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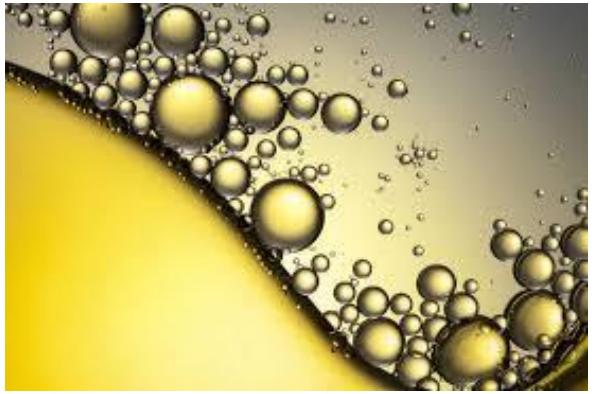

Update on Lipid Management: Guidelines and Treatment

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Spokane County Medical Society CME

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Disclosures

- Novo Nordisk: funding for investigator-initiated study
- Fractyl health: Site-PI for industry sponsored study

Learning Objectives

- Review the current landscape and recent advances in management of commonly encountered lipid disorders in clinical practice
- Highlight ongoing research and clinical trials that could alter treatment paradigms in the future

Case 1

- 46-year-old man with type 2 diabetes of 3 years duration.
- Current Medications: metformin 1000 mg twice daily, empagliflozin 25 mg daily, pravastatin 20 mg daily
- Exam: P70, BP 124/72, BMI 24.3 kg/m^2
- Labs:

HbA1c: 6.9%	LDL-cholesterol 115 mg/dL
Urine albumin/creatinine ratio: normal	Triglycerides 140 mg/dL
Normal BMP	Total cholesterol 185 mg/dL
Normal LFTs	HDL-cholesterol 42 mg/dL

BMP: basic metabolic panel
LFTs: liver function tests

What is the next best step in his management?

A. Calculate his 10-year risk for ASCVD before making any changes
B. Switch to rosuvastatin 10 mg daily
C. Continue pravastatin 20 mg daily
D. Add ezetimibe 10 mg daily

ASCVD: atherosclerotic cardiovascular disease

What is the next best step in his management?

A. Calculate his 10-year risk for ASCVD before making any changes
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C. Continue pravastatin 20 mg daily
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Case 1 Discussion

- Patient specific goal: primary prevention of an ASCVD event
- This patient's 10-year risk for an ASCVD event (ACC/AHA risk calculator): 4.4%
  - Threshold to begin statin therapy in patients without diabetes is ≥7.5%
- Patients with diabetes have higher ASCVD risk than general population; ASCVD is leading cause of morbidity and mortality in diabetes
- Patients with diabetes >40 years age and LDL-C >70 mg/dL warrant moderate-intensity statin therapy at least, irrespective of ASCVD risk score

ASCVD: atherosclerotic cardiovascular disease
ACC: American College of Cardiology
AHA: American Heart Association
LDL-C: Low density lipoprotein-cholesterol

Diabetes Care 2018;41:917–928.
J Am Coll Cardiol 2019;73:3168–3209.
Diabetes Care 2023;46(Suppl. 1):S158–S190.

Statin Therapy

High intensity statins (typical LDL-C lowering ≥50%)	Moderate intensity statins (typical LDL-C lowering 30-49%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1-4 mg

- 10-year ASCVD risk >20%
- Known ASCVD

- Multiple ASCVD risk factors
- Age 50-70 years

- No additional ASCVD risk factors
- Primary prevention
- 10-year risk ASCVD risk <20%

Treatment Goals in Patient with Diabetes

- 2018 ACC/AHA guidelines, 2022 ADA Guidelines: 50% LDL-C lowering
- 2023 ADA guidelines:
  - *10-year ASCVD risk >20% or multiple ASCVD risk factors*: 50% LDL-C lowering AND LDL-C <70 mg/dL
  - *Secondary prevention*: 50% LDL-C lowering AND LDL-C <55 mg/dL

ADA: American Diabetes Association

Cleve Clin J Med. 2020 Apr;87(4):231-239.
Diabetes Care 2023;46(Suppl. 1):S158–S190.

Case 2

- 63-year-old man, with no prior medical history, presents to you for follow up after having unstable angina 3 months ago. During his presentation, he did not require PCI to any vessel but was started on medications for coronary artery disease.
- Within 2 weeks of starting atorvastatin 80 mg, he developed severe muscle aches. The dose was lowered to 20 mg, and he still had persistent symptoms and so he stopped taking it.
- Current meds: Aspirin, Lisinopril, Metoprolol
- Exam: P68, BP 128/76, BMI 27.3 kg/m^2
- Labs: LDL-C 141 mg/dL, TG 130 mg/dL, TC 215 mg/dL, HDL-C 48 mg/dL, HbA1C 5.6%, CK 150 U/L, 25-hydroxy vitamin D 30 ng/mL.

