Lipids in Women: Time for a Paradigm Shift

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“Woman” was the term used in the original studies on the topic and was presumably used to describe female sex assigned at birth. I’ll be using it in the same context.

Disclosures

None

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Objectives

Conceptualize an approach to **integrate data** into a **patient-level** decision

- Understand the impact of hypercholesterolemia as a function of **time**, **concentration**, and **context** / **inflammation**
  - ASCVD is an product of time spent “under the curve”
  - Female hormones influence on cardiovascular disease differently
- Understand the impact of **sex-specific life events** on cardiovascular risk
  - Age of menarche, adverse pregnancy events, menopause

Not in scope: Secondary prevention, hypertriglyceridemia

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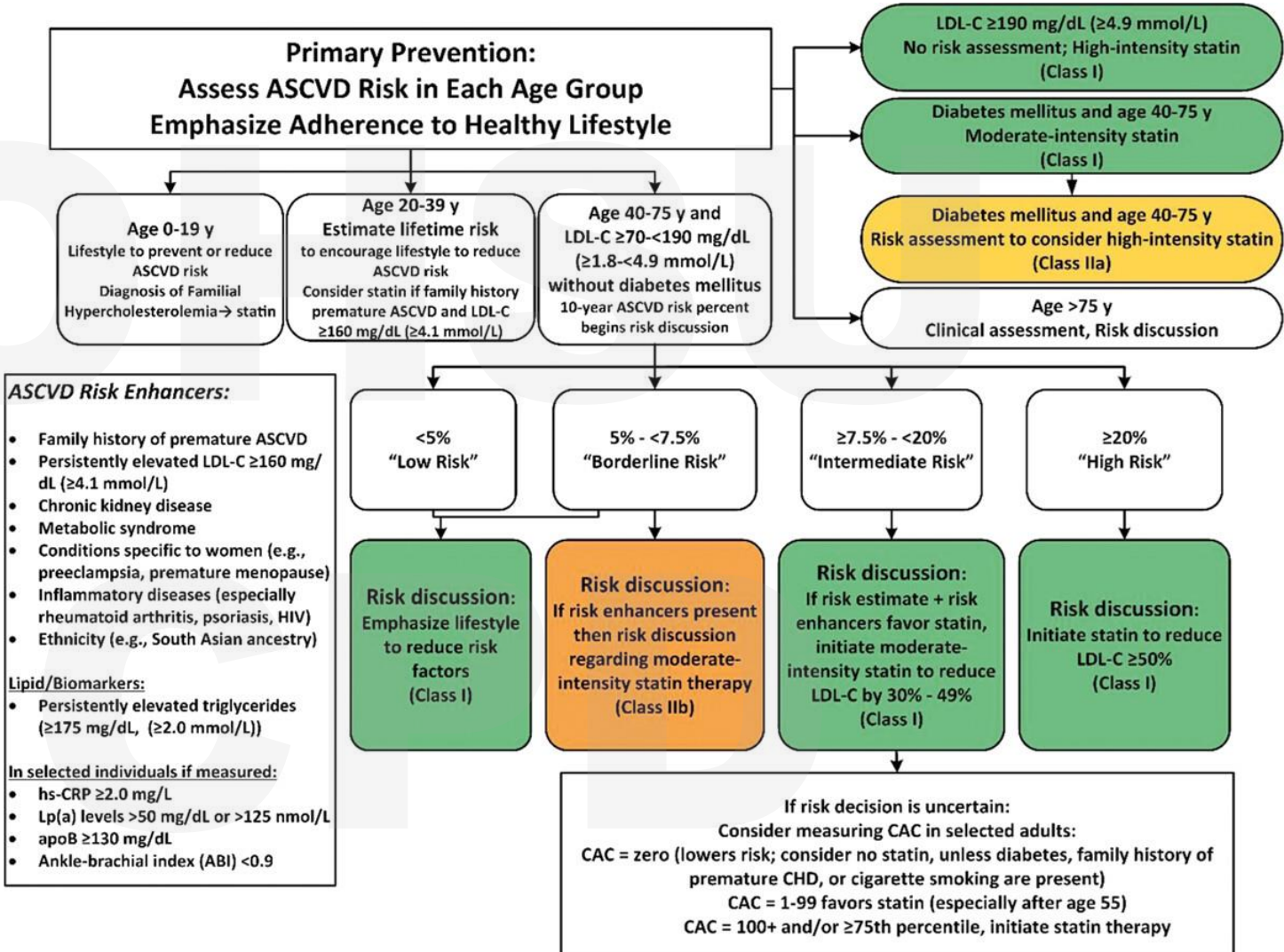
2018 Guideline

- PCSK9i data was newly published
  - Cost-prohibitive
- Primary prevention was NOT the focus of recent studies
- CAC testing was still relatively underutilized



2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association

American Heart Association.

Calculators

- Observational, logs many characteristics
- Determines relationship of variables to outcome
- Weighted equation derived to provide probability

Pooled-cohort equations (**PCE**, ~2013):

- 5 different datasets, 25,000 individuals
  - Strictly research protocols
- Specific to White and Non-black Hispanic patients
- No kidney disease
- 40-79

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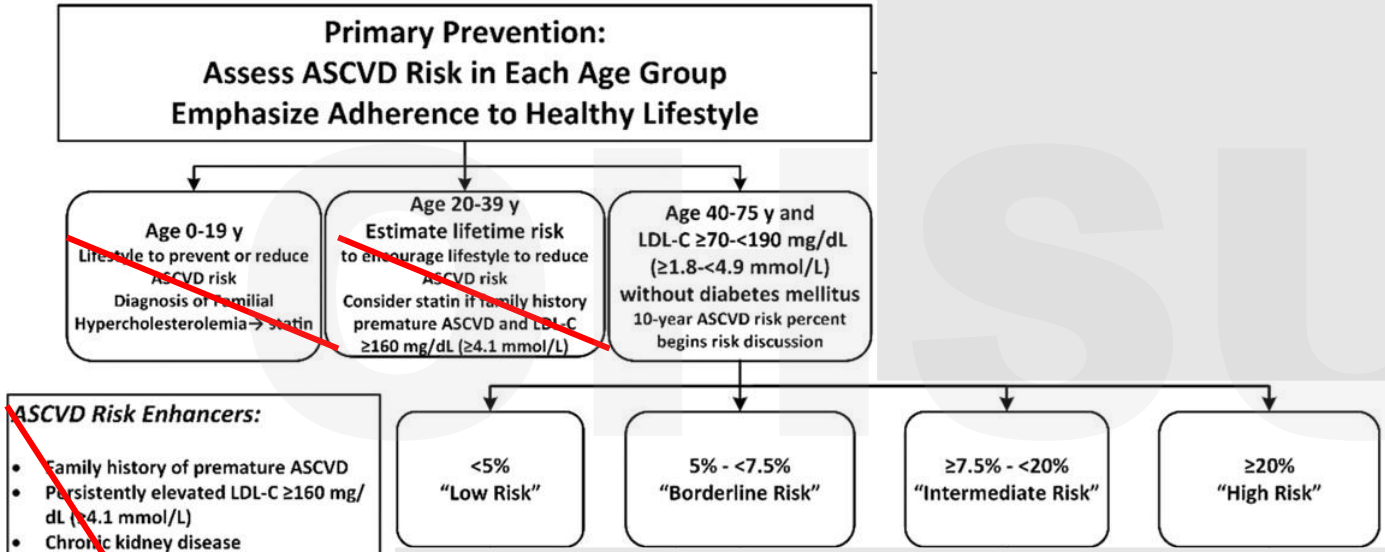
Predicting Risk of Cardiovascular Disease Events (**PREVENT**, 2023)

