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

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

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 mm³ with placebo and 5.8 mm³ with evolocumab (difference, −4.9 mm³ [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.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01813422

Published online November 15, 2016. Corrected on December 1, 2016.
Reducing 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. 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. 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.

Monoclonal antibodies against PCSK9 reduce LDL-C levels 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 LDL-C levels much lower than achieved previously. 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 (CSResearch) 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.

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 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. 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...
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.3,5,6,13-18

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

<table>
<thead>
<tr>
<th>Patients screened</th>
<th>2628</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1382</td>
</tr>
<tr>
<td>Did not meet inclusion criteria</td>
<td>845</td>
</tr>
<tr>
<td>Not statin intolerant</td>
<td>629</td>
</tr>
<tr>
<td>Did not meet IVUS criteria</td>
<td>102</td>
</tr>
<tr>
<td>Prior lipid-regulating therapy</td>
<td>74</td>
</tr>
<tr>
<td>No informed consent</td>
<td>24</td>
</tr>
<tr>
<td>No clinical indication for coronary angiography</td>
<td>11</td>
</tr>
<tr>
<td>Met exclusion criteria</td>
<td>562</td>
</tr>
<tr>
<td>Medical or laboratory</td>
<td>275</td>
</tr>
<tr>
<td>Baseline IVUS (poor image quality or stented vessel)</td>
<td>166</td>
</tr>
<tr>
<td>Unavailable for study visits or procedures</td>
<td>81</td>
</tr>
<tr>
<td>Participant unreliable</td>
<td>21</td>
</tr>
<tr>
<td>Unable to give informed consent or adhere to study requirements</td>
<td>10</td>
</tr>
<tr>
<td>Known sensitivity to treatment</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
</tbody>
</table>

| Included in primary analysis | 423 |
| Did not complete end point assessment | 63 |
| Died before final IVUS obtained | 44 |
| Final IVUS not obtained | 16 |

| Included in safety analysis | 484 |
| Did not receive study drug | 2 |

| Randomized | 486 |
| Received placebo as randomized | 484 |
| Never received study drug | 2 |

| Included in primary analysis | 423 |
| Did not complete end point assessment | 61 |
| Died before final IVUS obtained | 43 |
| Final IVUS not obtained | 15 |

| Included in safety analysis | 484 | 
| Did not receive evolocumab | 484 |

| Randomized to receive placebo | 486 |
| Received placebo as randomized | 484 |

| Randomized to receive evolocumab | 486 |
| Received evolocumab as randomized | 484 |

| Discontinued treatment | 35 |
| Patient preference | 19 |
| Adverse event | 11 |
| Lost to follow-up | 2 |
| Physician decision | 1 |
| Other | 2 |

| Discontinued treatment | 38 |
| Patient preference | 12 |
| Adverse event | 18 |
| Lost to follow-up | 3 |
| Died | 1 |
| Physician decision | 1 |
| Other | 3 |

| Did not complete end point assessment | 61 |
| Died before final IVUS obtained | 16 |
| Final IVUS not analyzable | 16 |

| Did not complete end point assessment | 61 |
| Died before final IVUS obtained | 43 |
| Final IVUS not obtained | 15 |

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

\[
PAV = \frac{\sum (EEM_{area} - \text{Lumen}_{area})}{\sum EEM_{area}} \times 100,
\]

where \(EEM_{area}\) is the cross-sectional area of the external elastic membrane and \(\text{Lumen}_{area}\) 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:

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

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.
Table 2. Baseline and On-Treatment Biochemical Measures and Blood Pressure in the Randomized Population Who Received Study Druga

