Lipid lowering: current status and future perspectives in the prevention of cardiovascular diseases

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14TH NATIONAL CONGRESS OF CARDIOLOGY
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13/12/2025

Baku, Hilton hotel conference hall

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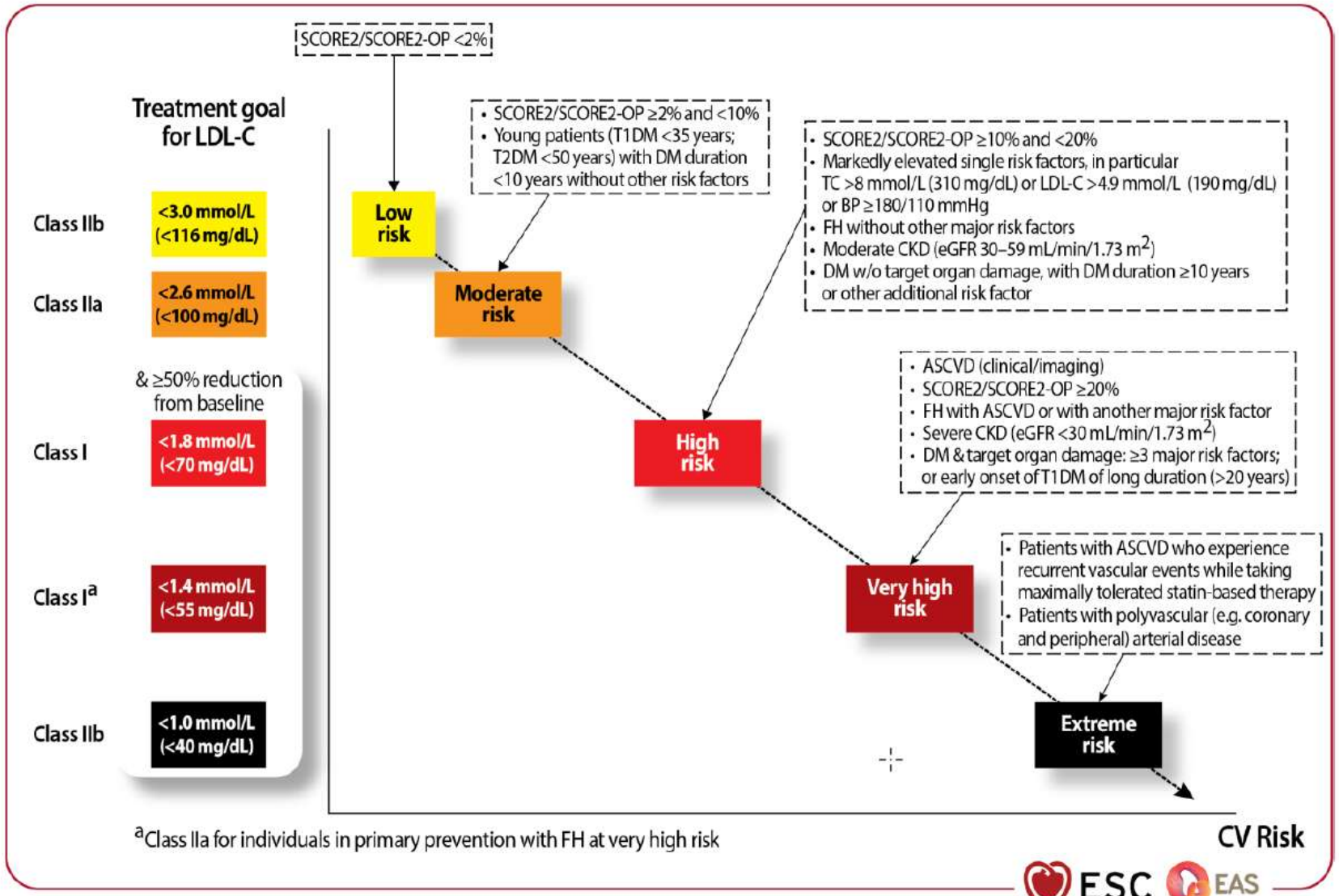
Figure 1

Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular risk.



2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias (European Heart Journal; doi: 10.1093/eurheartj/ehaf190)

Last 50 years in hypolipidemic hystory

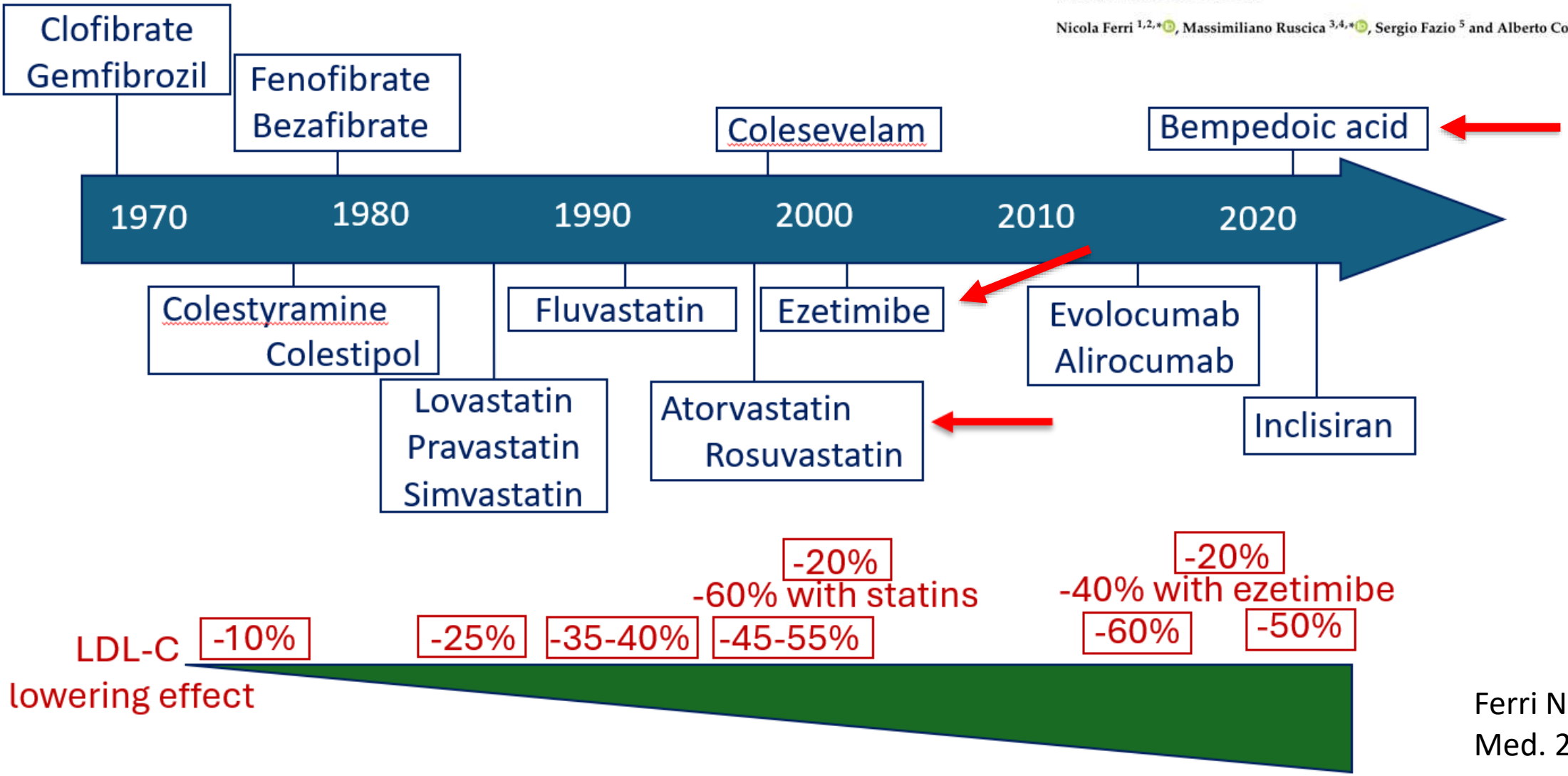
Journal of Clinical Medicine

MDPI

Review

Low-Density Lipoprotein Cholesterol-Lowering Drugs: A Narrative Review

Nicola Ferri [1,2,*], Massimiliano Ruscica [3,4,*], Sergio Fazio [5] and Alberto Corsini [3]



Ferri N et al J. Clin. Med. 2024, 13, 943

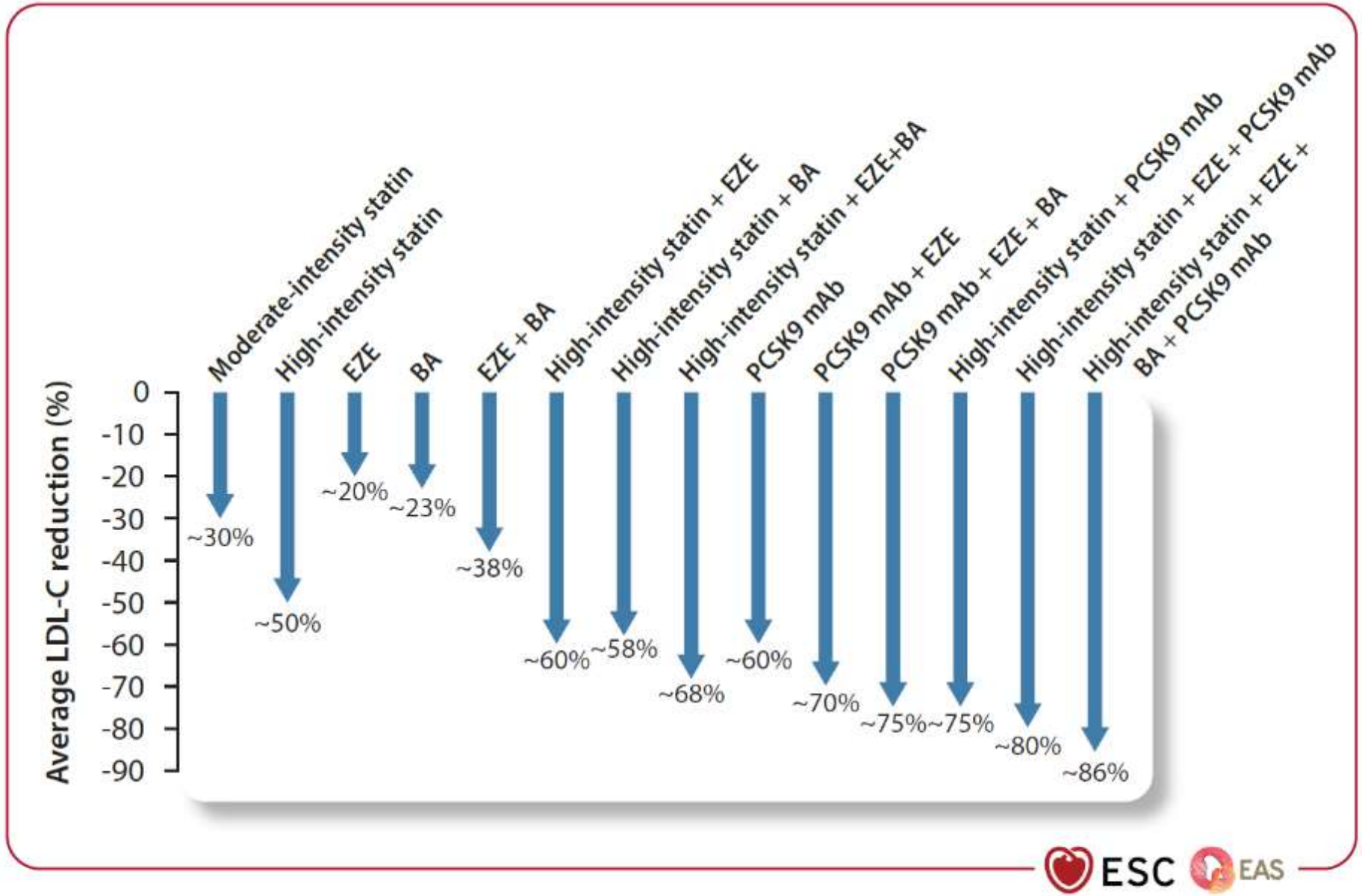


Figure 2 Average reduction in low-density lipoprotein cholesterol levels with different pharmacological therapies with proven cardiovascular benefits. BA, bempedoic acid; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody.

Established therapies

• Statins – inhibit HMG-CoA reductase, limit cholesterol byosinthesis, increase LDLR activity.

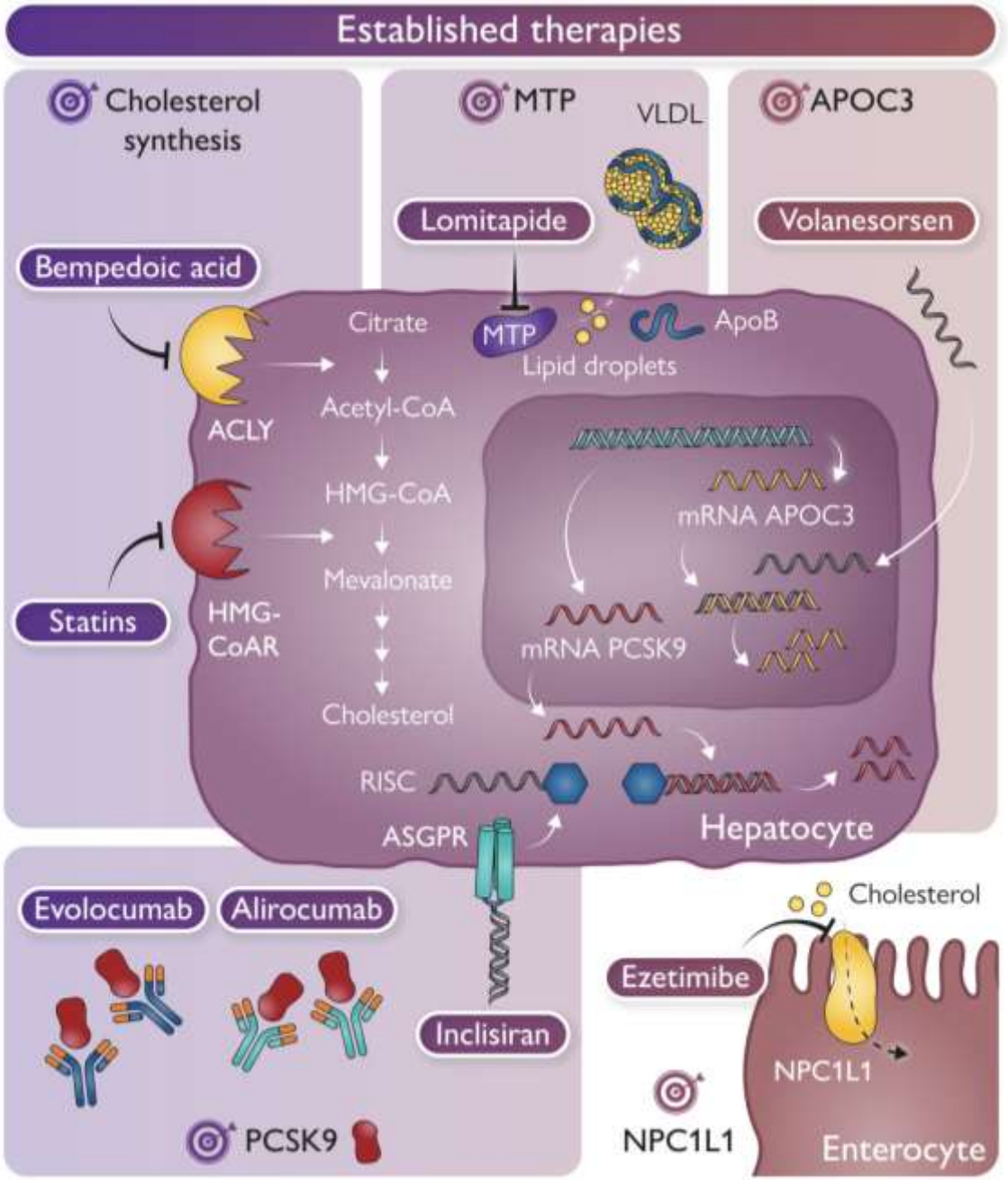
• Bempedoic acid – inhibits ATP citrate lyase, limits cholesterol byosinthesis, increases LDLR activity.

• Ezetimibe – inhibits intestinal cholesterol absorption (NPC1L1).

• PCSK9 inhibitors – prevent LDLR degradation, enhancing LDL-C clearance.

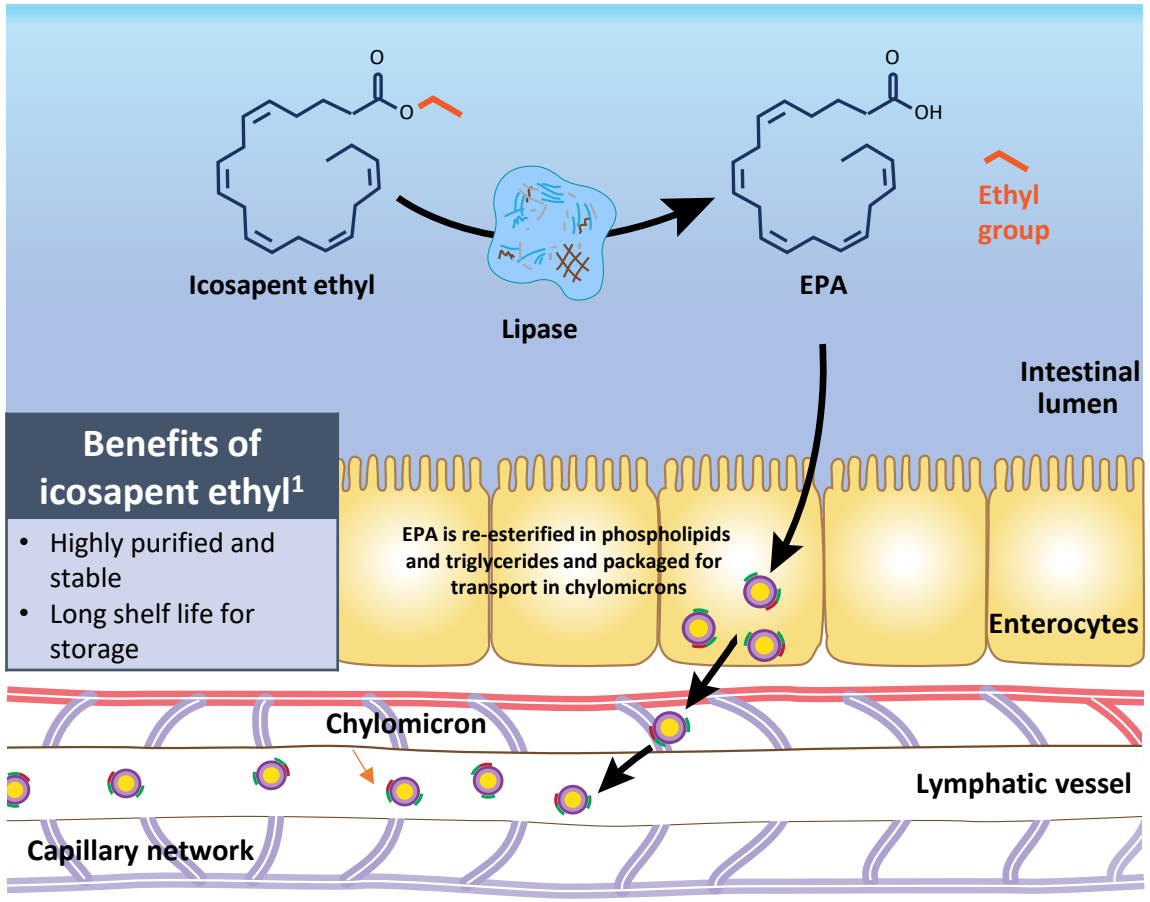
• MTP inhibitors – prevent VLDL synthesis.

• ApoC3 ASO – silences apoC3 mRNA, increases LPL activity.



