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Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

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IMPORTANCE Coronary plaques that are prone to rupture and cause adverse cardiac events are characterized by large plaque burden, large lipid content, and thin fibrous caps. Statins can halt the progression of coronary atherosclerosis; however, the effect of the proprotein convertase subtilisin kexin type 9 inhibitor alirocumab added to statin therapy on plaque burden and composition remains largely unknown.

OBJECTIVE To determine the effects of alirocumab on coronary atherosclerosis using serial multimodality intracoronary imaging in patients with acute myocardial infarction.

DESIGN, SETTING, AND PARTICIPANTS The PACMAN-AMI double-blind, placebo-controlled, randomized clinical trial (enrollment: May 9, 2017, through October 7, 2020; final follow-up: October 13, 2021) enrolled 300 patients undergoing percutaneous coronary intervention for acute myocardial infarction at 9 academic European hospitals.

INTERVENTIONS Patients were randomized to receive biweekly subcutaneous alirocumab (150 mg; n = 148) or placebo (n = 152), initiated less than 24 hours after urgent percutaneous coronary intervention of the culprit lesion, for 52 weeks in addition to high-intensity statin therapy (rosuvastatin, 20 mg).

MAIN OUTCOMES AND MEASURES Intravascular ultrasonography (IVUS), near-infrared spectroscopy, and optical coherence tomography were serially performed in the 2 non–infarct-related coronary arteries at baseline and after 52 weeks. The primary efficacy end point was the change in IVUS-derived percent atheroma volume from baseline to week 52. Two powered secondary end points were changes in near-infrared spectroscopy–derived maximum lipid core burden index within 4 mm (higher values indicating greater lipid content) and optical coherence tomography–derived minimal fibrous cap thickness (smaller values indicating thin-capped, vulnerable plaques) from baseline to week 52.

RESULTS Among 300 randomized patients (mean [SD] age, 58.5 [9.7] years; 56 [18.7%] women; mean [SD] low-density lipoprotein cholesterol level, 152.4 [33.8] mg/dL), 265 (88.3%) underwent serial IVUS imaging in 537 arteries. At 52 weeks, mean change in percent atheroma volume was −2.13% with alirocumab vs −0.92% with placebo (difference, −1.21% [95% CI, −1.78% to −0.65%], $P < .001$). Mean change in maximum lipid core burden index within 4 mm was −79.42 with alirocumab vs −37.60 with placebo (difference, −41.24 [95% CI, −70.71 to −11.77]; $P = .006$). Mean change in minimal fibrous cap thickness was 62.67 µm with alirocumab vs 33.19 µm with placebo (difference, 29.65 µm [95% CI, 11.75-47.55]; $P = .001$). Adverse events occurred in 70.7% of patients treated with alirocumab vs 72.8% of patients receiving placebo.

CONCLUSIONS AND RELEVANCE Among patients with acute myocardial infarction, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non–infarct-related arteries after 52 weeks. Further research is needed to understand whether alirocumab improves clinical outcomes in this population.

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Visual Abstract

Supplemental content

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Group Information: The PACMAN-AMI collaborators are listed in Supplement 5.

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Statins have been shown to reduce cardiovascular adverse events in patients with atherosclerotic disease.[1] In patients receiving statins with elevated low-density lipoprotein cholesterol (LDL-C) levels, the addition of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors resulted in profound reductions in LDL-C levels and an incremental reduction of ischemic cardiovascular events.[2,3]

The composition of atherosclerotic plaques largely affects their likelihood to progress or trigger acute coronary events.[4] Intracoronary imaging modalities can evaluate coronary plaque morphology and composition in vivo.[5] In accordance with histological evidence,[6] large atheroma burden assessed via intravascular ultrasonography (IVUS),[7] large lipid burden assessed via near-infrared spectroscopy (NIRS),[8] and presence of thin fibrous caps assessed via optical coherence tomography (OCT)[9] have been associated with a higher risk of subsequent cardiovascular adverse events. Intensive statin therapy has been shown to halt the progression of coronary atheroma burden[10,11] and might favorably affect plaque composition by reducing plaque lipid content and increasing the thickness of the fibrous cap.[12] Currently, there is limited evidence concerning the effect of PCSK9 inhibition on coronary plaque burden, composition, and phenotype. The risk of recurrent atherothrombotic events is particularly high in patients with acute myocardial infarction (AMI),[13] who derived early clinical benefit from intensive statin therapy.[14] Favorable effects of intensive lipid-modifying therapies on coronary atherosclerosis would be of particular relevance for patients with AMI, because the heightened risk of recurrent events is largely attributable to frequent coexistence of multiple nonobstructive lesions with high-risk characteristics[7] in the non-infarct-related arteries (non-IRAs) of these patients.

The PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) randomized trial[15] sought to determine the effect of early administration of the PCSK9 inhibitor alirocumab on coronary atherosclerosis, assessed by serial, 2-vessel, multimodality intracoronary imaging (IVUS, NIRS, and OCT) of the non-IRAs in patients presenting with AMI.

Key Points

Question Among patients with acute myocardial infarction, does the addition of the proprotein convertase subtilisin kexin type 9 inhibitor alirocumab to high-intensity statin therapy affect coronary atherosclerosis in non–infarct-related arteries?

Findings In this randomized clinical trial that included 300 patients, subcutaneous biweekly injection of alirocumab, compared with placebo, added to high-intensity statin therapy resulted in significantly greater reduction in the mean change in percent atheroma volume in non–infarct-related arteries after 52 weeks (−2.13% vs −0.92%).

Meaning Among patients with acute myocardial infarction, the addition of alirocumab, compared with placebo, to high-intensity statin therapy resulted in greater coronary plaque regression in non–infarct-related arteries after 52 weeks.

