ACC Latin America Conference 2017

FOURIER Clinical Trial

Session: 5 in 45: The Top 5 Clinical Trials You Need to Hear from ACC.17

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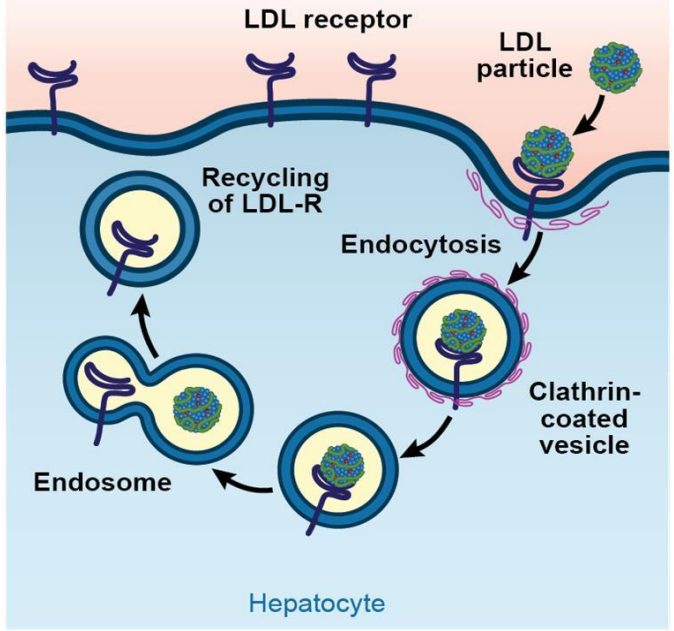
GLOBAL EXPERTS, LOCAL LEARNING

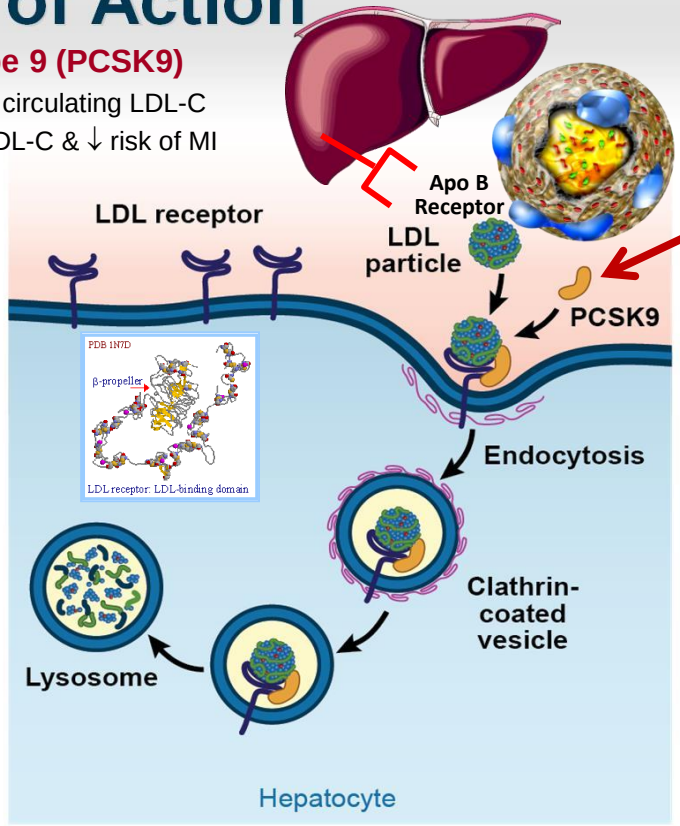
PCSK9 Mechanism of Action

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

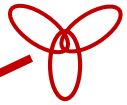
- Accompanies LDL-R towards degradation → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI



LDL Degradation and Recycling of LDL-R



PCSK9-Mediated Degradation of LDL-R



Fully human anti-PCSK9 mAb

Evolocumab

- Anti-PCSK9 mAb
- ↓ LDL-C ~ 60%
- Safe & well-tolerated in phase 2 & 3 studies
- Exploratory data suggested ↓ CV events

Lambert G, et al. *J. Lipid Res*. 2012;53:2515-2524.

