Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease:

Primary Results of the FOURIER-OLE (Open-Label Extension) Studies

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On Behalf of the FOURIER-OLE Investigators

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

This study was funded by Amgen Inc.

Background

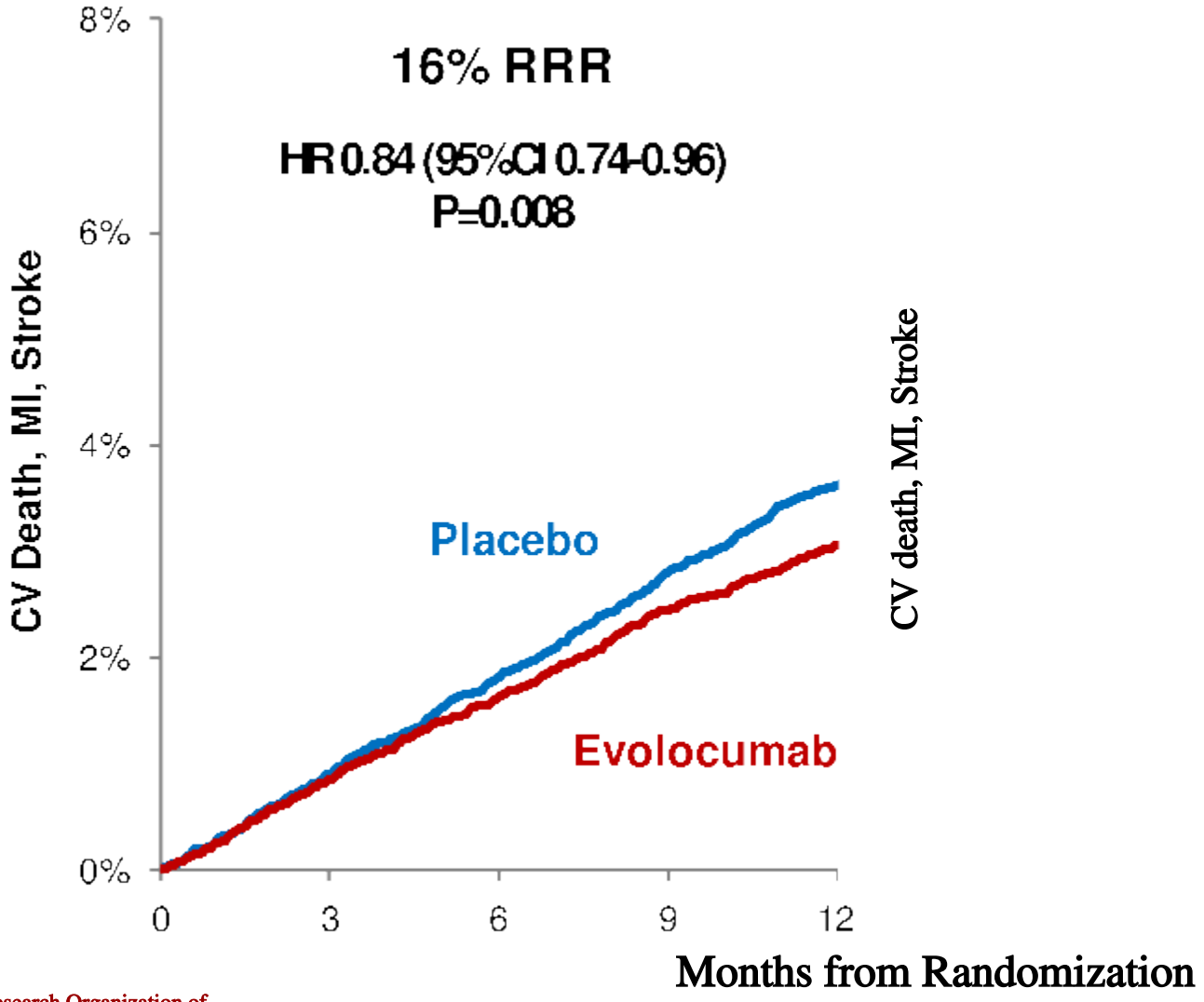
- In the FOURIER trial, 27,564 patients with stable ASCVD were randomized to the PCSK9 inhibitor evolocumab vs. placebo
- Evolocumab reduced the risk of MACE, but there was no observed effect on CV mortality
- However, the median follow-up was only 2.2 years

Background (2)

- Pivotal statin trials had median follow-up of 4-5 years and demonstrated both a lag effect (clinical benefit grew over time) and legacy effect (clinical benefit persisted in extended follow-up after the parent trial ended)

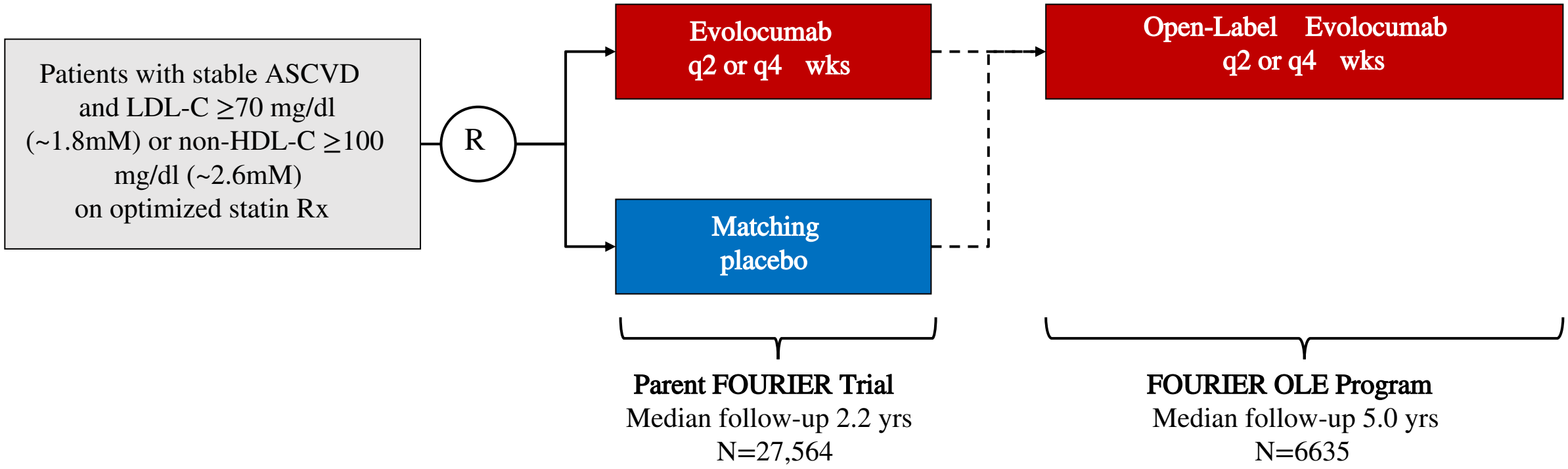
- Thus, very long-term data on safety and efficacy of LDL-C lowering with PCSK9 inhibition are needed

