

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

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Residual Risk After Acute Coronary Syndrome

- Remains high despite evidence-based preventive therapies
- Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
- Is reduced when LDL-C is lowered by
 - Statin therapy, compared with placebo¹
 - High-intensity, compared with moderate-intensity statin therapy²
 - Ezetimibe, compared with placebo, added to statin³

1. Schwartz GG, et al. JAMA 2001;285:1711-8. 2. Cannon CP, et al. NEJM 2004;350:1495-504.

3. Cannon CP, et al. NEJM 2015;372:2387-97.

Study Hypothesis

Alirocumab, versus placebo, reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Main Inclusion Criteria

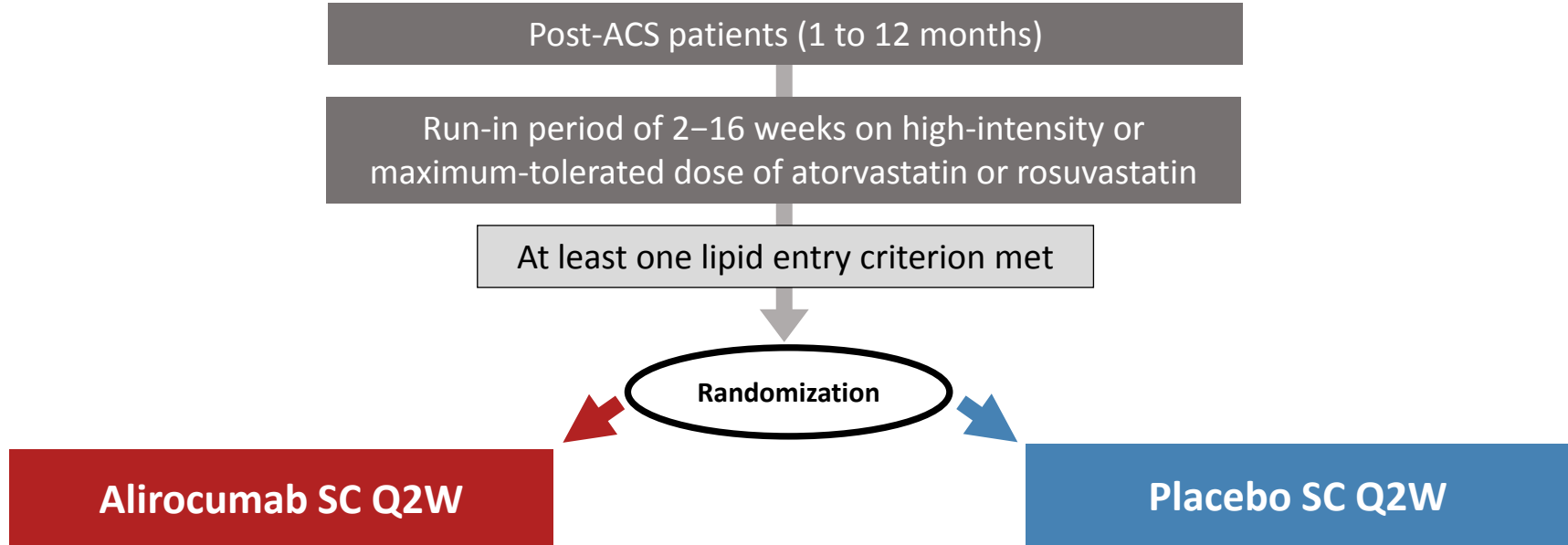
- **Age** ≥ 40 years
- **ACS**
 - 1 to 12 months prior to randomization
 - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
 - Atorvastatin 40 to 80 mg daily *or*
 - Rosuvastatin 20 to 40 mg daily *or*
 - Maximum tolerated dose of one of these agents for ≥ 2 weeks
- **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 m²
- Positive pregnancy test

