Il ruolo degli inibitori PCSK9

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Forum sulla gestione post - dimissione della terapia ipolipemizzante / metabolica

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BMC Medicine

Prevention of Cardiovascular Diseases

RESEARCH ARTICLE Open Access

Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials

Xin-Lin Zhang[1†], Qing-Qing Zhu[2†], Li Zhu[3†], Jian-Zhou Chen[1], Q
Li-Na Kang[1] and Biao Xu[1*]

Acbstract

Background: Inhibition of proprotein convertase subtilisin/kexin lower low-density lipoprotein cholesterol (LDL-C) levels. The purp and efficacy of anti-PCSK9 antibodies in randomized, controlled t

Methods: PubMed, EMBASE, CENTRAL databases, and recent cor rates of common adverse events. Efficacy outcomes included pe changes compared with placebo and ezetimibe, respectively.

Results: Twenty-five RCTs encompassing 12,200 patients were in firstly reported in our study by pooling together all evidence in F between anti-PCSK9 antibodies and placebo (or ezetimibe), exce rates of death (relative risk (RR): 0.43, 95 % confidence interval (C injection-site reactions (RR: 1.48, 95 % CI: 1.05 to 2.09, $P = 0.02$); e function (RR: 0.43, 95 % CI: 0.20 to 0.93, $P = 0.03$), both compared outcomes was detected between monthly 420 mg and biweekly evolocumab treatment significantly reduced LDL-C by −54.6 % (9 mg/dl (95 % CI: −88.9 to −68.9 mg/dl) versus placebo, and by −3 and increased high-density lipoprotein cholesterol (HDL-C) by 7.6 6.4 % (95 % CI: 4.3 to 8.4 %) versus ezetimibe. An equal or even 140 mg administration. Significant and favorable changes were a treatment. Biweekly 50 to 150 mg alirocumab lowered LDL-C by − by −29.9 % (95 % CI: −32.9 to −26.9 %) versus ezetimibe, and incre placebo.

Conclusions: Evolocumab and alirocumab were safe and well-tole antibodies substantially reduced the LDL-C level by over 50 %, incr changes in other lipids.

Keywords: PCSK9, Monoclonal antibody, Evolocumab, Alirocumab controlled trials

REVIEW

Annals of Internal Medicine

Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

A Systematic Review and Meta-analysis

Eliano Pio Navarese, MD, PhD*; Michalina Kołodziejczak, MD*; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D'Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD

Background: Guidelines rec for dyslipidemia. Monoclona convertase subtilisin/kexin typ approach.

Purpose: To assess the effica in adults with hypercholester

Data Sources: MEDLINE, Scholar; conference proceedi istry through 4 April 2015.

Study Selection: Phase 2 (RCTs) comparing treatment anti-PCSK9 therapy in adults

Data Extraction: Two inve data on study characteristics a rated risk of bias of trials. Pre all-cause and cardiovascular

Data Synthesis: Twenty-fou were included. Compared PCSK9 antibodies led to mar protein cholesterol levels (m

Intern Emerg Med (2017) 12:1043–1053
DOI 10.1007/s11739-017-1708-7

CrossMark

CE - SYSTEMATIC REVIEWS

PCSK9 inhibitors for treating dyslipidemia in patients at different cardiovascular risk: a systematic review and a meta-analysis

Alessandro Squizzato[1,2] · Matteo Basilio Suter[3] · Marta Nerone[3] · Robert Patrick Giugliano[4] · Francesco Dentali[1,2] · Andrea Maria Maresca[1] · Leonardo Campiotti[1] · Anna Maria Grandi[1] · Luigina Guasti[1]

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Abstract Statin-induced lowering of low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular morbidity and mortality, but many patients do not adequately reduce their LDL-C levels. Monoclonal antibodies targeting PCKS9 are currently in the advanced phase of development. We aimed to investigate the efficacy and safety of PCSK9 inhibitors in patients at different cardiovascular risk in a systematic review. Studies were searched on MEDLINE and EMBASE until January 2016. Differences in the outcomes among groups were expressed as mean differences, or pooled odds ratio (OR) and corresponding 95% confidence interval (CI), which were calculated using a fixed-effects and a random-effects model. Statistical heterogeneity was evaluated using the I^2 statistic. 22 RCTs and 8833 patients were included. Six studies were performed in patients affected by homozygous or heterozygous familial hypercholesterolemia, or with increased three in statin-naïve patients, and 10 in patients unable to achieve LDL-C target with statin therapy. PCSK9 inhibitors were associated with a statistically significant reduction of LDL-C (mean = −48.8%; 95% CI −54.1, −43.4; $I^2 = 94\%$) compared to control groups, and with a statistically significant reduction in death for any cause (OR = 0.34; 95% CI 0.17, 0.69; $I^2 = 0$) and a favorable trend for cardiovascular events (OR = 0.79; 95% CI 0.61, 1.02; $I^2 = 0\%$). PCSK9 inhibitors reduce LDL-C concentration in every group explored. A significant reduction in death by all cause was observed in the PCSK9 inhibitors groups, compared with control groups, even in the short time frame studied.

Keywords Lipid lowering drugs · PCSK-9 inhibitors · Monoclonal antibodies · Dyslipidemia

LDL reduction

Intern Emerg Med
DOI 10.1007/s11739-017-1708-7

Intern Emerg Med 2017

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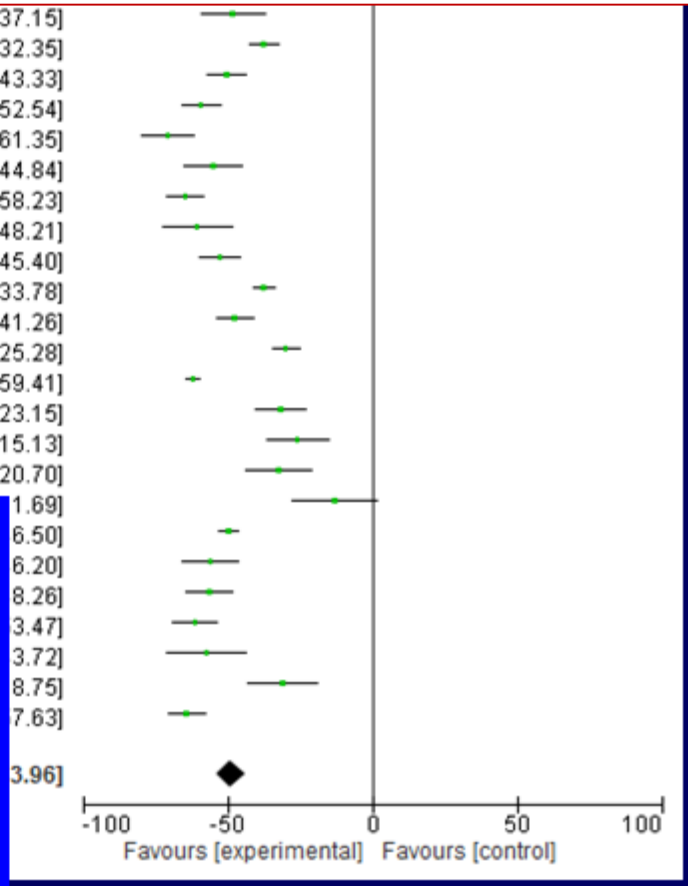
Study or Subgroup	PCSK9 Inhibitor Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Differe IV, Random
Ballantyne 2015	-54.2	27	46	-2.8	29.2	47	3.5%	-51.40 [-62.83,
DESCARTES 2014	-50.1	29.36	599	6.8	31.28	302	4.2%	-56.90 [-61.14
GAUSS 2012	-63	22.69	30	-14.8	21.63	32	3.6%	-48.20 [-59.25, -37.15]
GAUSS-2 2014	-52.6	15.97	102	-15.1	15	51	4.2%	-37.50 [-42.65, -32.35]
LAPLACE TIMI-57 2012	-51.3	22.63	80	-0.98	22.45	80	4.0%	-50.32 [-57.31, -43.33]
LAPLACE-2 A10 2014	-58.2	20.55	110	1	20.58	55	4.0%	-59.20 [-65.86, -52.54]
LAPLACE-2 A80 2014	-58.7	28.46	110	11.8	28.18	55	3.8%	-70.50 [-79.65, -61.35]
LAPLACE-2 R40 2014	-52.4	31.38	112	2.6	31.52	55	3.7%	-55.00 [-65.16, -44.84]
LAPLACE-2 R5 2014	-59.4	19.94	115	5.1	19.63	57	4.1%	-64.50 [-70.77, -58.23]
LAPLACE-2 S40 2014	-57	41.76	115	3.4	35.97	55	3.4%	-60.40 [-72.59, -48.21]
MENDEL 2012	-48	16.94	45	4.5	17.43	45	4.0%	-52.50 [-59.60, -45.40]
MENDEL-2 2014	-56.1	13.88	153	-18.6	13.45	77	4.3%	-37.50 [-41.22, -33.78]
ODISSEY COMBO I	-46.3	26	205	1.1	26.26	106	4.1%	-47.40 [-53.54, -41.26]
ODISSEY COMBO II	-50.6	30.25	467	-20.7	29.43	240	4.2%	-29.90 [-34.52, -25.28]
ODISSEY LONG TERM 2015	-61	27.38	1530	0.8	27.93	780	4.3%	-61.80 [-64.19, -59.41]
ODISSEY MONO 2014	-47.2	21.63	52	-15.6	22.14	51	3.9%	-31.60 [-40.05, -23.15]
ODISSEY OPTIONS I	-48.4	28.18	55	-22.6	28.39	53	3.6%	-25.80 [-36.47, -15.13]
ODISSEY OPTIONS II R 10	-49.6	28.41	48	-17.4	28.79	47	3.5%	-32.20 [-43.70, -20.70]
								1.69]
								6.50]
								6.20]
								8.26]
								3.47]
								3.72]
								8.75]
								7.63]
								3.96]



23 published studies on PCSK9 inhibitors

n = 8833 patients

MEDLINE and EMBASE database until January 2016

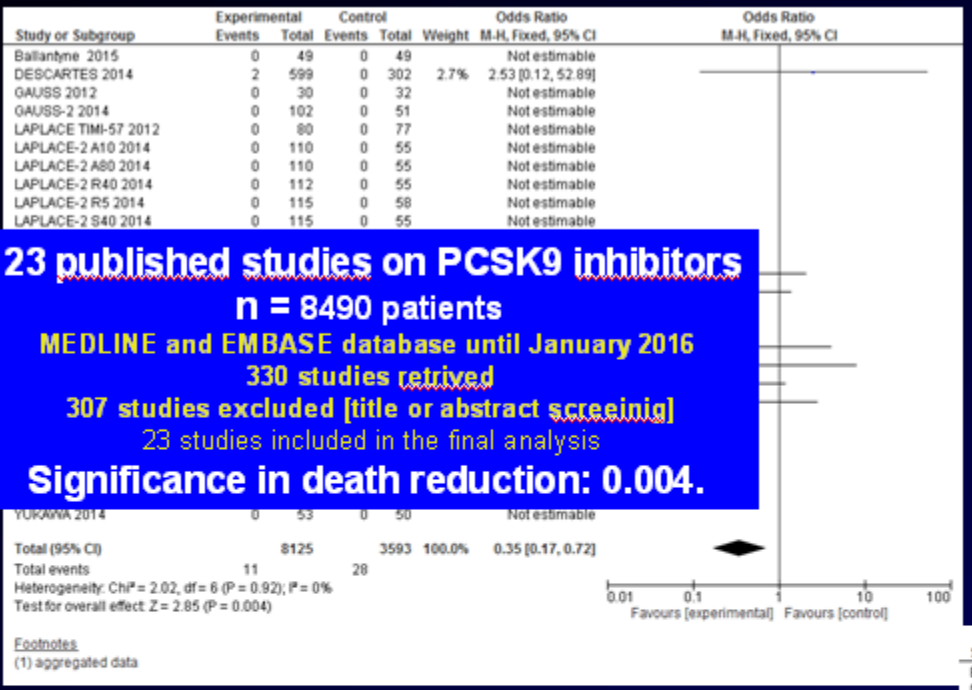
330 studies retrived

307 studies excluded [title or abstract screeinig]

23 studies included in the final analysis

mean difference in LDL-C reduction: - 48.86.

Mortalità tot



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ballantyne 2015	0	49	0	49		Not estimable
DESCARTES 2014	2	599	0	302	2.7%	2.53 [0.12, 52.89]
GAUSS 2012	0	30	0	32		Not estimable
GAUSS-2 2014	0	102	0	51		Not estimable
LAPLACE TIMI-57 2012	0	80	0	77		Not estimable
LAPLACE-2 A10 2014	0	110	0	55		Not estimable
LAPLACE-2 A80 2014	0	110	0	55		Not estimable
LAPLACE-2 R40 2014	0	112	0	55		Not estimable
LAPLACE-2 R5 2014	0	115	0	58		Not estimable
LAPLACE-2 S40 2014	0	115	0	55		Not estimable
YUKAWA 2014	0	53	0	50		Not estimable
Total (95% CI)		8125		3593	100.0%	0.35 [0.17, 0.72]
Total events	11		28			

Heterogeneity: Chi² = 2.02, df = 6 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.85 (P = 0.004)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Footnotes
(1) aggregated data

23 published studies on PCSK9 inhibitors
n = 8490 patients
MEDLINE and EMBASE database until January 2016
330 studies retrived
307 studies excluded [title or abstract screeinig]
23 studies included in the final analysis
Significance in death reduction: 0.004.

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CE - SYSTEMATIC REVIEWS

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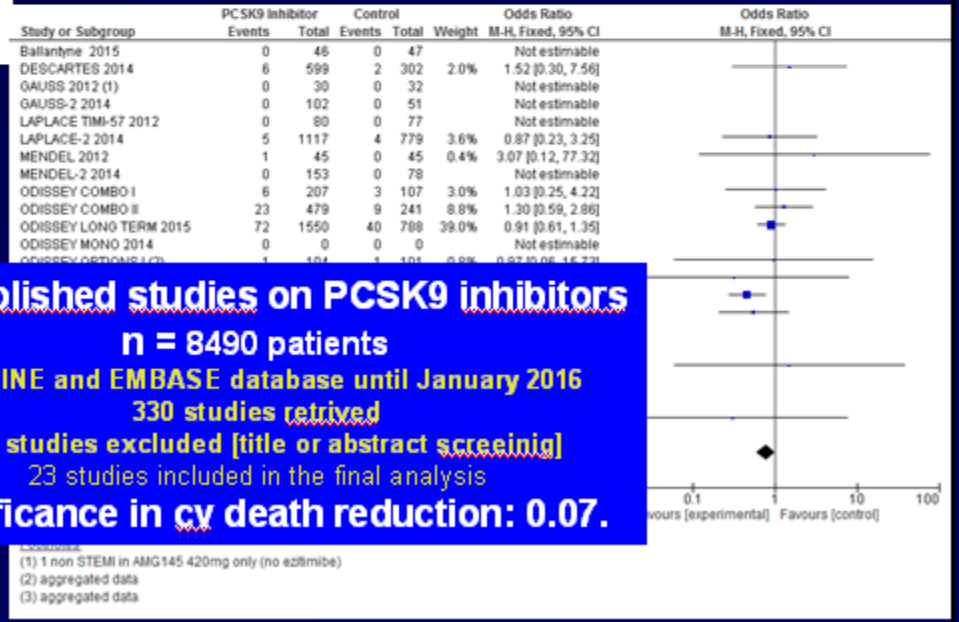
Mortalità cardiovascolare