PCI: percutaneous coronary intervention
TG: triglycerides
TC: total cholesterol
HDL-C: high density lipoprotein-cholesterol
CK: creatine kinase

What is the next best step in management?

A. Start rosuvastatin 5 mg daily
B. Start ezetimibe
C. Start evolocumab
D. Start high dose vitamin D supplementation

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Case 2 Discussion

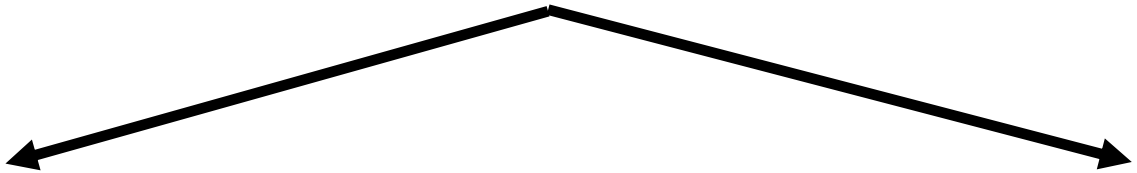
- Patient specific goal: Secondary prevention (of a subsequent ASCVD event)
- LDL-C on max-tolerated statin still >70 mg/dL*
- Warrants LDL-C lowering
- Is this statin intolerance?

*NOTE: patient does not have diabetes, so LDL-C target is different

2023 ACC/AHA Clinical Practice Guidelines for Chronic Coronary Disease. Circulation. 2023;148:e9–e119.

Statin Intolerance

- One or more adverse effects related to statin use
- Resolves with dose reduction or discontinuation
- MINIMUM of TWO statins tried – at least ONE at lowest approved daily dose



COMPLETE INTOLERANCE
Unable to take statin at any dose

PARTIAL INTOLERANCE
Maximal tolerated dose fails to achieve therapeutic target

National Lipid Association scientific statement on statin intolerance. Journal of Clinical Lipidology (2022) 16, 361–375.

Modifiable risk factors for Statin Intolerance

- Hypothyroidism
- Other therapies with potential drug-drug interactions (e.g., gemfibrozil, protease inhibitors, amiodarone, calcium channel blockers, azole antifungals, macrolides, immunosuppressants, colchicine)
- Alcohol use
- Strenuous exercise
- Vitamin D deficiency
- Obesity
- Diabetes

Journal of Clinical Lipidology (2022) 16, 361–375.

Approach to Statin Intolerance

- Prevalence: 5-30% (lowest in RCTs, higher in observational studies)
- Several studies have shown nocebo effect
- Treat modifiable risk factors
- Trial at least 2 statins, and at least one at lowest tolerated dose (including unconventional dosing – QOD, twice weekly etc.)
- While trying alternative statins, consider urgency to achieve LDL-C target
- Initiate alternative LDL-C lowering agents accordingly

RCT: randomized clinical trial
QOD: every other day

Eur Heart J. 2022 Sep 7;43(34):3213-3223.
Journal of Clinical Lipidology (2022) 16, 361–375.

Adjunctive LDL-C lowering agents

Medication	Mechanism of Action	LDL-C lowering	CV event lowering evidence
Ezetimibe	NPC1L1 inhibitor, inhibits intestinal absorption of cholesterol	15-20%	+ (IMPROVE-IT)
PCSK9 inhibitors (Monoclonal antibodies: evolocumab, alirocumab siRNA: inclisiran*)	Inhibit PCSK9, prevent LDLR degradation	50-60%	+ (ODYSSEY, FOURIER)
Bempedoic acid	ATP citrate lyase inhibitor, inhibits cholesterol synthesis	13-25%	+ (CLEAR OUTCOMES)

Less frequently used alternatives: bile acid resins, niacin, fibrates

* Cardiovascular outcome trial's results still pending

N Engl J Med 2015;372:2387-97.
N Engl J Med . 2018;379:2097–2107.
N Engl J Med . 2017;376:1713–1722.
N Engl J Med 2023; 388:1353-1364.