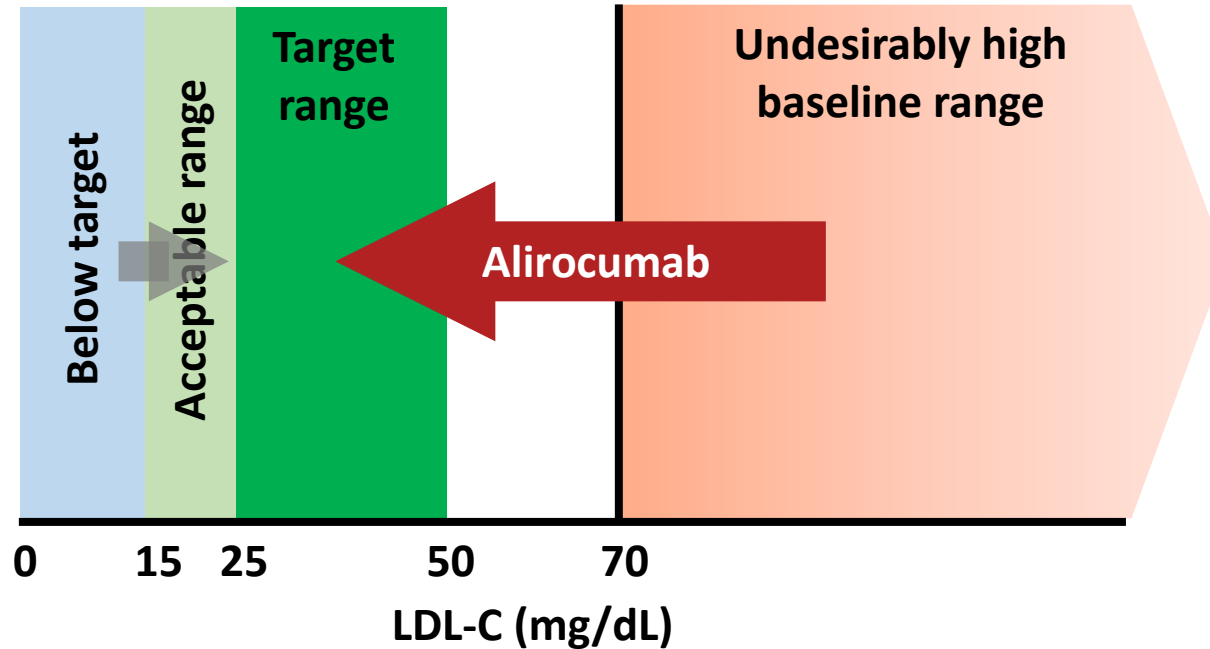
Treatment Assignment



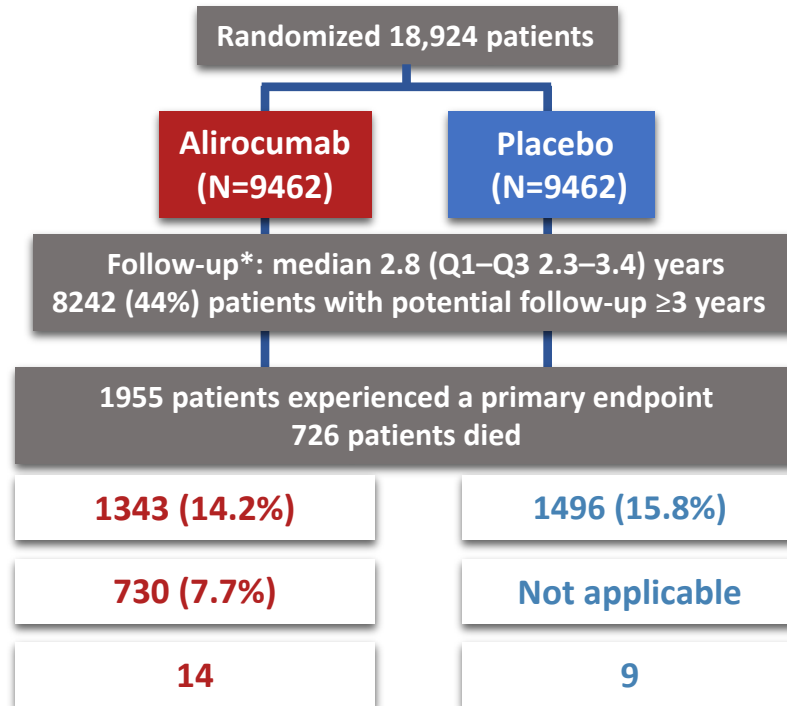
Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

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.



