

# Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

## The GLAGOV Randomized Clinical Trial

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**IMPORTANCE** Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

**OBJECTIVE** To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

**DESIGN, SETTING, AND PARTICIPANTS** The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.

**INTERVENTIONS** Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

**MAIN OUTCOMES AND MEASURES** The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.

**RESULTS** Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5 mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, -56.5 mg/dL [95% CI, -59.7 to -53.4];  $P < .001$ ). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, -1.0% [95% CI, -1.8% to -0.64%];  $P < .001$ ). The secondary efficacy parameter, normalized TAV, decreased 0.9 mm<sup>3</sup> with placebo and 5.8 mm<sup>3</sup> with evolocumab (difference, -4.9 mm<sup>3</sup> [95% CI, -7.3 to -2.5];  $P < .001$ ). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%];  $P < .001$  for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%];  $P < .001$  for TAV).

**CONCLUSIONS AND RELEVANCE** Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

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**R**educing levels of low-density lipoprotein cholesterol (LDL-C) with inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) is the cornerstone of contemporary care for patients with atherosclerotic cardiovascular disease. Analysis of data within individual statin trials and through meta-analyses suggests a consistent relationship between achieving lower LDL-C levels and reduction in major adverse cardiovascular events.<sup>1,2</sup> In parallel, trials using intravascular ultrasound (IVUS) have studied the effect of statins on coronary atherosclerosis and demonstrated a linear relationship between achieved LDL-C levels and reduction in atheroma burden.<sup>3-6</sup> However, major clinical outcome trials and IVUS studies have explored a range of achieved LDL-C levels, extending to a mean of approximately 60 mg/dL.<sup>3,5</sup>

Proprotein convertase subtilisin kexin type 9 (PCSK9) reduces LDL receptor recycling to the hepatic surface, thereby limiting removal of LDL particles from the circulation.<sup>7-9</sup> Monoclonal antibodies against PCSK9 reduce LDL-C levels when administered alone or in combination with statins.<sup>10,11</sup> Initial studies have demonstrated the feasibility of using the combination of statins and PCSK9 inhibitors to achieve LDL-C levels much lower than achieved previously.<sup>10,11</sup> However, to our knowledge, no trials to date have explored whether LDL-C lowering with a PCSK9 inhibitor reduces the rate of progression of coronary atherosclerosis, and no data exist assessing whether achieving very low LDL-C levels via combination therapy results in incremental benefits in reducing disease progression compared with statins alone. The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was designed to assess whether PCSK9 inhibition reduces progression of atherosclerosis as measured by IVUS.

## Methods

### Study Design

The GLAGOV trial was a multicenter, double-blind, placebo-controlled, randomized clinical trial. Randomization was stratified according to geographic region. The trial was designed by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) in collaboration with the sponsor. Institutional review boards at each site approved the protocol, and patients provided written informed consent. The study protocol and statistical analysis plan are available in [Supplement 1](#) and [Supplement 2](#), respectively, and the design of the trial has been described.<sup>12</sup>

Patients 18 years or older were eligible if they demonstrated at least 1 epicardial coronary stenosis of 20% or greater on clinically indicated coronary angiography and had a target vessel suitable for imaging with 50% or less visual obstruction. Patients were required to have been treated with a stable statin dose for at least 4 weeks and to have an LDL-C level of 80 mg/dL or higher or between 60 and 80 mg/dL (to convert LDL-C values to mmol/L, multiply by 0.0259) with 1 major or 3 minor cardiovascular risk factors. Major risk

### Key Points

**Question** Does treatment with a PCSK9 inhibitor modify coronary atherosclerosis disease progression?

**Findings** In this clinical trial in which 968 patients with coronary disease were treated with the PCSK9 inhibitor evolocumab or placebo monthly for 76 weeks and underwent serial intravascular ultrasound determination of coronary atheroma volume, lower low-density lipoprotein cholesterol levels were observed in the evolocumab group (36.6 vs 93.0 mg/dL), which also was associated with a reduction in percent atheroma volume for evolocumab (-0.95%) but not placebo (+0.05%) and a greater percentage of patients demonstrating plaque regression (64.3% vs 47.3%).

**Meaning** Addition of the PCSK9 inhibitor evolocumab to statin therapy produced greater low-density lipoprotein cholesterol lowering and atheroma regression.

factors included noncoronary atherosclerotic vascular disease, myocardial infarction or hospitalization for unstable angina in the preceding 2 years, or type 2 diabetes mellitus. Minor risk factors included current cigarette smoking, hypertension, low levels of high-density lipoprotein cholesterol, family history of premature coronary heart disease, high-sensitivity C-reactive protein (hsCRP) level of 2 mg/L or higher (to convert hsCRP values to nmol/L, multiply by 9.524), or age 50 years or older for men and 55 years or older for women.

