FOURIER Study

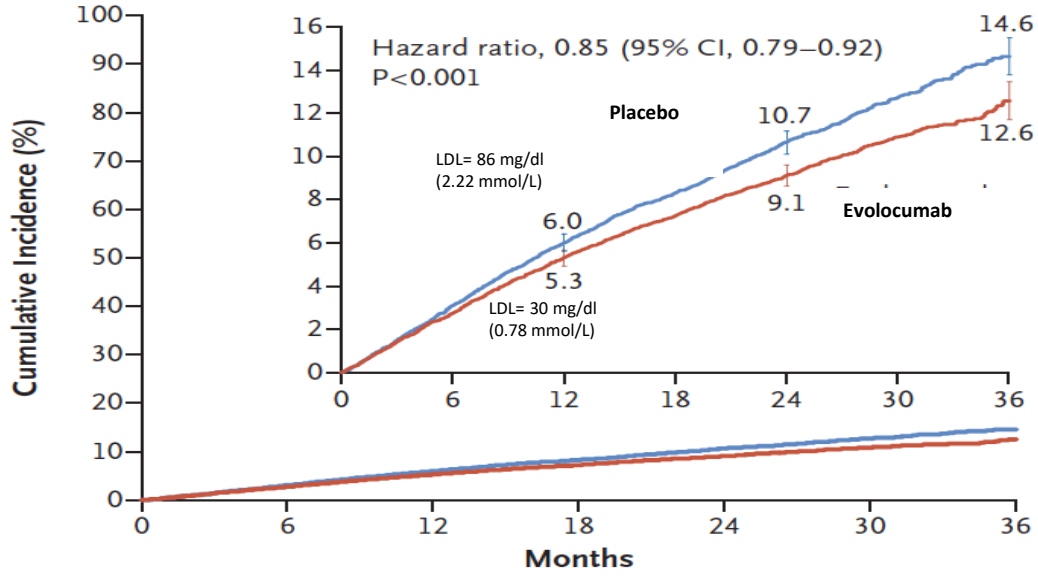
27,564 pts.

Atherosclerosis + Risk enhancer + **LDL ≥ 70 mg/dl* ApoB ≥ 80 mg/dl* Non-HDL ≥ 100 mg/dl***

*Despite ATV ≥ 20 mg/d

- **Evolocumab** 140 mg/2 weeks SC ó 420 mg/month
- **Placebo**

Primary Efficacy End Point



CV death, MI, stroke, Unst Ang., Cor. revasc.

Sabatine et al. N Engl J Med 2017; 376:1713-1722

Reunión Anual de la Sección de Riesgo Vascular y Rehabilitación Cardiaca de la SEC
San Sebastián Donostia 2018
25 y 26 de Mayo
Hotel Silken Amara plaza
www.reunionriesgovascularsec.com
info@ reunionriesgovascularsec.com
SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA
Sección de Riesgo Vascular y Rehabilitación Cardiaca

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

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.

Key Exclusion Criteria

- Uncontrolled hypertension
- NYHA class III or IV heart failure;

  LVEF <25% if measured
- History of hemorrhagic stroke
- Fasting triglycerides >400 mg/dL

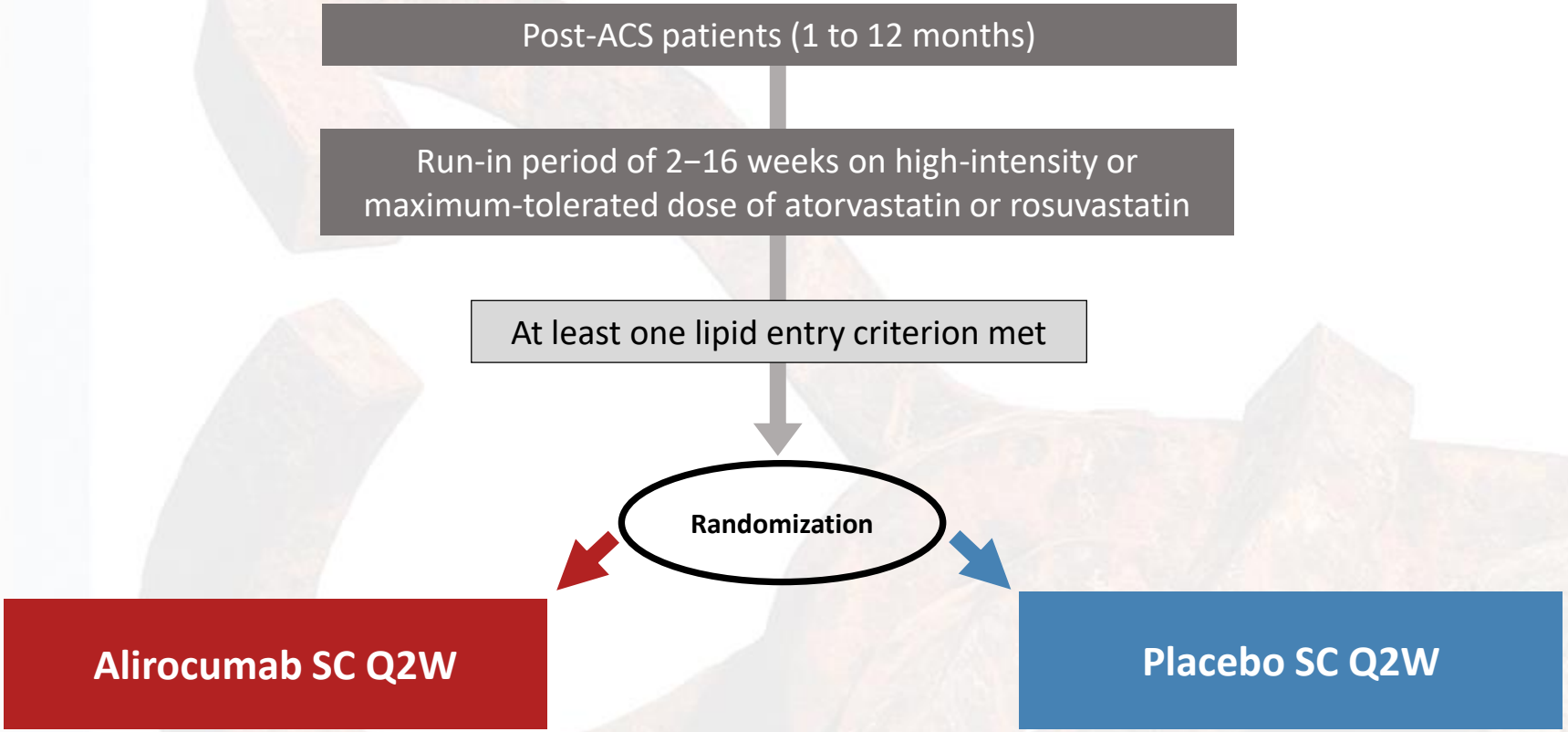
  (4.52 mmol/L)
- Use of fibrates other than fenofibrate or fenofibric acid
- Recurrent ACS within 2 weeks prior to randomization visit
  - Coronary revascularization performed within 2 weeks prior to randomization visit, or planned after randomization
- Liver transaminases >3 × ULN;

  hepatitis B or C infection
- Creatine kinase >3 × ULN
- eGFR <30 mL/min/1.73 m^2
- Positive pregnancy test

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal

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

Treatment Assignment

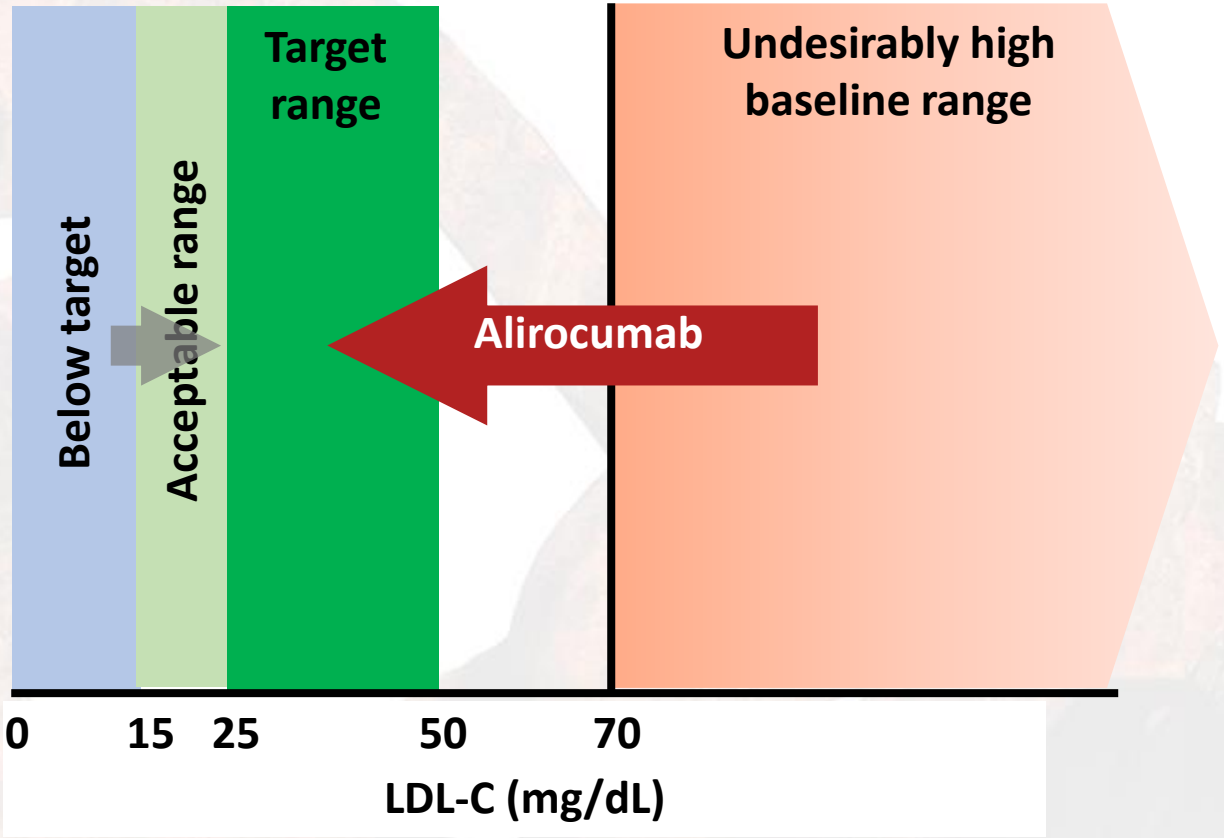


Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

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

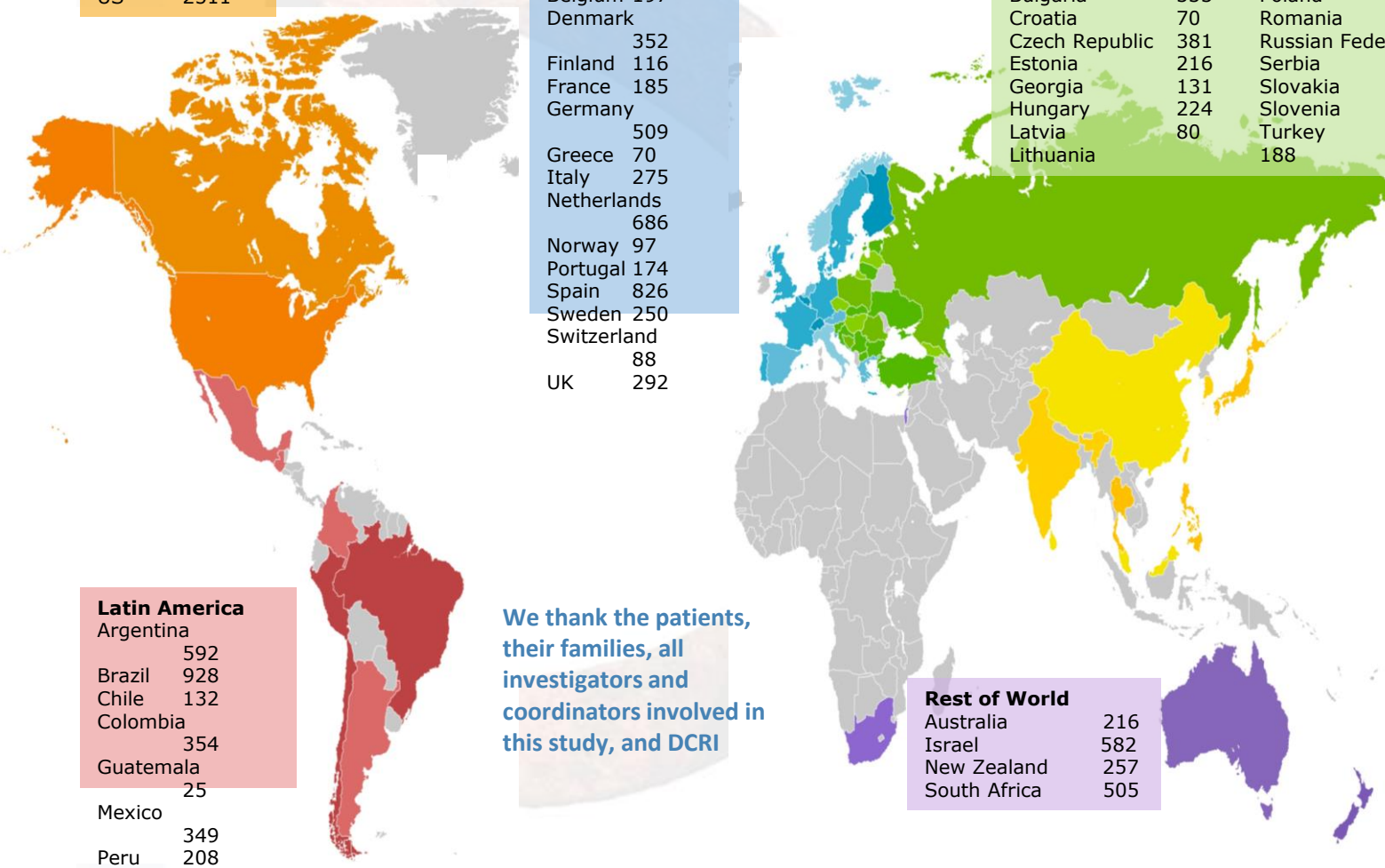
A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



