PCSK9FORUM

The Evolution of PCSK9 inhibitors; Pipedream or Evidence based Reality?

Kindly supplied by
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Director Emeritus, Metabolic & Atherosclerosis Research Center

Disclosures

Have received consulting fees related to development of PCSK9 inhibitors from Amgen, Regeneron/Sanofi, Genentech/Roche and BMS and other LDL drugs from AstraZeneca, Catabasis, CymaBay and Gemphire.
Lipid Advisory Panel for CVS/Caremark

The Evolution of PCSK9 inhibitors; Pipedream or Evidence based Reality?

- **What evidence do we need?**
  - Do PCSK9 inhibitors reduce LDL-C?
  - Do PCSK9 inhibitors reduce CVD?
  - Is there any additional CVD benefit to achieving very low LDL-C of <25 mg/dL with PCSK9 inhibitors?
  - Are PCSK9 inhibitors safe?
  - Are there safety concerns when achieving very low LDL-C <25 mg/dL with PCSK9 inhibitors?

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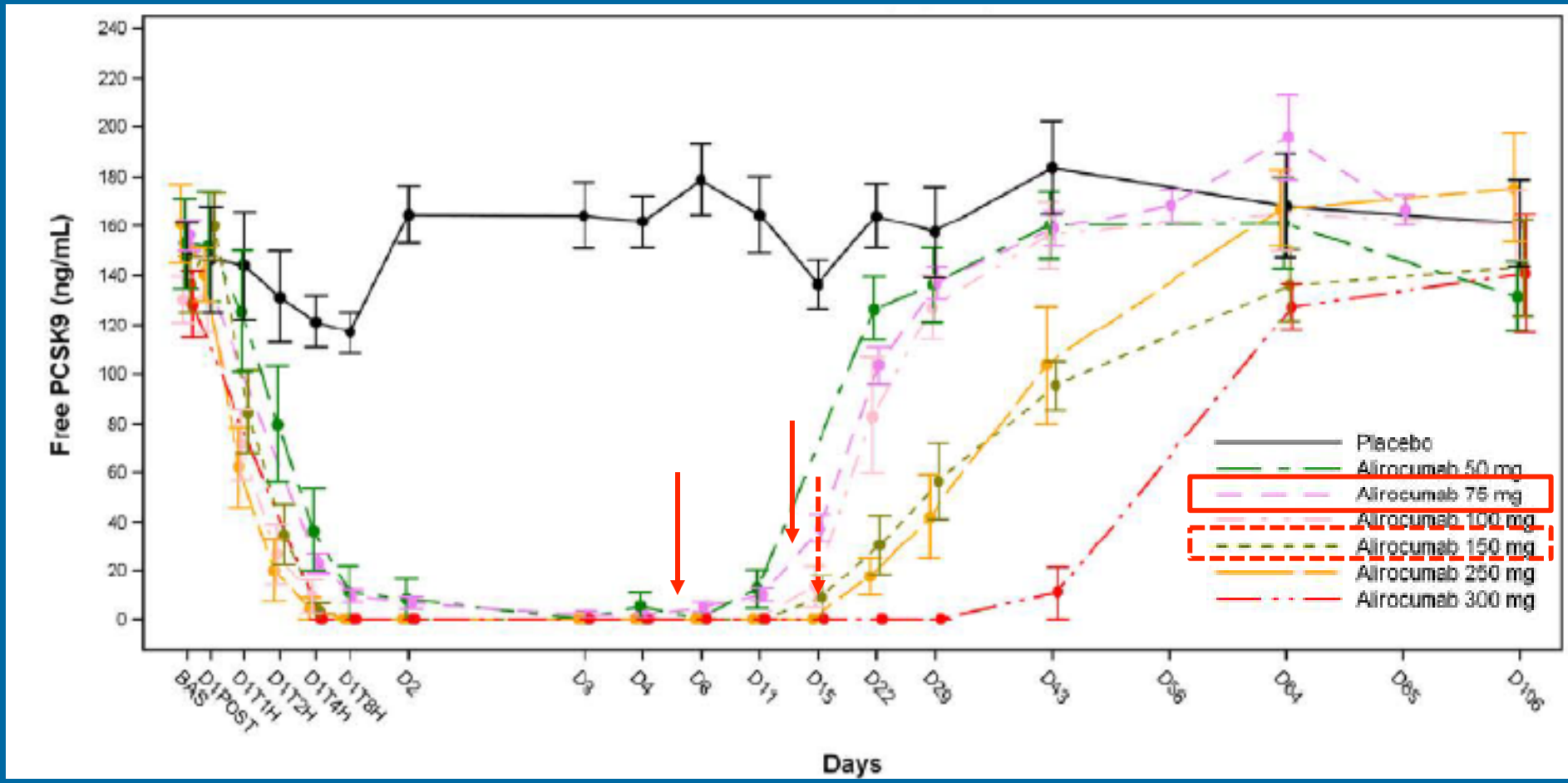
Do PCSK9 inhibitors lower LDL-C?

- Phase 1 trials with two mAbs have shown there is a maximal and stable 60% reduction in LDL-C once all PCSK9 is bound, which occurs at about 70-75 mg of a high affinity monoclonal antibody (mAb) like evolocumab and alirocumab
- Higher doses ***do not*** achieve further LDL-C reduction but do serve to provide ***stable LDL-C reduction for longer duration*** which in turn reduce the interval between doses/injections; rough rule of thumb is that 70-75 mg will reduce LDL-C 60% for 1 week, double the dose (140-150 mg) for two weeks and 3 x the 2 weeks dose (420-450 mg) is needed for 4 weeks
- Same 60% reduction in LDL-C is seen with appropriate dosing when added to diet alone, low and maximal dose statin or statin plus ezetimibe
- Patients with HeFH and nonFH respond the same and the response in HeFH is independent of underlying LDL receptor mutation/function
- Homozygous FH patients respond about half as well, with mean reductions in LDL-C of 31% to high doses, 420 mg Q4W, to evolocumab
- Statin adverse patients tolerate PCSK9 mAbs well
- In addition to LDL-C reductions there is robust 25-30% decrease in Lp(a)

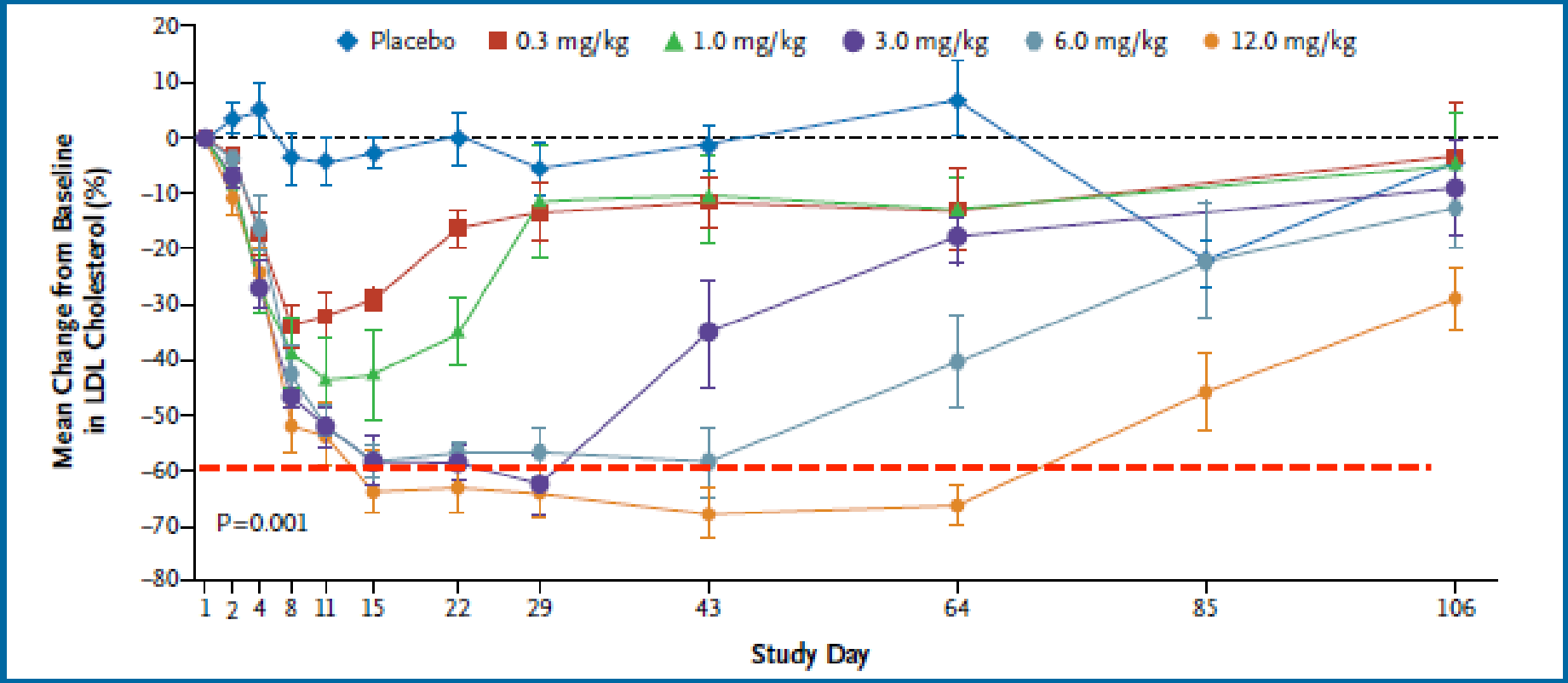
Free PCSK9 by Alirocumab dose: Pooled Phase 1 Studies:



Background information prepared by FDA for the panel member so EMD advisory committee – Fig 2

Alirocumab Briefing Document: Endocrine & Metabolic Advisory Committee Meeting [accessed Sept 14, 2015]
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM449865.pdf

