THE ABC'S OF PCSK9 INHIBITORS

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Tuesday, May 10, 2016

MR. FUJI & PROFESSOR TORU TANAKA

TONY GAREA & DEAN HO

THE HART FOUNDATION AND THE ROAD WARRIORS

THE BUSHWHACKERS

1. **Both** Alirocumab and Evolocumab are indicated as adjuncts to diet and maximally tolerated statin therapy for the treatment of adults with Heterozygous Familial Hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) requiring additional lowering of LDL-C.
2. Only Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies for patients with Homozygous Familial Hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

CURRENT INDICATIONS FOR USE OF THE PCSK9 INHIBITORS

LIMITATIONS OF USE

The effect of Alirocumab and Evolocumab on cardiovascular morbidity and mortality has not been determined

ALI-07224
08242015

ODYSSEY A Robust Clinical Development Program

HeFH	High CV Risk		
On top of max-tolerated statin	On top of max-tolerated statin	On top of typical statin doses	Not receiving statin
FH I (N=486)	COMBO I (N=316)	OPTIONS I (N=355)	MONO[2] (N=103)
FH II (N= 249)	COMBO II (N=720)	OPTIONS II (n=305)	**Statin intolerant**
HIGH FH (N=107)	CHOICE I (N=700)		ALTERNATIVE (N=314)
LONG TERM (N=2341)			CHOICE II[3] (N=200)
OLE[1] (N ≥1,000)	OUTCOMES (N=18,000)	← Ongoing	

- Large and robust trial program
- 14 trials with >24,300 patients
- Primary endpoint evaluated at 24 weeks
- Double-blind design (6, 12, 18, and 24 months)
- Evaluation of Q2W and Q4W dosing regimens and 75- and 150-mg doses
- >5,000 patient-years exposure[(4)]

All studies : every 2 weeks (Q2W) regimens (75/150 mg with potential dose ↑ from 75 –150 mg) except CHOICE I (300 mg Q4W) and II (150 mg Q4W)

1. Open-Label Extension open to HeFH patients included in other studies.
2. ODYSSEY MONO included patients at moderate CV risk.
3. ODYSSEY CHOICE II includes some patients on additional nonstatin lipid-lowering therapy.
4. ≥4,500 double-blind patient-years at completion of pivotal studies in initial submission.

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

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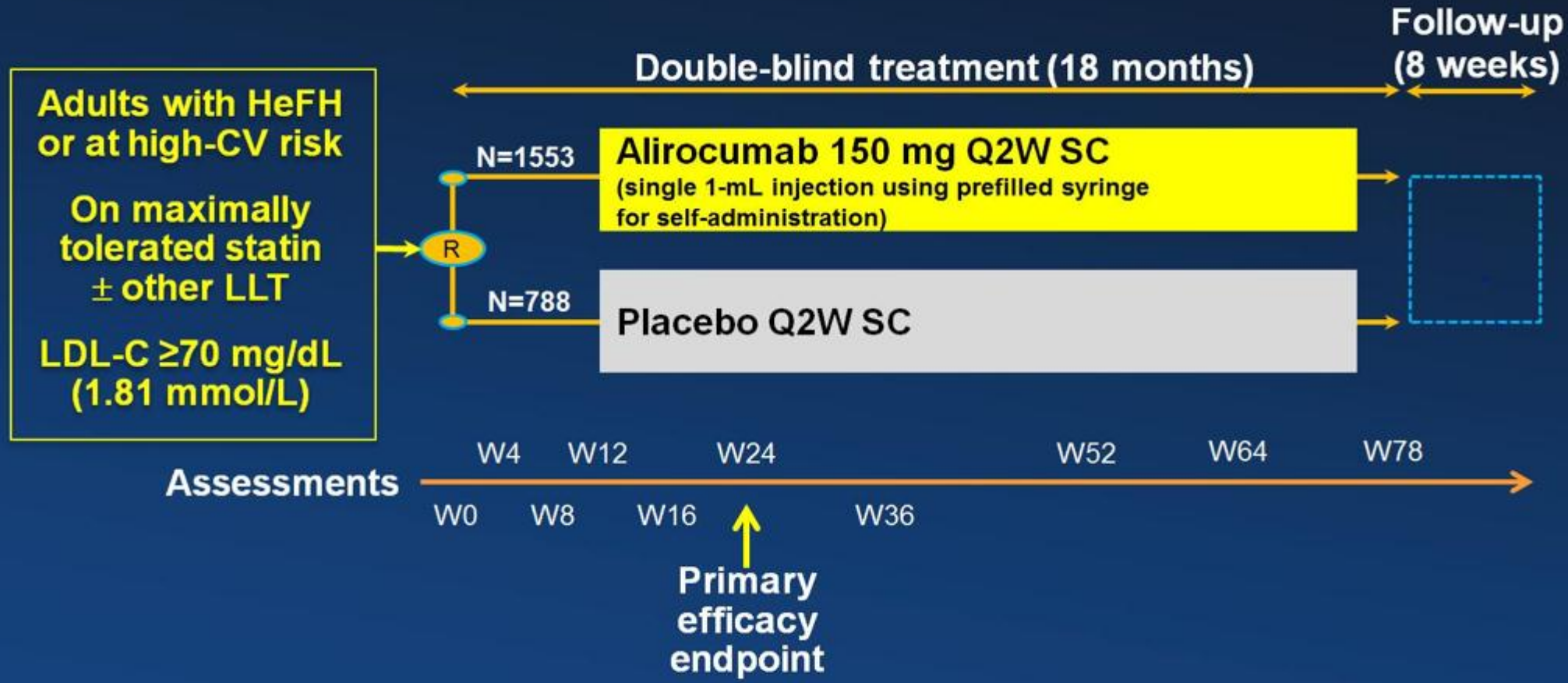
This study was funded by Sanofi and Regeneron Pharmaceuticals

Robinson JG et al. *N Engl J Med.* 2015; 372:1489-1499.

ODYSSEY LONG TERM
Study Design



CV=cardiovascular; HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; Q2W=every 2 weeks; SC=subcutaneous; W=week.
ClinicalTrials.gov identifier: NCT01507831.
Robinson JG et al. *N Engl J Med* 2015; 372:1489-1499. (Appendix)

Baseline Characteristics

Demographics and CV History and Risk Factors

All randomized patients	Alirocumab (N=1553)	Placebo (N=788)
Age, years, mean ± SD	60.4±10.4	60.6±10.4
Male sex, n (%)	983 (63.3)	474 (60.2)
White race, n (%)	1441 (92.8)	730 (92.6)
Cardiovascular history and risk factors:		
Body mass index, kg/m^2, mean±SD	30.2±5.7	30.5±5.5
HeFH, n (%)*	276 (17.8)	139 (17.6)
Coronary heart disease, n (%)	1055 (67.9)	552 (70.1)
Coronary heart disease risk equivalent, n (%)†	639 (41.1)	323 (41.0)
Type 2 diabetes, n (%)	542 (34.9)	267 (33.9)
Current smoker, n (%)	325 (20.9)	159 (20.2)
Calculated LDL-C, mean ± SD‡	122.7±42.6	121.9±41.4

*Diagnosed by genotyping in 40.2% of patients and by clinical criteria (WHO/Simon Broome) in 59.8% of patients (2 groups combined). †Coronary heart disease risk equivalents included: peripheral artery disease, ischemic stroke, moderate chronic kidney disease (eGFR 30 to <60 ml/min/1.73 m^2), or diabetes mellitus plus 2 or more additional risk factors (hypertension; ankle–brachial index of ≤0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or family history of premature coronary heart disease). ‡Calculated with the use of the Friedewald formula.