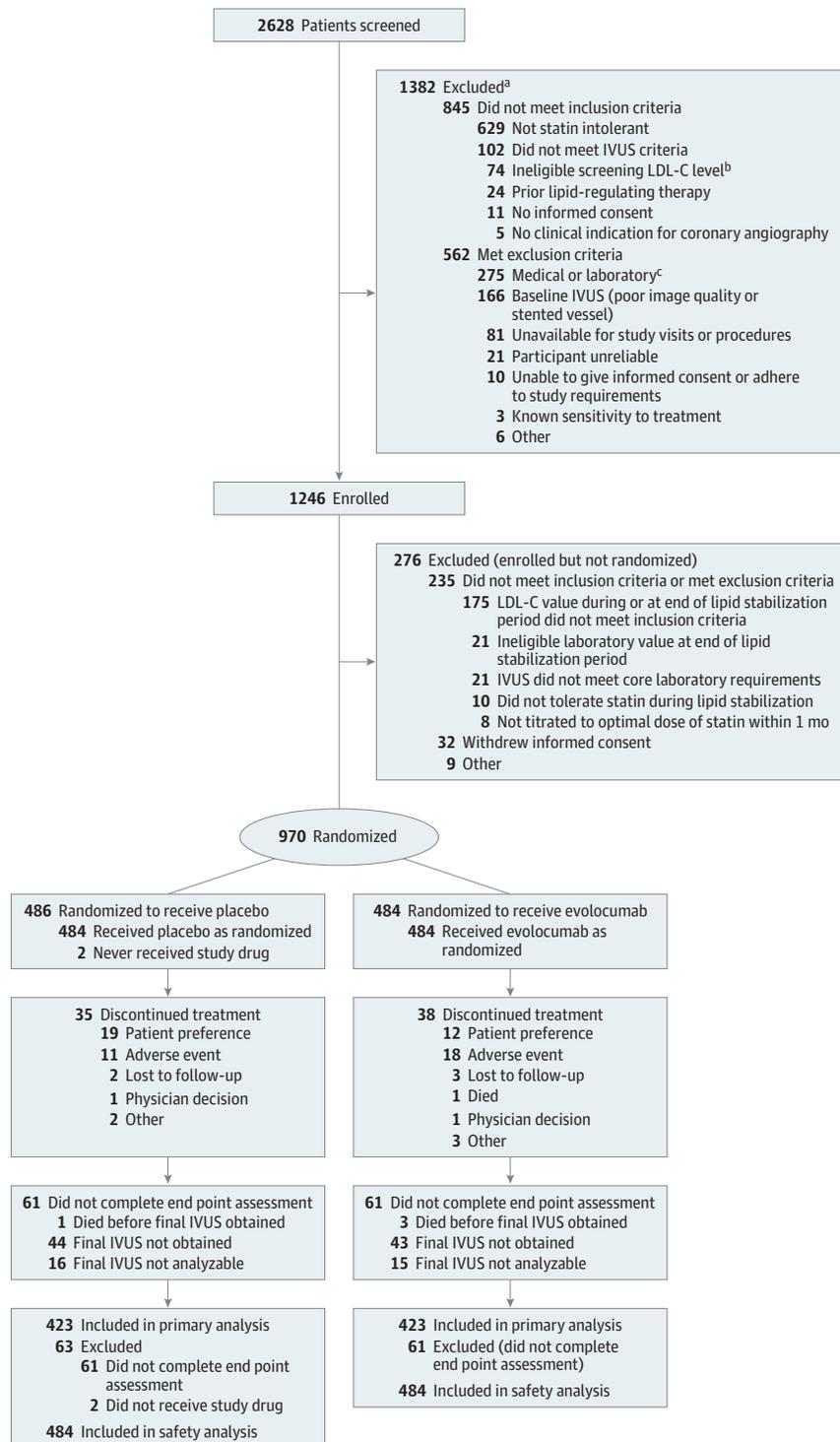
By design, patients with an entry LDL-C level between 60 and 80 mg/dL were limited to 25% of the total patient cohort. A 4-week lipid stabilization period was included for patients not currently taking lipid-modifying therapy at screening. Inclusion of patients intolerant to statins was limited to 10% of the total cohort. Patients were excluded if they had uncontrolled diabetes or hypertension, heart failure, renal dysfunction, or liver disease. Patients were asked to identify race/ethnicity according to fixed categories determined by the study protocol, to evaluate potential differences in concomitant treatment and disease progression.

Patients underwent randomization in a 1:1 allocation ratio with a block size of 4 using an interactive voice response system to treatment with evolocumab (420 mg) or placebo administered monthly via subcutaneous injection for 76 weeks. During the treatment period, patients underwent clinic visits at weeks 4, 12, 24, 36, 52, 64, and 76 and repeat IVUS imaging at week 78. A clinical events committee, blinded to treatment assignment, adjudicated cardiovascular events. An independent, unblinded data monitoring committee led by an academic cardiologist reviewed clinical trial safety during the study.

### Acquisition and Analysis of Ultrasound Images

After coronary angiography, baseline intravascular ultrasonography was performed. Previous reports have described the methods of image acquisition and analysis.<sup>3,5,6,13-18</sup> Imaging was performed in a single artery and screened by a core laboratory. Patients meeting prespecified requirements for image quality were eligible for randomization. At week

Figure 1. Flow of Patients Through the GLAGOV Randomized Clinical Trial



<sup>a</sup> Patients could be excluded for more than 1 reason; therefore, the sum of the criteria may be greater than the number of patients. CETP indicates cholesterylester transfer protein; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; IVUS, intravascular ultrasonography; LDL-C, low-density lipoprotein cholesterol.

<sup>b</sup> LDL-C level 80 mg/dL (2.07 mmol/L) or greater, with or without risk factors; less than 60 mg/dL (1.55 mmol/L); or 60 mg/dL or greater to less than 80 mg/dL.

<sup>c</sup> Clinically significant heart disease (154), hyperthyroidism or hypothyroidism (38), type 1 diabetes (27), history of malignancy (16), fasting triglyceride level greater than 400 mg/dL (4.52 mmol/L) (15), active liver disease or hepatic dysfunction (11), uncontrolled cardiac arrhythmia (4), creatine kinase level greater than 3 times upper limit of normal (2), history of hereditary muscular disorders (2), known active infection or systemic dysfunctions (2), New York Heart Association III or IV heart failure or left ventricular ejection fraction less than 30% (2), severe renal dysfunction (1), uncontrolled hypertension (1).