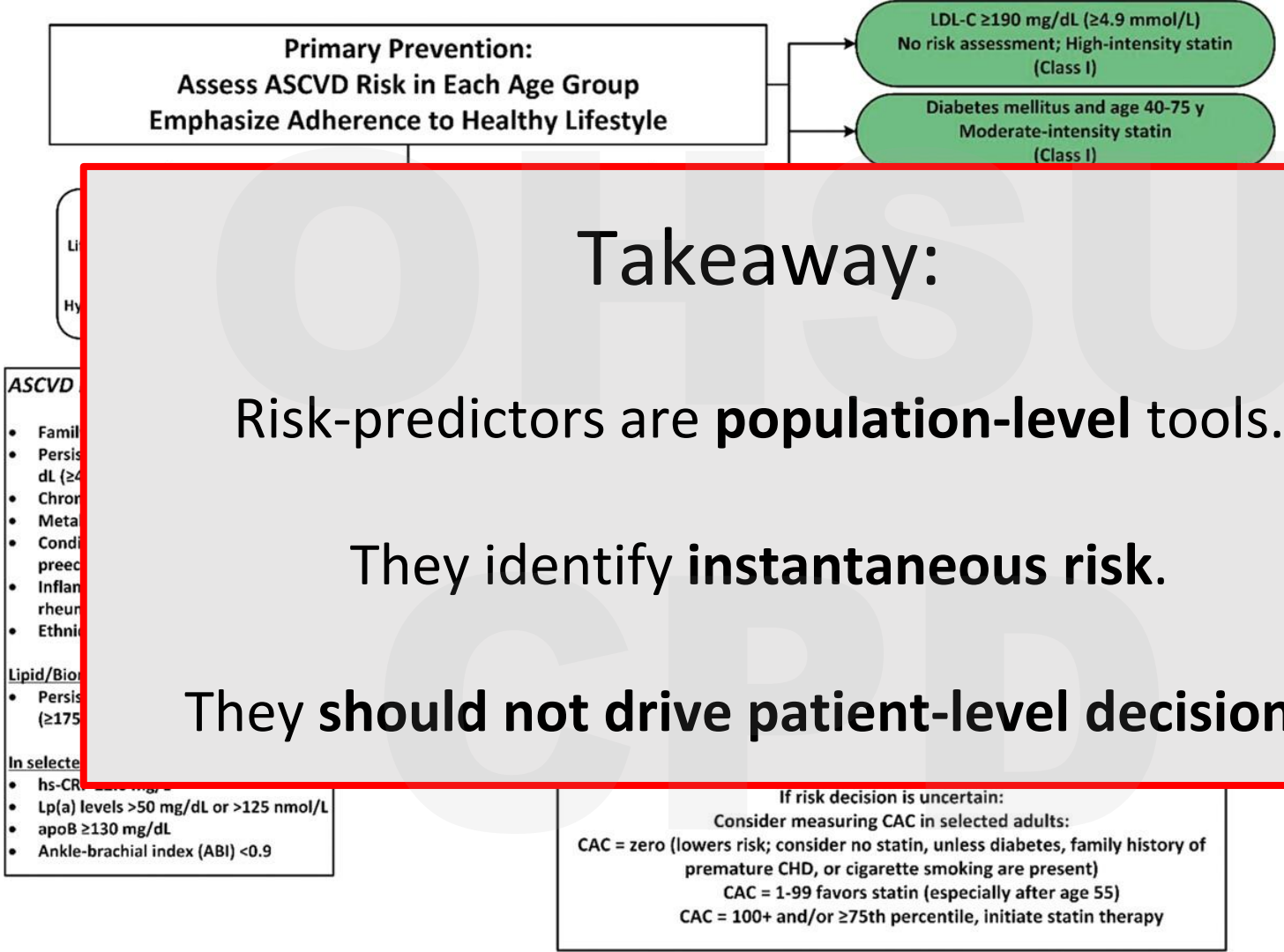
- 46 datasets, 6.6 million individuals
  - Includes EMR data
- 30-79 yo
- Many more risk factors included
  - Race excluded, but more accurate across races
  - Uses SDH based on zip code (social deprivation index)
  - Optional model: a1c, albuminuria
- Predicts other related outcomes
- NO prospective data

Table 12. Crosswalk Between 10-Year Risk ASCVD Estimates From PCE and PREVENT-ASCVD Equations

	Approximate Equivalent Ranges of 10-Year ASCVD Risk Estimates*	
Risk Group	PCE	PREVENT-ASCVD
Low	<5%	<3%
Borderline	5% to <7.5%	3% to <5%
Intermediate	7.5% to <20%	5% to <10%
High	≥20%	≥10%

2018 Guideline





2018 Guideline

Takeaway:

Risk-predictors are **population-level** tools.

They identify **instantaneous risk**.

They **should not drive patient-level decisions**.

New Framework: CPR

- Classify: **PREVENT**

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New Framework: CPR

- Classify: **PREVENT**
- **Personalize**

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New Framework: CPR

- Classify: **PREVENT**
- **Personalize**
- **Reclassify / Reassess**

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New Framework: CPR

- Classify: **PREVENT**
- **Personalize**
- **Reclassify / Reassess**

"Originally stratified as **LOW** risk by **PREVENT**;

Risk futher stratified based on:
h/o PET, CAC, and Lp(a).

Patient to be considered **HIGH** risk."

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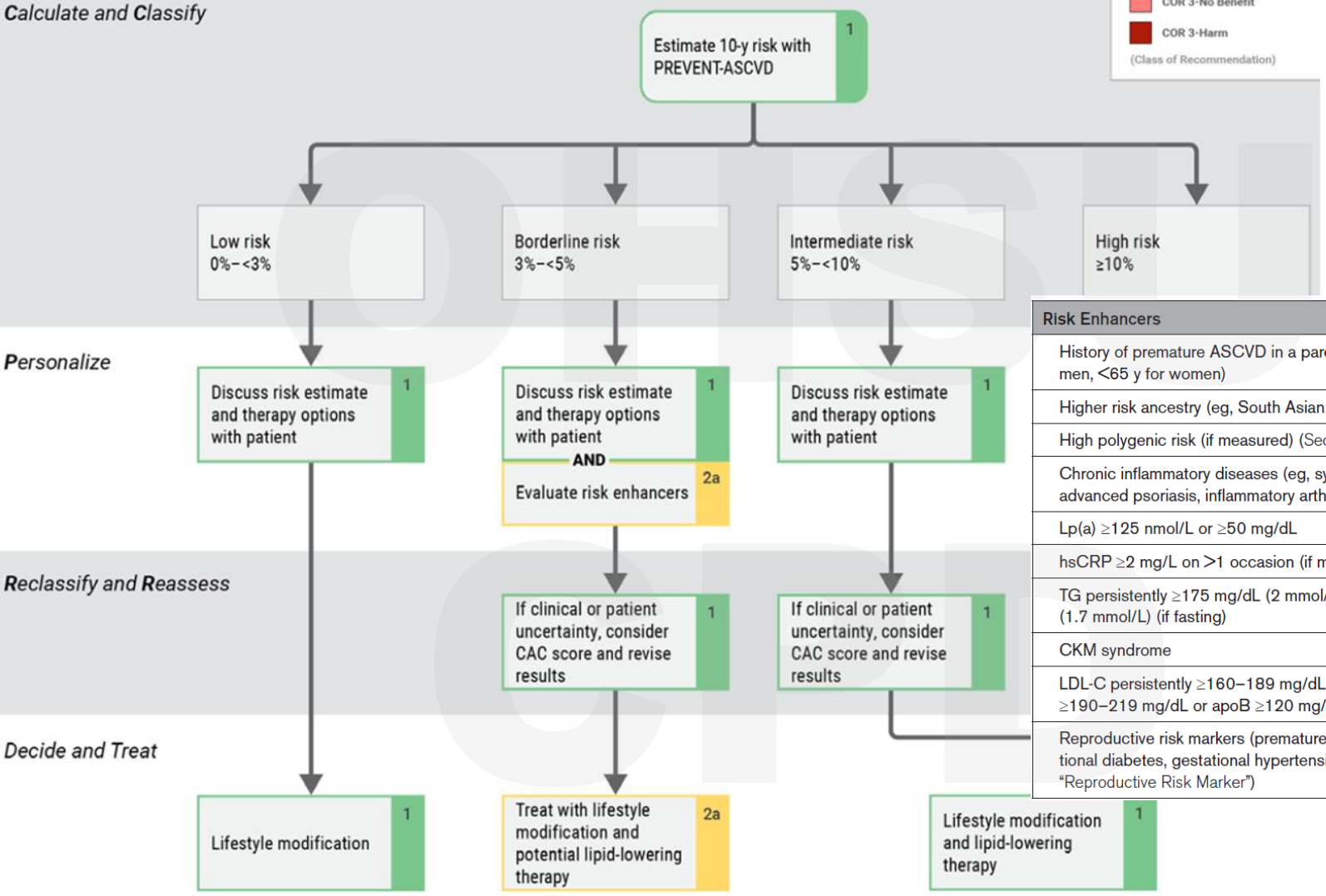


