

Updates in Dyslipidemia Management: LDL Management Across the Spectrum of Primary and Secondary Prevention

Pam R. Taub, MD, FACC, FAPSC

Founder and Director of Step Family Cardiac Rehabilitation and Wellness Center
Step Family Director's Endowed Chair
Director of Preventive Cardiology
Professor of Medicine
University of California San Diego Health System
San Diego, CA



1

Disclosure

Consultant: Amgen; Bayer; Boehringer Ingelheim; Eli Lilly; Jazz Pharma; Medtronic; Novartis; Novo Nordisk; Roche

Ownership Interest (Founder & Shareholder): Epirium Bio

Research Grant: Dysautonomia International Grant; Hillblom Network Grant; National Institutes of Health (NIH)

Steering Committee: Amgen; Boehringer Ingelheim; Cleerly; Medtronic; Merck; Novartis



2

Outline

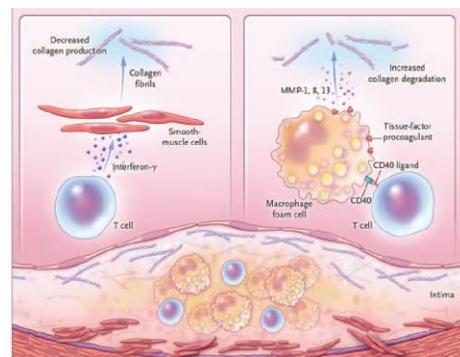
- Pathogenesis of Atherosclerosis
- Going Beyond LDL Cholesterol
- Review of Non-Statins Agents
- Role of Imaging in CV Risk Stratification
- Updates from the 2022 CC Expert Consensus Statement on Lipid Lowering
- Review of Recent Clinical Trials

UC San Diego Health

3

Pathogenesis of Atherosclerosis

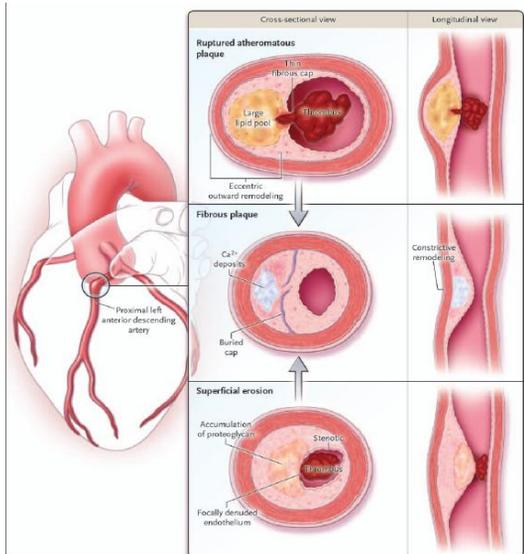
- **Atherosclerosis is a DIFFUSE DISEASE driven by inflammation, atherogenic lipoproteins, and in the acute phase - platelet aggregation.**
- A multi biomarker strategy is needed for better risk factor stratification.

Libby P. *N Engl J Med.* 2013;368:2004-2013

UC San Diego Health

4

Subclinical Plaque May Not Be Detected on Stress Testing or Coronary Angiography



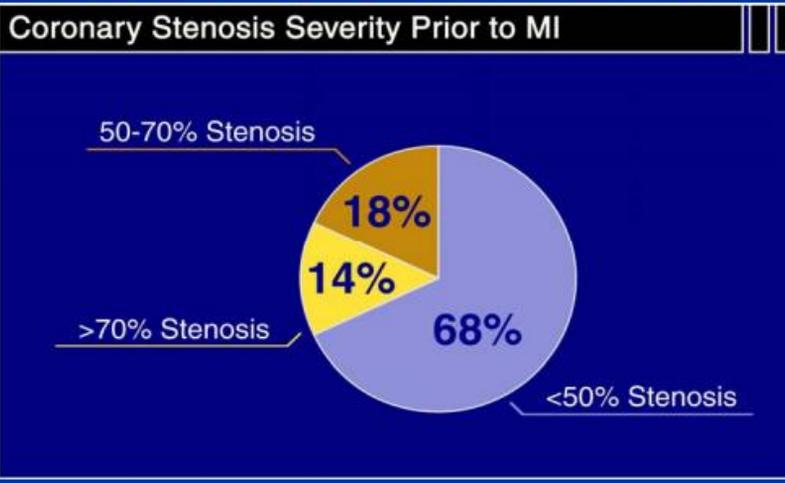
Libby P. *N Engl J Med.* 2013;368:2004-2013

- Serial angiographic studies reveal culprit lesion of a future acute MI often does not cause significant stenosis.
- Plaque can cause outward expansion of the artery wall which accommodates the growth of the plaque and minimizes luminal narrowing
- Luminal stenosis occurs late in the process of atherosclerosis
- Angiography is an assessment of luminal narrowing

