29º Congresso de Cardiologia do Estado da Bahia

Atualizações em Dislipidemias

LDL-c quanto menor, melhor?

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PREVENÇÃO

O QUE PRETENDEMOS ?

Reduzir LDL-c?

Reduzir RISCO?

Por que o LDL-c?

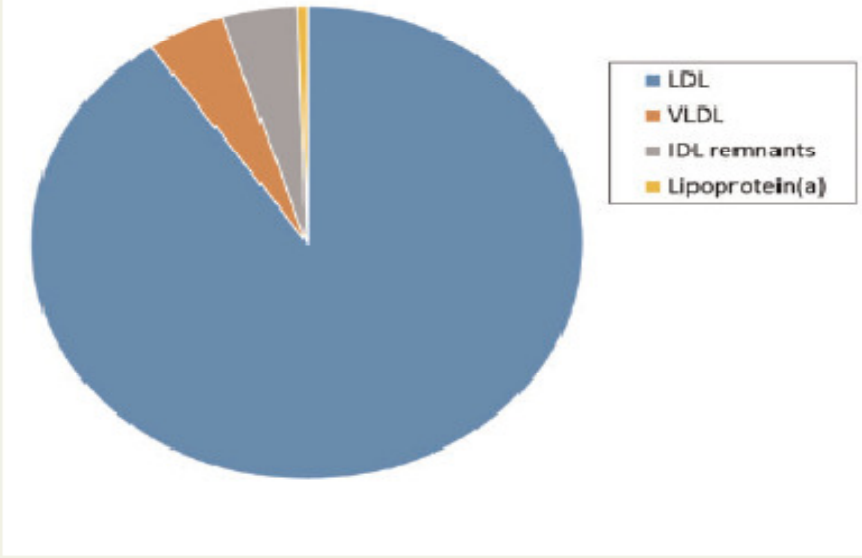
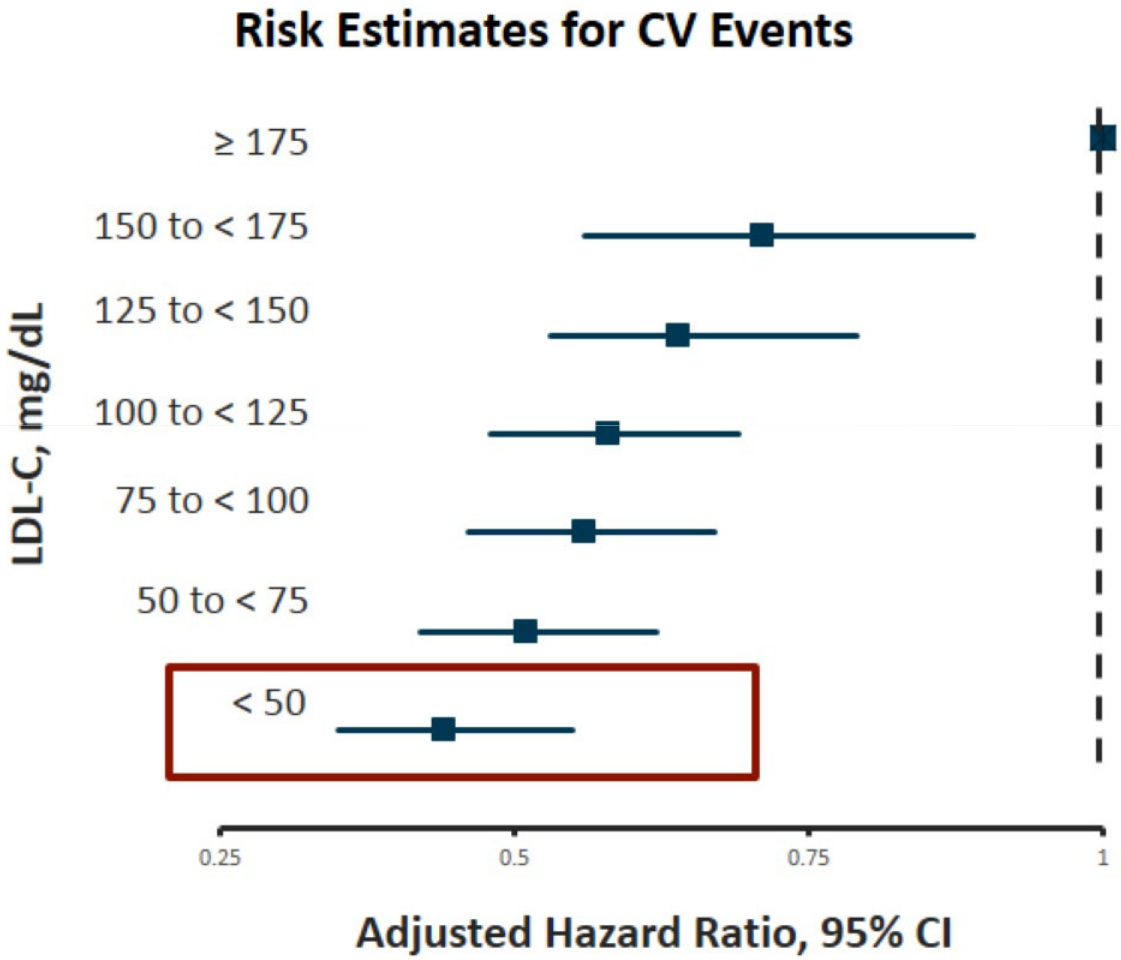


Figure 1 Relative concentration of apolipoprotein B (ApoB) contained in circulating lipoproteins in normolipidaemic individuals. ApoB content was calculated in nanomoles per litre using 500 000 as the defined molecular mass [i.e. low-density lipoprotein (LDL) 100 mg/dL or 2000 nmol/L, very low-density lipoprotein (VLDL) 5 mg/dL or 100 nmol/L, intermediate density lipoprotein (IDL) remnants 5 mg/dL or 100 nmol/L and lipoprotein(a) 10 nmol/l*]. *Based on population median.

