Supplemental Online Content

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Supplement 4. eMethods and eResults

This supplemental material has been provided by the authors to give readers additional information about their work.

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Statistical Methods

Initial sample size calculation

For the primary endpoint, we assumed a change in percent atheroma volume (PAV) of -0.5% in the placebo arm and -1.8% in the alirocumab arm, with a common standard deviation of 3.4% (as a consensus from SATURN11:3.0%[1], IBIS-4[2]: 3.4%, ASTEROID[3]: 4.0%) and an intraclass correlation coefficient of ICC=0.40 (estimated from IBIS4 data[2]). Given that m=1.8 vessels per patients are expected to be analyzed, this gives a design effect of D=1.4 [design effect computed as D = 1+ICC(m-1)]. If dropout was ignored, a total sample size of 176 patients would be necessary to reach a statistical power of 80% at a two sided alpha level of α=5%. Anticipating a dropout rate of 25% at the 12 month imaging follow-up, a total of n=220 patients should be recruited (110 per arm).

In case the GLAGOV randomized clinical trial reported considerably lower PAV regression compared with our current assumptions ($\leq$ 1.6% difference in the change in PAV with evolocumab vs palcebo), a protocol amendment of the present study would be submitted with a revised sample size calculation accounting for the GLAGOV results.

Revised sample size calculation

i. Primary Endpoint

The above-mentioned condition for the revised sample size calculation was met, since the between-group difference in change in PAV observed in GLAGOV was 1%.[4] We therefore revised our sample size calculation, considering a change in PAV of 1% (instead of 1.3% initially). Based on data from already enrolled patients with available one year follow-up at the time point of the revised sample size calculation (N=54), we also revised the expected number of vessels per patient (m=2.0 instead of 1.8 initially) and the expected dropout rate (10% instead of 25% initially). This was a superiority trial powered on the primary endpoint, change in PAV from baseline to 52 weeks. In the revised power calculation we assumed: (i) a difference in change in PAV of -1.0% (alirocumab vs placebo, based on the findings of the

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GLAGOV trial[4]); (ii) a standard deviation of 3.4% (as a consensus from SATURN[1]: 3.0%, IBIS-4[2]: 3.4%, ASTEROID[3]: 4.0%); and (iii) an intraclass correlation coefficient (ICC) of approximately 0.435 (estimated from IBIS-4 data[2]). We expected m=2.0 vessels per patients to be analyzed. The design effect was calculated by D = 1+ICC(m-1). If dropout was ignored, a total sample size of 264 patients would be required to reach a statistical power of 80% at a significance level of α=5% using a two-sided test. Anticipating a dropout rate of 10% (loss of patients undergoing follow-up imaging) at the week 52 imaging follow-up, a total of n=294 patients should be recruited (147 per arm).

ii. Powered Secondary Endpoints

- Change in lipid-core burden index at the 4-mm maximal segment ($maxLCBI_{4mm}$)

For the change in $maxLCBI_{4mm}$ from baseline to 52 weeks, we assumed: (i) a difference between PCSK9 arm and Placebo arm of 193.3 based on the observed difference in the YELLOW I trial[5] and the expected reduction in LDL-C levels in PACMAN-AMI (-40% with placebo and -75% with alirocumab), (ii) a standard deviation of 220 (estimated from the LRP trial[6]) and iii) a dropout rate of 10% at the week 52 imaging follow-up. Considering a total number of enrolled patients of n=294, a significance level of alpha=2.5% using a two-sided test, the trial would provide a power of more than 95% to detect the expected difference in the change in maxLCBI4mm of 193.3 between placebo and alirocumab if it was tested independently.

- Change in minimal cap thickness

For the change in minimal cap thickness from baseline to 52 weeks, we assumed: (i) a difference between PCSK9 arm and Placebo arm of 19.8μm for min cap thickness based on the observed difference in IBIS-4[7] and the expected reduction in LDL-C in PACMAN-AMI (-40% with placebo and -75% with alirocumab), (ii) a standard deviation of 44.8 (calculated from IBIS-4[7]); (iii) an intracluster correlation coefficient of approximately 0.57 (estimated from IBIS-4 data[7]); (iv) m=1.59 vessels per patient with fibroatheroma, according to the PACMAN-AMI matching substudy[8]), (v) 72% of the patients to show

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any fibroatheroma (PACMAN-AMI matching substudy[8]). Considering a dropout rate of 10% at the week 52 imaging follow-up, an expected 72% of patients showing fibroatheroma, a total number of enrolled patients of n=294, and a significance level of alpha=2.5% using a two-sided test, the trial would provide a power of 85% to detect the expected difference in the change in min. cap thickness of 19.8µm between placebo and alirocumab if it was tested independently.

