LDL-Cholesterol Lowering Drugs

Class	Drugs/Dose	MOA	ADME	ADRs/CI
HMG Co-A Reductase Inhibitors (Statins) • 1st line hyper-cholesteremia • 4-6 wks to reach max effect • double dose = NOT double effect only 6-7%	ALL • First line agents ↓cholest. • Major effect is on the ***liver*** • Effective with OD administration • Minor ↓ VLDL TGs:7-30% • Marginal ↑ HDL: 5-15%	• **REVERSIBLE COMPETITIVE INHIBITION OF HMG COA REDUCTASE** (higher affinity for the enz vs HMG CoA at least by 1000x) • Inhibits HMG CoA reductase = Inhibition of cholesterol synthesis in the liver = ↑ LDL-R = ↓ LDL (b/c reuptake of LDL/IDL in plasma due to ↑ LDL-R in liver) • **↑ expression of LDL R = promotes ↓ LDL/IDL from plasma** • **↓ cholesterol packg'd in VLDL =↓ LDL/IDL synthesized (b/c formed from VLDL) = ↓ VLDL = minor ↓ TG = ↑ HDL (b/c ↓ TG)** • **↓ LDL-C: 20-65%** <u>SAM: statin associated muscle syndrome</u> **CK (creatinine kinase)** = tissue enz (skeletal muscle) that is released during muscle breakdown **Myopathy:** muscle related pathology (umbrella term) **Myalgia:** muscle pain w/ **CK≤ ULN** (not any breakdown) = continue current dose, reduce dose, switch statin or d/c temp or intermittent dosing **Myositis:** myalgia with **CK>ULN (≤10ULN)** (muscle breakdown) = often d/c statin and re-start tx once pt asx and CK≤ULN **Rhabdomyolysis:** muscle breakdown **with CK >10x ULN +/- serum myoglobin w/ renal failure (dark urine = myoglobinuria)** = v rare, likely dose related, increased risk with concomitant fibrate, d/c statin and DO NOT rechallenge • <u>**Lipid targets:**</u> **Statin indicated condition (2* prevention) or 1*prevention:** LDL-C <2mmol/L or >50% ↓ LDL-C **LDL-C >5mmol/L:** >50%↓ LDL-C <u>**Study:**</u> • Statins risk of CV event in 1* and 2* prevention • ARR> in 2* prev. vs 1* • Small ARR w/ intensive vs mod dose tx in 2* prev • Higher intensity > lower intensity statin tx • ↓ LDL-C associated with ↓ risk of CV events • <u>**MEDCHEM**</u>: 7 sub. 3R, 5R dihydroxyheptanoic acid moiety = essential for inhibitory activity if have lactone ring = pro drug, if open then active	• First pass metabolism in the liver • ⊣ HMG CoA reductase = ⊣ Melavonic acid =⊣ Rho [Rho: constricts BV in smooth muscles, ↑ TPR) = **by ⊣ Rho = helps ↓ BP**	• 5-10% **GI upset**: cramps, gas, nausea, constipation; **Headache, rash, insomnia** • Cramps, weakness, pain – muscle sx (**SAMS = statin associated muscle syndrome**) • **N/V/D, elevated liver enzymes** • **Myopathy** (due to ↓ CoQ10 – block ATP produc.) • **Rhabdomyolysis** (rare) – mscl breakdown = liver failure) [>10xULN+/- serum myoglobin] – reversible if stop statin • Limited of patients who lack genes for LDL-R • <u>**CI**</u>**: pregnancy** (skeletal malformation in fetus), **lactation**, may cause small increase in A1C (***caution in DM***), **hepatotoxicity [3x>ULN – do liver fn test], hypersensitivity** • May be associated **with DM, cataracts** • ***Other drugs that <u>inhibit</u> statin metabolism*** ***↑[statin] = ↑ SEs of statins***: amiodarone, CCBs (diltiazem, verapamil +/- amlodipine), colchicine, cyclosporine)
	Simvastatin (P) **10-40mg/day**		• Short T ½ = 6 hrs – take @ night b/c that's when cholesterol is made in the liver	• <u>**CYP3A4 inhibitors**</u>: macrolides ab, grapefruit juice, azole antifungals, protease inhibits ***↑[statin] = ↑ SEs of statins*** • CYP3A4 inducers = ***↓[statin] =*** rifampin, carbamazepine, phenytoin, phenobarbital, St.Johns wort
