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Disclosures



Research Support to Institution

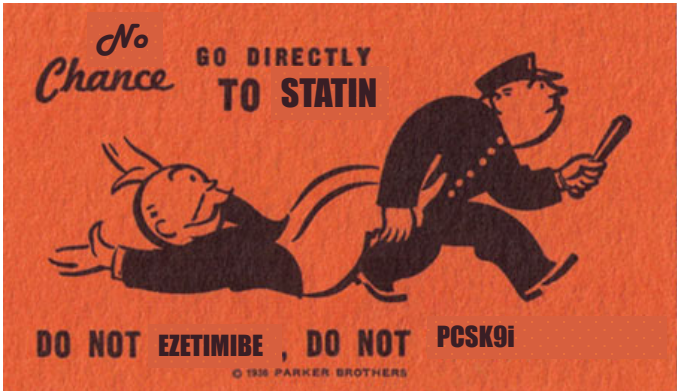
Amgen, Arrowhead



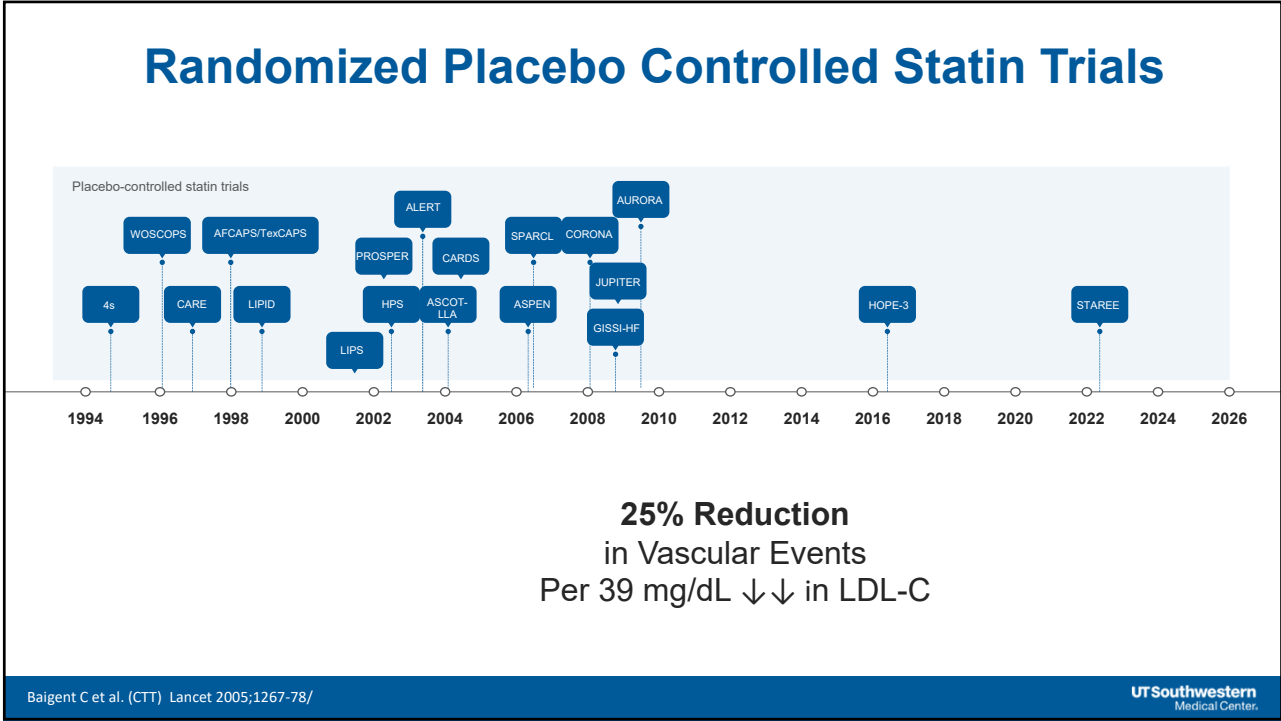
Consulting / Honoraria

Arrowhead, Eli Lilly, Merck, Amgen, New Amsterdam, Novartis, Genentech, Novo Nordisk

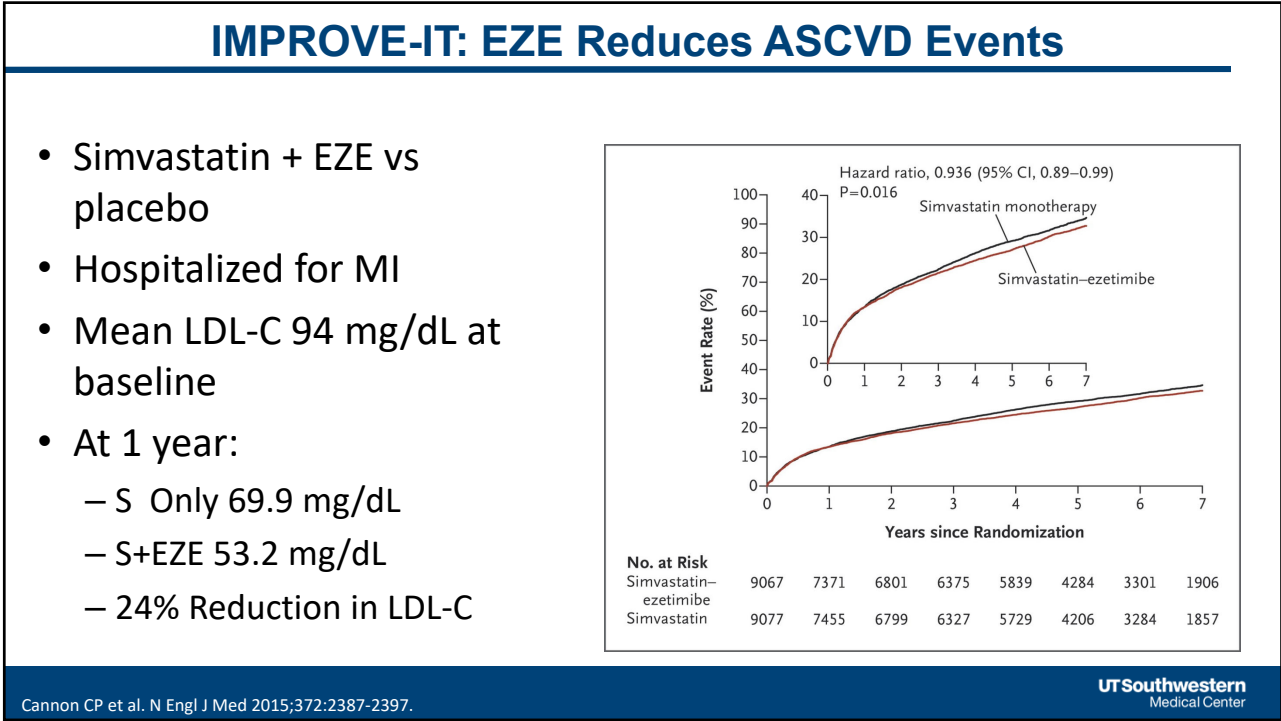
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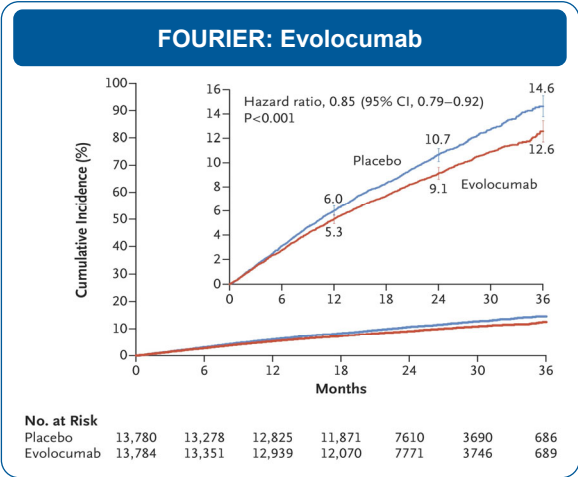


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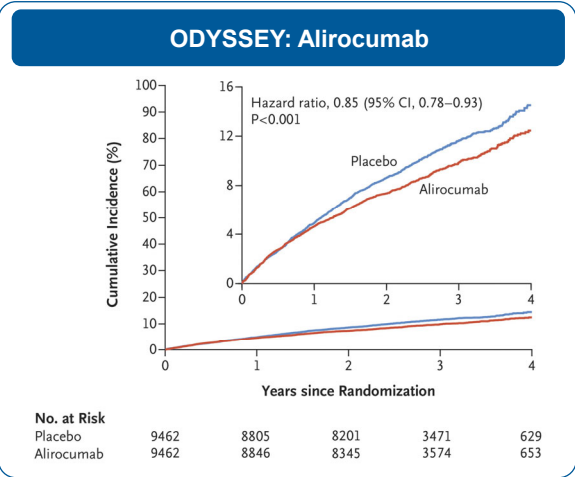


6

Clinical Trials: 15% Reduction in Events for PCSK9i



Sabatine MS et al. N Engl J Med 2017; 376:1713-1722

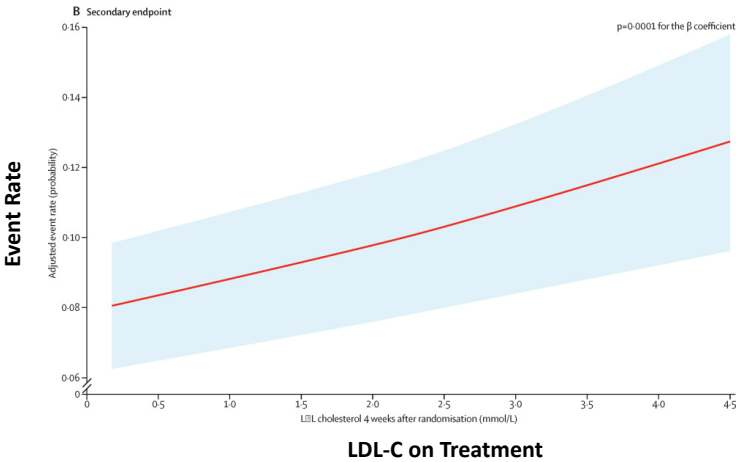


Schwartz GG et al. N Engl J Med 2018; 379:2097-2107

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FOURIER: No “floor” to benefit



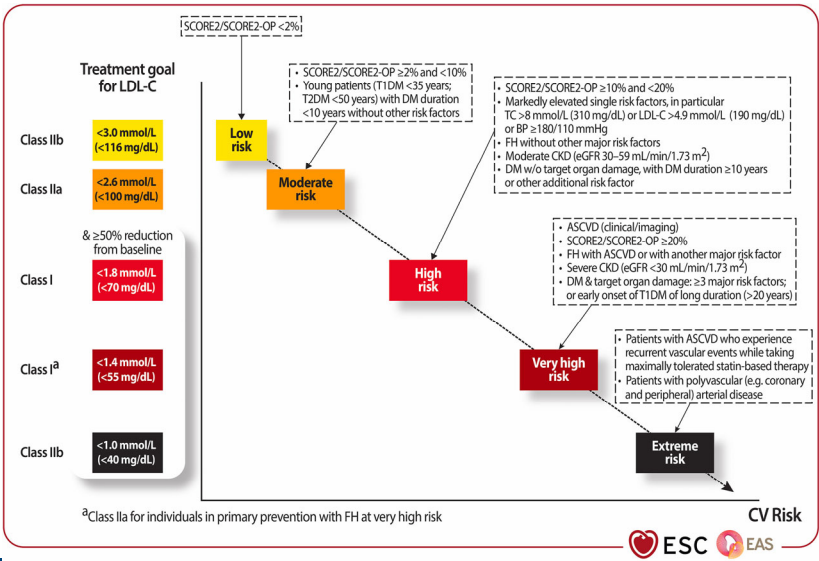
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Guigliano R et al. Lancet 390.2017

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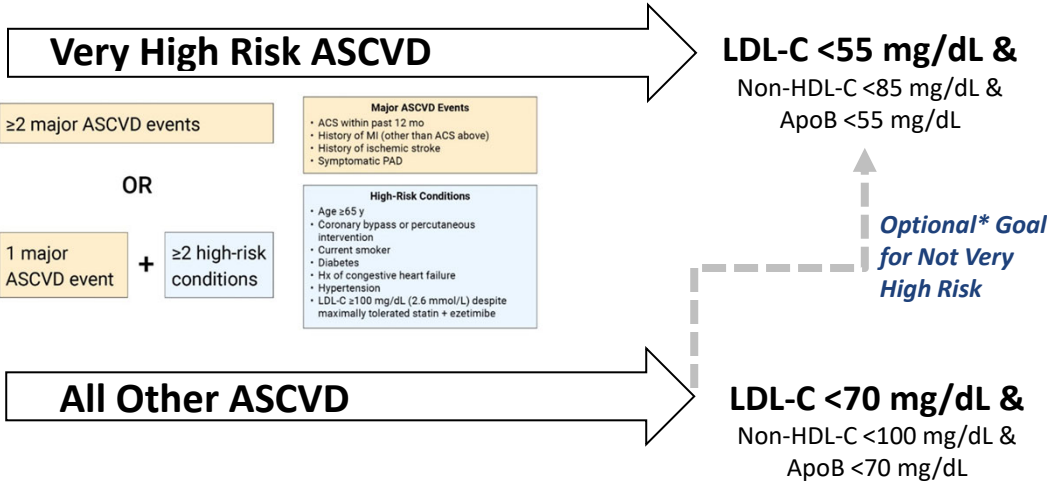
ESC/EAS: Lower is better



Mach F et al. 2025 Update of 2019 ESC/EAS Guidelines for the management of dyslipidemia. Atherosclerosis 209:2025

