Strategies for Individualizing Lipid Management: Non statin therapies

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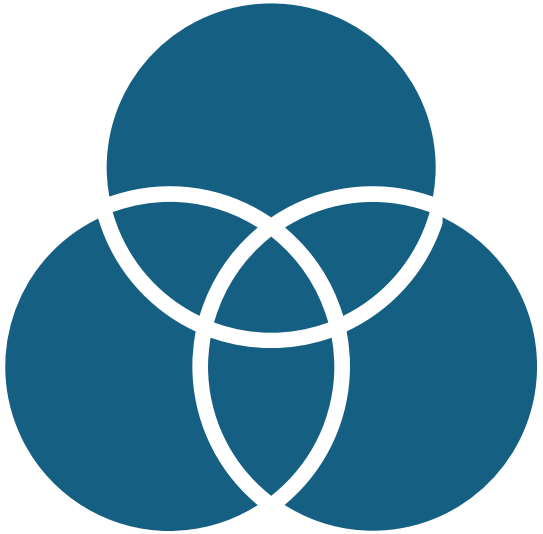
What is Preventive Cardiology

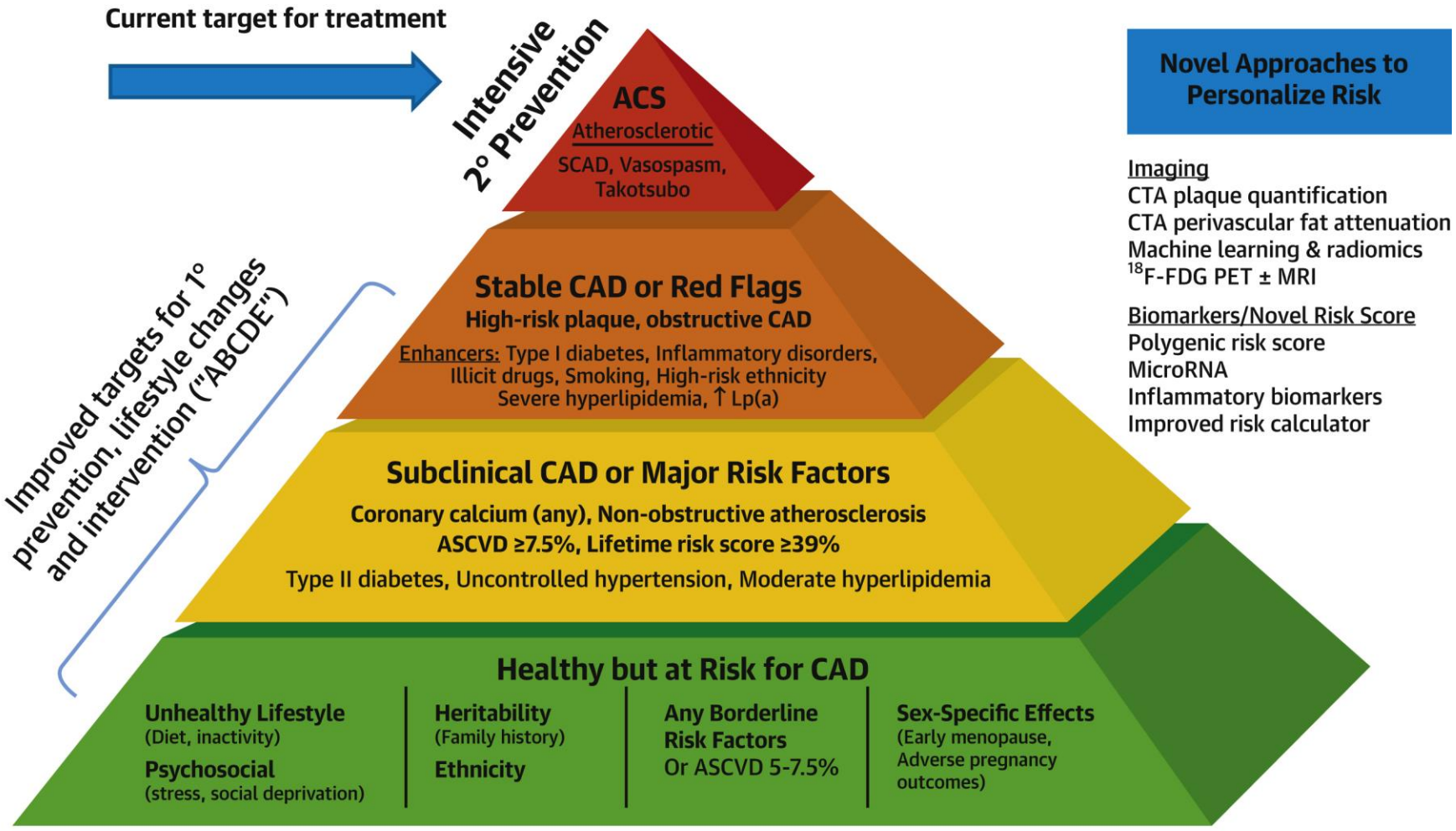
- Risk Assessment and identifying high risk primary prevention patients
- Personalized Risk Assessment
- Proactive management
- Early disease detection /Advanced Diagnostics
- Lifestyle Optimization
- Patient education and empowerment
- Medical management/Risk Reduction



Think C-P-R

- C- Calculate Risk
- P-Personalize
- Risk Reclassification

Primordial-Primary-Secondary Prevention



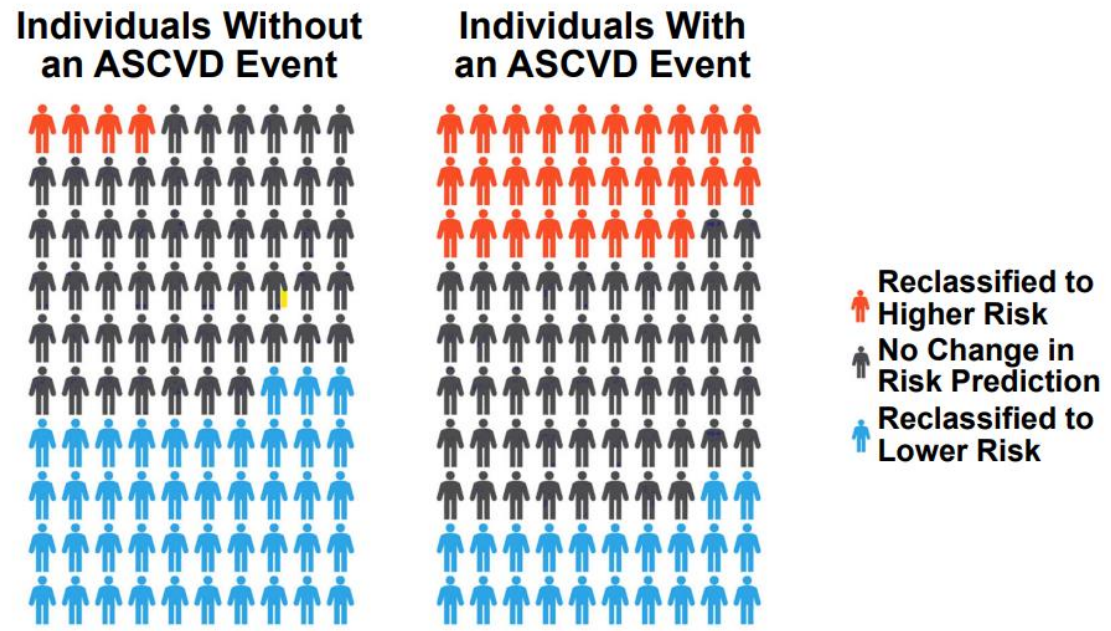
Novel Approaches to Personalize Risk

Imaging
CTA plaque quantification
CTA perivascular fat attenuation
Machine learning & radiomics
^{18}F-FDG PET ± MRI

Biomarkers/Novel Risk Score
Polygenic risk score
MicroRNA
Inflammatory biomarkers
Improved risk calculator

"Breaking the Cycle of Coronary Artery Disease in Young Adults"

