Women's Health 2024 | Beyond the Annual Visit

Love Story: Lipid Education for Women's Heart Health

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Disclosures

- Consultant to Sanofi, Novo Nordisk, Novartis, Boehringer-Ingelheim, Lilly, Amgen, Bayer, Medtronic, Jaxx, Edwards, and Esperion

Research Funding:

Grants:

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  - Impact of time-restricted feeding (TRF) on glucose homeostasis and mitochondrial function in patients with metabolic syndrome – The TIMET Study (NCT0405733)
- Hillblom Network Grant (PI: Taub PR) (NCT05365529)
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Clinical Trial Leadership:

- US National Lead/Steering Committee Member for: Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease (VICTORION-2P). (Sponsor: Novartis; NCT05030428)
- US National Lead/Steering Committee Member for: A Double-blind, Randomized, Placebo controlled, Multicenter Study Assessing the Impact of Olpasiran on Major Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease and Elevated Lipoprotein (a). (Sponsor: Amgen NCT05581303)
- Executive Steering Committee for VICTORIAN-1P Trial (Sponsor: Novartis)
- National Principal Investigator for the NIH RECOVER COVID Initiative (recovercovid.org) and responsible for design and execution of studies related to Post COVID Postural Orthostatic Tachycardia Syndrome.
- US National Lead/Steering Committee Member for MK0616 (oral PCSK9 inhibitor) Phase 3 program (Sponsor: Merck)
- Executive Steering Committee Member for TRANSFORM Trial (Sponsor: Cleerly)

Learning Objectives

- Demonstrate collective understanding of gender differences and challenges in optimizing LDL-C management for women, with a particular focus on practical considerations
- Analyze the changing landscape of LDL-C management in women by integrating the latest research findings and therapeutic insights

Talk Overview

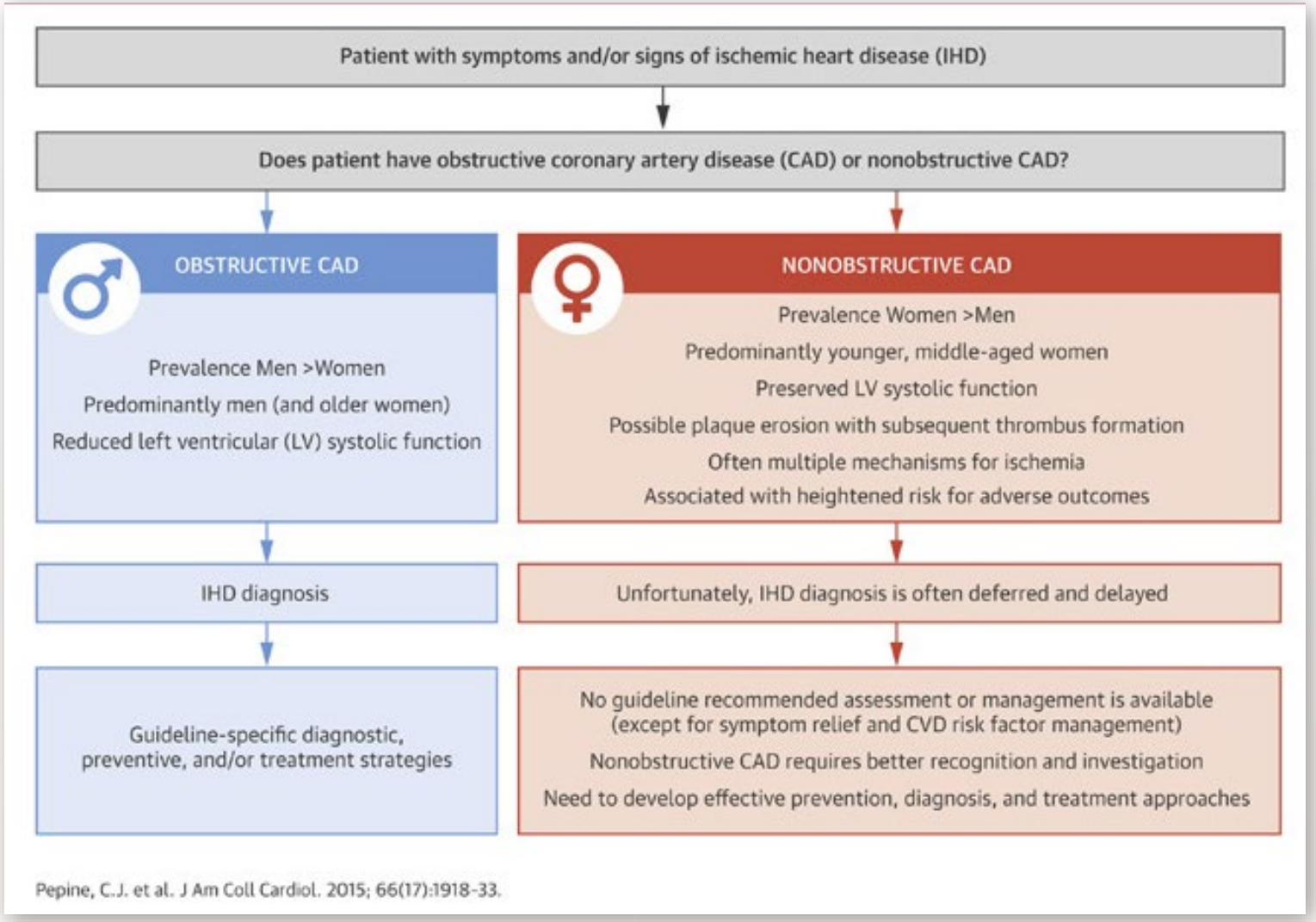
- **Speak Now:** Assessing Risk Status for CV Events in Women
- **Love Story:** LDL-C Goals and Testing
- **Shake It Off:** Managing LDL-C
- **Wildest Dreams:** Latest Nonstatin Therapy Management Approaches

Speak Now: Raise Awareness of Heart Disease in Women

Overview of CVD in Women

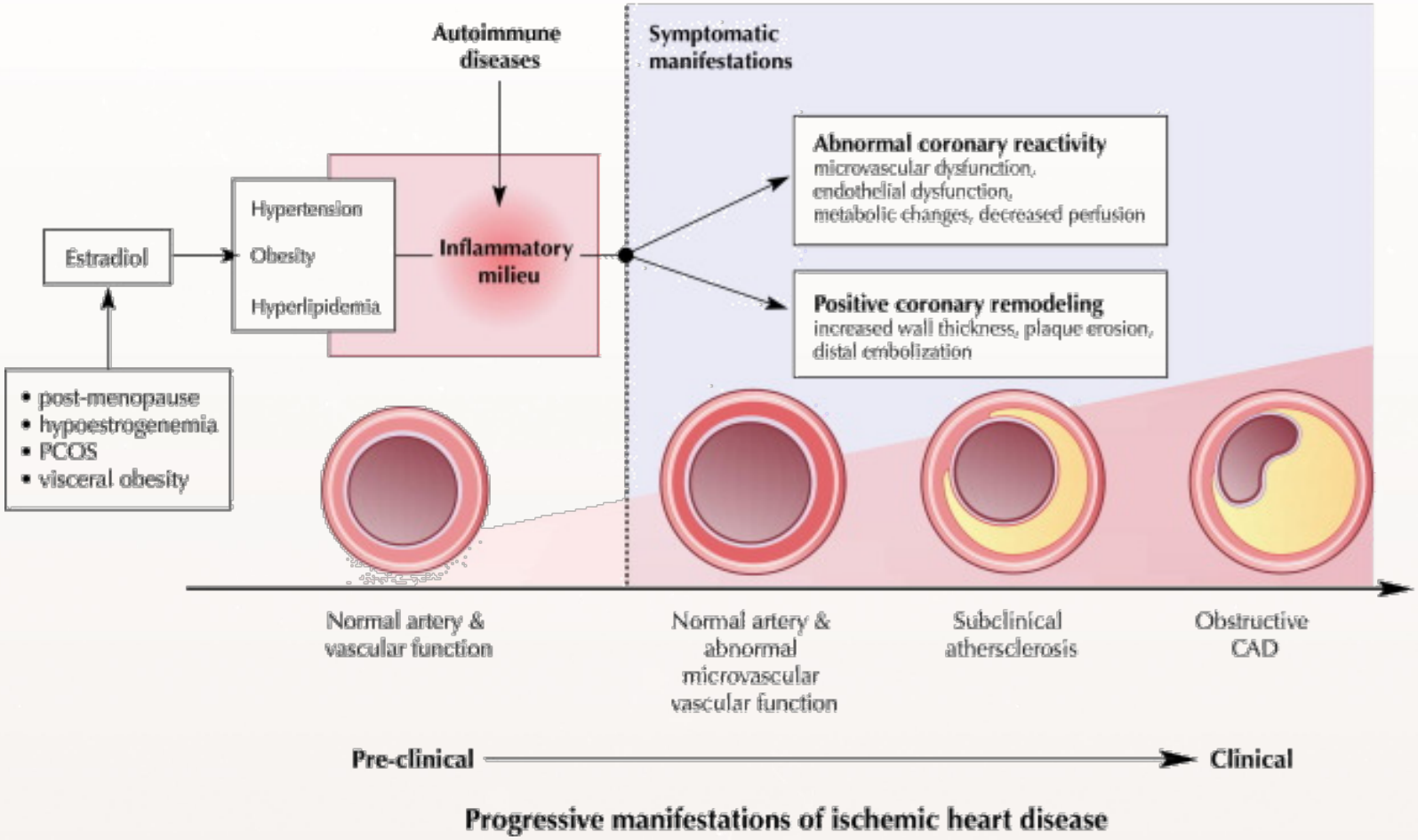
- Cardiovascular disease (CVD) accounts for 35% of all deaths in women worldwide
- 8.9 million women died from CVD in 2019
- Women have worse outcomes with acute myocardial infarction, yet women are less likely to receive guideline-indicated therapies
- Younger women are at the greatest risk for poor outcomes after acute myocardial infarction
- Women are understudied, underdiagnosed, undertreated, and underrepresented in clinical trials

Sex Differences in CAD



Pepine, C.J. et al. J Am Coll Cardiol. 2015; 66(17):1918-33.

Impact of Factors Unique to Women on CAD Progression



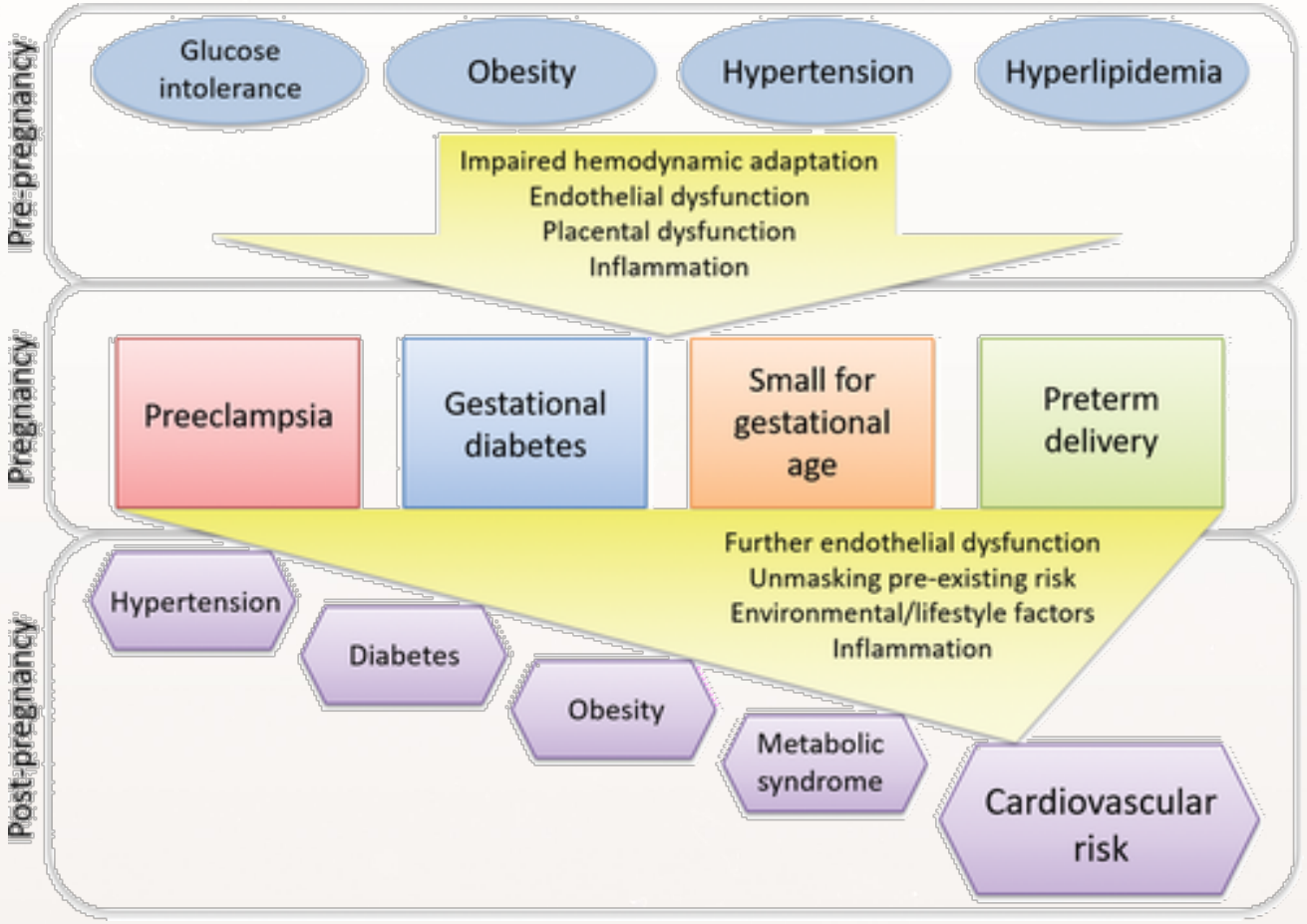
Shaw LJ, et al. J *Am Coll Cardiol*. 2009;54(17):1561-1575.