Ballantyne CM and Norata GD. EHJ 2025

Icosapent Ethyl Pharmacokinetics



Adapted from: Wang X, et al. *Curr Diab Rep*. 2020;20(11):65.[1]

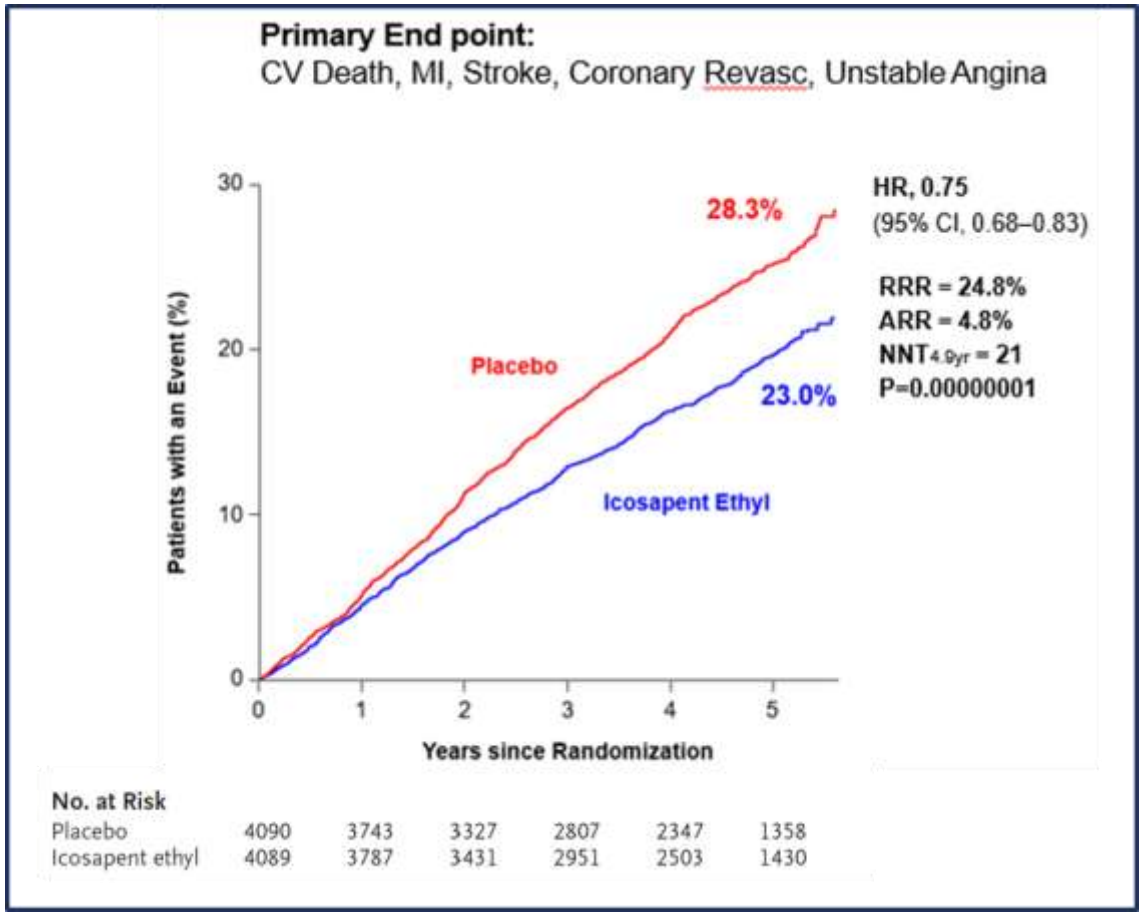
- Addition of ethyl ester enables:[2]
  - Greater purification
  - Higher concentration
  - Higher stability
  - Longer shelf life
- Icosapent ethyl is de-esterified to EPA in the small intestine and absorbed[2]
- Once absorbed, EPA is transported in blood inside chylomicrons.[2]
- Peak plasma concentrations of EPA ~5 hours.[2]
- 99% bound to plasma proteins.[2]
- Plasma elimination $t_{1/2}$ = 89 hours.[2]
- Elimination is by hepatic metabolism.[2]
- Does not undergo renal excretion.[2]

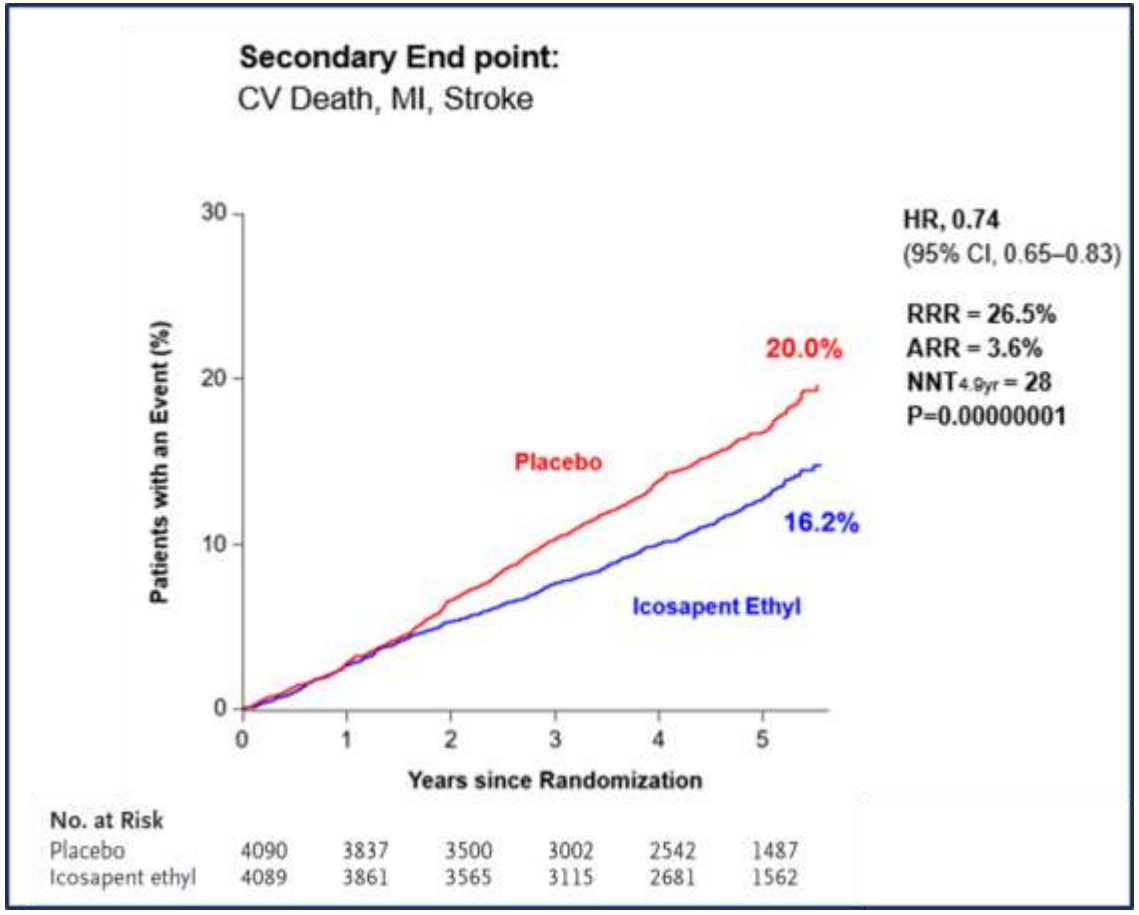
EPA, eicosapentaenoic acid; $t_{1/2}$, half-life.

1. Wang X, et al. *Curr Diab Rep*. 2020;20(11):65; **2.** Brinton EA, et al. *Lipids Health Dis*. 2017;16(1):23.

Primary and key secondary endpoints

Cumulative incidence for the primary and secondary efficacy composite end point in the 2 trial groups in a time-to-event analysis





;

Bhatt DL et al. *N Engl J Med.* 2019;380(1).

New Recommendations (6)

Recommendations	Class	Level
Recommendations for drug treatment of patients with hypertriglyceridaemia		
High-dose icosapent ethyl (2 x 2 g/day) should be considered in combination with a statin in high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride levels 135–499 mg/dL or 1.52–5.63 mmol/L) to reduce the risk of cardiovascular events.	IIa	B
Volanesorsen (300 mg/week) should be considered in patients with severe hypertriglyceridaemia (>750 mg/dL or >8.5 mmol/L) due to familial chylomicronaemia syndrome, to lower triglyceride levels and reduce the risk of pancreatitis.	IIa	B

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evinacumab in Patients with Refractory Hypercholesterolemia

Robert S. Rosenson, M.D., Lesley J. Burgess, M.D., Ph.D.,
Christoph F. Ebenbichler, M.D., Seth J. Baum, M.D., Erik S.G. Stroes, M.D., Ph.D.,
Shazia Ali, Pharm.D., Nagwa Khilla, M.S., Robert Hamlin, B.S., Robert Pordy, M.D.,
Yuping Dong, Ph.D., Vladimir Son, Ph.D., and Daniel Gaudet, M.D., Ph.D.

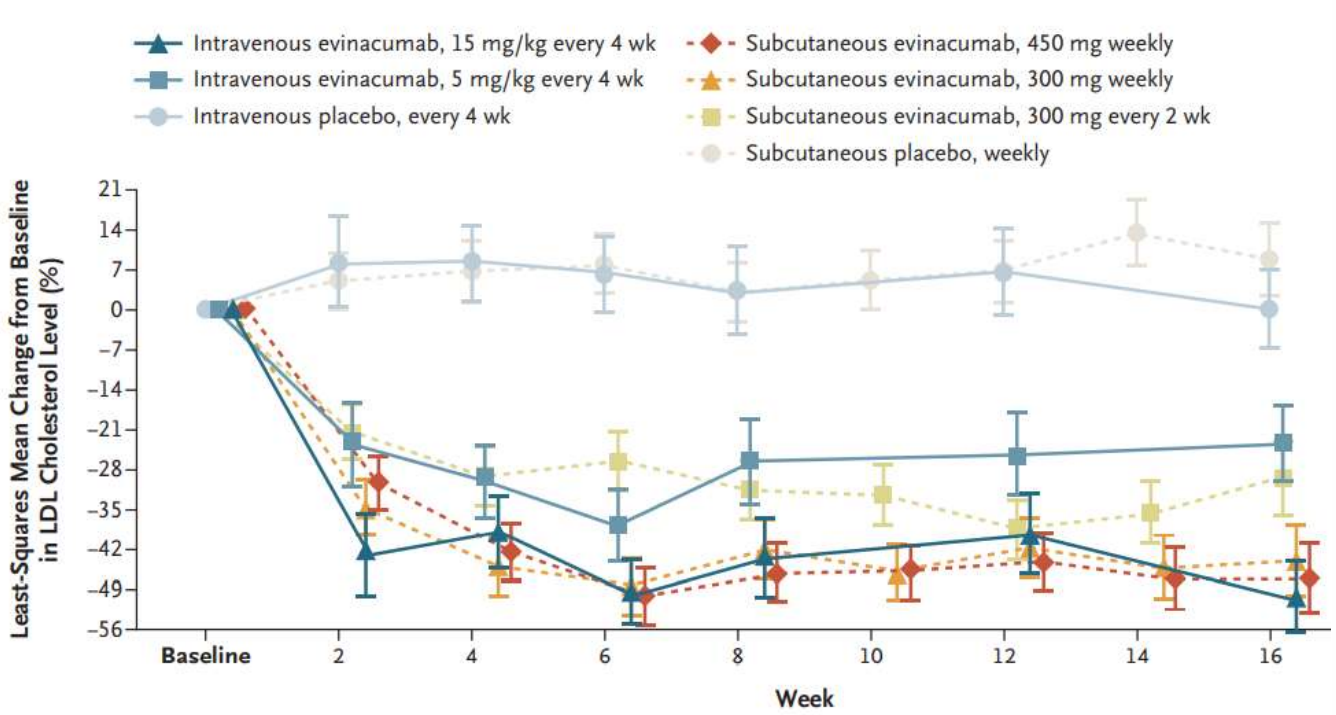
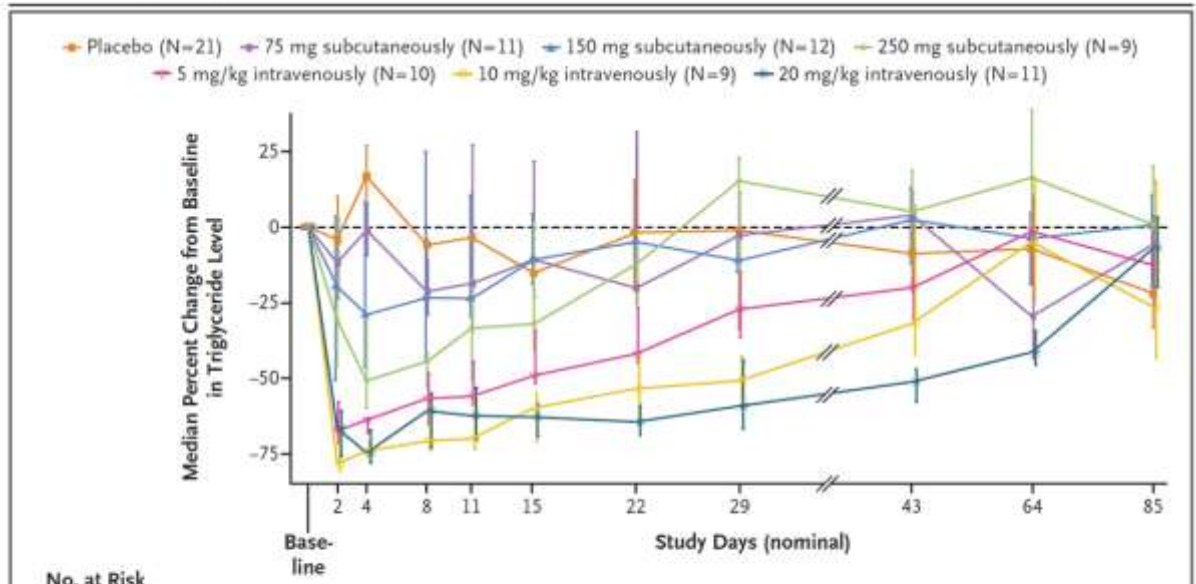
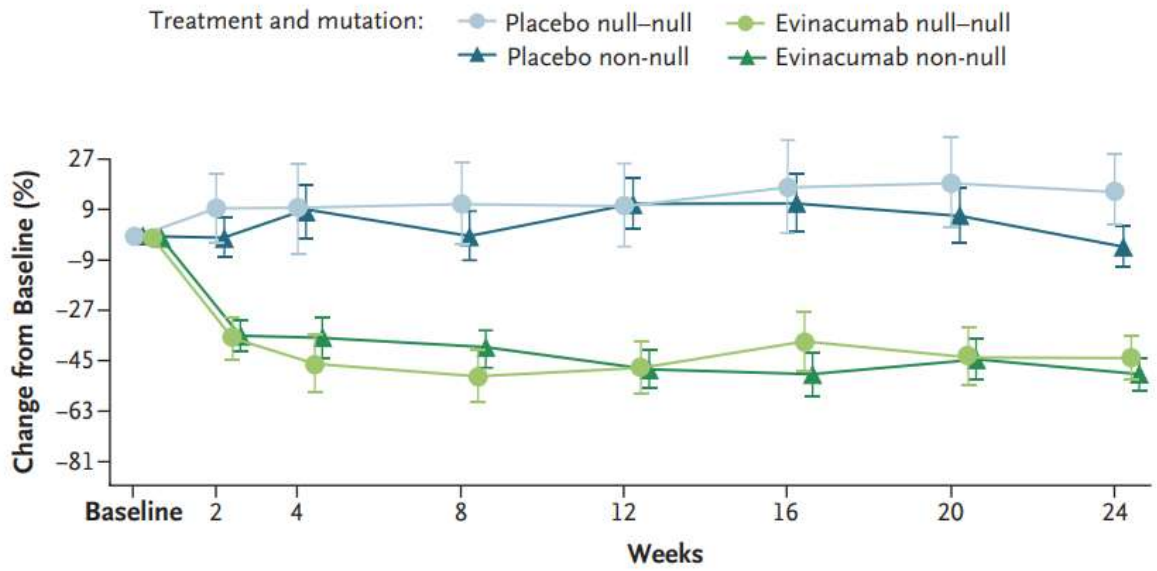


Figure 1. Least-Squares Mean Percent Change from Baseline in the Calculated Low-Density Lipoprotein Cholesterol Level at Week 16.



No. at Risk												
Placebo	21	21	21	21	20	18	19	19	19	18	19
75 mg subcutaneously	11	11	11	9	10	10	9	8	8	9	9
150 mg subcutaneously	12	12	12	12	12	12	11	11	10	8	8
250 mg subcutaneously	9	9	9	7	7	7	7	7	7	7	6
5 mg/kg intravenously	9	10	10	10	10	9	10	10	10	9	9
10 mg/kg intravenously	9	9	9	9	8	9	8	8	8	7	6
20 mg/kg intravenously	11	11	11	11	11	11	11	10	10	10	10

Figure 4. Effects of Inhibition of ANGPTL3 with a Monoclonal Antibody on Triglyceride Levels in Human Volunteers.



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

Figure 2. Percent Change in LDL Cholesterol Levels, According to Type of LDL-Receptor Variants.

Shown is the least-squares mean percent change from baseline in LDL cholesterol levels in the evinacumab group and the placebo group, according to the type of loss-of-function variant in the LDL receptor. Genetic variants that cause a virtually complete absence of LDL-receptor expression (null–null variants) result in higher LDL cholesterol levels than variants that partially reduce LDL-receptor activity (non-null variants). Patients with null–null variants have LDL-receptor activity of less than 15%.

The NEW ENGLAND JOURNAL of MEDICINE

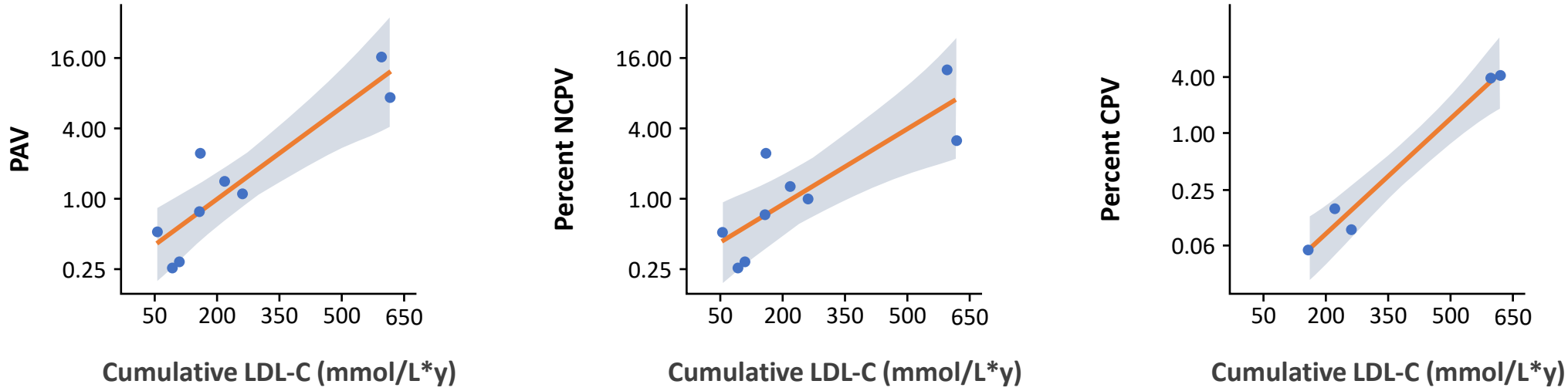
ESTABLISHED IN 1812 AUGUST 20, 2020 VOL. 383 NO. 8

Evinacumab for Homozygous Familial Hypercholesterolemia

Frederick J. Raal, M.D., Ph.D., Robert S. Rosenson, M.D., Laurens F. Reeskamp, M.D., G. Kees Hovingh, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Paolo Rubba, M.D., Shazia Ali, Pharm.D., Poulabi Banerjee, Ph.D., Kuo-Chen Chan, Ph.D., Daniel A. Gipe, M.D., Nagwa Khilla, M.S., Robert Pordy, M.D., David M. Weinreich, M.D., George D. Yancopoulos, M.D., Ph.D., Yi Zhang, Ph.D., and Daniel Gaudet, M.D., Ph.D., for the ELIPSE HoFH Investigators*

Cumulative LDL-C exposure was significantly correlated to plaque volume at baseline CCTA

- The median absolute atheroma volume was 18.8 mm^3 [IQR 2.8, 22.8] at baseline CCTA
- Every 10 mmol/L*year increment of cumulative LDL-C exposure was associated with a:
  - 5.8% (95% CI: 3.4–8.2, *P*<0.001) higher PAV
  - 4.6% (95% CI: 2.0–7.4, *P*=0.002) higher percent NCPV
  - 7.5% (95% CI: 6.3–8.7, *P*<0.001) higher percent CPV



CCTA, coronary computed tomography angiography; CI, confidence interval; CPV, calcified plaque volume; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NCPV, non-calcified plaque volume; PAV, percent atheroma volume

Schonck WAM *et al. JACC Cardiovasc Imaging* 2024. https://doi.org/10.1016/j.jcmg.2024.05.005

RNA Based Therapies

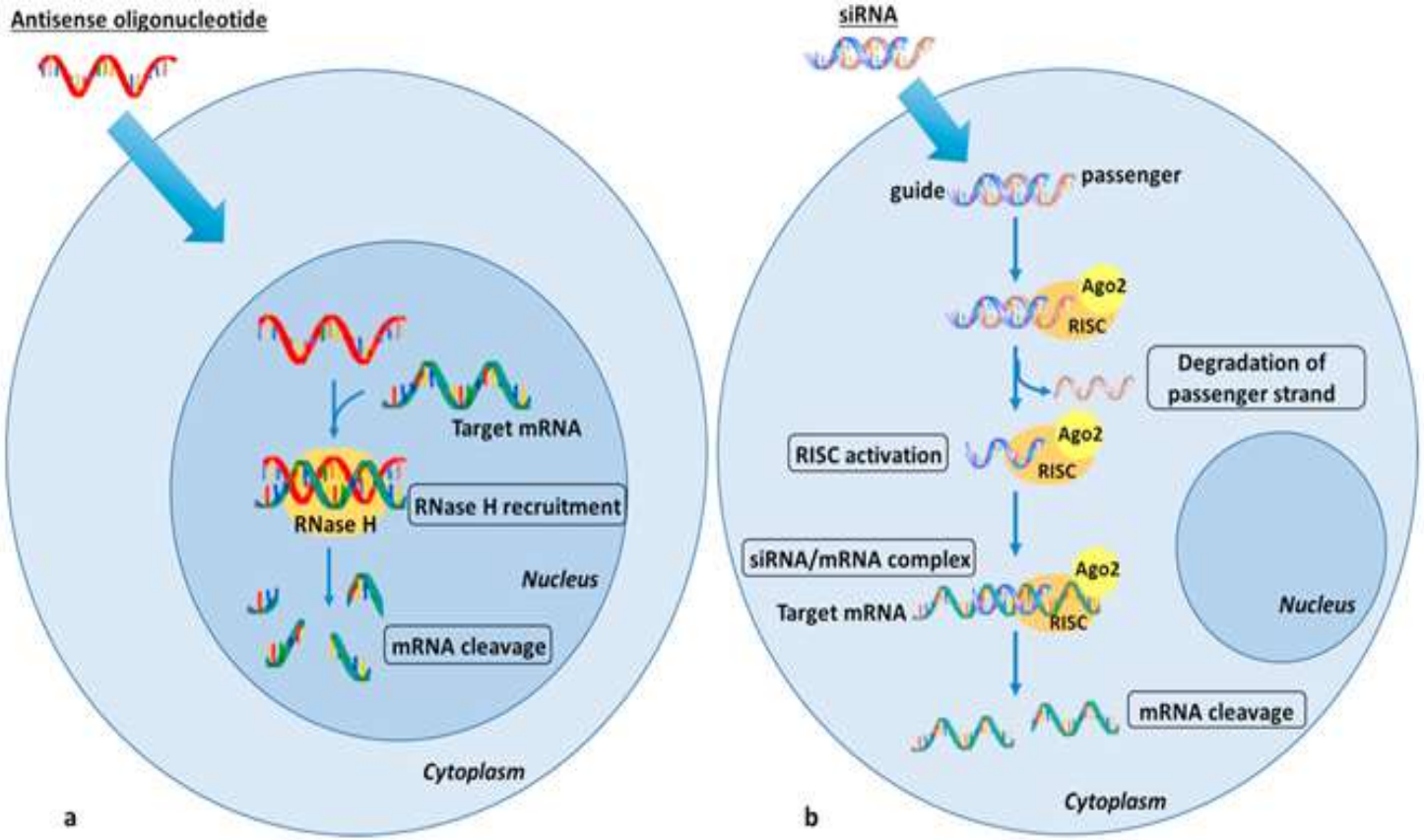
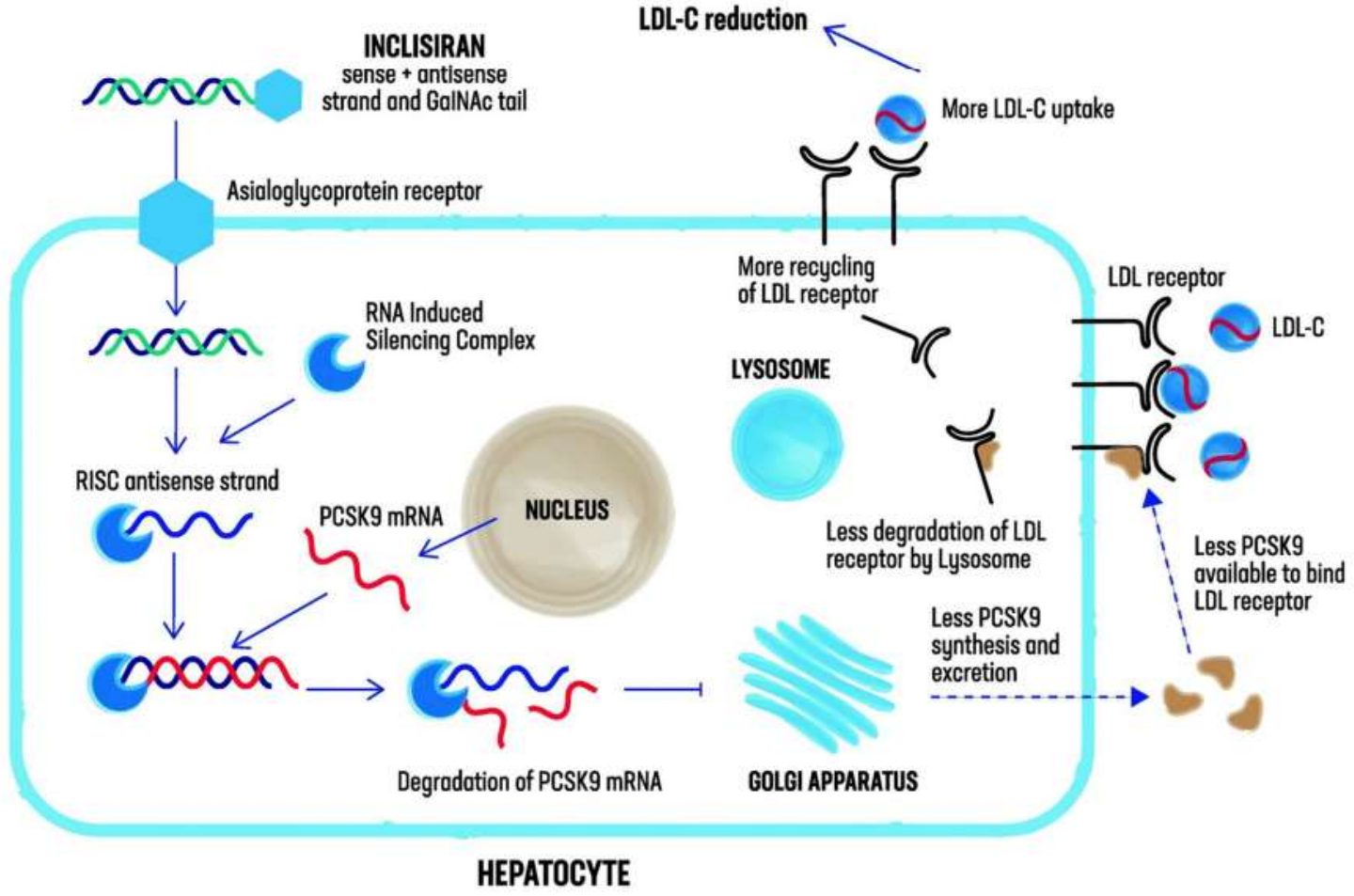


Fig. 1. *RNA-based therapeutic approaches: ASO and siRNA. Panel a)* antisense oligonucleotides (ASOs) control gene expression by the involvement of the RNase H1, an endoribonuclease that preferentially binds to the DNA-RNA hetero-duplex over RNA-RNA and DNA-DNA homo-duplexes. The final result is the selective cleavage of the RNA strand while the synthetic DNA strand remains intact and free to bind additional target mRNAs; *Panel b)* siRNAs are composed of two strands, the guide and the passenger. Once in the cytoplasm the two strands are separated with the guide loaded into the RISC and the passenger removed and degraded. When the complementary target mRNA has hybridized with part of the guide strand, an endonucleolytic cleavage of the mRNA is driven by a component of RISC, the Argonaute 2 (ago 2) protein.

