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Evolocumab in Patients without Known Atherosclerosis and with Diabetes:

Secondary Analysis from VESALIUS-CV

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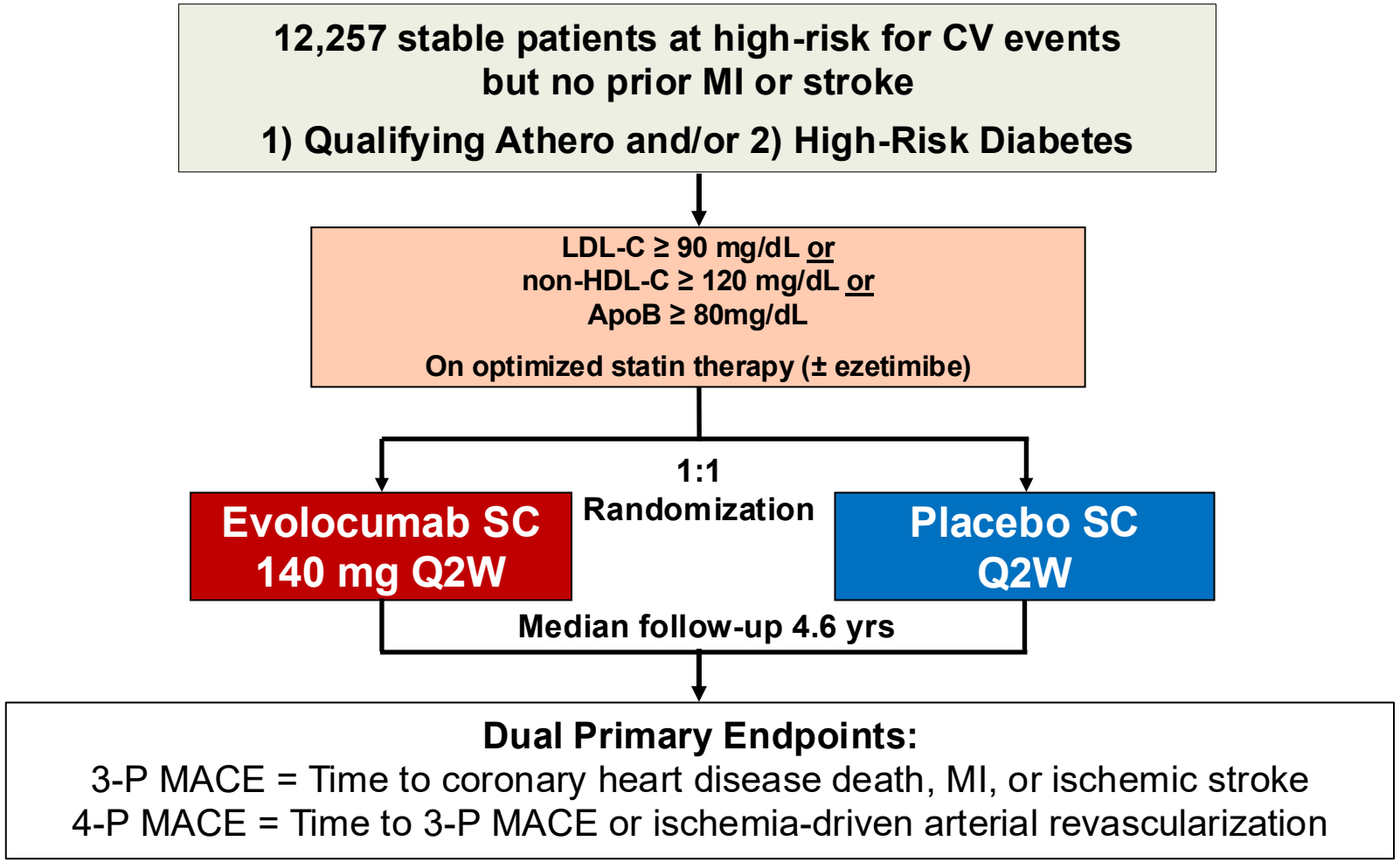
Vesalius-CV

Trial Design



Bohula EA, et al. *Am Heart J.* 2024;269:179-190.

No Known Significant Atherosclerosis Subgroup

- N = 3,655 patients (30% of VESALIUS-CV)

- No known significant atherosclerosis, defined as:
  - No prior arterial revascularization,
  - No known arterial stenosis ≥50%, and
  - No known coronary artery calcium (CAC) score ≥100 Agatston units

- Per protocol, all had high-risk diabetes defined as
  - ≥10 years duration, daily insulin use, or microvascular disease

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Baseline Characteristics

Demographics	N=3,655
Age (years)	65 [60, 70]
Female	57%
White	93%
Hispanic	23%

Co-morbidities	
High-risk diabetes	99.5%
BMI	31 [28-36]
Hypertension	88%
Current smoking	28%

Lipid-lowering therapy (LLT)	
Any LLT	89%
High-intensity LLT regimen	68%
Any statin	84%
High-intensity statin	64%
Ezetimibe	14%

Lipid Values (mg/dL)	
LDL-C	132 [108-156]
Non-HDL-C	163 [138-192]
Apolipoprotein B	110 [94-131]