Diabetes Impacts Women More Severely

- Premenopausal women with diabetes lose the protection against heart disease that nondiabetic women have and are 50% more likely to die from heart disease
- Elderly women with T2DM and end-stage renal disease have a significantly higher risk of death than men
- Women with diabetes are 4 times more likely to suffer a stroke than women without diabetes
- Cyclical hormonal changes make diabetes control more difficult in premenopausal women, and the risk of diabetic ketoacidosis is higher amongst women than men
- Across all countries, women tend to receive less intensive care and treatment for diabetes compared to men

Kapur A, Seshiah V. Indian *J Med Res*. 2017;146(5):553-556.

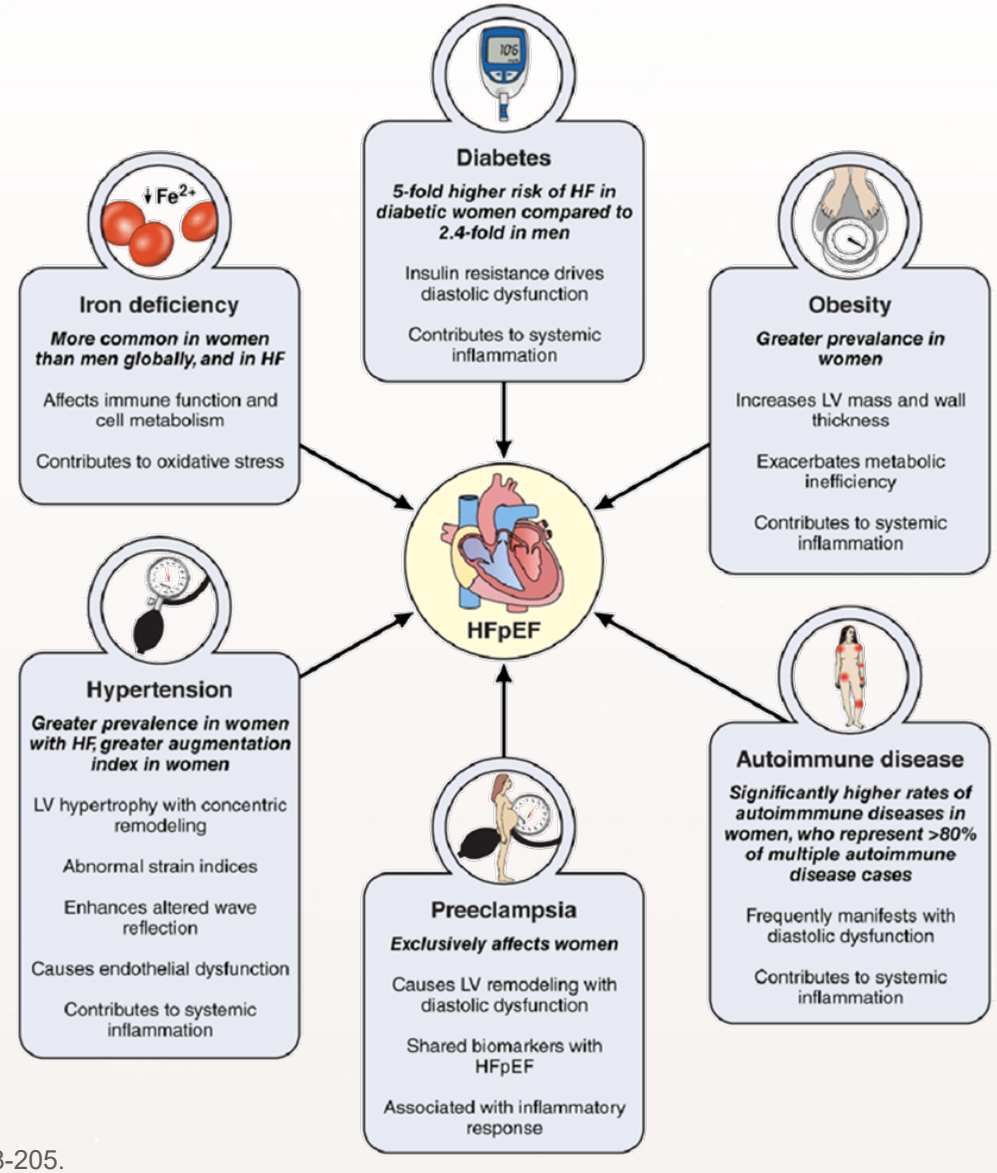
Associations Between Pre-Pregnancy Risk Factors, Adverse Pregnancy Outcomes, and Post-Pregnancy Cardiometabolic Risk Factors and Outcomes



Hauspurg A, et al. *Clin Cardiol*. 2018;41(2):239-246.

HFpEF Disproportionately Impacts Women

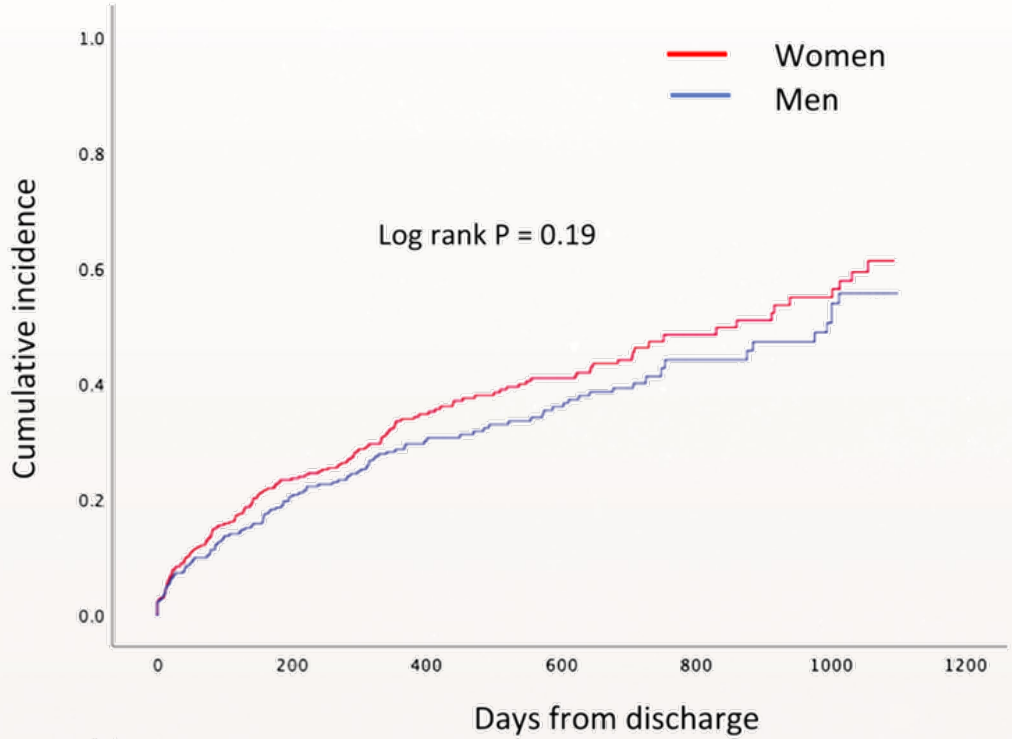
- HFpEF is intricately linked to T2DM and risk factors for T2DM
- Female sex was independently associated with the presence of diastolic dysfunction and worse clinical outcomes in a cohort of elderly patients with HFpEF



Beale AL, et al. *Circulation*. 2018;138(2):198-205.

Women With HFpEF Have Worse Outcomes

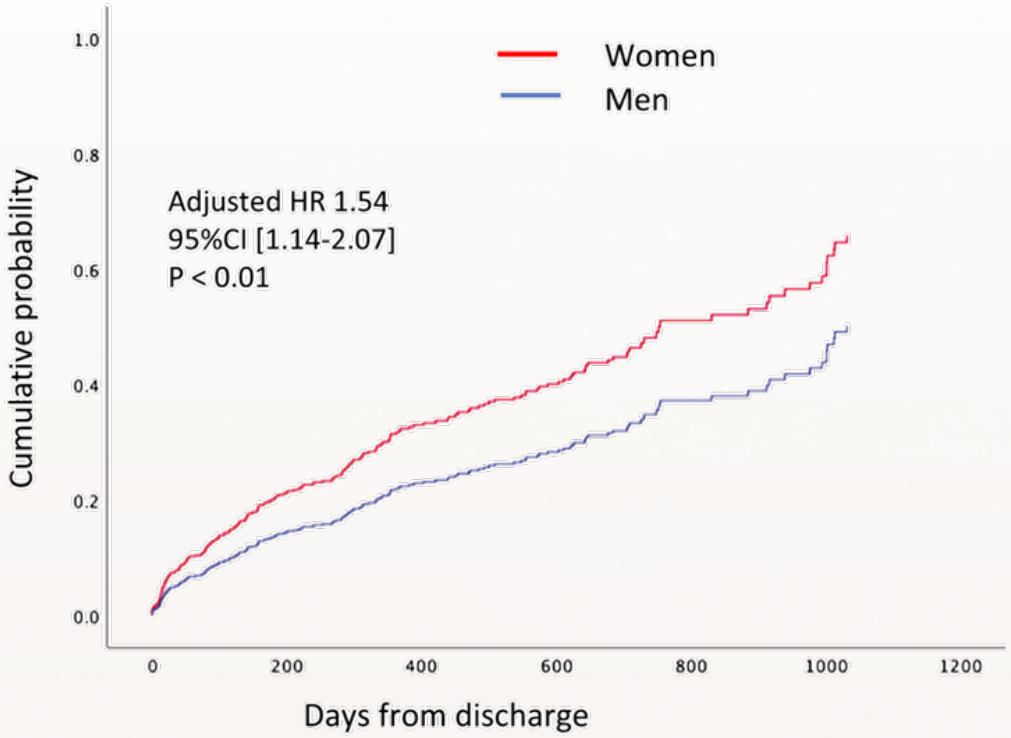
A Clinical endpoint (all-cause death and HF readmission)
Kaplan Meier curves



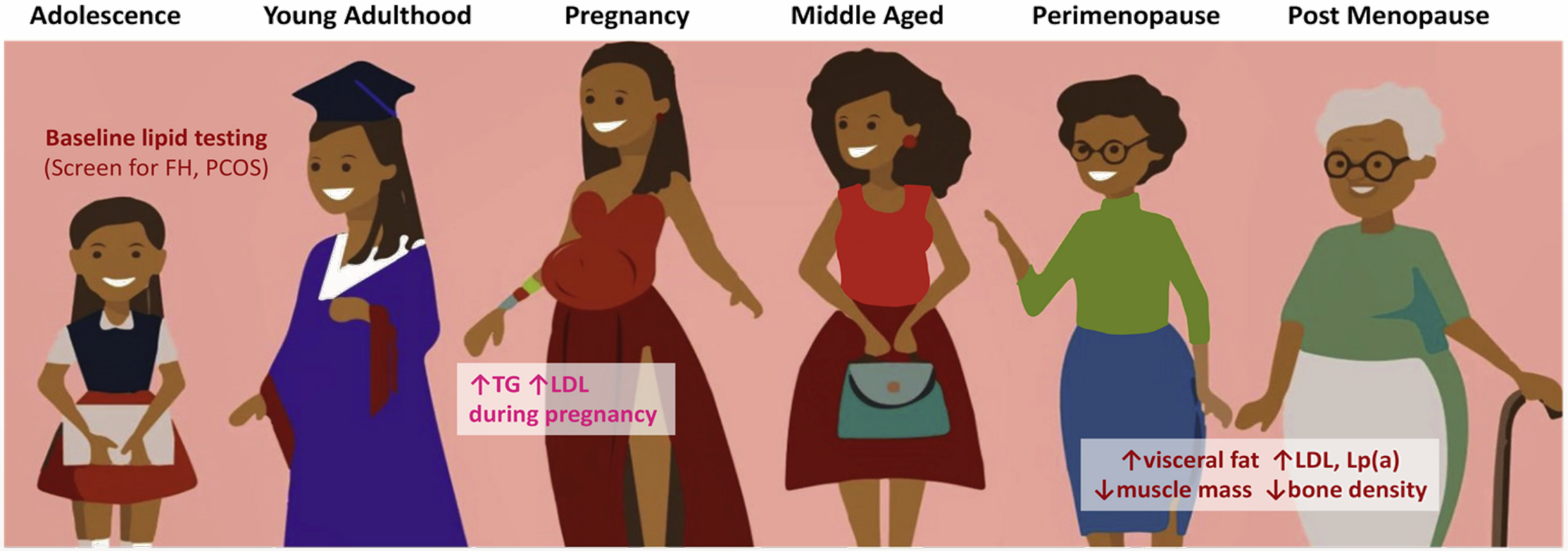
Number at risk

Women	481	261	149	118	43	32
Men	389	220	131	103	37	29

B Clinical endpoint (all-cause death and HF readmission)
Adjusted probablity curves



Sotomi Y, et al. *J Am Heart Assoc*. 2021;10(5):e018574.