Inclisiran



- A small interfering RNA that binds to PCSK9 m-RNA in hepatocytes, blocking PCSK9's translation and production
- The addition of GalNAc increases liver-specific uptake

Cleared from plasma in 24 hours preventing off target toxicity

No PCSK9 + Ab complex in plasma

Extended duration, biannual dosing adequate: may increase adherence

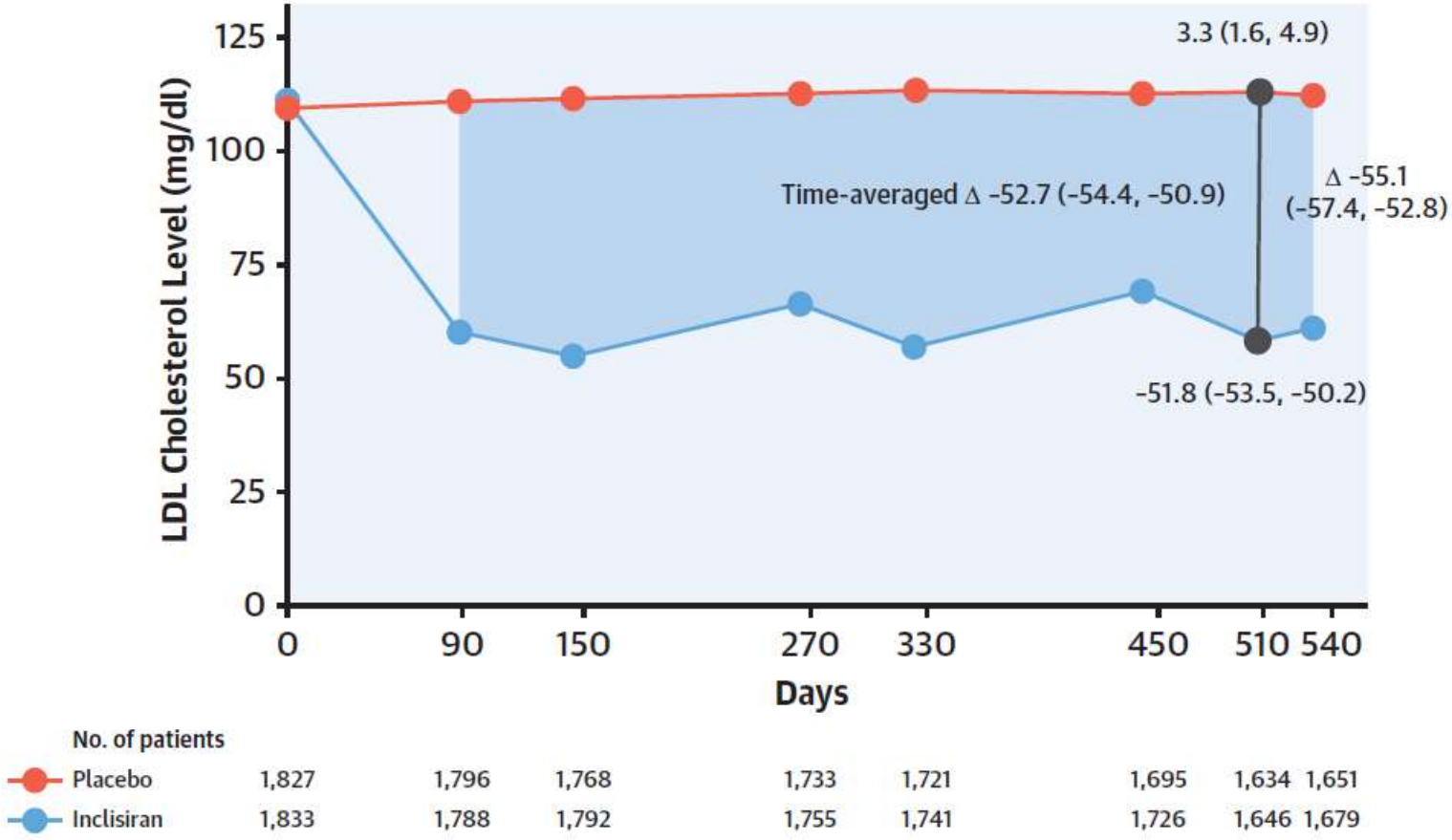
Sinning D and Landmesser U. Curr Cardiol Rep. 2020;22(12):176

ORION Studies

Trials	Patients	Endpoints
ORION-1	ASCVD (N=501)	LDL-C lowering (Phase II)
ORION-2	HoFH (N=10)	LDL-C lowering (Phase II)
ORION-3	ASCVD or ASCVD RE or HeFH (N=490)	LDL-C lowering (extension of ORION-1)
ORION-4	ASCVD or RE (N=15,000)	Cardiovascular M&M (Phase III)
ORION-5	HoFH (N=60)	LDL-C lowering (Phase III)
ORION-6	Hepatic impairment (N=24-32)	Pharmacokinetics
ORION-7	Renal impairment (N=31)	Pharmacokinetics
ORION-8	ASCVD, ASCVD risk equivalent, HeFH (N=3,460)	LDL-C lowering (extension of ORION -9, -10, -11)
ORION-9	HEFH (N=400)	LDL-C lowering (Phase III)
ORION-10	ASCVD (N=1,500)	LDL-C lowering (US) (Phase III)
ORION-11	ASCVD OR ASCVD RE (N=1,500)	LDL-C lowering (EU) (Phase III)
ORION-12	Healthy volunteers (N=200)	TQT

ORION Phase III pooled analysis:Efficacy

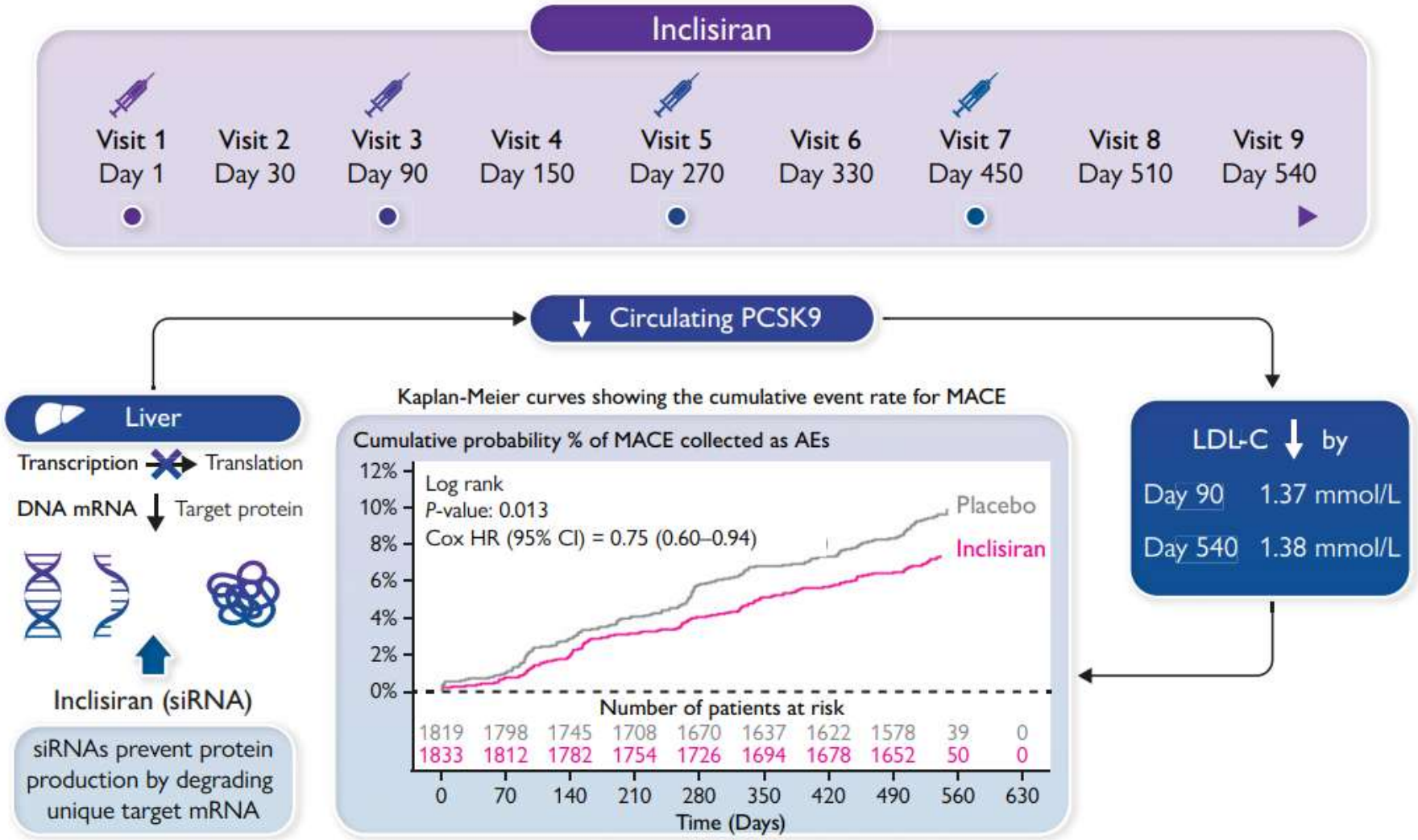
Durable and potent with consistent effect over 18 months



Adapted figure from fig 2(B)

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

Inclisiran and CV Events: patient-level analysis of phase III trials



Inclisiran was associated with a 26% lower probability of MACE ,
Not powered for outcome: hypothesis generating

Ray KK et al. European Heart Journal (2023); 44(2):129-138

Emerging therapies

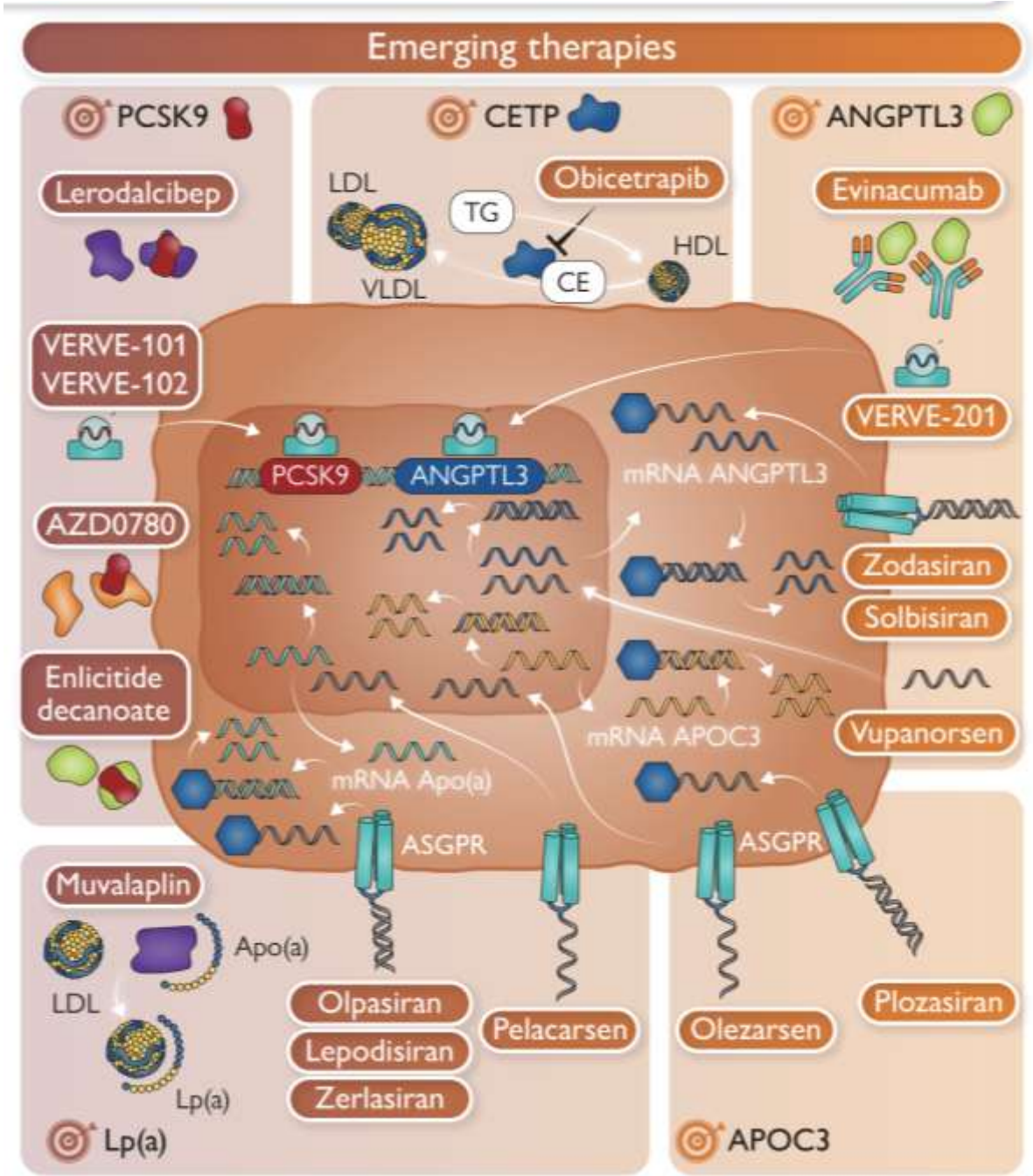
- Novel PCSK9 inhibitors – prevent LDLR degradation, enhancing LDL-C clearance.

- ANGPTL3 inhibition – lowers triglycerides and LDL-C independently of LDLR.

- ApoC-III inhibition – enhances LPL activity, improving TG-rich lipoprotein metabolism.

- CETP inhibition – increases catabolism of apoB-lipoproteins.

- Lp(a) reduction (antisense/siRNA) – addresses specific residual risk factor.



Ballantyne CM and Norata GD. EHJ 2025

ORIGINAL RESEARCH ARTICLE

Orally Bioavailable Macrocyclic Peptide That Inhibits Binding of PCSK9 to the Low Density Lipoprotein Receptor

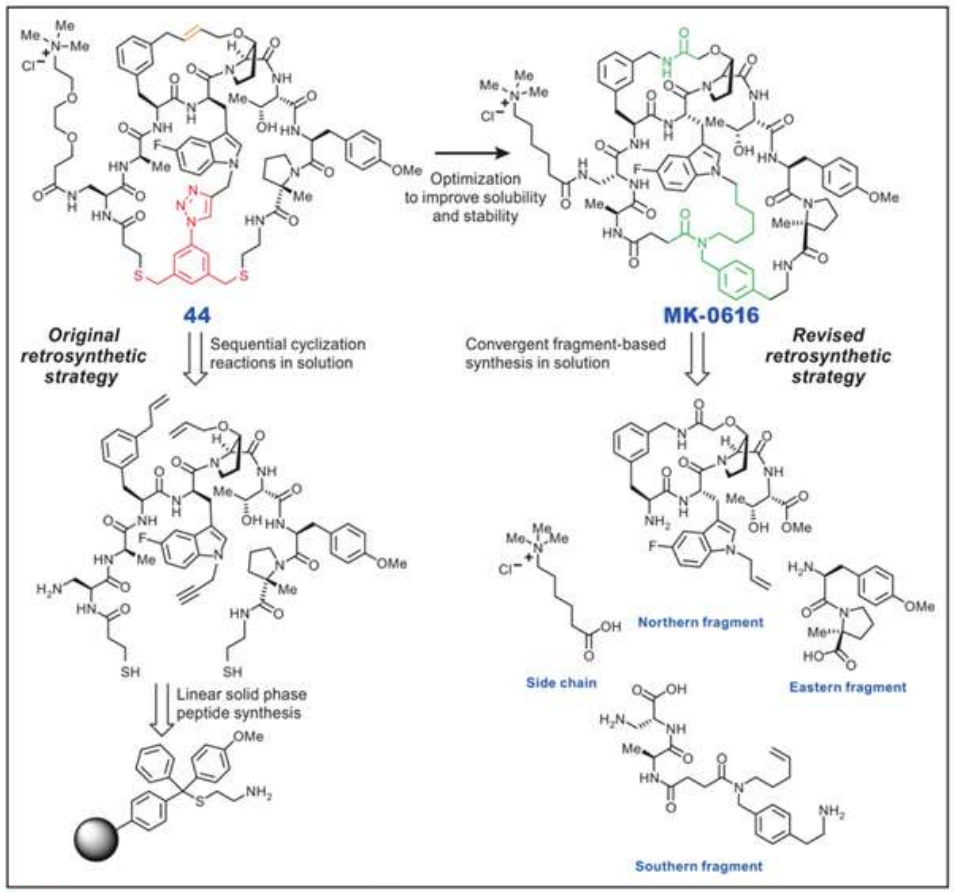


Figure 2. Redesigned synthesis and key features of MK-0616.
Critical modifications of 44 are replacement of the sulfide-based linker and central triazole (red to teal) and changing the northern olefin to an amide crosslinker (orange to teal).

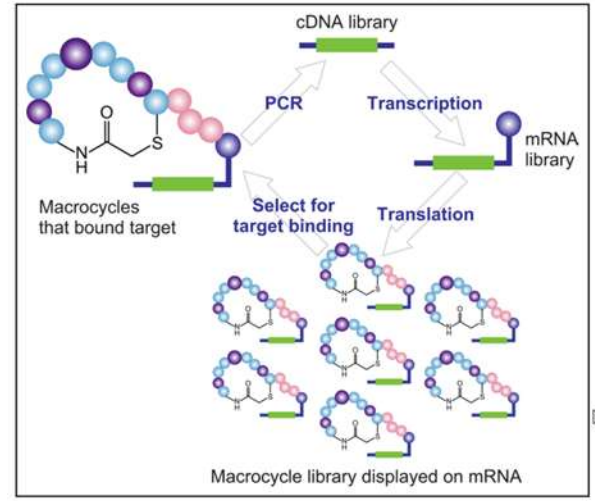


Figure 1. Messenger ribonucleic acid (mRNA) display screening platform.
mRNA display is a powerful in vitro affinity selection platform that allows screening of large, genetically encoded peptide libraries. The platform takes advantage of the transcription/translation machinery and post-translation cyclization, under cell-free conditions to prepare the libraries. A key feature is that the mRNA is covalently linked to its encoded peptide which enables amplification of desired peptides shown to interact with a target of interest. cDNA indicates complementary DNA (deoxyribonucleic acid); and PCR, polymerase chain reaction.

