

HDL, LDL Cholesterol Oh My!

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Description

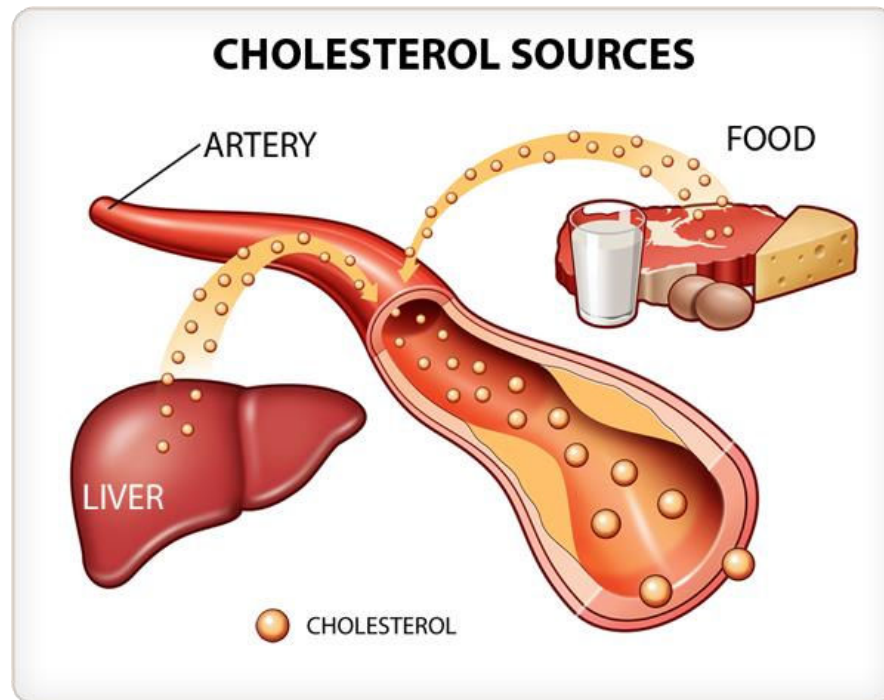
- ▶ This session will cover pharmacologic treatments for different components of a lipid panel. Using a case-based approach we will review treatment options for diverse clinical situations including patients who are “intolerant/allergic” to specific treatments. We will discuss the current variety of 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 ($\geq 130\text{mg/dl}$)**

