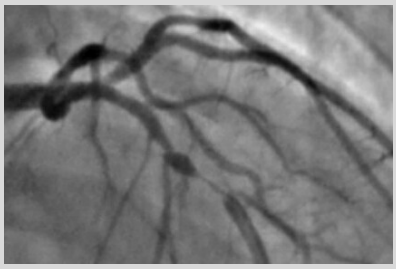

Preventive Cardiology

Atherosclerotic Cardiovascular Disease Risk Prediction & Coronary Artery Calcium Scoring

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Disclosures

- **Site PI, EVOLVE-MI**: A Pragmatic Randomized Multicenter Trial of EVOLocumab Administered Very Early to Reduce the Risk of Cardiovascular Events in Patients Hospitalized With Acute Myocardial Infarction (Amgen, Inc.)
- **Site Co-investigator, HORIZON**: A randomized double-blind, placebo-controlled, multicenter trial assessing the impact of lipoprotein(a) lowering with pelacarsen (TQJ230) on major cardiovascular events in patients with established cardiovascular disease (Novartis Pharm.)
- **Site Co-investigator, ACCLAIM-Lp(a):** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Lepodisiran on the Reduction of Major Adverse Cardiovascular Events in Adults with Elevated Lipoprotein(a) who have Established Atherosclerotic Cardiovascular Disease or Are at Risk for a First Cardiovascular Event (Eli Lilly & Co.)
- **Site Co-investigator, MUIR-3**: Double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of plozasiran (ARO-APOC3) in adults with hypertriglyceridemia. (Arrowhead Pharmaceuticals, Inc.)

Objectives

- Discuss the recommended **screening evaluation** and **risk prediction tools** for primary atherosclerotic cardiovascular disease (ASCVD) prevention.
- Reference the recently updated **recommended risk-based treatment goals** for primary and secondary ASCVD prevention.
- Understand the basic **technical aspects** of and **indications** for **coronary artery calcium** (CAC) scoring.

Common Questions

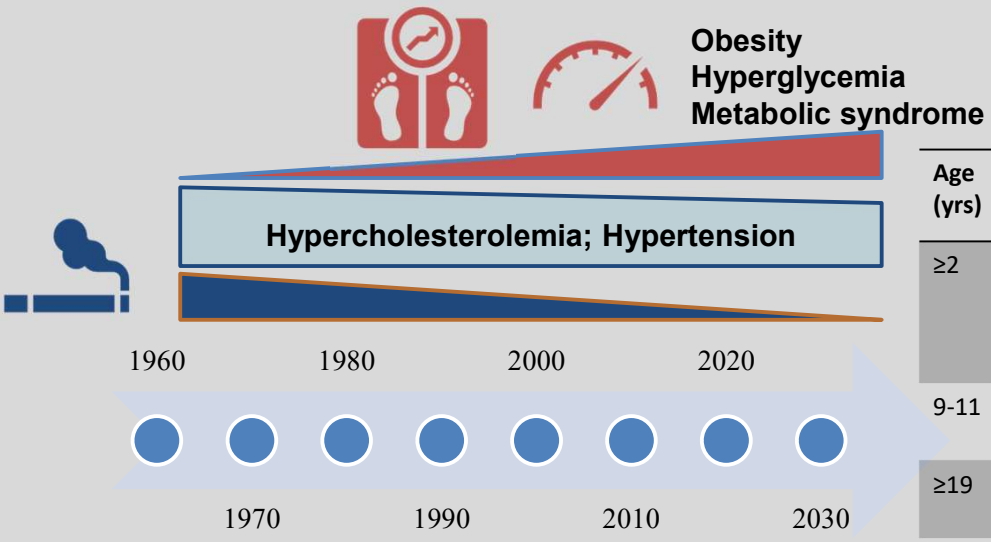
I was prescribed a statin, but do I really need it?

Is that risk estimate really applicable to me?

I'm on a statin, but should I have an even lower treatment goal?

Evolving Drivers of ASCVD

Lipid profile screening recommended, non-fasting OK; fasting if high TG

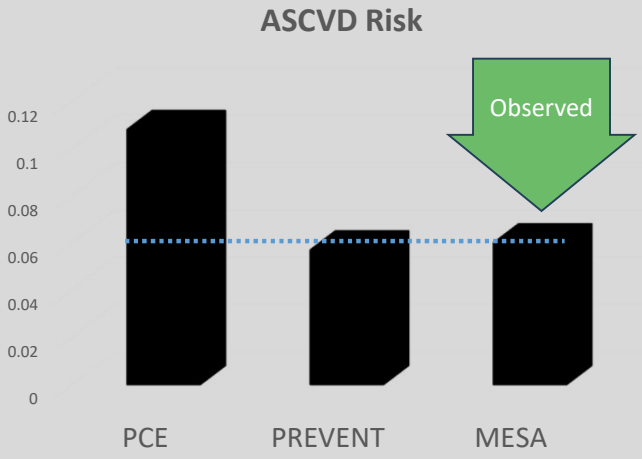


Age (yrs)	Population
≥2	1º or 2º relatives of individuals with premature ASCVD or FH (Class 2a)
9-11	Children not previously screened (Class 1)
≥19	Adults not previously screened (Class 1)

Writing Cmte Members; Blumenthal RS, et al. *J Am Coll Cardiol*. 2026 Mar 13:S0735-1097(25)10254-4.

PREVENT Model

- Predicting Risk of CVD Events (PREVENT) model released in 2023
- Includes ASCVD and/or heart failure outcomes
- Estimates 10- and 30-yr risk
- Optional refining predictors
  - Urine albumin-creatinine ratio
  - Hemoglobin A1c
  - Social deprivation index
- Risk better aligned with outcomes than pooled cohort eq.



Murphy BS, et al. *JACC Adv* 2025 Jun;4(6 Pt 1):101825.

