Practical Updates in Primary Care

Lipid Management Beyond Statins: Individualized LDL-C Lowering Strategies for ASCVD Risk Reduction

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Disclosures

- **Michael J. Blaha, MD, MPH:** Advisory Board—Bayer, Eli Lilly, Genentech, Idorsia, Merck, New Amsterdam, Novartis, Novo Nordisk; Consultant—Boehringer Ingelheim, Merck; Grant/Research Support—Bayer, Novo Nordisk; Speaker's Bureau—Novo Nordisk

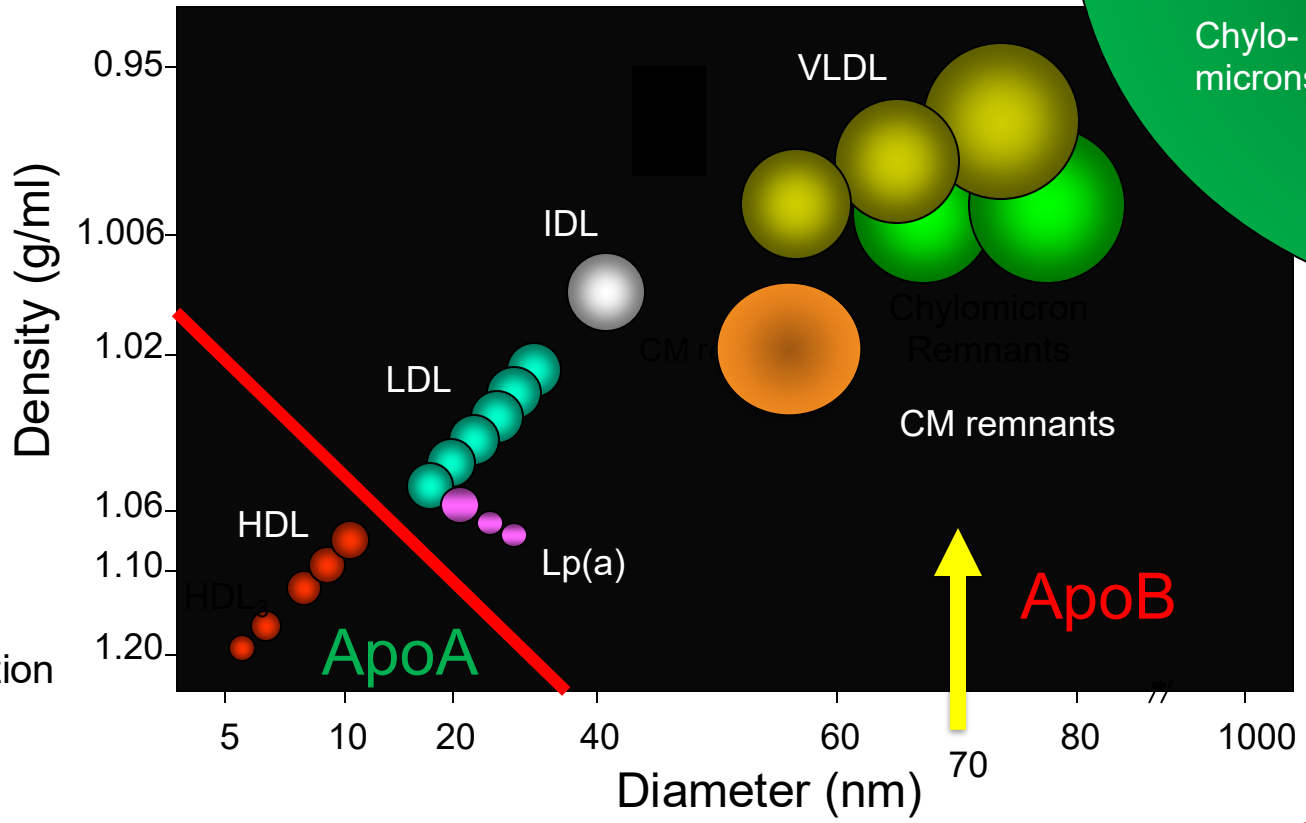
- **Jonathon Firnhaber, MD, MAEd, MBA** has nothing to disclose in relation to this activity

Learning Objectives

- Identify the pathophysiological roles of elevated LDL-C and Lp(a) as risk factors for ASCVD/CVD
- Evaluate guideline-directed lipid screening strategies to inform comprehensive CVD management
- Assess the efficacy and safety of newer and emerging non-statin lipid-lowering therapies for patients with or at risk of developing ASCVD
- Apply individualized, guideline-directed management plans that promote patient adherence and optimize LDL-C goal attainment in patients with ASCVD and persistently elevated lipids

LDL-C = low-density lipoprotein cholesterol; Lp = lipoprotein; ASCVD = atherosclerotic cardiovascular disease.

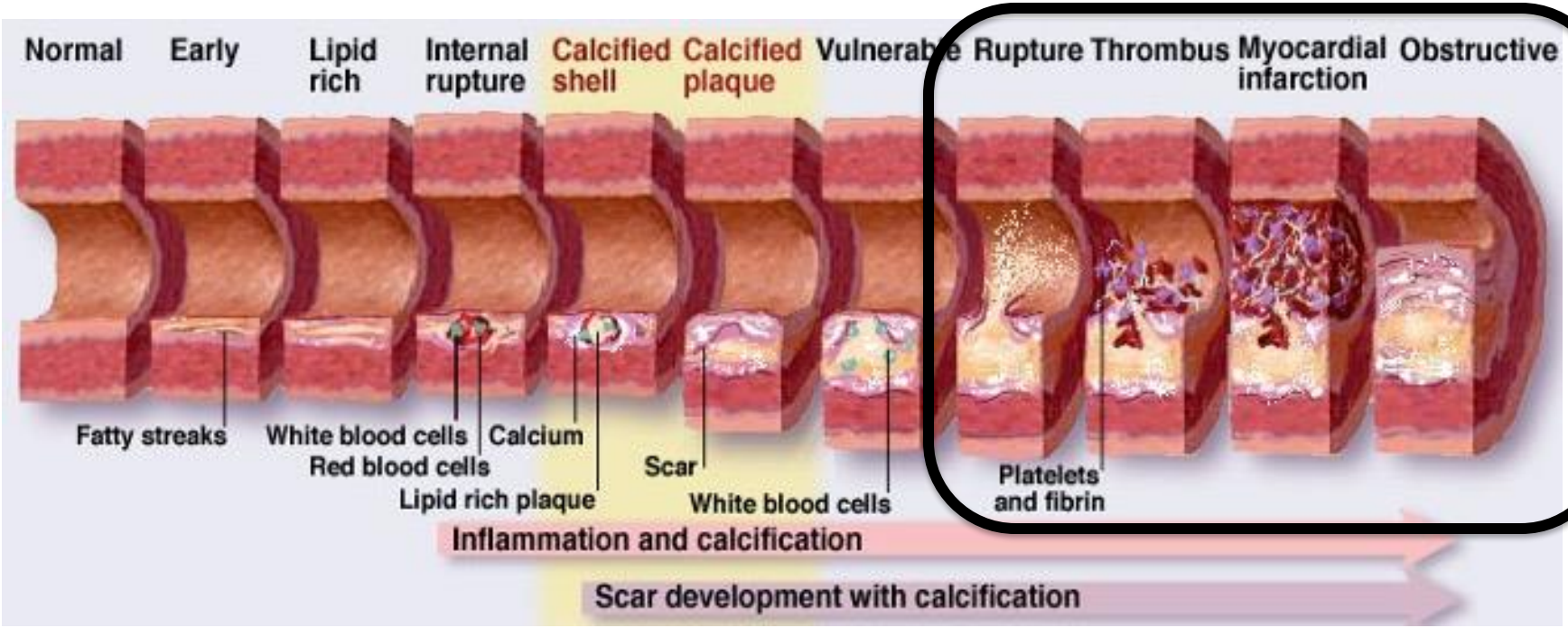
Lipoprotein Subclasses



Gel Fractionation

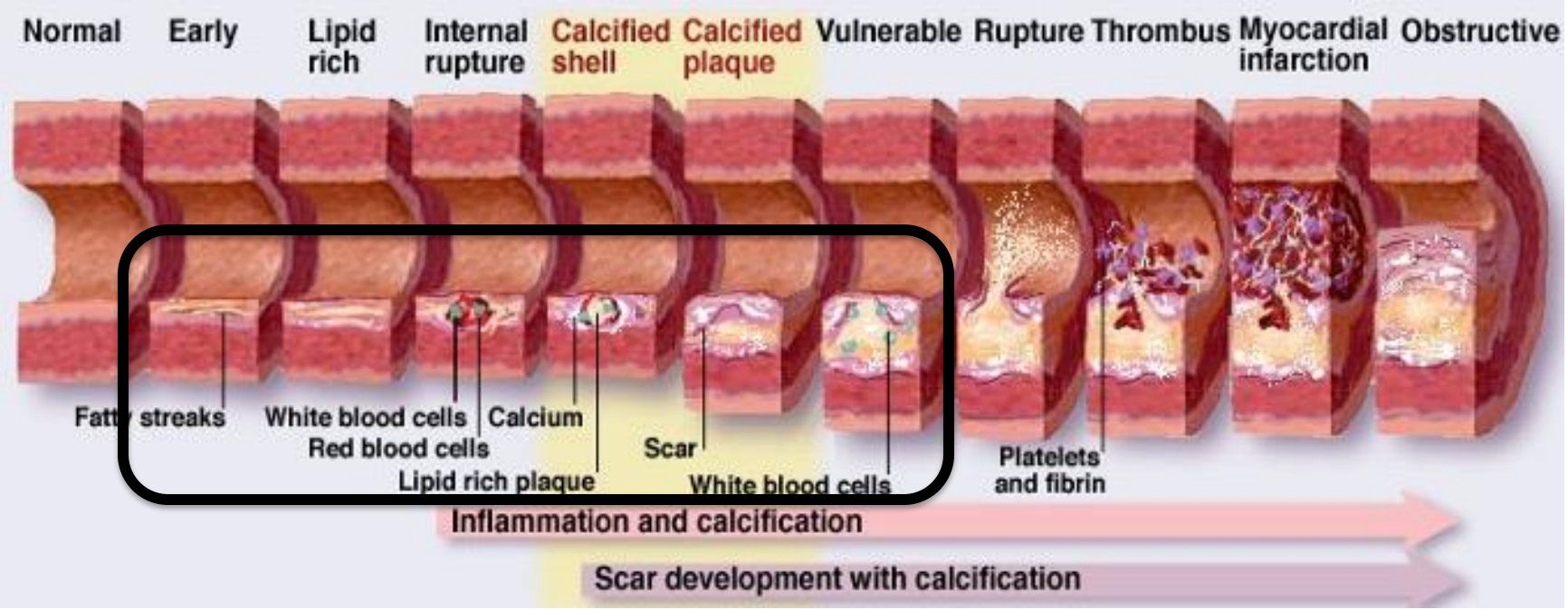
IDL = intermediate-density lipoprotein; CM = chylomicron; Apo = apolipoprotein.
Gofman/Berkeley Heart Lab.

Atherosclerosis Timeline



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Atherosclerosis Timeline



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Lipid Measurement across the Lifespan

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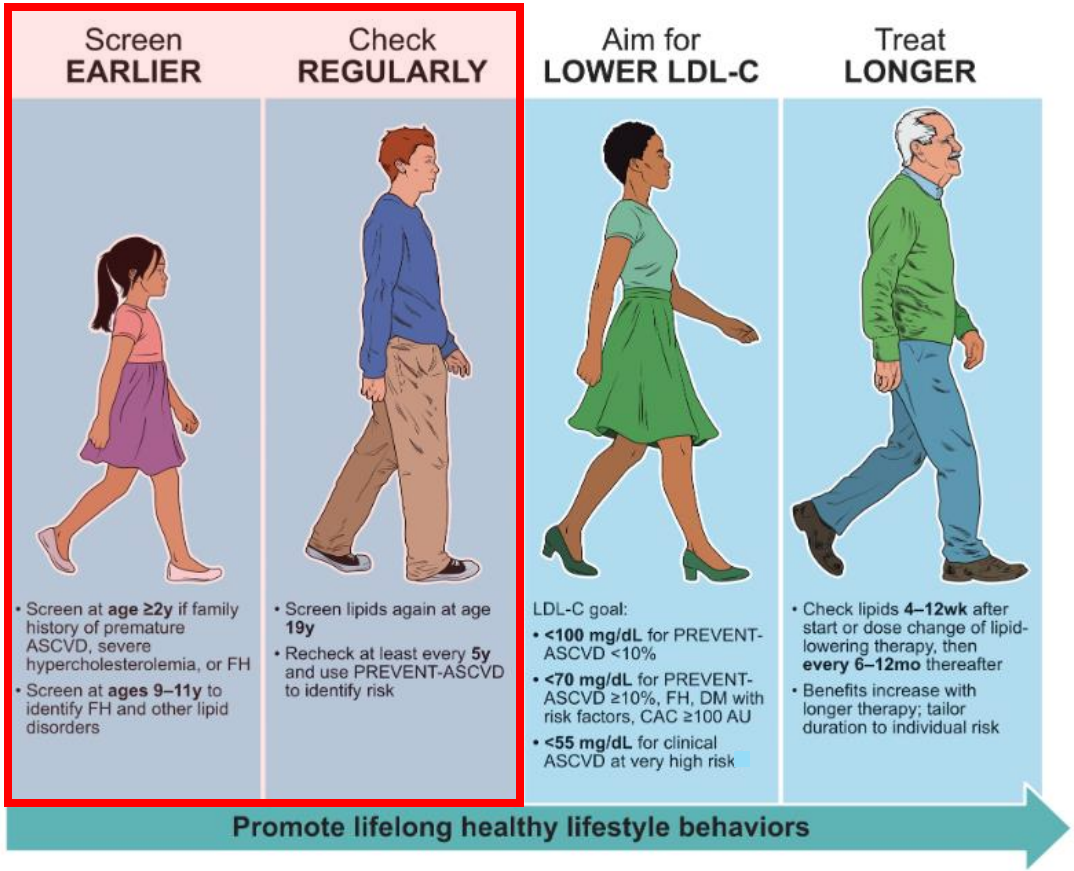
Screening in Adults and Children



COR	RECOMMENDATIONS
1	In adults, screening with a lipid profile is recommended beginning at age 19 years and at least every 5 years thereafter to identify treatable ASCVD risk, with frequent screening recommended for individuals with additional ASCVD risk factors.
1	In children 9 to 11 years of age not previously tested, it is recommended to screen with a lipid profile to identify familial hypercholesterolemia (FH) and other significant lipid disorders.
2a	In individuals with first- or second-degree relatives with premature ASCVD, severe hypercholesterolemia, or FH, it is reasonable to perform screening with a single lipid profile (eg, cascade screening) starting at ≥2 years of age to identify FH.

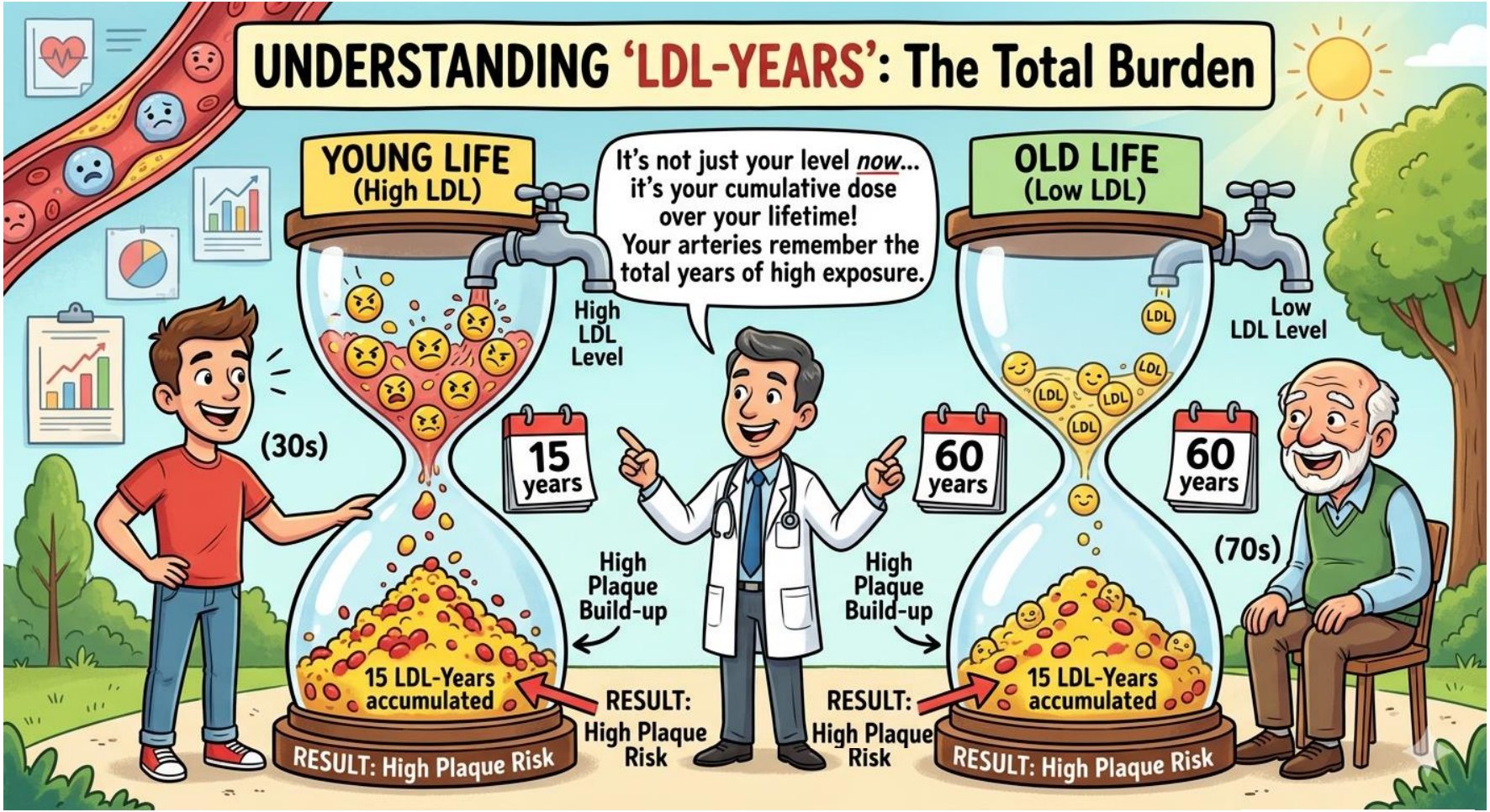
COR = class of recommendation.
Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

When to Do It & How Often



Wiggins BS, et al. *J Am Coll Cardiol*. 2026;87(19):2617-2623.

