Novel oral pathways in LDL-C lowering therapy: The new promise of CETPi

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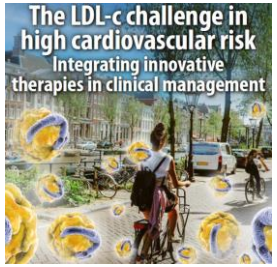
The LDL-c challenge in high cardiovascular risk - Integrating innovative therapies in clinical management



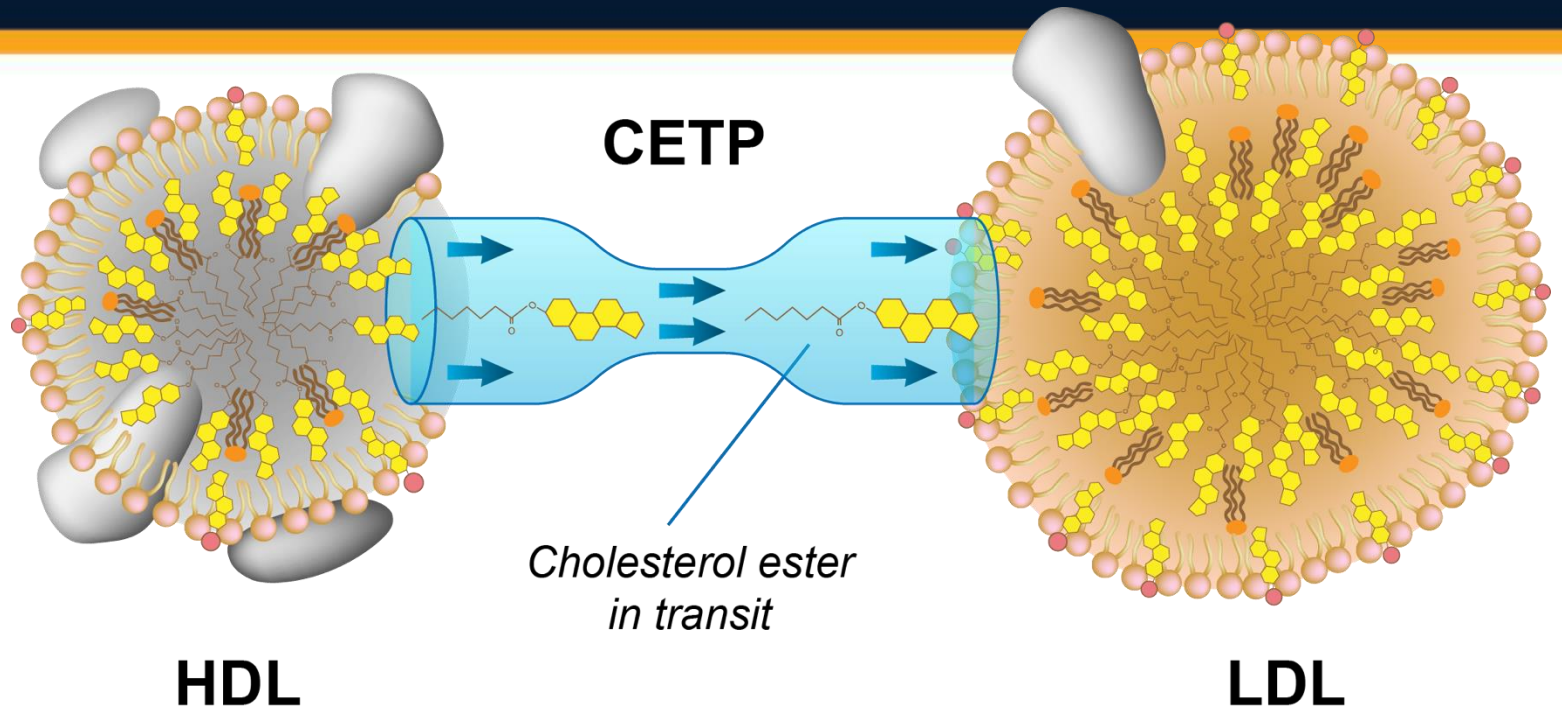
PHYSICIANS' ACADEMY FOR PACE-CME CARDIOVASCULAR EDUCATION

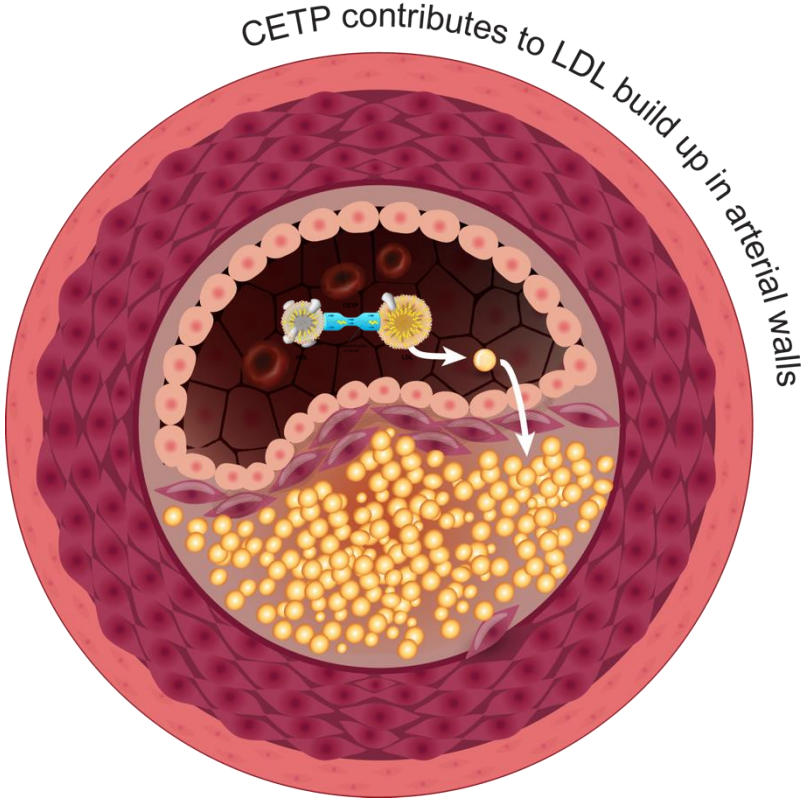
Disclosures

- Dr. Michos reports Consulting/Advisory Boards with Astra Zeneca, Amgen, Amarin, Bayer, Boehringer Ingelheim, Edwards Life Science, Esperion, Medtronic, Novartis, Novo Nordisk, and Pfizer

- Will be discussing investigational therapies (obicetrapib currently being studied in trials and not yet FDA or EMA approved or available for use)

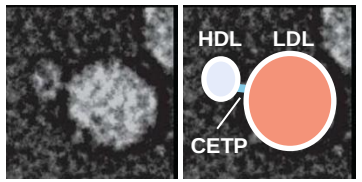
CETP transfers cholesterol esters from HDL to LDL





Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesterol esters from ***anti-atherogenic HDLs*** to ***pro-atherogenic LDLs***

