Nouvelles stratégies de gestion du risque lipidique

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- Clinical Trials, Consulting or Speaking: **Amarin, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Idorsia, Novartis, Novo-Nordisk, PhaseBio, Pfizer, Sanofi**

- Senior Associate Editor at ***Circulation***

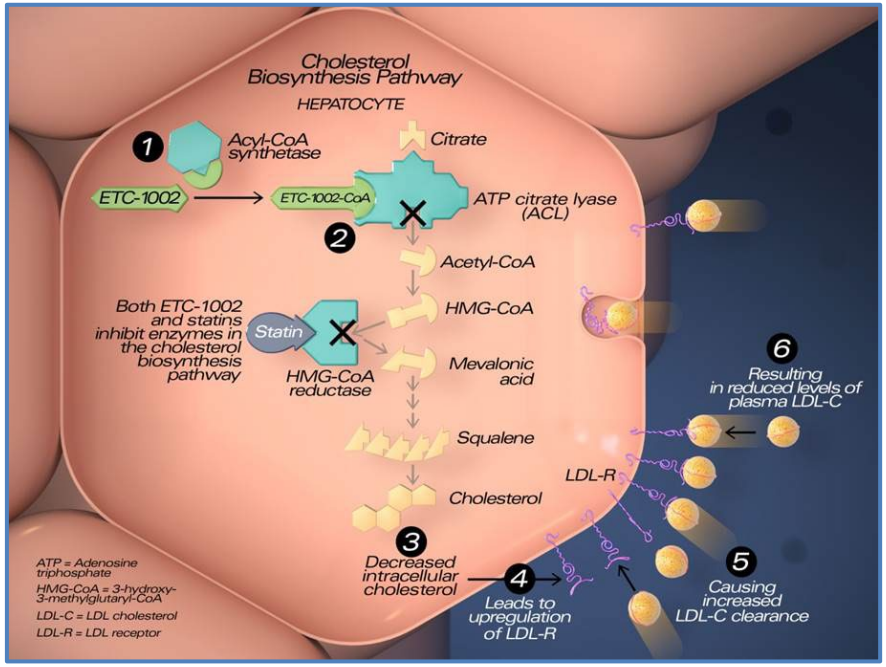
- Chief Medical Officer, **Bioquantis**

- Steering Committee chair for **ODYSSEY OUTCOMES, VICTORION-2P**

Optimizing management of dyslipidemias

- Lower LDL: beyond statins and ezetimibe
  - **Bempedoic acid**

Bempedoic acid



- **Bempedoic acid (BA) acts in the same cholesterol biosynthesis pathway as statins**
- **BA targets ATP-Citrate Lyase (ACL), an enzyme upstream of HMG-CoA reductase**
- **Up-regulates LDL receptors and lowers LDL-C**
- **The specific isozyme (ACSVL1) which converts BA into an active drug is not present in skeletal muscle**

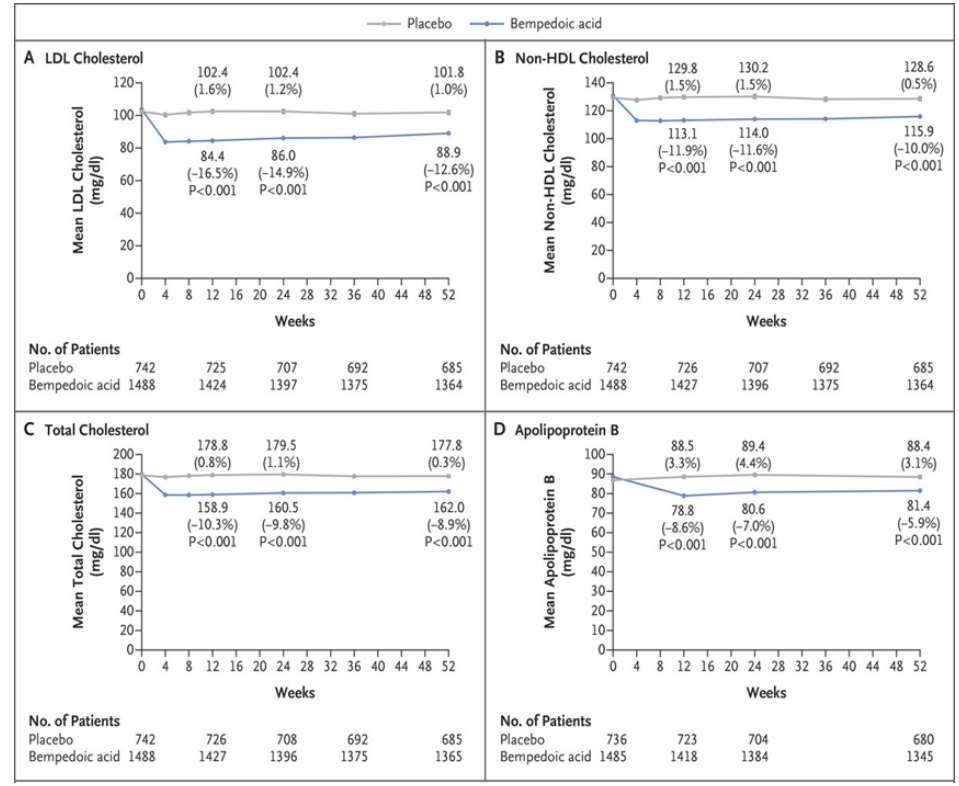
Adapted from Pinkosky et al. ***Nature Communications***. 2016 Nov 28; DOI: 10.1038/ncomms13457

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

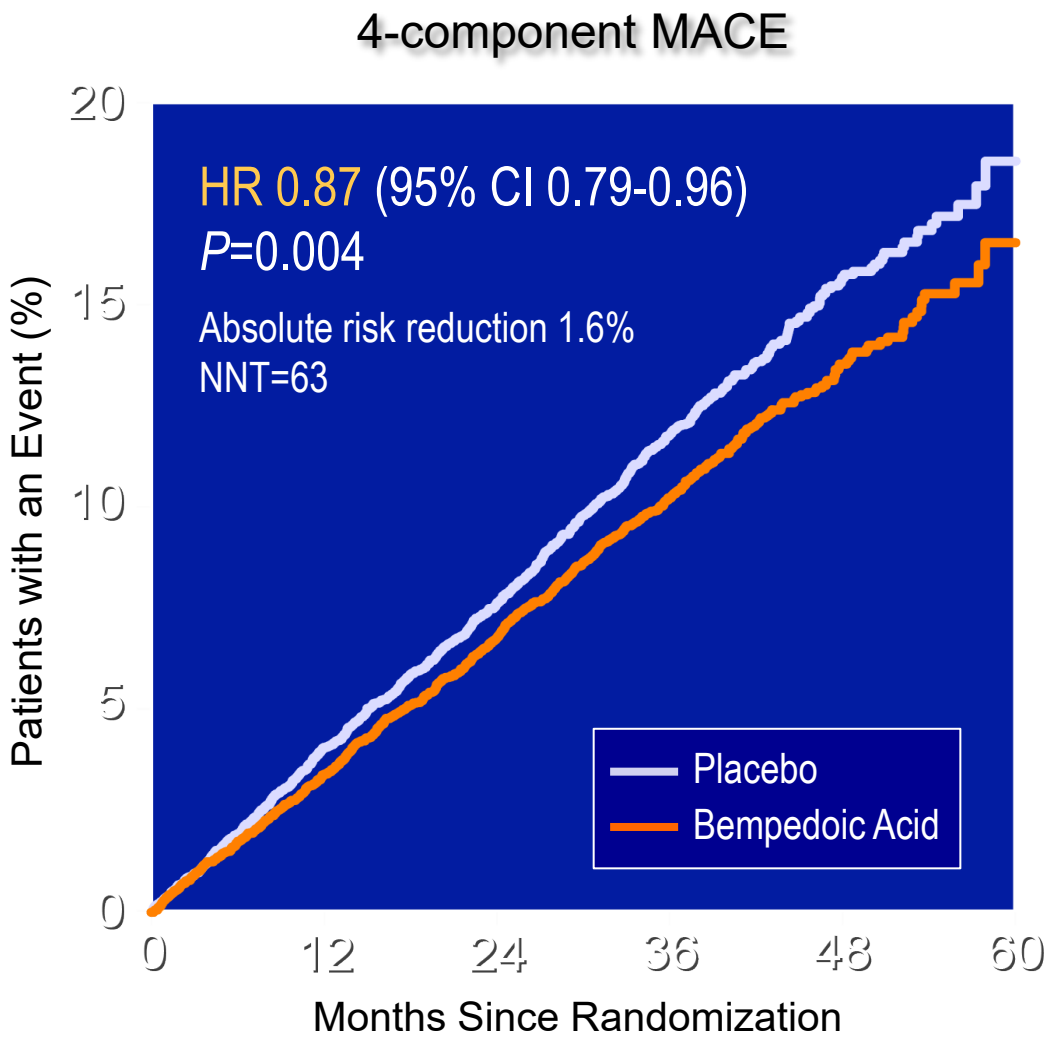
Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*

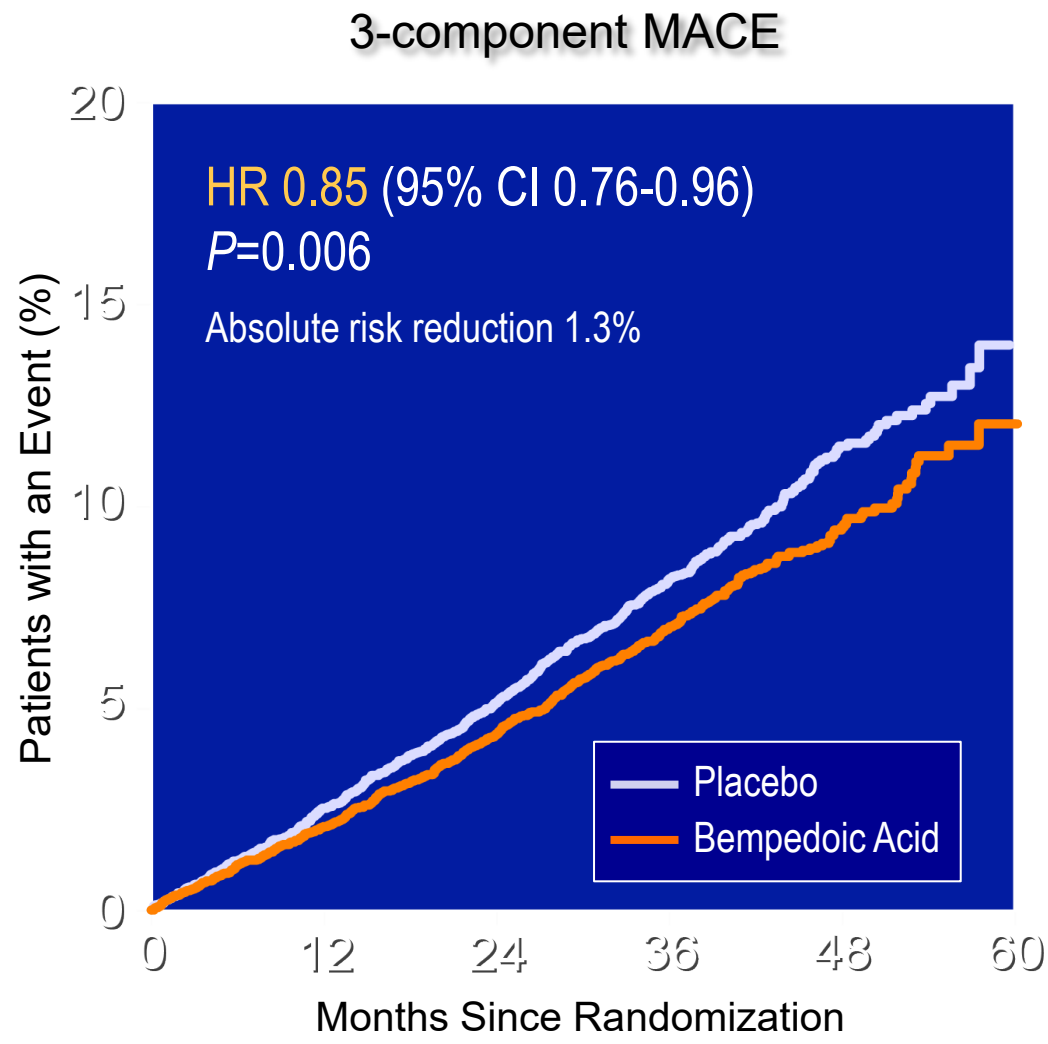


KK Ray et al. ***N Engl J Med*** 2019;380:1022-1032.

CLEAR OUTCOMES: effect of Bempedoic Acid on CV outcomes

Primary and First Key Secondary Cardiovascular End Points





Nissen et al. ***N Engl J Med*** 2023

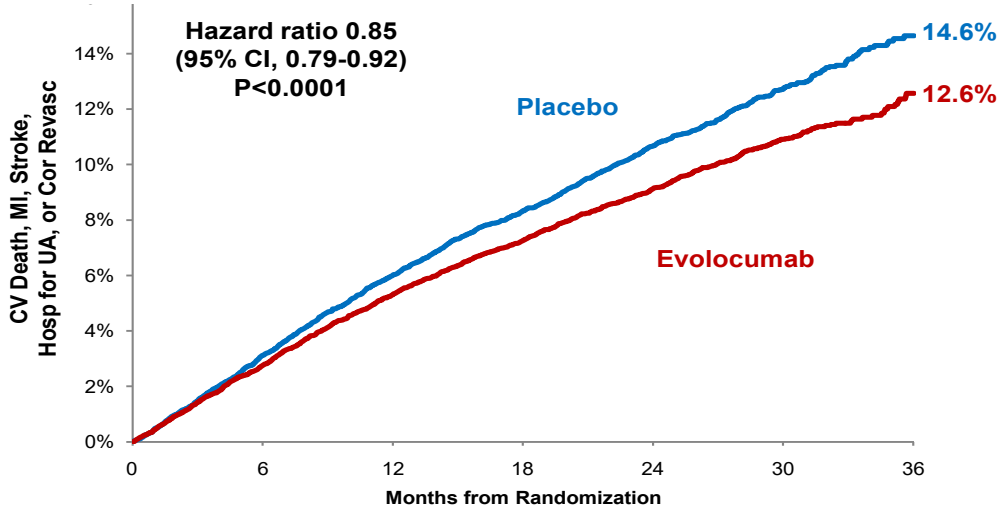
Optimizing management of dyslipidemias

- Lower LDL
  - Bempedoic acid
  - **PCSK9 inhibitors**
    - **Mabs**
    - **Inclisiran**
    - **Oral inhibitors**
    - **Gene editing**

FOURIER: benefit of evolocumab in patients with stable ASCVD

27,564 patients with stable ASCVD on moderate or high intensity statin

Primary endpoint:
CV death, MI, stroke, coronary revascularisation, or hospital admission for UA



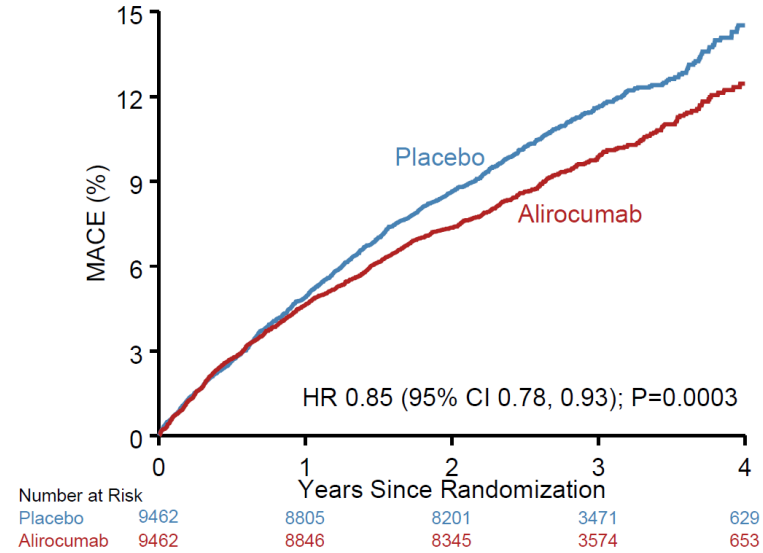
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Sabatine et al ***NEJM*** 2017

ODYSSEY OUTCOMES: benefit of alirocumab in patients with recent ACS

18,924 patients with recent ACS on maximum statin Rx

Primary endpoint: MACE

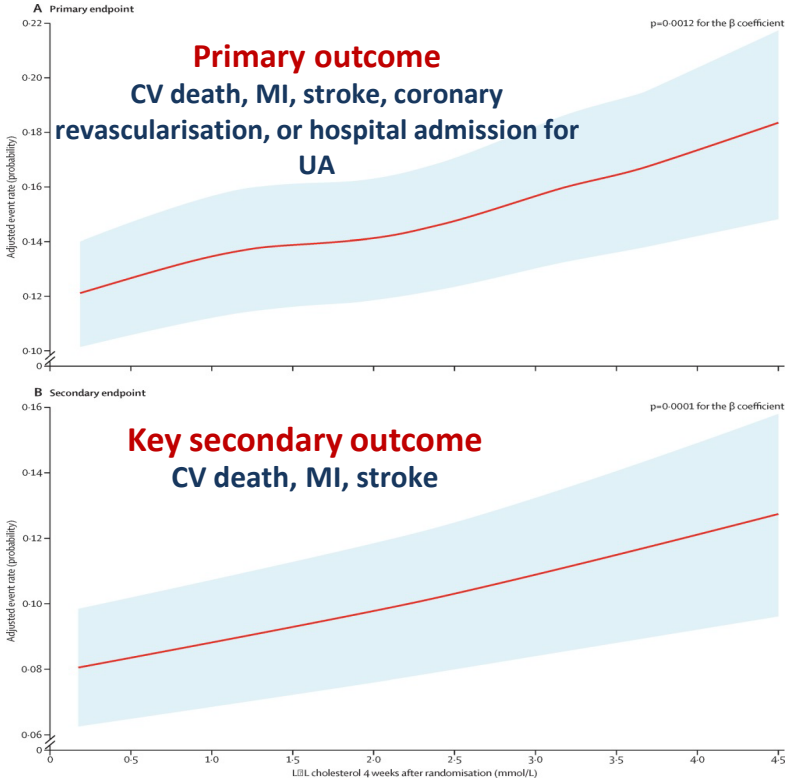


ARR based on cumulative incidence

Schwartz GG, Steg PG, et al. ***NEJM*** 2018

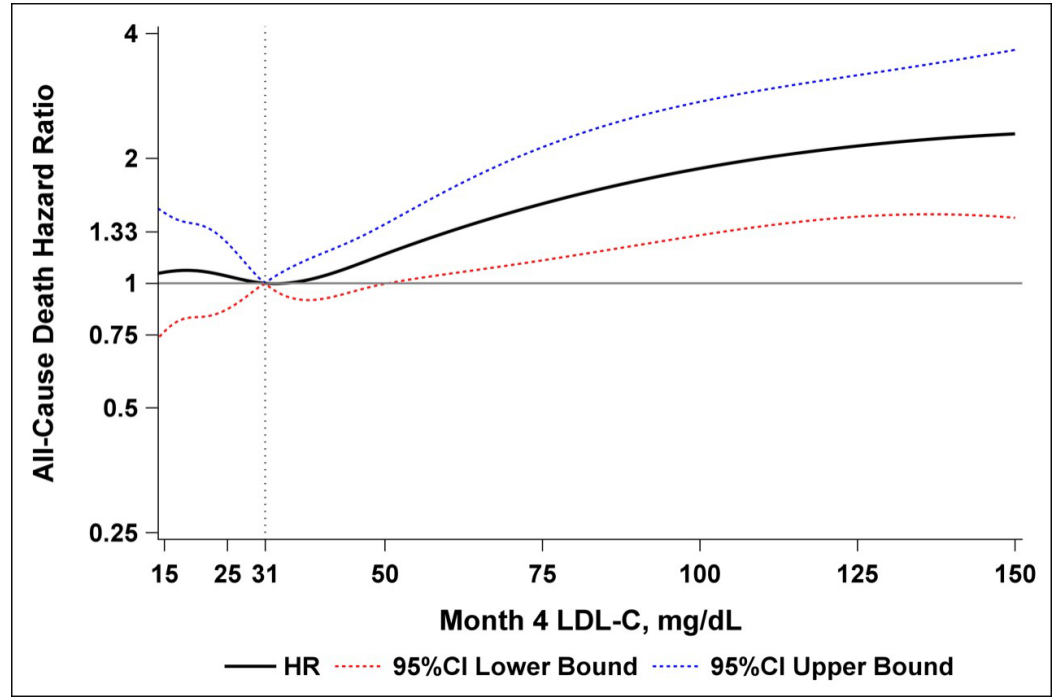
"Lower LDL-C is better"

Achieved LDL-cholesterol at 4 weeks and outcomes in the FOURIER trial



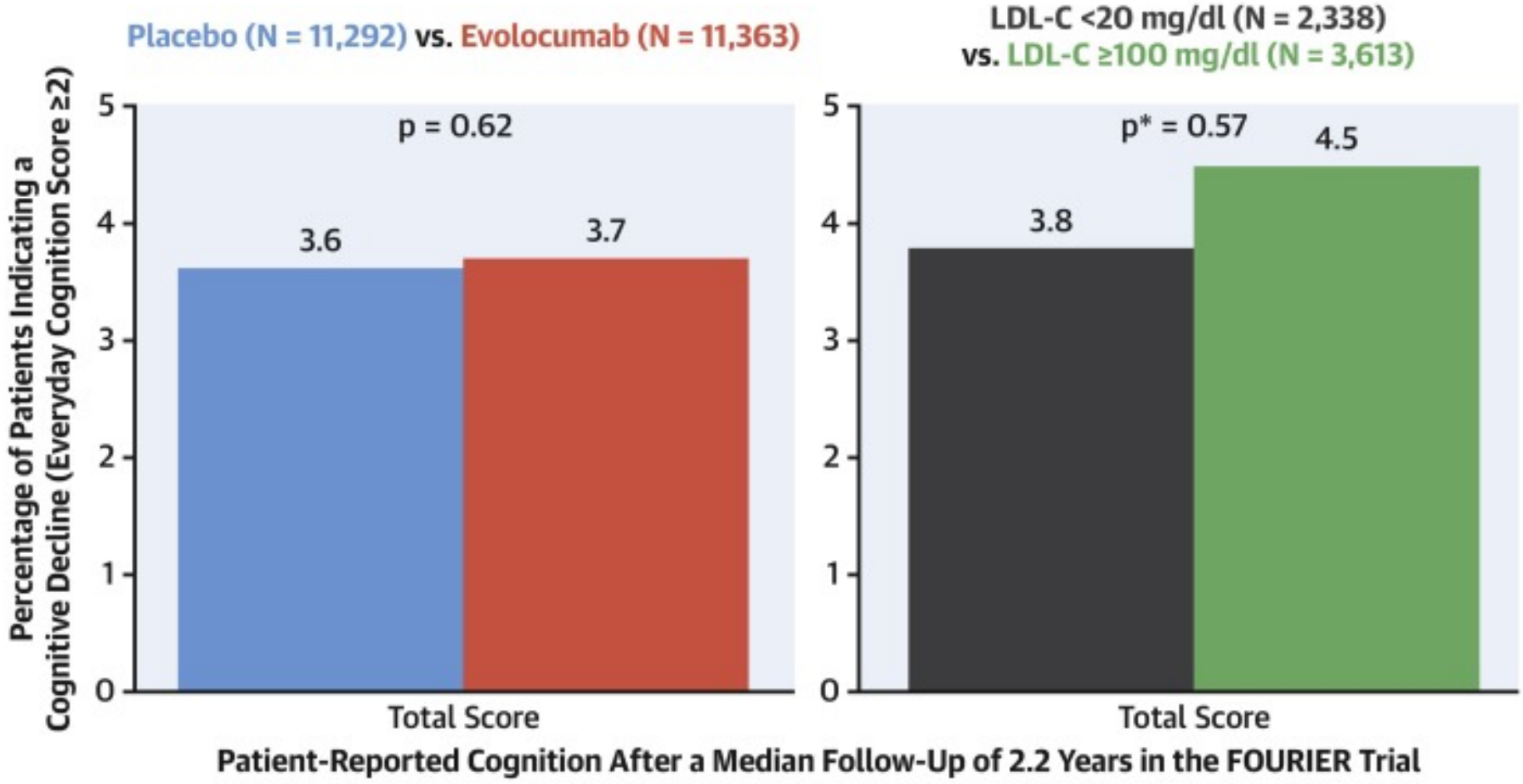
Giugliano et al. ***Lancet*** 2017;390:1962-71