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 484)</th>
<th>Evolocumab (n = 484)</th>
<th>On-Treatment Placebo (n = 484)</th>
<th>Evolocumab (n = 484)</th>
<th>Absolute Change (95% CI)</th>
<th>P Valueb</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mean (95% CI), mg/dL</td>
<td>166.2 (163.1 to 169.2)</td>
<td>166.1 (163.0 to 169.2)</td>
<td>169.1 (166.3 to 172.0)</td>
<td>108.6 (106.0 to 111.3)</td>
<td>&lt;.001</td>
<td>1.8 (−2.0 to 5.6)</td>
<td>−59.0 (−62.8 to −55.2)</td>
</tr>
<tr>
<td>LDL-Cc</td>
<td>92.4 (90.0 to 94.8)</td>
<td>92.6 (90.1 to 95.0)</td>
<td>93.0 (90.5 to 95.4)</td>
<td>36.6 (34.5 to 38.8)</td>
<td>&lt;.001</td>
<td>0.2 (−2.9 to 3.4)</td>
<td>−56.3 (−59.4 to −53.1)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>45.4 (44.2 to 46.5)</td>
<td>46.7 (45.5 to 47.8)</td>
<td>47.1 (46.0 to 48.2)</td>
<td>51.0 (49.8 to 52.1)</td>
<td>&lt;.001</td>
<td>0.7 (−0.1 to 1.6)</td>
<td>3.3 (2.4 to 4.1)</td>
</tr>
<tr>
<td>Triglycerides, median (IQR), mg/dLd</td>
<td>124.5 (90.0 to 173.0)</td>
<td>117.0 (88.0 to 155.0)</td>
<td>130.5 (100.3 to 177.2)</td>
<td>105.1 (82.5 to 141.6)</td>
<td>&lt;.001</td>
<td>8.1 (−0.4 to 16.6)</td>
<td>−10.9 (−19.4 to 2.5)</td>
</tr>
<tr>
<td>non–HDL-C, mean (95% CI), mg/dL</td>
<td>120.8 (117.9 to 123.7)</td>
<td>119.4 (116.5 to 122.3)</td>
<td>122.0 (119.3 to 124.7)</td>
<td>57.7 (55.2 to 60.2)</td>
<td>&lt;.001</td>
<td>1.1 (−2.7 to 4.8)</td>
<td>−62.3 (−66.0 to −58.5)</td>
</tr>
<tr>
<td>TC:HDL-C, mean (95% CI)</td>
<td>3.9 (3.6 to 3.9)</td>
<td>3.7 (3.6 to 3.9)</td>
<td>3.8 (3.7 to 3.9)</td>
<td>2.3 (2.2 to 2.3)</td>
<td>&lt;.001</td>
<td>−0.1 (−0.2 to 0.04)</td>
<td>−1.5 (−1.6 to −1.4)</td>
</tr>
<tr>
<td>Apolipoprotein, mean (95% CI), mg/dL</td>
<td>81.9 (80.1 to 83.6)</td>
<td>81.1 (79.3 to 82.9)</td>
<td>83.5 (81.8 to 85.2)</td>
<td>42.4 (40.8 to 44.0)</td>
<td>&lt;.001</td>
<td>0.3 (−2.0 to 2.6)</td>
<td>−40.3 (−42.6 to −38.0)</td>
</tr>
<tr>
<td>A-I</td>
<td>139.5 (137.2 to 141.9)</td>
<td>140.5 (138.3 to 142.8)</td>
<td>145.4 (143.4 to 147.4)</td>
<td>151.6 (149.5 to 153.7)</td>
<td>&lt;.001</td>
<td>3.5 (1.5 to 5.5)</td>
<td>8.5 (6.5 to 10.5)</td>
</tr>
<tr>
<td>B:A-I</td>
<td>0.60 (0.59 to 0.62)</td>
<td>0.59 (0.58 to 0.61)</td>
<td>0.59 (0.57 to 0.60)</td>
<td>0.29 (0.28 to 0.30)</td>
<td>&lt;.001</td>
<td>−0.02 (−0.04 to −0.001)</td>
<td>−0.3 (−0.33 to −0.29)</td>
</tr>
<tr>
<td>hsCRP, median (IQR), mg/L,e</td>
<td>1.6 (0.8 to 3.4)</td>
<td>1.6 (0.8 to 3.4)</td>
<td>1.4 (0.7 to 3.0)</td>
<td>1.4 (0.7 to 3.0)</td>
<td>.47</td>
<td>−0.3 (−1.3 to 0.6)</td>
<td>−0.4 (−1.3 to 0.6)</td>
</tr>
<tr>
<td>Lp(a), median (IQR), mg/dL</td>
<td>10.3 (3.9 to 50.7)</td>
<td>12.1 (4.6 to 57.1)</td>
<td>8.9 (3.9 to 48.1)</td>
<td>7.1 (2.5 to 46.7)</td>
<td>.07</td>
<td>−1.0 (−2.2 to 0.2)</td>
<td>−7.8 (−9.0 to −6.6)</td>
</tr>
<tr>
<td>Glucose, mean (95% CI), mg/dL,e</td>
<td>107.3 (104.6 to 110.1)</td>
<td>104.0 (101.8 to 106.2)</td>
<td>109.4 (106.9 to 112.0)</td>
<td>110.1 (107.8 to 112.3)</td>
<td>.72</td>
<td>3.9 (1.3 to 6.5)</td>
<td>7.8 (5.3 to 10.4)</td>
</tr>
<tr>
<td>Hba1c, mean (95% CI), %e</td>
<td>5.9 (5.8 to 6.0)</td>
<td>5.8 (5.8 to 5.9)</td>
<td>6.0 (5.9 to 6.1)</td>
<td>6.0 (5.9 to 6.1)</td>
<td>.85</td>
<td>0.2 (0.1 to 0.2)</td>
<td>0.2 (0.15 to 0.25)</td>
</tr>
</tbody>
</table>

Blood pressure, mean (95% CI), mm Hg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 484)</th>
<th>Evolocumab (n = 484)</th>
<th>On-Treatment Placebo (n = 484)</th>
<th>Evolocumab (n = 484)</th>
<th>Absolute Change (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>129.6 (128.2 to 131.0)</td>
<td>131.4 (130.1 to 132.7)</td>
<td>131.9 (130.8 to 133.1)</td>
<td>131.5 (130.4 to 132.5)</td>
<td>.55</td>
<td>0.9 (−0.7 to 2.5)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.7 (75.8 to 77.6)</td>
<td>78.0 (77.2 to 78.9)</td>
<td>78.5 (77.8 to 79.2)</td>
<td>78.6 (77.9 to 79.2)</td>
<td>.94</td>
<td>2.2 (1.0 to 3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: Apo, apolipoprotein; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); non–HDL-C, non–high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9, TC, total cholesterol.

SI conversion factors: To convert total cholesterol, LDL-C, HDL-C, and non–HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0013; to convert hCRP values to mg/L, multiply by 9.524; to convert Lp(a) values to μmol/L, multiply by 0.0357; to convert glucose values to mmol/L, multiply by 0.0555.

a On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all postbaseline 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 who were randomized and received at least 1 dose of study drug. Results expressed as mean (95% CI) at baseline and least squares mean (95% CI) for on-treatment values.

b P value for between-treatment group comparison.

c 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.

d Tested using Wilcoxon rank-sum test.