Evolocumab: Evidence of Lag Effect for MACE



Sabatine MS et al. *NEJM* 2017; 376:1713-22

Study Schema



US & Eastern Europe: NCT02867813
Western Europe: NCT03080935

Methods

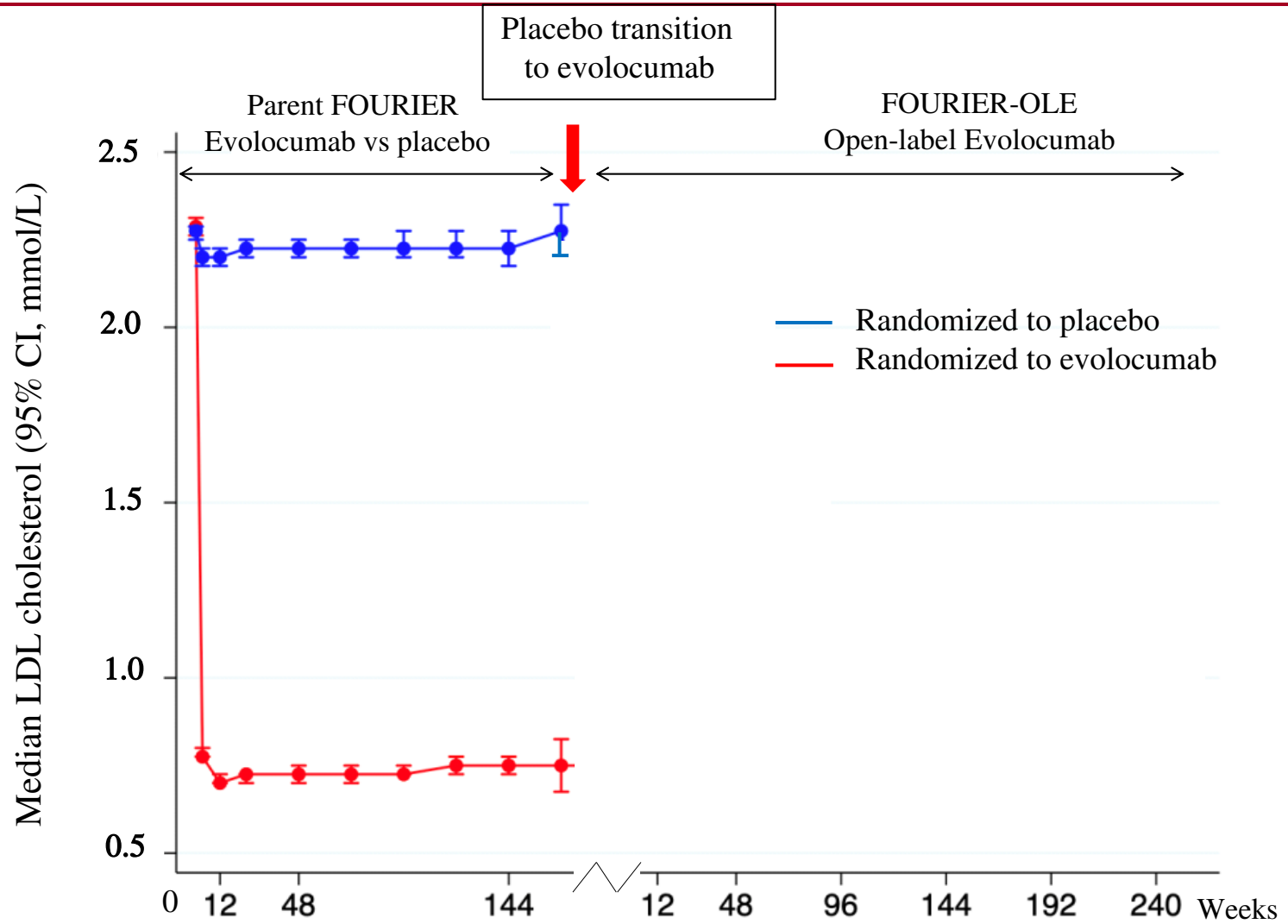
- Primary endpoint was incidence of adverse events
- MACE were prespecified exploratory endpoints and were reviewed by the TIMI Study Group Clinical Events Committee
- Safety evaluations included all patients in FOURIER-OLE who received ≥1 dose of study drug and for whom post-dose data were available. Patients were censored for safety analyses 30 days following permanent drug discontinuation or end-of-study (whichever was earlier).
- Analyses for major adverse cardiovascular events were conducted on an intention-to-treat basis and stratified by original treatment assignment at randomization