Patient Disposition



- Premature treatment discontinuation
- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
- Patients lost to follow-up (vital status)

*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)

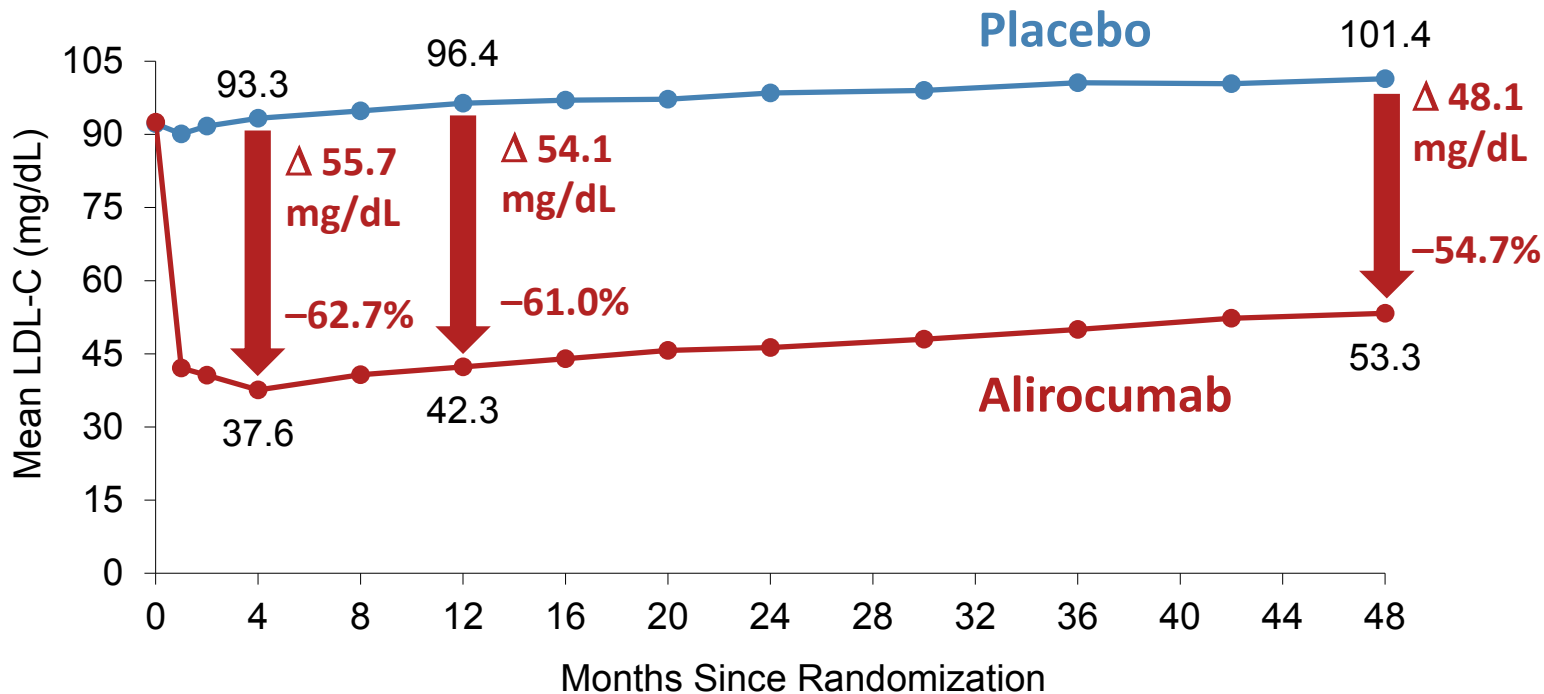
92.5% of patients qualified on the basis of LDL-C \geq 70 mg/dL

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)

