A novel CETP-inhibitor to target CV risk reduction: Where could it fit in future lipid management?

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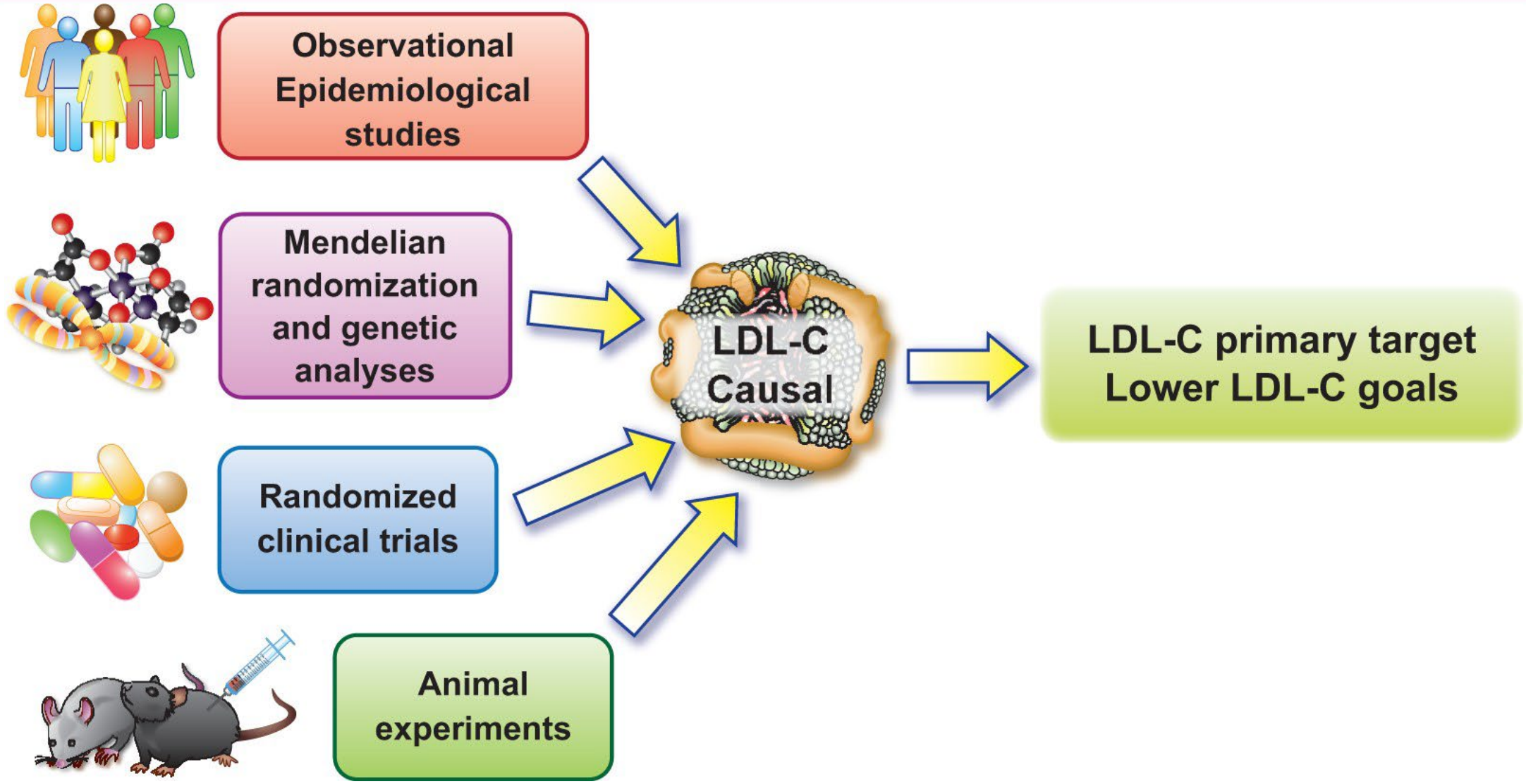
Disclosures

- Dr. Michos reports Consulting/Advisory Boards with Astra Zeneca, Amgen, Arrowhead, Bayer, Boehringer Ingelheim, Edwards Life Science, Eli Lilly, Esperion, Ionis Medtronic, Merck, New Amsterdam, Novartis, Novo Nordisk, and Zoll