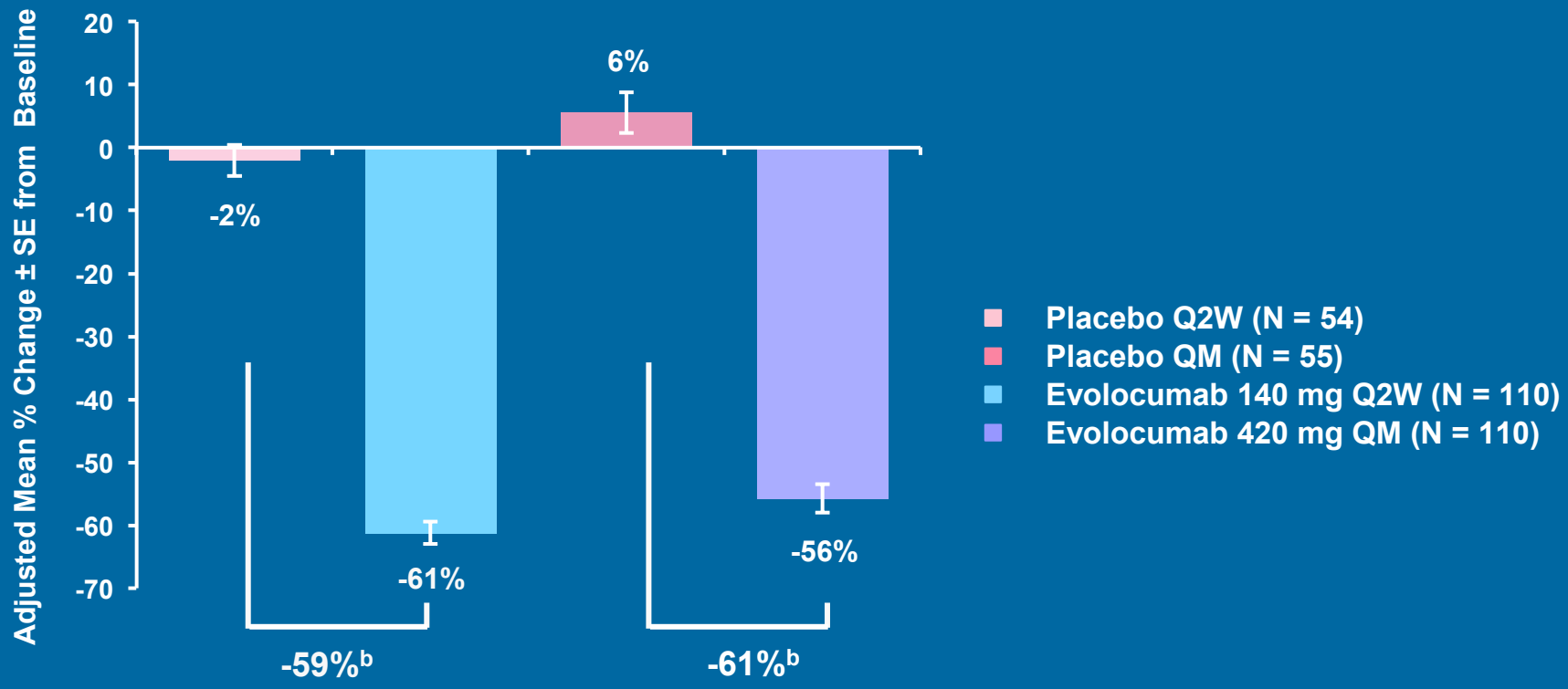
Alirocumab Phase 1 SAD Study: LDL-C Percentage Change From Baseline with IV dosing



3 mg/kg = 210 mg for 70 kg adult
6 mg/kg = 420 mg for 70 kg adult
12 mg/kg = 840 mg for 70 kg adult

Stein EA, et al. N Engl J Med. 2012;366(12):1108-18.

RUTHERFORD-2: Mean % Change in LDL-C[a] from Baseline to Week 12

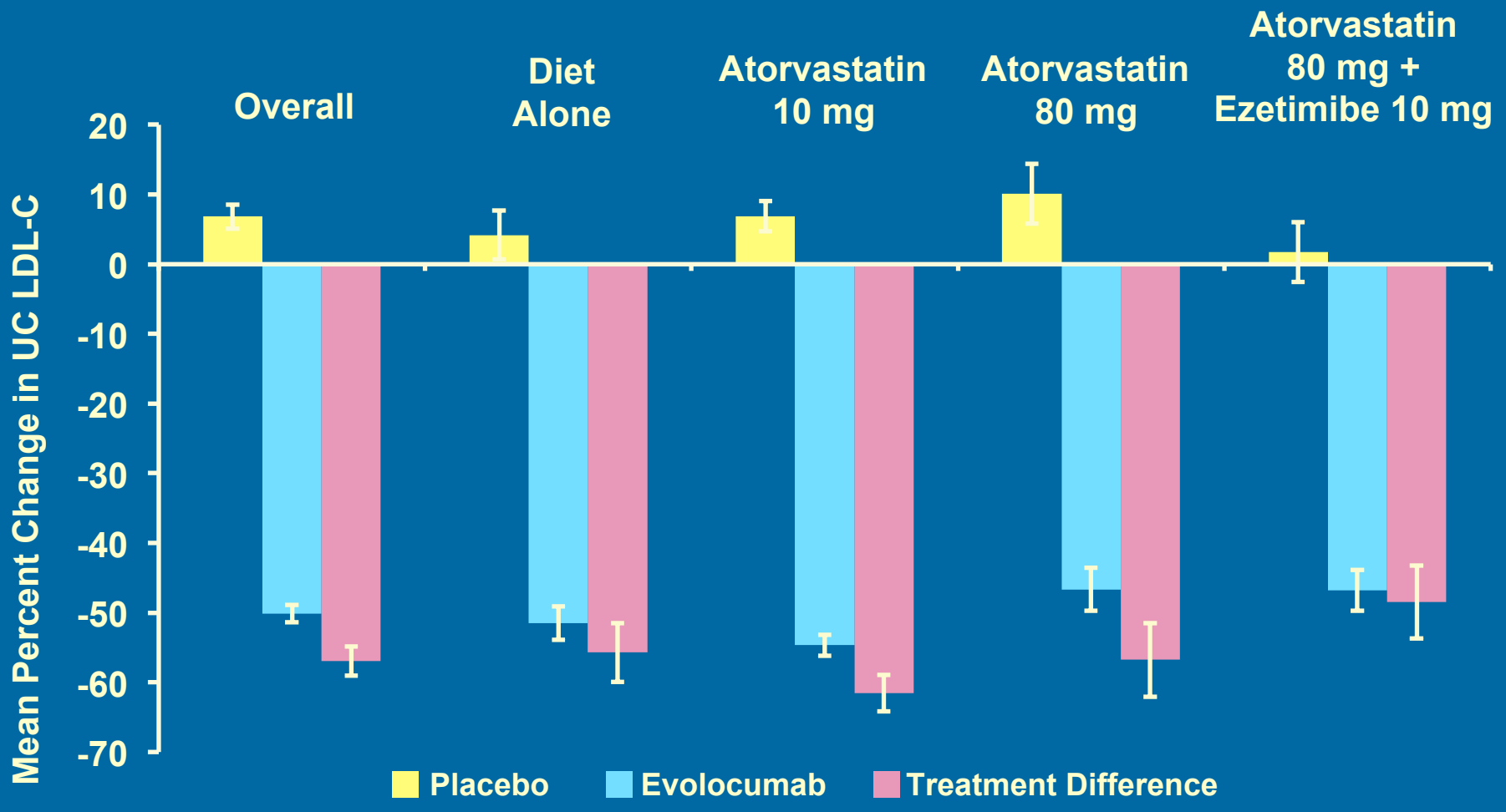


[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

[b] P < 0.001; placebo-adjusted treatment difference analyzed using repeated measures model which included treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates

LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly; SE, standard error

DESCARTES: % Change in LDL-C from baseline in patients on various background treatments



Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model
UC LDL-C at week 52

Blom et al NEJM 2014:370:1809-19

Phase B: Adverse Effects and Drug Discontinuations

	Ezetimibe (n=73)	Evolocumab (n=145)
Total muscle-related events	**21 (28.8%)**	**30 (20.7%)**
Myalgia, muscle pain or weakness	17 (23.3%)	25(17.2%)
Investigator reported CK Increase	1 (1.4%)	4 (2.8%)
Discontinuation of Treatment for Any Reason		
Discontinuation of oral treatment	14 (19.2%)	23 (15.9%)
Discontinued SC drug treatment	4 (5.5%)	7 (4.8%)
Discontinuation of Treatment for Muscle Symptoms		
Discontinued oral drug treatment	**5 (6.8%)**	**11 (7.6%)**
Discontinued SC drug treatment	**0 (0%)**	**1 (0.7%)**

Nissen SE et al JAMA. 2016;315:1580-90

RUTHERFORD-2: demographics and lipid parameters in HeFH patients in the genetic sub-analysis