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Primordial Prevention of Dyslipidemia: Childhood through Adulthood



COR	RECOMMENDATIONS
1	In children and healthy adults, healthy dietary patterns, regular physical activity, maintenance of a healthy weight, healthy sleep, stress management, and avoidance of tobacco products should be promoted and reinforced lifelong to reduce the risk for dyslipidemia and ASCVD.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

You Can't Treat What You Don't Measure

COR	RECOMMENDATIONS
1	Standard nonfasting or fasting lipid profile is recommended to document baseline lipid levels, estimate ASCVD risk, & guide initiation of lipid-lowering therapy (LLT).
1	With a family history of dyslipidemia or premature ASCVD, a known or suspected disorder in TG metabolism, or whose nonfasting lipid profile reveals a TG level ≥400 mg/dL (≥4.5 mmol/L), a fasting lipid profile should be performed to more accurately estimate LDL-C level.
1	In those who have undergone a standard lipid profile, use of either the Martin/Hopkins equation or the Sampson/NIH equation is preferred over calculation by the Friedewald equation to estimate LDL-C.
1	In those who have undergone a standard lipid profile, use of either the Martin/Hopkins equation or Sampson/NIH equation is preferred over direct LDL-C measurement to estimate LDL-C.
1	In those who have undergone a standard lipid profile, reporting of non-HDL-C is recommended for ASCVD risk assessment and to guide initiation and monitoring of lipid-lowering therapy.
3: No Benefit	Routine advanced lipoprotein testing to assess lipoprotein subclasses and parameters such as LDL particle size is NOT recommended to estimate ASCVD risk or guide initiation of LLT.

TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.
Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

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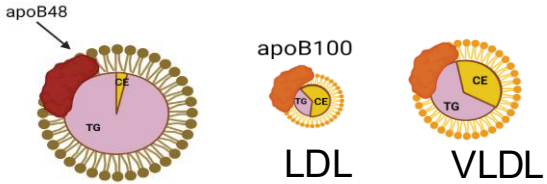
Role of ApoB and Lp(a) in Practice

Michael J. Blaha, MD, MPH

Consider ApoB to Assess Residual Lipid-Related Risk

ApoB measures all atherogenic particles and is more accurate compared to LDL-cholesterol

Screening with Apolipoprotein B (ApoB)





All atherogenic lipoproteins have a single apoB100 protein; apoB is not affected by fasting

In adults <u>on LLT</u>, particularly those with ASCVD, type 2 DM, &/or elevated TG, measurement of apoB is reasonable to guide decisions regarding further therapeutic intensification once LDL-C &/or non-HDL-C goals are achieved (<u>2a</u>)

In adults <u>not on LLT</u>, measurement of apoB may be reasonable to enhance ASCVD risk assessment, guide initiation of LLT, & characterize inherited lipid disorders (<u>2b</u>)

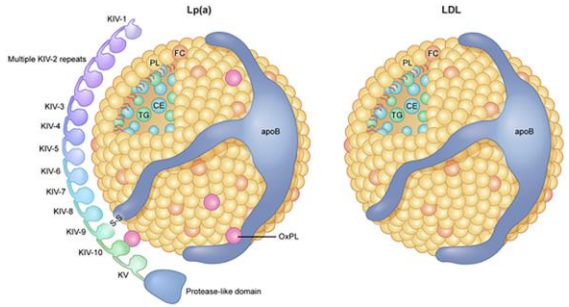
Particularly for secondary prevention, metabolic syndrome, diabetes, elevated TG

DM = diabetes mellitus.

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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Measure Lipoprotein(a) Once in All Adults



Lp (a) in nmol/L	ASCVD relative risk
450	4x
375	3x
250	2x
125	1.4x
75	Reference

Screening with Lp(a)

- Measurement of Lp(a) in all adults is recommended at least once for ASCVD risk assessment (1)
- In those with FH, premature ASCVD, or high Lp(a), cascade testing of 1st-degree relatives is recommended (1)



Lp(a) particles consist of an LDL-C-like particle bound to an apo(a) protein

Lp(a) levels are largely genetically determined and stable over one's lifetime

Repeat testing is generally not needed

If Lp(a) is elevated, intensify LDL-C lowering and aggressively control other ASCVD risk factors

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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Primary Prevention & Initial Risk Assessment

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Role of Individualized Benefit-Risk Discussion



Information

Clinician provides the best available evidence for treatment options, including the risks & benefits of each option



Patient-Centered Care

Treatment & care options take into consideration individual values & preferences



Shared Decision-Making

A collaborative decision about treatment or care is documented and shared with relevant stakeholders

COR	RECOMMENDATIONS
1	In individuals with dyslipidemia, clinicians and their patients should engage in a discussion of the patient's ASCVD risk, healthy lifestyle as the foundation of risk reduction, expected risk reduction benefits from LLT, possible harms and DDI, costs, and patient preferences to make individualized treatment decisions and/or consider additional options for evaluation to aid in decision-making.

Discussion should emphasize

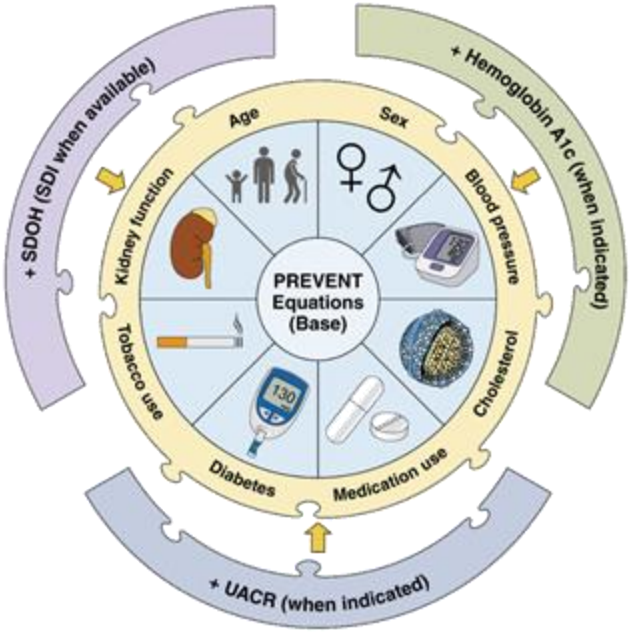
- Patient's ASCVD risk
- Consideration of additional options for evaluation
- Healthy lifestyle as the foundation of risk reduction
- Expected risk reduction benefits from lipid-lowering therapies
- Possible harms and drug-drug interactions
- Costs
- Administration frequency
- Patient preferences

DDI = drug-drug interaction.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

PREVENT-ASCVD Risk Calculator

COR	RECOMMENDATIONS
1	PREVENT-ASCVD equations should be used for risk assessment in adults aged 30-79 years without ASCVD or subclinical atherosclerosis, with LDL-C 70-189 mg/dL.



Approximate Equivalent Ranges of 10-yr ASCVD Risk Estimates

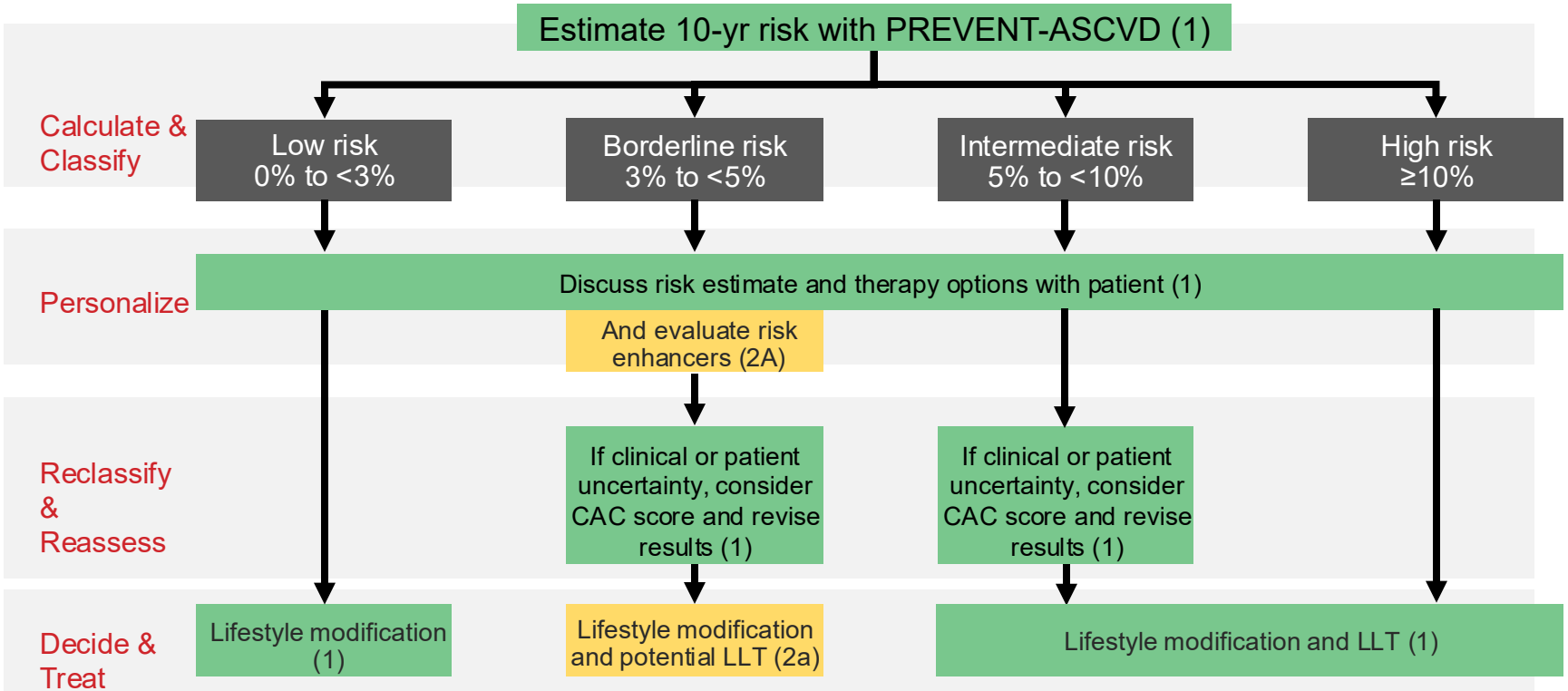
RISK	POOLED COHORT EQUATIONS	PREVENT-ASCVD
Low	<5%	<3%
Borderline	5 to <7.5%	3 to <5%
Intermediate	7.5 to <20%	5 to <10%
High	≥20%	≥10%

PREVENT = predicting risk of cardiovascular disease events; SDI = social deprivation index; SDOH = social determinants of health; UACR = urine albumin-to-creatinine ratio.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

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Calculate, Personalize, Reclassify (CPR) Framework



CAC = coronary artery calcium.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

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)
- 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)

COR	RECOMMENDATIONS
2a	In adults without ASCVD with a borderline 10-year ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, consideration of risk-enhancers is reasonable to personalize risk assessment and the potential benefit of initiating LLT as an adjunct to lifestyle management to reduce ASCVD risk.
2a	In adults without ASCVD with a borderline 10-year ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, if high-sensitivity C-reactive protein (hsCRP) is measured and is ≥2 mg/L on 2 successive occasions with no identifiable underlying cause of hsCRP elevation, high-intensity statin therapy can be useful to reduce the risk of ASCVD events.

hsCRP = high-sensitivity C-reactive protein; CKM = cardiovascular-kidney-metabolic.
Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

Reproductive Risk Markers

Adverse Pregnancy Outcomes with a Stronger Association with ASCVD Events

- Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)
- Gestational diabetes
- Small for gestational age (birthweight <10th percentile)
- Preterm delivery (before 37 weeks of gestation)
- Recurrent spontaneous pregnancy loss

Other Reproductive Risk Markers

- Early menarche (<10 yr old)
- Early menopause (<45 yr), especially if premature (<40 yr)
- Polycystic ovarian syndrome and irregular menses



COR	RECOMMENDATIONS
2a	In adults without ASCVD, consideration of reproductive risk markers, such as early menopause (<45 years of age) and history of adverse pregnancy outcomes is reasonable to personalize ASCVD risk assessment when considering the potential benefit of initiating LLT as an adjunct to lifestyle management for primary ASCVD prevention.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

Primary Prevention: 30-79 Years without ASCVD

Adults with LDL-C 70-189 mg/dL → Health behavior counseling (1) → Calculate 10-yr and 30-yr in ages 30-59 ASCVD risk using PREVENT-ASCVD (1) AND Have benefit-risk discussion (1)



- Low 10-yr risk (<3%)
- Borderline 10-yr risk (3% to <5%)
- Intermediate 10-yr risk (5% to <10%)
- High 10-yr risk (≥10%)

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

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Primary Prevention: 30-79 Years without ASCVD

Low-Intermediate 10-Yr Risk (<3% to 10%)	
COR	RECOMMENDATIONS
1	Low risk (<3%) + LDL <160 mg/dL → Health behavior counseling.
2a	Low risk + LDL 160-189 mg/dL or high 30-yr risk → Start moderate statin. Goal: ≥30% LDL-C reduction; LDL-C<100 mg/dL and non-HDL-C <130 mg/dL.
2a	Borderline risk (3% to <5%) → Moderate statin reasonable. Goal: ≥30% LDL-C reduction; LDL-C <100 mg/dL and non-HDL-C <130 mg/dL.
1	Intermediate risk (5% to <10%) → Start moderate- to high-intensity statin.
AND	
2a	Goal: LDL-C <100 mg/dL and non-HDL-C <130 mg/dL.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

Primary Prevention: 30-79 Years without ASCVD (Continued)



High 10-Yr Risk (≥10%)	
COR	RECOMMENDATIONS
1	Start high-intensity statin.
2a	Goal: ≥50% LDL-C reduction; LDL-C <70 mg/dL and non-HDL-C <100 mg/dL.
2a	If LDL-C and non-HDL-C goals still not achieved, add ezetimibe.
2b	If LDL-C and non-HDL-C goals still not achieved, add PCSK9 mAb or bempedoic acid.

mAb = monoclonal antibody.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.



