5 in 50- The Top 2018 Trials To Impact Your Practice-Prevention

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- Member, Steering Committee, Patient and Provider Assessment of Lipid Management (PALM) Registry at the Duke Clinical Research Institute (DCRI) [No financial remuneration].
- Associate Editor for Innovation, ACC.org

ODYSSEY OUTCOMES

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.

ODYSSEY OUTCOMES

Primary Efficacy Outcome

Time of first occurrence of:

- **Coronary heart disease (CHD) death, or**
- **Non-fatal MI, or**
- **Fatal or non-fatal ischemic stroke, or**
- **Unstable angina requiring hospitalization***

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the Duke Clinical Research Institute (DCRI). Members were unaware of treatment assignment and lipid levels

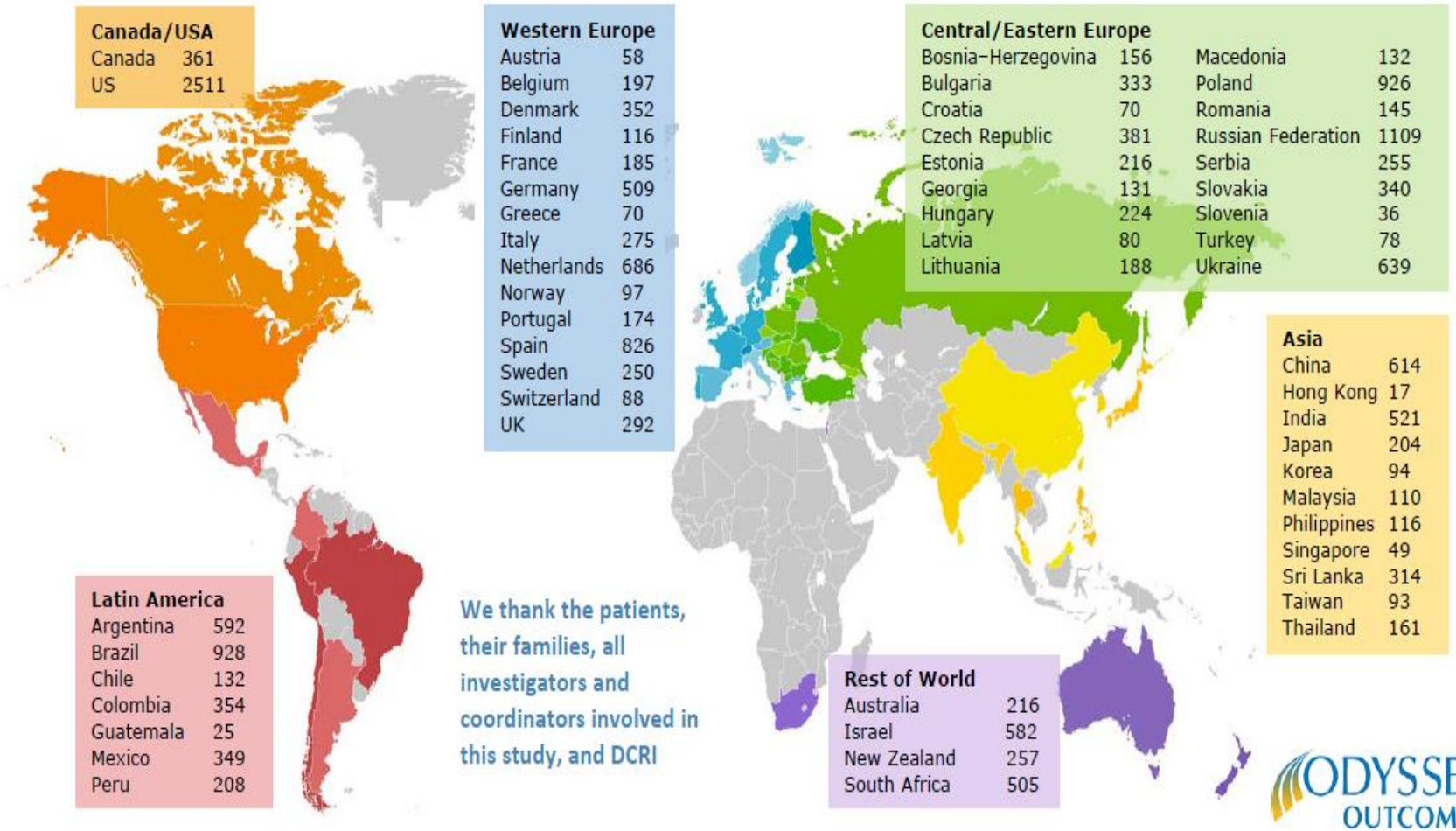
*Required all of the following:

1. Hospital admission >23 h for MI symptoms, ↑ tempo in prior 48 hours and/or ≥20 min of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

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

ODYSSEY OUTCOMES

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

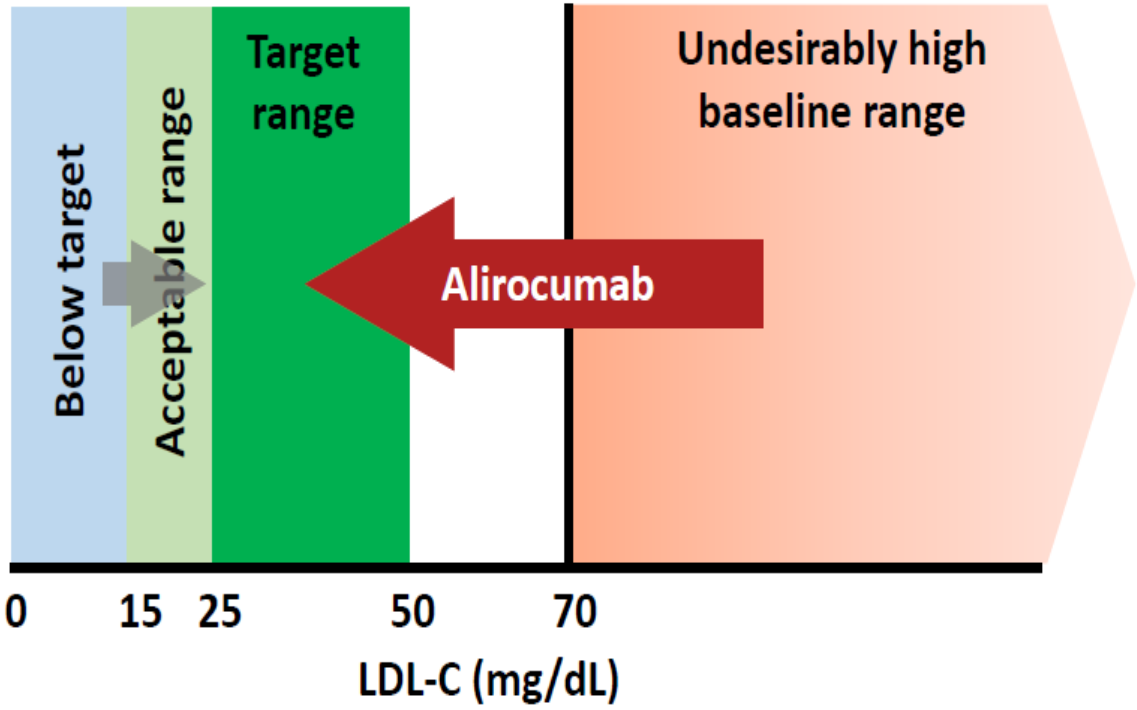
We thank the patients, their families, all investigators and coordinators involved in this study, and DCRI

