Reunión Anual de la Sección de Riesgo Vascular y Rehabilitación Cardiaca de la SEC

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA | Sección de Riesgo Vascular y Rehabilitación Cardiaca

San Sebastián Donostia

25 y 26 de Mayo 2018

Hotel Silken Amara plaza

Reunión anual de la Sección de Riesgo Vascular y Rehabilitación cardiaca

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA | Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

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#Cardiofighters: Preguntas clave en la identificación del paciente de alto riesgo vascular.

Cardiofighters: Dra. Almudena Castro, Dr. Domingo Marzal

Árbitro: Dr. Iñaki Lekuona

Preguntas clave en la identificación del paciente de alto riesgo vascular.

Escribir la URL siguiente:

http://amgendigital.es/cardiofighters

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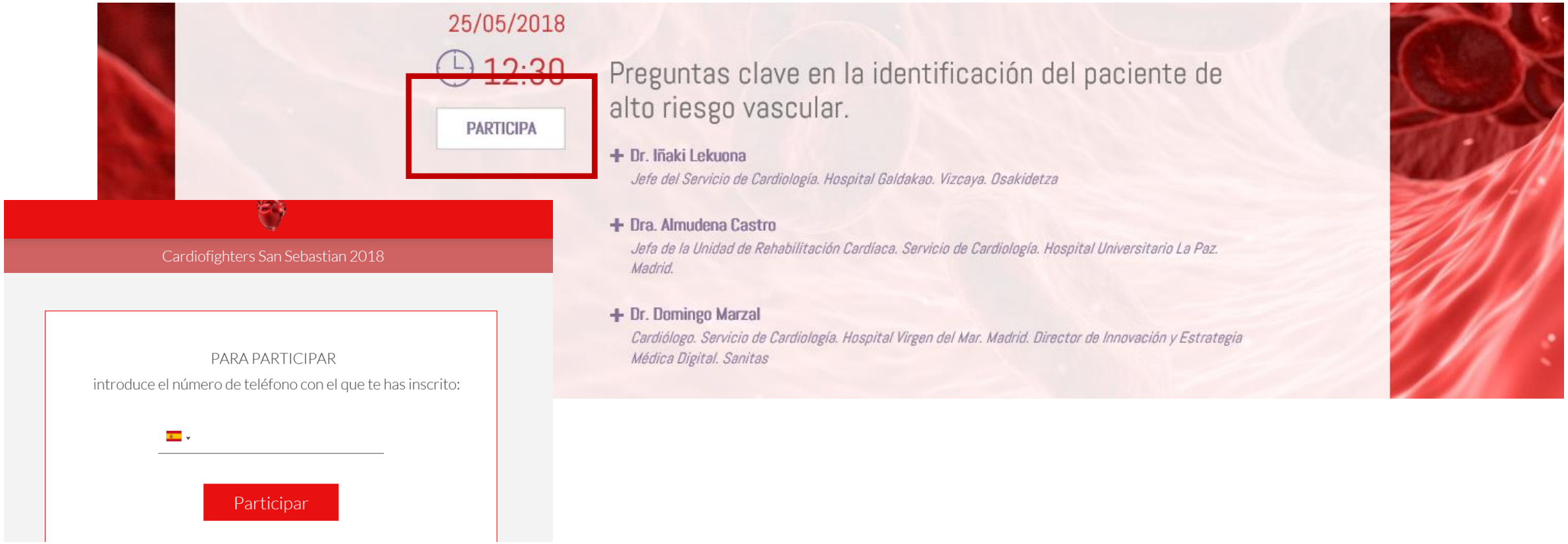
SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Sección de Riesgo Vascular y Rehabilitación Cardiaca

http://amgendigital.es/cardiofighters



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Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

www.amgendigital.es/cardiofighters

Introducir el número de teléfono móvil para participar en la sesión

IMPORTANTE

El número sólo se usará durante esta sesión y se eliminará su registro inmediatamente al acabar el evento.

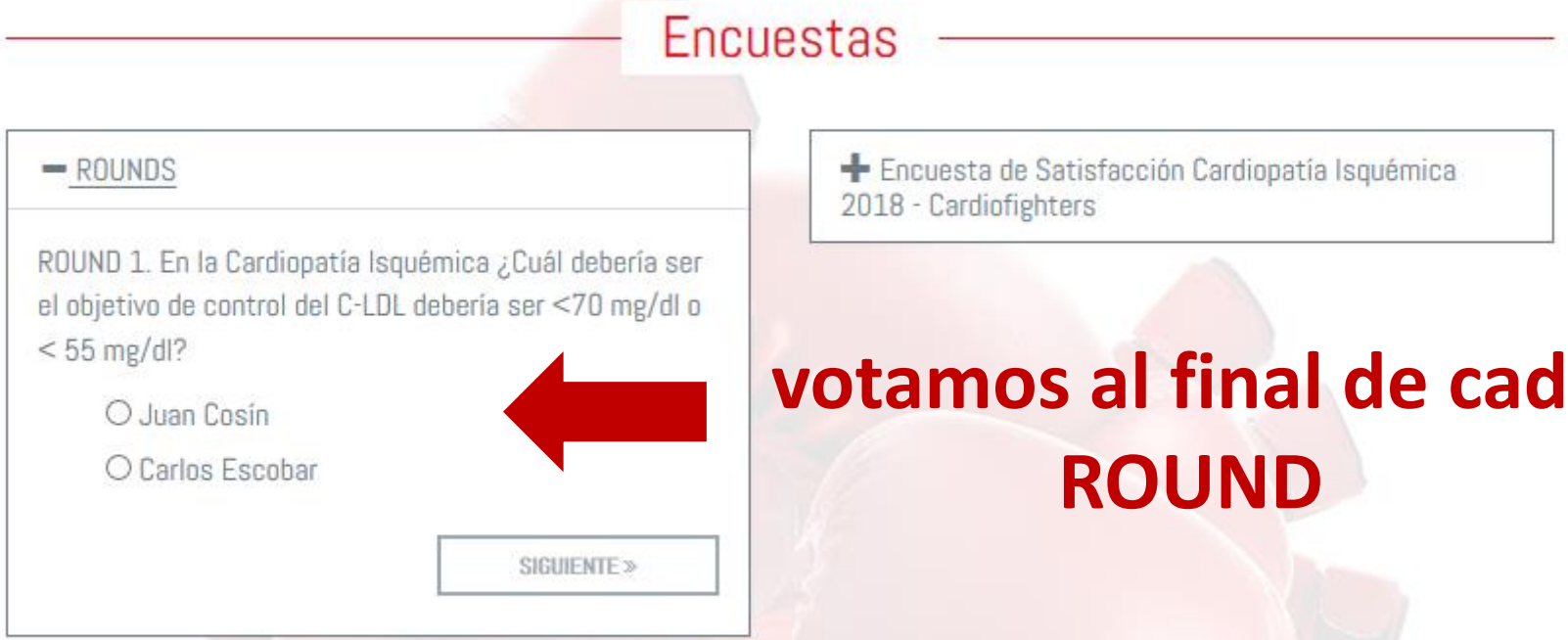
SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

Para votar por los #CardioFighters

Tenemos cuatro ROUNDs de preguntas



votamos al final de cada ROUND

Veremos las votaciones al final de cada round

NO OLVIDAR!!!!!

Rellenar la encuesta de satisfacción

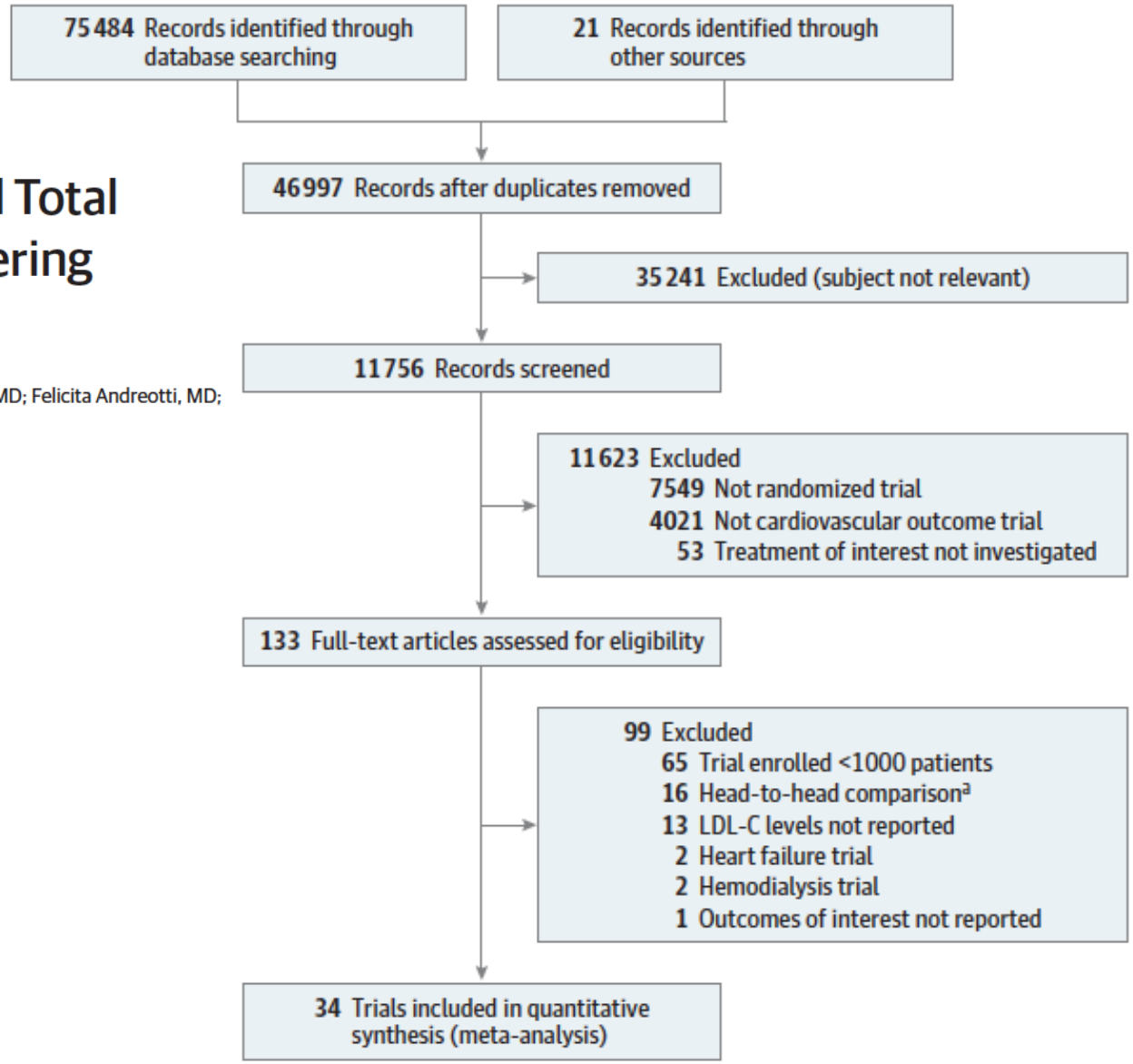
ROUND #1
Es verdad que
¿el c-LDL cuanto más bajo mejor?

JAMA | Original Investigation

Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering

A Systematic Review and Meta-analysis

Eliano P. Navarese, MD, PhD; Jennifer G. Robinson, MD, MPH; Mariusz Kowalewski, MD; Michalina Kołodziejczak, MD; Felicita Andreotti, MD; Kevin Bliden, MD; Udaya Tantry, PhD; Jacek Kubica, MD, PhD; Paolo Raggi, MD; Paul A. Gurbel, MD



Navarese E.P et al. JAMA. 2018;319(15):1566-1579

Source	Source	No.	No. (%) Women	History Diabetes	History Vascular Disease	History CAD	Median Follow-up, y	More Intensive LDL-C Lowering Treatment	More Intensive LDL-C Lowering Baseline LDL-C, Mean (SD), mg/dL	More Intensive LDL-C Lowering LDL-C Reduction, %	Less Intensive LDL-C Lowering Treatment	Less Intensive LDL-C Lowering Baseline LDL Mean (SD), mg/dL
4S,[7] 1994	MEGA,[37] 2006	8214	5547 (68)	1686 (21)	<1	<1	5.3	Pravastatin (10-20 mg) [n = 3866]	156.61 (17.79)	−22	Usual care [n = 3966]	156.61 (17
WOSCOPS,[21] 1995	SPARCL,[38] 2006	4731	1908 (40)	794 (17)	4731 (100)	0	4.9 (range, 4.0-6.6)	Atorvastatin (80 mg) [n = 2365]	132.7 (0.5)	−45	Placebo [n = 2366]	133.7 (0.5
CARE,[22] 1996	JUPITER,[9] 2008	17 802	6801 (30)	76 (<1)	0	0	1.9	Rosuvastatin (20 mg) [n = 8901]	108	−49	Placebo [n = 8901]	108
THE POST CABG Trial,[23] 1997	SEARCH,[39] 2010	12 064	2052 (17)	1267 (11)	12 064 (100)	12 064 (100)	6.7	Simvastatin (80 mg) [n = 6031]	96.67	>13	Simvastatin (20 mg) [n = 6033]	96.67
AFCAPS-TexCAPS,[24] 1998	HOPE-3,[40] 2016	12 705	5874 (46)	731 (6)	0	0	5.6	Rosuvastatin (10 mg) [n = 6361]	127.8 (36.1)	−26	Placebo [n = 6344]	127.9 (36.
LIPID,[8] 1998	SEAS,[41] 2008	1873	723 (39)	0%	0	0	4.4	Simvastatin (40 mg) + ezetimibe (10 mg) [n = 944]	140 (36)	−54	Placebo [n = 929]	139 (35)
GISSI-P,[25] 2000	SHARP,[42] 2011	9270	3470 (37)	2094 (23)	1393 (15)	0	4.9	Simvastatin (20 mg) + ezetimibe (10 mg) [n = 4650][b]	107.12 (34.03)	−30	Placebo [n = 4620]	107.50 (33
ALLHAT-LLT,[26] 2002	IMPROVE-IT,[2] 2015	18 144	4416 (24)	4933 (27)	18 144 (100)	18 144 (100)	6	Simvastatin (40 mg) + ezetimibe (10 mg) [n = 9077]	93.8	−43	Simvastatin (40 mg) [n = 9077]	93.8
GREACE,[27] 2002	ODYSSEY LONG TERM,[4] 2015	2341	884 (38)	809 (35)	2341 (100)[d]	1607 (69)	1.5	Alirocumab (150 mg every 2 wk) [n = 1553]	122.7 (42.6)	−53	Placebo [n = 788]	121.9 (41.
HPS,[28] 2002	OSLER 1 & 2,[5] 2015	4465	2210 (49)	599 (13)	1303 (29)	896 (20)	0.9	Evolocumab (140 mg every 2 wk or 420 mg every mo) [n = 2976]	120	−61	Usual care [n = 1489]	121
LIPS,[29] 2002	FOURIER,[3] 2017	27 564	6769 (25)	10 081 (37)	27 564 (100)	22 351 (81)	2.2 (IQR 1.4-3.6)	Evolocumab (140 mg every 2 wk or 420 mg every mo) [n = 13 784]	92	−61	Placebo [n = 13 780]	92
PROSPER,[30] 2002	SPIRE-1,[43] 2017	16 817	4439 (26)	8047 (48)	14 563 (87)	NA	0.6	Bococizumab (150 mg every 2 wk) [n = 8408]	93.8	−45	Placebo [n = 8409]	93.7
ALERT,[31] 2003	SPIRE-2,[43] 2017	10 621	3675 (35)	4986 (47)	8635 (81)	NA	1.1	Bococizumab (150 mg every 2 wk) [n = 5312]	133.9	−41	Placebo [n = 5309]	133.4
ASCOT-LLA,[32] 2003	All trials	270 288[e]					3.9					
A to Z,[33] 2004												
ALLIANCE,[34] 2004												
CARDS,[35] 2004												
PROVE IT-TIMI,[12] 22 2004												
TNT,[10] 2005												
IDEAL,[11] 2005												
ASPEN,[36] 2006												

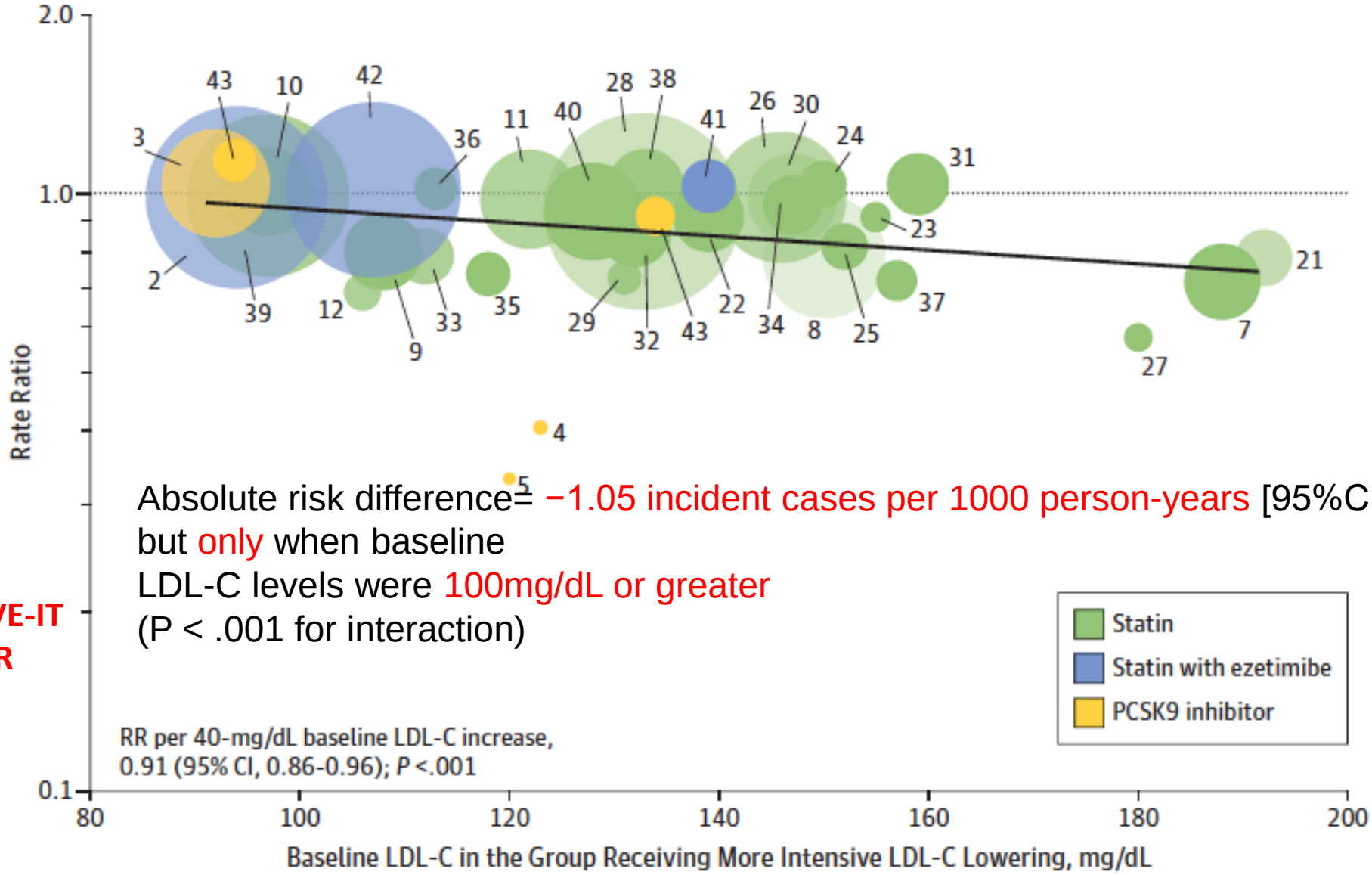
JUPITER

IMPROVE-IT

FOURIER

SPIREs

Meta-regression Analysis of **All-cause Mortality** by Baseline LDL-C Level (34 RCTs)



7: 4S
21: WOSCOPS
27: GRACE

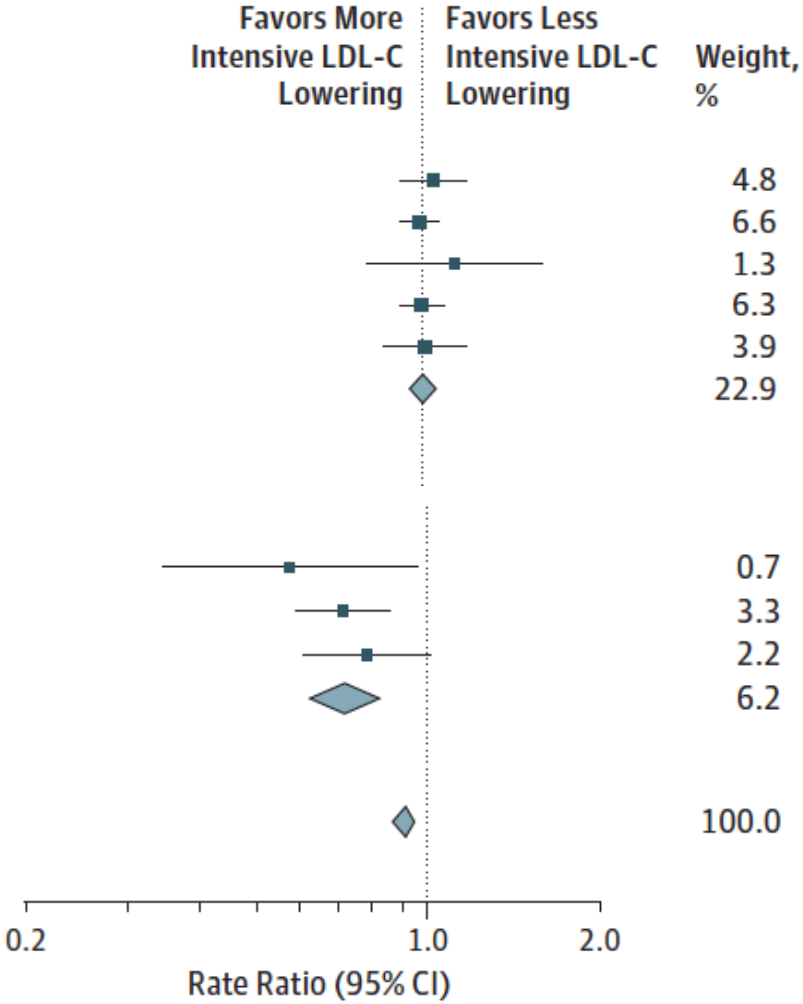
Absolute risk difference= −1.05 incident cases per 1000 person-years [95%CI, −1.59 to −0.51])
but only when baseline
LDL-C levels were 100mg/dL or greater
(P < .001 for interaction)

