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

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

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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

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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

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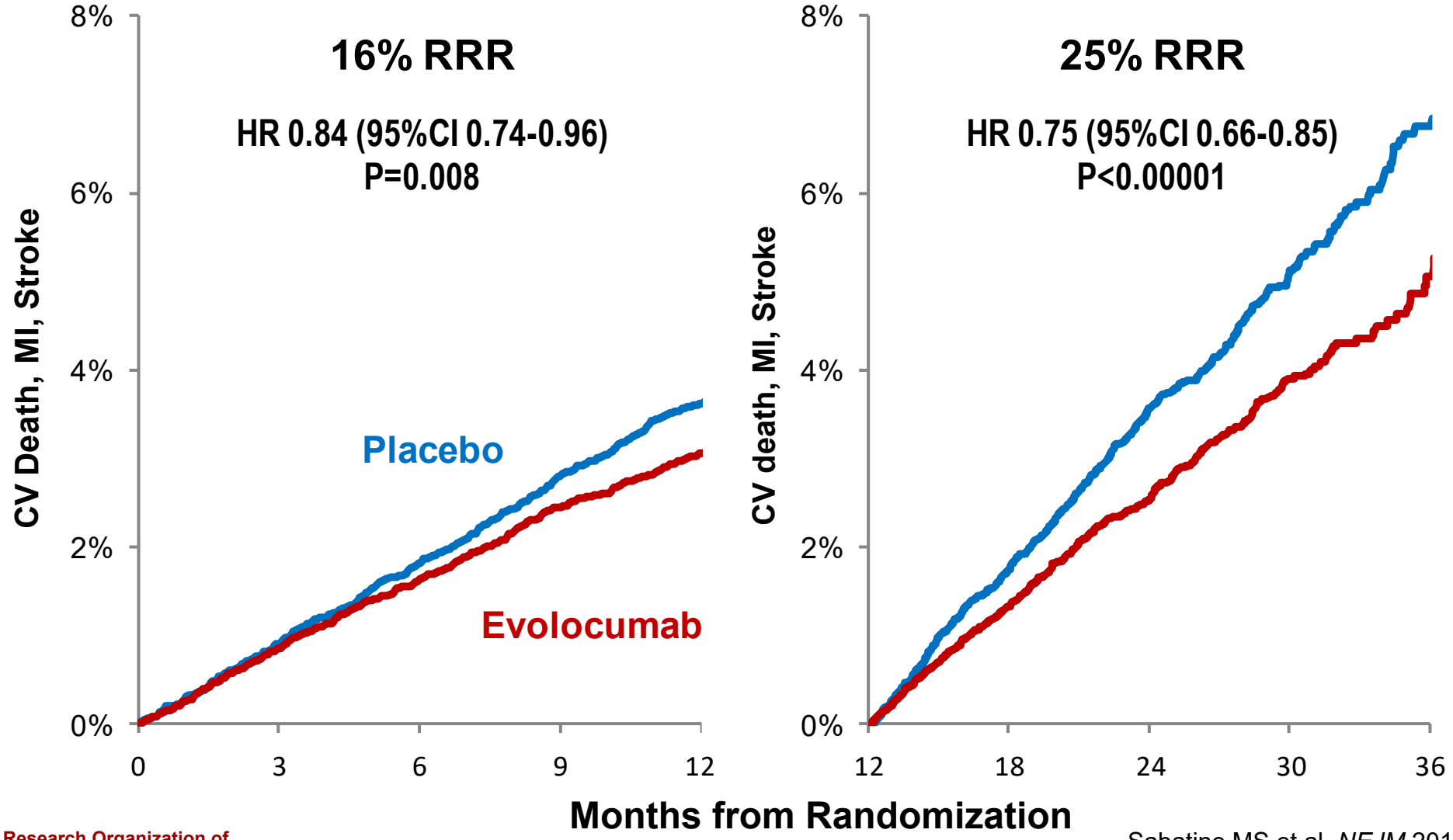
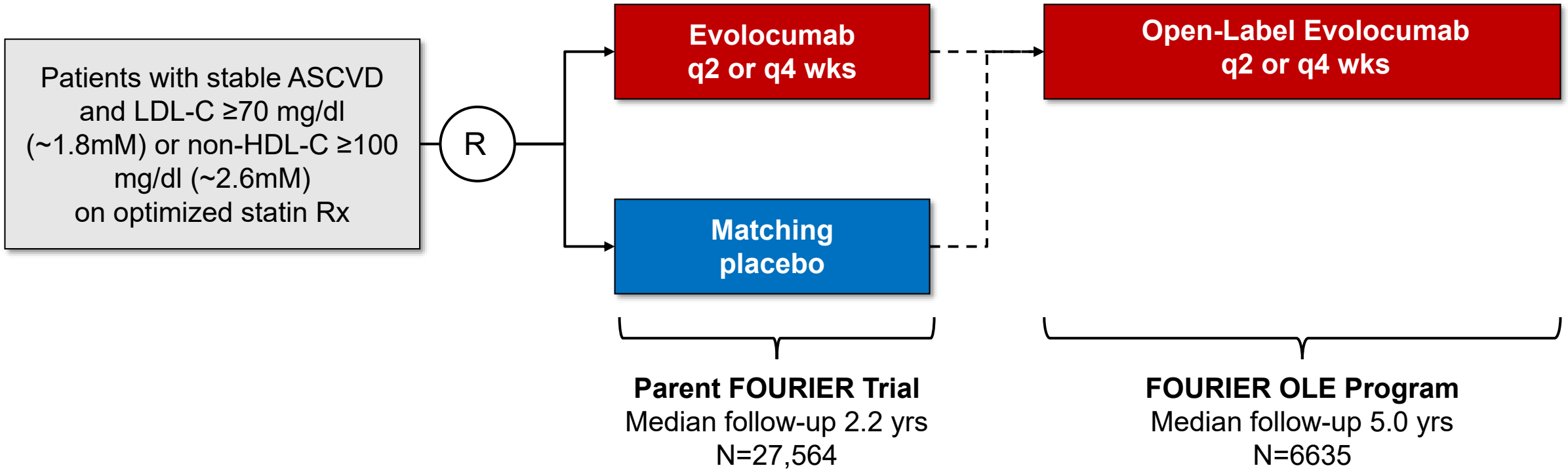
Evolocumab: Evidence of Lag Effect for MACE



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

Study Schema



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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)

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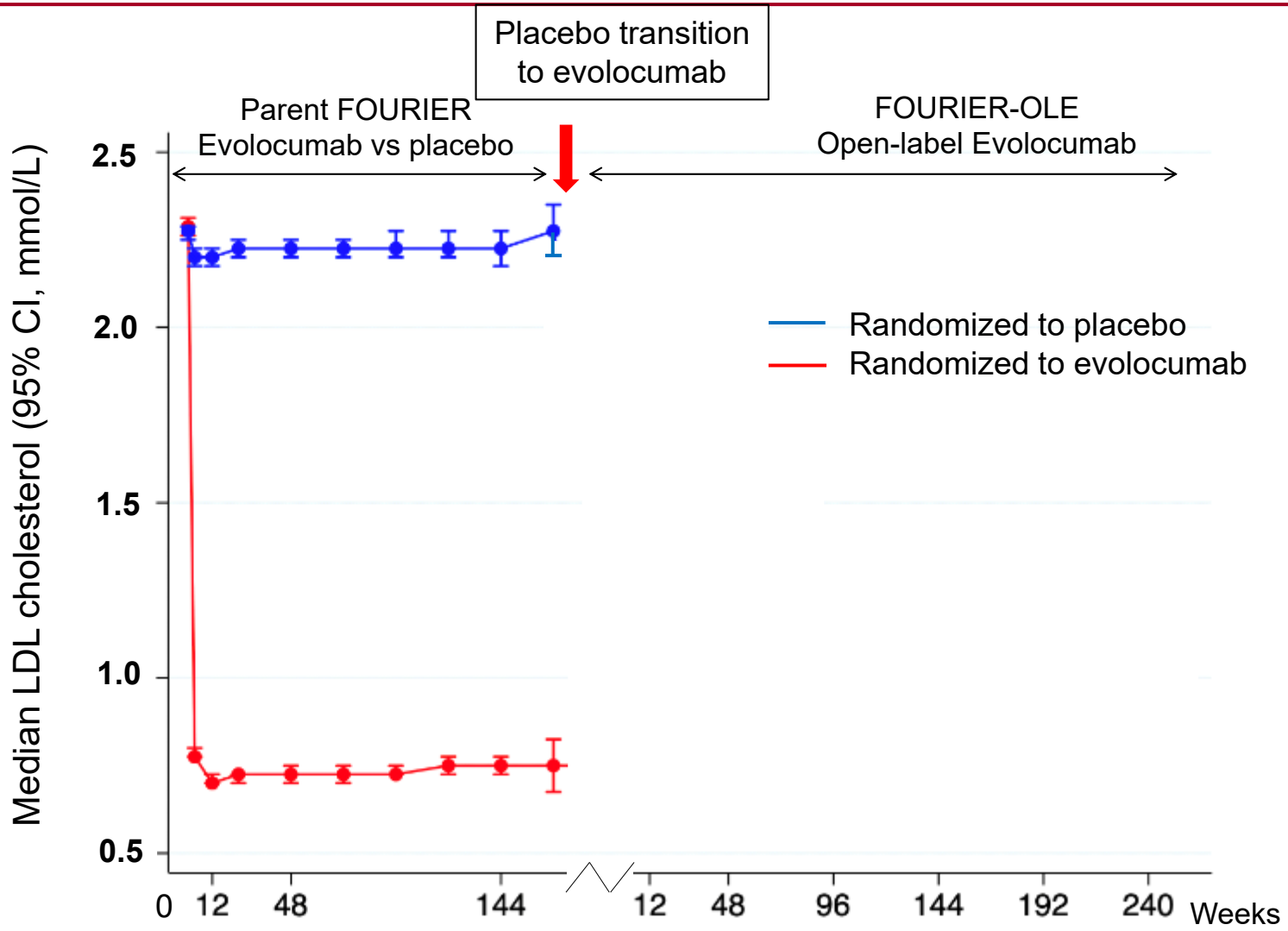
All comparisons P>0.05

