Victorian Heart Hospital

Impact of Obicetrapib on Major Adverse Cardiovascular Events: a Pooled Analysis of Phase 3 Clinical Trials

Stephen J Nicholls, Adam J Nelson, Kausik K Ray, Marc Ditmarsch, Douglas Kling, Andy Hsieh, Michael Szarek, John J Kastelein and Michael H Davidson

Monash Health

MONASH University

MONASH VICTORIAN HEART INSTITUTE

Disclosures

- Research support: AstraZeneca, Cyclarity, NewAmsterdam Pharma, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron and Liposcience
- Consulting and honoraria: AstraZeneca, Abcentra, Amarin, Akcea, Arrowhead, Cyclarity, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim, Vaxxinity, Scribe Therapeutics, Sequiris

CETP and Cardiovascular Risk

- Cholesteryl ester transfer protein (CETP) plays a pivotal role in lipid metabolism and presents an attractive target for inhibition
- Genomic studies and post hoc analyses of clinical trials demonstrated that the cardiovascular protection associated with low CETP activity results from low LDL-C and not high HDL-C levels
- CETP inhibitors decrease levels of atherogenic lipids and raise HDL-C
- Early CETP inhibitor programs focused on HDL-C raising and failed to consistently demonstrate a reduction in cardiovascular events

Obicetrapib

- Obicetrapib is a highly selective CETP inhibitor which was well tolerated in early clinical trials

- Obicetrapib lowers levels of LDL-C, apoB and Lp(a) and raises HDL-C, when administered as monotherapy or in addition to high intensity statins, in studies of high-risk patients with either familial hypercholesterolaemia or atherosclerotic cardiovascular disease

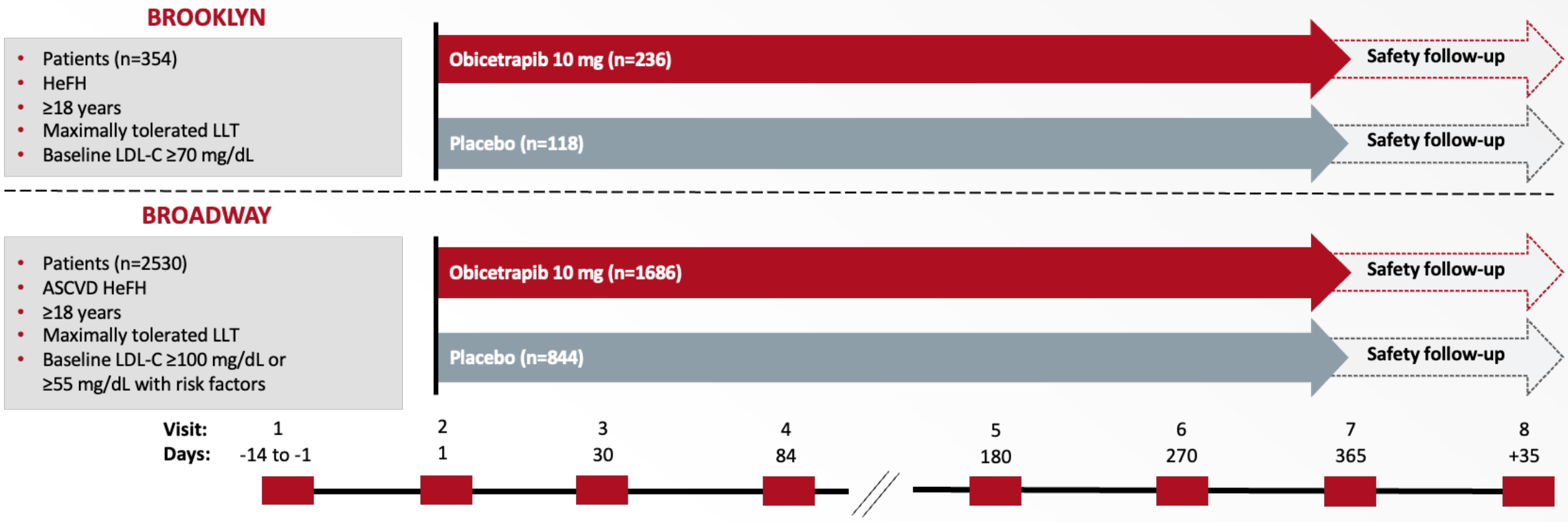
- The effects of obicetrapib on major adverse cardiovascular events (MACE) have not been investigated