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

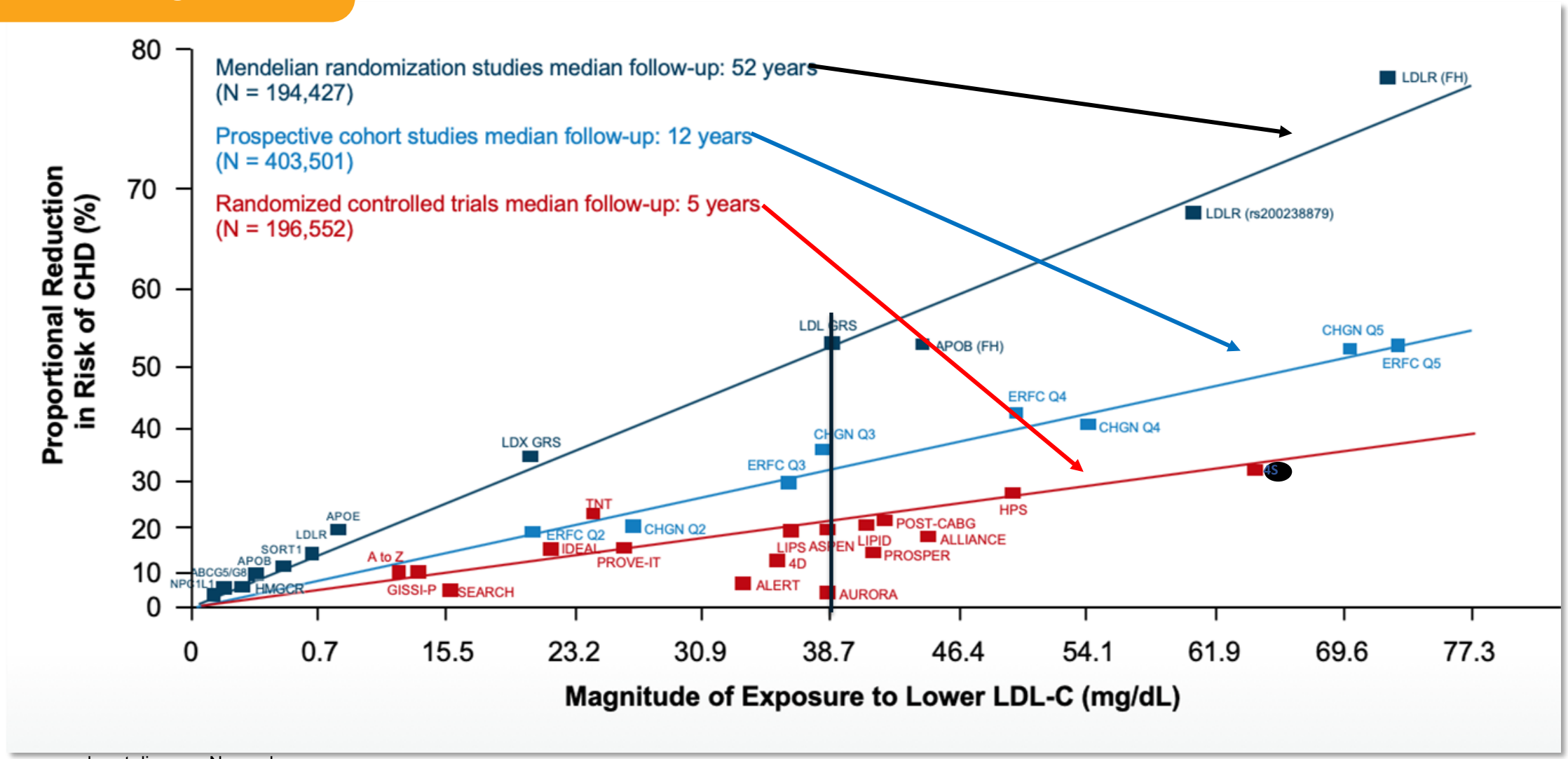
LDL is a causal agent in ASCVD pathogenesis



Tokgözoğlu L, Libby P. *Eur Heart J* 2022; 43(34):3198–3208

Genetics, Interventional, and Observational Data: Proportional Reduction in CHD Risk with Magnitude of LDL-C lowering

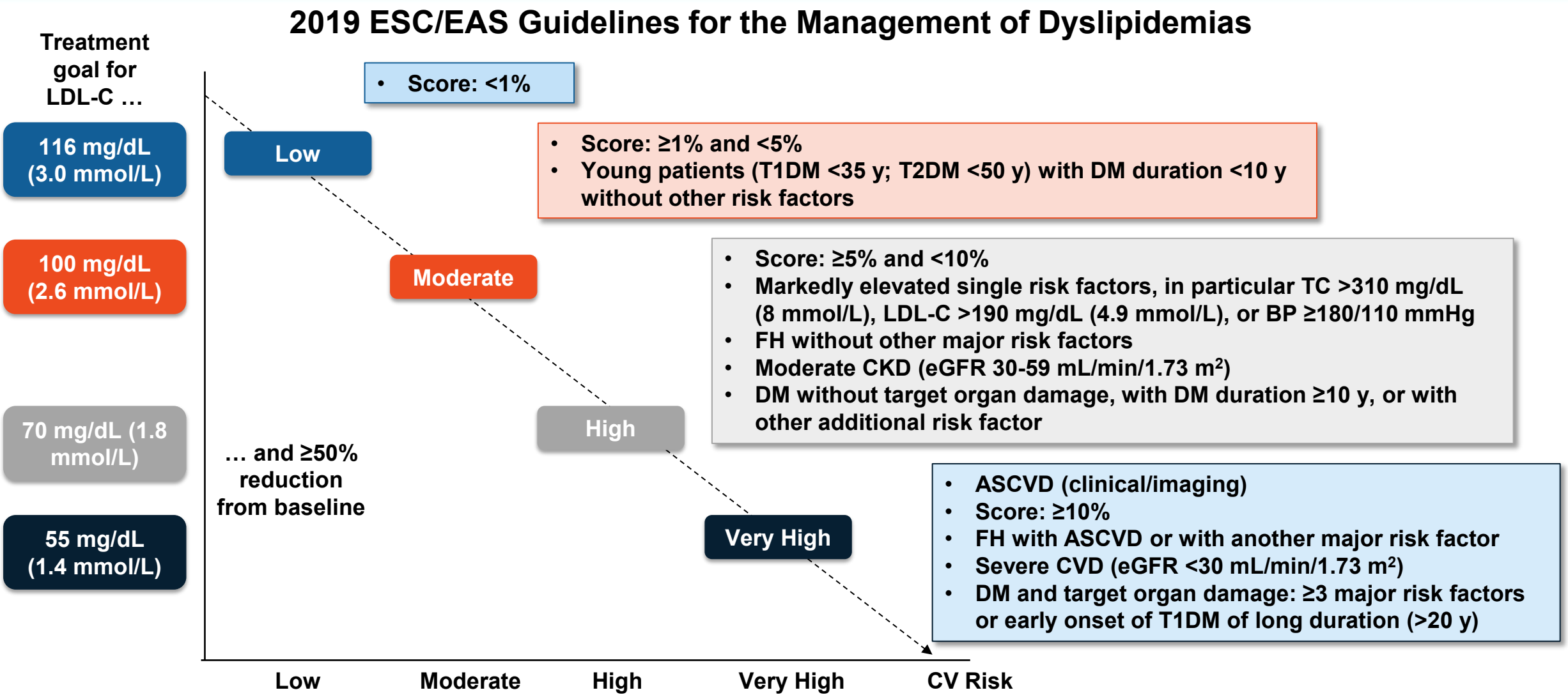
Lower LDL-C is better



CHD, coronary heart disease; N, number

Ference BA, et al. *European Heart Journal* 2017;38(32):2459-2472

ESC Guidelines: Treatment Goals for LDL-C Across Categories of Total Cardiovascular Disease Risk



Mach F et al. *Eur Heart J.* 2020;41:111-188.