Methods

Study Design and Patient Population

This trial was an investigator-initiated, multicenter, randomized, double-blind clinical trial conducted at 9 centers in 4 European countries (Switzerland, Austria, Denmark, and the Netherlands). All patients provided written informed consent, and the study was approved by the ethical committee at each site. The study protocol and statistical analysis plan are available in Supplements 1, 2, and 3, and the study design has been previously described.[15]

Patients 18 years or older who underwent urgent percutaneous coronary intervention (PCI) of the culprit lesion for treatment of ST-elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) were eligible for inclusion if they were considered suitable for intracoronary imaging, with angiographic evidence of coronary atherosclerosis but without significant obstructive disease (diameter stenosis >20% and <50% by visual estimate) in the proximal part of 2 non-IRAs. LDL-C levels, measured prior to PCI using a validated point-of-care assay, were required to be at least 125 mg/dL if patients had not been receiving a stable statin dose for at least 4 weeks or at least 70 mg/dL if patients had been receiving a stable statin dose for at least 4 weeks. Patients were excluded if they had left main or 3-vessel coronary artery disease (CAD), history of coronary artery bypass surgery, severe kidney dysfunction, liver disease, or known statin intolerance (eTable 1 in Supplement 4).

Randomization and Interventions

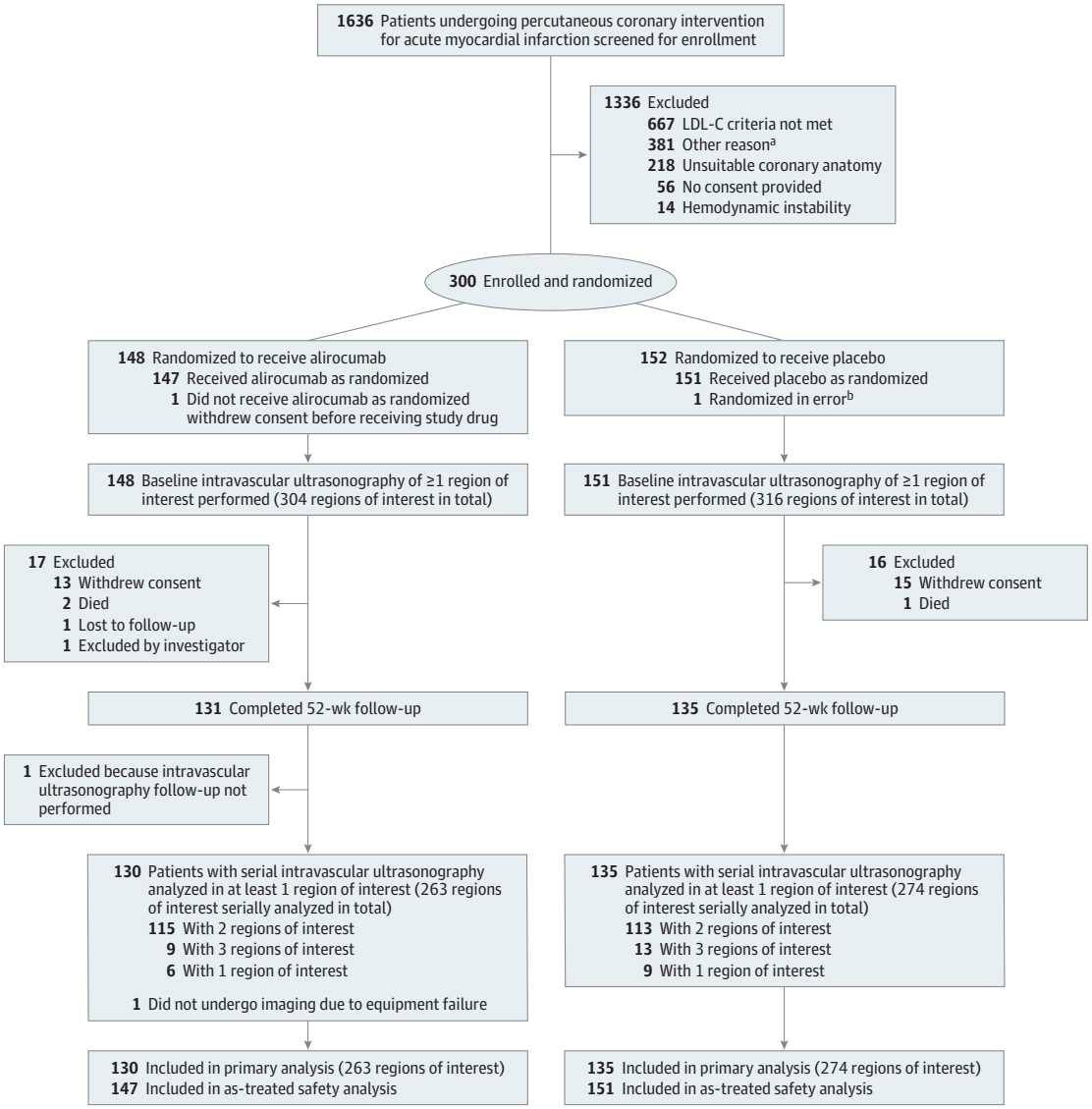
After PCI of the culprit lesion in the IRA, eligible patients underwent intracoronary imaging of the 2 non-IRAs and, if successful, they were randomly allocated in a 1:1 fashion to receive either 150-mg alirocumab or placebo, administered biweekly via subcutaneous injection for 52 weeks. Web-based randomization was performed using randomly varying block sizes of 2, 4, or 6 patients, stratified by study site, use of stable (≥4 weeks) statin treatment at presentation, and type of AMI (STEMI vs NSTEMI). The first dose of the study drug was administered within 24 hours after PCI, without dose adjustment during the study period. Patients in both treatment groups received 20 mg of rosuvastatin daily, without change in type or dose of statin during the course of the study (protocol-mandated statin treatment). During the treatment period, patients underwent clinical (on-site) visits at weeks 2, 4, 24, and 52; phone visits at weeks 8, 12, 36, and 48; and repeat intracoronary imaging at week 52.