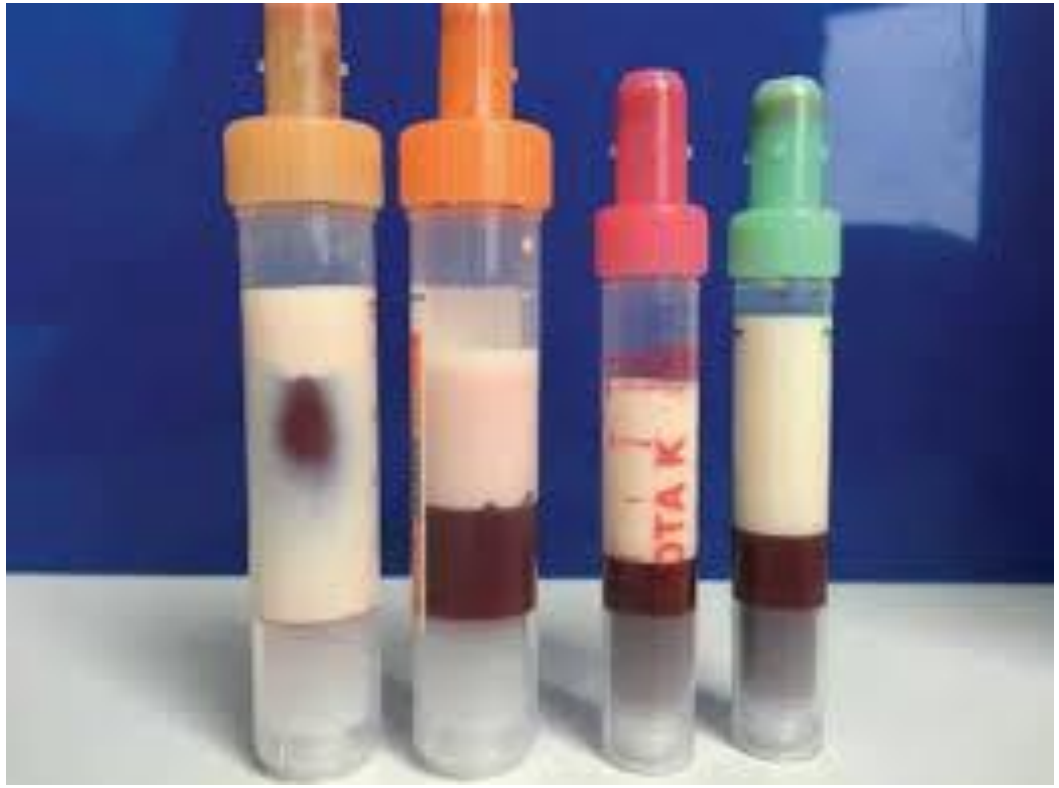
Case 3

- 62-year-old man with type 2 diabetes presents for routine follow up.
- Past medical history: Myocardial infarction 5 years ago, Hypertension, obesity
- Current Meds: Rosuvastatin 40 mg daily, Aspirin, Lisinopril, Metoprolol succinate, Metformin 1000 mg twice daily, Semaglutide 2 mg weekly, Empagliflozin 25 mg daily
- Exam: P 62, BP 110/60, BMI 27 kg/m^2
- Labs:

HbA1c: 6.6%	LDL-cholesterol 53 mg/dL
Urine albumin/creatinine ratio: normal	Triglycerides 335 mg/dL
Normal BMP	Total cholesterol 152 mg/dL
Normal LFTs	HDL-cholesterol 32 mg/dL

What is the next best step in management?

A. No changes necessary
B. Start glargine insulin
C. Start fenofibrate
D. Start icosapent ethyl



What is the next best step in management?

A. No changes necessary
B. Start glargine insulin
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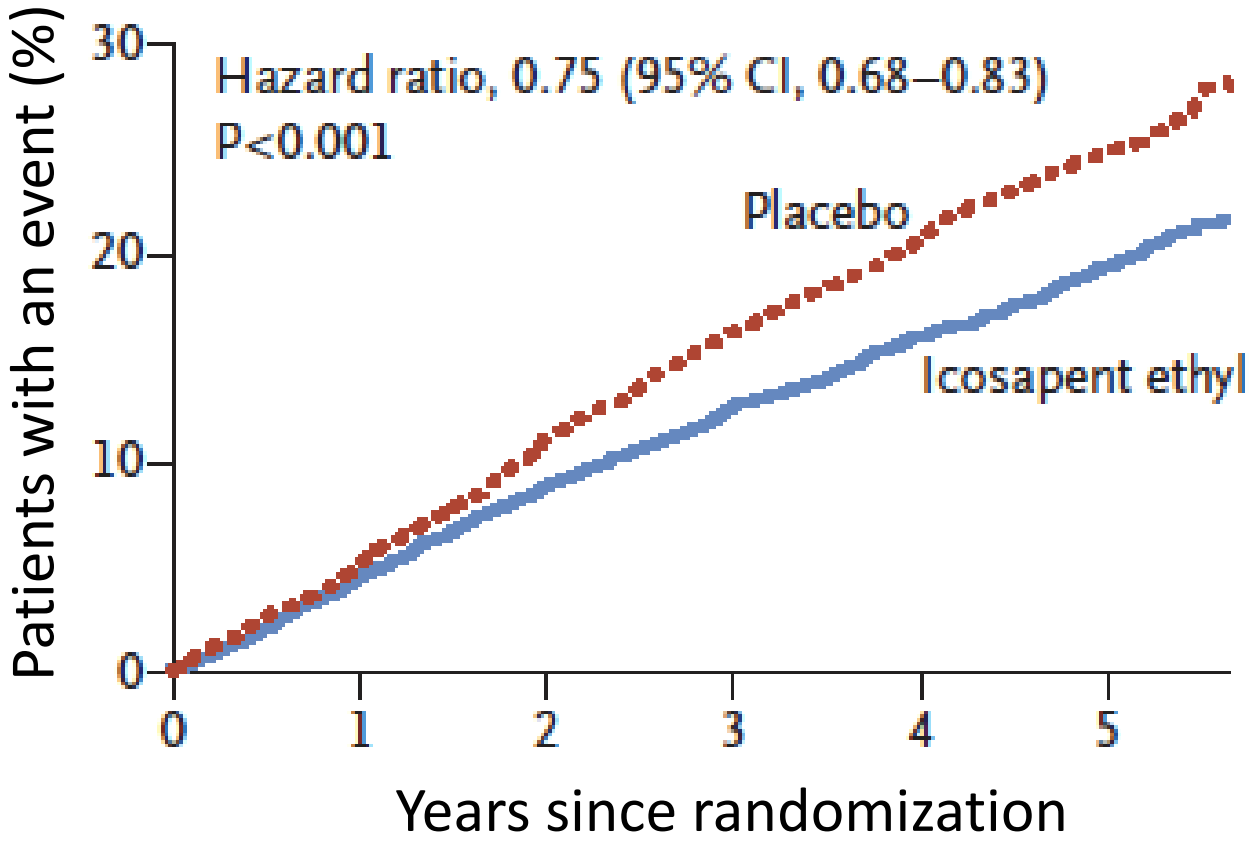
Case 3 Discussion

