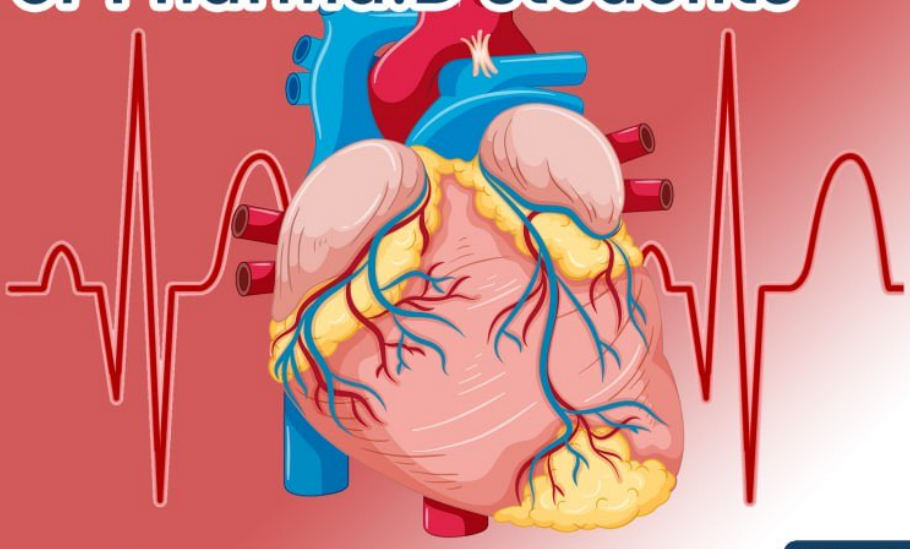
Cardiovascular System

For Pharma.D students





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تواصل معنا للتسجيل

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Calma Study

Dyslipidemia

- It's important to know all about dyslipidemia, because it's usually not a symptomatic disease. Patients go directly into complications (**atherosclerosis**).
- Cholesterol, triglycerides, and phospholipids circulate in the blood as **lipoproteins** ➔ chylomicrons, VLDL, IDL, LDL, and **HDL**.

Cholesterol ↑ TG↓

- Lipoproteins have apolipoproteins (Apos) on their surface → they help in transportation to the liver through ligand-receptor and secretions.
  Apos defect ➔less transportation ➔accumulation and dyslipidemia.
- Friedewald equation (fasting 9-12H):

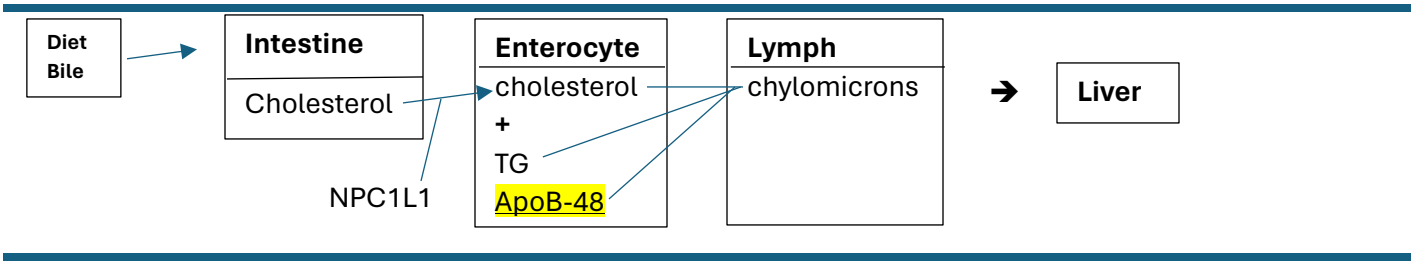
LDL = total cholesterol –(HDL + TG/5) (mg/dL) ..... (2.2)→mmol\L

VLDL = triglycerides (mg/dl)/5

The formula becomes incorrect if:
- **Serum triglycerides are > 400 mg/dL (4.52 mmol/L)**
- Chylomicrons are present
- Patient has familial dysbetalipoproteinemia

- **Non-HDL cholesterol** = total cholesterol – HDL cholesterol (non-fasting state)
- *Martin-Hopkins equation: LDL = total cholesterol – HDL – TG/adjustable factor*

