

# Impact of alirocumab on plaque regression and haemodynamics of non-culprit arteries in patients with acute myocardial infarction: a prespecified substudy of the PACMAN-AMI trial

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## KEYWORDS

- adjunctive pharmacotherapy
- clinical trials
- NSTEMI
- other imaging modalities
- QCA
- STEMI

## Abstract

**Background:** Treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on top of statins leads to plaque regression and stabilisation. The effects of PCSK9 inhibitors on coronary physiology and angiographic diameter stenosis (DS%) are unknown.

**Aims:** This study aimed to investigate the effects of the PCSK9 inhibitor alirocumab on coronary haemodynamics as assessed by quantitative flow ratio (QFR) and DS% by three-dimensional quantitative coronary angiography (3D-QCA) in non-infarct-related arteries (non-IRA) among acute myocardial infarction (AMI) patients.

**Methods:** This was a prespecified substudy of the randomised controlled PACMAN-AMI trial, comparing alirocumab versus placebo on top of rosuvastatin. QFR and 3D-QCA were assessed at baseline and 1 year in any non-IRA  $\geq 2.0$  mm and 3D-QCA DS%  $>25\%$ . The prespecified primary endpoint was the number of patients with a mean QFR increase at 1 year, and the secondary endpoint was the change in 3D-QCA DS%.

**Results:** Of 300 enrolled patients, 265 had serial follow-up, of which 193 underwent serial QFR/3D-QCA analysis in 282 non-IRA. At 1 year, QFR increased in 50/94 (53.2%) patients with alirocumab versus 40/99 (40.4%) with placebo ( $\Delta 12.8\%$ ; odds ratio 1.7, 95% confidence interval [CI]: 0.9 to 3.0;  $p=0.076$ ). DS% decreased by  $1.03 \pm 7.28\%$  with alirocumab and increased by  $1.70 \pm 8.27\%$  with placebo ( $\Delta -2.50\%$ , 95% CI:  $-4.43$  to  $-0.57$ ;  $p=0.011$ ).

**Conclusions:** Treatment of AMI patients with alirocumab versus placebo for 1 year resulted in a significant regression in angiographic DS%, whereas no overall improvement of coronary haemodynamics was observed. ClinicalTrials.gov: NCT03067844

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## Abbreviations

<b>AMI</b>	acute myocardial infarction
<b>DS%</b>	diameter stenosis
<b>LDL-C</b>	low-density lipoprotein cholesterol
<b>non-IRA</b>	non-infarct-related artery
<b>PCSK9</b>	proprotein convertase subtilisin/kexin type 9
<b>QFR</b>	quantitative flow ratio
<b>3D</b>	three-dimensional
<b>QCA</b>	quantitative coronary angiography

## Introduction

Hypercholesterolaemia negatively affects endothelial function, coronary vasodilator capacity<sup>1</sup> and coronary flow<sup>2</sup>. Statins are the first-line therapy for hypercholesterolaemia<sup>3,4</sup> and can counteract the unfavourable effects of elevated cholesterol blood levels on the coronary vasculature, by inducing stenosis regression<sup>5</sup> and improving coronary microvascular function<sup>6</sup>.

Monoclonal antibodies inhibiting the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme represent a valuable add-on therapy for patients who require additional low-density lipoprotein cholesterol (LDL-C)-lowering despite receiving statin therapy<sup>3,4</sup>. According to 3 randomised intracoronary imaging studies, PCSK9 inhibitors as compared to placebo induce plaque regression and stabilisation<sup>7-9</sup>. Whether atherosclerosis regression with PCSK9 inhibitors leads to an improvement of coronary physiology and changes in angiographic diameter stenosis (DS%) remains unknown to date.

Quantitative flow ratio (QFR) is a novel, non-hyperaemic method for assessing coronary haemodynamics from biplane coronary angiography using three-dimensional quantitative coronary analysis (3D-QCA) and Thrombolysis in Myocardial Infarction (TIMI) frame counting<sup>10,11</sup>. Previous observational evidence suggests that lipid-lowering therapy with statins is associated with an improvement in QFR<sup>12</sup> and regression in two-dimensional (2D)-QCA DS%<sup>13</sup>. However, the effects of PCSK9 inhibitors on QFR and 3D-QCA DS% have never been investigated.