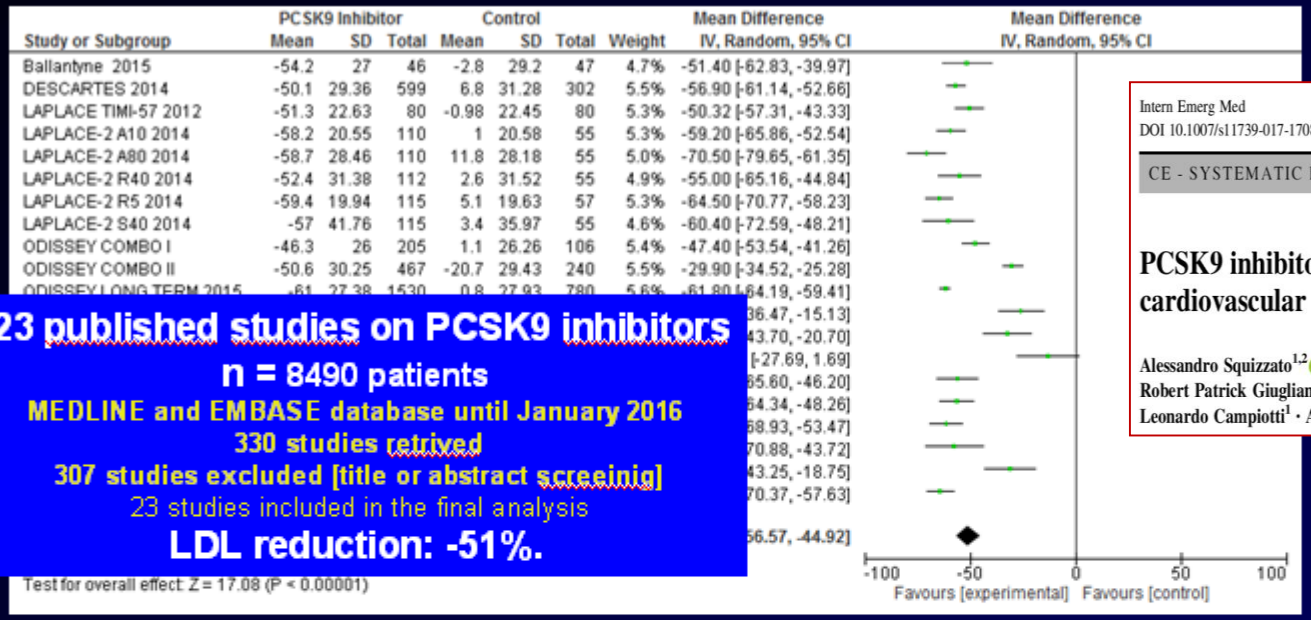
Study or Subgroup	PCSK9 Inhibitor Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ballantyne 2015	0	46	0	47		Not estimable
DESCARTES 2014	6	599	2	302	2.0%	1.52 [0.30, 7.56]
GAUSS 2012 (1)	0	30	0	32		Not estimable
GAUSS-2 2014	0	102	0	51		Not estimable
LAPLACE TIMI-57 2012	0	80	0	77		Not estimable
LAPLACE-2 2014	5	1117	4	779	3.6%	0.87 [0.23, 3.25]
MENDEL 2012	1	45	0	45	0.4%	3.07 [0.12, 77.32]
MENDEL-2 2014	0	153	0	78		Not estimable
ODISSEY COMBO I	6	207	3	107	3.0%	1.03 [0.25, 4.22]
ODISSEY COMBO II	23	479	9	241	8.8%	1.30 [0.59, 2.86]
ODISSEY LONG TERM 2015	72	1550	40	788	39.0%	0.91 [0.61, 1.35]
ODISSEY MONO 2014	0	0	0	0		Not estimable

Odds Ratio M-H, Fixed, 95% CI
0.1 1 10 100
vours [experimental] Favours [control]

Footnotes
(1) 1 non STEMI in AMG145 420mg only (no ezitimibe)
(2) aggregated data
(3) aggregated data

23 published studies on PCSK9 inhibitors
n = 8490 patients
MEDLINE and EMBASE database until January 2016
330 studies retrived
307 studies excluded [title or abstract screeinig]
23 studies included in the final analysis
Significance in cv death reduction: 0.07.

Sub-analysis: Lipid lowering regimen failure



Study or Subgroup	PCSK9 Inhibitor Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ballantyne 2015	-54.2	27	46	-2.8	29.2	47	4.7%	-51.40 [-62.83, -39.97]
DESCARTES 2014	-50.1	29.36	599	6.8	31.28	302	5.5%	-56.90 [-61.14, -52.66]
LAPLACE TIMI-57 2012	-51.3	22.63	80	-0.98	22.45	80	5.3%	-50.32 [-57.31, -43.33]
LAPLACE-2 A10 2014	-58.2	20.55	110	1	20.58	55	5.3%	-59.20 [-65.86, -52.54]
LAPLACE-2 A80 2014	-58.7	28.46	110	11.8	28.18	55	5.0%	-70.50 [-79.65, -61.35]
LAPLACE-2 R40 2014	-52.4	31.38	112	2.6	31.52	55	4.9%	-55.00 [-65.16, -44.84]
LAPLACE-2 R5 2014	-59.4	19.94	115	5.1	19.63	57	5.3%	-64.50 [-70.77, -58.23]
LAPLACE-2 S40 2014	-57	41.76	115	3.4	35.97	55	4.6%	-60.40 [-72.59, -48.21]
ODISSEY COMBO I	-46.3	26	205	1.1	26.26	106	5.4%	-47.40 [-53.54, -41.26]
ODISSEY COMBO II	-50.6	30.25	467	-20.7	29.43	240	5.5%	-29.90 [-34.52, -25.28]
ODISSEY LONG TERM 2015	-61	27.38	1530	0.8	27.93	780	5.6%	-61.80 [-64.19, -59.41]
								36.47, -15.13]
								43.70, -20.70]
								[-27.69, 1.69]
								65.60, -46.20]
								54.34, -48.26]
								68.93, -53.47]
								70.88, -43.72]
								43.25, -18.75]
								70.37, -57.63]
								56.57, -44.92]

Test for overall effect: Z = 17.08 (P < 0.00001)

Mean Difference IV, Random, 95% CI

-100 -50 0 50 100

Favours [experimental] Favours [control]

23 published studies on PCSK9 inhibitors

n = 8490 patients

MEDLINE and EMBASE database until January 2016

330 studies retrived

307 studies excluded [title or abstract screeinig]

23 studies included in the final analysis

LDL reduction: -51%.

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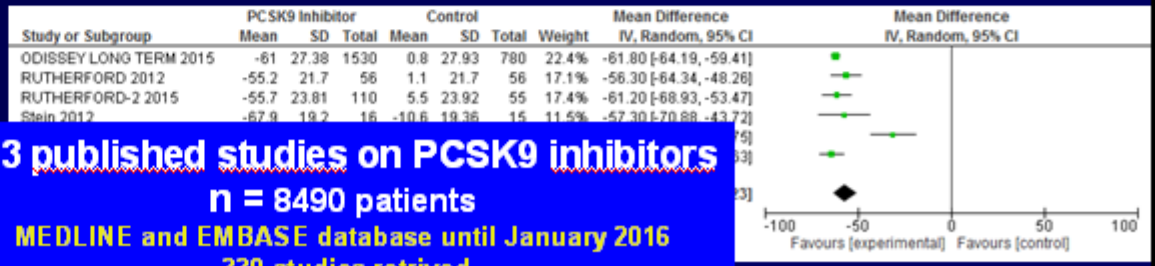
Sub-analysis: High risk pts



Study or Subgroup	PCSK9 Inhibitor Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ODISSEY LONG TERM 2015	-61	27.38	1530	0.8	27.93	780	22.4%	-61.80 [-64.19, -59.41]
RUTHERFORD 2012	-55.2	21.7	56	1.1	21.7	56	17.1%	-56.30 [-64.34, -48.26]
RUTHERFORD-2 2015	-55.7	23.81	110	5.5	23.92	55	17.4%	-61.20 [-68.93, -53.47]
Stein 2012	-67.9	19.2	16	-10.6	19.36	15	11.5%	-57.30 [-70.88, -43.72]

Mean Difference IV, Random, 95% CI

-100 -50 0 50 100

Favours [experimental] Favours [control]

23 published studies on PCSK9 inhibitors

n = 8490 patients

MEDLINE and EMBASE database until January 2016

330 studies retrived

307 studies excluded [title or abstract screeinig]

23 studies included in the final analysis

LDL reduction: -56.7%

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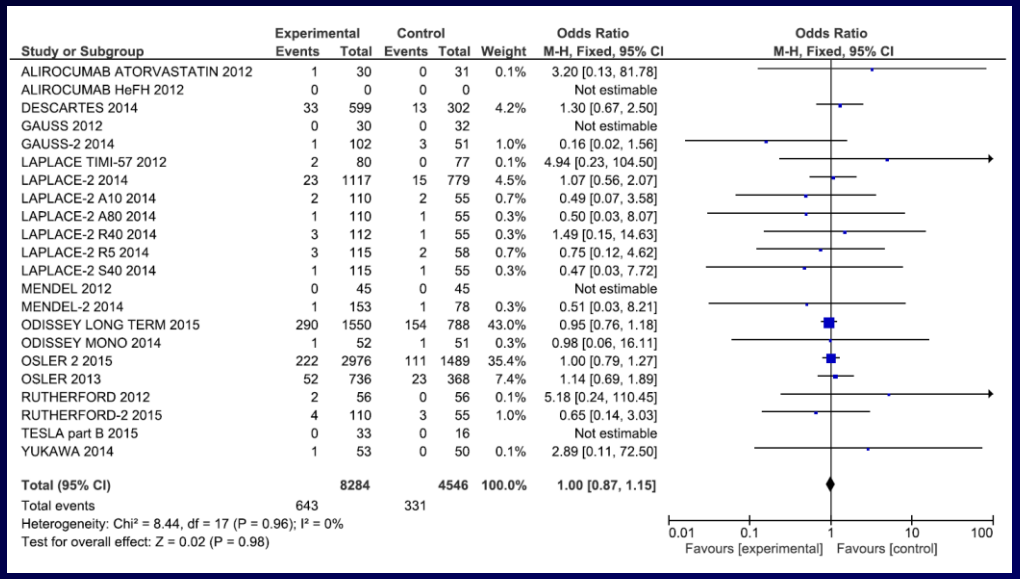
Serious Adverse Effects

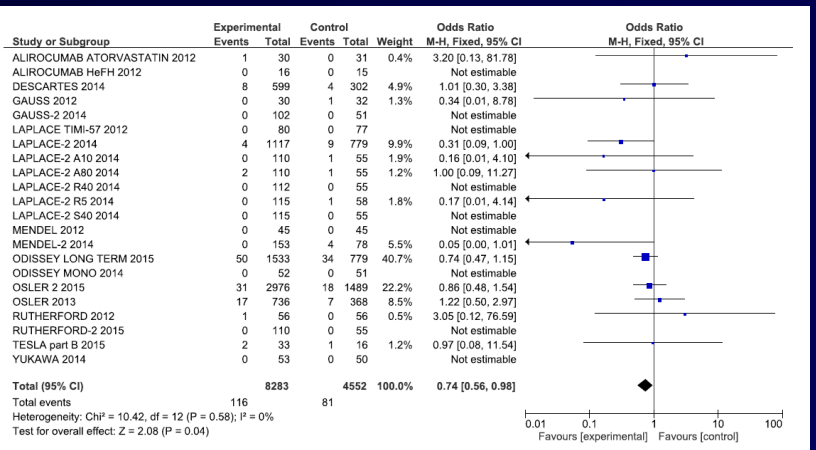


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ALIROCUMAB ATORVASTATIN 2012	1	30	0	31	0.1%	3.20 [0.13, 81.78]
ALIROCUMAB HeFH 2012	0	0	0	0		Not estimable
DESCARTES 2014	33	599	13	302	4.2%	1.30 [0.67, 2.50]
GAUSS 2012	0	30	0	32		Not estimable
GAUSS-2 2014	1	102	3	51	1.0%	0.16 [0.02, 1.56]
LAPLACE TIMI-57 2012	2	80	0	77	0.1%	4.94 [0.23, 104.50]
LAPLACE-2 2014	23	1117	15	779	4.5%	1.07 [0.56, 2.07]
LAPLACE-2 A10 2014	2	110	2	55	0.7%	0.49 [0.07, 3.58]
LAPLACE-2 A80 2014	1	110	1	55	0.3%	0.50 [0.03, 8.07]
LAPLACE-2 R40 2014	3	112	1	55	0.3%	1.49 [0.15, 14.63]
LAPLACE-2 R5 2014	3	115	2	58	0.7%	0.75 [0.12, 4.62]
LAPLACE-2 S40 2014	1	115	1	55	0.3%	0.47 [0.03, 7.72]
MENDEL 2012	0	45	0	45		Not estimable
MENDEL-2 2014	1	153	1	78	0.3%	0.51 [0.03, 8.21]
ODISSEY LONG TERM 2015	290	1550	154	788	43.0%	0.95 [0.76, 1.18]
ODISSEY MONO 2014	1	52	1	51	0.3%	0.98 [0.06, 16.11]
OSLER 2 2015	222	2976	111	1489	35.4%	1.00 [0.79, 1.27]
OSLER 2013	52	736	23	368	7.4%	1.14 [0.69, 1.89]
RUTHERFORD 2012	2	56	0	56	0.1%	5.18 [0.24, 110.45]
RUTHERFORD-2 2015	4	110	3	55	1.0%	0.65 [0.14, 3.03]
TESLA part B 2015	0	33	0	16		Not estimable
YUKAWA 2014	1	53	0	50	0.1%	2.89 [0.11, 72.50]
Total (95% CI)		**8284**		**4546**	**100.0%**	**1.00 [0.87, 1.15]**
Total events	643		331			

Heterogeneity: Chi² = 8.44, df = 17 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Transaminases elevation

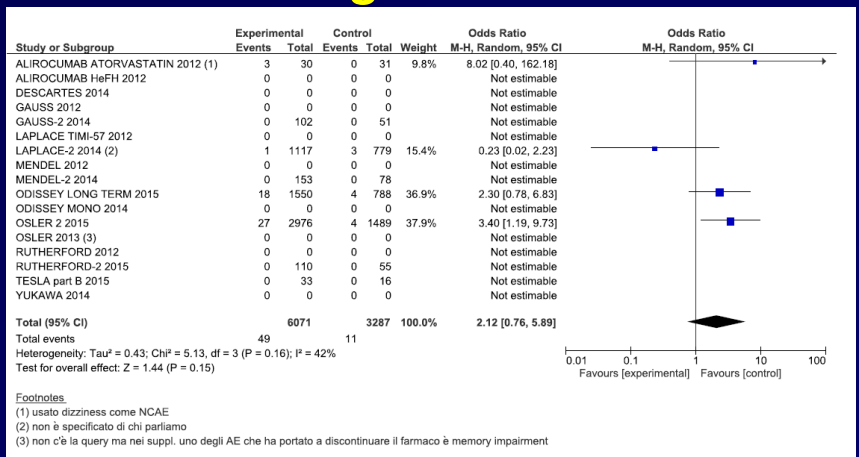


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ALIROCUMAB ATORVASTATIN 2012	1	30	0	31	0.4%	3.20 [0.13, 81.78]
ALIROCUMAB HeFH 2012	0	16	0	15		Not estimable
DESCARTES 2014	8	599	4	302	4.9%	1.01 [0.30, 3.38]
GAUSS 2012	0	30	1	32	1.3%	0.34 [0.01, 8.78]
GAUSS-2 2014	0	102	0	51		Not estimable
LAPLACE TIMI-57 2012	0	80	0	77		Not estimable
LAPLACE-2 2014	4	1117	9	779	9.9%	0.31 [0.09, 1.00]
LAPLACE-2 A10 2014	0	110	1	55	1.9%	0.16 [0.01, 4.10]
LAPLACE-2 A80 2014	2	110	1	55	1.2%	1.00 [0.09, 11.27]
LAPLACE-2 R40 2014	0	112	0	55		Not estimable
LAPLACE-2 R5 2014	0	115	1	58	1.8%	0.17 [0.01, 4.14]
LAPLACE-2 S40 2014	0	115	0	55		Not estimable
MENDEL 2012	0	45	0	45		Not estimable
MENDEL-2 2014	0	153	4	78	5.5%	0.05 [0.00, 1.01]
ODISSEY LONG TERM 2015	50	1533	34	779	40.7%	0.74 [0.47, 1.15]
ODISSEY MONO 2014	0	52	0	51		Not estimable
OSLER 2 2015	31	2976	18	1489	22.2%	0.86 [0.48, 1.54]
OSLER 2013	17	736	7	368	8.5%	1.22 [0.50, 2.97]
RUTHERFORD 2012	1	56	0	56	0.5%	3.05 [0.12, 76.59]
RUTHERFORD-2 2015	0	110	0	55		Not estimable
TESLA part B 2015	2	33	1	16	1.2%	0.97 [0.08, 11.54]
YUKAWA 2014	0	53	0	50		Not estimable
Total (95% CI)		**8283**		**4552**	**100.0%**	**0.74 [0.56, 0.98]**
Total events	116		81			

Heterogeneity: Chi² = 10.42, df = 12 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Neurocognitive AE



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ALIROCUMAB ATORVASTATIN 2012 (1)	3	30	0	31	9.8%	8.02 [0.40, 162.18]
ALIROCUMAB HeFH 2012	0	0	0	0		Not estimable
DESCARTES 2014	0	0	0	0		Not estimable
GAUSS 2012	0	0	0	0		Not estimable
GAUSS-2 2014	0	102	0	51		Not estimable
LAPLACE TIMI-57 2012	0	0	0	0		Not estimable
LAPLACE-2 2014 (2)	1	1117	3	779	15.4%	0.23 [0.02, 2.23]
MENDEL 2012	0	0	0	0		Not estimable
MENDEL-2 2014	0	153	0	78		Not estimable
ODISSEY LONG TERM 2015	18	1550	4	788	36.9%	2.30 [0.78, 6.83]
ODISSEY MONO 2014	0	0	0	0		Not estimable
OSLER 2 2015	27	2976	4	1489	37.9%	3.40 [1.19, 9.73]
OSLER 2013 (3)	0	0	0	0		Not estimable
RUTHERFORD 2012	0	0	0	0		Not estimable
RUTHERFORD-2 2015	0	110	0	55		Not estimable
TESLA part B 2015	0	33	0	16		Not estimable
YUKAWA 2014	0	0	0	0		Not estimable
Total (95% CI)		**6071**		**3287**	**100.0%**	**2.12 [0.76, 5.89]**
Total events	49		11			