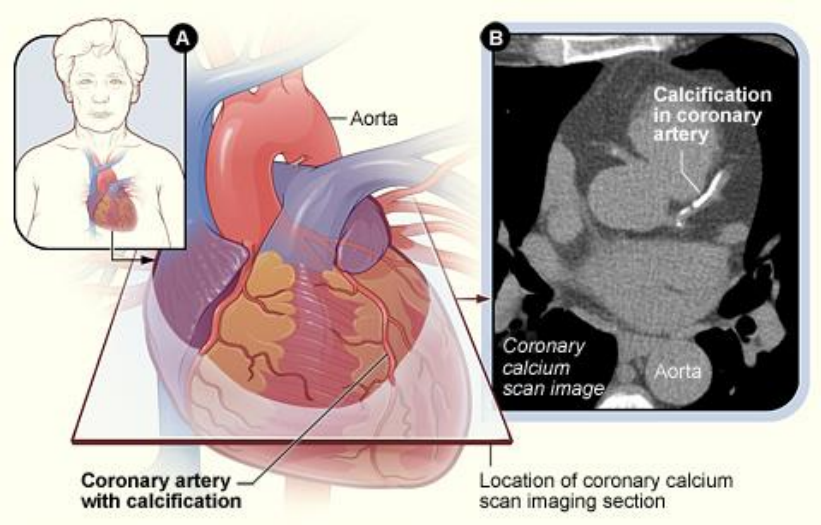
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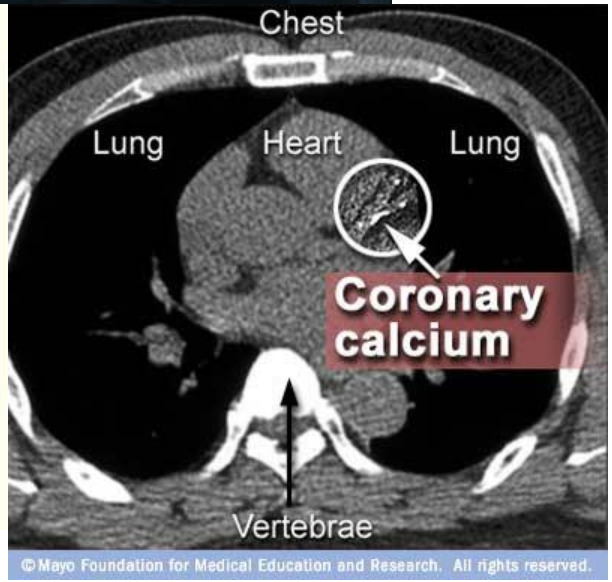
Coronary Artery Calcium Testing

Michael J. Blaha, MD, MPH



~1 mSv

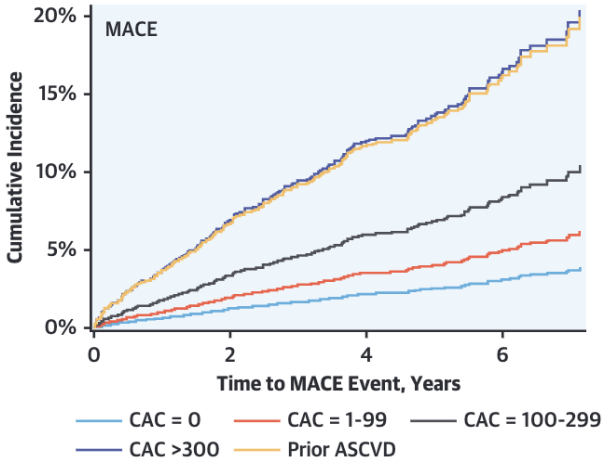


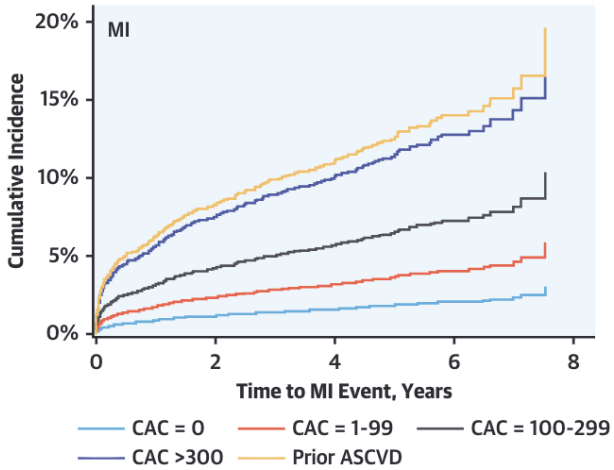


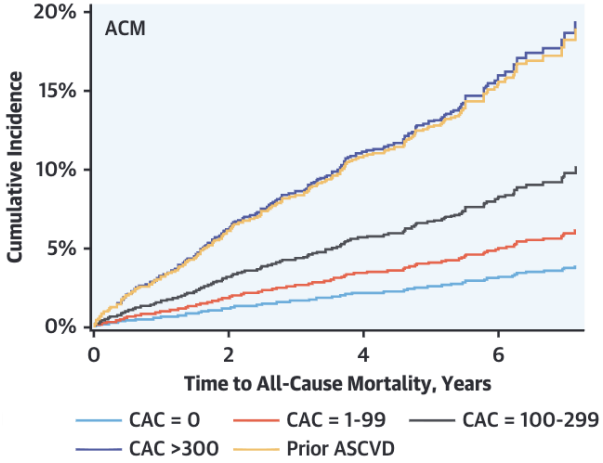
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Coronary Artery Calcium Scores and Cardiovascular Risk

Observational analysis of 4511 individuals with an elevated coronary artery calcium score compared to 438 individuals with established ASCVD (CONFIRM registry)







Individuals with a CAC score ≥300 face cardiovascular risks similar to those with established ASCVD

MACE = major adverse cardiovascular event; MI = myocardial infarction; ACM = all-cause mortality; CAC = coronary artery calcium.

Budoff MJ, et al. *JACC Cardiovasc Imaging*. 2023;16(9):1181-1189.

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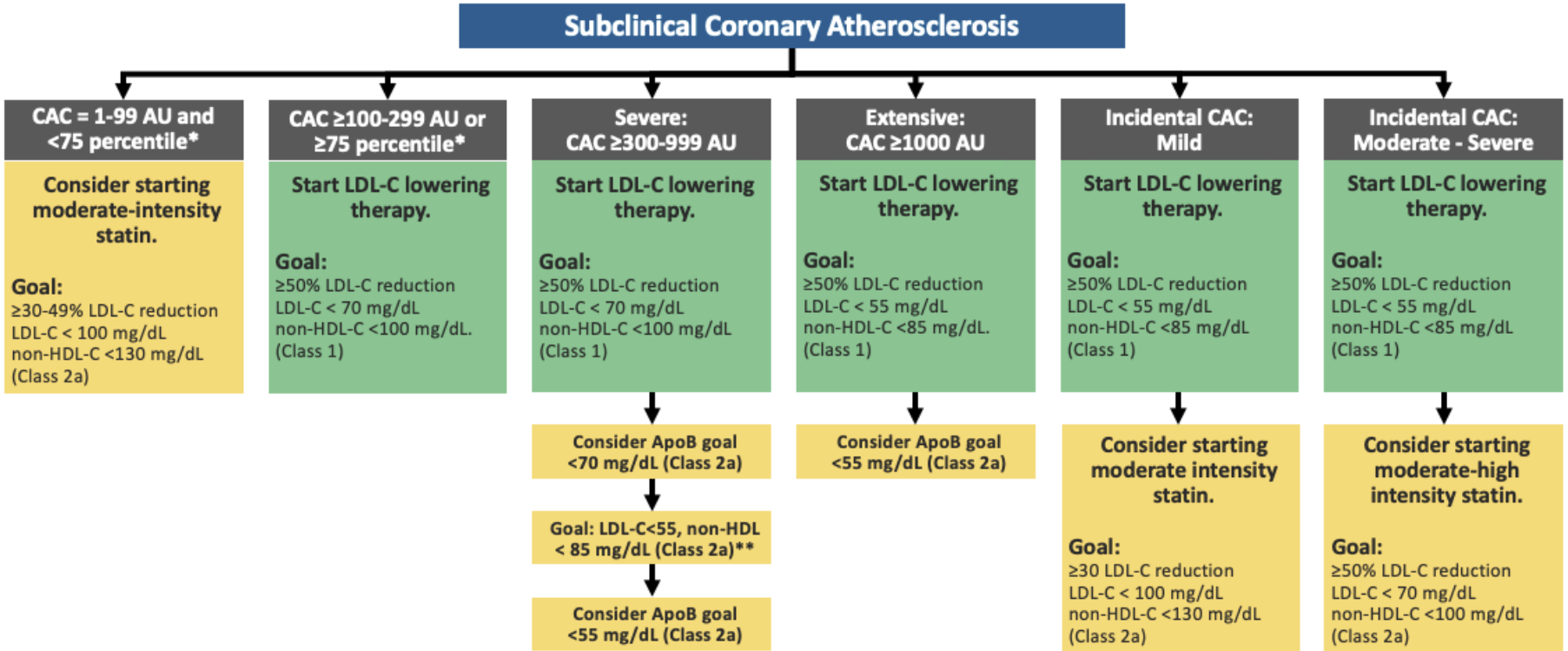
CAC Guidelines – 2018 → 2026

COR	LOE	
IIa	B-NR	In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.
I	B-R	In adults at intermediate risk and select adults at borderline risk with no prior ASCVD, if the decision regarding LLT remains uncertain, a CAC score should be used for further risk stratification and to guide the decision to withhold, postpone, or initiate therapy.

LOE = level of evidence.

Arnett DK, et al. *J Am Coll Cardiol*. 2019;74(10):1376-1414. Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

Lipid Goals in Patients with Coronary Artery Calcium

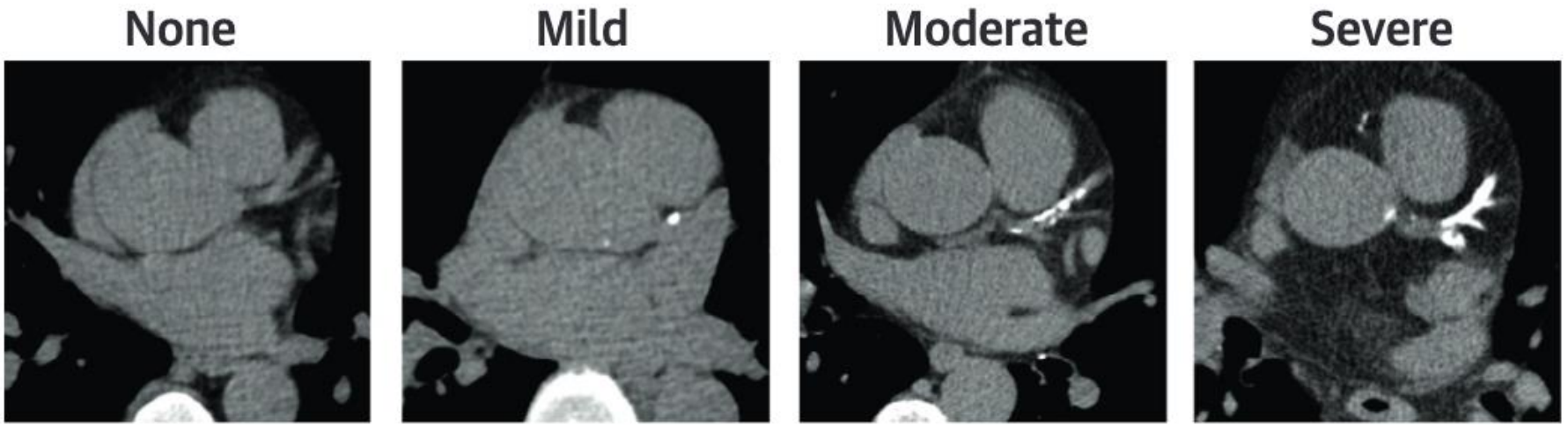


*Percentiles for age, sex, and race; **Optional.

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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Importance of Incidental Coronary Artery Calcium





Incidental CAC on a non-gated CT scan can also be used to guide therapy →
Class I recommendation

- If mild, LDL-C goal is <100 mg/dL
- If moderate or severe, LDL-C goal is <70 mg/dL

Absence of incidental CAC should not be used to defer therapy, given the low negative predictive value of non-gated scans

CT = computed tomography.

Parsa S, et al. *J Am Coll Cardiol*. 2024;83(16):1557-1567. Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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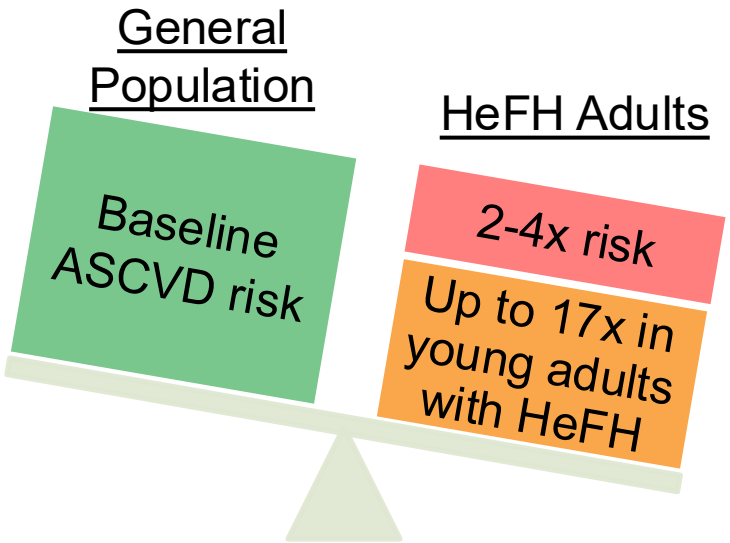


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Considerations in Familial Hypercholesterolemia

Michael J. Blaha, MD, MPH

Role of Risk Assessment in Heterozygous Familial Hypercholesterolemia



COR	RECOMMENDATIONS
2b	In adults with HeFH, FH-specific risk scores may be useful in predicting short-term ASCVD risk.
3: Harm	In adults with HeFH, standard risk assessment tools developed for the general population should NOT be used to calculate 10-yr or 30-yr ASCVD risk.

HeFH = heterozygous familial hypercholesterolemia.
Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

Genetic Testing for Familial Hypercholesterolemia

Genetic Testing

- Identify individuals meeting clinical suspicion
- Prevalence 1:250 → underdiagnosed

Variants

- LDLR
- ApoB
- PCSK9

Risk Stratification & Treatment

- Higher ASCVD risk, even with modest LDL
- Supports earlier LLT and cascade screening

COR	RECOMMENDATIONS
1	In adults with possible, probable, or definite FH, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH is beneficial to identify individuals at highest risk of cardiovascular events and to facilitate cascade screening.
2a	In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L) without an identified secondary cause, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH can be useful to identify those with FH who are at higher risk of ASCVD events.
2b	In adults with an elevated LDL-C of 160 to 189 mg/dL (4.1-4.9 mmol/L) without an identified secondary cause, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH may be considered to identify those with FH who are at higher risk of events.

LDLR = LDL-receptor.

Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

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Lipid Goals in Patients with Severe Hypercholesterolemia

Severe Hypercholesterolemia

- LDL-C ≥190 mg/dL (non-HDL-C ≥220 mg/dL, apoB ≥140 mg/dL)
- Very high lifetime ASCVD risk, even without other risk factors
- Often due to long-term LDL-C exposure (cumulative burden)



Always exclude secondary causes, including a ketogenic or high saturated fat diet, hypothyroidism, chronic kidney disease, nephrotic syndrome, steroids, etc.

	Patient Examples	LDL-C mg/dL	Non-HDL-C mg/dL	ApoB mg/dL
Severe hypercholesterolemia	• Without FH, ASCVD risk factors, and subclinical atherosclerosis	<100	<130	<90
Severe hypercholesterolemia	• With FH, ASCVD risk factors, and subclinical atherosclerosis	<70	<100	<70
Severe hypercholesterolemia	• With FH and ASCVD	<55	<85	<55

Adapted from Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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Secondary Prevention Risk Assessment

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Criteria for Defining "At Very High Risk" in Patients with ASCVD

At Very High Risk

≥2 major ASCVD events

OR

1 major ASCVD event
+
≥2 high-risk conditions

Major ASCVD Events

- Consider drug-drug interactions between lipid-lowering therapies and antiretroviral therapies

High-Risk Conditions

- Age ≥65
- Coronary bypass or percutaneous intervention
- Current smoker
- Diabetes
- Hx of congestive heart failure
- Hypertension
- LDL-C ≥100 mg/dL despite maximally tolerated statin + ezetimibe

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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Lipid Goals in Patients with Clinical ASCVD

	Patient Examples	LDL-C mg/dL	Non-HDL-C mg/dL	ApoB mg/dL
Secondary prevention – adults at very high risk	• ≥2 major ASCVD events • 1 major ASCVD event and ≥2 high-risk conditions	<55	<85	<55
Secondary prevention – adults not at very high risk	• 1 major ASCVD event and ≤1 high-risk condition • 0 major ASCVD events	<70 (optional goal <55)	<100 (optional goal <85)	<70 (optional goal <55)



LDL-C (along with non-HDL-C & apoB) goals are back

Adapted from Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

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Summary – LDL 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, and subclinical atherosclerosis	Severe hypercholesterolemia or HeFH with clinical ASCVD
Diabetes	Without ASCVD risk factors or diabetes-specific risk modifiers • ApoB goal: <90 mg/dL	Without ASCVD risk factors or diabetes-specific risk modifiers • 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, and 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
Hypertriglyceridemia	<50 yrs old with no additional risk enhancers	• With clinical ASCVD not at very high risk – ApoB goal: <70 mg/dL • Age 40-75 yrs with ≥1 ASCVD risk factor – ApoB goal: <70 mg/dL	• With clinical ASCVD at very high risk – ApoB goal: <55 mg/dL
Clinical ASCVD	N/A	Not at very high risk • Optional goal: LDL-C <55 mg/dL, non-HDL-C <85 mg/dL, and consider apoB goal <55 mg/dL	• At very high risk – ApoB goal: <55 mg/dL • With CKD

CKD = chronic kidney disease.

