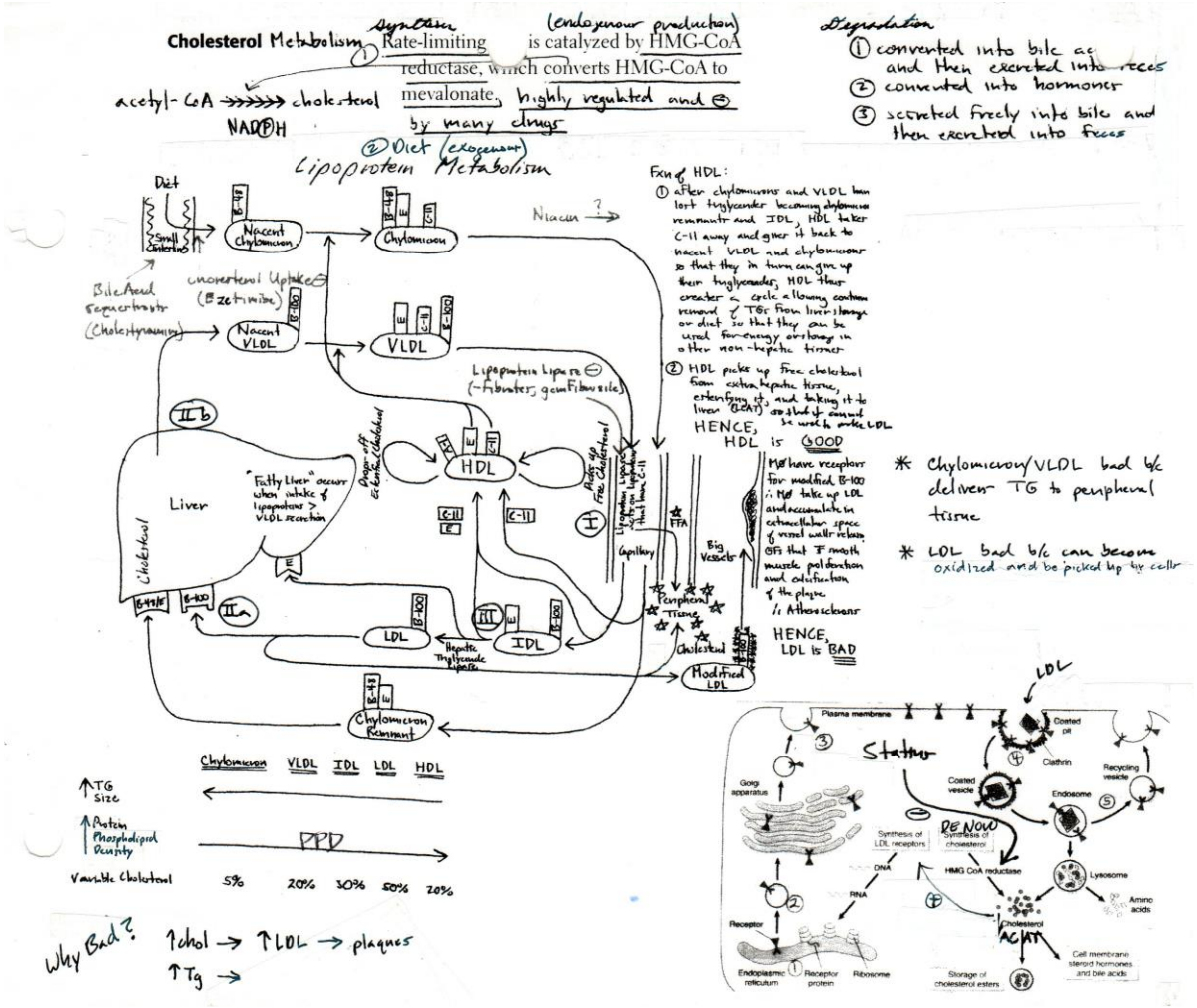
- Lipoproteins: hydrophobic core (TG + Cholesterol) and hydrophilic outer layer (PL + Apoproteins)
- Chylomicrons provide energy from food in form of TG to body and VLDLs provide energy from liver in form of TG to body with the enzyme, LPL, breaking down the TG into FFAs
- LDL provides cholesterol for synthesis of hormones, membranes, bile acid, etc
- HDL scavenges cholesterol that is made from broken down cells
- NB Lp(a) is several LDLs bound together by disulfide bound to apo(a), very thrombophilic



