Publicações de impacto no último ano em: Cardiologia Clinica

Dislipidemias

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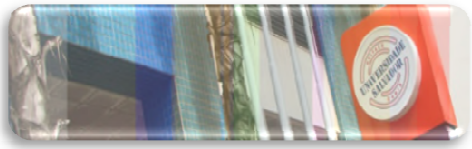
2017



Declaração de Potencial Conflito de Interesse

Conselho Federal de Medicina (Nº 1595/2000) e Vigilância Sanitária RDC 102/2000,

Nome do Palestrante: Nivaldo Filgueiras

Título da Apresentação: Dislipidemias: Year in Review 2017

CATEGORIAS DE POTENCIAL CONFLITO DE INTERESSE	INDÚSTRIA(S)
Patrocínio de transporte e/ou hospedagem em Congressos	Bayer
Patrocínio em estudos clínicos e/ ou experimentais subvencionados pela indústria	-
Ser conferencista / palestrante em eventos patrocinados pela indústria	Novartis, Merck Sharp Dohme, Pfizer
Participar de comitês normativos de estudos científicos patrocinados pela indústria	-
Receber apoio institucional da indústria	-
Preparo de textos científicos em periódicos patrocinados pela indústria	-
Ter ações da indústria	-

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease – HOPE 3

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)
Age — yr	65.8±6.4	65.7±6.3
Female sex — no. (%)	2951 (46.4)	2923 (46.1)
Cardiovascular risk factors — no. (%)		
Elevated waist-to-hip ratio	5540 (87.1)	5494 (86.6)
Recent or current smoking	1740 (27.4)	1784 (28.1)
Low HDL cholesterol level	2344 (36.8)	2244 (35.4)
Impaired fasting glucose or impaired glucose tolerance	809 (12.7)	807 (12.7)
Early diabetes mellitus	374 (5.9)	357 (5.6)
Family history of premature coronary heart disease	1675 (26.3)	1660 (26.2)
Early renal dysfunction	169 (2.7)	181 (2.9)
Hypertension	2403 (37.8)	2411 (38.0)
Presence of 2 risk factors	3002 (47.2)	2924 (46.1)
Presence of ≥3 risk factors	1545 (24.3)	1523 (24.0)
Blood pressure — mm Hg		
Systolic	138.04±14.92	138.06±14.62
Diastolic	81.85±9.38	81.90±9.26
Heart rate — beats/min	72.75±10.25	72.72±10.19
Body mass index†	27.15±4.78	27.07±4.77
Waist-to-hip ratio	0.94±0.08	0.94±0.08
Cholesterol — mg/dl‡		
Total	201.5±42.6	201.3±41.7
LDL	127.8±36.1	127.9±36.0
HDL	44.7±13.9	44.9±13.8
Triglycerides — mg/dl‡		

Critérios de Inclusão: ♂ 55 anos e ♀ ≥65 anos, que tinham pelo menos um dos seguintes fatores de risco cardiovascular: elevada relação cintura-quadril, ↓HDL, Tabagismo, disglicemia, história familiar de DAC precoce e disfunção renal.
Ou ♀ ≥ 60 com dois destes fatores.

Desfecho Primário: morte cardiovascular, IAM ou AVC não fatal.
O 2º resultado co-primário incluíram, adicionalmente, RM, IC e PCR.

Média de *follow-up*: 5,6 anos.

(published on April 2, 2016, at NEJM.org.)

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease – HOPE 3

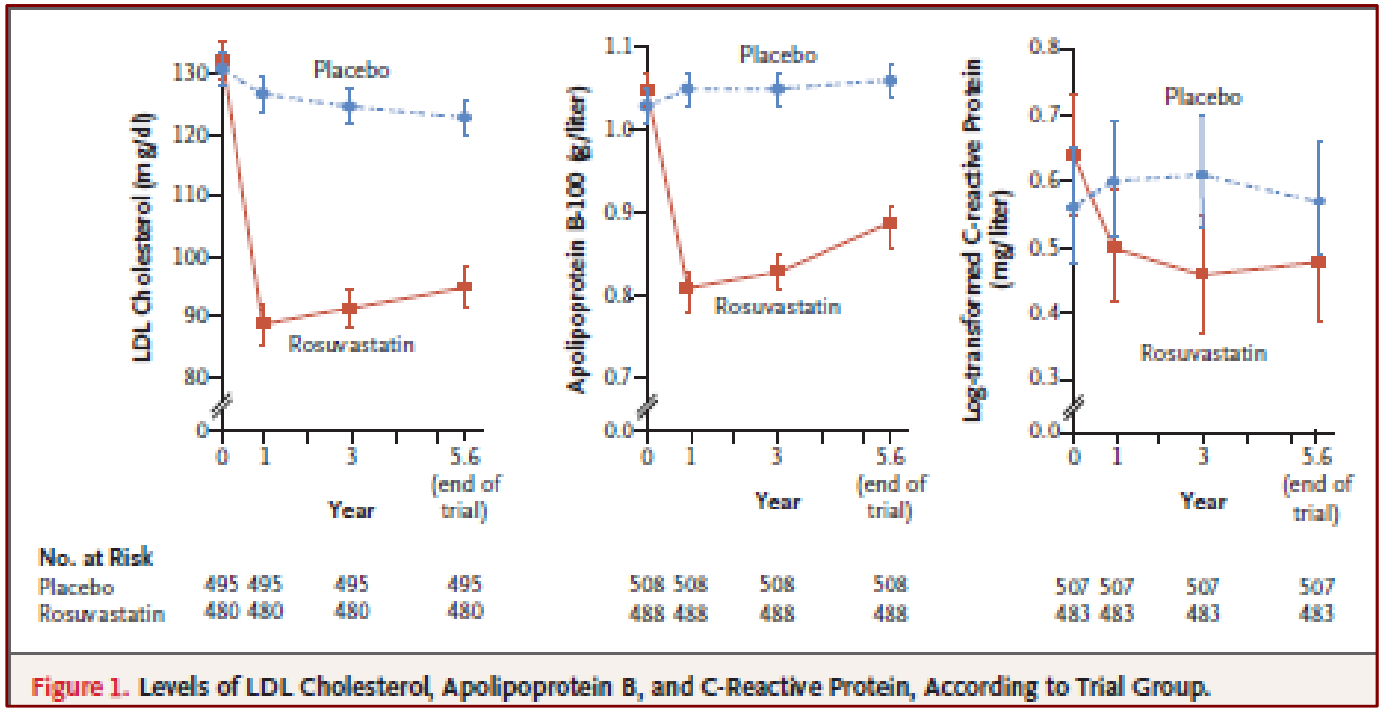


Figure 1. Levels of LDL Cholesterol, Apolipoprotein B, and C-Reactive Protein, According to Trial Group.

(published on April 2, 2016, at NEJM.org.)

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease – HOPE 3

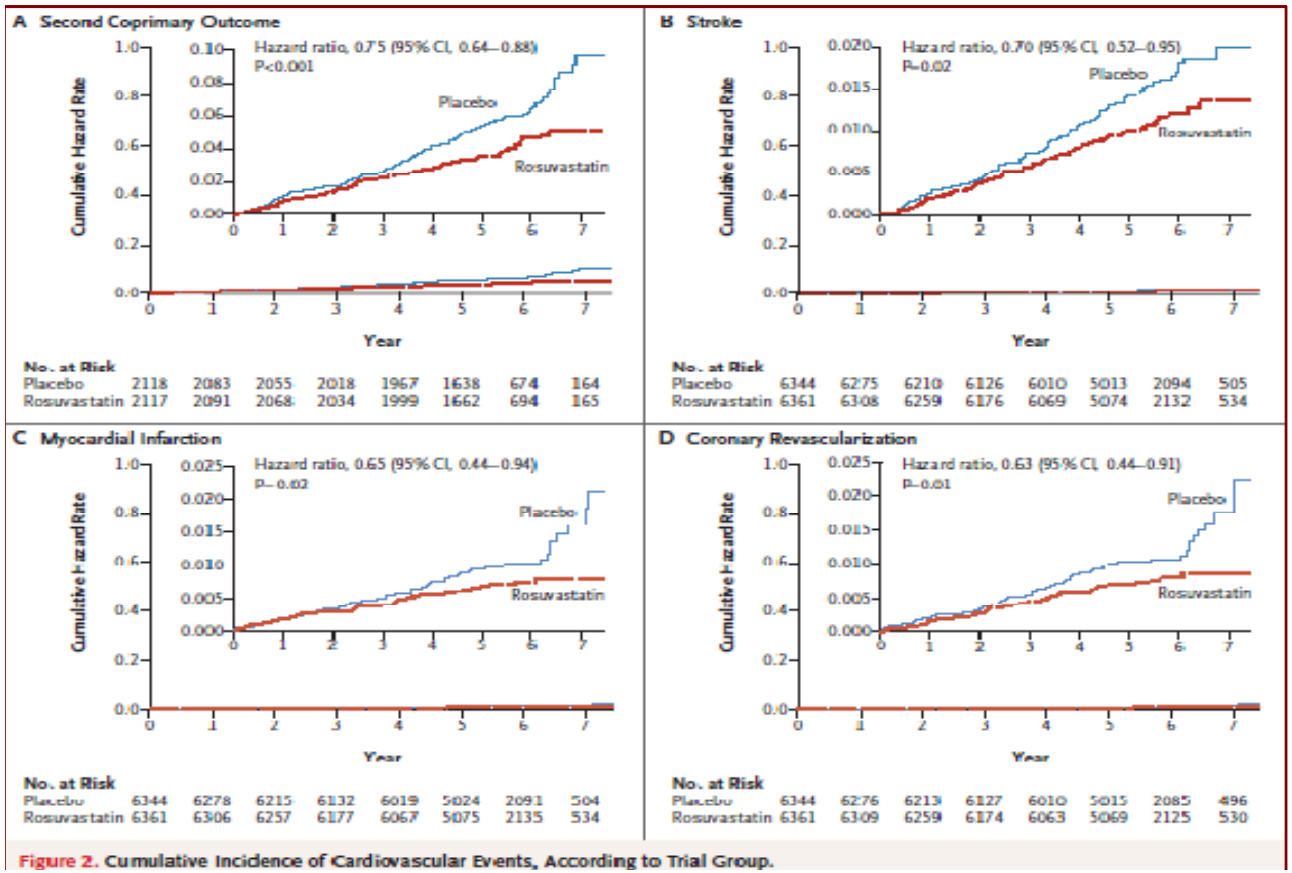


Figure 2. Cumulative Incidence of Cardiovascular Events, According to Trial Group.

Desfecho Primário: morte cardiovascular, IAM ou AVC não fatal.
O 2º resultado co-primário incluíram, adicionalmente, RM, IC e PCR.

Média de *follow-up*: 5,6 anos.

(published on April 2, 2016, at NEJM.org.)

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Rosuvastatin Group (N = 6361)	Placebo Group (N = 6344)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	235 (3.7)	304 (4.8)	0.76 (0.64–0.91)	0.002
Second coprimary outcome	277 (4.4)	363 (5.7)	0.75 (0.64–0.88)	<0.001
Secondary outcome — no. (%)	306 (4.8)	393 (6.2)	0.77 (0.66–0.89)	<0.001
Components of the coprimary and secondary outcomes — no. (%)				
Death from cardiovascular causes	154 (2.4)	171 (2.7)	0.89 (0.72–1.11)	
Myocardial infarction	45 (0.7)	69 (1.1)	0.65 (0.44–0.94)	
Stroke	70 (1.1)	99 (1.6)	0.70 (0.52–0.95)	
Resuscitated cardiac arrest	4 (0.1)	4 (0.1)	0.99 (0.25–3.97)	
Revascularization	56 (0.9)	82 (1.3)	0.68 (0.48–0.95)	
Heart failure	21 (0.3)	29 (0.5)	0.72 (0.41–1.26)	
Angina with evidence of ischemia	56 (0.9)	64 (1.0)	0.87 (0.61–1.24)	
Death from any cause — no. (%)	334 (5.3)	357 (5.6)	0.93 (0.80–1.08)	0.32
New-onset diabetes — no. (%)	232 (3.9)	226 (3.8)	1.02 (0.85–1.23)	0.82
Coronary heart disease — no. (%)‖	105 (1.7)	140 (2.2)	0.74 (0.58–0.96)	0.02
First and recurrent events of the second coprimary outcome‡				
No. of participants with ≥1 event	277	363		
No. of participants with ≥2 events	68	89		
No. of participants with ≥3 events	6	16		
Total no. of events	353	473	0.75 (0.64–0.89)	0.001
Hospitalizations — no. (%)§				
For cardiovascular causes	281 (4.4)	369 (5.8)	0.75 (0.64–0.88)	<0.001
For noncardiovascular causes	881 (13.9)	879 (13.9)	1.00 (0.91–1.10)	0.99

→ NNT=91

→ NNT=73

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease – HOPE 3

(published on April 2, 2016, at NEJM.org.)

The ACCELERATE Trial

Impact of the Cholesteryl Ester Transfer Protein Inhibitor Evacetrapib on Cardiovascular Outcome

Stephen J Nicholls
for the ACCELERATE investigators

Disclosure

Research support: AstraZeneca, Amgen, Anthera, Eli Lilly, Novartis, Cerenis The Medicines Company, Resverlogix, InfraReDx, Roche and LipoScience

Consulting and honoraria: AstraZeneca, Eli Lilly, Anthera, Merck, Takeda, Resverlogix, Sanofi-Aventis, CSL Behring, Esperion, Boehringer Ingelheim

ACCELERATE was sponsored by Eli Lilly and Company

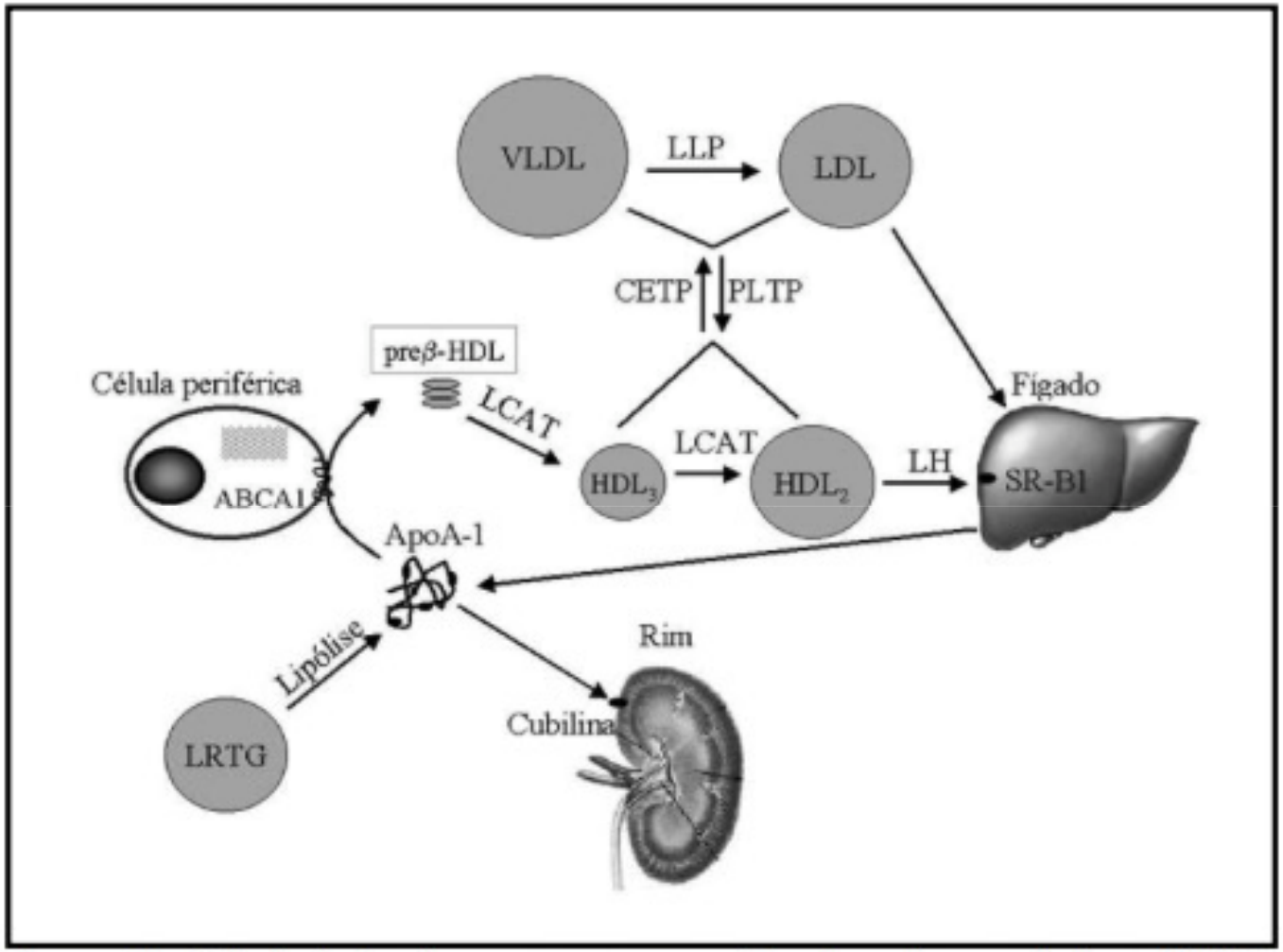
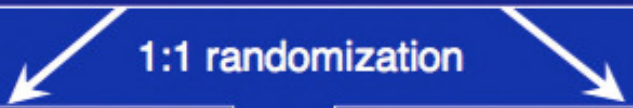


Figura 1 – *Principais vias do transporte reverso do colesterol e metabolismo da HDL*

ACCELERATE Trial Design

12,092 patients at high vascular risk, defined as:

- ACS within 30-365 days
- Peripheral arterial disease
- Diabetes with coronary disease
- Cerebrovascular disease

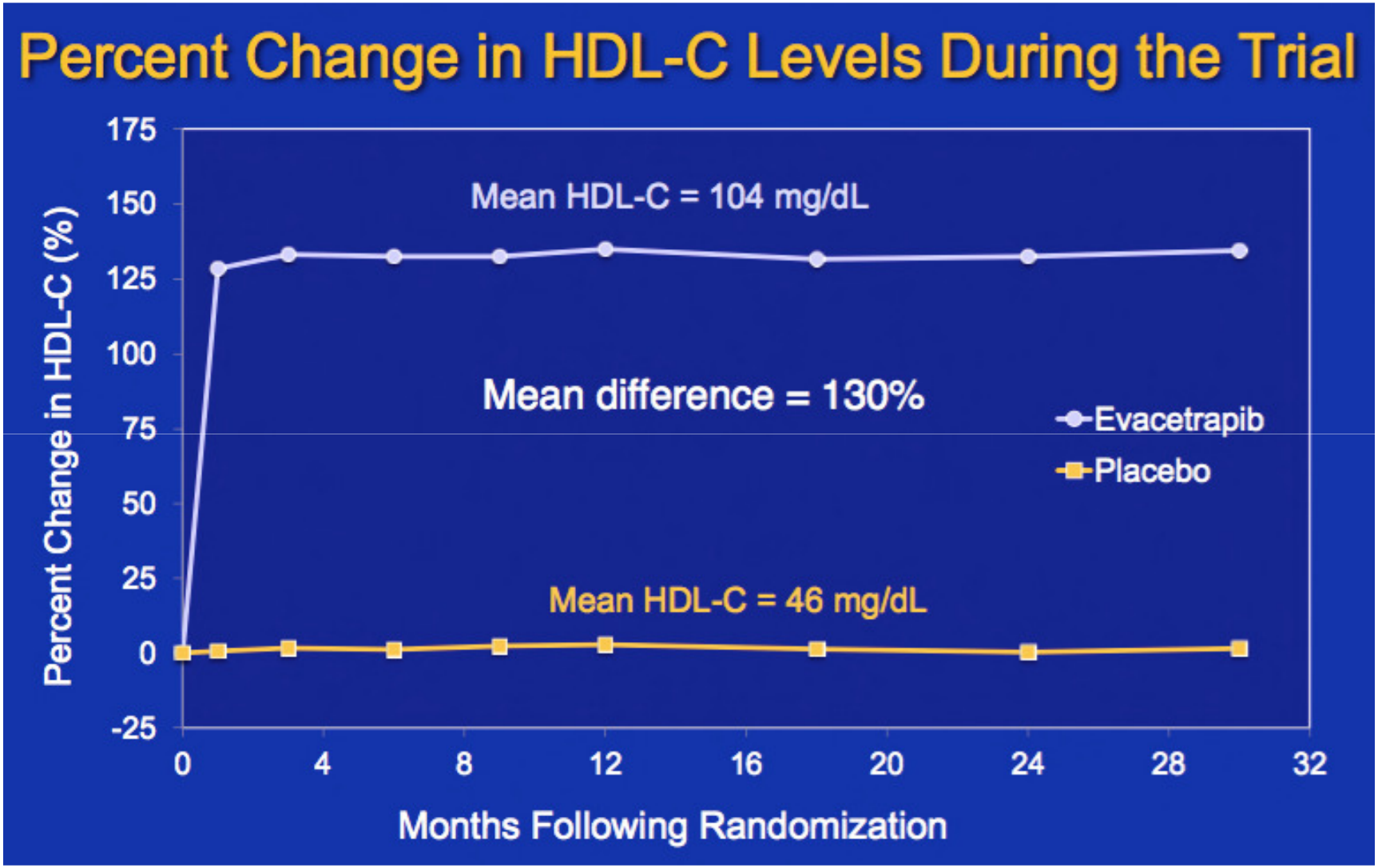


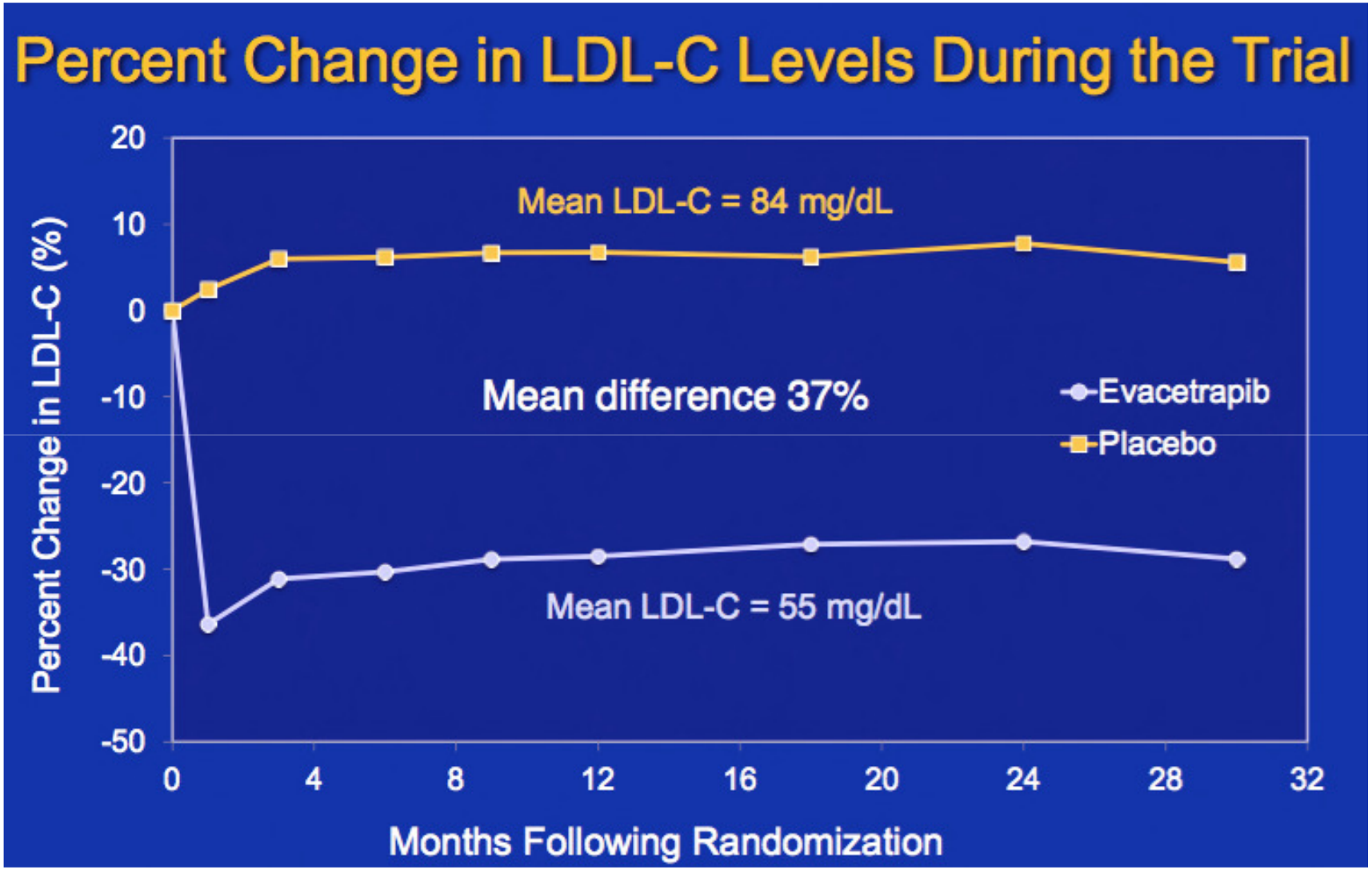
Evacetrapib 130 mg

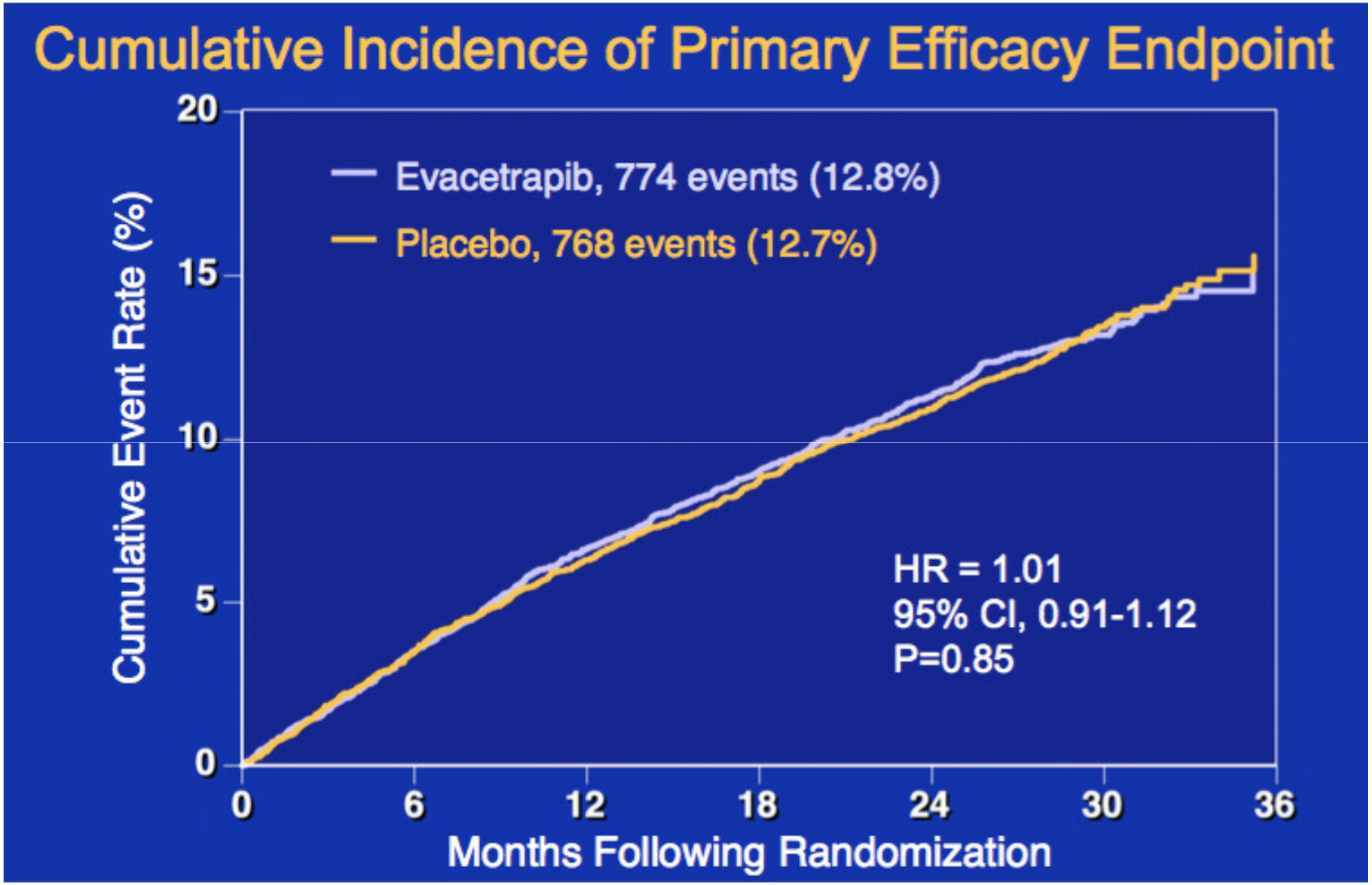
Placebo

- Event driven - Primary endpoint in 1670 patients (CV death, MI, stroke, coronary revascularization or hosp. for unstable angina)
- Minimum of 700 patients with hard events (CV death, MI or stroke), minimum of 1.5 years of follow-up per patient
- 84% power to detect a 13.5% reduction in the primary endpoint