Aim of Study

- To investigate the rate of cardiovascular events in patients treated with obicetrapib compared with placebo in a pooled analysis of two large phase 3 lipid lowering trials over 12 months of treatment in high cardiovascular risk cohorts

Phase 3 Clinical Trials of Obicetrapib

Pooled analysis of **BROOKLYN** (NCT05425745) and **BROADWAY** (NCT05142722), phase 3, randomized, double-blind, placebo-controlled trials evaluating the effect of Obicetrapib as an adjunct to maximally tolerated LLT



Statistical Analysis

- A pooled analysis of both clinical trials was performed as they involved administration of obicetrapib or placebo for 12 months
- Potential cardiovascular events were adjudicated by a central committee who were blinded to the treatment status of the patients
- Treatment group compared via proportional hazards modes and post hoc models determined whether treatment effects depended on time since randomization
- Restricted cubic spline models investigated the association between achieved levels of lipids and lipoproteins with the rate of MACE

Clinical Characteristics

Parameter	Placebo (N=962)	Obicetrapib (N=1922)
Age (yrs)	65.0	66.0
Females (%)	35.9	36.3
White race (%)	78.7	76.0
Body mass index (kg/m^2)	28.9	28.7
ASCVD (%)	82.4	82.5
Heterozygous FH (%)	27.0	26.9
Diabetes (%)	37.6	34.9
Hypertension (%)	78.4	76.5
Current smoker (%)	20.5	20.9

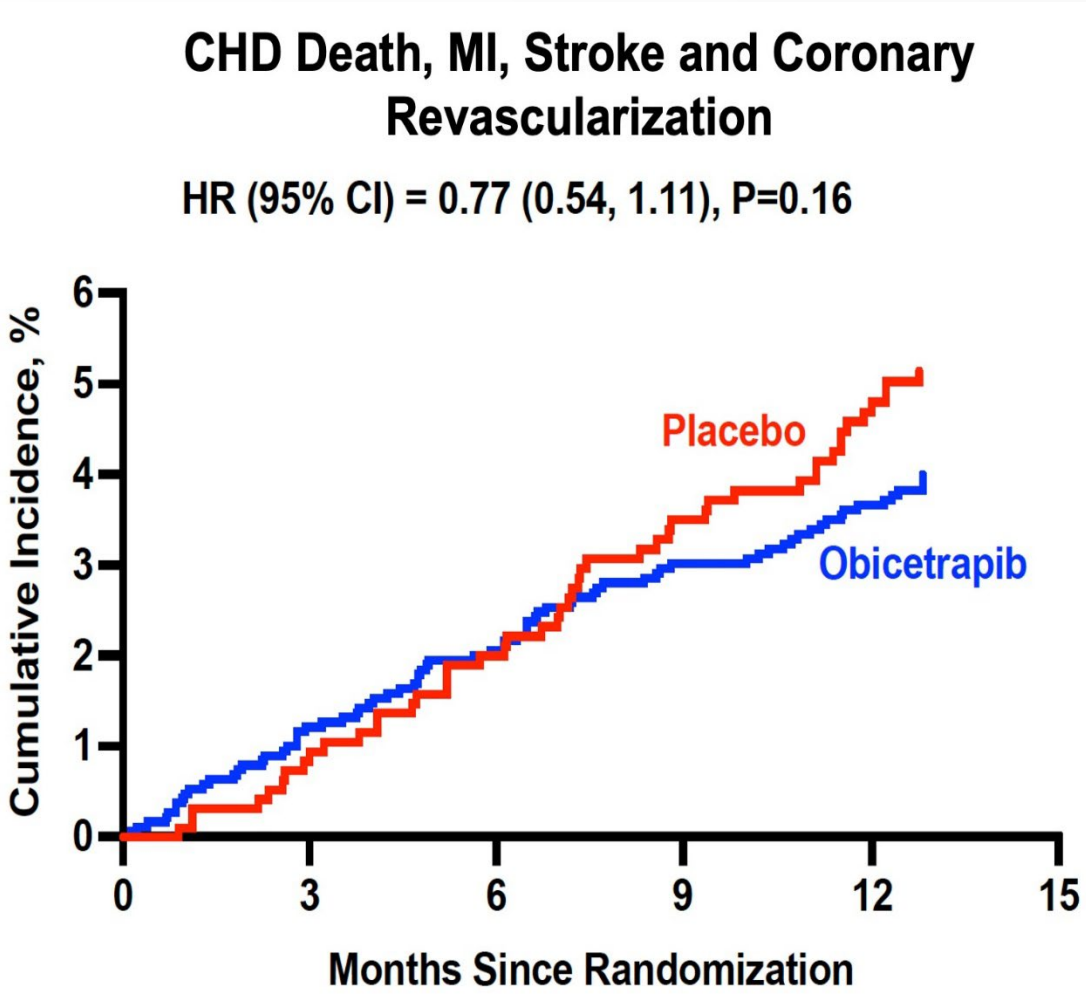
Concomitant Medications and Median Baseline Lipids

