Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial

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Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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Contents

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Background

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Background

- Intravascular ultrasound (IVUS) trials have studied the effect of statins on coronary atherosclerosis and demonstrated a linear relationship between achieved LDL-C levels and reduction in atheroma burden.
- Monoclonal antibodies against PCSK9 lower LDL-C when administered alone or in combination with statins. Initial studies have demonstrated the feasibility of using the combination of statins and PCSK9 inhibitors to achieve much lower LDL-C levels than previously studied.
- No trials to date have explored whether LDL-C lowering beyond that achievable with statins with a PCSK9 inhibitor results in incremental benefits on coronary artery disease compared with statins alone.
- The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial was designed to assess whether PCSK9 inhibition reduces progression of atherosclerosis as measured by IVUS.

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Methods

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GLAGOV: Objective

Objective

- To test the hypothesis that LDL-C lowering with a monthly subcutaneous injection of evolocumab 420 mg for 78 weeks will result in a significantly greater change from baseline in percentage atheroma volume (PAV) compared with placebo in subjects taking background statin therapy

Design

- A 78-week, randomized, double-blind, placebo-controlled, multicenter, phase 3 study.

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

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Note: mg/dL version

GLAGOV: Key Inclusion Criteria

- Men or women aged > 18 years
- Clinically indicated coronary angiogram, evidence of coronary disease
- LDL-C criteria met within 4 weeks of screening visit or, if applicable, at the end of lipid-stabilization period:
  - LDL-C ≥ 80 mg/dL, **OR**
  - LDL-C ≥ 60 but < 80 mg/dL in the presence of risk factors as shown in the table below:

Major Risk Factors (One Required)	• Non-coronary atherosclerotic vascular disease • Documented myocardial infarction or hospitalization for unstable angina within the last 2 years • Documented type 2 diabetes mellitus
OR	
Minor Risk Factors (Three Required)	• Age (men ≥ 50 years; women ≥ 55 years) • Hypertension (BP ≥ 140/90 mmHg or current use of antihypertensive medications) • Low HDL-C (men: < 40 mg/dL; women < 50 mg/dL) • Family history of premature coronary heart disease (first-degree male relative < 55 years of age or first-degree female relative < 65 years of age) • hs-CRP ≥ 2 mg/L • Cigarette smoking (current)

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Note: mmol/L version

GLAGOV: Key Inclusion Criteria

- Men or women aged > 18 years
- Clinically indicated coronary angiogram, evidence of coronary disease
- LDL-C criteria met within 4 weeks of screening visit or, if applicable, at the end of lipid-stabilization period:
  - LDL-C ≥ 2.07 mmol/L, **OR**
  - LDL-C ≥ 1.56 but < 2.07 mmol/L in the presence of risk factors as shown in the table below:

Major Risk Factors (One Required)	• Non-coronary atherosclerotic vascular disease • Documented myocardial infarction or hospitalization for unstable angina within the last 2 years • Documented type 2 diabetes mellitus
OR	
Minor Risk Factors (Three Required)	• Age (men ≥ 50 years; women ≥ 55 years) • Hypertension (BP ≥ 140/90 mmHg or current use of antihypertensive medications) • Low HDL-C (men: < 1.04 mmol/L; women < 1.30 mmol/L) • Family history of premature coronary heart disease (first-degree male relative < 55 years of age or first-degree female relative < 65 years of age) • hs-CRP ≥ 19.0 nmol/L • Cigarette smoking (current)

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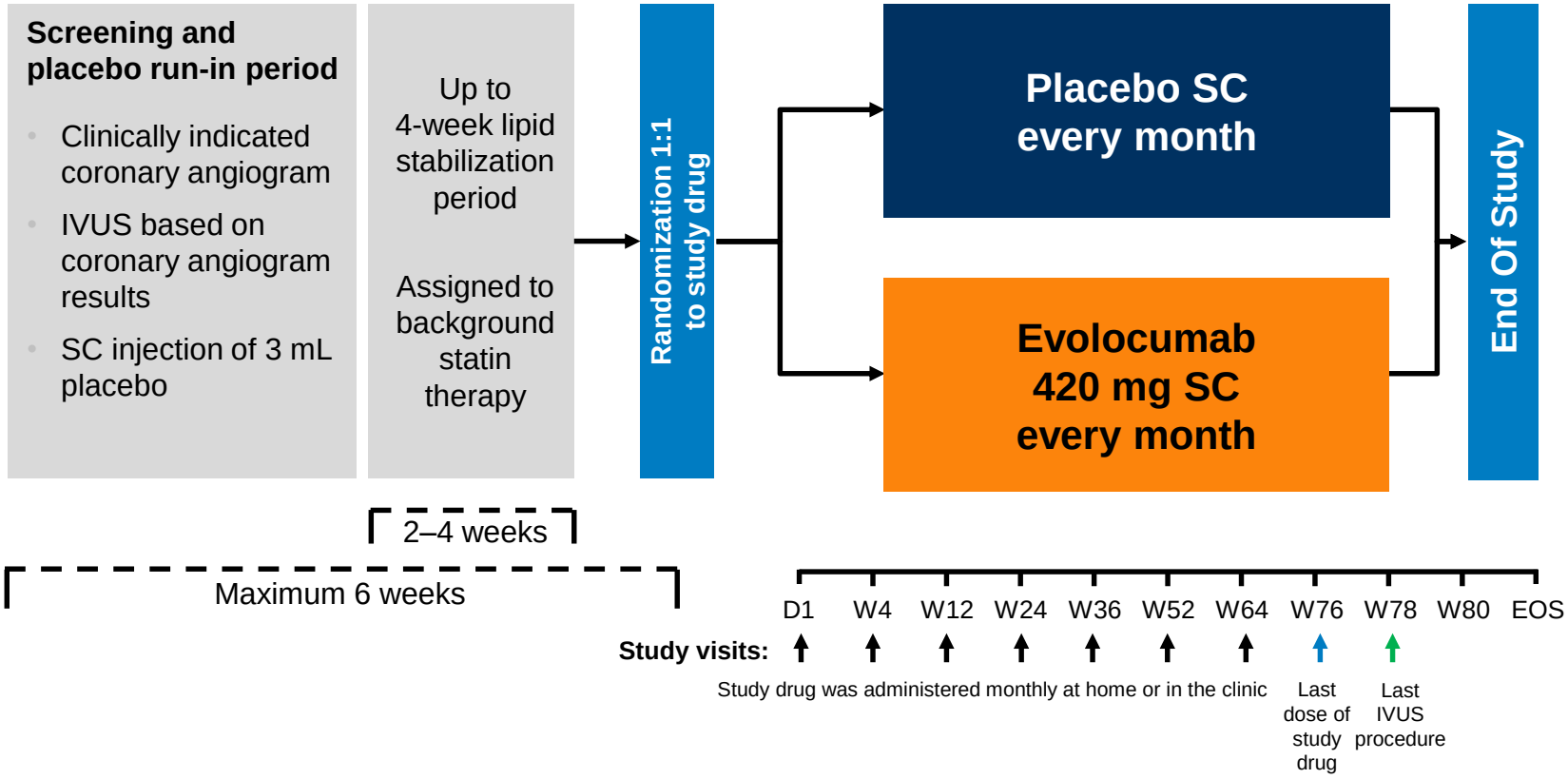
GLAGOV: Study Design



*Nominal change refers to the actual number, as opposed to percent change
D = day; IVUS = intravascular ultrasound; SC = subcutaneously; W = week.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

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GLAGOV: Study Endpoints

Endpoint	Description
Primary[1,2]	• Nominal change* in PAV from baseline to week 78, as determined by IVUS
Secondary[1,2]	• Nominal change* in TAV from baseline to week 78, as determined by IVUS • Proportion of patients demonstrating any reduction of PAV from baseline† • Proportion of patients demonstrating any reduction of TAV from baseline†
Exploratory[2]	• Incidence of adjudicated events (all-cause mortality, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure) • Change in lipid parameters

*Nominal change refers to the actual number, as opposed to percent change
†Proportion/percentage of subjects with regression is a group level summary statistics rather than a subject level endpoint
IVUS = intravascular ultrasound; PAV = percentage atheroma volume; TAV = total atheroma volume
1. Puri R, et al. *Am Heart J*. 2016;176:83-92. 2. Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951

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Note: mg/dL version

GLAGOV: Exploratory Post-Hoc Analysis

Analysis Type	Description
Exploratory Post-Hoc	• Comparison of the change in PAV and percentage of patients undergoing regression of PAV in those with an LDL-C < 70 mg/dL at baseline. • A locally weighted polynomial regression (LOESS) curve fitting was performed to examine the association between achieved LDL-C levels and disease progression

PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

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Note: mmol/L version

GLAGOV: Exploratory Post-Hoc Analysis

Analysis Type	Description
Exploratory Post-Hoc	• Comparison of the change in PAV and percentage of patients undergoing regression of PAV in those with an LDL-C < 1.81 mmol/L at baseline. • A locally weighted polynomial regression (LOESS) curve fitting was performed to examine the association between achieved LDL-C levels and disease progression

PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

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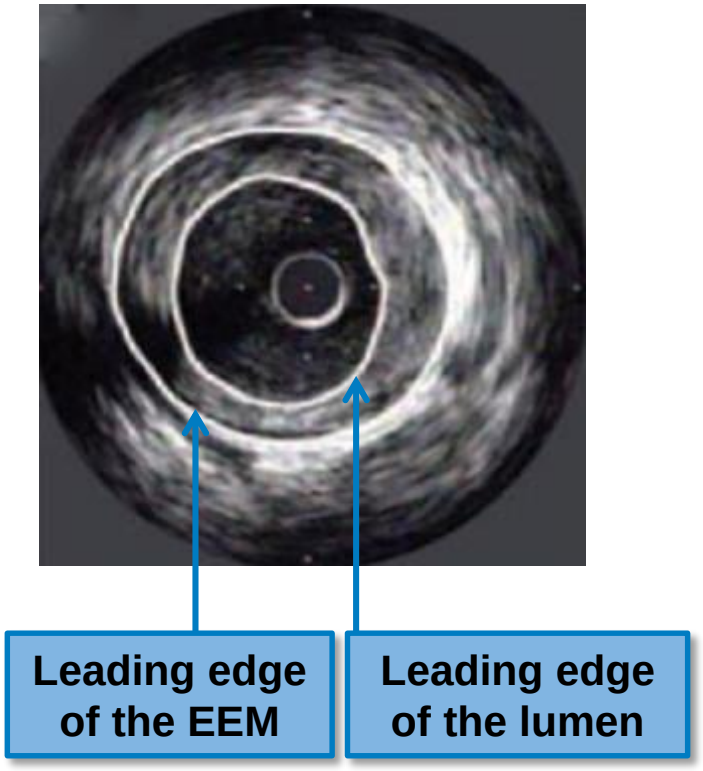
GLAGOV: Analysis of IVUS Imaging

- Plaque area is calculated as the area between the two leading edges
- Two measures of atheroma burden will be calculated for each patient
  - PAV is calculated as the proportion of the EEM volume occupied by atherosclerotic plaque

$$PAV = \frac{\Sigma(EEM_{area} - lumen_{area})}{\Sigma(EEM_{area})} \times 100$$

  - TAV is calculated as the summation of plaque areas in each measured cross-sectional image within the segment and subsequently normalized by the median number of images analyzed in the entire cohort to account for heterogeneity in segment length between subjects

$$TAV_{normalized} = \frac{\Sigma(EEM_{area} - lumen_{area})}{\text{Number of images in pullback}} \times \text{Median number of images in cohort}$$



IVUS = intravascular ultrasound; EEM = external elastic membrane; PAV = percentage atheroma volume; TAV = total atheroma volume.

