

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

  
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**#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.

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<http://amgendigital.es/cardiofighters>



# #CardioFighters

Reunión anual de la Sección Riesgo Vascular y  
Rehabilitación Cardíaca

BIENVENIDO A CARDIOFIGHTERS

*San Sebastián, 25 mayo 2018*



<http://amgendigital.es/cardiofighters>

25/05/2018

🕒 12:30

PARTICIPA

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

+ Dr. Iñaki Lekuona

*Jefe del Servicio de Cardiología. Hospital Galdakao. Vizcaya. Osakidetza*

+ Dra. Almudena Castro

*Jefa de la Unidad de Rehabilitación Cardíaca. Servicio de Cardiología. Hospital Universitario La Paz. Madrid.*

+ Dr. Domingo Marzal

*Cardiólogo. Servicio de Cardiología. Hospital Virgen del Mar. Madrid. Director de Innovación y Estrategia Médica Digital. Sanitas*

Cardiofighters San Sebastian 2018

PARA PARTICIPAR

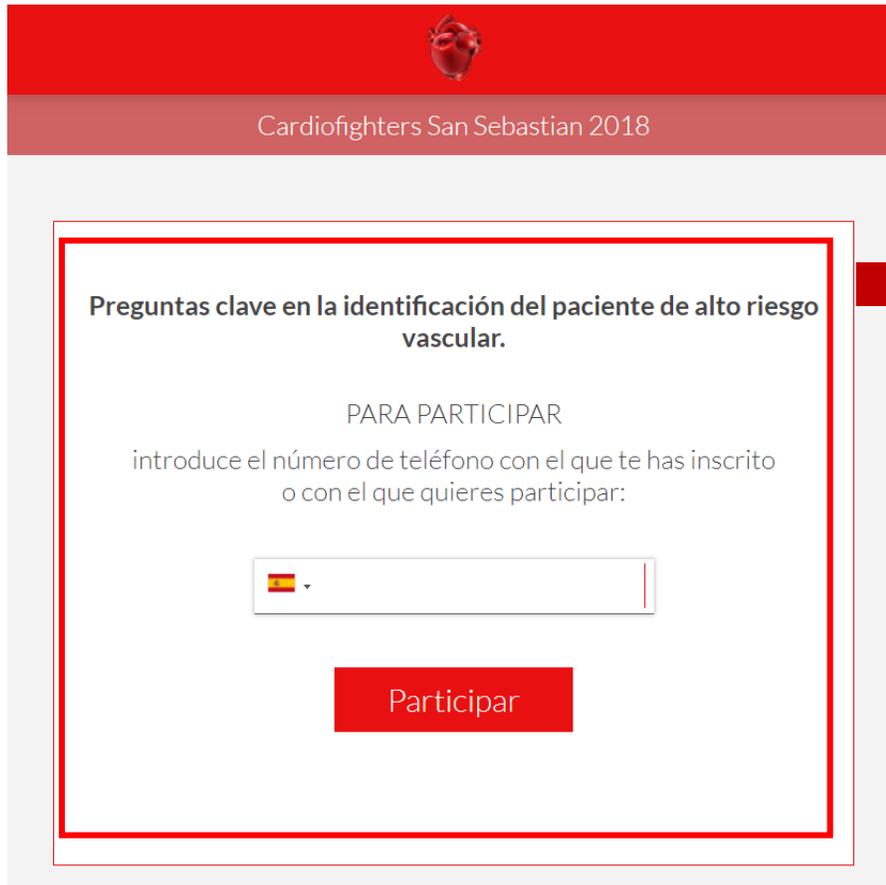
introduce el número de teléfono con el que te has inscrito:



Participar



# [www.amgendigital.es/cardiofighters](http://www.amgendigital.es/cardiofighters)



Cardiofighters San Sebastian 2018

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

PARA PARTICIPAR

introduce el número de teléfono con el que te has inscrito o con el que quieres participar:

Participar



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.



# Para votar por los #CardioFighters

## Tenemos cuatro ROUNDS de preguntas

### Encuestas

**- ROUNDS**

ROUND 1. En la Cardiopatía Isquémica ¿Cuál debería ser el objetivo de control del C-LDL debería ser <70 mg/dl o < 55 mg/dl?

Juan Cosín

Carlos Escobar

**←**

SIGUIENTE >>

**+ Encuesta de Satisfacción Cardiopatía Isquémica 2018 - Cardiofighters**

**votamos al final de cada ROUND**

**Veremos las votaciones al final de cada round**



# NO OLVIDAR!!!!

## Encuestas

### - ROUNDS

ROUND 1. En la Cardiopatía Isquémica ¿Cuál debería ser el objetivo de control del C-LDL debería ser <70 mg/dl o < 55 mg/dl?

- Juan Cosín
- Carlos Escobar

SIGUIENTE >>

+ Encuesta de Satisfacción Cardiopatía Isquémica 2018 - Cardiofighters

**Rellenar la encuesta de satisfacción**



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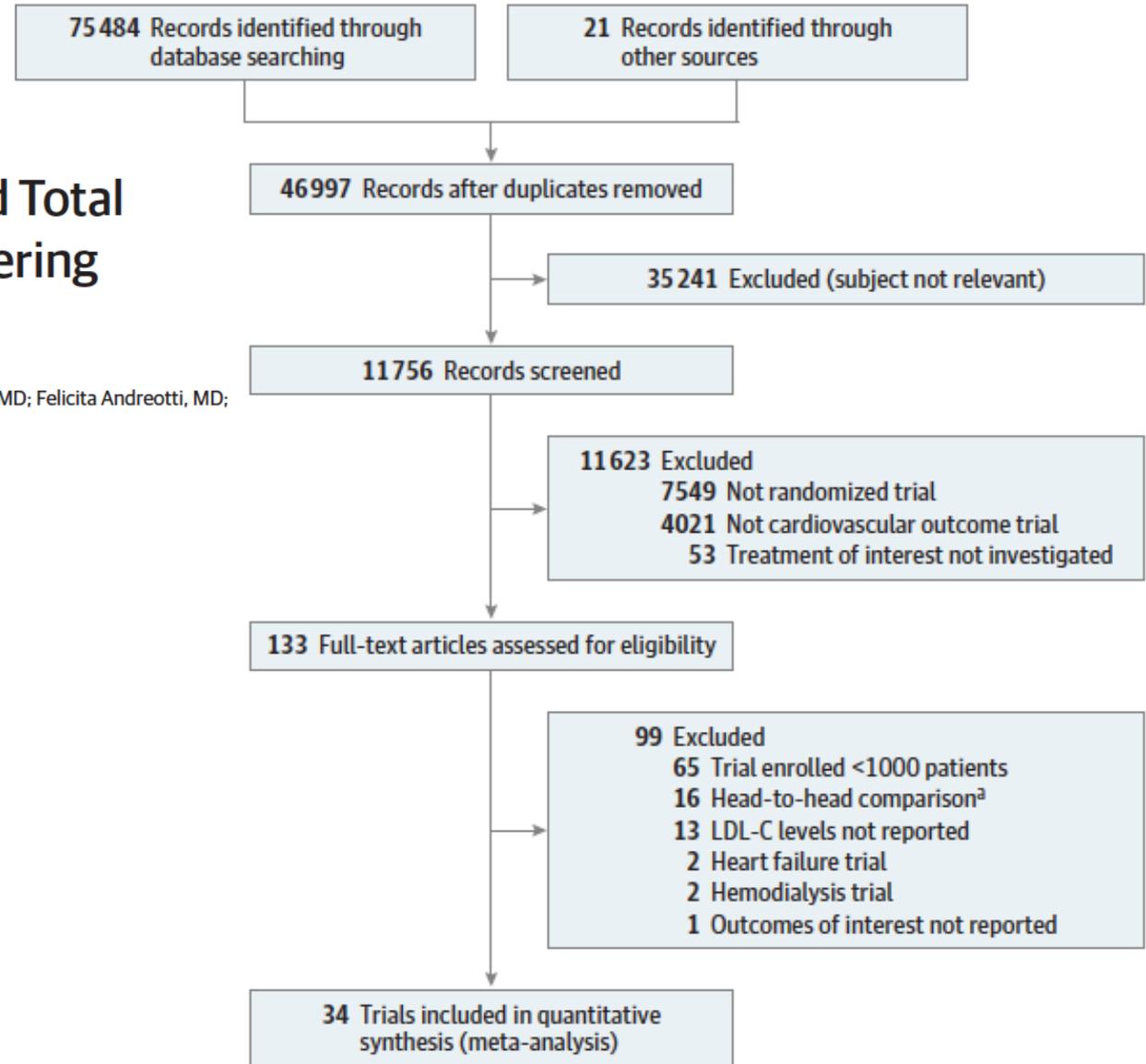
# **ROUND #1**

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



# 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



Source	No. (%)						Median Follow-up, y	More Intensive LDL-C Lowering		Less Intensive LDL-C Lowering		
	Source	No.	Women	Diabetes	Vascular Disease	CAD		Treatment	Baseline LDL-C, Mean (SD), mg/dL	LDL-C Reduction, %	Treatment	Baseline LDL-C, Mean (SD), mg/dL
4S, <sup>7</sup> 1994	MEGA, <sup>37</sup> 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 (17.79)
WOSCOPS, <sup>21</sup> 1995	SPARCL, <sup>38</sup> 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, <sup>22</sup> 1996	JUPITER, <sup>9</sup> 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, <sup>23</sup> 1997	SEARCH, <sup>39</sup> 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, <sup>24</sup> 1998	HOPE-3, <sup>40</sup> 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 (36.1)
LIPID, <sup>8</sup> 1998	SEAS, <sup>41</sup> 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, <sup>25</sup> 2000	SHARP, <sup>42</sup> 2011	9270	3470 (37)	2094 (23)	1393 (15)	0	4.9	Simvastatin (20 mg) + ezetimibe (10 mg) [n = 4650] <sup>b</sup>	107.12 (34.03)	-30	Placebo [n = 4620]	107.50 (34.03)
ALLHAT-LLT, <sup>26</sup> 2002	IMPROVE-IT, <sup>2</sup> 2015	18 144	4416 (24)	4933 (27)	18 144 (100)	18 144 (100)	6.7	Simvastatin (40 mg) + ezetimibe (10 mg) [n = 9077]	93.8	-43	Simvastatin (40 mg) [n = 9077]	93.8
GREACE, <sup>27</sup> 2002	ODYSSEY LONG TERM, <sup>4</sup> 2015	2341	884 (38)	809 (35)	2341 (100) <sup>d</sup>	1607 (69)	1.5	Alirocumab (150 mg every 2 wk) [n = 1553]	122.7 (42.6)	-53	Placebo [n = 788]	121.9 (41.6)
HPS, <sup>28</sup> 2002	OSLER 1 & 2, <sup>5</sup> 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, <sup>29</sup> 2002	FOURIER, <sup>3</sup> 2017	27 564	6769 (25)	10 081 (37)	27 564 (100)	22 551 (81)	2.2 (1.2-3.5)	Evolocumab (140 mg every 2 wk or 420 mg every mo) [n = 13 784]	92	-61	Placebo [n = 13 780]	92
PROSPER, <sup>30</sup> 2002	SPIRE-1, <sup>43</sup> 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, <sup>31</sup> 2003	SPIRE-2, <sup>43</sup> 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, <sup>32</sup> 2003	All trials	270 288 <sup>e</sup>					3.9					
A to Z, <sup>33</sup> 2004												
ALLIANCE, <sup>34</sup> 2004												
CARDS, <sup>35</sup> 2004												
PROVE IT-TIMI, <sup>12</sup> 2004												
TNT, <sup>10</sup> 2005												
IDEAL, <sup>11</sup> 2005												
ASPEN, <sup>36</sup> 2006												

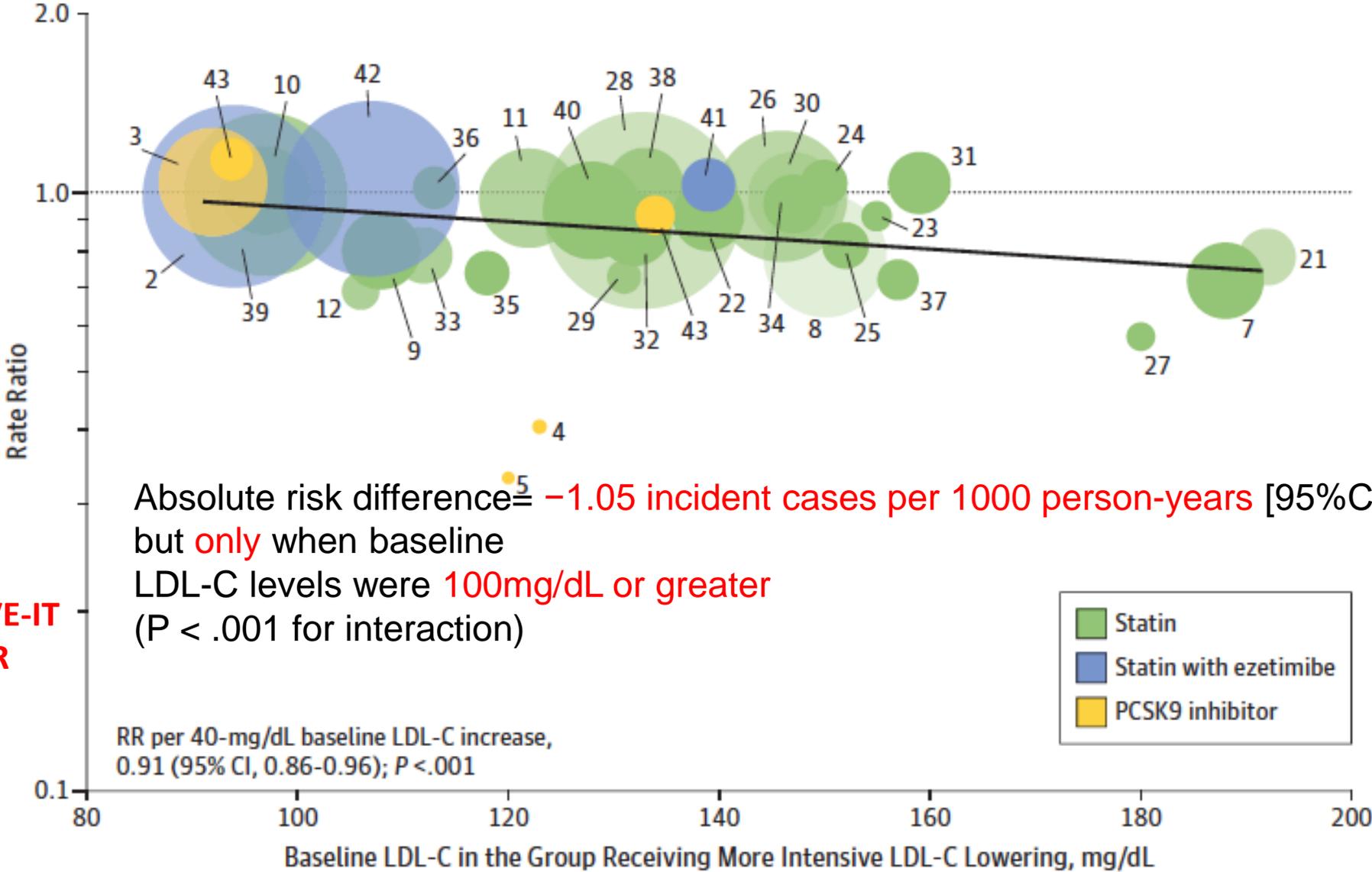
JUPITER

IMPROVE-IT

FOURIER

SPIREs

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



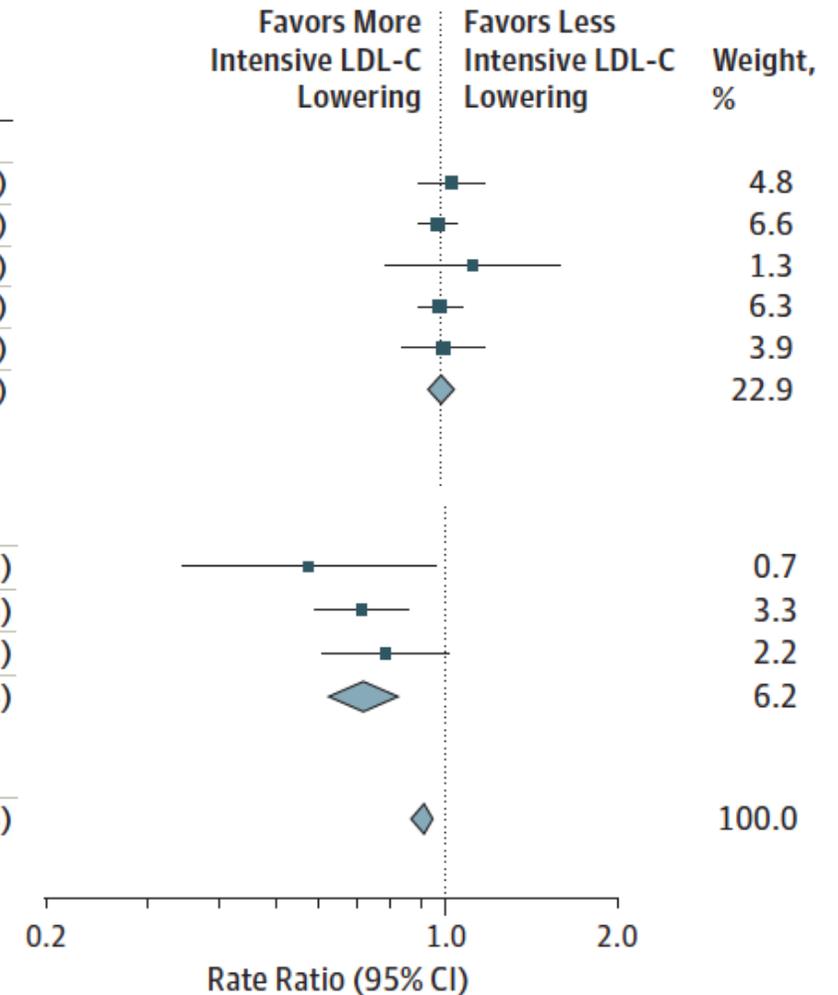
Absolute risk difference = **-1.05 incident cases per 1000 person-years** [95%CI, -1.59 to -0.51])  
 but **only** when baseline LDL-C levels were **100mg/dL or greater**  
 (P < .001 for interaction)

