Evolving Therapies in Dyslipidemia and ASCVD Risk Reduction: Putting It All Together in High-Risk Patients

MUSC Health
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Changing What's Possible

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Disclosures

Local PI (research), CLEAR Outcomes (ended 3/2023)

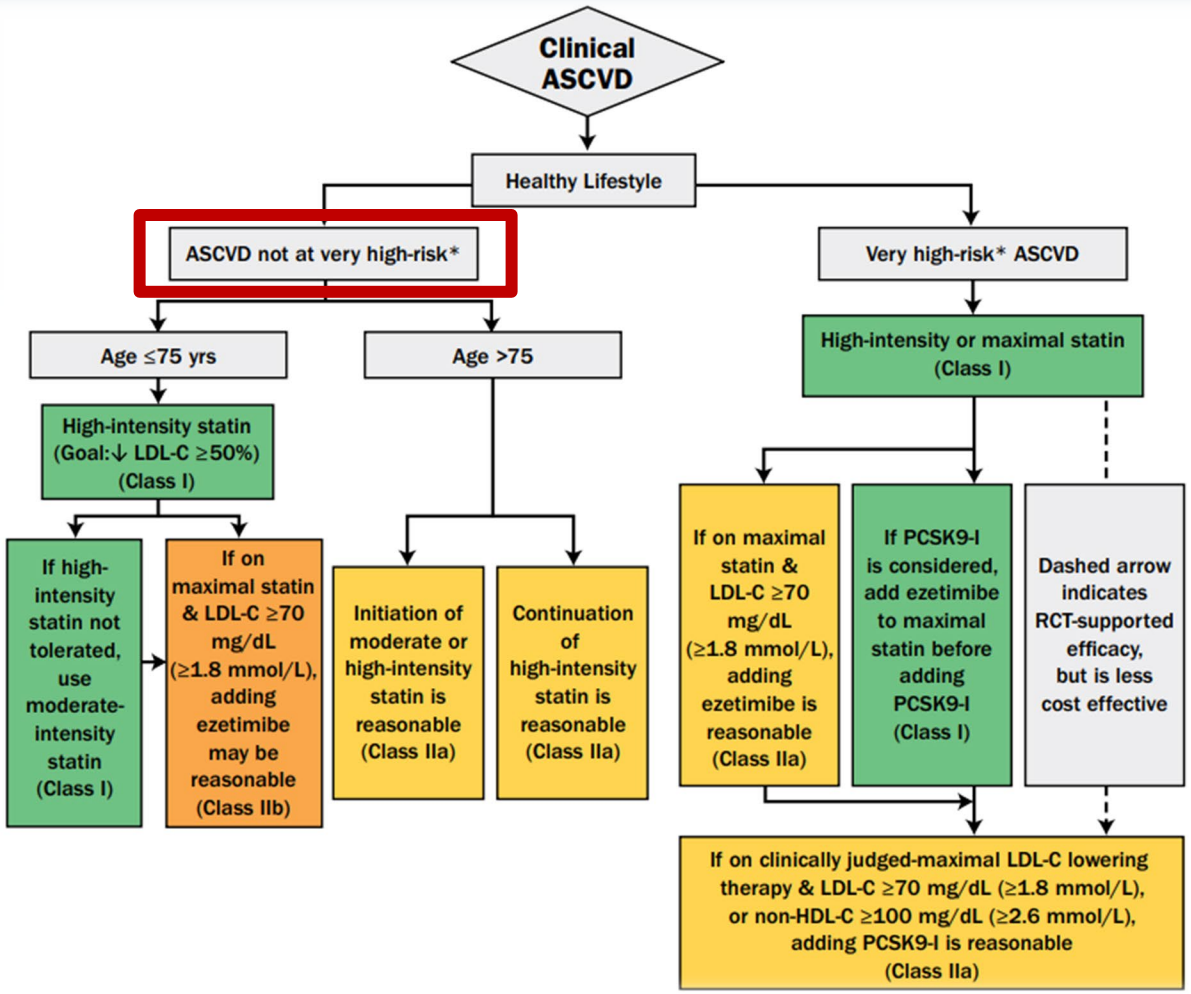
Mission Critical: Treating the High-Risk Patient

Who Is the Very High-Risk ASCVD Patient?

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

Other high-risk features

- 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



J Am Coll Cardiol. 2019;74(20):2496-507;
J Am Coll Cardiol. 2022 DOI: 10.1016/j.jacc.2022.07.006

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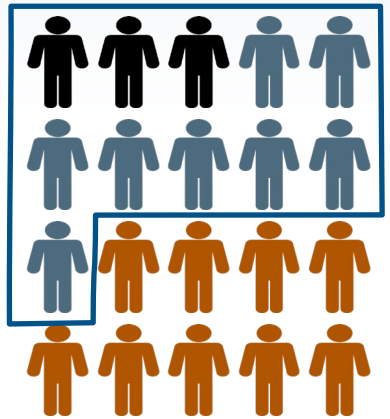
- Major ASCVD event with >1 risk conditions

Among 27,775 patients with a history of ASCVD in the MarketScan database on January 1, 2016



55.3% met the definition for very high risk

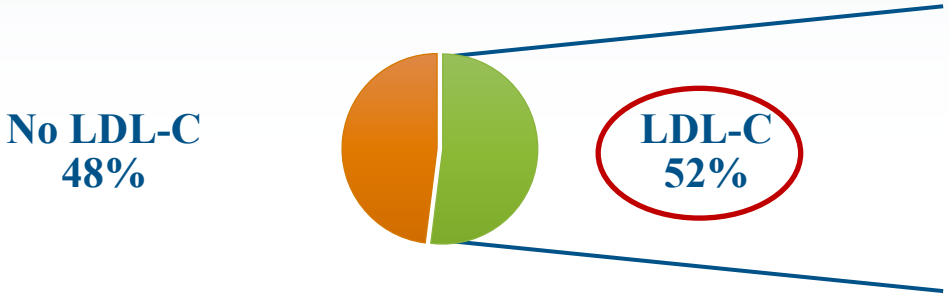
26.0% had multiple major ASCVD events

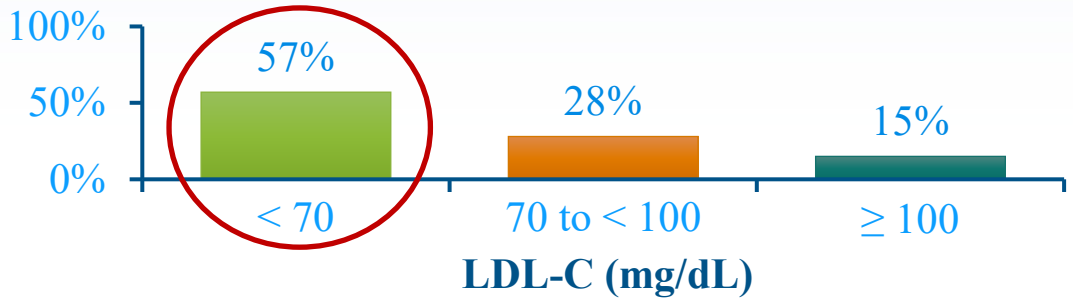
74.0% had a major ASCVD event and multiple high-risk conditions

J Am Coll Cardiol. 2019;74(20):2496-507;
J Am Coll Cardiol. 2022 DOI: 10.1016/j.jacc.2022.07.006

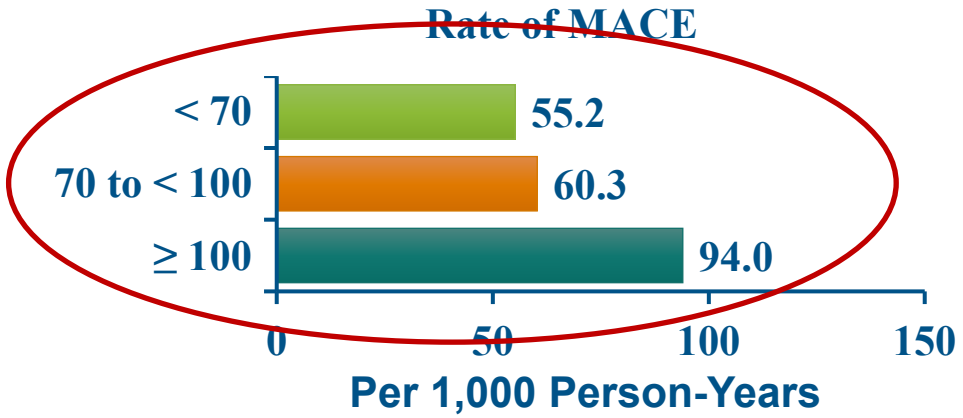
Reality Check:
Many Patients with ASCVD Not at LDL-C Goal

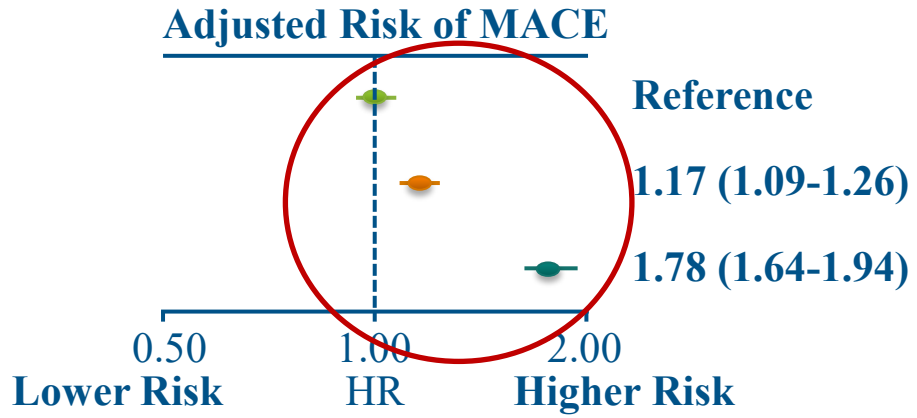
~1 of every 2 patients had LDL-C measured after PCI → **~1 of every 2 patients had LDL-C < 70 mg/dL**





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





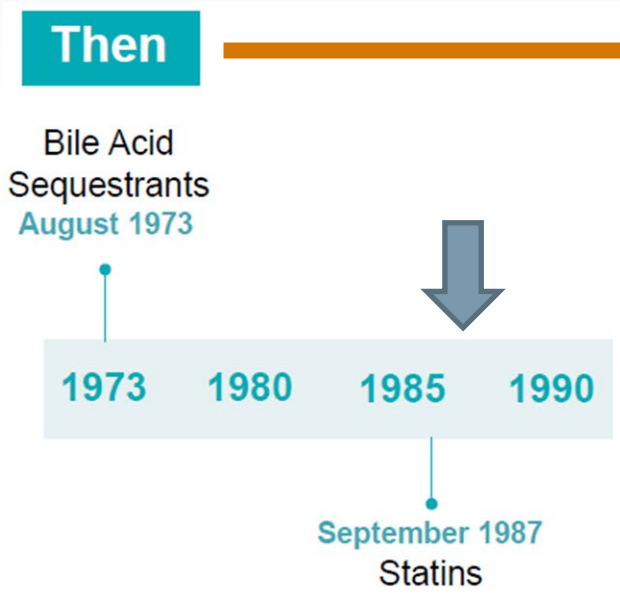
- 47,884 pts s/p PCI
- 3.2 yrs F/U

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

The LDL-C Treatment Journey

- What are the options for treatment of the high-risk patient?

The LDL-C Treatment Journey…



Lovastatin: 1987

Simvastatin: 1991

Pravastatin: 1991

Atorvastatin: 1996

Cerivastatin: 1997

- *Withdrawn: 2001*

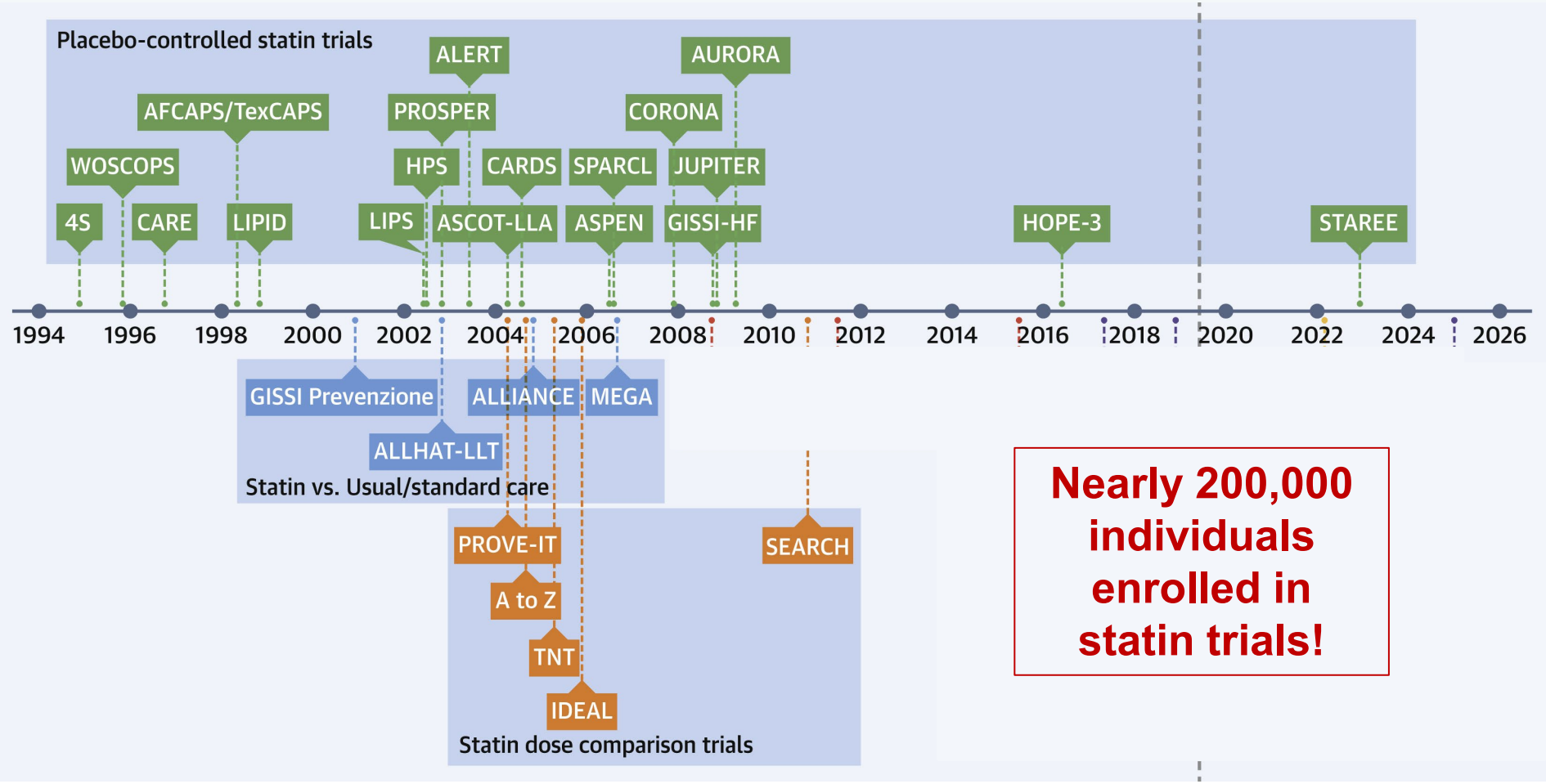
Fluvastatin: 2000

Rosuvastatin: 2003

Pitavastatin: 2009

37 yrs

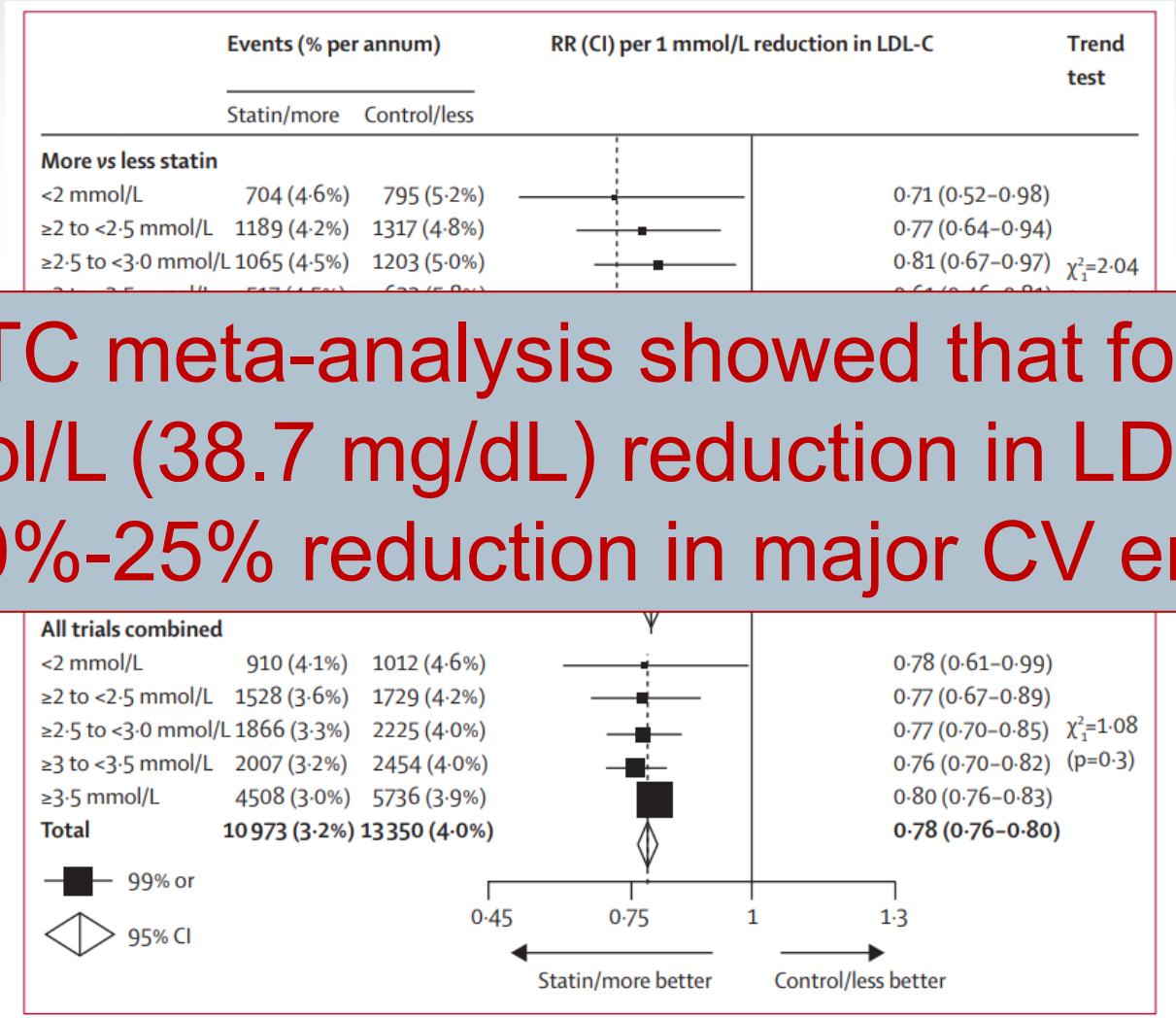
Timeline of Completed and Ongoing LDL Cholesterol–Lowering Cardiovascular Outcome Trials



Nearly 200,000 individuals enrolled in statin trials!

J Am Coll Cardiol 2020;75:1945–55

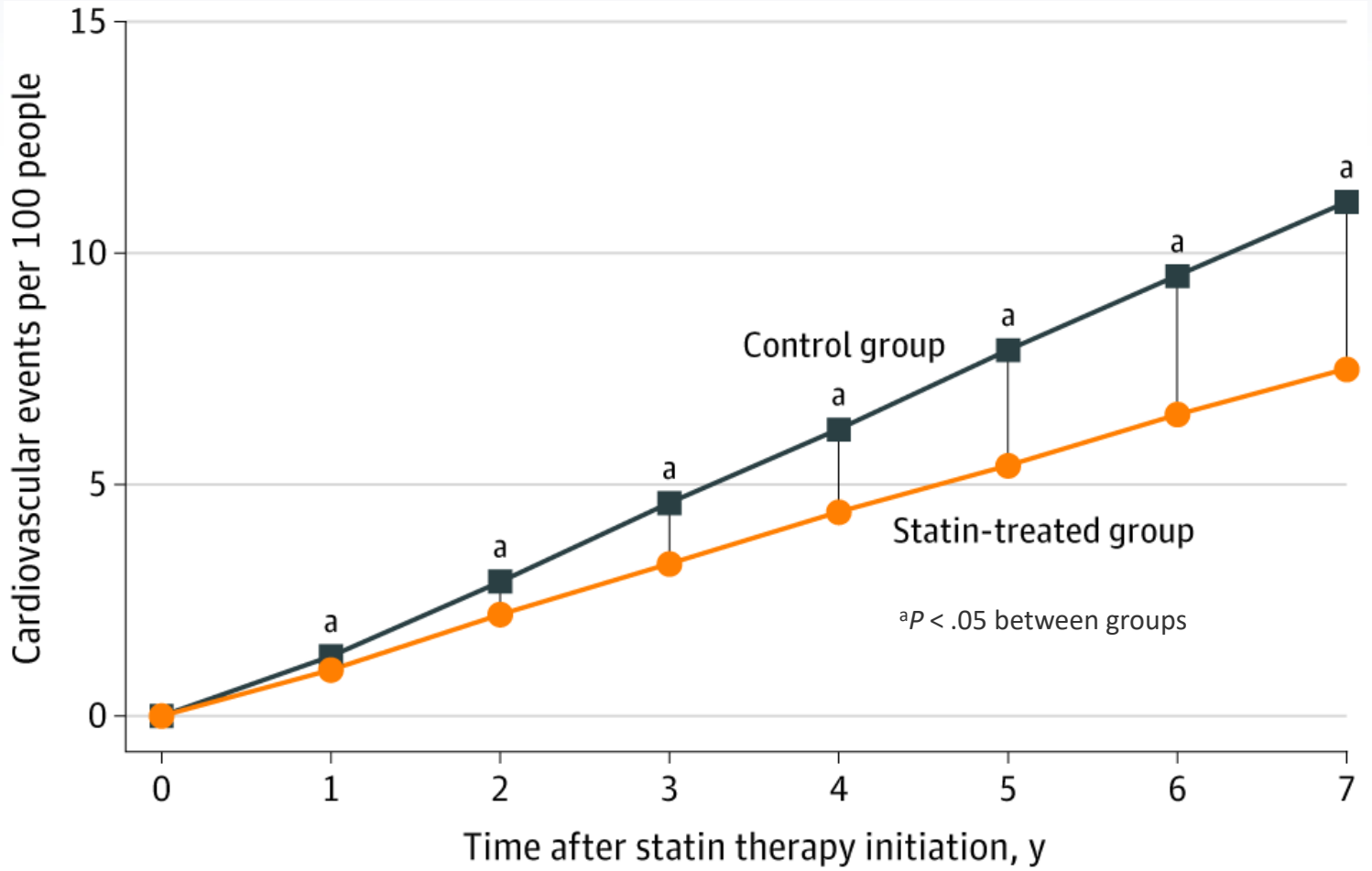
Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials



CTTC meta-analysis showed that for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C there is a 20%-25% reduction in major CV end points.

Lancet 2010; 376: 1670–81

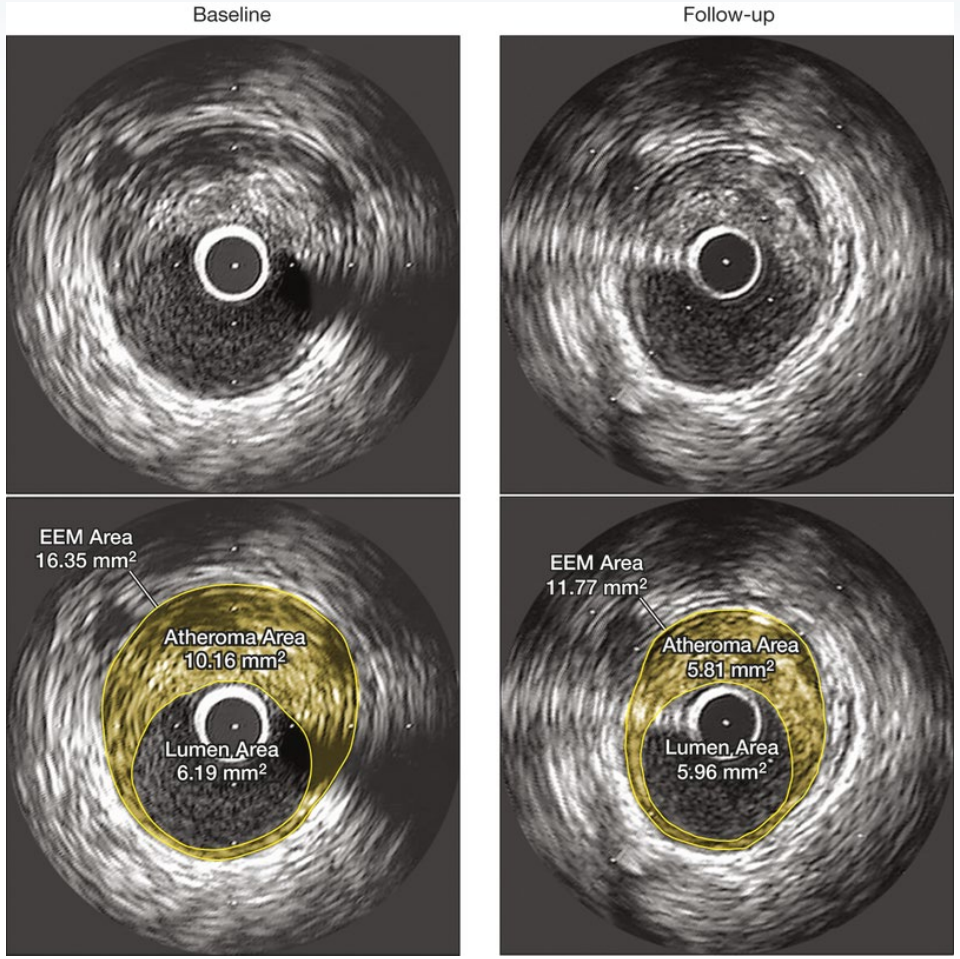
Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years
A Meta-analysis



Benefits of statin therapy increase steadily with longer follow-up

JAMA Intern Med. 2021;181(2):179-185.

Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis: The ASTEROID Trial



- To assess whether *very intensive statin therapy* could *regress* coronary atherosclerosis as determined by IVUS imaging.
- 349 patients underwent IVUS examination and received rosuvastatin 40 mg over 24 months

  Baseline LDL-C level of **130.4** (34.3) mg/dL declined to **60.8** (20.0) mg/dL, a mean reduction of 53.2% (P<.001).