Initiate lifestyle changes to ↓LDL

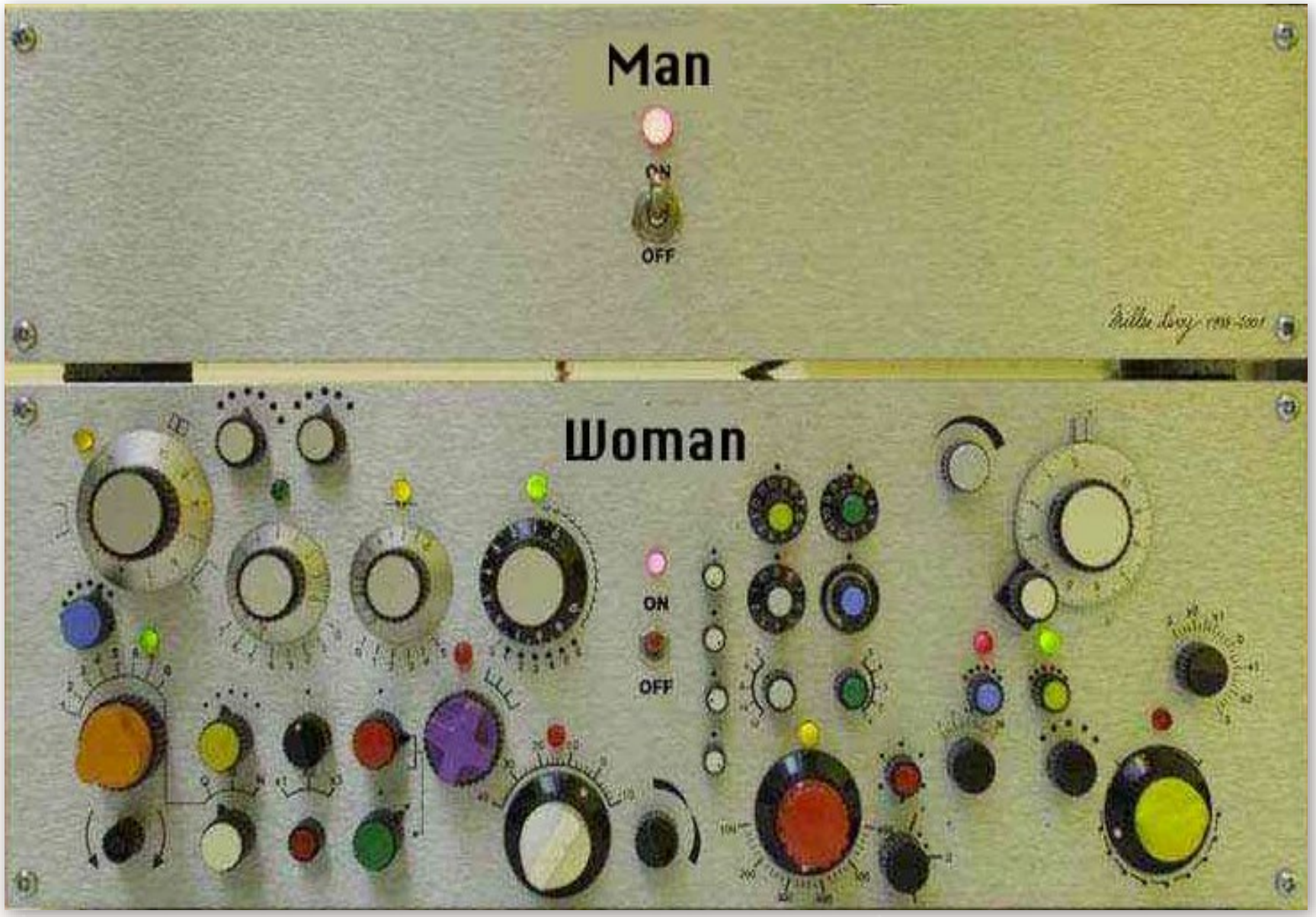
- Statins can be considered in pregnancy, weigh risks & benefits
- Preeclampsia & gestational DM ↑ASCVD risk

- Regular screening w/ lipid panel, blood pressure, HbA1c; treat lipids & modifiable risk factors
- Consider Coronary Artery Calcium score & Lp(a) for CV risk stratification

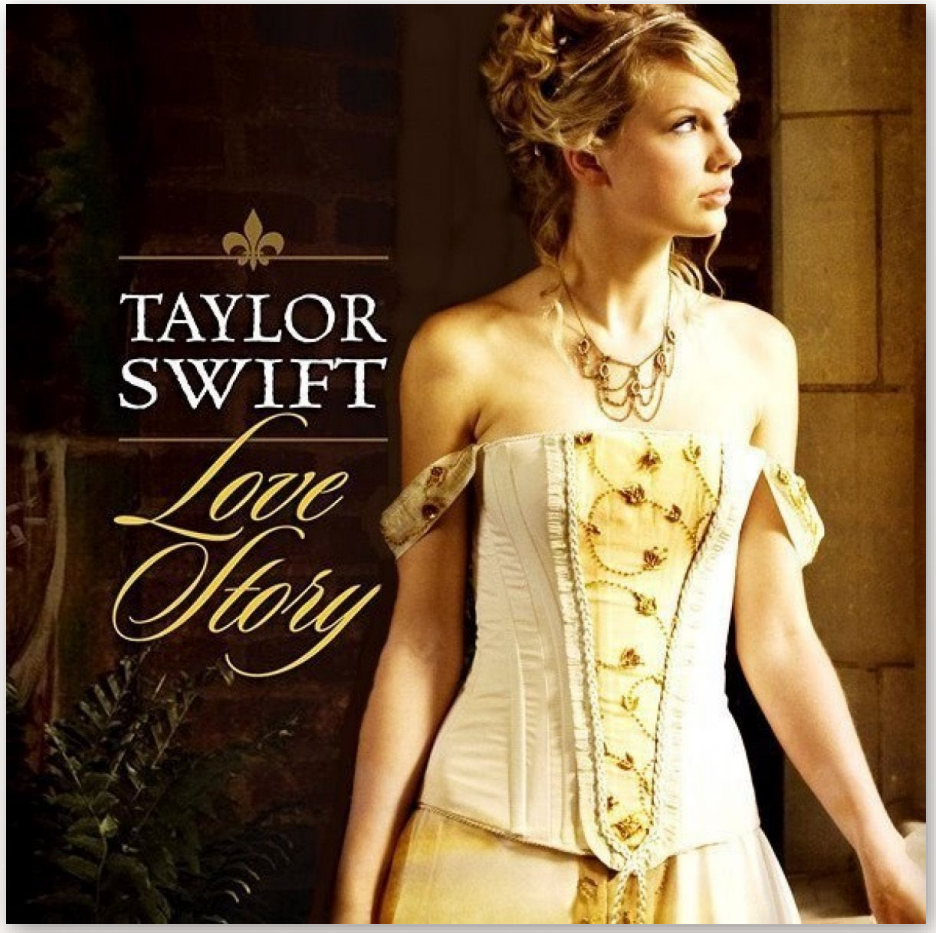
Personalized lipid management based on ASCVD risk

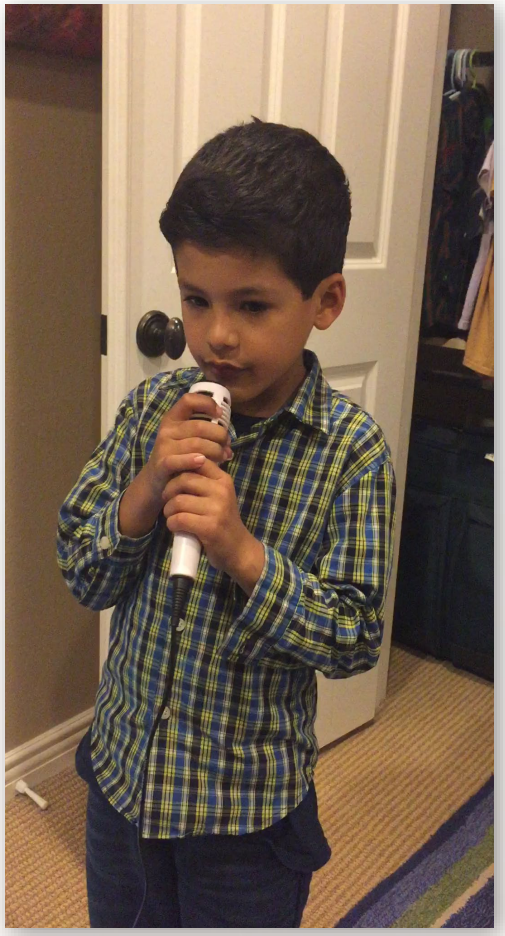
Increasing ASCVD risk

Patel N, et al. *Am J Prev Cardiol*. 2024;18:100666.

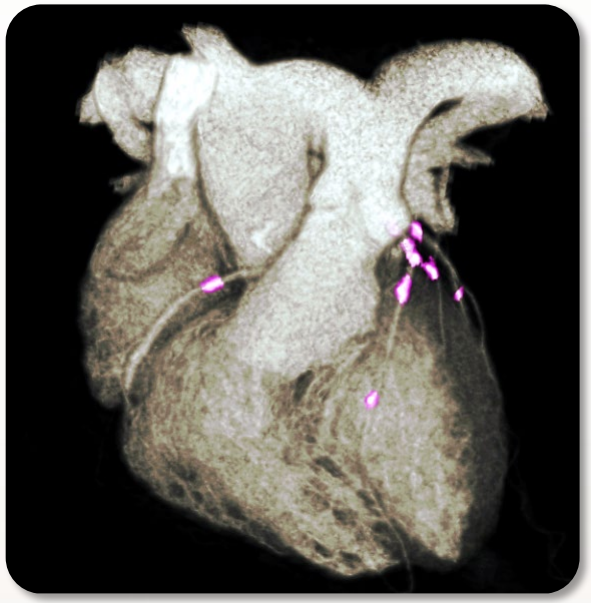

Man
ON
OFF
Woman
ON
OFF

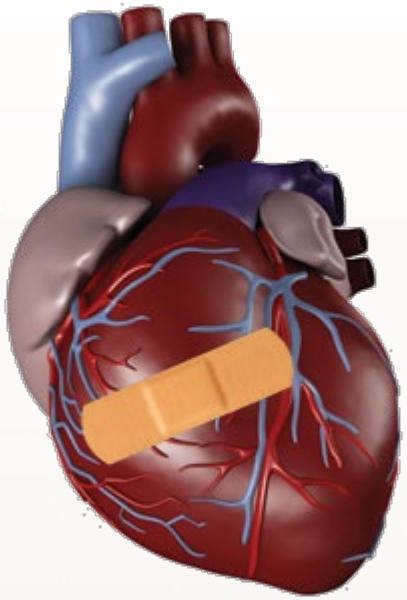
Love Story: Engage in Meaningful Relationships





Continuum of ASCVD Risk





Primary Prevention

High-Risk Primary Prevention
Advanced Subclinical Atherosclerosis?

Secondary Prevention

Blaha MJ. *Am J Cardiol*. 2016;118(6 Suppl):4A-12A.

2018 Blood Cholesterol Guideline | ASCVD Risk Enhancers

ASCVD Risk Enhancers:

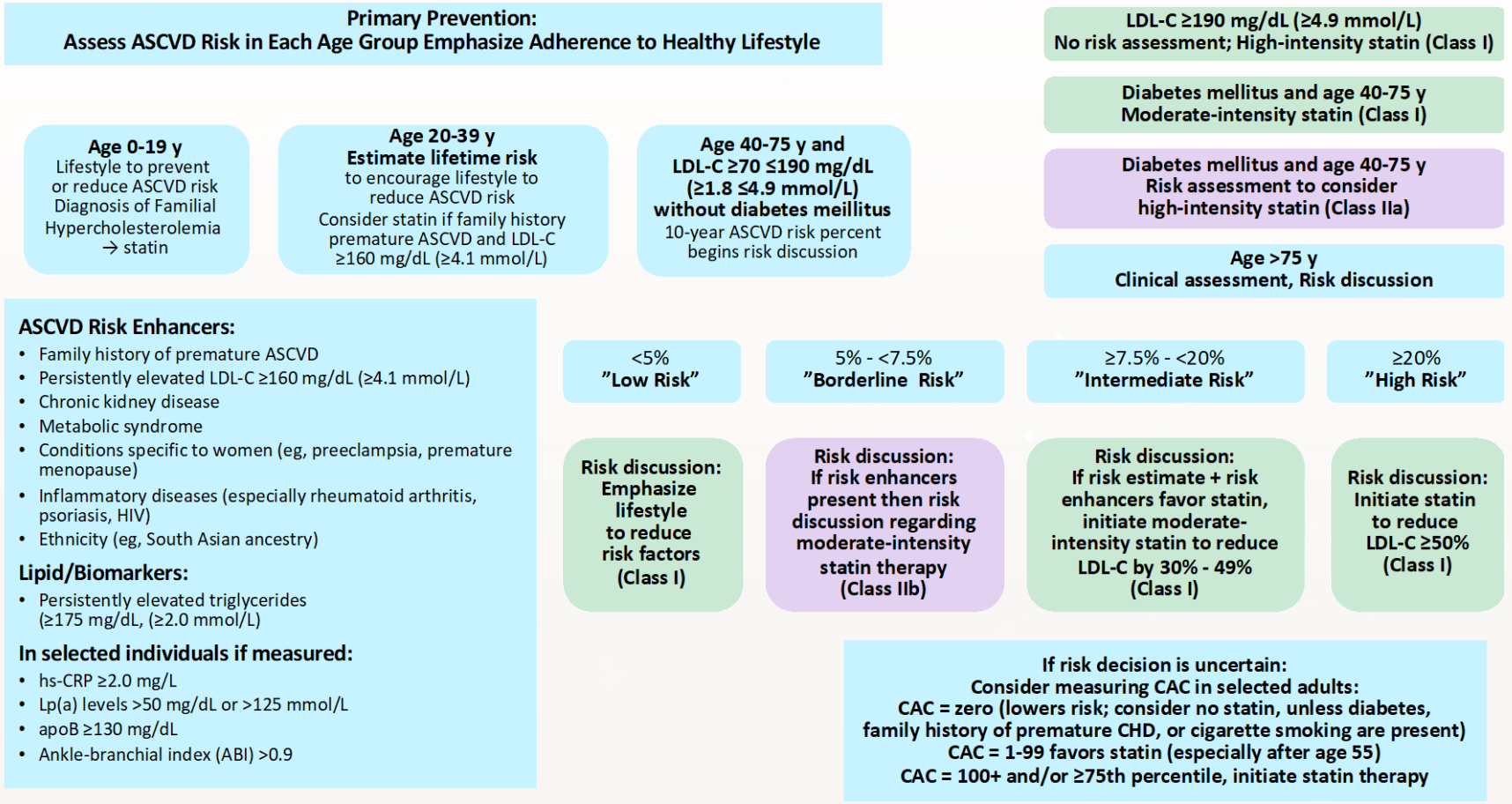
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- **Conditions specific to women (eg, preeclampsia, premature menopause)**
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asian ancestry)

Lipid/Biomarkers:

- Persistently elevated triglycerides (≥ 175 mg/dL or ≥ 2.0 mmol/L)

In selected individuals if measured:

- hs-CRP ≥ 2.0 mg/L
- Lp(a) levels > 50 mg/dL or > 125 mmol/L
- apoB ≥ 130 mg/dL
- Ankle-branchial index (ABI) < 0.9



Grundy SM, et al. *J Am Coll Cardiol*. 2019;73(24):e285-e350.