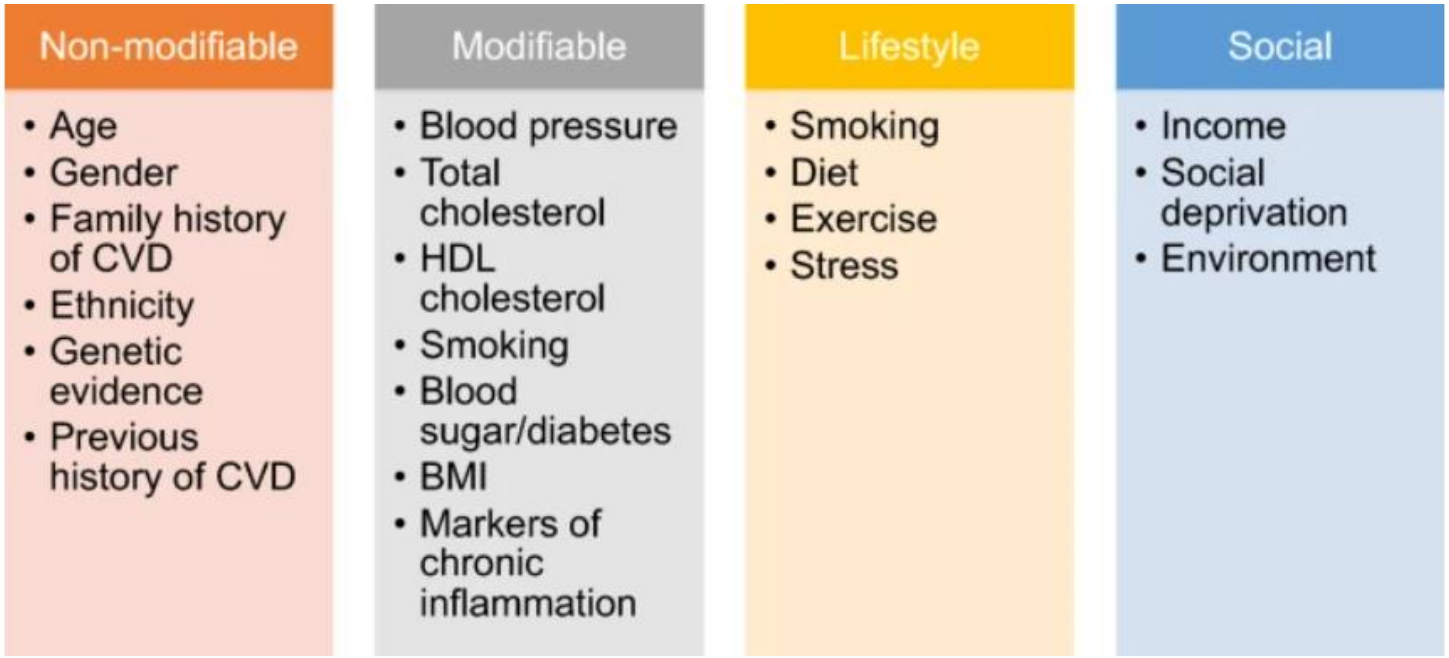
Risk Assessment: Prevent Calculator



- Intended for primary prevention in patients aged 30-79 years
  - 10-year risk estimates for individuals aged 30-79 years
  - 30-year risk estimates for individuals aged 30-59 years
- 10-year risk for CVD categories
  - Low risk (<5%)
  - Borderline risk (5%-7.4%)
  - Intermediate risk (7.5%-19.9%)
  - High risk (≥20%)

- Components
  - Sex
  - Age (range)
  - Total cholesterol (range)
  - HDL (range)
  - SBP (range)
  - BMI (range)
  - eGFR (range)
  - Diabetes, smoking status, antihypertensives, lipid Rx (yes/no)
  - Optional info: UACR, HbA1C, zip code [social deprivation index]

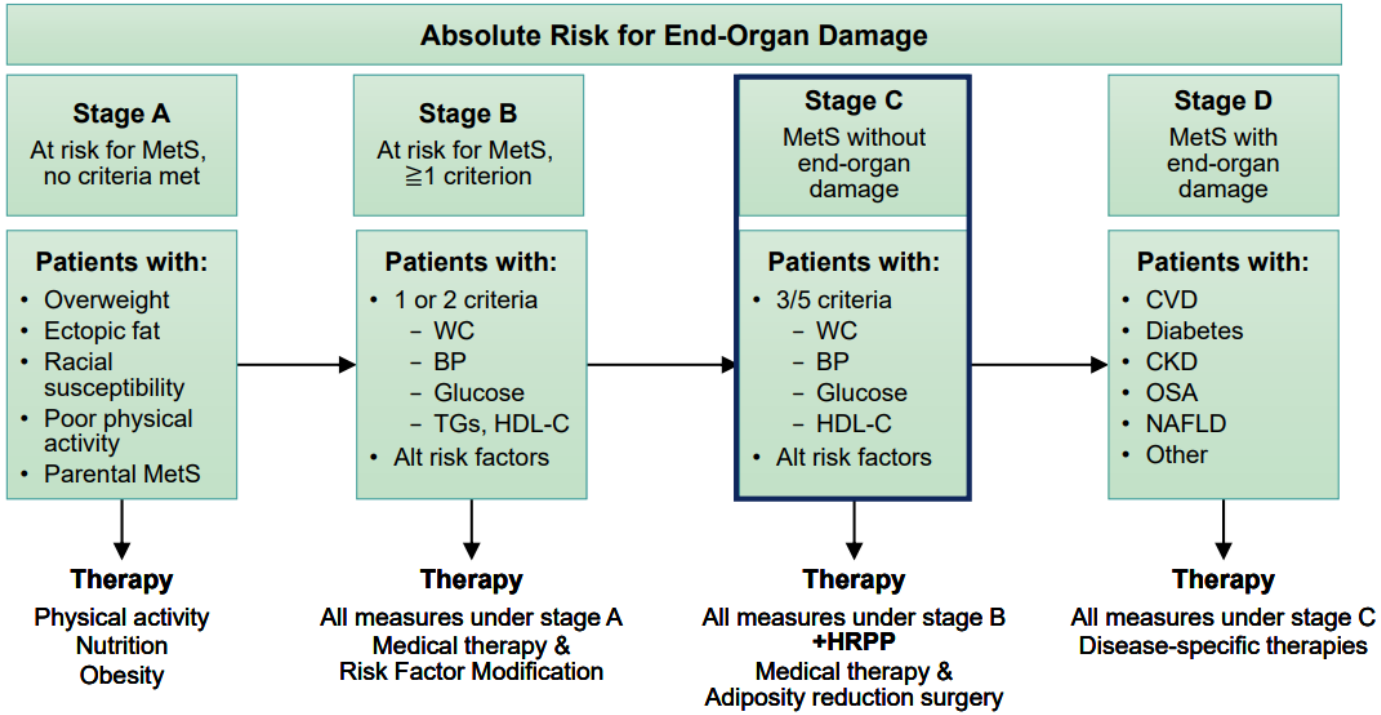
Cardiovascular Risk Factors: Modifiable and Non- Modifiable



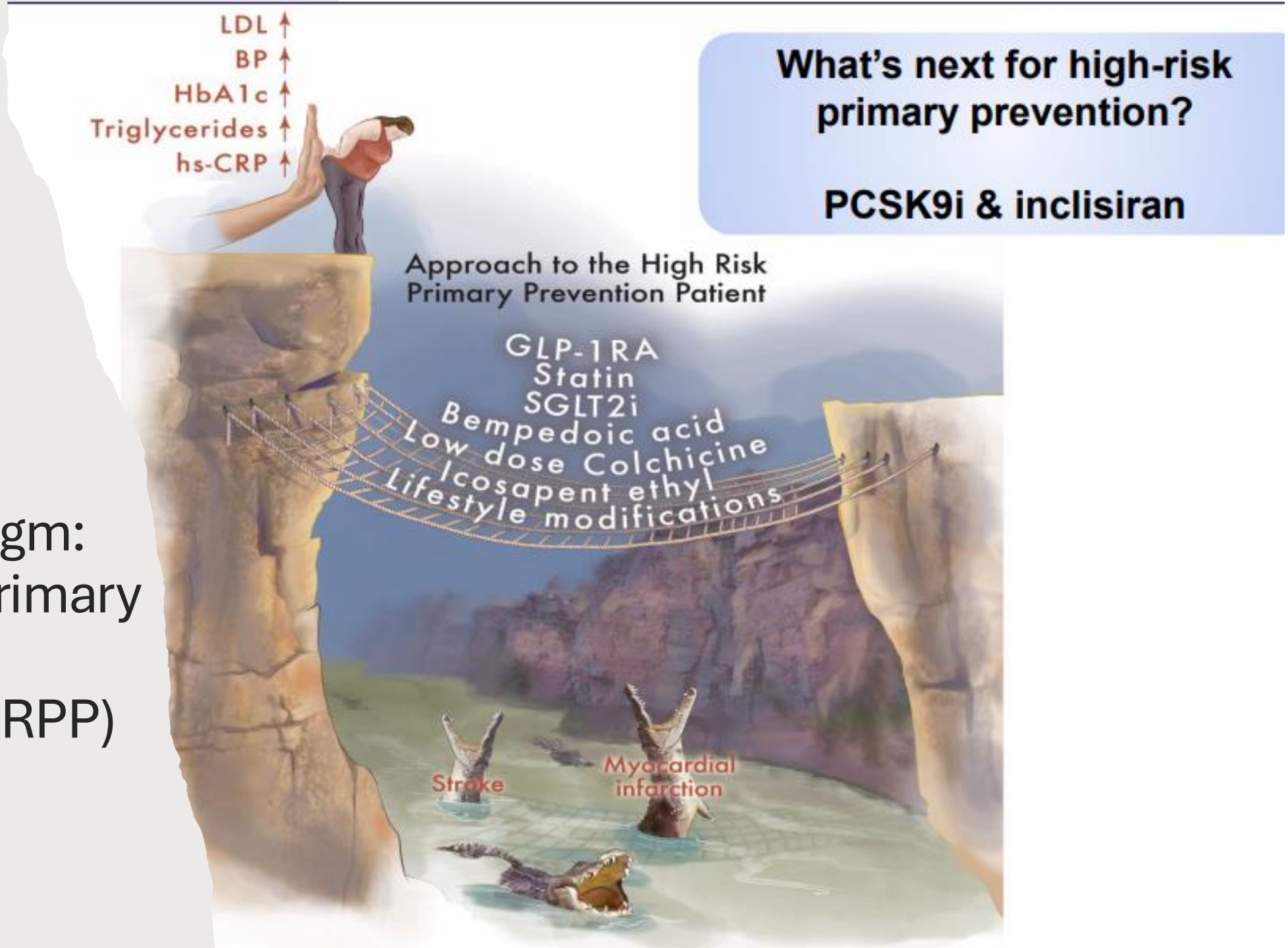
CV Risk Enhancers

- **Family history of premature ASCVD** (men aged <55 years; women aged <65 years)
- **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL [4.1-4.8 mmol/L); non–HDL-C 190-219 mg/dL [4.9-5.6 mmol/L]*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [≥150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; tally of 3 makes the diagnosis
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia**
- **High-risk races/ethnicities** (eg, South-Asian ancestry)
- **Lipids/biomarkers:** Associated with increased ASCVD risk
  - **Persistently* elevated, primary hypertriglyceridemia** (≥175 mg/dL)
  - If measured:
    1. **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    2. **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
    3. **Elevated apoB ≥130 mg/dL:** A relative indication for its measurement would be triglycerides ≥200 mg/dL. A level ≥130 mg/dL corresponds to LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor
    4. **ABI** <0.9

When do we start ?