Lower achieved LDL at Month 4 is associated with lower all-cause death



Steg PG et al. ***Circulation*** 2019

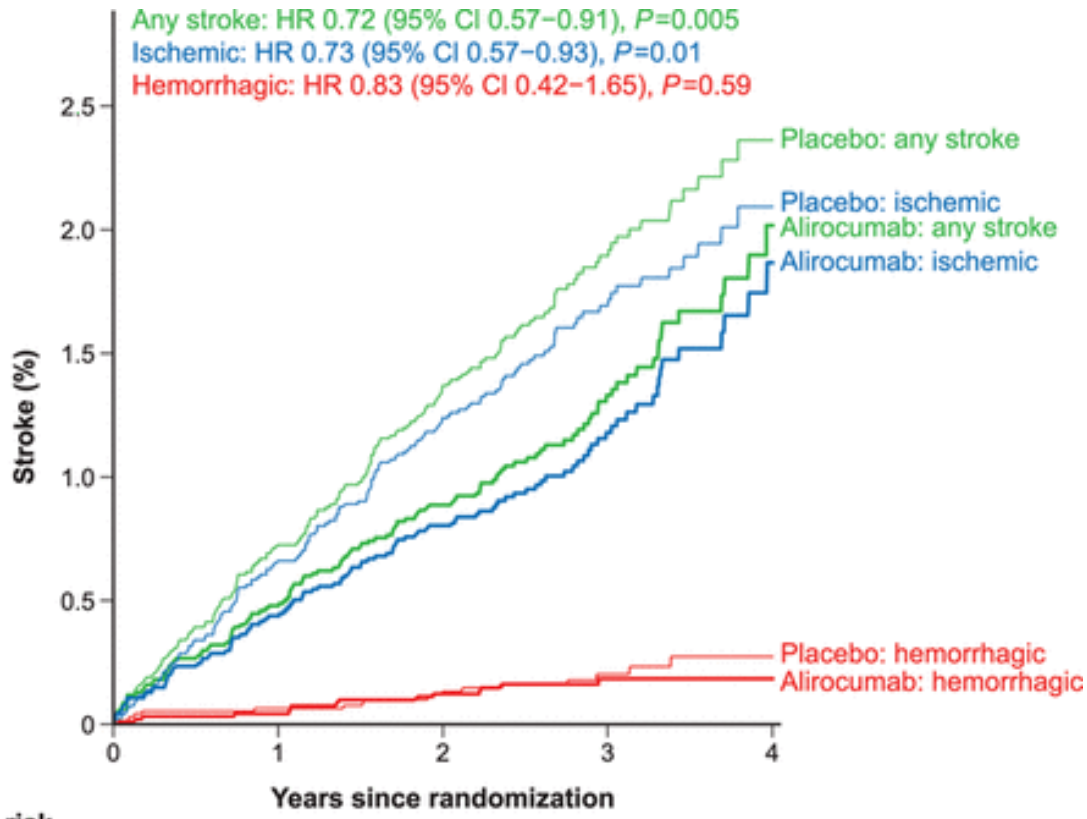
CENTRAL ILLUSTRATION: Percentage of Patients Indicating Cognitive Decline (Everyday Cognition Score ≥2) at the End of the Study by Treatment Arm and Achieved Low-Density Lipoprotein-Cholesterol Target at 4 Weeks



Patient-Reported Cognition After a Median Follow-Up of 2.2 Years in the FOURIER Trial

Gencer, B. et al. J Am Coll Cardiol. 2020;75(18):2283-93.

In ODYSSEY OUTCOMES, alirocumab reduced the risk of stroke and ischemic stroke without increasing the risk of hemorrhagic stroke

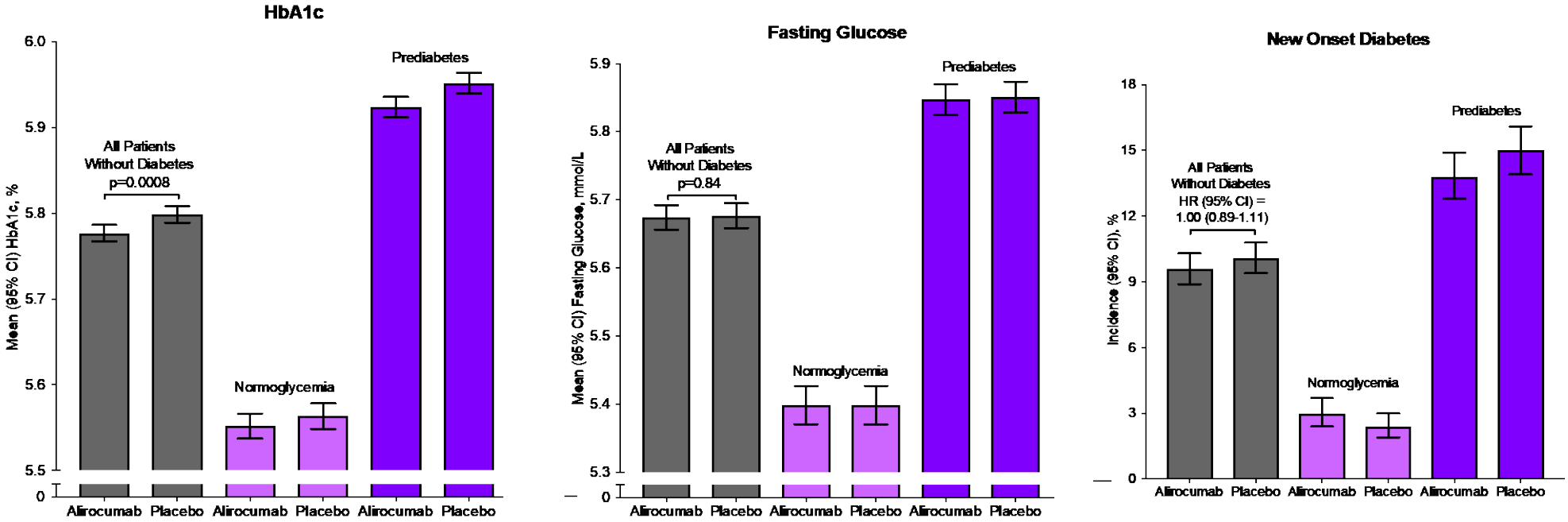


No apparent relation between low on treatment LDL and the incidence of hemorrhagic stroke in the Alirocumab arm

Jukema et al. ***Circulation*** 2019;140:2054-62

No adverse effects of alirocumab on glycemia

Post-randomization A1c, Fasting Glucose, and New-onset Diabetes by Baseline Glucometabolic Status in ODYSSEY OUTCOMES

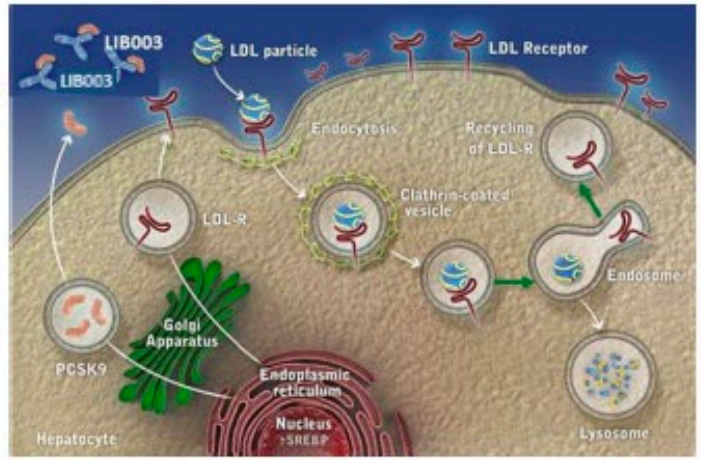


Analysis method for A1c and fasting glucose: repeated-measures mixed effects model; random effects = slope, intercept; fixed effects = treatment, baseline value, and time. Only post-randomization values prior to initiation of diabetes medication were included in the analysis.
*Without diabetes = prediabetes or normoglycemia.

Ray KK et al. ***Lancet Diabetes Endoc*** 2019

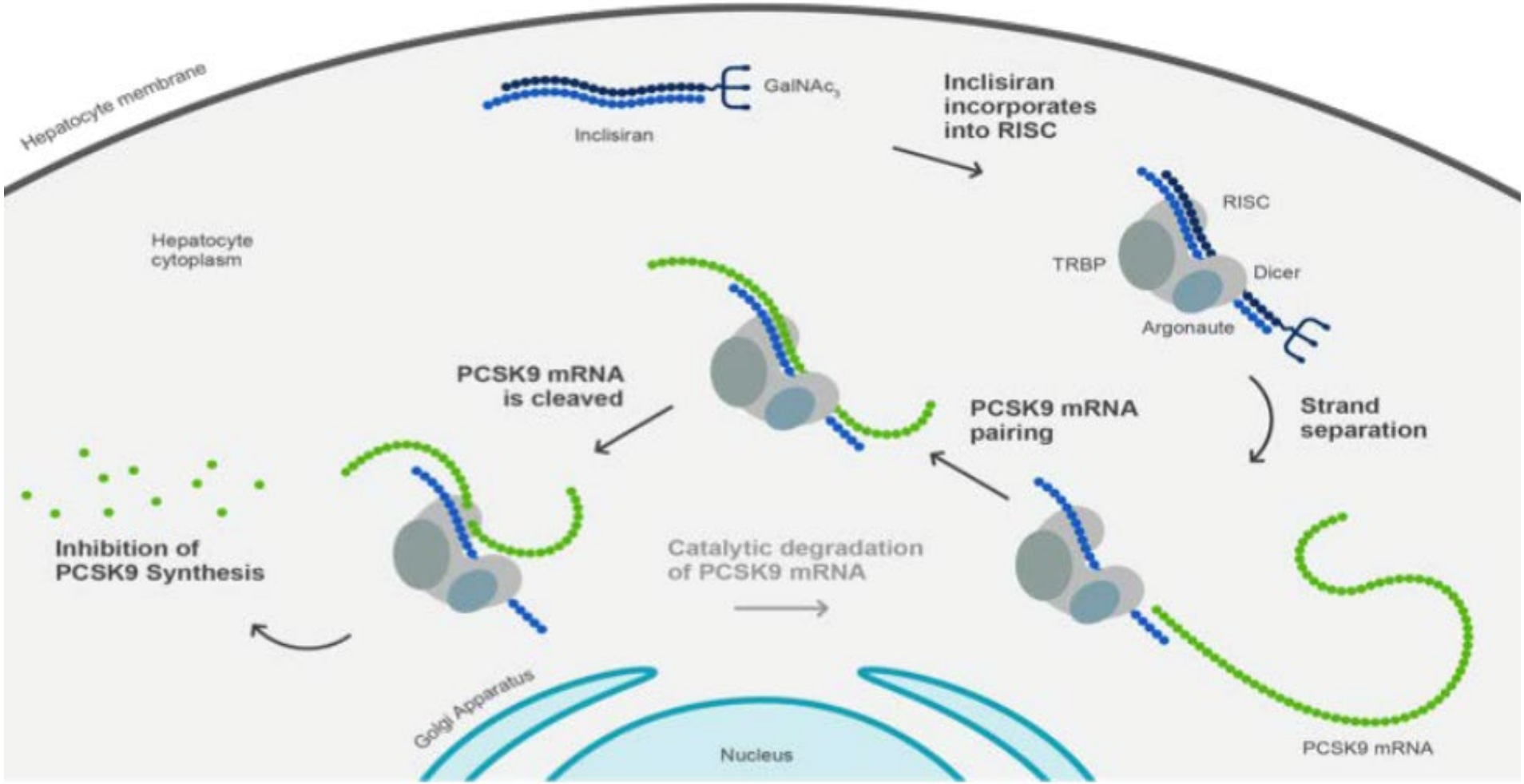
Lerodalcibep: a small binding protein with an anti-PCSK9 domain

- **Lerodalcibep** a small binding protein, consists of an 11kDa anti-PCSK9 domain (Adnectin), derived from human fibronectin, fused with human serum albumin with plasma half-life 12 to 15 days.



- Similar to mAbs, LIB003 binds to PCSK9, blocks PCSK9 binding to LDLR, preventing LDLR degradation, increasing LDLR recycling, enhancing LDL-C clearance, and lowers LDL-C levels.
- Different from mAbs, the small size (77kDa) and high solubility allows for a much smaller injection volume to achieve stable and prolonged LDL-C reductions between injections.
- Phase 2 trial established a 300 mg dose in 1.2 mL dosed monthly as highly effective, reducing LDL-C >70%

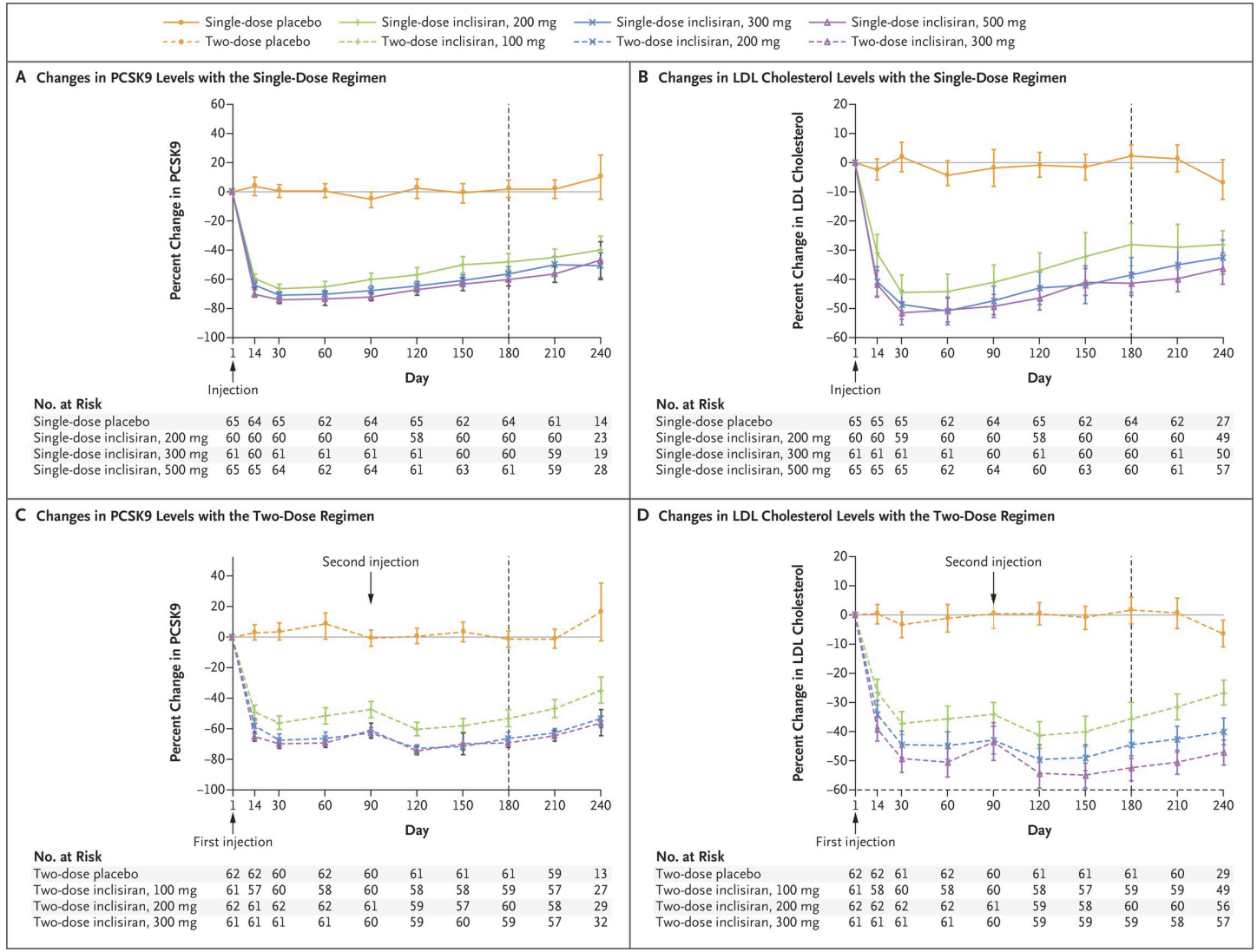
Inclisiran: a small interfering RNA (siRNA) targeted to PCSK9



RISC= RNA induced silencing complex

Whitehead et al. ***Nat Rev Drug Discov*** 2009;8:129-138

Sustained Effect of Inclisiran on PCSK9 and LDL Cholesterol Levels



No. at Risk

Single-dose placebo	65	64	65	62	64	65	62	64	61	14
Single-dose inclisiran, 200 mg	60	60	60	60	60	58	60	60	60	23
Single-dose inclisiran, 300 mg	61	60	61	61	61	61	60	60	59	19
Single-dose inclisiran, 500 mg	65	65	64	62	64	61	63	61	59	28

No. at Risk

Single-dose placebo	65	65	65	62	64	65	62	64	62	27
Single-dose inclisiran, 200 mg	60	60	59	60	60	58	60	60	60	49
Single-dose inclisiran, 300 mg	61	61	61	61	60	61	60	60	61	50
Single-dose inclisiran, 500 mg	65	65	65	62	64	60	63	60	61	57

No. at Risk

Two-dose placebo	62	62	60	62	60	61	61	61	59	13
Two-dose inclisiran, 100 mg	61	57	60	58	60	58	58	59	57	27
Two-dose inclisiran, 200 mg	62	61	62	62	61	59	57	60	58	29
Two-dose inclisiran, 300 mg	61	61	61	61	60	59	60	59	57	32

No. at Risk

Two-dose placebo	62	62	61	62	60	61	61	61	60	29
Two-dose inclisiran, 100 mg	61	58	60	58	60	58	57	59	59	49
Two-dose inclisiran, 200 mg	62	62	62	62	61	59	58	60	60	56
Two-dose inclisiran, 300 mg	61	61	61	61	60	59	59	59	58	57

Ray KK et al. ***N Engl J Med*** 2017;376:1430-1440

Ongoing Inclisiran CV Outcomes trials

Placebo-controlled, double-blind, randomized studies

	Objective	Participants	Countries	Treatment	Status
ORION-4	Impact of Inclisiran on 4P-MACE in ps with established CV disease	Established CV disease (N= 15000)	UK/USA	Inclisiran sodium 300 mg (284 mg inclisiran) or placebo SQ	Ongoing
VICTORION-2 Prevent	Impact of Inclisiran on 3-P MACE in pts with established CV disease	Established CV disease (N= 15000) - on stable dose atorvastatin ≥40 mg QD or Rosuvastatin ≥20 mg QD - LDL-c ≥0,7 g/L	International	Inclisiran sodium 300 mg (284 mg inclisiran) or placebo SQ	Ongoing

https://clinicaltrials.gov/ct2/show/NCT05030428 - V2P
https://clinicaltrials.gov/ct2/show/NCT03705234 - ORION 4

Design of a knowledge-based mechanistic model of atherosclerotic cardiovascular disease for *in silico* trials

D. Angoulvant[1], P. Amarenco[2], A. Bastien[3], E. Bechet[4], F. Boccara[5], JP. Boissel[4], B. Cariou[6], E. Courcelles[4], S. Granjeon-Noriot[4], G. Mahé[7], E. Peyronnet[4], L. Portal[3], S. Porte[4], Y. Wang[4], P.G. Steg[8]

[1] Cardiology department, Hôpital Trousseau, CHRU de Tours & EA4245, Université de Tours, Tours, France, [2] Department of Neurology and Stroke center, APHP, Bichat Hospital, Université Paris-Cité Paris, France and McMaster University, Population Health Research Institute, Hamilton, Ontario, Canada, [3] Novartis, Rueil Malmaison, France, [4] Novadiscovery, Lyon, France, [5] Sorbonne Université, GRC n°22, C2MV, Inserm UMR_S 938, Centre de Recherche Saint-Antoine, ICAN, Cardiologie, Hôpital Saint Antoine APHP, Paris, France, [6] Nantes Université, CHU Nantes, CNRS, Inserm, institut du thorax, Nantes, France, [7] Vascular Medicine Unit, CHU Rennes, Univ Rennes CIC1414, Rennes, France, [8] Université Paris-Cité, APHP, Hôpital Bichat, and INSERM U-1148/LVTS, Paris, France

PURPOSE

This study aims at building a **knowledge-based mechanistic model of atherosclerotic cardiovascular disease** (**ASCVD**). Once validated, the model will be used to run ***in silico* clinical trials** to compare the benefit of inclisiran, an siRNA targeting PCSK9 mRNA, vs other lipid-lowering therapies (LLT) on cardiovascular (CV) events in patients with ASCVD.

METHODS

- **ASCVD pathophysiological mechanisms** and **therapeutic mechanisms of action** were described into a knowledge model following an extensive literature review.
- Every piece of knowledge extracted from the literature was awarded a **strength of evidence** grading to allow **tracking of uncertainty** in the model.
- A panel of **multidisciplinary clinical experts** reviewed knowledge models and subsequent modelling hypotheses to **validate their relevance**.
- Knowledge was translated into **mathematical equations**. Each functional relationship between entities was represented by a biochemical/biophysical reaction with its reaction rate. A system of ordinary differential equations provided dynamics of modelled biological entities over time.
- **A calibration and validation strategy** was defined with the panel of experts by selecting relevant randomized clinical trials and registry data, that the model should be able to reproduce.
- **Inter-patient variability** was accounted for by virtual populations* by making a set of model parameters vary.

CONCLUSIONS

A mechanistic computational model of ASCVD (including 72 biological entities, 750 parameters) was built from knowledge and calibrated. The next step is validation before using the model to run *in silico* clinical trials.

In silico clinical trials provide an attractive option to complement randomized clinical trials by **adding comparative effectiveness data** and **facilitating demonstration of drug benefit**.