2: IMPROVE-IT
3: FOURIER
43: SPIRE

Navarese E.P et al. JAMA. 2018;319(15):1566-1579

Meta-analysis of **All-cause Mortality** Stratified by Baseline LDL-C Level

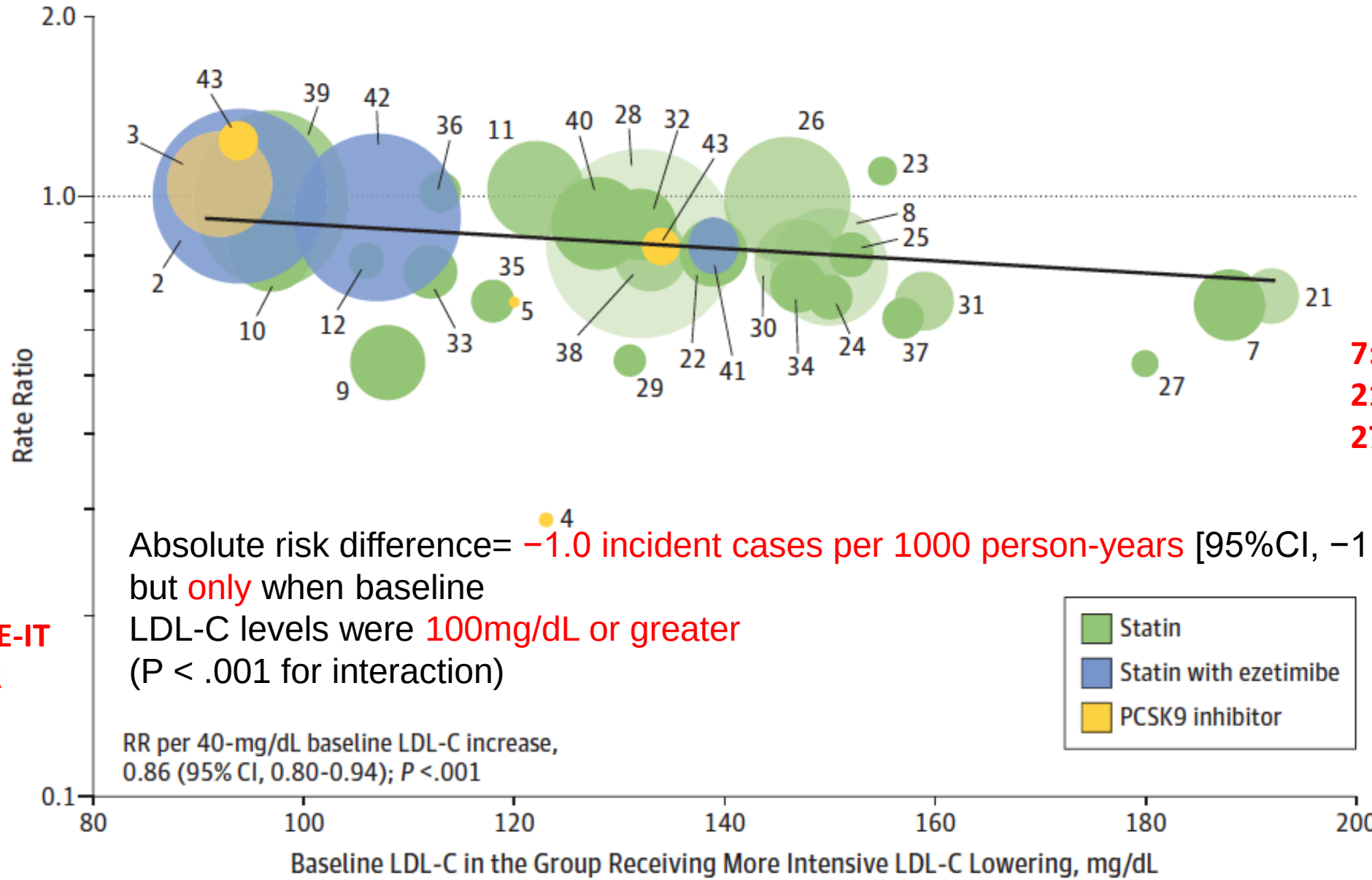
Study and Subgroup	No. of Patients With Event/Total No. (%) More Intensive LDL-C Lowering	Less Intensive LDL-C Lowering	Rate Ratio (95% CI)	Weight, %
Baseline LDL-C <100 mg/dL				
FOURIER,[3] 2017	444/13 784 (3.22)	426/13 780 (3.09)	1.04 (0.91-1.19)	4.8
IMPROVE-IT,[2] 2015	1215/9067 (13.40)	1231/9077 (13.56)	0.99 (0.91-1.07)	6.6
SPIRE-1,[43] 2017	66/8408 (0.78)	58/8409 (0.69)	1.14 (0.80-1.62)	1.3
SEARCH,[39] 2010	964/6031 (15.98)	970/6033 (16.08)	0.99 (0.91-1.09)	6.3
TNT,[10] 2005	284/4995 (5.69)	282/5006 (5.63)	1.01 (0.86-1.19)	3.9
Subtotal	2973/42 285 (7.03)	2967/42 305 (7.01)	1.00 (0.95-1.06)	22.9
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_4 = 0.99$ ($P = .91$); $I^2 = 0\%$				
Overall effect: $z = 0.11$ ($P = .92$)				
Baseline LDL-C ≥160 mg/dL				
GREACE,[27] 2002	23/800 (2.88)	40/800 (5.00)	0.57 (0.34-0.96)	0.7
4S,[7] 1994	182/2221 (8.19)	256/2223 (11.52)	0.71 (0.59-0.86)	3.3
WOSCOPS,[21] 1995	106/3302 (3.21)	135/3293 (4.10)	0.78 (0.61-1.01)	2.2
Subtotal	311/6323 (4.92)	431/6316 (6.82)	0.72 (0.62-0.84)	6.2
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 1.17$ ($P = .56$); $I^2 = 0\%$				
Overall effect: $z = 4.38$ ($P < .001$)				
Total	9651/136 299 (7.08)	10 311/133 989 (7.70)	0.92 (0.88-0.96)	100.0
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_{33} = 60.79$ ($P = .002$); $I^2 = 46\%$				
Overall effect: $z = 3.80$ ($P < .001$)				
$P < .001$ for interaction (<100 mg/dL vs ≥100 mg/dL)				



4.3 fewer deaths per 1000 person-years

Navarese E.P et al. JAMA. 2018;319(15):1566-1579

Meta-regression Analysis of **Cardiovascular Mortality** by Baseline LDL-C Level



7: 4S
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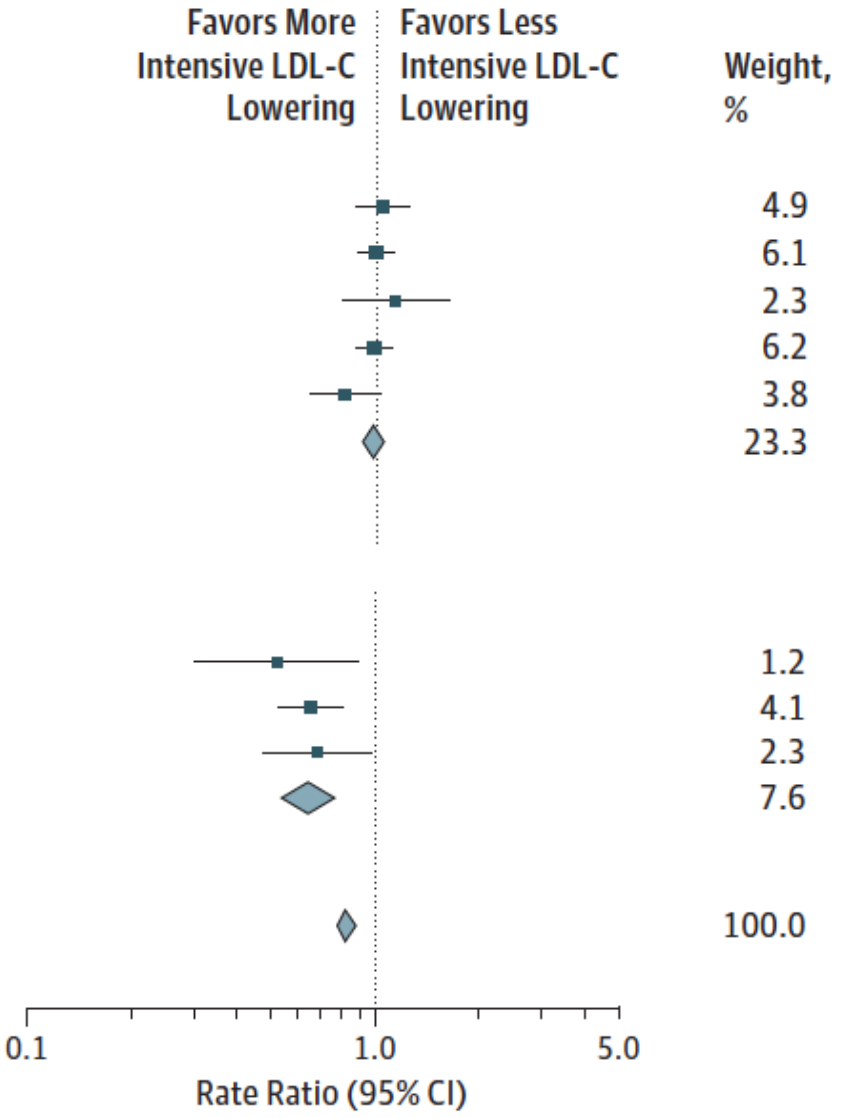
Absolute risk difference= −1.0 incident cases per 1000 person-years [95%CI, −1.59 to −0.51])
but only when baseline
LDL-C levels were 100mg/dL or greater
(P < .001 for interaction)

2: IMPROVE-IT
3: FOURIER
43: SPIRE

Navarese E.P et al. JAMA. 2018;319(15):1566-1579

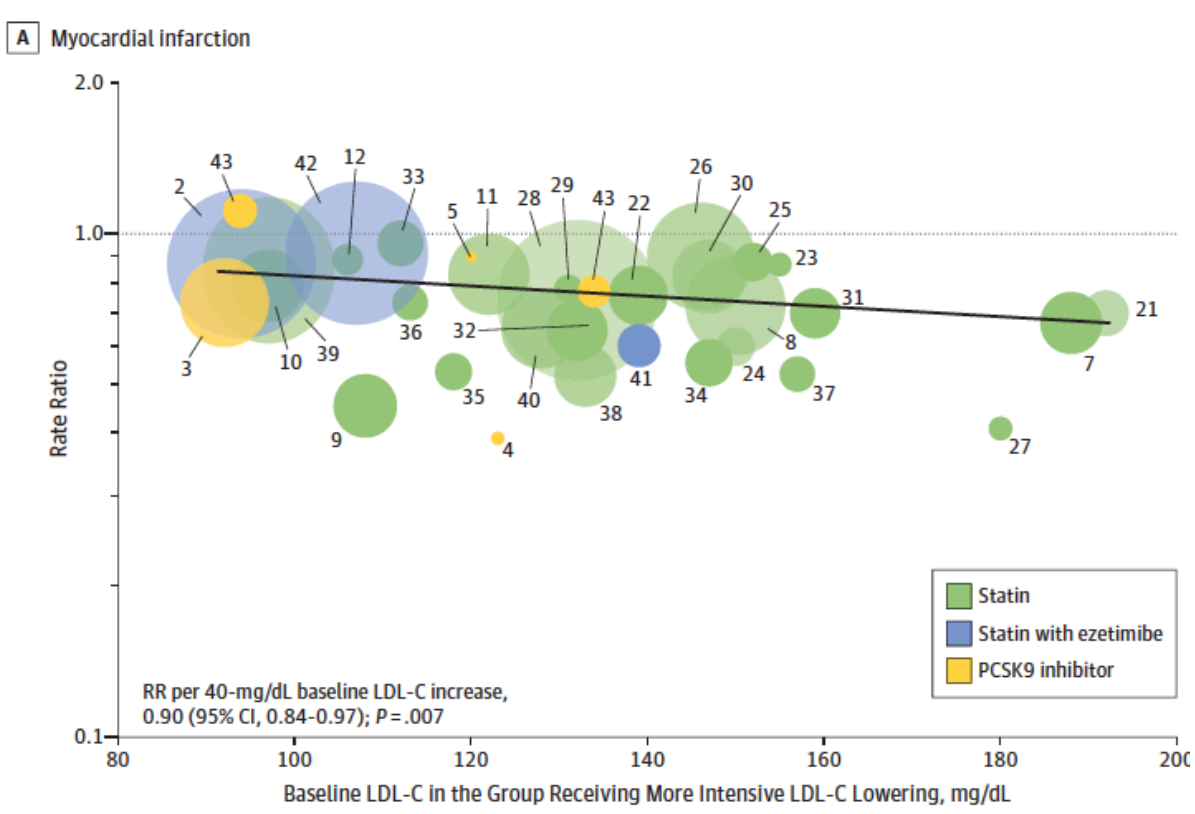
Meta-analysis of Cardiovascular Mortality Stratified by Baseline LDL-C Level

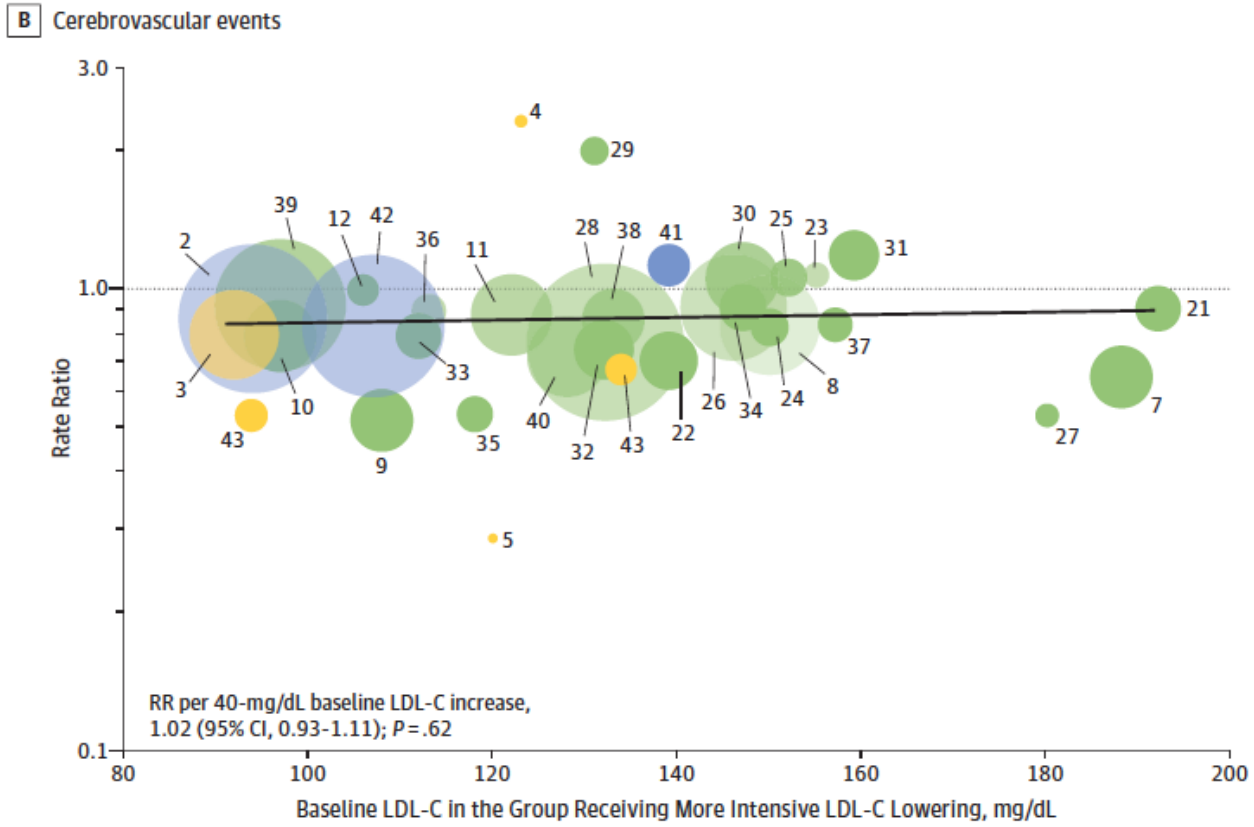
Study and Subgroup	No. of Patients With Event/Total No. (%) More Intensive LDL-C Lowering	Less Intensive LDL-C Lowering	Rate Ratio (95% CI)	Weight, %
Baseline LDL-C <100 mg/dL				
FOURIER,[3] 2017	251/13784 (1.82)	240/13780 (1.74)	1.05 (0.88-1.25)	4.9
IMPROVE-IT,[2] 2015	537/9067 (5.92)	538/9077 (5.93)	1.00 (0.89-1.13)	6.1
SPIRE-1,[43] 2017	37/8408 (0.44)	30/8409 (0.36)	1.14 (0.80-1.62)	2.3
SEARCH,[39] 2010	565/6031 (9.37)	572/6033 (9.48)	0.99 (0.88-1.11)	6.2
TNT,[10] 2005	126/4995 (2.52)	155/5006 (3.10)	0.81 (0.64-1.03)	3.8
Subtotal	1516/42285 (3.59)	1535/42305 (3.63)	0.99 (0.92-1.06)	23.3
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_4 = 3.83$ ($P = .43$); $I^2 = 0\%$				
Overall effect: $z = 0.32$ ($P = .75$)				
Baseline LDL-C ≥160 mg/dL				
GREACE,[27] 2002	20/800 (2.50)	38/800 (4.75)	0.53 (0.31-0.90)	1.2
4S,[7] 1994	136/2221 (6.12)	207/2223 (9.31)	0.66 (0.53-0.82)	4.1
WOSCOPS,[21] 1995	50/3302 (1.51)	73/3293 (2.22)	0.68 (0.48-0.98)	2.3
Subtotal	206/6323 (3.26)	318/6316 (5.03)	0.65 (0.54-0.77)	7.6
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.67$ ($P = .72$); $I^2 = 0\%$				
Overall effect: $z = 4.84$ ($P < .001$)				
Total	4738/136299 (3.48)	5457/133989 (4.07)	0.84 (0.79-0.89)	100.0
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_{33} = 65.59$ ($P = .002$); $I^2 = 50\%$				
Overall effect: $z = 5.37$ ($P < .001$)				
$P < .001$ for interaction (<100 mg/dL vs ≥100 mg/dL)				



Navarese E.P et al. JAMA. 2018;319(15):1566-1579

Meta-regression Analysis of **MACEs** by Baseline LDL-C Level





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JAMA | Original Investigation

Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering

A Systematic Review and Meta-analysis

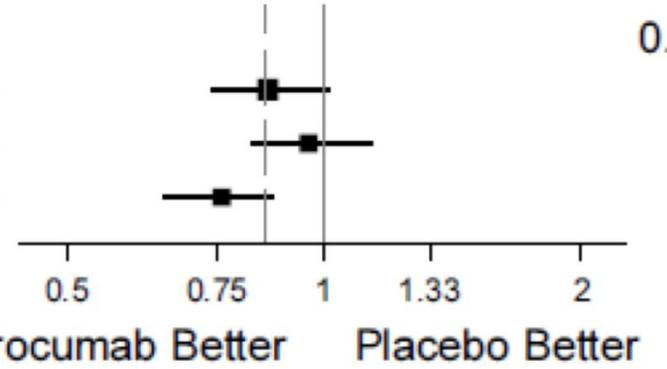
Eliano P. Navarese, MD, PhD; Jennifer G. Robinson, MD, MPH; Mariusz Kowalewski, MD; Michalina Kołodziejczak, MD; Felicita Andreotti, MD; Kevin Bliden, MD; Udaya Tantry, PhD; Jacek Kubica, MD, PhD; Paolo Raggi, MD; Paul A. Gurbel, MD

CONCLUSIONS AND RELEVANCE In these meta-analyses and meta-regressions, more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels. This association was not present when baseline LDL-C level was less than 100 mg/dL, suggesting that the greatest benefit from LDL-C–lowering therapy may occur for patients with higher baseline LDL-C levels.