Significant reductions in

PAV for the entire vessel

Atheroma volume in the most diseased

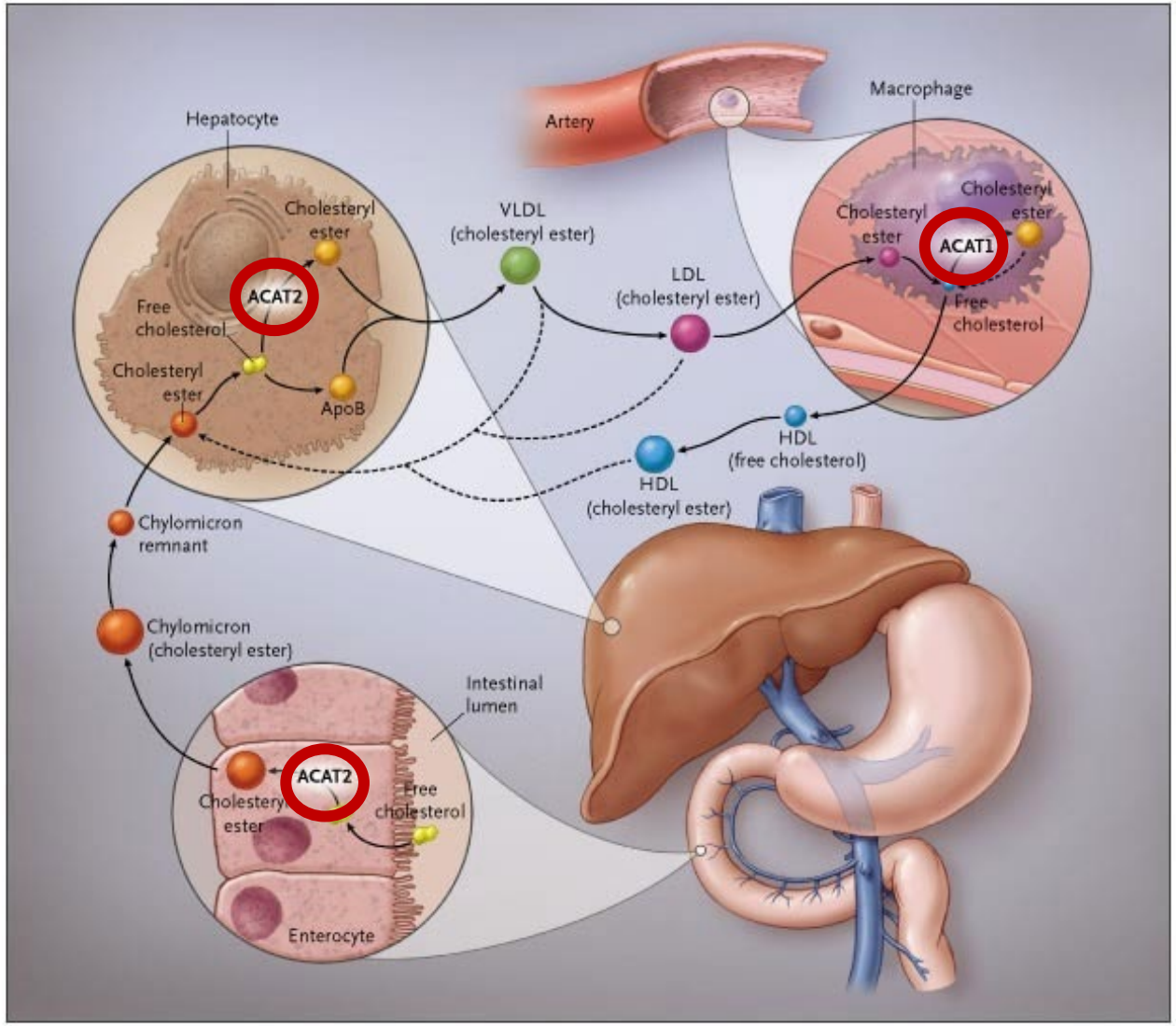
Total atheroma volume

JAMA. 2006 Apr 5;295(13):1556-65

Beyond Statins…

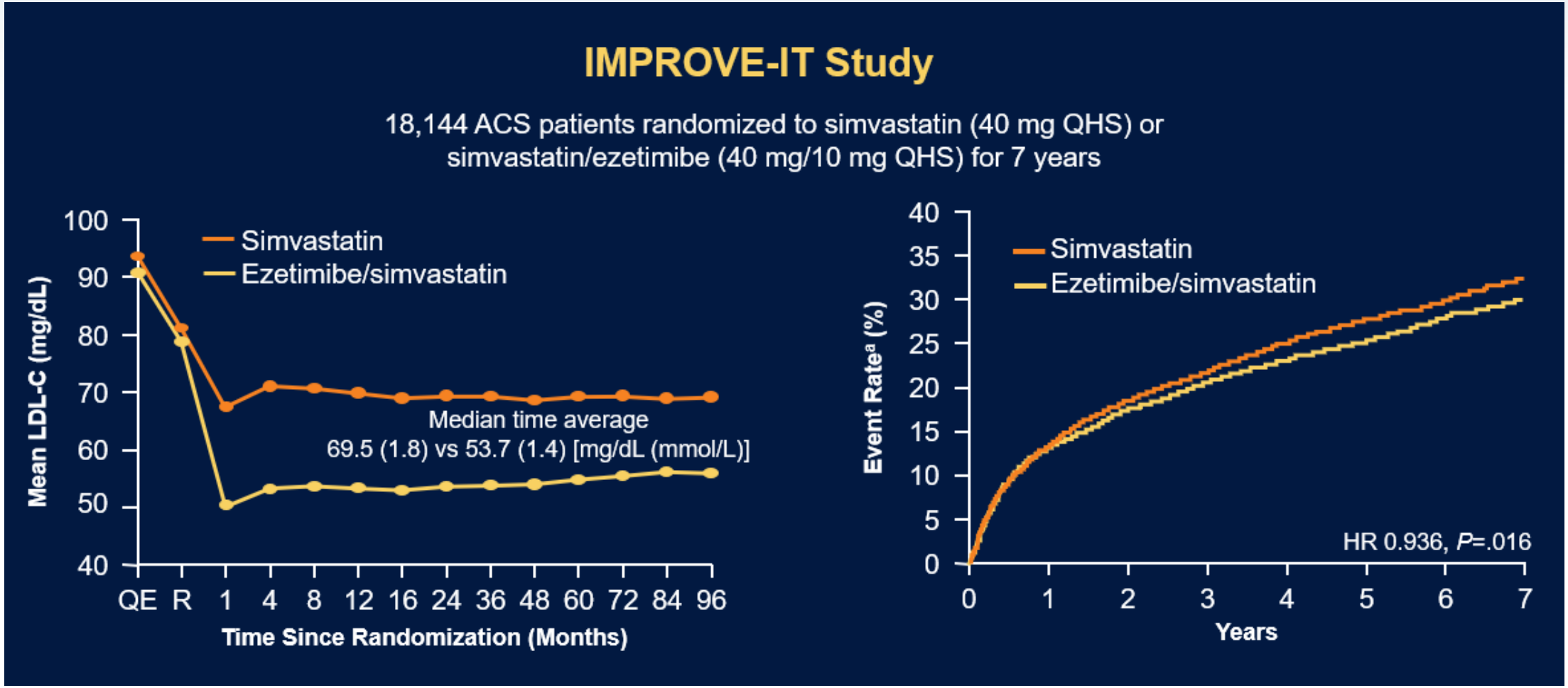
Ezetimibe (2002)

- Discovered as part of program to identify ACAT inhibitors for lipid lowering
  - Catalyzes formation CE from cholesterol and long-chain fatty-acid-acyl CoA to store and transport cholesterol
- Weak ACAT inhibitor, but lowered cholesterol
  - Different mechanism?
- At time of U.S. approval in 2002, target not known
  - › Inhibits NPC1L1 sterol transporter



N Engl J Med 2006; 354:1253-1263

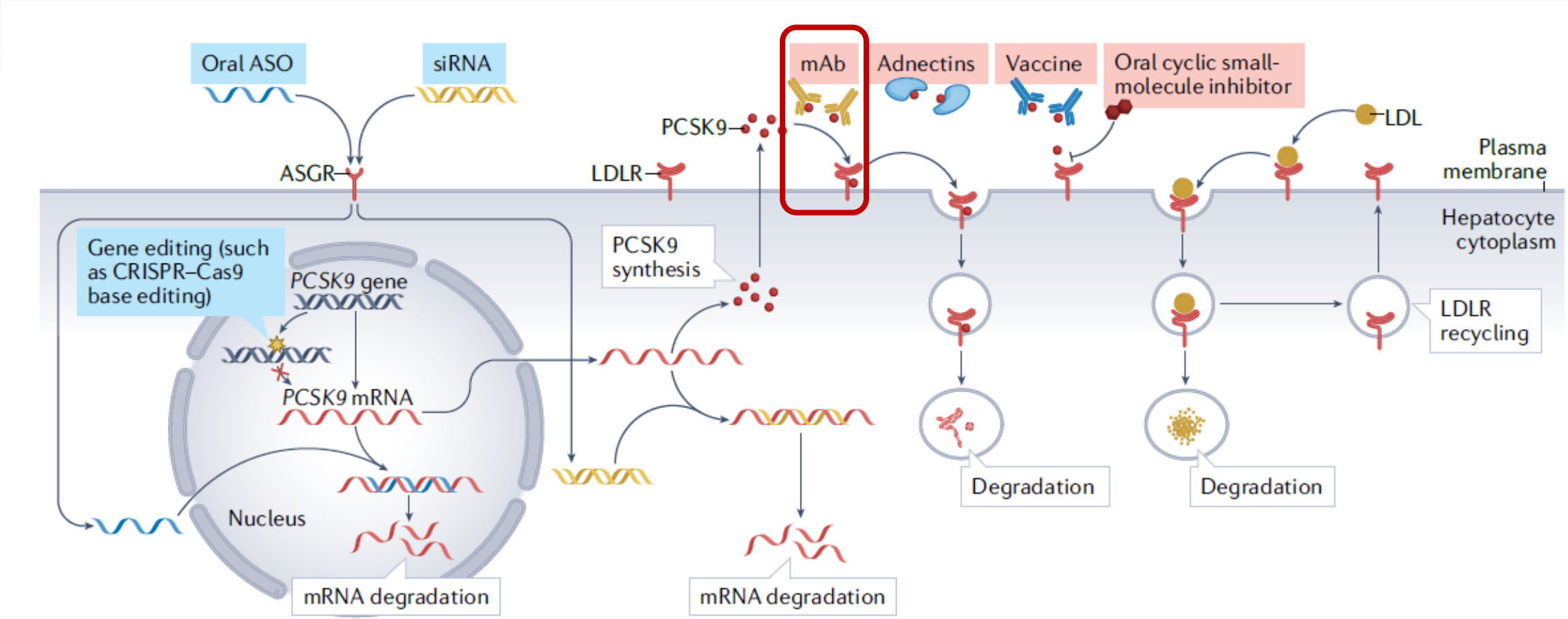
Impact of Ezetimibe in ACS



N Engl J Med. 2015;372:2387-97

PCSK9-targeted interventions: Monoclonal Ab (2015)

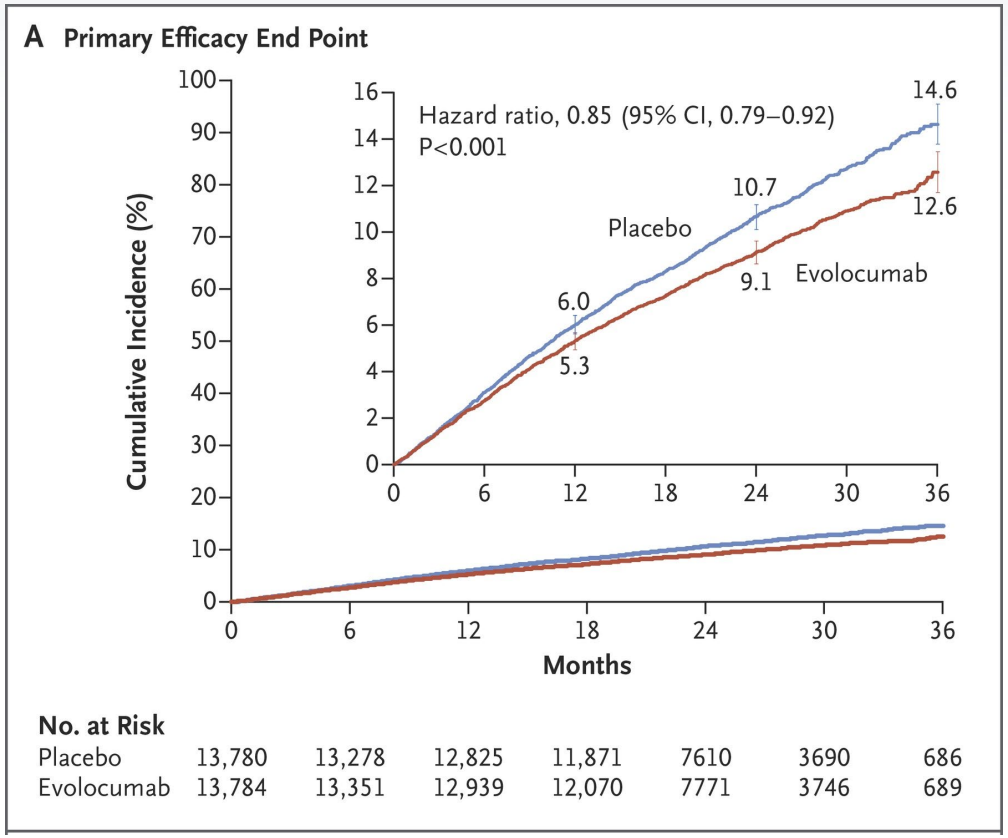
- Bind PCSK9 to prevent targeted breakdown of LDL-R in lysozymes



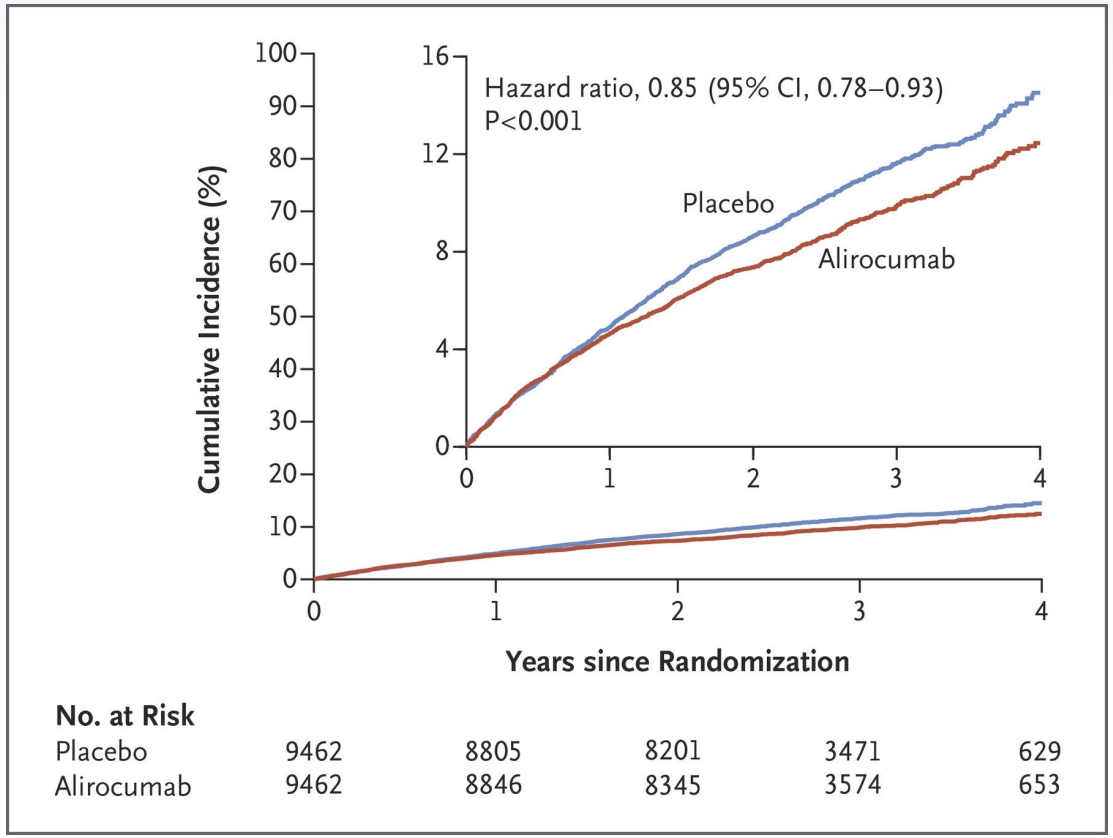
Nature Rev Cardiol.2021;18;805-6

PCSK9 mAb CV Outcomes Trials

FOURIER

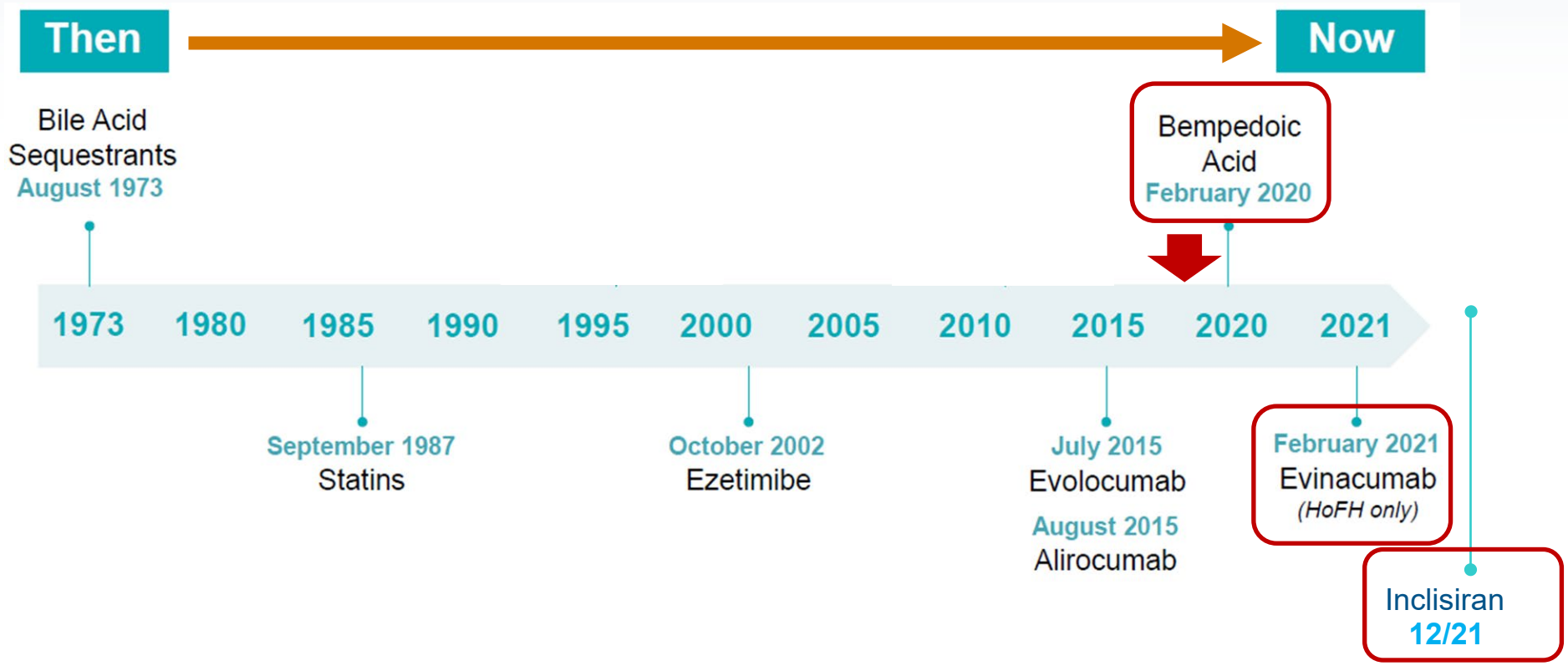


ODYSSEY Outcomes



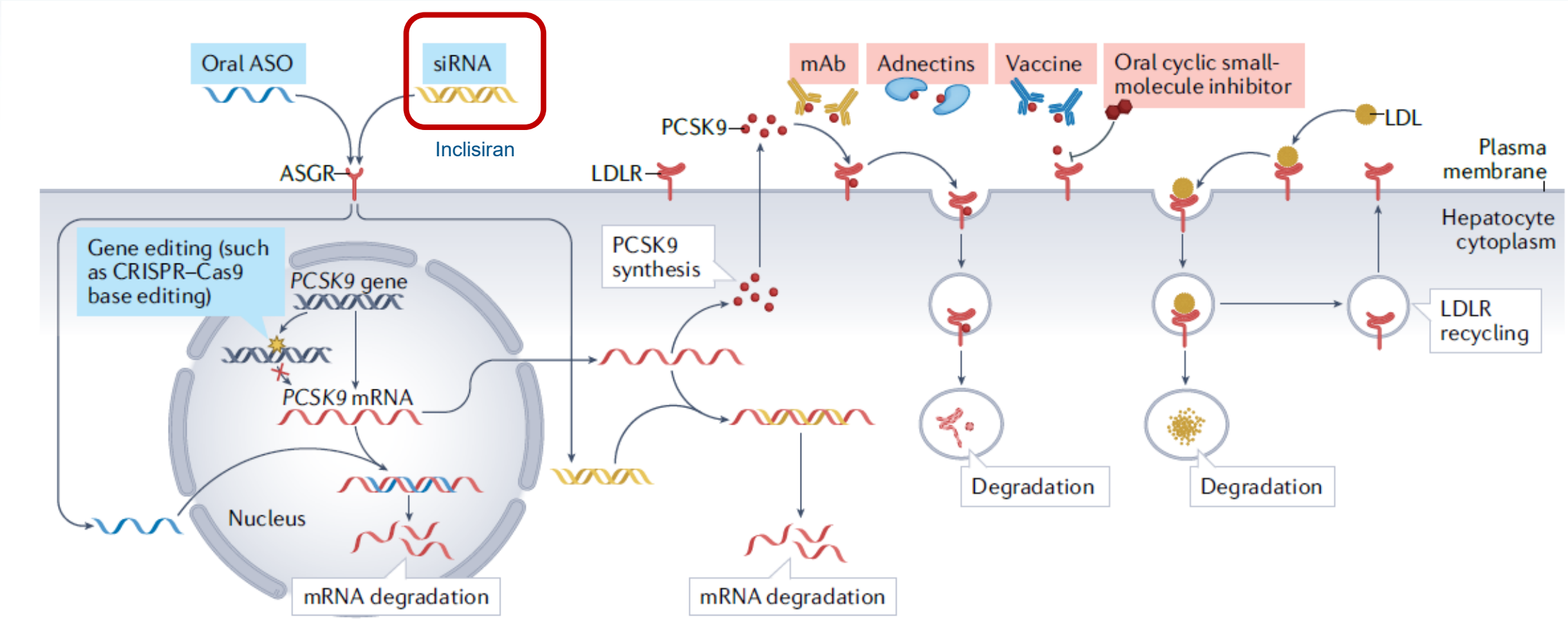
N Engl J Med. 2017;376(16):1527-39;
N Engl J Med 2018; 379:2097-2107

The LDL-C Treatment Journey…



PCSK9-targeted interventions: Inclisiran (12/21)

- Results in degradation of mRNA for PCSK9 in cytoplasm

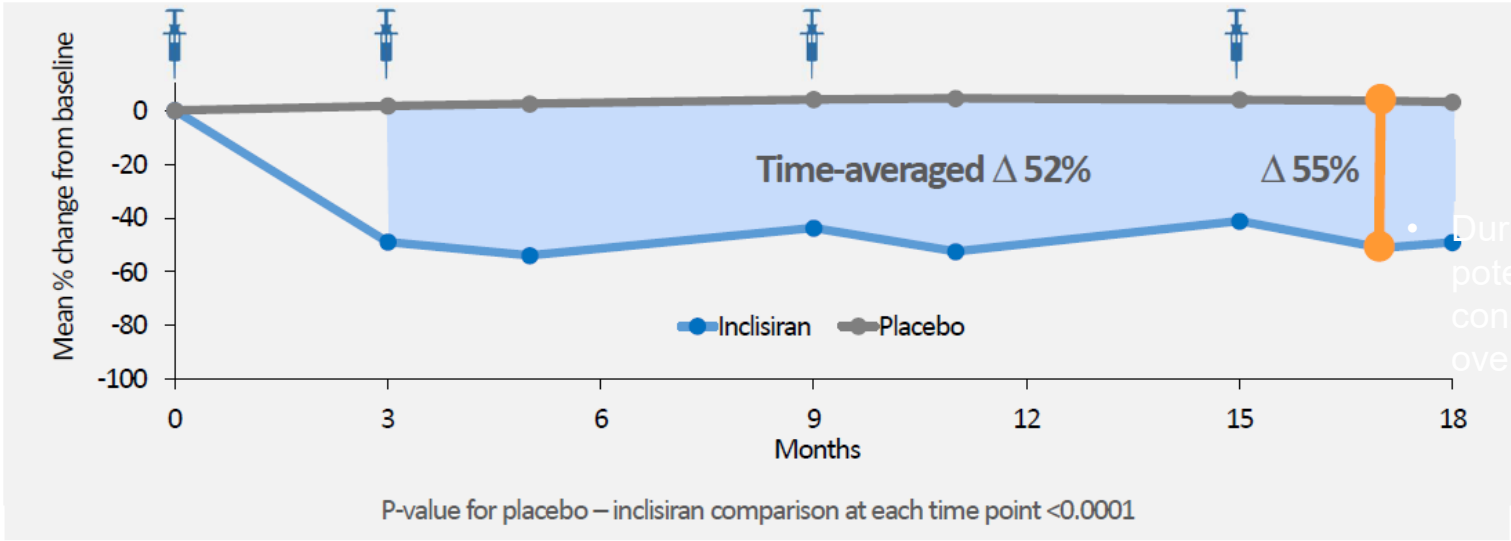


Nature Rev Cardiol.2021;18;805-6

ORION Phase III pooled analysis: Efficacy

ORION-9	ORION-10	ORION-11
HeFH[1]	ASCVD (CHD, CVD, PAD)	ASCVD (CHD, CVD, PAD)
Stable on a low-fat diet		ASCVD risk equivalents • Type 2 diabetes • 10-year risk ≥20% • HeFH[1]

- Percent change in LDL-C over time – observed values in ITT patients



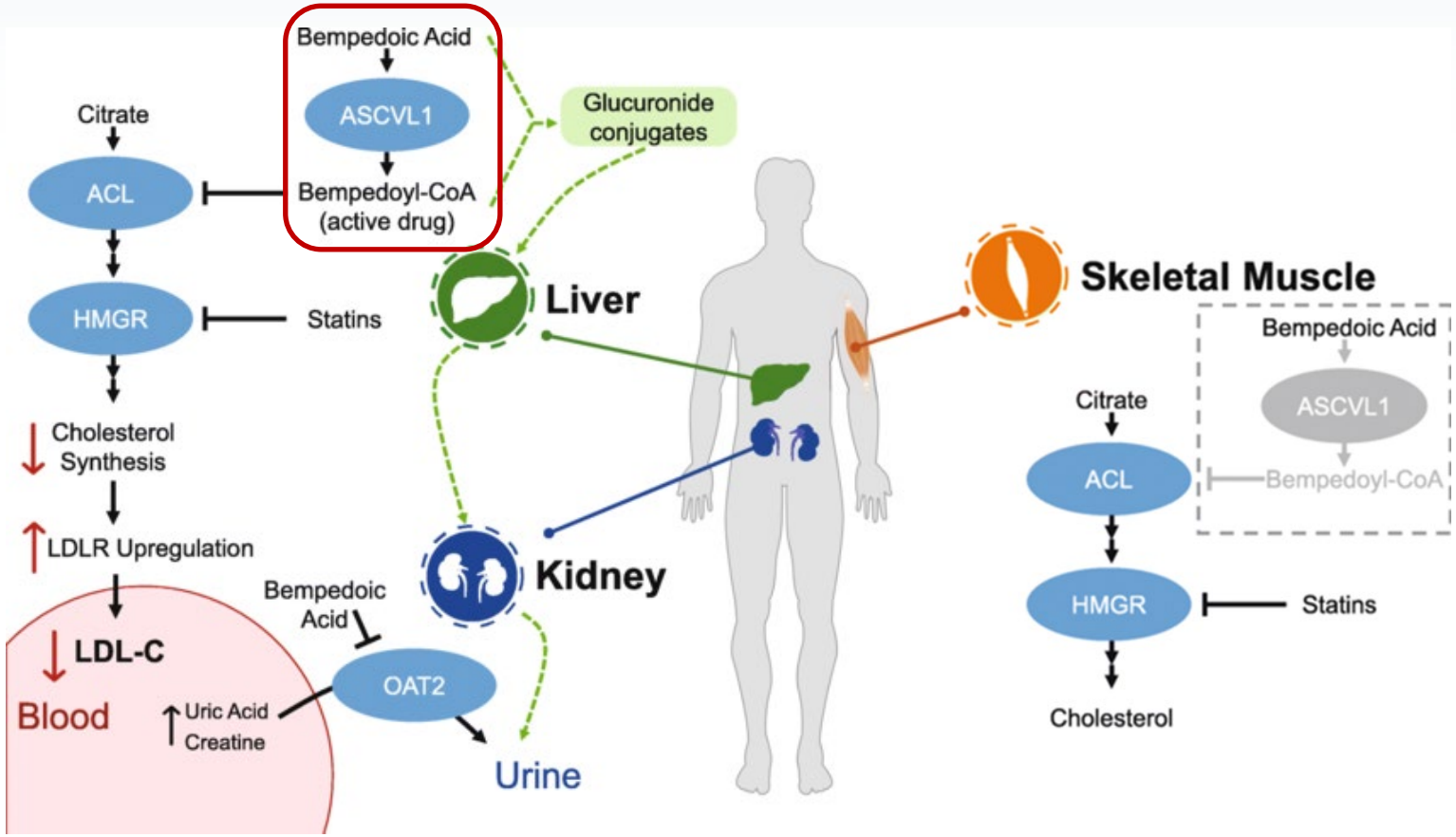
P-value for placebo – inclisiran comparison at each time point <0.0001

J Am Coll Cardiol. 2021;77:1182-93

Ongoing Inclisiran Trials

Trial	Patients	Major Inclusion Criteria	Study Outcomes
ORION-4 (NCT03705234)	N = 15,000	• High-risk ASCVD • ASCVD risk equivalent	CV outcomes trial and long-term efficacy and safety study. Median follow-up of 5 years (2026)
VICTORION-1P	N = 14,000	High-risk 1° prevention	CV outcomes trial (4/2029)
VICTORION-2P	N = 15,000	ASCVD	CV outcomes trial. Up to 72 months (2027)

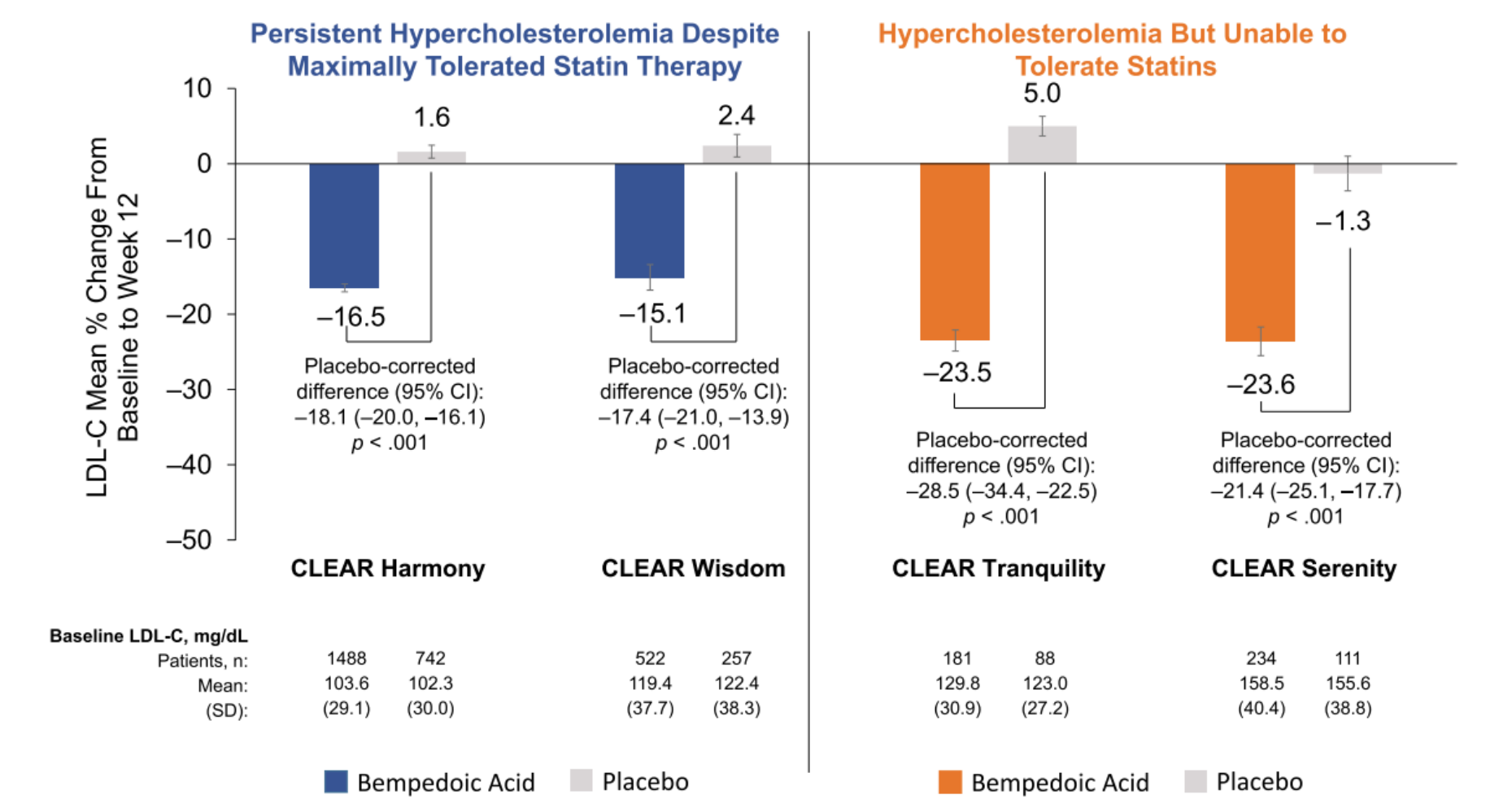
Bempedoic Acid Mechanism of Action (2/2020)



- Prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated BA acts in same cholesterol synthesis pathway as statins
  - Inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Activated bempedoic acid is ***not*** present in skeletal muscle
- LDL-C lowering
  - ~15% to 17% when added to statin
  - ~24% as monotherapy

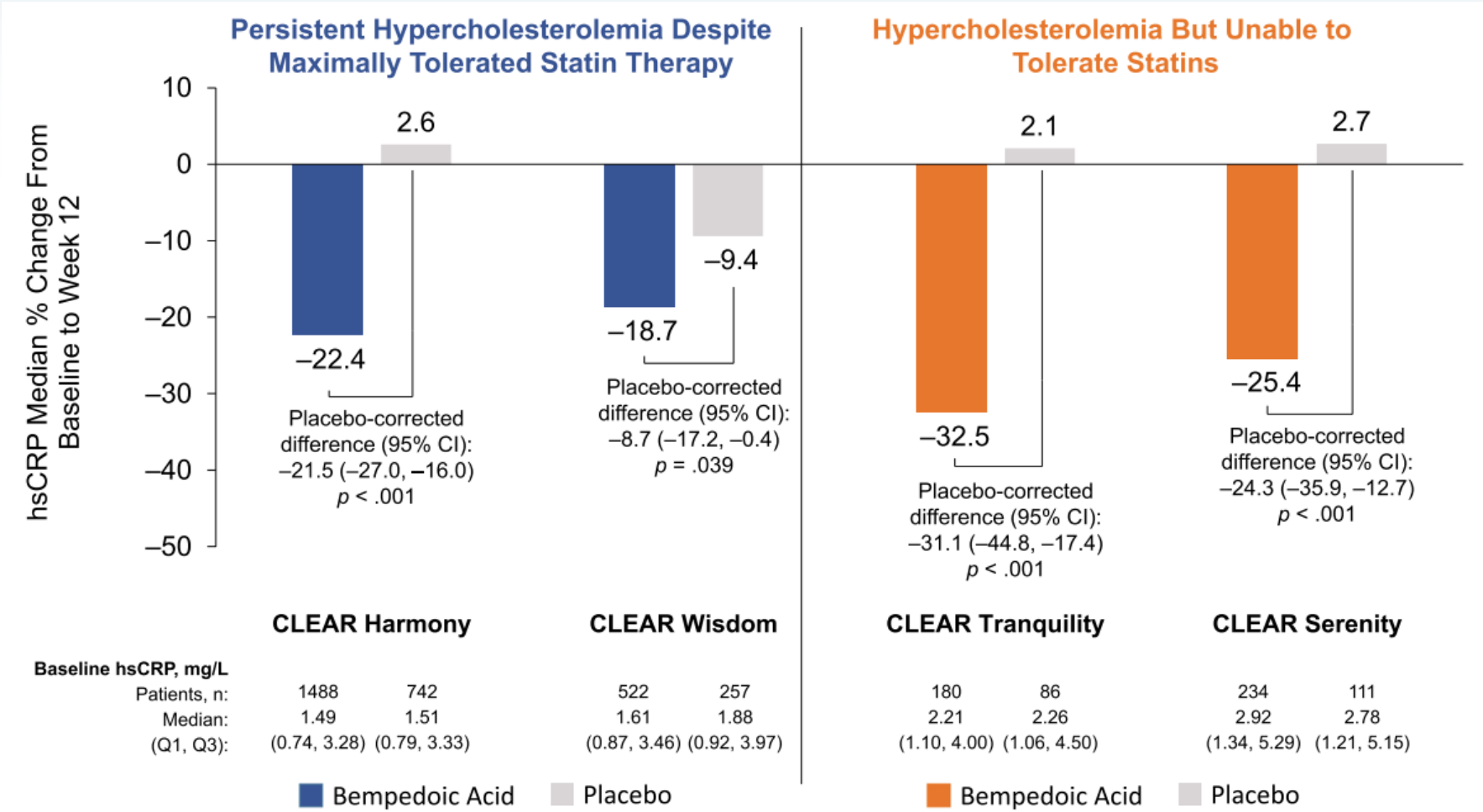
Cardiovascular Drugs and Therapy (2021) 35:853–864

Effects of BA on LDL-C at 12 weeks



Cardiovascular Drugs and Therapy (2021) 35:853–864

Effects of BA on hsCRP at 12 weeks



Cardiovascular Drugs and Therapy (2021) 35:853–864

CLEAR Outcomes

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Steven E. Nissen, M.D., A. Michael Lincoff, M.D., Danielle Brennan, M.S., Kausik K. Ray, M.D., Denise Mason, B.S.N., John J.P. Kastelein, M.D., Paul D. Thompson, M.D., Peter Libby, M.D., Leslie Cho, M.D., Jorge Plutzky, M.D., Harold E. Bays, M.D., Patrick M. Moriarty, M.D., et al., for the CLEAR Outcomes Investigators*

- Double-blind RCT of patients with statin-intolerance
  - Patients with ASCVD or at high risk for ASCVD (DM, CAC >400 AU)
- Assigned to receive oral bempedoic acid, 180 mg daily, or placebo
- Primary end point: 4-component composite of MACE
  - CV death, nonfatal MI, nonfatal stroke, or coronary revascularization

N Engl J Med 2023; 388:1353-1364

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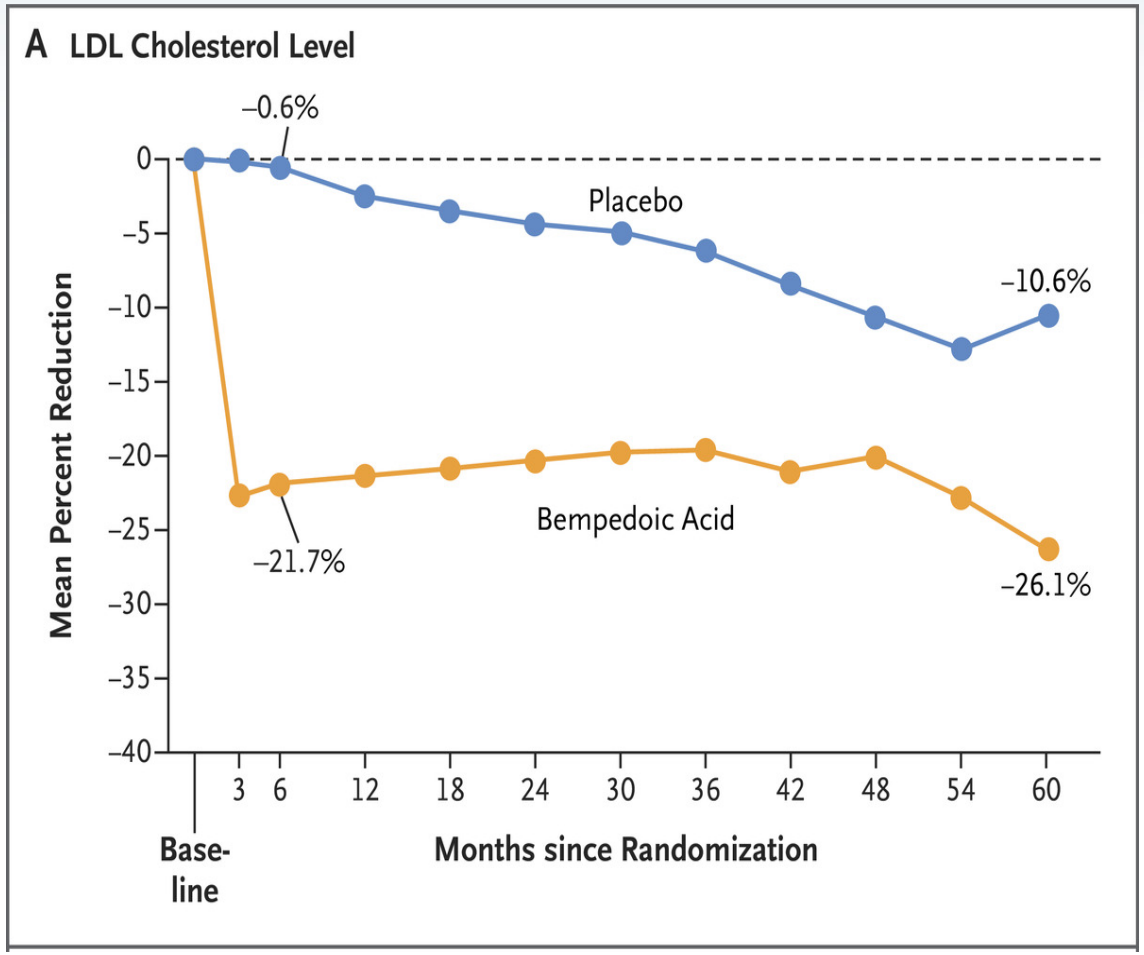
- Mean (±SD) age: 65.5 ± 9.0 years
- Female: 6740 patients (48.2%)
- Diabetes: 6373 (45.6%)
- Previous ASCVD: 9764 (69.9%)
- Statin therapy: 3174 (22.7%)
- Ezetimibe: 1612 (11.5%)

- Mean LDL-C: 3.59 mmol/L (139.0 mg/dL)
- Mean HDL-C: 1.28 mmol/L (49.5 mg/dL)
  Median TG: 1.8 mmol/L (159.0 mg/dL)
- Median hsCRP: 2.3 mg/L

N Engl J Med 2023; 388:1353-1364

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients: CLEAR Outcomes

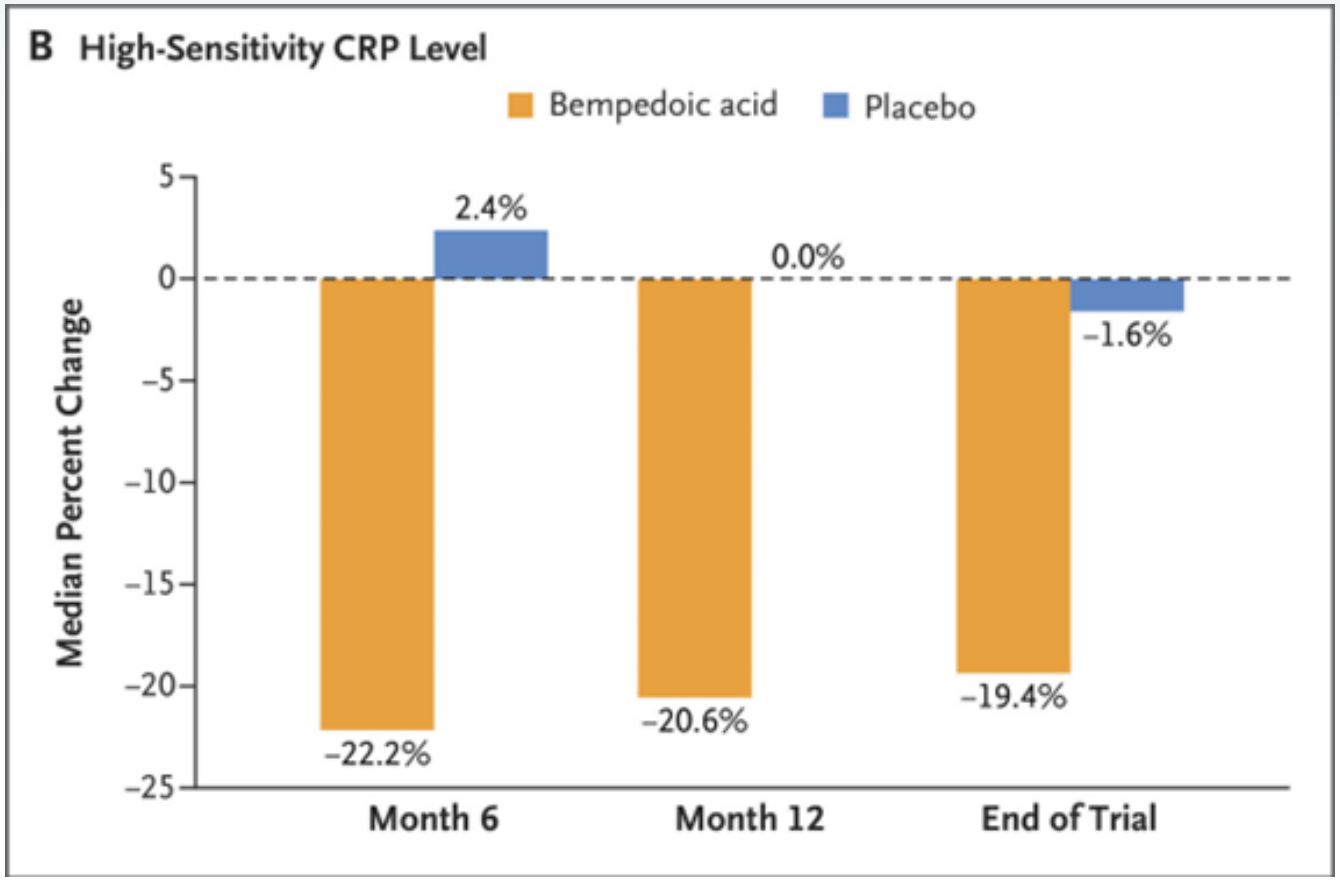


- Time-averaged difference in reduction in LDL-C between BA group and placebo group over duration of the trial was 22.0 mg/dL (0.57 mmol per liter)
- Difference in % reduction was 15.9 percentage points in favor of BA

N Engl J Med 2023; 388:1353-1364

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients: CLEAR Outcomes

- % change in median hsCRP level was −21.6% (95% CI, −23.7 to −19.6) in favor of BA



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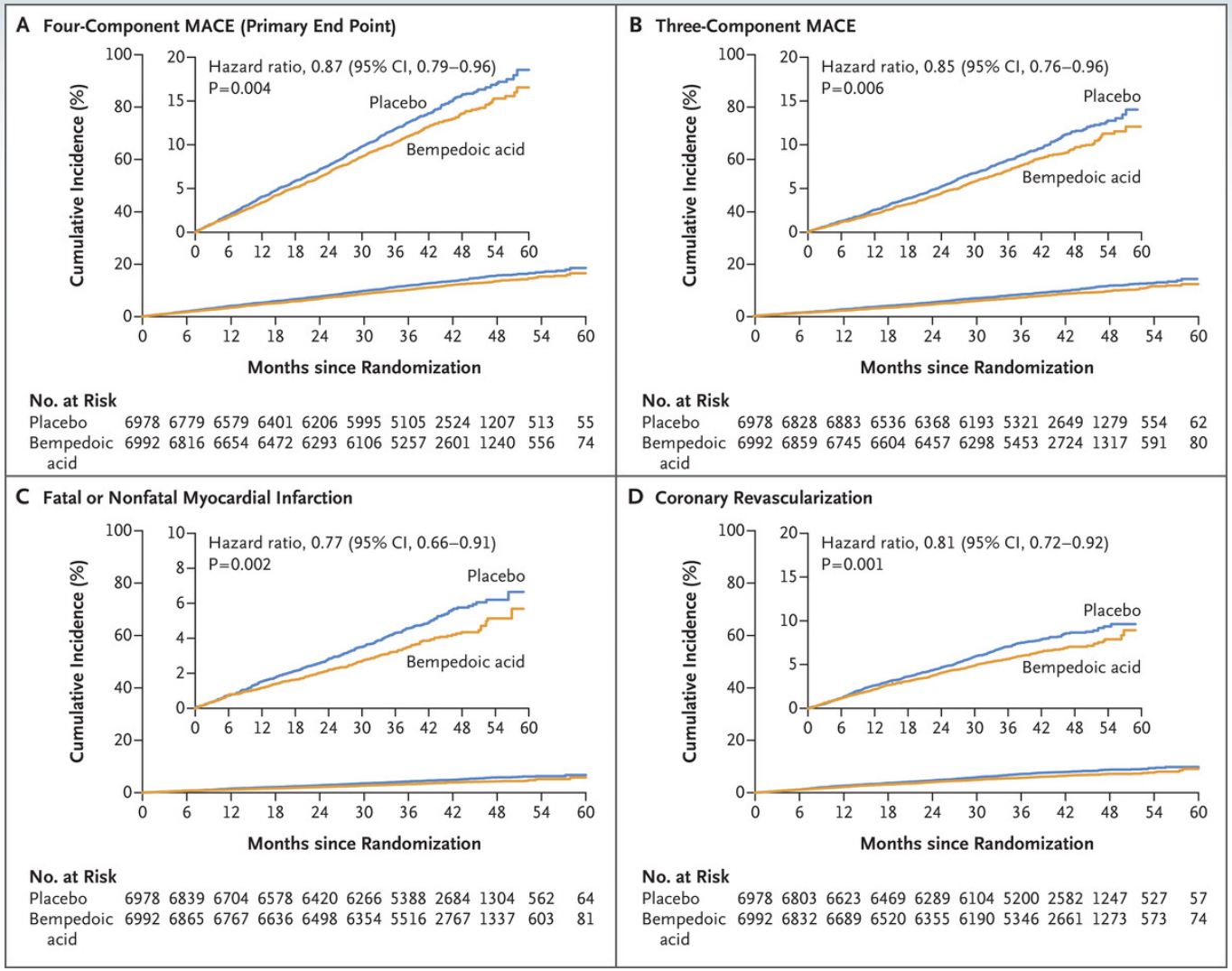
Cumulative Incidence of CV Events



- BA associated with lower risk of 4-component MACE (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization), 3-component MACE, fatal or nonfatal MI, and coronary revascularization
- Fatal or nonfatal stroke, CV death, and death from any cause did not differ significantly between BA group and placebo group

N Engl J Med 2023; 388:1353-1364

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients: CLEAR Outcomes

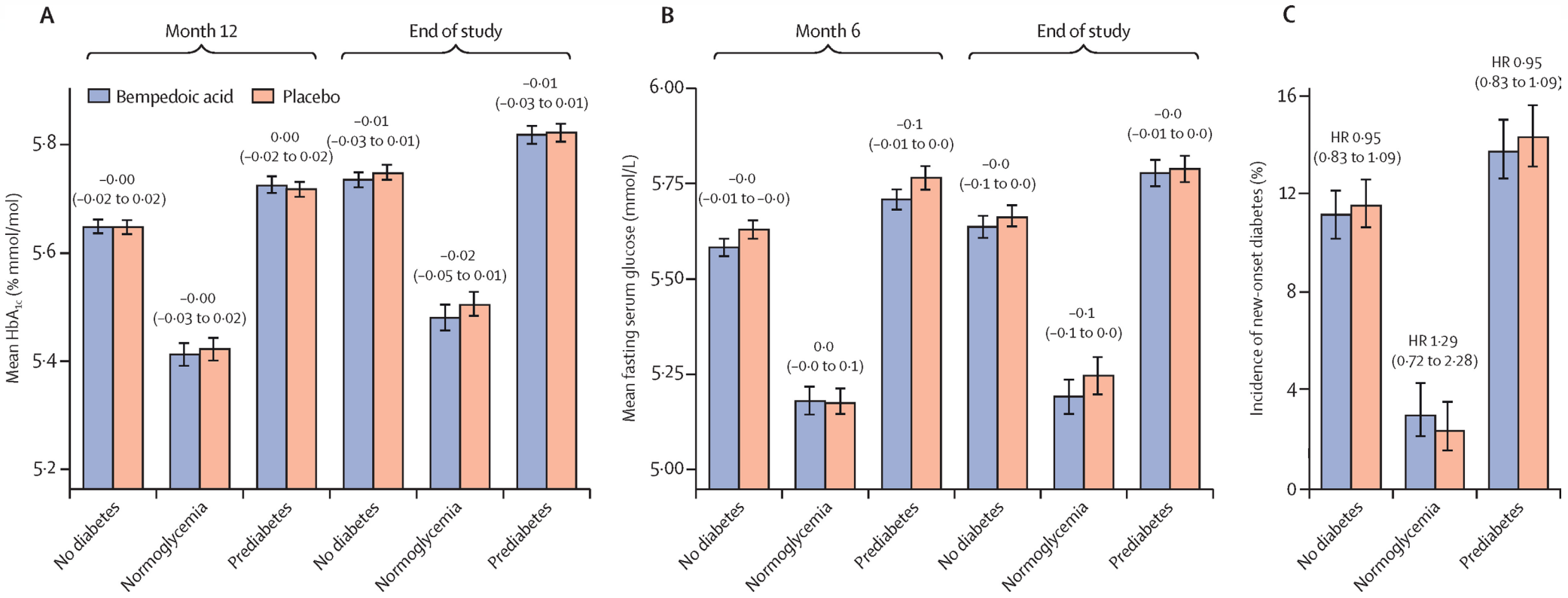
- Overall, prespecified adverse events similar in both trial groups
  - Except for
    - Elevations in hepatic-enzyme levels: 4.5% in BA group vs. 3.0% in placebo group
    - Renal events: 11.5% in BA group vs. 8.6% in placebo group
    - Hyperuricemia: 10.9% BA group vs. 5.6% placebo group
      - Incidence of gout (3.1% vs. 2.1%)
    - Cholelithiasis: 22% BA group vs. 1.2% placebo group

  - Myalgias: 5.6% BA group vs. 6.8% placebo group
    - Rhabdomyolysis in 8 patients (0.06%)
      - One in each trial group met diagnostic criteria for rhabdomyolysis

N Engl J Med 2023; 388:1353-1364

CLEAR Outcomes: Risk of new onset DM, glycemic control

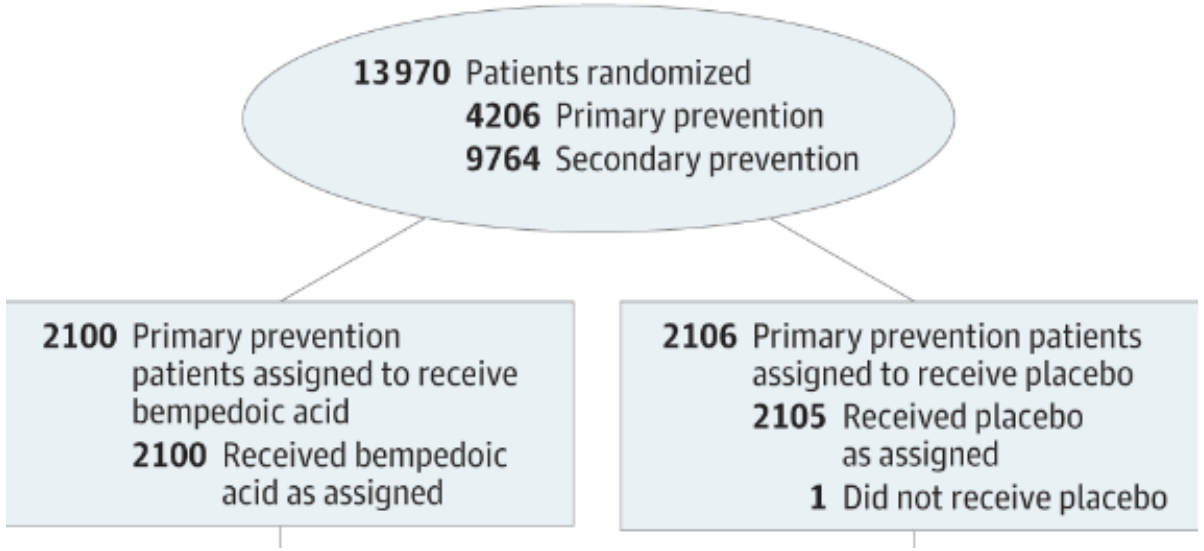
- Patients with DM had significant relative and absolute reductions in MACE-4 endpoints with BA compared to placebo (HR 0·83; 95% CI 0·72–0·95; absolute risk reduction of 2·4%)
- No evidence of effect modification across glycemic strata (interaction p=0·42)
- New-onset DM similar between BA and placebo groups



Lancet Diabetes Endocrinol. 2024; 12: 19–28

Bempedoic acid for primary prevention of CV events in statin intolerant patients: CLEAR Outcomes

- Among 13,970 patients enrolled, 4206 (30%) were high risk of CV outcomes but without prior event
- Prespecified subgroup analysis of effects of BA on MACE in primary prevention population



JAMA. 2023;330(2):131-140

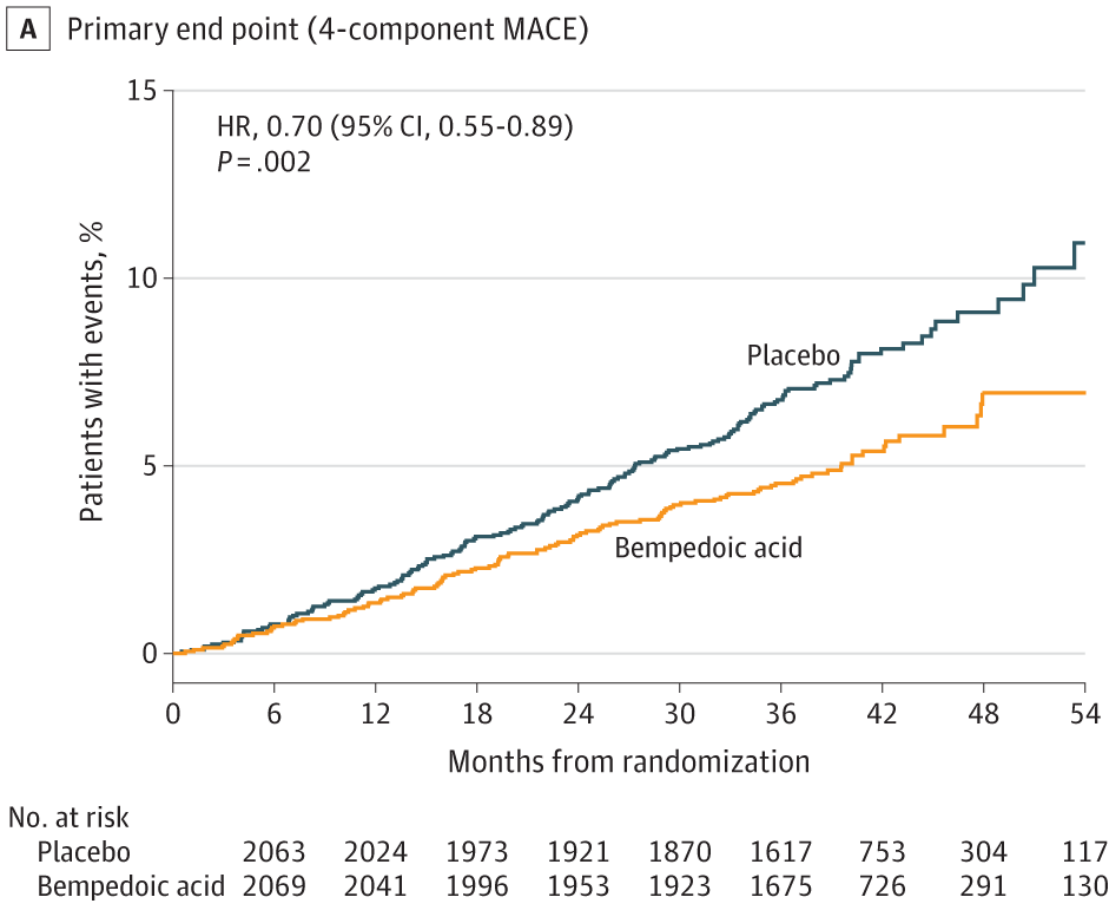
Bempedoic acid for primary prevention of CV events in statin intolerant patients: CLEAR Outcomes

Effects on lipids and inflammatory biomarkers

	Bempedoic acid			Placebo			Bempedoic acid vs placebo after 6 mo of treatment	
	Observed mean (SD) or median (IQR)			Observed mean (SD) or median (IQR)				
End point	Baseline	6 mo	Change, baseline to 6 mo (95% CI)[a]	Baseline	6 mo	Change, baseline to 6 mo (95% CI)[a]	Difference (95% CI)[a]	Difference, % (95% CI)[a]
Lipids, mg/dL								
Total cholesterol	228.5 (40.2)	191.1 (43.5)	−37.3 (−38.9 to −35.8)	229.1 (42.3)	225.2 (48.0)	−3.4 (−5.0 to −1.9)	−33.9 (−36.1 to −31.7)	−14.8 (−15.7 to −13.8)
HDL-C	51.1 (13.5)	47.6 (14.7)	−3.4 (−3.8 to −3.0)	50.9 (13.7)	50.9 (14.1)	−0.05 (−0.4 to 0.3)	−3.35 (−3.87 to −2.82)	−6.9 (−7.9 to −5.9)
LDL-C	142.2 (34.5)	108.2 (36.4)	−34.0 (−35.3 to −32.6)	142.7 (35.9)	138.6 (41.1)	−3.8 (−5.1 to −2.4)	−30.2 (−32.1 to −28.3)	−21.3 (−22.7 to −19.9)
Non-HDL-C	177.4 (38.7)	143.5 (41.8)	−34.0 (−35.5 to −32.5)	178.2 (41.2)	174.4 (46.6)	−3.4 (−4.8 to −1.9)	−30.6 (−32.7 to −28.5)	−17.3 (−18.5 to −16.1)
Triglycerides	162.0 (120.5 to 216.5)	156.0 (111.0 to 219.0)	−6.0 (−9.0 to −3.0)	161.5 (123.5 to 215.5)	160.0 (117.0 to 217.0)	−2.0 (−3.5 to 0.5)	−4.25 (−7.5 to −1.0)	−3.2 (−5.1 to −1.3)
	Baseline	12 mo	Change, baseline to 12 mo (95% CI)[b]	Baseline	12 mo	Change, baseline to 12 mo (95% CI)[b]	After 12 mo of treatment	After 12 mo of treatment
hsCRP, mg/L	2.39 (1.2 to 4.5)	1.75 (0.87 to 3.49)	−0.34 (−0.42 to −0.29)	2.44 (1.2 to 4.6)	2.52 (1.2 to 5.0)	0.01 (−0.04 to 0.09)	−0.56 (−0.68 to −0.44)	−21.5 (−25.4 to −17.6)