Rest of World	
Australia	216
Israel	582
New Zealand	257
South Africa	505

ODYSSEY OUTCOMES 18

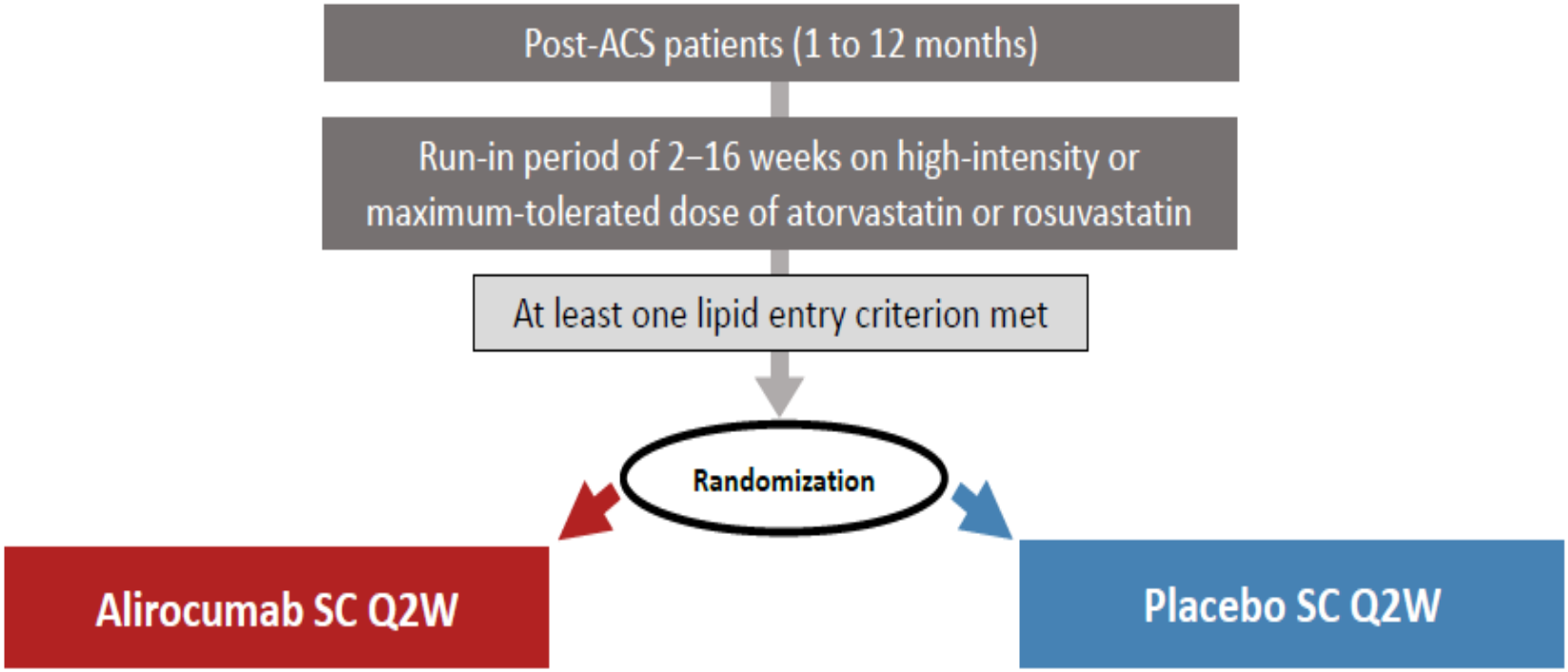
A Target Range for LDL-C

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.