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

ODYSSEY OUTCOMES: 18,924 patients randomized at 1315 sites in 57 countries, Nov 2, 2012 – Nov 11, 2017



Canada/USA

Canada	361
US	2511

Western Europe

Austria	58
Belgium	197
Denmark	352
Finland	116
France	185
Germany	509
Greece	70
Italy	275
Netherlands	686
Norway	97
Portugal	174
Spain	826
Sweden	250
Switzerland	88
UK	292

Central/Eastern Europe

Bosnia–Herzegovina	156	Macedonia	132
Bulgaria	333	Poland	926
Croatia	70	Romania	145
Czech Republic	381	Russian Federation	1109
Estonia	216	Serbia	255
Georgia	131	Slovakia	340
Hungary	224	Slovenia	36
Latvia	80	Turkey	78
Lithuania	188	Ukraine	639

Asia

China	614
Hong Kong	17
India	521
Japan	204
Korea	94
Malaysia	110
Philippines	116
Singapore	49
Sri Lanka	314
Taiwan	93
Thailand	161

Latin America

Argentina	592
Brazil	928
Chile	132
Colombia	354
Guatemala	25
Mexico	349
Peru	208

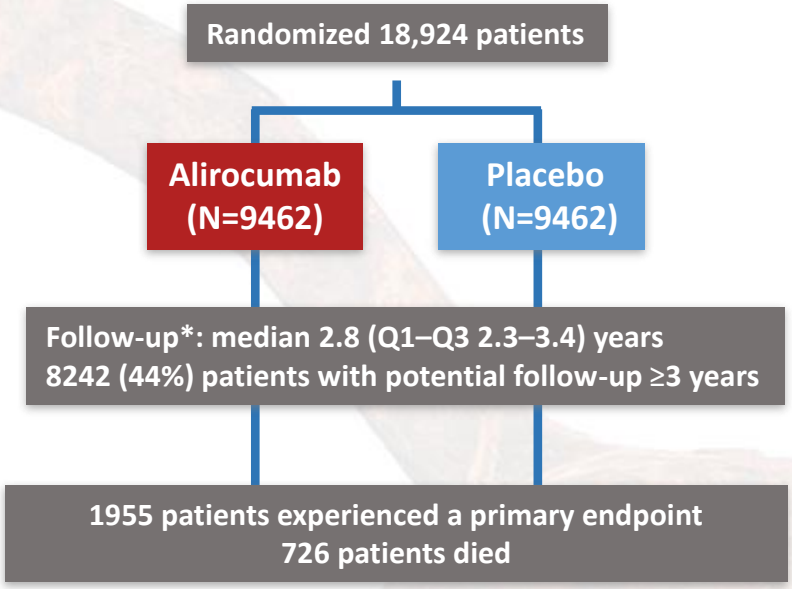
We thank the patients, their families, all investigators and coordinators involved in this study, and DCRI

Rest of World

Australia	216
Israel	582
New Zealand	257
South Africa	505

ODYSSEY OUTCOMES

Patient Disposition



	Alirocumab (N=9462)	Placebo (N=9462)
• Premature treatment discontinuation	1343 (14.2%)	1496 (15.8%)
• Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)	730 (7.7%)	Not applicable
• Patients lost to follow-up (vital status)	14	9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

Baseline Demographics

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age, years, median (Q1–Q3)	58 (52–65)	58 (52–65)
Female, n (%)	2390 (25.3)	2372 (25.1)
Medical history, n (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Prior MI	1790 (18.9)	1843 (19.5)

Baseline Index Events

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Time from index ACS to randomization, months, median (Q1–Q3)	2.6 (1.7–4.4)	2.6 (1.7–4.3)
ACS type, n (%)		
NSTEMI	4574 (48.4)	4601 (48.7)
STEMI	3301 (35.0)	3235 (34.2)
Unstable angina	1568 (16.6)	1614 (17.1)
Revascularization for index ACS, n (%)	6798 (71.8)	6878 (72.7)

Baseline Lipid Characteristics

Characteristic, mg/dL, median (Q1–Q3)	Alirocumab (N=9462)	Placebo (N=9462)
LDL-C	87 (73–104)	87 (73–104)
Non-HDL-C	115 (99–136)	115 (99–137)
Apolipoprotein B	79 (69–93)	80 (69–93)
HDL-C	43 (37–50)	42 (36–50)
Triglycerides	129 (94–181)	129 (95–183)
Lipoprotein(a)	21 (7–59)	22 (7–60)

92.5% of patients qualified on the basis of LDL-C ≥70 mg/dL

Baseline Lipid-Lowering Therapy

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)

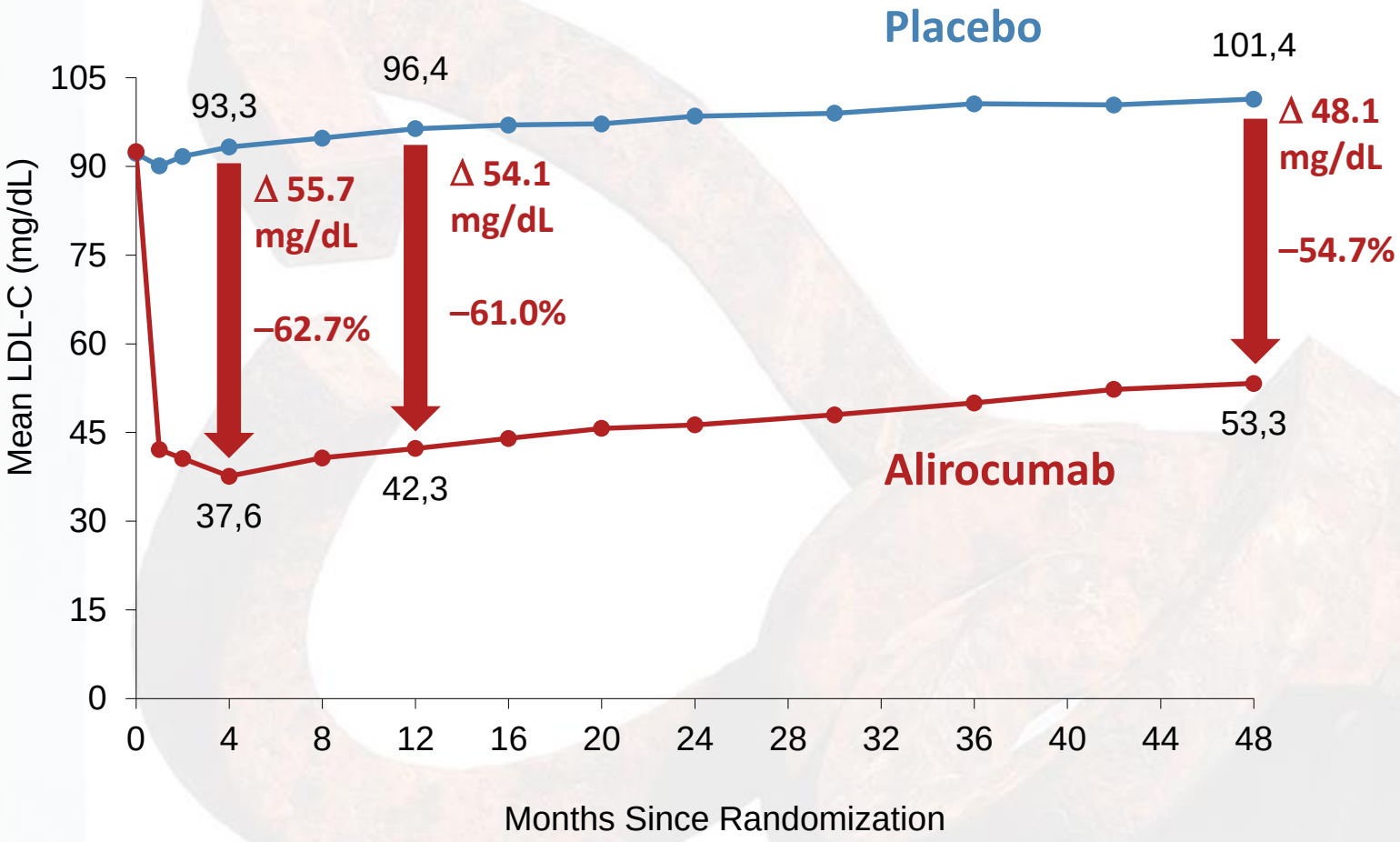
*Patients not on statins were authorized to participate if tolerability issues were present and documented

Guideline-Recommended Post-ACS Medications

Medication, n (%)	**Alirocumab (N=9462)**	**Placebo (N=9462)**
Aspirin	9050 (95.6)	9036 (95.5)
$P2Y_{12}$ antagonist	8296 (87.7)	8245 (87.1)
ACE-I/ARB	7356 (77.7)	7360 (77.8)
Beta-blocker	7998 (84.5)	7992 (84.5)

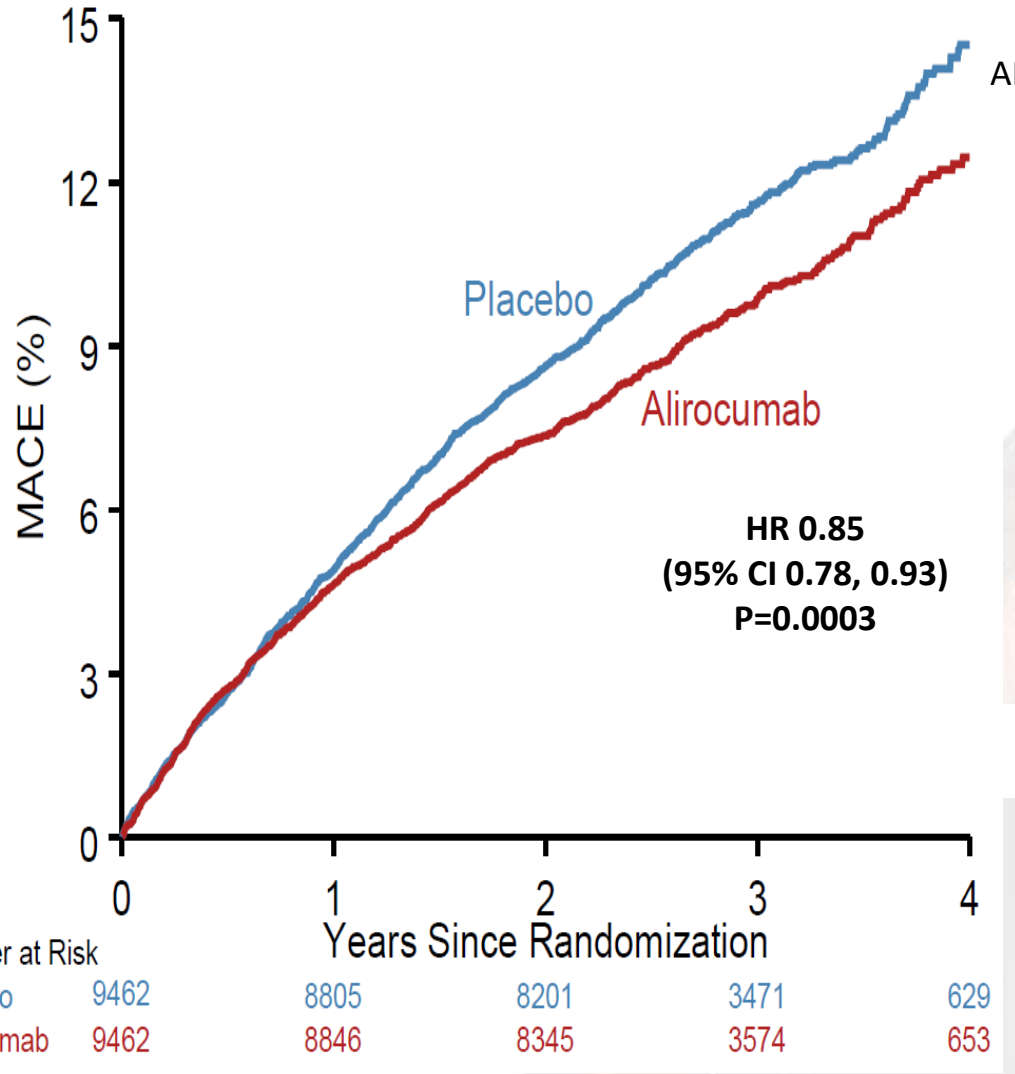
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