Pooled data; no difference between treatment arms

% or median and interquartile range

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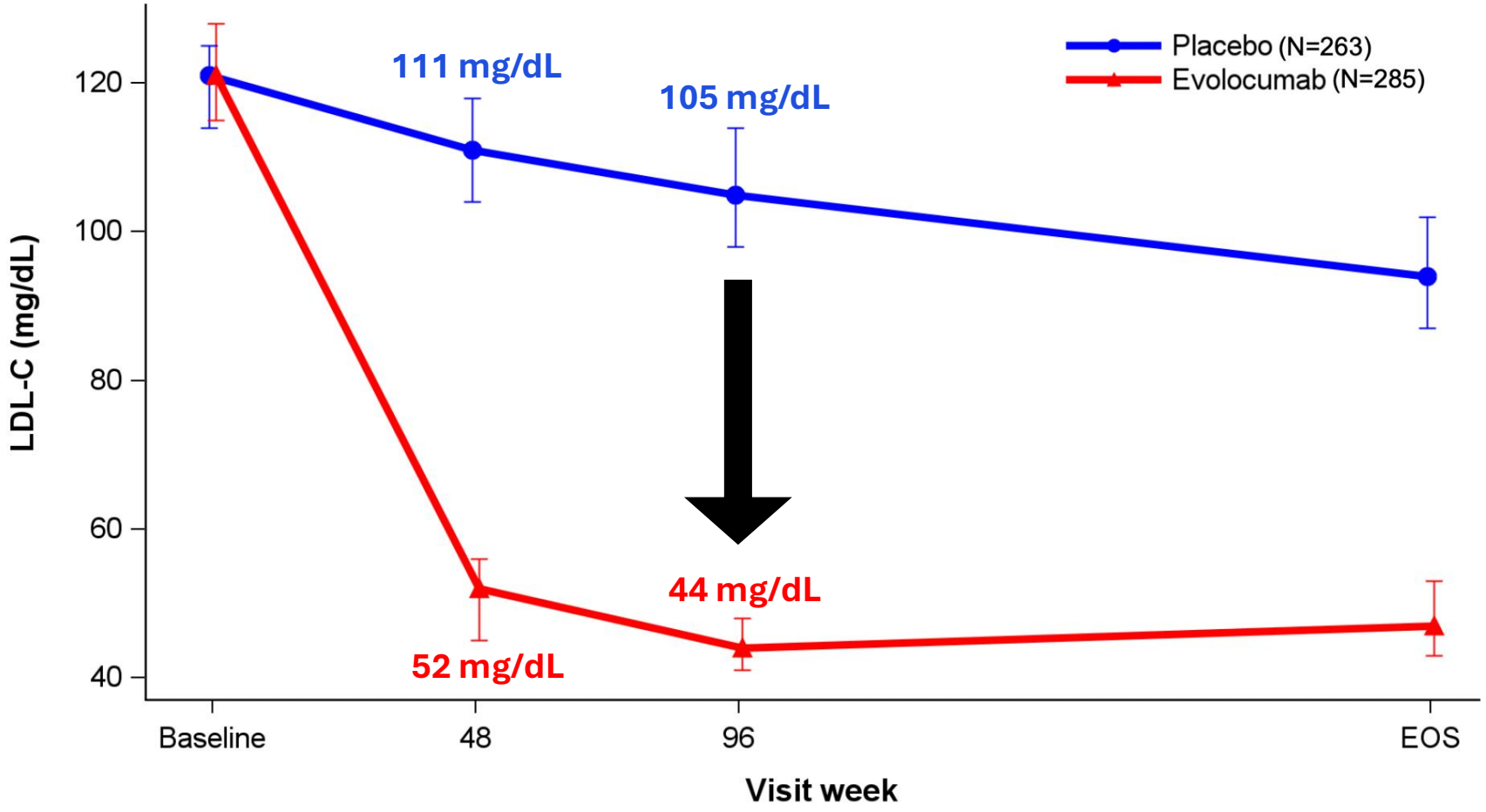
Effect of Evolocumab on LDL-C in Lipid Substudy



N=548 in the Lipid Substudy
Values presented as Medians

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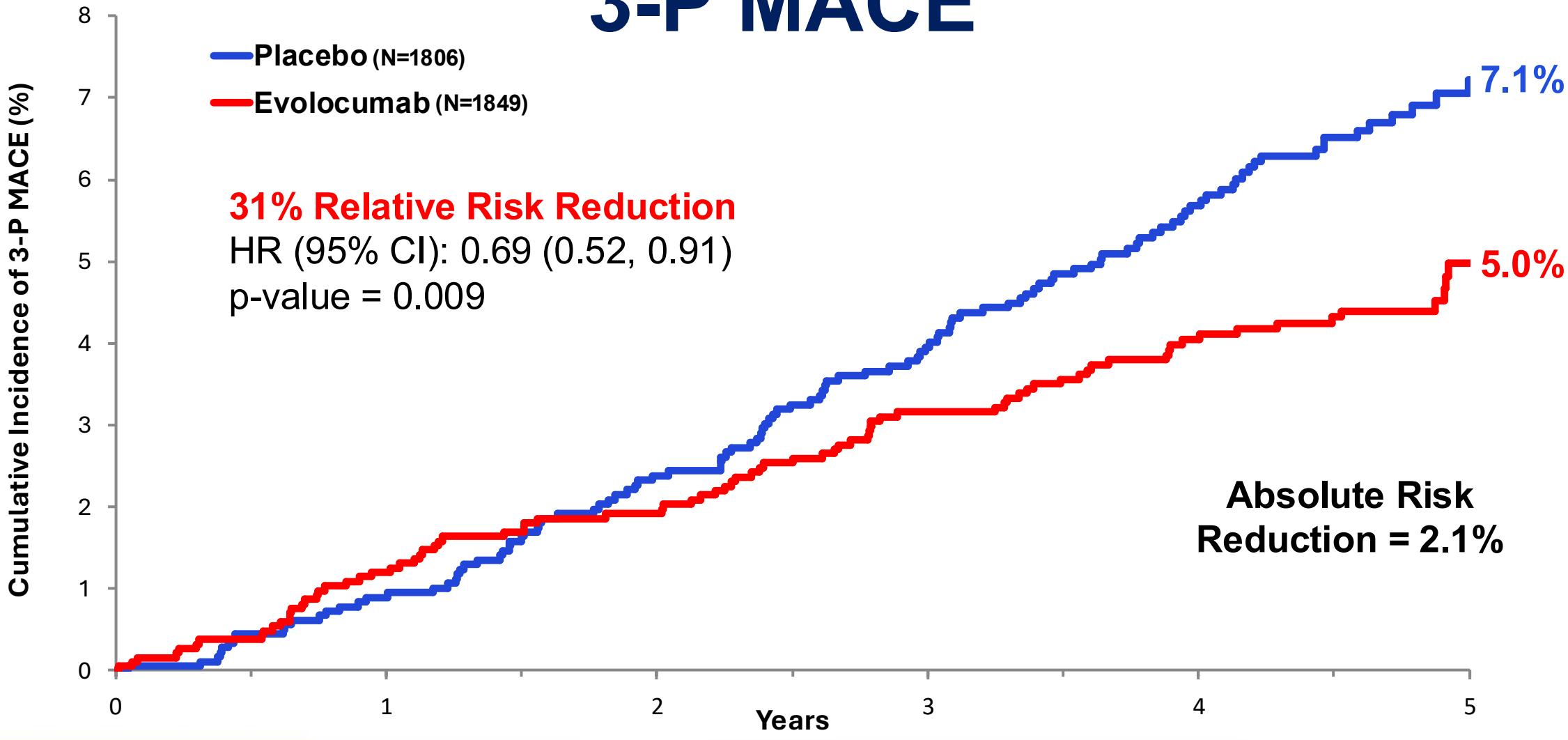
Dual Primary Endpoints: 3-P MACE