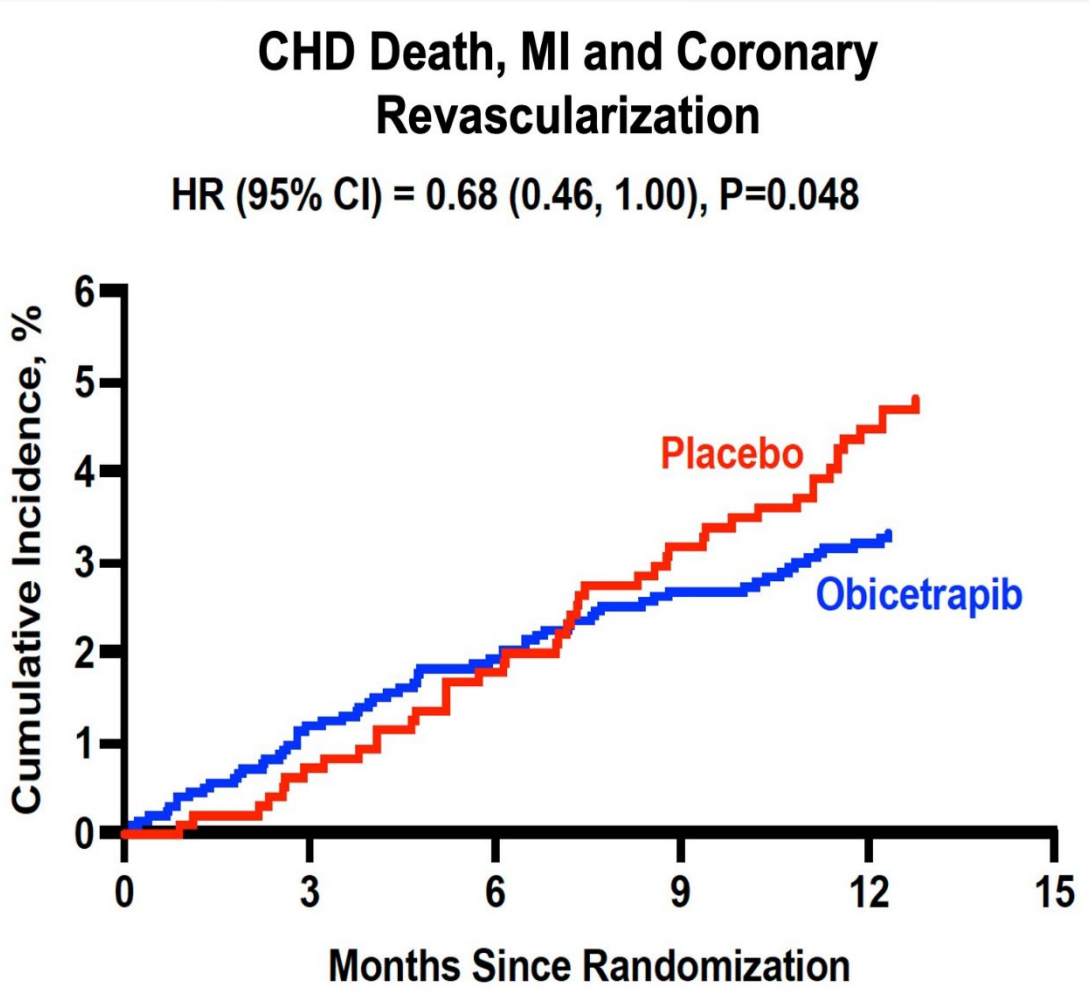
Parameter	Placebo (N=962)	Obicetrapib (N=1922)
Statins (%)	91.6	90.6
High intensity statins (%)	68.7	69.6
Ezetimibe (%)	29.0	30.2
PCSK9 inhibitor (%)	6.1	4.9
LDL cholesterol (mg/dL)	92.0	93.0
HDL cholesterol (mg/dL)	48.0	48.0
Triglycerides (mg/dL)	127.0	122.0
Non-HDL cholesterol (mg/dL)	116.0	116.0
Apolipoprotein B (mg/dL)	88.0	88.0
Lipoprotein(a) (nmol/L)	40.0	40.5