LDL as a Risk Factor



Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64:485-494.

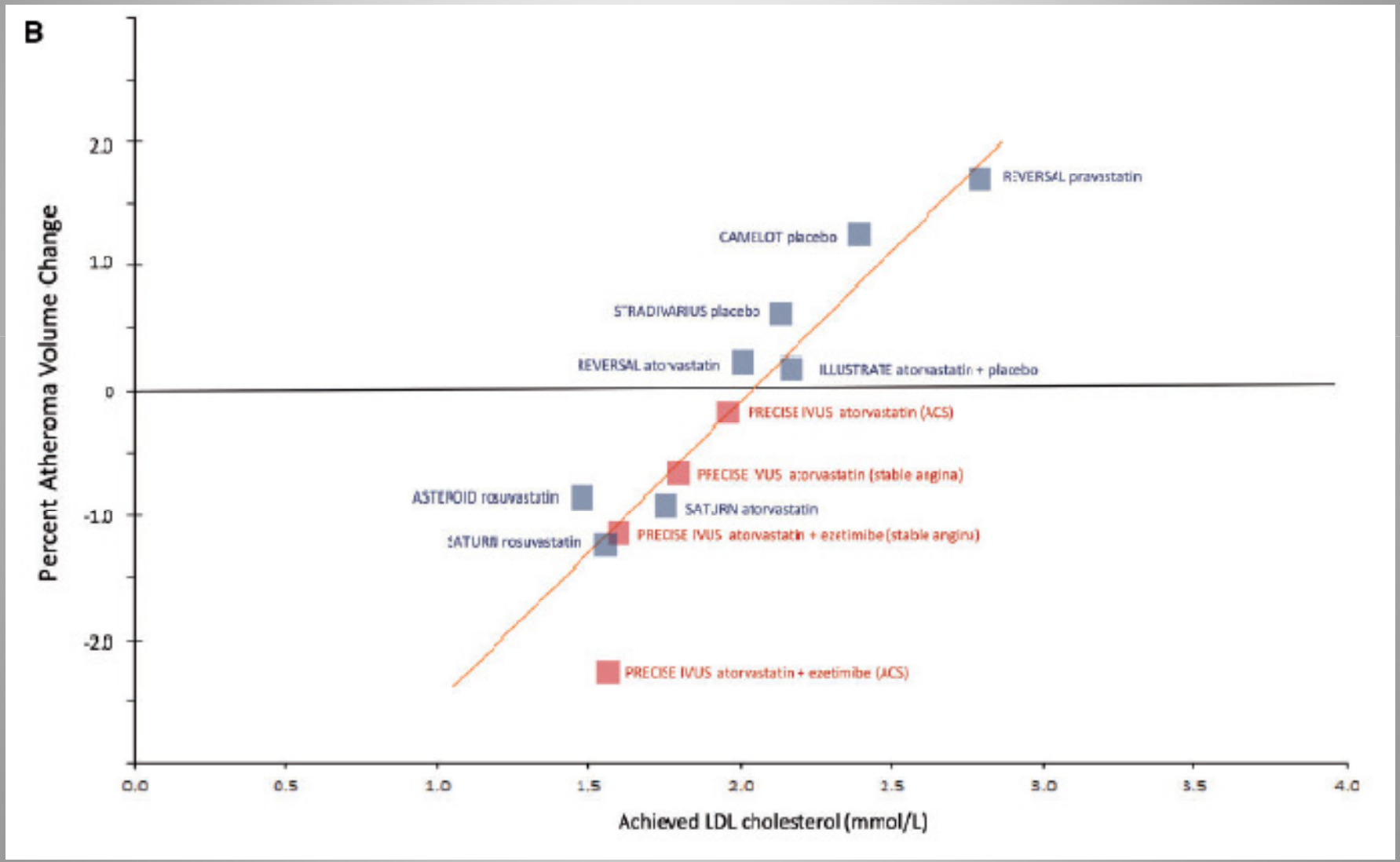
Por que reduzir LDL-c?