UC San Diego Health

5

Low Grade Stenoses Cause Most Infarctions

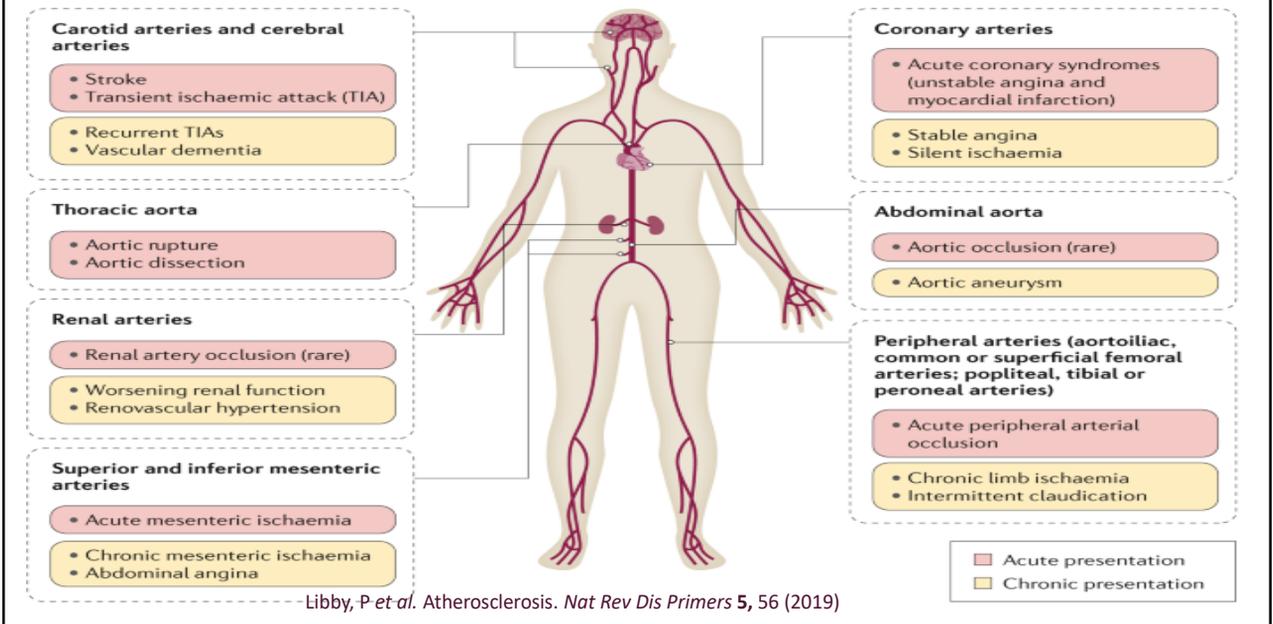


Falk E et al., *Circulation*, 1995

UC San Diego Health

6

Atherosclerosis Is a Systemic Disease



7

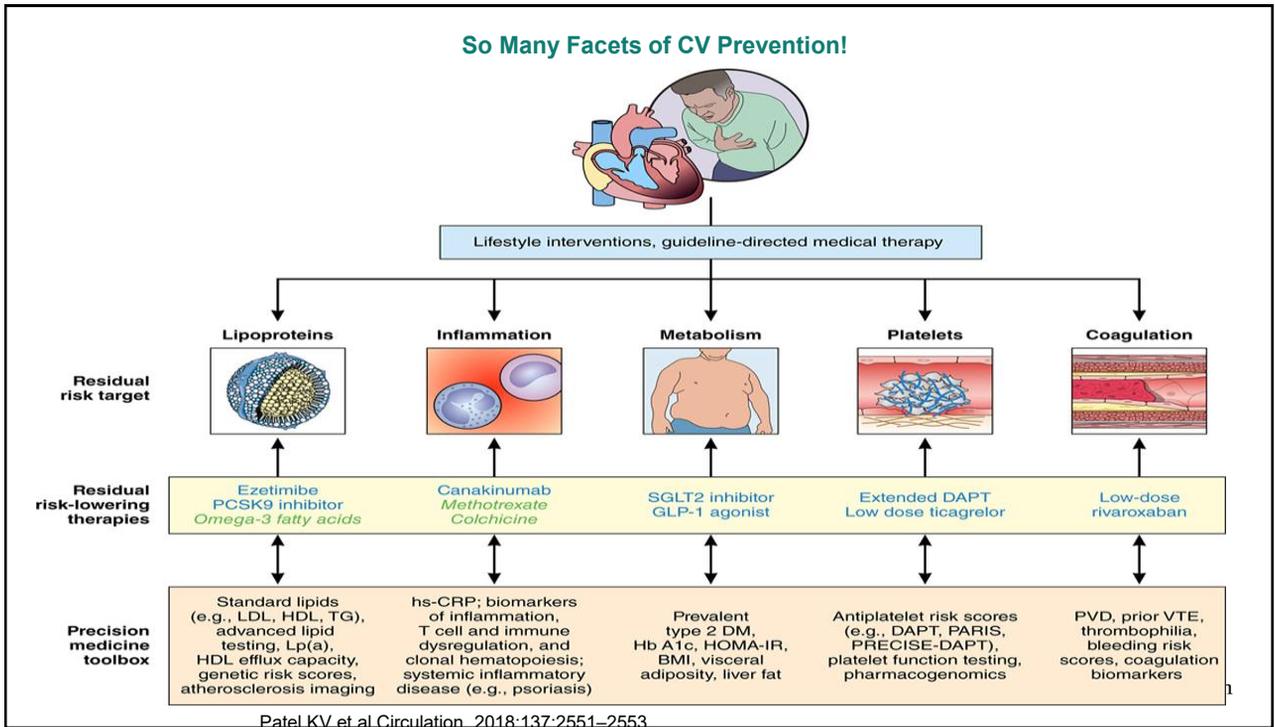
Beyond LDL Cholesterol

- LDL-C: amount of cholesterol in LDL particles
- LDL-P: number of LDL particles
- Apo-B: reflection of number of atherogenic particles
- Non-HDL: (Total cholesterol - HDL) amount of cholesterol in atherogenic particles
- Low HDL and high TG are associated with higher LDL-P
 - If triglycerides are high there will be less space for cholesterol and it may take more LDL particles to carry a given amount of cholesterol



UC San Diego Health

8

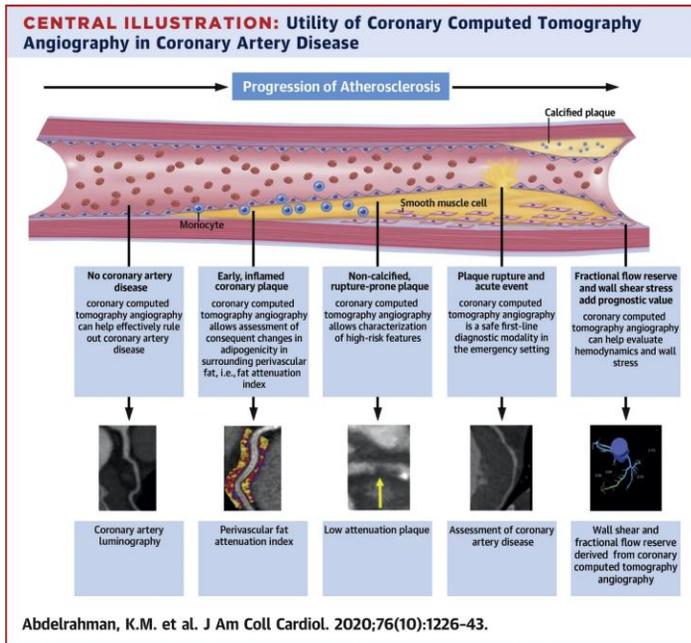


9



10

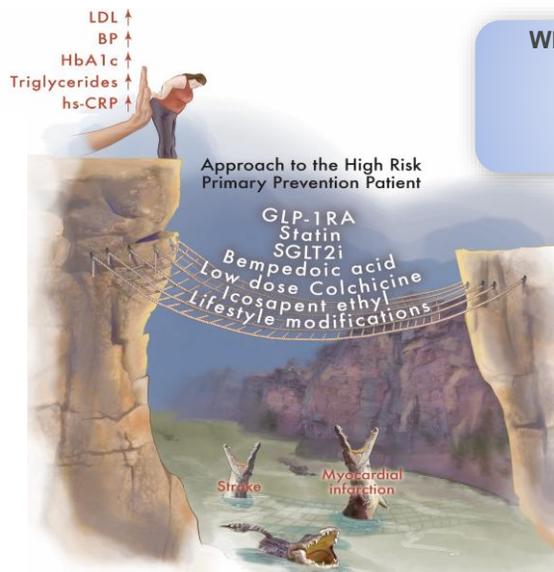
There Is a Continuum in ASCVD



UC San Diego Health

11

High Risk Primary Prevention (HRPP) Patients: The New Paradigm



What's next for high-risk primary prevention?
PCSK9i & inclisiran HF Prevention!