Effect on LDL-C



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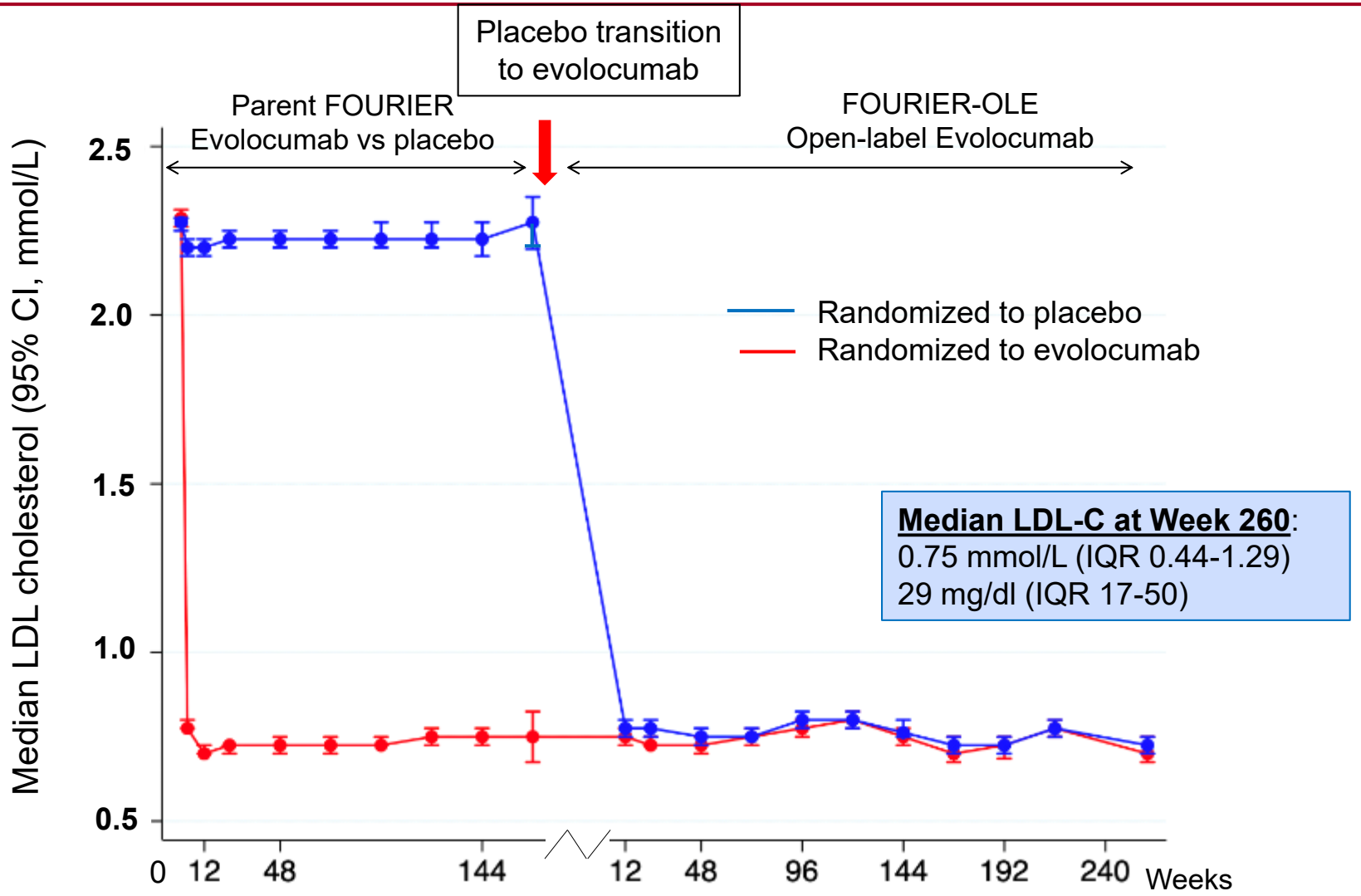
Effect on LDL-C



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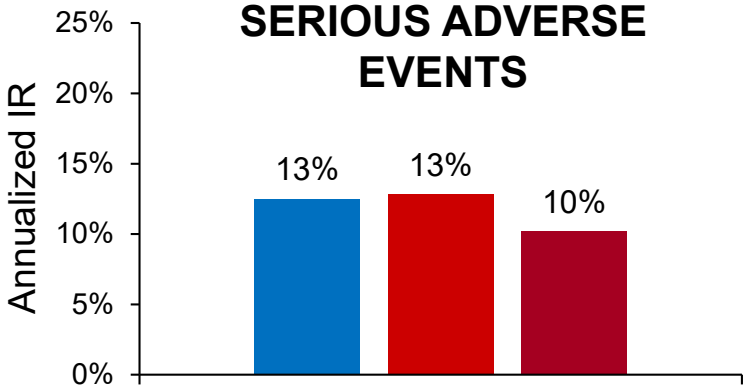
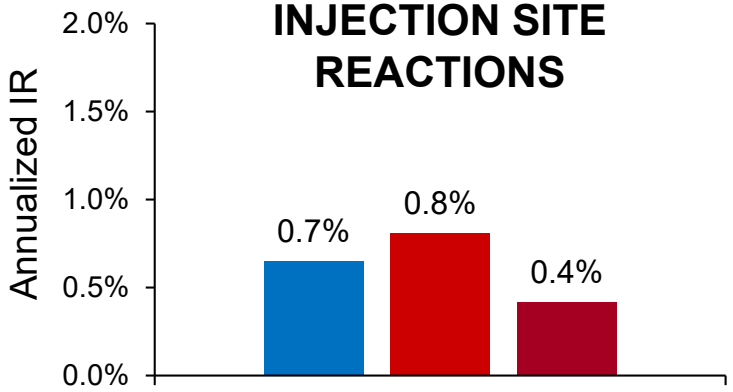
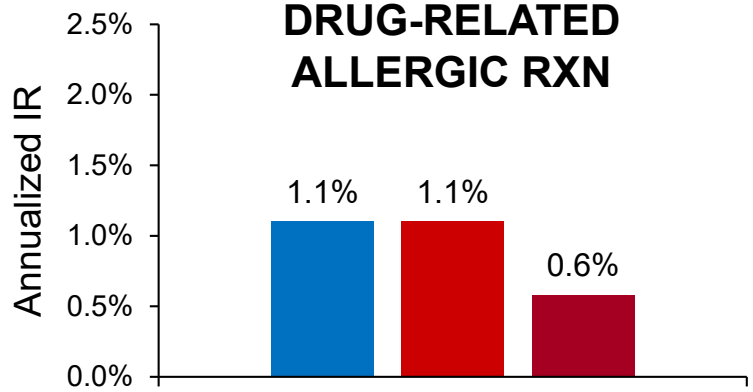
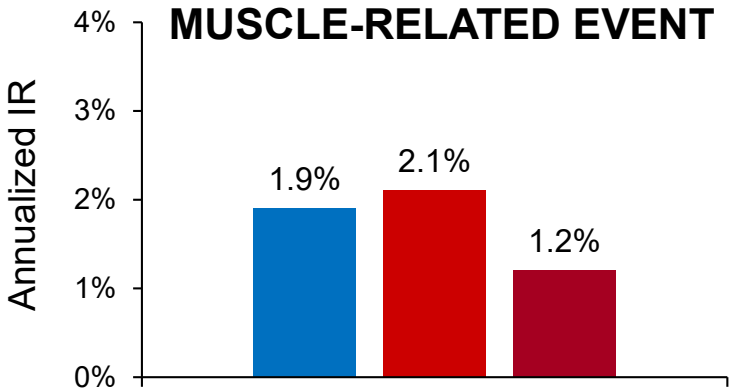
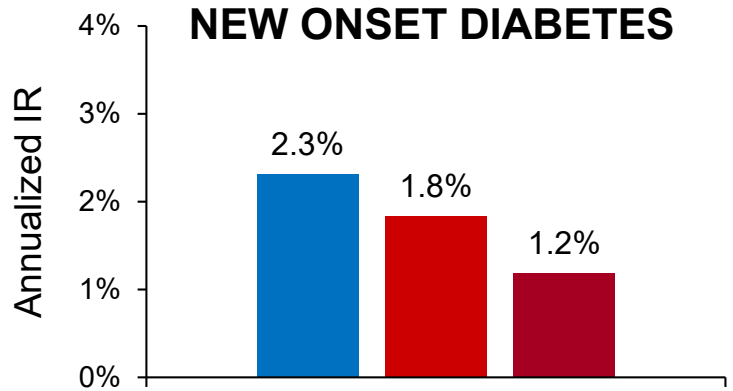
Long-Term Safety