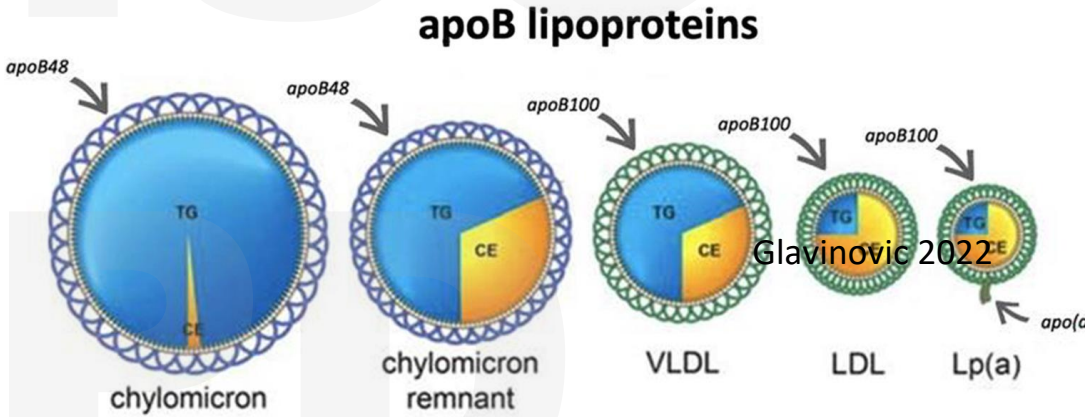
Risk Enhancers
History of premature ASCVD in a parent or sibling (onset age <55 y for men, <65 y for women)
Higher risk ancestry (eg, South Asian, Filipino)
High polygenic risk (if measured) (Section 4.2.3.5, "Polygenic Risk Scores")
Chronic inflammatory diseases (eg, systemic lupus, rheumatoid arthritis, advanced psoriasis, inflammatory arthritis)
Lp(a) ≥125 nmol/L or ≥50 mg/dL
hsCRP ≥2 mg/L on >1 occasion (if measured)
TG persistently ≥175 mg/dL (2 mmol/L) (if nonfasting) and ≥150 mg/dL (1.7 mmol/L) (if fasting)
CKM syndrome
LDL-C persistently ≥160–189 mg/dL (4.1–4.9 mmol/L), non–HDL-C ≥190–219 mg/dL or apoB ≥120 mg/dL*
Reproductive risk markers (premature menopause, preeclampsia, gestational diabetes, gestational hypertension, preterm delivery; Section 4.2.3.4, "Reproductive Risk Marker")

Assessing Residual Risk

Residual risk: biomarkers identifying previously unappreciated risk factors

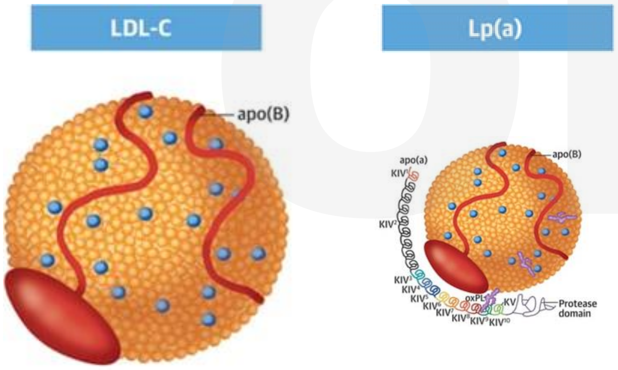
ApoB100 ("**ApoB**")

- **Better predicts** cardiovascular risk
- characterizes all relevant atherogenic particles
- Avoids calculation inaccuracies due to **triglycerides**



Glavinovic 2022

Lipoprotein (a)
(aka “LP little a”)



- **Smaller**, more atherogenic particle
- Lab identifies # “Kringle IV” repeats

Recommendation: Test at least once

Directly lowered by estrogen

Lp(a) increases by 20-30% in post-menopausal patients

Anagnostis 2016

Table 4. ASCVD Risk Related to Lp(a) Concentrations*

Lp(a) concentration nmol/L (mg/dL)	ASCVD Relative Risk: Increase Compared With Population Median (20 nmol/L, 7 mg/dL)
430 nmol/L (180 mg/dL)	4-fold
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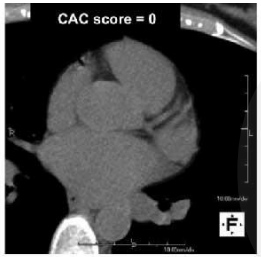
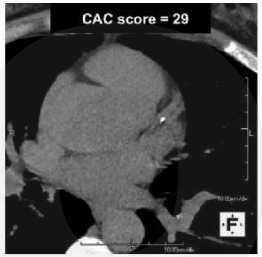
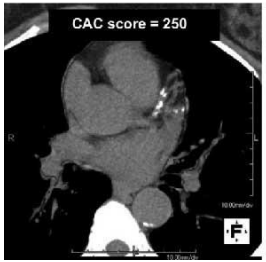
125 nmol/L (50 mg/dL)	1.4-fold
75–124 nmol/L (30-49 mg/dL)	1.2-fold
<75 nmol/L (<30 mg/dL)	Reference

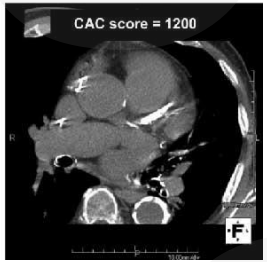
Adapted from 2026 Dyslipidemia Guideline, derived from UK Biobank Study (Alver et al 2019)

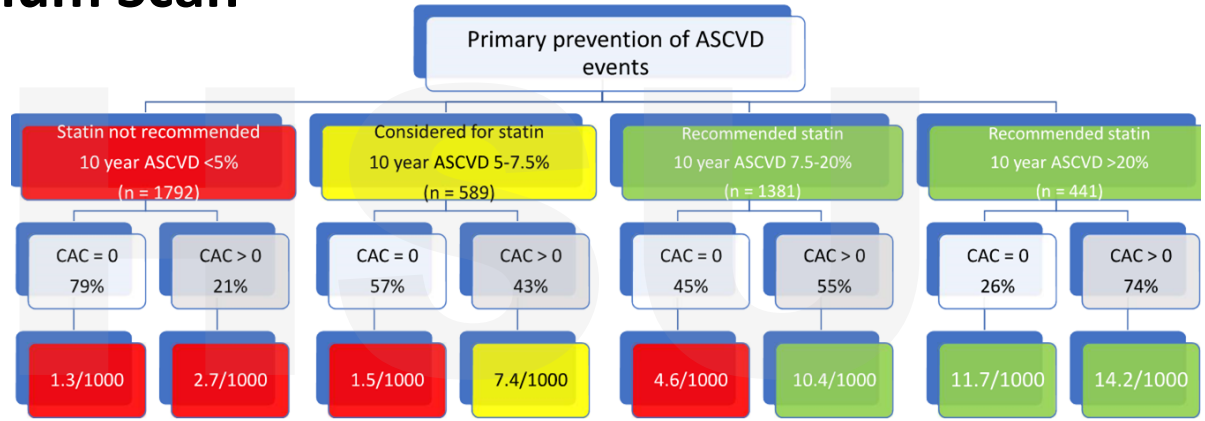
Coronary Artery Calcium Scan











Adapted from Nasir K et al. **J Am Coll Cardiol** 2015. 66(15);1657-68.

Coverage Considerations:

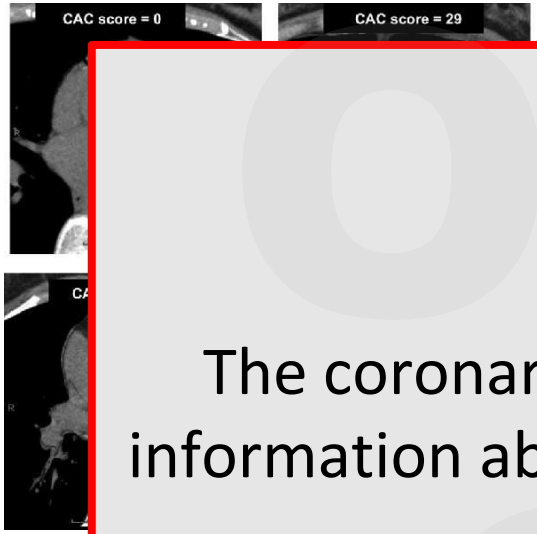
- Non-smoker
- No other indication for statin
- 40-75 yo

Out of pocket at OHSU: $299

CALCIUM SCORE	*INTERPRETATION*	*RISK OF MYOCARDIAL INFARCTION/STROKE AT 10 YEARS*
0	Very low risk	<1%
1–100	Low risk	<10%
101–400	Moderate risk	10-20%
101-400 and >75th Percentile	Moderately high risk	15-20%
>400	High risk	>20%

(Blaha et al., 2016; Chua et al., 2020; Greenland et al., 2018)

Coronary Artery Calcium Scan



Primary prevention of ASCVD events

...nded statin
...SCVD >20%
= 441)

CAC > 0
74%

14.2/1000

...15. 66(15);1657-68.