Therefore, in a substudy of the randomised controlled double-blind PACMAN-AMI (Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction. A Serial, Multivessel, Intravascular Ultrasound, Near-Infrared Spectroscopy And Optical Coherence Tomography Imaging Study) trial<sup>14</sup>, we aimed to assess the effects of the PCSK9 inhibitor alirocumab added to high-intensity statin therapy with rosuvastatin on QFR and DS% by 3D-QCA in non-obstructive coronary lesions located in non-infarct related arteries (non-IRA), 1 year after acute myocardial infarction (AMI).

## Methods

### STUDY DESIGN AND MAIN RESULTS OF THE PACMAN-AMI TRIAL

The design and primary results of the PACMAN-AMI trial have been published previously<sup>7,14</sup>. Briefly, PACMAN-AMI was an investigator-initiated, randomised, double-blind, placebo-controlled,

European multicentre study to evaluate the effect of intensive lipid-lowering therapy with alirocumab added to high-intensity statin therapy with rosuvastatin on coronary atherosclerosis by multimodality intracoronary imaging with intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT) in patients with AMI undergoing percutaneous coronary intervention (PCI). Detailed inclusion and exclusion criteria have been reported elsewhere<sup>14</sup>. In brief, patients were eligible if they had 1) 2 non-IRA suitable for intracoronary imaging with non-obstructive atherosclerotic disease (visual estimate >20 to <50% angiographic DS%); 2) LDL-C levels  $\geq$ 125 mg/dl, if patients were statin-naïve or had not been on a stable ( $\geq$ 4 weeks) statin regimen at the time of screening; or 3) LDL-C  $\geq$ 70 mg/dl, if patients were on an unchanged statin treatment for  $\geq$ 4 weeks prior to study enrolment. The study was conducted at 9 academic centres in Switzerland (5), Austria (1), Denmark (1) and the Netherlands (2). A total of 300 patients were randomised in a 1:1 ratio to either alirocumab subcutaneous 150 mg biweekly or a matching placebo between 9 May 2017 and 7 October 2020. Web-based randomisation was performed using randomly varying block sizes of 2, 4, or 6 patients, stratified by study site; use of stable ( $\geq$ 4 weeks) statin treatment at presentation; and type of AMI (ST-elevation myocardial infarction vs non-ST-elevation myocardial infarction). All patients underwent serial coronary angiography and intravascular imaging at baseline and 1-year follow-up. The PACMAN-AMI main trial findings indicate that alirocumab added to rosuvastatin as compared to placebo leads to a 5% plaque regression, according to IVUS, plaque stabilisation as evidenced by a 59% increase in minimum fibrous cap thickness (minFCT), according to OCT, and a 30% decrease of lipid pool, according to NIRS<sup>7</sup>.

### PACMAN-AMI QFR SUBSTUDY

This was a prespecified substudy of the PACMAN-AMI trial<sup>7</sup> to assess QFR and 3D-QCA DS% in non-IRA with a proximal reference diameter  $\geq$ 2.0 mm and >25% DS% as assessed by 3D-QCA (**Central illustration**). The 25% threshold was based on previous QCA studies<sup>5,15,16</sup>. The sample size was determined by the main trial<sup>14</sup>. Analysis was per intention to treat. QFR-specific exclusion criteria included the absence of 2 projections with angles  $\geq$ 25° apart, lack of isocentre calibration, substantial vessel overlap or vessel foreshortening, severe tortuosity, poor contrast, ostial left main or right coronary artery (RCA) stenosis, TIMI flow  $\leq$ 2, tachycardia >100/min, and atrial or ventricular arrhythmia.

