

What do I need to know about Lp(a): the ins and outs

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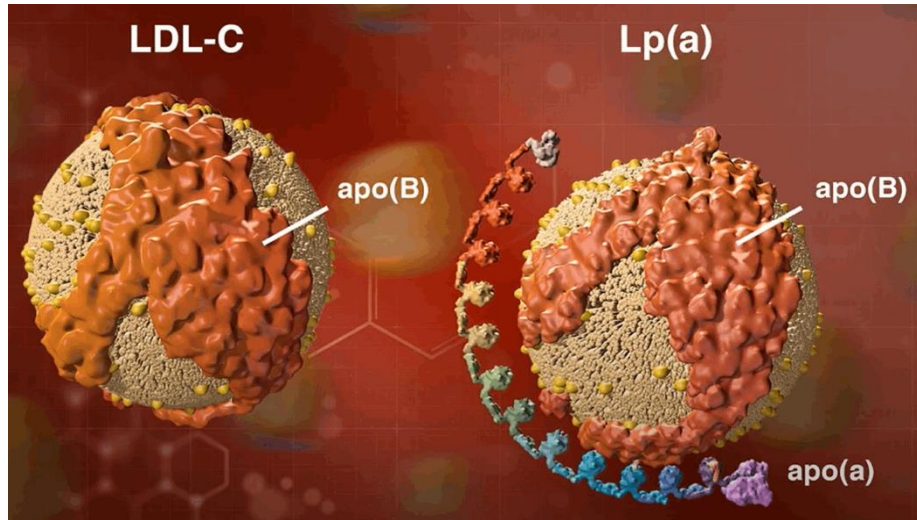
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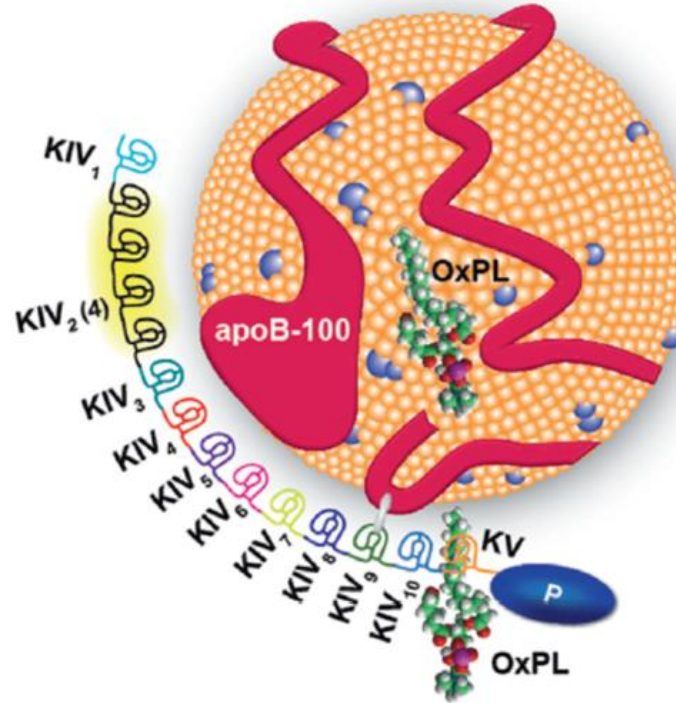
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Lp(a) – structure & importance



The Lp(a) particle is composed of 2 parts:

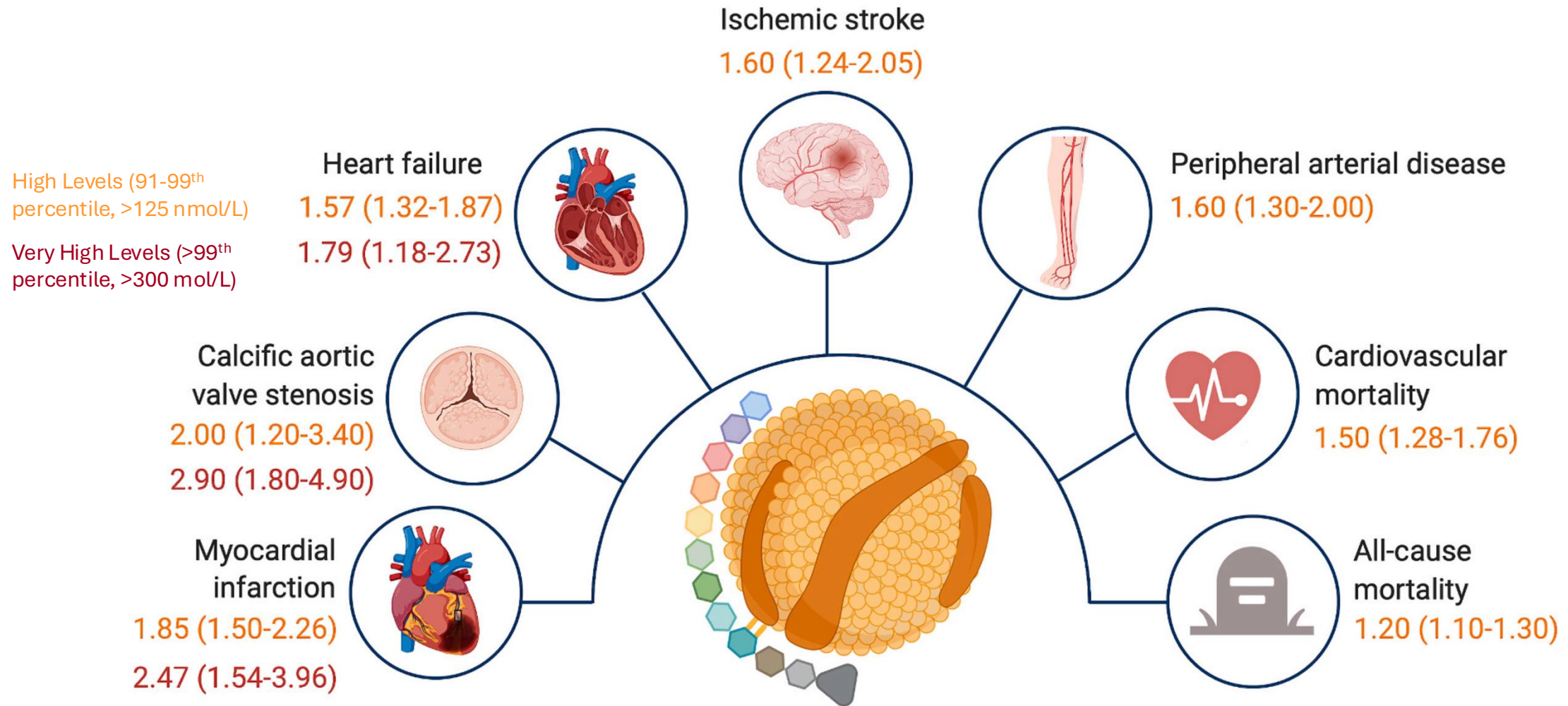
- LDL-like particle with apoB-100
- Apo(a) covalently bound to apoB-100 by disulfide bonds



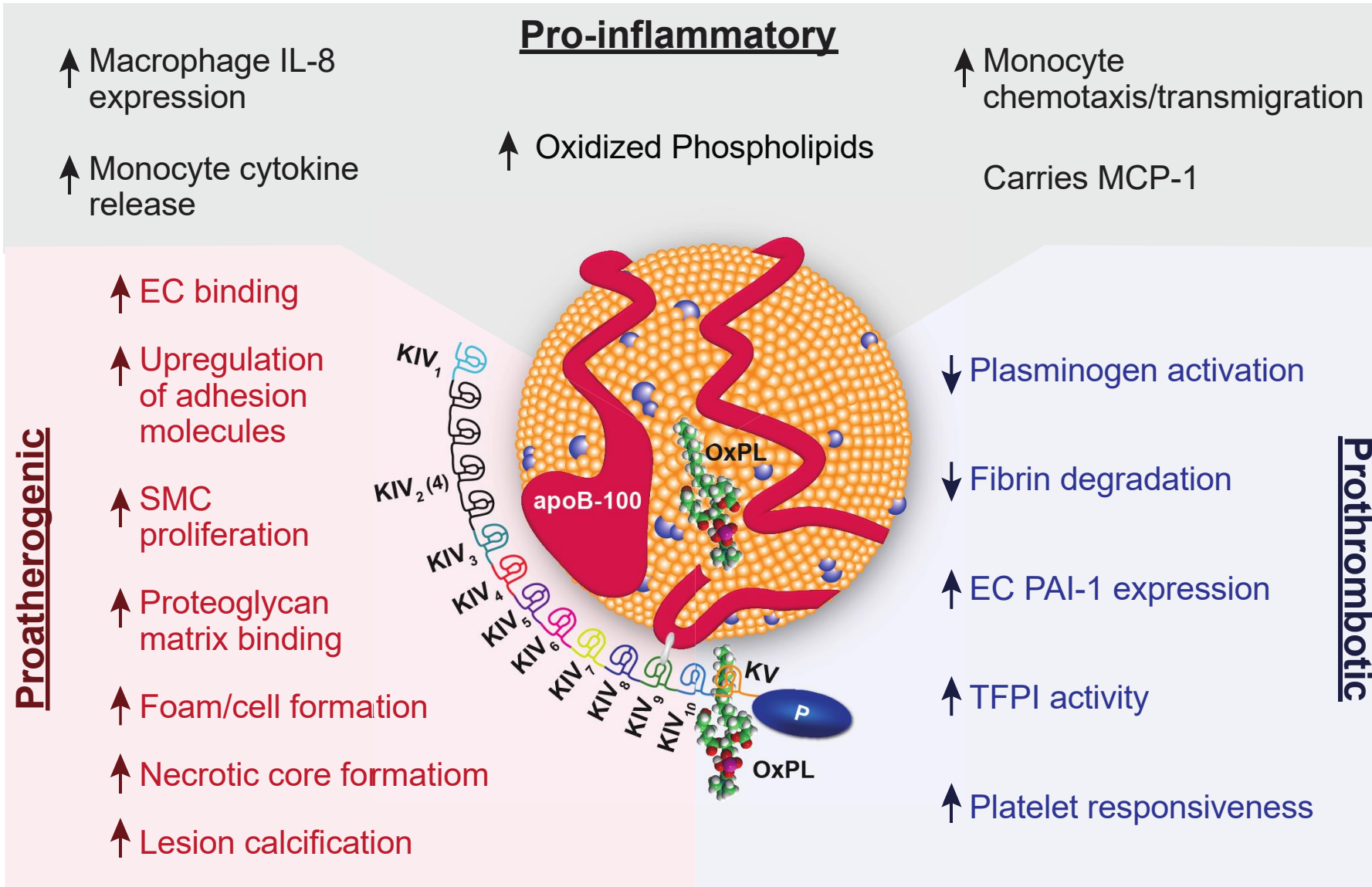
apo(a) contains 10 KIV types, an inactive protease-like domain, and oxidized phospholipids

- Independent, causal risk factor for ASCVD
- 20% of world has elevated levels $\cong 1.4B$, in US: 65M (>50 mg/dL or 125 nmol/L)
- 90% genetically determined (*LPA*), without significant effect of diet or environment
- On a per particle basis, 6X more atherogenic than LDL

