HDL, LDL Cholesterol Oh My!

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Description

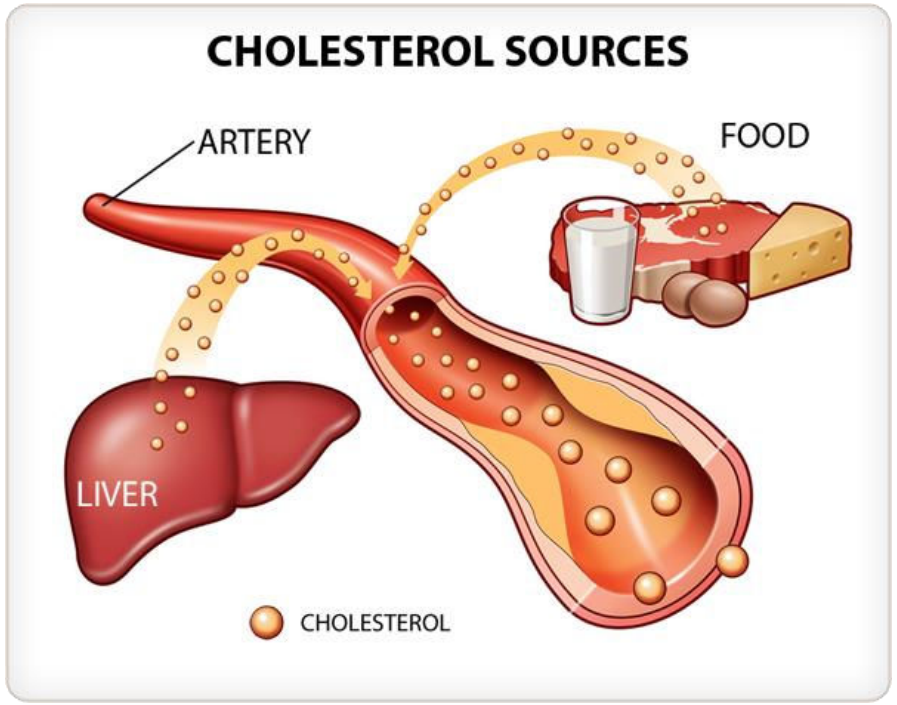
- This session will cover pharmacologic treatments for different components of a lipid panel. Using a case-based approach we will review treatment options for diverse clinical situations including patients who are “intolerant/allergic” to specific treatments. We will discuss the current variety of pharmacologic options for treatment of dyslipidemia.

Objectives

- Analyze lipid panels and identify cardiovascular risk for diverse patients.
- Discuss lipid lowering medications and the indications for use in clinical practice.
- Describe challenges in initiating lipid lowering therapies

Why does it matter?

- 2023 American Heart Association- Heart Disease and Stroke Statistics



25.5 %
of adults in the USA have elevated **LDL (≥ 130mg/dl)**

Lipid Panel Components

- Non-HDL – calculated as: Total cholesterol- HDL.
- Non-HDL includes LDL and other types of cholesterol such as VLDL
- Optimal: Less than 130mg/dL