New Paradigm: High Risk Primary Prevention Patients (HRPP)



HRPP: WHAT to look for

Definition

- 3 or more of:
  - Waist circumference (WC) ≥102 cm (40 in) (men) or ≥88 cm (35 in) (women)
  - Triglycerides ≥150 mg/dL*
  - HDL-C <40 mg/dL (men), <50 mg/dL (women)*
  - SBP ≥130 mmHg and/or DBP ≥85 mmHg*
  - Fasting glucose ≥100 mg/dL*

*or taking a medication to address this problem

WC cutoff for South Asian population is ≥90 cm (35.5 in) for males and ≥80 cm (31.5 in)for females

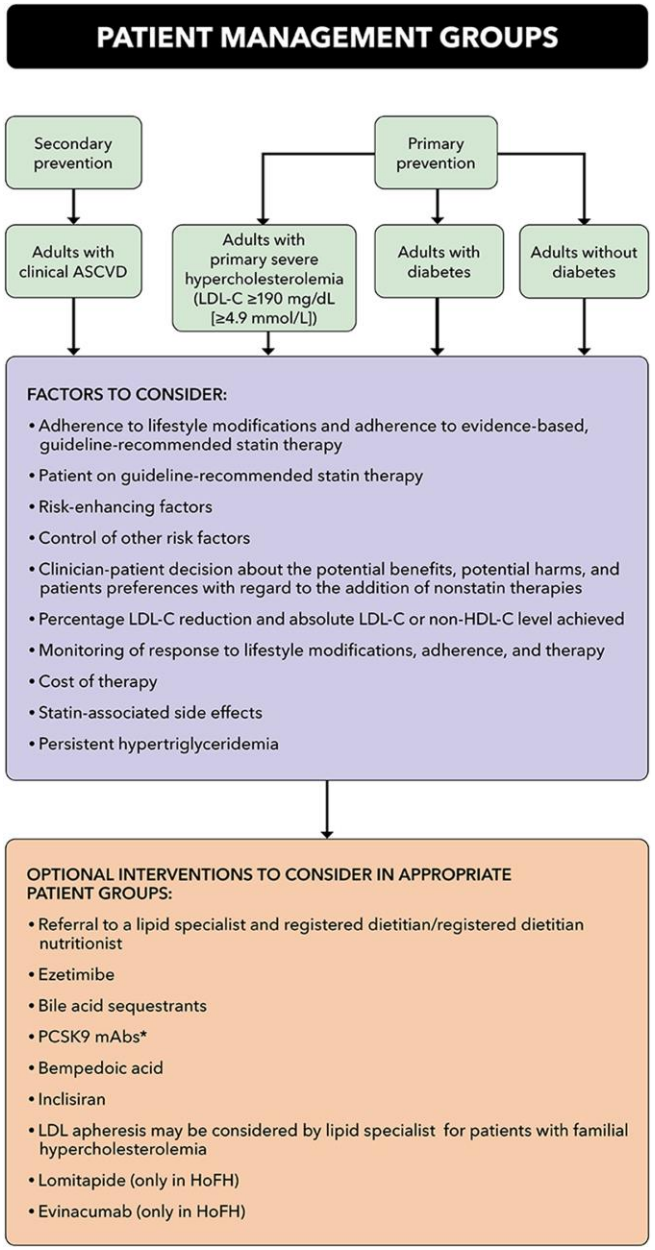
Risk

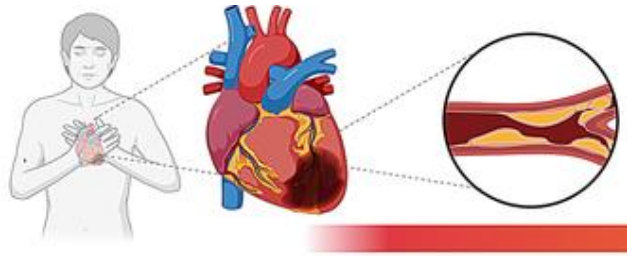
- 2x risk of developing cardiovascular disease over 5-10 years
- 5-fold increase in risk of type 2 diabetes mellitus

Prevalence

- 34% of the US has metabolic syndrome
- Obesity with metabolic syndrome:
  - 65% of men, 56% of women

Primary vs Secondary Prevention Groups





Primary ASCVD Risk Reduction

Risk Assessment

PREVENT
ACC/AHA Pooled Cohort Equations (PCE)
QRISK 3
JBS3
SCORE 2

Coronary Artery Calcium Score

Genetic risk markers

- Lipoprotein (a)
- Polygenic risk score

ASCVD "Risk Enhancers"

- Family hx of premature ASCVD
- Primary hypercholesterolemia
- Chronic kidney disease
- Metabolic syndrome
- Preeclampsia
- Premature menopause
- Chronic inflammatory disease
- South Asian ancestry
- Peristent hypertriglyceridemia (≥175 mg/dL nonfasting)
- Elevated hs-CRP ≥2.0 mg/L
- Elevated Lipoprotein (a) ≥125 nmol/L
- Elevated Apoprotein B ≥130 mg/dL
- Ankle-brachial index <0.9

Treatment Indications

Familial hypercholesterolemia with LDL-C ≥190 mg/dL

Diabetes mellitus in individuals aged 40-75 years

Individuals aged 40-75 years with LDL-C ≥70 to <190 mg/dL without diabetes mellitus

"High ASCVD Risk"
PCE predicted risk ≥20%

"Intermediate ASCVD Risk"
PCE predicted risk ≥7.5% to <20%

"Borderline ASCVD Risk"
PCE predicted risk 5% to <7.5%
+ risk enhancers

Management

Therapeutic lifestyle modification

Lipid Lowering Therapies

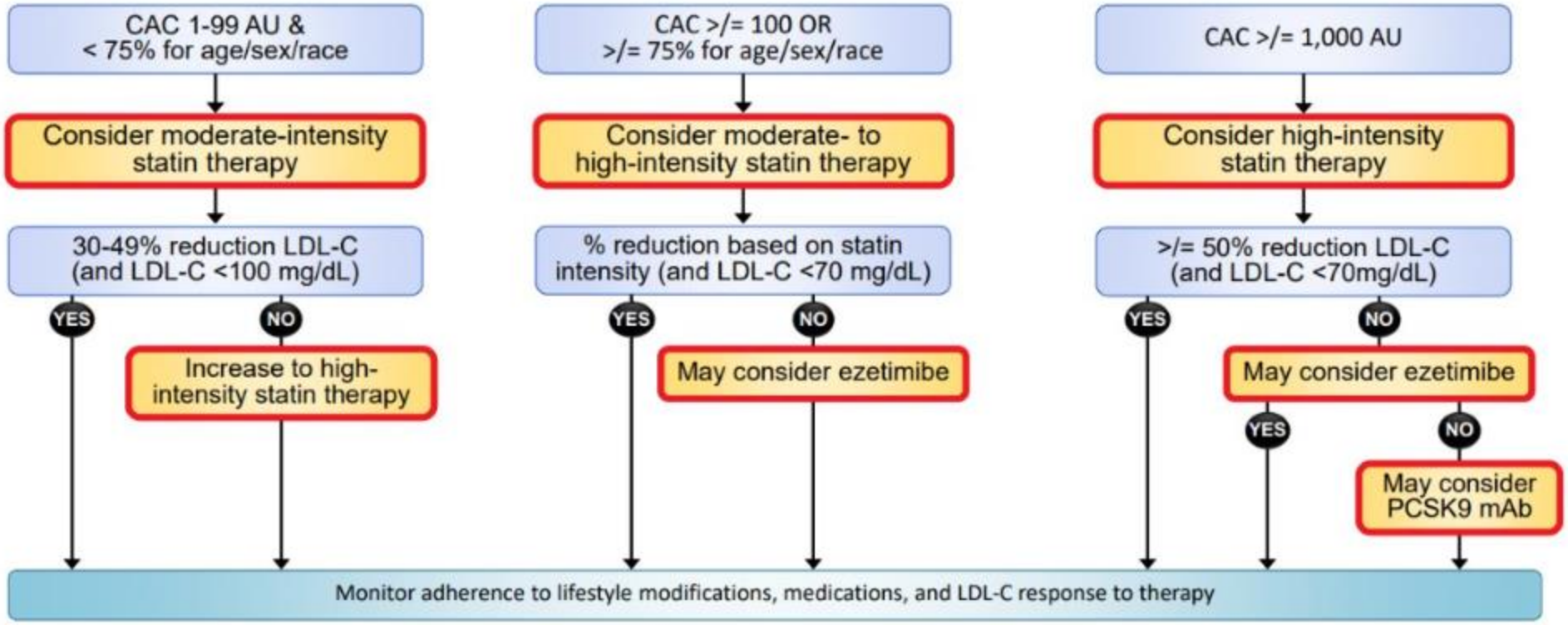
- Statin
- Ezetimibe
- PCSK9 inhibitor
- Bempedoic Acid
- Icosapent Ethyl