**2: IMPROVE-IT**  
**3: FOURIER**  
**43: SPIRE**

**7: 4S**  
**21: WOSCOPS**  
**27: GRACE**

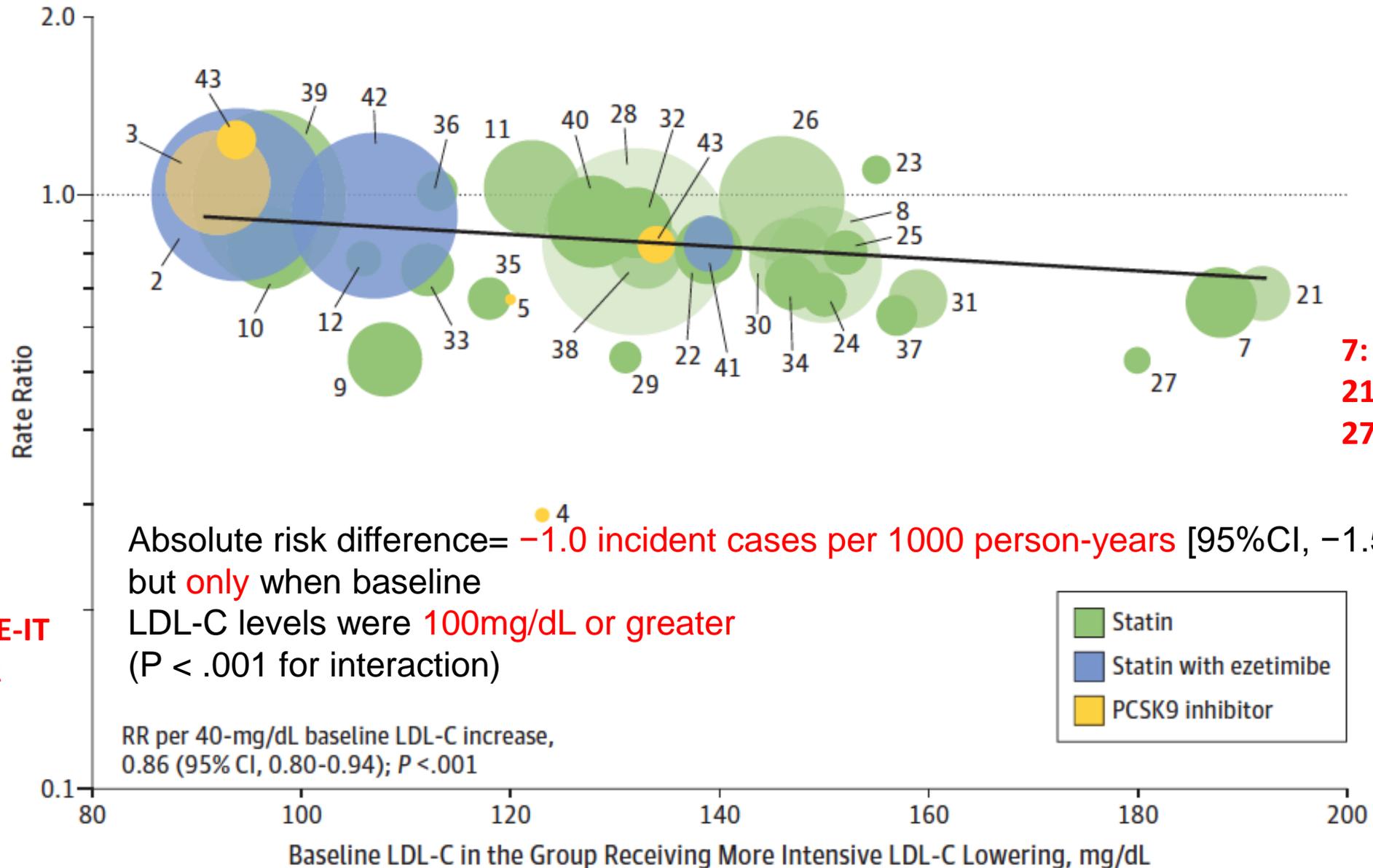
# Meta-analysis of **All-cause Mortality** Stratified by Baseline LDL-C Level

Study and Subgroup	No. of Patients With Event/Total No. (%)		Rate Ratio (95% CI)
	More Intensive LDL-C Lowering	Less Intensive LDL-C Lowering	
<b>Baseline LDL-C &lt;100 mg/dL</b>			
FOURIER, <sup>3</sup> 2017	444/13 784 (3.22)	426/13 780 (3.09)	1.04 (0.91-1.19)
IMPROVE-IT, <sup>2</sup> 2015	1215/9067 (13.40)	1231/9077 (13.56)	0.99 (0.91-1.07)
SPIRE-1, <sup>43</sup> 2017	66/8408 (0.78)	58/8409 (0.69)	1.14 (0.80-1.62)
SEARCH, <sup>39</sup> 2010	964/6031 (15.98)	970/6033 (16.08)	0.99 (0.91-1.09)
TNT, <sup>10</sup> 2005	284/4995 (5.69)	282/5006 (5.63)	1.01 (0.86-1.19)
Subtotal	2973/42 285 (7.03)	2967/42 305 (7.01)	1.00 (0.95-1.06)
Heterogeneity: $\tau^2=0.00$ ; $\chi^2_4=0.99$ ( $P=.91$ ); $I^2=0\%$			
Overall effect: $z=0.11$ ( $P=.92$ )			
<b>Baseline LDL-C <math>\geq 160</math> mg/dL</b>			
GREACE, <sup>27</sup> 2002	23/800 (2.88)	40/800 (5.00)	0.57 (0.34-0.96)
4S, <sup>7</sup> 1994	182/2221 (8.19)	256/2223 (11.52)	0.71 (0.59-0.86)
WOSCOPS, <sup>21</sup> 1995	106/3302 (3.21)	135/3293 (4.10)	0.78 (0.61-1.01)
Subtotal	311/6323 (4.92)	431/6316 (6.82)	0.72 (0.62-0.84)
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)
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 $\geq 100$ mg/dL)			



4.3 fewer deaths per 1000 person-years

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



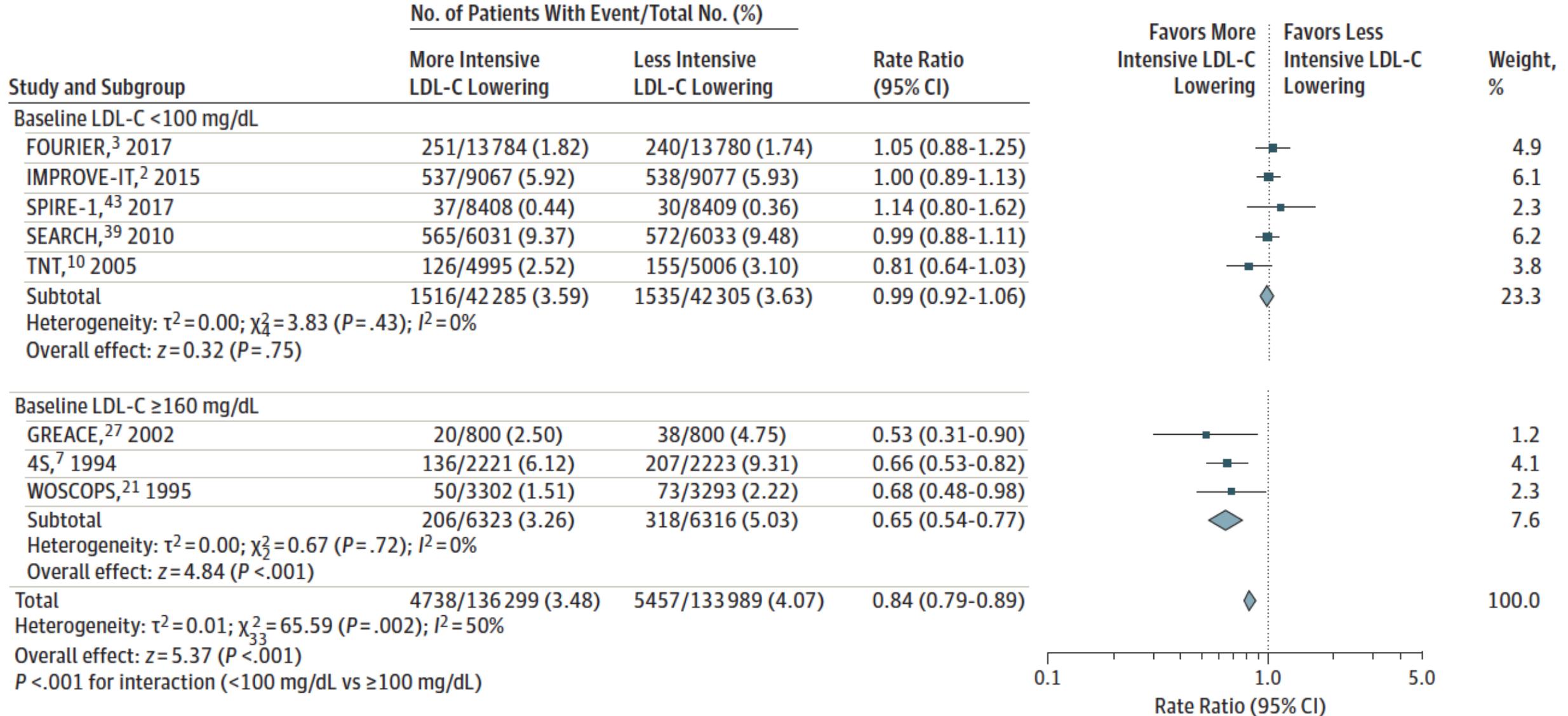
**7: 4S**  
**21: WOSCOPS**  
**27: GRACE**

**2: IMPROVE-IT**  
**3: FOURIER**  
**43: SPIRE**

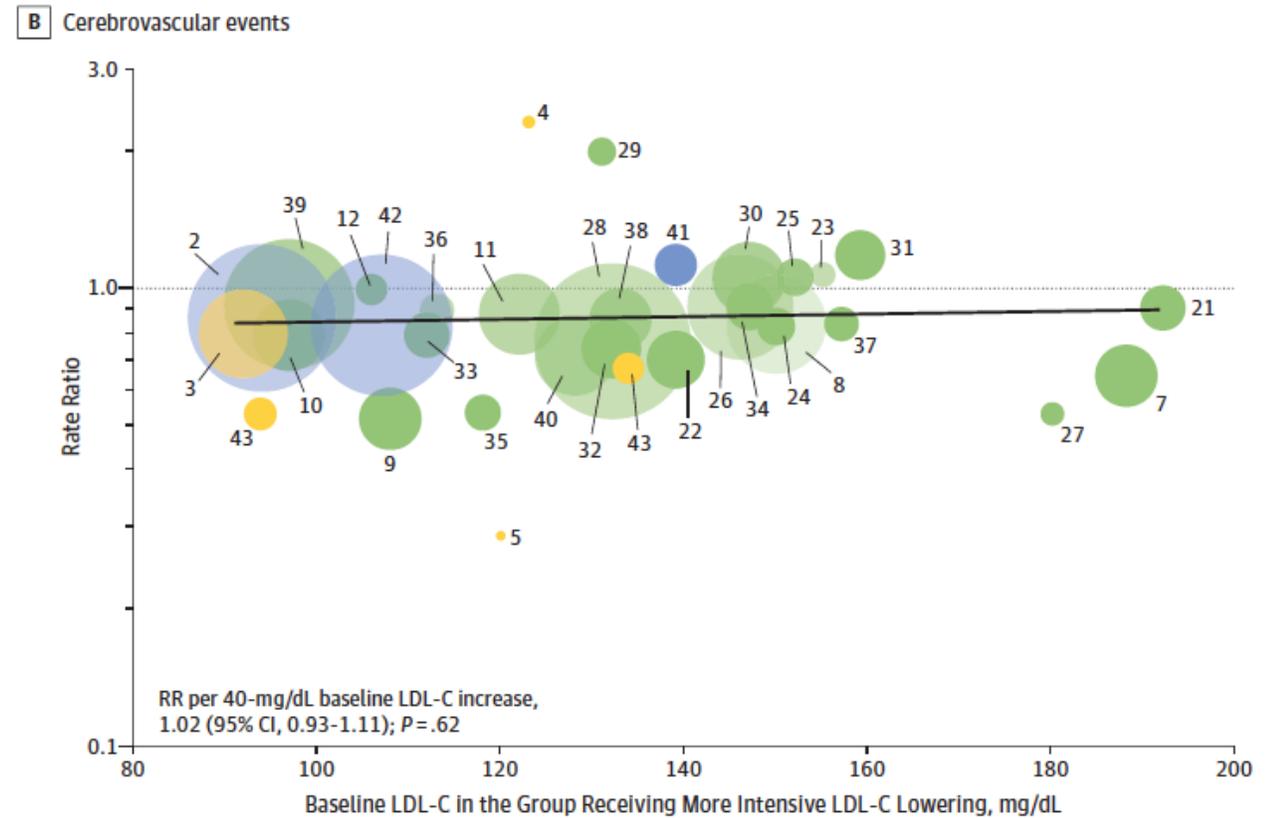
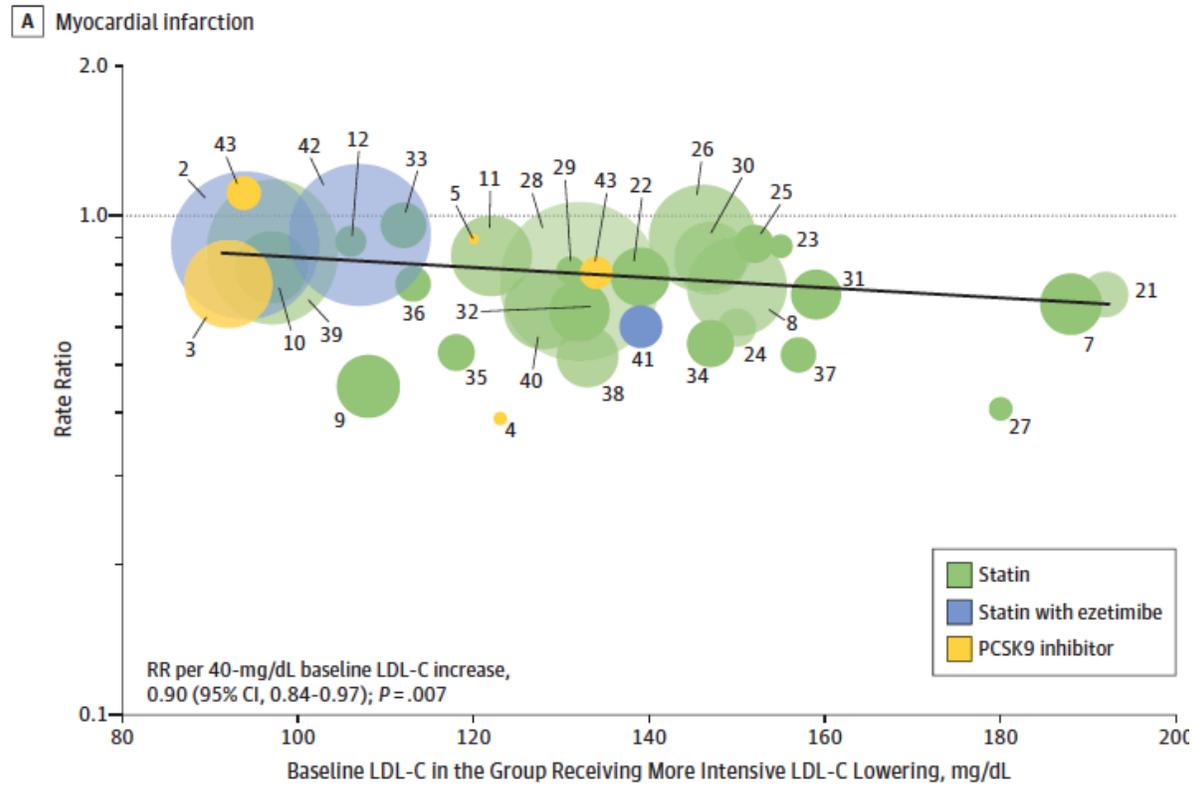
Absolute risk difference = **-1.0 incident cases per 1000 person-years** [95%CI, -1.59 to -0.51])  
 but **only** when baseline LDL-C levels were **100mg/dL or greater**  
 (P < .001 for interaction)

RR per 40-mg/dL baseline LDL-C increase,  
 0.86 (95% CI, 0.80-0.94); P < .001

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



# Meta-regression Analysis of **MACES** by Baseline LDL-C Level



# 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

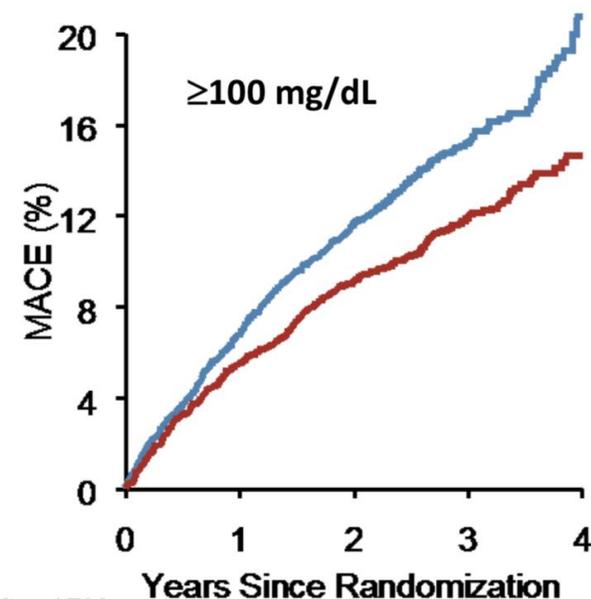
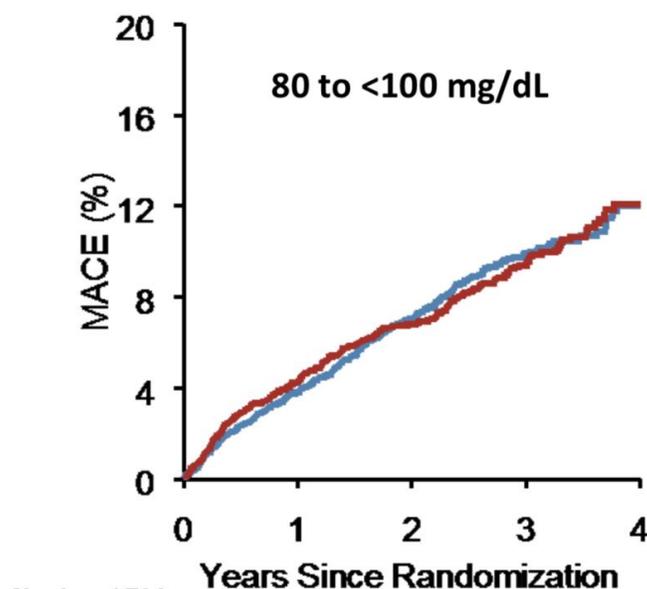
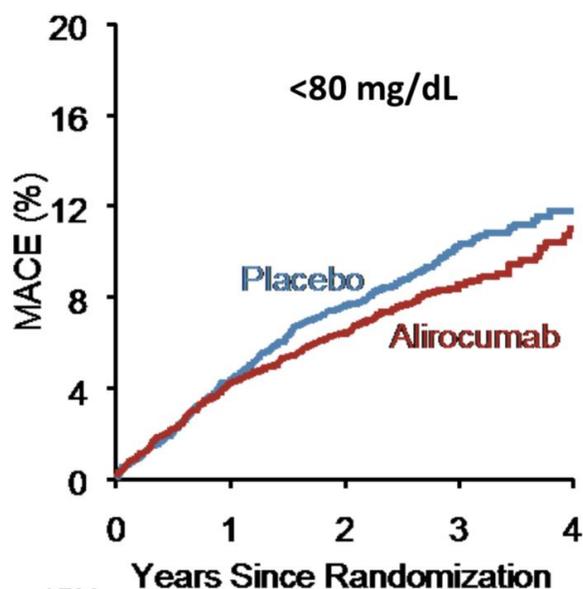


**CONCLUSIONS AND RELEVANCE** In these meta-analyses and meta-regressions, more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels. This association was not 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.

# Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%)		HR (95% CI)	p-value*
		Alirocumab	Placebo		
<b>LDL (mg/dL)</b>					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

	0	1	2	3	4
Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233

Number at Risk

	0	1	2	3	4
Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

Number at Risk

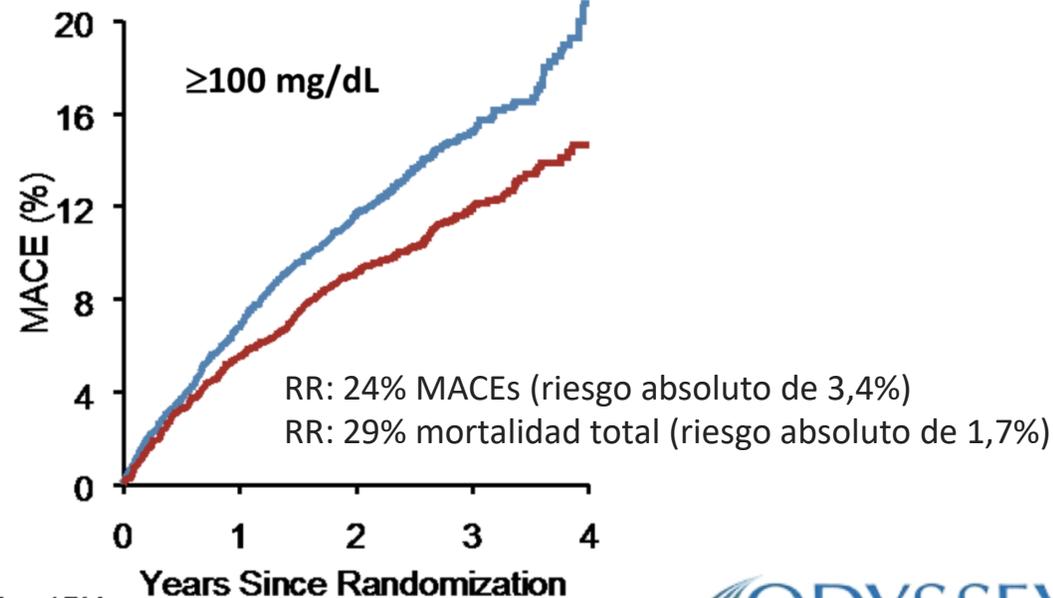
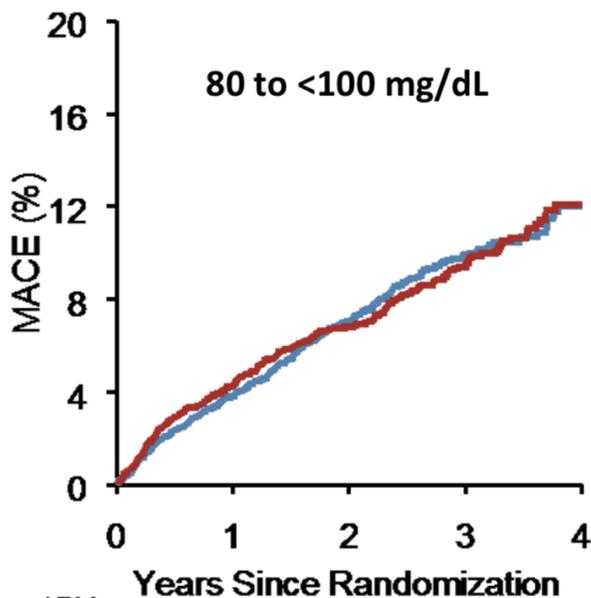
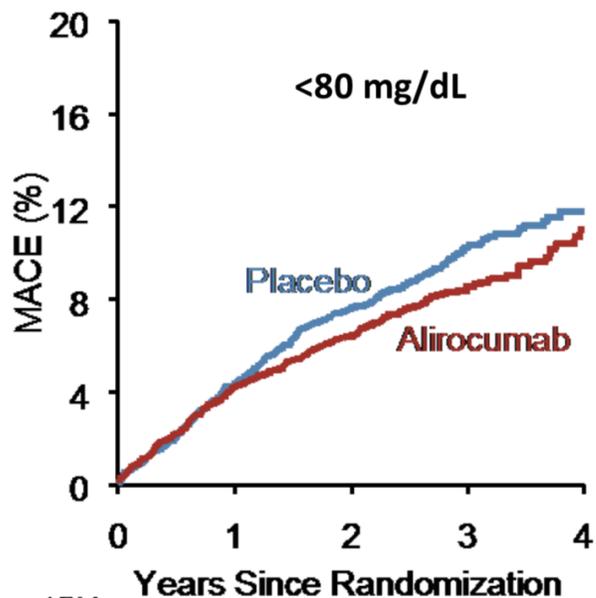
	0	1	2	3	4
Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207



# Primary Efficacy in Main Prespecified Subgroups

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# 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 ...”



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



# ESC Congress 2016, Rome



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

## Recommendations for lipid control



# ASCVD Risk Factor Modifications Algorithm



## Dyslipidemia

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



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

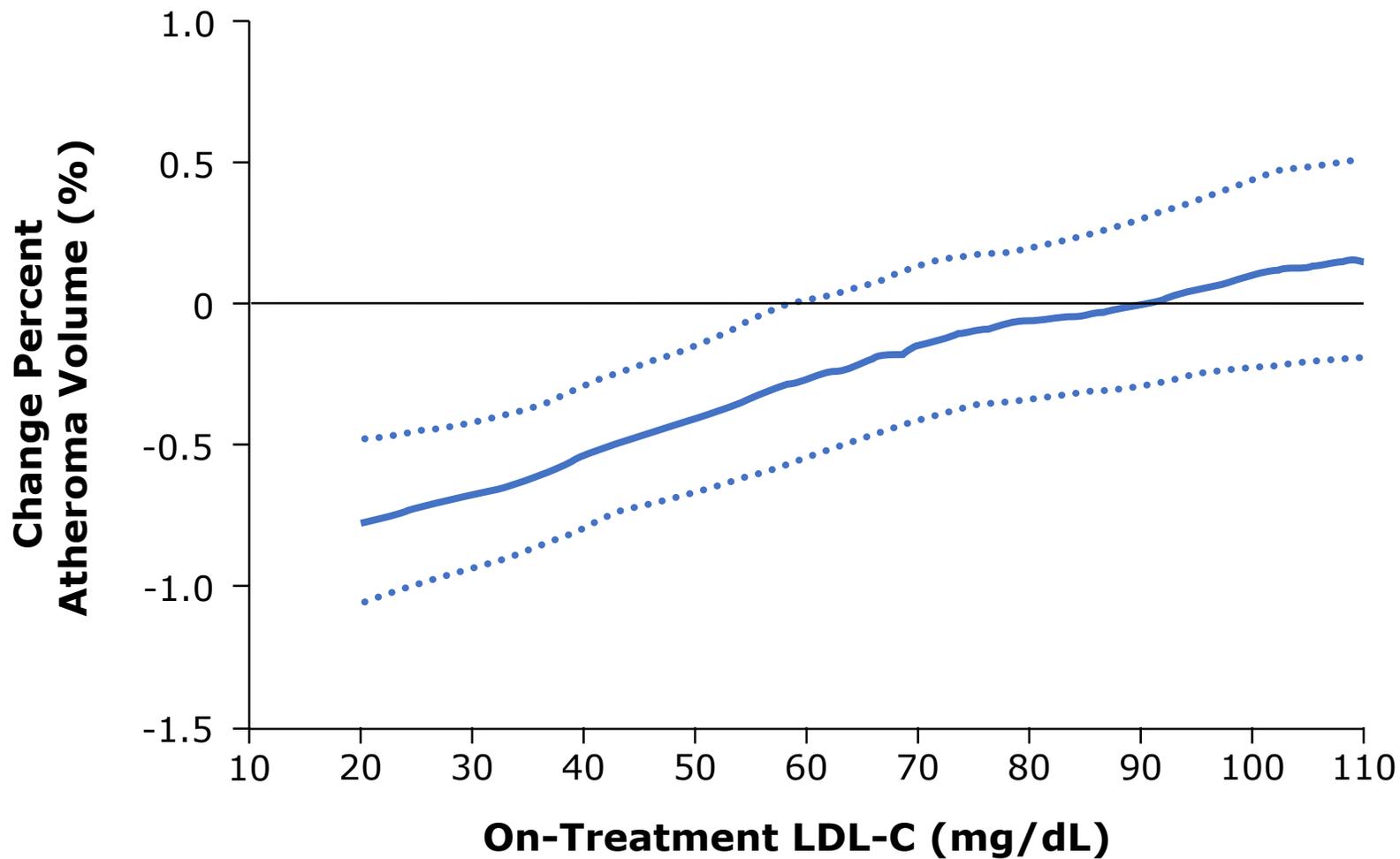
A Meta-Analysis of Statin Trials

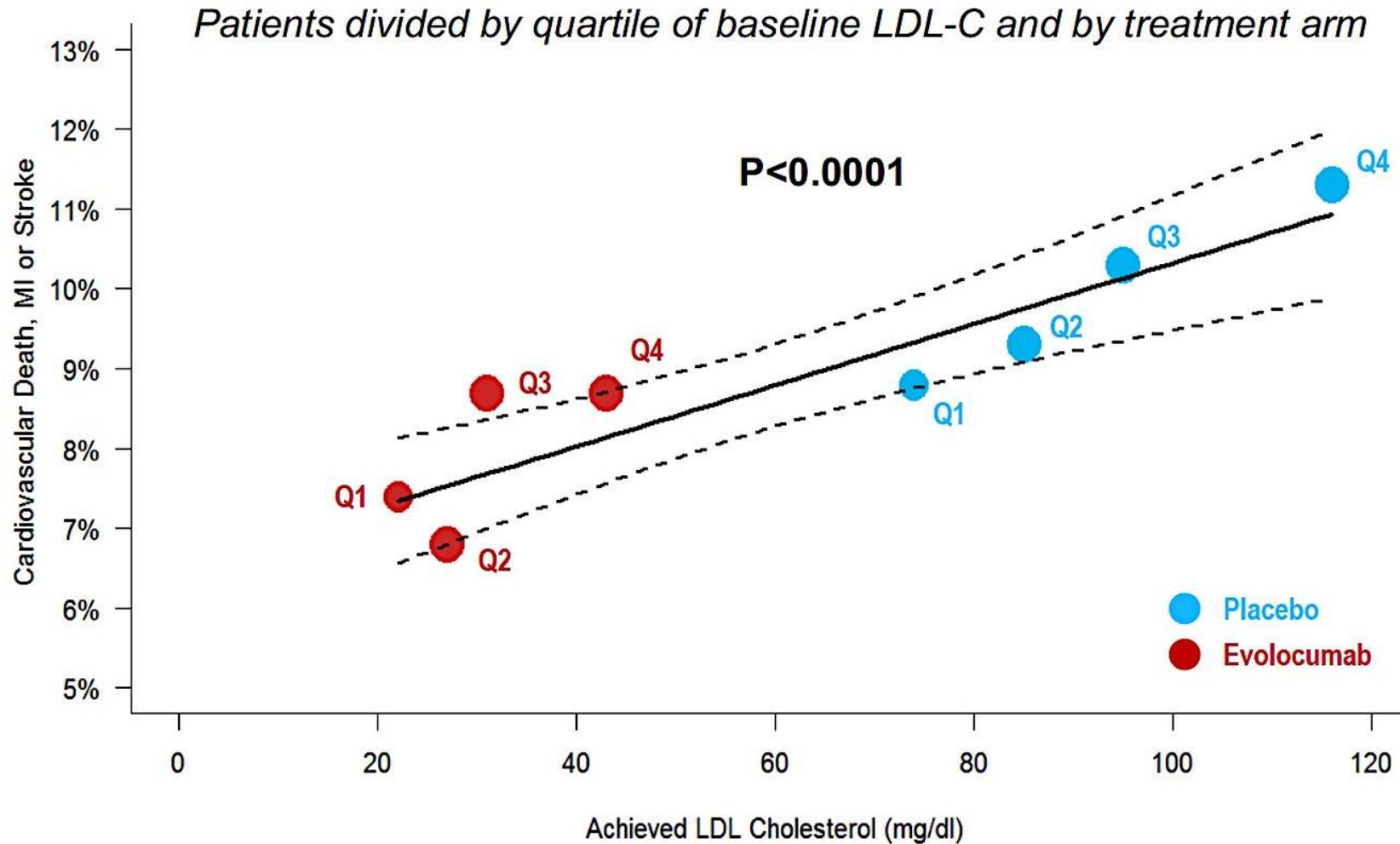
## Risk for Major Cardiovascular Events by Achieved LDL-C Concentration

Achieved On-Trial LDL-C Concentration, mg/dl (mmol/l)

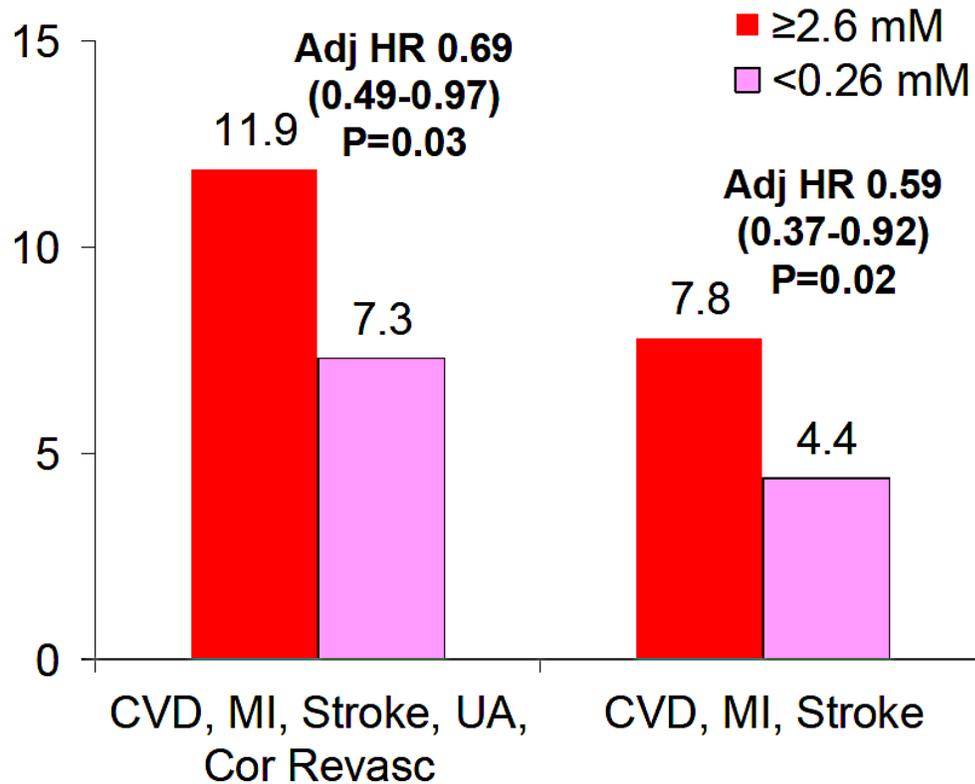
	<b>&lt;50 (&lt;1.29) (n = 4,375)</b>	<b>50-&lt;75 (1.29-&lt;1.94) (n = 10,395)</b>	<b>75-&lt;100 (1.94-&lt;2.58) (n = 10,091)</b>	<b>100-&lt;125 (2.58-&lt;3.23) (n = 8,953)</b>	<b>125-&lt;150 (3.23-&lt;3.88) (n = 3,128)</b>	<b>150-&lt;175 (3.88-&lt;4.52) (n = 836)</b>	<b>≥175 (≥4.52) (n = 375)</b>
Major 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)