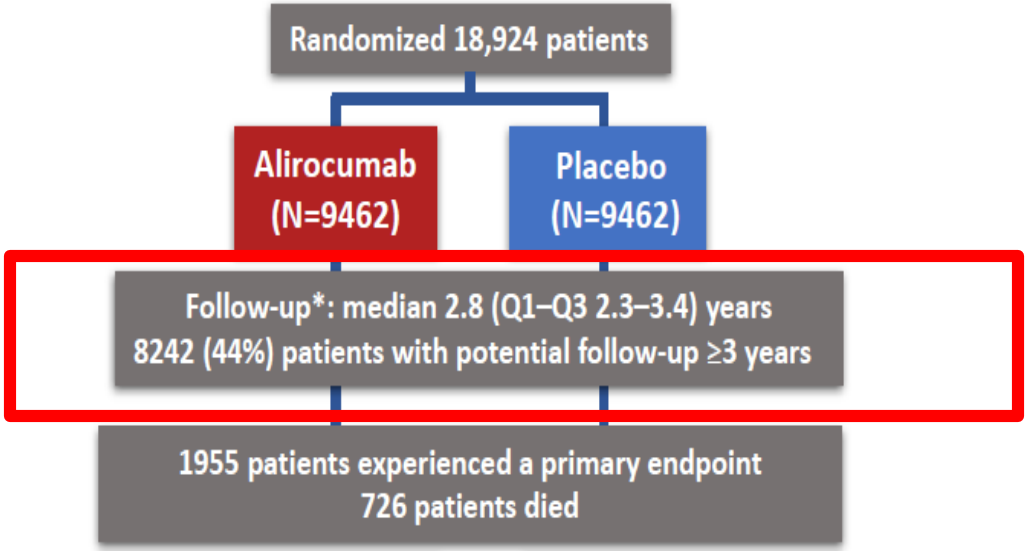
Treatment Assignment



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.

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

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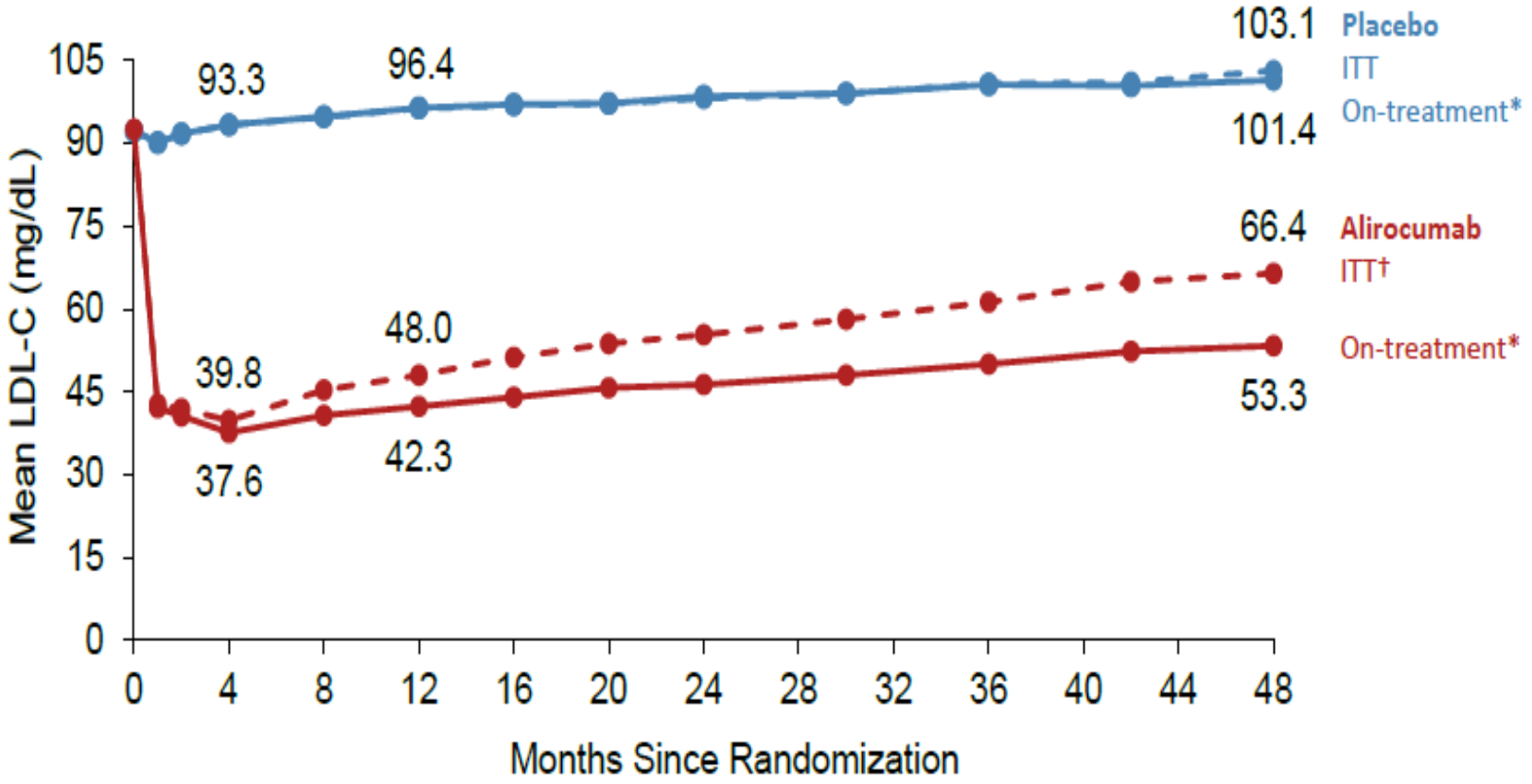
Baseline Lipid-Lowering Therapy