Therapeutic Goals

LDL-C ≤100 mg/dL
(preferably <70 mg/dL if PCE risk >20%)

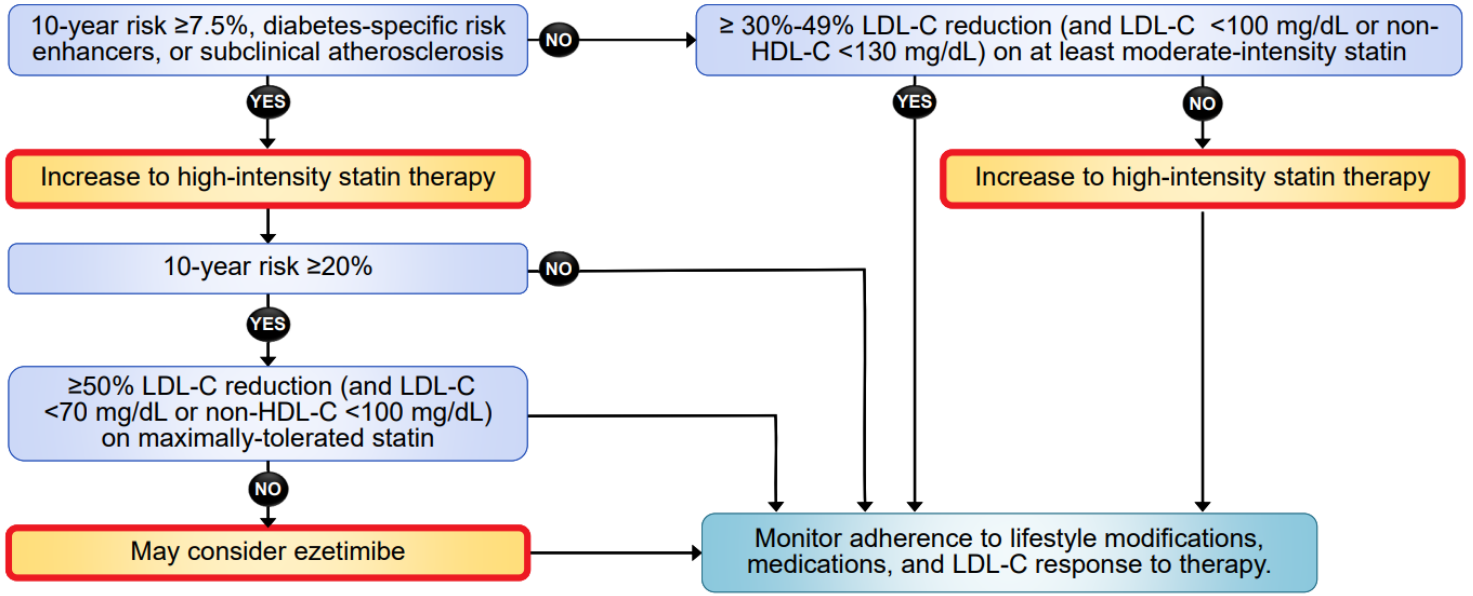
non-HDL <130 mg/dL
(preferably <100 mg/dL if PCE risk >20%)

Calcium scoring (CAC) Management



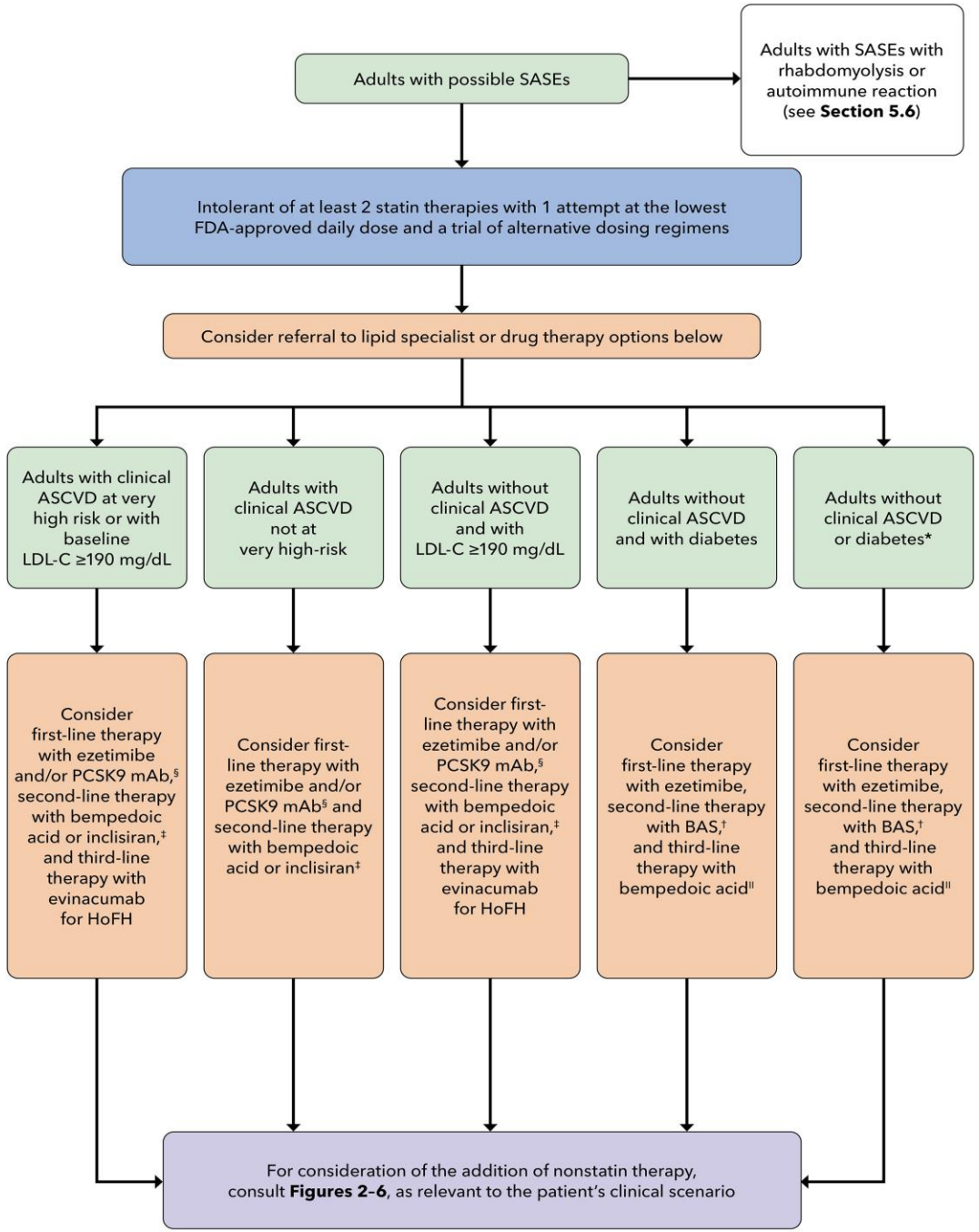
If noted coronary calcifications on alternative imaging- No additional value in obtaining CAC Score.

Statin therapy is still the cornerstone of treatment



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

Non-statin Therapies options



Summary of Data of Pharmacotherapy Lipid Lowering Data

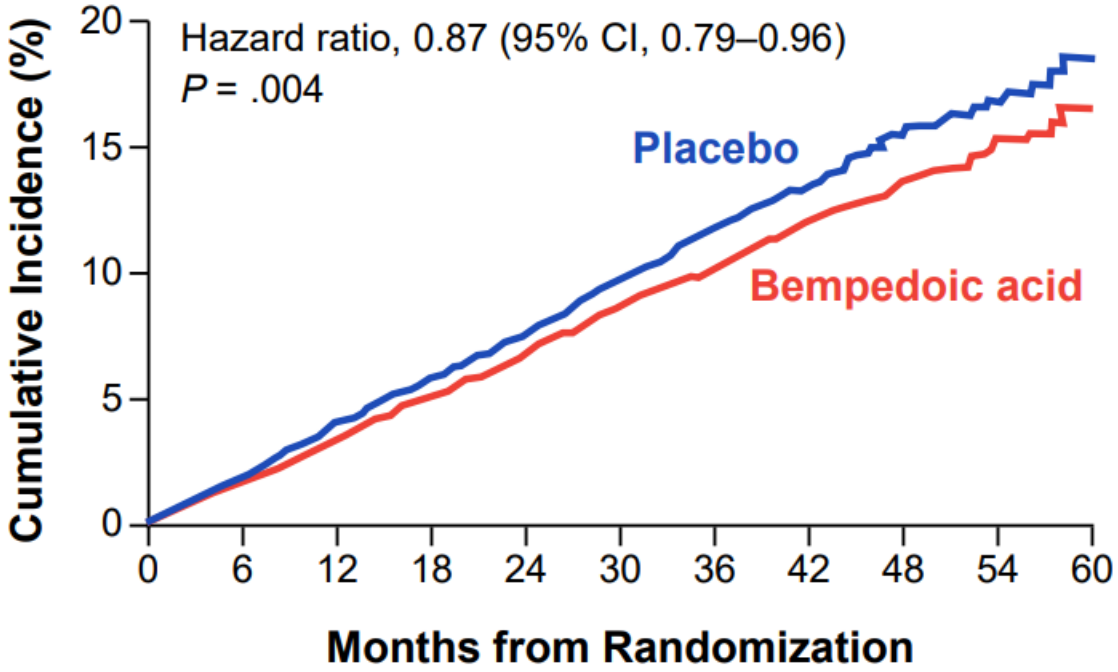
	LDL-C Reduction	HDL-C	TG	LP(a)	CV RR Reduction 1° / 2° Prevention
Statins	18-63%	↑ 5-15%	↓ 7-30%	neutral	25-39% / 19-34%
Ezetimibe	18%	↑ 1%	↓ 7%	neutral	~~minimal data~~ / 6.4%
PCSK9 inhibitors	40-60%	neutral	↓	↓ ~20-30%	19-25%* / 17%*
Bile acid sequestrants	15-30%	↑ 3-5%	0 or ↑	neutral	19% / minimal data
Inclisiran	~50-60%	↑ ~5%	↓ ~7-12%	↓ ~15-20%	no data / 26%*
Bempedoic acid	18%	↓ 6%	↑ 3%	neutral	30% / +/- 13%