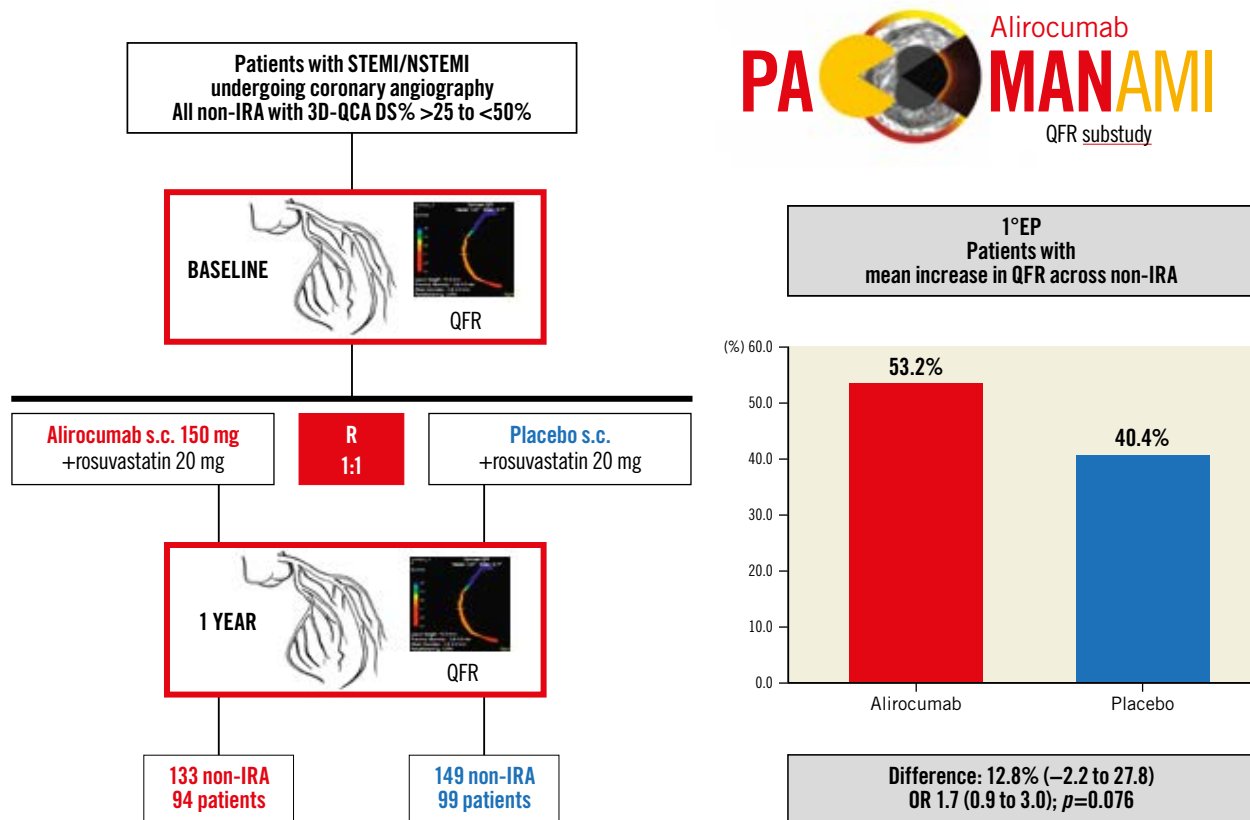
### CORONARY ANGIOGRAPHY

Coronary angiographies at baseline and 1-year follow-up were performed after the administration of 100-200  $\mu$ g intracoronary nitroglycerine using standard projections.

### QFR AND 3D-QCA ANALYSIS

QFR and 3D-QCA were assessed at baseline and 1-year follow-up by experienced analysts blinded to treatment allocation, intracoronary imaging findings, and patient outcomes at the Bern University

## CENTRAL ILLUSTRATION PACMAN-AMI QFR substudy design and primary endpoint result



PACMAN-AMI QFR substudy study design (left) and results of the primary endpoint (1°EP) (right). DS%: percent diameter stenosis; non-IRA: non-infarct-related artery; NSTEMI: non-ST-elevation myocardial infarction; OR: odds ratio; QFR: quantitative flow ratio; s.c.: subcutaneous; STEMI: ST-elevation myocardial infarction; 3D-QCA: three-dimensional quantitative coronary angiography

Hospital core lab, using a dedicated software (QAngio XA 3D, version 1.2; Medis Medical Imaging Systems). All non-IRA with  $\geq 2.0$  mm proximal reference diameter and DS% >25% according to 3D-QCA were eligible for QFR measurement. Whole-vessel contrast QFR using frame counting<sup>10</sup> was measured from the ostium to a distal landmark at a minimum of 1.5 mm distal vessel reference diameter, as reported previously<sup>17</sup>. The conventional QFR cutoff of  $\leq 0.80$  was used to detect significant ischaemia<sup>10,11</sup>.

#### INTRA- AND INTEROBSERVER RELIABILITY

For intra- and interobserver reliability analysis, repeated QFR and 3D-QCA analyses by 2 independent core lab analysts including 10 randomly assigned vessels were used.