Percent Change in HDL-C Levels During the Trial




Percent Change in LDL-C Levels During the Trial
Percent Change in LDL-C (%)
20
10
0
-10
-20
-30
-40
-50
Mean LDL-C = 84 mg/dL
Mean difference 37%
Mean LDL-C = 55 mg/dL
Evacetrapib
Placebo
0
4
8
12
16
20
24
28
32
Months Following Randomization


Cumulative Incidence of Primary Efficacy Endpoint
Cumulative Event Rate (%)
20
15
10
5
0
Evacetrapib, 774 events (12.8%)
Placebo, 768 events (12.7%)
HR = 1.01
95% CI, 0.91-1.12
P=0.85
0
6
12
18
24
30
36
Months Following Randomization

Adverse Clinical and Biochemical Events

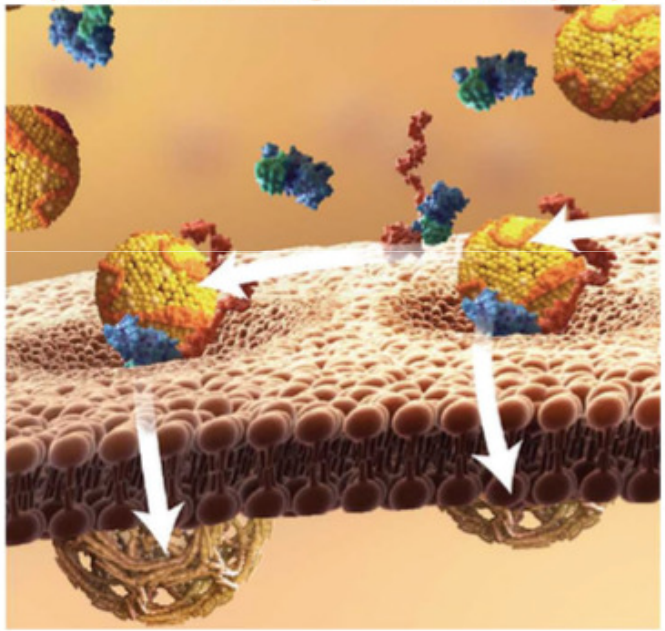
Parameter	Placebo	Evacetrapib	*P* Value
Discontinuation due to adverse events	8.7%	8.6%	0.86
ALT >3x ULN	0.7%	0.6%	0.31
Bilirubin >2x ULN	0.3%	0.1%	0.06
CK >3x ULN	3.1 %	2.3%	<0.01
Median change in hsCRP	-8%	+4.6%	<0.01
New onset diabetes	183 (3.0%)	149 (2.5%)	0.06
Investigator-reported hypertension	609 (10.1%)	686 (11.4%)	<0.05
Ventricular tachycardia	45 (0.7%)	28 (0.5%)	<0.05

Conclusions

- Despite a 37% decrease in LDL-C and a 130% increase in HDL-C, evacetrapib did not reduce the primary composite endpoint of major adverse CV events.
- A borderline significant (p=0.06) reduction in all-cause mortality was observed in the evacetrapib group.
- The failure of decreases in LDL-C to result in an overall morbidity-mortality benefit emphasizes the limitations of surrogate endpoints.
- The findings continue to challenge the hope that CETP inhibition might successfully address residual CV risk.

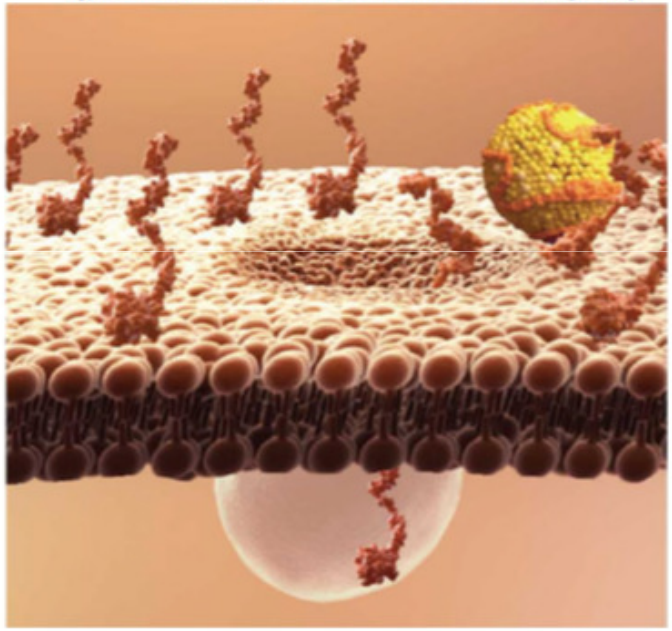
A inibição da PCSK9 permite a reciclagem do receptor de LDL

Função elevada da PCSK9
(por exemplo, ganho de função)



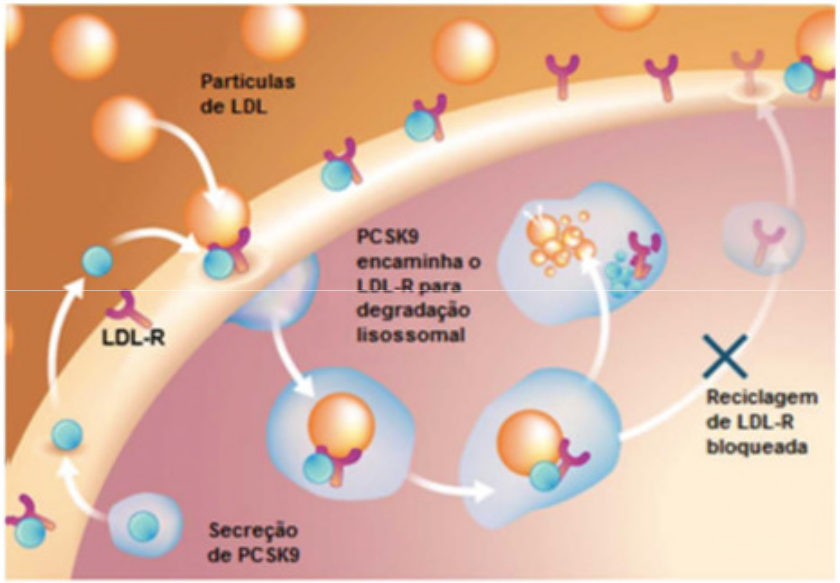
Menos LDL-Rs[1–3]
Maior LDL-C plasmático

Função diminuída da PCSK9
(por exemplo, perda da função)

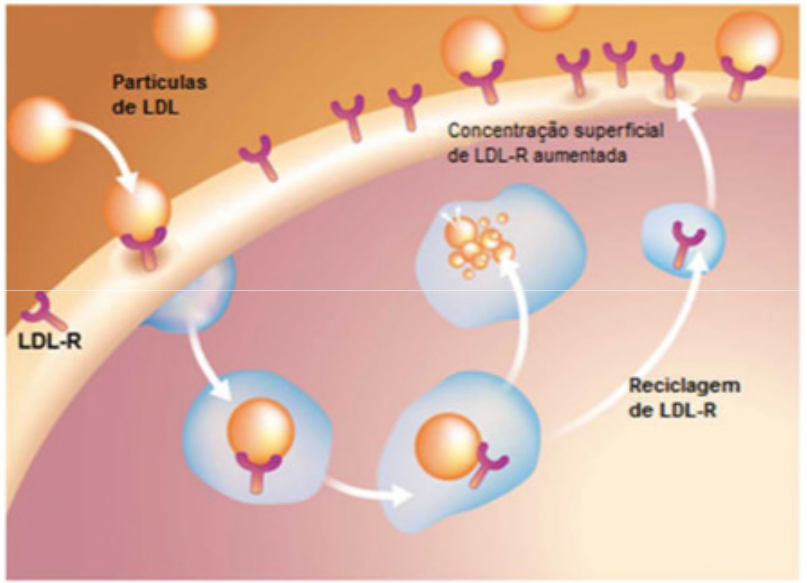


Mais LDL-Rs[2,3]
Menor LDL-C plasmático

Variantes genéticas de PCSK9 demonstram sua importância na regulação dos níveis de LDL



Ganho de Função PCSK9
= <u>Menos</u> LDL-Rs[1,3,5]



Perda de Função PCSK9
= <u>Mais</u> LDL-Rs[1,4,5]

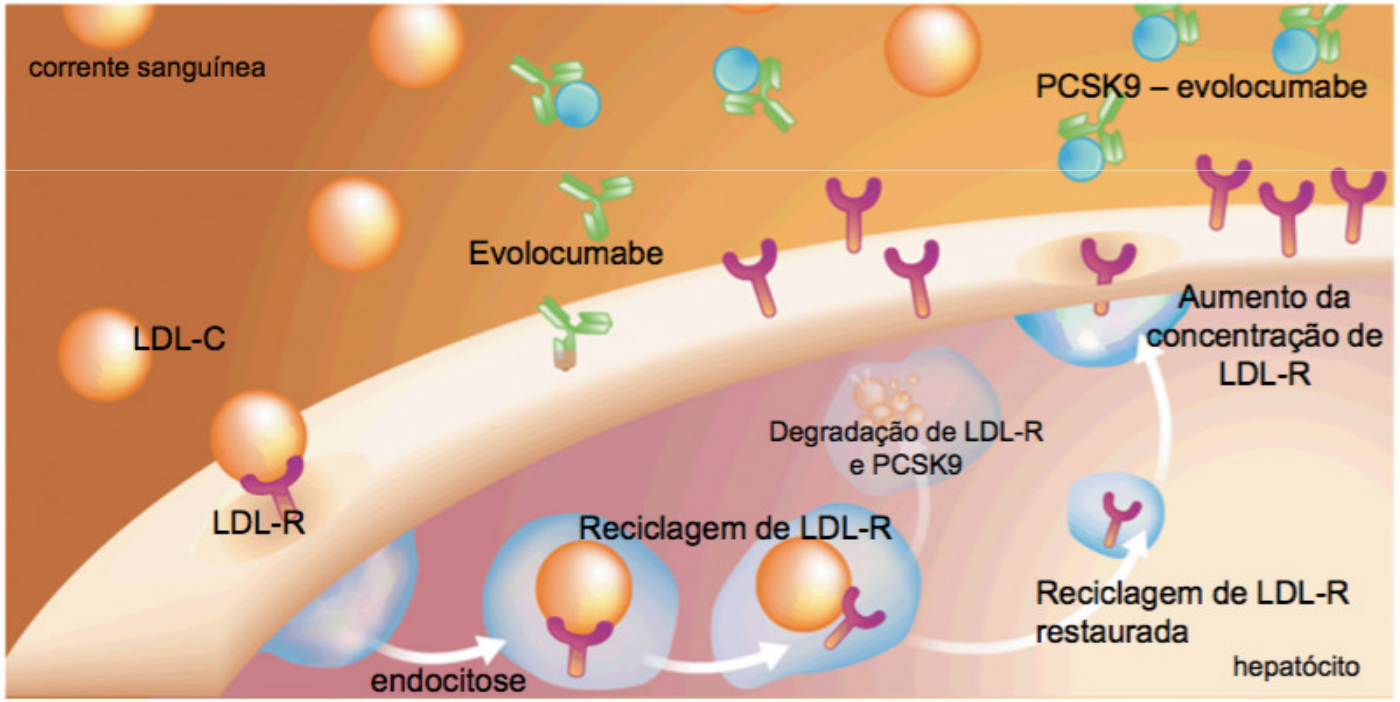
- **Mutações no gene PCSK9 humano que levam à perda da função de PCSK9 são encontradas em 1 – 3% da população[1-3]**

Evolocumabe é um tratamento inovador. Ele inibe a PCSK9, bloqueando, assim, a interação de PCSK9 – LDL-R, aumentando a expressão de LDL-R e a eliminação de LDL-C

Presença de evolocumabe = ausência de PCSK9

➡ Mais LDL-R

➡LDL-C menor no plasma



Research

Original Investigation

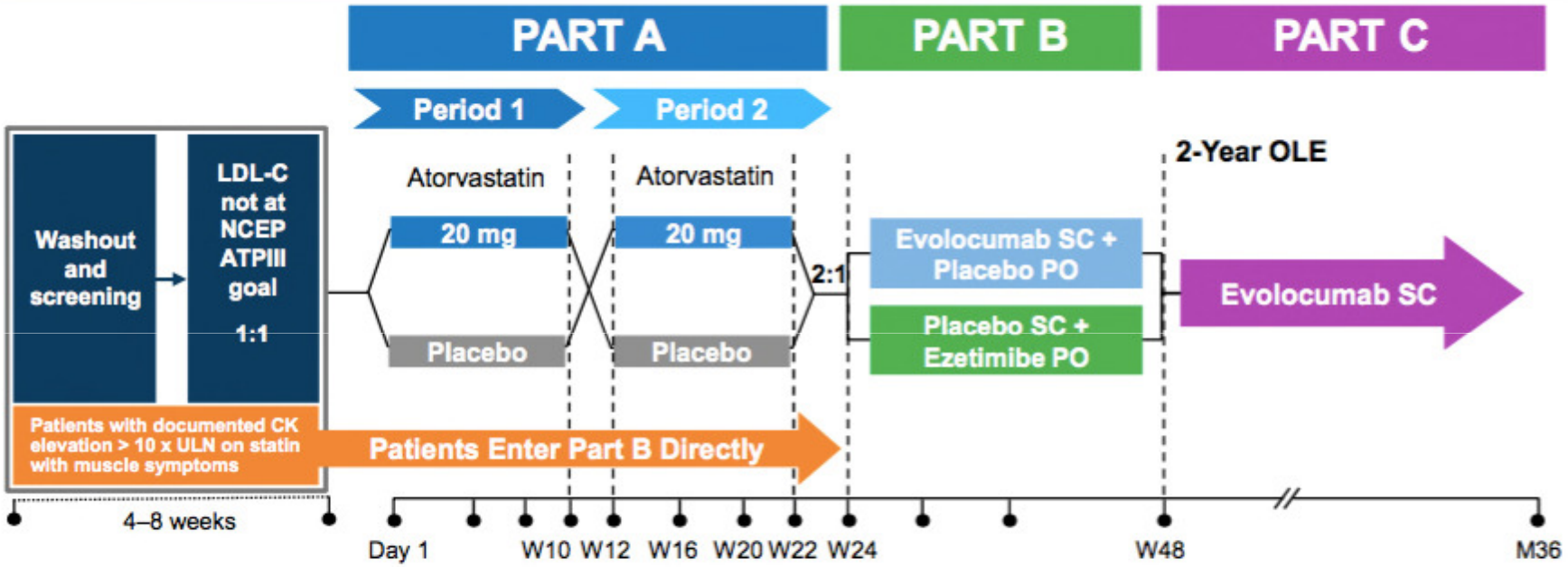
Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance
The GAUSS-3 Randomized Clinical Trial

Steven E. Nissen, MD; Erik Stroes, MD, PhD; Ricardo E. Dent-Acosta, MD; Robert S. Rosenson, MD; Sam J. Lehman, MBBS, PhD; Naveed Sattar, MD, PhD; David Preiss, MD; Eric Bruckert, MD; Richard Češka, MD; Norman Lepor, MD; Christie M. Ballantyne, MD; Ioanna Gouni-Berthold, MD; Mary Elliott, MS; Danielle M. Brennan, MS; Scott M. Wasserman, MD; Ransi Somaratne, MD, MBA; Rob Scott, MD; Evan A. Stein, MD, PhD; for the GAUSS-3 Investigators

JAMA. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608

ACC 2016

GAUSS-3: Study Design*



- **Co-primary endpoints:** Mean percent change from baseline in LDL-C at weeks 22 and 24; percent change from baseline in LDL-C at week 24[1,2]
- **Key co-secondary endpoints:**† Means at weeks 22 and 24 and at week 24 for change from baseline in LDL-C, LDL-C < 70 mg/dL (1.81 mmol/L), percent change from baseline in total cholesterol, non–HDL-C, ApoB, total cholesterol/HDL-C, ApoB/ApoA1[1,2]

GAUSS-3: Study Population

511 patients* aged ≥ 18 to ≤ 80 years

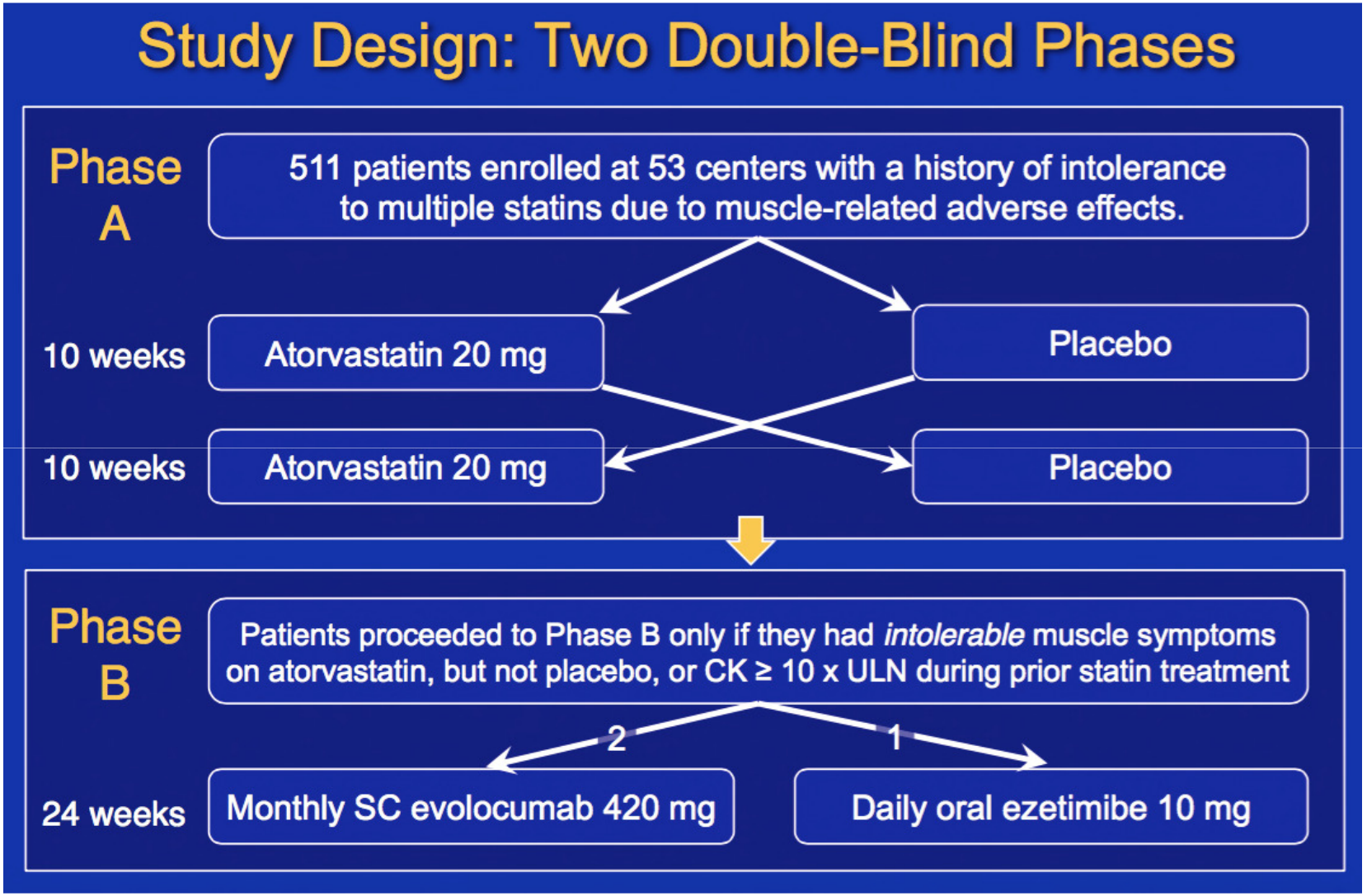
LDL-C above target level specified in the NCEP ATP III for appropriate CHD risk category

Patients with history of statin intolerance defined as:

- inability to tolerate atorvastatin 10 mg QD and any other statin at any dose OR
- inability to tolerate ≥ 3 statins† OR
- documented history of CK elevation >10 x ULN with muscle symptoms while on statins

*Only patients whose symptoms resolved or improved when statin dose was decreased or discontinued were randomized; †One of which must be at the lowest-approved starting average daily dose and two other statins at any dose. The lowest average starting dose was defined as 5 mg rosuvastatin, 10 mg simvastatin, 40 mg pravastatin, 20 mg lovastatin, 40 mg fluvastatin, or 2 mg pitavastatin

Study Design: Two Double-Blind Phases



Baseline Laboratory Values

Lipid parameters, mean (SD)	Phase A			Phase B		
	All Randomized (N = 491*)	Atorvastatin followed by PBO (N = 245*)	PBO followed by atorvastatin (N = 246)	Total qualifying for phase B (N = 218)	Randomized to Ezetimibe (N = 73)	Randomized to evolocumab (N = 145)
TC, mg/dL	300.5 (71.2)	300.0 (75.3)	301.0 (67.0)	307 (74.7)	308.0 (73.8)	306.5 (75.4)
LDL-C, mg/dL	212.3 (67.9)	212.0 (72.2)	212.7 (63.6)	219.9 (72.0)	221.9 (70.2)	218.8 (73.1)
HDL-C, mg/dL	50.9 (15.7)	51.0 (16.3)	50.9 (15.1)	49.8 (15.4)	50.2 (15.5)	49.7 (15.4)
Triglycerides, mg/dL†	170 (121.5, 231)	168.5 (115.5, 228.5)	172.8 (123.5, 231.5)	171.3 (127, 233)	162.5 (127, 231)	176.0 (128, 233.5)
Lp(a) nmol/L†	32.0 (15, 146)	33.5 (15, 156.5)	28.0 (14, 144)	31.0 (15, 156)	38.0 (18, 164)	29 (12.5, 152.5)
hsCRP, mg/L†	1.6 (0.8, 3.4)	1.4 (0.8, 2.8)	1.7 (0.9, 4.1)	1.7 (0.9, 3.6)	1.7 (0.9, 3.8)	1.7 (0.9, 3.6)

GAUSS-3 Summary

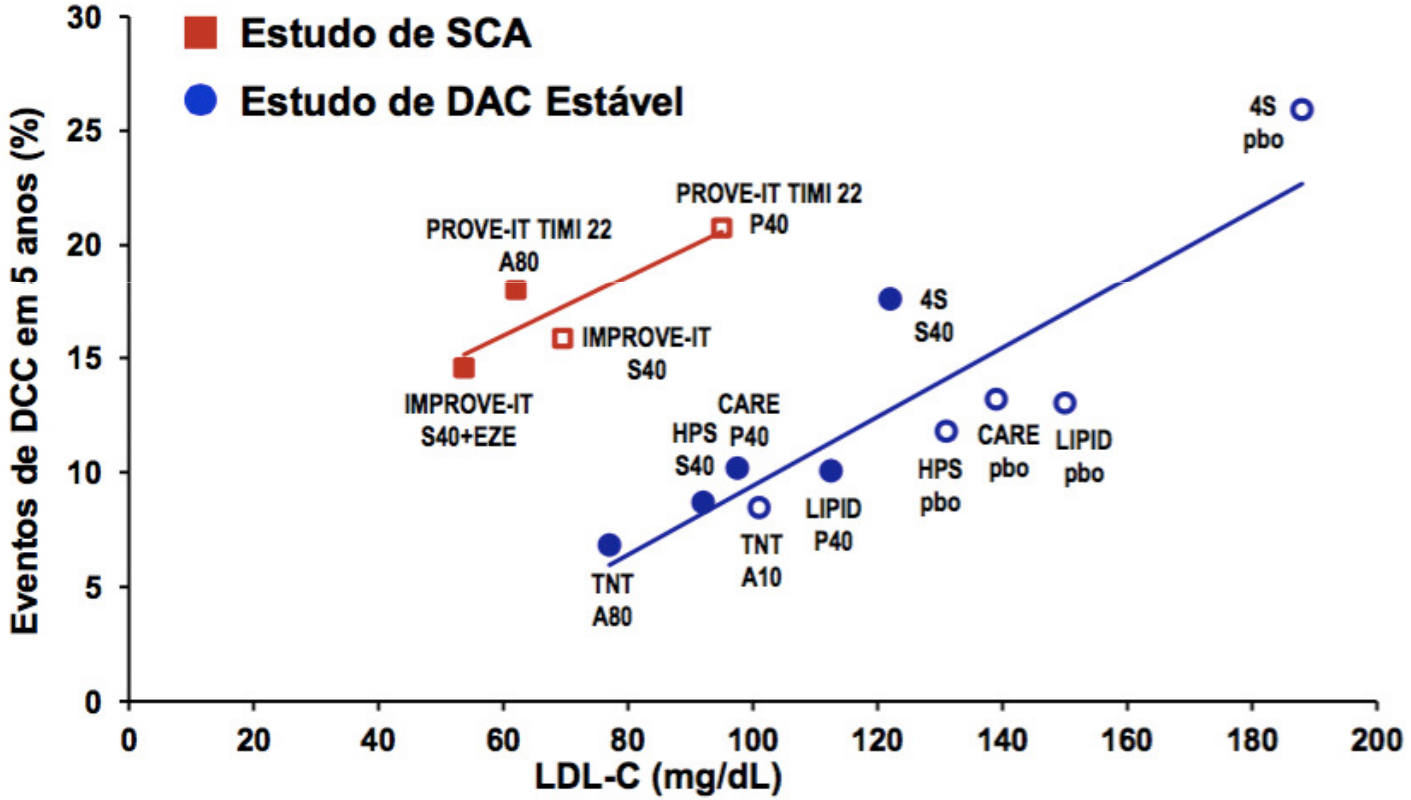
- In patients with statin-associated muscle symptoms, with symptoms during atorvastatin rechallenge, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C and other atherogenic lipoproetins after 24 weeks. Further studies are needed to assess long-term efficacy and safety of evolocumab for this indication.
- Both ezetimibe and evolocumab were well tolerated during the trial, with 5 ezetimibe patients (6.8%) and 1 evolocumab patient (0.7%) discontinuing active treatment due to muscle-related adverse events. However, 11 evolocumab-treated patients (7.6%) discontinued oral placebo for muscle symptoms.