- CETP activity increases circulating LDL-C levels



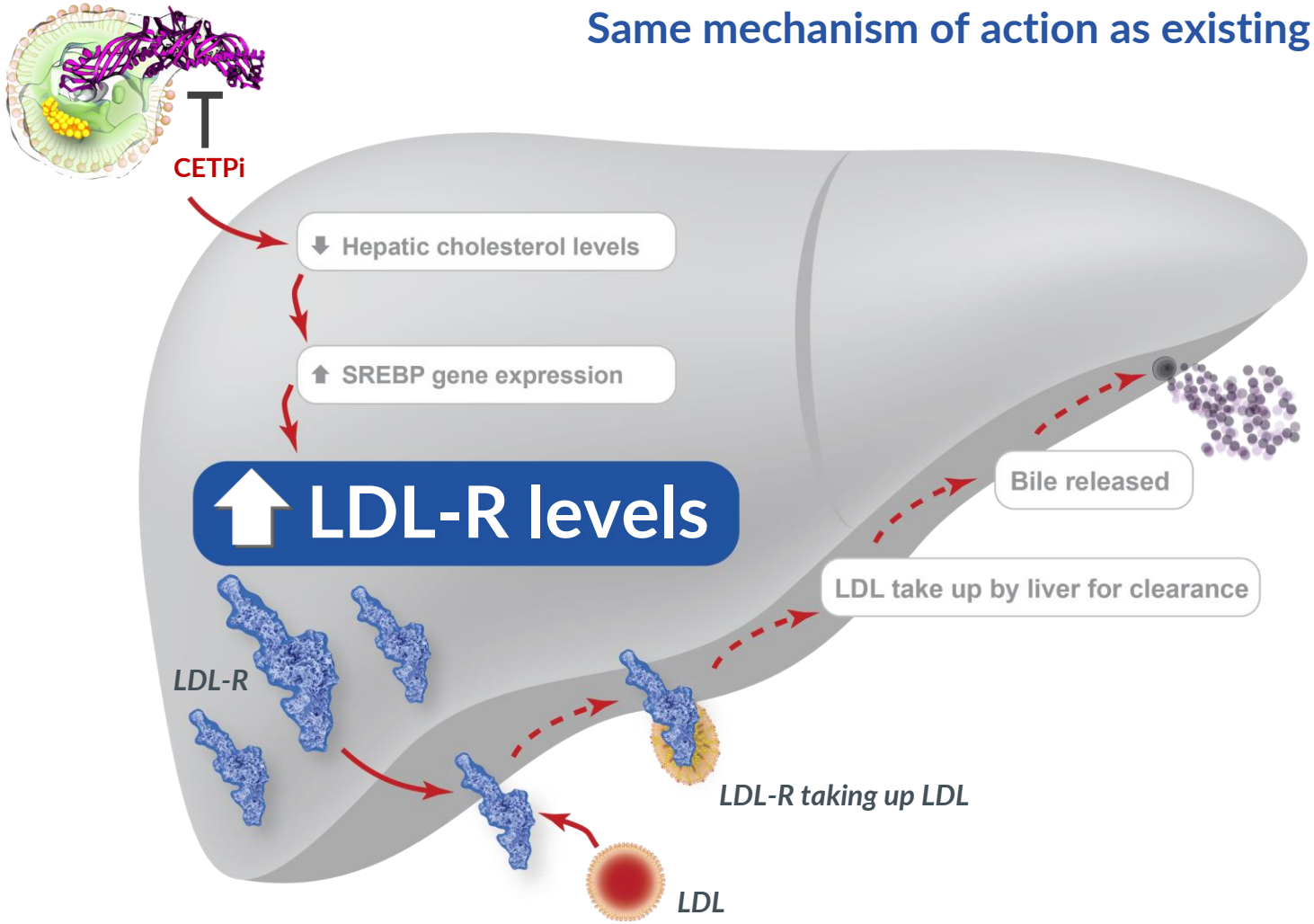
Electron micrograph of HDL, LDL, CETP

Electron micrograph (key)

- Note: Figures adapted from Meng Zhang, at al., Assessing the mechanisms of cholesteryl ester transfer protein inhibitors, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1862(12), 2017, 1606-1617, and from Lei D, et al., Insights into the Tunnel Mechanism of Cholesteryl Ester Transfer Protein through All-atom Molecular Dynamics Simulations, J Biol Chem., 2291(27), 2016, 14034-14044.

CETPi decreases hepatic cholesterol resulting in upregulation of LDL-R and improved LDL and ApoB clearance through the liver

Same mechanism of action as existing LDL-lowering drugs



Decrease in hepatic cholesterol

↓

Increase in hepatic LDL receptors

↓

Decrease in plasma LDL levels

Adapted from:
Millar JS, et al., Anacetrapib lowers LDL by increasing ApoB clearance in mildly hypercholesterolemic subjects. J Clin Invest. 2015 Jun;125(6):2510-22. doi: 10.1172/JCI80025.
van der Tuin SJ, et al., Anacetrapib reduces (V)LDL cholesterol by inhibition of CETP activity and reduction of plasma PCSK9. J Lipid Res. 2015 Nov;56(11):2085-93. doi: 10.1194/jlr.M057794

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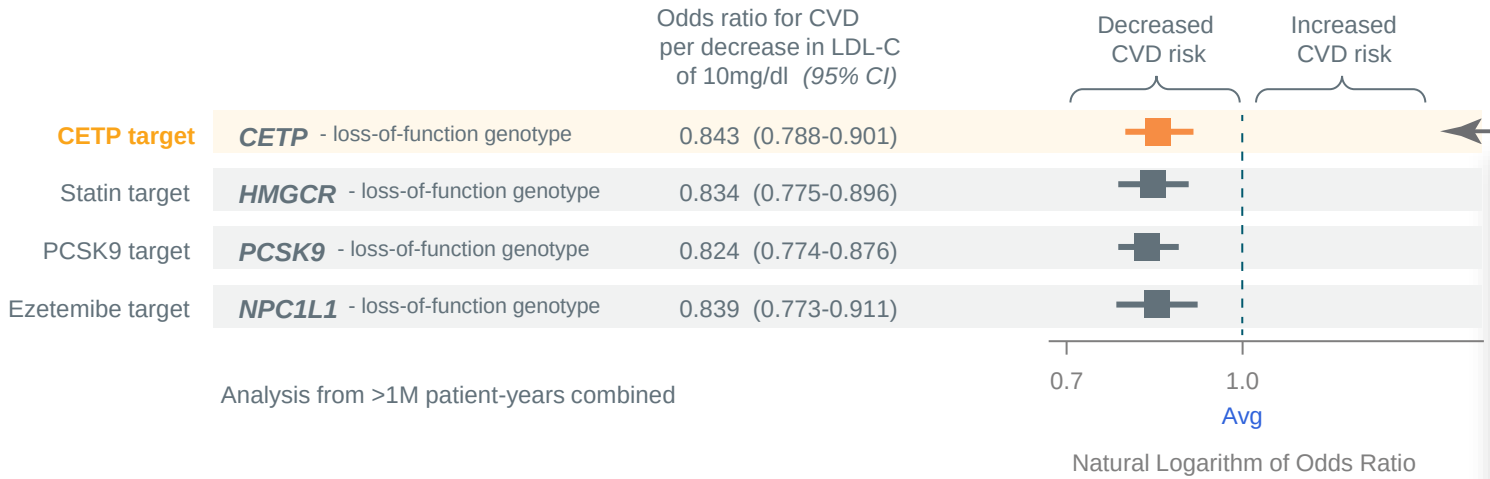
CETP inhibition has Mendelian randomization evidence that links reducing LDL-C to reducing ASCVD

Analysis of effects of genetic scores on the risk of cardiovascular disease (CVD)



- A **16% reduction** in CVD risk is observed for every 10mg/dl LDL-C decrease in patients with loss-of-function CETP genotypes
- This is ~equivalent with the level of CVD risk reduction observed in patients with loss-of-function genotypes in each of the proteins targeted by **statins**, **PCSK9 modulators**, and **ezetimibe**, respectively

KEY CONCLUSIONS:

1. **MECHANISM-AGNOSTIC RISK REDUCTION**
   Regardless of mechanism the same absolute lowering in LDL-C results in the same reduction in CVD risk
2. **HIGHLY PREDICTABLE CLINICAL EFFICACY**
   The consistency of benefit observed across loss-of-function genotypes in all four drug target genes indicates a very high predictability and probability of success for how clinically efficacious CEPTi-induced LDL-C lowering will be

Ference, Brian A., et al. "Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk." JAMA 2017; 318: 947-956

CETP, HDL-C, and the risk of Coronary Heart Disease (CHD)

- Initially it was not appreciated that loss-of-function mutations in the CETP gene do not only lead to increased HDL-C, but also to lower LDL-C, non-HDL and apoB

- We therefore now understand that inhibiting CETP lowers CHD risk by lowering atherogenic lipids/lipoproteins (e.g. LDL-C and apoB), NOT by increasing HDL-C