Robinson JG et al. *N Engl J Med*. 2015;372:1489-1499.

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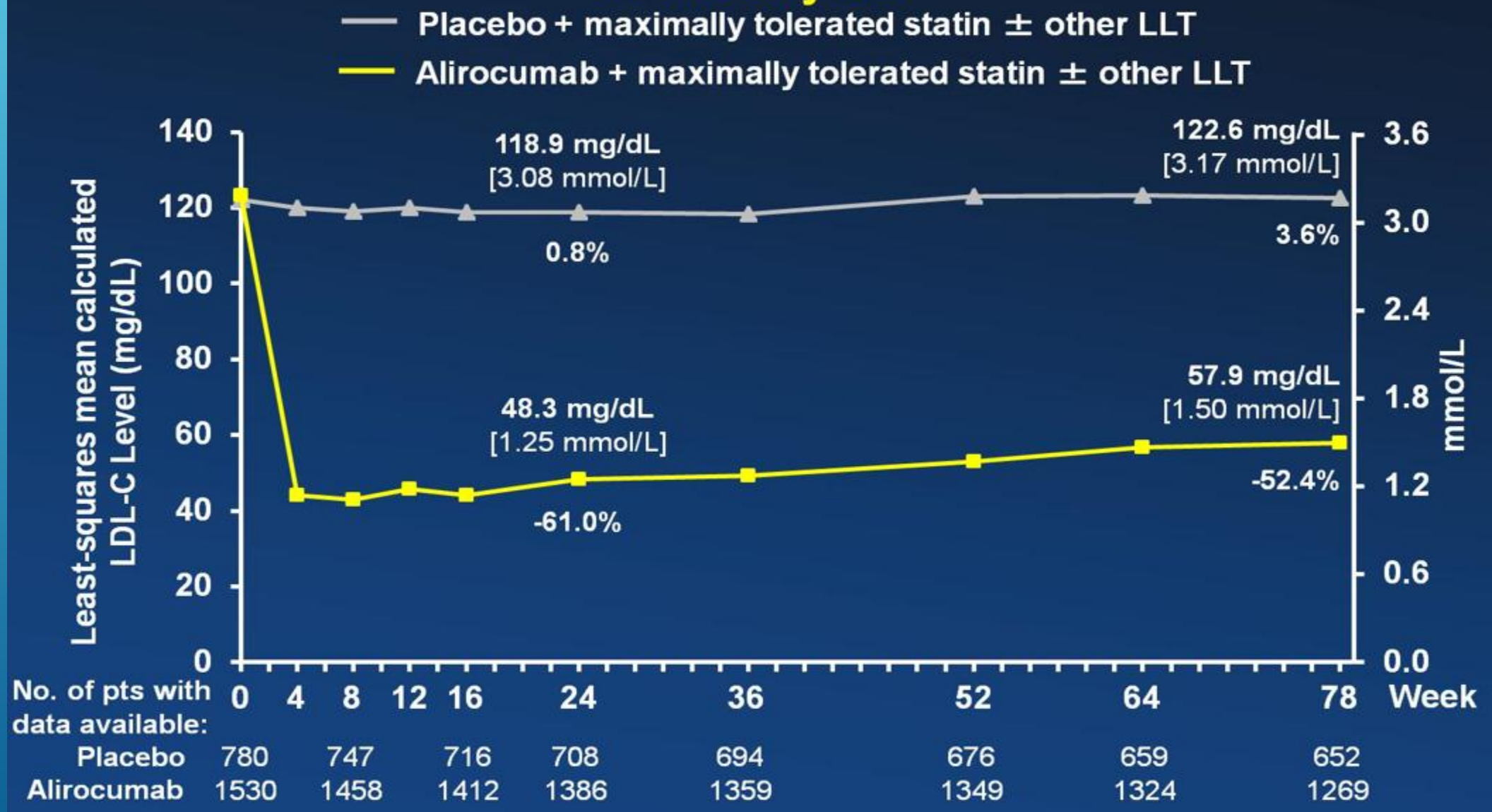
Calculated LDL-C Levels over Time

ITT Analysis



Robinson JG et al. *N Engl J Med*. 2015;372:1489-1499.

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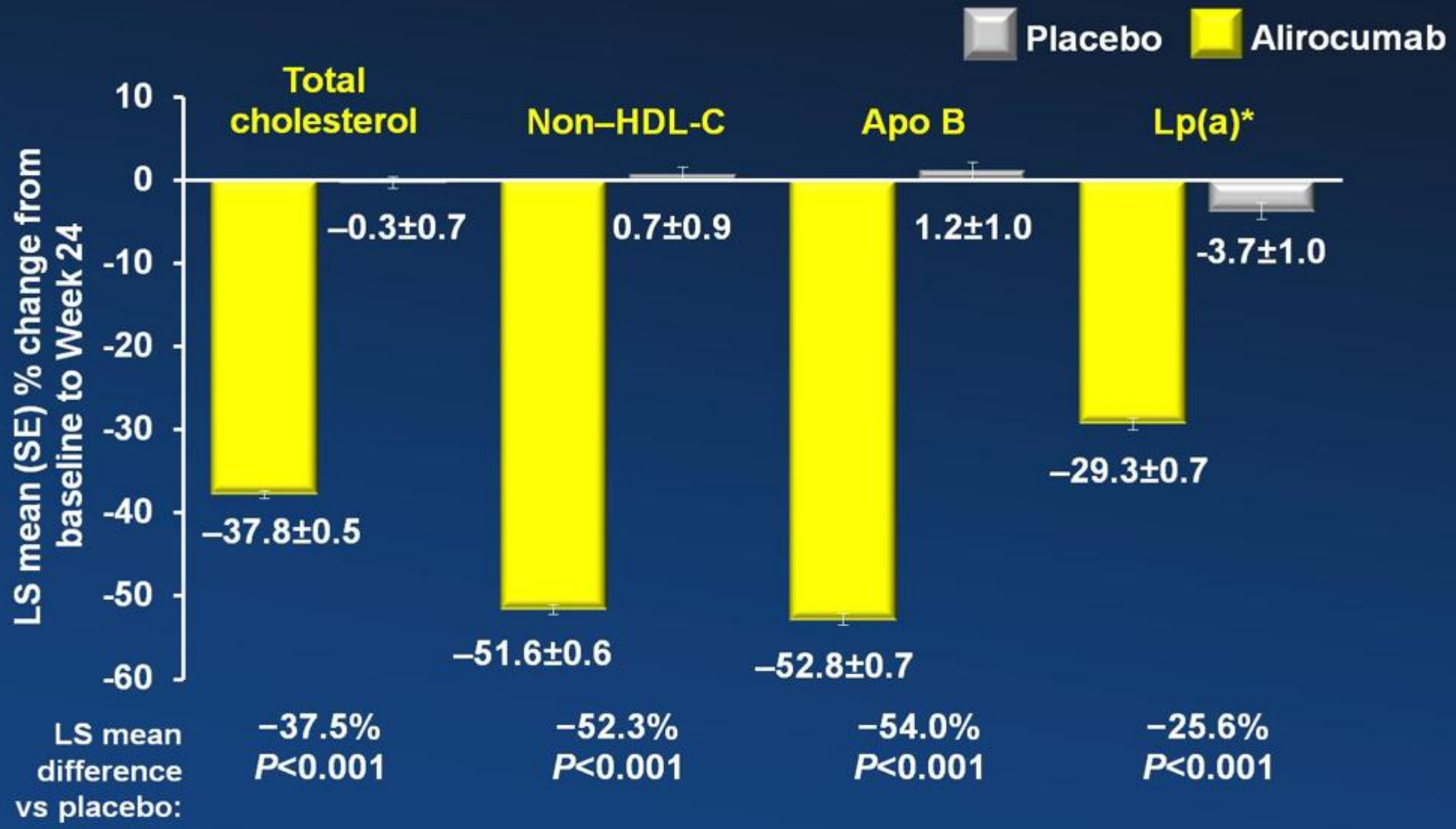
Change from Baseline to Week 24:

Total Cholesterol, Non–HDL-C, Apo B, and Lp(a) (ITT)



These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.

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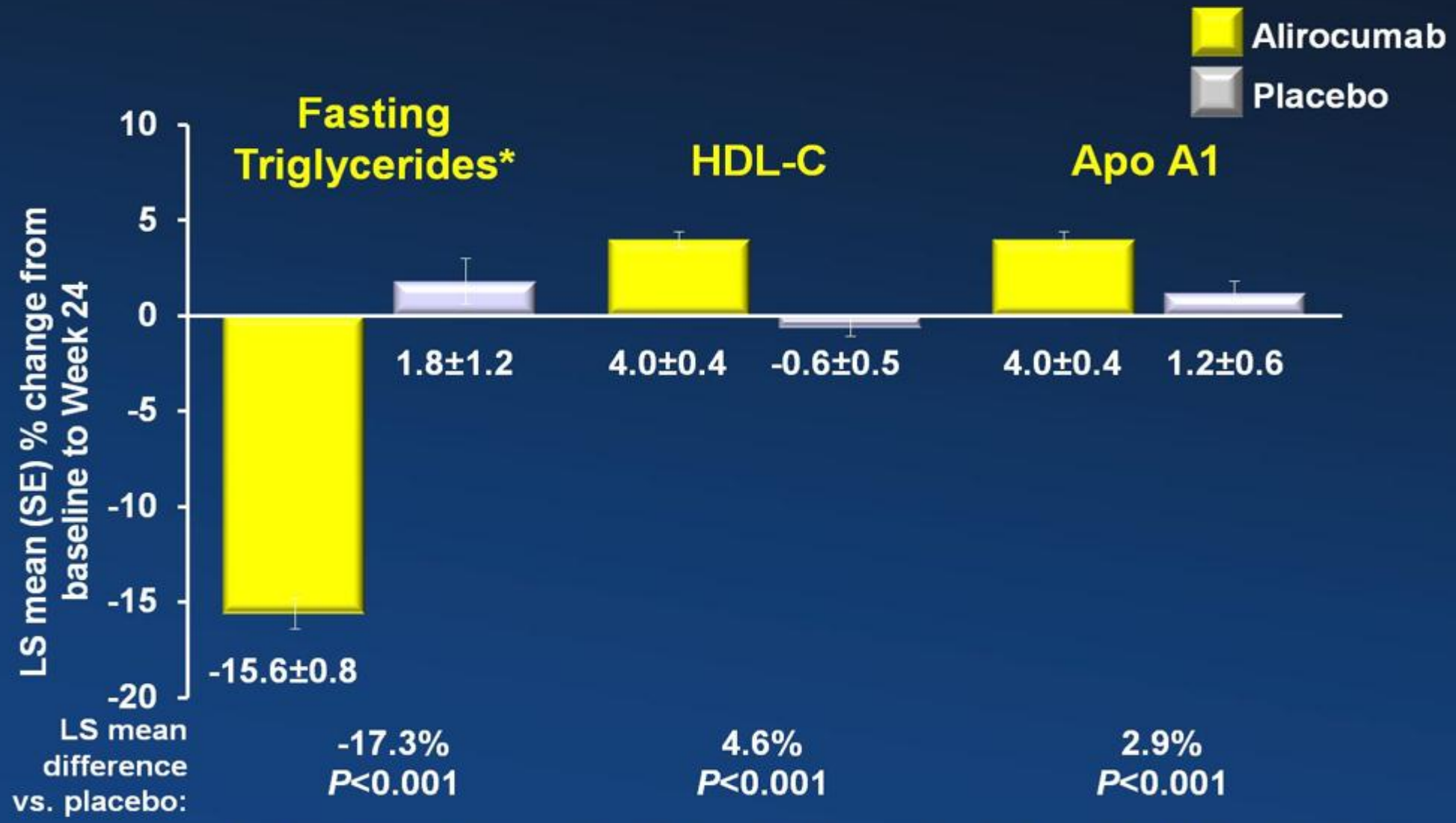
Change from Baseline to Week 24