PREVENT Model: Inputs

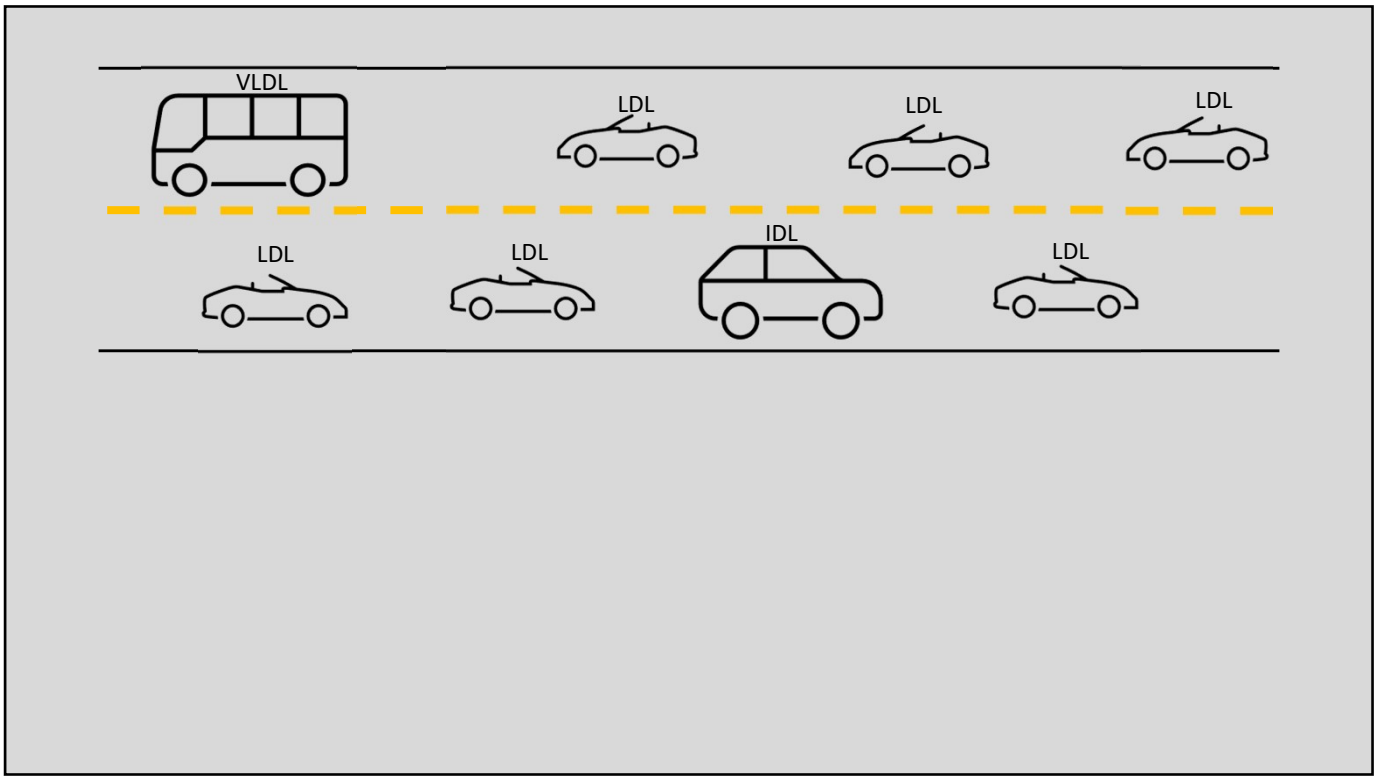
LDL not included

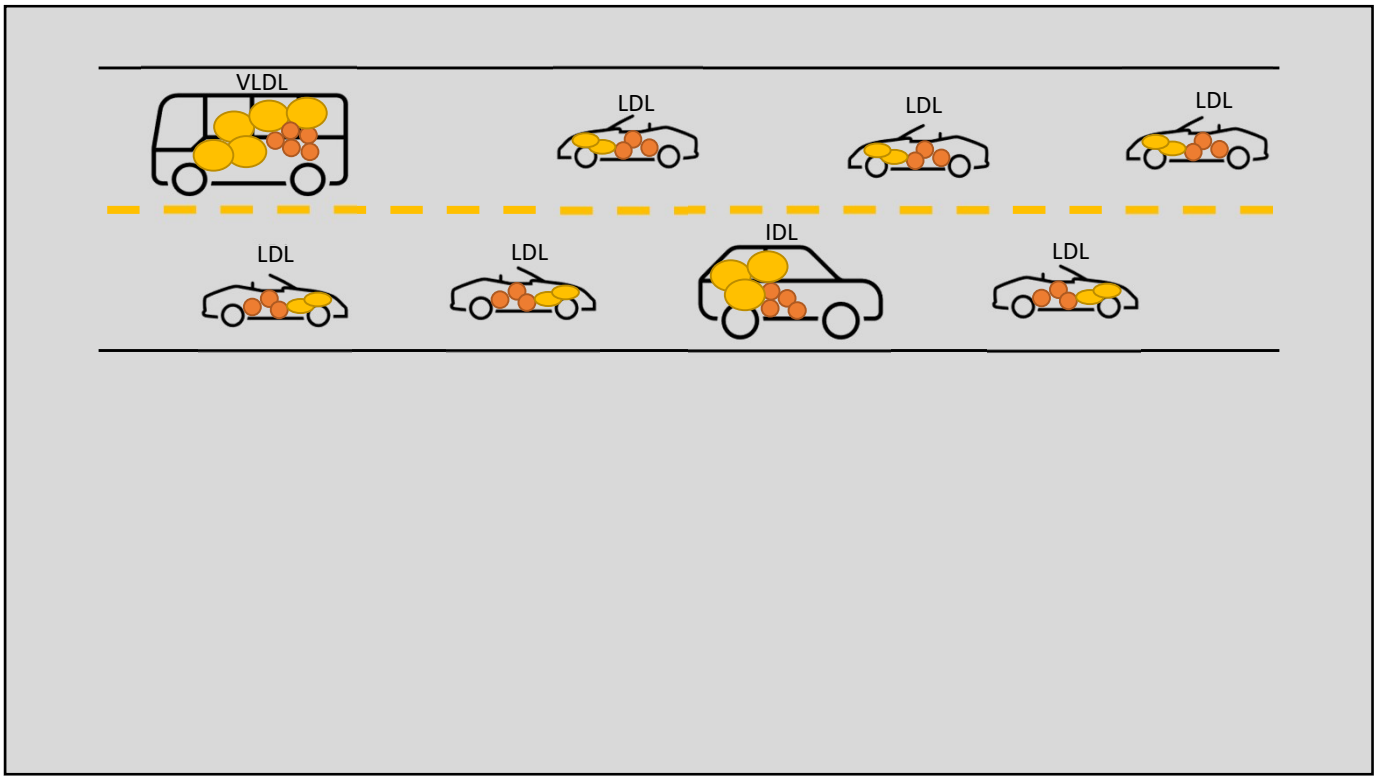
Variable	Categorical / Nominal	Numeric
Required inputs	Sex Smoking status Diabetes mellitus Lipid-lowering medication use Anti-hypertensive medication use	Age Total cholesterol HDL cholesterol eGFR (ml/min/1.73m^2)
Optional inputs	Zip Code (corresponds to the social deprivation index)	Urine albumin creatinine ratio Hemoglobin A1c

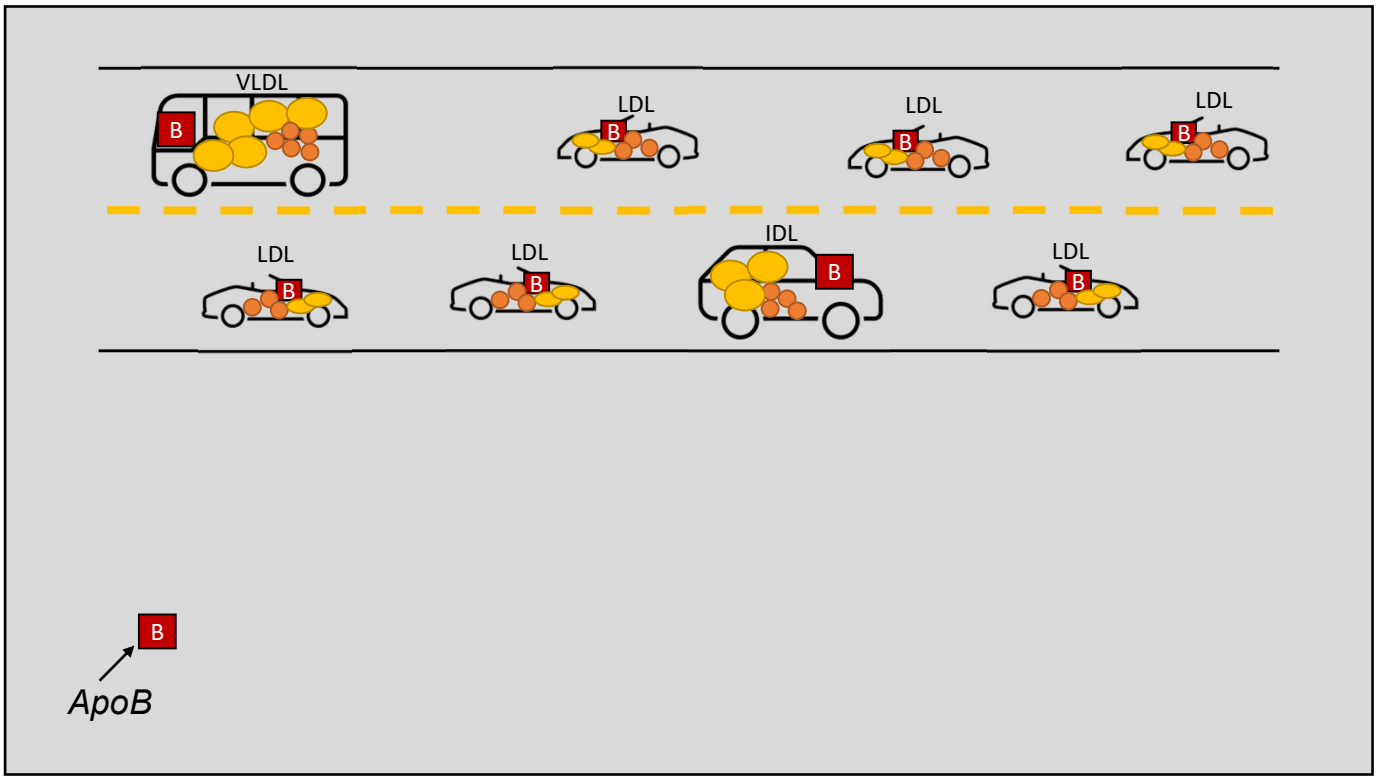
Khan SS, et al. *Circulation* 2024;149(6):430–449