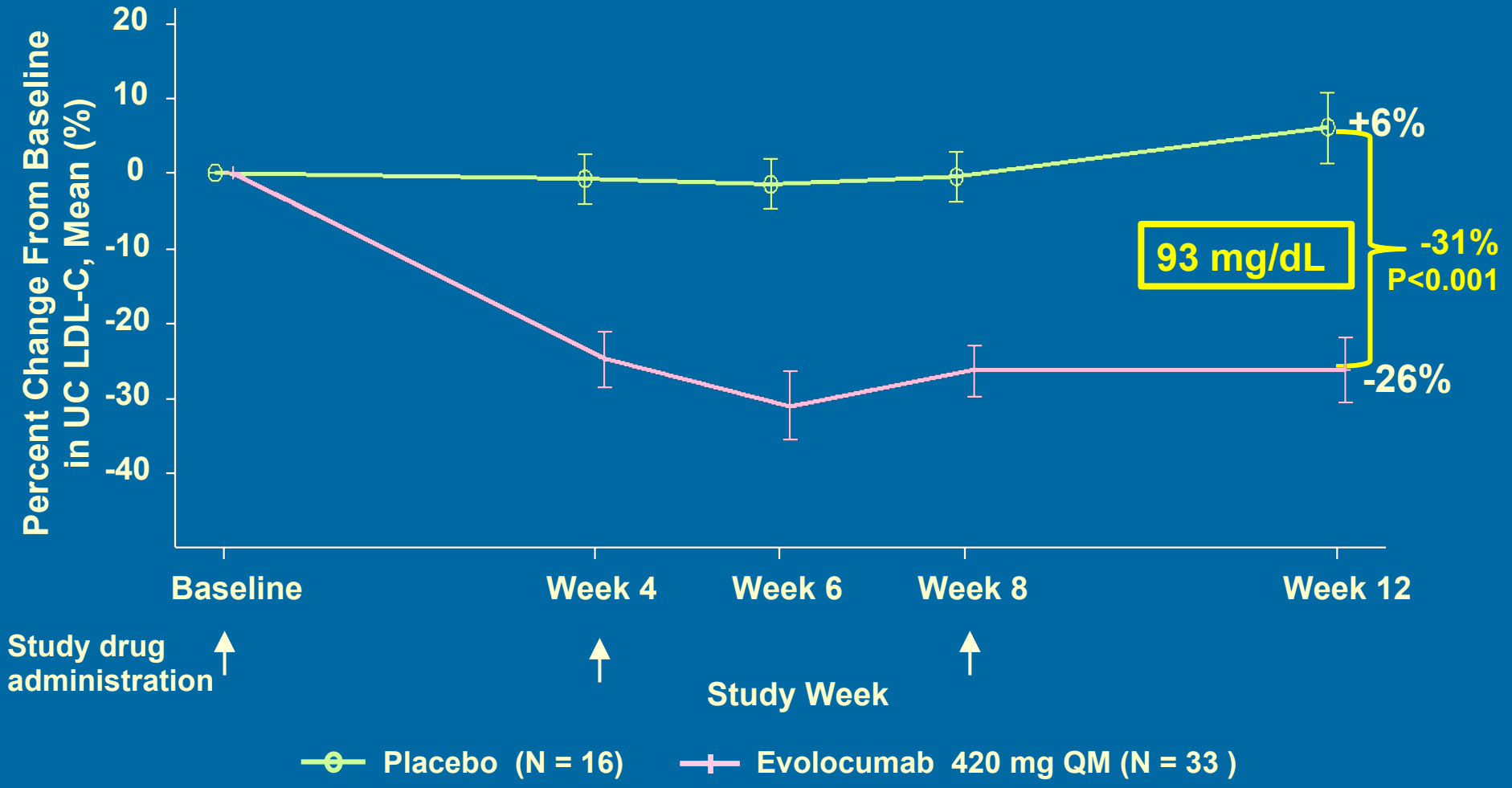
Mutations causative of familial hypercholesterolaemia were found in 80% (211/264) of patients who consented to the genetic analysis

	LDLR Mutation (n=195)				
	Negative (n=66)	Defective (n=75)	Unclassified (n=54)	Apo B Mutation (n=9)	HoFH/Compound HeFH (n=7)
Age (years), mean (SD)	48·1 (13·0)	49·5 (12·3)	51·0 (12·8)	57·1 (11·2)	53 (10·3)
Coronary artery disease, n (%)	23 (34·8)	15 (20·0)	23 (42·6)	2 (22·2)	4 (57·1)
LDL-C (mg/dL), mean (SD)	170 (50)	153 (39)	154 (46)	143 (39)	205 (108)
Apo B (mg/dL), mean (SD)	120 (30)	110 (20)	120 (30)	100 (20)	150 (60)
LDL-C reduction* at wk 12 (mean %)	61%	62%	64%	51%	68%

*evolocumab 140 mg every 2 weeks

Raal, et al. Lancet 2014;385:331-40

TESLA part B: Percent Change in UC LDL-C From Baseline to Week 12



Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values.

Raal, et al. Lancet 2014;385:341-50

Homozygous FH TESLA part B: LDL-C Lowering by Type of Mutation

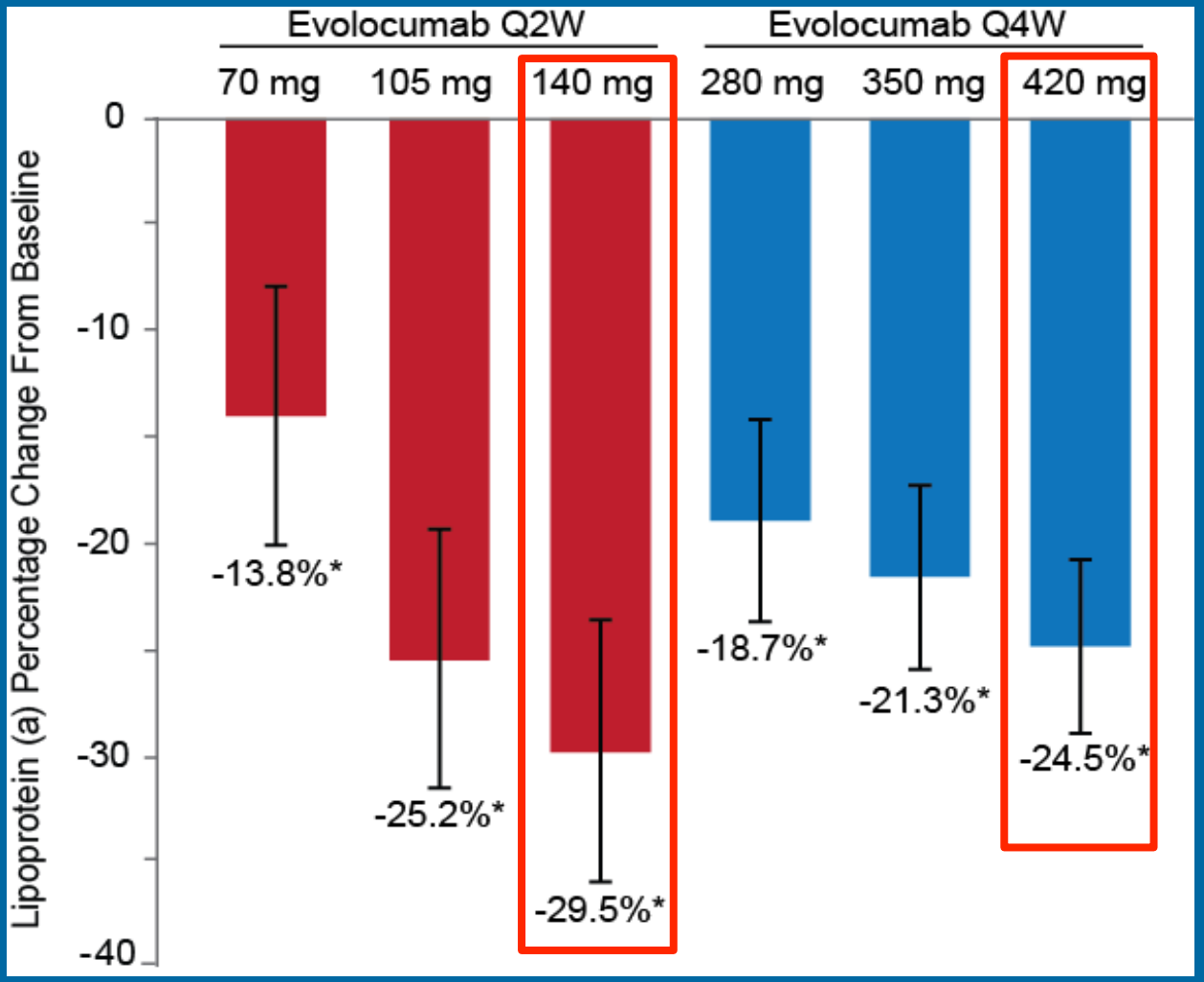
Percent Change from Baseline in UC LDL-C at Week 12, Mean (SE)

Mutation Status	N	Placebo	Evolocumab 420 mg QM	Treatment Difference
All	49	7.9 (5.3)	-23.1 (3.8)	-30.9 (6.4)*
LDLR				
Defective/any†	28	11.2 (5.1)	-29.6 (3.4)	**-40.8 (6.1)‡**
Defective/defective	13	15.1 (7.3)	-31.8 (5.8)	**-46.9 (9.4)‡**
Negative/defective	9	3.5 (5.8)	-21.0 (4.0)	**-24.5 (7.0)§**
Unclassified‖	22	3.8 (11.7)	-17.9 (8.8)	**-21.7 (13.9)**
Median (Q1, Q3)		7.2 (0.0, 9.9)	-39.2 (-48.8, -14.6)	-
Negative/negative	1	-	10.3	-
LDLR Heterozygous	1	-	-55.7	-
Apolipoprotein B	2	-10.8, 13.1	-	-
ARH	1	-	3.5	-

Data are least squares (LS) mean for groups with sufficient data; otherwise actual value at week 12. LS mean is from the repeated measures model, which includes treatment group, screening LDL, scheduled visit and the interaction of treatment with scheduled visit as covariates. *Adjusted P-value < 0.001; †Receptor defective in at least one of two affected alleles. ‡ Nominal P-value < 0.001; §Nominal P-value = 0.013; ‖Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group).

Raal, et al. Lancet 2014;385:341-50

Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145):a Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials



Error bars represent standard error.