** A Virtual Population is a collection of virtual patients. Each virtual patient is generated by drawing randomly a value for each parameter of the model (eg age, sex, reaction rate constants) from the parameter distributions derived from available data sets and literature, or determined during calibration.*

***Abbreviations** - anti-PCSK9 mAb: anti-PCSK9 monoclonal antibody, ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, eGFR: estimated glomerular filtration rate, HDL: High density lipoproteins, hsCRP: high sensitivity C-reactive protein, LDL: low density lipoprotein, LDLR: LDL receptor, Lp(a): lipoprotein(a), LLT: lipid-lowering therapies, PAD: peripheral arterial disease, PCSK9: proprotein convertase subtilisin/kexin type 9, NPC1L1: Niemann–Pick C1-like 1, 3P-MACE: 3 point major adverse cardiovascular events, MALE: Major adverse limb events, RCT: reverse cholesterol transport, VLDL: very low density lipoprotein, VSMC: vascular smooth muscle cells.*

RESULTS – An ASCVD model predicting lipoprotein levels and CV events to support the development of new LLT

An ASCVD knowledge model synthesizes pathophysiology

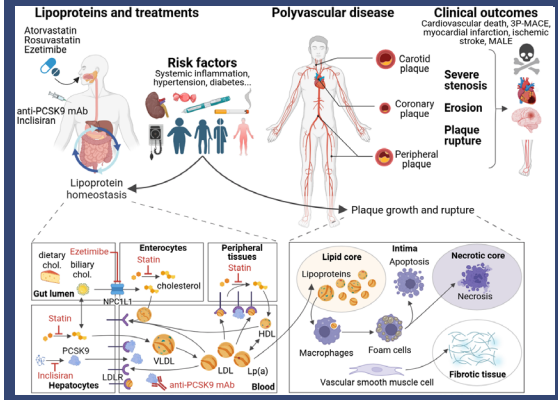


Figure 1: Multi-scale *in silico* model combining lipoprotein homeostasis, efficacy of lipid lowering treatments, atherosclerotic plaque growth and rupture leading to clinical outcomes and impact of risk factors (not exhaustively listed) on the pathophysiology.

Knowledge is translated into a mathematical model (eg. ASCVD plaque submodel)

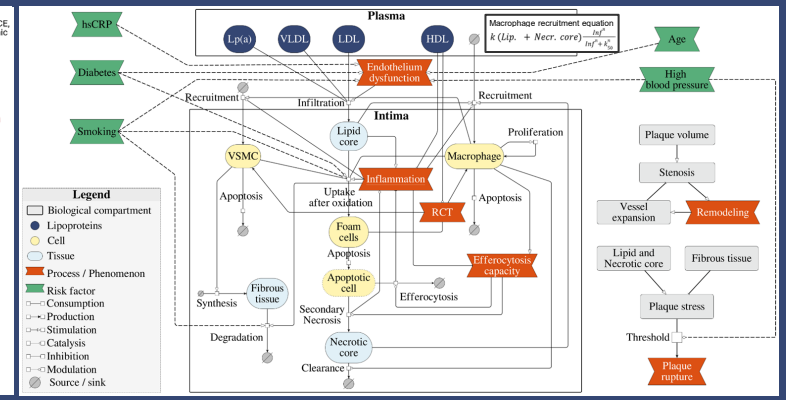


Figure 2: Graphical representation of the plaque growth and rupture submodel describing interactions between biological entities (eg. lipoproteins, macrophage, VSMC and foam cells) involved in atherosclerosis plaque evolution, atherosclerosis patho-physiological processes, and impact of risk factors (eg. diabetes, hypertension and smoking).

The model is calibrated to reproduce inclisiran effect on LDL-C levels

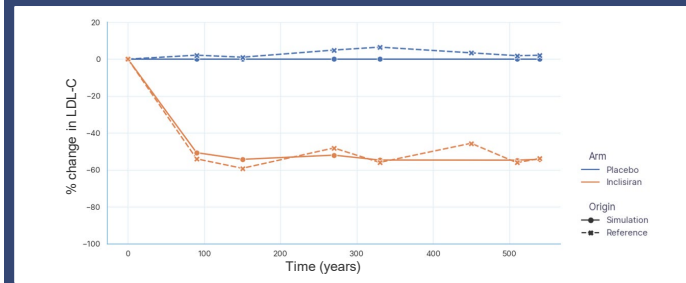


Figure 3: Comparison of population-mean percentage change in LDL-C levels following inclisiran (orange) or placebo (blue) administered as add-on to background LLT (statin with or without ezetimibe) as observed in ORION 10 trial (dotted lines; N=780 per arm) Ray et al. (2020) vs simulated by the model with a calibrated virtual population (solid lines; N=780).

The model is calibrated to reproduce evolocumab effect on CV outcomes

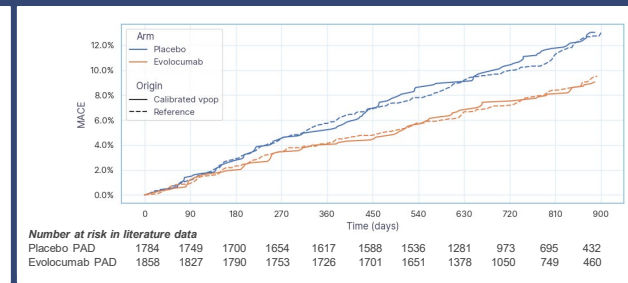


Figure 4: MACE (first occurrence of CV death, MI or stroke) by treatment (evolocumab in orange, placebo in blue) in patients with symptomatic PAD as observed in FOURIER (dashed lines) Bonaca et al. (2018) and simulated in a virtual population (solid lines, N=929). *Note that all strokes are modeled as a consequence of a plaque rupture.*

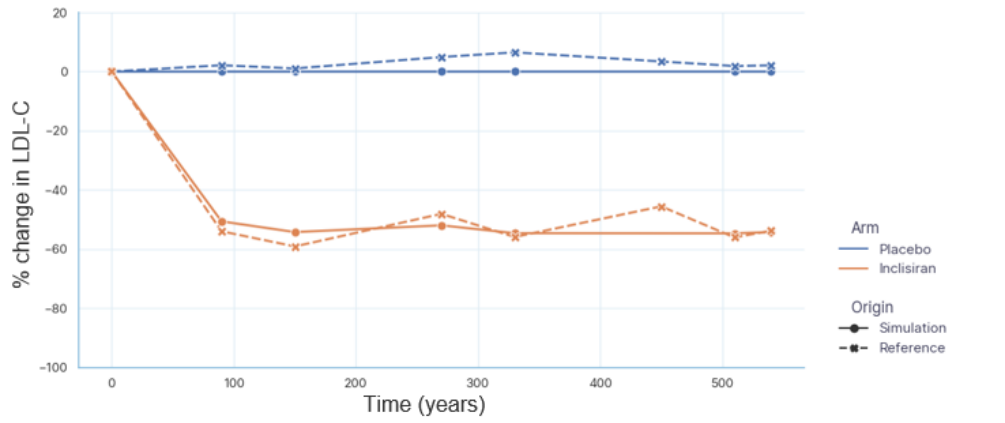
Angoulvant D, et al. ***Eur J Prev Cardiol***. 2024

Calibration

Mechanistic modeling based on knowledge

Calibration: iterative process of determining the values and/or the distributions of unknown model parameters in order to achieve a realistic behavior of the model.

The model is calibrated to reproduce inclisiran effect on LDL-C levels



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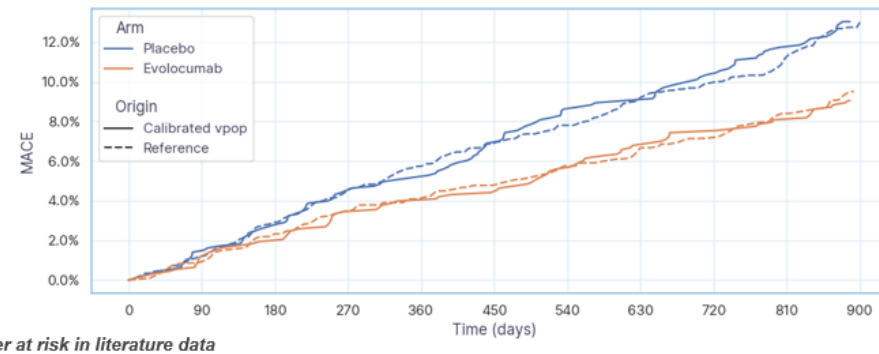


Number at risk in literature data

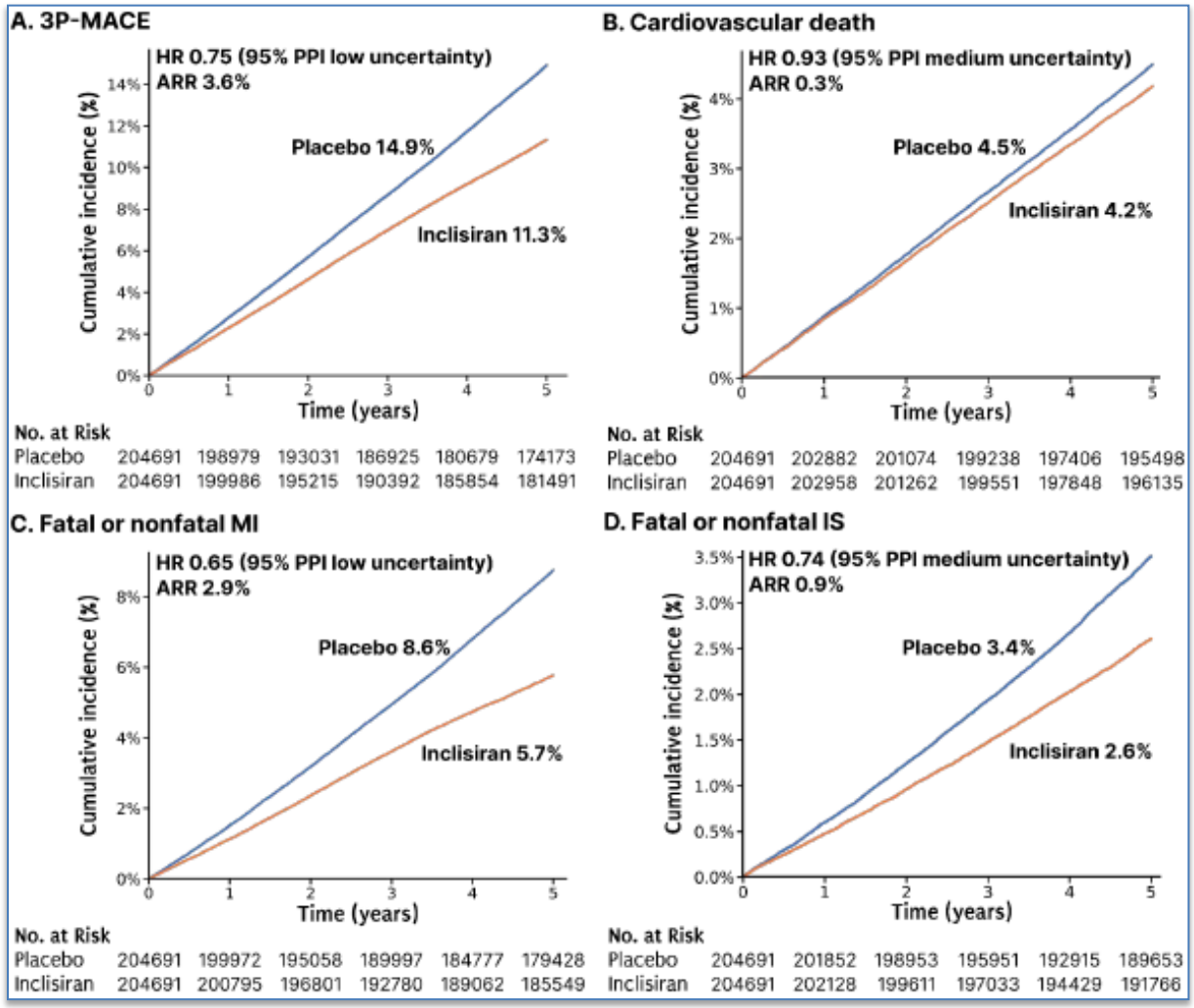
Placebo PAD	1784	1749	1700	1654	1617	1588	1536	1281	973	695	432
Evolocumab PAD	1858	1827	1790	1753	1726	1701	1651	1378	1050	749	460

Figure 4: MACE (first occurrence of CV death, MI or stroke) by treatment (evolocumab in orange, placebo in blue) in patients with symptomatic PAD as observed in FOURIER (dashed lines) Bonaca et al. (2018) and simulated in a virtual population (solid lines, N=929). *Note that all strokes are modeled as a consequence of a plaque rupture.*

Angoulvant D, et al. ***Eur J Prev Cardiol***. 2024

Predicting the efficacy of inclisiran on cardiovascular outcomes in patients with established atherosclerotic cardiovascular disease: primary results of the *in silico* SIRIUS trial

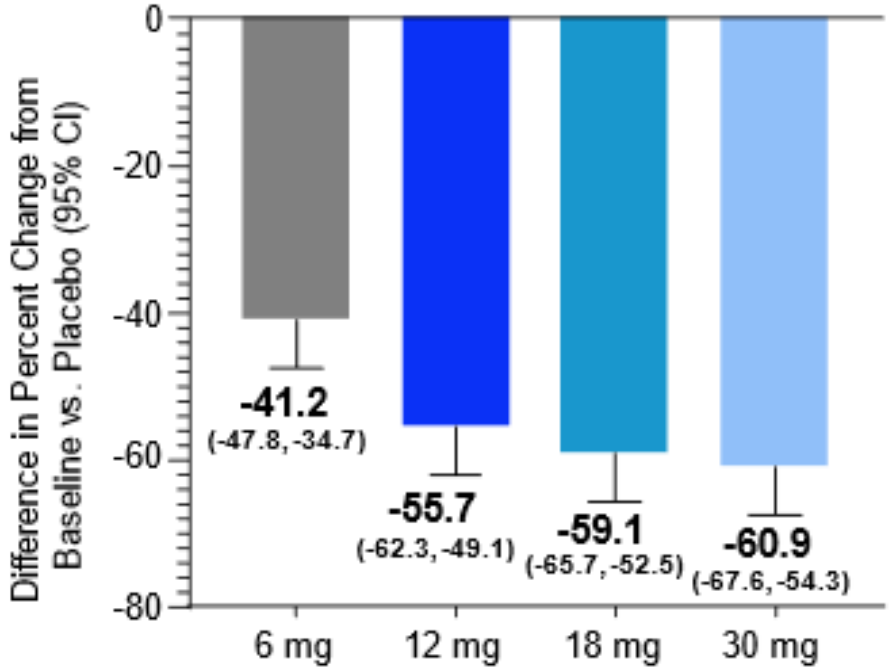
D. Angoulvant[1], P. Amarenco[2], A. Bastien[3], E. Bechet[4], F. Boccara[5*], JP. Boissel[4], B. Cariou[6], E. Courcelles[4], A. Diatchenko[4], A. Filipovics[3], S. Granjeon-Noriot[4], R. Kahoul[4], G. Mahé[7], E. Peyronnet[4], L. Portal[3], S. Porte[4], Y. Wang[4], P.G. Steg[8]



Angoulvant D et al. ***EAS*** 2024

A phase II trial of MK-0616, an oral PCSK9 inhibitor

LDL-C at Week 8



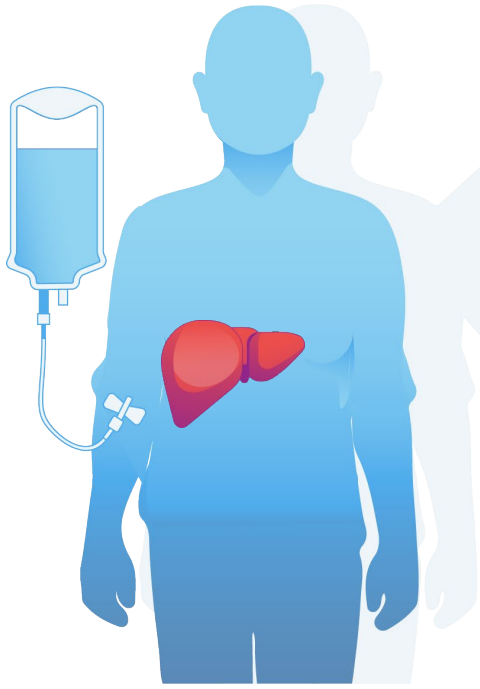
- LDL-C reduction from Baseline to Week 8 superior to placebo ($p<0.001$) for all doses of MK-0616
- Near-complete efficacy achieved by 2 weeks with persistent effect over the 8 -week treatment period
- Results generally consistent across prespecified subgroups

Efficacy Population: All participants who received ≥1 dose, had ≥1 observation for the analysis endpoint, and had baseline data for those analyses that require baseline data.

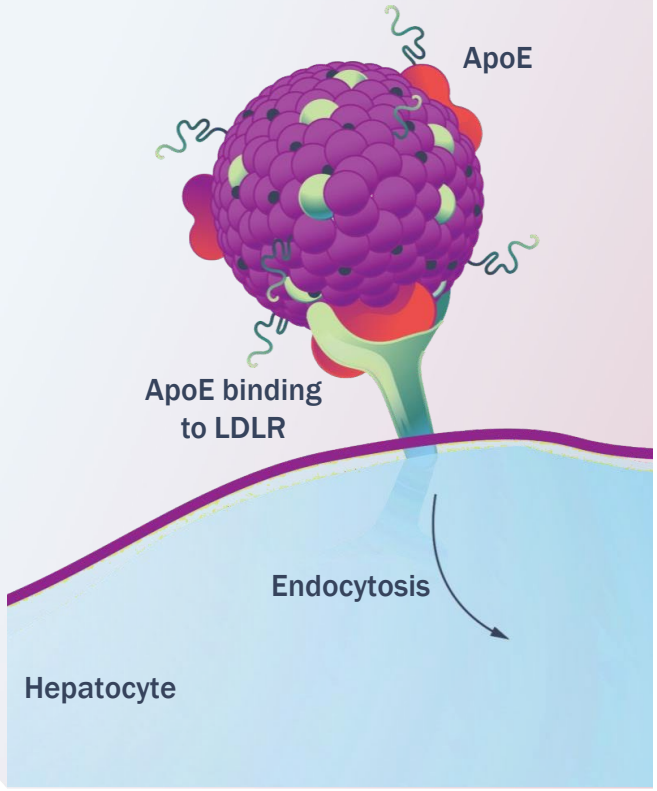
Ballantyne CM et al. ***J Am Coll Cardiol*** 2023; 81:1553-1564.

Uptake of the VERVE-101 LNP into hepatocytes occurs primarily by endocytosis through LDLR

IV infusion of LNP



VERVE-101 LNP Uptake

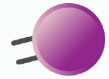


RNA Components

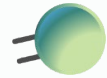
mRNA encoding adenine base editor

Guide RNA targeting *PCSK9*

LNP Components



Ionizable lipid



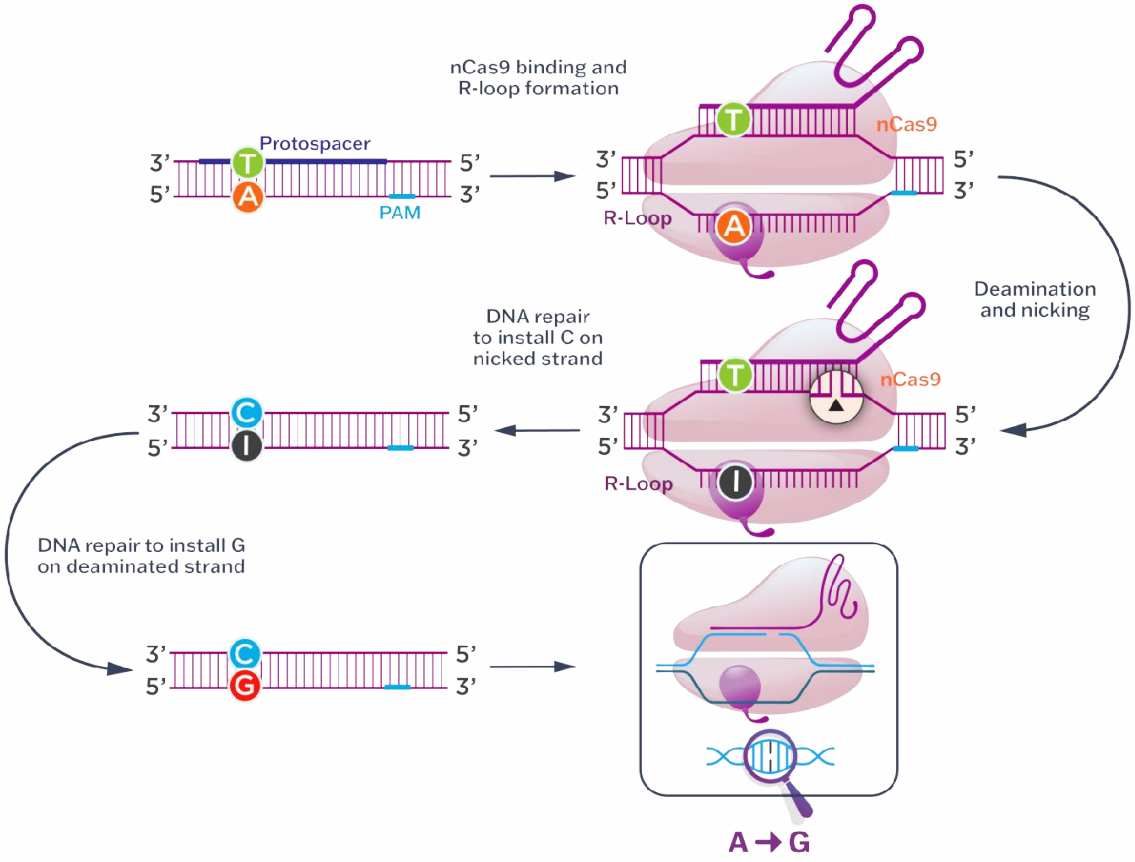
DSPC

PEG

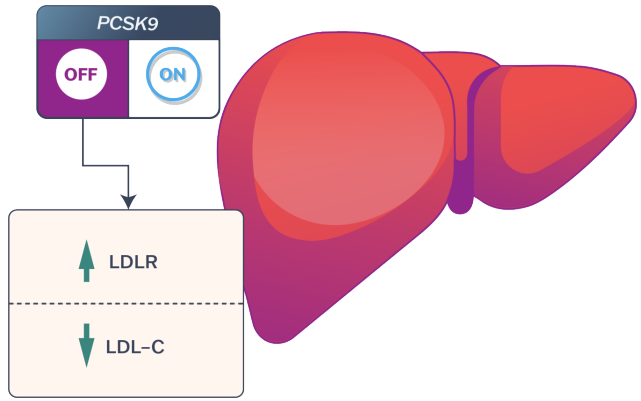
Cholesterol

ApoE, apolipoprotein E

In the hepatocyte, the mRNA is translated to ABE protein which pairs with the gRNA to ultimately make a single spelling change in the PCSK9 DNA sequence to turn it off: <u>think pencil and eraser</u>