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

Practical Updates in Primary Care

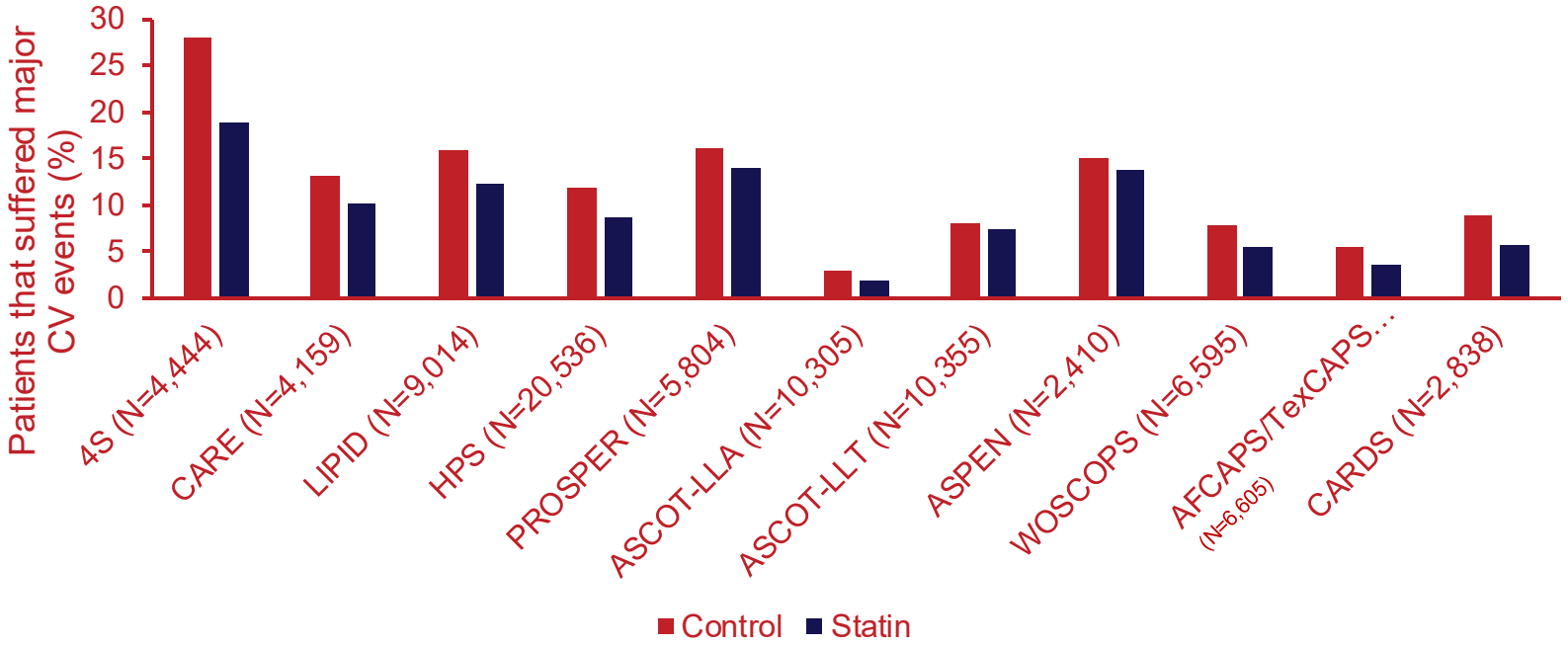


Practical Updates in Primary Care

New and Emerging Lipid-Lowering Therapies

Michael J. Blaha, MD, MPH

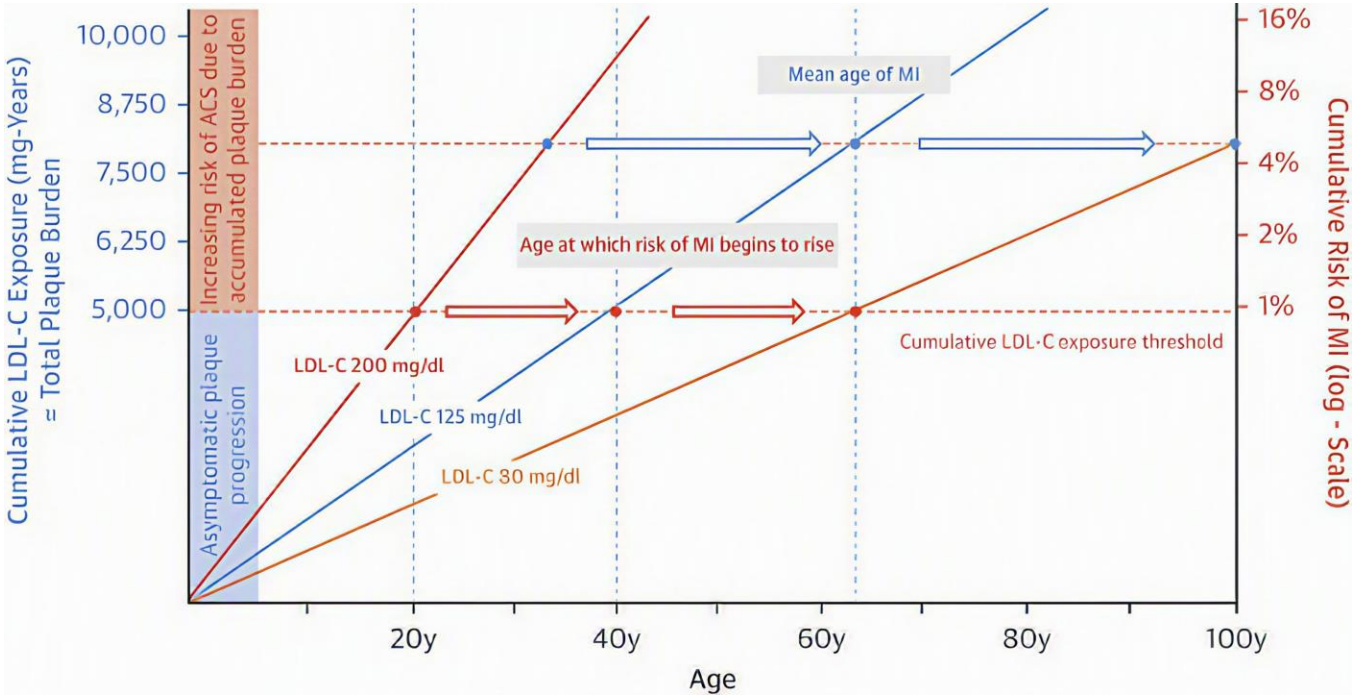
Residual Risk Remains after Marked Reduction of LDL-C in 12 Major Statin Trials



Sampson UK, et al. *Curr Atheroscler Rep*. 2012;14(1):1-10.

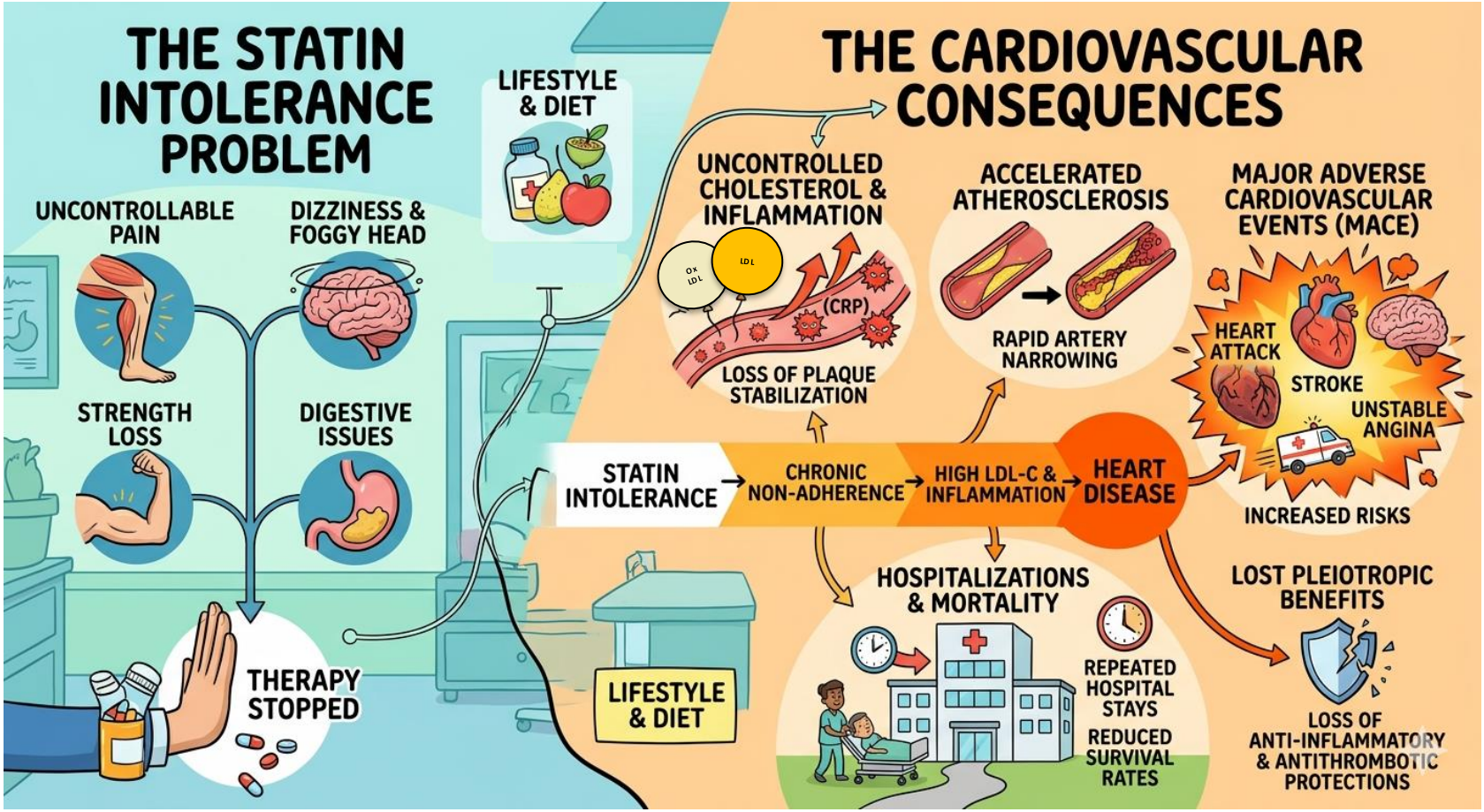
Practical Updates in Primary Care

Cumulative Effect of LDL on Risk of Atherosclerotic Cardiovascular Disease



Ference BA, et al. *J Am Coll Cardiol*. 2018;72(10):1141-1156.

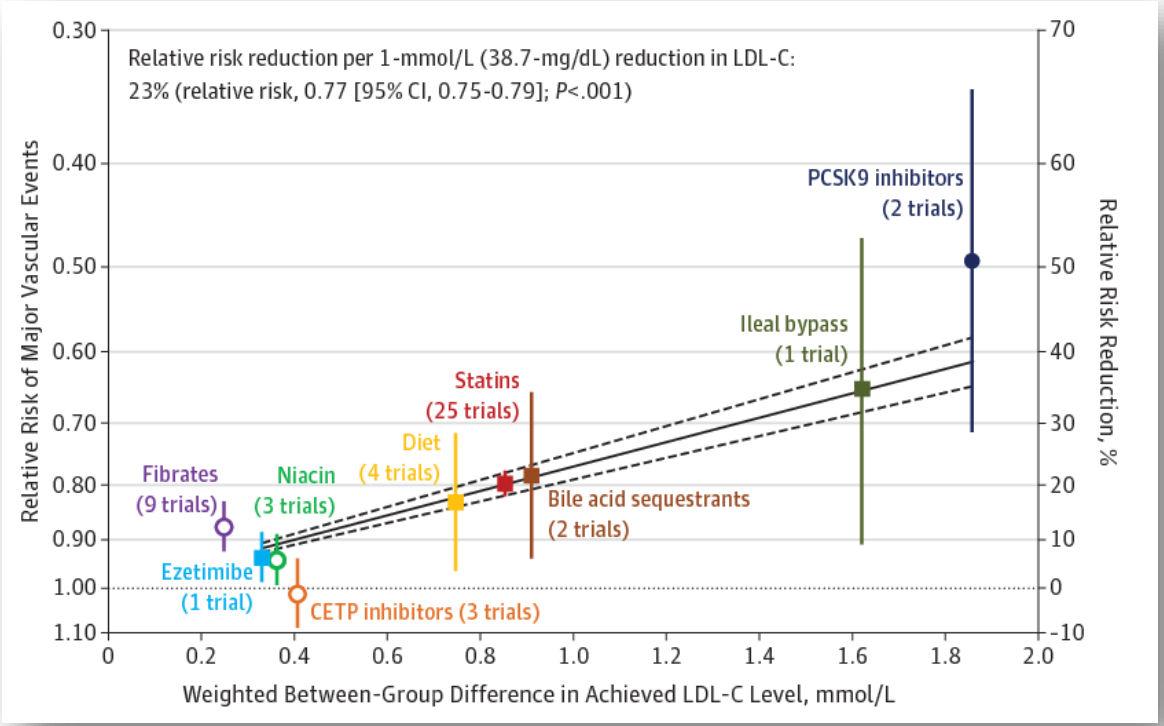
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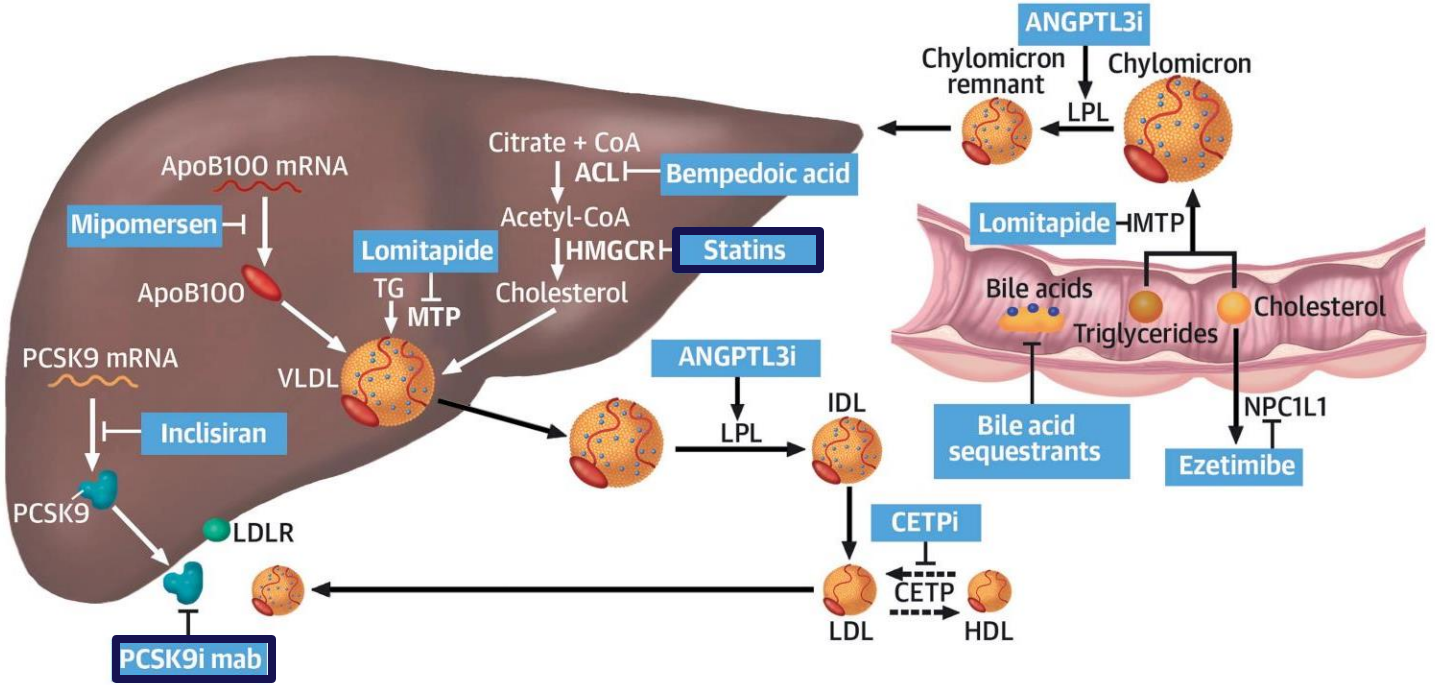
Association between LDL-C Lowering and CV Risk Reduction among Different Therapeutic Interventions



Silverman MG, et al. *JAMA*. 2016;316(12):1289-1297.

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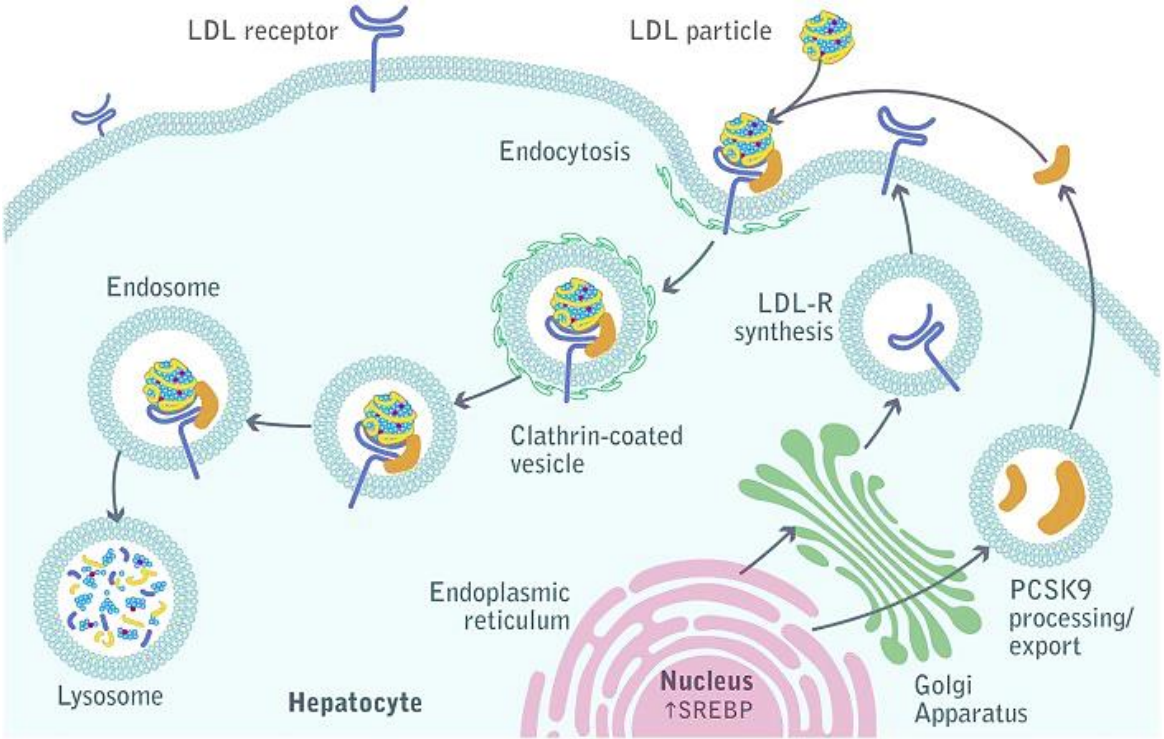
CENTRAL ILLUSTRATION: Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies



Nurmohamed NS, et al. *J Am Coll Cardiol*. 2021;77(12):1564-1575.