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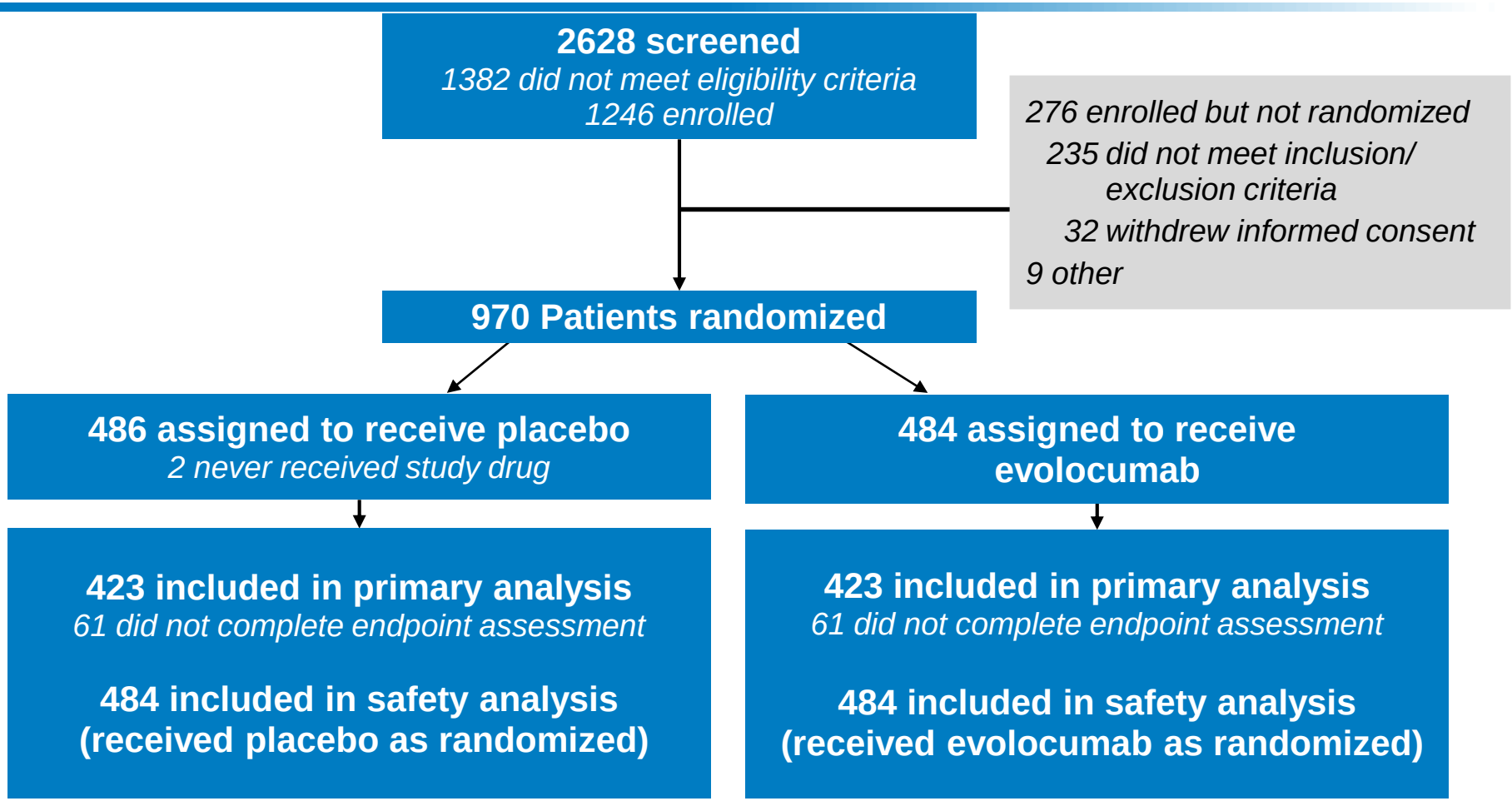
GLAGOV: Disposition of Patients During the Study



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Baseline Characteristics

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GLAGOV: Baseline Characteristics of Randomized Patients

Parameter*	Placebo (N = 484)	Evolocumab (N = 484)
Age, years	59.8±8.8	59.8±9.6
Men, n (%)	350 (72.3)	349 (72.1)
White, n (%)	452 (93.4)	456 (94.2)
BMI	29.5±5.0	29.4±5.0
Hypertension, n (%)	405 (83.7)	398 (82.2)
Previous PCI, n (%)	188 (38.8)	189 (39.0)
Previous MI, n (%)	171 (35.3)	169 (34.9)
Smoking, n (%)	113 (23.3)	124 (25.6)
Diabetes, n (%)	104 (21.5)	98 (20.2)
Baseline statin use,* n (%)	476 (98.3)	478 (98.8)
High intensity†, n (%)	290 (59.9)	280 (57.9)
Moderate intensity, n (%)	185 (38.2)	196 (40.5)
Low intensity, n (%)	1 (0.2)	2 (0.4)
Baseline ezetimibe use,* n (%)	9 (2.1)	9 (2.1)
Baseline medications		
Anti-platelet therapy, n (%)	465 (96.1)	454 (93.8)
Beta-blocker, n (%)	370 (76.4)	362 (74.8)
ACE inhibitor, n (%)	264 (54.5)	260 (53.7)
ARB, n (%)	92 (19.0)	87 (18.0)

Age and BMI expressed as mean ± standard deviation. *Baseline statin and ezetimibe use is defined as subject treated with statin or ezetimibe therapy at the end of the lipid stabilization period at randomization. †High intensity statin as defined by ACC/AHA criteria

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Note: mg/dL version

GLAGOV: Biochemical Measures

Parameter	Baseline		On-treatment		P-Value*	Absolute Change (95% CI)		P-Value*
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)		Placebo (n = 484)	Evolocumab (n = 484)	
Total cholesterol, mg/dL mean (95%CI)	166.2 (163.1 to 169.2)	166.1 (163 to 169.2)	169.1 (166.3 to 172)	108.6 (160 to 111.3)	< 0.001	1.8 (-2.0 to 5.6)	-59.0 (-62.8 to -55.2)	< 0.001
LDL-C, mg/dL† mean (95%CI)	92.4 (90 to 94.8)	92.6 (90.1 to 95.0)	93.0 (90.5 to 95.4)	36.6 (34.5 to 38.8)	< 0.001	0.2 (-2.9 to 3.4)	-56.3 (-59.4 to -53.1)	< 0.001
Lp(a), mg/dL median (IQR)	10.9 (3.9 to 50.7)	12.1 (4.6 to 57.1)	8.9 (3.9 to 48.1)	7.1 (2.5 to 46.7)	0.07	-1.0 (-2.2 to 0.2)	-7.8 (-9.0 to -6.6)	< 0.001
hs-CRP (mg/L) median (IQR)‡	1.6 (0.8 to 3.4)	1.6 (0.8 to 3.4)	1.4 (0.7 to 3.0)	1.4 (0.7 to 3.0)	0.47	-0.3 (-1.3 to 0.6)	-0.4 (-1.3 to 0.6)	0.35

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †When the calculated LDL-C level is less than 40 mg/dL or triglyceride level is greater than 400 mg/dL, ultracentrifugation LDL-C was determined from the same blood sample. ‡Tested using Wilcoxon rank-sum test. Final measurements are used for on-treatment values. Absolute changes are presented as least-squares means (95% CIs).

LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a)

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Note: mmol/L version

GLAGOV: Biochemical Measures

Parameter	Baseline		On-treatment			Absolute Change (95% CI)		
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*
Total cholesterol, mmol/L mean (95%CI)	4.30 (4.22 to 4.38)	4.30 (4.22 to 4.38)	4.37 (4.31 to 4.45)	2.81 (4.14 to 2.88)	< 0.001	0.05 (-0.05 to 0.15)	-1.53 (-1.63 to -1.43)	< 0.001
LDL-C, mmol/L† mean (95%CI)	2.39 (2.33 to 2.46)	2.40 (2.33 to 2.46)	2.41 (2.34 to 2.47)	0.95 (0.89 to 1.00)	< 0.001	0.00 (-0.08 to 0.09)	-1.46 (-1.54 to -1.38)	< 0.001
Lp(a), µmol/L median (IQR)	0.39 (0.14 to 1.81)	0.43 (0.16 to 2.04)	0.32 (0.14 to 1.72)	0.25 (0.09 to 1.67)	0.07	-0.04 (-0.08 to 0.01)	-0.28 (-0.32 to -0.24)	< 0.001
hs-CRP (nmol/L) median (IQR)‡	15.24 (7.62 to 32.4)	15.24 (7.62 to 32.38)	13.33 (6.67 to 28.57)	13.33 (6.67 to 28.57)	0.47	-2.86 (-12.38 to 5.71)	-3.81 (-12.38 to 5.71)	0.35

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †When the calculated LDL-C level is less than 1.04 mmol/L or triglyceride level is greater than 4.52 mmol/L, ultracentrifugation LDL-C was determined from the same blood sample. ‡Tested using Wilcoxon rank-sum test. Final measurements are used for on-treatment values. Absolute changes are presented as least-squares means (95% CIs).

LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a)

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Note: mg/dL version

GLAGOV: Biochemical Measures *(continued)*

Parameter	Baseline		On-treatment			Absolute Change (95% CI)		
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*
HDL-C, mg/dL mean (95%CI)	45.4 (44.2 to 46.5)	46.7 (45.5 to 47.8)	47.1 (46.0 to 48.2)	51.0 (49.8 to 52.1)	< 0.001	0.7 (-0.1 to 1.6)	3.3 (2.4 to 4.1)	< 0.001
TG, mg/dL† median (IQR)	124.5 (90.0 to 173)	117.0 (88 to 155)	130.5 (100.3 to 177.2)	105.1 (82.5 to 141.6)	< 0.001	8.1 (-0.4 to 16.6)	-10.9 (-19.4 to -2.5)	< 0.001
ApoA, mg/dL mean (95%CI)	139.5 (137.2 to 141.9)	140.5 (138.3 to 142.8)	145.4 (143.4 to 147.4)	151.6 (149.5 to 153.7)	< 0.001	3.5 (1.5 to 5.5)	8.5 (6.5 to 10.5)	< 0.001
ApoB, mg/dL mean (95%CI)	81.9 (80.1 to 83.6)	81.1 (79.3 to 82.9)	83.5 (81.8 to 85.2)	42.4 (40.8 to 44.0)	< 0.001	0.3 (-2.0 to 2.6)	-40.3 (-42.6 to 38.0)	< 0.001

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †Tested using Wilcoxon rank-sum test.

HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; Apo = Apolipoprotein

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Note: mmol/L version

GLAGOV: Biochemical Measures *(continued)*

Parameter	Baseline		On-treatment			Absolute Change (95% CI)		
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*
HDL-C, mmol/L mean (95%CI)	1.18 (1.14 to 1.20)	1.21 (1.18 to 1.24)	1.22 (1.19 to 1.25)	1.32 (1.29 to 1.35)	< 0.001	0.02 (-0.00 to 0.04)	0.09 (0.06 to 0.11)	< 0.001
TG, mmol/L† median (IQR)	1.41 (1.01 to 1.95)	1.32 (0.99 to 1.75)	1.47 (1.13 to 2.00)	1.18 (0.93 to 1.60)	< 0.001	0.09 (-0.00 to 0.18)	-0.12 (-0.22 to -0.03)	< 0.001
ApoA, mg/dL mean (95%CI)	139.5 (137.2 to 141.9)	140.5 (138.3 to 142.8)	145.4 (143.4 to 147.4)	151.6 (149.5 to 153.7)	< 0.001	3.5 (1.5 to 5.5)	8.5 (6.5 to 10.5)	< 0.001
ApoB, mg/dL mean (95%CI)	81.9 (80.1 to 83.6)	81.1 (79.3 to 82.9)	83.5 (81.8 to 85.2)	42.4 (40.8 to 44.0)	< 0.001	0.3 (-2.0 to 2.6)	-40.3 (-42.6 to 38.0)	< 0.001

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †Tested using Wilcoxon rank-sum test.

HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; Apo = Apolipoprotein

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Note: mg/dL version

GLAGOV: Biochemical Measurements for Diabetes and Blood Pressure

Parameter	Baseline		On-treatment		P-Value*	Absolute Change (95% CI)		P-Value*
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)		Placebo (n = 484)	Evolocumab (n = 484)	
Glucose, mg/dL†,‡ mean (95%CI)	107.3 (104.6 to 110.1)	104.0 (101.8 to 106.2)	109.4 (106.9 to 112.0)	110.1 (107.8 to 112.3)	0.72	3.9 (1.3 to 6.5)	7.8 (5.3 to 10.4)	0.02
HbA1c, %‡ mean (95%CI)	5.9 (5.8 to 6.0)	5.8 (5.8 to 5.9)	6.0 (5.9 to 6.1)	6.0 (5.9 to 6.1)	0.85	0.2 (0.1 to 0.2)	0.2 (0.15 to 0.25)	0.09
Systolic blood pressure, mmHg mean (95%CI)	129.6 (128.2 to 131.0	131.4 (130.1 to 132.7)	131.9 (130.8 to 133.1)	131.5 (130.4 to 132.5)	0.55	0.9 (-0.7 to 2.5)	-1.3 (-2.9 to 0.4)	0.007
Diastolic blood pressure, mmHg mean (95%CI)	76.7 (75.8 to 77.6)	78.0 (77.2 to 78.9)	78.5 (77.8 to 79.2)	78.6 (77.9 to 79.2)	0.94	2.2 (1.0 to 3.3)	0.9 -0.2 to 1.99)	0.01

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †Tested using Wilcoxon rank-sum test. ‡Final measurements are used for on-treatment values. Absolute changes are presented as least-squares means (95% CIs)

Hb = hemoglobin

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Note: mmol/L version

GLAGOV: Biochemical Measurements for Diabetes and Blood Pressure

Parameter	Baseline		On-treatment		P-Value*	Absolute Change (95% CI)		P-Value*
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)		Placebo (n = 484)	Evolocumab (n = 484)	
Glucose, mmol/L†,‡ mean (95%CI)	5.90 (5.81 to 6.11)	5.77 (5.65 to 5.89)	6.07 (5.93 to 6.22)	6.11 (5.98 to 6.23)	0.72	0.22 (0.07 to 0.36)	0.43 (0.29 to 0.58)	0.02
HbA1c, %‡ mean (95%CI)	5.9 (5.8 to 6.0)	5.8 (5.8 to 5.9)	6.0 (5.9 to 6.1)	6.0 (5.9 to 6.1)	0.85	0.2 (0.1 to 0.2)	0.2 (0.15 to 0.25)	0.09
Systolic blood pressure, mmHg mean (95%CI)	129.6 (128.2 to 131.0	131.4 (130.1 to 132.7)	131.9 (130.8 to 133.1)	131.5 (130.4 to 132.5)	0.55	0.9 (-0.7 to 2.5)	-1.3 (-2.9 to 0.4)	0.007
Diastolic blood pressure, mmHg mean (95%CI)	76.7 (75.8 to 77.6)	78.0 (77.2 to 78.9)	78.5 (77.8 to 79.2)	78.6 (77.9 to 79.2)	0.94	2.2 (1.0 to 3.3)	0.9 -0.2 to 1.99)	0.01

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †Tested using Wilcoxon rank-sum test. ‡Final measurements are used for on-treatment values. Absolute changes are presented as least-squares means (95% CIs)

Hb = hemoglobin

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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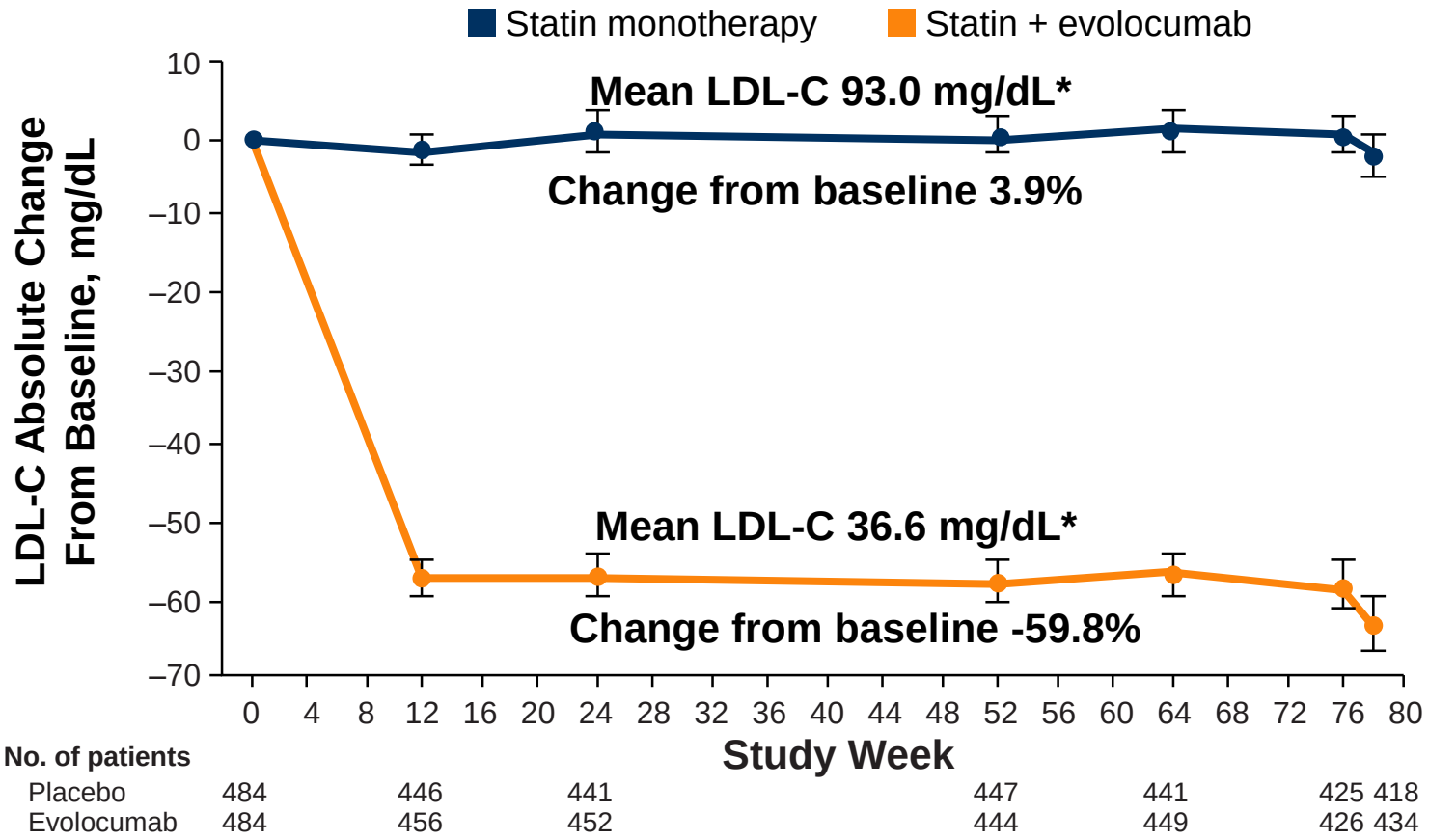
Note: mg/dL version

Mean Absolute Change in LDL-C



Absolute change for evolocumab-statin group: -56.3 (-59.4 to -53.1); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

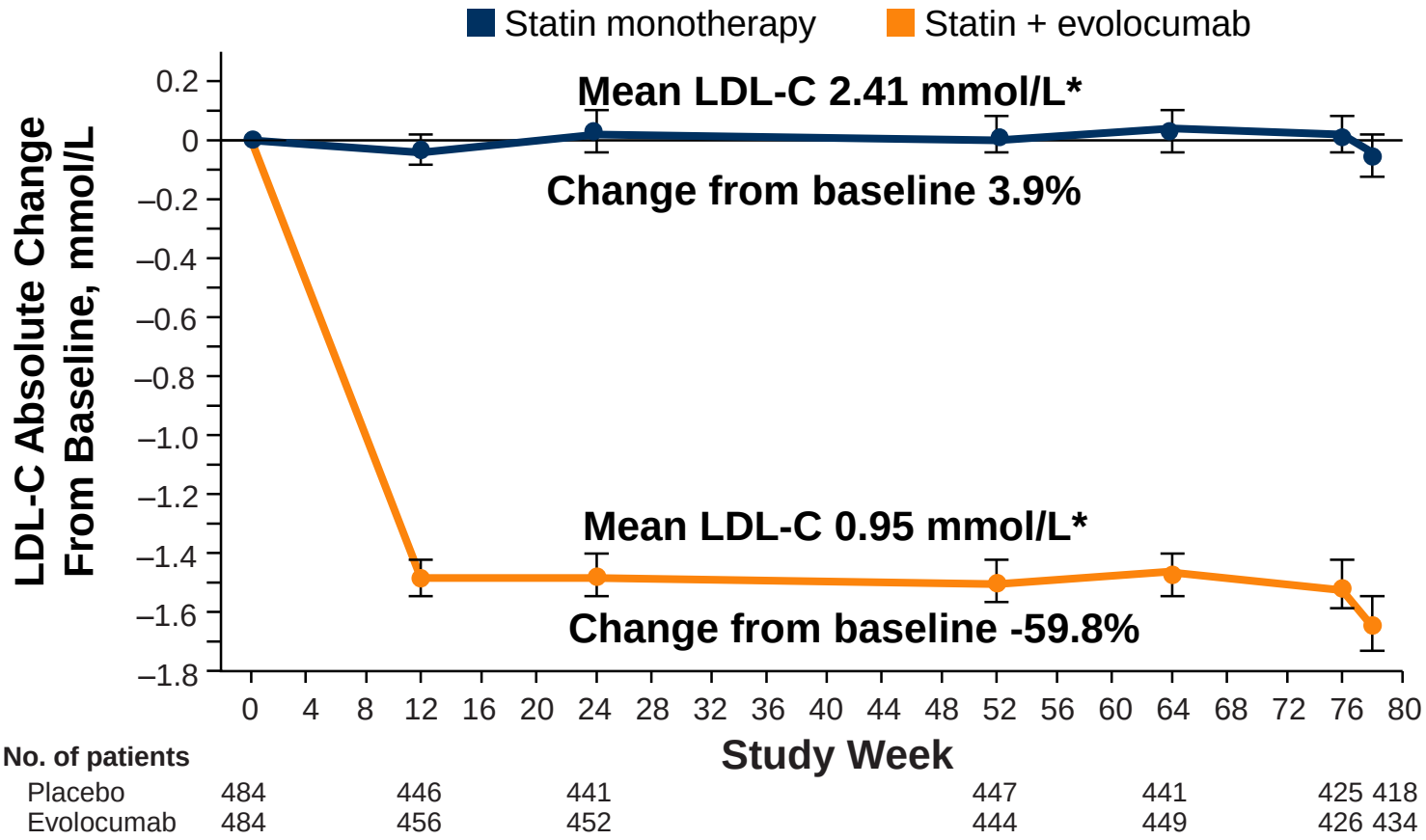
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation.