A-to-G change disrupts a splice donor site and inactivates the *PCSK9* gene



nature

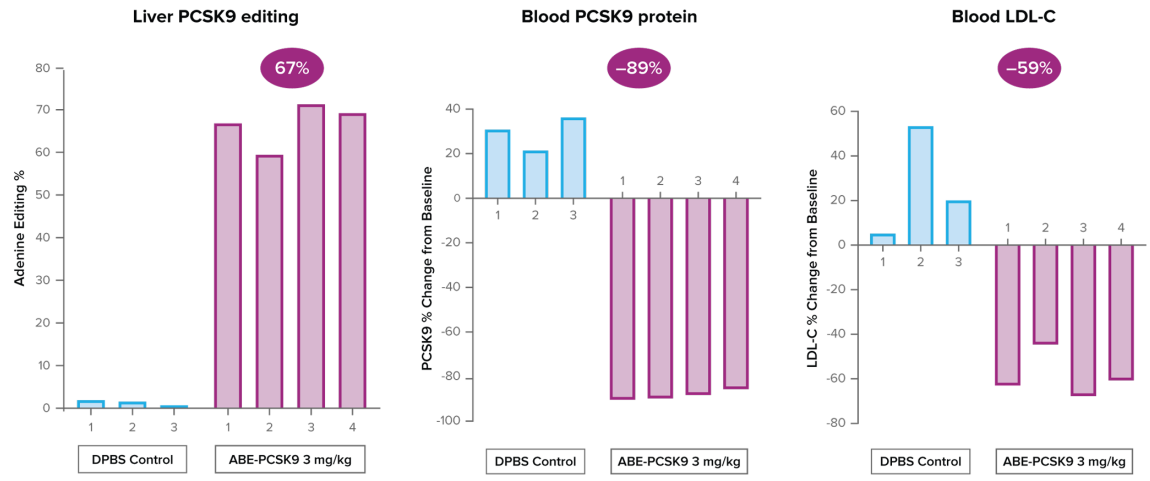
Nature | Vol 593 | 20 May 2021 |

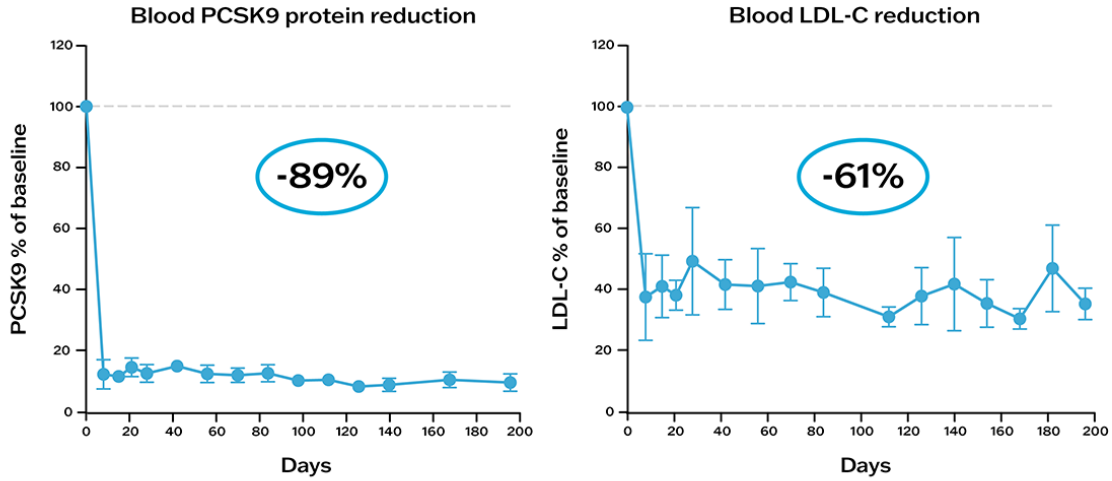
Article

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

Gene-editing technologies, which include the CRISPR–Cas nucleases[1–3] and CRISPR base editors[4,5], have the potential to permanently modify disease-causing genes in patients[6]. The demonstration of durable editing in target organs of nonhuman primates is a key step before in vivo administration of gene editors to patients in clinical trials. Here we demonstrate that CRISPR base editors that are delivered in vivo using lipid nanoparticles can efficiently and precisely modify disease-related genes in living cynomolgus monkeys (*Macaca fascicularis*). We observed a near-complete knockdown of *PCSK9* in the liver after a single infusion of lipid nanoparticles, with concomitant reductions in blood levels of PCSK9 and low-density lipoprotein cholesterol of approximately 90% and about 60%, respectively; all of these changes remained stable for at least 8 months after a single-dose treatment. In addition to supporting a 'once-and-done' approach to the reduction of low-density lipoprotein cholesterol and the treatment of atherosclerotic cardiovascular disease (the leading cause of death worldwide[7]), our results provide a proof-of-concept for how CRISPR base editors can be productively applied to make precise single-nucleotide changes in therapeutic target genes in the liver, and potentially in other organs.

CrisprCas9 Gene editing to inhibit PCSK9 (NHP)

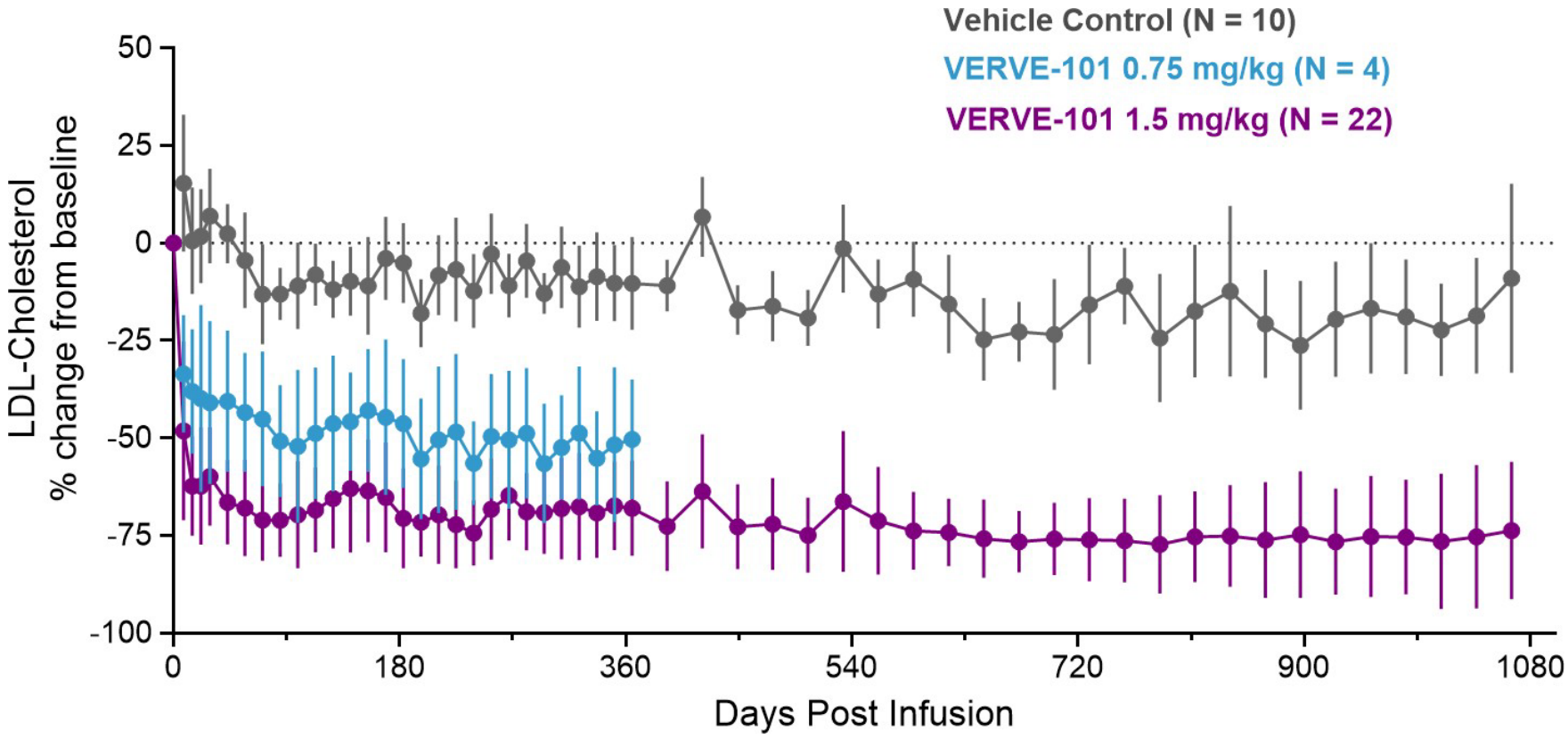




Each data point represents a consecutive measurement from n = 4 cynomolgus monkeys

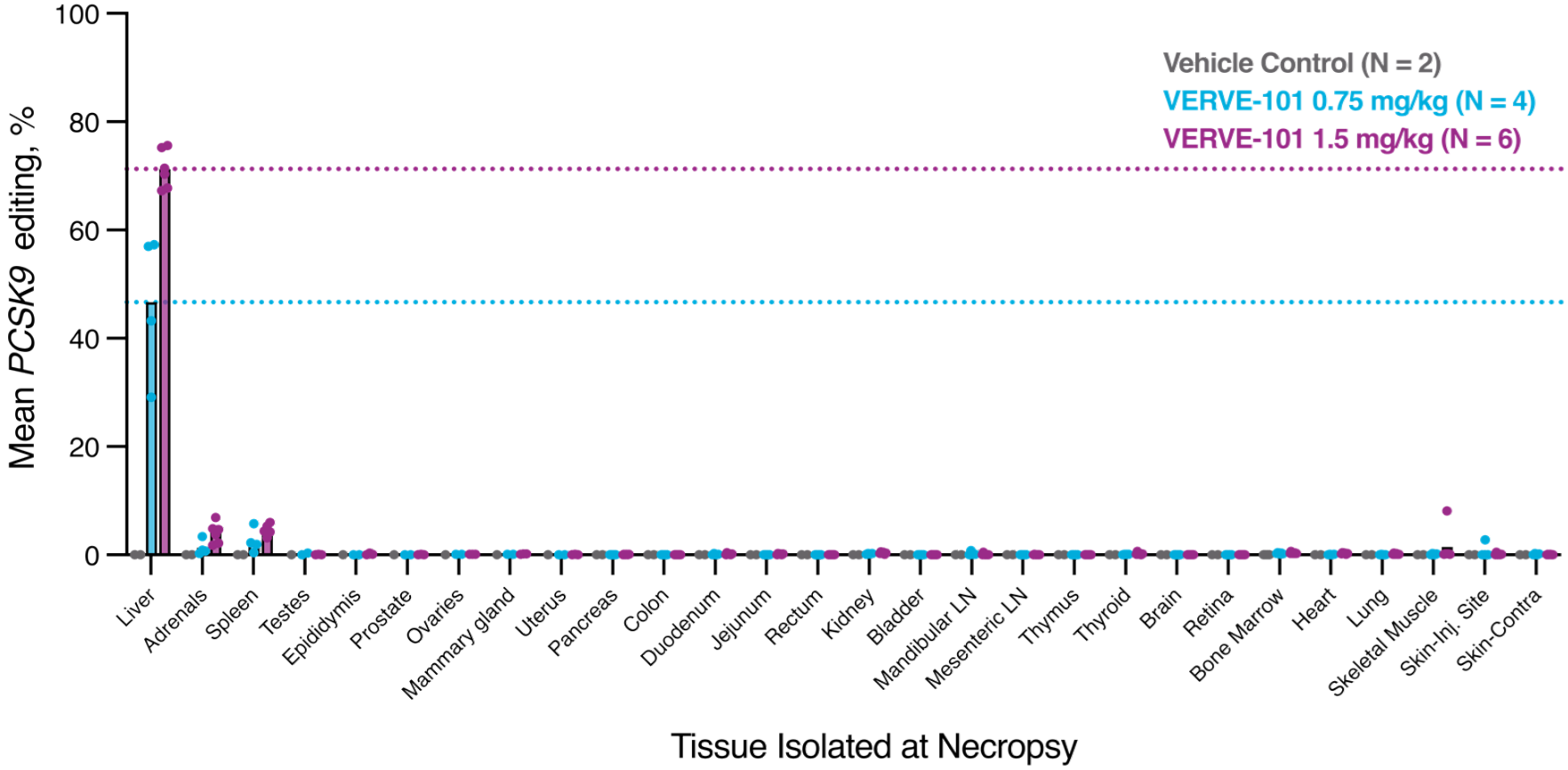
Vervetx.com

Durability in non-human primates: a single infusion of VERVE-101 reduced blood LDL-C for 3 years

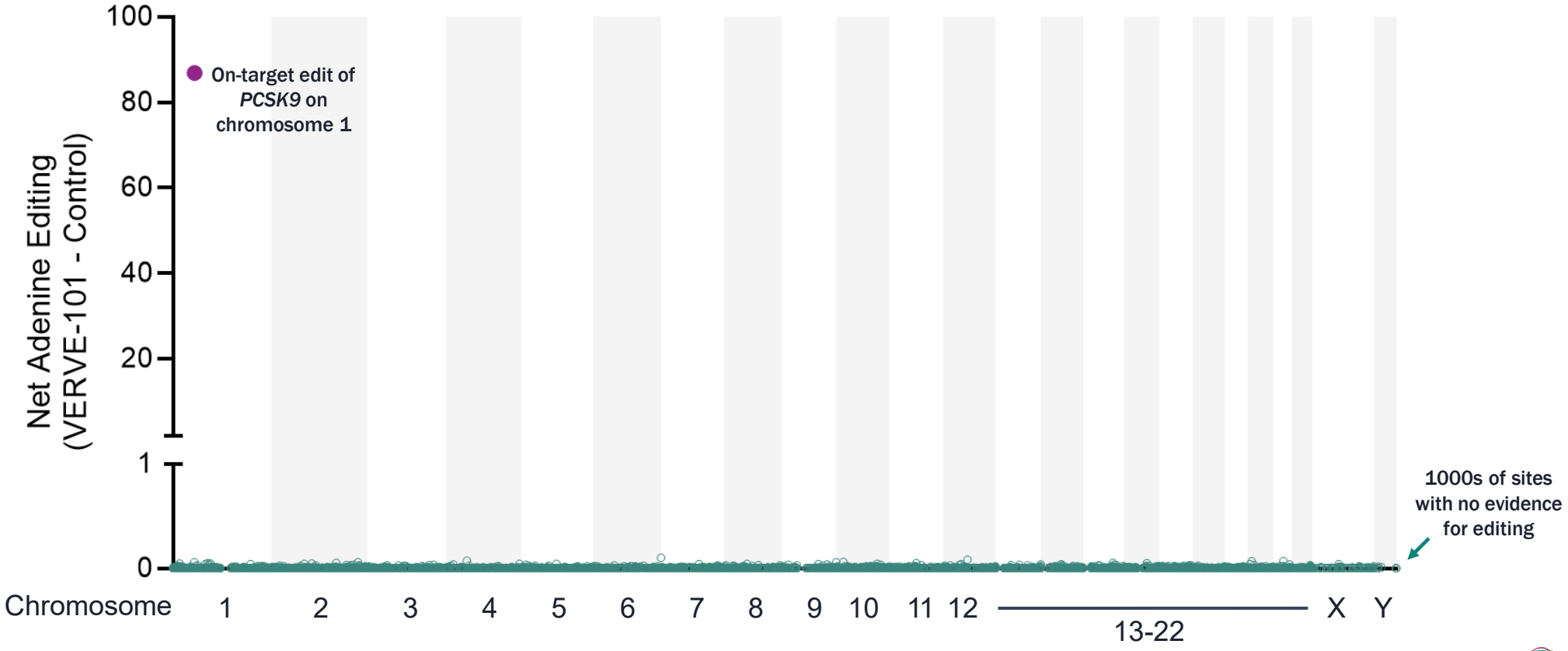


NHP, non-human primate
Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point
Reductions are time-weighted average change from baseline

NHP data demonstrate that VERVE-101 is predominantly taken up by the liver



No off-target editing was observed with VERVE-101 in analysis of ~6000 candidate sites in primary human hepatocytes *in vitro*



Heart-1 is a first-in-human Phase 1b trial designed to evaluate the safety and tolerability of VERVE-101

heart-1

First-in-human, open-label, single ascending dose study in patients with HeFH and high risk for cardiovascular events

13 patients dosed

STUDY POPULATION SUMMARY

- Males and females (age 18 to 75)
- HeFH and established ASCVD
- High cholesterol despite treatment

TREATMENT

- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered by single IV infusion

HeFH Heterozygous familial hypercholesterolemia

- Serious, inherited form of high cholesterol
- Lifelong elevations in LDL-C and premature ASCVD
- Estimated three million adult patients in EU/US[1]

Data as of Oct. 3, 2024; Clinical trial registration: NCT05398029
Women of childbearing potential are excluded from the study. LDL-C threshold for inclusion value varies by country-specific protocol.
Ongoing treatment for high cholesterol for participants consists of maximum tolerated statin and/or ezetimibe (statin intolerant allowed).
Dosing based on weight for participants ≤ 100 kg; participants > 100 kg are dosed on an assumed 100 kg weight.
EU, European Union; US, United States
1. de Ferranti SD, et al. *Circulation*. 2016;133;1067-1072; 2. Vallejo-Vaz AJ, et al. *Lancet*. 2021;398(10312):1713-1725.

verve THERAPEUTICS

Efficacy: Heart-1 provides human proof-of-concept for *in vivo* base editing of the *PCSK9* gene with VERVE-101

heart-1

13

patients dosed

- Dose-dependent reductions in blood PCSK9 protein & LDL-C
- Mean PCSK9 protein reductions of >60% for two higher dose cohorts (0.45 and 0.6 mg/kg)
- Mean LDL-C reductions of 42% at 0.45 mg/kg (n=6) and 57% at 0.6 mg/kg (n=1)[1]

As of data cut off date of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.
1. Means are based on time-averaged reduction in LDL-C and PCSK9 protein from day 28 through last available follow up; observations from one participant dosed at 0.45 mg/kg censored after change in lipid lowering therapy from baseline more than 6 months after VERVE-101 treatment; effective dose for participant at 0.6 mg/kg was ~0.5 mg/kg.

verve THERAPEUTICS

Safety: Laboratory abnormalities (transient, reversible) after LNP infusion led to pause in enrollment

heart-1

13

patients dosed

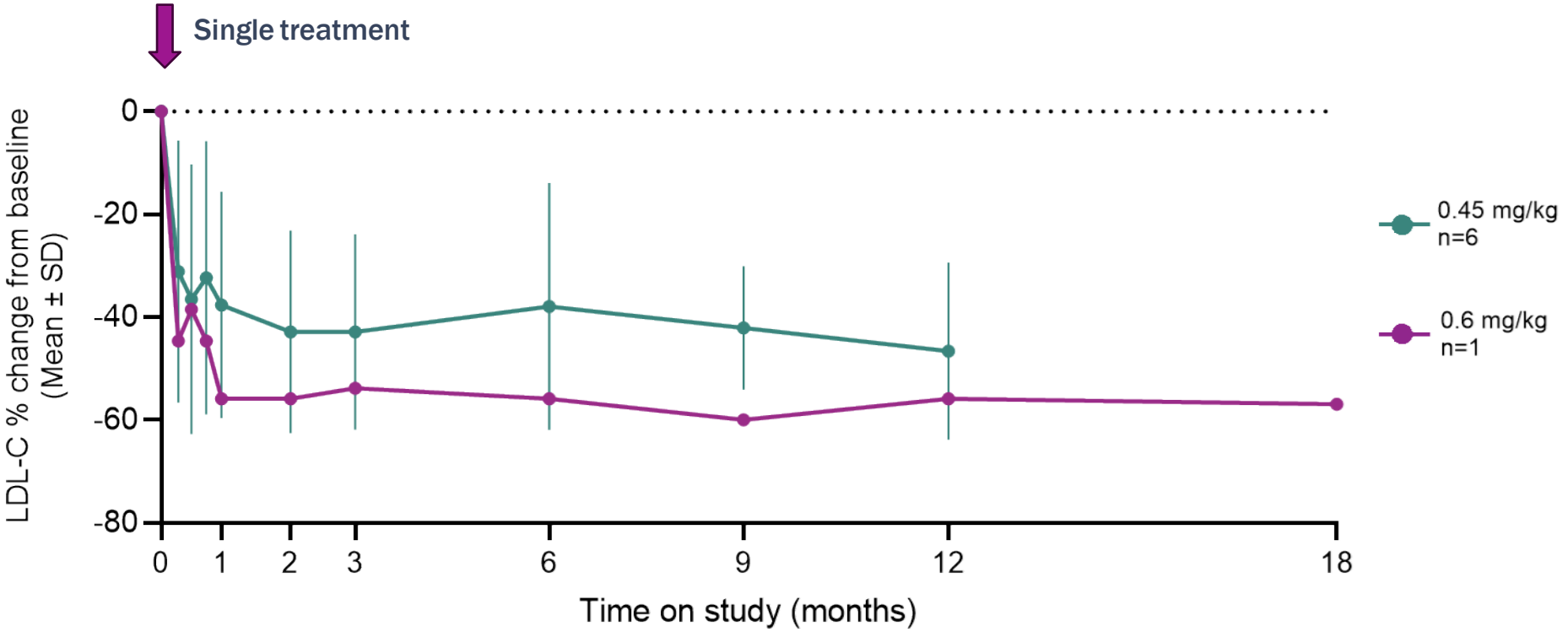
- Mild-to-moderate infusion reactions and transient, asymptomatic ALT increases
- Transient laboratory abnormalities in one patient of ALT increase and grade 3 SAE of drug-induced thrombocytopenia
- Cardiovascular events consistent with severe ASCVD population
- No new treatment-related adverse events occurred more than 2 days after treatment

Enrollment paused pending completion of investigation of laboratory abnormalities; preliminary findings support hypothesis that laboratory abnormalities attributable to LNP

As of data cut off date of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.
AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event

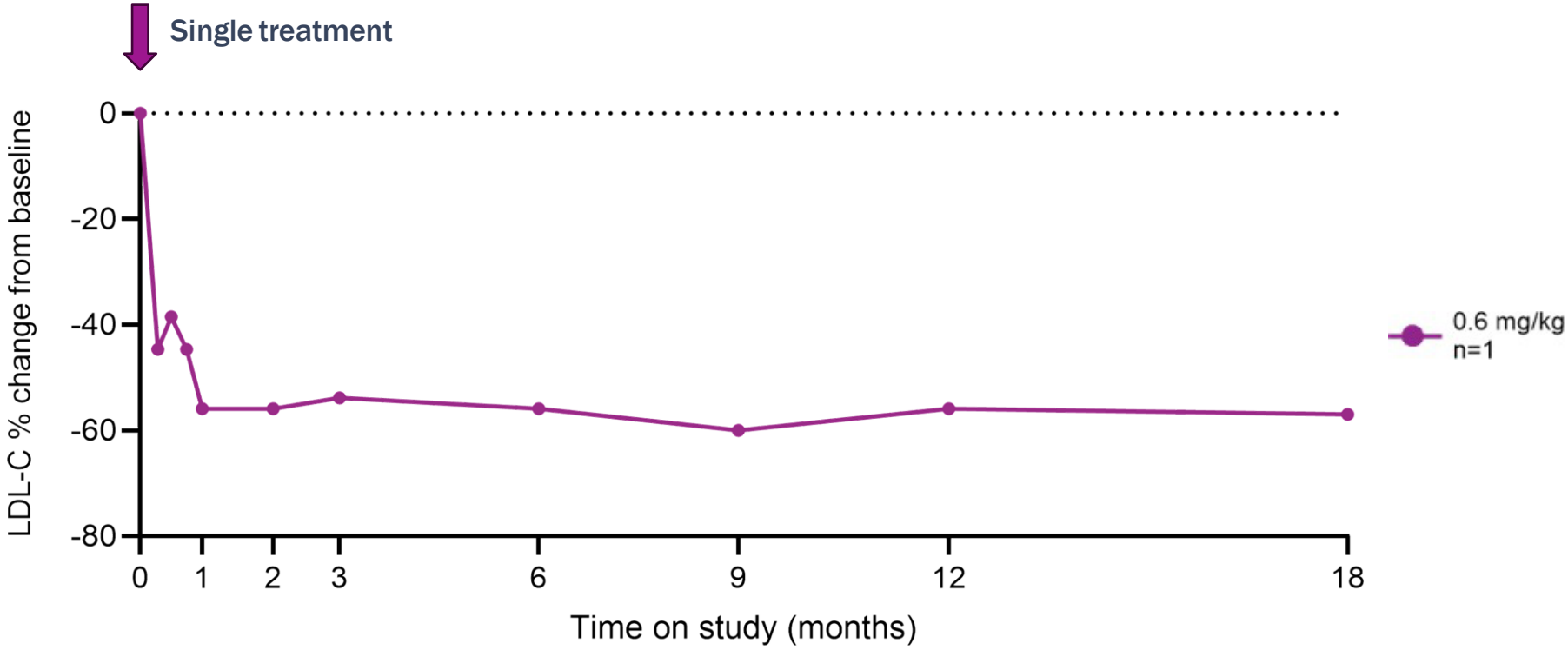
verve THERAPEUTICS

Durability in humans: Evidence for sustained LDL-C reduction following single VERVE-101 treatment in two higher dose cohorts



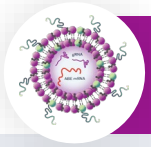
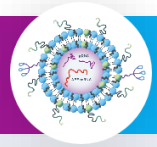
As of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned. Participants in 0.45 mg/kg cohort have variable duration of follow up, with n=6 at 6 months and n=3 at 9 months and 12 months. One of the six 0.45 mg/kg participants intensified statin therapy from baseline more than 6 months after VERVE-101 treatment.
SD, standard deviation

Durability: Proof-of-concept for LDL-C lowering extends to 18 months in participant dosed at 0.6 mg/kg



As of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.