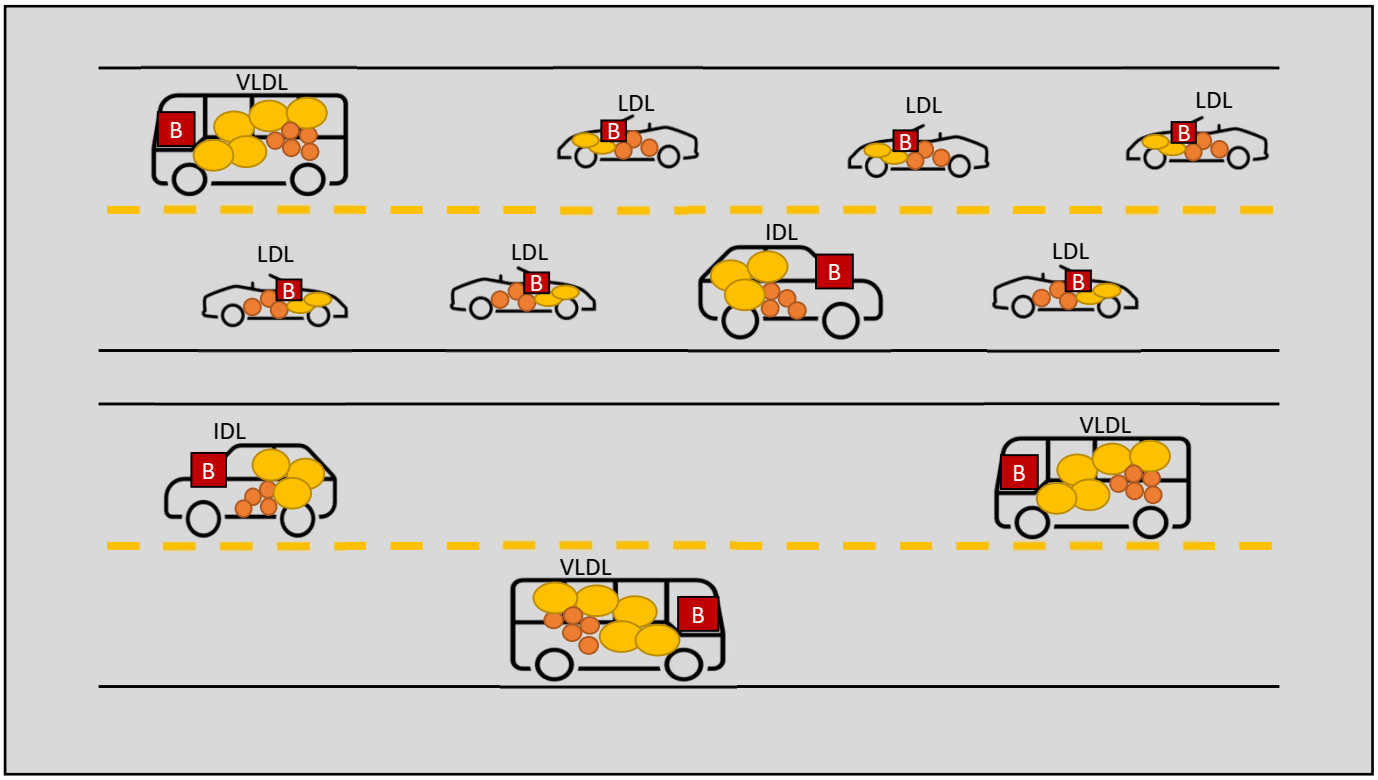
Lipoprotein Analogy

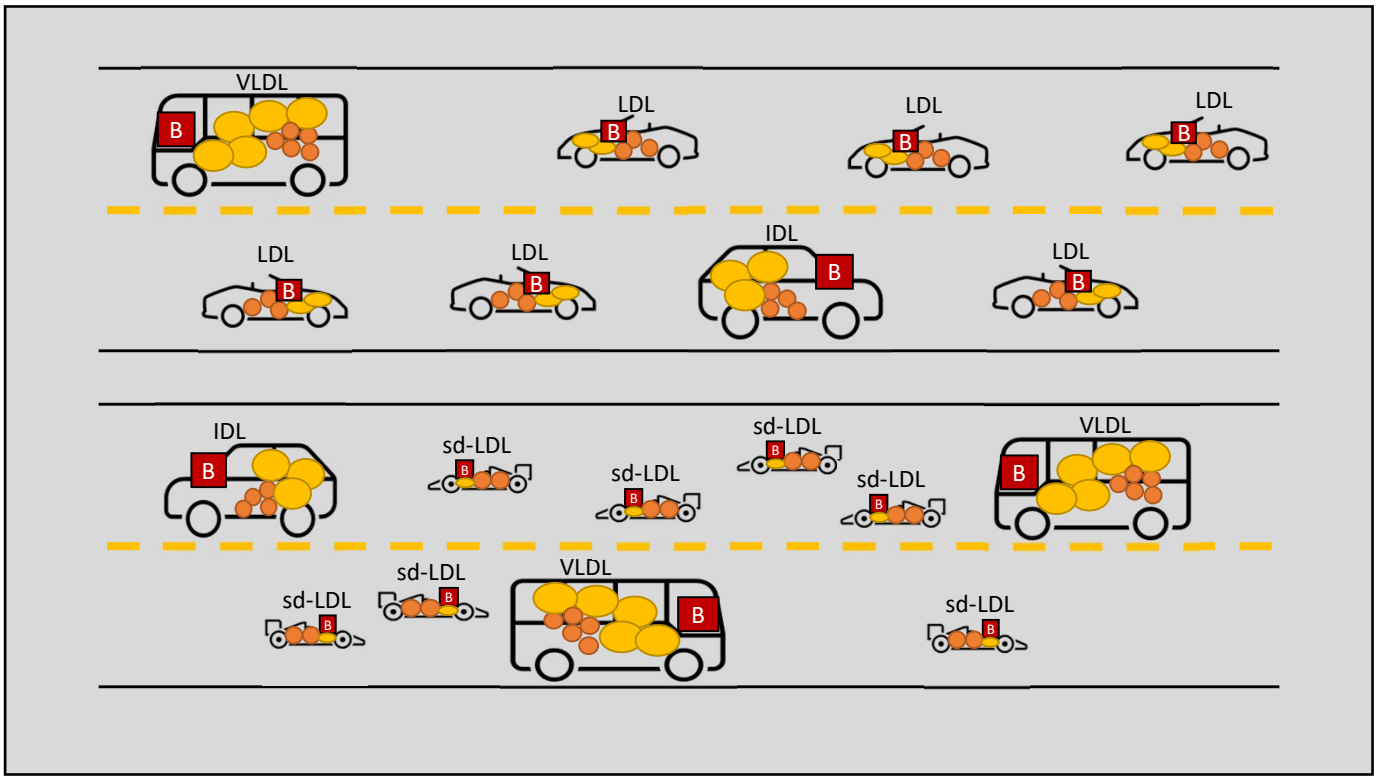
Concept adapted from Sniderman, A. D., et al. (2019). *JAMA Cardiol* 4(12): 1287-1295. | Graphics original.


VLDL
LDL
LDL
LDL
LDL
LDL
IDL
LDL


VLDL
LDL
LDL
LDL
LDL
LDL
IDL
LDL


VLDL
LDL
LDL
LDL
LDL
LDL
IDL
LDL
B
ApoB


VLDL
LDL
LDL
LDL
LDL
LDL
IDL
LDL
IDL
VLDL
VLDL
B


VLDL
LDL
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VLDL
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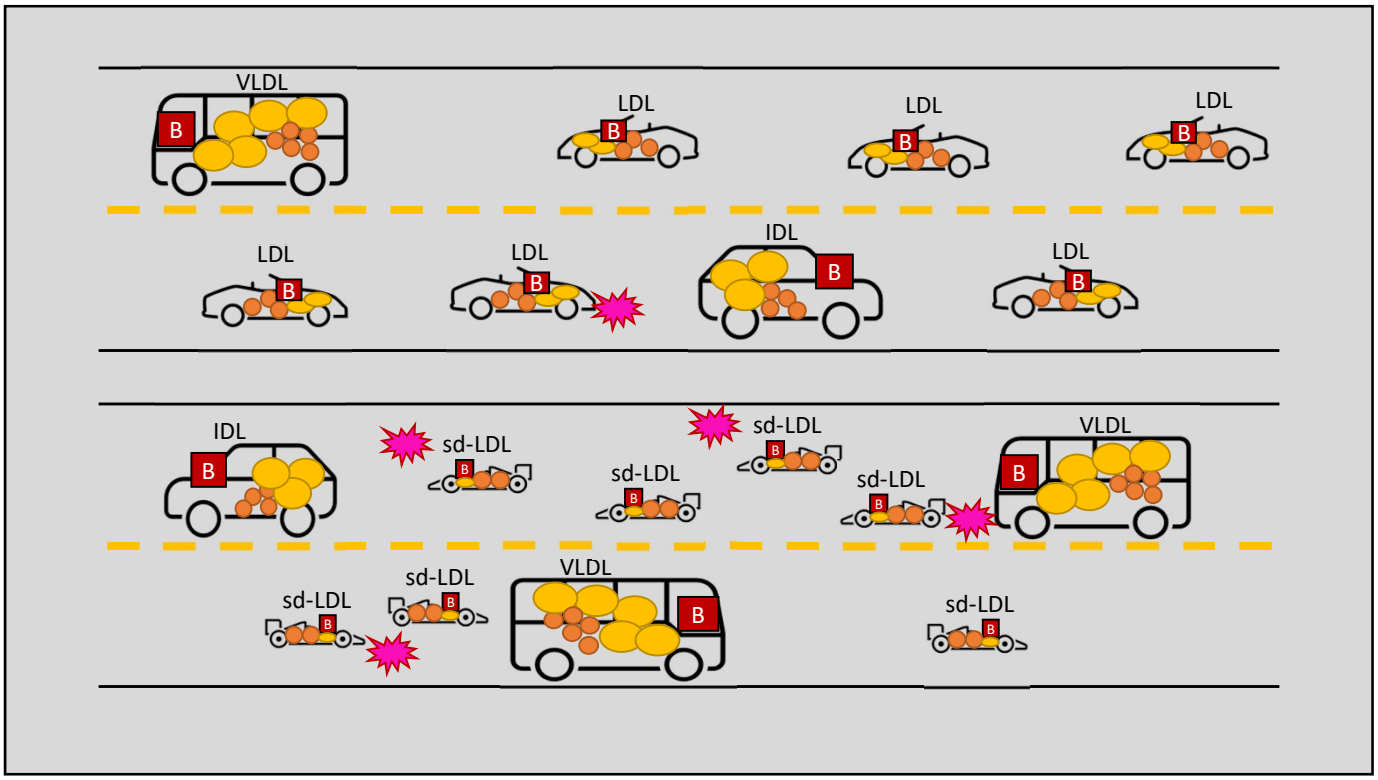
VLDL
sd-LDL


