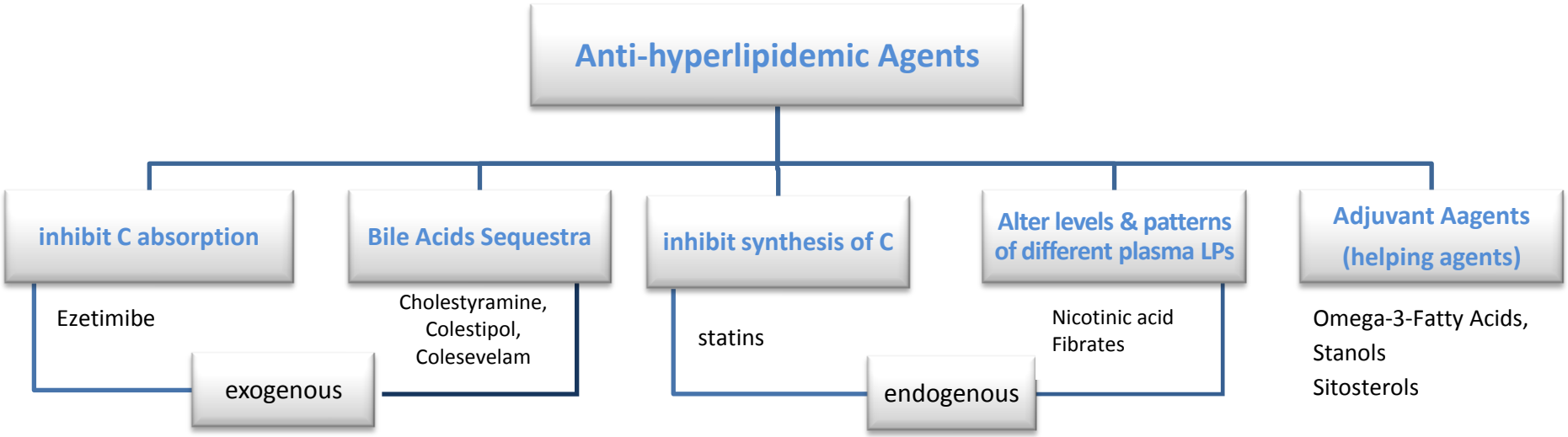
Treatment of hyperlipidemia



Hyperlipoproteinemia	Lipid Derangement	Treatment
Type I	**TGs**	
Type IIa	C	Statins + Sequestrants
Type IIb	**TG & C**	Fibrates, Statins, Niacin
Type III	**TG & C**	Fibrates
Type IV	TGs	Fibrates
Type V	**TG & C**	

Inhibiting Cholesterol absorption in intestine	**e.g., Ezetimibe**
M.O.A	- **Block NPC1L1** (responsible for C transport) → decrease C in liver → upregulate LDL receptors → blood LDL decrease - **LDL decreases 20%, TG decreases 8%, HDL increases 4%**
Pharmacokinetics	- Absorption in intestines - $t_{1/2}$ = 22hrs , level peaks in 12-14hrs - **Undergoes enteorohepatic circulation (prolong action of drug)** - **80% of the drug is excreted in feces** - **Drug level ↑if with statins & ↓ if with cholystyramine**
Uses	- prevention of low risk of CHD (mono therapy) - In moderate/severe ↑ LDL (As Combination Therapy with statins)
Adverse Effects	Not common. GIT disturbance, headach, fatigue, artheralgia & myalgia. Seldom reversible impairment of hepatic function

Bile Acids Sequestrant	**e.g.** Cholestyramine, Colestipol, Colesevelam **(polymeric cation exchange resins)**
M.O.A	- binds to BA (bile acids) → prevent their recycling in liver → ↑ fecal excretion → ↓BA will ↓ C absorption → upregulation of LDL receptors → ↑hepatic C uptake → decrease C levels in blood - LDL decreases 15-30%, TG and VLDL increases (intial & transient), HDL increases 3-5%
Uses	- Hyperlipidemia - Pruritus - Digitalis poisoning
Adverse effects	- ↑ GIT bloating, diarrhea, constipation, dyspepsia - ↓ absorption of fat soluble vitamins *(A, D, E, K)* - Dry flaking skin
Contraindication	- Diverticulitis - Chronic constipation. - Severe hypertriglyceridemia - Type IIb Hyperlipoproteinemia
Drug interaction	- ↓ absorption of some drugs; Digoxin, Thiazides, Furosemide, Propranolol, L-thyroxin, warfarin anticoagulant **these drugs must be taken 1 hr before or 4 hrs after sequestrantes**