- Patient specific goal: Secondary prevention (of a subsequent ASCVD event)
- Glycemic control has been optimized and weight-sparing and CV protective agents have been added and titrated to max-dose
- BP well controlled
- On high-intensity statin, LDL-C goal of < 55 mg/dL has been achieved
- Residual risk: from elevated triglycerides and low HDL-C

CV: cardiovascular

REDUCE-IT Trial – Icosapent ethyl

- Known ASCVD or diabetes+ other CV risk factors
- On statin, LDL-C 41-100 mg/dL, Triglycerides 135-499 mg/dL
- Randomized to icosapent ethyl 2 g twice daily or placebo; ~5-year f/u
- Composite primary end-point of CV death, non-fatal MI, non-fatal stroke, coronary revascularization or unstable angina
- Result: 25% relative risk reduction in primary end-point with icosapent ethyl



N Engl J Med 2019; 380:11-22.

Triglyceride-lowering agents

- ACCORD study: no ASCVD reduction with fenofibrate + statin combination in patients with diabetes
- AIM-HIGH study: no ASCVD reduction with niacin+ statin combination; trial halted early due to increase in ischemic stroke
- If fasting triglycerides are >500 mg/dL, risk of pancreatitis is high, so may need to consider addition of fibrate and evaluate for secondary causes of hypertriglyceridemia (diet, alcohol, chronic liver or kidney disease, hypothyroidism)

N Engl J Med 2010;362:1563–1574.
N Engl J Med 2011;365:2255–2267.

Case 4

- 57-year-old woman presents to discuss her cardiovascular risk. She has a past medical history of hypertension. She underwent menopause at age 50 years. There is no family history of heart disease/stroke. She has no symptoms currently.
- Race: White. Substance use: never smoked, no alcohol or other substances.
- Current meds: Lisinopril
- Exam: P 80, BP 146/76, BMI 26 kg/m^2
- Labs: TC 220 mg/dL, HDL-C 45 mg/dL, TG 145 mg/dL, LDL-C 146 mg/dL.

Case 4

- You calculate her 10-year risk of ASCVD using the ACC/AHA risk calculator and it is 5.46%. You reassure her that she is not at a risk level that warrants lipid lowering therapy. However, she is not satisfied and asks to get a coronary artery calcium (CAC) test.
- What is the next best step in her management?

A. Order a CAC
B. Tell her a CAC won't add anything here and start atorvastatin 40 mg daily
C. Order a treadmill stress test
D. Refer her to cardiology

Case 4

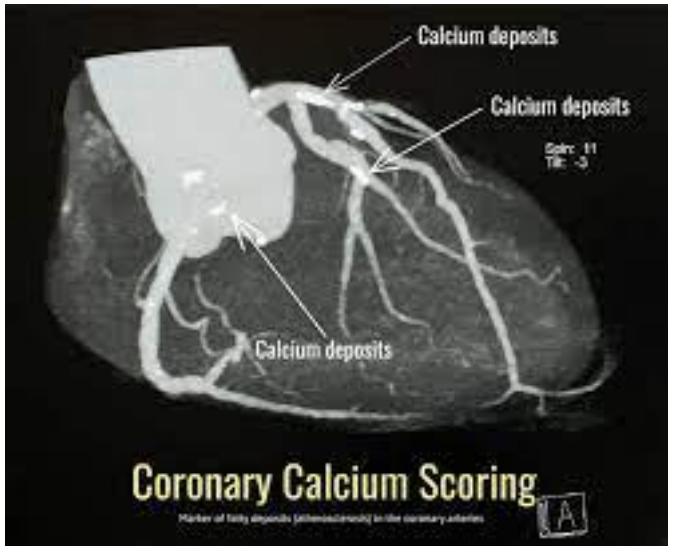
- What is the next best step in her management?

