NATURE-Legacy: A Naturally Randomized Trial Comparing the Benefit of Earlier to Later LDL and SBP Lowering among Persons without Cardiovascular Disease

Brian A. Ference, M.D., M.Phil., M.Sc., F.A.C.C., F.E.S.C.

On behalf of:

Brian A Ference, MD, MPhil, MSc; Thatcher B. Ference, BEng; John E. Deanfield, CBE; Kausik K Ray, MD, MPhil, and Stephen J. Nicholls, MD, PhD

ESC Late-Breaking Clinical Science: lipids and cardiovascular risk
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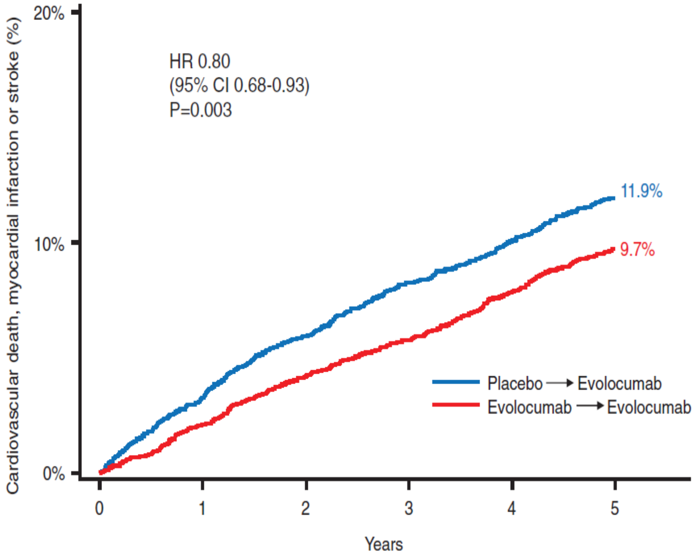
Background and Motivation

- A persistent 'legacy benefit' has been reported for both LDL and SBP lowering therapies in observational follow-up studies of RCTs
- Participants randomized to both LDL & SBP lowering therapies in HOPE-3 had 29% lower risk of MACE, and 15% legacy benefit after the trial
- Mendelian randomization studies demonstrate that lifelong sustained LDL & SBP lowering produces much larger reductions in risk than observed in RCTs – suggesting the benefit of lowering LDL & SBP in HOPE-3 could have been much larger if LDL & SBP lowering started earlier

FOURIER OLE – Legacy Benefit

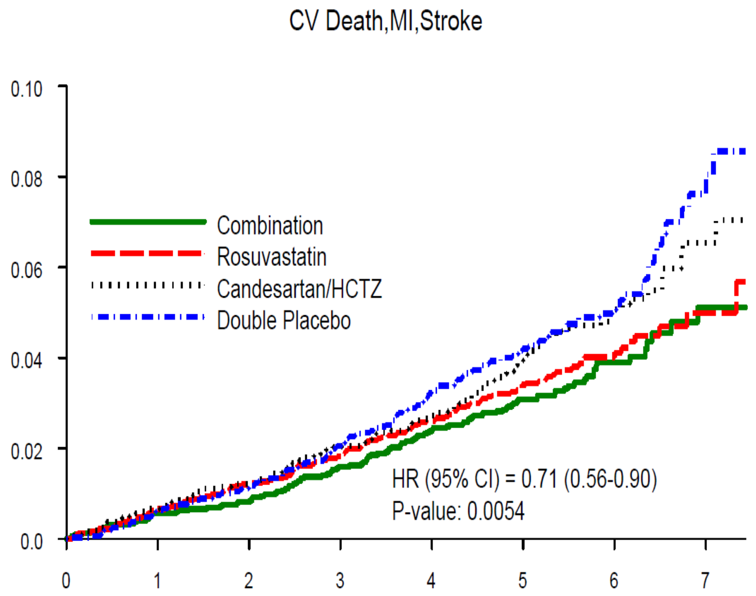
All participants were treated with evolocumab after RCT



O'Donoghue ML, et al. Circulation. 2022;146:1109–1119.

HOPE-3 Trial

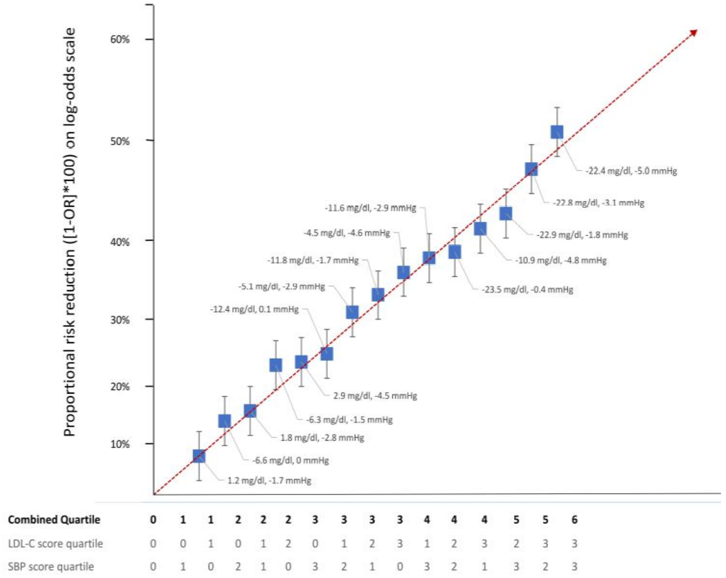
2x2 factorial design



Yusuf S, et al. N Engl J Med 2016;374:2032-43.

