Evolocumab Outcomes Trial – FOURIER

SC-AT-AMG145-01252 0526

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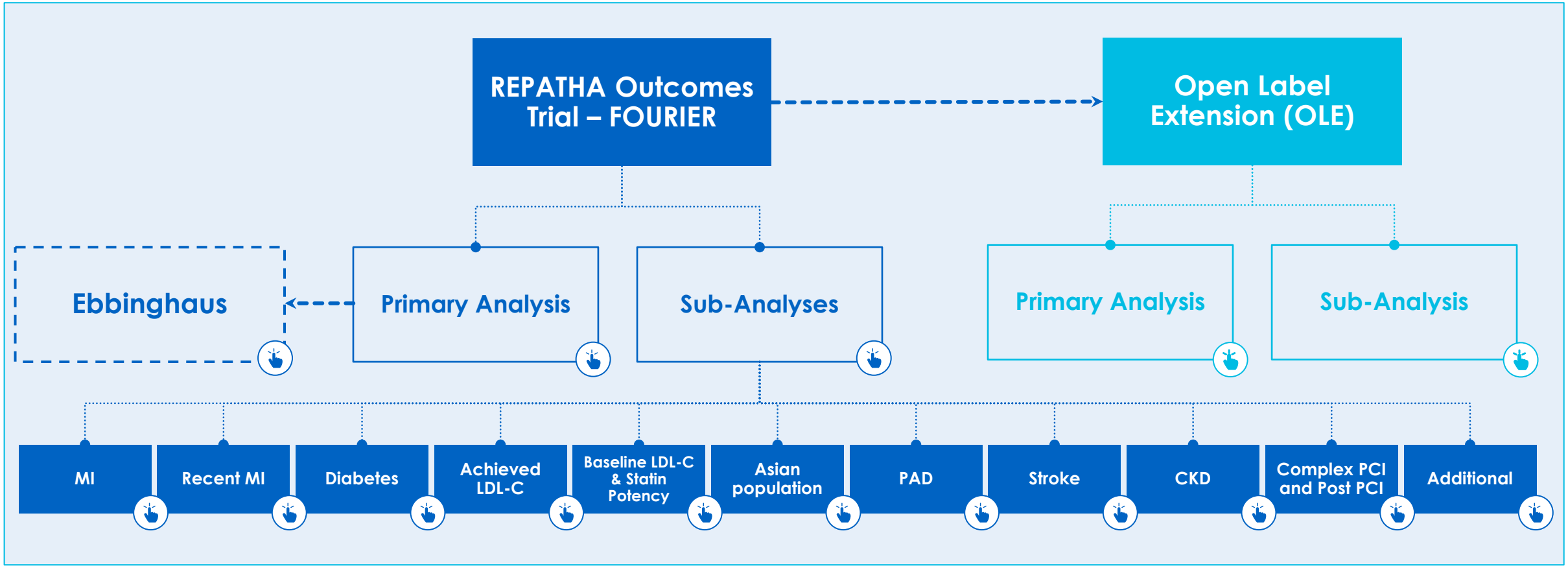

FOURIER: Primary Analysis

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

Additional Information

Baseline Lipid-Lowering Therapies and Lipid Parameters Were Balanced Between Treatment Arms

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Statin use – n (%)		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe – n (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications – n/total n (%)		
Aspirin and/or $P2Y_{12}$ inhibitor	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB and/or aldosterone antagonist	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Lipid measures - Median (IQR) – mg/dL		
LDL cholesterol	92 (80, 109)	92 (80, 109)
Total cholesterol	168 (151, 188)	168 (151, 189)
HDL cholesterol	44 (37, 53)	44 (37, 53)
Triglycerides	134 (101, 183)	133 (99, 181)
Lp(a) - nmol/L	37 (13, 166)	37 (13, 164)

Note: mmol/L version

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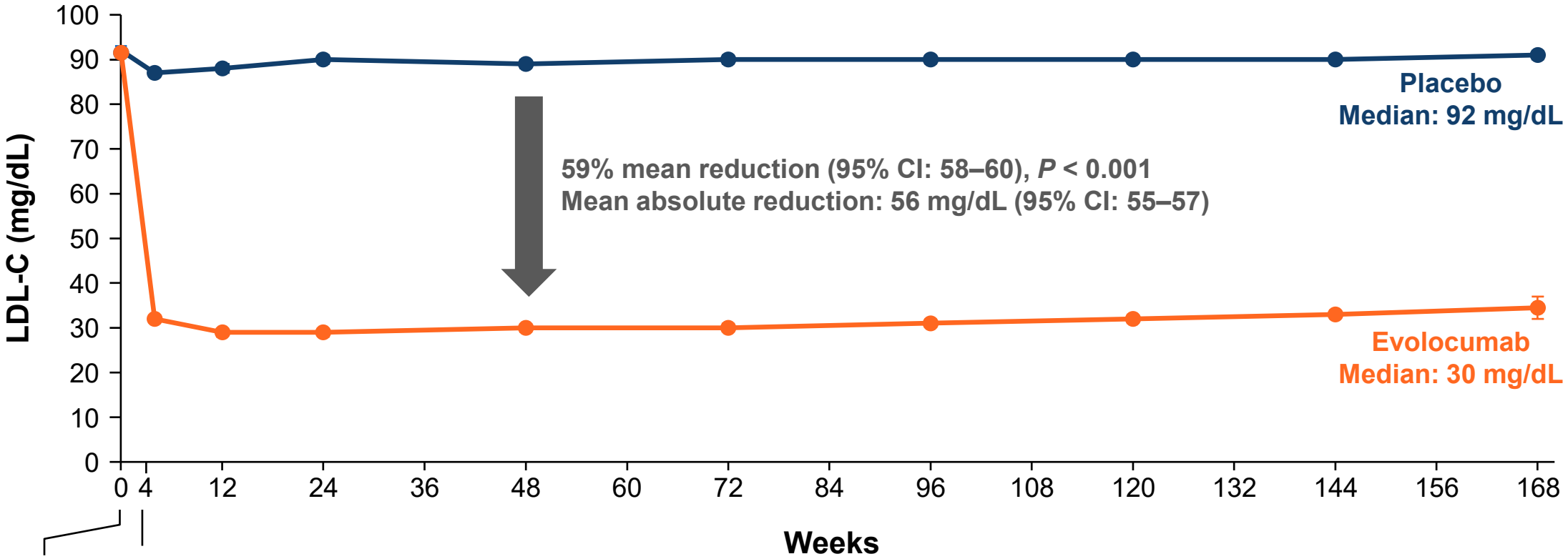
ACE inhibitor or ARB and/or aldosterone antagonist	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Lipid measures - Median (IQR) – mmol/L		
LDL cholesterol	2.38 (2.07, 2.82)	2.38 (2.07, 2.82)
Total cholesterol	4.34 (3.90, 4.86)	4.34 (3.90, 4.89)
HDL cholesterol	1.14 (0.96, 1.37)	1.14 (0.96, 1.37)
Triglycerides	1.51 (1.14, 2.07)	1.50 (1.12, 2.04)
Lp(a) - nmol/L	0.96 (0.34, 4.29)	0.96 (13, 4.24)

AMGEN

Significant LDL-C Reduction in Evolocumab Group Compared With Placebo Group



No. at risk											
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6,926	3,352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6,958	3,323	768

Note: mmol/L version

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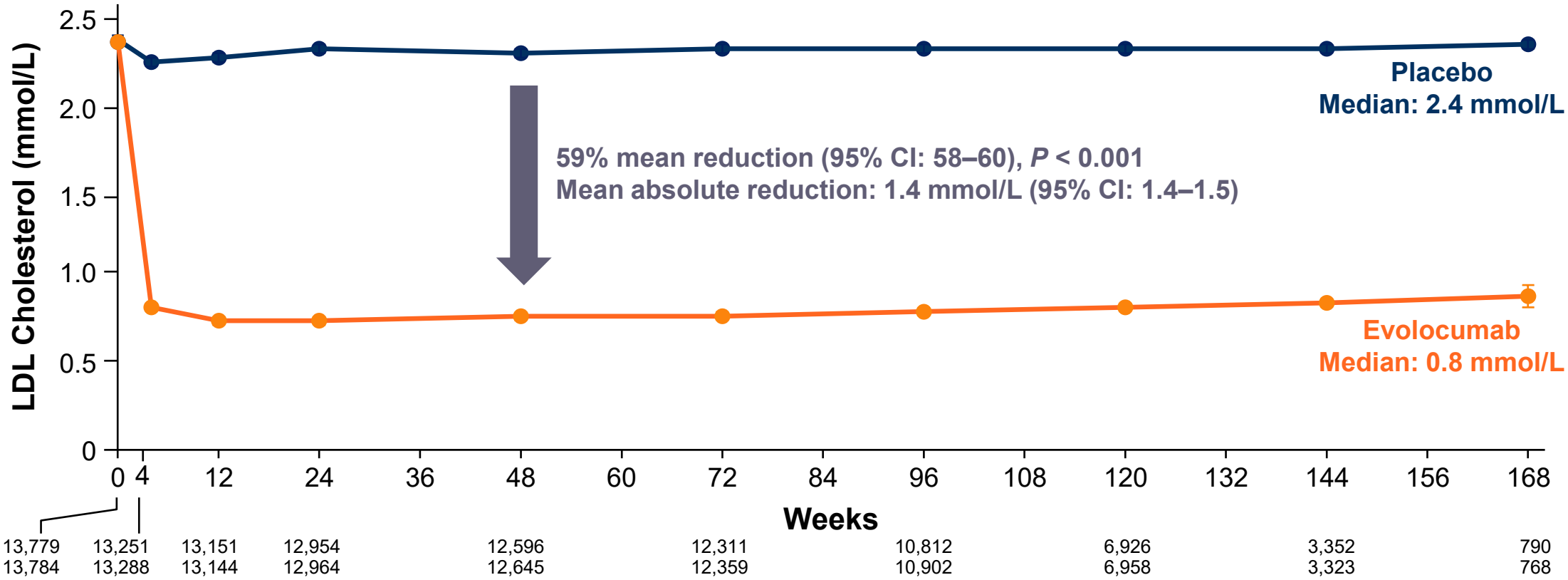
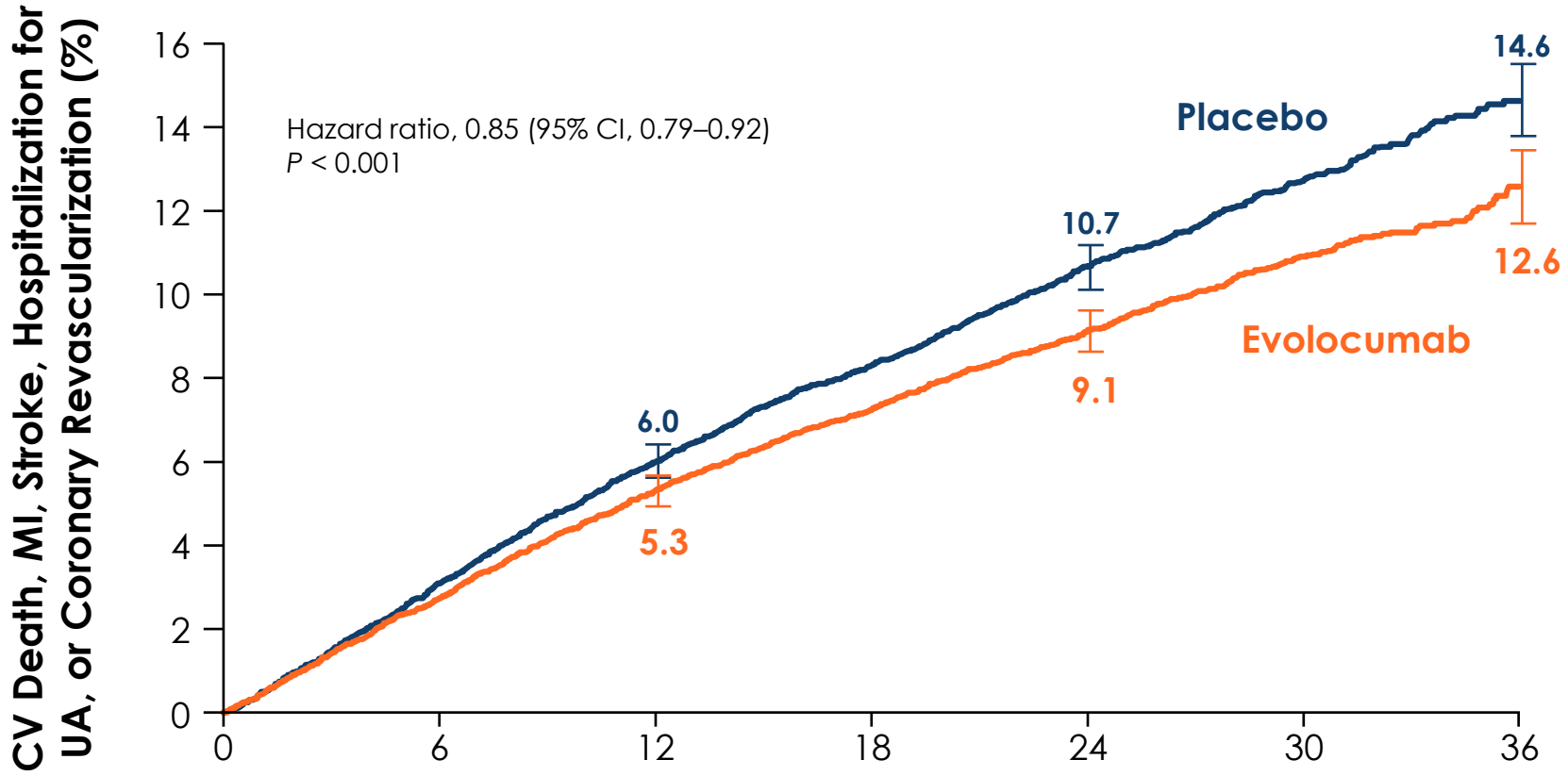


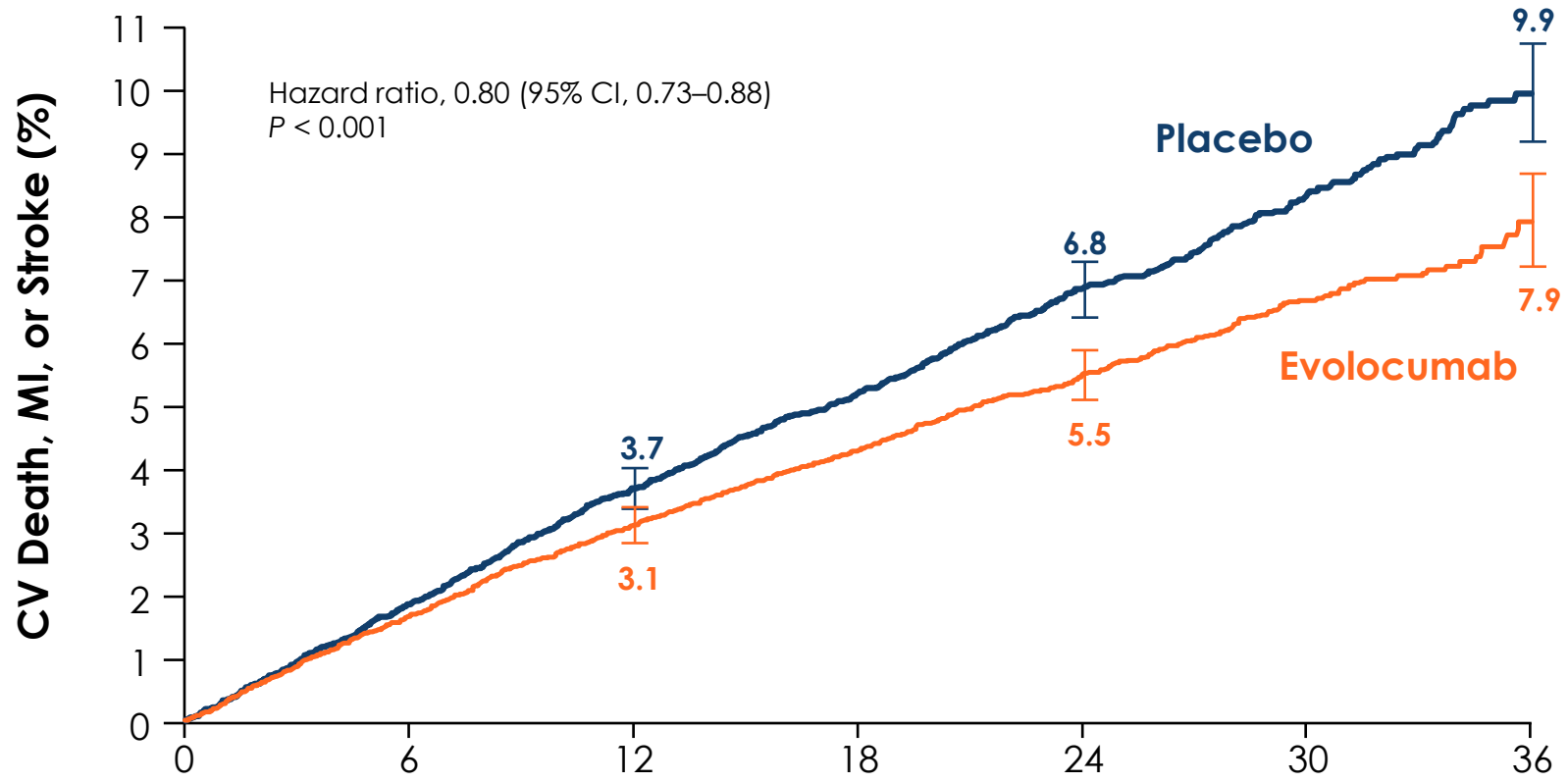
No. at risk													
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6,926	3,352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6,958	3,323	768

Evolocumab Reduced 5-Point MACE by 15% vs Placebo



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689

Evolocumab Reduced 3-Point MACE by 20% vs Placebo



No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7,944	3,893	731
Evolocumab	13,784	13,501	13,241	12,456	8,094	3,935	724

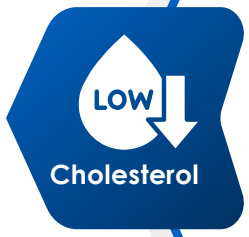
No Notable Differences in the Rate of AEs, SAEs, or AEs Leading to Discontinuation

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3,410 (24.8)	3,404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)

Incidence of Neurocognitive Events, Cataracts, and New-Onset Diabetes Was Similar Between the Evolocumab and Placebo Arms

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Injection-site reaction	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results - n/total n (%)		
Aminotransferase > 3x ULN	240/13,543 (1.8)	242/13,523 (1.8)
Creatinine kinase > 5x ULN	95/13,543 (0.7)	99/13,523 (0.7)

Summary



When added to statin therapy, evolocumab reduced LDL-C by 59% from baseline compared with placebo,

Evolocumab significantly reduced the risk of cardiovascular events by 15% and 20% for the primary and key secondary composite endpoints, respectively

A Landmark analysis showed that the magnitude of risk reduction was 19% and 23% beyond the first year for the primary and secondary endpoint, respectively

No notable differences were observed in the rate of AEs, SAEs, or AEs leading to discontinuation between the evolocumab and placebo arms

FOURIER: Sub-Analyses

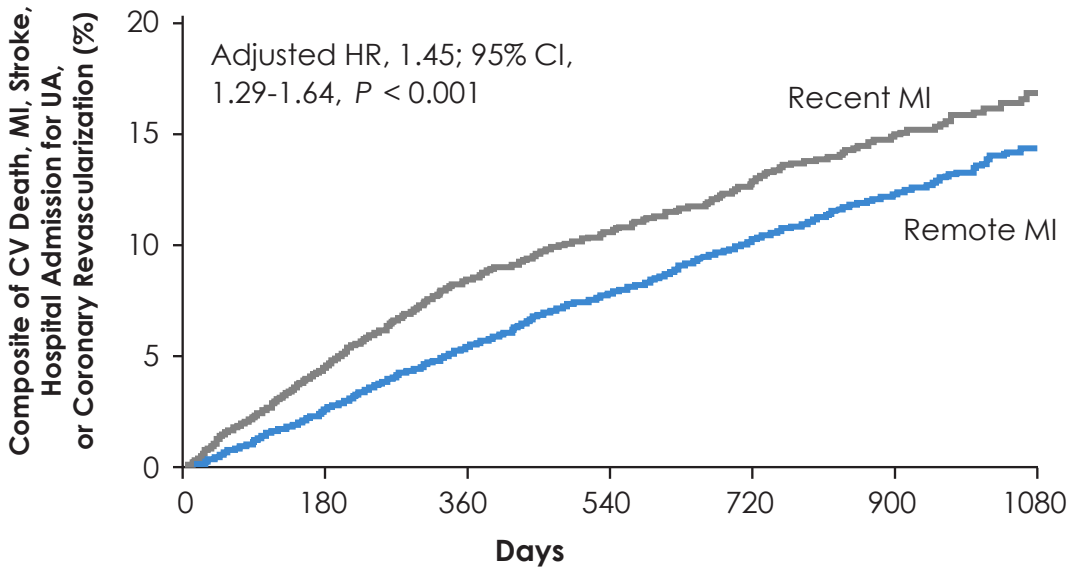
Sub-Analysis: Recent MI

Gencer B, et al. *JAMA Cardiology*. 2020;5:952-957.

Additional Information

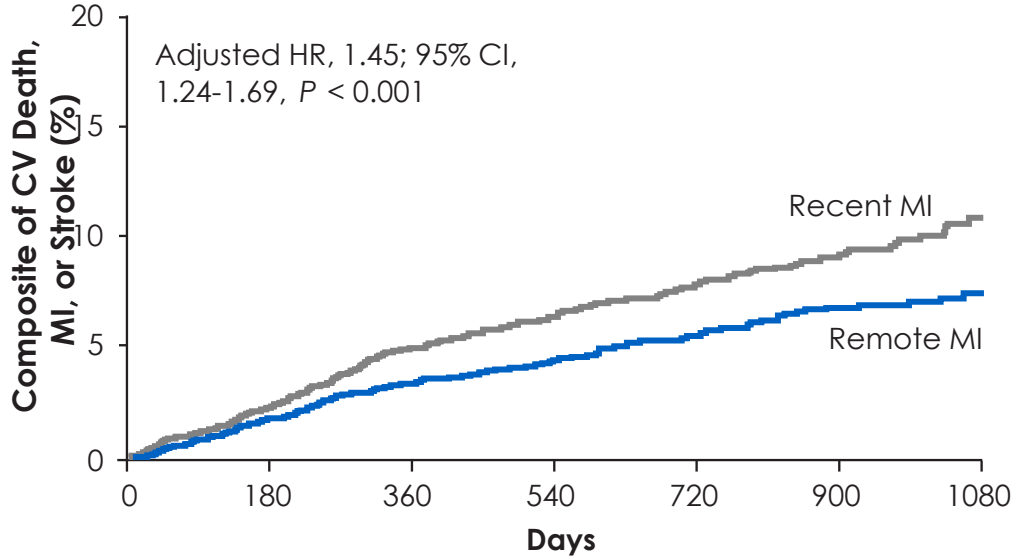
In the Placebo Arm, the Incidences of Both 5-Point MACE (17.2% vs 14.4%) and 3-Point MACE (10.9% vs 9.5%) Were Higher in Patients With Recent MI vs Those With Remote MI

5-Point MACE



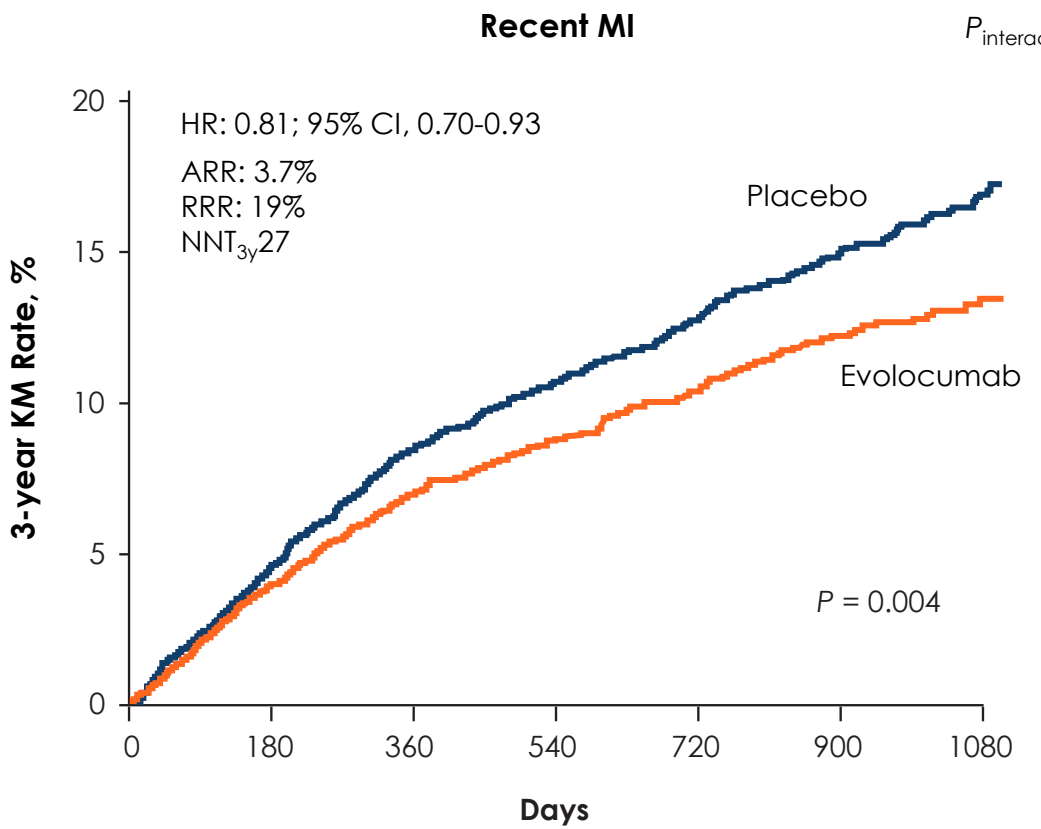
No. at Risk							
Recent MI	2,890	2,748	2,628	2,462	1,716	999	309
Remote MI	8,301	8,034	7,770	7,204	4,695	2,298	468

3-Point MACE

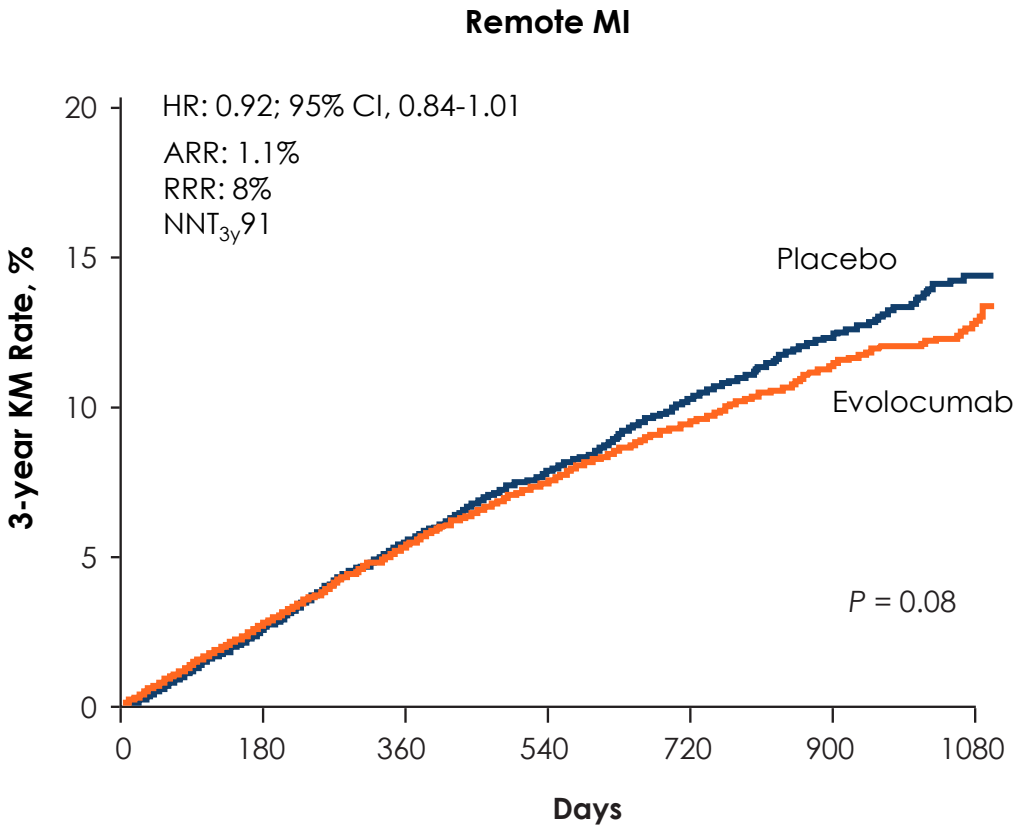


No. at Risk							
Recent MI	2,890	2,813	2,732	2,586	1,823	1,066	330
Remote MI	8,301	8,124	7,949	7,456	4,896	2,433	502

Patients Treated With Evolocumab Within 1 Year of Their Most Recent MI Tended to Experience Greater CV Risk Reduction for 5-Point MACE



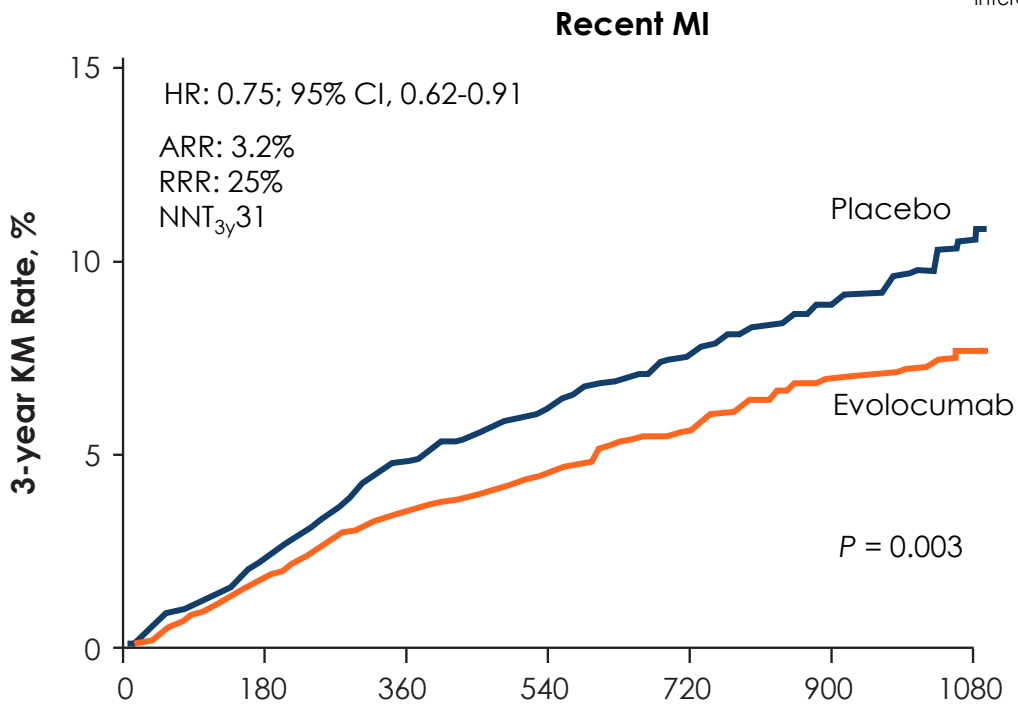
No. at Risk							
Placebo	2,890	2,748	2,628	2,462	1,716	999	309
Evolocumab	2,821	2,696	2,602	2,470	1,705	988	299



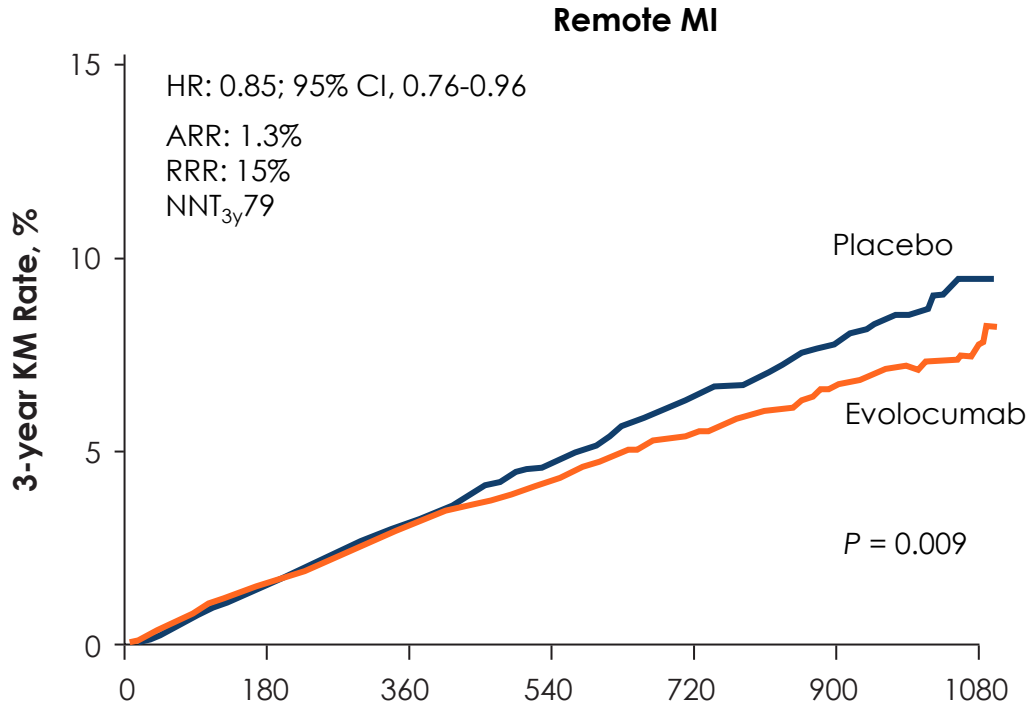
No. at Risk							
Placebo	8,301	8,034	7,770	7,204	4,695	2,298	468
Evolocumab	8,308	8,058	7,796	7,286	4,791	2,332	480

Patients Treated With Evolocumab Within 1 Year of Their Most Recent MI Tended to Experience Greater CV Risk Reduction for 3-Point MACE

$P_{interaction}$ = 0.24



No. at Risk							
Placebo	2,890	2,813	2,732	2,586	1,823	1,066	330
Evolocumab	2,821	2,754	2,697	2,582	1,793	1,045	317



No. at Risk							
Placebo	8,301	8,124	7,949	7,456	4,896	2,433	502
Evolocumab	8,308	8,142	7,984	7,537	5,008	2,457	507

Summary

In patients with a recent MI, within 1 year, evolocumab reduced the relative risk of CV death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization by 19% and CV death, MI, or stroke by 25%

Patients with recent MI were at a higher risk of CV events and showed greater ARRs with evolocumab than those with more remote MIs

Sub-Analysis: MI with high-risk features:

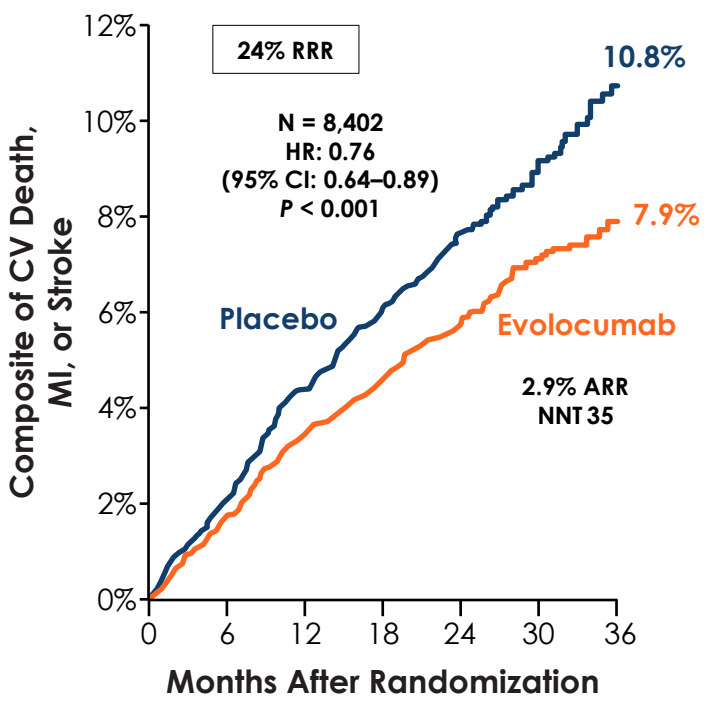
- recent MI
- multiple prior MIs
- residual multivessel coronary artery disease

Sabatine MS, et al. *Circulation*. 2018;138:756-766.