AMGEN Cardiovascular

Note: mmol/L version

Mean Absolute Change in LDL-C



Absolute change for evolocumab-statin group: -1.46 (-1.54 to -1.38); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation.

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Results

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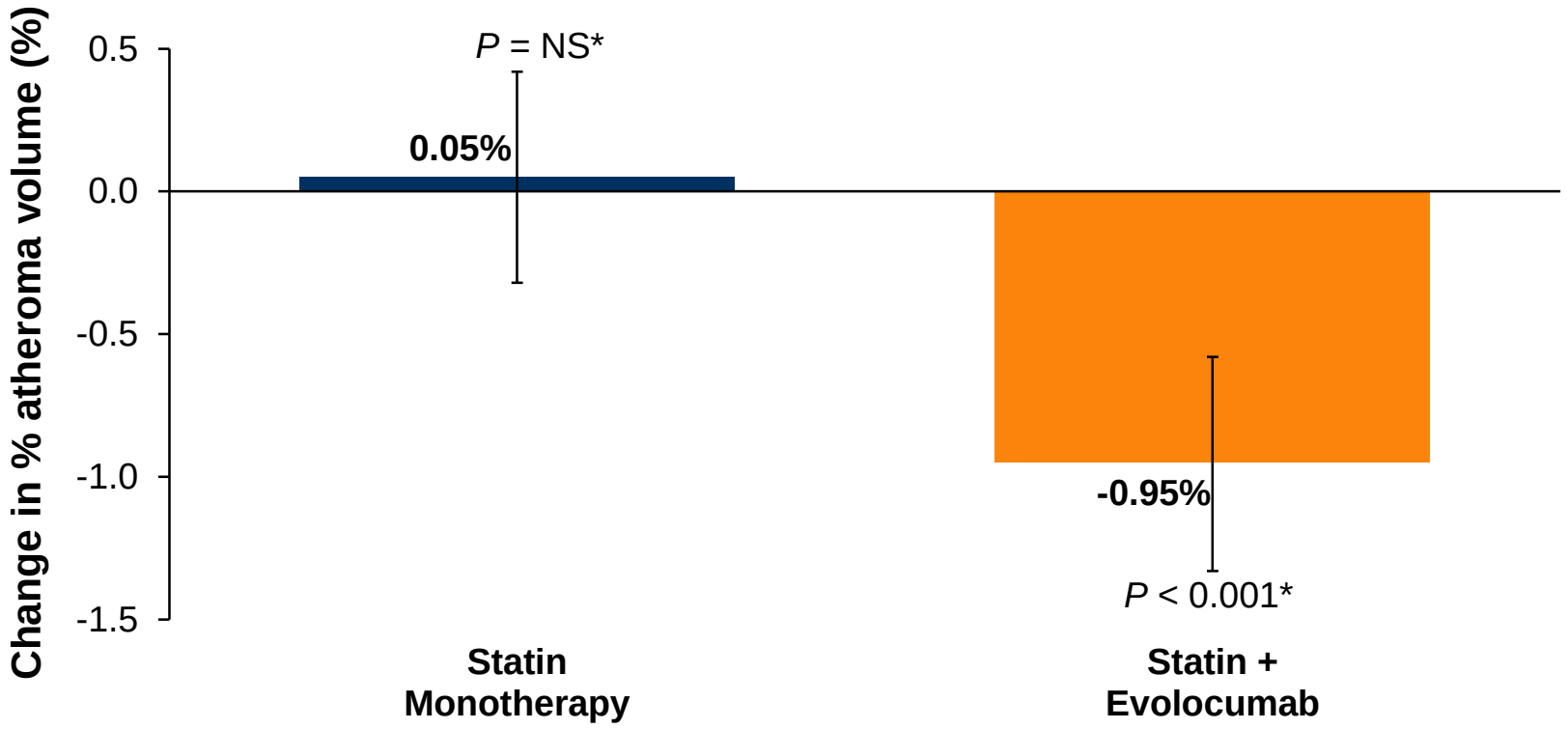
Primary Endpoint: Nominal Change in PAV From Baseline to Week 78



Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001

Data shown are least-squares mean (95% CI). PAV = Percent Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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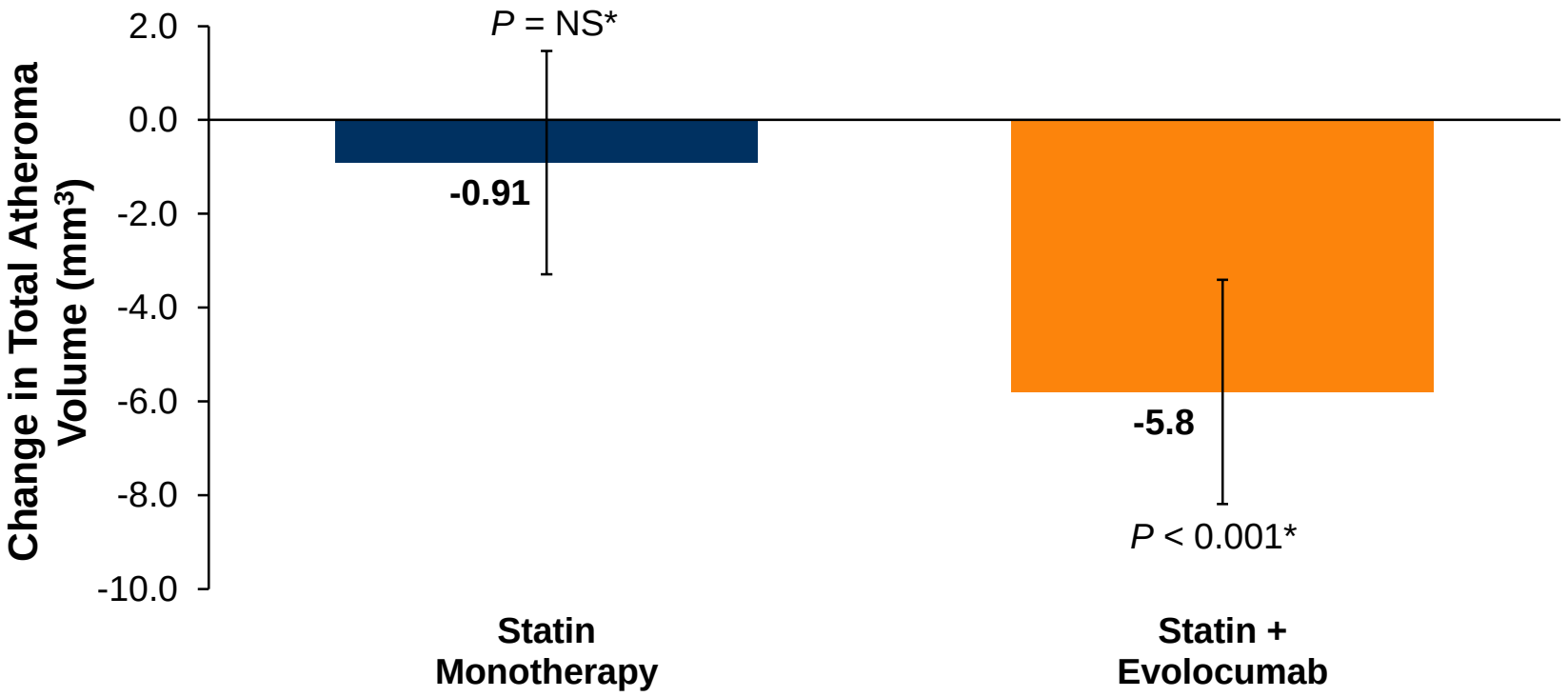
Secondary Endpoint: Nominal Change in TAV From Baseline to Week 78



Difference between groups: -4.9mm³ (-7.3 to -2.5); *P* < 0.001

Data shown are least-squares mean (95% CI). TAV = Total Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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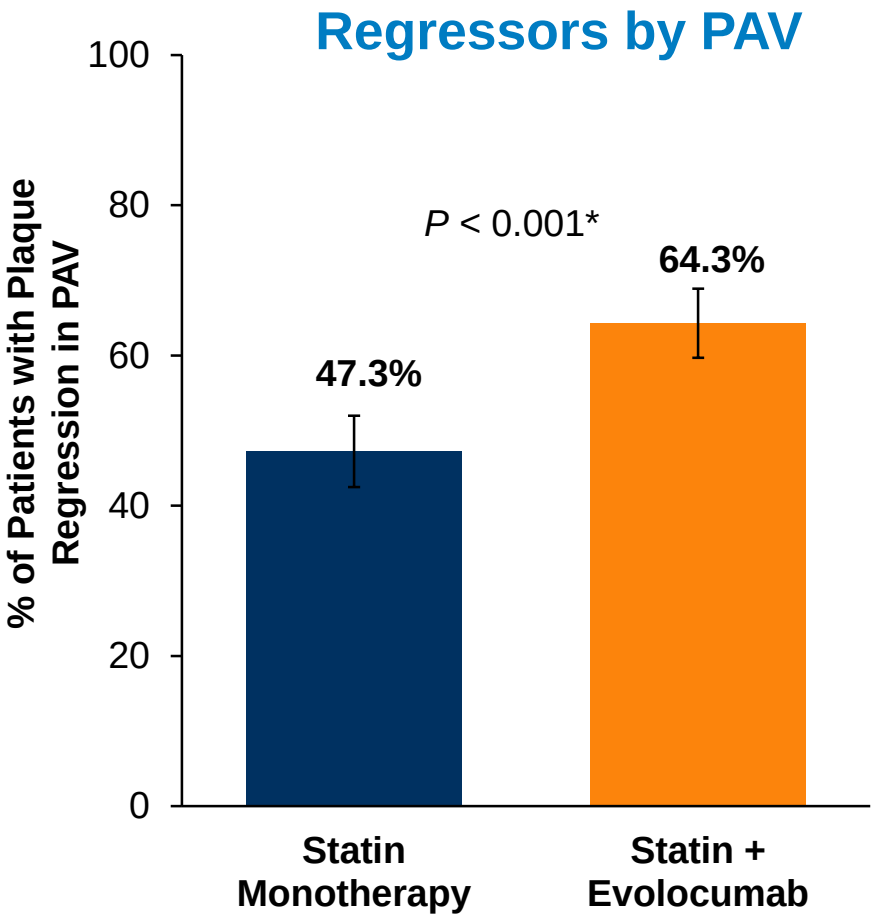
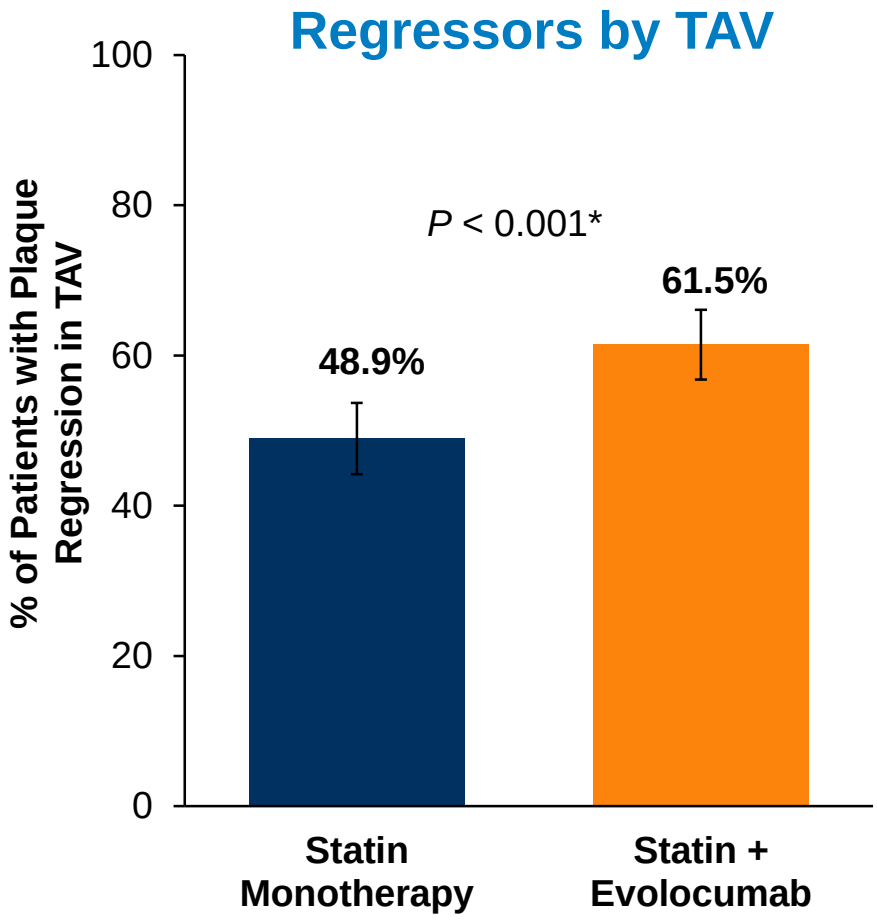
Secondary Endpoint: Percent of Patients Showing Regression in PAV and TAV