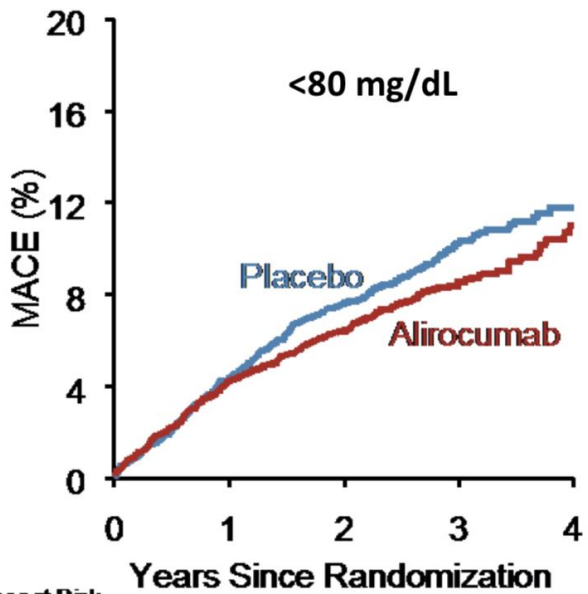
Navarese E.P et al. JAMA. 2018;319(15):1566-1579

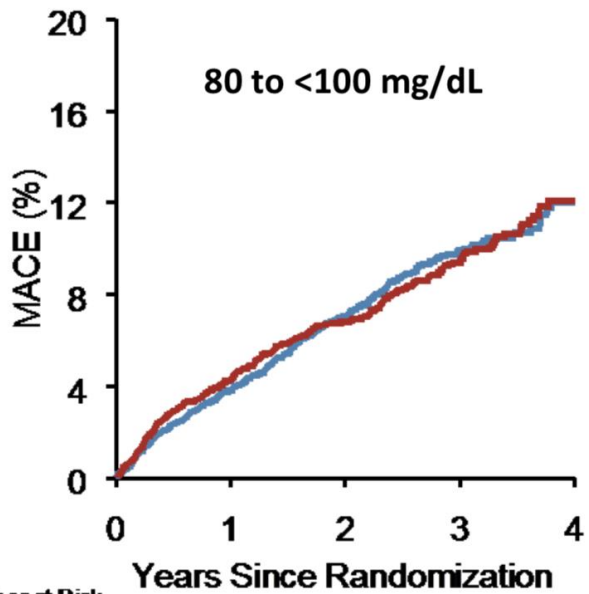
Primary Efficacy in Main Prespecified Subgroups

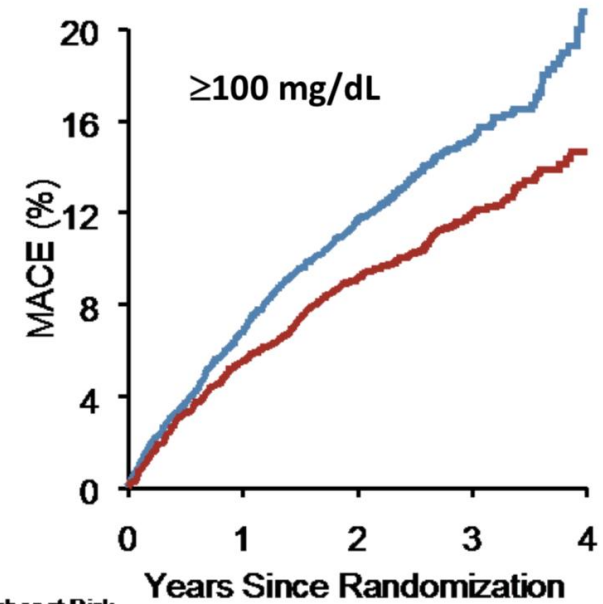
Subgroup	Patients	Incidence (%) Alirocumab	Incidence (%) Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction







Number at Risk						
Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233

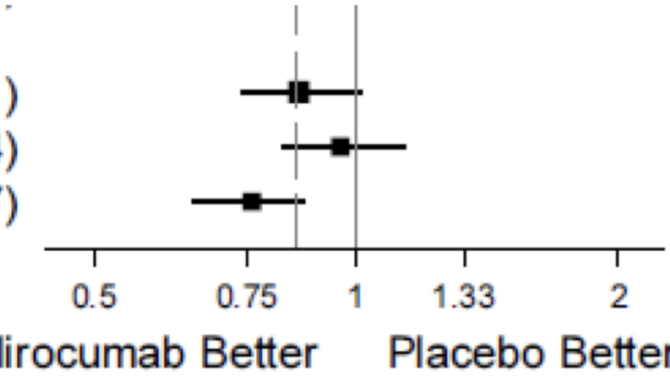
Number at Risk						
Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

Number at Risk						
Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

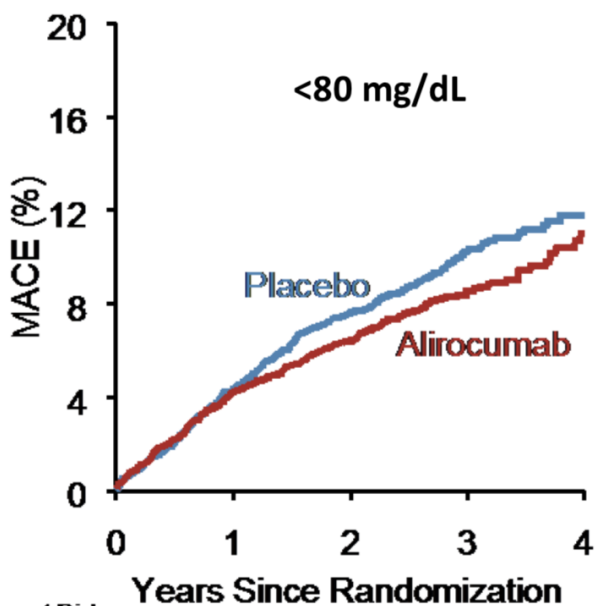
ODYSSEY OUTCOMES

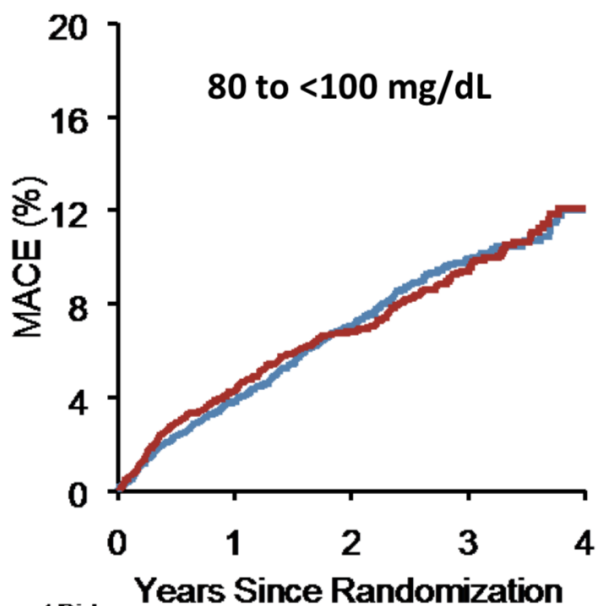
Primary Efficacy in Main Prespecified Subgroups

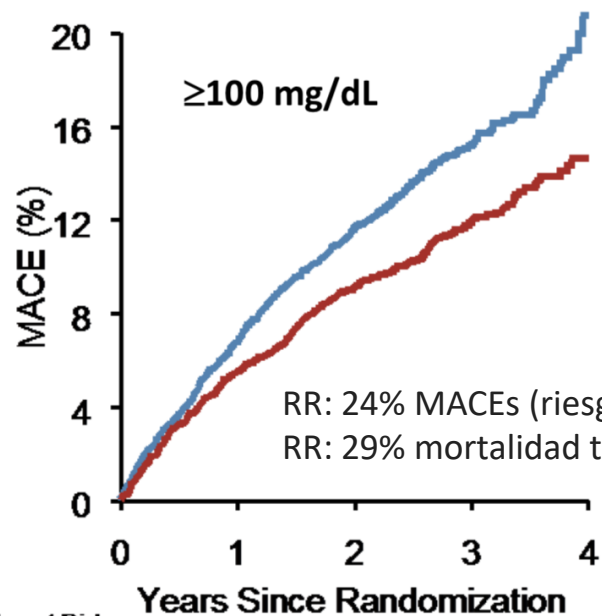
Subgroup	Patients	Incidence (%) Alirocumab	Incidence (%) Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction







RR: 24% MACEs (riesgo absoluto de 3,4%)
RR: 29% mortalidad total (riesgo absoluto de 1,7%)

Number at Risk					
Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233

Number at Risk					
Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

Number at Risk					
Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

ODYSSEY OUTCOMES

The Nobel Prize in Physiology or Medicine 1985

Michael S. Brown
Prize share: 1/2

Joseph L. Goldstein
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein *"for their discoveries concerning the regulation of cholesterol metabolism"*

"… a level of LDL-cholesterol in plasma of **25 mg/dL** would be sufficient …"

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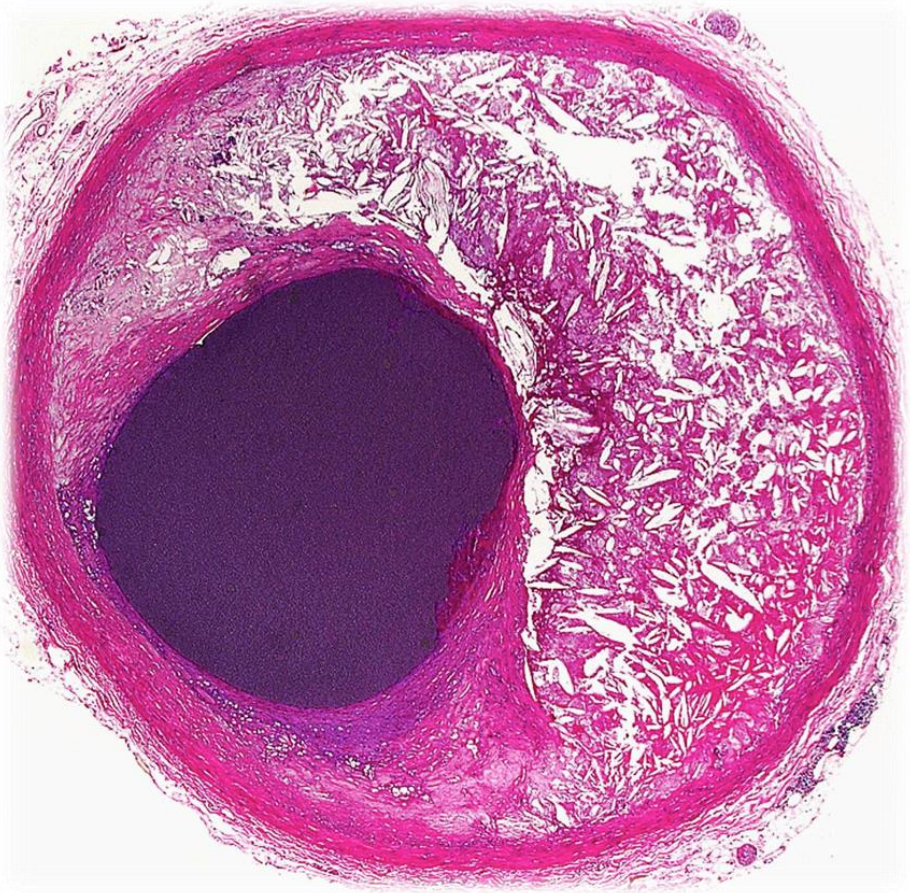
Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

ESC Congress 2016, Rome

Braunwald contundente: "LDL por encima de 50 mg/dl es Tóxico para la especie" #ESCcongress



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Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

2016 European Guidelines on cardiovascular disease prevention in clinical practice

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

EUROPEAN SOCIETY OF CARDIOLOGY

Recommendations	Class [a]	Level [b]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

Recommendations for lipid control

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Sección de Riesgo Vascular y Rehabilitación Cardiaca

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Piepoli MF, et al. Eur Heart J. 2016;37:2315-81; Catapano AL, et al. Eur Heart J. 2016

ASCVD Risk Factor Modifications Algorithm

Dyslipidemia

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:

- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

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Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

Garber AJ, et al. Endocr Pract. 2018;24:91-120

Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events

A Meta-Analysis of Statin Trials

Risk for Major Cardiovascular Events by Achieved LDL-C Concentration

	Achieved On-Trial LDL-C Concentration, mg/dl (mmol/l)						
	<50 (<1.29) (n = 4,375)	50-<75 (1.29-<1.94) (n = 10,395)	75-<100 (1.94-<2.58) (n = 10,091)	100-<125 (2.58-<3.23) (n = 8,953)	125-<150 (3.23-<3.88) (n = 3,128)	150-<175 (3.88-<4.52) (n = 836)	≥175 (≥4.52) (n = 375)
Major cardiovascular events	194 (4.4)	1,185 (11.4)	1,664 (16.5)	1,480 (16.5)	557 (17.8)	184 (22.0)	123 (32.8)
Unadjusted HR (95% CI)	0.20 (0.16-0.25)	0.40 (0.33-0.48)	0.50 (0.42-0.60)	0.48 (0.40-0.58)	0.51 (0.42-0.62)	0.64 (0.51-0.81)	1.00 (ref)
Adjusted HR (95% CI)*	0.44 (0.35-0.55)	0.51 (0.42-0.62)	0.56 (0.46-0.67)	0.58 (0.48-0.69)	0.64 (0.53-0.79)	0.71 (0.56-0.89)	1.00 (ref)
Major coronary events	129 (2.9)	918 (8.8)	1,431 (14.2)	1,336 (14.9)	492 (15.7)	170 (20.3)	107 (28.5)
Unadjusted HR (95% CI)	0.15 (0.12-0.20)	0.36 (0.29-0.43)	0.50 (0.41-0.61)	0.51 (0.42-0.62)	0.53 (0.43-0.65)	0.69 (0.54-0.88)	1.00 (ref)
Adjusted HR (95% CI)*	0.47 (0.36-0.61)	0.53 (0.43-0.65)	0.58 (0.48-0.71)	0.62 (0.51-0.75)	0.67 (0.55-0.83)	0.78 (0.61-0.99)	1.00 (ref)
Major cerebrovascular events	72 (1.6)	315 (3.0)	302 (3.0)	205 (2.3)	91 (2.9)	21 (2.5)	23 (6.1)
Unadjusted HR (95% CI)	0.47 (0.29-0.74)	0.62 (0.41-0.95)	0.52 (0.34-0.79)	0.38 (0.25-0.58)	0.47 (0.30-0.75)	0.41 (0.23-0.74)	1.00 (ref)
Adjusted HR (95% CI)*	0.36 (0.22-0.59)	0.46 (0.30-0.71)	0.49 (0.32-0.75)	0.45 (0.29-0.69)	0.58 (0.36-0.91)	0.43 (0.24-0.78)	1.00 (ref)

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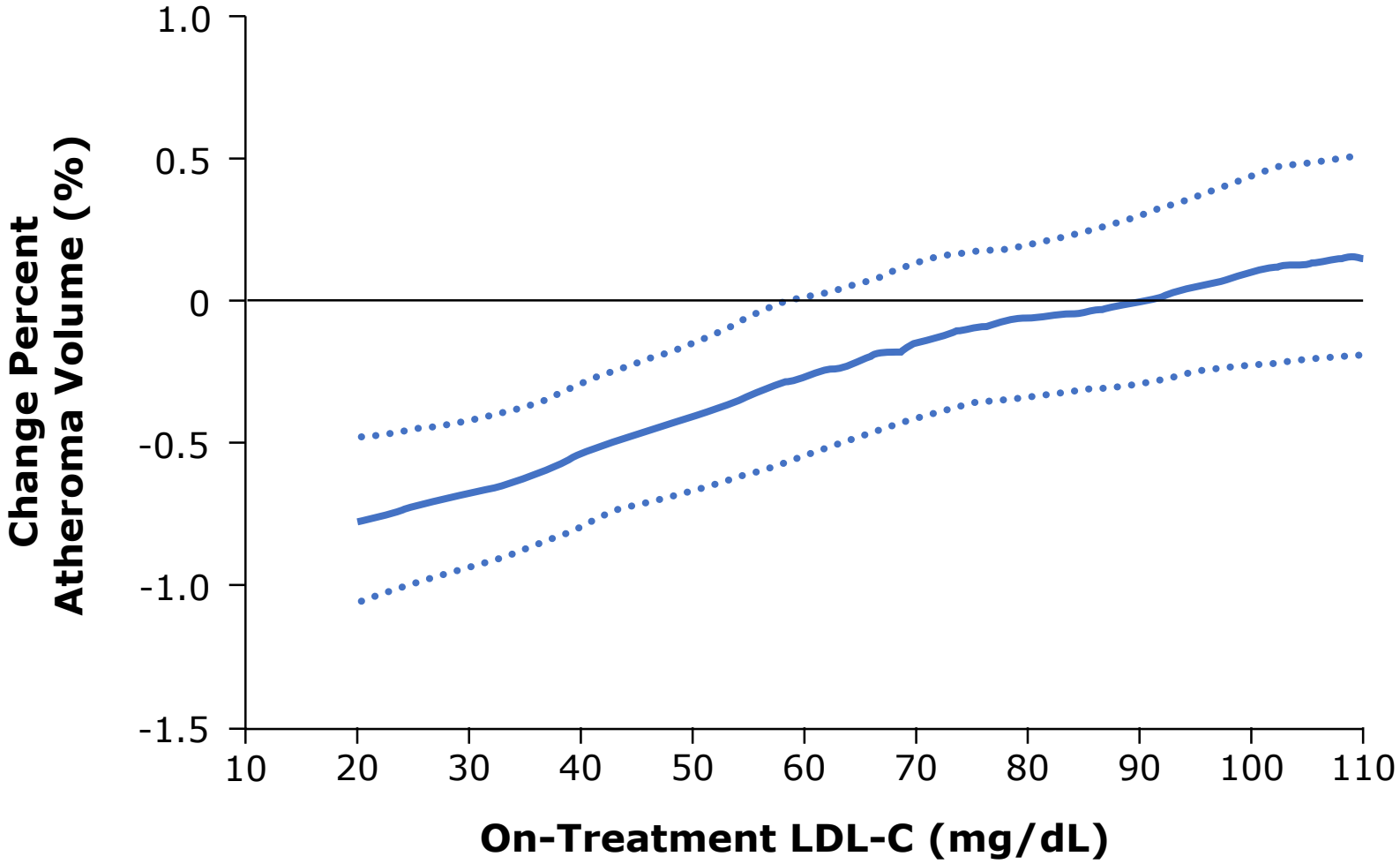
Boekholdt SM, et al. J Am Coll Cardiol. 2014;64:485-94