Sever P & Mackay J. ***Br J Cardiol*** **2014;21:91-3**
Giugliano RP, ***et al. Lancet*** **2012;380:2007-17**
Sabatine MS, ***et al. NEJM*** **2015;372:1500-9**

Methods & Objectives:

- *N*= 27,564 patients + follow-up (median) 2.2 years
- Atherosclerotic CV disease and LDL-C ≥ 70 mg/dL; receiving statin therapy
- Patients randomly assigned to receive subcutaneous injections of evolocumab:

140 mg every 2 weeks ***or*** 420 mg monthly	matching placebo
Follow-up Q 12 weeks	Follow-up Q 12 weeks

- Test whether the addition of evolocumab reduces the incidence of major CV events
- Examine the long-term safety & tolerability of evolocumab as well as to investigate the efficacy and safety of achieving unprecedented low levels of LDL-C
- Primary efficacy endpoint: *composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization*
- Key Secondary Efficacy Endpoint: *composite of CV death, MI, or stroke*

***N Engl J Med* 2017;376(18):1713-22.**

FOURIER - Characteristics of the Patients at Baseline

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	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 Argentina, Brazil, Chile, and Colombia	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)

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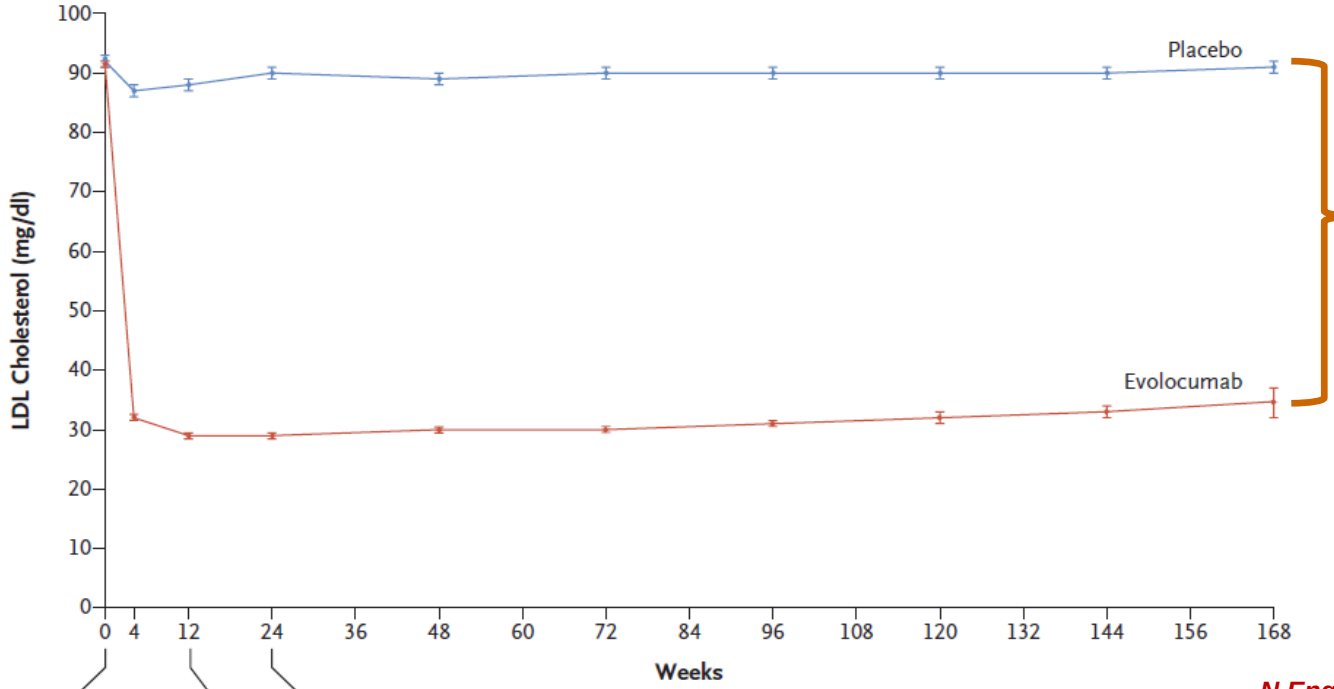
FOURIER - LDL-Cholesterol Levels Over Time



"to investigate the efficacy and safety of achieving unprecedented low levels of LDL-C"