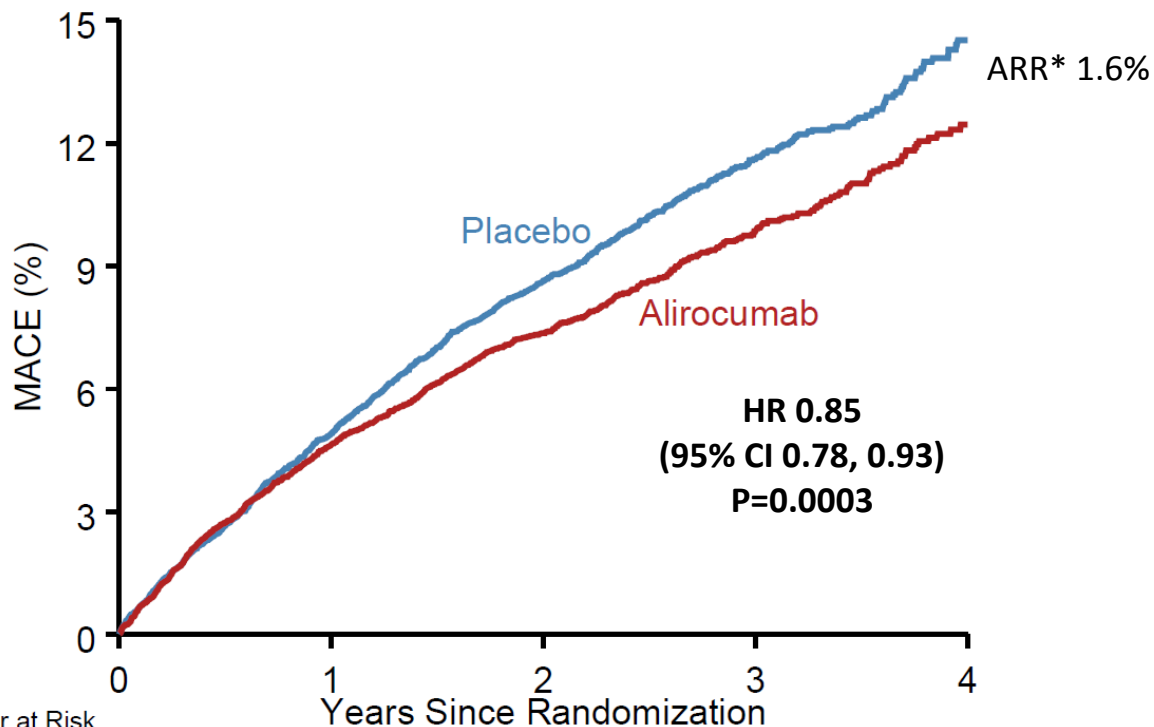
*Patients not on statins were authorized to participate if tolerability issues were present and documented

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

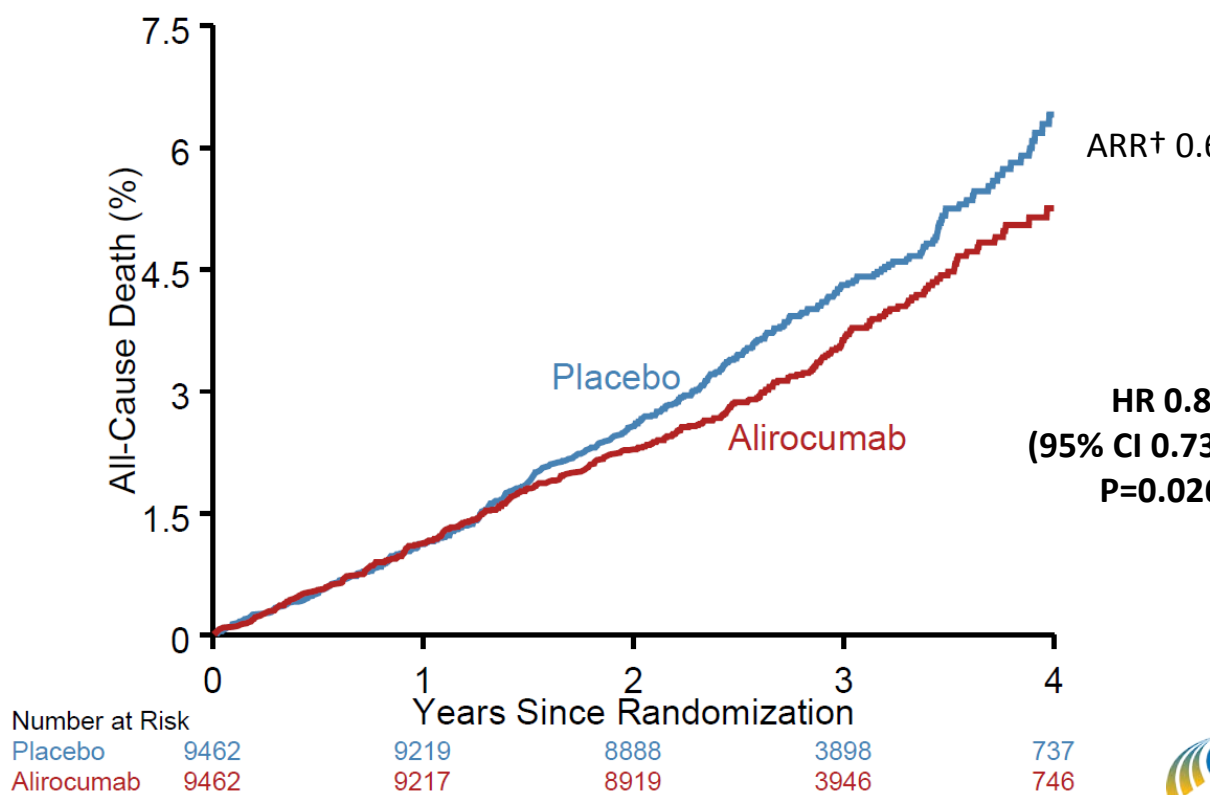
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	903 (9.5)	1052 (11.1)	0.85 (0.78, 0.93)	0.0003
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
Non-fatal MI	626 (6.6)	722 (7.6)	0.86 (0.77, 0.96)	0.006
Ischemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57, 0.93)	0.01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