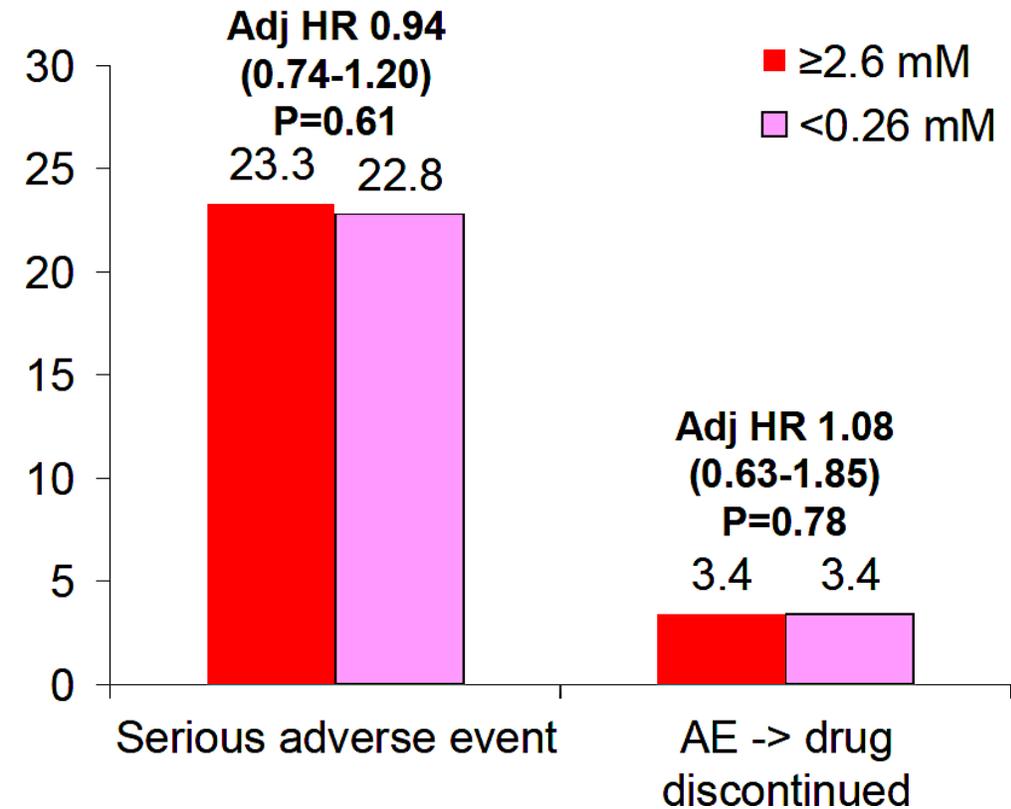




## Cardiovascular efficacy



## Safety



---

# 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



## Pharmacological treatment of hypercholesterolemia

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

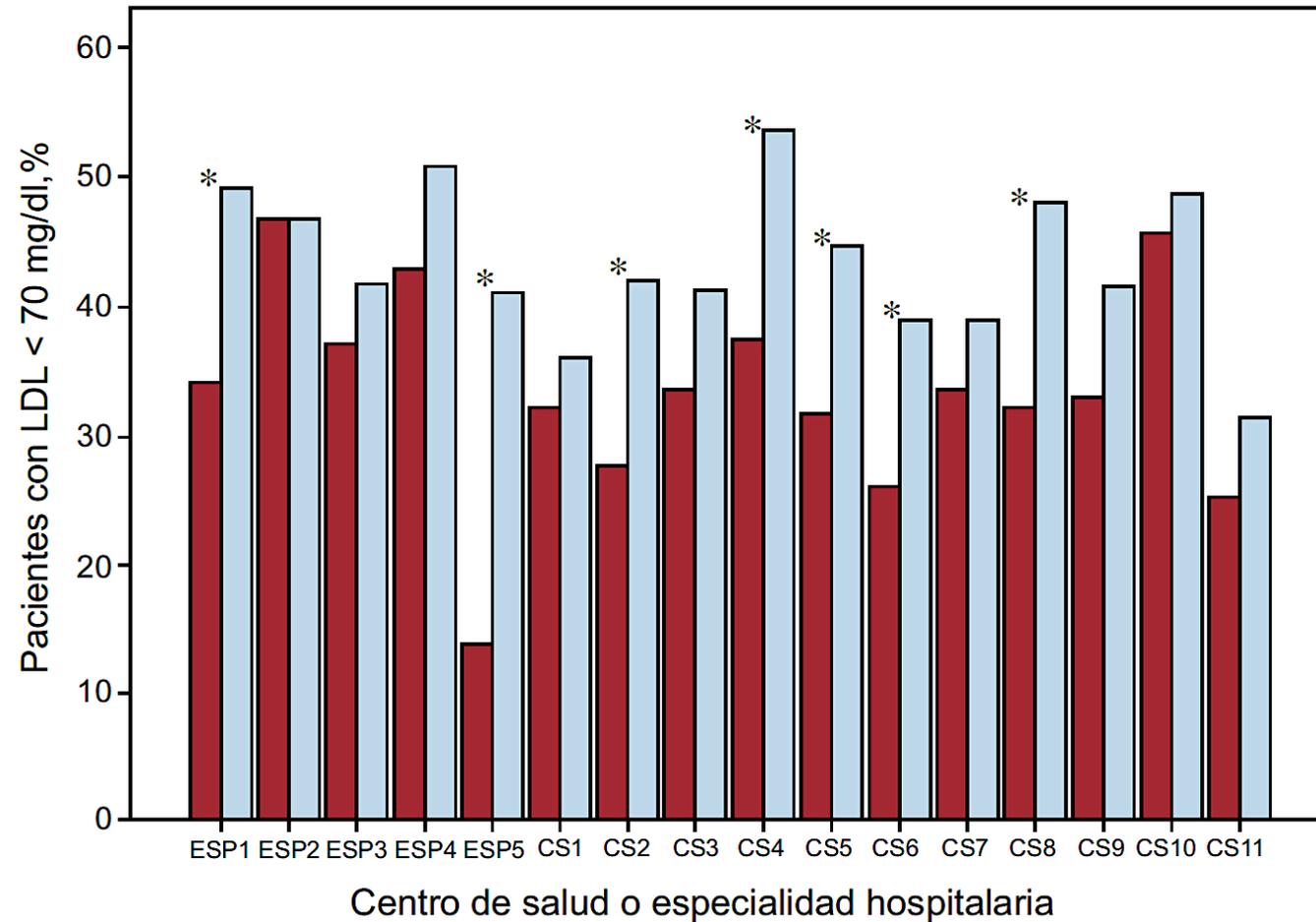
**Ila**

**C**



# COLIPAR project

■ Pre-COLIPAR  
■ Post-COLIPAR



# 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

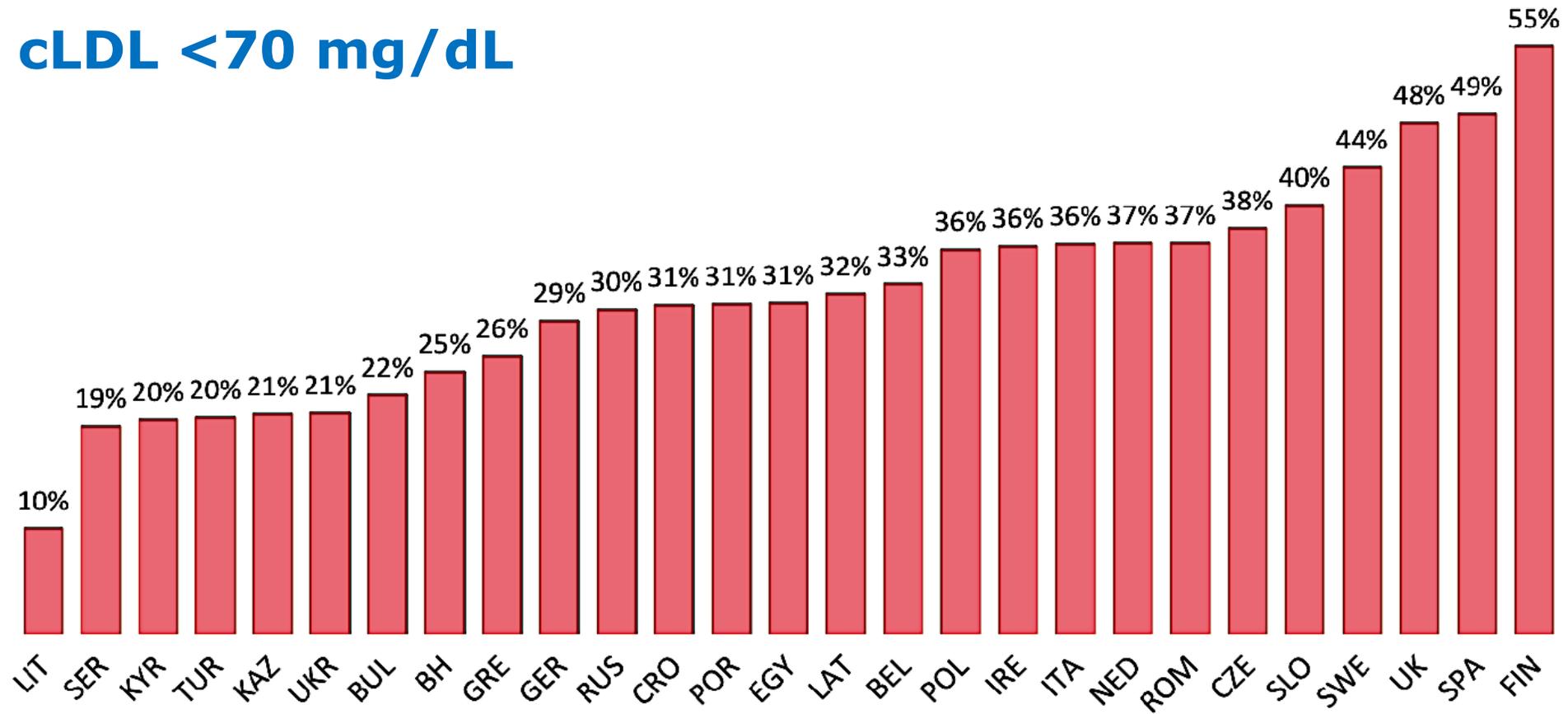
## Grado de cumplimiento de objetivos lipídicos

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

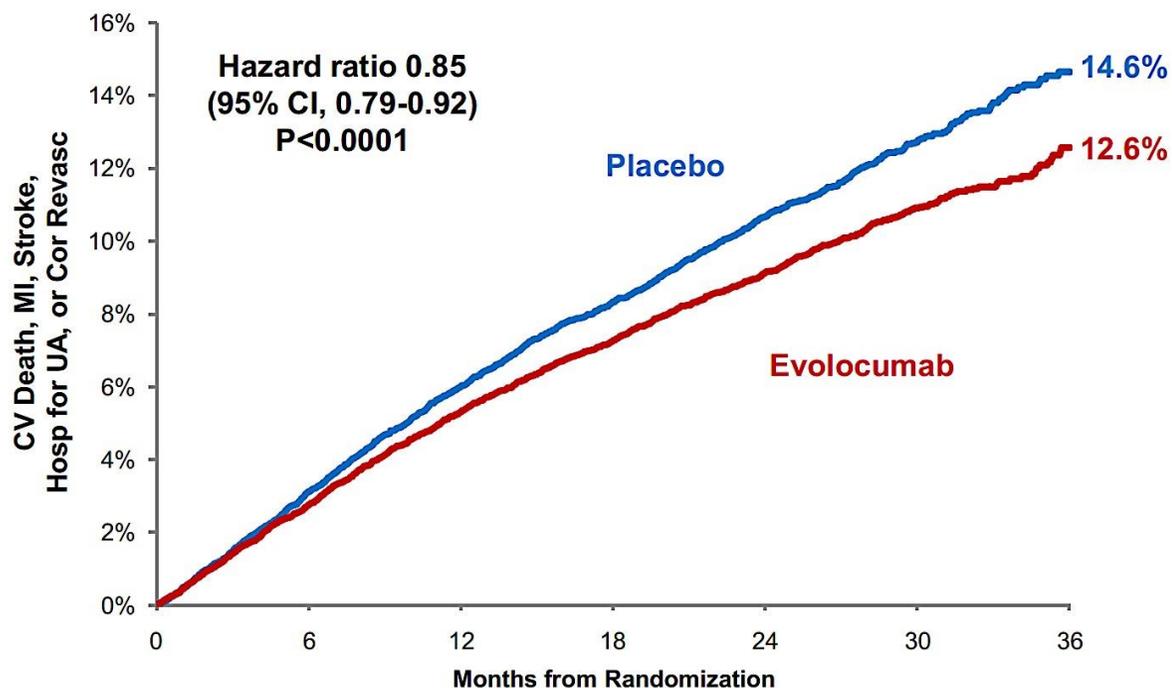




## cLDL <70 mg/dL



## Primary endpoint

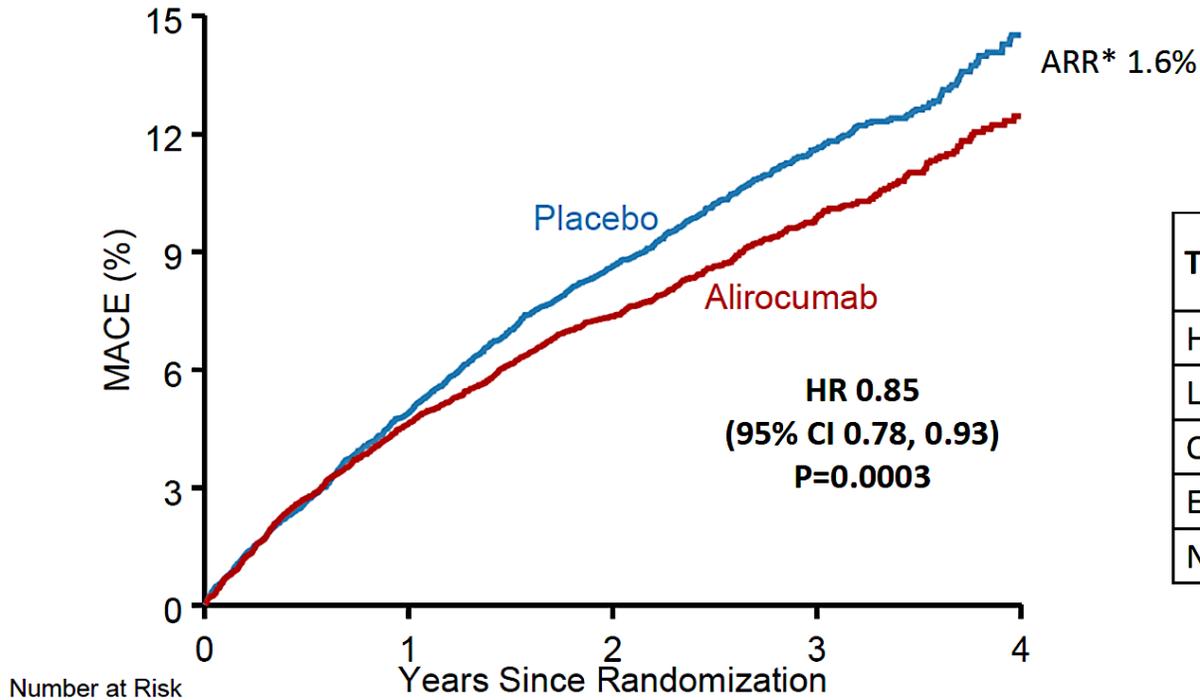


Characteristic	Value
<b>Statin use (%)*</b>	
High-intensity	<b>69</b>
Moderate-intensity	<b>30</b>
<b>Ezetimibe use (%)</b>	<b>5</b>
<b>Median lipid measures (IQR) – mg/dL</b>	
LDL-C	<b>92 (80-109)</b>
Total cholesterol	<b>168 (151-189)</b>
HDL-C	<b>44 (37-53)</b>
Triglycerides	<b>133 (100-182)</b>



# ODYSSEY OUTCOMES

## Primary Efficacy Endpoint



## Baseline characteristics

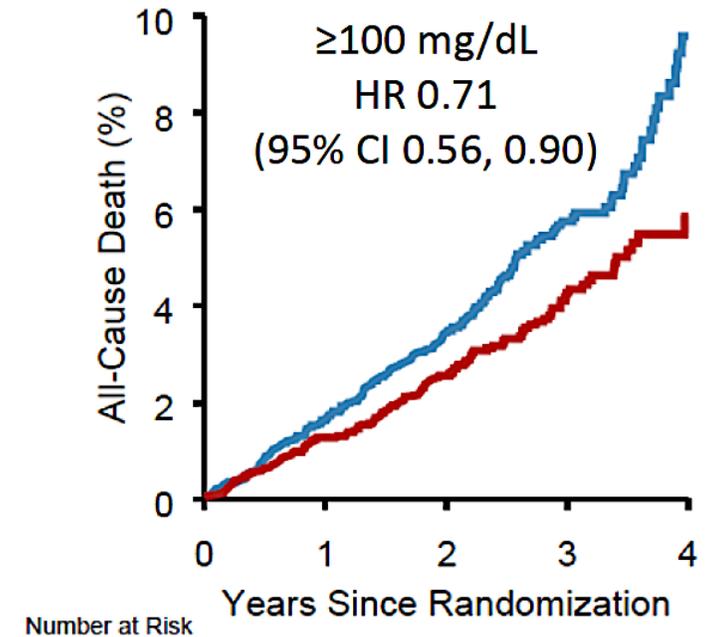
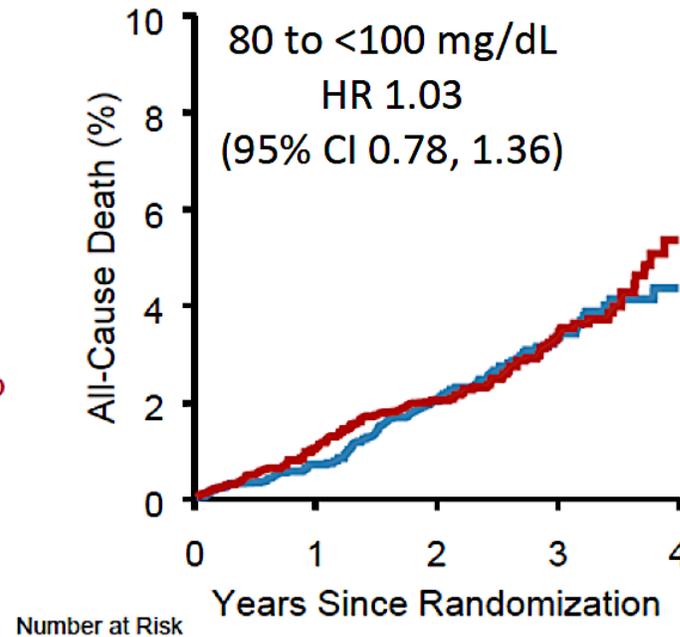
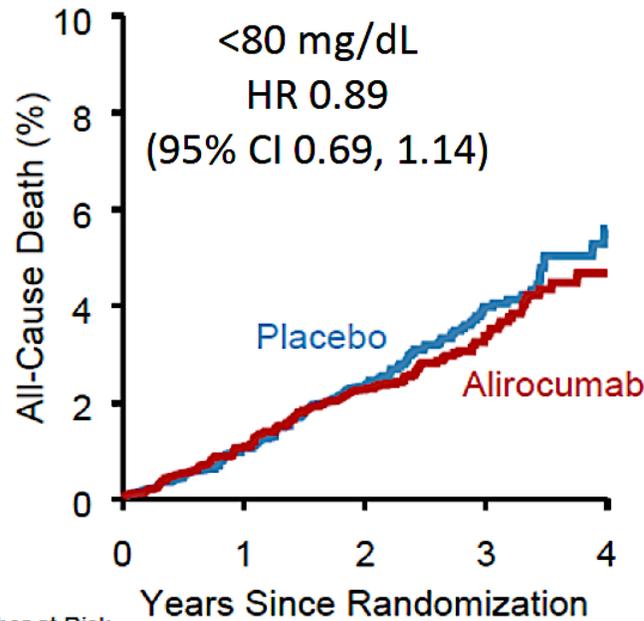
Therapy, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
High-dose atorvastatin/rosuvastatin	8380 (88.6)	8431 (89.1)
Low-/moderate-dose atorvastatin/rosuvastatin	830 (8.8)	777 (8.2)
Other statin	19 (0.2)	27 (0.3)
Ezetimibe, with or without statin	269 (2.8)	285 (3.0)
No lipid-lowering therapy*	87 (0.9)	91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

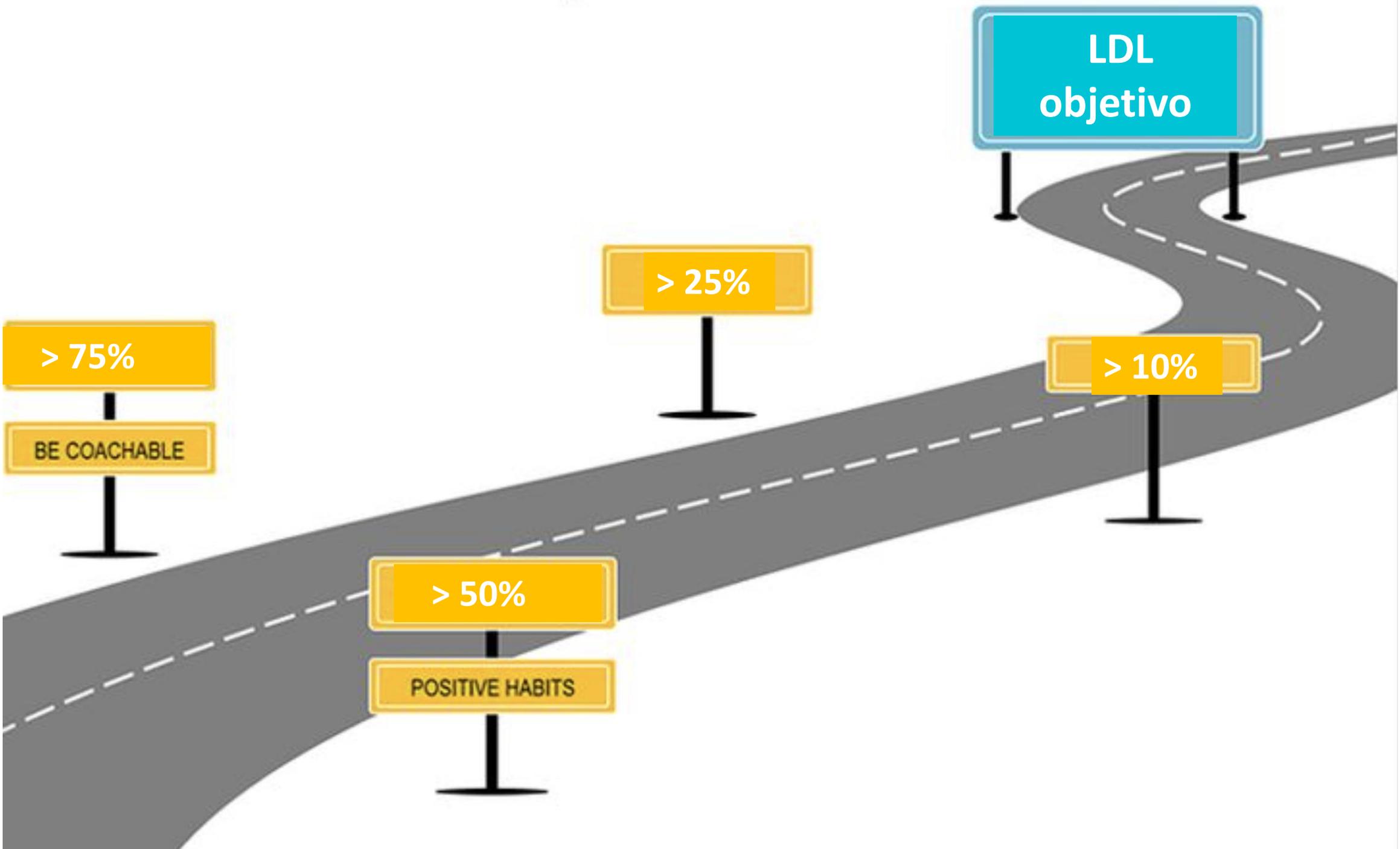


# ODYSSEY OUTCOMES

## Post hoc analysis all-cause death

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





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

$$%A + \%B (1 - \%A) + \%C \{1 - [\%A + \%B (1 - \%A)]\} \dots$$

%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

[http://tools.acc.org/ldl/ldlc\\_lowering\\_therapy/index.html#!/content/calculator/](http://tools.acc.org/ldl/ldlc_lowering_therapy/index.html#!/content/calculator/)



**#CardioFighters**





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  $\leq$  437 mg/dl podrían alcanzar los objetivos de LDL recomendados para la prevención secundaria.