Heterogeneity: Tau² = 0.43; Chi² = 5.13, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.44 (P = 0.15)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Footnotes
(1) usato dizziness come NCAE
(2) non è specificato di chi parliamo
(3) non c'è la query ma nei suppl. uno degli AE che ha portato a discontinuare il farmaco è memory impairment

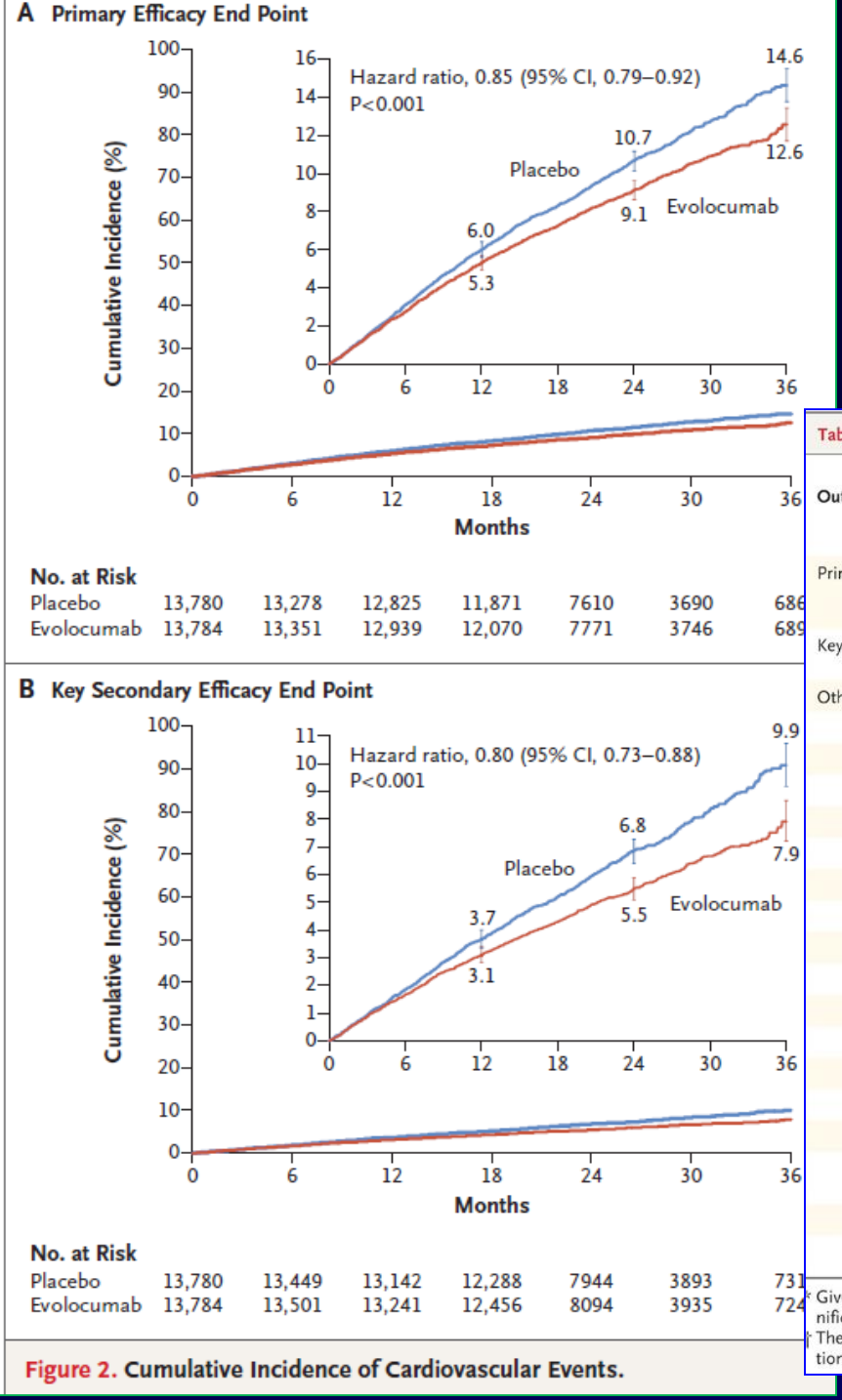


Figure 2. Cumulative Incidence of Cardiovascular Events.

The NEW ENGLAND JOURNAL

NEJM 2017

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

* Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary end points should be considered significant, whereas all other P values should be considered exploratory.
† The Cholesterol Treatment Trialists Collaboration (CTTC) composite end point consists of coronary heart death, nonfatal myocardial infarction, stroke, or coronary revascularization.

Cardiovascular Events

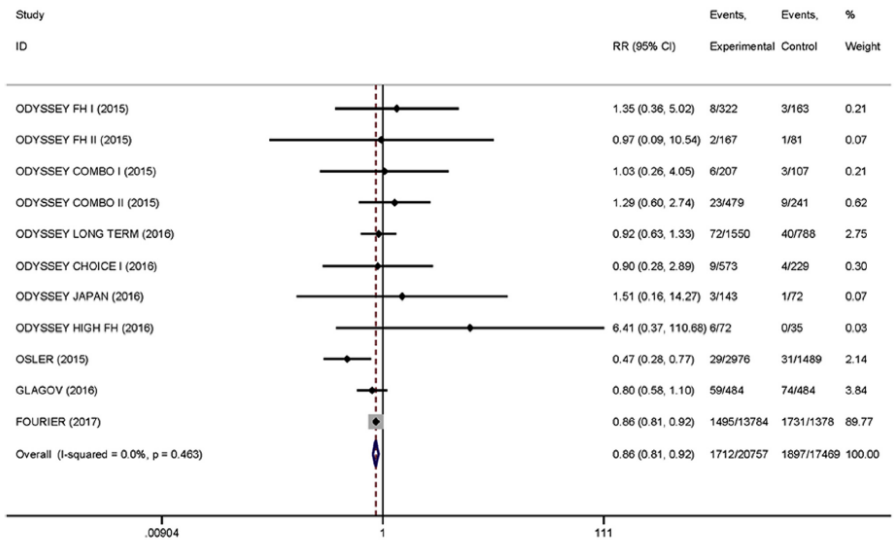
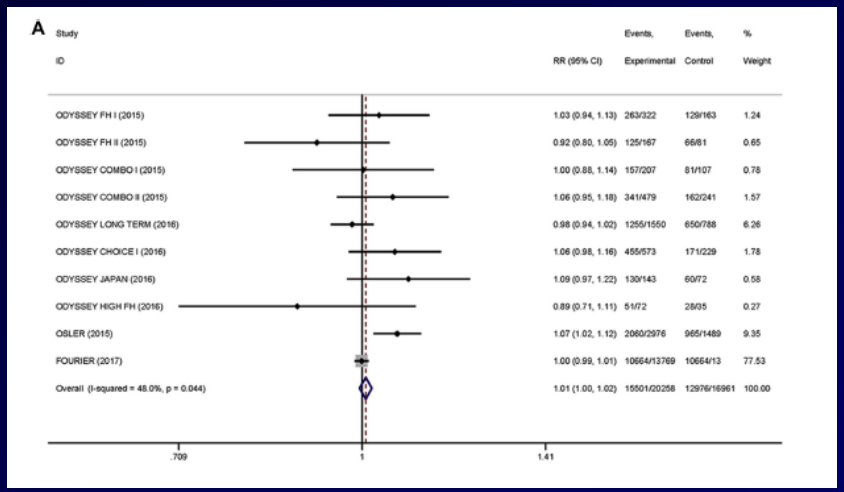


Figure 3 Forest plots depicting the effect of PCSK9 antibody therapy on cardiovascular events. CI, confidence interval; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; OSLER, Open-Label Study of Long-Term Evaluation Against LDL-C trial; PCSK9, proprotein convertase subtilisin/kexin type 9; RR, relative risk.

Adverse Events



Journal of Clinical Lipidology (2018) 12, 277–291

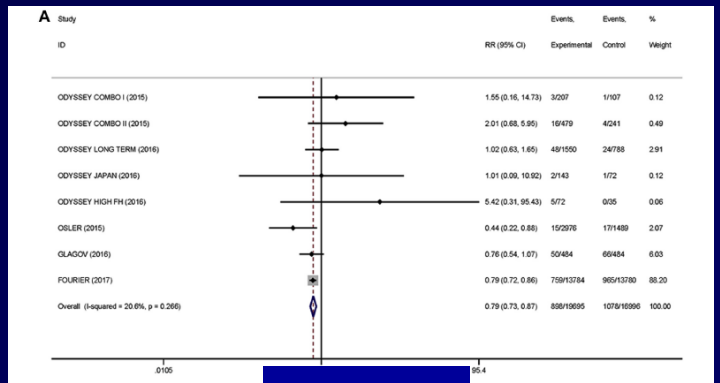
Journal of Clinical Lipidology

Long-term efficacy and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibodies: A meta-analysis of 11 randomized controlled trials

Jie Bai, MD, Li-lin Gong, PhD, Qi-fu Li, PhD, Zhi-hong Wang, PhD*

Check for updates

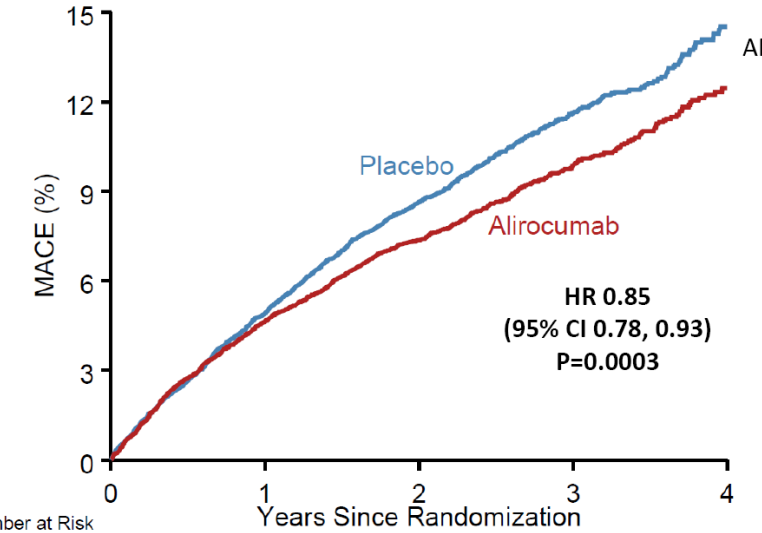
Coronary revasc.



Stroke

Figure 6 Forest plots depicting the effect of PCSK9 antibody therapy on (A) coronary revascularization, and (B) stroke. CI, confidence interval; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; OSLER, Open-Label Study of Long-Term Evaluation Against LDL-C trial; PCSK9, proprotein convertase subtilisin/kexin type 9; RR, relative risk.

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher, **Ph. Gabriel Steg**

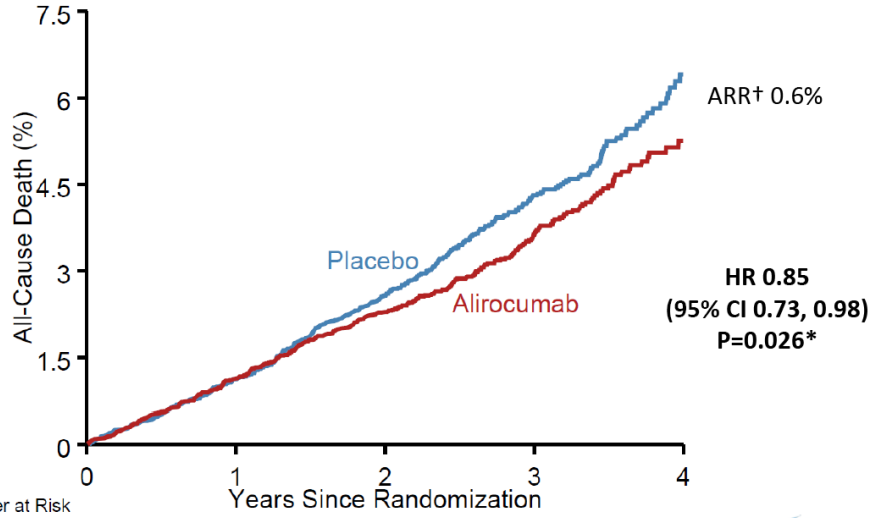
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402

ODYSSEY OUTCOMES

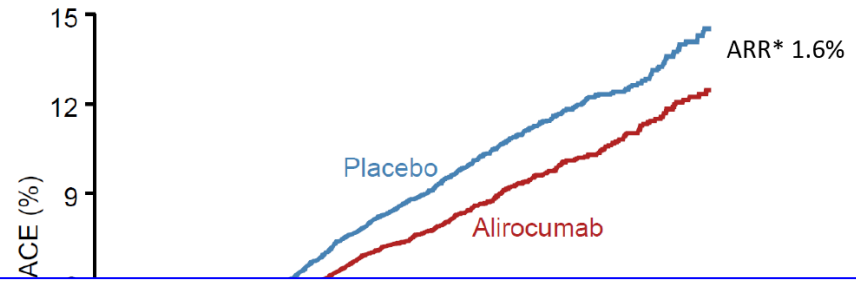
All-Cause Death



*Nominal P-value

†Based on cumulative incidence

Primary Efficacy Endpoint: MACE



The ODYSSEY OUTCOMES Trial: Topline Results

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ClinicalTrials.gov: NCT01663402

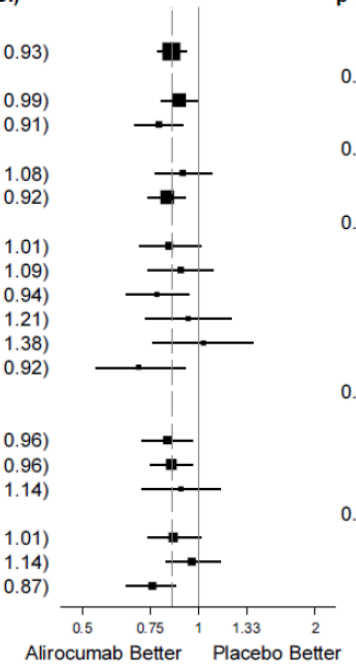
ODYSSEY OUTCOMES

MACE: (
non-fata
ischemi
unstable
hospital

*Based on cu
incidence

Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
Overall	18924	9.5	11.1	0.85 (0.78, 0.93)	
Age					0.19
< 65 Yr	13840	8.5	9.5	0.89 (0.80, 0.99)	
≥ 65 Yr	5084	12.4	15.5	0.79 (0.68, 0.91)	
Sex					0.35
Female	4762	10.7	11.8	0.91 (0.77, 1.08)	
Male	14162	9.2	10.9	0.83 (0.74, 0.92)	
Region					0.40
Eastern Europe	5437	7.9	9.3	0.84 (0.70, 1.01)	
Western Europe	4175	9.1	10.0	0.90 (0.74, 1.09)	
North America	2871	13.7	17.1	0.78 (0.65, 0.94)	
South America	2588	9.1	9.7	0.94 (0.73, 1.21)	
Asia	2293	7.7	7.6	1.03 (0.76, 1.38)	
Rest of World	1560	12.2	16.7	0.70 (0.54, 0.92)	
Time from Index Event to Randomization					0.85
<2 Months	6178	10.3	12.3	0.83 (0.71, 0.96)	
2 - <6 Months	9518	9.6	11.1	0.85 (0.75, 0.96)	
≥6 Months	3228	8.0	8.7	0.90 (0.71, 1.14)	
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

ODYSSEY OUTCOMES

0.6%

0.85
.73, 0.98)
026*

*Nominal P-value
†Based on cumulative incidence

ODYS
OUTC

The NEW ENGLAND JOURNAL of MEDICINE 2017

ORIGINAL ARTICLE

Cognitive Function in a Randomized Trial of Evolocumab

Robert P. Giugliano, M.D., François Mach, M.D., Kenton Zavitz, Ph.D., Christopher Kurtz, M.D., Kyungah Im, Ph.D., Estella Kanevsky, M.S., Jingjing Schneider, Ph.D., Huei Wang, Ph.D., Anthony Keech, M.D., Terje R. Pedersen, M.D., Marc S. Sabatine, M.D., M.P.H., Peter S. Sever, Ph.D., F.R.C.P., Jennifer G. Robinson, M.D., M.P.H., Narimon Honarpour, M.D., Ph.D., Scott M. Wasserman, M.D., and Brian R. Ott, M.D., for the EBBINGHAUS Investigators*