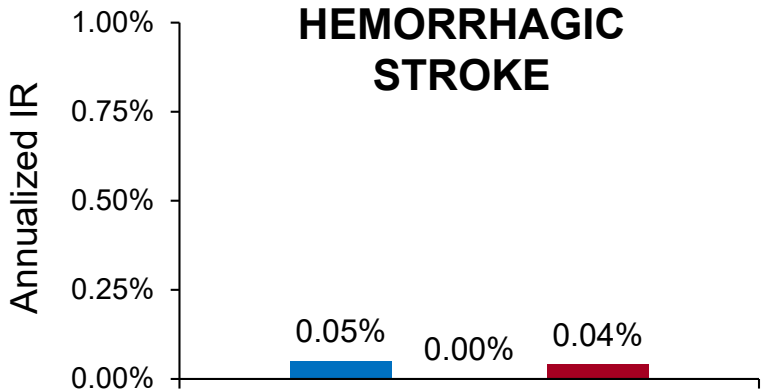












Placebo Phase FOURIER
Evolocumab Phase FOURIER
Evolocumab Phase FOURIER & OLE

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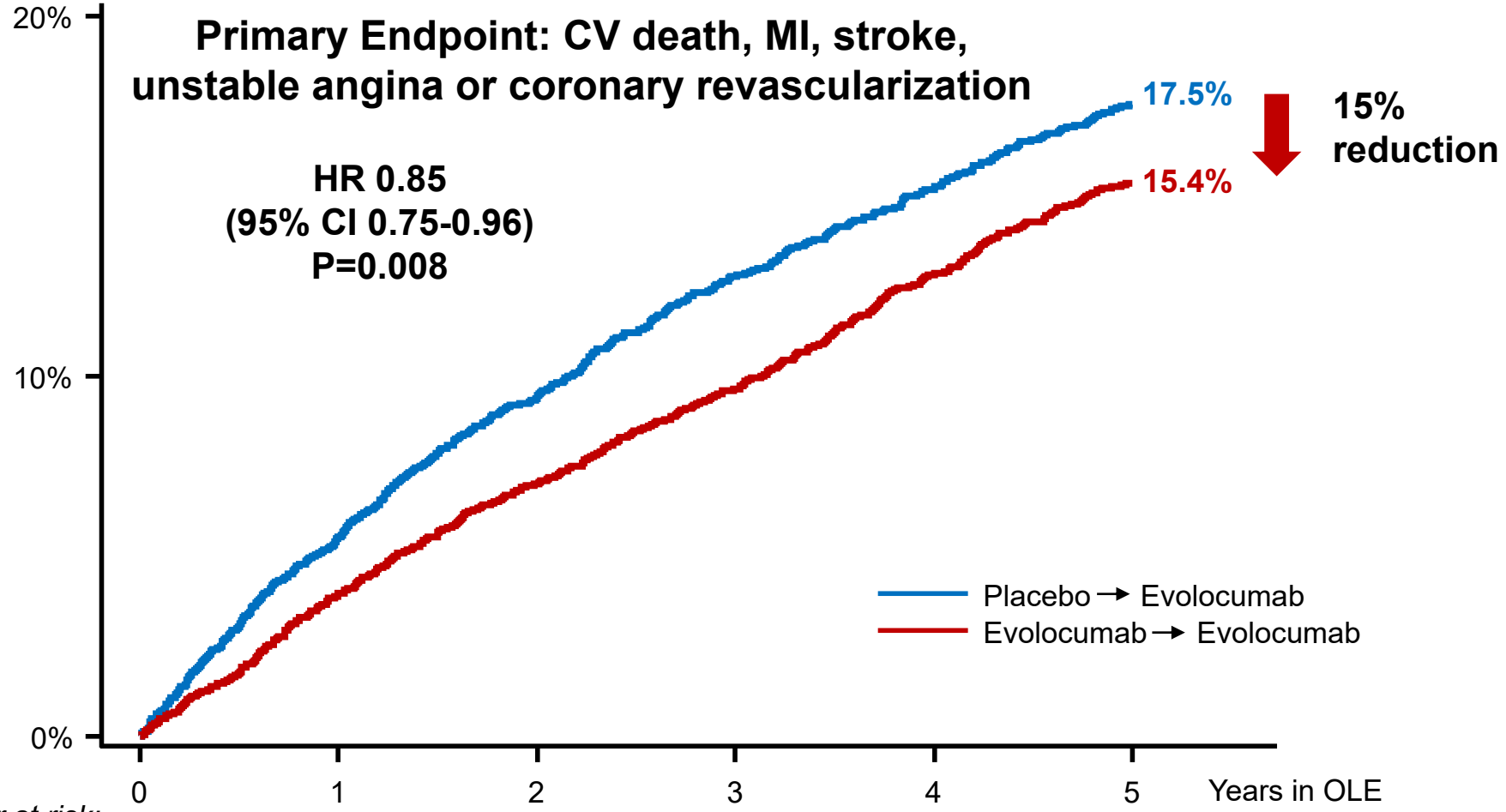
Efficacy during FOURIER-OLE



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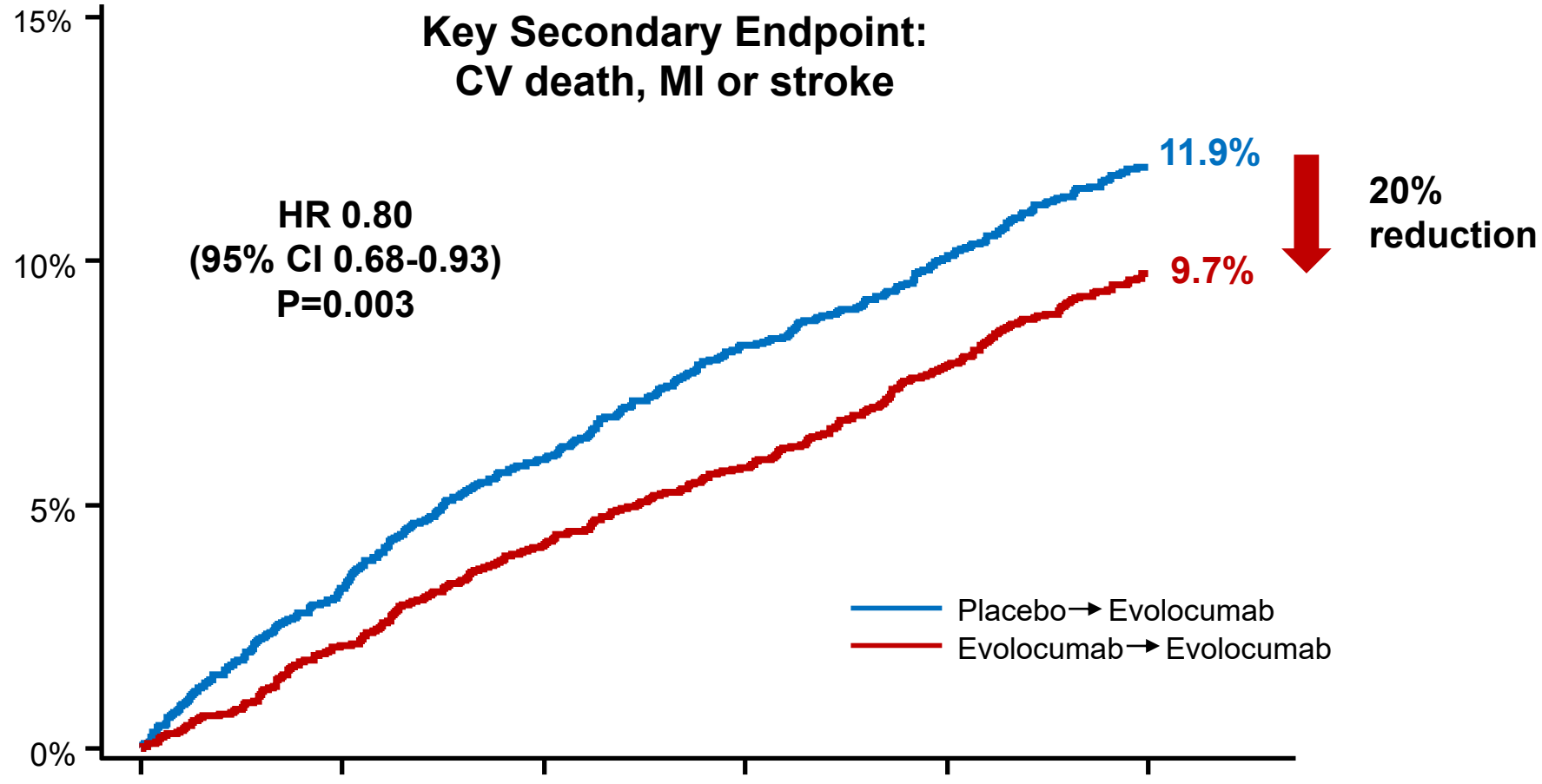
Efficacy during FOURIER-OLE



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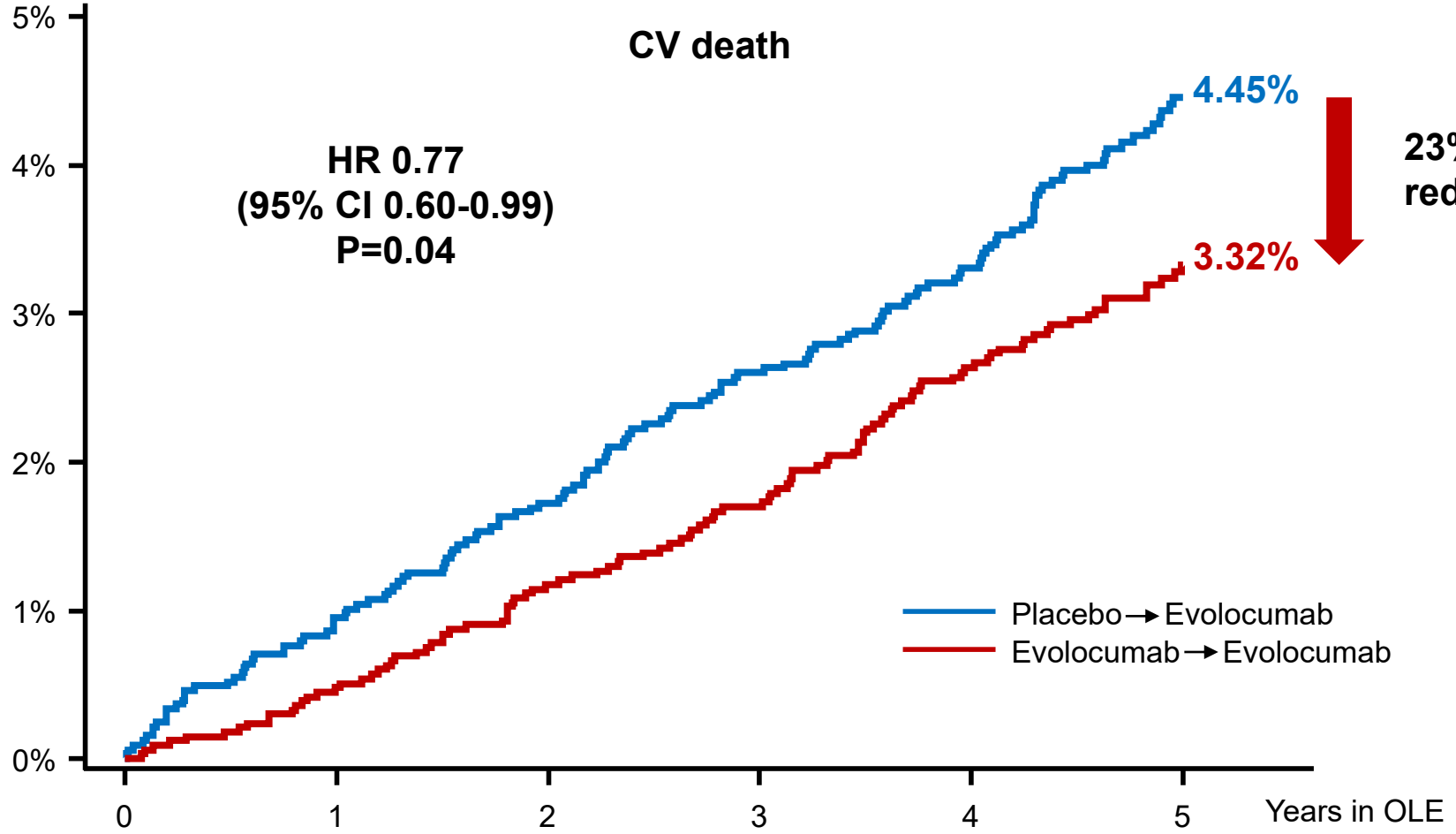
Efficacy during FOURIER-OLE Time Period



Number at risk:

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

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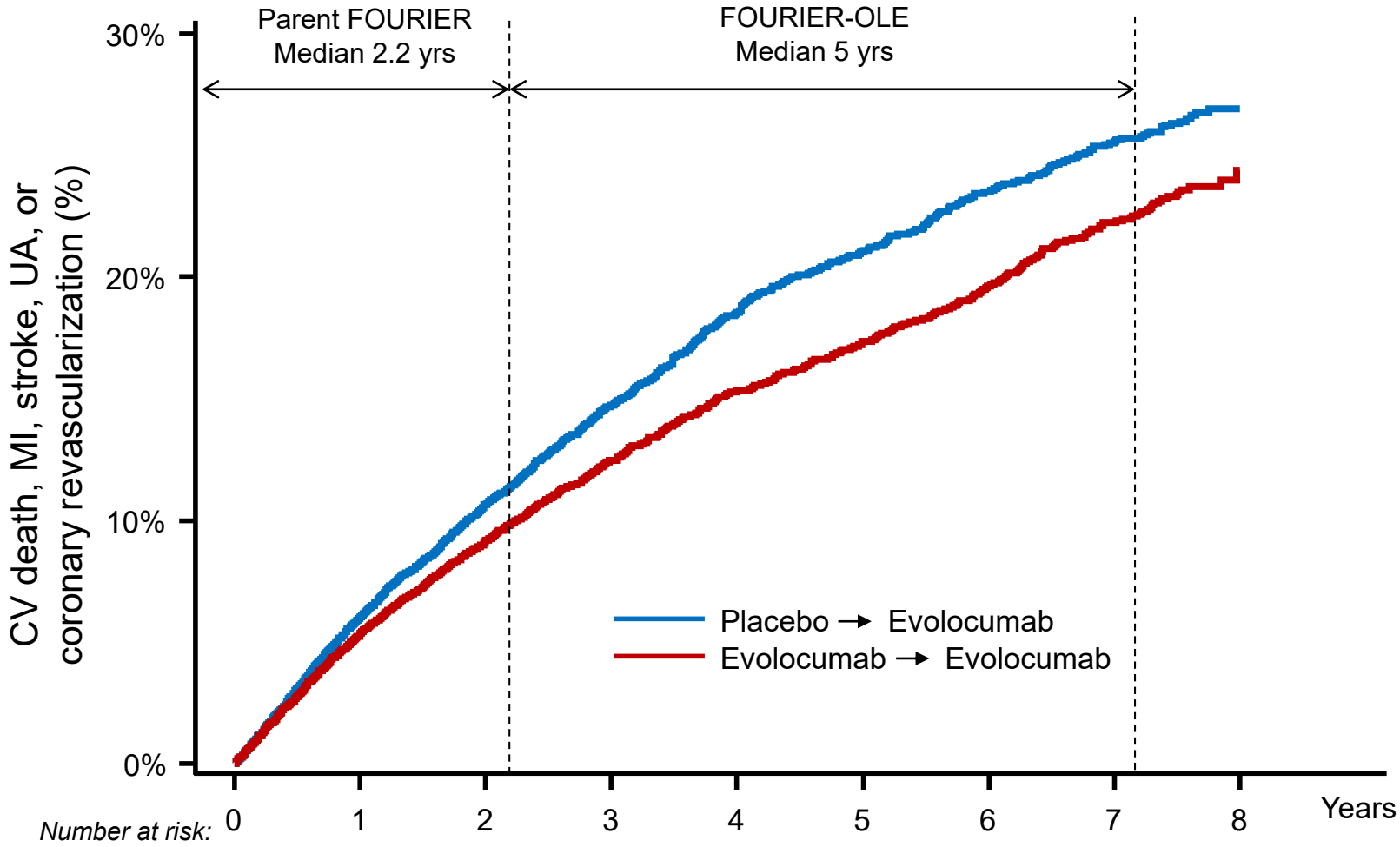
Efficacy during FOURIER & FOURIER-OLE

FOURIER Primary Endpoint



Number at risk:

	0	1	2	3	4	5	6	7	8
Placebo-Evolocumab	13780	12822	8467	3260	2654	2526	2372	1498	189
Evolocumab-Evolocumab	13784	12937	8683	3389	2814	2699	2550	1569	165

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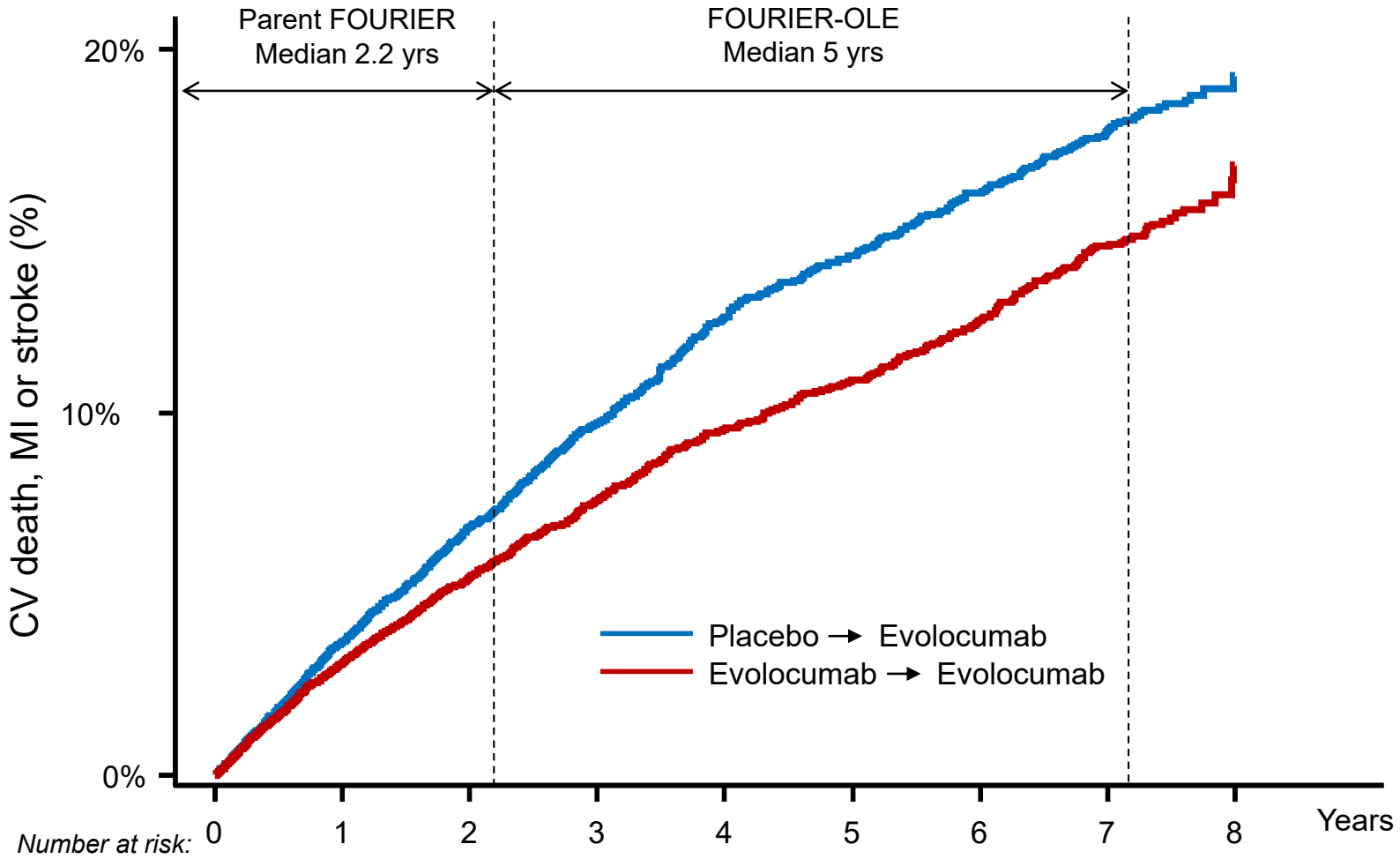
Efficacy during FOURIER & FOURIER-OLE

FOURIER Key Secondary Endpoint



Number at risk:	0	1	2	3	4	5	6	7	8
Placebo-Evolocumab	13780	13140	8846	3470	2861	2757	2621	1664	216
Evolocumab-Evolocumab	13784	13240	9051	3617	3046	2946	2810	1746	185

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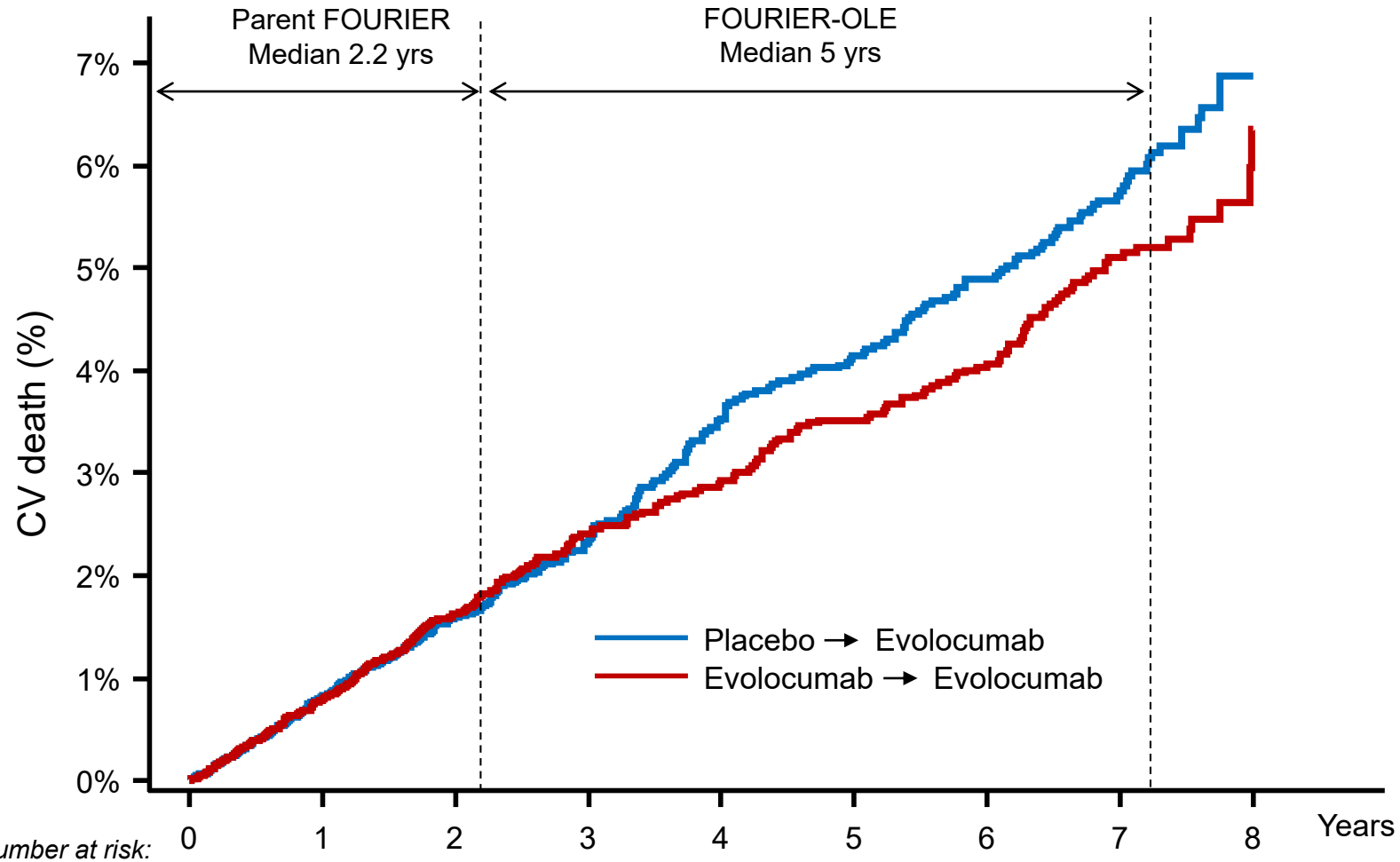
Efficacy during FOURIER & FOURIER-OLE