Ahlers M...Taub P. Am J Prev Cardiol. 2025 Aug 22;23:101265

UC San Diego Health

12

Metabolic Syndrome: The Tipping Point of High-Risk Primary Prevention

Definition

Three or more of the following criteria:

- Waist circumference ≥ 102 cm (Men) or ≥ 88 cm (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

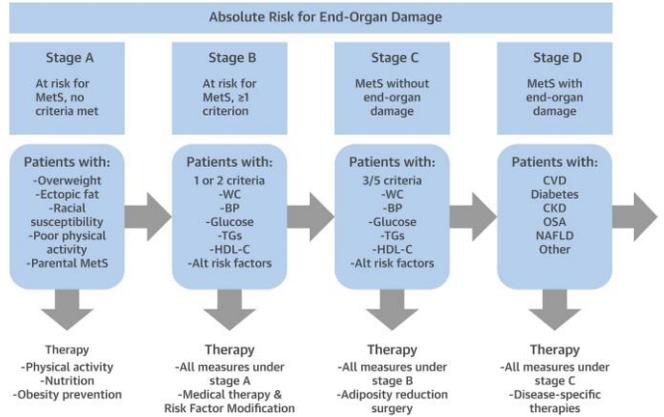
Waist circumference cutoff for South Asian population is ≥ 90 cm for males and ≥ 80 cm for females

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 U.S. has metabolic syndrome
- Obese population living with metabolic syndrome:
 - 65% of men, 56% of women

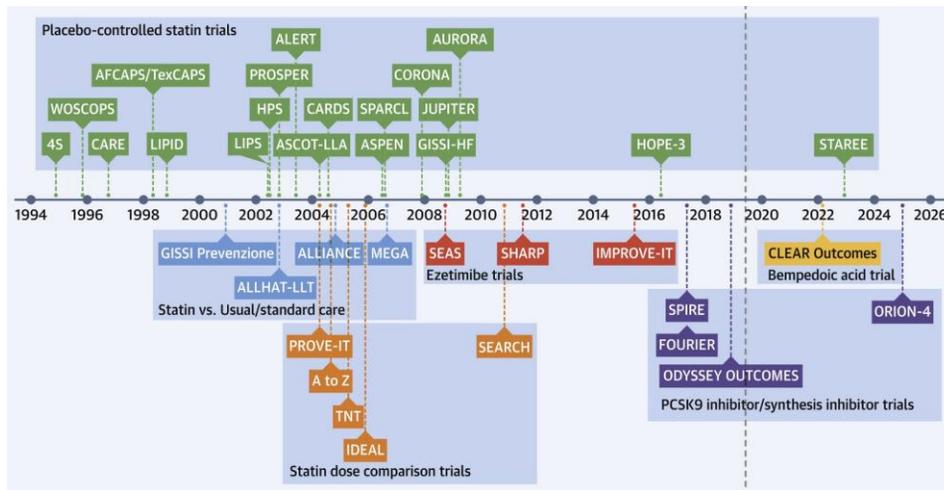


Alberti KG, Eckel RH, Grundy SM et al. Circulation 2009; 120:1640-1645
Sperling LS et al. JACC 2014 66:(9)

UC San Diego Health

13

Timeline of Non-Statin Agents Clinical Trials



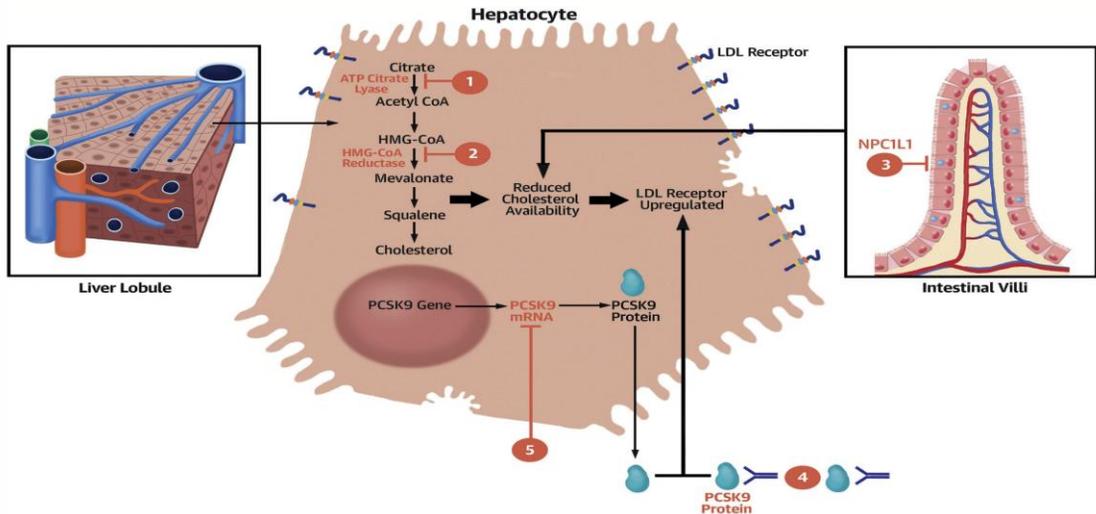
Priess, D et al. J Am Coll Cardiol. 2020 75 (16) 1945-1955

UC San Diego Health

14

Review of Mechanism of Action of Non-Statins Agents

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

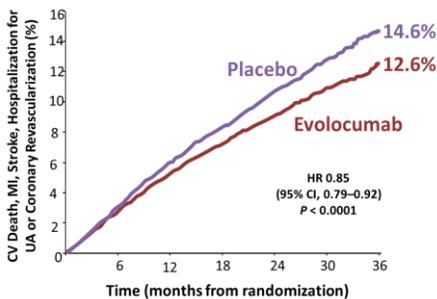


Preiss, D. et al. *J Am Coll Cardiol.* 2020;75(16):1945-55.

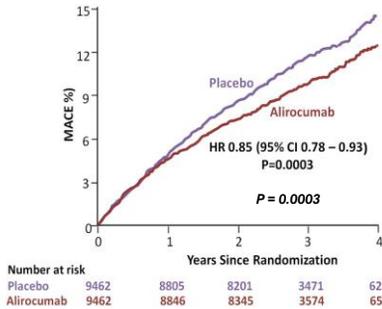
15

PCSK9i Cardiovascular Outcome Trials

FOURIER: Cumulative Incidence of MACE in Months After Randomization¹



ODYSSEY: Cumulative Incidence of MACE per Year After Randomization²



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.

UC San Diego Health

16

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

Vulnerable Plaque



Stable Plaque



Reduced lipid core
Thickened fibrous cap

ACS, acute coronary syndrome

Nicholls SJ et al. *JACC Cardiovasc Imaging*. 2022; 15(7):1308-21; Nissen SE et al. *JAMA* 2004; 291:1071-80; Nicholls SJ et al. *JAMA* 2016;316:2373-2384; *JAMA*. 2022;327(18):1771-1781.

UC San Diego Health

17

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.