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3-P MACE = coronary heart death, MI, or ischemic stroke
Absolute Risk Reduction (ARR) assessed at 5 years

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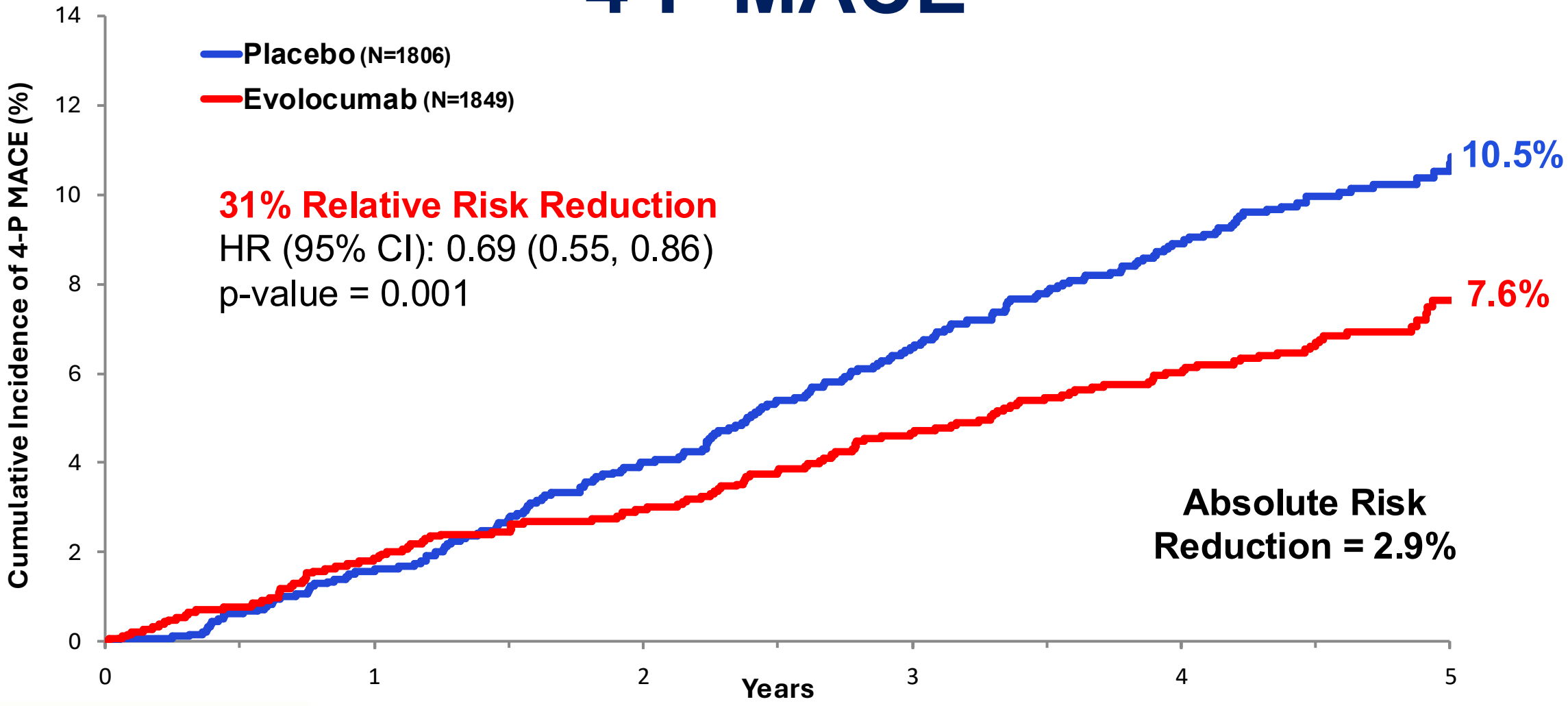
Dual Primary Endpoints: 4-P MACE



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4-P MACE = coronary heart death, MI, ischemic stroke, or IDR
IDR, ischemia-driven revascularization
Absolute Risk Reduction (ARR) assessed at 5 years