*** P < 0.001**

Raal et al JACC 2014;():. doi:10.1016/j.jacc.2014.01.006 Online First

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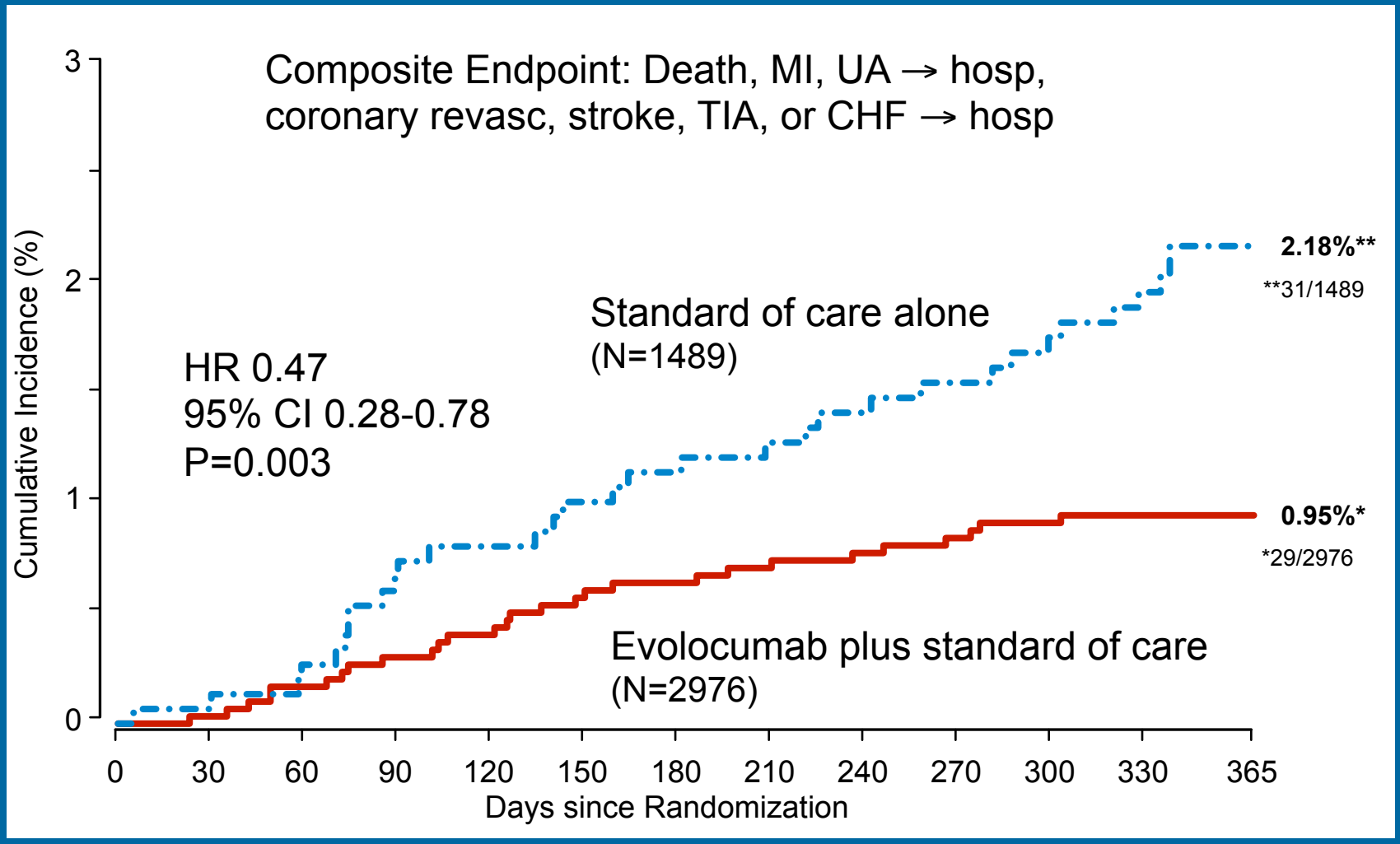
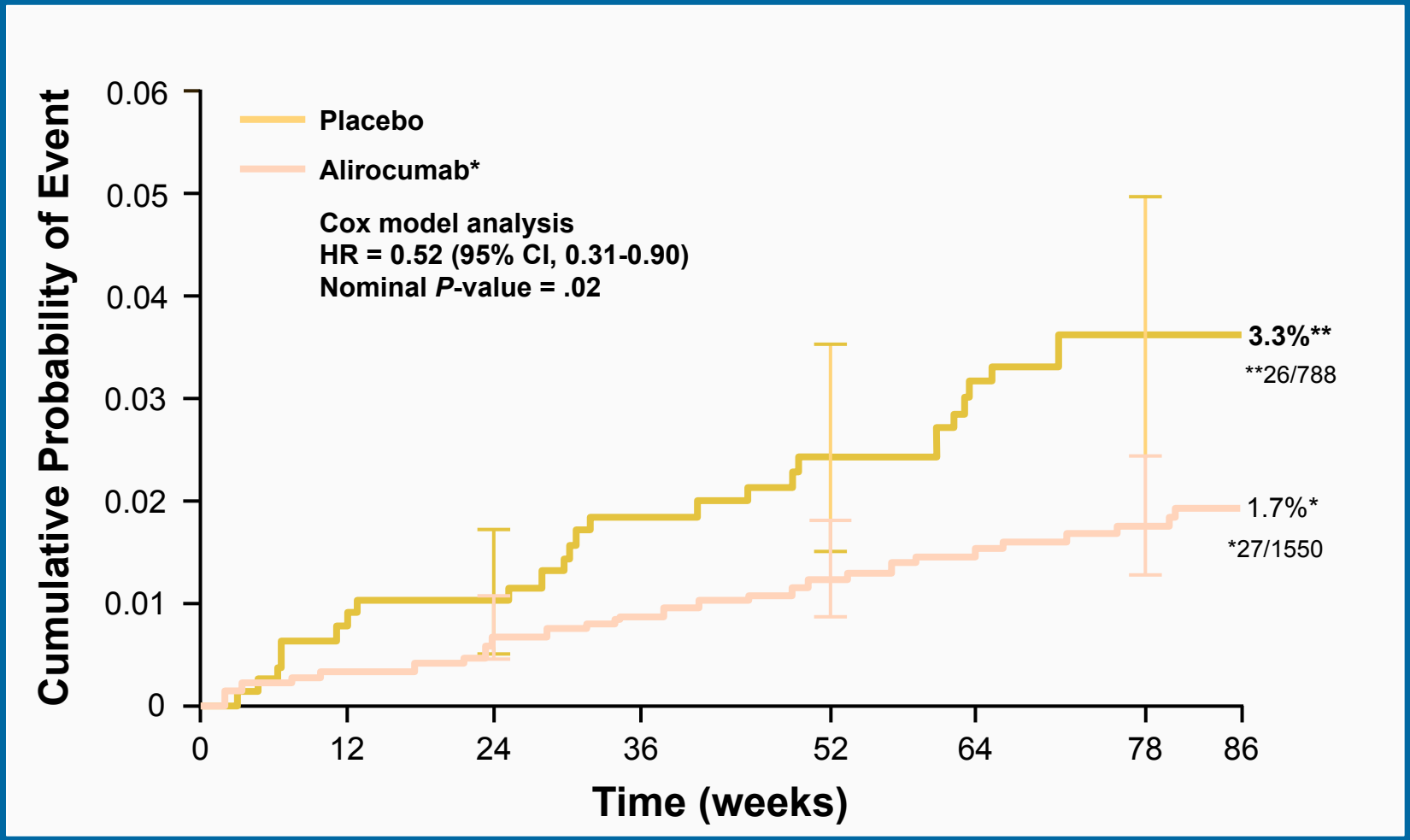
Evolocumab OSLER Trial: Cumulative Incidence of Cardiovascular Events¶



¶CVD clinical outcomes (prespecified, exploratory): adjudicated by TIMI Study Group CEC, blinded to treatment
Included death, myocardial infarction, unstable angina requiring hospitalization, revascularization, stroke or transient ischemic attack and Heart failure requiring hospitalization

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

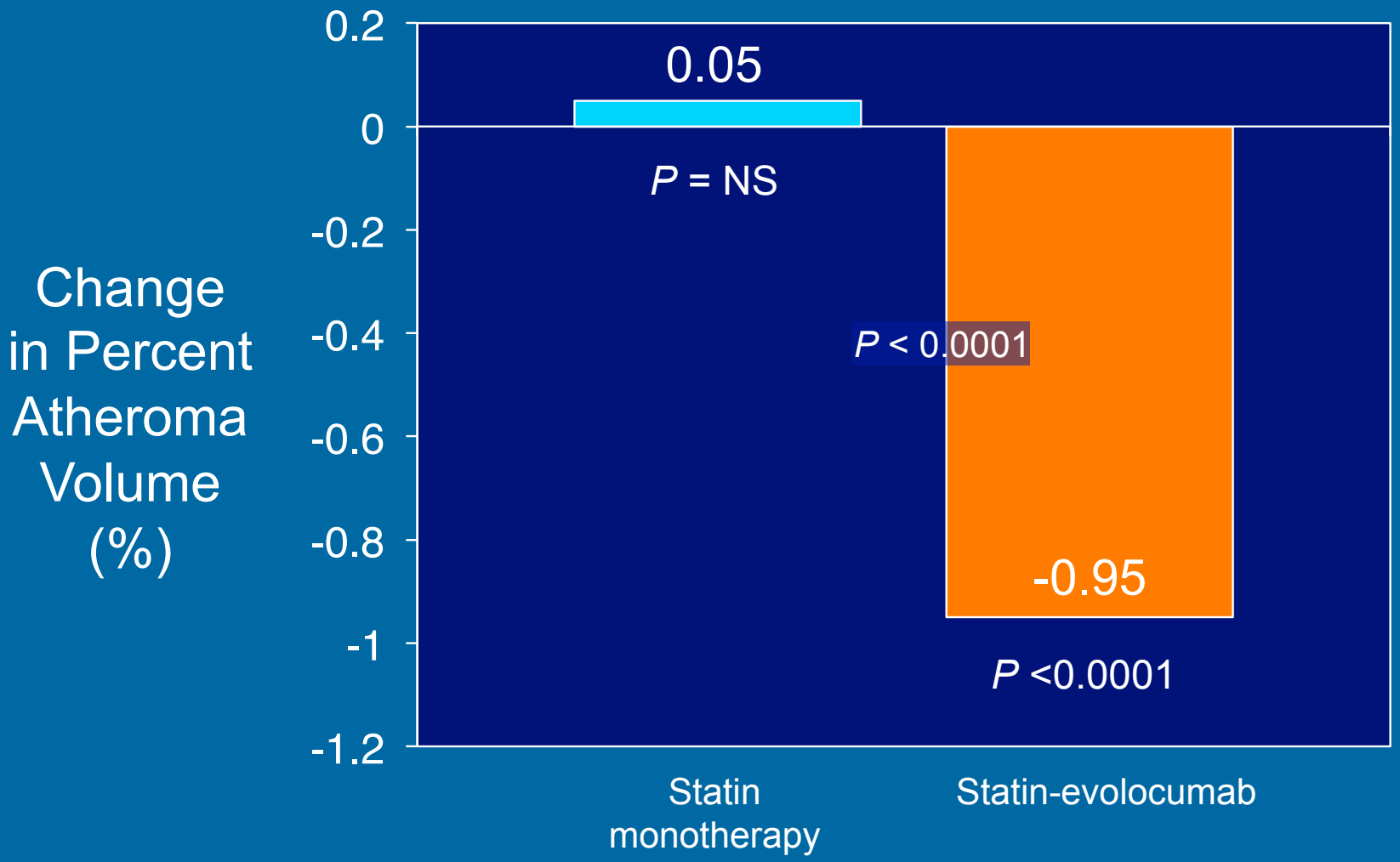
Alirocumab: ODYSSEY Long-term Cumulative Incidence of Cardiovascular Events¶