Primary Efficacy Endpoint: MACE



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

*Based on cumulative incidence

Primary Efficacy and Components

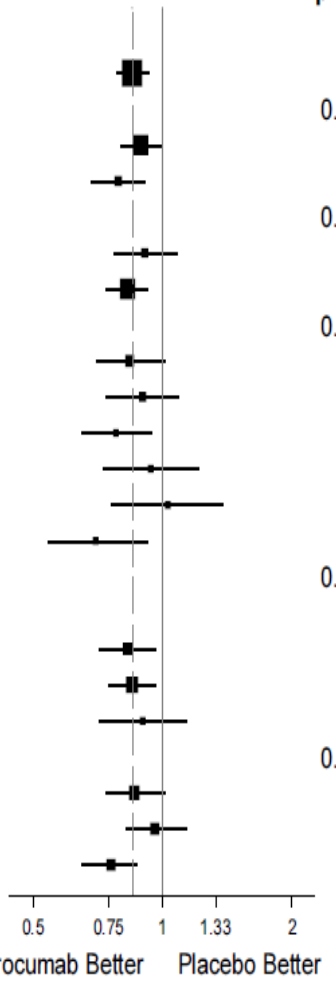
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

Odyssey: Hierarchical testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	1199 (12.7)	1349 (14.3)	0.88 (0.81, 0.95)	0.001
Major CHD event	793 (8.4)	899 (9.5)	0.88 (0.80, 0.96)	0.006
CV event	1301 (13.7)	1474 (15.6)	0.87 (0.81, 0.94)	0.0003
Death, MI, ischemic stroke	973 (10.3)	1126 (11.9)	0.86 (0.79, 0.93)	0.0003
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
CV death	240 (2.5)	271 (2.9)	0.88 (0.74, 1.05)	0.15
All-cause death	334 (3.5)	392 (4.1)	0.85 (0.73, 0.98)	0.026*

Primary Efficacy in Main Prespecified Subgroups

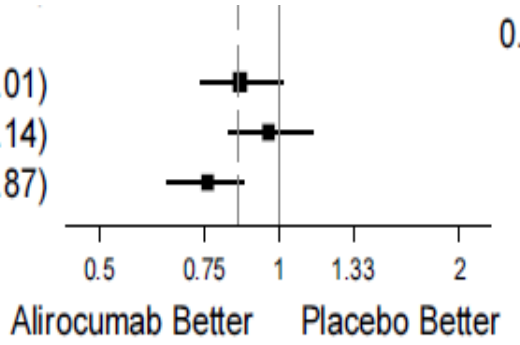
Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
Overall	18924	9.5	11.1	0.85 (0.78, 0.93)	
Age					0.19
< 65 Yr	13840	8.5	9.5	0.89 (0.80, 0.99)	
≥ 65 Yr	5084	12.4	15.5	0.79 (0.68, 0.91)	
Sex					0.35
Female	4762	10.7	11.8	0.91 (0.77, 1.08)	
Male	14162	9.2	10.9	0.83 (0.74, 0.92)	
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)	



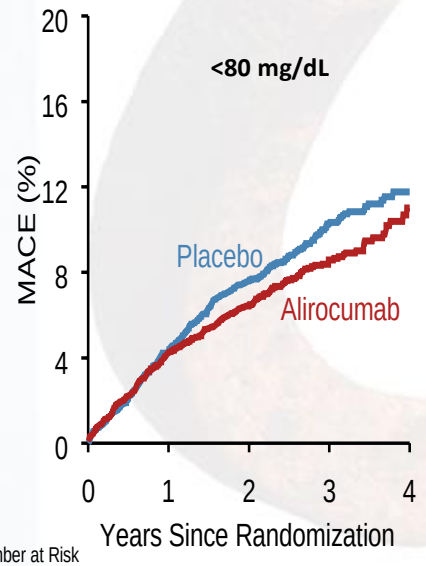
*P-values for interaction

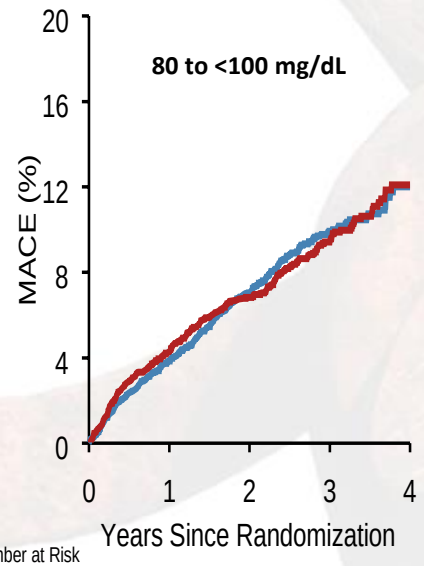
Primary Efficacy in Main Prespecified Subgroups

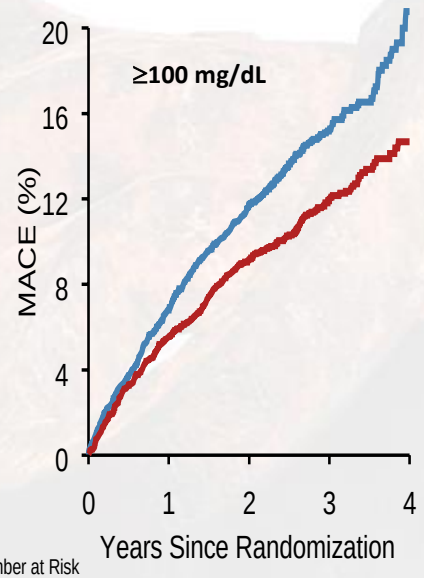
Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction







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

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

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

Odyssey: Events in patients with LDL ≥100 mg/dl

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

Safety (1)

Treatment-emergent adverse events, n (%)	**Alirocumab (N=9451)**	**Placebo (N=9443)**
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	**Alirocumab**	**Placebo**
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

Safety (2)

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢ These are the patients who may benefit most from treatment

ARR, absolute risk reduction

ESC Guidelines in dyslipidemias

Table 27 **Recommendations for lipid-lowering therapy in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention**

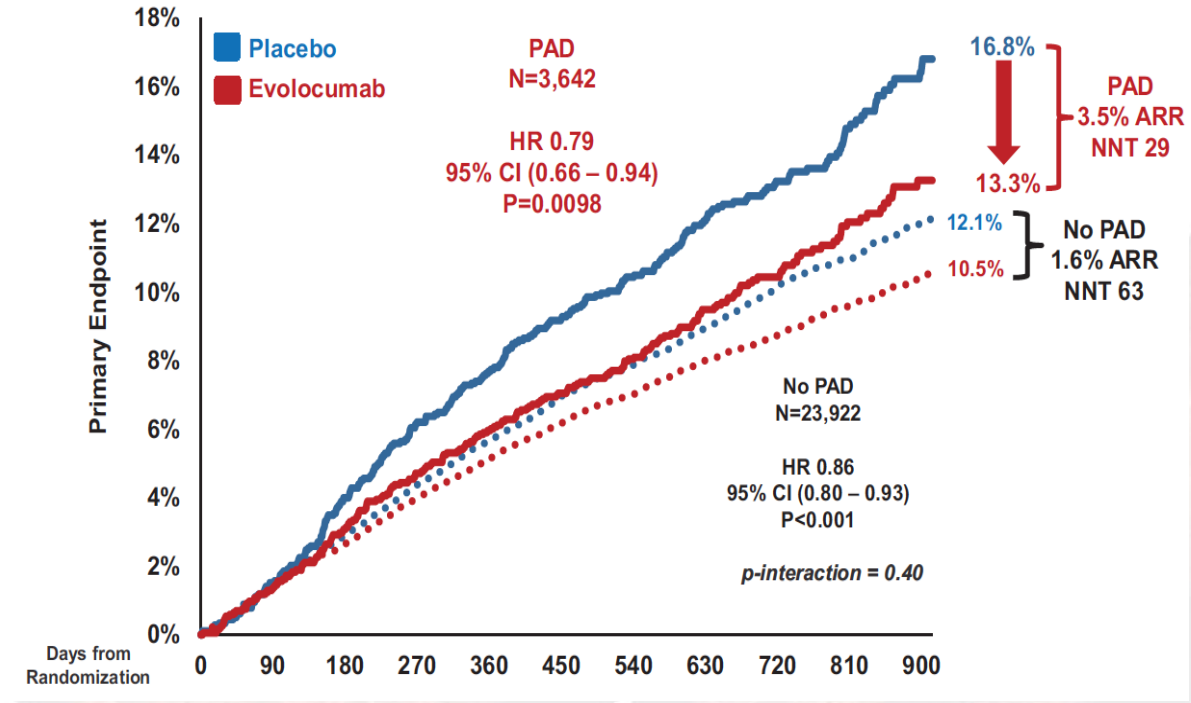
Recommendations	Class [a]	Level [b]	Ref [c]
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	I	A	64, 358–360
If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients.	IIa	B	63
If the LDL-C target is not reached with the highest tolerable statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin intolerant patients or in whom a statin is contra-indicated.	IIb	C	115, 116
Lipids should be re-evaluated 4–6 weeks after ACS to determine whether target levels of LDL-C <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) have been reached and whether there are any safety issues. The therapy dose should then be adapted accordingly.	IIa	C	
Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTE-ACS.	IIa	A	363–365

Catapano A, et al. Eur Heart J 2016;37:2999-3058

FOURIER Study

The reduction of the absolute risk of adverse events with evolocumab is more marked in patients with PAD

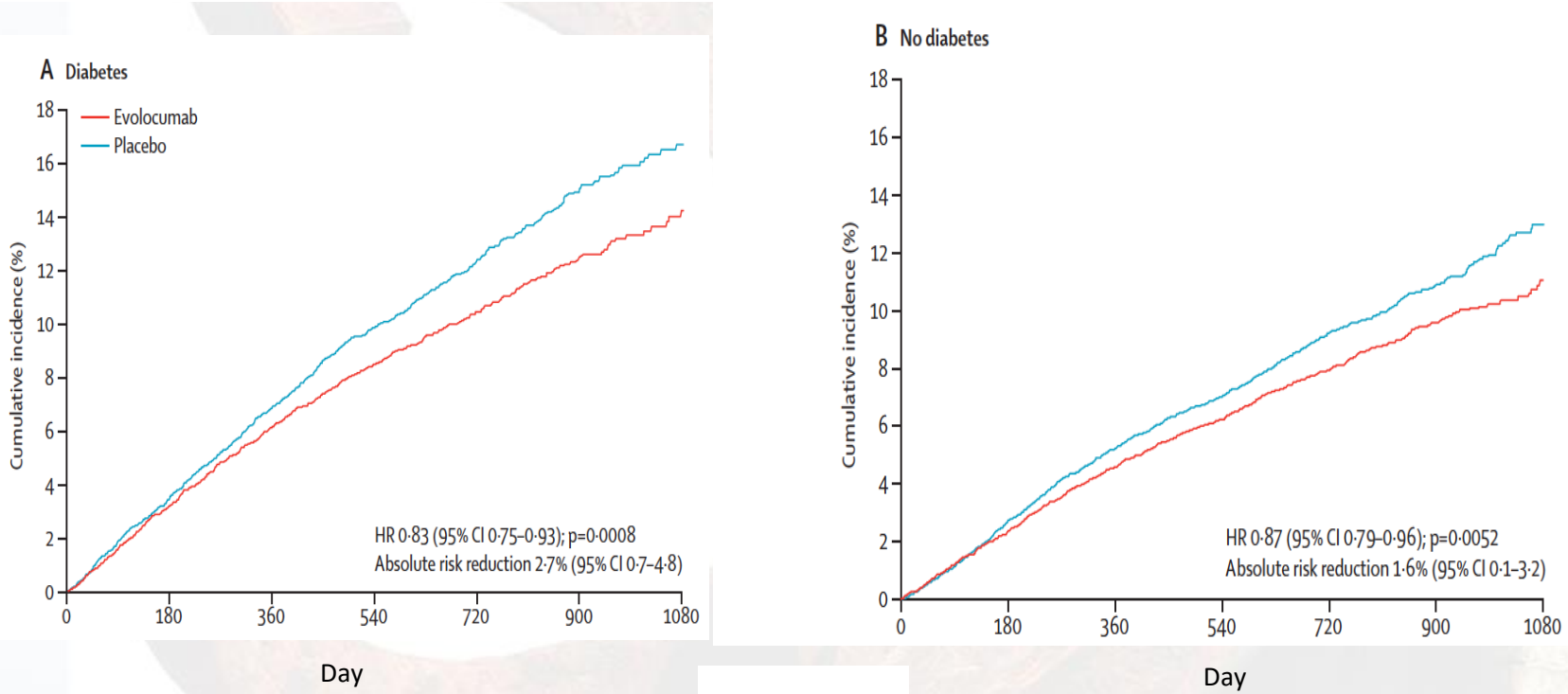
*CV death, MI, stroke, Unstable Angina, Cor revascularization