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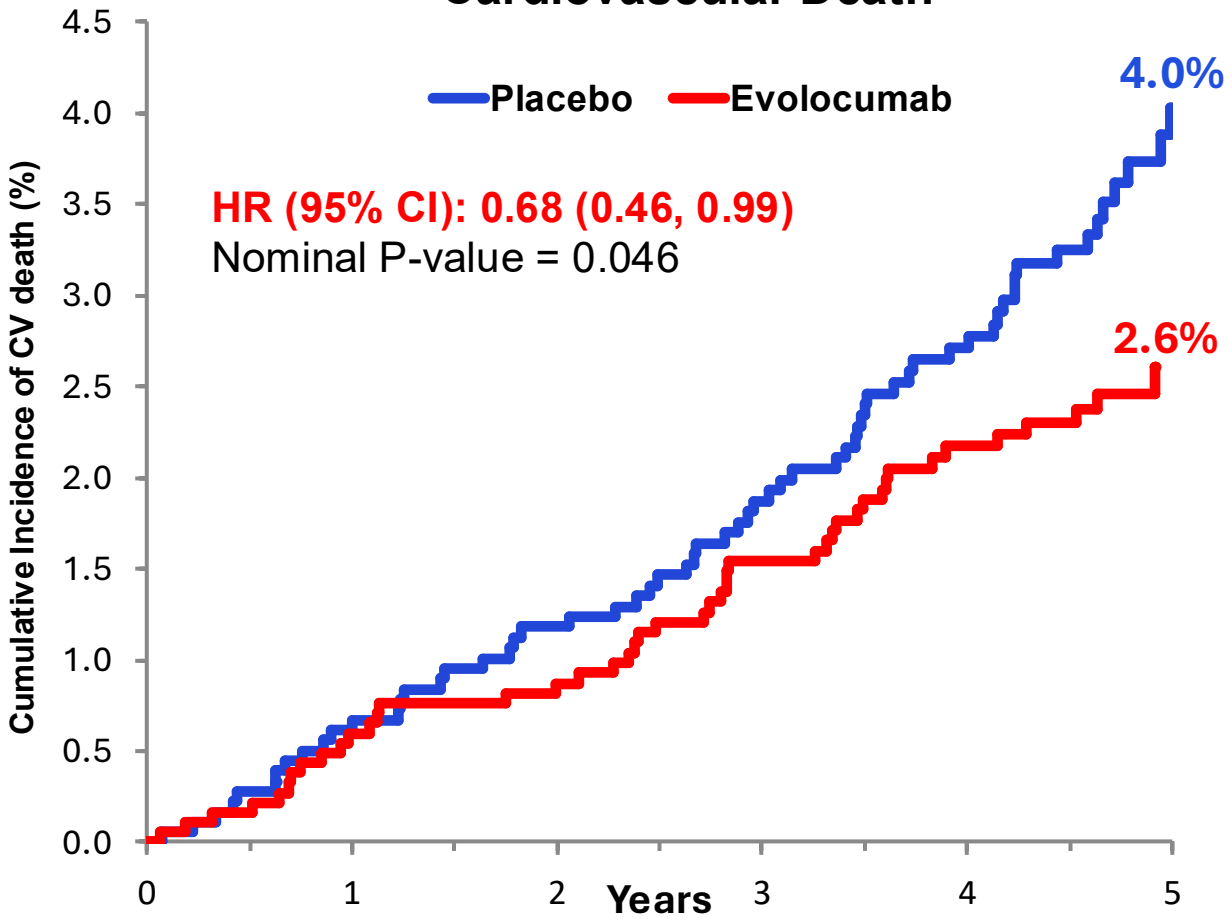
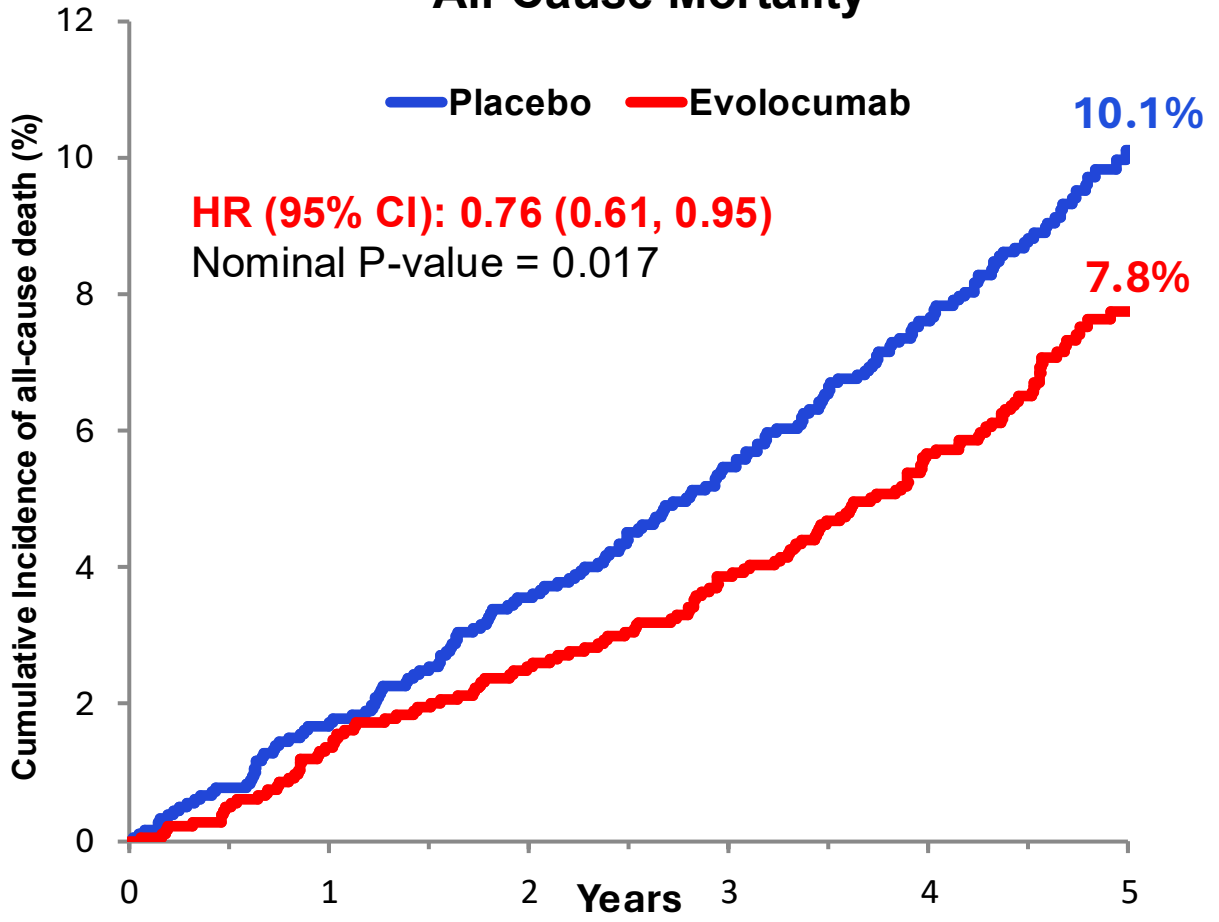
Mortality