GAUSS 3

Conclusions

- A substantial proportion (42.6%) of patients with a history of muscle-related statin intolerance have symptoms when re-challenged with atorvastatin 20 mg, but not placebo.
- A smaller fraction of patients (26.5%) report muscle-related symptoms when administered placebo, but not atorvastatin.
- In patients with statin-associated muscle symptoms, evolocumab, compared with ezetimibe, produced significantly larger reductions in LDL-C and other atherogenic lipoproteins.

Dados de estudo clínico suportam a obtenção de níveis menores de LDL-C, independentemente do LDL-C basal



[Para converter, 100 mg/dL=2,59 mmol/L].

Lipid Lowering Efficacy of Bococizumab Among 4,449 High Risk Patients

The SPIRE Lipid Lowering Trials

Safety and Cardiovascular Efficacy of Bococizumab Among 27,438 High Risk Patients

The SPIRE 1 and SPIRE 2 Cardiovascular Outcome Trials

SPIRE

Lipid Lowering Efficacy of Bococizumab Among 4,449 High Risk Patients

The SPIRE Lipid Lowering Trials

Safety and Cardiovascular Efficacy of Bococizumab Among 27,438 High Risk Patients

The SPIRE 1 and SPIRE 2 Cardiovascular Outcome Trials

Paul M Ridker, MD, MPH

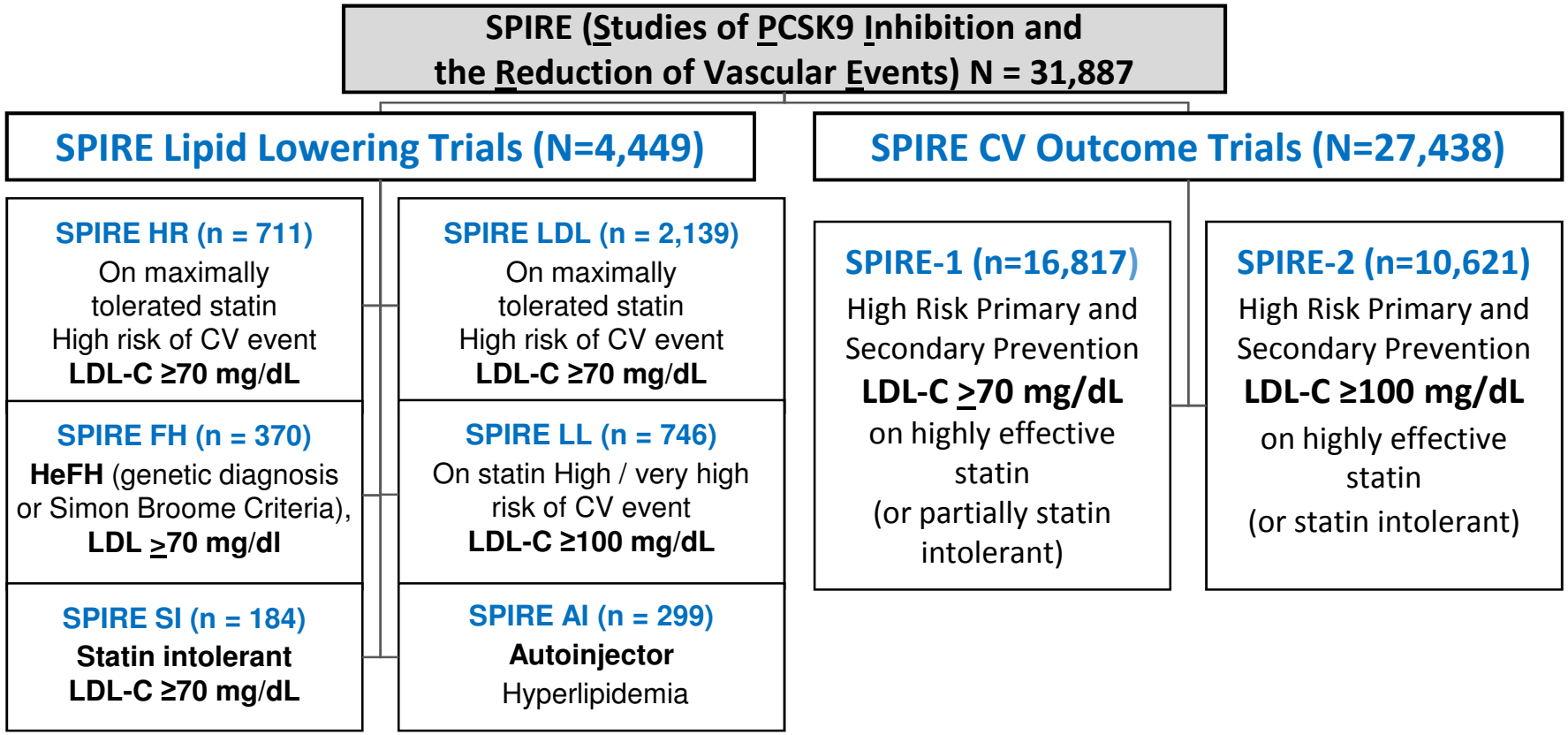
Brigham and Women's Hospital, Boston MA

Studies of **P**CSK9 **I**nhibition and the **R**eduction in vascular **E**vents (SPIRE)

Bococizumab Development Program

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

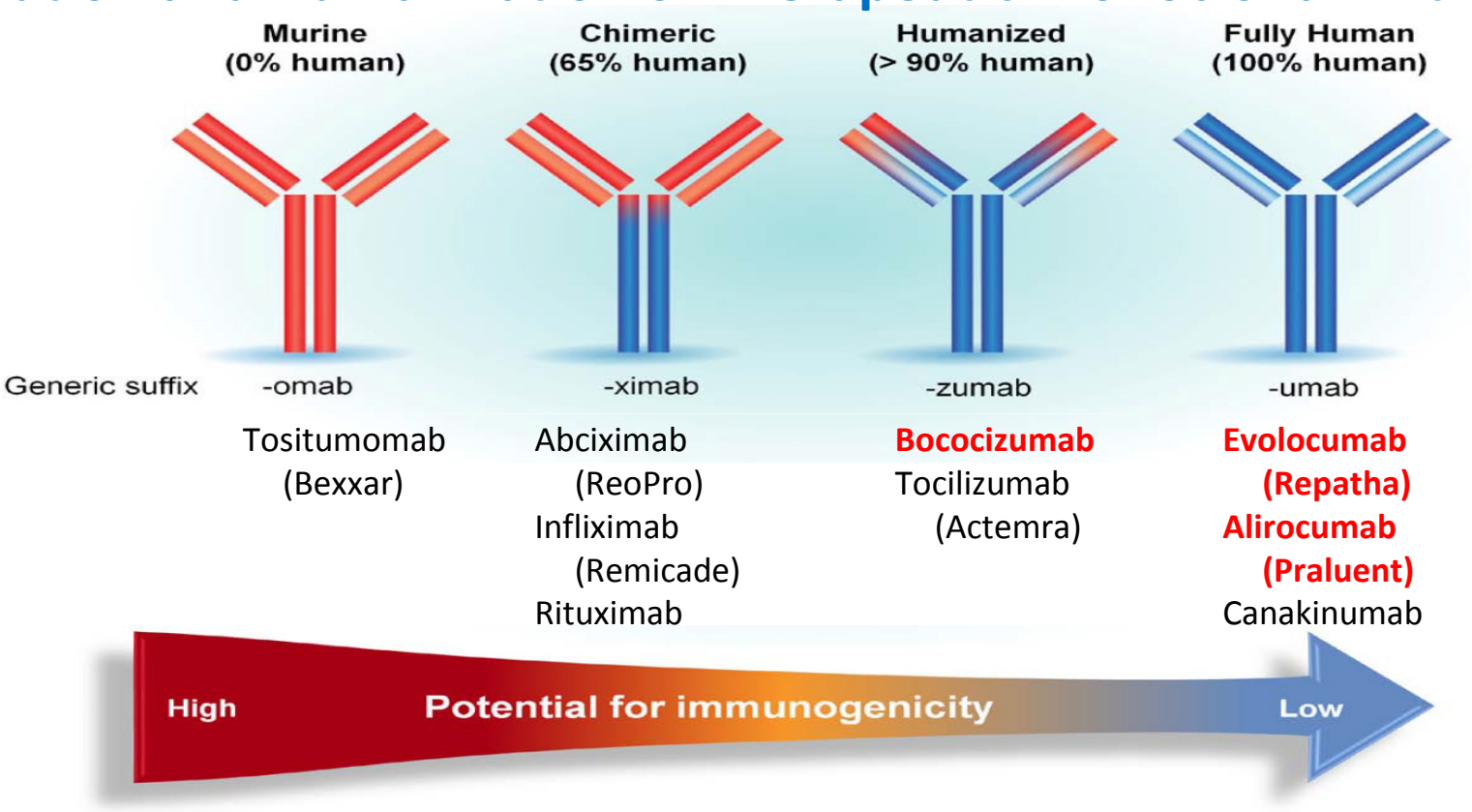
The SPIRE Bococizumab Clinical Development Program



Ridker et al, Am Heart J 2016;178:135-144

Ridker ACC 2017

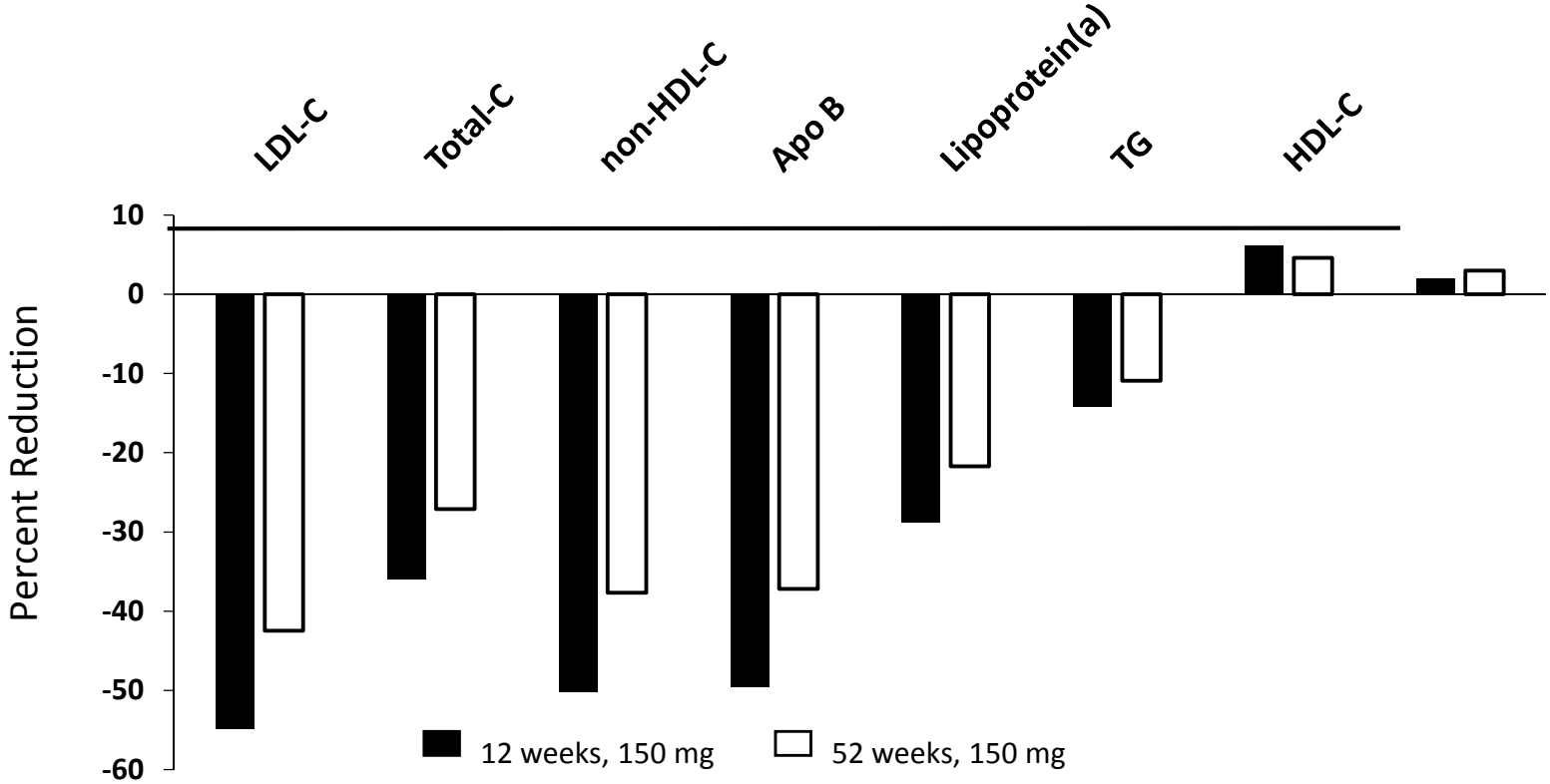
Evolution and Humanization of Therapeutic Monoclonal Antibodies



Adapted from Foltz IN, Karow M, Wasserman SM. Circulation 2013; 127:2222-2230.

The SPIRE Bococizumab Lipid Lowering Trials :

Unanticipated Attenuation of Efficacy for All Lipid Parameters at 52 weeks



Ridker ACC 2017

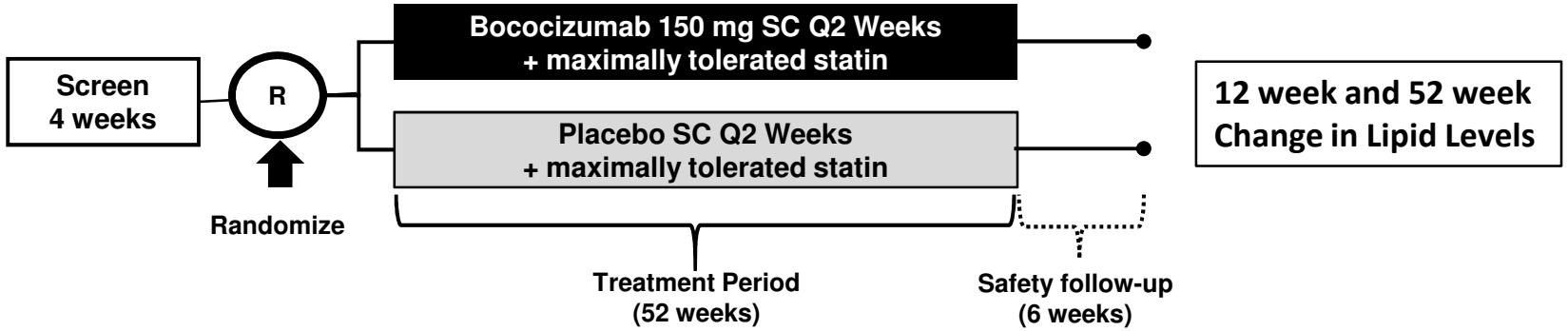
Impact of the SPIRE Lipid Lowering Trials on the SPIRE-1 and SPIRE-2 Cardiovascular Outcomes Trials

On the basis of the completed SPIRE Lipid Lowering trials, the sponsor elected on November 1, 2016 to discontinue further development of bococizumab.

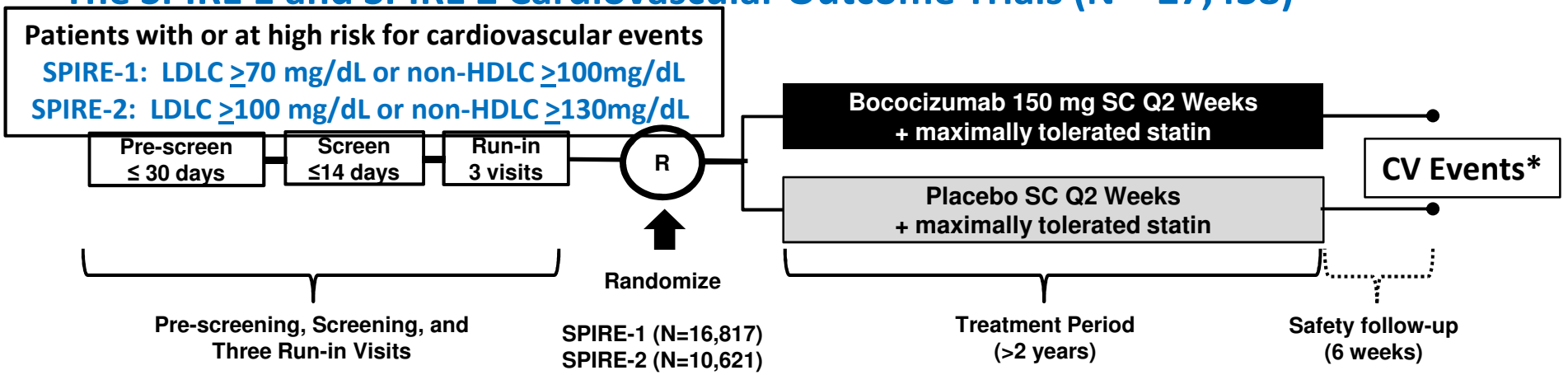
As a consequence of the data in the SPIRE Lipid Lowering trials, the sponsor elected to prematurely stop the ongoing SPIRE-1 and SPIRE-2 outcome trials which had, at that time, randomized 27,438 patients worldwide.

That decision was made with no knowledge by the sponsor or the investigators of any unblinded data within the SPIRE-1 or SPIRE-2 trials.

The Six SPIRE Lipid Lowering Trials (N=4,449)



The SPIRE 1 and SPIRE 2 Cardiovascular Outcome Trials (N = 27,438)



*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

Ridker ACC 2017

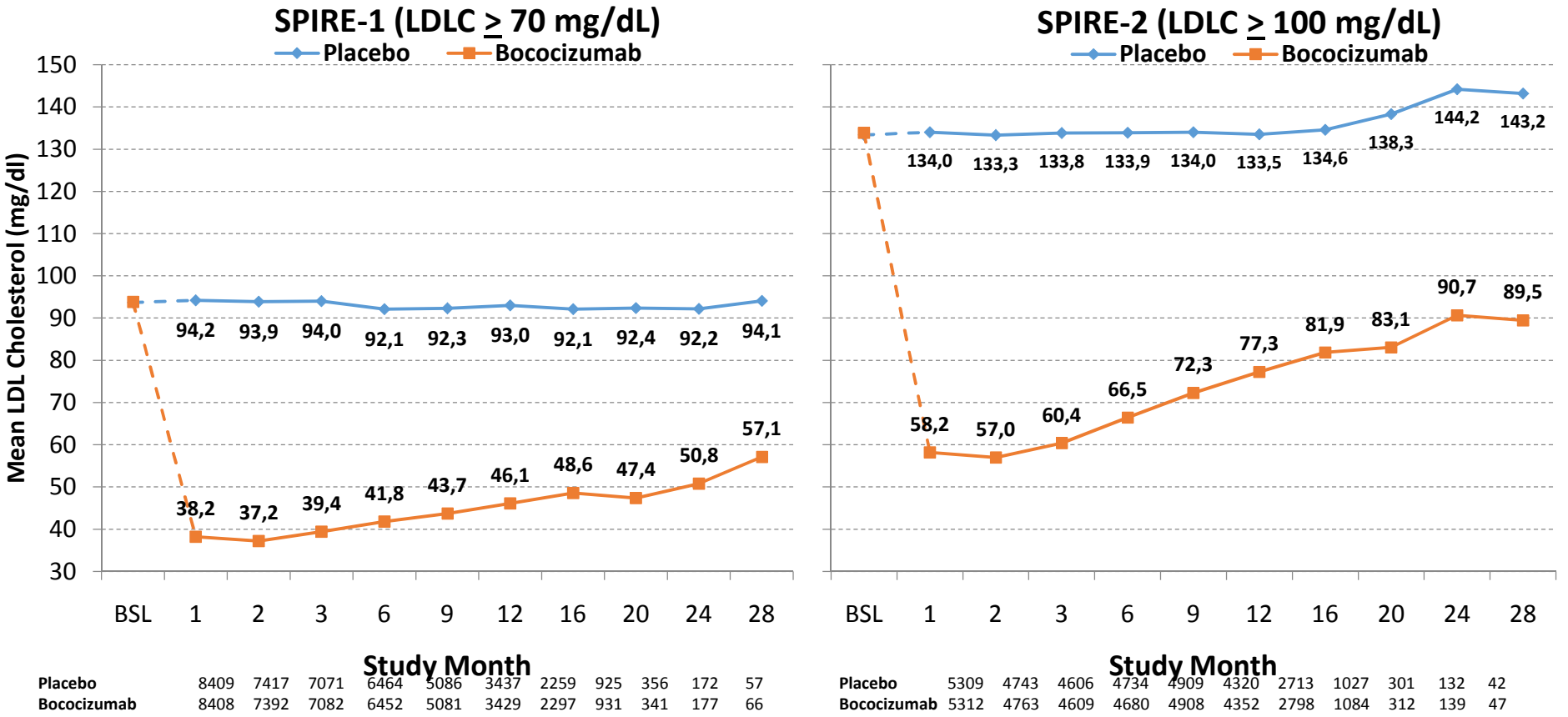
The SPIRE-1 and SPIRE-2 Cardiovascular Outcomes Trials: Baseline Clinical Characteristics

Characteristic	SPIRE-1 Bococizumab (N=8408)	SPIRE-1 Placebo (N=8409)	SPIRE-2 Bococizumab (N=5212)	SPIRE-2 Placebo (N=5309)
Age (years)	63.3	63.3	62.2	62.6
Female (%)	26.3	26.5	34.1	35.1
Diabetes (%)	48.3	47.4	47.8	46.1
Smokers (%)	22.8	23.0	27.7	26.6
FH (%)	1.7	1.8	7.0	7.6
Statin Use (%)	99.1	99.2	83.2	83.1
Primary Prevention (%)	13.0	13.8	18.9	18.5
LDLC (mg/dL)	94	94	134	133
Apo B (mg/dL)	80	80	106	106
TG (mg/dL)	124	125	157	154
Lp(a) (mg/dL)	19	19	19	20
hsCRP (mg/L)	1.8	1.7	2.3	2.3
Absolute risk (MACE+)*	3.02 per 100 person-years		4.19 per 100 person-years	

* Placebo group event rate

Ridker ACC 2017

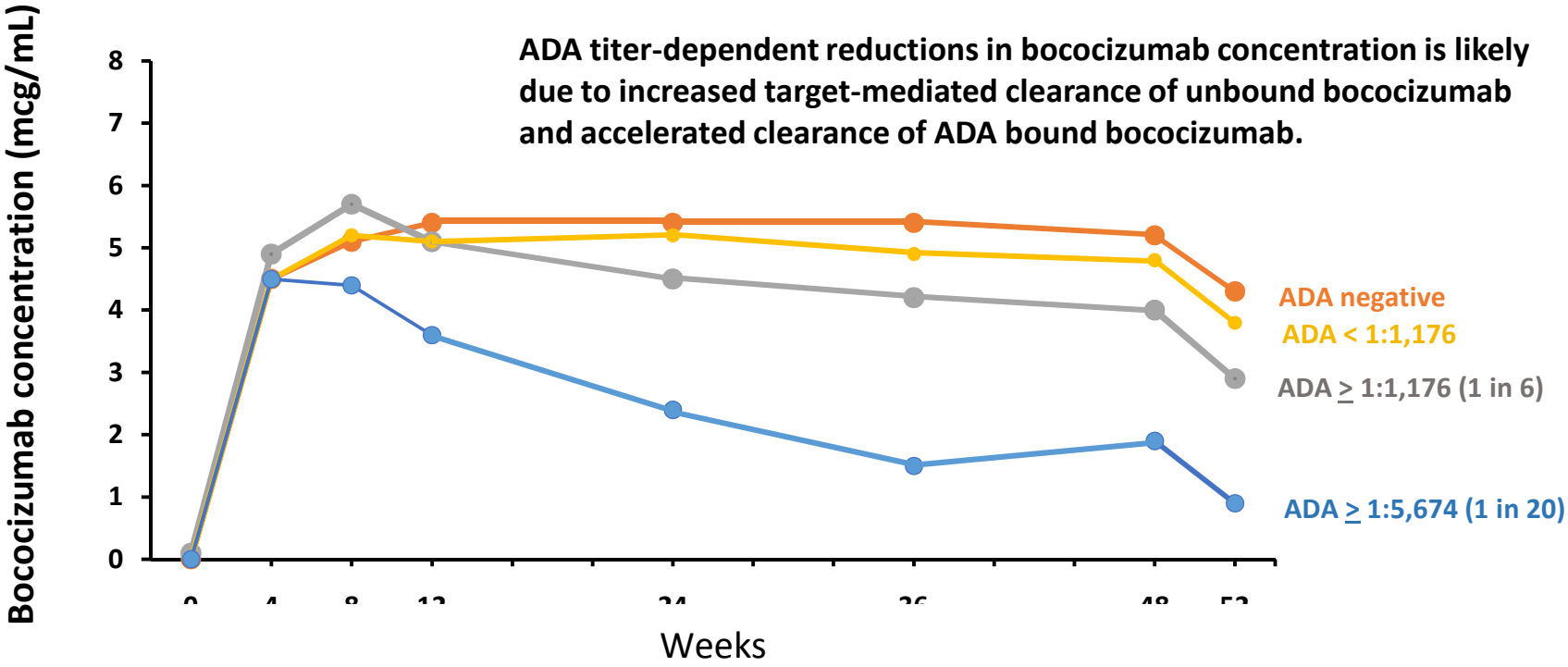
The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Confirmation of Attenuation in LDLC Reduction Over Time