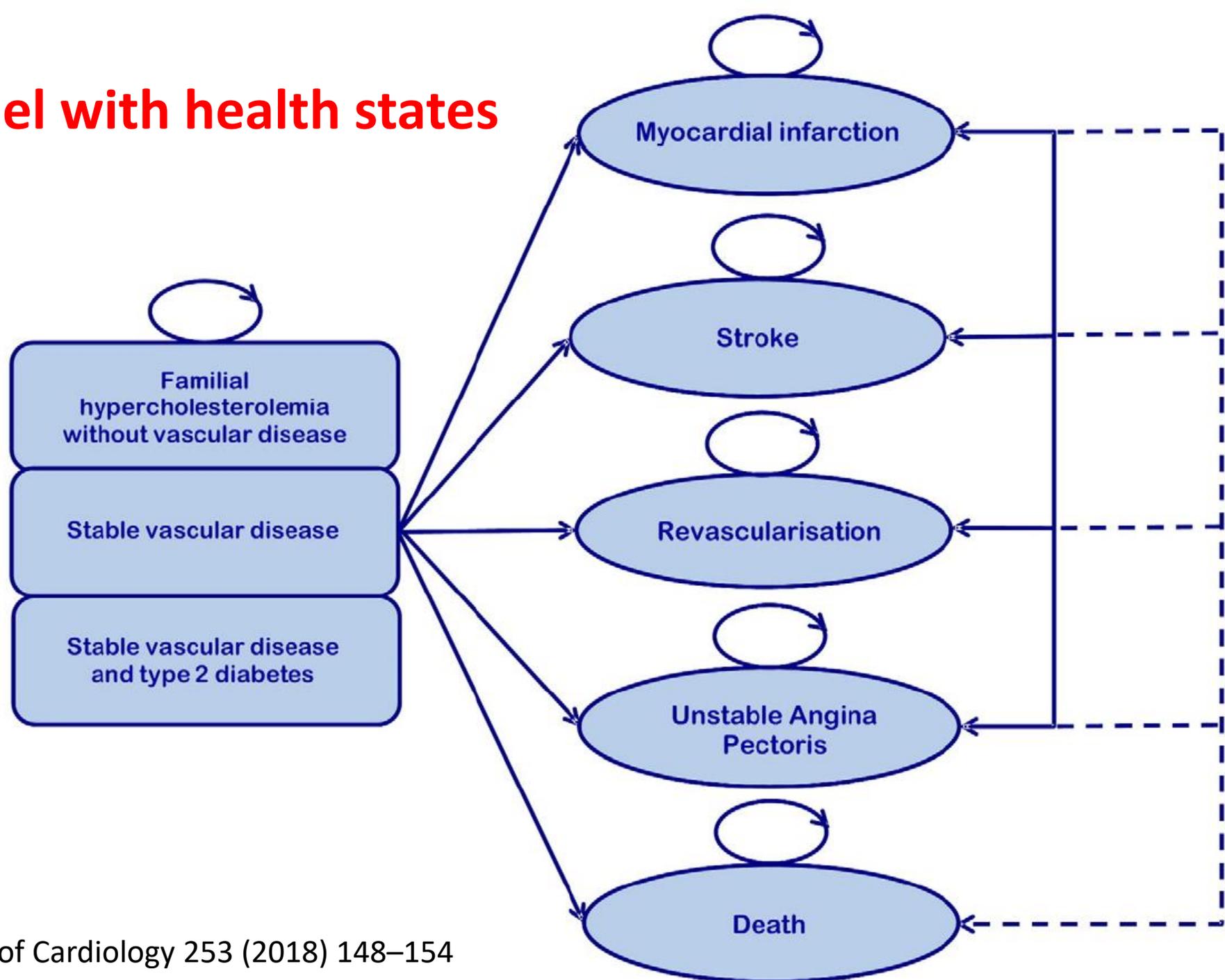
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# ROUND #3

## ¿Son coste-efectivos los iPCSK9?



# Markov model with health states

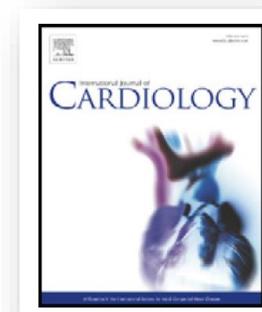


# Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease

	Familial hypercholesterolemia		Vascular disease and 10-year MACE risk $\geq 20\%$		Vascular disease and 10-year MACE risk $\geq 30\%$		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

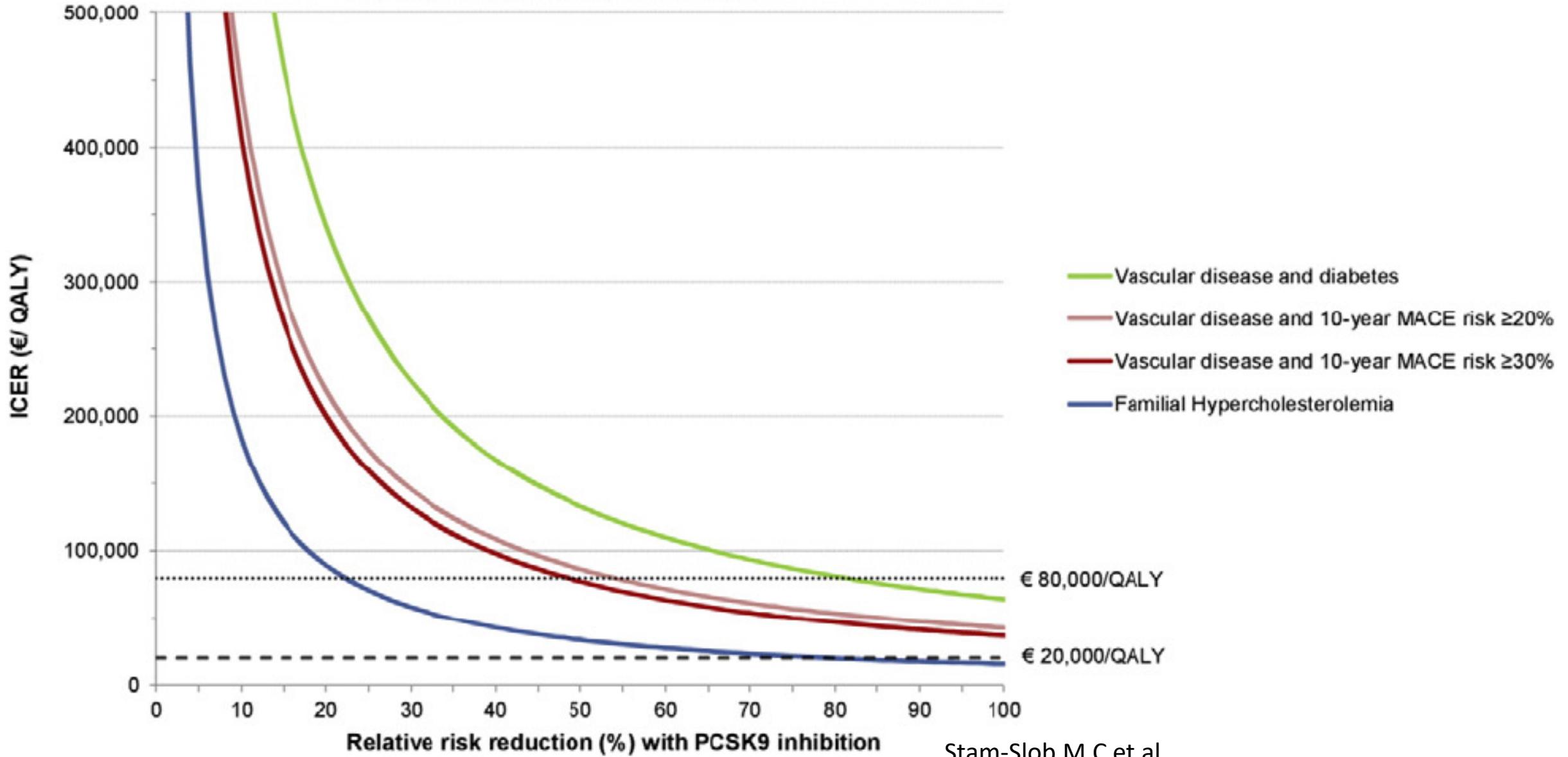
Stam-Slob M.C et al.

International Journal of Cardiology 253 (2018) 148–154



Parámetros del modelo	
Concepto	Valor medio
<b>Coste fármacos anual (euros)</b>	
<i>Evolocumab (PVL con descuento aplicable)</i>	4.969,74
<i>Ezetimiba</i>	668,33 <sup>B</sup>
<i>Estatinas</i>	104,87 <sup>9</sup> Atorvastatina 80 mg: 441,6 euros/año
<b>Coste eventos cardiovasculares (euros)</b>	
<i>Muerte cardiovascular</i>	5.014,27
<i>Muerte por infarto de miocardio</i>	3.912,66
<i>Muerte por accidente cerebrovascular</i>	4.994,57
<i>Muerte por cualquier causa</i>	0
<i>Infarto de miocardio</i>	3.912,66
<i>Hospitalización por angina inestable</i>	2.765,74
<i>Accidente cerebrovascular</i>	4.994,57      Ictus fase aguda 9.000 euro/años
<i>Isquémico</i>	4.994,57
<i>Hemorrágico</i>	5.545,22
<i>Revascularización coronaria</i>	5.924,87
<b>Riesgo relativo<sup>a</sup></b>	
<i>Todo el seguimiento</i>	
<i>Medida primaria<sup>b</sup></i>	0,85 (IC95%, 0,79-0,92)
<i>Medida secundaria<sup>c</sup></i>	0,80 (IC95%, 0,73-0,88)
<i>Año seguimiento</i>	
<i>Medida primaria<sup>b</sup></i>	0,88 (IC95%, 0,80-0,97)
<i>Medida secundaria<sup>c</sup></i>	0,84 (IC95%, 0,74-0,96)

**B. ICERs for PCSK9i versus standard lipid-lowering therapy  
for annual PCSKi drug costs of €4,500**



# Cost-Effectiveness PCSK9 inhibitors ...

## Artículo original

### Coste-efectividad e impacto presupuestario del tratamiento con evolucumab frente a estatinas y ezetimípara para la hipercolesterolemia en España

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Palabras clave:  
Efectividad cardiovascular  
Prevención secundaria  
Análisis de costes y costes  
Anticuerpos monoclonales PCSK9

## RESUMEN

**Introducción y objetivos:** Analizar la razón de coste-efectividad y el tratamiento con evolucumab (inhibidor de la PCSK9) para pacientes en Sistema Nacional de Salud español.  
**Método:** Se realizaron, desde la perspectiva del sistema sanitario y presupuestario, modelos de árbol de decisión y Markov, basándose en el 6 de mortalidad (FOURIER). Las alternativas comparadas fueron evolucumab 55 mg cada 4 semanas o estatinas más ezetimípara conjuntamente. La medida de efectividad utilizada fue el número de eventos cardiovasculares evitados por paciente tratado durante 5 años. El coste sanitario promedio de los pacientes tratados a 20 € de 11.134,78 euros y de 393.83 euros con el estándar (estatinas + ezetimípara) incrementó los 600.000 euros por evento cardiovascular evitado (morte cardiovascular, infarto de miocardio, accidente cerebrovascular isémico o revascularización coronaria); segunda: incluye los 3 primeros de Markov mostró un coste promedio de 471.417,37 frente a 13.948,49 € respectivamente. El tratamiento con evolucumab en hipercolesterolemia (entre 3 y 6,1 millones de euros, lo que supone una diferencia de 2,5-€ de tratamiento estándar (2017). Para el año 2021, en hipercolesterolemia secundaria), la diferencia osciló entre 204,3 y 1.364,7 millones de euros. **Conclusiones:** El evolucumab se asocia con menor frecuencia de eventos (ineficiente para los pacientes susceptibles de recibirlo en el Sistema Nacional de Salud Española de Cardiología. Publicado por Elsevier España, S.L.U.).

### Cost-effectiveness and budget impact of Treatment With Statins and Ezetimibe for Hypercholesterolemia in Spain

## ABSTRACT

**Introduction and objectives:** To analyze the cost-effectiveness ratio and budget impact (PCSK9 inhibitor) for patients in secondary prevention in Spain.  
**Method:** A budget impact analysis, decision tree and Markov models, we health systems perspective, based on the only study with mortality and is alternatives compared were evolucumab vs statins, and dual therapy (population). The measure of effectiveness used was the number of cardiovascular events avoided. The cost of treatment was based on the number of cardiovascular events avoided. The incremental cost-effectiveness ratio (ICER) was calculated. The incremental cost-effectiveness ratio (ICER) was calculated. The incremental cost-effectiveness ratio (ICER) was calculated.

\* Autor para correspondencia: Escuela Analítica de Salud Pública, Campus Universitario de Cartuja, Apartado de Correos 2070, 18080 Correo electrónico: antonioolryde@campusjuntadeandalucia.es (A. Olry de Labry Lima).

## ARTICLE IN PRESS

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

Radya Kumar<sup>1</sup>, Andrew Tonkin<sup>1</sup>, Danny Liew<sup>1</sup>, Ella Zomer<sup>2,3</sup>

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**Keywords:**  
Cost-effectiveness  
PCSK9 inhibitors  
Lipids  
Cardiovascular disease  
Prevention

**Abstract**  
Background: For patients in whom statins are not tolerated or effective as their additional treatment, PCSK9 inhibitors (PCSK9i) represent a new class of lipids-lowering drugs that can reduce low-density lipoprotein cholesterol (LDL-C) levels by up to 50% and lower cardiovascular risk. We evaluated the cost-effectiveness of PCSK9i in Australia to estimate a realistic cost-effectiveness ratio (ICER) compared to placebo in the prevention of CVD.  
Methods and results: A Markov cohort state-transition model was developed in a sample of 1000 individuals based on data from the Further Cardiovascular Outcomes in Subjects with Elevated Risk (FOURIER) trial population. The model, which compared PCSK9i (evolucumab) to statins plus ezetimibe, was run for 5 years. The model showed that PCSK9i was cost-effective compared to statins plus ezetimibe for the prevention of CVD. The ICER was \$48,358 per quality-adjusted life year (QALY) saved. The model showed that PCSK9i was cost-effective compared to statins plus ezetimibe for the prevention of CVD. The ICER was \$48,358 per quality-adjusted life year (QALY) saved. The model showed that PCSK9i was cost-effective compared to statins plus ezetimibe for the prevention of CVD. The ICER was \$48,358 per quality-adjusted life year (QALY) saved.

### 1. Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are highly effective at reducing low-density lipoprotein cholesterol (LDL-C) levels and lowering CVD risk [1] and currently comprise first-line therapy in the treatment of hyperlipidaemia and prevention of CVD [2]. Previous research has demonstrated that a decrease of 1 mmol/L LDL-C results in an approximate 20% decrease in risk of CVD major vascular events [1,3].

However, statins are suitable for approximately 5 to 10% of individuals, predominantly due to intolerance or ineffectiveness as monotherapy [4]. For such people, the new class of lipid-lowering agents, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), represents an alternative treatment option. Randomized controlled trials of PCSK9i thus far have demonstrated reductions in LDL-C levels by

>50% compared to placebo [5]. More recent outcomes research with PCSK9i inhibitor (RUI) (FOURIER) trial reported that on top of the PCSK9i evolucumab reduced the risk of CVD events compared to statins plus ezetimibe, but it rarely outperforms [6].

This study sought to determine the cost-effectiveness of PCSK9i from the Australian perspective.

**2. Methods**  
**2.1. Model structure**

A Markov state-transition model was developed to estimate the cost-effectiveness of PCSK9i compared to statins plus ezetimibe in the prevention of CVD. The model was run for 5 years.

**2.2. Model inputs**  
The model inputs were based on data from the FOURIER trial population. The model was run for 5 years.

**2.3. Model outputs**  
The model outputs were the incremental cost-effectiveness ratio (ICER) and the number of quality-adjusted life years (QALYs) saved.

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Manuscript accepted 10 October 2017

LEADING ARTICLE

### Are PCSK9 Inhibitors Cost Effective?

Max J. Korman<sup>1</sup>, Neil Retherford<sup>2</sup>, Ina Sömbö Kristjánsson<sup>3</sup>, Turbjörn Wafar<sup>4</sup>

<sup>1</sup>Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Australia

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**Abstract**  
The objective of this study was to review available health economic evaluations of PCSK9i (proprotein convertase subtilisin/kexin type 9) inhibitors. These drugs reduce low-density lipoprotein cholesterol levels and cardiovascular risk, but their cost-effectiveness has been questioned. We searched Medline and Embase for economic evaluations in any language at any time. Studies were included if they analyzed any PCSK9i inhibitor compared with either statin alone or in combination with ezetimibe or any other therapy considered standard prior to the introduction of PCSK9i inhibitors. We found ten full health economic evaluations of PCSK9i inhibitors, two from Europe and eight from the United States (US). Six of the eight from the US were from two different countries that analyzed PCSK9i inhibitors at different stages through the development of evidence. All studies generally reported incremental cost-effectiveness ratios above suggested thresholds for cost-effectiveness, except one study from Spain. The results of this review indicate that PCSK9i

inhibitors in general are not cost effective at lower prices, but lower prices may change this.

**Keywords:**  
Health economic evaluations  
Health economics  
PCSK9 inhibitors  
Cost-effectiveness

### 1 Introduction

Since the introduction of statins in the lowering treatment of cardiovascular disease has become one of the most important treatments in the prevention of cardiovascular disease, it has played a crucial role in ending CVD. The United Kingdom and France [1]. ezetimibe, up to 60% reduction in low cholesterol can be achieved. This can do so in the range of 1.8–2.6 mmol patients cannot reach the desired reduction and need additional treatments. Other patients do not tolerate statins. Here, proprotein convertase subtilisin/kexin type 9 inhibitors represent a new class of PCSK9i inhibitors can reduce LDL cholesterol by an additional 60% on top of diet, statin and ezetimibe. This combination therapy makes it

Electronic supplementary material: The online version of this article (<https://doi.org/10.1007/s12012-018-0071-0>) contains supplementary material, which is available to authorized users.

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Current Cardiology Reports (2018) 20:51  
<https://doi.org/10.1007/s12012-018-0098-8>

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

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

Parth Shah<sup>1</sup>

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**Abstract**  
Purpose of Review This review aims to explore and summarize the current literature on the cardiovascular health care burden and the cost-effectiveness of the PCSK9 inhibitors. Recent findings The CVD remains the largest cause of mortality in the USA, presenting substantial costs reaching \$55.5 billion in 2014 and projected to rise to \$1.1 trillion by 2035. The PCSK9 inhibitors have a net LDL lowering, but in price of ~14,000–14,600 per patient per year coupled with ~2.2–2.8 years of cost data has created many controversies surrounding its cost-effectiveness. To determine the cost-effective inhibition, various simulation models and risk-based stratification and case-by-case patient approaches have which need to be assessed as per the ODYSSEY and long-term CVD outcomes. Summary Further studies are warranted to evaluate the long-term CVD event rates of patients on the statins in true cost-effectiveness.

**Keywords:**  
Allopathy  
Evolucumab  
PCSK9  
Cardiovascular  
Cholesterol  
Lipoprotein (a)

### Introduction

The cardiovascular diseases (CVD) remain the leading cause of death globally with the mortality rates between 481 and 680 deaths per 100,000 people in western Europe, northern Asia, Middle East, and some parts of Africa [1]. There were 42.7 million cases of CVD worldwide with 17.92 million deaths as per the 2015 estimate [1]. The CVD remains the number one cause of mortality in the USA, accounting for about one in three deaths [2]. The striking CVD statistics from 2013 show that ~2200 Americans die due to the CVD every day, one death every 40 s [3–5]. The stroke caused 1 in 20 deaths while the coronary heart disease (CHD) caused 1 in 7 deaths in 2013 [1, 3–5]. Each year, approximately 795,000 Americans continue to experience a new recurrent stroke and ~

965,000 Americans have a new or recurrent stroke [3–5]. In addition, there are also ~160 in strokes each year [2].

However, as per the American Heart Association's actions on prevalence of CVD in 2015, (102.7 million Americans had at least one disease: hypertension, coronary heart disease, heart failure, or atrial fibrillation) in 2035, the CVD burden is expected to increase [6–8].