Takeaway:

The coronary artery calcium scan provides you information about the patient's **current physiology**.

It is one of the **best risk-stratification** tools

Cove
- N
- N
- 40-75 yo

Out of pocket at OHSU: $299

		...AT 10 YEARS
Percentile		
>400	High risk	>20%

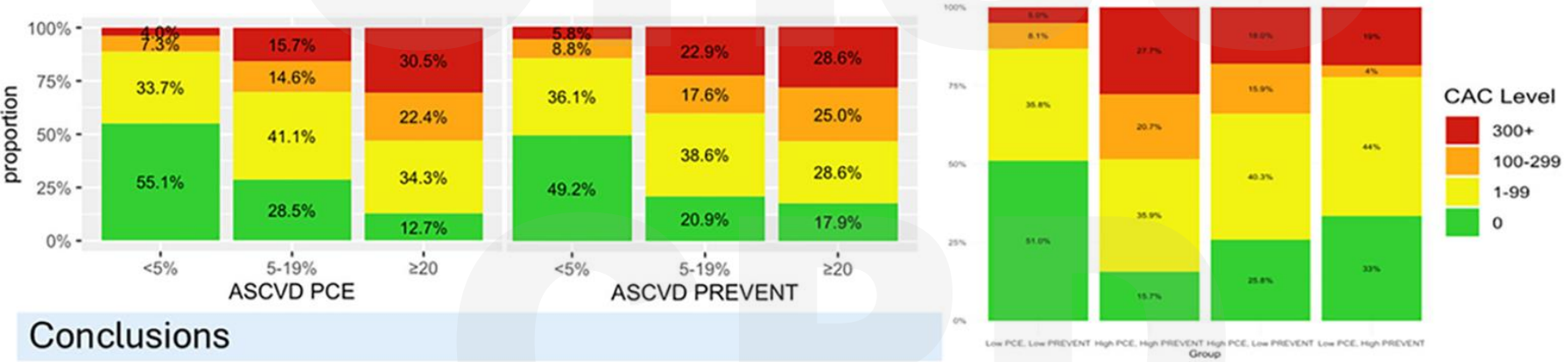
(Blaha et al., 2016; Chua et al., 2020; Greenland et al., 2018)

Coronary Artery Calcium Burden Across the Pooled Cohort Equation versus the American Heart Association PREVENT Risk Calculator

Methods

- Retrospective analysis of 7,610 asymptomatic patients who underwent coronary artery calcium scoring, with 10-year ASCVD risk calculated using both PCE and PREVENT equations.

Results

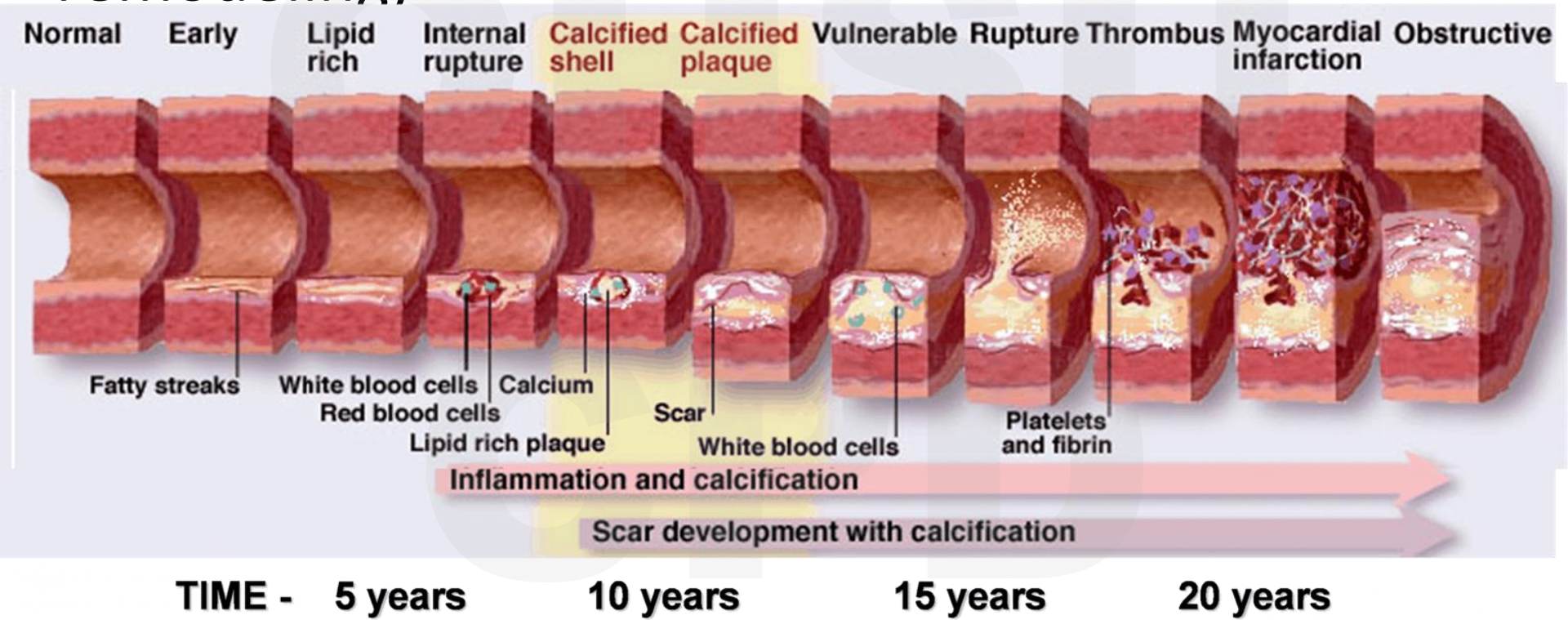


Conclusions

- Significant prevalence of non-zero CAC was observed in low-risk patients (45% PCE, 51% PREVENT), while substantial CAC heterogeneity existed in borderline-intermediate risk groups
- CAC scoring provides critical risk reclassification beyond traditional risk calculators, with 13% of concordant low-risk patients having CAC >100

Greshon et al. 2025

Pathophysiology: Macro-scale (Glagov remodeling)