Relationship Between LDL-C Reduction and CHD Relative Risk

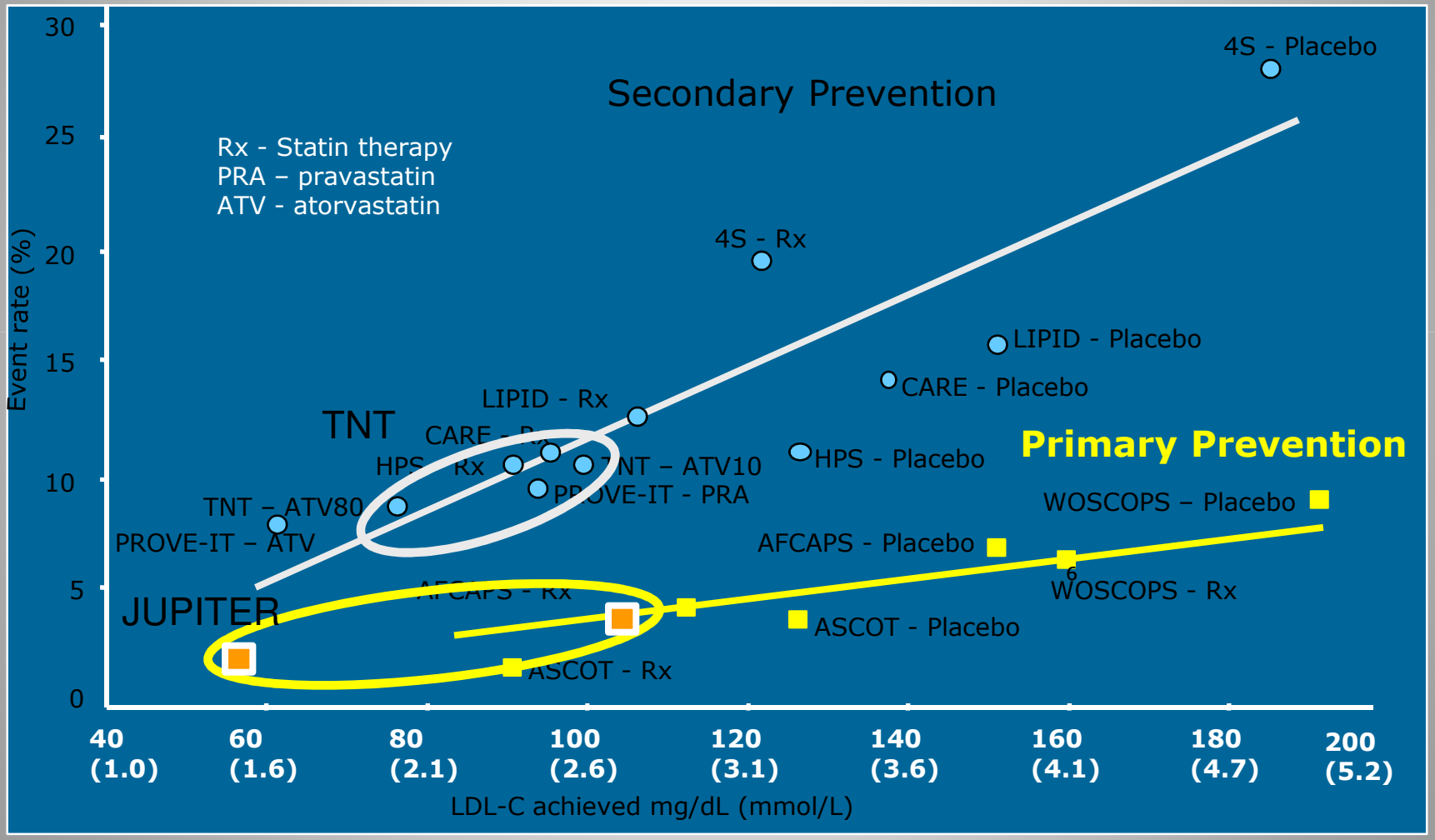
Study/Type	Year	Intervention	LDL-C, % Reduction	Nonfatal MI/CHD, Death, % Reduction (95% CI)
Diet				
London hospitals	1965	Low-fat diet	11	3 (−54, 39)
Oslo	1966	PUFA	16	25 (−10, 48)
MRC	1968	Soy oil	18	16 (−32, 46)
Los Angeles	1969	PUFA	17	17 (−29, 46)
Sydney	1978	PUFA	4	−65 (−185, 4)
BAS				
Upjohn	1978	Colestipol	13	38 (−11, 65)
NHLBI	1984	Cholestyramine	21	53 (−44, 85)
LRC	1984	Cholestyramine	13	17 (−9, 37)
Surgery				
POSCH	1998	Ileal bypass	38	31 (−1, 53)
Statin				
4S	1994	Simvastatin	35	31 (21, 39)
WOSCOPS	1995	Pravastatin	26	30 (15, 43)
CARE	1996	Pravastatin	28	23 (7, 36)
LIPID	1998	Pravastatin	25	22 (13, 31)
AFCAPS/TexCAPS	1998	Lovastatin	26.5	37 (20, 50)
HPS	2002	Simvastatin	30	26 (19, 32)
PROSPER	2002	Pravastatin	27	17 (3, 30)
ALERT	2003	Fluvastatin	32	25 (−2, 44)
ASCOT-LLA	2003	Atorvastatin	35	35 (17, 50)
CARDS	2004	Atorvastatin	40	35 (3, 56)

Robinson et al. *J Am Coll Cardiol*. 2005;46:1855-1862.

LDL colesterol e regressão de placa, Mais baixo é melhor?



LDL colesterol e benefícios nos ensaios clínicos
Mais baixo é melhor?