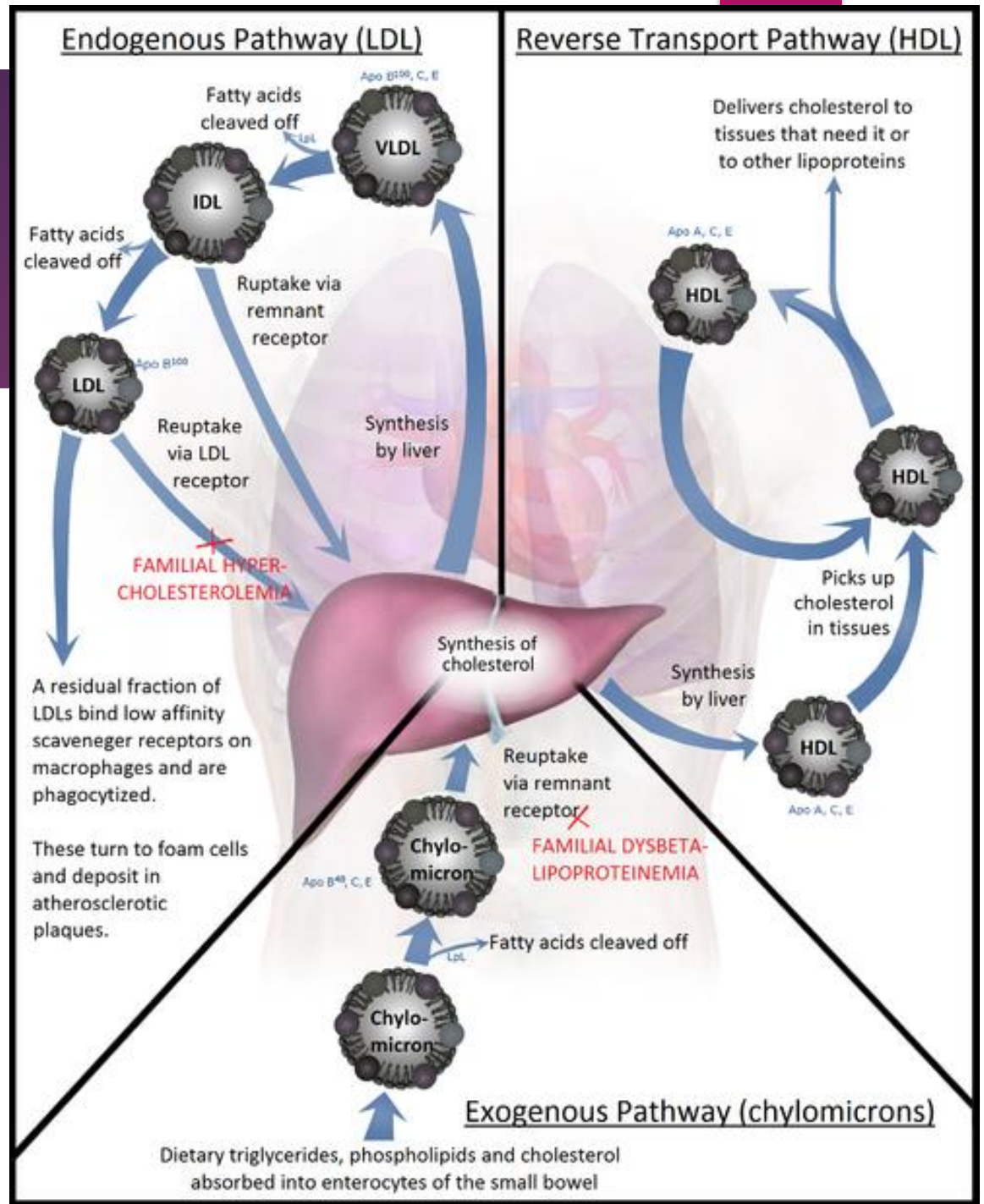
Component	Range
Total Cholesterol	200 - 240 mg/dl <200 mg/dl preferred High is >240 mg/dl
LDL	100 - 129 mg/dl
HDL	>40 mg/dl
Triglycerides	< 150 mg/dL Borderline high: 150 to 199 mg/dL High: 200 to 499 mg/dL Very high: Above 500 mg/dL

Low Density Lipoprotein and the Liver

- LDL-R at hepatocyte surface
- LDL binds to LDL-R
- LDL-R with LDL enters cell
- LDL-R releases LDL
- LDL-R returns to surface & LDL destroyed by lysosome

Lipid metabolism

Lowering LDL



HDL

- At risk levels- HDL <40 mg/dl in men and <50mg/dl in women
- Multiple studies no cardiovascular protection in HDL >60
- FIELD and ACCORD trials
  - Did not demonstrate a reduction in cardiovascular outcomes in patients with diabetes patients, despite a significant increase in HDL-C

Barter, P. and Genest, J. HDL cholesterol and ASCVD risk stratification: A debate. Atherosclerosis 283 (2019) 7–12.