e Final measurements are used for on-treatment values. Absolute changes are presented as least squares means (95% CIs).
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 α 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.19 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 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 μmol/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 mm³, P = .45 compared with baseline) and decreased by 5.8 mm³ in the evolocumab group (P < .001) compared with baseline; between-group difference, −4.9 mm³ [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
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%]; \( P < .001 \)).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 423)</th>
<th>Evolocumab (n = 423)</th>
<th>Between Group Differences, Least Squares Means (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td>37.2 (36.4 to 38.0)</td>
<td>36.4 (35.6 to 37.2)</td>
<td>−0.76 (−1.9 to 0.4)</td>
<td>.18</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>37.1 (36.0 to 38.0)</td>
<td>36.4 (35.5 to 37.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total atheroma volume, mm³</td>
<td>191.4 (183.2 to 199.6)</td>
<td>187.0 (179.1 to 194.8)</td>
<td>−4.3 (−15.6 to 7.0)</td>
<td>.63</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>175.8 (164.0 to 187.4)</td>
<td>174.6 (164.1 to 183.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up at 78 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td>37.3 (36.5 to 38.1)</td>
<td>35.6 (34.8 to 36.4)</td>
<td>−1.7 (−2.8 to −0.6)</td>
<td>.002</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>36.8 (35.7 to 37.8)</td>
<td>35.7 (34.8 to 36.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total atheroma volume, mm³</td>
<td>190.6 (182.5 to 198.7)</td>
<td>181.5 (174.1 to 188.9)</td>
<td>−8.9 (−19.9 to 2.0)</td>
<td>.23</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>174.4 (164.3 to 186.6)</td>
<td>169.6 (160.9 to 180.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change From Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean (95% CI)</td>
<td>0.05 (−0.32 to 0.42)</td>
<td>−0.95 (−1.33 to −0.58)</td>
<td>−1.0 (−1.8 to −0.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( P ) value for change from baseline</td>
<td>.78</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total atheroma volume, mm³</td>
<td>−0.91 (−1.29 to 1.47)</td>
<td>−5.80 (−8.19 to −3.41)</td>
<td>−4.9 (−7.3 to −2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( P ) value for change from baseline</td>
<td>.45</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with regression, % (95% CI)</td>
<td>47.3 (42.5 to 52.0)</td>
<td>64.3 (59.7 to 68.9)</td>
<td>17.0 (10.4 to 23.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total atheroma volume</td>
<td>48.9 (44.2 to 53.7)</td>
<td>61.5 (56.8 to 66.1)</td>
<td>12.5 (5.9 to 19.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* The \( P \) value for comparison between treatments for change from baseline were generated from an analysis of covariance.

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 \( A_1c \) 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
of coronary atherosclerosis as measured by IVUS. Both the primary and secondary IVUS efficacy measures showed atheroma volume 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%, \( P < .001 \)). Similar results were observed for the principal secondary end point, TAV (between-group difference, −4.9 mm\(^3\); \( P < .001 \)). 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 the treatment group receiving the combination of a statin and PCSK9 inhibitor (between-group difference, 17.0%; \( P < .001 \)) showed regression of coronary atherosclerosis. Similar results were observed for TAV, with more patients achieving regression with combination therapy.

### Table

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Placebo</th>
<th>Evolocumab</th>
<th>Placebo</th>
<th>Evolocumab</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>195</td>
<td>206</td>
<td></td>
<td>0.14 (−5.16 to 5.44)</td>
<td></td>
<td>−0.83 (−6.43 to 4.78)</td>
</tr>
<tr>
<td>≥ Median</td>
<td>228</td>
<td>217</td>
<td></td>
<td>0.11 (−5.80 to 6.02)</td>
<td></td>
<td>−0.77 (−6.32 to 4.79)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>115</td>
<td>117</td>
<td></td>
<td>0.45 (−5.21 to 6.12)</td>
<td></td>
<td>−0.85 (−6.54 to 4.85)</td>
</tr>
<tr>
<td>Men</td>
<td>308</td>
<td>306</td>
<td></td>
<td>0.00 (−5.61 to 5.61)</td>
<td></td>
<td>−0.78 (−6.31 to 4.76)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>397</td>
<td>399</td>
<td></td>
<td>0.11 (−5.55 to 5.78)</td>
<td></td>
<td>−0.79 (−6.41 to 4.83)</td>
</tr>
<tr>
<td>Other (^b)</td>
<td>26</td>
<td>24</td>
<td></td>
<td>0.30 (−4.93 to 5.53)</td>
<td></td>
<td>−0.88 (−5.74 to 3.97)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>145</td>
<td>142</td>
<td></td>
<td>0.16 (−5.49 to 5.81)</td>
<td></td>
<td>−0.71 (−6.46 to 5.04)</td>
</tr>
<tr>
<td>Yes</td>
<td>278</td>
<td>281</td>
<td></td>
<td>0.11 (−5.53 to 5.74)</td>
<td></td>
<td>−0.84 (−6.33 to 4.65)</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>95</td>
<td>110</td>
<td></td>
<td>0.15 (−6.60 to 6.89)</td>
<td></td>
<td>−0.65 (−6.87 to 5.57)</td>
</tr>
<tr>
<td>No</td>
<td>328</td>
<td>313</td>
<td></td>
<td>0.12 (−5.16 to 5.40)</td>
<td></td>
<td>−0.85 (−6.18 to 4.49)</td>
</tr>
<tr>
<td>Baseline PAV (^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>209</td>
<td>220</td>
<td></td>
<td>0.83 (−4.69 to 6.35)</td>
<td></td>
<td>−0.06 (−5.52 to 5.41)</td>
</tr>
<tr>
<td>Yes</td>
<td>214</td>
<td>203</td>
<td></td>
<td>−0.56 (−5.99 to 4.86)</td>
<td></td>
<td>−1.60 (−6.87 to 3.67)</td>
</tr>
<tr>
<td>No</td>
<td>298</td>
<td>281</td>
<td></td>
<td>0.05 (−5.93 to 6.04)</td>
<td></td>
<td>−0.51 (−6.42 to 5.41)</td>
</tr>
<tr>
<td>Baseline TAV (^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>210</td>
<td>214</td>
<td></td>
<td>0.48 (−5.32 to 6.27)</td>
<td></td>
<td>−0.37 (−5.79 to 5.04)</td>
</tr>
<tr>
<td>Yes</td>
<td>213</td>
<td>209</td>
<td></td>
<td>−0.22 (−5.62 to 5.17)</td>
<td></td>
<td>−1.23 (−6.85 to 4.39)</td>
</tr>
<tr>
<td>No</td>
<td>328</td>
<td>313</td>
<td></td>
<td>0.12 (−5.16 to 5.40)</td>
<td></td>
<td>−0.85 (−6.18 to 4.49)</td>
</tr>
<tr>
<td>Baseline non–HDL-C (^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>204</td>
<td>212</td>
<td></td>
<td>0.19 (−5.07 to 5.46)</td>
<td></td>
<td>−1.09 (−6.28 to 4.10)</td>
</tr>
<tr>
<td>≥ Median</td>
<td>214</td>
<td>199</td>
<td></td>
<td>0.05 (−5.93 to 6.04)</td>
<td></td>
<td>−0.51 (−6.42 to 5.41)</td>
</tr>
<tr>
<td>Baseline PCSK9 (^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>215</td>
<td>203</td>
<td></td>
<td>0.02 (−5.73 to 5.77)</td>
<td></td>
<td>−0.73 (−6.18 to 4.71)</td>
</tr>
<tr>
<td>Yes</td>
<td>201</td>
<td>209</td>
<td></td>
<td>0.23 (−5.27 to 5.73)</td>
<td></td>
<td>−0.87 (−6.62 to 4.88)</td>
</tr>
<tr>
<td>No</td>
<td>328</td>
<td>313</td>
<td></td>
<td>0.12 (−5.41 to 5.70)</td>
<td></td>
<td>−0.74 (−6.42 to 4.94)</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>133</td>
<td>149</td>
<td></td>
<td>0.14 (−5.41 to 5.70)</td>
<td></td>
<td>−0.74 (−6.42 to 4.94)</td>
</tr>
<tr>
<td>No</td>
<td>290</td>
<td>274</td>
<td></td>
<td>0.11 (−5.56 to 5.79)</td>
<td></td>
<td>−0.83 (−6.35 to 4.70)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>87</td>
<td>88</td>
<td></td>
<td>0.43 (−4.90 to 5.77)</td>
<td></td>
<td>−0.85 (−5.70 to 3.99)</td>
</tr>
<tr>
<td>No</td>
<td>336</td>
<td>335</td>
<td></td>
<td>0.04 (−5.66 to 5.75)</td>
<td></td>
<td>−0.78 (−6.54 to 4.97)</td>
</tr>
<tr>
<td>Prior statin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>379</td>
<td>372</td>
<td></td>
<td>0.14 (−5.49 to 5.77)</td>
<td></td>
<td>−0.72 (−6.18 to 4.74)</td>
</tr>
<tr>
<td>No</td>
<td>290</td>
<td>274</td>
<td></td>
<td>−0.01 (−5.73 to 5.70)</td>
<td></td>
<td>−1.38 (−7.65 to 4.89)</td>
</tr>
<tr>
<td>Statin intensity per ACC/AHA (^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>255</td>
<td>253</td>
<td></td>
<td>0.07 (−5.46 to 5.61)</td>
<td></td>
<td>−0.71 (−6.20 to 4.78)</td>
</tr>
<tr>
<td>Moderate/low</td>
<td>168</td>
<td>170</td>
<td></td>
<td>0.20 (−5.59 to 5.99)</td>
<td></td>
<td>−0.92 (−6.62 to 4.78)</td>
</tr>
</tbody>
</table>