Supplementary references

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eTable 1. Inclusion and Exclusion Criteria

Inclusion criteria

- Male or female, age ≥18 years at screening
- Acute myocardial infarction: acute ST-segment elevation myocardial infarction (STEMI) with pain onset within ≤24h, or non-ST segment elevation myocardial infarction (NSTEMI), with at least one coronary segment (culprit lesion) requiring PCI
- LDL-C ≥70 mg/dL (≥1.8 mmol/L) assessed prior to, or during PCI in patients who have been receiving any stable statin regimen within ≥ 4 weeks prior to enrollment; OR LDL-C ≥125 mg/dL (≥3.2 mmol/L) in patients who are statin-naïve or have not been on stable statin regimen for ≥ 4 weeks prior to enrollment
- At least two major native coronary arteries ("target vessels") each meeting the following criteria for intracoronary imaging immediately following the qualifying PCI procedure:
  - Angiographic evidence of <50% reduction in lumen diameter by angiographic visual estimation
  - Target vessel deemed to be accessible to imaging catheters and suitable for intracoronary imaging in the proximal (50mm) segment ("target segment")
  - Target vessel may not be a bypass (saphenous vein or arterial) graft or a bypassed native vessel
  - Target vessel must not have undergone previous PCI within the target segment
  - Target vessel is not candidate for intervention at the time of qualifying PCI or over the following 6 months in the judgment of the Investigator
- Hemodynamic stability allowing the repetitive administration of nitroglycerine
- Ability to understand the requirements of the study and to provide informed consent
- Willingness of patient to undergo follow-up intracoronary imaging

Exclusion criteria

- Left-main disease, defined as ≥50% reduction in lumen diameter of the left main coronary artery by angiographic visual estimation
- Three-vessel disease, defined as ≥70% reduction in lumen diameter of three major epicardial coronary arteries by angiographic visual estimation or in major branches of one or more of these arteries, irrespective of the localization (proximal 50mm or more distal localization) of the obstructive lesions
- History of coronary artery bypass surgery
- TIMI flow <2 of the infarct-related artery after PCI

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- Unstable clinical status (hemodynamic or electrical instability)
- Significant coronary calcification or tortuosity deemed to preclude IVUS, NIRS and OCT evaluation
- Uncontrolled cardiac arrhythmia, defined as recurrent and symptomatic ventricular tachycardia or atrial fibrillation with rapid ventricular response not controlled by medications in the past 3 months prior to screening
- Severe renal dysfunction, defined by estimated glomerular filtration rate <30 ml/min/1.73m^2
- Active liver disease or hepatic dysfunction
- Known intolerance to rosuvastatin OR known statin intolerance
- Known allergy to contrast medium, heparin, aspirin, ticagrelor or prasugrel
- Known sensitivity to any substances to be administered, including known statin intolerance
- Patients who previously received alirocumab or other PCSK9 inhibitor
- Patient who received cholesterol ester transfer protein inhibitors in the past 12 months prior to screening
- Treatment with systemic steroids or systemic cyclosporine in the past 3 months
- Known active infection or major hematologic, metabolic, or endocrine dysfunction in the judgment of the Investigator
- Planned surgery within 12 months
- Patients who will not be available for study-required visits in the judgment of the Investigator
- Current enrollment in another investigational device or drug study
- History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
- Estimated life expectancy less than 1 year
- Female of childbearing potential (age <50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy.

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eTable 2. Pre-Specified Secondary Endpoints not Reported in the Present Manuscript

- High-sensitivity troponin T
- N-terminal B-type natriuretic peptide
- Tumor-necrosis factor a
- Interleukin-1b
- Interleukin-6
- Cystatine
- Myeloperoxidase
- Sirtuin-1
- Sirtuin-6
- PCSK9

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eTable 3. Medications at Discharge after Hospitalization for the Index Event