Triglycerides

- Moderate risk 175-499 mg/dl
- Severe risk >500 mg/dl

Personal Photos: M. Bowers

What should you measure?

- Apolipoprotein B- measure in patients with hypertriglyceridemia, DM and with obesity at least once.
- Lp(a)- measure once to establish genetic risk for ASCVD.
- Non-HDL-C= Total Cholesterol - HDL-C

ASCVD Calculator-

Use in age 40-79

- Age
- Gender
- Race
- Yes/No- Diabetes, Smoker, treatment for Hypertension

Total Cholesterol

HDL Cholesterol

Systolic BP

Calculating Risk

11.3% Current 10-Year ASCVD Risk

Lifetime ASCVD Risk: **50%** Optimal ASCVD Risk: **1.3%**

Current Age * 56
Age must be between 20-79

Sex * Male | ✔ Female

Race * ✔ White | African American | Other

Systolic Blood Pressure (mm Hg) * 148
Value must be between 90-200

Diastolic Blood Pressure (mm Hg) 86
Value must be between 60-130

Total Cholesterol (mg/dL) * 280
Value must be between 130 - 320

HDL Cholesterol (mg/dL) * 35
Value must be between 20 - 100

LDL Cholesterol (mg/dL) 189
Value must be between 30-300

History of Diabetes? * ✔ Yes | No

Smoker: * Yes | Former | ✔ No

On Hypertension Treatment? * Yes | ✔ No

On a Statin? ✔ Yes | No

On Aspirin Therapy? ✔ Yes | No

Evaluating Risk- Low to Very High

Cardiovascular Risk	Low	Moderate	High	Very High
Risk Factors	Score<1%	Score 1-5% T1DM<35 yr) and T2DM <50yr without other RF	Score >5% and <10% Elevated RF BP>180/110 Mod CKD DM>10 yr or additional RF	Score ≥10% ASCVD FH with ASCVD or with additional RF Severe CKD DM & target organ damage
Upper TARGET level of plasma LDL-C concentration	3.0 mmol/L (116 mg/dL)	2.6mmol/L (100 mg/dL)	1.8 mmol/L (70 mg/dL)	1.4 mmol/L (55mg/dL)

BE CAREFUL- Bias in Calculator

Options for race do not include options for multiethnic individuals.

May **underestimate** risk in the following patients:

- Diverse racial/ethnic groups
- Lower socioeconomic status
- Chronic inflammatory diseases

May **overestimate** risk in the following patients:

- Higher socioeconomic status
- Connected to health care for preventive healthcare services.

Risk Enhancers

- + Family history (women <65 and men <55 yrs)
- LDL 160-189mg/dl
- CKD
- Metabolic syndrome
- Chronic inflammatory diseases
- Early menopause (<40 yr) or h/o pre-eclampsia
- South Asian ethnicity

Factors that influence lipid panel results

- Pregnancy ↑
- Non-fasting
  - Triglycerides are most impacted
- Glycemic control

GUIDELINES FOR HYPERLIPIDEMIA

ESC/EAS 2019

- Define risk
  - Very high, high, moderate and low
- Identify treatment threshold
  - LDL <55 mg/dl
- Rec pharm treatment
  - Max statin + ezetimibe
  - Consider PCSK9 inhibitor

AHA/ACC 2018

- Define risk
  - Multiple major ASCVD events or one major
- Identify treatment threshold
  - LDL <70mg/dl
- Rec pharm treatment
  - Max statin + ezetimibe
  - Consider PCSK9 inhibitor

2023 American Diabetes Association

Guidelines for lipid lowering in patients with DM

Patient Characteristics	LDL target
Diabetes	Less than 70 mg/dl or no greater than 55mg/dl based on CV risk
Age 40-75 with DM and 1 or more atherosclerotic RF	Reduce LDL by 50% from baseline and target less than 70 mg/dl
Addition of ezetimibe of PCSK9 inhibitor in addition to statis	LDL remains >70 mg/dl on max tolerated statin