Summary of previous CETP inhibitors

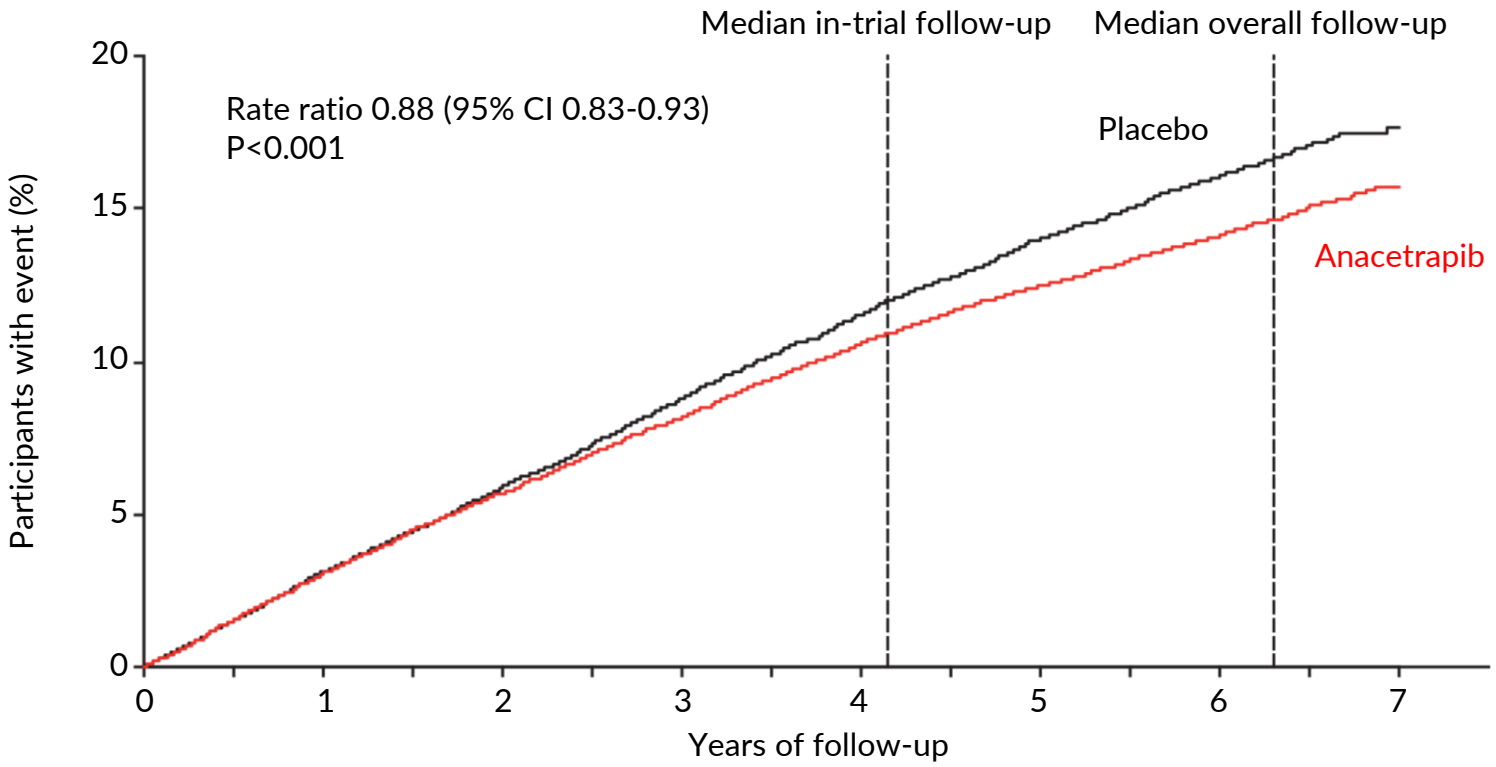
Drug	CETP inhibition	LDL-C reduction	HDL-C increase	ApoB	Significant trials	Results	Other
Torcetrapib	≥80%	-20%	65%	-16%	ILLUMINATE (2006)	Terminated due to increased death and CV events	
Dalcetrapib	37%	-7%	26%	-2%	Dal-OUTCOMES (2012)	Terminated for futility	Decrease in onset of DM
Evacetrapib	83%	-26%	98%	16%	ACCELERATE (2017)	Terminated for futility	Decrease in onset of DM Lp(a) -32% (100mg)
Anacetrapib	90%	-41% (-17%)*	104%	-18%	REVEAL (2017, 2021)	MACE -9% MACE -20% in 2.3 yr f/u	Decrease in onset of DM Lp(a) -25% 4+ year half-life

- *Reduced LDL-C by 41% (direct assay); reduced 17% in subgroup (2000 patients) measured by beta quantification

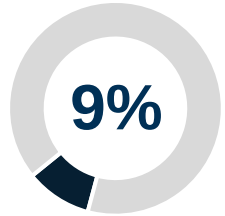
- Barter, PJ. et al, N Engl J Med 2007; 357:2109-2122 ; Schwartz, GG, et, al., N Engl J Med 2012; 367:2089-2099; Lincoff, AM. et al,. N Engl J Med 2017; 376:1933-1942; The HPS3/TIMI55–REVEAL Collaborative Group, N Engl J Med 2017; 377:1217-1227; The HPS3/TIMI55-REVEAL Collaborative Group, European Heart Journal, Volume 43, Issue 14, 7 April 2022
- Nicholls, SJ., et. al, Evacetrapib alone or in combination with statins lowers lipoprotein(a) and total and small LDL particle concentrations in mildly hypercholesterolemic patients, JCL, December 17, 2015DOI:https://doi.org/10.1016/j.jacl.2015.11.014

Historical effects of CETP inhibitors were found in reducing cardiovascular events

REVEAL: Effects of anacetrapib on first major coronary event



Reduction of MACE



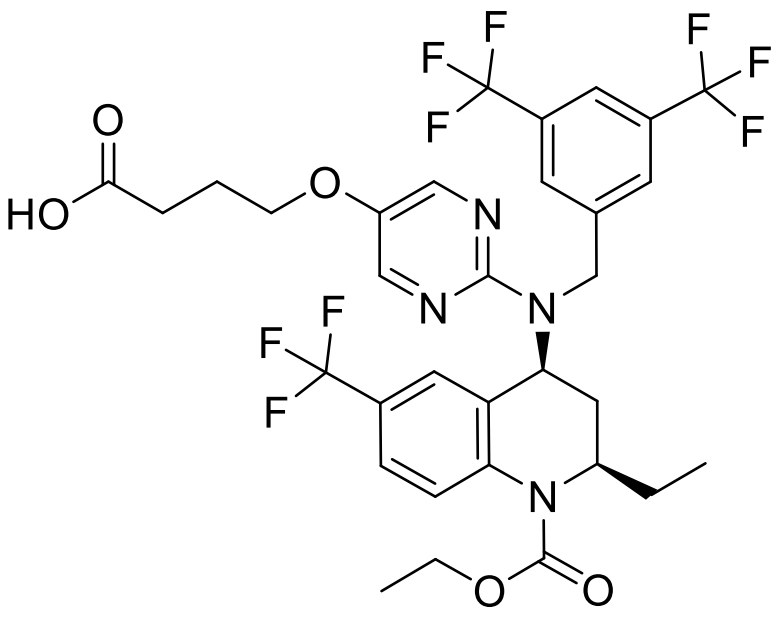
At 4.1 years

Additional reduction at 6.3 years

The positive impacts of CETP inhibition on major coronary incidents increased with extended follow-up, with no unfavorable outcomes in non-vascular death or illness

- CETP, cholesteryl ester transfer protein; MACE, major adverse cardiovascular events.
- HPS3/TIMI55-REVEAL Collaborative Group; et al. *Eur Heart J*. 2022;43(14):1416-1424.

Obicetrapib



- Obicetrapib is a selective CETP inhibitor undergoing clinical development for reducing both LDL-C and the incidence of major adverse cardiovascular events
- **At equipotent dosages obicetrapib reduces CETP activity to a greater extent than both anacetrapib and evacetrapib resulting in greater efficacy for LDL-C lowering**
- The potency of obicetrapib comes from a series of crystallography experiments that have shown that CETP inhibitors located at the narrow N-terminal neck of the hydrophobic tunnel of CETP are able to restrict the lipid flow through this tunnel
- By introducing hydrophilic structures into obicetrapib, it is the most polar of all CETP inhibitors and has a LogP of 4.9 versus 9.2 for anacetrapib and 7.9 for evacetrapib (less lipophilic)

- Nicholls, SJ et al., Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial, Nature Medicine,11 August 2022, 10.1038/s41591-022-01936-7, https://www.nature.com/articles/s41591-022-01936-7

ROSE study: Obicetrapib and High Intensity Statin therapy (HIS)

Objective **To evaluate the effect of obicetrapib on top of HIS on LDL-C**

Inclusion criteria

- A stable dose of HIS (A 40 / 80; R 20 / 40) 8 weeks prior to screening
- Fasting LDL-C levels >1.8 mmol/L