Lifelong Lower LDL & SBP

2x2 factorial design – randomized by nature



Ference BA, et al. JAMA 2019; 322(14):1381 1391.

Objectives

- Primary: Quantify the legacy benefit of early compared to later LDL & SBP lowering among persons without cardiovascular disease
  - Relying exclusively on randomized evidence to answer the *counterfactual causal question*: what would have happened if LDL & SBP lowering had started earlier among participants enrolled in the HOPE-3 Trial?
- Secondary: Introduce the Naturally Randomized Target Trial
  - A novel study design that combines evidence from Mendelian randomization & randomized trials into the same study - to directly compare the benefit of earlier and later interventions to slow the progression of common diseases using the same inclusion criteria, primary outcome definition, time zero, analytical methods, and follow-up duration

Study Design

- **Naturally Randomized Target Trial:** protocol outline
  - Identify HOPE-3 as 'target trial' evaluating benefit of lowering both LDL & SBP among persons without cardiovascular disease
  - Screen 440,000 participants enrolled in the UK Biobank to identify participants who:
    - Meet all HOPE-3 inclusion and exclusion criteria
    - Survived to age 65.8 (mean age at enrollment in HOPE-3) without having had a clinical cardiovascular event
  - Create genetic instrumental variable scores for LDL & SBP to produce same magnitude of LDL & SBP lowering as in HOPE-3
    - Use the genetic instrumental variables to partition participants into groups randomized by nature for factorial analyses
  - Estimate the legacy benefit of earlier compared to later LDL & SBP lowering by directly comparing event rate & cumulative event curves over 5.6 years of follow-up (the median duration of follow-up in HOPE-3) among participants who were:
    - Randomized to both LDL & SBP lowering therapies or double placebo beginning at median age of 65.8 in HOPE-3, or
    - Randomized by nature to lifelong exposure to the same magnitude of lower LDL & SBP achieved in HOPE-3, and who survived to age 65.8 without a history of cardiovascular disease) - using age 65.8 as time zero for this group
- **Primary Outcome:** as defined by the first co-primary endpoint in HOPE-3
  - Major Adverse Cardiovascular Events (MACE): Composite of first occurrence of MI, stroke, or cardiovascular death
- **Primary Analysis:** for all comparisons between randomized groups
  - Primary analysis compared *time to first MACE* using proportional hazard models
  - **LEGACY BENEFIT** was defined as the *difference in residual risk of MACE* among participant randomized to early or later LDL & SBP lowering expressed as a Legacy Benefit Hazard Ratio (HR; 95% CI))