VLDL
LDL
LDL
LDL
LDL
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IDL
LDL
IDL
sd-LDL
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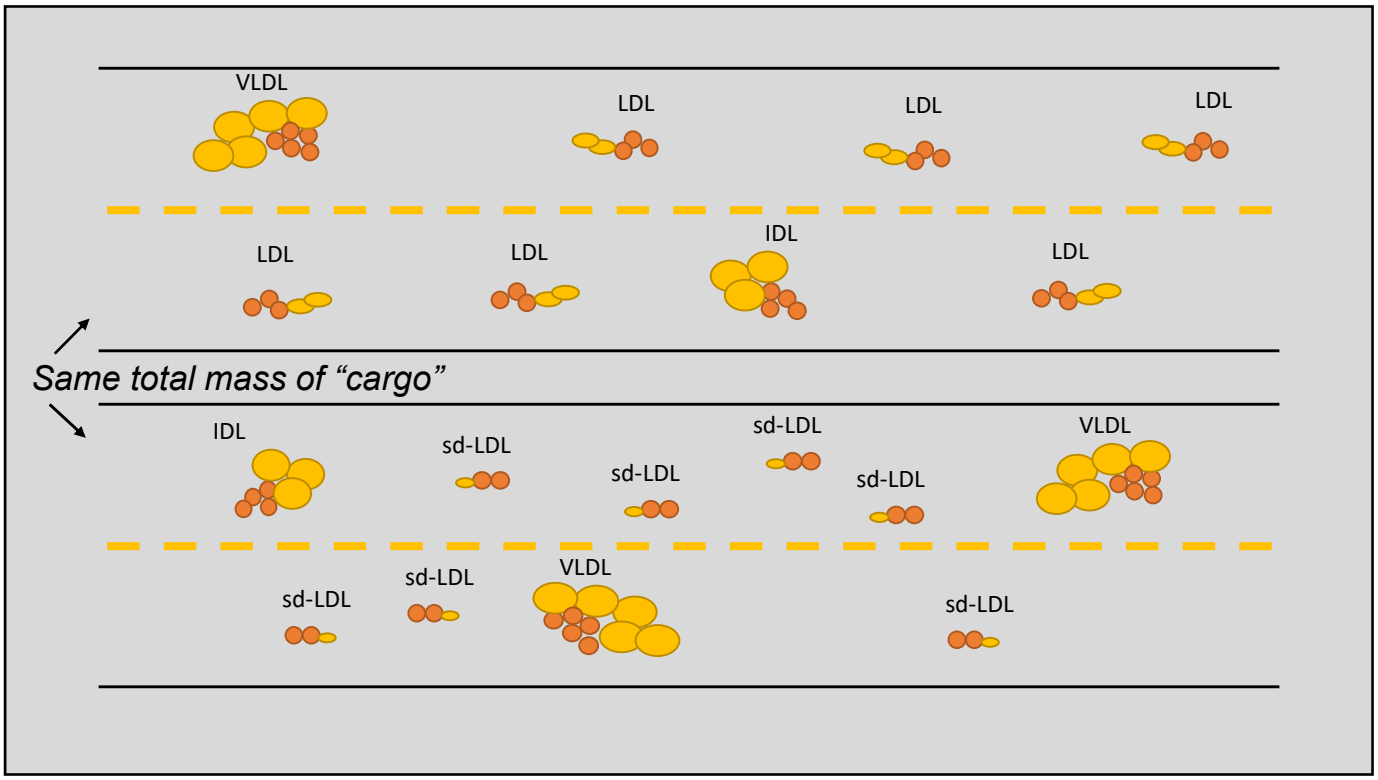
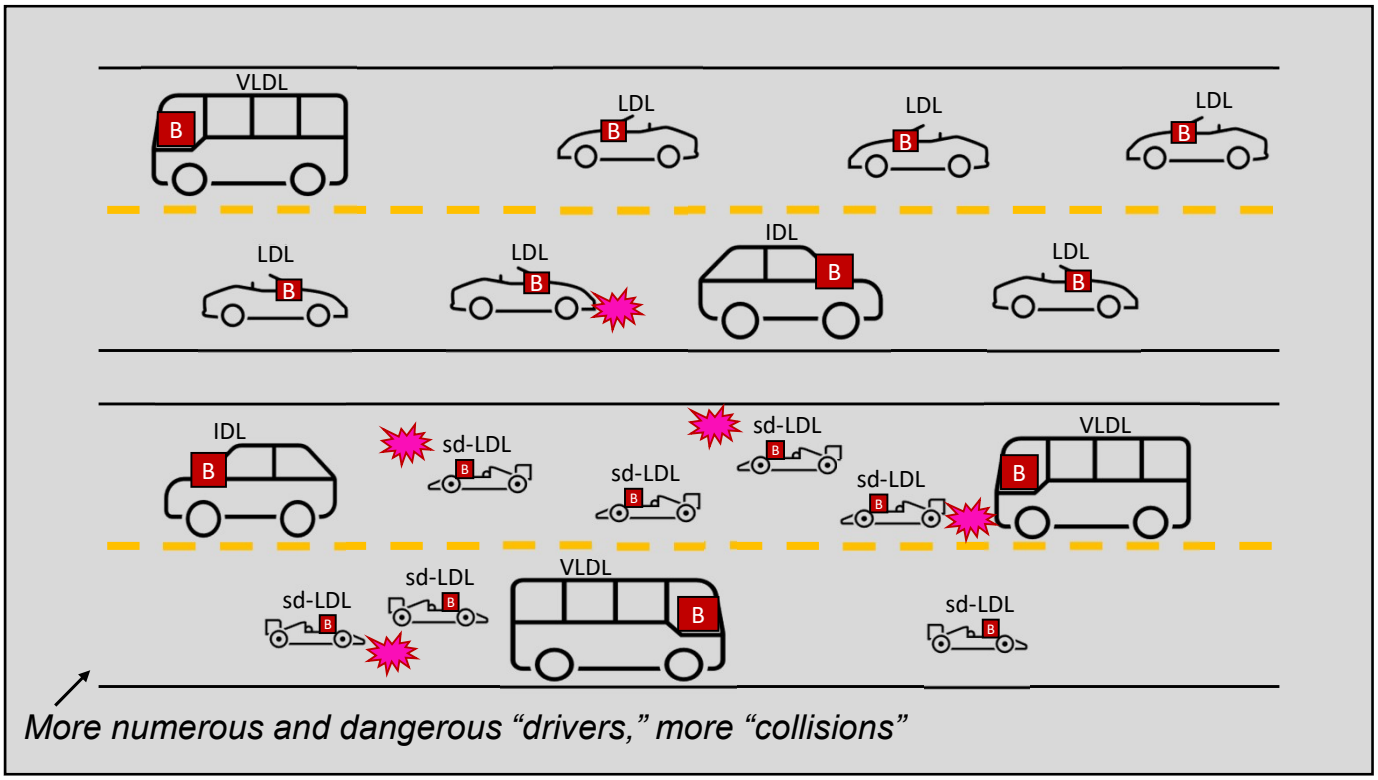
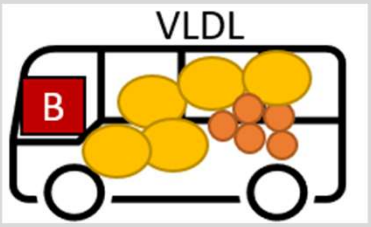
sd-LDL
sd-LDL
VLDL
sd-LDL
sd-LDL
VLDL
sd-LDL

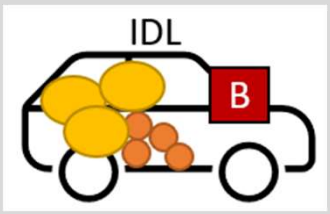

VLDL
LDL
LDL
LDL
LDL
LDL
IDL
LDL
Same total mass of "cargo"
IDL
sd-LDL
sd-LDL
sd-LDL
sd-LDL
VLDL
sd-LDL
sd-LDL
VLDL
sd-LDL


VLDL
LDL
LDL
LDL
LDL
LDL
IDL
LDL
IDL
sd-LDL
sd-LDL
sd-LDL
sd-LDL
VLDL
sd-LDL
sd-LDL
VLDL
sd-LDL
More numerous and dangerous "drivers," more "collisions"

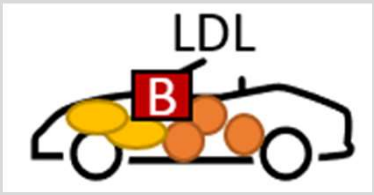
Apolipoprotein B

- **ApoB and non-HDL-C** levels **correlate with risk** better than LDL-C
- When discordance exists, ApoB is the best predictor of risk
- **ApoB measurement is reasonable** to guide treatment (Class 2a)
  - Especially in CKD metabolic syndrome, T2DM, elevated TG





LDL is one of many "dangerous vehicles on the road"



Best Predictor

ApoB > **non-HDL-C** > **LDL-C**

Writing Cmte Members; Blumenthal RS, et al. *J Am Coll Cardiol*. 2026 Mar 13:S0735-1097(25)10254-4.