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

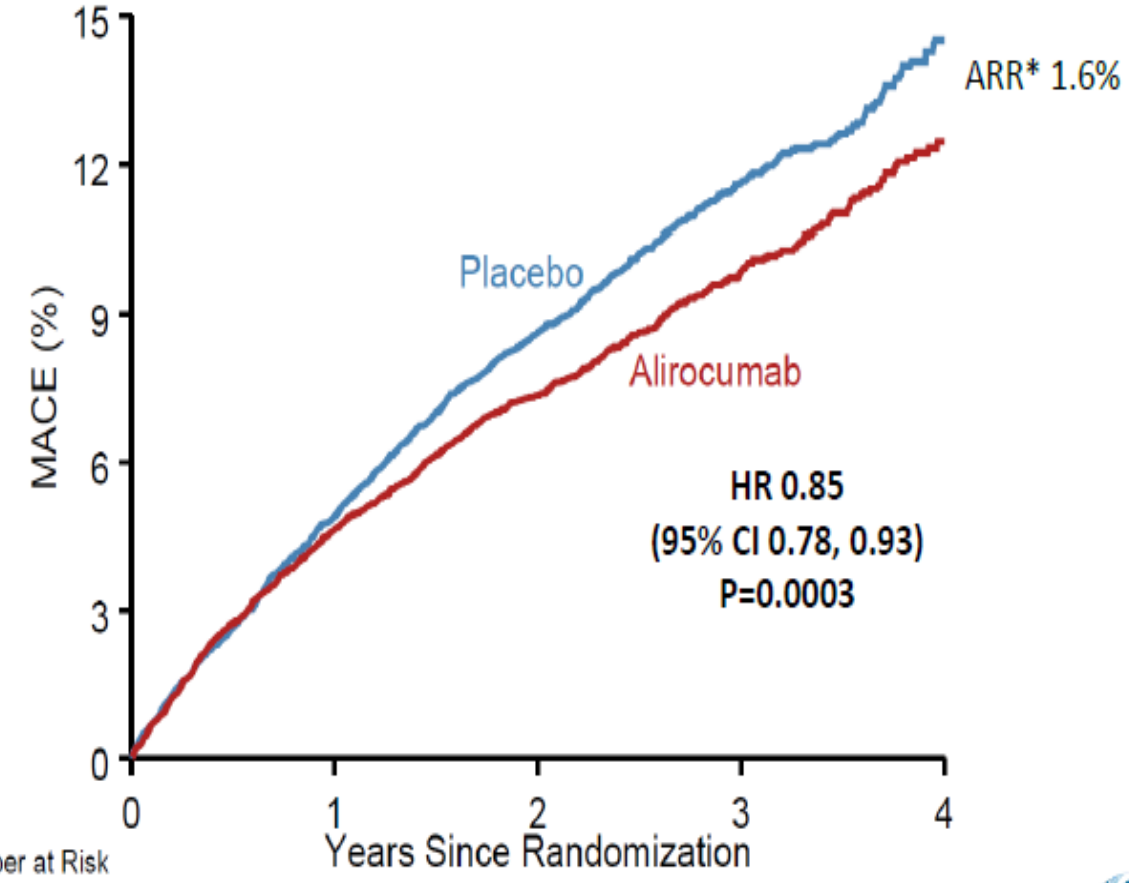
LDL-C: ITT and On-Treatment Analyses



*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

ODYSSEY OUTCOMES 28

Primary Efficacy Endpoint: MACE



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

*Based on cumulative incidence

ODYSSEY OUTCOMES

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***

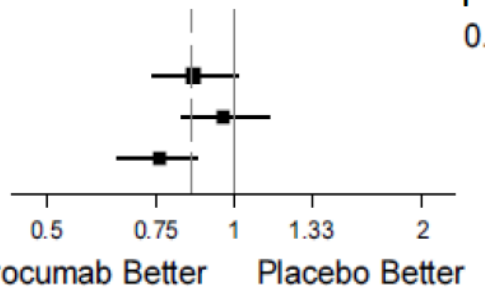
*Nominal P-value

ODYSSEY OUTCOMES