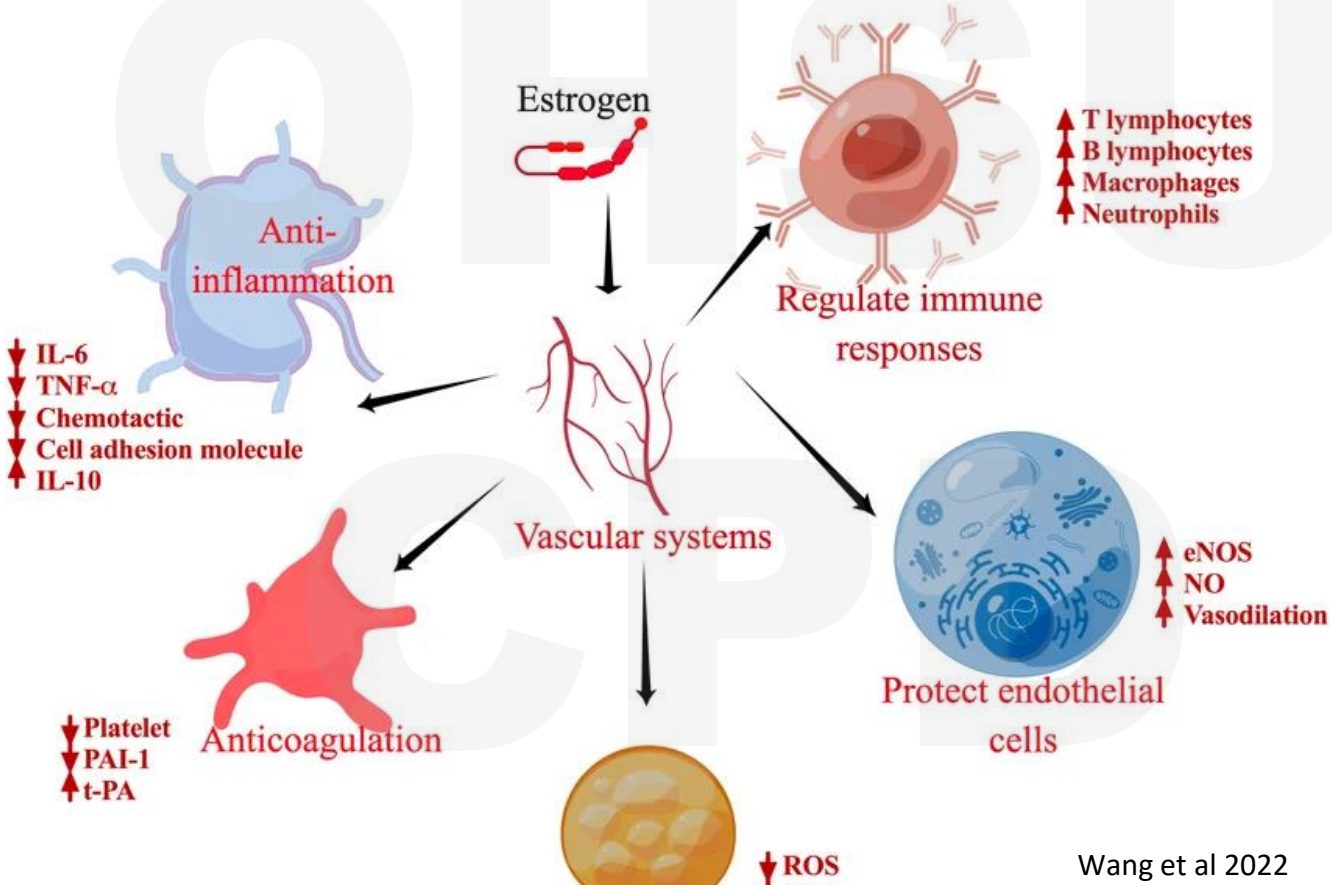


MI @ 55 (M); @ 65 (F)

Lipids in the female lifespan

13 yo	Early or late **menarche** increases the risk of cardiovascular disease.
20 - 45 yo	Cardiovascular risk can be challenging to mitigate in **childbearing years**; **pregnancy** is an incredibly useful risk stratification tool.
52 yo	**Menopausal transition** represents an increase cardiovascular risk; menopause hormone therapy should pay attention to risk
80 yo	**Prognosis** (or average lifespan) should be a major factor in decisions regarding medication initiation.

Estrogen protects the vasculature



Wang et al 2022

“Traditional risk factors” affect women differently

- **Diabetes**: **2x** risk relative to men (3-7x higher than baseline)[1]
- **Obesity**: 1.64x versus 1.46x[1]
- **Tobacco** use (if >45yo): 1.25x risk relative to men[2]
    - Significantly higher if also using oral contraceptives

1) Rajendran 2023
2) Huxley 2011

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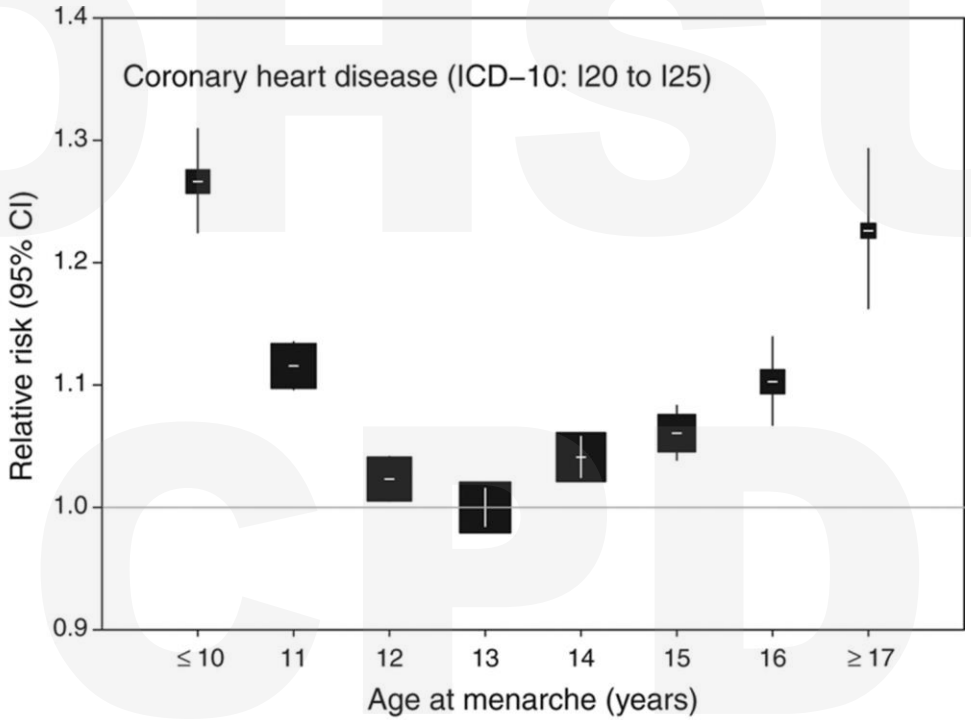
Age at Menarche Influences Risk



Mean age at menarche (years)	9.9	11	12	13	14	15	16	17.4
Number with incident CHD	3477	12,759	12,121	16,199	15,064	8784	3614	1360
RR (95% CI)	1.27 (1.22, 1.31)	1.12 (1.10, 1.14)	1.02 (1.01, 1.04)	1.00 (0.98, 1.02)	1.04 (1.02, 1.06)	1.06 (1.04, 1.08)	1.10 (1.07, 1.14)	1.23 (1.16, 1.29)

Canoy et al. 2014

Pregnancy as **risk stratification**

Adverse Pregnancy Outcomes: Associations with ASCVD

- Hypertensive disorders of pregnancy: 2-3x
  - 3x risk of stroke
  - Develop subclinical ASCVD 5 years earlier than those w/o APO
  - Earlier PET leads to higher ASCVD risk
- Gestational diabetes: 1.2-2x
- Low birth weight: 1.12x
  - <2.5 kg: 4x
  - 2.5-3kg: 3x
  - 3-3.5kg: 2x
- Miscarriage (2+ vs 0): 1.37x
  - Stillbirth: 2x
  - Nulliparous postmenopausal w/ h/o infertility: 1.36x

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125 nmol/L (50 mg/dL)	1.4-fold	75 %ile
75–124 nmol/L (30-49 mg/dL)	1.2-fold	
<75 nmol/L (<30 mg/dL)	Reference	

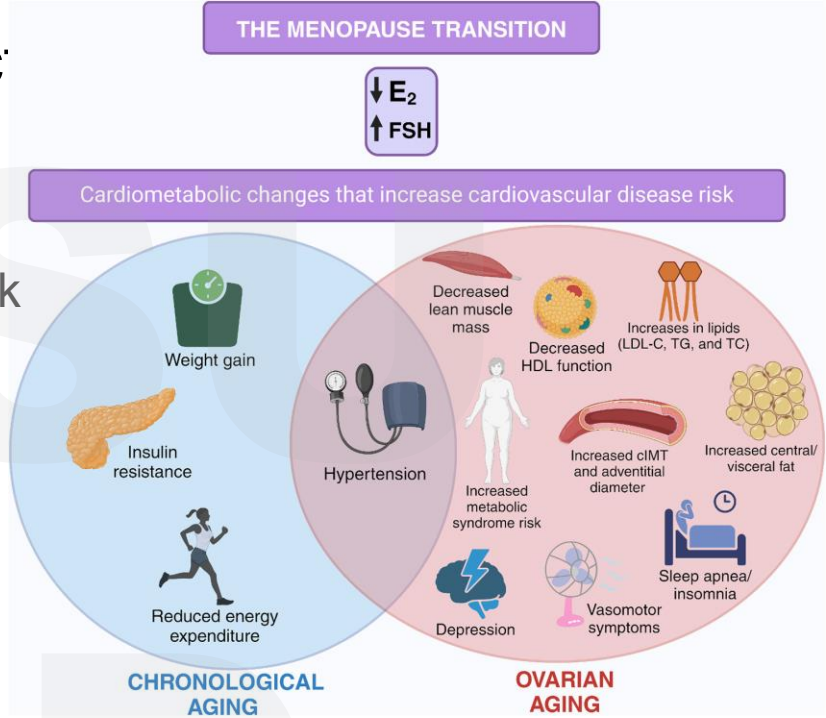
Menopause: Underscores the protec effects of ovarian functioning