Cholesterol



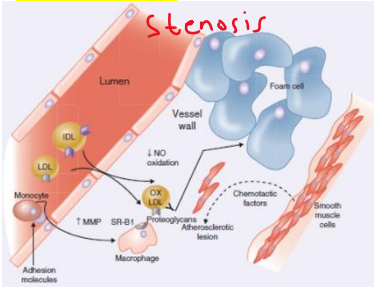
- Mature HDL interacts with chylomicrons and takes cholesterol back to the liver by SR-B1 receptor. Chylomicron remnants (VLDL, LDL) react with hepatic lipase and then bind to LDL receptor and be taken up by liver.
- Cholesterol is synthesized in the liver through multiple reactions:

HMG CoA —(HMG CoA reductase)→ Mevalonic acid ..... ➔ **Cholesterol Esters**

Rate limiting step → target for drugs: **Statin.**

CE, TG, Apo B-100 → VLDL —(LPL)→ IDL —(HL)→ LDL

If stays in blood vessels it may cause **atherosclerosis**. They migrate into the vessel wall and undergo oxidation. Oxidized LDL reduces **nitric oxide** (vasodilator) ➔ vasoconstriction.



Macrophage's role is to phagocyte OX LDL. ↑↑↑ OX LDL ➔foam cells. Accumulation of foam cells makes the atherosclerotic plaque and stenosis of blood vessel.

Underlying causes of dyslipidemia are so many. Just remember these 2 primary causes:

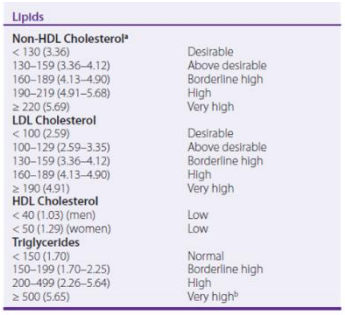
1. Familial hypercholesterolemia (defect in LDL-receptor)
2. Familial hypertriglyceridemia (defect in LPL or Apos)

Secondary causes:

- Anorexia nervosa. CKD. Hypothyroidism. Obesity. NS.
- Drugs ➔ B-blocker, thiazide, isotretinoin

Treatment

- The primary goal in treatment is the LDL & non-HDL. If TG was above 500mg/dl, in this case TG is the primary goal. Once you lower TG under 500 → switch to LDL as primary goal



Lipids	
Non-HDL Cholesterol[a]	
< 130 (3.36)	Desirable
130–159 (3.36–4.12)	Above desirable
160–189 (4.13–4.90)	Borderline high
190–219 (4.91–5.68)	High
≥ 220 (5.69)	Very high
LDL Cholesterol	
< 100 (2.59)	Desirable
100–129 (2.59–3.35)	Above desirable
130–159 (3.36–4.12)	Borderline high
160–189 (4.13–4.90)	High
≥ 190 (4.91)	Very high
HDL Cholesterol	
< 40 (1.03) (men)	Low
< 50 (1.29) (women)	Low
Triglycerides	
< 150 (1.70)	Normal
150–199 (1.70–2.25)	Borderline high
200–499 (2.26–5.64)	High
≥ 500 (5.65)	Very high[b]

These numbers are not used in management. Just notice that abnormal HDL is a low HDL.

Remember the desirable values.

Guidelines:

2018 ➔ percentage of reduction →50% (ASCVD, LDL>190, DM with risk factors)
→30% intermediate-risk patients with DM and ASCVD

2020➔LDL goal → <55mg/dL for extreme risk
→<70 for very high risk
→<100 for moderate to high risk
→<130 for low risk

NOTE: it's important to determine whether you're treating for primary or secondary prevention. **As a secondary prevention statin should be started regardless of the lipid profile**. (MI patient with LDL 50)

Statin for primary prevention →LDL ≥ 190 mg/dL
→DM, age 40 to 75 years regardless of LDL cholesterol levels

Patients age 40-75 and medically free. According to 10 years ASCVD risk assessment (PCE):

<5% (low risk)	5-7,5% (borderline)	7.5-19.9% (intermediate)	≥20% (high risk)
Lifestyle	Discussion (risk enhancers)	Discussion (favor statin) or CAC score reduce 30-49%	Statin reduce >50%

ASCVD risk enhancers:

- Family history
- LDL >160
- TG >175
- CKD

***CAC score (0→no statin, 1-99→favor, 100+→statin)**

Age (20-30)→give statin if (family history of premature ASCVD, LDL >160)

Age <19→ genetic disorder (familial hypercholesterolemia)

Once the decision to initiate statin therapy is made, the **dose intensity** is based on the patient's specific statin-benefit group.