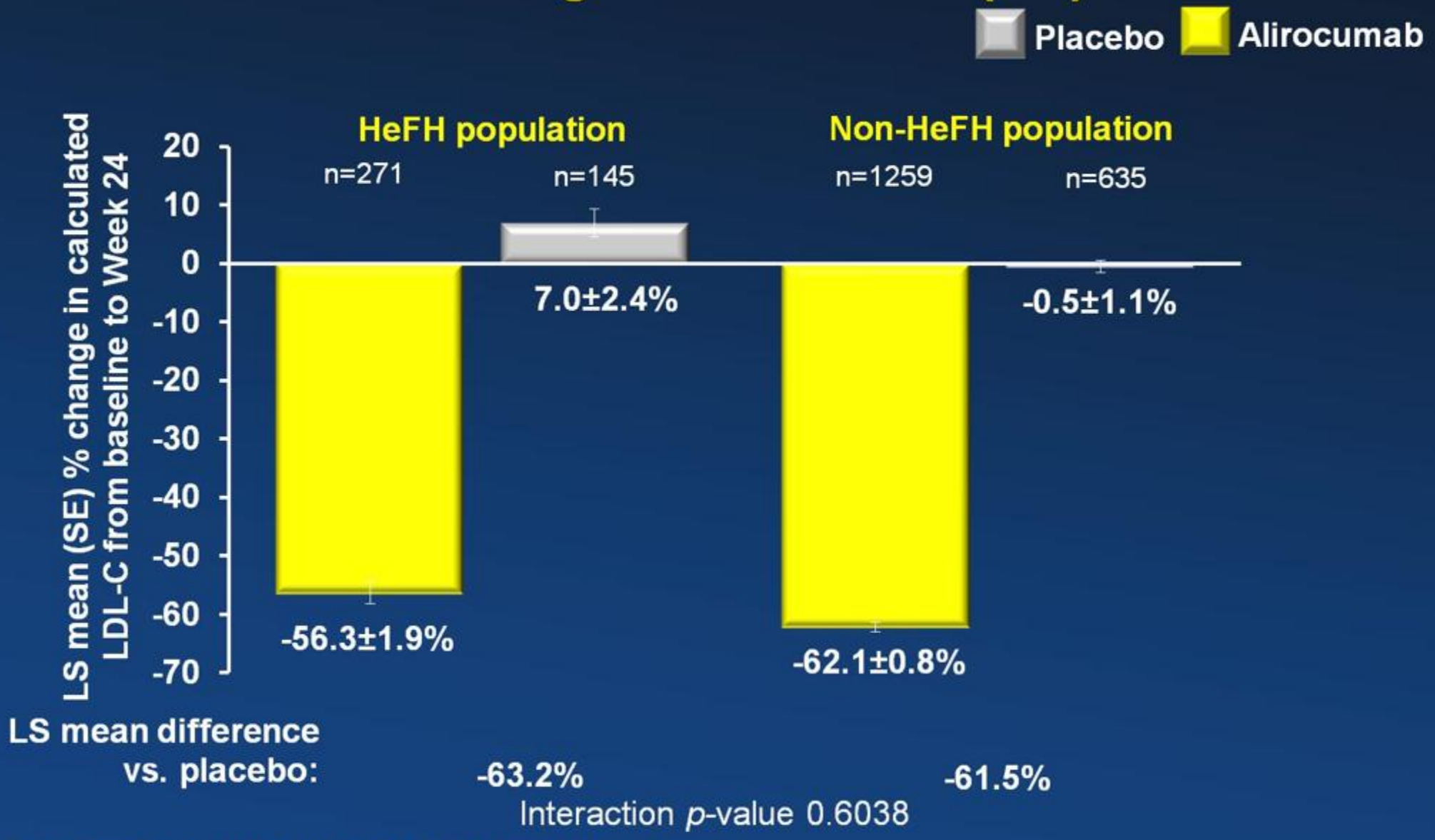
Fasting Triglycerides, HDL-C, and Apo A1 (ITT)



These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.

Change in LDL-C from Baseline to Week 24

According to HeFH status (ITT)



Robinson JG et al. *N Engl J Med* 2015;372:1489-1499. (Appendix)

Cardiovascular Adverse Events of Interest

Number of patients (%)	Alirocumab (n=1550)	Placebo (n=788)	*P*-value*
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68

MACE (a composite of the first 4 categories): 27/1550 in the Alirocumab patients (1.7%) versus 26/788 in the placebo group (3.3%); HR = 0.52; p = 0.02).

**P*-values are provided for descriptive purposes only.

Robinson JG, et al. *N Engl J Med*. 2015;372:1489-1499.

Adverse Events
Summary

Number of patients (%)	Alirocumab (N=1550)	Placebo (N=788)	*P*-value*
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08

- **Mean study-drug exposure in the 1550 alirocumab-treated patients and 788 placebo patients:**
  - **70 weeks**
  - **2061 patient-years of exposure to alirocumab 150 mg Q2W**

**P*-values are provided for descriptive purposes only.

Robinson JG, et al. *N Engl J Med* 2015; 372:1489-1499.

Adverse Events By System Organ Class
Comparable in Patients With 2 Consecutive LDL-C <25 mg/dL

% (n) of patients	Alirocumab (n=1550)	Alirocumab group with LDL-C <25 mg/dL (N=575)	Placebo (n=788)
Infections and infestations	48.3% (748)	42.3% (243)	48.6% (383)
Musculoskeletal and connective tissue disorders	30.1% (467)	26.1% (150)	30.7% (242)
Gastrointestinal disorders	20.5% (318)	16.7% (96)	20.6% (162)
Nervous system disorders	18.6% (289)	12.9% (74)	19.7% (155)
General disorders and administration-site conditions	16.1% (250)	11.3% (65)	17.8% (140)
Injury, poisoning, and procedural complications	15.5% (241)	13.2% (76)	15.7% (124)
Respiratory, thoracic, and mediastinal disorders	11.7% (182)	8.9% (51)	12.6% (99)
Cardiac disorders	11.0% (171)	10.6% (61)	12.9% (102)
Metabolism and nutrition disorders	10.2% (158)	9.6% (55)	9.3% (73)
Skin and subcutaneous tissue disorders	10.1% (156)	8.3% (48)	9.4% (74)
Vascular disorders	8.6% (133)	5.4% (31)	10.0% (79)
Eye disorders	7.0% (108)	7.0% (40)	6.2% (49)
Psychiatric disorders	6.5% (101)	5.2% (30)	8.5% (67)
Laboratory investigations	6.4% (99)	4.3% (25)	5.5% (43)
Renal and urinary disorders	5.5% (85)	4.7% (27)	6.6% (52)
Reproductive system and breast disorders	3.2% (50)	2.8% (16)	3.4% (27)
Neoplasms, benign, malignant, and unspecified	3.0% (47)	3.8% (22)	4.3% (34)
Blood and lymphatic system disorders	3.0% (46)	2.4% (14)	3.7% (29)
Ear and labyrinth disorders	2.4% (37)	1.7% (10)	3.9% (31)
Hepatobiliary disorders	1.7% (27)	1.4% (8)	2.3% (18)

Robinson JG, et al. *N Engl J Med.* 2015;372:1489-1499. (Appendix)

Treatment-Emergent Neurocognitive Adverse Events

Number of patients (%)	Alirocumab (n=1550)	Alirocumab with LDL-C <25 mg/dL (N=575)	Placebo (n=788)
Any neurocognitive disorder†	18 (1.2)	3 (0.5)	4 (0.5)
Amnesia	5 (0.3)	0	0
Memory impairment	4 (0.3)	0	1 (0.1)
Confusional state	4 (0.3)	1 (0.2)	1 (0.1)
Confusion postoperative	1 (<0.1)	0	0
Dementia	1 (<0.1)	1 (0.2)	1 (0.1)
Disorientation	1 (<0.1)	0	0
Disturbance in attention	1 (<0.1)	0	1 (0.1)
Frontotemporal dementia	1 (<0.1)	1 (0.2)	0
Reading disorder	1 (<0.1)	0	0
Transient global amnesia	1 (<0.1)	0	0
Vascular encephalopathy	1 (<0.1)	0	0

†These terms were selected using custom *Medical Dictionary for Regulatory Activities (MedDRA)* queries that were based on five high-level group terms: deliria (including confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; and mental impairment disorders.