78, patients underwent a second ultrasonographic examination within the same artery. Using digitized images, personnel unaware of treatment status performed measurements of the lumen and external elastic membrane in images within

a matched artery segment. Measurement personnel were blinded to the sequence of imaging studies (baseline vs follow-up). The accuracy and reproducibility of this method have been reported.<sup>3,5,6,13-18</sup>

**Table 1. Baseline Characteristics of Patients in the Randomized Population Who Received Study Drug (N = 968)<sup>a</sup>**

Parameter	No. (%)	
	Placebo (n = 484)	Evolocumab (n = 484)
Age, mean (SD), y	59.8 (8.8)	59.8 (9.6)
Men	350 (72.3)	349 (72.1)
Race/ethnicity		
White	452 (93.4)	456 (94.2)
Black or African American	5 (1.0)	4 (0.8)
Asian	16 (3.3)	14 (2.9)
Native Hawaiian or other Pacific islander	0	1 (0.2)
American Indian or Alaska native	2 (0.4)	0
Multiple	6 (1.2)	7 (1.4)
Other	3 (0.6)	2 (0.4)
BMI, mean (SD) <sup>b</sup>	29.5 (5.0)	29.4 (5.0)
Hypertension	405 (83.7)	398 (82.2)
Previous PCI	188 (38.8)	189 (39.0)
Previous MI	171 (35.3)	169 (34.9)
Smoking	113 (23.3)	124 (25.6)
Diabetes	104 (21.5)	98 (20.2)
Baseline statin use <sup>c</sup>	476 (98.3)	478 (98.8)
Intensity <sup>d</sup>		
High	290 (59.9)	280 (57.9)
Moderate	185 (38.2)	196 (40.5)
Low	1 (0.2)	2 (0.4)
Baseline ezetimibe use <sup>c</sup>	9 (2.1)	9 (2.1)
Baseline medications		
Antiplatelet therapy	465 (96.1)	454 (93.8)
β-Blocker	370 (76.4)	362 (74.8)
ACE inhibitor	264 (54.5)	260 (53.7)
ARB	92 (19.0)	87 (18.0)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention.

<sup>a</sup> Clinical characteristics and concomitant medications of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up.

<sup>b</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>c</sup> Baseline statin and ezetimibe use is defined as patient treated with statin or ezetimibe therapy at the end of the lipid stabilization period at randomization.

<sup>d</sup> High intensity: atorvastatin (≥40 mg), rosuvastatin (≥20 mg), simvastatin (≥80 mg). Moderate intensity: atorvastatin (10-40 mg), rosuvastatin (5-20 mg), simvastatin (20-80 mg), pravastatin (≥40 mg), lovastatin (≥40 mg), fluvastatin (80 mg), pitavastatin (≥2 mg). Low intensity: atorvastatin (<10 mg), rosuvastatin (<5 mg), simvastatin (<20 mg), pravastatin (<40 mg), lovastatin (<40 mg).

The primary efficacy measure, percent atheroma volume (PAV), was calculated using the following equation:

$$PAV = \Sigma(EEM_{\text{area}} - \text{Lumen}_{\text{area}}) / \Sigma EEM_{\text{area}} \times 100,$$

where  $EEM_{\text{area}}$  is the cross-sectional area of the external elastic membrane and  $\text{Lumen}_{\text{area}}$  is the cross-sectional area of the lumen. The change in PAV was calculated as the PAV at 78 weeks minus the PAV at baseline. A secondary measure of

efficacy, normalized total atheroma volume (TAV), was calculated using the following equation:

$$TAV_{\text{normalized}} = (EEM_{\text{area}} - \text{Lumen}_{\text{area}}) / \text{Number of Images in Pullback} \times \text{Median Number of Images in Cohort},$$

where the average plaque area in each image was multiplied by the median number of images analyzed in the entire cohort to compensate for differences in segment length between patients. Change in normalized TAV was calculated as the TAV at 78 weeks minus the TAV at baseline. Regression was defined as any decrease in PAV or TAV from baseline.

### Efficacy End Points

The primary efficacy end point was the nominal change in PAV from baseline to week 78 as described above. Secondary efficacy end points included, in sequential order of testing, nominal change in TAV from baseline to week 78 as described above and the proportion of patients demonstrating any reduction of PAV from baseline and any reduction of TAV from baseline. Exploratory end points included the 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) and change in lipid parameters. Additional exploratory post hoc analyses included comparison of the change in PAV and percentage of patients undergoing regression of PAV in those with an LDL-C level less than or greater than 70 mg/dL at baseline. Locally weighted polynomial regression (LOESS) curve fitting was performed to examine the association between achieved LDL-C levels and disease progression.