Cardiovascular Death



All-Cause Mortality



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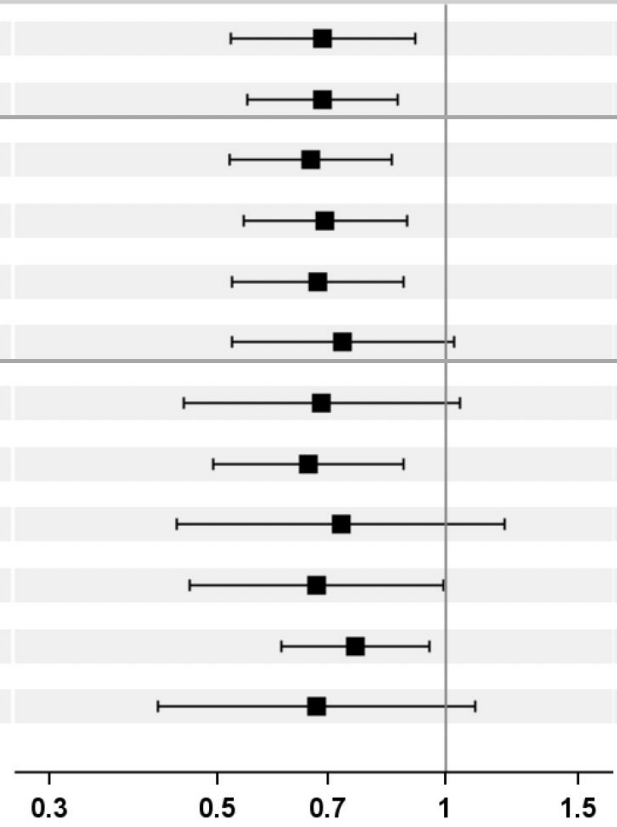
Secondary Endpoints

	Endpoint	n (%) Evolocumab	Placebo	HR (95% CI)
Dual-Primary Endpoints	3-P MACE	83 (4.5)	117 (6.5)	0.69 (0.52, 0.91)
	4-P MACE	127 (6.9)	178 (9.9)	0.69 (0.55, 0.86)
Secondary Composite Endpoints	MI/ Ischemic stroke/ IDR	106 (5.7)	154 (8.5)	0.66 (0.52, 0.85)
	CHD death/ MI/ IDR	106 (5.7)	148 (8.2)	0.69 (0.54, 0.89)
	CV death/ MI/ Ischemic stroke	96 (5.2)	137 (7.6)	0.68 (0.52, 0.88)
	CHD death/ MI	59 (3.2)	79 (4.4)	0.73 (0.52, 1.02)
Secondary Individual Components	MI	37 (2.0)	53 (2.9)	0.69 (0.45, 1.04)
	IDR	77 (4.2)	113 (6.3)	0.66 (0.49, 0.88)
	CHD death	27 (1.5)	36 (2.0)	0.73 (0.44, 1.20)
	CV death	44 (2.4)	63 (3.5)	0.68 (0.46, 0.99)
	All-cause death	136 (7.4)	172 (9.5)	0.76 (0.61, 0.95)
	Ischemic stroke	28 (1.5)	40 (2.2)	0.67 (0.42, 1.09)