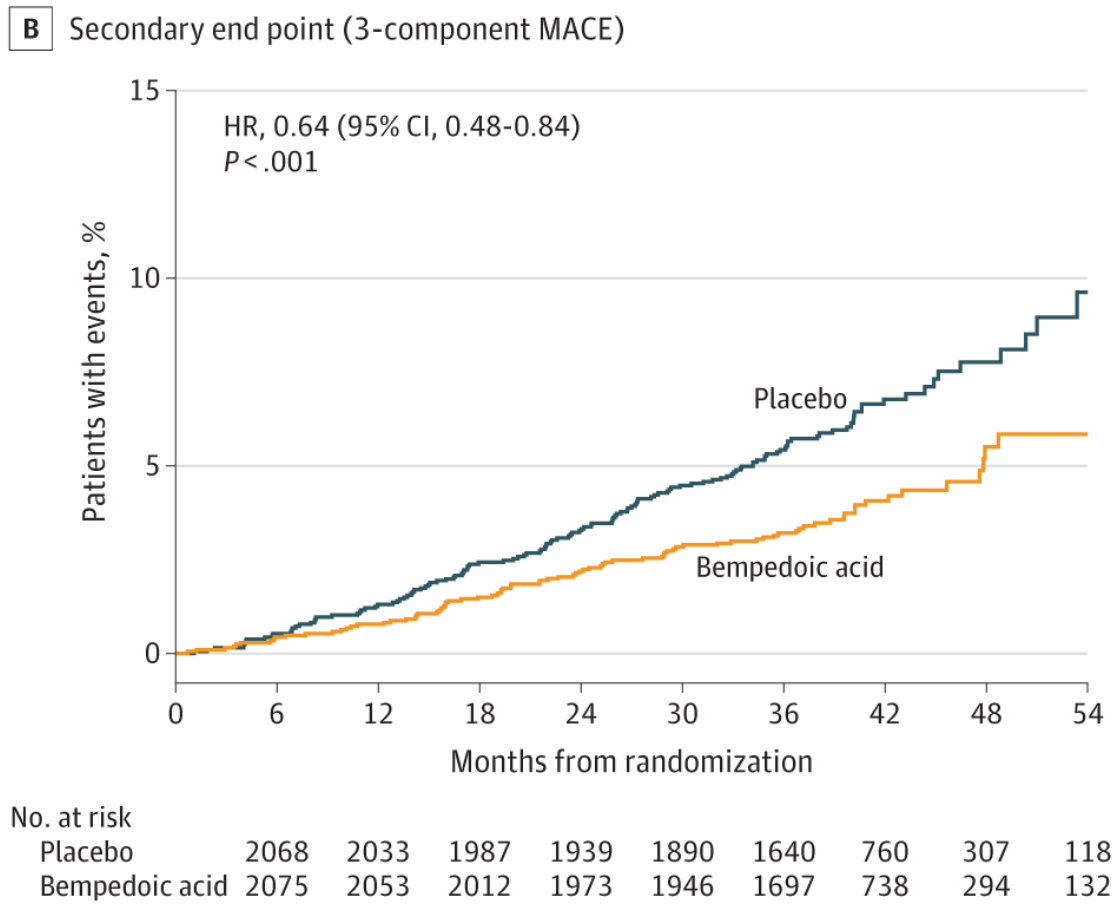
JAMA. 2023;330(2):131-140

Bempedoic acid for primary prevention of CV events in statin intolerant patients: CLEAR Outcomes



No. at risk

Placebo	2063	2024	1973	1921	1870	1617	753	304	117
Bempedoic acid	2069	2041	1996	1953	1923	1675	726	291	130

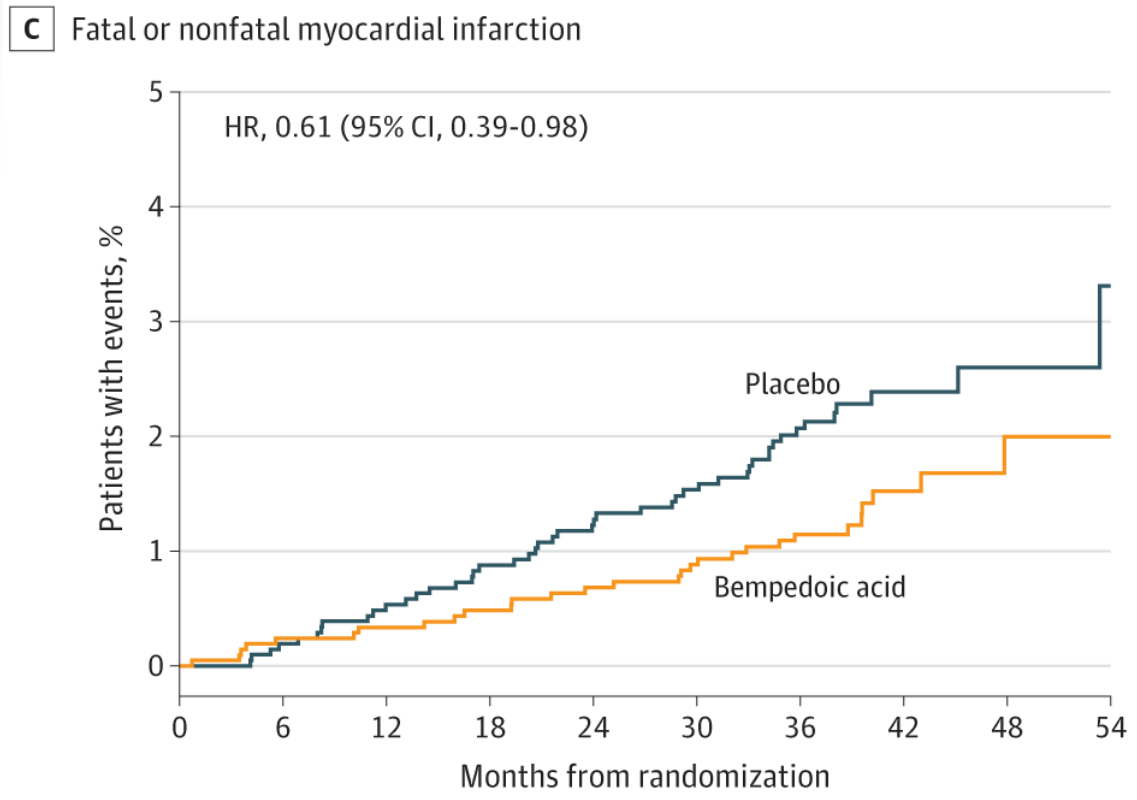


No. at risk

Placebo	2068	2033	1987	1939	1890	1640	760	307	118
Bempedoic acid	2075	2053	2012	1973	1946	1697	738	294	132

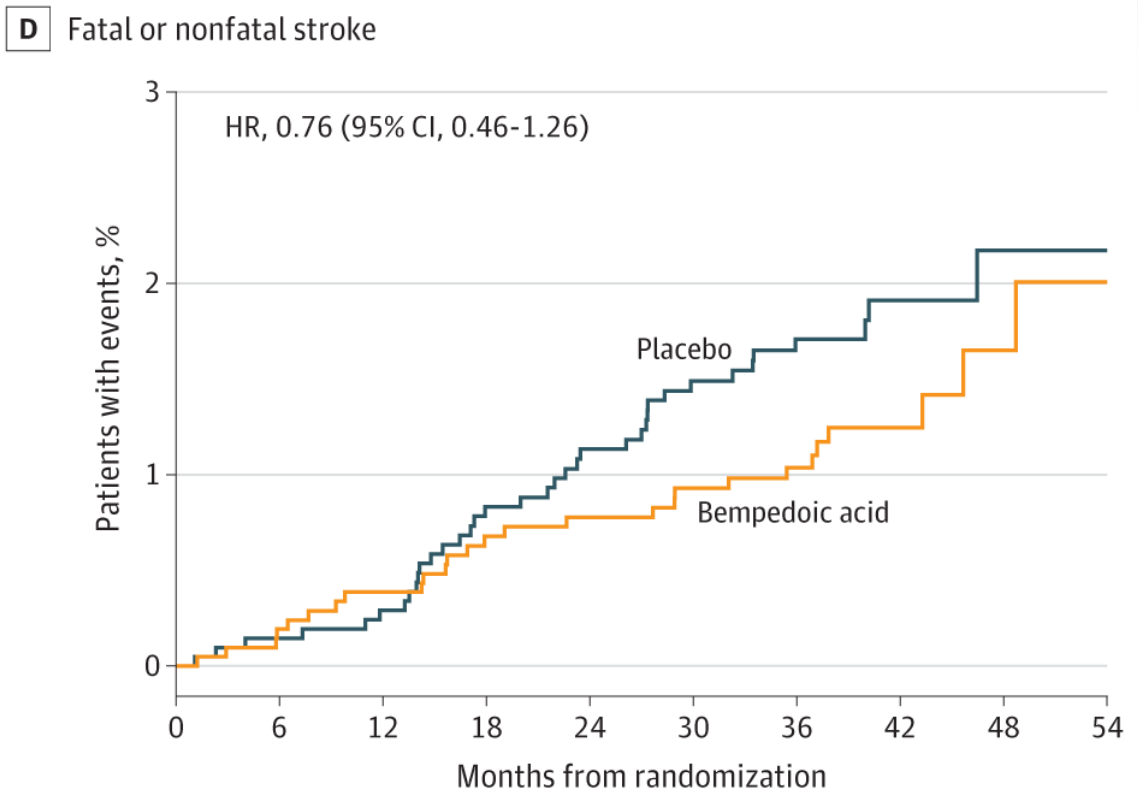
JAMA. 2023;330(2):131-140

Bempedoic acid for primary prevention of CV events in statin intolerant patients: CLEAR Outcomes



No. at risk

Placebo	2069	2037	2000	1955	1913	1661	769	311	119
Bempedoic acid	2079	2059	2022	1984	1959	1709	747	295	133

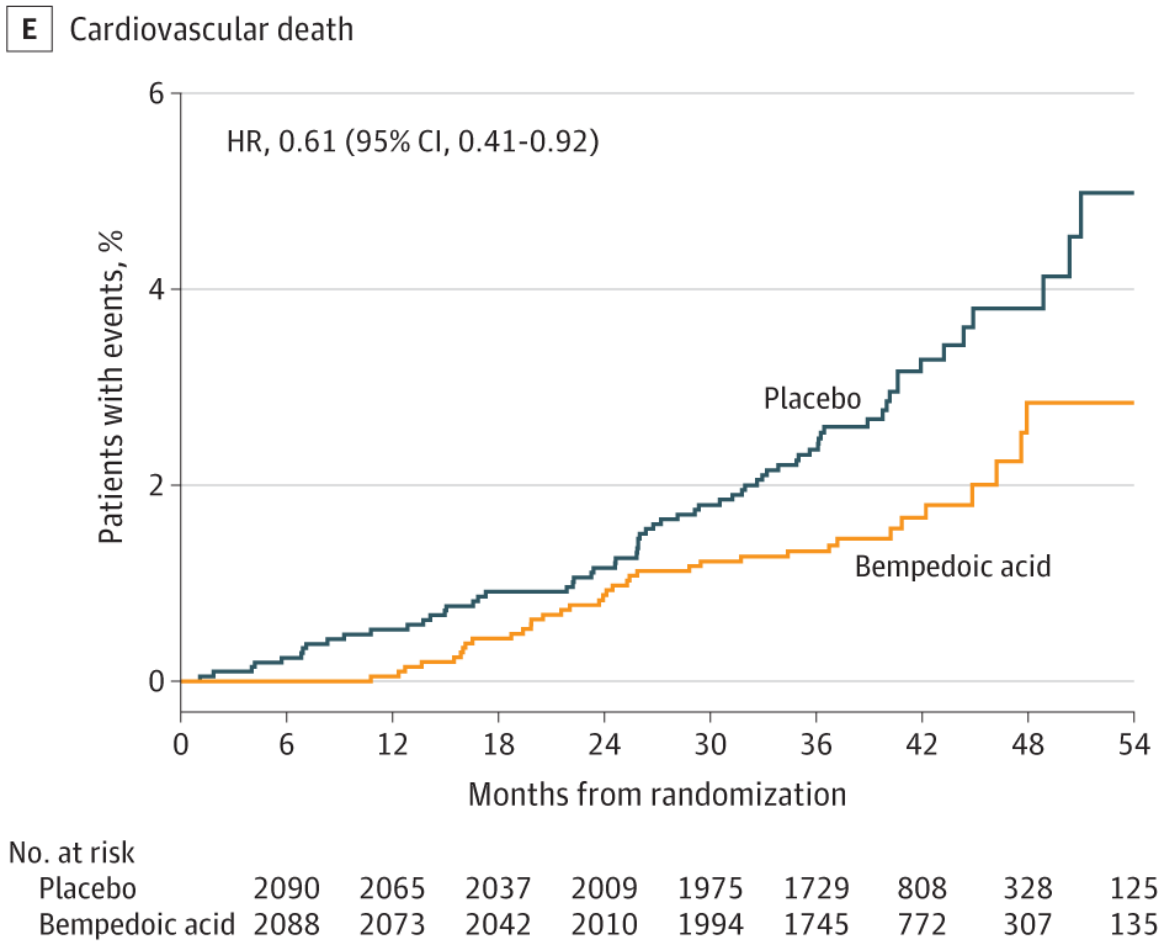


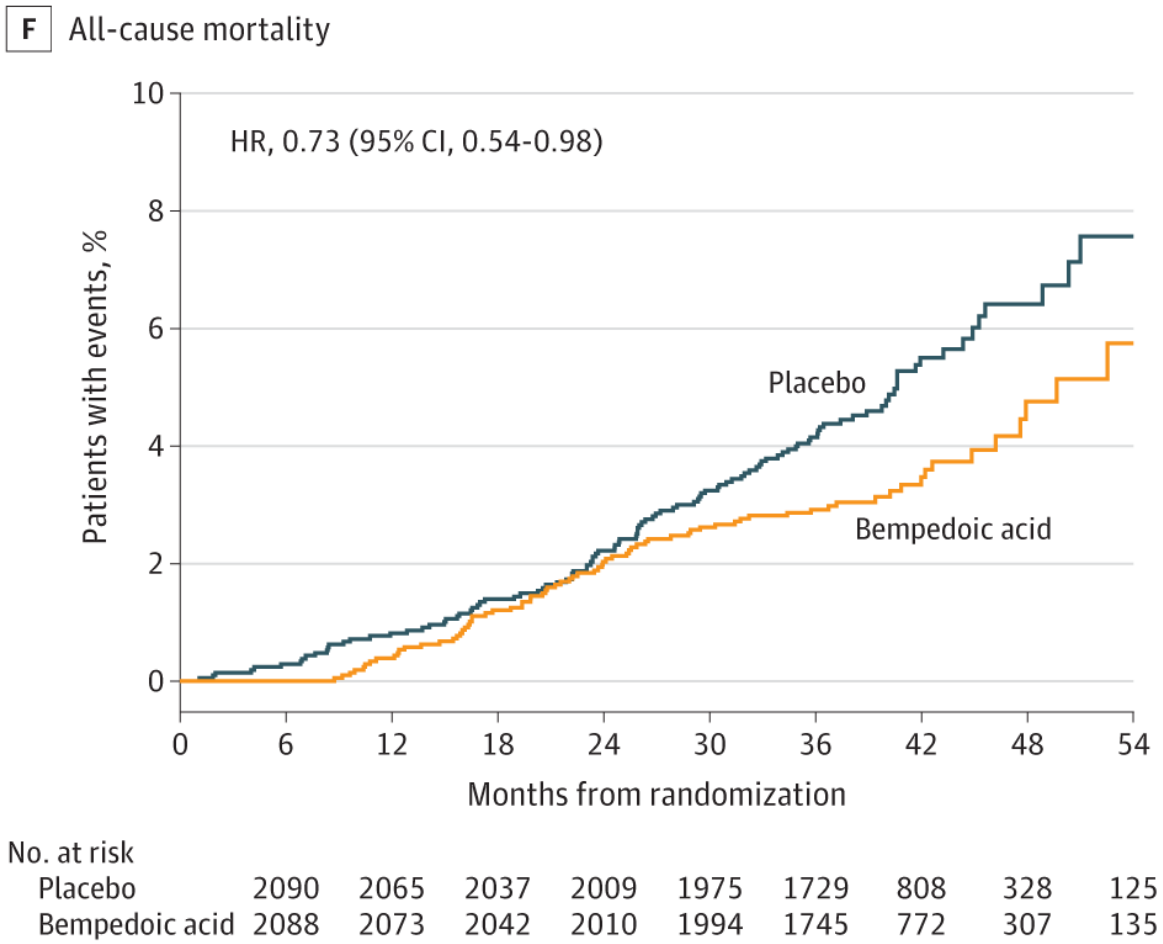
No. at risk

Placebo	2071	2042	2002	1959	1913	1664	777	315	122
Bempedoic acid	2080	2058	2019	1983	1959	1710	751	301	133

JAMA. 2023;330(2):131-140

Bempedoic acid for primary prevention of CV events in statin intolerant patients: CLEAR Outcomes





JAMA. 2023;330(2):131-140

Bempedoic acid for primary prevention of CV events in statin intolerant patients: CLEAR Outcomes

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

4206 Patients randomized

2100
Bempedoic acid
180-mg oral dose administered daily

2106
Placebo
Matching placebo

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

JAMA. 2023;330(2):131-140

Total Cardiovascular Events: CLEAR Outcomes

JAMA Cardiology | Original Investigation

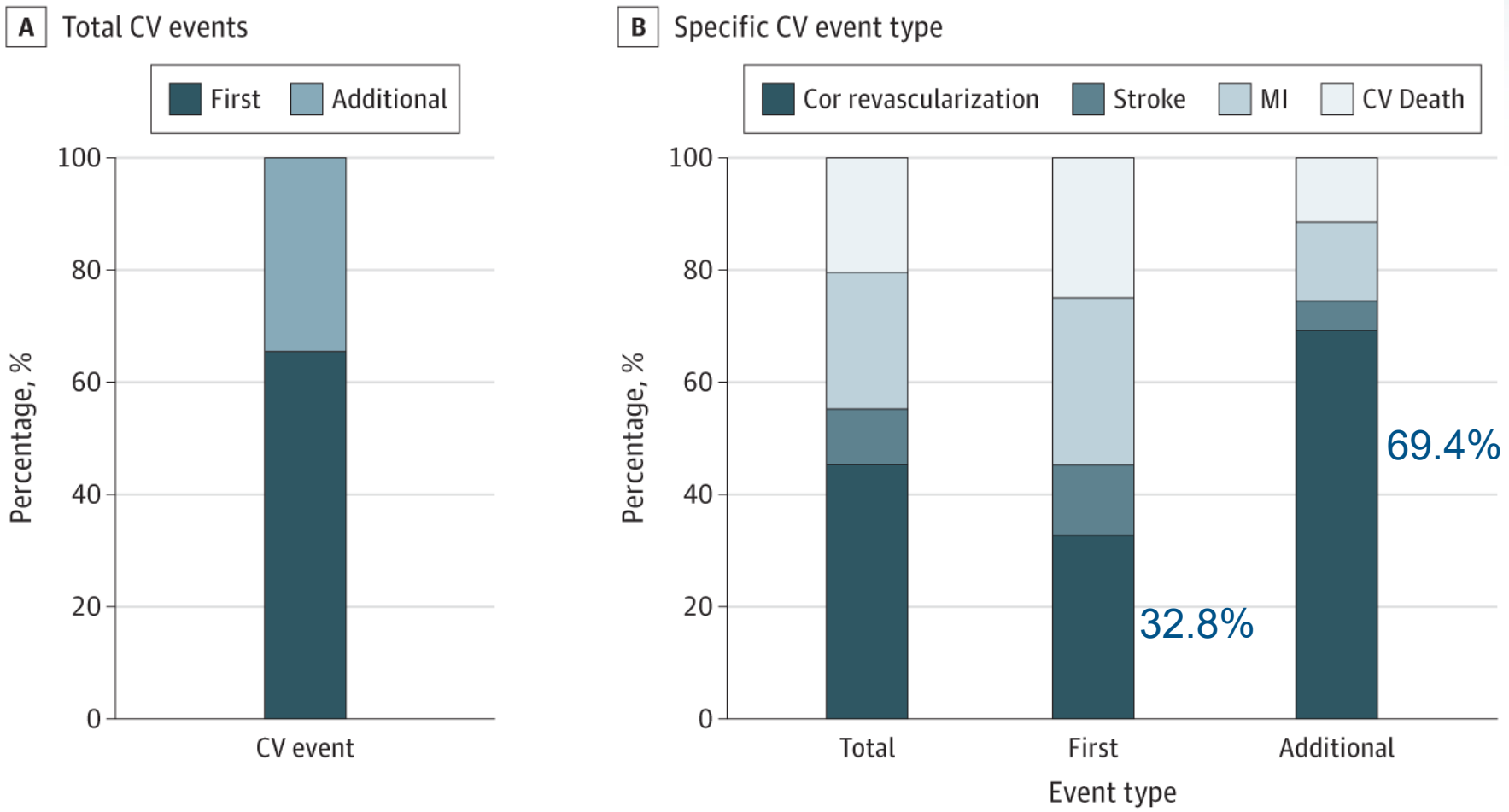
Impact of Bempedoic Acid on Total Cardiovascular Events
A Prespecified Analysis of the CLEAR Outcomes Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Adam J. Nelson, MBBS, PhD; A. Michael Lincoff, MD; Danielle Brennan, MS; Kausik K. Ray, MD, MPhil; Leslie Cho, MD; Venu Menon, MD; Na Li, PhD; LeAnne Bloedon, MS; Steven E. Nissen, MD

JAMA Cardiol. 2024;9(3):245-253

Total Cardiovascular Events: CLEAR Outcomes

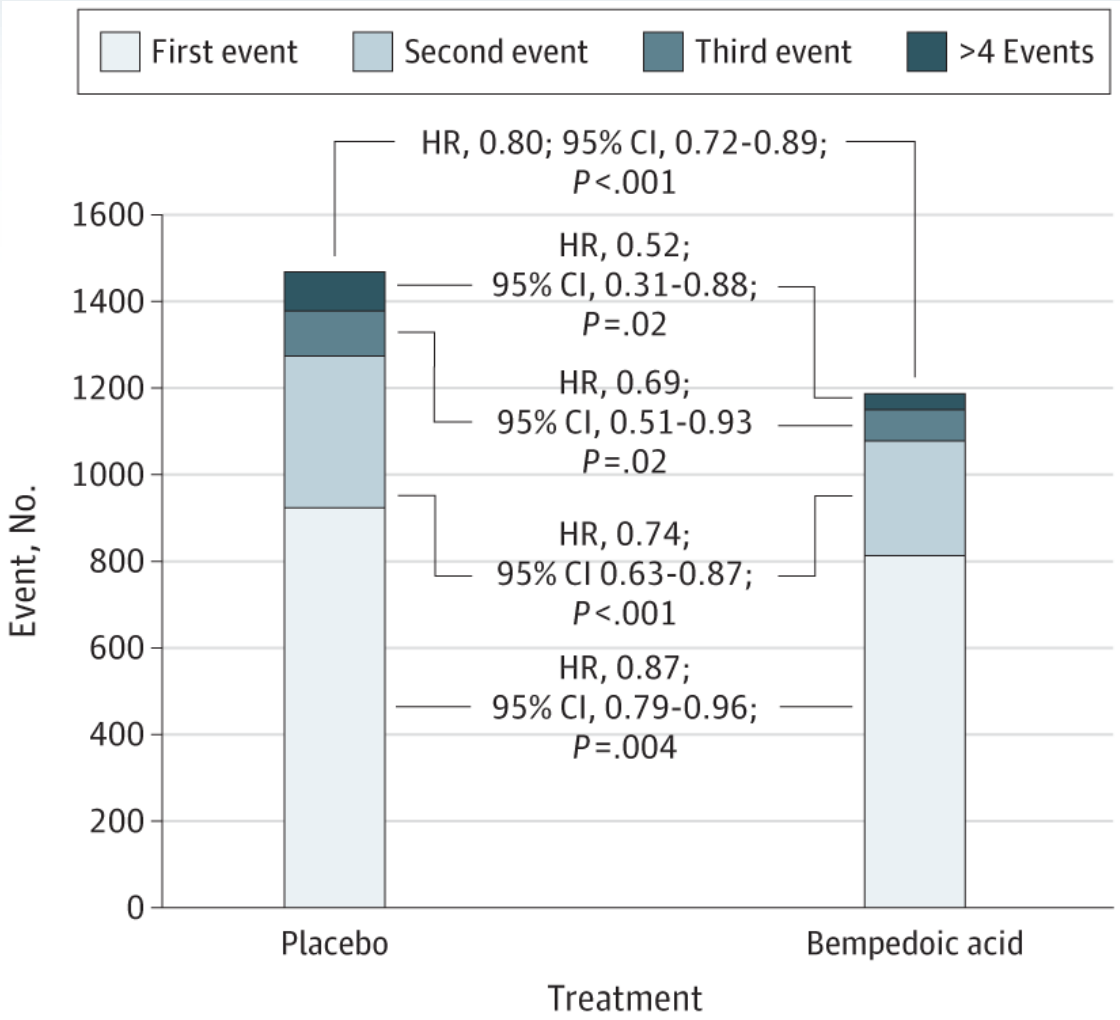
- Total of 1746 first MACE-4 events
- 915 additional MACE events in 612 patients
- Coronary revascularization represented 32.8% (573 of 1746) of first events and 69.4% (635 of 915) of additional events



JAMA Cardiol. 2024;9(3):245-253

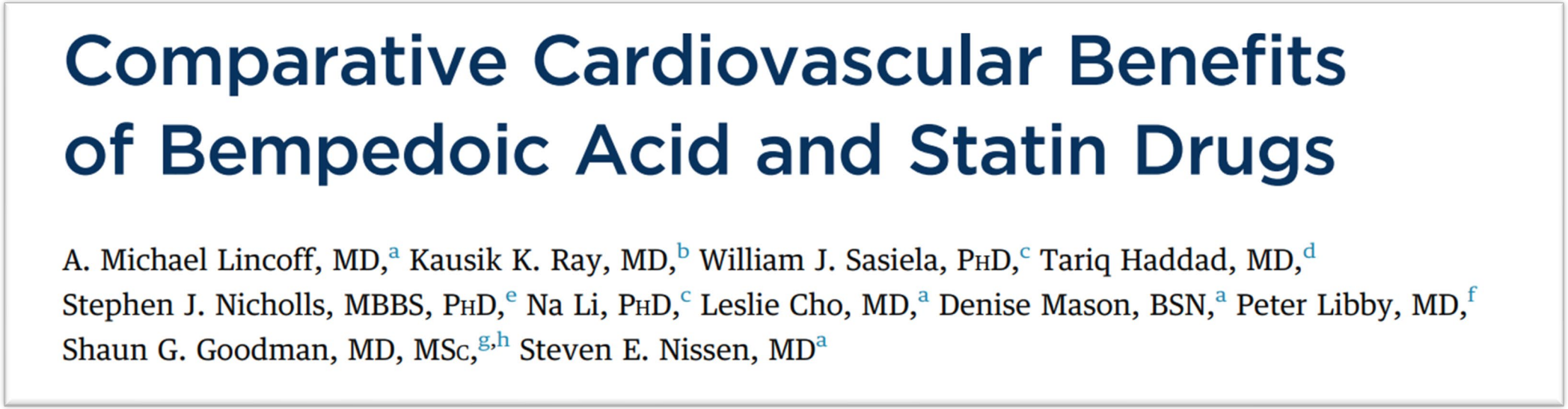
Impact of BA on total CV events: CLEAR Outcomes

- Lowering LDL-C level with BA reduced total number of CV events in patients with high CV risk, statin intolerance, and elevated LDL-C levels.