UC San Diego Health

18

	PCSK9 Inhibitors	Inclisiran
Dosing	Every two weeks or once a month	Three doses in first year followed by 2 does in subsequent years
Cost (List Price)	\$5850 yearly	\$9,750 in year one \$6,500 in subsequent years
Price to the Patient	Copays can range from \$5 to \$500 per month	For Medicare patients with part B coverage copay is 0.

UC San Diego Health

19

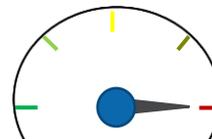
Statin Intolerance

- 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 acceptable regimen may require modification of the statin, statin dose, and/or dosing regimen

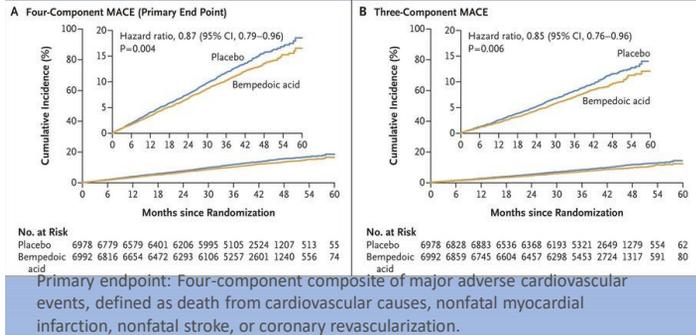
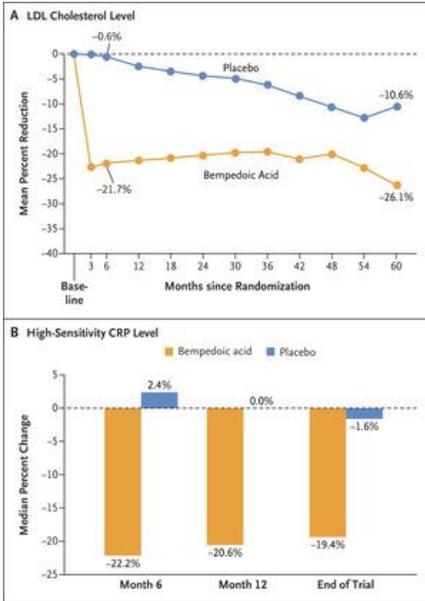
Bruckert et al. *Cardiovasc Drugs Ther* 2005;19:403-14. Palapinyo S, Nissen S. *JAMA*. 2016;315:1580-1590.
<https://www.lipid.org/nla/scientific-statement-statin-intolerance-new-definition-and-key-considerations-ascvd-risk>

UC San Diego Health

20

20

Clear Outcomes Study



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 et al; N Engl J Med. 2023 Mar 4. doi: 10.1056

UC San Diego Health

21

JAMA

QUESTION In statin-intolerant primary prevention patients at high cardiovascular risk, does bempedoic acid reduce major adverse cardiovascular events?

CONCLUSION Treatment with bempedoic acid in primary prevention patients has the potential to reduce major adverse cardiovascular events.

POPULATION

2481 Women
1725 Men

Statin-intolerant adults without a prior cardiovascular event
Mean age: 68 years

LOCATIONS

1250 Centers worldwide

INTERVENTION



2100
Bempedoic acid
180-mg oral dose administered daily



2106
Placebo
Matching placebo

4206 Patients randomized

PRIMARY OUTCOME

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

FINDINGS

Composite end point occurrence

Bempedoic acid
5.3% (111 of 2100 patients)

Placebo
7.6% (161 of 2106 patients)

Risk reduction was significant:
Adjusted hazard ratio, **0.70**
(95% CI, 0.55-0.89); P=.002

© AMA

Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA*. Published online June 24, 2023. doi:10.1001/jama.2023.9696

- 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.

UC San Diego Health

22

FDA Label Update March 2024 Based on CLEAR OUTCOMES

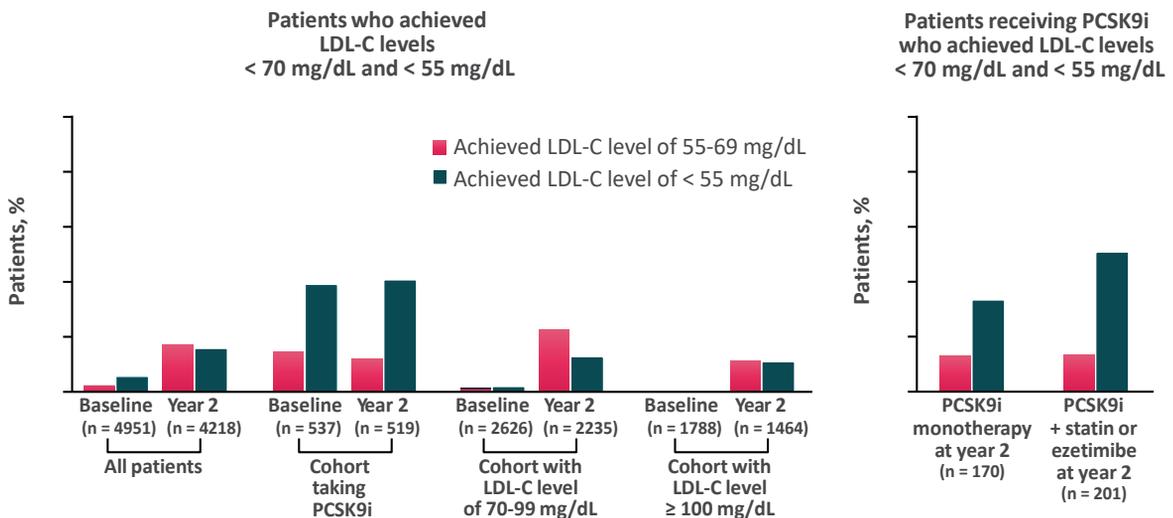
- The bempedoic acid component of NEXLIZET and NEXLETOL is indicated to reduce the risk of myocardial infarction and coronary revascularization in adults **who are unable to take recommended statin therapy (including those not taking a statin)** with:
 - established cardiovascular disease (CVD), or
 - **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.

www.accessdata.fda.gov/drugsatfda_docs/label/2024/211616s012s013lbl.pdf

UC San Diego Health

23

GOULD: Combination Therapy Required to Achieve Target LDL-C



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

UC San Diego Health

24

24

53-year-old Male Presented Last Year with Exertional Dyspnea, Admitted for NSTEMI

- Managed with stent in LAD; started lipid-lowering therapy at time of angiogram
- **Hx:** Hypertension, mild CKD (eGFR 52 mL/min/1.73m²).
- **Meds:** Rosuvastatin 40 mg qd, ezetimibe 10 mg qd, lisinopril 20 mg qd, aspirin 81 mg qd.
- **Family Hx:** Father had high cholesterol and died of MI at age 47; one sister with high cholesterol who takes statin therapy.
- **Labs:** LDL-C 110 mg/dL, HDL-C 50 mg/dL, TG 110 mg/dL, Total-C 182 mg/dL.

What Is the Next Best Step in Management?