9

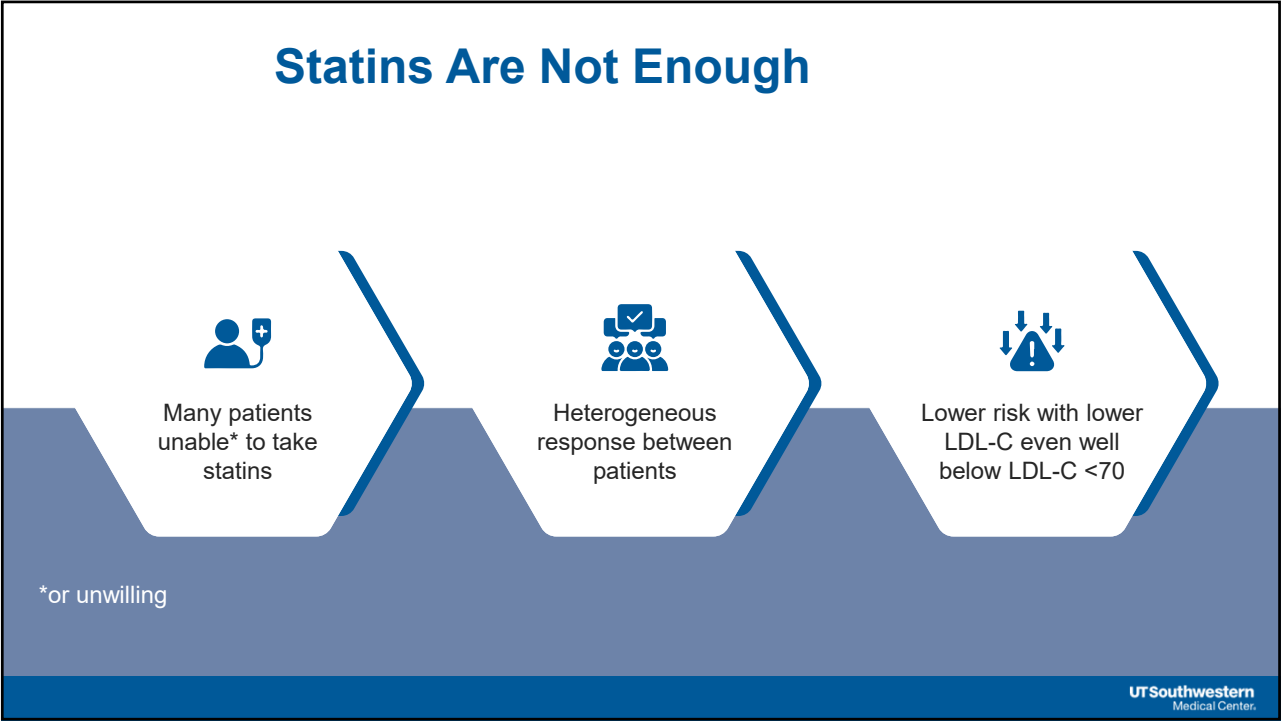
2026 AHA/ACC: Lower is better in ASCVD



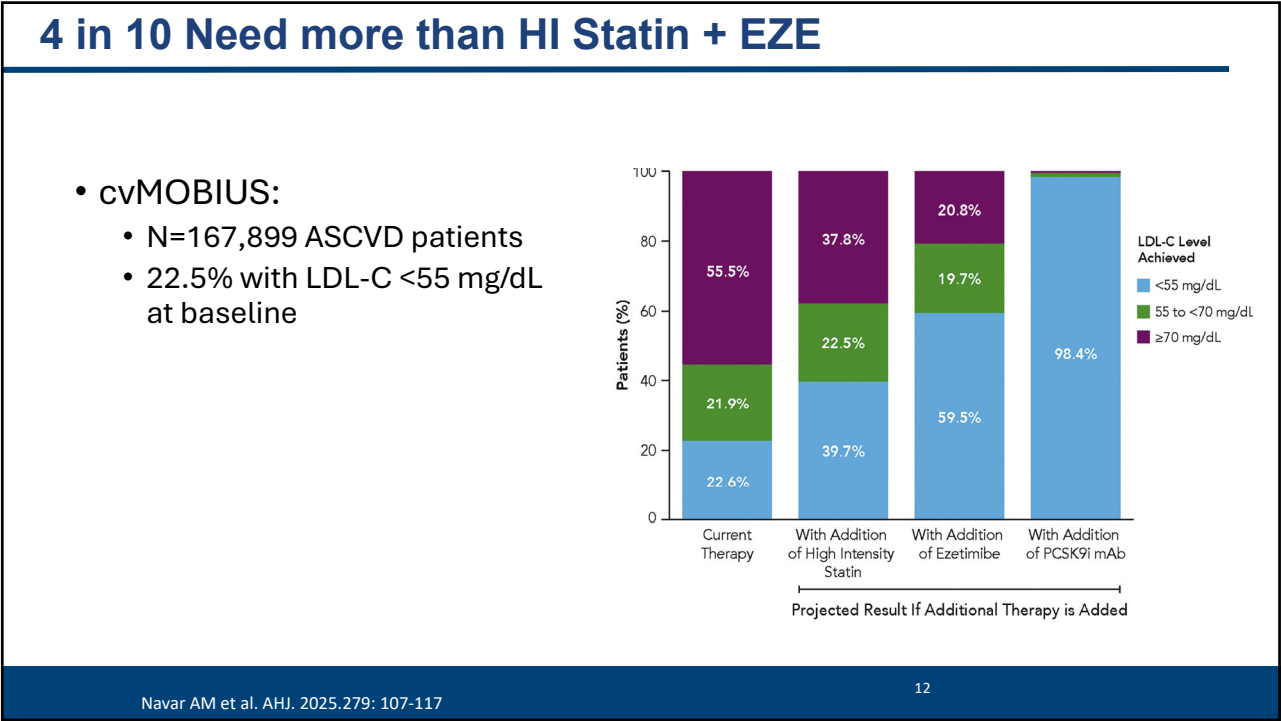
Blumenthal R et al. 2026 ACC/AHA Multisociety Dyslipidemia Guideline. JACC. 2026 :S0735-1097(25)10254-4.

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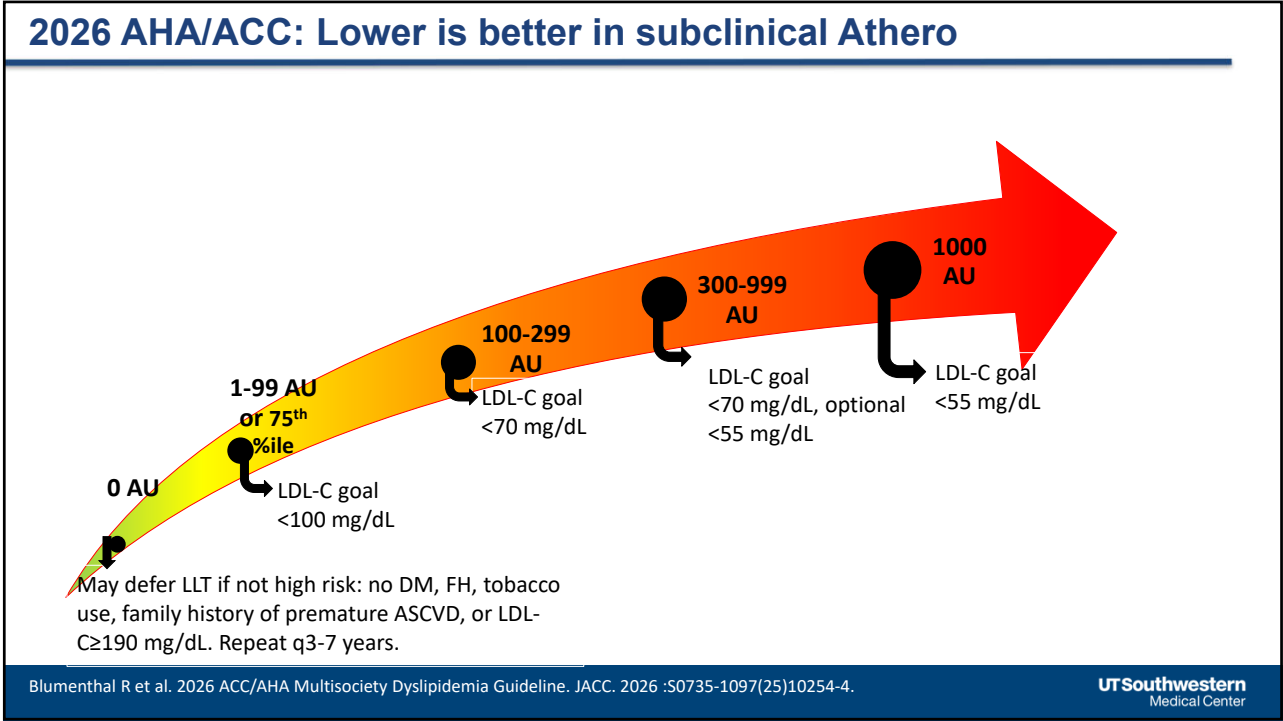
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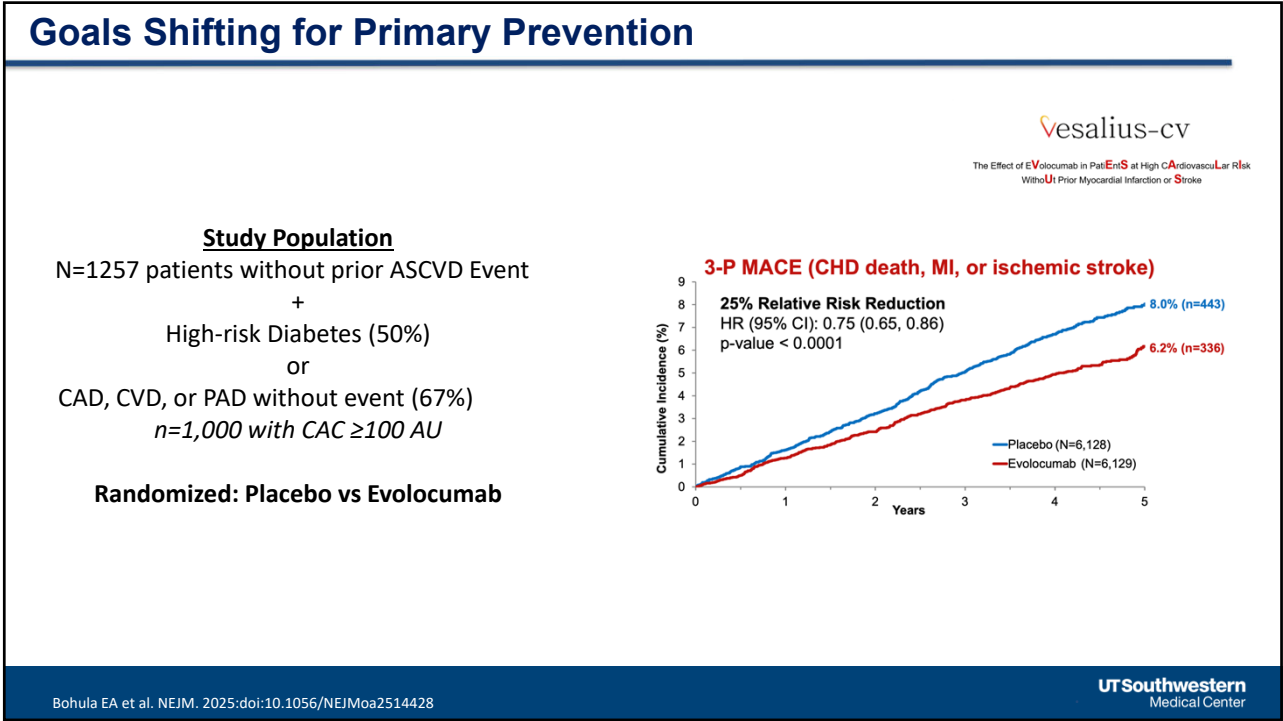
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Novel Therapies for LDL-C Lowering



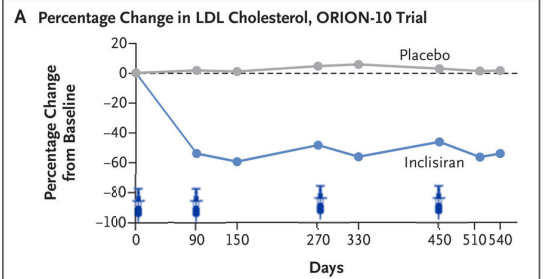
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Inclisiran: Anti-PCSK9 siRNA

ORION-10 Phase 3
n=1561 with ASCVD in the US
LDL-C >70 mg/dL on statin

A Percentage Change in LDL Cholesterol, ORION-10 Trial



	0	90	150	270	330	450	510	540
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

54%
LDL-C

CVOT Ongoing
NCT05030428
Estimated
completion:
October 2027

Ray KK, .. Kastelein JP. NEJM 2020;382:1507-1519

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Lerodalcibep: A monthly, injectable PCSK9i small binding protein

Study Design

N=922 randomized 2:1 lerodalcibep vs placebo

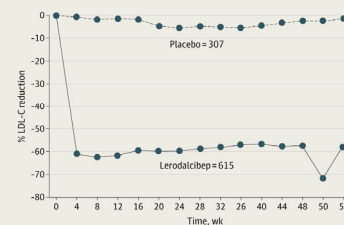
1.2 mL SC monthly

Shelf stable up to 3 months

LDL-C Reduction over Time

FINDINGS

Lerodalcibep dosed monthly for 1 y, significantly reduced LDL level in patients with CVD and at high risk for CVD compared with placebo (difference, -56.2%; 95% CI, -60.5% to -51.9%; $P < .001$)