¶post-hoc analysis not specified in the study protocol - included cardiovascular event categories which comprise the endpoint in ODYSSEY Outcomes (Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome).

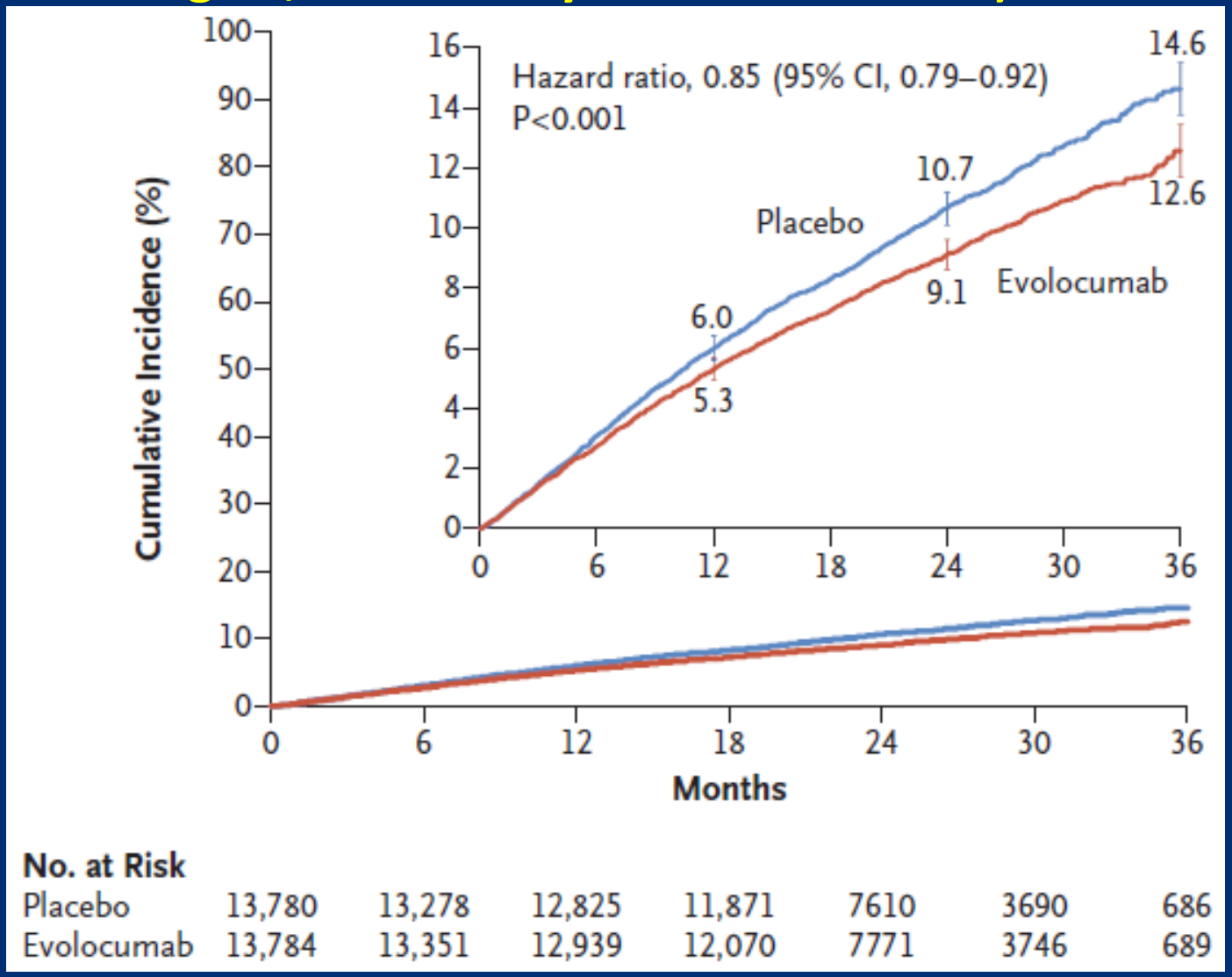
Robinson JG et al. N Engl J Med 2015;372:1489-1499

GLAGOV Primary Endpoint: Percent Atheroma Volume



Nicholls SJ et al JAMA Published online November 15, 2016 doi:10.1001/jama.2016.16951

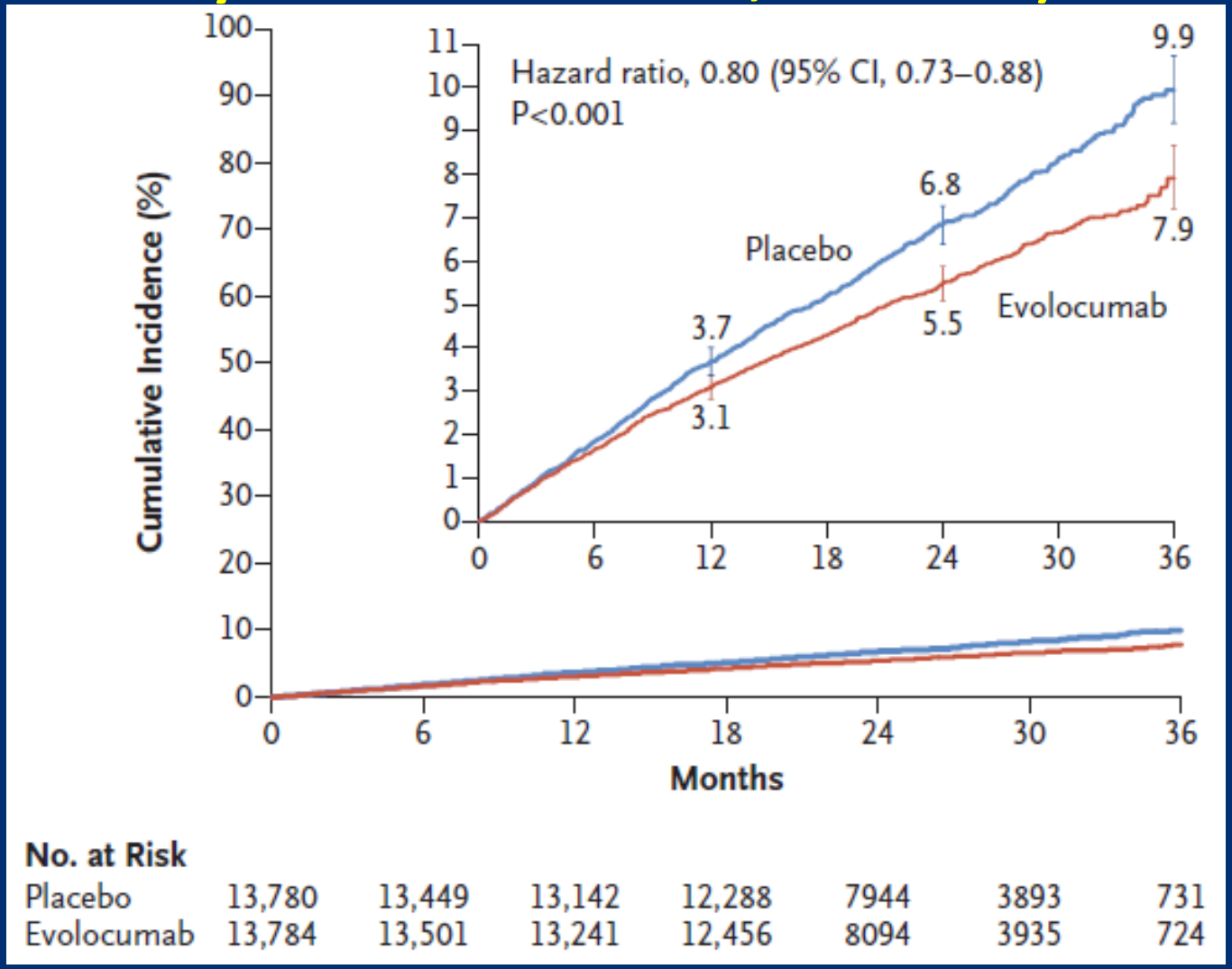
FOURIER: Cumulative Incidence of CVD events *Primary End Point* (composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)



P values calculated using log-rank tests

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664.

FOURIER: Cumulative Incidence of CVD events for key secondary efficacy end point (the composite of CV death, myocardial infarction, or stroke)



P values calculated using log-rank tests

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664.