Baseline Characteristics of OLE Population at Randomization

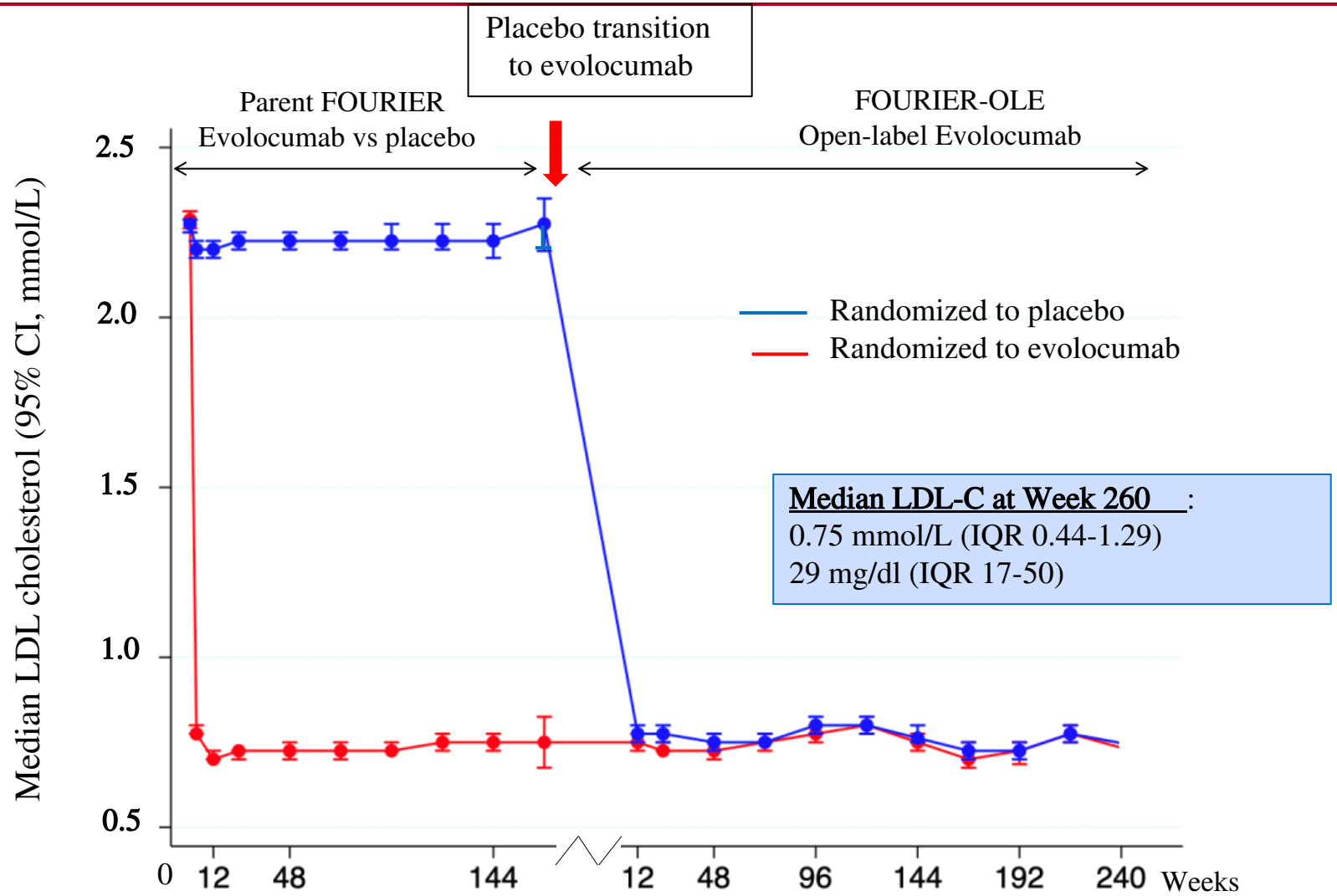
		Initial allocation in parent FOURIER trial	
		Placebo (N=3280)	Evolocumab (N=3355)
Demographics	Age (mean, years)	62	62
	Male sex (%)	76	77
	White race (%)	96	95
Region (%)	Europe	66	67
	United States	34	33
Type of athero (%)	Myocardial infarction	84	84
	Non-hemorrhagic stroke	16	16
	Peripheral artery disease	14	15
CV risk factors (%)	Hypertension	85	82
	Diabetes mellitus	35	33
	Current cigarette use	27	26
Meds at time of enrollment in FOURIER (%)	High-intensity statin use	76	77
	Ezetimibe	5.5	6.0
LDL-C at randomization (median, IQR)	mmol/L	2.4 (2.1-2.8)	2.4 (2.1-2.8)
	mg/dl	91 (80-109)	92 (80-108)