Medication	**Alirocumab** n=148	**Placebo** n=152
Statin	147 (99.3%)	151 (99.3%)
Rosuvastatin 20mg	141 (95.3%)	142 (93.4%)
High-intensity statin therapy[a]	144 (97.3%)	148 (97.4%)
Ezetimibe	0 (0.0%)	0 (0.0%)
Any antiplatelet drug	147 (99.3%)	151 (99.3%)
Dual antiplatelet therapy	144 (97.3%)	150 (98.7%)
Aspirin	144 (97.3%)	150 (98.7%)
Clopidogrel	8 (5.4%)	8 (5.3%)
Ticagrelor	115 (77.7%)	122 (80.3%)
Prasugrel	24 (16.2%)	21 (13.8%)
Novel oral anticoagulant	4 (2.7%)	4 (2.6%)
Vitamin K antagonist	4 (2.7%)	3 (2.0%)
ACE inhibitor	109 (73.6%)	105 (69.1%)
ARB	15 (10.1%)	21 (13.8%)
β-blocker	116 (78.4%)	126 (82.9%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

In the alirocumab group, one missing value in all variables. In the placebo group, one patient excluded short after randomization has missing values in all variables.

[a] Defined as atorvastatin ≥40mg or rosuvastatin ≥20mg.

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eTable 4. Medications at 52-Week Follow-up

Medication	**Alirocumab** n=131	**Placebo** n=135
Statin	128 (97.7%)	134 (99.3%)
Rosuvastatin 20mg	115 (87.8%)	126 (93.3%)
High-intensity statin therapy[a]	116 (88.5%)	128 (94.8%)
Ezetimibe	2 (1.5%)	3 (2.2%)
Any antiplatelet drug	129 (98.5%)	135 (100%)
Dual antiplatelet therapy	106 (80.9%)	125 (92.6%)
Aspirin	124 (94.7%)	134 (99.3%)
Clopidogrel	9 (6.9%)	9 (6.7%)
Ticagrelor	82 (62.6%)	97 (71.9%)
Prasugrel	20 (15.3%)	20 (14.8%)
Novel oral anticoagulant	7 (5.3%)	4 (3.0%)
Vitamin K antagonist	3 (2.3%)	0 (0.0%)
ACE inhibitor	71 (54.2%)	77 (57.0%)
ARB	32 (24.4%)	30 (22.2%)
β-blocker	104 (79.4%)	99 (73.3%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

[a] Defined as atorvastatin ≥40mg or rosuvastatin ≥20mg.

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eTable 5. Baseline Characteristics of Patients in the Randomized Population Who Received Study Drug With and Without Serial IVUS Imaging

Characteristics	Serial IVUS (n=265)	No serial IVUS (n=35)
Age (y)	57.8 (9.3)	64.0 (11.1)
Female sex	43 (16.2%)	13 (37.1%)
Body mass index[a]	28.0 (4.3)	25.9 (4.3)
Diabetes mellitus	26 (9.8%)	5 (14.3%)
Arterial hypertension	113 (42.6%)	17 (48.6%)
Current smoking	129 (48.7%)	13 (37.1%)
Family history of CAD	88 (33.2%)	10 (28.6%)
Previous myocardial infarction	6 (2.3%)	1 (2.9%)
Previous PCI	7 (2.6%)	0 (0.0%)
Peripheral arterial disease	5 (1.9%)	1 (2.9%)
Type of acute myocardial infarction		
NSTEMI	122 (46.0%)	20 (57.1%)
STEMI	143 (54.0%)	15 (42.9%)
Baseline medications		
Antiplatelet therapy	26 (9.8%)	5 (14.3%)
Statin	34 (12.8%)	3 (8.6%)
High-intensity statin[b]	18 (6.8%)	2 (5.7%)
Ezetimibe	1 (0.4%)	0 (0.0%)
β-blocker	24 (9.1%)	5 (14.3%)
ACE inhibitor	21 (7.9%)	3 (8.6%)
ARB	32 (12.1%)	9 (25.7%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; IVUS, intravascular ultrasound; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation acute myocardial infarction.

Values are count (%) or mean (SD).

In the patient population without serial IVUS, one patient excluded short after randomization has missing values in all variables except “Age” and ”Type of acute myocardial infarction”. One additional value was missing for BMI in the patient population without serial IVUS.

