



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

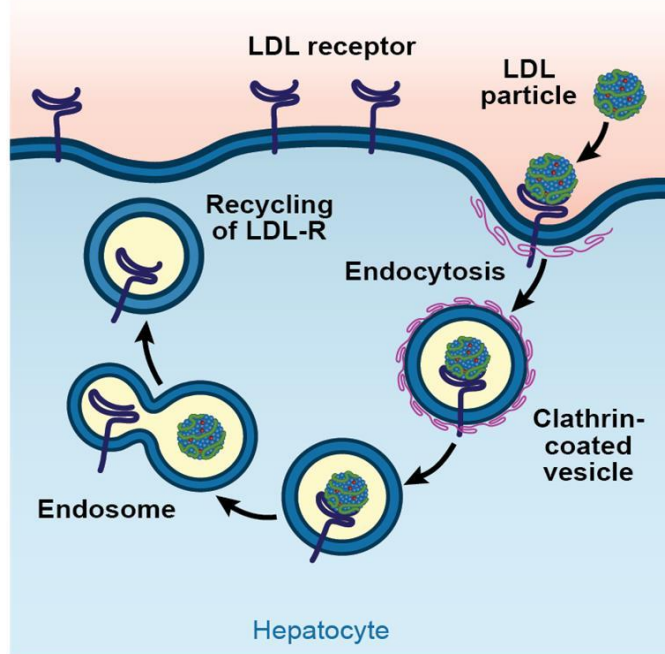
PCSK9 Mechanism of Action



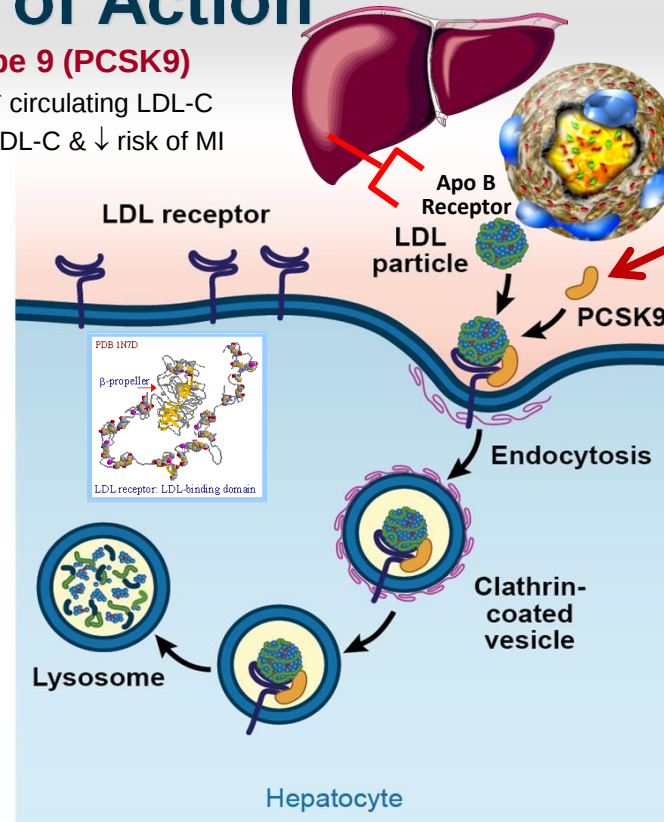
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Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

- Accompanies LDL-R towards degradation $\rightarrow$ $\uparrow$ circulating LDL-C
- Loss-of-fxn genetic variants $\rightarrow$ $\uparrow$ LDL-R $\rightarrow$ $\downarrow$ LDL-C & $\downarrow$ 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
- $\downarrow$ LDL-C $\sim$ 60%
- Safe & well-tolerated in phase 2 & 3 studies
- Exploratory data suggested $\downarrow$ CV events

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:



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- 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
Follow-up Q 12 weeks