Robinson JG, et al. *N Engl J Med.* 2015;372:1489-1499. (Appendix)

ODYSSEY LONG TERM
Conclusions

- This large-scale trial of 2341 high-risk patients provides data on the long-term efficacy and safety of alirocumab treatment over a 78-week period when added to a maximally tolerated dose of statin with or without other LLT
- Overall, alirocumab reduced LDL-C levels by 62% vs placebo at 24 weeks
  - LDL-C reduction in the alirocumab group was consistent over the 78-week treatment period

Robinson JG, et al. *N Engl J Med*. 2015;372:1489-1499.

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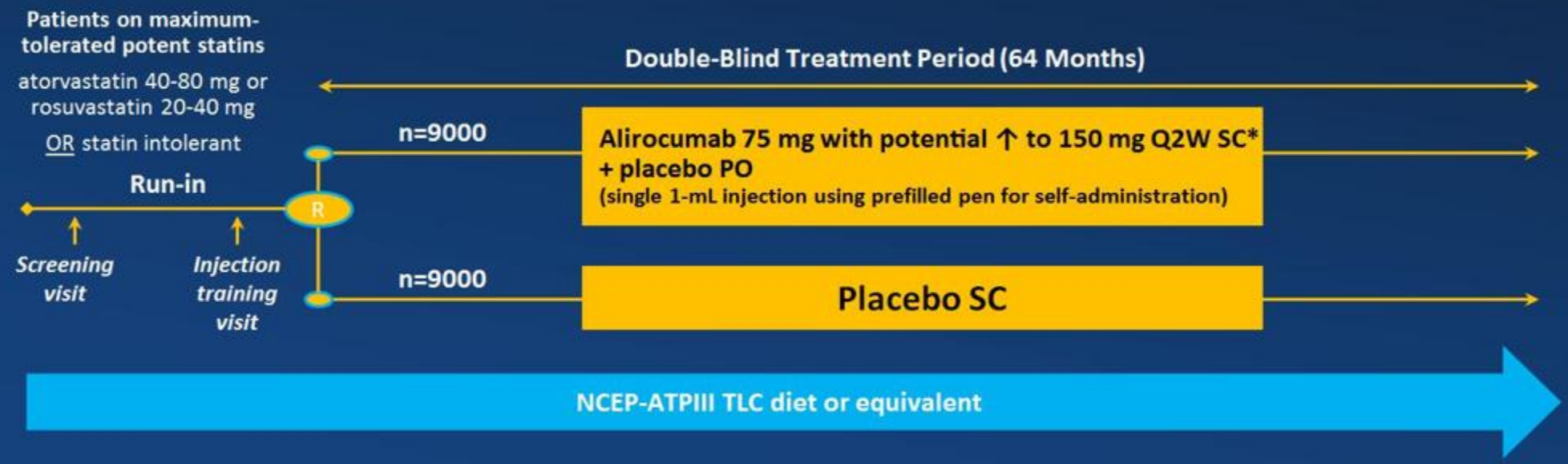
ODYSSEY OUTCOMES – Study Design

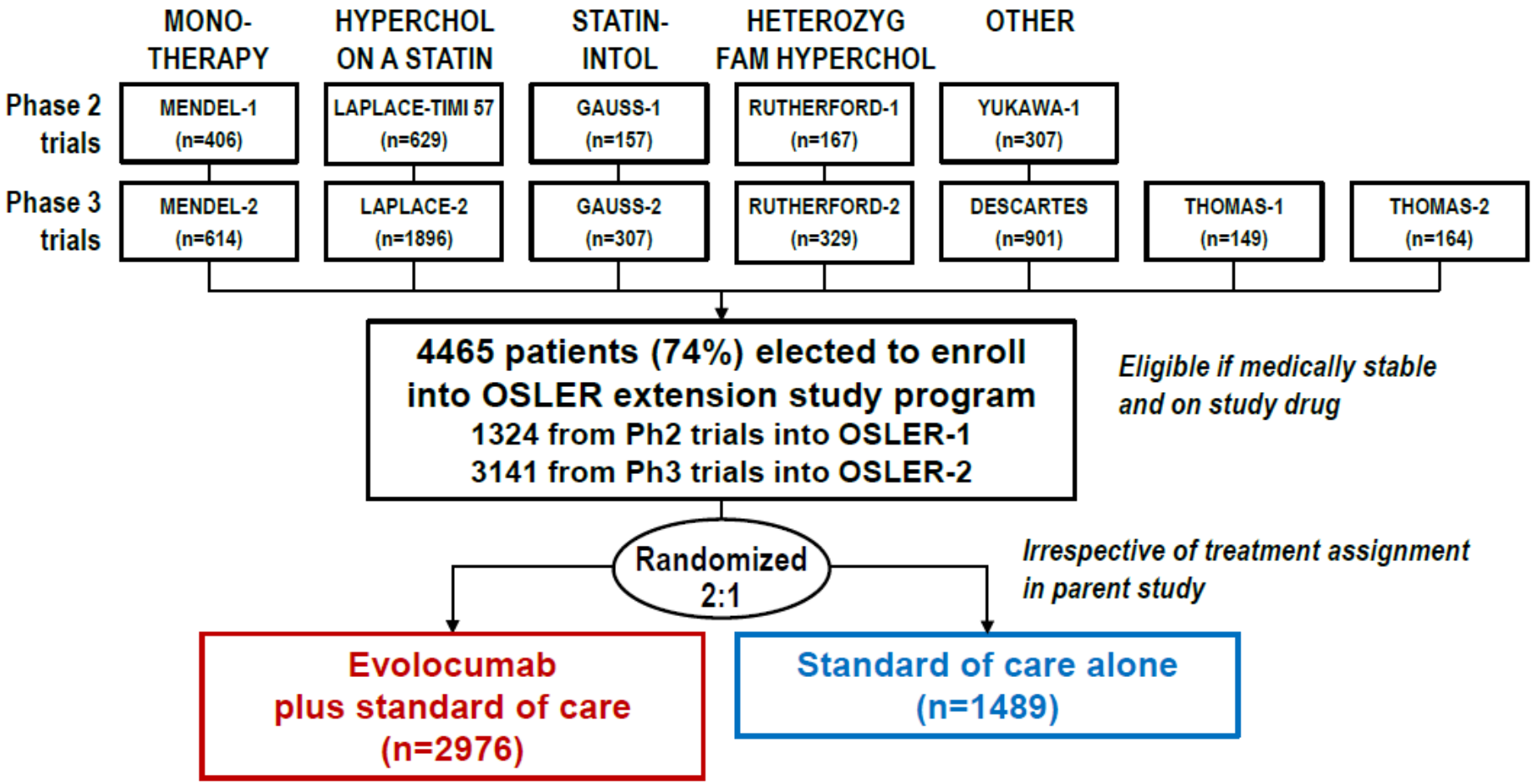
Population	Lipid criteria at entry	Primary endpoint
• Patients 4-52 weeks post-ACS • Age ≥ 40	• LDL-C ≥70 mg/dL [≥1.81 mmol/L] OR • ApoB ≥80 mg/dL [≥0.8 mmol/L] OR • Non-HDL-C ≥100 mg/dL [≥2.59 mmol/L]	• Composite of – CHD death – Nonfatal MI – Ischemic stroke – High-risk UA requiring hospitalization



ACS=acute coronary syndrome; CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; Q2W=every other week; SC=subcutaneous; TLC=therapeutic lifestyle changes; UA=unstable angina.
*Dose titrated up to 150mg Q2W at Month 2 if LDL-C ≥50 mg/dL(1.29 mmol/L) at Month 1 visit.