A. Order a CAC

B. Tell her a CAC won't add anything here and start atorvastatin 40 mg daily

C. Order a treadmill stress test

D. Refer her to cardiology



Case 4 Discussion

- Patient specific goal: Primary prevention
- Patient's calculated risk for ASCVD is below treatment threshold, however, patient is concerned and not satisfied with this recommendation
- NLA recommends using CAC in patients with borderline or intermediate risk, where the perceived risk is higher or lower than the calculated risk for ASCVD and there is inability to decide on how to treat
- Can also consider CAC in patient with low risk but positive family history of premature ASCVD
- Do not use in patients with known ASCVD

NLA: National Lipid Association

J Clin Lipidol. 2021 Jan-Feb;15(1):33-60.

LDL-C Goals per Guidelines in Patients without Diabetes

Primary Prevention

- First calculate 10-year ASCVD risk in age 40-75 years
- Categorize as low (<5%), borderline (5-7.5%), intermediate (7.5-20%) or high risk (>20%)
- Consider risk-enhancing factors – if present, usually favor statin therapy
- If undecided on therapy, consider CAC
- LDL-C reduction goal 30-49% in intermediate risk, 50% in high risk

2018 ACC/AHA Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.

Risk-Enhancing Factors

- Family h/o premature ASCVD
- Metabolic syndrome
- CKD
- h/o pre-eclampsia
- Premature menopause
- Chronic inflammatory diseases
- High risk ethnic groups (eg. South Asians)

- LDL-C ≥ 160 mg/dL persistently
- TG ≥ 175 mg/dL persistently
- Apo B ≥ 130 mg/dL
- hs-CRP ≥ 2 mg/L
- Lp (a) ≥ 50 mg/dL or 125 nmol/L
- ABI < 0.9

J Am Coll Cardiol . 2019 Jun 25;73(24):e285-e350.

Coronary Artery Calcium Testing

- Non-contrast CT scan (no specific scanner or preparation needed)
- Radiation exposure: 1mSv (~ mammogram levels)
- Report should give total Agatston score and individual coronary artery values
- Good reproducibility of results (interscan variability for non-zero values ~12%)

J Clin Lipidol. 2021 Jan-Feb;15(1):33-60.

How to interpret CAC results?

- Total score: best predictor of 5–10-year risk of ASCVD event; use in all patients
- Percentile score:
  - Calculated by entering data into MESA CAC reference tool (https://www.mesa-nhlbi.org/Calcium/input.aspx)
  - Better estimate of longitudinal risk relative to peers
  - Best used in patients 45-50 or >70 years age
- Can also use the MESA CAC CHD risk calculator

MESA: Multi-ethnic study of atherosclerosis
CHD: Coronary Heart Disease

J Clin Lipidol. 2021 Jan-Feb;15(1):33-60.

Treatment Decision Based on CAC Score

CAC Score	Decision
0	Defer statin (if no diabetes, smoking or family history)
1-99	Favor statin; esp if age ≥ 55 years
≥ 100 but < 300	Start medium intensity statin
≥300	Start high intensity statin Goal: ≥50% LDL-C reduction and <70 mg/dL

J Clin Lipidol. 2021 Jan-Feb;15(1):33-60.

Other noteworthy points regarding CAC

- Presence of diffuse CAC elevation or left main coronary CAC elevation are higher risk
- In patients with severe hypercholesterolemia (>190 mg/dL), CAC of 0 does not preclude need for long-term treatment
- In DM patients, age 40-75 years, statin is indicated regardless of CAC score, but if CAC >100, consider high-intensity statin
- In DM patients aged 30-39 years with long DM duration (type 1 ≥20 years, type 2 ≥ 10 years), other CV risk factors or microangiopathy, CAC may be used to consider statin initiation
- In DM patients >75 years (primary prevention), CAC=0 may defer statin therapy
- Statins can modestly increase CAC, but still predict risk

J Clin Lipidol. 2021 Jan-Feb;15(1):33-60.

DM: diabetes mellitus

Serial CAC measurements

- If CAC=0, repeat CAC in:
  - <5% risk: 5-7 years
  - 5-19.9%: 3-5 years
  - ≥20% or DM: 3 years
- If there is progression of CAC by >20-25% per year, need to aggressively lower LDL-C

J Clin Lipidol. 2021 Jan-Feb;15(1):33-60.