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;**9**(2):269-279

LaRosa JC *et al. N Engl J Med* 2005;**352**:e-version

IMPROVE-IT
Enrollment and Study Period

Assumptions

- 1% clinical benefit for every 1.6-mg/dL difference in LDL-C
- **15-mg/dL incremental reduction in LDL-C with ezetimibe**
- 25% reduction in treatment effect in first 6 mo

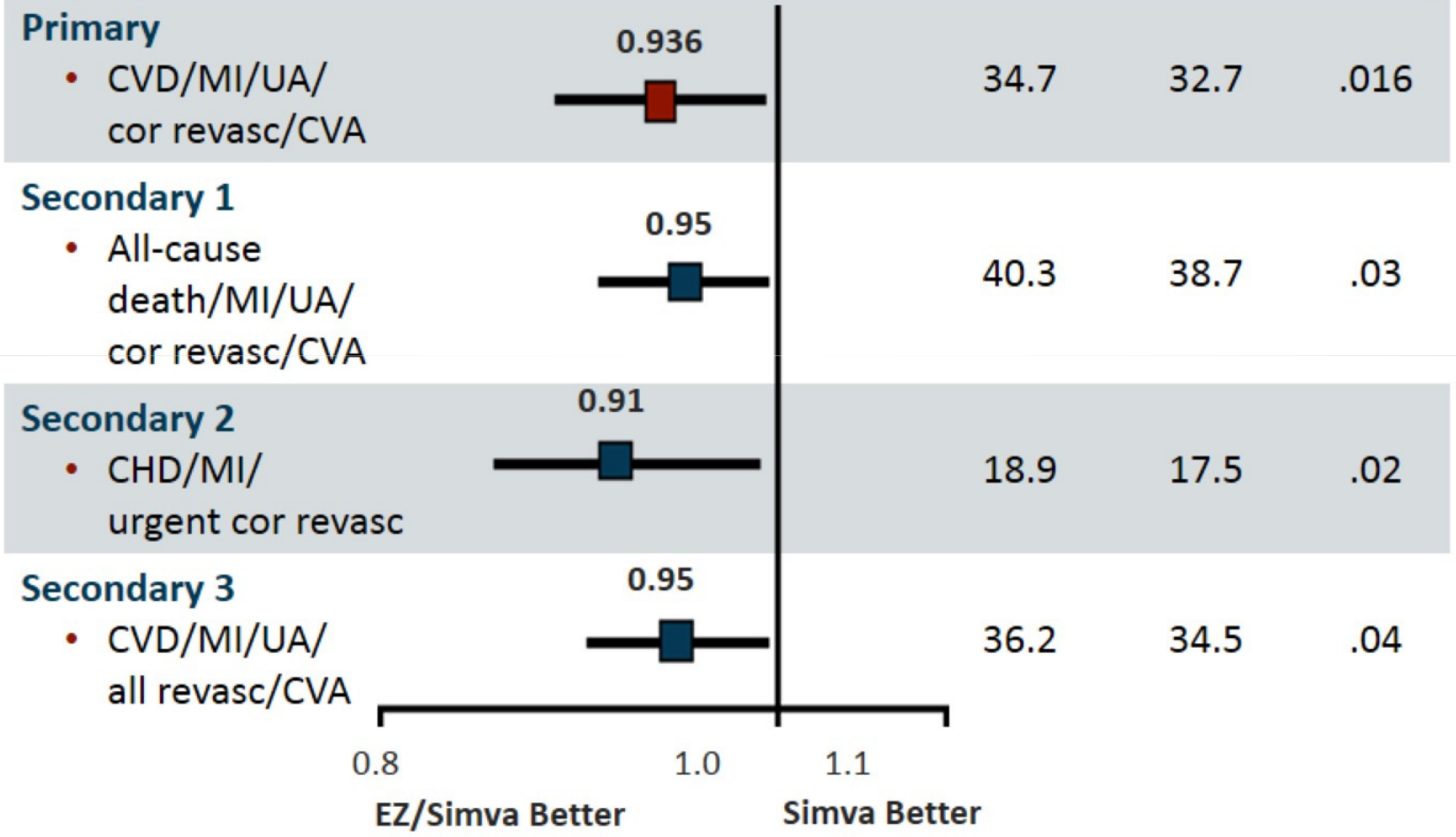
→ **9.375% treatment effect for primary endpoint**

Required to detect difference in LDL-C level between treatment groups

- Large study population: N=18,144
- Long study period: 7-y follow-up; 9 y total

Cannon CP, et al. *Am Heart J.* 2008;156:826-832.