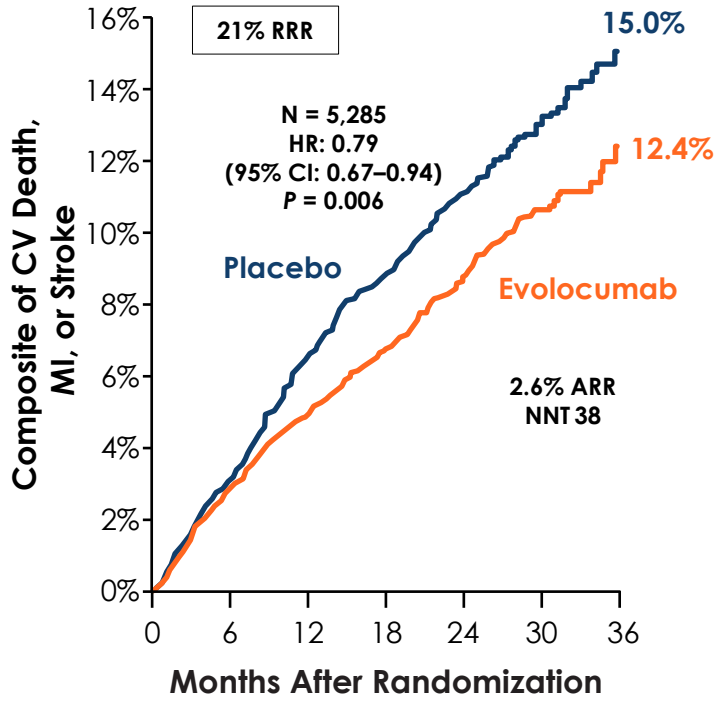
Additional Information

Patients With Higher Baseline CV Risk Benefitted from Intensive LDL-C Lowering With Evolocumab, with >20% RRR in 3-Point MACE

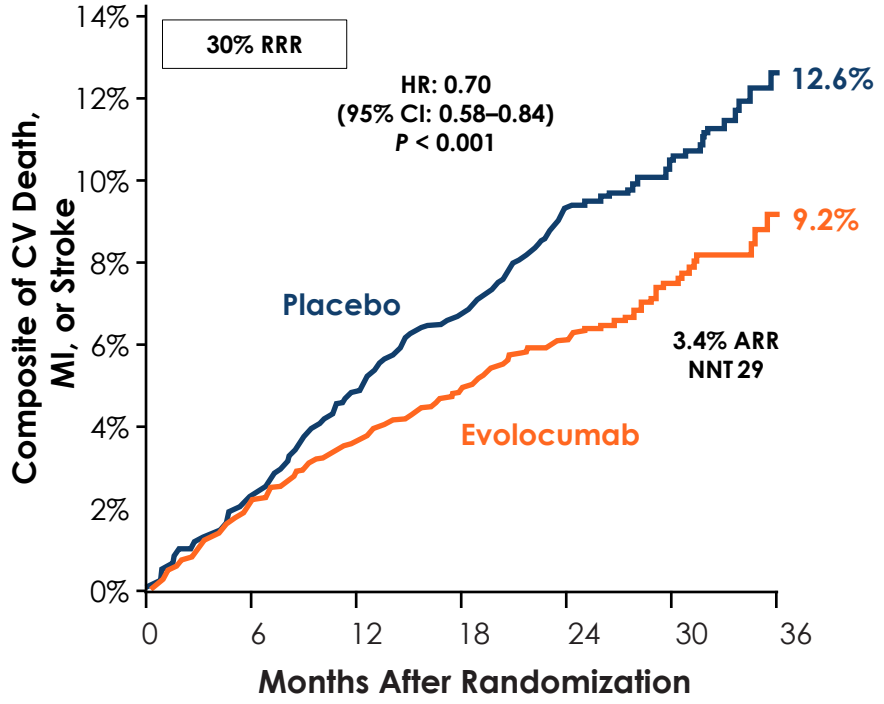
Recent MI (< 2 Years)



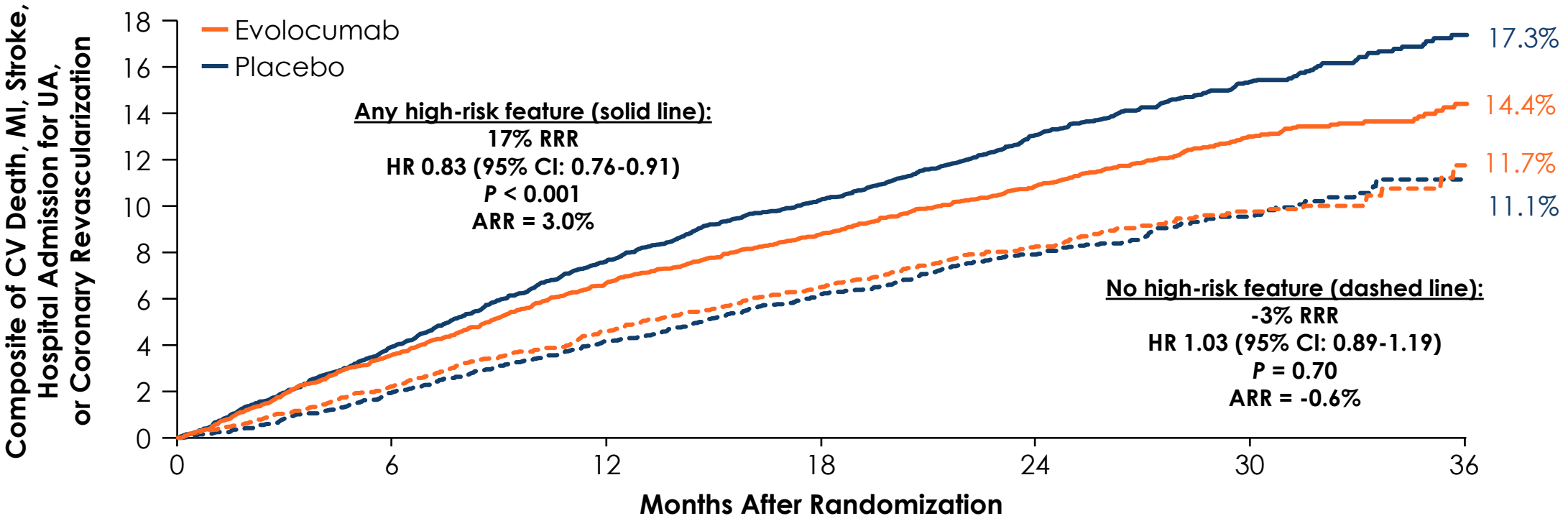
Multiple Events (≥ 2 Prior MIs)



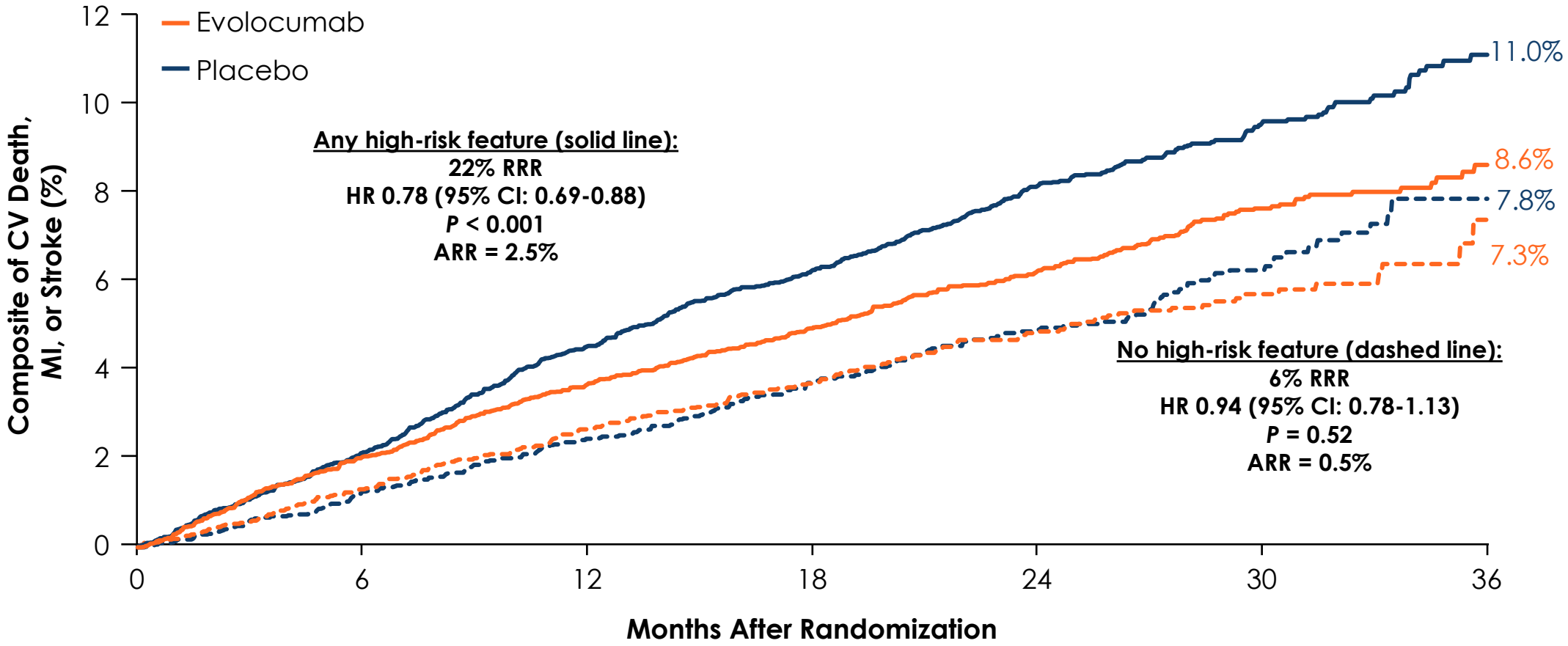
Multivessel Disease



In Patients With at Least One High-Risk Feature, Evolocumab Reduced the Risk of 5-Point MACE by 17%



In Patients With at Least One High-Risk Feature, Evolocumab Reduced the Risk of 3-Point MACE By 22%



Summary

Among the subgroup of patients with prior MI, those with a more recent MI, multiple prior MIs, or residual multivessel CAD experienced substantial relative and absolute risk reductions with LDL-C lowering with evolocumab

Patients with the greatest burden of coronary atherosclerosis have the greatest potential for clinical benefit from aggressive LDL-C lowering

Overall Summary: Evolocumab Treatment Reduced CV death, MI, and Stroke in Patients With MI

There were 22,351 MI patients within the FOURIER trial (81% of overall trial)

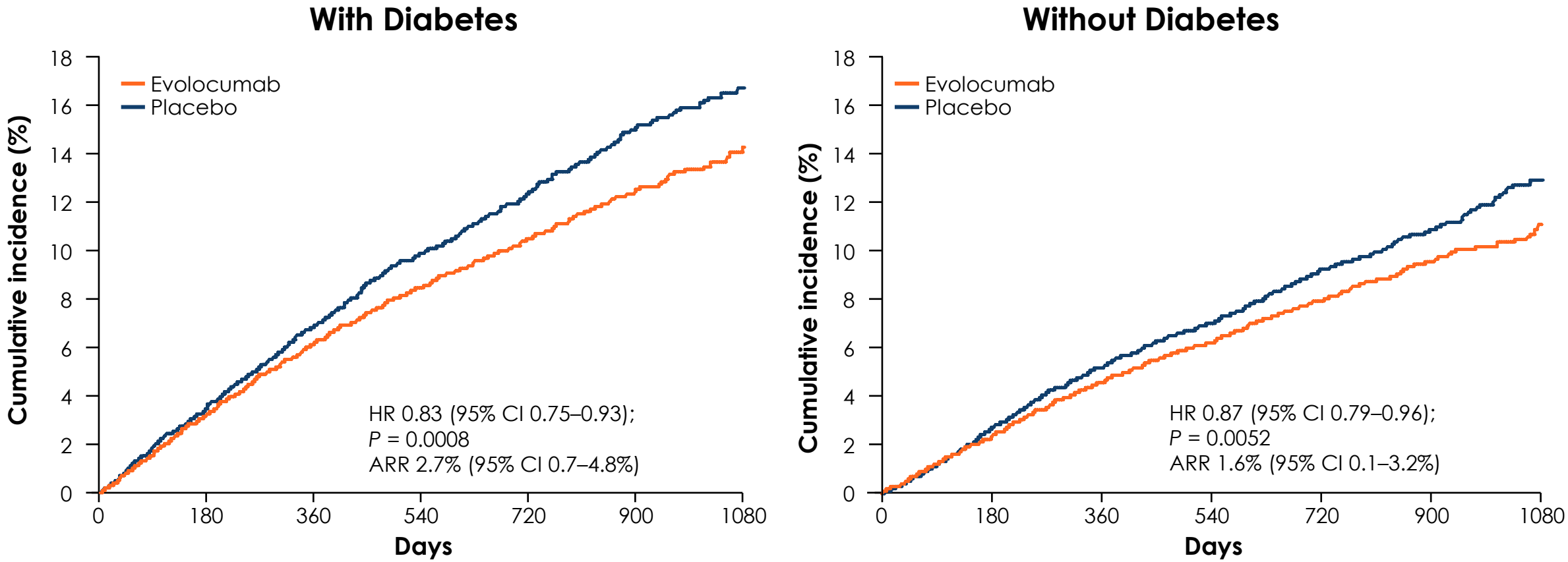
Type of MI Patient: **Prior MI** N = 22,351	Type of MI Patient: **≥ 2 Prior MIs** N = 5,285	Type of MI Patient: **Recent MI <2 years** N = 8,402	Type of MI Patient: **Recent MI <1 year** N = 5,711
ARR 1.9%	ARR 2.6%	ARR 2.9%	ARR 3.2%
RRR 18%	RRR 21%	RRR 24%	RRR 25%
NNT 54	NNT 38	NNT 35	NNT 31

Sub-Analysis: Diabetes

Sabatine MS, et al. *Lancet Diab Endocrinol.* 2017;5:941-950.

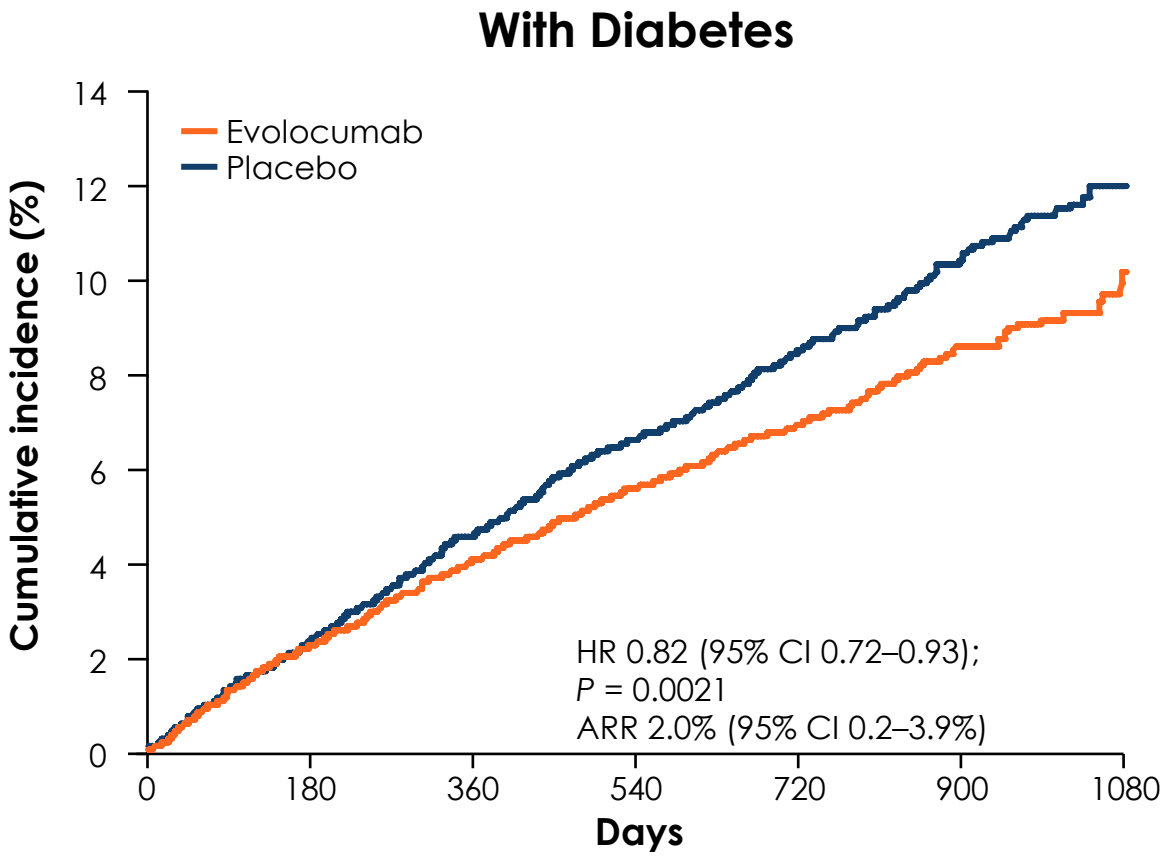
Additional Information

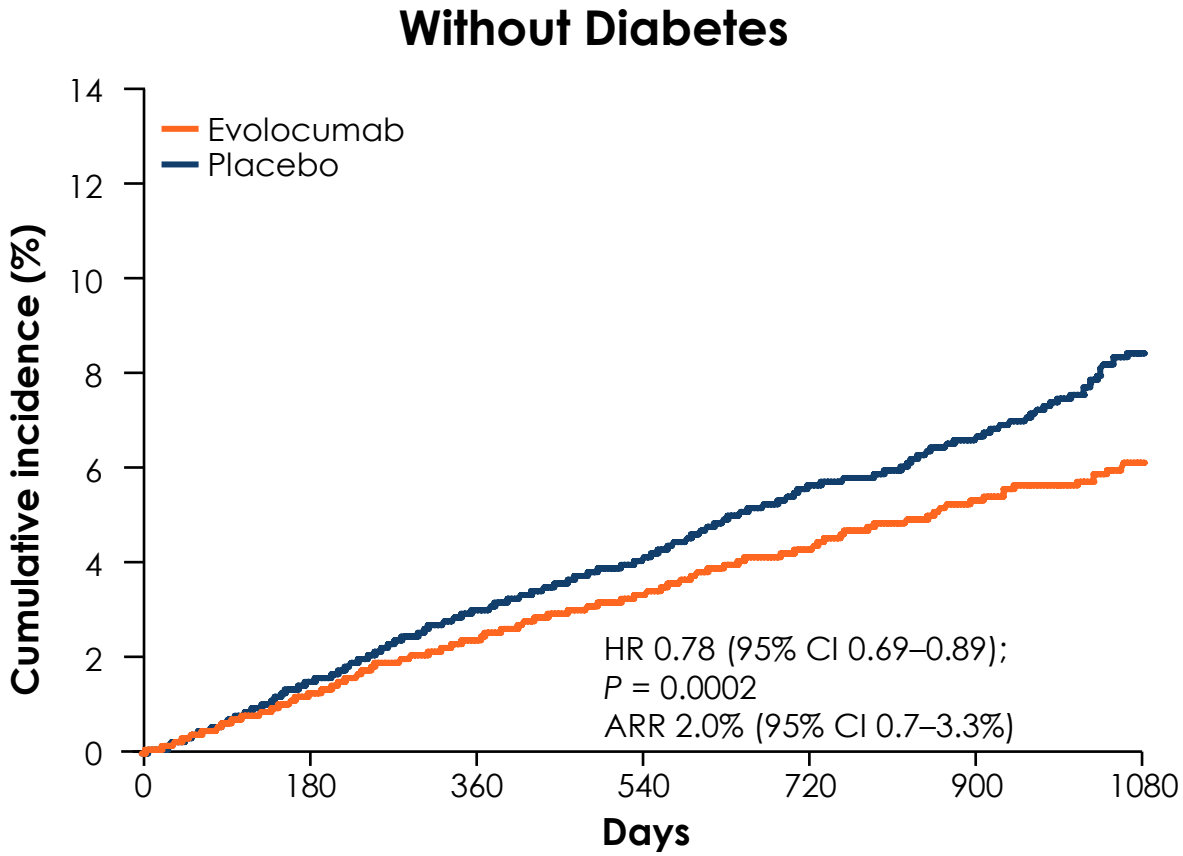
Patients With Diabetes Treated With Evolocumab Showed a Greater ARR Than Those Without Diabetes for 5-Point MACE



The $P_{interaction}$ value between baseline diabetes status and efficacy of evolocumab was 0·60.

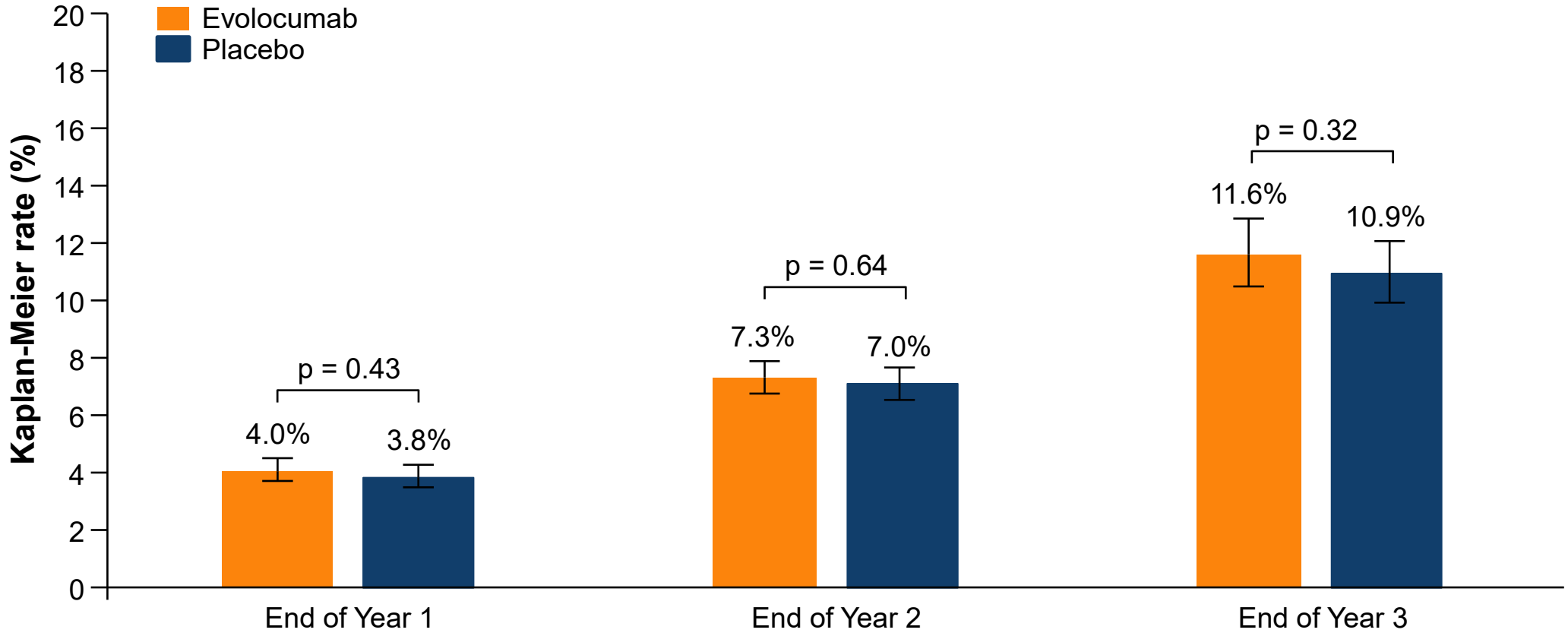
Evolocumab Significantly Reduced Cardiovascular Outcomes Irrespective of Baseline Diabetes Status for 3-Point MACE



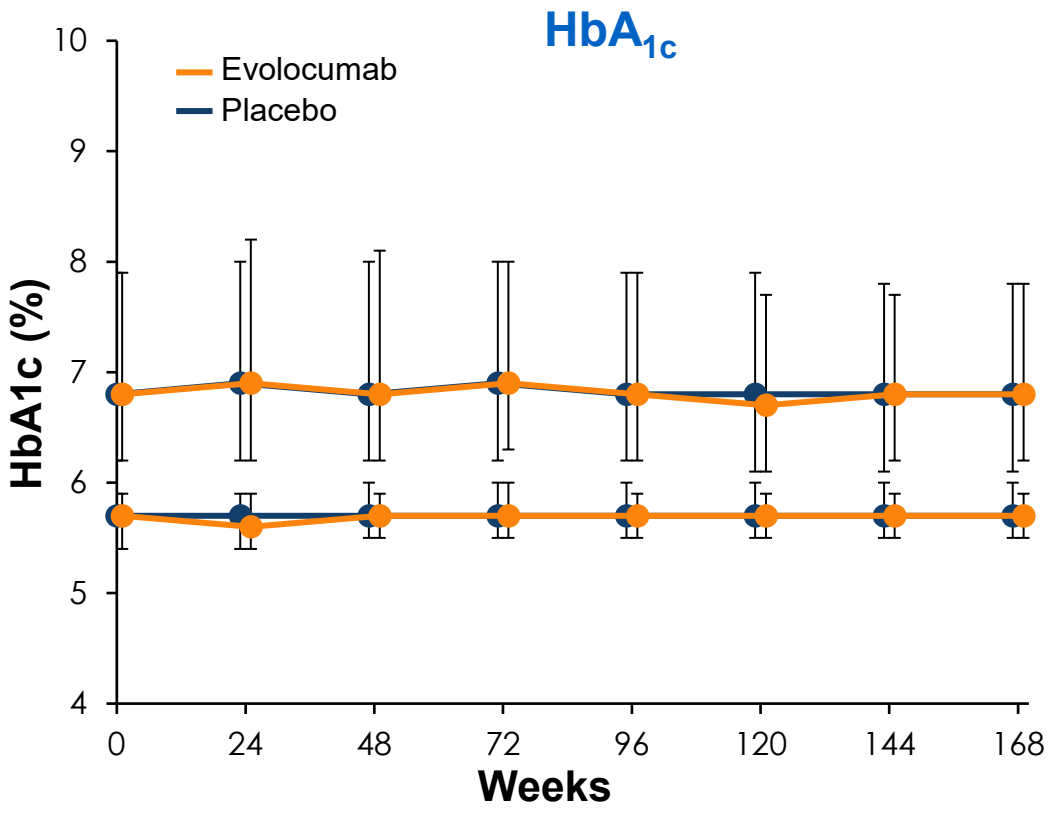


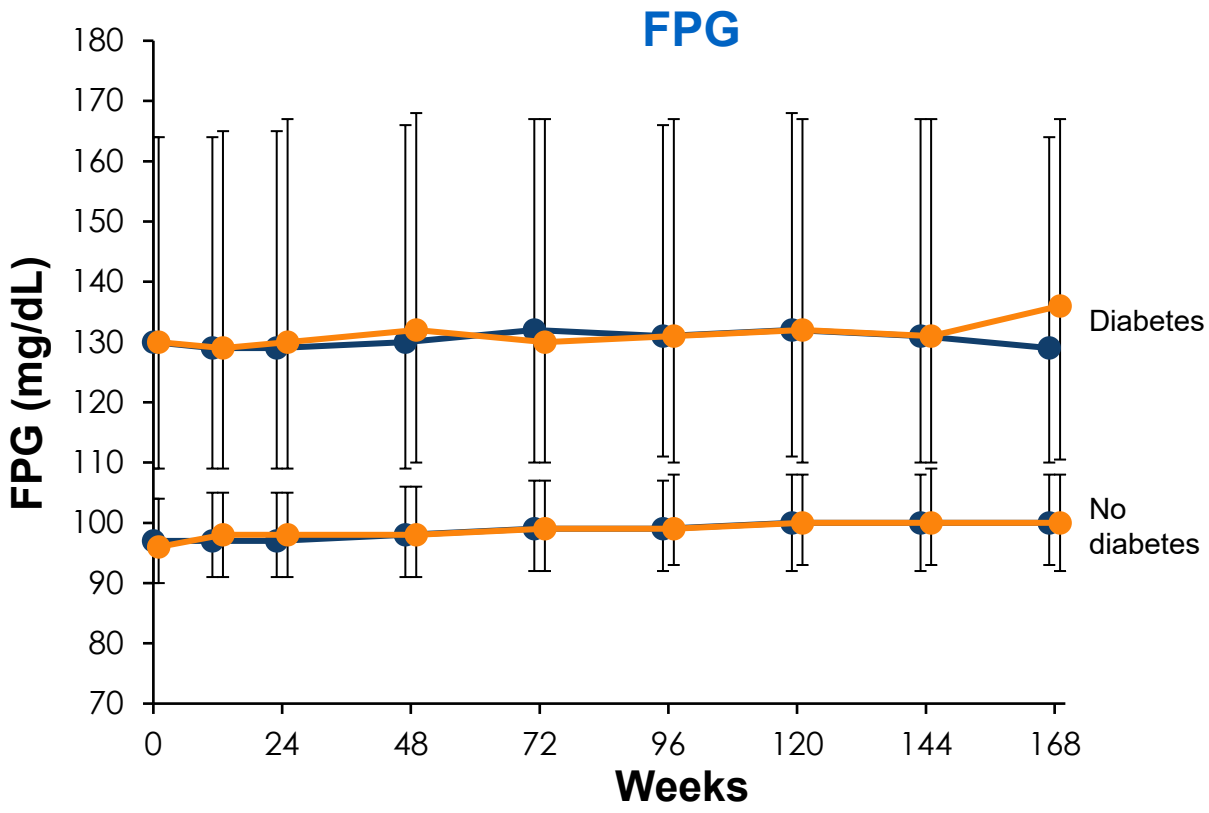
The $P_{interaction}$ value between baseline diabetes status and efficacy of evolocumab was 0·65