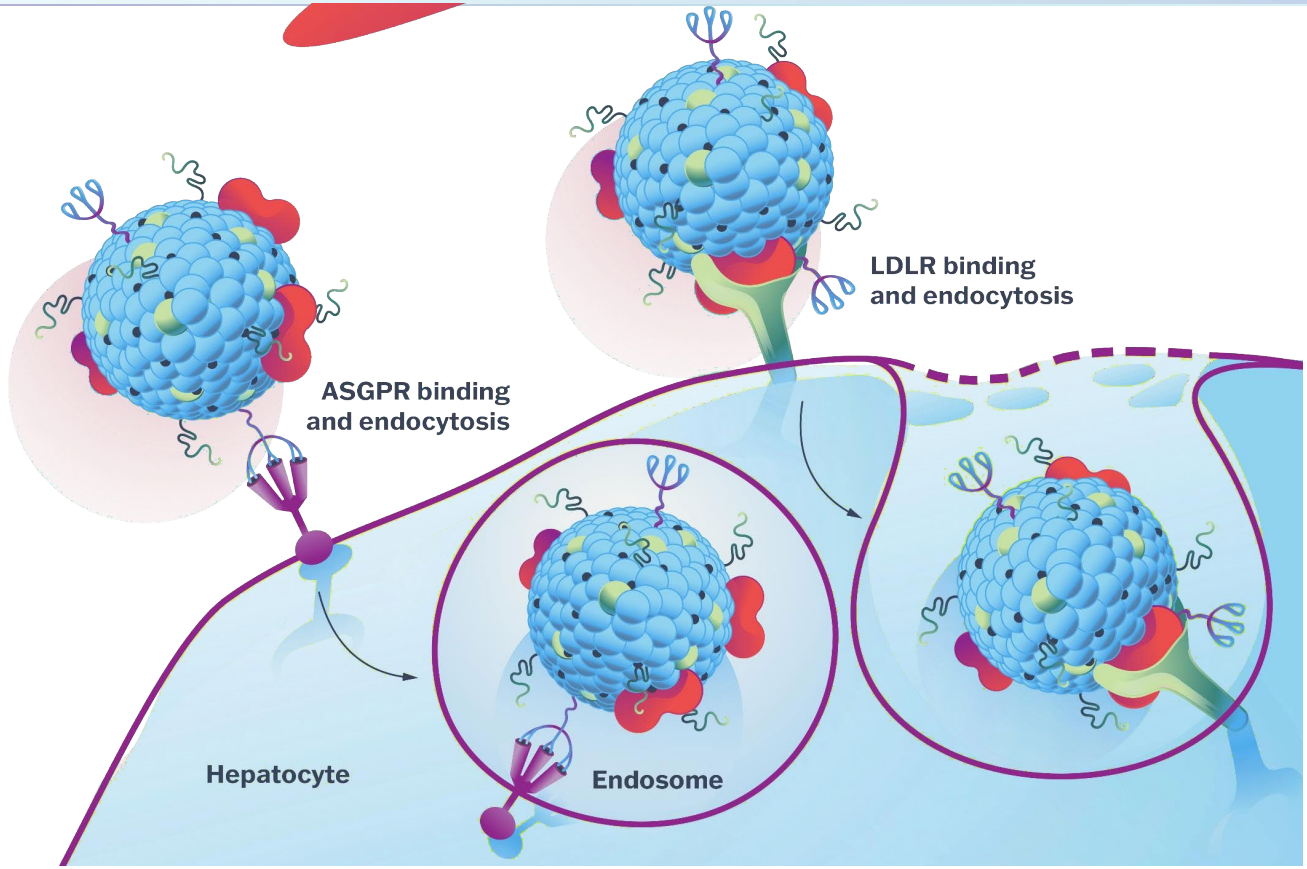
VERVE-102 retains the same ABE mRNA and guide RNA but switches out the LNP formulation and adds a liver-targeting ligand (GalNAc)

	 VERVE-101	 VERVE-102
TARGET	*PCSK9* gene	
ADENINE BASE EDITOR (ABE)	Same adenine base editor (ABE) used in both product candidates	
GUIDE RNA	Same guide RNA (gRNA) targeting *PCSK9*	
IONIZABLE LIPID	ALC-0307	LP000001
PEG LIPID	ALC-0159	DMG-PEG$_{2000}$
LIVER-TARGETING LIGAND	—	GalNAc

- Ionizable lipid and PEG-lipid in VERVE-102 have been well-tolerated in >80 patients (third-party clinical trials)
- Addition of GalNAc in VERVE-102 allows for LDLR- or ASGPR-mediated uptake into hepatocytes

ASGPR: asialoglycoprotein receptor

VERVE-102 is designed to enter hepatocytes through either ASGPR or LDLR



- GalNAc may enable more robust delivery in setting of LDLR-deficiency, present in some patients with familial hypercholesterolemia
- GalNAc-LNP has shown high specificity for liver in nonclinical biodistribution analysis

Heart-2 is a Phase 1b trial designed to evaluate VERVE-102; clinical data expected in 1st half of 2025

heart-2

First-in-human, open-label trial in adults with HeFH and/or premature coronary artery disease (CAD)

Single Ascending Dose

Three to nine participants per cohort receive a single dose

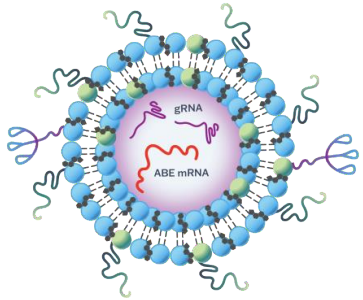
STUDY POPULATION SUMMARY

- Males and females (age 18 to 65)
- HeFH and/or premature CAD
- Require additional LDL-C lowering despite maximally tolerated oral therapies

TRIAL ENDPOINTS

- Primary: Safety and tolerability
- Pharmacokinetics of VERVE-102
- Changes in blood PCSK9 and LDL-C

VERVE-102



First patient dosed in 2Q 2024

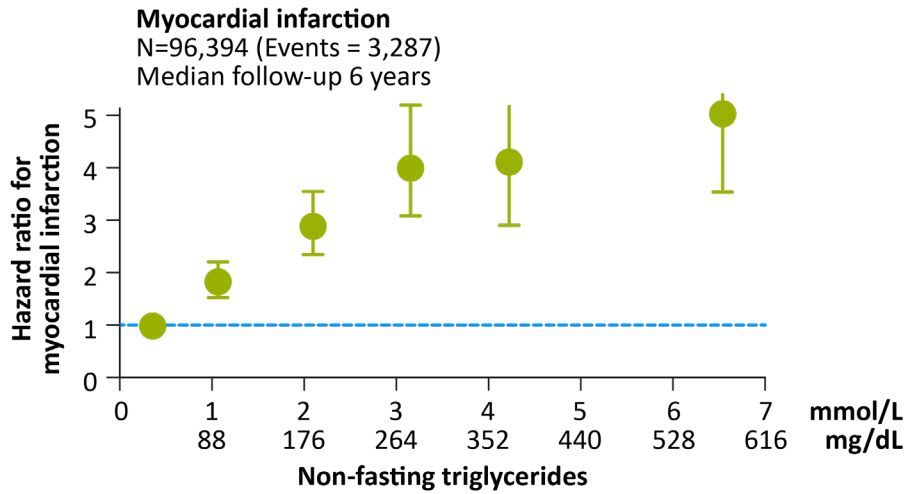
Clinical trial registration: NCT06164730
Women of childbearing potential are excluded from the study.

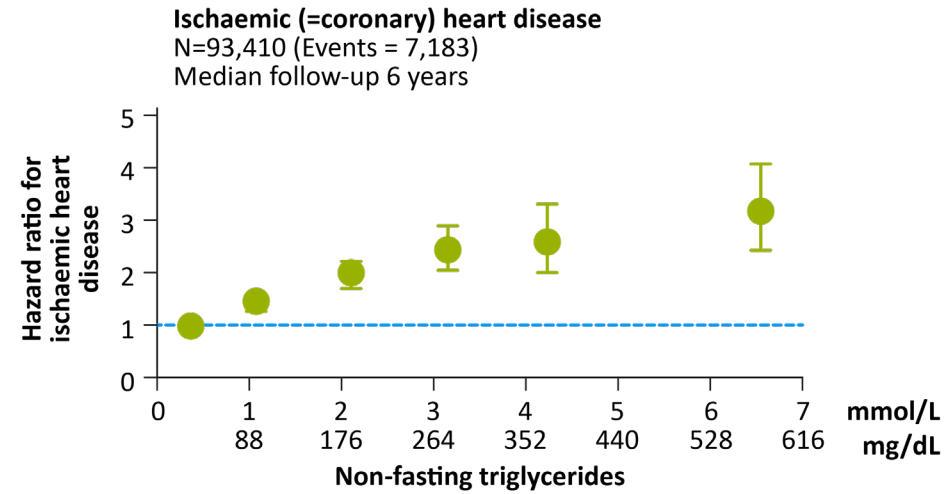
verve THERAPEUTICS

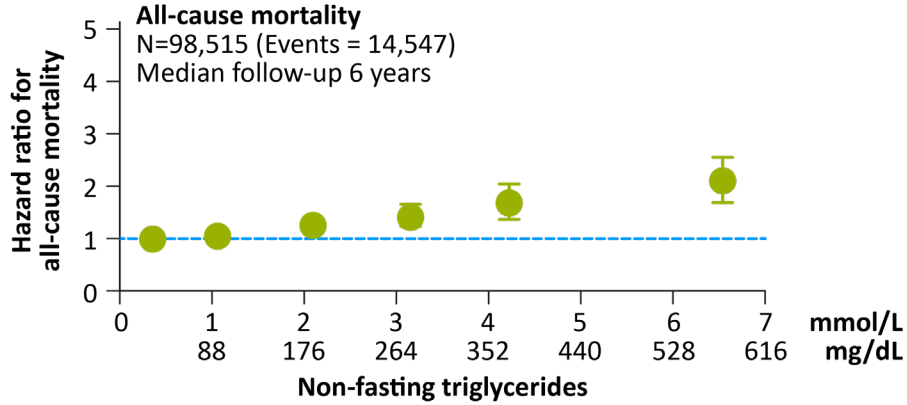
Optimizing management of dyslipidemias

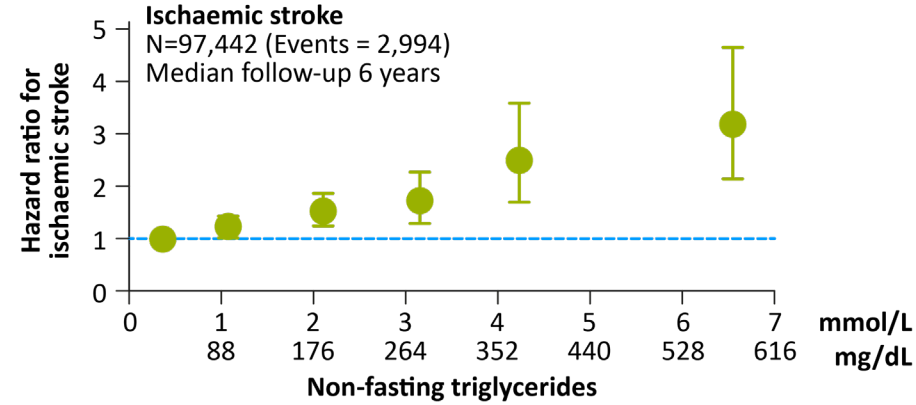
- Lower LDL
- **Addressing elevated triglycerides**

Hypertriglyceridaemia and CVD risk
The Copenhagen City Heart Study





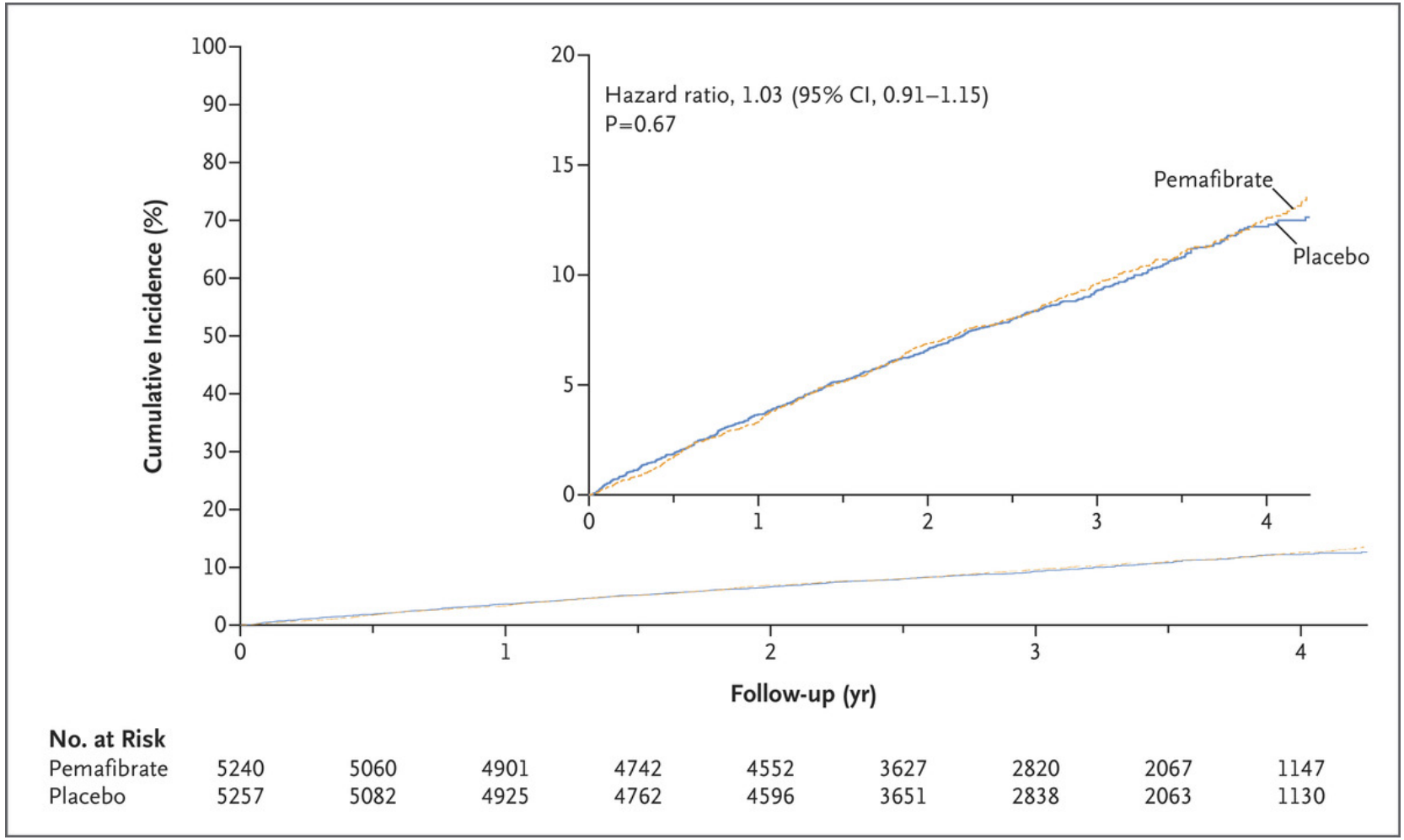




Adapted from: Nordestgaard BG et al. Lancet 2014; Aug 16;384(9943):626-635; Nordestgaard BG. Circ Res. 2016 Feb 19;118(4):547-63

PROMINENT: pemafibrate for CV prevention

Cumulative Incidence of Cardiovascular Events



No. at Risk

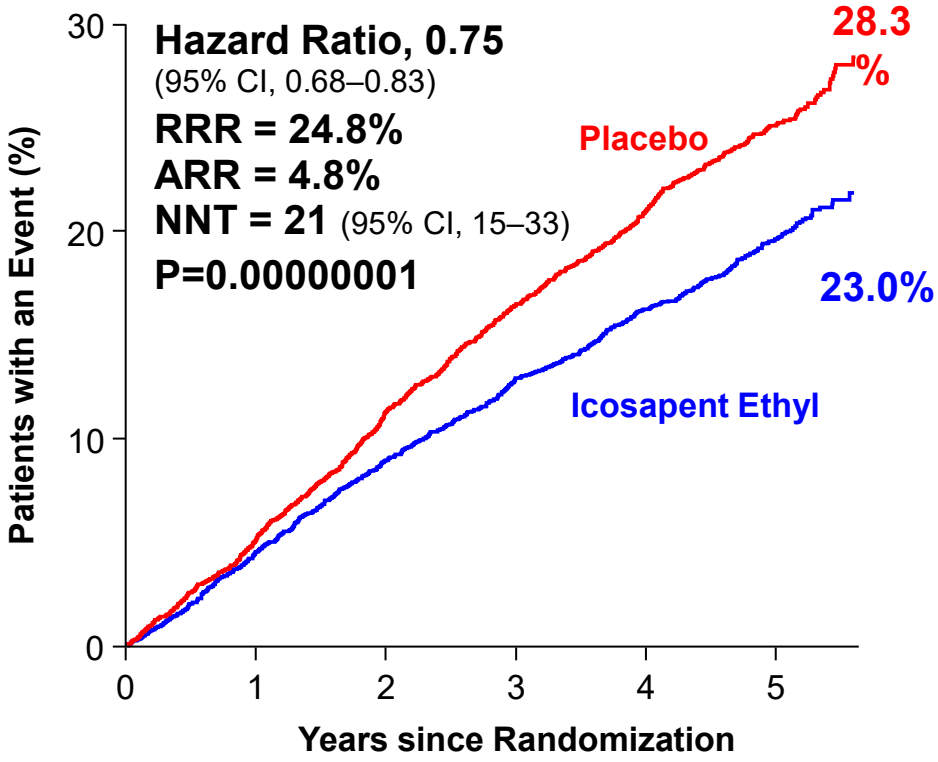
Pemafibrate	5240	5060	4901	4742	4552	3627	2820	2067	1147
Placebo	5257	5082	4925	4762	4596	3651	2838	2063	1130

A Das Pradhan et al. ***N Engl J Med* 2022.** DOI: 10.1056/NEJMoa2210645

REDUCE IT: CV risk reduction with 4 g purified EPA/d in statin-treated pts at high risk with elevated TGs

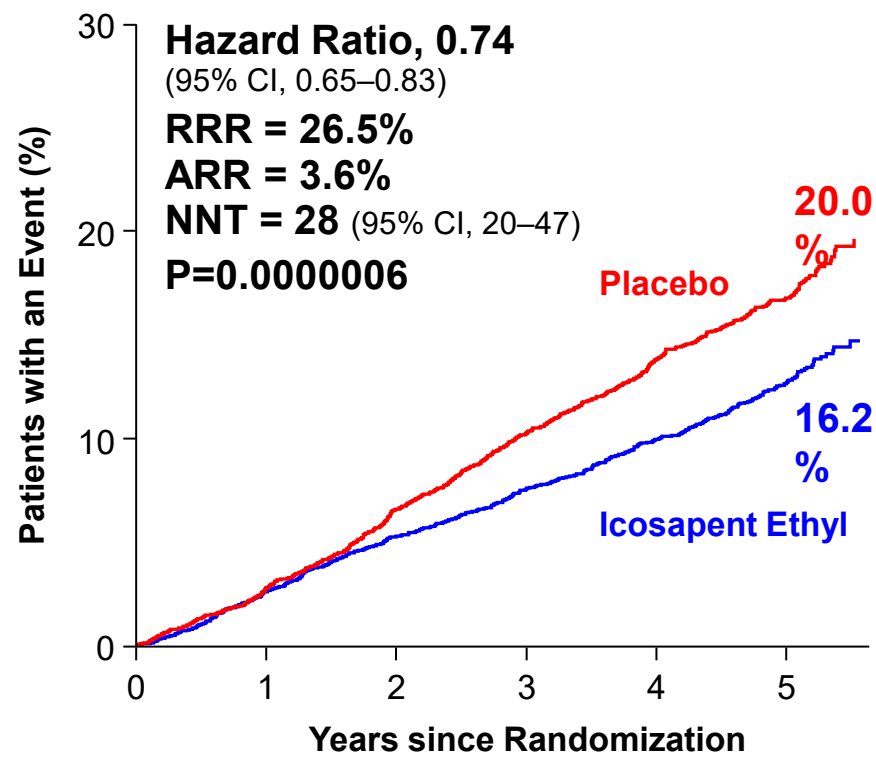
Primary Composite Endpoint:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



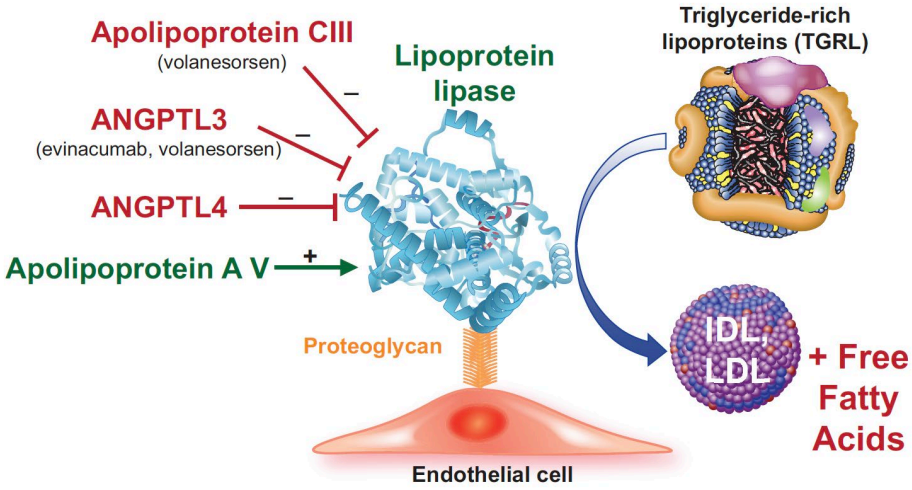
Key Secondary Composite Endpoint:

CV Death, MI, Stroke



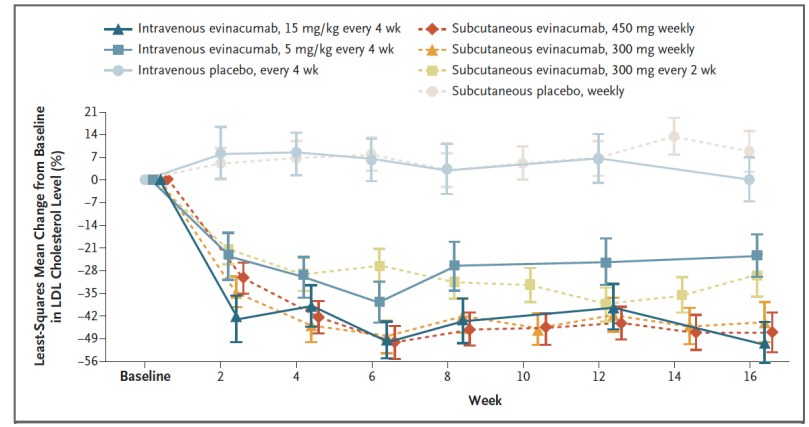
Bhatt DL, Steg PG, Miller M, et al. ***N Engl J Med.*** 2019

Targeting LPL to reduce triglycerides ?