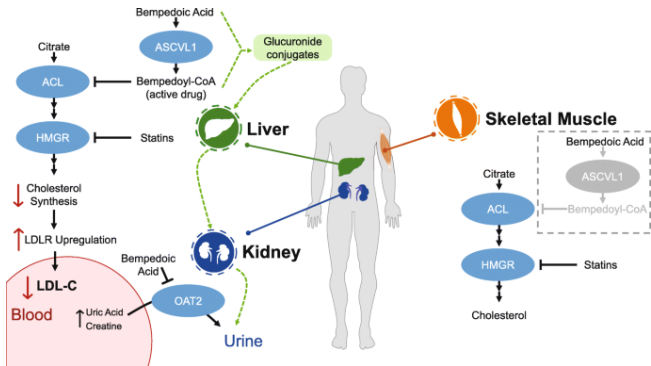
Percent change in LDL level from baseline at wk 52:
Lerodalcibep, -56.3%
Placebo, -0.1%

Klug EQ et al. JAMA Cardiol. Published online July 3, 2024

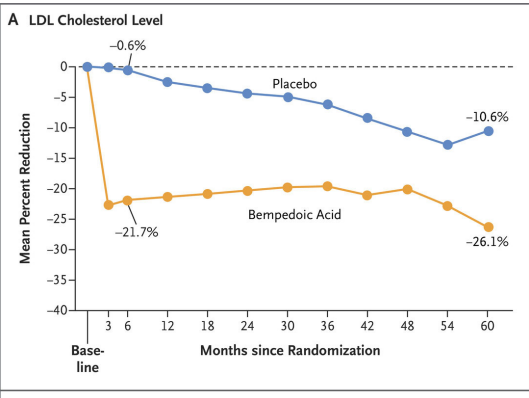
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Bempedoic acid: 21% LDL-C lowering



CLEAR-Outcomes: LDL-C over Time



Ballantyne C .. Saseen JJ. Cardio Drugs and Therapy 2021;35:853-864 ; Nissen S et al NEJM 2023

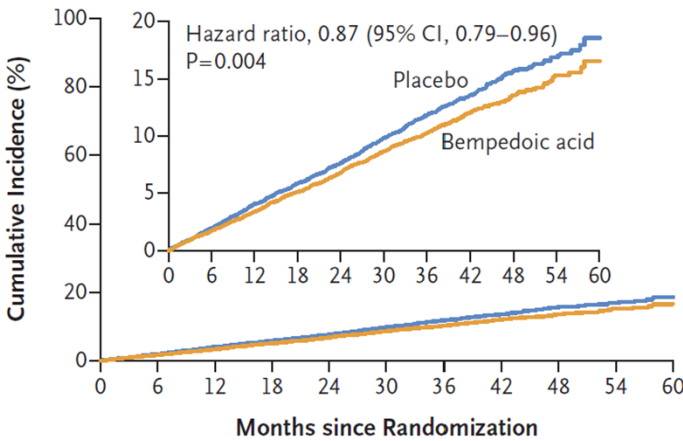
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CLEAR OUTCOMES: CV benefit in statin intolerance

Primary and Secondary Prevention

A Four-Component MACE (Primary End Point)

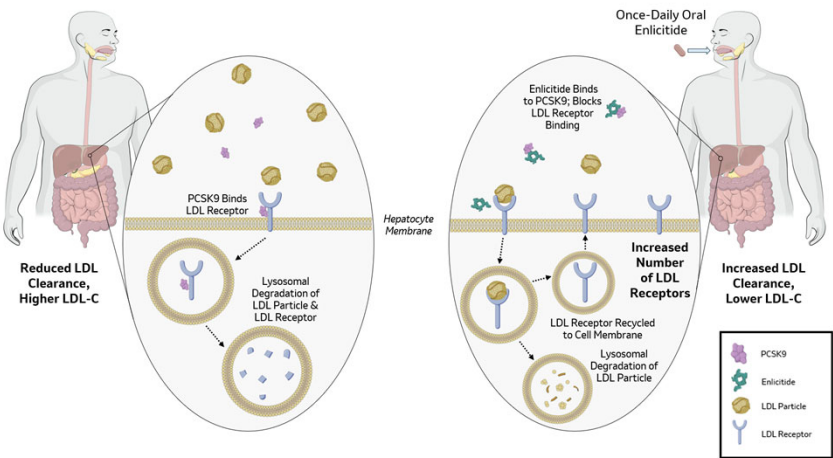


Nissen S et al NEJM 2023

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Eniclitide Mechanism of Action

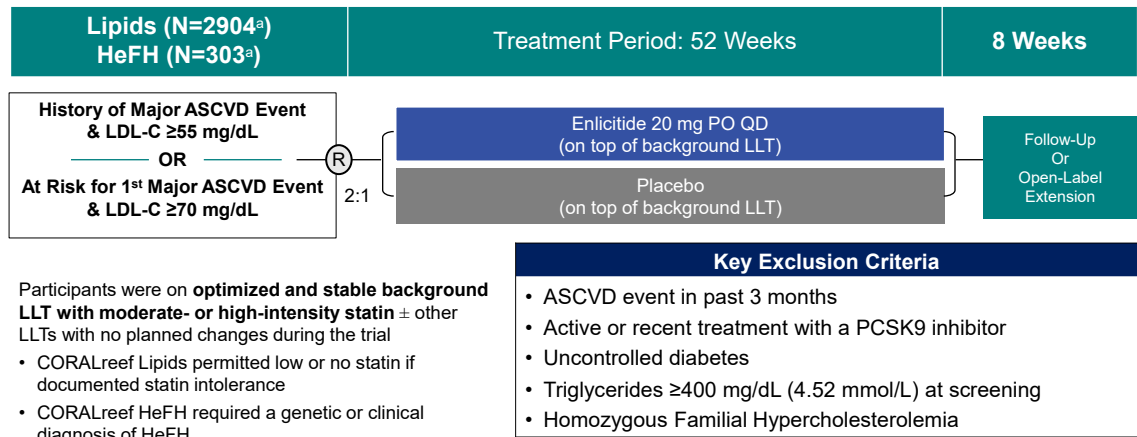


Hwang J, Peterson ED, Gupta A, Decicco E, Sarnes E, Navar AM. Prescriber Uptake and Use of Novel Lipid-Lowering Therapies. J Am Heart Assoc. 2025 May 6;14(9):e040768. doi: 10.1161/JAHA.125.040768. Epub 2025 May 2. PMID: 40314342; PMCID: PMC12184243.

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Study Designs: CORALreef Lipids AND HeFH Studies

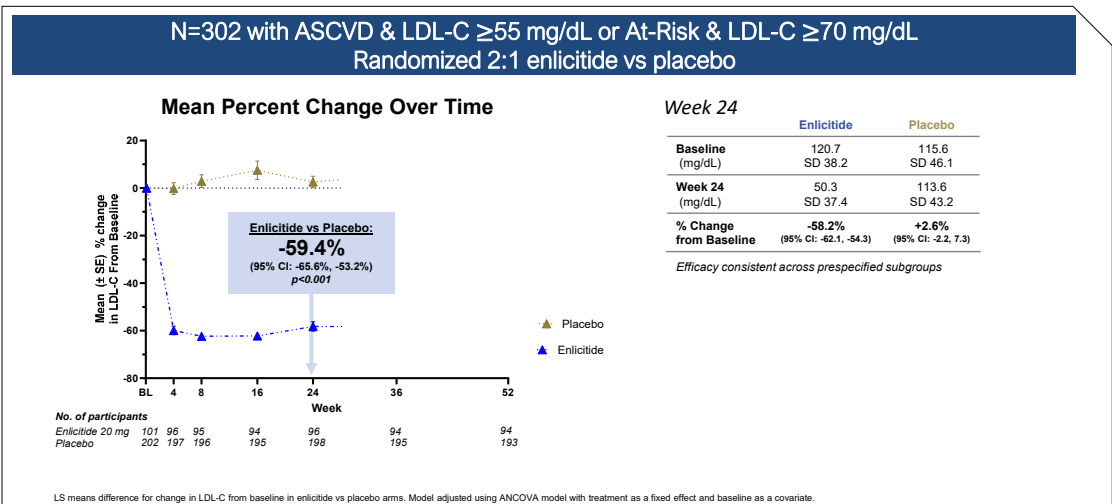


^a Modified ITT population: number of participants randomized who received at least 1 dose of study intervention

Presented ACC 2026

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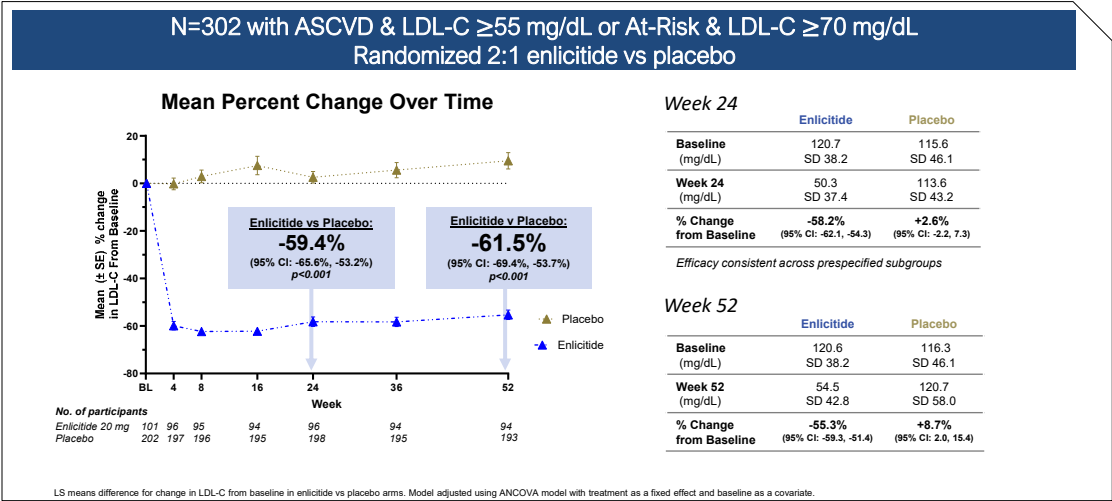
CORAL-Reef HeFH: Enlicotide in HeFH



Ballantyne C et al. JAMA 2026 Jan 13;335(2):129-139.

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CORAL-Reef HeFH: Enlicitide in HeFH

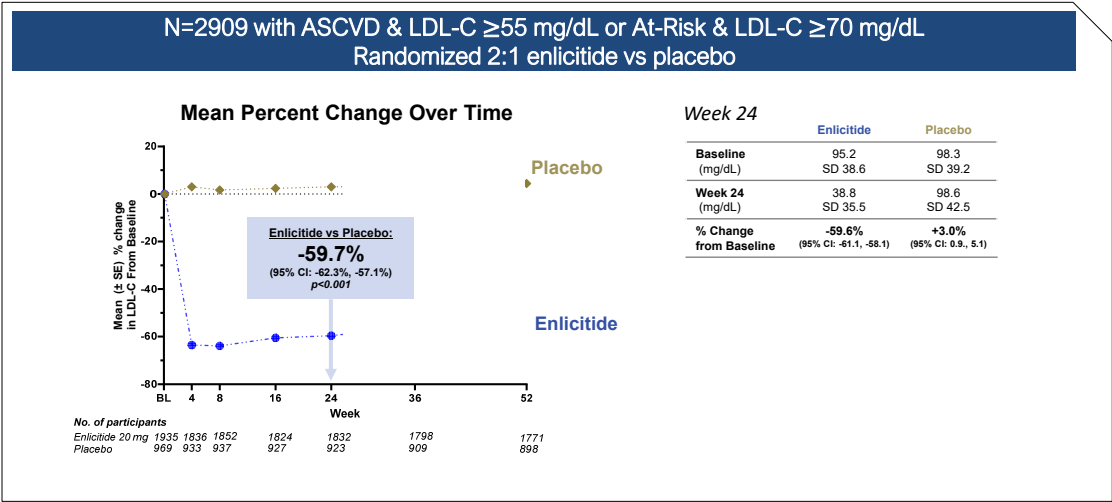


Ballantyne C et al. JAMA 2026 Jan 13;335(2):129-139.

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CORAL-Reef lipids: Enlicitide in ASCVD or At-Risk

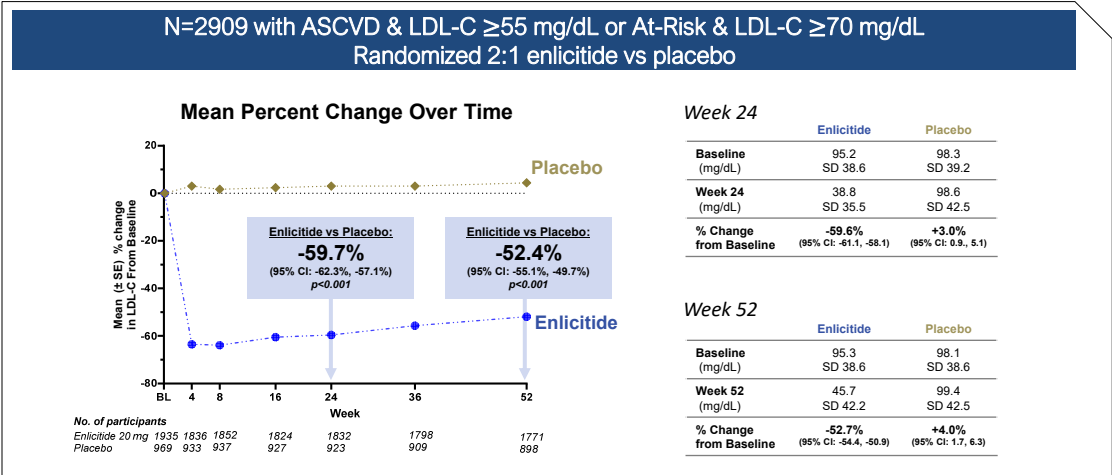


Navar AM et al. N Engl J Med 2026;394:529-539

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CORAL-Reef lipids: Enlicitide in ASCVD or At-Risk



Navar AM et al. N Engl J Med 2026;394:529-539

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Non-HDL-C, ApoB, and Lp(a) at Week 24

	CORALreef Lipids	CORALreef HeFH
Endpoint	Enlicitide vs placebo LS Means Difference (95% CI)	
Non-HDL-C	-53.4% (-55.5%, -51.2%) p<0.001	-53.0% (-58.5%, -47.4%) p<0.001
ApoB	-50.3% (-52.1%, -48.5%) p<0.001	-49.1% (-54.0%, -44.3%) p<0.001
Lp(a)	-28.2% (-30.3%, -26.0%) p<0.001	-27.5% (-34.3%, -20.6%) p<0.001

CORALreef Lipids: Adjusted using ANCOVA model with treatment and the stratification factors (renal function and geographic region) as fixed effects and baseline as a covariate.
CORALreef HeFH: Adjusted using ANCOVA model with treatment as a fixed effect and baseline as a covariate

Navar AM et al. N Engl J Med 2026;394:529-539, Ballantyne C et al. JAMA 2026 Jan 13;335(2):129-139.