Ridker ACC 2017

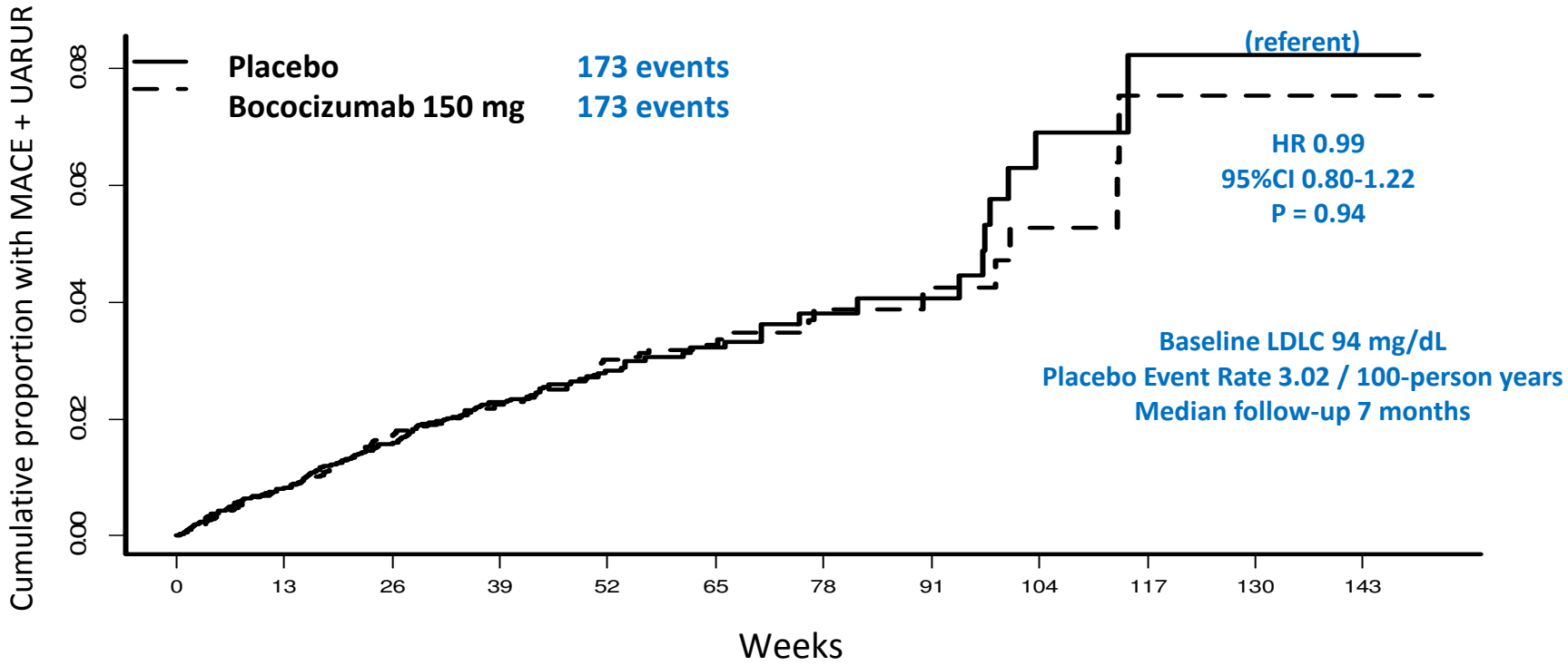
The SPIRE Bococizumab Lipid Lowering Trials :

Impact of Antidrug Antibodies (ADAs) on Plasma Bococizumab Concentration Over Time



Ridker ACC 2017

The SPIRE-1 Cardiovascular Outcomes Trial: Baseline LDLC ≥ 70 mg/dL Primary Pre-Specified Endpoint*

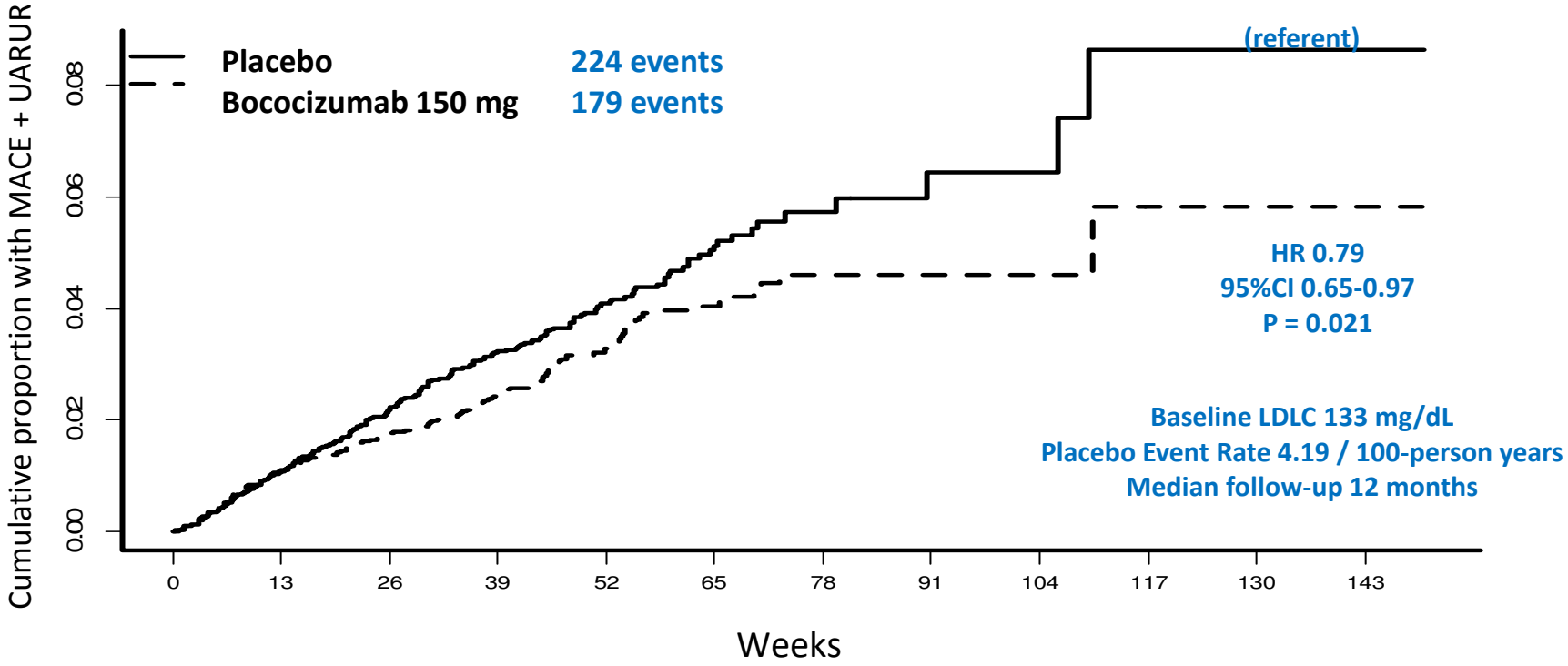


*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

Ridker ACC 2017

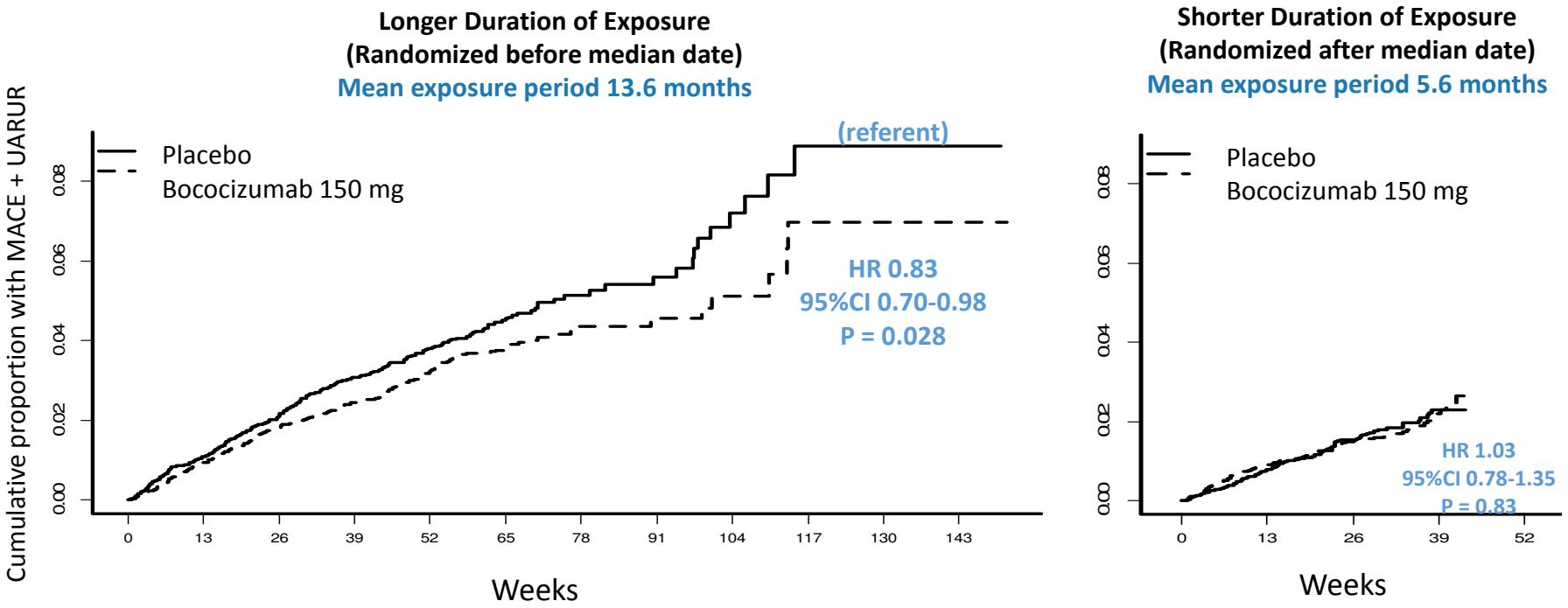
The SPIRE-2 Cardiovascular Outcomes Trial: Baseline LDLC ≥ 100 mg/dL Primary Pre-Specified Endpoint*



*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Combined Trials Primary Endpoint*, Stratified By Duration of Exposure



*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

Ridker ACC 2017

Conclusions:

The SPIRE Lipid Lowering Trials and the SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials

1. PCSK9 inhibition with bococizumab reduces LDLC by 55 to 60% when given as an adjunct to statin therapy, but this effect is significantly attenuated over time in 10 to 15% of patients due to the development of anti-drug antibodies. This effect is specific to bococizumab (a humanized monoclonal antibody) and has not been seen with either evolocumab or alirocumab (fully human monoclonal antibodies). This immunogenicity also explains the higher rate of injection site reactions observed with bococizumab.

2. Bococizumab is also associated with wide individual variability in LDLC response even among those who do not develop anti-drug antibodies. This suggests that on-treatment measures of LDLC will be important for clinical practice. Whether similar individual variability in LDLC response is present for evolocumab and alirocumab is uncertain.

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

Conclusões:

The SPIRE Lipid Lowering Trials and the SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials

1. Inibidor do PCSK9 bococizumab reduz LDLC em 55 a 60% quando usado associado a terapia com estatina, mas este efeito é significantemente atenuado ao longo do tempo em 10 a 15% dos pacientes devido ao desenvolvimento de anticorpos anti-droga. Este efeito é específico com o bococizumab (anticorpo monoclonal humanizado) e não tem sido observado com evolocumab or alirocumab (anticorpo monoclonal totalmente humano). Esta imunogenicidade também explica a alta taxa de reações no sítio de injeção observado com bococizumab.

2. Bococizumab foi também associado com variabilidade individual de resposta no LDLC mesmo naqueles pacientes que não desenvolveram anticorpos anti-droga. Isto sugere que dosagem do LDLC nos pacientes em tratamento, serão importantes na prática clínica.

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

Conclusions:

The SPIRE Lipid Lowering Trials and the SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials

3. Despite anti-drug antibody production, variation in individual response, and early trial termination, bococizumab significantly reduced cardiovascular event rates in the higher-risk SPIRE-2 trial of those with LDLC ≥100 mg/dL, but not in the lower-risk SPIRE-1 trial of those with LDLC ≥70 mg/dL.

4. Consistent with the hypothesis that "lower is better for longer", clinical benefits were greater and statistically significant in analyses of those who achieved and sustained greater absolute as well as relative reductions in LDLC. These data thus support the use of PCSK9 inhibitors in selected patients as an adjunct to aggressive statin therapy.

N Engl J Med 2017; 376:1527-1539April 20, 2017DOI: 10.1056/NEJMoa1701488

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial

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Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Background

- **Intravascular ultrasound (IVUS) trials have studied the effect of statins on coronary atherosclerosis and demonstrated a linear relationship between achieved LDL-C levels and reduction in atheroma burden.**
- **Monoclonal antibodies against PCSK9 lower LDL-C when administered alone or in combination with statins. Initial studies have demonstrated the feasibility of using the combination of statins and PCSK9 inhibitors to achieve much lower LDL-C levels than previously studied.**
- **No trials to date have explored whether LDL-C lowering beyond that achievable with statins with a PCSK9 inhibitor results in incremental benefits on coronary artery disease compared with statins alone.**
- **The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial was designed to assess whether PCSK9 inhibition reduces progression of atherosclerosis as measured by IVUS.**

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

GLAGOV: Objective

Objective

- **To test the hypothesis that LDL-C lowering with a monthly subcutaneous injection of evolocumab 420 mg for 78 weeks will result in a significantly greater change from baseline in percentage atheroma volume (PAV) compared with placebo in subjects taking background statin therapy**

Design

- **A 78-week, randomized, double-blind, placebo-controlled, multicenter, phase 3 study.**

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

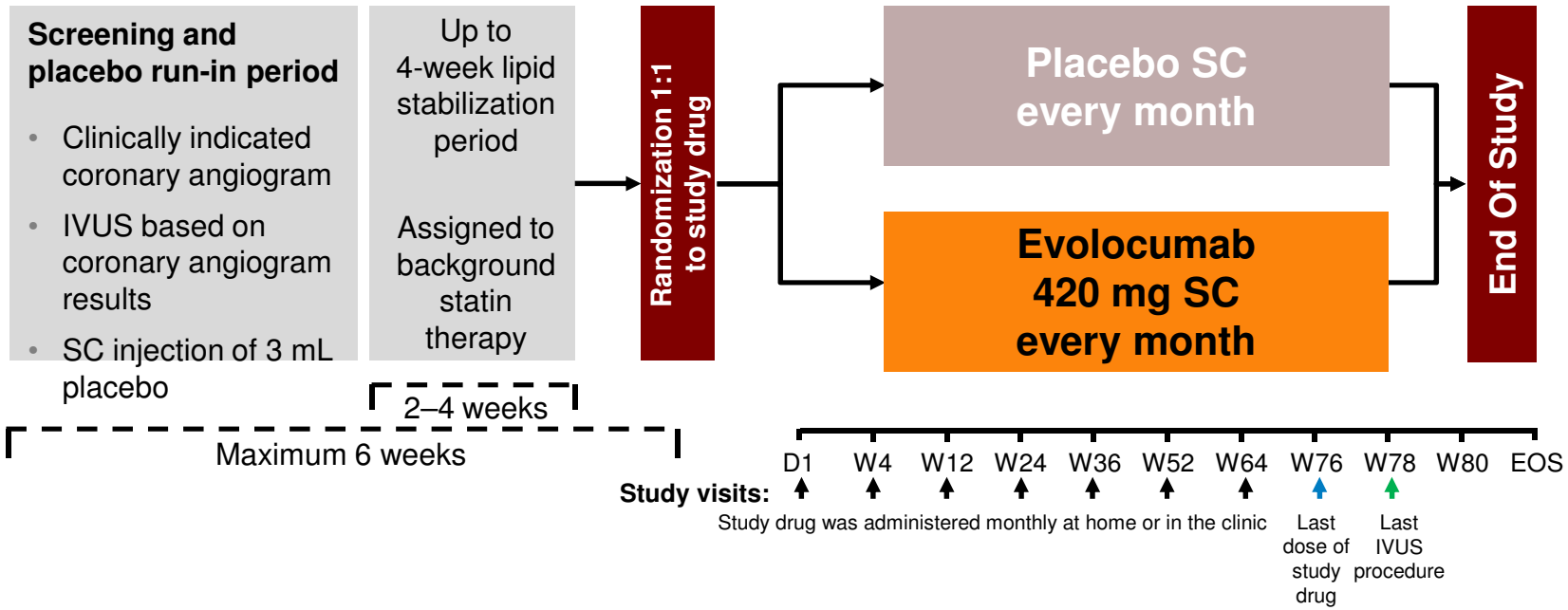
GLAGOV: Key Inclusion Criteria

- **Men or women aged □ 18 years**
- **Clinically indicated coronary angiogram, evidence of coronary disease**
- **LDL-C criteria met within 4 weeks of screening visit or, if applicable, at the end of lipid-stabilization period:**
  - LDL-C ≥ 80 mg/dL, **OR**
  - LDL-C ≥ 60 but < 80 mg/dL in the presence of risk factors as shown in the table below:

Major Risk Factors (One Required)	• Non-coronary atherosclerotic vascular disease • Documented myocardial infarction or hospitalization for unstable angina within the last 2 years • Documented type 2 diabetes mellitus
OR	
Minor Risk Factors (Three Required)	• Age (men ≥ 50 years; women ≥ 55 years) • Hypertension (BP ≥ 140/90 mmHg or current use of antihypertensive medications) • Low HDL-C (men: < 40 mg/dL; women < 50 mg/dL) • Family history of premature coronary heart disease (first-degree male relative < 55 years of age or first-degree female relative < 65 years of age) • hs-CRP ≥ 2 mg/L • Cigarette smoking (current)

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

GLAGOV: Study Design



*Nominal change refers to the actual number, as opposed to percent change
D = day; IVUS = intravascular ultrasound; SC = subcutaneously; W = week.
Puri R, et al. *Am Heart J.* 2016;176:83-92.

GLAGOV: Study Endpoints

Endpoint	Description
Primary[1,2]	• Nominal change* in PAV from baseline to week 78, as determined by IVUS
Secondary[1,2]	• Nominal change* in TAV from baseline to week 78, as determined by IVUS • Proportion of patients demonstrating any reduction of PAV from baseline† • Proportion of patients demonstrating any reduction of TAV from baseline†
Exploratory[2]	• Incidence of adjudicated events (all-cause mortality, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure) • Change in lipid parameters

*Nominal change refers to the actual number, as opposed to percent change
†Proportion/percentage of subjects with regression is a group level summary statistics rather than a subject level endpoint
IVUS = intravascular ultrasound; PAV = percentage atheroma volume; TAV = total atheroma volume
1. Puri R, et al. *Am Heart J*. 2016;176:83-92. 2. Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951

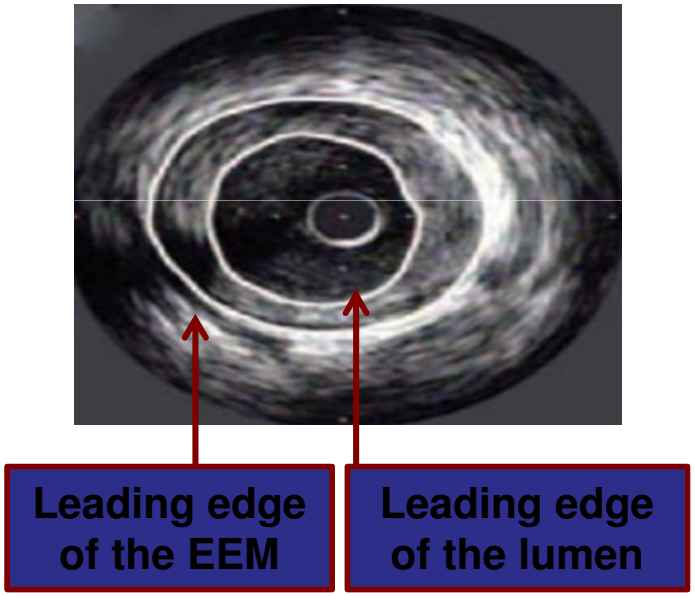
GLAGOV: Analysis of IVUS Imaging

- Plaque area is calculated as the area between the two leading edges
- Two measures of atheroma burden will be calculated for each patient
  - PAV is calculated as the proportion of the EEM volume occupied by atherosclerotic plaque

$$PAV = \frac{\Sigma(EEM_{area} - lumen_{area})}{\Sigma(EEM_{area})} \times 100$$

  - TAV is calculated as the summation of plaque areas in each measured cross-sectional image within the segment and subsequently normalized by the median number of images analyzed in the entire cohort to account for heterogeneity in segment length between subjects

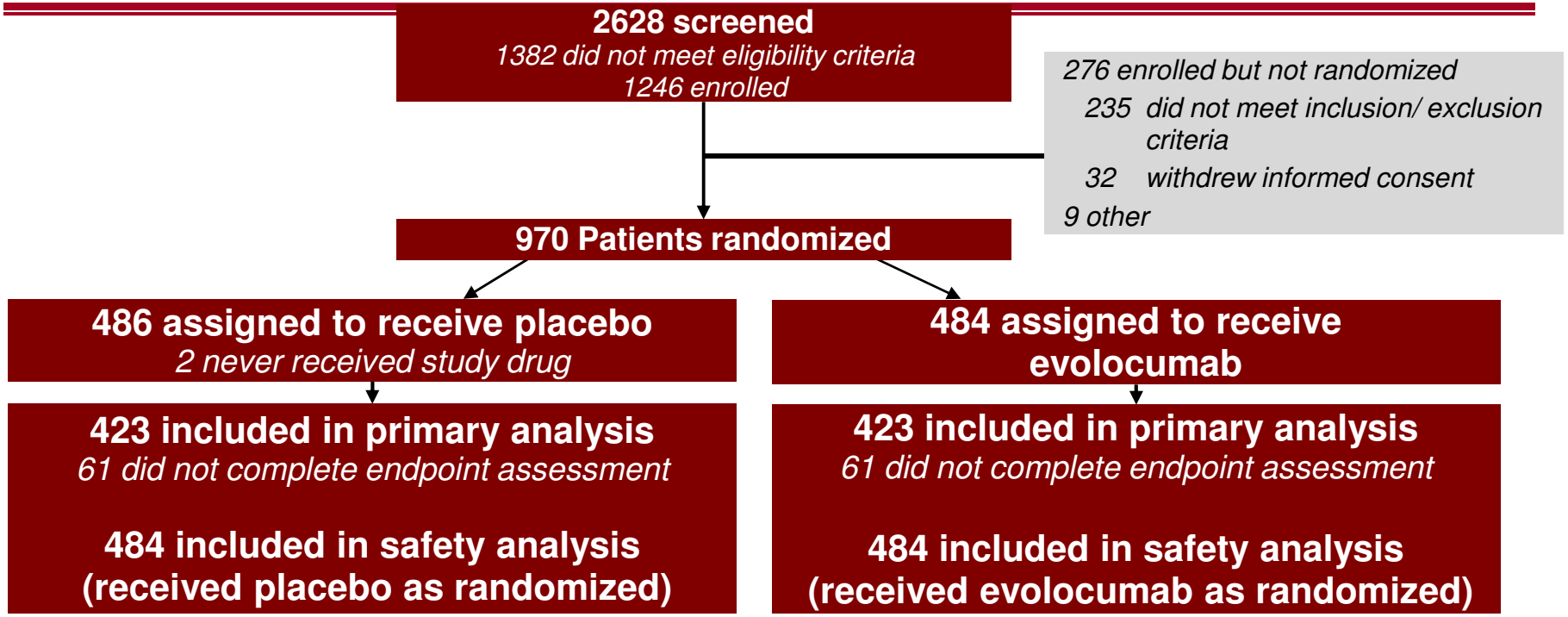
$$TAV_{normalized} = \frac{\Sigma(EEM_{area} - lumen_{area})}{\text{Number of images in pullback}} \times \text{Median number of images in cohort}$$



IVUS = intravascular ultrasound; EEM = external elastic membrane; PAV = percentage atheroma volume; TAV = total

Puri R, et al. *Am Heart J.* 2016;176:83-92.
Nicholls SJ, et al. *JAMA.* [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951

GLAGOV: Disposition of Patients During the Study



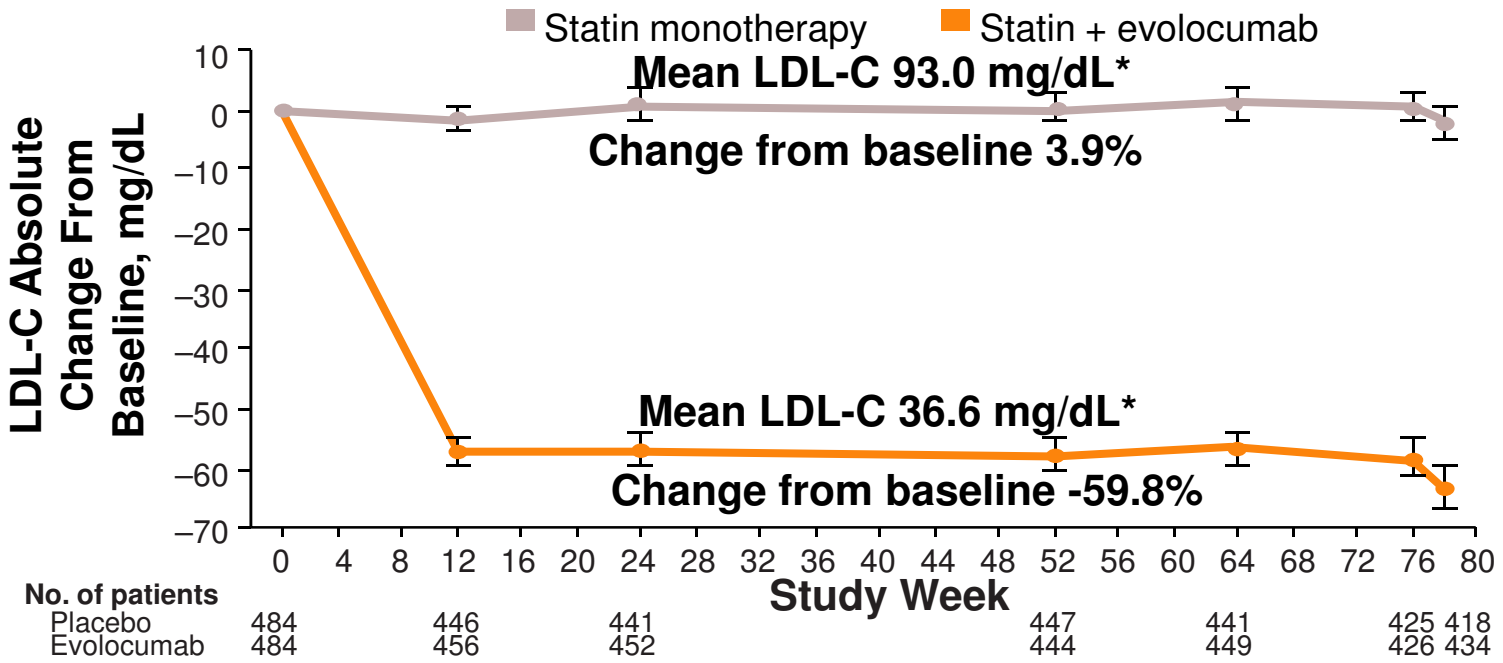
Adapted from: Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