Case 5

- 63-year-old man comes to you for routine visit.
- Past medical history: Myocardial infarction in 2015 (LAD stented), ischemic stroke in 2019, abnormal stress test (for angina) in 2022 (LCx stented), Hypertension, Obesity.
- Current Meds: Aspirin, Clopidogrel, Lisinopril, Metoprolol succinate, Rosuvastatin 40 mg daily (since 2015), Ezetimibe 10 mg daily (since 2019), evolocumab 140 mg every 2 weeks (since 2022).
- Exam: P66, BP 124/74, BMI: 32 kg/m^2

LAD: left anterior descending coronary artery
LCX: left circumflex coronary artery

Case 5

- Labs: LDL-C 220 mg/dL (2015) -> 105 mg/dL (2019) -> 90 mg/dL (2022) -> 42 mg/dL (now). TG and HDL-C are normal. HbA1C is 5.4%.
- Patient is free of any symptoms. What is the next best step in management?

A. No tests or interventions needed at this time
B. Increase evolocumab to 420 mg monthly
C. Check Lp(a) levels
D. Check Apo B levels

Case 5

What is the next best step in management?

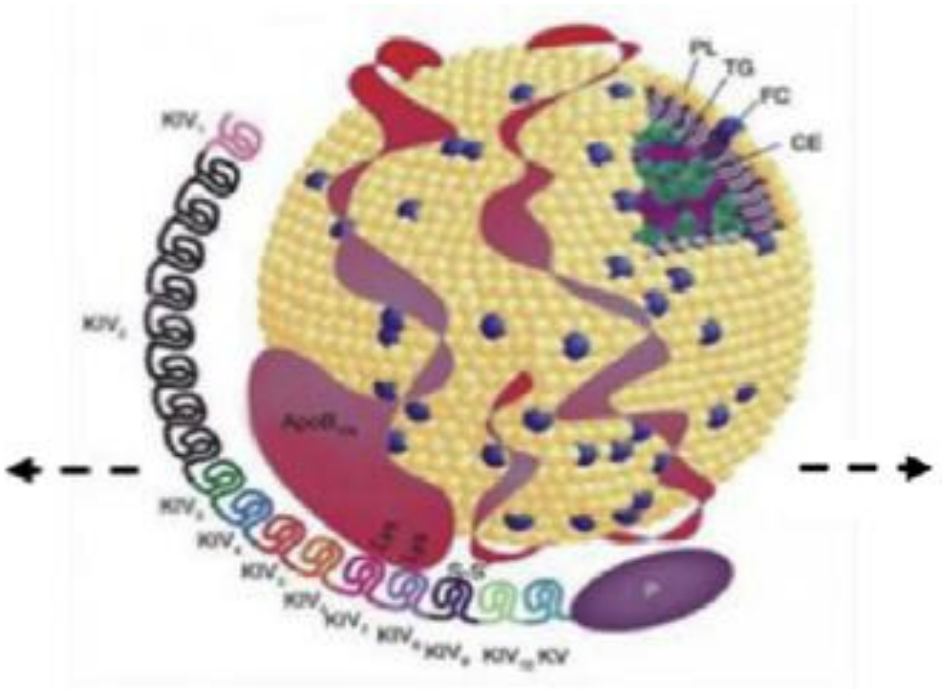
A. No tests or interventions needed at this time
B. Increase evolocumab to 420 mg monthly
C. Check Lp(a) levels
D. Check Apo B levels

Case 5 Discussion

- Patient specific goal: Secondary prevention
- Patient has had recurring ASCVD events, and required escalation of lipid-lowering therapy multiple times
- LDL-C currently at goal on triple-drug therapy
- Apo B levels are helpful in patients with elevated triglycerides
- Is there evidence of harm from elevated Lp(a) regardless of LDL-C levels?
- Who are candidates for Lp(a) testing?
- What to do with an elevated Lp(a)?

Lp(a) and Cardiovascular Disease

- 2 components: LDL-like particle and Apolipoprotein (a)
- Apo (a) has homology with plasminogen and inhibits fibrinolysis
- Associated with higher risk of CAD, ischemic stroke, PAD and CV mortality
- Lp(a) concentrations are a CV risk factor, independent of other known ASCVD risk factors (including LDL-C)



CAD: coronary artery disease
PAD: peripheral arterial disease
CV: cardiovascular

J Clin Lipidol. 2019 May-Jun;13(3):374-392.

Lp(a) Value Considerations

- Assays have not been harmonized or standardized; report can be in mg/dL or nmol/L but cannot be easily compared
- Ethnic variations exist in percentiles and associated ASCVD risk
- 2018 ACC/AHA guidelines recommend using Lp(a) ≥125 nmol/L (or ≥50 mg/dL) as a risk enhancing factor
- 2022 NLA position statement recommends using Lp(a) ≥ 100 nmol/L as a risk enhancing factor

J Am Coll Cardiol 2019;73:3168–3209.
J Clin Lipidol. 2022 Sep-Oct;16(5):e77-e95.