ClinicalTrials.gov. ODYSSEY OUTCOMES Study. http://clinicaltrials.gov/ct2/show/NCT01663402. Accessed May 14, 2015.
Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1.

OSLER Program



Median follow-up of 11.1 months (IQR 11.0-12.8)
7% discontinued evolocumab early
96% completed follow-up

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

Trial Sponsor: Amgen

Original Article

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

N Engl J Med
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The NEW ENGLAND JOURNAL of MEDICINE

Methods

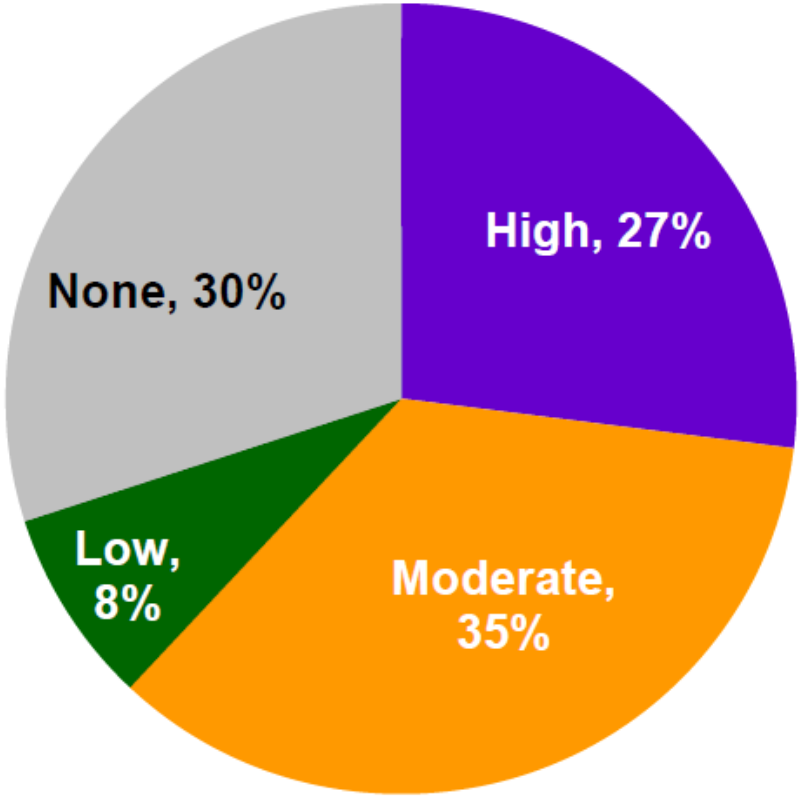
- **Evolocumab**
  - Open-label; subcutaneous injections
  - Dosed either 140 mg q 2 wk or 420 mg q month (similar ↓ LDL-C)
- **Endpoints**
  - Adverse events (primary) & tolerability
  - LDL-cholesterol (secondary) & other lipid parameters
  - Cardiovascular (CV) clinical outcomes (prespecified, exploratory): adjudicated by TIMI Study Group CEC, ***blinded to treatment***
    - Death
    - Coronary: myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization
    - Cerebrovascular: stroke or transient ischemic attack (TIA)
    - Heart failure (HF) requiring hospitalization

Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**58 (11)**
Male sex (%)	**51**
Cardiovascular risk factor (%)	**80**
Hypertension	52
Diabetes mellitus	13
Metabolic syndrome	34
Current cigarette use	15
Family hx of premature CAD	24
Known familial hyperchol.	10
Known vascular disease (%)	**25**
Coronary	20
Cerebrovascular or Peripheral	9