IDR, ischemia-driven arterial revascularization

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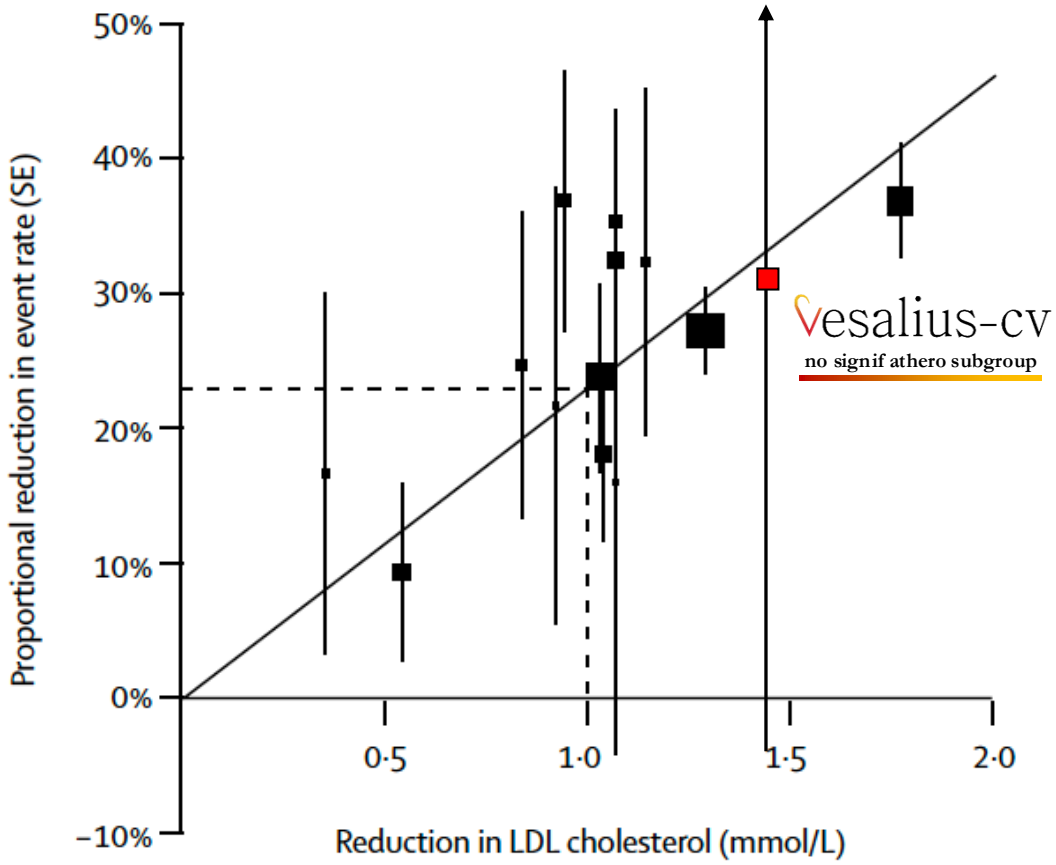
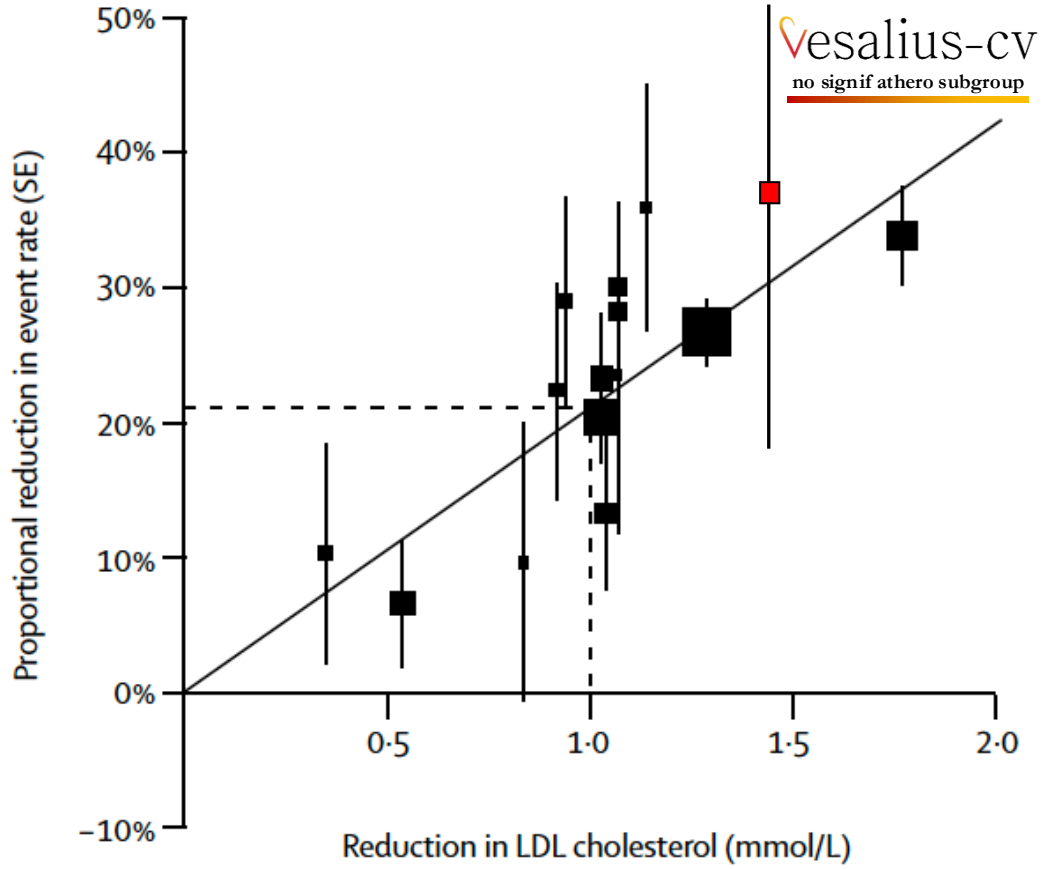
CTTC Meta-regression

Major Coronary Events [MCE]
(Death due to AMI, MI)



Major Vascular Events [MVE]
(MCE, fatal/non-fatal stroke, cor revasc)

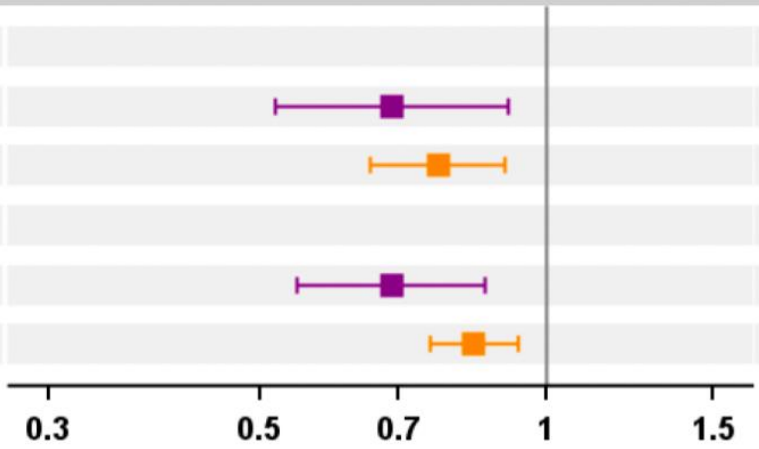


CTTC (Cholesterol Treatment Trialists' Collaboration): pooling of data from the 1° & 2° prevention statin CV outcomes trials.

Lancet. 2005;366:1267-78.
Lancet. 2010;376:1670-81.

Without vs With Known Significant Athero

Dual Primary Endpoints	n (%) Evolocumab	Placebo	HR (95% CI)	Interaction p-value
3-P MACE				
W/O significant Athero	83 (4.5)	117 (6.5)	0.69 (0.52, 0.91)	
W/ significant Athero	253 (5.9)	326 (7.5)	0.77 (0.65, 0.91)	
4-P MACE				
W/O significant Athero	127 (6.9)	178 (9.9)	0.69 (0.55, 0.86)	
W/ significant Athero	620 (14.5)	729 (16.9)	0.84 (0.76, 0.94)	