The estimation of the cardiovascular imperfect science with the ACC/AHA guideline having its limitations such as its narrow CVD events, and limiting the tips and systemic blood pressure [9, 10]. For a risk of the atherosclerotic cardiovascular as opposed to the short-term 10-year risk general incorporation of soft ASCVD outcomes based factors, transient ischemic attack intermittent classification, since a large younger individuals suffer from soft A Leung et al. concluded that two in

Published online: 19 May 2018

Research

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

Alfredo Armata, PhD, Jonathan C. Hong, MD, MPH, Rohan Khora, MD, Sahar S. Vrank, MD, PhD, Harish M. Natarajan, MD, Siba Khuram Nasir, MD, MPH

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**Abstract**  
Purpose of Review This review aims to explore and summarize the current literature on the cardiovascular health care burden and the cost-effectiveness of the PCSK9 inhibitors. Recent findings The CVD remains the largest cause of mortality in the USA, presenting substantial costs reaching \$55.5 billion in 2014 and projected to rise to \$1.1 trillion by 2035. The PCSK9 inhibitors have a net LDL lowering, but in price of ~14,000–14,600 per patient per year coupled with ~2.2–2.8 years of cost data has created many controversies surrounding its cost-effectiveness. To determine the cost-effective inhibition, various simulation models and risk-based stratification and case-by-case patient approaches have which need to be assessed as per the ODYSSEY and long-term CVD outcomes. Summary Further studies are warranted to evaluate the long-term CVD event rates of patients on the statins in true cost-effectiveness.

**Keywords:**  
Allopathy  
Evolucumab  
PCSK9  
Cardiovascular  
Cholesterol  
Lipoprotein (a)

**Introduction**  
The cardiovascular diseases (CVD) remain the leading cause of death globally with the mortality rates between 481 and 680 deaths per 100,000 people in western Europe, northern Asia, Middle East, and some parts of Africa [1]. There were 42.7 million cases of CVD worldwide with 17.92 million deaths as per the 2015 estimate [1]. The CVD remains the number one cause of mortality in the USA, accounting for about one in three deaths [2]. The striking CVD statistics from 2013 show that ~2200 Americans die due to the CVD every day, one death every 40 s [3–5]. The stroke caused 1 in 20 deaths while the coronary heart disease (CHD) caused 1 in 7 deaths in 2013 [1, 3–5]. Each year, approximately 795,000 Americans continue to experience a new recurrent stroke and ~

965,000 Americans have a new or recurrent stroke [3–5]. In addition, there are also ~160 in strokes each year [2].

However, as per the American Heart Association's actions on prevalence of CVD in 2015, (102.7 million Americans had at least one disease: hypertension, coronary heart disease, heart failure, or atrial fibrillation) in 2035, the CVD burden is expected to increase [6–8].

The estimation of the cardiovascular imperfect science with the ACC/AHA guideline having its limitations such as its narrow CVD events, and limiting the tips and systemic blood pressure [9, 10]. For a risk of the atherosclerotic cardiovascular as opposed to the short-term 10-year risk general incorporation of soft ASCVD outcomes based factors, transient ischemic attack intermittent classification, since a large younger individuals suffer from soft A Leung et al. concluded that two in

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#CardioFighters



# 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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## 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.<sup>1</sup> 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.<sup>2</sup> These costs are projected to nearly double by 2030.<sup>3</sup> 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 26% (more vs less statins) reduction in rates of any major CVD event across 26 randomized trials.<sup>3</sup> Results from the Improved Reduction of

## 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.

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Clin. Cardiol. (in press)  
DOI: 10.1002/clc.22535



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



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# ROUND #4

## ¿Hay perfiles para iPCSK9?

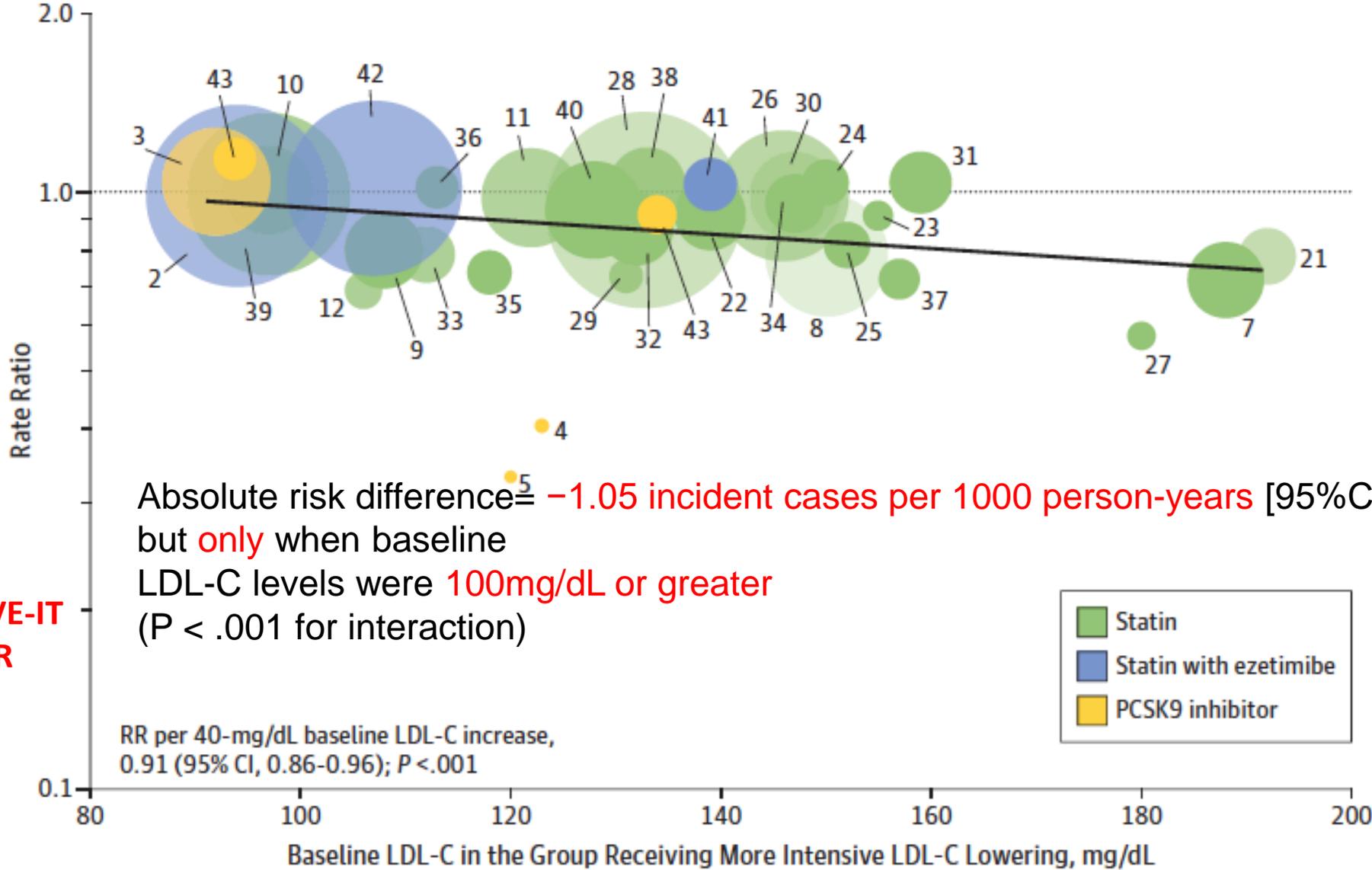
Paciente 68 años con IAM previo, c-LDL 89, enfermedad de 2 vasos y DM2

VS

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



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

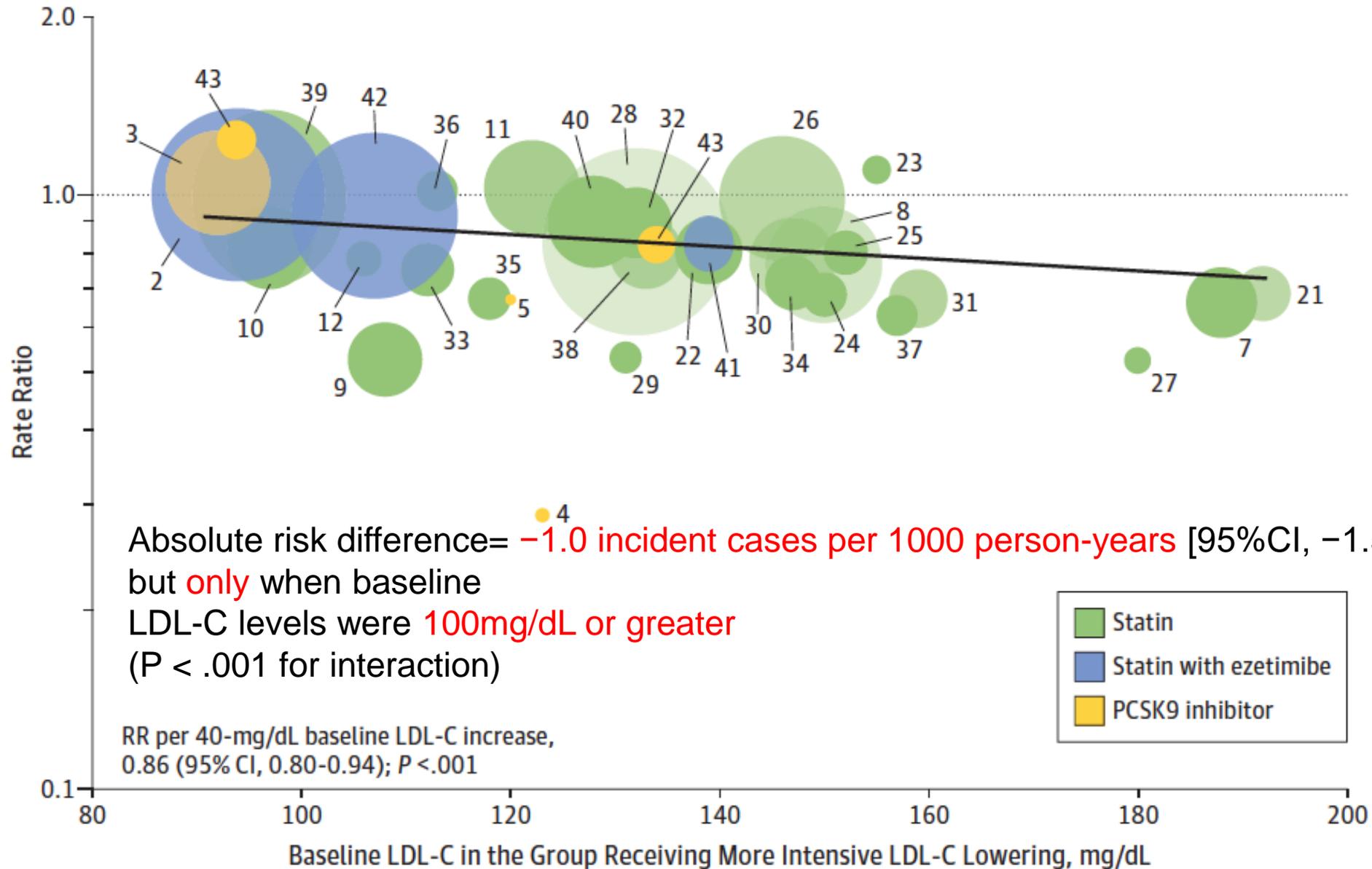


**7: IMPROVE-IT**  
**21: FOURIER**  
**27: SPIRE**

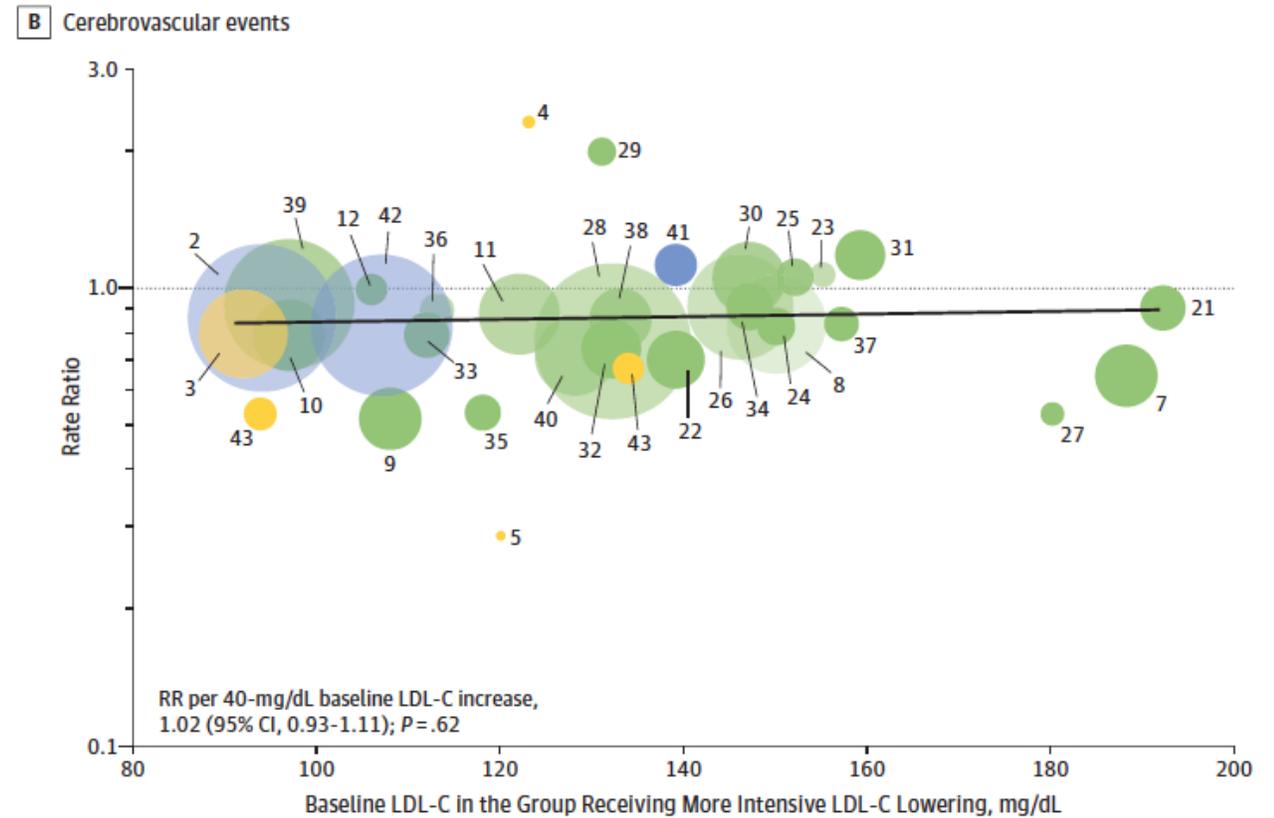
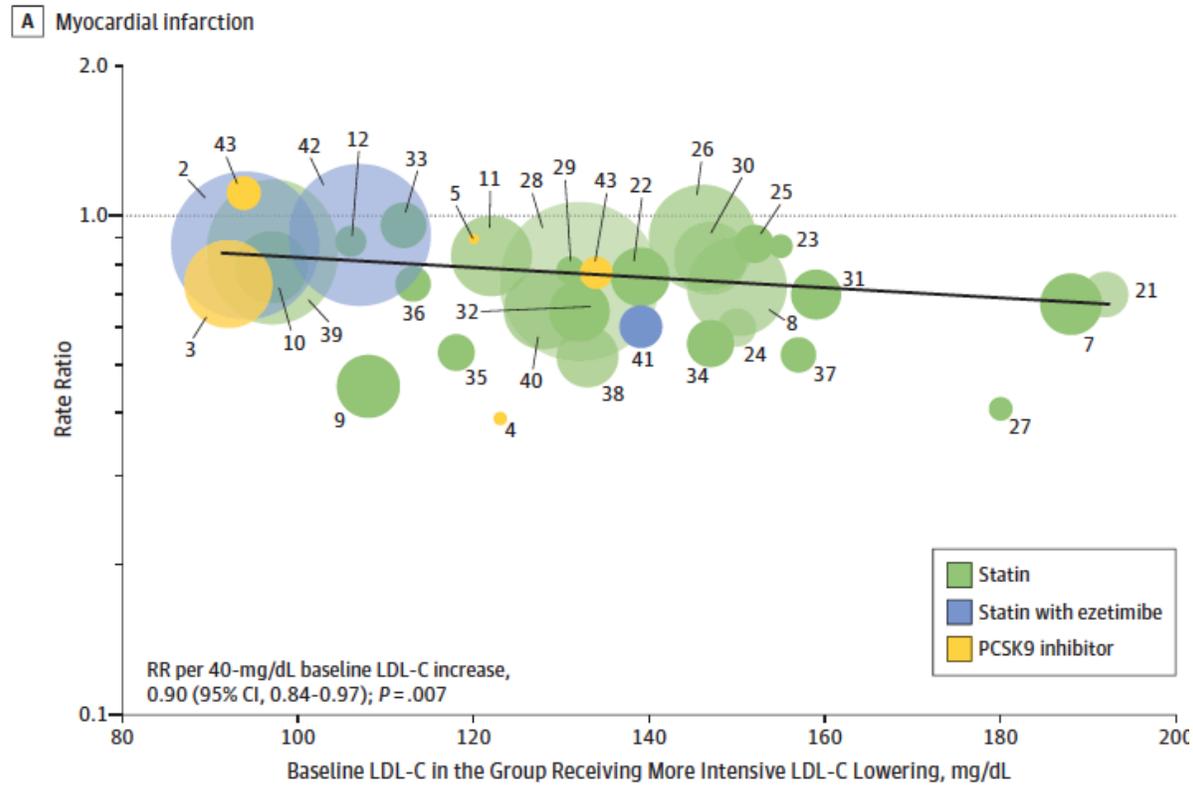
**2: IMPROVE-IT**  
**3: FOURIER**  
**43: SPIRE**



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



# Meta-regression Analysis of **MACES** by Baseline LDL-C Level



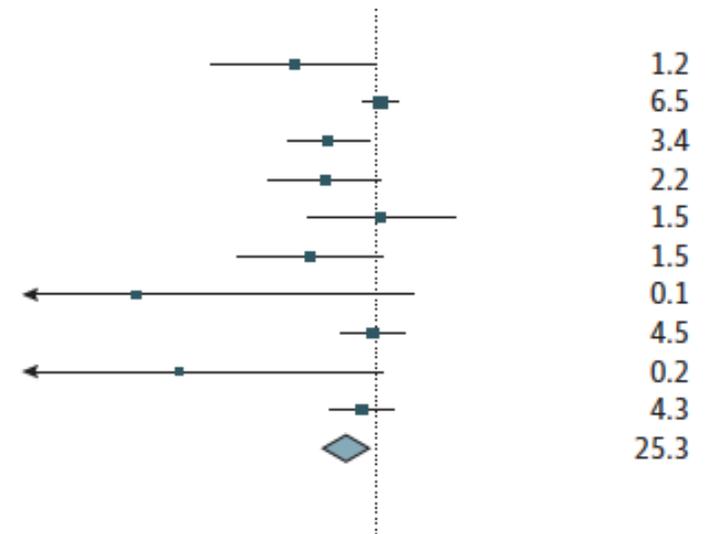
# Meta-analysis of **All-cause Mortality** Stratified by Baseline LDL-C Level