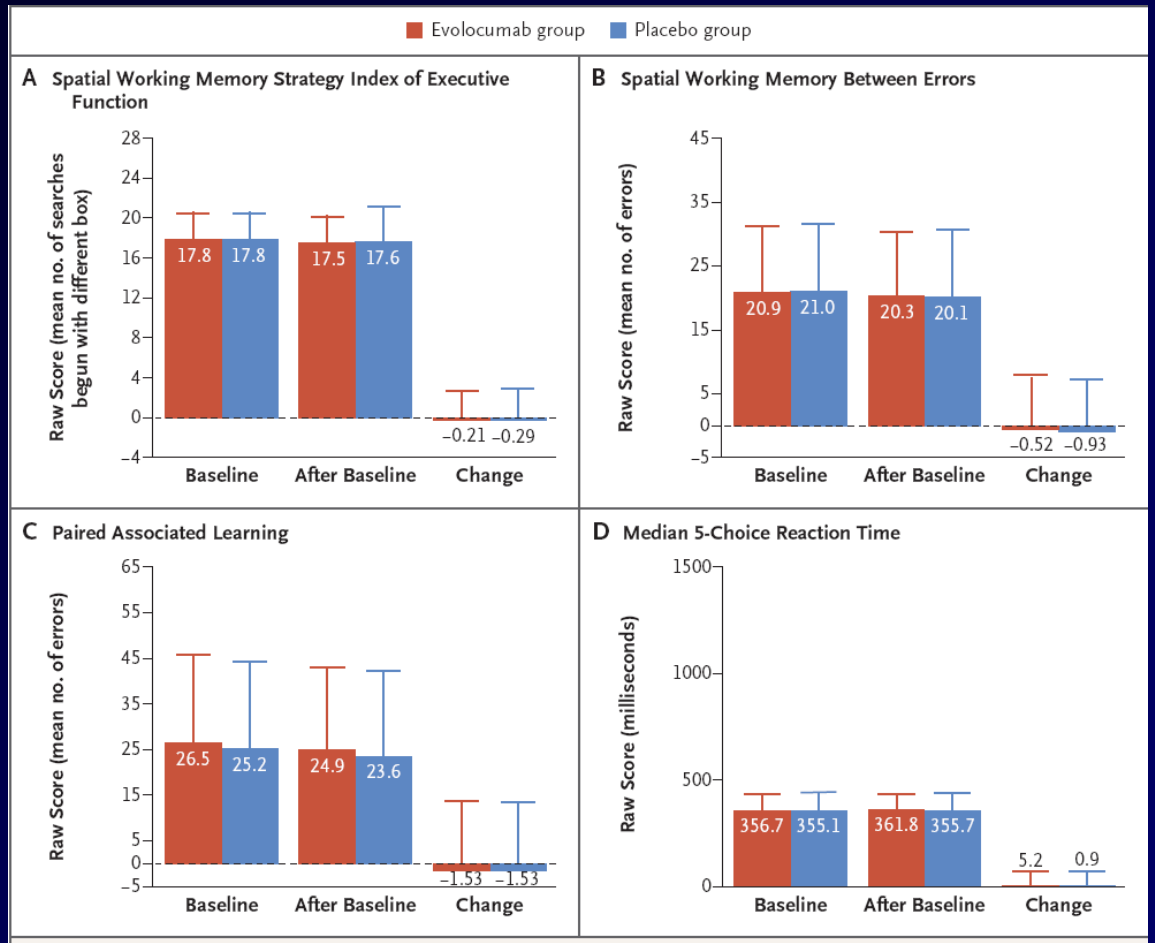
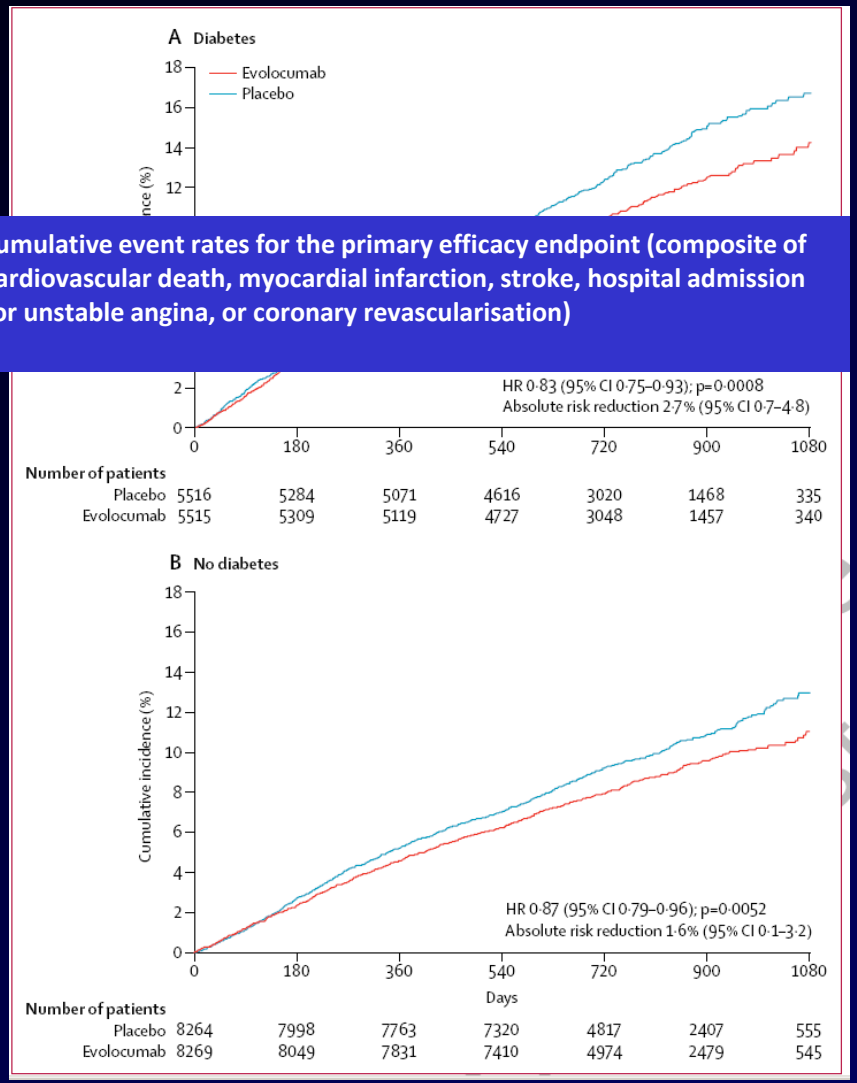


Figure 1. Primary and Secondary Cambridge Neuropsychological Test Automated Battery (CANTAB) End Points.

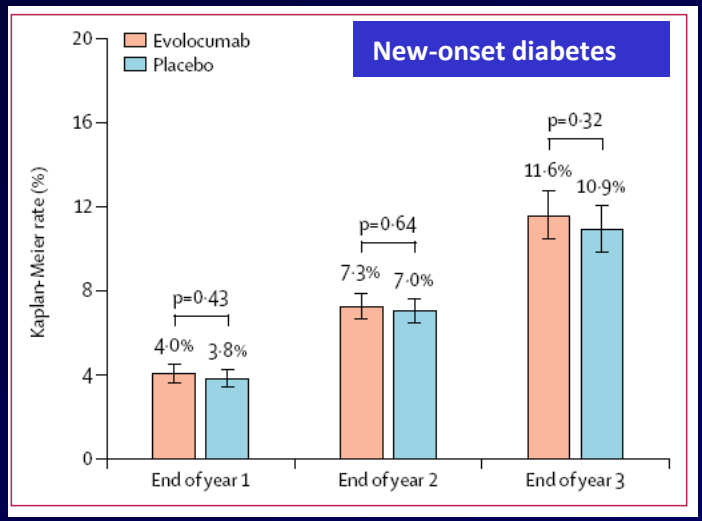
Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

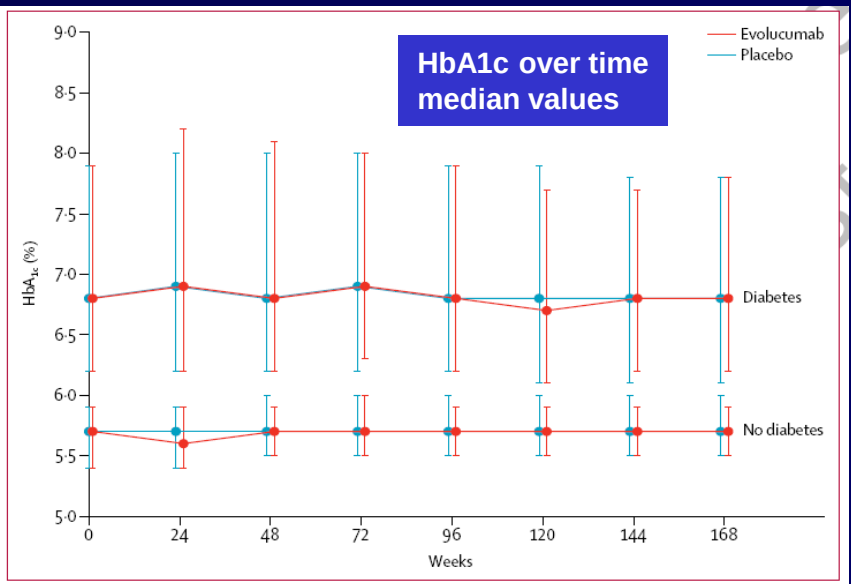
Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

2017



cumulative event rates for the primary efficacy endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation)





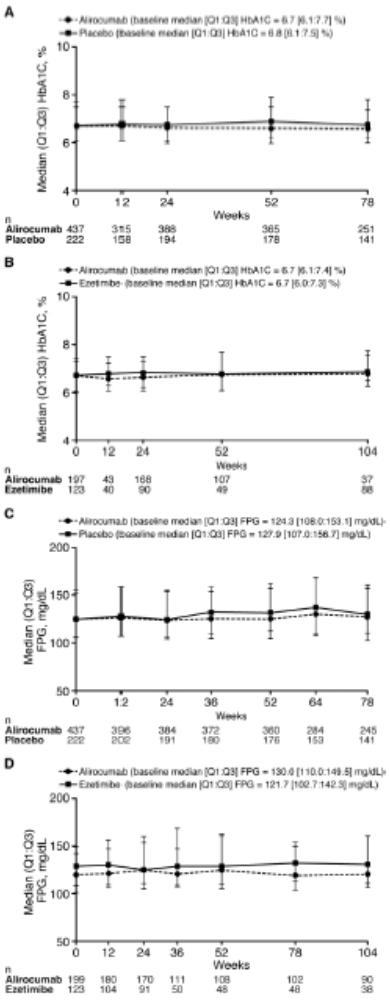
Efficacy and safety of alirocumab among individuals with diabetes mellitus and atherosclerotic cardiovascular disease in the ODYSSEY phase 3 trials

Running title: Alirocumab efficacy and safety in DM and ASCVD

Om P. Ganda MD[1] | Jorge Plutzky MD[2] | Santosh K. Sanganalmath MD, PhD[3] | Maja Bujas-Bobanovic PharmD[4] | Andrew Koren MD[5] | Jonas Mandel MSc[6,7] | Alexia Letierce PhD[6] | Lawrence A. Leiter MD[8]

Diabetes Obes Metab. 2018 May 26

FIGURE 3. Median HbA1C values over time in (A) placebo-controlled and (B) ezetimibe-controlled pools and FPG values over time in (C) placebo-controlled and (D) ezetimibe-controlled pools



CONCLUSION:
Alirocumab significantly reduced LDL-C and other atherogenic lipid parameters, and was generally well tolerated in persons with DM and ASCVD.

Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Ioanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanevsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators

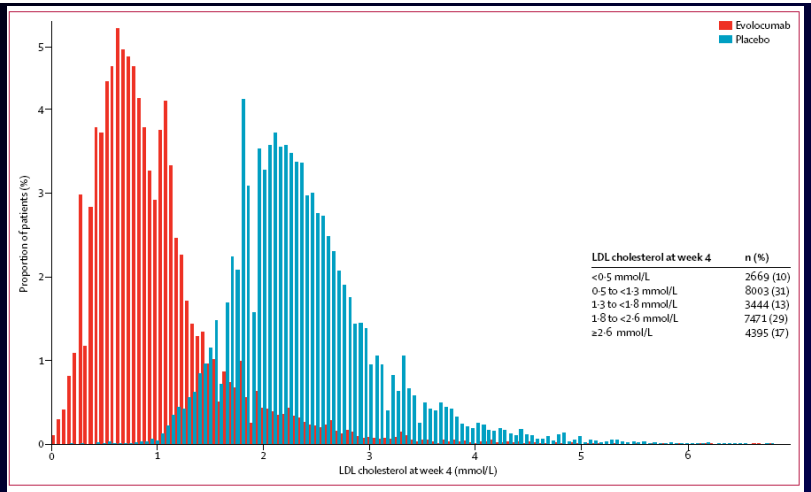


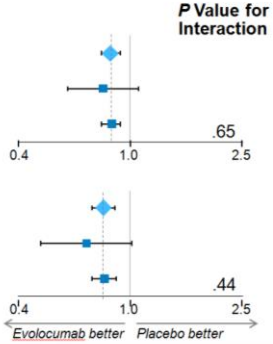
Figure 1: **Distribution of achieved LDL-cholesterol concentrations at 4 weeks in patients who did not have a primary efficacy or prespecified safety event before the study**
Red bars are evolocumab (median 0·8 mmol/L, IQR 0·5–1·2). Blue bars are placebo (median 2·2 mmol/L, IQR 1·9–2·7).

Primary and Key Secondary Endpoints Stratified by Baseline LDL-C

Efficacy outcomes by baseline LDL-C level

Number Events		Primary Endpoint	HR (95% CI)
Evo	Placebo		
86	106	**LDL-C < 70 mg/dL**	0.80 (0.60-1.07)
1258	1457	**LDL-C ≥ 70 mg/dL**	0.86 (0.79-0.92)
		All	0.85 (0.79-0.92)

Number Events		Key Secondary Endpoint	
Evo	Placebo		
48	68	**LDL-C < 70 mg/dL**	0.70 (0.48-1.01)
768	945	**LDL-C ≥ 70 mg/dL**	0.81 (0.73-0.89)
		All	0.80 (0.73-0.88)



Evolocumab significantly reduced risk for the primary and key secondary endpoints in those with baseline LDL-C < 70 mg/dL and ≥ 70 mg/dL, with no evidence of effect modification due to baseline LDL-C level

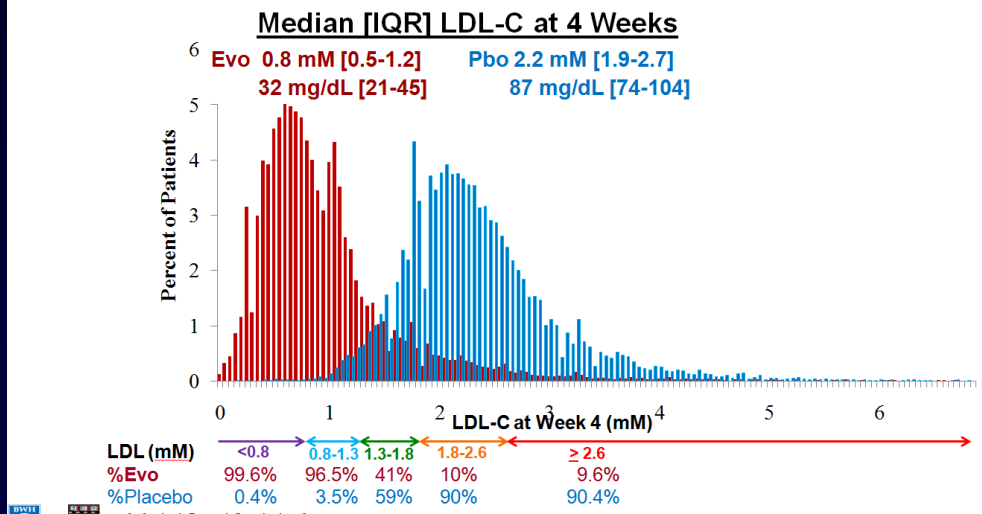
HRs and 95% CIs are shown for the primary (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization) and the key secondary (composite of cardiovascular death, myocardial infarction, and stroke) efficacy composite endpoints in the total population and in patients with baseline LDL-C levels < 70 mg/dL (1.8 mmol/L) vs those with LDL-C levels of at least 70 mg/dL (1.8 mmol/L).
CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein.