Early menopause (<45 yo): 1.3x CVD risk
Premature ovarian failure (<40 yo): 1.55x CVD risk

Surgical menopause:
- <45 yo (on MHT): 1.3x
  - Non-significant >45
- <50 not on MHT: 1.98x
- <50 and ONLY hysterectomy: 1.17x

Vasomotor symptoms:
- Late (post-menopause): 1.69x
  - Association falls after age 60
- Early (pre-menopause): 1.38x
- Severe (≥ 6 days / 2 weeks): 1.5x

Zhu et al. 2019 (review)



Uddenberg et al 2024

Increases in LDL, ApoB, Lp(a), TG

Reduction in HDL function (higher not better)

MHT: Developing understanding of CVD risk

Raising the question:

Nurse's study (1991): Maybe protective

HERS (1998): Actually probably harmful

- HERS II (2002): Not helpful for prevention

Establishing the precedent:

WHI (2002): initial analysis was broadly interpreted as "***HRT causes CVD***"

Adding nuance: Timing hypothesis

Rossow et al (2007): Secondary analysis of WHI

DOPS (2012)

Confirming suspicions:

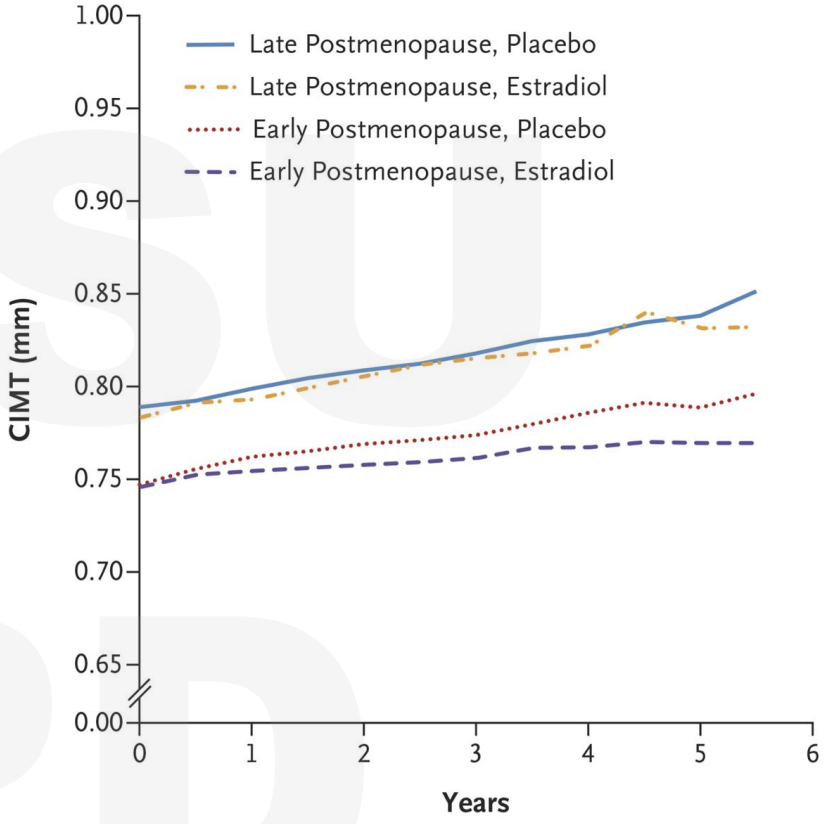
low risk in early menopause

ELITE (2016) and KEEPS (2019) : biomarker progression is less in treated group closer to menopause

Menopause Hormonal Therapy: CVD

Takeaway:

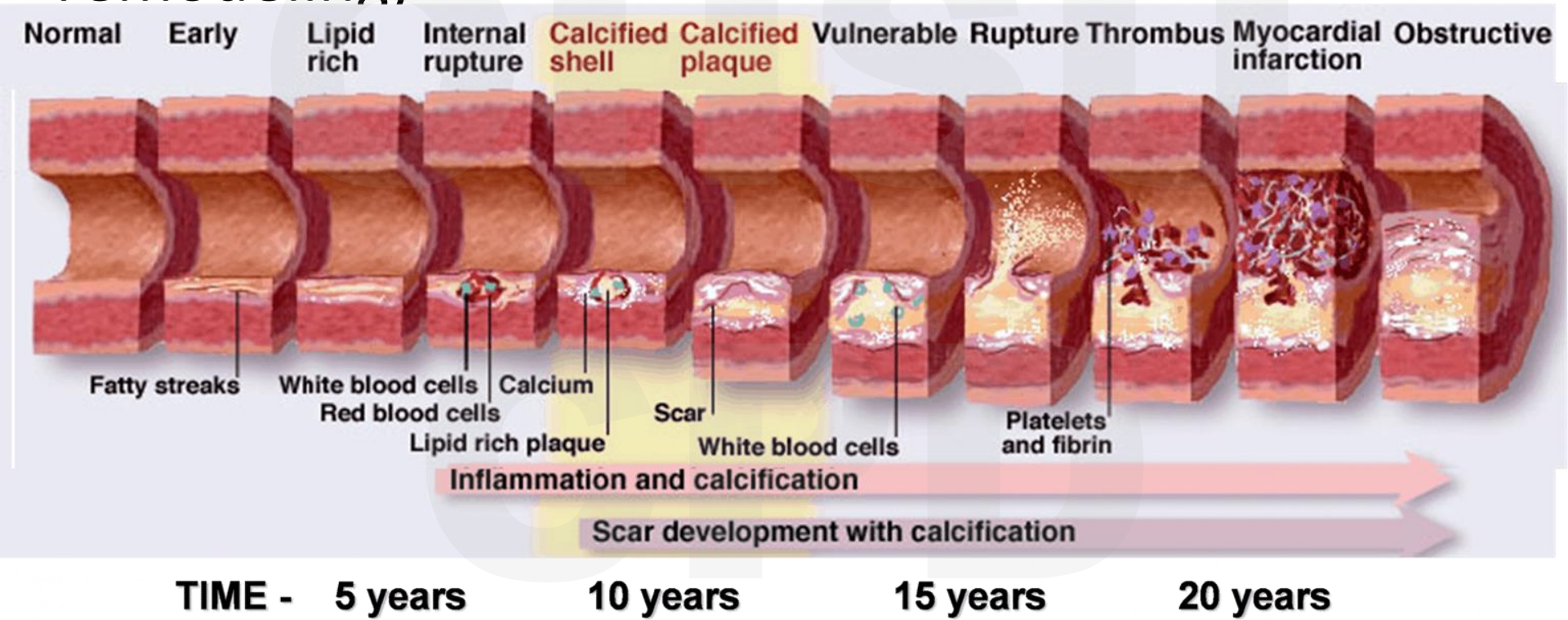
MHT in low risk women initiated **near menopause does not have a significant net effect on CVD**



No. of Participants							
With CIMT data	643	533	522	515	424	295	56
Who completed or discontinued study	0	106	119	128	215	345	582
Without CIMT data	0	4	2	0	4	3	5

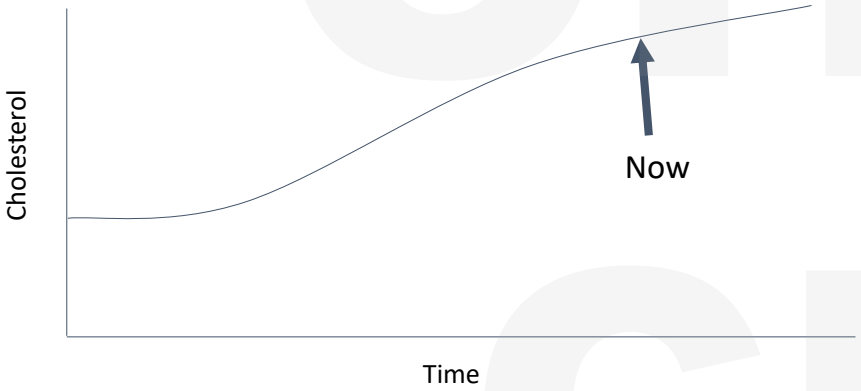
ELITE (2016) + KEEPS (2019)

Pathophysiology: Macro-scale (Glagov remodeling)



MI @ 55 (M); @ 65 (F)