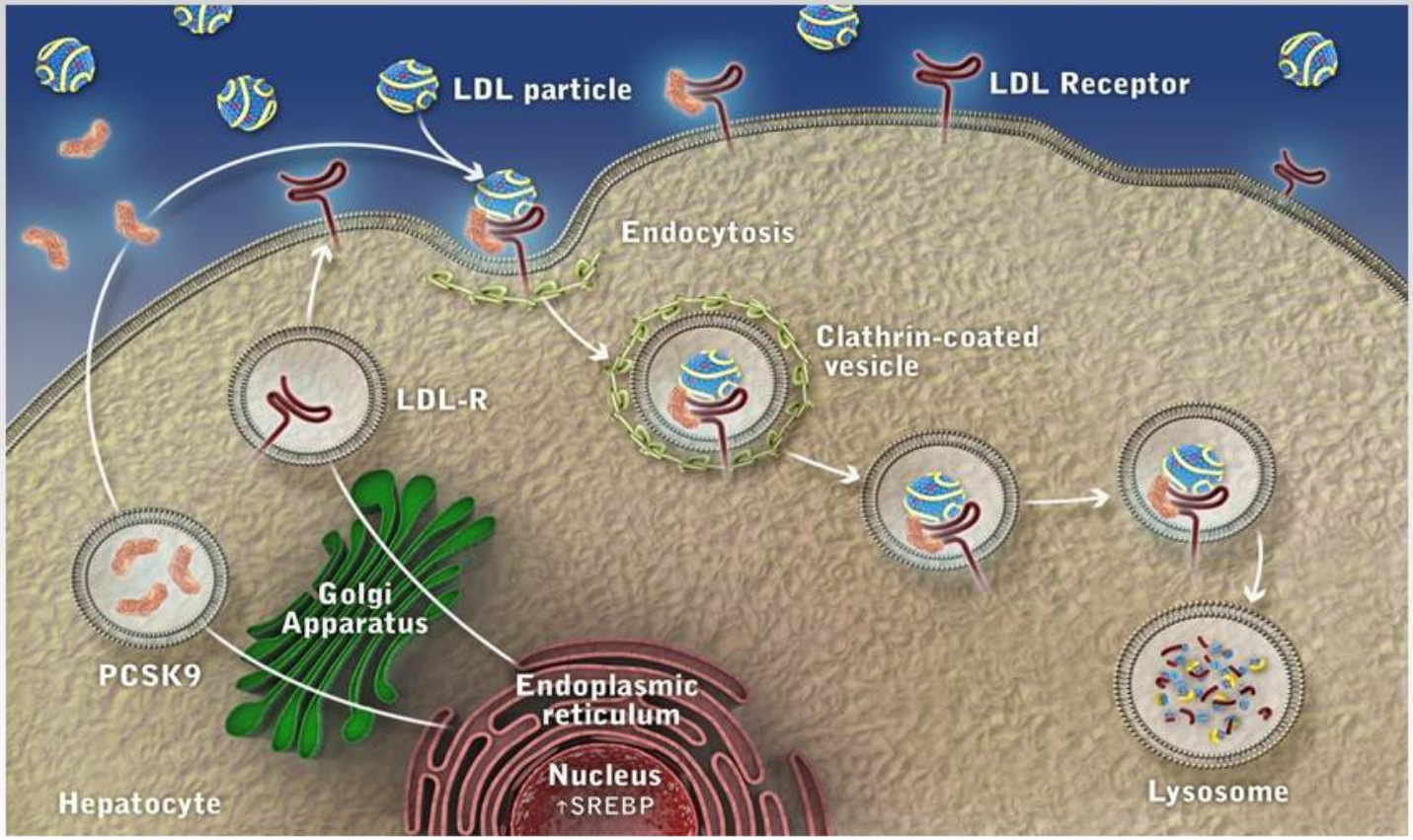
IMPROVE-IT
Efficacy



cor revasc, ≥ 30 d after randomization; all revasc ≥ 30 d.
*7-y event rates (%).
Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397.

Nova Era na Redução de LDL-c

The Role of PCSK9 in the Regulation of LDL-Receptor Expression



LIPID & METABOLIC

McKenney J. ACC; 2012.

theheart.org from WebMD | Medscape EDUCATION

RCTs (Phase 3 Trials) With PCSK9 Inhibitors (vs. placebo or ezetimibe) Recently Published or Presented

RCT	Study Design	Net LDL-C Reduction (%)
DESCARTES	Long-term efficacy and safety	-49 to -62
LAPLACE-2	Combination therapy with statins	-63 to -75
GAUSS-2	Statin intolerance	-37 to -39
MENDEL-2	Monotherapy	-39 to -40
RUTHERFORD-2	Heterozygous FH	-60 to -66
TESLA	Homozygous FH	-31
ODYSSEY MONO	Comparison with ezetimibe in patients with hypercholesterolemia at moderate CV risk	-32
ODYSSEY COMBO II	Comparison with ezetimibe	-30
ODYSSEY FH I and II	Heterozygous FH	-51 to -58
ODYSSEY LONG TERM	Combination with statins	-62
ODYSSEY ALTERNATIVE	Statin intolerance	-30
ODYSSEY HIGH FH	Severe heterozygous FH	-39
ODYSSEY COMBO I	On top of maximally tolerated statins ± other lipid-lowering drugs in high-risk patients	-24 to -49
ODYSSEY OPTIONS I and II	Comparison of different strategies to further reduce LDL-C in high-risk patients not at goal	-20 to -37

De Backer J, et al. *Eur Heart J.* 2015;36:214-218.

PCSK9 Inhibitor CV Outcomes Trials

	Evolocumab	Alirocumab	Bococizumab	
Sponsor	Amgen	Sanofi/Regeneron	Pfizer	
Trial	**FOURIER**	**ODYSSEY Outcomes**	**SPIRE I**	**SPIRE II**
Sample size	27,500	18,000	17,000	9000
Patients	MI, stroke, or PAD	4-52 weeks post-ACS	High risk for CV event	
Statin	Atorva ≥20 mg or equiv	Evid-based med Rx	Lipid-lowering Rx	
LDL-C, mg/dL (mmol/L)	≥70 (≥1.8)	≥70 (≥1.8)	70-99 (1.8-2.6)	≥100 (≥2.6)
PCSK9i dosing	q2w or q4w	q2w	q2w	
Endpoint	1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hosp for UA	CV death, MI, stroke, or urgent revasc	
Completion	12/2017	1/2018	8/2017	

Robinson JG, et al. *N Engl J Med.* 2015;372:1489-1499.
http://www.clinicaltrials.gov (NCT01764633/ NCT01975376/NCT01975389)