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Safety and Tolerability

	CORALreef Lipids		CORALreef HeFH	
	Enlicitide	Placebo	Enlicitide	Placebo
	N=1935 n (%)	N=969 n (%)	N=202 n (%)	N=101 n (%)
≥1 Adverse events (AEs)	1244 (64.3)	602 (62.1)	157 (77.7)	77 (76.2)
Serious AEs	191 (9.9)	116 (12.0)	9 (4.5)	4 (4.0)
Moderate or severe AEs	649 (33.5)	314 (32.4)	62 (30.7)	33 (32.7)
Discontinued intervention due to an AE	60 (3.1)	40 (4.1)	4 (2.0)	3 (3.0)
Deaths ^a	13 (0.7)	7 (0.7)	1 (0.5)	0

High adherence with study intervention and dosage instructions (≥96% in both studies) across treatment groups

AE = Adverse Event. The table summarizes on-treatment AEs that occurred after the first dose and up to either the last dose before rollover into the open label extension or up to the 8-week follow-up period after the last dose. ^aIn CORALreef Lipids, three deaths occurred >8 weeks after the last dose and are not included here. In CORALreef HeFH, one participant (enlicitide group) experienced an ischemic stroke and cardiovascular death; neither the stroke nor death were deemed related to study intervention by the investigator.

Navar AM et al. N Engl J Med 2026;394:529-539, Ballantyne C et al. JAMA 2026 Jan 13;335(2):129-139.

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CORALreef AddOn Study Design

N = 301

Treatment Period^a: 56 Days

8 weeks

History of major ASCVD event & LDL-C ≥55 mg/dL
OR
At intermediate to high risk for first major ASCVD event & LDL-C ≥70 mg/dL

Ⓡ

2:1:1:2

Enlicitide 20 mg QD (on top of statins); n = 101

Bempedoic acid 180 mg QD (on top of statins); n = 50

Ezetimibe 10 mg QD (on top of statins); n = 50

Bempedoic acid 180 mg QD + Ezetimibe 10 mg QD (on top of statins); n = 100

Follow-Up or OLE

Participants were on **stable background statin therapy (low-, moderate-, or high-intensity)** ± other permitted^b LLTs with no planned changes during the trial

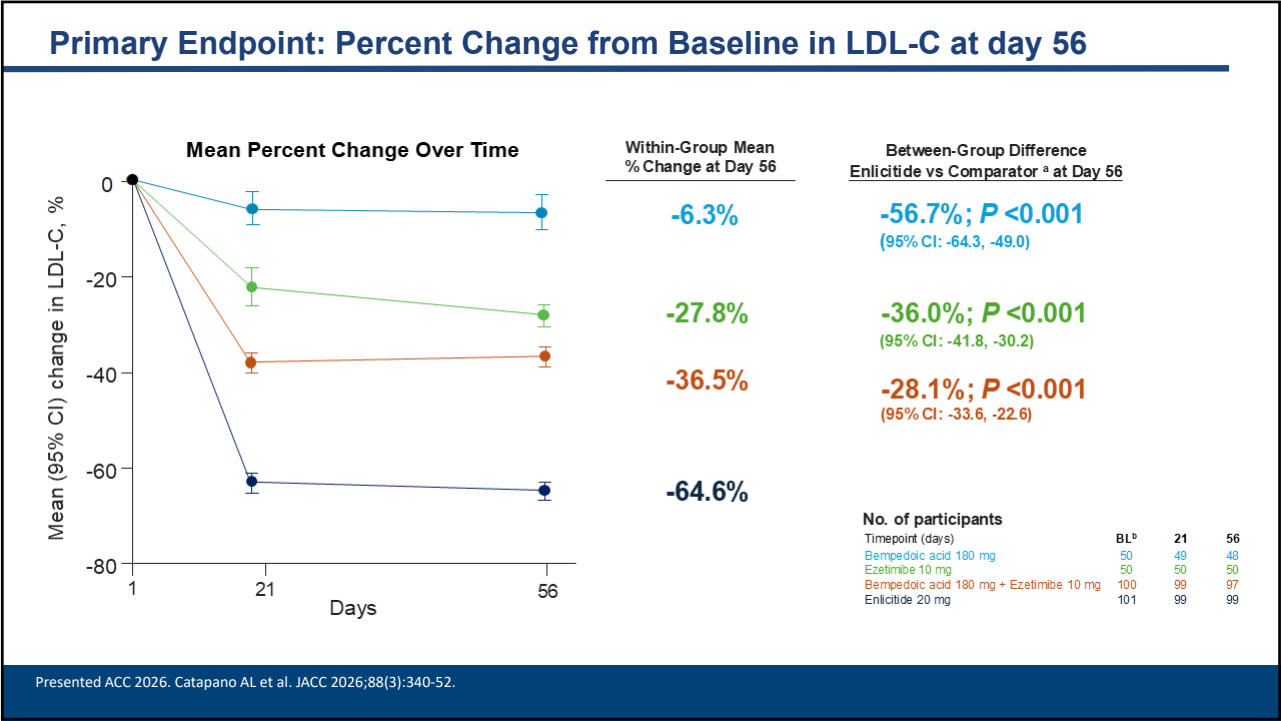
Key Exclusion Criteria

- ASCVD event in past 3 months
- Active or recent treatment with a PCSK9 inhibitor
- Active or recent treatment with bempedoic acid or ezetimibe
- Triglycerides ≥400 mg/dL (4.52 mmol/L) at screening

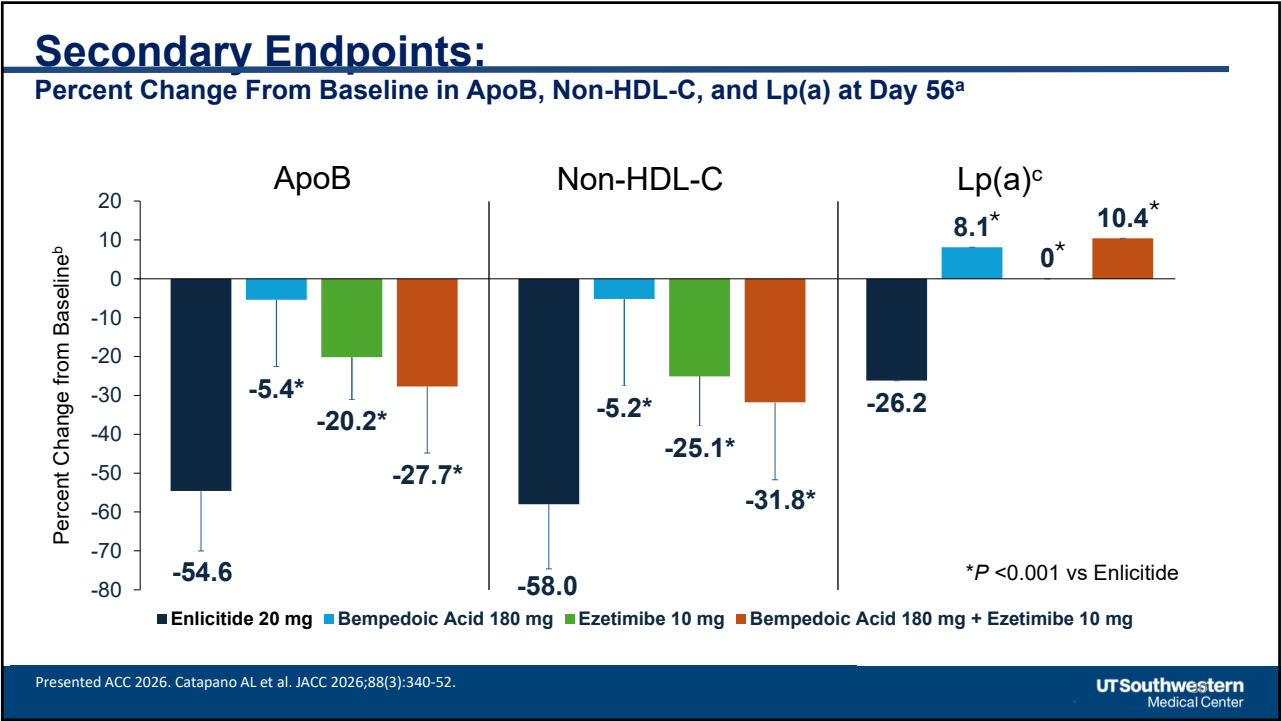
Presented ACC 2026. Catapano AL et al. JACC 2026;88(3):340-52.

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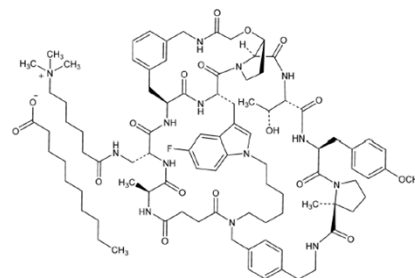
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Enlicitide Pharmacology

- **Safe in renal and hepatic impairment**
Not metabolized-
Eliminated intact via glomerular filtration
eGFR <30? = 26% higher exposure
→ not clinically meaningful
- **No DDIs** with: lithium,
levothyroxine, digoxin, warfarin,
atorvastatin, alendranote, lisinopril
or oral semaglutide
- Effective half life 14 hours,
terminal half life 244 hours



https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/220848Orig1s000lbl.pdf

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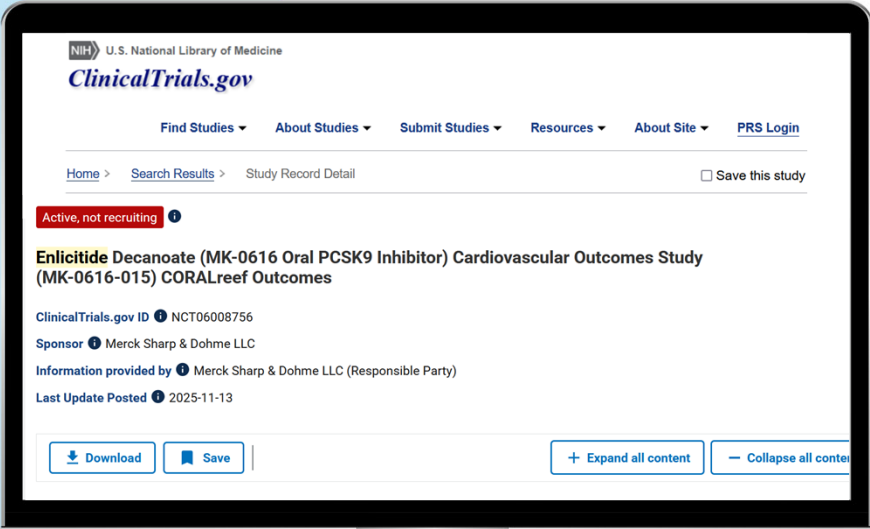
FAQs: Enlicitide Administration

- Take on an empty stomach in the morning *with water, black coffee, or plain tea*
 - Wait 30 minutes before eating (giving 30 minutes after a meal reduces AUC by 50%)
- Okay to take with other medications
- Miss a dose?
 - Take ≥30 minutes before next meal
- When to repeat LDL-C?
 - As soon as 4 weeks after initiation



https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/220848Orig1s000lbl.pdf

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Active, not recruiting

Enlicitide Decanoate (MK-0616 Oral PCSK9 Inhibitor) Cardiovascular Outcomes Study (MK-0616-015) CORALreef Outcomes

ClinicalTrials.gov ID **NCT06008756**
Sponsor **Merck Sharp & Dohme LLC**
Information provided by **Merck Sharp & Dohme LLC (Responsible Party)**
Last Update Posted **2025-11-13**

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- N=14,550
Estimated completion:
November 2029
- Established
ASCVD & LDL-C
≥70 mg/dL
- OR High Risk &
LDL-C ≥90 mg/dL

33

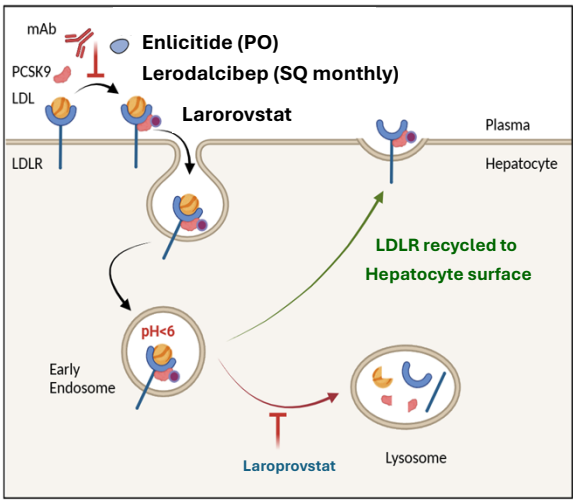
What else is on the horizon?