Bonaca et al. Circulation 2017

FOURIER Study

The reduction of the relative risk of the primary end point* with evolocumab is similar in pts with/without diabetes ($P_{interaction}$=0.60) but higher in terms of absolute risk



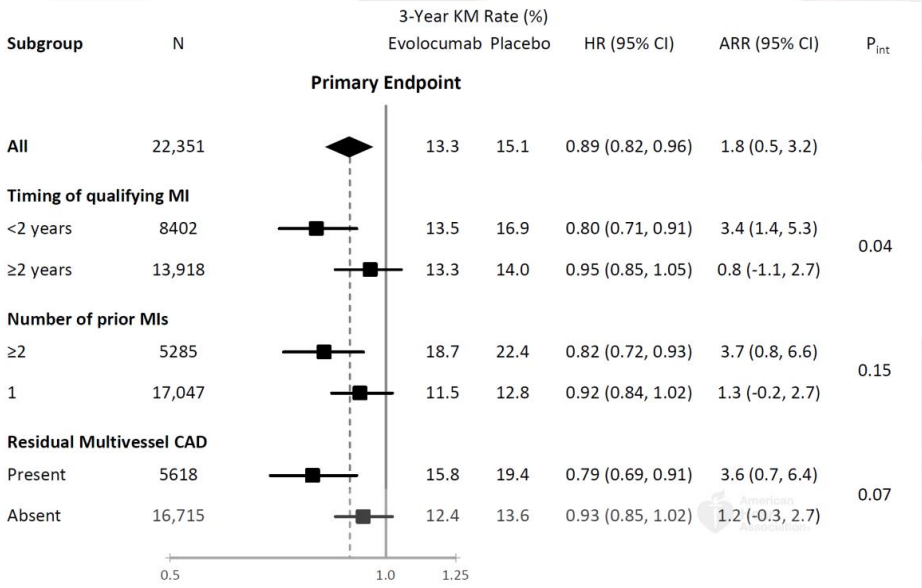
*CV death, MI, stroke, Unstable Angina, Cor revascularization

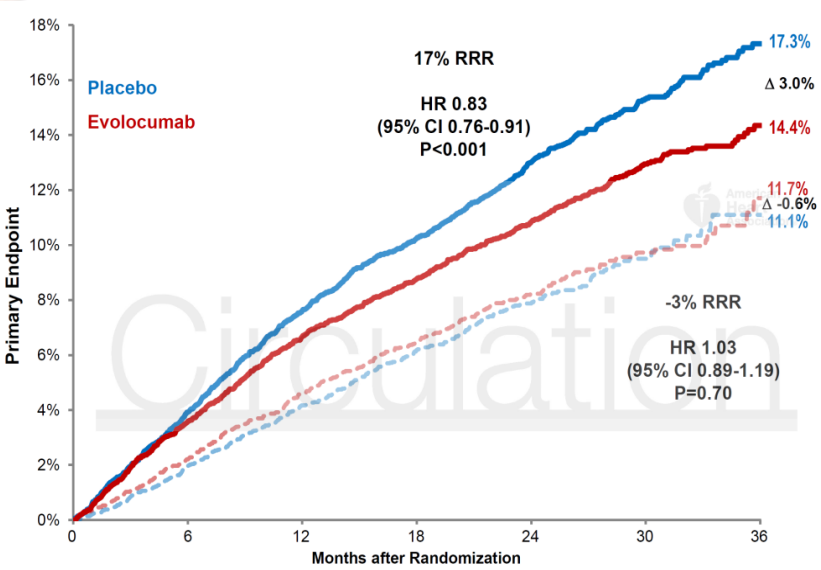
Sabatine et al. Lancet Diabetes Endocrinol 2017;5:941-50

FOURIER and severity of CAD

The 22,351 pts. with a prior MI were characterized based on:

- -Time from most recent MI
- -Number of prior MIs
- -Presence of multivessel disease (≥ 40% stenosis in ≥ 2 large vessels)

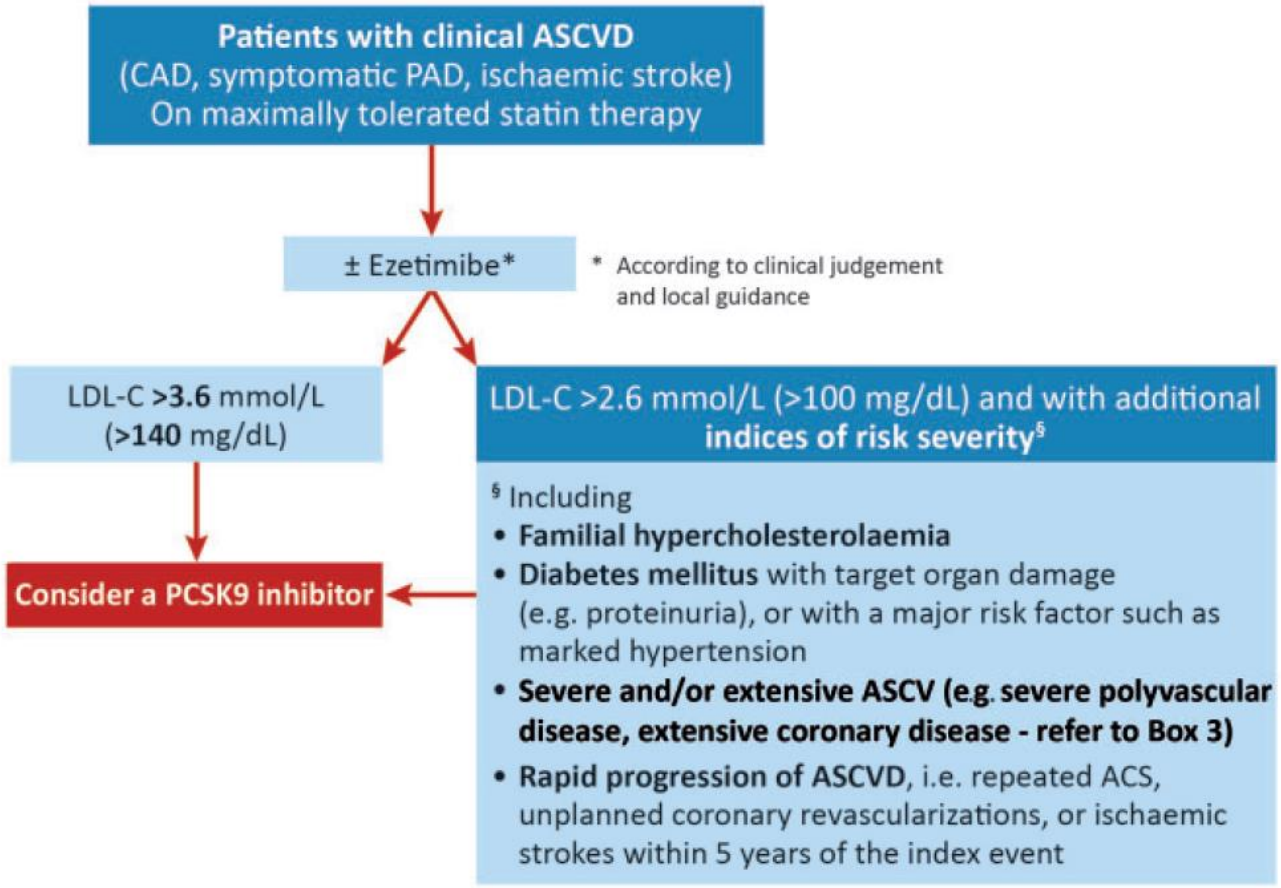




SOLID LINES: Pts. With a least 1 high-risk feature
DASHED LINES: Pts. Without high-risk features

Sabatine MS, et al. Circulation 2018;in press

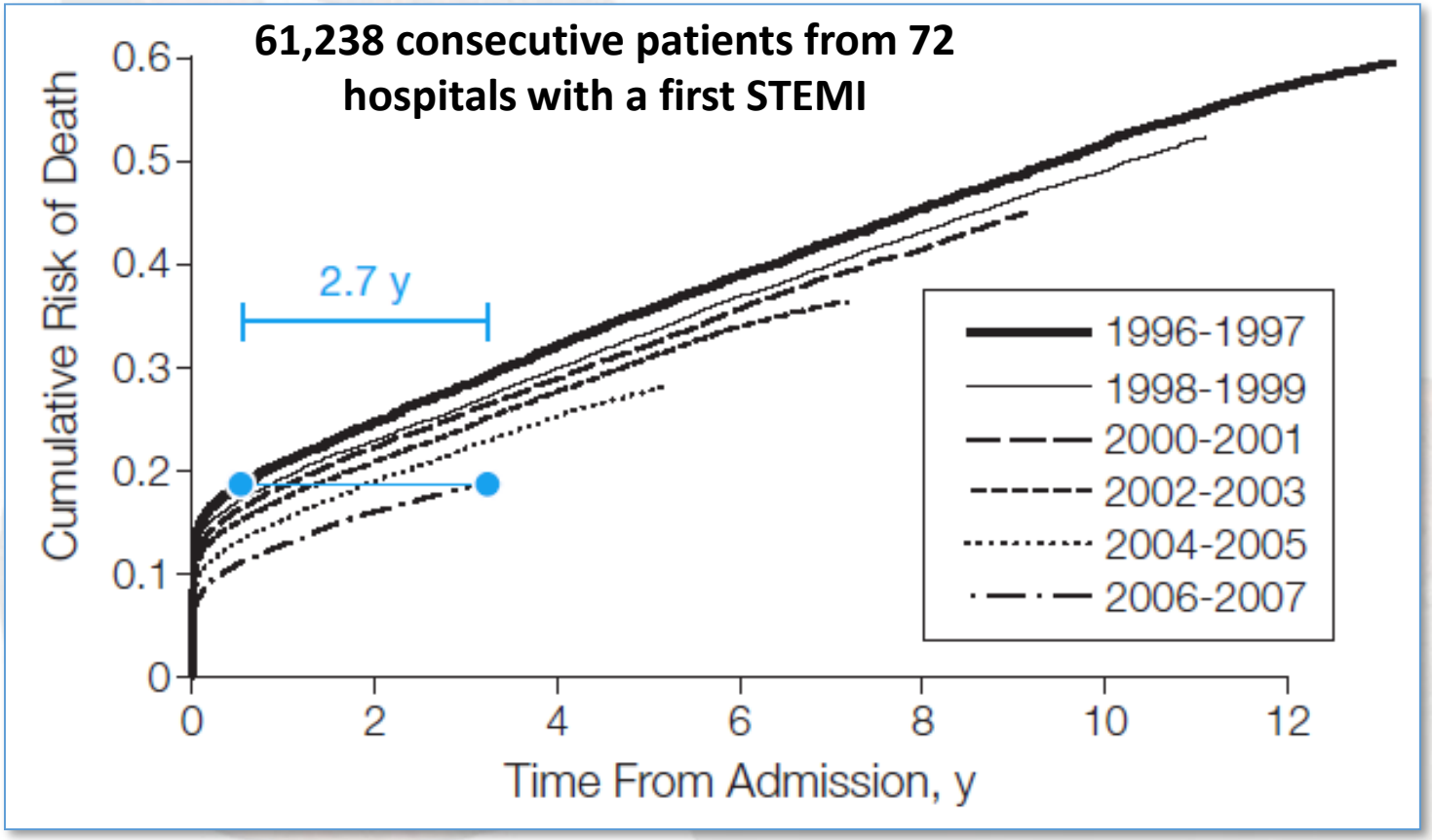
2017 Update ESC/EAS on PCSKi



Landmesser U, Chapman MJ, et al. Eur Heart J 2018;39:1131-1143

Decreasing mortality post-STEMI

Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA)