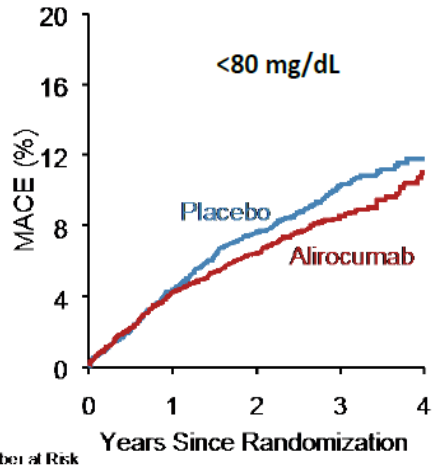
Is There a Sweet Spot Where PCKS9i Have the Most Impact?

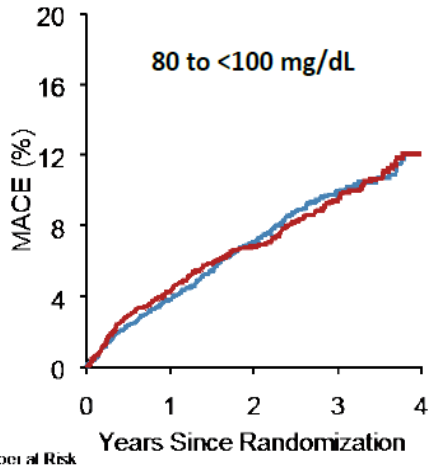
Primary Efficacy in Main Prespecified Subgroups

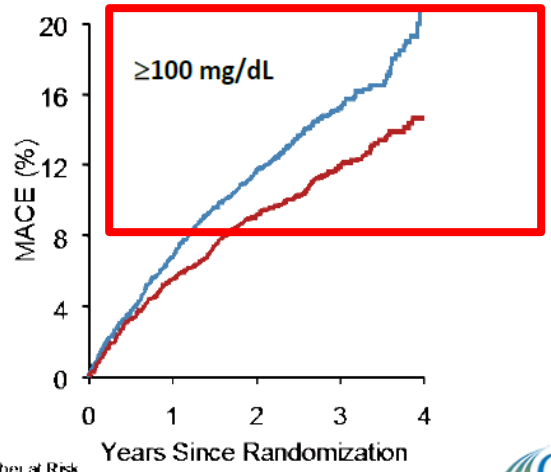
Subgroup	Patients	Incidence (%) Alirocumab	Incidence (%) Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction







Number at Risk						
Placebo	3683	3347	3122	1290	256
Alirocumab	3681	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