The impact of hypercholesterolemia is a function of **time**, **concentration**, and **context** / **inflammation**



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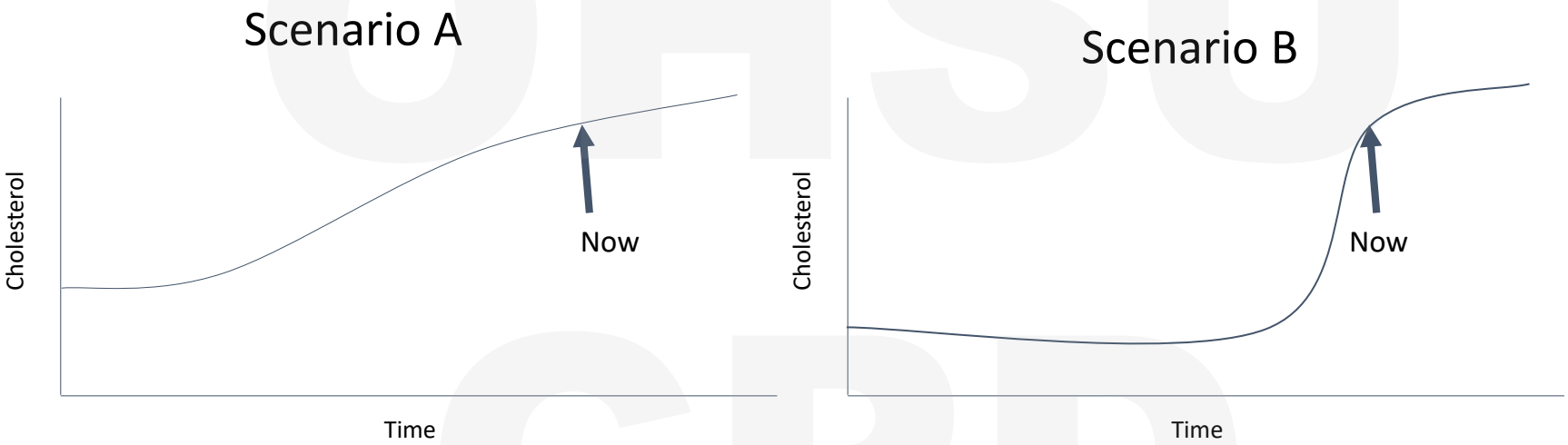
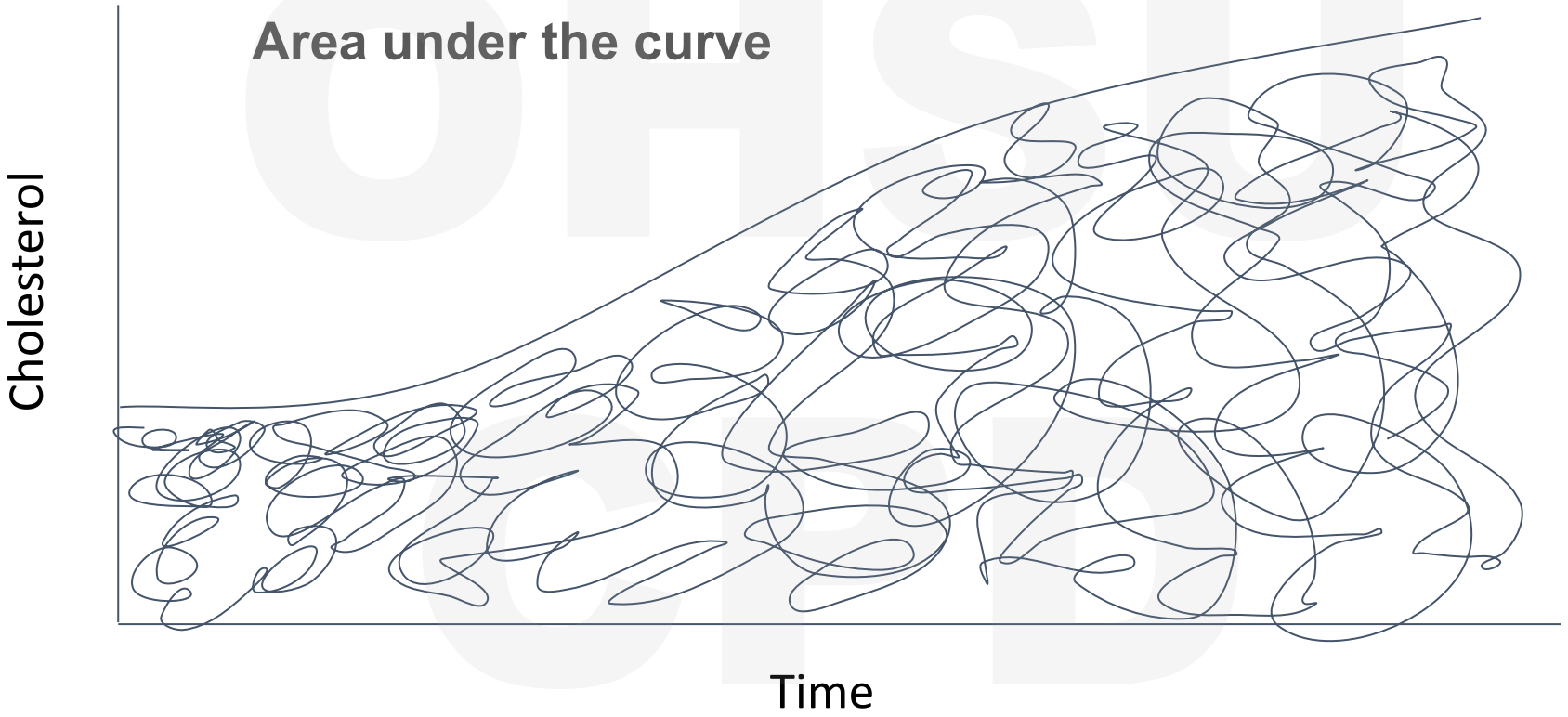


OHSU CPD

The impact of hypercholesterolemia is a function of **time**, **concentration**, and **context** / **inflammation**:



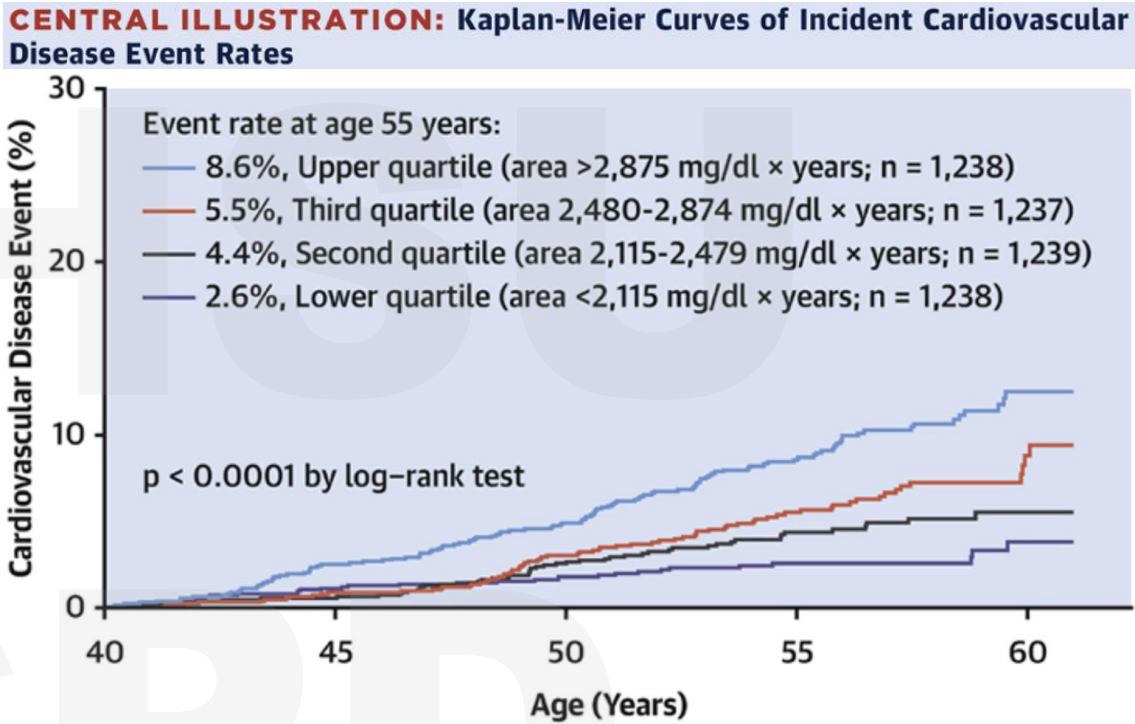
Exposure to higher cholesterol in **healthy young adults** leads to higher events at **age 55**