In Patients Without Diabetes at Baseline, There Was No Difference in the Incidence of NODM Between Evolocumab And Placebo



HbA1c and FPG Levels Remained Similar Between Treatment Groups in Patients With or Without Diabetes





Safety Parameters Were Similar Across Treatment Groups, Regardless of Diabetes Status

Outcome	With Diabetes			Without Diabetes	
	No. of patients			No. of patients	
	Evolocumab (n = 5,513)	Placebo (n = 5,502)		Evolocumab (n = 8,256)	Placebo (n = 8,254)
Adverse events					
Any	4,327 (78.5)	4,307 (78.3)		6,337 (76.8)	6,337 (76.8)
Serious	1,497 (27.2)	1,467 (26.7)		1,913 (23.2)	1,937 (23.5)
Thought to be treatment-related and leading to discontinuation of study drug	65 (1.2)	73 (1.3)		161 (2.0)	128 (1.6)
Injection-site reaction	96 (1.7)	75 (1.4)		200 (2.4)	144 (1.7)
Allergic reactions	180 (3.3)	150 (2.7)		240 (2.9)	243 (2.9)
Muscle-related	241 (4.4)	230 (4.2)		441 (5.3)	426 (5.2)
Cataract	107 (1.9)	106 (1.9)		121 (1.5)	136 (1.6)
Neurocognitive event	79 (1.4)	79 (1.4)		138 (1.7)	123 (1.5)
Laboratory results					
Aminotransferase >3x ULN	89 (1.6)	85 (1.6)		151 (1.9)	157 (1.9)
Creatinine kinase >5x ULN	28 (0.5)	33 (0.6)		67 (0.8)	66 (0.8)

Summary

Patients with diabetes had a higher risk of events for both the 5-point MACE and 3-point MACE compared with patients without diabetes

Evolocumab significantly reduced the risk for both the 5-point MACE and 3-point MACE in patients with diabetes, consistent with patients who were not diabetic

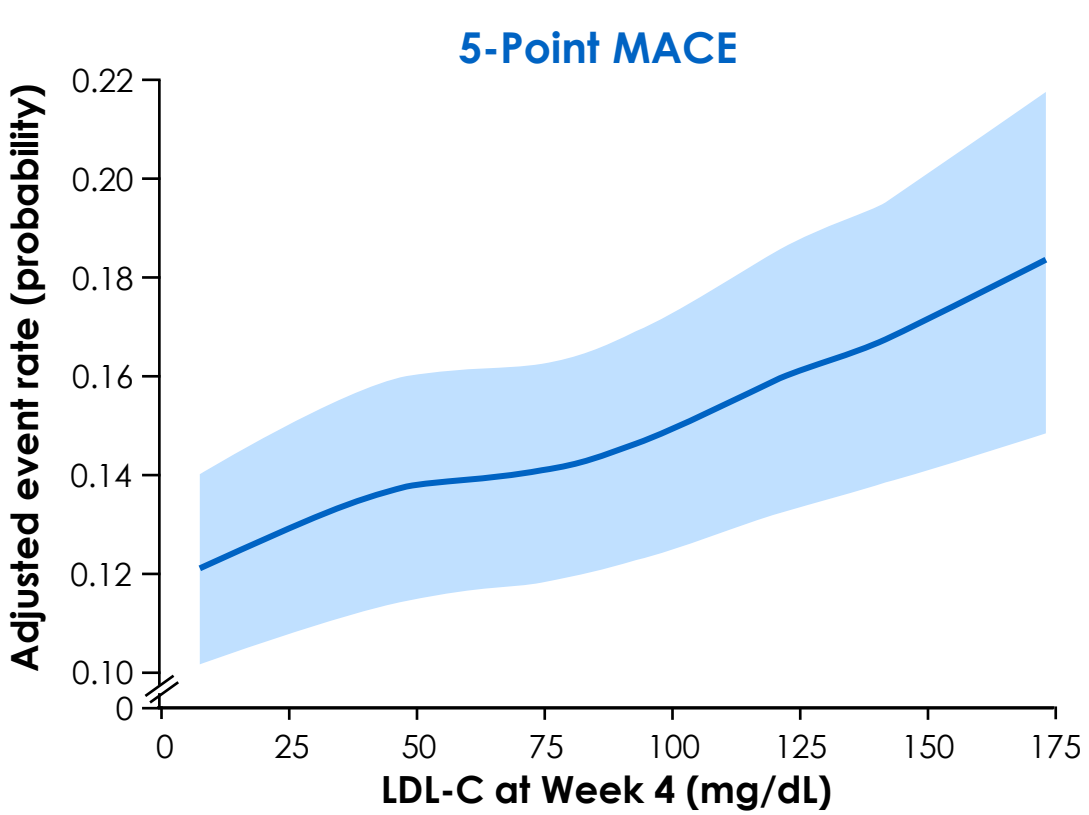
No differences in the development of NODM, glycemia, or other safety parameters were observed over the median 2.2-year study duration

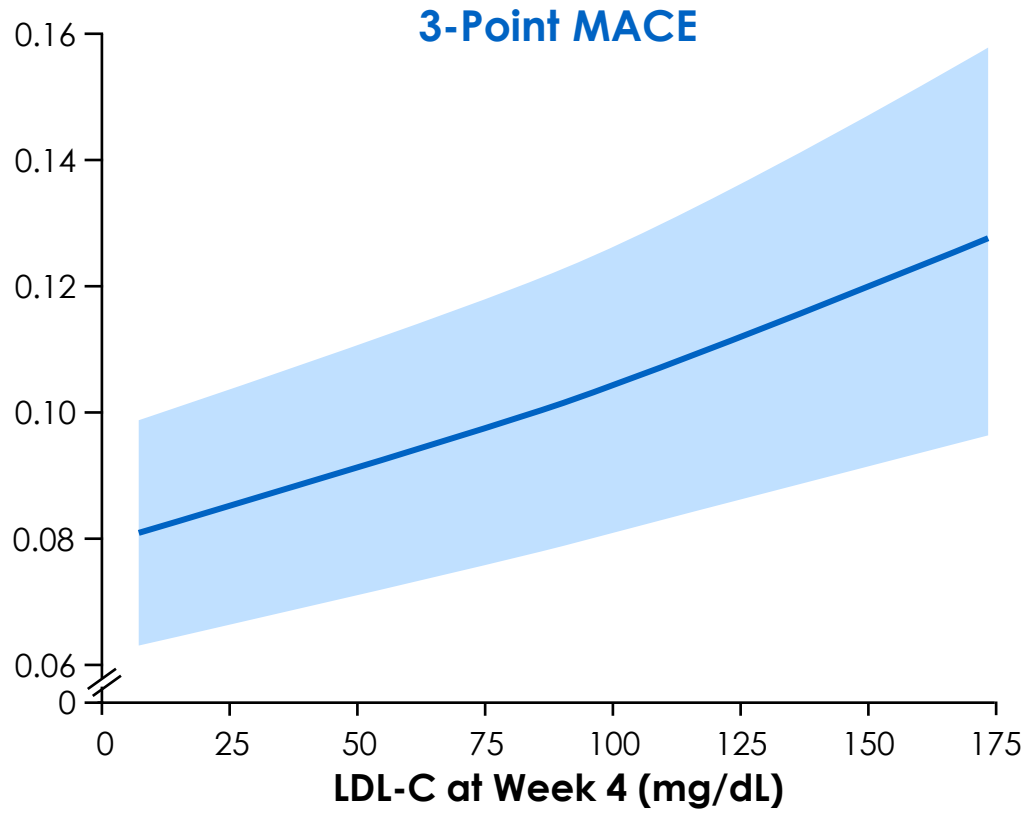
Sub-Analysis: Achieved LDL-C

Giugliano RP, et al. *Lancet*. 2017;390:1962-1971.

Additional Information

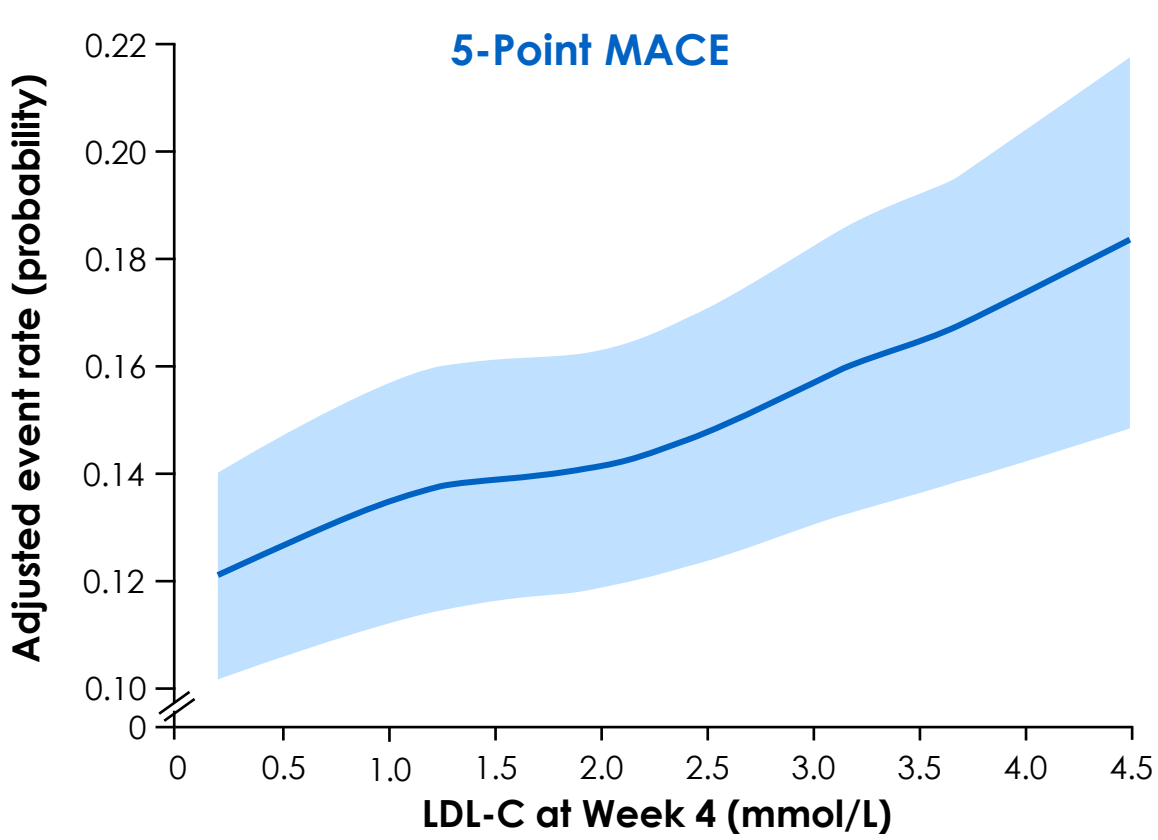
Risk of the 5-Point MACE and 3-Point MACE Was Progressively Lower as the Achieved LDL-C at Week 4 Was Reduced

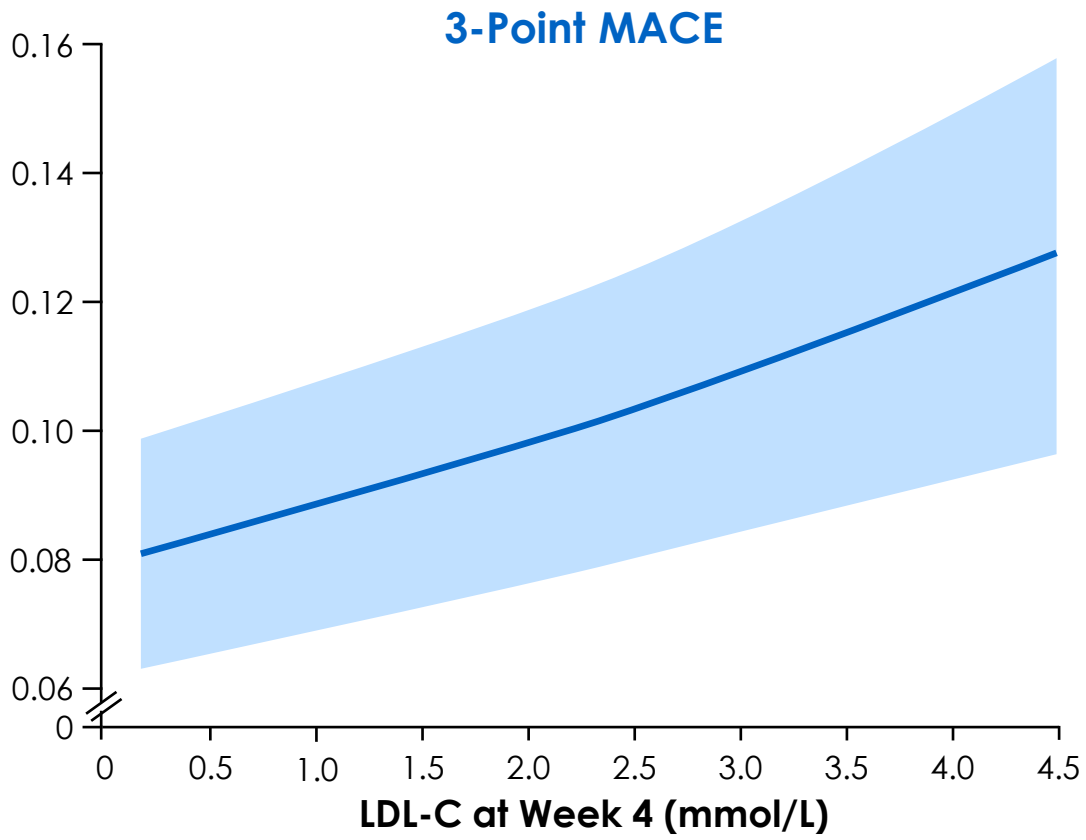




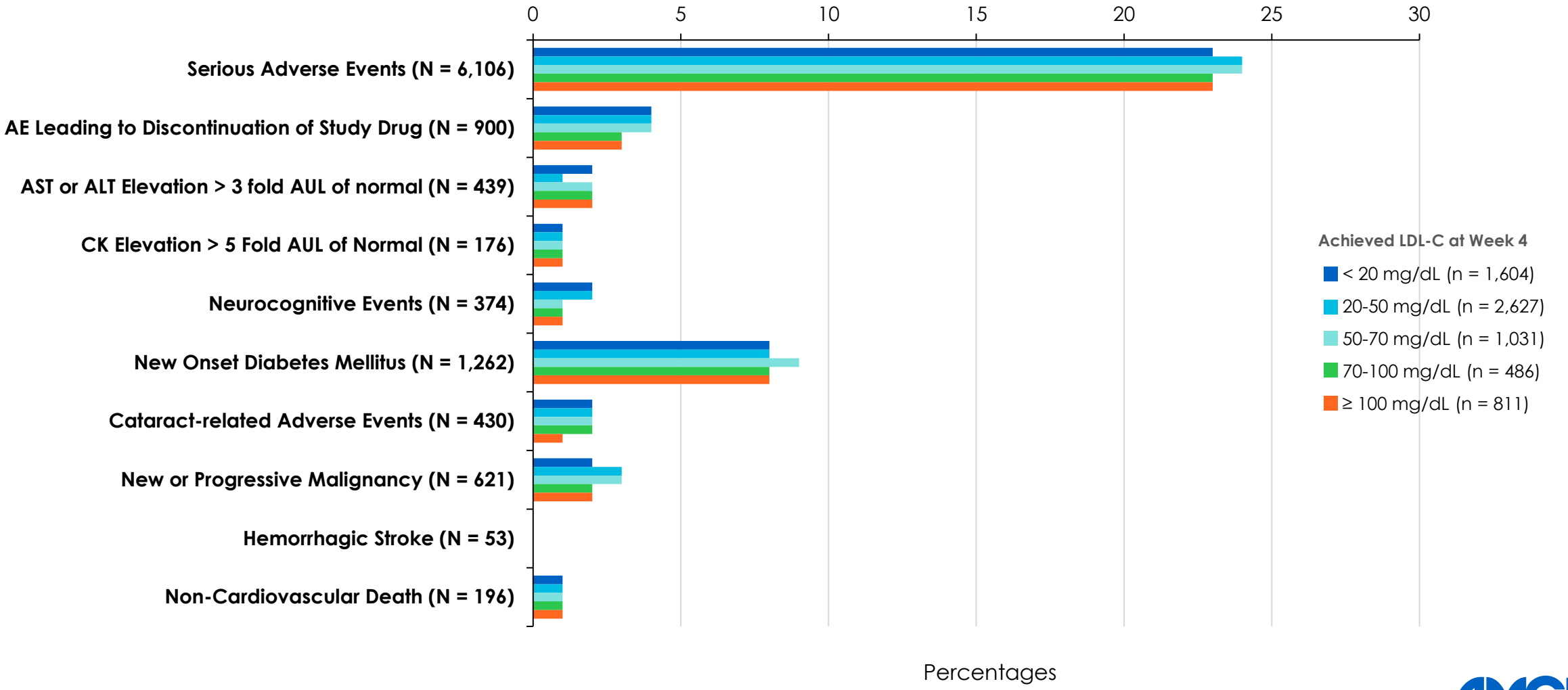
Note: mmol/L version

Risk of the 5-Point MACE and 3-Point MACE Was Progressively Lower as the Achieved LDL-C at Week 4 Was Reduced



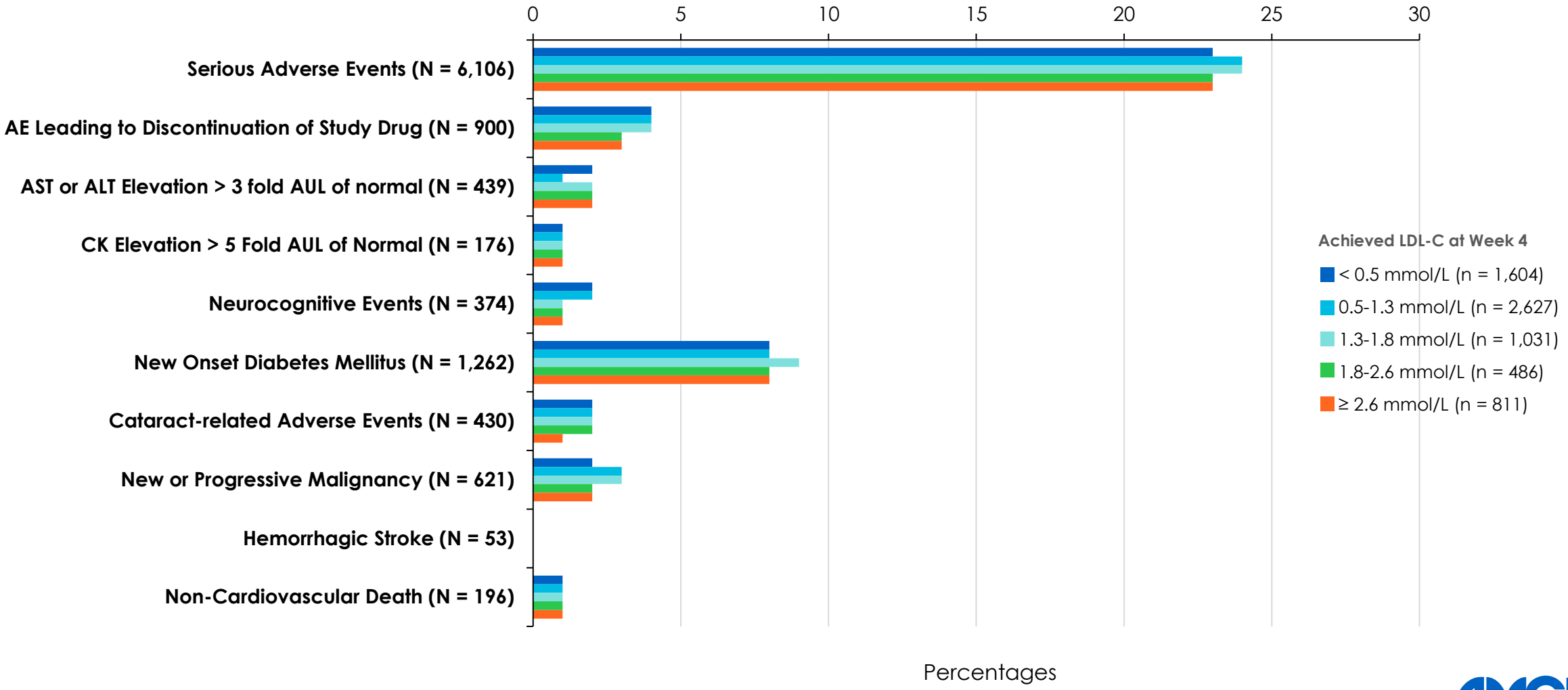


No Significant Differences in Major Safety Events Across the Five Very Low Achieved LDL-C Groups



Note: mmol/L version

No Significant Differences in Major Safety Events Across the Five Very Low Achieved LDL-C Groups



Summary

Patients who achieved progressively lower LDL-C levels at week 4 experienced continued lower CV event rates with no evidence of a plateau and no increase in adverse events

This relationship between lower LDL-C and lower risk for major CV outcomes extended even to the bottom 1st percentile of LDL-C < 7.7 mg/dL

Targeting LDL-C levels below current guidelines and recommendations should be considered to prevent recurrent events in high-risk patients

Note: mmol/L version

Summary

Patients who achieved progressively lower LDL-C levels at week 4 experienced continued lower CV event rates with no evidence of a plateau and no increase in adverse events

This relationship between lower LDL-C and lower risk for major CV outcomes extended even to the bottom 1st percentile of LDL-C < 0.2 mmol/L

Targeting LDL-C levels below current guidelines and recommendations should be considered to prevent recurrent events in high-risk patients

Sub-Analysis: Baseline LDL-C & Statin Potency

Giugliano RP, et al. *JAMA Cardiology*. 2017;2:1385-1391.

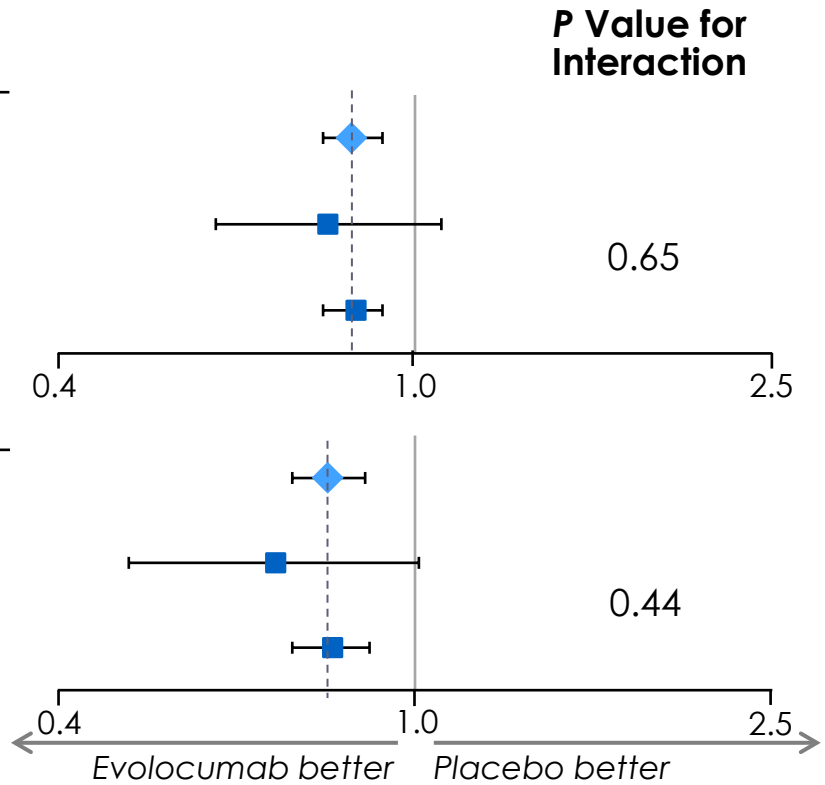
Additional Information

Evolocumab Significantly Reduced the Risk for 5-Point MACE and 3-Point MACE With No Evidence of Effect Modification Due to Baseline LDL-C Level

Efficacy outcomes by baseline LDL-C level

Number Events		5-Point MACE	HR (95% CI)
Evo	Placebo	**All**	0.85 (0.79-0.92)
86	106	**LDL-C < 70 mg/dL**	0.80 (0.60-1.07)
1258	1457	**LDL-C ≥ 70 mg/dL**	0.86 (0.79-0.92)

Number Events		3-Point MACE	
Evo	Placebo	**All**	0.80 (0.73-0.88)
48	68	**LDL-C < 70 mg/dL**	0.70 (0.48-1.01)
768	945	**LDL-C ≥ 70 mg/dL**	0.81 (0.73-0.89)



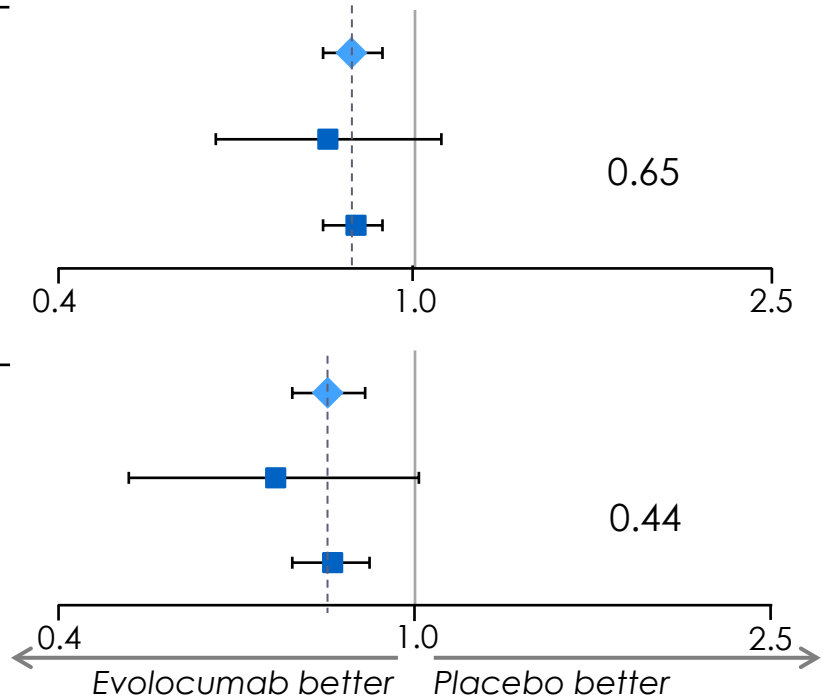
Note: mmol/L version

Evolocumab Significantly Reduced the Risk for 5-Point MACE and 3-Point MACE With No Evidence of Effect Modification Due to Baseline LDL-C Level

Efficacy outcomes by baseline LDL-C level

Number Events		5-Point MACE	HR (95% CI)	*P* Value for Interaction
Evo	Placebo	**All**	0.85 (0.79-0.92)	
86	106	**LDL-C < 1.8 mmol/L**	0.80 (0.60-1.07)	0.65
1258	1457	**LDL-C ≥ 1.8 mmol/L**	0.86 (0.79-0.92)	

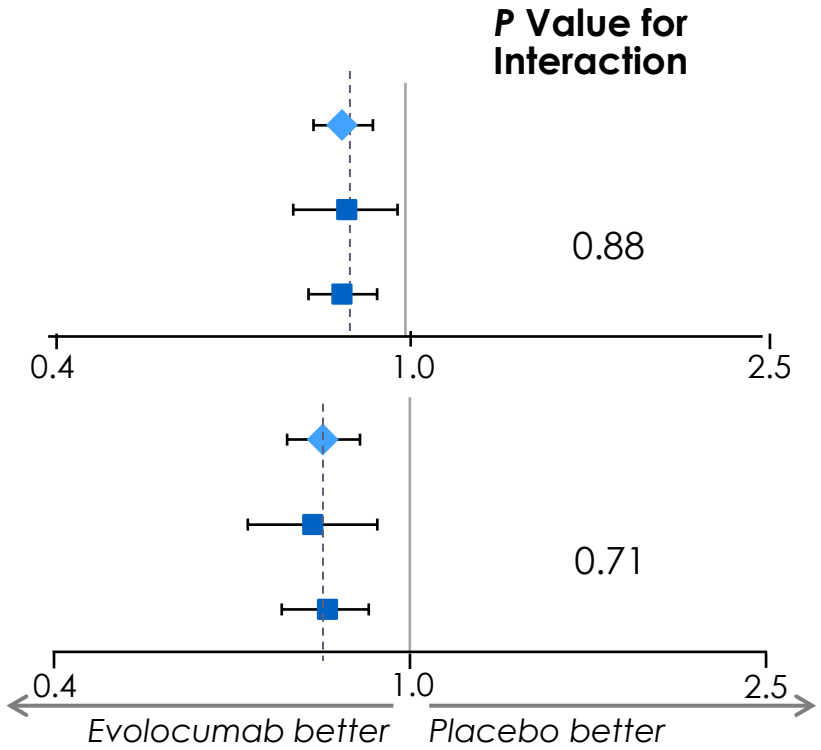
Number Events		3-Point MACE		
Evo	Placebo	**All**	0.80 (0.73-0.88)	
48	68	**LDL-C < 1.8 mmol/L**	0.70 (0.48-1.01)	0.44
768	945	**LDL-C ≥ 1.8 mmol/L**	0.81 (0.73-0.89)	



Evolocumab Significantly Reduced the Risk for 5-Point MACE and 3-Point MACE in Patients Receiving Statin Therapy, With No Evidence of Effect Modification Due to Background Statin Intensity

Efficacy outcomes by potency of background statin

Number Events		5-Point MACE	HR (95% CI)
Evo	Placebo	**All**	0.85 (0.79-0.92)
421	489	**Maximum intensity statin**	0.86 (0.75-0.98)
923	1074	**Less intense statin**	0.85 (0.78-0.93)
Number Events		**3-Point MACE**	
Evo	Placebo	**All**	0.80 (0.73-0.88)
246	315	**Maximum intensity statin**	0.78 (0.66-0.92)
570	698	**Less intense statin**	0.81 (0.72-0.90)



Incidence of AEs and Serious AEs Was Similar Between Evolocumab and Placebo Groups Irrespective of Baseline LDL-C Levels

Outcome	< 70 mg/dL (n = 2,033)		≥ 70 mg/dL (n = 25,491)	
	Evolocumab (n = 1,030)	Placebo (n = 1,003)	Evolocumab (n = 12,739)	Placebo (n = 12,752)
Serious AE	268 (26.0)	274 (27.3)	3,142 (24.7)	3,130 (24.5)
AE related to study drug and leading to therapy discontinuation	19 (1.8)	19 (1.9)	207 (1.6)	182 (1.4)
Injection site reaction	30 (2.9)	16 (1.6)	266 (2.1)	203 (1.6)
Muscle-related event	49 (4.8)	60 (6.0)	633 (5.0)	596 (4.7)
Cataract	19 (1.8)	16 (1.6)	209 (1.6)	226 (1.8)
New-onset diabetes (CEC adjudicated)	45/509 (8.8)	53/475 (11.2)	632/7,828 (8.1)	591/7,864 (7.5)
Neurocognitive event	17 (1.7)	12 (1.2)	200 (1.6)	190 (1.5)
AST or ALT level > 3 times normal	27 (2.7)	23 (2.3)	213 (1.7)	219 (1.7)
Creatine kinase level > 5 times normal	9 (0.9)	9 (0.9)	86 (0.7)	90 (0.7)

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Note: mmol/L version

Incidence of AEs and Serious AEs Was Similar Between Evolocumab and Placebo Groups Irrespective of Baseline LDL-C Levels

Outcome	< 1.8 mmol/L (n = 2,033)		≥ 1.8 mmol/L (n = 25,491)	
	Evolocumab (n = 1,030)	Placebo (n = 1,003)	Evolocumab (n = 12,739)	Placebo (n = 12,752)
Serious AE	268 (26.0)	274 (27.3)	3,142 (24.7)	3,130 (24.5)
AE related to study drug and leading to therapy discontinuation	19 (1.8)	19 (1.9)	207 (1.6)	182 (1.4)
Injection site reaction	30 (2.9)	16 (1.6)	266 (2.1)	203 (1.6)
Muscle-related event	49 (4.8)	60 (6.0)	633 (5.0)	596 (4.7)
Cataract	19 (1.8)	16 (1.6)	209 (1.6)	226 (1.8)
New-onset diabetes (CEC adjudicated)	45/509 (8.8)	53/475 (11.2)	632/7,828 (8.1)	591/7,864 (7.5)
Neurocognitive event	17 (1.7)	12 (1.2)	200 (1.6)	190 (1.5)
AST or ALT level > 3 times normal	27 (2.7)	23 (2.3)	213 (1.7)	219 (1.7)
Creatine kinase level > 5 times normal	9 (0.9)	9 (0.9)	86 (0.7)	90 (0.7)