PCE vs. PREVENT Model: Output

Risk category (10-yr ASCVD)	Pooled cohort equations	PREVENT model (new)
Low	< 5%	< 3%
Borderline	5 – 7.5%	3 – 5%
Intermediate	7.5% – 20%	5 – 10%
High	≥ 20%	≥ 10%

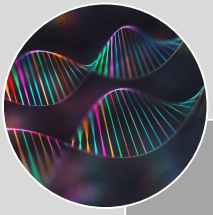
- Estimates from contemporary **PREVENT-ASCVD** equations are about **40-50% lower** than older pooled cohort equations (PCE) values
- **Similar numbers of US adults recommended** to consider statin therapy using PCE ≥ 5% or PREVENT-ASCVD 10-yr risk of ≥ 3%
- **Net benefit** (benefit > potential harm) for statin treatment threshold: **≥ 3%**

Writing Cmte Members; Blumenthal RS, et al. *J Am Coll Cardiol*. 2026 Mar 13:S0735-1097(25)10254-4.

ASCVD Risk Enhancing Factors

Cardiovascular-kidney-metabolic (CKM) syndrome
Chronic inflammatory diseases
Reproductive risk markers

Elevated lipoprotein(a) >125 nmol/l
Elevated triglycerides (≥ 150 fasting)
LDL-C persistently ≥ 160 mg/dl
hsCRP ≥ 2 mg/dl (≥ 2 occasions)

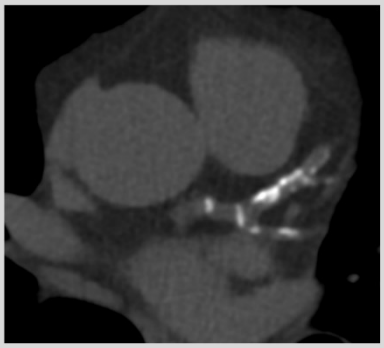


Family history of premature CAD
Ancestry (e.g. South Asian, Filipino)
High polygenic risk

Writing Cmte Members; Blumenthal RS, et al. *J Am Coll Cardiol*. 2026 Mar 13:S0735-1097(25)10254-4.

Coronary Artery Calcium Scoring

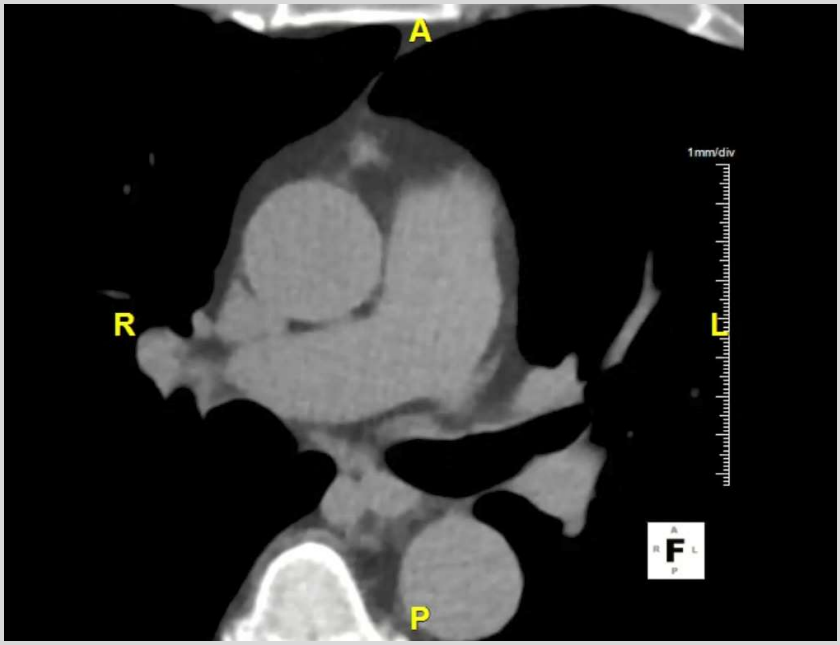
- Acquisition
  - Axial imaging, non-contrast
  - Prospective triggering
  - Potential 120 kVP
  - Current 120-150 mAs
- Radiation exposure usually ≤ 1.5 mSv
- Scoring using Agatston method
- Slice thickness 2.5-3 mm



Density factor	Peak HU of calcium
0	0-129
1	130-199
2	200-299
3	300-399
4	≥400

Harfi TT, Cardona A, Rajpal S, Villines TC. Am. Coll. Cardiology Self Assessment Program, 2021

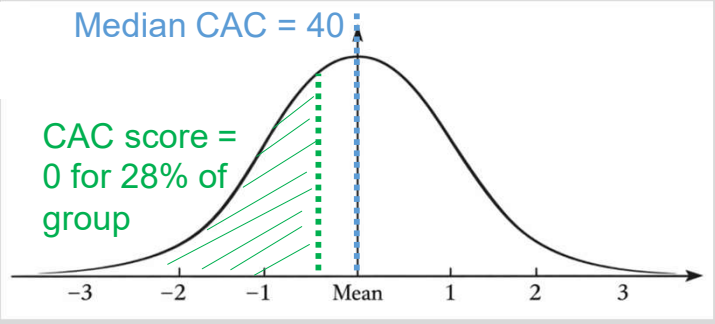
Video - Coronary Artery Calcium Scoring - CT Images



MESA CAC Normative Values

- Multi-Ethnic Study of Atherosclerosis (MESA): prospective, multi-ethnic cohort **without diabetes or known ASCVD**
- Follow-up for 10 yrs

62-year-old white males



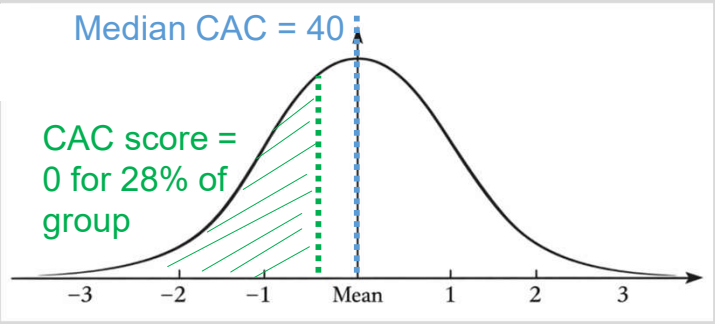
McClelland RL, et al. *Circulation*. 2006;113(1):30-37.

MESA CAC Normative Values

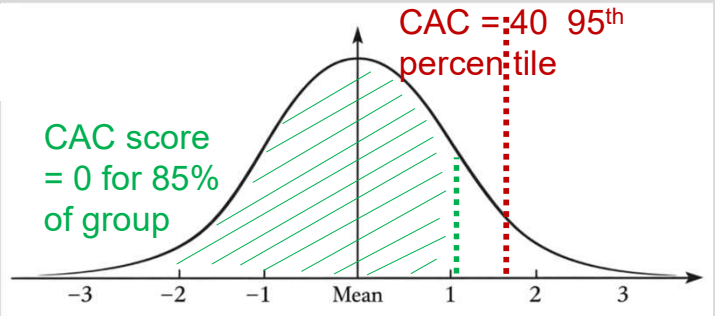
- Multi-Ethnic Study of Atherosclerosis (MESA): prospective, multi-ethnic cohort **without diabetes or known ASCVD**
- Follow-up for 10 yrs

Examples, both with CAC score of 40 Agatston Units

62-year-old white males



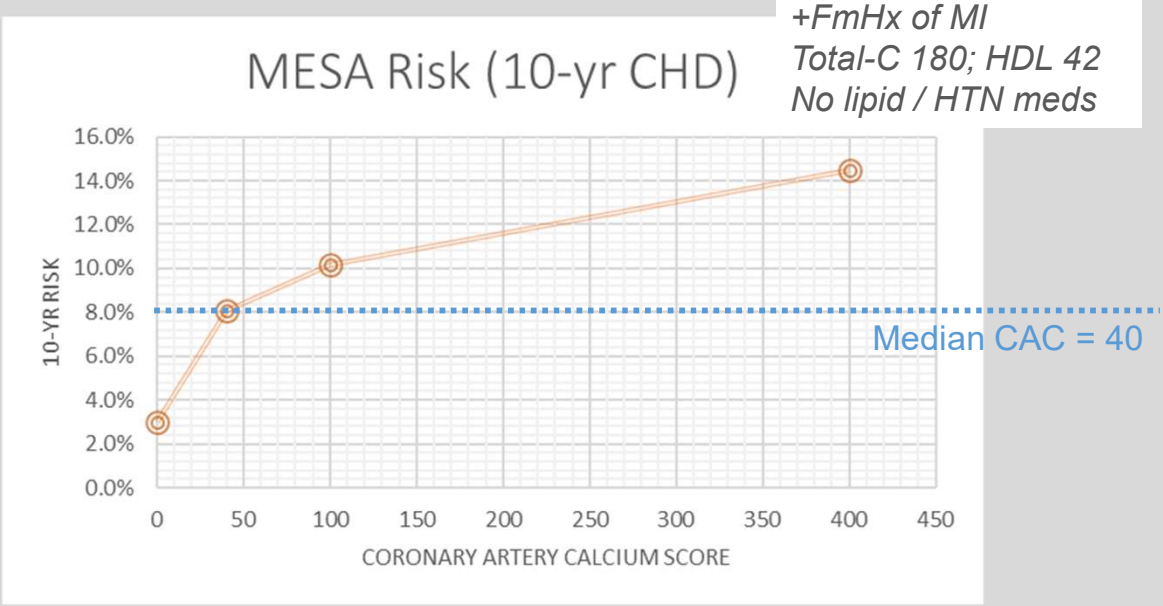
50-year-old black females



McClelland RL, et al. *Circulation*. 2006;113(1):30-37.