GLAGOV: Baseline Characteristics of Randomized Patients

Parameter*	Placebo (N = 484)	Evolocumab (N = 484)
Age, years	59.8±8.8	59.8±9.6
Men, n (%)	350 (72.3)	349 (72.1)
White, n (%)	452 (93.4)	456 (94.2)
BMI	29.5±5.0	29.4±5.0
Hypertension, n (%)	405 (83.7)	398 (82.2)
Previous PCI, n (%)	188 (38.8)	189 (39.0)
Previous MI, n (%)	171 (35.3)	169 (34.9)
Smoking, n (%)	113 (23.3)	124 (25.6)
Diabetes, n (%)	104 (21.5)	98 (20.2)
Baseline statin use,* n (%)	476 (98.3)	478 (98.8)
High intensity, n (%)	290 (59.9)	280 (57.9)
Moderate intensity, n (%)	185 (38.2)	196 (40.5)
Low intensity, n (%)	1 (0.2)	2 (0.4)
Baseline ezetimibe use,* n (%)	9 (2.1)	9 (2.1)
Baseline medications		
Anti-platelet therapy, n (%)	465 (96.1)	454 (93.8)
Beta-blocker, n (%)	370 (76.4)	362 (74.8)
ACE inhibitor, n (%)	264 (54.5)	260 (53.7)
ARB, n (%)	92 (19.0)	87 (18.0)

Age and BMI expressed as mean ± standard deviation. *Baseline statin and ezetimibe use is defined as subject treated with statin or ezetimibe therapy at the end of the lipid stabilization period at randomization. †High intensity statin as defined by ACC/AHA criteria

Mean Absolute Change in LDL-C

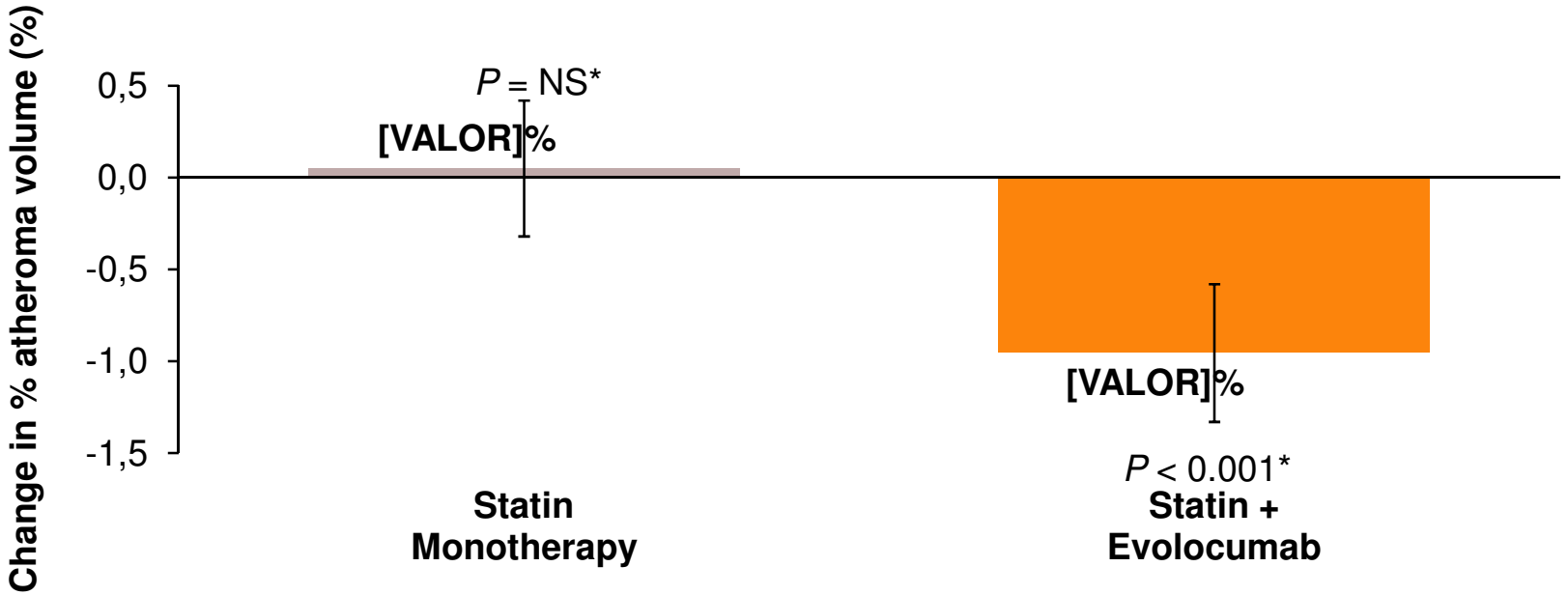


Absolute change for evolocumab-statin group: -56.3 (-59.4 to -53.1); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation.

Primary Endpoint: Nominal Change in PAV From Baseline to Week 78



Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001

Data shown are least-squares mean (95% CI). PAV = Percent Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Clinical and Biochemical Adverse Events in the Safety Population*

Parameter	Placebo (N = 484)	Evolocumab (N = 484)
Clinically important adverse events, n (%)		
Injection site reactions	0 (0)	2 (0.4)
Myalgia	28 (5.8)	34 (7.0)
Neurocognitive events[a]	6 (1.2)	7 (1.4)
New diagnosis of diabetes mellitus†	18 (3.7)	17 (3.6)
Abnormality in laboratory value, n (%)‡		
Aspartate or alanine aminotransferase >3xULN	2 (0.5)	2 (0.5)
Total bilirubin >2xULN	2 (0.5)	1 (0.3)
Creatine phosphokinase >5xULN	3 (0.7)	3 (0.7)
Creatinine >ULN	5 (1.0)	3 (0.6)
Anti-Evolocumab binding antibody	NA	1 (0.2)
Anti-Evolocumab neutralizing antibody	NA	0 (0)

*All patients who received at least one dose of study drug were included in the safety analyses (n = 968)

†Neurocognitive events and new diagnosis diabetes mellitus as reported by investigators as adverse events. ‡The denominator for both placebo and evolocumab with normal value at baseline in 958. There were a total of 10 patients with missing safety laboratory data, clinical and laboratory adverse events, and reasons for discontinuation in the safety population.

NA = Not Available; ULN = Upper Limit of Normal

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Reasons for Discontinuation*

Discontinuation from Treatment – n	Placebo (N = 484)	Evolocumab (N = 484)
Number of patients	35	38
Reason for discontinuation		
Preference of patient	19	12
Adverse Event	11	18
Lost to follow-up	2	3
Death	0	1
Physician decision	1	1
Other	2	3

*All patients who received at least one dose of study drug were included in the safety analyses (n=968)
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Adjudicated Cardiovascular Events in the Safety Population*

Parameter	Placebo (N = 484)	Evolocumab (N = 484)
Cardiovascular events, n (%)†		
Death	4 (0.8)	3 (0.6)
Non-fatal myocardial infarction	14 (2.9)	10 (2.1)
Non-fatal stroke	3 (0.6)	2 (0.4)
Hospitalization for unstable angina	4 (0.8)	3 (0.6)
Coronary revascularization	66 (13.6)	50 (10.3)
First major adverse cardiovascular event	74 (15.3)	59 (12.2)

*All patients who received at least one dose of study drug were included in the safety analyses (n=968)
†Total number of cardiovascular events included 2 events occurring during the period between the last scheduled visit and the end of the safety assessment period.
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

GLAGOV Summary

- **In statin-treated patients with symptomatic coronary disease, addition of evolocumab, 420 mg monthly for 18 months:**
  - Achieved LDL-C levels averaging 36.6 mg/dL compared with 93 mg/dL for a statin alone.
  - Produced regression, mean change in PAV of -0.95% for evolocumab-statin treated group, compared with statin only patients, whose mean change in PAV was +0.05% ($P < 0.001$).
  - Produced regression (change in PAV <0) in a greater percentage of patients; 64% for evolocumab-statin treated patients vs. 47% in statin only patients ($P < 0.001$).
- **No new safety signals were observed**
- **Further studies assessing the effects of PCSK9 inhibition on clinical outcomes are pending.**

PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

FOURIER

Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session

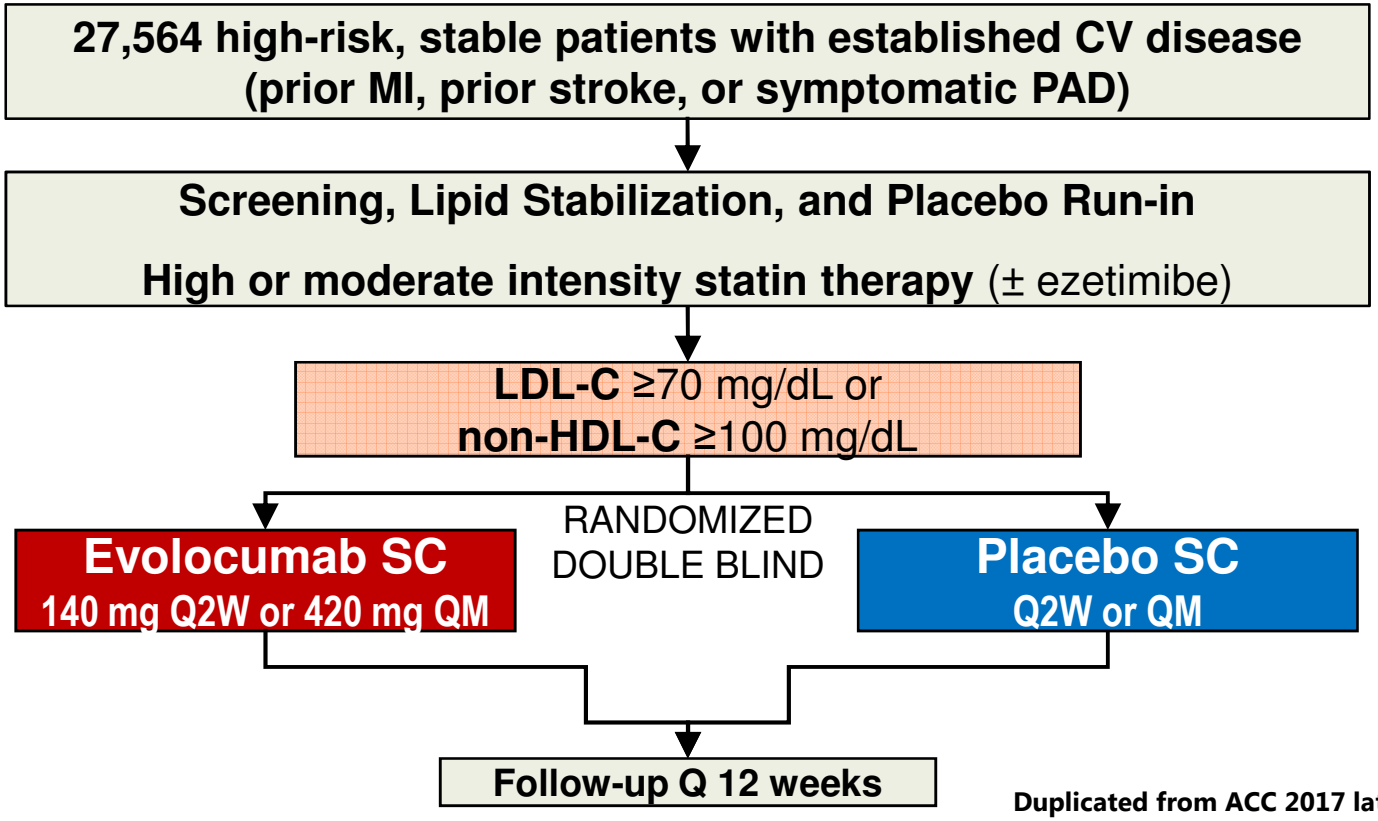
Late-Breaking Clinical Trial

March 17, 2017

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

Duplicated from ACC 2017 late-breaking session

Trial Design



Duplicated from ACC 2017 late-breaking session

Sabatine MS et al. *Am Heart J* 2016;173:94-101

Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**63 (9)**
Male sex (%)	**75**
Type of cardiovascular disease (%)	
Myocardial infarction	**81**
Stroke (non-hemorrhagic)	**19**
Symptomatic PAD	**13**
Cardiovascular risk factor (%)	
Hypertension	**80**
Diabetes mellitus	**37**
Current cigarette use	**28**

Median time from most recent event ~3 yrs

Duplicated from ACC 2017 late-breaking session

Pooled data; no differences between treatment arms

Lipid Lowering Therapy & Lipid Levels at Baseline

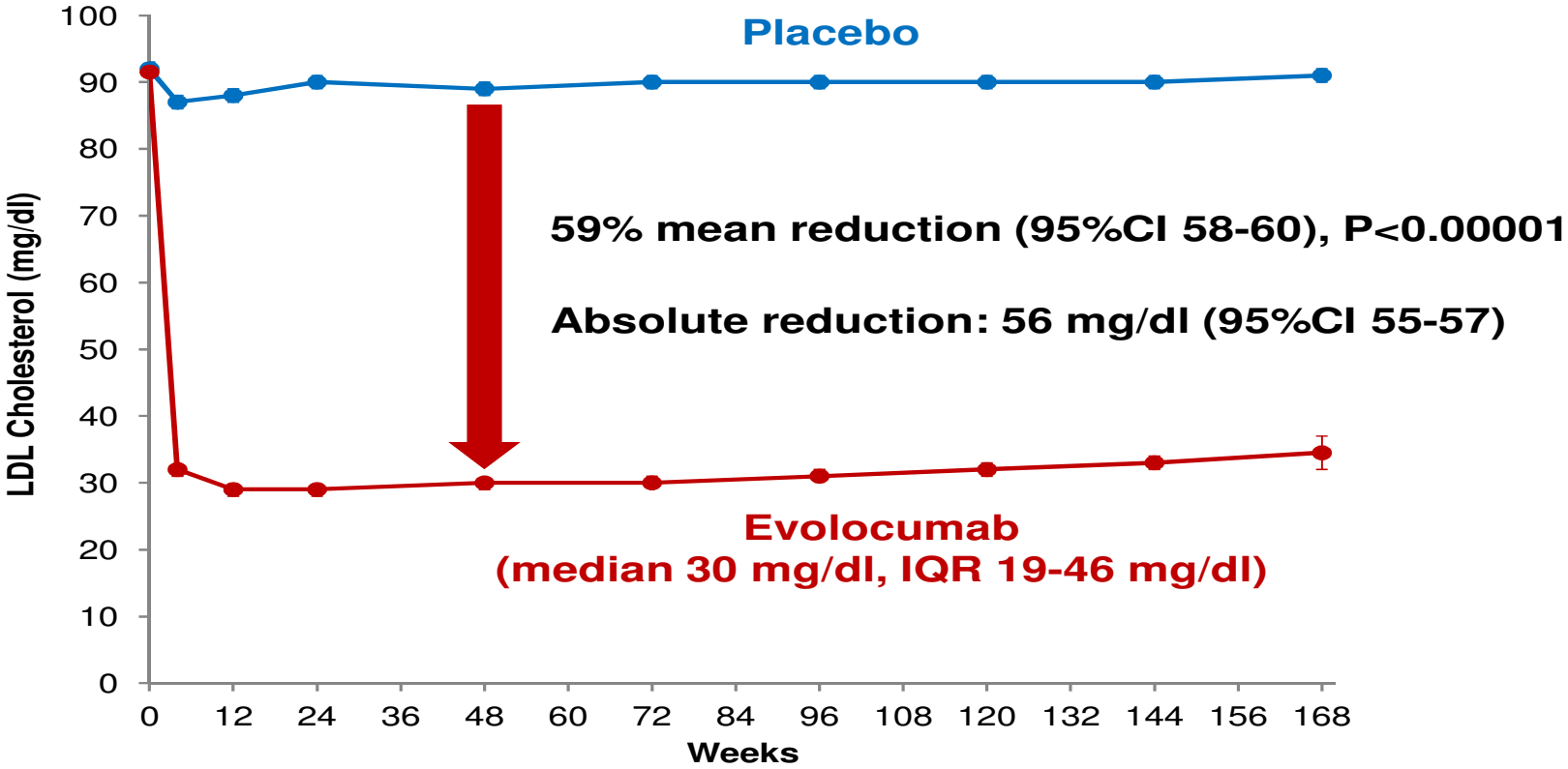
Characteristic	Value
Statin use (%)*	
High-intensity	**69**
Moderate-intensity	**30**
Ezetimibe use (%)	**5**
Median lipid measures (IQR) – mg/dL	
LDL-C	**92 (80-109)**
Total cholesterol	**168 (151-189)**
HDL-C	**44 (37-53)**
Triglycerides	**133 (100-182)**

*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Duplicated from ACC 2017 late-breaking session

Pooled data; no differences between treatment arms

LDL Cholesterol



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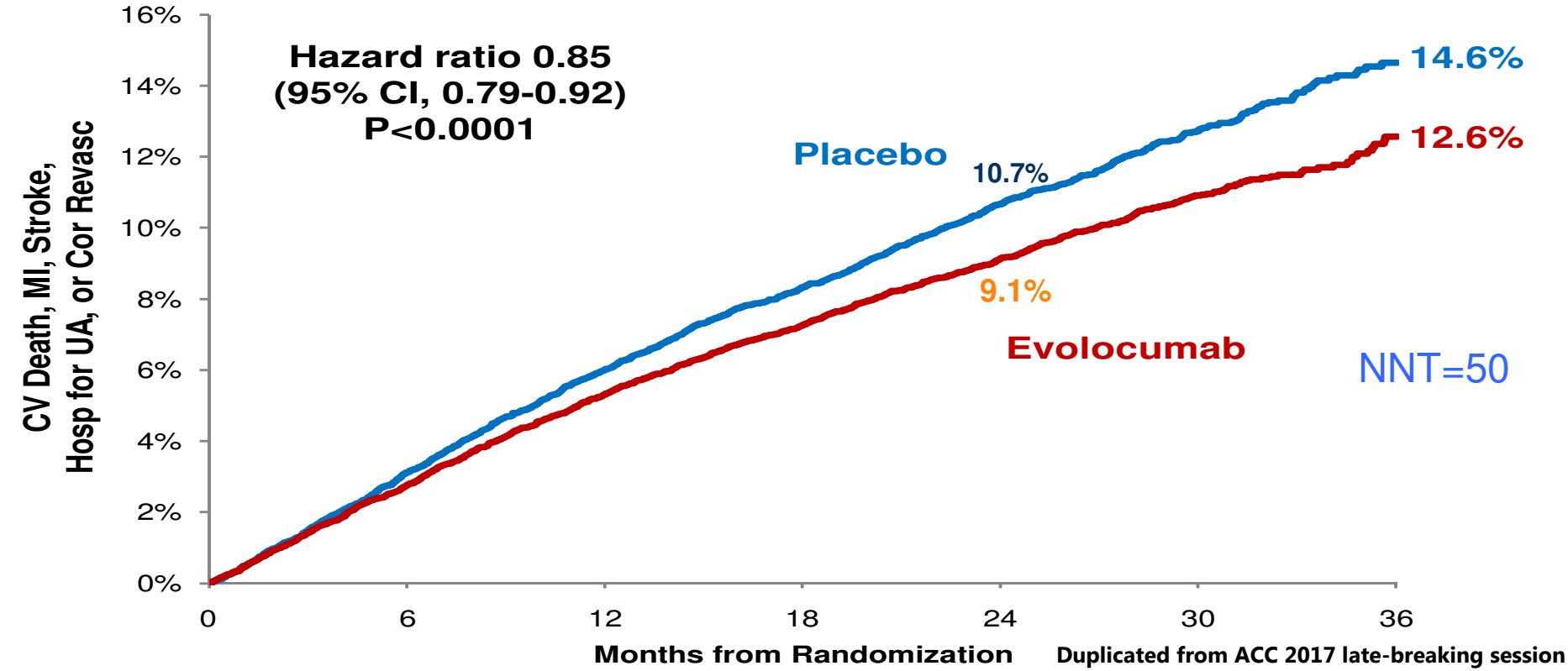
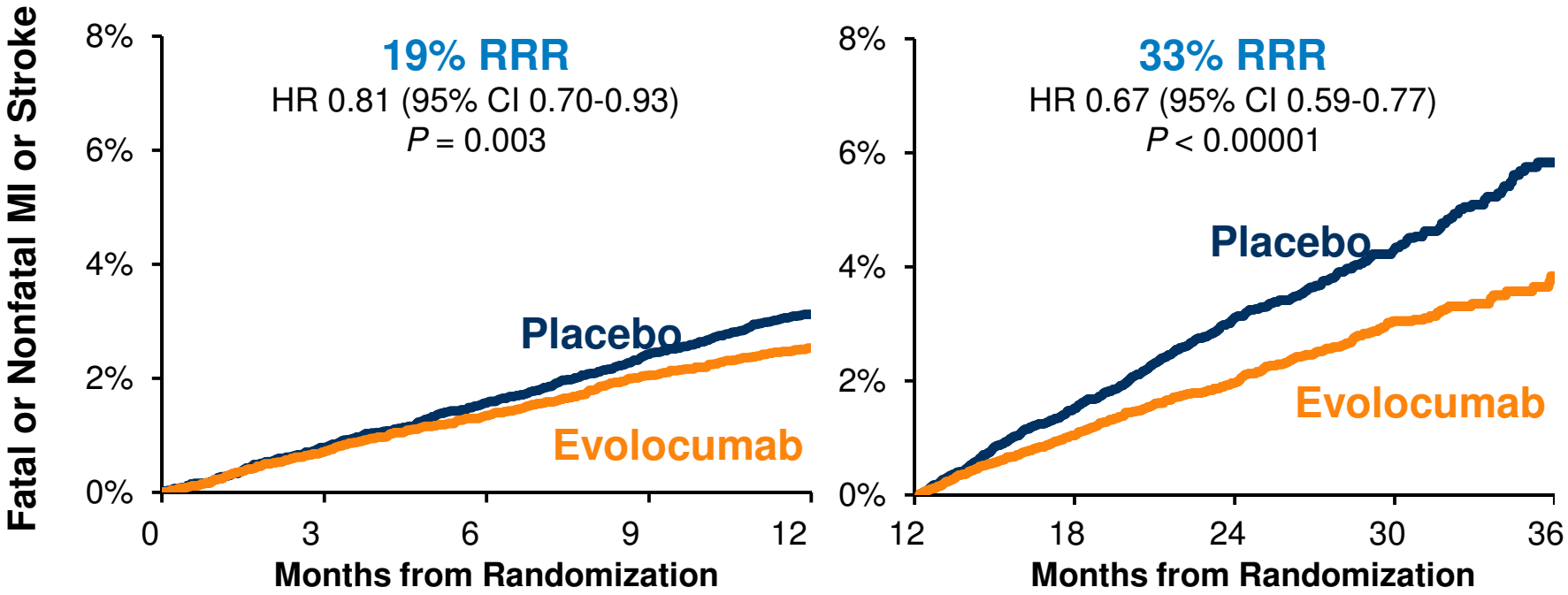
Primary Endpoint



N Engl J Med 2017; 376:1713-1722 May 4, 2017DOI: 10.1056/NEJMoa1615664

Fatal or Nonfatal MI or Stroke



Sabatine MS, et al. *American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial*. Washington, D.C. March 17, 2017.