#### ENDPOINTS

The prespecified primary endpoint was the number of patients with a mean increase in QFR across non-IRA from baseline to follow-up<sup>14</sup>. Secondary endpoints were the continuous change in DS% by

3D-QCA and the continuous change in QFR from baseline to follow-up<sup>14</sup>. Since many stenotic lesions have been reported to better respond to lipid-lowering therapy<sup>18,19</sup> and the potential effect of alirocumab can be blunted by an expectedly high baseline QFR related to the trial inclusion criteria of only non-obstructive non-IRA, we performed a non-prespecified sensitivity analysis that excluded vessels with the least flow limitation, using an empirical threshold of QFR >0.95 in the absence of prior data. Further, on the patient level, we quantified the relationship between QFR (lowest per patient) and DS% (highest per patient) and intracoronary imaging variables (i.e., IVUS: percentage atheroma volume [PAV; highest per patient]; NIRS: maximum lipid core burden index 4 mm [maxLCBI4 mm; highest per patient]; and OCT: minFCT [lowest per patient]).

#### STATISTICAL ANALYSIS

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]) and categorical variables are presented as counts with percentages. Baseline characteristics, baseline

medications and laboratory values were compared using the Student's t-test or Fisher's exact test, as appropriate. QFR variables at baseline were compared using Wilcoxon tests. For the primary endpoint (an increase or decrease in vessel QFR), we used a logistic model to compare the odds of a QFR increase between the alirocumab and the placebo groups. We report the corresponding odd ratios (OR) with 95% confidence intervals (95% CI) and associated p-values. The continuous change between groups for secondary QFR/3D-QCA variables were computed using mixed-effect models; we fitted the interaction between groups (alirocumab or placebo) and timepoints (baseline or follow-up) as fixed effects and patient identity as a random effect. These models account for repeated measures for a given vessel (baseline and follow-up) and for multiple vessels per patient. We report marginal differences between arms with robustified 95% CI. Intra- and interobserver agreement were assessed by intraclass correlation coefficients. All analyses were conducted in Stata 17 (Stata Corp) and R version 4.2.1 (R Foundation for Statistical Computing). Significance tests were 2-tailed with a significance level set to 0.05.

## Results

### PATIENT POPULATION

Of 300 enrolled patients, 265 underwent serial angiography. Among these, serial QFR was performed in 193 patients with a total of 282 non-IRA (64% of the trial population). The most frequent exclusion criteria were the absence of any non-IRA with >25% stenosis, the absence of 2 appropriate projections  $\geq 25^\circ$  apart, or a missing isocentre calibration (**Figure 1**). The mean age was 58 years, 19% were female, 9% had diabetes mellitus, and the baseline LDL-C level was  $152.4 \pm 33.7$  mg/dl. The non-IRA analysed were most frequently in the left anterior descending artery (LAD) territory (39%), followed by the left circumflex (LCx; 34%) and the RCA (27%) territory (**Table 1**). Patient baseline characteristics, non-IRA analysed, and laboratory values are reported in **Table 1**. The characteristics of included versus excluded patients from the PACMAN-AMI QFR substudy were comparable (**Supplementary Table 1**). At 1 year, LDL-C levels decreased to  $23.1 \pm 21.0$  mg/dl in the alirocumab arm compared to  $78.3 \pm 32.7$  mg/dl in the placebo arm ( $p < 0.001$ ). Treatment adherence at 1 year is shown in **Supplementary Table 2**.

### INTRA- AND INTEROBSERVER AGREEMENT

Intraobserver agreement analysis for continuous QFR yielded an intraclass correlation coefficient (ICC) of 0.96 (95% CI: 0.86-0.99) and  $R^2$ (adjusted) of 0.92 ( $p < 0.001$ ). For 3D-QCA DS% ICC was 0.99 (95% CI: 0.96-1.00) and  $R^2$ (adjusted) was 0.98 ( $p < 0.001$ ).

Interobserver agreement analysis for QFR yielded an ICC of 0.94 (0.79-0.99) and  $R^2$ (adjusted) of 0.90 ( $p < 0.001$ ). For 3D-QCA DS% maybe put on next line ICC to make more legible as it is hard to see the space between "3D-QCA" and "DS%" and "ICC" was 0.95 (95% CI: 0.82-0.99) and  $R^2$ (adjusted) was 0.90 ( $p < 0.001$ ).