JAMA Cardiol. 2024;9(3):245-253

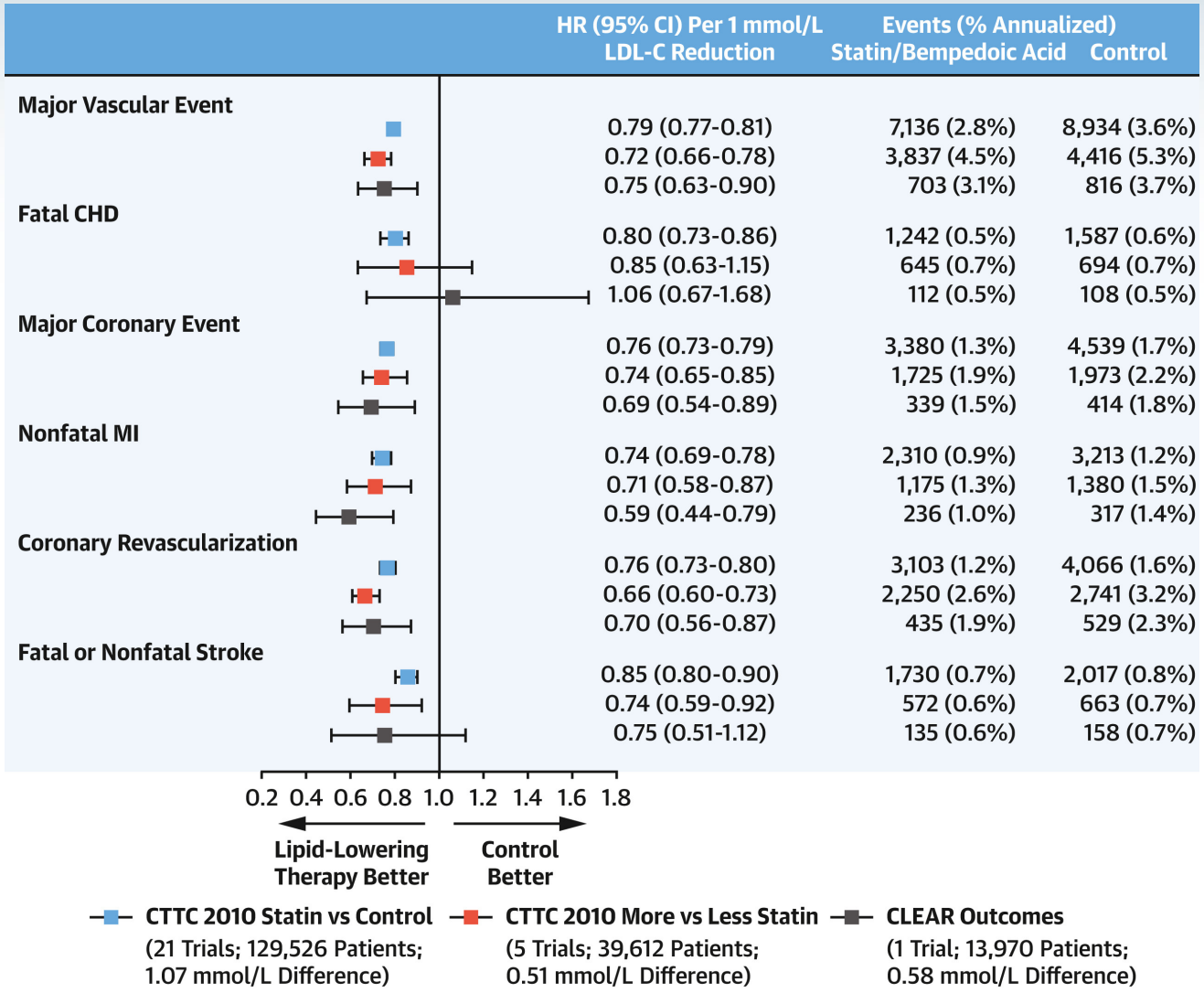
Comparative Cardiovascular Benefits of Bempedoic Acid and Statin Drugs



J Am Coll Cardiol 2024;84:152–162

Comparative Cardiovascular Benefits of Bempedoic Acid and Statin Drugs

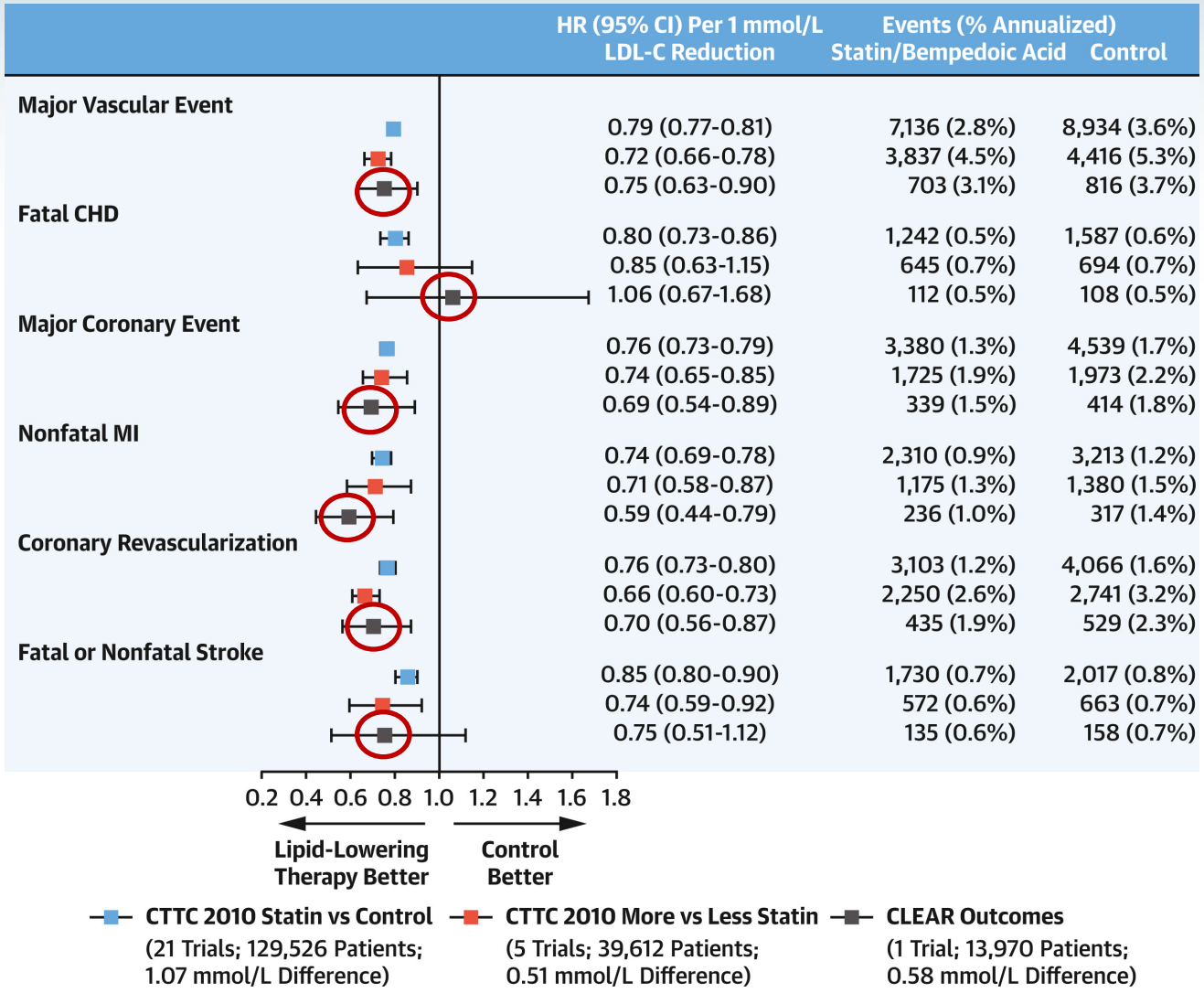
- Compare treatment effect of BA with statins
- Methodology of CTTC to outcomes among 13,970 CLEAR Outcomes trial patients
- CTTC endpoint: “major vascular event” was composite of CHD death, nonfatal MI, nonfatal stroke, or coronary revascularization
- HRs for CTTC-defined endpoints were normalized to 1 mmol/L differences in LDL-C levels between BA and placebo groups
- Every 1 mmol/L (38.7 mg/dL) reduction in LDL-C over 1 year was associated with 22% reduction in major vascular events



J Am Coll Cardiol 2024;84:152–162

Comparative Cardiovascular Benefits of Bempedoic Acid and Statin Drugs

- Normalized risk reductions were similar for BA and statins for endpoints of major vascular events, major coronary events, nonfatal myocardial infarction, and coronary revascularization.

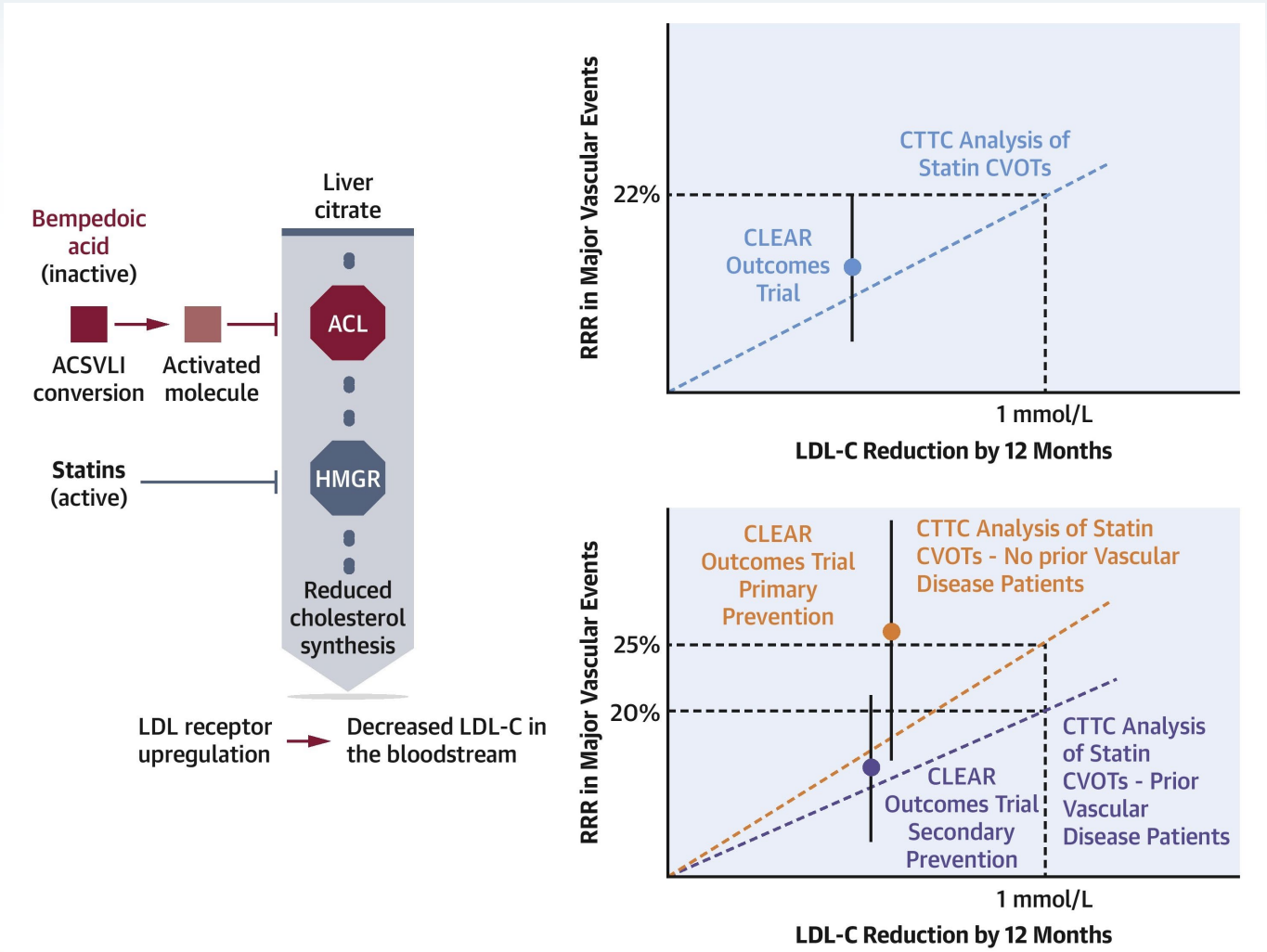


J Am Coll Cardiol 2024;84:152–162

Comparative Cardiovascular Benefits of Bempedoic Acid and Statin Drugs

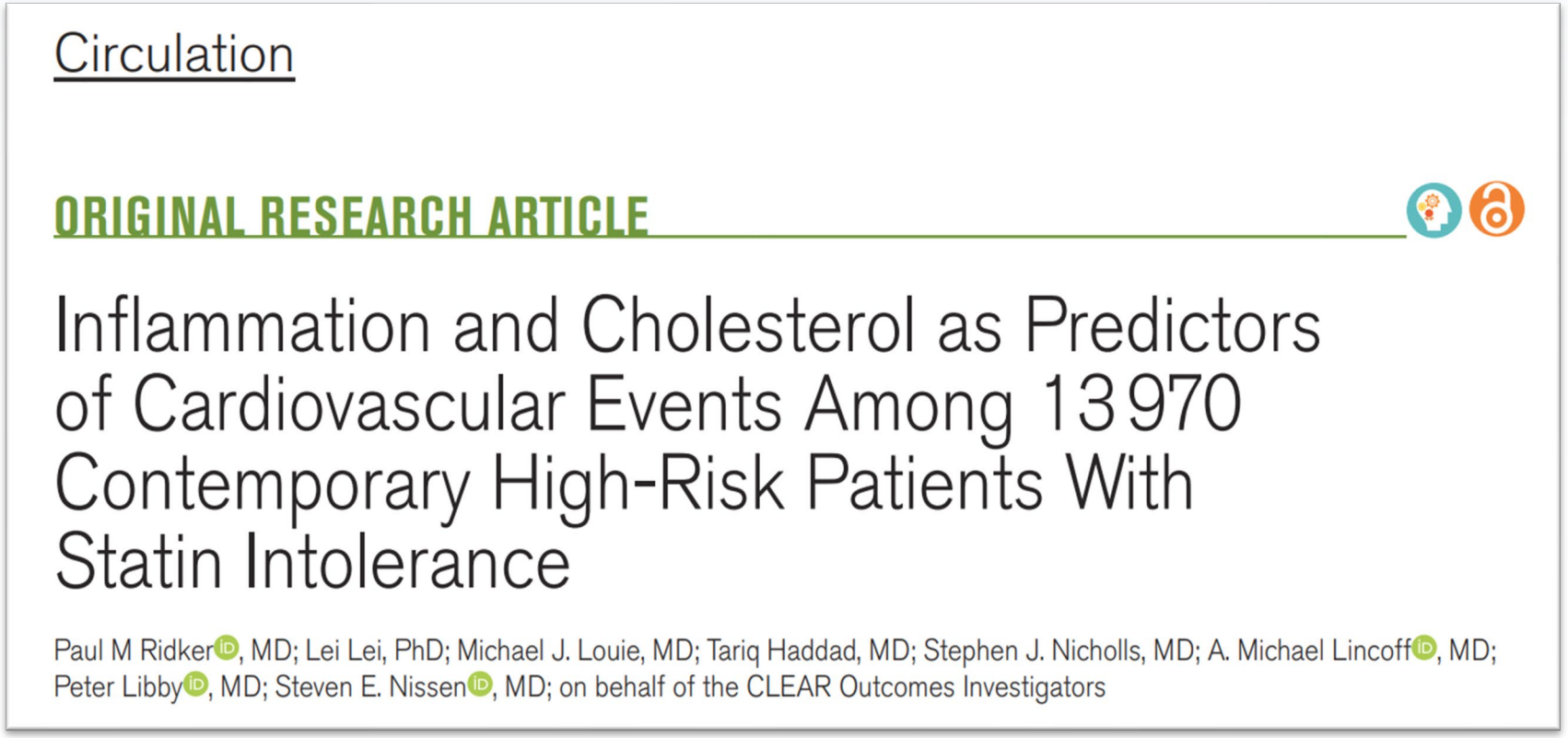
- Current analysis using methodology of the CTTC to show that extent of clinical event reduction with BA is similar to that achieved with statins for a given magnitude of LDL-C lowering

Reduction in Vascular Events by BA compared with statins



J Am Coll Cardiol 2024;84:152–162

Inflammation and cholesterol as predictors of CV Risk: CLEAR Outcomes



Circulation

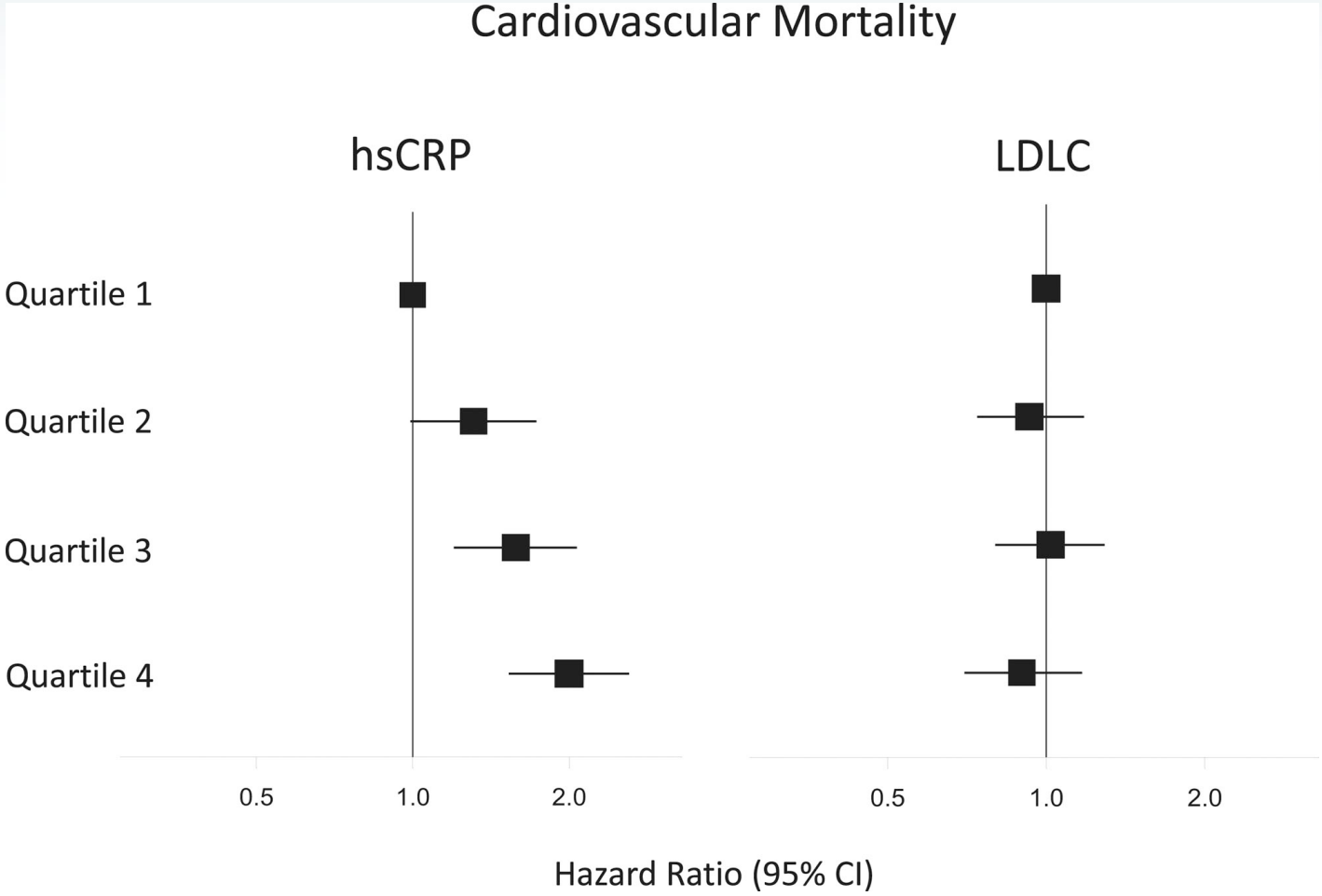
ORIGINAL RESEARCH ARTICLE

Inflammation and Cholesterol as Predictors of Cardiovascular Events Among 13 970 Contemporary High-Risk Patients With Statin Intolerance

Paul M Ridker, MD; Lei Lei, PhD; Michael J. Louie, MD; Tariq Haddad, MD; Stephen J. Nicholls, MD; A. Michael Lincoff, MD; Peter Libby, MD; Steven E. Nissen, MD; on behalf of the CLEAR Outcomes Investigators

Circulation. 2024;149:28–35

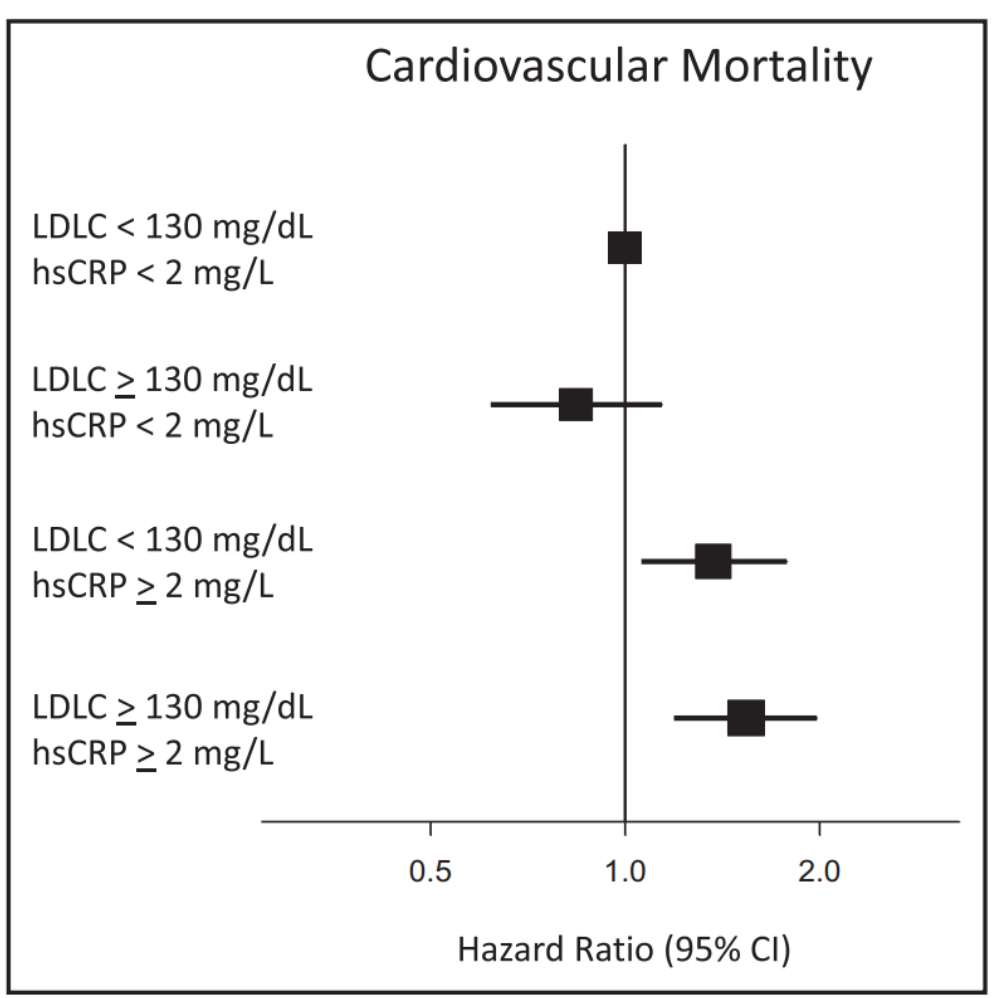
Inflammation and cholesterol as predictors of CV Risk: CLEAR Outcomes



Comparison of increasing quartiles of hsCRP (left) to increasing quartiles of LDLC (right) for CV mortality

Circulation. 2024;149:28–35

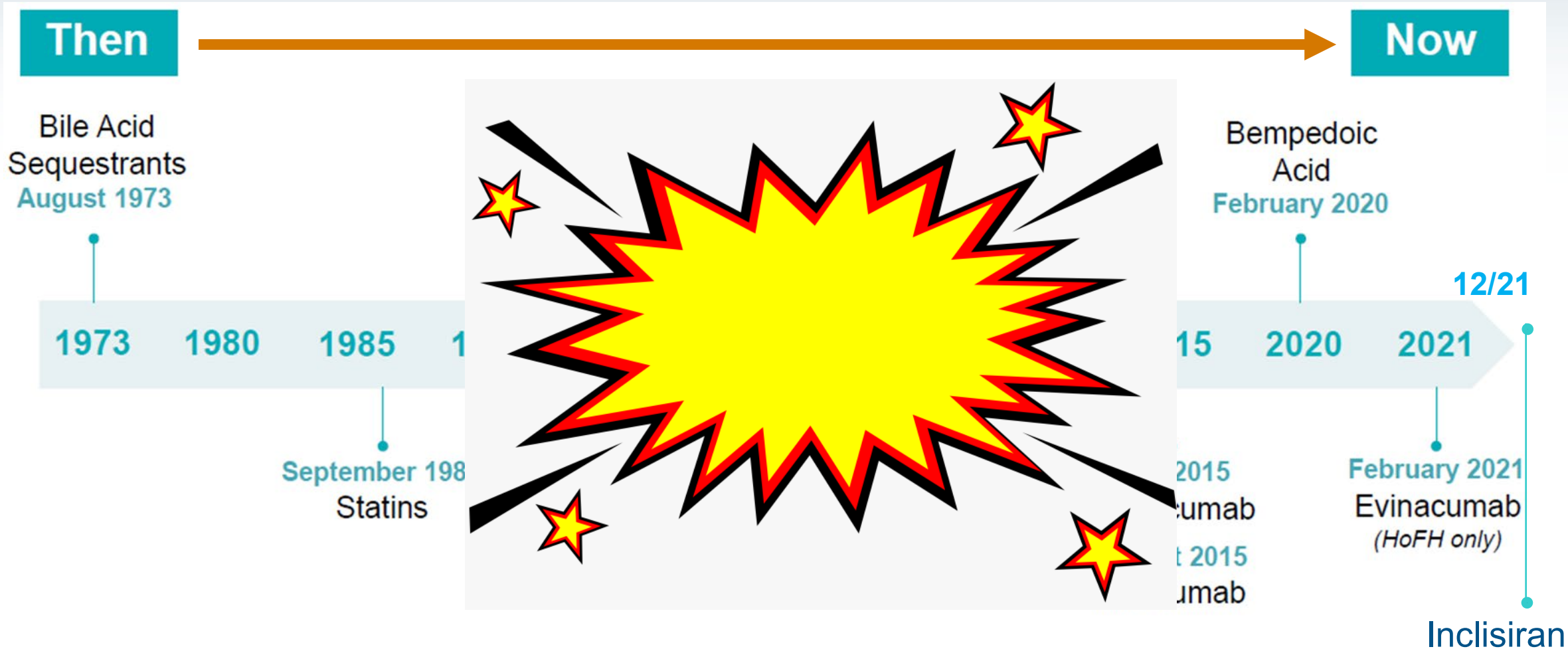
Inflammation and cholesterol as predictors of CV Risk: CLEAR Outcomes



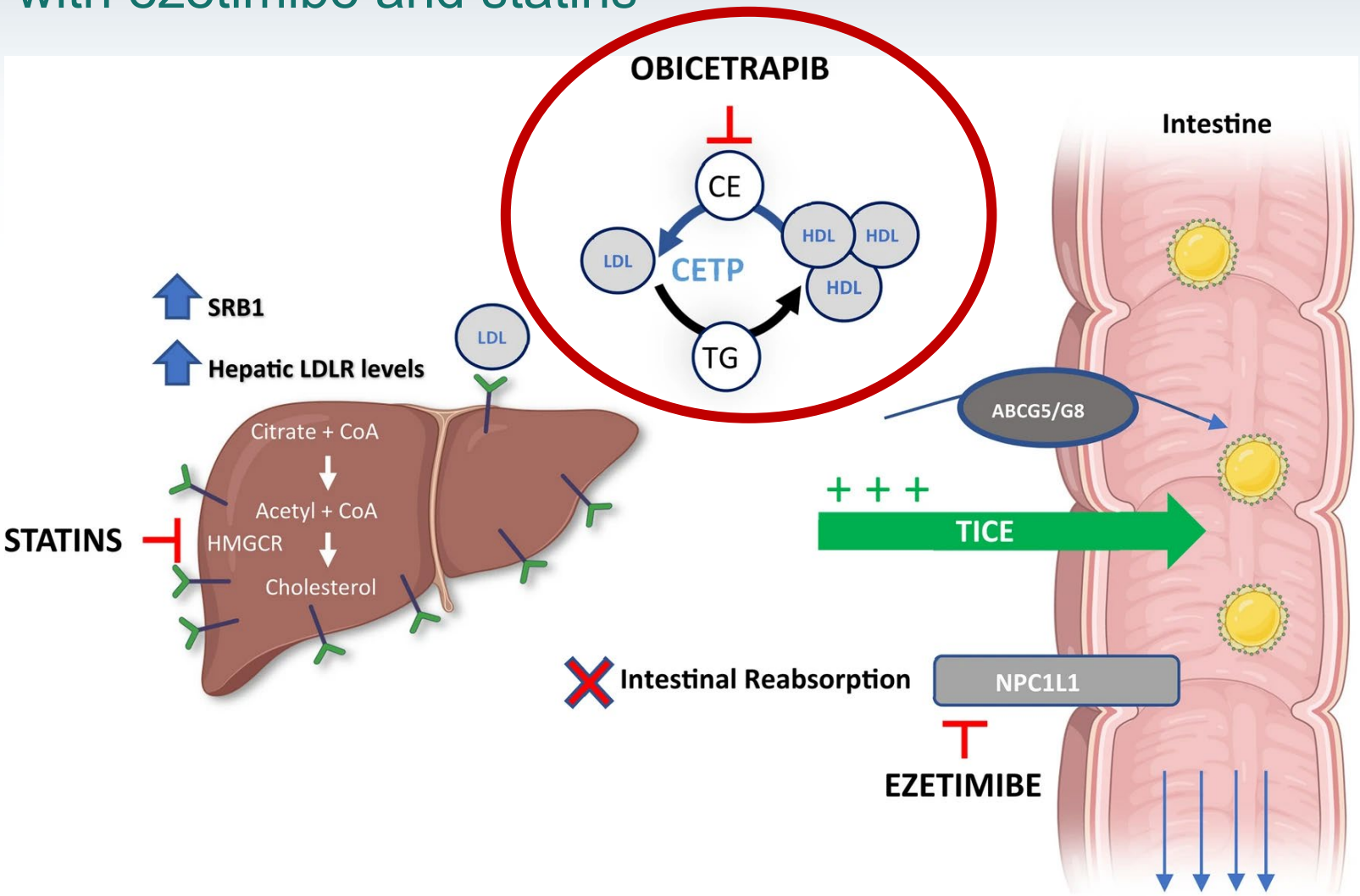
- Risks for MACE, CV mortality, and all-cause mortality significantly higher for those with above-median compared with below-median hsCRP, irrespective of LDLC strata (all P values ≤0.001)
- hsCRP predicted risk for future CV events and death more strongly than hyperlipidemia assessed by LDL-C

Circulation. 2024;149:28–35

Novel Lipid-Modifying Agents in Development



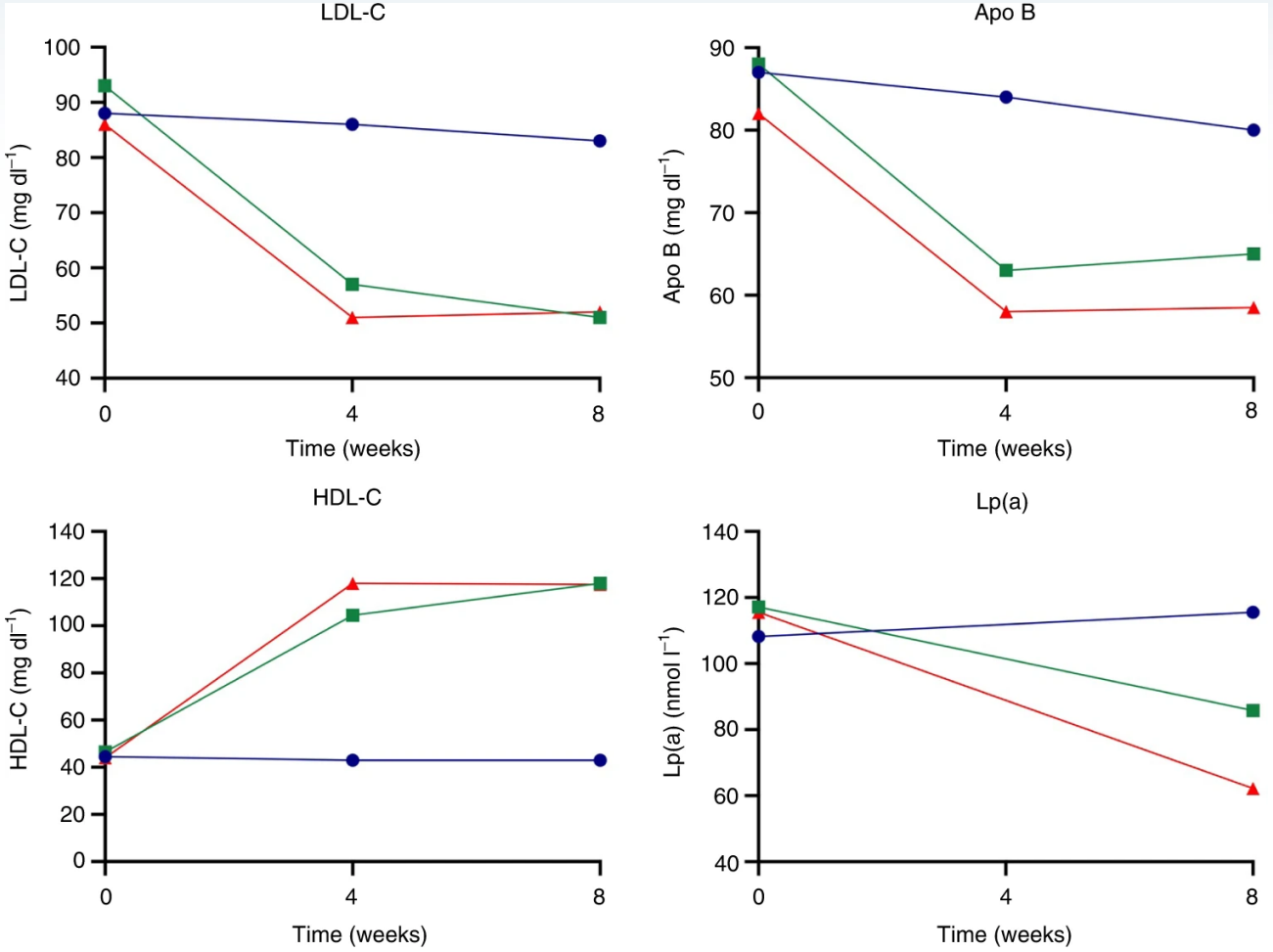
Obicetrapib: Proposed mechanisms of action for LDL-C lowering in combination with ezetimibe and statins



- Impairs transfer of CE from HDL to ApoB-containing particles
- Increase transintestinal cholesterol excretion
- Increased catabolic rate of LDL and ApoB

CETP inhibition: Obicetrapib

- CETP: promotes transfer CE from HDL to apoB containing lipoproteins
- RCT in dyslipidaemic patients (n = 120, median LDL-C 88 mg dl−1) on high-intensity statin (ROSE trial)
- At equipotent dosages obicetrapib reduces CETP activity >anacetrapib and evacetrapib
  - 5 mg or 10 mg obicetrapib
    - Up to 51% in LDL-C
    - Decreased apoB by up to 30%
    - Decreased non-HDL-C by up to 44%
    - Increased HDL-C by up to 165%



Nature Medicine.2022;28:1672–1678

BROOKLYN: Evaluate the Effect of Obicetrapib in Patients with HeFH on Top of Maximum Tolerated Lipid-Modifying Therapies 354 participants across ten countries in North America, Europe, and Africa

- 354 participants with HeFH across 10 countries in North America, Europe, and Africa
- Met primary endpoint
  - LS mean reduction in LDL-C
    - 36.3% ($p<0.0001$) at day 84
    - 41.5% ($p<0.0001$) at 1 year
- Reductions in nonHDL-C, Lp(a), and apoB

https://ir.newamsterdampharma.com/news-releases/news-release-details/newamsterdam-pharma-announces-positive-topline-data-pivotal. Accessed 20 September 2024.