Lp(a) increased the risk of ASCVD, CAVS, and HF in Copenhagen Heart Study

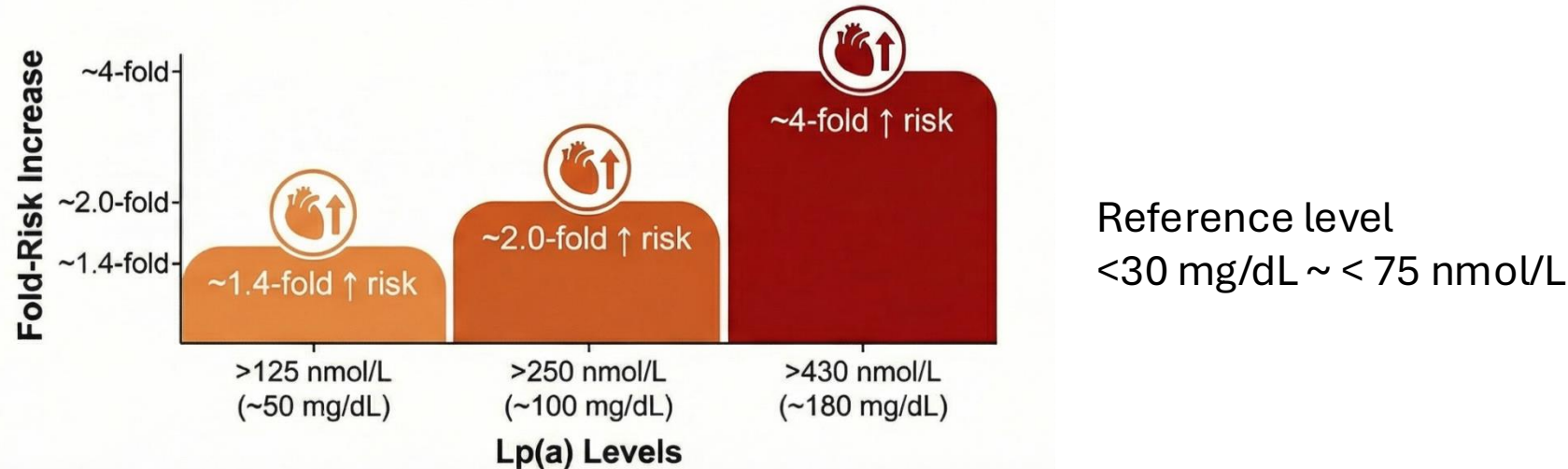


Lp(a) - Pathophysiology



Lp(a) – 2026 ACC/AHA Dyslipidemia Guidelines

Recommendations for Measurement of Lipoprotein (a)		
COR	LOE	Recommendations
1	B-NR	1. In all adults, measurement of Lp(a) concentration is recommended at least once for ASCVD risk assessment.
1	B-NR	2. In individuals with FH, premature ASCVD, or high Lp(a), cascade testing of first-degree family members for high Lp(a) concentration is recommended to identify those at increased ASCVD risk.
1	B-NR	3. For individuals undergoing measurement of Lp(a), use of laboratories employing assays that are insensitive to apo(a) isoforms and traceable to official reference standard materials is recommended to more accurately measure Lp(a) and characterize ASCVD risk.

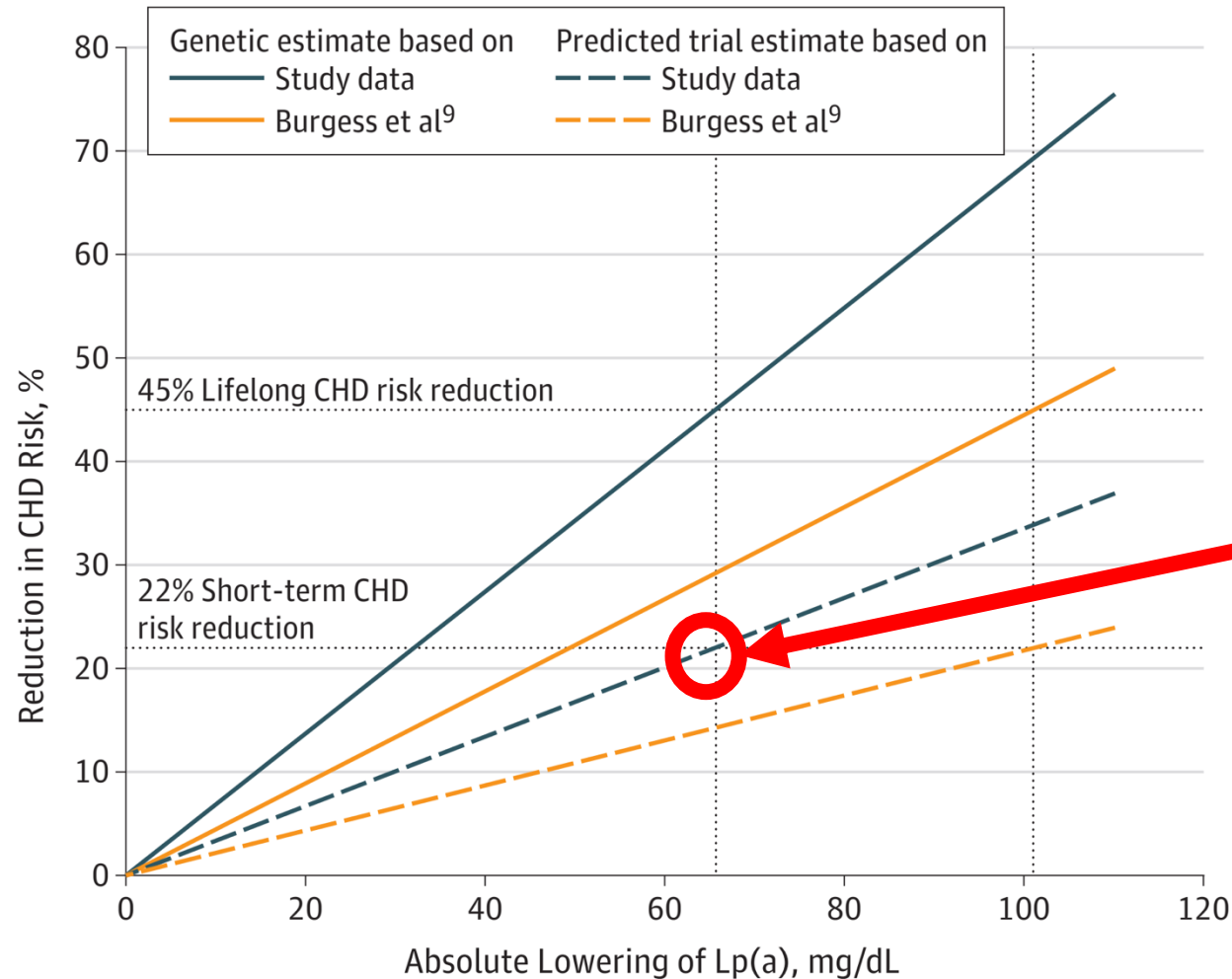


Lp(a) – 2026 ACC/AHA Dyslipidemia Guidelines

- Risk enhancer: Lp(a) ≥ 125 nmol/L or ≥ 50 mg/dL → favors statin therapy in borderline to intermediate risk individuals (10-year ASCVD risk 3 to $<10\%$)
- Higher levels of Lp(a) are found in non-Hispanic Black individuals, but associated increase in CVD relative risk is similar to other groups.
- Elevated Lp(a) is associated with a higher population-attributed risk for MI among South Asian and Latin American people.
- Liposorber lipoprotein apheresis - Clinically diagnosed familial hypercholesterolemic heterozygotes with Lp(a) ≥ 60 mg/dL (or 130 nmol/L) and either documented coronary artery disease or documented peripheral artery disease

Recommendations for the Approach to Patients With Elevated Lp(a)		
COR	LOE	Recommendations
1	B-NR	1. In all individuals with elevated Lp(a) (≥ 125 nmol/L or ≥ 50 mg/dL), optimal early control of modifiable cardiovascular risk factors is recommended to reduce ASCVD risk.
1	B-R	2. In individuals with clinical ASCVD and elevated Lp(a) who have not achieved LDL-C and non-HDL-C treatment goals on maximally tolerated statin therapy, the addition of a PCSK9 mAb with proven cardiovascular benefit is recommended to achieve treatment goals and reduce ASCVD risk.

Lp(a) vs LDL-C lowering & CVD risk

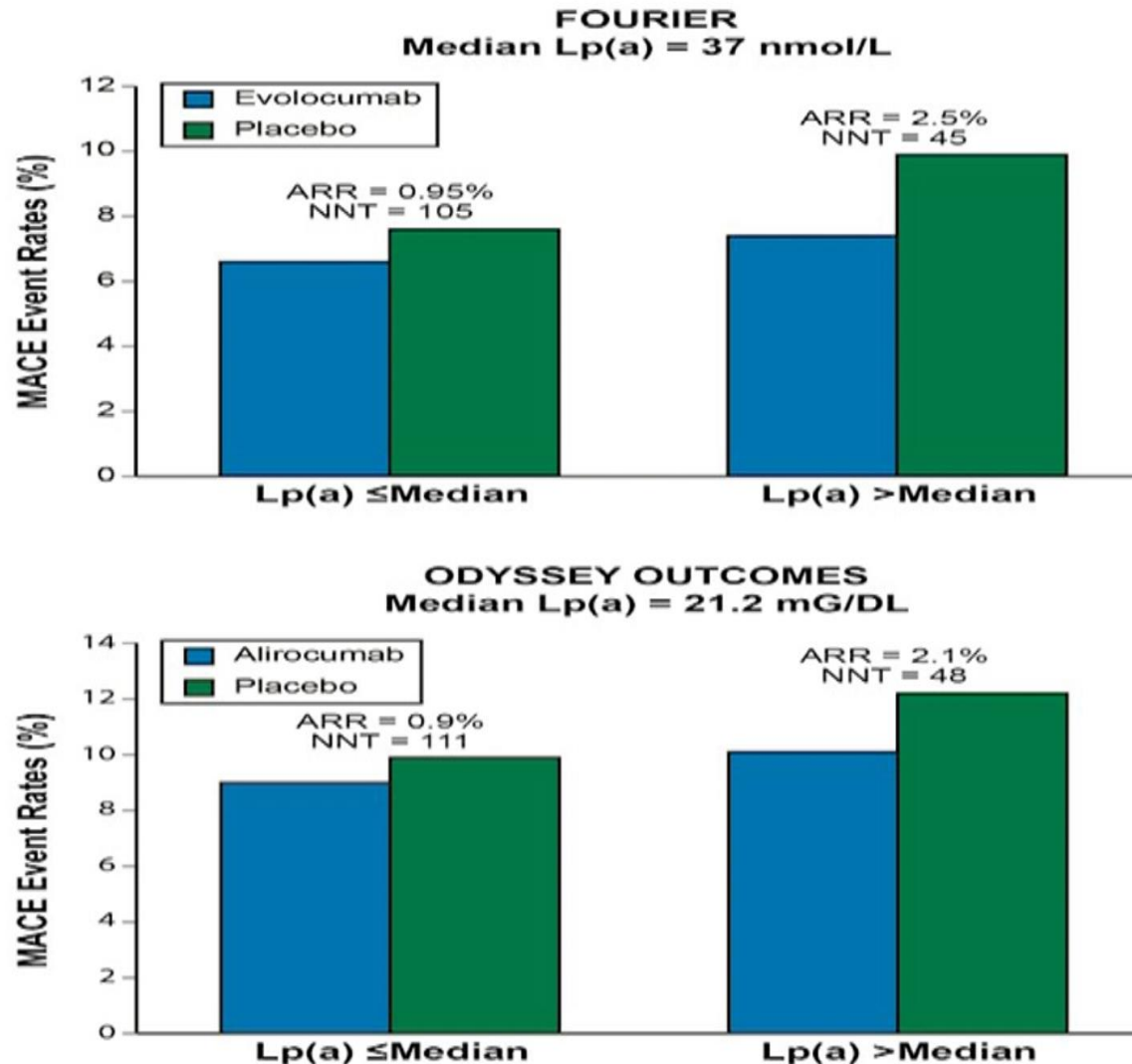


In order to achieve same reduction of CVD (22%) as seen in CTT by 1 mmol/L LDL-C reduction (38 mg/dL), Lp(a) needs to be reduced by 66 mg/dL

Is available LLT useful in reducing Lp(a) levels?