Familial Dyslipidemia 10% (II/IV most common) Fredrickson Classification

- Other: Tangier's Dz, Familial HDL Deficiency, Familial Hypoalphalipoproteinemia, etc

Class	Name	Lipoprotein	Etiology
Type I	Exogenous Hyperlipidemia	Nl LDL High TG	AD mutation of lipoprotein lipase or ApoCII resulting in a syndrome where you have ab pain, HSM, eruptive xanthomas, lipemia retinalis, pancreatitis, memory loss, paresthesia, peripheral neuropathy (NB no increased r/o CAD), Tx: low fat diet, medium chain TG, fat soluble vitamins
Type IIa	Familial Hypercholesterolemia (FH)	High LDL (>250) Nl TG	AD mutation of the LDL Receptor (binds ApoB) resulting in decreased production, premature CAD and tendon xanthomas, TC 250-500 (Hetero) 600-1000 (Homo), discovered by Dr. Brown & Dr. Goldstein, Tx: statins, bile acid binders
Type IIb	Familial Combined Hyperlipidemia (FCH)	High LDL (200-250) High TG	Unknown but likely polygenic (combination of IIa with increased VLDL), Tx: statins + fibrates VERY COMMON, 1% of population, 10% of premature CAD pts
Type III	Familial Dysbetalipoproteinemia	Same as Type IIb	AD mutation of ApoE such that lipoproteins w/ ApoE aka IDL cannot be taken up, usually there is concurrent DM, Obesity, hypoTH, Tx: Niacin
Type IV	Endogenous Hyperlipidemia	Same as Type I	Secondary Causes of overproduction of ApoV and VLDL resulting premature CAD and NIDDM

Type V	Familial Hypertriglyceridemia	Same as Type I	Combination of I and IV, Tx: Niacin and Fibrates

Secondary Dyslipidemia 90%

	LDL	TG	HDL
Low	Cancer HyperTH Cirrhosis		Social: Smoking Diet: High Carb Diet Endo: Obesity, DM Meds: Androgens, BB
High	Age Diet: High Calorie Diet Meds: HAART, BB, OCPs, Steroids, HCTZ, PIs, Propofol Endo: HypoTH, DM, Obesity, Cushing, Pregnancy Renal: CKD w/ Nephrotic Syndrome	Same as LDL + Diet: EtOH	Social: Weight Training, Red Wine Endo: Losing Weight

Diet

- Trans/hydrogenated increase LDL decrease HDL therefore very bad
- Saturated & Polyunsaturated decrease LDL decrease HDL therefore bad
- Monounsaturated decrease LDL increase HDL therefore good

Clinical Features

- Familial Hyperlipidemia
  - Eruptive Xanthoma (pimple like lesions on buttocks/elbows/forearms) and Xanthalesma (soft yellow plaque on eyelids) seen in Type I/IV/V (TG)
  - Tendon Xanthoma (hard yellow mass on extensor tendons of fingers/Achilles) seen in Type II (LDL)
  - Tuberous Xanthoma (hard yellow mass on elbows/knees) seen in Type III (TG + LDL)
  - Yellow Palmar Crease (creases in palms are yellow) seen in Type III (IDL)
  - Corneal Arcus (lipid deposition on cornea)
  - Lipemia Retinalis (retinal vessels are white)
  - Pancreatitis (TG>500)
  - Lactescent Serum
- Secondary Hyperlipidemia
  - Asymptomatic

Diagnosis

Friedewald Formula

Calculated Measured

LDL = Total Cholesterol – HDL – TG/5

TC ≈ LDL + HDL + TG

200 ≈ 120 + 50 + 150/5

	TC	LDL	HDL	TG
Low			<40	
Optimal		<100	40-60	
Near Optimal	<200	100-130		<150
Border High	200-240	130-160	>60	150-200
High	>240	160-190		200-500
Very High		>190		>500