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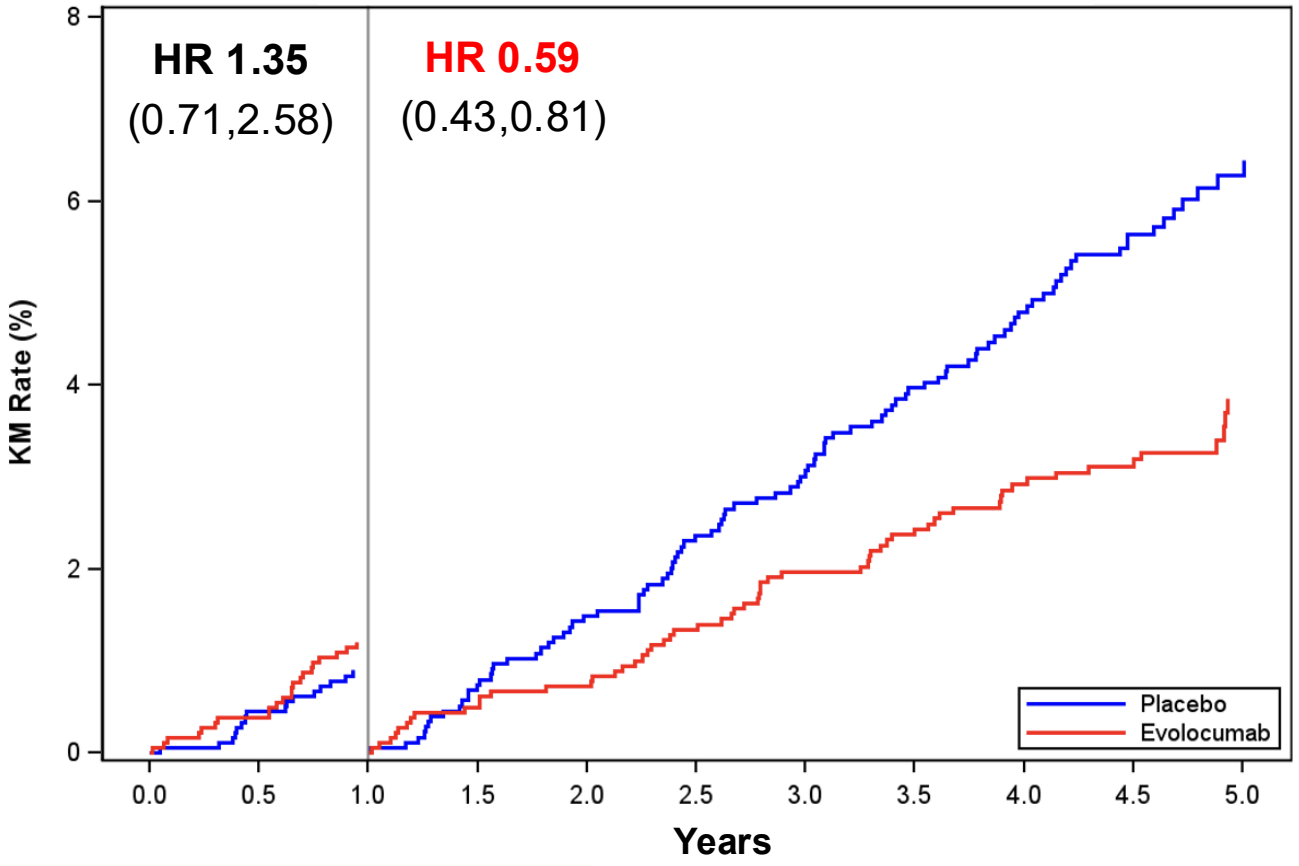
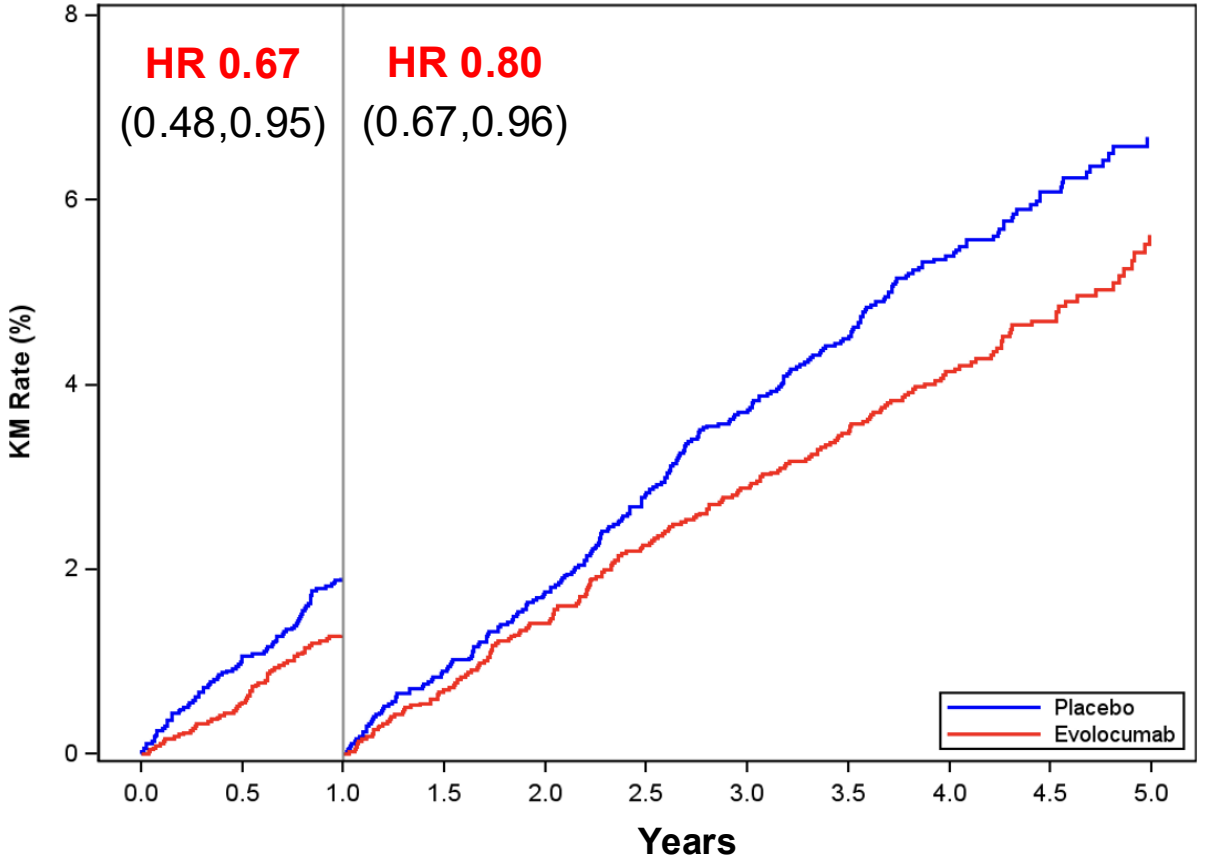
Effect After 1 Year by Athero Status (3-P)