Achieved LDL-C and change in PAV



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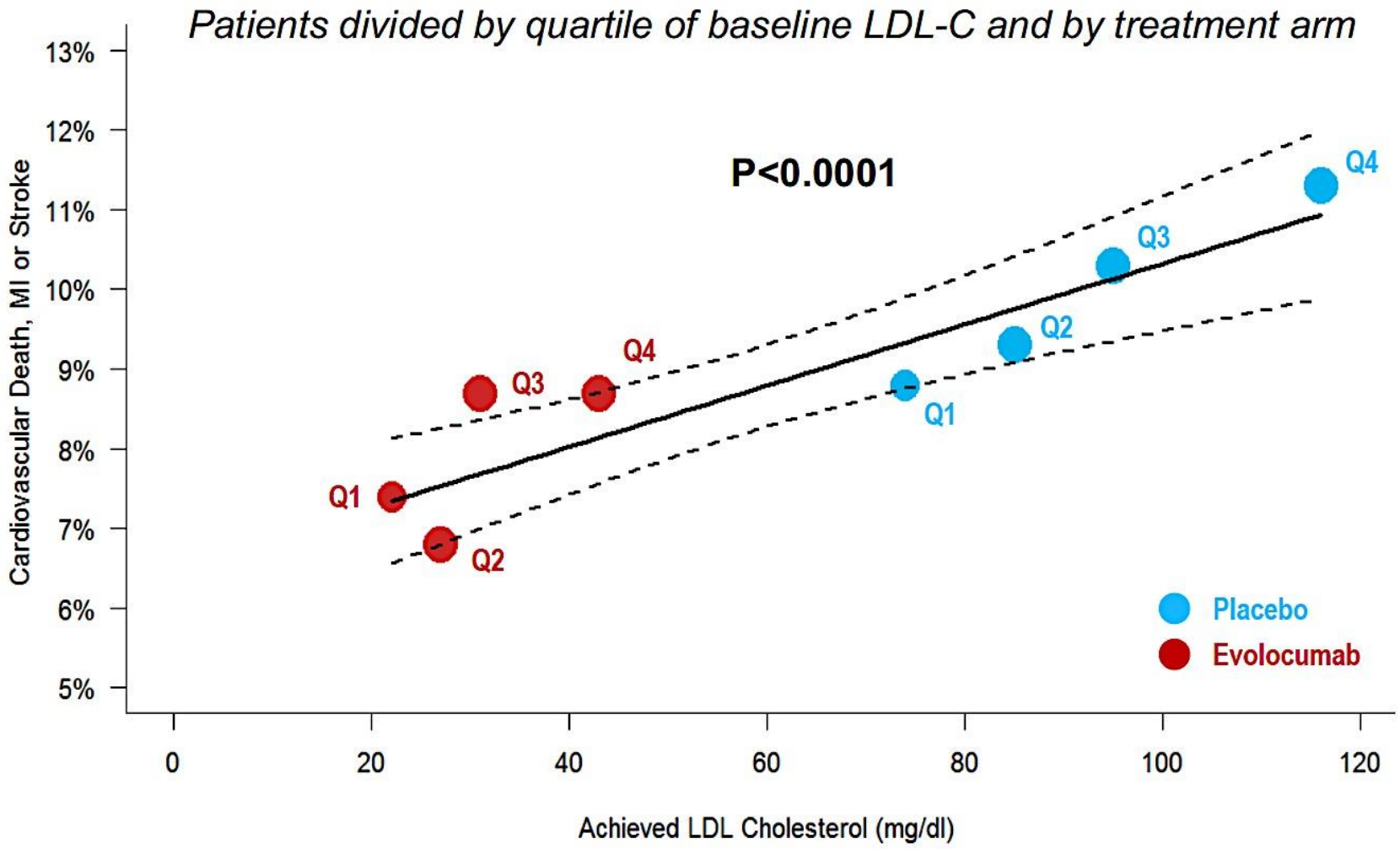
Nicholls SJ, et al. JAMA, 2016;316:2373-84

lower LDL-C is better



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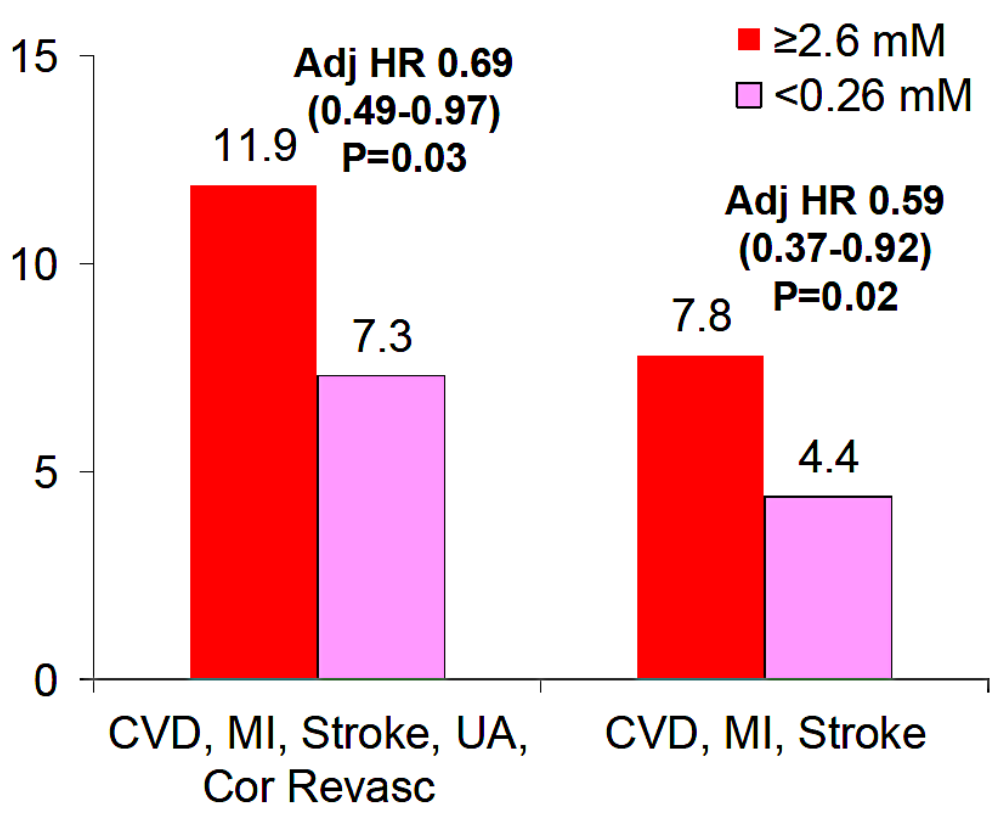
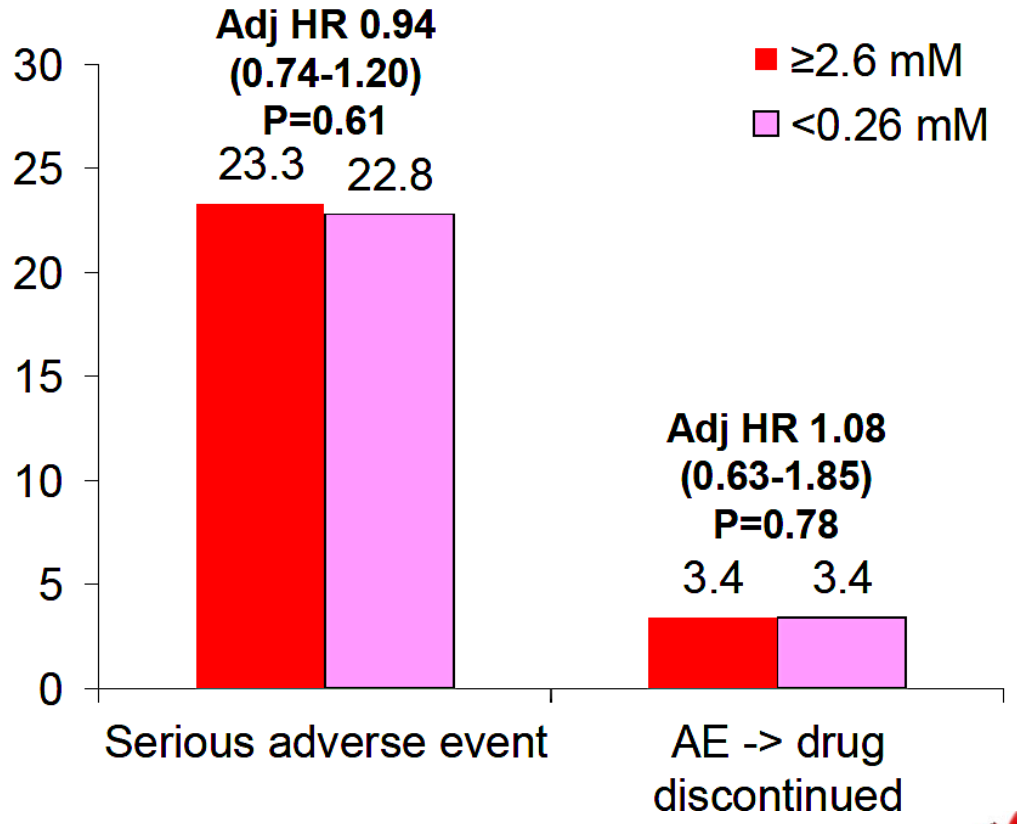
Sabatine MS, et al. N Engl J Med. 2017;376:1713-22

504 patients with LDL-C <10 mg/dL at 4 weeks

Cardiovascular efficacy



Safety



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Sección de Riesgo Vascular y Rehabilitación Cardiaca

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Giugliano RP, et al. Lancet. 2017;390:1962-71

ROUND #2
¿Hacen faltan iPCSK9 más allá de estatinas y ezetimibe?

Pharmacological treatment of hypercholesterolemia

Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A

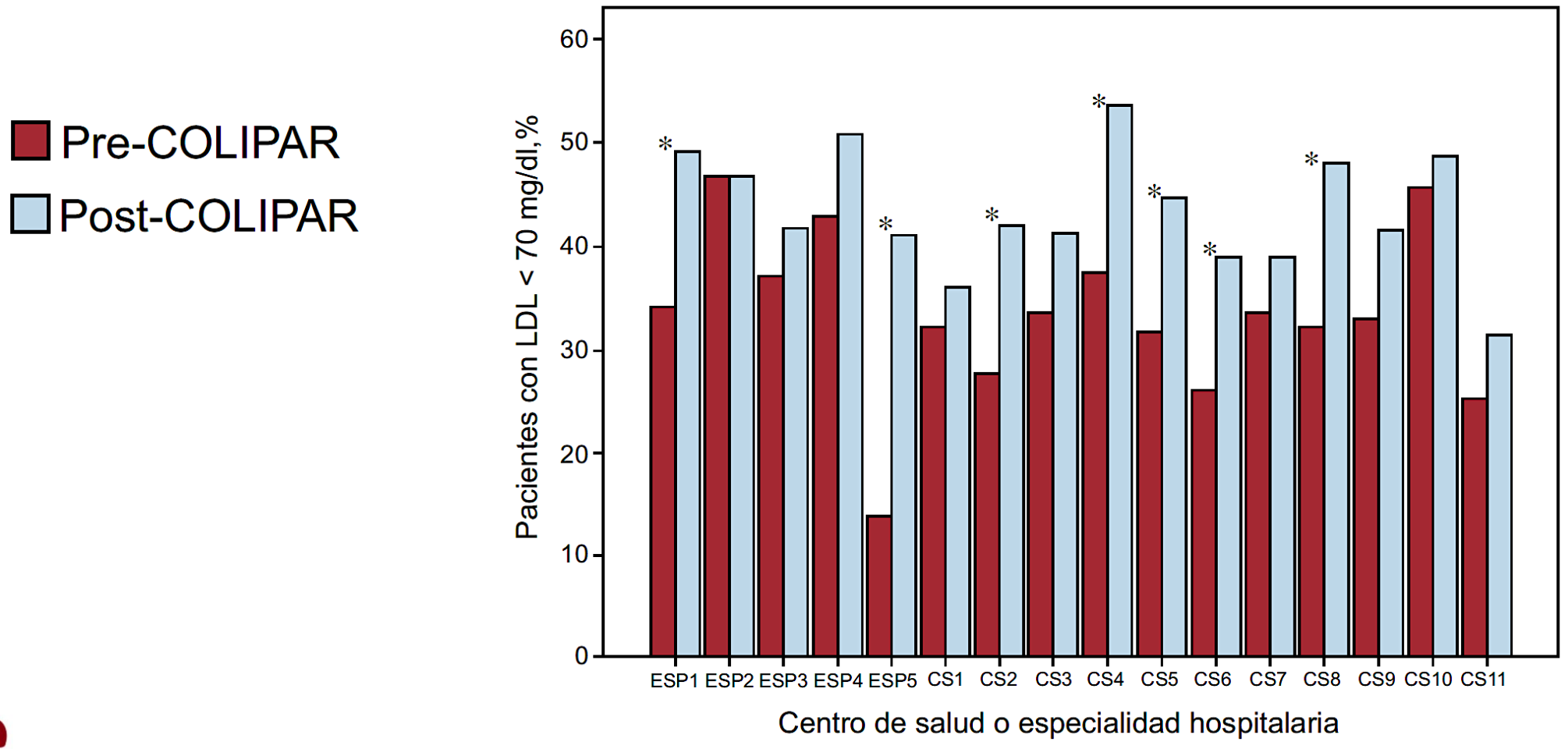
Catapano AL, et al. Eur Heart J. 2016

Pharmacological treatment of hypercholesterolemia

In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C

Catapano AL, et al. Eur Heart J. 2016

COLIPAR project



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Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

Cosin J, et al. Rev Esp Cardiol. 2017 (online)

Control lipídico en pacientes con enfermedad coronaria del Área de Salud de Cáceres (España) estudio LIPICERES

Distribución de pacientes por rangos de edad y género

	Total (mg/dl)	Hombres (mg/dl)	Mujeres (mg/dl)	p
CT	144,0 ± 33,6	141,9 ± 33,5	149,9 ± 33,2	< 0,005
cLDL	73,0 ± 28,8	72,4 ± 28,8	74,9 ± 28,7	0,3

Grado de cumplimiento de objetivos lipídicos

mg/dl	Total (%)	Varones (%)	Mujeres (%)	p
cLDL < 70	52,3	52,7	51,2	0,7
cLDL < 100	83,6	84,6	80,7	0,2

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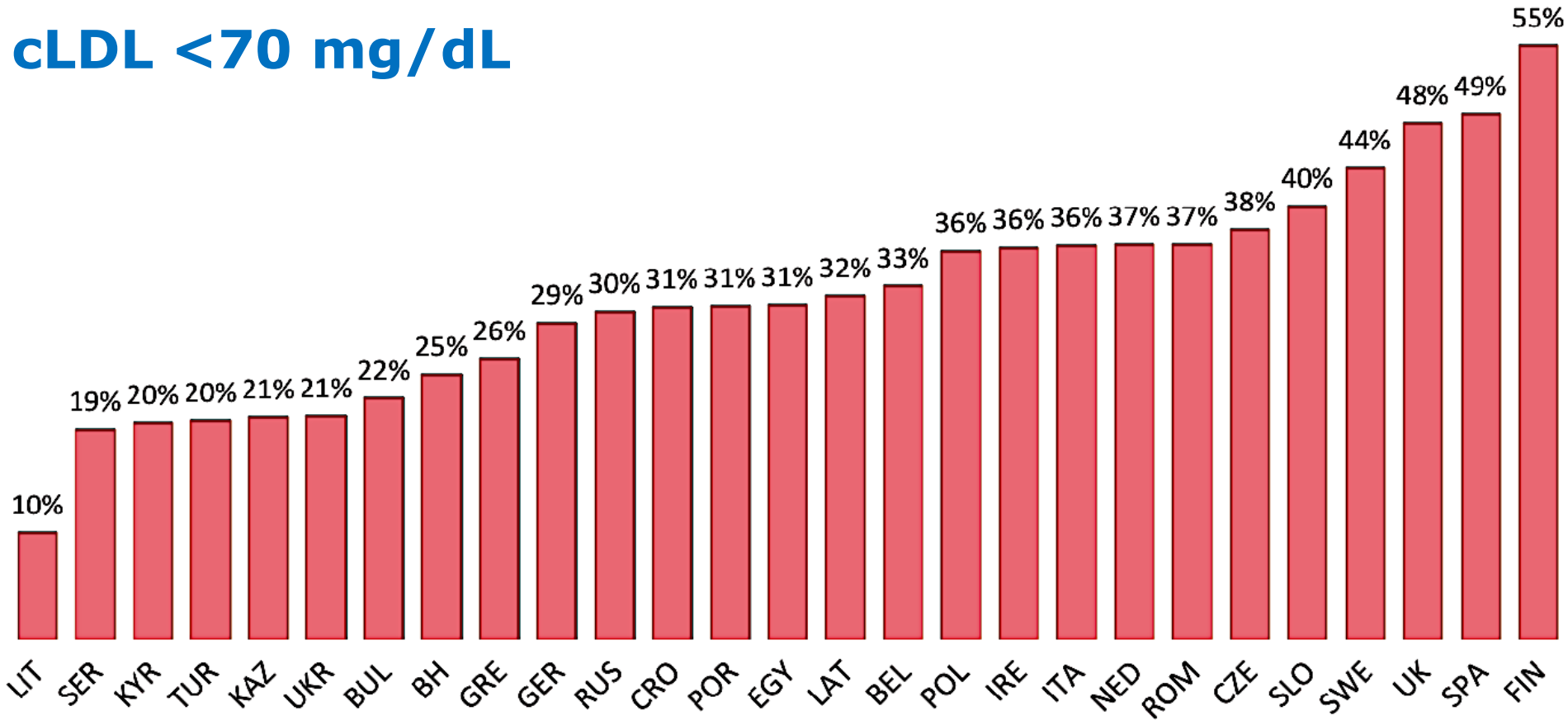
Gómez-Barrado JJ, et al. Clin Investig Arterioscler. 2017;29:13-9

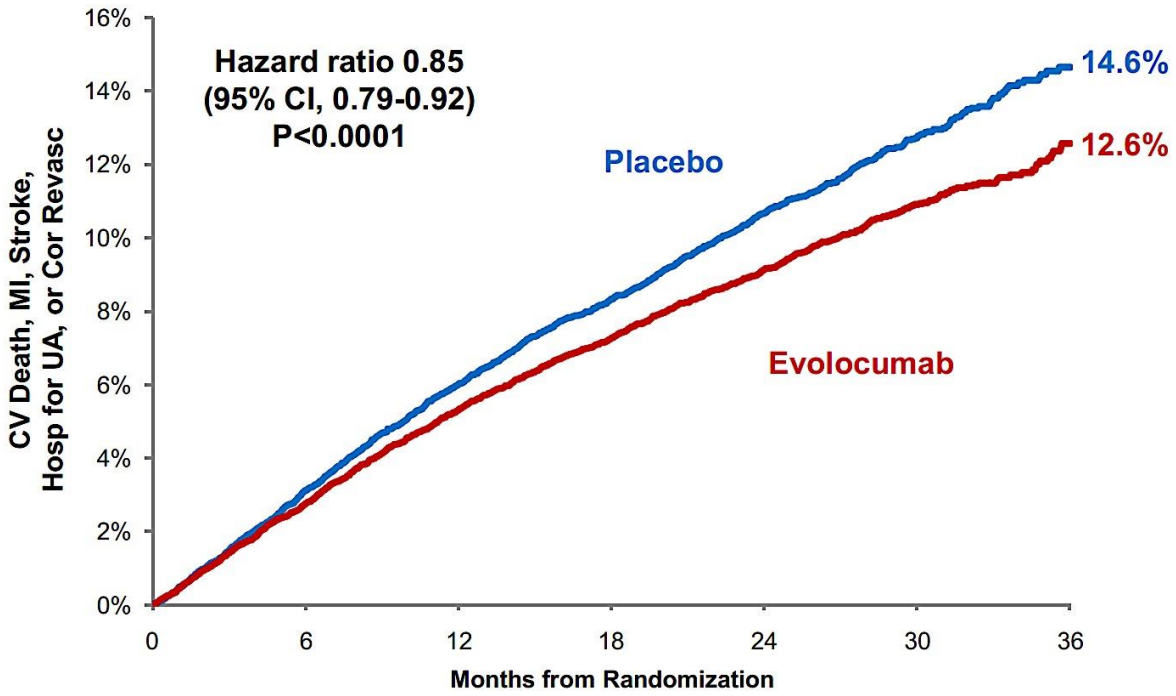
ESC European Society of Cardiology

cLDL <70 mg/dL



fourier

Primary endpoint



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)**

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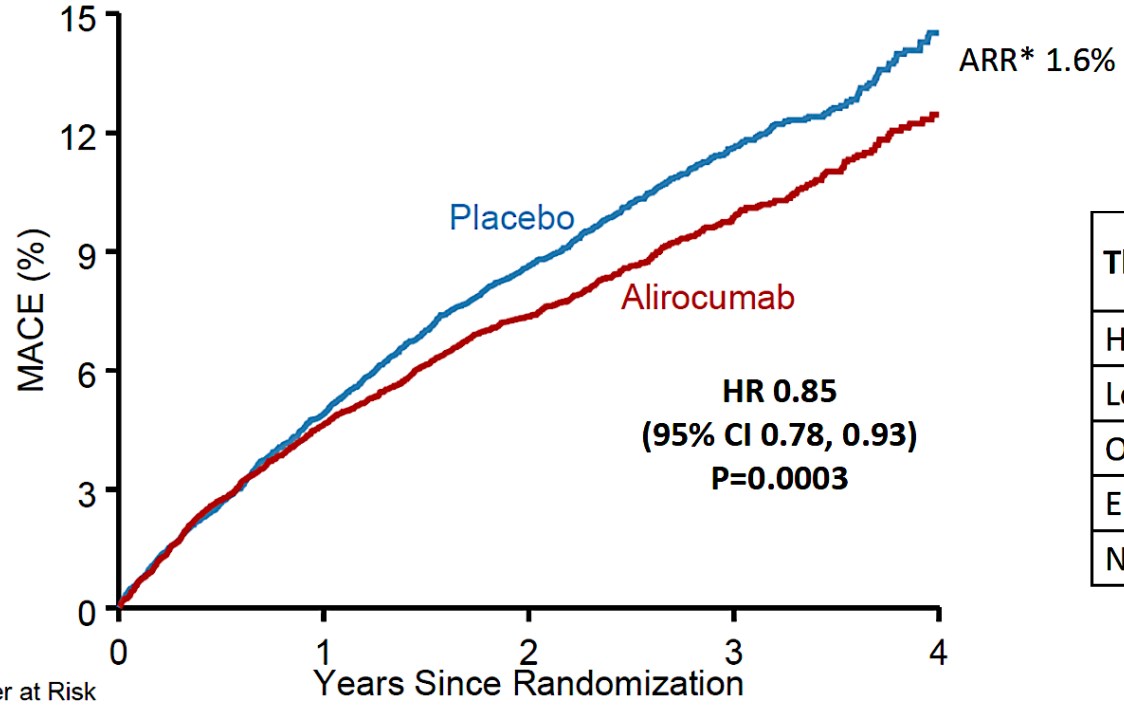
Sabatine MS, et al. N Engl J Med. 2017;376:1713-22

ODYSSEY OUTCOMES

Primary Efficacy Endpoint



Baseline characteristics

Therapy, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
High-dose atorvastatin/rosuvastatin	8380 (88.6)	8431 (89.1)
Low-/moderate-dose atorvastatin/rosuvastatin	830 (8.8)	777 (8.2)
Other statin	19 (0.2)	27 (0.3)
Ezetimibe, with or without statin	269 (2.8)	285 (3.0)
No lipid-lowering therapy*	87 (0.9)	91 (1.0)