- Fasting Lipid Panel (FLP) = measures TC, HDL, TG and calculates LDL
- Same look at "non-HDL" (TC-HDL) which is theoretically the sum of all atherogenic proteins (LDL + Lp(a) + IDL + VLDL) and may be a better predictor of plaque formation than just LDL
- NB the cholesterol content of chylomicrons is minimal
- screen every adult >20yo if +RFs or >35yoM/>45yoF if –RFs and then Q5yrs if nl or Q1yr if abnl
- TG can be falsely elevated in the NON-fasting state therefore since LDL is calculated based on this value pt should fast 9-12 hrs b/c if not then the LDL might be falsely lowered b/c of a high TG but normal TC and HDL
- Lipid levels are stable for up to 24hrs
- recent evidence suggests that increased TG in the form of VLDL is an independent cardiac RF, therefore the goal is to lower BOTH LDL and VLDL = "non-HDL cholesterol"
- there is evidence that LDL particle size specifically small dense LDL is a contributor to CAD there some argue ordering an LDL subclass panel called an MMR ("big and fluffy is better")
- Other Labs to Consider = TSH, cortisol, LFTs, BUN, Cr, glucose, etc

Treatment

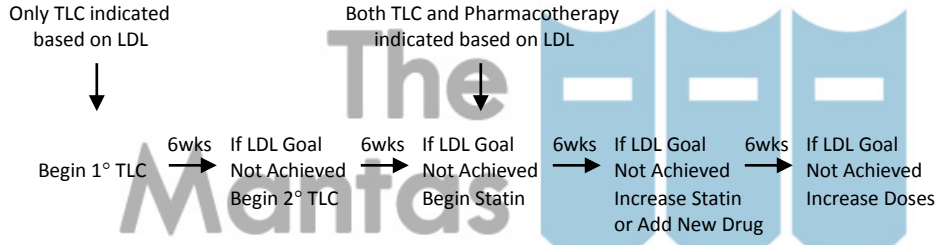
Risk Assessment/Management of Cholesterol using National Cholesterol Education Program (NCEP) & Adult Treatment Panel III (ATP III) Guidelines		
Category	**LDL Goal**	**Tx**
CAD or CAD Equivalent: DM or any atherosclerotic dz (PVD, AAA, CVA) or Framingham 10yr Risk of ≥20%	<70-100	TLC: start if >100 Meds: start if >130
Framingham 10yr Risk of 10-20%	<130	TLC: start if >130 Meds: start if >160
Framingham 10yr Risk of ≤10%	<160	TLC: start if >160 Meds: start if >190

- NB Heart Protection Study and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) showed that lowering LDL by 30 below recommendations below may be beneficial
- Framingham Risk
  - Smoker
  - HTN (>140/90 or any BP if pt is one an anti-hypertensive)
  - HDL<40 (subtract a RF if HDL >60)
  - Age (M>45, W>55)
  - FHx of Premature CAD (1°M<55yo, 1°F<65yo)

Therapeutic Lifestyle Changes (TLC)

- 1°: decrease intake of saturated fat/cholesterol (Step 1 Diet), increased physical activity, decrease weight
- 2°: increase plant stanols/sterols and soluble fiber (Step 2 Diet)