[a] Calculated as weight in kilograms divided by height in meters squared

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

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eTable 6. Clinical and Biochemical Adverse Events

	Alirocumab N=147[a]	**Placebo N=151[a]**
Any adverse event	104 (70.7%)	110 (72.8%)
Serious adverse event[b]	47 (32.0%)	50 (33.1%)
Adverse events resulting in study drug discontinuation	2 (1.4%)	0 (0.0%)
Cardiovascular events		
Coronary revascularization – ischemia driven[c]	12 (8.2%)	28 (18.5%)
Revascularization of *de novo* lesion – ischemia driven[c]	7 (4.8%)	17 (11.3%)
Target-lesion revascularization[d] – ischemia driven[c]	5 (3.4%)	12 (7.9%)
All-Cause death	2 (1.4%)	1 (0.7%)
Cardiac death	2 (1.4%)	0 (0.0%)
Myocardial infarction	2 (1.4%)	3 (2.0%)
Stroke / TIA	0 (0.0%)	1 (0.7%)
Adverse events of special interest		
Local injection site reaction	9 (6.1%)	5 (3.3%)
General allergic reaction	5 (3.4%)	0 (0.0%)
Neurocognitive event	3 (2.0%)	0 (0.0%)
ALT increase > 3x ULN	1 (0.7%)	0 (0.0%)

Abbreviations: ALT, alanine transaminase; TIA, transient ischemic attack; ULN, upper limit of normal. Only the first event of each type per patient is included.

Results expressed a count (percentage).

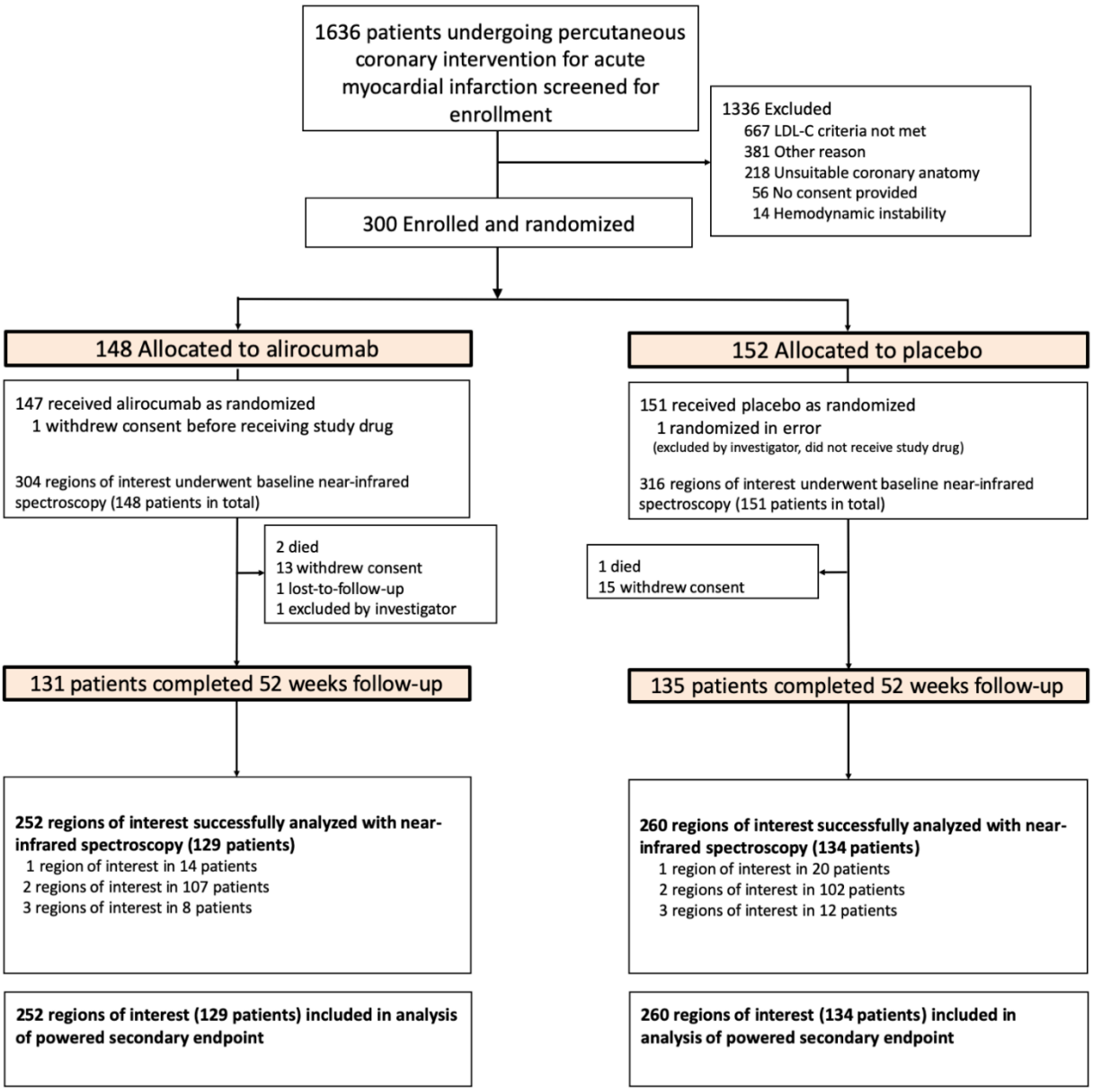
[a] Includes patients who received at least one dose of the study drug.
[b] Serious adverse events were defined as events that resulted in death; or were life-threatening; or required inpatient hospitalization or prolongation of existing hospitalization; or resulted in persistent or significant disability/incapacity; or were congenital anomaly/birth defects; or were medically important events.
[c] Ischemia driven revascularization was defined as revascularization in the presence of angina symptoms and >50% stenosis by quantitative coronary angiography; or >70% stenosis by quantitative coronary angiography in the absence of angina; or a positive fractional flow reserve (<0.80).
[d] Indicates revascularization in a stent implanted during index coronary intervention.