No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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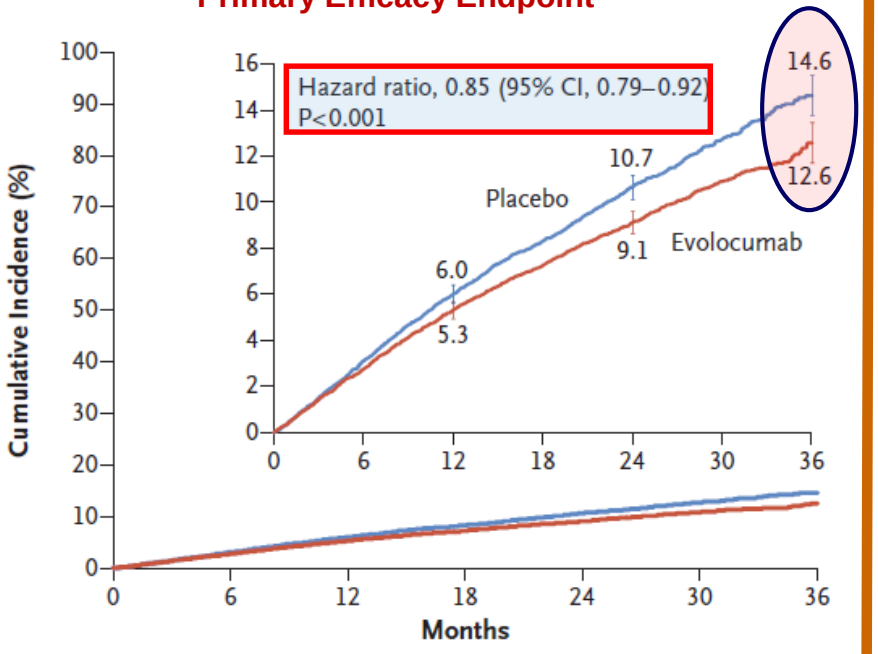
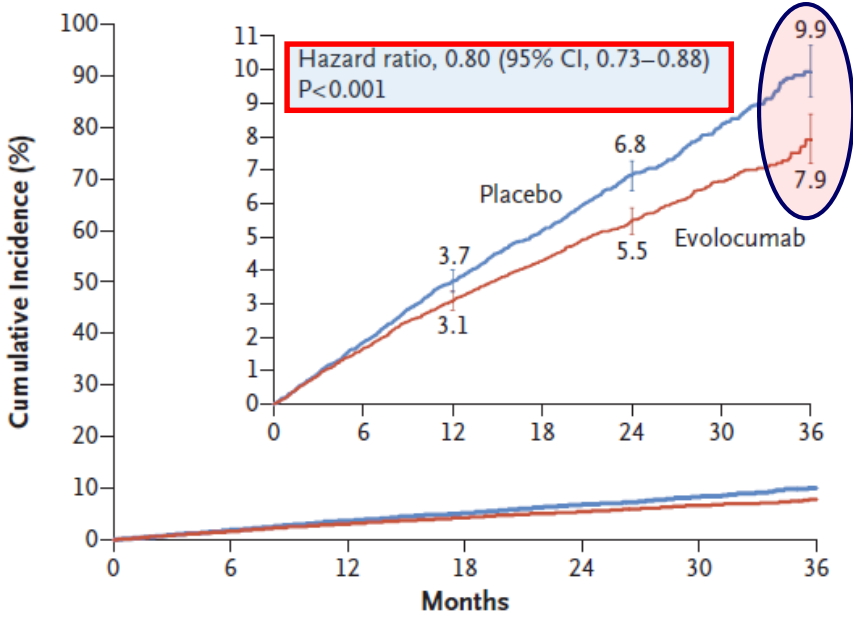
FOURIER - *Primary & Key Secondary* Efficacy Endpoints

Primary Efficacy Endpoint



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

Key Secondary Efficacy Endpoint



No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7944	3893	731
Evolocumab	13,784	13,501	13,241	12,456	8094	3935	724

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FOURIER - Secondary Endpoints