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.

\(^a\) Median values: age, 60 years; PAV, 36.88%; TAV, 175.08 mm\(^3\); non–HDL-C, 115 mg/dL; PCSK9, 315 ng/mL.

\(^b\) Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska native, multiple, or other.

\(^c\) 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).
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,20–23 statins are considered essential in global guidelines for managing the care of patients with clinically manifest coronary heart disease.24,25 However, many patients do not achieve optimal LDL-C reduction26 or experience cardiovascular events despite statin therapy.27 Furthermore, some patients report inability to tolerate full therapeutic doses of statins.28 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.29 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 antibodies. 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.30 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.24,25 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.24,25 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

---

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 484)</th>
<th>Evolocumab (n = 484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>14 (2.9)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>4 (0.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>66 (13.6)</td>
<td>50 (10.3)</td>
</tr>
<tr>
<td>First major adverse cardiovascular event</td>
<td>74 (15.3)</td>
<td>59 (12.2)</td>
</tr>
<tr>
<td>Clinically important adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>28 (5.8)</td>
<td>34 (7.0)</td>
</tr>
<tr>
<td>Neurocognitive events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (1.2)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>New diagnosis diabetes mellitus&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (3.7)</td>
<td>17 (3.6)</td>
</tr>
<tr>
<td>Abnormality in laboratory value&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate or alanine aminotransferase &gt;3× ULN</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Total bilirubin &gt;2× ULN</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Creatine phosphokinase &gt;5× ULN</td>
<td>3 (0.7)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Creatinine &gt;ULN</td>
<td>5 (1.0)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Antievolocumab binding antibody</td>
<td>NA</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Antievolocumab neutralizing antibody</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
Evolocumab and Coronary Disease Progression in Statin-Treated Patients

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

Correction: This article was corrected online on December 1, 2016, for an incorrect data point in the Discussion.

Published Online: November 15, 2016. doi:10.1001/jama.2016.16951

Author Affiliations: South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia (Nicholls); Department of Cardiovascular Medicine, Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, Ohio (Nicholls, Puri, Cho, Borgman, Brennan, Nissen); Libin Cardiovascular Institute, University of Calgary, Calgary, Alberta, Canada (Andersen); The Methodist DeBakey Heart and Vascular Center, Section of Cardiovascular Research, Baylor College of Medicine, Houston, Texas (Ballantyne); Academic Medical Center, Department of Vascular Medicine, University of Amsterdam, Amsterdam, the Netherlands (Kastelein); Deutsches Herzcenter München, Technische Universität München, Munich, Germany (Koenig); ESHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany (Koenig); Department of Internal Medicine, University of Ulm Medical Center, Ulm, Germany (Koenig); Apteon Inc, Thousand Oaks, California (Somaratne, Kassahun, Wasserman, Scott); Department of Cardiology, University of Szeged, Hungary (Ungi); Department of Interventional Cardiology, Cardiology Institute, Jagiellonian University, College of Medicine and the John Paul II Hospital, Krakow, Poland (Podolec); Department of Cardiology, Cansius Wilhelmina Hospital, Nijmegen, the Netherlands (Oude Ophuis); Department of Cardiology, Noordwest Ziekenhuis, Amstelveen, the Netherlands (Cornel).