MESA CAC-Revised Risk

62 year-old male
No DM or smoking
+FmHx of MI
Total-C 180; HDL 42
No lipid / HTN meds



Blaha MJ, et al. *J Am Heart Assoc* 2021 Mar 16;10(6):e019351. https://mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx

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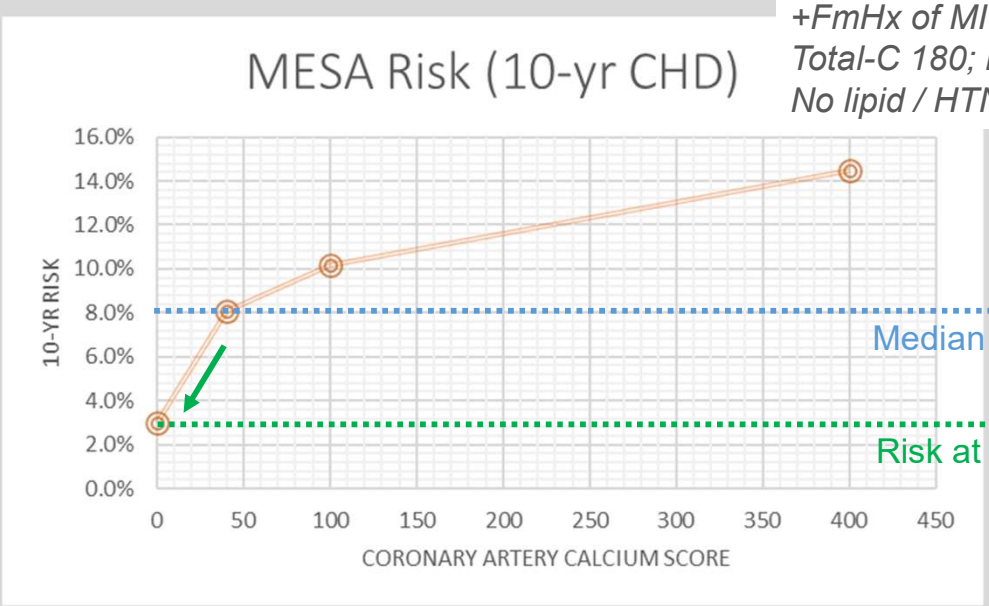

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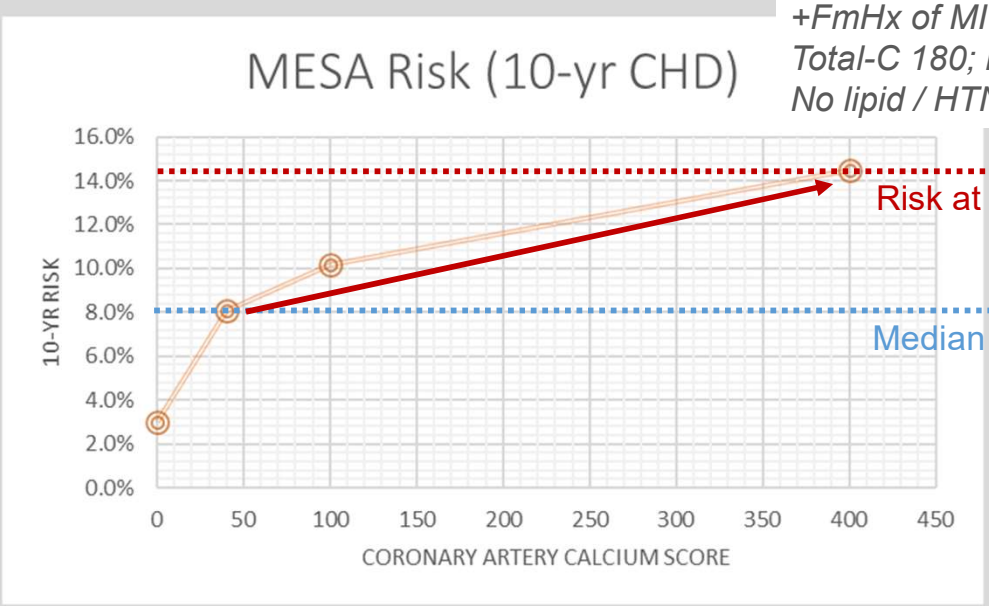

Blaha MJ, et al. *J Am Heart Assoc* 2021 Mar 16;10(6):e019351. https://mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx

Risk-Based Treatment Goals

Population (selected/abridged)	LDL-C goal (mg/dl)	Non-HDL goal (mg/dl)	ApoB goal (mg/dl)
Primary prevention, low-intermediate risk PREVENT-ASCVD <10%	< 100	< 130	**< 90** With TG ≥ 150
Primary prevention, high risk PREVENT-ASCVD ≥10% **Diabetes mellitus, with risk factors**	< 70	< 100	**< 70** With TG ≥ 150
Subclinical atherosclerosis [CAC scores in Agatston u.] Mild (CAC score 1-99 and <75th%ile) Moderate (CAC 100-299, or ≥75th%ile) Severe (CAC 300-999) Extensive (CAC ≥ 1000)	 < 100 < 70 < 55* < 55	 < 130 < 100 < 85* < 55	 < 55*[*optional]
Clinical ASCVD	< 70 (< 55*)	< 100 (< 85*)	< 55*
Clinical ASCVD, very high risk / with CKD	< 55	< 85	< 55

Writing Cmte Members; Blumenthal RS, et al. *J Am Coll Cardiol*. 2026 Mar 13:S0735-1097(25)10254-4.

Key Points

- The **PREVENT** calculator has replaced and is more contemporarily accurate than the prior Pooled Cohort Equation model
- Statin treatment and achievement of specific lipoprotein goals (LDL, Non-HDL, and/or ApoB) should be considered when the **PREVENT-ASCVD 10-yr risk ≥ 3%**
- **Risk enhancing factors** may lead to significant deviation from the initial calculated risk estimates and require clinical judgement
- Coronary artery calcium **(CAC) assessment can guide treatment** strategies powerfully in primary ASCVD prevention

The Lp(a) Paradigm Change

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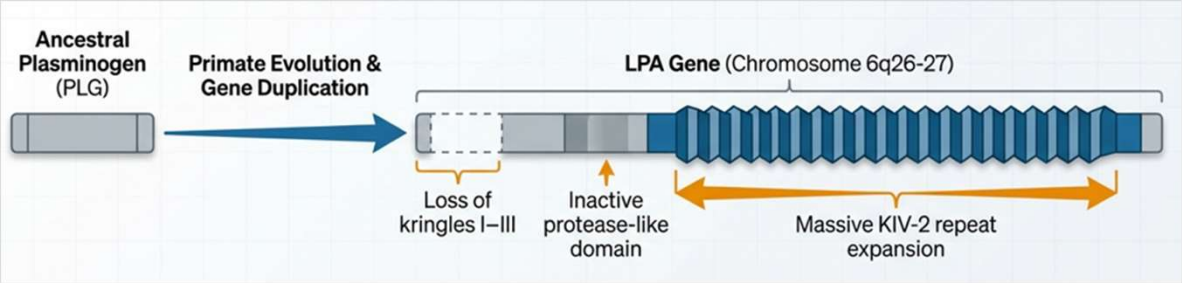
MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Objectives

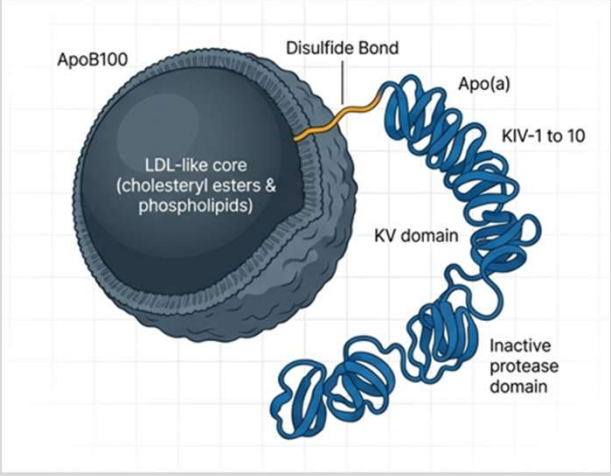
- Review the origin, structure and function of Lp(a)
- Discuss the role of Lp(a) in cardiovascular disease
- Outline contemporary management strategies for elevated Lp(a)
- Discuss future perspectives
- Review the role of aspirin in primary prevention
- Present the case for hsCRP use in ASCVD risk