	Lovastatin (P) 20-80mg/day			
	Atorvastatin (synthetic) **10-80mg/day** "super statins" ***[↓LDL 35-60%]***		• T ½ = 14-19 hrs (longer) so can be taken at any time)	
	Fluvastatin 20-80mg/day			• **CYP 2C9 metabolism** = also used in warfarin, so if used with warfarin, caution b/c will ↑ [warfarin]
	Rosuvastatin (synthetic) <u>most potent</u> **5-40mg/day** "super statins" ***[↓LDL 40-65%]***		• Longer T ½ so can be taken at any time	• 40mg daily CI in Asian patients or patients with pre-disposing factors for myopathy/rhabdomyolysis • ***Separate Rosuvastatin + Mg/Al antacids by 2 hrs (b/c ↓ [statin])***
	Pravastatin 10-40mg/day		• ↑ Hydrophilicity =↓ penetration into membrane of peripheral cells = improves hepatic selectivity (↓ Vd) = ↓ SEs • Metabolized in the gut and secreted in the kidney so <u>**not affected by CYP 450 enz**</u>	
Bile Acid Sequestrants **"Cole"** **PO**	**Colestipol** (mesh, pKa: 9-10.5 not charged) Granules –mix w fluid/pulpy fruits, soups): 5-30g/day Tabs (swallow whole): 2-16g/day	• **Sequestrants are large positively charged polymers that biologically inert and water insoluble bind to negatively charged bile = prevent bile reabsorp** • **MoA:** block re-absorption of bile from the ileum in small intestine (95-97% of bile reabsorbed) and <u>blocks reabsorption of free cholesterol</u>= more cholesterol gets broken down into bile in the liver = ↓ cholesterol in the liver • Net effect: ↑ production of LDL-R = ↓cholesterol • Over time **efficacy is blunted** (b/c liver can still produce cholesterol (HMG CoA reductase) and then ↓ LDL-R but ***still effective b/c block free cholesterol still*** • **↓ LDL-C: 15-30%**	• Efficacy is blunted over time • Limited SEs b/c stay in gut • Study: no CV outcome data	• <u>**SEs:**</u> Diarrhea, flatulence, abdominal pain, constipation, bloating • <u>**CI:**</u> hypersensitivity, biliary obstruction • Multiple drug interactions (space by ≥2hr) • **Decreased absorption of negatively charged drugs** (digoxin, propranolol, anti-coags like warfarin, HCTZ – take 1 hr before or 4 hrs after) **and fat-soluble vitamins (Vitamins A, D, E, & K) →** *would ↓ [their]* • **Can be taken in pregnancy √**
	Colesevelam tabs (swallow whole): 3 tabs BID w/meal (each tab: 625mg)			
	Cholestyramine (4* ammonium = charges, higher absorption)			
Cholesterol Absorption Inhibitor	**Ezetimibe** 10mg/day PO Study: solo↓ LDL-C and did not ↓ CV event but w/ statin did , no change in mortality	• Inhibitor of <u>**intestinal**</u> cholesterol absorption at brush border – **inhibits NPC1L1** = as a result ↓ chylomicrons =↓ CM = ↓cholesterol delivery to liver (main effect) and eventually ↓VLDL and ↓ LDL (indirect effect b/c ↓cholesterol, will ↑LDL-R in liver) • NPC1L1= transporter responsible for cholesterol reabsorption in intestine • **Monotherapy/Combination with statin** (promote clearance of LDL from blood into liver by LDL-R) • **↓ LDL-C: 18-20%** w/ statin tx	• Long T ½ :22 hrs • Can be co-administered w statins b/c diff MoA • Rapidly metabolized to **glucuronide** (400x potency of EZE) =prolong action	• **SEs:** diarrhea, headache, URTI, fatigue, sinusitis, increased liver enz (w/ statins), arthralgias • <u>**CI:**</u> **pregnancy/lactation, active hepatic diseased or unexplained liver enz elevation (w/ statins), hypersensitivity**