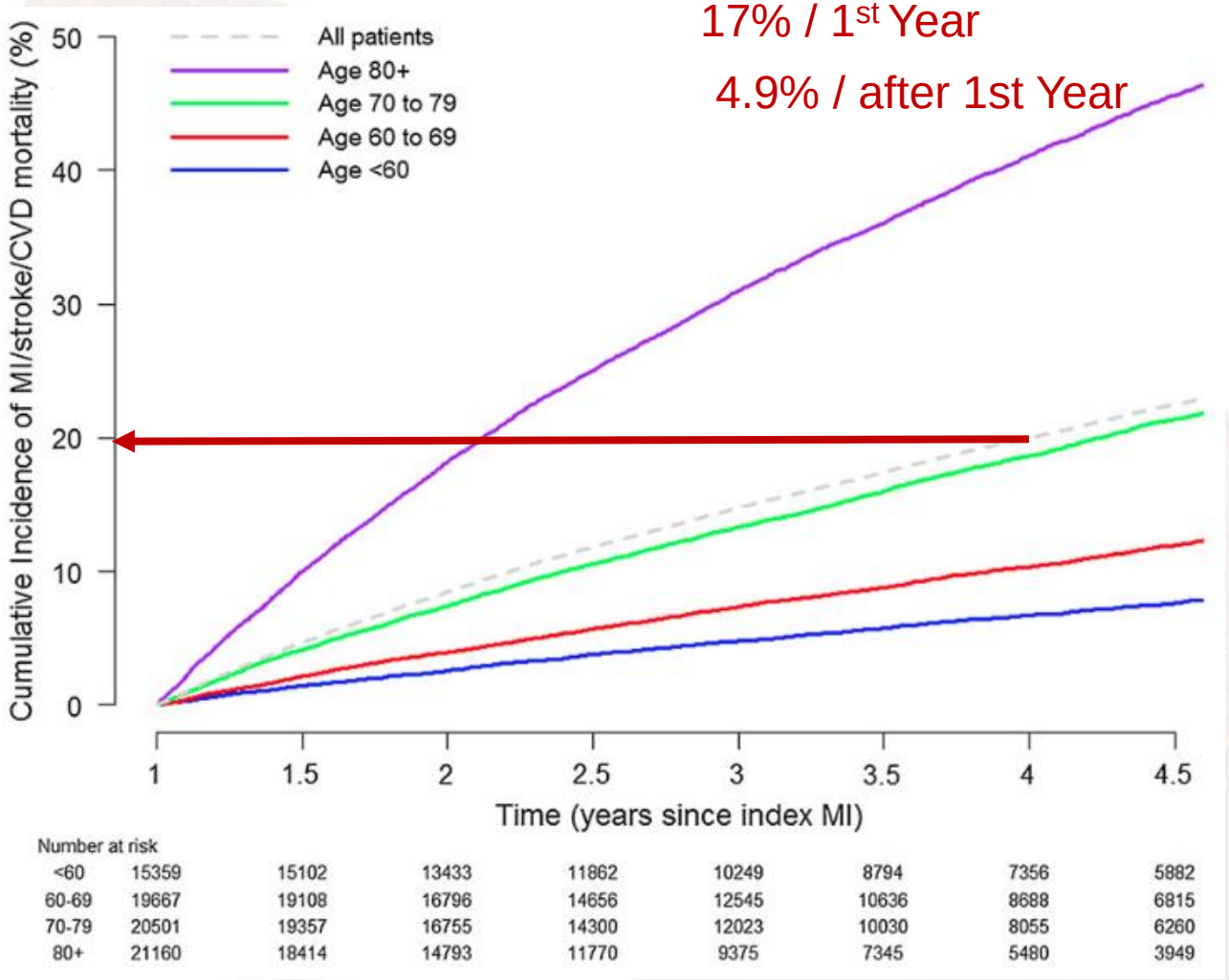


Jernberg et al *JAMA* 2011;305:1677-84

Outcome after MI

17% / 1st Year

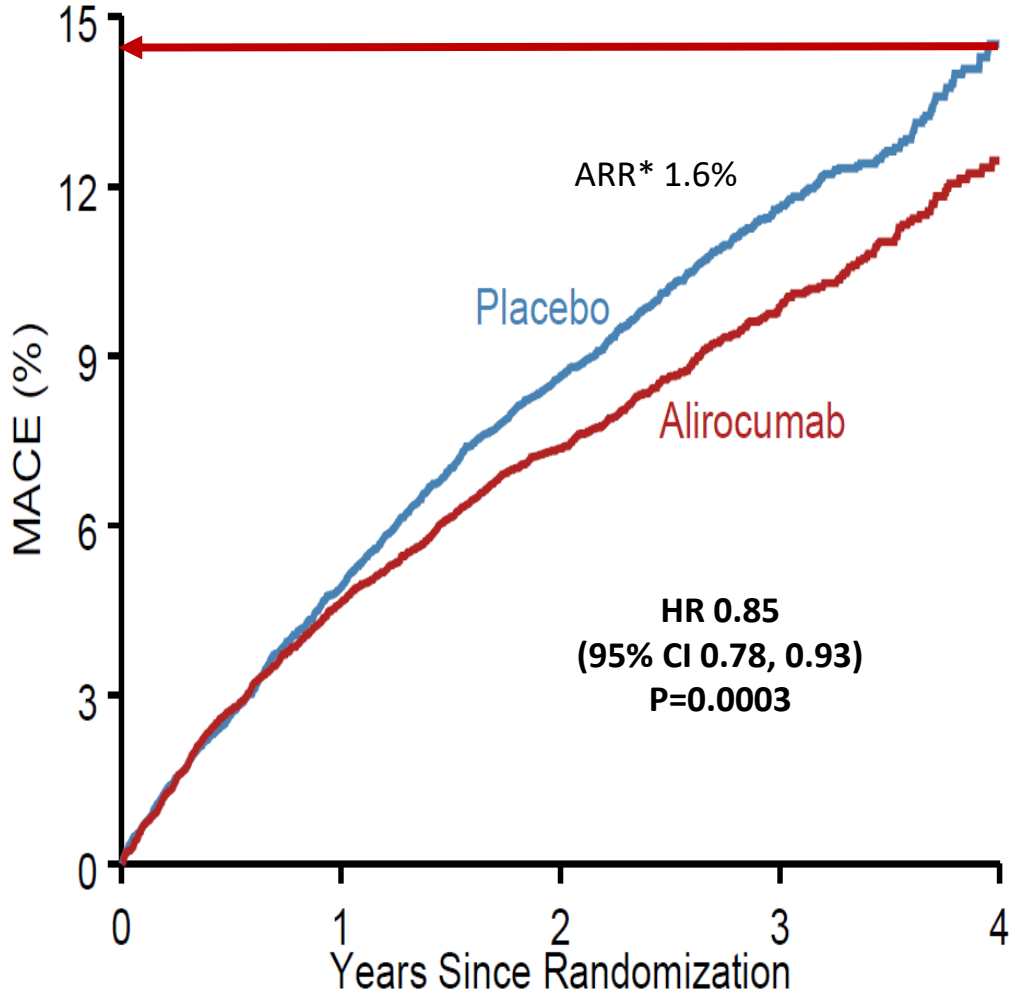
4.9% / after 1st Year



Jernberg et al., Eur Heart Journal 2015; 36, 1163–1170

Odyssey:Primary Efficacy end point

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



Odyssey: Hierarchical testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	1199 (12.7)	1349 (14.3)	0.88 (0.81, 0.95)	0.001
Major CHD event	793 (8.4)	899 (9.5)	0.88 (0.80, 0.96)	0.006
CV event	1301 (13.7)	1474 (15.6)	0.87 (0.81, 0.94)	0.0003
Death, MI, ischemic stroke	973 (10.3)	1126 (11.9)	0.86 (0.79, 0.93)	0.0003
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
CV death	240 (2.5)	271 (2.9)	0.88 (0.74, 1.05)	0.15
All-cause death	334 (3.5)	392 (4.1)	0.85 (0.73, 0.98)	0.026*

Odyssey: Events in patients with LDL ≥100 mg/dl

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

Odyssey: Background therapy

Medication, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
Aspirin	9050 (95.6)	9036 (95.5)
$P2Y_{12}$ antagonist	8296 (87.7)	8245 (87.1)
ACE-I/ARB	7356 (77.7)	7360 (77.8)
Beta-blocker	7998 (84.5)	7992 (84.5)

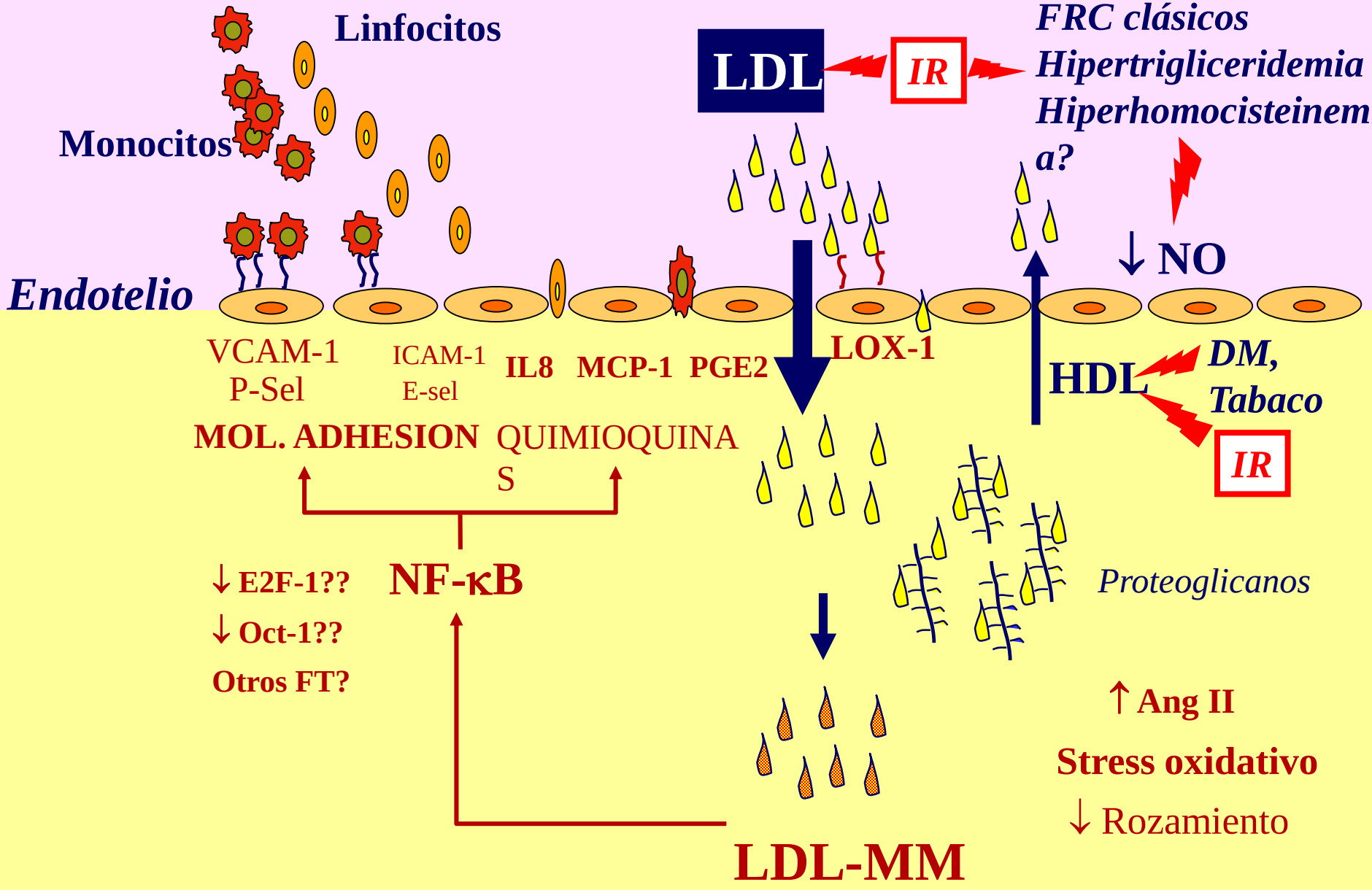
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Odyssey: Lipid-lowering therapy

	ODYSSEY OUTCOMES (N=18,312)	FOURIER (N=27,564)
Lipid-lowering therapies		
High-intensity statin (%)	89.5	69.2
Moderate/Low-intensity statin (%)	7.8	30.4
Ezetimibe (%)	2.9	5.1
Median LDL-C (mg/dL)	86.5	91.5
Total cholesterol (mg/dL)	160.0	167.0
HDL cholesterol (mg/dL)	42.5	44.0
Triglycerides (mg/dL)	129.2	133.0

Sabatine, et al. Am Heart J. 2016;173:94-101
Schwartz GG, et al. Am Heart J. 2014;168:682-689.e1.