Cardiovascular adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment. Statistical analyses were independently performed at CTU Bern, Bern, Switzerland.

Acquisition and Analysis of Intracoronary Imaging

Intracoronary imaging with the combined NIRS-IVUS catheter and OCT were performed in at least 2 proximal non-IRAs

Figure 1. Flow of Patients in the PACMAN-AMI Randomized Clinical Trial



LDL-C indicates low-density lipoprotein cholesterol.

[a] Specific reasons for other exclusions were not documented at the site of evaluation. See eTable 1 in Supplement 4 for additional inclusion and exclusion criteria.

[b] Excluded by investigator and did not receive study drug.

at baseline. At week 52, patients underwent a second intracoronary imaging in the identical localization of the same arteries, using identical catheter types. The methods of image acquisition and analysis were previously described.[15] Images of all modalities were analyzed at independent core laboratories (IVUS and NIRS: Cardialysis, Rotterdam, The Netherlands; OCT: Bern University Hospital, Bern, Switzerland) by experienced analysts unaware of treatment allocation and temporal sequence (baseline or follow-up imaging).

For IVUS, lumen and external elastic membrane were analyzed every 1 mm in matched regions of interest (ROI). The arterial lumen and external elastic membrane borders were segmented from digitized IVUS images. For NIRS, identical ROI as those used for IVUS analyses were analyzed and the 4-mm segment with maximum lipid core burden index was identified within the ROI. OCT recordings were analyzed every 0.4 mm within the matched ROI.[15] Fibrous cap thickness (FCT) was measured in the presence of any frames with OCT-fibroatheroma at both time points using a validated, semiquantitative method.[16]

Biochemical Assessment

Blood samples were obtained prior to PCI, at week 4, and week 52. Blood samples were immediately processed and stored at −80 °C locally and subsequently transferred to a central biobank. All central biochemical analyses were conducted by the Department of Clinical Chemistry, University of Zurich, Switzerland.

Table 1. Baseline Characteristics of Patients in a Study of Alirocumab vs Placebo Added to High-Intensity Statin on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction

Characteristics[a]	No. (%)	
	Alirocumab (n = 148)	Placebo (n = 152)[d]
Demographic characteristics		
Age, mean (SD), y	58.4 (10.0)	58.6 (9.4)
Women	24 (16.2)	32 (21.1)
Men	124 (83.8)	119 (78.3)
BMI, mean (SD)	27.3 (4.1)	28.2 (4.5)
Medical history[b]		
Current smoking	77 (52.0)	65 (42.8)
Arterial hypertension	60 (40.5)	70 (46.1)
Diabetes	12 (8.1)	19 (12.5)
Insulin-dependent diabetes	4 (2.7)	4 (2.6)
Previous myocardial infarction	2 (1.4)	5 (3.3)
Previous PCI	2 (1.4)	5 (3.3)
Peripheral arterial disease	2 (1.4)	4 (2.6)
Family history of CAD	44 (29.7)	54 (35.5)
Statin use	17 (11.5)	20 (13.2)
High-intensity statin[c]	11 (7.4)	9 (5.9)
Ezetimibe use	0	1 (0.7)
Other cardiac medications		
ARB	20 (13.5)	21 (13.8)
Antiplatelet therapy	14 (9.5)	17 (11.2)
β-Blocker	12 (8.1)	17 (11.2)
ACE inhibitor	12 (8.1)	12 (7.9)
Type of acute myocardial infarction		
NSTEMI	70 (47.3)	72 (47.4)
STEMI	78 (52.7)	80 (52.6)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

[a] Age and body mass index were normally distributed.

[b] Determined through medical record review.

[c] Atorvastatin ≥40 mg or rosuvastatin ≥20 mg.

[d] In the placebo group, due to exclusion immediately following randomization, 1 patient had missing values in all variables except "Age" and "Type of acute myocardial infarction." One additional value was missing for BMI in the placebo group.

Outcomes

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

$$PAV = [\Sigma(EEM_{CSA} - Lumen_{CSA})/\Sigma EEM_{CSA}] \times 100$$

where EEM_{CSA} is the cross-sectional external elastic membrane area and $Lumen_{CSA}$ is the luminal cross-sectional area.

Normalized total atheroma volume was the secondary IVUS efficacy measure. The main NIRS efficacy parameter was maximum lipid core burden index within 4 mm; an additional secondary measure was total LCBI within the entire imaged ROI. The main OCT efficacy measure was minimal FCT. Other OCT measures were mean FCT and mean angular extension of macrophages (details provided in Supplement 1). Larger maximum lipid core burden index within 4-mm values (indicating greater plaque lipid content) and smaller minimal FCT values (indicating plaques with thinner fibrous caps) are recognized features of high-risk atherosclerotic plaques associated with a greater risk of causing adverse cardiac events.[4,6,8,9]

The primary outcome was change in PAV via IVUS from baseline to week 52. Two powered secondary end points were change in maximum lipid core burden index within 4 mm via NIRS and change in minimal FCT via OCT from baseline to week 52. Other secondary end points were change in normalized total atheroma volume via IVUS, change in total LCBI via NIRS, and changes in mean FCT and in mean angular extension of macrophages via OCT (Supplement 1).[15] Secondary non-imaging-related end points included the incidence of adjudicated events (all-cause mortality, cardiac death, myocardial infarction, ischemia-driven coronary revascularization, and stroke or transient ischemic attack) and adverse events and changes in biomarkers (total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides, lipoprotein(a), apolipoprotein A and apolipoprotein B1, and high-sensitivity C-reactive protein). Prespecified secondary end points not reported in this article are listed in eTable 2 in Supplement 4. A post hoc exploratory outcome was the percentage of patients per treatment group with regression (ie, any reduction) of PAV from baseline to week 52.