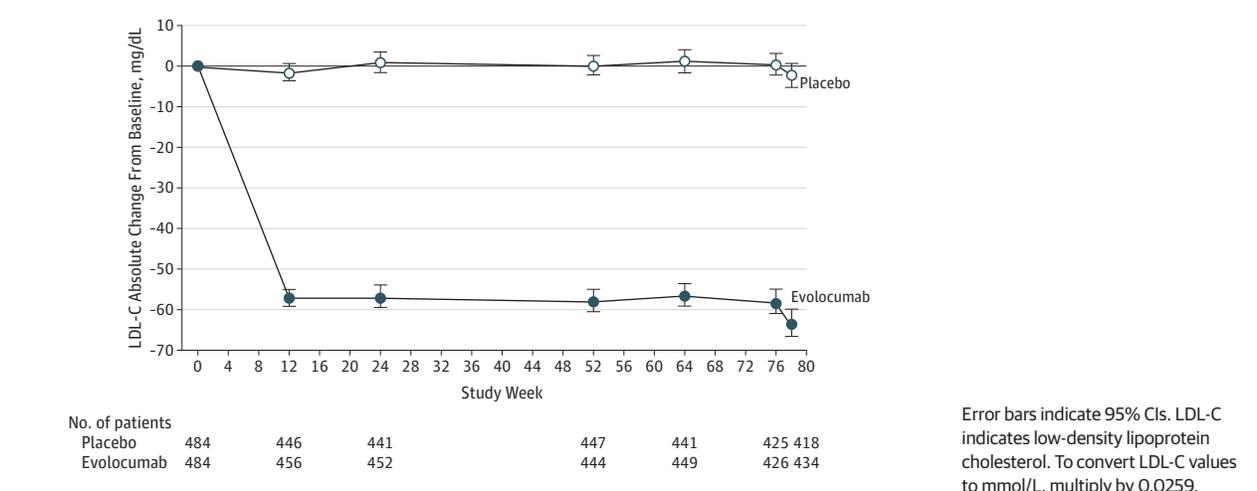
### Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Inc). For continuous variables with an approximately normal distribution, means and standard deviations are reported. For variables not normally distributed, medians and interquartile ranges (IQRs) are reported. IVUS efficacy parameters are reported as least squares means (95% CIs) and treatment groups compared using analysis of covariance on rank-transformed data with adjustment for baseline value and geographic region. On-treatment lipoprotein levels are reported as time-weighted means (95% CIs) and compared using analysis of covariance, with adjustment for treatment group and geographic region. Time-weighted averages for each laboratory parameter were created by the summation of the product between each measurement and time interval between each visit divided by the total time.

A step-down statistical approach was applied to investigate the primary and secondary end points. First, the primary end point was tested at the .05 significance level, then the secondary end points were tested at the .05 significance level in the sequential order as listed in section 4.1.2 in the statistical analysis plan (Supplement 2). A sensitivity analysis using multiple imputation was performed to impute missing primary end point data. The imputation model included variables for treatment group, background statin therapy intensity, region, baseline LDL-C level, baseline PAV, age, and sex



Figure 2. Mean Absolute Change in LDL-C Level



as covariates. Subgroup analyses on the primary end point were conducted using subgroups specified in section 7.4 of the statistical analysis plan (Supplement 2). Subgroup × treatment interactions were tested. An additional exploratory analysis was conducted in patients with baseline LDL-C level less than or greater than 70 mg/dL.

For the change in the primary efficacy parameter, PAV, a sample size of 356 patients in each treatment group was required to provide 90% power at a 2-sided  $\alpha$  of .05 to detect a nominal treatment difference of 0.71%, assuming a 2.9% standard deviation. A difference of 0.5% has been previously reported to distinguish patients who experience cardiovascular events from those who do not.<sup>19</sup> Assuming a withdrawal rate of 25%, 950 randomized patients were required.

All reported *P* values are 2-sided; *P* < .05 was considered statistically significant.

## Results

### Patient Characteristics

The disposition of patients enrolled in the study is shown in Figure 1. From May 3, 2013, to January 12, 2015, 968 patients at 197 centers were randomized and received study drug, 484 to the evolocumab treatment group and 484 to the placebo group. Eight hundred forty-six patients (87.2%) had evaluable IVUS imaging at both baseline and follow-up. Of these patients, 423 were in the placebo group and 423 in the evolocumab group. Mean exposure to study drug was 17.6 months. Table 1 reports the baseline characteristics of randomized patients. At the time of randomization, 58.9% were receiving high-intensity statin therapy and 39.4% moderate-intensity therapy, with 1.4% of patients not treated with a statin. At baseline, patients had a mean LDL-C level of 92.5 (SD, 27.2) mg/dL and median hsCRP level of 1.6 (IQR, 0.8-3.4) mg/L. No significant differences in these parameters were observed between patients who had evaluable follow-up IVUS imaging and those who did not (eTable 1 in Supplement 3).

### Biochemical Measurements

Table 2 summarizes the baseline and on-treatment laboratory values for the 846 patients who underwent follow-up IVUS imaging. During 76 weeks of treatment, time-weighted mean LDL-C levels were 93.0 mg/dL in the placebo group and 36.6 mg/dL in the evolocumab group (*P* < .001), representing a 0.2-mg/dL increase in the placebo group compared with a 56.3-mg/dL decrease in the evolocumab group (between-group difference, -56.5 mg/dL [95% CI, -59.7 to -53.4]; *P* < .001) (Figure 2). Evolocumab-treated patients demonstrated greater reductions in levels of apolipoprotein B (-40.3 vs 0.3 mg/dL; between-group difference, -40.6 mg/dL [95% CI, -42.9 to -38.3]; *P* < .001), triglycerides (-10.9 vs 8.1 mg/dL; between-group difference, -19.1 mg/dL [95% CI, -27.5 to -10.6]; *P* < .001) (to convert to mmol/L, multiply by 0.0113), and lipoprotein(a) (-7.8 vs -1.0 mg/dL; between-group difference, -6.7 mg/dL [95% CI, -7.9 to -5.5]; *P* < .001) (to convert to  $\mu$ mol/L, multiply by 0.0357) and greater increases in levels of high-density lipoprotein cholesterol (3.3 vs 0.8 mg/dL; between-group difference, 2.5 mg/dL [95% CI, 1.7 to 3.4]; *P* < .001) (to convert to mmol/L, multiply by 0.0259). Median hsCRP levels during treatment were 1.4 mg/L (IQR, 0.7-3.0) in the placebo group and 1.4 mg/L (IQR, 0.7-3.0) in the evolocumab group (*P* = .48).