Disfunción Endotelial



Luz Vascular

Linfocitos

CE progenitoras

Monocitos

PDGF CTGF
TGF-β

Plaquetas

Endotelio

MMP

IR → Macrófagos

CML

Ang II

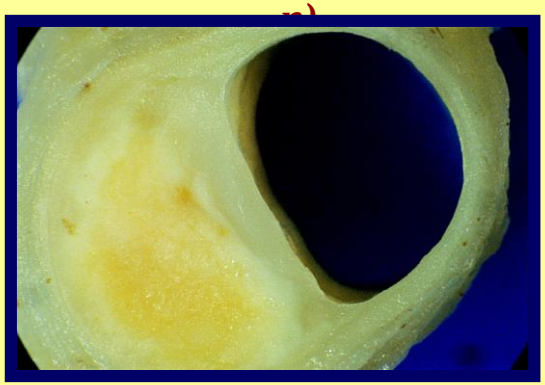
Espumosas

Diabete
(Glicosilación

Ang II

LDL-MM

LDLox



*IR-Carbamilación

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

Key Exclusion Criteria

- Uncontrolled hypertension
- NYHA class III or IV heart failure; LVEF <25% if measured
- History of hemorrhagic stroke
- Fasting triglycerides >400 mg/dL (4.52 mmol/L)
- Coronary revascularization performed within 2 weeks prior to randomization visit, or planned after randomization
- Liver transaminases >3 × ULN; hepatitis B or C infection
- Creatine kinase >3 × ULN
- eGFR <30 mL/min/1.73 m^2
- Positive pregnancy test

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal

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

ODYSSEY OUTCOMES

EZT in ESC Guidelines on dyslipidemia

Recommendations for LL therapy in patients with moderate-severe CKD

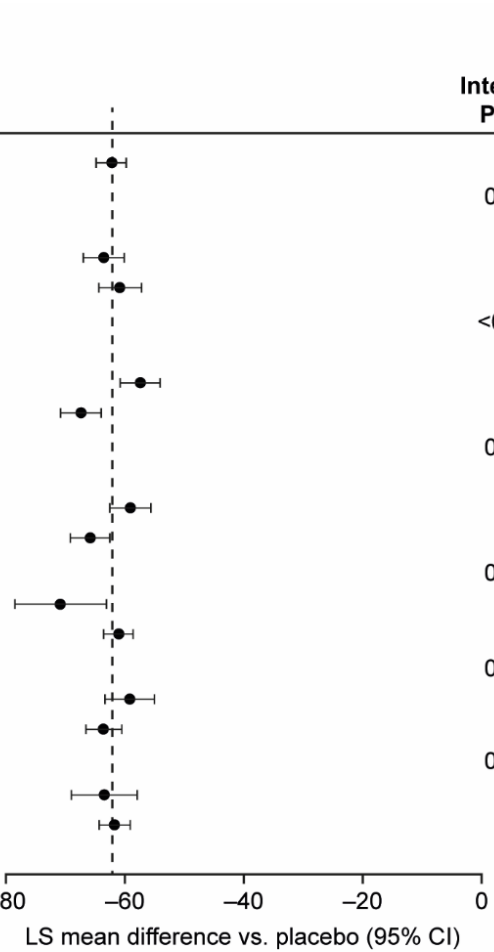
Recommendations	Class [a]	Level [b]	Ref [c]
Patients with stage 3–5 CKD have to be considered at high or very high CV risk.	I	A	388–392
The use of statins or statin/ezetimibe combination is indicated in patients with non-dialysis-dependent CKD.	I	A	393, 394, 397
In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	III	A	395, 396
In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, these drugs should be continued, particularly in patients with CVD.	IIa	C	

Catapano A, et al. Eur Heart J 2016;37:2999-3058

Effect of alirocumab on lipids in different subgroups

LONG-TERM

Subgroup	Alirocumab n	Alirocumab LS mean (SE)	Placebo n	Placebo LS mean (SE)	Interaction P value
Overall	1530	–61.0 (0.7)	780	0.8 (1.0)	
History of MI/Ischemic stroke					0.2835
Yes	734	–63.0 (1.1)	375	0.3 (1.5)	
No	796	–59.2 (1.0)	405	1.3 (1.4)	
Baseline total PCSK9 level					<0.0001
Below median	736	–60.1 (1.1)	376	–2.8 (1.5)	
At or above median	740	–62.2 (1.1)	381	5.1 (1.5)	
Baseline free PCSK9 level					0.0076
Below median	728	–59.4 (1.1)	387	–0.5 (1.5)	
At or above median	748	–62.8 (1.1)	370	2.9 (1.5)	
Moderate CKD					0.0210
Yes	174	–62.0 (2.2)	73	8.7 (3.4)	
No	1356	–60.9 (0.8)	707	0.0 (1.1)	
Diabetes					0.0957
Yes	545	–60.0 (1.3)	273	–1.0 (1.8)	
No	985	–61.6 (0.9)	507	1.8 (1.3)	
HeFH					0.6038
Yes	271	–56.3 (1.9)	145	7.0 (2.4)	
No	1259	–62.1 (0.8)	635	–0.5 (1.1)	

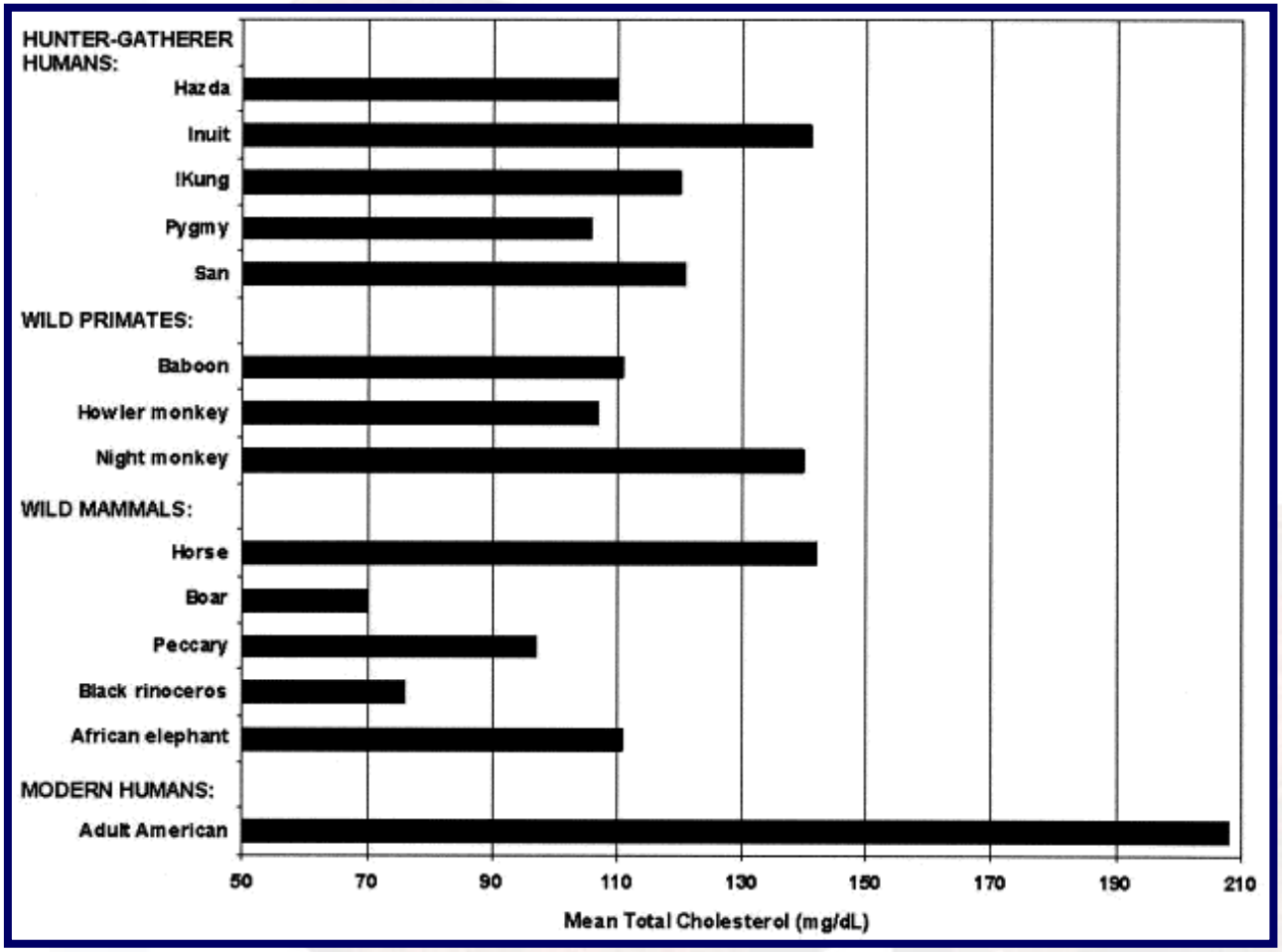


Robinson JG et al. NEJM 2015

Treatment targets and goals for CV prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids LDL-C is the primary target[a]	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[b] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Perhaps not!

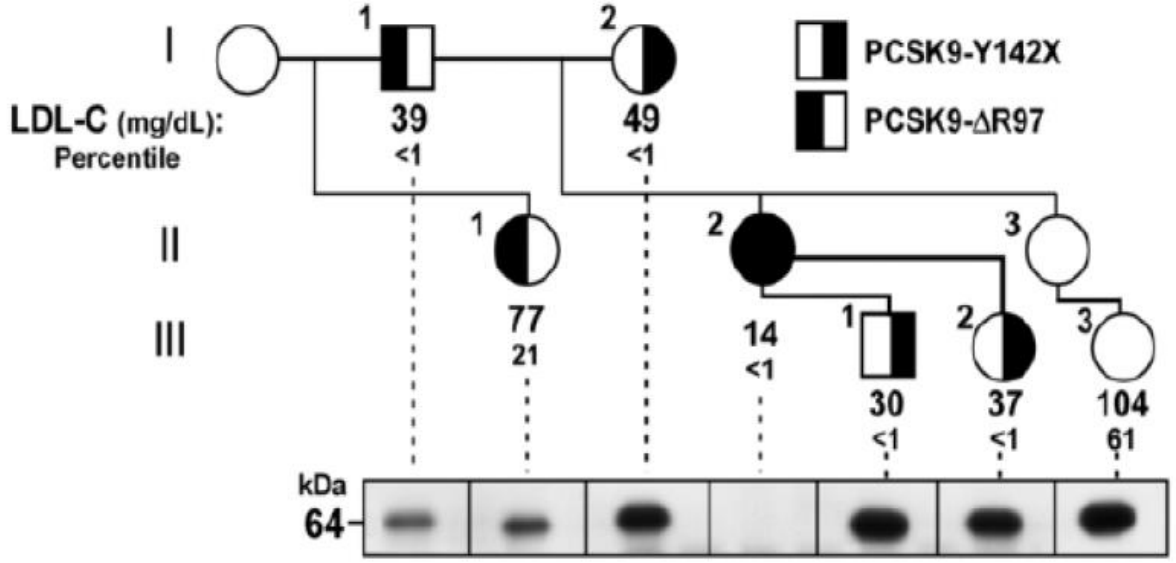


LDL in healthy neonates is 30-70 mg/dl!

O'Keefe et al; *J Am Coll Cardiol* 2004;43:2142-2146

Compound heterozygote with 2 PCSK9 loss of function mutations: Very low LDL-C; no adverse health consequences

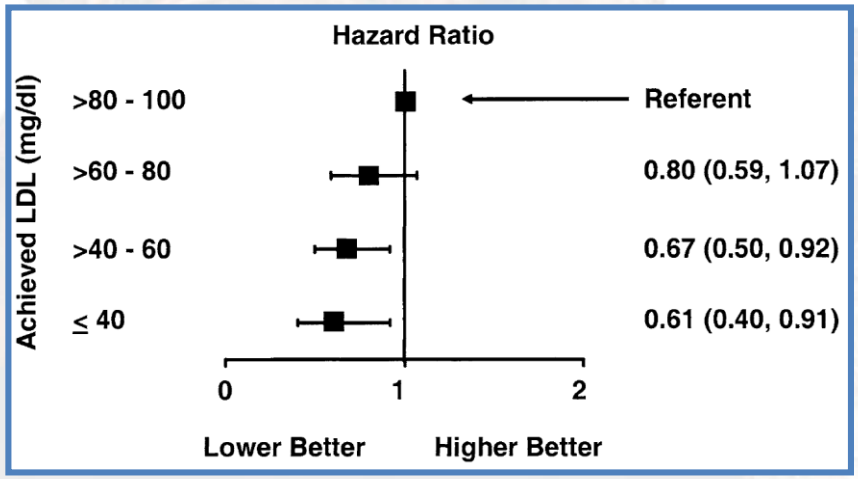
- 32 yo AA woman
- Compound heterozygote for 2 PCSK9 loss of function mutations
- LDL-C = 14 mg/dL



Zhao et al. Am J Hum Genet 2006;79:514-23

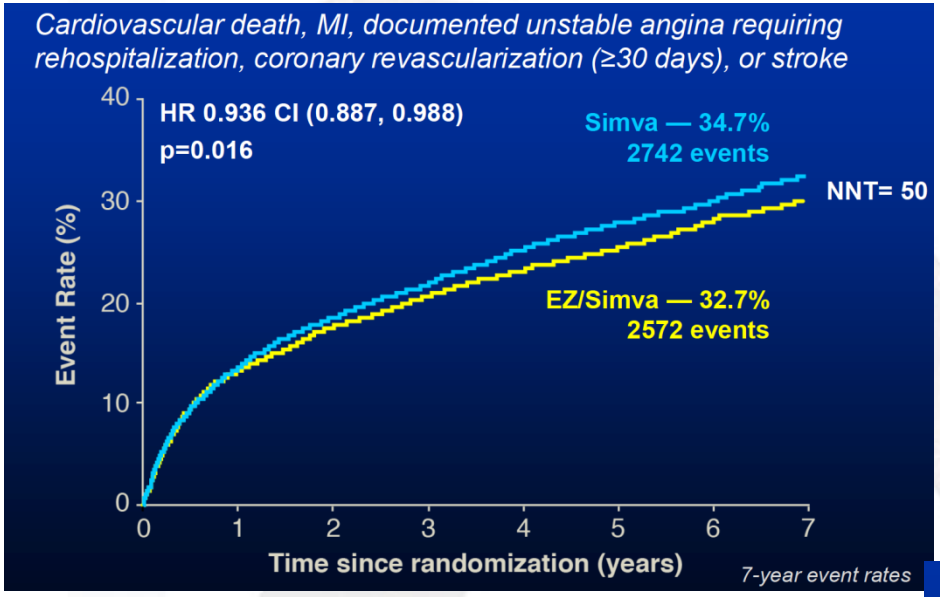
PROVE-IT Study and very low LDL

Safety Measure	Achieved LDL Cholesterol (mg/dl) >80–100 n = 256	>60–80 n = 576	>40–60 n = 631	<40 n = 193	p Trend
Muscle side effects*					
Myalgia	6.4	4.3	6.2	5.7	0.75
Myositis	0.4	0.6	0.6	0	0.64
CK >3× ULN	2.3	0.7	1.9	1.0	0.18
CK >10× ULN	0	0	0.3	0	0.45
Rhabdomyolysis	0	0	0	0	1.0
Liver side effects					
ALT >3× ULN	3.2	3.0	3.2	2.6	0.98
Study drug discontinued because of LFT	2.0	2.6	2.4	1.6	0.83
Other					
Hemorrhagic stroke	0.4	0.2	0	0	0.12
Retinal AE	0.4	0.9	1.0	0	0.48
Suicide/trauma death	0	0	0	0	1.0
Study drug discontinued because of any AE	10.2	9.4	9.7	9.8	0.99