Johns et al

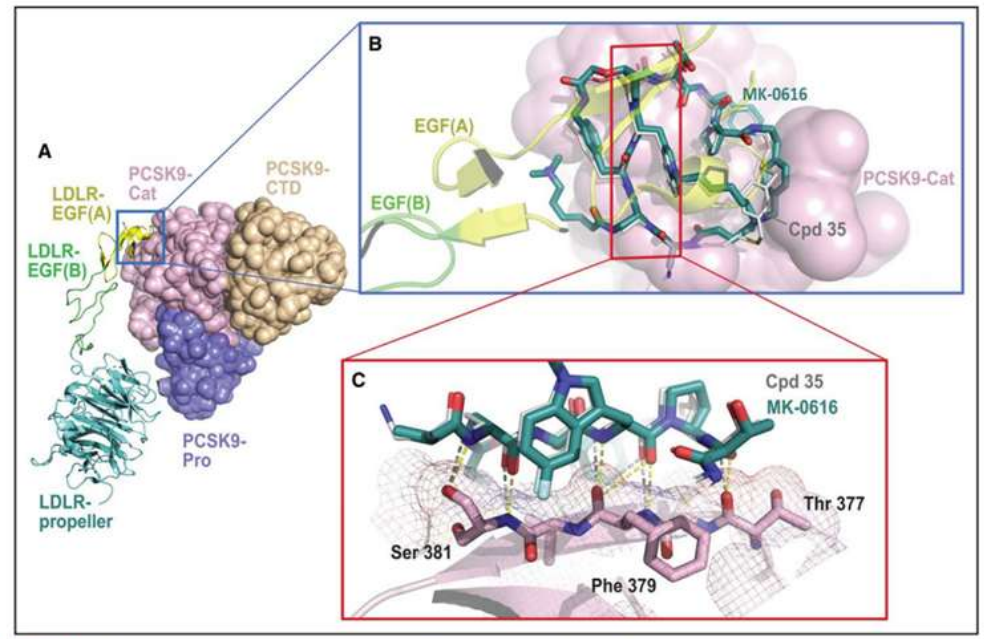
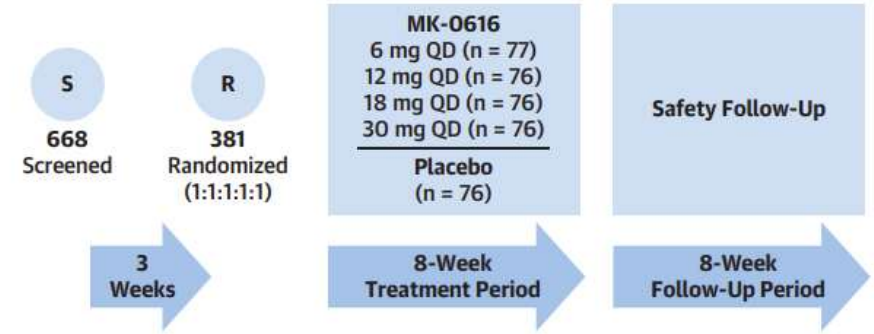


Figure 3. MK-0616-PCSK9 (proprotein convertase subtilisin/kexin type 9) complex.
A, Interaction of PCSK9 catalytic domain and prodomain with the LDLR epidermal growth factor and β-propeller domains, respectively, from PDB ID: 3P5B.[21] **B**, Modeling MK-0616 from related crystal structures (PDB IDs: 6XID, 6XIE, 7SSG, and 7SSH)[18,20] suggests MK-0616 (deep teal) interacts with a flat surface on the PCSK9 catalytic domain (pink surface), interrupting the interaction with the EGF(A) domain (transparent yellow) of LDLR. Compound 35 (PDB ID: 7S5H), a closely related analog of Compound 44,[18,20] is shown in white sticks, overlaid with MK-0616 to illustrate the binding site similarity. **C**, MK-0616 and Compound 35[18,20] can form key hydrogen bonds with T377, F379, and S381 of PCSK9-Cat domain. Cpd 35 indicates Compound 35; EGF, epidermal growth factor; LDLR-EGF, LDL receptor-EGF; PCSK9-Cat, PCSK9-catalytic doman; PCSK9-CTD, PCSK9-C-terminal domain; Phe 379, phenylalanine 379; Ser 381, serine 381; and Thr 377, threonine 377.

CENTRAL ILLUSTRATION A Phase 2b Study of MK-0616, an Oral PCSK9 Inhibitor

Study Design



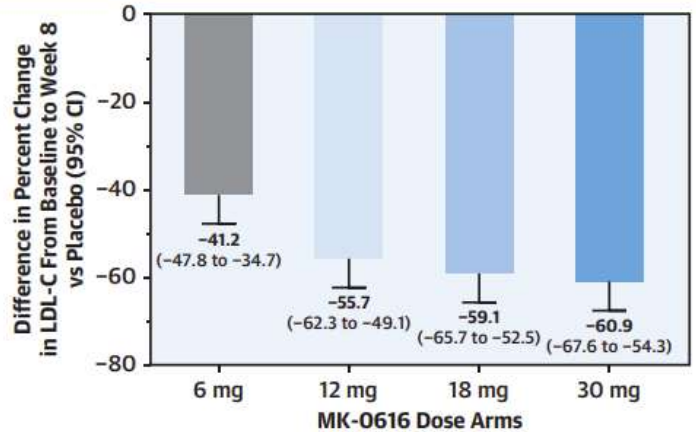
Baseline Participant Characteristics *(n = 381 Randomized Participants)*

Female: 49.3%
Mean LDL-C: 119.5 mg/dL

ASCVD Risk Category:
Clinical ASCVD: 38.6%
Intermediate/High ASCVD Risk: 56.4%
Borderline ASCVD Risk: 4.7%

Statin Intensity:
No Statin: 39.4%
Low-to-Moderate Intensity: 34.6%
High Intensity: 26.0%

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

Ballantyne CM, et al. J Am Coll Cardiol. 2023;81(16):1553-1564.

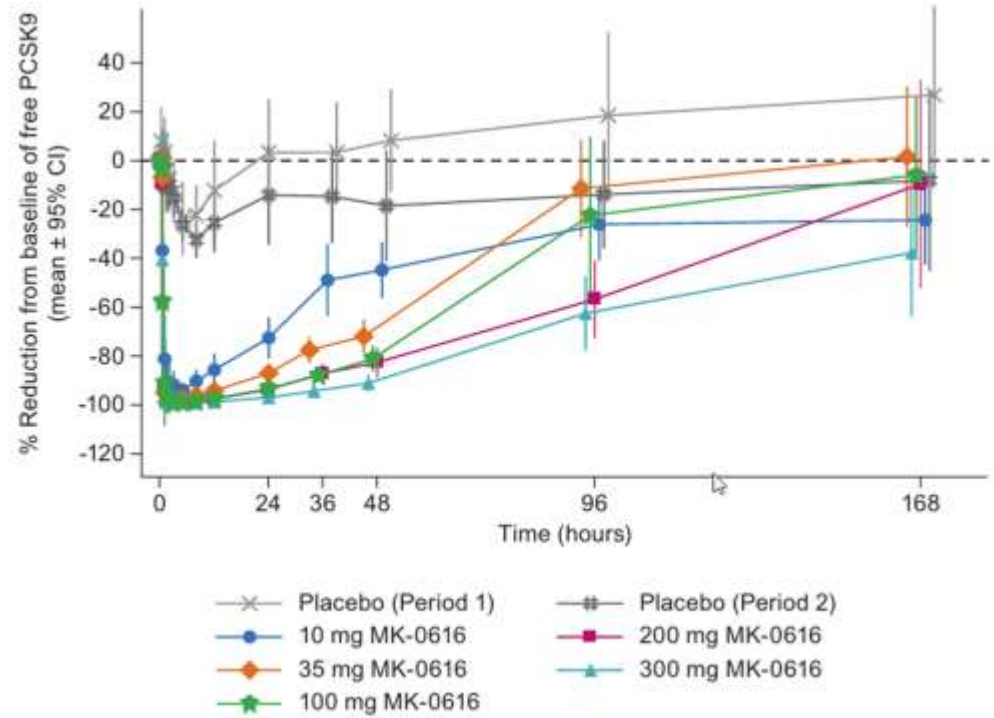
This Phase 2b, randomized, controlled trial randomized 381 participants for 16 weeks including an 8-week treatment period and an 8-week follow-up period. **(Lower left)** The forest plot shows statistically significant ($P < 0.001$) reductions in LDL-C at Week 8 of treatment for all MK-0616 doses vs placebo. AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; QD = once daily.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 81, NO. 16, 2023

ORIGINAL INVESTIGATIONS

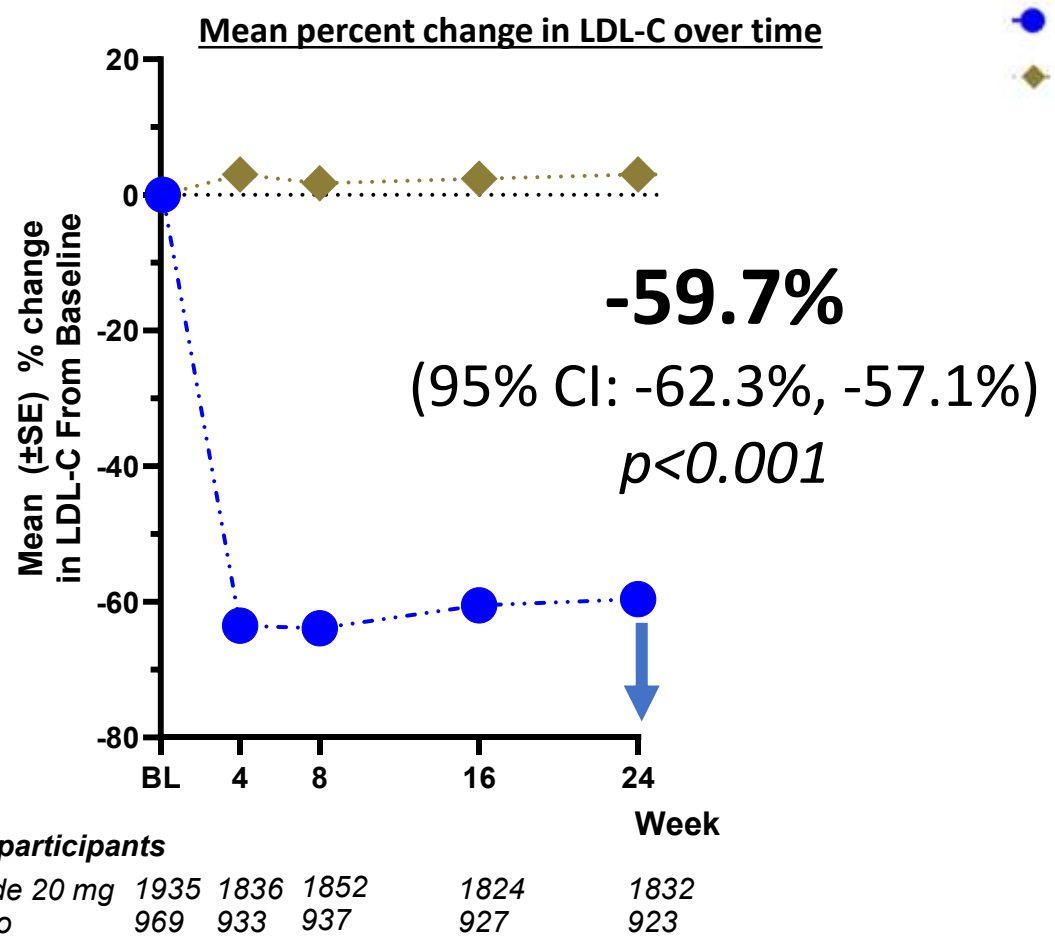
Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616

Christie M. Ballantyne, MD,[a] Puja Banka, MD,[b] Gustavo Mendez, MD,[c] Raymundo Garcia, MD,[d] Julio Rosenstock, MD,[e] Anthony Rodgers, MS,[b] Geraldine Mendizabal, MD,[b] Yale Mitchel, MD,[b] Alberico L. Catapano, MDISC, PHD[f,g]



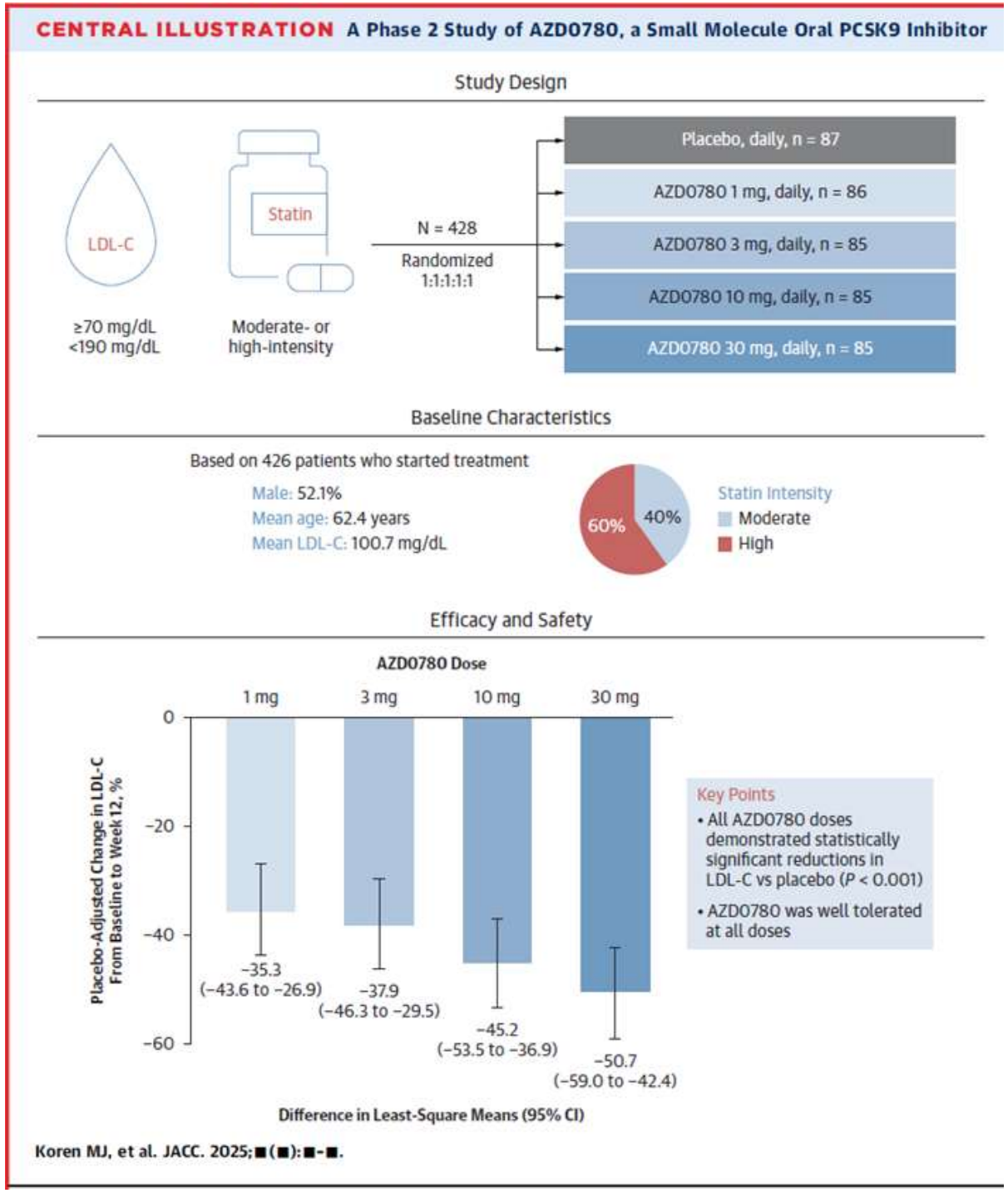
Robust LDL-C Reduction at Week 24

Post-hoc Re-analysis



	Enlicitide	Placebo
Baseline	95.2 mg/dL *SD 38.6*	98.3 mg/dL *SD 39.2*
Week 24	38.8 mg/dL *SD 35.5* **-59.6%**	98.6 mg/dL *SD 42.5* **+3.0%**

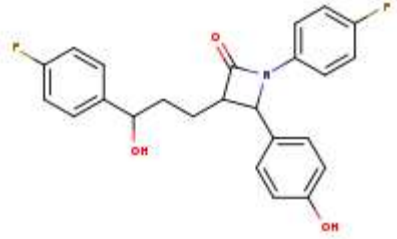
Beta-quantification-derived LDL-C values of ≤0 treated as missing and MH LDL-C used if available.



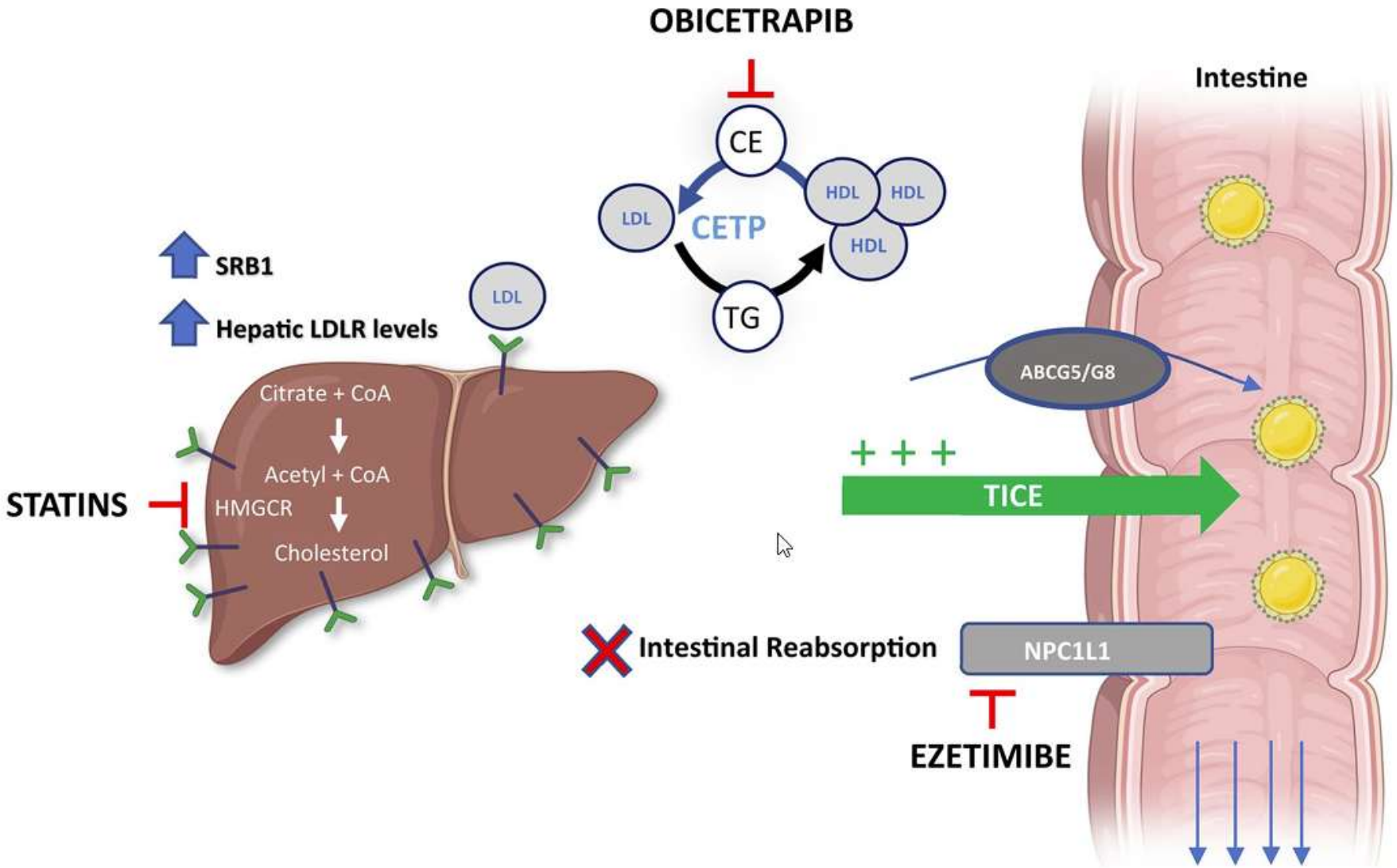
An Oral PCSK9 Inhibitor for Treatment of Hypercholesterolemia

The PURSUIT Randomized Trial

Michael J. Koren, MD,[a] Rick B. Vega, PhD,[b] Nikhil Agrawal, MD,[c] Yuejia Xu, PhD,[d] April M. Barbour, PhD,[e] Hongtao Yu, PhD,[e] Emelie Wallerstedt, PhD,[f] Debra Carter, MD,[g] Jessica Middlemiss, BSc,[h] Lee Twaddle, BSc,[h] Michael C. McCarthy, MD,[i] Jaya B. Rosenmeier, MD, PhD[i]



AZD0780 (LAROPROVSTAT) inhibits lysosomal trafficking of PSCK9-LDLR complexes and prevents PCSK9-induced LDLR degradation

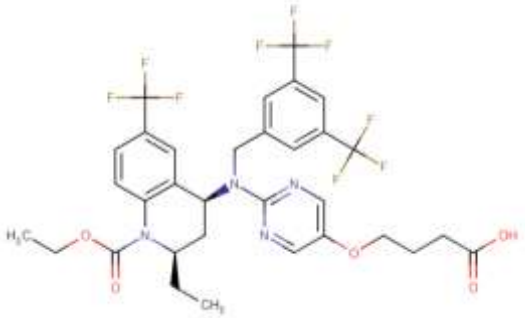


Current Atherosclerosis Reports (2024) 26:35–44

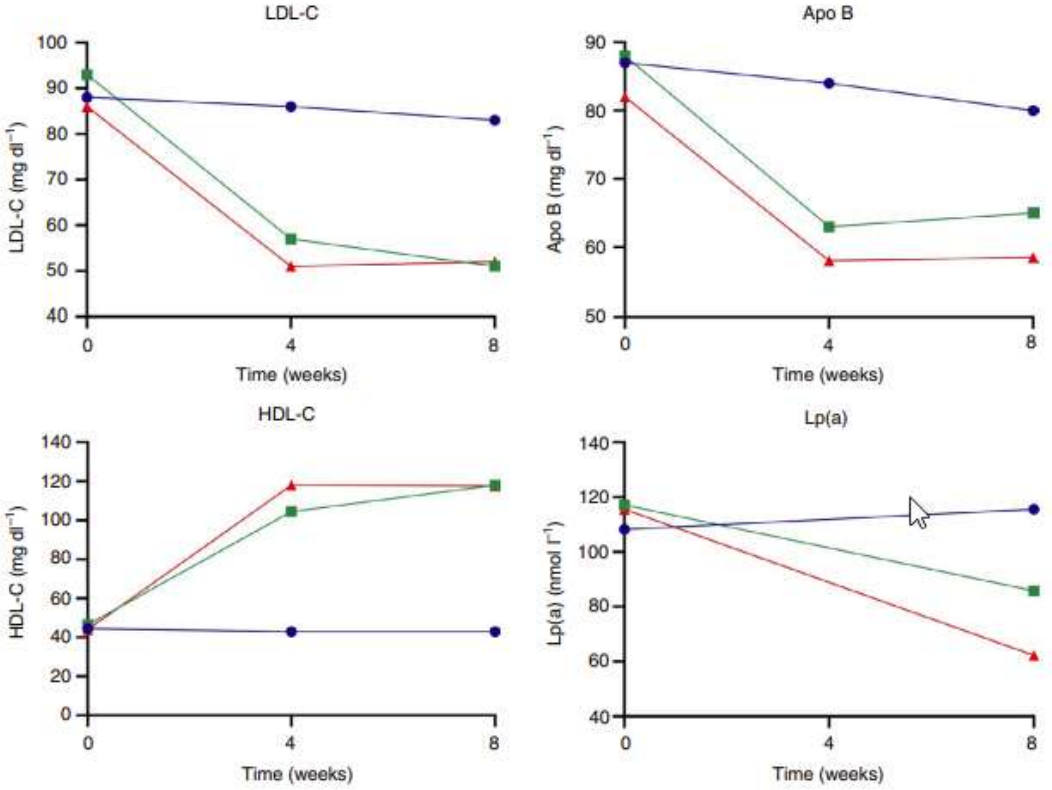
Proposed mechanisms of action for low-density lipoprotein cholesterol lowering with the combination of obicetrapib with ezetimibe on top of statins. Abbreviations: ABCG5/G8, ATP-binding cassette sub-family G member 5/member 8; CE, cholesteryl ester; CoA, coenzyme A; HDL, high-density lipoprotein; HMGCR, hydroxy-3-methylglutaryl coenzyme A reductase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; NPC1L1, Niemann Pick C-1 Like-1; TG, triglyceride; SRB1, scavenger receptor class B, type 1; TICE, transintestinal cholesterol excretion (used with permission from Elsevier from: Ballantyne CM, et al. J Clin Lipidol. 2023. https://doi.org/10.1016/j.jacl.2023.05.098, permission conveyed through Copyright Clearance Center, Inc.) [35•]

Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial

Stephen J. Nicholls[1,2], Marc Ditmarsch[2], John J. Kastelein[3], Scott P. Rigby[4], Douglas Kling[2], Danielle L. Curcio[2], Nicholas John Alp[5] and Michael H. Davidson[2]



The ongoing phase II OCEAN trial[145] will assess obicetrapib as a combination therapy with ezetimibe in patients with LDL cholesterol levels of >1.8 mmol/l and >2.5 mmol/l. The PREVAIL trial[146], a cardiovascular outcomes study to evaluate obicetrapib in patients with ASCVD, started recruitment in 2022 and will follow about 9,000 participants over the next 4 years.