CV Death



Number at risk:

Placebo-Evolocumab	13780	13590	9399	3753	3167	3098	2996	1965	268
Evolocumab-Evolocumab	13784	13598	9464	3826	3270	3204	3109	1988	237

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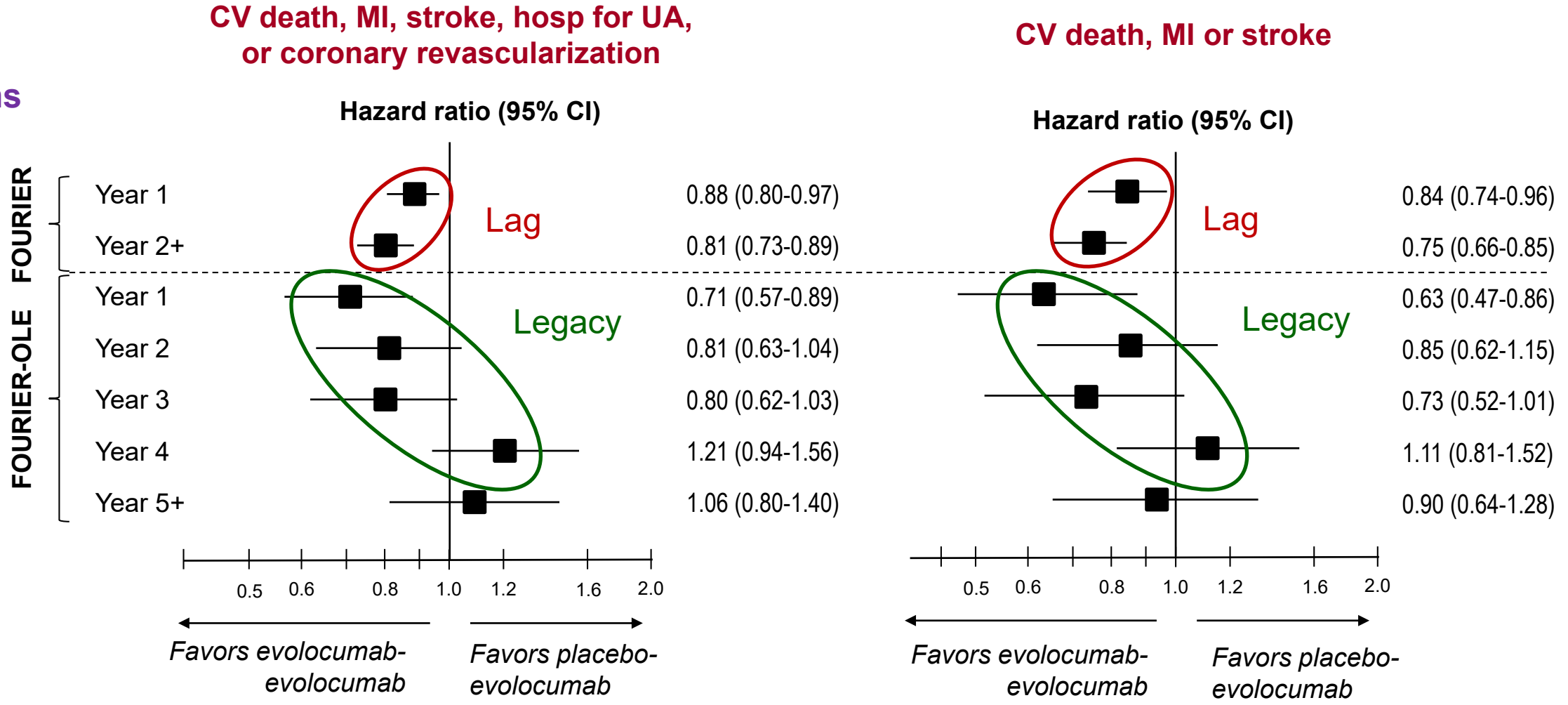
MACE by Year of Study

LDL-C Δ between arms

1.6 mM (62 mg/dl)

0.0 mM



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

Association Between Achieved LDL-Cholesterol and Long-term Cardiovascular and Safety Outcomes: An Analysis of the FOURIER and FOURIER-OLE Studies

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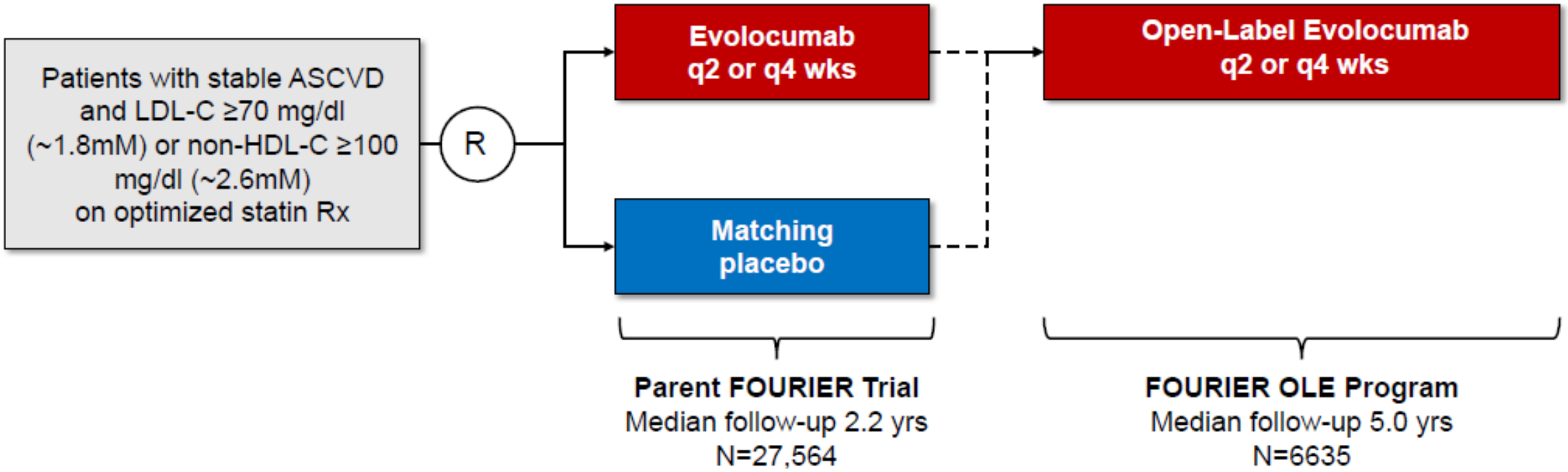
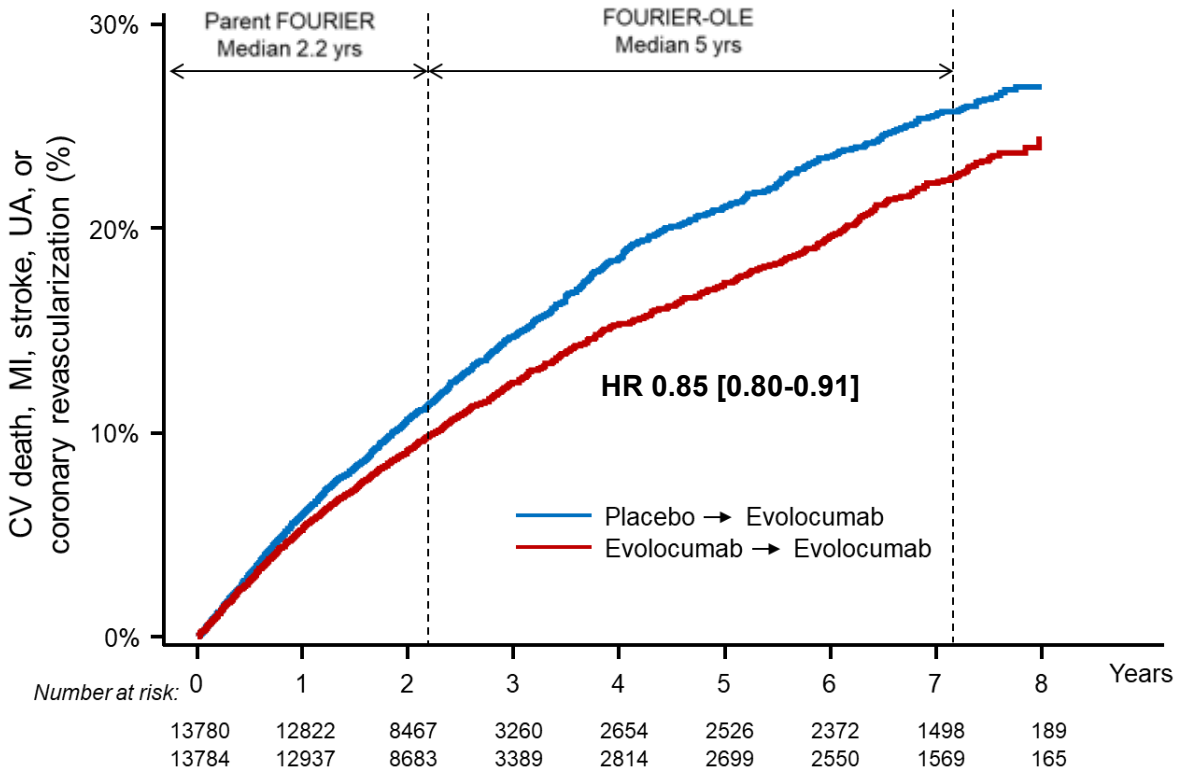
Study Schema: FOURIER and FOURIER-OLE