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



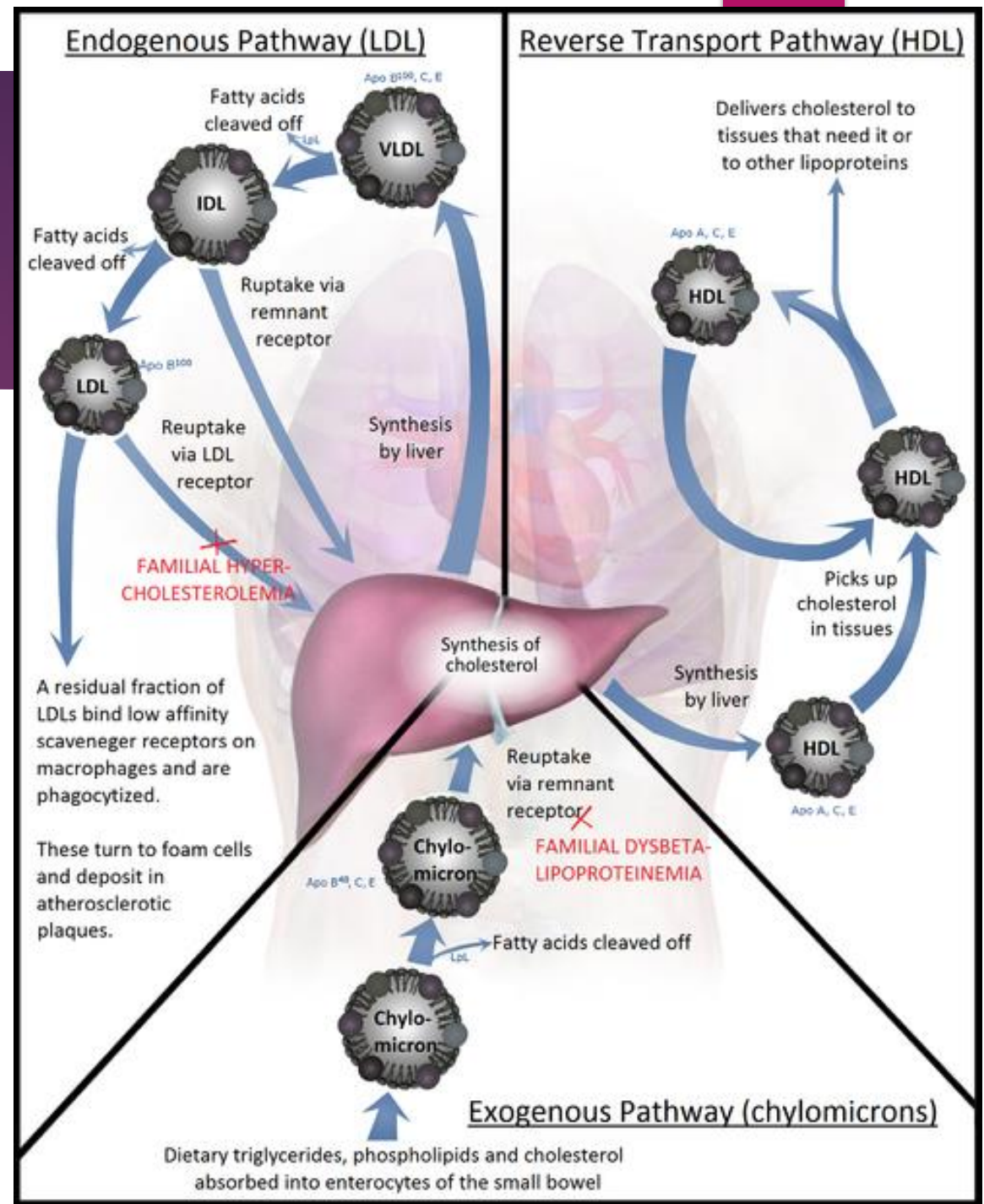
LDL-R releases LDL



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

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 Total Cholesterol
- ▶ Gender HDL Cholesterol
- ▶ Race Systolic BP
- ▶ Yes/No- Diabetes, Smoker, treatment
for Hypertension

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 or PCSK9 inhibitor in addition to statin	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 $\text{CrCl} < 50 \text{ ml/min}$

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 $\frac{1}{2}$ life is 89 hrs.
- ▶ Key Adverse Effects:
 - ▶ 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



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High Intensity	Moderate Intensity	Low Intensity
Daily dose lowers LDL-C on average, approximately $\geq 50\%$	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 Pitavastatin 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)

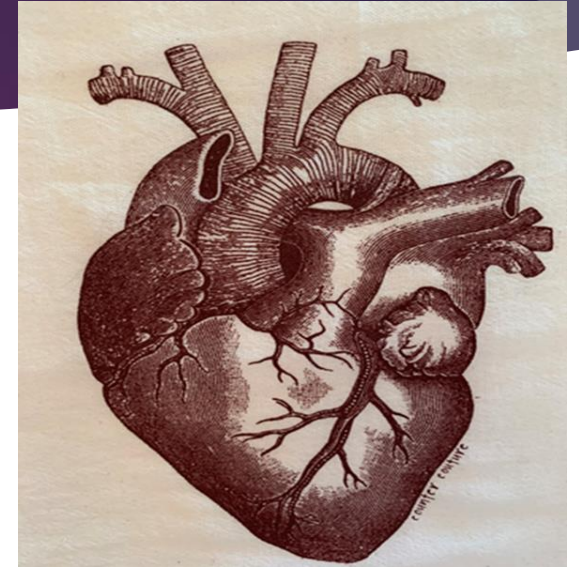
PK and PD-Inclisiran

- ▶ 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

- ▶ Barter, P. and Genest, J. HDL cholesterol and ASCVD risk stratification: A debate. *Atherosclerosis* 283 (2019) 7–12.
- ▶ Dybiec J, Baran W, Dąbek B, Fularski P, Młynarska E, Radzioch E, Rysz J, Franczyk B. Advances in Treatment of Dyslipidemia. *International Journal of Molecular Sciences*. 2023; 24(17):13288. <https://doi.org/10.3390/ijms241713288>
- ▶ Grundy et al, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143
- ▶ 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.

Key References

- ▶ Lloyd-Jones D, Morris P, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2022 Oct, 80 (14) 1366–1418. <https://doi.org/10.1016/j.jacc.2022.07.006>
- ▶ Merćep I, Strikić D, Slišković AM, Reiner Ž. New Therapeutic Approaches in Treatment of Dyslipidaemia-A Narrative Review. *Pharmaceuticals (Basel)*. 2022 Jul 7;15(7):839. doi: 10.3390/ph15070839. PMID: 35890138; PMCID: PMC9324773.
- ▶ 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:\[Epub ahead of print\]](#).

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.