BROOKLYN: Evaluate the Effect of Obicetrapib in Patients with HeFH on Top of Maximum Tolerated Lipid-Modifying Therapies 354 participants across ten countries in North America, Europe, and Africa

- Obicetrapib well-tolerated and AE comparable to placebo
- No increase in blood pressure
- Treatment discontinuation 7.6% obicetrapib vs 14.4% placebo

	Placebo N=118 n (%)	Obicetrapib 10 mg N=234 n (%)	Total N=352 n (%)
Any TEAEs	83 (70.3)	149 (63.7)	232 (65.9)
Any study drug related TEAEs	8 (6.8)	10 (4.3)	18 (5.1)
Any TEAEs leading to discontinuation of study drug	8 (6.8)	10 (4.3)	18 (5.1)
Any TESAEs	8 (6.8)	13 (5.6)	21 (6.0)

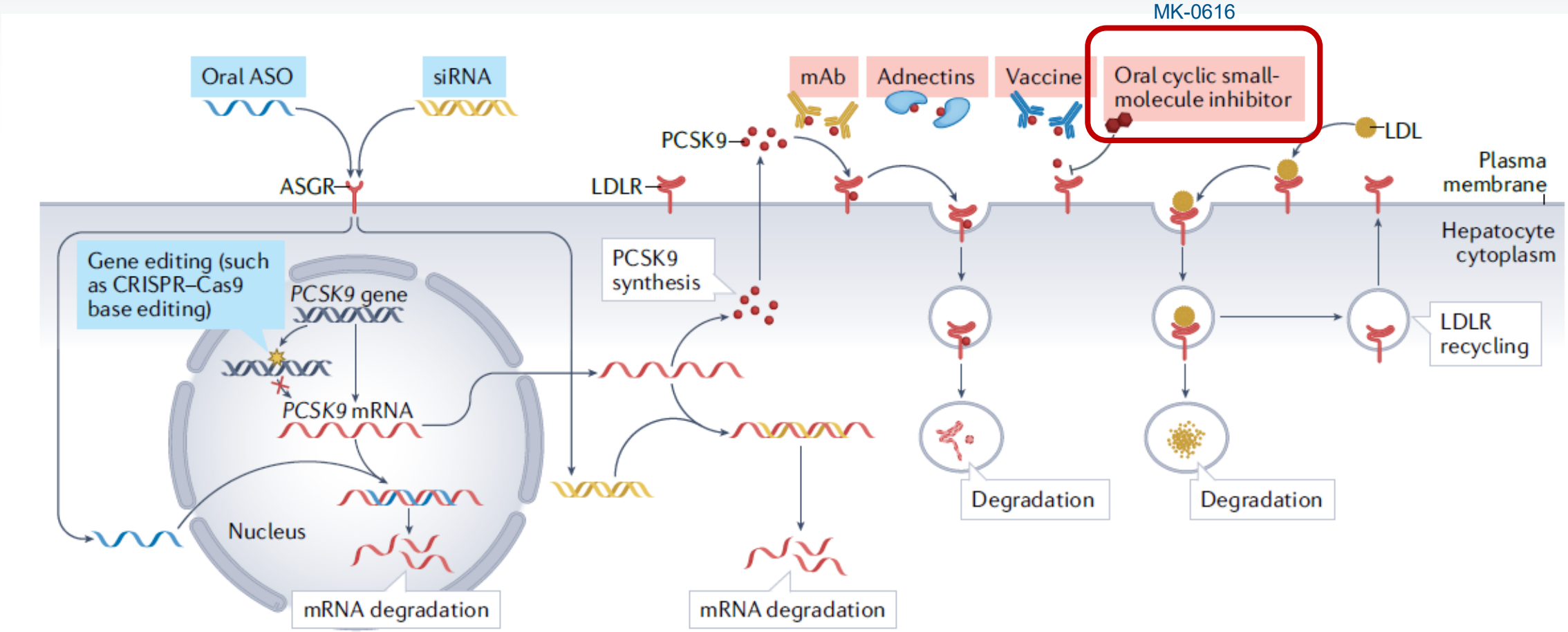
ir.newamsterdampharma.com/news-releases/news-release-details/newamsterdam-pharma-announces-positive-topline-data-pivotal. Accessed 20 September 2024.

PREVAIL Trial: Cardiovascular Outcome Study to Evaluate the Effect of Obicetrapib in Patients With CVD

- RCT to evaluate effect of obicetrapib 10 mg in participants with ASCVD who are not adequately controlled despite maximally tolerated lipid-lowering therapy
- Primary outcome: risk of CV death, MI, stroke and non-elective coronary revascularization
- N = 9000
- Estimated completion: end 12/2026

NCT05202509

PCSK9-targeted interventions: Enlicitide decanoate

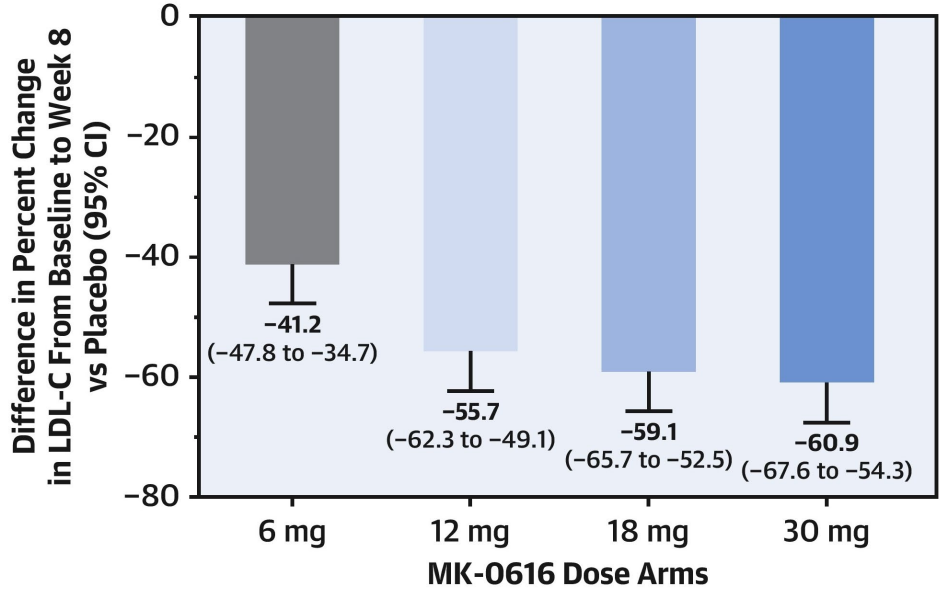


Nature Rev Cardiol.2021;18;805-6

Phase 2b Randomized Trial of Oral PCSK9 Inhibitor MK-0616 (enlicitide decanoate)

- LDL-C reduction from baseline to Week 8 superior to placebo ($p<0.001$) for all doses of MK-0616
- Near-complete efficacy achieved by 2 weeks with persistent effect over the 8-week treatment period
- Results generally consistent across prespecified subgroups

Efficacy *(n = 380 Treated Participants)*



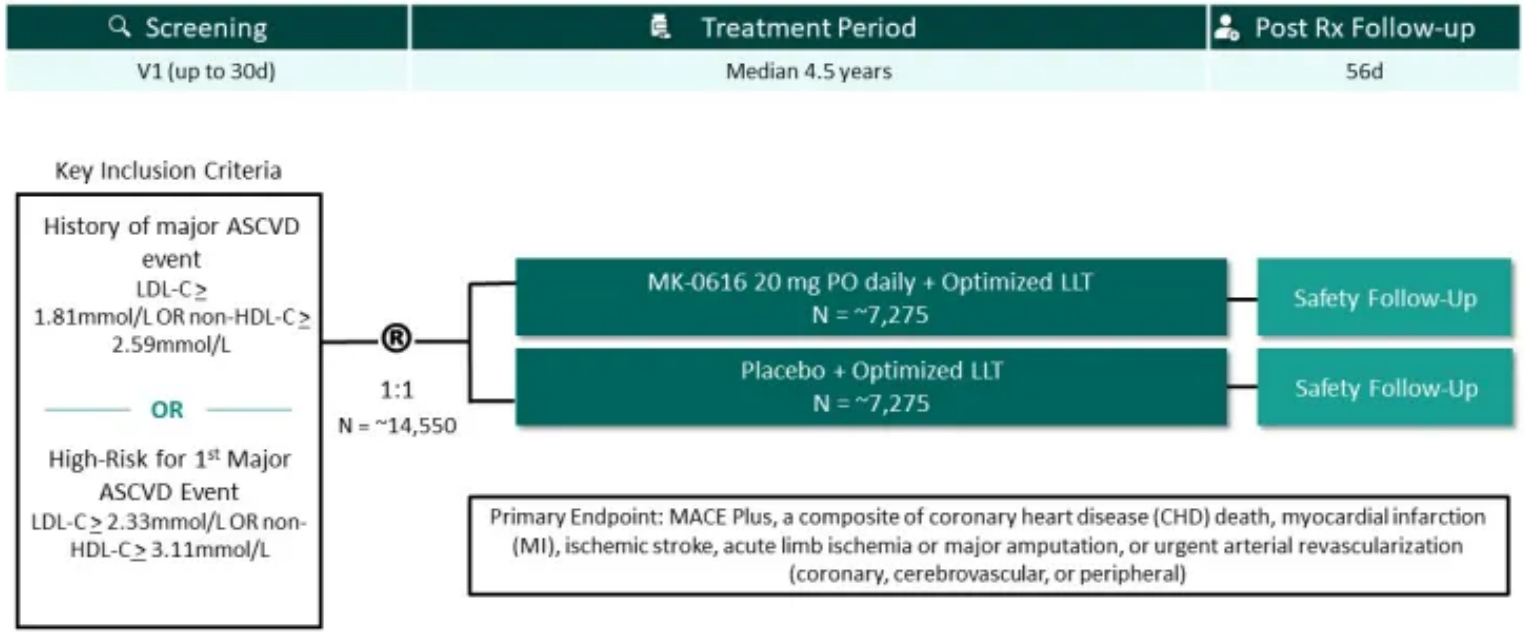
Key Points

- All doses of MK-0616 demonstrated statistically superior reductions in LDL-C vs placebo with up to 60.9% placebo-adjusted reduction from baseline values
- MK-0616 was well tolerated with no overall trends in AEs across treatment groups

J Am Coll Cardiol. 2023;81(16):1553-1564

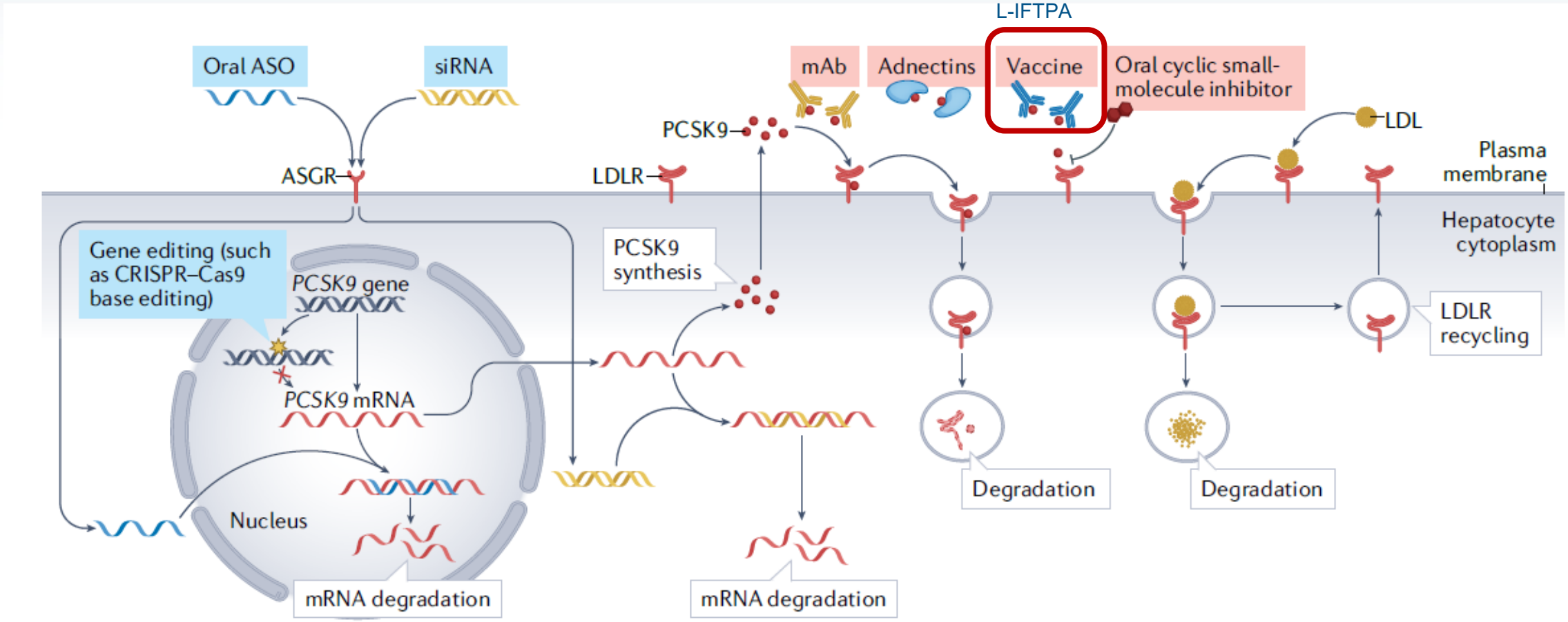
TIMI-77: CORALreef Outcomes

- Phase 3 RCT of efficacy and safety of MK-0616 (enrolling)
- 4,550 participants with high cardiovascular risk
- Evaluate efficacy of MK-0616 vs placebo in increasing time to 1st MACE (CHD death, ischemic stroke, MI, acute limb ischemia or major amputation, or urgent arterial revascularization)
- Completion 11-29-2029



PCSK9-targeted interventions: PCSK9 vaccines

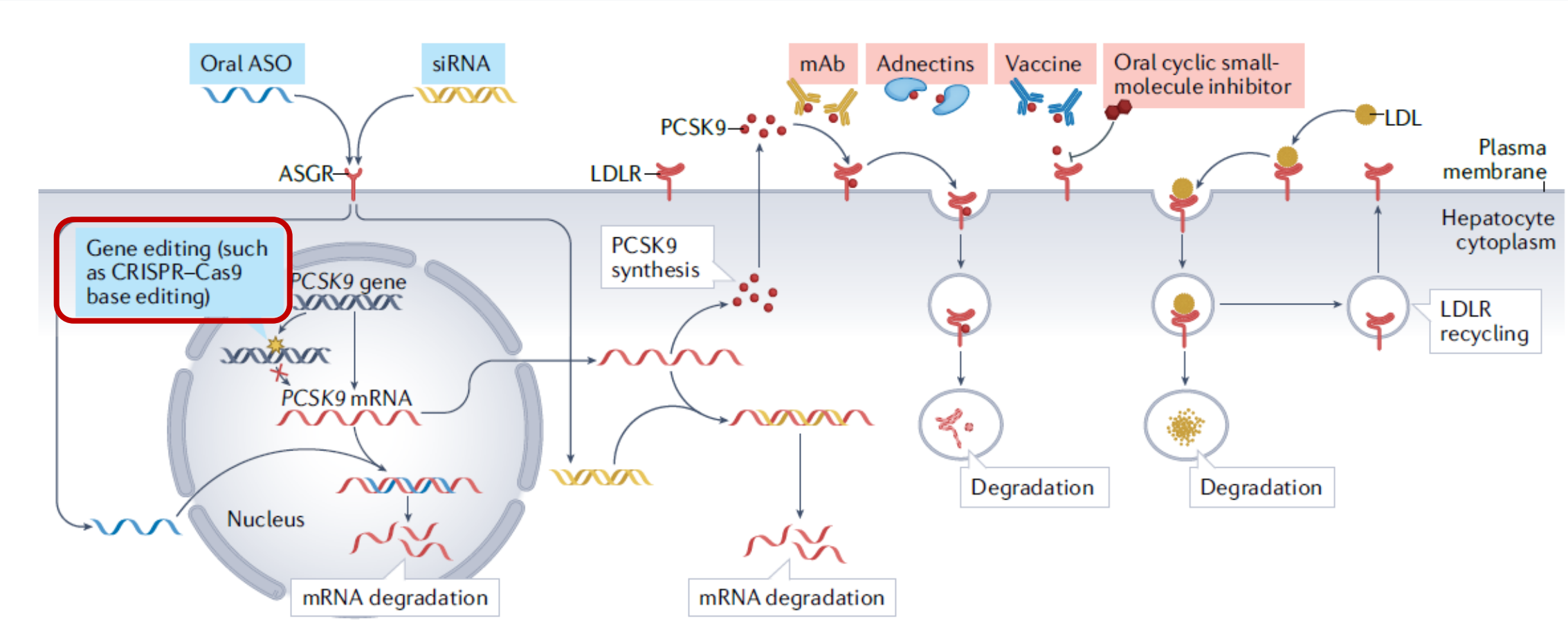
- Vaccines against PCSK9 to trigger generation of host anti-PCSK9 antibodies and neutralize PCSK9/LDLR interactions (Clinical data lacking)



Nature Rev Cardiol.2021;18;805-6

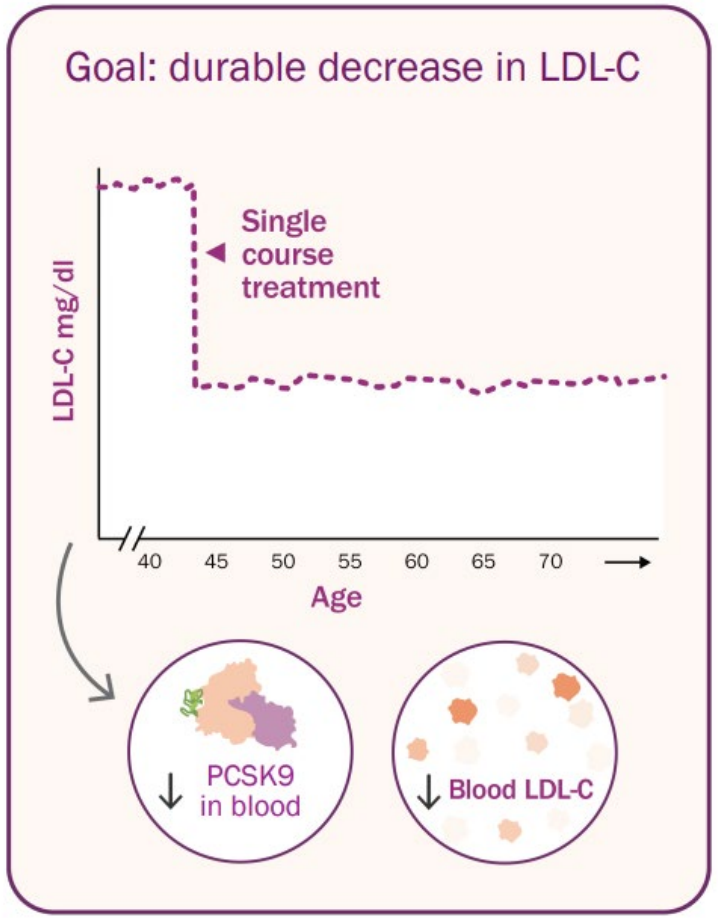
PCSK9-targeted interventions: Gene editing (VERVE 101)

- Gene editing technologies: Once and done



Nature Rev Cardiol.2021;18;805-6

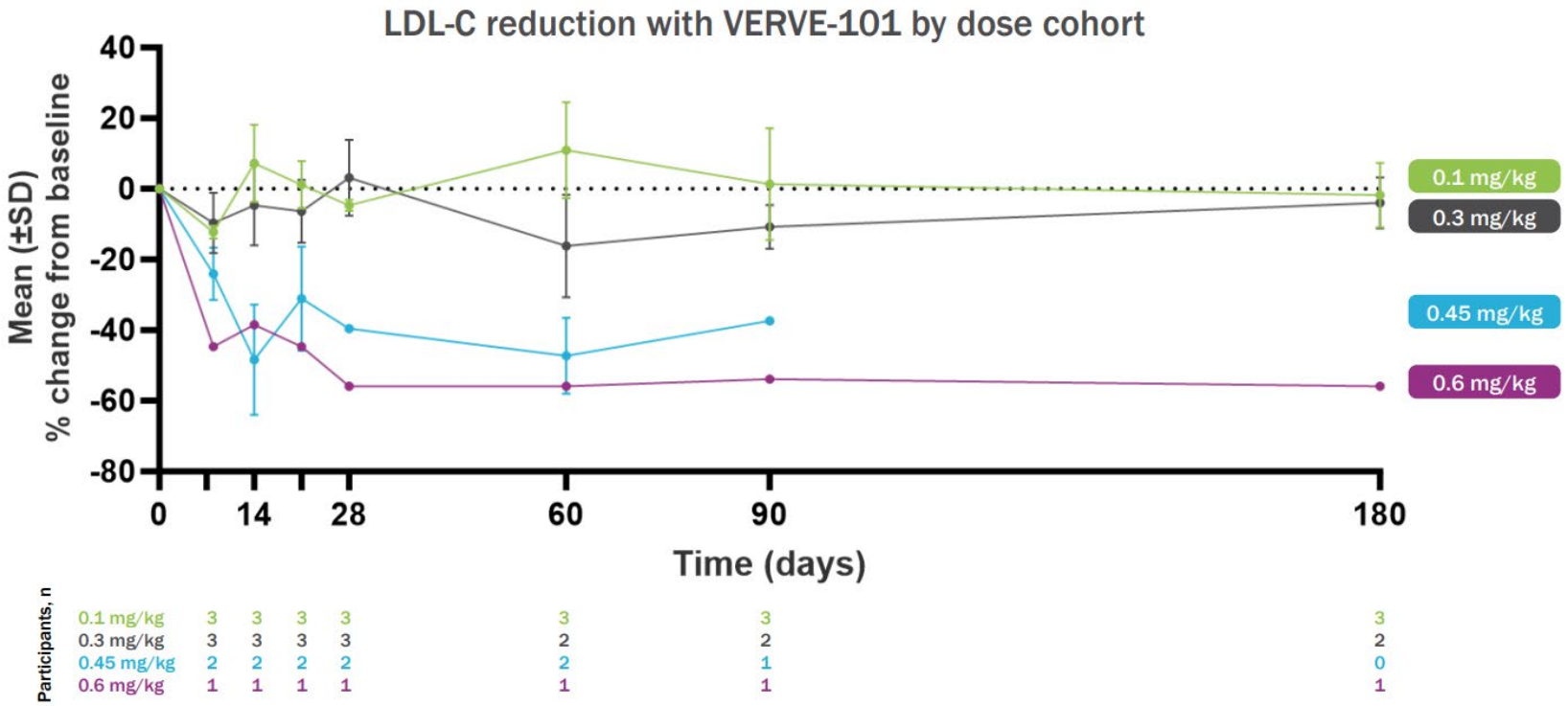
VERVE-101 Phase 2b



TARGET	INDICATION	TECHNOLOGY	DEVELOPMENT STATUS
			Research / IND-enabling / Clinical
PCSK9 (VERVE-101)	Heterozygous familial hypercholesterolemia; ASCVD	Base Editor	
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia; ASCVD	Base Editor	
ANGPTL3 (VERVE-201)	Homozygous familial hypercholesterolemia; Refractory Hypercholesterolemia	Base Editor	
LPA	ASCVD patients with high blood Lp(a)	Novel Editor	
Undisclosed	Undisclosed ASCVD	Base Editor	
Undisclosed	Undisclosed liver disease	Novel Editor	

VERVE-101 Phase 2b

Durable 55% reduction in LDL-C extending up to 180 days in the single participant in the highest dose cohort

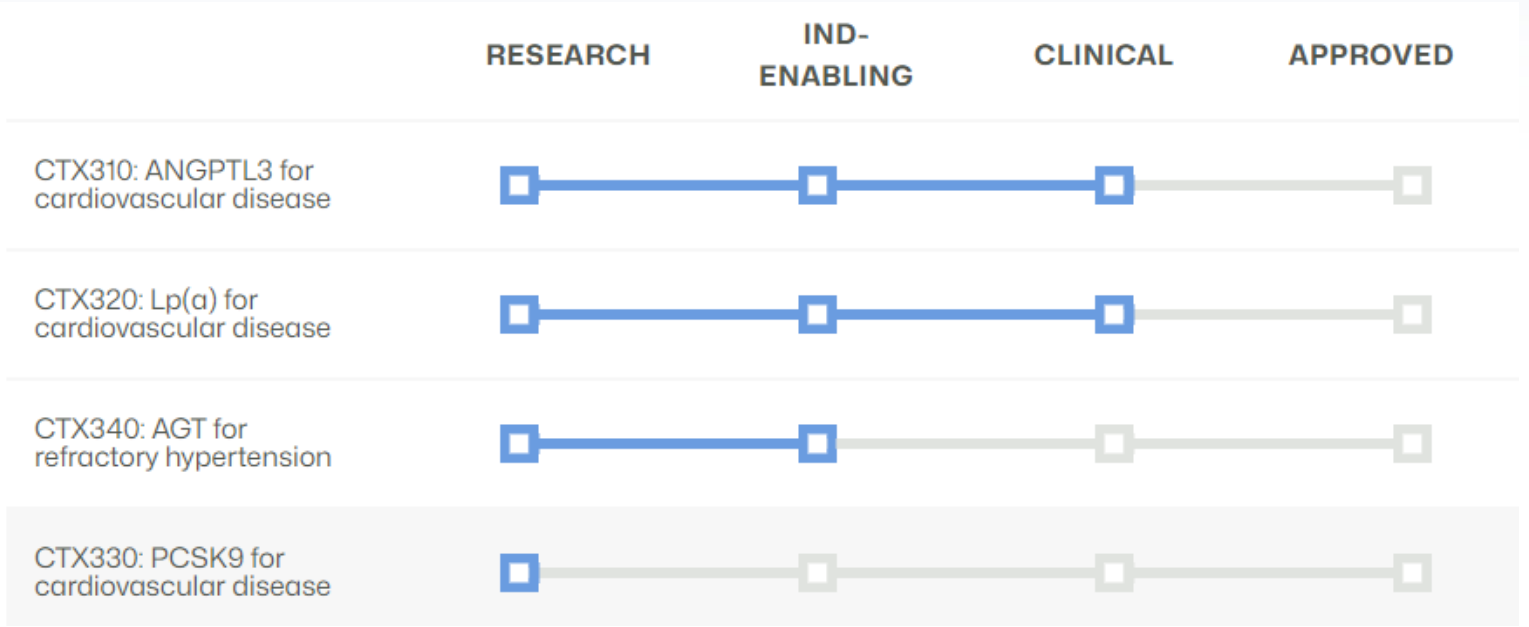


As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned
SD, standard deviation

Kathersan S, presented ESC, August 2023

CRISPR Technology

- Other CRISPR development programs
  - CTX310 ANGPTL3
  - CTX320 Lp(a)
  - CTX330 PCSK9



https://crisprtx.com/focus-areas/in-vivo
Accessed 9/20/24

Novel Therapies in HoFH

- *Statins, CAI, PCSK9 inhibitors, ACL inhibitors all work by upregulating the LDL receptor*
- *In HoFH, absent or defective LDL receptor*
  - *Limited efficacy of available agents*
- *Need for agents that lower LDL-C independently of LDL receptor*

What's the Difference?