Treatment Algorithm



Agent,	LDL	HDL	TG	SEs
HMG-CoA Reductase Inhibitor (decreasing denovo chol production leading to increased LDL receptors) only 50% of the cardioprotective effects of statin is decreasing LDL), Anti-Inflammatory, Increase NO, Reverses Endothelial Dysfxn, Stabilizes Plaques **Average LDL decrease at 20mg** **Rosuvastatin (Crestor) 53%** **Atorvastatin (Lipitor) 46%** **Simvistatin (Zocor) 35%** **Lovastatin (Mevacor) 29%** **Pravastan (Pravachol) 24%** **Fluvastastin (Lescol) 17%**	↓ 15-55%	↑ 5-15%	↓ 7-30%	• NB SEs are not class-specific so if one statin has SEs switch to another statin • Myopathy: Sx (weakness, pain, etc of big muscle groups like quads), 1-5% w/ CK<10xULN, 0.1-0.5% CK>10xULN, 0.00005% Rhabdo, RFs: old age, female, low BMI, hypoTH, DM, renal failure, liver failure, concomitant use of fibrates/macrolides/antifungals/cyclosporine, dose related, you don't have to follow muscle enz just symptoms, check CK @ initiation and then if symptomatic (stop Tx if >10xULN, have pt take Coenzyme Q10 100-200mg PO QD x2wks then after 2wks restart another statin) NB SEARCH Trial showed that there is a link with a SNP at gene SLCO1B1 • Hepatitis: 1-2% >3xULN LFTs, incidence with 1% progressing to symptomatic hepatitis, dose related, monitor LFTs @ initiation, @ 3mos, then Q1yr thereafter (stop Tx or switch to different statin if >3xnl) • Increased Plasma Levels w/ Garlic or St. Johns Wort (except for Pravechol), macrolides, cyclopsorin, antifungals, etc vs Decreased Plasma Levels w/ Diltiazem or Protease Inhibitors (except for Pravechol)
Bile Acid Sequestrant **Cholestyramine (Questran)** **Colesevelam (Welchol)** **Colestipol (Colestid)**	↓ 15-30%	↑ 3- 5%	No Change	• ↓ADEK vitamins and fat soluble drugs (therefore take drugs 4hrs before or after) • Can increase TG • Lower GI Distress
GI Cholesterol Uptake Inhibitor **Ezetimibe (Zetia)**	↓ 15%	↑ 2%	↓ 2%	• Myopathy & Hepatitis (but mild so try not to combine w/ statins or fibrates)
Inhibit Liver Production of VLDL **Nicotinic acid /Niacin (Niaspan)**	↓ 5-25%	↑ 15-35%	↓ 20-50%	• Red Flushed Face (uncomfortably warm w/ pruritis) - Start with low dose and increase every few weeks - decreased when ASA 325mg administered 30 min prior and take with meals - this effect only lasts a few weeks • Hyperglycemia • Hyperuricemia • Best to use Rx b/c OTC SR Niacin is associated w/ liver failure and non-SR Niacin

				you have to take TID, in addition the actual dose is unreliable
Lipoprotein Lipase Stimulant **Fenofibrate (Tricor, Trilipex)** **Gemfibrozil (Lopid)**	↓ 5-20%	↑10-20%	↓ 20-50%	• Myopathy (hence do not add to statins except fenofibrate which does NOT increase r/o statin induced myopathy) • Older Drug (clofibrate) was associated w/ increased mortality, cholelithiasis, hepatic cancer!!!

- Approach
  - 1st High **LDL**: **statin, increase statin, add bile acid sequestrant or cholesterol uptake inhibitor or switch statin to fibrate**
  - 2nd High **TG**: first address LDL as above and then if still high then **Ω-3FAs** (↓ TG by 20-50%, OTC supplements or the highly concentrated prescription form Lovaza/Omacor, SEs: interference w/ plt fxn, upper GI distress, taste bad, eructation) or **Niacin** or **Statin/Fibrates**
  - 3rd Low **HDL**: first address LDL and TG as above and then if still low then **diet/social changes (above)** and then if low then **Niacin** or **Statin/Fibrates** (NB alcohol intake actually increases HDL)
- Takes 4-6wks after starting Tx therefore 6-8wks before you make a change, f/u Q3-6mo
- Combinations: Vytorin (Simvistatin + Ezetimibe), Advicor (Lovestatin + Niacin), Caudet (Atorvastatin + Amlodipine), Simcor (Niacin + Simvastatin)
- **ILLUMINATE Trial** showed that the new LDL lowering drug, torcetrapib, caused higher mortality despite lowering LDL
- Vytorin (Simvistatin + Ezetimibe) lowers LDL more than statin alone but the **ENHANCE trial** has shown that there is NO more decrease in carotid intimal thickening than with statin alone as this has been shown to be the best noninvasive surrogate marker for CAD then combination does not decrease CAD any more (problems with study: you are looking at a surrogate marker not CAD directly, the study was too short, not a lot of pts, did not look at mortality/morbidity outcome)
- There is evidence that WelChol also lowers glucose therefore good in pts w/ T2DM