Dyslipidemia medication classes

Class of Medication	LDL reduction
Statin	Reduce LDL by 30-50%
Bile Acid Sequestrants	Reduce LDL by 15-30%
Ezetimibe	Reduce LDL by 20%
PCSK9 inhibitor	Reduce LDL by 80%
siRNA inhibitor	Reduce LDL by 46-51%
ACL inhibitor	Reduce LDL by 24.6%

Hypertriglyceridemia medications

- Fibrates
  - Gemfibrozil and Fenofibrate-
    - Synergistic effects when added to a statin may confer a cardiovascular benefit in metabolic syndrome.

- **Icosapent Ethyl**

Kim NH, Kim SG. Fibrates Revisited: Potential Role in Cardiovascular Risk Reduction. Diabetes Metab J. 2020 Apr;44(2):213-221. doi: 10.4093/dmj.2020.0001. PMID: 32347023; PMCID: PMC7188966.

Fenofibrates

- Stimulates lipoprotein lipase enhancing VLDL breakdown

- May increase size of LDL particles
  - Lower LDL 5–20% (with normal TG)
  - May raise LDL (with high TG)
  - Lower TG 20–50%
  - Raise HDL 10–20%

Fenofibrates

- Multiple drug interactions
- Contraindicated with severe renal or hepatic dysfunction
- Monitor LFT's
- Reduce dose with CrCl<50ml/min

Icosapent Ethyl

- It is a pure EPA Omega 3 fatty acid
- Indications: Add to maximally tolerated dose of a statin and/or in patients with triglycerides ≥500 mg/dl
- Icosapent Ethyl is approved to be used with a **statin** in certain high risk groups with high triglycerides to lower the risk of outcomes like a heart attack or stroke.

PK and PD-Icosapent Ethyl

- MOA: enhances triglyceride clearance from circulating VLDL and reduced liver lipogenesis
- Absorption: small intestine
- Metabolism: liver
- Elimination: plasma ½ life is 89 hrs.

- <u>Key Adverse Effects</u>:
  - Atrial fibrillation- especially if h/o atrial fib
  - Bleeding, peripheral edema, gout, joint pain

Dosing and Treatment-Icosapent Ethyl

Dosing:

- Total dose = 4 gms/day
- Comes in 0.5gram or 1 gm capsules
- Taken with food twice a day

REDUCE IT trial

- Icosapent Ethyl at a dose of 4 gms/day reduced risk of:
  - Major total CV event by 25%
  - Major first CV event by 30% in high risk pt on statin with DM and other RF with triglyceride 150-499mg/dl and LDL 41-100 mg/dl
  - Benefit not only from reducing triglycerides; reducing **inflammation**

Omega 3 Fatty Acids

- In doses of > 6g/day can reduce triglycerides
- If elevated levels of triglycerides 15 g/day can reduce level by up to 50%

HMG-CoA reductase inhibitors - STATIN

- Decrease LDL
- Reduce triglycerides
- Increase HDL production
- Contraindicated in pregnancy

High Intensity	Moderate Intensity	Low Intensity
Daily dose lowers LDL-C on average, approximately ≥ 50%	Daily dose lowers LDL-C on average, approximately 30 to >50%	**Daily dose lowers LDL-C by 30%**
Atorvastatin 40-80mg Rosuvastatin 20-(40)mg	**Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40mg Lovastatin 40mg Pravastatin 40-80mg Fluvastatin 40mg BID Pitavastsatin 2-4mg**	**Simvastatin 10mg Pravastatin 10-20mg Lovastatin 20mg Fluvastatin 20-40mg Pitavastatin 1mg**

Commons side effects of statins

Symptoms	Evidence	Predisposing factors	Frequency
Myalgias	RCTs Cohorts/observational	Age, low BMI, female sex, high-risk medications, comorbidities, Asian ancestry, excess alcohol, high levels of physical activity, and trauma	Infrequent
Transaminase elevation 3 × ULN	RCTs/cohorts/observational Case reports		Infrequent
New Onset Diabetes Mellitus	RCT and meta-analysis	High intensity statin treatment, metabolic syndrome	More common if: BMI≥30, fasting blood glucose ≥100 mg/dL; metabolic syndrome, or A1c ≥6%.