Sample Size Calculation

In the initial protocol, a sample size of 220 patients was powered to detect a between-group difference of 1.3% in change in PAV. Per the protocol, the power analysis was revised after the publication of the GLAGOV trial.[17] The revised sample size calculation assumed a between-group difference of 1.0% in change in PAV (based on the PAV regression in previous IVUS trials of high-intensity statins[10,11,17]), an SD of 3.4%, an intraclass correlation coefficient of 0.435, and 2 vessels imaged per patient. Anticipating a 10% dropout rate, 294 patients would provide 80% power at a 2-sided α of .05. This sample size provided 95% power to detect a difference in the change in maximum lipid core burden index within 4 mm of 193.3[12] and 85% power to detect a difference in the change in minimal FCT of 19.8 μm between groups[18] (powered secondary end points). More details are provided in Supplement 4.

Statistical Analysis

For the primary end point, powered secondary end points, and other secondary imaging end points, the statistical comparisons between groups were performed using mixed-effect models by fitting the interaction between group (alirocumab or placebo) and time point (baseline or follow-up) as fixed effects and patient identity as the random effect. These models account for repeated measures for a given vessel (baseline and follow-up) and for the multiple vessels imaged per patient. For biomarker secondary end points, statistical comparisons between groups were performed using mixed-effect repeated models at the patient level. The difference between treatments is reported as the marginal difference (with 95% CIs) computed from the mixed-effect models. The primary analysis was performed on the full analysis set, which included all patients with available serial IVUS data. Patients were analyzed

Table 2. Absolute Change in Biochemical Measures From Baseline to 52 Weeks in the As-Treated Groups[a]

Measurement[b]	Baseline, mean (SD)		Week 52, mean (SD)		Change from baseline to week 52, (95% CI)			
	Alirocumab (n = 126)[c]	Placebo (n = 132)[d]	Alirocumab (n = 126)[c]	Placebo (n = 132)[d]	Alirocumab (n = 126)[c]	Placebo (n = 132)[d]	Difference in change (95% CI)	*P* value[e]
Cholesterol, mg/dL								
Total	206.8 (34.6)	203.9 (35.2)	84.3 (27.6)	139.2 (33.4)	−122.5 (−128.8 to −116.3)	−64.8 (−71.5 to −58.0)	−57.8 (−66.9 to −48.6)	<.001
LDL-C	154.8 (30.9)	150.9 (36.3)	23.6 (23.8)	74.4 (30.5)	−131.2 (−137.0 to −125.4)	−76.5 (−83.2 to −69.8)	−54.7 (−63.5 to −45.9)	<.001
HDL-C	41.3 (10.2)	41.3 (10.1)	48.3 (11.2)	45.0 (11.6)	7.0 (5.8 to 8.2)	3.7 (2.5 to 5.0)	3.3 (1.5 to 5.0)	<.001
Non-HDL-C	165.7 (34.5)	162.9 (35.3)	36.1 (27.3)	94.4 (32.2)	−129.7 (−136.0 to −123.3)	−68.5 (−75.0 to −61.9)	−61.2 (−70.2 to −52.1)	<.001
Triglycerides, mg/dL[f]	107.4 (63.9)	111.0 (84.3)	94.2 (47.0)	126.0 (77.9)	−13.2 (−23.8 to −2.6)	15.0 (3.9 to 26.1)	−24.4 (−36.5 to −12.4)	<.001
Lipoprotein(a), mg/dL[f]	30.9 (42.7)	34.5 (39.6)	28.4 (41.6)	42.9 (49.4)	−2.5 (−4.5 to −0.6)	8.3 (5.8 to 10.9)	−4.9 (−6.4 to −3.4)	<.001
Apolipoprotein AI, mg/dL	113.6 (19.6)	114.3 (18.2)	132.0 (20.1)	126.1 (21.1)	18.4 (15.9 to 20.9)	11.8 (9.1 to 14.5)	6.6 (2.9 to 10.2)	<.001
Apolipoprotein B, mg/dL	115.4 (21.9)	113.6 (23.1)	32.3 (18.6)	72.6 (20.7)	−83.1 (−87.1 to −79.1)	−41.0 (−45.2 to −36.8)	−42.1 (−47.9 to −36.4)	<.001
High-sensitivity CRP, mg/L[f]	6.4 (13.3)	5.7 (10.9)	1.9 (2.8)	2.4 (4.9)	−4.5 (−6.8 to −2.2)	−3.3 (−5.3 to −1.2)	−0.4 (−1.2 to 0.4)	.34

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert total cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert high-sensitivity CRP values to nmol/L, multiply by 9.524.

[a] Analyses were performed on the full analysis set (265 patients), but 7 patients were excluded due to missing serial biomarker data (258 patients included in the biomarker analyses). Difference in change between groups are marginal differences (95% CI) computed from mixed-effect models.

[b] Reference value for total cholesterol is <193 mg/dL; LDL-C, <116 mg/dL; HDL-C, >39 mg/dL; non–HDL-C, <151 mg/dL; triglycerides, <77 mg/dL; lipoprotein(a), <30 mg/dL; apolipoprotein AI, >125 mg/dL; apolipoprotein B, <100 mg/dL; high-sensitivity CRP, <1.0 mg/L.

[c] Four patients in the alirocumab group with missing data were excluded from the analysis.

[d] Three patients in the placebo group with missing data were excluded from the analysis.

[e] *P* value for between-group comparison.