Per cent changes from baseline for LDL-C and HDL-C as conferred by CETP inhibitors

CETP inhibitor	Dose (mg)	LDL-C (mmol/L) % change from baseline	HDL-C (mmol/L) % change from baseline	Years
Torcetrapib	60	−15.7	33.1	2006
Dalcetrapib	600	−5.4	26.4	2009
Anacetrapib	100	−23.4	138.1	2010
Evacetrapib	100	−22.3	94.6	2011
Obicetrapib	5	−45.3	157.1	2015

Open in a sepa

Shown is the change in LDL-C and HDL-C levels of the different CETP inhibitors.
CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-densi cholesterol.

Fig. 2 | Median lipoprotein lipid concentrations. a–d, LDL-C concentrations measured by the Friedewald formula (**a**), Apo B (**b**), HDL-C (**c**) and Lp(a) (**d**) for the placebo (blue), obicetrapib 5 mg (green) and obicetrapib 10 mg (red) groups ($n = 40$ each), administered on a background of high-intensity statin treatment at baseline and after 4 and 8 weeks of treatment (only after 8 weeks of treatment for Lp(a)).

Numohamed NS et al Cardiovasc Res. 2022 Oct; 118(14): 2919–2931

Fixed-dose combination of obicetrapib and ezetimibe for LDL cholesterol reduction (TANDEM): a phase 3, randomised, double-blind, placebo-controlled trial

Ashish Sarraju, Danielle Brennan, Kierstyn Hayden, Amanda Stronczek, Anne C Goldberg, Erin D Michos, Darren K McGuire, Denise Mason, Grace Tercek, Stephen J Nicholls, Douglas Kling, Annie L Neild, John Kastelein, Michael Davidson, Marc Ditmarsch, Steven E Nissen

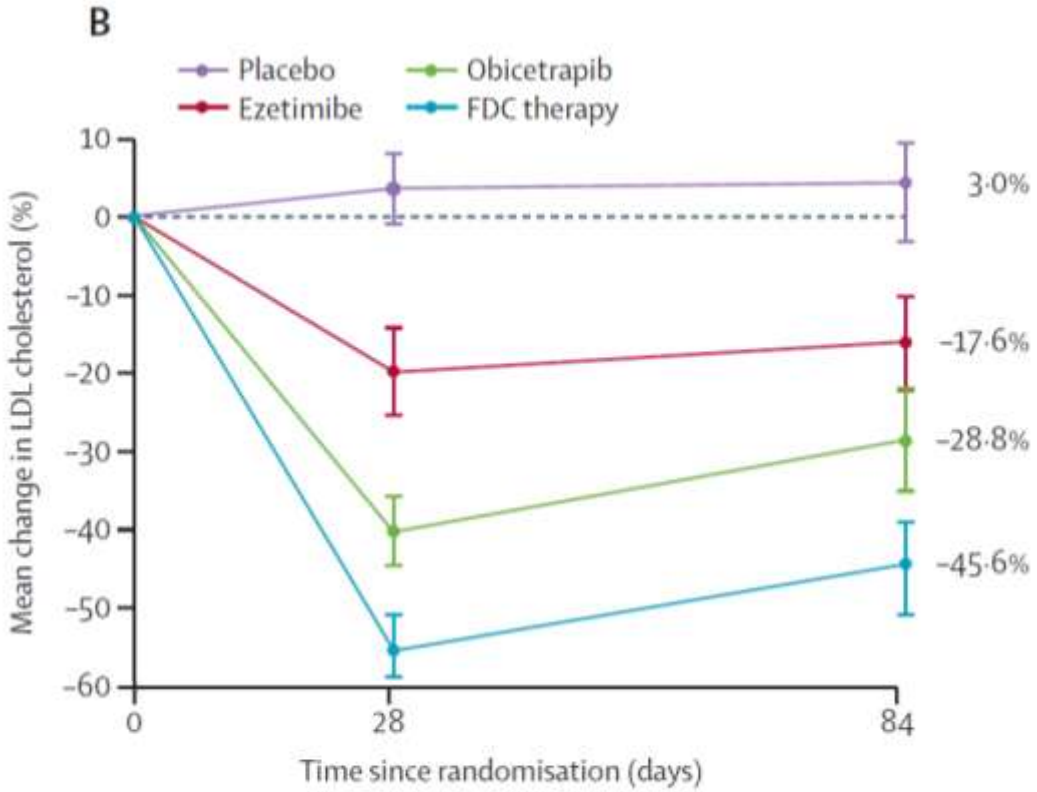
Inclusion criteria

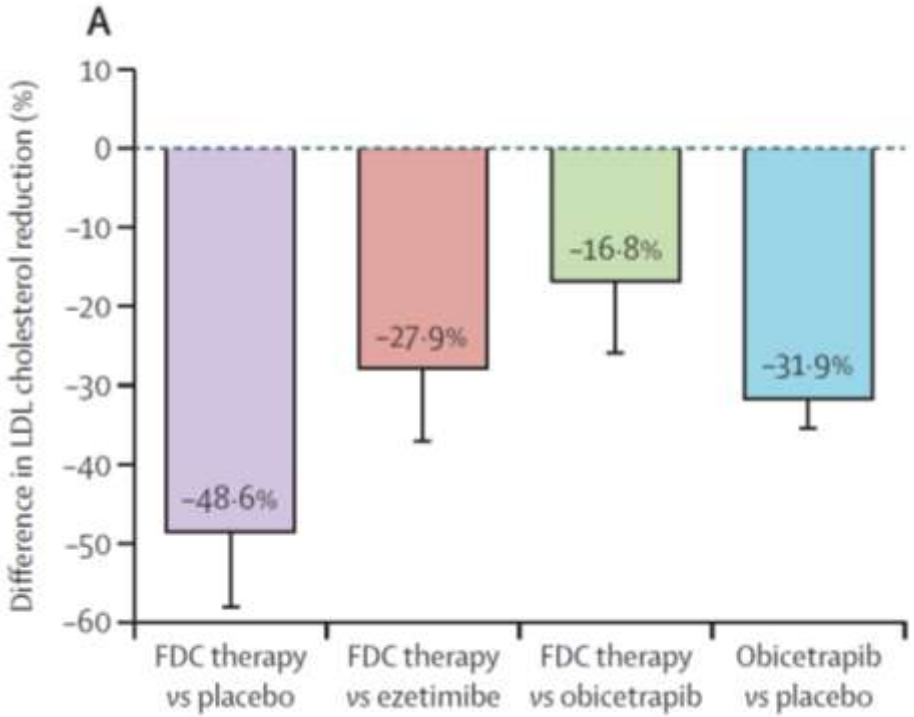
Pre-existing or high risk for ASVCD or
heFH with LDL-C ≥ 70 mg/dL

obicetrapib 10 mg plus ezetimibe 10 mg FDC obicetrapib
obicetrapib 10 mg monotherapy
ezetimibe 10 mg monotherapy
Placebo

Endpoint

Percent change in the LDL-C level from baseline to day 84

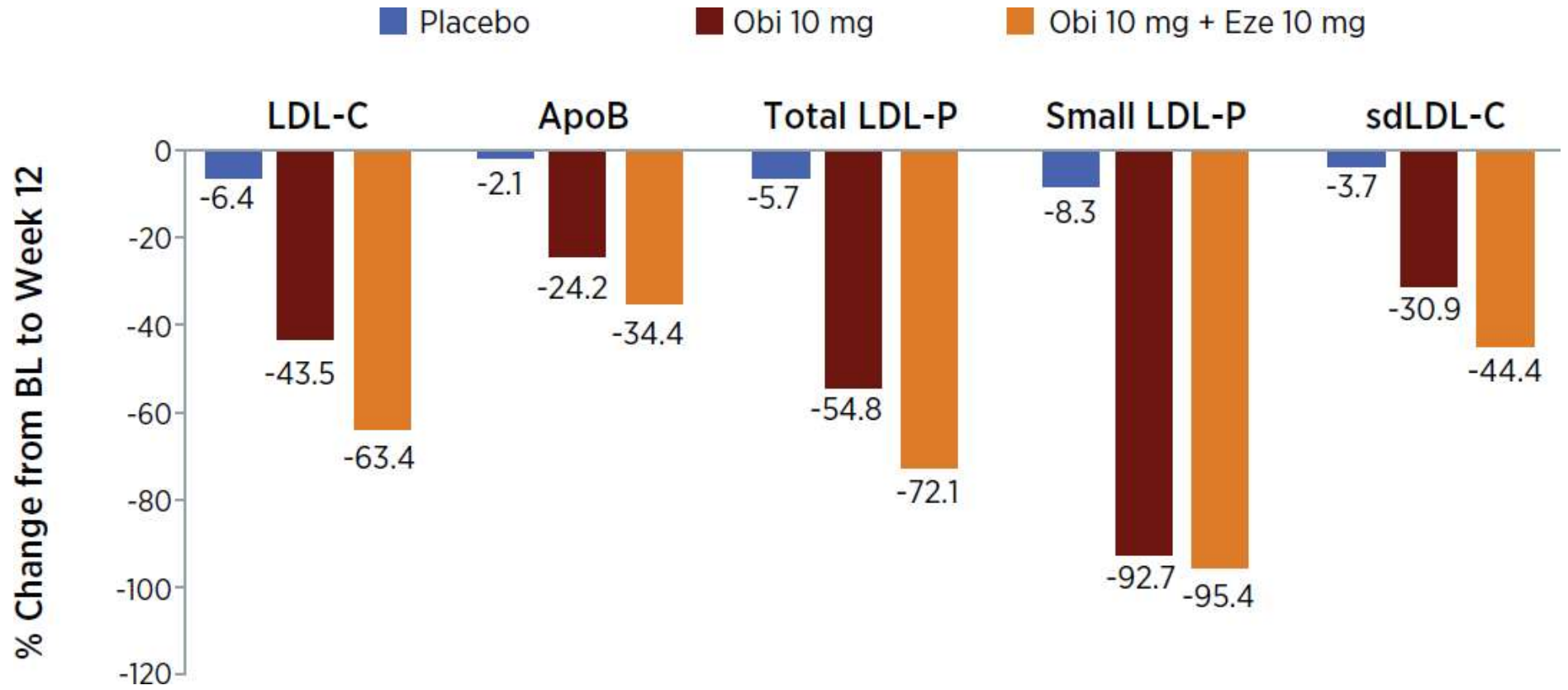




Lancet 2025; 405: 1757–68

ROSE 2 trial: obicetrapib + ezetimibe + HIS
% change in atherogenic lipoproteins from baseline

- Obi, obicetrapib*; Eze, ezetimibe; HIS, high-intensity statin Ballantyne CM, et al. J Clin Lipidol 2023;17(4):491-503
- Davidson MH et al. Presentation at American College of Cardiology Scientific Sessions 2024



JAMA | Preliminary Communication

Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation
A Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Steven E. Nissen, MD; Cynthia Fleming, RN, MSN; Shweta Urva, PhD; Jeffrey Suico, PhD; Paul H. Berg, MS; Helle Linnebjerg, PhD; Giacomo Ruotolo, MD, PhD; P. Kellie Turner, PharmD, PhD; Laura F. Michael, PhD

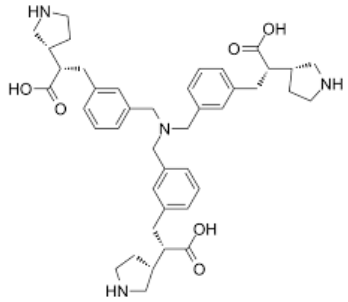
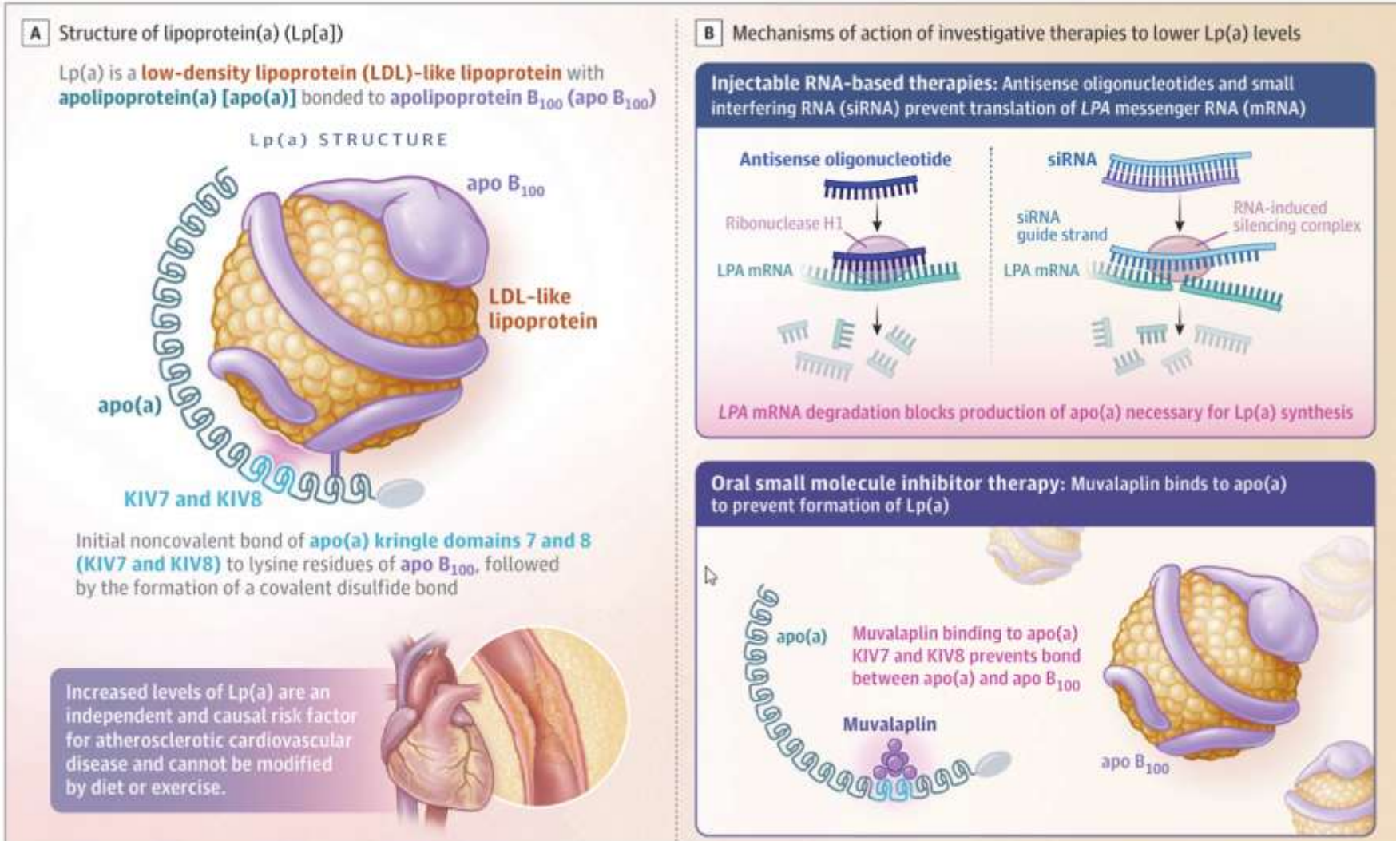
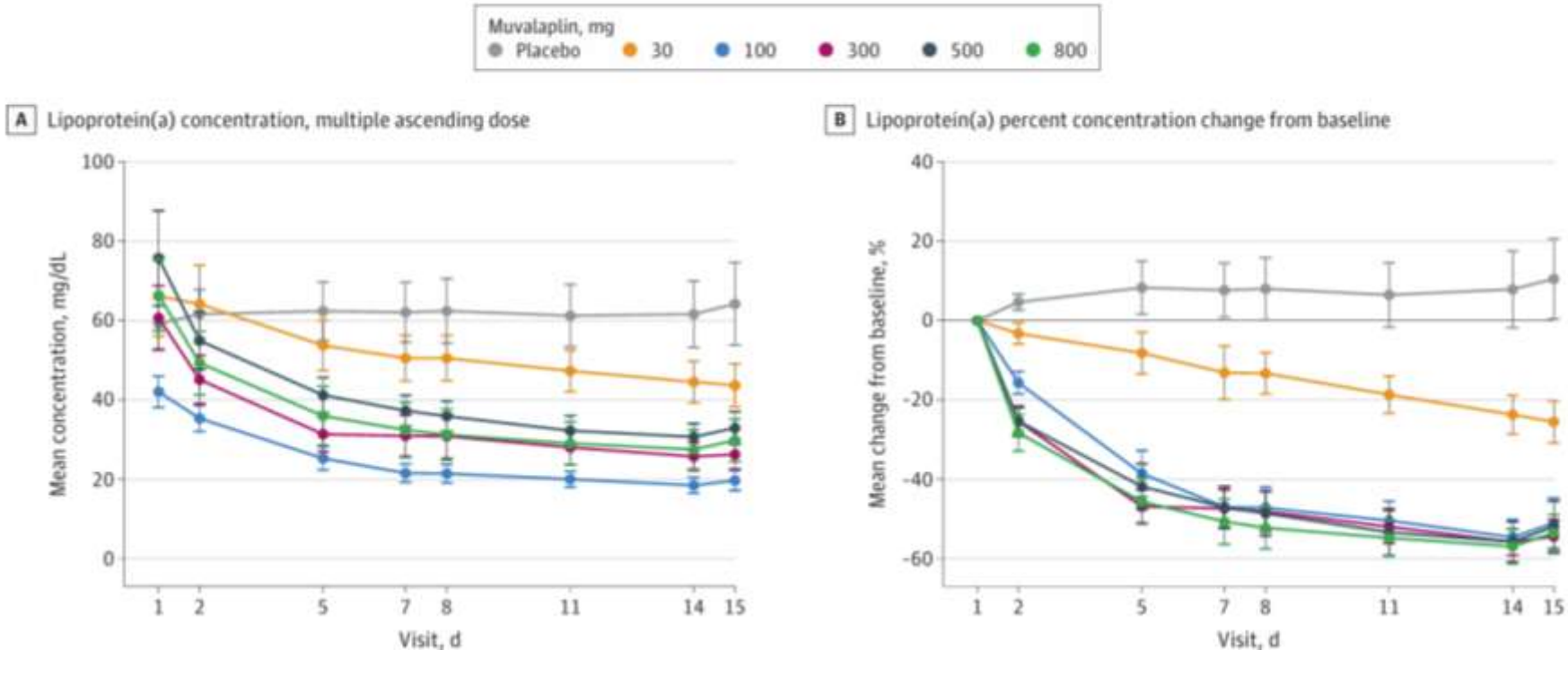


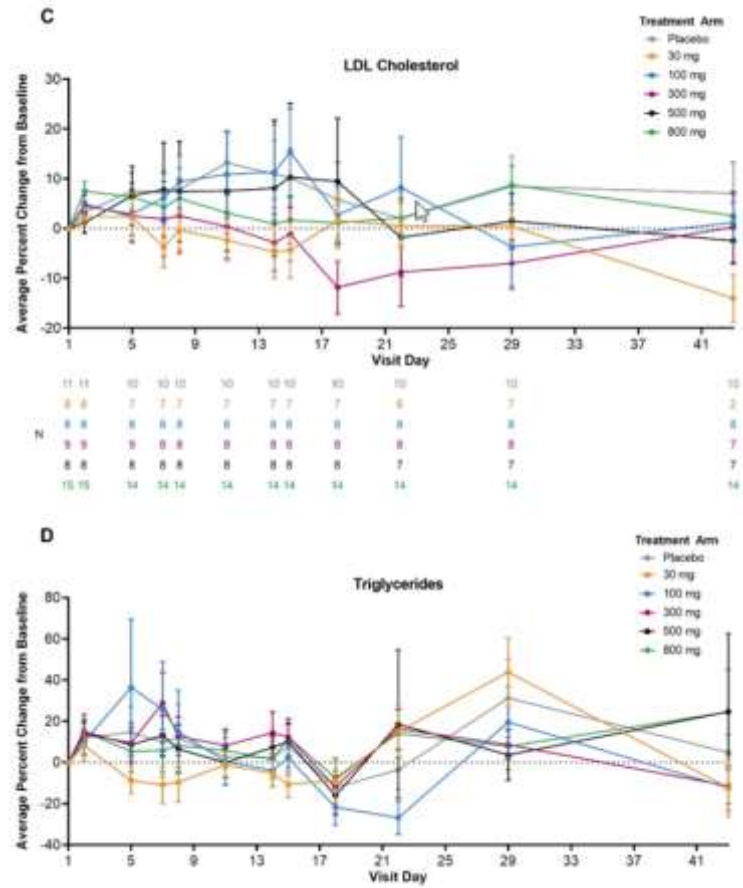
Figure 1. Lipoprotein(a) Biology and Therapeutic Approaches to Lower Lipoprotein(a)



JAMA.2023;330 (11):1042-1053

Figure 4. Effect of Multiple Daily Doses of Muvalaplin on Lipoprotein(a) and Plasminogen Activity



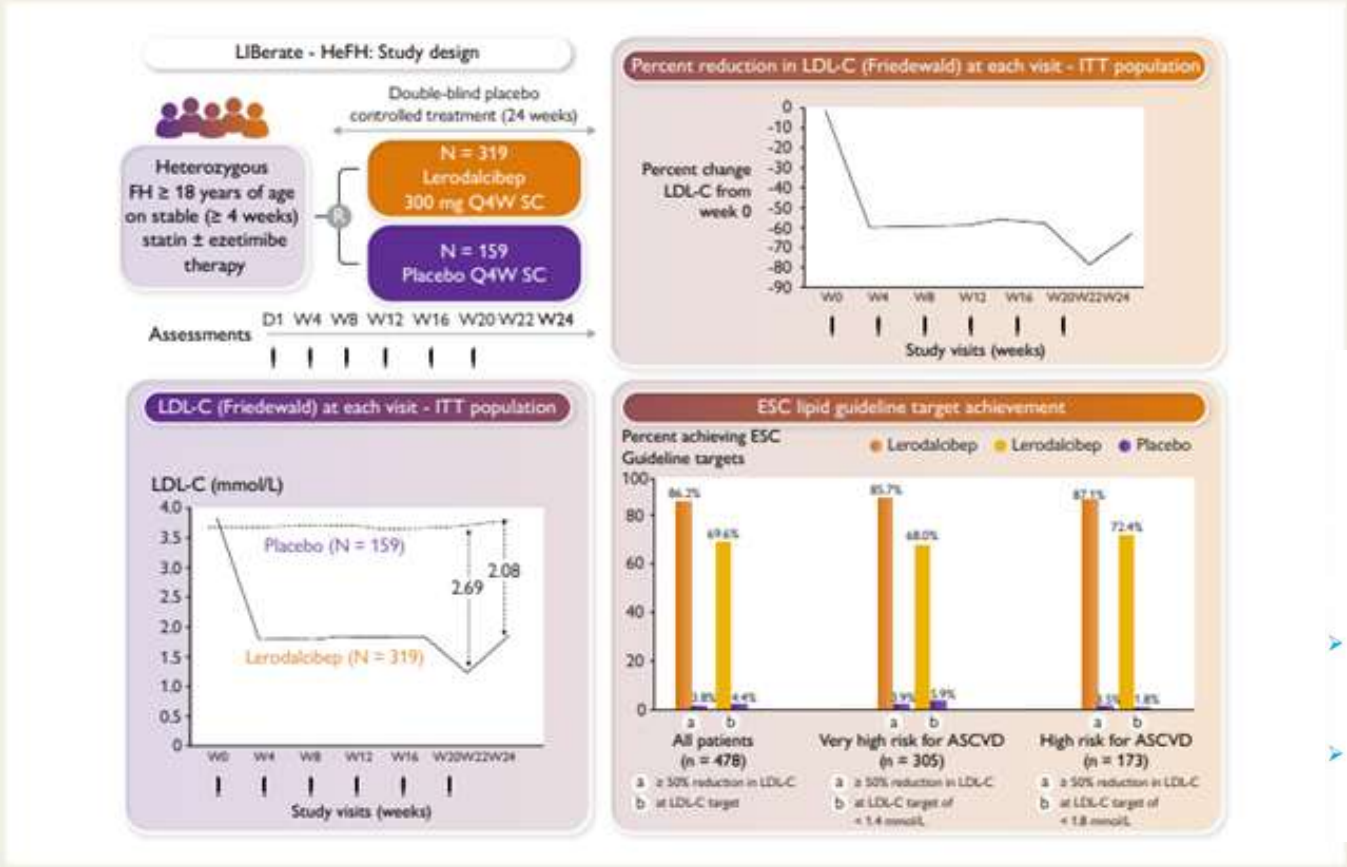


JAMA.2023;330(11):1042-1053.