Median Percent Change in Lipids and Lipoproteins

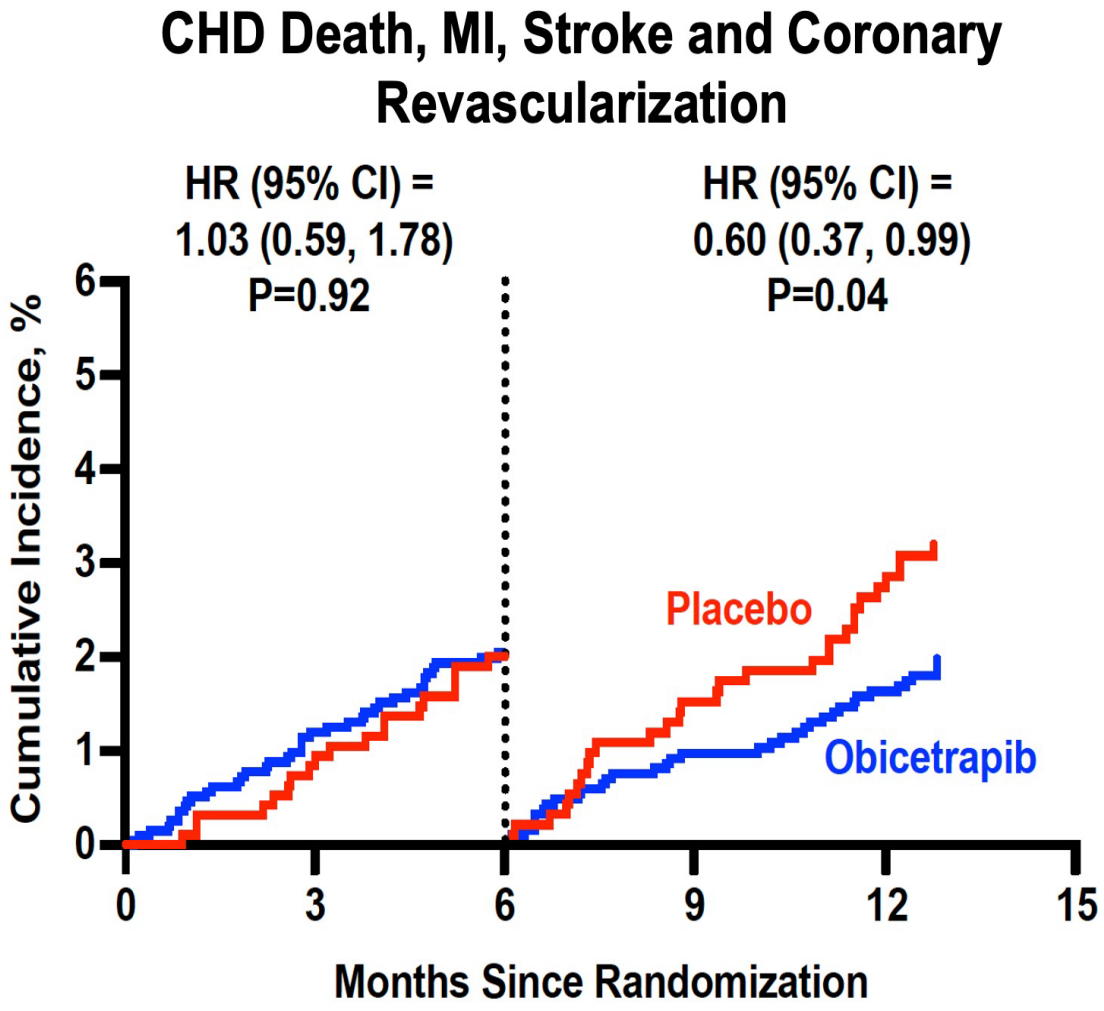
Parameter	Placebo (N=962)	Obicetrapib (N=1922)	P Value
LDL cholesterol (%)	-4.6	-37.8	<0.0001
HDL cholesterol (%)	1.5	140.0	<0.0001
Triglycerides (%)	-2.3	-6.7	0.009
Non-HDL cholesterol (%)	-3.7	-32.4	<0.0001
Apolipoprotein B (%)	-3.6	-21.7	<0.0001
Lipoprotein(a) (%)	0	-32.5	<0.0001