Monitoring Lipids on Therapy

- Measure fasting lipids between 4- 12 weeks after starting statin or dose change
- Measure every 12 months after achieving target

PCSK9 inhibitor

- PCSK9 inhibitor is monoclonal antibody which blocks endogenous PCSK9.
- Prevents degradation of LDL-C receptors
- Results in reduced amount of circulating LDL.
- Increases the clearance of LDL by 43 to 58%

PCSK9 inhibitor

- Alirocumab and Evolocumab
- Administered by injection every 2-4 weeks.
- Prior authorization
- Alirocumab cost- average $670 down to $370 with drug coupon (Can cost over $1000)

PCSK9 inhibitor

Clinical Trial Results

- ODYSSEY- Alirocumab + atorvastatin compared to others
  - Lowered LDL by 54%

- LAPLACE-2- Evolocumab + ezetimibe or placebo
  - Lowered LDL by 66%

PCSK9 inhibitor

Clinical Trial Results

- FOURIER- Evolocumab + statin
  - 15% reduction in composite endpoints of MI, CVA and hospitalizations for cardiac or death.

- New 2023- LDL <20 mg/dl lower risk of adverse cardiovascular outcomes if ASCVD present

Ezetimibe

- Inhibits absorption of cholesterol by 54% at brush border of small intestine

Results:

- **Increased** expression of hepatic LDL receptors
- **Reduced** cholesterol content of atherogenic particles
- **Decreased** intestinal delivery of cholesterol to the liver

Ezetimibe

- LDL ~ ↓ 18%
- Total Cholesterol ~ ↓ 10-17%
- Triglycerides ~ ↓ 8-14%
- HDL ~ ↑ 1-3%

- Monotherapy 18% LDL reduction
- Synergistic effect when combined with statin 25% and may be higher

Case

- 52 yo male comes in for followup on mixed hyperlipidemia. He has been on:

  Rosuvastatin 40 mg daily

  Fenofibrate 150 mg daily

- Fasting Lipid panel today: (Glucose is normal)
  - Total Cholesterol 184 mg/dl
  - LDL 94 mg/dl
  - HDL 65 mg/dl
  - Triglycerides 415 mg/dl

Inclisiran

- Indications: Add to maximally tolerated dose of a statin in patients ASCVD or heterozygous familial hyperlipidemia
- ORION 10 trial (USA) N=1561 LDL reduction 51.3%
- ORION 11 trial N= 1617 LDL reduction 45.8%

  (Europe and South Africa)

PK and PD-Inclisiran

- MOA: small interfering RNA treatment to reduce LDL-cholesterol

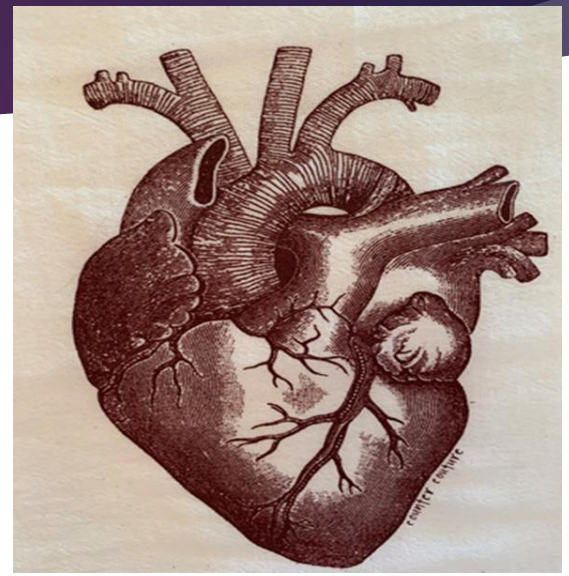
- Absorption: subcutaneous, peak at 4 hrs post injection
- Metabolism: liver
- Elimination: renal