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Alternative mechanisms to target PCSK9

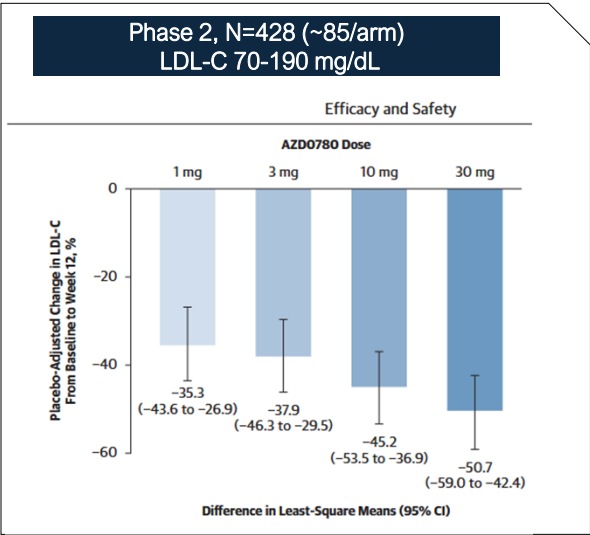


CTD, c-terminal domain; mAb, monoclonal antibody; PCSK9, Proprotein Convertase Subtilisin/Kexin type 9
Figure - Refer to: Vega RB *et al.* Presented at AHA 2025, Abstract MP496. / Ferri N & Marodin G. *Atheroscler Plus.* 2024;59:25-31; 2. Vega RB *et al.* Presented at AHA 2025, Abstract MP496.

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Laroprostat (AZD0780): Oral small molecule PCSK9 disruptor



- N=15,100
Estimated completion: October 2029
- Established ASCVD & LDL-C ≥75 mg/dL
- OR High Risk & LDL-C ≥1000 mg/dL

Koren MJ *et al.* JACC 2025;85(21):1996-2007.

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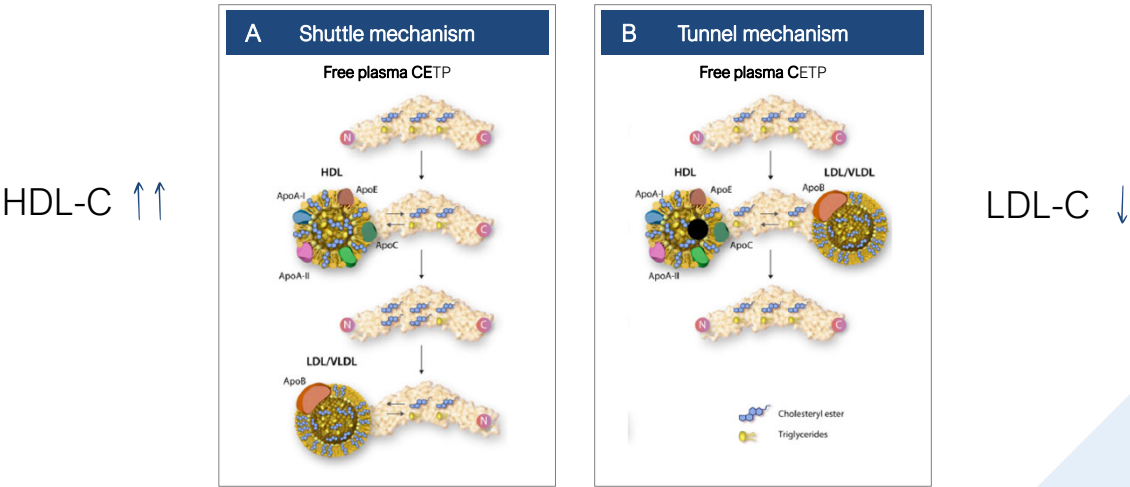
Indirect Comparison to other PCSK9i Therapies

	Enlicitide (20 mg qd) Week 24 ^a	Alirocumab (75 mg q2w) Week 24 ^b	Evolocumab (140 mg q2w or 420 mg q4w) Week 48 ^c	Lerodalcicbep (300 mg q month) Week 52 ^d	Inclisiran (284 mg q3m->q6m) Day 510 ^{e,f}	Laroprostat (30 mg daily) Week 52 ^g
MOA	Disrupts PCSK9 binding to LDLR				Inhibits PCSK9 translation in hepatocytes	Prevents lysosomal degradation of PCSK9-LDLR complex
Route	Oral*	SQ	SQ	SQ	SQ	Oral
LDL-C	-60%	-62%	-59%	-56%	-50 to -52%	-51%
Non-HDL-C	-53%	-52%	-52%	-47%	-44% to -47%	-45%
ApoB	-50%	-53%	-49%	-43%	-40 to -43%	-40%
Lp(a)	-28% Lp(a) is from individual studies not head-to-head comparisons. Differences in study design including population, and endpoint measurement may affect relative lipid lowering.	-29%	-27%	-20%	-19% to -26%	-20%

*Beta-quantification-derived LDL-C values of ≤0 treated as missing, and MH LDL-C used if available. ^bRobinson JG et al. *N Engl J Med.* 2015;372(16):1489-99; ^cSabatine MS et al. *N Engl J Med.* 2017;376(18):1713-1722; ^dMITT analysis for LDL-C, ITT for others. Lp(a) median reduction : Klug EQ et al. *JAMA Cardiol* 2024;9(9):800-7. ^eRay KK et al. *N Engl J Med.* 2020;382(16):1507-1519; ^fLEQVIO* (inclisiran) injection, for subcutaneous use (Prescribing Information) www.accessdata.fda.gov/drugsatfda_docs/label/2021/214017lbl.pdf. ^gKoren MJ et al. *JACC* 2025;85(21)

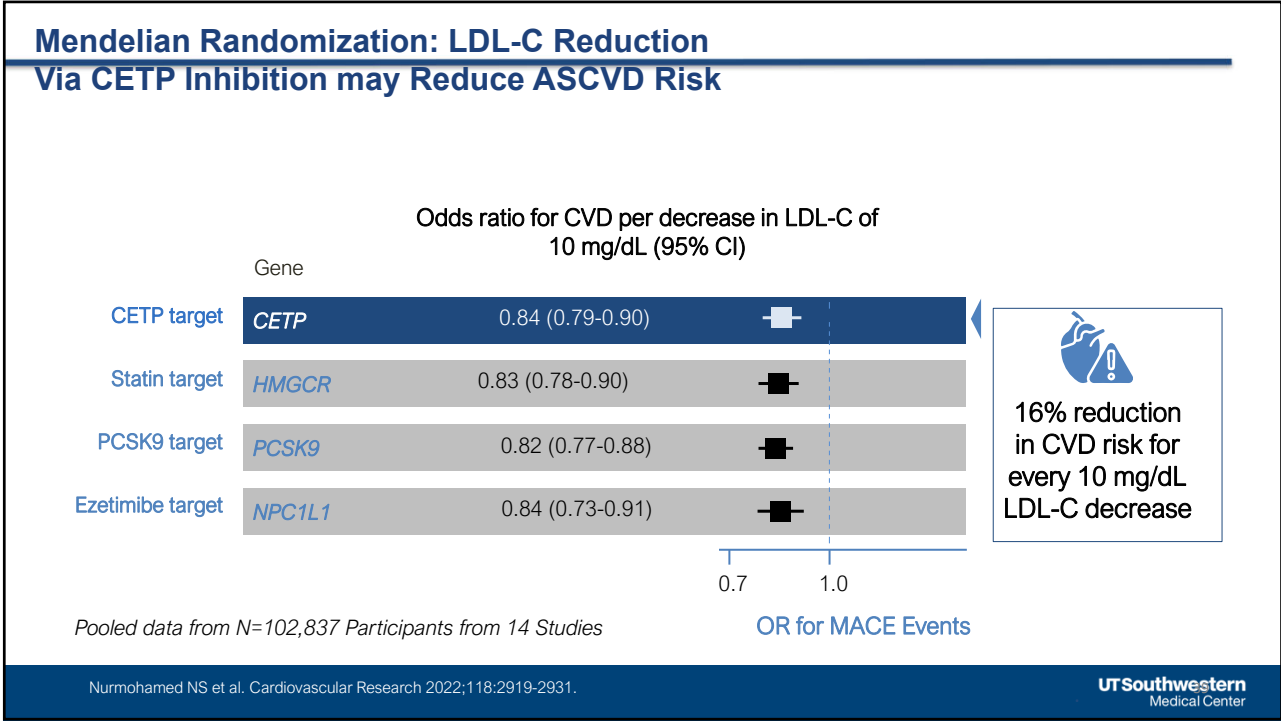
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CETP: Potential Next Addition to LDL Lowering Toolkit

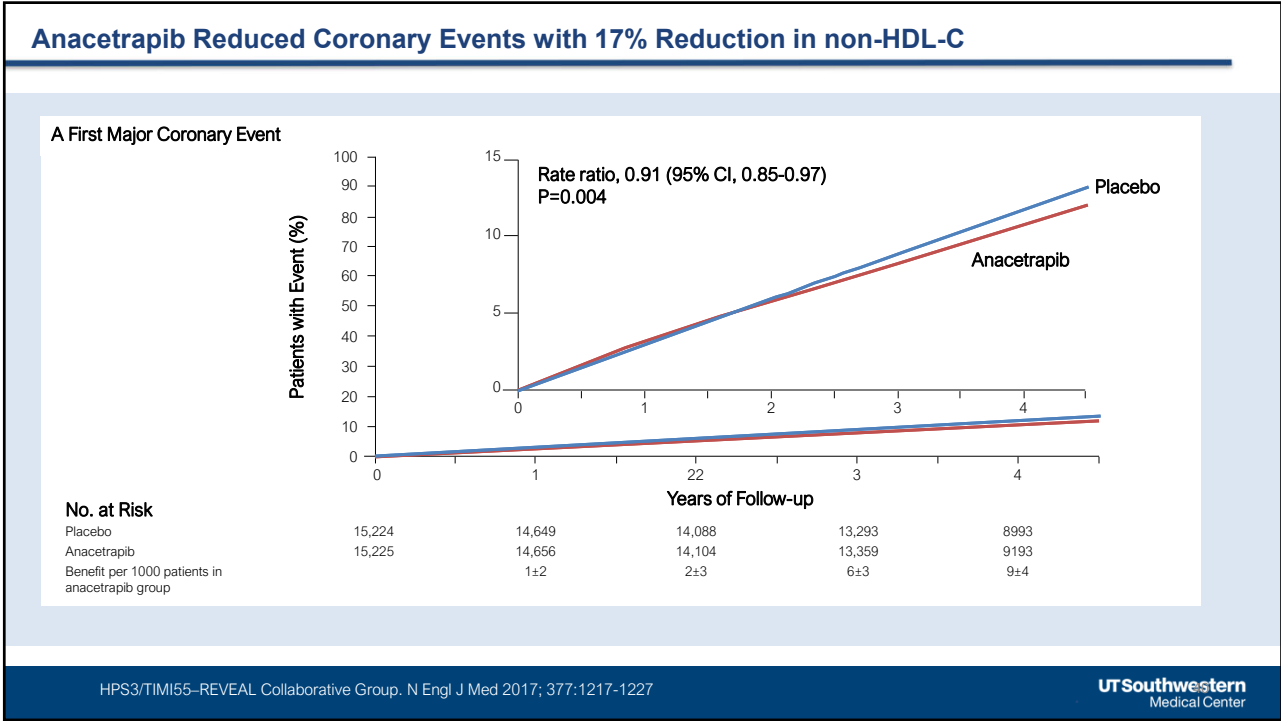


Nurmohamed NS et al. *Cardiovascular Research* 2022;118:2919-2931.