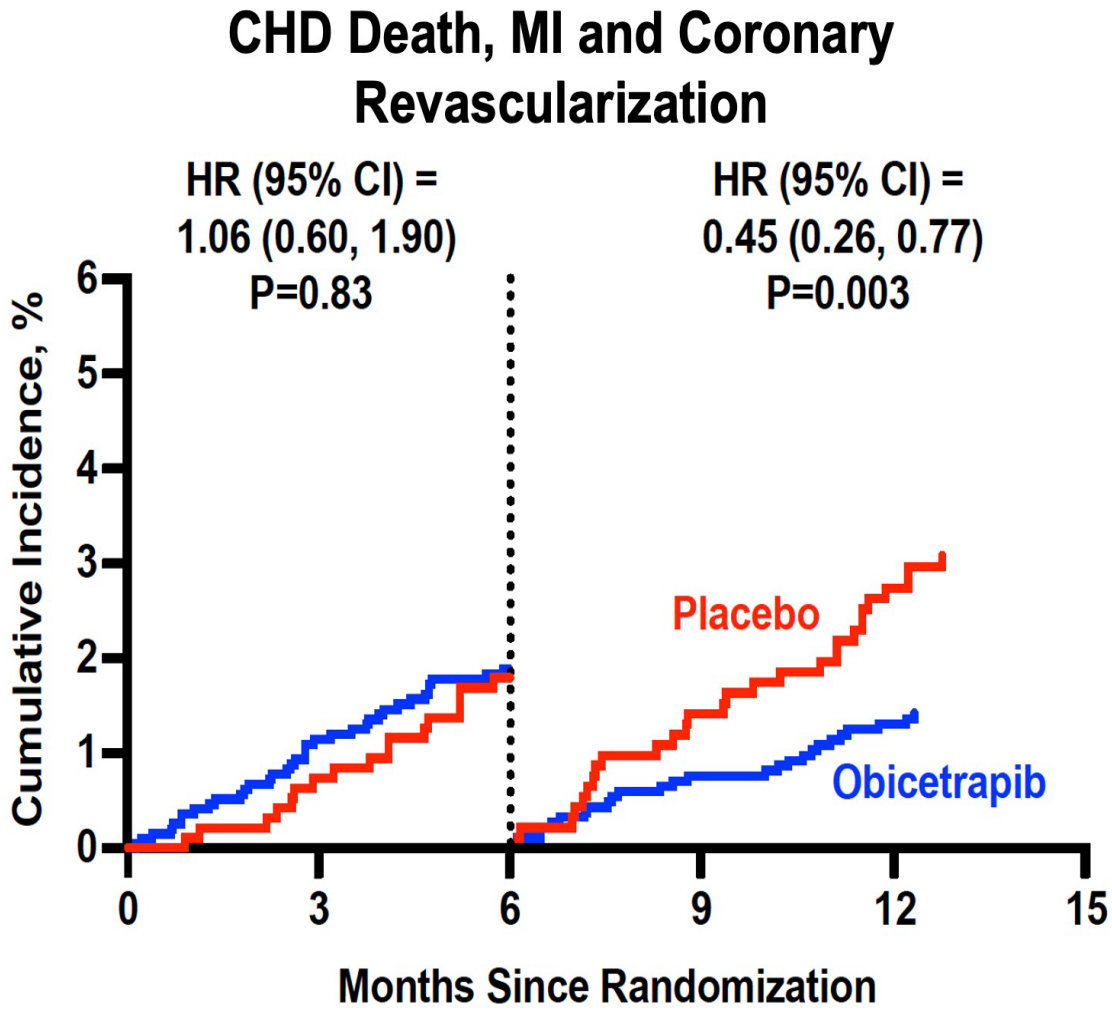
Obicetrapib and Major Adverse Cardiovascular Events