### QFR

At baseline, the median QFR was 0.96 (0.91-0.98) in the alirocumab arm and 0.96 (0.91-0.99) in the placebo arm ( $p = 0.593$ )

(**Supplementary Figure 1A, Table 2**). Overall, 96.8% ( $n = 273$ ) of vessels had QFR  $> 0.80$ . The number of patients with a mean QFR increase across non-IRA from baseline to 1-year follow-up was 50 of 94 (53%, 95% CI: 43.2-63.0) in the alirocumab arm versus 40 of 99 (40%, 95% CI: 31.3-50.3) in the placebo arm (difference 13%, 95% CI: -2.2 to 27.8; OR 1.7, 95% CI: 0.9-3.0;  $p = 0.076$ ) (**Central illustration, Figure 2A, Table 2**). The between-group comparison of the change in continuous QFR from baseline to follow-up was not performed because of the small difference (**Supplementary Figure 1A, Table 2**). A sensitivity analysis considering only non-IRA with QFR  $\leq 0.95$  showed a significantly higher number of patients with a mean QFR increase on alirocumab ( $n = 37$  of 57; 65%, 95% CI: 51.9-76.0) compared to placebo ( $n = 22$  of 50; 44%, 95% CI: 31.2-57.7) (difference 21%, 95% CI: 0.5-41.3; OR 2.4, 95% CI: 1.1-5.2;  $p = 0.031$ ) (**Table 2**).

### 3D-QCA

At baseline, the mean DS% was  $36.96 \pm 7.88\%$  in the alirocumab arm and  $36.63 \pm 8.46\%$  in the placebo arm ( $p = 0.742$ ) (**Supplementary Figure 1B, Table 2**). In total, 92.9% ( $n = 262$ ) of vessels had a DS%  $< 50\%$ . Vessels in the alirocumab arm were larger (including larger minimum lumen diameter [MLD]) ( $p = 0.004$ ) than in the placebo arm, whereas area stenosis ( $p = 0.715$ ) and lesion length ( $p = 0.999$ ) were similar between the treatment groups (**Table 2**). The mean change in DS% was  $-1.03 \pm 7.28\%$  in the alirocumab arm compared to  $+1.70 \pm 8.27\%$  in the placebo arm (difference in change  $-2.50\%$ , 95% CI: -4.43 to -0.57;  $p = 0.011$ ) (**Figure 2B, Table 2**). In the sensitivity analysis considering only non-IRA with QFR  $\leq 0.95$ , this difference was more pronounced (alirocumab  $-1.53 \pm 7.63\%$  vs placebo  $+2.74 \pm 9.67\%$ , difference in change  $-4.11\%$ , 95% CI: -7.41 to -0.80;  $p = 0.015$ ) (**Supplementary Table 3**).