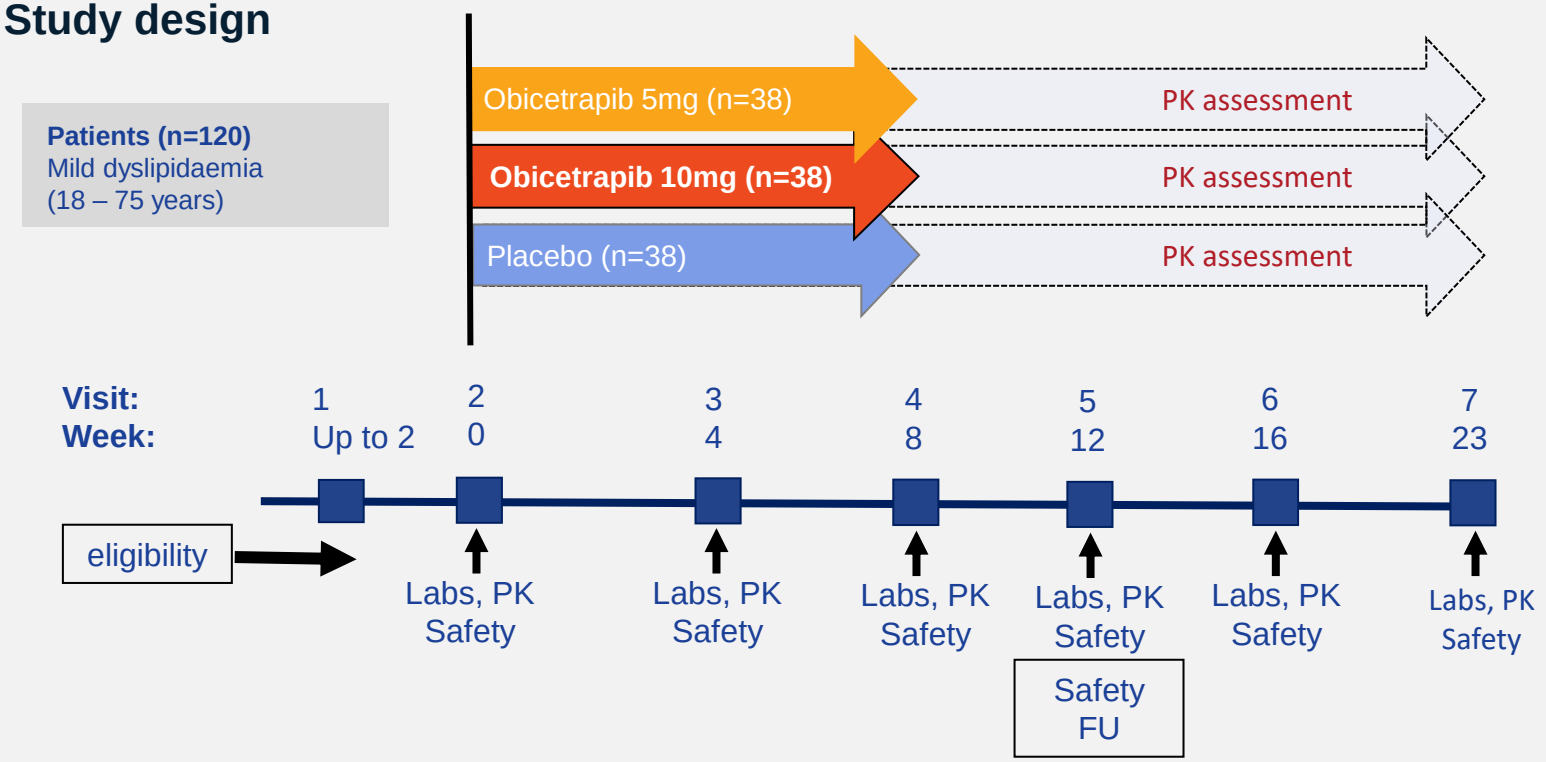
Exclusion criteria

- Current significant CV disease
- Diagnosis of type 1 or type 2 diabetes mellitus;
- Uncontrolled hypertension

Primary efficacy endpoint

- Percent change from baseline in LDL-C compared to the placebo group

Study design



Pre-specified assessment of LDL-C levels by preparative ultra-centrifugation and Friedewald

NLA Scientific Session, Late Breaking Sessions, June 4, 2022

Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

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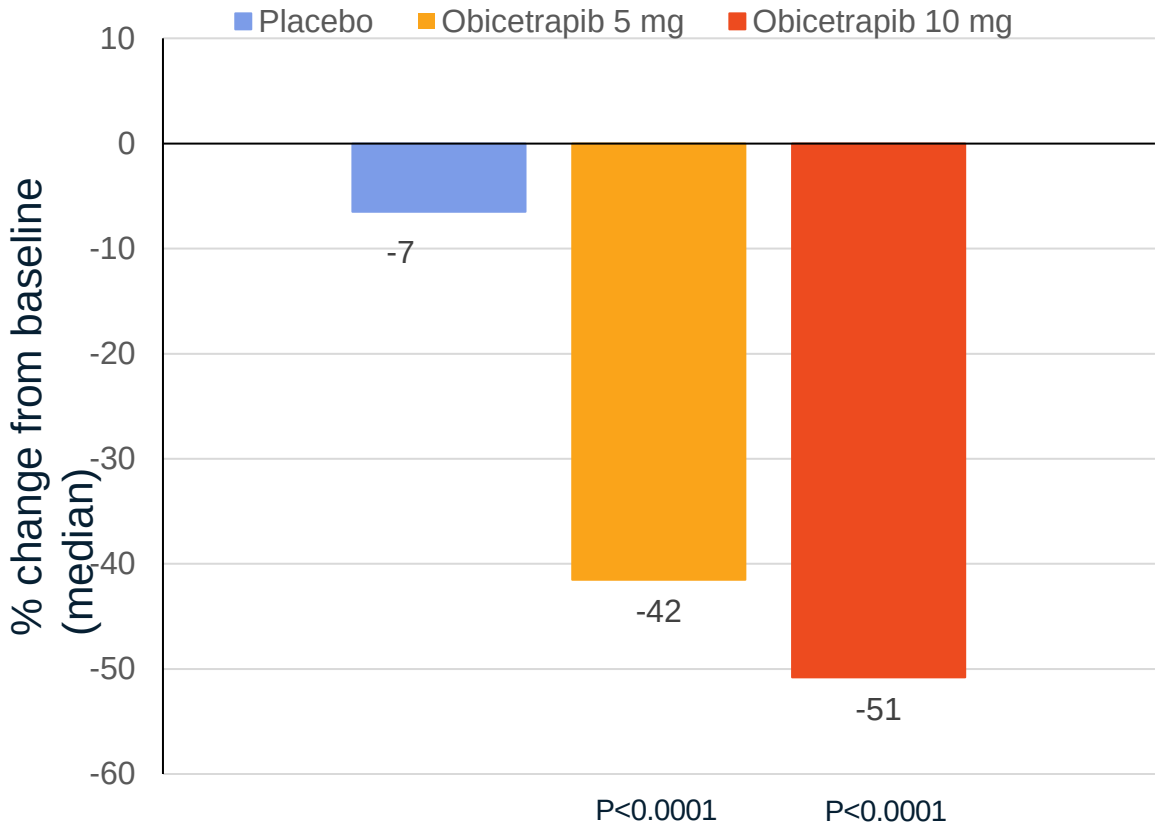
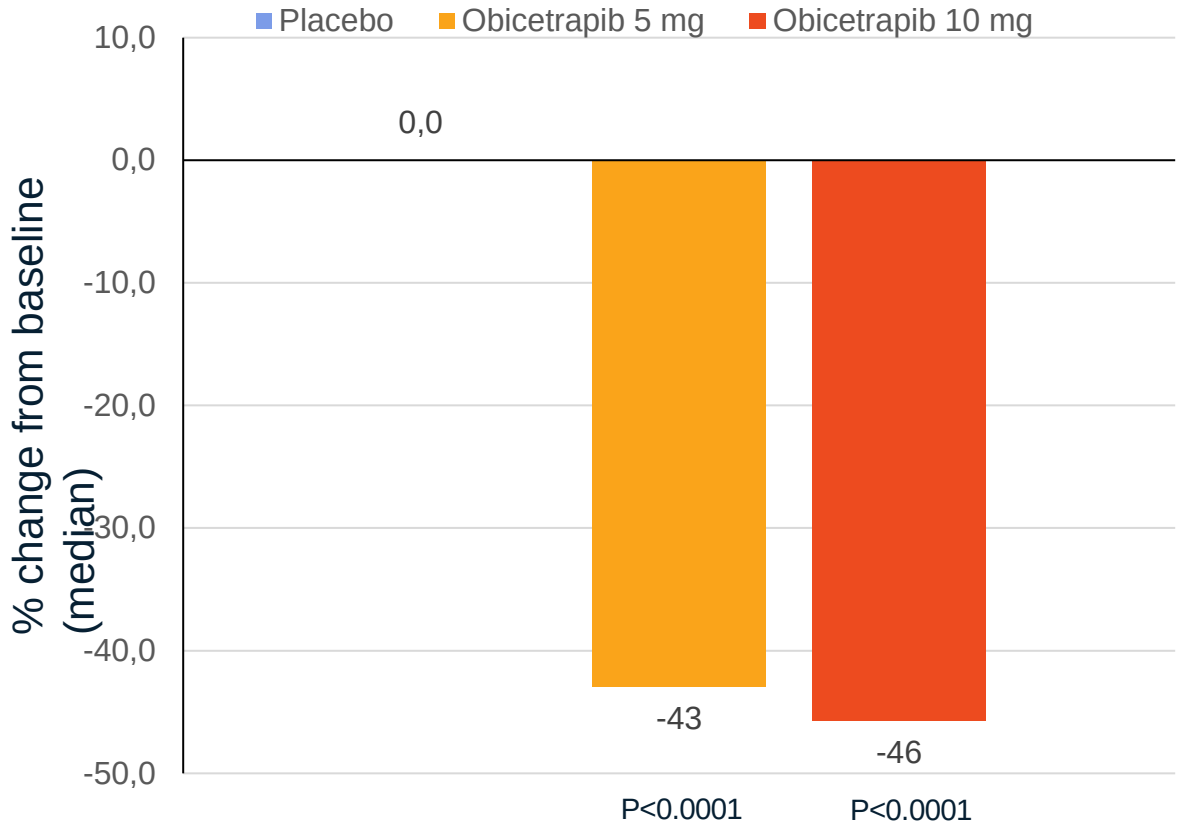
LDL-C Percent change from baseline by different measurement approaches