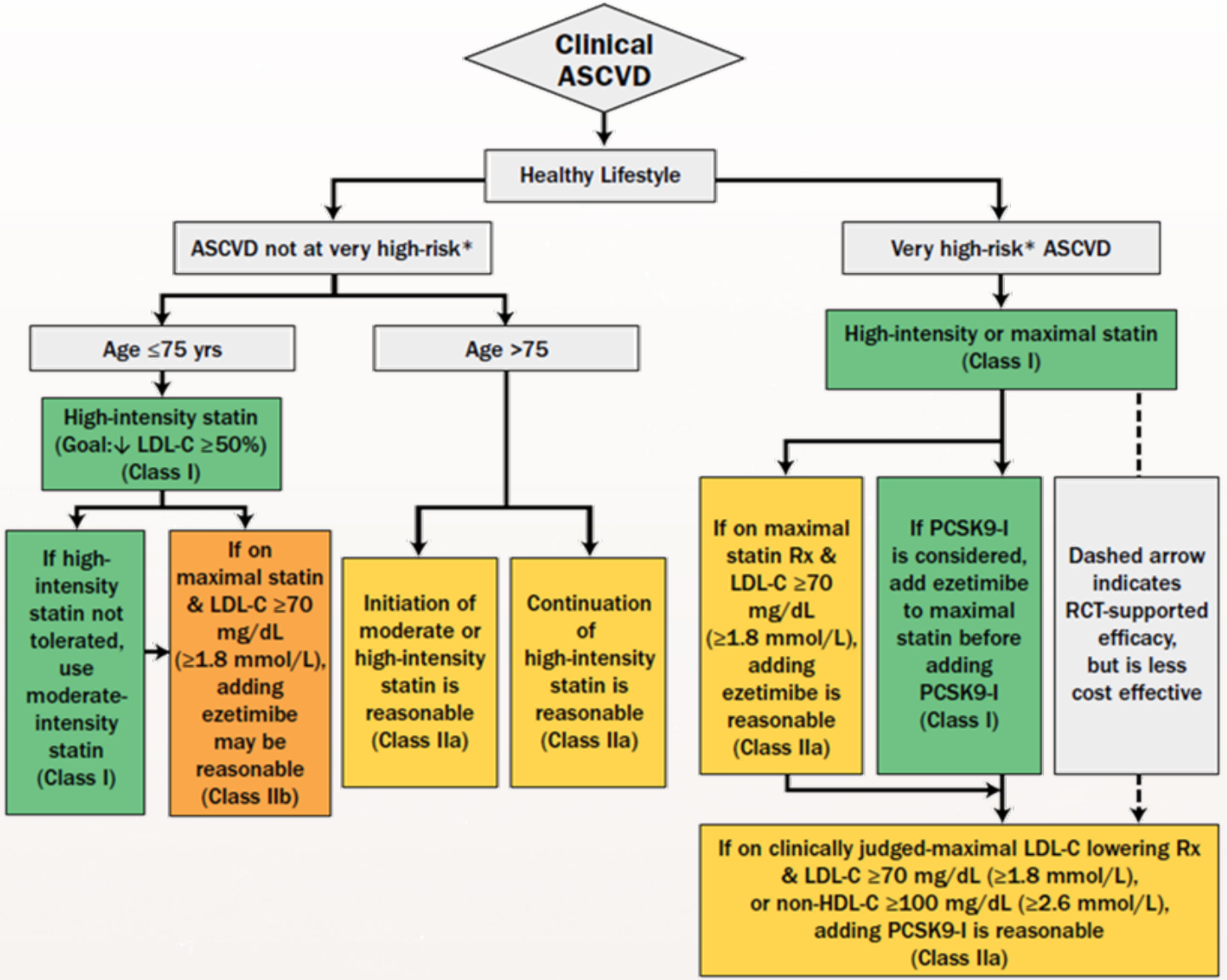
Very-High-Risk Features

- Recent ACS
- History of prior MI
- History of ischemic stroke
- Symptomatic PAD

- Age ≥ 65 years
- HeFH
- Prior CABG or PCI
- Diabetes
- Hypertension
- Chronic kidney disease
- Current smoking
- LDL-C ≥ 2.6 mmol/L (100 mg/dL) on statin and ezetimibe
- History of HF

- Recurrent ASCVD events
- Major ASCVD event with ≥ 1 risk conditions

Secondary Prevention in Patients with Clinical ASCVD



Grundy SM, et al. *Circulation*. 2019;139(25):e1046-e1081.

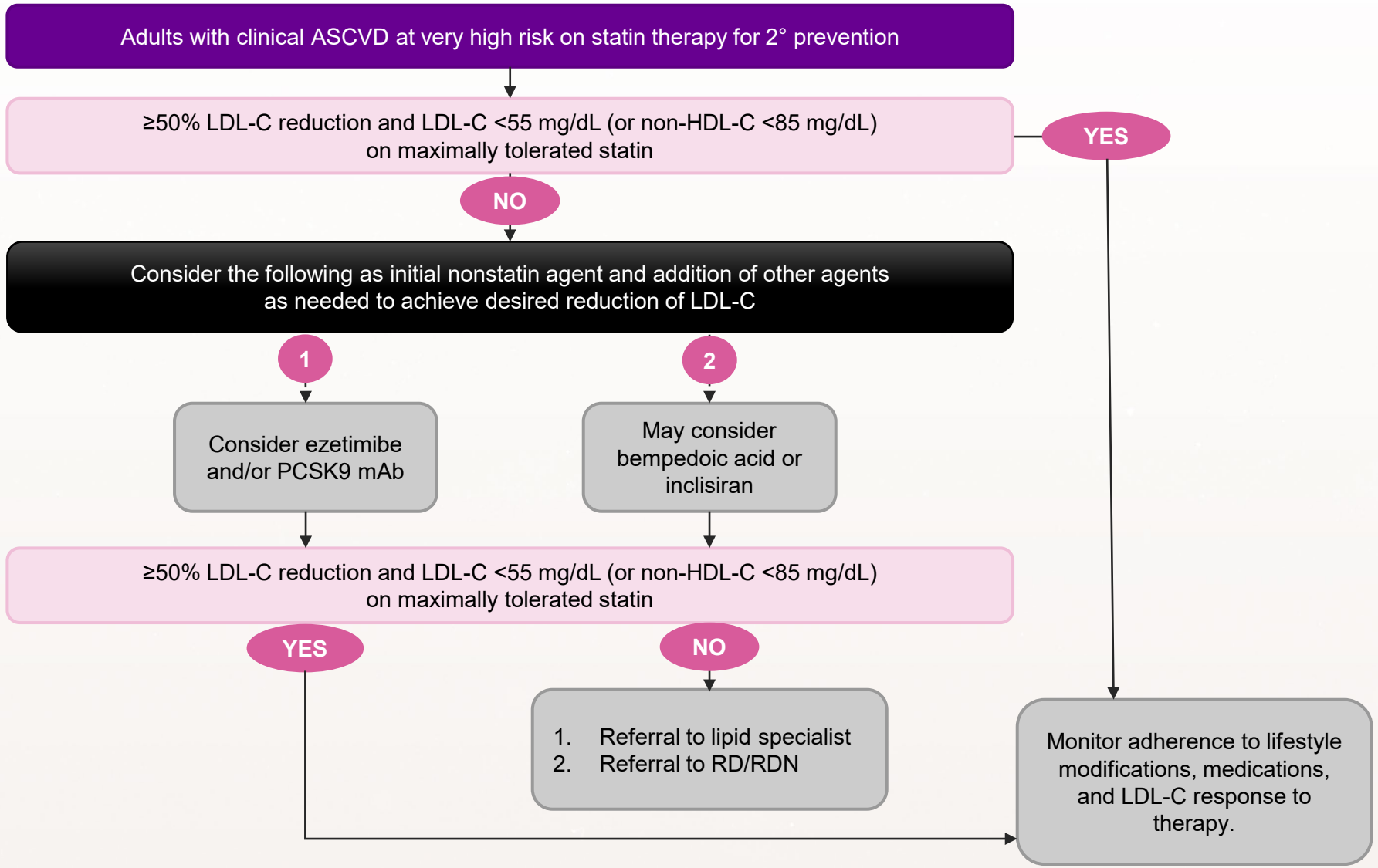
*Very High Risk for Future ASCVD events**

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

Grundy SM, et al. *J Am Coll Cardiol*. 2019;73(24):e285-e350.

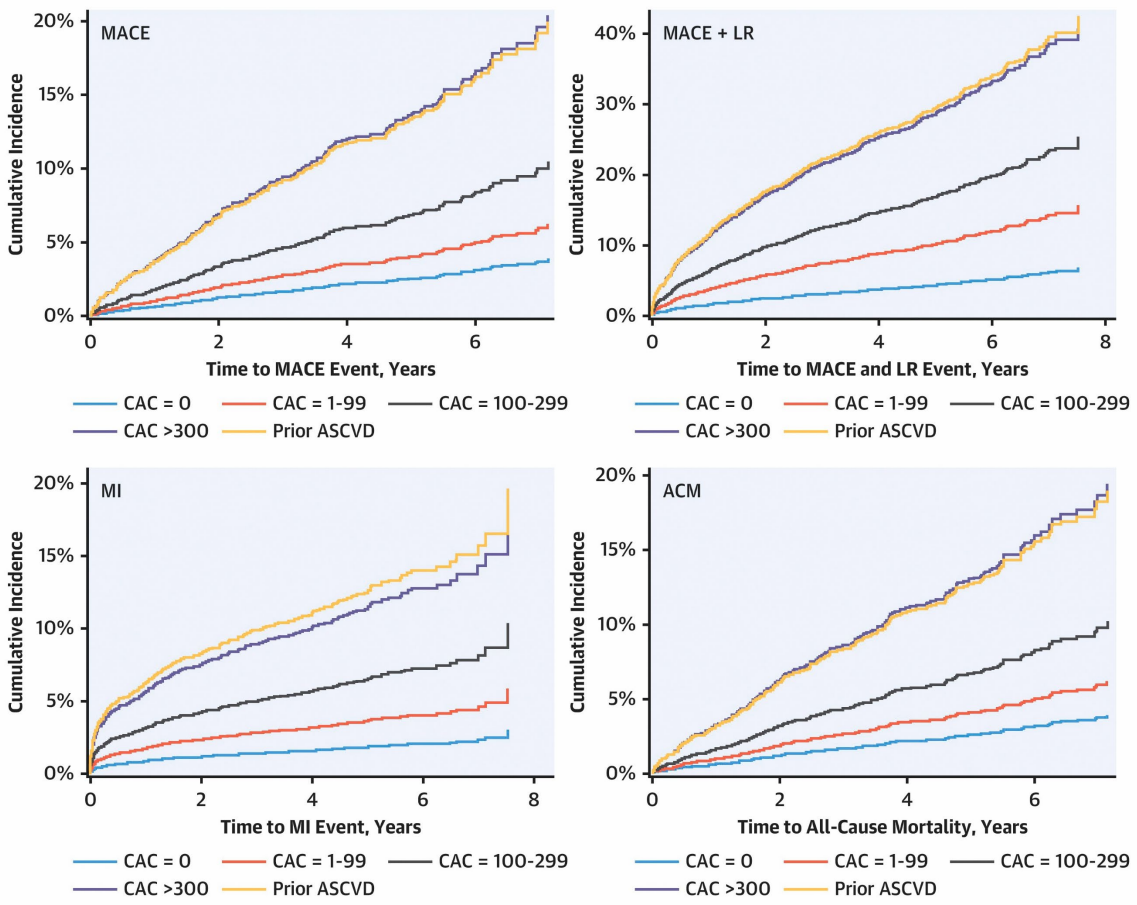
2022 ACC Expert Consensus Decision Pathway



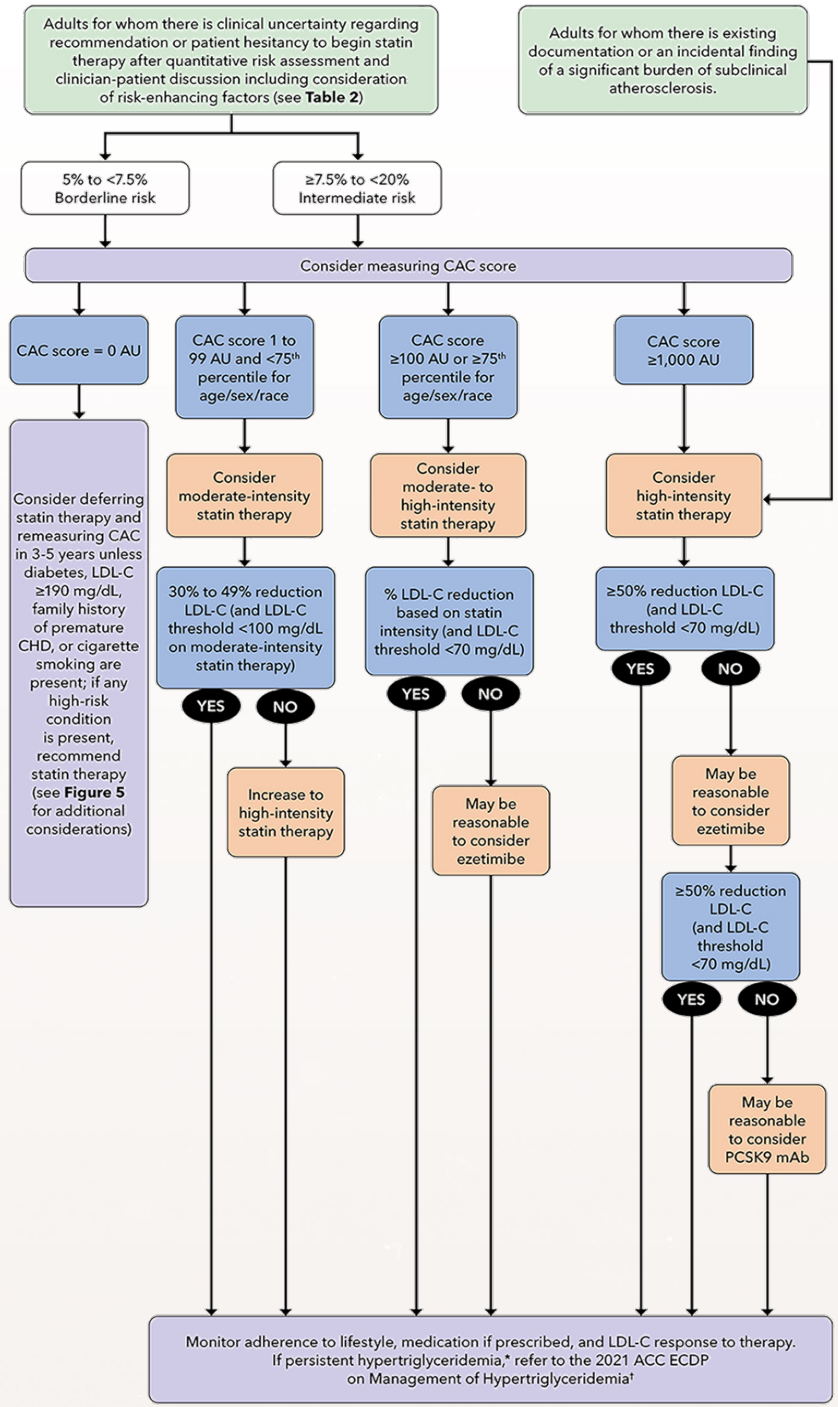
Lloyd-Jones DM, et al. J Am Coll Cardiol. 2022;80(14):1366-1418.