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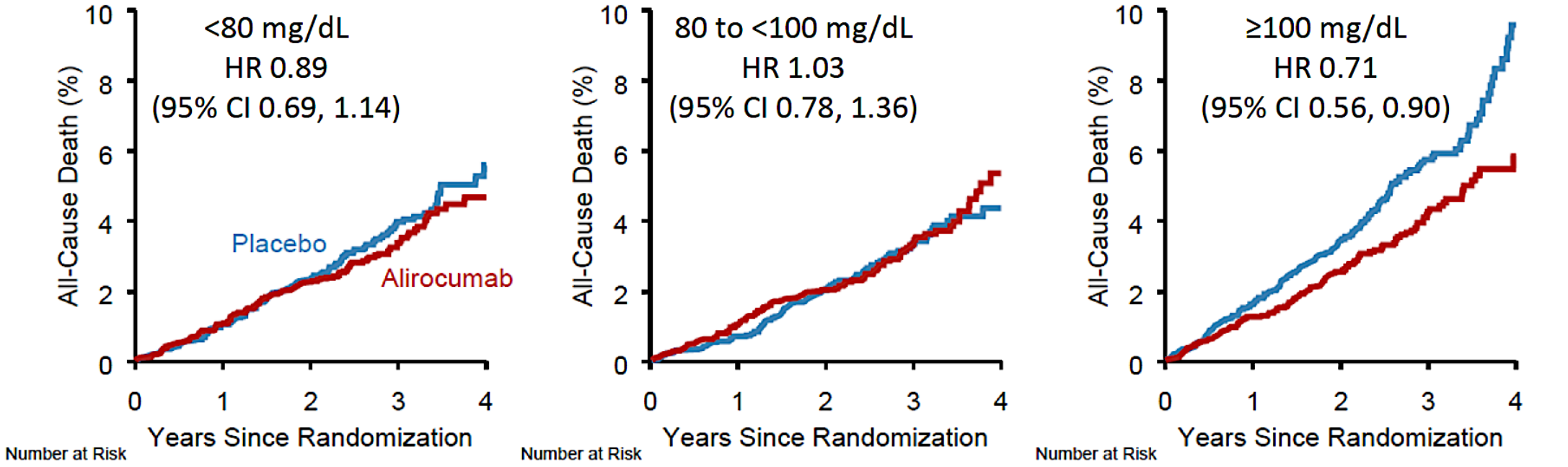
Schwartz GG, et al. ACC congress, Orlando 2018

ODYSSEY OUTCOMES

Post hoc analysis all-cause death

ARR* 1.7% $P_{interaction}$=0.12



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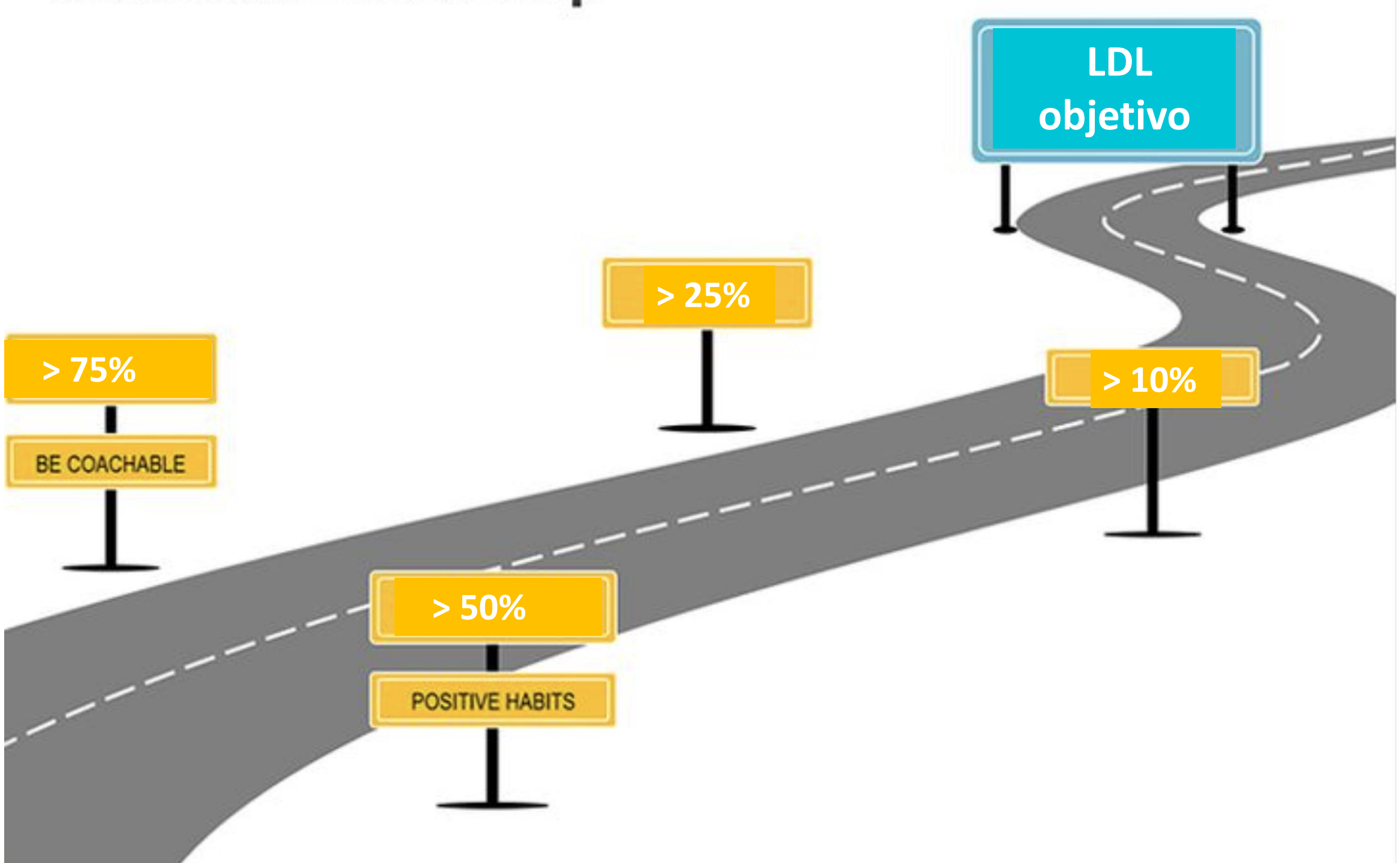
Schwartz GG, et al. ACC congress, Orlando 2018


LDL
objetivo
> 25%
> 75%
BE COACHABLE
> 10%
> 50%
POSITIVE HABITS

Máxima reducción de colesterol unido a lipoproteínas de baja densidad alcanzable con combinaciones farmacológicas. Cuando 50 más 20 suma 60

%A + %B (1 – %A) + %C {1 – [%A + %B (1 – %A)]}…

%A es la reducción teórica de lipoproteínas de baja densidad inducida por el fármaco A, %B es la inducida por el fármaco B y %C es la inducida por el fármaco C.

Aplicación de la fórmula al ejemplo del texto:

0,5 + 0,2 (1 – 0,5) + 0,6 {1 – [0,5 + 0,2 (1-0,5)]} =

0,5 + 0,2 (0,5) + 0,6 {1 – [0,5 + 0,2 (0,5)]} =

0,5 + 0,1 + 0,24 = 0,84

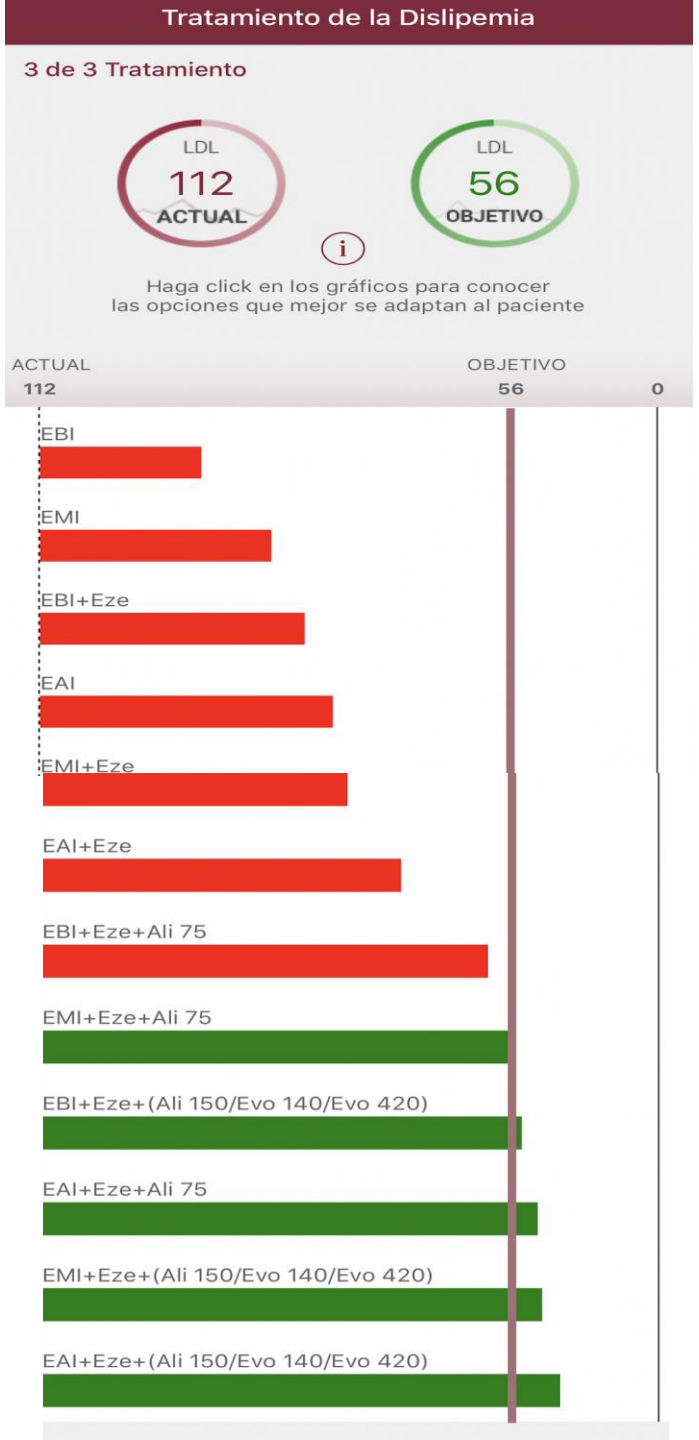
Reducción teórica de lipoproteínas de baja densidad expresada en el porcentaje inducido por los fármacos en monoterapia o en combinación

Fármacos en monoterapia o en combinación	Reducción teórica del cLDL (%)
Estatina de intensidad baja	30
Estatina de intensidad moderada	40
Estatina de intensidad alta	50
Ezetimiba	20
Inhibidor de PCSK9	60
Estatina de intensidad baja + ezetimiba	44
Estatina de intensidad moderada + ezetimiba	52
Estatina de intensidad alta + ezetimiba	60
Estatina de intensidad baja + inhibidor de PCSK9	72
Estatina de intensidad moderada + inhibidor de PCSK9	76
Estatina de intensidad alta + inhibidor de PCSK9	80
Estatina de intensidad baja + ezetimiba + inhibidor de PCSK9	78
Estatina de intensidad moderada + ezetimiba + inhibidor de PCSK9	80
Estatina de intensidad alta + ezetimiba + inhibidor de PCSK9	84

Masana L. Cartas científicas. Rev Esp Cardiol. 2016;69(3):337–349

http://tools.acc.org/ldl/ldlc_lowering_therapy/index.html#!/content/calculator/

LipidApp



https://secardiologia.es/multimedia/apps/7988-lipidapp

Marzal D.

Máxima reducción de colesterol unido a lipoproteínas de baja densidad alcanzable con combinaciones farmacológicas. Cuando 50 más 20 suma 60

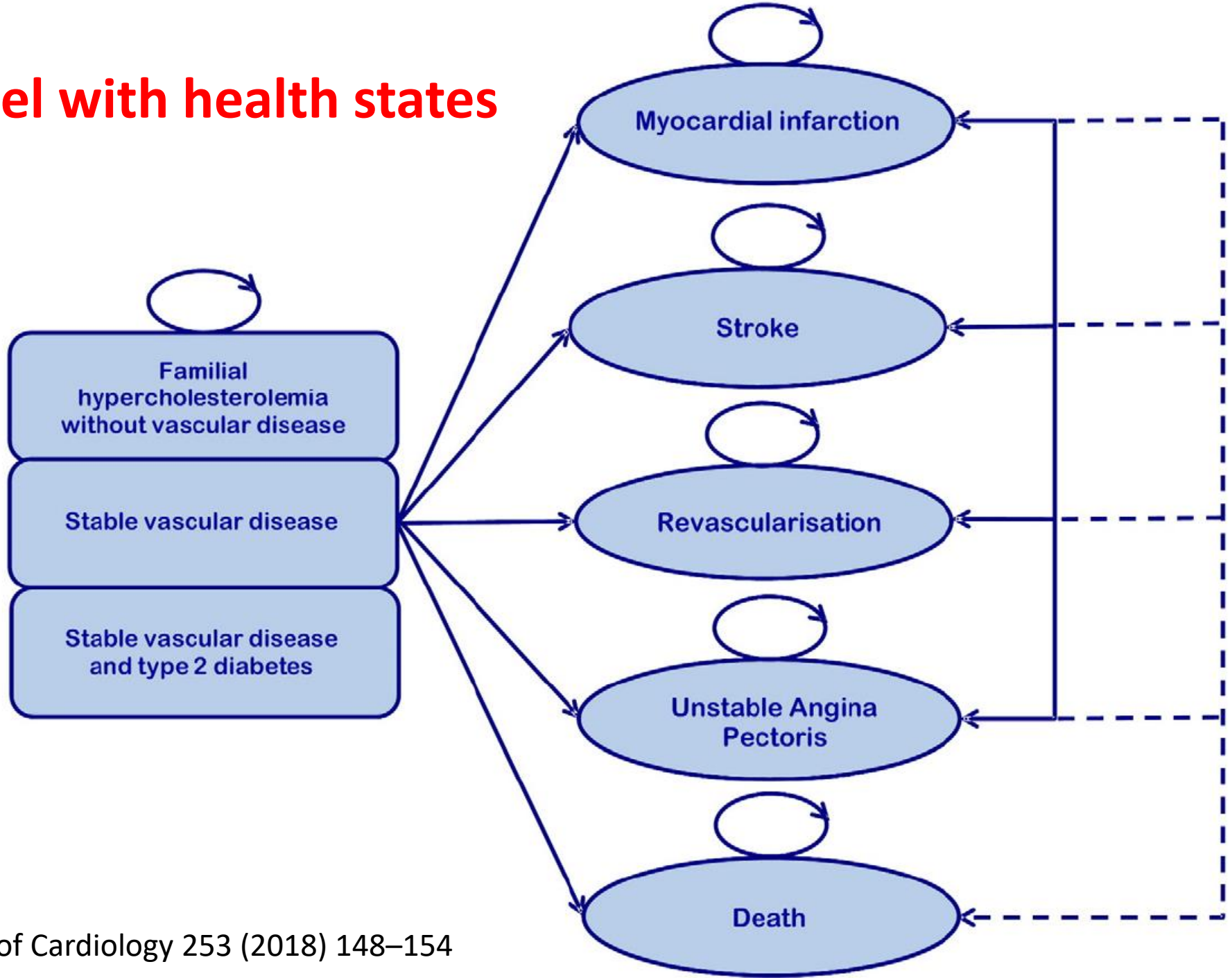
Por ejemplo, cuando se emplean estatinas en monoterapia (con un efecto máximo de reducción de LDL del 50%), solo los pacientes con LDL < 140 mg/dl alcanzarán los objetivos de prevención secundaria (LDL < 70 mg/dl). Con el uso de una estatina más ezetimiba (capacidad máxima de reducción de LDL del 60%), solo los pacientes con LDL < 175 mg/dl alcanzarán los objetivos de prevención secundaria.

Con la terapia triple (capacidad de reducción de LDL del 84%), prácticamente todos los pacientes con LDL ≤ 437 mg/dl podrían alcanzar los objetivos de LDL recomendados para la prevención secundaria.

Masana L. Cartas científicas. Rev Esp Cardiol. 2016;69(3):337–349

ROUND #3
¿Son coste-efectivos los iPCSK9?

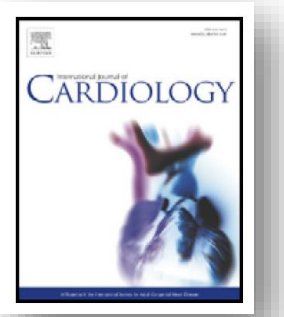
Markov model with health states



Stam-Slob M.C et al.
International Journal of Cardiology 253 (2018) 148–154

Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease

	Familial hypercholesterol-emia		Vascular disease and 10-year MACE risk ≥20%		Vascular disease and 10-year MACE risk ≥30%		Vascular disease and diabetes	
	Standard therapy	PCSK9 inhibition	Standard therapy	PCSK9 inhibition	Standard therapy	PCSK9 inhibition	Standard therapy	PCSK9 inhibition
Costs per patient (€)								
Treatment	11,606	123,112	5087	52,684	4247	44,149	6155	63,489
Event and post-event care	13,858	10,766	22,030	22,232	21,085	20,593	46,404	54,155
Total	25,464	133,878	27,116	74,916	25,331	64,742	52,559	117,644
Expected age at death	73		76		78		76	
Life-years gained		2.3		0.36		0.32		0.40
QALYs gained		1.4		0.25		0.22		0.22
ICER (€/QALY)		78,485		193,726		176,735		295,543



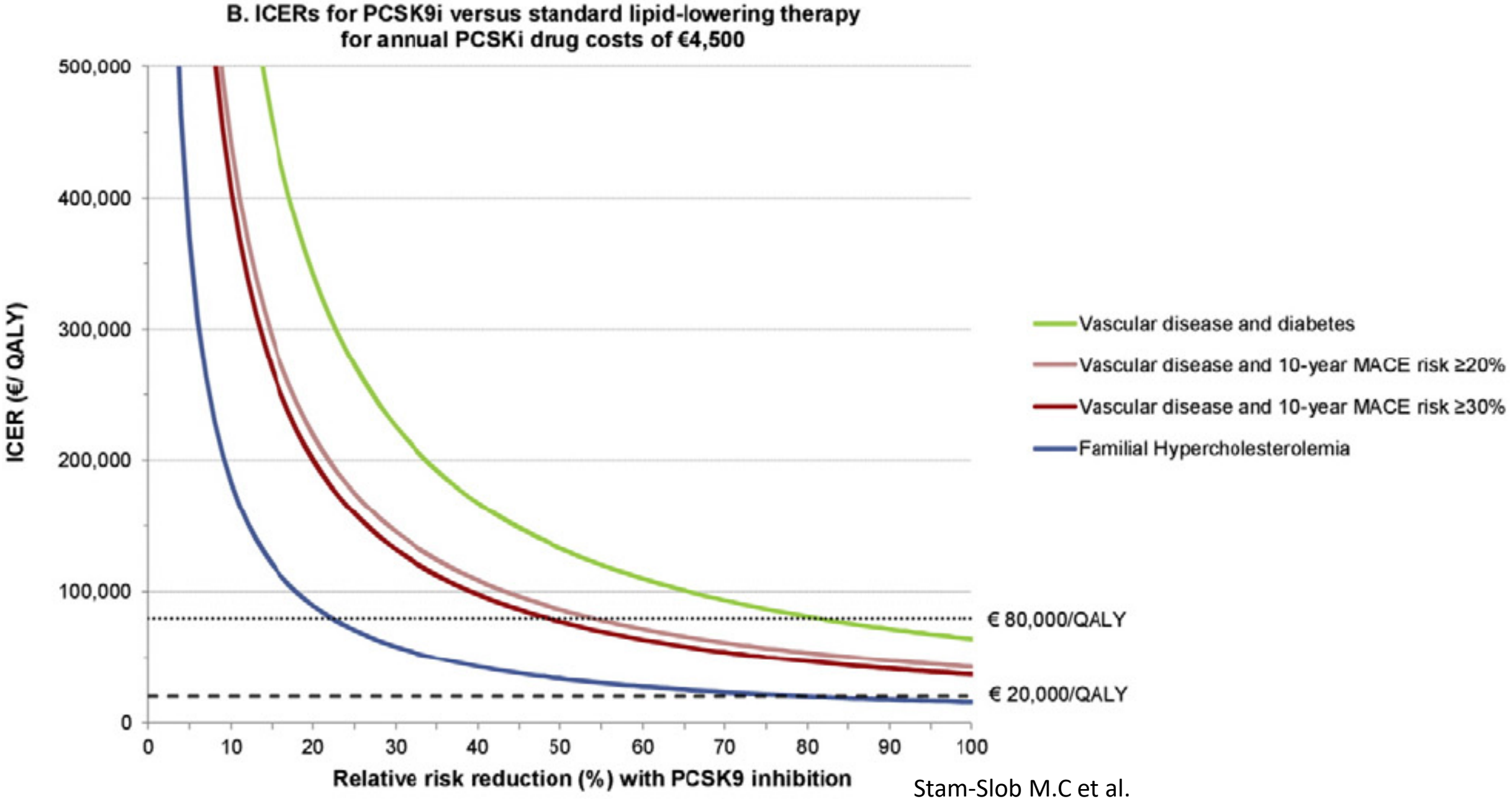
Stam-Slob M.C et al.
International Journal of Cardiology 253 (2018) 148–154

Parámetros del modelo	
Concepto	Valor medio
Coste fármacos anual (euros)	
Evolocumab (PVL con descuento aplicable)	4.969,74
Ezetimiba	668,33[8]
Estatinas	104,87[9]
Coste eventos cardiovasculares (euros)	
Muerte cardiovascular	5.014,27
Muerte por infarto de miocardio	3.912,66
Muerte por accidente cerebrovascular	4.994,57
Muerte por cualquier causa	0
Infarto de miocardio	3.912,66
Hospitalización por angina inestable	2.765,74
Accidente cerebrovascular	4.994,57
Isquémico	4.994,57
Hemorrágico	5.545,22
Revascularización coronaria	5.924,87
Riesgo relativo[a]	
Todo el seguimiento	
Medida primaria[b]	0,85 (IC95%, 0,79-0,92)
Medida secundaria[c]	0,80 (IC95%, 0,73-0,88)
Año seguimiento	
Medida primaria[b]	0,88 (IC95%, 0,80-0,97)
Medida secundaria[c]	0,84 (IC95%, 0,74-0,96)

Atorvastatina 80 mg: 441,6 euros/año

Ictus fase aguda 9.000 euro/años

A. Olry de Labry Lima et al. Rev Esp Cardiol. 2018. doi.org/10.1016/j.recesp.2018.02.013



Stam-Slob M.C et al.
International Journal of Cardiology 253 (2018) 148–154

Cost-Effectiveness PCSK9 inhibitors …

Artículo original

Coste-efectividad e impacto presupuestario del tratamiento con evolocumab frente a estatinas y ezetimiba para la hipercolesterc en España

Antonio Olry de Labry Lima[a,b,c,*], Vicente Gimeno Ballester[d], Jesús Francisco Sierra Antonio Matas Hoces[f], Julio González-Outón[g] y Emilio Jesús Alegre del Rey[h]

ARTICLE IN PRESS

International Journal of Cardiology

The cost-effectiveness of PCSK9 inhibitors – The Australian healthcare perspective

Radya Kumar [1], Andrew Tonkin [1], Danny Liew [1], Ella Zomer *[,1]

PharmacoEconomics

LEADING ARTICLE

Are PCSK9 Inhibitors Cost Effective?