### Primary and Secondary IVUS End Points

Changes in IVUS measures of plaque burden are summarized in Table 3. The primary efficacy measure, PAV, did not change in the placebo group (0.05%, *P* = .78 compared with baseline) and decreased by 0.95% in the evolocumab group (*P* < .001 compared with baseline; between-group difference, -1.0% [95% CI, -1.8% to -0.64%]; *P* < .001). The secondary efficacy measure, TAV, did not change in the placebo group (-0.9 mm<sup>3</sup>, *P* = .45 compared with baseline) and decreased by 5.8 mm<sup>3</sup> in the evolocumab group (*P* < .001 compared with baseline; between-group difference, -4.9 mm<sup>3</sup> [95% CI, -7.3 to -2.5]; *P* < .001). More evolocumab-treated patients exhibited PAV regression (64.3% vs 47.3%, *P* < .001) and TAV

Table 3. Primary and Secondary Study End Points as Evaluated on Intravascular Ultrasonography

Parameter	Placebo (n = 423)	Evolocumab (n = 423)	Between Group Differences, Least Squares Means (95% CI)	P Value
<b>Baseline</b>				
Percent atheroma volume				
Mean (95% CI)	37.2 (36.4 to 38.0)	36.4 (35.6 to 37.2)	-0.76 (-1.9 to 0.4)	.18
Median (95% CI)	37.1 (36.0 to 38.0)	36.4 (35.5 to 37.5)		
Total atheroma volume, mm <sup>3</sup>				
Mean (95% CI)	191.4 (183.2 to 199.6)	187.0 (179.1 to 194.8)	-4.3 (-15.6 to 7.0)	.63
Median (95% CI)	175.8 (164.0 to 187.4)	174.6 (164.1 to 183.1)		
<b>Follow-up at 78 wk</b>				
Percent atheroma volume				
Mean (95% CI)	37.3 (36.5 to 38.1)	35.6 (34.8 to 36.4)	-1.7 (-2.8 to -0.6)	.002
Median (95% CI)	36.8 (35.7 to 37.8)	35.7 (34.8 to 36.5)		
Total atheroma volume, mm <sup>3</sup>				
Mean (95% CI)	190.6 (182.5 to 198.7)	181.5 (174.1 to 188.9)	-8.9 (-19.9 to 2.0)	.23
Median (95% CI)	174.4 (164.3 to 186.6)	169.6 (160.9 to 180.7)		
<b>Change From Baseline</b>				<b>P Value for Between Groups<sup>a</sup></b>
Percent atheroma volume				
Least squares mean (95% CI)	0.05 (-0.32 to 0.42)	-0.95 (-1.33 to -0.58)	-1.0 (-1.8 to -0.64)	<.001
P value for change from baseline	.78	<.001		
Total atheroma volume, mm <sup>3</sup>				
Least squares mean (95% CI)	-0.91 (-3.29 to 1.47)	-5.80 (-8.19 to -3.41)	-4.9 (-7.3 to -2.5)	<.001
P value for change from baseline	.45	<.001		
Patients with regression, % (95% CI)				
Percent atheroma volume	47.3 (42.5 to 52.0)	64.3 (59.7 to 68.9)	17.0 (10.4 to 23.6)	<.001
Total atheroma volume	48.9 (44.2 to 53.7)	61.5 (56.8 to 66.1)	12.5 (5.9 to 19.2)	<.001

<sup>a</sup> The P value for comparison between treatments for change from baseline were generated from an analysis of covariance. Primary and secondary end points as evaluated on intravascular ultrasonography

at baseline and 78-week follow-up with changes from baseline. Results expressed as mean (SD) and median (95% CI) for continuous variables and percentage for categorical variables at baseline and follow-up.

regression (61.5% vs 48.9%,  $P < .001$ ). For all prespecified subgroups, there was no statistical evidence of interaction (Figure 3; eTable 2 in Supplement 3). Specifically, there was no difference in treatment effect observed in patients stratified according to baseline LDL-C level. Imputation modeling for patients who did not have evaluable IVUS imaging at follow-up demonstrated similar findings, with a decrease in PAV with placebo (-0.02%) and evolocumab (-1.05%) (between-group difference, -1.03% [95% CI, -1.51% to -0.55%];  $P < .001$ ).

### Exploratory Post Hoc Analyses

In 144 patients with baseline LDL-C levels less than 70 mg/dL, evolocumab treatment, compared with placebo, was associated with favorable effects on the change in PAV (-1.97% vs -0.35%; between-group difference, -1.62% [95% CI, -2.50% to -0.74%];  $P < .001$ ). In this subgroup, the percentage of patients with regression of PAV for evolocumab compared with placebo was 81.2% vs 48.0% (between-group difference, 33.2% [95% CI, 18.6% to 47.7%];  $P < .001$ ). A LOESS plot showed a linear relationship between achieved LDL-C level and PAV progression for LDL-C levels ranging from 110 mg/dL to as low as 20 mg/dL (Figure 4).