Drug	Change in serum Lp(a) levels
Statins	↑ 0 to 20%
Ezetimibe	↓ 0-7%
Bempedoic acid	↓ 2-3%
Niacin	↓ 10-20%
Lomitapide	↓ 3-17%
Evinacumab	↓ 18%
Estrogen	↓ 20%
Inclisiran	↓ 22%
Alirocumab, Evolocumab, Lerodalcicibep	↓ 20-27%
Enlicitide	↓ 30-35%
Obicetrapib	↓ 35-45%
Lipoprotein apheresis	↓ 60-75% (immediate); 25-45% (time averaged)

PCSK9 mAbs and Lp(a) reduction



Post-hoc analyses of PCSK9 mAb trials:

Larger MACE ↓ effect size in patients with higher Lp(a) levels at baseline

Emerging/Novel LLT to reduce Lp(a) levels

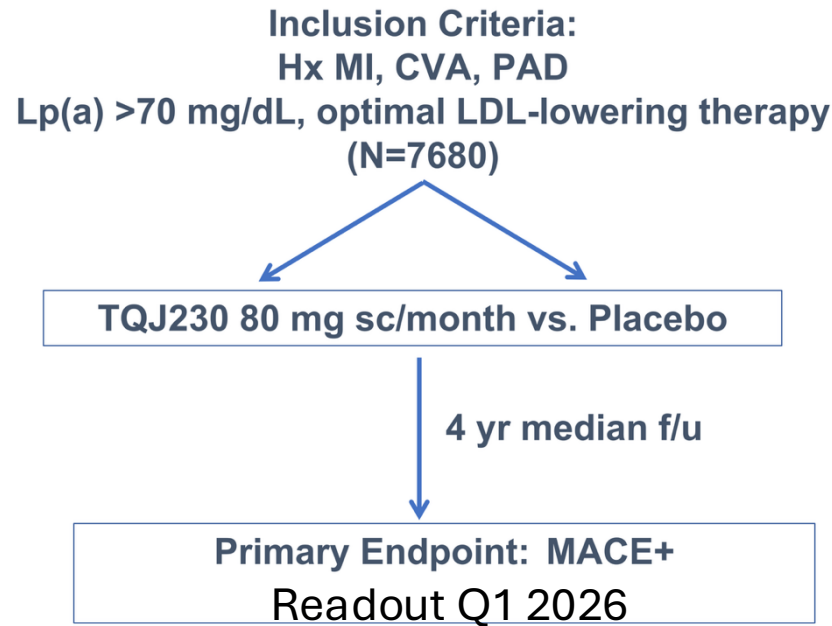
1. Pelacarsen (ASO)
2. Olpasiran (**siRNA**)
3. Lepodisiran
4. Zerlasiran
5. Muvalaplin
6. Others (Obicetrapib ~45-50% in BROOKLYN trial, Crispr-Cas9: VERVE/Eli Lilly; HRS5346 Merck/Jiangsu Hengrui)

Drug	Reduction in serum Lp(a) levels
Pelacarsen	↓ 80%
Olpasiran	↓ 97-101%
Lepodisiran	↓ 94%
Zerlasiran	↓ 86%
Muvalaplin	↓ 85%

Lp(a) drugs in the pipeline

Drug	Company	Trial	MOA	Inclusion	Dosing	Lp(a) reduction (time averaged)	Readout
Pelacarsen	Novartis	HORIZON outcomes	ASO	Very high risk ASCVD (MI/isch stroke/PAD), >70 mg/dL (~175 nmol/L)	80 mg SQ q 4 wks	80%	2026 Q3
Olpasiran	Amgen	OCEAN(a) outcomes	siRNA	MI or cor revasc+RF, > 200 nmol/L	150 mg SQ q 12 wks	97-101%	2027 Q4
Lepodisiran	Eli Lilly	ACCLAIM-Lp(a)	siRNA	ASCVD or high risk pri prevention, > 175 nmol/L	400 mg SQ q 6 mo x 3, then q 12 mo	94%	2029 Q1
Zerlasiran	Silence therapeutics	Not started yet (phase 2 ALPACAR360)	siRNA	?	?450 mg SQ q 6 mo	86%	-
Muvalaplin	Eli Lilly	MOVE Lp(a) (phase 2: KRAKEN)	Disrupts Lp(a) assembly	10450 participants with ASCVD or at high risk	120 mg po qd	85%	2031

Pelacarsen Lp(a)HORIZON trial (NCT04023552)

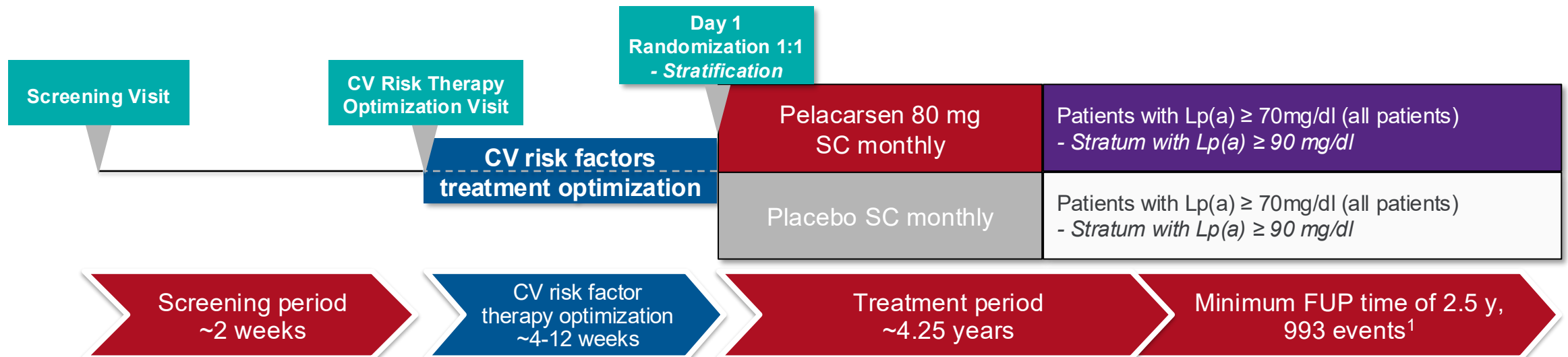


n = 8323; randomized, double-blind, placebo-controlled CVOT. Recruitment complete

Inclusion criteria: Lp(a) $\geq$ 70 mg/dL ($\sim$ 150 nmol/L); pre-existing ASCVD (MI, ischemic stroke, or PAD)

Primary endpoint: time to MACE-4 (CV death/non-fatal MI/non-fatal ischemic stroke/urgent coronary revasc)

FRONTIERS CAVS : mild or moderate AS progression in 50-80 yo (NCT05646381) (change in echo peak velocity and CT AV calcium score)



Lp(a)HORIZON: Negative Primary Endpoint — Is Lp(a) Lowering Dead?

Lp(a)HORIZON Topline (Sept 4, 2026)

- Pelacarsen (ASO) vs placebo, n=8,323, established CVD, Lp(a) ≥70 mg/dL
- Primary endpoint (CV death/MI/stroke/urgent revasc): **NOT MET**
- Substantial Lp(a) lowering achieved; acceptable safety profile
- ≥90 mg/dL co-primary subgroup result not yet reported
- Full data pending presentation at AHA 2026 Chicago

Why This Isn't the End of the Lp(a) Story

- Causality rests on decades of Mendelian randomization data — independent of this one drug's outcome
- Absolute (not just %) Lp(a) reduction may have been insufficient at lower end of eligible range
- Aggressive background GDMT (low LDL-C) may have diluted residual, Lp(a)-attributable risk
- Trial duration (~4-5y) may be short relative to a CETP-inhibitor-like delayed-benefit pattern (eg anacetrapib)

Ongoing Trials — The Real Test of Hope

OCEAN(a)-Outcomes (olpasiran, siRNA, ~6,000 pts) — deeper/more uniform Lp(a) lowering (90-98%)

ACCLAIM-Lp(a) (Iepodisiran, Eli Lilly) — Phase 3, ongoing

Zerlasiran & muvalaplin (oral) — earlier-phase siRNA/small-molecule agents

Bottom Line

One drug, one degree of lowering, one population, one duration — **missed the mark**, not falsified the hypothesis

OCEAN(a)-Outcomes will inform whether near-complete Lp(a) suppression changes events

Lp(a)HORIZON topline: field check, not field closed

What failed?

Pelacarsen ASO



Primary CV outcome negative

No statistically significant reduction in 4-point MACE vs placebo in the overall population despite lower Lp(a).

Trial frame

8,323 patients

established CVD + elevated Lp(a)

Lp(a) ≥ 70 mg/dL

prespecified ≥ 90 mg/dL analysis

4-point MACE

CV death, nonfatal MI, nonfatal stroke, urgent hospitalized revascularization

What it means now

Not a causal obituary

Negative at the tested dose, duration, population, event mix, and background therapy — not proof that Lp(a) lowering cannot work.

Await other siRNA drug trials

Key missing pieces: achieved absolute Lp(a), on-treatment exposure, adherence, LDL-C/background therapy, event components, ≥ 90 mg/dL subgroup, and safety.