Preparative Ultra-centrifugation



Friedewald



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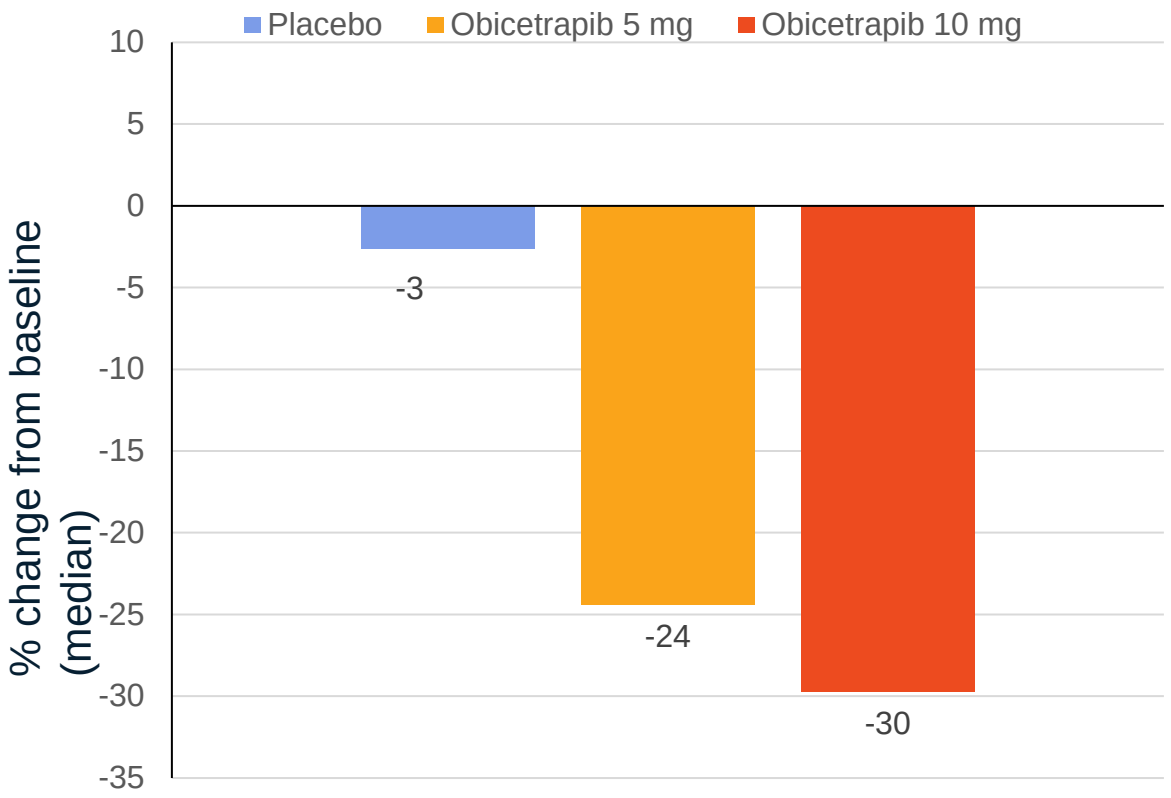
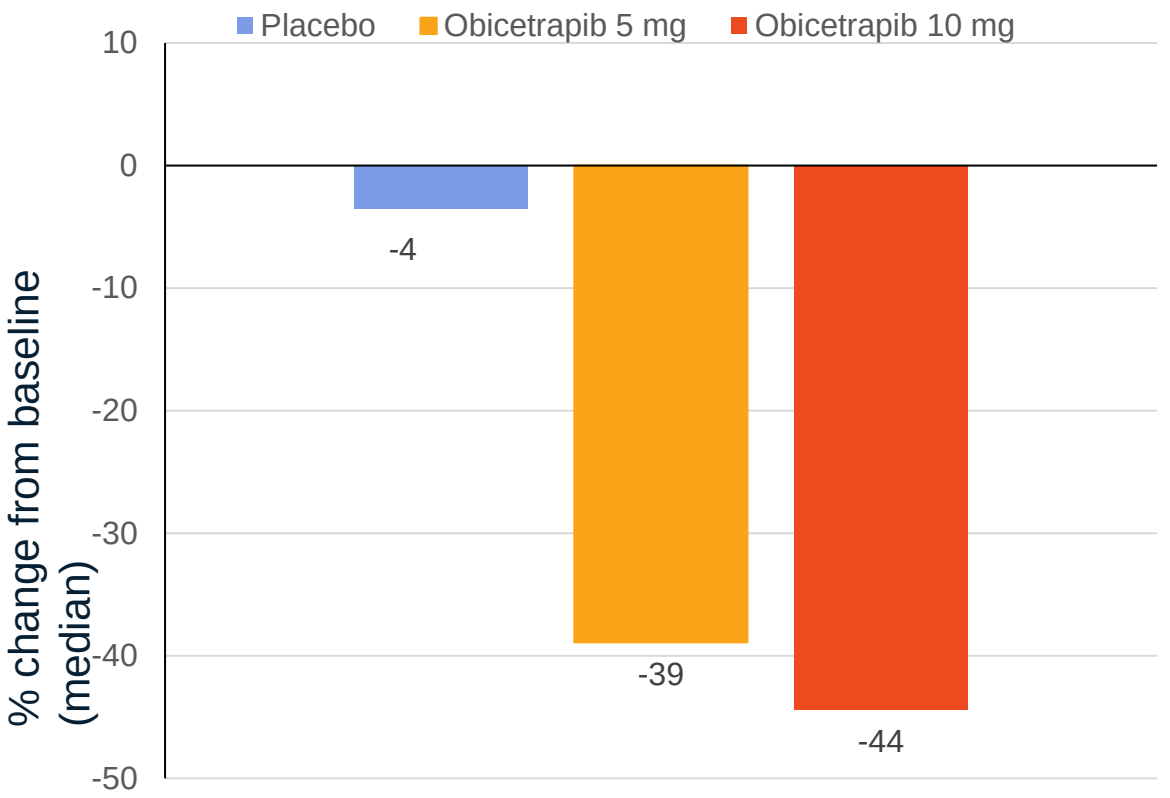
ApoB & non-HDL-C Percent change from baseline