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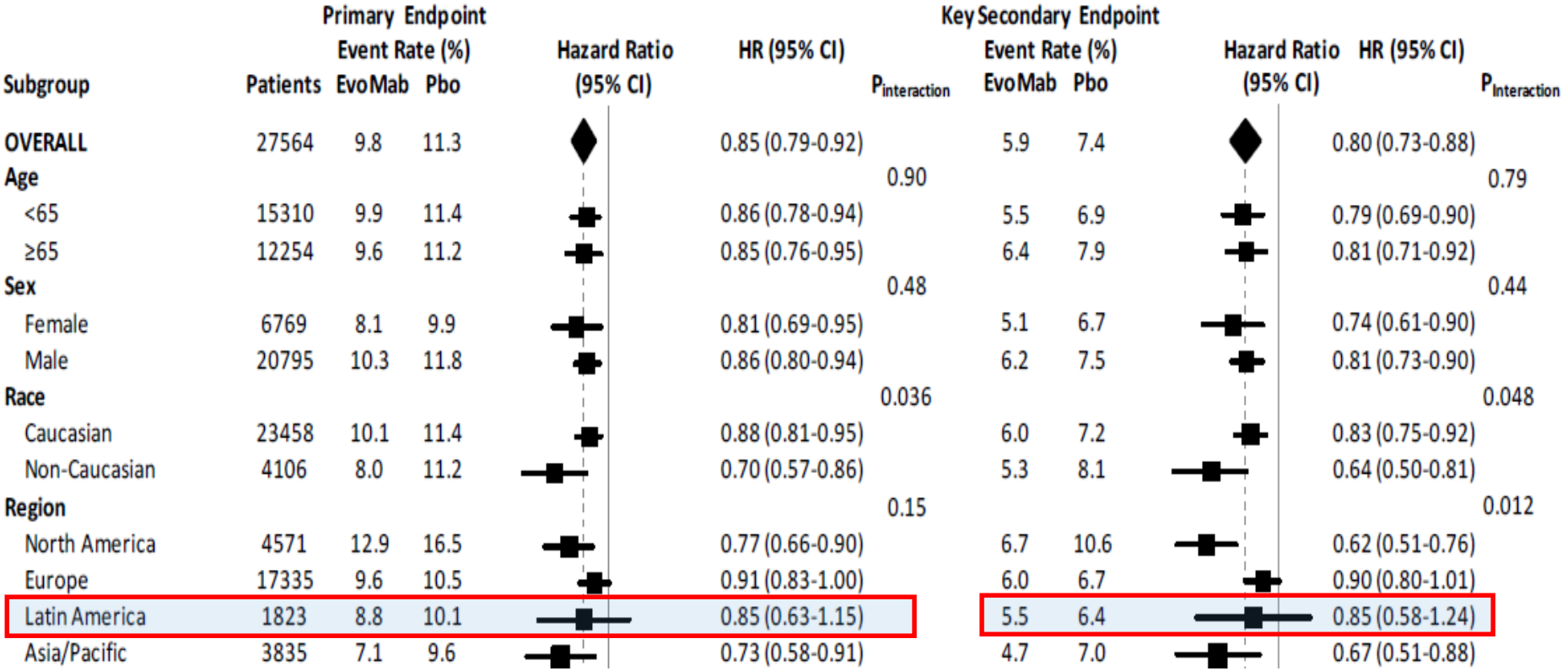
Outcome	Evolocumab (N = 13,784)	Placebo (N = 13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