2022 ACC Expert Consensus Decision Pathway – Nonstatin Therapy Summary (Simplified)

≥50% reduction in LDL-C on maximal tolerated statin AND achievement of risk-based LDL-C thresholds

LDL-C Threshold	<55 mg/dL (1.4 mmol/L)	<70 mg/dL (1.8 mmol/L)	<100 mg/dL (2.6 mmol/L)
Steps* to Achieve LDL-C Threshold	Adults With ASCVD at Very High Risk, incl. FH	Adults with ASCVD Not at Very High Risk	Adults Without ASCVD and baseline LDL-C ≥190 mg/dL
1st	Maximum tolerated **statin**	Maximum tolerated **statin**	Maximum tolerated **statin**
2nd	Add **ezetimibe**	Add **ezetimibe**	Add **ezetimibe**
3rd	Consider adding **PCSK9 mAb**	Consider adding **PCSK9 mAb**	Consider adding **PCSK9 mAb**
4th	Consider **bempedoic acid**	Consider **bempedoic acid**	Consider **bempedoic acid**
5th	Consider **inclisiran**	Consider **inclisiran**	Consider **inclisiran**

*Lifestyle therapies are recommended for all patients with ASCVD and/or major ASCVD risk factors.
Referral to a registered dietitian nutritionist may be considered at any step to individualize nutrition recommendations.

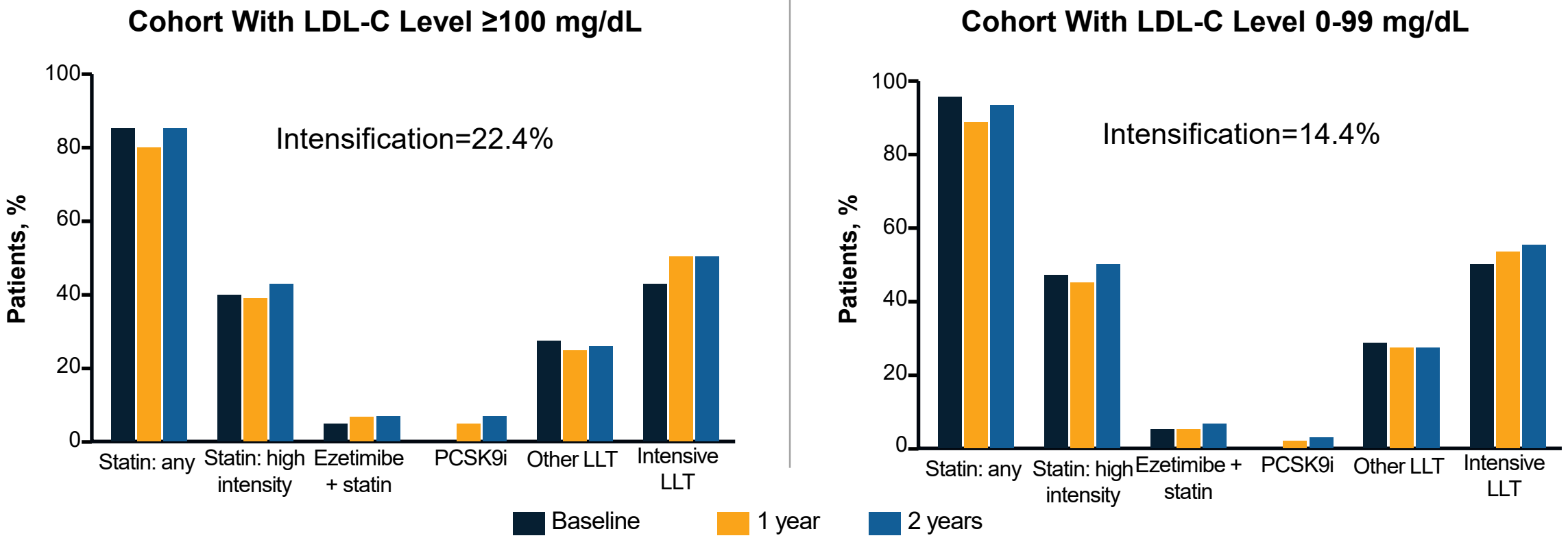
ACC, American College of Cardiology; mAb, monocolonal antibody

Lloyd-Jones DM, et al. *J Am Coll Cardiol* 2022 Oct 4;80(14):1366-1418.