ApoB



Non-HDL-C



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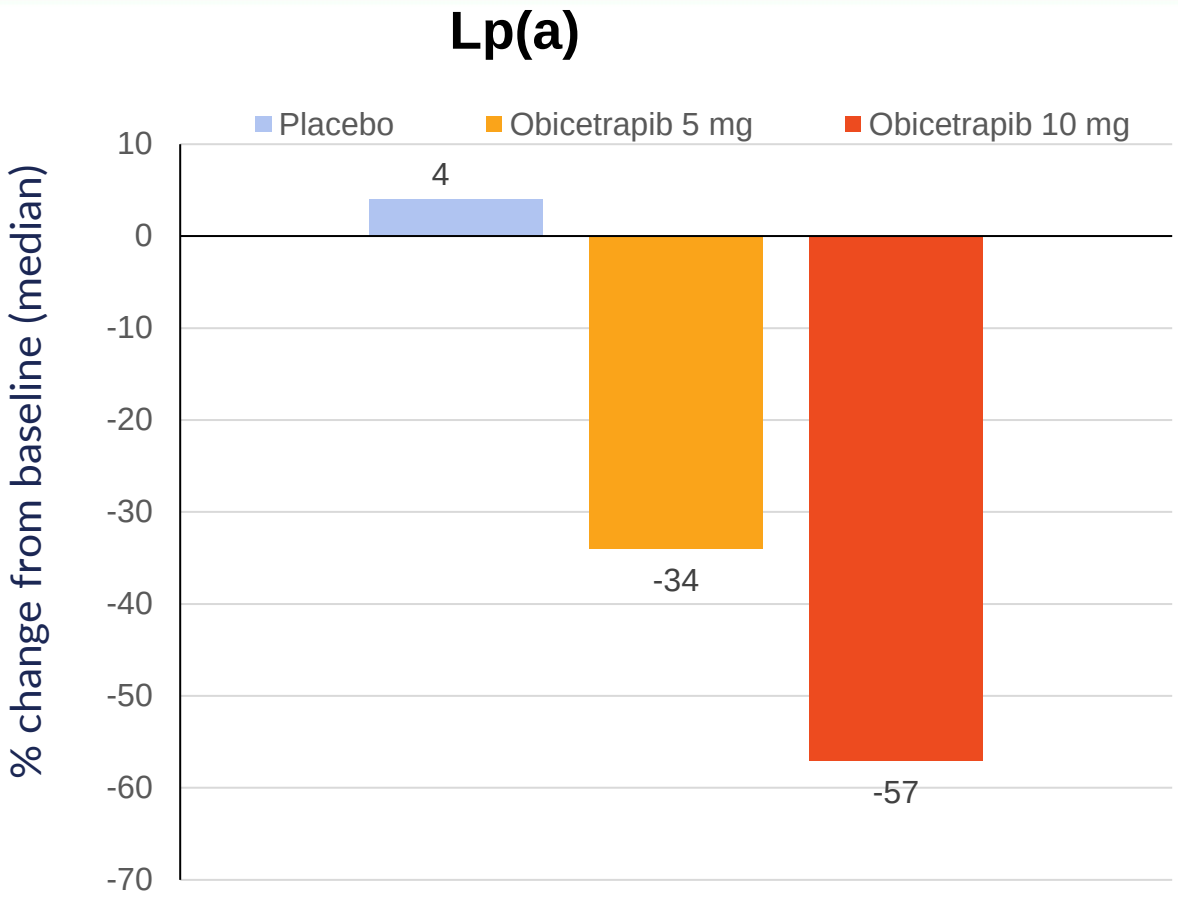
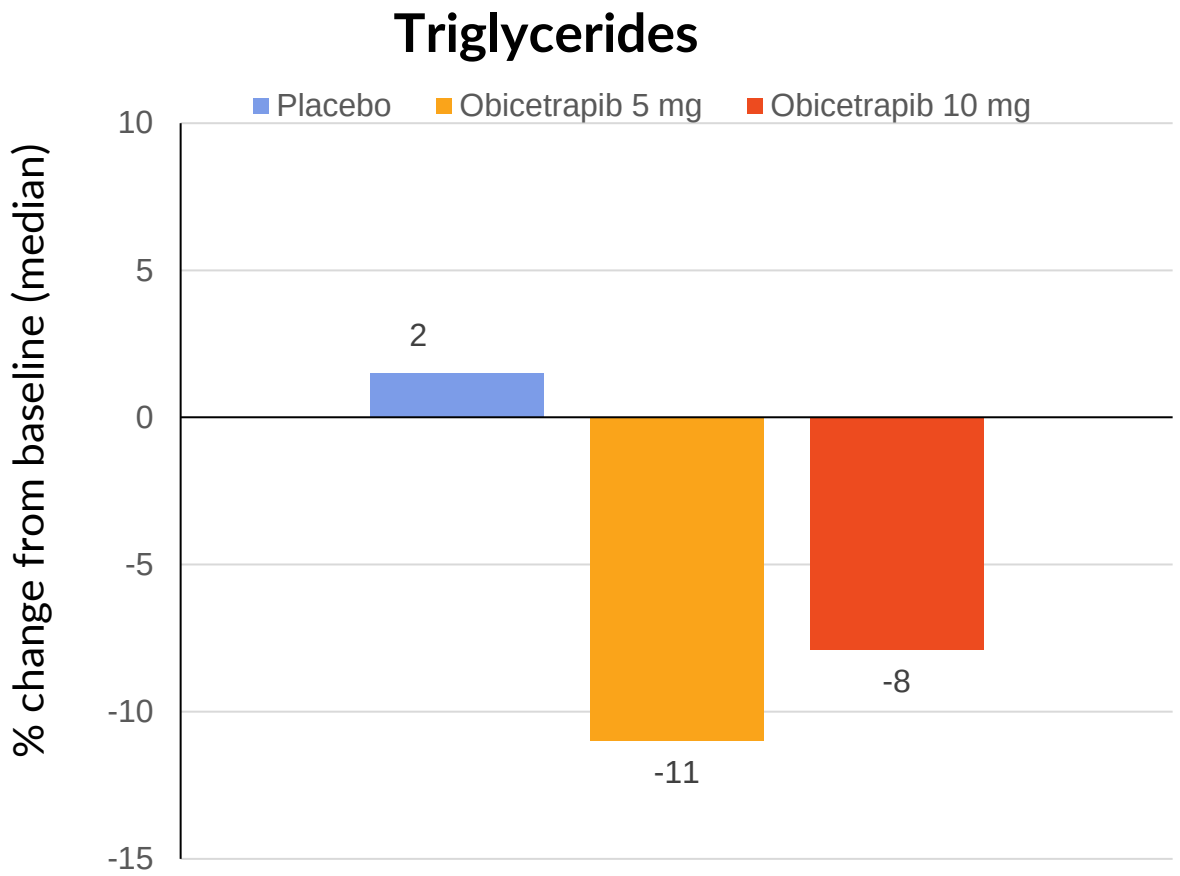
Lp(a) and Triglycerides Percent change from baseline





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ROSE Conclusions

- Obicetrapib 5 and 10 mg on top of HIS therapy was well tolerated
- Obicetrapib 5 and 10 mg on top of HIS therapy reduced median LDL-C levels by -42% and -51% from baseline, respectively
- Obicetrapib LDL-C lowering comparable at all baseline LDL-C levels
- Obicetrapib LDL-C lowering is not mitigated in combination with HIS
- Obicetrapib LDL-C lowering is similar with both LDL-C quantitation methods
- Obicetrapib has potential to be a valuable addition for high risk ASCVD patients who do not achieve their target LDL-C guideline goals despite the use of HIS therapy.

NLA Scientific Session, Late Breaking Sessions, June 4, 2022

Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

ROSE 2 Trial: obicetrapib + ezetimibe and high-intensity statin therapy

Objective To evaluate the effect of obicetrapib 10mg in combination with ezetimibe 10mg on top of HIS on LDL-C

Inclusion criteria

- Stable dose of high-intensity statins (A 40/80, R 20/40) 8 weeks before screening
- Fasting LDL-C levels >70 mg/dL (1.8 mmol/L)