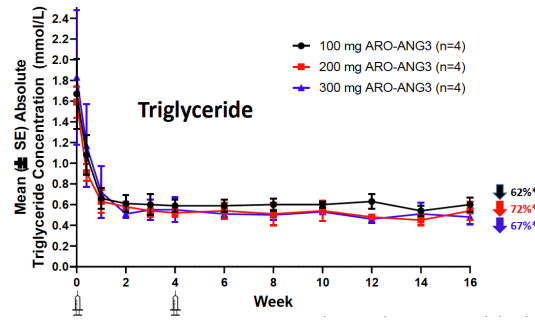
Tokgözoglu ***EHJ*** 2022

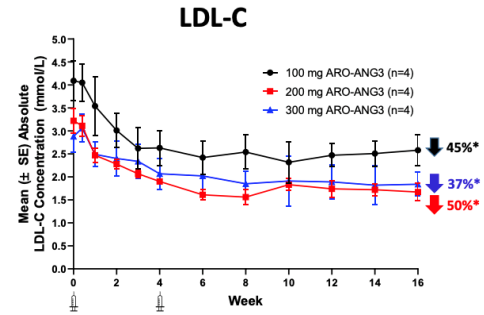
Evinacumab in Patients with Refractory Hypercholesterolemia



R S. Rosenson et al. ***NEJM*** 2020

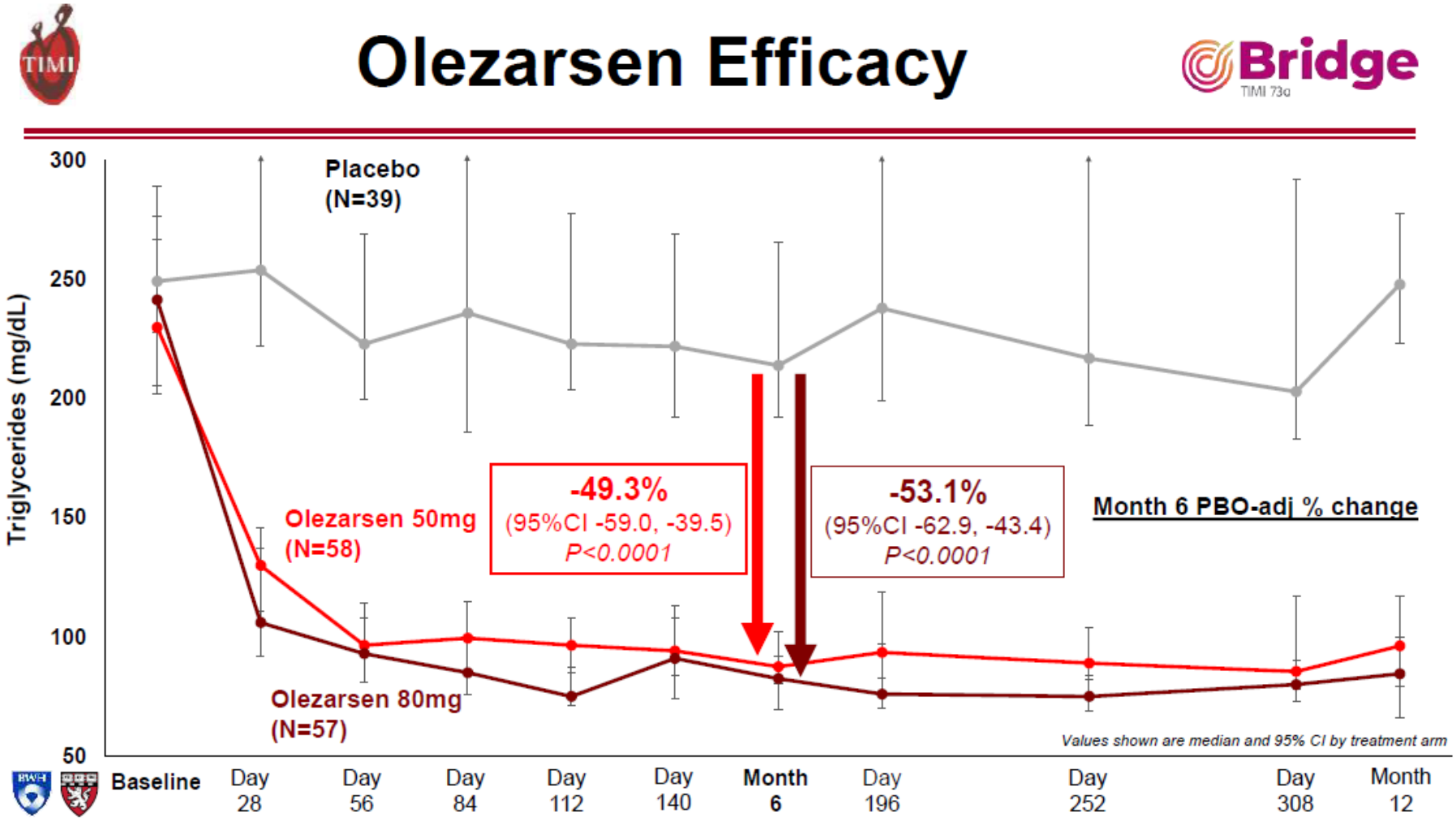
ARO-ANG3 in adults with mixed dyslipidemia (ARCHES-2)





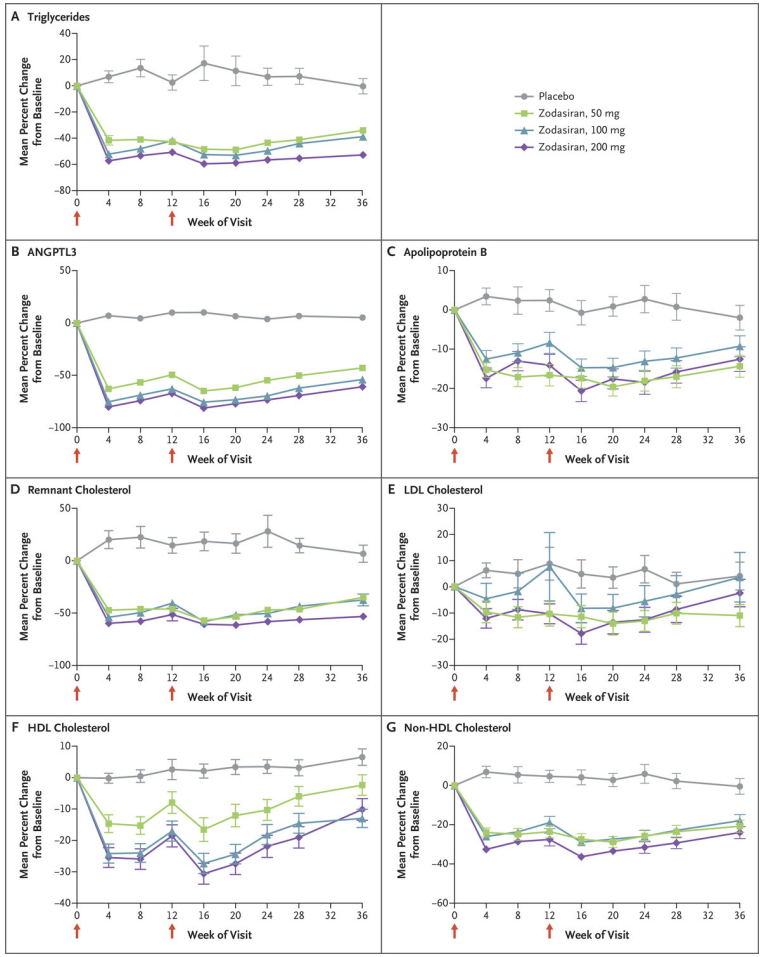
G F Watts et al. ***ESC*** 2020

Inhibition of Apo C3 in pts at high CV risk with moderate HTG



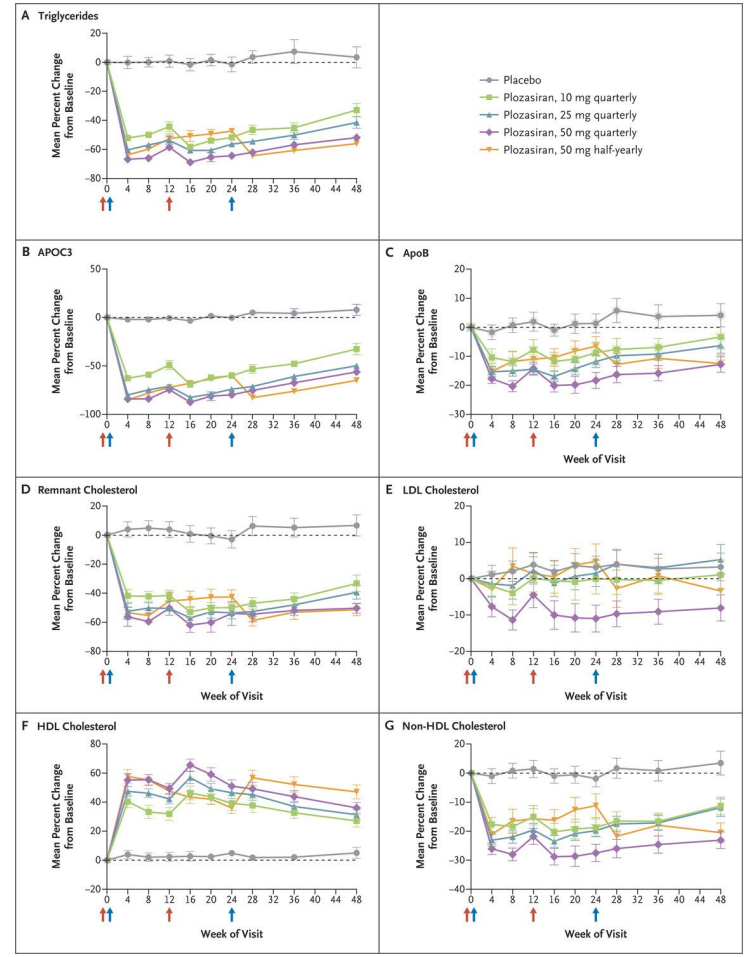
Bergmark B et al. ***N Engl J Med*** 2024

Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia



Rosenson RS et al. ***NEJM*** 2024

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



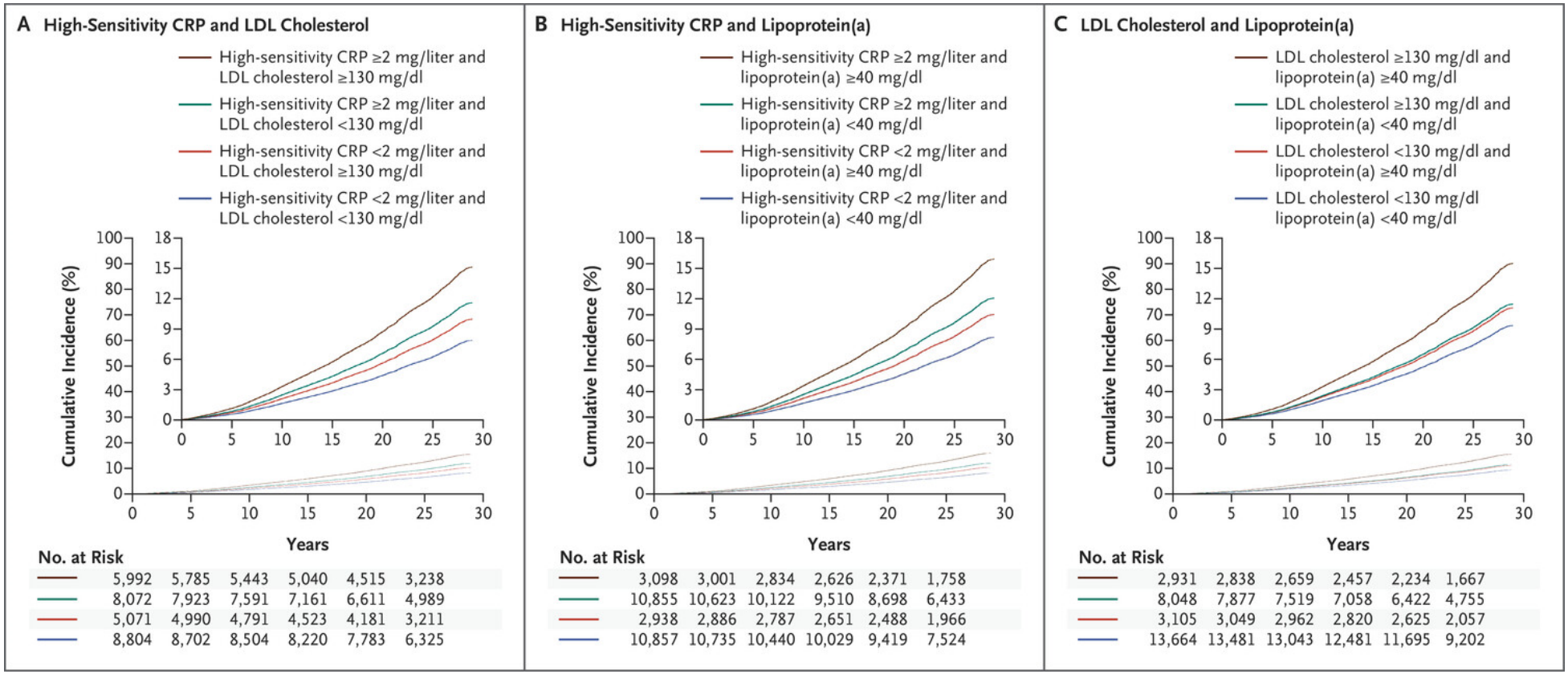
Ballantyne CM et al. ***NEJM*** 2024

Optimizing management of dyslipidemias

- Earlier and lower LDL for longer
- Addressing elevated triglycerides
- **Addressing Lp(a)**

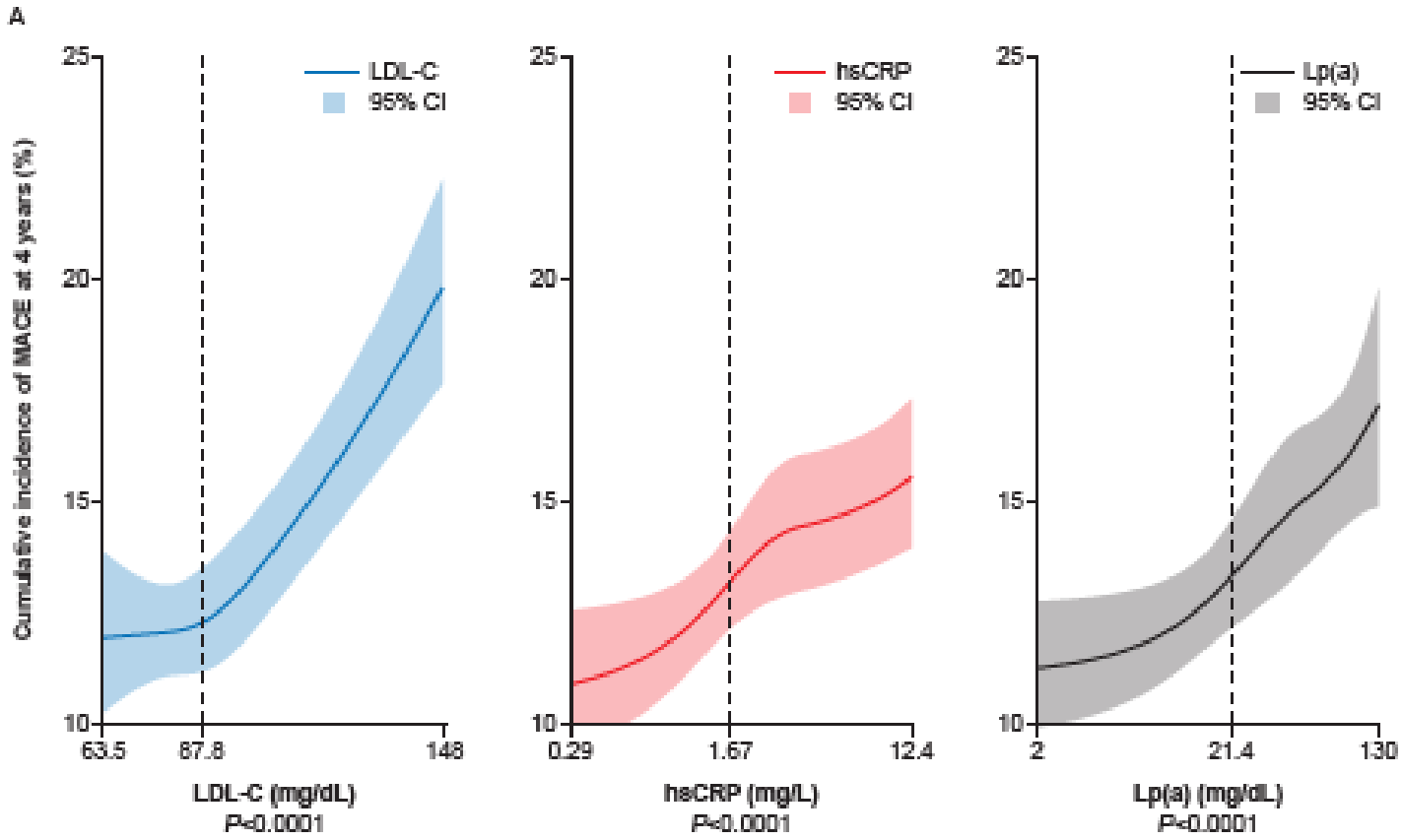
Joint effect of hs-CRP, LDL-c and Lp(a) on MACE

WHS (Women's Health Study) 30 year follow-up



Ridker P et al. ***N Engl J Med*** 2024

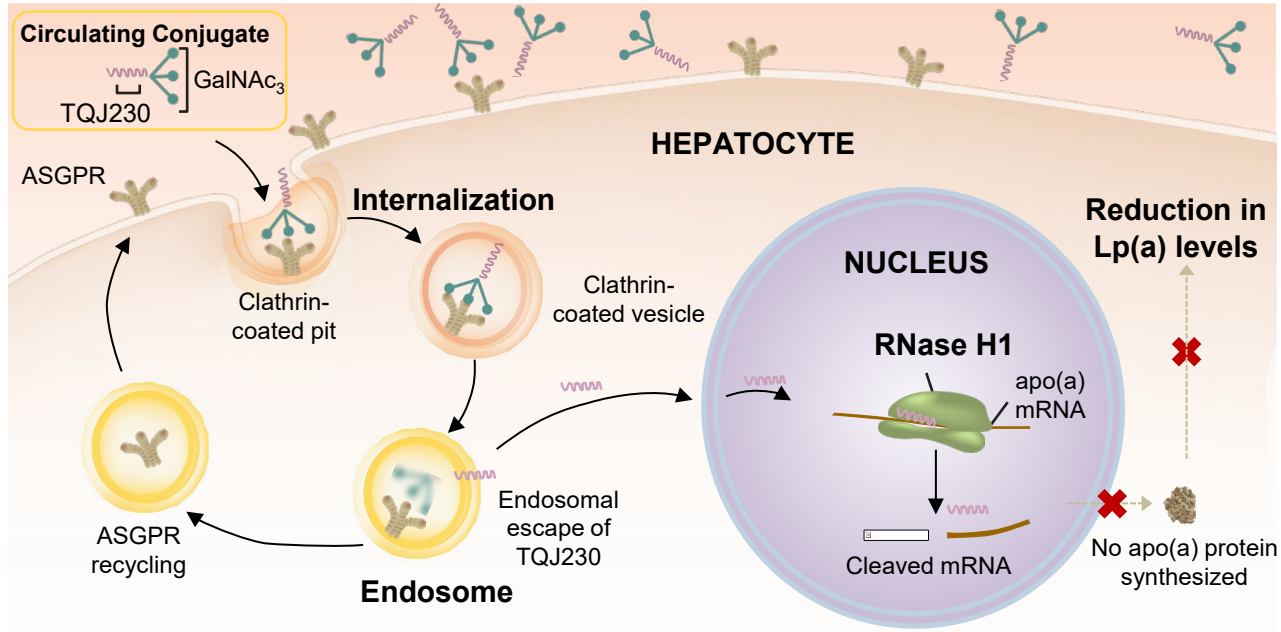
Independent relation between LDLc, hs-CRP, and Lp(a) and future CV events after ACS on High-Intensity Statin Therapy.
An Analysis of the Placebo Arm of ODYSSEY OUTCOMES



Steg PG et al. ***AHA 2023***

Pelacarsen: an ASO targeting apo(a) mRNA

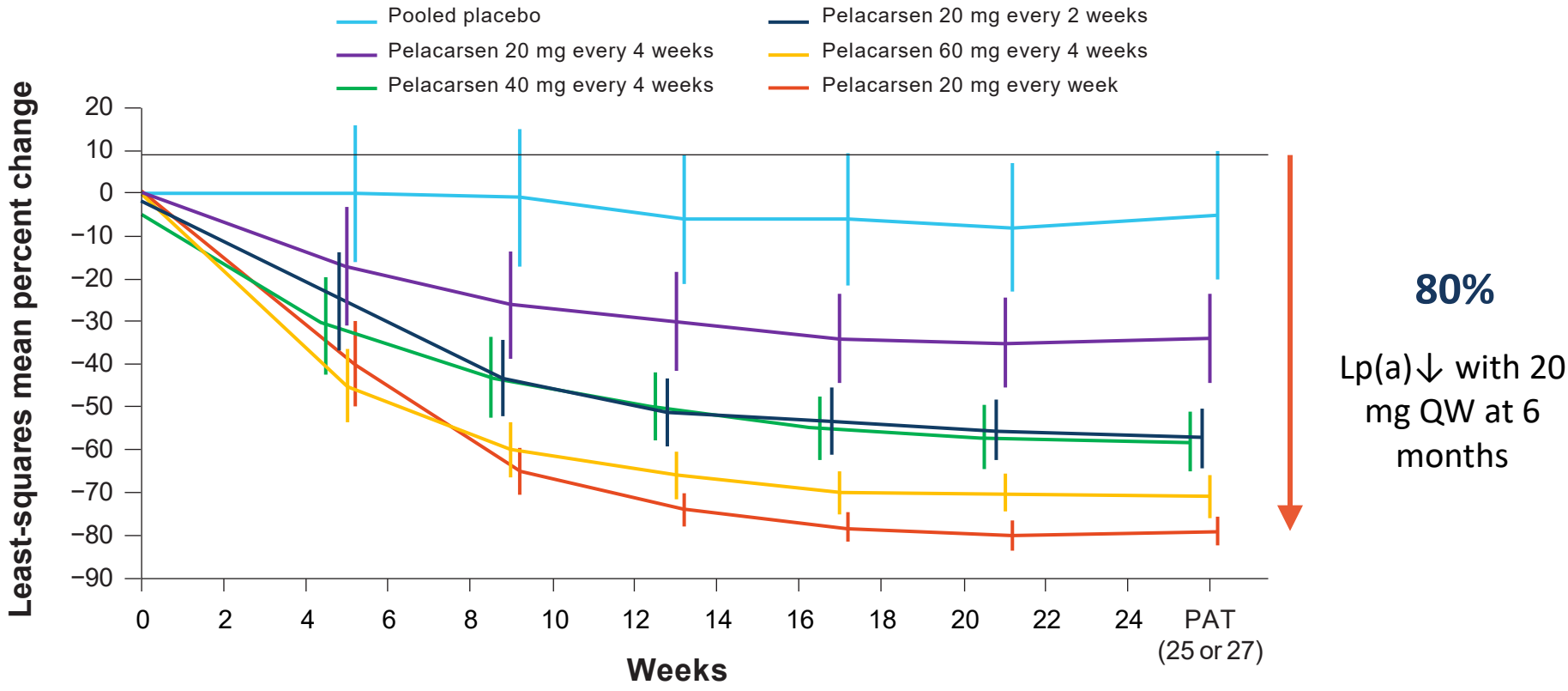
- **Pelacarsen** is a $GalNAc_3$-conjugated, 2′-MOE chimeric 2.5 generation ASO targeting apo(a) mRNA[1,2]
- The $GalNAc_3$ moiety acts as a ligand for ASGPR in hepatocytes[3], which mediates selective uptake of TQJ230 by the liver
- In the hepatocytes, **Pelacarsen** selectively binds to a region spanning exon 24-25 splice site of **apo(a) mRNA**
- **RNase H1** cleaves apo(a) mRNA in the ASO-RNA heteroduplex thereby preventing the synthesis of the apo(a) protein[1] and lowers the levels of circulating Lp(a)



1. Novartis, data on file; 2. Viney et al. ***Lancet***. 2016;388:2239-2253; 3. Seth, et al. ***J Clin Invest***. 2019;129(3):915-925; 4. Prakash TP. ***Nucleic Acids Res***. 2014;42:8796-807.