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Incidence of AEs and Serious AEs Was Similar Between Evolocumab and Placebo Groups for Those Receiving Maximal and Submaximal-Potency Statin Therapy

Outcome	Maximal Potency Background Statin (n = 7,524)		Submaximal Potency Background Statin (n = 20,001)	
	Evolocumab (n = 3,754)	Placebo (n = 3,770)	Evolocumab (n = 10,015)	Placebo (n = 9,986)
Serious AE	979 (26.1)	1,010 (26.8)	2,431 (24.3)	2,394 (24.0)
Adverse event related to study drug and leading to drug discontinuation	53 (1.4)	53 (1.4)	173 (1.7)	148 (1.5)
Injection site reaction	84 (2.2)	68 (1.8)	212 (2.1)	151 (1.5)
Muscle-related event	207 (5.5)	194 (5.1)	475 (4.7)	462 (4.6)
Cataract	53 (1.4)	64 (1.7)	175 (1.7)	178 (1.8)
New-onset diabetes (CEC adjudicated)	214/2,385 (9.0)	176/2,383 (7.4)	463/5,952 (7.8)	468/5,956 (7.9)
Neurocognitive event	64 (1.7)	63 (1.7)	153 (1.5)	139 (1.4)
AST or ALT level > 3 times normal	84 (2.3)	81 (2.2)	156 (1.6)	161 (1.6)
Creatine kinase level > 5 times normal	28 (0.8)	33 (0.9)	67 (0.7)	66 (0.7)

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Summary

Evolocumab reduced the risk for both 5-Point MACE and 3-Point MACE regardless of baseline LDL-C level or maximal statin therapy

No new safety signals were observed in either subgroup, although a higher incidence of NODM was observed in the evolocumab treatment arm for those receiving maximal-potency statin therapy at baseline

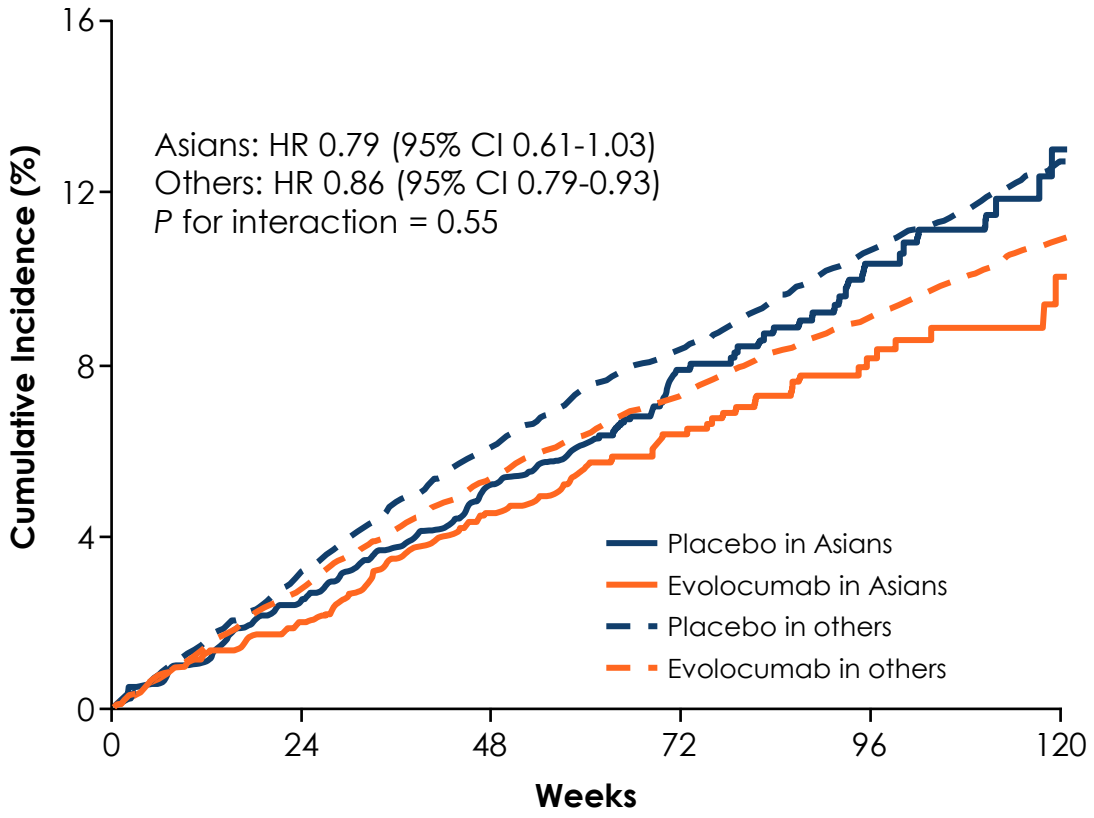
Sub-Analysis: Asian Population

Keech AC, et al. *Circ J.* 2021;85:2063-2070.

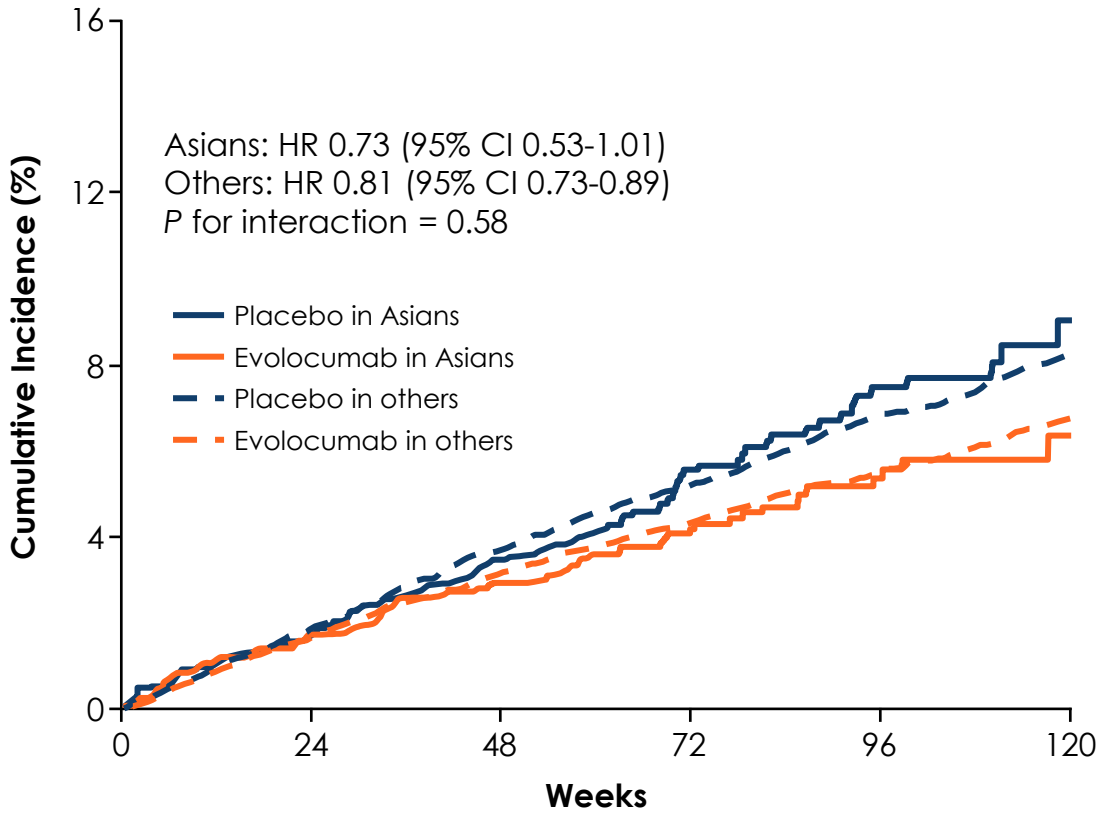
Additional Information

Reduction in Risk of the 5-Point MACE and 3-Point MACE With Evolocumab Were Similar Between Asians and Others

5-Point MACE by Treatment and Race



3-Point MACE by Treatment and Race



There Were No Key Differences Between Evolocumab and Placebo in Safety Among Asians and Other Ethnic Population

Event	Asians			Others			*P* Value for Interaction
	Evolocumab	Placebo	*P* Value	Evolocumab	Placebo	*P* Value	
Adverse events							
New-onset diabetes, n (%)	88 (13.6)	85 (13.6)	0.99	589 (7.7)	559 (7.2)	0.33	0.72
Hemorrhagic stroke, n (%)	7 (0.5)	4 (0.3)	0.55	22 (0.2)	21 (0.2)	0.87	0.48
Investigator-reported neurocognitive event, n (%)	20 (1.5)	31 (2.3)	0.10	197 (1.6)	171 (1.4)	0.17	0.047
Cognitive decline (ECog score ≥ 2), n (%)	30 (2.6)	20 (1.8)	0.18	388 (3.8)	381 (3.8)	0.85	0.22
Laboratory							
Aminotransferase level > 3-fold the upper limit of the normal range	12 (0.9)	24 (1.8)	0.04	228 (1.9)	218 (1.8)	0.63	0.04
Binding antibody,%	0.90	0	-	0.26	0	-	-

Summary

LDL-C reductions with evolocumab treatment compared with placebo were statistically larger among Asian subjects than in others (66% vs 58%; P < 0.001), regardless of statin dose and body weight (P < 0.001)

The relative risk reductions in CV events with evolocumab in Asians were comparable to those seen in others, without any safety concerns

There were no excess serious adverse events noted among Asians who received evolocumab compared with placebo

The findings from this trial provide reassurance that no dose modification is required in Asian patients treated with evolocumab

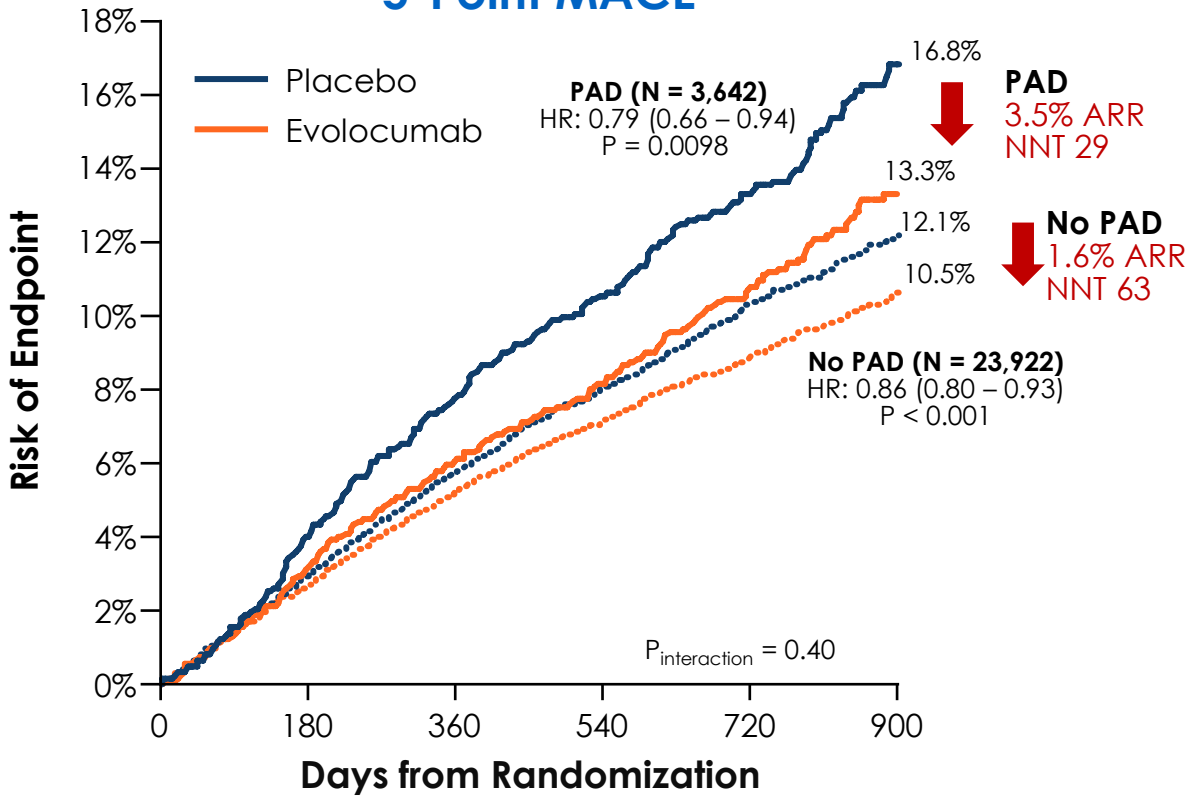
Sub-Analysis: PAD

Bonaca MP, et al. *Circulation*. 2018;137:338-350.

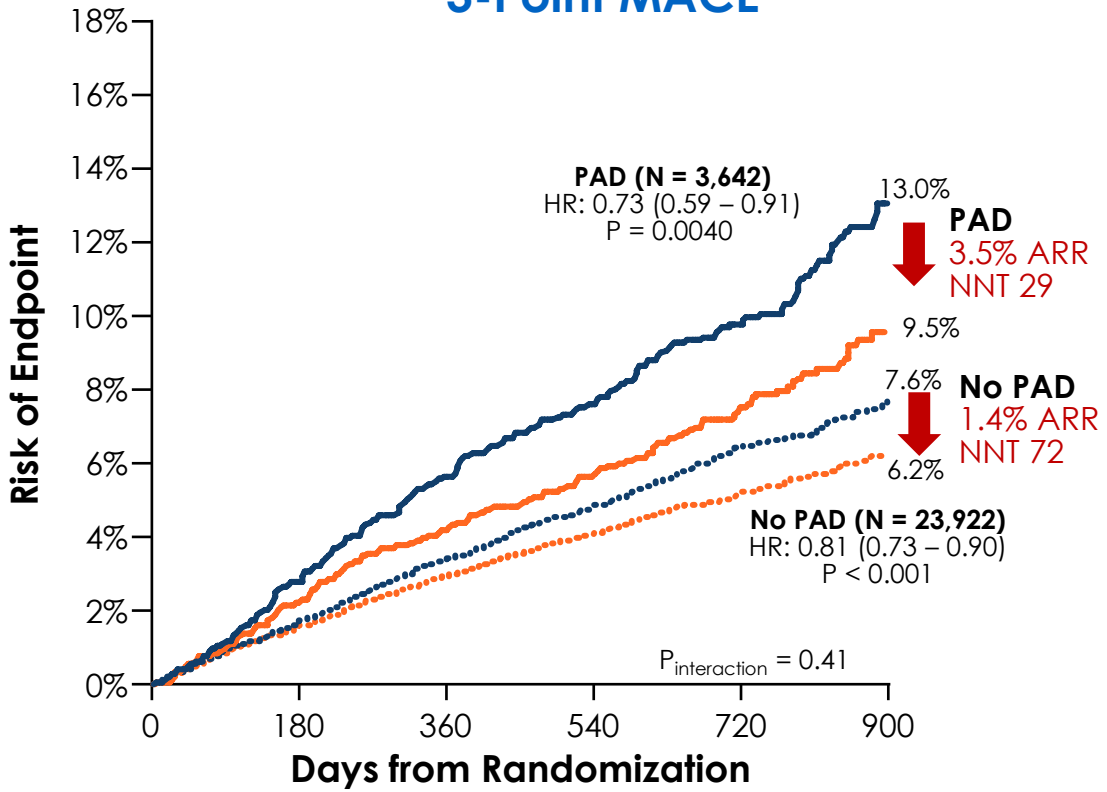
Additional Information

Patients With a History of PAD Treated With Evolocumab Experienced a Consistent RRR and Greater ARR for Both the 5-Point MACE and 3-Point MACE Compared With Those Without a History of PAD

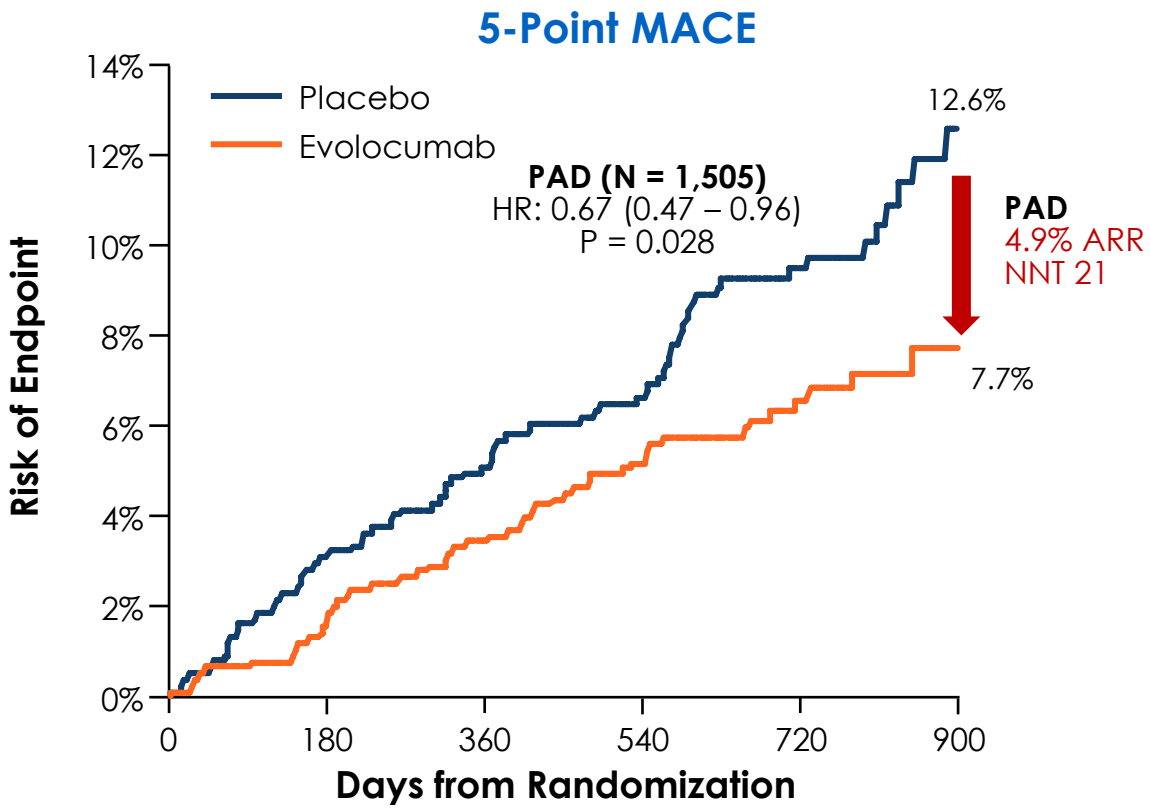
5-Point MACE

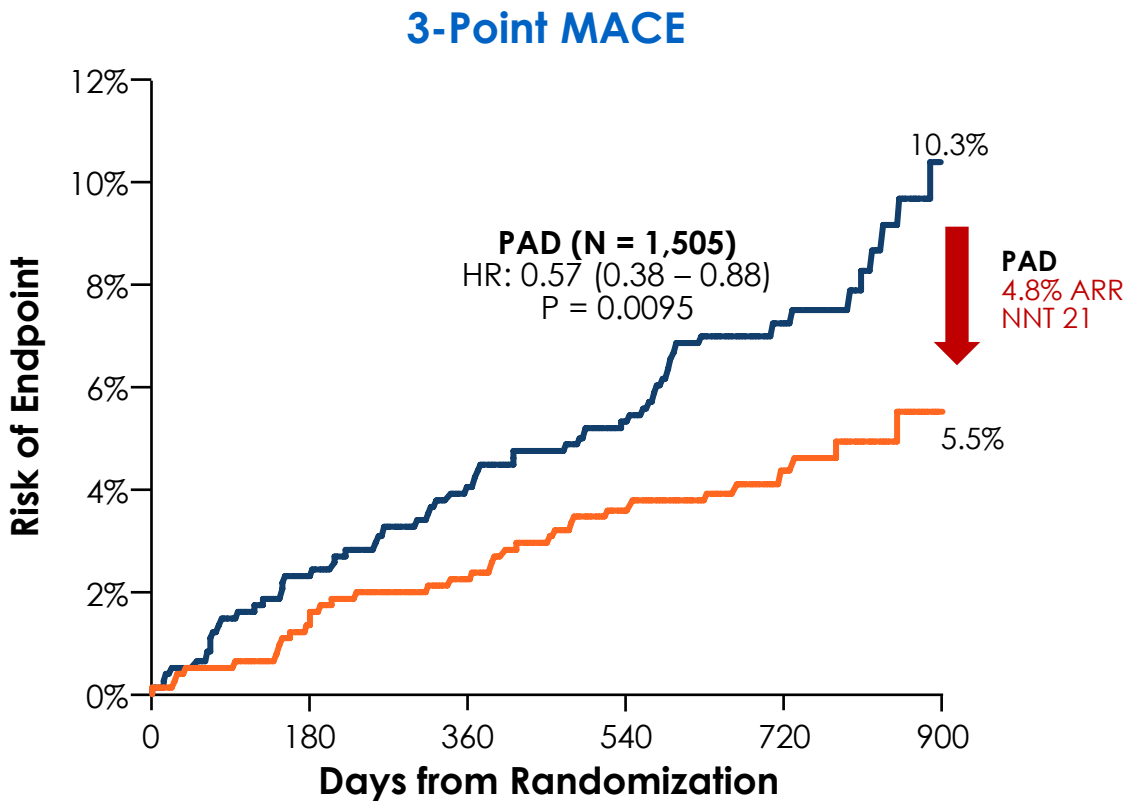


3-Point MACE

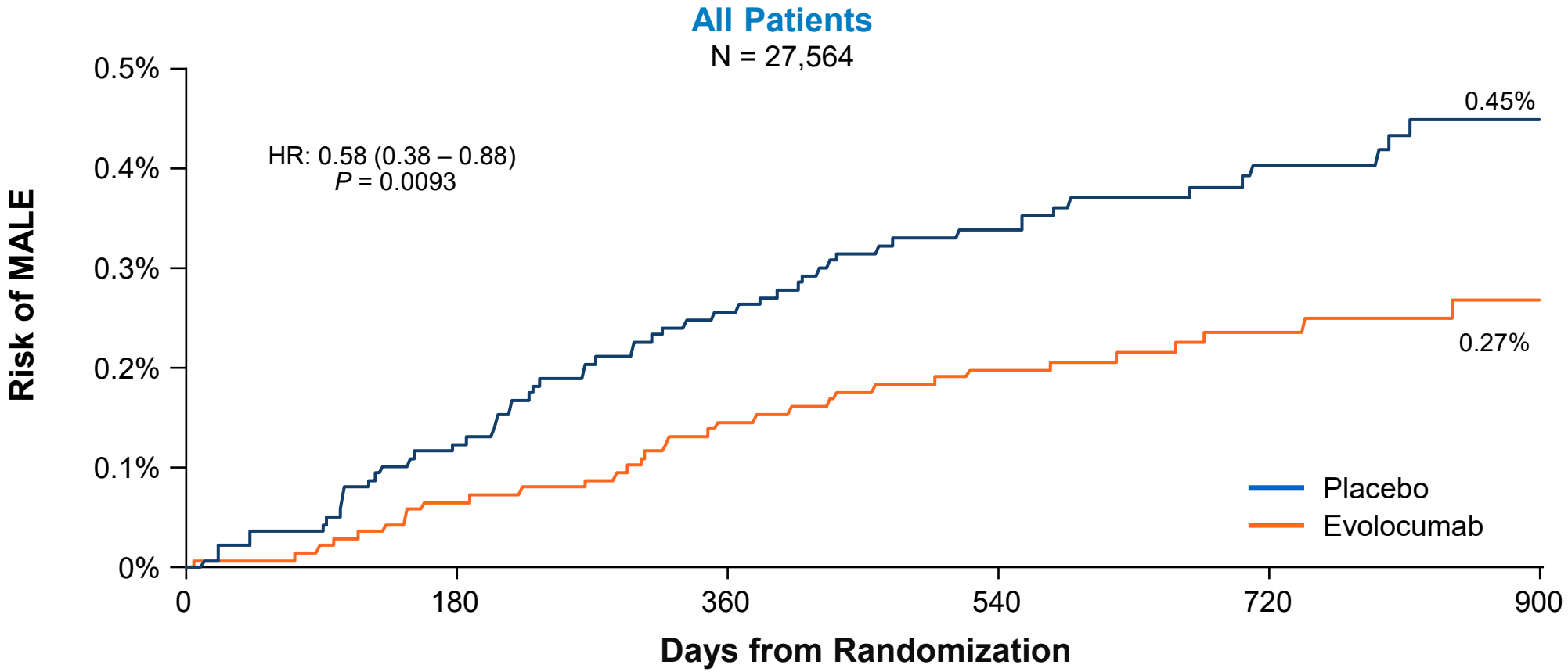


Patients With a History of PAD Without Prior MI or Stroke Showed a Greater ARR With Evolocumab Compared With Placebo





Evolocumab Reduced the Relative Risk of MALE (by 42%) in Patients, Irrespective of a History of PAD



In Patients With a History of PAD, Incidence of AEs and Serious AEs Was Similar Between Evolocumab and Placebo Groups

	Placebo N = 1,780	Evolocumab N = 1,856
Adverse events, n (%)		
Any	1,408 (79.1%)	1,481 (79.8%)
Serious	624 (35.1%)	601 (32.4%)
Thought to be related to the study agent and leading to discontinuation of study regimen	27 (1.5%)	24 (1.3%)
Injection-site reaction	32 (1.8%)	26 (1.4%)
Allergic reaction	47 (2.6%)	54 (2.9%)
Muscle-related event	79 (4.4%)	94 (5.1%)
Rhabdomyolysis	1 (0.1%)	2 (0.1%)
Cataract	43 (2.4%)	24 (1.3%)
Adjudicated case of new-onset diabetes	67 (6.7%)	80 (8.3%)
Neurocognitive event	31 (1.7%)	28 (1.5%)
Laboratory results, n (%)		
Aminotransferase level >3x ULN	31 (1.8%)	27 (1.5%)
Creatine Kinase level >5 ULN	15 (0.9%)	5 (0.3%)

Summary

Evolocumab lowered LDL-C by 59% and significantly reduced the risk for 5-Point MACE and 3-Point MACE, and MALE endpoints in patients with history of PAD, consistent with patients without PAD

Given the greater underlying CV risk of patients with a history of PAD, a larger ARR for the 5-Point MACE was observed with evolocumab treatment in patients with PAD compared with those without (3.5% vs 1.6%)

Benefits extend to PAD patients without prior history of MI or stroke (ARR for MACE or MALE of 6.3%, NNT 16 at 2.5 years)

No new safety signals were observed

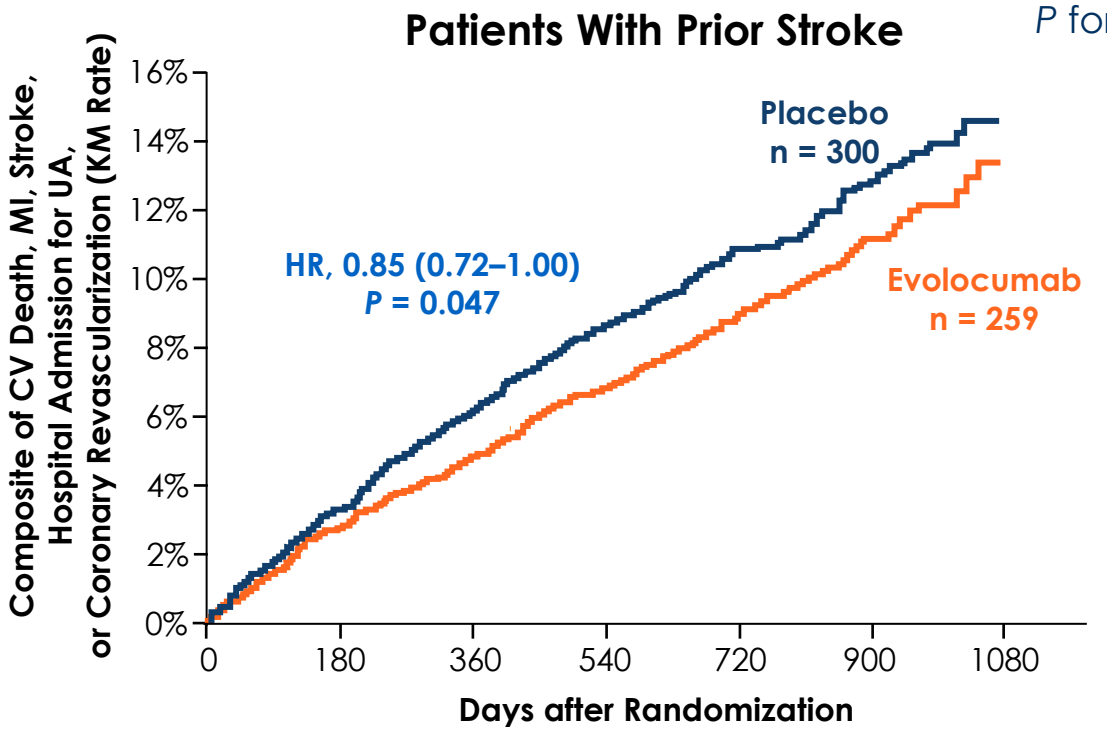
Sub-Analysis: Stroke

Giugliano RP, et al. *Stroke*. 2020;51:1546-1554.