AMGEN Cardiovascular

Table S3 - Event Rates and Adjusted Risk of Efficacy Endpoints by Achieved LDL-C Group at Four Weeks

Endpoint	n (%)	Adjusted HR (95% CI)	P_{trend} of Adjusted HRs
Primary Efficacy Composite*			<0·0001
<0·5 mmol/L	217 (8·1)	0·76 (0·64-0·90)	
0·5-1·3 mmol/L	769 (9·6)	0·85 (0·76-0·96)	
1·3-1·8 mmol/L	354 (10·3)	0·94 (0·82-1·09)	
1·8-2·6 mmol/L	793 (10·6)	0·97 (0·86-1·09)	
≥ 2·6 mmol/L	521 (11·9)	referent	
CV death, MI, or stroke			<0·0001
<0·5 mmol/L	134 (5·0)	0·69 (0·56-0·85)	
0·5-1·3 mmol/L	455 (5·7)	0·75 (0·64-0·86)	
1·3-1·8 mmol/L	223 (6·5)	0·87 (0·73-1·04)	
1·8-2·6 mmol/L	498 (6·7)	0·90 (0·78-1·04)	
≥ 2·6 mmol/L	345 (7·8)	referent	
Cardiovascular death			0·83
<0·5 mmol/L	42 (1·6)	0·99 (0·67-1·47)	
0·5-1·3 mmol/L	140 (1·7)	1·07 (0·80-1·43)	
1·3-1·8 mmol/L	54 (1·6)	0·99 (0·69-1·43)	
1·8-2·6 mmol/L	134 (1·8)	1·14 (0·85-1·53)	
≥ 2·6 mmol/L	77 (1·8)	referent	
Myocardial infarction			<0·0001
<0·5 mmol/L	71 (2·7)	0·59 (0·45-0·78)	
0·5-1·3 mmol/L	266 (3·3)	0·69 (0·57-0·84)	
1·3-1·8 mmol/L	141 (4·1)	0·87 (0·69-1·09)	
1·8-2·6 mmol/L	297 (4·0)	0·85 (0·71-1·03)	
≥ 2·6 mmol/L	214 (4·9)	referent	
Stroke			0·0054
<0·5 mmol/L	45 (1·7)	0·81 (0·55-1·18)	
0·5-1·3 mmol/L	103 (1·3)	0·63 (0·47-0·85)	
1·3-1·8 mmol/L	56 (1·6)	0·81 (0·57-1·14)	
1·8-2·6 mmol/L	134 (1·8)	0·90 (0·68-1·20)	
≥ 2·6 mmol/L	92 (2·1)	referent	
Coronary revascularization			<0·0001
<0·5 mmol/L	111 (4·2)	0·63 (0·50-0·78)	
0·5-1·3 mmol/L	446 (5·6)	0·78 (0·67-0·91)	
1·3-1·8 mmol/L	215 (6·2)	0·91 (0·76-1·09)	
1·8-2·6 mmol/L	471 (6·3)	0·91 (0·78-1·05)	
≥ 2·6 mmol/L	326 (7·4)	referent	
Unstable angina			0·73
<0·5 mmol/L	44 (1·6)	1·18 (0·80-1·74)	
0·5-1·3 mmol/L	132 (1·6)	1·04 (0·78-1·39)	
1·3-1·8 mmol/L	51 (1·5)	0·95 (0·66-1·37)	
1·8-2·6 mmol/L	129 (1·7)	1·09 (0·82-1·47)	
≥ 2·6 mmol/L	80 (1·8)	referent	

Achieved LDL-C at 4 Weeks



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

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Conclusions

- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 1 mM)
- A strong progressive relationship of achieved LDL-C and CV events seen, down to LDL <0.26 mM (<10 mg/dL)
- No excess in safety events with very low achieved LDL-C <0.5 mM (<20 mg/dL) at 2.2 years

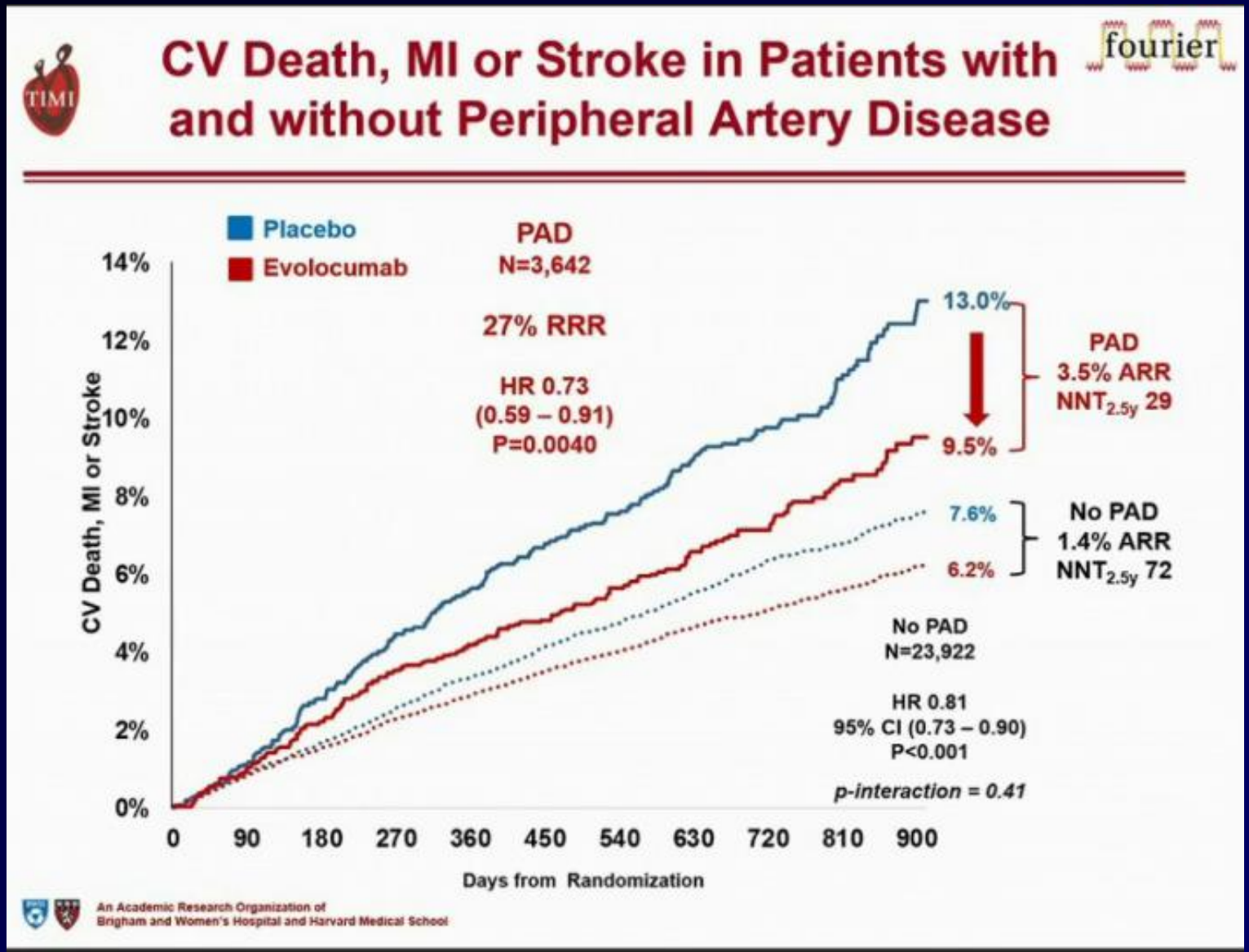
These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease

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

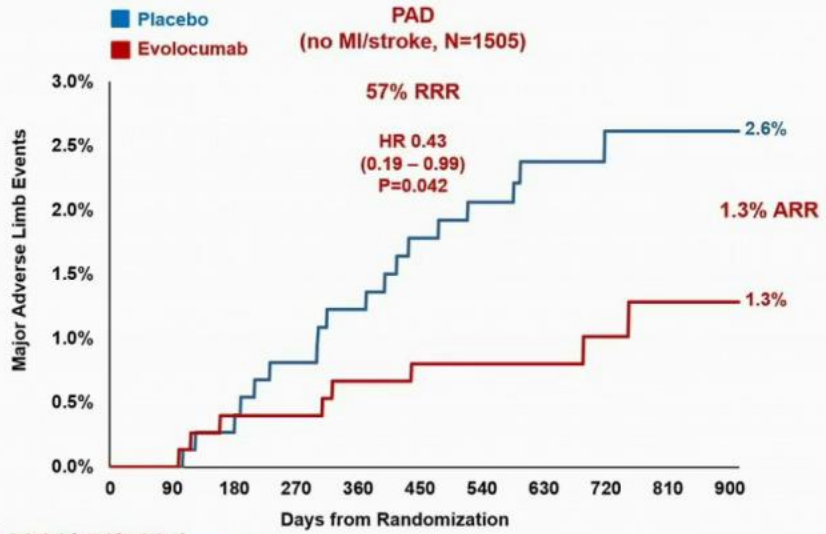
Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

2017 Scientific Sessions OnDemand

Evolocumab and Outcomes in Patients With Peripheral Artery Disease



Major Adverse Limb Events in Patients with PAD and no MI or Stroke



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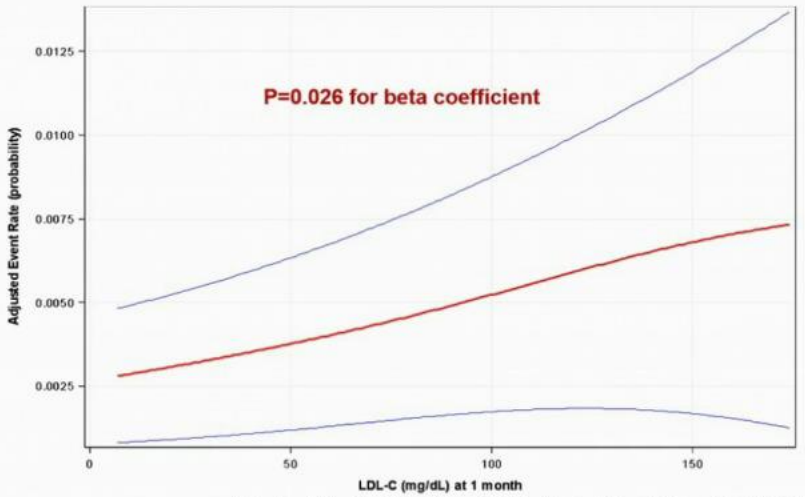
Achieved LDL-C and Major Adverse Limb Events



adjusted for significant (p<0.05) predictors of LDL-C cholesterol at 1 month after randomization including age, BMI, LDL-C at baseline, male sex, race, randomized in North America, current smoker, high intensity statin.

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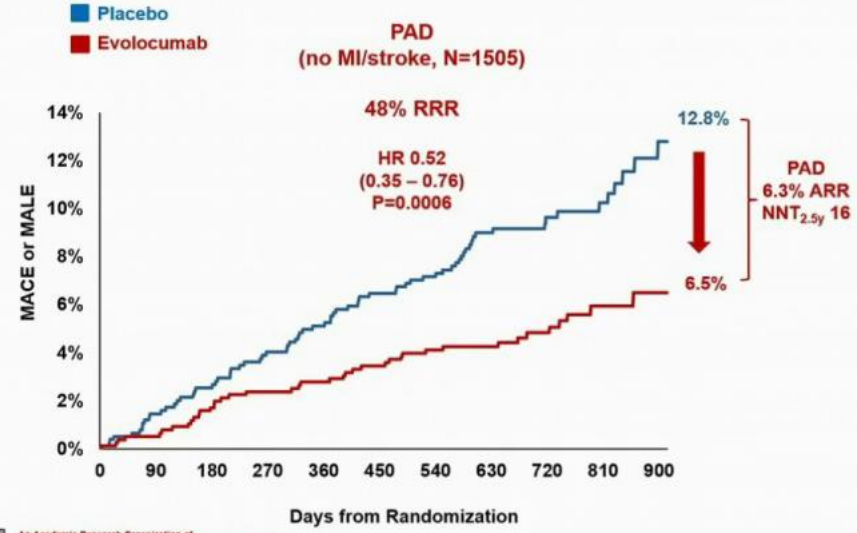
MACE or MALE
In Patients with PAD and no MI or Stroke



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Summary

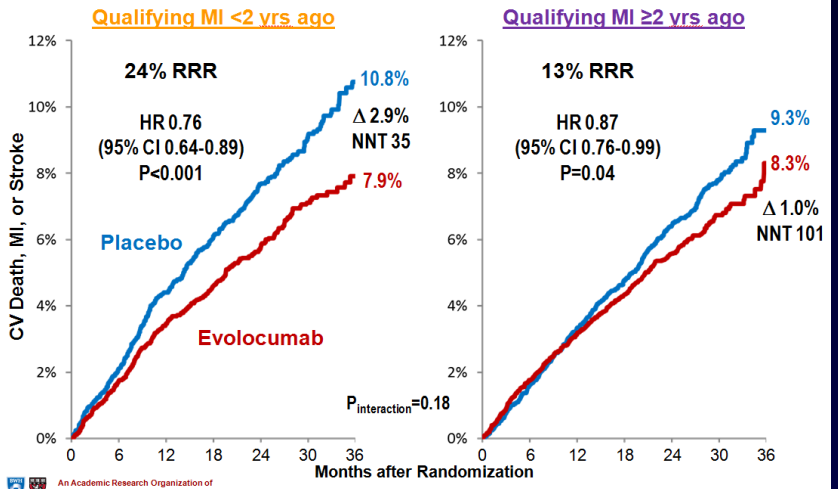
- Patients with PAD are at heightened risk of MACE and MALE
- LDL-C lowering with evolocumab in patients with PAD:
  - Reduces major adverse CV events with robust ARR
  - Reduces major adverse limb events
- Benefits extend to PAD without prior MI or stroke with an ARR for MACE or MALE of 6.3% (NNT 16) at 2.5 years

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

Conclusion

LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of MI or stroke, to reduce the risk of MACE and MALE

Benefit of EvoMab Based on Time from Qualifying MI



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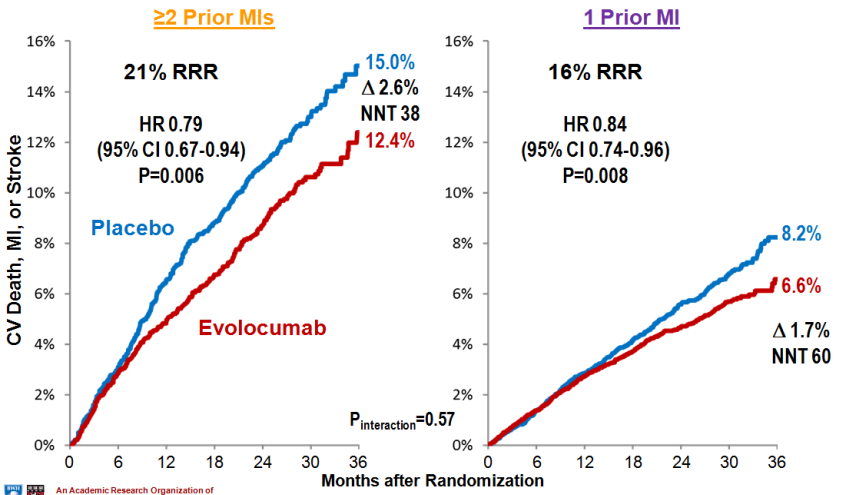
Sabatine MS et al. Circulation 2018. Published online April 6, 2018

Benefit of EvoMab Based on # of Prior MIs



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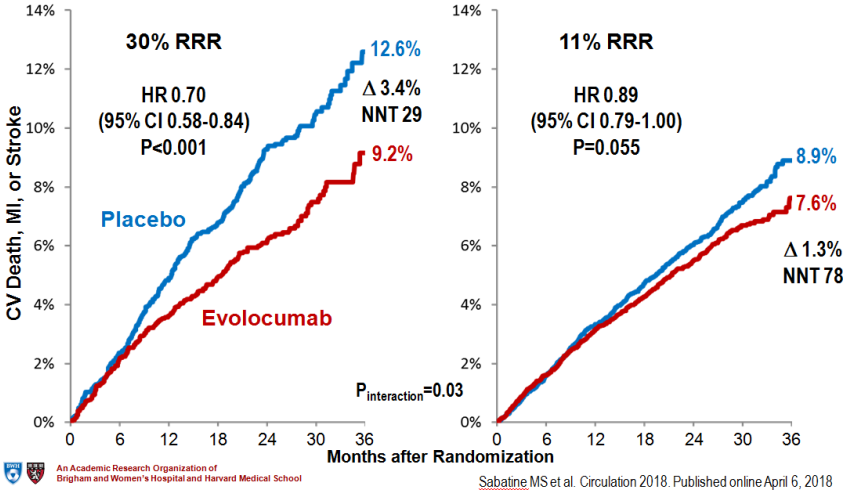
Sabatine MS et al. Circulation 2018. Published online April 6, 2018