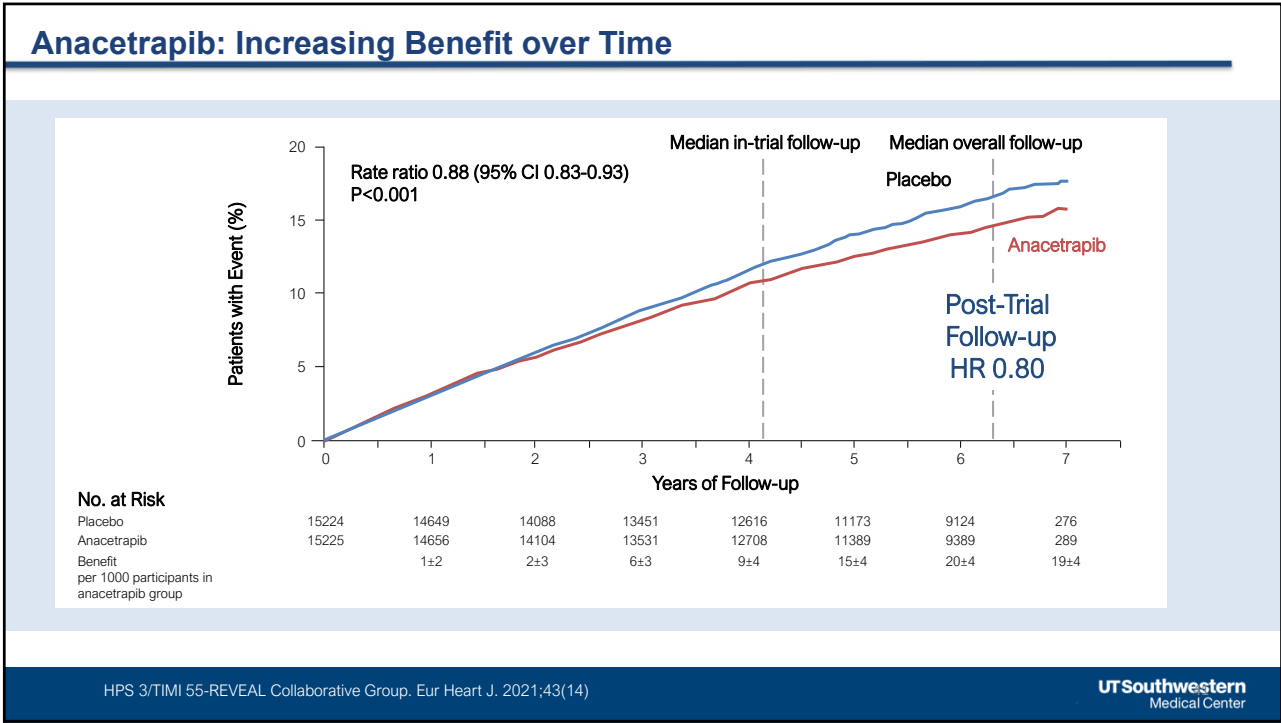
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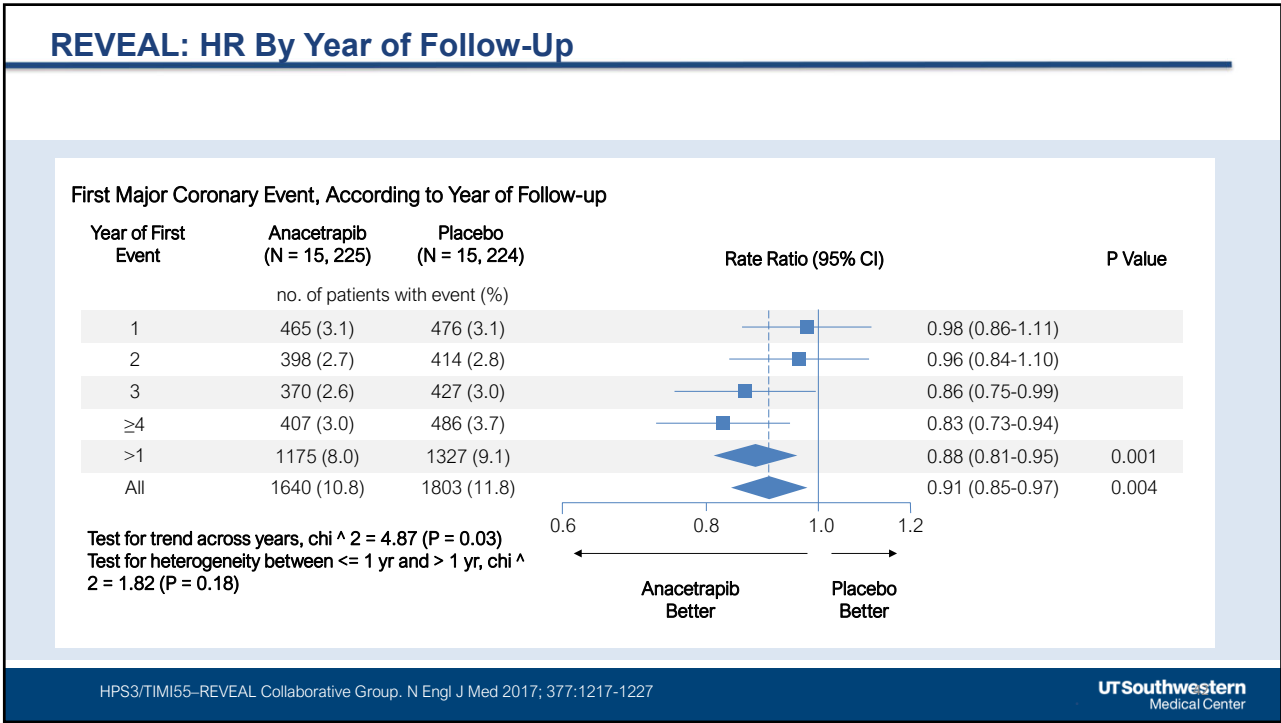
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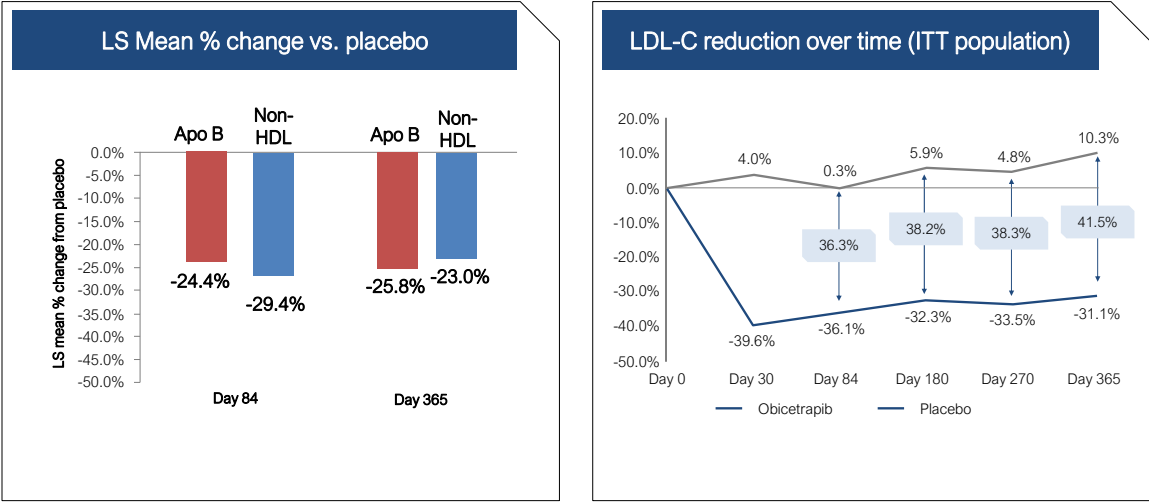
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BROADWAY: Obicetrapib vs placebo in ASCVD or HeFH

n=2530 2:1 obi vs placebo, mean LDL-C 98 mg/dL



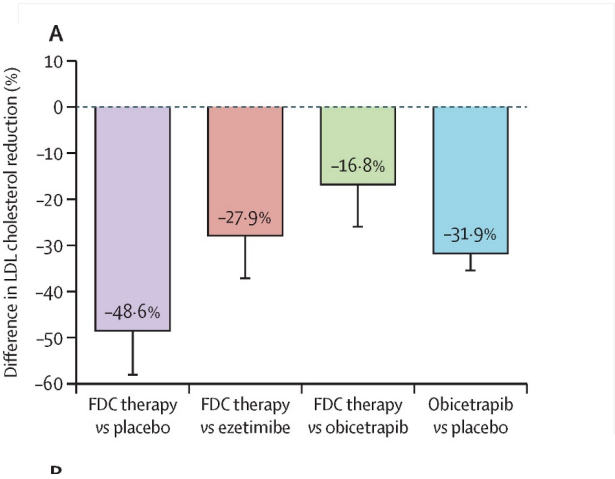
Nicholls SJ et al. NEJM 2025;393:51-61

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Obicetrapib + Ezetimibe: TANDEM Trial

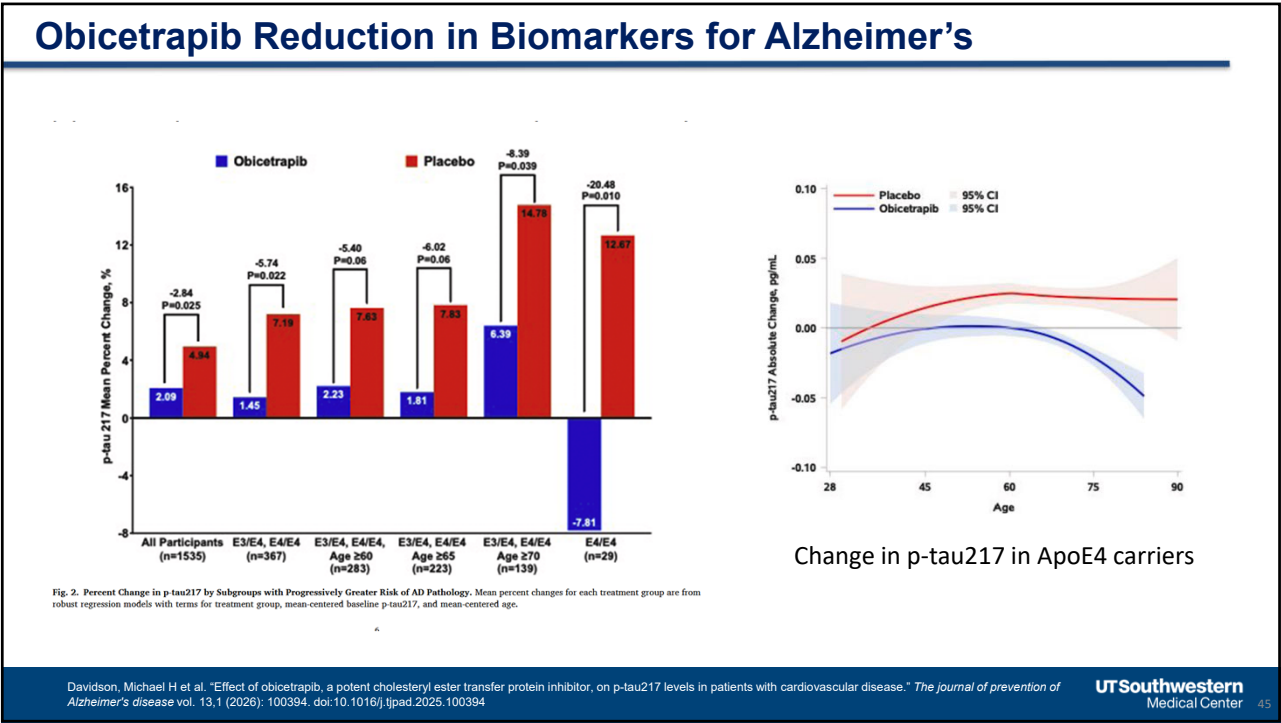
Obicetrapib + EZE: TANDEM Trial



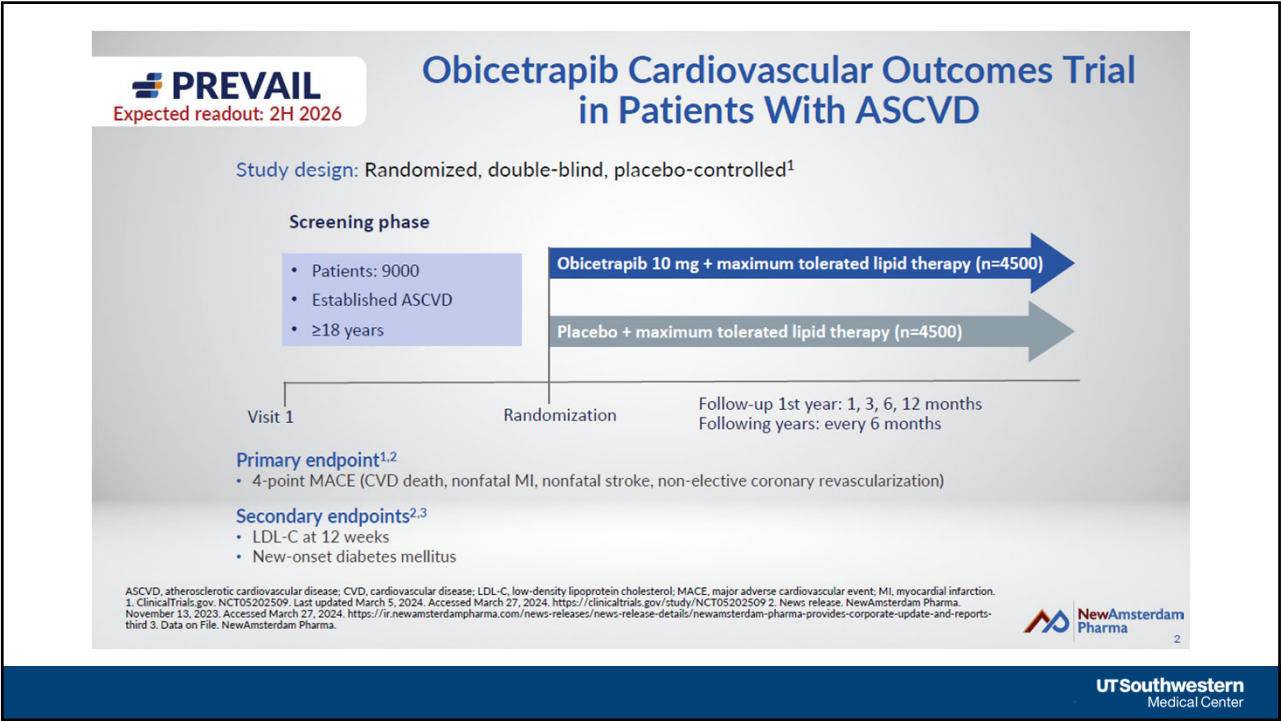
Sarraj A et al. Lancet 405(10491) 2025; Nicholls SJ et al. NEJM 2025;393:51-61.

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What am I most excited about?

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Combo Therapy – 1 pill >80% LDL-C Reduction?