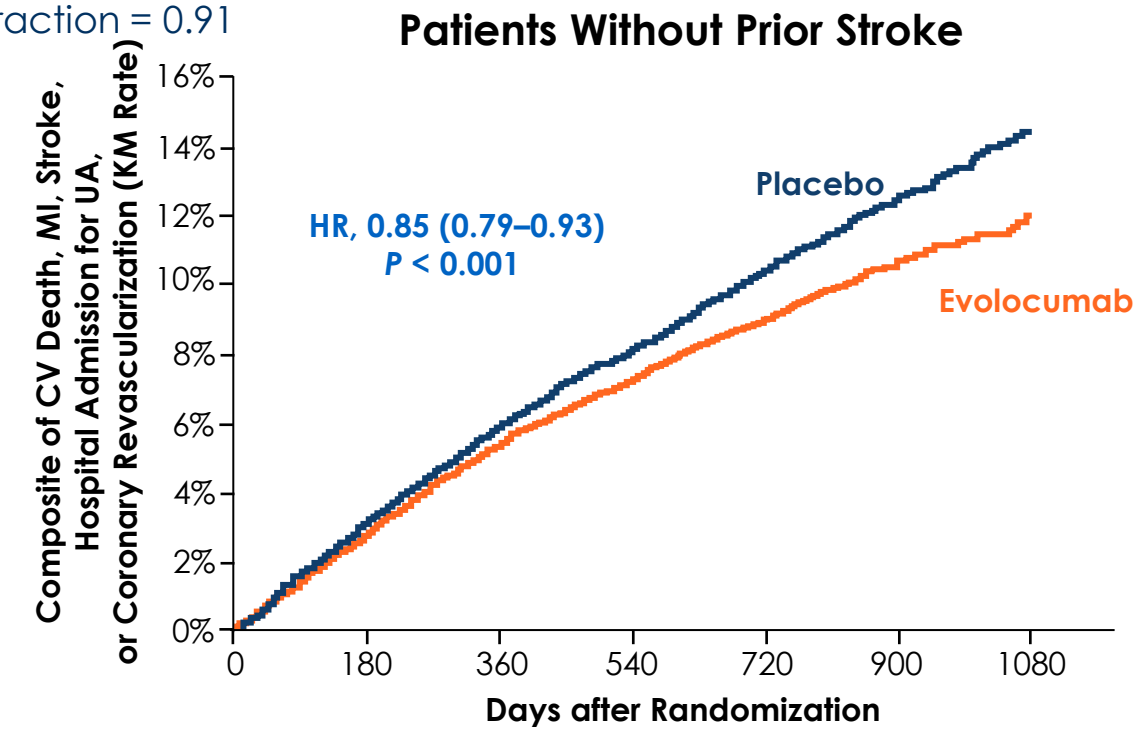
Additional Information

Evolocumab Demonstrated a Similar Reduction in First Occurrence of the 5-Point MACE Regardless of Baseline Stroke Status

P for interaction = 0.91



Placebo	2,651	2,547	2,457	2,224	1,457	651	148
Evolocumab	2,686	2,595	2,526	2,293	1,498	664	138



Placebo	11,129	10,731	10,369	9,647	6,219	3,039	635
Evolocumab	11,098	10,756	10,415	9,777	6,340	3,082	662

Evolocumab Demonstrated a Similar Reduction in All Stroke, Ischemic Stroke, and Composite of Ischemic Stroke or TIA

Endpoint	Prior Stroke		
	Placebo (N = 2,651) n (%)	Evolocumab (N = 2,686) n (%)	Hazard Ratio (95% CI)
Primary composite	300 (11.3)	259 (9.6)	0.85 (0.72–1.00)
Key secondary composite	224 (8.4)	202 (7.5)	0.89 (0.74–1.08)
Any stroke	105 (4.0)	95 (3.5)	0.90 (0.68–1.19)
Ischemic stroke	86 (3.2)	80 (3.0)	0.92 (0.68–1.25)
Hemorrhagic stroke	14 (0.63)	14 (0.61)	0.99 (0.47–2.07)
Myocardial infarction	100 (3.8)	75 (2.8)	0.74 (0.55–1.00)
Coronary revascularization	128 (4.8)	89 (3.3)	0.68 (0.52–0.90)
Unstable angina	33 (1.2)	29 (1.1)	0.86 (0.52–1.42)
Cardiovascular death	65 (2.5)	73 (2.7)	1.11 (0.80–1.56)
Ischemic stroke or TIA	113 (4.3)	102 (3.8)	0.89 (0.68–1.17)

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No Difference in Hemorrhagic Stroke Was Observed With Evolocumab vs Placebo, Regardless of Prior History of Stroke

End Point	Placebo, n (%)	Evolocumab, n (%)	95% CI	P Value
	N = 13,780	N = 13,784	Hazard ratio	
All stroke	262 (1.9)	207 (1.5)	0.79 (0.66–0.95)	0.01
Ischemic	226 (1.6)	171 (1.2)	0.75 (0.62–0.92)	0.005
Hemorrhagic	**25 (0.18)**	**29 (0.21)**	**1.16 (0.68–1.98)**	**0.59**
Unknown	14 (0.10)	13 (0.09)	0.93 (0.44–1.97)	0.84
Ischemic stroke or TIA	295 (2.1)	229 (1.7)	0.77 (0.65–0.92)	0.003
TIA	76 (0.55)	61 (0.44)	0.80 (0.57–1.12)	0.20

Similar to the Overall FOURIER Population, Adverse Events Were Similar Across Treatment Groups, Regardless of Stroke Status

Outcome	No Prior Stroke (N = 22,196)		Prior Stroke (N = 5,329)	
	Placebo (N = 11,110)	Evolocumab (N = 11,086)	Placebo (N = 2,646)	Evolocumab (N = 2,683)
Treatment emergent adverse events – no. of patients (%)				
Any	8,585 (77.3)	8,561 (77.2)	2,059 (77.8)	2,103 (78.4)
Serious	2,666 (24.0)	2,669 (24.1)	738 (27.9)	741 (27.6)
Any leading to discontinuation of study drug	442 (4.0)	449 (4.1)	131 (5.0)	159 (5.9)
Injection-site reaction	166 (1.5)	228 (2.1)	46 (1.7)	54 (2.0)
Allergic reaction	312 (2.8)	331 (3.0)	81 (3.1)	89 (3.3)
Muscle-related event	546 (4.9)	570 (5.1)	110 (4.2)	112 (4.2)
Rhabdomyolysis	6 (0.05)	7 (0.06)	5 (0.19)	1 (0.04)
Cataract	198 (1.8)	173 (1.6)	44 (1.7)	55 (2.0)
Adjudicated case of new-onset diabetes	538 (7.8)	563 (8.2)	106 (7.2)	114 (7.6)
Neurocognitive event	149 (1.3)	164 (1.5)	53 (2.0)	53 (2.0)
Laboratory results – no. of patients/total no. (%)				
Aminotransferase level > 3 times ULN	198/10,921 (1.8)	204/10,909 (1.9)	44/2,602 (1.7)	36/2,634 (1.4)
Creatine kinase level > 3 times ULN	71/10,921 (0.7)	74/10,909 (0.7)	28/2,602 (1.1)	21/2,634 (0.8)

Summary

Among the patients with prior ischemic stroke, evolocumab safely reduced LDL-C levels to a median of 27.1 mg/dL and reduced the risk of future cardiovascular events, including ischemic stroke and TIA

Evolocumab significantly reduced all stroke, ischemic stroke, and ischemic stroke/TIA, with no increase in hemorrhagic stroke

Note: mmol/L version

Summary

Among the patients with prior ischemic stroke, evolocumab safely reduced LDL-C levels to a median of 0.7 mmol/L and reduced the risk of future cardiovascular events, including ischemic stroke and TIA

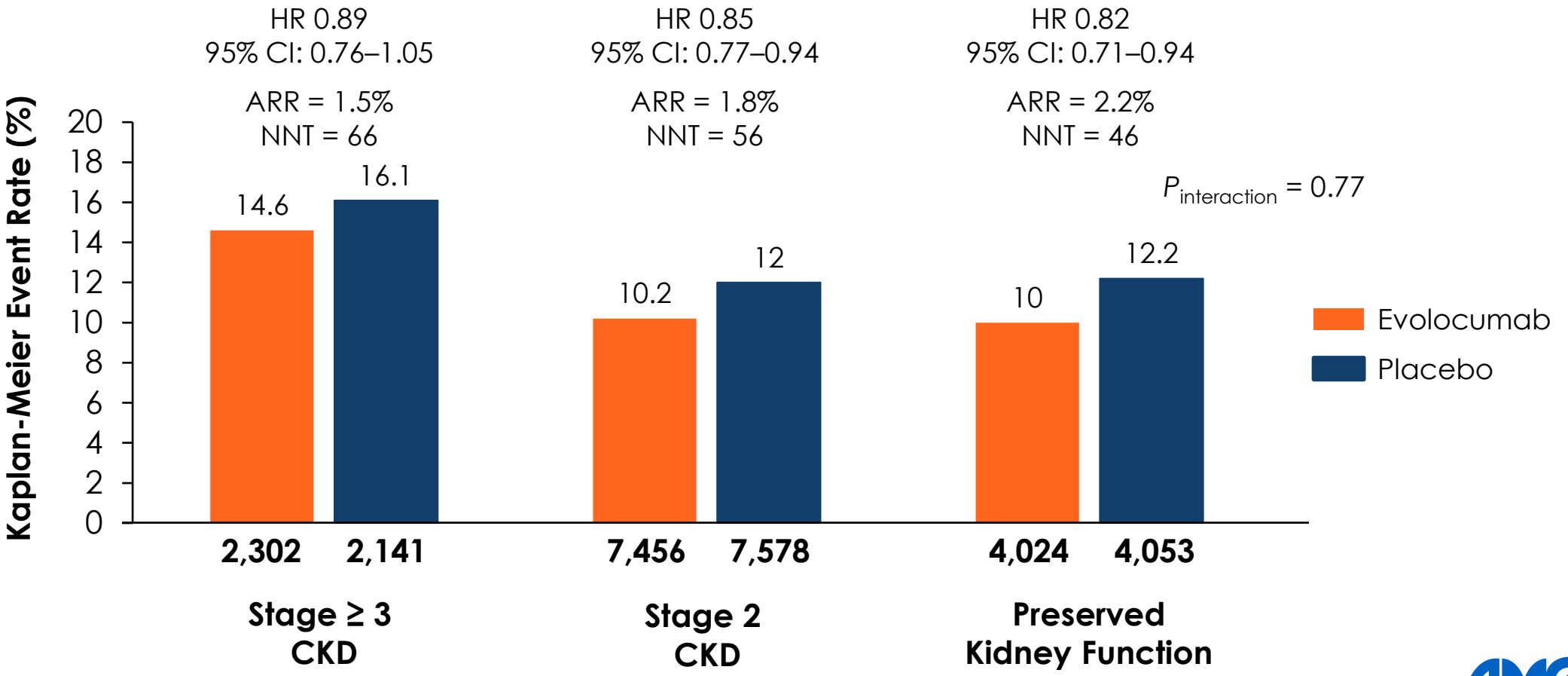
Evolocumab significantly reduced all stroke, ischemic stroke, and ischemic stroke/TIA, with no increase in hemorrhagic stroke

Sub-Analysis: CKD

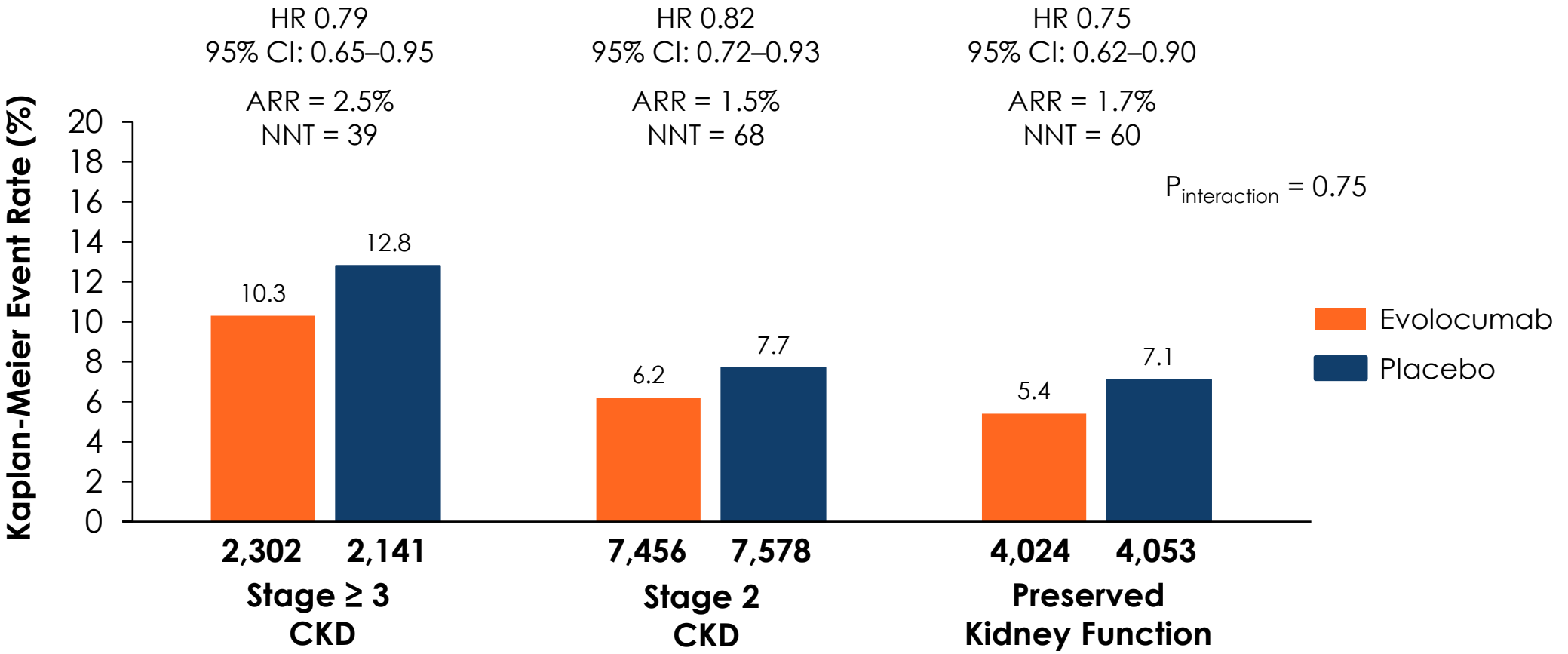
Charytan DM, et al. *J Am Coll Cardiol*. 2019;73:2961-2970.

Additional Information

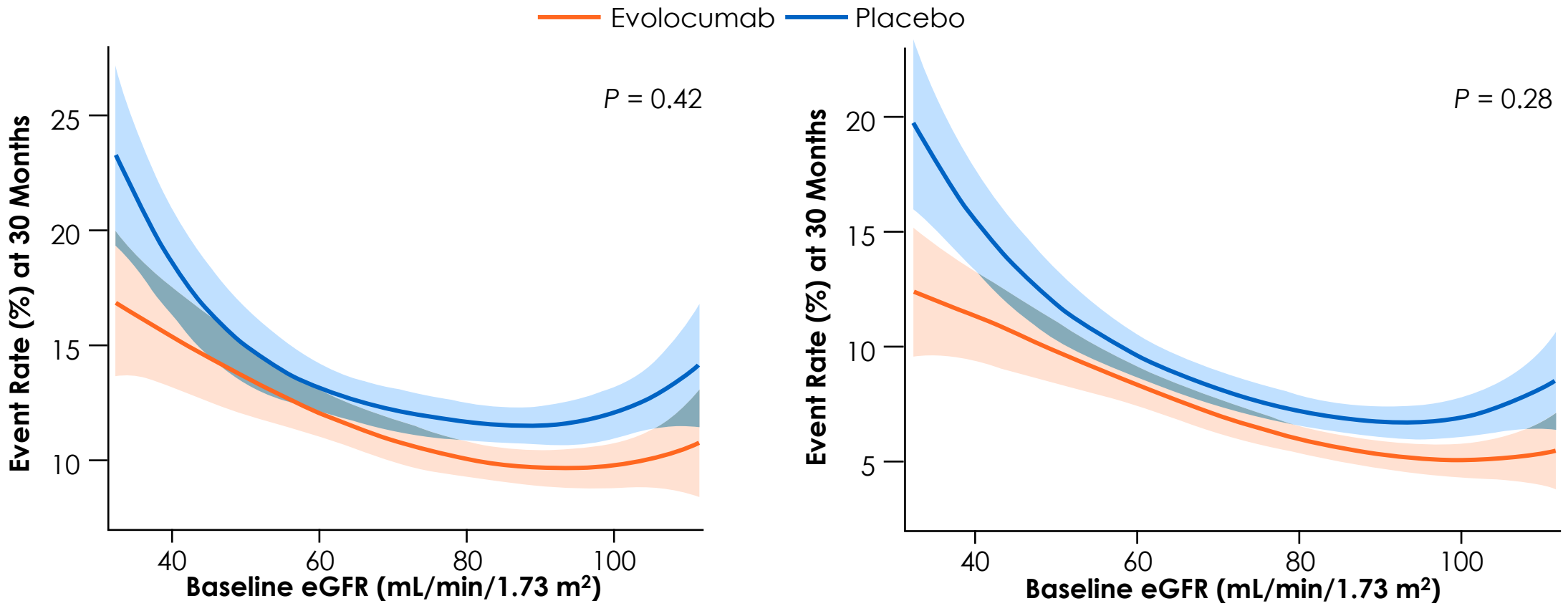
The ARRs for 5-Point MACE Were Numerically Larger Among Those With Stage ≥ 3 CKD vs Stage 2 CKD and Preserved Kidney Function



The ARRs for the Key 3-Point MACE Were Numerically Larger Among Those With Stage ≥ 3 CKD vs Stage 2 CKD and Preserved Kidney Function



Given Higher Event Rates at Lower eGFR, the Absolute Reduction With Evolocumab in the 5-Point MACE and 3-Point MACE Was More Robust With Advancing CKD



Summary

Relative risk reductions for the primary and key secondary CV outcomes were similar regardless of CKD stage

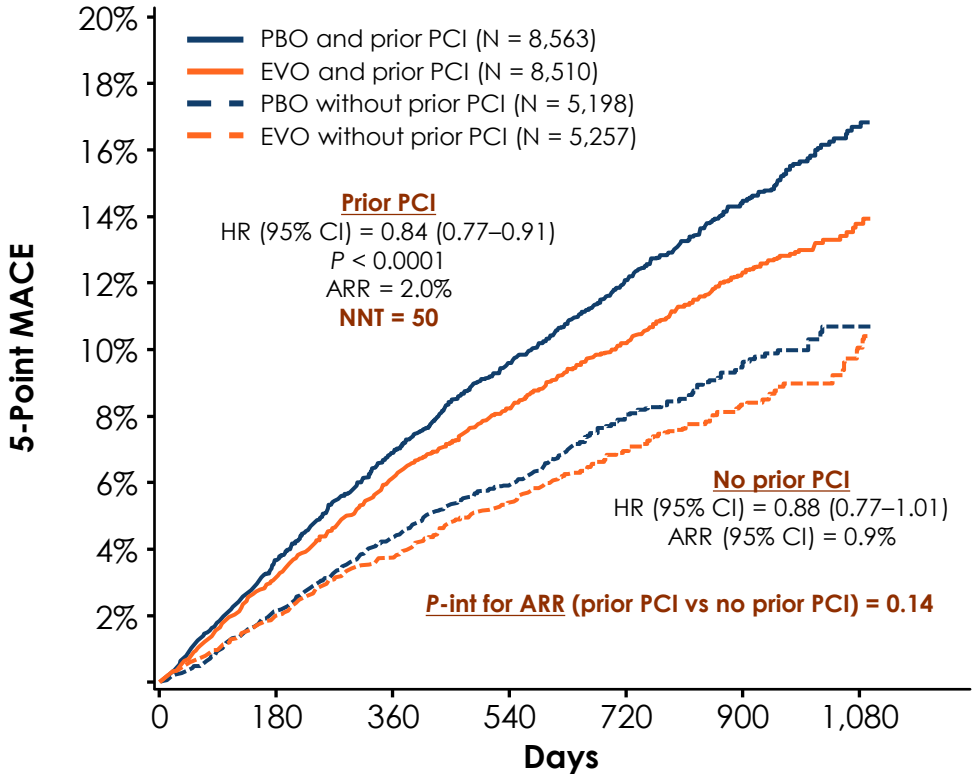
However, with higher event rates at lower eGFR, the absolute reduction in CV death, MI or stroke with evolocumab was more robust with more advanced CKD

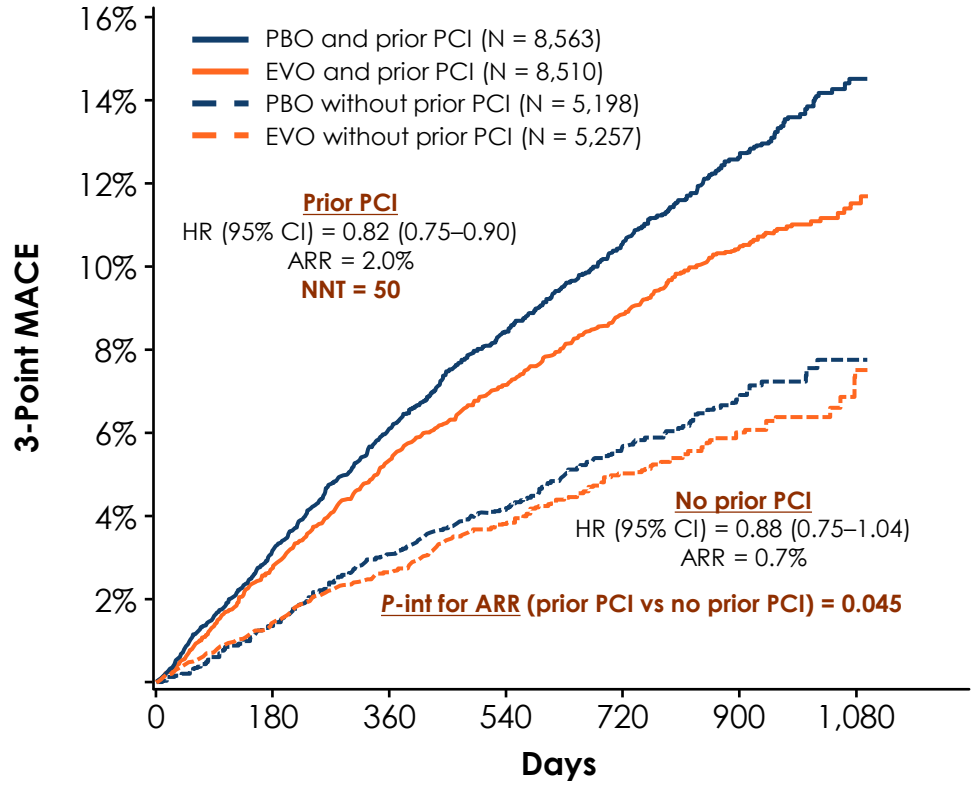
Sub-Analysis: Complex PCI and Post PCI

Furtado RHM, et al. *Circ Cardiovasc Interv*. 2022;15:e011382.

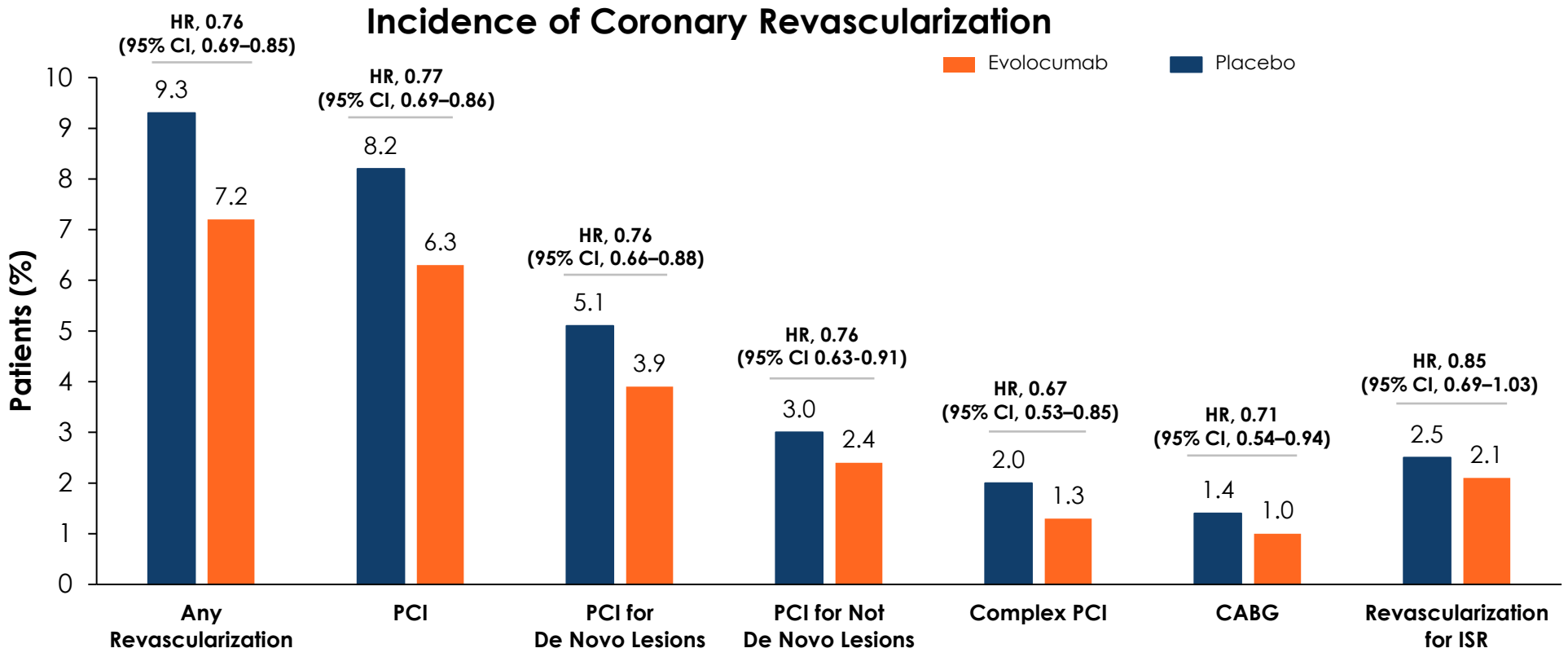
Additional Information

The Relative Reduction in 5-Point MACE Risk Was Similar, and ARR in 3-Point MACE Was Significantly Greater With Evolocumab in Patients With Prior PCI





In Patients With Prior PCI, Evolocumab Reduced the Risk of Overall Coronary Revascularization Procedures With Consistent Effects for PCI, CABG, and Several Types of Revascularization Procedures



Summary

Evolocumab reduces the risk of MACE in patients with prior PCI including the risk of coronary revascularization, with directionally consistent effects across several types of revascularization procedures, including PCI for ISR or graft failure, complex PCI, and CABG

The relative risk reductions for MACE were similar with evolocumab in patients with and without prior PCI; the higher baseline risk in the former led to numerically higher absolute risk reduction with evolocumab

Sub-Analysis: Additional

FOURIER Sub-analyses Not Listed in This Deck

	Sub-analysis	Associated Publication
1	hs-CRP	Bohula EA, et al. *Circulation*. 2018
2	LDL-C interindividual variation	Qamar A, et al. *JAMA Cardiol*. 2019
3	Total CV events	Murphy SA, et al. *JAMA Cardiology*. 2019
4	Genetic risk	Marston NA, et al. *Circulation*. 2020
5	Age and gender	Sever P, et al. *Eur J Prev Cardiol*. 2021
6	MI type and size	Wiviott SD, et al. *JAMA Cardiol*. 2020

FOURIER Parent Trial
> 30 Published Sub-analyses

5 analyses on LDL-C

- **Achieved LDL-C** (2017)
- **Low LDL-C and max potency statins** (2017)
- **LDL-C reduction by baseline LDL-C** (2020)
- **LDL-C interindividual variation** (2018)
- **LDL-C below 1 mmol/L** (2021)

10 analyses on high-risk subgroups

- **Diabetes** (2017)
- **Metabolic syndrome** (2020)
- **PAD** (2018)
- **Stroke** (2020)
- **CKD** (2019)
- **Lp(a)** (2019)
- **Evolocumab in patients with prior PCI** (2020)
- **hs-CRP** (2018)
- **LDL receptor loss of function** (2020)
- **Triglycerides** (2018)

4 analyses to advance patient identification

- **Methods for estimating LDL-C levels** (2018)
- **Genetic risk score for stroke** (2020)
- **High-sensitivity troponin** (2021)
- **Biomarker risk prediction** (2021)

3 analyses on patient subgroups

- **Age and gender** (2020)
- **Asian patients** (2020)
- **SLR and meta-analysis on efficacy of lowering LDL-C in elderly patients** (2020)

5 analyses on the impact of Repatha® on additional clinical outcomes

- **Venous thromboembolism** (2020)
- **Everyday cognition** (2020)
- **Aortic stenosis** (2020)
- **Acute arterial events** (2021)
- **Complex coronary disease requiring revascularization** (2021)

4 analyses focused on MI subgroups and outcomes

- **MI (< 2 years, # prior MI, MV disease)** (2018)
- **Recent MI (< 1 year)** (2020)
- **Total CV events** (2019)
- **MI type and size** (2020)

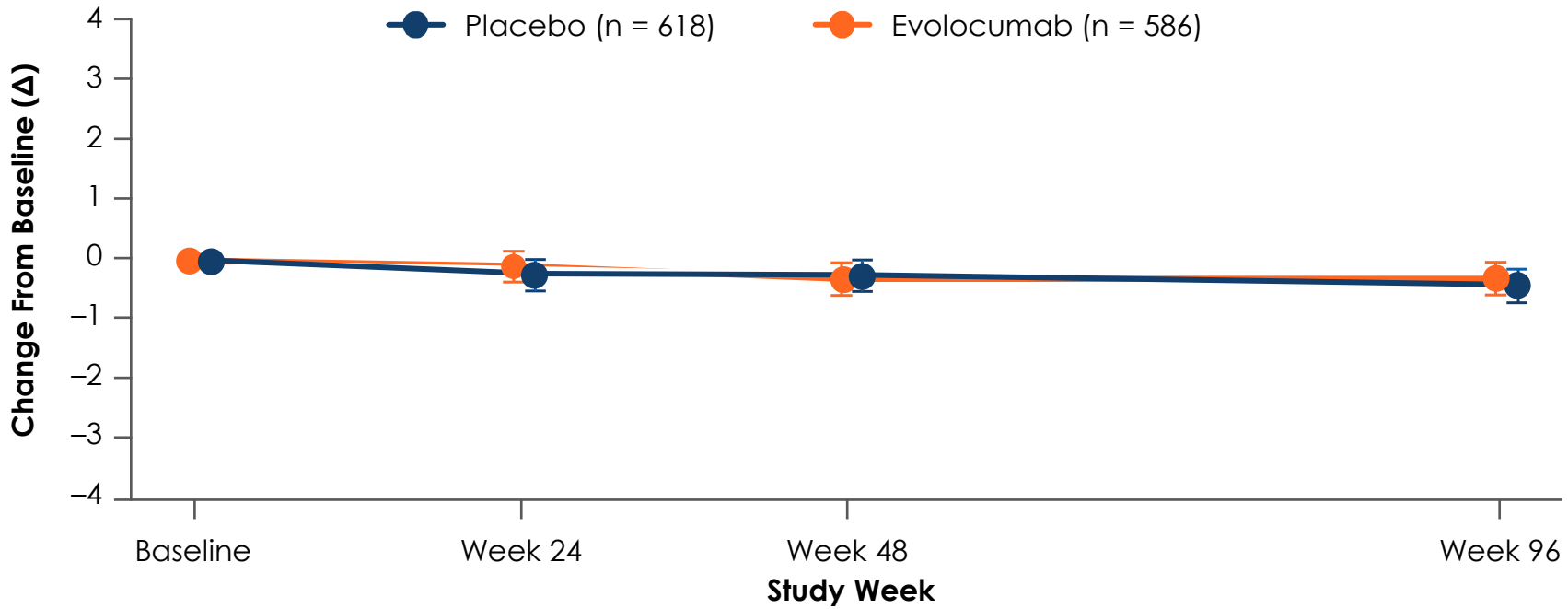
EBBINGHAUS Study

Giugliano RP, et al. *N Engl J Med*. 2017;377:633-643.