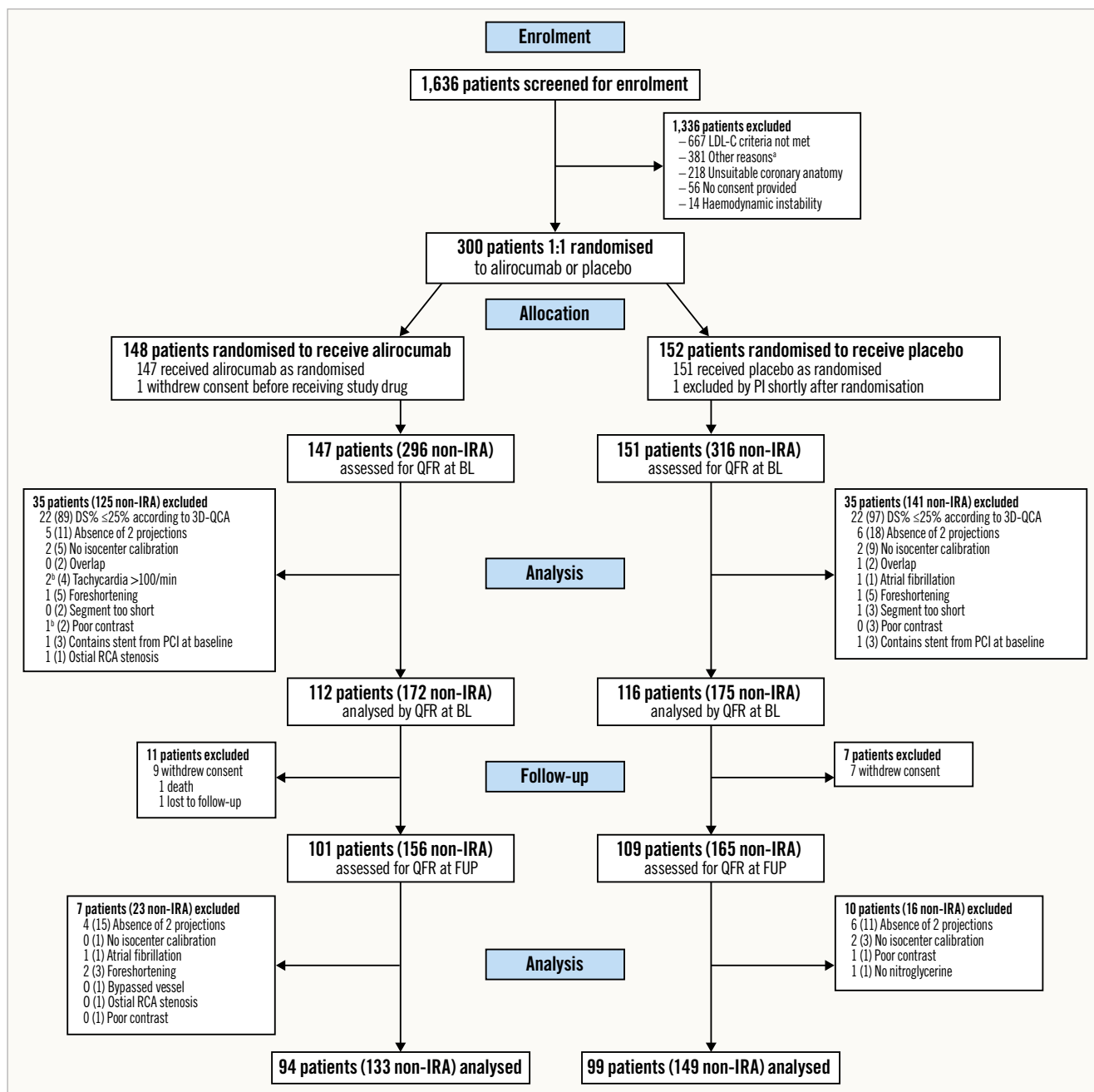
In the exploratory analyses, we observed an association between change in DS% and on-treatment LDL-C (**Figure 3, Supplementary Figure 2**). Further, we observed a trend towards more pronounced DS% reduction with a higher degree of baseline stenosis (**Figure 4**) and increasing raw differences in the change in DS% between treatment groups favouring alirocumab, reaching  $-3.98\%$  with baseline DS%  $> 45\%$  (**Supplementary Figure 3**).

### ASSOCIATION BETWEEN QFR AND DS% WITH INTRACORONARY IMAGING FINDINGS

For both QFR and DS%, there were significant associations with PAV and maxLCB14 mm at baseline and at follow-up (**Supplementary Figure 4, Supplementary Figure 5**), and for QFR, there was a trend towards an association with minFCT at baseline (**Supplementary Figure 6**). There were no significant associations between the change in DS% and the change in intracoronary imaging variables (**Supplementary Figure 7**).

## Discussion

PACMAN-AMI QFR represents the first prespecified, multicentre, randomised controlled trial substudy to assess the effects of intensive lipid-lowering therapy with the PCSK9 inhibitor alirocumab



**Figure 1.** CONSORT flow diagram. <sup>a</sup>Specific reasons for other exclusions were not documented at the site of evaluation. See Table 1 in Supplement 4 in the main publication<sup>8</sup> for additional inclusion and exclusion criteria. <sup>b</sup>This patient fulfilled both exclusion criteria. BL: baseline; DS%: diameter stenosis; FUP: follow-up; LDL-C: low-density lipoprotein cholesterol; non-IRA: non-infarct related artery; PCI: percutaneous coronary intervention; PI: principal investigator; QFR: quantitative flow ratio; RCA: right coronary artery; 3D-QCA: three-dimensional quantitative coronary angiography

added to rosuvastatin on coronary haemodynamics as assessed by QFR and 3D-QCA DS% in non-obstructive non-IRA lesions of AMI patients. The salient findings of this study can be summarised as follows: 1) treatment with the PCSK9 inhibitor alirocumab for 1 year did not result in a statistically significant difference in the number of patients with a QFR increase compared to placebo. The results, after excluding vessels with the least flow limitation (i.e., QFR  $>$ 0.95), suggest that alirocumab may exert a small but significant beneficial

effect on coronary haemodynamics in more flow-limiting disease. 2) Patients on alirocumab showed statistically significant regression of DS% by 1.0% compared to a 1.7% increase with placebo.