- Key Adverse Effects:
  - injection site reaction, arthralgia, UTI, bronchitis

Dosing and Treatment-Inclisiran

Dosing: 284 mg/1.5 ml syringe in a single dose

- Initial dose at 1 month and 3 months
- Subsequent: every 6 months



Personal Photo: M. Bowers

Case

- 67 yo female with dyslipidemia, T2DM and multiple major cardiovascular events within the previous 12 months.

  Atorvastatin 80 mg daily Ezetimibe 10 mg daily

- Fasting Lipid Panel
  - TC 190 mg/dl HDL 33mg/dl
  - LDL 102 mg/dl Triglycerides 168 mg/dl

- **What are your options for treatment?**

Bempedoic Acid

- FDA approved in February 2020
- Oral ATP citrate lyase inhibitor (ACL)
- Indication: Add on therapy to diet, max tolerated statin in HeFH or pt with ASCVD who need further LDL lowering
- Dosing- 180 mg daily

PK and PD- Bempedoic Acid

- MOA: small molecule pro-drug that inhibits an enzyme in cholesterol pathway, upstream from HMG-CoA reductase. Upregulation of LDL receptor with increased LDL clearance.

- Absorption: onset of action within 3.5 hrs
- Metabolism: Liver
- Elimination: Urine

- Key Adverse Effects: URI, hyperuricemia, muscle spasms, back pain, pain in hands and feet, anemia and elevated liver enzymes

Clinical Trials- Bempedoic Acid

- CLEAR Tranquility (N=269)
  - Patients on ezetimibe who were statin intolerant and LDL >100mg/dl
  - At 3 months- 28.5% reduction in LDL
- CLEAR Serenity (N=345)
  - Similar population
  - At 6 months – 21.4% reduction in LDL

Clinical Trials- Bempedoic Acid

- CLEAR Outcomes N= 13,970 Randomized 1:1 with placebo, all high risk for CVD and statin intolerant *
- 180 mg dose
- Median follow up 40.6 months
- MACE 11.7% vs 13.3%
- LDL change in 6 months 21.1 vs 0.8mg/dl

Nissen SE, Lincoff AM, Brennan D, et al., on behalf of the CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med* 2023;Mar 4:[Epub ahead of print].

Case

- 54 yo who identifies as female, PMH: CAD (PCI to RCA), dyslipidemia, OSA who c/o myalgias in both legs with ongoing statin use.
- Lipid panel
  - TC 240 LDL 122 HDL 44 Triglycerides 120
- Current CV meds: Atorvastatin 20 mg daily, Ezetimibe 10 mg daily.

Medications in clinical trials

- **Pelacarsen**- antisense oligonucleotide that binds to hepatocyte apo(a) mRNA and prevents the translation of apolipoprotein(a).
- Results in lower circulating Lp(a) now in phase III clinical trials
- Administered subcutaneously at a dosage scheme 20 mg up to 60 mg over several weeks.
- Reduction in Lp(a) circulating levels by 35% up to 80%.
- Adverse effects: malaise, myalgias, arthralgias and injection site reactions.
- **Olezarsen**- antisense oligonucleotide also in phase III clinical trials

Other Medications in clinical trials

- Volanesorsen (antisense oligonucleotide) focuses on reducing triglyceride and triglyceride rich particles such as chylomicrons.
- European Medicines Agency approved NOT FDA approved
- Subcutaneous administration once a week.

Key References

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Summary

- Analyze lipid panels and identify cardiovascular risk for diverse patient populations
- Discuss lipid lowering medications and the indications for use in clinical practice.
- Describe challenges in initiating lipid lowering therapies.