1.6% vs. 3.4% ARR, NNT 64 vs. 29

ODYSSEY OUTCOMES

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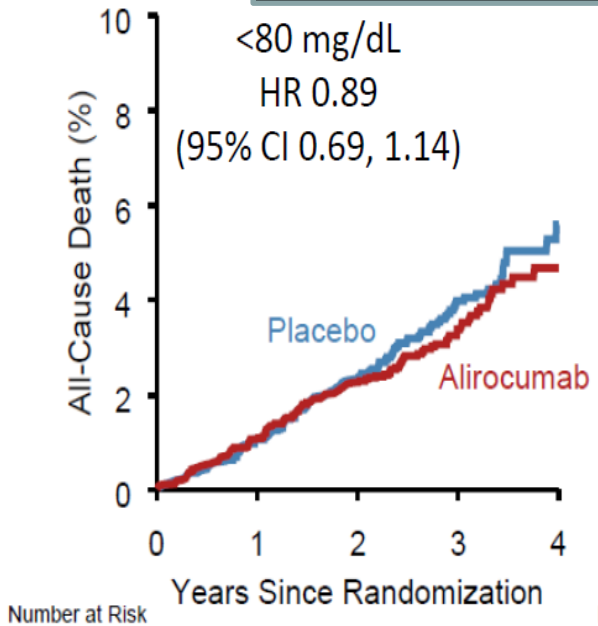
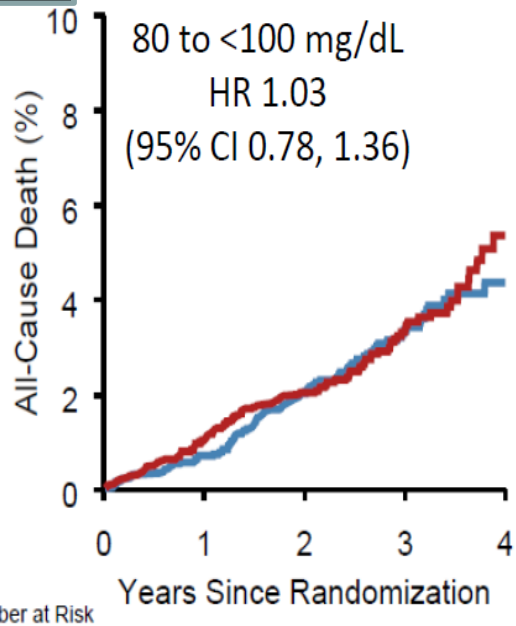
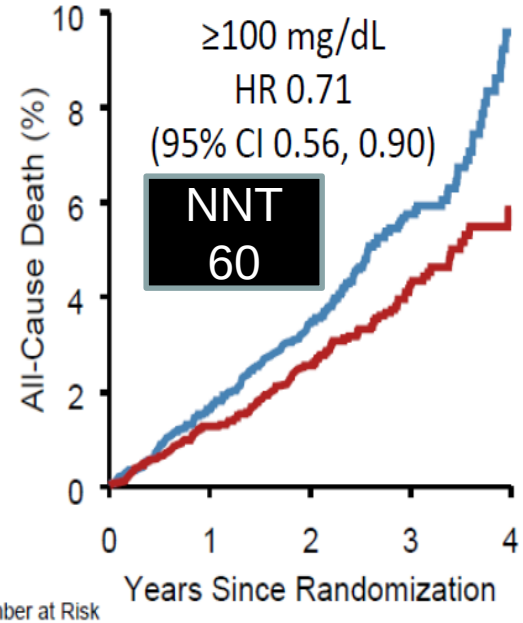
Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR = 0.6% for all patients, NNT 163

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







Number at Risk					
Placebo	3583	3486	3349	1426	285
Alirocumab	3581	3488	3358	1452	269

Number at Risk					
Placebo	3062	3001	2894	1325	228
Alirocumab	3066	2992	2907	1308	237

Number at Risk					
Placebo	2815	2732	2645	1147	224
Alirocumab	2814	2739	2655	1186	240

*Based on cumulative incidence

ODYSSEY OUTCOMES

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)

ODYSSEY OUTCOMES vs. FOURIER

Trial Design	ODYSSEY OUTCOMES	FOURIER
Patient population	Post ACS	Stable ASCVD
LDL-C criteria (mg/dL)	≥70	≥70
Median Baseline LDL-C (mg/dL)	87	92
On high intensity statin	89%; 33% on statin prior to ACS	69%
PCSK9 dosing	Alirocumab 75 or 150 mg Q2W, titrated to target LDL-C (15-50 mg/dl)	Evolocumab 140 mg Q2Wor 420 mg Q4W
Duration of follow-up (months)	33.6 (44% with ≥36 months)	26.4
Primary endpoint	4-point: CHD death, MI, ischemic stroke, UA requiring hospitalization	5-point: CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization

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ODYSSEY OUTCOMES vs. FOURIER

Efficacy	ODYSSEY OUTCOMES	FOURIER
Change in LDL-C (Absolute – mg/dL)	54	56
% change in LDL-C (on-treatment arm)	↓61%	↓59%
Relative reduction in primary endpoint	15%	15%
All-cause mortality	↓15% (P=0.026*)	↑4% (NS)

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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