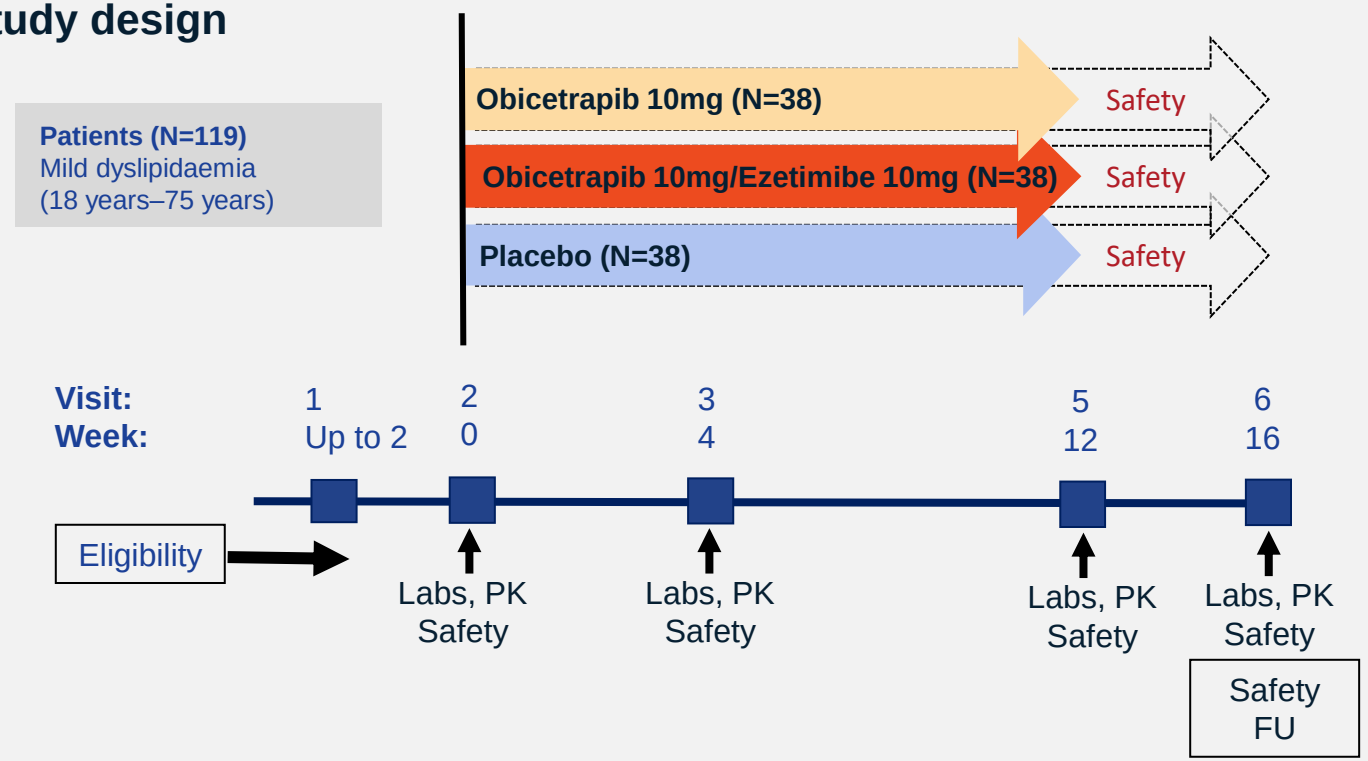
Exclusion criteria

- Current significant CV disease
- HbA1c ≥10%
- Uncontrolled hypertension

Primary efficacy endpoint

- Percent change from baseline in LDL-C compared with the placebo group

Study design



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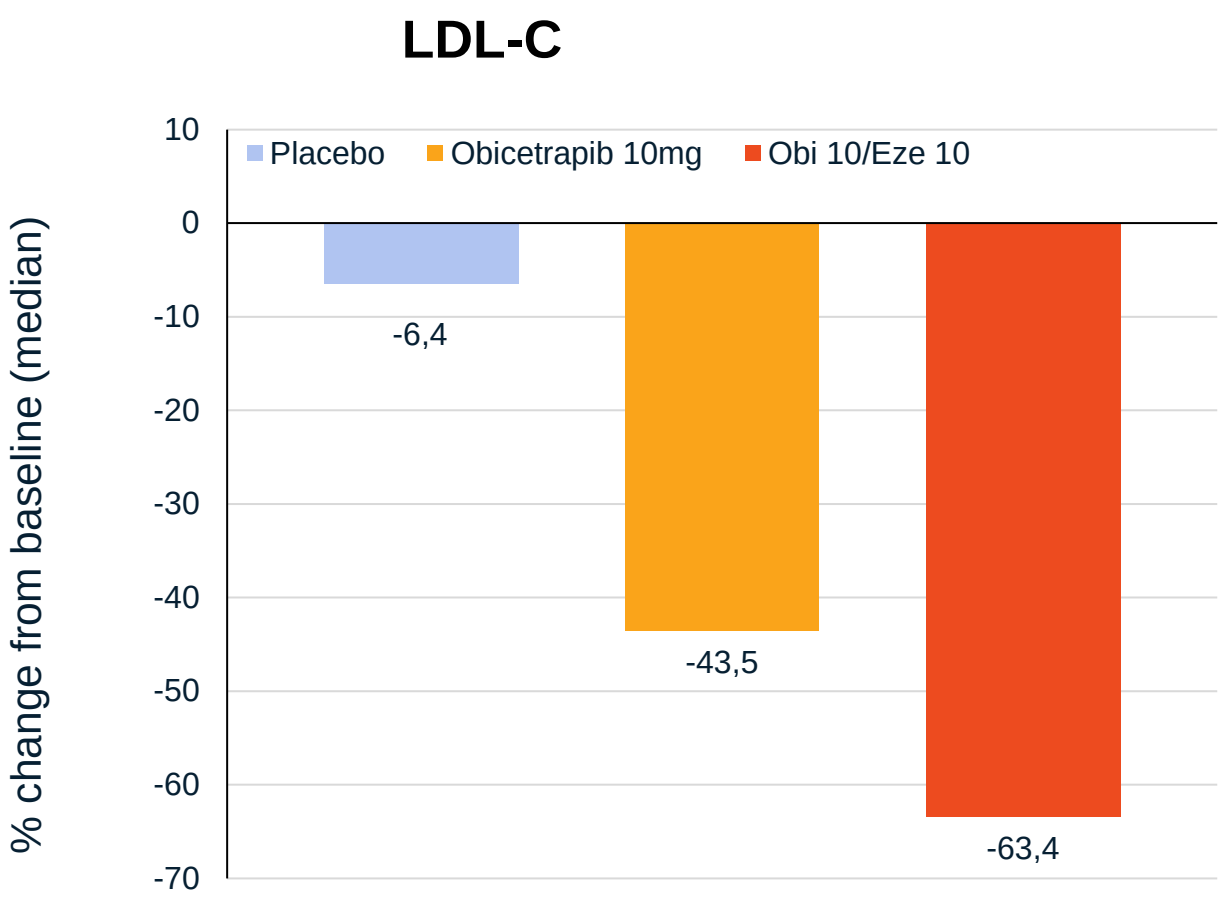
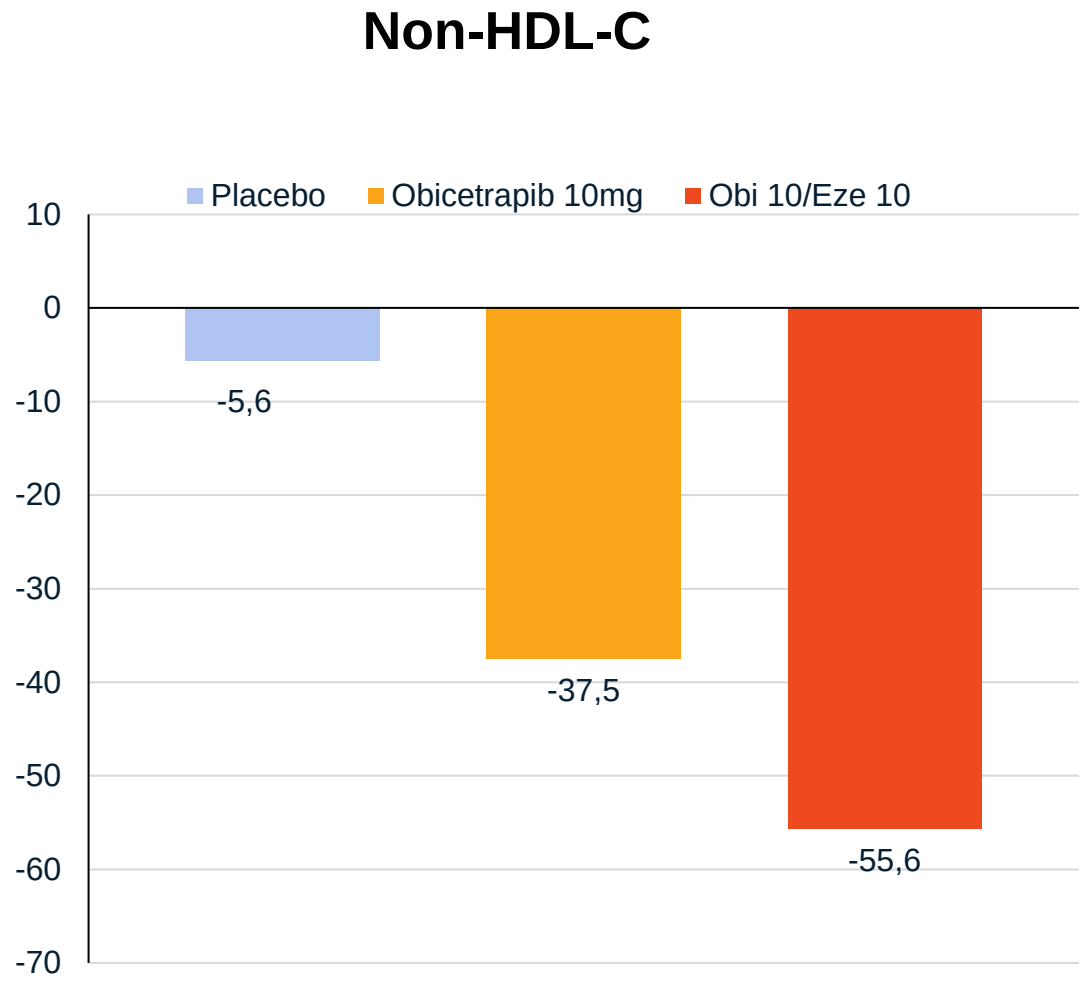
LDL-C in mg/dL and percent change from baseline