CAC Sore >300 = Same Risk as Patients With ASCVD

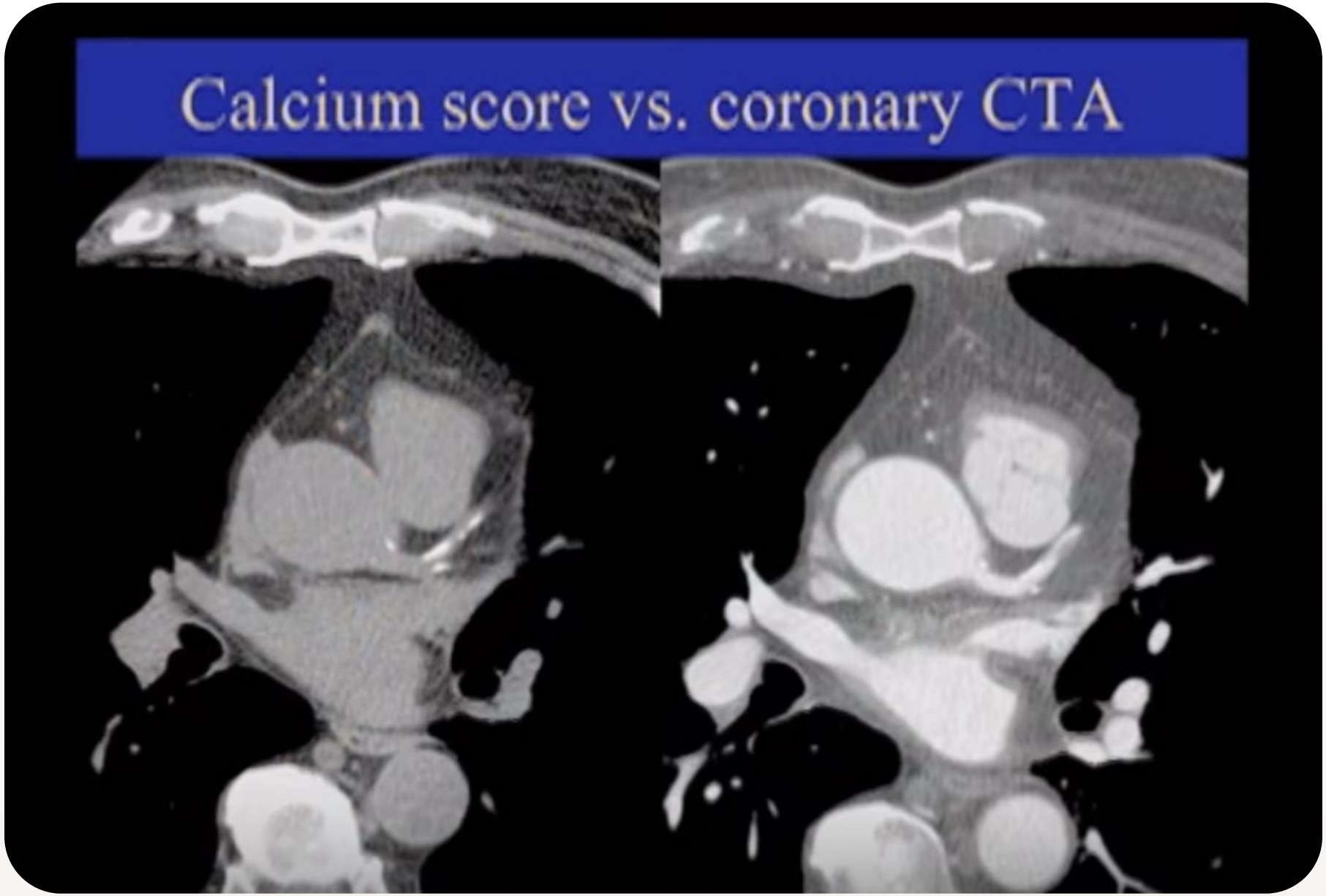
CENTRAL ILLUSTRATION: Event Rates by CAC Score Categories for MACE Compared to Prior ASCVD Patients



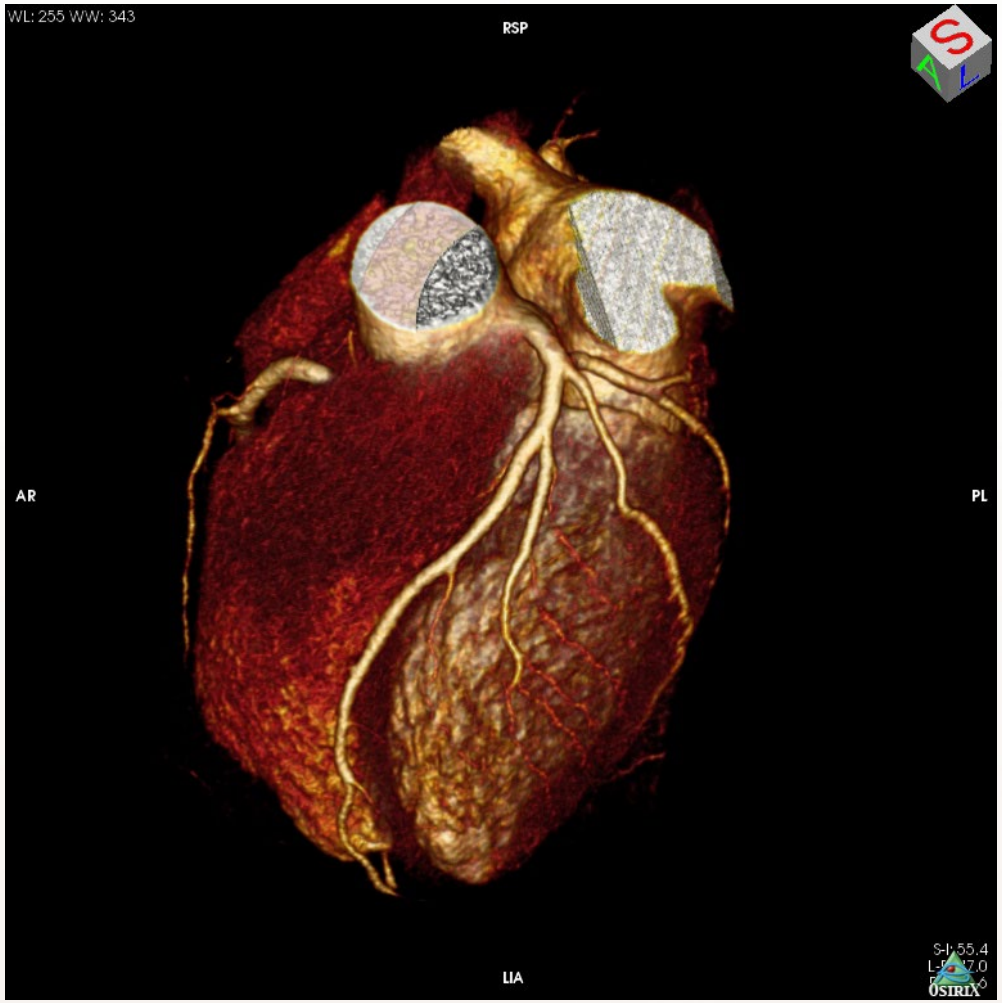
Budoff MJ, et al. J Am Coll Cardiol Img. 2023;16(9):1181-1189.



Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2022;80(14):1366-1418.


Calcium score vs. coronary CTA

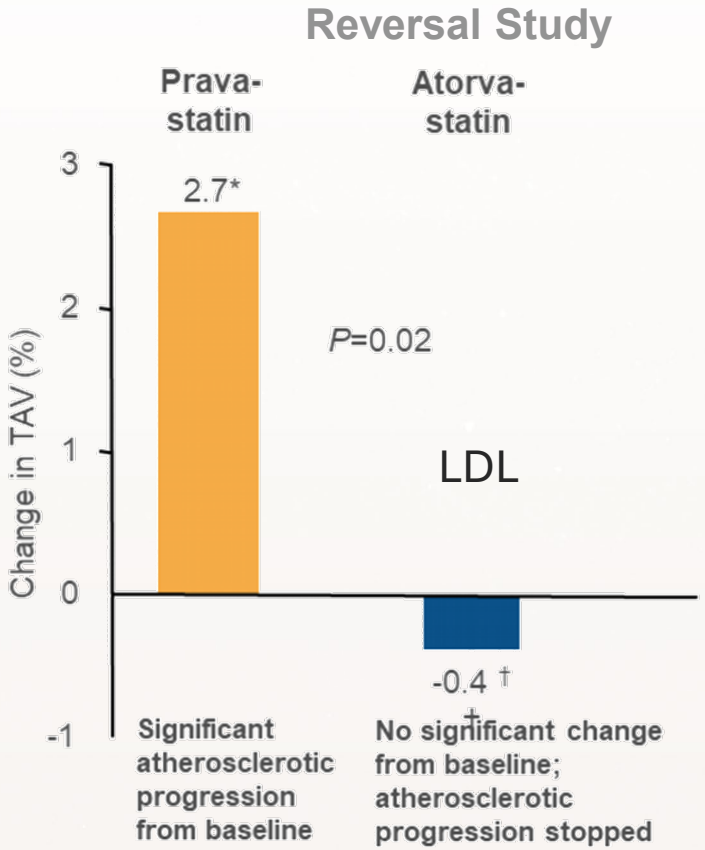
Coronary CT Angiography: Best Imaging Modality for Plaque Characterization

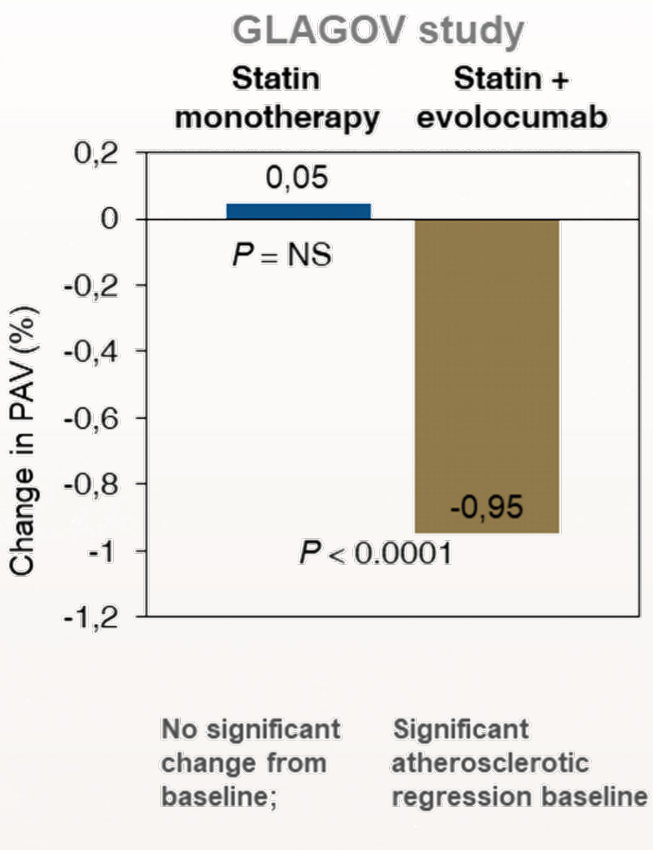


Chen, Pourmorteza, McVeigh, et al. NIH – UCSD.

Shake It Off: Exercise Daily to Reduce Risk of Cardiovascular Disease

Plaque Stabilization vs Plaque Regression Depends on LDL Achieved





LDL of 36 or lower resulted in significant plaque regression

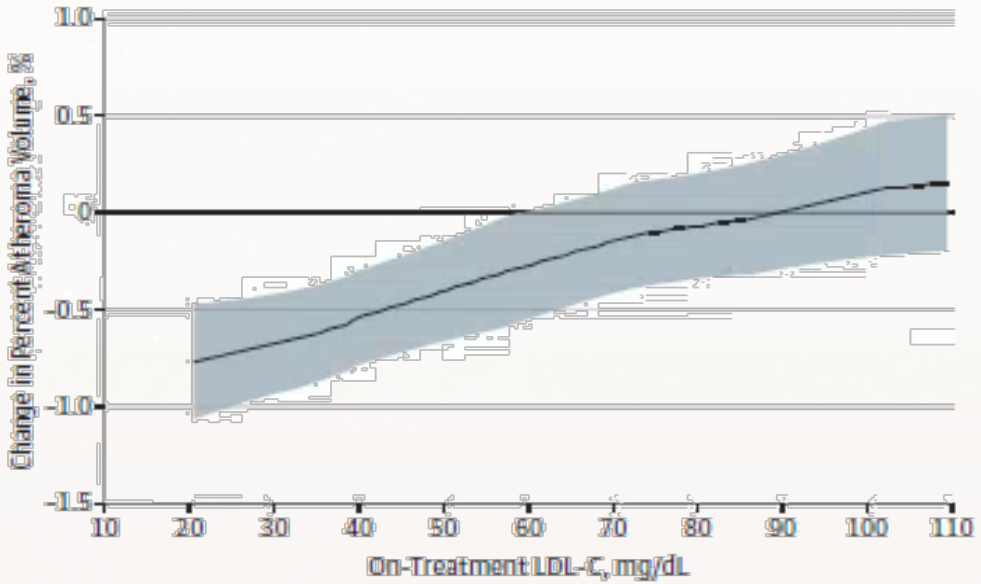
LDL in pravastatin group: 110
LDL in atorvastatin group: 79

LDL in statin group: 93
LDL in statin + PCSK9i group: 36

Nissen SE, et al. *JAMA*. 2004;291(9):1071-1080.
Nicholls SJ, et al. *JAMA*. 2016;316(22):2373-2384.