Main Secondary Efficacy Endpoints: 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*

*Nominal P-value

All-Cause Death



*Nominal P-value

†Based on cumulative incidence

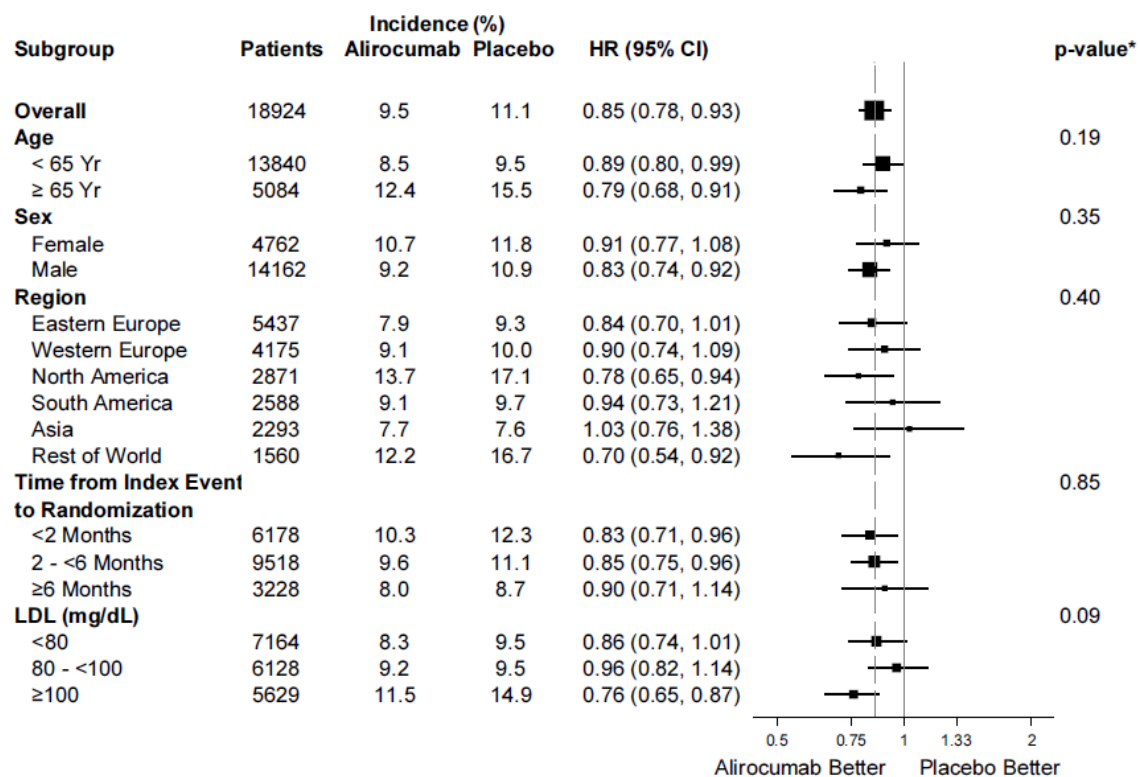


Other Efficacy Endpoints

Endpoint n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Lo P-
Ischemia-driven coronary revascularization	731 (7.7)	828 (8.8)	0.88 (0.79, 0.97)	C