BWH TIMI

3-P MACE Without Known Athero



3-P MACE With Known Athero



Landmarked analysis for first and subsequent years

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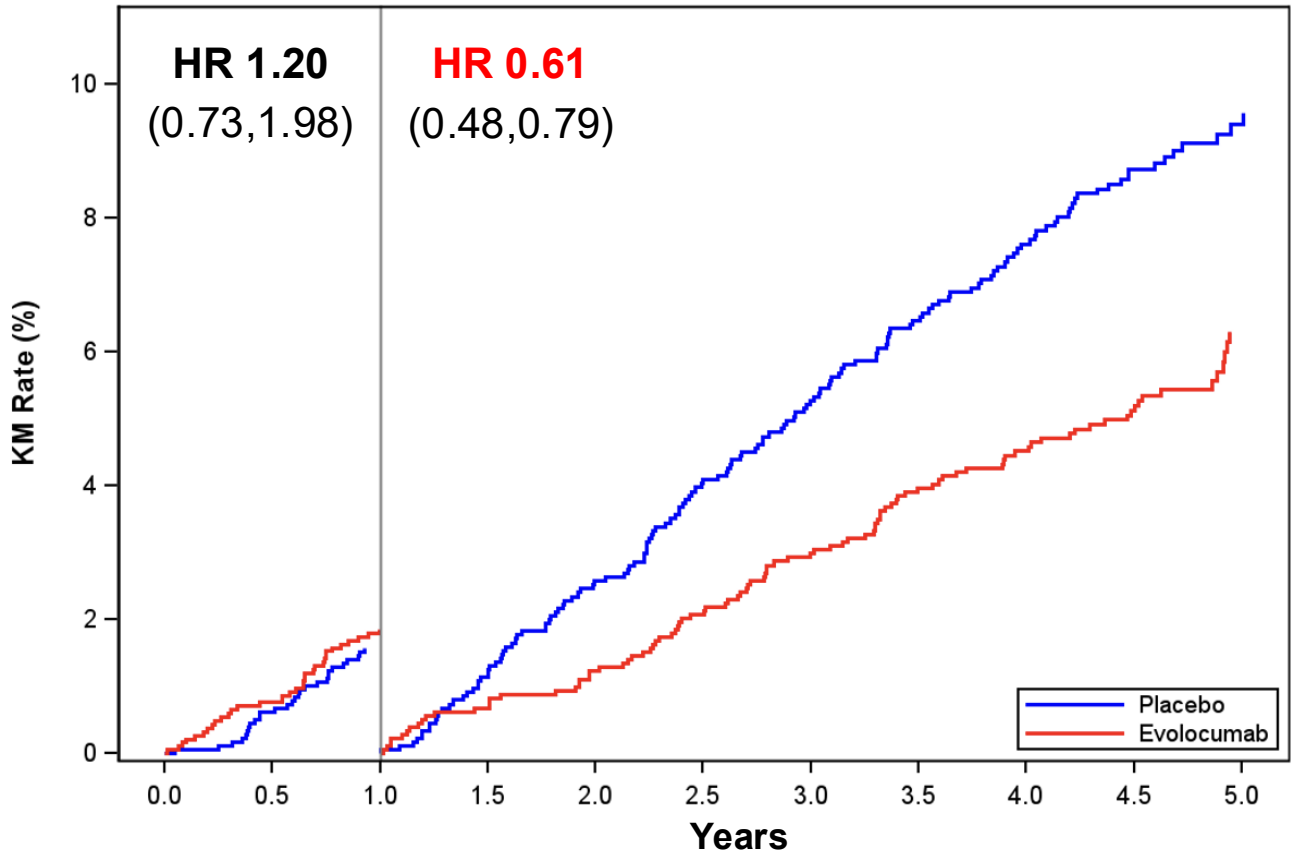
Effect After 1 Year by Athero Status (4-P)

4-P MACE Without Known Athero



4-P MACE With Known Athero

Landmarked analysis for first and subsequent years

Limitations

- **Systematic imaging was not required,** and some may have had undiagnosed significant atherosclerosis. However, this reflects guideline recommendations and clinical practice.

- **All patients had high-risk diabetes mellitus**, therefore validation in other types of high-risk patients without known atherosclerosis will be important.

Summary

In high-risk primary prevention patients without known significant atherosclerosis and with diabetes, addition of the PCSK9 mAb, evolocumab, to baseline LLRx resulted in:

- Median achieved LDL-C of 44 mg/dL (1.14 mmol/L)
- 31% ↓ in 3-P MACE and 4-P MACE
- ~40% ↓ in MACE after the first year
- 32% ↓ in CV death, MI or ischemic stroke
- Lower rates of cardiovascular and all-cause death

Conclusions

- The benefits seen in this subgroup support intensification of lipid-lowering therapy beyond statins earlier in the atherosclerotic cardiovascular disease process
- The consistency of the magnitude of clinical benefit with that expected from CTTC underscores the value of lowering LDL-C down to ~40 mg/dL in these patients
- ***Thus, these data strongly support that in these lower-risk patients we should be targeting LDL-C goals typically reserved for very high-risk secondary prevention patients***

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TIMI Study Group

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

Marston NA, Bohula EA, Bhatia KA, et al; VESALIUS-CV Investigators

Evolocumab to Reduce First Major Cardiovascular Events in Patients Without Known Significant Atherosclerosis and With Diabetes

Results From the VESALIUS-CV Trial

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