- A. No change to management as he is already on high intensity statin
- B. Add bempedoic acid
- C. Add PCSK9i
- D. Switch rosuvastatin to atorvastatin 80 mg

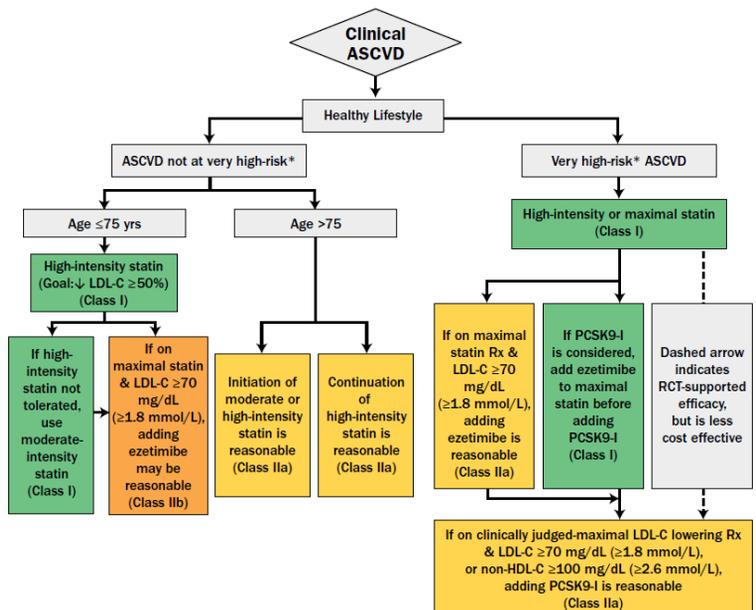


Very High-risk Features

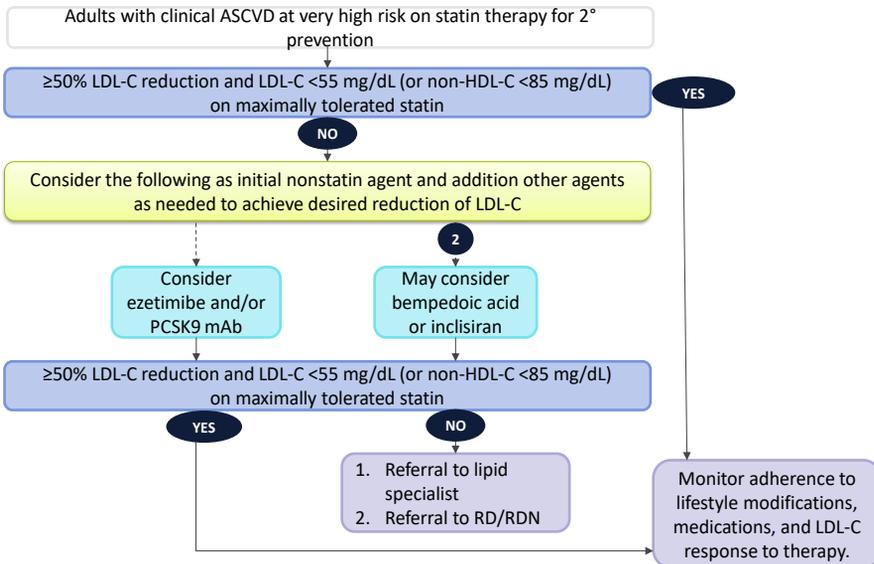
- Recent ACS
- History of prior MI
- History of ischemic stroke
- Symptomatic PAD
- Age ≥65 years
- HeFH
- Prior CABG or PCI
- Diabetes
- Hypertension
- Chronic kidney disease
- Current smoking
- LDL-C ≥ 2.6 mmol/L (100 mg/dL) on statin and ezetimibe
- History of HF
- Recurrent ASCVD events
- Major ASCVD event with ≥1 risk conditions

<https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624>

Secondary Prevention in Patients with Clinical ASCVD



2022 ACC Expert Consensus Decision Pathway



UC San Diego Health

• Writing Committee, Lloyd-Jones DM, Morris PB, et al. *J Am Coll Cardiol.* 2022;S0735-1097(22)05594-2.

27

Screening for Atherosclerosis

Risk Factors vs Disease

Numerous Risk Factors

- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

Examples of Arterial Structure Tests

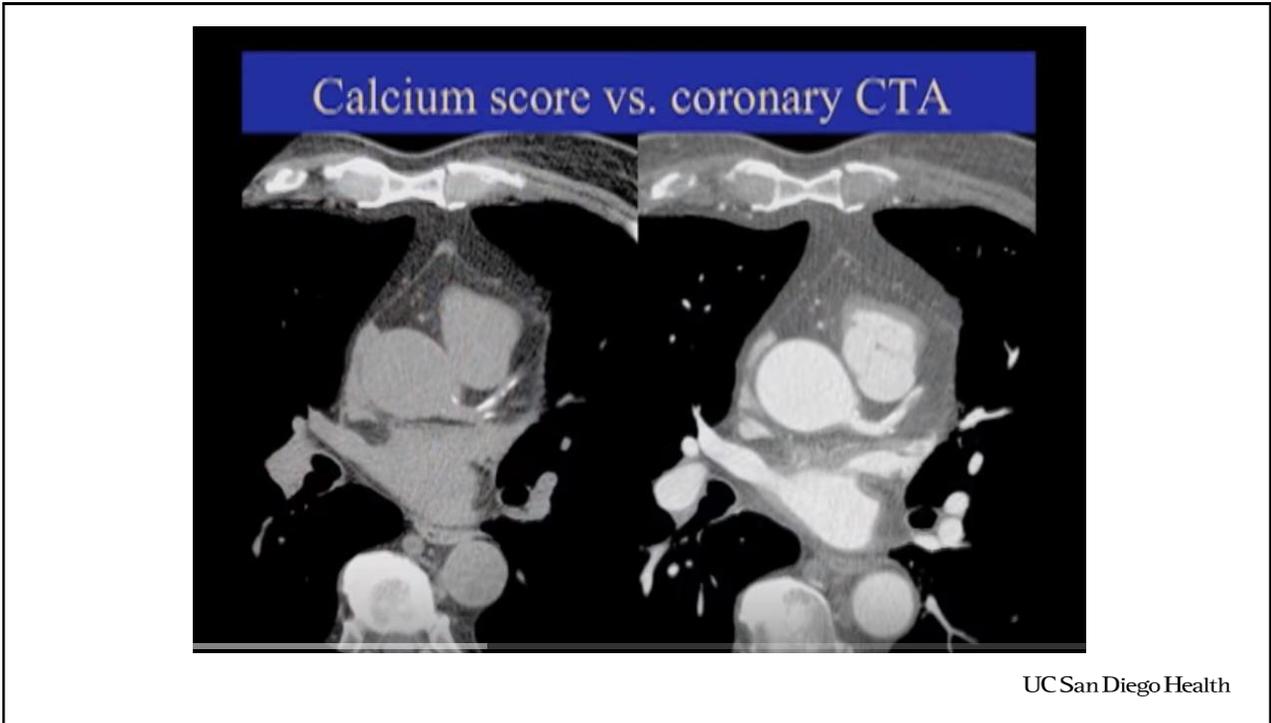
- Carotid IMT and Plaque Measured by Ultrasound
- Aortic and Carotid Plaque Detected by MRI
- Coronary Calcium Score Measured by CT
- Ankle Brachial Index
- Brachial Vasoreactivity Measured by Ultrasound
- Vascular Compliance Measured by Radial Tonometry
- Microvascular Reactivity Measured by Fingertip Tonometry