GLAGOV Study: Benefit of LDL Lowering on Plaque Regression

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



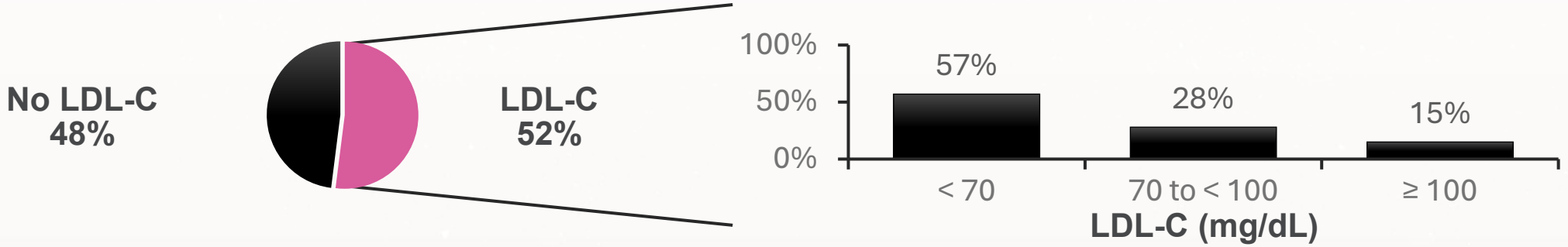
Local regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.

Nicholls SJ, et al. *JAMA*. 2016;316(22):2373-2384.

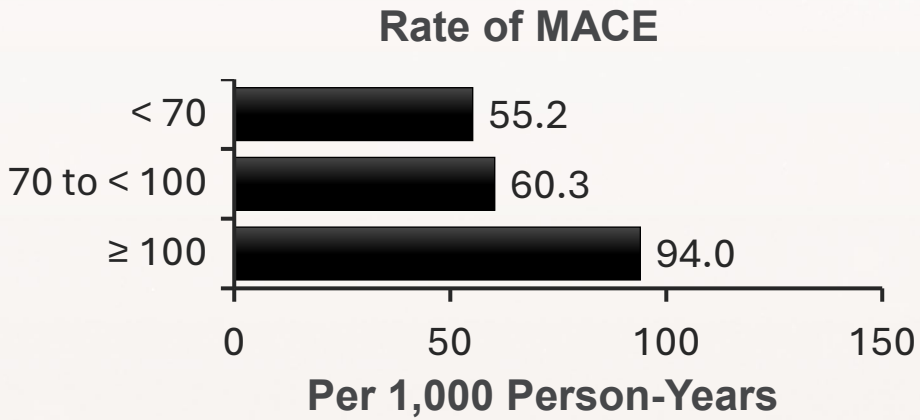
Reality Check: Many Patients With ASCVD Not at LDL-C Goal

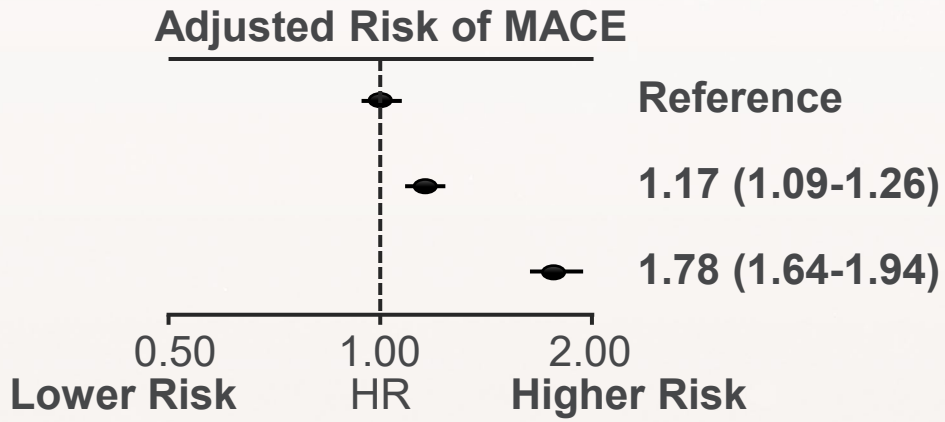
~1 of every 2 patients had LDL-C measured after PCI

~1 of every 2 patients had LDL-C < 70 mg/dL



Higher LDL-C after PCI was associated with a higher risk of MACE





Sud M, et al. *J Am Coll Cardiol*. 2020;76(12):1440-1450.

GOULD Registry: High-Risk Patients With ASCVD

GOULD is a multicenter observational registry that describes lipid-lowering therapy patterns among patients with clinical ASCVD + LDL-C ≥ 70 mg/dL (or taking a PCSK9i) in the United States

N = 5006

Enrolled from Dec 2016 - Jul 2018

Cohort 1

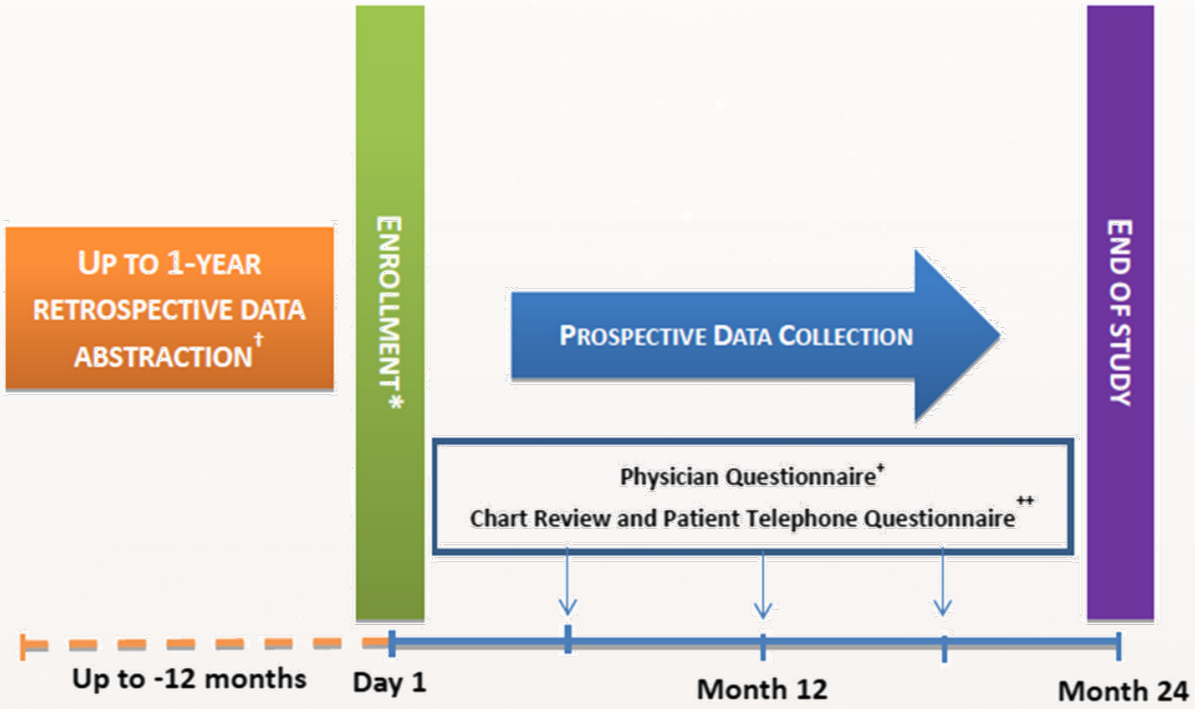
Patients taking PCSK9i at baseline

Cohort 2

Patients with LDL-C ≥ 100 mg/dL

Cohort 3

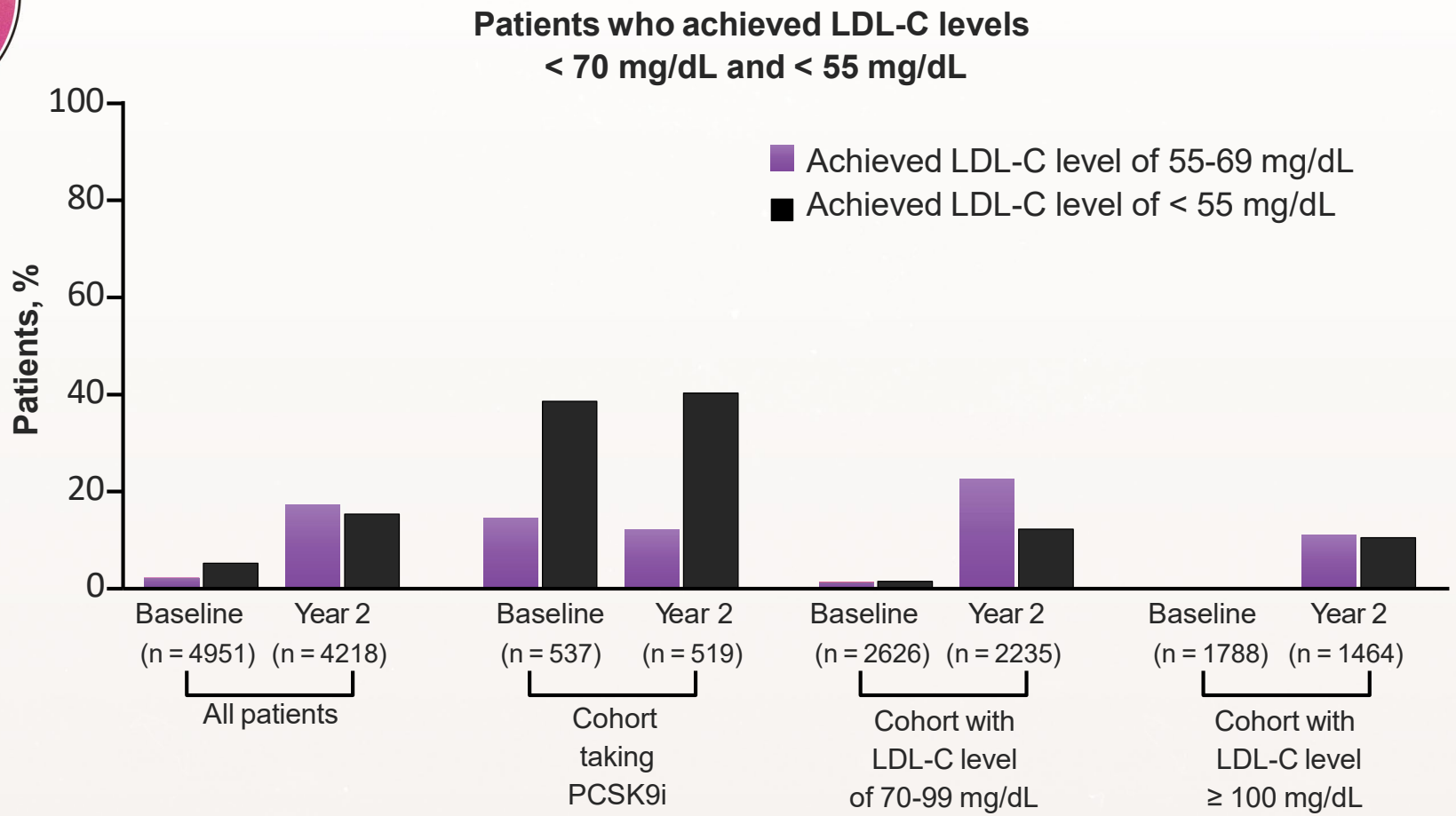
Patients with LDL-C 70–99 mg/dL

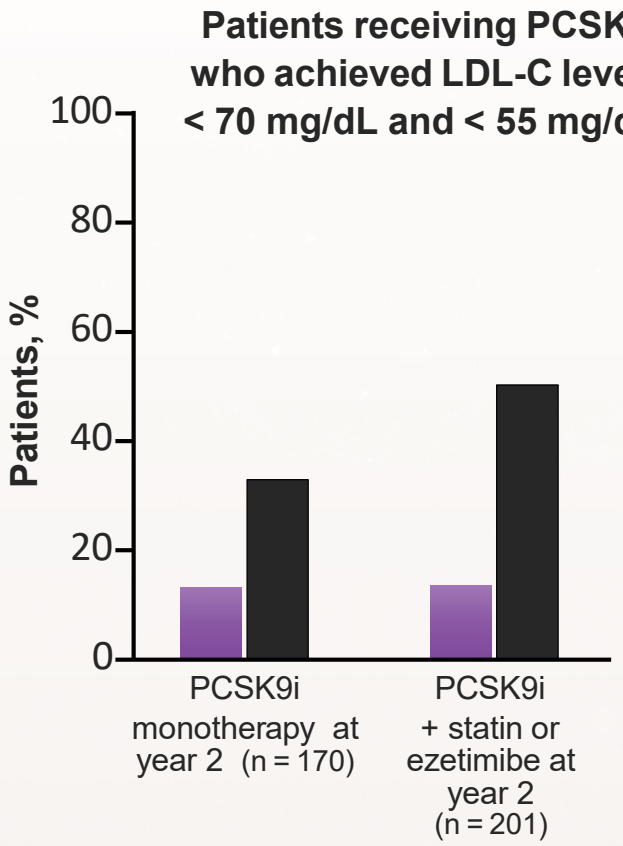


PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Cannon CP, et al. *Am Heart J*. 2020;219:70-77.