*RCT evidence of ASCVD risk reduction when added to statin therapy

New Clinical Trial Data on Non-Statin Therapies

CLEAR Outcomes Trial: Bempedoic Acid

- N = 13,970 patients with (1) ASCVD or at high risk, (2) LDL-C ≥100 mg/dL, and (3) statin intolerance
- Primary endpoint: 13% RR reduction in MACE
- Secondary endpoints:
  - 15% RR reduction in nonfatal MI, nonfatal stroke, or CV death
  - 13% RR reduction in fatal & nonfatal MI
  - 19% RR reduction in coronary revascularization



HRPP Bempedoic Acid Reduced CV Events

POPULATION

2481 Women
1725 Men

Statin-intolerant adults without a prior cardiovascular event

Mean age: **68** years

LOCATIONS

1250
Centers worldwide

INTERVENTION

4206 Patients randomized

2100
Bempedoic acid
180 mg qd

2106
Placebo
Matching placebo

PRIMARY OUTCOME

Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization (MACE)

FINDINGS

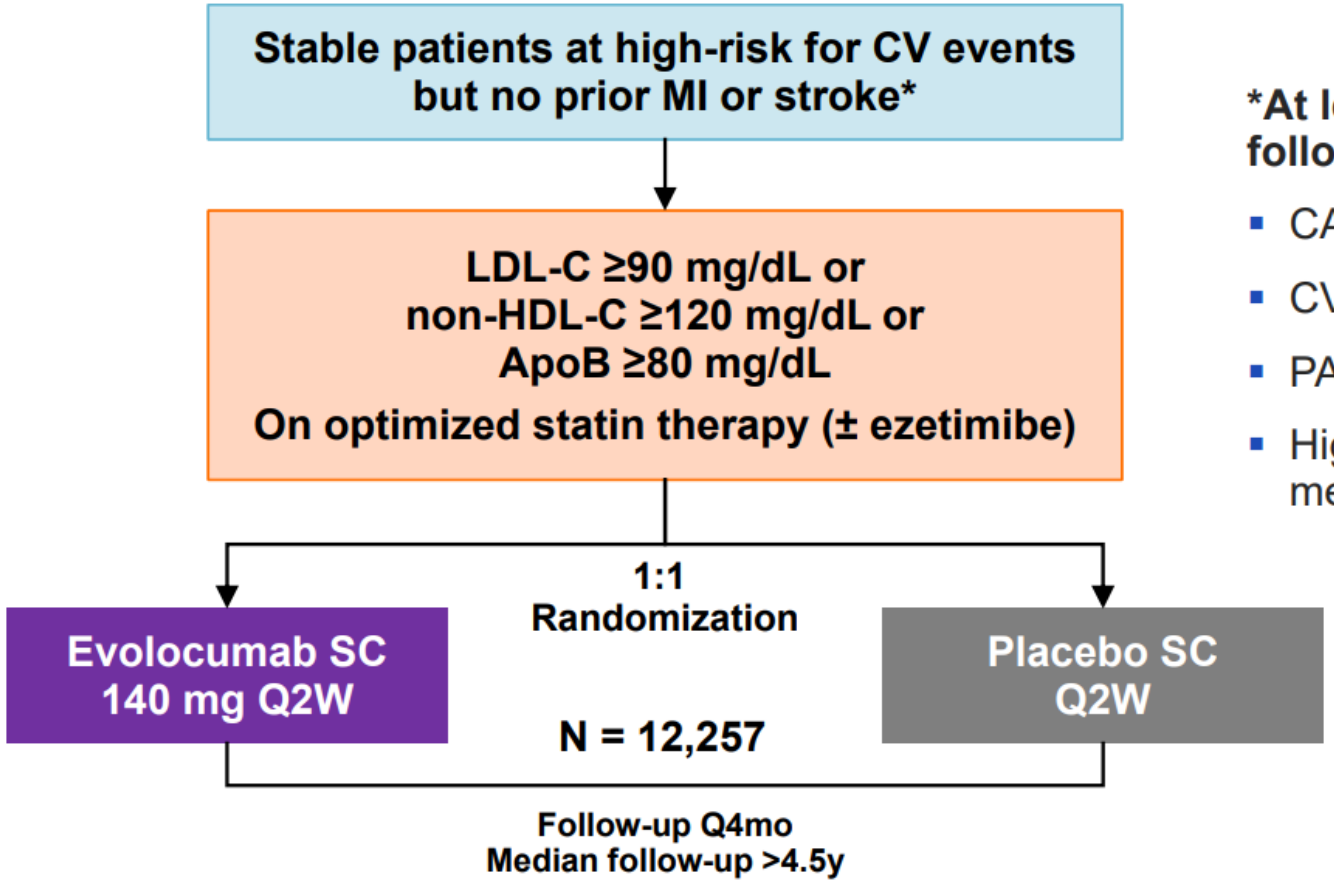
Composite end point occurrence

Bempedoic acid
5.3%
(111 of 2100 patients)

Placebo
7.6%
(161 of 2106 patients)

Relative Risk Reduction
30%
HR 0.70 (95% CI, 0.55-0.89) P = .002

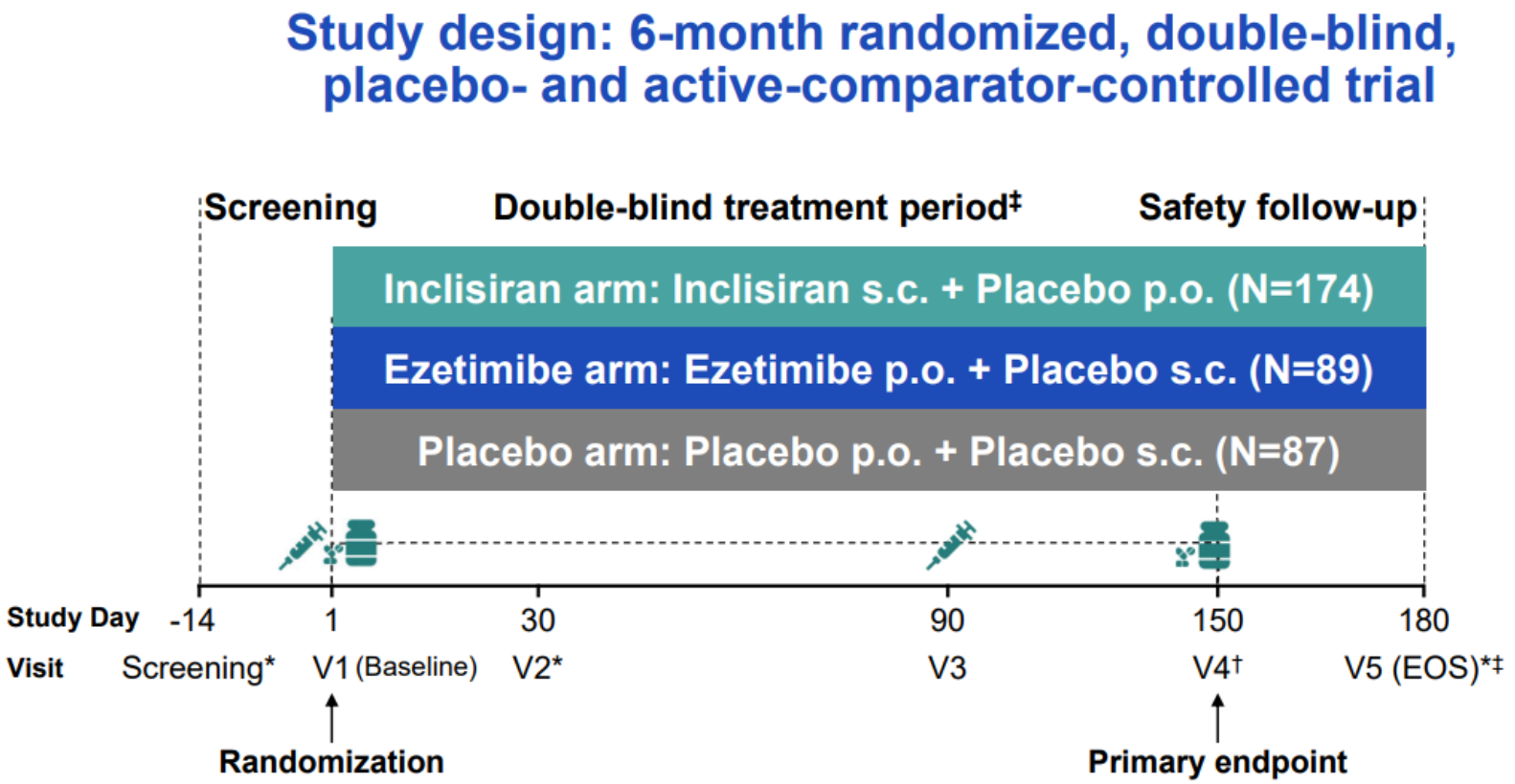
VESALIUS-CV: Evolovcumob for risk reduction in HRPP