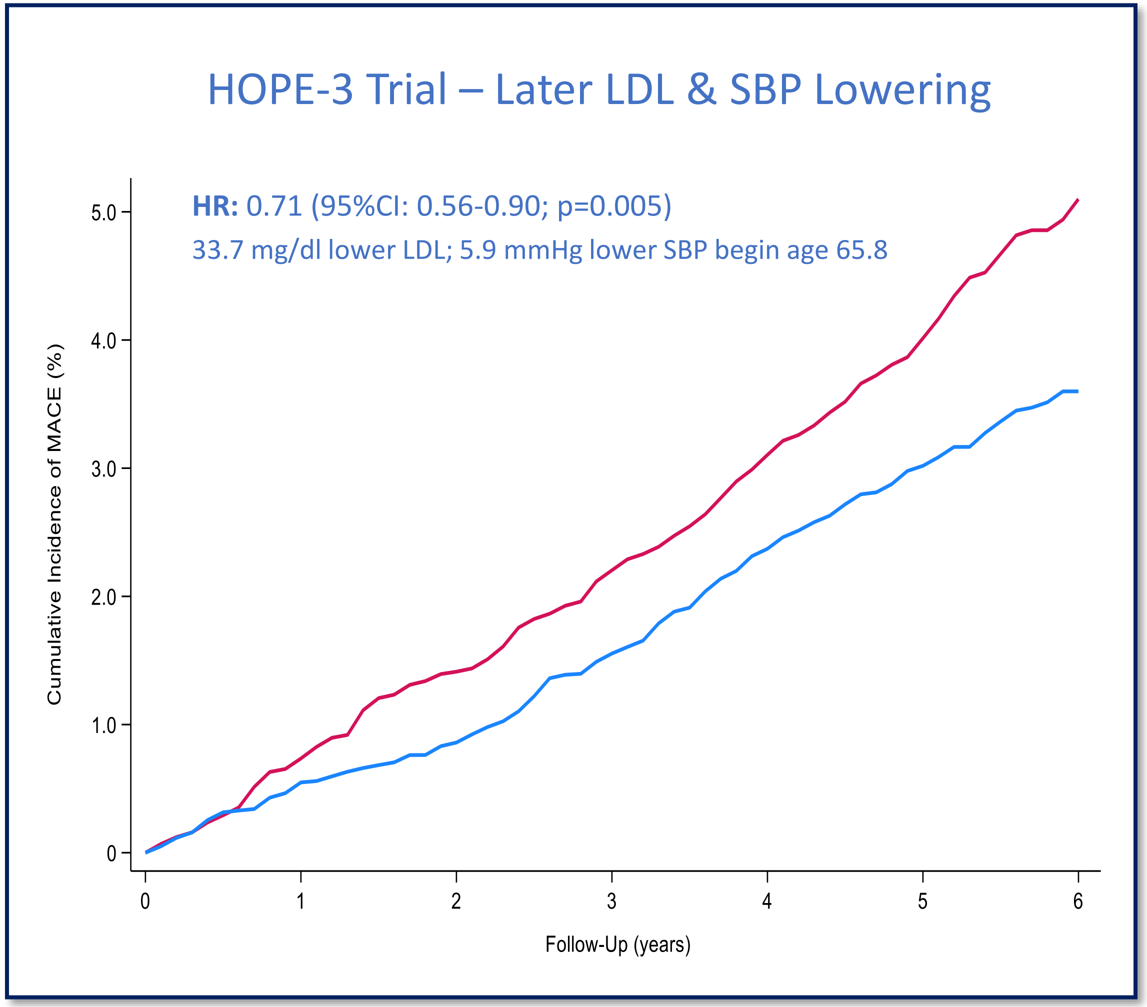
Baseline Characteristics

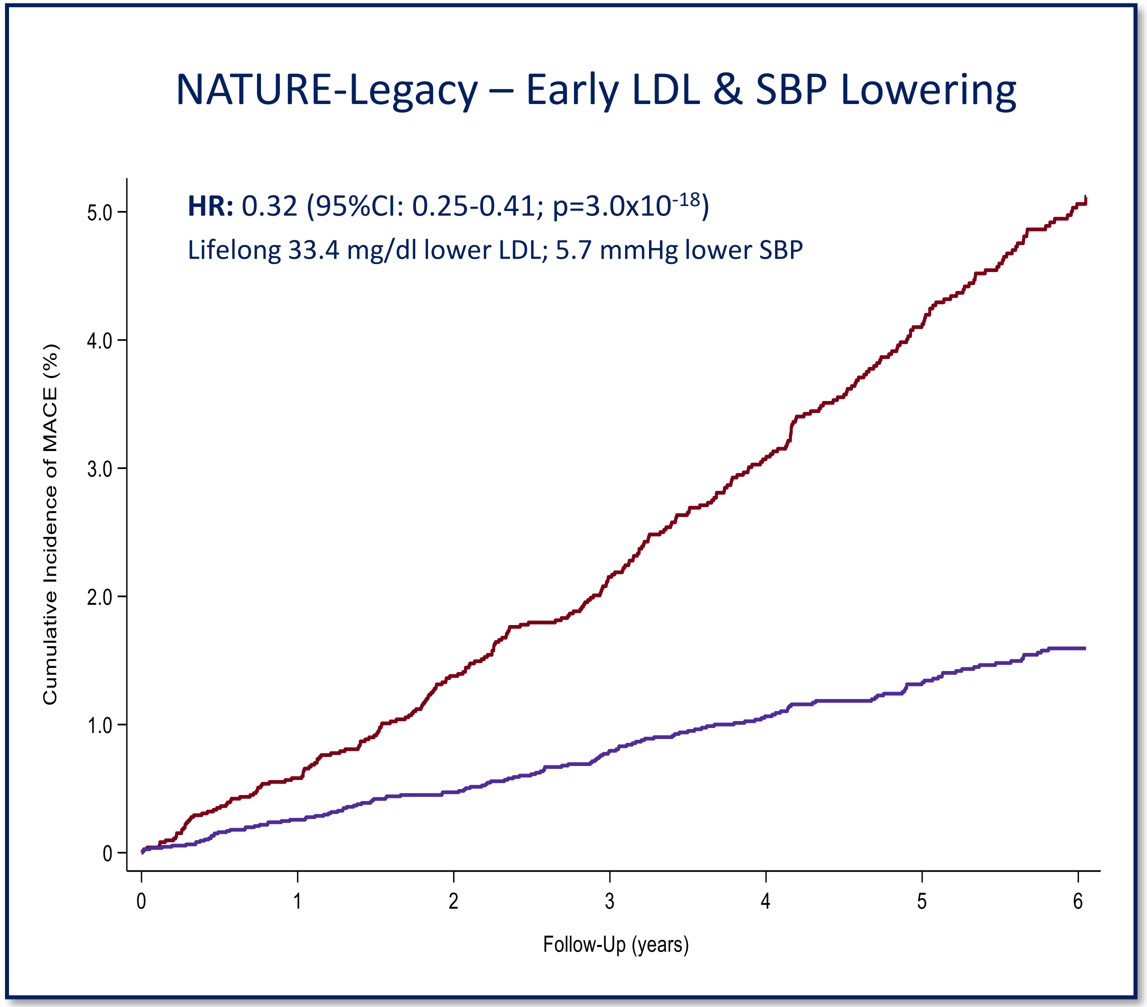
- Of 12,705 participants in HOPE-3: 3168 were randomized to placebo & 3180 to both LDL & SBP lowering therapies - 270 had a first MACE
- Of 208,990 UK Biobank participants who met all HOPE-3 inclusion criteria: 130,370 survived to age 65.8 years without a history of cardiovascular disease and were included in this study - 4,551 experienced a first MACE during the 5.6 years of follow-up after age 65.8