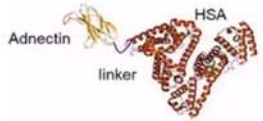
ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–9
https://doi.org/10.1093/eurheartj/ehad596
FASTTRACK CLINICAL RESEARCH
Clinical trials

Long-term efficacy and safety of lerodalcibep in heterozygous familial hypercholesterolaemia: the LIBerate-HeFH trial

Frederick Raal [1]*, Nyda Fourie [2], Russell Scott [3], Dirk Blom [4], Matthys De Vries Basson [5], Meral Kayikcioglu [6], Kate Caldwell [7], David Kallend [7] and Evan Stein [7], for the LIBerate-HeFH Investigators†



Lerodalcibep, a novel anti-proprotein convertase subtilisin/kexin type 9 gene small binding protein for the management of heterozygous familial hypercholesterolaemia. ASCVD, atherosclerotic cardiovascular disease; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; ITT, intention to treat; LDL-C, low-density lipoprotein cholesterol; SC, subcutaneous.

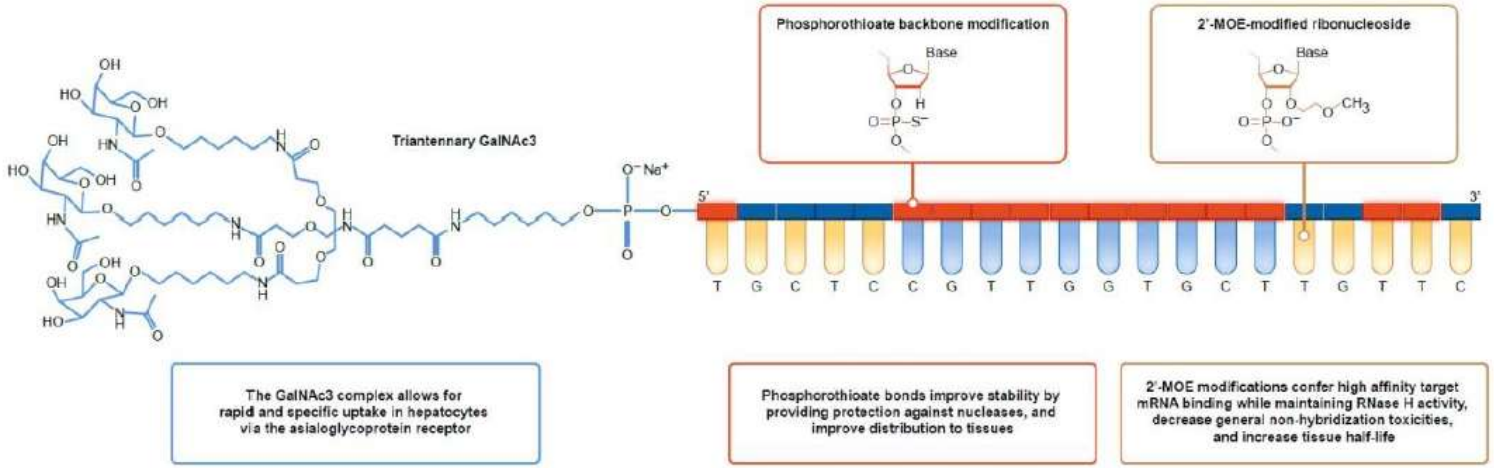


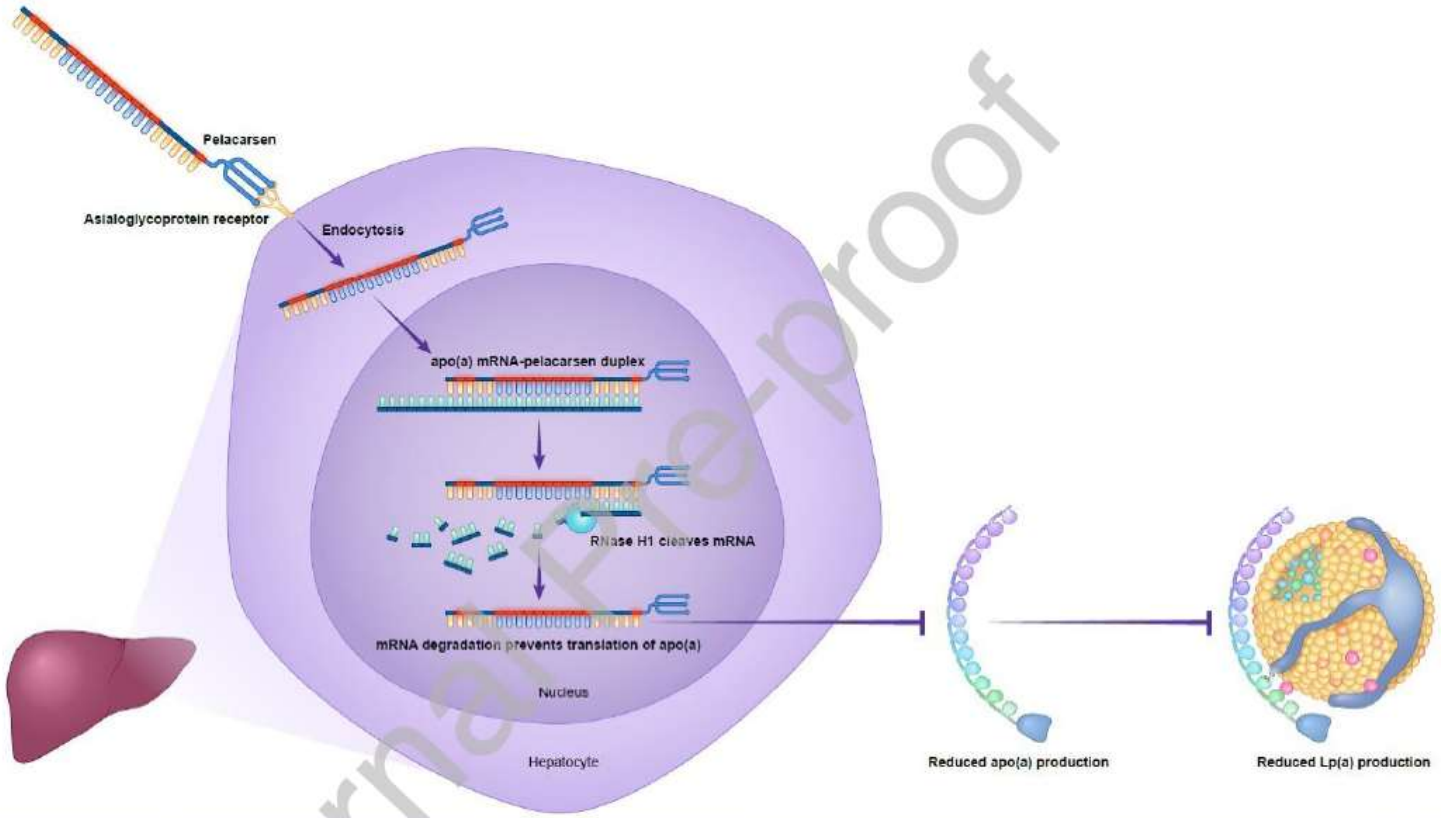
- Similar to mAbs, Lerodalcibep binds to PCSK9, blocks the interaction between PCSK9 and LDLR, preventing LDLR degradation, increasing LDLR recycling, enhancing LDL-C clearance, and lowers LDL-C levels.
- Prolonged stability at room temperature, small size (77kDa), high binding affinity and solubility allows for less frequent smaller injection volume than mAbs to achieve stable and prolonged LDL-C reductions between injections.

Lerodalcibep, a novel small recombinant fusion protein of PCSK9–binding domain (adnectin)

Gene silencing therapies for lipid lowering

Drug	Molecular target	% reduction of target expression	% reduction in LDL-C / Lp(a) / apoB / TG
Inclisiran	PCSK9 (hepatic mRNA)	≈75% PCSK9↓	≈50% LDL-C↓
Volanesorsen	APOC3 (hepatic mRNA)	≈84% apoC-III↓	≈77% plasma TG↓
Olezarsen	APOC3 (hepatic mRNA)	≈73% apoC-III↓ (80 mg)	≈60.6% plasma TG↓ (6 mo)
Plozasiran	APOC3 (hepatic mRNA)	≈77% apoC-III↓	≈57% plasma TG↓
Zodasiran	ANGPTL3 (hepatic mRNA)	≈74% ANGPTL3↓ (200 mg)	≈63% plasma TG↓ (24 wk)
Solbisiran	ANGPTL3 (hepatic mRNA)	Reported ANGPTL3↓ (quant. NR in paper)	≈50% plasma TG↓ (Phase 2)
Pelacarsen	LPA / apo(a) (hepatic mRNA)	≥80% Lp(a)↓	≥80% Lp(a)↓
Olpasiran	LPA / apo(a) (hepatic mRNA)	≈95% Lp(a)↓	≈95% Lp(a)↓
Zerlasiran	LPA / apo(a) (hepatic mRNA)	≈82–86% Lp(a)↓	≈82–86% Lp(a)↓
Lepodisiran	LPA / apo(a) (hepatic mRNA)	≈93.9–95% Lp(a)↓	≈93.9–95% Lp(a)↓





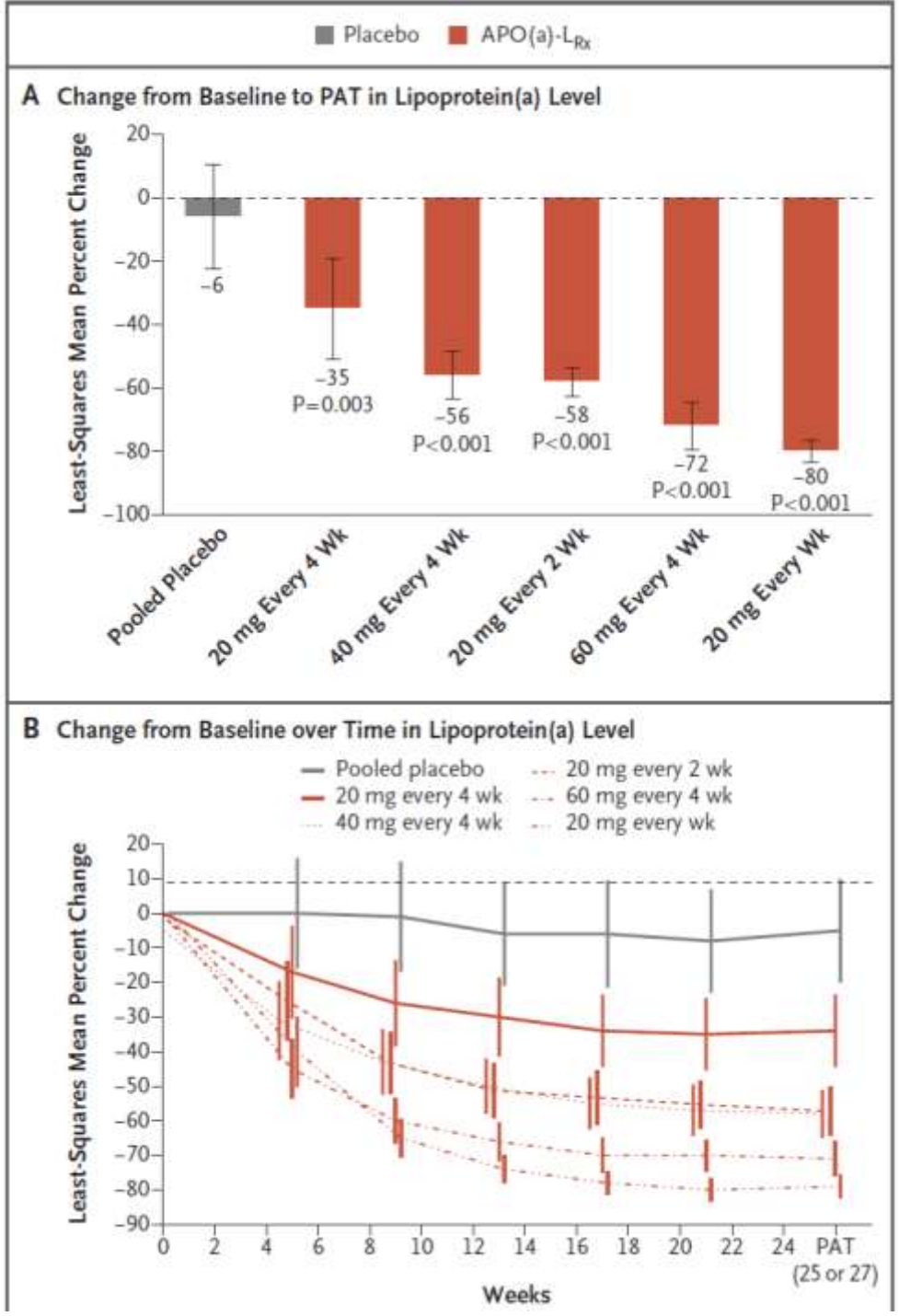
Journal of Clinical Lipidology
Available online 16 June 2025
In Press, Journal Pre-proof What's this?

Review Article

[illegible] lowering effect

[illegible] MD [illegible], Sasha N Goonewardena MD [illegible]
Harpreet S Bhatia MD, MAS [a], Archna [illegible]
Patrick M Moriarty MD [d]

Pelacarsen



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

Tsimikas S et al N Engl J Med 2020;382:244-55.

Table 2. Absolute Change from Baseline at 6 Months of Exposure.*

Measure	APO(a)-L_{Rx}					Pooled Placebo (N=47)
	20 mg Every 4 Wk (N=48)	40 mg Every 4 Wk (N=48)	20 mg Every 2 Wk (N=48)	60 mg Every 4 Wk (N=47)	20 mg Every Wk (N=48)	
Lipoprotein(a) — nmol/liter	−95.9±94.4	−116.9±71.7	−130.3±66.1	−149.5±67.4	−187.8±80.3	−15.2±34.6
Lipoprotein(a) — mg/dl	−38.4±7.7	−46.8±28.7	−52.1±26.4	−59.8±27.0	−75.1±32.1	−6.1±13.8
OxPL-apoB — nmol/liter	−8.0±10.3	−11.3±11.0	−12.2±7.9	−14.9±10.3	−20.1±8.5	3.7±8.1
OxPL-apo(a) — nmol/liter	−16.8±14.3	−24.5±20.1	−25.9±17.2	−33.3±16.8	−41.6±16.5	−12.3±14.7
LDL cholesterol — mg/dl	−5.6±27.4	−13.5±30.1	−13.2±19.8	−8.2±17.3	−16.4±14.8	−1.2±17.8
Apolipoprotein B — mg/dl	−2.2±17.4	−8.3±18.2	−6.3±11.6	−3.9±13.5	−10.9±10.9	0.6±12.0
Total cholesterol — mg/dl	−3.9±32.1	−11.6±32.1	−11.6±24.4	−3.9±23.2	−11.6±20.9	−3.9±21.3
HDL cholesterol — mg/dl	0.0±6.2	0.0±9.7	3.7±8.9	3.7±11.6	3.7±10.1	0.0±6.6
Triglycerides — mg/dl	−8.9±32.8	−8.9±31.0	0.0±52.3	0.0±50.5	−8.9±41.6	0.0±51.4
hsCRP — mg/liter	−0.9±4.24	−0.7±4.24	−0.3±2.84	−0.5±2.22	−0.1±6.30	−0.8±5.13

* Plus–minus values are means ±SD. The primary analysis time point was at 6 months of exposure: week 25 in the groups that received monthly doses and week 27 in the groups that received more frequent doses. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

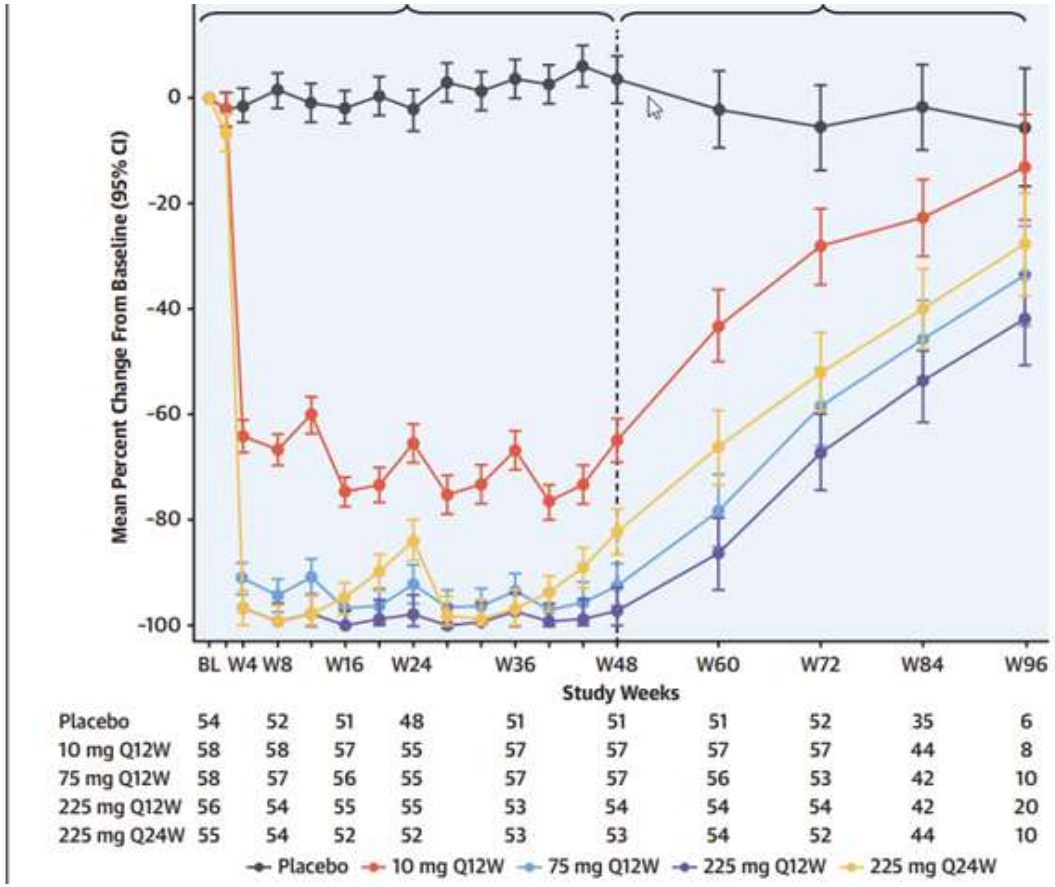
Tsimikas S et al N Engl J Med 2020;382:244-55.