Therapy	LDL↓	Intensity	Administration	Acceptance
High-Intensity Statin	45–55%	High	Oral daily	★★★★
FDC Bempedoic acid + Ezetimibe	40%	High	Oral daily	★★★★
FDC Statin + Ezetimibe	60–65%	Very High	Oral daily	★★★★★
Future FDC: Statin + Bempedoic acid + Ezetimibe	65–70%	Very High	Oral daily	★★★★★ ?
+ PCSK9i AB, adnektin or siRNA (s.c. injection)	70–80%	Ultra	s.c. q2–4w; siRNA q 6 mo	★★★★
+ PCSK9i Enlicitide or Laroprostat (oral)	70–80%	Ultra	Oral daily	★★★★★ ?
Future FDC: oral PCSK9i + statin	>85%	Maximal	Oral daily	★★★★★ ?
Future PCSK9-DNA therapy	>50%	Cure	once per lifetime	★?

A Clinical Trial of Enlicitide and Rosuvastatin in Healthy Adults (MK-0616-039)

ClinicalTrials.gov ID ⓘ NCT07300280

Sponsor ⓘ Merck Sharp & Dohme LLC

Information provided by ⓘ Merck Sharp & Dohme LLC (Responsible Party)

Last Update Posted ⓘ 2026-03-18

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Study Details

Researcher View No Results Posted Reco

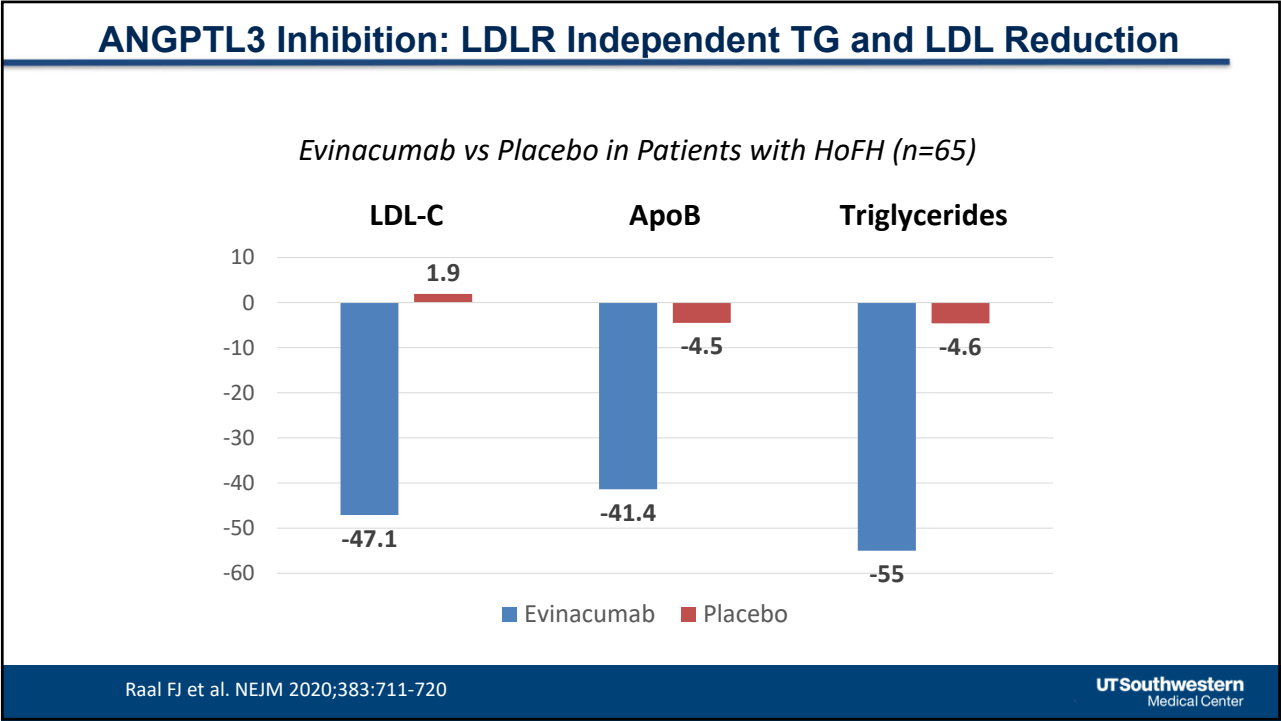
Study Overview

Brief Summary

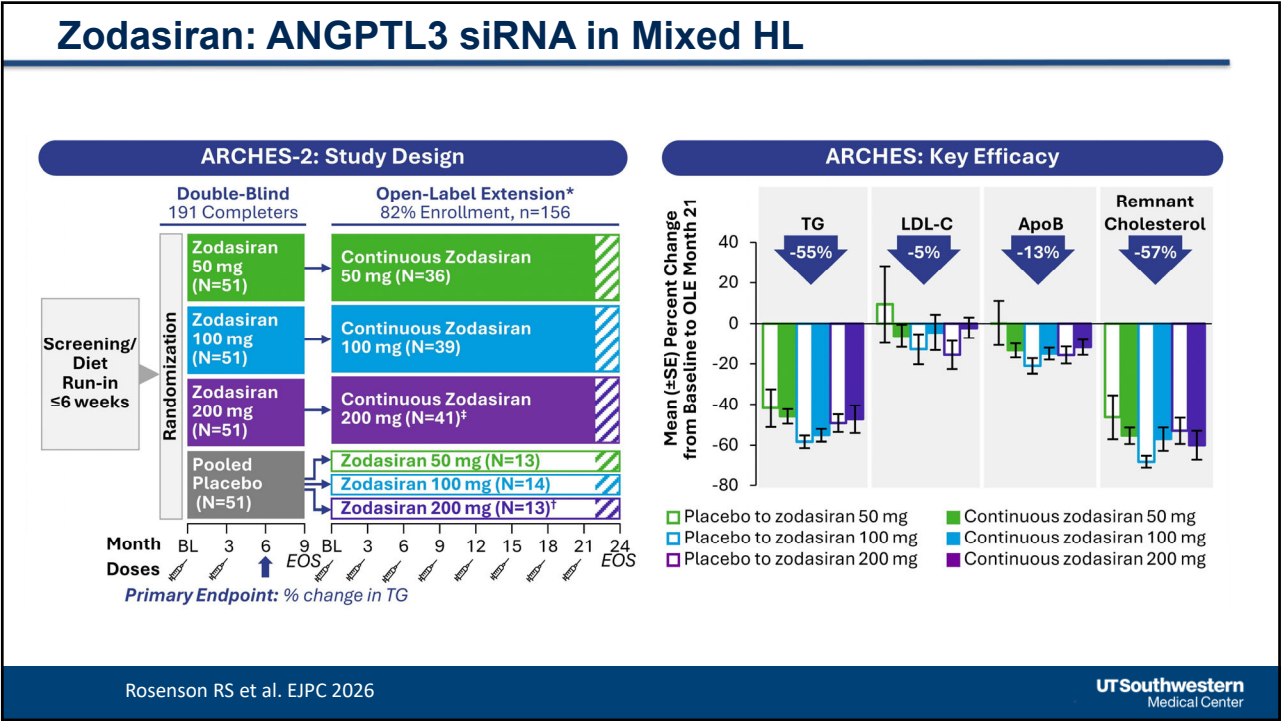
This goal of this trial is to learn about two medicines, enlicitide and rosuvastatin, in healthy people. Researchers will compare the amounts of enlicitide and rosuvastatin in a person's body over time, when they are given as separate medicines and when they are combined into one tablet.

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PCSK9 LOF Associated with Lower LDL-C

nature genetics

LETTERS

Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in *PCSK9*

Jonathan Cohen^{1,3}, Alexander Pertsemidis^{2,3}, Ingrid K Kotowski⁴, Randall Graham¹, Christine Kim Garcia^{1,3} & Helen H Hobbs^{1,4}

The low-density lipoprotein receptor (LDLR) prevents hypercholesterolemia and atherosclerosis by removing low-density lipoprotein (LDL) from circulation. Mutations in the gene encoding either LDLR or its ligand (APOB) cause severe hypercholesterolemia. Missense mutations in *PCSK9*, encoding a serine protease in the secretory pathway, also cause hypercholesterolemia¹. These mutations are probably gain-of-function mutations, as overexpression of *PCSK9* in the liver of mice produces hypercholesterolemia^{2,3} by reducing LDLR number. To test whether loss-of-function mutations in *PCSK9* have the opposite effect, we sequenced the coding region of *PCSK9* in 128 subjects (50% African American) with low plasma levels of LDL and found two nonsense mutations (Y142X and C679X). These mutations were common in African Americans (combined frequency, 2%) but rare in European Americans (<0.1%) and were associated with a 40% reduction in plasma levels of LDL cholesterol. These data indicate that common sequence variations have large effects on plasma cholesterol levels in selected populations.

PCSK9 encodes a 692-amino acid glycoprotein, also called neural apoptosis-regulated convertase 1 (NARIC-1), that is expressed most abundantly in the liver, small intestine and kidney (Fig. 1a)⁴. *PCSK9* is a proprotein convertase subtilisin/kexin type 9 serine protease that

Figure 1 Functional domains and haplotypes of *PCSK9*. (a) *PCSK9* contains a 30-amino acid signal peptide (SP) followed by a prodomain. The prodomain undergoes autocatalytic processing to release a 14 kDa peptide from the N terminus. The catalytic domain, which contains the catalytic triad of aspartate (D), histidine (H) and serine (S), as well as a highly conserved asparagine (N), is followed by a P domain and a cysteine-rich C-terminal domain. The sites of the three missense mutations associated with hypercholesterolemia are indicated below the prodomain. (b) Haplotypes of subjects with 425C⁻G (Y142X) and 2033C⁻A (C679X) mutations (indicated) and in 142 noncarriers.

Two nonsense mutations in *PCSK9* ~2% of Black DHS Participants

LDL-C levels in African American DHS participants with and without a *PCSK9* LOF

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Lifelong Reduction in ASCVD Risk

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

ABSTRACT

BACKGROUND

A low plasma level of low-density lipoprotein (LDL) cholesterol is associated with reduced risk of coronary heart disease (CHD), but the effect of lifelong reductions in plasma LDL cholesterol is not known. We examined the effect of DNA-sequence variations that reduce plasma levels of LDL cholesterol on the incidence of coronary events in a large population.

METHODS

We compared the incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization) over a 15-year interval in the Atherosclerosis Risk in Communities study according to the presence or absence of sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) that are associated with reduced plasma levels of LDL cholesterol.

RESULTS

Individuals with *PCSK9* LOF Variants

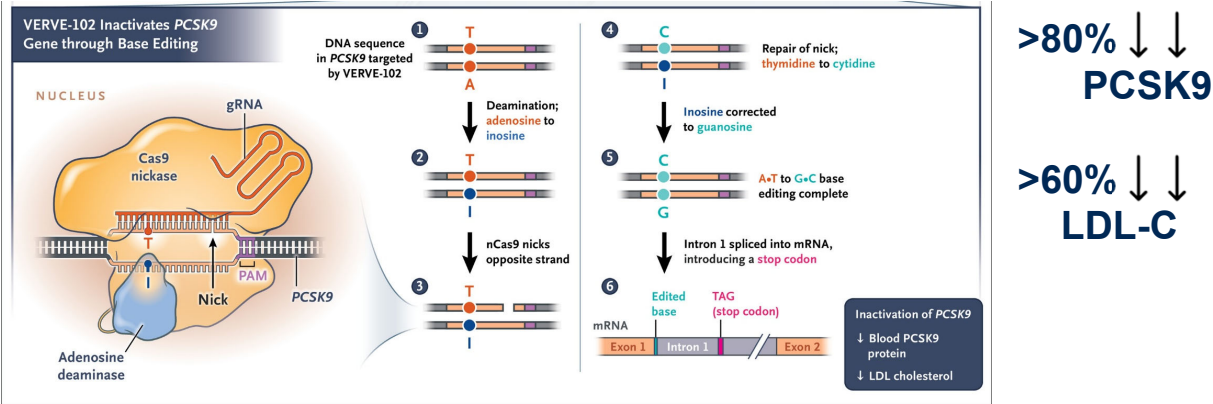
1 variant:
-15% ↓ in LDL-C → 47% ↓ ↓ CHD risk

2 variants
-28% ↓ in LDL-C → 88% ↓ ↓ CHD Risk

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Gene Editing: Cheating the Genetic Lottery

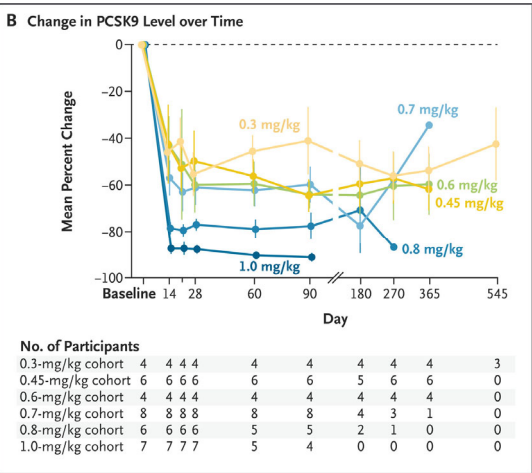


Vafai SB, et al. In Vivo Base Editing of PCSK9 with VERVE-102 for Hypercholesterolemia. N Engl J Med. 2026 Aug 13;395(7):648-659. doi: 10.1056/NEJMoa2601283. Epub 2026 May 25. PMID: 42187087

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Sustained Effect Beyond Hepatocyte Lifespan



Vafai SB. In Vivo Base Editing of PCSK9 with VERVE-102 for Hypercholesterolemia. N Engl J Med. 2026 Aug 13;395(7):648-659. doi: 10.1056/NEJMoa2601283. Epub 2026 May 25. PMID: 42187087.