Benefit of EvoMab Based on Multivessel Disease



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

Sabatine MS et al. Circulation 2018. Published online April 6, 2018

Summary

- Patients (1) closer to their most recent MI,
  (2) with multiple prior MIs, or
  (3) with multivessel disease
  are at 34-90% ↑ risk for major vascular events
- These patients experience substantial:
  - relative risk reductions (21-30%) and
  - absolute risk reductions (2.6-3.4% over 3 yrs)
  with intensive LDL-C lowering w/ the PCSK9i evolocumab

These readily ascertainable clinical features offer one approach to tailoring therapy

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

Sabatine MS et al. Circulation 2018. Published online April 6, 2018

Characterization of Types and Sizes of Myocardial Infarction Reduced with Evolocumab in FOURIER

Stephen D Wiviott, Robert P Giugliano, David A Morrow, Gaetano M De Ferrari, Basil S Lewis, Kurt Huber, Julia F Kuder, Sabina A Murphy, Danielle M Forni, Christopher Kurtz, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen, Marc S Sabatine

On behalf of the FOURIER Investigators

American Heart Association Scientific Sessions
November 13, 2017

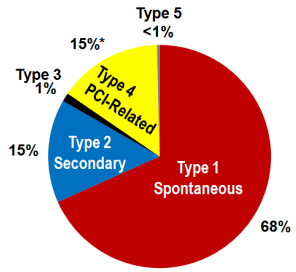
SC-EU-AMG145-00780
Approved November 2017

SC-IT-AMG145-00302_11_2017

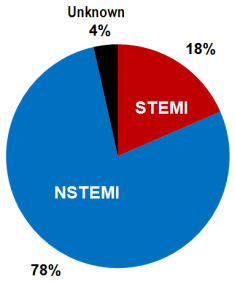
Type of MI

1288 total myocardial infarctions occurred in the trial

Universal MI Type

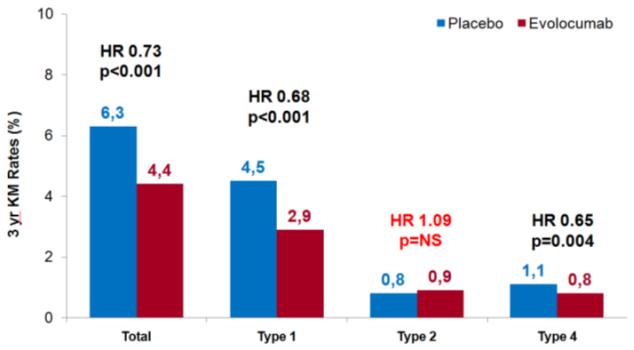


ECG Categorization



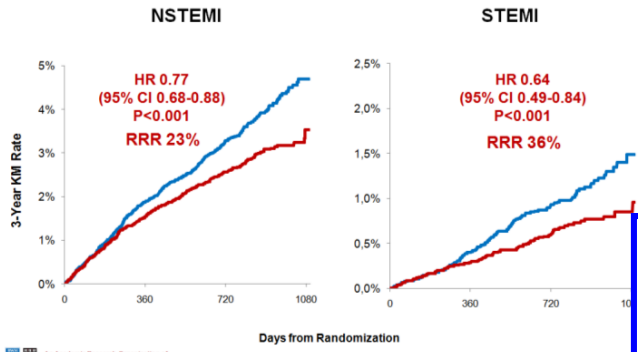
*25 Type 4a, 99 Type 4b, 70 Type 4c

Effect of Evolocumab by Universal MI Type



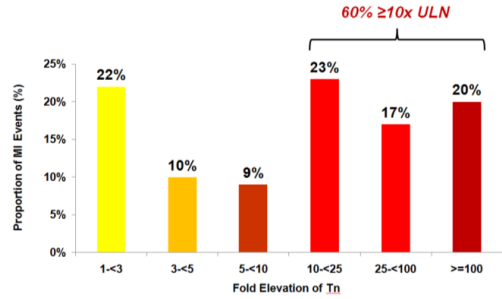
Due to small numbers, Types 3 and 5 are not presented individually

Effect of Evolocumab by MI Type: NSTEMI and STEMI

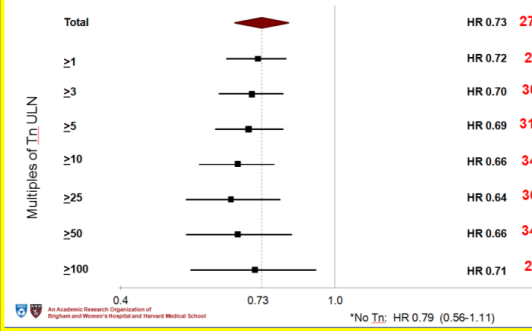


MI Size

1288 total MI, 1150 with Tn Size Data



Effect of Evolocumab by MI Size Based on Peak Tn/ULN*



*No Tn: HR 0.79 (0.56-1.11)

Summary

- MI was the commonest of the first primary composite outcomes in this population with stable atherosclerosis
- Type 1 (spontaneous) and NSTEMI categories predominated
- Addition of the PCSK9 inhibitor evolocumab to statin therapy reduced MI, with consistent reductions of:
  - Larger MI
  - Spontaneous & PCI-related MI [w/ no effect on Type 2 (ischemic mismatch)]
  - STEMI and NSTEMI
- MI reduction tended to be greater after the 1st 6 months of therapy. The relatively short trial period may, therefore have limited the overall effect.

Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER

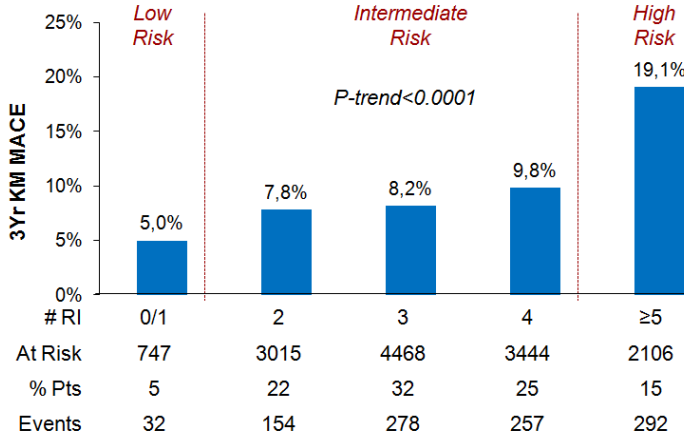
Erin A Bohula[1], David A Morrow[1], Terje R. Pedersen[2], Estella Kanevsky[1], Sabina A Murphy[1], Robert P Giugliano[1], Peter S. Sever[3], Anthony C. Keech[4], and Marc S Sabatine[1]

[1]TIMI Study Group, Brigham & Women's Hospital, Boston, MA, USA
[2]Ullevål University Hospital, Oslo, Norway
[3]Imperial College, London, UK
[4]University of Sydney, Sydney, Australia

RESULTS

Figure 1: Risk Stratification for MACE with Placebo

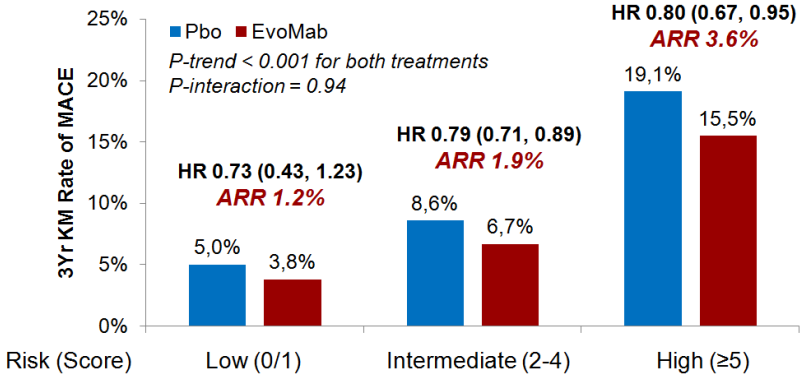
Risk Indicators	Points
CHF	1
HTN	1
Age ≥ 75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR < 60	1
Current Smoking	1
Prior MI	1
Max Possible	10



- The integer-based scheme showed a strong, graded relationship with the rate of CV death, MI or CVA and the components at 3 yrs in both treatment arms (Fig 1; p-trend < 0.0001 for all endpoints; c-statistic = 0.61 [0.67 in prior validation set]).

RESULTS

Figure 3: MACE by Risk Category & Randomized Treatment



- Low-risk pts had a 1.2% ARR, intermediate-risk a 1.9% ARR and high-risk a 3.6% ARR in MACE at 3 years with EvoMab vs Pbo, ***translating to a NNT3Yr of 83, 53 and 28***, respectively (Fig 3).

American Heart Association. life is why | SCIENTIFIC SESSIONS

ORION-1

Inclisiran inhibits PCSK9 synthesis by RNA interference

Planned interim analysis of a multi-center randomized controlled dose-finding trial

Kausik K Ray, Ulf Landmesser, Lawrence A Leiter, David Kallend, Peter Wijngaard
Robert Dufour, Timothy Hall, Mahir Karakas, Traci Turner, Frank LJ Visseren,
R Scott Wright, and John JP Kastelein

On behalf of the ORION-1 investigators

Background and rationale
Inclisiran: Under investigation for LDL-C lowering

- ASCVD remains a challenge to global health[1]
- LDL-C reduction is a proven strategy to prevent ASCVD[2]
- Statins are the cornerstone of treatment but with limitations[2]
- mAbs that block PCSK9 have demonstrated significant LDL-C lowering with or without statins[3,4]
- mAbs that block PCSK9 require 12-24 s.c. injections per year (totaling ~2-5 grams)[5,6]
- Administrative and financial burdens leave room for more efficient agents
- RNAi a highly efficient approach to inhibit PCSK9 synthesis in the liver[7,8]
- Phase I 300 mg s.c. inclisiran lowered LDL-C ~50% for 4-6 months (n=69)[9]

1: World Health Organization
2: AHA guidelines on dyslipidemia
3: Sabatine MS et al. N Engl J Med 2015;372:1500-9
4: Robinson JG et al. N Engl J Med 2015;372:1489-99
5: https://www.repathahcp.com/dosing
6: https://www.praluenthcp.com/dosing
7: Wittrup A & Lieberman J Nature Rev Gen 2015;16: 543-52
8: Fitzgerald K et al. Lancet 2013;9911:60-8
9: Fitzgerald K et al. N Engl J Med online publication 2016 November 13

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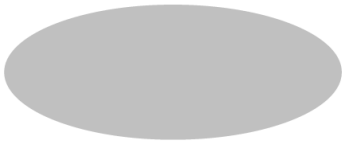
PCSK9 synthesis inhibition via RNA interference
Inclisiran harnesses a natural catalytic process

- Synthetic double strand 21-23mer oligonucleotide
- 3x GalNAc at sense 3' end enables hepatic-specific uptake via ASGP receptor
- Chemically modified to prevent RNAse degradation
- Dicer separates antisense strand – and incorporates it into RISC
- RISC degrades PCSK9 mRNA catalytically to halt PCSK9 protein synthesis in the liver

RISC - RNA induced silencing complex



- RISC degrades PCSK9 mRNA catalytically to halt PCSK9 protein synthesis in the liver

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Patient population
High cardiovascular risk and elevated LDL-C

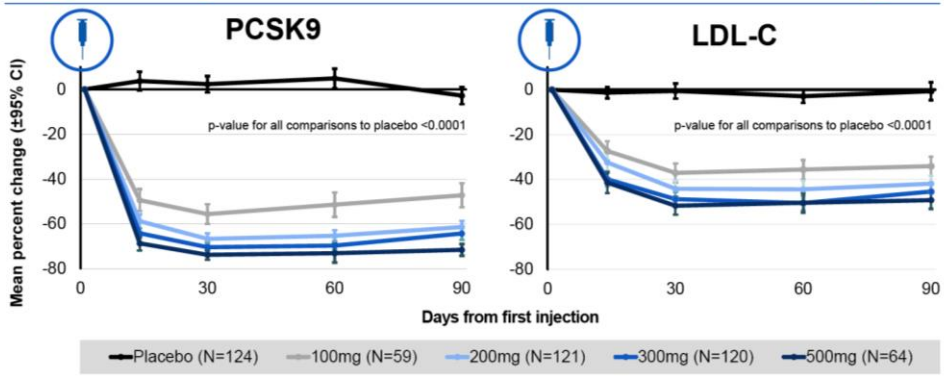
Inclusion criteria

- Age ≥18 years
- With ASCVD - LDL-C >70 mg/dL
- High risk primary prevention LDL-C >100
- TG <400 mg/dL
- eGFR ≥30 mL/min
- Maximally tolerated statin
- Stable lipid Rx for ≥30 days

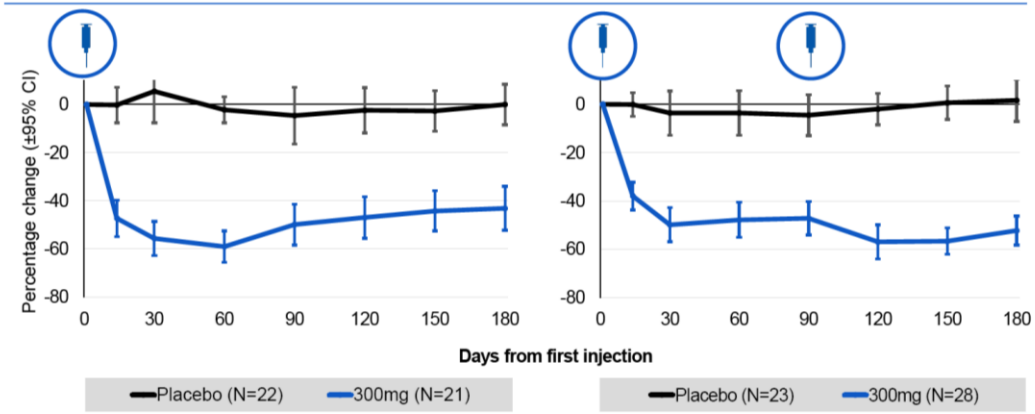
Exclusion criteria

- Significant comorbidity
- HbA1c ≥10%
- NYHA Class II-IV HF
- MACE <6 months
- Uncontrolled BP
- Active liver disease
- Pregnancy or risk | nursing
- Cognitive impairment

Efficacy of one dose of inclisiran up to day 90
Significant, durable PCSK9 and LDL-C lowering

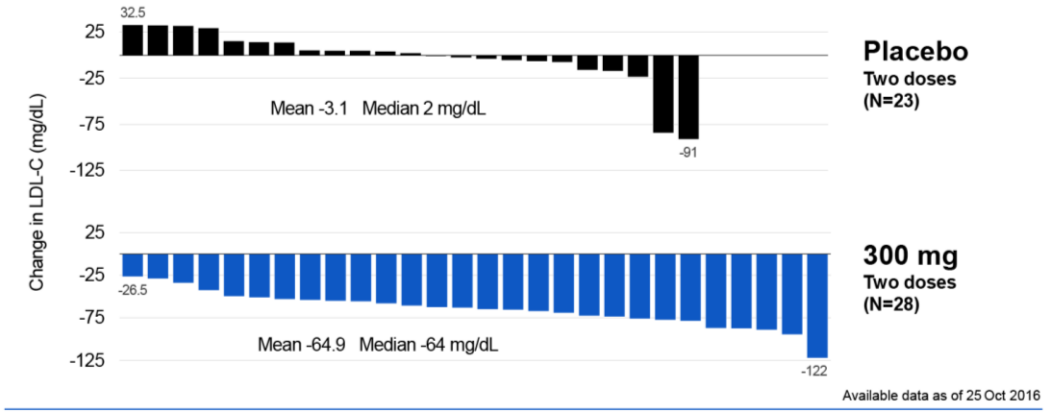


One dose and two doses of inclisiran up to day 180
Efficacy of 300 mg versus placebo on LDL-C



Available data as of 25 Oct 2016

Individual patient response at day 180
Absolute change in LDL-C from baseline



Available data as of 25 Oct 2016

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Conclusions
Inclisiran: Phase III-ready investigational compound

- Inclisiran inhibits PCSK9 synthesis by RNA interference and lowers LDL-C significantly
  - One dose of 300 mg achieves mean 51% LDL-C reduction
  - Two doses of 300 mg achieve mean 57% LDL-C reduction
- Inclisiran is well tolerated with no material safety issues
- Potential for biannual or triannual dosing affirmed
- Results of ORION-1 support start of Phase III
- The efficacy, safety and dosing profile of inclisiran are likely to ensure significant and durable reductions in LDL-C and thus potentially impact cardiovascular outcomes