Pooled data; no differences between treatment arms

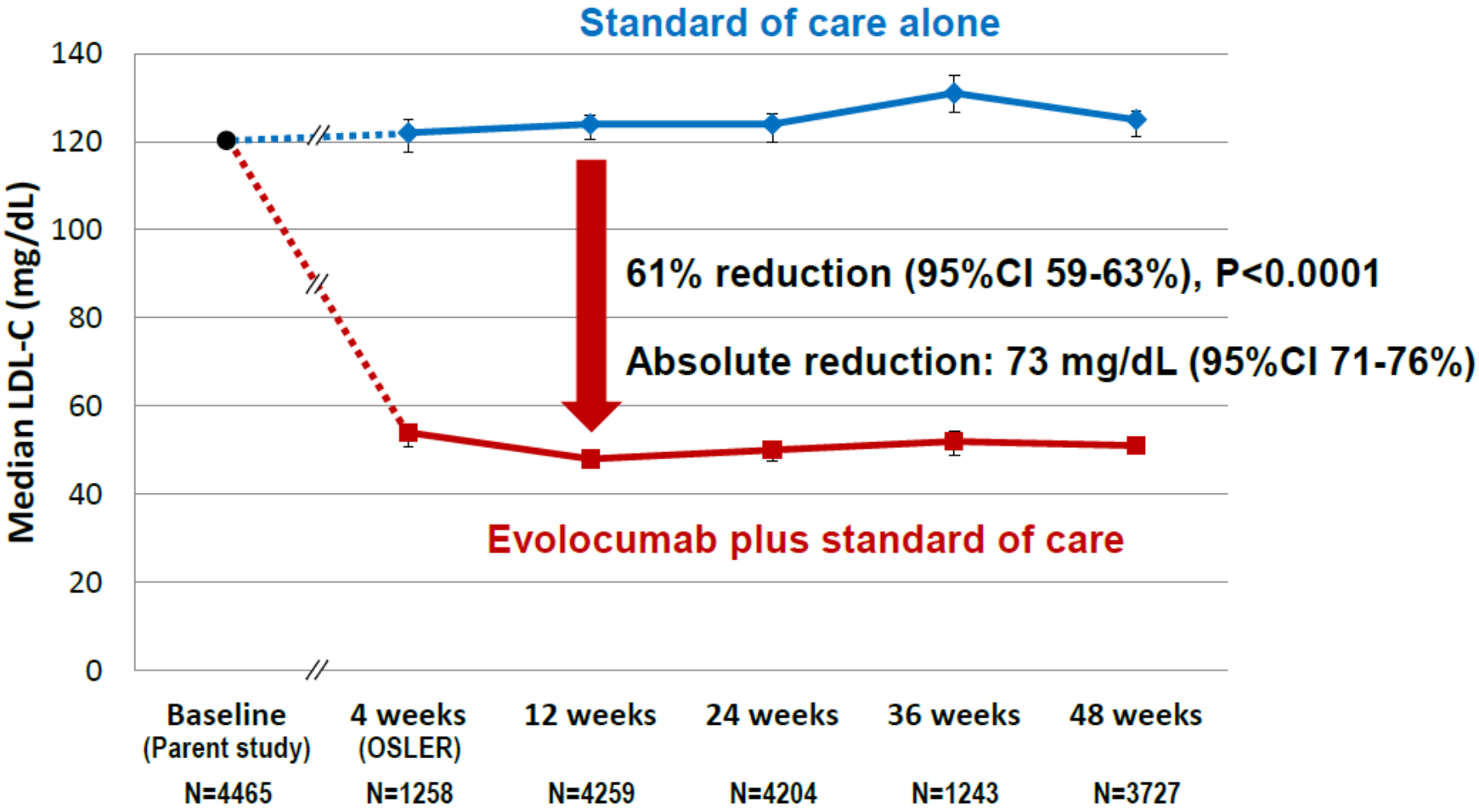
Statin Use & Intensity



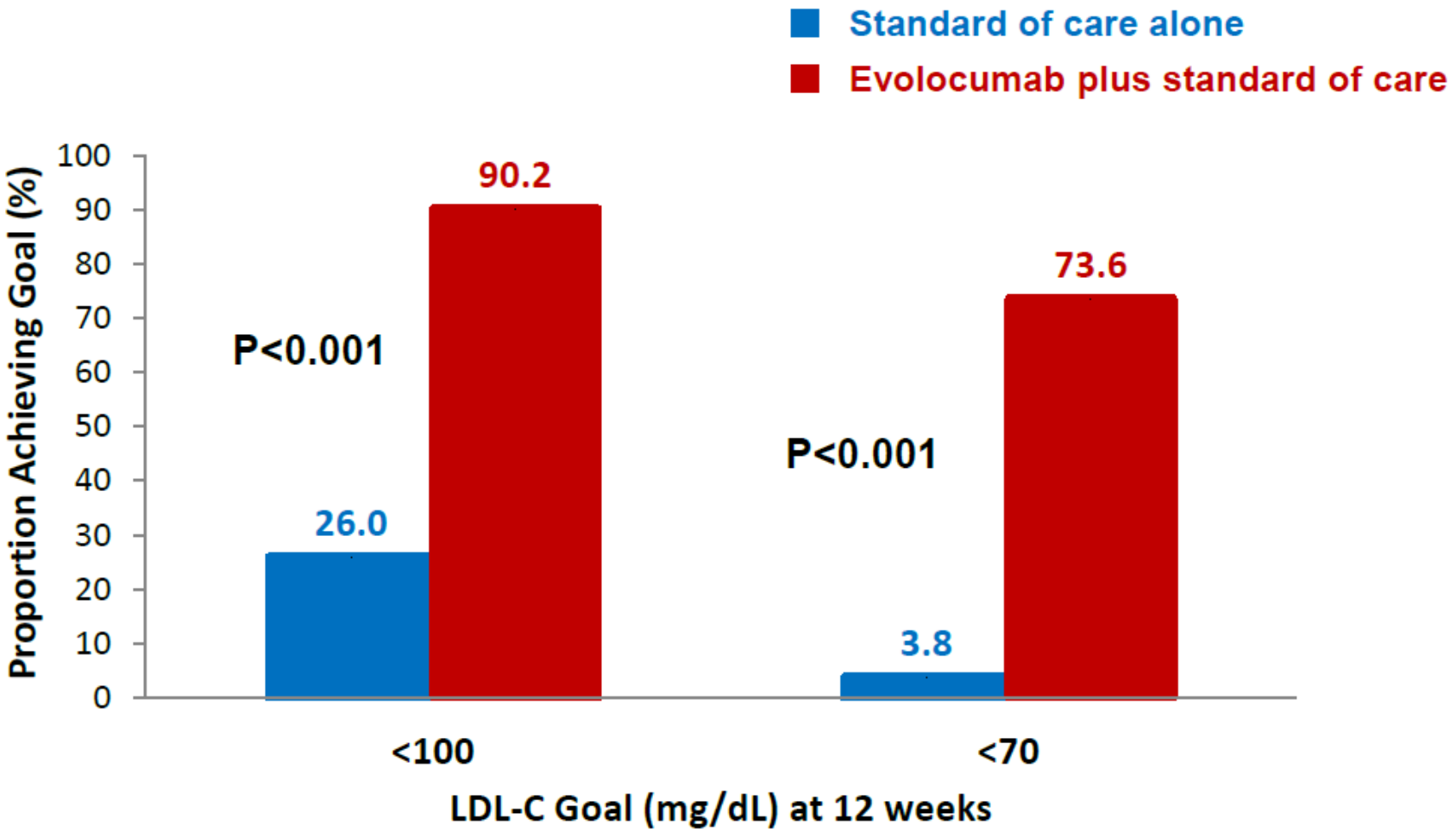
Pooled data at the start of OSLER; no differences between treatment arms

High: ↓ LDL-C by ~≥50% (eg, atorvastatin ≥40 mg/d or equivalent)
Moderate: ↓ LDL-C by ~30-50% (eg, simvastatin 20-40 mg/d or equivalent)
Low: ↓ LDL-C by ~<30% (eg, pravastatin ≤20 mg/d or equivalent)

LDL Cholesterol

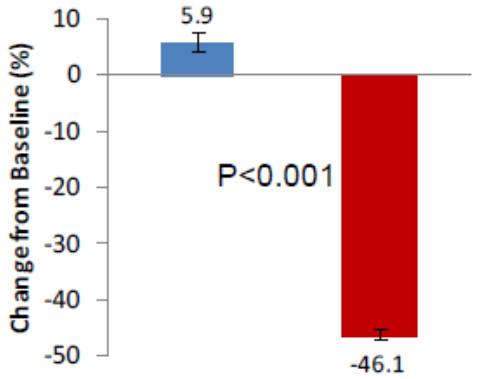


LDL Cholesterol Goals

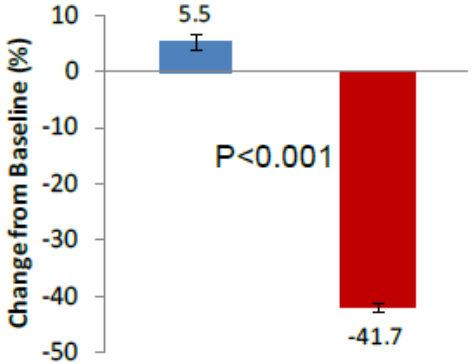


Other Lipid Parameters

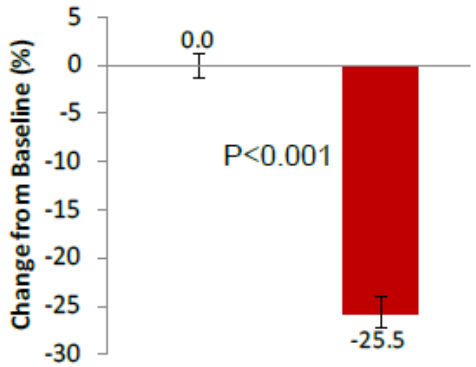
52% ↓ in Non-HDL-C



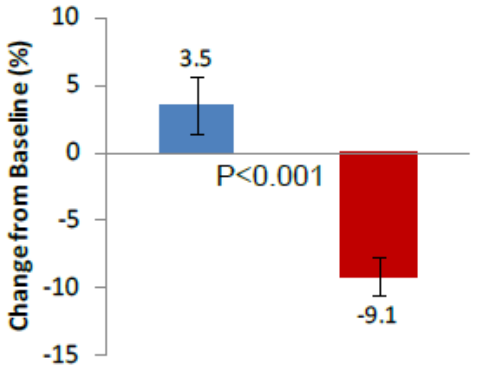
47% ↓ in ApoB



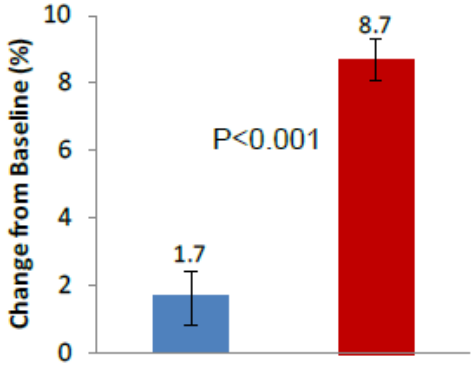
26% ↓ in Lp(a)



