓ levels of LDL
Indications	Approved as adjunctive for treatment of very high TGs	Given as food supplement before meal in hypercholestrolemia

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

Q1: Colestipol belongs to which group of the following antihyperlipidemic drugs ?
A- Cholesterol absorption inhibitors
B-Cholesterol synthesis inhibitors
C-Bile acid seqesterants -
D-None of the above

Q2: The long duration of action of Ezetimibe is due to which one of the following?
A-It can be given IV
B-Absorbed in intestine
C-It undergoes enterohepaic circulation
D-It is a prodrug

Q3: The first line of treatment of hyperlipidemia and the most efficacious group is
A-Fibrates
B-Statins
C-Omega-3-FA
D-All of them

Q4: A 60-years old hyperlipidemic man who was diagnosed last year with gouty arthritis, what drug should be avoided to prescribe in such a condition?
A-Ezetimibe
B-Nicotinic acid
C-Fibrates
D-Statins

Q5: What is the serious adverse effect of fibrate if taken by alcoholics:
A- Rhabdomyolysis
B- Sensation of warmth
C- Purities
D- None of the above

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

Q6: A 75-years old woman was diagnosed with hypertriglyceridemia, the doctor described one of the fibrates drugs for her but she told him that she is taking an anticoagulant (warfarin).
What precaution should be done by the doctor in this condition :
A-Cut of warfarin
B-Displace fibrate by another drug
C-Adjust the dose of warfrine
D-No precaution should be done

Q7: Which one of the following groups must take statins even in case they don't have increased LDL levels because they have increased thrombotic profile and prone to have low LDL levels
A-Asthmatic patient
B-Hypertensive patient
C-Diabetics
D-Pregnant woman

Q8: Statins drugs that are metabolized by CYP3A4 will show decreased efficacy with which one of the following drugs
A-Macrolides
B-Metrodinazole
C-Phenytoin
D-Cyclosporine

Q9: What is the contraindication of statins ?
A-Pregnancy
B-Under age of 18
C-Hypertensive patients
D-A&B

Q10: What is the mechanism of action of nicotinic acids
A- Blocking of peroxisomes proliferator-activated receptors (PPARs)
B- Inhibit lipolysis in adipose tissue and decrease cAMP
C- HMG CoA reductase inhibitors
D- Blocks sterol transporter

PHARMACOLOGY 433

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We hope that we made this lecture easier for you

Good Luck !