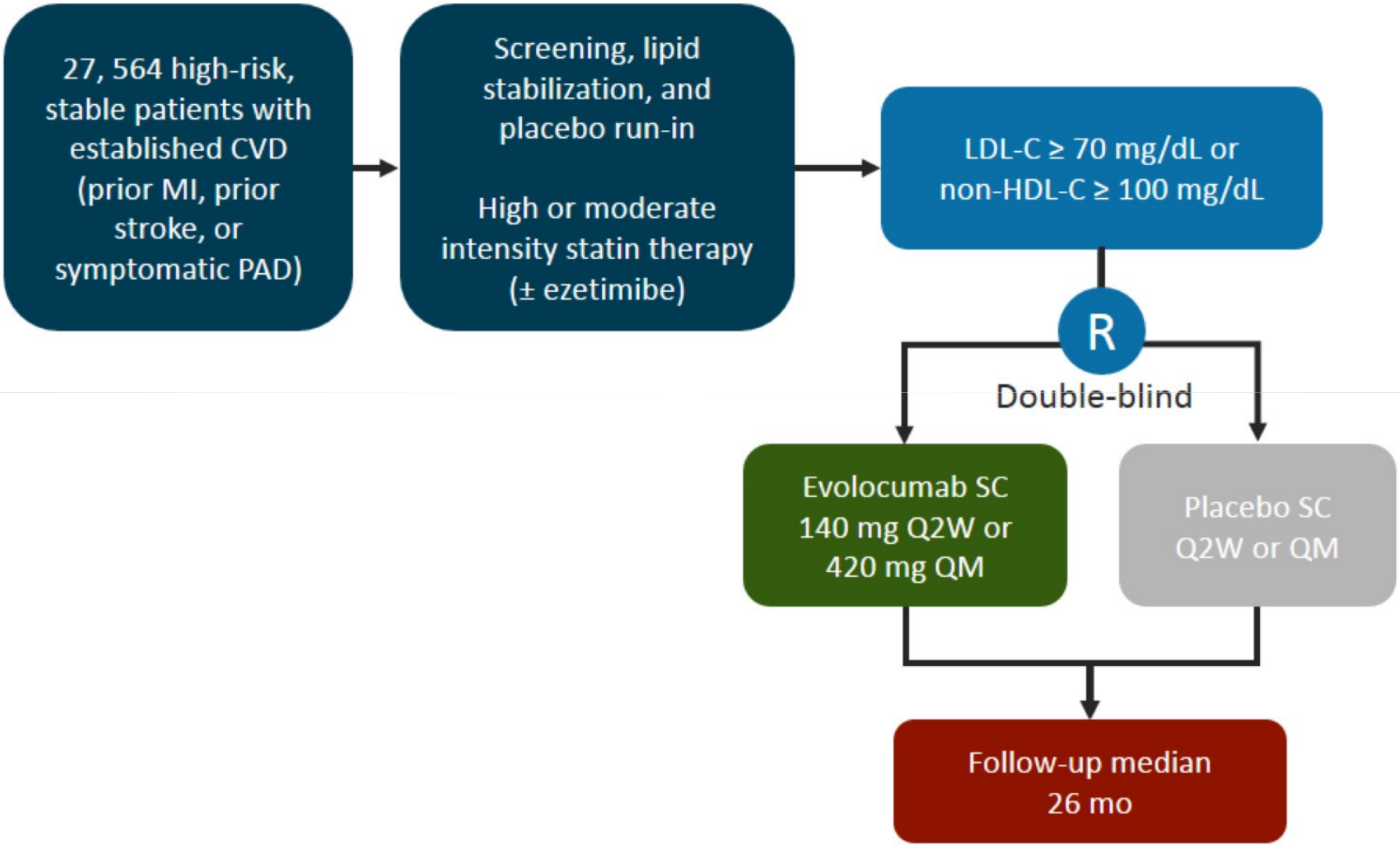
Medscape EDUCATION

theheart.org from WebMD

FOURIER: Cardiovascular Outcomes With PCSK9 Inhibition

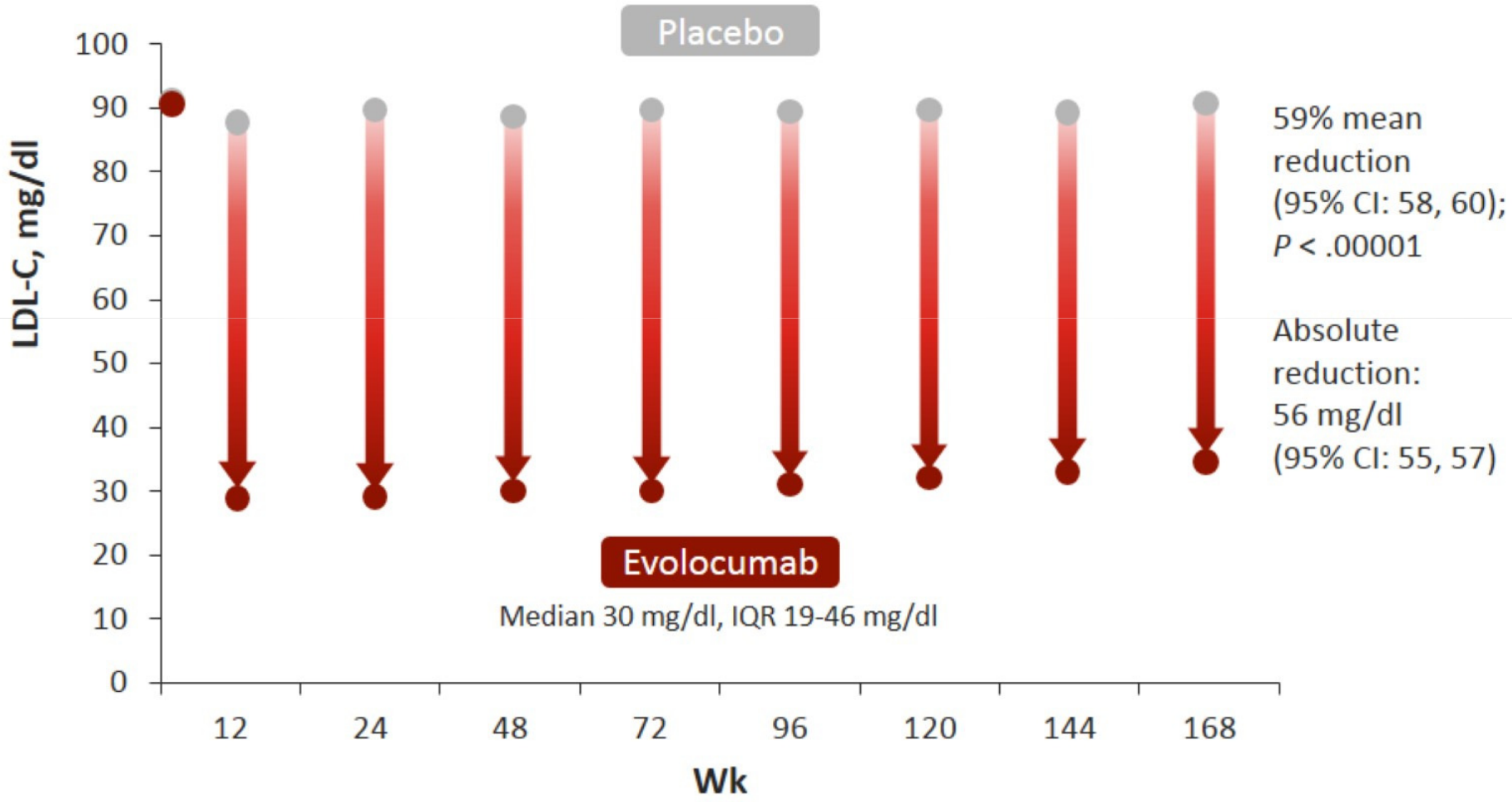
Marc S. Sabatine, MD
Professor of Medicine
Harvard Medicine School
Chairman, TIMI Study Group
Lewis Dexter, MD Distinguished Chair