Additional Information

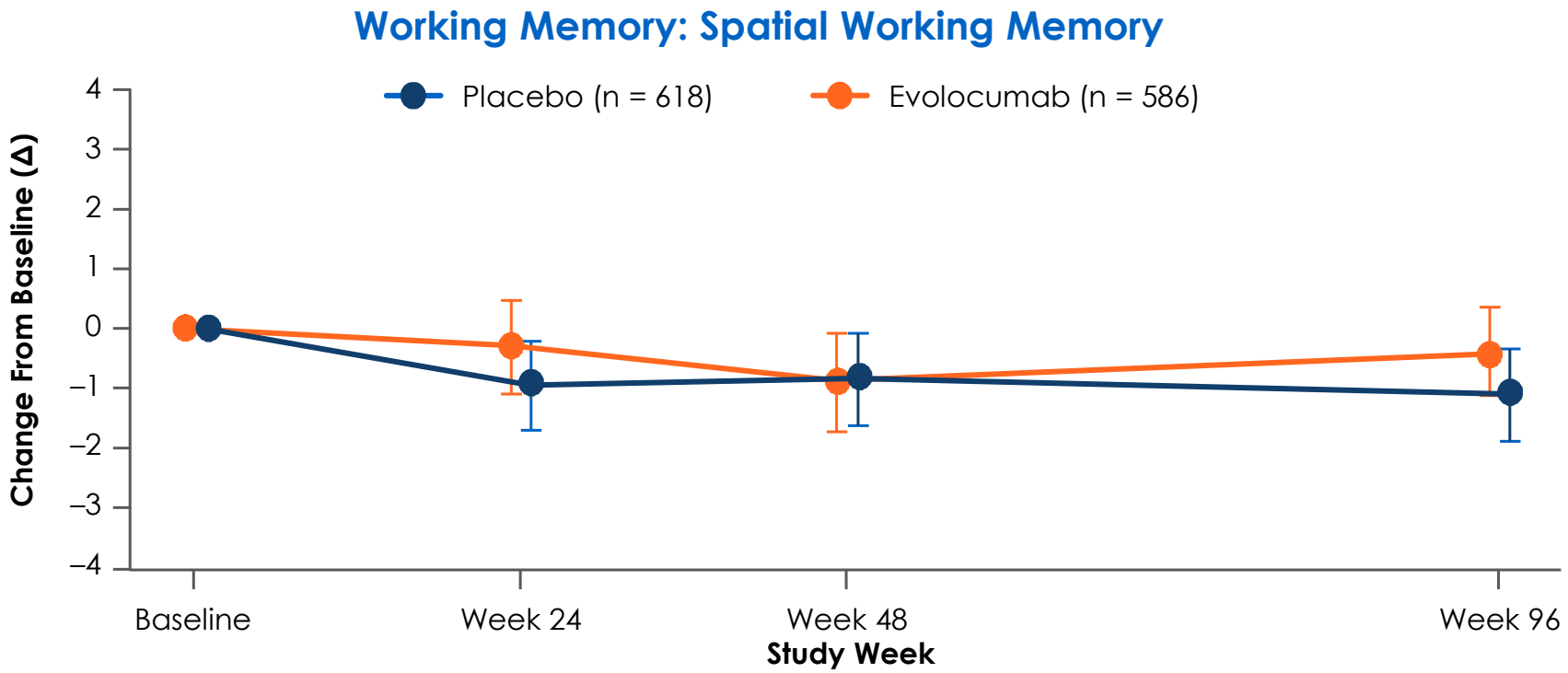
Spatial Working Memory Strategy Index of Executive Function Was Similar for Placebo and Evolocumab Groups From Baseline to Week 96

Executive Function: Spatial Working Memory Strategy Index of Executive Function



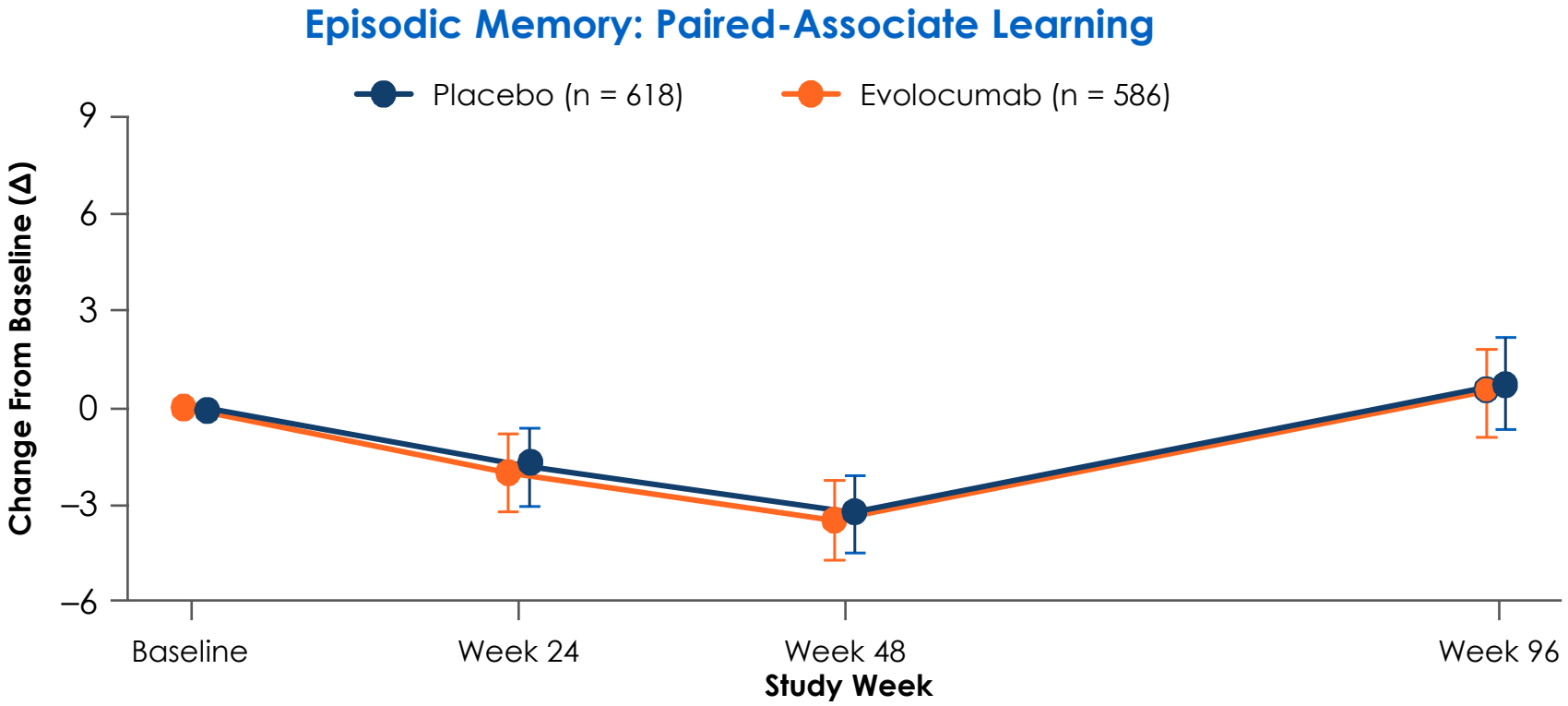
Placebo n =	618	601	585	565
Evolocumab n =	586	576	560	544

Working Memory Scores Remained Similar for Both Groups Across Study Time Points



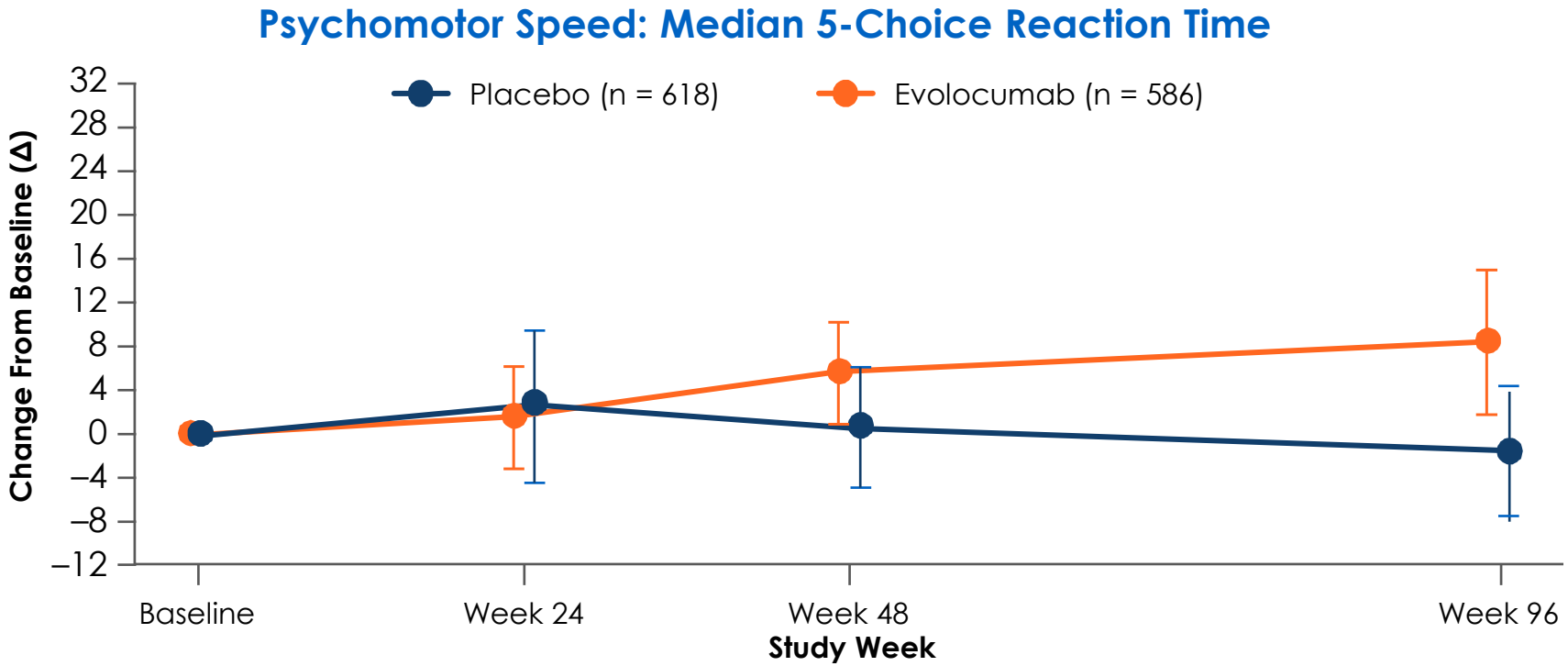
Placebo n =	618	601	585	565
Evolocumab n =	586	576	560	544

Episodic Memory Scores Were Similar for Both the Groups at All Study Time Points



Placebo n =	618	597	584	563
Evolocumab n =	586	575	558	542

Psychomotor Speed Scores Did Not Significantly Differ for Both the Groups

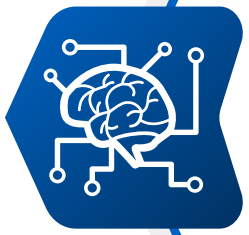


Placebo n =	614	591	579	556
Evolocumab n =	585	572	554	538

Summary

Treatment with evolocumab had no effect on the executive function of the patients

Treatment with evolocumab had no significant impact on working memory, episodic memory, or psychomotor speed across all time points

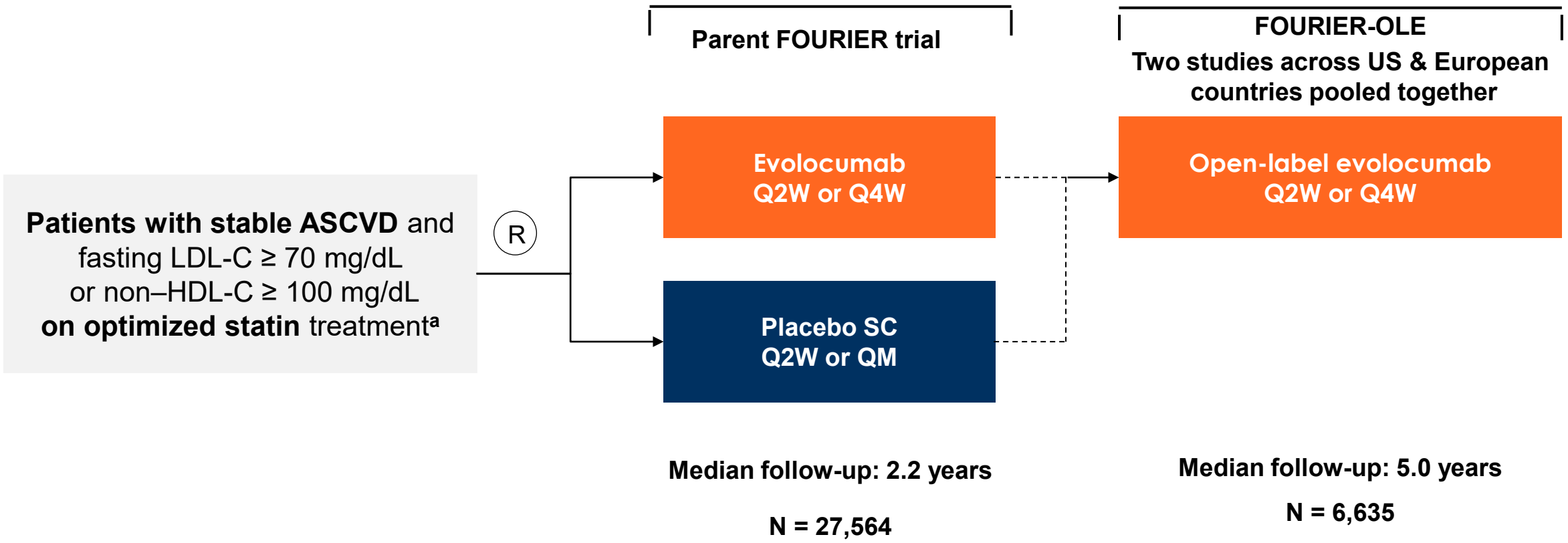


Over a median of 19 months, there was no discernible change in cognitive function between the groups

Open Label Extension (OLE): Primary analysis

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

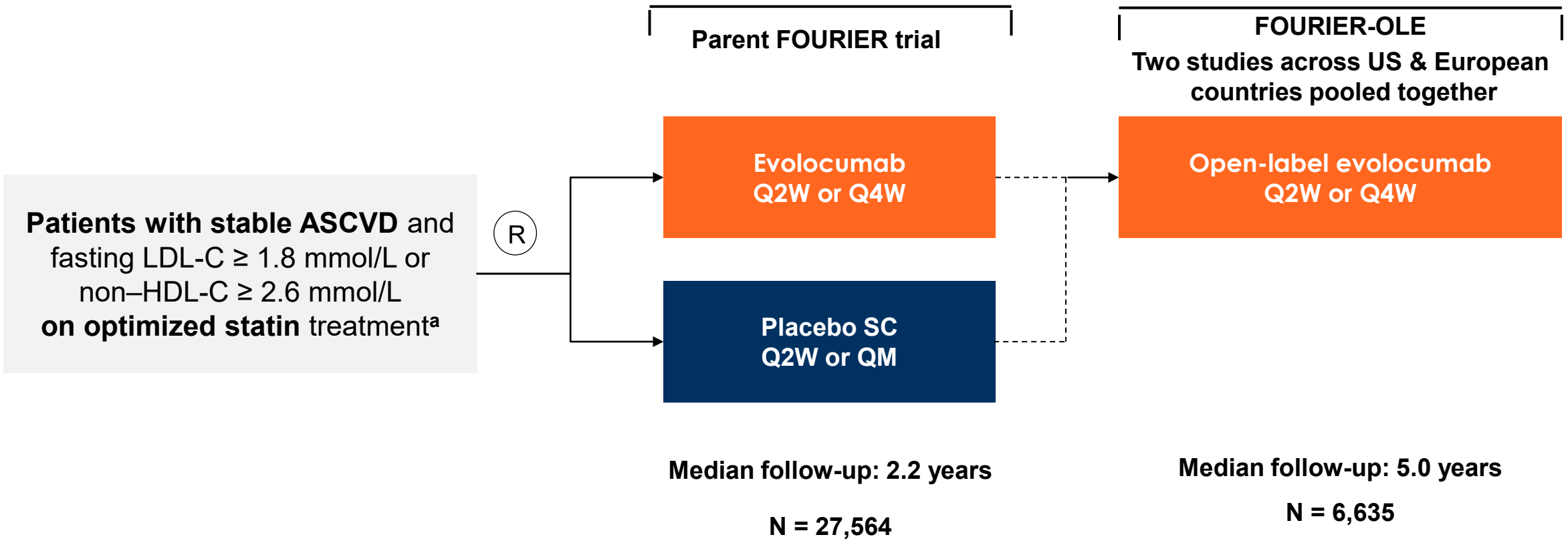
FOURIER-OLE: Designed to assess long-term safety and included prespecified exploratory CV outcomes



FOURIER OLE data are based on a pooled analysis of data from two underlying studies, one in Western Europe and one in the US and Eastern Europe. The pooled analysis was published and is presented here. When interpreting results of pooled analyses, consider that there may be differences in the individual studies data, including study design features and patient demographics and that the pooled results may differ from those of the individual studies themselves.

Note: mmol/L version

FOURIER-OLE: Designed to assess long-term safety and included prespecified exploratory CV outcomes



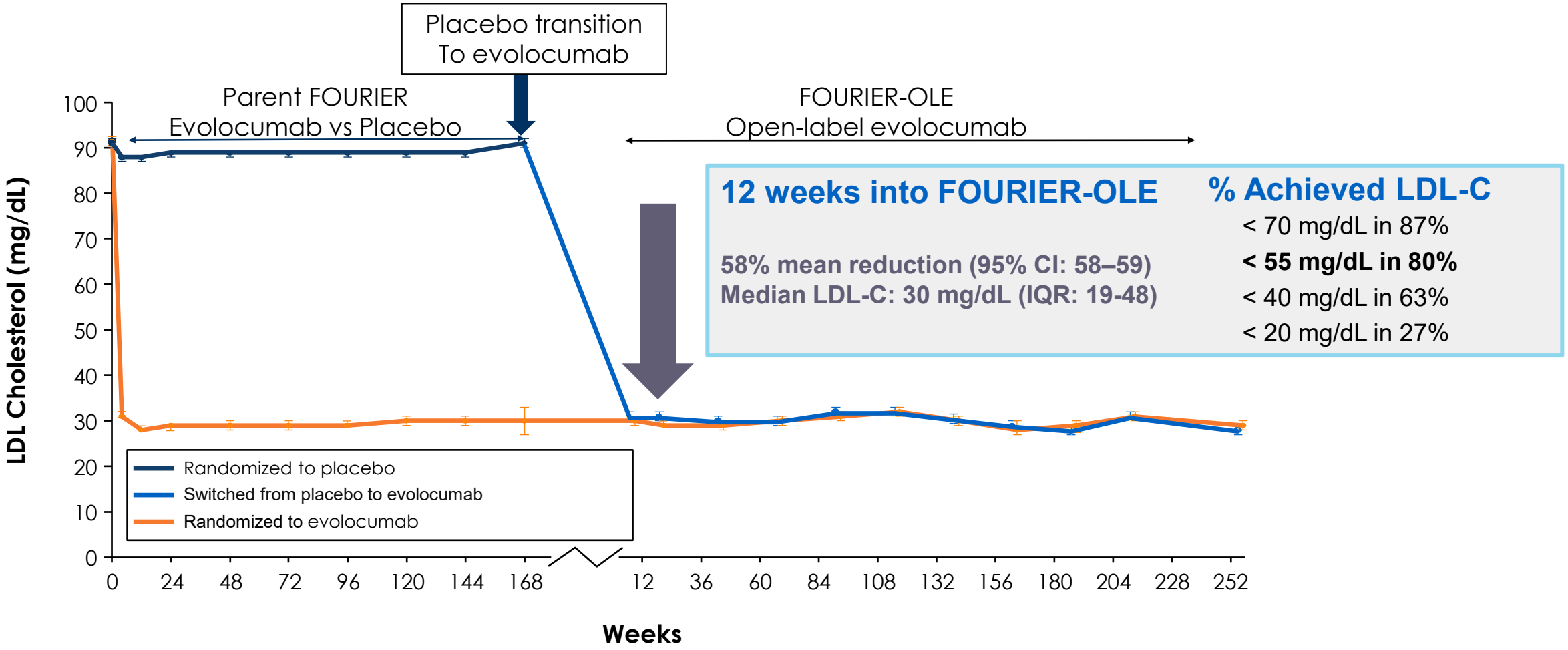
FOURIER OLE data are based on a pooled analysis of data from two underlying studies, one in Western Europe and one in the US and Eastern Europe. The pooled analysis was published and is presented here. When interpreting results of pooled analyses, consider that there may be differences in the individual studies data, including study design features and patient demographics and that the pooled results may differ from those of the individual studies themselves.

Considerations of FOURIER-OLE Analyses

- All patients were treated with evolocumab resulting in no concurrent placebo arm
- Cannot exclude that unmeasured confounders may have existed between patients originally randomized to evolocumab versus placebo
- Patients needed to have survived the parent FOURIER trial to be enrolled in FOURIER-OLE such that the extension population would be expected to be at somewhat lower risk
- Not all patients in the FOURIER parent or extension studies were on high-intensity statin or ezetimibe, but effect modification was not observed in FOURIER on the basis of background therapy
- Study sites were provided with their patients' treatment assignment after FOURIER completely closed, which could introduce bias

Patients who participated in FOURIER-OLE were overall similar to those who participated in the parent trial, thereby allowing reasonably unconfounded exploratory comparisons between groups

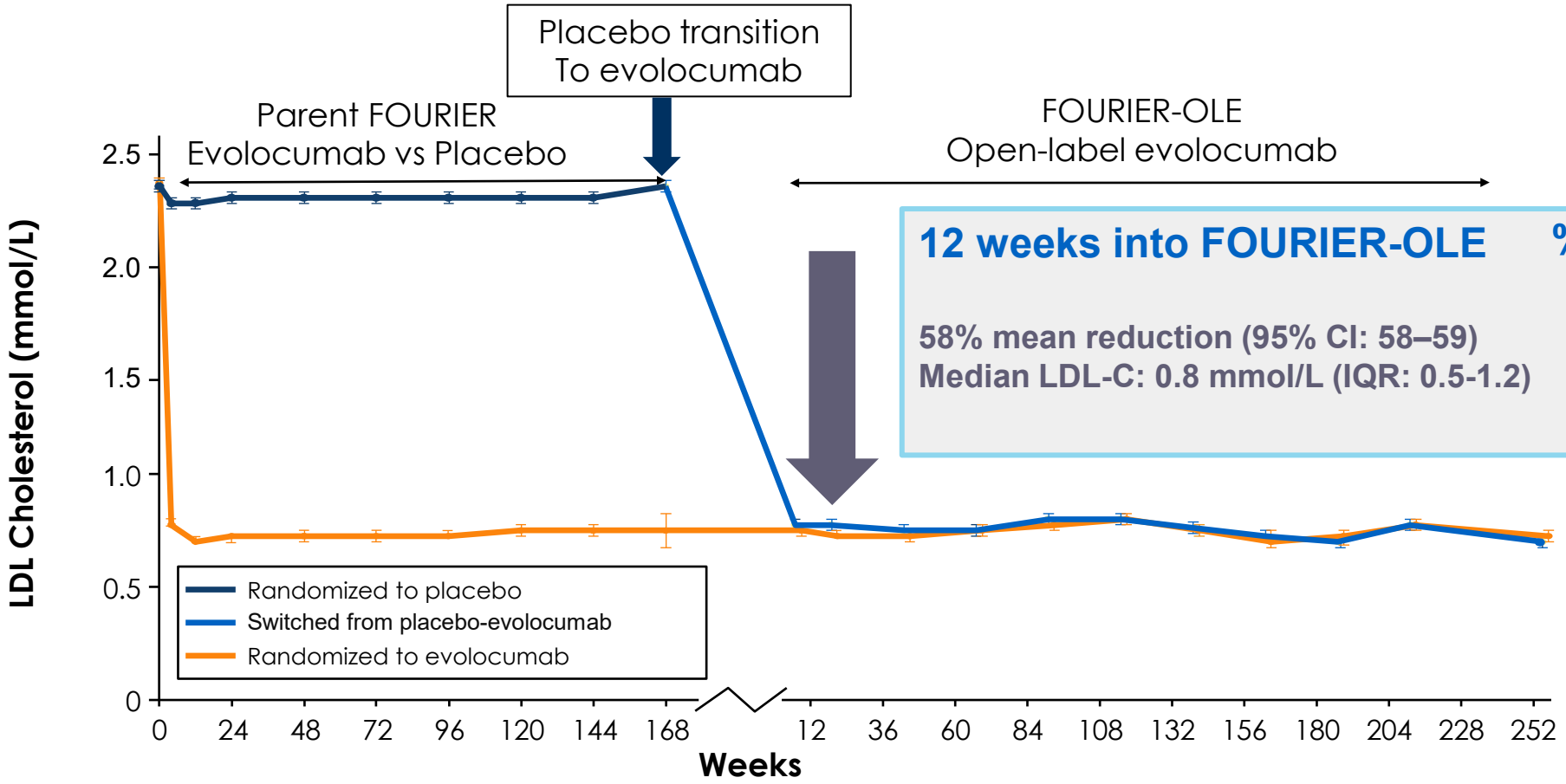
FOURIER-OLE: LDL-C was consistently reduced by evolocumab for median >5 years (maximum 8.4 years across parent & OLE)



86 Open-label trials are not blinded or controlled, and inherently subject to self-selection bias

Note: mmol/L version

FOURIER-OLE: LDL-C was consistently reduced by evolocumab for median >5 years (maximum 8.4 years across parent & OLE)



12 weeks into FOURIER-OLE

58% mean reduction (95% CI: 58–59)
Median LDL-C: 0.8 mmol/L (IQR: 0.5-1.2)

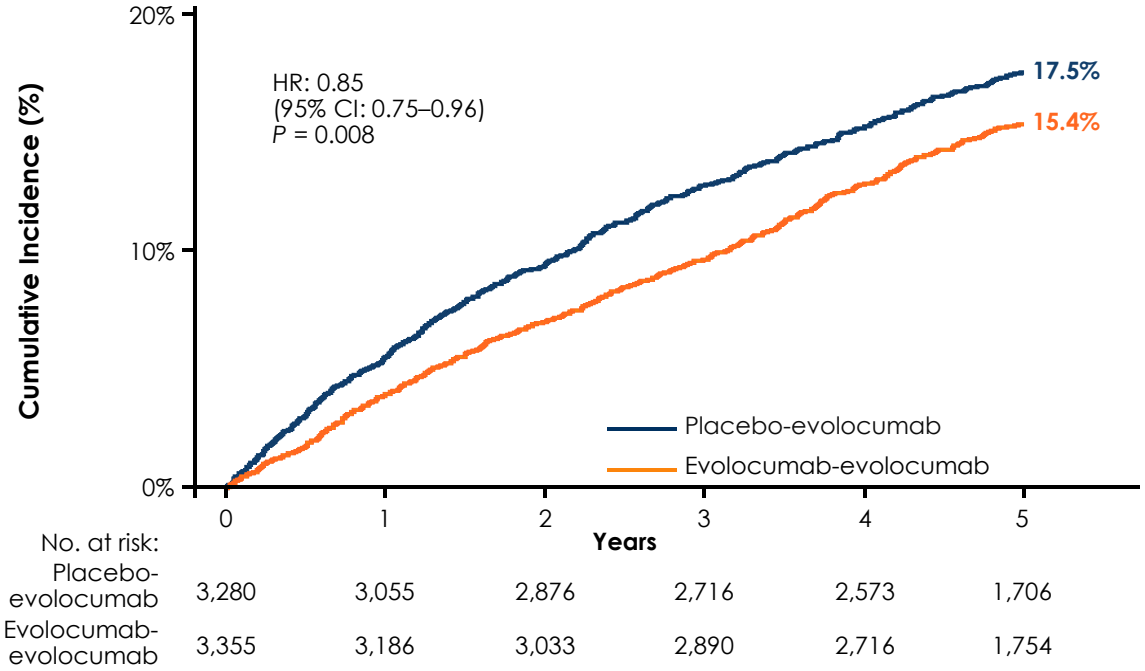
% Achieved LDL-C

< 1.8 mmol/L in 87%
< 1.4 mmol/L in 80%
< 1.0 mmol/L in 63%
< 0.5 mmol/L in 27%

A Lower Risk (15%) of 5-Point MACE Was Observed in Patients Originally Randomized to Evolocumab in the Parent Trial Compared With Placebo

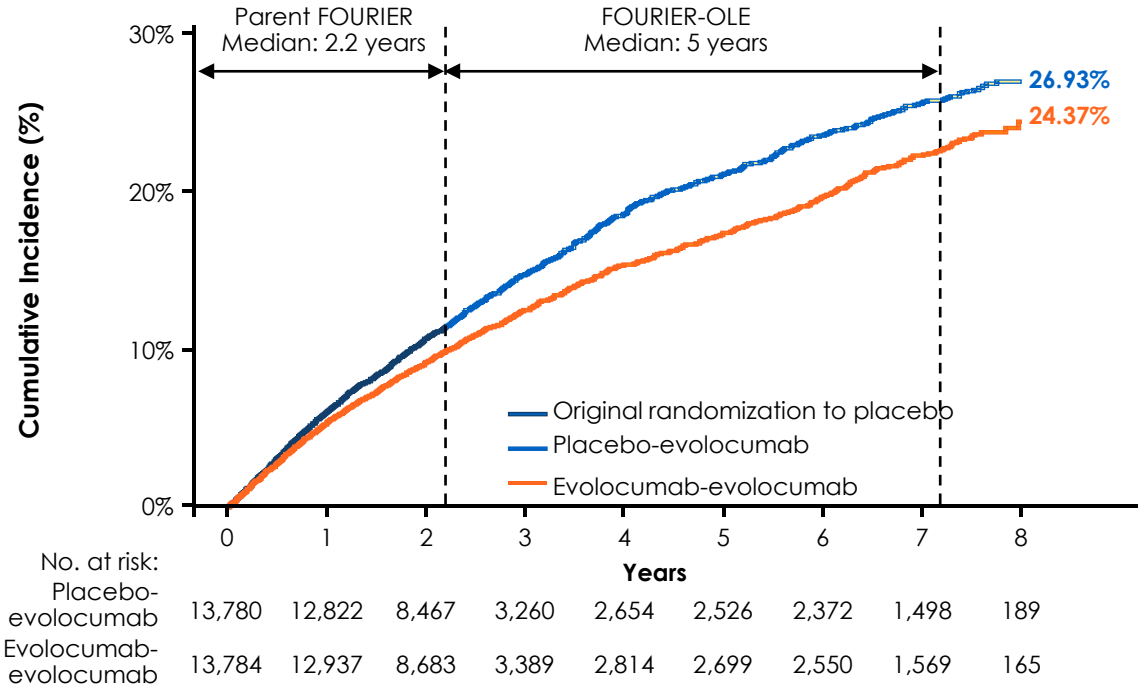
Prespecified Exploratory Analysis – CV death, MI, stroke, hospitalization for UA, or CoR

FOURIER-OLE[1]



No. at risk:						
Placebo-evolocumab	3,280	3,055	2,876	2,716	2,573	1,706
Evolocumab-evolocumab	3,355	3,186	3,033	2,890	2,716	1,754

Parent FOURIER + FOURIER-OLE[2]



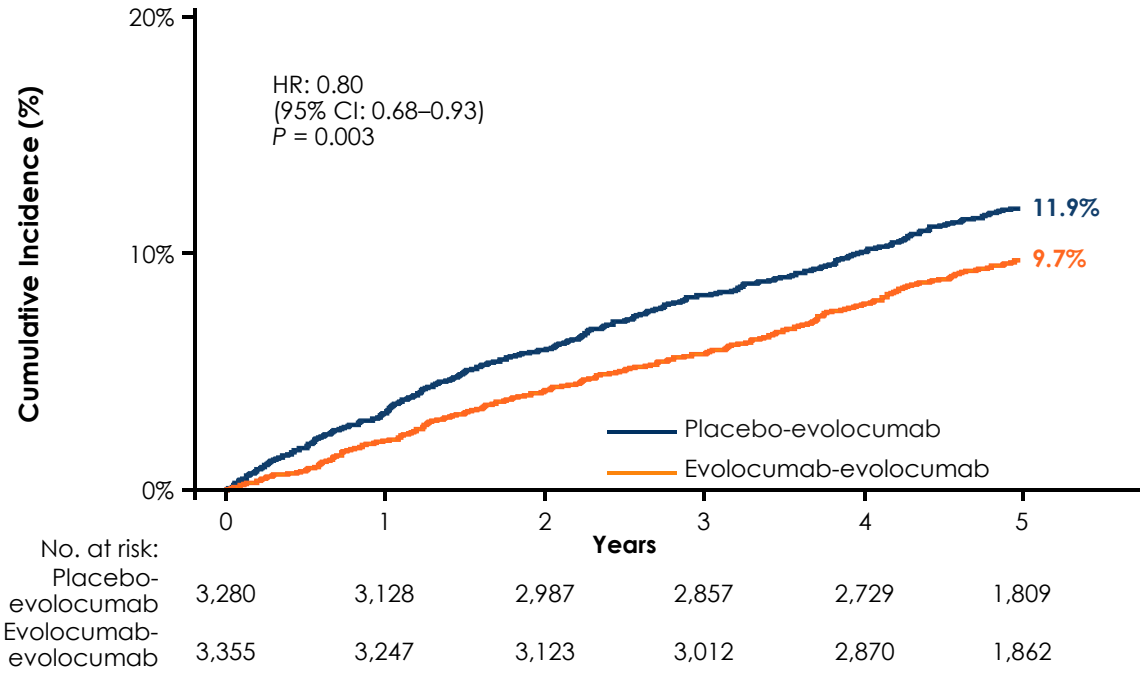
No. at risk:									
Placebo-evolocumab	13,780	12,822	8,467	3,260	2,654	2,526	2,372	1,498	189
Evolocumab-evolocumab	13,784	12,937	8,683	3,389	2,814	2,699	2,550	1,569	165

Note: Open-label trials are not blinded or controlled, and inherently subject to self-selection bias. CV outcomes were prespecified, but considered exploratory. No statistical conclusions can be drawn from this exploratory analysis.

A Lower Risk (20%) of 3-Point MACE Was Observed in Patients Originally Randomized to Evolocumab in the Parent Trial Compared With Placebo

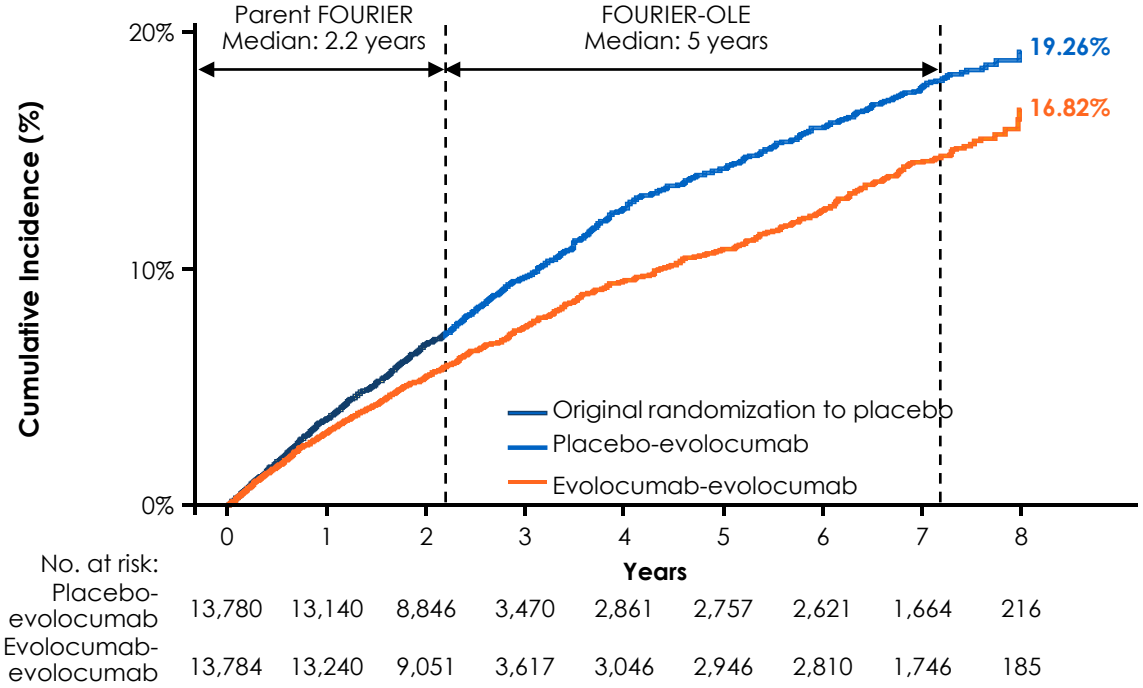
Prespecified Exploratory Analysis – CV death, MI, or stroke

FOURIER-OLE[1]



No. at risk:						
Placebo-evolocumab	3,280	3,128	2,987	2,857	2,729	1,809
Evolocumab-evolocumab	3,355	3,247	3,123	3,012	2,870	1,862

Parent FOURIER + FOURIER-OLE[2]



No. at risk:									
Placebo-evolocumab	13,780	13,140	8,846	3,470	2,861	2,757	2,621	1,664	216
Evolocumab-evolocumab	13,784	13,240	9,051	3,617	3,046	2,946	2,810	1,746	185

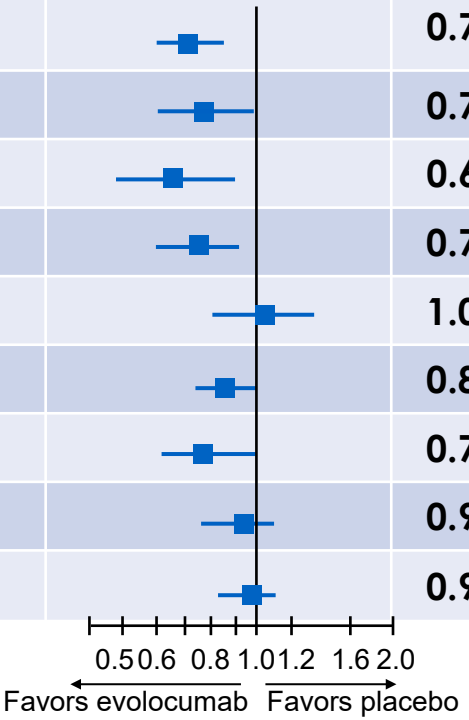
Note: Open-label trials are not blinded or controlled, and inherently subject to self-selection bias. CV outcomes were prespecified, but considered exploratory. No statistical conclusions can be drawn from this exploratory analysis.