Inhibiting C synthesis	**Statins e.g. Simvastatin, Lovastatin, Fluvastatin, Atorvastatin, Pravastatin,** Rosuvastatin
M.O.A	- **HMGCoA Reductase INHIBITORS:** a) ↓hepatic C synthesis→ ↓ hepatic intracellular C b) ↑synthesis of LDL receptors →↑ clearance of LDL c) ↓secretion of VLDL & ↑uptake of non-HDL-C - **blocking signaling molecules responsible for progress of inflammation, vulnerability & athrothrombosis** (Improve endothelial function,↓vascular inflammation,↓platelet aggregability, Stabilization of atherosclerotic plaque, Antithrombotic actions, Enhanced fibrinolysis) - **+ve osteoclast apoptosis** - **↑synthetic activity in osteoblasts** - **Immune suppression.** - **↓LDL 18-55%, ↑ HDL 5-10%, ↓ TG & VLDL 10-30%**
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 bcz C Synthesis > at night)*lypophylic drugs - t½ = 14/19hrs → Atorvastatin/Rosuvastatin (taken any time) *hydrophilic drugs
Uses	- 1st prevention in hyperlipidemia with risk of developing ischemic insults and Type IIa Hyperlipoprotinemia (mono therapy) - 2nd prevention all ischemic insults as transient ischemic attacks, stroke, subtypes of ACSs up to AMI. (mono therapy) - Mixed dyslipidaemias (Combination Therapy) - In diabetics (hypertriglyceridemia & low HDL) (Combination Therapy)
Adverse effects	- **liver toxicity** (due↑serum transaminase) - **myalgia or myositis** (↑CK is measured) - **blood in urine and Rhabdomyolysis "** excretion of myoglobin in the urine" (renal failure happen) - **others** ↑lenticular opacity, insomnia, rash, GIT disturbance
Drug interaction	- CYP3A4 , Drug inducers (Phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones) → ↓ efficacy & Drug inhibitors (e.g.macrolide antibiotics, cyclosporine, ketoconazole)↑ toxicity of Simvastatin, Lovastatin, Atorvastatin - CYP2C9, Drug inhibitors (ketoconazole, metronidazole, sulfinpyrazone, amiodarone, and cimetidine) ↑ toxicity of fluvastatin & rosuvastatin

Fibrates	**Fenofibrate (F), Bezafibrate, Gemfibrozil (G)** (Nuclear Transcription Factors)	
M.O.A	- Peroxisome Proliferator Activator Receptor [PPARa] AGONISTS - FA oxidation (↓ TGs in plasma,↓ VLDL Formation by liver) -(↓LDL 5-20%,↑ HDL 10-20% > (G),↓ TG & VLDL 20-50%,↓ Fibrinogen,↓ Vascular inflammation > (G),↑ glucose tolerance > (F))	
Pharmacokinetics	**Gemfibrozil** 100% BV 95% protein binding (pass through placenta) Hepatic metabolism (CYP3A4) t ½ = 1.5hrs 94% renal, 6% feces excretion	**Fenofibrate** less BV 99% protein binding Glucuronidation metabolism t ½ = 20 hrs 60% renal, 25% feces excretion
Uses	- Hypertriglcyredemia; Type IV lipoproteinemia (mono therapy use G) - Mixed dyslipidaemia and in diabetes (combined therapy use F) * *F uricosuric action help in insulin resistance syndrome* - As Combined therapy with other lipid lowering drugs; in severe treatment-resistant dyslipidaemia.	
Adverse effects	- G.I.T upset, headache, fatigue, weight gain - Rash, urticaria, hair loss - Myalagia, myositis, rhabdomyolysis → acute renal failure	
Contraindication	- Renal or hepatic impairment - Pregnant or nursing women - Gall-bladder disease & morbid obesity - In hypoalbuminaemia - In alcoholics - Clofibrate *cause Gall stones, Cancer, hypoglycemia, ADRS*	
Drug interaction	- They displace warfarin from their protein binding sites → ↑ bleeding tendency - They ↓ metabolism of lipophylic statins → toxicity → myalgia, myositis	

Nicotinic acid	**Is known as Vit B_3. Its amide derivative nicotinamide has no lipid lowering effects**
M.O.A	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 & VLDLformation, This eventually ↓LDL & ↑ HDLIn plasma:↑ LPL activity →↑ VLDL & CMs clearance ↓LDL 5-25%, ↑ HDL 15-30%, ↓ TG & VLDL 20-50%, ↓ LP(a), ↓ Fibrinogen, ↑Tissue plasminogen activator
Uses	- Type IIa hypercholestrolemia - Type IIb hypercholesterolemia & any combined hyperlipidemia - Patient with hypertriglyceridemia & low HDL-C. - Hyperchylomicronemia
Adverse effects	- Sensation of warmth & flushing (prostaglandin induced /-ve by aspirin ½ h before niacin). - Pruritus, rash, dry skin - Dypepsia: nausea, vomiting, reactivation of peptic ulcer *(↓ if taken after meal).* - Reversible ↑ liver enzymes →hepatotoxicity. - Impairment of glucose tolerance → overt diabetes - ↑ uric acid
Contraindication	- Gout, Peptic ulcer, Hepatotoxicity, Diabetes mellitus

Adjuvant agents	**Omega-3-FA**	**β- sitosterol** (found in plants with structure similar to C)
M.O.A	- **decrease TGs** Inhibit enzymes involved in TG synthesis FA oxidation - **vascular protection** Inhibit platelet function Prolong bleeding time Anti-inflammatory effect	Compete with dietary & biliary C absorption→ ↓ levels LDL levels ±10%
Uses	Approved as adjunctive for treatment of very high TGs	Given as food supplement before meal in hypecholestrolemia
Adverse effects	- Eructation, dyspepsia, altered taste - Can worsen glycemic control in diabetics - Can increase bleeding tendencies	- GIT ; nausea, vomiting, diarrhea, gases,constipation… - Impotence & ↓ sex drive - Avoided in pregnancy & breast feeding