CARDIA trial

"Coronary Artery Risk Development in Young Adults"

n = 4958 asymptomatic adults 18-30 yo (1985-1986)

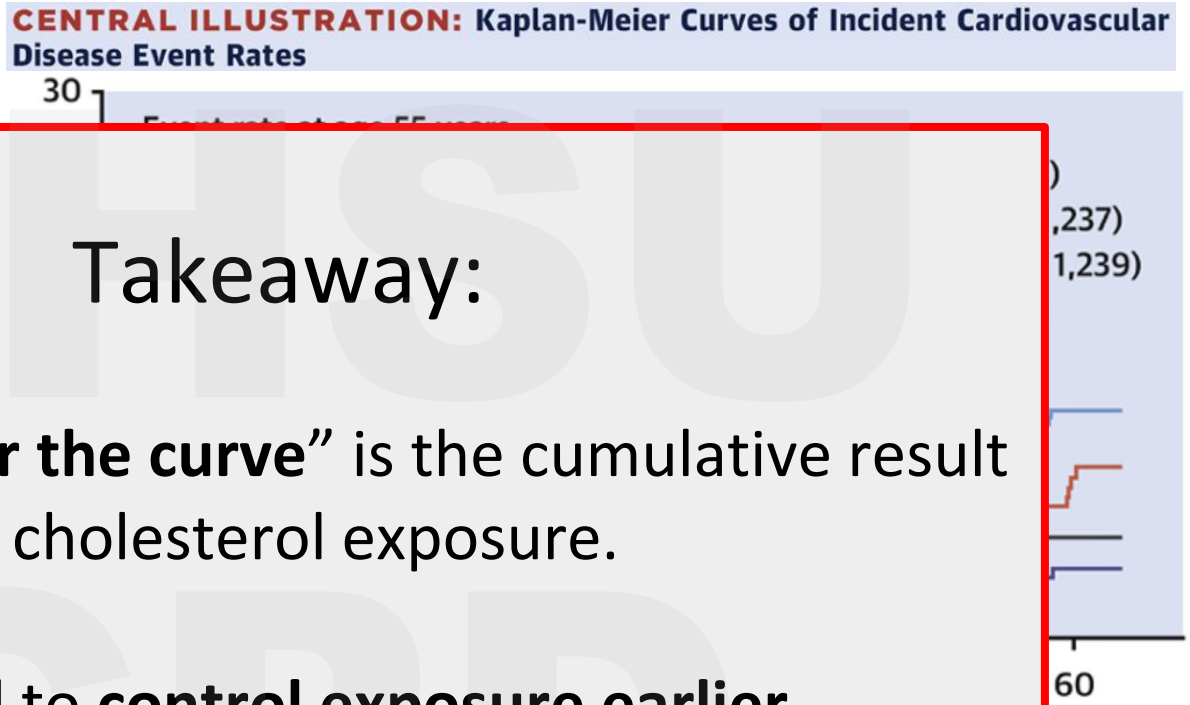
Methods: tracked LDL-c over time, measure event rate at 55 years old



Outcome: Composite (nonfatal coronary heart disease, stroke, transient ischemic attack, heart failure hospitalization, cardiac revascularization, peripheral arterial disease intervention, or cardiovascular death)

Domanski et al 2020

CARDIA trial



"Corc
Deve
Adult

n = 4
adult

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time,
55 ye

Outcome
ischemic attack, heart failure hospitalization, cardiac revascularization, peripheral arterial disease intervention, or cardiovascular death)

Takeaway:

The "**Area under the curve**" is the cumulative result of cholesterol exposure.

We need to **control exposure earlier**.

Domanski et al 2020

Treatment Goals

Patient population	LDL-C <100 mg/dL (2.6 mmol/L) Non–HDL-C <130 mg/dL (3.4 mmol/L)	LDL-C <70 mg/dL (1.8 mmol/L) Non–HDL-C <100 mg/dL (2.6 mmol/L)	LDL-C <55 mg/dL (1.4 mmol/L) Non–HDL-C <85 mg/dL (2.2 mmol/L)
Primary prevention	PREVENT-ASCVD <10% • If TG ≥150 mg/dL to 499 mg/dL, apoB goal: <90 mg/dL	PREVENT-ASCVD ≥10% • If TG ≥150 mg/dL to 499 mg/dL, apoB goal: <70 mg/dL	N/A
Severe hypercholesterolemia	**Without** FH, ASCVD risk factors, and subclinical atherosclerosis	**With** FH, ASCVD risk factors, or subclinical atherosclerosis	Severe hypercholesterolemia or HeFH with clinical ASCVD
Diabetes	**Without** ASCVD risk factors or diabetes-specific risk modifiers • apoB goal: <90 mg/dL	**With** ASCVD risk factors or diabetes-specific risk factors • apoB goal: <70 mg/dL	N/A
Subclinical atherosclerosis	CAC = 1–99 AU and <75th percentile for age, sex, and race	• CAC ≥100 to 299 AU or ≥75th percentile for age, sex, race • CAC ≥300 to 999 AU ◦ Optional goal: LDL-C <55 mg/dL, non–HDL-C <85 mg/dL and consider apoB goal <55 mg/dL	CAC ≥1000 AU

Treatment Goals

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Primary prevention			
Severe hypercholesterolemia			
Diabetes			
Subclinical atherosclerosis			

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Evolocumab in Patients without a Previous Myocardial Infarction or Stroke

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Intensive control in

Primary prevention

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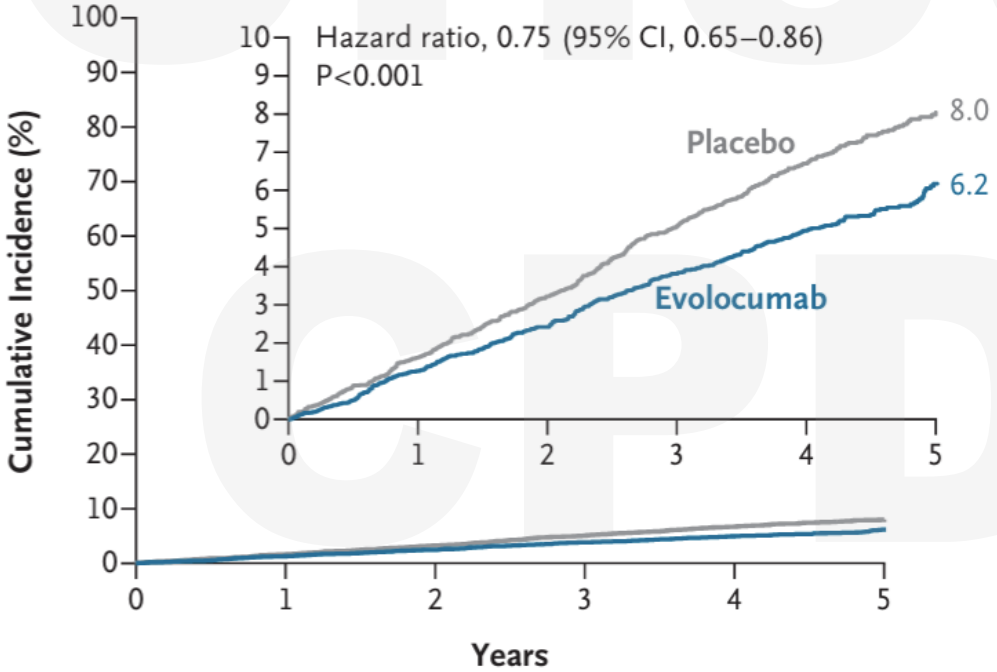
Evolocumab in Patients without a Previous Myocardial Infarction or Stroke

3-point MACE



Achieved LDL in evolucumab arm: 45 mg/dL

Takeaways

- The impact of hypercholesterolemia is a product of **time**, **concentration**, and **context** / **inflammation**
- Calculated risk is the **starting point** for clinical decision making
- **Patient** AND **sex-specific** factors should dictate your risk stratification
- The 2026 guidelines provide specific targets for cholesterol management that are **more aggressive** and **more directive** than prior guidelines.
    - Aggressive management drives better outcomes

Questions?