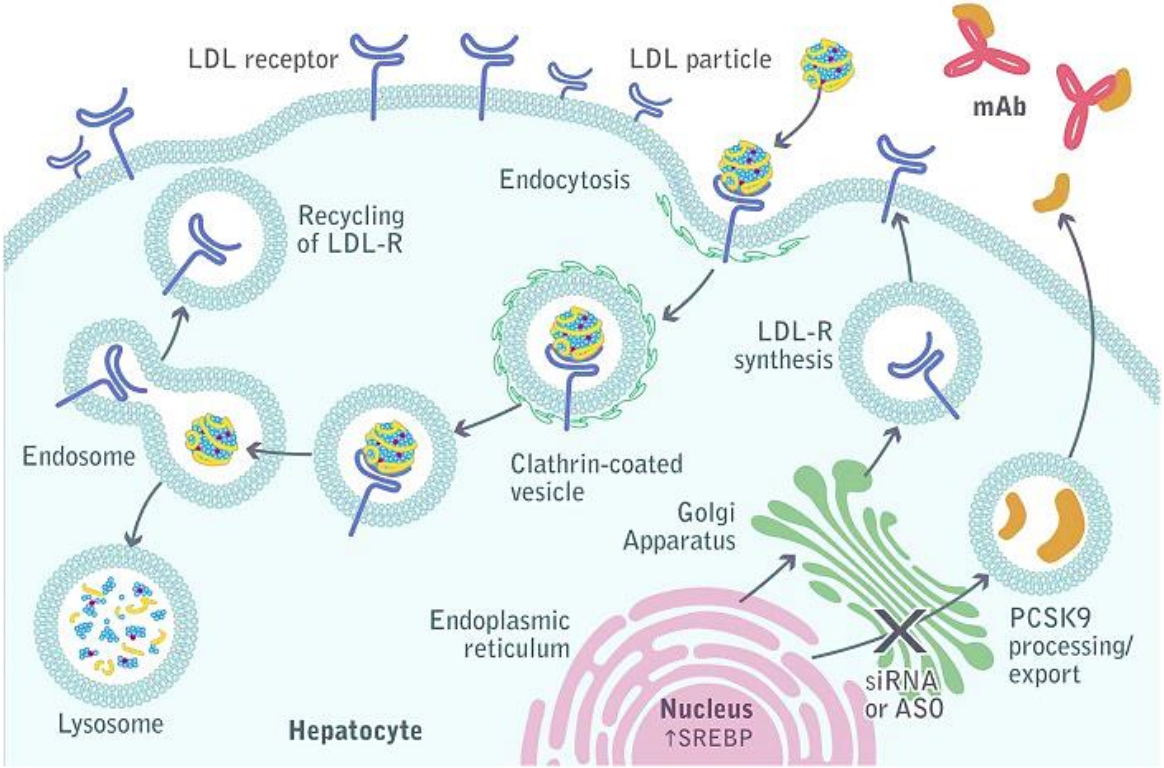
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PCSK9 Promotes the Degradation of the LDL-Receptor and Prevents it from Recycling to the Cell Membrane



Practical Updates in Primary Care

PCSK9 Inhibitors Are Monoclonal Antibodies That Bind to PCSK9, Prevent Association with LDL-Receptor, and Therefore Decrease LDL-Receptor Degradation

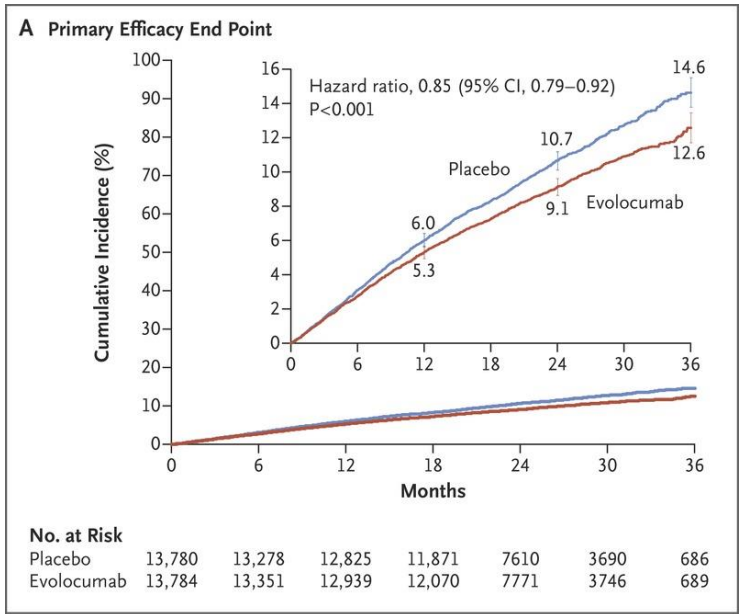


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Major Trial Evidence for PCSK9i

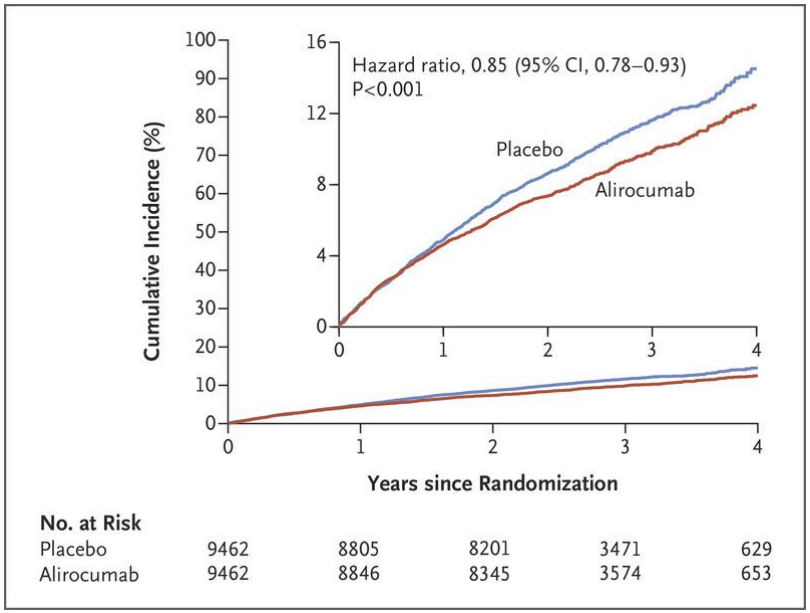
FOURIER

27,564 pts w/ ASCVD
Median 2.2 yrs
LDL-C 92 → 30



ODYSSEY Outcomes

18,924 pts w/ ACS
Median 2.8 yrs
LDL-C 92 → 30 → 48 → 66



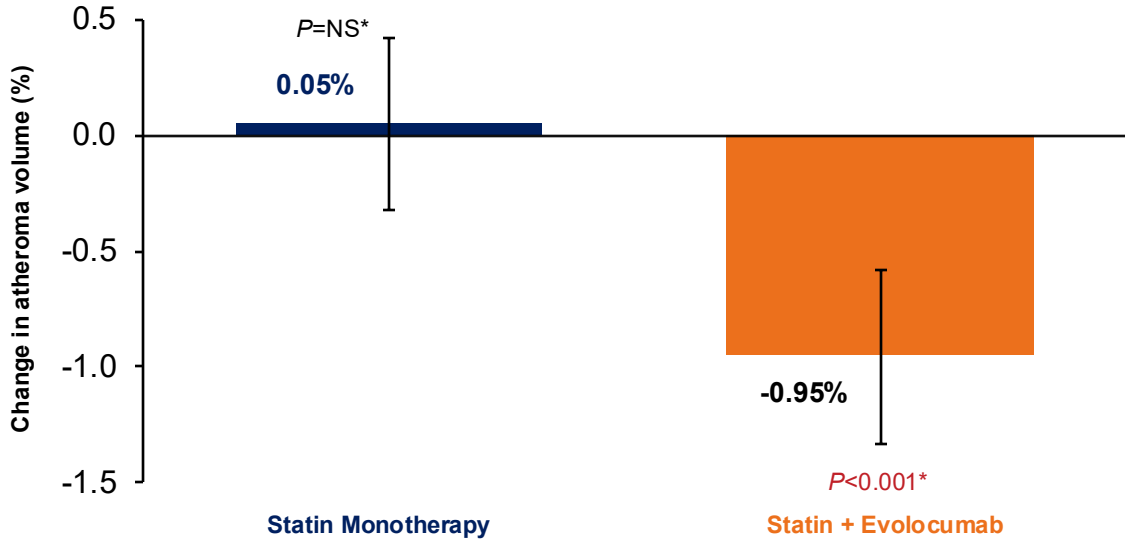
ACS = acute coronary syndrome.

Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722. Schwartz GG, et al. *N Engl J Med*. 2018;379(22):2097-2107.

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EVOLOCUMAB – GLAGOV Trial

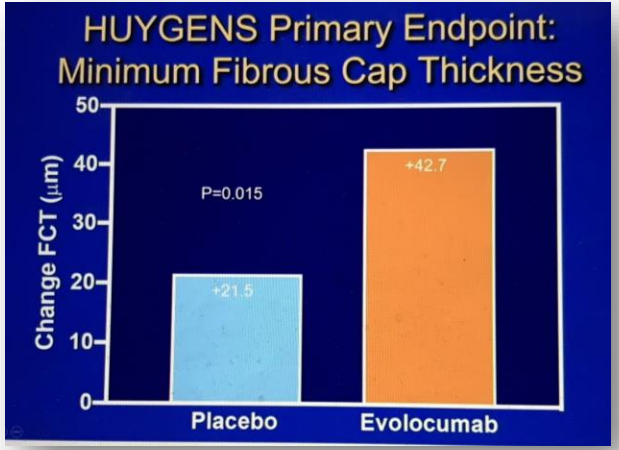
Primary Endpoint: Nominal Change in PAV on IVUS from Baseline to Week 78

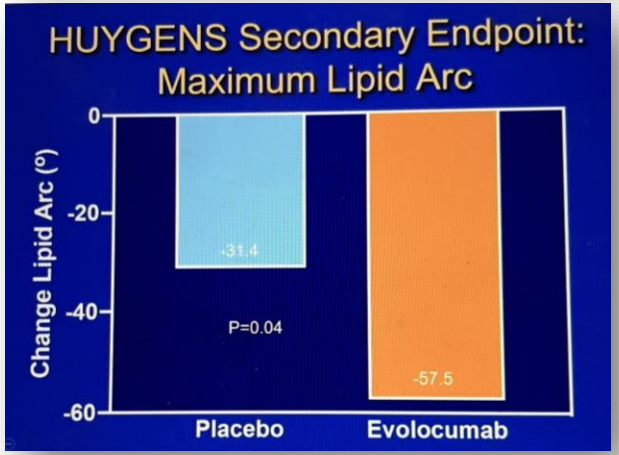


Mean change in coronary atherosclerotic plaque burden, as measured by percent atheroma volume, from baseline to Week 78 (vs placebo) was -1.0% (-1.8, -0.64; *P*<0.001)

Data shown are least-squares mean (95% CI).
***Comparison vs baseline.**
PAV = percent atheroma volume; IVUS = intravascular ultrasound; NS = not significant.
Nicholls SJ, et al. *JAMA*. 2016;316(22):2373-2384.

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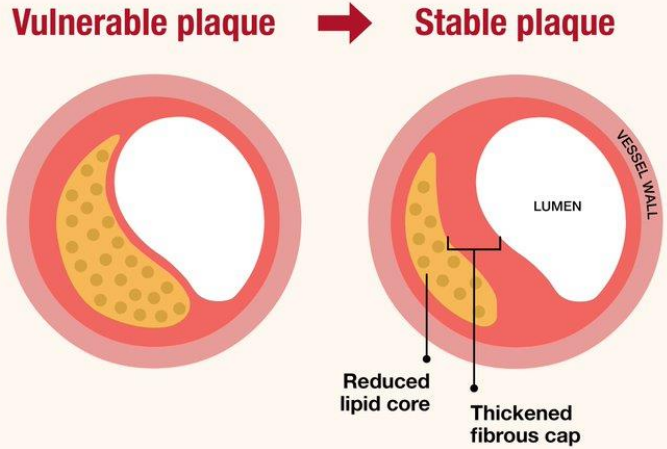




ESC
European Society of Cardiology

HUYGENS

Evolocumab and changes in plaque composition on OCT

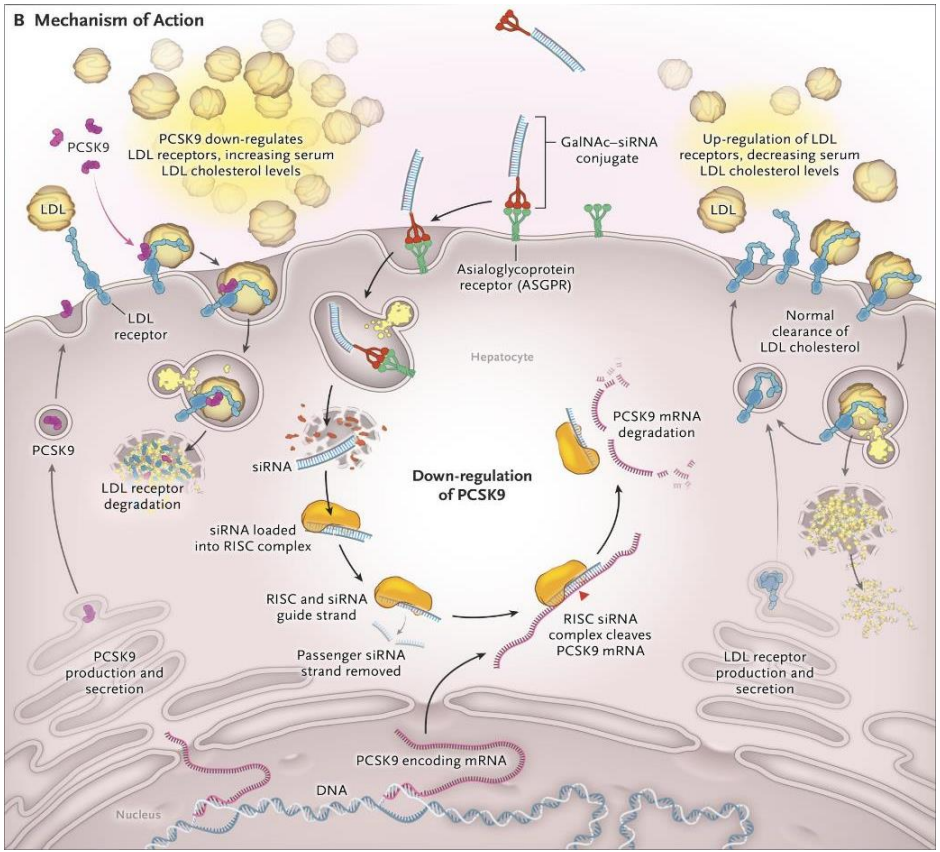


FCT = fibrous cap thickness; OCT = optical coherence tomography.

Nicholls SJ, et al. *JACC Cardiovasc Imaging*. 2022;15(7):1308-1321.

Practical Updates in Primary Care

Inclisiran

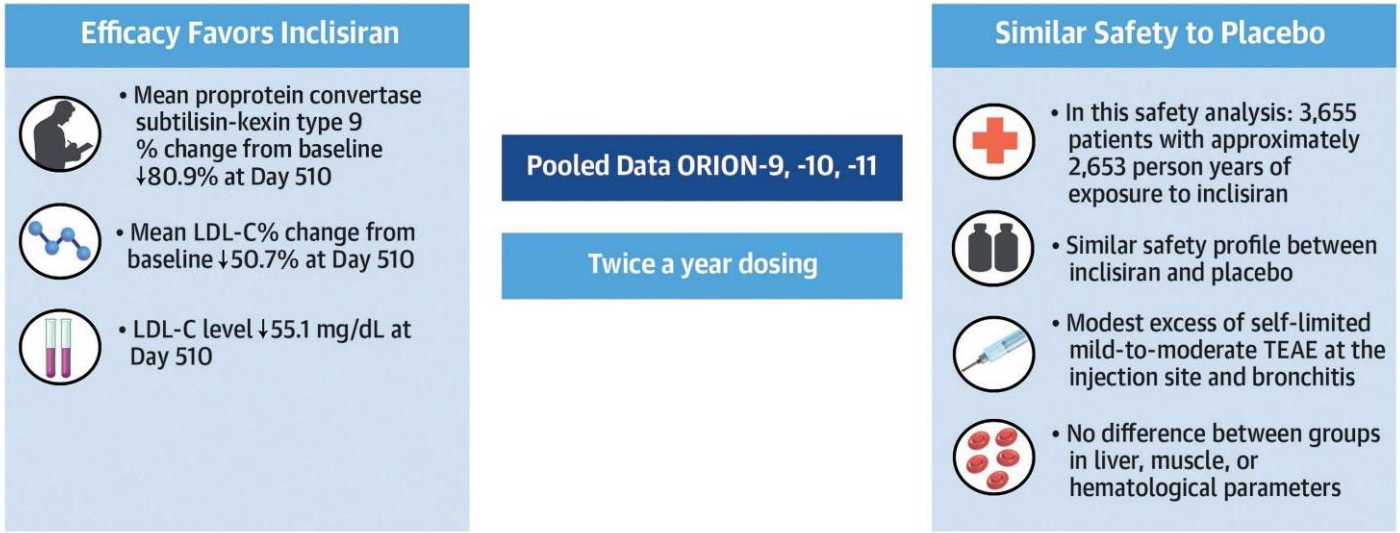


- Short-chain, synthetic, small interfering RNA (siRNA) that inhibits translation of PCSK9; binds to the mRNA precursor, which then undergoes degradation
- Indication: Secondary prevention in patients with ASCVD and HeFH
- Administered: Subcutaneously with an initial dose followed by dosing at 3 months and then every 6 months thereafter
- Inclisiran approved by EMA in Dec 2020, UK NICE in 2021, FDA approval Dec 2021

Rosenson RS, et al. *J Am Coll Cardiol*. 2018;72(3):314-329. Ray KK, et al. *N Engl J Med*. 2020;382(16):1507-1519.