matching placebo
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



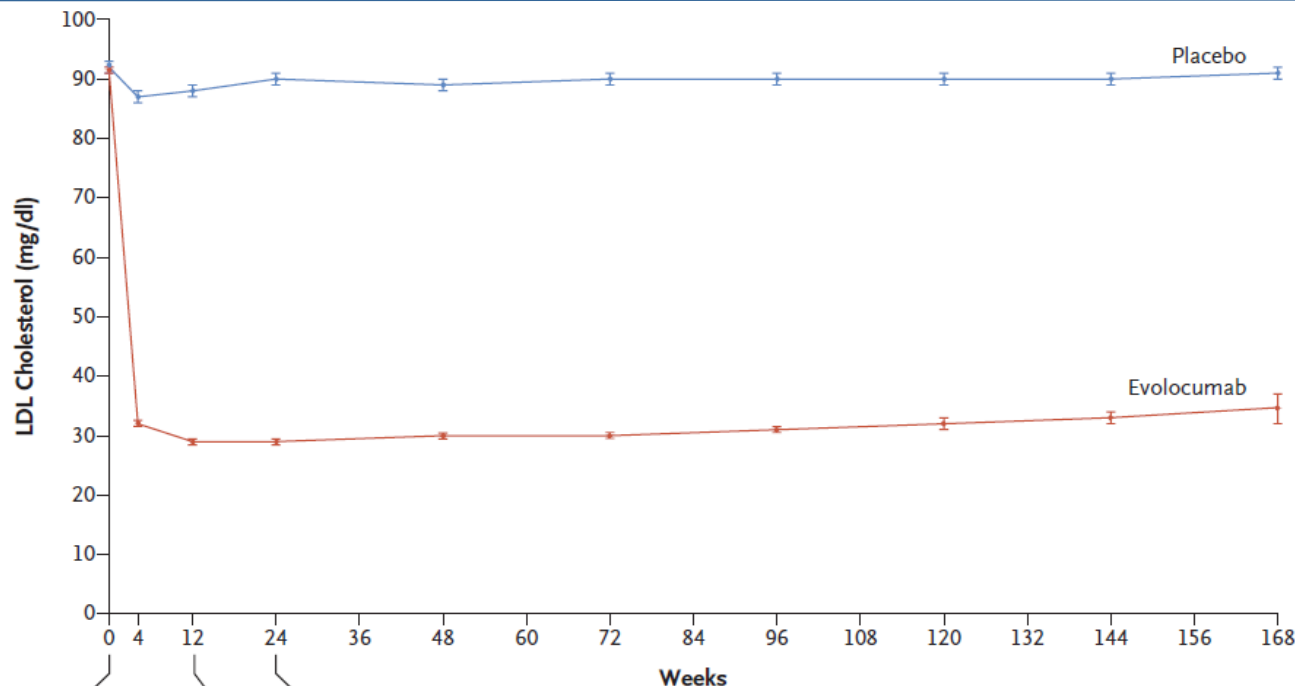
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Table 1. Characteristics of the Patients at Baseline.*

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	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

Absolute difference (mg/dl)

Percentage difference

P value

54	58	57	56	55	54	52	53	50
57	61	61	59	58	57	55	56	54
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

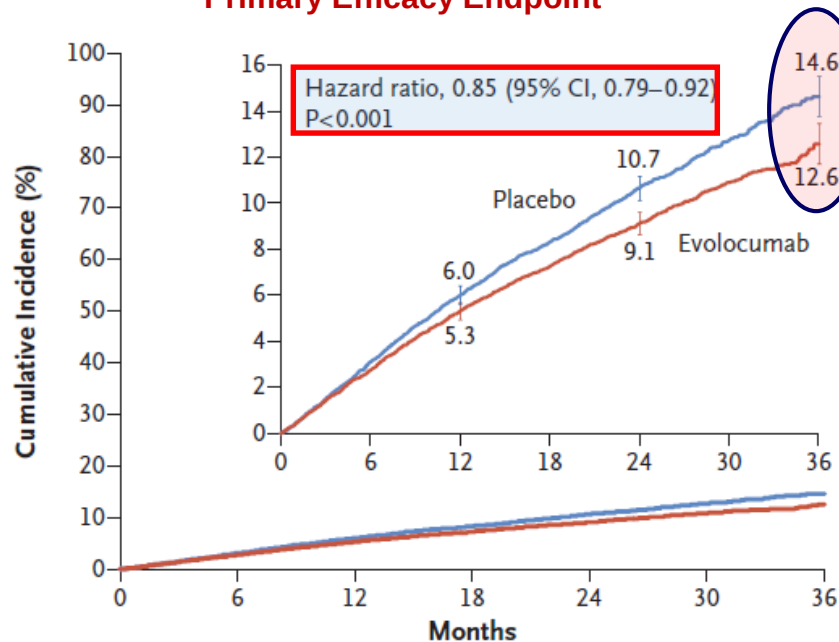
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FOURIER - Primary & Key Secondary Efficacy Endpoints



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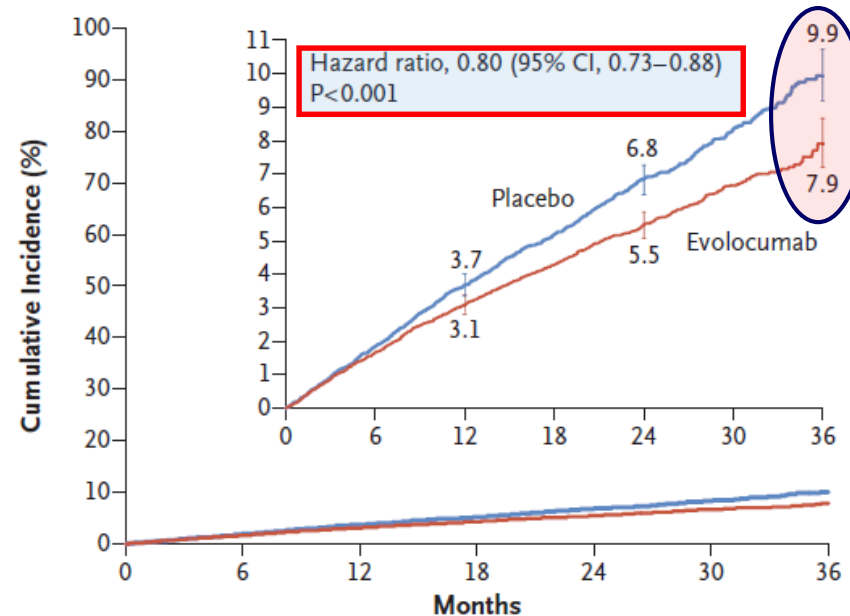
Primary Efficacy Endpoint