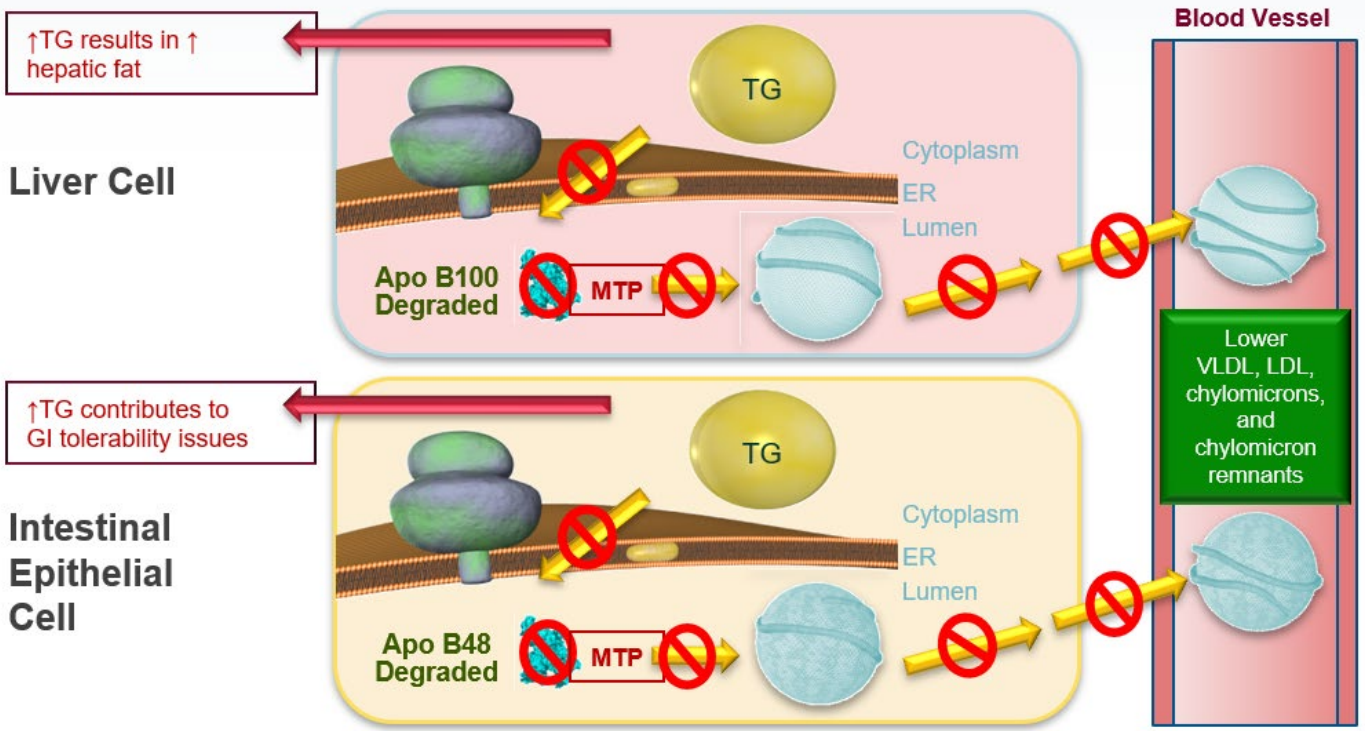
Know Familial Hypercholesterolemia (FH)

HeFH and HoFH

					
HeFH (common)	1 gene	>190 mg/dL	30-60 years	Most respond to drug therapy	Common 1 in 250
HoFH (rare)	2 genes	>400 mg/dL	Childhood	Poor response to drug therapy	Rare 1 in 300,000

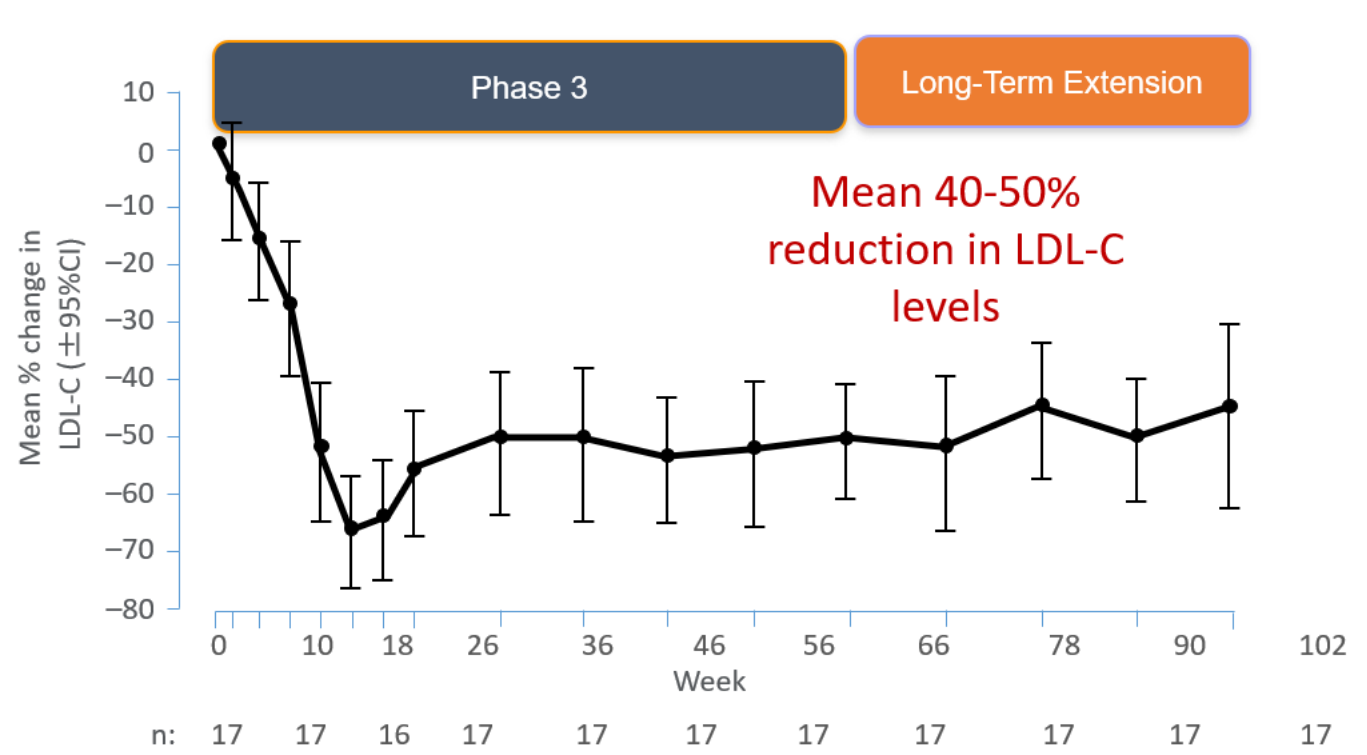
Lomitapide: 2012

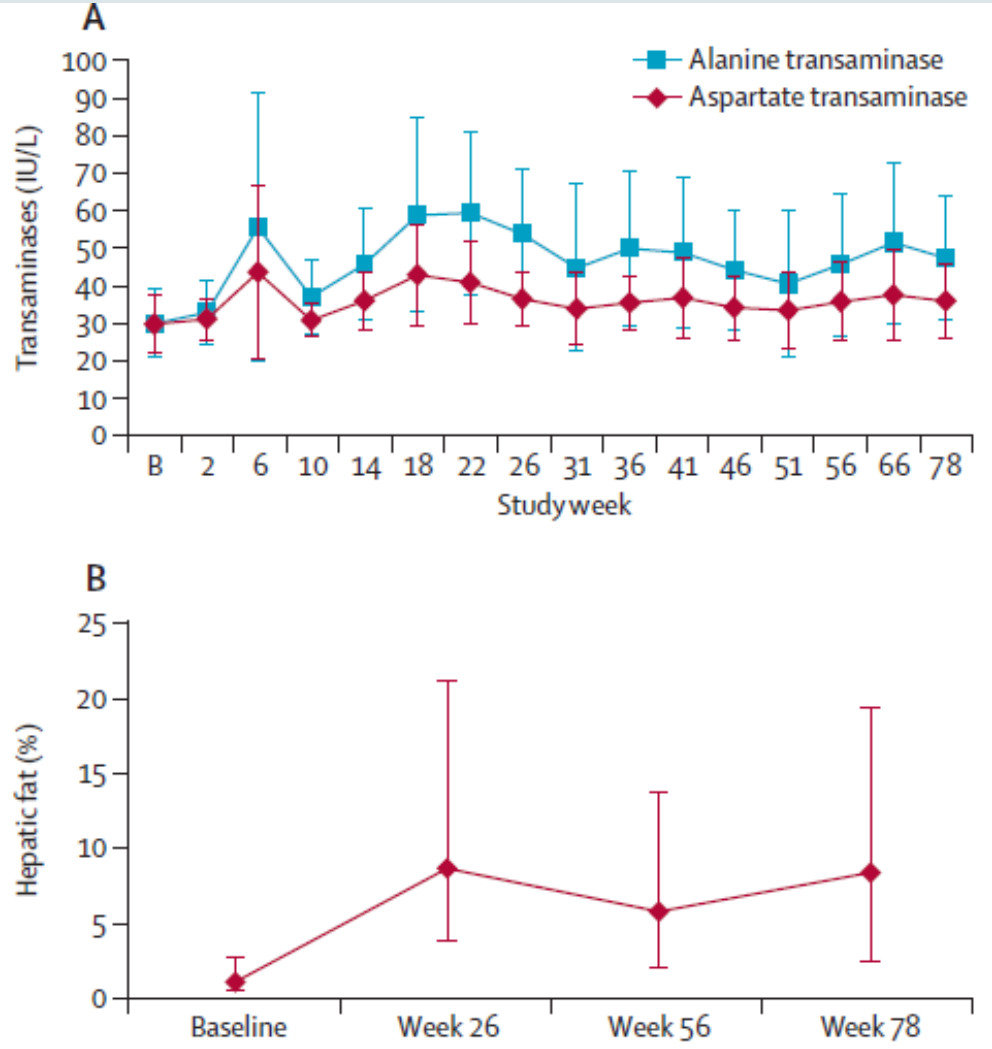
- Inhibitor of MTP
  - Enzyme that lipidates apoB
- ***Lowers LDL-C independently of LDL receptor***
- Approved in patients with HoFH
- Adverse effects
  - Increase in hepatic fat
  - GI tolerability issues



J Lipid Res. 2003;44:22-32

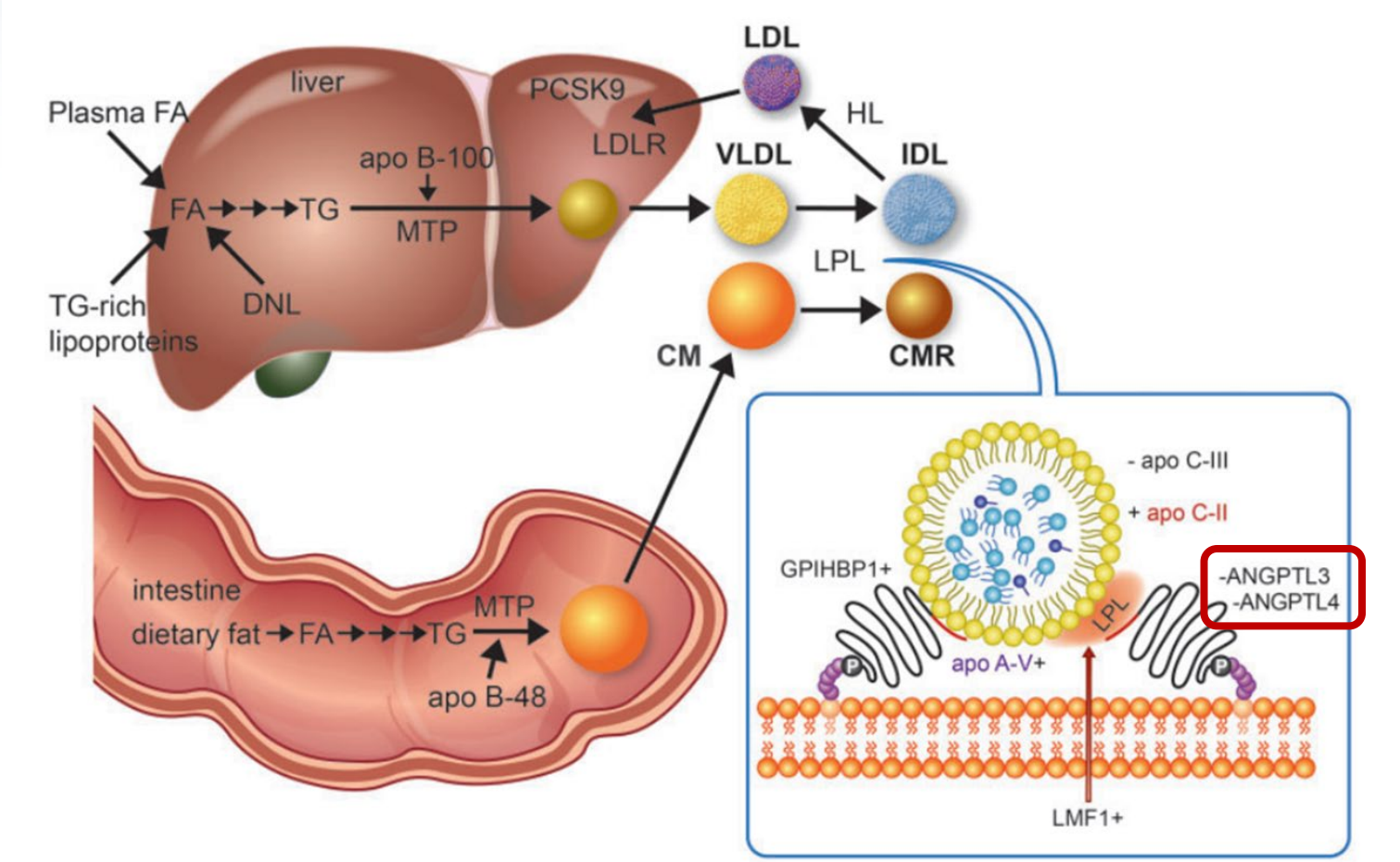
Mean percent change from baseline in LDL-C by study visit (Week 126 completers population)





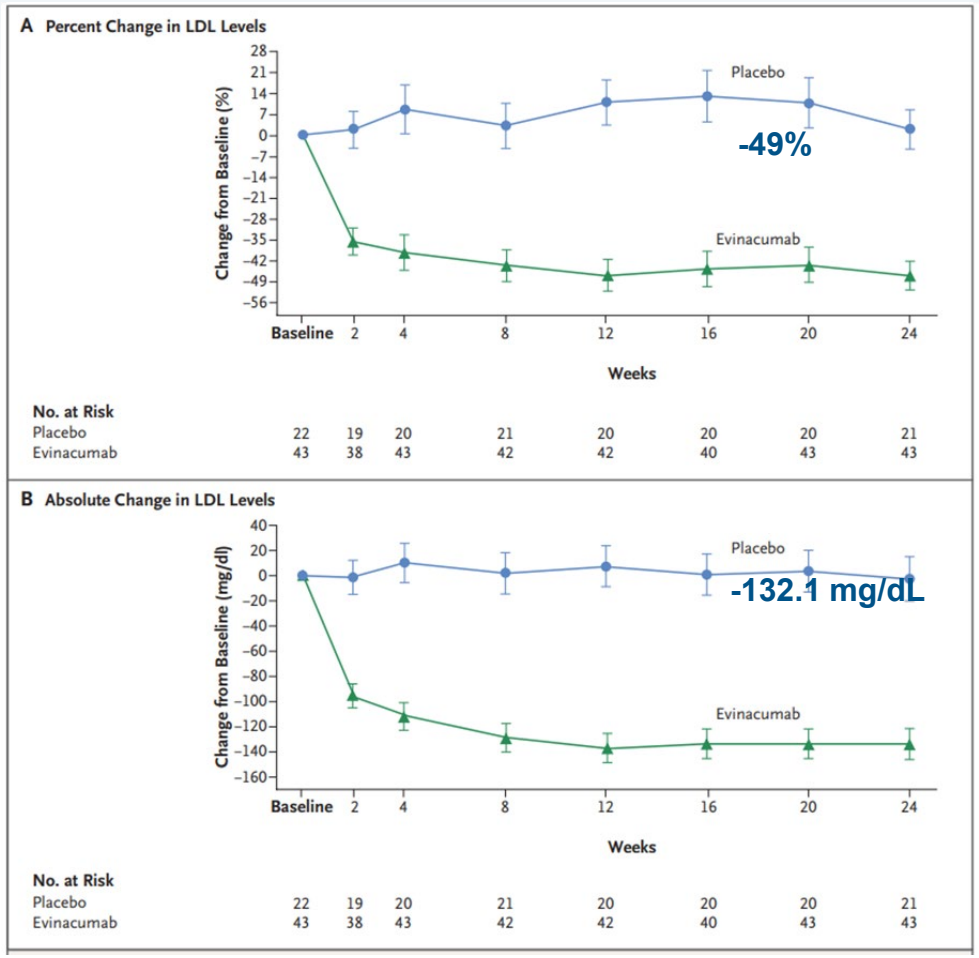
Cuchel M. et al. Circulation. 2013; 128: A16516.
Presented at 2013 AHA Scientific Sessions.

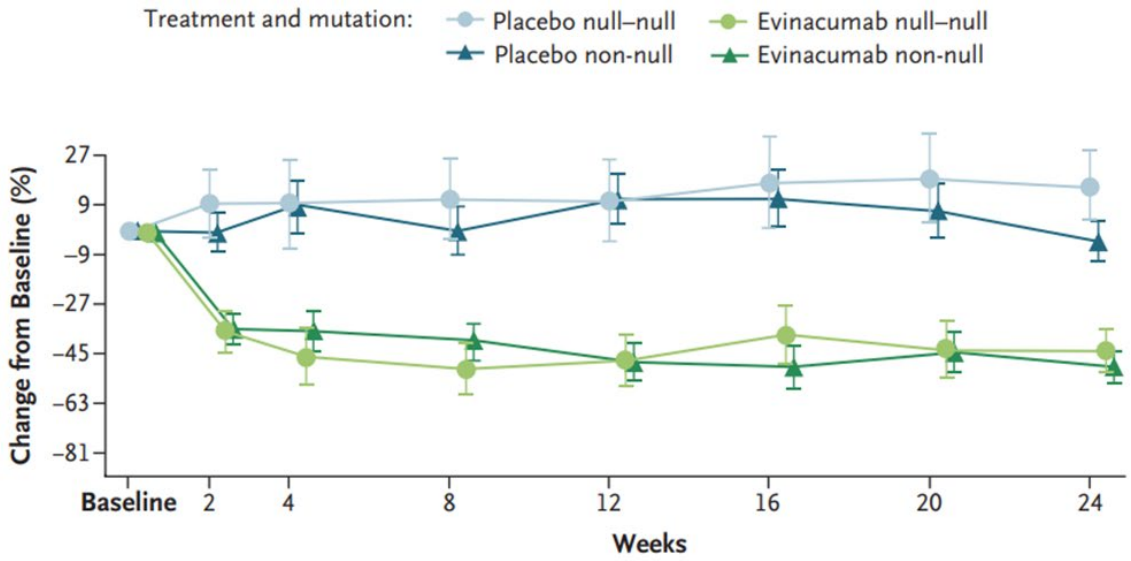
Evinacumab: ANGPTL3 inhibition



- Evinacumab: fully human monoclonal antibody that is inhibitor of ANGPTL3
- ANGPTL3 is inhibitor of LPL and EL
  - Plays a key role in lipid metabolism by increasing the levels of TGs and other lipids
- LOF variants associated with low levels of both LDL-C and TGs
  - 41% lower risk of CAD, despite presence of low levels of HDL-C
- Both ANGPLT3 loss-of-function variants and ANGPTL3 pharmacologic inhibition *reduce LDL-C levels independently of LDLR*

Evinacumab in HoFH



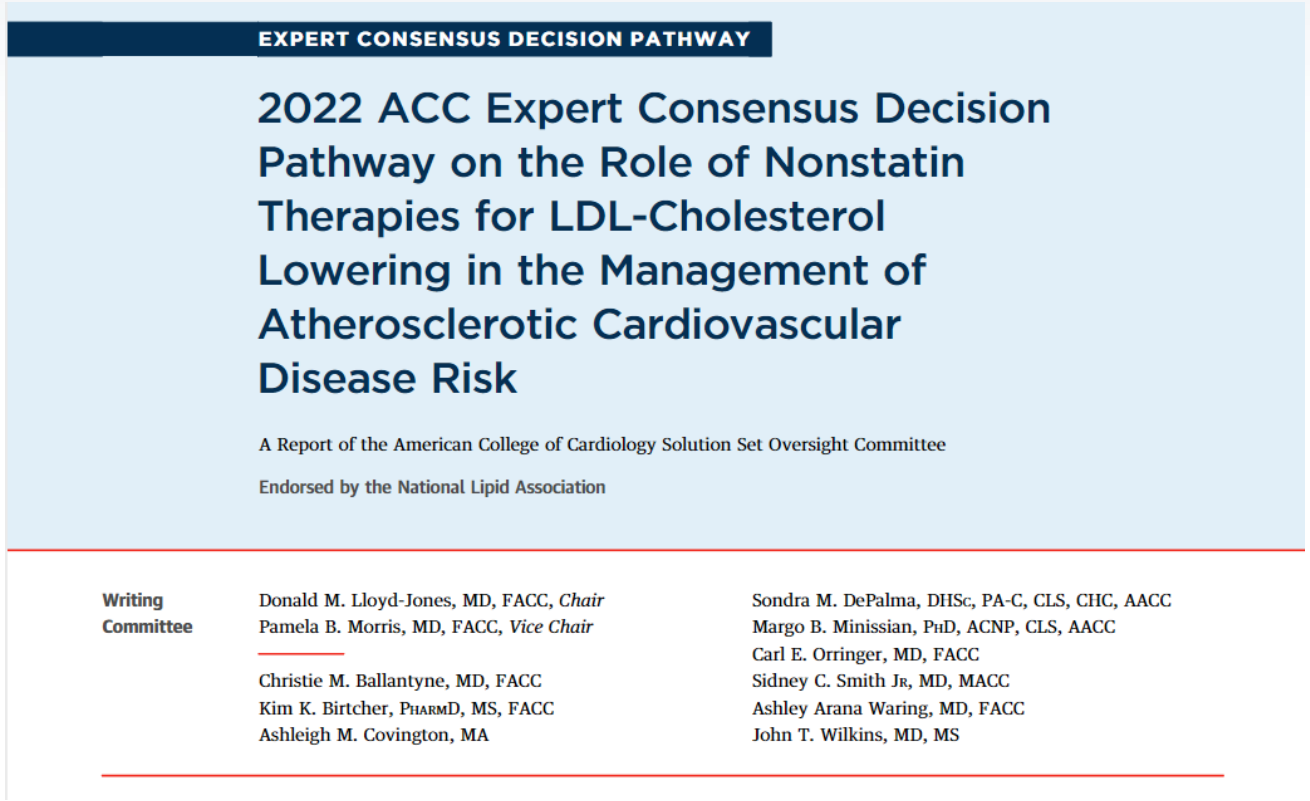


No. at Risk								
Placebo null–null	6	4	6	6	6	6	6	6
Placebo non-null	16	15	14	15	14	14	14	15
Evinacumab null–null	15	14	15	15	14	15	15	15
Evinacumab non-null	28	24	28	27	28	25	28	28

N Engl J Med 2020;383:711-20.

Evolving Science, Treatments, and Guidance

August 26th, 2022



EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

Writing Committee

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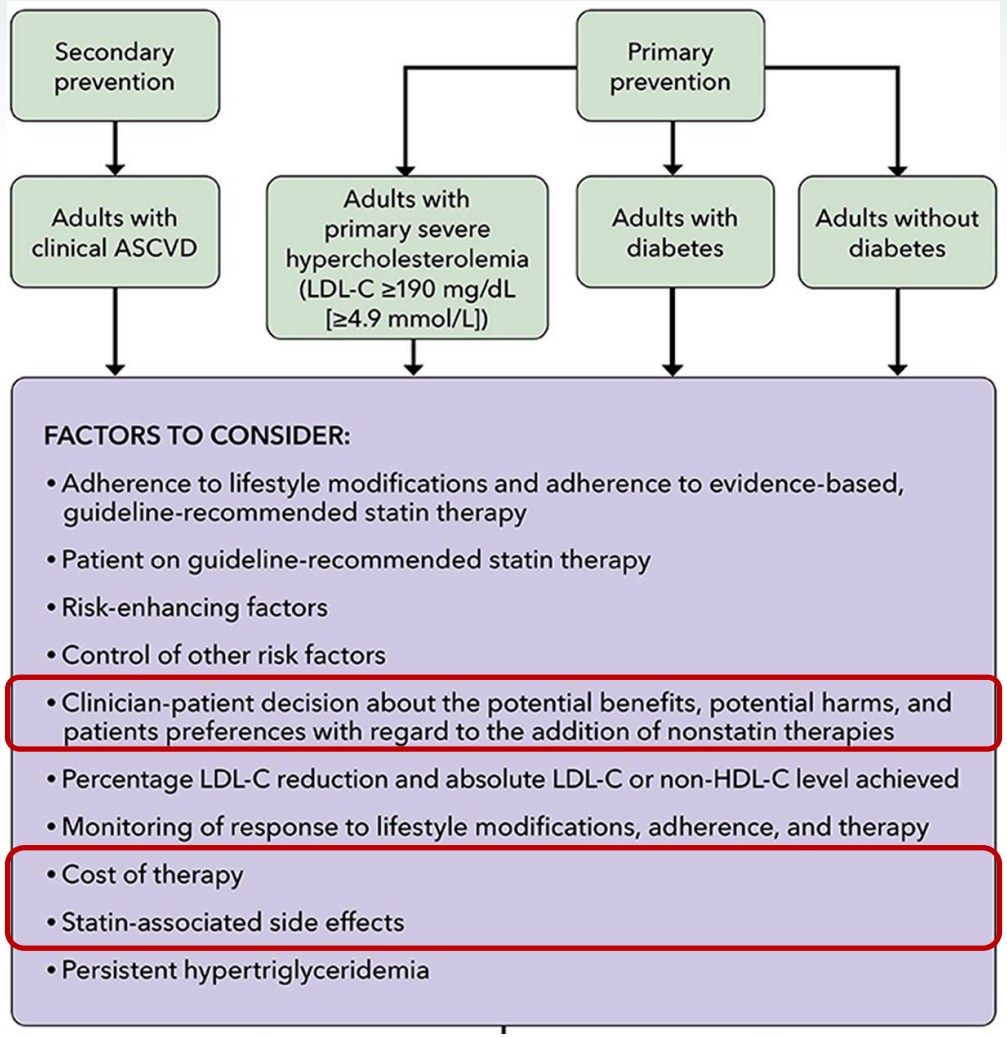
doi.org/10.1016/j.jacc.2022.07.006

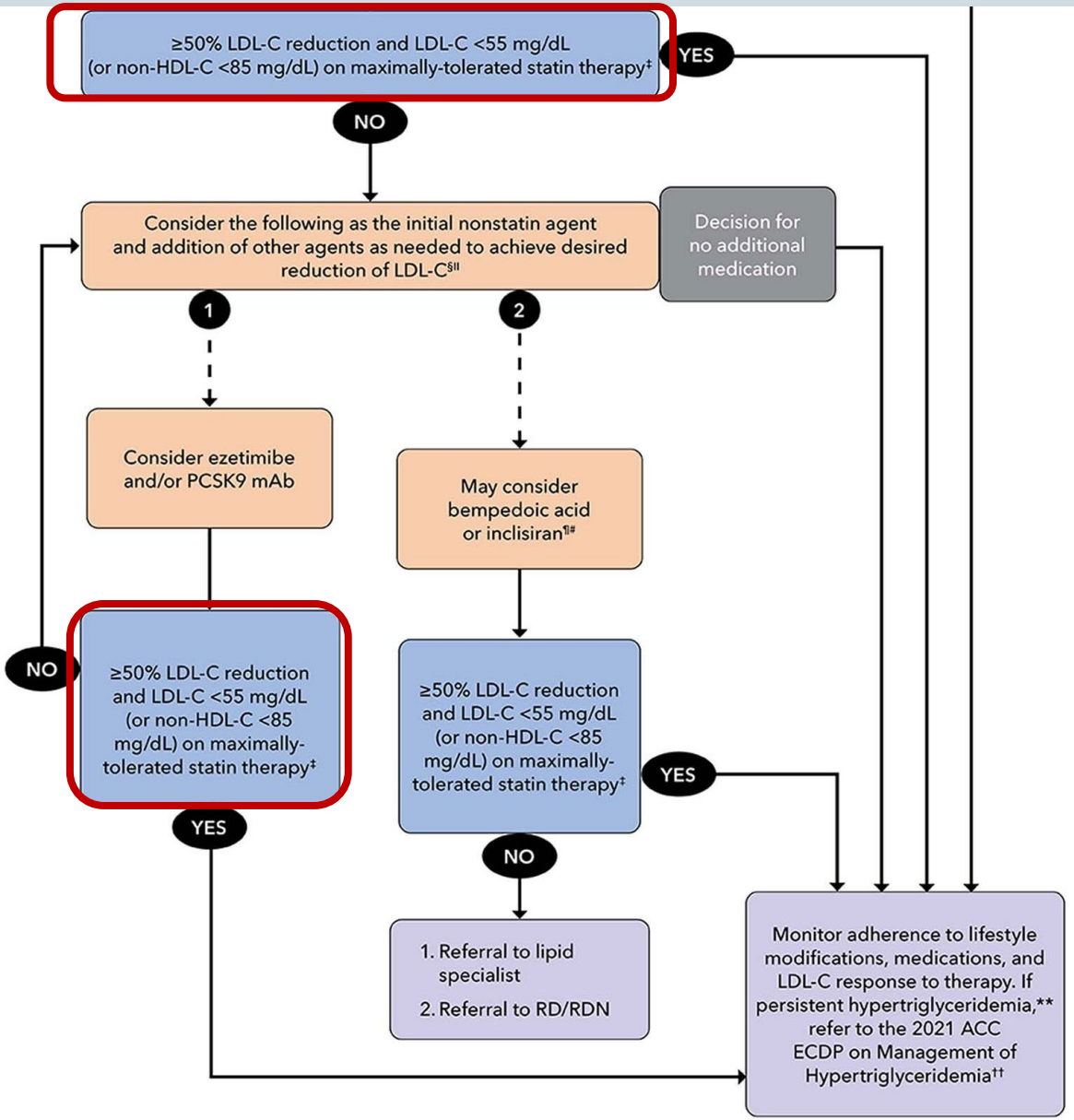
Clinical Decision Making



ASCVD at Very High Risk

In view of evidence demonstrating CV outcomes benefits of LDL-C to lower levels, new lower LDL-C threshold of 55 mg/dL for addition of non-statin therapies.