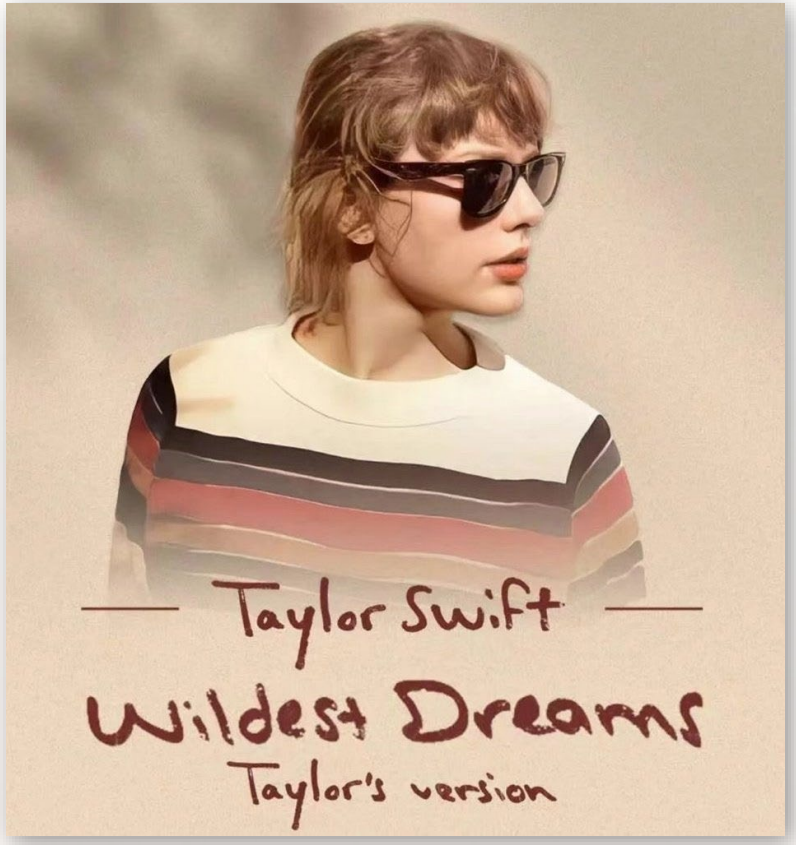
GOULD: Combination Therapy Required to Achieve Target LDL-C





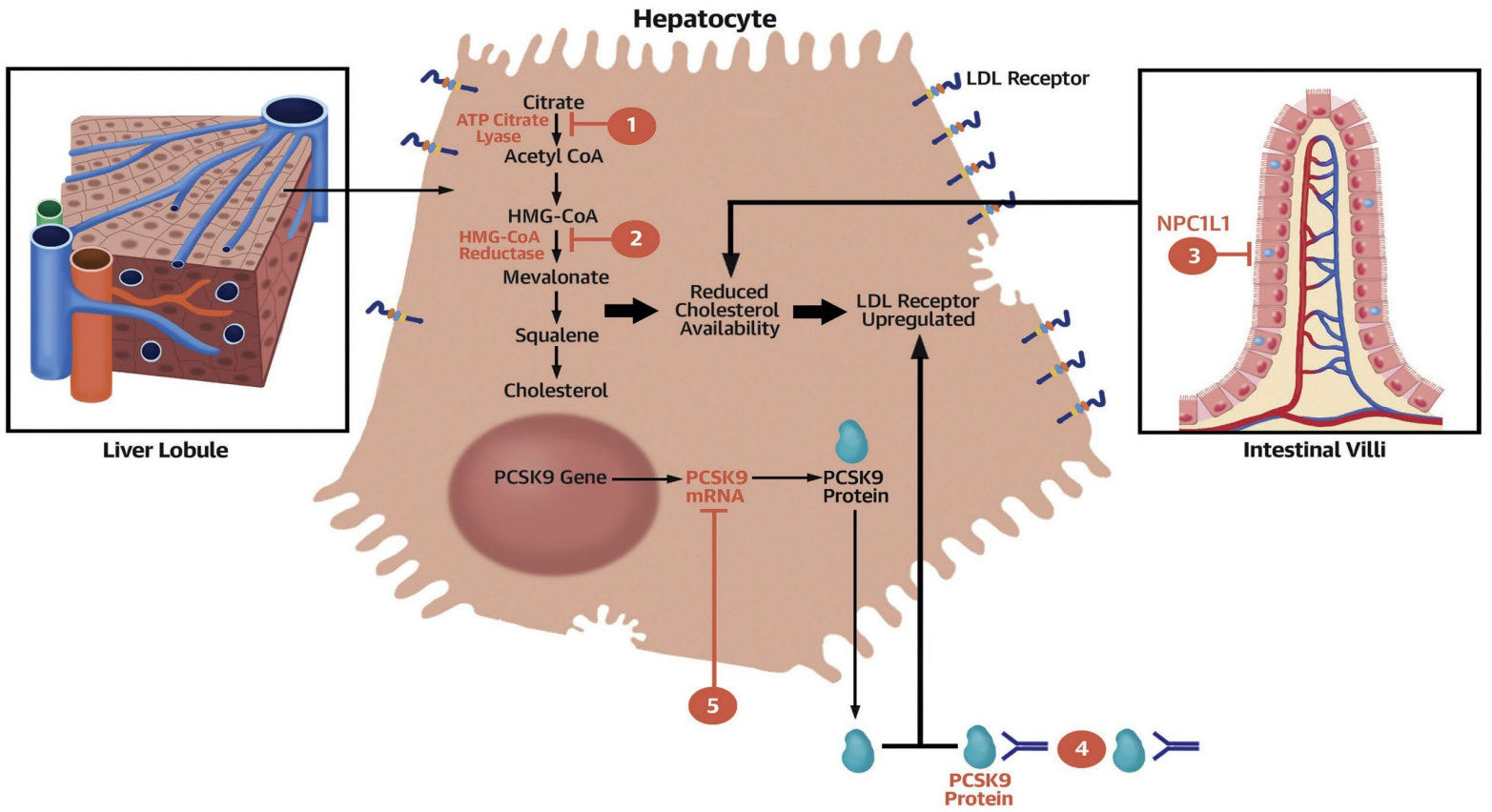
Cannon CP, et al. JAMA Cardiol. 2021;6(9):1060-1068.

Wildest Dreams: New Science Is Giving Us So Many Options for Lipid Lowering



Review of Mechanism of Action of Nonstatin Agents

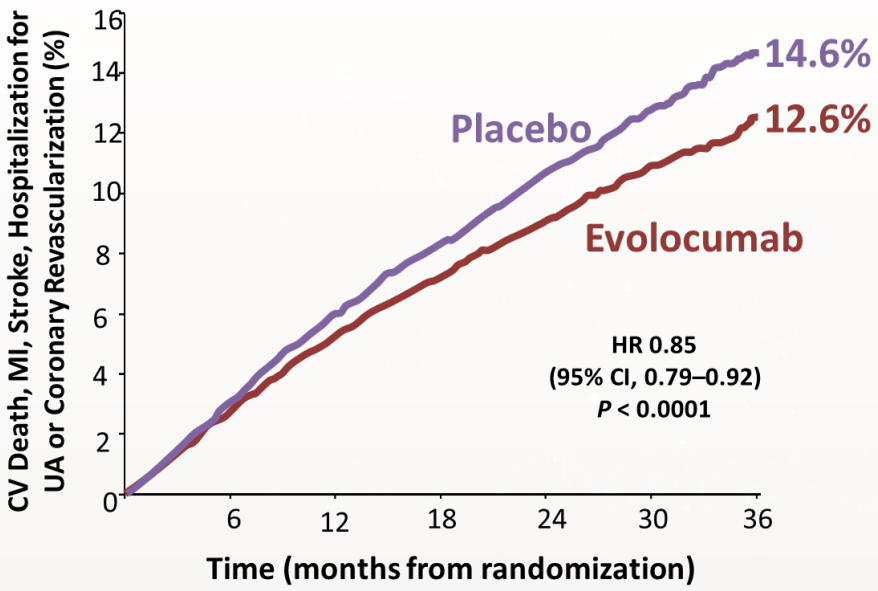
CENTRAL ILLUSTRATION: Schematic Diagram of the Mechanisms of Action of Statins, PCSK9 Inhibitors, PCSK9 Synthesis Inhibitors, and Bempedoic Acid



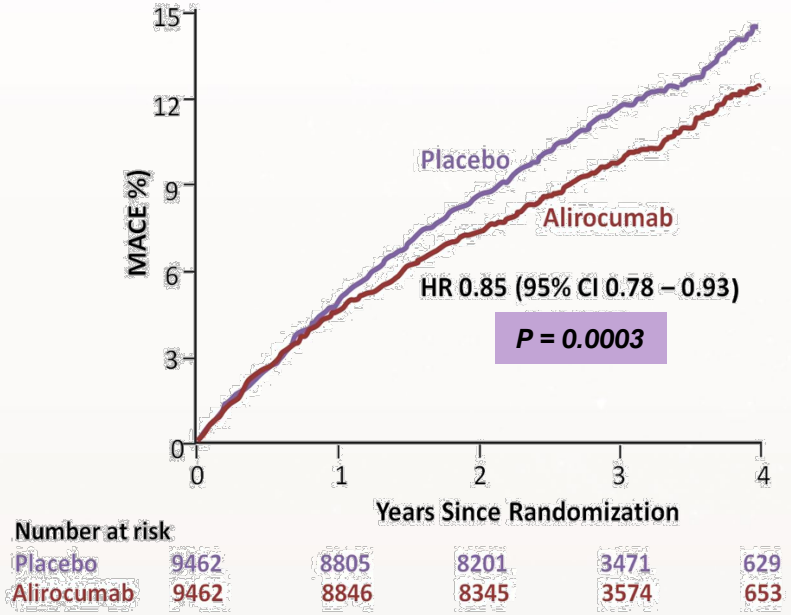
Preiss, D. et al. J Am Coll Cardiol. 2020;75(16):1945–55.

PCSK9i Cardiovascular Outcome Trials

FOURIER: Cumulative Incidence of MACE in Months After Randomization[1]



ODYSSEY: Cumulative Incidence of MACE per Year After Randomization[2]



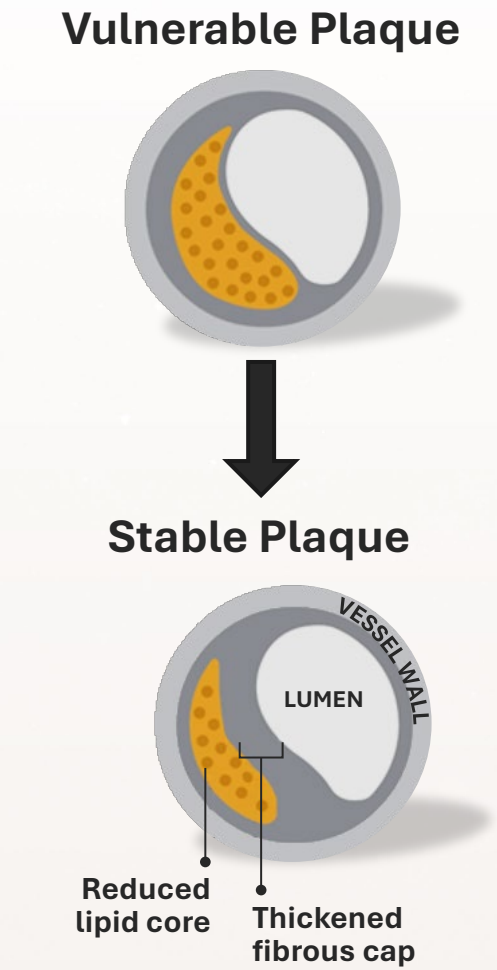
Efficacy	FOURIER	ODYSSEY OUTCOMES
Change in LDL-C (Absolute mg/dL)	56	53
% change in LDL-C (on-treatment arm)	↓59%	↓61%

MACE, major adverse cardiovascular event; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; UA, unstable angina.

1. Sabatine MS, et al; FOURIER Steering Committee and Investigators. *N Engl J Med*. 2017;376(18):1713-1722. 2. Schwartz GG, et al; ODYSSEY OUTCOMES Committees and Investigators. *N Engl J Med*. 2018;379(22)2097-2107.

Stabilization and Regression of Vulnerable Plaque With PCSK9 Inhibitors

- **Studies in ACS:**
  - HUYGENS: Evolocumab vs placebo
  - GLAGOV: Evolocumab vs placebo
  - PACMAN-AMI: Alirocumab vs placebo
- **Results:**
  - In patients with ACS, treatment with PCSK9i led to significantly greater plaque regression vs placebo
  - Plaque regression was related to degree of LDL-C lowering



ACS, acute coronary syndrome.

Nicholls SJ, et al. *JACC Cardiovasc Imaging.* 2022;15(7):1308-1321. Nissen SE, et al. *JAMA.* 2004;291(9):1071-1080. Nicholls SJ, et al. *JAMA.* 2016;316(22):2373-2384. Räber L,et al. *JAMA.* 2022;327(18):1771-1781.

Summary of Safety and Efficacy of Inclisiran

Efficacy Favors Inclisiran

- Mean proprotein convertase subtilisin-kexin type 9 % change from baseline ↓80.9% at Day 510
- Mean LDL-C% change from baseline ↓50.7% at Day 510
- LDL-C level ↓55.1 mg/dL at Day 510

Pooled Data ORION-9, -10, -11

Twice a year dosing

Now FDA-approved as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including HeFH. (*July 2023*)

Similar Safety to Placebo

- In this safety analysis: 3,655 patients with approximately 2,653 person years of exposure to inclisiran
- Similar safety profile between inclisiran and placebo
- Modest excess of self-limited mild-to-moderate TEAE at the injection site and bronchitis
- No difference between groups in liver, muscle, or hematological parameters

Wright RS, et al; ORION Phase III Investigators. *J Am Coll Cardiol*. 2021;77(9):1182-1193.
Inclisiran. Prescribing Information. Revised July 2023.