Data shown are percent (95% CI)
PAV = percentage atheroma volume; TAV = total atheroma volume
*Between-treatment group comparison
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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GLAGOV Primary & Secondary Endpoints at Baseline and Week 78

Parameter	Baseline		At week 78	
	Placebo (n = 423)	Evolocumab (n = 423)	Placebo (n = 423)	Evolocumab (n = 423)
PAV,% mean (95% CI)	37.2 (36.4 to 38.0)	36.4 (35.6 to 37.2)	37.3 (36.5 to 38.1)	35.6 (34.8 to 36.4)
TAV, mm^3 mean (95% CI)	191.4 (183.2 to 199.6)	187.0 (179.1 to 194.8)	190.6 (182.5 to 198.7)	181.5 (174.1 to 188.9)

PAV = percentage atheroma volume; TAV = total atheroma volume

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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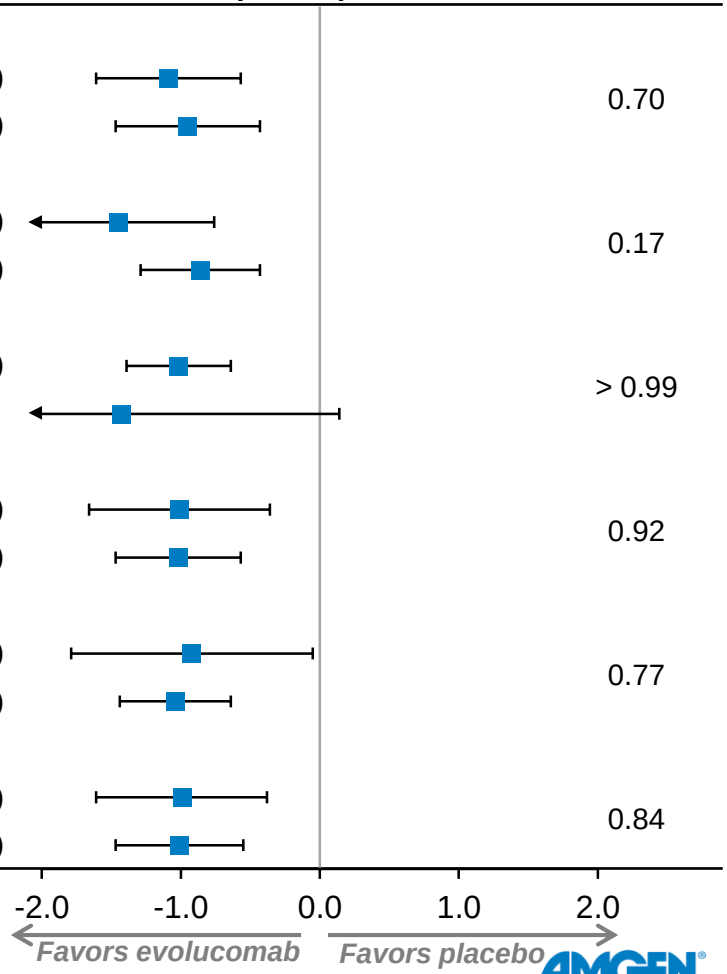
Prespecified Subgroup Analysis of Change in PAV

Subgroups	Placebo N	Evolocumab N	Treatment Difference (95% CI)	P-value Interaction
Age*				
< median	195	206	-1.09 (-1.61, -0.57)	0.70
≥ median	228	217	-0.95 (-1.47, -0.43)	
Sex				
Women	115	117	-1.45 (-2.15, -0.76)	0.17
Men	308	306	-0.86 (-1.29, -0.43)	
Race				
White	397	399	-1.02 (-1.39, -0.64)	> 0.99
Non-White	26	24	-1.43 (-3.00, 0.14)	
Prior Myocardial Infarction				
Yes	145	142	-1.01 (-1.66, -0.36)	0.92
No	278	281	-1.02 (-1.47, -0.57)	
Current Cigarette Use				
Yes	95	110	-0.92 (-1.79, -0.05)	0.77
No	328	313	-1.04 (-1.44, -0.64)	
Family History of Premature CHD				
Yes	133	149	-0.99 (-1.61, -0.38)	0.84
No	290	274	-1.01 (-1.47, -0.55)	



Results expressed as least-squares means (95%CI)
*Median values: Age 60 years
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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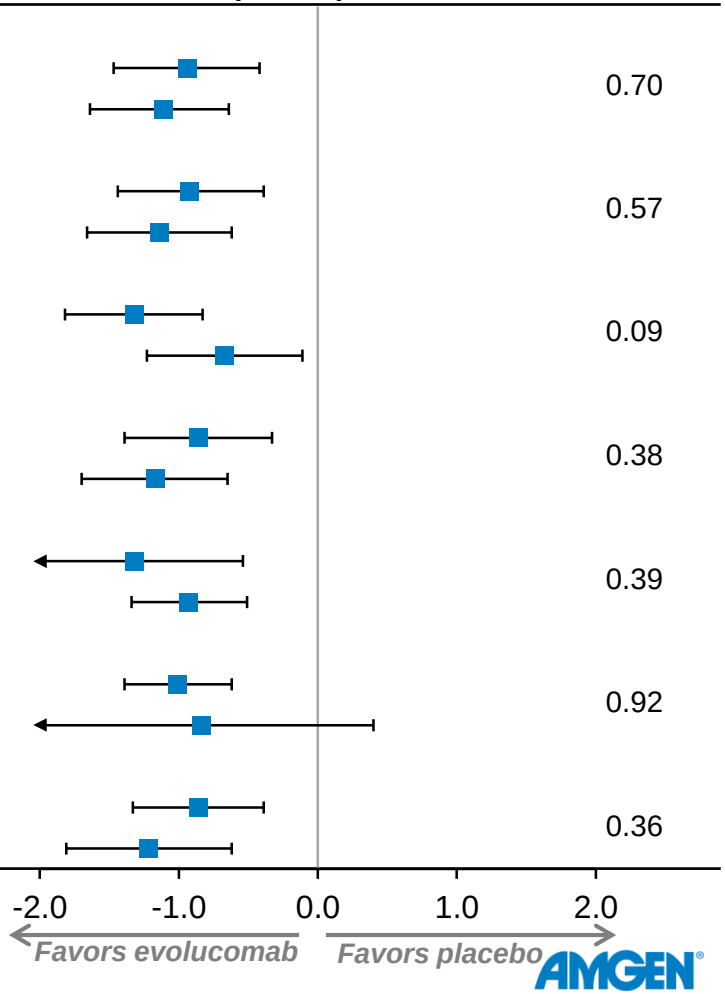
Prespecified Subgroup Analysis of Change in PAV

Subgroups	Placebo N	Evolocumab N	Treatment Difference (95% CI)	P-value Interaction
Baseline PAV*				
< median	209	220	-0.94 (-1.47, -0.42)	0.70
≥ median	214	203	-1.11 (-1.64, -0.64)	
Baseline TAV*				
< median	210	214	-0.92 (-1.44, -0.39)	0.57
≥ median	213	209	-1.14 (-1.66, -0.62)	
Baseline Non-HDL-C*				
< median	204	212	-1.32 (-1.82, -0.83)	0.09
≥ median	214	199	-0.67 (-1.23, -0.11)	
Baseline PCSK9*				
< median	215	203	-0.86 (-1.39, -0.33)	0.38
≥ median	201	209	-1.17 (-1.70, -0.65)	
Type 2 Diabetes Mellitus				
Yes	87	88	-1.32 (-2.10, -0.54)	0.39
No	336	335	-0.93 (-1.34, -0.51)	
Prior Statin Use				
Yes	379	372	-1.01 (-1.39, -0.62)	0.92
No	44	51	-0.84 (-2.09, 0.40)	
Statin Intensity per ACC/AHA				
High	255	253	-0.86 (-1.33, -0.39)	0.36
Moderate/Low	168	170	-1.22 (-1.81, -0.62)	



Results expressed as least-squares means (95%CI)
*Median values: PAV 36.88%; TAV 175.08mm^3; Non-HDL: 115 mg/dL; PCSK9: 315 ng/mL
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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Exploratory Post-Hoc Analyses