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CENTRAL ILLUSTRATION: Inclisiran With Summary About Safety and Efficacy



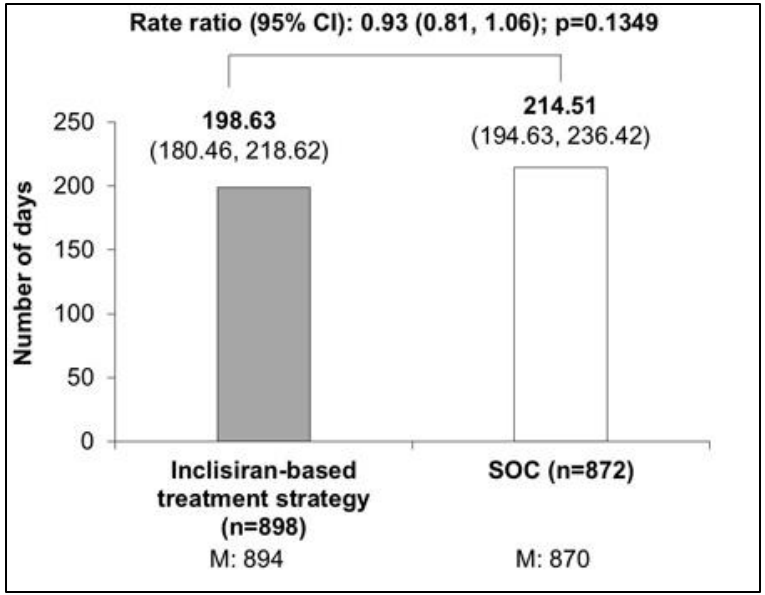
Wright RS, et al. *J Am Coll Cardiol*. 2021;77(9):1182-1193.

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VICTORION-Difference (Phase 4):

Effect of Inclisiran-Based Treatment Strategy, in Combination with Individually Optimized Statin Therapy, on Quality of Life and Muscle-Related Pain vs Standard of Care

Annualized rate (95% CI) of days with pain from Day 1 to Day 360 in the VICTORION-Difference study population (full analysis set)



Fewer participants in the inclisiran vs SOC arm experienced a muscle-related adverse event (11.9% vs 19.2%; odds ratio = 0.57; 95% CI: 0.43, 0.74).

SOC = standard of care.

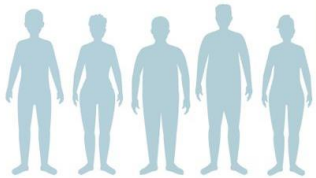
Landmesser U, et al. *Circulation*. 2025;152(Suppl 3):4360376.

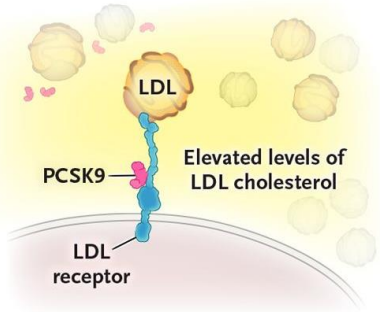
A Placebo-Controlled Trial of the Oral PCSK9 Inhibitor Enlicitide

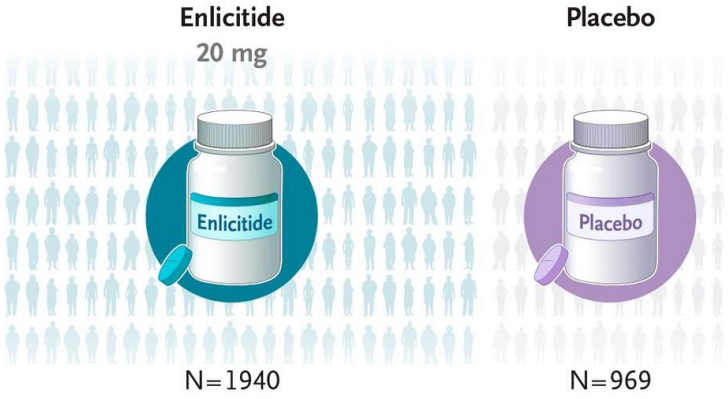
A Research Summary based on Navar AM et al. | 10.1056/NEJMoa2511002 | Published on February 5, 2026

Participants

- 2909 adults
- Mean age, 63 years
- Men: 61%; Women: 39%



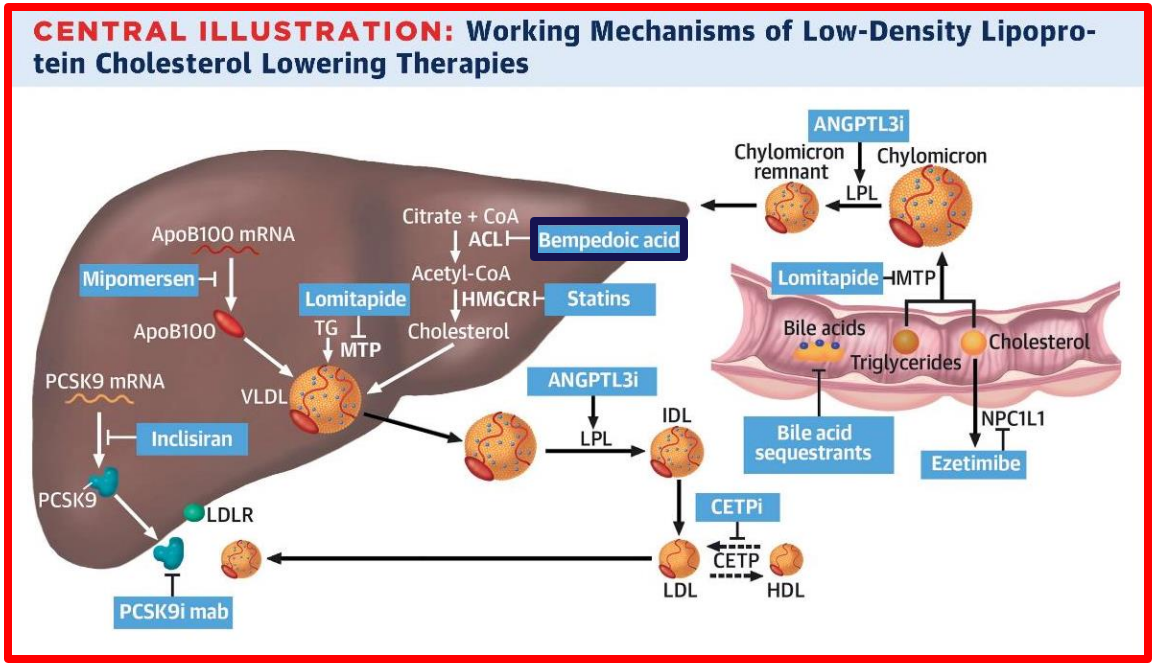




Navar AM, et al. *N Engl J Med*. 2026;394(6):529-539.

Practical Updates in Primary Care

Bempedoic Acid

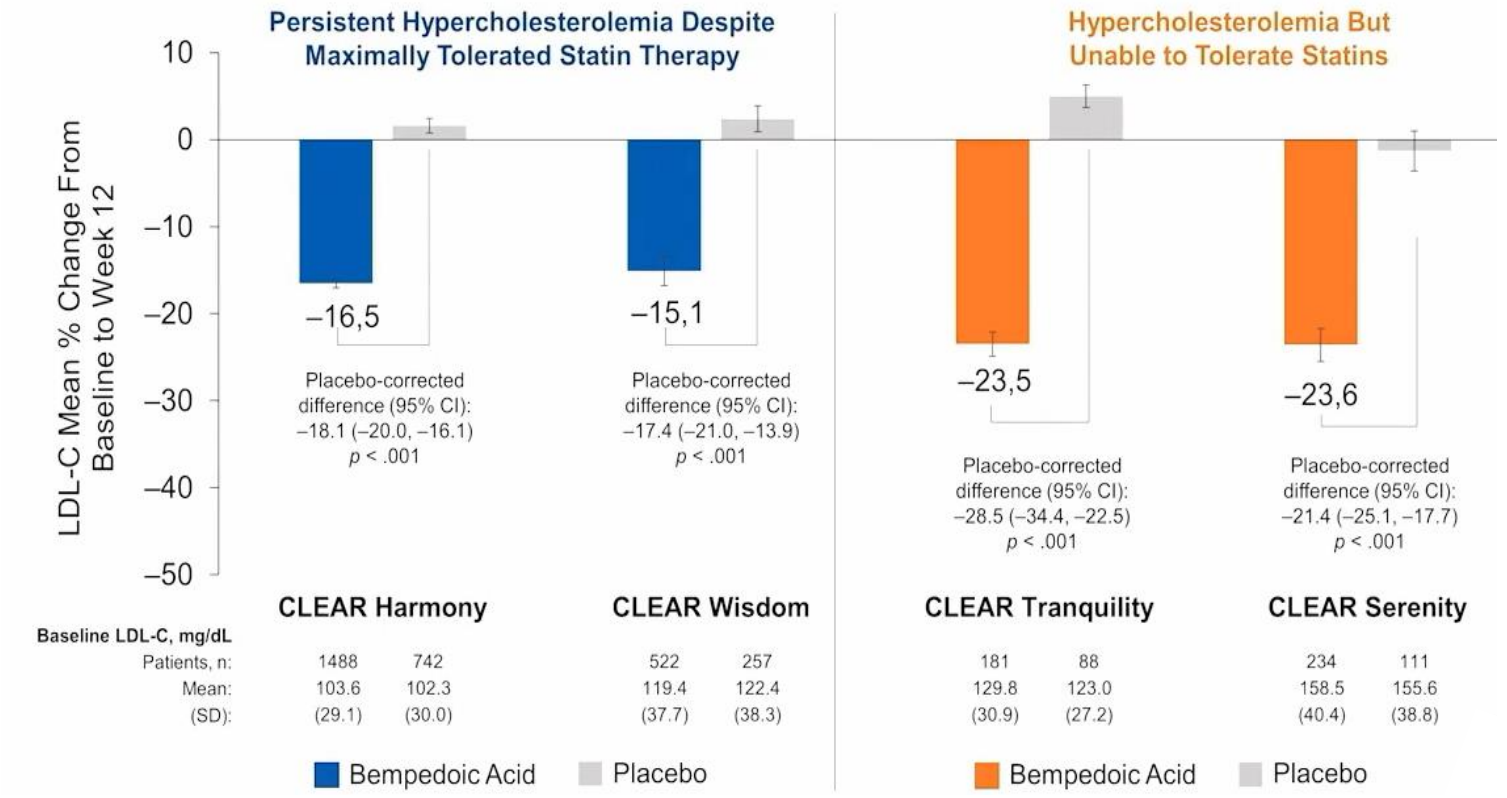


- Inhibits ATP-citrate lyase (ACL), enzyme upstream of HMG-CoA reductase inhibitor in the cholesterol synthesis pathway
- Prodrug activated in the liver
- Activated by ACSVL1, which is not present in muscle

Nurmohamed NS, et al. *J Am Coll Cardiol*. 2021;77(12):1564-1575.

Practical Updates in Primary Care

Effect of Bempedoic Acid on LDL-C after 12 Weeks of Treatment

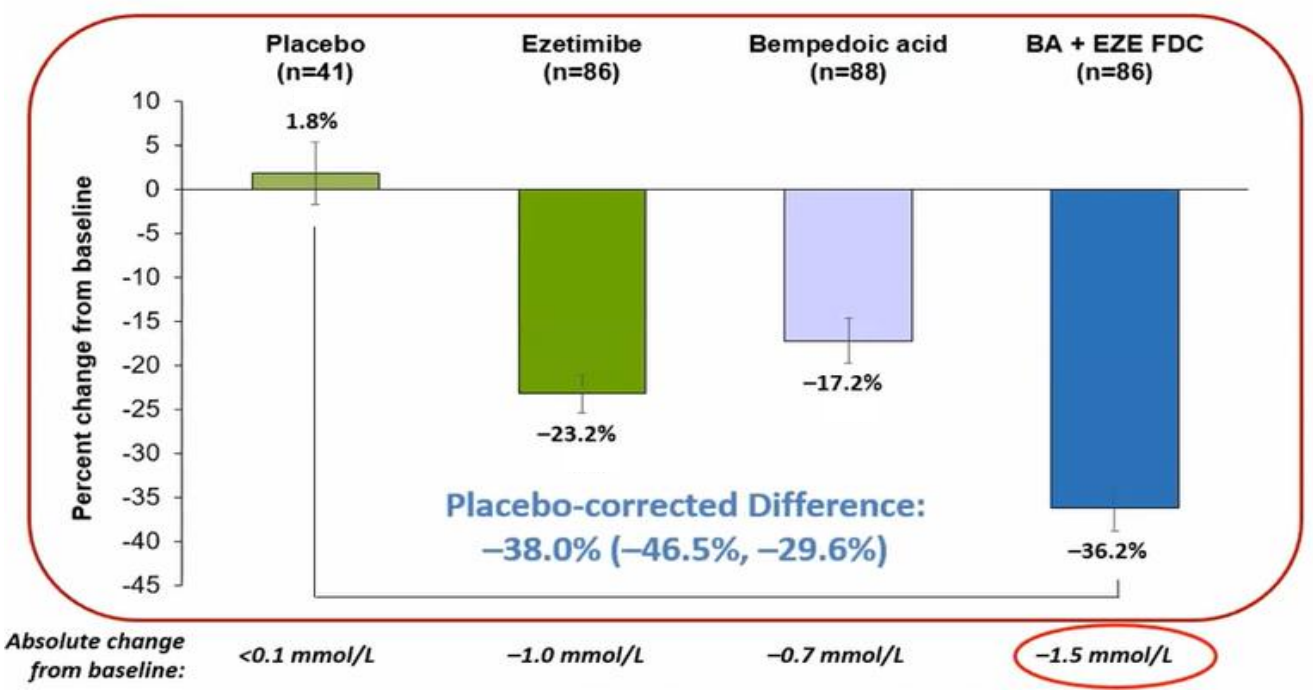




Ballantyne CM, et al. *Cardiovasc Drugs Ther*. 2021;35(4):853-864.

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Percent Change from Baseline in LDL Level at Week 12





BA = bempedoic acid; EZE = ezetimibe; FDC = fixed-dose combination.
Ballantyne CM, et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Practical Updates in Primary Care

CLEAR Outcomes



RESEARCH SUMMARY

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen SE et al. DOI: 10.1056/NEJMoa2215024

CLINICAL PROBLEM

Bempedoic acid is an ATP citrate lyase inhibitor that reduces low-density lipoprotein (LDL) cholesterol levels without the elevated risk of musculoskeletal adverse effects associated with statins. Although the goal of reducing LDL cholesterol levels is to prevent adverse cardiovascular events, studies of the effects of bempedoic acid on cardiovascular events are lacking.

CLINICAL TRIAL

Design: An international, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of bempedoic acid for the prevention of adverse cardiovascular events in statin-intolerant patients.

Intervention: 13,970 patients 18 to 85 years of age at increased cardiovascular risk who were unable or unwilling to take guideline-recommended doses of statins were assigned to receive 180 mg of oral bempedoic acid or placebo daily. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

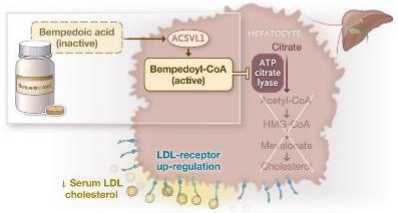
Efficacy: After a median follow-up of 40.6 months, the incidence of major adverse cardiovascular events was significantly lower in the bempedoic acid group than in the placebo group.

Safety: The incidences of adverse events were similar in the two groups overall; however, the bempedoic acid group had higher incidences of elevated hepatic enzymes, renal impairment, hyperuricemia, gout, and cholelithiasis.

LIMITATIONS AND REMAINING QUESTIONS

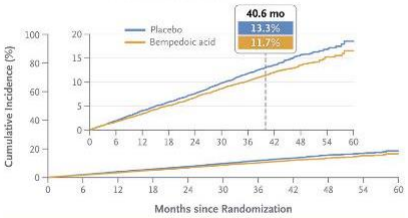
- The trial included only patients who were unable or unwilling to take statins, and therefore the mean LDL cholesterol level was high at baseline. The findings cannot be generalized to populations with lower LDL cholesterol levels.