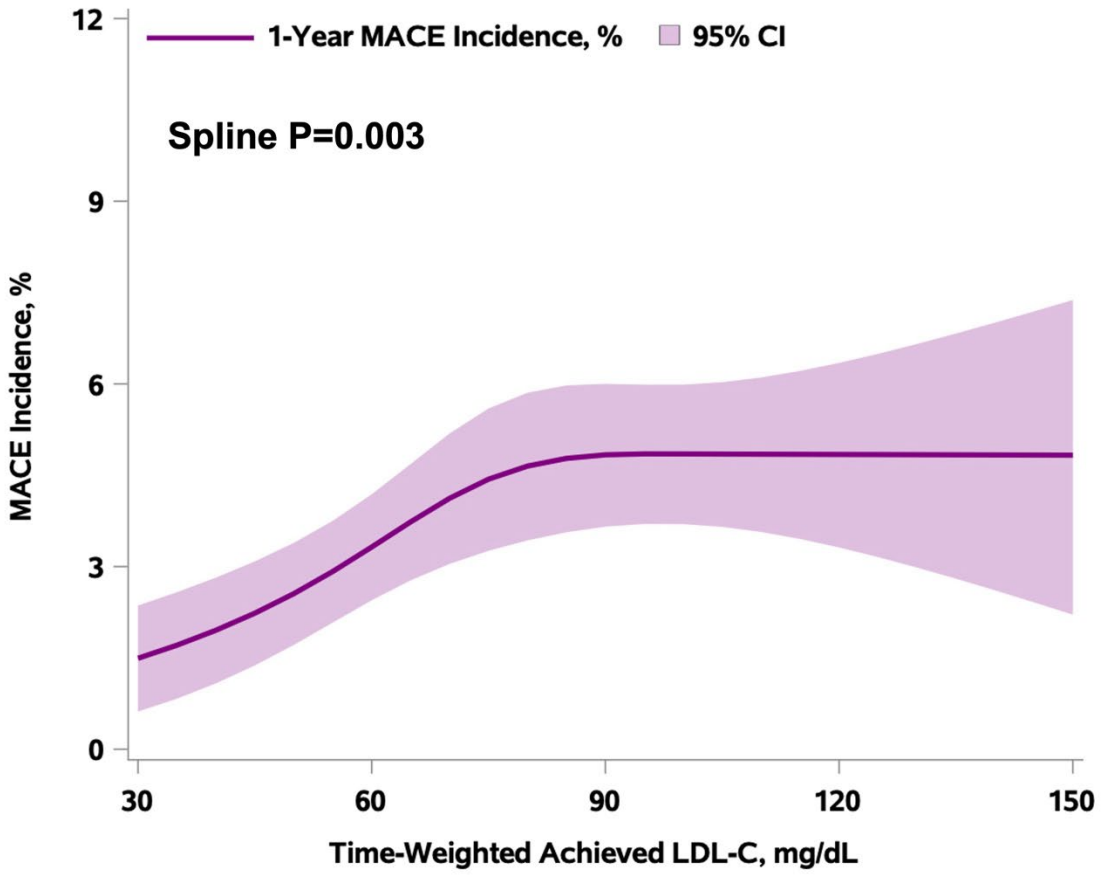


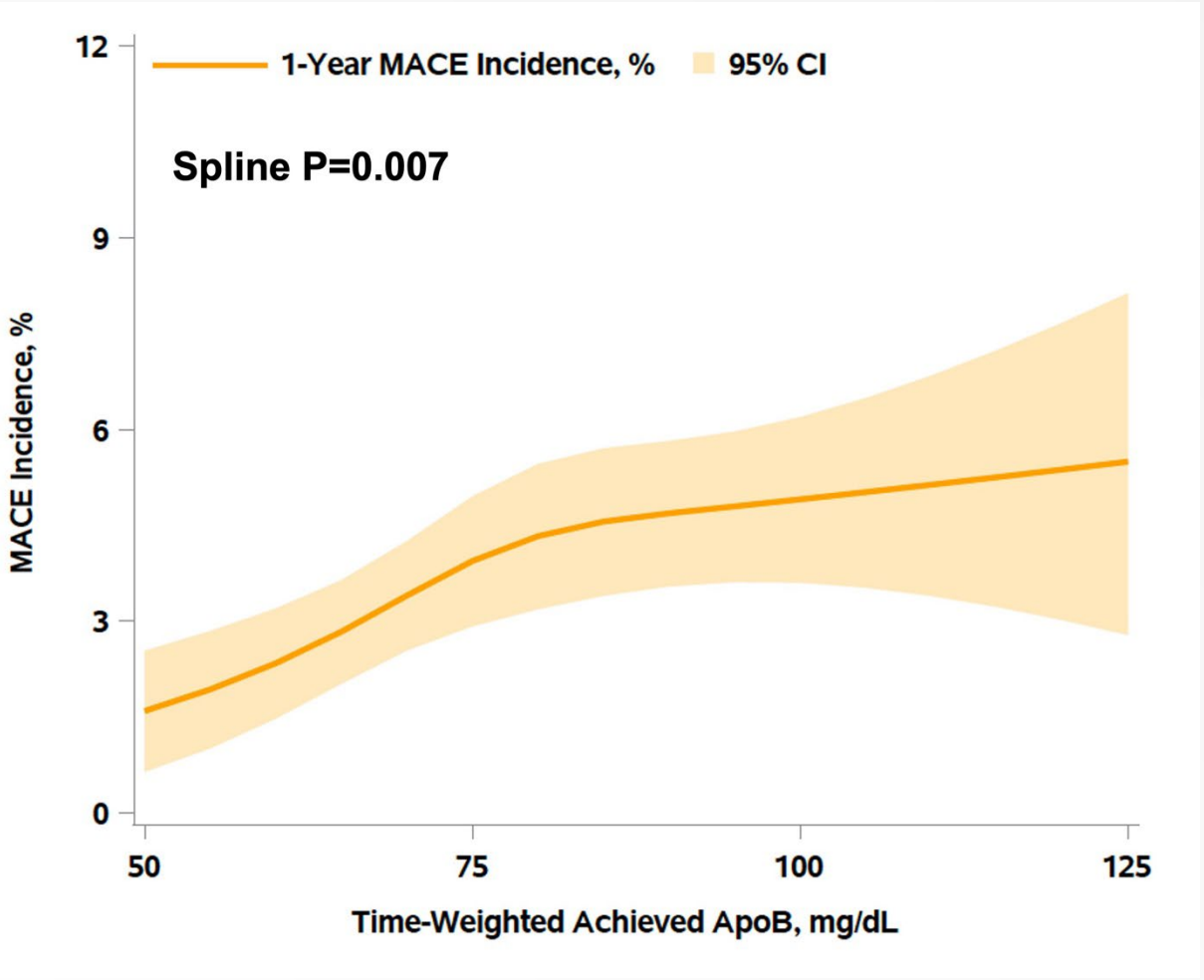
Landmark analysis of study duration



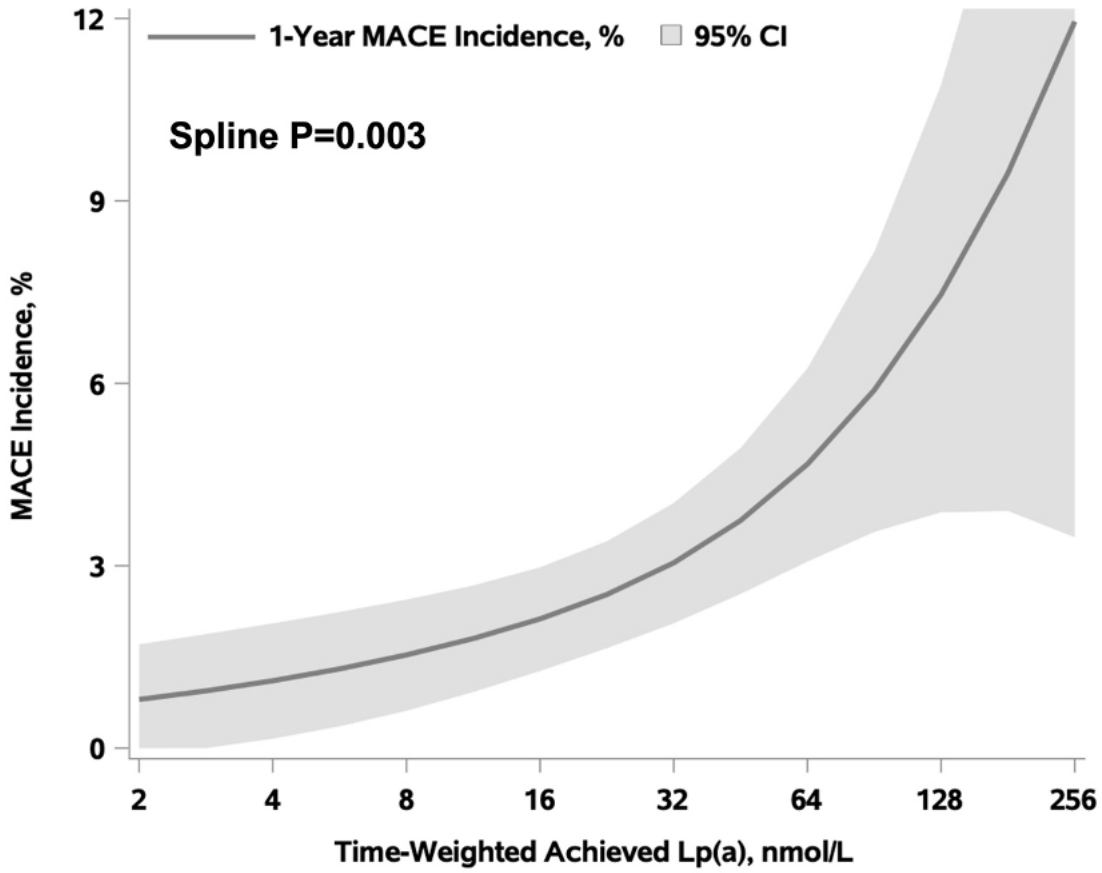


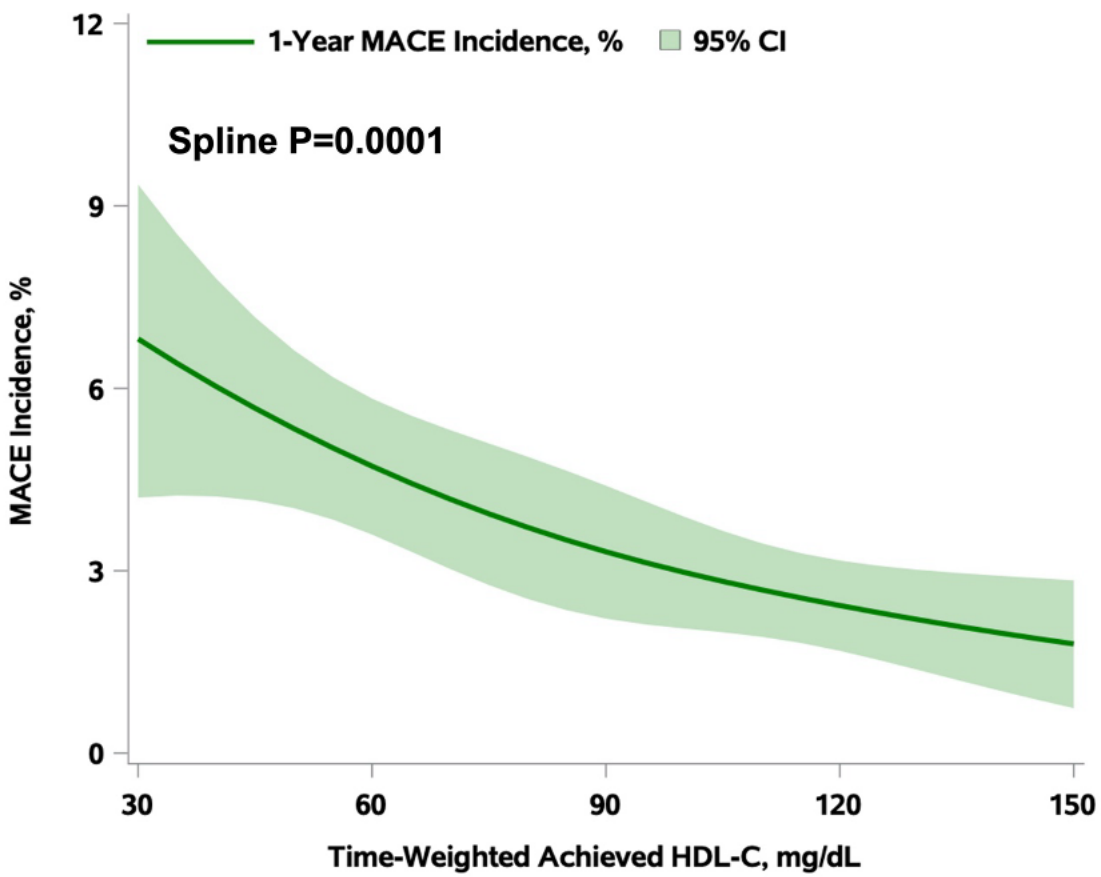
Achieved Levels of LDL-C and ApoB and MACE rates





Achieved Levels of Lp(a) and HDL-C and MACE Rates





Conclusion

- This pooled analysis of phase 3 trials demonstrates a reduction in cardiovascular events with obicetrapib
- Achieved levels of LDL-C, apoB, Lp(a) and HDL-C associate with the ongoing risk of cardiovascular events
- These findings suggest that obicetrapib has the potential to be a useful therapeutic for the prevention of cardiovascular disease
- The ultimate impact of obicetrapib on cardiovascular events is being evaluated in the ongoing PREVAIL trial of 9000 patients