eTable 7. Complications Related to Intracoronary Imaging Procedures

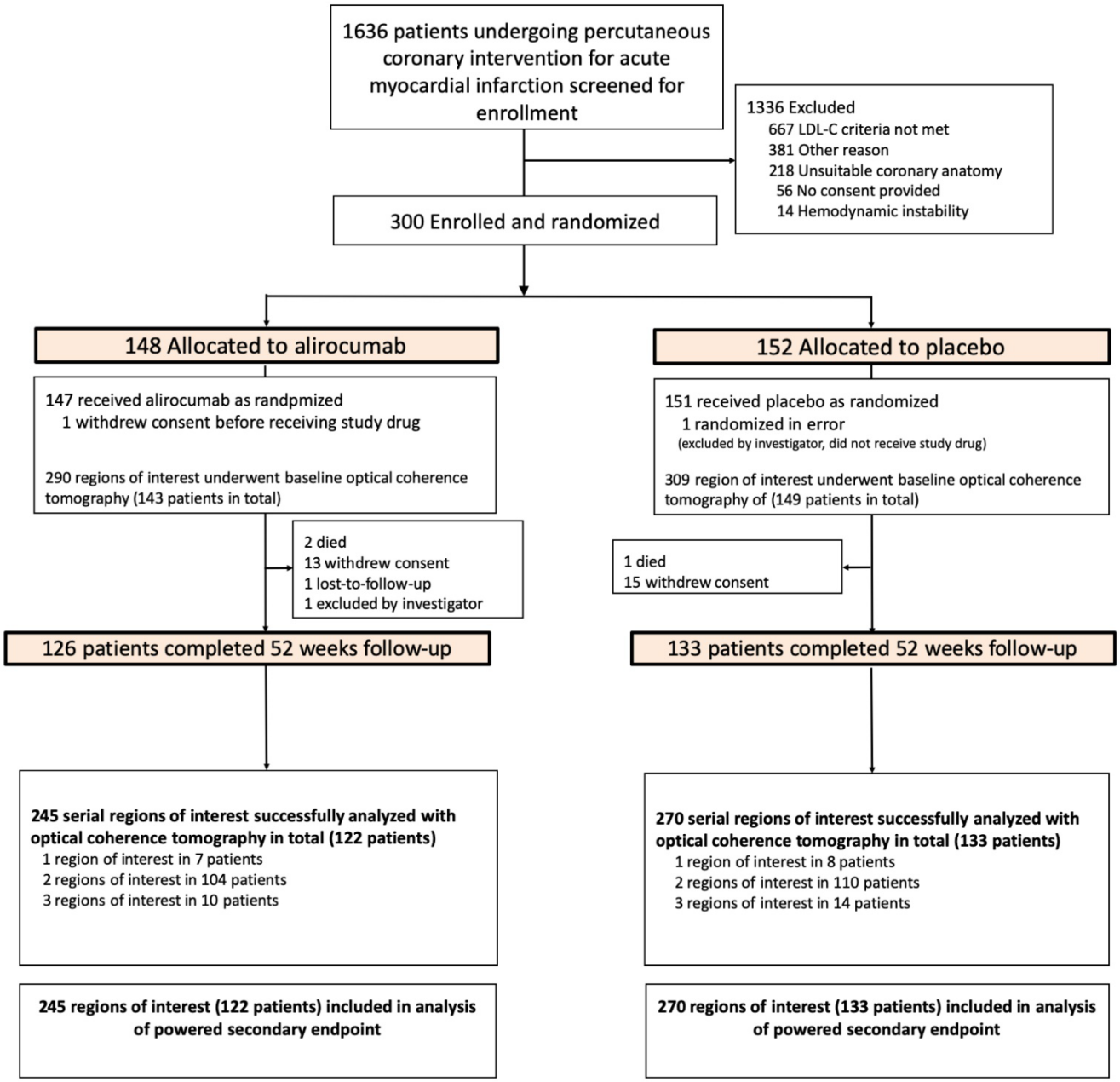
Imaging related complications	Number of patients (%)*	Alirocumab	Placebo
Any	7 (2.3)	4	3
Arrhythmia	3 (1.0)	1	2
Air embolism	2 (0.7)	1	1
Spasm	2 (0.7)	2	0
Perforation	0	0	0
Dissection	0	0	0