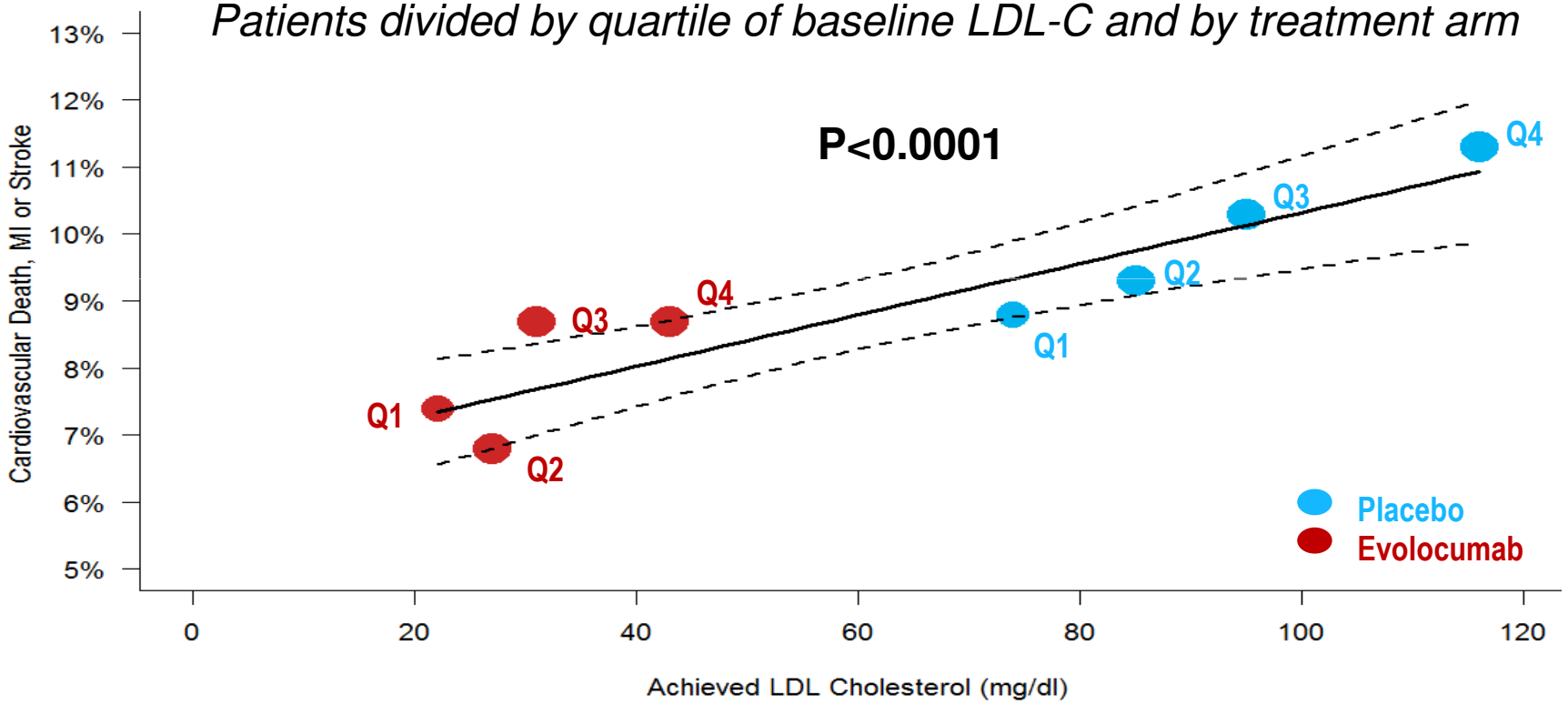
Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	**12.6**	**14.6**	**0.85 (0.79-0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Hosp for unstable angina	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91-1.19)**

Duplicated from ACC 2017 late-breaking session

Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm



Duplicated from ACC 2017 late-breaking session

Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

Conclusões

- ***Os resultados do FOURIER confirmam e reforçam a tese do colesterol.***
- ***A redução do LDL-C por meio da inibição da PCSK9 é eficaz na redução do risco cardiovascular.***
- ***A inibição da PCSK9 é segura.***
- ***Uma limitação do Fourier é a duração média mais curta do acompanhamento (mediana de 2,2 anos).***
- ***O ODYSSEY OUTCOMES será o mais longo estudo de desfecho cardiovascular com um inibidor da PCSK9.***

N Engl J Med 2017; 376:1713-1722 May 4, 2017DOI: 10.1056/NEJMoa1615664

Overview of ODYSSEY Phase III Program

22 global trials, including more than 29,000 patients across more than 3,000 study centers

HeFH population

Add-on to max tolerated statin (± other LMT)

- **ODYSSEY OLE** (LTS13463) N=1000
  18 months **[Ongoing]**
- **ODYSSEY FH I** (EFC12492) N=486
  18 months ✓
- **ODYSSEY FH II** (CL1112) N=249
  18 months ✓
- **ODYSSEY HIGH FH** (EFC12732) N=107
  18 months ✓
- **ODYSSEY LONG TERM** (LTS11717) N=2,341
  18 months ✓
- **ODYSSEY JAPAN** (EFC 13672) N=216
  12 months ✓
- **ODYSSEY APPRISE** (LPS14245) N=1300
  3 – 30 months **[Ongoing]**
- **ODYSSEY ESCAPE** (R727-CL-1216) N=63
  4 months ✓

HC in high CV risk population

Add-on to max tolerated statin (±other LMT)

- **ODYSSEY OUTCOMES (EFC11570) N=18,600**
  Event-driven, 2 year minimum follow-up
  Enrollment Completed Nov 2015 [Ongoing]
- **ODYSSEY COMBO I** (EFC11568) N=316
  12 months ✓
- **ODYSSEY COMBO II** (EFC11569) N=720
  24 months ✓
- **ODYSSEY EAST** (EFC13389) N=600
  6 months **[Ongoing]**
- **ODYSSEY KT** (EFC14074) N=199
  6 months ✓
- **ODYSSEY DM – Insulin** (LTS14354) N=500
  6 months **[Ongoing]**
- **ODYSSEY DM – Dyslipidemia** (LTS14355)
  6 months **[Ongoing]**

Additional populations/studies

- **ODYSSEY MONO** (EFC11716) N=103
  6 months ✓
- **ODYSSEY ALTERNATIVE** (CL1119) N=314
  6 months (+OLE) ✓
- **ODYSSEY OPTIONS I** (CL1110) N=355
  6 months ✓
- **ODYSSEY OPTIONS II** (CL1118) N=305
  6 months ✓
- **ODYSSEY CHOICE I** (CL1308)
  300 mg Q4w dosing , 12 months ✓
- **ODYSSEY CHOICE II** (EFC13786) N=233
  150 mg Q4W dosing, 6 months (+OLE) ✓
- **ODYSSEY NIPPON** (EFC14305) N=159
  3 months (+OLE) ✓

✓ Primary endpoint met; data presented or published

LONG TERM: Desenho do Estudo

Objetivo primário: Avaliar a segurança de longo prazo, tolerabilidade e eficácia do Alirocumabe

J. Robinson et al., *N Engl J Med* 2015 372:1489-1499 (Apêndice)

LONG TERM: Características demográficas

Todos os pacientes com estatina máx. tolerada de base ± outra TRL	Alirocumabe (N=1553)	Placebo (N=788)
Idade, anos, média (DP)	**60,4** (10,4)	**60,6** (10.4)
Sexo masculino, % (n)	**63,3%** (983)	**60,2%** (474)
Raça, branca, % (n)	**92,8%** (1441)	**92,6%** (730)
IMC, kg/m², média (DP)	**30,2** (5,7)	**30,5** (5.5)
HeFH, % (n)	**17,8%** (276)	**17,6%** (139)
História de DAC, % (n)	**67,9%** (1055)	**70,1%** (552)
Equivalente de risco CV, % (n)	**41,1%** (639)	**41,0%** (323)
Diabetes tipo 2, % (n)	**34,9%** (542)	**33,9%** (267)
Qualquer estatina,[a] % (n)	**>99,9%** (1552)	**99,9%** (787)
Alta dose de estatina,[b] % (n)	**46,8%** (727)	**46,8%** (369)
Qualquer TRL menos estatina, % (n)	**28,1%** (437)	**27,9%** (220)
Ezetimibe, % (n)	**13,9%** (216)	**15,0%** (118)

[a]Os pacientes deveriam receber rosuvastatin a 20–40 mg QD, atorvastatina 40–80 mg QD, ou sinvastatina 80 mg QD a não ser que não tolerada e/ou outra dose apropriada administrada a critério do investigador.
[b]Alta dose de estatina: atorvastatina 40–80 mg, rosuvastatina 20–40 mg, ou sinvastatina 80 mg diariamente.
Robinson JG, et al. *N Engl J Med.* 2015;372(16):1489-1499.

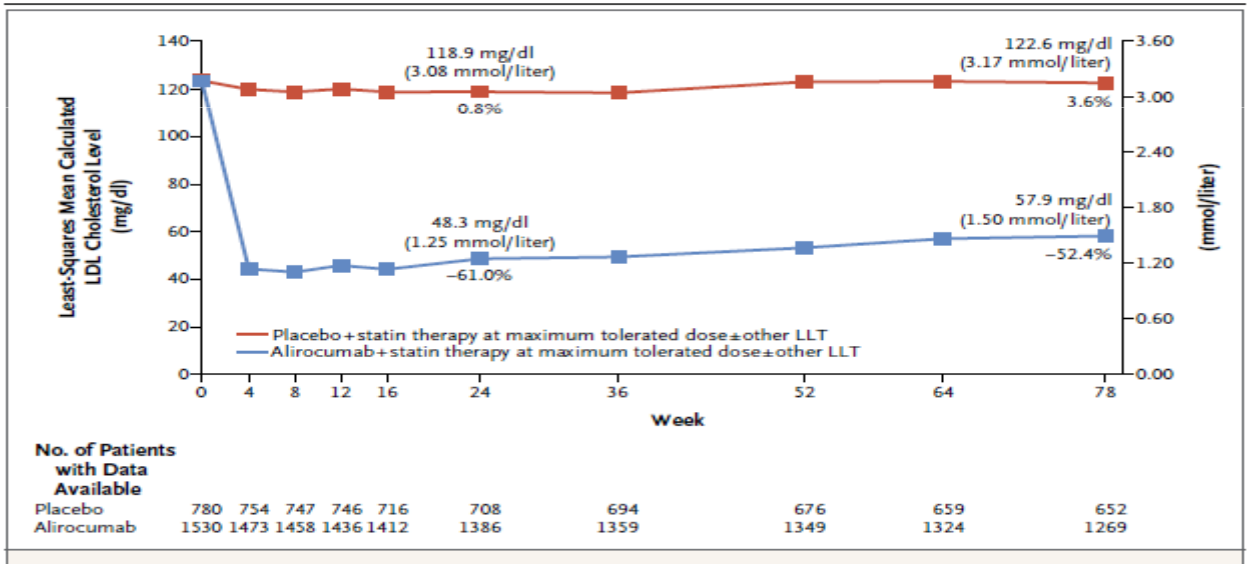
J. Robinson et al., *N Engl J Med* 2015 372:1489-1499 (Apêndice)

The NEW ENGLAND JOURNAL of MEDICINE

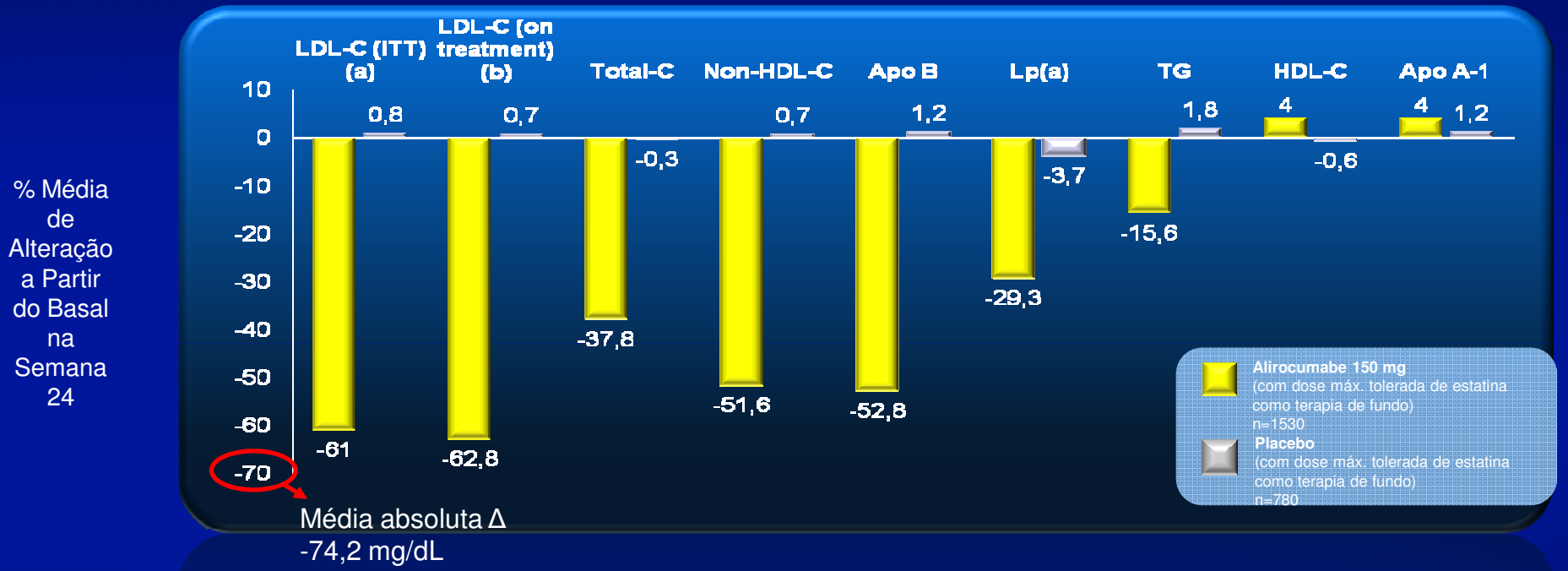
ESTABLISHED IN 1812 APRIL 16, 2015 VOL. 372 NO. 16

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Robinson JG et al



LONG TERM: *Endpoints* de Eficácia na Semana 24



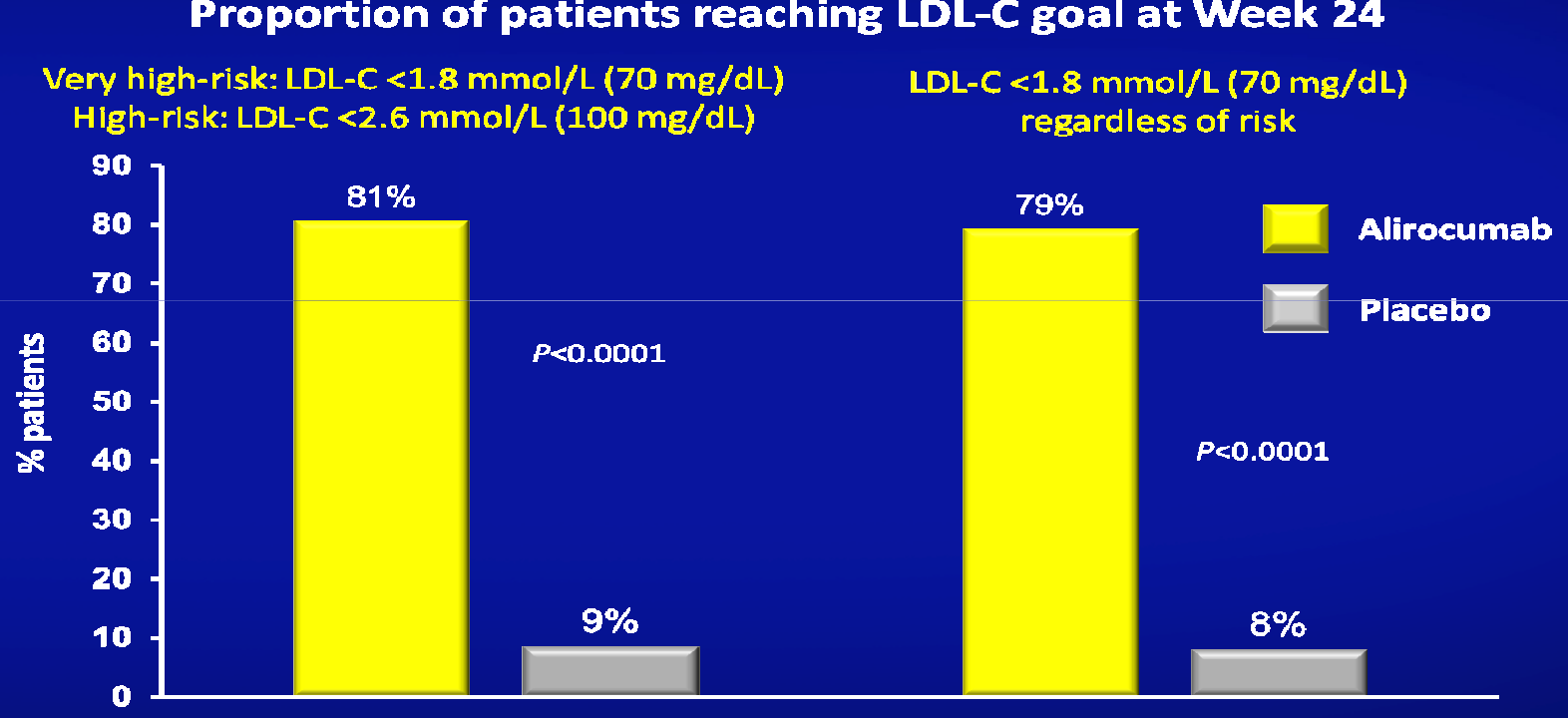
A média de LDL-C no basal foi de 122,8mg/dL no grupo Alirocumabe e122,0mg/dL no grupo placebo

(a) Análise ITT – população com intenção de tratar, inclui todos os dados sobre lipídios durante todo o estudo, independente da adesão ao tratamento em estudo.

(b) Análise durante o tratamento – análise restrita ao período em que os pacientes realmente receberam o tratamento.

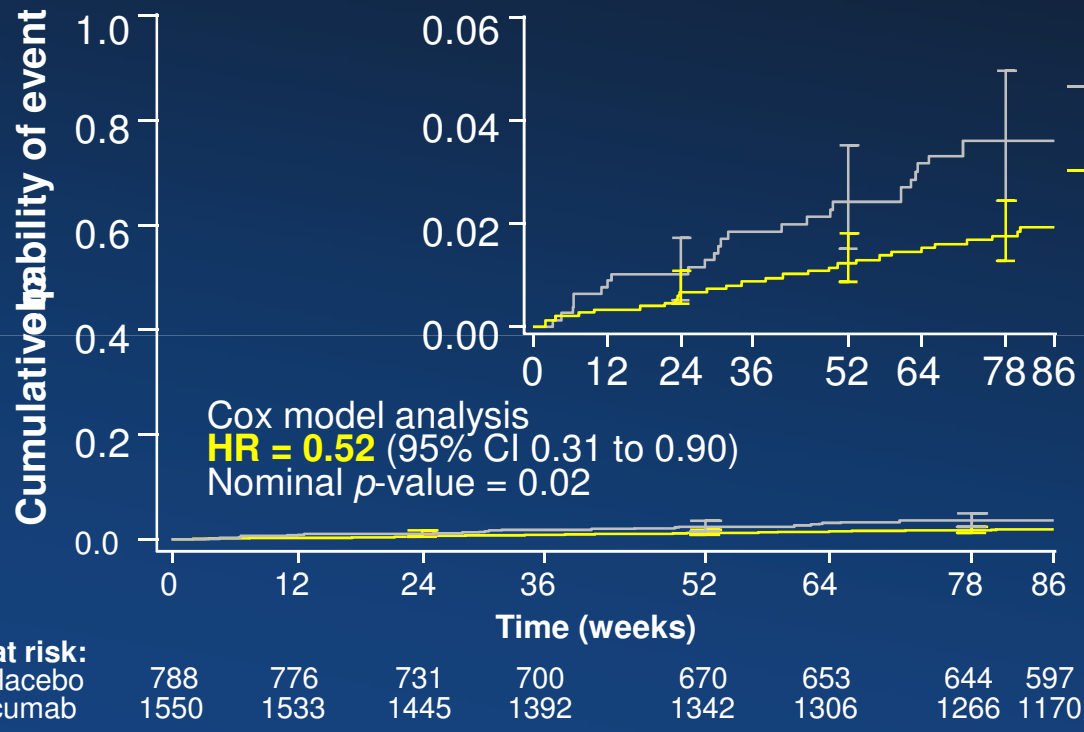
J. Robinson et al., *N Engl J Med* 2015 372:1489-1499 (Apêndice)

LONG TERM : proporção de pacientes atingindo a meta de LDL-C na Semana 24



J. Robinson et al., *N Engl J Med* 2015 372:1489-1499

Post hoc Analysis of Adjudicated Major Adverse Cardiovascular Events*



Placebo + maximally tolerated statin ± other LLT

Alirocumab + maximally tolerated statin ± other LLT

No. at risk:

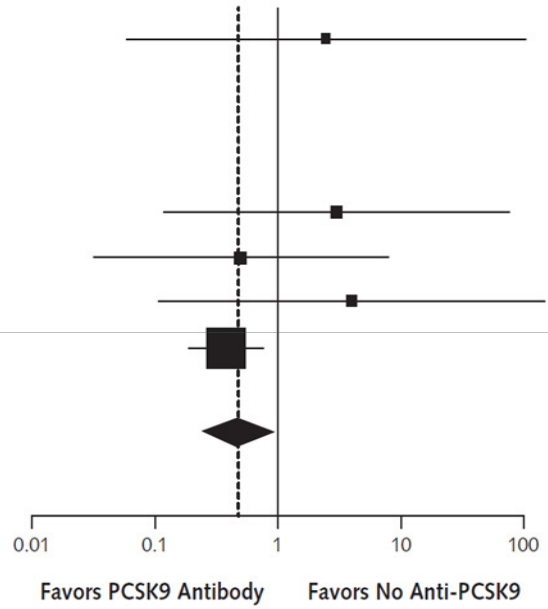
Placebo	788	776	731	700	670	653	644	597
Alirocumab	1550	1533	1445	1392	1342	1306	1266	1170

*Based on primary endpoint for the ODYSSEY OUTCOMES trial, including CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization.Unstable angina requiring hospitalization was considered based on strict criteria / clear progression of ischemia.

Robinson JG et al. *NEJM* 2015; 372:1489-99.

NAVARESE Meta-Analysis

Study	Events/Total, *n/N*		Odds Ratio (95% CI)	Weight, %
	PCSK9 Antibody	No Anti-PCSK9		
DESCARTES	1/599	0/302	2.51 (0.06–102.80)	3.0
LAPLACE-TIMI 57	0/158	0/157	–	0.0
McKenney et al	0/31	0/31	–	0.0
MENDEL	0/90	0/135	–	0.0
ODYSSEY ALTERNATIVE	1/126	0/125	3.02 (0.12–75.06)	4.0
ODYSSEY COMBO I	1/209	1/107	0.51 (0.03–8.23)	5.4
ODYSSEY FH I and FH II	2/490	0/245	4.02 (0.11–147.57)	3.2
ODYSSEY LONG TERM	14/1553	18/788	0.39 (0.19–0.79)	84.3
TESLA Part B	0/33	0/16	–	0.0
Fixed-effect model	19/3289	19/1906	0.49 (0.26–0.93)	100
Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.4492$				
Test for overall effect: $Z = -2.17$ ($P = 0.030$)				



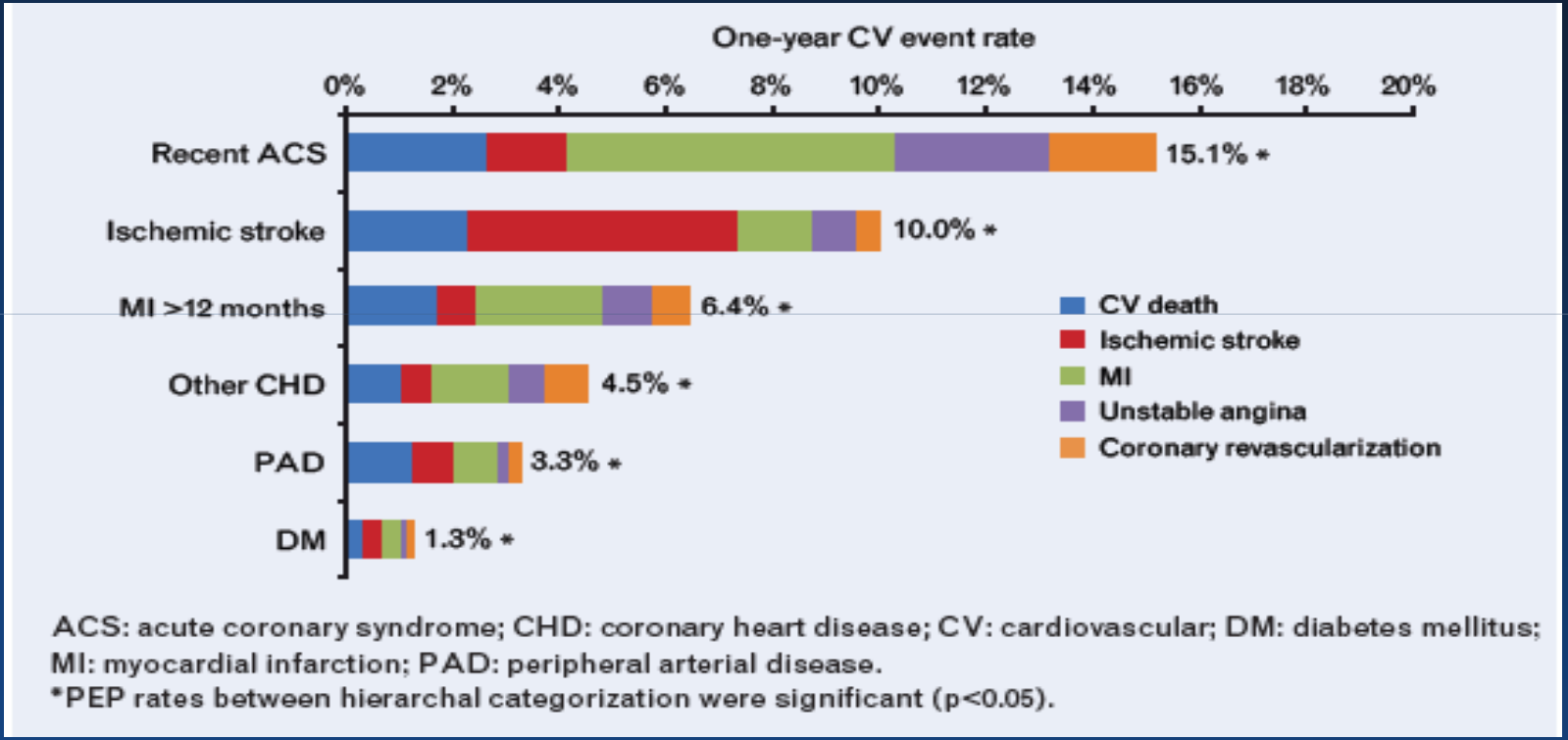
10 RCTs were analyzed amongst the 24 of NAVARESE meta-analysis to assess reduction in MI

PCSK9i resulted in a statistically significant reduction in MI compared with no anti-PCSK9: 0.58%

(OR, 0.49 [CI, 0.26 to 0.93]; *P* = 0.030)

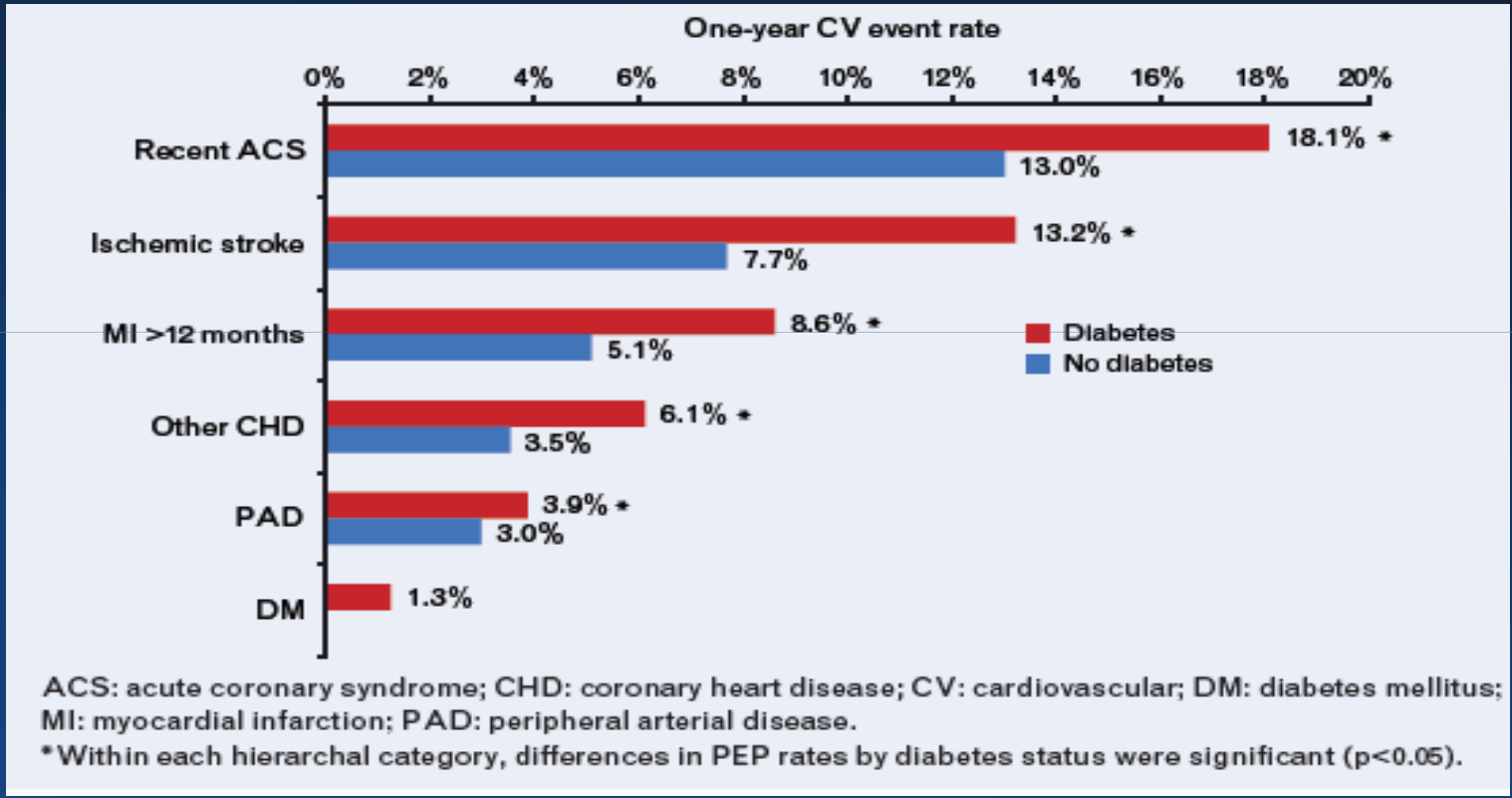
Navarese EP. *Ann Intern Med.* 2015.;163: 42-45.