Links: Full Article | NEJM Quick Take | Editorial | Science behind the Study



Four-Component Composite of Major Adverse Cardiovascular Events

HR, 0.87 (95% CI, 0.79–0.96); P=0.004



Adverse Events

	Bempedoic acid (N=7001)	Placebo (N=6964)
	no. of patients (%)	
Any adverse event	6040 (86.3)	5919 (85.0)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

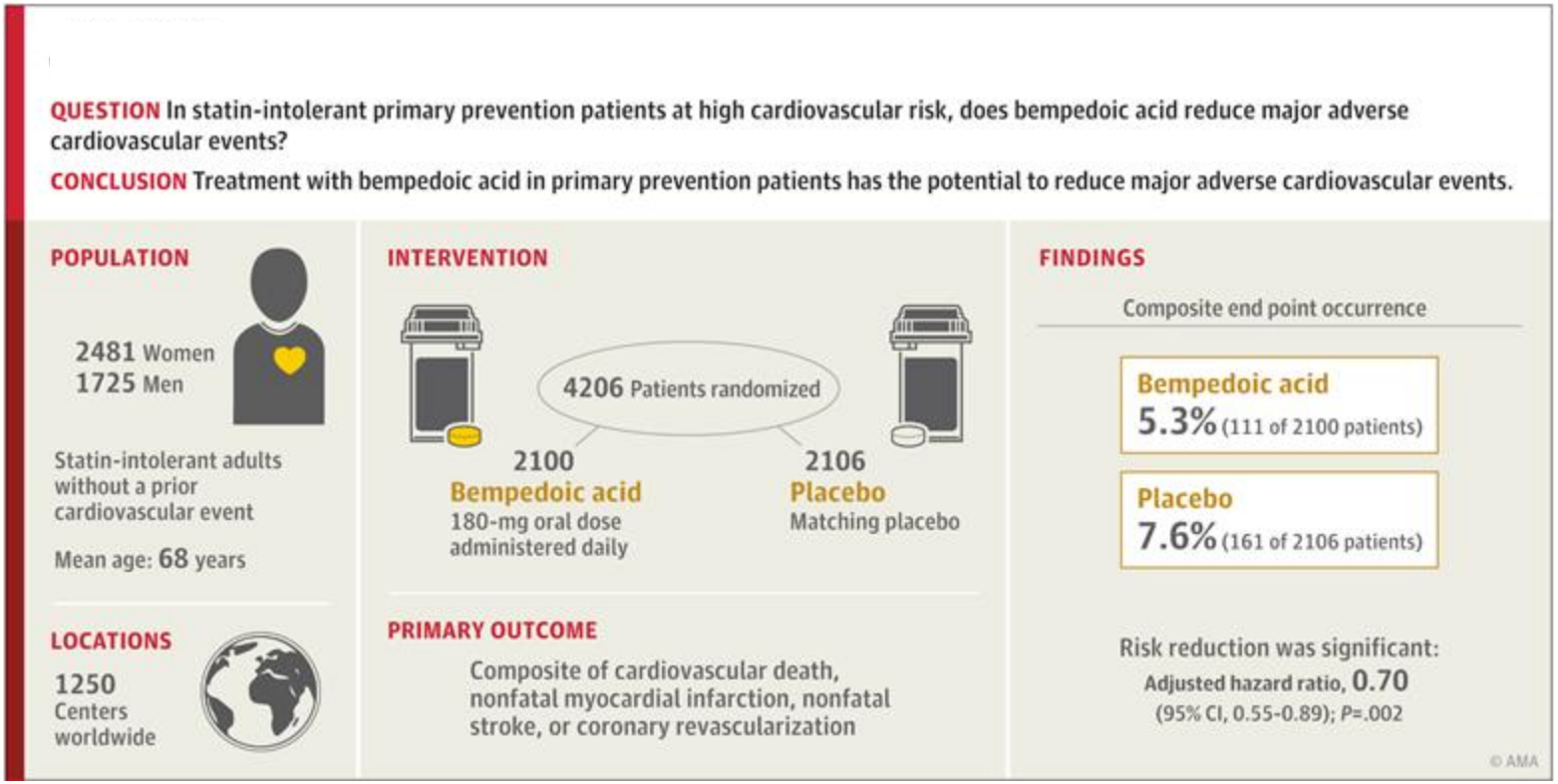
CONCLUSIONS

Among patients at increased cardiovascular risk who were unable or unwilling to take statins, treatment with bempedoic acid significantly reduced the risk of major adverse cardiovascular events.

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

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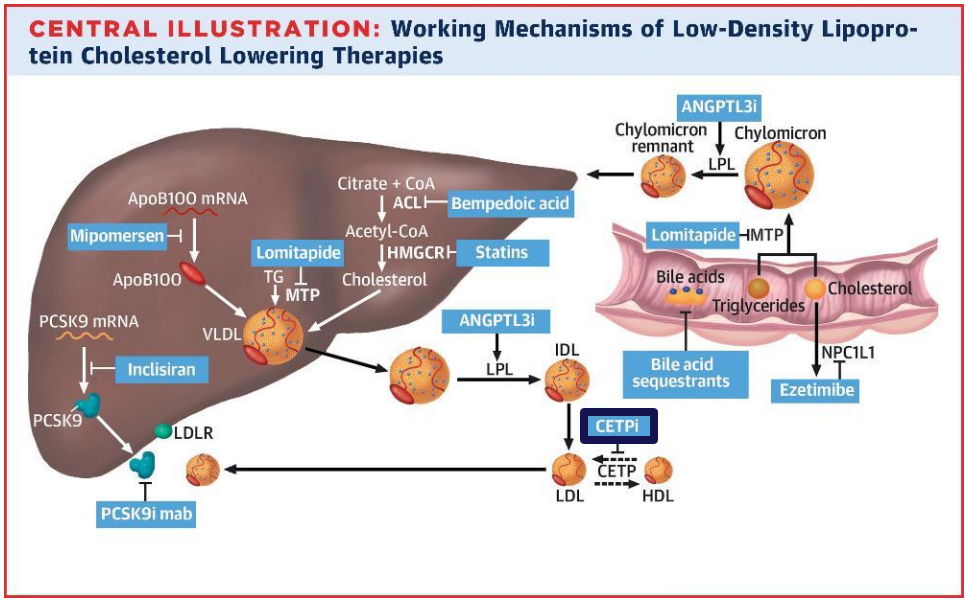
CLEAR Outcomes – Primary Prevention



Nissen SE, et al. *JAMA*. 2023;330(2):131-140.

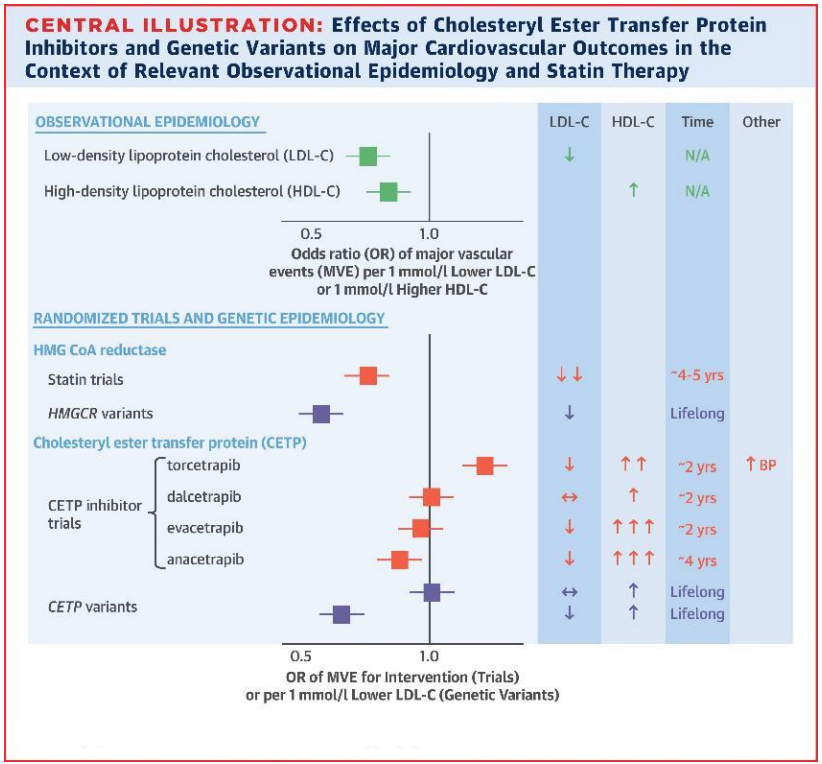
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Obicetrapib (CETP Inhibitor)





TA-8995 lowers LDL-C by 45%

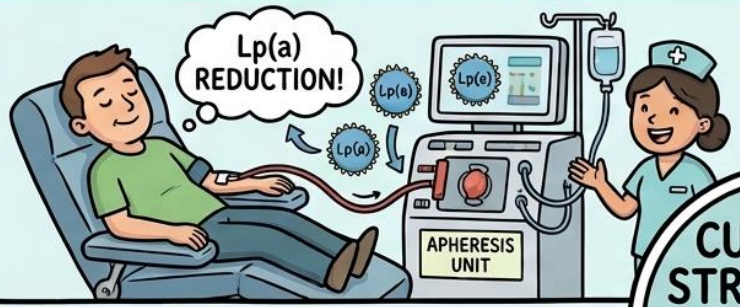


Nurmohamed NS, et al. *J Am Coll Cardiol*. 2021;77(12):1564-1575. Armitage J, et al. *J Am Coll Cardiol*. 2019;73(4):477-487.

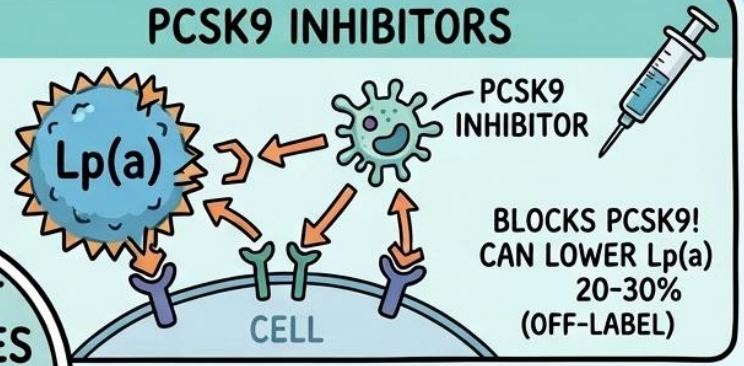
Practical Updates in Primary Care

EXISTING THERAPIES FOR LOWERING LIPOPROTEIN(a)

1 LIPORPOTEIN APHERESIS



2 PCSK9 INHIBITORS



CURRENT STRATEGIES & GOALS

- REDUCE TOTAL CARDIOVASCULAR RISK

3 NIACIN (VITAMIN B3)



MAY LOWER Lp(a) BY APPROX. 20-30%, BUT NOT RECOMMENDED

4 HORMONE THERAPY



GENERALLY, NOT RECOMMENDED FOR THIS PURPOSE

ADDITIONAL APPROACHES



ASPIRIN CONSIDERATION



MANAGE OVERALL RISK

KEY TAKEAWAY: **TEST ONCE**

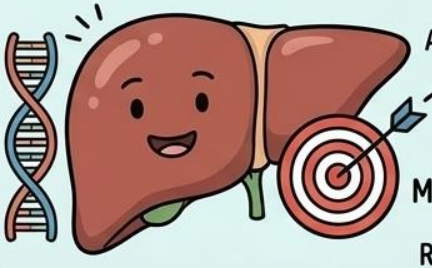


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EMERGING THERAPIES IN PHASE 3 TRIALS FOR LOWERING LIPOPROTEIN(a)

1 ANTISENSE OLIGONUCLEOTIDES (ASO)



TARGETS LIVER!

ASO

apo(a) mRNA

BLOCKS apo(a) MRNA PRODUCTION. POTENTIAL REDUCTIONS > 80%.

2 SMALL INTERFERING RNA (siRNA)

LIVER CELL



Lp(a) siRNA

RISC

apo(a)

apo(a)

apo(a) mRNA

WHY ASO & siRNA?



GENE SILENCING! HALTS apo(a) ASSEMBLY. POTENTIAL REDUCTIONS > 80%.

KEY GOALS OF PHASE 3 TRIALS

- ✓ 1. ESTABLISH SAFETY
- ✓ 2. PROVE Lp(a) LOWERING EFFICACY
- ✓ 3. DEMONSTRATE REDUCTION OF CARDIOVASCULAR EVENTS (MACE)

3 SMALL MOLECULE ORAL DRUGS

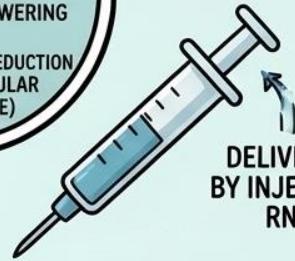


ORAL PILL DEVELOPMENT!

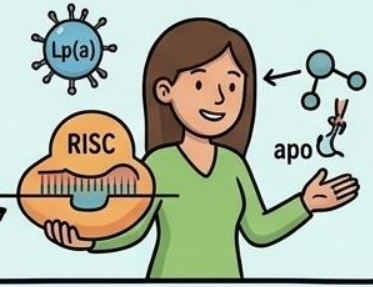
apo(a) apo(b)

Lp(a)

INHIBITS FORMATION. POTENTIAL REDUCTIONS 70-90%.



DELIVERED BY INJECTION RNA



ADDITIONAL TRIAL CONSIDERATIONS



CARDIOVASCULAR RISK PREDICTION



LONG-TERM TRIAL DURATION



DIVERSE ENROLLMENT

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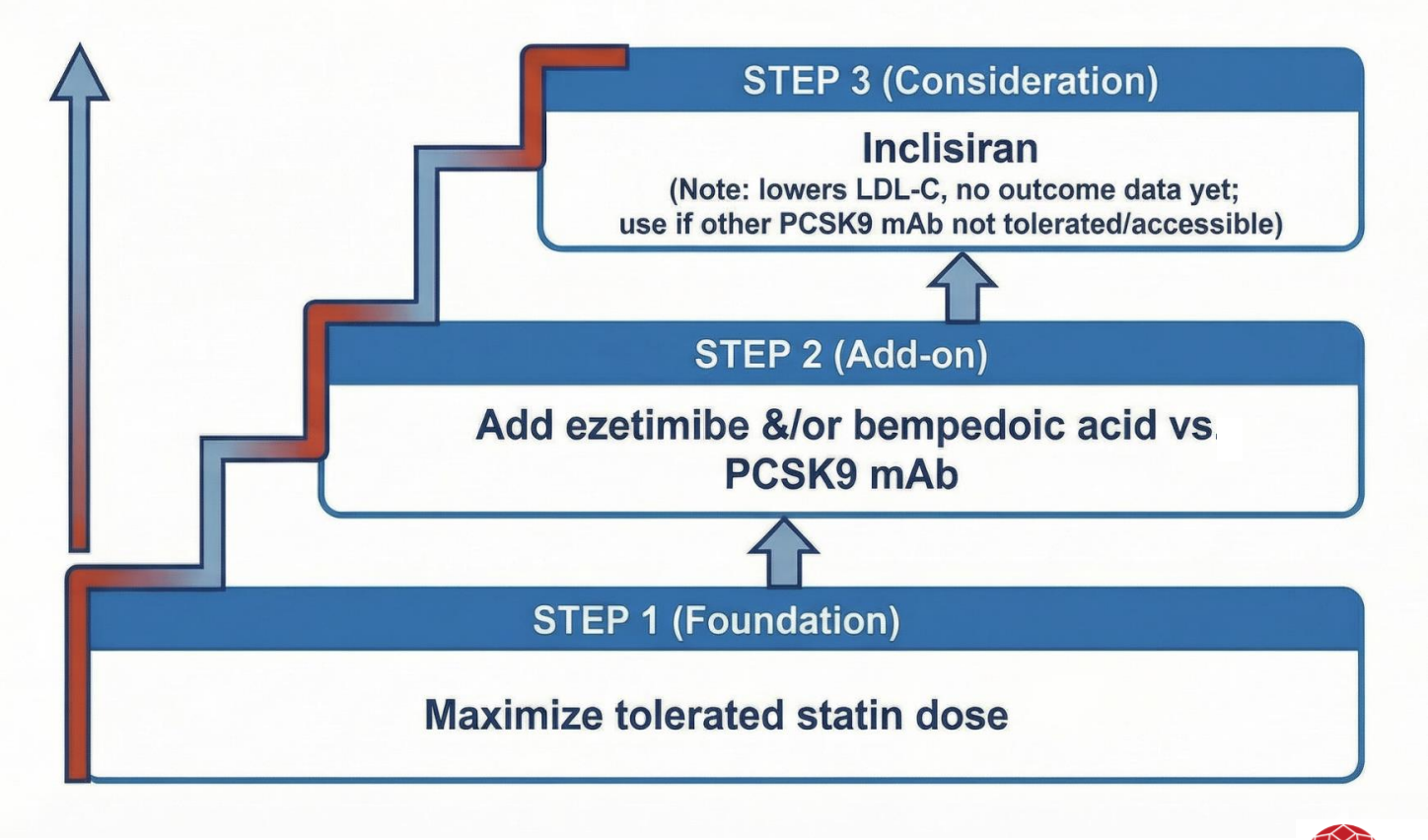


Practical Updates in Primary Care

Guideline Algorithms

Michael J. Blaha, MD, MPH

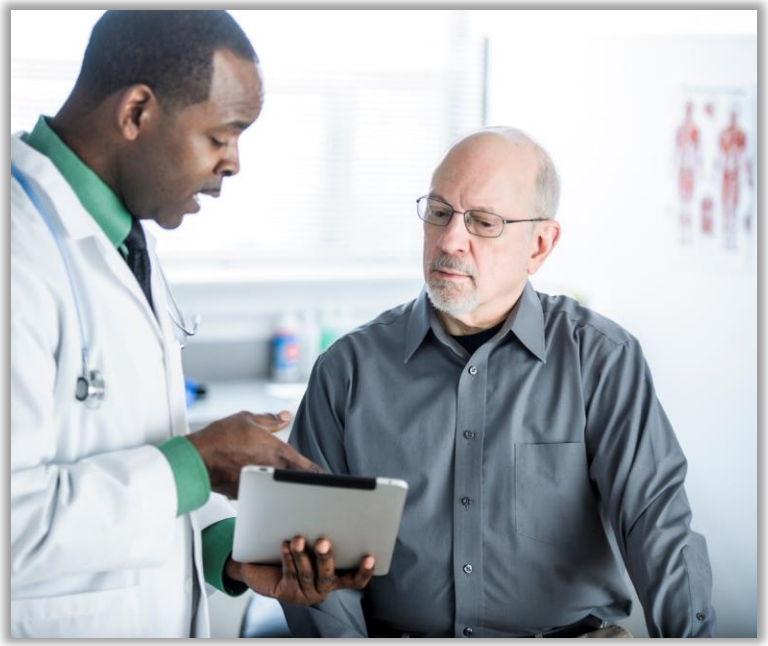
General – How to Sequence LLT



Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

Practical Updates in Primary Care

Severe Hypercholesterolemia with Clinical or Genetic Confirmation of Homozygous Familial Hypercholesterolemia



COR	RECOMMENDATIONS
1	Refer to lipid specialist.
1	Maximally tolerated statin recommended.
2a	Add ezetimibe, PCSK9 mAb, or bempedoic.
2b	Add evinacumab if LDL ≥100 persists.
2b	Consider lomitapide with monitoring.