Nonstatins Are Underused in Patients with ASCVD

Observational registry of 5006 patients with ASCVD enrolled between December 2016 and July 2018 seeking to assess change in lipid-lowering therapy over 2 years (GOULD Registry)

Two-thirds remained at an LDL-C level >70 mg/dL (1.8 mmol/L)

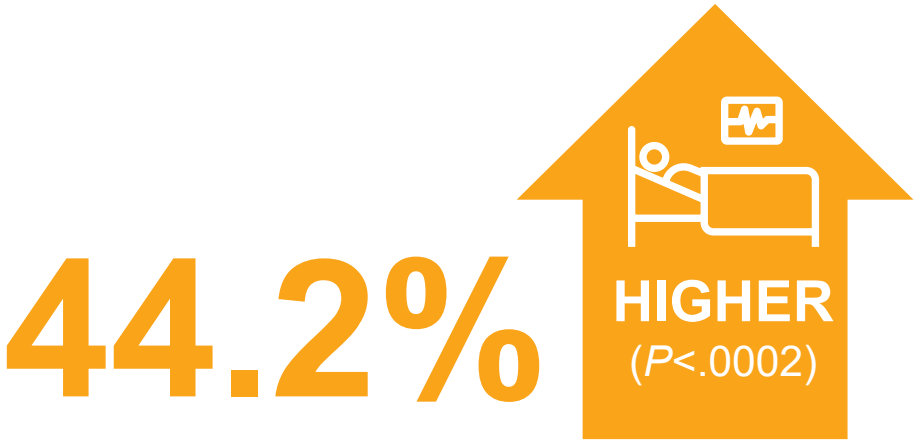


GOULD, Getting to an Improved Understanding of LDL-C and Dyslipidemia Management; LLT, lipid-lowering therapy

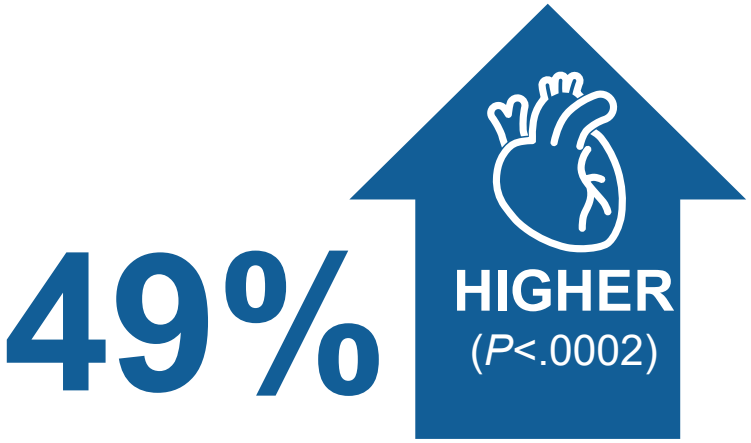
Cannon CP, et al. *JAMA Cardiol.* 2021;6(9):1060-1068.

Clinical Consequences of Insufficient LDL-C Management: Family Heart Foundation study

A retrospective analysis assessed the annual CV event rates in 56,349 high-risk patients who were above LDL-C threshold or below LDL-C threshold for at least 70% of the study period (≥48 mo)



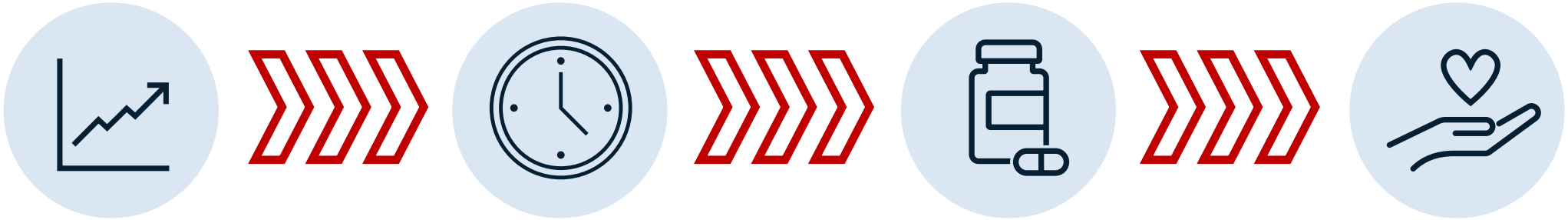
"Above LDL-C Threshold" group had an annual incidence rate of first cardiac events **44.2% higher** (*P*<.0002) than those in the **"Below LDL-C Threshold"** group



Total **cardiac events** (first and subsequent) in the **"Above LDL-C Threshold"** group were **49% higher** (*P*<.0002) than those in the **"Below LDL-C Threshold"** group

Family Heart Database™.

LDL-C Treatment Gap



- Most high-risk patients remain persistently above guideline-recommended LDL-C thresholds
- Patients with LDL-C below thresholds remained there for only brief time periods
- Insufficient prescribing of combination LLTs by clinicians elevates the risk for ASCVD events
- High-risk patients whose LDL-C remains persistently above recommended thresholds have a significantly increased risk of major CV events

Family Heart Database™.

LLT, lipid lowering therapy; ASCVD, atherosclerotic cardiovascular disease

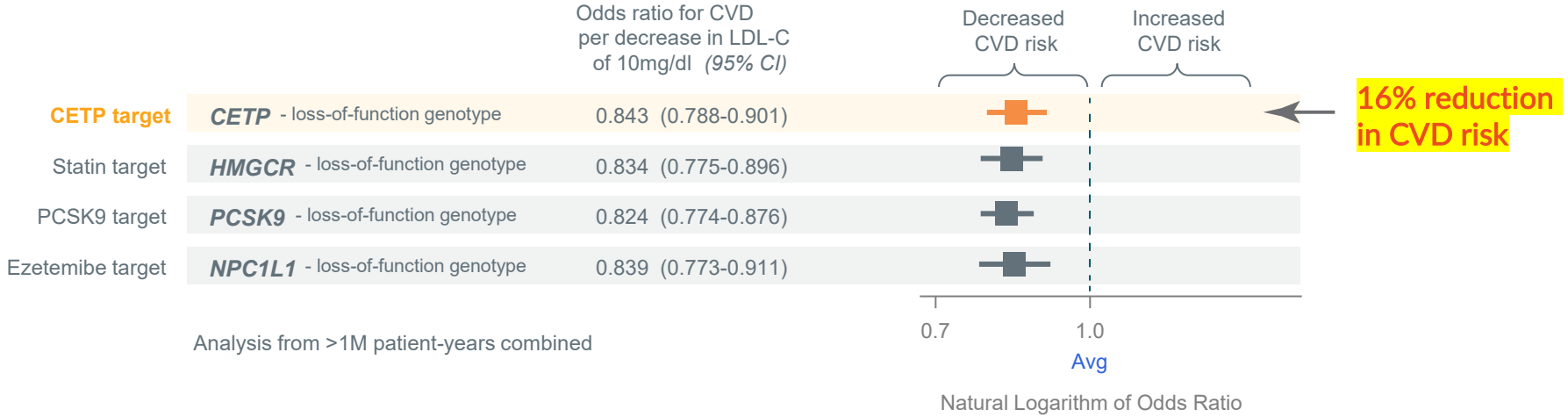
The Clinical Paradox…and a call to Action