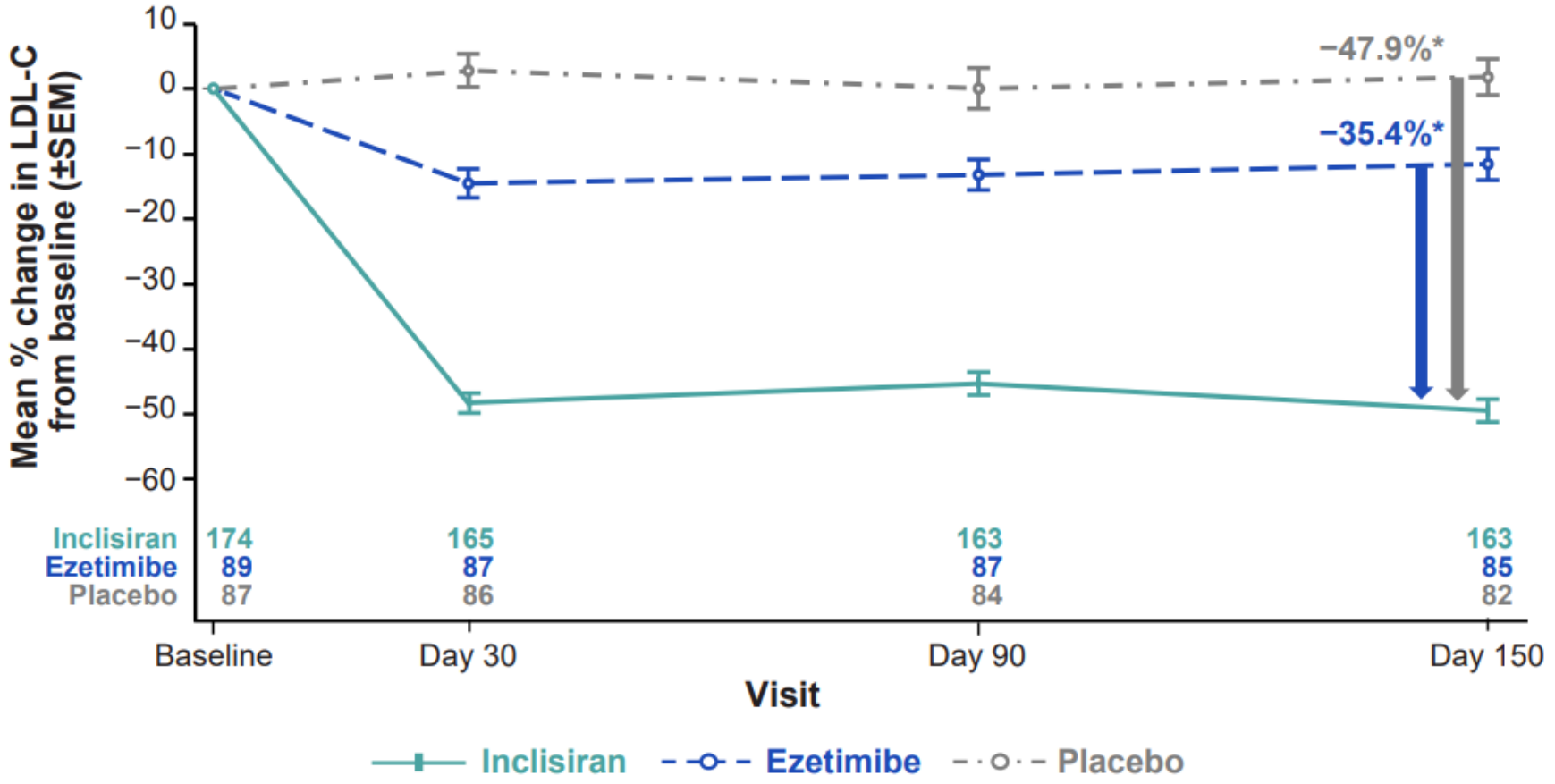
***At least one of the following:**

- CAD *without MI*
- CVD *without stroke*
- PAD
- High-risk diabetes mellitus

VICTORIAN-MONO: inclisiran as monotherapy



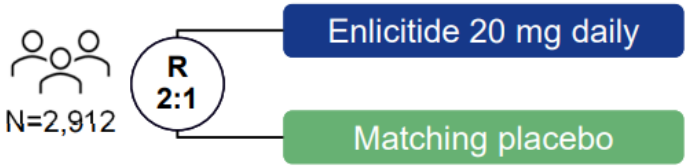
LS mean percentage change in LDL-C from baseline to Day 150 between inclisiran and placebo was −47.9% and that between inclisiran and ezetimibe was −35.4% ($p<0.0001$ for both)



Taub PR et al J Am Coll Cardiol. 2025 Jul 22;86(3):196-208

CORALreef Lipids
enclicitide (oralPCSK 9 inhibitors) LDL-c Reduction

Trial Design



Key Inclusion Criteria

- Patients with EITHER
  ASCVD and LDL-C > 55 mg/dL, OR
  No ASCVD and LDL-C >7 0mg/dL
- Stable LLT, including a statin

Key Exclusion Criteria

- Recent (3 mo) ASCVD event
- Active/Recent PCKS9i Tx
- Uncontrolled diabetes
- TG >400 mg/dL @ screening

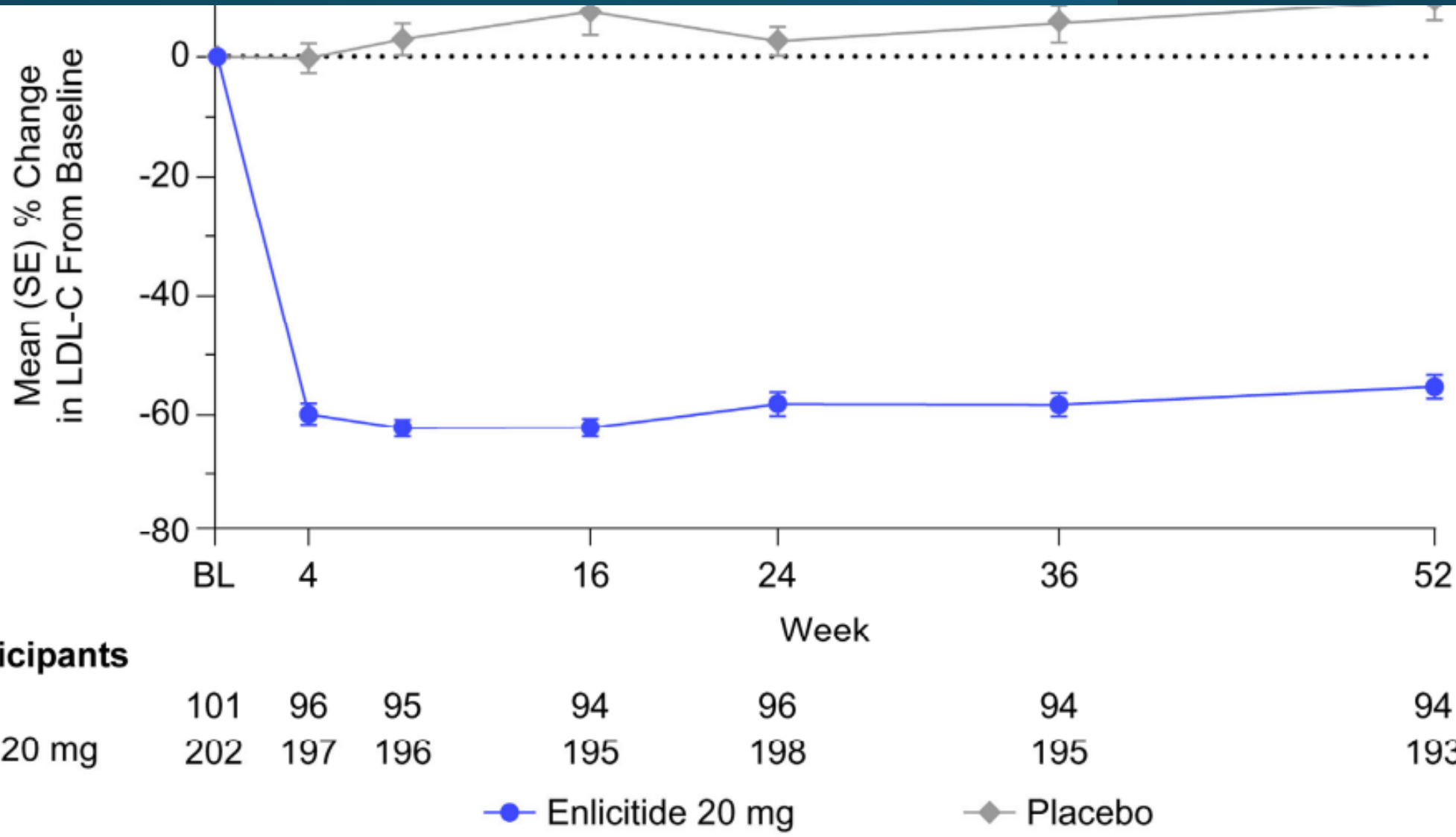
Primary Outcomes

- LDL-C percent change from baseline @ 24-weeks
  - **-59.4%** (95%CI: -65.6%, -53.2%; p<0.001)
- Percent of participants with AEs
  - Similar rate of serious AEs
    (**10% enlicitide vs 12% placebo**)
- Percent of participants with discontinuation secondary to AEs
  - Similar proportion disenrolled secondary to AEs
    (**3% enlicitide vs 4% placebo**)

Secondary Outcomes

- LDL-C percent change from baseline @ 52 weeks
  - **-61.5%** (95% CI: -69.4%, -53.7%; p<0.001)

Ballantyne CM et al. JAMA. Published online November 09, 2025.