	High Intensity	Moderate Intensity	Low Intensity
LDL-C Lowering[a]	≥ 50%	30%–49%	< 30%
Statins	Atorvastatin (40[b])–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg Pravastatin 40 (80) mg Lovastatin 40 (80) mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 1–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

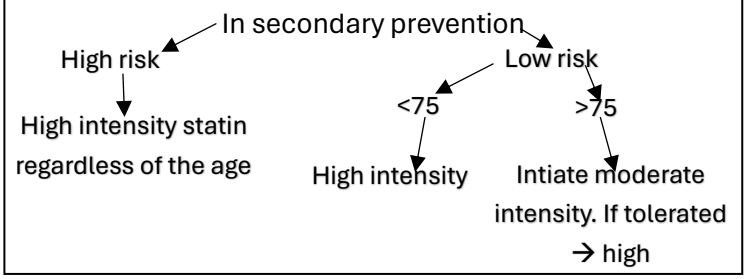
If you were using high intensity statin with no benefits, don't increase the dose.

LDL > 190 → high intensity

DM → moderate to high intensity.
If the patient has CV risk →High intensity

No DM but high risk → high intensity

In secondary prevention we favor high intensity



**** high risk →multiple ASCVD OR 1 ASCVD with risk factors**

Follow up → 4-12 weeks. If statin was not affective→Moderate intensity →high intensity →high intensity → combine drugs (but first make sure that LDL is still the target not TG)

First-line add-on therapies→ ezetimibe then PCSK9 inhibitors (most effective add-on but expensive).

But if statin is not tolerated →PCSK9 inhibitors is the first line

Second-line add-on therapies→ Bile acid sequestrants

- According to the **NLA → non-HDL cholesterol is a better primary target for modification than LDL cholesterol.**

Recommendations for Treatment

1- Screening →All adults >20 years are screened at least every 5 years.
→2-20 years →if their parents have premature CHD or cholesterol >240 mg/dL.

2- Rule Out Secondary Causes of Dyslipidemia.

3- Identify Patients with Very High-Risk Conditions.

4- Treatment of Elevated Triglycerides.

CV risk factors:
***Age (male >45. Female >55)**
***family history of 1st degree relative (male <55. Female <65)**
***hypertension**
***smoking**

TG >500 mg/dL →increased risk of pancreatitis especially when >1000 mg/dL

- TG >1000 mg/dL →Niacin, fibrates, and long-chain omega-3 fatty acids
- TG 500-999 mg/dL→TG-lowering agent **OR** a statin (if not already on statin)
- TG 200-499 mg/dL→statins
- TG ≥150 mg/dL ASCVD or DM and ≥ 2 risk factors for CV disease →add **icosapent ethyl (OM3FA)**
- TG ≥300 mg/dL→ avoid Bile acid sequestrants (As monotherapy)
- renal dysfunction→ Fibrate therapy needs to be used with caution
- stage 4 or 5 CKD → Gemfibrozil should not be used

Pharmacotherapy

Statins (HMG-CoA Reductase Inhibitors)

↓↓↓LDL ↓TG ↑HDL

- Pleiotropic effects➔ ↓lipoprotein oxidation → ↑nitric oxide →Inhibit thrombosis.
- Taken at night ≠ (long half-life →atorvastatin, rosuvastatin → anytime).
- Maximum effect on lipids for statins is generally 4 to 6 weeks.

adverse effects:

- Liver toxicity (AST, ALP) →reported in <2%
- Myalgia (muscle pain)
- Myopathy →muscle weakness or pain with CK >10X the upper limit
- **Rhabdomyolysis** →50% is drug–drug interactions (CK >40X the upper limit)
  →↑Creatinine, with myoglobinuria and brown urine (Rare)

Risk factors:

- Small body
- Higher doses
- Female .. Age ≥ 65 years
- Exercise
- CKD, DM
- **Multiple medications**

Fibrates (Gemfibrozil), cyclosporine, antifungals, macrolide, protease inhibitors, nefazodone, verapamil, amiodarone, large quantities of grapefruit juice and alcohol

Monitoring ➔ **CK elevation**

<3X	3-10X	>10X	>40X
Continue	Continue and repeat a CK in 1 week. Decreasing → continue increasing → stop	Stop statin, and increase fluid intake	Hospitalization

****Patient assessment for symptoms of myopathy should be done 6-12 weeks after starting or changing therapy and at each visit**

Once the patient's muscle symptoms have resolved, clinicians have several options to treat that patient's dyslipidemia:

1- Lower dose
2- Use hydrophilic-type statins such as pravastatin and rosuvastatin
3- Non-statin lipid-lowering agents (not preferred option because of **Pleiotropic effects** of statin)