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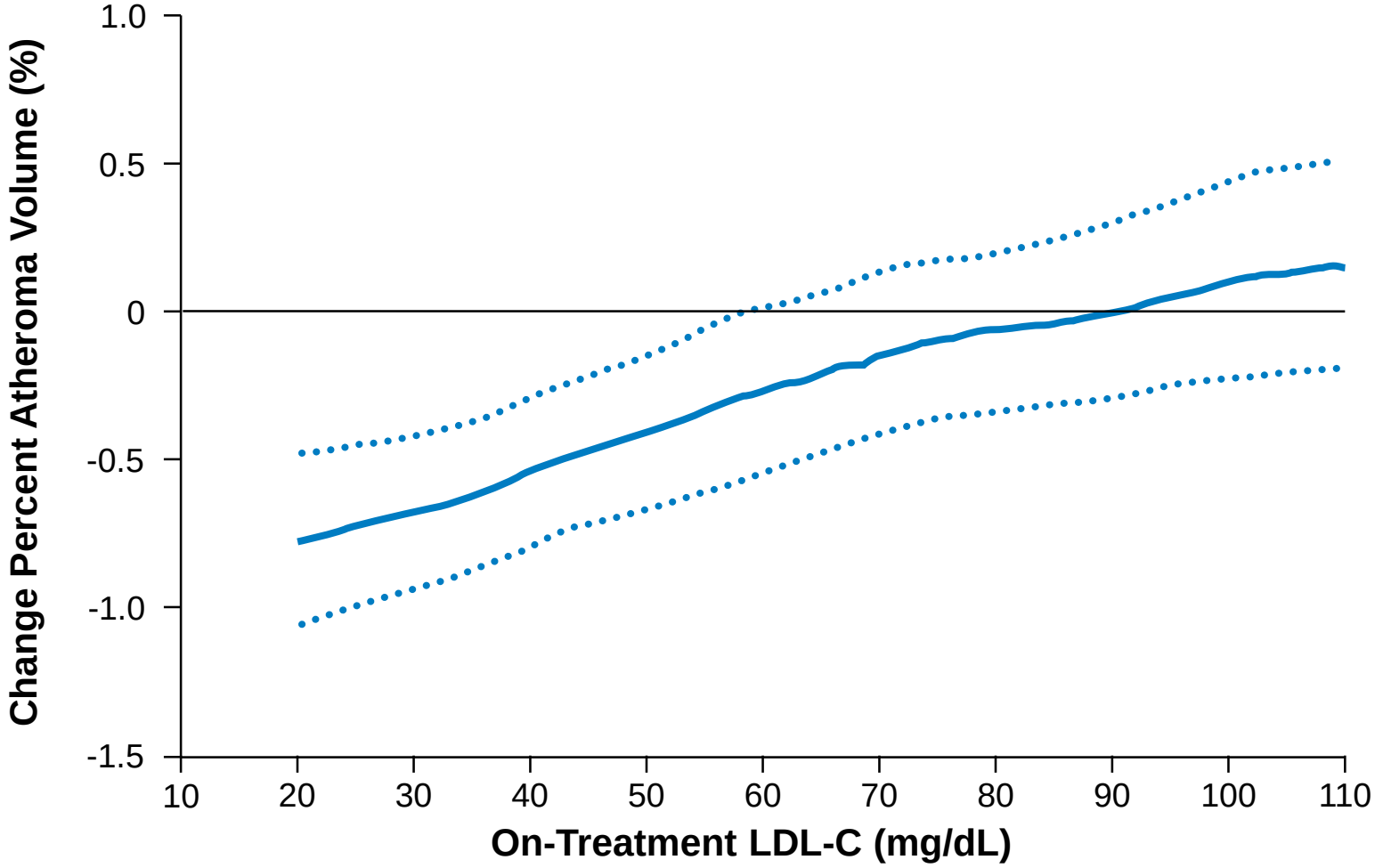
Note: mg/dL version

Exploratory Analysis: Achieved LDL-C and Change in PAV in All Patients



Local regression (LOESS) curve illustrating the association (with 95% CI) between achieved LDL-C levels and change in PAV in all patients undergoing serial IVUS evaluation. PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016] doi: 10.1001/jama.2016.16951.

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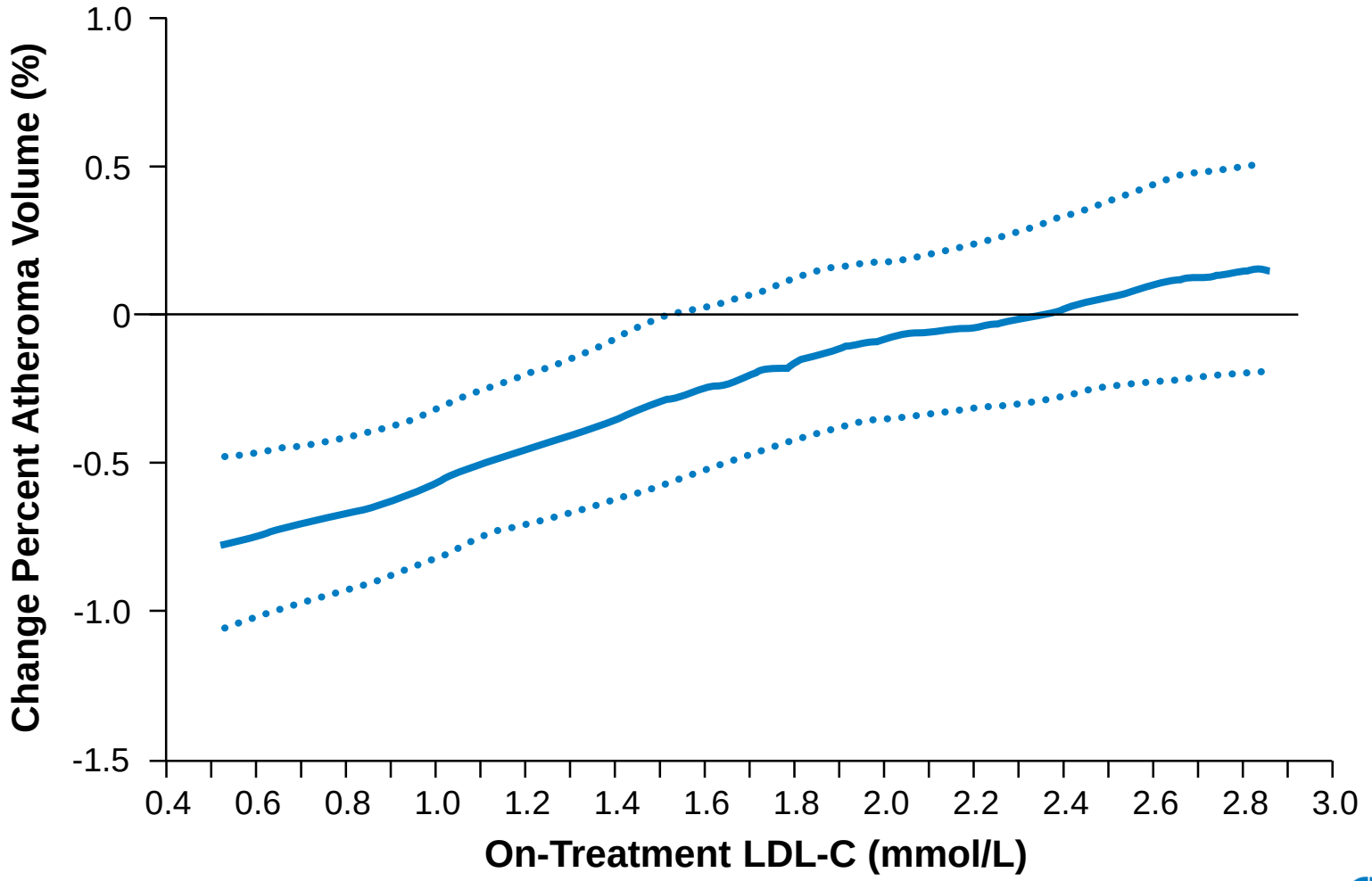
Note: mmol/L version

Exploratory Analysis: Achieved LDL-C and Change in PAV in All Patients



Local regression (LOESS) curve illustrating the association (with 95% CI) between achieved LDL-C levels and change in PAV in all patients undergoing serial IVUS evaluation. PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016] doi: 10.1001/jama.2016.16951.

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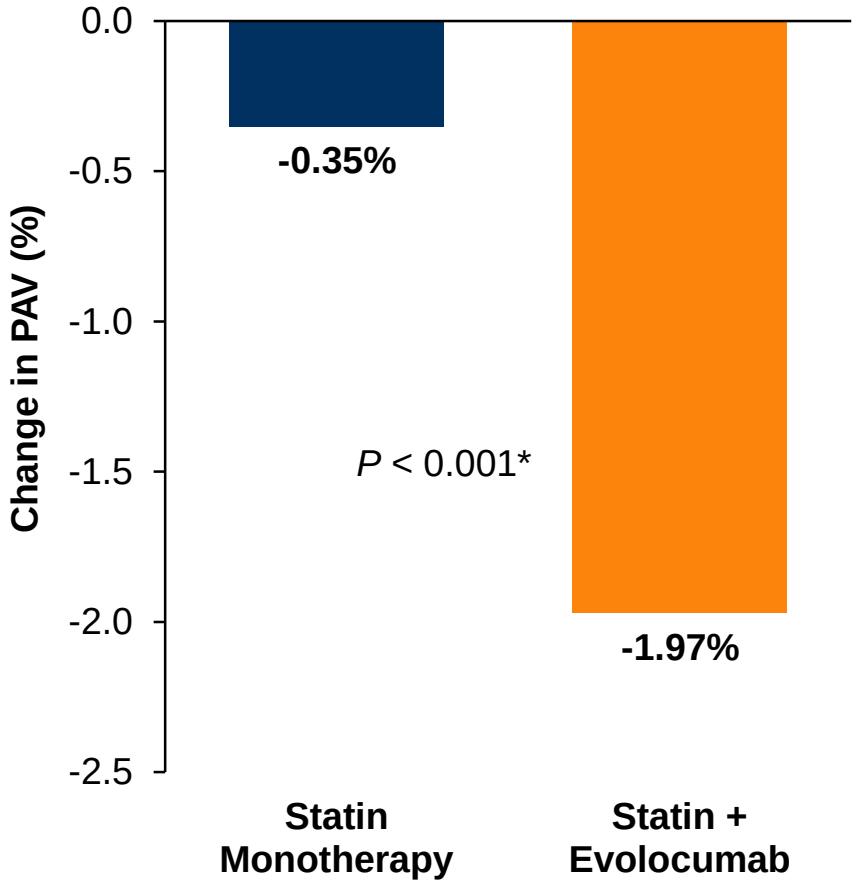
Note: mg/dL version

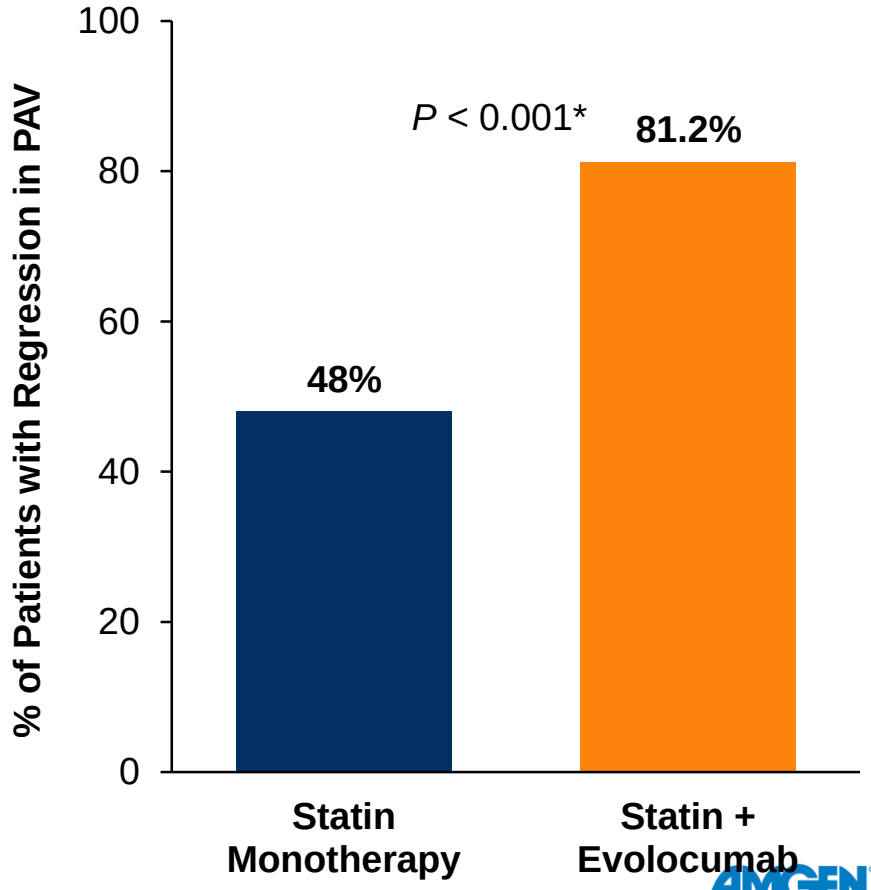
Exploratory Subgroup: Change in PAV & Regression in Patients with LDL-C < 70 mg/dL at Baseline