- IMPROVE-IT treatment group: 54 mg/dL
- FOURIER/ODYSSEY Outcomes: 30 mg/dL



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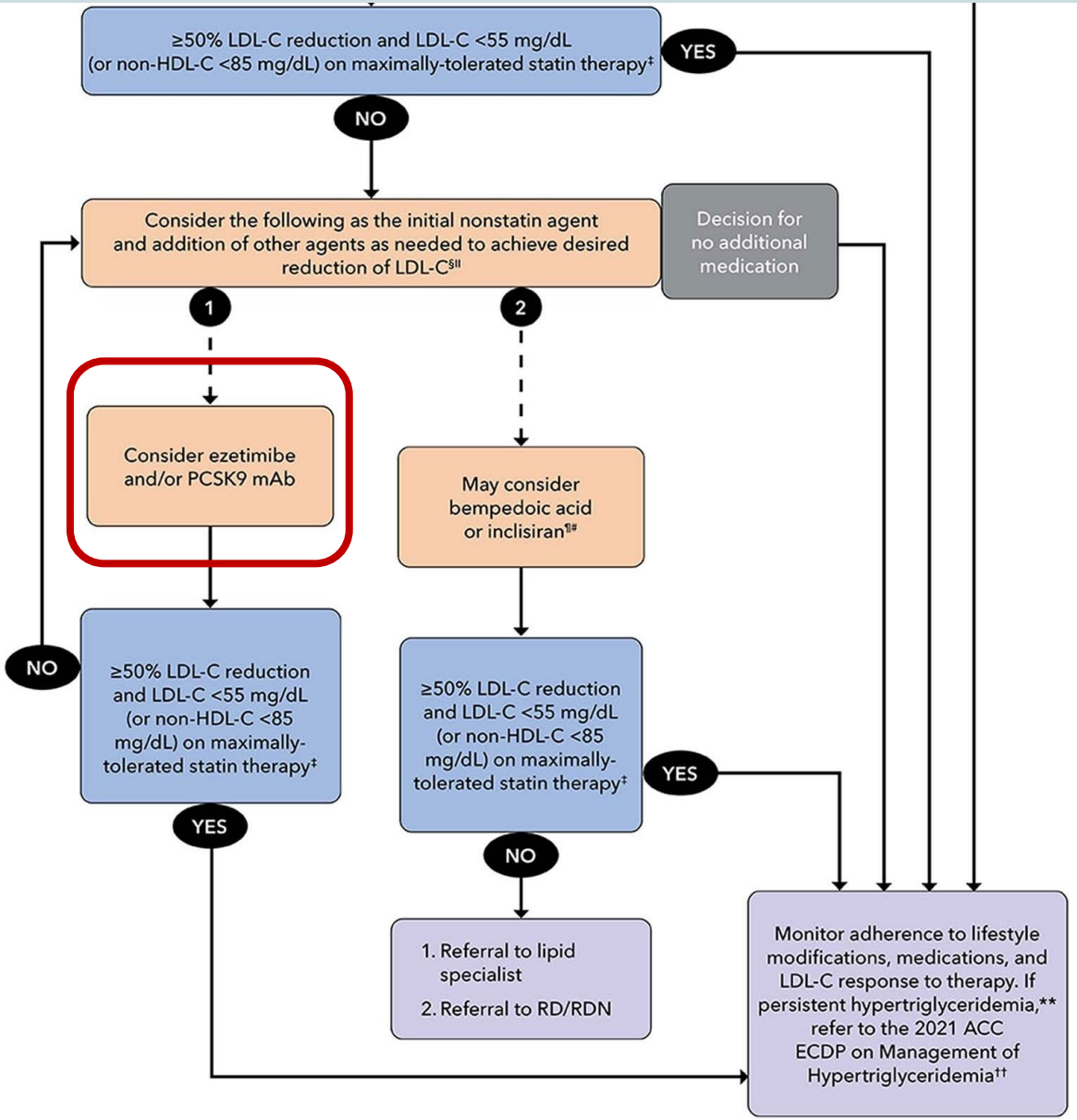
ASCVD at Very High Risk

- In patients with clinical ASCVD at very high risk who require greater LDL-C reduction than any additional therapy alone can expect to achieve, may be reasonable to consider simultaneous addition of 2 agents to reduce risk of recurrent events more rapidly
  - Combination therapy with high-intensity or maximally tolerated statin therapy and ezetimibe
  - Maximally tolerated statin therapy with or without ezetimibe and PCSK9 mAb



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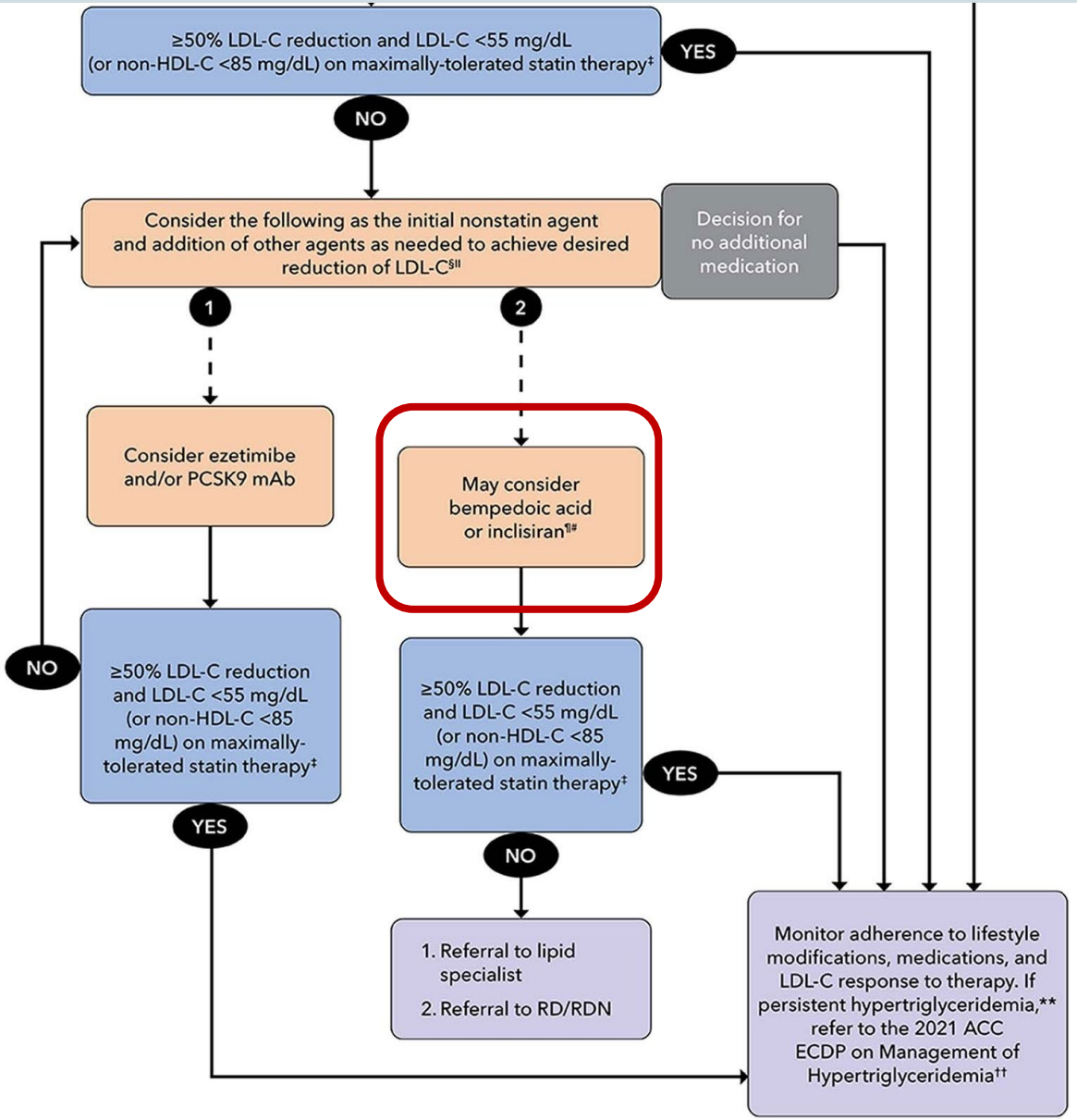
- PCSK9 mAb and ezetimibe are 1st line non-statin therapies
  - CV outcomes trial published for all 3 agents

- Bempedoic acid and inclisiran as 2nd line non-statin therapies
  - Likely to change recommendation for bempedoic acid with publication of CLEAR Outcomes



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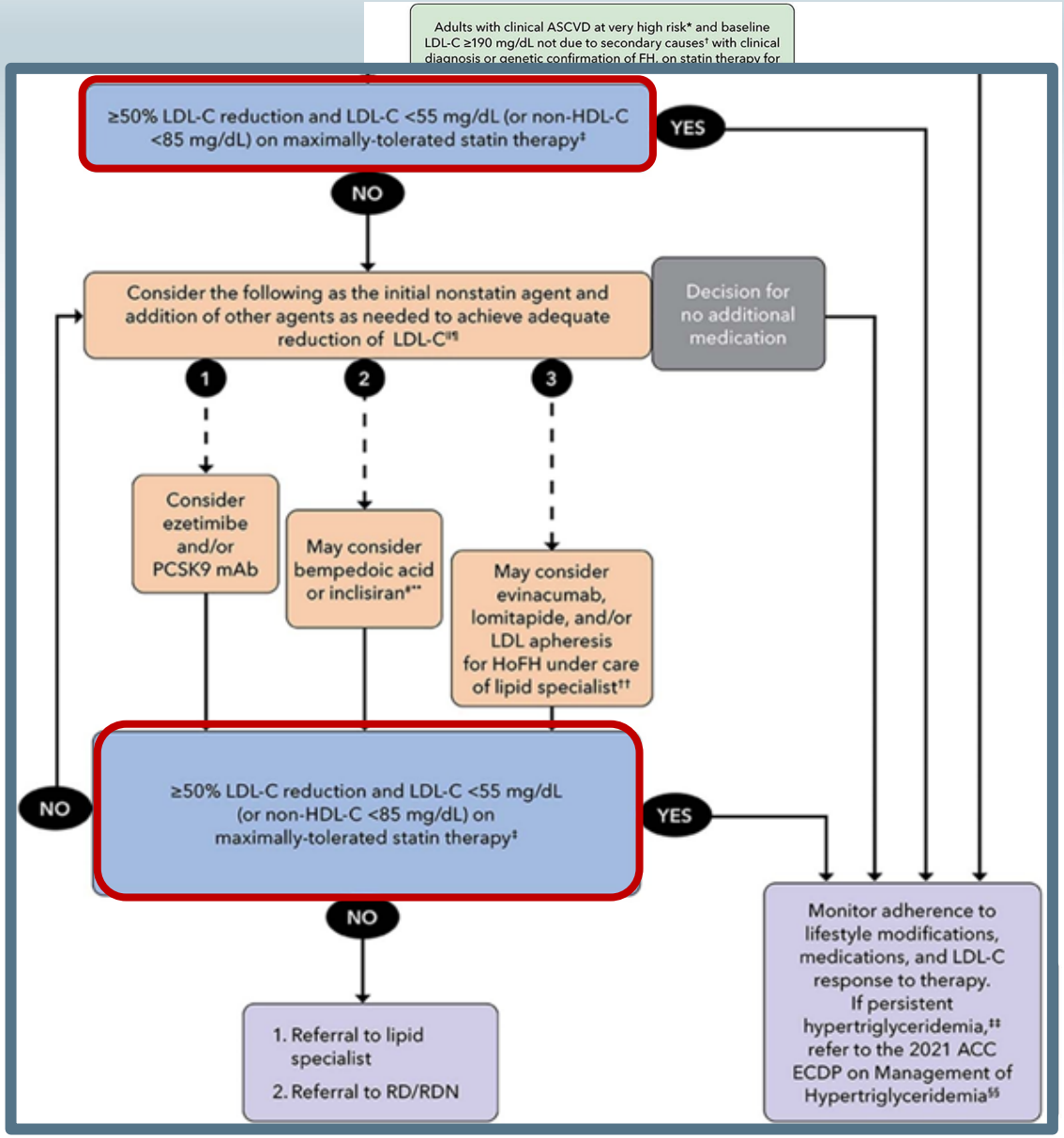
ASCVD and FH

Patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL and a *clinical diagnosis or genetic confirmation* of FH may be at very high risk

- Intensification of therapy and addition of nonstatin therapies should be considered if <50% reduction in LDL-C or *LDL-C ≥55 mg/dL* on maximally tolerated statin therapy
- Additional non-statin options include evinacumab, lomitapide, and/or LDL apheresis



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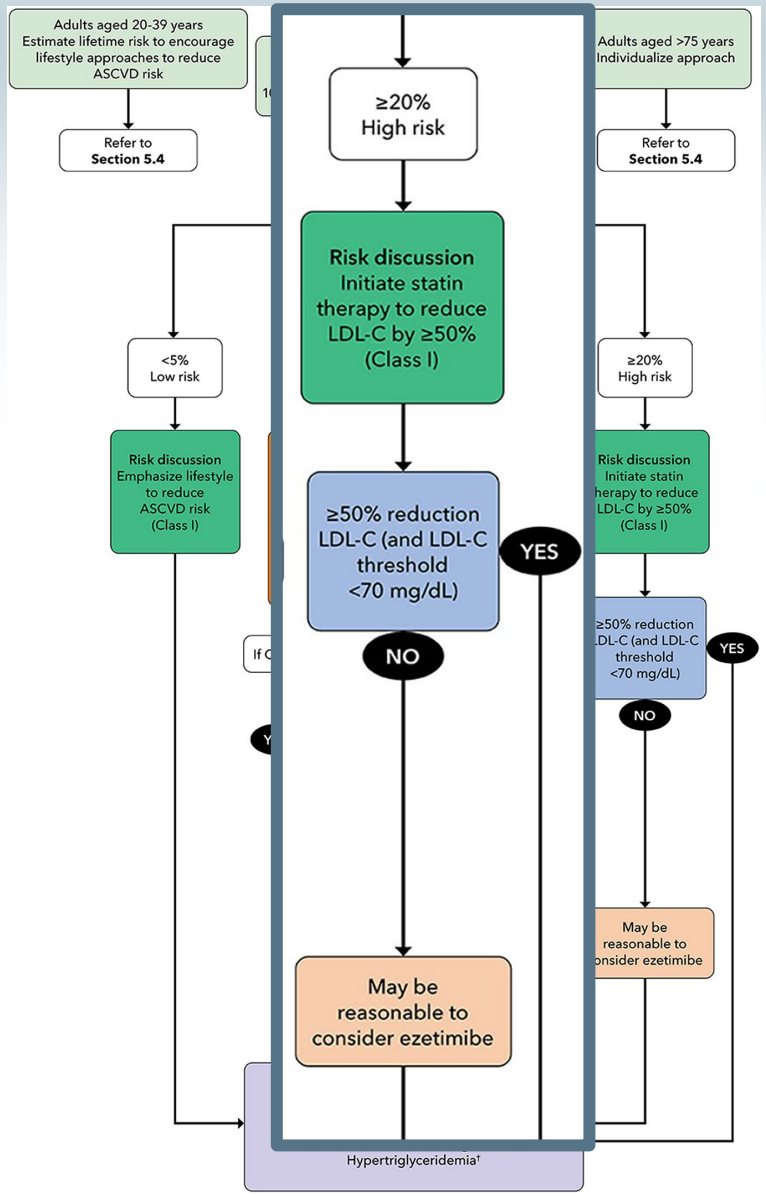
High Risk Primary Prevention

Addition of recommendation for use of ezetimibe in pts with 10-year ASCVD risk ≥20%



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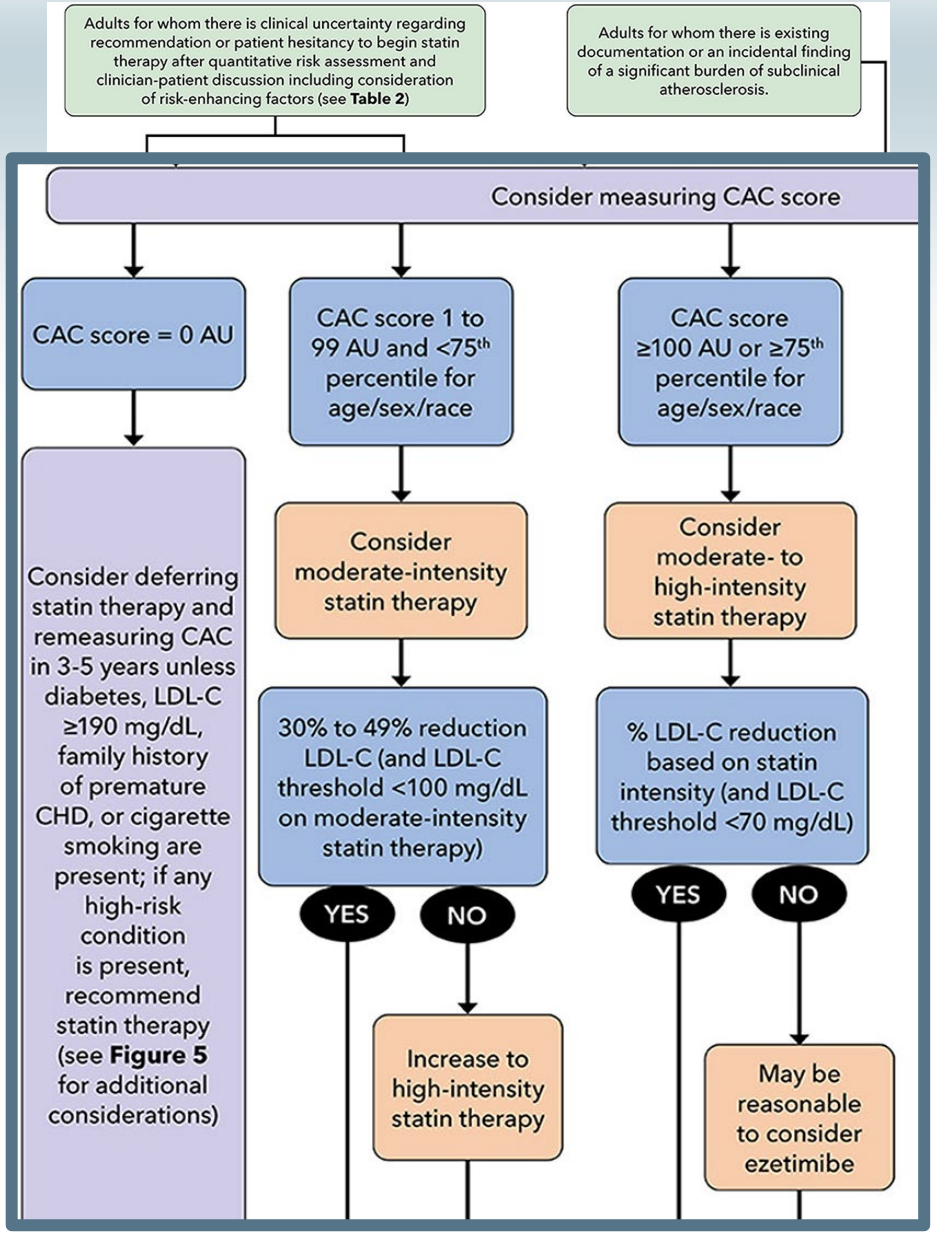
Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment

For those with CAC score of 0 AU, in absence of diabetes, LDL-C ≥190 mg/dL, family history of premature CHD, or active cigarette smoking

- Reasonable to defer statin therapy with a plan for CAC reassessment in 3-5 years.

For those with a CAC score of 1-99 AU and <75th percentile, moderate-intensity statin therapy is reasonable.

- MESA identified individuals with a CAC score >100 AU or ≥75th percentile as having 10-year incidence of hard ASCVD events of >7.5%
  - Supports the initiation of moderate- or high-intensity statin therapy.
- Titration to high-intensity statin therapy may be considered if the patient achieves <30% LDL-C reduction or LDL-C ≥100 mg/dL.



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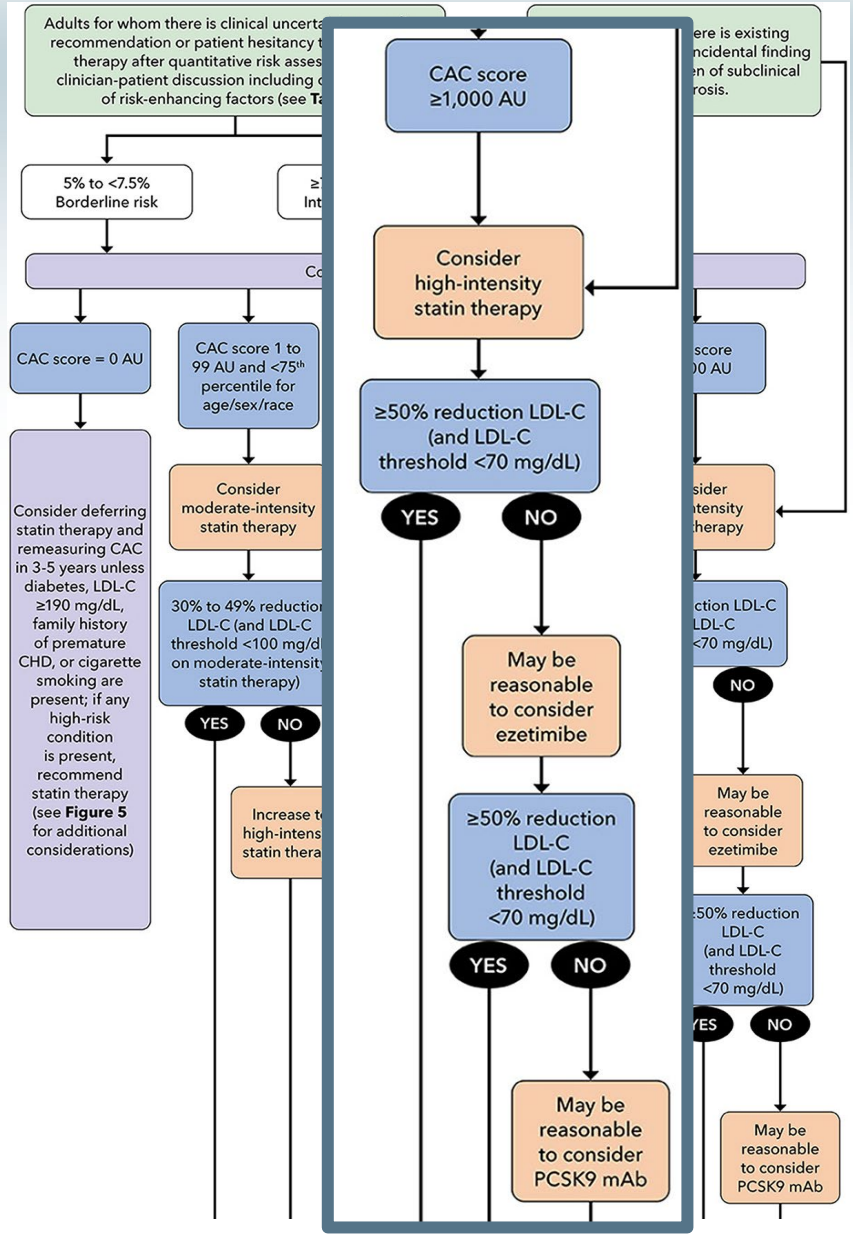
Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment

CAC scores ≥1,000 AU

- Data from CAC Consortium and MESA demonstrated very high annual clinical ASCVD event rates in individuals not on baseline statin therapy (3.3 per 100 person-years)
- Based on the high ASCVD risk in such individuals, if maximally tolerated statin and ezetimibe therapy results in inadequate lowering of LDL-C, with <50% LDL-C reduction or LDL-C ≥70 mg/dL, the addition of a PCSK9 mAb may be considered.
  - Bempedoic acid not added due to absence of CVOTs



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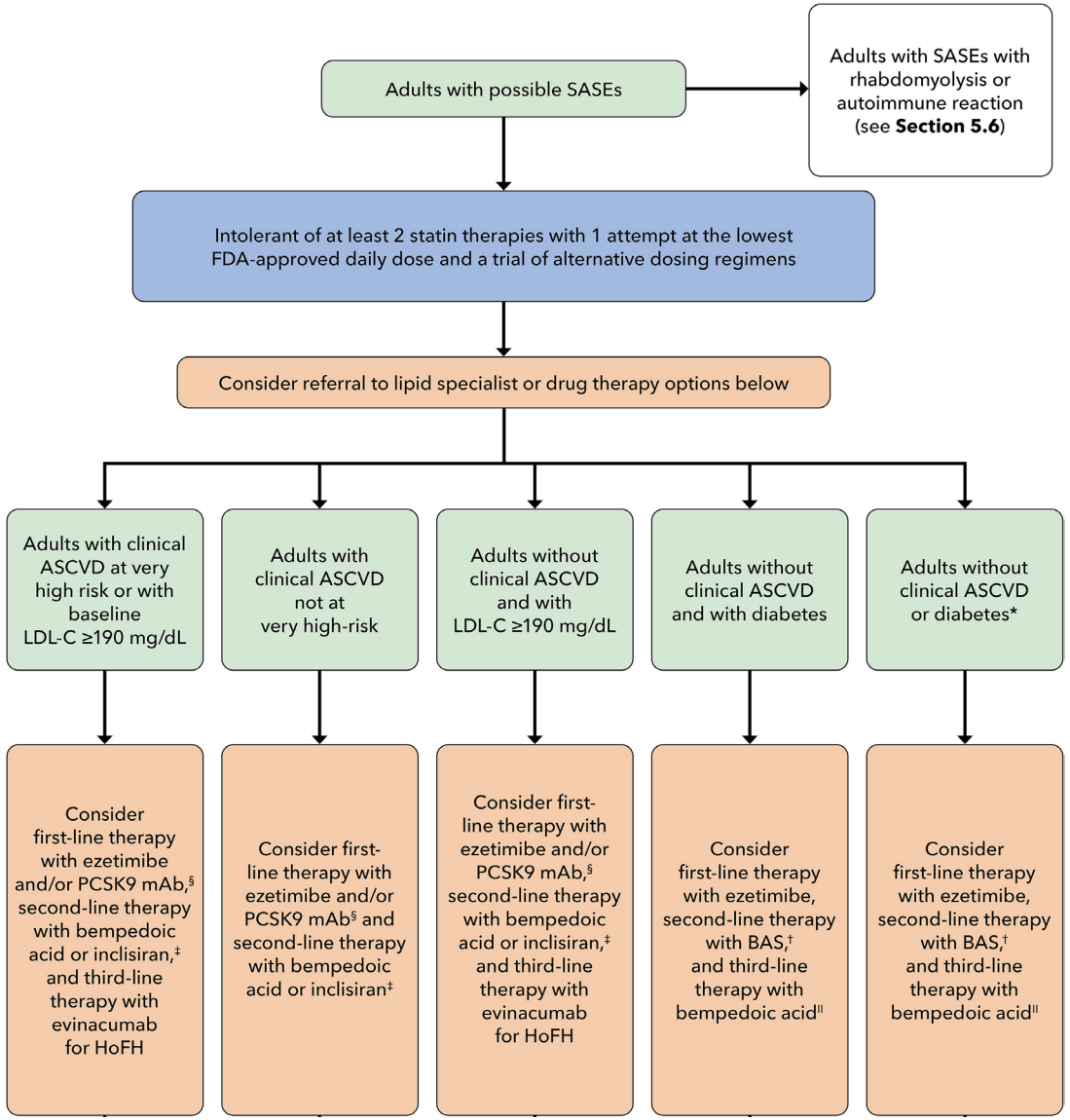
Adults With Possible Statin-Associated Side Effects

Use of CAC assessment may be particularly useful in primary prevention patients with SASEs.

- CAC score of 0 AU in a patient with documented SASEs at borderline or intermediate risk
  - Could reinforce a decision to defer lipid-lowering therapy (provided the patient does not have diabetes, heavy current smoking, or a strong family history)
- CAC score of ≥100 AU or ≥75th percentile
  - Should reinforce efforts to find evidence-based LDL-C–lowering strategies to reduce the ASCVD risk in such a patient



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Summary

Foundation of therapy remains statins

Additional evidence-based non-statins

- Ezetimibe
- PCSK9 mAB
- Bempedoic acid

Therapy with outcomes trials in progress

- Inclisiran

Novel therapies in development

- Obicetrapib
- MK-0616
- ASO/siRNA therapies [PCSK9, ANGPTL3]
- Gene editing

- **HoFH-specific therapies**
  - Lomitapide
  - Evinacumab
  - (LDL apheresis)

Thank you!