Why hope remains

The next trials are not duplicates

Olpasiran

siRNA; Phase 2 $>95\%$ Lp(a) reduction; OCEAN(a)-Outcomes n $\approx$ 7,297

Lepodisiran

long-duration siRNA; ALPACA $\approx 94\%$ time-averaged reduction; ACCLAIM ongoing

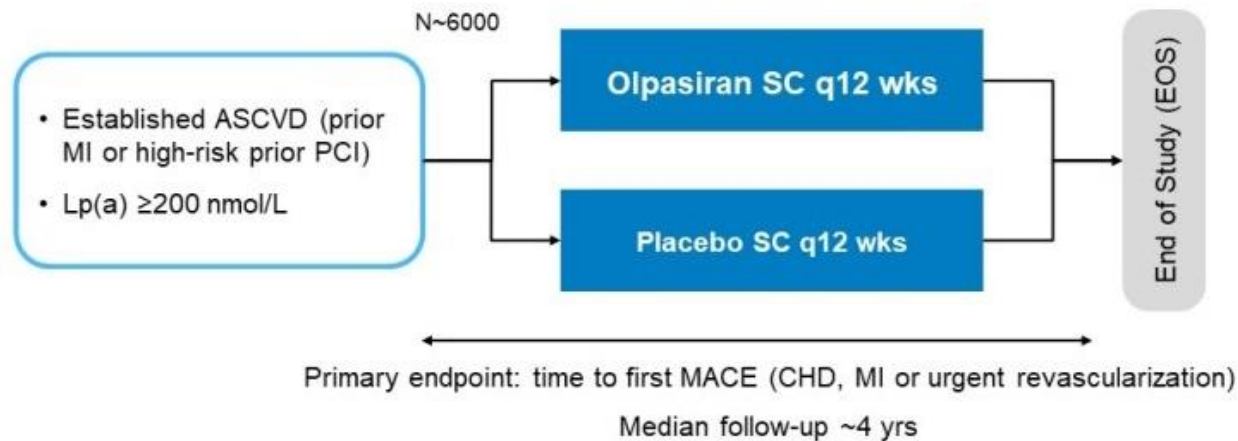
Muvalaplin

oral assembly inhibitor; KRAKEN ≈ 48 – 86% reduction; Phase III outcomes ongoing

Hope rests on deeper / more durable lowering, better phenotyping, and component/subgroup signals — not blind faith.

Bottom line: wounded hypothesis, active pipeline

Olpasiran OCEAN(a) Outcomes (TIMI75; NCT05581303)



- n = 7297; randomized, double-blind, placebo-controlled CVOT. Recruitment completed. Readout Q4 2026
- 18-85 yrs
- Lp(a) $\geq$ 200 nmol/L; history of MI type 1 AND/OR
- coronary revascularization (eg, PCI) + $\geq$ 1 additional risk factor (eg, PAD, age>65, multivessel PCI, residual coronary stenosis >50%, ischemic stroke, DM)
- Assigned to 150 mg olpasiran SC q 12 weeks vs placebo
- Time to MACE-3: CHD death, MI, urgent coronary revasc, whichever occurs first

Lepodisiran ACCLAIM-Lp(a) (NCT06292013)

- n= 12,500 (est); recruitment ongoing, 5.5 yrs, readout ~ 2029
- Lp(a) $\geq$ 175 nmol/L; includes patients with either established ASCVD with a previous event/revascularization, OR *high risk primary prevention* individuals a) >55 years with CAD/carotid stenosis/PAD (i.e. without a previous event/revasc); b) a combination of risk factors putting them at high risk of a first event (eg CAC>300 AU); c) or, FH
- Time to 1st occurrence: MACE-4 (CV death/non-fatal MI/non-fatal ischemic stroke/urgent coronary revasc)

Zerlasiran ALPACAR-360 (Silence Therapeutics)

POPULATION

132 Men
46 Women



Adults aged 18 to 80 years
with atherosclerotic
cardiovascular disease

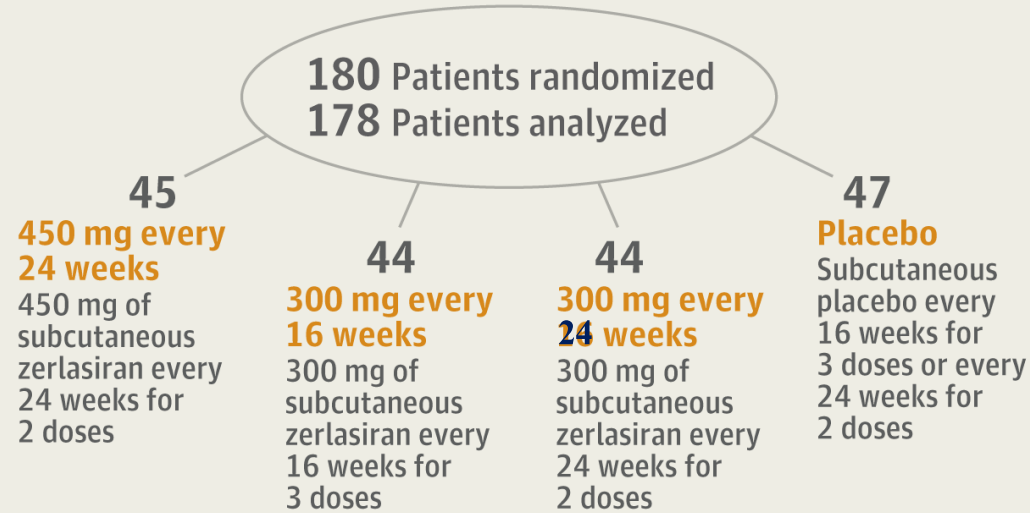
Mean age: **64** years
DM 16%

LOCATIONS

26
Research sites
worldwide



INTERVENTION



PRIMARY OUTCOME

Least-squares mean time-averaged percent change in serum lipoprotein(a) concentration vs placebo from baseline to 36 weeks

FINDINGS

Change in serum lipoprotein(a) concentration vs placebo

450 mg every 24 weeks

-85.6% (95% CI, -90.9% to -80.3%)

300 mg every 16 weeks

-82.8% (95% CI, -88.2% to -77.4%)

300 mg every 24 weeks

-81.3% (95% CI, -86.7% to -76.0%)

All 3 zerlasiran treatment groups produced a $\geq 80\%$ time-averaged reduction in serum lipoprotein(a) concentration compared with placebo

Also 15% ↓ in apoB, 25.1% ↓ in LDL-C

Inclusion:

Lp(a) ≥ 125 nmol/L
Median Lp(a) 213 nmol/L

Exclusion:

Recent acute CV event
GFR < 30
History of liver disease or heart failure

Muvalaplin - KRAKEN trial (Eli Lilly)

Oral small molecule inhibitor therapy: Muvalaplin binds to apo(a) to prevent formation of Lp(a)



Inclusion:

Phase 2, Lp(a) ≥ 175 nmol/L

Age ≥ 40 with high CV risk (CAD in 70-80%, ischemic stroke, PAD, type 2 DM 33%, FH)

Exclusion:

Uncontrolled hypertension/DM
GFR < 30

Recent CV procedure

Case: A 37-Year-Old Man with a Normal LDL-C

Presentation

- 37-year-old man, referred for risk assessment after his father's MI at age 44
- Asymptomatic. Runs three times weekly. Never smoked. BMI 24.
- BP 122/76. No diabetes. No medications.
- **Family history**
 - Father: MI at 44, CABG at 51. Paternal uncle: MI at 49. Paternal grandfather: sudden death at 52.
- **He has been told repeatedly that his cholesterol is "fine" and that his lifestyle is exemplary.**

- **LDL-C 112 mg/dL looks unremarkable. apoB 118 mg/dL does not.**
- Each Lp(a) particle carries one apoB-100. At 430 nmol/L, Lp(a) is contributing a substantial number of atherogenic particles that LDL-C does not represent
- A meaningful fraction of the reported LDL-C is itself Lp(a)-cholesterol — the "corrected" LDL-C is lower, while the particle burden is higher
- **This is exactly the patient in whom ordering apoB and Lp(a) changes how you treat the patient.**

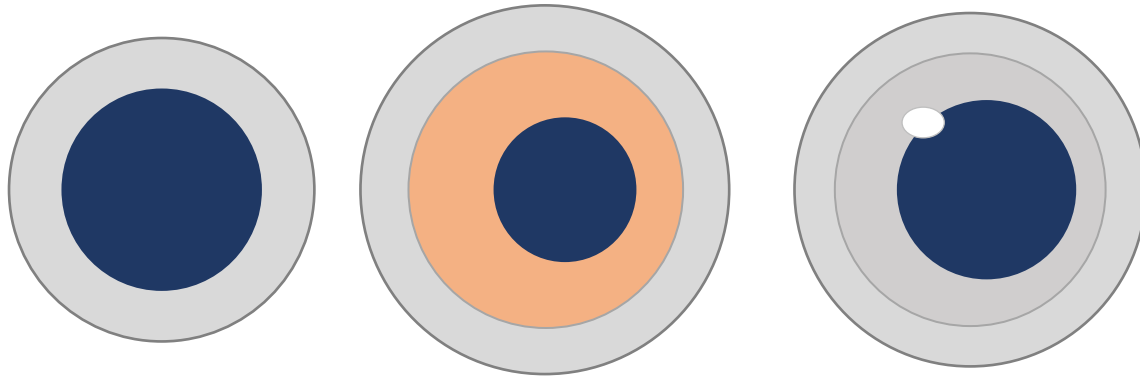
Laboratory	Result	Interpretation
Total cholesterol	186 mg/dL	Normal
LDL-C (calculated)	112 mg/dL	Unremarkable
HDL-C	52 mg/dL	Normal
Triglycerides	108 mg/dL	Normal
apoB	118 mg/dL	Elevated — discordant
Lp(a)	430 nmol/L (~180 mg/dL)	Very high (>95th %ile)
hsCRP	0.8 mg/L	Low
HbA1c, TSH, creatinine	Normal	No secondary cause

What the calculator says — and why it is useless here

- **PREVENT-ASCVD 10-year risk: well under 5%.**
- By 10-year risk alone, this man does not obviously warrant pharmacotherapy
- He has had 37 years of markedly elevated atherogenic particle exposure and a strong family history
- **The 30-year estimate, and the risk-enhancer designation of Lp(a) ≥125 nmol/L, increase his risk ~4X at 430 nmol/L**
- **Discussion point: would you treat now, or image first?**

Case: CAC = 0, But the CCTA Is Not Normal

What a CAC score cannot see



Normal segment

Preserved lumen,
no wall thickening

This patient

Non-calcified plaque with
positive remodeling, CAC = 0

Older patient

Calcified plaque,
abnormal CACS

The imaging result

- **Coronary artery calcium score: 0**
- **CCTA:**
 - Eccentric non-calcified plaque in the proximal LAD with positive remodeling, producing approximately 30-40% diameter stenosis. Additional non-calcified plaque in the proximal RCA. No obstructive disease. No high-risk features beyond positive remodeling.
- **Total plaque burden is abnormal for a 37-year-old by any published normative standard.**
- **The CAC score of zero was not a false negative. It was an accurate measurement of the wrong thing.**

Why this matters — and where the "power of zero" breaks down

- Calcification is a late, reparative phase of atherosclerosis. In young patients, plaque is predominantly non-calcified and therefore invisible to CAC scoring.
- **The negative predictive value of CAC = 0 is derived largely from older cohorts. It degrades substantially under age 45, and further in the presence of a strong family history or a powerful genetic risk factor such as very high Lp(a).**
- Elevated Lp(a) has been associated with greater non-calcified and low-attenuation plaque burden and with faster plaque progression — precisely the phenotype CAC misses.
- **Practical rule: in a young patient with very high Lp(a) and premature family history, CAC = 0 should not end the evaluation. If you are going to image, image with CCTA.**

Case: Clinical Management of Elevated Lp(a) Today- What Can We Do Now

Immediate

- **High-intensity statin**
 - Rosuvastatin 20 mg or atorvastatin 40 mg. He has documented plaque; this is no longer primary prevention in the conventional sense.
- **Target**
 - LDL-C <70 mg/dL and apoB <80 mg/dL, with a low threshold to go lower given the plaque and the Lp(a).
- **Recheck at 6-8 weeks**
 - Lipids and apoB. Add ezetimibe/PCSK9i if not at goal.