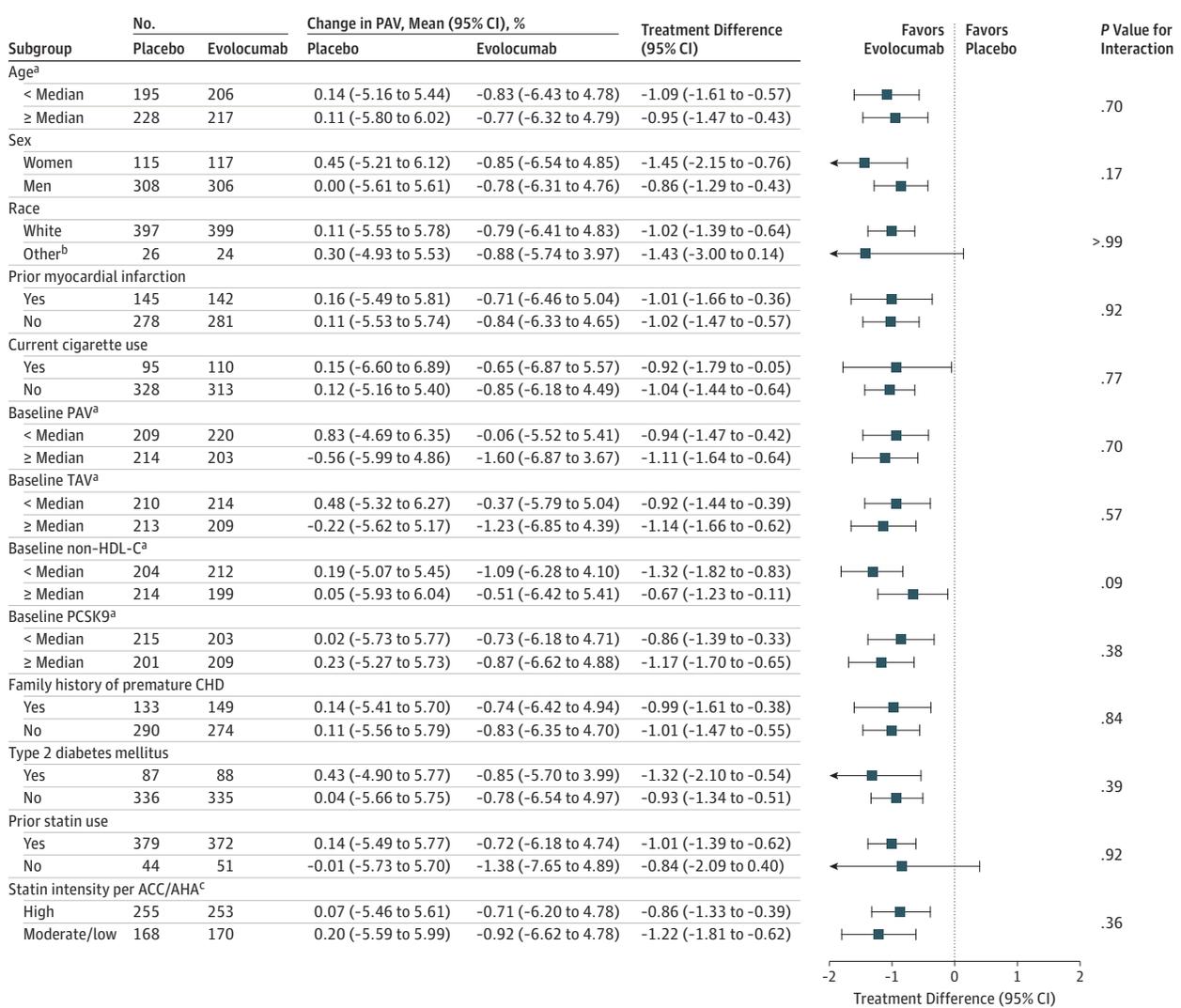
### Exploratory Clinical Events and Laboratory Adverse Events

Table 4 describes centrally adjudicated clinical events, clinical adverse events, laboratory abnormalities, and reasons for study discontinuation. Although the study was not powered to assess effects on cardiovascular events, exploratory analysis revealed numerically fewer adverse cardiovascular outcomes (12.2% vs 15.3%), nonfatal myocardial infarctions (2.1% vs 2.9%), and coronary revascularization procedures (10.3% vs 13.6%) in the evolocumab vs placebo groups. Administration of evolocumab was well tolerated, with no significant excess in rate of injection site reactions (0.4% vs 0%), myalgia (7.0% vs 5.8%), and neurocognitive events (1.4% vs 1.2%). The rates of laboratory abnormalities were low in both groups. Only 1 patient (0.2%) developed antievolocumab antibodies, and none had neutralizing antibodies detected. Hemoglobin A<sub>1c</sub> levels did not change in either treatment group.

### Discussion

The GLAGOV trial demonstrated that addition of the PCSK9 inhibitor evolocumab in patients treated with moderate- or high-intensity statin therapy had a favorable effect on progression

Figure 3. Prespecified Subgroup Analysis of Change in Percent Atheroma Volume From Baseline to Week-78 Follow-up



Results expressed as least squares means with 95% CIs. ACC/AHA indicates American College of Cardiology/American Heart Association; LDL-C indicates low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9; PAV, percent atheroma volume; TAV, total atheroma volume.

<sup>a</sup> Median values: age, 60 years; PAV, 36.88%; TAV, 175.08 mm<sup>3</sup>; non-HDL-C, 115 mg/dL; PCSK9, 315 ng/mL.

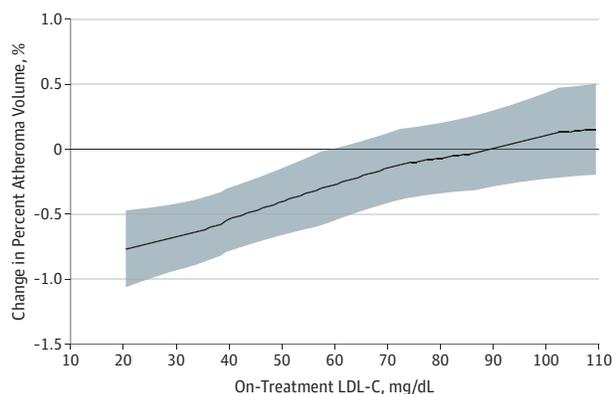
<sup>b</sup> Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska native, multiple, or other.