Baseline Characteristic	HOPE-3 Participants	HOPE-3 Eligible Participants
No. Participants	6,348	130,370
Median age at beginning of study (y)	65.8	65.8
Female Sex (%)	*46.2*	*20.2*
BMI (kg/m2)	27.1	28.2
WHR	0.94	0.94
Median fasting glucose - mg/dl	95.4	90.3
Early diabetes mellitus (%)	5.8	5.1
Median C-reactive protein (mg/L)	2.0	1.6
HDL-C (mmol/L)	1.2	1.3
LDL-C (mmol/L)	3.3	3.5
Non-HDL-C (mmol/L)	4.1	4.2
apoB (mg/dL)	102.9	103.0
SBP (mmHg)	138	143
Treatment for Hypertension (%)	37.9	32.2
European ancestry (%)	*20.0*	*100*
Current Smoker (%)	*27.7*	*9.7*

Reduction in MACE for earlier compared to later LDL and SBP lowering

- In HOPE-3, treatment led to 33.7 mg/dl lower LDL and 5.9 mmHg lower SBP; and a 29% lower rate of MACE over 5.6 years of follow-up
- Participants randomized by nature to lifelong exposure to the same reduction in LDL & SBP had a 68% lower rate of MACE over 5.6 years of follow-up after age 65.8 – a 3.3-fold greater reduction in MACE (on log scale) for the same LDL & SBP reduction