Hospitalization for CHF	176 (1.9)	179 (1.9)	0.98 (0.79, 1.20)	



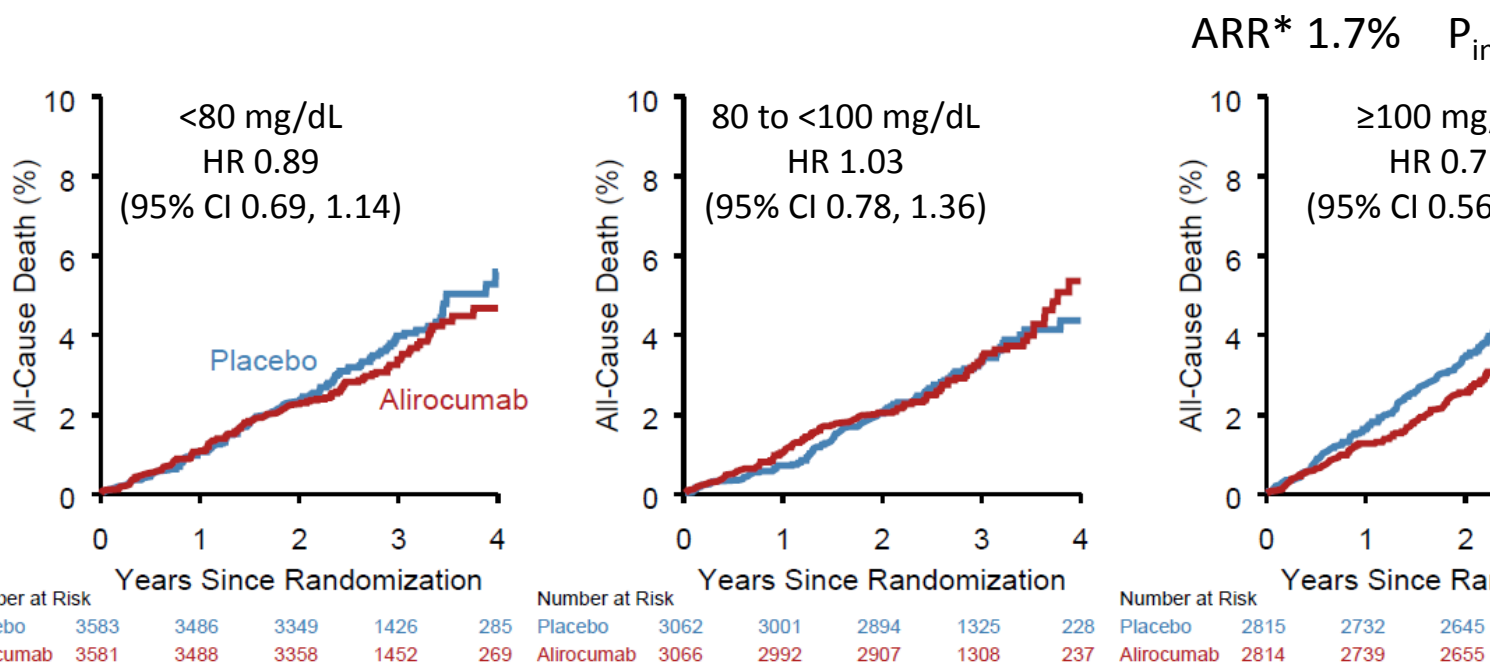
Primary Efficacy in Main Prespecified Subg



*P-values for interaction



Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups



*Based on cumulative incidence



Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL 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 study



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