Examples of Arterial Function Tests

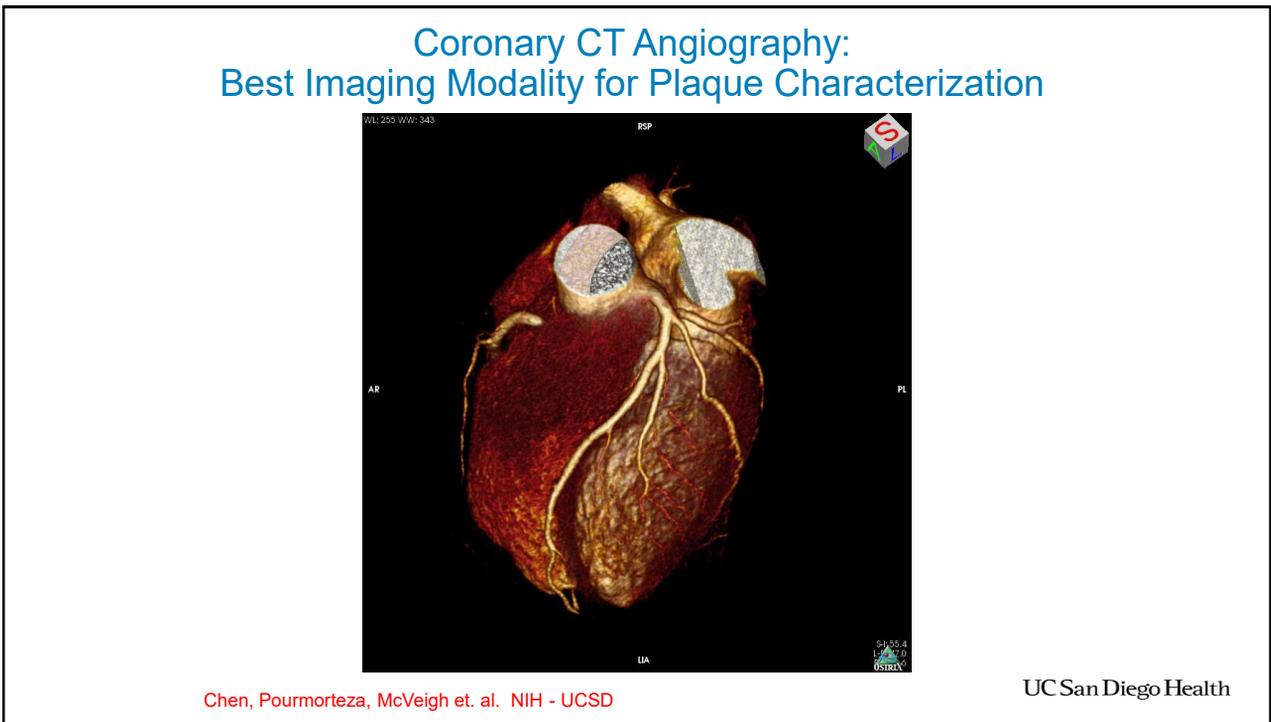
<https://doi.org/10.1161/CIRCULATIONAHA.107.707984>