FOURIER-OLE: Earlier initiation of evolocumab reduced the risk of several major adverse CV events vs Later Initiation

Prespecified Exploratory Analysis

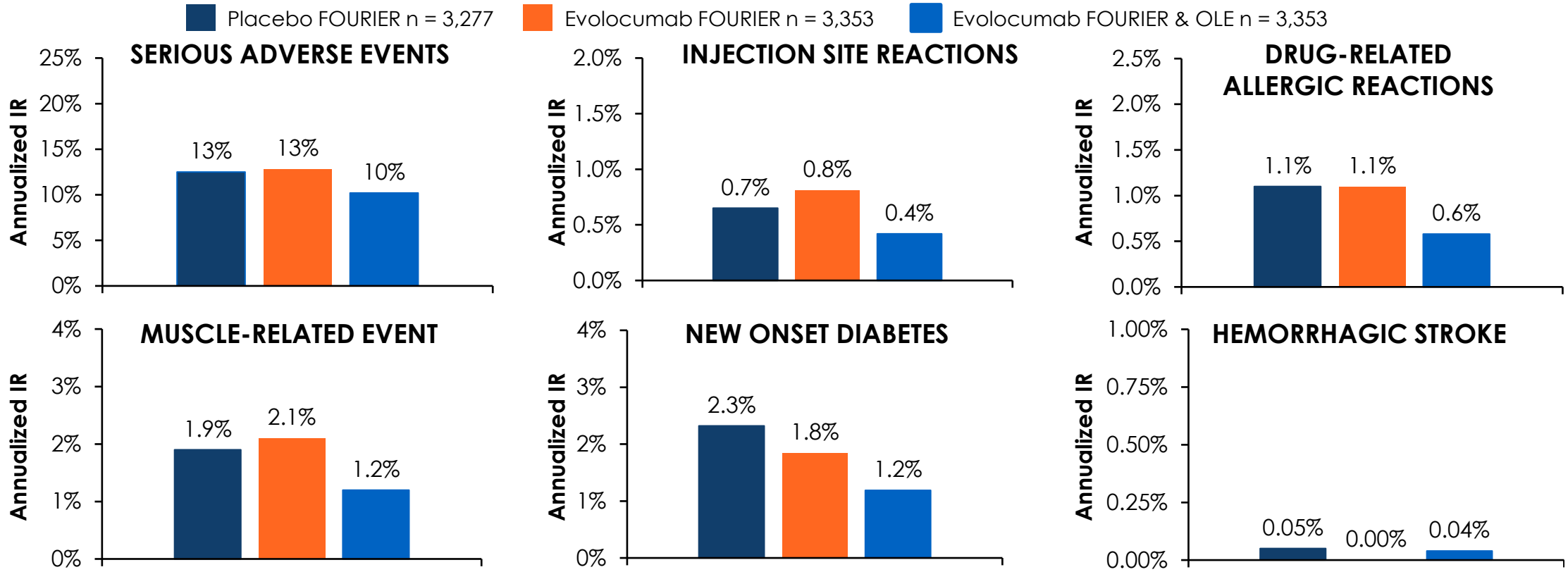
Original Randomization Groups in FOURIER

	Placebo (N=3280)		Evolocumab (N=3355)		Hazard Ratio (95% confidence interval)
CV Events	# patients with event	Incidence rate	# patients with event	Incidence rate	
Coronary heart disease death or myocardial infarction	267	1.82%	199	1.30%	**0.72 (0.60-0.86)**
Cardiovascular death	138	0.90%	107	0.68%	**0.77 (0.60-0.99)**
Coronary heart disease death	97	0.63%	64	0.40%	**0.65 (0.48-0.90)**
Myocardial infarction	194	1.32%	151	0.99%	**0.75 (0.60-0.93)**
Stroke	94	0.63%	102	0.66%	**1.05 (0.80-1.39)**
Coronary Revascularization	313	2.20%	280	1.88%	**0.85 (0.73-1.00)**
Urgent Revascularization	166	1.13%	132	0.87%	**0.77 (0.61-0.96)**
Elective Revascularization	178	1.22%	174	1.15%	**0.93 (0.76-1.15)**
All-cause mortality	344	2.23%	338	2.14%	**0.97 (0.83-1.13)**



Open-label trials are not blinded or controlled, and inherently subject to self-selection bias. CV outcomes were prespecified, but considered exploratory. No statistical conclusions can be drawn from this exploratory analysis. Component analyses were not pre-specified and not adjusted for multiplicity, the results on the individual components need cautious interpretation and could represent chance findings

The Annual Incidence Rates of Safety Events of Interest in Patients Who Entered FOURIER OLE Were Consistent With the Established Safety Profile



FOURIER-OLE Trial

Summary

- The FOURIER OLE included a sub-set of 6,635 patients from FOURIER where all patients received evolocumab:
- The FOURIER-OLE trial has the longest follow-up to date of a PCSK9i:
  - Median follow-up in the OLE was 5 years with a maximum exposure to evolocumab in the FOURIER parent + OLE studies of 8.4 years and a maximum safety follow-up of 8.6 years

- Evolocumab demonstrated consistent LDL-C lowering and safety profile through long-term follow up

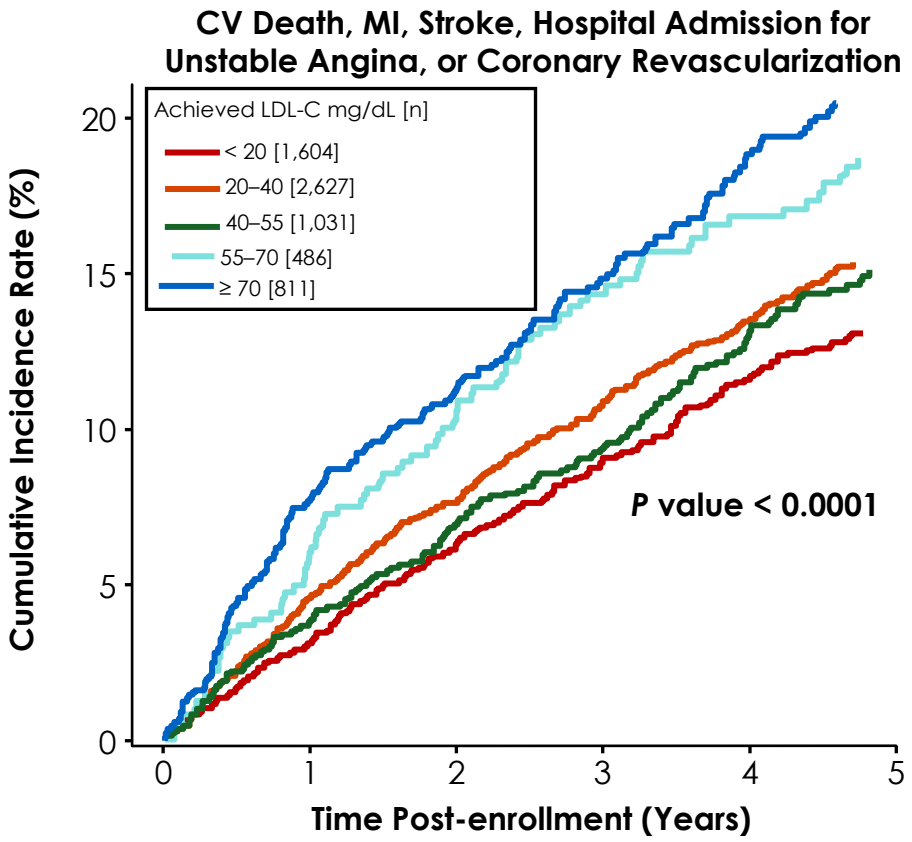
- Although not placebo-controlled and exploratory:
  - Pre-specified CV outcomes showed continued divergence in the risk of MACE
  - Patients who started evolocumab earlier in the parent trial experienced greater reductions in component endpoints CV death, MI, and coronary revascularization than those who initiated evolocumab later in FOURIER OLE

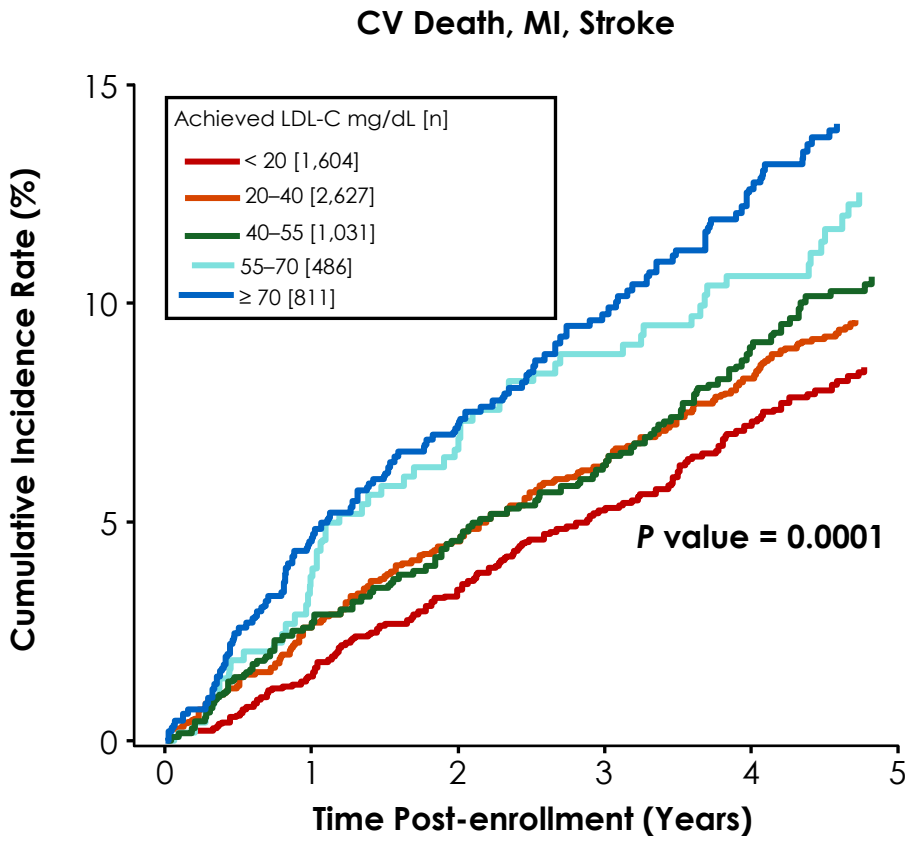
Open Label Extension (OLE) Sub-analysis: Achieved LDL-C

Gaba P, et al. *Circulation*. 2023;147:1192-1203.

Additional Information

For 5-Point and 3-Point MACE, A Gradient of Lower Event Rates was Observed With Lower Achieved LDL-C Categories

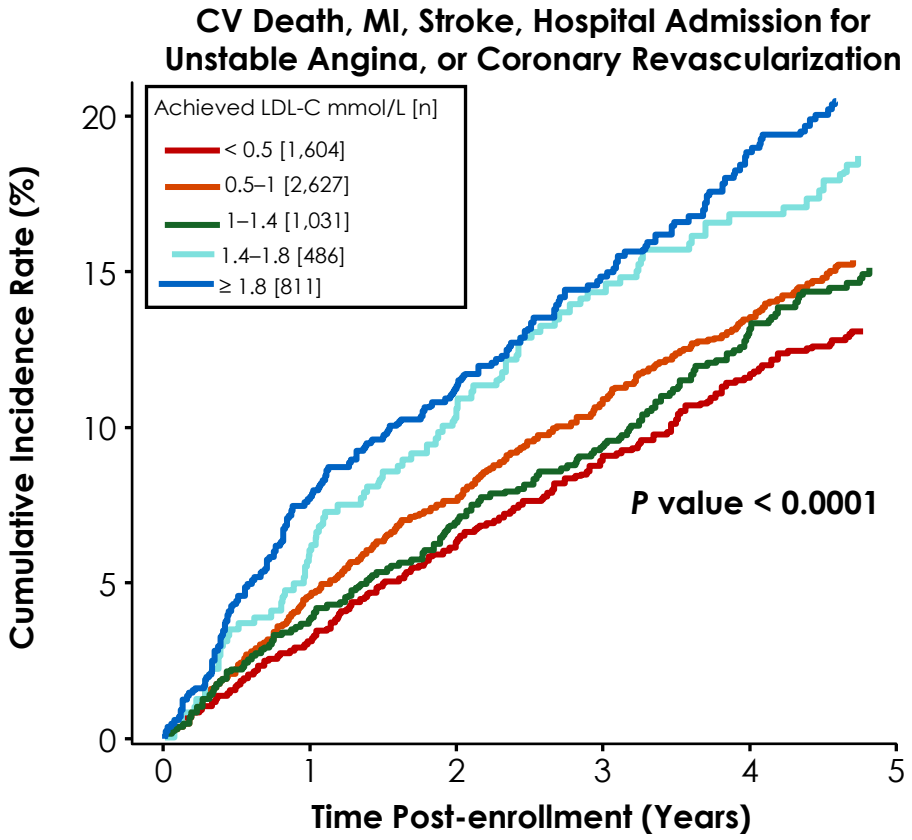


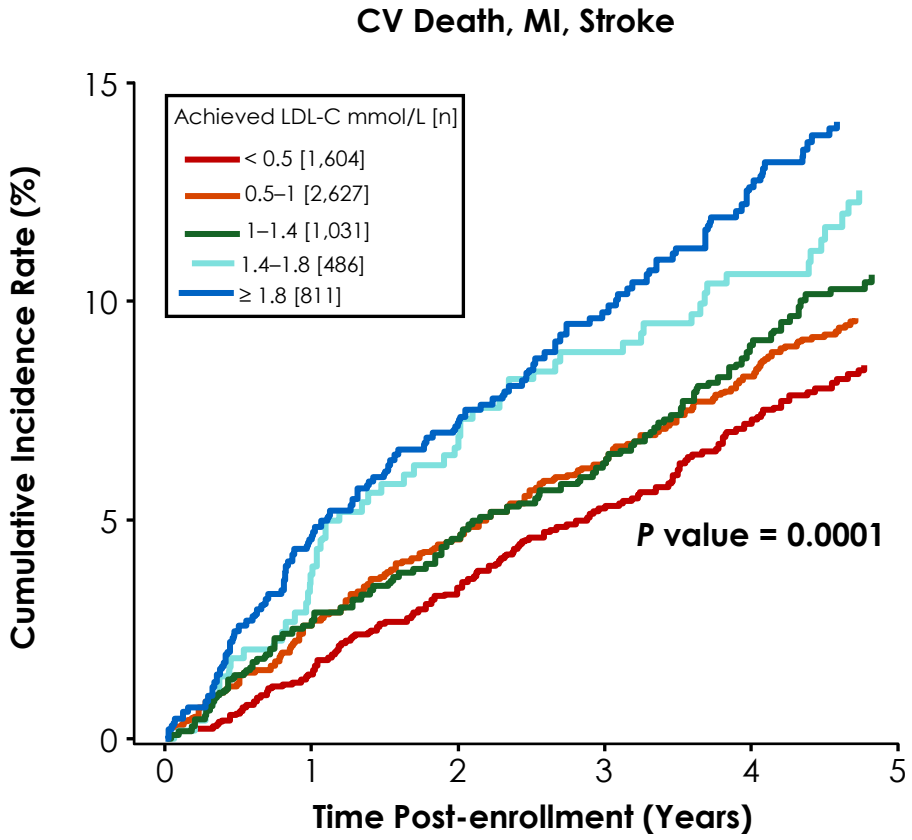


Prespecified Exploratory Analysis – 5-point MACE: CV death, MI, stroke, hospitalization for UA, or CoR; 3-Point MACE - CV death, MI, stroke

Note: mmol/L version

For 5-Point and 3-Point MACE, A Gradient of Lower Event Rates was Observed With Lower Achieved LDL-C Categories

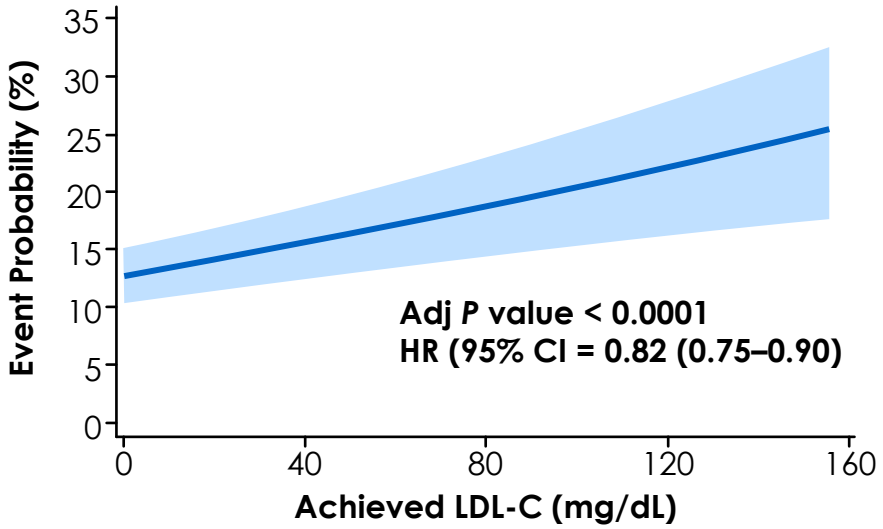




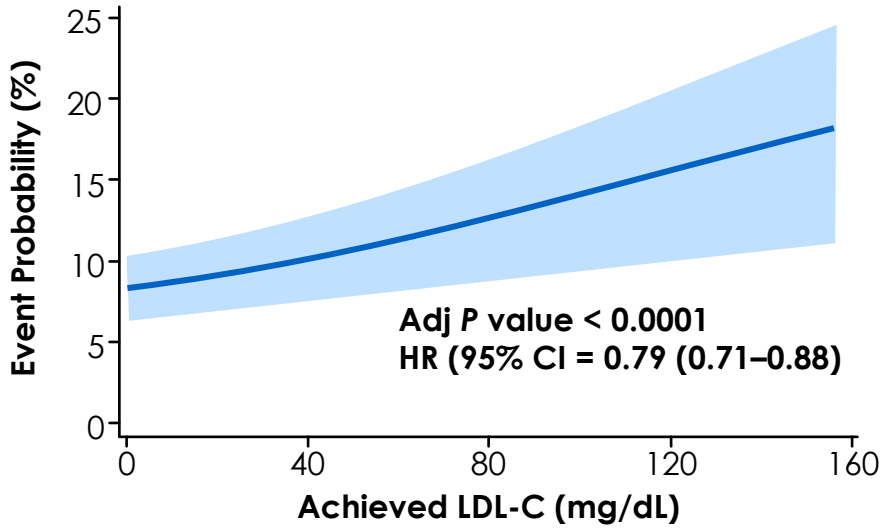
Prespecified Exploratory Analysis – 5-point MACE: CV death, MI, stroke, hospitalization for UA, or CoR; 3-Point MACE - CV death, MI, stroke

A Monotonic Relationship Observed Between Achieved LDL-C Level and Cardiovascular Efficacy Outcomes in FOURIER-OLE

5-Point MACE



3-Point MACE

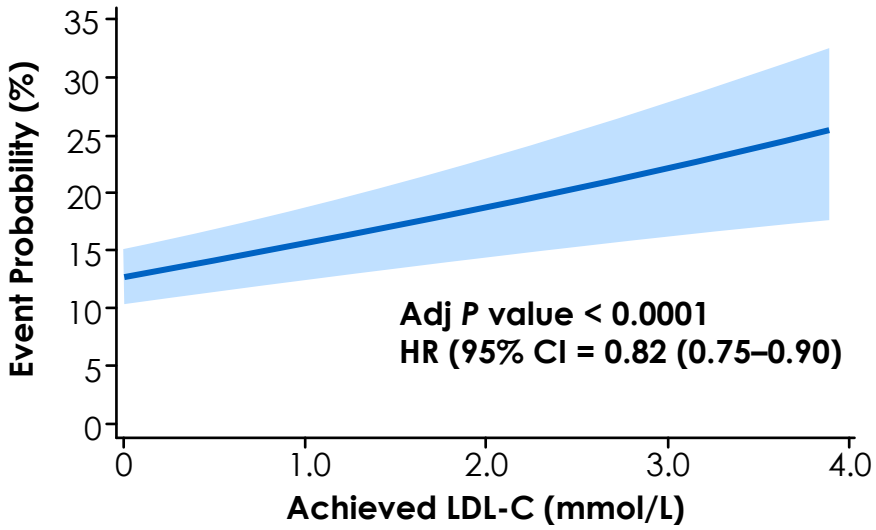


Prespecified Exploratory Analysis – 5-point MACE: CV death, MI, stroke, hospitalization for UA, or CoR; 3-Point MACE - CV death, MI, stroke

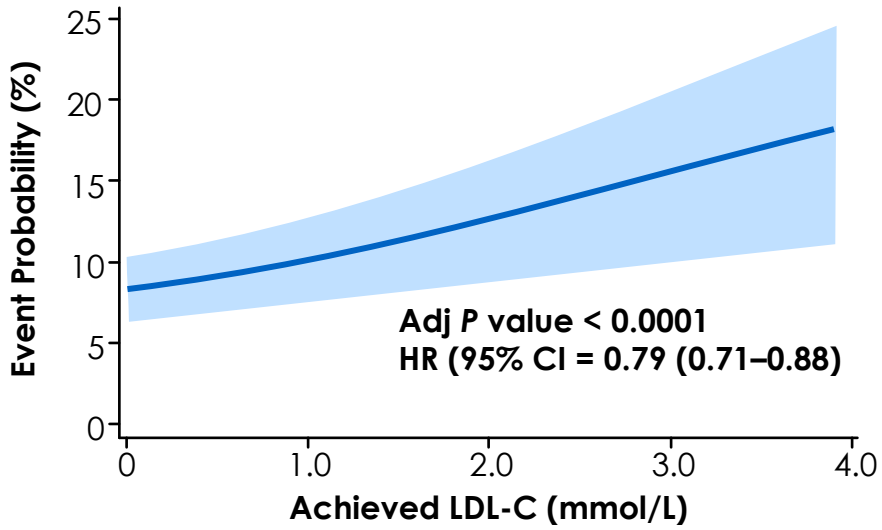
Note: mmol/L version

A Monotonic Relationship Observed Between Achieved LDL-C Level and Cardiovascular Efficacy Outcomes in FOURIER-OLE

5-Point MACE

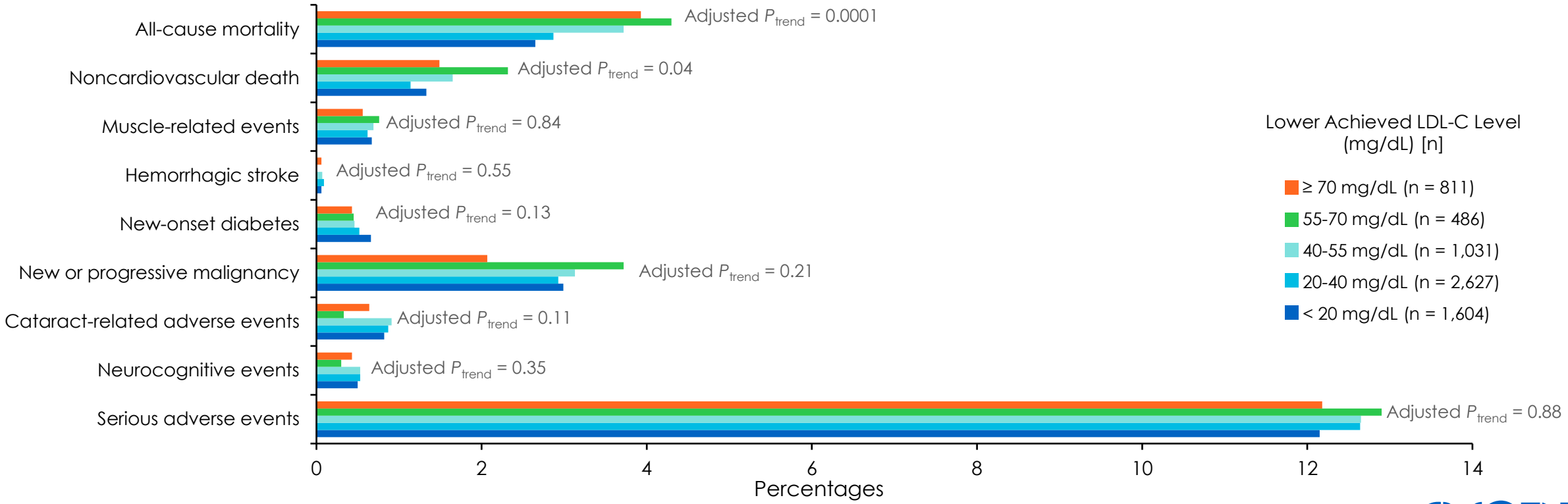


3-Point MACE



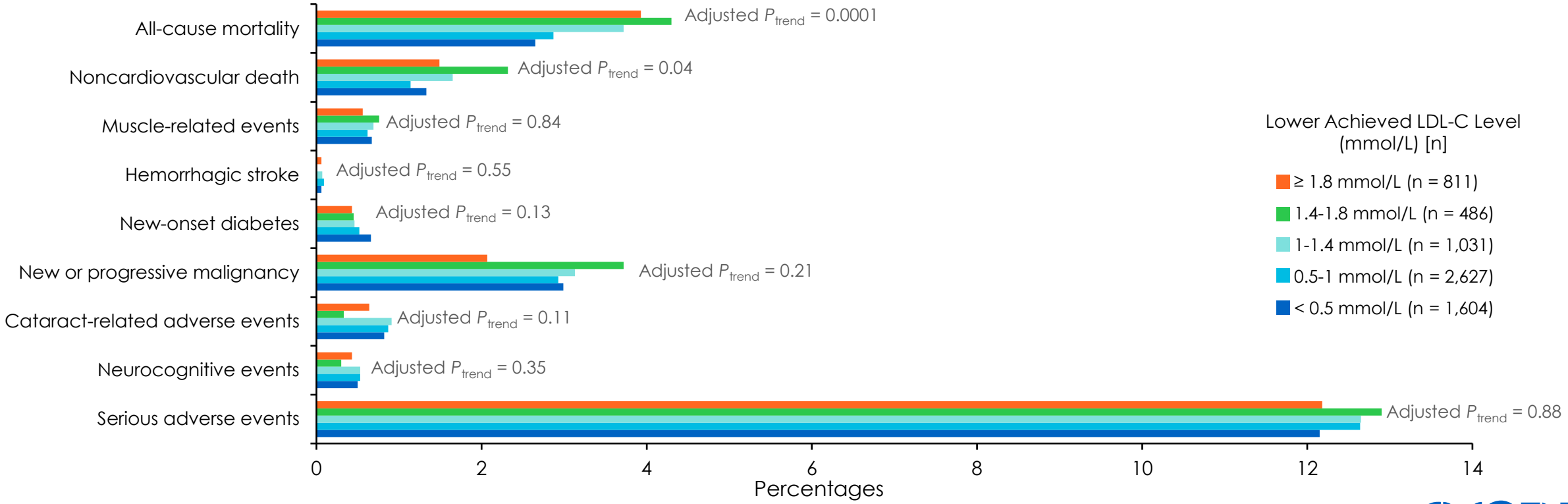
Prespecified Exploratory Analysis – 5-point MACE: CV death, MI, stroke, hospitalization for UA, or CoR; 3-Point MACE - CV death, MI, stroke

No Clear Monotonic Trends Between Lower Achieved LDL-C Level and the Risk of Safety Outcomes Except for All-Cause Mortality, Which Was Lowest Among Those With Lower Achieved LDL-C Levels

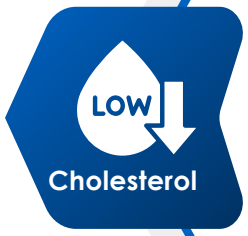


Note: mmol/L version

No Clear Monotonic Trends Between Lower Achieved LDL-C Level and the Risk of Safety Outcomes Except for All-Cause Mortality, Which Was Lowest Among Those With Lower Achieved LDL-C Levels



Summary

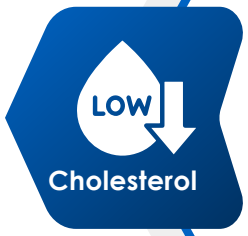


A monotonic relationship was observed between lower achieved LDL-C levels, down to very low LDL-C levels < 20 mg/dL, and a lower risk of cardiovasicular outcomes during an extended follow-up of 8.6 years across the FOURIER parent and OLE studies

No relationship between achieved LDL-C levels and safety was observed except for reduced risk in all-cause mortality with lower LDL-C levels

Note: mmol/L version

Summary



A monotonic relationship was observed between lower achieved LDL-C levels, down to very low LDL-C levels < 0.5 mmol/L, and a lower risk of cardiovascular outcomes during an extended follow-up of 8.6 years

No relationship between achieved LDL-C levels and safety was observed except for reduced risk in all-cause mortality with lower LDL-C levels

Backup Slides

FOURIER Parent Trial: Objectives

FOURIER: **F**urther cardiovascular **OU**tcomes **R**esearch with PCSK9 **I**nhibition in subjects with **E**levated **R**isk

- Designed to test whether patients with established cardiovascular disease who are already on optimal cardiovascular therapy, including high to moderate intensity statins, benefit from maximal LDL-C reduction with evolocumab.
- Additionally, the clinical efficacy and safety of achieving unprecedented levels of low LDL-C with evolocumab was evaluated.
- Global randomized, placebo-controlled, double-blind trial (n = 27,564; 49 countries; 1,242 sites).