Max J. Korman[1] · Kjetil Retterstøl[2,3] · Ivar Sønbø Kristiansen[4] · Torbjørn Wisløff[4,5]

Current Cardiology Reports (2018) 20:51

LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

Economic Evaluation of the PCSK9 Inhibitors in Prevention of the Cardiovascular Diseases

Parth Shah[1]

JAMA Cardiology | Brief Report

Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers Insights Derived From the FOURIER Trial

Alejandro Arrieta, PhD; Jonathan C. Hong, MD, MHS; Rohan Khera, MD; Salim S. Virani, MD, PhD; Harlan M. Krumholz, MD, SM; Khurram Nasir, MD, MPH

Sección de Riesgo Vascular y Rehabilitación Cardiaca

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Cost-Effectiveness of Evolocumab in the US Payer Context

Quality and Outcomes

Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States

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Department of Global Health Economics (Gandra), Department of Clinical Development (Somaratne), Amgen Inc., Thousand Oaks, California; Economic Modeling Center (Villa, Lothgren), Amgen (Europe) GmbH, Zug, Switzerland; Ahmanson-UCLA Cardiomyopathy Center, Division of Cardiology (Fonarow), Geffen–UCLA School of Medicine, Los Angeles, California; Department of Health Economics (Lindgren), the Swedish Institute for Health Economics, Lund, Sweden; Department of Learning, Informatics, Management and Ethics (Lindgren), Karolinska Institute, Stockholm, Sweden; Department of Health Economics (van Hout), University of Sheffield, Sheffield, United Kingdom

ABSTRACT

Randomized trials have shown marked reductions in low-density lipoprotein cholesterol (LDL-C), a risk factor for cardiovascular disease (CVD), when evolocumab is administered. We hypothesized that evolocumab added to standard of care (SOC) vs SOC alone is cost-effective in the treatment of patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic CVD (ASCVD) with or without statin intolerance and LDL-C >100 mg/dL. Using a Markov cohort state transition model, primary and recurrent CVD event rates were predicted considering population-specific trial-based mean risk factors and calibrated against observed rates in the real world. The LDL-C–lowering effect from population-specific phase 3 randomized studies for evolocumab was used together with estimated LDL-C–lowering effect on CVD event rates per 38.67-mg/dL LDL-C lowering from a statin-trial meta-analysis. Costs and utilities were included from published sources. Evolocumab treatment was associated with both increased cost and improved quality-adjusted life-years (QALY): HeFH (incremental cost: US$153 289, incremental QALY: 2.02, incremental cost-effectiveness ratio: US$75 863/QALY); ASCVD (US$158 307, 1.12, US$141 699/QALY); and ASCVD with statin intolerance (US$136 903, 1.36, US$100 309/QALY). Evolocumab met both the American College of Cardiology/American Heart Association (ACC/AHA) and World Health Organization (WHO) thresholds in each population evaluated. Sensitivity and scenario analyses confirmed that model results were robust to changes in model parameters. Among patients with HeFH and ASCVD with or without statin intolerance, evolocumab added to SOC may provide a cost-effective treatment option for lowering LDL-C using ACC/AHA intermediate/high value and WHO cost-effectiveness thresholds. More definitive information on the clinical and economic value of evolocumab will be available from the forthcoming CVD outcomes study.

Introduction

Approximately 86 million people in the United States have cardiovascular disease (CVD); it accounts for 1 out of every 3 deaths and remains the leading cause of death.[1] Despite the widespread use of statins, the economic burden associated with CVD is onerous, with > US$650 billion spent on CVD-related costs annually in the United States.[1,2] These costs are projected to nearly double by 2030.[1] The cost-effectiveness of new therapies has become increasingly important as healthcare costs continue to rise and information about making tradeoffs becomes critical.

Low-density lipoprotein cholesterol (LDL-C) has been established as a modifiable risk factor for CVD. A meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration (CTTC) found that every 38.67-mg/dL (1 mmol/L) reduction in LDL-C with statin therapy results in a 21% (statins vs control) and 28% (more vs less statins) reduction in rates of any major CVD event across 26 randomized trials.[3] Results from the Improved Reduction of

Amgen Inc. supported this analysis. Dr. Fonarow, Dr. Lindgren, and Dr. van Hout have served as consultants to Amgen Inc. Dr. Gandra, Dr. Villa, Dr. Lothgren, and Dr. Somaratne are employees and stockholders in Amgen.
The authors have no other funding, financial relationships, or conflicts of interest to disclose.
Additional Supporting Information may be found in the online version of this article.

Received: December 14, 2015
Accepted with revision: January 20, 2016
Accepted: February 7, 2016
Clin. Cardiol. (in press)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22535
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SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Sección de Riesgo Vascular y Rehabilitación Cardiaca

#CardioFighters

Gandra SR, et al. Clin Cardiol. 2016

Coste-efectividad e impacto presupuestario del tratamiento con evolocumab frente a estatinas y ezetimiba para la hipercolesterolemia en España

Parámetros del modelo	
Concepto	Valor medio
Coste fármacos anual (euros)	
Evolocumab (PVL con descuento aplicable)	4.969,74
Ezetimiba	668,33[8]
Estatinas	104,87[9]
Coste eventos cardiovasculares (euros)	
Muerte cardiovascular	5.014,27
Muerte por infarto de miocardio	3.912,66
Muerte por accidente cerebrovascular	4.994,57
Muerte por cualquier causa	0
Infarto de miocardio	3.912,66
Hospitalización por angina inestable	2.765,74
Accidente cerebrovascular	4.994,57
Isquémico	4.994,57
Hemorrágico	5.545,22
Revascularización coronaria	5.924,87
Riesgo relativo[a]	
Todo el seguimiento	
Medida primaria[b]	0,85 (IC95%, 0,79-0,92)
Medida secundaria[c]	0,80 (IC95%, 0,73-0,88)

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Olry de Labry Lima A, et al. Rev Esp Cardiol. 2018 (in press)

ROUND #4
¿Hay perfiles para iPCSK9?

Paciente 68 años con IAM previo, c-LDL 89, enfermedad de 2 vasos y DM2

vs

Paciente de 79 años 1er IAM hace 1 año c-LDL 116

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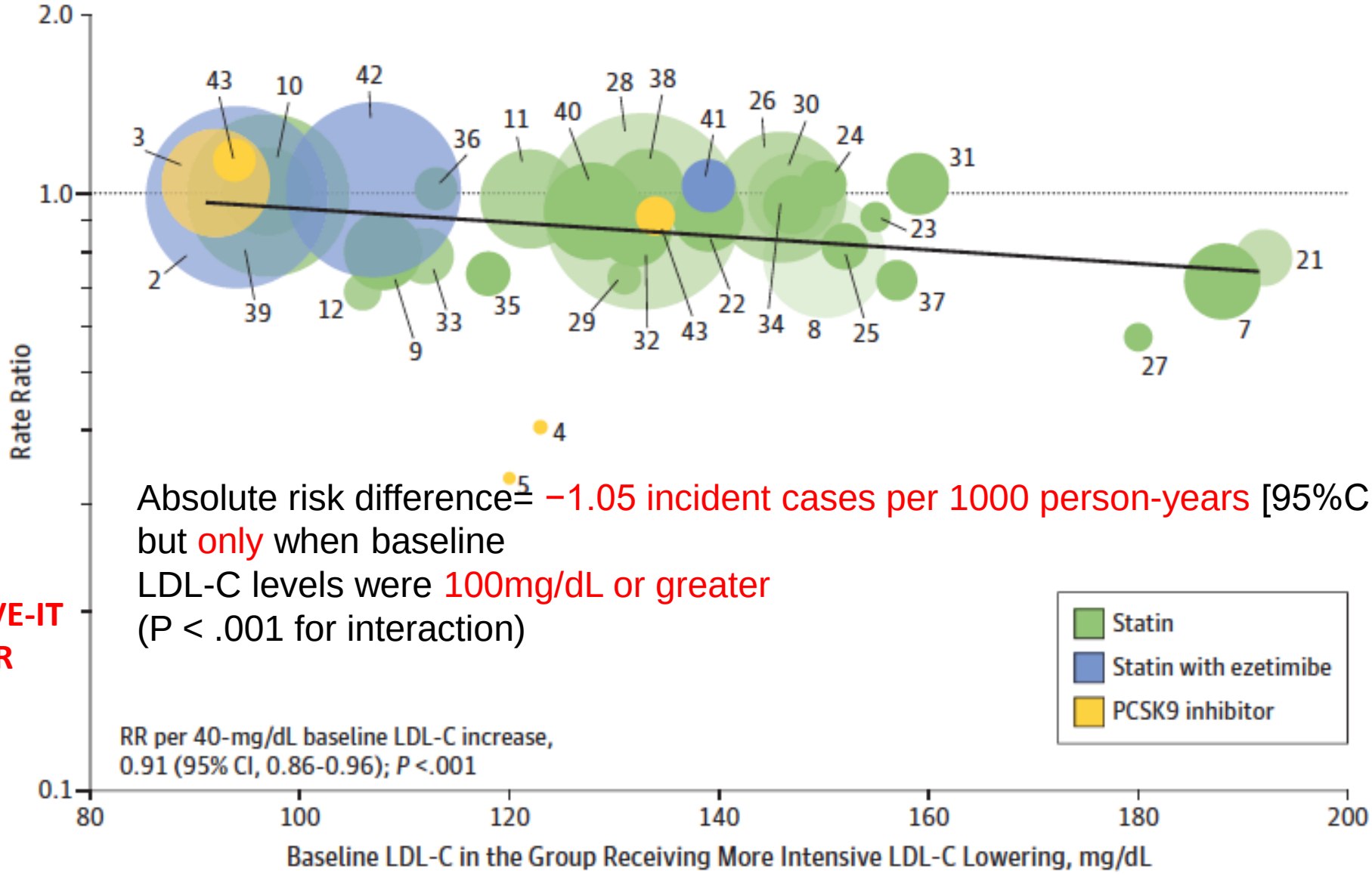
Meta-regression Analysis of **All-cause Mortality** by Baseline LDL-C Level (34 RCTs)



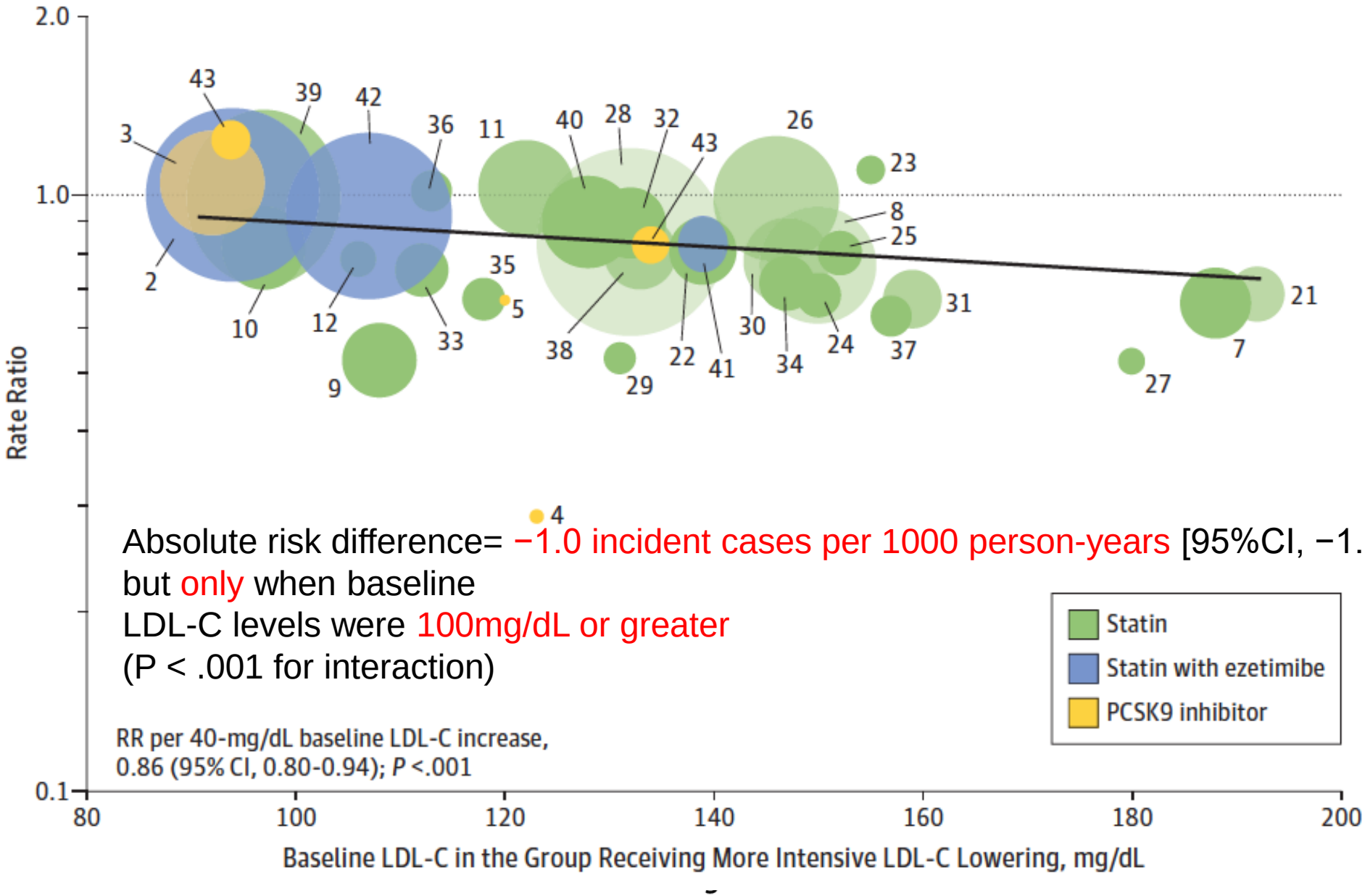
Absolute risk difference= −1.05 incident cases per 1000 person-years [95%CI, −1.59 to −0.51])
but only when baseline
LDL-C levels were 100mg/dL or greater
(P < .001 for interaction)

7: IMPROVE-IT
21: FOURIER
27: SPIRE

2: IMPROVE-IT
3: FOURIER
43: SPIRE

Navarese E.P et al. JAMA. 2018;319(15):1566-1579

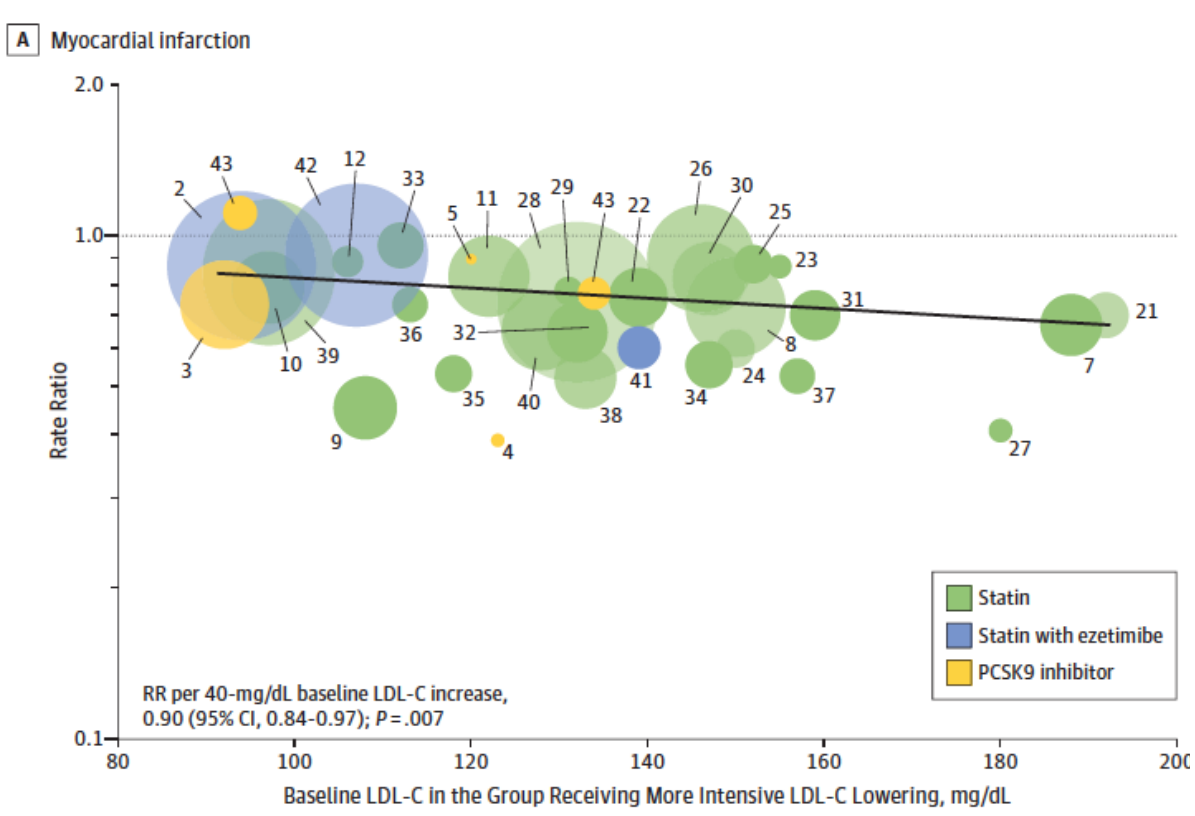
Meta-regression Analysis of **Cardiovascular Mortality** by Baseline LDL-C Level

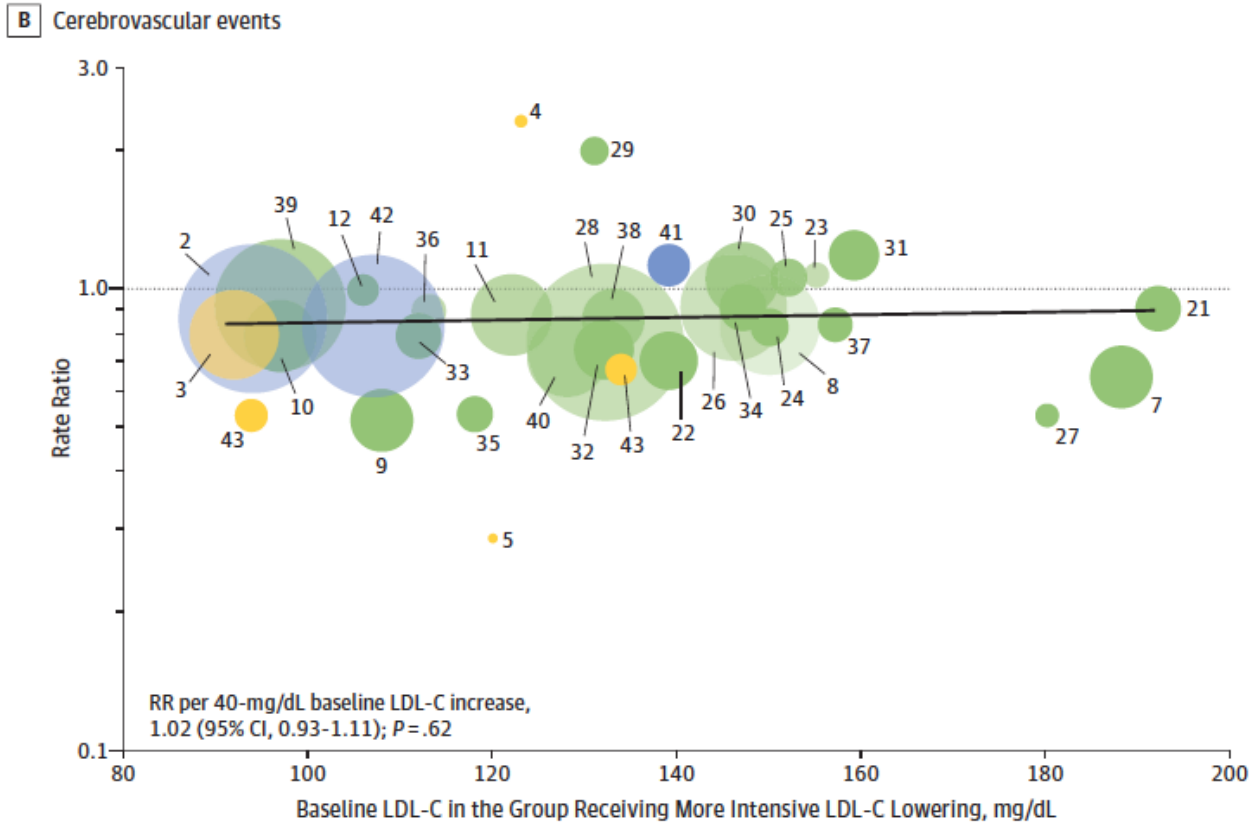


Absolute risk difference= −1.0 incident cases per 1000 person-years [95%CI, −1.59 to −0.51])
but only when baseline
LDL-C levels were 100mg/dL or greater
(P < .001 for interaction)