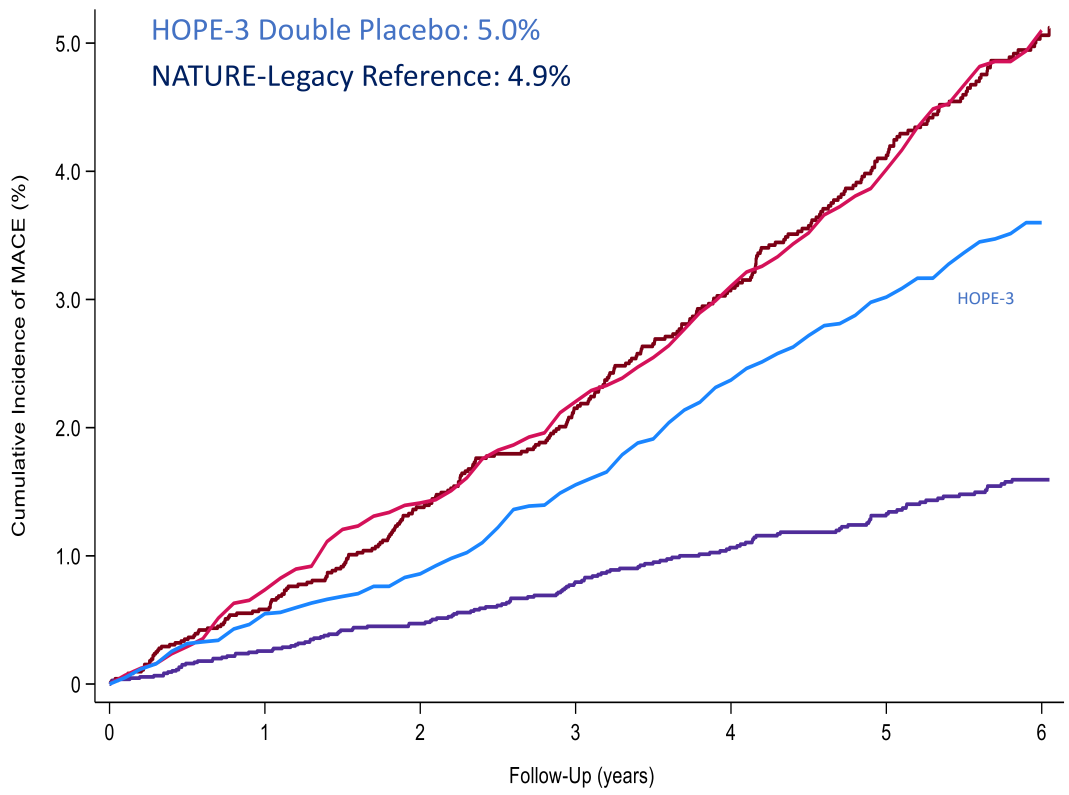




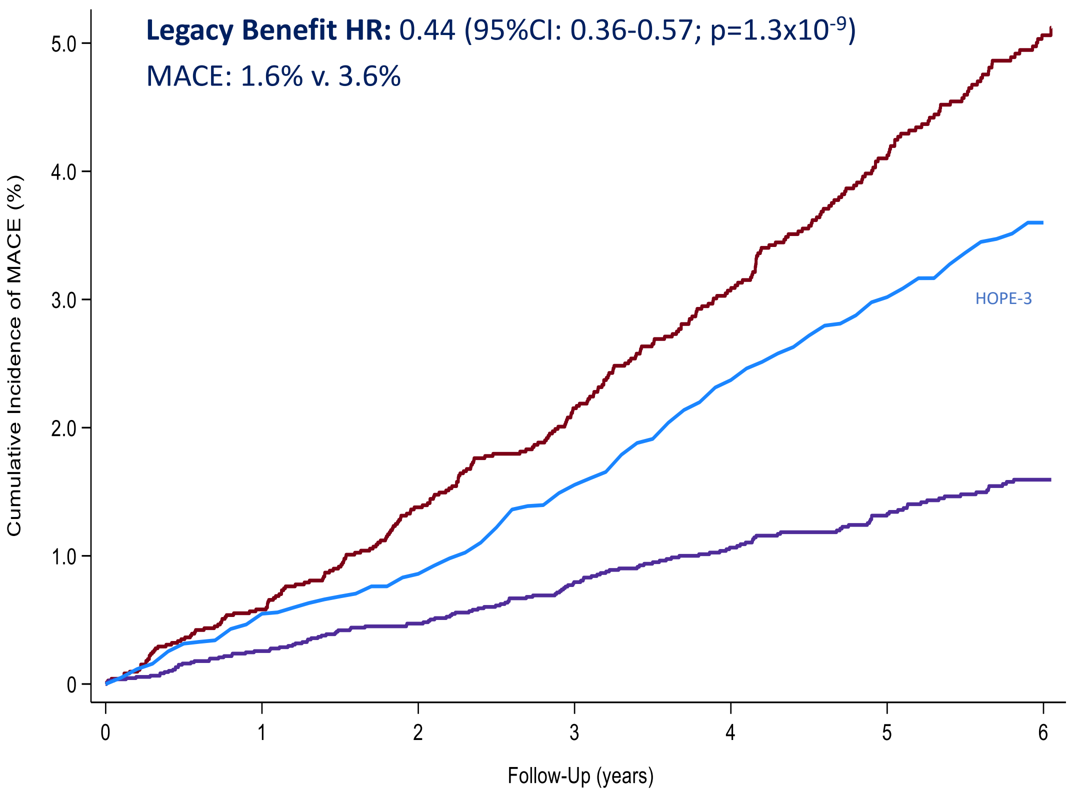
Legacy benefit of earlier compared to later LDL and SBP lowering

- MACE rates among participants randomized to placebo in HOPE-3 and the reference group by nature were very similar (5.0% v. 4.9%), permitting estimation of legacy benefit by directly comparing residual risk among participants randomized to early and later LDL & SBP lowering
- Participants randomized by nature to lifelong lower LDL & SBP ***had a 56% lower residual risk of MACE*** compared to participants randomized to the same magnitude of LDL & SBP lowering beginning at age 65.8 in HOPE-3