As Populações Alvo são aquelas de maior risco CV



ACS: acute coronary syndrome; CHD: coronary heart disease; CV: cardiovascular; DM: diabetes mellitus; MI: myocardial infarction; PAD: peripheral arterial disease.
*PEP rates between hierarchal categorization were significant ($p<0.05$).

As Populações Alvo são aquelas de maior risco CV

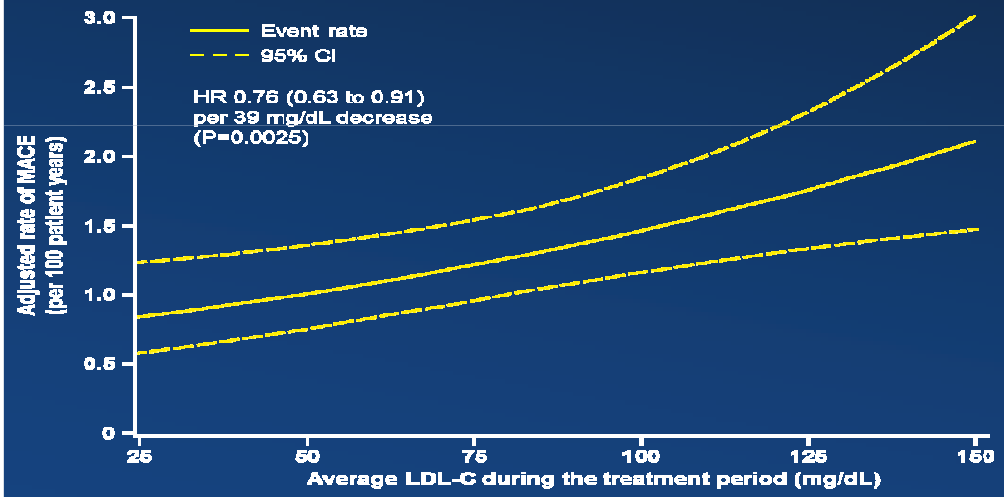


ACS: acute coronary syndrome; CHD: coronary heart disease; CV: cardiovascular; DM: diabetes mellitus; MI: myocardial infarction; PAD: peripheral arterial disease.

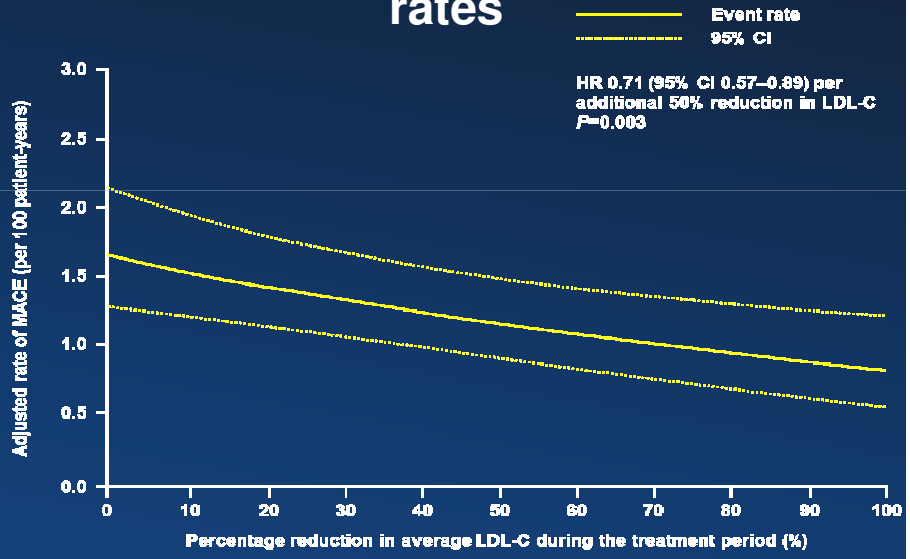
*Within each hierarchal category, differences in PEP rates by diabetes status were significant ($p<0.05$).

Emerging Evidence from ODYSSEY Program: Achieved LDL vs. MACE

Continuous relationship between lower achieved LDL-C levels and lower CV risk



Greater LDL-C % reduction from baseline and lower ASCVD event rates



Adjusted MACE rate by average LDL-C (absolute or % reduction from baseline) during treatment period.
Multivariate analysis adjusted on baseline characteristics; pool of Phase 3 ODYSSEY trials.

Alirocumab Reduces Major Cardiovascular Events in Individuals with Atherosclerotic Cardiovascular Disease: A Post-Hoc Analysis of ODYSSEY LONG TERM

Jennifer G Robinson,[1] Michel Farnier,[2] William J Sasiela,[3] Tu Nguyen,[4] Jonas Mandel,[5] John JP Kastelein[6]

[1]University of Iowa, Iowa City, IA, USA; [2] Point Médical, Dijon, France; [3]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [4]Sanofi US, Bridgewater, NJ, USA; [5]Sanofi, Chilly-Mazarin, France and IviData Stats, Levallois-Perret, France; [6]Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands.

Poster presented at the American College of Cardiology 66th Annual Scientific Session, March 17–19, 2017, Washington, DC, USA.
[Presentation number: 1203-305]

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

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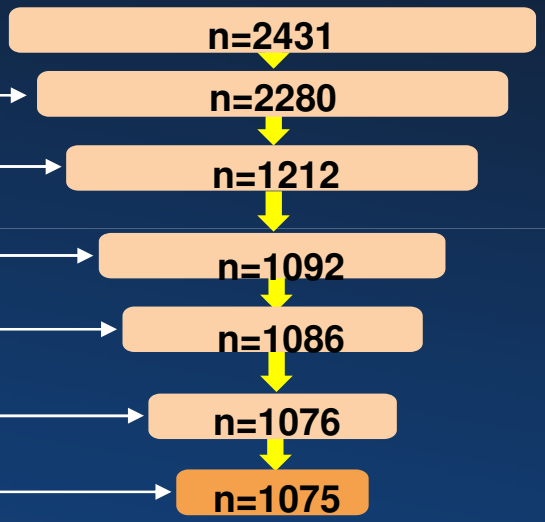
Inclusion Criteria for the *Post-hoc* ODYSSEY LONG TERM ASCVD Subgroup Analysis

- The Phase 3 ODYSSEY LONG TERM study investigated the efficacy and safety of alirocumab 150 mg Q2W versus placebo over 78 weeks in individuals at high-risk of cardiovascular events[1]

Total randomized patients in LONG TERM[1]

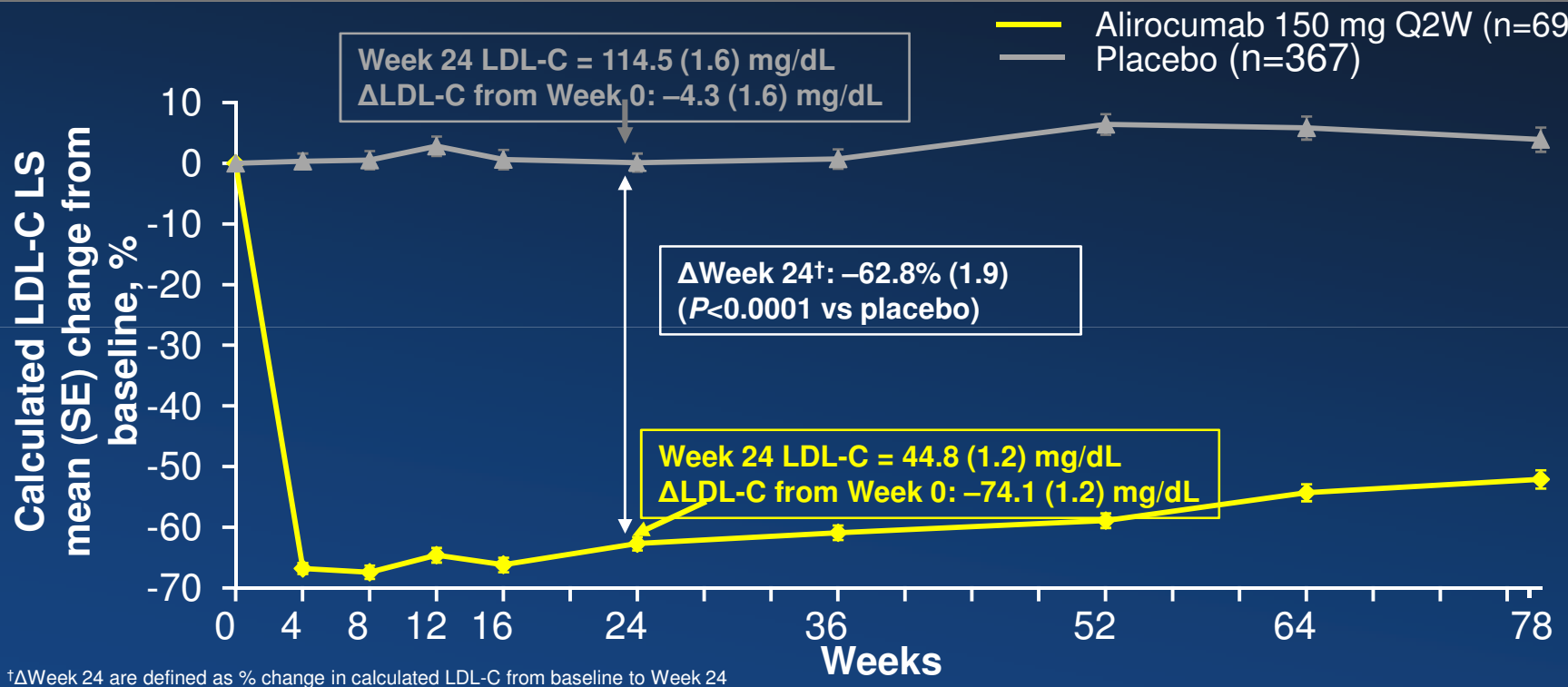


- Age ≥40 to ≤85 years
- History of clinically evident ASCVD (MI, ischemic stroke, PAD)
- ≥1 major risk factor† or ≥2 minor risk factors‡
- Most recent LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL before randomization
- Most recent TGs ≤400 mg/dL before randomization
- No known history of uncontrolled/recurrent ventricular tachycardia[2]

†Including diabetes mellitus type 1 or 2, age ≥65 years at randomization, MI or non-hemorrhagic stroke within 6 months of screening, additional history of MI or stroke, daily smoking, history of PAD if selected by history of MI, or stroke. ‡Including history of non-MI related coronary revascularization, residual CAD with ≥40% stenosis in ≥2 large vessels, most recent HDL-C <40 mg/dL for men and <50 mg/dL for women before randomization, most recent hsCRP >2 mg/L before randomization, metabolic syndrome, most recent LDL-C ≥130 mg/dL, or non-HDL-C ≥160 mg/dL before randomization
ASCVD, atherosclerotic cardiovascular disease; CAD, coronary arterial disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; Q2W, every two weeks; TGs, triglycerides.

1. Robinson JG et al. N Engl J Med. 2015;372:1489–1499. 2. Robinson JG et al. Presented at ACC 2017. Poster number 1203-305

Percent Change in Calculated LDL-C over Time: Individuals with ASCVD with and without HeFH from LONG TERM (ITT Population)



†ΔWeek 24 are defined as % change in calculated LDL-C from baseline to Week 24

ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q2W, every 2 weeks; SE, standard error

Robinson JG et al. Presented at ACC 2017. Poster number 1203-305

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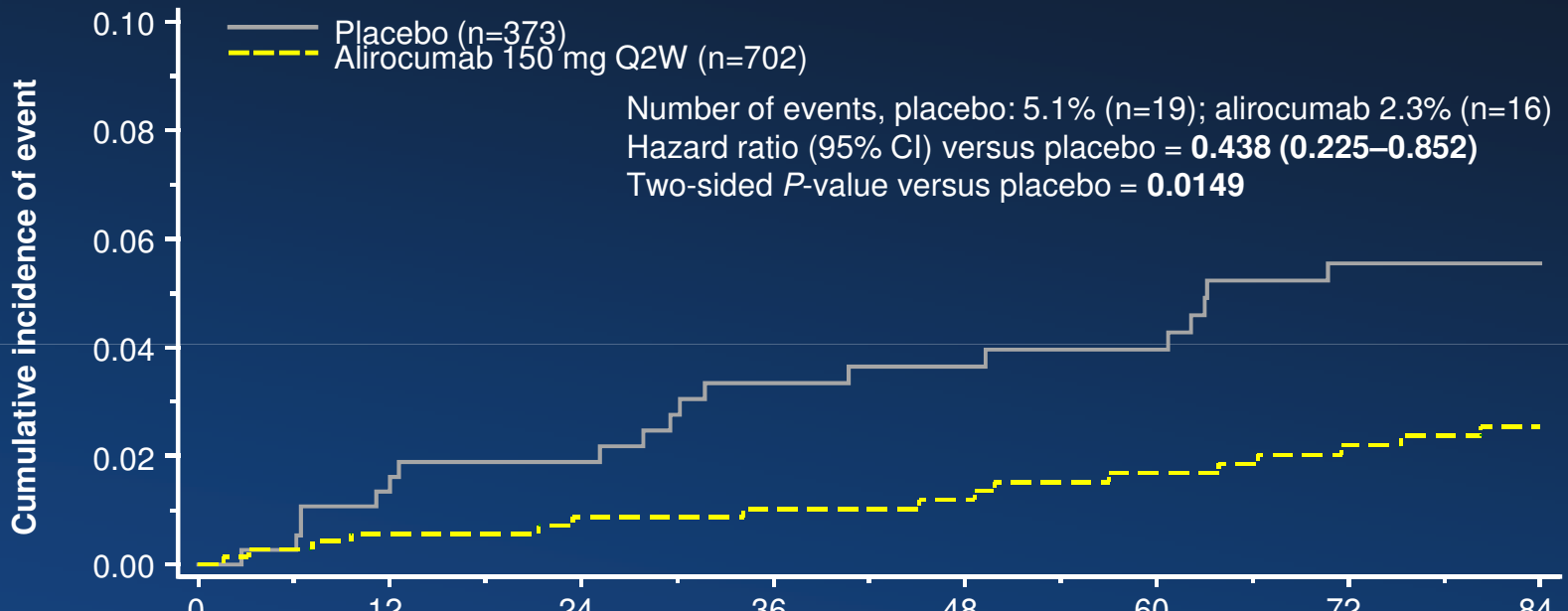
Kaplan–Meier Cumulative Incidence Curve for Time to First Event: Individuals with ASCVD with and without HeFH from LONG TERM (Safety Population)



Number at Risk

Placebo	373	364	340	322	308	304	294	289
Alirocumab	702	692	650	631	604	594	569	555

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HeFH, heterozygous familial hypercholesterolemia; Q2W, every two weeks.

Robinson JG et al. Presented at ACC 2017. Poster number 1203-305

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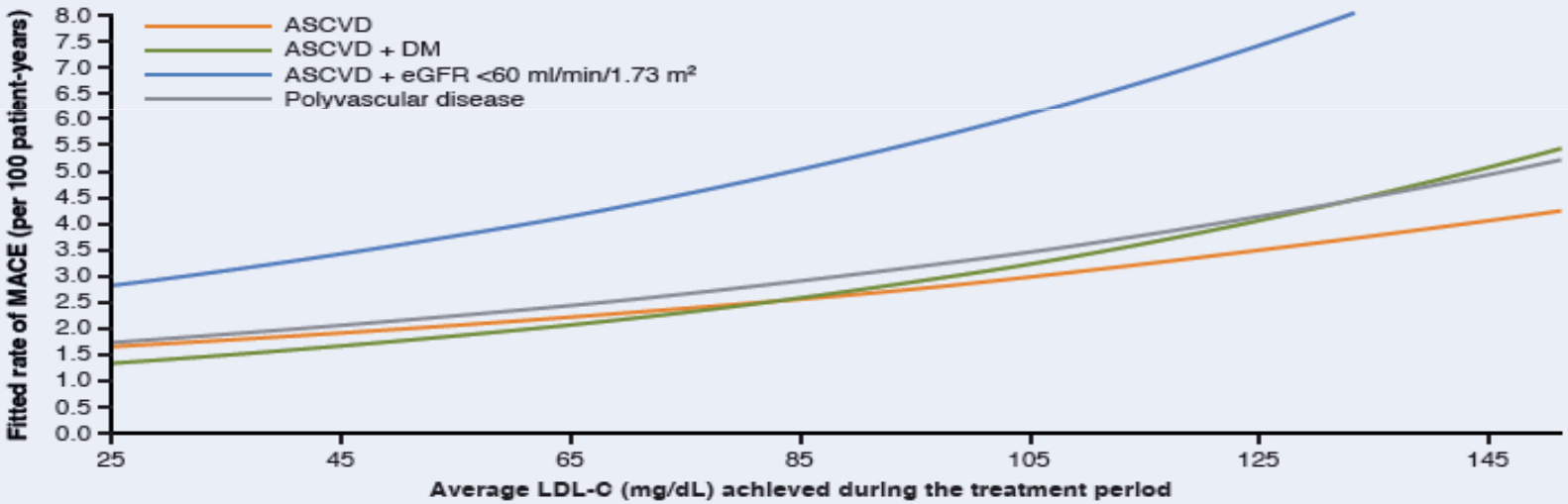
Lower On-Treatment Low-Density Lipoprotein Cholesterol is Associated with Lower Cardiovascular Risk in Very High-Risk Patients with Atherosclerotic Cardiovascular Disease: Analyses from the ODYSSEY Trials

Figure 2. Adjusted rate of MACE by average LDL-C achieved during the treatment period in all patients with ASCVD and in high-risk subgroups with comorbid DM, PoVD, or eGFR <60 mL/min/1.73 m² at baseline (multivariate analysis adjusted on baseline characteristics, safety population; pool of 10 Phase 3 ODYSSEY trials)

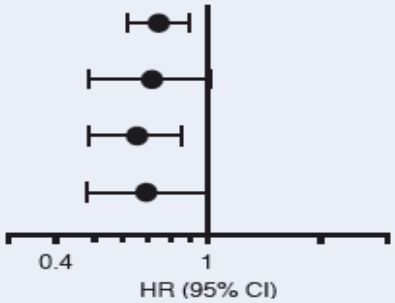


Event rate and 95% CI determined from a multivariate Poisson model, with adjustment for age, diabetes, prior history of MI or stroke, baseline LDL-C and smoking status. Average LDL-C during the treatment period determined from the area under the curve (using trapezoidal method), taking into account all LDL-C values up to end of treatment period or occurrence of MACE event, whichever came first. For patients with no post-baseline LDL-C, LDL-C at baseline was used; two patients with missing baseline LDL-C were excluded from the multivariate analysis.

Lower On-Treatment Low-Density Lipoprotein Cholesterol is Associated with Lower Cardiovascular Risk in Very High-Risk Patients with Atherosclerotic Cardiovascular Disease: Analyses from the ODYSSEY Trials

Figure 3. Relationship between MACE and each 39 mg/dL lower average LDL-C in very high-risk ASCVD subgroups (safety population; pool of 10 Phase 3 ODYSSEY trials)

Population	n	HR (95% CI) per 39 mg/dL lower LDL-C	Adjusted rate (%) of MACE per 100 patient-years (95% CI)		
			Mean achieved LDL-C 40 mg/dL	Mean achieved LDL-C 79 mg/dL	Mean achieved LDL-C 120 mg/dL
Overall ASCVD	3503	0.75 (0.62 to 0.90)	1.81 (1.12 to 2.94)	2.44 (1.59 to 3.76)	3.34 (2.11 to 5.28)
Polyvascular disease	943	0.71 (0.49 to 1.01)	1.94 (0.75 to 5.01)	2.75 (1.18 to 6.37)	3.96 (1.63 to 9.60)
ASCVD + DM	980	0.65 (0.49 to 0.86)	1.55 (0.67 to 3.58)	2.41 (1.12 to 5.19)	3.83 (1.72 to 8.54)
ASCVD + eGFR <60 mL/min/1.73 m²	660	0.69 (0.48 to 1.00)	3.26 (1.27 to 8.35)	4.77 (2.07 to 11.00)	7.13 (2.93 to 17.35)



HR calculated using Cox multivariable regression analysis, adjusted for age, gender, diabetes (except for the ASCVD+DM analysis), prior MI/stroke, baseline LDL-C and smoking, Adjusted rates of MACE obtained by a Poisson model adjusted for the same variables; rates are provided for a subject with averaged characteristics and different levels of LDL-C under treatment.

Lower On-Treatment Low-Density Lipoprotein Cholesterol is Associated with Lower Cardiovascular Risk in Women: Analyses from the ODYSSEY Trials of Alirocumab versus Control

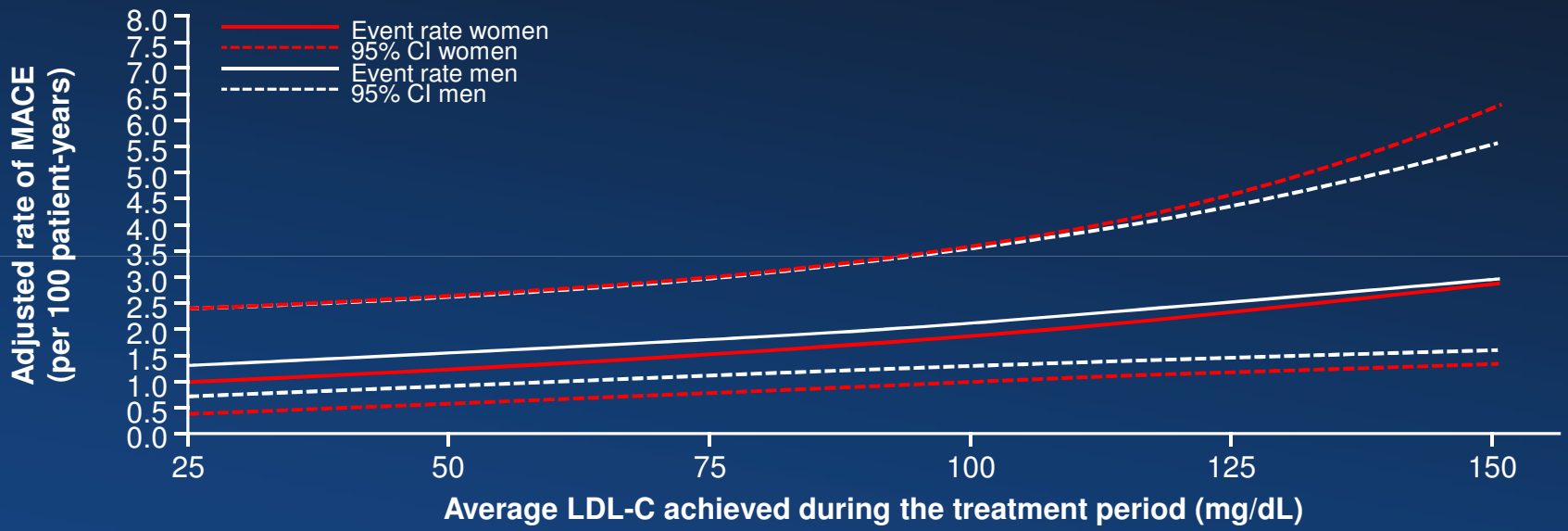
Antonio J Vallejo-Vaz,[1] Henry N Ginsberg,[2]
Michael H Davidson,[3] Robert H Eckel,[4] Christopher P Cannon,[5]
L. Veronica Lee,[6] Laurence Bessac,[7] Robert Pordy,[8]
Alexia Letierce,[9] Kausik K Ray[1]

[1]Imperial Centre for Cardiovascular Disease Prevention, Imperial College London, London, UK;
[2]Columbia University, New York, NY, USA; [3]Department of Medicine, University of Chicago Medicine, Chicago, IL, USA; [4]University of Colorado, Anschutz Medical Campus, Aurora, CO, USA;
[5]Harvard Clinical Research Institute, Boston, MA, USA; [6]Sanofi, Bridgewater, NJ, USA; [7]Sanofi, Paris, France; [8]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [9]Sanofi, Chilly-Mazarin, France

Poster presented at the American College of Cardiology 66th Annual Scientific Session, March 17–19, 2017, Washington, DC, USA.
(Presentation number: 1204-331 / 331)

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Adjusted Rate of MACE by Average LDL-C Achieved During Treatment in Women and Men (Safety Population)



Event rate and 95% CI determined from a multivariate Poisson model, with adjustment for age, diabetes, prior history of MI or stroke, baseline LDL-C and smoking status. Average LDL-C during the treatment period determined from the area under the curve (using trapezoidal method), taking into account all LDL-C values up to end of treatment period or occurrence of MACE, whichever came first. For patients with no post-baseline LDL-C, LDL-C at baseline was used; two patients with missing baseline LDL-C were excluded from the multivariate analysis

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction

Vallejo-Vaz AJ et al. Presented at ACC 2017. Poster number 1204-331 / 331

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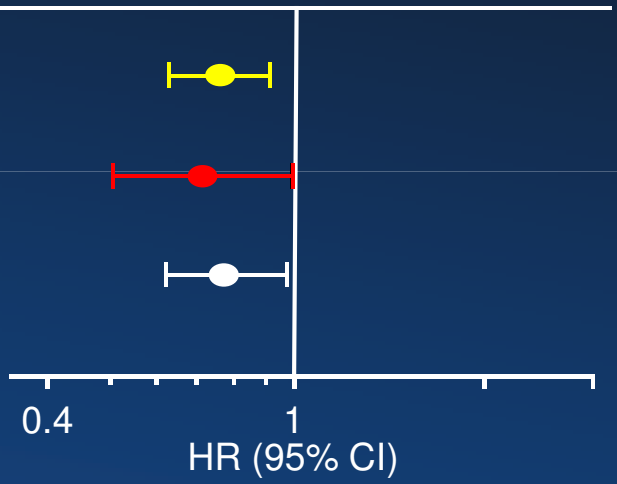
Risk of MACE Associated with Each 39 mg/dL On-Treatment Reduction in LDL-C in Women and Men (Safety Population)

Population	n	Adjusted HR (95% CI) per 39 mg/dL lower LDL-C	*P-value*†
Overall cohort	4972	0.76 (0.63–0.91)	0.0025
Women	1882	0.71 (0.51–0.99)	0.0459
Men	3090	0.78 (0.63–0.98)	0.0297



†*P*-values are for each 39 mg/dL decrease in LDL-C. HR calculated using multivariable Cox regression, adjusted for age, diabetes mellitus, prior MI/stroke, baseline LDL-C, and smoking

CI, confidence interval; HR, hazard ration; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction

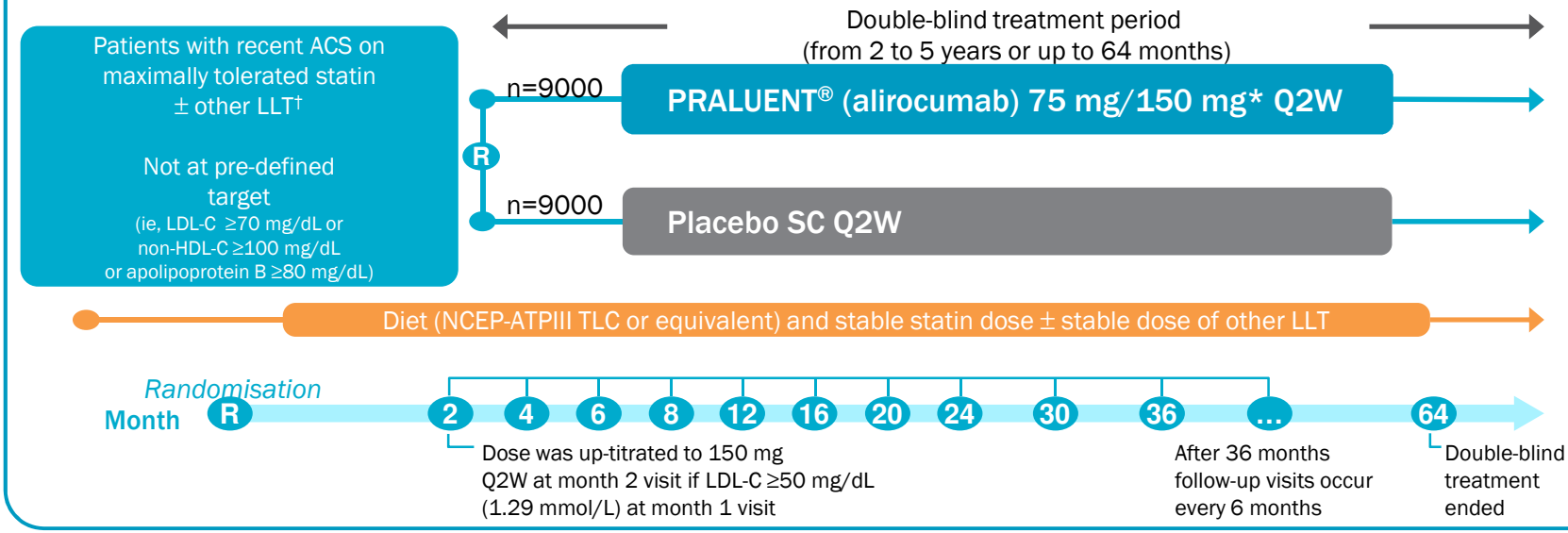
SANOFI

Vallejo-Vaz AJ et al. Presented at ACC 2017. Poster number 1204-331 / 331

REGENERON

ODYSSEY OUTCOMES – Study Design

A randomised, double-blind, placebo-controlled study



*Dose titrated up to 150 mg Q2W at month 2 if LDL-C ≥50 mg/dL (1.29 mmol/L) at month 1 visit.
†Atorvastatin 40-80 mg or rosuvastatin 20-40 mg OR maximally tolerated dose of statin (can be 0 mg).
Dose down-titration to 75 mg Q2W if dose is 150 mg Q2W or substitution by placebo if dose is 75 mg Q2W occurs when LDL-C ≤0.65 mmol/L (25 mg/dL) on 2 consecutive measures.