*in a total of 567 imaging procedures (baseline and week 52)

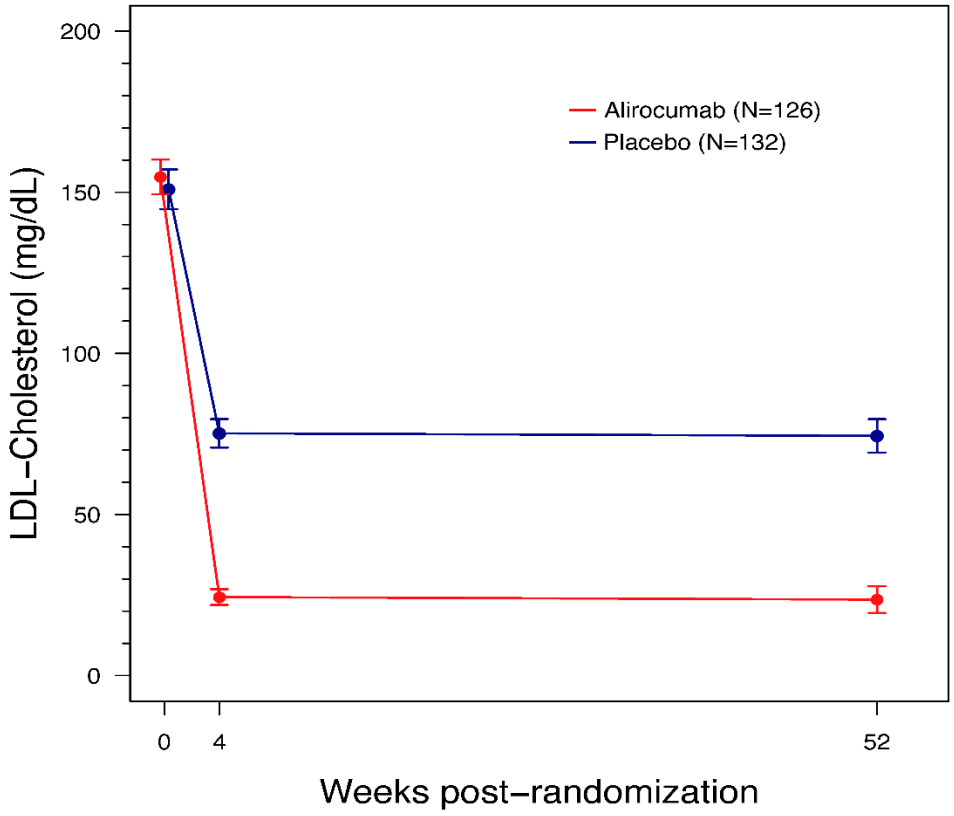
eFigure 1. Flow of Patients in the PACMAN-AMI Randomized Clinical Trial with Respect to Imaging with Near-Infrared Spectroscopy



eFigure 2. Flow of Patients in the PACMAN-AMI Randomized Clinical Trial with Respect to Imaging with Optical Coherence Tomography



eFigure 3. Mean Low-Density Lipoprotein Cholesterol Levels During the Trial



Values are means and 95% confidence intervals. Sample size: 259 patients (7 missing due to missing LDL-C values).

To convert LDL-C values to mmol/L, multiply by 0.0259.