Lp(a) Testing Candidates

- 2019 ESC/EAS guidelines and 2022 NLA position statement:
  - Documented ASCVD (esp if recurrent events on lipid lowering therapy)
  - Severe hypercholesterolemia or familial hypercholesterolemia
  - Premature ASCVD in self or 1st degree relative, particularly in absence of traditional risk factors
- 2018 ACC/AHA do not provide guidance on Lp(a) testing
- 2021 Canadian Cardiovascular Society Guidelines:
  - Recommend one-time Lp(a) measurement in all patients
  - Recommend earlier and more intensive lipid lowering therapy in patients with Lp(a) >100 nmol/L

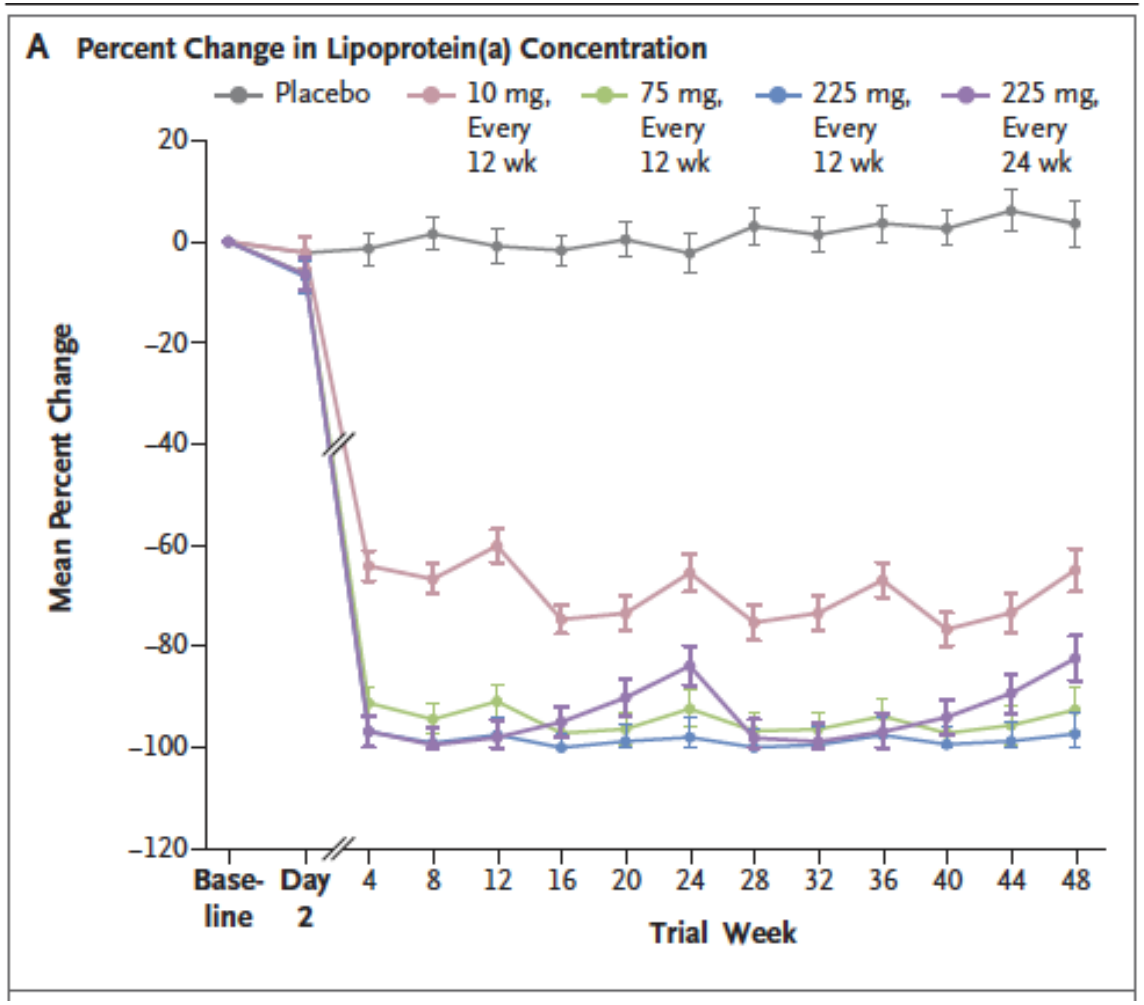
Can J Cardiol. 2021 Aug;37(8):1129-1150.