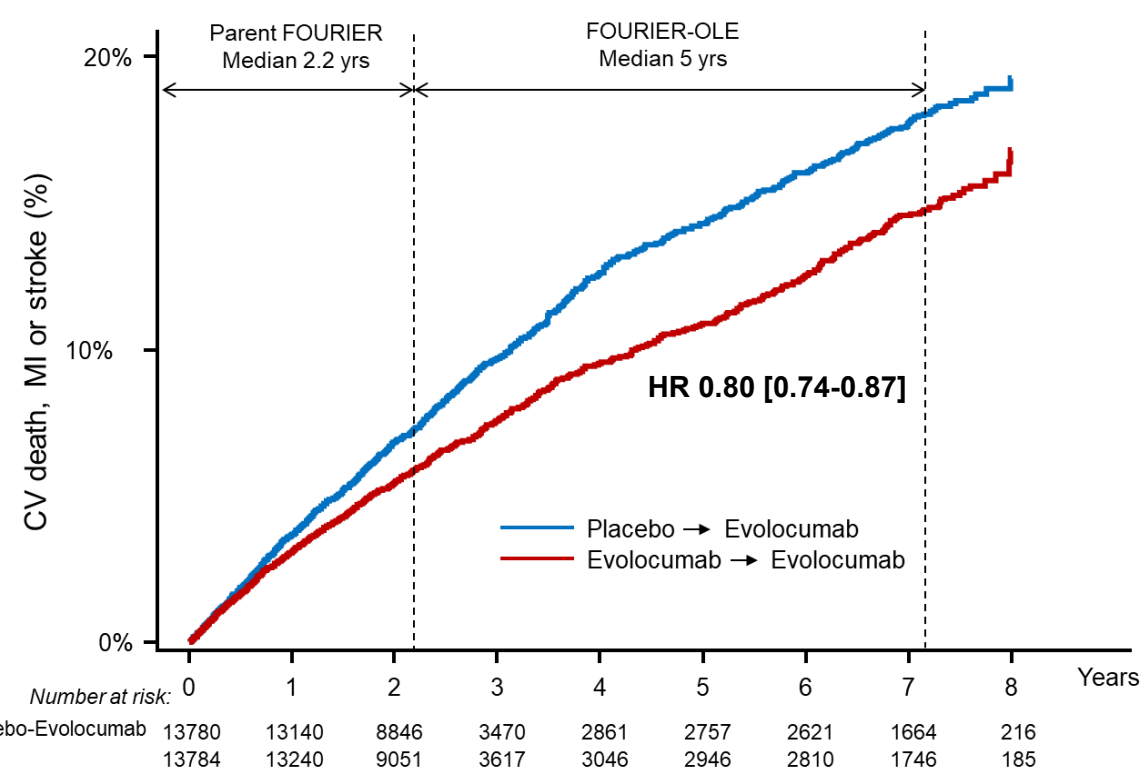
Sabatine et al. *NEJM* 2017; 376: 1713-1722.
O'Donoghue et al. *Circulation* 2022; 146:1109-1119.

Results of FOURIER and FOURIER-OLE – CV Outcomes

Primary Efficacy Endpoint

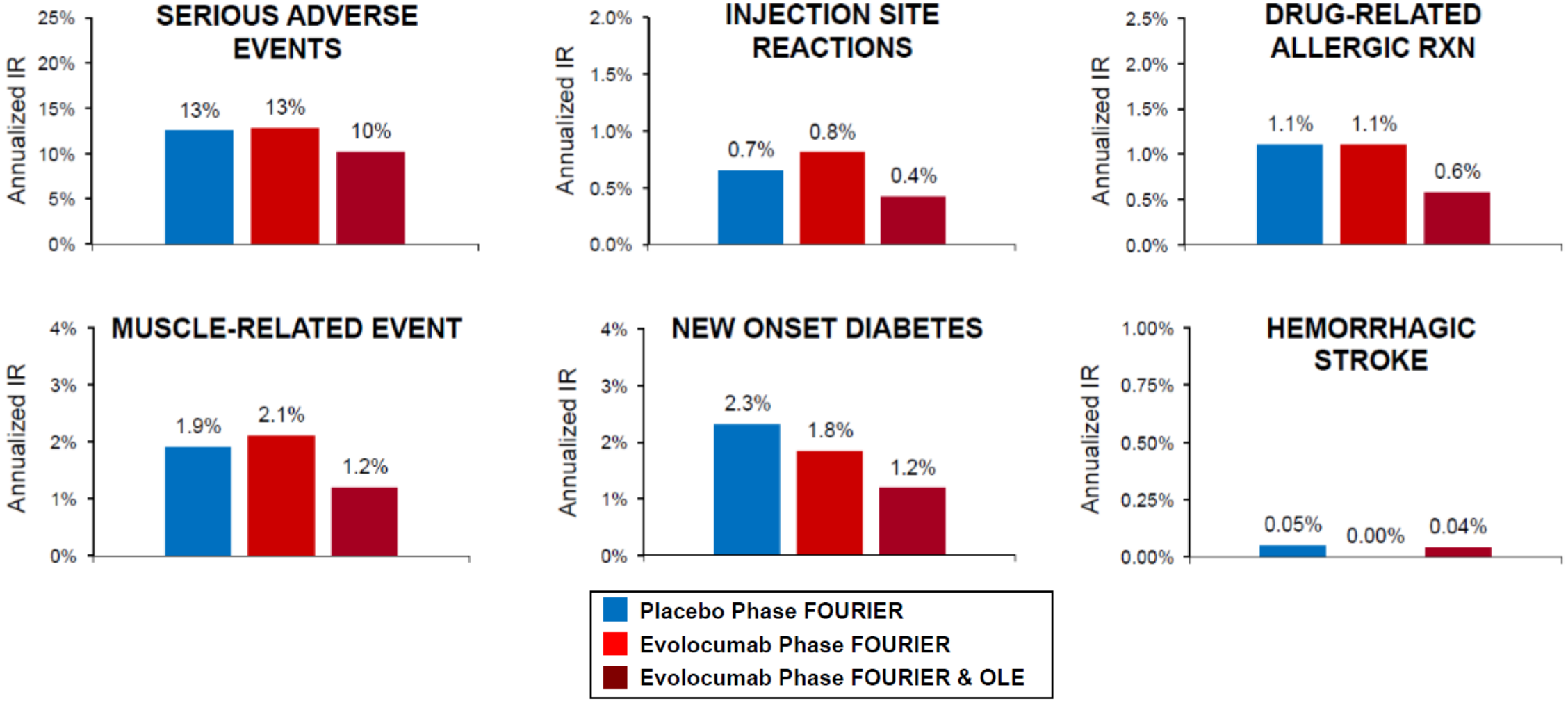


Key Secondary Efficacy Endpoint



O'Donoghue et al. *Circulation* 2022; 146:1109-1119.

Results of FOURIER-OLE - Safety



O'Donoghue et al. *Circulation* 2022; 146:1109-1119.

Evidence Gap

The optimal achieved LDL-C level with regards to cardiovascular and safety outcomes in the long term remains unclear.

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Objective

To explore the relationship between achieved LDL-C levels and the occurrence of long-term adverse cardiovascular and safety outcomes, down to very low (<20 mg/dL) achieved LDL-C levels.

Methods

- **Patients divided into 6 categories based on achieved LDL-C: <20, 20-<40, 40-<55, 55-<70, 70-<100, and ≥100 mg/dL**
- **CV outcomes**
  - Primary: CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina
  - Key secondary: CV death, MI, or stroke
- **Safety outcomes**
  - Serious adverse events, muscle-related events, new-onset diabetes mellitus, cataract-related adverse events, neurocognitive events, hemorrhagic stroke, malignancy, and non-CV death

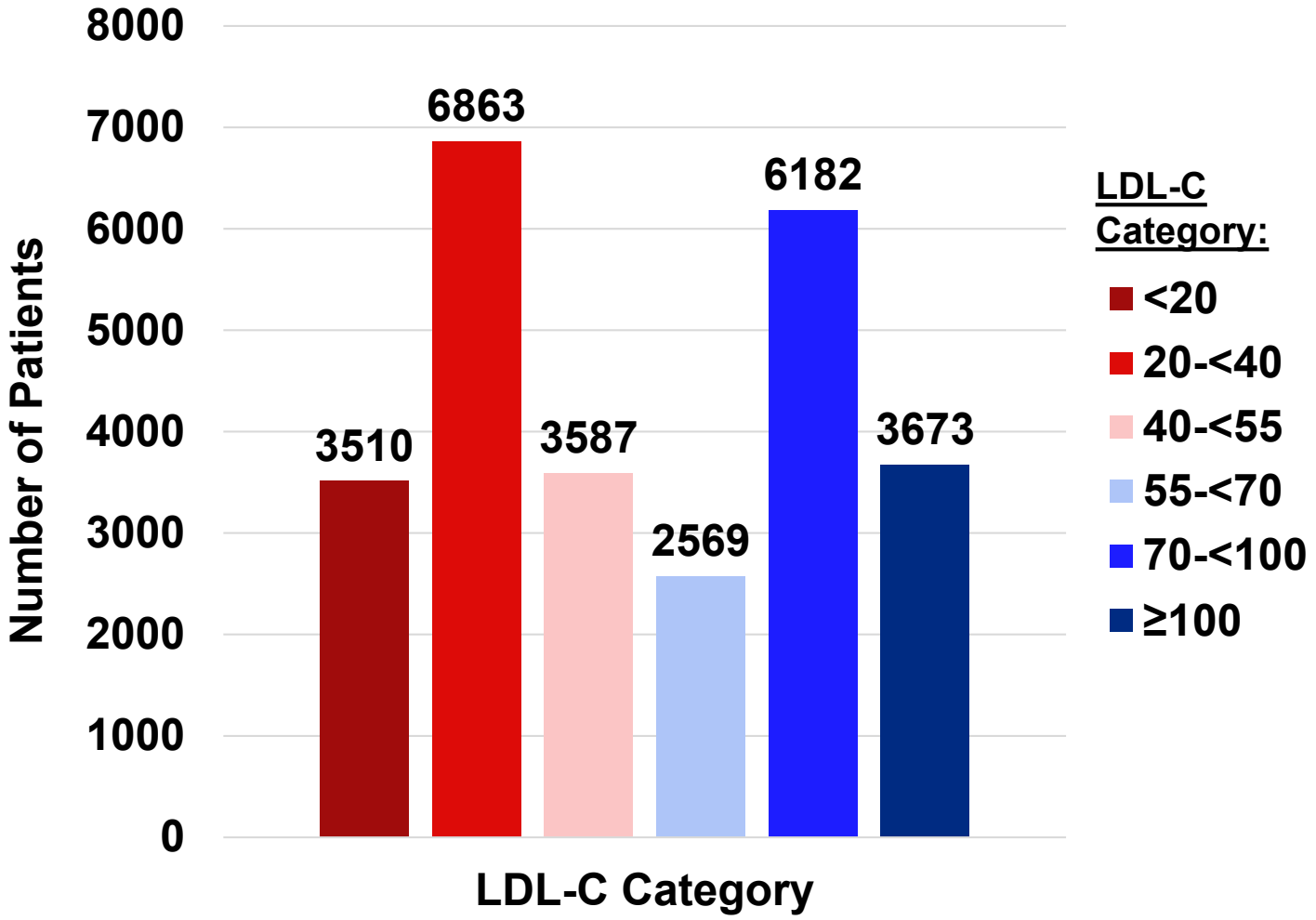
Methods (cont'd)

- Examined trends in baseline characteristics
- Annualized incidence rates and 95% confidence intervals were calculated for all cardiovascular and safety outcomes
- Multivariable models adjusted for baseline characteristics associated with achieved LDL-C, including age, BMI, sex, race, current smoker, prior MI, prior non-hemorrhagic stroke, history of diabetes, history of peripheral arterial disease, high-intensity statin use, ezetimibe use, and participation in OLE.