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

Practical Updates in Primary Care

Secondary Prevention of ASCVD in Adults at Very High Risk



Clinical ASCVD in adults at very high risk:	
COR	RECOMMENDATIONS
1	High-intensity statin therapy should be initiated to achieve ≥50% lowering in LDL-C and a goal of LDL-C <55 mg/dL and non-HDL-C <85 mg/dL, and to reduce risk of ASCVD events.
1	For those on maximally tolerated statin therapy, ezetimibe and/or a PCSK9 mAb should be added to achieve a goal of LDL-C <55 mg/dL and non-HDL-C <85 mg/dL to reduce risk of ASCVD events.
2a	For those on maximally tolerated statin, it is reasonable to add bempedoic acid to a statin, with or without ezetimibe and/or PCSK9 mAb, to reach an LDL-C goal of <55 mg/dL and non-HDL-C <85 mg/dL to reduce risk of ASCVD events.
2a	For those on maximally tolerated statin therapy with or without ezetimibe, it is reasonable to add inclisiran in those unable to tolerate or obtain evolocumab or alirocumab, or those with a strong preference for less frequent dosing to achieve an LDL-C goal of <55 mg/dL and non-HDL-C <85 mg/dL.

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.

Practical Updates in Primary Care

Secondary Prevention in Patients Not at Very High Risk

Clinical ASCVD in adults not at very high risk	
COR	RECOMMENDATIONS
1	High-intensity statin Rx should be initiated to achieve ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL + non-HDL-C <100 mg/dL to reduce risk of recurrent ASCVD events.
2a	For those on maximally tolerated statin Rx, it is reasonable to add ezetimibe, a PCSK9 mAb, or bempedoic acid to achieve a goal of LDL-C <70 mg/dL + non-HDL-C <100 mg/dL to reduce risk of ASCVD events.
2a	For those on maximally tolerated statin therapy, it is reasonable to add ezetimibe, a PCSK9 mAb, or bempedoic acid to achieve a goal of LDL-C <55 mg/dL and non-HDL-C <85 mg/dL, and to reduce risk of ASCVD events.

Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757.



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Individualizing LDL-C Management: Adherence, Health Equity, and Shared Decision-Making

Jonathon Firnhaber, MD, MAEd, MBA

Barriers to Adherence

- Patient factors
  - Poor ASCVD awareness – we perceive problems differently than our patients do
  - Unintentional nonadherence
  - Nocebo effect



Desai NR, et al. *Clin Cardiol*. 2022;46(1):13-21.

Nocebo Effect

Registry studies have indicated that the most common reason for declining or discontinuing statin therapy is *fear of adverse events*.

- Nocebo effect describes a situation where a negative outcome occurs due to a *belief* that the intervention will cause harm; the term nocebo comes from the Latin “to harm”
- For adverse reactions to medicines, nocebo implies that patients are more likely to experience an adverse effect if they *expect or are worried about the adverse effect*; the adverse effects may be physically experienced by the patient
- Example: adverse effects experienced by patients *taking a placebo* during a clinical trial

The nocebo effect may have a *larger effect on clinical outcomes* than the placebo effect, as negative perceptions are formed much faster than positive ones.

Barriers to Adherence

- Patient factors
  - Poor ASCVD awareness – we perceive problems differently than our patients do
  - Unintentional nonadherence
  - Nocebo effect

  - And people spend time on social media

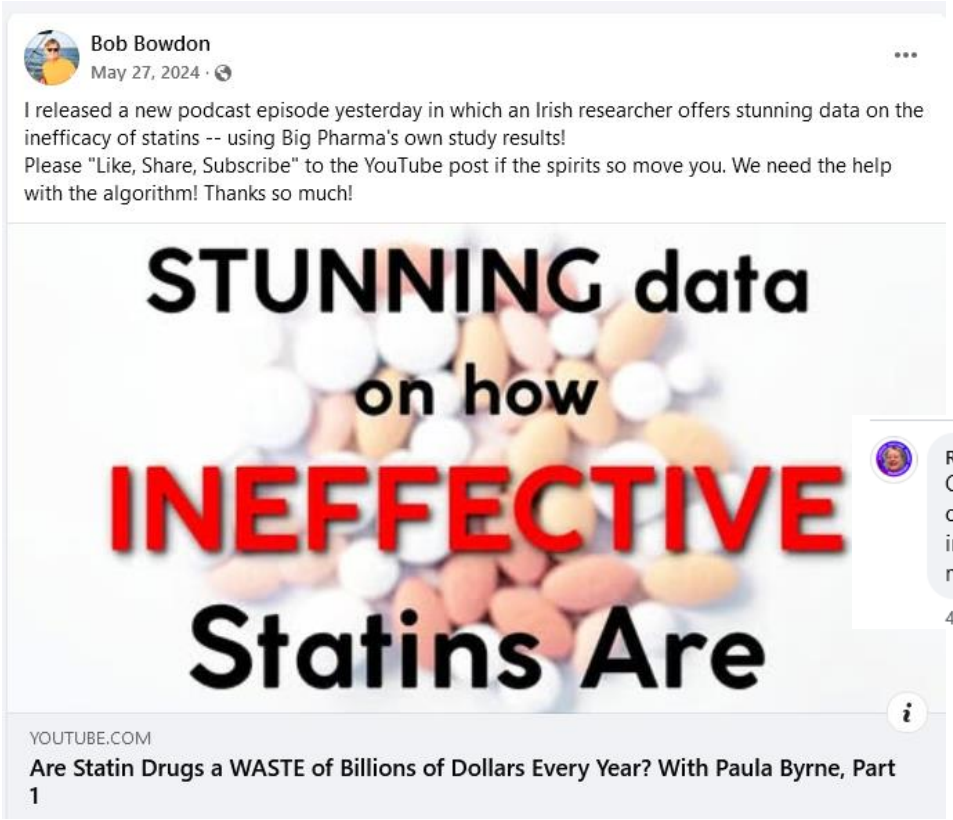
Desai NR, et al. *Clin Cardiol*. 2022;46(1):13-21.

Social Media Misinformation

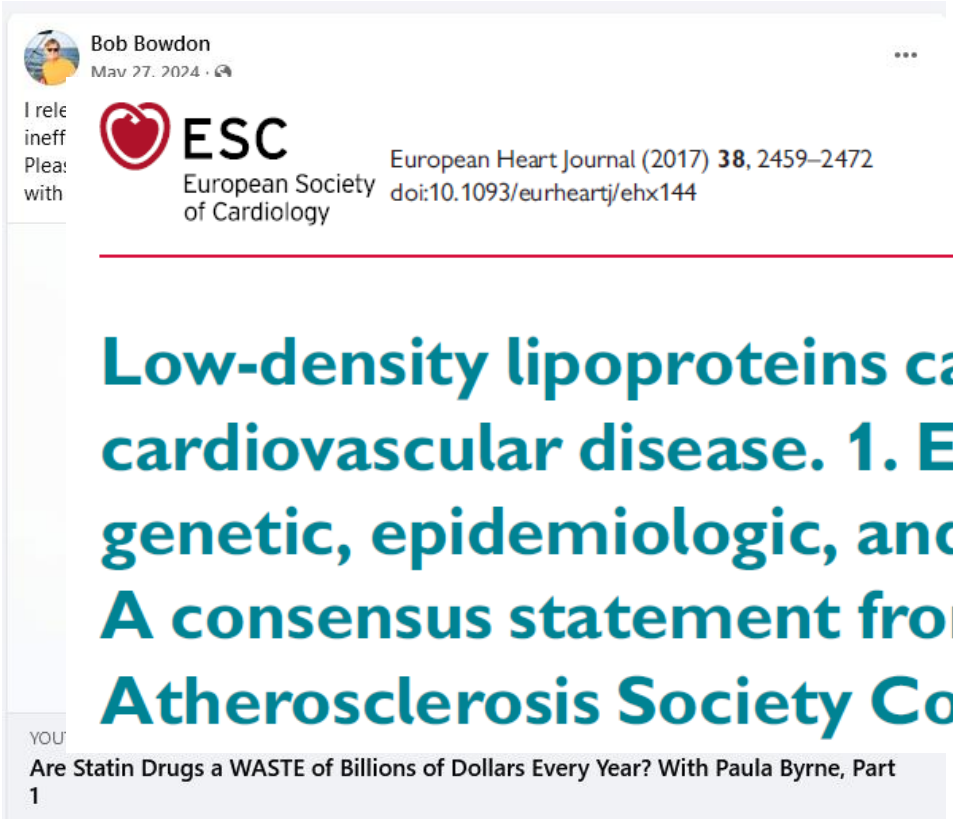


Facebook. Accessed June 23, 2026. https://www.facebook.com/groups/587055831344762/; https://www.facebook.com/groups/106409759391807/about.

Social Media Misinformation



YouTube. Accessed June 23, 2026. https://www.youtube.com/watch?v=6Fu2VMLjvT0.



Ference BA, et al. *Eur Heart J*. 2017;38(32):2459-2472.

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Modifiable Factors Associated with Statin Intolerance

- Hypothyroidism
- Alcohol use
- Strenuous exercise
- Vitamin D deficiency
- Obesity
- Diabetes
- Potential drug-drug interactions (eg, gemfibrozil, protease inhibitors, amiodarone, calcium channel blockers, azole antifungals, macrolides, immunosuppressants, colchicine)

Barriers to Adherence

- Patient factors
  - Poor ASCVD awareness – we perceive problems differently than our patients do
  - Unintentional nonadherence
  - Nocebo effect

- Therapy factors
  - Cost, inconvenience
  - True side effects

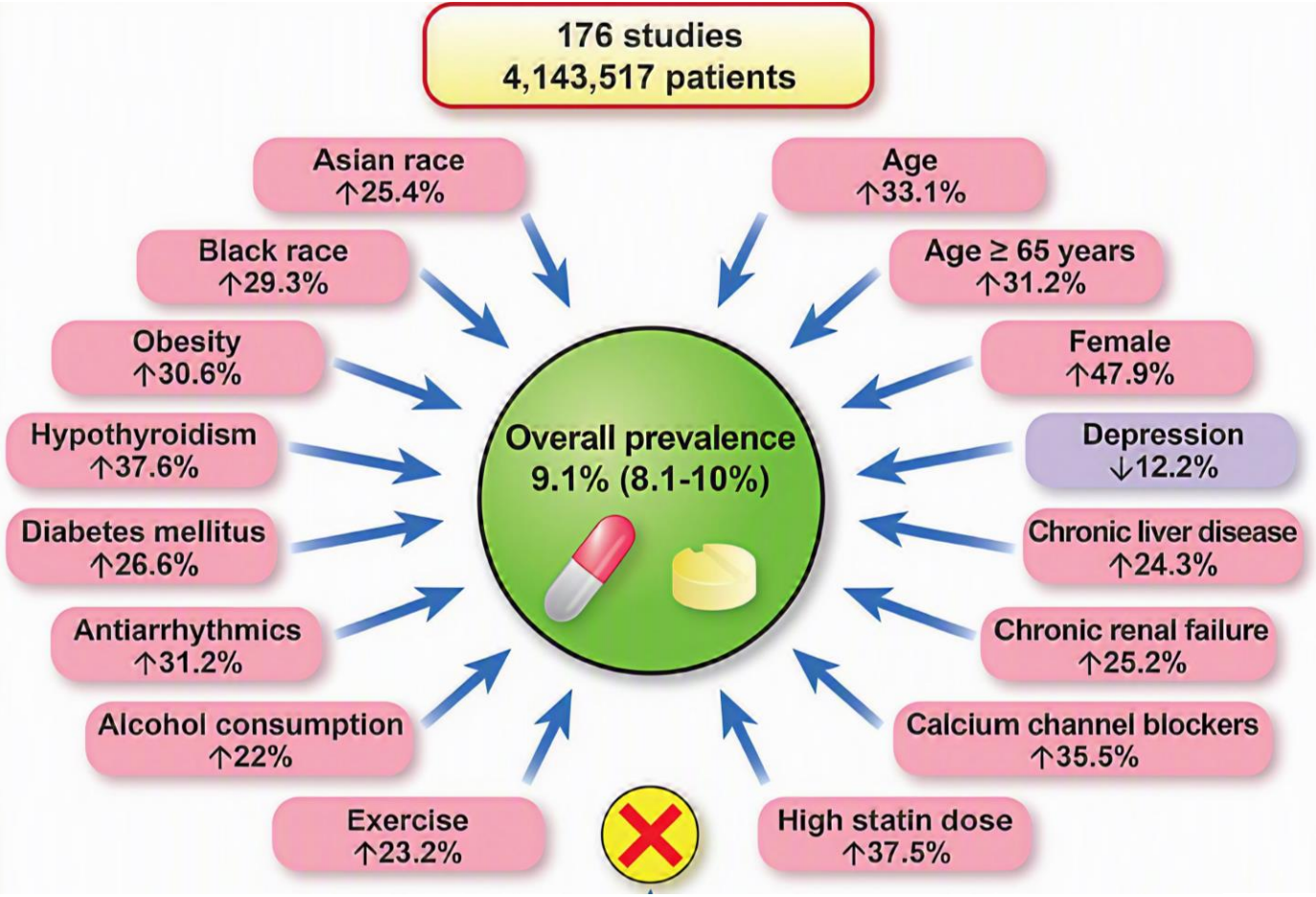
Desai NR, et al. *Clin Cardiol*. 2022;46(1):13-21.

Prevalence of Statin Intolerance: A Meta-Analysis

176 studies [112 randomized controlled trials (RCTs);
64 cohort studies] with 4,143,517 patients

- The overall prevalence of statin intolerance (SI) was 9.1% – even lower when using the international definitions: National Lipid Association, International Lipid Expert Panel, European Atherosclerosis Society (7.0, 6.7, 5.9%)
- The prevalence of SI in RCTs was significantly lower compared with cohort studies [4.9% (4.0-6.0%) vs 17% (14-19%)]
- Prevalence of statin intolerance was found to be similar between patients who received lipophilic (4%) and hydrophilic (5%) statins

SI = statin intolerance; RCTs = randomized controlled trials.
Bytyçi I, et al. *Eur Heart J.* 2022;43(34):3213-3223.



Bytyçi I, et al. *Eur Heart J*. 2022;43(34):3213-3223.

Practical Updates in Primary Care

National Lipid Association Recommendations

- The consensus is that the body of evidence supporting the efficacy of statin therapy to reduce ASCVD risk is compelling, and therefore, it is recommended that multiple strategies should be attempted to achieve statin tolerance whenever feasible

- In high- and very high-risk patients who are statin-intolerant, clinicians should *consider initiating non-statin therapy while additional attempts are made to identify a tolerable statin* in order to limit the time of exposure to elevated levels of atherogenic lipoproteins

Healthcare Disparities

- PALM (Patient and Provider Assessment of Lipid Management) registry
  - 5693 adults recommended for statin; 26.5% not on therapy
  - 47.0% of untreated, statin-eligible patients were never offered a statin
  - Compared with current statin users, patients who were *never offered a statin* were more likely to be
    - Female (51.1% vs 39.4%) and of
    - Black (20.9% vs 12.1%) or
    - Hispanic (14.0% vs 10.1%) ethnicity

Bradley CK, et al. *J Am Heart Assoc*. 2019;8(7):e011765.

Shared Decision-Making

1. *Calculate* risk
2. *Present* treatment options
3. *Explore* patient values, preferences, concerns, goals
4. *Reach* consensus



Himmelfarb CRD, et al. *Circulation*. 2023;148(11):912-931. Stiggelbout AM, et al. *BMJ*. 2012;344:e256.

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Key Learning Points



- Ignoring the nocebo effect (*expectation* of side effects leading to *perceived* side effects) doesn't make it not happen; proactively discuss medication concerns
- Statin side effects do occur; modifying drug / dose / dosing interval / competing comorbidities / drug class can improve patients' ability to adhere to therapy
- Awareness of disparities in treatment recommendations is the first step in eliminating those disparities
- Shared decision-making involves honest, proactive discussion