FOURIER: Primary, Secondary and select other CVD endpoints

Outcome	Evolocumab (N=13784) N Pts (%)	Placebo (N=13780) N (%)	Hazard Ratio (95% CI)	P Value
Primary End Point*	1344 (12.6%)	1563 (14.6%)	0.85 (0.79-0.92)	<0.001
Secondary End Point#	816 (7.8%)	1013 (9.9%)	0.80 (0.73-0.88)	<0.001
Myocardial infarction	468 (4.4)	639 (6.3)	0.73 (0.65-0.82)	<0.001
Stroke	**207 (2.2)**	**262 (2.6)**	**0.79 (0.66-0.95)**	**0.01**
Ischemic	171 (1.9)	226 (2.2)	0.75 (0.62-0.92)	
Hemorrhagic	29 (0.2)	25 (0.2)	1.16 (0.68-1.98)	
Unknown	13 (0.1)	14 (0.2)	0.93 (0.44-1.97)	
Coronary revascularization	**759 (7.0)**	**965 (9.2)**	**0.78 (0.71-0.86)**	**<0.001**
Urgent	403 (3.7)	547 (5.4)	0.73 (0.64-0.83)	
Elective	420 (3.9)	504 (4.6)	0.83 (0.73-0.95)	

*cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization
#cardiovascular death, myocardial infarction, or stroke
Based on the hierarchical nature of the statistical testing, the P values for the primary and key secondary endpoint should be considered statistically significant whereas all other P values should be considered nominal.
Percentages are 3-year Kaplan-Meier rates

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664.

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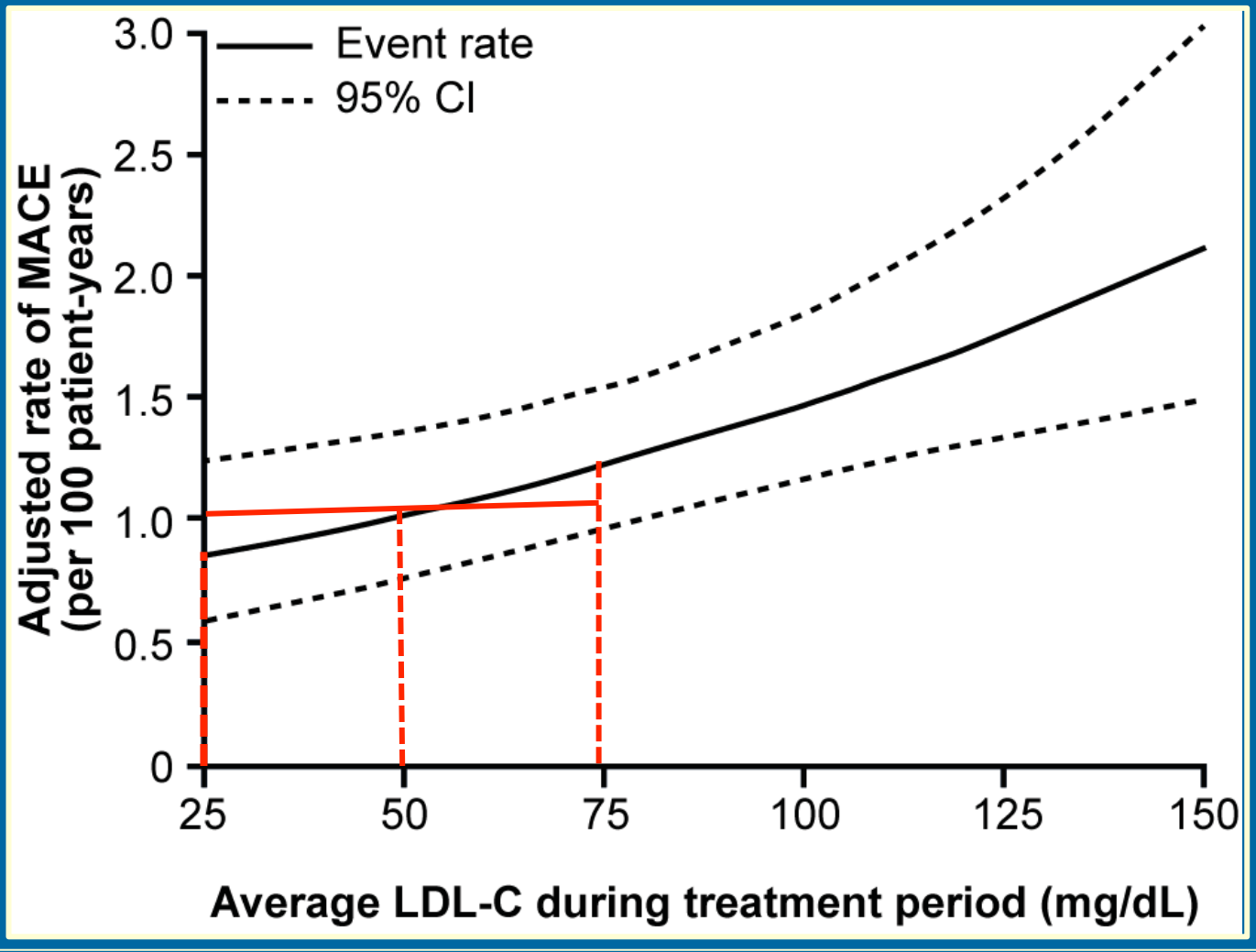
RELATIONSHIP BETWEEN MACE AND ACHIEVED LDL-C IN PHASE 3 ODYSSEY TRIALS OF ALIROCUMAB VERSUS CONTROL*

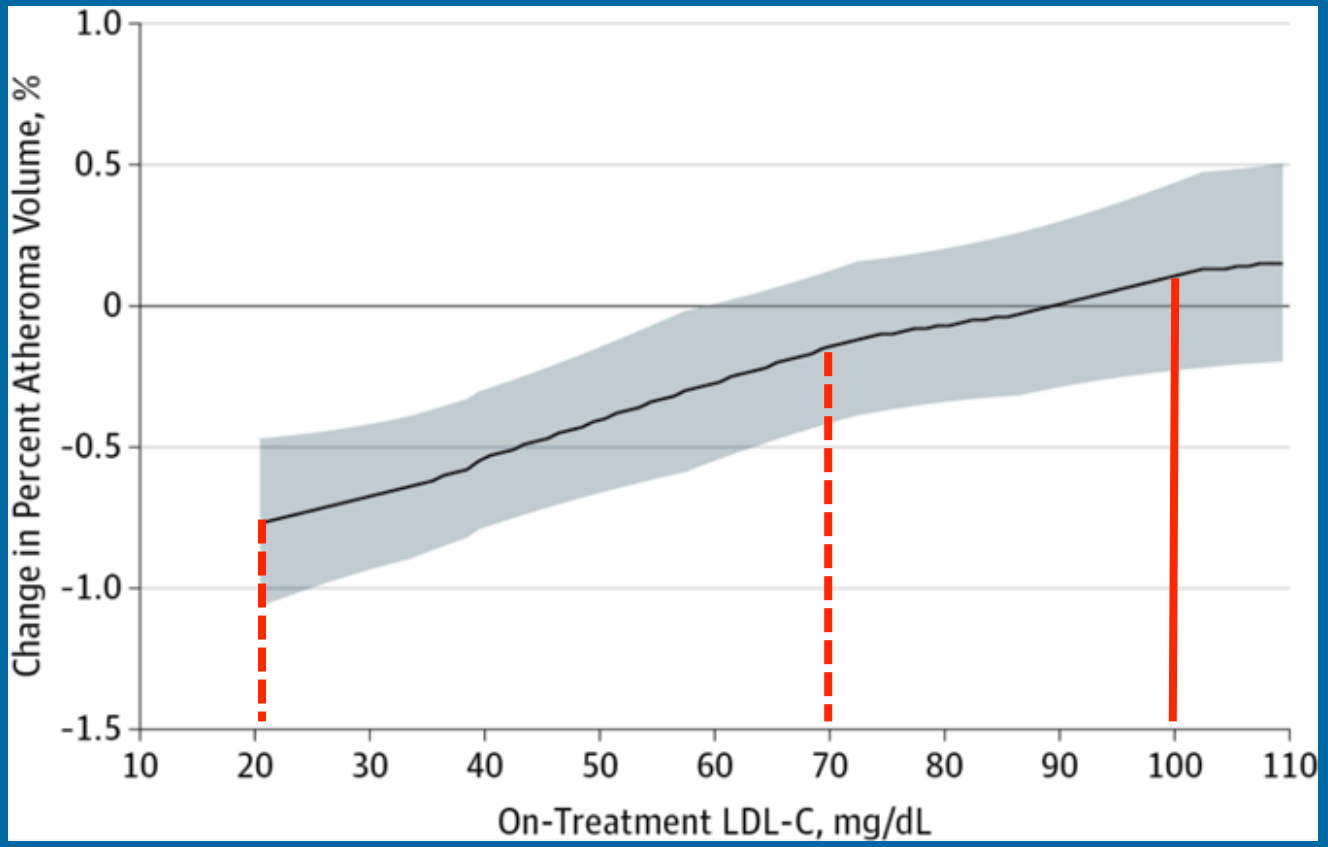


Conclusion: a continuous relationship between 24% lower MACE risk and 39 mg/dL lower on-Rx LDL-C was observed without limit, even down to *mean* level of 25 mg/dL

*ODYSSEY FH I, FH II, HIGH FH, LONG TERM, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE and MONO studies: median time to events 36 wks 4974 patients treated with ALI, placebo or EZE experienced a total of 104 CVD events

Ray et al https://doi.org/10.1161/CIRCULATIONAHA.116.024604 Originally published October 24, 2016