Same visit

- **Cascade testing**
 - Lp(a) and a lipid panel for both parents, all siblings, and his children when age-appropriate. Given the pedigree, screen for FH in parallel.
- **Blood pressure and tobacco**
 - Treat aggressively to goals
- **Aspirin**
 - Reasonable to discuss given documented plaque, young age, and low bleeding risk — as a shared decision, consider genotyping

Longitudinal

- **Do not repeat the Lp(a)**
 - Document it once
- **Flag for trial eligibility**
 - Check current Lp(a) trial criteria; trials of patients with subclinical disease.
- **Aortic valve**
 - Auscultate annually; baseline echo is reasonable given the Lp(a) level.
- **Re-image?**
 - No routine interval CCTA. Repeat only if it would change management.

Questions

- Would you have imaged at all, or treated on the Lp(a) and family history alone?
- Does the presence of non-calcified plaque change your LDL-C target — and on what evidence?
- Would you start aspirin in this man? Would your answer change if he were 62?
- Is a PCSK9 inhibitor justifiable here if he reaches LDL-C 68 mg/dL on a statin plus ezetimibe?
- At what age would you screen his children?

Incorrect measures:

- **Reassure him because the CAC score was zero.**
- **Defer treatment pending a positive Lp(a)-lowering drug trial.**
- **Serial checks of Lp(a) levels to "follow the trend."**
- **Niacin, supplements, or a dietary fads aimed at Lp(a).**
- **Not do cascade testing for his relatives.**

Summary

1. Elevated Lp(a) levels are seen in 20-25% of the world's population and are causally associated with ~1.5-3 x increase in CAD, stroke, PAD, HF, and AS.
2. Several lines of indirect evidence suggest that lower Lp(a) levels may be associated with lower rates of MACE (observational, Mendelian randomization, PCSK9 mAb therapies, etc).
3. At least 5 agents are being tested in patients with high Lp(a) and established ASCVD, or elevated CV risk, or calcific aortic valve stenosis.
4. The long term efficacy and safety of these approaches will become clearer over the next 1-5 years.

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Thank You!



Navigating Lipid Management During The Childbearing Years

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Disclosures

Nothing to disclose

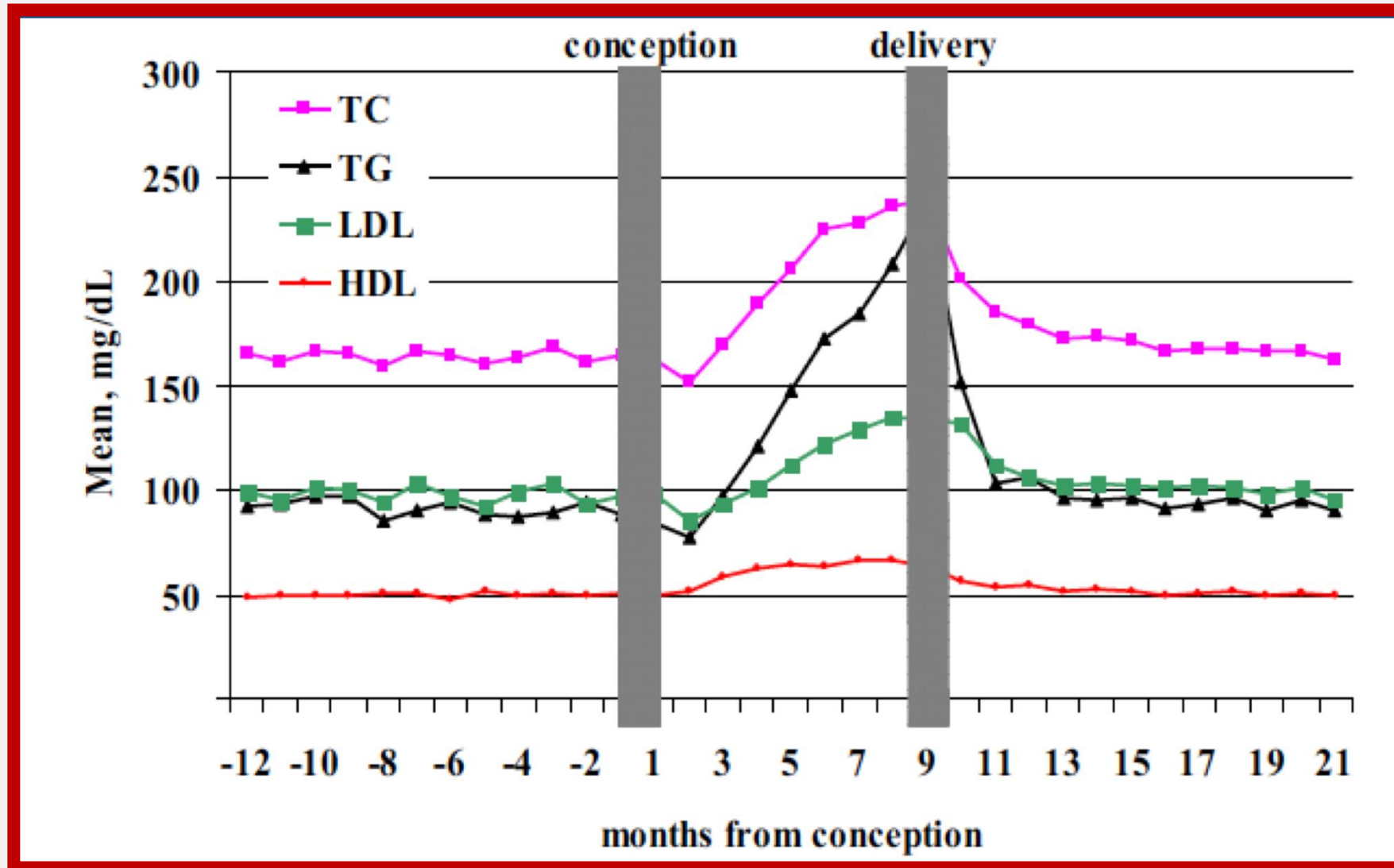


***A ship is always safe at the shore—
but that is not what it is built for.***

-Albert Einstein



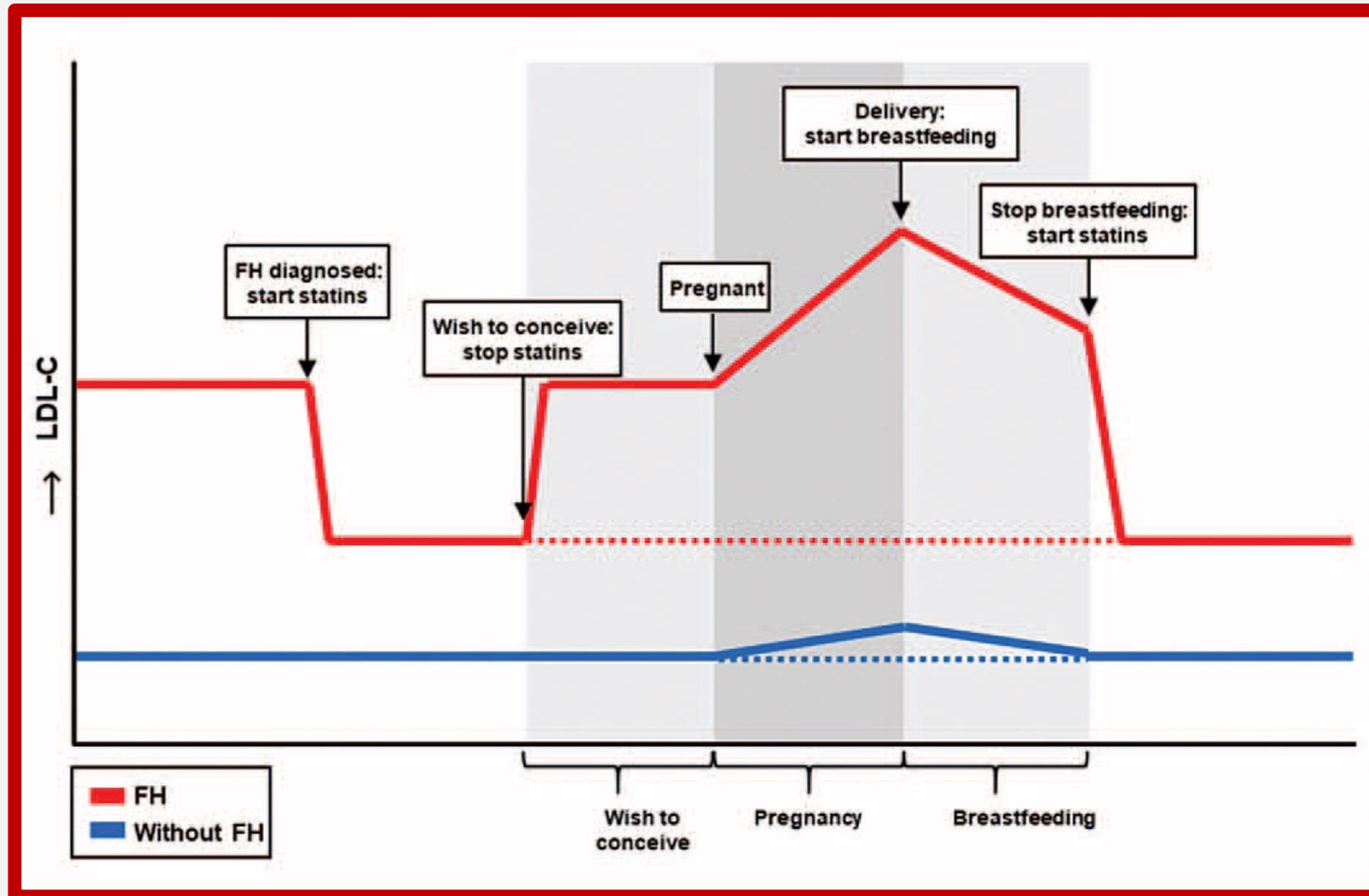
Normal Pregnancy: Changes in Lipid Levels