[f] End point was log-transformed to achieve normality of the model residuals (values shown are on the original [ie, not log-transformed] scale).

according to their randomization group. Patients with missing data were excluded from the primary analysis. The stratification variables used in the stratified randomization were not included in the model for the primary analysis; stratification variables were included in a post hoc sensitivity analysis, with type of myocardial infarction (STEMI vs NSTEMI) and use of stable (≥4 weeks) statin treatment at presentation (yes vs no) fitted as fixed effects and site identity as a random intercept. Analyses for the secondary end points were performed in the full analysis set excluding patients with missing serial data for the considered end point (imaging or biomarker). For binary outcomes, treatment groups were compared using logistic regression. Analyses of adverse events included patients who received at least 1 administration of the study drug. Adverse events were summarized per treatment group by keeping only the first event of each type per patient.

Statistical tests were 2-sided and the significance level was set at .05. For the primary and powered secondary outcomes, a gatekeeping procedure was applied, whereby the primary end point was first tested at an α level = .05. If the *P* value was ≥.05, *P* values for the powered secondary end points were not interpreted; if the *P* value was <.05, the significance level was equally split between the 2 powered secondary end points using Bonferroni correction (ie, significance level set to .025). Because of the potential for type I error due to multiple comparisons, findings for analyses of the other secondary end points should be interpreted as exploratory. Statistical analyses were performed using Stata, version 17 (StataCorp LLC), and R software, version 3.6.2 (R Core Team).

Results

Patient Characteristics

From May 9, 2017, through October 7, 2020, a total of 300 patients (52.7% presenting with STEMI and 47.3% with NSTEMI) were randomized to receive treatment with alirocumab (n = 148) or placebo (n = 152) (**Figure 1**; eFigures 1 and 2 in Supplement 4). Clinical characteristics of patients are summarized in **Table 1**. A total of 298 patients (99.3%) received at least 1 study drug administration. At the time of randomization, 37 patients (12.3%) were receiving any statin therapy. A total of 283 patients (94.3%) were receiving 20-mg rosuvastatin at hospital discharge and 241 patients (90.6%) were receiving 20-mg rosuvastatin at 52 weeks (eTables 3 and 4 in Supplement 4). At baseline, a mean of 2.1 arteries per patient were imaged; 265 patients (88.3%) had evaluable serial IVUS data in 537 arteries. Baseline characteristics of patients who underwent serial IVUS imaging and those who did not are shown in eTable 5 in Supplement 4.

Biochemical Analyses

Table 2 summarizes laboratory measurements for patients who underwent serial IVUS imaging. At baseline, the mean (SD) LDL-C level was 152.8 (33.8) mg/dL (n = 258). At week 52, the mean (SD) LDL-C level was 74.4 (30.5) mg/dL in the placebo group (n = 132) and 23.6 (23.8) mg/dL in the alirocumab group (n = 126) (*P* < .001), representing a 76.5 (95% CI, −83.2 to −69.8) mg/dL decrease in the placebo group and a 131.2

Table 3. Primary and Secondary Imaging Outcomes Assessed by Intravascular Ultrasonography, Near-Infrared Spectroscopy, and Optical Coherence Tomography[a]

Outcome	Baseline, mean (SD)		Week 52, mean (SD)		Change from baseline to week 52, mean (95% CI)		Difference in change (95% CI)	*P* value[b]
	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab	Placebo		
Primary								
No. of vessels imaged with intravascular ultrasonography (No. of patients)	263 (130)	274 (135)	263 (130)	274 (135)				
Percent atheroma volume, %	40.91 (8.61)	43.01 (9.84)	38.78 (8.20)	42.09 (9.94)	−2.13 (−2.53 to −1.73)	−0.92 (−1.28 to −0.56)	−1.21 (−1.78 to −0.65)	<.001
Secondary								
Normalized total atheroma volume, mm^3[c]	261.37 (121.42)	250.41 (112.69)	235.25 (107.89)	235.44 (107.72)	−26.12 (−30.07 to −22.17)	−14.97 (−18.14 to −11.80)	−11.55 (−17.44 to −5.66)	<.001
Patients with percent atheroma volume regression, No. (%)[d]			110 (84.6)	89 (65.9)			18.7% (7.8 to 29.6); odds ratio, 2.8 (95% CI, 1.6 to 5.2)	
No. of vessels imaged with near-infrared spectroscopy (No. of patients)	252 (129)	260 (134)	252 (129)	260 (134)				
Maximum lipid core burden index at 4 mm[e]	260.60 (184.49)	276.23 (195.65)	181.17 (171.93)	238.63 (194.51)	−79.42 (−100.39 to −58.46)	−37.60 (−57.40 to −17.80)	−41.24 (−70.71 to −11.77)	.006
Total lipid core burden index	73.16 (76.39)	82.11 (84.19)	43.86 (57.03)	69.73 (82.35)	−29.30 (−37.52 to −21.08)	−12.38 (−20.66 to −4.10)	−17.29 (−28.98 to −5.60)	.004
No. of vessels imaged with optical coherence tomography (No. of patients)	245 (122)	270 (133)	245 (122)	270 (133)				
Minimal fibrous cap thickness, μm[e]	106.97 (70.19) [173 vessels (105 patients)][f]	110.53 (84.98) [197 vessels (116 patients)][f]	169.64 (97.78) [173 vessels (105 patients)][f]	143.72 (84.03) [197 vessels (116 patients)][f]	62.67 (48.84 to 76.50)	33.19 (22.22 to 44.16)	29.65 (11.75 to 47.55)	.001
Mean fibrous cap thickness, μm	328.74 (97.25) [173 vessels (105 patients)][f]	328.91 (112.58) [197 vessels (116 patients)][f]	419.69 (108.79) [173 vessels (105 patients)][f]	391.27 (100.29) [197 vessels (116 patients)][f]	90.95 (72.96 to 108.94) [173 vessels (105 patients)]	62.36 (46.23 to 78.50) [197 vessels (116 patients)]	28.22 (3.21 to 53.23)	.03
Mean angular extension of macrophages, °	58.54 (20.81) [232 vessels (121 patients)][g]	57.57 (22.51) [251 vessels (131 patients)][g]	32.57 (21.01) [232 vessels (121 patients)][g]	41.62 (22.25) [251 vessels (131 patients)][g]	−25.98 (−29.35 to −22.61) [232 vessels (121 patients)]	−15.95 (−19.02 to −12.87) [251 vessels (131 patients)]	−10.08 (−14.72 to −5.43)	<.001