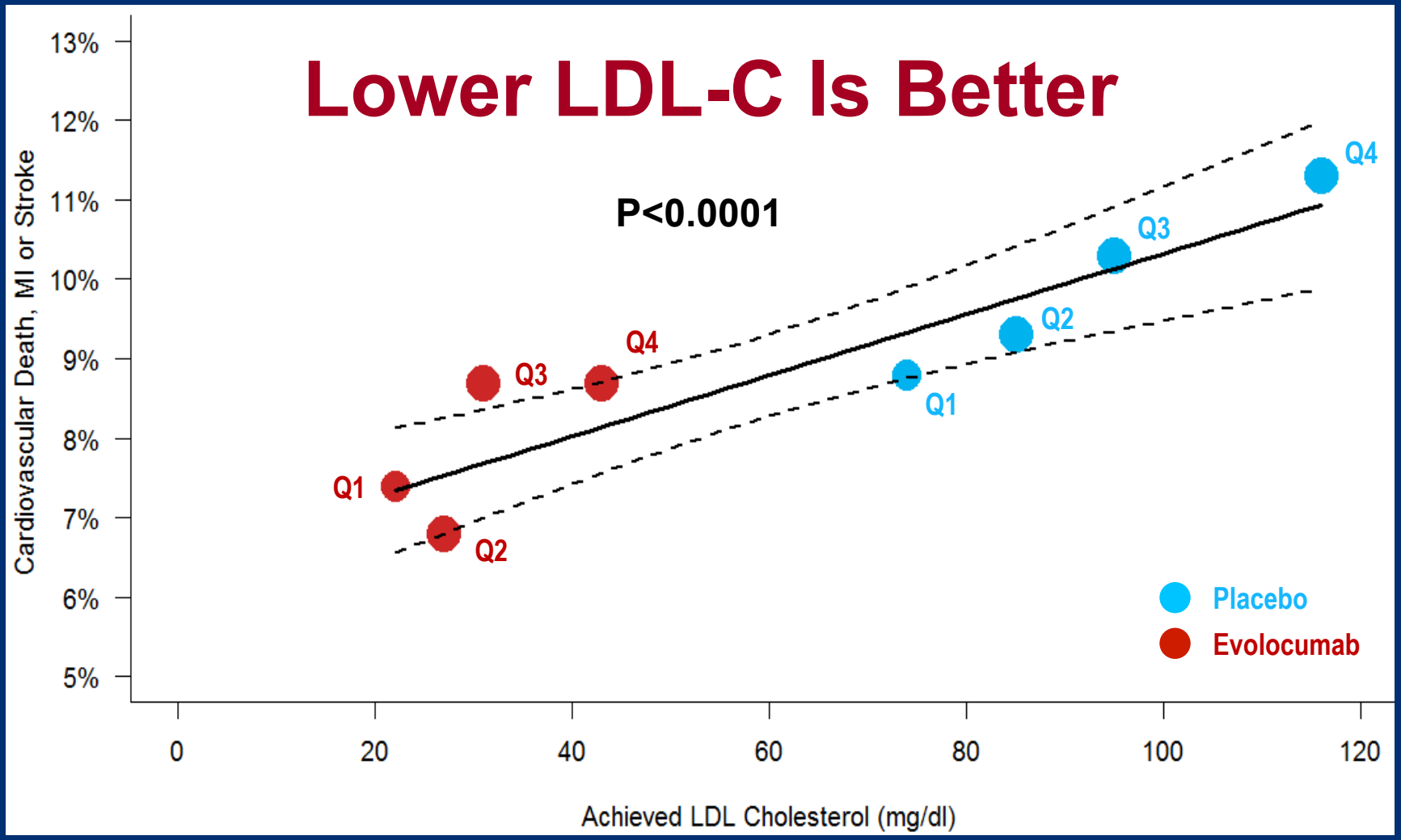
GLAGOV: Post Hoc Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



Shaded area represents 95% confidence intervals
Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range.

Nicholls SJ et al JAMA Published online November 15, 2016 doi:10.1001/jama.2016.16951

FOURIER: Secondary Endpoints by quartile of baseline LDL-C and treatment arms



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FOURIER: Clinical Adverse Events

Clinical Adverse Event	Evolocumab (N=13784) N Pts (%)	Placebo (N=13780) N (%)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Leading to discontinuation of study drug	**608 (4.4)**	**573 (4.2)**
Injection-site reaction	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	**228 (1.7)**	**242 (1.8)**
Adjudicated new-onset diabetes*	677 (8.1)	644 (7.7)
Neurocognitive event	**217 (1.6)**	**202 (1.5)**

*Denominators of 8337 and 8339, respectively, because patients with prevalent diabetes at the start of the trial were excluded

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664.

FOURIER: Laboratory Adverse Events

Laboratory Parameter	Evolocumab (N=13784) N Pts (%)	Placebo (N=13780) N (%)
Aminotransferase >3x ULN	240 (1.8)	242 (1.8)
Creatinine kinase>5x ULN	95 (0.7)	99 (0.7)

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Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy

A PROVE IT-TIMI 22 Substudy

Stephen D. Wiviott, MD,*† Christopher P. Cannon, MD, FACC,*†
David A. Morrow, MD, MPH, FACC,*† Kausik K. Ray, MD,† Marc A. Pfeffer, MD, PHD, FACC,*
Eugene Braunwald, MD, MACC,*† for the PROVE IT-TIMI 22 Investigators
Boston, Massachusetts

Déjà vu, all over again?

Concerns of increased hemorrhagic stroke or cognitive impairment

Wiviott SD et al JACC 2005; 46:1411-16

How low should we reduce LDL-C?

Major Safety and Efficacy Outcomes (% of Subjects)

Safety Measure	Achieved LDL Cholesterol (mg/dl) >80–100 n = 256	>60–80 n = 576	>40–60 n = 631	<40 n = 193	p Trend
Other					
Hemorrhagic stroke	0.4	0.2	0	0	0.12
Retinal AE	0.4	0.9	1.0	0	0.48
Suicide/trauma death	0	0	0	0	1.0
Study drug discontinued because of any AE	10.2	9.4	9.7	9.8	0.99
Major efficacy measures					
Death	1.1	1.4	1.3	0.5	0.59
CHD death	0.5	0.5	0.6	0.0	0.06
Myocardial infarction	1.0	0.7	0.5	0.6	0.009
Any stroke	0.8	0.9	0.6	1.6	0.32
Primary composite*	26.1	22.2	20.4	20.4	0.10

efficacy. These data identify no intrinsic safety concern of achieving low LDL and, therefore, a strategy of intensive treatment need not be altered in patients achieving very low LDL

Wiviott SD et al JACC 2005; 46:1411-16

IMPROVE-IT: Adverse Events by achieved LDL-C

	LDL-C in mg/dL at Month 1				Trend P-value
	<30	30–<50	50–<70	≥70	
	(n=969)	(n=4755)	(n=5482)	(n=3989)	
AE leading to drug discontinuation	6.9	6.9	6.5	6.5	0.38
AST or ALT ≥3x ULN	4.6	4.5	4.4	4.8	0.68
Myalgia with CK elevation per investigator	9.7	9.0	8.8	9.2	0.90
Myopathy per CEC	0	0.1	0.1	0.2	0.41
Rhabdomyolysis per CEC	0	0.1	0.1	0.2	0.16
Memory impairment/altered mental status	2.1	2.5	2.9	2.3	0.97
Hemorrhagic stroke	0.3	0.8	0.4	0.6	0.57

Conclusions: Patients who reached an LDL-C <30 mg/dL at month 1 had no differences in safety events, including adverse events leading to discontinuation, LFT elevations, muscle-related events, memory impairment, or hemorrhagic stroke compared to those with higher LDL-C levels. These data support continuation of intensive lipid lowering therapy without modification in patients achieving very low LDL levels.

Guigliano RP, et al. Europe Heart J 2015, 36 (abstract supplement)

Osler: Adverse Events by Achieved LDL-C

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	SOC Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	**0.5**	**1.2**	**0.8**	**1.0**	**0.9**	**0.3**
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

ODYSSEY LONG TERM Study: Neurocognitive TEAEs: Safety Analysis

	Alirocumab (N=1550)	Alirocumab with 2 consecutive LDL-C <25 mg/dL (N = 575)	Placebo (N=788)
Neurocognitive disorders - no. of patients (%)*	**18 (1.2)**	**3 (0.5)**	**4 (0.5)**
Amnesia	5 (0.3)	0	0
Memory impairment	4 (0.3)	0	1 (0.1)
Confusional state	4 (0.3)	1 (0.2)	1 (0.1)
Confusion postoperative	1 (<0.1)	0	0
Dementia	1 (<0.1)	1 (0.2)	1 (0.1)
Disorientation	1 (<0.1)	0	0
Disturbance in attention	1 (<0.1)	0	1 (0.1)
Frontotemporal dementia	1 (<0.1)	1 (0.2)	0
Reading disorder	1 (<0.1)	0	0
Transient global amnesia	1 (<0.1)	0	0
Vascular encephalopathy	1 (<0.1)	0	0

Robinson JG, et al. N Engl J Med. 2015;372:1489-99 – appendix Table S6.