Author Contributions: Drs Nicholls and Nissen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Nicholls, Ballantyne, Cho, Kastelein, Yang, Wasserman, Scott, Borgman, Nissen.

Acquisition, analysis, or interpretation of data: Nicholls, Puri, Anderson, Kastelein, Koenig, Somaratne, Kassahun, Yang, Wasserman, Scott, Ungi, Podolec, Oude Ophuis, Cornel, Brennan, Nissen.

Drafting of the manuscript: Nicholls, Cho, Scott, Cornel, Nissen.

Critical revision of the manuscript for important intellectual content: Nicholls, Puri, Anderson, Ballantyne, Cho, Kastelein, Koenig, Somaratne, Kassahun, Yang, Wasserman, Scott, Ungi, Podolec, Oude Ophuis, Borgman, Brennan, Nissen.

Statistical analysis: Nicholls, Yang, Brennan.

Obtained funding: Wasserman, Scott, Nissen.

Administrative, technical, or material support: Nicholls, Puri, Kastelein, Koenig, Wasserman, Scott, Borgman, Nissen.


Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Dr Nicholls reported receiving research support from AstraZeneca, Cereris, Amgen, Novartis, Eli Lilly, Anthera, LipoScience, Roche, Sanofi-Regeneron, and Resverlogix and receiving honoraria from or serving as a consultant for Amgen, AstraZeneca, Roche, Esparion, Eli Lilly, Abbott, Pfizer, Merck, Takeda, LipoScience, Omthera, Novo Nordisk, Sanofi Regeneron, Atherosvera, Anthera, CSL Behring, and Boehringer Ingelhein. Dr Puri reported receiving consulting fees from Sanofi Aventis and Cereris. Dr Koenig reported receiving research support from Abbott, Roche Diagnostics, Bedermann, and Singulex and receiving honoraria from or serving as a consultant for Novartis, AstraZeneca, Amgen, Pfizer, Sanofi, Berlin-Chemie, The Medicines Company, GlaxoSmithKline, DaiCor, and Kowa. Dr Podolec reported receiving honoraria from or serving as a consultant for Amgen, The Medicines Company, Pfizer, GlaxoSmithKline, AstraZeneca, Polyphor Ltd, and Janssen Research & Development LLC. Dr Oude Ophuis reported receiving consulting fees from Astra Pharmaceuticals, GlaxoSmithKline, Amgen, and Boston Pharmaceuticals. Dr Nissen reported receiving research support from Amgen, Abbvie, AstraZeneca, Cerenis, Eli Lilly, Esperion Therapeutics, Novo-Nordisk, The Medicines Company, Orexigen, Pfizer, and Takeda and consulting for a number of pharmaceutical companies without financial compensation (all honoraria, consulting fees, or any other payments from any for-profit entity are paid directly to charity, so neither income nor any tax deduction is received). Dr Cornel reported receiving consultant fees from Amgen, Merck, Sanofi, and AstraZeneca. No other authors reported disclosures.

Funding/Support: This study was sponsored by Amgen Inc.

Role of the Funder/Sponsor: Amgen Inc participated actively in designing the study in collaboration with the steering committee and developing the protocol written by the steering committee, provided logistical support during the trial in terms of site management in collaboration with CSRResearch, and performed all site monitoring. The sponsor maintained the trial database. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where statistical analyses were performed by an independent statistician, Danielle Brennan, MS. The results reported in the manuscript are the results of the analyses performed by Ms Brennan. The lead for Novartis, AstraZeneca, Amgen, Pfizer, Sanofi, Berlin-Chemie, The Medicines Company, GlaxoSmithKline, DaiCor, and Kowa. Dr Podolec reported receiving honoraria from or serving as a consultant for Amgen, The Medicines Company, Pfizer, GlaxoSmithKline, AstraZeneca, Polyphor Ltd, and Janssen Research & Development LLC. Dr Oude Ophuis reported receiving consulting fees from Astra Pharmaceuticals, GlaxoSmithKline, Amgen, and Boston Pharmaceuticals. Dr Nissen reported receiving research support from Amgen, Abbvie, AstraZeneca, Cerenis, Eli Lilly, Esperion Therapeutics, Novo-Nordisk, The Medicines Company, Orexigen, Pfizer, and Takeda and consulting for a number of pharmaceutical companies without financial compensation (all honoraria, consulting fees, or any other payments from any for-profit entity are paid directly to charity, so neither income nor any tax deduction is received). Dr Cornel reported receiving consultant fees from Amgen, Merck, Sanofi, and AstraZeneca. No other authors reported disclosures.

Funding/Support: This study was sponsored by Amgen Inc.