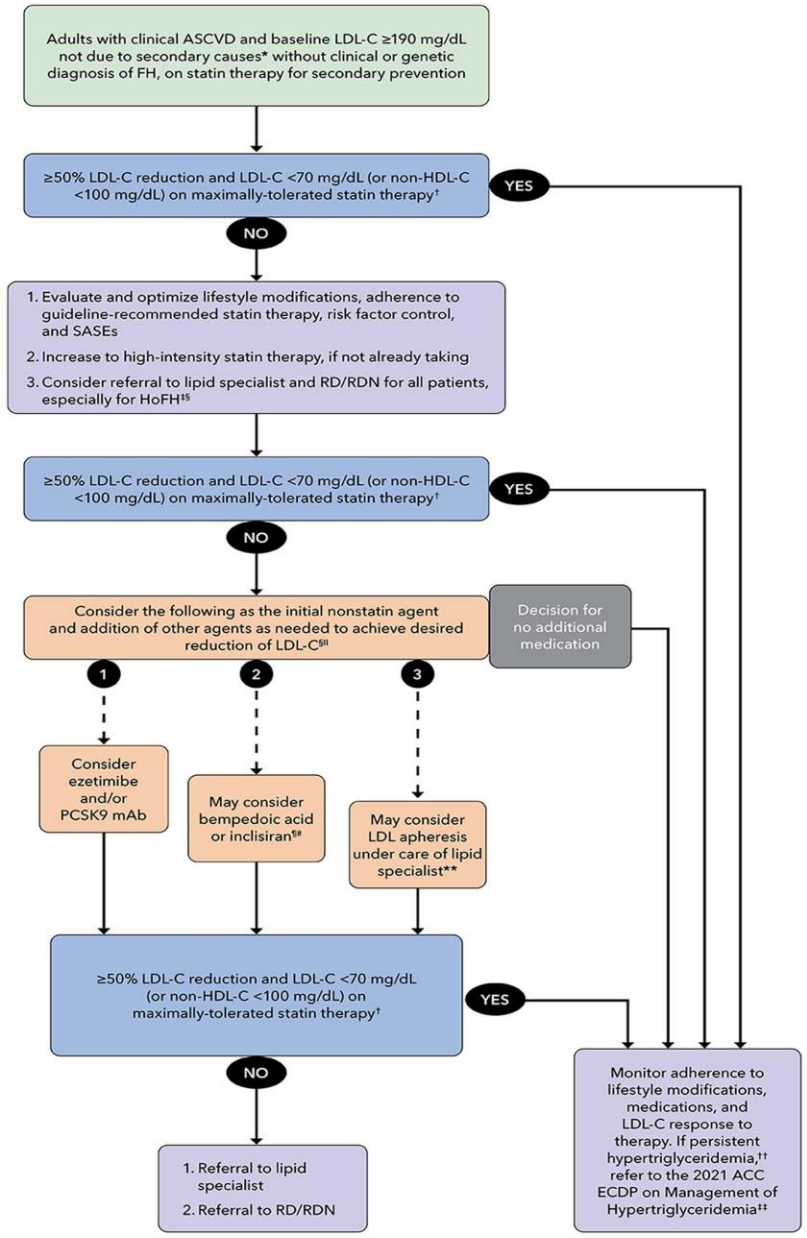
Ballantyne CM et al. JAMA. Published online November 09, 2025.

PCSK9 Targeting Therapies

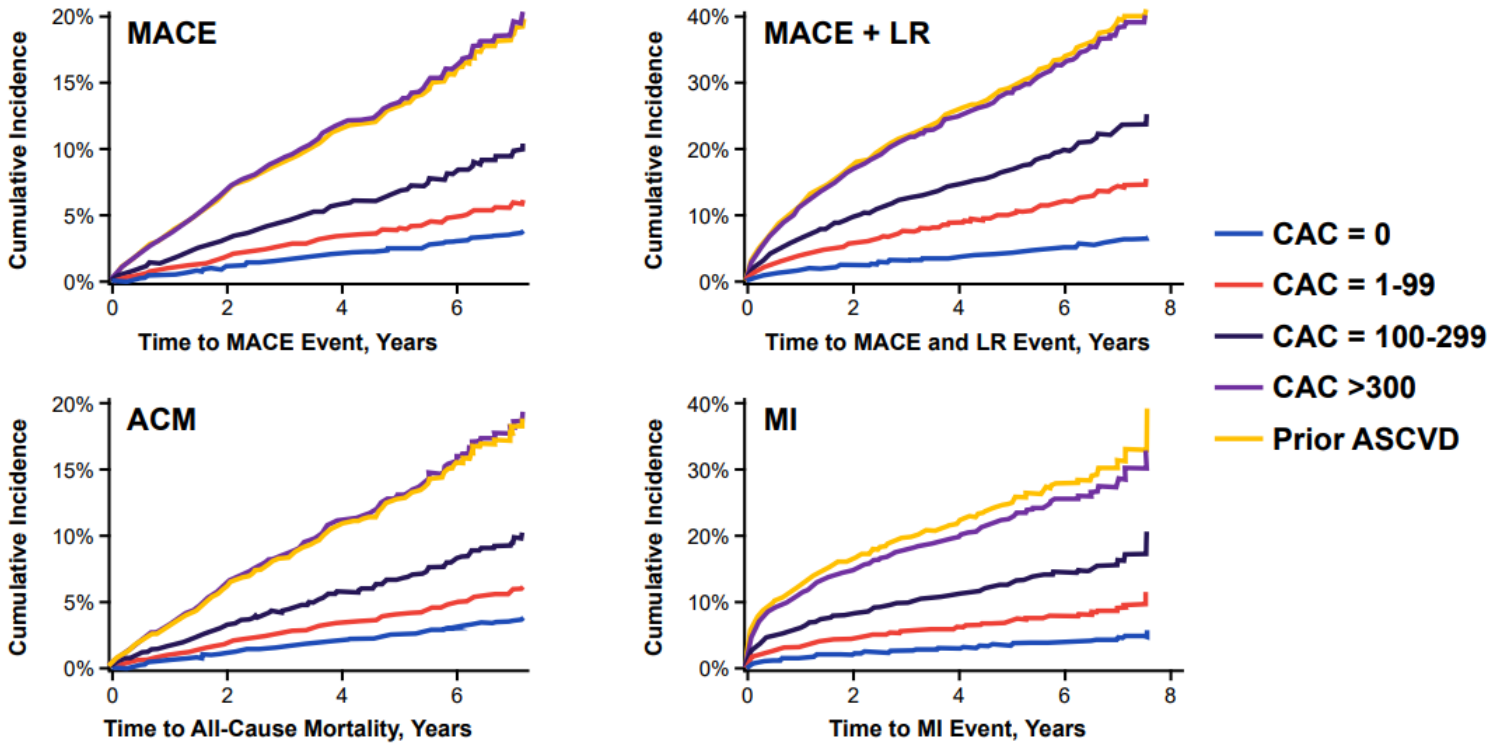
Injectable PCSK9 mAbs	**Injectable Small Interfering RNA**	**Oral Small-molecule PCSK9 antagonist**
Alirocumab, Evolocumab	*Inclisiran*	*Enlicitide*
Human monoclonal antibodies bind circulating PCSK9 to prevent its binding to LDL receptors.	siRNA binds PCSK9 mRNA, causing its degradation and inhibiting the production of PCSK9	Enlicitide prevents PCSK9 binding at the LDL receptor.