The EBBINGHAUS cognitive function trial

- In FOURIER parent trial neurocognitive events not different between evolocumab 1.6% and placebo 1.5%
- Randomized 1974 patients to EBBINGHAUS sub-study
- Cognitive function assessed in 3 ways at baseline and end of study;
  - battery of cognitive tests
  - questionnaires included memory, organization, planning skills,
  - physician-reported cognitive adverse events
- There were no differences between evolocumab and placebo in any of these measures
- An exploratory analysis assessed patients according to their achieved LDL;
  - Compared results of those with LDL-C <25, 25 to 40, >40 mg/dL
  - **No differences according to the achieved LDL-C in their cognitive function**

Giugliano RP ACC March 18, 2017; http://www.ajmc.com/conferences/acc-2017/dr-robert-p-giugliano-on-the-results-of-the-ebbinghaus-evolocumab-cognitive-study#sthash.x7y5ECCl.dpuf,

Adverse Experience Summary in Patients with LDL-C values <25 mg/dL, <15 mg/dL and ≥25 mg/dL in Global Safety Pool

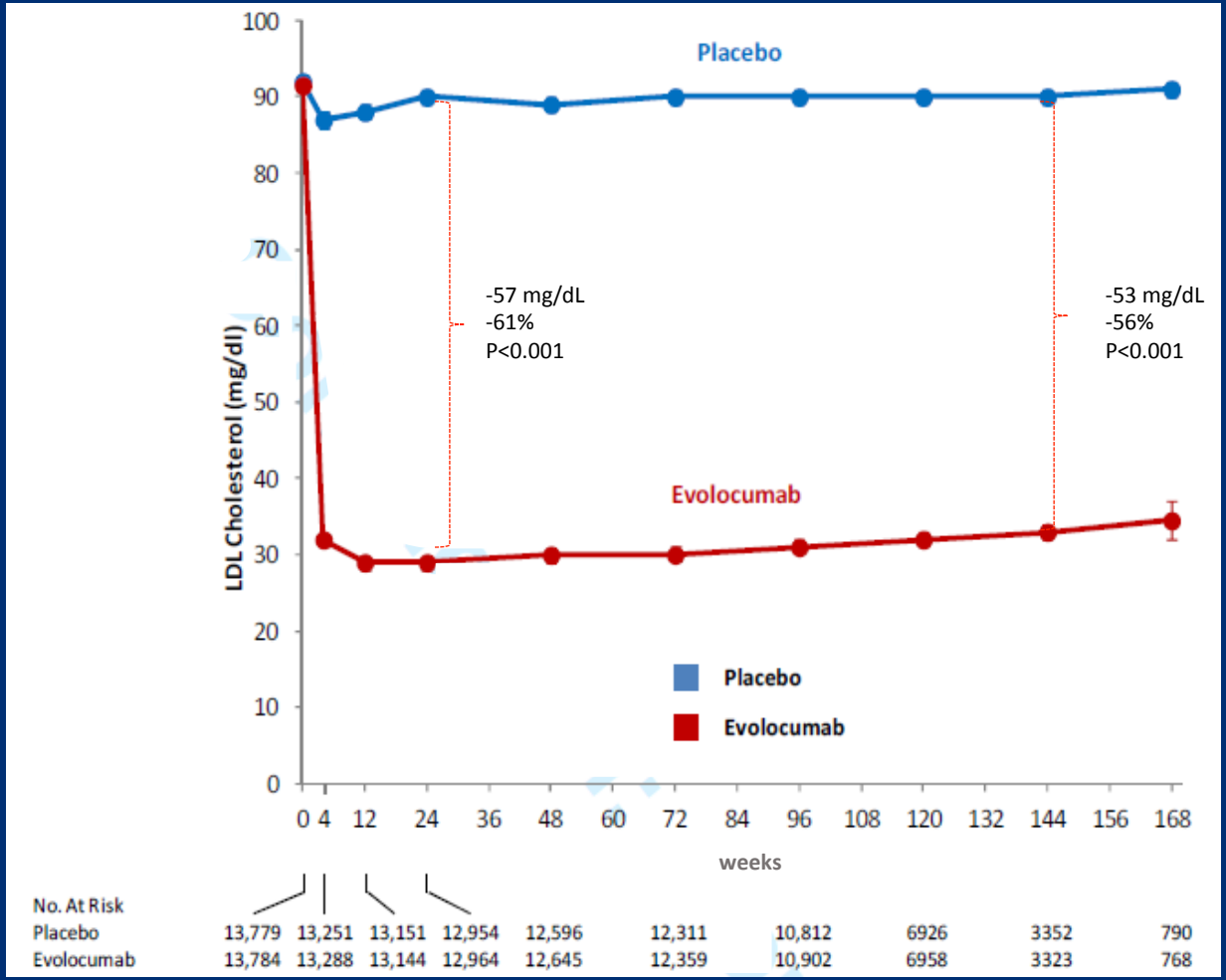
Primary system organ class, % Preferred term, %	Overall Alirocumab (n=3340)	≥2 LDL-C <25 mg/dL (n=796)	≥2 LDL-C <15 mg/dL (n=288)	LDL-C ≥25 mg/dL (n=2544)
Gastrointestinal disorders	17.0%	12.7%	10.1%	16.7%
Diarrhea	4.3%	3.0%	1.4%	4.0%
Nausea	2.2%	0.9%	1.0%	2.5%
General disorders and administration-site conditions	15.1%	10.2%	6.9%	15.5%
Injection-site reaction	5.7%	3.0%	3.5%	5.9%
Fatigue	2.8%	2.6%	2.4%	2.7%
Non-cardiac chest pain	1.6%	1.8%	0.3%	1.5%
Nervous system disorders	14.9%	10.3%	9.0%	15.1%
Dizziness	3.0%	1.8%	1.4%	3.2%
Headache	4.6%	1.8%	1.4%	4.8%
Hemorrhagic stroke	0.1%	0	0	0.1%

Favorable safety profile

The information provided in the safety database of 3340 patients treated with alirocumab at the 75 or 150 mg Q2W doses (global exposure of 3451 patient-years) supports that the drug was well tolerated. The overall occurrences of SAEs and premature withdrawals were comparable between treatment groups. Deaths were rare and less frequently reported for alirocumab than control. In patients who had at least 2 consecutive values of LDL-C < 25 or <15 mg/dL, no safety effects were identified in analyses of the AEs of interest. Across all treatment groups in

Alirocumab Briefing Document: Endocrine & Metabolic Advisory Committee Meeting [accessed Sept 14, 2015]
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM449865.pdf

FOURIER: LDL Cholesterol¥ over time



LDL-C at 48 weeks

LDL-C	Evolocumab	Placebo
Median (IQR)	30 (19,46)	85
≤70 mg/dL	87%	18%
≤40 mg/dL¥	67%	o.5%
≤25 mg/dL¥	42%	<0.1%

P<0.001 for all treatment comparisons

¥LDL-C calculated using the Friedewald equation, except if <40 mg/dL or if TG >400 mg/dL; then LDL-C measured by preparative ultracentrifugation.

*Shown are median values with 95% confidence intervals in the two arms

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664.

FOURIER: Clinical Adverse Events

Clinical Adverse Event	Evolocumab (N=13784) N Pts (%)	Placebo (N=13780) N (%)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Leading to discontinuation of study drug	**608 (4.4)**	**573 (4.2)**
Injection-site reaction	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	***228 (1.7)***	***242 (1.8)***
Adjudicated new-onset diabetes*	677 (8.1)	644 (7.7)
Neurocognitive event	**217 (1.6)**	**202 (1.5)**
Hemorrhagic Stroke	***29 (0.2)***	***25 (0.2)***

*Denominators of 8337 and 8339, respectively, because patients with prevalent diabetes at the start of the trial were excluded

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664.

Adverse Events and Laboratory Measurements in Combined SPIRE-1 and SPIRE-2.*

Adverse Events and Laboratory Measurements	Bococizumab			Placebo
	All LDL Cholesterol Values	≥1 LDL Cholesterol Value ≤25 mg/dl	No LDL Cholesterol Value ≤25 mg/dl	
	number of patients (rate per 100 patient-yr)			
Adverse events				
Number of patients evaluated	13,707	6285	7259	13,697
Any adverse event	8,727 (169.3)	4049 (166.1)	4637 (173.1)	8,289 (149.1)
Serious adverse event	1,995 (19.5)	876 (18.2)	1097 (20.5)	1,999 (19.7)
Adverse event resulting in drug discontinuation	684 (6.3)	246 (4.8)	421 (7.5)	466 (4.2)
Injection-site irritation	1,663 (16.8)	785 (16.9)	875 (16.7)	398 (3.6)
Injection-site reaction	1,084 (10.4)	524 (10.8)	558 (10.2)	142 (1.3)
Myalgia	405 (3.7)	160 (3.1)	245 (4.3)	371 (3.4)
Arthralgia	425 (3.9)	185 (3.6)	240 (4.2)	392 (3.6)
Newly diagnosed diabetes	242 (4.2)	139 (4.9)	103 (3.5)	250 (4.2)
Cataract	125 (1.1)	46 (0.9)	79 (1.3)	124 (1.1)
Fatigue	293 (2.6)	110 (2.1)	183 (3.2)	253 (2.3)
Headache	356 (3.2)	134 (2.6)	220 (3.8)	308 (2.8)
Hypersensitivity	22 (0.2)	9 (0.2)	13 (0.2)	19 (0.2)

Ridker PM et al NEJM published on March 17, 2017, DOI: 10.1056/NEJMoa1701488

Are there safety concerns when achieving very low LDL-C <25 mg/dL with PCSK9 inhibitors?

Conclusions:

- Reduction of LDL-C with evolocumab to a median of 30 mg/dL, with nearly 6,000 patients <25 mg/dL and 3,500 patients below 19 mg/dL, was not associated with any major safety concerns such as hemorrhagic stroke, cognitive impairment or cataracts
- No increase in cognitive dysfunction with LDL-C <25 mg/dL compared to higher LDL-C or placebo
- LDL-C <25 mg/dL in 6285 patients treated with bococizumab was associated with fewer cataracts (0.9%) than the 1.3% in the 7259 patients with LDL-C >25 mg/dL and no different from placebo (1.1%)

Sabatine M et al NEJM 2017 DOI: 10.1056/NEJMoa1615664
Ridker PM et al NEJM published on March 17, 2017, DOI: 10.1056/NEJMoa1701488.

Does reducing LDL cholesterol to low and very low levels have additional benefit on CVD events or safety concerns?

Conclusion:

- Patients achieving very low LDL-C levels (<25 mg/dL and even <15 mg/dL) do not show any increase in clinical or laboratory side effects compared to those with higher LDL-C or control groups in properly randomized studies
- The CVD event and IVUS data shows additional benefit from low (~40 mg/dL; 1 mmol/L) and very low LDL-C (25 mg/dL;0.4 mmol/L) and increased CVD events when LDL-C remains elevated
- ***Based on current evidence the real safety concern is under treatment of LDL-C, not too low LDL-C!***
- Safety and benefit data for very low LDL-C based on increased LDL clearance via upregulation of the LDL receptor (statins, ezetimibe and PCSK9 inhibition), plus unreliability of Friedewald LDL-C when LDL-C <50 mg/dL suggest eliminating lower limit for LDL-C (as for hsCRP).

The Evolution of PCSK9 inhibitors;
No Pipedream - Definitely Evidence based Reality!