Navarese E.P et al. JAMA. 2018;319(15):1566-1579

Meta-regression Analysis of **MACEs** by Baseline LDL-C Level





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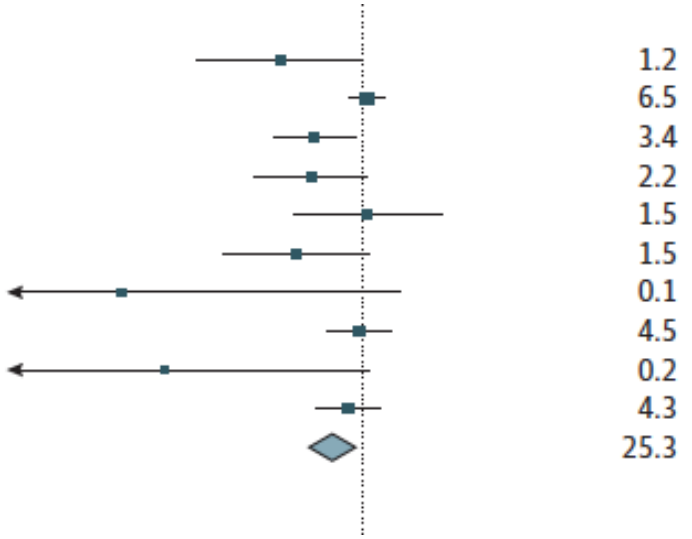
Navarese E.P et al. JAMA. 2018;319(15):1566-1579

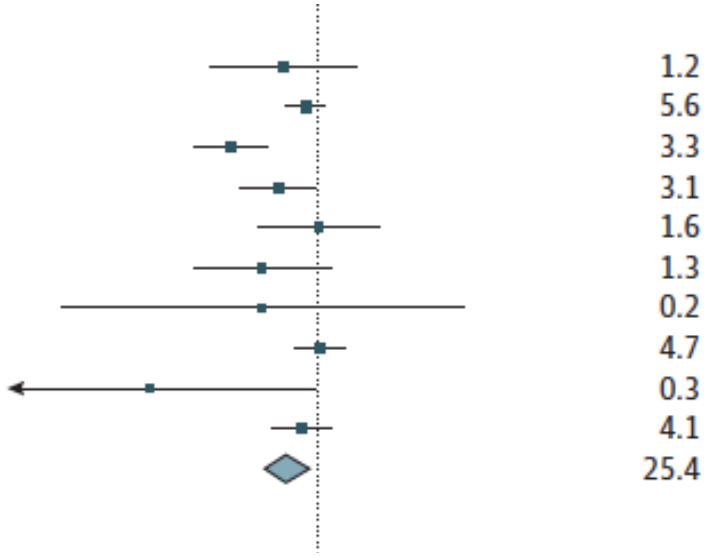
Meta-analysis of **All-cause Mortality** Stratified by Baseline LDL-C Level

Baseline LDL-C 100-129 mg/dL				
PROVE IT-TIMI 22,[12] 2004	46/2099 (2.19)	66/2063 (3.20)	0.69 (0.47-1.00)	1.2
SHARP,[42] 2011	1142/4650 (24.56)	1115/4620 (24.13)	1.02 (0.94-1.11)	6.5
JUPITER,[9] 2008	198/8901 (2.22)	247/8901 (2.77)	0.80 (0.66-0.97)	3.4
A to Z,[33] 2004	104/2265 (4.59)	130/2232 (5.82)	0.79 (0.61-1.02)	2.2
ASPEN,[36] 2006	70/1211 (5.78)	68/1199 (5.67)	1.02 (0.73-1.42)	1.5
CARDS,[35] 2004	61/1429 (4.27)	82/1412 (5.81)	0.74 (0.53-1.02)	1.5
OSLER 1 & 2,[5] 2015	4/2976 (0.13)	6/1489 (0.40)	0.33 (0.09-1.18)	0.1
IDEAL,[11] 2005	366/4439 (8.25)	374/4449 (8.41)	0.98 (0.85-1.13)	4.5
ODYSSEY LONG TERM,[4] 2015	8/1553 (0.52)	10/788 (1.27)	0.41 (0.16-1.03)	0.2
HOPE-3,[40] 2016	334/6361 (5.25)	357/6344 (5.63)	0.93 (0.80-1.08)	4.3
Subtotal	2333/35884 (6.50)	2455/33497 (7.33)	0.88 (0.79-0.98)	25.3
Heterogeneity: $\tau^2=0.01$; $\chi^2_9=19.23$ ($P=.02$); $I^2=53\%$				
Overall effect: $z=2.35$ ($P=.02$)				



Meta-analysis of **CV Mortality** Stratified by Baseline LDL-C level

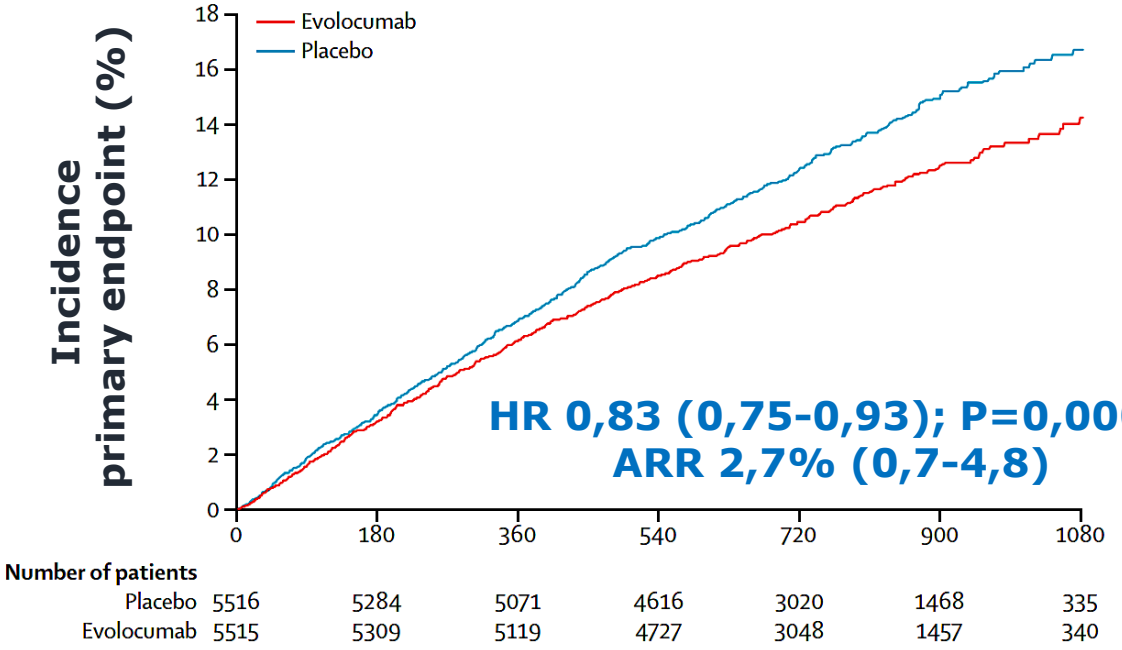
Baseline LDL-C 100-129 mg/dL				
PROVE IT-TIMI 22,[12] 2004	23/2099 (1.10)	29/2063 (1.41)	0.78 (0.45-1.35)	1.2
SHARP,[42] 2011	361/4650 (7.76)	388/4620 (8.40)	0.92 (0.80-1.07)	5.6
JUPITER,[9] 2008	83/8901 (0.93)	157/8901 (1.76)	0.53 (0.41-0.69)	3.3
A to Z,[33] 2004	83/2265 (3.66)	109/2232 (4.88)	0.75 (0.56-1.00)	3.1
ASPEN,[36] 2006	38/1211 (3.14)	37/1199 (3.09)	1.02 (0.65-1.60)	1.6
CARDS,[35] 2004	25/1429 (1.75)	37/1412 (2.62)	0.67 (0.40-1.11)	1.3
OSLER 1 & 2,[5] 2015	4/2976 (0.13)	3/1489 (0.20)	0.67 (0.15-2.98)	0.2
IDEAL,[11] 2005	223/4439 (5.02)	218/4449 (4.90)	1.03 (0.85-1.24)	4.7
ODYSSEY LONG TERM,[4] 2015	4/1553 (0.26)	7/788 (0.89)	0.29 (0.08-0.99)	0.3
HOPE-3,[40] 2016	154/6361 (2.42)	171/6344 (2.70)	0.90 (0.72-1.12)	4.1
Subtotal	998/35884 (2.78)	1156/33497 (3.45)	0.81 (0.68-0.95)	25.4
Heterogeneity: $\tau^2=0.03$; $\chi^2_9=22.99$ ($P=.02$); $I^2=61\%$				
Overall effect: $z=2.59$ ($P=.01$)				

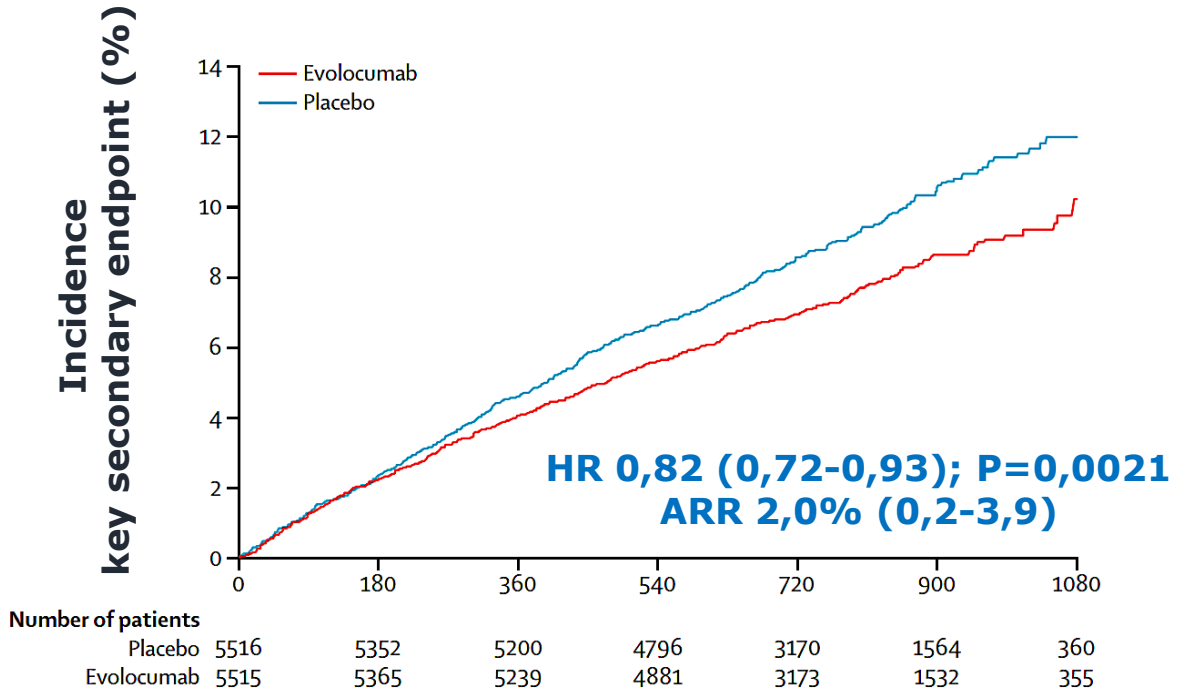


Navarese E.P et al. JAMA. 2018;319(15):1566-1579

subgroup diabetes

patients with diabetes





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Sección de Riesgo Vascular y Rehabilitación Cardiaca

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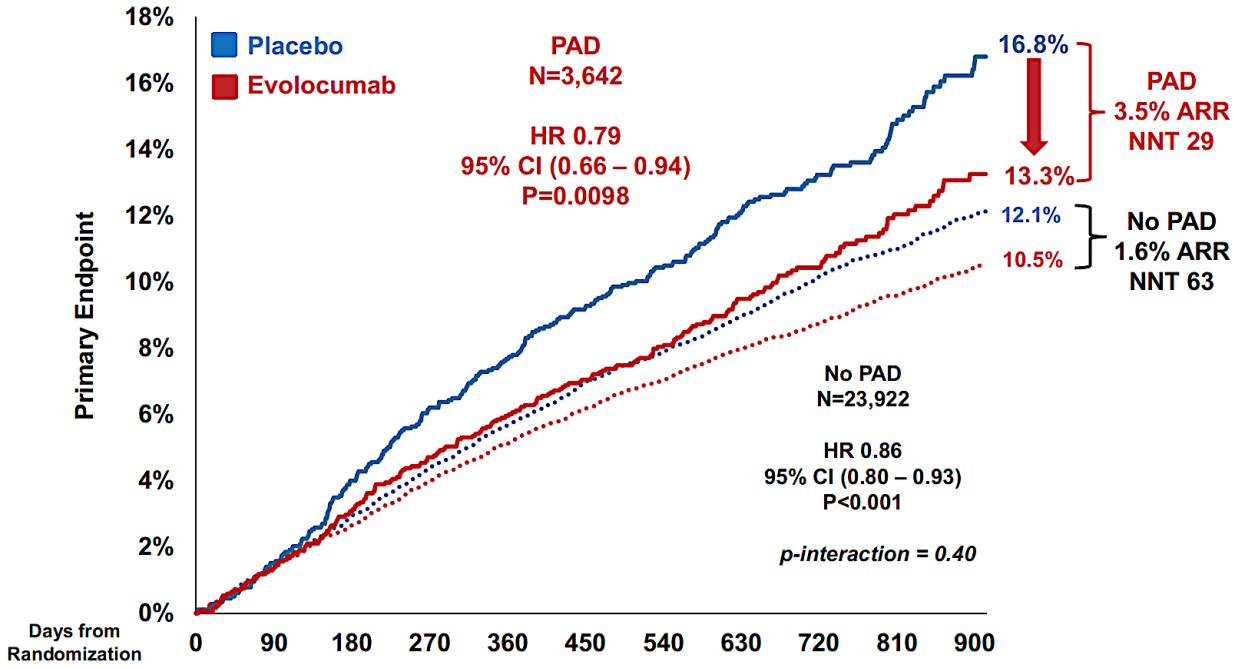
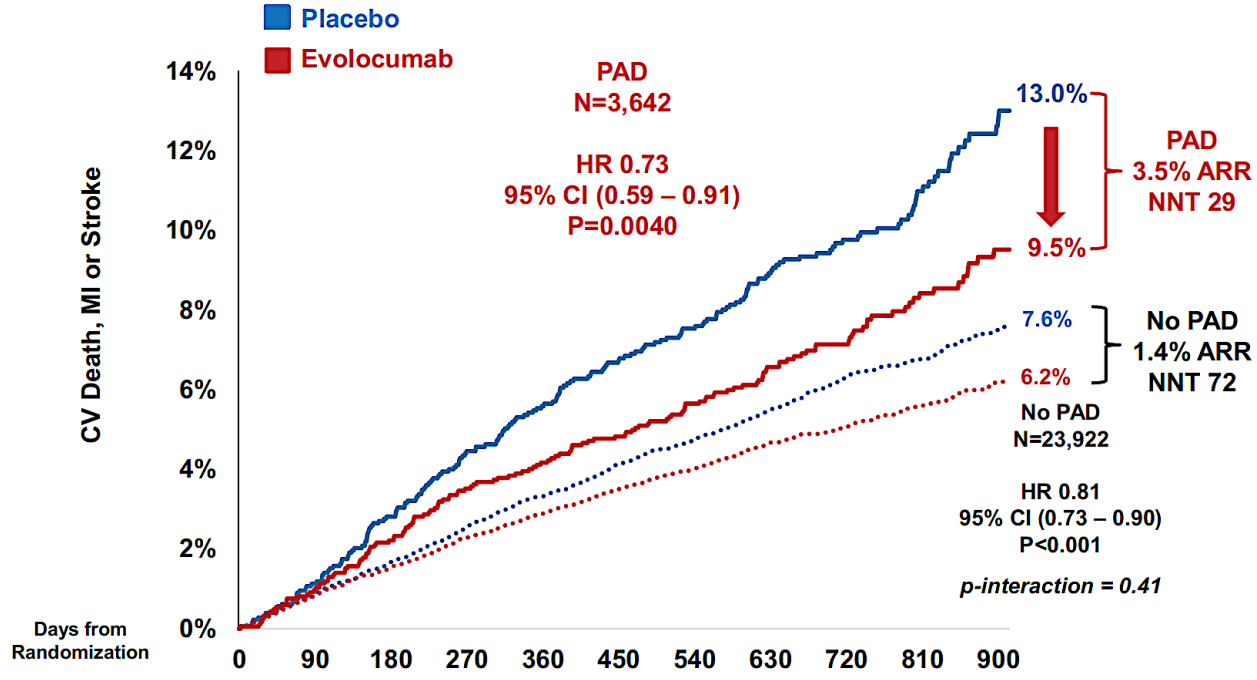
Sabatine MS, et al. Lancet Diabetes Endocrinol. 2017;5:941-50

subgroup PAD

patients with and without PAD





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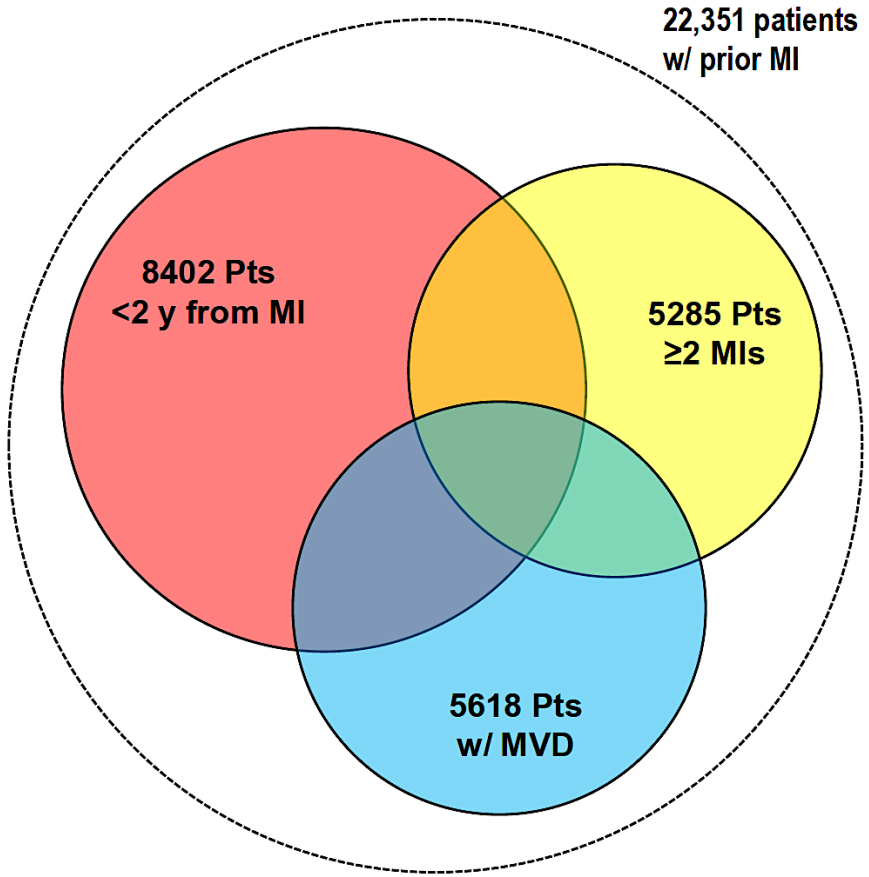
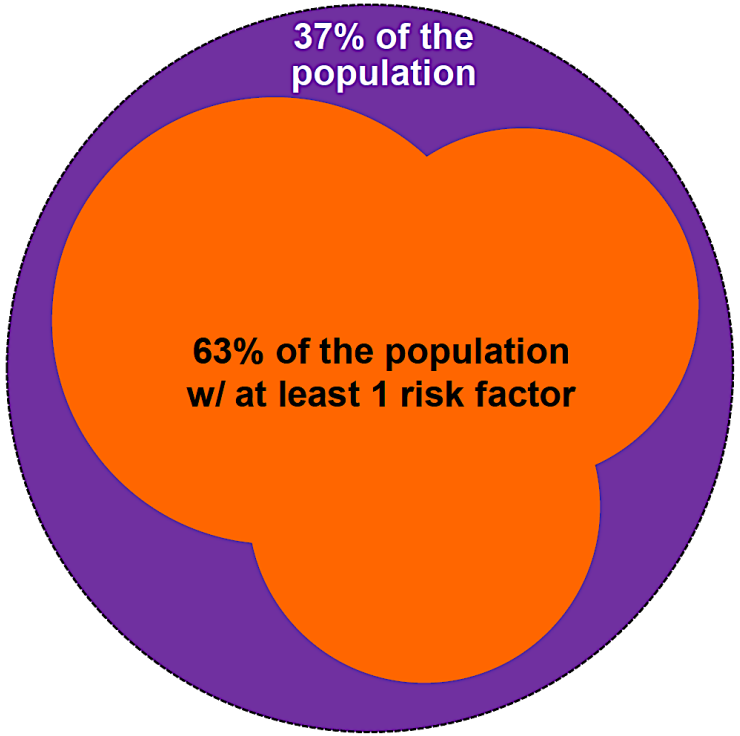
Bonaca MP, et al. Circulation. 2018;137:338-50