All comparisons P>0.05

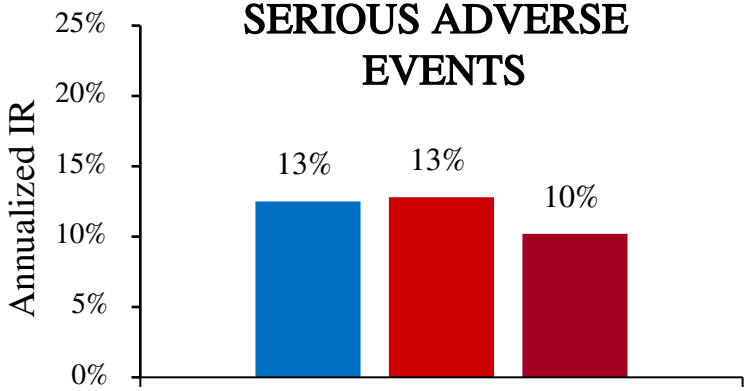
Effect on LDL-C

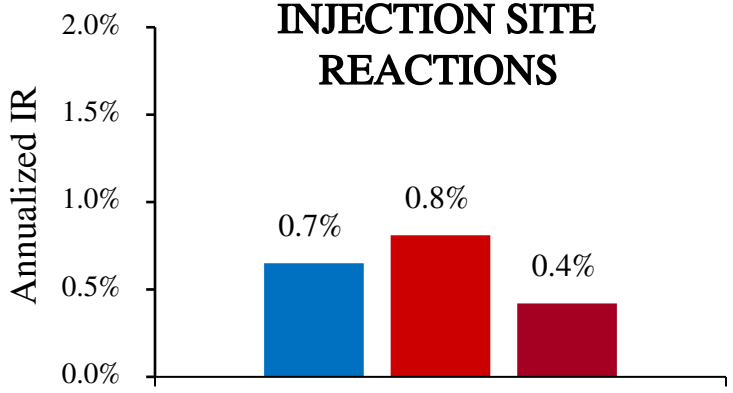


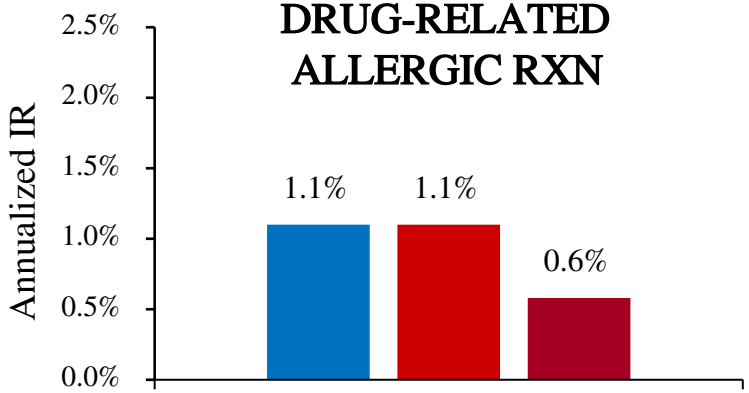
Effect on LDL-C

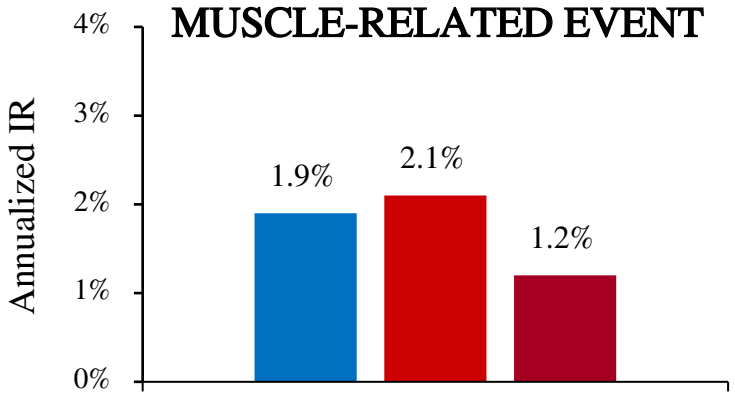


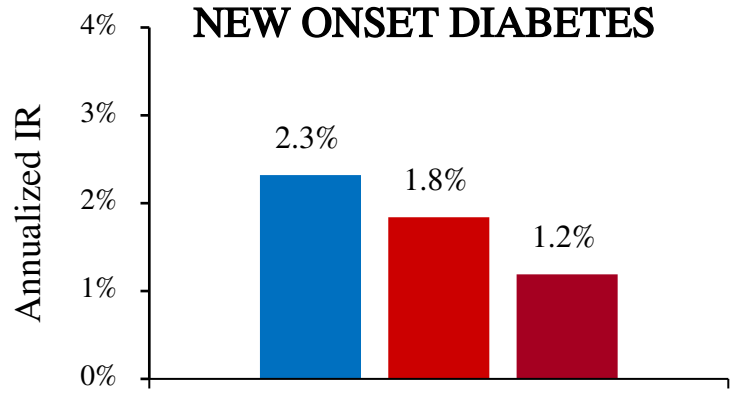
Long-Term Safety