Effect of Lipid-lowering Therapies on Lp(a)

Drug	Lp(a) lowering	Comments
Statin	None	
Niacin	23%	AIM-HIGH and HPS2-THRIVE studies showed no ASCVD reduction and showed increased harm from therapy
PCSK9i	20-30%	FOURIER and ODYSSEY OUTCOMES trials showed greatest MACE reduction in those with highest Lp(a)
Lomitapide	20-25%	Not recommended for ASCVD reduction
Lp(a) apheresis	60%	Drug-resistant hypercholesterolemia

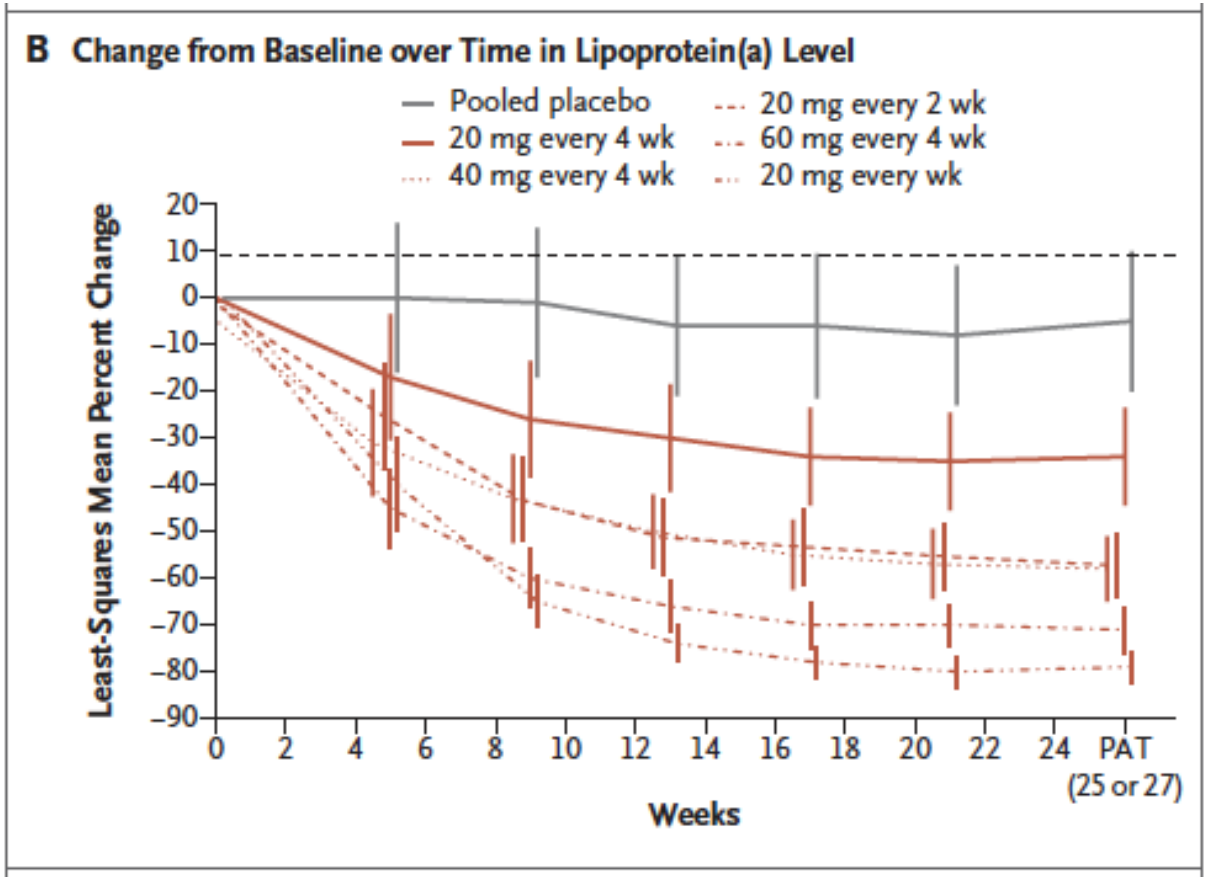
Metabolism. 2016 Nov;65(11):1664–1678 Epub 2016 Aug 31.
N Engl J Med 2014; 371:203-212.
N Engl J Med. 2014 Jul17;371(3):288–290.
Circulation. 2019 Mar 19;139(12):1483–1492.
Atherosclerosis Supplements. 2018;32:24–25.
Eur Heart J. 2017 Dec 21;38(48):3555–3559.
J Lipid Res. 2012 Aug;53(8):1670–1678 Epub 2012 May 24.

Clinical Trials to Lower Lp(a)



Olpasiran – phase 2

N Engl J Med. 2022 Nov 17;387(20):1855-1864.



Pelacarsen – phase 2

N Engl J Med 2020;382:244-55.

Take Home Points

- Patients with diabetes, age >40 years, LDL-C>70 mg/dL, warrant statin therapy to lower CV risk
  - Consider LDL-C goals of <70 mg/dL (primary) and <55 mg/dL (secondary)
- Look for modifiable causes for statin intolerance, trial at least 2 statins and at lowest doses, try non-statin agents (-> ezetimibe -> PCSK9i)
- In patients with high CV risk, who have achieved LDL-C target, but have elevated TG, low HDL-C, consider use of icosapent ethyl
- In primary prevention candidates at borderline/intermediate CV risk, consider using CAC to make decisions regarding therapy
- Lp(a) lowering therapies are emerging, so consider testing in patients with established ASCVD or very high risk for ASCVD

THANK YOU

QUESTIONS?