<sup>c</sup> High intensity: atorvastatin (≥40 mg), rosuvastatin (≥20 mg), simvastatin (≥80 mg). Moderate intensity: atorvastatin (10-40 mg), rosuvastatin (5-20 mg), simvastatin (20-80 mg), pravastatin (≥40 mg), lovastatin (≥40 mg), fluvastatin (80 mg), pitavastatin (≥2 mg). Low intensity: atorvastatin (<10 mg), rosuvastatin (<5 mg), simvastatin (<20 mg), pravastatin (<40 mg), lovastatin (<40 mg).

of coronary atherosclerosis as measured by IVUS. Both the primary and secondary IVUS efficacy measures showed atherosclerosis regression during 18 months of therapy in patients treated with the combination of evolocumab and statins and absence of regression in patients treated with a statin alone. Compared with baseline, for the primary IVUS end point, PAV, patients in the placebo treatment group demonstrated no decrease in atheroma burden (0.05%,  $P = .78$ ), whereas patients in the evolocumab group showed a significant reduction in PAV (-0.95%,  $P < .001$ ), for a between-group difference of -1.01% ( $P < .001$ ). Similar results were observed for the principal secondary end point, TAV (between-group difference, -4.9mm<sup>3</sup>;

$P < .001$ ). These findings provide evidence that PCSK9 inhibition produces incremental benefits on coronary disease progression in statin-treated patients.

This trial also evaluated the percentage of patients demonstrating regression of coronary atherosclerosis, defined as any change in PAV or TAV less than zero. Using this definition, for the primary end point, PAV, approximately 47% of patients in the placebo group experienced regression, compared with 64% of the treatment group receiving the combination of a statin and PCSK9 inhibitor (between-group difference, 17.0%;  $P < .001$ ). Similar results were observed for TAV, with more patients achieving regression with combination

**Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume**

Local regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.

therapy (between-group difference, 12.5%;  $P < .001$ ). This is the first clinical trial, to our knowledge, to show incremental effects on regression in patients who had been treated with moderate or intensive statin therapy prior to entry into the study. It is also the first, to our knowledge, to demonstrate a reduction in atherosclerotic disease progression by IVUS for a nonstatin LDL-C-lowering therapy.

After demonstrating major clinical benefits in multiple large outcomes trials,<sup>20-23</sup> statins are considered essential in global guidelines for managing the care of patients with clinically manifest coronary heart disease.<sup>24,25</sup> However, many patients do not achieve optimal LDL-C reduction<sup>26</sup> or experience cardiovascular events despite statin therapy.<sup>27</sup> Furthermore, some patients report inability to tolerate full therapeutic doses of statins.<sup>28</sup> Inadequate LDL-C reduction and presence of high residual risk suggests that additional therapies will be required to deliver maximally effective cardiovascular prevention. PCSK9 regulation of hepatic LDL receptor expression has provided a potentially useful target for therapeutic modulation to address residual cardiovascular risk in statin-treated patients, particularly with the observation that PCSK9 levels rise in response to statin administration.<sup>29</sup> In the current trial, almost every patient was treated with a statin prior to study entry, and addition of the PCSK9 inhibitor evolocumab provided incremental reduction in LDL-C levels and atheroma volume.

Favorable effects were observed in the GLAGOV trial on disease progression without an increase in the incidence of myalgias, elevations in hepatic transaminase levels, or new-onset diabetes. However, the number of treated patients was relatively small, and further safety assessments will require analysis of large ongoing clinical outcome trials. Subcutaneous injections were well tolerated, with injection site reactions reported in only 2 evolocumab-treated patients, a low rate of detection of antidrug antibodies, and no neutralizing anti-

**Table 4. Clinical and Biochemical Adverse Events in the Safety Population**

Parameter	No. (%)	
	Placebo (n = 484)	Evolocumab (n = 484)
Cardiovascular events <sup>a</sup>		
Death	4 (0.8)	3 (0.6)
Nonfatal myocardial infarction	14 (2.9)	10 (2.1)
Nonfatal 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)
Clinically important adverse events		
Injection site reaction	0	2 (0.4)
Myalgia	28 (5.8)	34 (7.0)
Neurocognitive events <sup>b</sup>		
New diagnosis diabetes mellitus <sup>b</sup>	6 (1.2)	7 (1.4)
Abnormality in laboratory value <sup>c</sup>		
Aspartate or alanine aminotransferase >3× ULN	2 (0.5)	2 (0.5)
Total bilirubin >2× ULN	2 (0.5)	1 (0.3)
Creatine phosphokinase >5× ULN	3 (0.7)	3 (0.7)
Creatinine >ULN	5 (1.0)	3 (0.6)
Antievolocumab binding antibody	NA	1 (0.2)
Antievolocumab neutralizing antibody	NA	0

Abbreviations: NA, not available; ULN, upper limit of normal.

<sup>a</sup> Total number of cardiovascular events included 2 events occurring during the period between the last scheduled visit and the end of safety assessment period.

<sup>b</sup> Neurocognitive events and new diagnosis diabetes mellitus as reported by investigators as adverse events.

<sup>c</sup> The denominator for both placebo and evolocumab with normal value at baseline is 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.

bodies. These safety findings are consistent with prior observations showing no apparent excess in adverse events among statin-treated patients achieving very low LDL-C levels.<sup>30</sup>

Subgroup analyses showed no heterogeneity in the favorable effects of PCSK9 inhibition on disease progression. Regression with evolocumab was observed regardless of baseline LDL-C levels. An LDL-C level of 70 mg/dL represents the most stringent target level recommended by any global guideline for cholesterol treatment.<sup>24,25</sup> In patients with a baseline LDL-C level less than 70 mg/dL, post hoc analysis in the current trial demonstrated regression in PAV in more than 80% of patients with combination therapy. This observation is supportive of current treatment guidelines recommending intensive lipid lowering in patients at high cardiovascular risk.<sup>24,25</sup> While these findings are reassuring, it is important to note that subgroup analyses cannot definitively characterize the potential efficacy or harm of a novel treatment strategy in distinct patient cohorts. At best, these analyses can generate hypotheses requiring further validation in prospective studies.