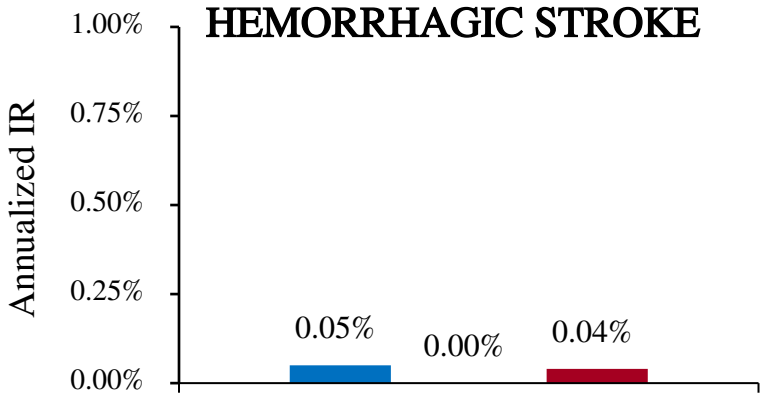






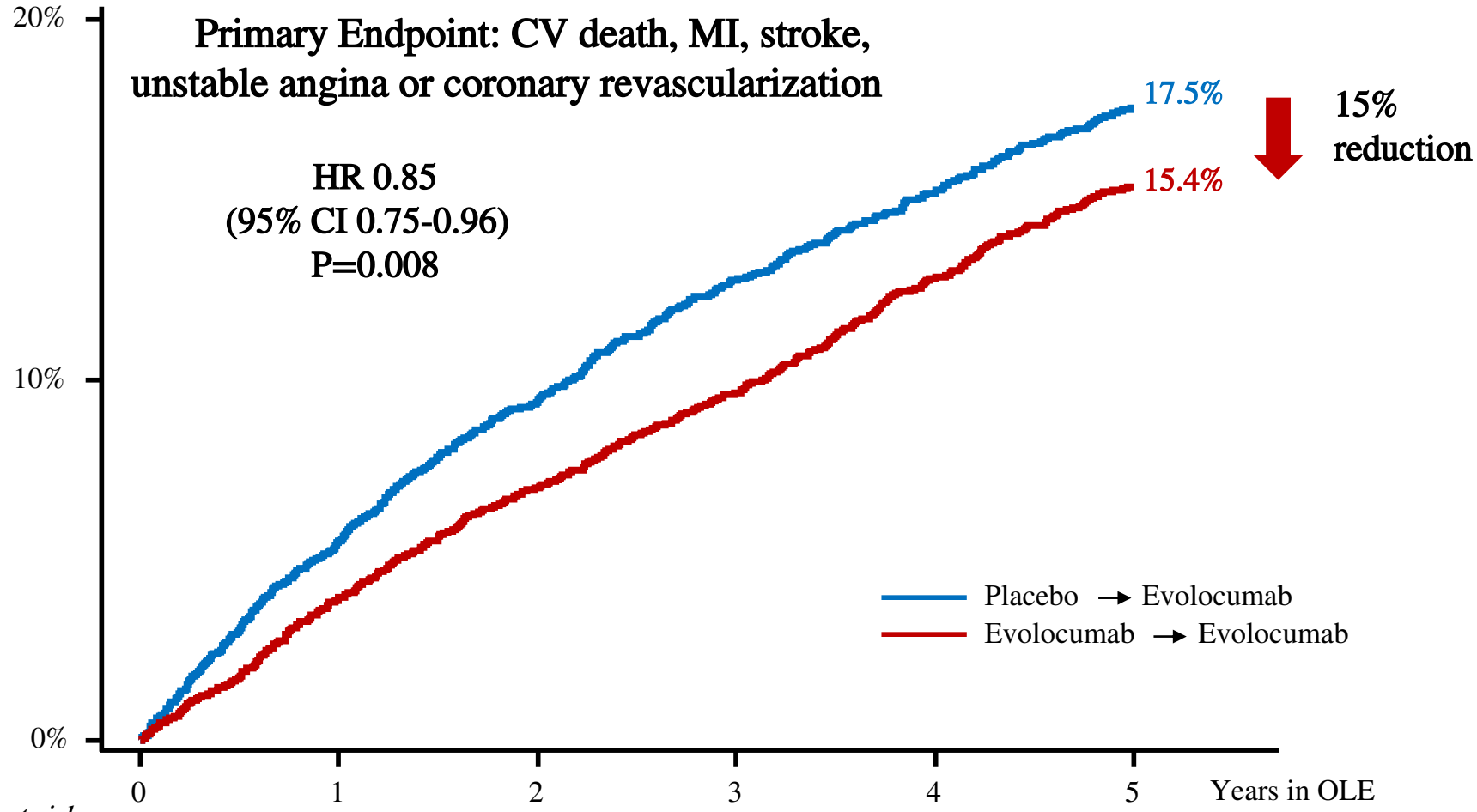






Placebo Phase FOURIER
Evolocumab Phase FOURIER
Evolocumab Phase FOURIER & OLE

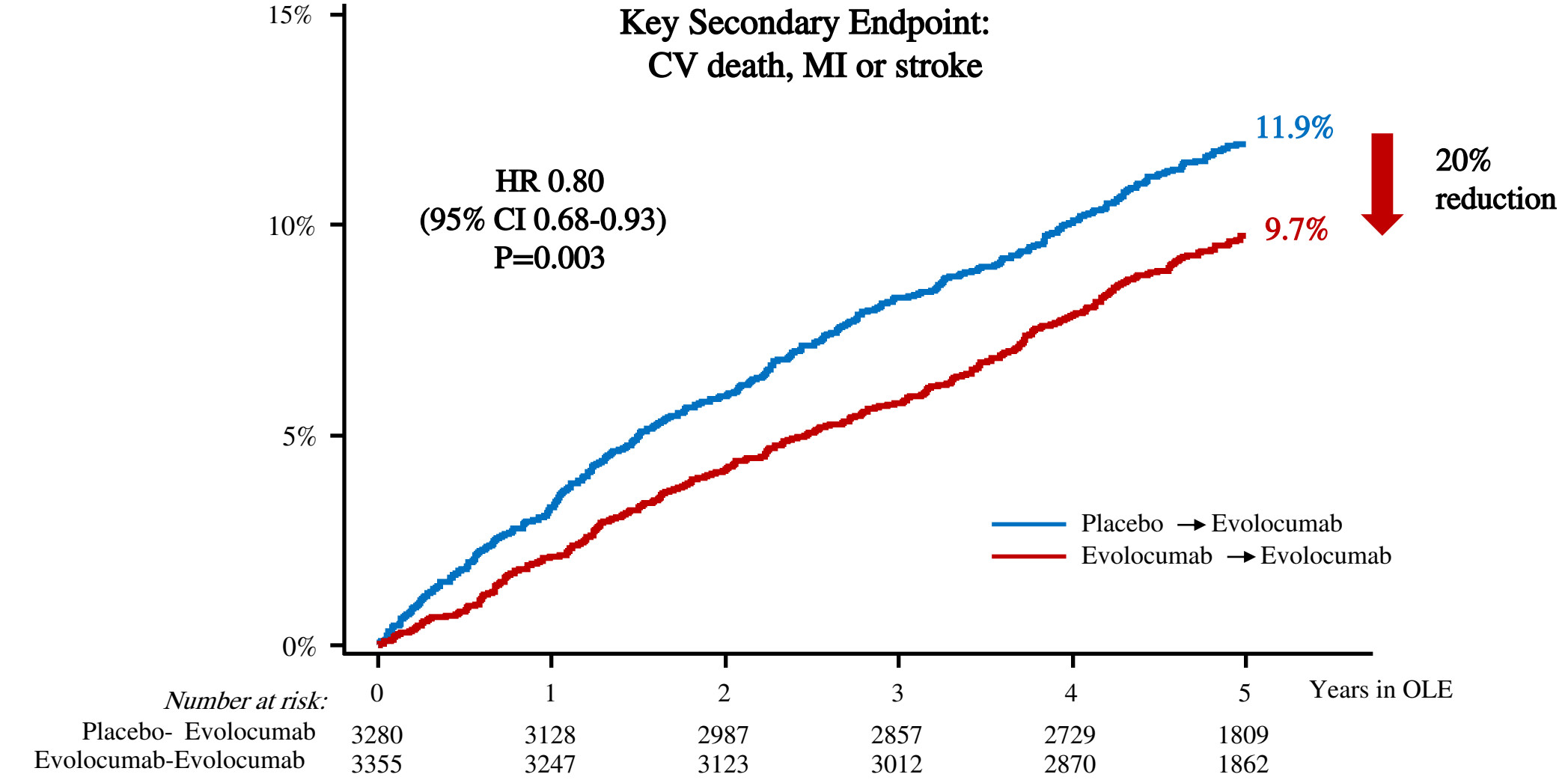
Efficacy during FOURIER- OLE



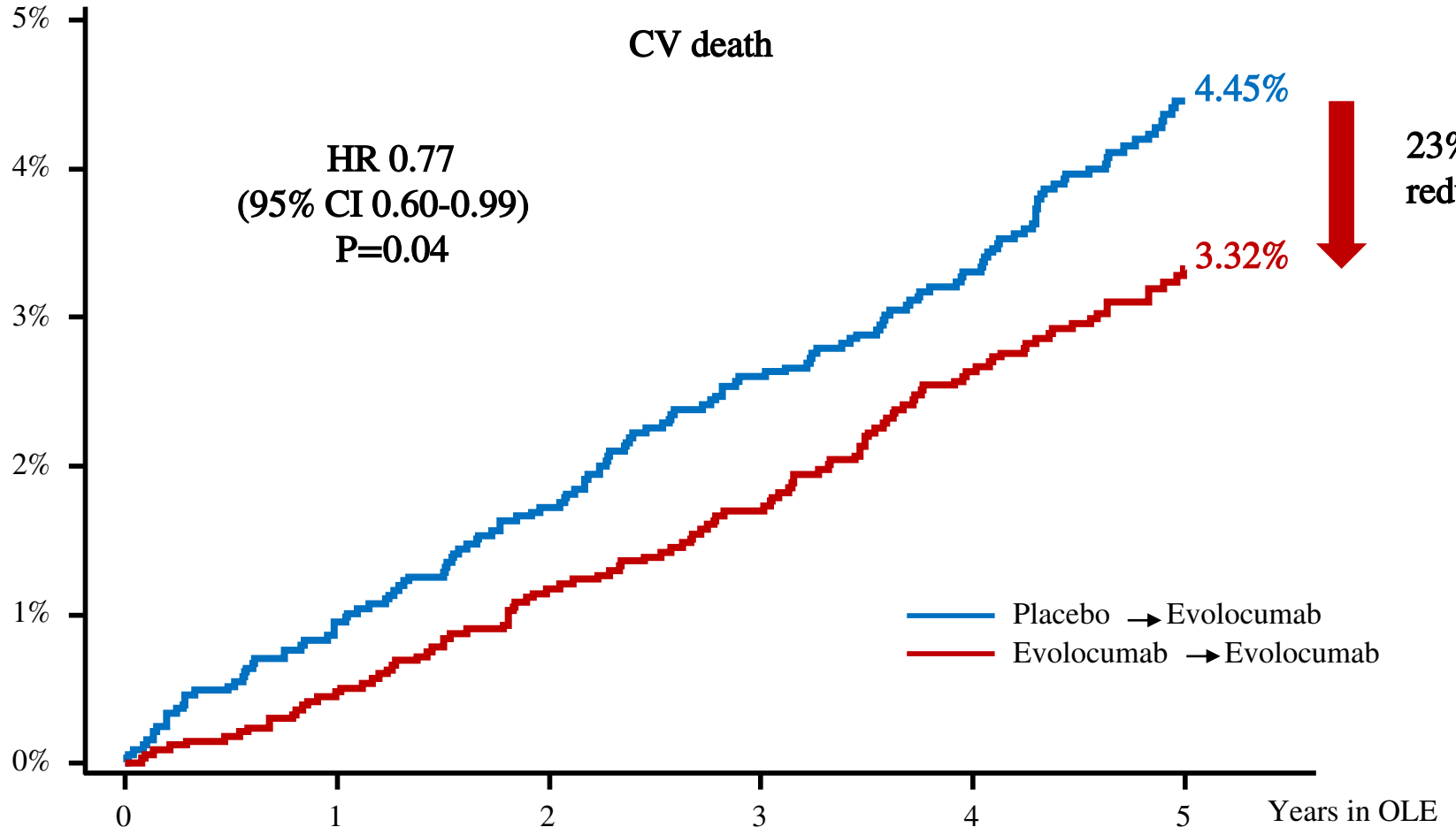
Number at risk:

Placebo- Evolocumab	3280	3055	2876	2716	2573	1706
Evolocumab-Evolocumab	3355	3186	3033	2890	2716	1754

Efficacy during FOURIER- OLE



Efficacy during FOURIER- OLE Time Period

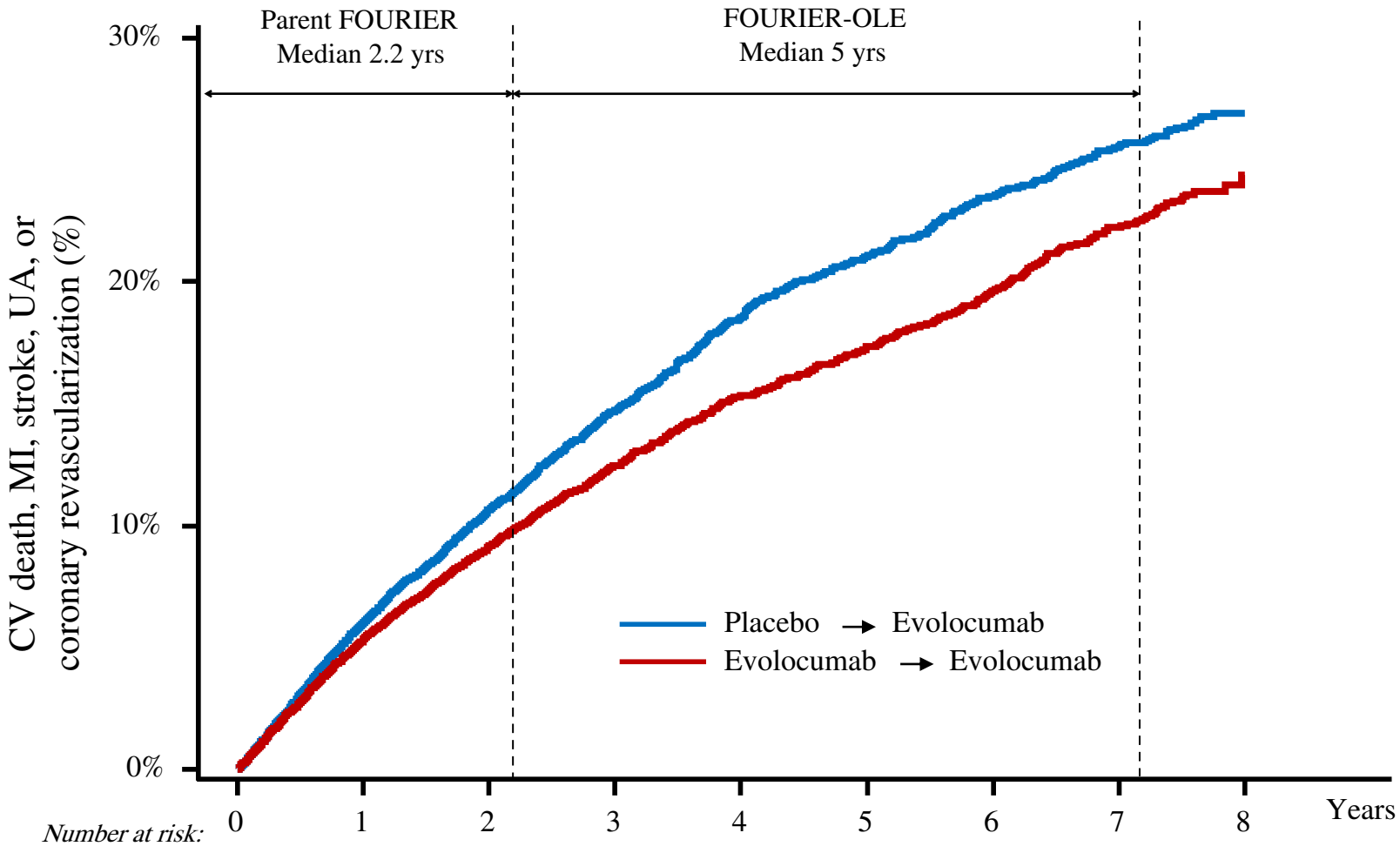


Number at risk:

Placebo- Evolocumab	3280	3223	3155	3081	2991	2049
Evolocumab-Evolocumab	3355	3314	3244	3173	3080	2069