#### EFFECTS OF LIPID-LOWERING ON CORONARY HAEMODYNAMICS

Several observational studies suggest an interplay between lipid levels and coronary haemodynamics. Coronary flow reserve

**Table 1. Patient baseline characteristics.**

		N	Alirocumab (N=94)	N	Placebo (N=99)	p-value
Age, years		94	58.7±9.8	99	58.1±8.3	0.65
Sex, female		94	14 (15)	99	22 (22)	0.20
Type of AMI	NSTEMI	94	44 (47)	99	45 (46)	0.89
	STEMI		50 (53)		54 (54)	
Statin/LDL-C status at baseline	- On statin for at least 4 weeks prior to PCI and LDL-C ≥70 mg/dl	94	10 (11)	99	14 (14)	0.52
	- No statin and LDL-C ≥125 mg/dl		84 (89)		85 (86)	
BMI, kg/m <sup>2</sup>		94	27.4±3.8	99	28.4±4.6	0.10
Systolic blood pressure, mmHg		94	125.0±21.1	99	127.1±20.4	0.48
Diastolic blood pressure, mmHg		94	74.4±12.5	99	74.8±14.7	0.84
Heart rate, beats/min		94	80.2±15.5	99	76.2±12.7	0.05
Family history of CAD or CVD		94	28 (30)	99	35 (35)	0.44
Peripheral arterial disease		94	2 (2)	99	3 (3)	1.00
Diabetes mellitus		94	8 (9)	99	10 (10)	0.81
Diabetes type	Type 1	94	2 (2)	99	0 (0)	0.18
	Type 2		6 (6)		10 (10)	
Arterial hypertension		94	40 (43)	99	43 (43)	1.00
Hypercholesterolaemia		94	77 (82)	99	80 (81)	0.86
Active smoker		94	52 (55)	99	44 (44)	0.15
Previous myocardial infarction		94	1 (1)	99	2 (2)	1.00
Previous PCI		94	1 (1)	99	2 (2)	1.00
Premature <sup>a</sup> CAD, cerebral or peripheral vascular disease		94	16 (17)	99	17 (17)	1.00
Non-IRA analysed by QFR/3D-QCA	LAD	133	50 (38)	149	59 (40)	0.56
	LCx		46 (35)		51 (34)	0.97
	RCA		37 (28)		39 (26)	0.94
Laboratory values	Baseline LDL-C, mg/dl	94	155.6±30.3	99	149.2±36.6	0.19
	Haematocrit, l/l	93	0.4±0.0	94	0.4±0.0	0.28
	Haemoglobin, g/dl	94	12.0±5.1	99	12.1±4.9	0.89
	White blood cell count, G/l	93	10.4±3.8	99	10.6±3.7	0.61
	HbA1c, %	87	5.8±0.9	91	5.8±0.9	0.72
	Creatinine, µmol/l	94	76.7±14.7	98	75.4±14.4	0.55
	Peak CK, U/l	91	7,560±1,190	94	491±641	0.06
	Peak hs-troponin, ng/l	92	1,354±3,269	94	726±1,494	0.09

Values are mean±standard deviation (SD) or number (%). p-values are from Student's t-tests or Fisher's exact tests. <sup>a</sup><55 years in males and <60 years in females (first degree relatives). AMI: acute myocardial infarction; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CK: creatine kinase; CVD: cardiovascular disease; hs: high sensitivity; LAD: left anterior descending artery; LCx: left circumflex artery; LDL-C: low-density lipoprotein cholesterol; non-IRA: non-infarct-related artery; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction; TIA: transitory ischaemic attack; 3D-QCA: three-dimensional quantitative coronary angiography

(CFR) was shown to be reduced in patients with hypercholesterolaemia even in the absence of angiographically significant coronary artery disease<sup>2</sup>. Impaired endothelial function and coronary vasodilator capacity related to hypercholesterolaemia have been postulated as mechanistic explanations for this<sup>1</sup>. Lipid-lowering therapy can counteract the negative effects of hypercholesterolaemia on the coronary vasculature by inducing stenosis regression<sup>5</sup>, regression of diffuse disease without focal stenosis, and improving microvascular function, as evidenced by an increase in CFR (in the absence of epicardial stenosis) under statin therapy<sup>6</sup> or LDL-C

apheresis<sup>20</sup>. Further evidence exists from NIRS studies, where an association between LCBI and fractional flow reserve (FFR)<sup>21,22</sup> has been reported.