The definitive evidence supporting PCSK9 inhibitors as a clinically effective therapeutic strategy relies on the ability of

these drugs to reduce cardiovascular adverse events. Prior reports have demonstrated an association between both the burden and rate of progression of coronary atherosclerosis and cardiovascular outcomes.<sup>19,31</sup> Although the current findings of the effect of evolocumab on disease progression are promising, completion of ongoing large cardiovascular outcome trials of PCSK9 inhibitors is needed to provide definitive information on the efficacy and safety of these drugs.

Only approximately two-thirds of patients achieved atheroma regression, despite achieving very low LDL-C levels with evolocumab. However, the GLAGOV trial evaluated patients after 18 months of treatment, a relatively short duration of therapy in comparison with other recent studies of high-intensity statin treatment that treated patients for 24 months. It remains possible that a greater percentage of patients would demonstrate regression at these low LDL-C levels with more prolonged treatment. Nonetheless, the GLAGOV trial suggests that there may be biological limitations on the percentage of patients who can achieve regression with highly effective LDL-C lowering and that other factors contribute to disease progression in the remaining patients. Investigation of other factors influencing disease progression in the setting of very low achieved LDL-C levels could be useful in identifying novel therapeutic targets.

This trial has several limitations. The study examined the effects of PCSK9 inhibition on disease progression in patients presenting for a clinically indicated coronary angiogram. It remains unknown whether similar effects would be observed in asymptomatic patients receiving statins for secondary prevention. Although patient retention in this trial (87%) was better than in previous IVUS studies, the results may have been influenced by patients who did not complete the trial. We addressed this issue by imputing results for patients who did not complete the trial, but imputation is not an entirely satisfactory approach to missing data. The study focused on the role of PCSK9 inhibition on atheroma volume but did not characterize effects on atheroma morphology, which was investigated in a prespecified substudy not yet analyzed.

## Conclusions

Among patients with angiographic coronary artery disease treated with statins, addition of subcutaneous evolocumab, compared with placebo, resulted in a greater decrease in percent atheroma volume after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

### ARTICLE INFORMATION

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## REFERENCES

- LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352(14):1425-1435.
- Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670-1681.
- Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med.* 2011;365(22):2078-2087.
- Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA.* 2007;297(5):499-508.
- Nissen SE, Nicholls SJ, Sipahi I, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA.* 2006;295(13):1556-1565.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004;291(9):1071-1080.
- Abifadel M, Varret M, Rabès JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet.* 2003;34(2):154-156.
- Maxwell KN, Breslow JL. Adenoviral-mediated expression of Pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype. *Proc Natl Acad Sci U S A.* 2004;101(18):7100-7105.
- Seidah NG, Benjannet S, Wickham L, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. *Proc Natl Acad Sci U S A.* 2003;100(3):928-933.
- Robinson JG, Nedergaard BS, Rogers WJ, et al; LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA.* 2014;311(18):1870-1882.
- Blom DJ, Hala T, Bolognese M, et al; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med.* 2014;370(19):1809-1819.
- Puri R, Nissen SE, Somaratne R, et al. Impact of PCSK9 inhibition on coronary atheroma progression: rationale and design of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV). *Am Heart J.* 2016;176:83-92.
- Nissen SE, Nicholls SJ, Wolski K, et al; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA.* 2008;299(13):1561-1573.
- Nissen SE, Nicholls SJ, Wolski K, et al; STRADIVARIUS Investigators. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *JAMA.* 2008;299(13):1547-1560.
- Nissen SE, Tardif JC, Nicholls SJ, et al; ILLUSTRATE Investigators. Effect of torcetrapib on the progression of coronary atherosclerosis [published correction appears in *N Engl J Med.* 2007;357(8):835]. *N Engl J Med.* 2007;356(13):1304-1316.
- Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA.* 2003;290(17):2292-2300.
- Nissen SE, Tuzcu EM, Brewer HB, et al; ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Investigators. Effect of ACAT inhibition on the progression of coronary atherosclerosis. *N Engl J Med.* 2006;354(12):1253-1263.
- Nissen SE, Tuzcu EM, Libby P, et al; CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA.* 2004;292(18):2217-2225.
- Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol.* 2010;55(21):2399-2407.
- Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344(8934):1383-1389.
- Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339(19):1349-1357.
- Sacks FM, Pfeffer MA, Moye LA, et al; Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335(14):1001-1009.
- Shepherd J, Cobbe SM, Ford I, et al; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995;333(20):1301-1307.
- Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25, pt B):2889-2934.
- Catapano AL, Graham I, De Backer G, et al; Authors/Task Force Members. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR) [published online August 27, 2016]. *Eur Heart J.* doi: 10.1093/eurheartj/ehw272
- Jones PH, Nair R, Thakker KM. Prevalence of dyslipidemia and lipid goal attainment in statin-treated subjects from 3 data sources: a retrospective analysis. *J Am Heart Assoc.* 2012;1(6):e001800.
- Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol.* 2005;46(7):1225-1228.
- Nissen SE, Stroes E, Dent-Acosta RE, et al; GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA.* 2016;315(15):1580-1590.
- Mayne J, Dewpura T, Raymond A, et al. Plasma PCSK9 levels are significantly modified by statins and fibrates in humans. *Lipids Health Dis.* 2008;7:22.
- Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E; PROVE IT-TIMI 22 Investigators. Can low-density lipoprotein be too low? the safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol.* 2005;46(8):1411-1416.
- Puri R, Nissen SE, Shao M, et al. Coronary atheroma volume and cardiovascular events during maximally intensive statin therapy. *Eur Heart J.* 2013;34(41):3182-3190.