Role of the Funder/Sponsor: Amgen Inc participated actively in designing the study in collaboration with the steering committee and developing the protocol written by the steering committee, provided logistical support during the trial in terms of site management in collaboration with CSRResearch, and performed all site monitoring. The sponsor maintained the trial database. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where statistical analyses were performed by an independent statistician, Danielle Brennan, MS. The results reported in the manuscript are the results of the analyses performed by Ms Brennan. The lead for Novartis, AstraZeneca, Amgen, Pfizer, Sanofi, Berlin-Chemie, The Medicines Company, GlaxoSmithKline, DaiCor, and Kowa. Dr Podolec reported receiving honoraria from or serving as a consultant for Amgen, The Medicines Company, Pfizer, GlaxoSmithKline, AstraZeneca, Polyphor Ltd, and Janssen Research & Development LLC. Dr Oude Ophuis reported receiving consulting fees from Astra Pharmaceuticals, GlaxoSmithKline, Amgen, and Boston Pharmaceuticals. Dr Nissen reported receiving research support from Amgen, Abbvie, AstraZeneca, Cerenis, Eli Lilly, Esperion Therapeutics, Novo-Nordisk, The Medicines Company, Orexigen, Pfizer, and Takeda and consulting for a number of pharmaceutical companies without financial compensation (all honoraria, consulting fees, or any other payments from any for-profit entity are paid directly to charity, so neither income nor any tax deduction is received). Dr Cornel reported receiving consultant fees from Amgen, Merck, Sanofi, and AstraZeneca. No other authors reported disclosures.

Funding/Support: This study was sponsored by Amgen Inc.

Role of the Funder/Sponsor: Amgen Inc participated actively in designing the study in collaboration with the steering committee and developing the protocol written by the steering committee, provided logistical support during the trial in terms of site management in collaboration with CSRResearch, and performed all site monitoring. The sponsor maintained the trial database. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where statistical analyses were performed by an independent statistician, Danielle Brennan, MS. The results reported in the manuscript are the results of the analyses performed by Ms Brennan. The lead for Novartis, AstraZeneca, Amgen, Pfizer, Sanofi, Berlin-Chemie, The Medicines Company, GlaxoSmithKline, DaiCor, and Kowa. Dr Podolec reported receiving honoraria from or serving as a consultant for Amgen, The Medicines Company, Pfizer, GlaxoSmithKline, AstraZeneca, Polyphor Ltd, and Janssen Research & Development LLC. Dr Oude Ophuis reported receiving consulting fees from Astra Pharmaceuticals, GlaxoSmithKline, Amgen, and Boston Pharmaceuticals. Dr Nissen reported receiving research support from Amgen, Abbvie, AstraZeneca, Cerenis, Eli Lilly, Esperion Therapeutics, Novo-Nordisk, The Medicines Company, Orexigen, Pfizer, and Takeda and consulting for a number of pharmaceutical companies without financial compensation (all honoraria, consulting fees, or any other payments from any for-profit entity are paid directly to charity, so neither income nor any tax deduction is received). Dr Cornel reported receiving consultant fees from Amgen, Merck, Sanofi, and AstraZeneca. No other authors reported disclosures.

Funding/Support: This study was sponsored by Amgen Inc.

Role of the Funder/Sponsor: Amgen Inc participated actively in designing the study in collaboration with the steering committee and developing the protocol written by the steering committee, provided logistical support during the trial in terms of site management in collaboration with CSRResearch, and performed all site monitoring. The sponsor maintained the trial database. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where statistical analyses were performed by an independent statistician, Danielle Brennan, MS. The results reported in the manuscript are the results of the analyses performed by Ms Brennan. The lead for Novartis, AstraZeneca, Amgen, Pfizer, Sanofi, Berlin-Chemie, The Medicines Company, GlaxoSmithKline, DaiCor, and Kowa. Dr Podolec reported receiving honoraria from or serving as a consultant for Amgen, The Medicines Company, Pfizer, GlaxoSmithKline, AstraZeneca, Polyphor Ltd, and Janssen Research & Development LLC. Dr Oude Ophuis reported receiving consulting fees from Astra Pharmaceuticals, GlaxoSmithKline, Amgen, and Boston Pharmaceuticals. Dr Nissen reported receiving research support from Amgen, Abbvie, AstraZeneca, Cerenis, Eli Lilly, Esperion Therapeutics, Novo-Nordisk, The Medicines Company, Orexigen, Pfizer, and Takeda and consulting for a number of pharmaceutical companies without financial compensation (all honoraria, consulting fees, or any other payments from any for-profit entity are paid directly to charity, so neither income nor any tax deduction is received). Dr Cornel reported receiving consultant fees from Amgen, Merck, Sanofi, and AstraZeneca. No other authors reported disclosures.

Funding/Support: This study was sponsored by Amgen Inc.
Evolocumab and Coronary Disease Progression in Statin-Treated Patients

Original Investigation Research

academic investigator (Dr Nicholls) wrote the manuscript and is responsible for the accuracy and completeness of the data. Analysis of the data and the analysis while the steering committee and coordinating center had confidentiality agreements with the sponsor; the contract study specified that a copy of the study database be provided to CSResearch for independent analysis. While employees of the sponsor are coauthors of the manuscript, they provided input to the drafts. The academic authors had unrestricted rights to publish the results. The manuscript was modified after consultation with coauthors. The final decision on content was exclusively retained by the academic authors.

Intravascular Ultrasound Core Laboratory Staff: Karlane King, William Magyar, Brett Babb, Eva Balazs, Allen Borowski, Anne Colagiovanni, Patrick Hoeflinger, Erin Mayock, Jill Odabashian, Roman Poliszczuk