in CV Medicine
Brigham and Women's Hospital
Boston, Massachusetts

FOURIER Trial Design



Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]; Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

FOURIER: LDL-C Reduction



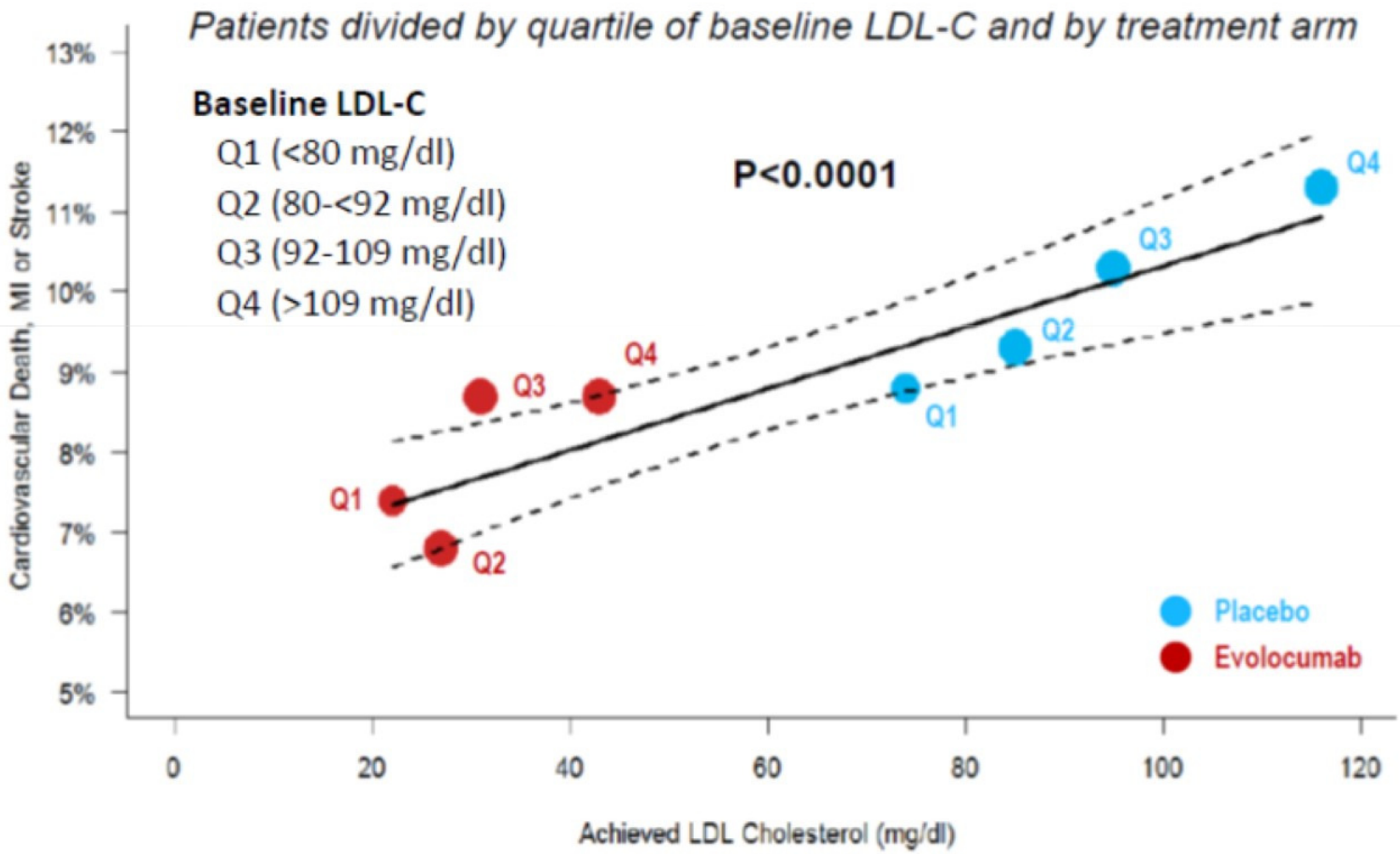
Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