The LPA gene was created by duplication of the plasminogen gene



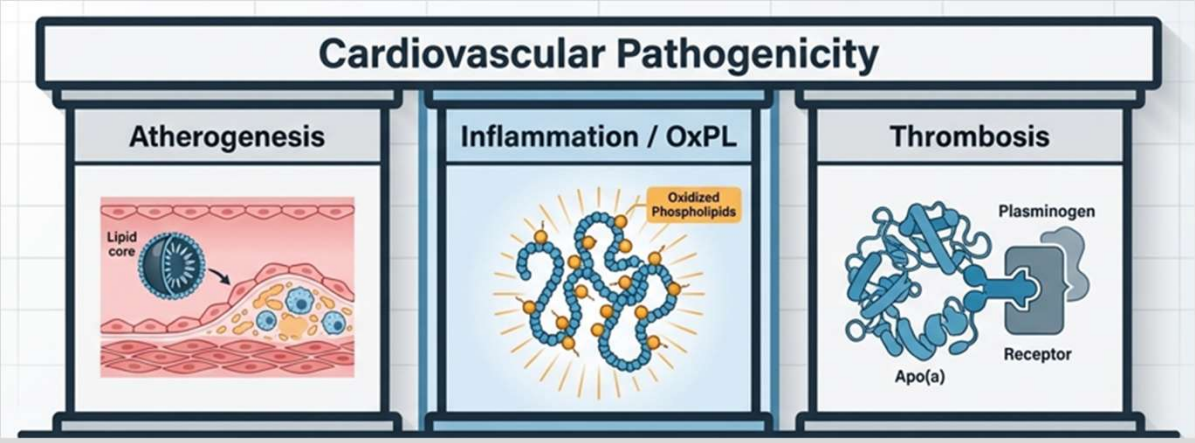
McLean et al. Nature 1987
Lawn et al. PNAS 1997

Lp(a) is an LDL-like particle with covalently linked apo(a)



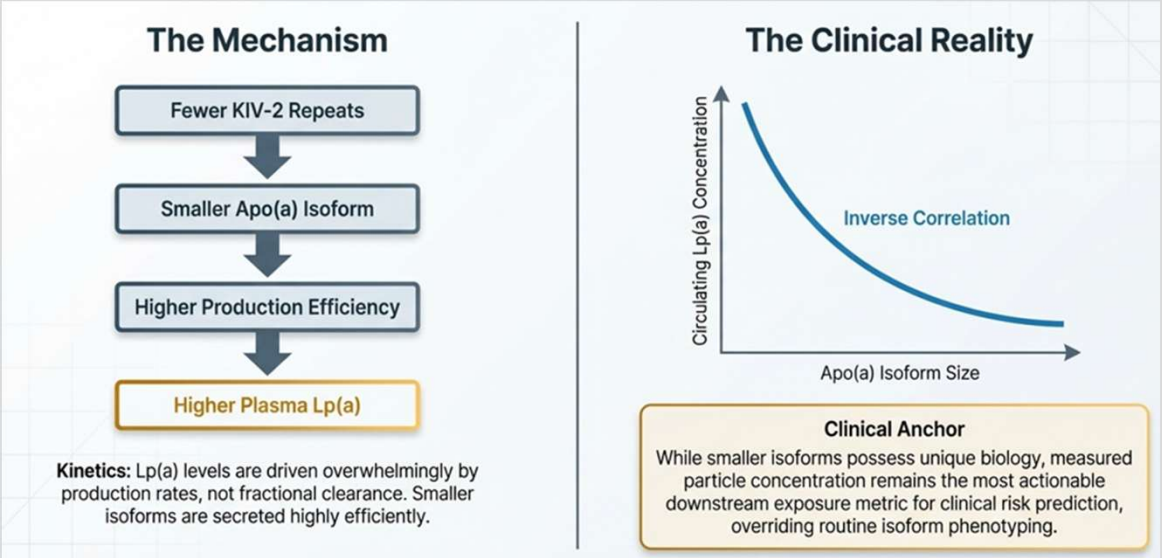
Nordestgaard et al. Eur Heart J 2010

Lp(a) has multiple atherogenic effects



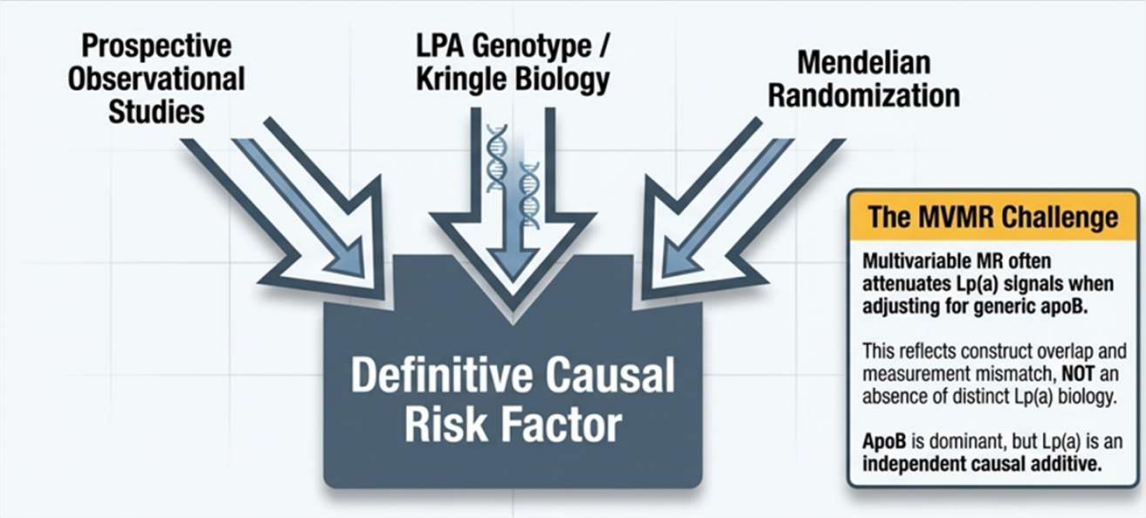
Kroneberg F et al. Circulation 1999
Tsimikas S et al. JACC 2012

Lp(a) levels are genetically determined



Utermann et al. JCI 1987
Lackner et al. JCI 1991

Multiple lines of evidence converge on Lp(a) as an important ASCVD risk factor



Clarke et al. NEJM 2009
Kamstrup et al. JAMA 2009

2026 AHA guidelines for dyslipidemia

Measure Lp(a) at least once in adulthood

Elevated Lp(a) is an ASCVD risk enhancer

Risk Thresholds	
≥ 125 nmol/L →	~1.4x increased MI/Stroke risk
≥ 250 nmol/L →	≥ 2.0x increased risk

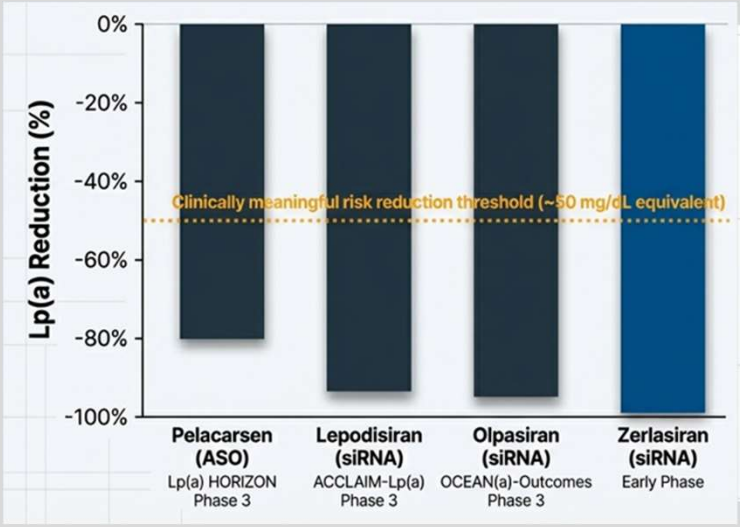
Blumenthal et al. Circulation 2026

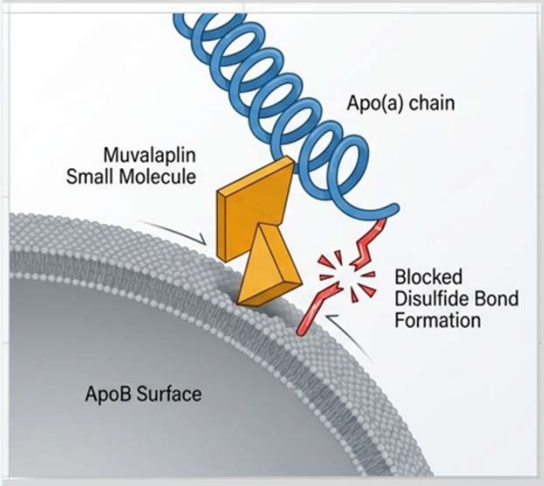
Current lipid lowering drugs have small if any effects on Lp(a)

Therapy Class	Effect on Lp(a)
Statins	None / Slight Increase
Ezetimibe / Bempedoic Acid / Fibrates	None
PCSK9i (mAbs) / Inclisiran	-20% to -30%
Niacin	-20% to -30%
Lipoprotein Apheresis	High reduction

Wilson et al. JCL 2022

Highly anticipated therapies for Lp(a) in the near future





Zhang et al. Eur Heart J 2026

2026 Bottom Line

The Biomarker is Settled:

Lp(a) is a genetically determined, causal cardiovascular risk factor driving atherogenesis, OxPL inflammation, and thrombosis.