Diego Health

28

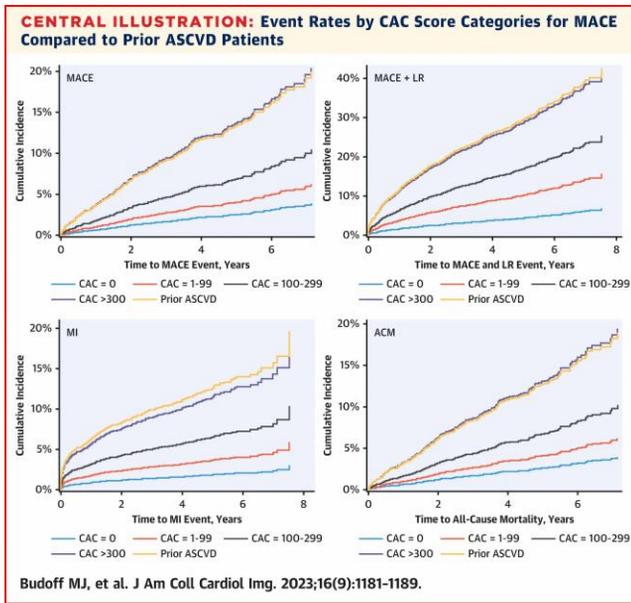


29



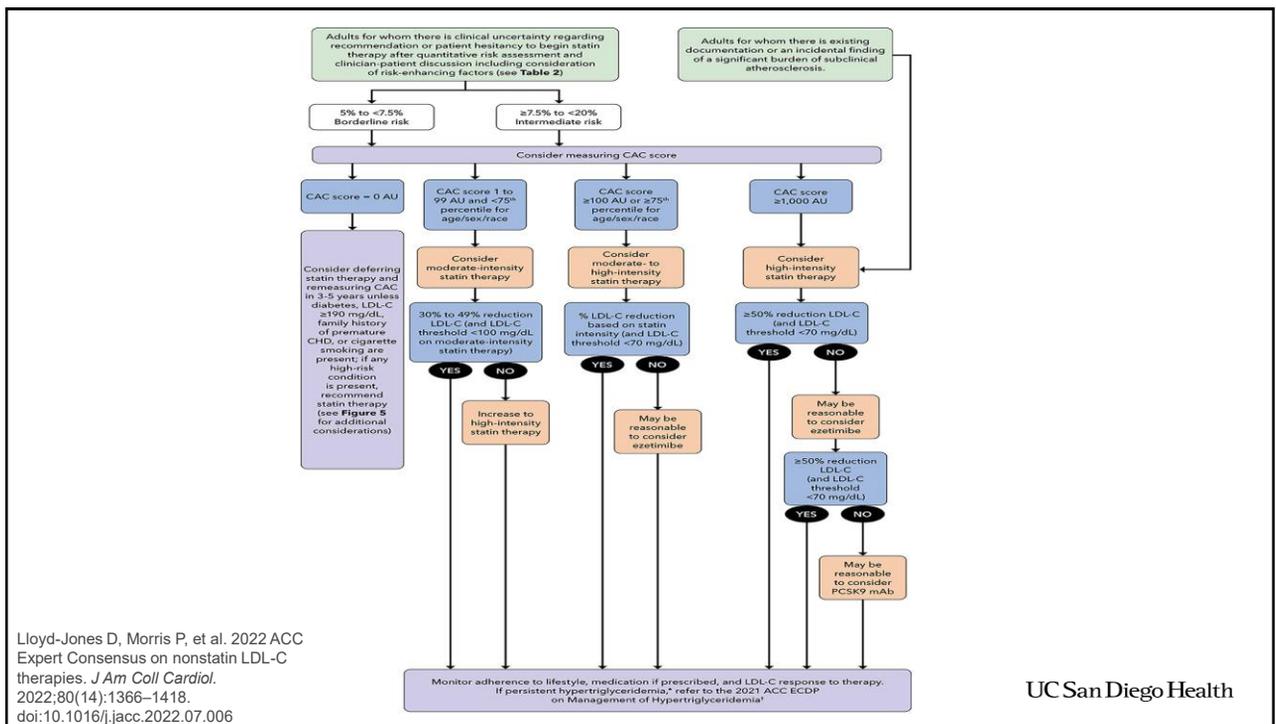
30

CAC Score >300 = Same Risk as Patients with ASCVD



UC San Diego Health

31



32

68-year-old Woman with Hypercholesterolemia, Hypertension, T2D

- Current smoker (20 pack/years).
- Father had MI at age 58.
- PE: BP 120/74 mmHg, BMI 28 kg/m².
- Labs: TC 188 mg/dL, HDL 42 mg/dL, TG 139 mg/dL, LDL 118 mg/dL
- Imaging: Coronary Calcium Score of 400
- Meds: Ezetimibe 10 mg daily, lisinopril 20 mg daily, valsartan 160 mg daily.
- History of intolerance to statins (has tried multiple statins at the lowest doses and was unable to tolerate)

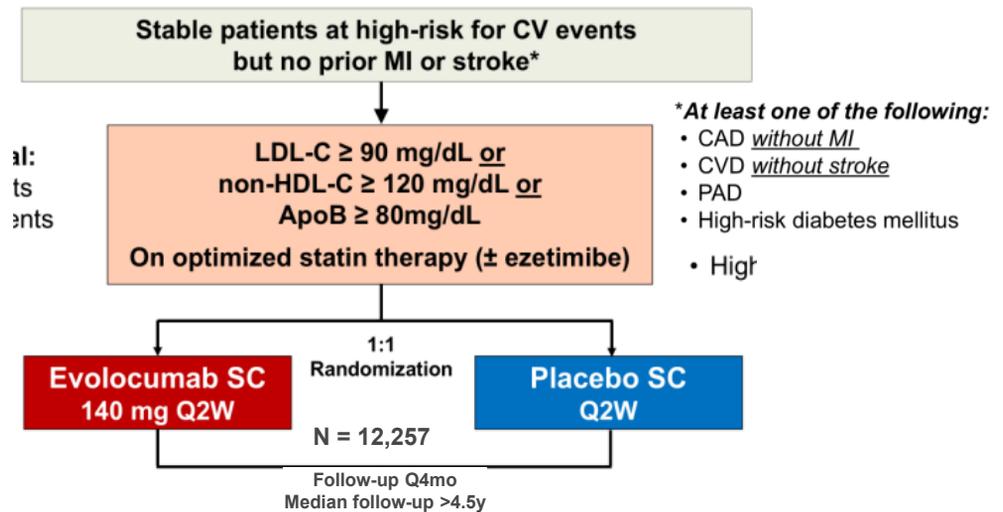
What Do You Recommend?

- A. No change to current Management
- B. Switch to Bempedoic Acid/Ezetimibe
- C. Rechallenge with low-dose statin
- D. Add Icosapent Ethyl



33

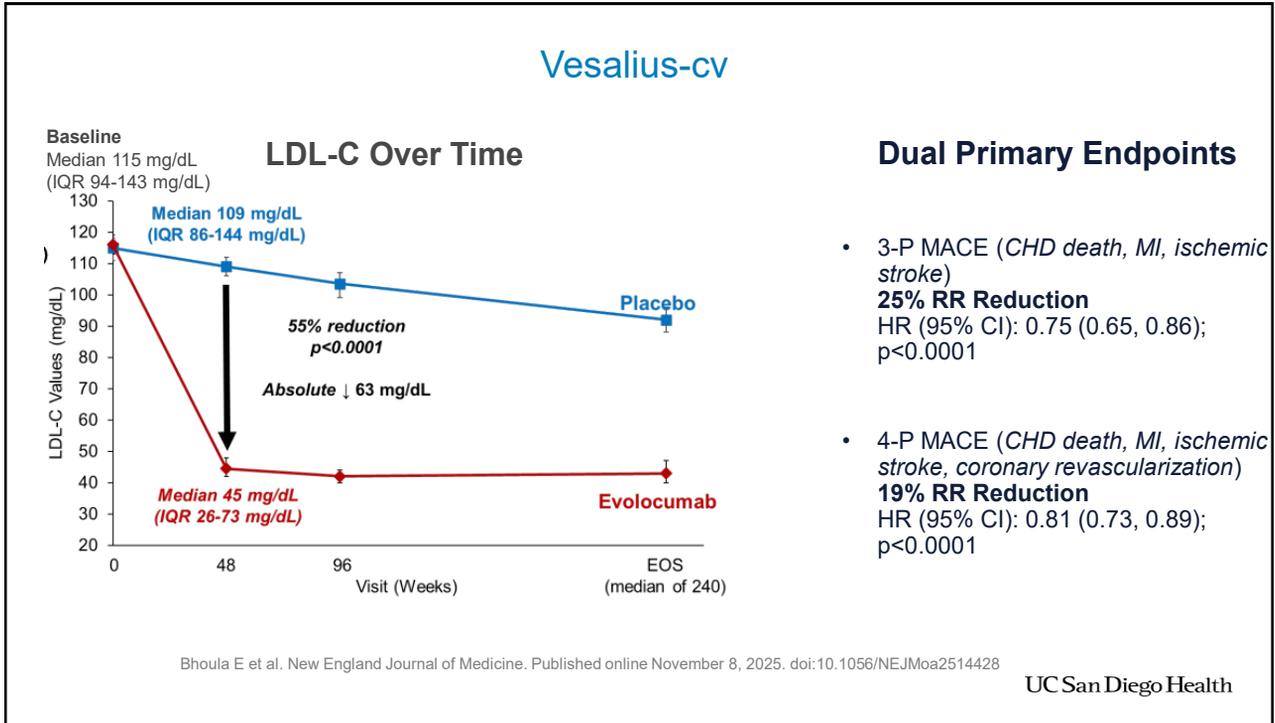
Vesalius-CV



Bohula EA, et al. *Am Heart J.* 2024;269:179-190

UCSanDiegoHealth

34



35

CORALreef Lipids: Oral PCSK9 Inhibitor

Trial Design

N=2,912

Key Inclusion Criteria

- Patients with EITHER ASCVD and LDL-C > 55 mg/dL, OR No ASCVD and LDL-C > 70mg/dL
- Stable LLT, including a statin