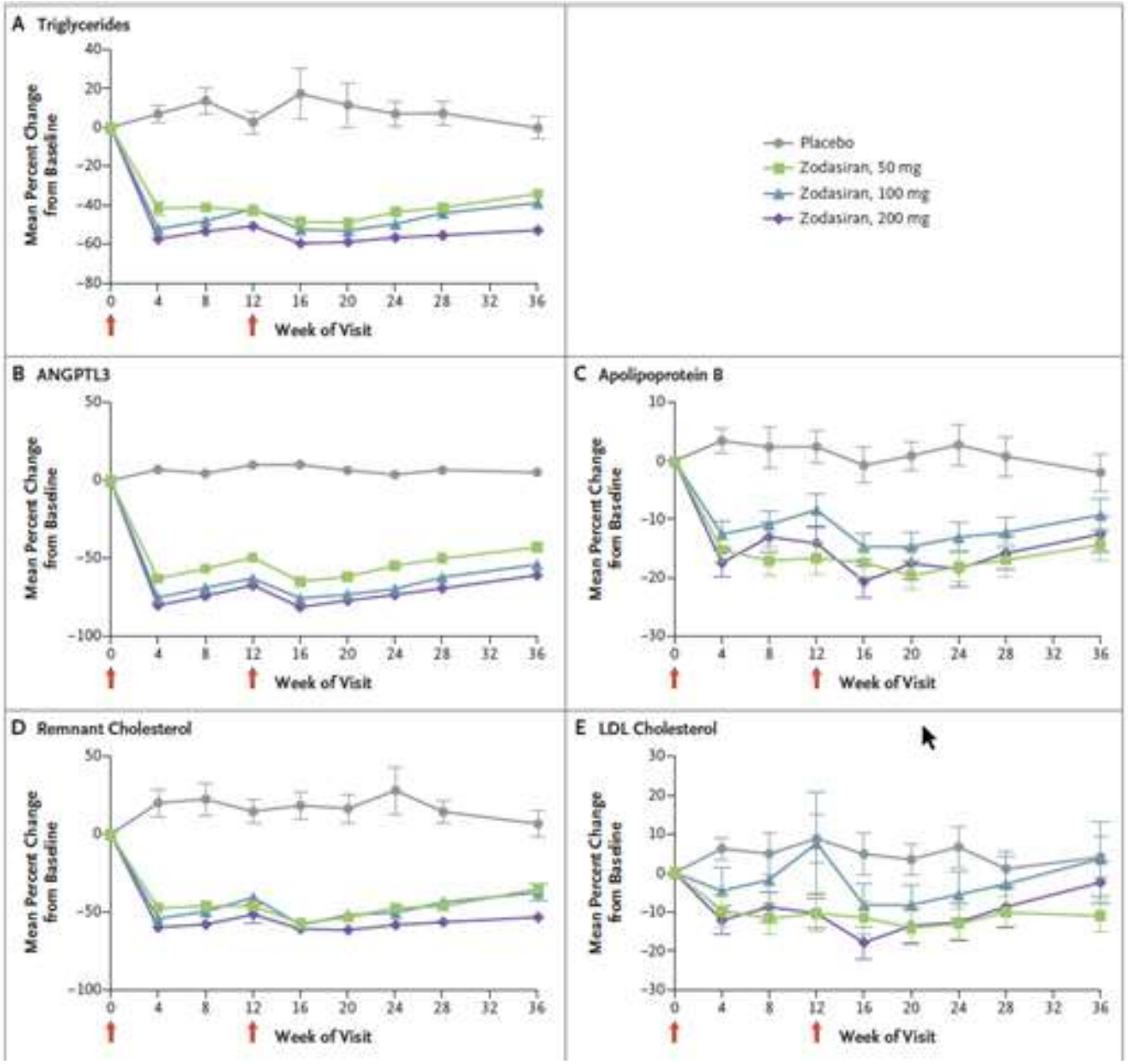
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 84, NO. 9, 2024

The Off-Treatment Effects of Olpasiran on Lipoprotein(a) Lowering

OCEAN(a)-DOSE Extension Period Results

Michelle L. O'Donoghue, MD, MPH,[a] Robert S. Rosenson, MD,[b] J. Antonio G. López, MD,[c] Norman E. Lepor, MD,[d] Seth J. Baum, MD,[e,f] Elmer Stout, MD,[g] Daniel Gaudet, MD, PhD,[h] Beat Knusel, PhD,[c] Julia F. Kuder, MA,[a] Sabina A. Murphy, MPH,[a] Huei Wang, PhD,[c] You Wu, PhD,[c] Trupti Shah, MD, MPH,[c] Jingying Wang, PhD,[c] Tomasz Wilmanski, MPH, PhD,[c] Winnie Sohn, PhD,[c] Helina Kassahun, MD,[c] Marc S. Sabatine, MD, MPH,[a] for the OCEAN(a)-DOSE Trial Investigators

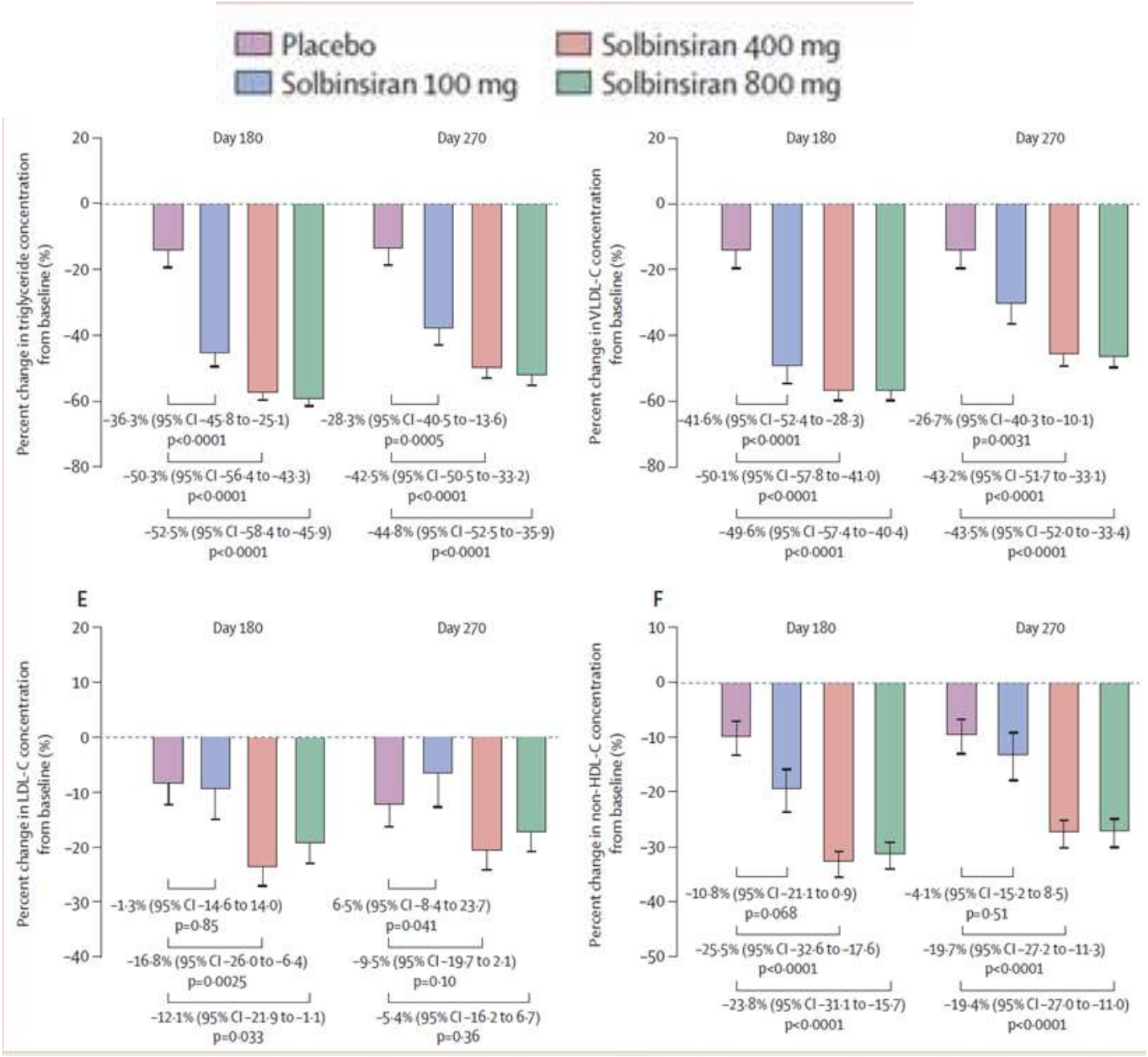




Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia

Robert S. Rosenson, M.D., Daniel Gaudet, M.D., Ph.D., Robert A. Hegele, M.D., Christie M. Ballantyne, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Kathryn J. Lucas, M.D., Javier San Martin, M.D., Rong Zhou, Ph.D., Ma'an Muhsin, M.D., Ting Chang, Ph.D., Jennifer Hellawell, M.D., and Gerald F. Watts, D.Sc., Ph.D., M.D., for the ARCHES-2 Trial Team*

N Engl J Med 2024;391:913-25.



Durability and efficacy of solbinsiran, a GalNAc-conjugated siRNA targeting ANGPTL3, in adults with mixed dyslipidaemia (PROLONG-ANG3): a double-blind, randomised, placebo-controlled, phase 2 trial

Kausik K Ray, Ena Oru, Robert S Rosenson, Jeremiah Jones, Xiaosu Ma, Jennie Walgren, Axel Haupt, Subodh Verma, Daniel Gaudet, Stephen J Nicholls, Giacomo Ruotolo

Lancet. 2025 Mar 28:S0140-6736(25)00507-0. doi: 10.1016/S0140-6736(25)00507-0.

Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridaemia and at high cardiovascular risk

Jean-Claude Tardif[1]*, Ewa Karwatowska-Prokopczuk [2], Eric St. Amour[3], Christie M. Ballantyne[4], Michael D. Shapiro [5], Patrick M. Moriarty[6], Seth J. Baum [7], Eunju Hurh [2], Victoria J. Bartlett [2], Joyce Kingsbury[2], Amparo L. Figueroa[2], Veronica J. Alexander [8], Joseph Tami[8], Joseph L. Witztum[9], Richard S. Geary[8], Louis St. L. O'Dea[2], Sotirios Tsimikas [8,10]*, and Daniel Gaudet [11]; for the Olezarsen Study Investigators

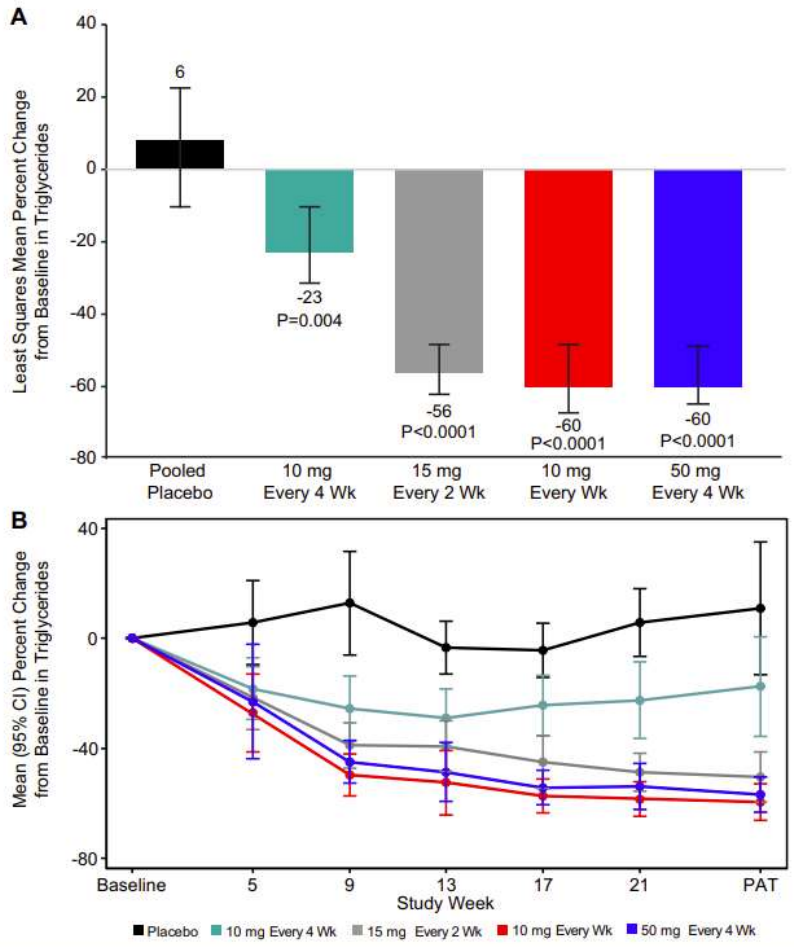
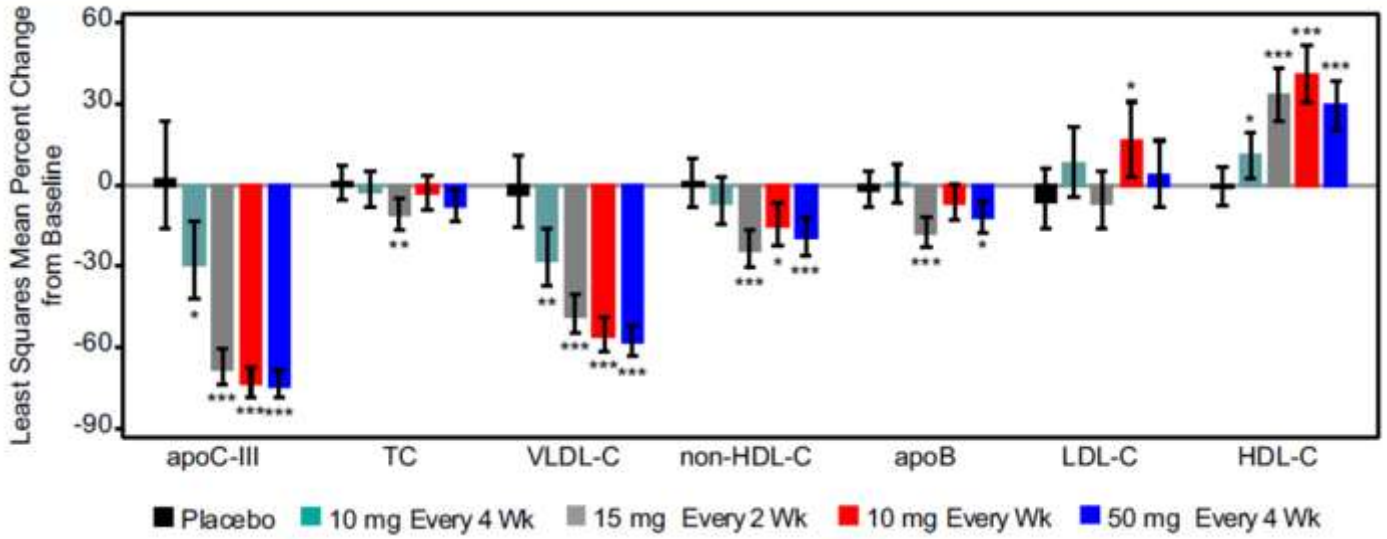
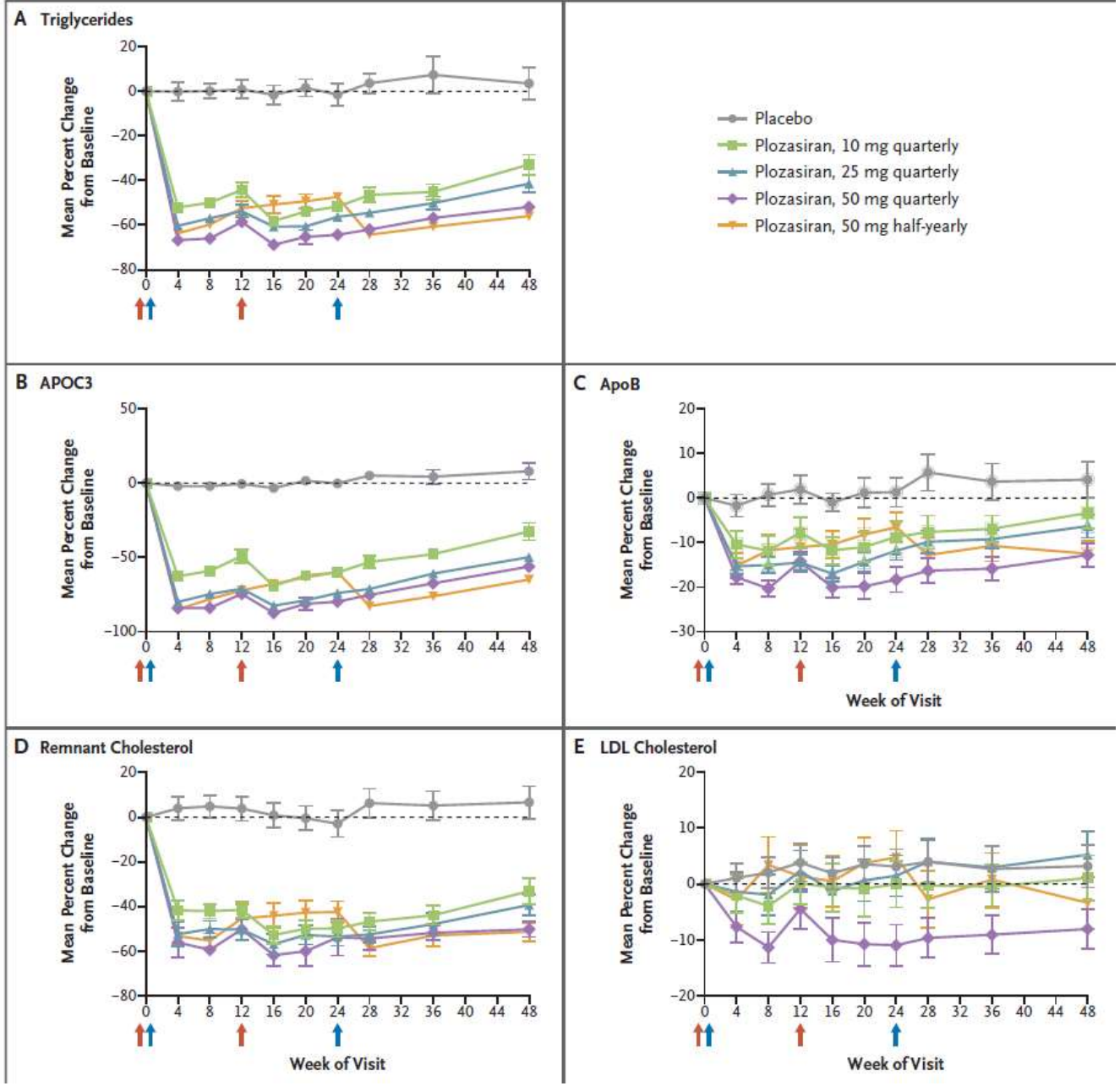


Figure 1 Effect of olezarsen on fasting triglyceride levels. (*A*) The least squares mean percent changes in triglycerides from baseline to the primary analysis timepoint. (*B*) The temporal changes in triglycerides in each of the dose groups. Error bars denote 95% confidence interval. Primary analysis timepoint was Week 27 for weekly dosing, and Week 25 for monthly dosing. The least squares mean of percent change from baseline (95% confidence interval) in each treatment group and the *P*-value of each olezarsen treatment group vs. the pooled placebo group were estimated using an ANCOVA model with the treatment group as the fixed factor and log-transformed baseline value as the covariate.



Tardif JC et al European Heart Journal (2022) 43, 1401–1412



Plozasiran, an RNA Interference Agent Targeting APOC3, for Mixed Hyperlipidemia

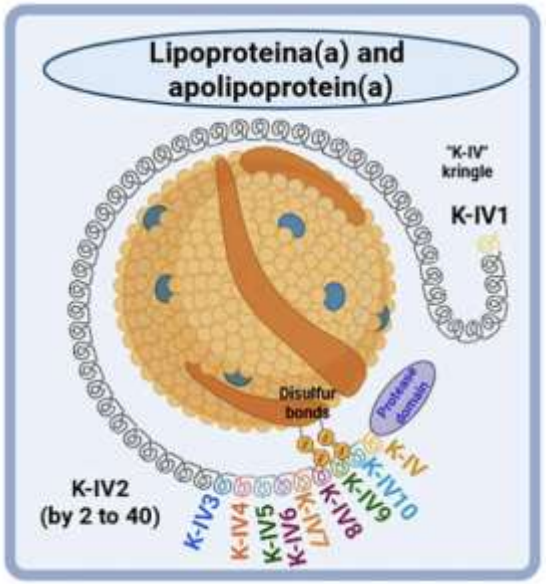
Christie M. Ballantyne, M.D., Szilard Vasas, M.D., Masoud Azizad, M.D., Peter Clifton, M.B., B.S., Ph.D., Robert S. Rosenson, M.D., Ting Chang, Ph.D., Stacey Melquist, Ph.D., Rong Zhou, Ph.D., Ma'an Mushin, M.D., Nicholas J. Leeper, M.D., Jennifer Hellawell, M.D., and Daniel Gaudet, M.D., Ph.D.

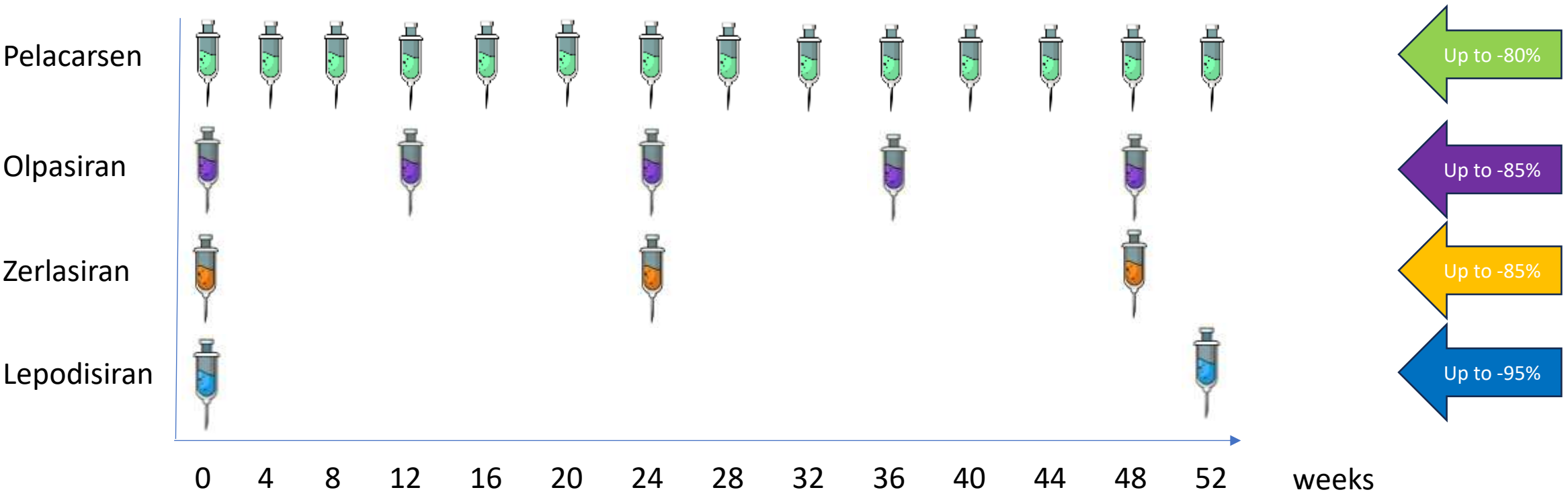
N Engl J Med 2024;391:899-912.