[a] Analyses were conducted on vessel-level values at 2 time points (baseline and week 52) using repeated-measures mixed-effect models accounting for the multiple vessels per patient. For continuous variables, values are vessel-level mean (SD), or vessel-level mean change (95% CI). Difference in change are marginal differences computed from mixed-effect models. For the categorical variable "Patients with PAV regression," values are count (%) and the corresponding odds ratio with associated 95% CIs.

[b] *P* value for between-group comparison.

[c] Normalized total atheroma volume was calculated as mean atheroma area multiplied by the median length of the regions of interest.

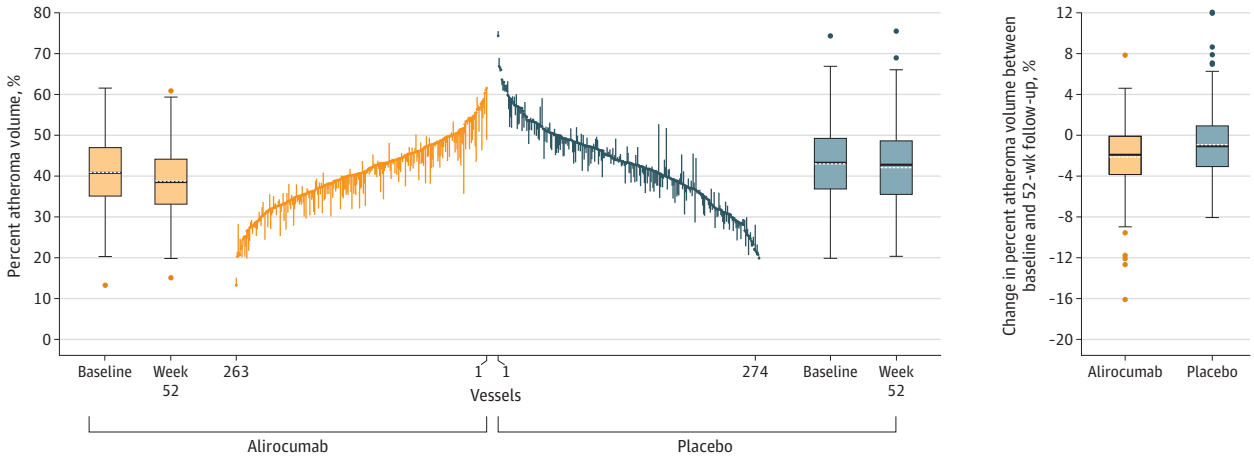
[d] Patients with PAV regression are those with negative change in PAV from baseline averaged across vessels.

[e] Powered secondary end point.

[f] No. of imaged vessels (No. of patients) with fibroatheromas.

[g] No. of imaged vessels (No. of patients) with macrophages.

Figure 2. Changes in Percent Atheroma Volume via Intravascular Ultrasonography in Patients Treated With Alirocumab vs Placebo Added to High-Intensity Statin Therapy



The parallel line plot contains 1 vertical line for each imaged vessel, which extends from the baseline value to the value at 52 weeks. Descending lines indicate a reduction (ie, regression) in percent atheroma volume over time, whereas ascending lines indicate an increase (ie, progression) in percent atheroma volume. Baseline values are placed in ascending order for the alirocumab group and descending order for the placebo group. The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line indicating the median and the dashed white line indicating the mean. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 IQRs from the first and third quartiles. Dots indicate more extreme values.

(95% CI, −137.0 to −125.4) mg/dL decrease in the alirocumab group from baseline (between-group difference, −54.7 mg/dL [95% CI, −63.5 to −45.9]; $P < .001$) (eFigure 3 in Supplement 4). Patients receiving alirocumab demonstrated significantly greater reductions in triglycerides, lipoprotein(a), and apolipoprotein B, without statistically significant difference in high-sensitivity C-reactive protein (Table 2).

Primary Outcome

The primary efficacy end point, change in mean PAV from baseline, showed significantly greater reduction in the alirocumab group compared with the placebo group (−2.13% [95% CI, −2.53% to −1.73%] vs −0.92% [95% CI, −1.28% to −0.56%]; between-group difference, −1.21% [95% CI, −1.78% to −0.65%]; $P < .001$) (**Table 3** and **Figure 2**).

Secondary IVUS Outcomes

Reduction in mean normalized total atheroma volume was significantly greater in the alirocumab group compared with the placebo group (−26.12 [95% CI, −30.07 to −22.17] vs −14.97 [95% CI, −18.14 to −11.80] mm^3; $P < .001$) (Table 3).

Secondary NIRS Outcomes

The powered secondary NIRS end point, change in maximum lipid core burden index within 4 mm, showed significantly greater reduction in the alirocumab group vs the placebo group (−79.42 vs −37.60; between-group difference, −41.24 [95% CI, −70.71 to −11.77]; $P = .006$) (Table 3). Mean total LCBI decreased to a significantly greater extent in alirocumab-treated vs placebo-treated patients (−29.30 vs −12.38; between-group difference, −17.29 [95% CI, −28.98 to −5.60]; $P = .004$).