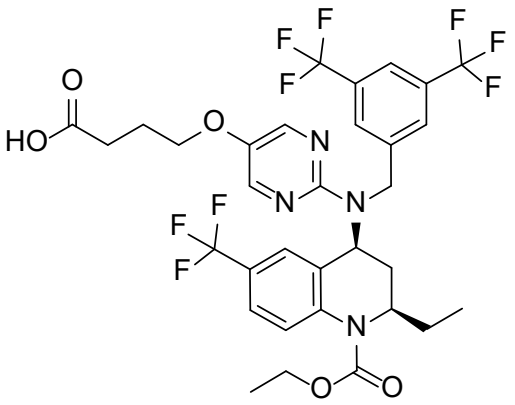
> “Atherosclerosis represents a clinical paradox: it is potentially the most preventable or treatable chronic disease, yet it remains the greatest cause of disability and death throughout the world. This does not have to be the case.”

Makover ME, et al. *Am J Prev Cardiol*. 2022;12:100371. doi: 10.1016/j.ajpc.2022.100371

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

- Obicetrapib* is a selective CETP inhibitor undergoing clinical development for reducing both LDL-C and the incidence of major adverse cardiovascular events

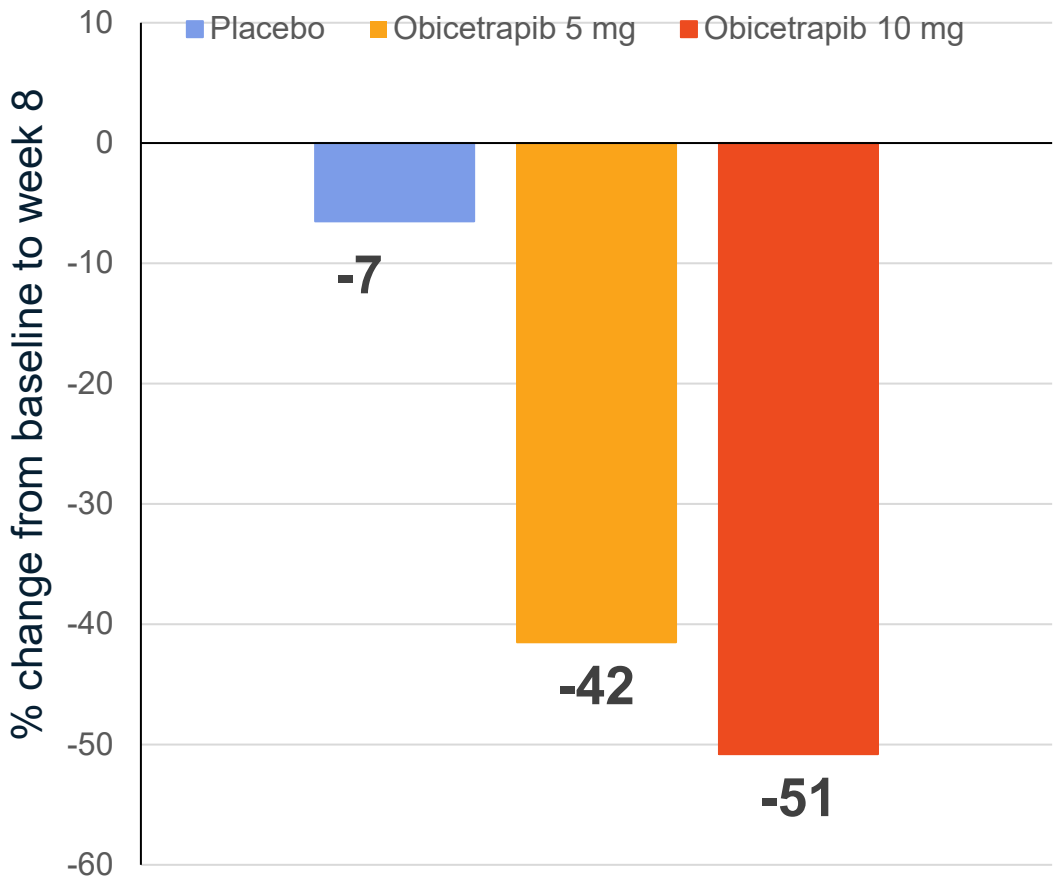
***Obicetrapib is an investigational agent; not commercially available**

Avg, average; CVD, cardiovascular disease; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase

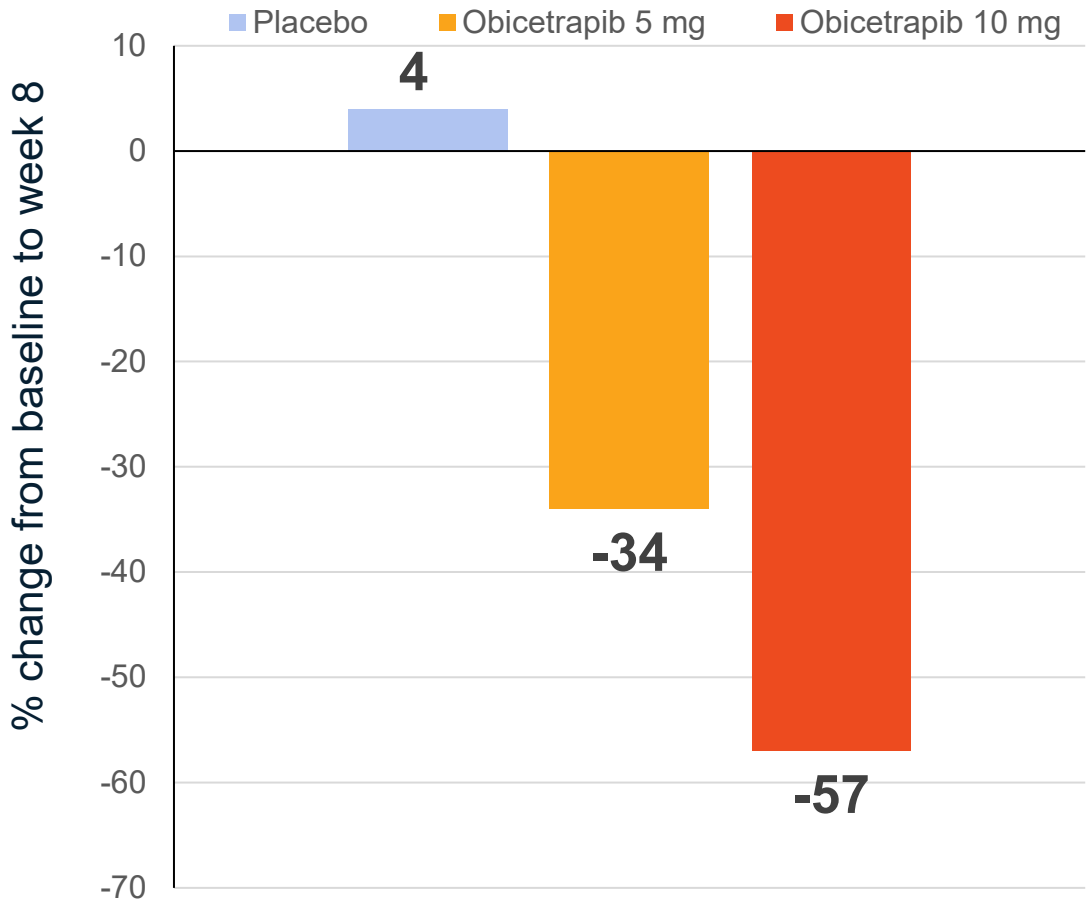
Ference, Brian A., et al. "Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk." JAMA 2017; 318: 947-956

ROSE Trial (Obicetrapib* + HIS)
LDL-C and Lp(a) % change from baseline

LDL-C Preparative Ultra-centrifugation



Lp(a)