Baseline LDL-C 100-129 mg/dL

PROVE IT-TIMI 22, <sup>12</sup> 2004	46/2099 (2.19)	66/2063 (3.20)	0.69 (0.47-1.00)
SHARP, <sup>42</sup> 2011	1142/4650 (24.56)	1115/4620 (24.13)	1.02 (0.94-1.11)
JUPITER, <sup>9</sup> 2008	198/8901 (2.22)	247/8901 (2.77)	0.80 (0.66-0.97)
A to Z, <sup>33</sup> 2004	104/2265 (4.59)	130/2232 (5.82)	0.79 (0.61-1.02)
ASPEN, <sup>36</sup> 2006	70/1211 (5.78)	68/1199 (5.67)	1.02 (0.73-1.42)
CARDS, <sup>35</sup> 2004	61/1429 (4.27)	82/1412 (5.81)	0.74 (0.53-1.02)
OSLER 1 & 2, <sup>5</sup> 2015	4/2976 (0.13)	6/1489 (0.40)	0.33 (0.09-1.18)
IDEAL, <sup>11</sup> 2005	366/4439 (8.25)	374/4449 (8.41)	0.98 (0.85-1.13)
ODYSSEY LONG TERM, <sup>4</sup> 2015	8/1553 (0.52)	10/788 (1.27)	0.41 (0.16-1.03)
HOPE-3, <sup>40</sup> 2016	334/6361 (5.25)	357/6344 (5.63)	0.93 (0.80-1.08)
Subtotal	2333/35884 (6.50)	2455/33497 (7.33)	0.88 (0.79-0.98)

Heterogeneity:  $\tau^2 = 0.01$ ;  $\chi^2 = 19.23$  ( $P = .02$ );  $I^2 = 53\%$

Overall effect:  $z = 2.35$  ( $P = .02$ )



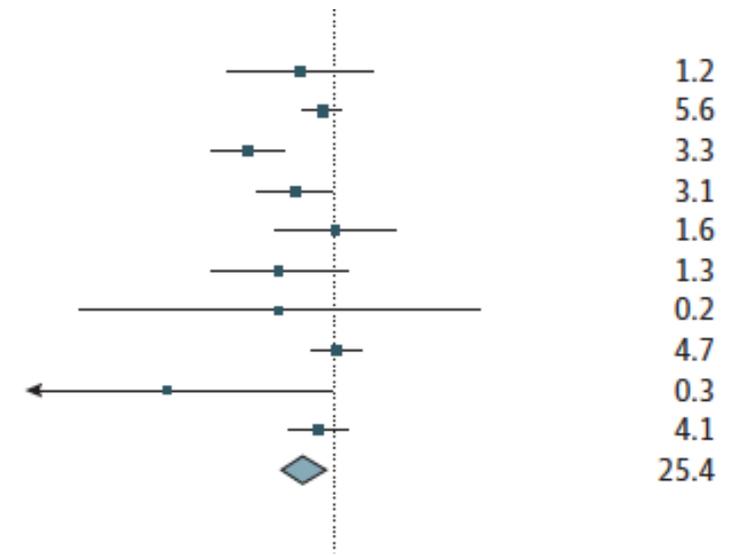
# Meta-analysis of **CV Mortality** Stratified by Baseline LDL-C level

Baseline LDL-C 100-129 mg/dL

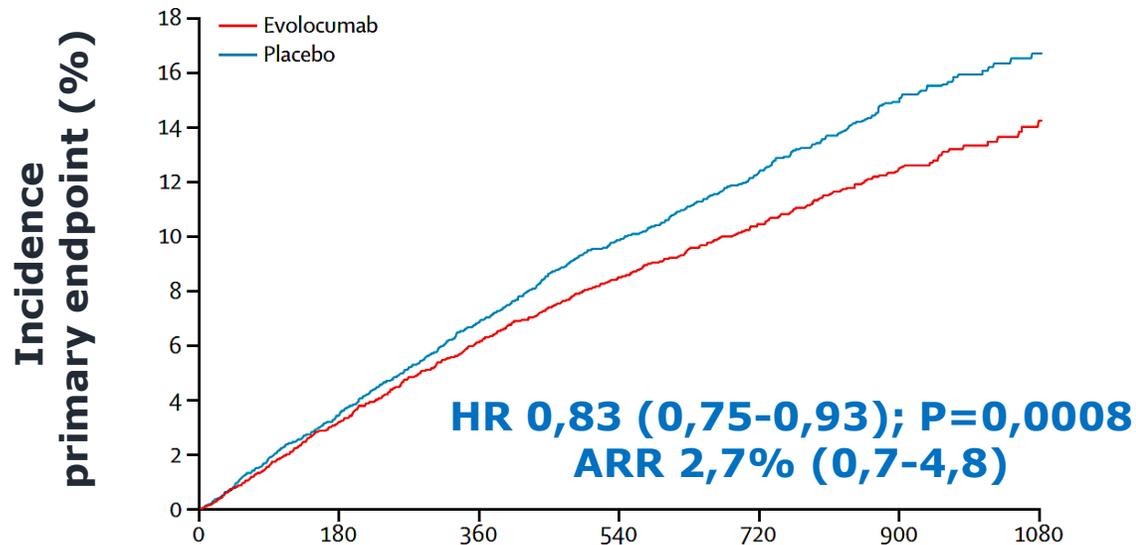
PROVE IT-TIMI 22, <sup>12</sup> 2004	23/2099 (1.10)	29/2063 (1.41)	0.78 (0.45-1.35)
SHARP, <sup>42</sup> 2011	361/4650 (7.76)	388/4620 (8.40)	0.92 (0.80-1.07)
JUPITER, <sup>9</sup> 2008	83/8901 (0.93)	157/8901 (1.76)	0.53 (0.41-0.69)
A to Z, <sup>33</sup> 2004	83/2265 (3.66)	109/2232 (4.88)	0.75 (0.56-1.00)
ASPEN, <sup>36</sup> 2006	38/1211 (3.14)	37/1199 (3.09)	1.02 (0.65-1.60)
CARDS, <sup>35</sup> 2004	25/1429 (1.75)	37/1412 (2.62)	0.67 (0.40-1.11)
OSLER 1 & 2, <sup>5</sup> 2015	4/2976 (0.13)	3/1489 (0.20)	0.67 (0.15-2.98)
IDEAL, <sup>11</sup> 2005	223/4439 (5.02)	218/4449 (4.90)	1.03 (0.85-1.24)
ODYSSEY LONG TERM, <sup>4</sup> 2015	4/1553 (0.26)	7/788 (0.89)	0.29 (0.08-0.99)
HOPE-3, <sup>40</sup> 2016	154/6361 (2.42)	171/6344 (2.70)	0.90 (0.72-1.12)
Subtotal	998/35884 (2.78)	1156/33497 (3.45)	0.81 (0.68-0.95)

Heterogeneity:  $\tau^2 = 0.03$ ;  $\chi^2 = 22.99$  ( $P = .02$ );  $I^2 = 61\%$

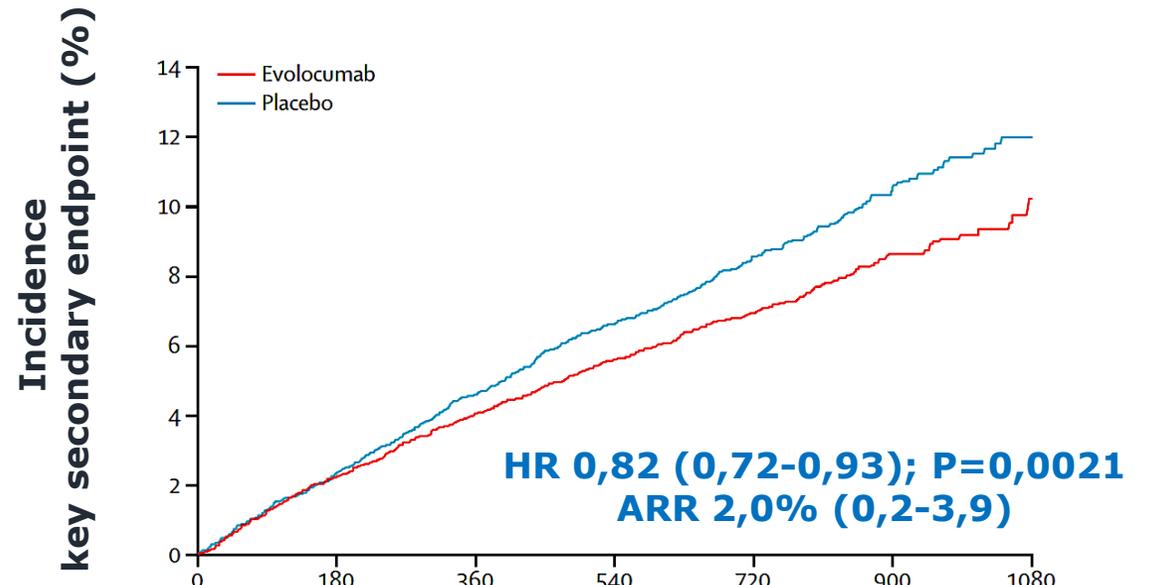
Overall effect:  $z = 2.59$  ( $P = .01$ )



## patients with diabetes



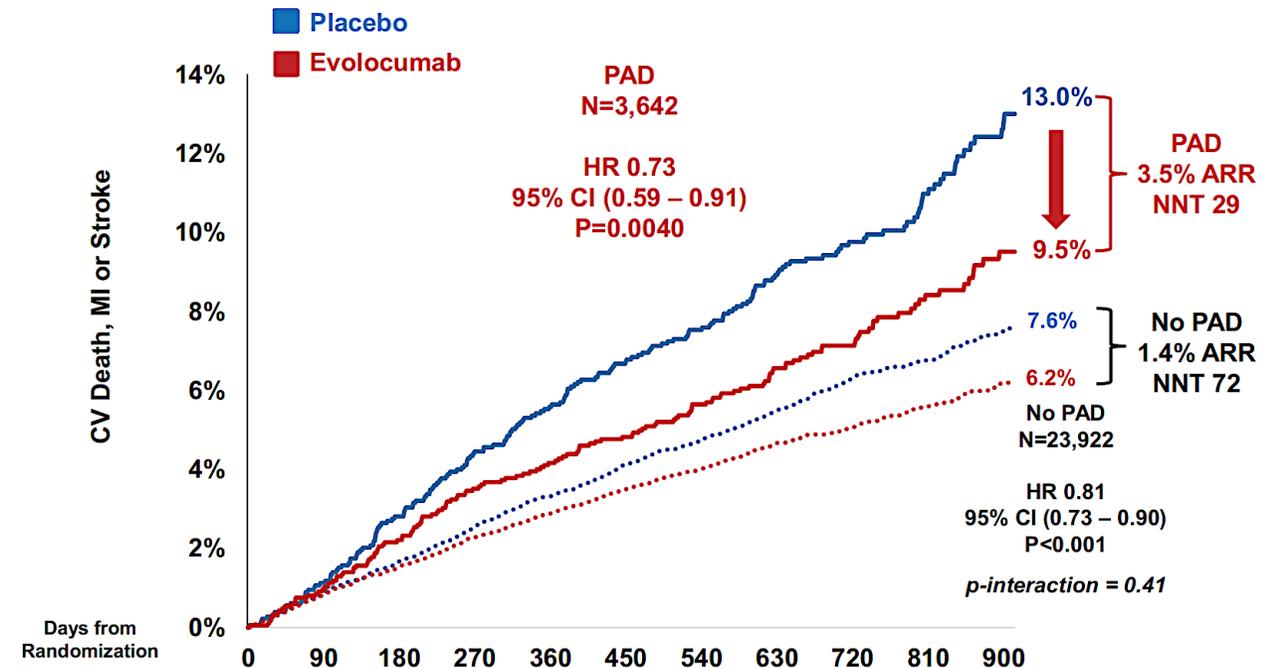
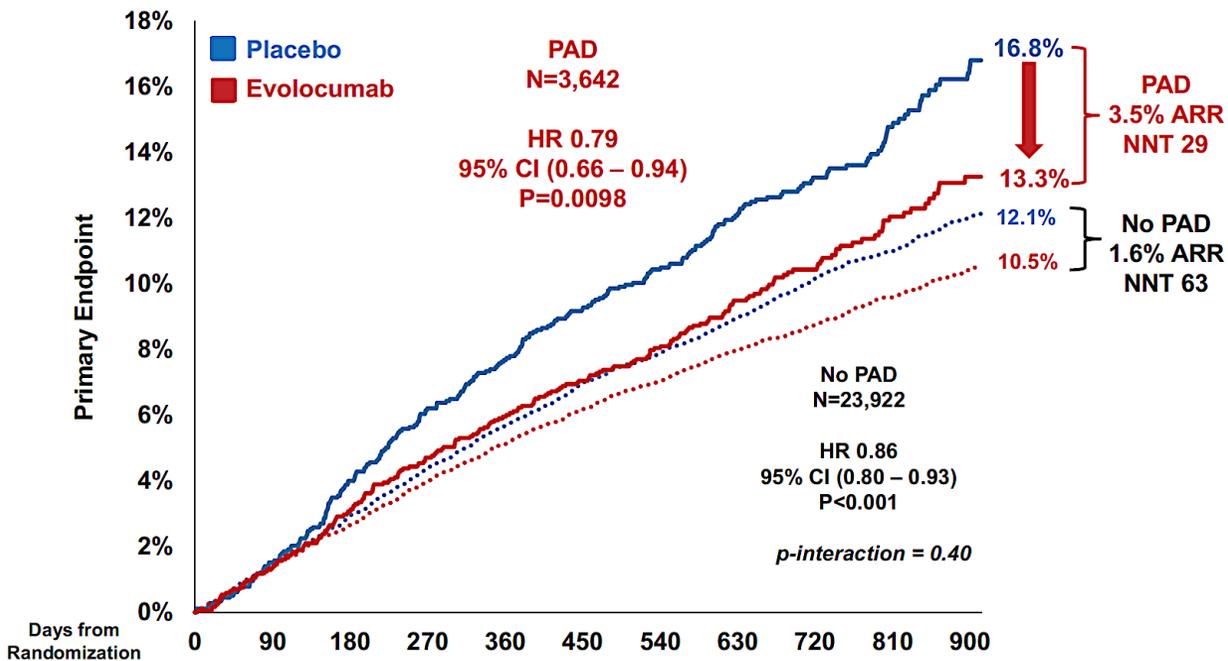
Number of patients	0	180	360	540	720	900	1080
Placebo	5516	5284	5071	4616	3020	1468	335
Evolocumab	5515	5309	5119	4727	3048	1457	340



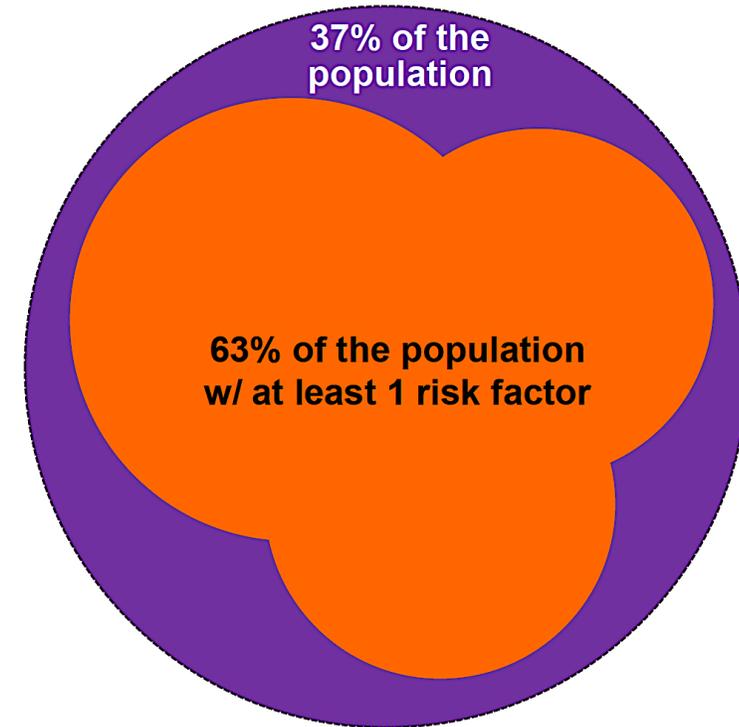
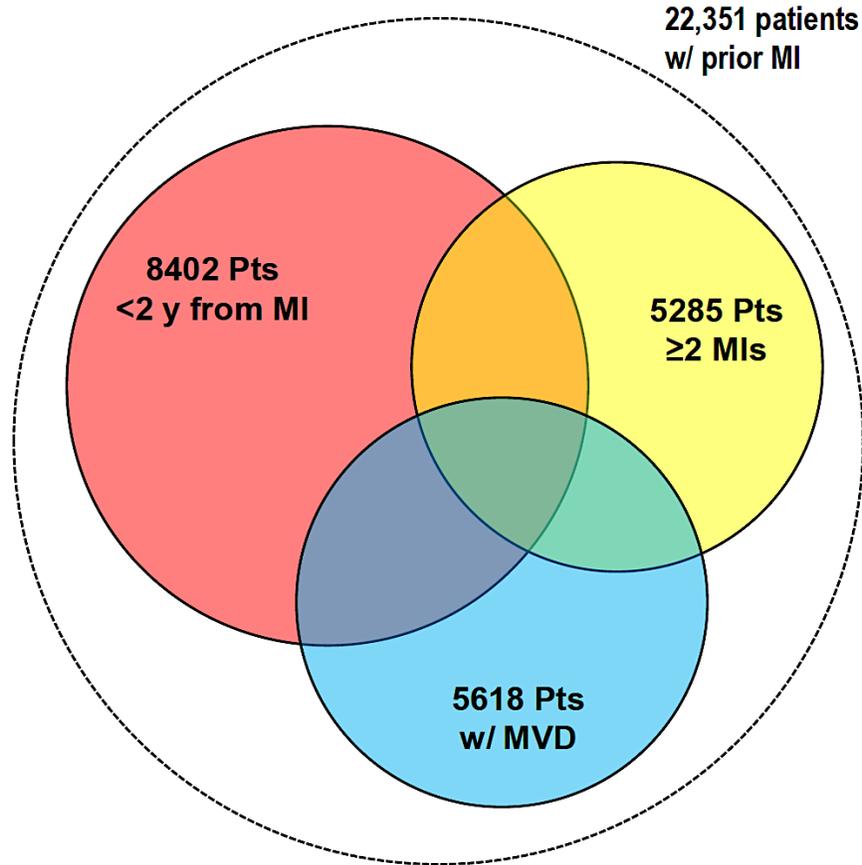
Number of patients	0	180	360	540	720	900	1080
Placebo	5516	5352	5200	4796	3170	1564	360
Evolocumab	5515	5365	5239	4881	3173	1532	355