Secondary OCT Outcomes

The powered secondary OCT end point, change in mean minimal FCT, showed a significantly greater increase in the alirocumab group (62.67 µm [95% CI, 48.84-76.50]) compared with the placebo group (33.19 µm [95% CI, 22.22-44.16]) (between-group difference, 29.65 µm [95% CI, 11.75-47.55]); $P = .001$) (Table 3). Patients in the alirocumab group showed significantly greater increase in mean FCT vs the placebo group (between-group difference, 28.22 µm [95% CI, 3.21-53.23]; $P = .03$) and greater reduction in mean angular extension of macrophages (difference, −10.08° [95% CI, −14.72° to −5.43°]; $P < .001$).

An example of a coronary plaque displaying reductions in PAV and maximum lipid core burden index within 4 mm and increase in minimal FCT is shown in **Figure 3**.

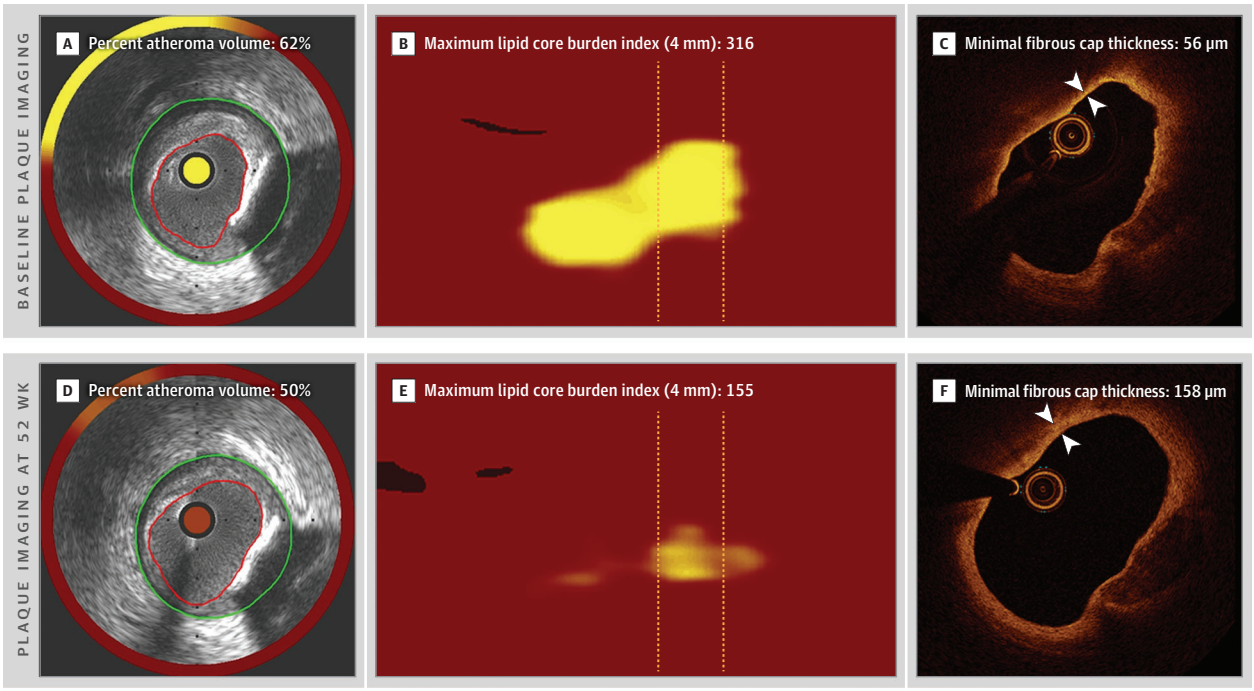
Secondary Clinical Outcomes

The number of centrally adjudicated clinical events in the alirocumab vs the placebo group were 2 (1.4%) vs 1 (0.7%) for all-cause mortality, 2 (1.4%) vs 0 for cardiac death, 2 (1.4%) vs 3 (2.0%) for myocardial infarction, and 12 (8.2%) vs 28 (18.5%) for ischemia-driven coronary revascularization (eTable 6 in Supplement 4).

Adverse Events

The frequency of adverse events with alirocumab vs placebo was 6.1% vs 3.3% for injection site reactions, 2.0% vs 0% for neurocognitive events, 0.7% vs 0% for increase in alanine transaminase levels greater than 3 times the upper limit of normal, and 3.4% vs 0% for general allergic reactions. Complications related to the intracoronary imaging procedure were reported

Figure 3. Example of Plaque Regression, Lipid Regression, and Fibrous Cap Thickening in a Trial Patient



All images were obtained from the same lesion in the same patient and matched for the 2 time points of intracoronary imaging investigation. For intravascular ultrasonography (IVUS), external elastic lamina borders (green line) and lumen borders (red line) are superimposed and a reduction in percent atheroma volume from 62% to 50% is indicated. Note the calcification (solid white linear structure) extending between 3 and 5 hours in this matched IVUS cross section in panels A and D. For near-infrared spectroscopy, a reduction in maximum lipid core burden index (4 mm) was measured; the dotted lines in panels B and E indicate the 4-mm region with greatest lipid accumulation. For optical coherence tomography, an increase in minimal fibrous cap thickness (noted by white arrows in panels C and F) from 56 µm to 158 µm was measured.

in 7 patients (2.3%) (eTable 7 in Supplement 4), all of which were transient and without clinical sequelae.

Exploratory Post Hoc Analyses

In a post hoc analysis that included the stratification variables in the model comparing the primary outcome between treatment groups, the difference in change in PAV was −1.21% ([95% CI, −1.78% to −0.64%]; $P < .001$). In another post hoc analysis, a significantly higher percentage of patients in the alirocumab vs the placebo group showed PAV regression, ie, any reduction in PAV from baseline to week 52 (84.6% vs 65.9%; $P < .001$) (Table 3).