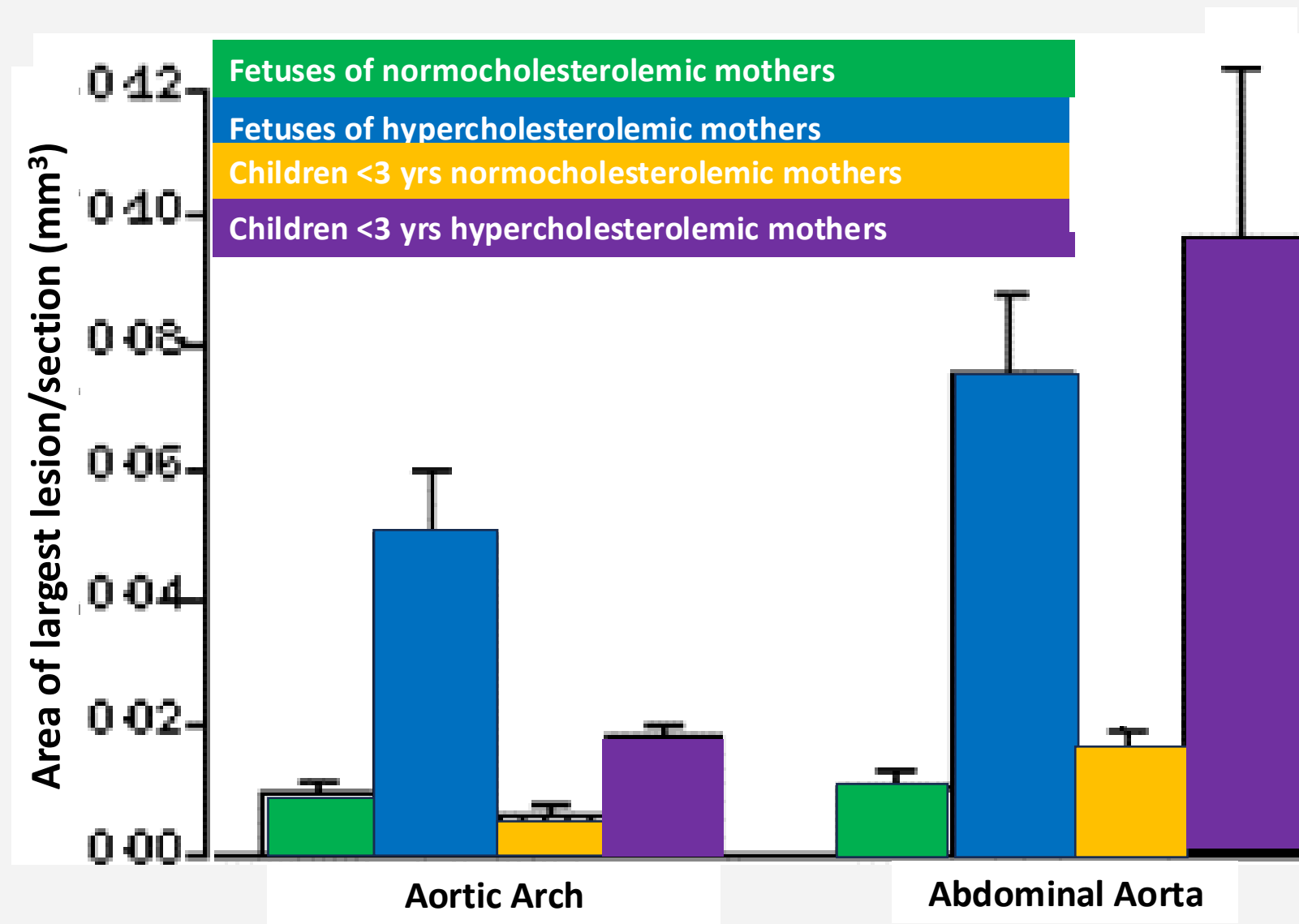
8 out of 10 women of childbearing age have never had their cholesterol levels checked, despite clear guidelines to get a first lipid blood test early in adulthood



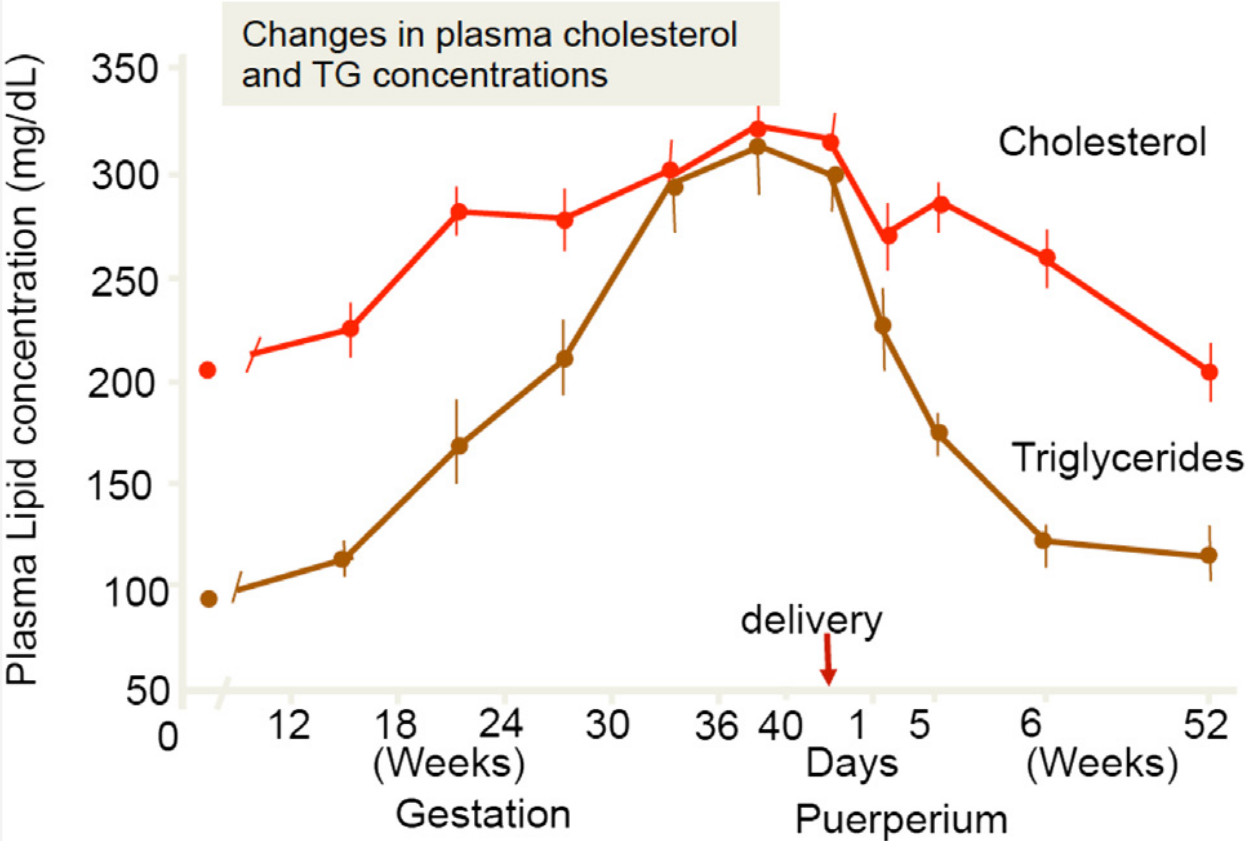
LDL-C Levels During Pregnancy in Women With and Without FH



Influence of Maternal Hypercholesterolemia During Pregnancy on Progression of Early Atherosclerotic Lesions In Childhood



Changes in Cholesterol and TG



Condition	Incidence	Odds Ratio of Increased Risk with Increase in TG
Pregnancy Induced Hypertension	4.9%	1.60
Preeclampsia	3.7%	1.69
Preterm Birth	5.3%	1.69
Large for Gestational Age	9.3%	1.48

The Obstetrician & Gynaecologist 2023;25:196–209
J Clin Endocrinol Metab, November 2012, 97(11):3917–3925



Start With A Preconception Lipid Visit

Create the plan before a positive pregnancy test.



- 1 Define risk**
ASCVD, HeFH/HoFH, prior events, LDL-C burden, pancreatitis
- 2 Clarify timeline**
Pregnancy intention, contraception, fertility treatment, breastfeeding goals
- 3 Document baseline**
Fasting lipid panel; consider Lp(a) once; ApoB selectively
- 4 Reconcile therapy**
Identify agents to stop, continue, or replace
- 5 Build handoffs**
Cardiology, MFM/OB, lipid specialist, pharmacist, dietitian

Nutrition Is Treatment, Not A Placeholder

Match the nutrition prescription to the lipid phenotype and pregnancy needs.



LDL-predominant

- Mediterranean-style pattern
- Replace saturated fat with unsaturated fat
- Soluble fiber and minimally processed foods
- Appropriate gestational weight gain



TG-predominant

- Eliminate alcohol
- Reduce refined carbohydrate and added sugar
- Address diabetes and secondary causes
- Severe TG: specialist-directed low-fat plan



Support adherence

- Registered dietitian
- Food access and cultural fit
- Nausea and appetite limitations
- Avoid overly restrictive counseling

Lipid Lowering Agents

Bile Acid
Sequestrants

Omega-3
Fatty Acids

Fibrates

Niacin

Ezetimibe

PCSK9
Inhibitors

Lomitapide

Mipomersen

Inclisiran



Perinatal Outcomes After Statin Exposure During Pregnancy

Retrospective cohort 1,443,657 pregnant women

First infant born 2004-2014

Characteristic	Cohort, No. (%)		RR (95% CI) ^a
	Statin exposed (n = 469)	Statin unexposed (n = 4690)	
Neonatal outcome			
Preterm birth (<37 wk)	118 (25.2)	343 (7.3)	1.99 (1.46-2.71) ^b
Low birth weight (<2500 g)	72 (15.4)	312 (6.7)	1.51 (1.05-2.16) ^c
Very low birth weight (<1500 g)	17 (3.6)	24 (0.5)	2.41 (0.90-6.44)
Apgar score (<7)			
At 1 min	44 (9.4)	105 (2.2)	1.83 (1.04-3.20) ^c
At 5 min	9 (1.9)	21 (0.4)	0.96 (0.24-3.90)
Congenital anomaly	55 (11.7)	289 (6.2)	1.24 (0.81-1.90)
Fetal distress	31 (6.6)	158 (3.4)	1.01 (0.55-1.86)



Meta-Analysis of Pravastatin

5 studies published between 2003 and 2022

To evaluate the role of pravastatin, use prior to 20 weeks of gestation

Preeclampsia
61%

Preterm Birth
58%

IUGR
45%

NICU Admission
77%

FDA requests removal of strongest warning against using cholesterol-lowering statins during pregnancy; still advises most pregnant patients should stop taking statins
Breastfeeding not recommended in patients who require statins



Bile Acid Sequestrants: Useful, But Not “Free”

The non-systemic option can complicate triglycerides, tolerability, and absorption.



Where they fit

- Pregnancy or lactation
- Hypercholesterolemia without hypertriglyceridemia
- When medication is needed and statin is not used

What to watch

- Baseline and follow-up triglycerides
- Constipation and GI burden
- Drug and vitamin absorption considerations

How to make it work

- Medication timing plan
- Hydration and fiber strategy
- Repeat lipids if clinical status changes

Do not use a “pregnancy-safe” label without checking the patient’s triglyceride phenotype.