Statin Intolerance

- Statin nonadherence: up to 20% of patients prescribed a statin stop it due to side effects
- GAUSS-3 study: blinded, placebo-controlled statin rechallenge in patients with history of statin-associated muscle symptoms
  - 43% had statin intolerance
- PRIMO study: 7,924 patients on high-dose statins
  - 10.5% reported myalgias (38% with lifestyle-limiting side effects)

NLA 2022 Update: Statin Intolerance

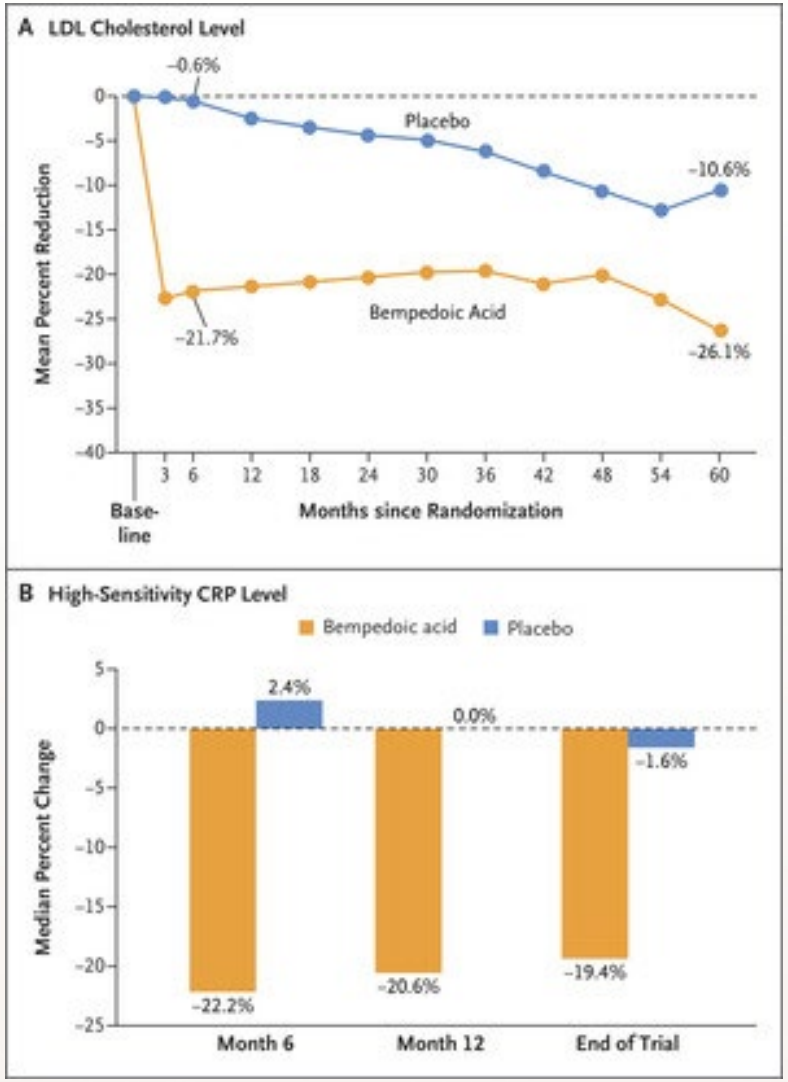
Partial Intolerance:
Ability to tolerate a lower dose of statin than is required to achieve the desired therapeutic objective

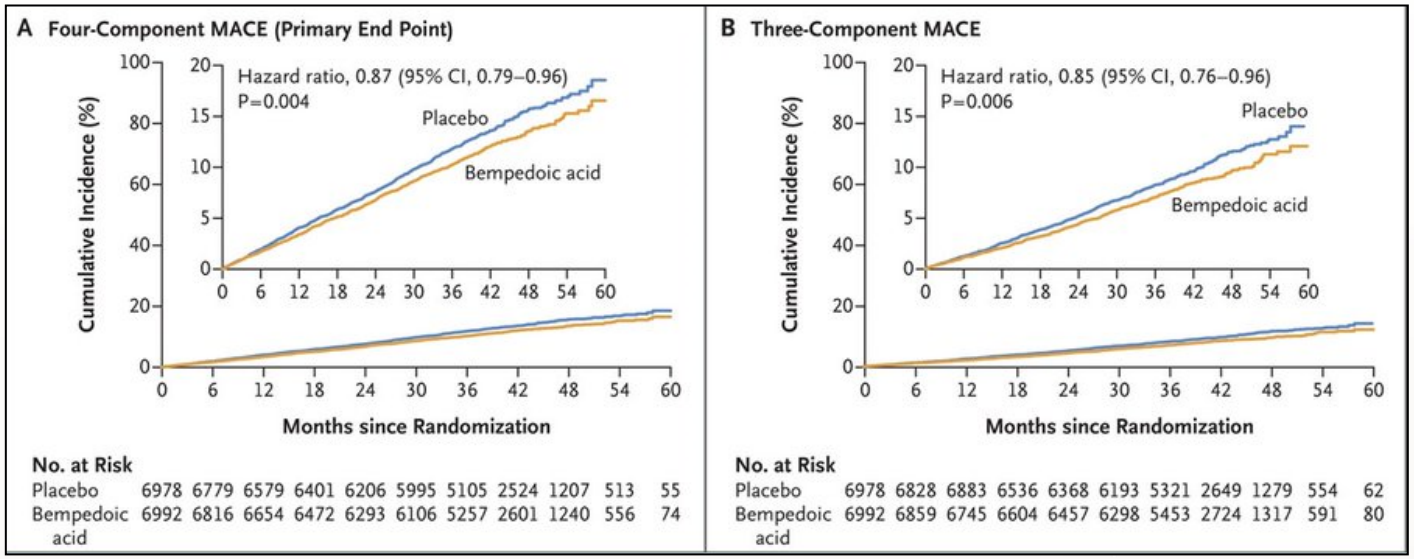
Complete Intolerance:
Patient is unable to tolerate any statin dose or regimen

Finding a tolerable statin regimen may require modification of the statin, statin dose, and/or dosing regimen

Bruckert E, et al. *Cardiovasc Drugs Ther.* 2005;19(6):403-414. Nissen SE, et al. *JAMA*. 2016;315(15):1580-1590.
https://www.lipid.org/nla/scientific-statement-statin-intolerance-new-definition-and-key-considerations-ascvd-risk

Clear Outcomes Study



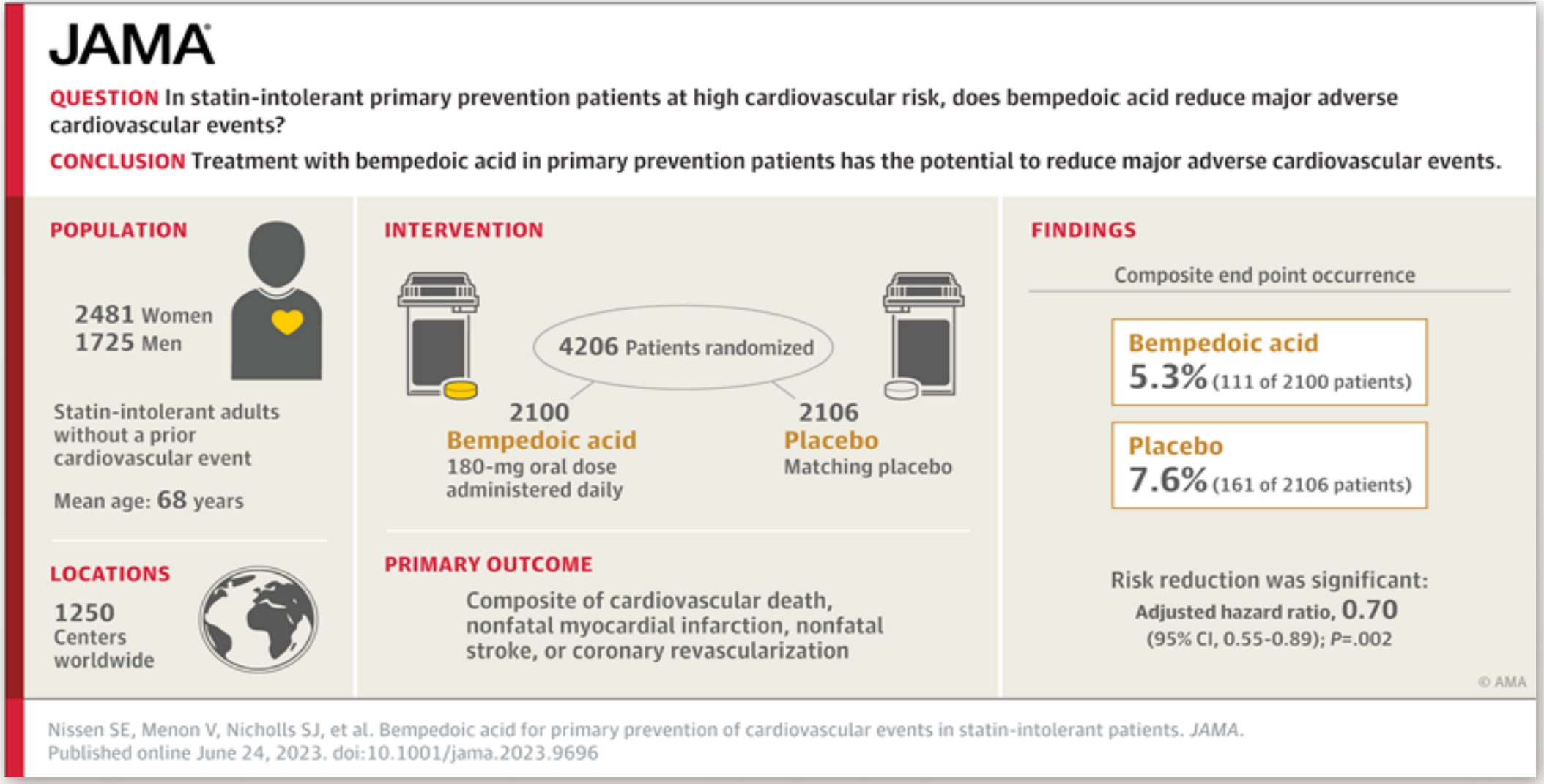


Primary endpoint: Four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

Key Takeaways:

- Patients with statin intolerance (high percentage are women; 48% women in trial) are undertreated and need more aggressive LDL lowering
- 13% RRR with bempedoic acid in composite MACE at 40 months; NNT 63
- Bempedoic acid is well tolerated and improves CV outcomes

Nissen SE, et al. *N Engl J Med*. 2023;388(15):1353-1364.



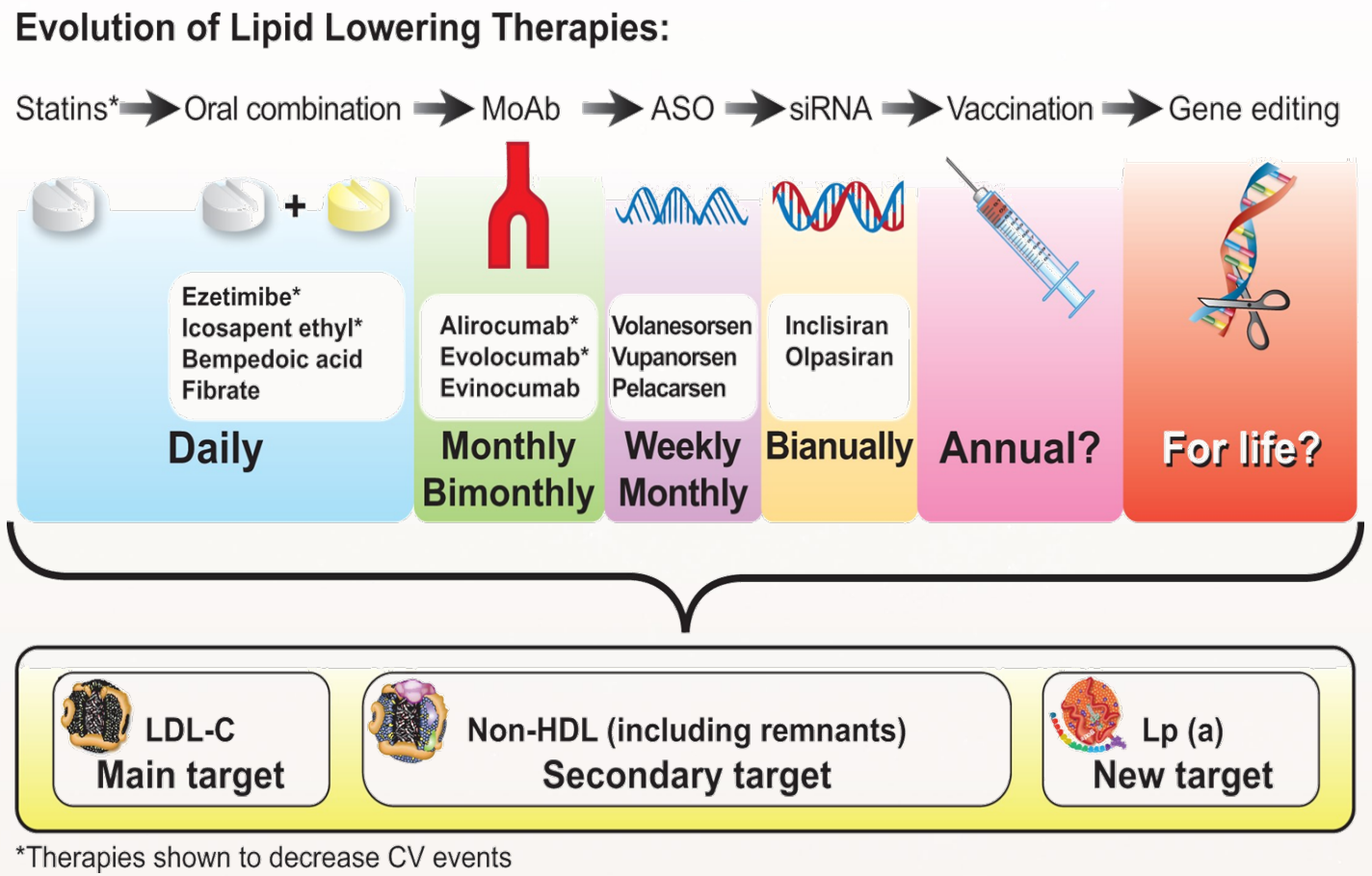
Key Takeaways:

- The high-risk primary prevention population has a high event rate, and this subgroup had even more benefit; NNT 44
- There was an all-cause mortality benefit for this subgroup

FDA Label Update March 2024 Based on CLEAR OUTCOMES

- The bempedoic acid component of NEXLIZET and NEXLETOL is indicated to reduce the risk of myocardial infarction and coronary revascularization in adults **who are unable to take recommended statin therapy (including those not taking a statin)** with:
  - established cardiovascular disease (CVD), or
  - **at high risk for a CVD event but without established CVD.**
- As an adjunct to diet:
  - NEXLIZET, alone or in combination with other LDL-C-lowering therapies, to reduce LDL-C in adults with primary hyperlipidemia, including HeFH.
  - NEXLETOL, in combination with other LDL-C-lowering therapies, or alone when concomitant LDL-C-lowering therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia, including HeFH.

The Future of Lipid-Lowering Therapies



Tokgözoğlu L, Libby P. *Eur Heart J*. 2022;43(34):3198-3208.

Conclusions

- Cardiovascular disease continues to be the #1 killer of women
- LDL-C is the single most modifiable risk factor
- Most high-risk patients with ASCVD are not at LDL-C goal
- Combination therapy with statin and nonstatin agents is needed to achieve LDL goals
- Patients with elevated CAC scores >300 should be considered secondary prevention
- Get the LDL as low as you can for secondary prevention

Women's Health 2024

Beyond the Annual Visit

THANK YOU