Discussion

In this trial, the addition of the PCSK9 inhibitor alirocumab to high-intensity statin therapy in patients presenting with AMI resulted in favorable effects on coronary atherosclerosis, assessed by 2-vessel imaging applying a combination of 3 intracoronary imaging modalities. The primary IVUS efficacy end point showed significantly greater PAV regression during 52 weeks of therapy in patients treated with the combination of alirocumab and high-intensity statin therapy compared with statin monotherapy. Favorable changes were also observed for the powered secondary end points, including a greater reduction in lipid burden, assessed by NIRS, and greater increase in minimal FCT, assessed by OCT. Taken together, PCSK9 inhibition initiated early in the acute setting of AMI produced incremental benefits on coronary plaque evolution, composition, and phenotype compared with the favorable effects of intensive statin therapy alone.

The extent of PAV regression (2.13%) in the active treatment group of this trial was larger than observed on previous reports and the mean LDL-C levels achieved (23.6 mg/dL) were lower compared with previous IVUS trials of statins[10,11] and the GLAGOV trial assessing the PCSK9 inhibitor evolocumab.[17] When interpreting the present findings in the context of those of the GLAGOV trial (0.95% PAV regression and LDL-C of 36.6 mg/dL while receiving treatment with evolocumab), important differences in study design should be considered. The GLAGOV trial included patients with stable CAD already receiving statin therapy with median LDL-C of 92.5 mg/dL at the time of randomization,[17] whereas patients in this study presented with an AMI and 88% of 300 patients were statin-naive with higher baseline LDL-C levels. PAV at baseline, which has been reported to correlate positively with the achieved PAV reduction with statins[19] or evolocumab,[20] was greater in this study (mean PAV, 42%) compared with the GLAGOV trial (mean PAV, 36.4%).[17] Thereby, concomitant initiation of a high-intensity statin and a PCSK9 inhibitor resulted in a PAV regression that is approximately the sum of the

PAV regression seen previously with statins (1.0%-1.2%)[10,11] and that observed with evolocumab in patients already receiving statin therapy (0.95%).[17]

The presence of a large lipid pool, thin fibrous cap, and marked inflammatory cell infiltration are essential characteristics of plaques prone to rupture and trigger potentially fatal coronary events.[4,6] Following evidence of plaque delipidation with statins in preclinical and human histological studies,[21,22] intensive statin treatment has been suggested to reduce NIRS-defined LCBI in patients with obstructive CAD.[12] This trial found a significant reduction in maximum lipid core burden index within 4 mm in the placebo (statin monotherapy) group and a significantly greater reduction in the alirocumab group. These findings provide new evidence by representing the largest serial NIRS study to date to examine the effects of lipid-lowering treatment on the lipid content of coronary plaques. Of clinical relevance, the Lipid Rich Plaque[8] and PROSPECT II studies[23] showed that greater LCBI as assessed by NIRS in nonobstructive lipid-rich lesions correlated with future ischemic cardiovascular events. Contrary to this trial, a substudy of the GLAGOV trial found no significant effect of evolocumab on plaque morphology as assessed by IVUS-virtual histology analysis, likely due to limitations inherent to the applied imaging method.[24]

OCT is the only imaging modality with sufficient spatial resolution to quantify FCT in vivo.[5,25] This trial found a significantly greater increase in minimal FCT with alirocumab vs placebo. These findings build on previous evidence of FCT increase from smaller, serial OCT studies with statins[18,26] and are consistent with the findings of the HUYGENS trial, demonstrating a mean increase in minimal FCT of 29.8 µm with placebo and 62.3 µm with evolocumab among 135 patients with NSTEMI.[27] The CLIMA study showed that the presence of 4 OCT markers of presumed plaque vulnerability was associated with increased risk of subsequent ischemic cardiovascular events; among these markers, minimal FCT less than 75 µm showed the strongest correlation with clinical prognosis.[9] Although it is reasonable to assume that fibrous cap thickening is a marker of plaque stabilization,[4,6] the clinical relevance of the increase in minimal FCT observed in this trial remains unclear.

This trial did not show an increase in the incidence of adverse events in patients treated with alirocumab. Although the number of treated patients was relatively small, the tolerability of alirocumab in this study is consistent with the findings of large outcome trials of PCSK9 antibodies[2,3] and a trial assessing the in-hospital initiation of evolocumab in patients with acute coronary syndromes.[28]

The favorable effects of alirocumab on coronary atherosclerosis were observed at mean LDL-C levels while receiving treatment below the treatment goals recommended in current guidelines.[29] These findings might provide the mechanistic rationale in favor of early initiation of very intensive LDL-C-lowering treatment in the acute setting of AMI—a patient population characterized by increased risk of recurrent atherothrombotic events, largely attributable to disease progression in nonculprit lesions.[7,30] In view of the early clinical benefit of intensive statin therapy initiated in hospital in patients with AMI,[14,31] the clinical effects of early initiation of PCSK9 inhibition—an approach endorsed for select patients with AMI according to a consensus-based recommendation in current European guidelines[32]—require additional research.

Limitations

This trial has several limitations. First, baseline PAV was numerically higher in the placebo group; however, based on the previously reported positive correlation between baseline PAV and achieved PAV regression,[19,20] this imbalance is more likely to have led to underestimation rather than overestimation of the effect of alirocumab on PAV regression. Second, although patient retention (88%) was better than in previous IVUS studies, patients who did not complete the trial might have had changes in coronary atherosclerosis that differed from those in patients who completed the trial. Third, the number of patients in this study is modest and smaller compared with previous serial IVUS studies[10,11,17]; however, the power increased by investigating two arteries per patient, and statistical significance was reached for the primary as well as the powered secondary end points.

Conclusions

Among patients with acute myocardial infarction, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non-infarct-related arteries after 52 weeks. Further research is needed to understand whether alirocumab improves clinical outcomes in this population.

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