FOURIER - Efficacy Endpoints in Key Subgroups

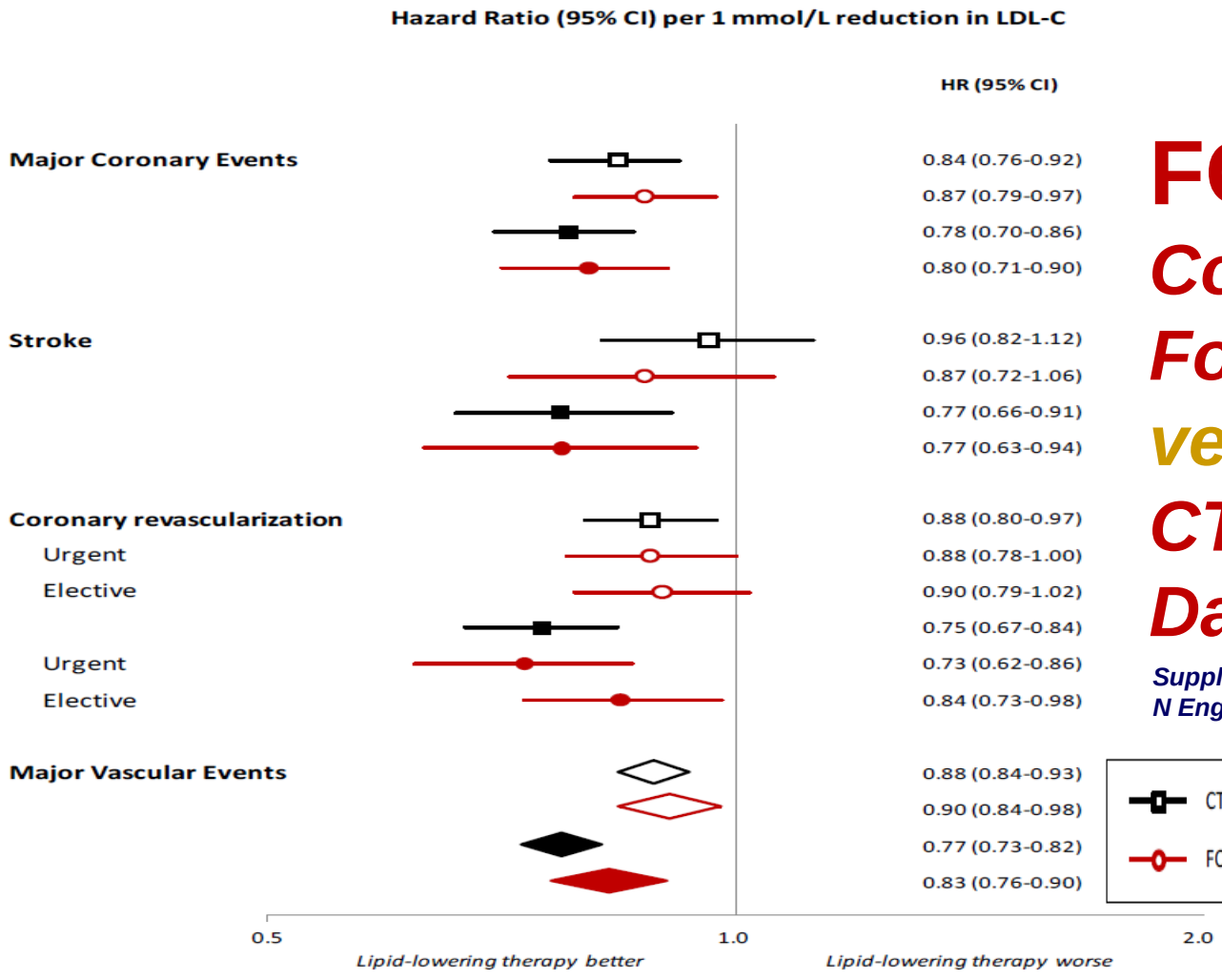


Subgroup	Patients	Primary Endpoint Event Rate (%) EvoMab	Pbo	Hazard Ratio (95% CI)	HR (95% CI)	$P_{interaction}$	Key Secondary Endpoint Event Rate (%) EvoMab	Pbo	Hazard Ratio (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	9.8	11.3		0.85 (0.79-0.92)		5.9	7.4		0.80 (0.73-0.88)	
Age						0.90					0.79
<65	15310	9.9	11.4		0.86 (0.78-0.94)		5.5	6.9		0.79 (0.69-0.90)	
≥65	12254	9.6	11.2		0.85 (0.76-0.95)		6.4	7.9		0.81 (0.71-0.92)	
Sex						0.48					0.44
Female	6769	8.1	9.9		0.81 (0.69-0.95)		5.1	6.7		0.74 (0.61-0.90)	
Male	20795	10.3	11.8		0.86 (0.80-0.94)		6.2	7.5		0.81 (0.73-0.90)	
Race						0.036					0.048
Caucasian	23458	10.1	11.4		0.88 (0.81-0.95)		6.0	7.2		0.83 (0.75-0.92)	
Non-Caucasian	4106	8.0	11.2		0.70 (0.57-0.86)		5.3	8.1		0.64 (0.50-0.81)	
Region						0.15					0.012
North America	4571	12.9	16.5		0.77 (0.66-0.90)		6.7	10.6		0.62 (0.51-0.76)	
Europe	17335	9.6	10.5		0.91 (0.83-1.00)		6.0	6.7		0.90 (0.80-1.01)	
Latin America	1823	8.8	10.1		0.85 (0.63-1.15)		5.5	6.4		0.85 (0.58-1.24)	
Asia/Pacific	3835	7.1	9.6		0.73 (0.58-0.91)		4.7	7.0		0.67 (0.51-0.88)	

Supplementary Appendix (page55). N Engl J Med 2017;376(18):1713-22.

FOURIER

*Comparison of Fourier Data versus CTT Collaboration Data**



Supplementary Appendix
***N Engl J Med* 2017;376(18):1713-22.**

* Data from Cholesterol Treatment Trialists Collaboration (CTT) are from *Lancet 2010;376:1670-81*

FOURIER - Adverse Events Results in Both Groups

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	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)

Muchas Gracias a todos

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