Cohort & Follow-Up

- 26,384 patients with achieved LDL-C levels in FOURIER and/or FOURIER-OLE
- 19,960 patients in FOURIER alone with a median follow-up 2.0 years
- 6,429 patients also participated in FOURIER-OLE with median follow up 4.9 years
- Including FOURIER & FOURIER-OLE, maximum follow-up 8.6 years

Achieved LDL-C Categories



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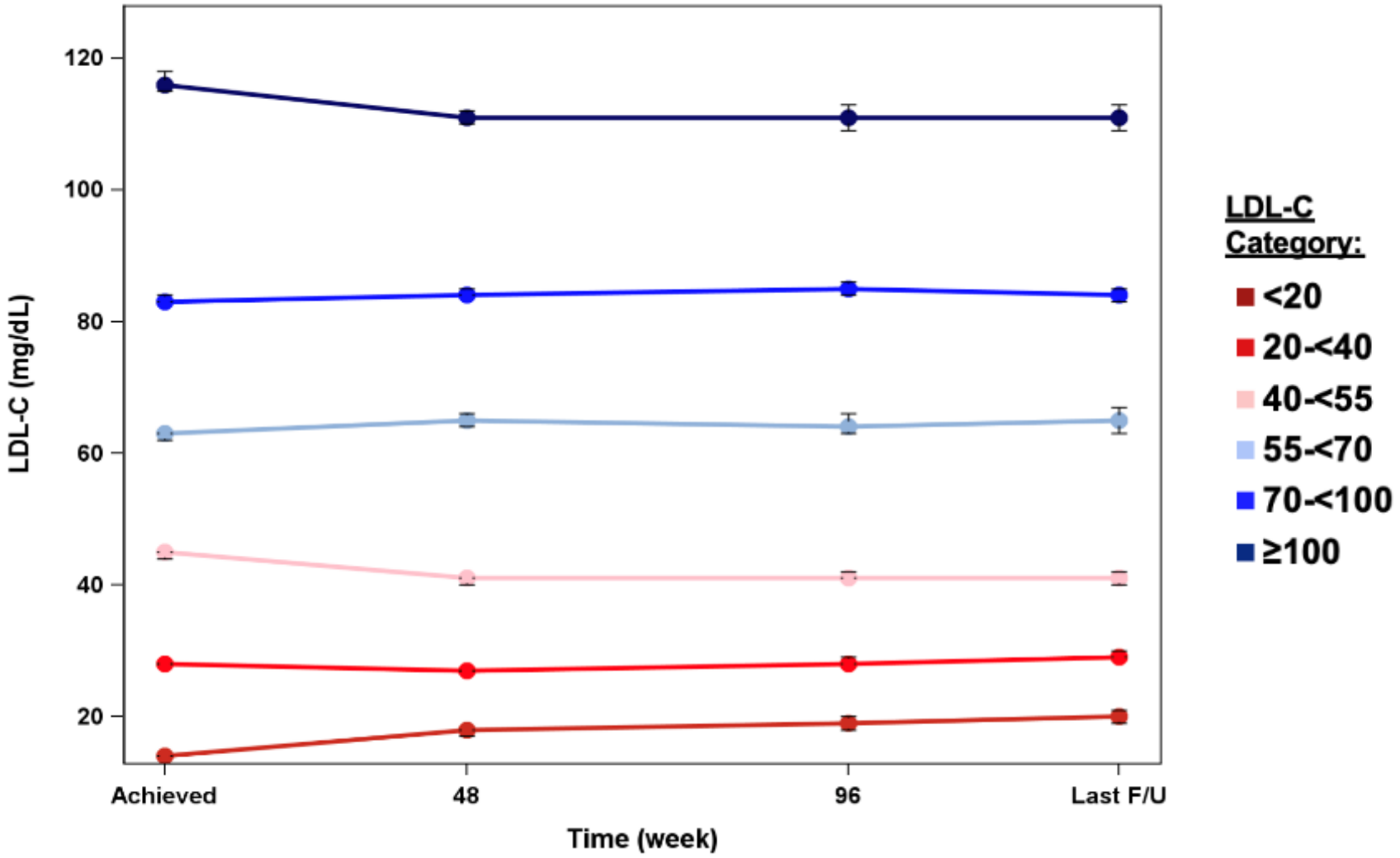
Achieved LDL-C Over Time



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Baseline Characteristics by Achieved LDL-C

	Achieved LDL-C level (mg/dL)						
	<20	20-<40	40-<55	55-<70	70-<100	≥100	P_{trend}
Age, mean (SD), yrs	63.5±8.7	63.2±8.8	61.6±8.9	62.0±9.3	62.7±9.0	61.2±9.0	<0.0001
Male	83.7%	78.9%	71.4%	71.4%	74.6%	70.7%	<0.0001
BMI, mean (SD), kg/m²	28.4±4.4	29.1±4.7	30.3±5.7	30.1±5.7	29.4±5.3	29.5±5.1	<0.0001
White race	84.0%	87.4%	87.0%	82.2%	82.5%	86.1%	0.0003
Prior MI	82.2%	81.6%	81.0%	79.3%	81.7%	79.9%	0.037
Non-hemorrhagic CVA	18.9%	18.3%	18.8%	19.7%	19.8%	20.8%	0.0019
Diabetes mellitus	34.9%	33.9%	40.6%	42.0%	35.8%	35.6%	0.051
Current smoker	26.6%	26.2%	28.0%	28.9%	28.7%	32.6%	<0.0001
High-intensity statin	65.8%	69.1%	72.5%	69.6%	68.2%	71.4%	0.0043
Baseline LDL-C, median (IQR), mg/dL	82 (75, 94)	90 (79, 103)	95 (81, 112)	85 (74, 107)	90 (81, 102)	115 (101, 137)	<0.0001

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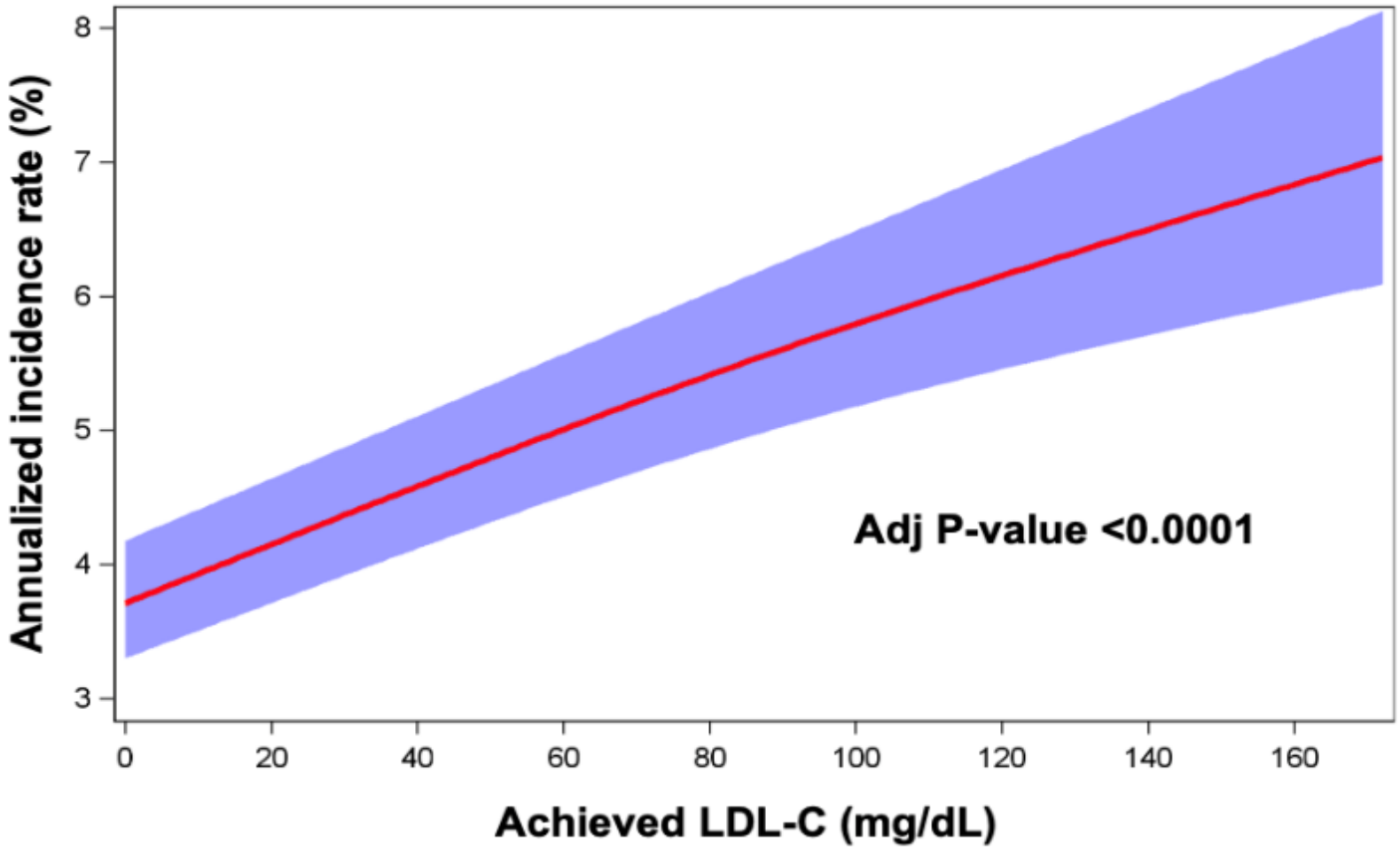
CV Outcomes and Achieved LDL-C