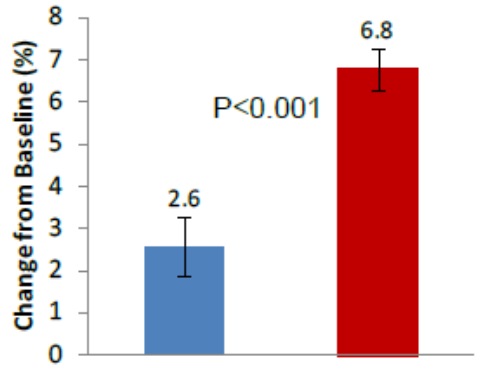
13% ↓ in Triglycerides



7% ↑ in HDL-C



4% ↑ in ApoA1

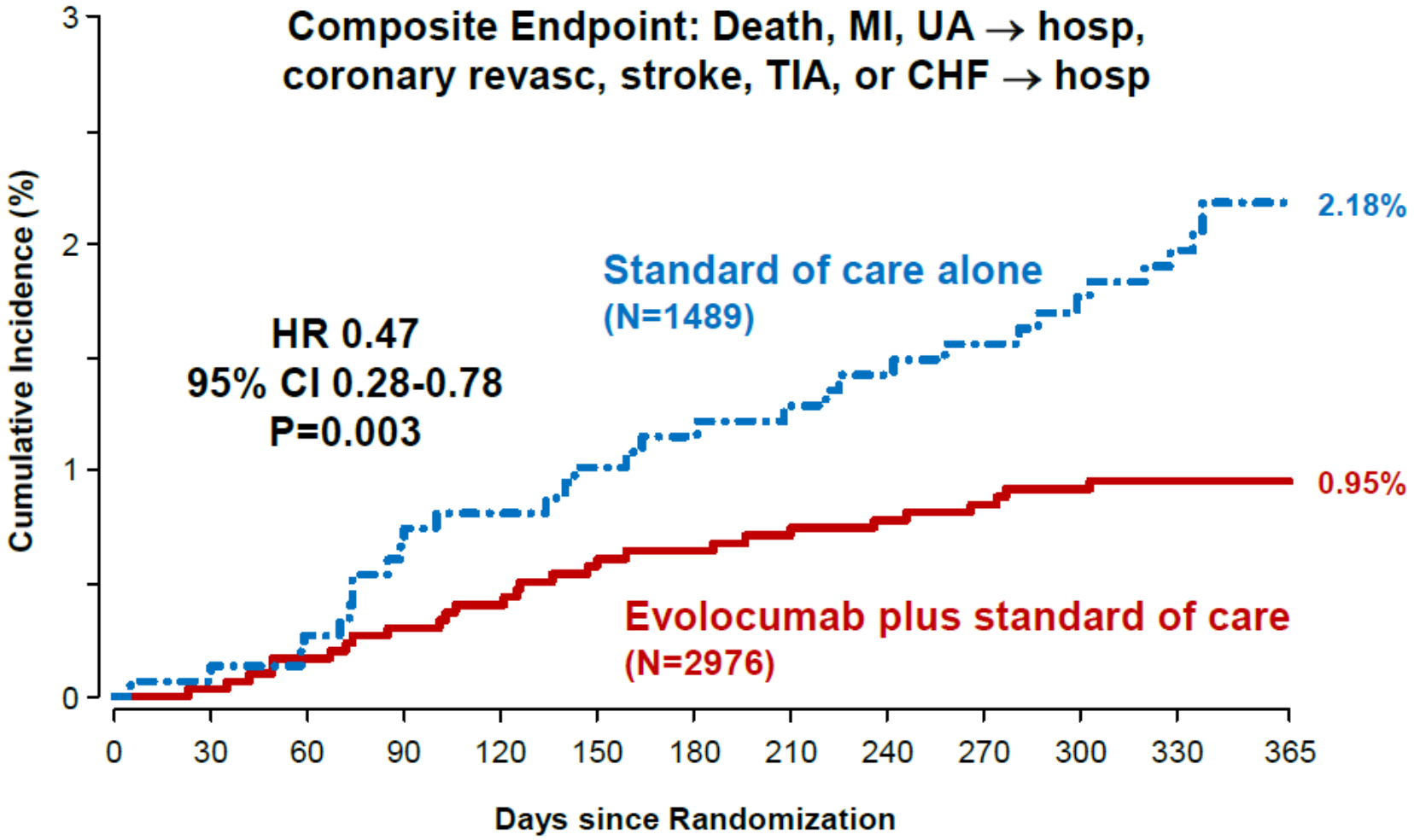


Week 12 data; values are means
except for TG and Lp(a) which are medians

Standard of care alone

Evolocumab plus standard of care

Cardiovascular Outcomes



Safety

	Evolocumab + stnd of care (N=2976)	Standard of care alone (N=1489)
Adverse events (%)		
Any	69.2	64.8
Serious	7.5	7.5
Leading to discontinuation of evolocumab	2.4	n/a
Injection-site reactions	4.3	n/a
Muscle-related	6.4	6.0
Neurocognitive	0.9	0.3
Laboratory results (%)		
ALT or AST >3×ULN	1.0	1.2
Creatine kinase >5×ULN	0.6	1.2

Adverse Events by Achieved LDL-C

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	Stnd of Care Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Summary for Evolocumab

- ↓ LDL-C by 61% at 12 weeks
  - Absolute decrease of 73 mg/dL
  - Median achieved LDL-C of 48 mg/dL
- ↓ CV outcomes by 53% over 1 year
  - Prespecified, exploratory outcome with relatively few events
  - Event curves diverged early & continued to separate over time
  - Consistent effect on death, coronary, and cerebrovasc. events
  - Consistent effect in major subgroups
- Appeared to be safe and well-tolerated
  - AEs largely balanced, good tolerability in this extension study
  - No gradient in incidence of any AE by achieved LDL-C, including in those with LDL-C <25 mg/dL

1) Monotherapy
2) Statin-intolerant patients
3) Elevated levels of Lp(a)

POSSIBLE FUTURE USES OF THE PCSK9 INHIBITORS