According to studies➔ ↑CK up to 5X stop statin and start another lipid-lowering drug.
1st Evolocumab (PCSK9) > ezetimibe

- Increased risk for development of DM
- Cognitive impairment, such as memory loss, confusion →reversible
- Pravastatin and pitavastatin have **least** drug-drug interactions. **lovastatin and simvastatin having the highest risk of drug–drug interactions**
- Cyclosporine and gemfibrozil can inhibit drug transporters and increase statin concentrations

	Cholesterol Absorption Inhibitors (ezetimibe)	Bile Acid Sequestrants (Cholestyramine, colestipol, colesevelam)	Adenosine Triphosphate Citrate Lyase Inhibitors (Bemedoic)
Lowering LDL	-18%	15%-30%	15%-25%
MOA	Blocks NPC1L1 ↓cholesterol → upregulation of LDL receptor	highly charged molecules that bind to bile acids. no absorption→ loss of bile causes a compensatory conversion of hepatic cholesterol to bile → upregulation of LDL receptors	Bempedoic acid decreases conversion of citrate to cytosolic acetyl-CoA carboxylase → creating less substrate for cholesterol
NOTE	compensatory increase in cholesterol biosynthesis→ taken with statin	1.They do not lower TG and might increase them. 2.used when there is no better option	1.No effect on TG 2.Doesn't need renal or hepatic adjustment
Effect time	2 weeks	2 to 4 weeks	
Adverse effect	contraindicated in patients with active liver diseae	Nausea, constipation→increase fluids and fibers. →spacing if vitamin D is taken	In general it's tolerable but may cause **hyperuricemia** (caution with gout)

Niacin (Vit. B3) ➔At doses higher than those used as a nutritional supplement.

- Inhibits FA release from adipose tissue and FA and TG production in liver cells
- This results in a reduction in the number of VLDL particles secreted
- This leads to an overall reduction in LDL cholesterol and a decrease in the number of small dense LDL particles
- It also reduces the uptake of HDL-Apo A1 particles and increases uptake of cholesterol esters by the liver, thus improving the efficiency of reverse cholesterol transport between HDL particles and vascular tissue

Mainly used to lower TG.
Side effects: flushing →use aspirin or nsaid 30 min before. Take it with food. Slow titration

- **Niacin products labeled as "no flush" do not contain nicotinic acid and therefore have no therapeutic role in the treatment of lipid disorders**
- **Effect time ➔ 3 to 5 weeks**

Fibrates ➔**The most effective TG-lowering drugs**

MOA: Activation of PPAR-α → reduction in TG-rich lipoproteins (VLDL and IDL)

They contraindicated in patients with gallbladder disease, liver dysfunction, or severe kidney dysfunction.

Fenofibrate & Gemfibrozil ➔ Fenofibrate is favored, less side effects and less drug-drug interactions (better with statin)

- Risk of bleeding is increased in patients taking both a fibrate and warfarin→increased INR
- Fibrates is not used to lower LDL as monotherapy as it may increase or decrease LDL.

Effect time ➔ Fenofibrate → 2 weeks Gemfibrozil→ 3 to 4 weeks

Omega-3 Fatty Acids Eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]

Adverse effects: →use with caution with patients having hypersensitivity to fish
→doses >3g daily increases risk of hemorrhagic stroke for patients taking anticoagulant or antiplatelet

Microsomal Triglyceride Transport Inhibitors (Lomitapide)

***pregnancy category X**

***It is primarily metabolized by CYP 3A4 (D/DI)**

MOA: Inhibition of microsomal TG transfer protein

FDA approved for the management of patients with homozygous FH

Antisense Oligonucleotide Inhibitor of Apo B-100 Synthesis (Mipomersen)

- **Once-weekly SC inj → injection site reaction**
- **MOA: antisense inhibitor of Apo B-100 synthesis**
- **FDA approved for the management of patients with homozygous FH**
- **It is not a substrate for CYP metabolism →minimal (*D/DI*)**
- **Pregnancy category B**

PCSK9 inhibitors (Alirocumab and evolocumab) →expensive

SC inj → **injection site reaction**

PCSK9 → LDL receptor degredation

MOA: Human monoclonal antibodies that bind to PCSK9.
PCSK9 inhibition → ↑LDL receptor →↑LDL cleared by liver

FDA approved for heterozygous FH and homozygous FH

Side effects: nasopharyngitis, influenza, UTI, URTI

- **Patients with genetic forms of hypercholesterolemia such as FH)→ require ≥ 3 drugs to manage their disorder → to obtain a minimum of ≥ 50% reduction in LDL cholesterol**