ESC European Society of Cardiology
Cardiovascular Research (2025) **121**, 1969–1971
https://doi.org/10.1093/cvr/cvaf153
CLINICAL COMMENTARIES
CARDIOVASCULAR RESEARCH Onlife

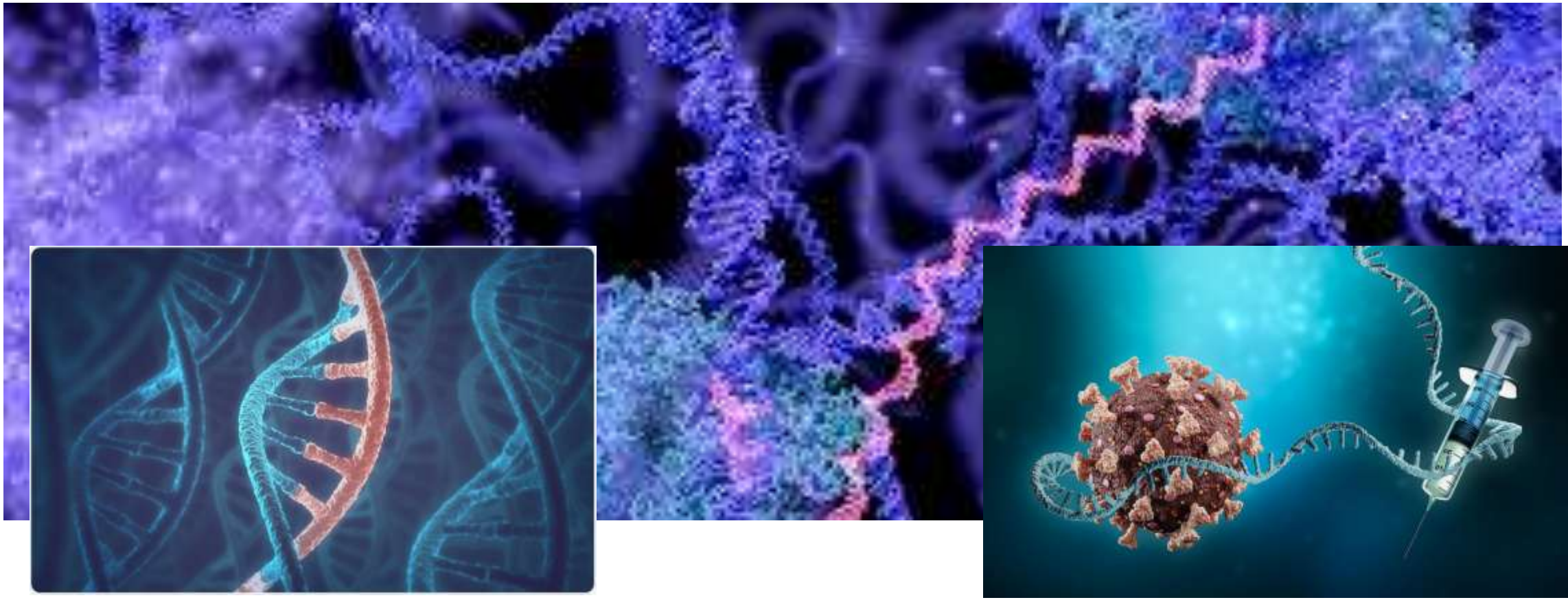
The new generation of small interfering RNAs directed against apoprotein(a): focus on the safety and efficacy of zerlasiran and lepodisiran

Andrea Baragetti and Giuseppe Danilo Norata*





From DNA to RNA and back

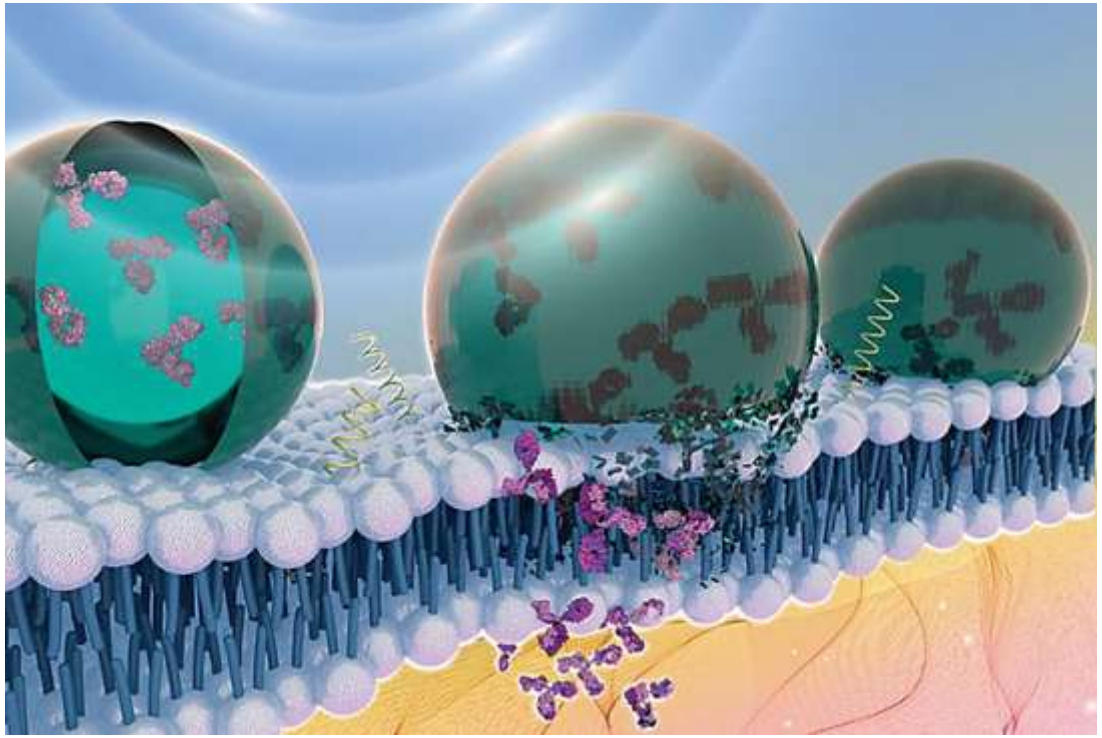


Gene Editing

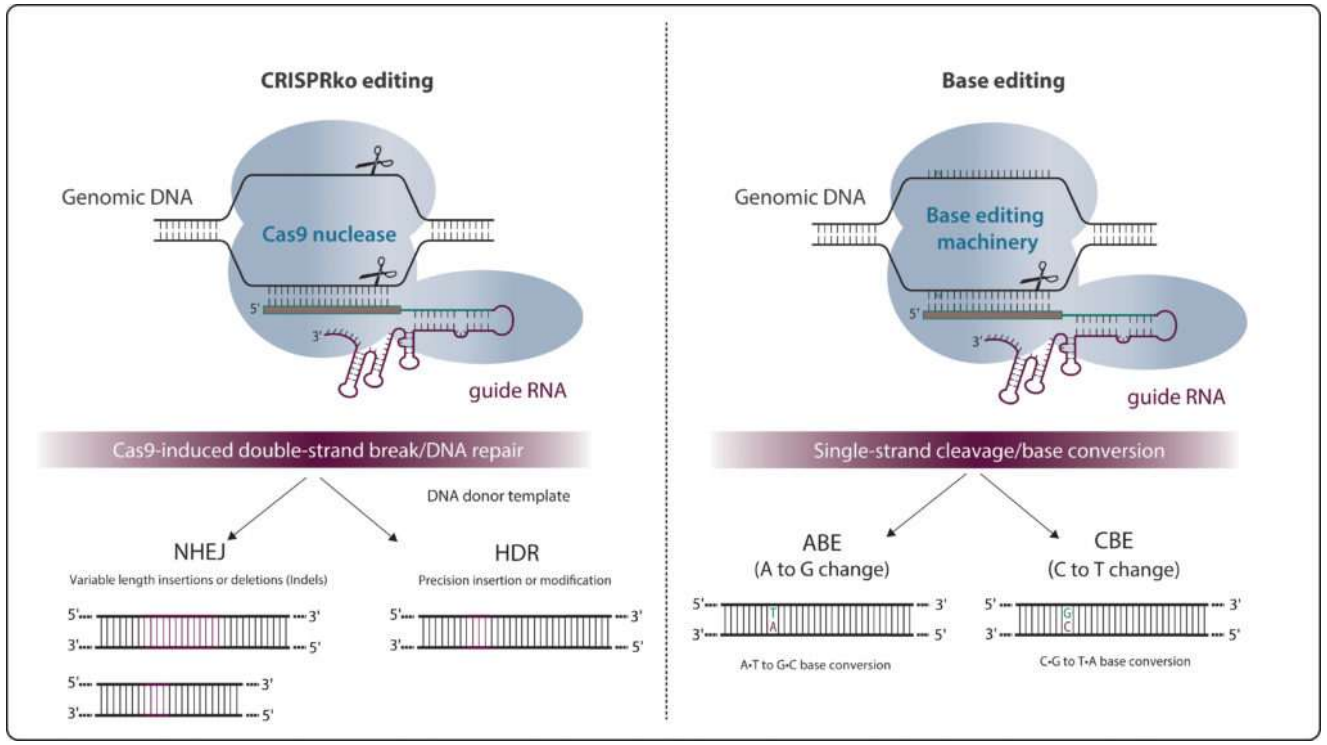
Gene Silencing

Gene Editing in humans

Non-viral selective delivery (LNP)



CRISPR 2.0

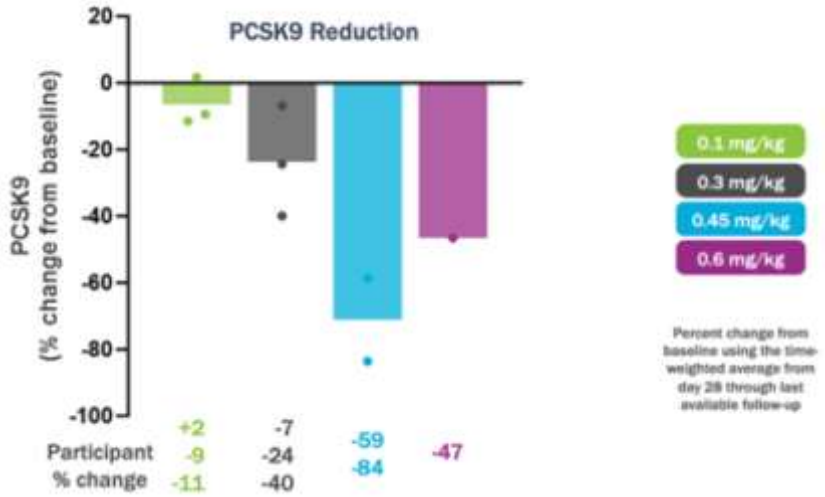


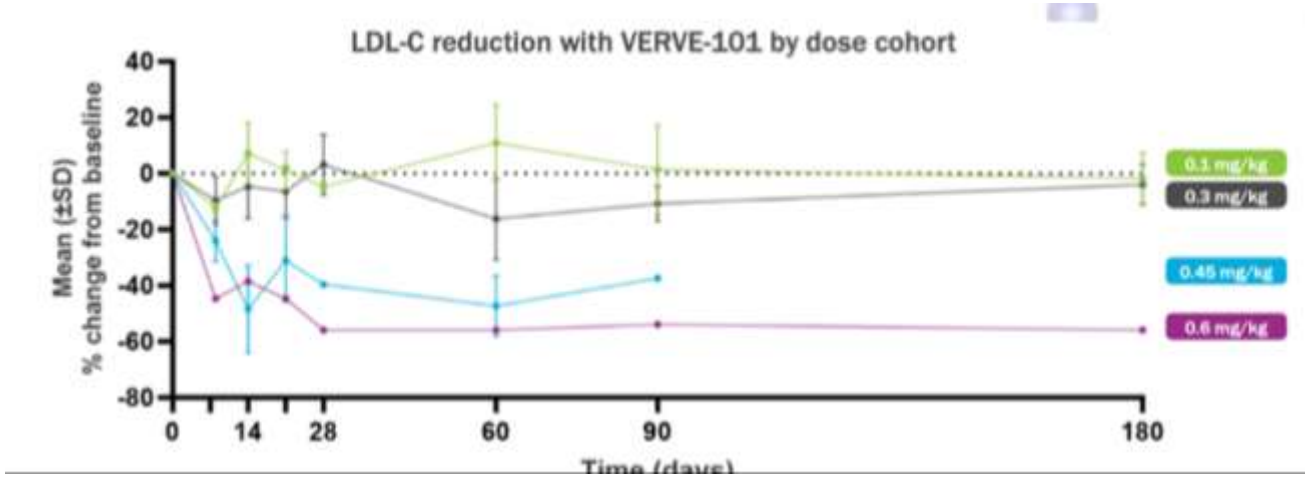
ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2024) **10**, 87–88
https://doi.org/10.1093/ehjcvp/pvad095
PHARMAPULSE

First-in-human trial of PCSK9 gene editing therapy for lowering cholesterol: a new frontier in cardiovascular pharmacotherapy? News from AHA

Basil S. Lewis *

- Delivered via LNP-encapsulated mRNA encoding a Cas9 nickase–adenine base editor + sgRNA.
- Aim: one-time edit to inactivate PCSK9 and permanently lower LDL-C.
- Population: Adults with HeFH + ASCVD with uncontrolled LDL-C despite maximal therapy.



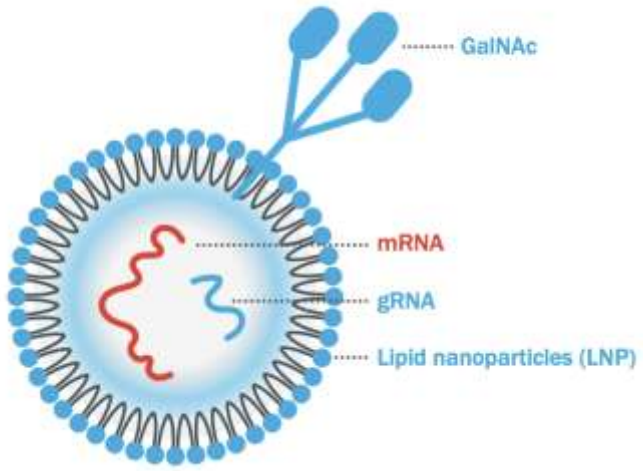


- No treatment-related deaths or SAEs.
- Two mild infusion reactions (Grade 1–2).
- One Grade 3 drug-related AE (ALT ˇ and thrombocytopenia) in high-dose cohort ® temporary enrollment pause (Apr 2024).

Gene Editing in humans: PCSK9 VERVE-102

VERVE-102 uses an adenine base editor + gRNA targeting PCSK9 in hepatocytes, delivered via GalNAc-LNP.

Population: Adults with HeFH + ASCVD with uncontrolled LDL-C despite maximal therapy.



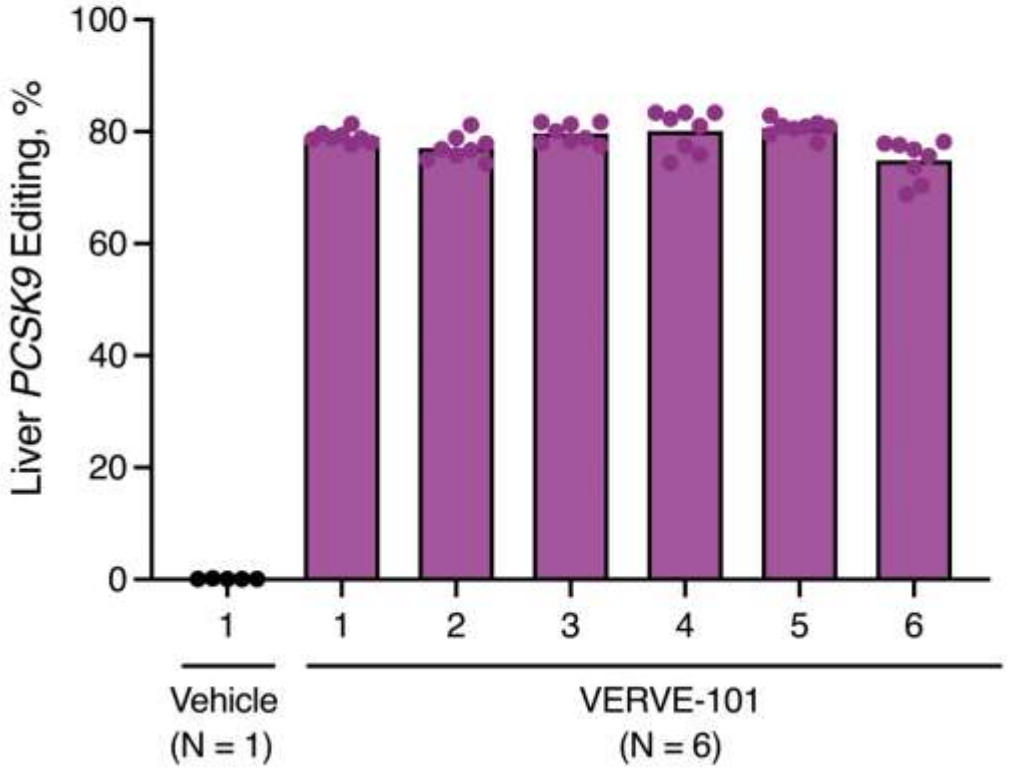
Dose (mg/kg)	n of patients	PCSK9 reduction	LDL-C reduction
0.3	4	-46%	-21%
0.4	6	-53%	-41%
0.6	4	-60%	-53% (max -69%)

Safety Summary

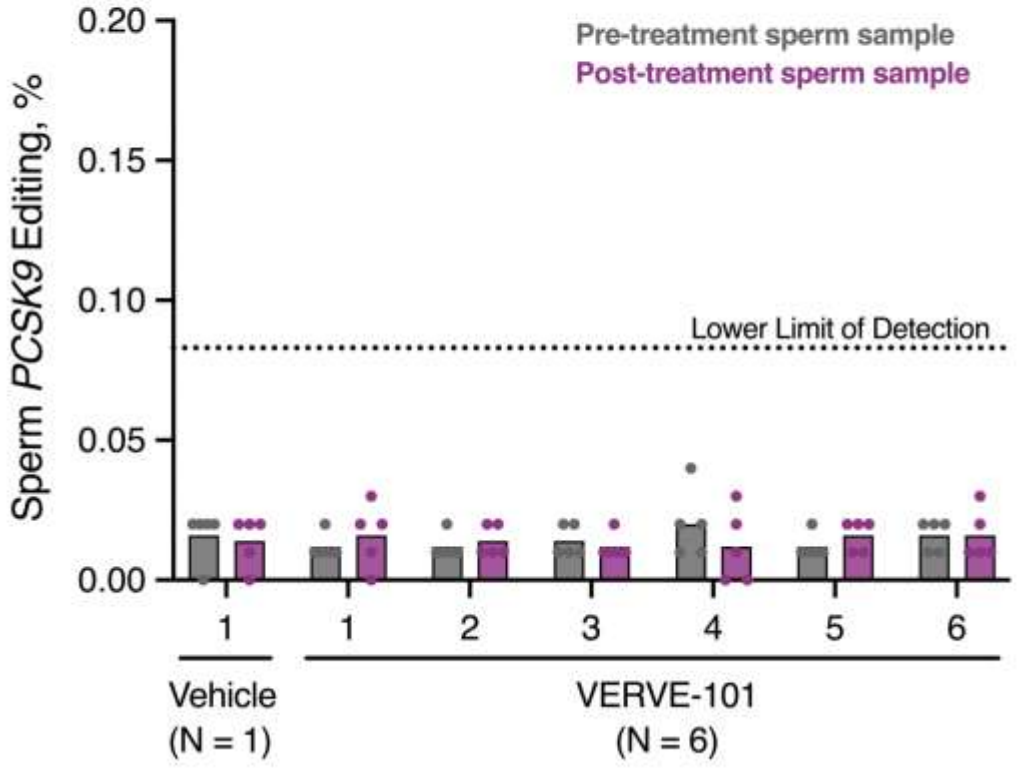
- No treatment-related serious adverse events (SAEs) or dose-limiting toxicities (DLTs).
- No clinically significant ALT, AST, bilirubin, or platelet changes.
- One Grade-2 infusion reaction, transient and resolved with acetaminophen.

Safety of PCSK9 Gene Editing

6 NHPs treated with VERVE-101
Mean liver *PCSK9* editing 79%



Sequencing of sperm noted
no detectable *PCSK9* editing



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ORIGINAL ARTICLE

Phase 1 Trial of CRISPR-Cas9 Gene Editing Targeting ANGPTL3

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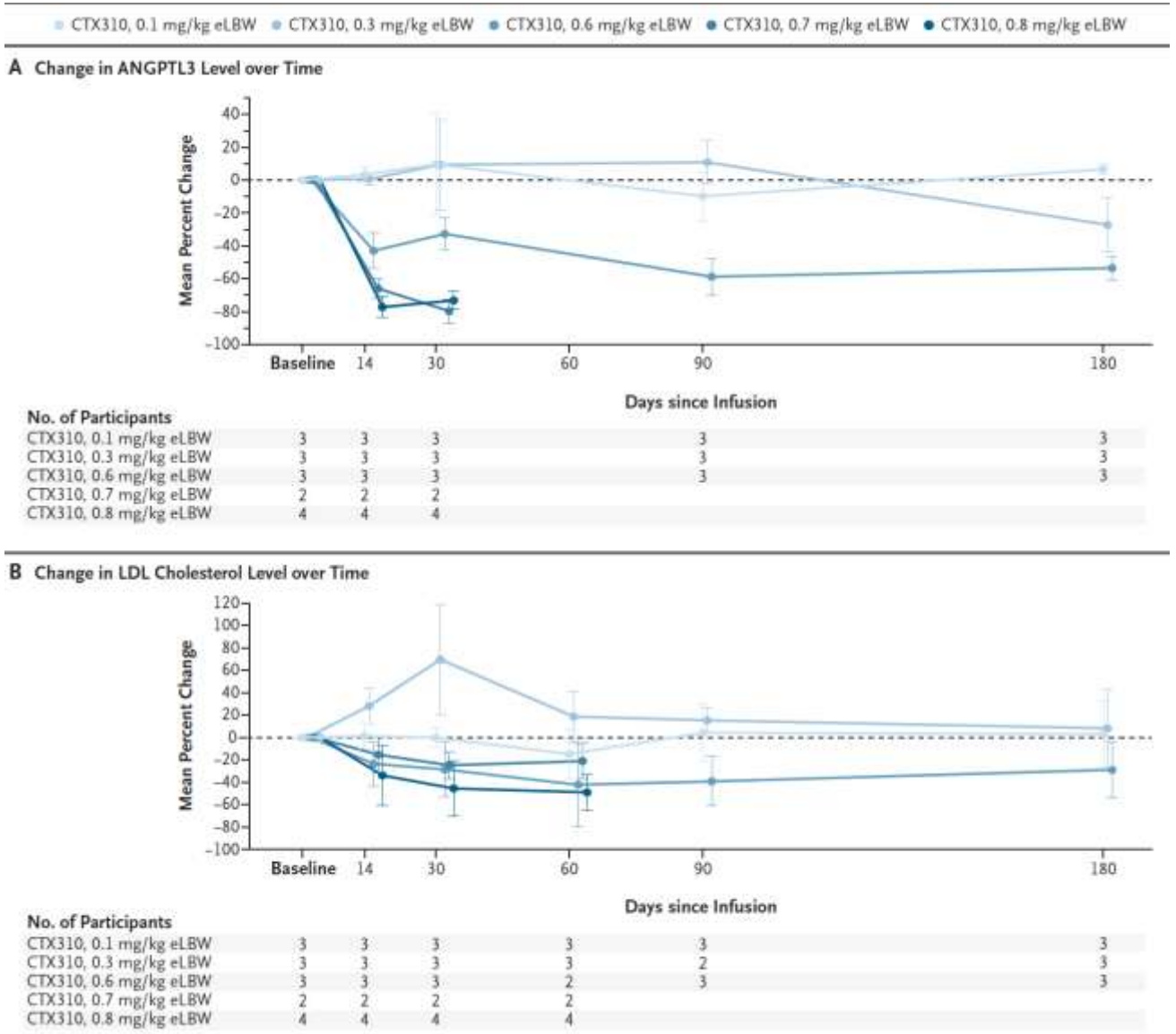
Table 2. Adverse Events.

Adverse Event	All Participants (N=15)
	no. (%)
Death*	1 (7)
Any serious adverse event†	2 (13)
Serious adverse events related to CTX310	0
Any investigator-reported adverse event‡	14 (93)
Grade 1§	4 (27)
Grade 2¶	9 (60)
Grade 3	0
Grade 4	0
Grade 5*	1 (7)
Adverse event of special interest related to CTX310‡‖	4 (27)
Allergic or localized reaction	1 (7)
Infusion-related reaction**	3 (20)
Elevation in level of AST or ALT††	1 (7)

CTX310 uses an adenine base editor + gRNA targeting ANGPTL3 in hepatocytes, delivered via GalNAc-LNP.

Population: 15 Adults who had uncontrolled hypercholesterolemia, hypertriglyceridemia, or mixed dyslipidemia and were receiving maximally tolerated lipid-lowering therapy.



Thanks