Secondary Prevention:

Non statin therapies



CAC score > 300 is ASCVD equivalent

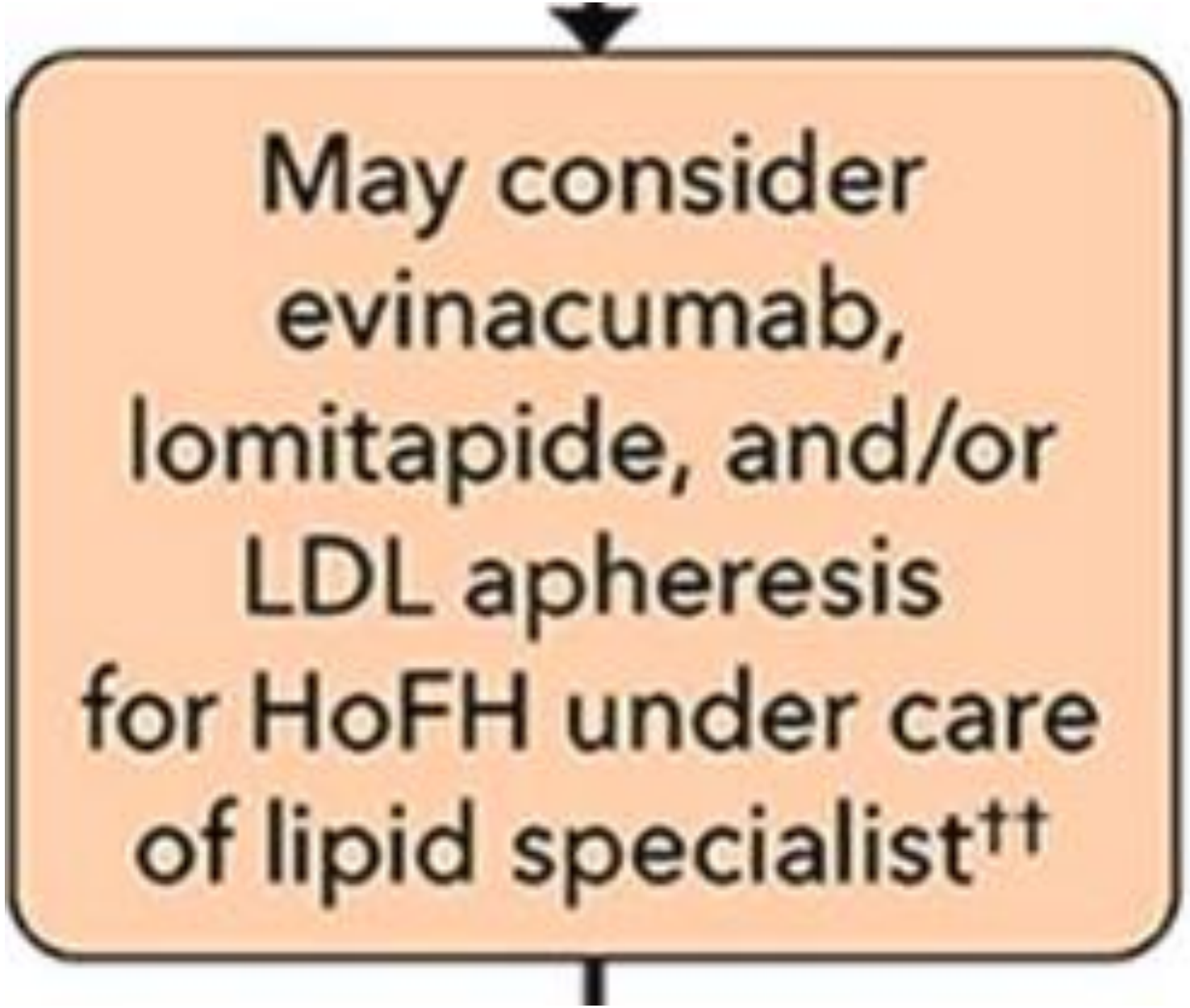


Budoff MJ, et al. *J Am Coll Cardiol Img*. 2023;16(9):1181-1189.

Considerations for FH

Heterozygous FH	LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)	Presence of 1 abnormal LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) Diagnosed as heterozygous FH if LDL-C–raising defect positive and LDL-C <160 mg/dL (4 mmol/L) Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes Presence of both abnormal LDL-C–raising gene defects (LDL receptor, apoB, or PCSK9) and LDL-C–lowering gene variant(s) with LDL-C <160 mg/dL (4 mmol/L)
Homozygous FH	LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed FH, positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) or autosomal-recessive FH If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 years of age, homozygous FH highly likely	Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL–raising gene defects (LDL receptor, apoB, or PCSK9); includes the rare autosomal-recessive type Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

Primary Severe Hypercholesteremia/ FH additional options



Hypertriglyceremia

- **Fibrates**: For patients whose triglycerides remain ≥500 mg/dL after general measures and optimal LDL lowering therapy who **do not** warrant additional ASCVD risk reduction, any prescription strength omega-3 fatty acid (including icosapent ethyl) or a fibrate (fenofibrate preferred) is reasonable
- **Icosapent ethyl (V*asepa*) :** patients whose triglycerides remain ≥150 mg/dL after general measures and optimal LDL lowering therapy who warrant additional ASCVD risk reduction (ie, those with established ASCVD
- or diabetes mellitus plus ≥2 risk factors for ASCVD), use icosapent ethyl over other triglyceride lowering therapies
- -NOT over the counter fish oil (no efficacy data)

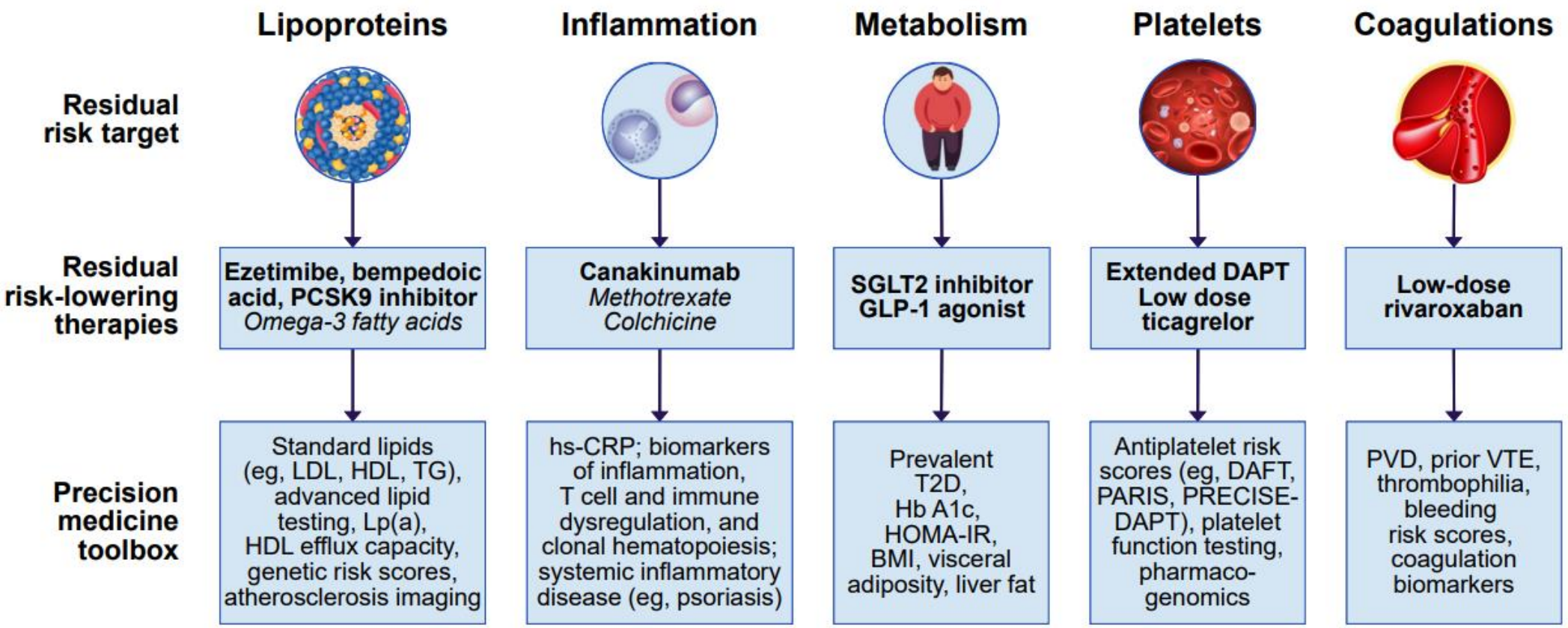
- **Olezarsen (*Tyngolza*)** : FCS, severe hypertriglyceremia with inclusion criteria

- **Ploasiran (Redemplo) :** FCS, severe hypertriglyceremia with inclusion criteria

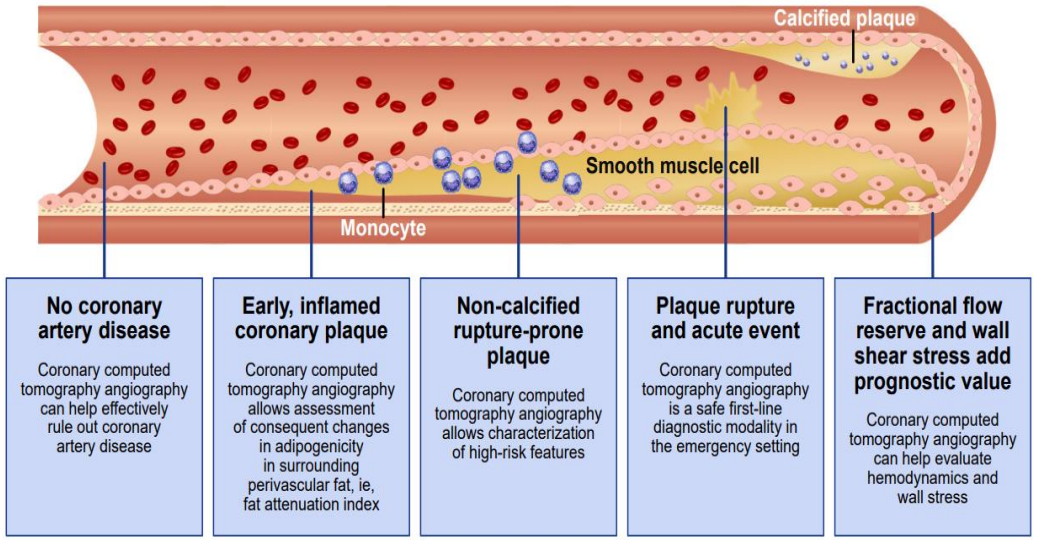
What's Next?

Advancing therapies in Risk Reduction

Beyond Lifestyle Modifications and Lipid therapy



Next frontier—AI generated plaque analysis



Thank you

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