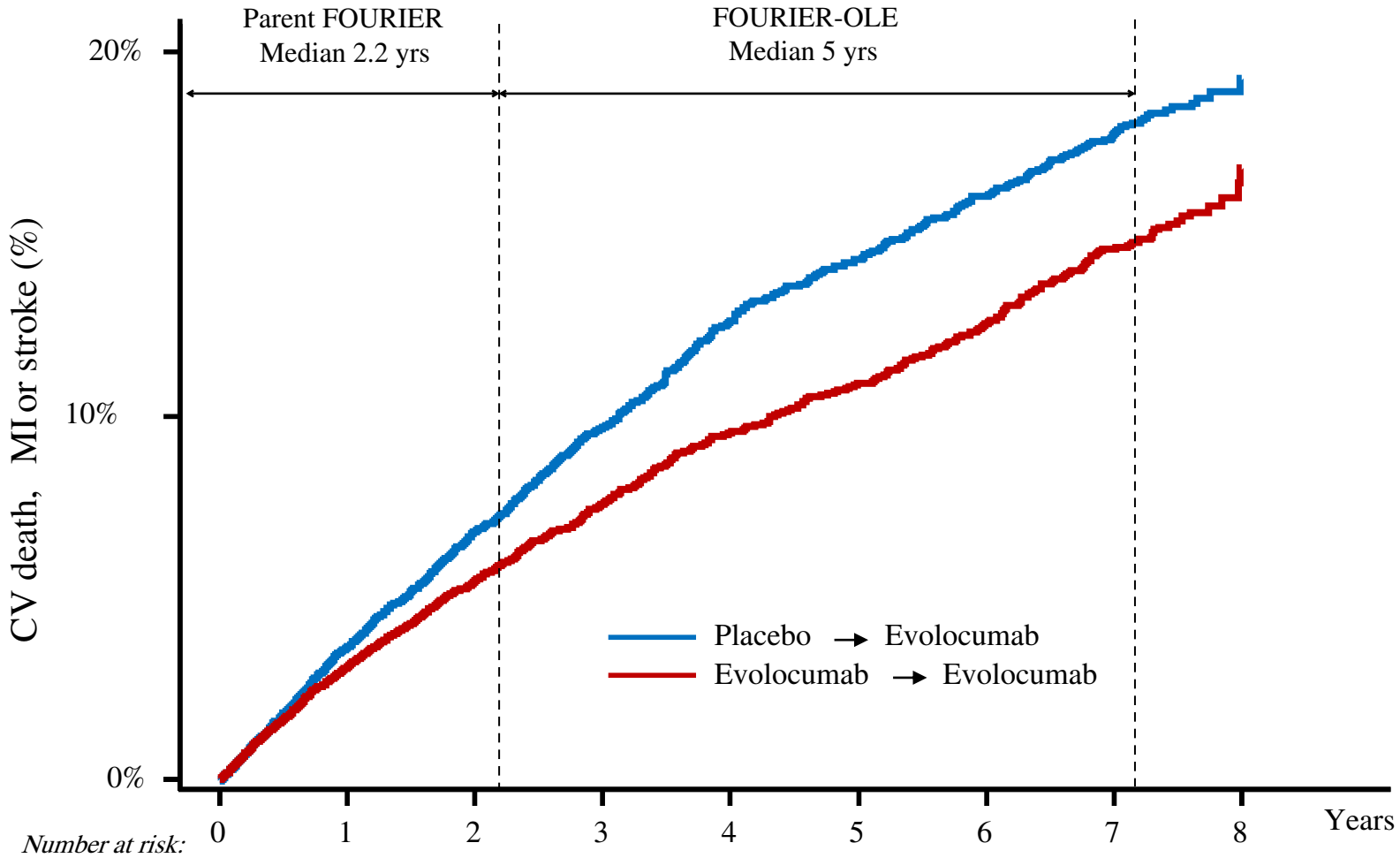
Efficacy during FOURIER & FOURIER-OLE

FOURIER Primary Endpoint



Efficacy during FOURIER & FOURIER-OLE

FOURIER Key Secondary Endpoint

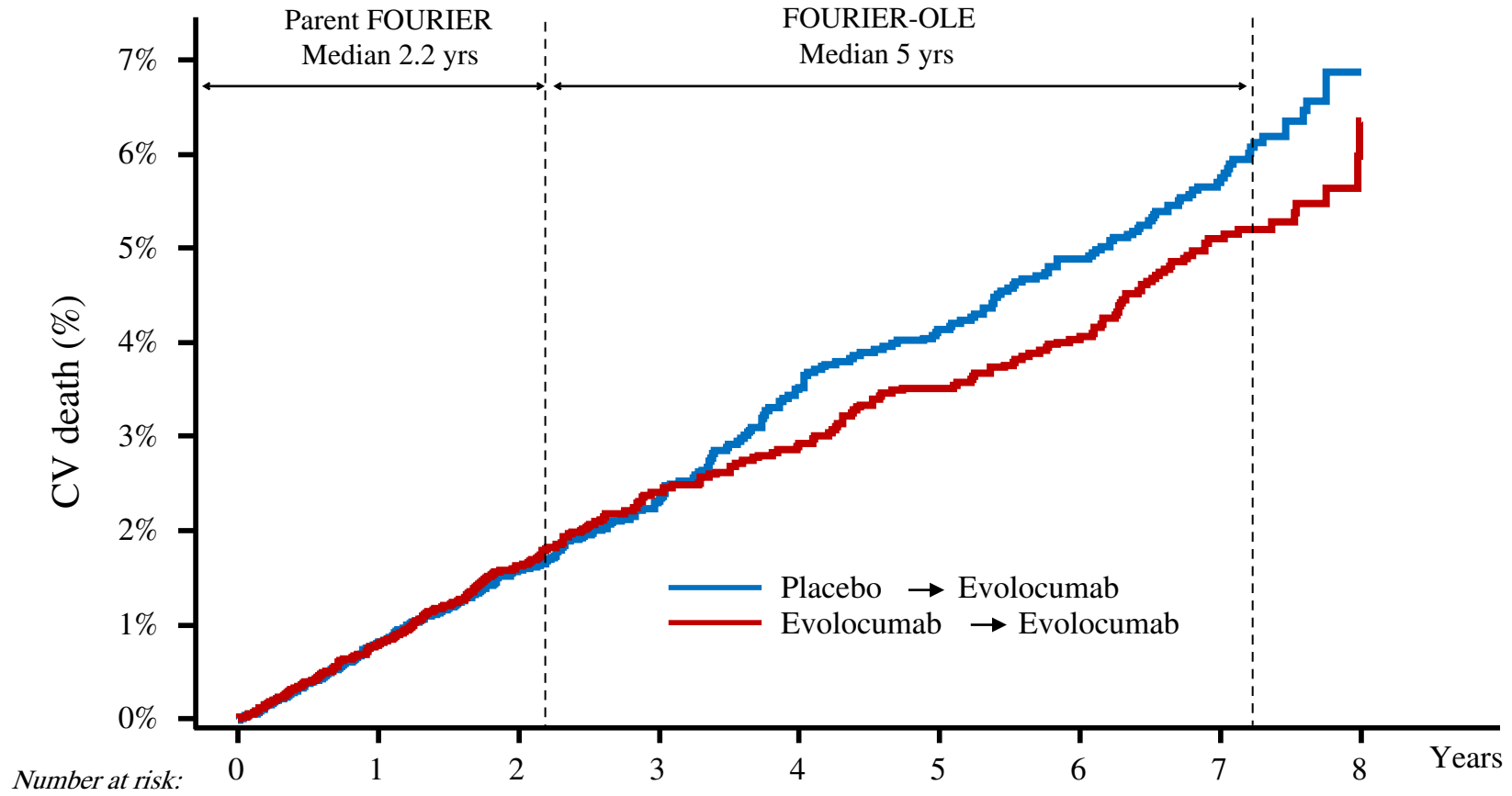


Number at risk:

Placebo- Evolocumab	13780	13140	8846	3470	2861	2757	2621	1664	216
Evolocumab-Evolocumab	13784	13240	9051	3617	3046	2946	2810	1746	185

Efficacy during FOURIER & FOURIER-OLE

CV Death



Number at risk:

	0	1	2	3	4	5	6	7	8
Placebo- Evolocumab	13780	13590	9399	3753	3167	3098	2996	1965	268
Evolocumab-Evolocumab	13784	13598	9464	3826	3270	3204	3109	1988	237

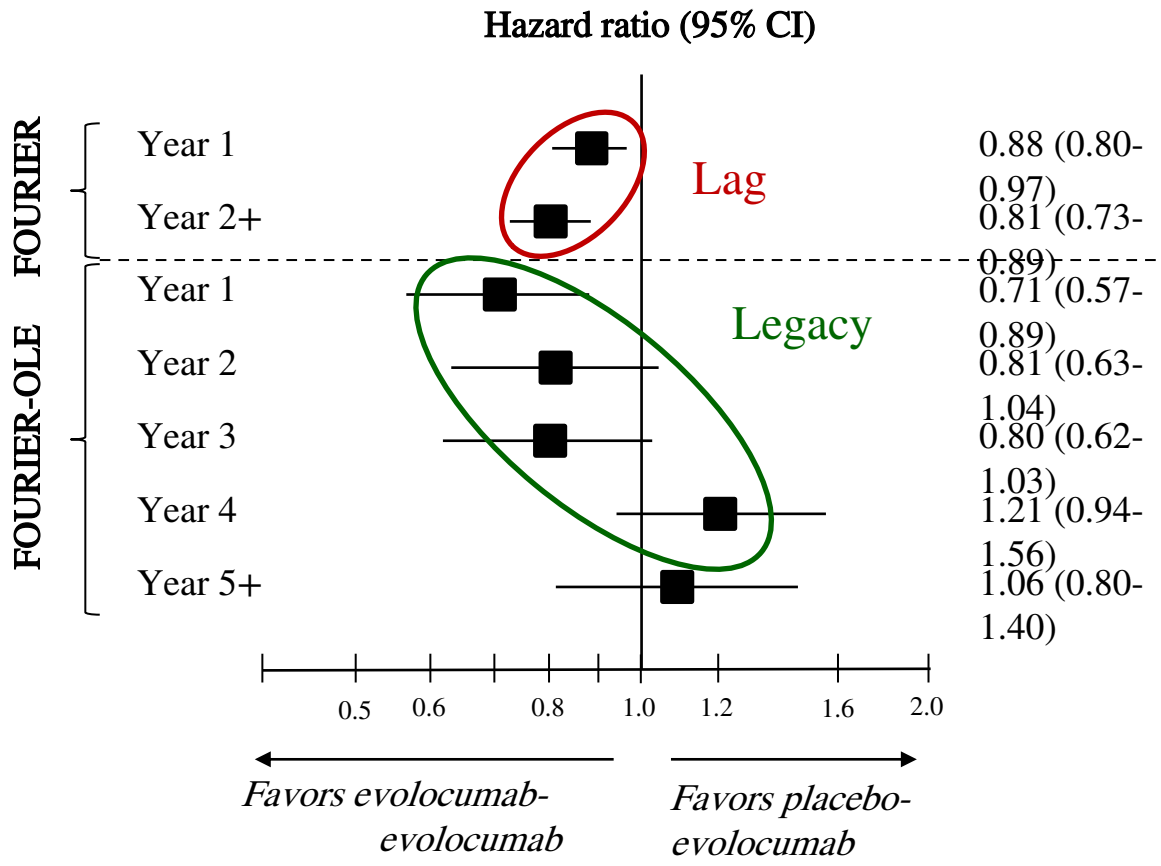
MACE by Year of Study

LDL-C Δ between arms

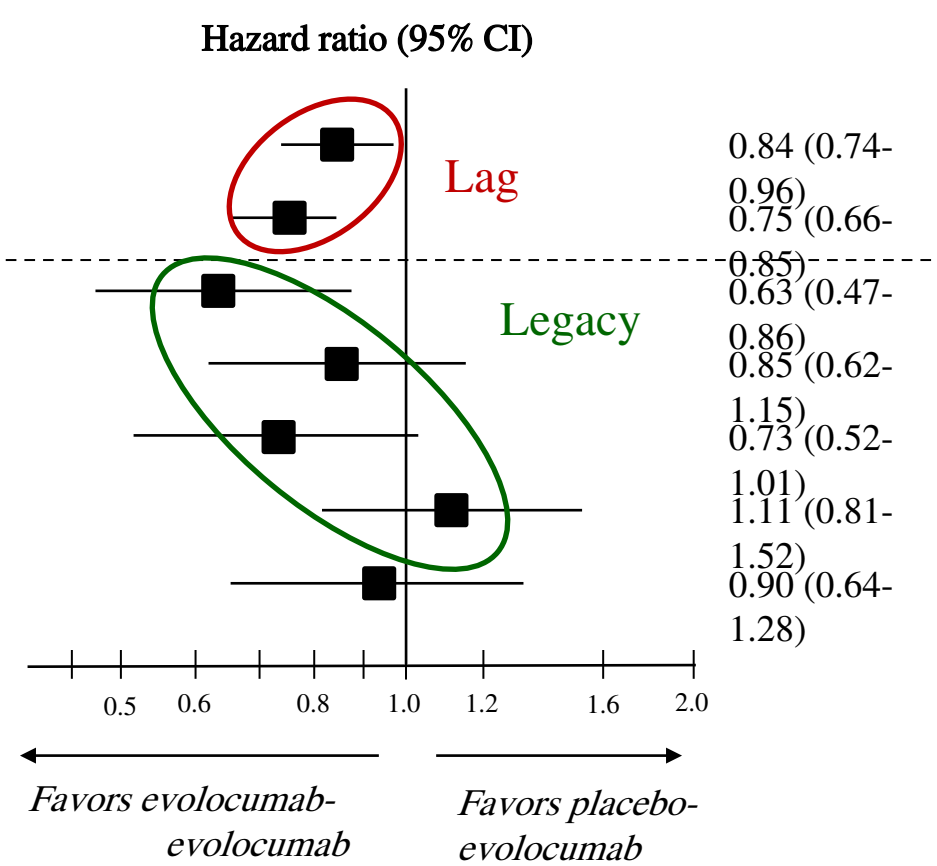
1.6 mM (62 mg/dl)

0.0 mM

CV death, MI, stroke, hosp for UA, or coronary revascularization



CV death, MI or stroke



Summary

- Long-term use of evolocumab with median follow-up of more than 7 years appears both safe and well-tolerated
- Earlier initiation of evolocumab is associated with continued accrual of cardiovascular benefit, including cardiovascular mortality, over the next several years
- These findings argue for early initiation of a marked and sustained LDL-C reduction to maximize clinical benefit

Circulation

CIRCULATION. 2022; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.122.061620

LONG-TERM EVOLOCUMAB IN PATIENTS WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

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