subgroup high risk MI patients





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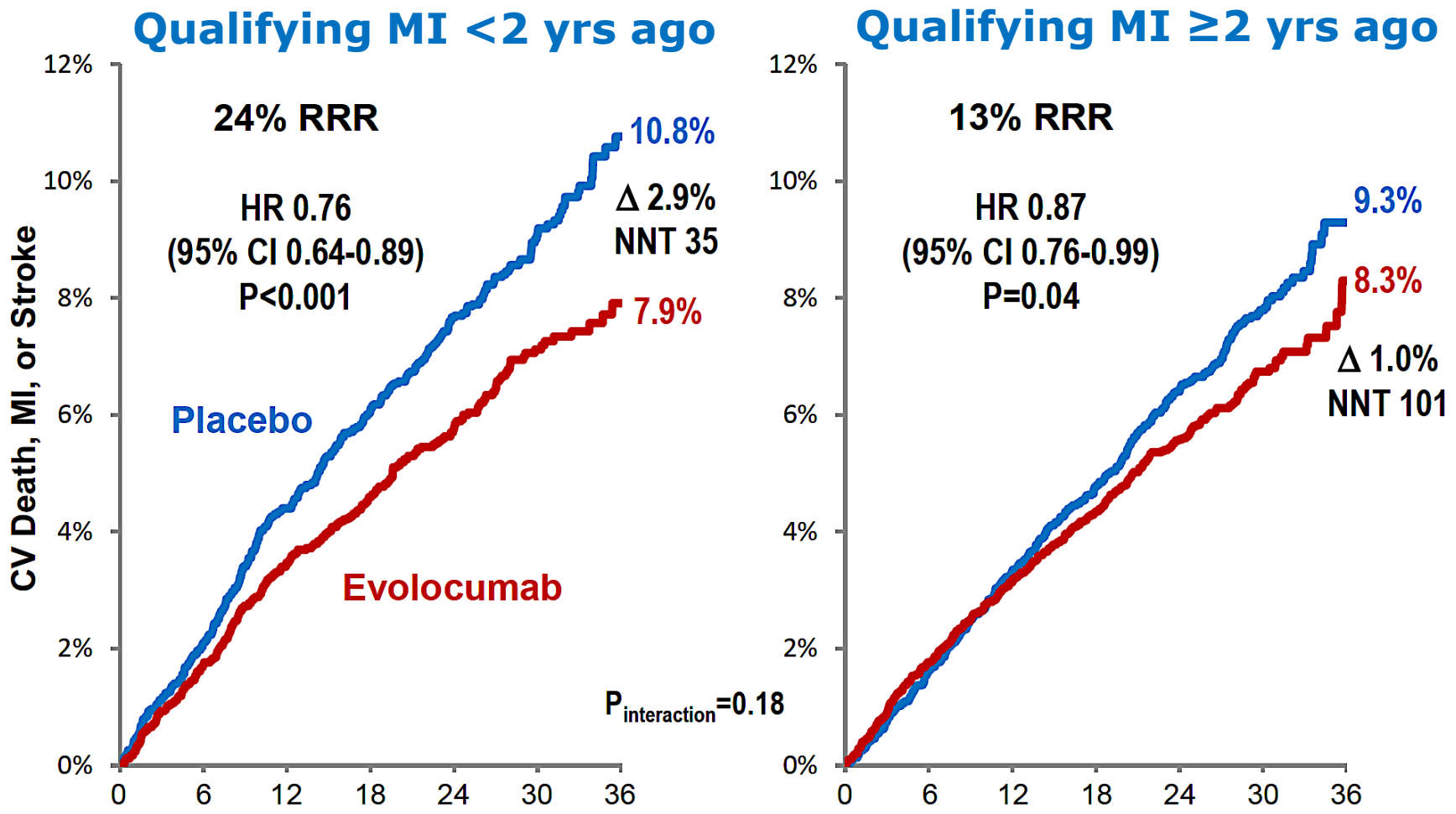
Sabatine MS, et al. AHA congress, Anhaeim 2017

Benefit of Evolocumab based on time from qualifying MI



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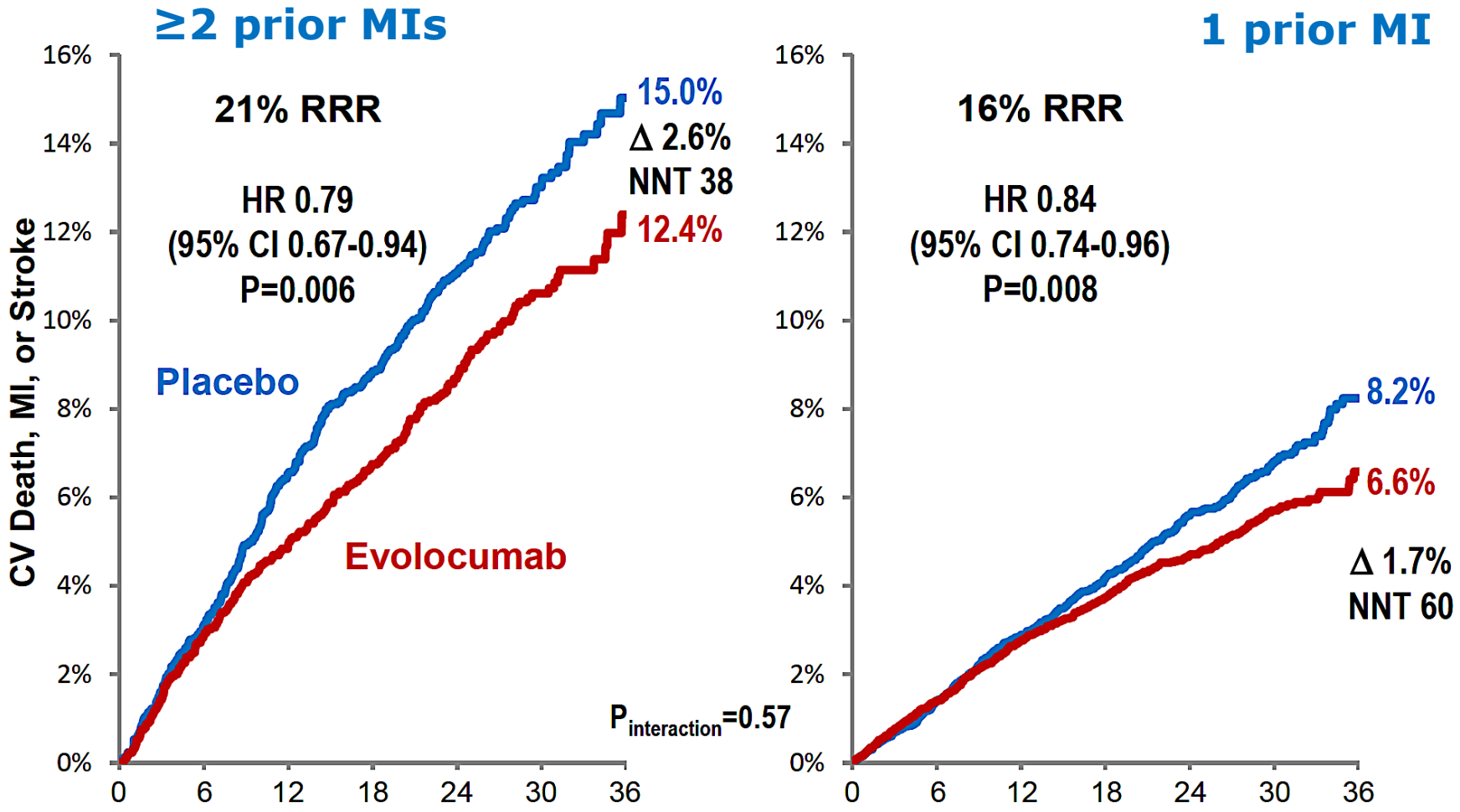
Sabatine MS, et al. AHA congress, Anhaeim 2017

Benefit of Evolocumab based on number of prior MIs



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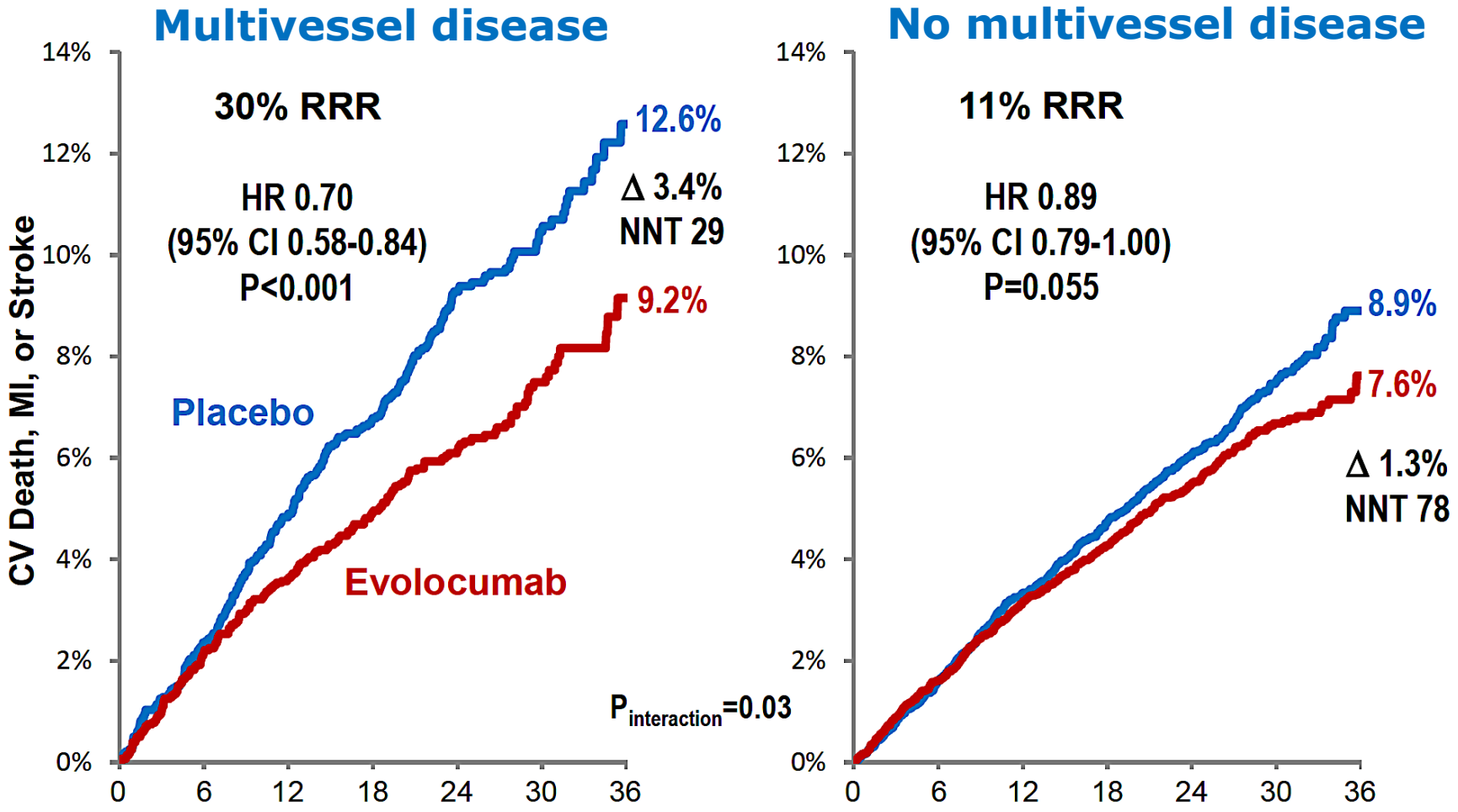
Sabatine MS, et al. AHA congress, Anhaeim 2017

Benefit of Evolocumab based on multivessel disease



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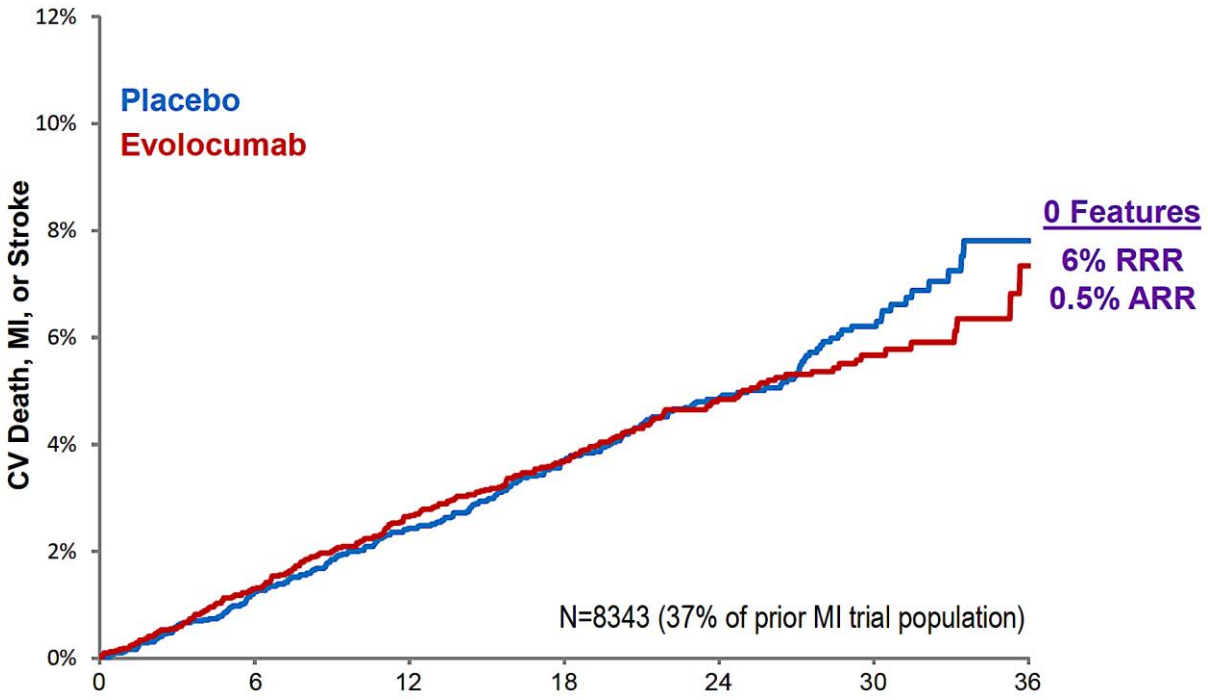
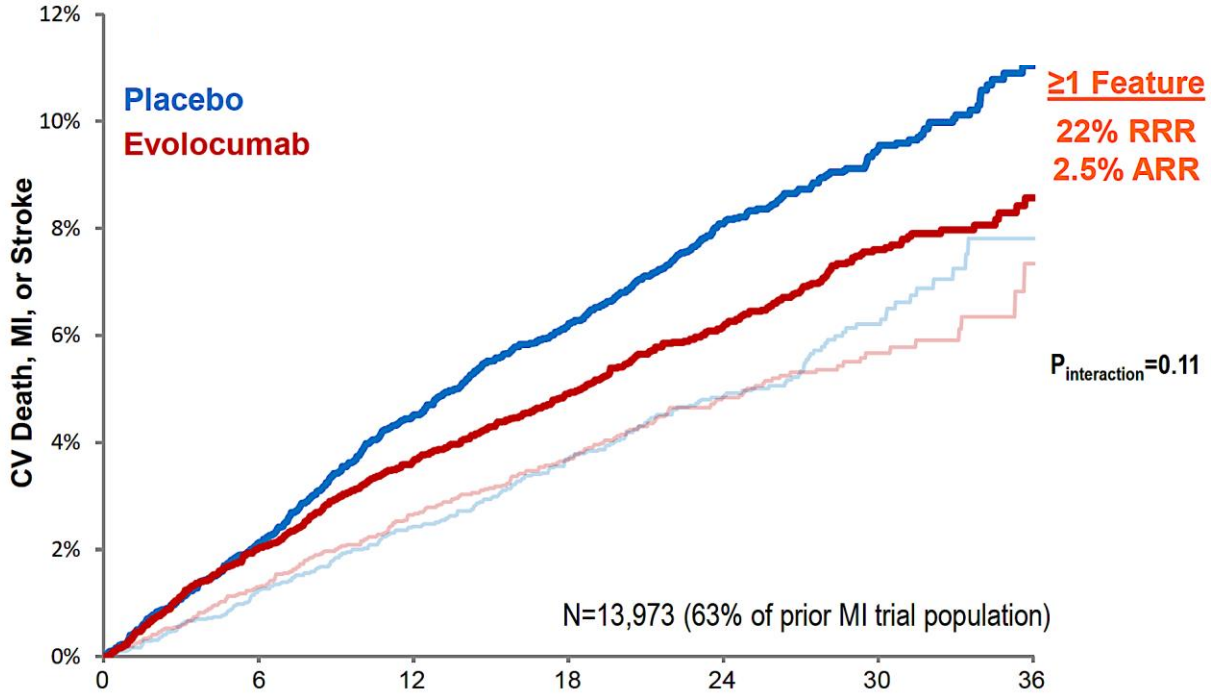
Sabatine MS, et al. AHA congress, Anhaeim 2017

Benefit of Evolocumab based on number of high-risk MI features

High-risk feature:
<2 yrs qualifying MI, ≥2 Prior MIs, or residual MVD





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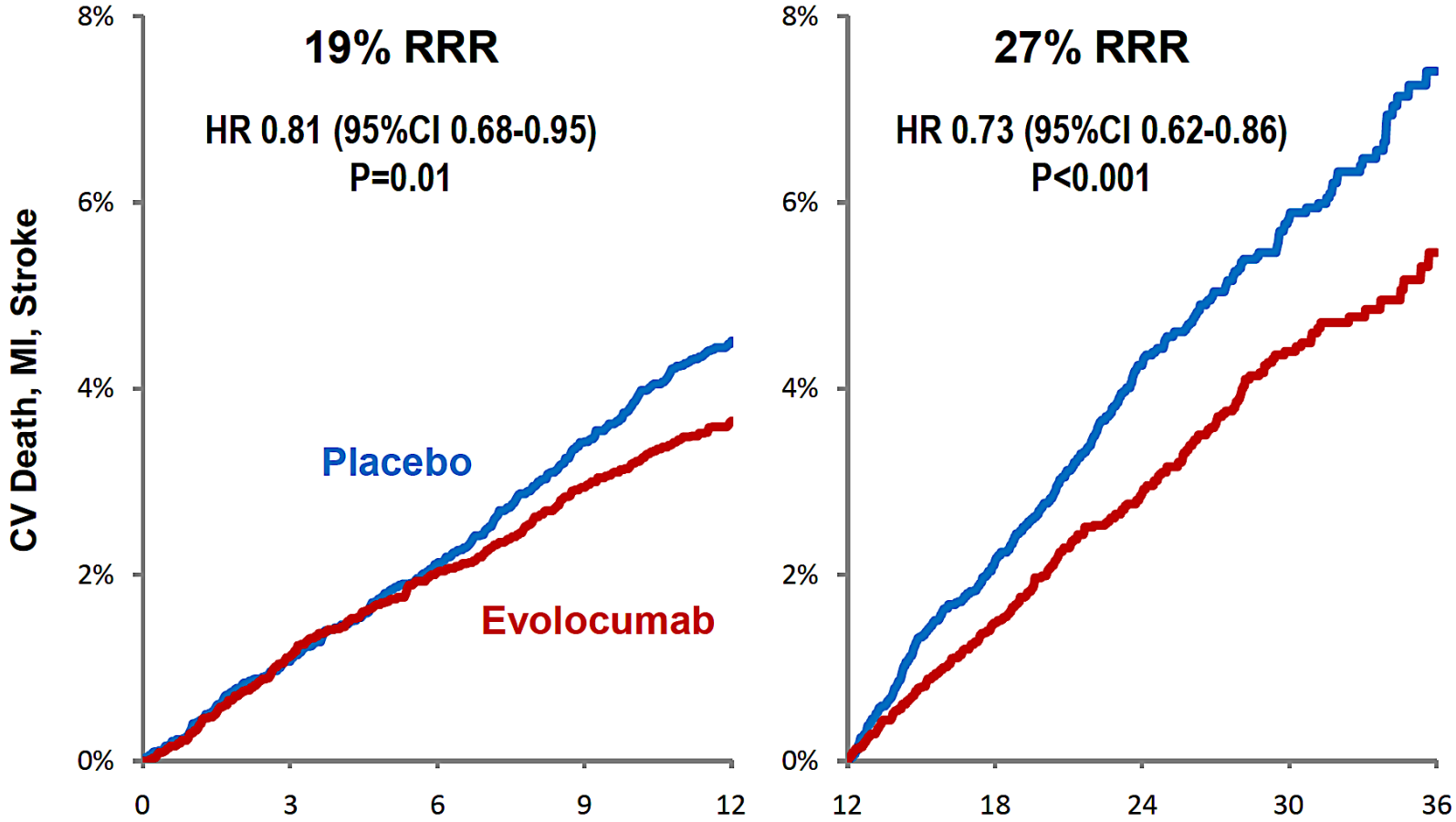
Sabatine MS, et al. AHA congress, Anhaeim 2017

Landmarck analyses in patients with/without high-risk MI features



High-risk feature:
<2 yrs MI,
≥2 Prior Mis,
or residual MVD

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Sabatine MS, et al. AHA congress, Anhaeim 2017

http://amgendigital.es/cardiofighters

Preguntas

http://amgendigital.es/cardiofighters

Cierre y conclusiones