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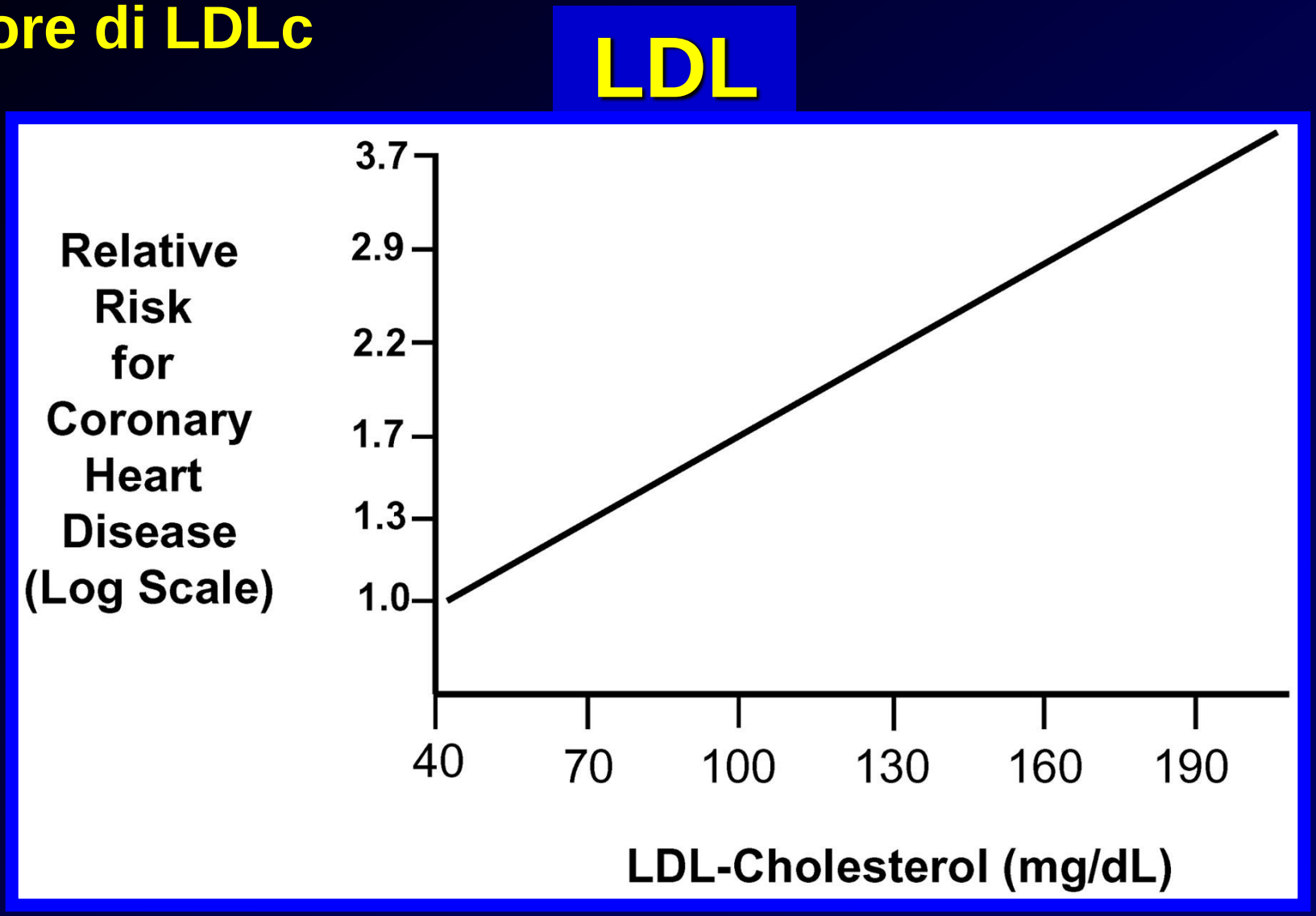
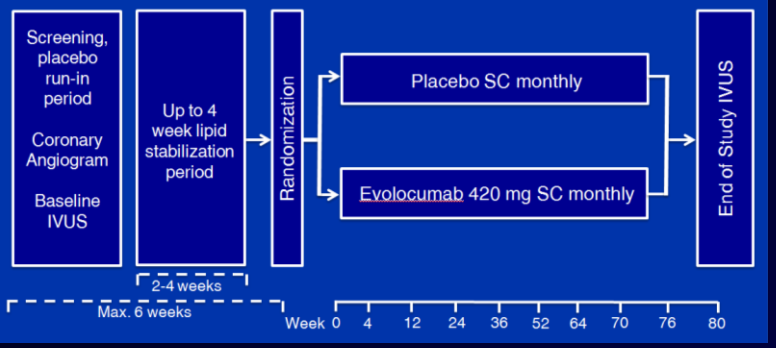
FENOTIPO:
valore di LDLc



Grundy 2004

GLAGOV Trial Schematic

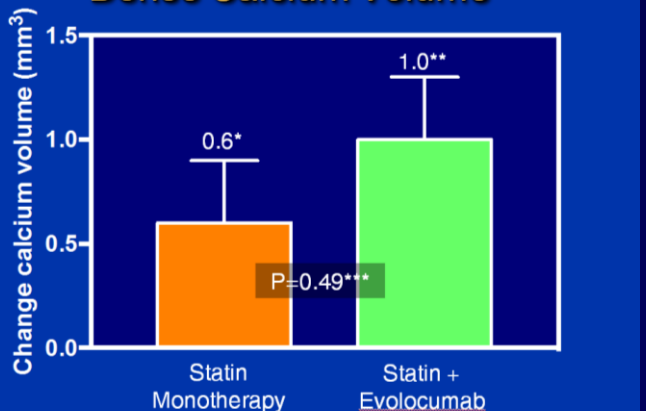
968 patients with angiographic CAD, stable statin dose and LDL-C ≥80 mg/dL OR 60-80 mg/dL and 1 major or 3 minor risk factors



GLAGOV VH Substudy

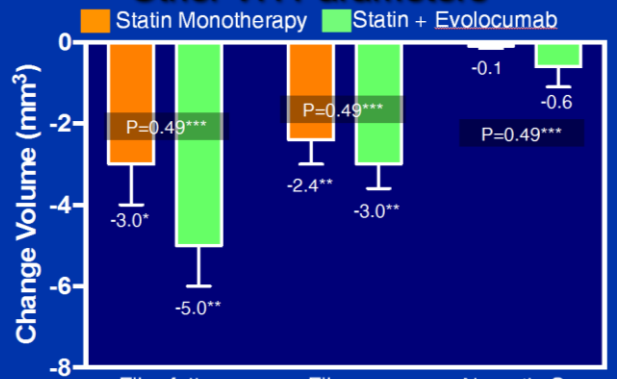
- Determine if evolocumab produced changes in VH-derived plaque components (dense calcium, fibrous, fibrofatty, necrotic core) compared with placebo in 331 patients with evaluable VH imaging.
- The prespecified statistical plan sought to compare changes in volumetric measures, adjusting for baseline values and multiple comparisons.
- The primary endpoint was the absolute change in dense calcium volume from baseline to week 78.

Primary Endpoint: Change in Normalized Dense Calcium Volume



* P<0.05 and ** P<0.001 compared with baseline (exploratory analysis). *** Hochberg adjusted p value

Secondary Endpoint: Change in Volume of Other VH Parameters



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Characterization of Types and Sizes of Myocardial Infarction Reduced with Evolocumab in FOURIER

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On behalf of the FOURIER Investigators

American Heart Association Scientific Sessions
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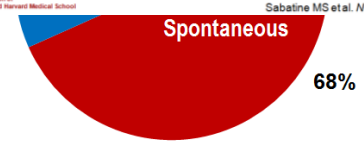
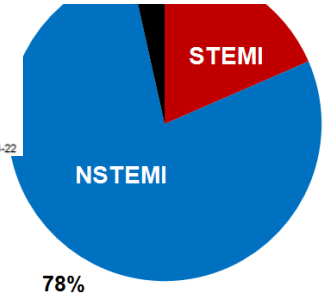
SC-EU-AMG145-00780
Approved November 2017

SC-IT-AMG145-00302_11_2017

Types of CV Ou

Endpoint	Evolocum (N=13,78		
	3-yr Ka		
CVD, MI, stroke, UA, or revasc	12.6		
CV death, MI, or stroke	7.9		
Cardiovascular death	2.5		
MI	4.4		
Stroke	2.2		
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86)

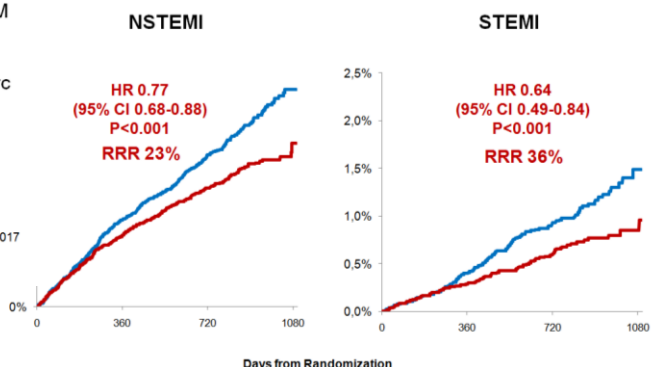




Sabatine MS et al. *NEJM* 2017; 376:1713-22

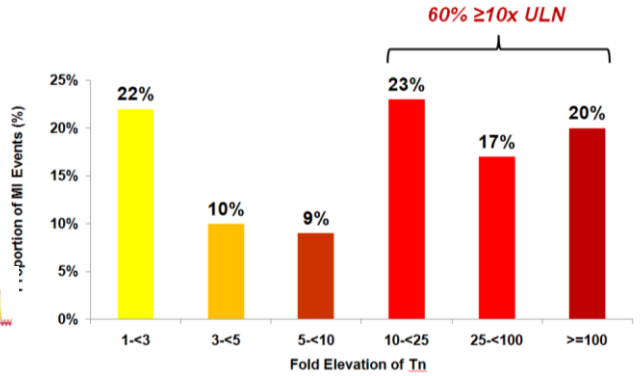
*25 Type 4a, 99 Type 4b, 70 Type 4c

Effect of Evolocumab by MI Type: NSTEMI and STEMI

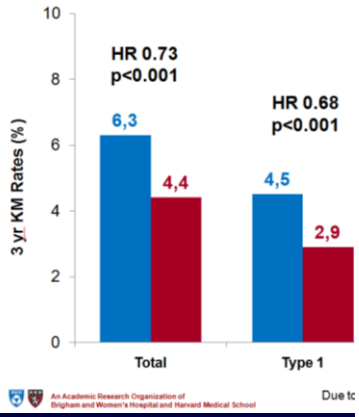


MI Size

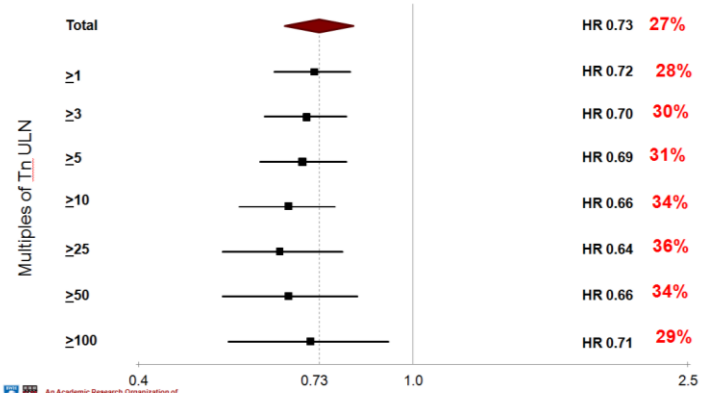
1288 total MI, 1150 with Tn Size Data



Effect of Evolocumab by Universal MI Type



Effect of Evolocumab by MI Size Based on Peak Tn/ULN*



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Summary

- MI was the commonest of the first primary composite outcomes in this population with stable atherosclerosis
- Type 1 (spontaneous) and NSTEMI categories predominated
- Addition of the PCSK9 inhibitor evolocumab to statin therapy reduced MI, with consistent reductions of:
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The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,
Ph. Gabriel Steg
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402

ODYSSEY OUTCOMES

Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented
Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

The ODYSSEY OUTCOMES Trial: Topline Results

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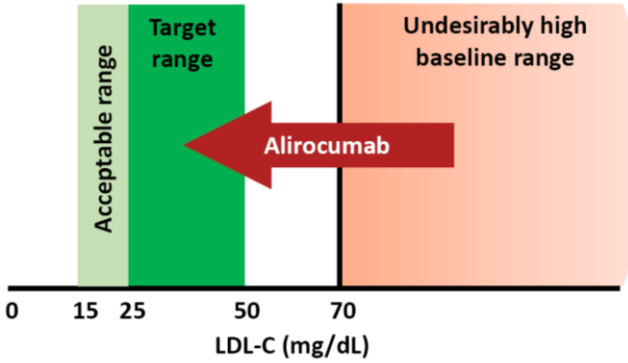
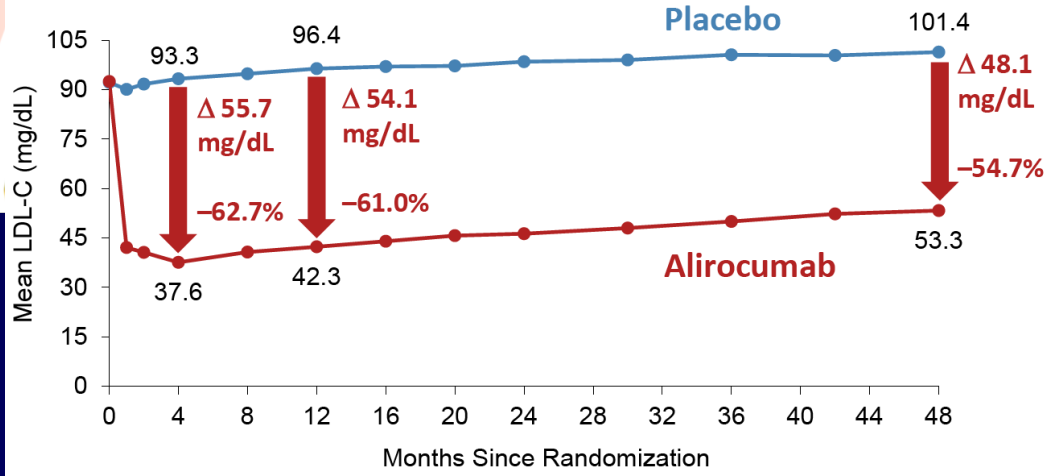
ClinicalTrials.gov: NCT01663402