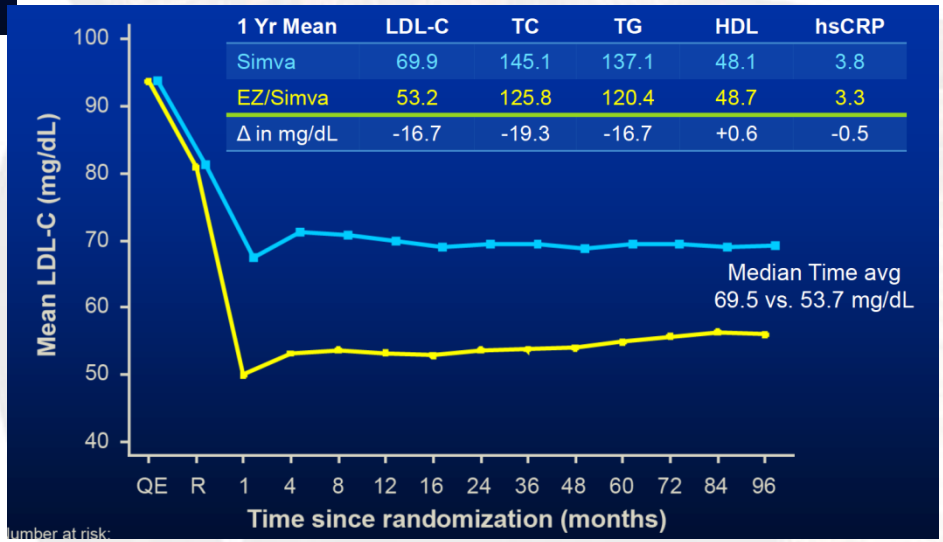


Wiviott et al. J Am Coll Cardiol 2005;46:1411-16

Ezetimibe: IMPROVE-IT study

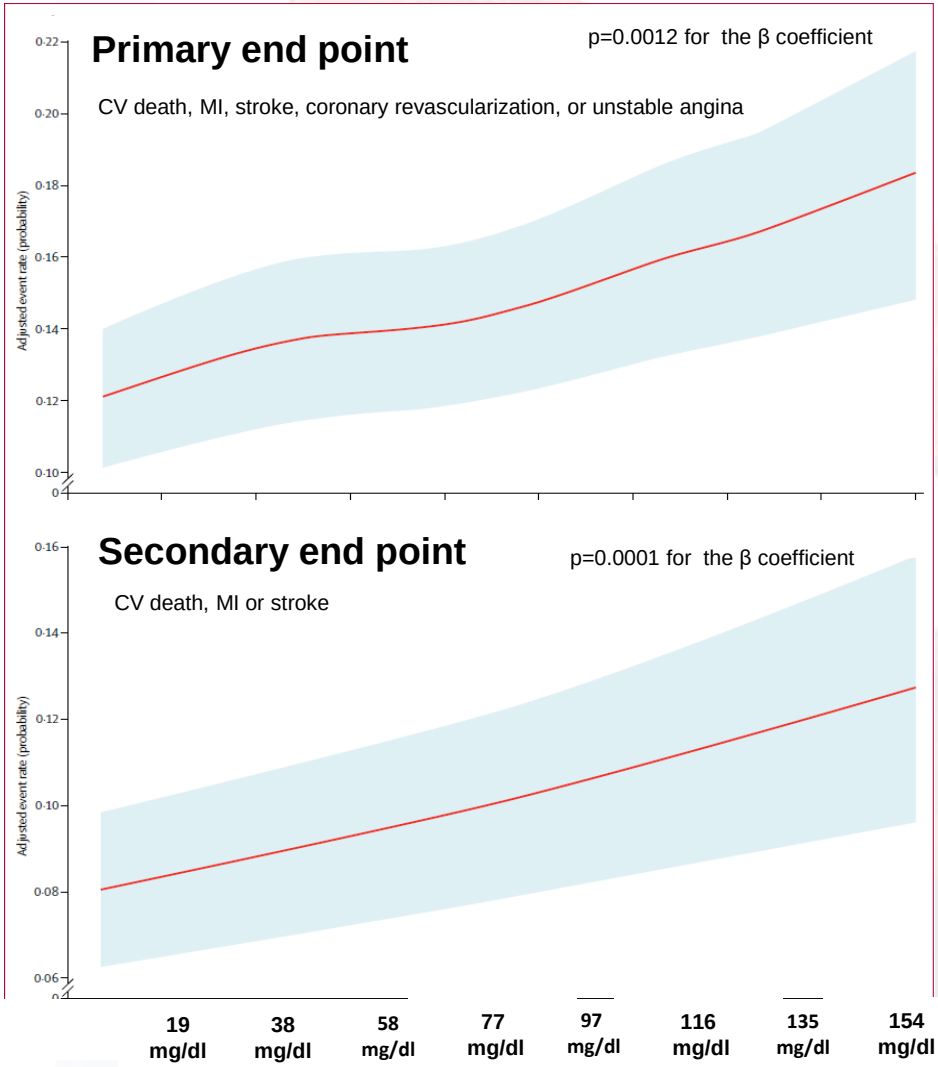


La reducción de LDL de 69.5 a 53.7 mg/dl se asociaba a menos eventos CV



AHA, November 2014

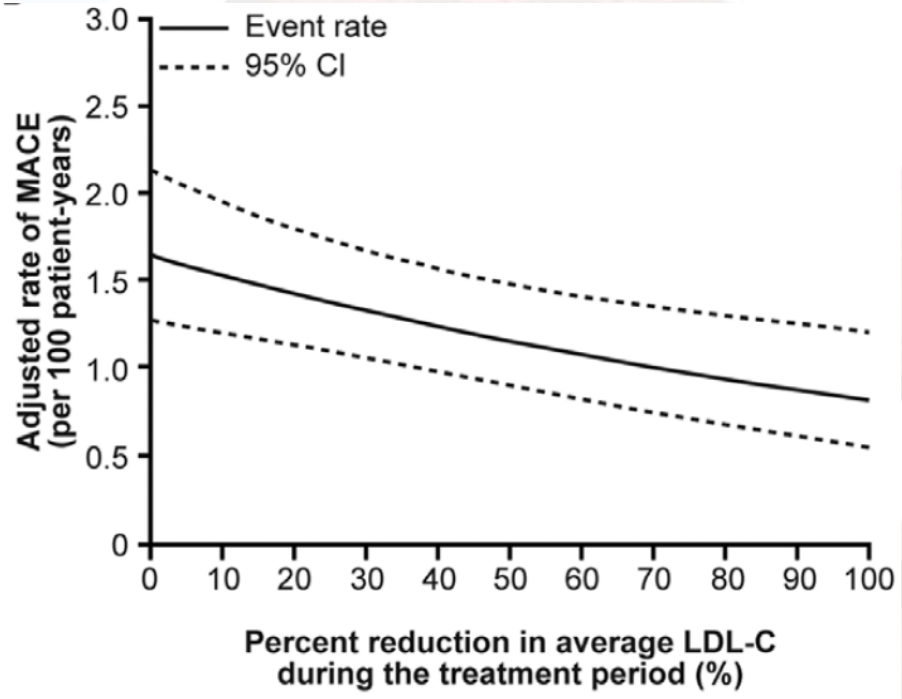
PCSK9i FOURIER Study

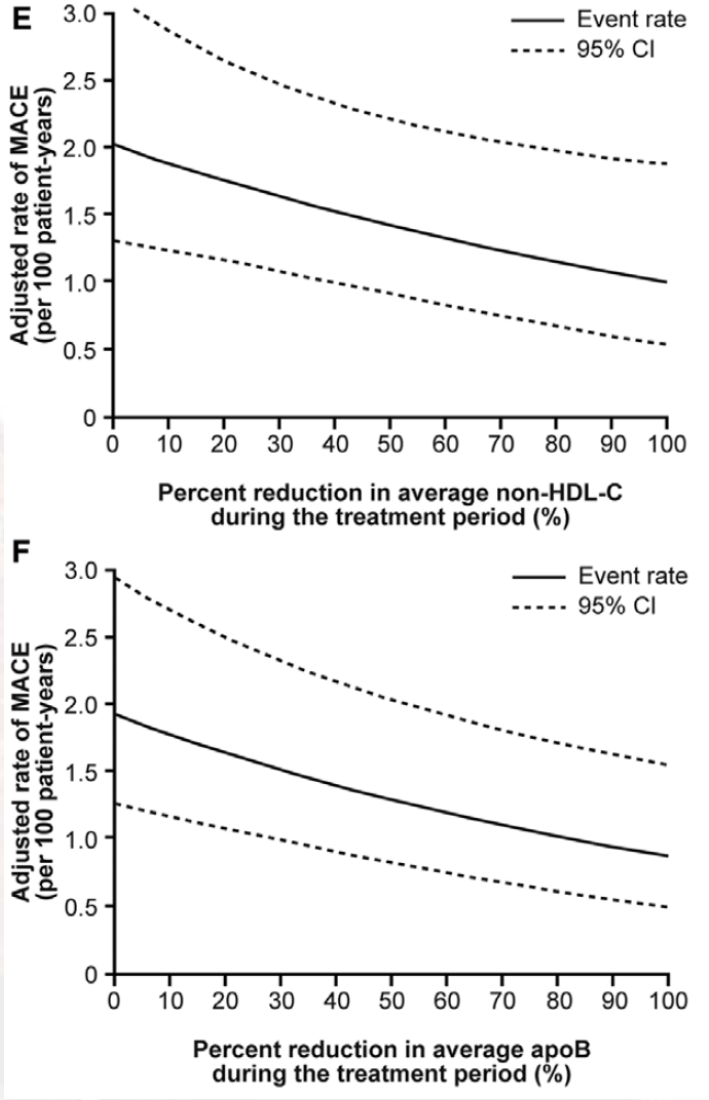


Giugliano RP et al; Lancet 2017;online

Event reduction with alirocumab

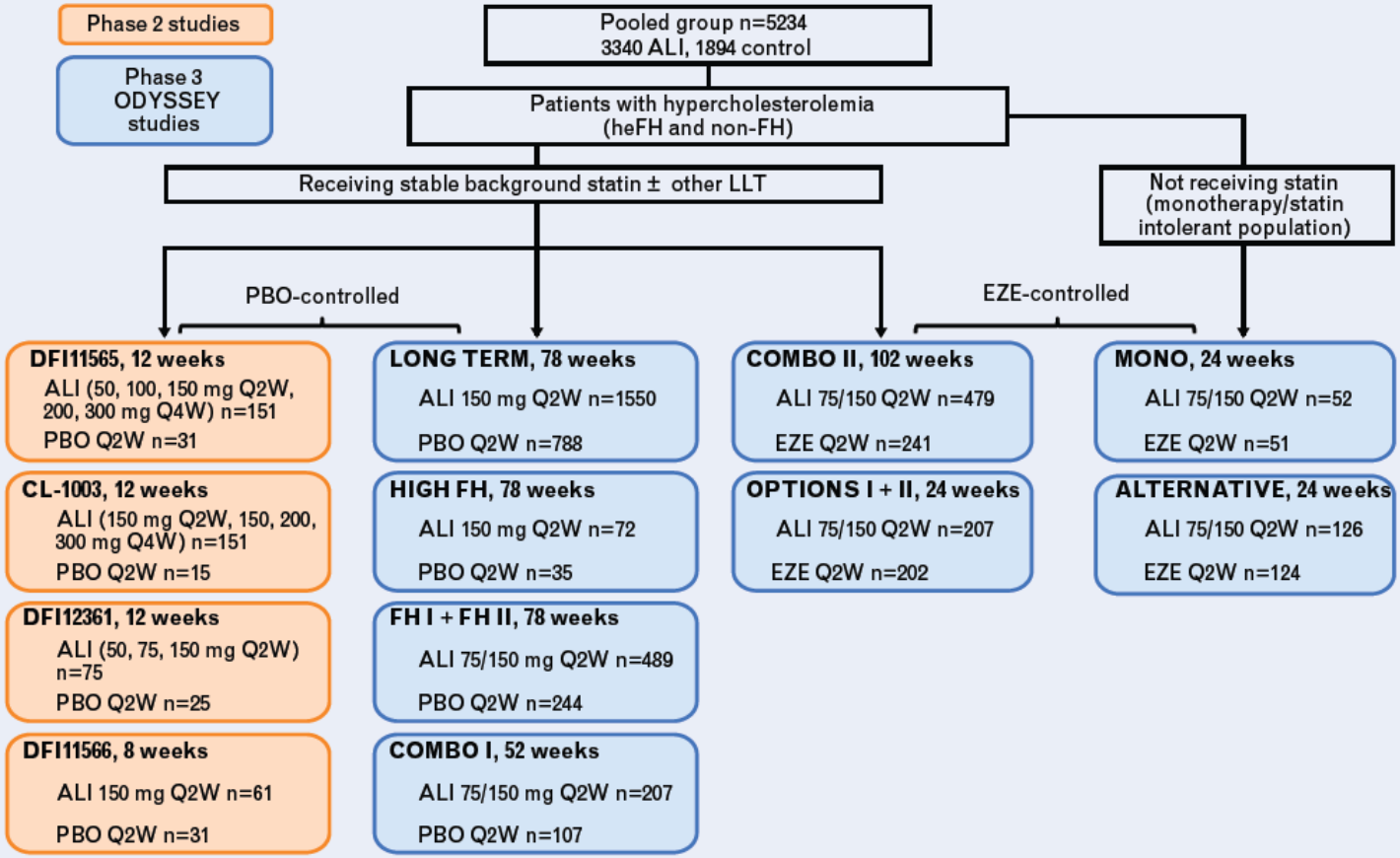
Risk of MACE and LDL reduction





Ray K, et al. Circulation 2016;134:1931-43

Safety of alirocumab in 14 clinical trials

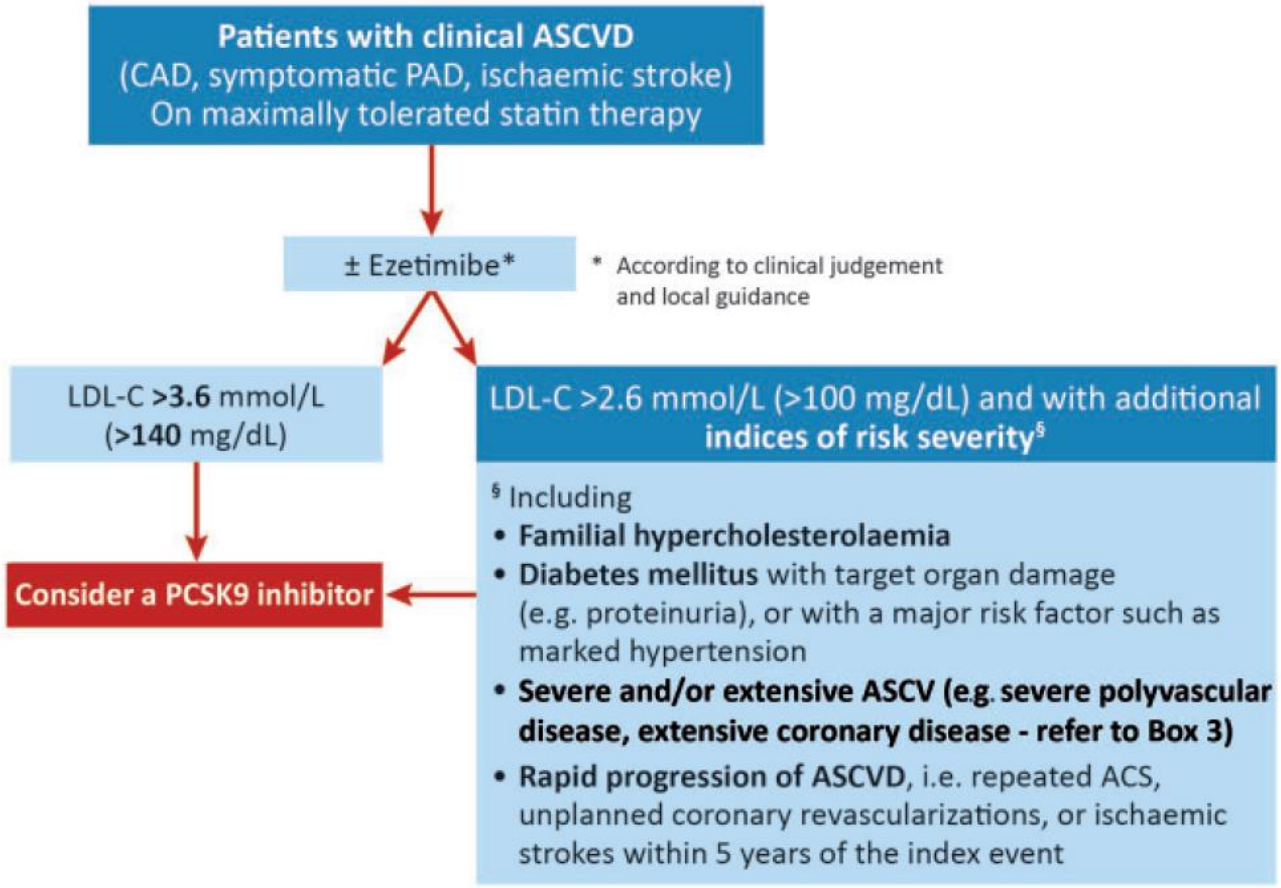


Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)	LONG TERM alirocumab ≥2 LDL-C <25 mg/dL (n=562)
Infections and infestations	36.3% (687)	38.5% (1286)	34.0% (271)	35.4% (102)	39.0% (219)
Nasopharyngitis	9.3% (176)	9.8% (326)	8.3% (66)	10.1% (29)	10.0% (56)
Upper respiratory tract infection	6.7% (126)	6.1% (203)	4.5% (36)	5.2% (15)	5.7% (32)
Urinary tract infection	4.1% (77)	4.1% (137)	4.6% (37)	4.9% (14)	5.5% (31)
Influenza	3.9% (73)	5.2% (173)	3.6% (29)	4.2% (12)	4.1% (23)
Bronchitis	3.3% (63)	3.8% (126)	4.4% (35)	3.1% (9)	5.2% (29)
Sinusitis	2.7% (51)	2.6% (87)	2.6% (21)	3.1% (9)	3.0% (17)
Lower respiratory tract infection	1.4% (26)	1.6% (53)	2.0% (16)	2.1% (6)	2.8% (16)
Gastroenteritis	2.3% (43)	1.9% (62)	0.6% (5)	1.0% (3)	0.7% (4)
Musculoskeletal and connective tissue disorders	25.2% (478)	24.2% (808)	21.1% (168)	20.1% (58)	22.6% (127)
Back pain	4.3% (82)	4.0% (133)	4.3% (34)	4.2% (12)	5.0% (28)
Arthralgia	5.0% (95)	4.0% (134)	3.1% (25)	2.1% (6)	3.2% (18)
Myalgia	4.8% (91)	4.9% (162)	3.1% (25)	3.8% (11)	3.0% (17)
Muscle spasms	2.4% (45)	2.8% (94)	2.5% (20)	3.5% (10)	2.8% (16)
Pain in extremity	3.4% (64)	2.4% (81)	2.1% (17)	1.4% (4)	2.1% (12)
Osteoarthritis	2.2% (42)	2.1% (69)	1.8% (14)	1.0% (3)	2.1% (12)