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A Cautionary Tale



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Misinformation threatens public health

STATIN NATION

BLOG CONTACT THE BOOK STATIN NATION

OWN STATIN PACKAG ADDITION

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The Dark Side of Statins

by Duane Graveline MD, MPH

Plus The Wonder of Cholesterol

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STORY AT-A-GLANCE

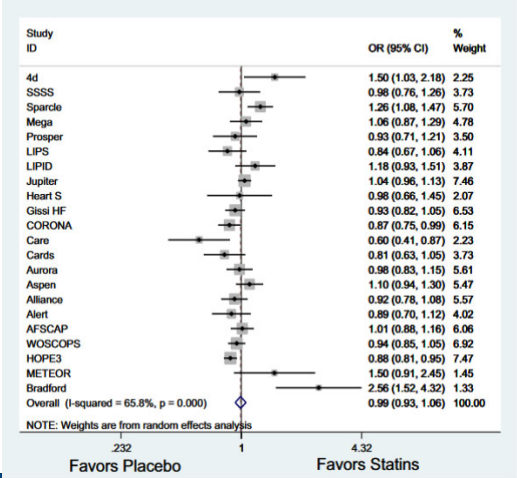
The number of people suffering from heart disease and stroke continues to rise, despite pharmaceutical interventions, including statin medications recommended for high cholesterol levels

Statin focus on reducing cholesterol your body produces naturally.

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RCTs: No difference between Placebo/Statin in Discontinuation due to Intolerance

Meta-Analysis of Randomized Trials



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Riaz H et al. AJC. 2017;120:774-81

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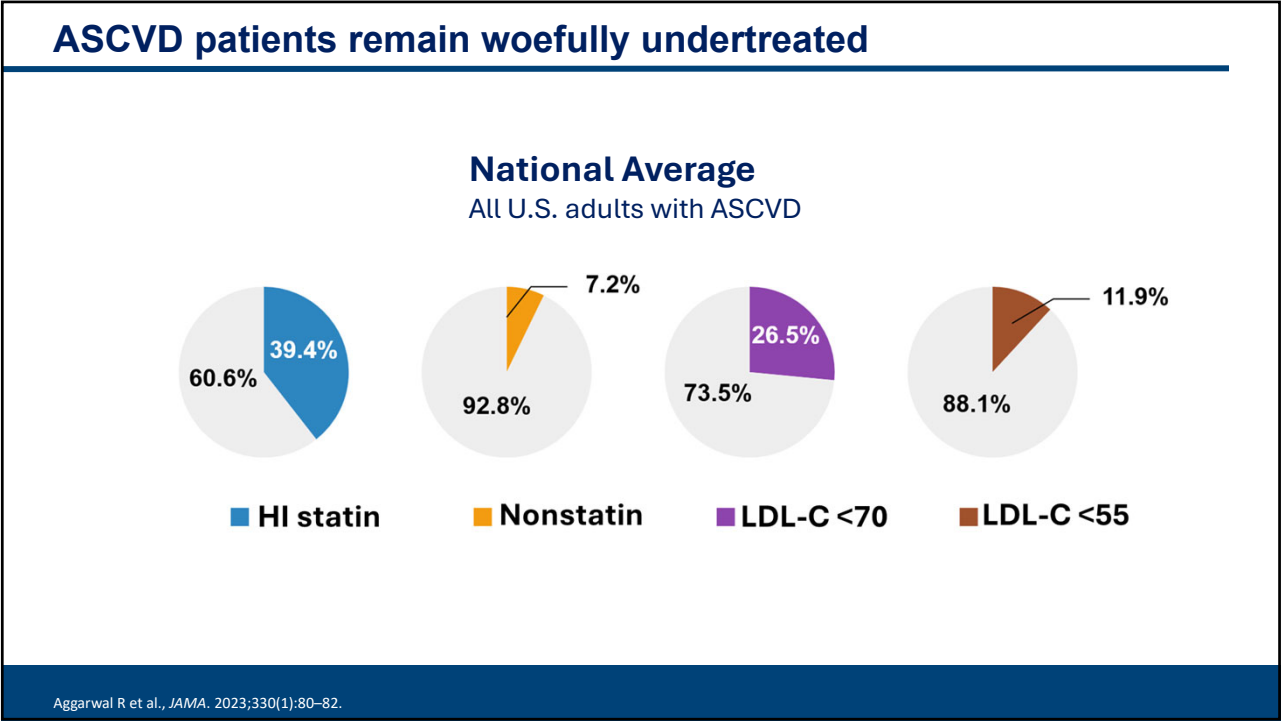
The Nocebo Effect: Side Effect Fears Fuel Actual Experience



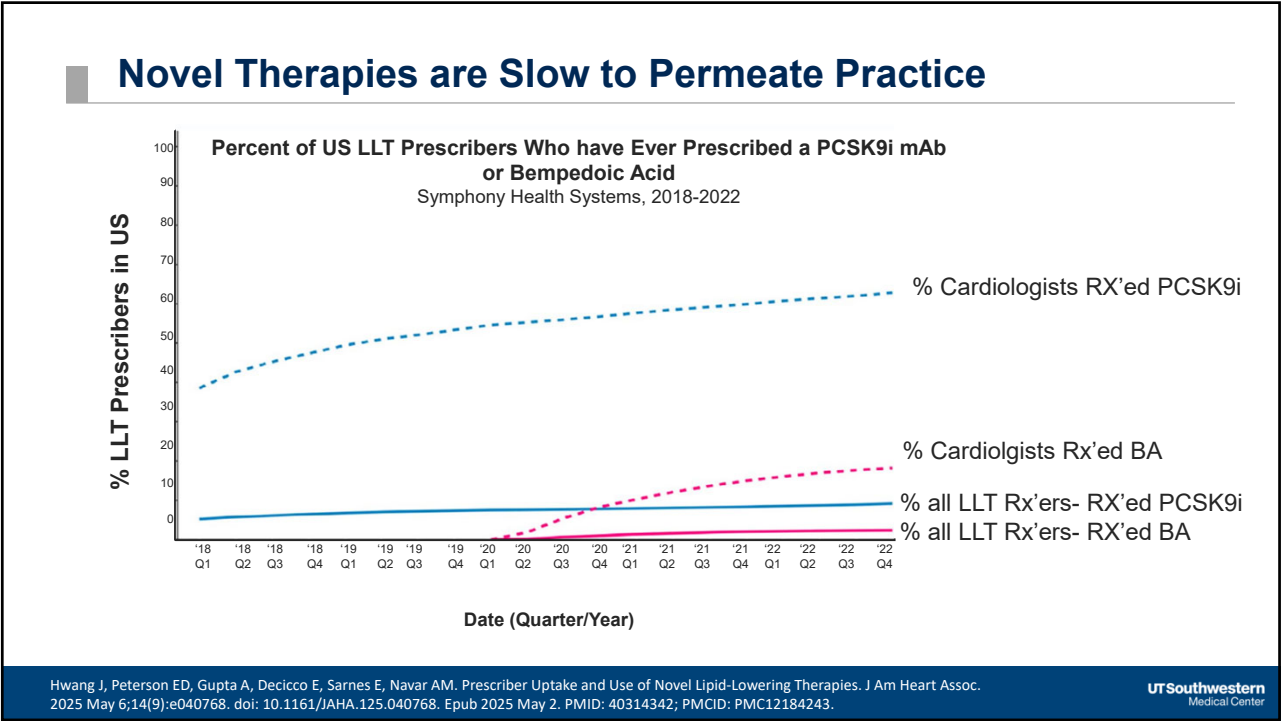
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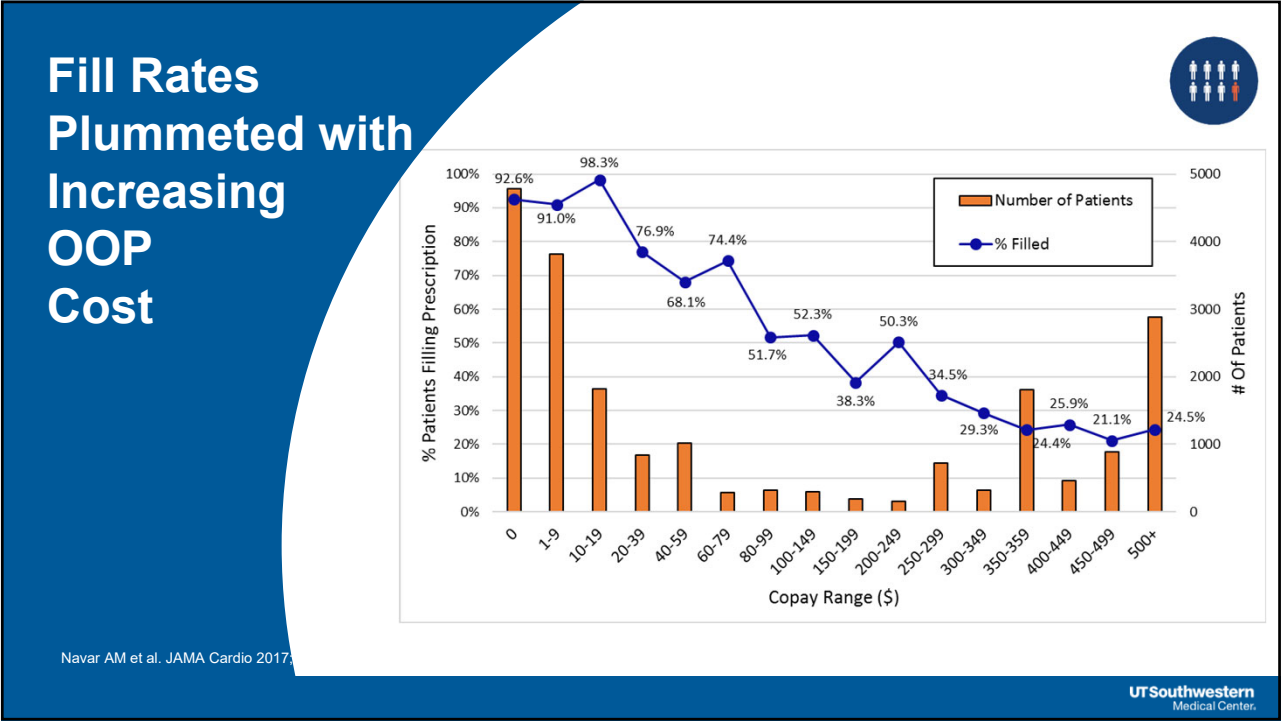
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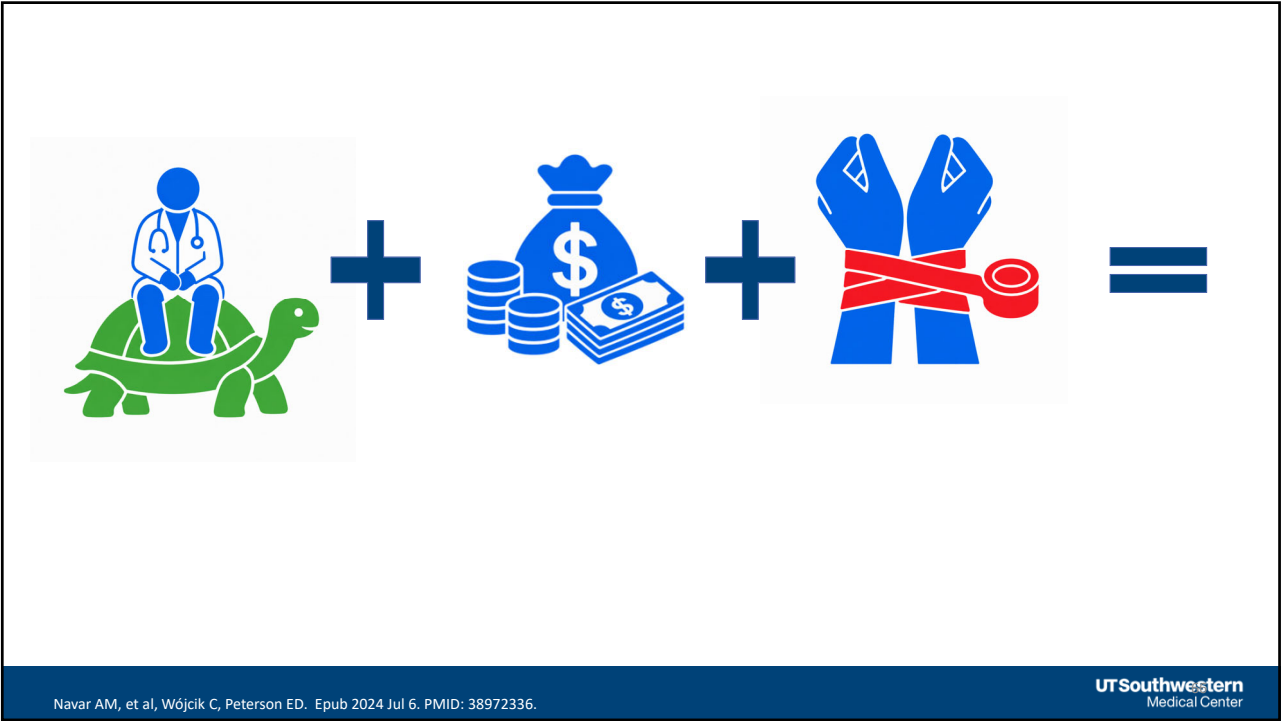
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>50% of ASCVD Patients with LDL-C >70 mg/dL

Navar AM, et al, Wójcik C, Peterson ED. Epub 2024 Jul 6. PMID: 38972336.

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The Future is Bright!

- Multiple novel therapies being added to the LDL-C lowering armamentarium
- Alternative LDL lowering pathways offer potential for more CV benefit
- Without broader uptake of **both old and new** LDL lowering therapies we will never achieve their full potential

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