A Target Range for LDL-C

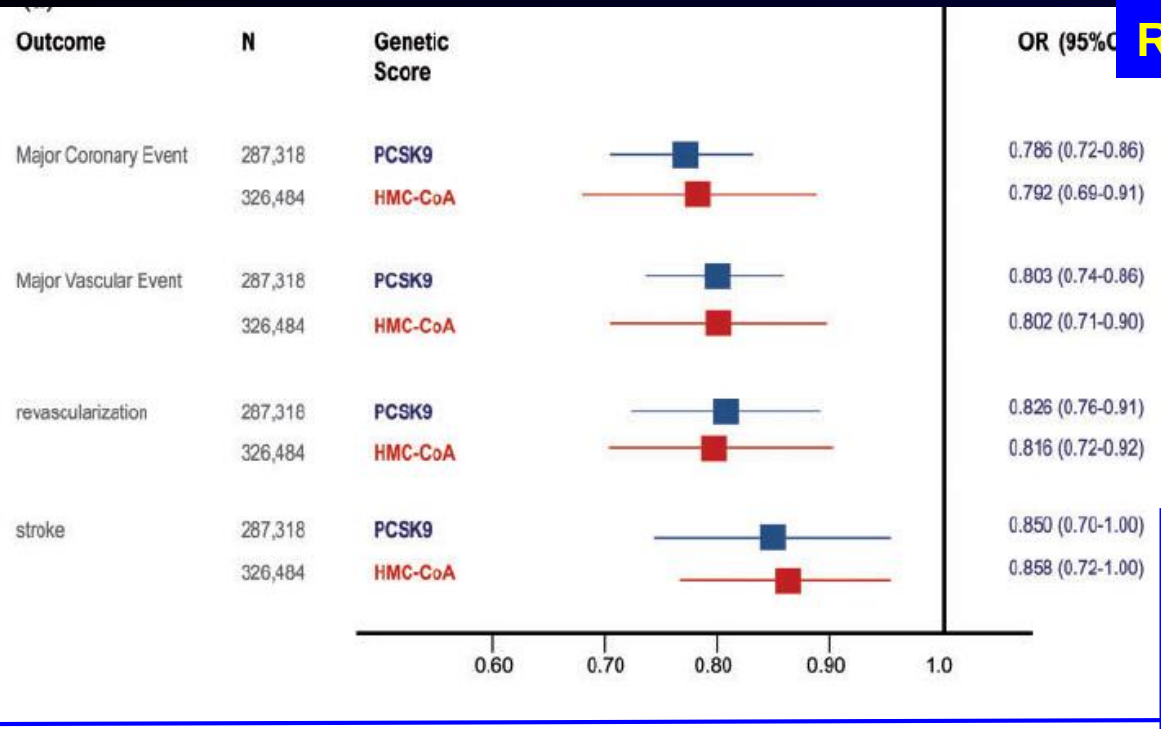


Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

LDL-C: On-Treatment Analysis



Randomizzazione mendeliana



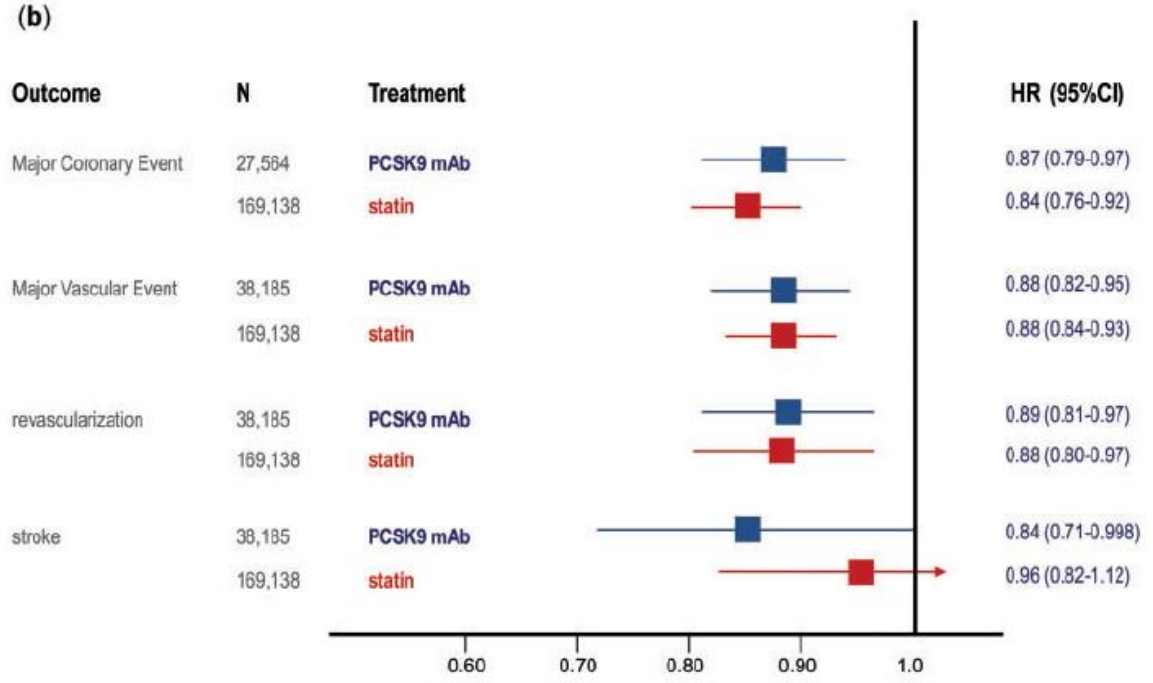
Effect of variants that mimic PCSK9 inhib as compared to variants that mimic statins on the risk of various cardiovascular outcomes per 0.25mmol/L reduction in LDLc

European Heart Journal (2017) 0, 1–6
doi:10.1093/eurheartj/ehx450

CURRENT OPINION

Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration

Brian A. Ference[1], Christopher P. Cannon[2], Ulf Landmesser[3], Thomas F. Lüscher[4], Alberico L. Catapano[5*†], and Kausik K. Ray[6†]



Effect of PCSK9 Inhib per mmol/L reduction in LDL-C in a meta-analysis of the FOURIER and SPIRE-2 trials during the first year of treatment as compared with the effect of statins during the first year of treatment per mmol/L reduction in LDL-C as reported by the Cholesterol Treatment Trialists (CTT) Collaboration

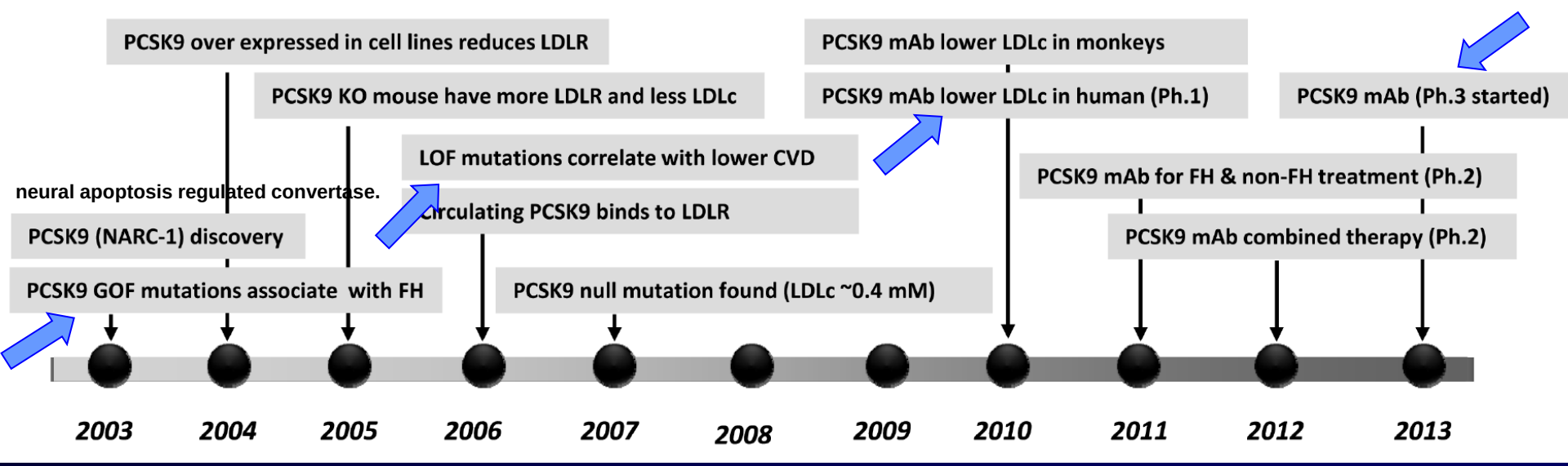
Studi di intervento

PCSK9

A Key Modulator of Cardiovascular Health

Nabil G. Seidah, Zuhier Awan, Michel Chrétien, Majambu Mbikay

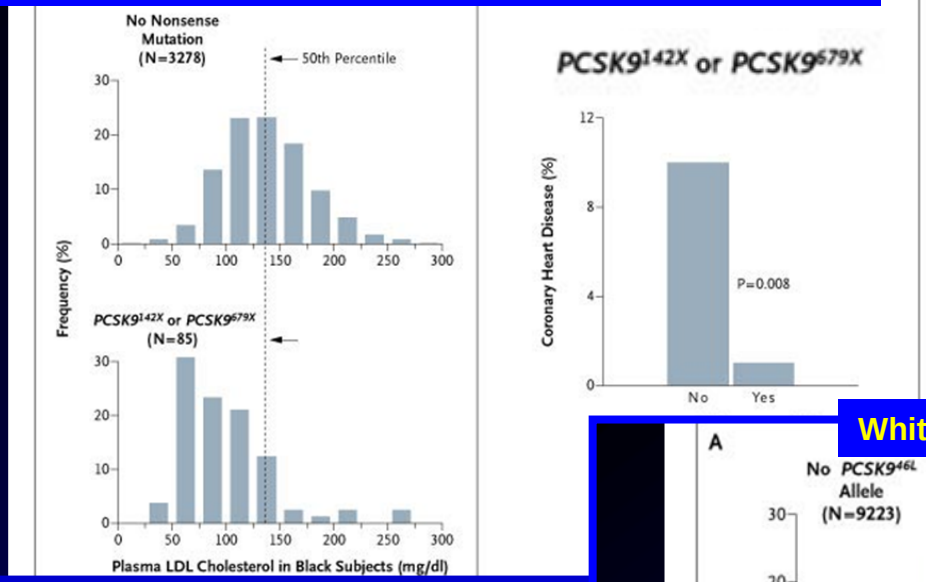
Circ Res. 2014;



conversion of an inactive secretory precursor into active product(s) is catalyzed by a special group of proteases denoted as the proprotein convertases (PCs). From 1990 to 1999, 8 mammalian PCs were discovered and shown to be responsible for the tissue-specific processing of various secretory Precursors. The ninth and last member of the family, known as PC subtilisin kexin 9 (PCSK9), was reported in early 2003.

adult liver hepatocytes ++, small intestine, Kidney ,pancreas, developing CNS, embryonic ts; Ts specificity

Black Subjects, Presence or Absence of a *PCSK9142X* or *PCSK9679X* Allele.



Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coror
Subjects, According to the Presence or Absence of a *PCSK914*
In Panel A, the distribution of plasma LDL cholesterol levels at baseline among
PCSK9142X or *PCSK9679X* allele (top) is compared with the distribution of levels
of these two alleles (bottom). Panel B shows the percentage of participants from
coronary heart disease at baseline and in whom coronary heart disease develop
convert values for LDL cholesterol to millimoles per liter,

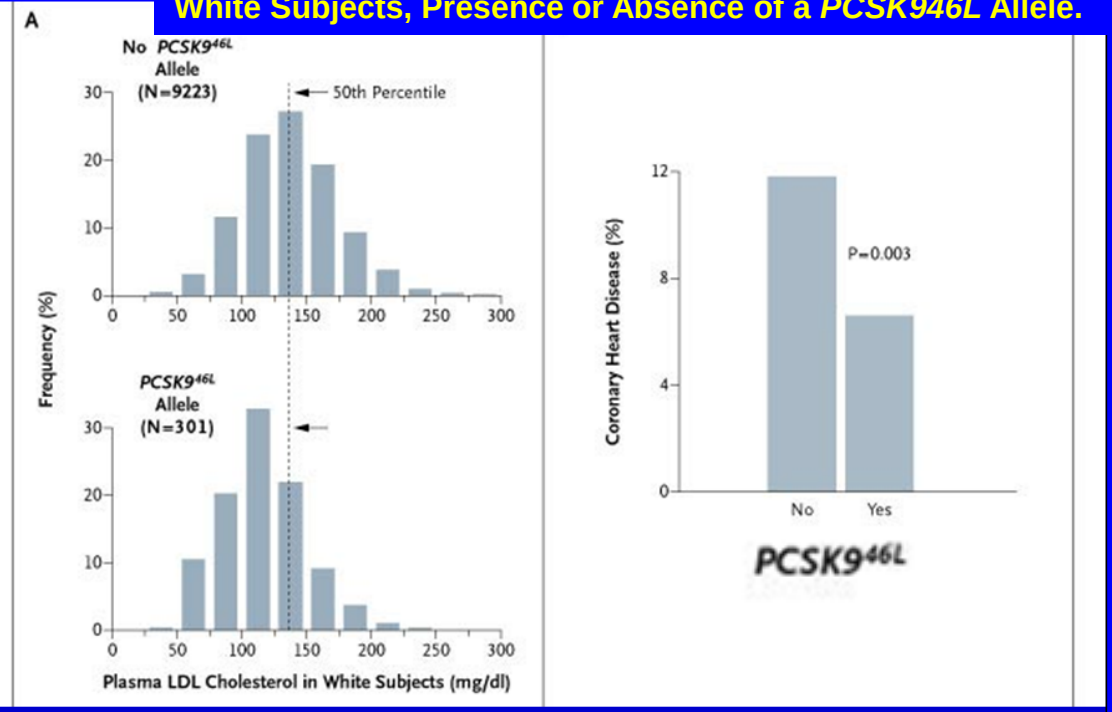
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

White Subjects, Presence or Absence of a *PCSK946L* Allele.



Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK946L* Allele.

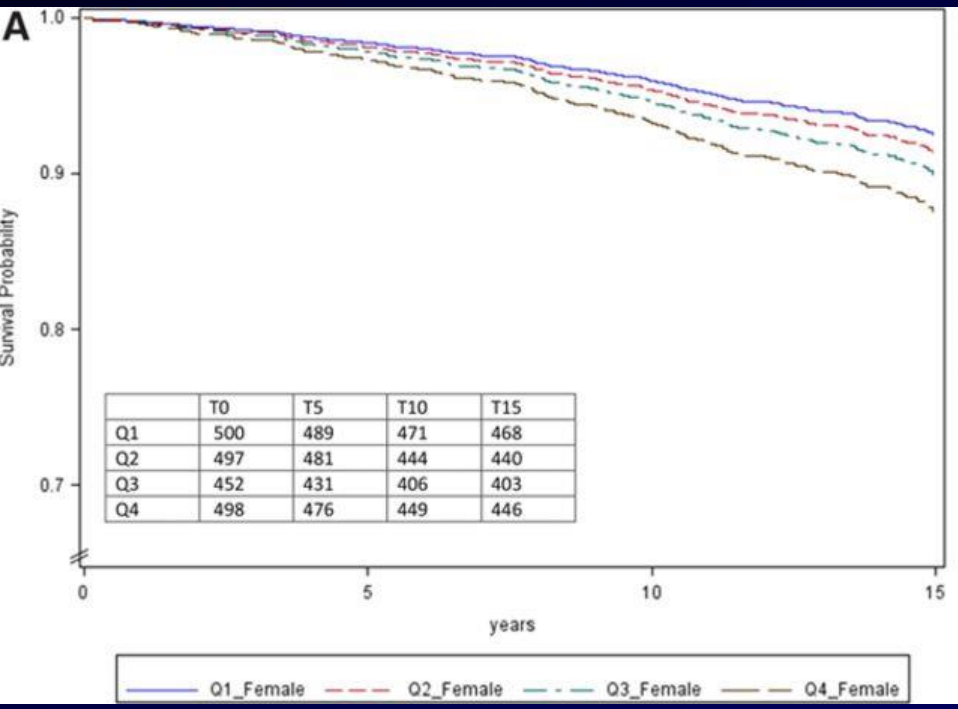
In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 9223 white subjects who did not have a *PCSK946L* allele (top) is compared with the distribution of levels among the 301 white subjects who were either heterozygous or homozygous for this allele (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

Cohen NEJM 2006

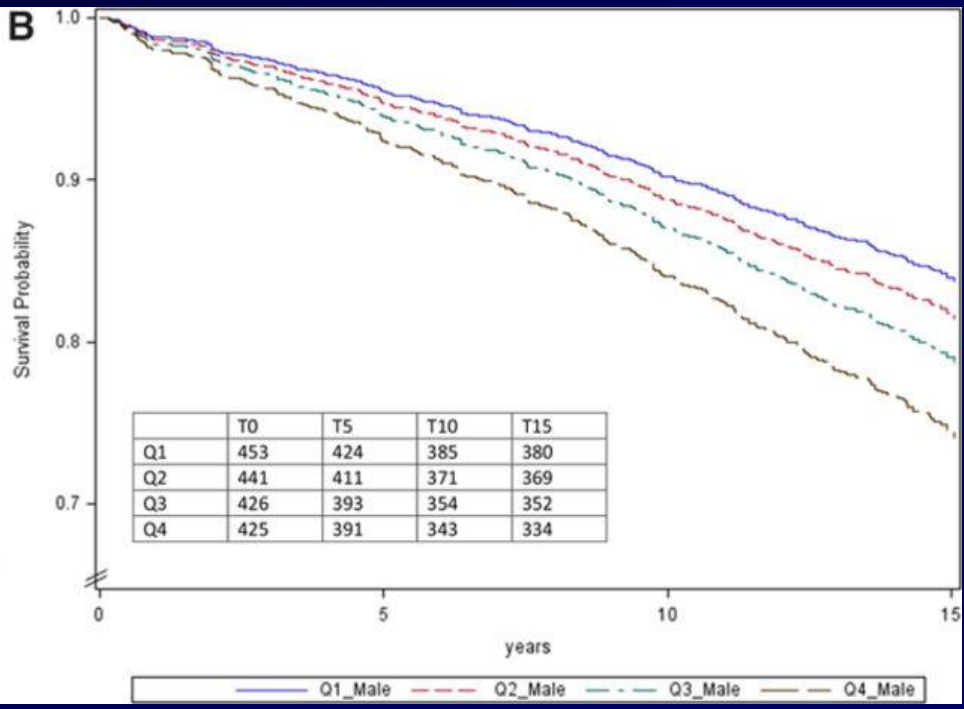
Circulating Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Predicts Future Risk of Cardiovascular Events Independently of Established Risk Factors

Karin Leander, Anders Mälarstig, Ferdinand M. van't Hooft, Craig Hyde, Mai-Lis Hellénius, Jason S. Troutt, Robert J. Konrad, John Öhrvik,Anders Hamsten and Ulf de Faire

Circulation 2016



	T0	T5	T10	T15
Q1	500	489	471	468
Q2	497	481	444	440
Q3	452	431	406	403
Q4	498	476	449	446



	T0	T5	T10	T15
Q1	453	424	385	380
Q2	441	411	371	369
Q3	426	393	354	352
Q4	425	391	343	334