Study Investigators: Argentina: M. Amuchastegui (Hospital Privado Centro Medico de Cordoba), D. Grinfield (Hospital Español de La Plata–IDYAC), F. Kozak (Instituto Cardiovascular de Rosario), P. Liva (Instituto de Cardiologia de Corrientes Juana Francisca Cabral), A. Lorenzetti (Fundacion Ruscudela), G. Migliaro (Hospital Britancio de Buenos Aires), E. Moreyra (Sanatorio Alende, A. Padilla (Instituto Cardiovascular Buenos Aires Icda). Australia: C. Aroney (Holy Spirit Northside Hospital), G. Bellamy (John Hunter Hospital), D. Bhullar (Sir Charles Gairdner Hospital), N. Cox (Footscray Hospital), S. Duffy (Alfred Hospital), D. Bhullar (Sir Charles Gairdner Hospital), N. Cox (Footscray Hospital), S. Duffy (Alfred Hospital), D. Muller (St Vincent's Hospital), C. Mussap (Liverpool Hospital), A. Sinhal (Flinders Medical Centre), W. Van Gaal (The Northern Hospital), D. Walters (Prince Charles Hospital), M. Worthley (Royal Adelaide Hospital), Belgium: E. Benit (Jessa Ziekenhuis–Campus Virge Jesse), S. Haine (Universitet Ziekenhuis Antwerpen), J. Jalmad (Centre Hospitalier Universitaire de Charleroi–Hopital Civil Marie Curie), D. Schoors (Universitet Ziekenhuis Brussel), B. Scott (Ziekenhuis Network Antwerpen Middelheim), M. Volix (Ziekenhuis Oost-Limburg Campus Sint-Jan). Brazil: P. Caramori (Hospital Sao Lucas da Pontifícia Universidade Catolica do Rio Grande do Sul), J. Costa Junior (Instituto Dante Pazzanese de Cardiologia), P. Lemos Neto (Instituto do Coracao do Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo), V. Lima (Impressando da Santa Casa de Misericordia of Porto Alegre), A. Schaan de Quadros (Instituto de Cardiologia do Rio Grande do Sul), Conodic. L. Bilodeau (McGill University Health Centre Royal Victoria Hospital), C. Constance (Hospital Maisonneuve Rosemont), A. Dell Siega (Victoria Heart Institute Foundation), M. Dorsch (Royal Alexandra Hospital), J. Ducas (St Boniface Hospital), V. Dzavik (Toronto General Hospital), P. Garg (London Health Sciences Centre, University Hospital), M. Kutyk (St Michaels Hospital), T. McPherson (Health Sciences Centre, Montana) (Centre integre de sante et des services sociaux de Laval, Hôpital Cite de la Sante), J. Rodes-Cabau (Institut Universitaire de Cardiologie et de pneumologie de Quebec), E. Schampaert (Hopital du Sacre Coeur de Montreal), F. Speer (Foothills Medical Centre University of Calgary), R. Teskey (Saint John Regional Hospital), L. Title (Queen Elizabeth II Health Sciences Center), R. Welsh (University of Alberta Hospital). Chile: C. Pincetti Jofre (Centro de Investigacion Clinica del Sur), Czech Republic: Z. Cofoul (Krajsa nemocnice Treni), (Fakultni nemocnice Brno), T. Kovarkin (Vseobecná fakultní nemocnice v Praze), J. Vojacek (Fakultni nemocnice Hradec Králové). Denmark: H. Kjærulf Jensen (Aarhus Universitetet Hospital), France: D. Angouiant (Centre Hospitalier Regionale Universitaire de Tours–Hopital Trousseau), J. Bonnet (Centre Hospitalier Universitaire de Marseille–Hopital de la Timone), P. Coste (Centre Hospitalier Universitaire de Bordeaux, Hopital Haut-Leveque), A. Lafont (Hopital Euvropéen Georges Pompidou), F. Schiele (Centre Hospitalier Regional Universitaire de Besancon, Hopital Jean Minjouz), E. Teiger (Hopital Henri Mondor), Germany: D. Endemann (Universitatsklinikum Regensburg), T. Rassaf (Universitatsklinikum Essen), S. Reith (Universitatsklinikum Aachen), J. Währle (Universitatsklinikum Ulm). Greece: N. Kalkas (General Hospital of Attika KAT), G. Kochiadakis (Ziekenhuisnetwork Antwerpen Vavouranakis (General Hospital of Athens Ipokrateio). Hungary: I. Edes (Debrencen Egyetem Klinikai Korzet), I. Horvath (Pecsi Tudomanyegyetem Klinikai Korzet), R. Kiss (Margarvs Hercules Egyszegy), B. Merkely (Semmelweis Egyetem), B. Nagybacsi (Cardiocenter Korzet orvostudomanti). I. Ungi (Szeged) (Tudomanyegyetem, Altalans Orvostudomanty kar). A. Zsidos (Betegapal romlal Rend–Budai Irgalmamensd Korzet). Ireland: I. Gudmundsdottir (Landspitalit National University Hospital). Ireland: B. MacNeill (Galway University Hospital), R. Murphy (St James Hospital), J. O’Brien (Mater Misericordiae). Japan: M. Kikuta (Kanazawa University Hospital), M. Kuroda (Osaka University Hospital). Korea: J. Kim (Hanyang University Hospital), M. Park (Seoul National University Bundang Hospital), K. Min (Seoul National University Boramae Medical Center), G. M. Park (Chung Among Medical University). Lativa: L. Padilla (Hospital Sao Lucas da Pontifícia Universidade de Sao Paulo). Lithuania: S. Talmu (Krajska Klinikos Streika). Malaysia: A. Bin Ruhani (Hospital Tengku Ampuan Afzan), H. Gan (Glengees Medical Centre), Mexico: A. Alcocer Gamba (Instituto de Investigaciones Queretaro), M. de los Rios Ibarra (Centro para el Desarrollo de la Medicina y de Asistencia Medica Especializada SC). Netherlands: A. Gosseling (Isala Kliniken), A. Heestermans (Noordwest Ziekenhuisgroep), J. Herman (Onze Lieve Vrouwe Gasthuis), J. Ielov (Katharina Ziekenhuis), A. Oude Ophuis (Carusius-Wilhelmina Ziekenhuis), R. Roesink (St Adriaan Ziekenhuis, locatie Nieuwegein), P. Smits (Maasticht Ziekenhuis), A. Van Boven (Medisch Centrum Leeuwarden), N. Van Royen (Vrije Universiteit Medisch Centrum), M. Voskuil (Universitair Medisch Centrum Utrecht), M. Winkens (Elsbieren-Tweesteden Ziekenhuis), Norway: L. Gullestad (Oslo University Hospitals). Philippines: A. Ferrerillo (Philippine Heart Center). Poland: R. Dudek (Szpital Uniwersytecki w Krakowie), A. Lubinsky (SPZOZ Uniwersytecki Szpital Kliniczny im. Nowotomejski Medyczny w Lodz–Centralny Szpital Wete), J. Podolec (Krakowski Szpital Specjalistyczny im. Jana Pawla II), J. Prokopczuk (Polsko-Amerykanskie Kliniki Serca), Russia: S. Abogov (FSBI Russian scientific center of surgery na academic B V Petrovskyi), O. Barbarash (FSBI Heart and Vessels Diseases complex problems Scientific Research Institution), M. Bubnova (FSBI State Scientific Research Center for Preventive Medicine of MoH of RF), M. Ezhov (FSBI Russian Cardiology Research and Production Complex), A. Kamminy (FSBI Russian Cardiology Research and Production Complex). Singapore: A. Wong (National Heart Centre Singapore). South Africa: I. Ebrahim (Unitas Hospital), F. Hellig (Sunninghill Hospital), A. Horak (Vincent Pallotti Hospital), E. Klap (Professional Surfers), J. Saiman (Kilis River Hospital), South Korea: Y. S. Cho (Seoul National University Bundang Hospital), W. Kim (Yung Hee University Hospital), S. H. Kim (Seoul Metropolitan Government Seoul National University Boramae Medical Center), G. M. Park (Chung Among Medical University). South Korea: L. Bilodeau (McGill University Health Centre). Spain: A. Cequier (Fundacion Ciutat Sanitaria i de Bellvitge), J. Hernandez Garcia (Hospital Clinico Universitario Virgen de la Victoria), R. Moreno Gomez (Hospital Clinico Universitario LA Paz), J. Otaegi Irureta (Hospital Universitari Vall d’Hebron), J. Rondan Murillo (Hospital de Cabueñes), M. Roffi (Hospital Clinico Universitario de Santander), J. Zamorano Gomez (Hospital Universitario Ramon y Cajal). Sweden: F. Böhm (Karolinska University Hospital), M. Götberg (Skånes Universitetssjukhus), J. Odestedt (Sahlgrenska University Hospital), K. Wachtell (Universitetssjukhuset Örebro). United Kingdom: A. Zaman (Freeman Hospital), United States: A. DiGiolamio (University of Florida and Shands Hospital), C. Bhagwat (Cardiovascular Research of Northwet Indiana LLC), E. Bridakis (Dallas Veterans Affairs Medical Center), M. Budoff (Harbor University of California Medical Center), M. Burke (Abbott Northwestern Hospital Minneapolis Heart Institute), P. Cambier (Morton Plant Meadow Health Care), L. Cannon (Cardiac and Vascular Research Center of Northern Michigan), R. Chilton (Audie L. Murphy Memorial Veteran Affairs Hospital), R. Christofferson (North Ohio Heart), A. Chu (Amarillo Heart Clinical Research Institute Inc.), R. Dave (University of California at Los Angeles), V. DeGeare (Norton Cardiovascular Associates), B. Duffy (Aultman Cardiology Clinical Trials), B. Ennis (TCA Research), B. Erickson (Saint Joseph's Hospital Health System), L. Everett (Covenant Medical Center, Michigan Cardiovascular Institute), M. Fikry (University at St Thomas Health Science Center at Saint Anthony Medical Arts Research Clinic), W. Felten (MidMichigan Medical Center Midland), I. Gilchrist (Penn State Milton South Hershey Medical Center), R. Gudipati (Michigan Cardiovascular Institute), T. Haldis (Sanford Heart Center), W. Herzog (Johns Hopkins University), S. Karas (Health First Inc), S. Kassas (Covenant Medical Center, Michigan Cardiovascular Institute), M. Koren (Jacksonville Center for Clinical Research), G. Kumukian (Suburban Hospital), B. Rusnick (Cardiovascular Associates Research LLC), D. Lee (Bay Regional Medical Center), J. Maddux (International Heart Institute of Montana), E. Mahmud (University of California at Los Angeles).
Research Original Investigation