Patients with LDL-C < 70 mg/dL at Baseline (n = 144)

Percent Atheroma Volume



Fraction Showing Regression



*Between-treatment group comparison
PAV = percentage atheroma volume
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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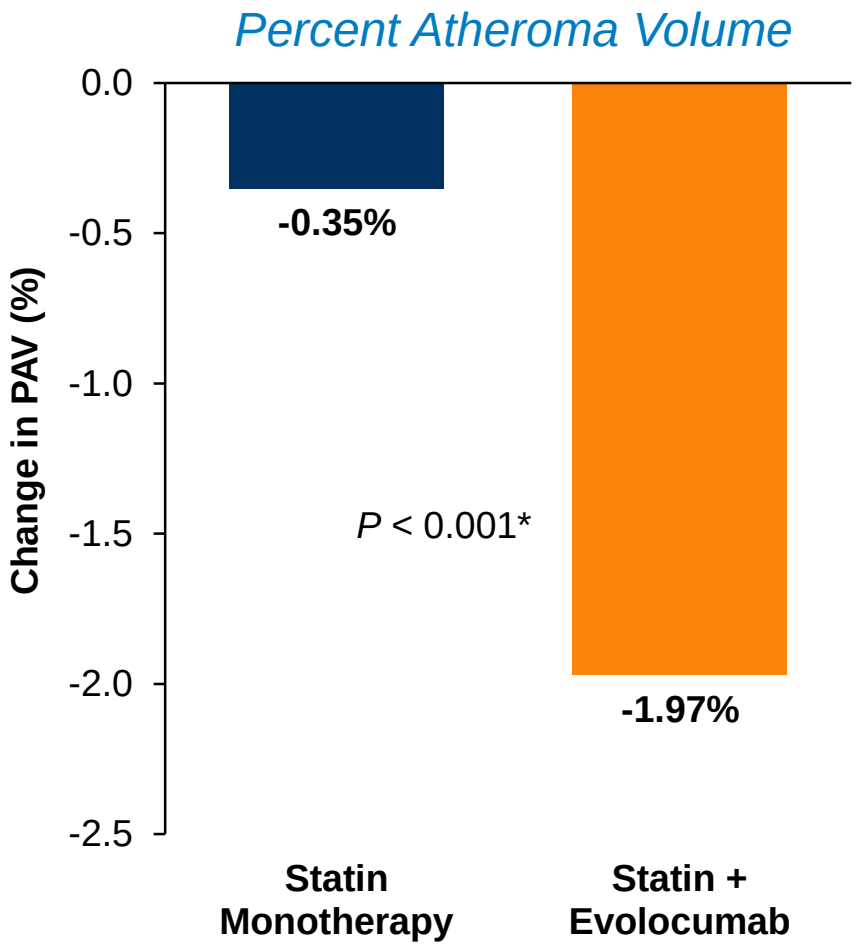
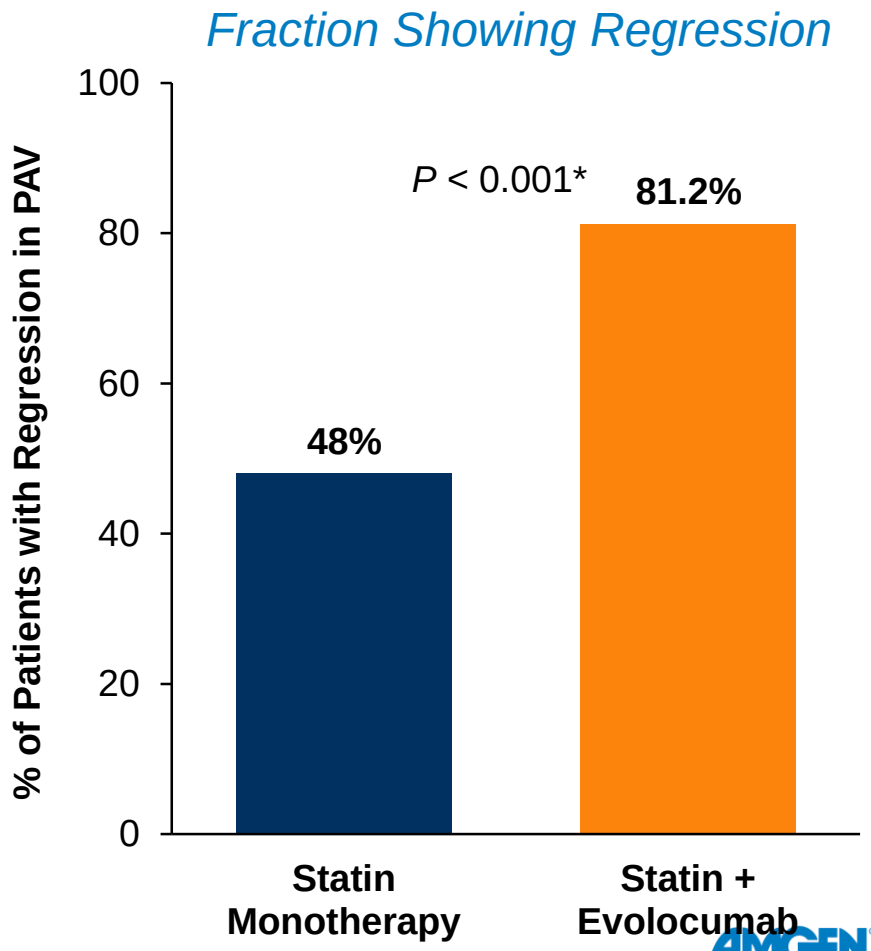
Note: mmol/L version

Exploratory Subgroup: Change in PAV & Regression in Patients with LDL-C < 1.81 mmol/L at Baseline

Patients with LDL-C < 1.81 mmol/L at Baseline (n = 144)





*Between-treatment group comparison
PAV = percentage atheroma volume
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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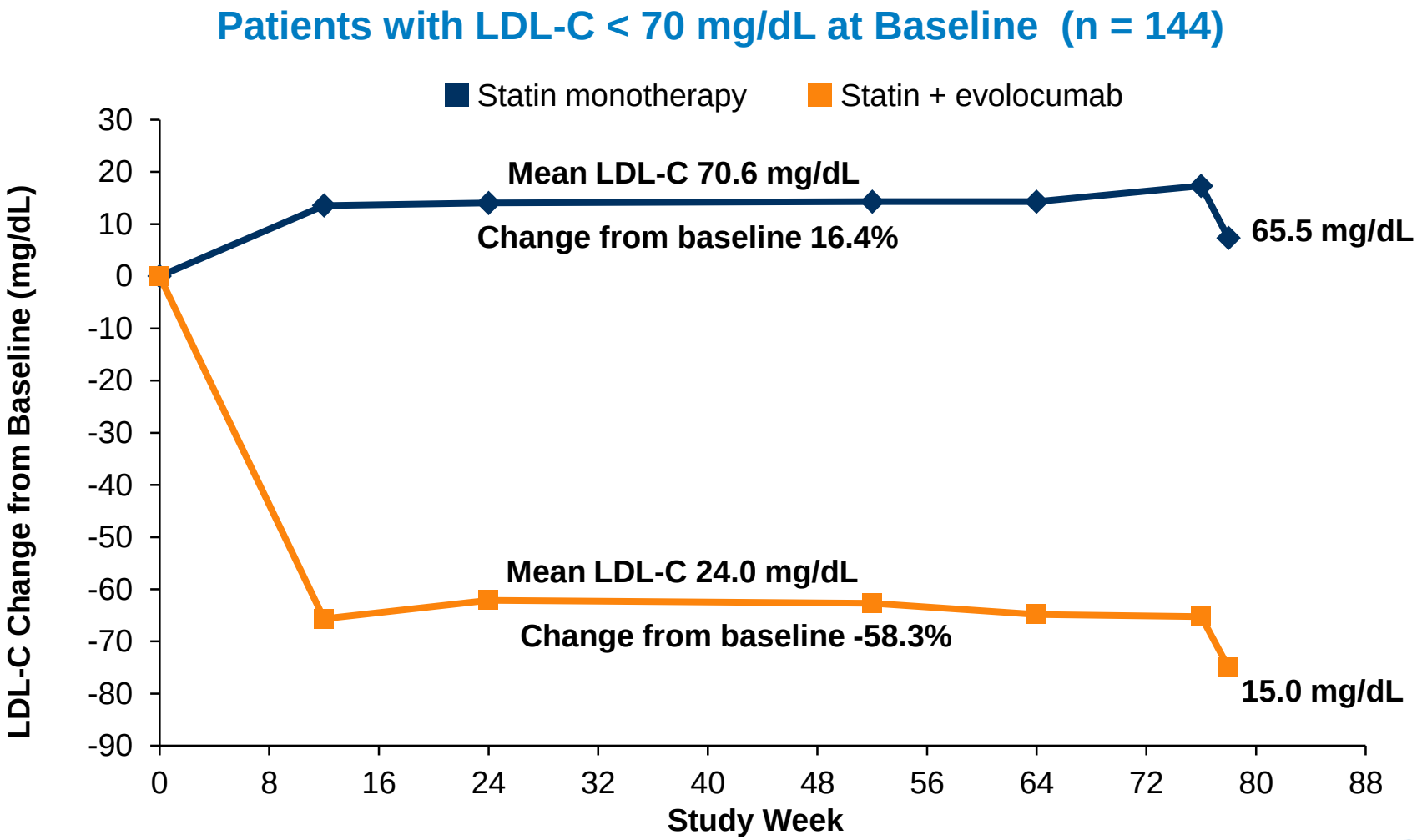
Note: mg/dL version

Exploratory Subgroup: LDL-C Change from Baseline in Patients with LDL-C < 70 mg/dL at Baseline



Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation

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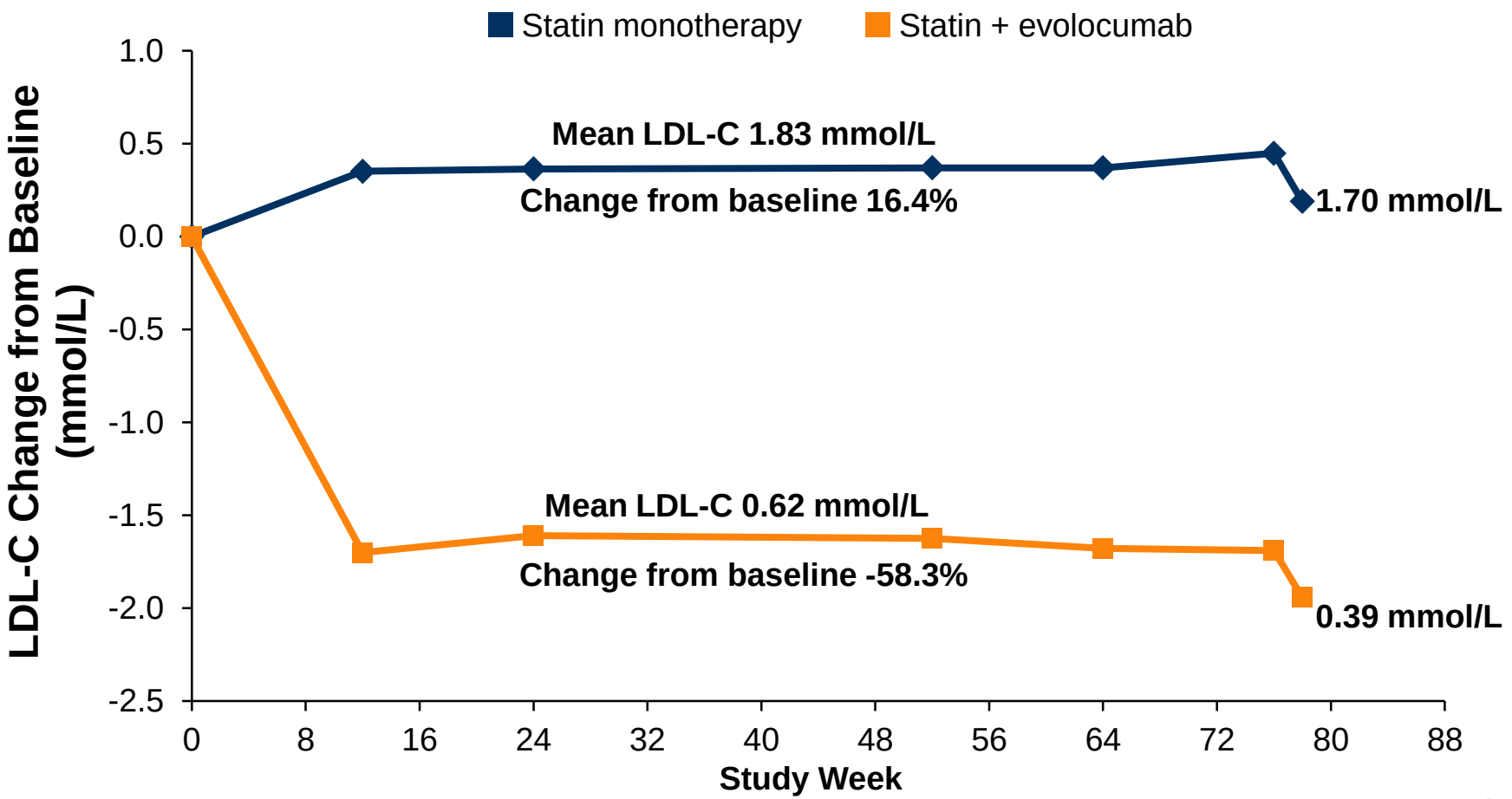
Note: mmol/L version

Exploratory Subgroup: LDL-C Change from Baseline in Patients with LDL-C < 1.81 mmol/L at Baseline



Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation

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Safety

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Clinical and Biochemical Adverse Events in the Safety Population*

Parameter	Placebo (N = 484)	Evolocumab (N = 484)
Clinically important adverse events, n (%)		
Injection site reactions	0 (0)	2 (0.4)
Myalgia	28 (5.8)	34 (7.0)
Neurocognitive events[a]	6 (1.2)	7 (1.4)
New diagnosis of diabetes mellitus†	18 (3.7)	17 (3.6)
Abnormality in laboratory value, n (%)‡		
Aspartate or alanine aminotransferase >3xULN	2 (0.5)	2 (0.5)
Total bilirubin >2xULN	2 (0.5)	1 (0.3)
Creatine phosphokinase >5xULN	3 (0.7)	3 (0.7)
Creatinine >ULN	5 (1.0)	3 (0.6)
Anti-Evolocumab binding antibody	NA	1 (0.2)
Anti-Evolocumab neutralizing antibody	NA	0 (0)

*All patients who received at least one dose of study drug were included in the safety analyses (n = 968)

†Neurocognitive events and new diagnosis diabetes mellitus as reported by investigators as adverse events. ‡The denominator for both placebo and evolocumab with normal value at baseline in 958. There were a total of 10 patients with missing safety laboratory data, clinical and laboratory adverse events, and reasons for discontinuation in the safety population.

NA = Not Available; ULN = Upper Limit of Normal

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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Reasons for Discontinuation*

Discontinuation from Treatment – n	Placebo (N = 484)	Evolocumab (N = 484)
Number of patients	35	38
Reason for discontinuation		
Preference of patient	19	12
Adverse Event	11	18
Lost to follow-up	2	3
Death	0	1
Physician decision	1	1
Other	2	3

*All patients who received at least one dose of study drug were included in the safety analyses (n=968)

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Adjudicated Cardiovascular Events in the Safety Population*

Parameter	Placebo (N = 484)	Evolocumab (N = 484)
Cardiovascular events, n (%)†		
Death	4 (0.8)	3 (0.6)
Non-fatal myocardial infarction	14 (2.9)	10 (2.1)
Non-fatal stroke	3 (0.6)	2 (0.4)
Hospitalization for unstable angina	4 (0.8)	3 (0.6)
Coronary revascularization	66 (13.6)	50 (10.3)
First major adverse cardiovascular event	74 (15.3)	59 (12.2)

*All patients who received at least one dose of study drug were included in the safety analyses (n=968)
†Total number of cardiovascular events included 2 events occurring during the period between the last scheduled visit and the end of the safety assessment period.
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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Summary

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Note: mg/dL version

GLAGOV Summary

- In statin-treated patients with symptomatic coronary disease, addition of evolocumab, 420 mg monthly for 18 months:
  - Achieved LDL-C levels averaging 36.6 mg/dL compared with 93 mg/dL for a statin alone.
  - Produced regression, mean change in PAV of -0.95% for evolocumab-statin treated group, compared with statin only patients, whose mean change in PAV was +0.05% ($P < 0.001$).
  - Produced regression (change in PAV <0) in a greater percentage of patients; 64% for evolocumab-statin treated patients vs. 47% in statin only patients ($P < 0.001$).
- No new safety signals were observed
- Further studies assessing the effects of PCSK9 inhibition on clinical outcomes are pending.

PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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Note: mmol/L version

GLAGOV Summary

- In statin-treated patients with symptomatic coronary disease, addition of evolocumab, 420 mg monthly for 18 months:
  - Achieved LDL-C levels averaging 0.95 mmol/L compared with 2.41 mmol/L for a statin alone.
  - Produced regression, mean change in PAV of -0.95% for evolocumab-statin treated group, compared with statin only patients, whose mean change in PAV was +0.05% ($P < 0.001$).
  - Produced regression (change in PAV <0) in a greater percentage of patients; 64% for evolocumab-statin treated patients vs. 47% in statin only patients ($P < 0.001$).
- No new safety signals were observed
- Further studies assessing the effects of PCSK9 inhibition on clinical outcomes are pending.

PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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Back-Up

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Note: mg/dL version

GLAGOV: Optimal Statin Therapy

- Optimal statin therapy was defined as an effective dose of atorvastatin 20 mg or equivalent titrated to achieve target LDL-C (reduction or goal) as defined by regional guidelines

Atorvastatin	20 – 80 mg	**Pravastatin**	80 mg
Simvastatin	40 – 80 mg	**Lovastatin**	80 mg
Rosuvastatin	5 – 40 mg	**Pitavastatin**	4 mg

- Highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent was recommended where locally approved

Subjects with LDL-C > 100 mg/dL not receiving highly effective statin therapy	Attestation required from the investigator that higher dose statin therapy was inappropriate for the subject*
Subjects not on a optimal tolerated dose of atorvastatin (or equivalent)	Lipid-stabilization period (2–4 weeks) entry for initiation or titration of atorvastatin to achieve optimization
Subjects with statin intolerance (≤ 10% of total study population)	Enrollment allowed†

Once subjects were randomized, no further alterations in lipid-lowering therapies were permitted

*Higher dose not tolerated, dose not available in that country, or other significant clinical concern; †As the effect of PSCK9-induced LDL-C lowering on changes in coronary atheroma volume in this special patient subgroup was felt to be an important subinvestigation.
LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Puri R, et al. *Am Heart J*. 2016;176:83-92.

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Note: mmol/L version

GLAGOV: Optimal Statin Therapy

- Optimal statin therapy was defined as an effective dose of atorvastatin 20 mg or equivalent titrated to achieve target LDL-C (reduction or goal) as defined by regional guidelines

Atorvastatin	20 – 80 mg	**Pravastatin**	80 mg
Simvastatin	40 – 80 mg	**Lovastatin**	80 mg
Rosuvastatin	5 – 40 mg	**Pitavastatin**	4 mg

- Highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent was recommended where locally approved

Subjects with LDL-C > 2.6 mmol/L not receiving highly effective statin therapy	Attestation required from the investigator that higher dose statin therapy was inappropriate for the subject*
Subjects not on a optimal tolerated dose of atorvastatin (or equivalent)	Lipid-stabilization period (2–4 weeks) entry for initiation or titration of atorvastatin to achieve optimization
Subjects with statin intolerance (≤ 10% of total study population)	Enrollment allowed†

Once subjects were randomized, no further alterations in lipid-lowering therapies were permitted

*Higher dose not tolerated, dose not available in that country, or other significant clinical concern; †As the effect of PSCK9-induced LDL-C lowering on changes in coronary atheroma volume in this special patient subgroup was felt to be an important subinvestigation.
LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Puri R, et al. *Am Heart J*. 2016;176:83-92.

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2013 ACC/AHA Blood Cholesterol Guidelines

High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Specific statins and doses are noted in bold that were evaluated in RCTs (17,18,46-48,64-67,69-78) included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (47).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline. DOI: 10.1161/01.cir.0000437738.63853.7a.

GLAGOV: Key Exclusion Criteria

- Clinically significant heart disease, which, in the opinion of the principal investigator, is likely to require coronary bypass surgery, PCI, cardiac transplantation, or surgical valve repair and/or replacement during the course of the study
- NYHA class III or IV or last known left ventricular ejection fraction < 30%
- CABG surgery < 6 weeks prior to the qualifying IVUS
- Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication
- Uncontrolled hypertension at day 1, defined as a resting systolic blood pressure of ≥ 180 mmHg
- Type 1 diabetes mellitus or poorly controlled type 2 diabetes (HbA_{1c} > 9%) at screening
- Use of CETP inhibition treatment within 12 months prior to randomization
- Any prior use of PCSK9 inhibitor therapy
- Laboratory values:
  - TG level > 400 mg/dL at screening
  - eGFR < 30 mL/min/1.73m^2
  - AST or ALT > 2 x ULN
  - Creatine kinase > 3 x ULN
  - TSH < LLN or TSH > 1.5 x ULN
- Consumption of any of the following drugs for more than 2 weeks in the last 3 months prior to LDL-C screening: systemic cyclosporine, systemic steroids, or isotretinoin

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CABG = coronary artery bypass surgery; CETP = cholesteryl ester transfer protein; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; LLN = lower limit of normal; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9; TG = triglyceride; TSH = thyroid stimulating hormone; ULN = upper limit of the normal.

Puri R, et al. *Am Heart J*. 2016;176:83-92.

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GLAGOV: Acquisition of IVUS Imaging

- Imaging was performed in a single artery and screened by a core laboratory; at week 78 the second IVUS examination was within the same artery
- Characteristics of the coronary artery for the IVUS examinations:
  - longest and least angulated coronary artery containing no lumen stenosis of more than 50% throughout a target segment of at least 40 mm in length
  - No prior revascularization
  - Not the culprit vessel responsible for a previous myocardial infarction
- The imaging catheter was advanced as distally as possible within the vessel
- Continuous images were acquired while the catheter was withdrawn back to the aorta by a motor drive at a constant speed of 0.5 mm per second

IVUS = intravascular ultrasound.

Puri R, et al. *Am Heart J*. 2016;176:83-92.
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Primary Efficacy Population and Safety Population

Study Analysis Groups	Definition	n
Primary Efficacy Population	Required evaluable IVUS imaging at both baseline and follow-up	846
Safety Population	All randomized patients who received at least one dose of study drug were included in the safety analyses	968

IVUS = intravascular ultrasound.

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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