FOURIER: CV Outcomes

Endpoint	Evolocumab (N = 13,784)	Placebo (N = 13,780)	HR (95% CI)
CVD, MI, stroke, UA or revasc	12.3	14.6	0.85 (0.79, 0.92)
CV death, MI, or stroke	7.9	9.9	0.80 (0.73, 0.88)
CV death	2.5	2.4	1.05 (0.88, 1.25)

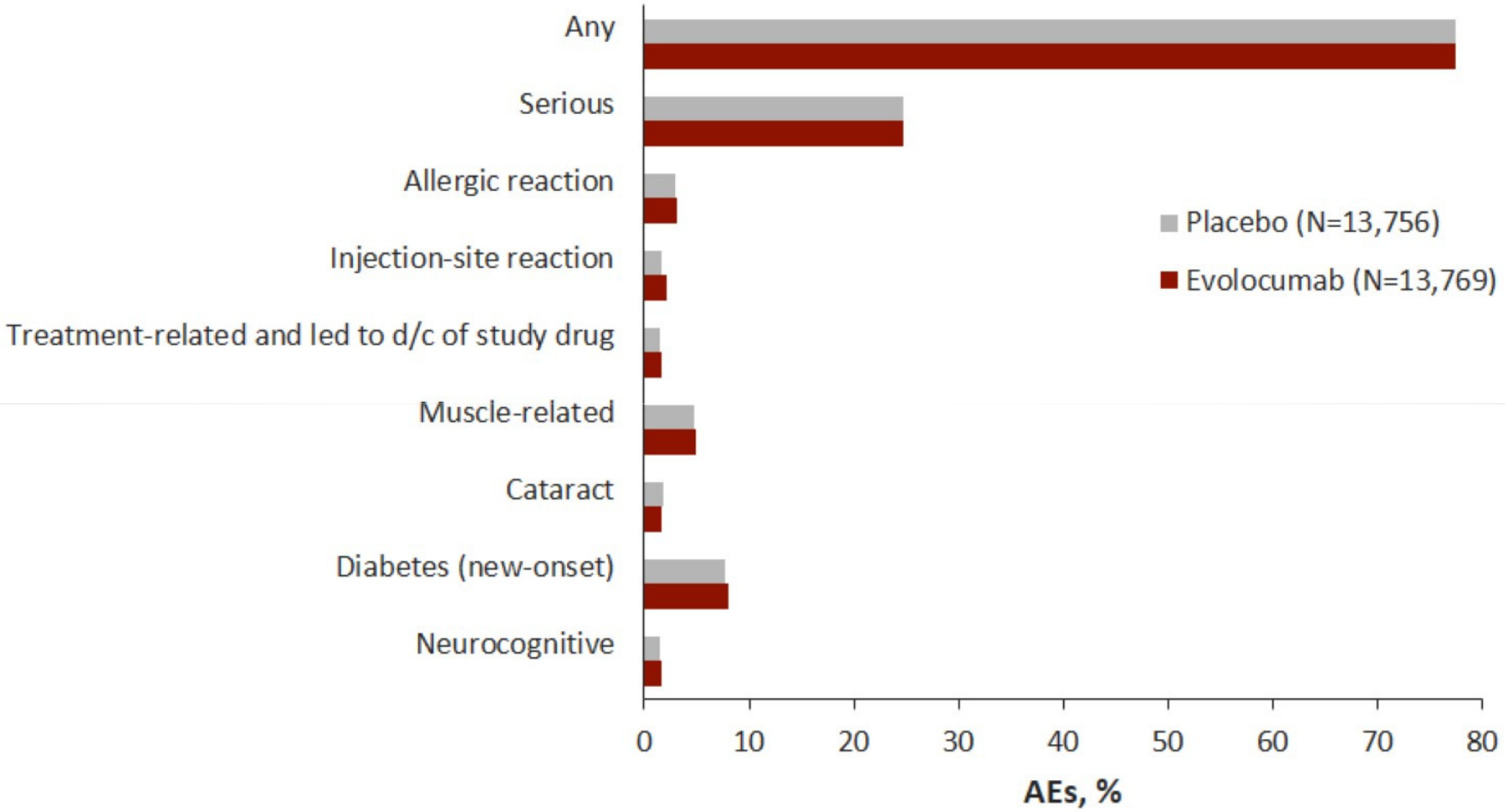
Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

FOURIER: Lower LDL-C Is Better



Sabatine MS, et al. ACC.17.

FOURIER: Safety



Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

Critérios de Causalidade
LDL-c vs DCV Aterosclerótica

Plausibilidade Biológica

Força da Associação

Gradiente Biológico

Sequência Temporal

Especificidade

Consistência

Redução de Risco com intervenções que reduzem LDL-C