FOURIER Parent Trial: Cardiovascular Outcomes Trial in ASCVD Patients on Background Lipid-Lowering Therapy

Randomized, double-blind, placebo-controlled, multinational clinical trial[1-3]

Screening/Key Eligibility Criteria

- Age 40–85 years
- MI, stroke, or PAD
- Additional risk factors (one major or two minor)
- Optimal background lipid therapy (including effective dose of statin ± ezetimibe)
- LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL

Randomization 1:1

Evolocumab SC
140 mg Q2W or 420 mg QM
(per patient preference)
N = 13,784

Placebo SC
Q2W or QM
(per patient preference)
N = 13,780

End of Study

Objective

- To test the clinical efficacy and safety of evolocumab when added to a statin in patients with clinically evident vascular disease

Endpoints

- **Primary:** Composite of CV death, MI, stroke, hospitalization for UA, or CoR
- **Key secondary:** Composite of CV death, MI, or stroke
- **Other secondary:** All-cause death, CoR; CV death or hospitalization for heart failure; ischemic stroke or TIA

Maximum approximately 15 weeks

D1 W4 W12 W24 Q24W

Number of key 2^0 endpoints achieved

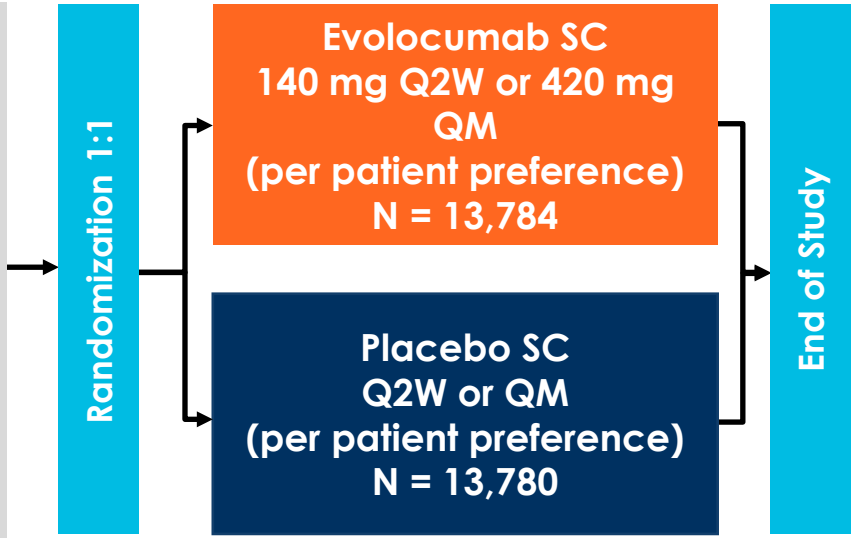
Note: mmol/L version

FOURIER Parent Trial: Cardiovascular Outcomes Trial in ASCVD Patients on Background Lipid-Lowering Therapy

Randomized, double-blind, placebo-controlled, multinational clinical trial[1-3]

Screening/Key Eligibility Criteria

- Age 40–85 years
- MI, stroke, or PAD
- Additional risk factors (one major or two minor)
- Optimal background lipid therapy (including effective dose of statin ± ezetimibe)
- LDL-C ≥ 1.8 mmol/L or non–HDL-C ≥ 2.6 mmol/L

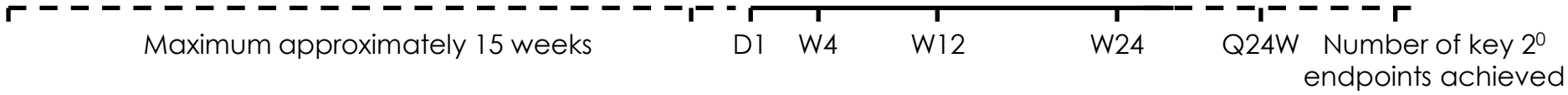


Objective

- To test the clinical efficacy and safety of evolocumab when added to a statin in patients with clinically evident vascular disease

Endpoints

- **Primary:** Composite of CV death, MI, stroke, hospitalization for UA, or CoR
- **Key secondary:** Composite of CV death, MI, or stroke
- **Other secondary:** All-cause death, CoR; CV death or hospitalization for heart failure; ischemic stroke or TIA



Evolocumab Outcomes Trial: Key Eligibility Criteria

- Men or women aged 40–85 years
- Clinically evident CVD (prior MI, prior non-hemorrhagic stroke, or symptomatic PAD)
- At least 1 major additional risk factor (e.g., diabetes, current smoker, MI or non-hemorrhagic stroke at ≤ 6 months of screening) or 2 minor additional risk factors (e.g., history of non-MI–related coronary revascularization, metabolic syndrome, LDL-C ≥ 130 mg/dL or non–HDL-C ≥ 160 mg/dL)
- Fasting LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL on an optimized stable lipid-lowering therapy
  - At least atorvastatin 20 mg daily or equivalent +/- ezetimibe

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Note: mmol/L version

Evolocumab Outcomes Trial: Key Eligibility Criteria

- Men or women aged 40–85 years
- Clinically evident CVD (prior MI, prior non-hemorrhagic stroke, or symptomatic PAD)
- At least 1 major additional risk factor (e.g., diabetes, current smoker, MI or non-hemorrhagic stroke at ≤ 6 months of screening) or 2 minor additional risk factors (e.g., history of non-MI–related coronary revascularization, metabolic syndrome, LDL-C ≥ 3.4 mmol/L or non–HDL-C ≥ 4.1 mmol/L)
- Fasting LDL-C ≥ 1.8 mmol/L or non–HDL-C ≥ 2.6 mmol/L on an optimized stable lipid-lowering therapy
  - At least atorvastatin 20 mg daily or equivalent +/- ezetimibe

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Baseline Characteristics

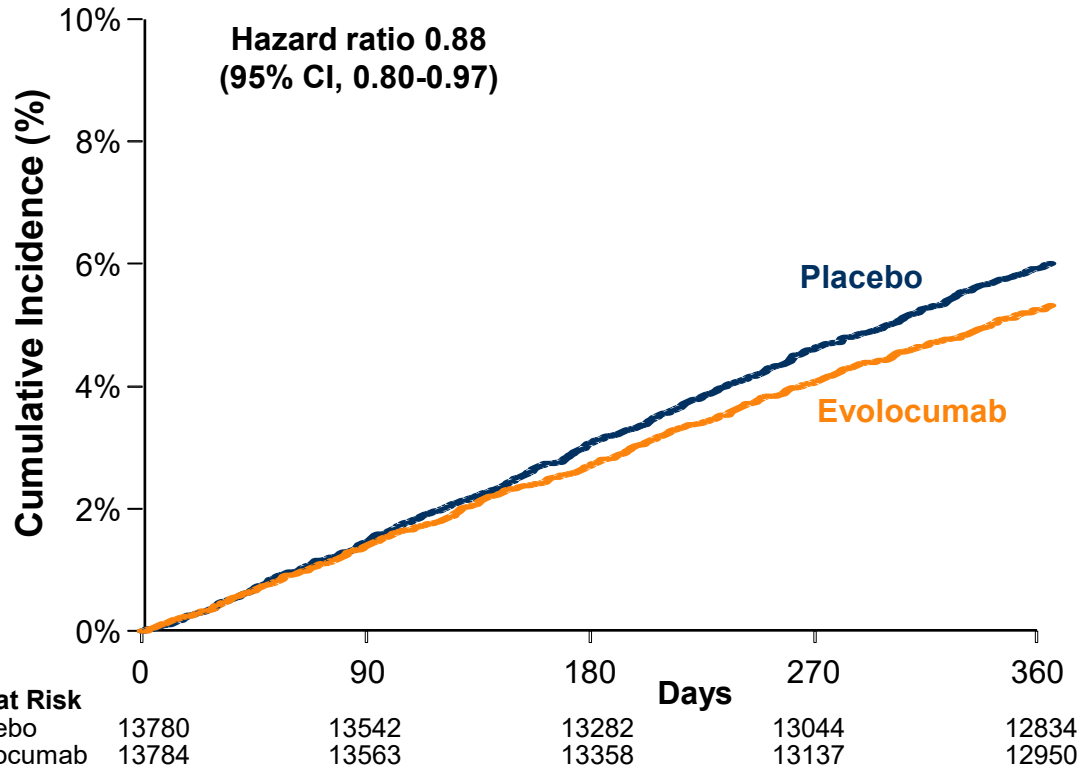
Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Demographics		
Age – y (SD)	62.5 (9.1)	62.5 (8.9)
Male sex – n (%)	10,397 (75.4)	10,398 (75.5)
White race – n (%)	11,748 (85.2)	11,710 (85.0)
Weight – kg (SD)	85.0 (17.3)	85.5 (17.4)
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)

Baseline CV Risk Factors

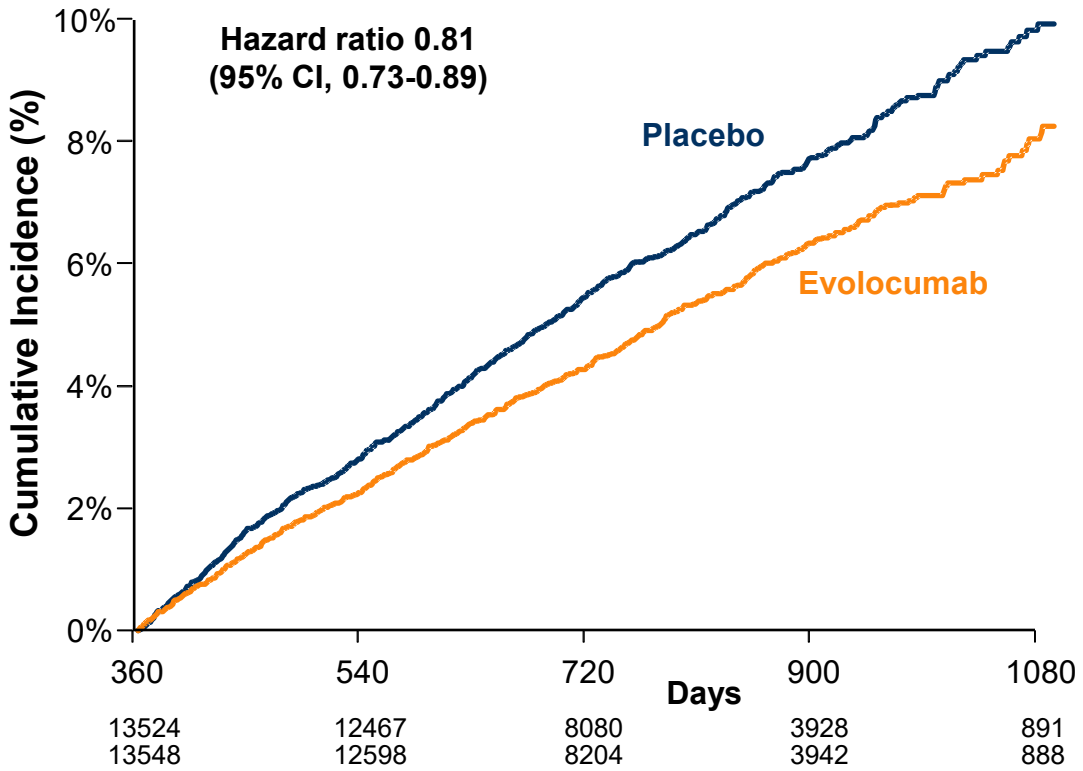
Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Type of atherosclerosis – n (%)		
MI	11,145 (80.9)	11,206 (81.3)
Time from most recent prior MI – yr (IQR)	3.4 (1.0-7.4)	3.3 (0.9-7.7)
Non-hemorrhagic stroke	2,686 (19.5)	2,651 (19.2)
Time from most recent prior stroke – yr (IQR)	3.2 (1.1-7.1)	3.3 (1.1-7.3)
Peripheral artery disease – n (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension – n/total n (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus – n (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use – n/total n (%)	3,854/13,783 (28.0)	3,923/13,779 (28.5)

Landmark Analysis of Primary Endpoint

Year 1: RRR 12%



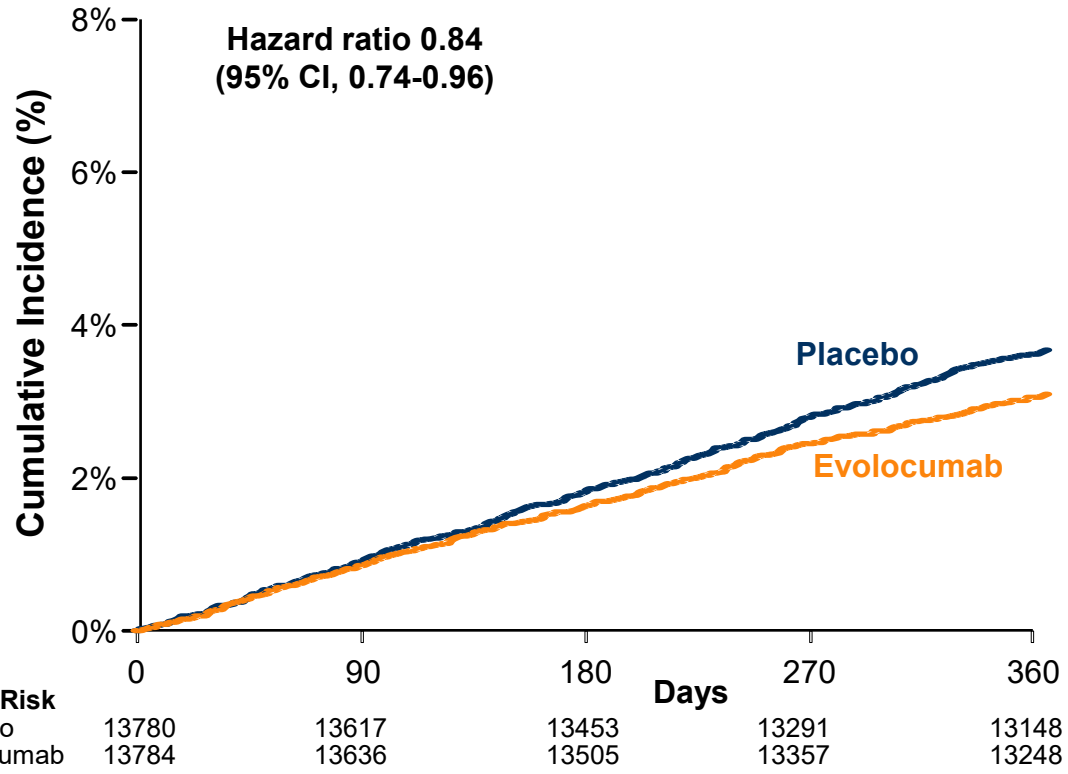
> Year 1: RRR 19%



Longer duration of treatment and follow up suggests larger risk reduction

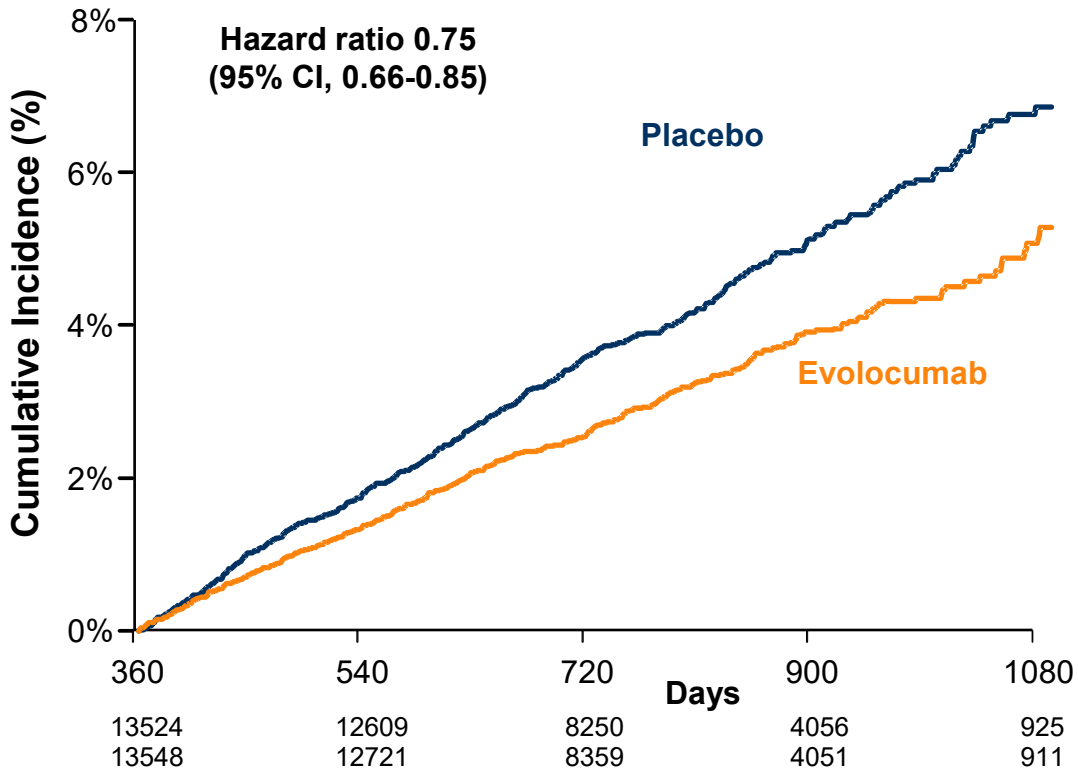
Landmark Analysis of Key Secondary Endpoint

Year 1: RRR 16%



No. at Risk					
Placebo	13780	13617	13453	13291	13148
Evolocumab	13784	13636	13505	13357	13248

> Year 1: RRR 25%



13524	12609	8250	4056	925
13548	12721	8359	4051	911

Longer duration of treatment and follow up suggests larger risk reduction

MI Sub-analysis: Objective and Methods

- This prespecified subanalysis of the FOURIER trial evaluated the efficacy of evolocumab in three subgroups
  - Number of prior MIs
  - Timing of prior MIs
  - Presence of residual multivessel cardiovascular disease
- 22,351 patients from the FOURIER trial with a history of prior MI were included in this prespecified subanalysis
- Patients were stratified based on the timing of prior MIs (< 2 years, n = 8,402 [38%]; ≥ 2 years, n = 13,918 [62%]), the number of prior MIs (≥ 3, n = 1,123 [5%]; ≥ 2, n = 5,285 [24%]; 1, n = 17,047 [76%]), and the presence of coronary disease, defined as ≥ 40% stenosis in ≥ 2 large vessels (n = 5,618 [25%])
- The relative and absolute risk reductions in major vascular events including the 5-point MACE and 3-point MACE with evolocumab in these three subgroups were compared
- Landmark analyses assessed the risk of cardiovascular outcomes in patients with at least one high-risk feature (n = 13,973 [63%]) and without a high-risk feature (n = 8,343 [37%])

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Recent MI Sub-analysis: Objective and Methods

- This prespecified secondary analysis sought to evaluate the risks of major adverse cardiovascular events as a function of time from the date of the qualifying MI and determine the effect of evolocumab on cardiovascular outcomes in patients with an MI within 12 months
- Patients with prior MI (N = 22,320) from the FOURIER trial were included in this prespecified secondary analysis
- Patients were categorized as having a recent MI (from 1 to 12 months prior to randomization) or a remote MI (> 12 months prior to randomization)
- The risks of the 5-point MACE and 3-point MACE were compared between evolocumab and placebo in patients with recent versus remote MI
- Data were collected from February 2013 to November 2016 and analyzed between May 2019 and February 2020

Diabetes Sub-analysis: Objectives and Methods

- This prespecified subanalysis of the FOURIER trial evaluated the efficacy and safety of evolocumab in patients with diabetes at baseline, and assessed any changes in glycemic parameters or development of NODM
- All 27,564 patients in the FOURIER trial were stratified according to diabetic status at baseline (n = 11,031 [40%] diabetic; n = 16,533 [60%] not diabetic)
- Those categorized with diabetes met one of the following criteria:
  - Reported clinical history of diabetes (91% of cases), HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL (2% of cases), or as determined by medical history review by the clinical events committee (7% of cases)
- A post hoc analysis included patients without diabetes but who were considered to be pre-diabetic according to the following baseline measurements:
  - HbA1c of 5.7%–6.4% or FPG of 100–125 mg/dL
- Risk of NODM was assessed according to criteria defined by the ADA and NDIC
- All patients were included in this analysis (not grouped by statin or evolocumab)

Note: mmol/L version

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- Those categorized with diabetes met one of the following criteria:
  - Reported clinical history of diabetes (91% of cases), HbA1c ≥ 6.5%, FPG ≥ 7.0 mmol/L (2% of cases), or as determined by medical history review by the clinical events committee (7% of cases)
- A post hoc analysis included patients without diabetes but who were considered to be pre-diabetic according to the following baseline measurements:
  - HbA1c of 5.7%–6.4% or FPG of 5.5–6.9 mmol/L
- Risk of NODM was assessed according to criteria defined by the ADA and NDIC
- All patients were included in this analysis (not grouped by statin or evolocumab)

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Achieved LDL-C Subanalysis: Objectives and Methods

- This prespecified subanalysis of the FOURIER trial sought to explore if there is an LDL-C level beyond which no additional benefit is observed by stratifying among achievement of progressively lower LDL-C levels
- Patients were included if they had an LDL-C assessment at week 4 and did not experience a primary efficacy or prespecified safety event prior to the 4-week visit (n = 25,982 [n = 13,013 evolocumab; n = 12,969 placebo])
- The efficacy and safety of very low LDL-C was assessed according to the achievement of LDL-C at week 4 and categorized into the following five prespecified subgroups, regardless of treatment assignment:
  - < 20 mg/dL
  - 20 to < 50 mg/dL
  - 50 to < 70 mg/dL
  - 70 to < 100 mg/dL
  - ≥ 100 mg/dL
- A post hoc ultra-low LDL-C analysis was also conducted in patients who achieved LDL-C < 15 mg/dL (n = 1,335) and < 10 mg/dL (n = 504) at week 4, compared with patients with LDL-C ≥ 100 mg/dL (n = 4,395)

Note: mmol/L version

Achieved LDL-C Sub-analysis: Objectives and Methods

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- The efficacy and safety of very low LDL-C was assessed according to the achievement of LDL-C at week 4 and categorized into the following five prespecified subgroups, regardless of treatment assignment:
  - < 0.5 mmol/L
  - 0.5 to < 1.4 mmol/L
  - 1.4 to < 1.8 mmol/L
  - 1.8 to < 2.6 mmol/L
  - ≥ 2.6 mmol/L
- A post hoc ultra-low LDL-C analysis was also conducted in patients who achieved LDL-C < 0.4 mmol/L (n = 1,335) and < 0.3 mmol/L (n = 504) at week 4, compared with patients with LDL-C ≥ 2.6 mmol/L (n = 4,395)

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Achieved LDL-C Sub-analysis: Methods Cont'd

- A subset of patients who participated in EBBINGHAUS, an embedded study within the FOURIER trial, who had a baseline cognitive test prior to or on the first day of study drug and did not experience an efficacy or prespecified safety event prior to the measurement of LDL-C at 4 weeks were also evaluated according to the five achieved LDL-C prespecified subgroups (n = 1,154)
- Using CANTAB, the primary endpoint assessed executive function with the spatial working memory strategy index and secondary endpoints assessed working memory, episodic memory, and psychomotor speed, as well as a global composite score

Baseline LDL-C & Statin Potency Sub-analysis: Objectives and Methods

- This secondary ad hoc analysis of the FOURIER trial evaluated whether more intensive lowering of LDL-C with evolocumab provides further benefit in the following two subgroups[1]
  - Patients starting with LDL-C < 70 mg/dL at baseline
  - Patients receiving maximal-potency statin therapy
- All 27,564 patients in the FOURIER trial were included in an intention-to-treat analysis[1,]
- Outcomes were compared across the two subgroups based on baseline LDL-C† and on background moderate (n = 8,392, 30.4%) or high (n = 19,103, 69.3%) intensity statin therapy[1,2,]
  - LDL-C < 70 mg/dL n = 2,034, 7.4%) vs LDL-C ≥ 70 mg/dL (n = 25,529, 92.6%) at baseline[1]
  - Maximal (n = 7,533, 27.3%) vs submaximal potency background statin at randomization (n = 20,031, 72.7%)[1]

Note: mmol/L version

Baseline LDL-C & Statin Potency Sub-analysis: Objectives and Methods

- This secondary ad hoc analysis of the FOURIER trial evaluated whether more intensive lowering of LDL-C with evolocumab provides further benefit in the following two subgroups[1]
  - Patients starting with LDL-C < 1.8 mmol/L at baseline
  - Patients receiving maximal-potency statin therapy
- All 27,564 patients in the FOURIER trial were included in an intention-to-treat analysis[1,]
- Outcomes were compared across the two subgroups based on baseline LDL-C† and on background moderate (n = 8,392, 30.4%) or high (n = 19,103, 69.3%) intensity statin therapy[1,2,]
  - LDL-C < 1.8 mmol/L (n = 2,034, 7.4%) vs LDL-C ≥ 1.8 mmol/L (n = 25,529, 92.6%) at baseline[1]
  - Maximal (n = 7,533, 27.3%) vs submaximal potency background statin at randomization (n = 20,031, 72.7%)[1]

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Asian Population Sub-analysis: Objectives and Methods

- To address potential concerns that the response to evolocumab may be different in the Asian patient population, a FOURIER subgroup analysis on the efficacy and safety of evolocumab in Asian vs other races was conducted

- Patient population:
  - Self-reported to be Asian: n = 2,723
  - Reported to be of other racial backgrounds, mainly Caucasian: n = 24,841

- Outcomes assessed:
  - 5-point MACE
  - 3-Point MACE
  - Safety
  - LDL-C lowering

Baseline Usage of High-Intensity Statin Was Less Frequent in Asians

Characteristics	Asians (N = 2,723)	Others (N = 24,841)	P Value
Lipid-lowering therapy, n (%)			
Statin			< 0.001
High intensity	**906 (33.3)**	**18,197 (73.3)**	
Moderate intensity	1,816 (66.7)	6,576 (26.5)	
Low, unknown, or no data	1 (0.0)	68 (0.3)	
Ezetimibe	101 (3.7)	1,339 (5.4)	< 0.001
Other cardiovascular medications, n (%)			
Aspirin, P2Y12 inhibitor, or both	2,571 (94.5)	22,861 (92.1)	< 0.001
β-blocker	1,637 (60.2)	19,178 (77.3)	< 0.001
Renin-angiotensin-aldosterone inhibitor	1,685 (61.9)	19,848 (80.0)	< 0.001

PAD Sub-analysis: Objectives

- Three main hypotheses were tested:
  - Risk of MACE would be greater with patients with PAD compared with those with coronary or cerebrovascular disease without PAD
  - Absolute risk reduction in MACE with evolocumab would be greater in patients with PAD due to consistent relative risk reduction in patients with PAD compared with those without
  - Risk of MALE would be significantly reduced by LDL-C lowering with evolocumab, extending to very low levels of LDL-C

PAD Sub-analysis: Methods

- All 27,564 patients in the FOURIER trial were assessed for clinically evident ASCVD including a history of symptomatic PAD, prior MI, and prior ischemic stroke
- Patients with a history of symptomatic lower extremity PAD at baseline met one of the following criteria (n = 3,642 [13.2%]):
  - Intermittent claudication and ABI < 0.85 (n = 2,518 [69.3%]), or
  - Prior peripheral revascularization procedure (n = 2,067 [56.8%]) or limb amputation due to atherosclerotic disease (n = 126 [3.5%])
- MALE was an outcome of interest, in addition to the 5-point MACE and 3-point MACE, in this prespecified subanalysis of patients with a history of PAD
  - Limb outcomes were adjudicated by two vascular medicine specialists (blinded)
- A post hoc exploratory analysis included assessment of endpoints in a more specific population of patients with a history of PAD without prior MI or stroke

Stroke Sub-analysis: Objectives and Methods

- This prespecified analysis of the FOURIER trial evaluated the efficacy and safety of evolocumab in prevention of stroke and stroke subtypes in the overall study population and in patients stratified by prior stroke status at baseline
- In this analysis, the benefit of evolocumab on prevention of overall stroke and stroke subtypes in the overall FOURIER study population and by subgroups according to a history of stroke at baseline (prior ischemic stroke, n = 5,337; no prior stroke, n = 22,227) was assessed
- The primary prespecified study endpoint was the time to the first of any of the following events: cardiovascular death, myocardial infarction, stroke (ischemic or hemorrhagic), hospitalization for unstable angina, or coronary revascularization
- All stroke (combined ischemic, hemorrhagic, and strokes of unknown type) and the composite of all stroke or TIA were prespecified secondary endpoints; also, the subgroup of patients with prior ischemic stroke was prespecified

CKD Sub-analysis: Objective and Methods

- This post hoc analysis of the FOURIER trial analyzed CV and renal outcomes of evolocumab therapy according to kidney function at baseline
- 27,554 patients from FOURIER were included in this secondary analysis
- The primary renal endpoint examined change in eGFR overtime
- Secondary renal endpoints included a 30%, 40%, or 50% decline in eGFR
- Individuals were classified according to standard CKD stages based on the level of eGFR:
  - Preserved kidney function (eGFR ≥ 90 mL/min/1.73 m^2)
  - Stage 2 (mild impairment) CKD (eGFR 60 to < 90 mL/min/1.73 m^2)
  - Stage ≥ 3 CKD (< 60 mL/min/1.73 m^2)
- A secondary analysis subdivided stage 3 CKD into stage 3a (eGFR 45 to < 60 mL/min/1.73 m^2) and 3b (eGFR < 45 mL/min/1.73 m^2)

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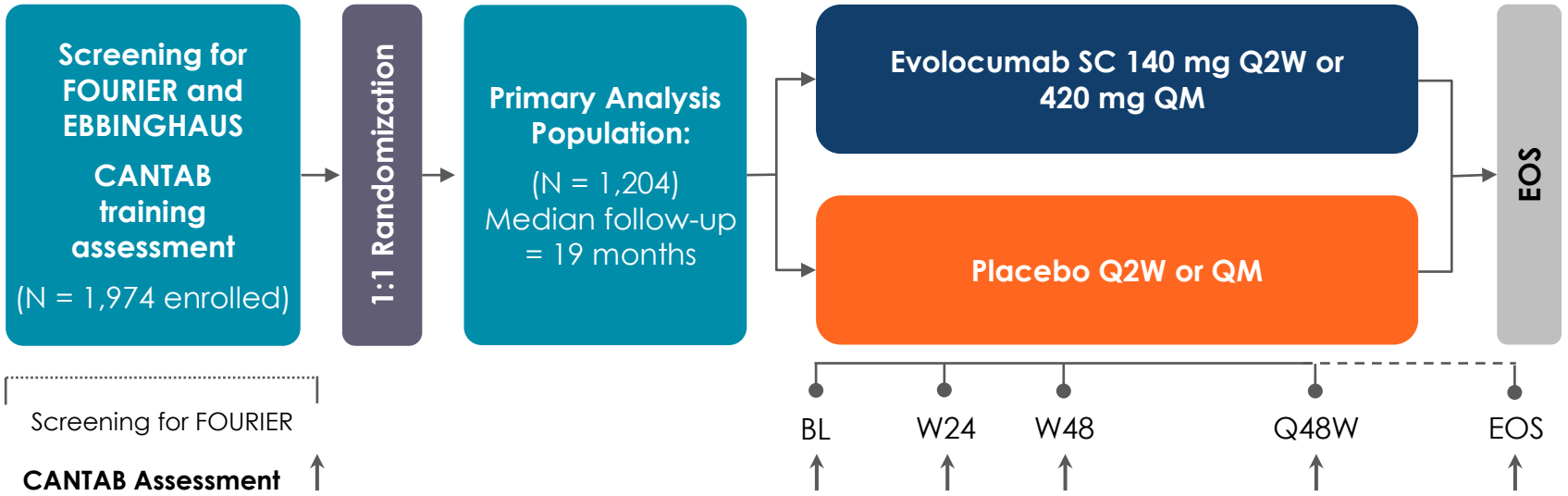
Complex PCI and Post-PCI Sub-analysis: Objective and Methods

- This prespecified subanalysis of the FOURIER trial evaluated the efficacy of evolocumab in patients with prior history of PCI
- 17,073 patients from the FOURIER trial with a history of PCI were included in this prespecified subanalysis
- The primary endpoint of the study was time to MACE, the key secondary endpoint was the composite of cardiovascular death, MI, or stroke, and the exploratory endpoint was the occurrence of MCEs
- In patients with and without prior PCI, evolocumab versus placebo was compared over serial LDL-C measurements
- Patients assigned to receive evolocumab versus placebo were stratified according to their prior PCI status, and event rates were compared for MACE, MCE, and their component rates

EBBINGHAUS: Study Design

A randomized, double-blind, placebo-controlled, multicenter, phase 3 study in a subset of patients who were enrolled in the FOURIER trial



Primary Endpoint[1,2]

- **Change over time in executive function**, as assessed by the SWM strategy index of executive function, in patients receiving evolocumab compared to placebo

Secondary Endpoints[1,2]

- **Change over time[d] in working memory**, as assessed by the SWM test between-errors score
- **Change over time in episodic memory**, as assessed by the PAL total errors-adjusted
- **Change over time in psychomotor speed**, as assessed by the median 5-choice RTI

- **Primary analysis population (N = 1,204)**: patients with CANTAB assessments at baseline (on or before the first dose of blinded study drug) and at least one follow-up CANTAB assessment
- **Full analysis population (N = 1,974)**: includes the primary analysis population and patients whose first CANTAB assessment occurred after the first dose of blinded study drug

Open Label Extension (OLE): Achieved LDL-C Sub-analysis Objective and Methods

- The prespecified secondary analysis of the FOURIER-OLE trial examined the relationship between achieved LDL-C level (available in 6,559 patients) and the incidence of subsequent cardiovascular and safety outcomes
- The primary efficacy endpoint in the FOURIER-OLE trial was the composite of cardiovascular death, MI, stroke, coronary revascularization, or hospital admission for unstable angina
- The key secondary efficacy endpoint was the composite of cardiovascular death, MI, or stroke
- There were nine safety endpoints evaluated, including serious adverse events, new or recurrent cancers (excluding nonmelanoma skin cancer), cataract-related adverse events, hemorrhagic stroke, new-onset diabetes, neurocognitive adverse events, muscular-related events, noncardiovascular death, and all-cause mortality

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