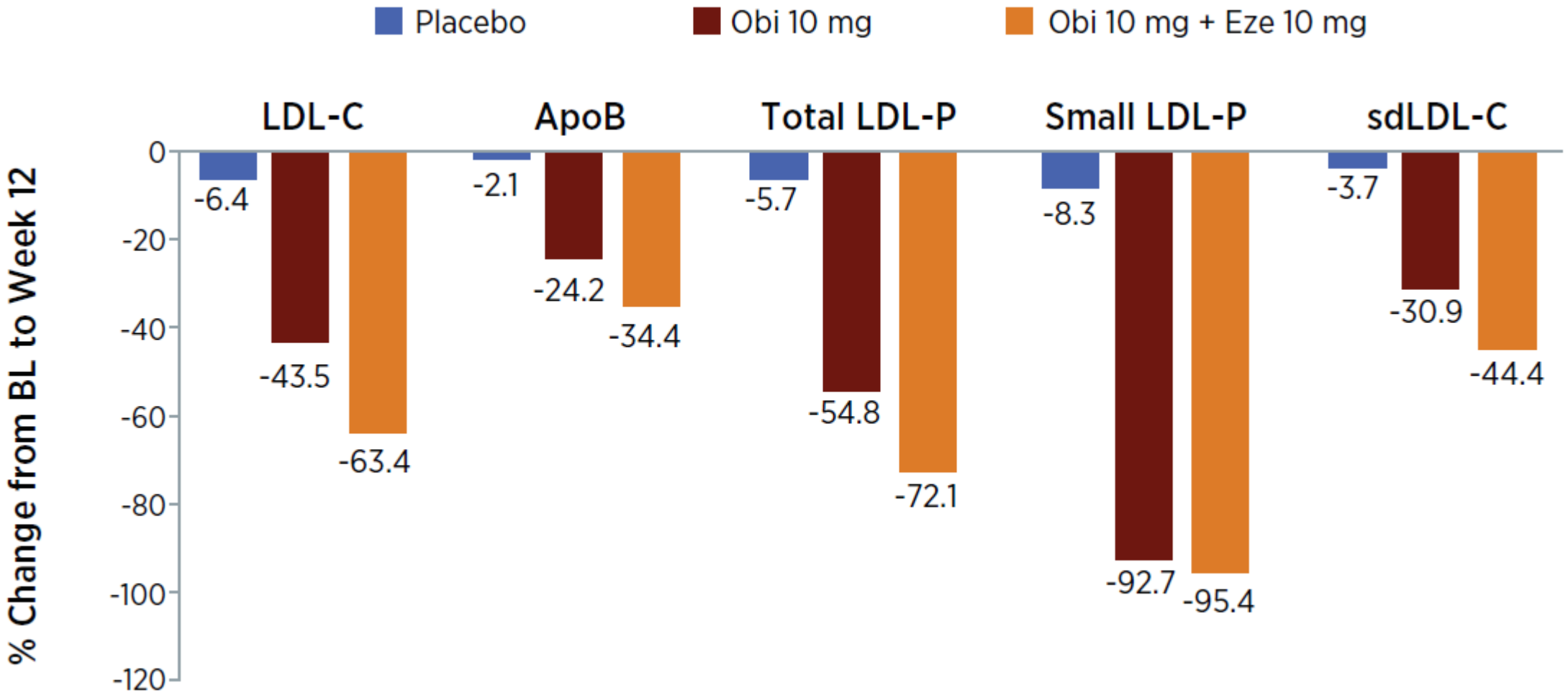
HIS, high-intensity statin

*Obicetrapib is an investigational agent; not commercially available

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

ROSE 2 trial: obicetrapib + ezetimibe + HIS

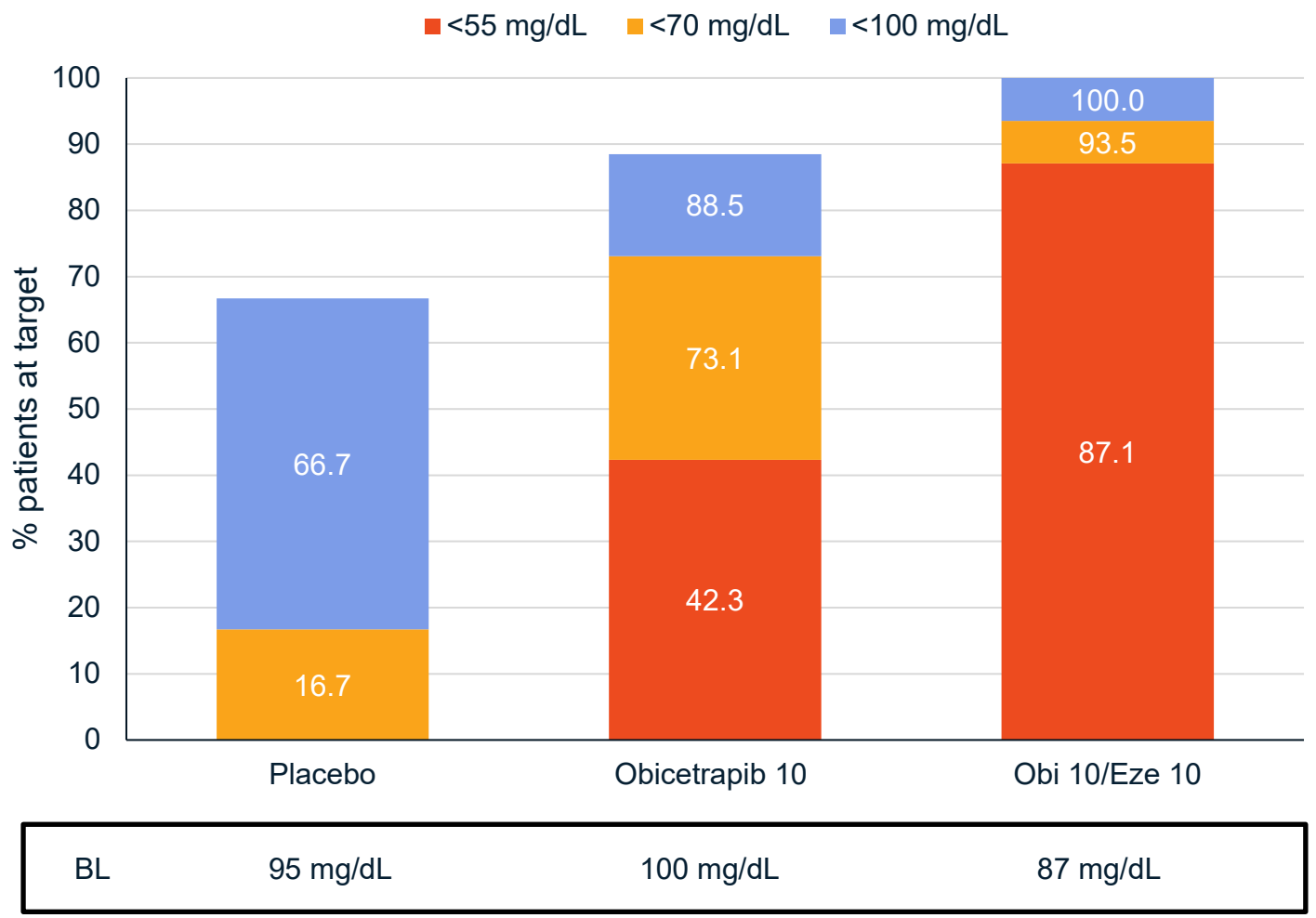
% change in atherogenic lipoproteins from baseline



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

ROSE 2 trial: LDL-C target attainment



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

Ballantyne CM, et al. J Clin Lipidol 2023;17(4):491-503

Rose 2 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); treatment-emergent serious adverse events (TESAEs).