MACE Rates in Placebo & Reference Groups



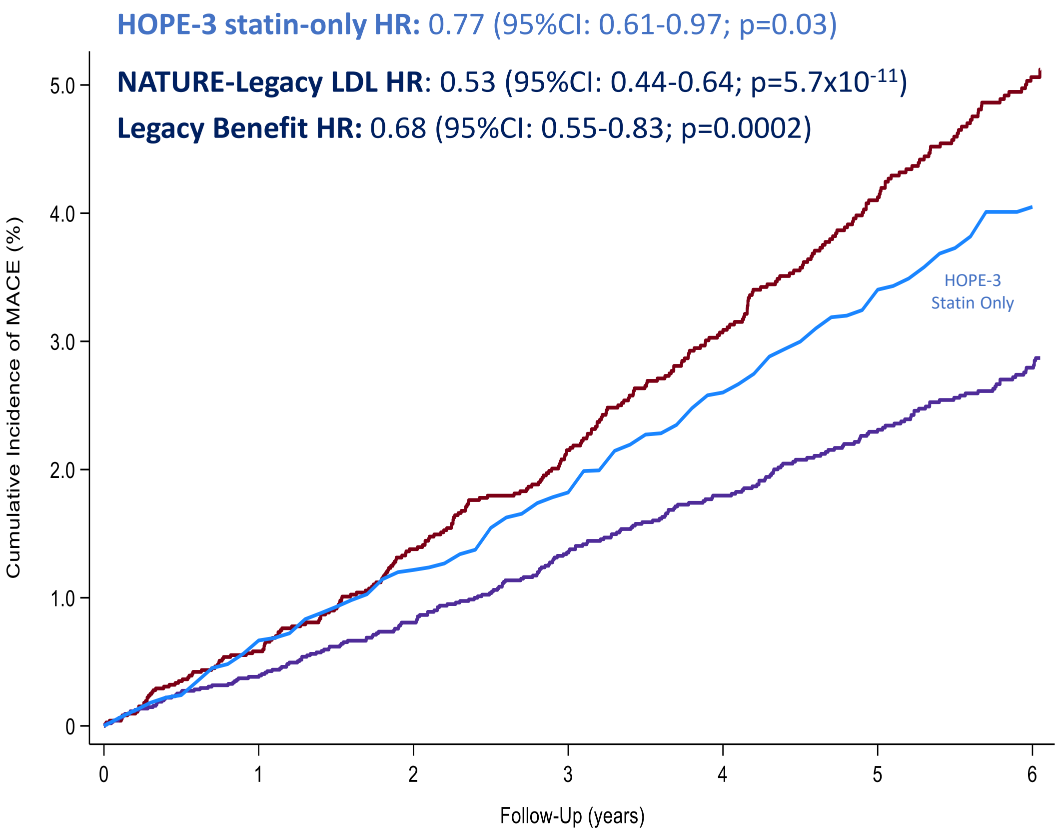
Legacy Benefit of Early LDL & SBP Lowering



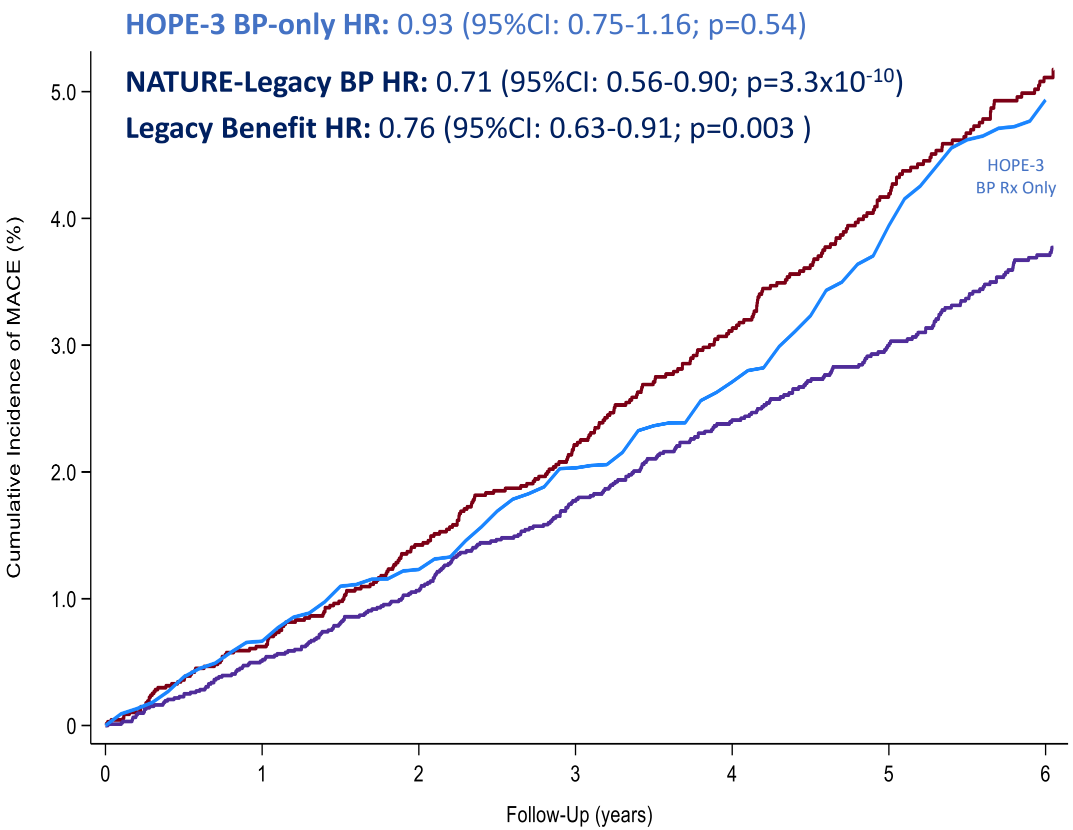
Independent & additive legacy benefit of earlier LDL and SBP lowering