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

FOURIER - Secondary Endpoints

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



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Outcome	Evolocumab (N = 13,784)	Placebo (N = 13,780)	Hazard Ratio (95% CI)	P Value*
<i>no. of patients (%)</i>				
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

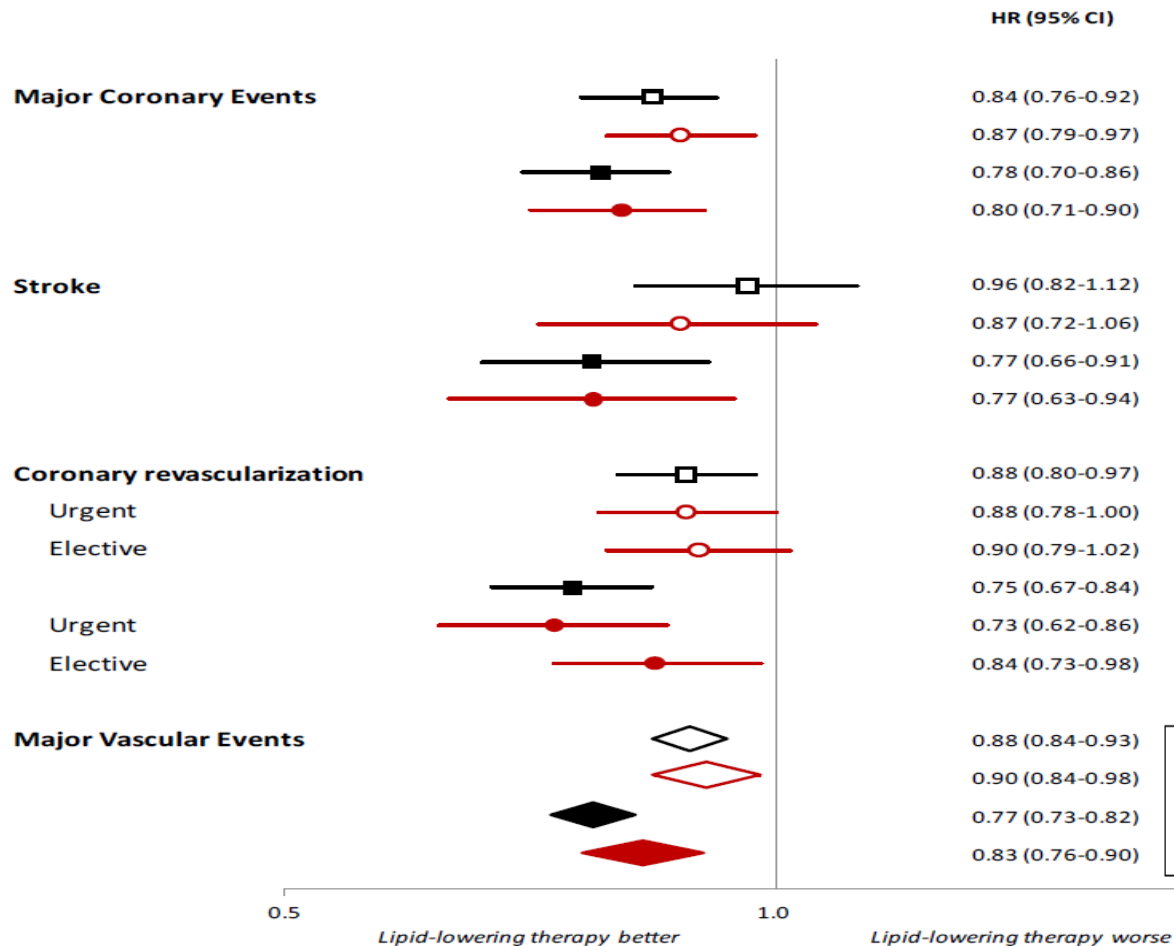
FOURIER - Efficacy Endpoints in Key Subgroups



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Subgroup	Primary Endpoint			Hazard Ratio (95% CI)	HR (95% CI)	P _{Interaction}	Key Secondary Endpoint			Hazard Ratio (95% CI)	HR (95% CI)	P _{Interaction}
	Patients	EvoMab	Pbo				Event Rate (%)					
							EvoMab	Pbo				
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.



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Comparison of Fourier Data versus CTT Collaboration Data*

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

 CTTC Meta-analysis Year 0-1
  CTTC Meta-analysis Year 1-2
 FOURIER Year 0-1
  FOURIER Year 1-2

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

FOURIER - Adverse Events Results in Both Groups



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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 reactions*	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)

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