Ballantyne CM, et al. J Clin Lipidol 2023;17(4):491-503

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

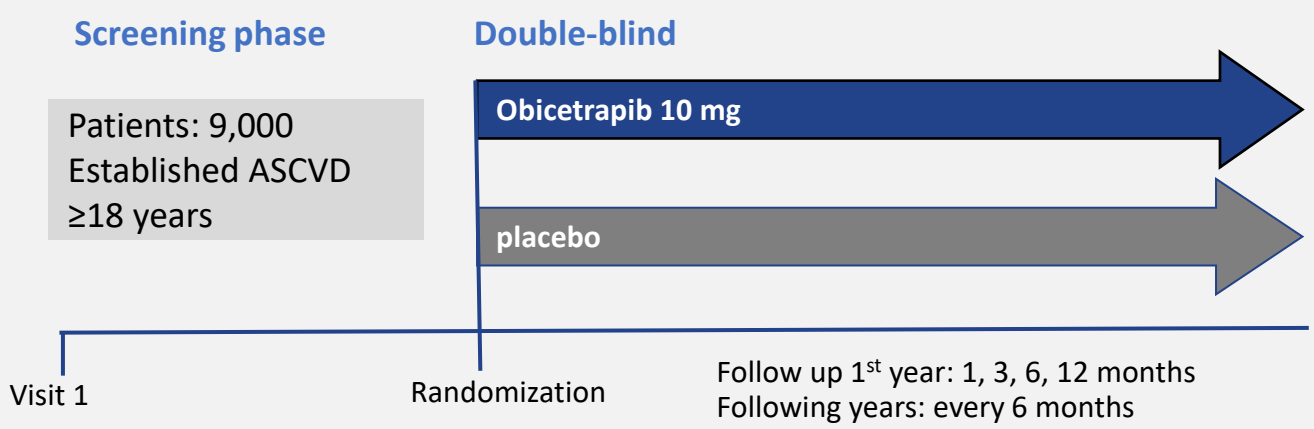
Main exclusion criteria

- 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)

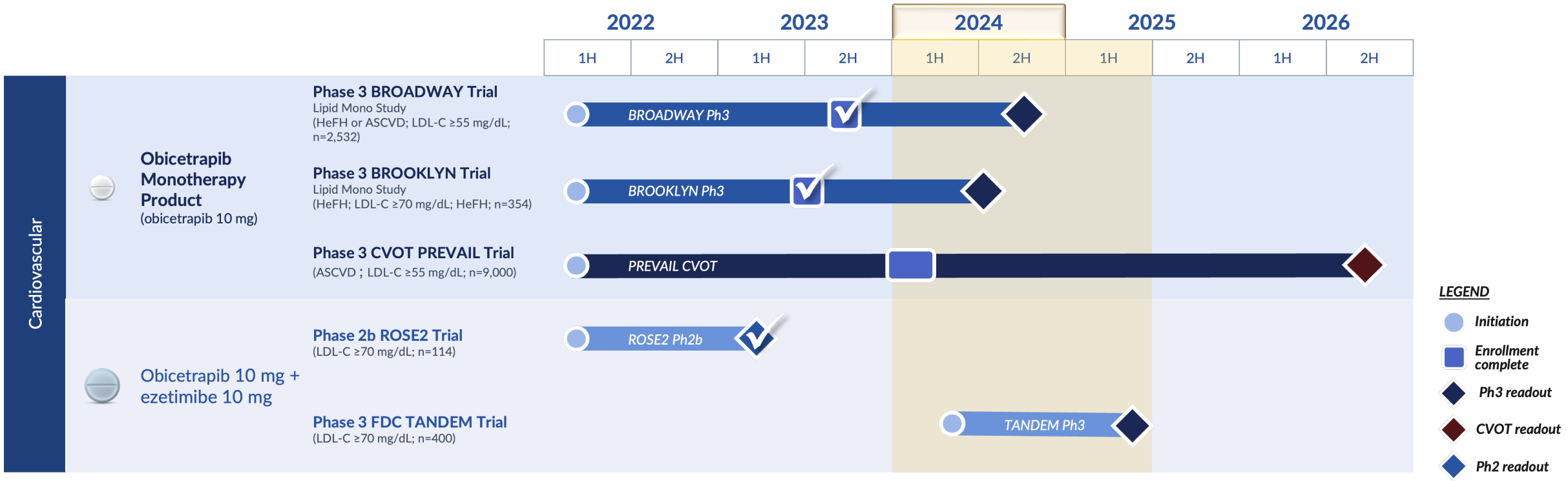
Secondary objective

- LDL-c at 12 weeks
- New-onset diabetes mellitus;

NCT05202509

*Obicetrapib is an investigational agent; not commercially available

Obicetrapib franchise projected clinical development program



- ASCVD=atherosclerotic cardiovascular disease; CVOT=cardiovascular outcomes trial; FDC=fixed-dose combination; HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein-cholesterol.
  Note: Other than as noted, the pipeline represents trials that are currently ongoing. Projections are subject to inherent limitations. Actual results may differ from expectations. The timing of regulatory submissions is subject to additional discussions with regulators.

Conclusions

- LDL-C is causal for ASCVD and is the primary target for cholesterol lowering
- Recent clinical guidance recommends even lower LDL-C levels in those at highest ASCVD risk
- There is a pressing need to close gaps in LDL-C management
- Current non-statin oral add-on lipid-lowering therapies reduce LDL-C individually by 20-25%, whereas potent injectable therapies have had limited uptake.
- As a result, there remains a high unmet need for effective, safe oral therapies to be used as an adjunct to high-intensity statins.
- Obicetrapib, an oral, once-daily low-dose CETP inhibitor, robustly reduces atherogenic lipoprotein particles and cholesterol concentrations when added to high-intensity statin (HIS) therapy and in combination with ezetimibe on top of HIS - can normalize the lipoprotein profile of patients to reflect a physiological profile.
- This supports the potential for obicetrapib to fill the treatment gap for patients with elevated LDL-C who are unable to achieve treatment objectives with currently available therapies
- As such, obicetrapib may be a promising agent for the treatment of ASCVD, with a CVOT in progress, and it is anticipated to be the first-in-class CETP inhibitor available for clinical use.