Medication Map: Pregnancy And Lactation

Therapy	Pregnancy	Lactation	Clinical use
Statins	Usually stop	Usually avoid	Consider continuation only in selected FH/ASCVD after benefit–risk discussion
Bile acid sequestrants	Reasonable	Reasonable	Hypercholesterolemia without high TG Monitor GI effects and TG
Fibrate	After 1st trimester if TG ≥ 500	Individualize	Lifestyle adjunct to reduce pancreatitis risk
High-dose omega-3 ethyl esters	Reasonable if TG ≥ 500	Individualize	Adjunct for severe fasting hypertriglyceridemia
Lipoprotein apheresis	Reasonable in HoFH	Reasonable in HoFH	Specialist center for severe inherited disease



Considerations in Pregnancy and Lactation

COR	RECOMMENDATIONS
1	Persons of childbearing age with hypercholesterolemia who <i>are not at high risk for ASCVD</i> and plan to become pregnant should <u>stop statin therapy 1 to 2 months before attempting to become pregnant or as soon as pregnancy is discovered</u> to avoid uncertain risks to the fetus.
2a	In <i>pregnant or lactating individuals with HoFH</i> , it is reasonable to undergo <u>lipoprotein apheresis</u> to lower LDL-C and reduce ASCVD risk.
2a	In pregnant individuals with <i>severe fasting hypertriglyceridemia TG ≥500 mg/dL [5.7 mmol/L]</i> , the use of <u>fibrates (after the 1st trimester) or high-dose omega-3 ethyl esters</u> is reasonable as an adjunct to lifestyle management to lower TG levels and reduce the risk of pancreatitis.



Considerations in Pregnancy and Lactation



COR	RECOMMENDATIONS
2a	In pregnant or lactating individuals with hypercholesterolemia but without hypertriglyceridemia , the use of <u>bile acid sequestrants</u> is reasonable to lower LDL-C.
2b	In pregnant individuals with FH or a history of clinical ASCVD , it <u>may be reasonable to continue statin</u> therapy to lower LDL-C and ASCVD risk following individualized benefit-risk discussion.

Lipid Management: Key Takeaways

Care should reflect the lipid phenotype, maternal risk and reproductive stage.

Plan before pregnancy. Reassess through lactation.



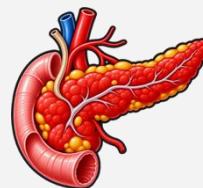
LDL-C

Prioritize lifestyle. Use bile acid sequestrants selectively when triglycerides are not elevated.



FH or ASCVD

Individualize statin decisions. Consider lipoprotein apheresis in HoFH.



TG ≥ 500 mg/dL

Reduce pancreatitis risk with a tailored diet and specialist-directed therapy.

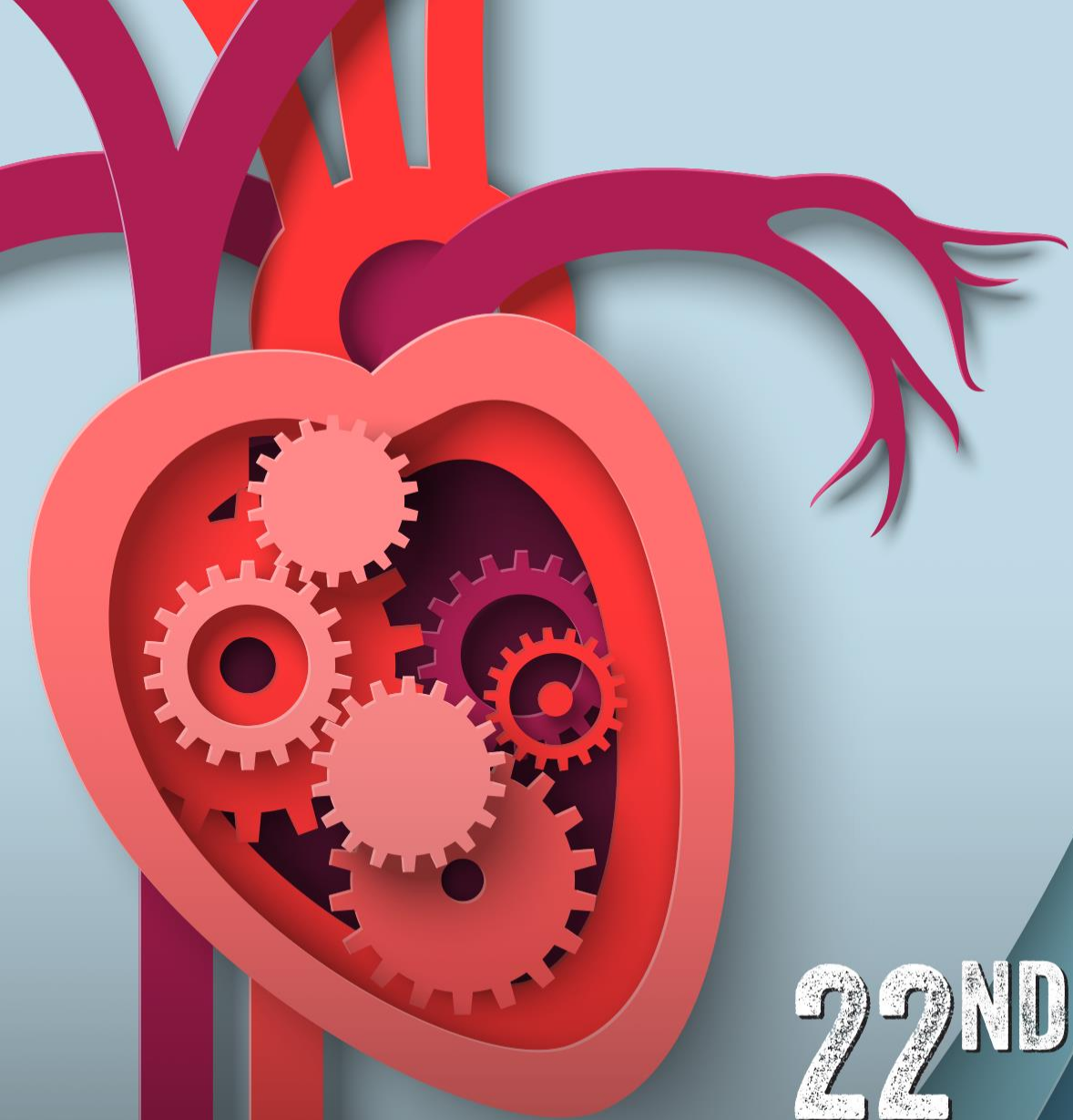


Postpartum

Balance lactation goals with maternal risk and plan when to resume therapy.

Thank You!





22ND ANNUAL MEETING & SCIENTIFIC SESSION



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Cardiovascular risk assessment in the age of PREVENT

Tammy Polonsky, MD, MSCI
University of Chicago Medicine



First, a case

- 33 yo woman referred to cardiology for palpitations
- PMH notable for hepatic steatosis, polyendocrine metabolic ovarian syndrome, IBS
- Meds – famotidine 20 mg BID
- SH – lives with her mother who does the cooking, doesn't track sodium, also eats out regularly
- FH – no premature CVD



Case, continued

- HR 88 BP 148/88, 250 lbs BMI 40.4 kg/m²
- Physical exam unremarkable
- Potassium 3.4, AST/ALT 46/108, Hba1c 5.9%
- Total cholesterol 215 HDL 44 TG 94 LDL 153
- BP has been high before, has only seen specialists, not primary care



The American Heart Association PREVENT™ Online Calculator

About the PREVENT Equations

 [Online Calculator](#)

Results for ASCVD

Estimated **10-year**
risk of ASCVD

2%

Estimated **30-year**
risk of ASCVD

12.7%



The American Heart Association PREVENT™ Online Calculator

Results for CVD

Estimated **10-year**
risk of CVD

2.9%

Estimated
PREVENT-Age

57
Years

Estimated **30-year**
risk of CVD

19.6%

Estimated 30 year
PREVENT-CVD risk

88th
percentile

In comparison, by age 60,
average woman's
risk of breast cancer is
3.54% (according to AI)



Foundation of risk assessment – Framingham Heart Study



1948	Framingham Heart Study begins	1970	Atrial fibrillation increases stroke risk 5-fold
1956	Findings on progression rheumatic heart disease reported	1976	Menopause found to increase the risk of heart disease
1957	High blood pressure and high cholesterol levels shown to increase likelihood of heart disease	1978	Psychosocial factors found to affect heart disease
1959	Some heart attacks discovered to be “silent” (causing no pain)	1988	High levels of HDL cholesterol found to reduce risk of death
1960	Cigarette smoking found to increase the risk of heart disease	1994	Enlarged left ventricle (one of two lower chambers of the heart) shown to increase the risk of stroke
1961	The term “risk factor” introduced	1996	Progression from hypertension to heart failure described
1961	Cholesterol level, blood pressure, and electrocardiogram abnormalities found to increase the risk of heart disease	1998	Framingham Heart Study researchers identify that atrial fibrillation is associated with an increased risk of all-cause mortality
1967	Physical activity found to reduce the risk of heart disease and obesity to increase the risk of heart disease	1998	Development of simple coronary disease prediction algorithm involving risk factor categories to allow physicians to predict multivariate coronary heart disease risk in patients without overt CHD
1970	High blood pressure found to increase the risk of stroke		



Initial Framingham risk score

- For primary prevention population without diabetes
- Predicted 10-year risk of coronary heart disease (myocardial infarction or coronary death)
- Variables included age, sex, total and HDL cholesterol, SBP, use of antihypertensive medication, smoking status



From Framingham Risk Score to Pooled Cohort Equations 2013

- Provided more contemporary cohorts that better represented modern prevalence of risk factors
- More geographically and racially diverse
- Included 10-year and lifetime risk of ASCVD for adults ages 40-75
- Included stroke as an outcome
- Variable for race (Black and white)
- Variable for diabetes status