Evoculobam and Coronary Disease Progression in Statin-Treated Patients

San Diego, H. Malave (Saint Joseph's Hospital of Atlanta), A. R. Masud (Buffalo Heart Group), J. McCay (Doyestown Hospital), D. Meneses (University of Michigan Health System), S. Mikesel (Saint Luke's Hospital Association of Duluth WhiteSide Institute), M. Miller (Novant Health Heart and Vascular Institute), J. Morrow (CB Flock Research Corporation), E. O. Leary (The University of Nebraska Medical Center), D. Palmer (Wichita Falls Heart Clinic), E. Panetta (HealthEast Medical Research Institute), P. Patel (University of California at Irvine Medical Center), W. Penny (Veterans Affairs San Diego Healthcare System), M. Rothenberg (Atlantic Clinical Research Collaborative), A. Seto (Long Beach Veterans Affairs Medical Center), M. Sheikh (University of Toledo), M. Sheth (Parkway Cardiology Associates), G. Soliman (Heart Center Research LLC), D. Spriggs (Clearwater Cardiovascular Consultants), J. Strain (The Valley Hospital), R. Waksman (MedStar Washington Hospital Center), R. Weibel (University of Missouri Health System), K. Ziada (University of Kentucky Gill Heart Institute).

Additional Contributions: Craig Balog, BS (CSResearch), provided statistical support; Kelly Hanlon, MBA (Amgen Global Study Lead GLAGOV/Clinical Operations, Study Management & Operations), provided study supervision and administrative support of the trial; and Kelly Kevin, BSC, and Tim Palmer (Amgen Global Statistical Programming) provided statistical support. These individuals are paid employees of CSResearch (Balog) and Amgen (Hanlon, Kevin, Palmer).

REFERENCES