Screening is Mandatory:

Measure once. Treat high levels as a definitive risk enhancer warranting aggressive global risk reduction.

The Ultimate Question:

We can now lower Lp(a) by 80-99%. The ongoing Phase 3 trials will answer the definitive question: **Will specific Lp(a) reduction yield the hard cardiovascular event reductions predicted by human genetics?"**

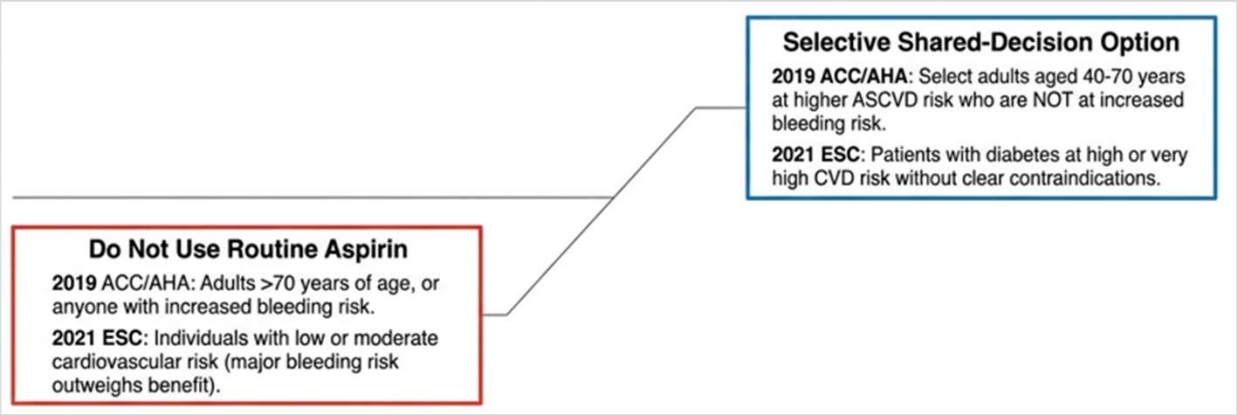
Aspirin in primary prevention

Recent aspirin trials weaken the case for primary prevention use

Trial	Population	Efficacy Signal	Bleeding Signal
ASPREE	19,114 healthy older adults (median age 74)	CV events 10.7 vs 11.3 per 1,000 PY Not Significant	Major hemorrhage 8.6 vs 6.2 per 1,000 PY
ASCEND	15,480 adults with diabetes	MACE 8.5% vs 9.6%	Major bleeding 4.1% vs 3.2%
ARRIVE	12,546 moderate-risk adults (nondiabetic)	Primary endpoint 4.3% vs 4.5% No Benefit	GI bleeding 0.97% vs 0.46%

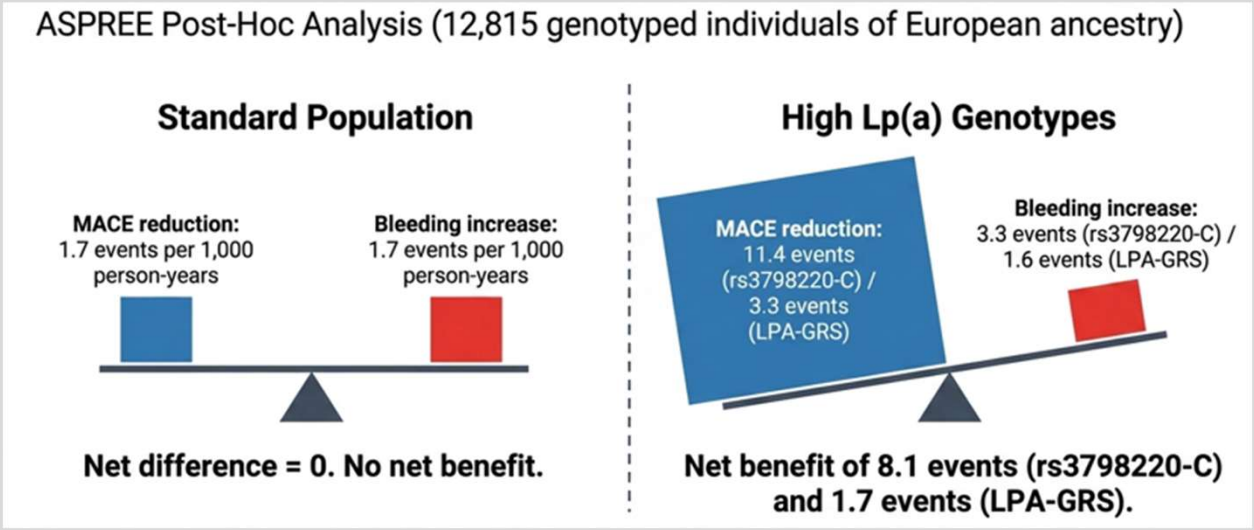
McNeil et al. NEJM 2018
ASCEND Collaborative Group. NEJM 2018
Gaziano et al. Lancet 2018

Society guidelines limit role of aspirin for primary prevention



Arnett et al. Circulation 2019
Visseren et al. Eur. Heart J. 2021

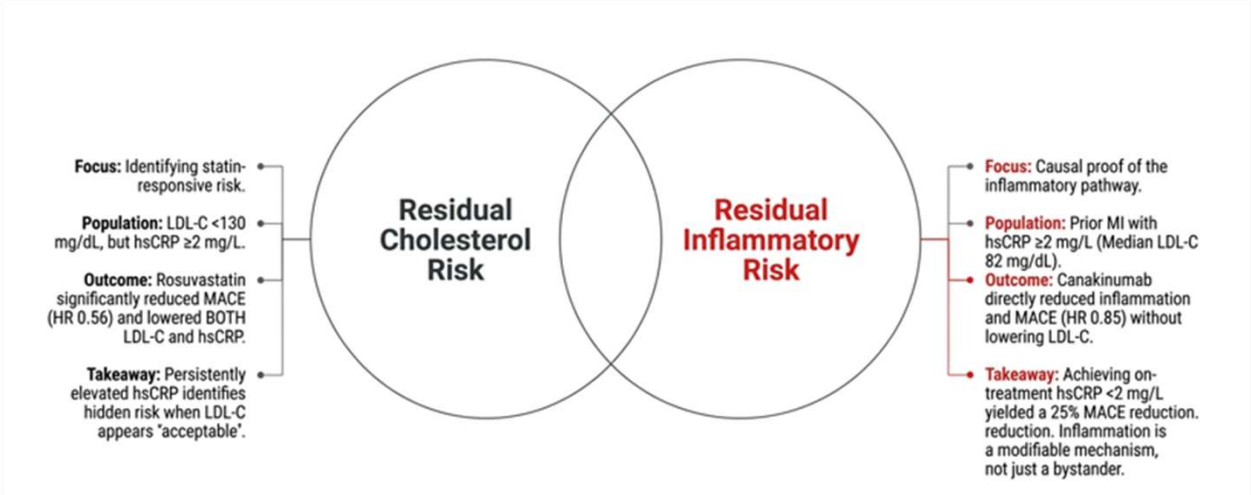
The role of Lp(a) as an effect modifier for aspirin



Lacaze et al. JACC 2022

hsCRP in primary prevention

The inflammatory cascade in atherosclerosis



Ridker et al. NEJM 2008
Ridker et al. NEJM 2017

The role of hsCRP in primary prevention

2026 ACC/AHA/Multisociety Dyslipidemia Guideline Framework

hsCRP ≥2 mg/L (measured on >1 occasion)

Low Risk (<3%)	Borderline Risk (3% to <5%)	Intermediate Risk (5% to <10%)	High Risk (≥10%)

Clinical Applications

Primary Prevention: Used to personalize treatment when baseline risk is uncertain or underestimated by standard lipid assessment. Strengthens the case for statin therapy.

Secondary Prevention: Signals residual inflammatory risk even when LDL-C is aggressively controlled.

Crucial Caveat

Do not over-interpret single values; always evaluate for active infection, trauma, or nonvascular autoimmune inflammatory causes before escalating therapy.

Blumenthal et al. Circulation 2026