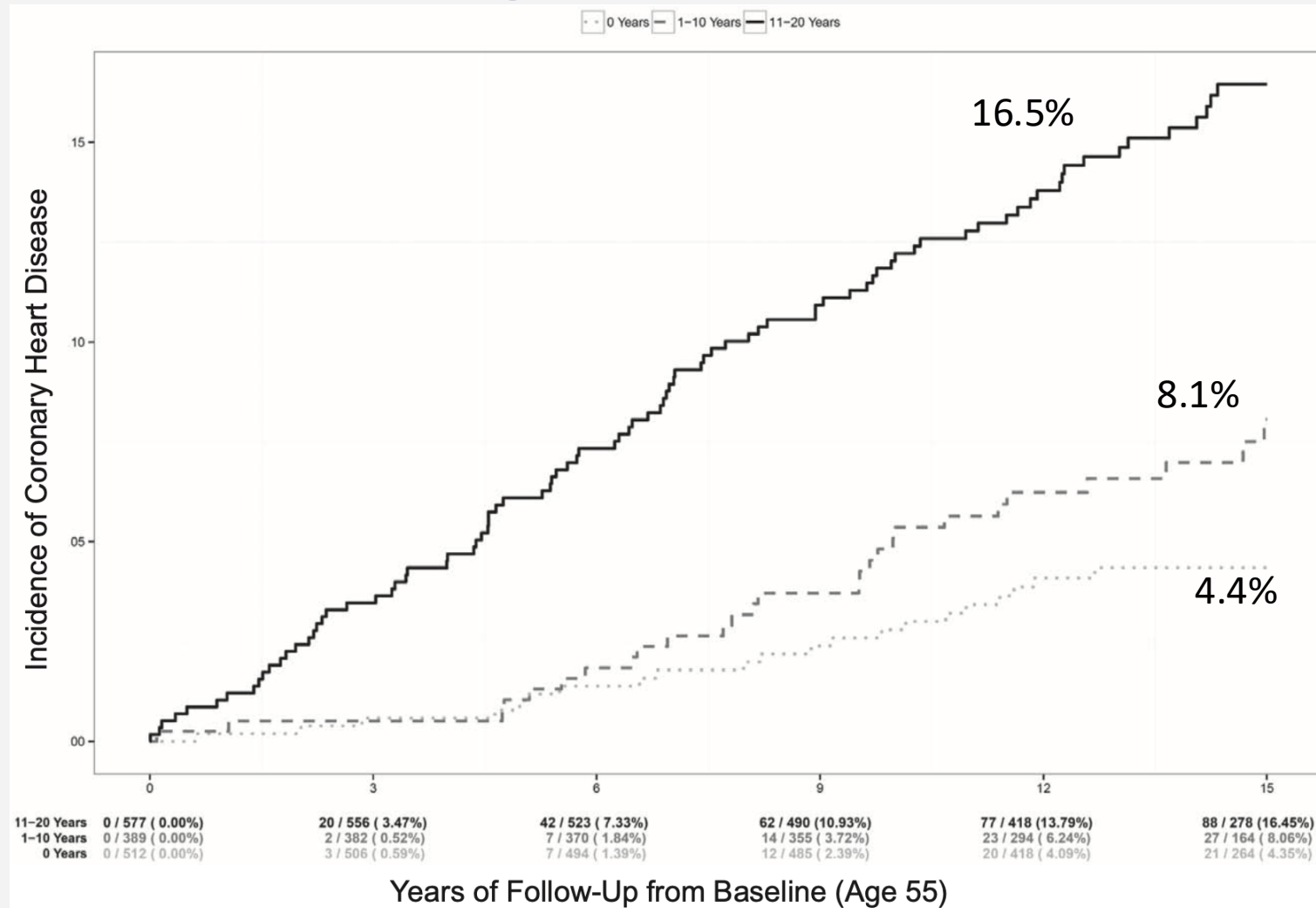
Importance of “lifetime risk”

- Participants of CARDIA, ages 32-47 at time of exam

	Men			Women		
	Low Short-Term Risk/Low Lifetime Risk	Low Short-Term Risk/High Lifetime Risk	High Short-Term Risk	Low Short-Term Risk/Low Lifetime Risk	Low Short-Term Risk/High Lifetime Risk	High Short-Term Risk
CARDIA						
Age-adjusted baseline CAC prevalence, %	9.8	16.7*	26.9*	2.3	7.1*	20.6*
CAC positive/total	50/543	117/704	36/120	18/808	55/770	9/43
Baseline CAC (Agatston) score, adjusted mean (SE)	6.8 (5.2)	12.9 (4.6)	50.7 (11.2)*	1.7 (0.9)	3.3 (0.9)	19.5 (3.7)*

Berry et al. *Circulation* 2009

15-year risk of CHD based on years of exposure to non-HDL >160 mg/dl



Navar-Boggin et al.
Circulation
2015;131:451-458



Evolution in prevention

- PCE shown in several populations to overestimate risk
- Health care disparities between white and Black adults in US is related to structural factors such as racism, access to care, not biological factors
- Greater understanding of interplay between kidney disease, metabolic factors and CVD (CKM syndrome)
- Rising incidence of heart failure
- Expansion in medications to treat heart failure and metabolic risk
- Greater sophistication in use electronic health record data in research



Changes in risk assessment with PREVENT

- Includes real-world contemporary patient data
- Includes 2nd database of lab data
- Adds BMI and eGFR to risk calculator
- Optional addition of zip code, UACr, A1c
- Expands age range to 30-79
- Expands outcomes to CVD, ASCVD and HF
- Reports 10-year and 30-year risk
- Better calibrated and so more accurate than PCE
- 10-year risk estimates average 40-50% lower than with PCE leading to changes in risk thresholds used for lipid-lowering therapy



The American Heart Association PREVENT™ Online Calculator

[About the PREVENT Equations](#)

[Online Calculator](#)

CVD

ASCVD

Heart Failure

Sex*

☒ Male ☐ Female

Age (years)*

30-79

SBP (mmHg)*

90-200

Total Cholesterol (mg/dL)*

130-320

HDL Cholesterol (mg/dL)*

20-100

eGFR (mL/min/1.73m²)*

15-140

BMI (kg/m²)*

18.5-39.9

Diabetes

Any history of diabetes.

☒ No ☐ Yes

Current Smoking

Any cigarette use within the last 30 days

☒ No ☐ Yes

Lipid-lowering medication

Current use of statin medication to lower cholesterol

☒ No ☐ Yes

Anti-hypertensive medication

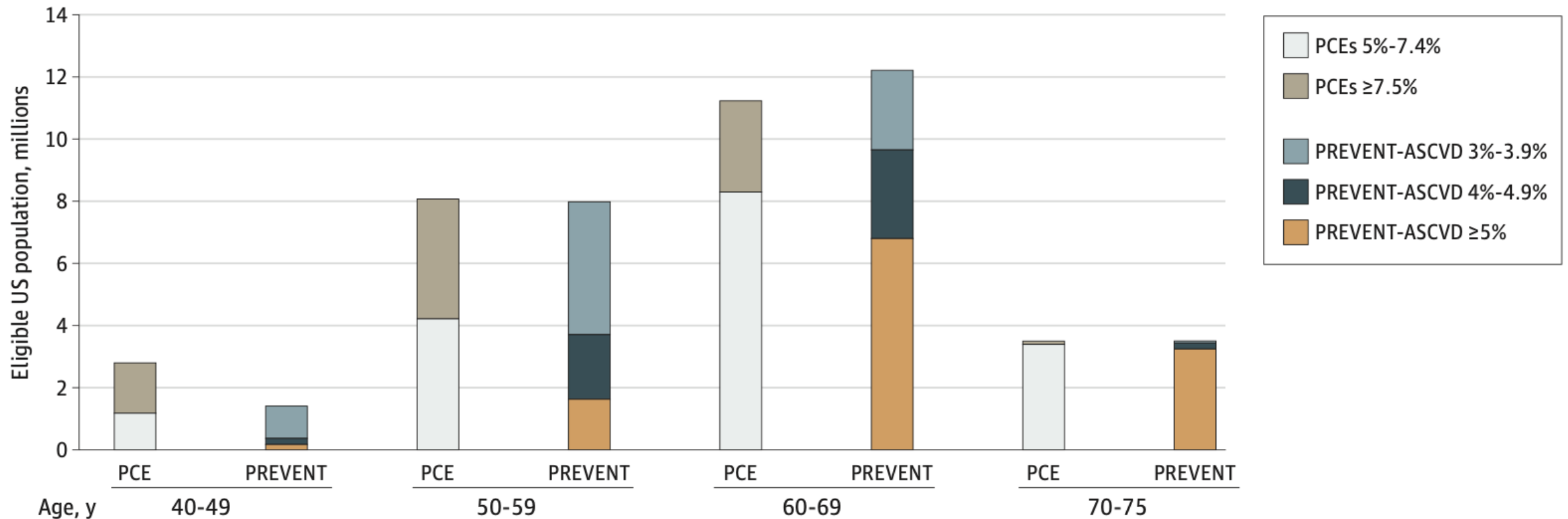
Current use of any medication for hypertension

☒ No ☐ Yes



Statin eligibility based on PREVENT vs PCE

11.8 million adults with PREVENT score >5%, 17 million adults with PCE $\geq$ 7.5%



SS Khan et al. *JAMA Cardiol* 2025



How NOT to use PREVENT

- 28 yo woman with known high cholesterol presents to resident primary care clinic
- Has been told for many years she has high cholesterol
- Father had stents in his early 50s
- Siblings on cholesterol medication
- Her most recent LDL was 180 mg/dL, wants to know if she should take medication
- Faculty preceptor in clinic said shouldn't start medication yet because too young to calculate a PREVENT score



What risk scores can and cannot do

- CAN provide an important first step in shared decision-making
- CANNOT be used to determine whether to treat patients with familial hypercholesterolemia
- CANNOT fully encompass all of the factors that may affect a person's eligibility for lipid-lowering therapy
 - Risk enhancing factors help further personalize risk assessment
 - Not all factors that affect a person's risk will be included in a risk score



Back to our patient



Use of Risk-Based Thresholds for Initiation of BP Treatment in Adults

BP Level-Only

Does the patient have an average BP $\geq 140/90$ mm Hg?

YES

Initiate antihypertensive medications to lower BP and reduce CVD risk for primary or secondary prevention of CVD

1

NO

Risk-Based Thresholds for Initiation of BP Treatment for Adults*

Does the patient have existing clinical CVD (CHD, stroke, HF)?

YES

Initiate antihypertensive medications to lower BP and reduce CVD risk if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg for secondary prevention of CVD

1

NO

Does the patient have diabetes or CKD, or is the patient at increased short-term risk of CVD (10-year PREVENT-CVD risk $\geq 7.5\%^{\dagger}$)?

YES

Initiate antihypertensive medications to lower BP and reduce CVD risk if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg for primary prevention of CVD

1

NO

Initiate antihypertensive medications to lower BP if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg after 3-6 months of lifestyle intervention

1

LEGEND

- COR 1
- COR 2a
- COR 2b
- COR 3-No Benefit
- COR 3-Harm

(Class of Recommendation)



2025 High Blood Pressure

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2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Recommendations for Diagnostic Approach to CKM Staging (Continued)

COR	LOE	Recommendations
2a	B-NR	2. Among adults at intermediate 10-y risk for ASCVD (PREVENT -ASCVD 5% to <10%) or select adults at borderline risk for ASCVD (PREVENT -ASCVD 3% to <5%) for whom decisions about preventive therapies remains uncertain, the presence of subclinical coronary atherosclerosis identified via coronary artery calcium (CAC) can be beneficial for informing optimal CVD prevention . ⁴⁻⁶
2a	B-NR	3. Among adults with increased predicted 10-y risk of HF (PREVENT -HF ≥5%), evaluation for pre-HF using cardiac biomarkers (natriuretic peptides [B-type natriuretic peptide (BNP) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)], high-sensitivity cardiac troponin [hs-cTn]) can be beneficial to guide additional diagnostic testing (eg, cardiac imaging) and coordinated care for optimal HF prevention . ⁷⁻¹⁰



Back to our patient

- Referred to dietitian to discuss lowering sodium intake
- Agreed to measure her pressure everyday, scheduled for virtual visit in 6 weeks
- Seeing endocrine next month for PMOS
- Referred to hepatology for hepatic steatosis
- Deferred discussions of lipid-lowering therapy until after blood pressure resolved