Musculoskeletal pain	1.4% (27)	1.9% (65)	1.0% (8)	1.0% (3)	1.4% (8)
Gastrointestinal disorders	16.8% (318)	17.0% (567)	12.7% (101)	10.1% (29)	13.7% (77)
Diarrhea	3.9% (74)	4.3% (142)	3.0% (24)	1.4% (4)	3.9% (22)
Nausea	2.5% (47)	2.2% (74)	0.9% (7)	1.0% (3)	0.9% (5)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)	LONG TERM alirocumab ≥2 LDL-C <25 mg/dL (n=562)
General disorders and administration-site conditions	14.9% (282)	15.1% (504)	10.2% (81)	6.9% (20)	11.0% (62)
Injection-site reaction	3.9% (73)	5.7% (191)	3.0% (24)	3.5% (10)	3.6% (20)
Fatigue	2.5% (48)	2.8% (93)	2.6% (21)	2.4% (7)	3.0% (17)
Non-cardiac chest pain	1.8% (35)	1.6% (54)	1.8% (14)	0.3% (1)	2.0% (11)
Nervous system disorders	14.9% (283)	14.9% (497)	10.3% (82)	9.0% (26)	11.2% (63)
Dizziness	3.6% (69)	3.0% (100)	1.8% (14)	1.4% (4)	1.4% (8)
Headache	4.6% (87)	4.6% (153)	1.8% (14)	1.4% (4)	1.8% (10)
Hemorrhagic stroke	0.1% (1)	0.1% (2)	0	0	0
Metabolism and nutrition disorders	6.3% (120)	6.9% (232)	7.0% (56)	7.3% (21)	8.0% (45)
Type 2 diabetes mellitus	0.7% (14)	1.1% (36)	1.8% (14)	1.4% (4)	2.5% (14)
Diabetes mellitus	1.3% (24)	1.2% (39)	1.5% (12)	2.4% (7)	1.4% (8)
Eye disorders	3.7% (71)	4.6% (152)	5.3% (42)	6.9% (20)	6.4% (36)
Cataract	0.9% (17)	0.8% (26)	1.5% (12)	2.4% (7)	1.8% (10)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2.5% (48)	2.5% (85)	2.8% (22)	2.4% (7)	3.0% (17)

Data from LONGTERM, FH I, FH II, HIGH FH and COMBO II taken from a pre-specified analysis prior to study completion, which included safety data at least 52 weeks for all continuing patients.

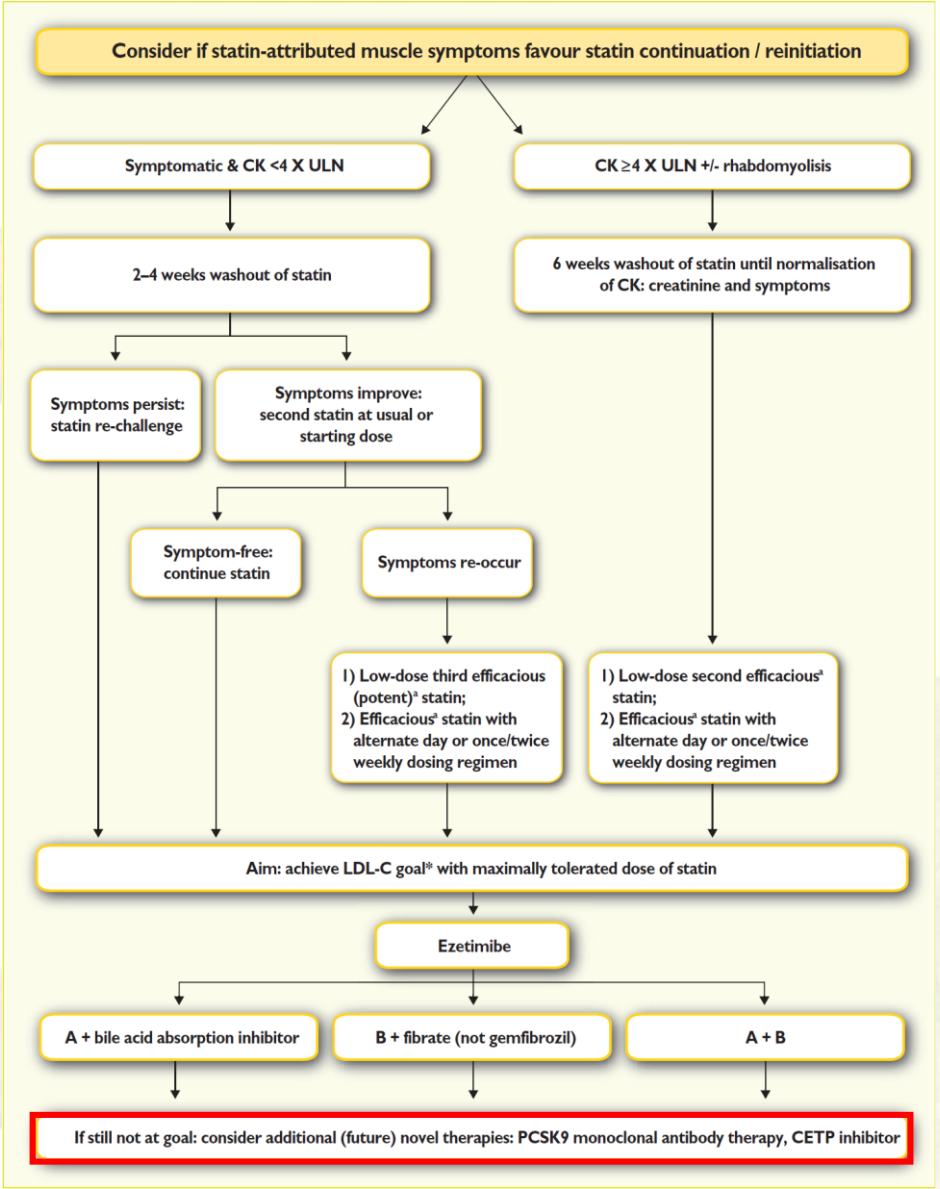
2017 Update ESC/EAS on PCSKi



Landmesser U, Chapman MJ, et al. Eur Heart J 2018;39:1131-1143

Guías Dislipemia ESC 2016

Algoritmo para tratamiento de molestias musculares en pacientes con estatinas



Catapano A et al. Eur Heart J 2016