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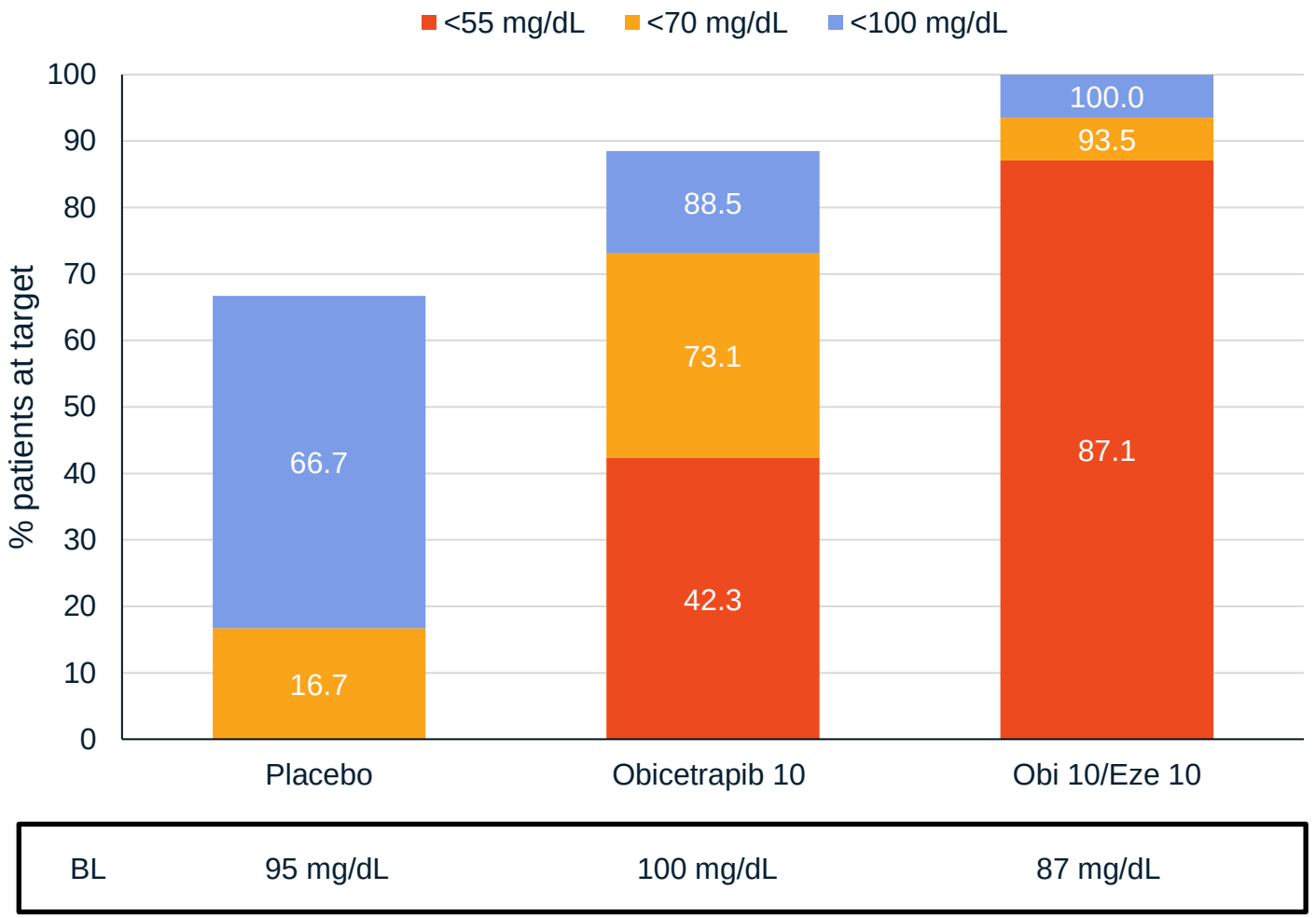
LDL-C target attainment



BL	95 mg/dL	100 mg/dL	87 mg/dL

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Safety: TEAEs, TESAEs, and withdrawal overview (safety population)

	Placebo N= 40, N (%)	Obicetrapib 10 mg N= 39, N (%)	Obi 10 mg / Eze 10 mg N= 40, N (%)
TEAEs (%)			
TEAEs	16 (40)	8 (20.5)	11 (27.5)
Related TEAEs	2 (5.0)	4 (10.3)	5 (12.5)
Severe TEAEs	2 (5.0)	1 (2.6)	0 (0)
TESAEs			
TESAEs, total	1 (2.5)	1 (2.6)	0 (0)
Deaths	0	0	0
Withdrawal's study / medication			
TEAEs leading to discontinuation of study drug	2 (5.0)	2 (5.1)	1 (2.5)

N=total number of subjects in each treatment group.
n=number of subjects who experienced an event.
%=100 x n/N.

Treatment emergent adverse events (TEAE)

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Rose 2 Trial Conclusions

- Obicetrapib 10 mg and the combination of obicetrapib 10 mg + ezetimibe 10 mg were observed to reduce median LDL-C levels by -43.5% and -63.4%, respectively, on top of HIS therapy
- The combination of obicetrapib 10 mg + ezetimibe 10 mg was observed to reduce total LDL particles and small LDL particles by 72.1% and 95.4%, respectively
- 87.1% of patients taking the combination of obicetrapib 10 mg + ezetimibe 10 mg were observed to achieve an LDL-C level <55 mg/dL
- Obicetrapib 10 mg and the combination of obicetrapib 10 mg and ezetimibe 10 mg on top of HIS therapy were well tolerated
- These data support the continued development of a fixed dose combination of obicetrapib 10 mg plus ezetimibe 10 mg

Obicetrapib Cardiovascular Outcome Trial in ASCVD patients

PREVAIL

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

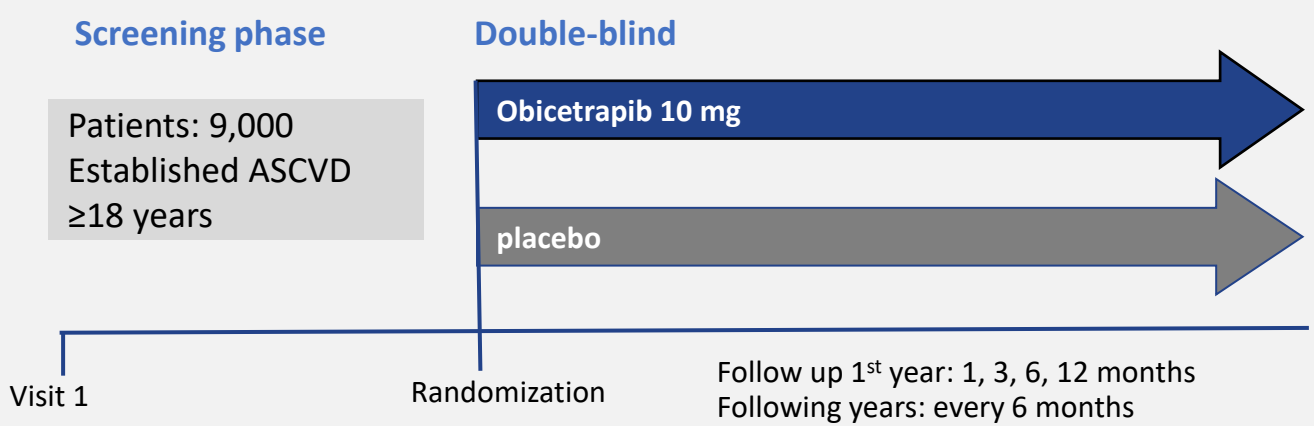
Main exclusion criteria

- 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 12 weeks
- New-onset diabetes mellitus;

NCT05202509

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What's Hot in CVD Prevention?

Lipid Management!!

THANK YOU!

Questions??

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