Lp(a)-lowering effect of Pelacarsen was observed within 1 month, with maximal effect reached by Week 16

Change from baseline over time in Lp(a) level



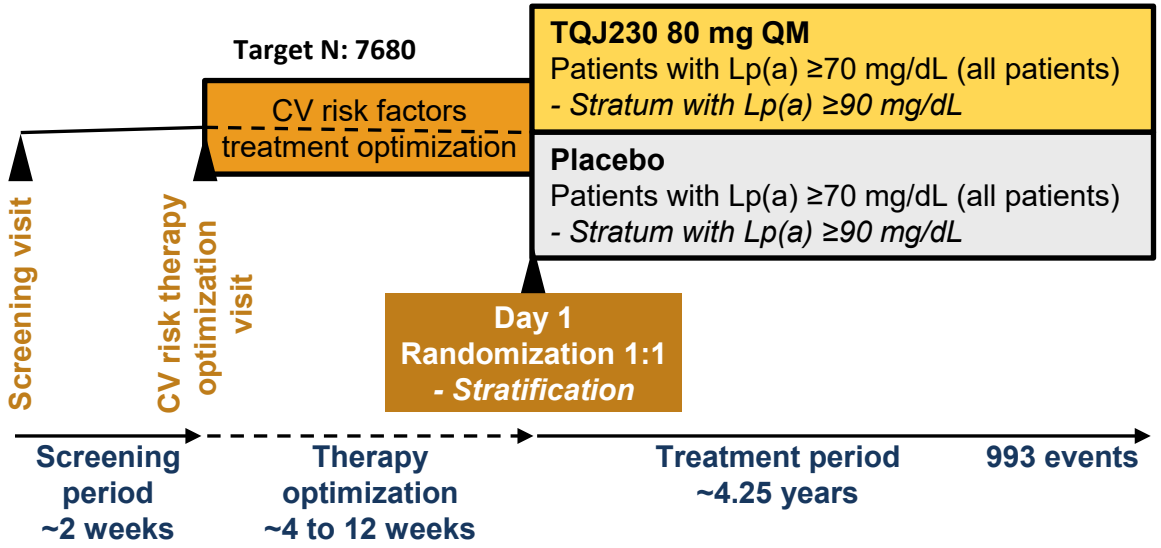
Error bars indicate 95% confidence intervals

Tsimikas, et al. ***N Engl J Med***. 2020;382(3):244-255.

Lp(a), lipoprotein A. PAT, primary analysis time point.

Lp(a)HORIZON: Phase III CV outcomes trial with Pelacarsen

Randomized double-blind, parallel group, placebo-controlled, multicenter study to assess effect of TQJ230 on MACE in patients with established CV disease



Objectives

- To demonstrate the superiority of TQJ230 versus placebo in reducing the risk of MACE (MI, stroke, CV death or urgent coronary revascularization) in the overall study population and in a subpopulation of patients with Lp(a) ≥90 mg/dL

Study population

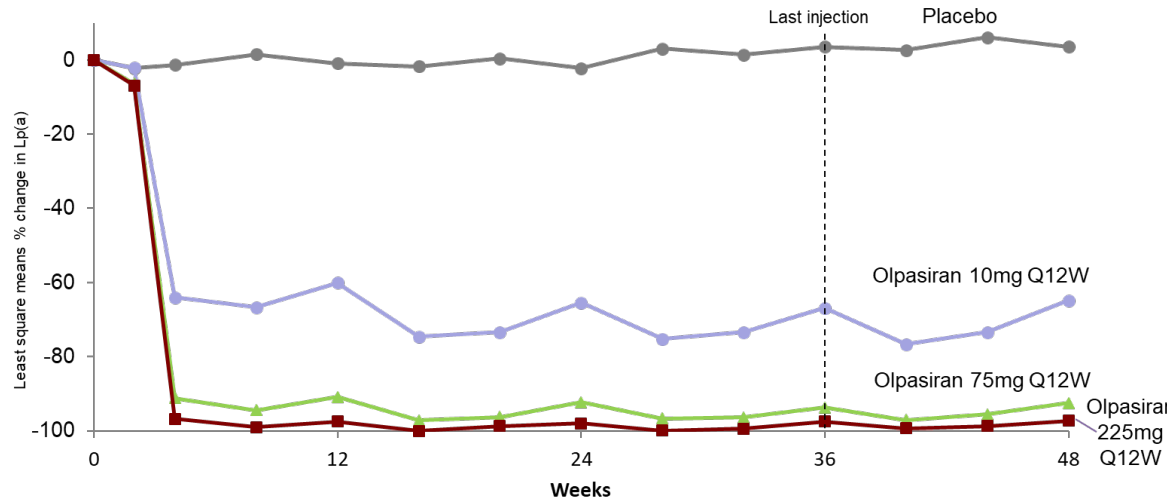
- Patients with established CV disease (prior MI, stroke, PAD) and Lp(a) ≥70 mg/dL

https://clinicaltrials.gov/ct2/show/NCT04023552;

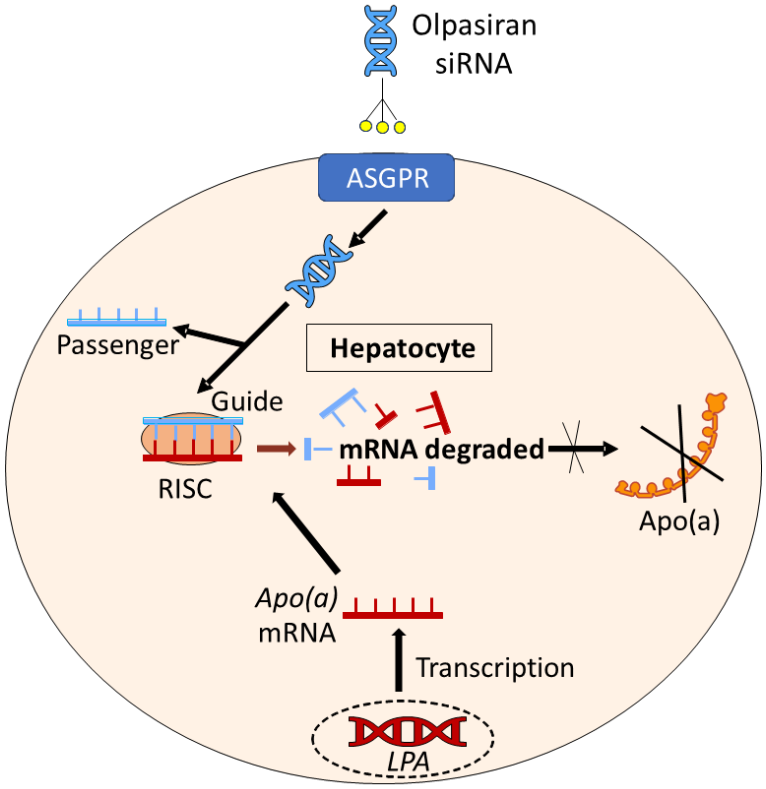
Olpasiran an siRNA targeted to Lp(a)

phase II results

Changes in Lp(a) Through Follow-Up



O'Donoghue et al ***NEJM*** 2022

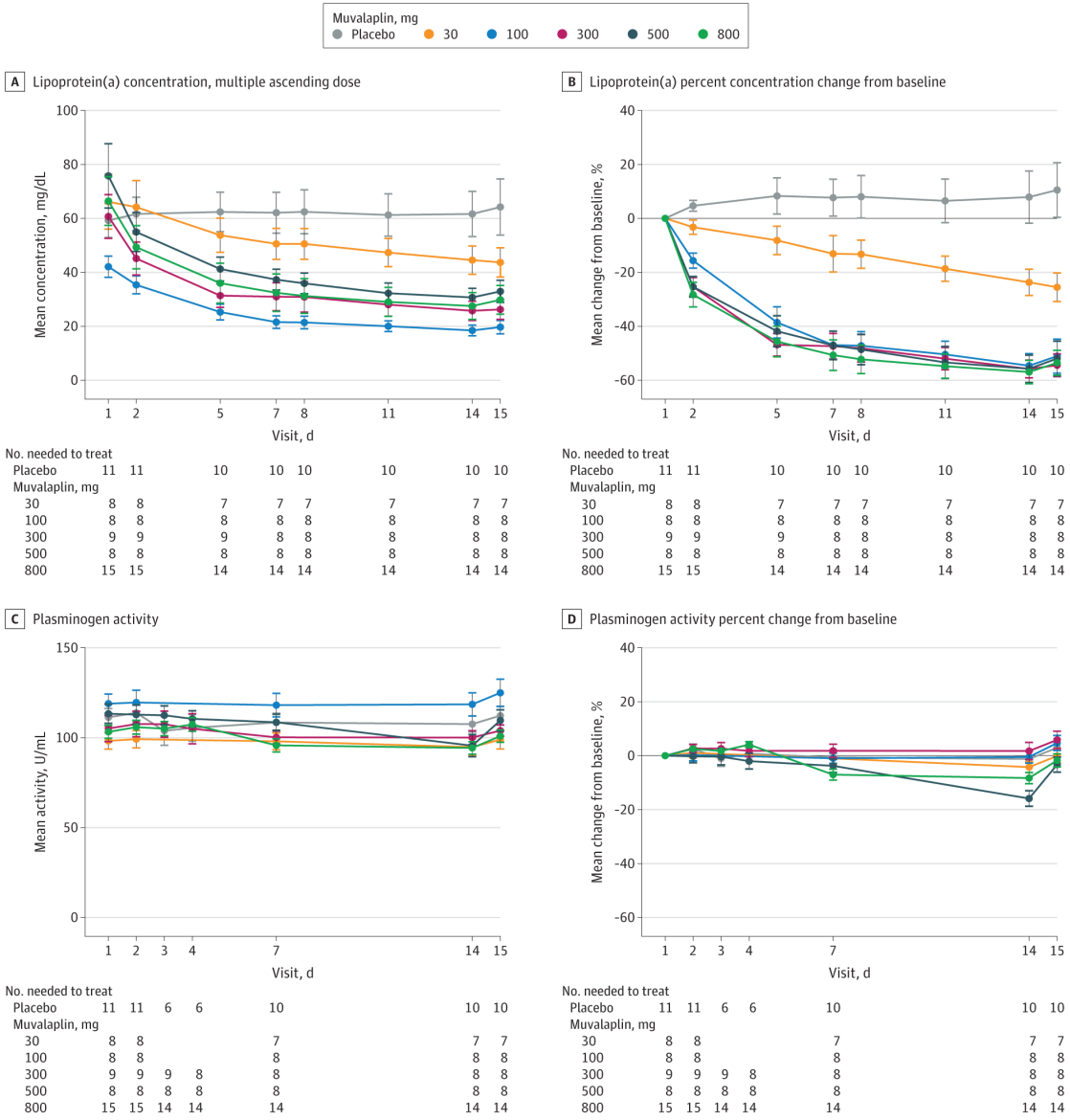


- Small interfering RNA directed to the liver.
- The antisense strand is loaded into an RNA-induced silencing complex (RISC) in the hepatocyte.
- The complex then binds to apo(a) mRNA, leading to its degradation and preventing protein translation.

O'Donoghue ML et al., ***Am Heart J*** 2022;251:61-69

The effect of Olpasiran on CV outcomes is being tested in the ongoing OCEAN-Lp(a) Trial

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



Effect of Multiple Daily Doses of Muvalaplin on Lipoprotein(a) and Plasminogen ActivityDosing began on day 1, and the values shown from day 1 are from before dosing began.

A, The absolute change in lipoprotein(a) (Lp[a]) levels in participants with levels of 30 mg/dL or higher.

B, The mean percent change from baseline in Lp(a) levels over time.

C, The absolute change in plasminogen activity.

D, The mean percent change from baseline in plasminogen activity in the same participants and during the same time shown in panels A and B.

Data markers indicate the mean; error bars, SEM.

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Phase 2 Trial of Zerlasiran: Multiple doses of an siRNA Targeting Lipoprotein(a) over 60 weeks

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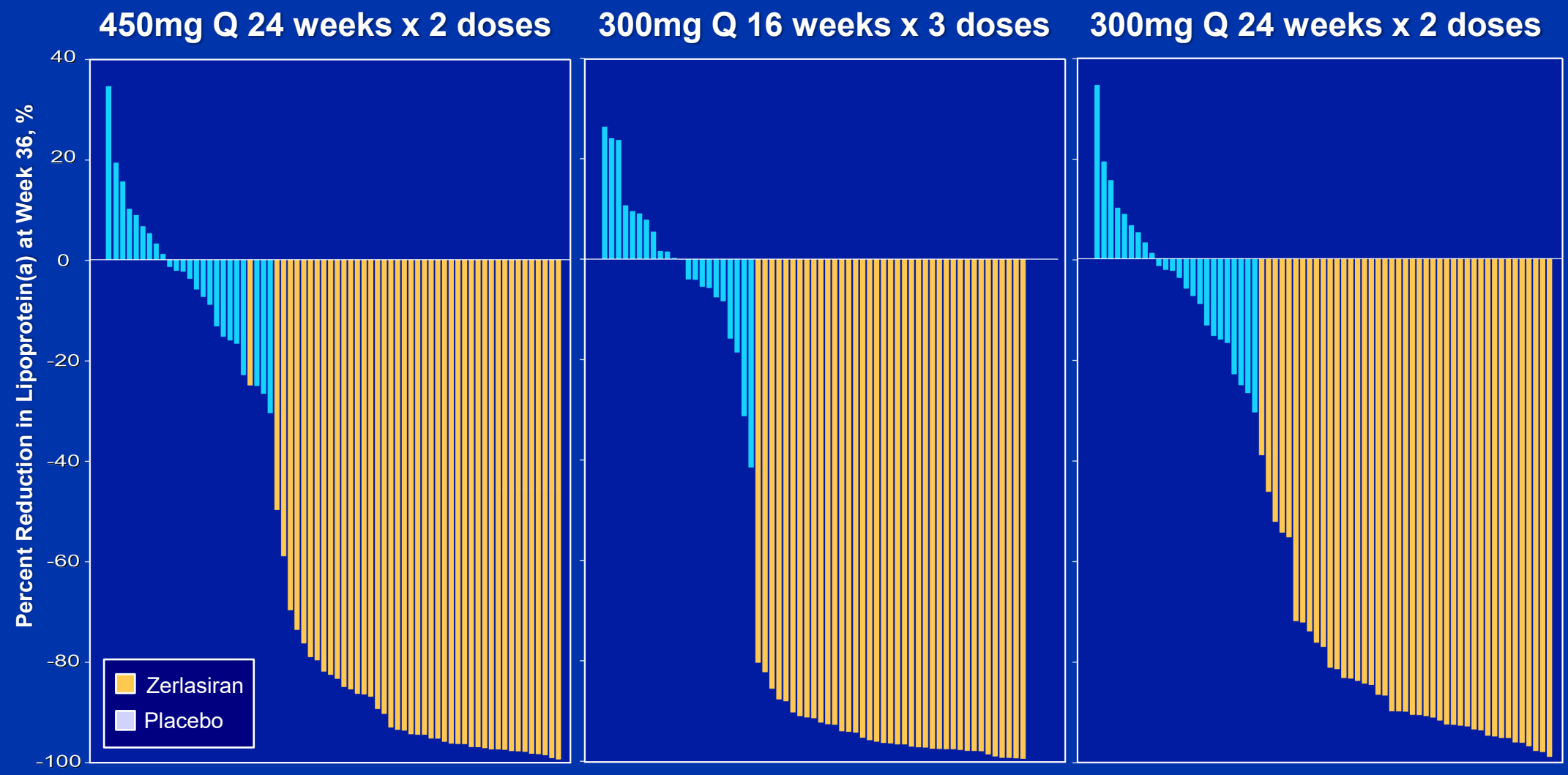
Disclosure

Consulting: Many pharmaceutical companies

Clinical Trials: AbbVie, Arrowhead, AstraZeneca, Bristol Myers Squibb, Encarda, Eli Lilly, Esperion, Medtronic, New Amsterdam, Novartis, Silence Therapeutics.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

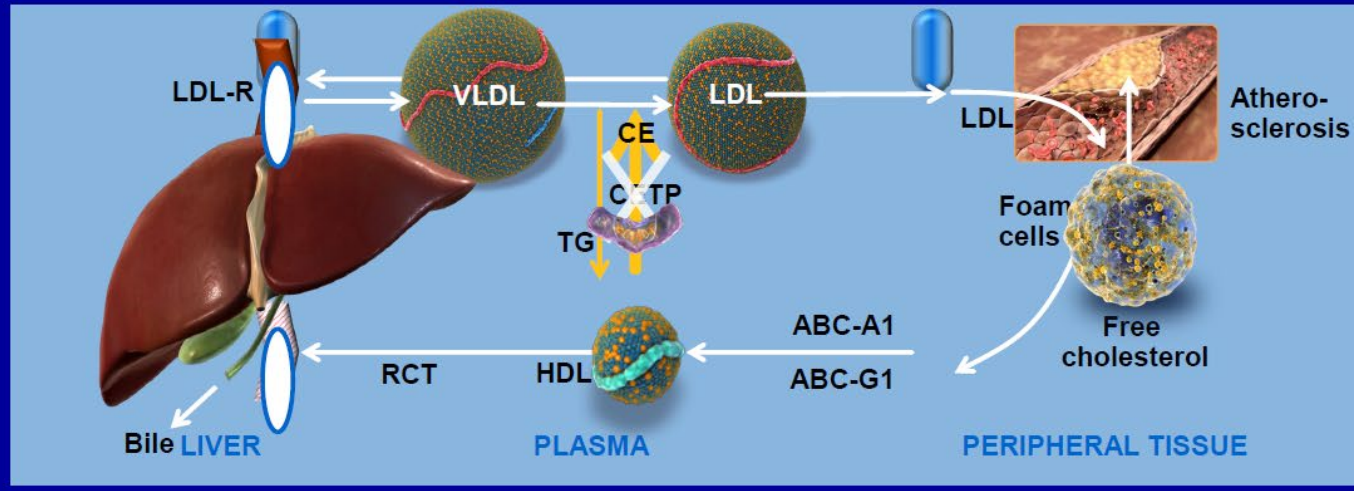
Waterfall Plots: Consistency of Lipoprotein(a) Lowering



Optimizing management of dyslipidemias

- Earlier and lower LDL for longer time
- Addressing elevated triglycerides
- Addressing Lp(a)
- **Addressing CETP**

Why Target CETP?
Does it have a Role in Atherosclerosis?



- Human CETP deficiency is associated with marked increases in HDL-C[1]
- CETP activity is inversely correlated with plasma HDL-C[1]
- Reduction in CETP activity is associated with a marked reduction in the cholesterol burden in TG-rich particles in both fasting and postprandial phases[2,3]
- Decreasing CETP activity has consistently inhibited atherosclerosis in animal models[1]

[1]Barter et al. *Arterioscler Thromb Vasc Biol*. 2003;23:160–167; [2]Contacos et al. *Atherosclerosis*.1998;141:87–98;
[3]Guerin et al. *Arterioscler Thromb Vasc Biol.* 2008;28:148–154.