ACS: Acute Coronary Syndromes LLT: Lipid-Lowering Therapy Q2W: Every 2 weeks

ClinicalTrials.gov. ODYSSEY OUTCOMES Study. http://clinicaltrials.gov/ct2/show/NCT01663402. Accessed May 14, 2015.
Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1.

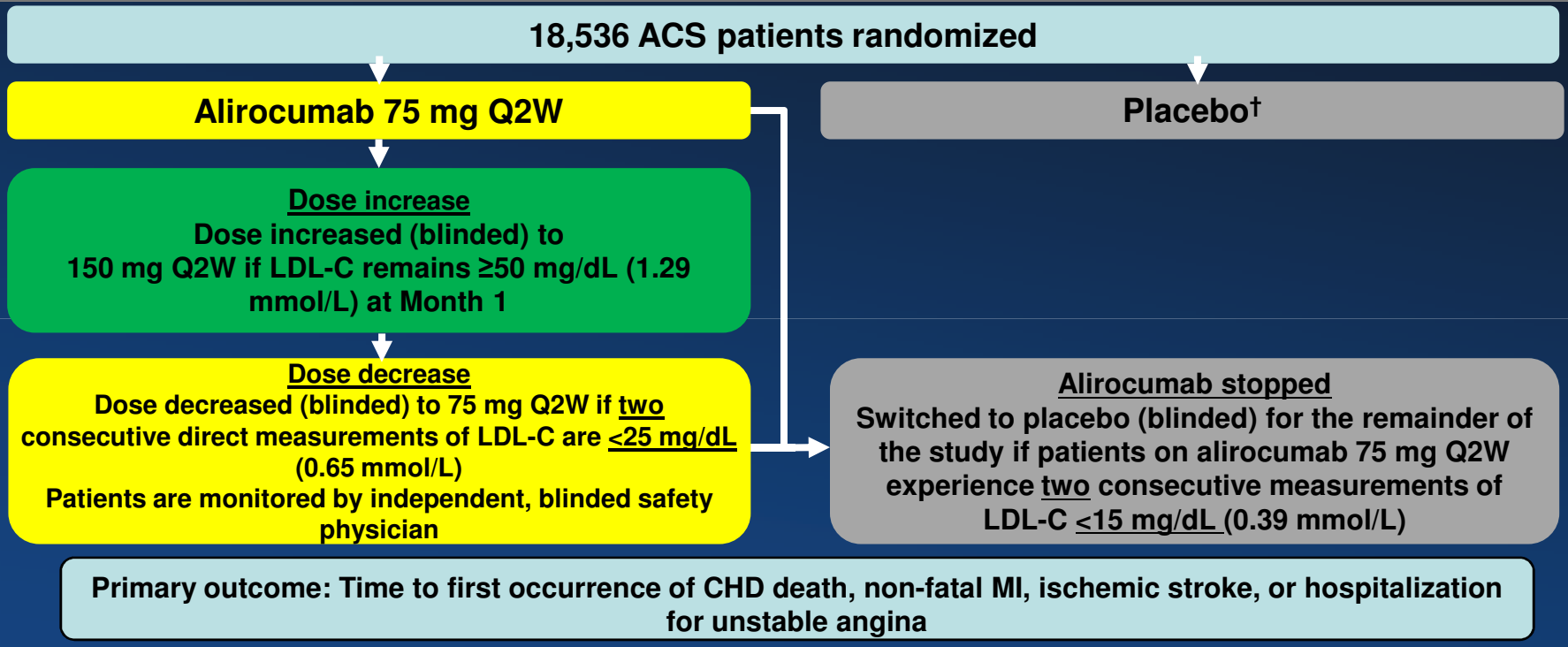
SANOFI REGENERON

Use of High-Intensity Statin Therapy Post-Acute Coronary Syndrome in the Ongoing ODYSSEY OUTCOMES Trial of Alirocumab, a Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibody, versus Placebo: Interim Baseline Data

Shaun G Goodman, Gregory G Schwartz, Deepak L Bhatt, Vera Bittner, Rafael Diaz, Corinne Hanotin, Robert A Harrington, J Wouter Jukema, Angèle Moryusef, Robert Pordy, Matthew T Roe, William J Sasiela, Michael Szarek, Jean-Francois Tamby, Harvey White, Andreas Zeiher, Philippe Gabriel Steg, for the ODYSSEY OUTCOMES Investigators

Poster presented at the American College of Cardiology 66th Annual Scientific Session, March 17–19, 2017, Washington, DC, USA.
(Presentation number: 1203-307 / 307)
This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Treatment Assignment and Primary Outcome Measures



†Placebo maintained for the duration of the study

ACS, acute coronary syndrome; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; Q2W, every two weeks.

Goodman SG et al. Presented at ACC 2017. Poster number 1203-307 / 307

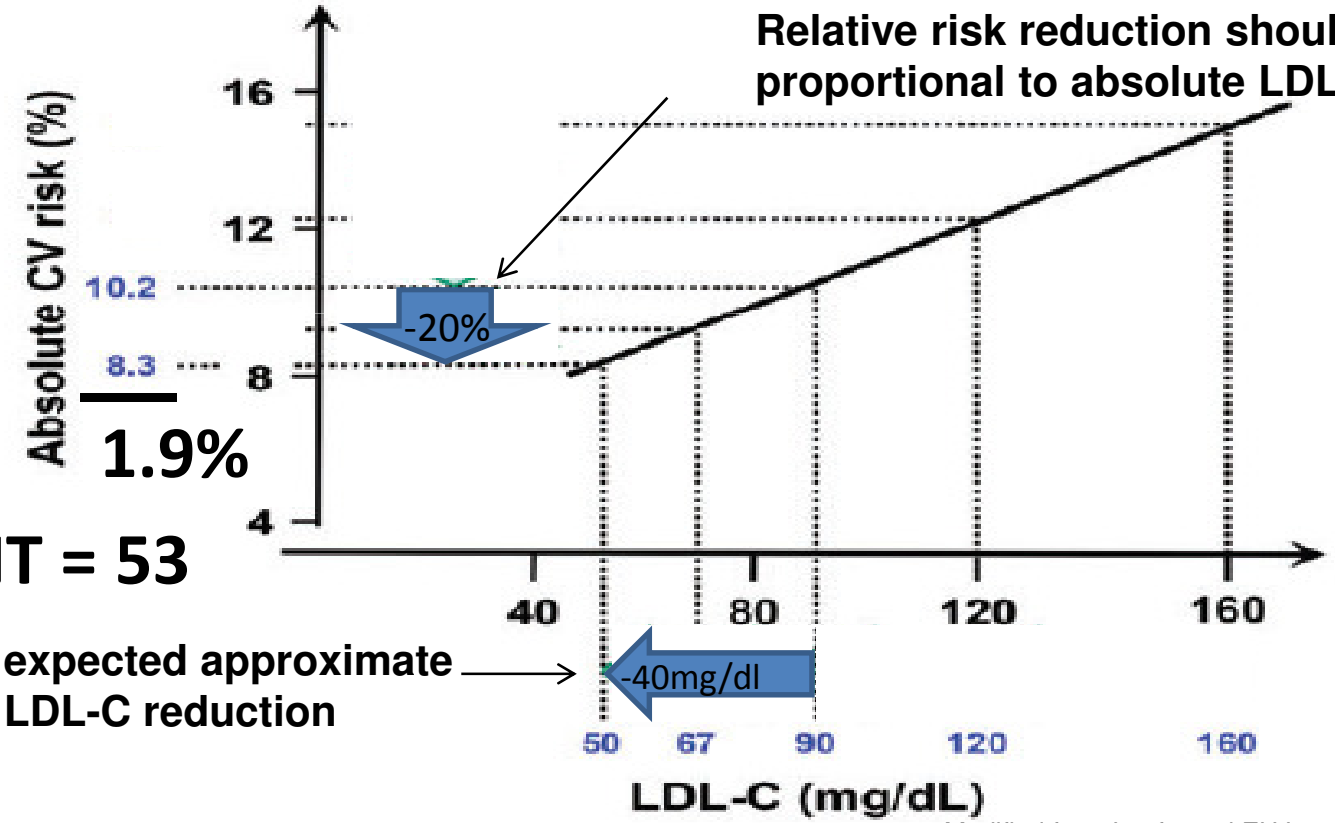
Key differences between ODYSSEY OUTCOMES & FOURIER

	ODYSSEY OUTCOMES N=18,000	FOURIER N=27,500
Population	Patient with a coronary event within a year (ACS)	MI, stroke, PAD
Baseline Demographics	Diabetes: 24% 35% prior CAD + 20% recurrent Prior Stroke: 3% Prior PAD: 4%	Diabetes: 34% MI: 81% Stroke: 19% PAD: 13%
Median baseline LDL-C	86.5	91.5
Statin background	**Maximally tolerated** High-intensity 89% Moderate-intensity: 8%	High-intensity 69% Moderate-intensity: 30%
Dosing regimen	75Q2W -> 150Q2W if LDL-C ≥50 mg/dL	140Q2W/420QM No titration
Primary endpoint Differences	CHD death	CV Death Coronary revascularization
Duration (exposure)	**2-to-5 years follow-up**	1-to-3.5 years follow-up

SANOFI REGENERON

ODYSSEY Estimated Relationship between LDL-C reduction and risk reduction

Based on statins and CTT
Relative risk reduction should be proportional to absolute LDL reduction



1.9%

NNT = 53

expected approximate LDL-C reduction

Modified from Laufs et al EHJ 2015

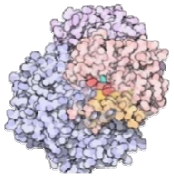
ODYSSEY OUTCOMES: Key Scientific Points

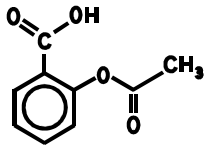
- ***ODYSSEY OUTCOMES is the longest randomized PCSK9i CVOT trial with estimated mean double-blind follow-up of 3 years and a maximum of 5 years at trial completion.***

- **Odyssey Outcomes will be overpowered for primary endpoint** Odyssey Outcomes may provide greater power to see effect on mortality

- ***Elements of the ODYSSEY OUTCOMES trial are different from FOURIER, including:***
  - ***A longer follow-up***
  - ***A higher risk patient population***
  - ***Treat to goal approach***
  - ***Higher proportion of patients on high intensity statin***
  - ***Inclusion of CHD death as a component of primary composite endpoint***
  - ***Unstable Angina definition***
  - **Odyssey Outcomes population predominantly statin naïve** at entry (2/3)

Biologic and Small Molecule Drugs

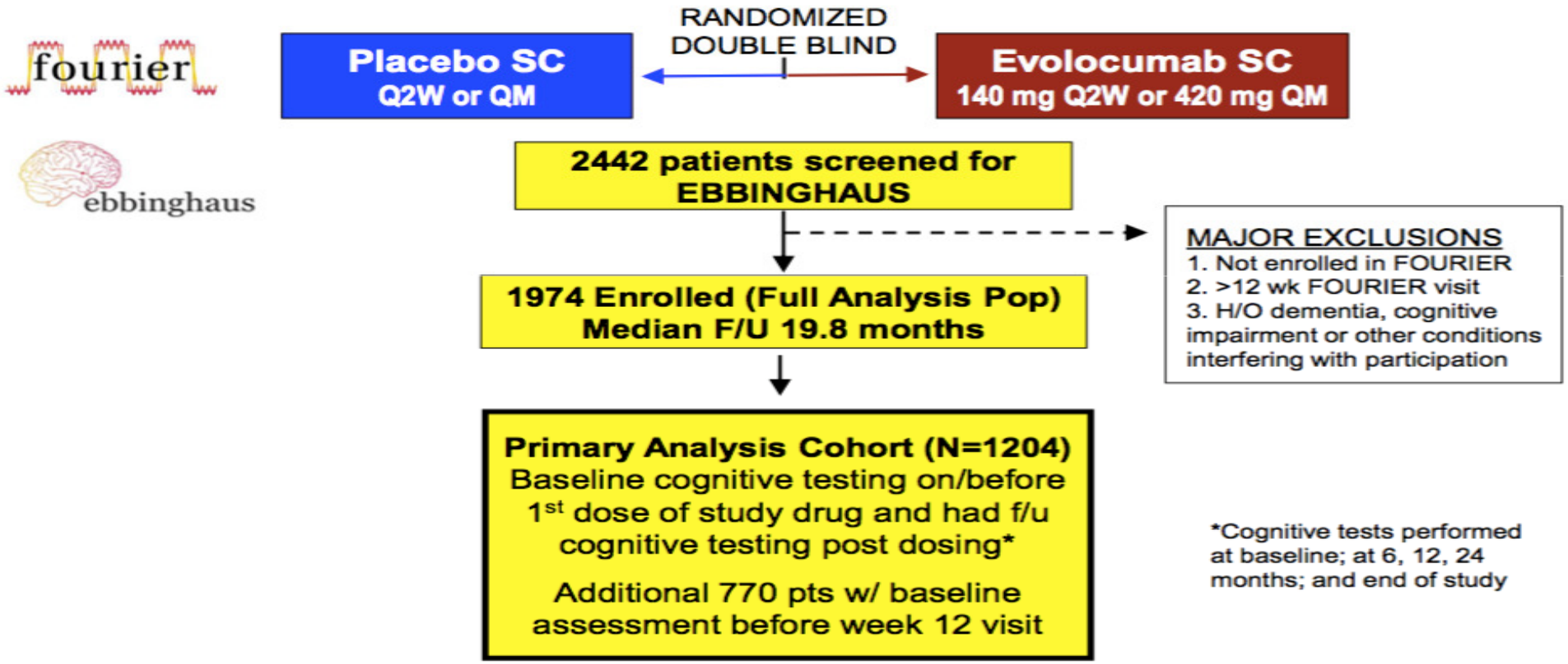




Large Molecule (Biologic)[1]	Small Molecule (Drug)[1]
Extremely high specificity[2]	Good specificity[2]
Parenteral administration[3]	Commonly administered orally[3]
Eliminated primarily by cellular endocytosis, phagocytosis and target-mediated clearance[3,4]	Metabolised and eliminated primarily by liver and kidneys[3,4]
Unlikely to have drug-drug interaction[4]	May have drug-drug interactions[4]
Longer half-life, less frequent administration[4]	Shorter half-life, more frequent administration[4]
Produced by genetically engineered cells or purified from natural sources[3]	Synthesised chemically or purified from natural sources[3]
Typically do not cross blood-brain barrier[5]	Some cross blood-brain barrier[5]
Can be immunogenic[4]	Rarely immunogenic[4]

1. Generics and Biosimilars Initiative. (2012, June 29). http://www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs; Accessed 13 April 2015. **2.** Webb, D.R., *et al. Biochemical Pharmacology*. 2013;85(2):147-152. **3.** Vugumeyster Y *et al. World Journal of Biological Chemistry*. 2013;*3*(4):73-92. **4.** Catapano, AL *et al. Atherosclerosis*. 2013;228(1):18-28. **5.** Gabathuler. *Neurobiology of Disease*. 2010;48-57.

Trial Design



Giugliano RP et al. *Clin Card* 2017;40:59–65

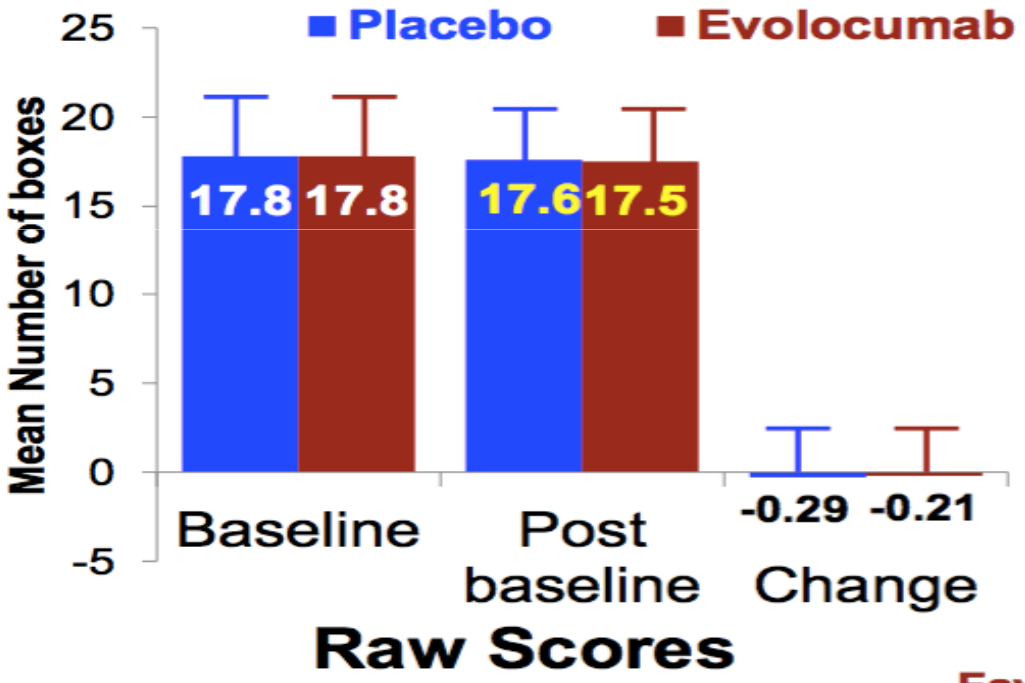
Endpoints

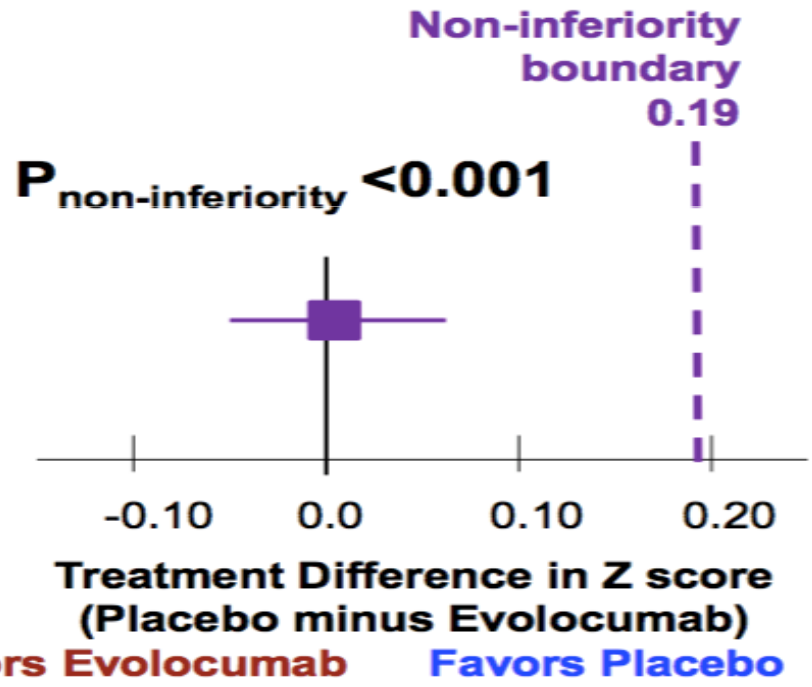
1. **Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform.**
   Assessed at baseline, 6, 12, 24, 48 mos and study end.
   - **Primary:** **Spatial working memory strategy index of executive function**
   - Secondary: Spatial working memory between errors
     Paired associates learning
     Reaction time
   - Exploratory: Global score (combines above 4 tests)
2. **Patient survey of everyday cognition* at study end**
3. **Investigator report of cognitive AEs**

*Memory and executive function domains

Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931
Giugliano RP et al. *Clin Card* 2017;40:59-65

Primary Endpoint
Spatial Working Memory Strategy Index

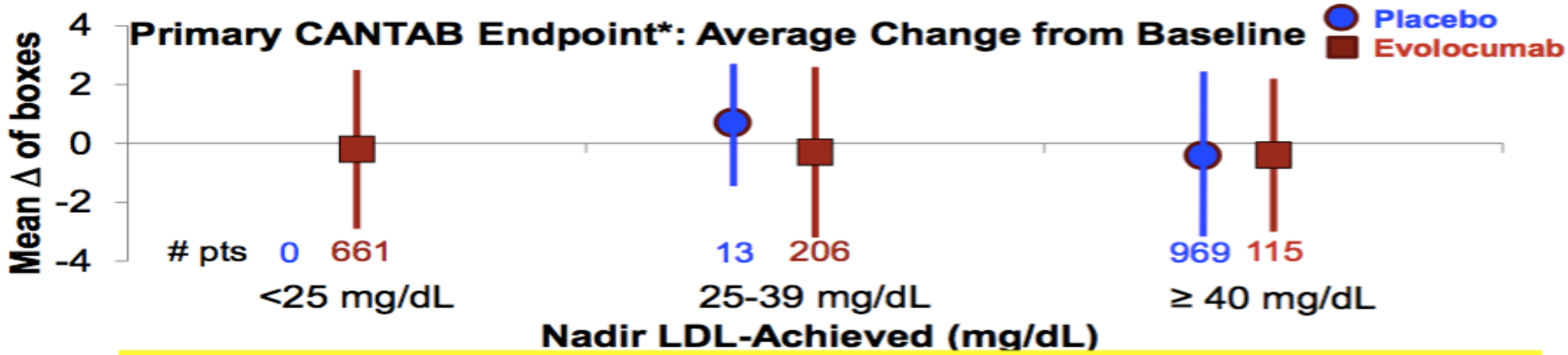




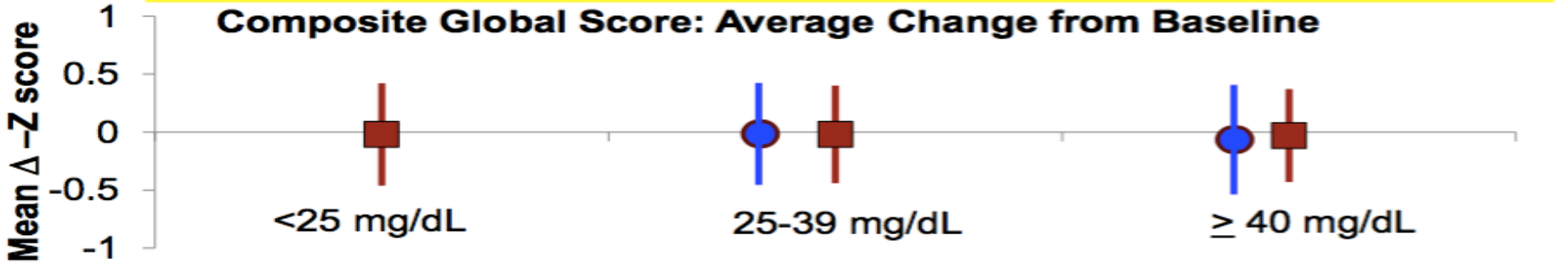
P_{NI} is from fixed estimate

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)

ebbinghaus



P=NS across LDL values achieved and also between treatments



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

Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

Patient Self-Report: 23 Questions Regarding Everyday Cognition

All Patients	Placebo (N=781) Mean (SD)	Evolocumab (N=800) Mean (SD)	P-Value
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
Total Score	**1.13 (0.33)**	**1.14 (0.33)**	**0.42**

Patient self-report at end of study as compared to randomization, graded as

1. *Better or no change*
2. *Questionable / occasionally worse*
3. *Consistently a little worse*
4. *Consistently much worse*

Lower scores represent better cognition

Results shown are in the full study population

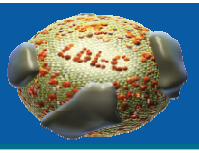
Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. **No differences btw evolocumab vs placebo**
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL**

O que muda depois do ACC17?



- *Os resultados do SPIRE 2 e do FOURIER confirmam e reforçam a tese do colesterol.*
- *A redução do LDL-C por meio da inibição da PCSK9 é agora comprovadamente eficaz na redução do risco cardiovascular.*
- *A inibição da PCSK9 é segura.*
- *O Programa SPIRE confirma a importância do uso de anticorpos monoclonais totalmente humanos.*
- *O ODYSSEY OUTCOMES será o mais longo estudo de desfecho cardiovascular com um inibidor da PCSK9; avaliará uma população de mais alto risco cardiovascular; e testará uma estrategia terapeutica com titulação de dose baseada na necessidade do paciente.*

Obrigado!