Key Exclusion Criteria

- Recent (3 mo) ASCVD event
- Active/Recent PCSK9i 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% enicitude vs 12% placebo**)
- Percent of participants with discontinuation secondary to AEs
 - Similar proportion disenrolled secondary to AE's (**3% enicitude vs 4% placebo**)

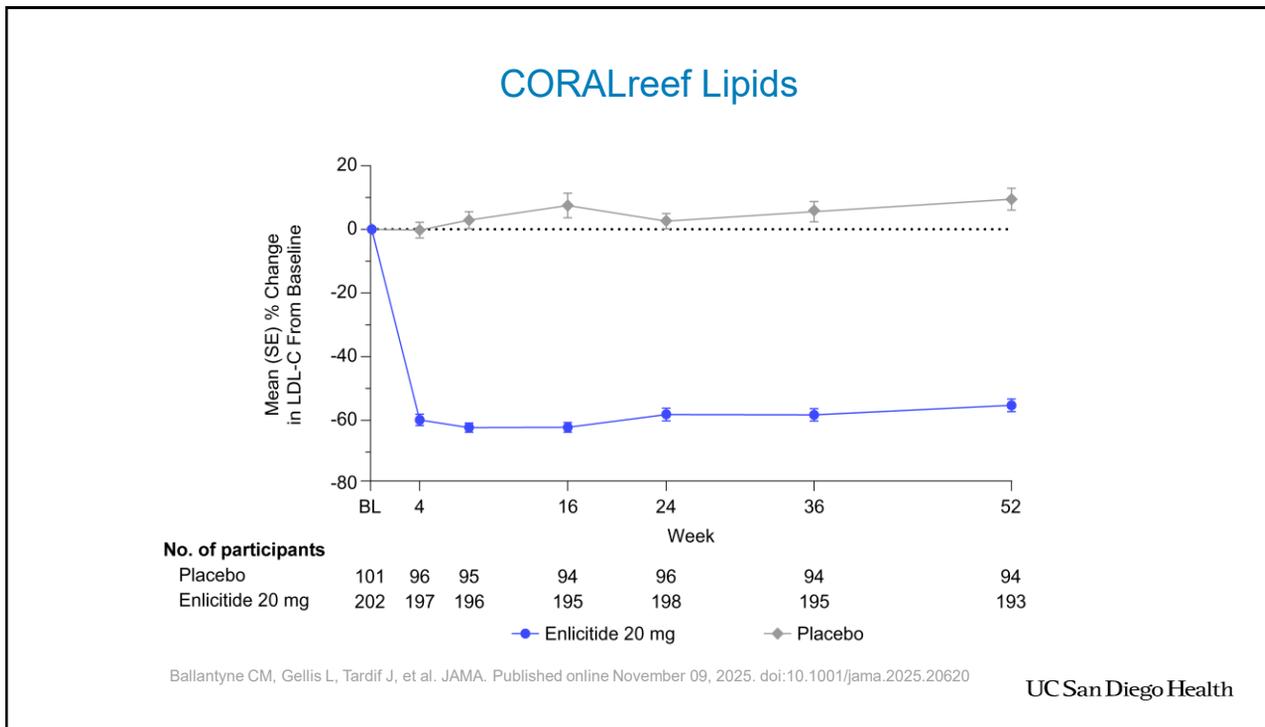
Secondary Outcomes

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

Ballantyne CM, Gellis L, Tardif J, et al. JAMA. Published online November 09, 2025. doi:10.1001/jama.2025.20620

UC San Diego Health

36



37

LDL-lowering Pharmacotherapy: Summary of Clinical Trial 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%	no data / 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

Expert Panel. JAMA. 2001;285:2486; Ray, et al. N Engl J Med. 2020; 382:1507-151; Data compiled from various package inserts; Zhang Y, et al. Frontiers in Pharmacology (2023); Ray KK, Raal FJ, Kallend DG, et al; ORION Phase III Investigators. Eur Heart J. 2023;44(2):129-138.; Sabatine MS, et al. N Engl J Med. 2017 May 4;376(18):1713-1722.; Turgeon, Ricky D. et al. Canadian Journal of Cardiology, Volume 34, Issue 12, 1600 – 1605.; (4S). Lancet. 1994 Nov 19;344(8934):1383-9.; Heart Protection Study Collaborative Group. Lancet. 2002 Jul 6;360(9326):7-22.; Lloyd SM, et al. PLoS One. 2013 Sep 2;8(9):e72642.; Bosch J, et al. Eur Heart J. 2021 Aug 17;42(31):2995-3007.; Ridker PM, et al. Lancet. 2012 Aug 11;380(9841):565-71.; Cannon CP, et al. N Engl J Med. 2015;372(25):2387-2397.; JAMA. 1984 Jan 20;251(3):351-64. Nissen SE, Menon V, Nicholls SJ, et al. JAMA. 2023;330(2):131-140.

UC San Diego Health

38

Putting It All Together

Quantity
Calories should be limited to 1,600 - 3,000 per day based on age, sex, & activity level, focusing on nutrient dense, whole foods.

Quality
The Mediterranean Diet & DASH Diet have the most evidence for CVD prevention. Fiber supports microbiome diversity & reduces inflammation.

Timing
Time-restricted eating with a 14-hour fasting interval has benefits for weight loss & potential CVD prevention.

Patient Engagement
Patients may be referred to cardiac rehab, dietitians, or shared medical appointments for education & support.

Bays H, Taub PR, et al. American Journal of Preventive Cardiology 2021

UC San Diego Health

39

The Future of Lipid Lowering Therapies

Evolution of Lipid Lowering Therapies:

Statins* → Oral combination → MoAb → ASO → siRNA → Vaccination → Gene editing

 Ezetimibe* Icosapent ethyl* Bempedoic acid Fibrate Daily	 Alirocumab* Evolocumab* Evinocumab Monthly Bimonthly	 Volanesorsen Vupanorsen Pelacarsen Weekly Monthly	 Inclisiran Olpasiran Bianually	 Annual?	 For life?
---	--	---	---	--------------------	----------------------

LDL-C
Main target

Non-HDL (including remnants)
Secondary target

Lp (a)
New target

*Therapies shown to decrease CV events

Tokgozoglul and Libby P. Eur Heart J, Volume 43, Issue 34, 7 September 2022, Pages 3198–3208, <https://doi.org/10.1093/eurheartj/ehab841>

UC San Diego Health

40

Conclusions

- There is a continuum of CV risk
- Statins are the cornerstone of therapy in patients with hyperlipidemia
- Ezetimibe is a useful non-statin adjunct to statin therapy
- PCSK9 inhibitors reduce LDL cholesterol, non-HDL, have a favorable safety profile and cause beneficial plaque remodeling
- Bempedoic acid and inclisiran are non-statin options for LDL lowering
- Get the LDL as low as you can for secondary prevention

UC San Diego Health