- Both early LDL lowering and early SBP lowering were associated with large legacy benefits that were independent and additive
- The legacy benefit of lifelong lower LDL (32%) and the legacy benefit from lifelong lower SBP (24%) summed to the legacy benefit for lifelong exposure to the combination of both lower LDL & SBP (56%)

Legacy Benefit of Early LDL Lowering



Legacy Benefit of Early SBP Lowering



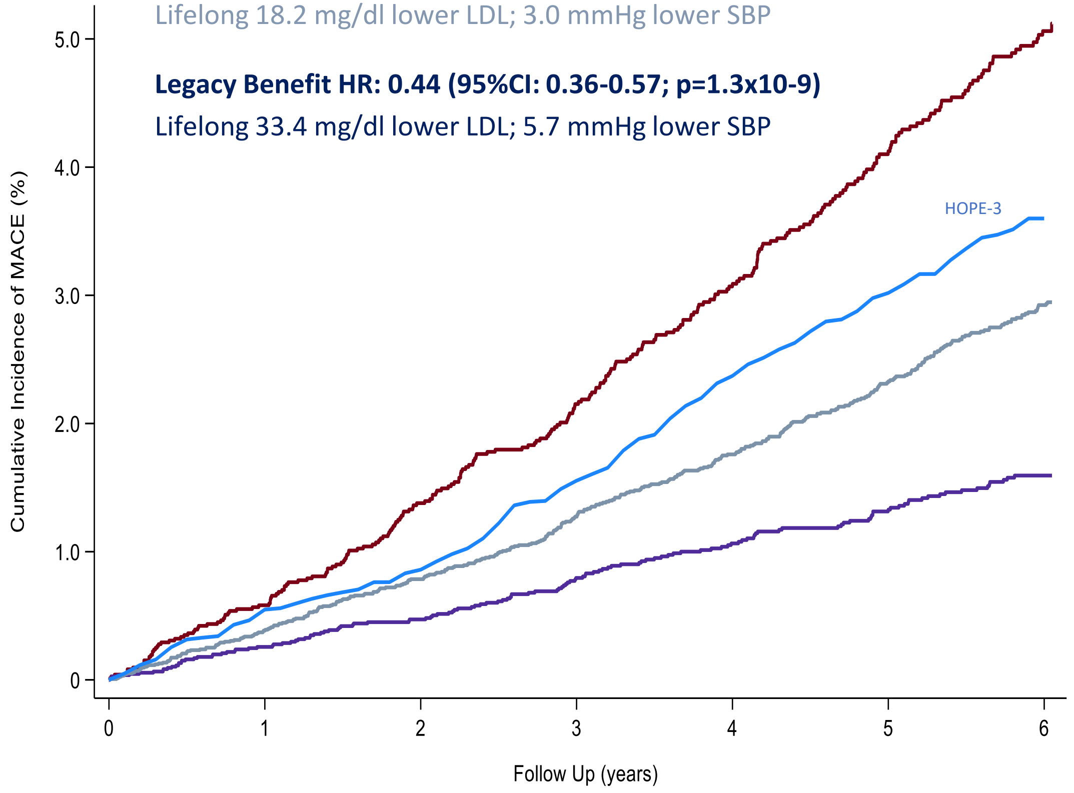
Dose Response for legacy benefit of earlier LDL and SBP lowering

- Lifelong exposure to just 11 mg/dL lower LDL and 2.5 mmHg lower SBP resulted in similar reduction in MACE (31% v. 29%) and similar residual risk (3.4 v. 3.6%) as lowering LDL by 33.7 mg/dl and SBP by 5.9 mmHg starting at age 65.8 years in HOPE-3
- Modest early sustained LDL & SBP lowering can produce large legacy benefits that reduce residual risk of MACE as effectively as much larger reductions in LDL & SBP started later in life

Legacy Benefit Dose Response

Legacy Benefit HR: 0.71 (95%CI: 0.58-0.82; p=0.0001)
Lifelong 18.2 mg/dl lower LDL; 3.0 mmHg lower SBP