## patients with and without PAD

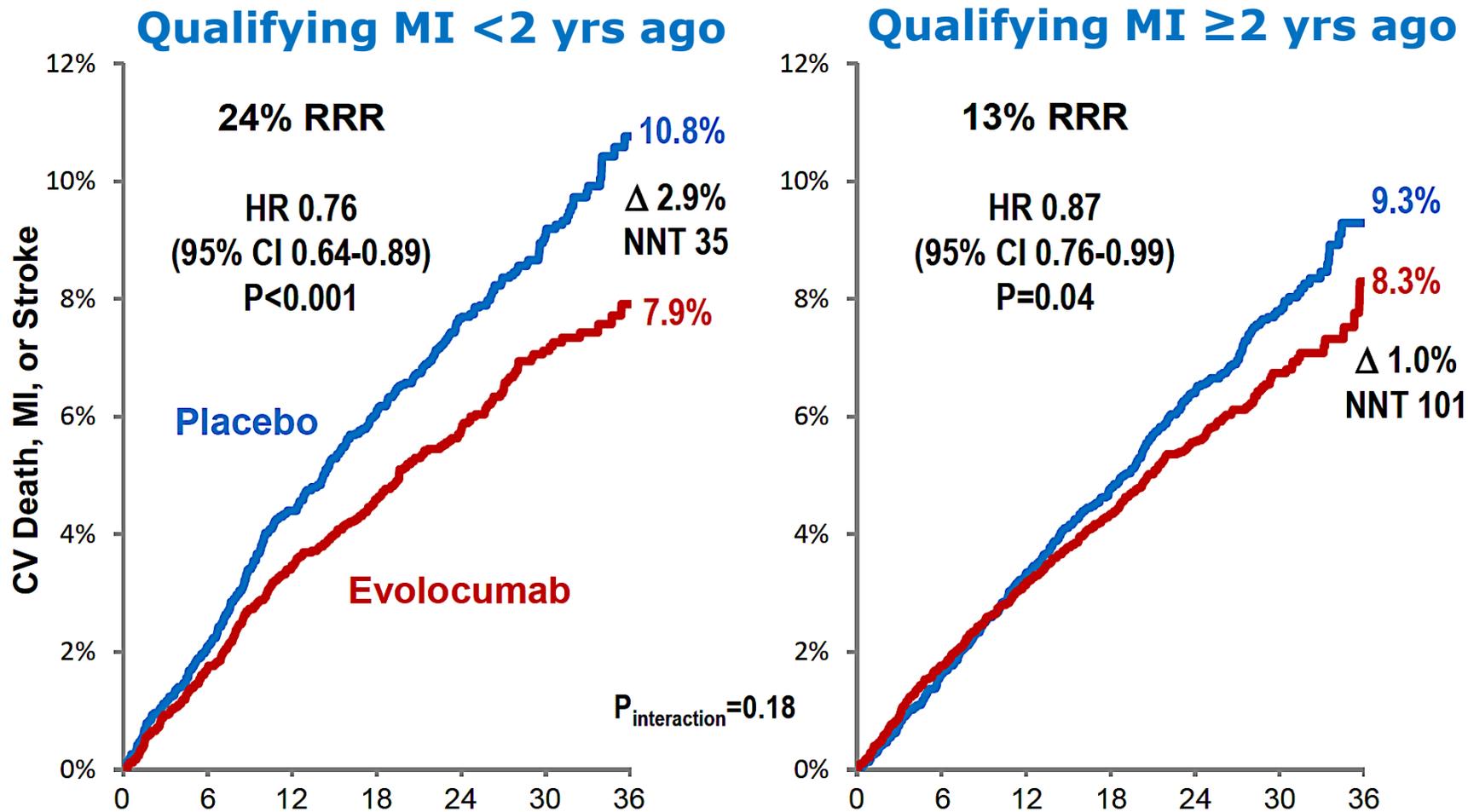


# subgroup high risk MI patients



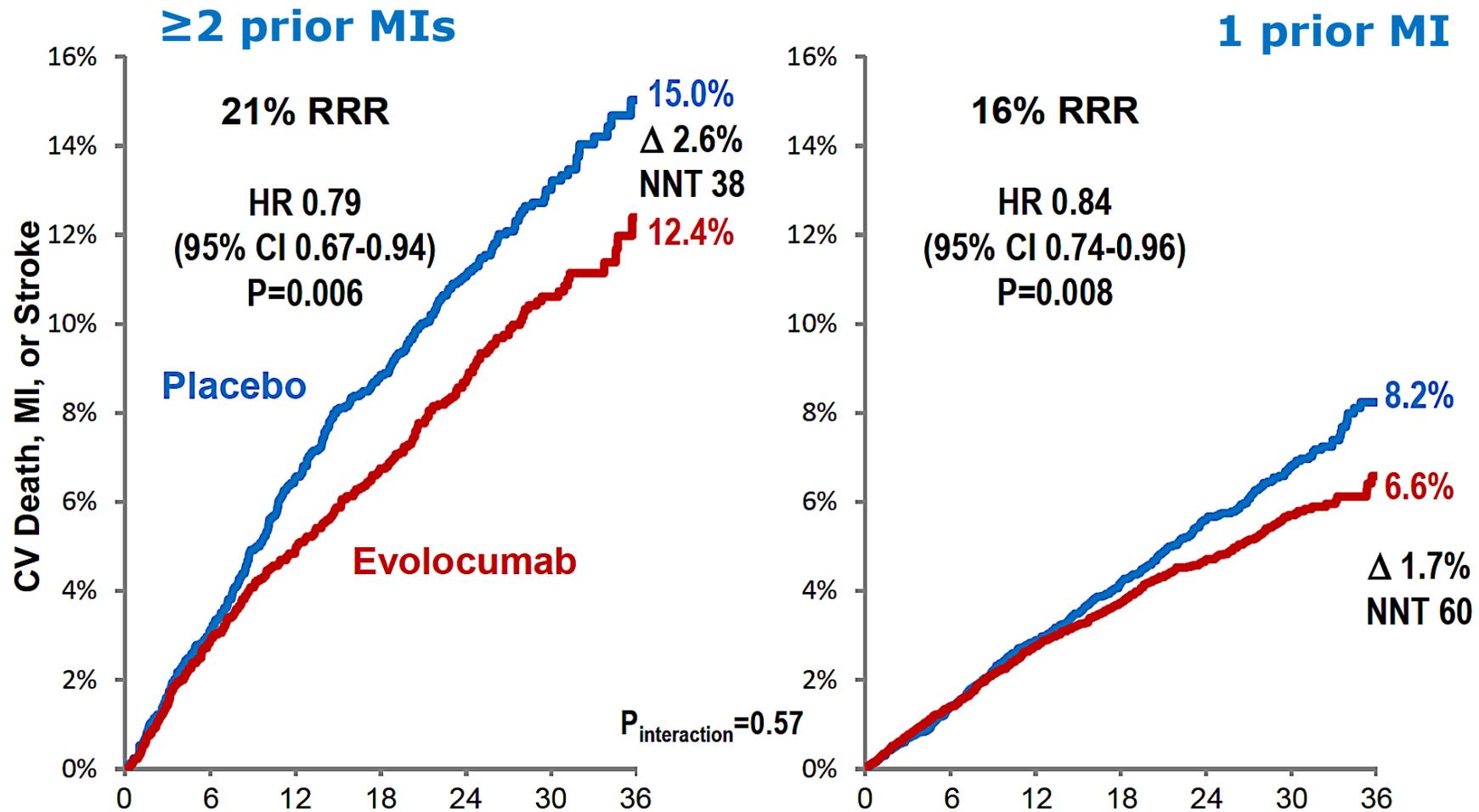


# Benefit of Evolocumab based on time from qualifying MI

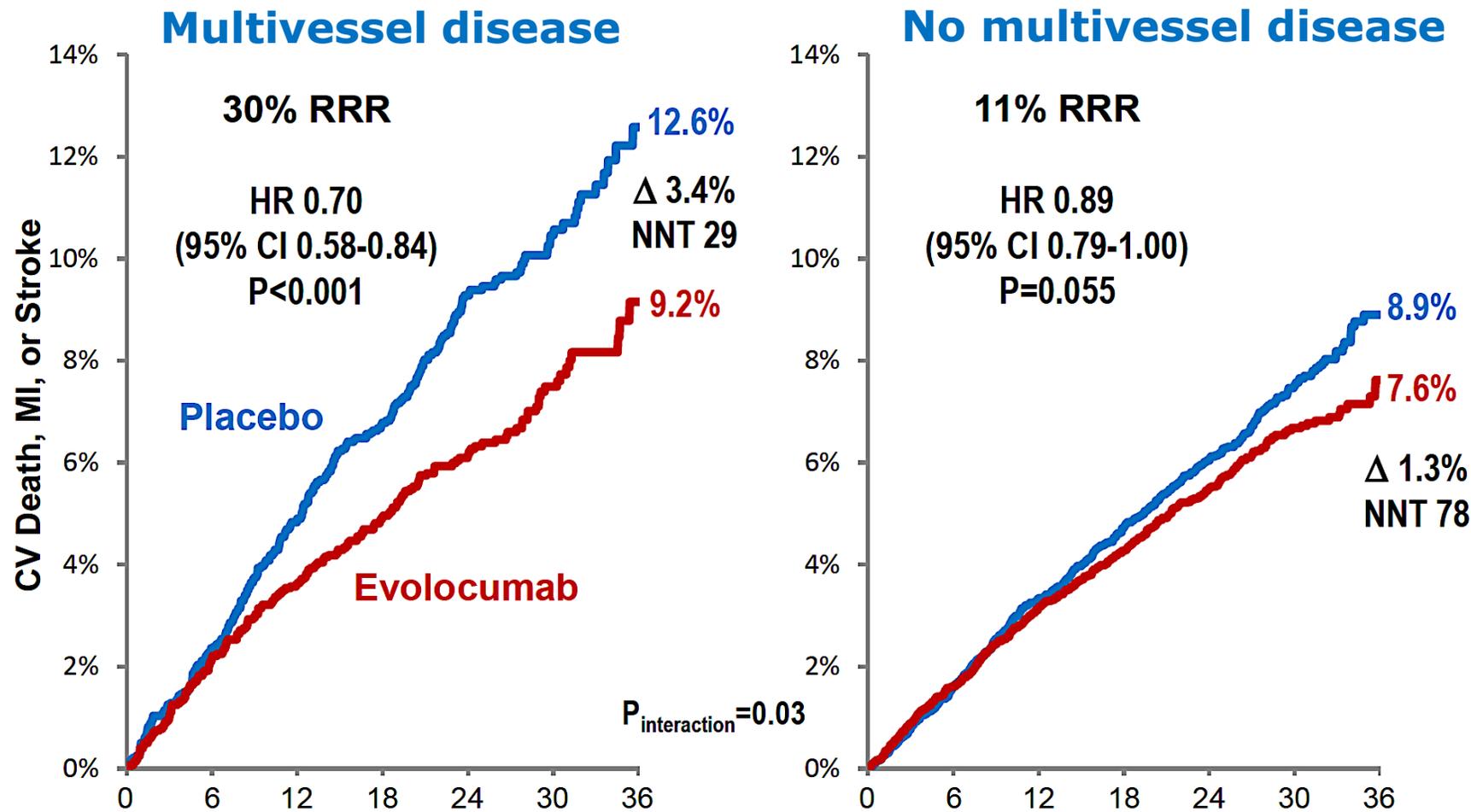




# Benefit of Evolocumab based on number of prior MIs



# Benefit of Evolocumab based on multivessel disease

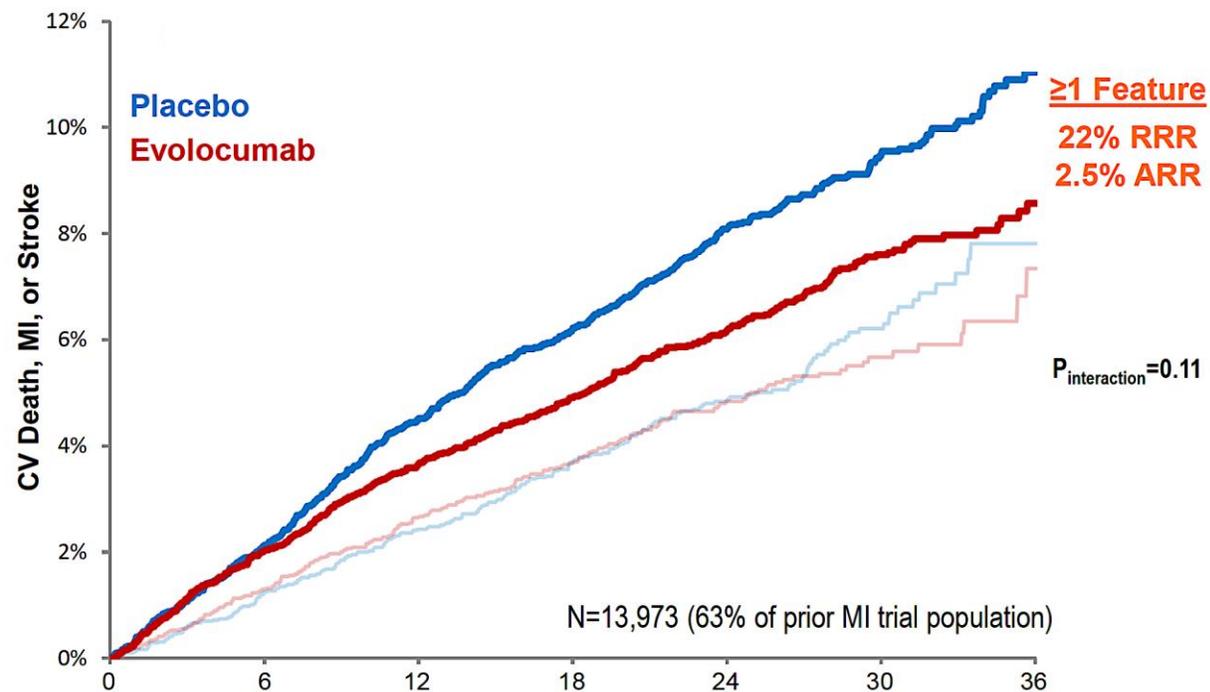
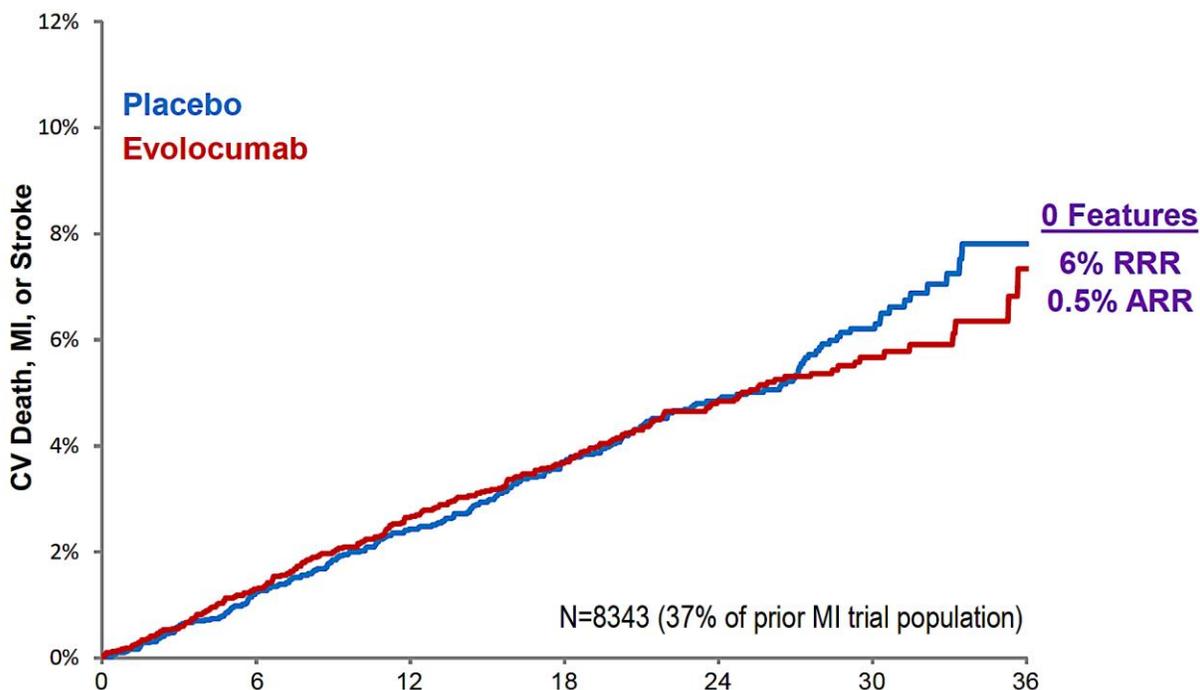


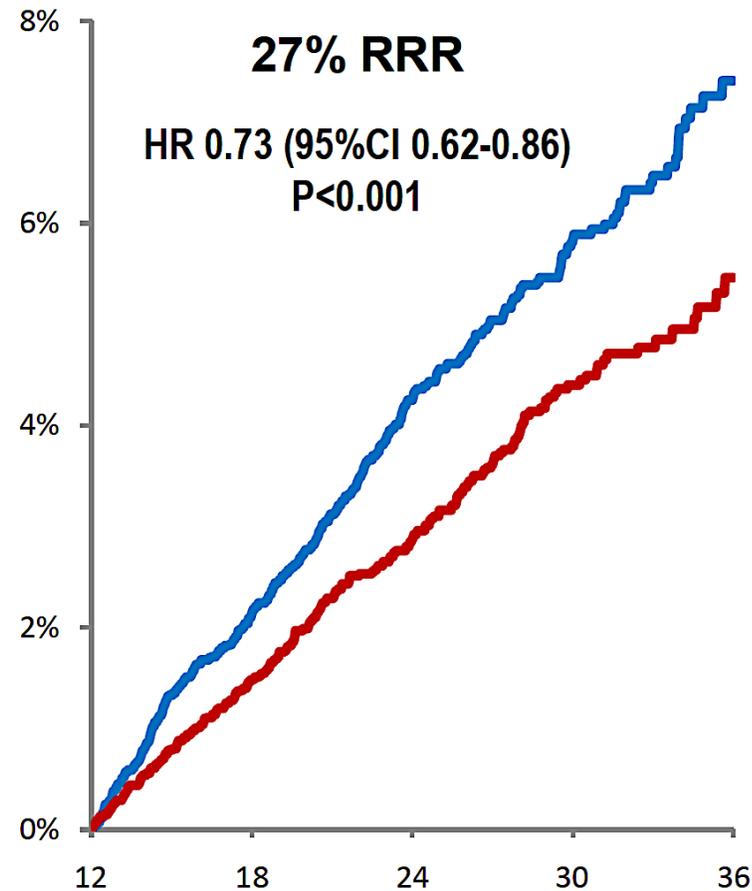
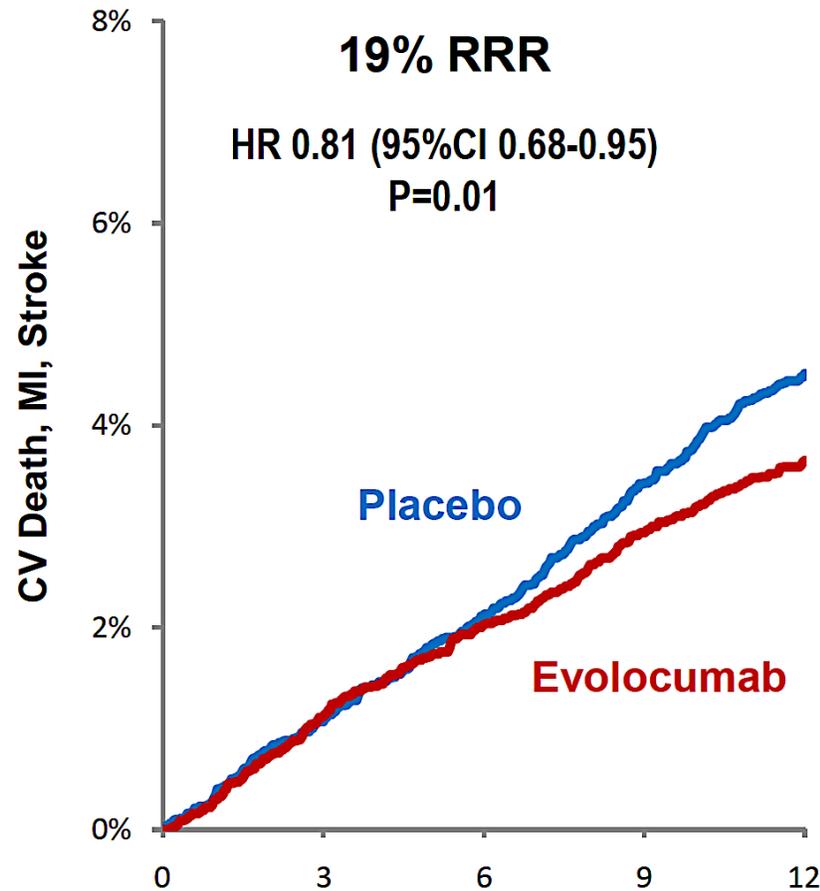


# Benefit of Evolocumab based on number of high-risk MI features

## High-risk feature:

<2 yrs qualifying MI,  $\geq 2$  Prior MIs, or residual MVD





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



<http://amgendigital.es/cardiofighters>

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# Preguntas



<http://amgendigital.es/cardiofighters>

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# Cierre y conclusiones