Primary endpoint: CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina



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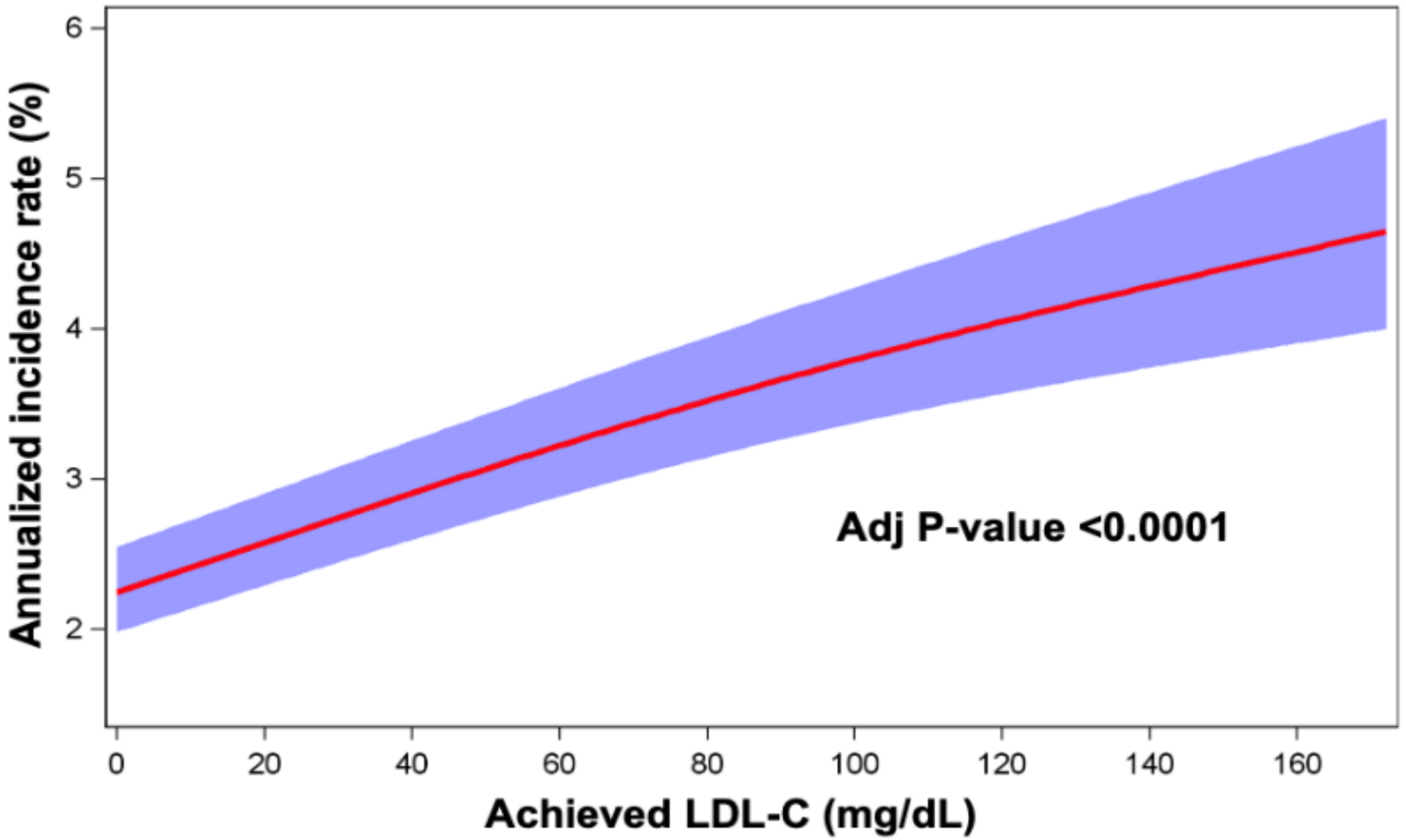
CV Outcomes and Achieved LDL-C

Key secondary endpoint: CV death, MI, or stroke



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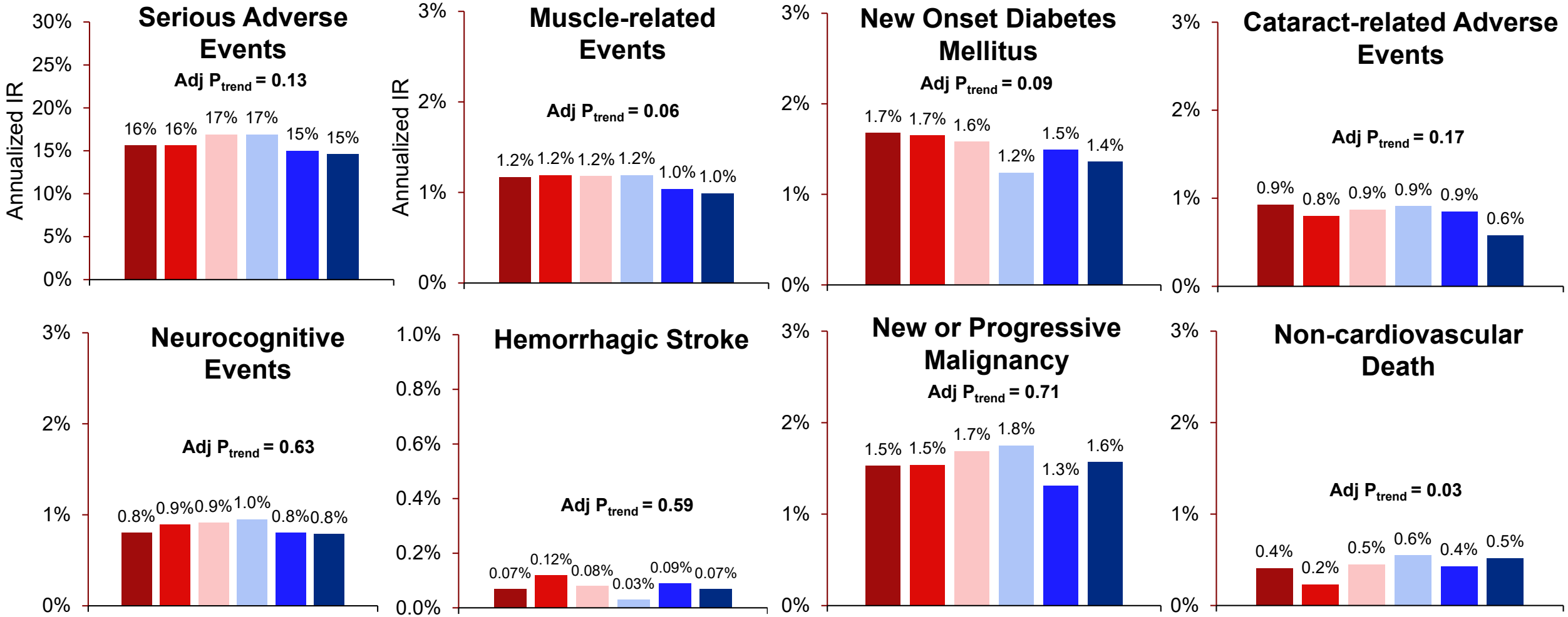
Safety and Achieved LDL-C



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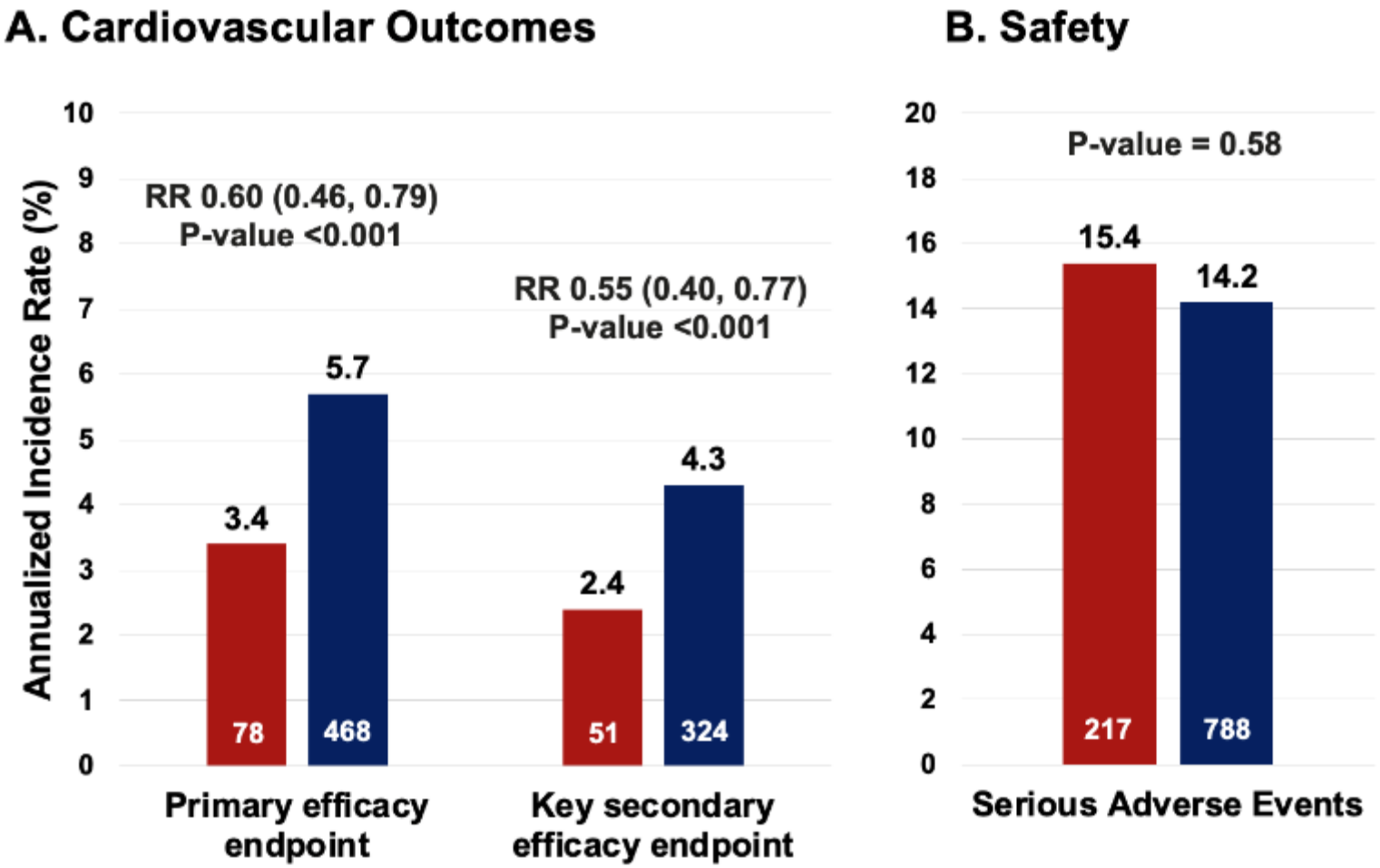
MACE & Safety w/ LDL-C <10 vs ≥100 mg/dL



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Limitations

- All patients enrolled in FOURIER had stable ASCVD with baseline LDL-C ≥70 mg/dL and non-HDL ≥ 100 mg/dL on GDMT, and thus findings may not be applicable to all patients in general practice
- Comparisons based on a post-randomization variable and, despite multivariable analysis, may be subject to residual confounding

Summary & Conclusions

- Monotonic relationship between lower achieved LDL-C levels, down to very low LDL-C levels <20 mg/dL, and a lower risk of cardiovascular events up to 8.6 years of follow-up
- No serious safety concerns with low LDL-C during the extended follow up period
- **Altogether, these data suggest that targeting a very low LDL-C level is both effective and safe for patients with atherosclerotic cardiovascular disease**