PCSK9 Inhibitors	**MAbs: Evolocumab** **Alirocumab** 75-150mg SC q2wk SC injections q2-4 wks	• Used if need additional cholesterol lowering therapy – used in cases of familial hypercholesterolemia • **Inhibits PCSK9 by binding to LDL-R = prevents degradation of LDL-R = increases LDL-R = ↓ cholesterol** [.:. PCSK9 cannot bind to LDL-R]	• <u>**Study:**</u> pt taking statin + PCSK9 inhib = reduces CV events but not mortality • T ½ = 11-17 days (Rapatha)	• <u>**SEs:**</u> URTI, rash injection site reactions, muscle aches, N/D, nasopharyngitis • <u>**CI**</u>: hypersensitivity; Not studied in pregnancy • **↓ LDL-C: 40-70% with statin tx**

VLDL-TGs Lowering Drugs				
Class	**Drugs/Dose**	**MOA**	**ADME**	**ADRs/CI**
Fibric Acid Derivates [Fibrates] **For severe hyperTG**	• Clofibrate (P) • **Fenofibrate (P):** 67-200g/day • **Bezafibrate:** 200-600mg/day • **Gemfibrozil**: 1200mg divided in 2 doses/day	• ***most effective at ↓VLDL (TGs): ↓20-50% of TGs** ****primarily used to ↓ risk of pancreatitis** • **Not effective in ↓LDL [5-20%]; ↑ HDL [transcription of ApoA-1]** **Note:** ↓ TG = ↓ clearance of HDL (CETP) • 1) Primarily as PPARa agonists → stim PPARa R = ↑ oxidation FAs in liver =↓ VLDL production striated muscle (+kidney/heart) • 2) ↑ LPL activity = ↑ breakdown of TGs =↑ CL of TGs (VLDL) **Med Chem:** • Coordinated by H bonds • Gem: more susceptible to CYP 3A4 metabolism b/c hydrophobic appendage • P = long hair sheep dog	• **Study:** ↓ LDL ↓ TG no Δ in CV events/ mortality	• **May cause**: GI intolerance, gallstones, risk of myopathy • **SEs:** N/D/weight-gain, skin rash, muscle cramps/stiffness • **CI: Gemfibrozil w/ statin**, gallbladder dx, severe CKD, hypersensitivity, lactation
Vascepa	• **Icosapent Ethyl** [analogue of **Omega 3 FA**]: 2 x 1g caps BID	• 1. ↑ beta oxidation of FA's = ↓ production/accelerates CL of TGs + slows production of VLDL • 2. blocks formation of FA = ↓ TG = ↓ VLDL • 3. FA (once formed) converted into TG (blocks DGAT) [DGAT= converts FA → TG] • 4. stim LPL = ↓ VLDL/TG	• **Study:** ↓ risk CV event in statin tx pt with ↑TGs (≥150mg/dL)	• **CI: pregnancy/lactation** • Small afib /flutter **Study:** • No benefit to Omega-3-PUFA supplementation in the prevention of CVD – • No change in CV events or mortality in DM patients OR men ≥50, women ≥55 yrs (primary) • **Icosapent ethyl** (purified EPA) 2000mg PO BID = ↓ CV events/CV death but all cause mortality = no change
Vitamin B3	• **Niacin (Vitamin B3)**	• Niacin Rs are GPCRs (Gi) = decrease in adipocyte lipolysis • = inhibition of lipolysis in adipose = **↓ TGs (at start)** = ↓cholesterol (after several days of tx) • No mobilization of FFA = liver cant makes VLDL = **↓ LDL** • **Causes vasodilation and lipid lower activity (unlike its amide analogue – requires COOH)** • **↓ LDL-C by 5-25% and ↑ HDL-C by 20-35%** • **Med Chem:** requires COOH	• High affinity = niacin R 1/ hydroxycarboxylic acid R2 • Low affinity= NR2/ HCAR3 • **Study**: ↑HDL, ↓ LDL, no Δ CV events serious AEs:↑diabetes, bleeding, infections	• **CI:** active peptic ulcer disease, active hepatic disease, severe DM, gout, arterial hemorrhage, hypersensitivity • **Lots of SEs: flushing** *(PG mediated, ↓ w/ tolerance, dose after meals or HS)* dyspepsia, dysglycemia, hypotension, inc liver enz/hepatotoxicity, gout, rash, thrombocytopenia, myopathy (w/ statins) **ER niacin** =↓ flushing = ↑ risk of hepatoxicity **Flush-free niacin** = contains inositol = does not absorb and does not work (don't get drug) = basically placebo

http://chd.bestsciencemedicine.com/calc2.html