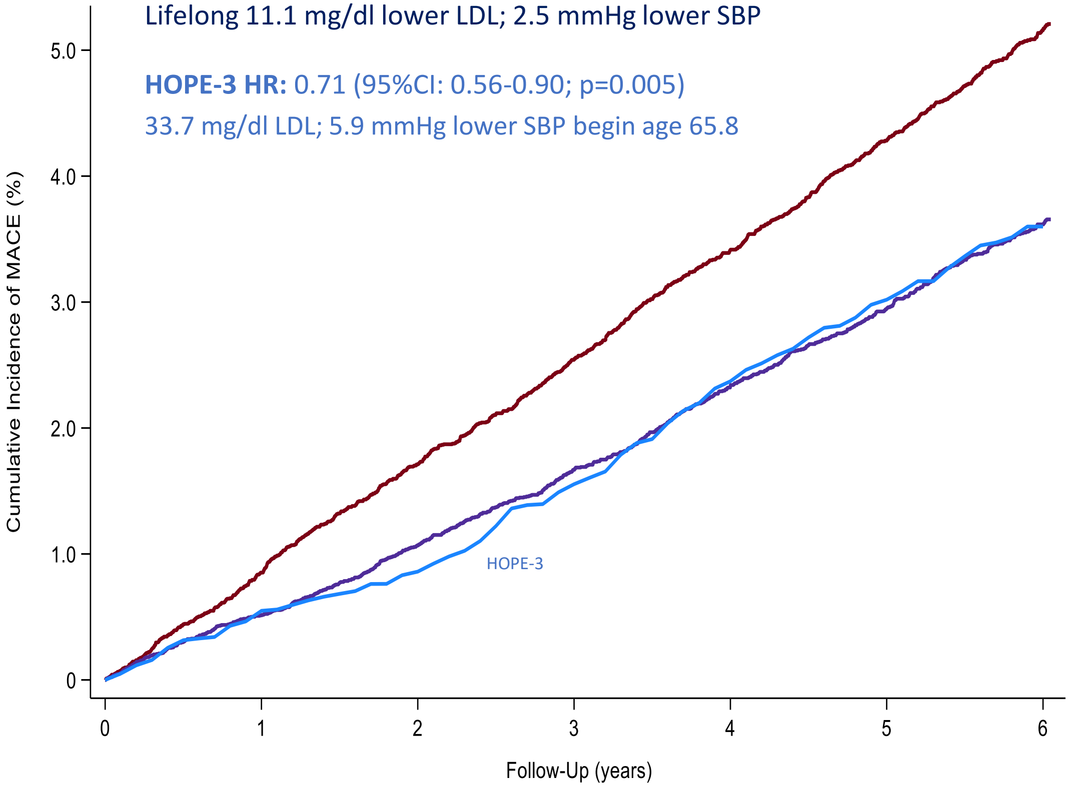
Legacy Benefit HR: 0.44 (95%CI: 0.36-0.57; p=1.3x10-9)
Lifelong 33.4 mg/dl lower LDL; 5.7 mmHg lower SBP



Legacy Benefit of Modest Early LDL & SBP lowering

NATURE-Legacy HR: 0.69 (95%CI: 0.63-0.76; $p=4.5x10^{-15}$)
Lifelong 11.1 mg/dl lower LDL; 2.5 mmHg lower SBP

HOPE-3 HR: 0.71 (95%CI: 0.56-0.90; p=0.005)
33.7 mg/dl LDL; 5.9 mmHg lower SBP begin age 65.8



Conclusions

- Early LDL & SBP lowering is associated with a large, dose-dependent legacy benefit:
  - Large legacy benefit provides a powerful rationale for early intervention to slow disease progression - because a large legacy benefit would not be possible unless early sustained LDL & SBP lowering prevents cardiovascular events by slowing the progression of atherosclerotic cardiovascular disease
  - Therefore, the duration of LDL & SBP lowering may be more important than the magnitude of LDL & SBP lowering
- Large legacy benefit from earlier compared to later LDL & SBP refines our understanding of residual risk:
  - Residual risk is not the result of medication failure or undiscovered causes of cardiovascular events
  - Instead, residual risk appears to be largely determined by the amount of atherosclerotic plaque and arterial wall injury that accumulates before LDL or SBP lowering is started
  - Therefore, the legacy benefit from early sustained LDL and SBP lowering to slow the progression of atherosclerosis and arterial wall injury may be the most effective way to reduce residual risk
- Directly refutes commonly held assumption that the benefit of lowering LDL & SBP is constant over time
  - Large legacy benefit would not be possible if the benefit of lowering LDL & SBP was constant over time and determined only by the amount of LDL & SBP Lowering and not the duration of lowering
  - Current Guidelines and economic models do not consider legacy benefit & therefore substantially underestimate both the clinical and economic benefit of early sustained LDL & SBP lowering to slow disease progression

One more thought …

- This study can serve as an exemplar for how to achieve the U.S. FDA's objective of combining advanced causal reasoning methods with the results of randomized trials to generate evidence for regulatory approval
- The Naturally Randomized Target Trial study design introduces a causally robust experimental framework relying exclusively on randomized evidence to directly compare the benefit of earlier and later interventions which cannot be easily captured in a short-term randomized trial.
- As a result, this study design could set a precedent for how to combine evidence from Mendelian randomization with the results of randomized trials to help close the evidence gap that has long delayed innovation in how we prevent atherosclerotic cardiovascular events

Thank You