Brooklyn Study Design

Main Inclusion Criteria

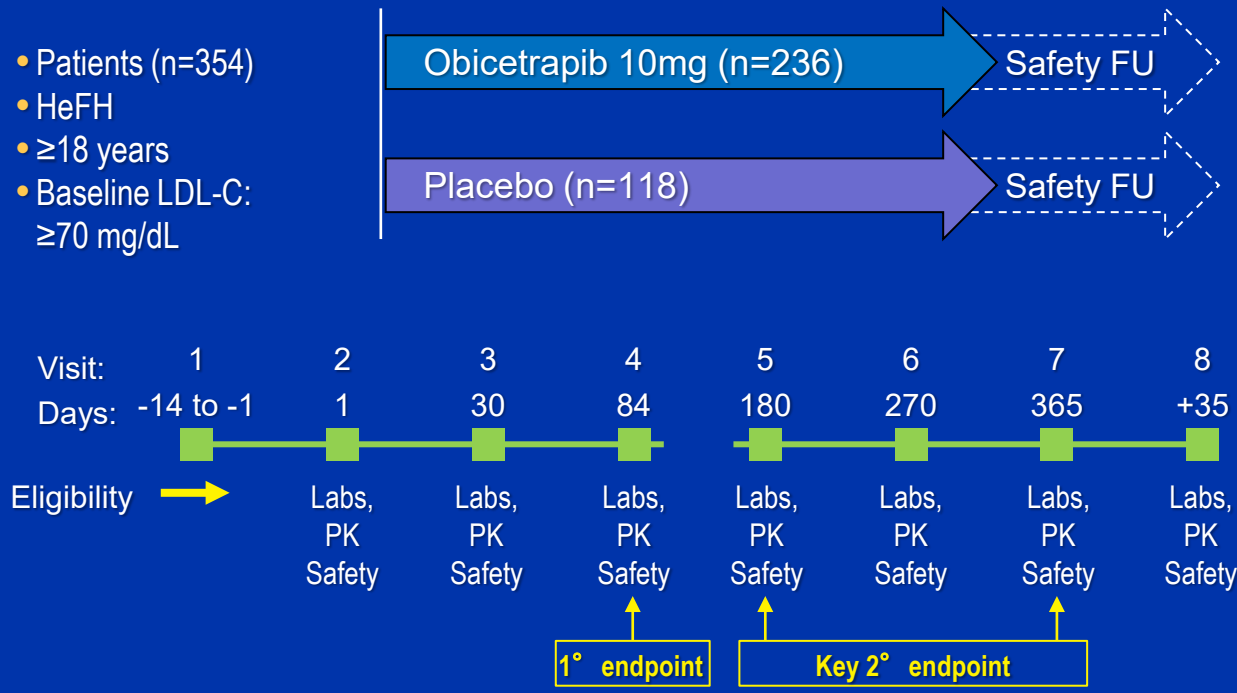
- HeFH diagnosed by
  - Genetic confirmation
  - WHO criteria / Dutch Clinical Network
  - Simon Broome criteria
- On maximally tolerated lipid lowering therapy
- LDL-C ≥ 70mg/dL
- TG ≤ 400mg/dL

Exclusion Criteria

- CV event in the last 3 months
- HoFH
- Uncontrolled hypertension

Study Design: Randomized, double-blind, placebo-controlled

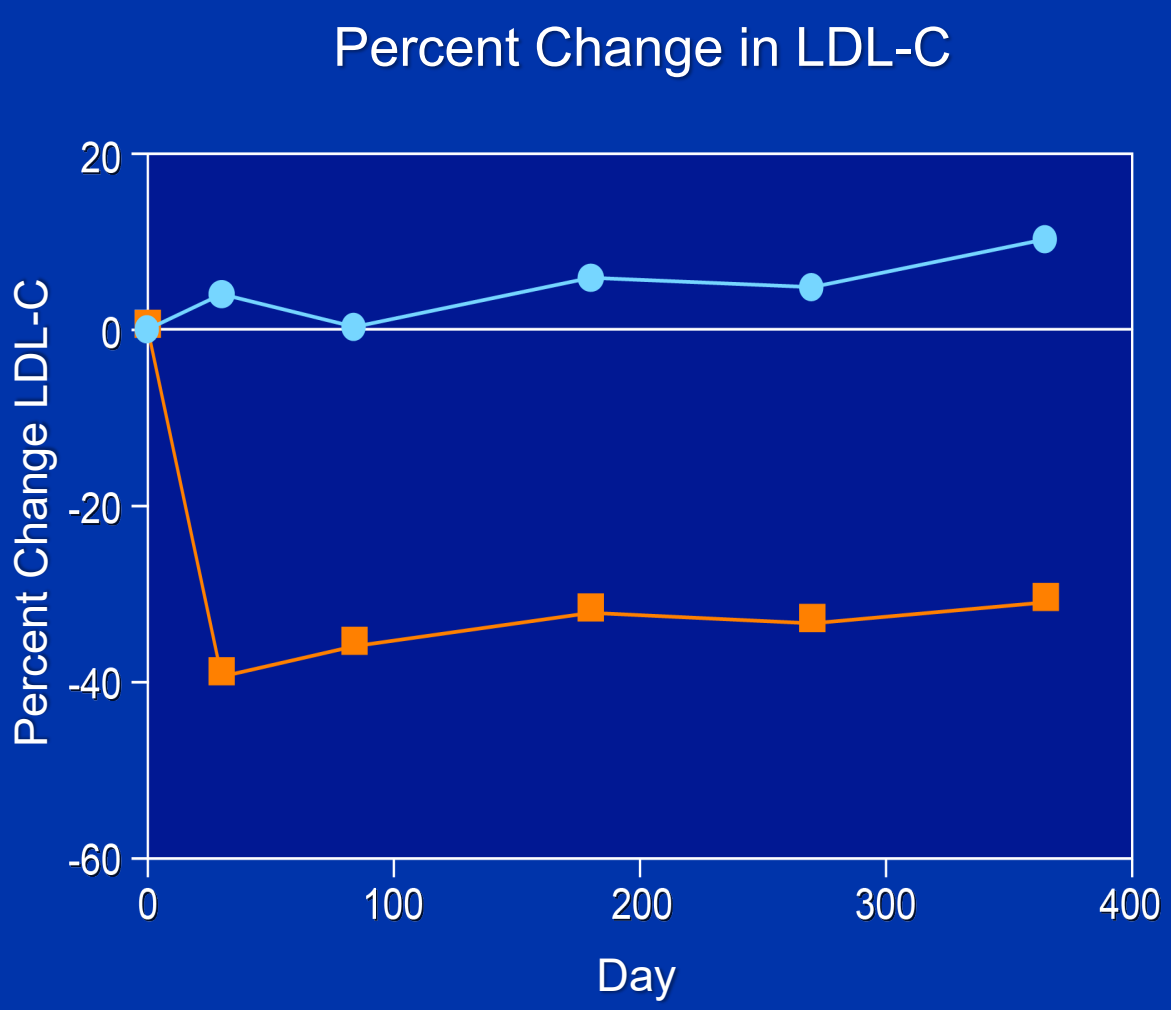
- Patients (n=354)
- HeFH
- ≥18 years
- Baseline LDL-C: ≥70 mg/dL

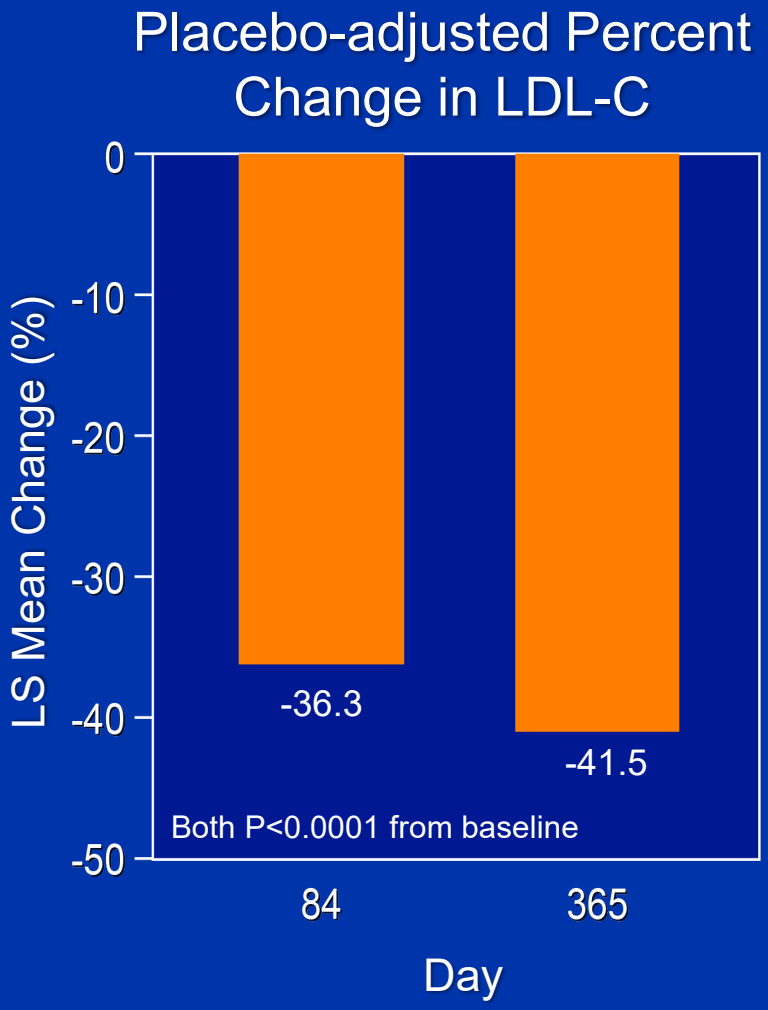


Primary endpoint: percent change in LDL-C from baseline to day 84
Secondary endpoints: change in LDL-C at day 365 and changes in other lipid parameters and percent of patients achieving a LDL-C <100 mg/dL at day 84

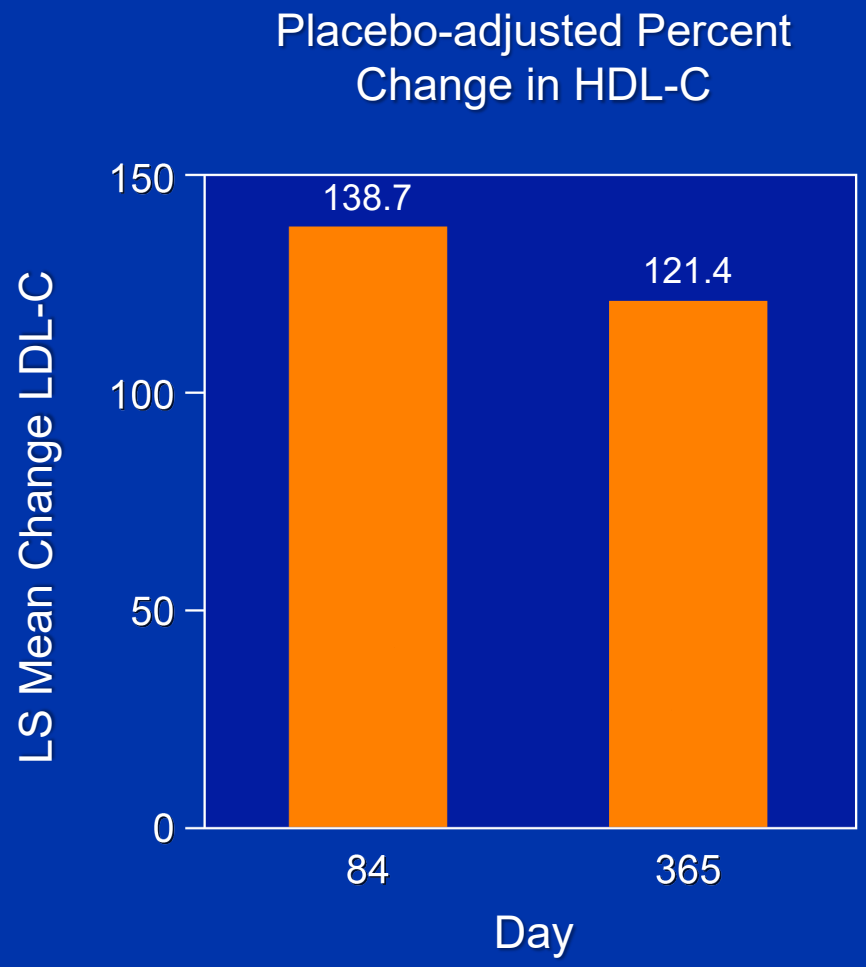
Nicholls S et al. ***AHA 2024***

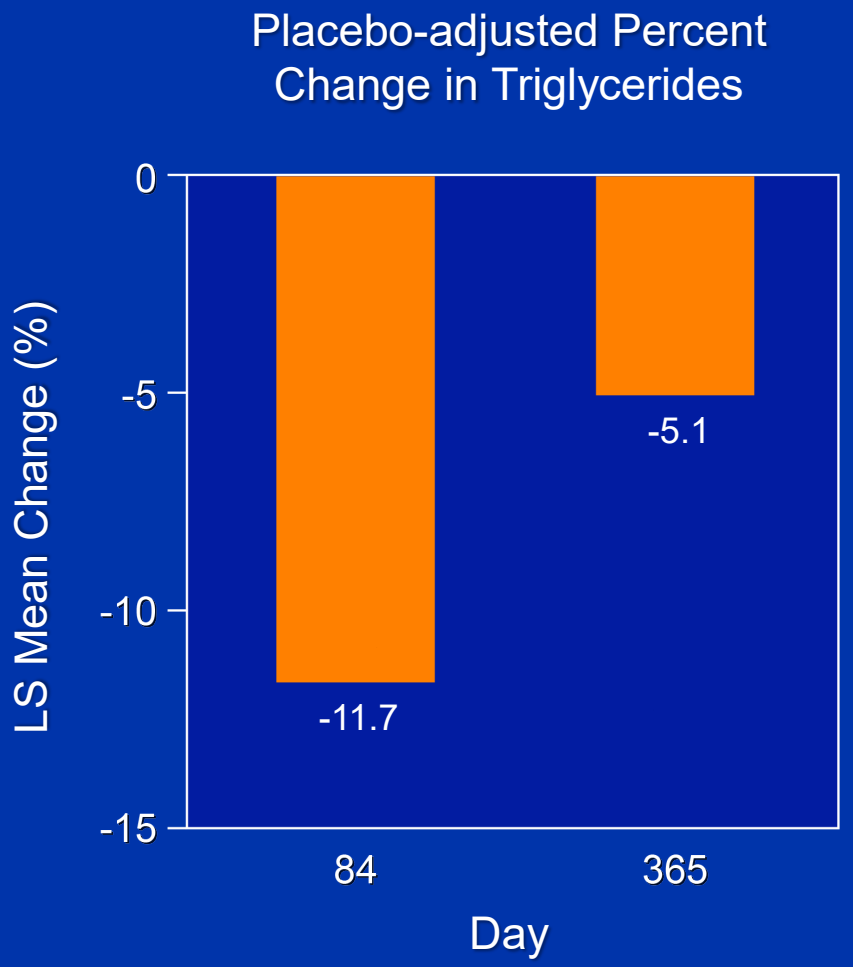
Percent Change in LDL-C with Obicetrapib





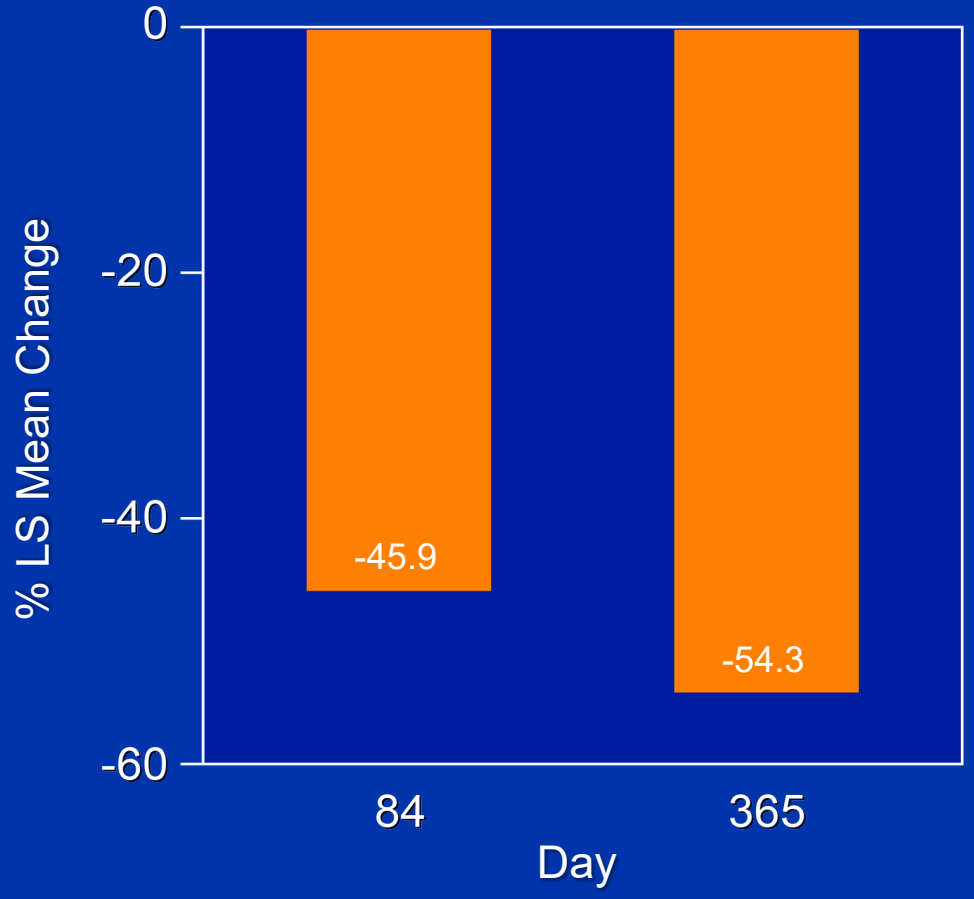
Percentage Change in HDL-C and Triglycerides



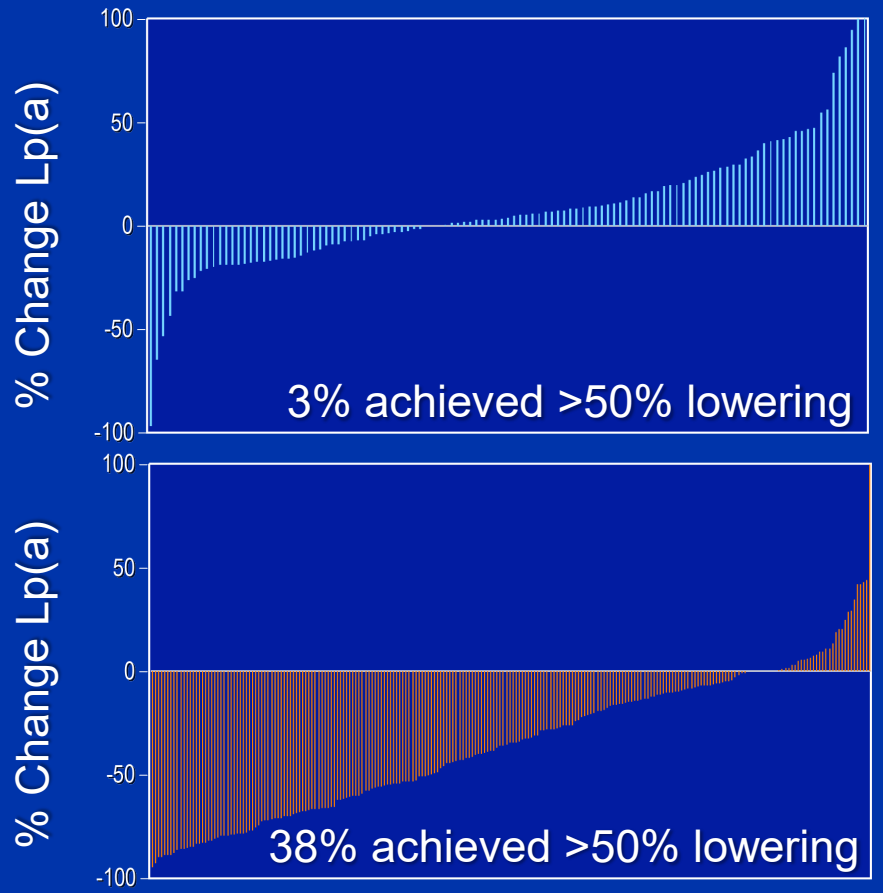


Percent Changes in Lp(a)

Placebo-adjusted Percent Change in Lp(a)



Individual Percent Changes in Lp(a)



PREVAIL Obicetrapib CV outcome trial is designed to show reduction of cardiovascular morbidity and mortality in patients with established ASCVD

Rationale

Patients with established ASCVD on maximally tolerated lipid-lowering therapy, including high-intensity statins, who are unable to get to their guideline goals, are at high risk for cardiovascular events, have an unmet medical need and therefore require additional lipid-lowering therapy

Objective

To evaluate the potential of Obicetrapib to reduce cardiovascular mortality and morbidity in patients with established ASCVD

Main inclusion criteria

- Established ASCVD
- Max tolerated lipid-modifying therapy
- LDL-C level ≥ 70 < 100 mg/dL + 1 RF
  - Recent MI (3-12 months)
  - T2DM
  - TG >150 mg/dL
  - HDL-C <40 mg/dL

  Or

  LDL-C ≥ 100 mg/dL

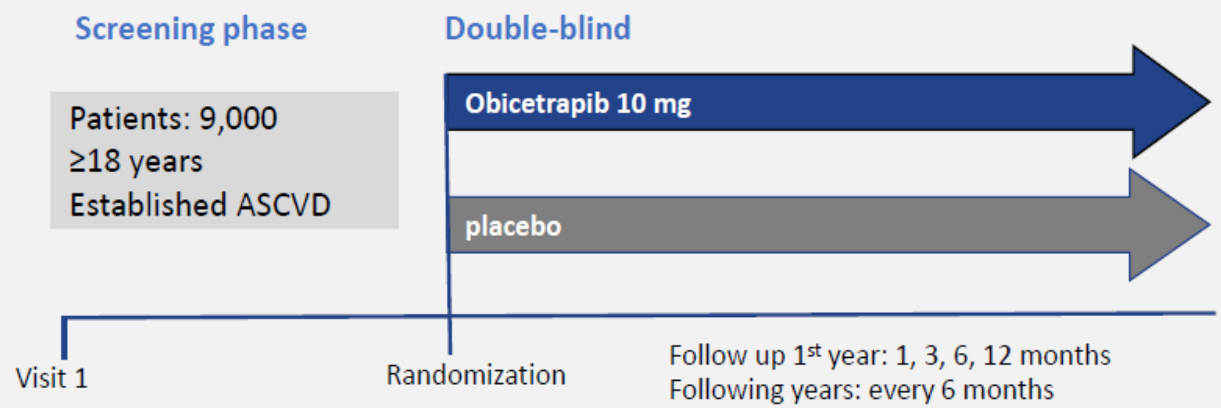
Main exclusion criteria

- Poorly controlled diabetes (HbA1c >10%)
- Hypertension
- Congestive heart failure
- Severe anemia
- Liver disease
- Chronic kidney disease

Strategy

- Duration if 959 primary endpoint events occur or the last randomized patient has been followed for a minimum of 2.5 years

Study design: Randomized, double-blind, placebo-controlled



Primary endpoint

- 4 point MACE (CVD death, non-fatal MI, non-fatal stroke, non-elective coronary revascularization)

Secondary objective

- LDL-c at 1-year
- New-onset diabetes mellitus;

https://clinicaltrials.gov/ct2/show/NCT05202509

Optimizing management of dyslipidemias: outcomes trials matter !

- **LDL**
  - Bempedoic acid — **CLEAR OUTCOMES**
  - PCSK9 inhibitors
    - Mabs — **FOURIER-ODYSSEY**
    - Inclisiran — **ORION4- VICTORION-2P, V1P**
    - Oral inhibitors — **CORAL REEF**
    - Gene editing — **Coming up**
- **Triglycerides**
  - Fibrates — **PROMINENT – FIELD, etc…**
  - Icosapent ethyl — **REDUCE IT**
  - ANGPTL3, APO CIII — **Coming up**
- **Lp(a)** — **HORIZONS – OCEAN**
- **CETPi: Obicetrapib** — **PREVAIL**