#### EFFECTS OF LIPID-LOWERING ON QFR

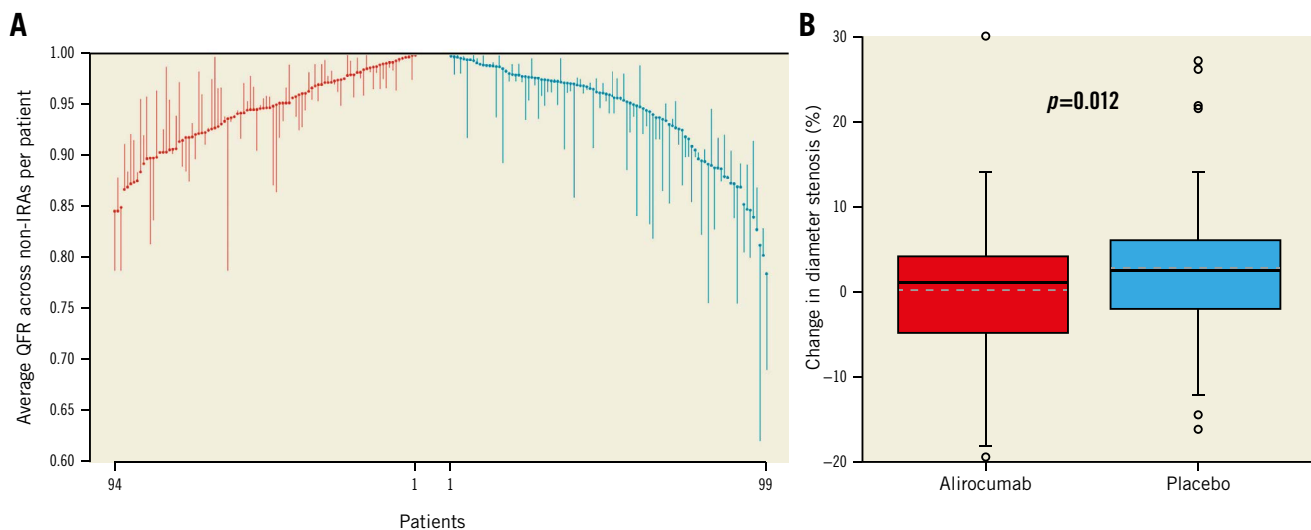
Lipid-lowering therapy may affect QFR by DS% regression<sup>5</sup>, improvement in microvascular function<sup>6</sup>, as well as changes in proximal or distal vessel diameters<sup>23</sup>.

Takenaka et al<sup>12</sup> measured QFR in deferred lesions with >50% stenosis at baseline and at 6- to 18-month follow-up in a cohort

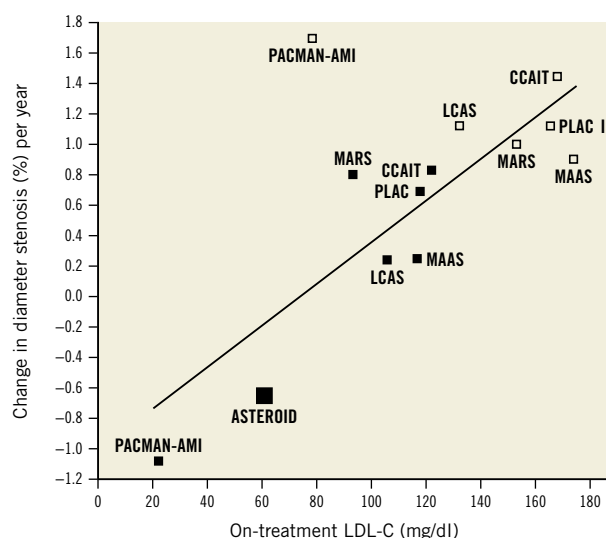
**Table 2. Quantitative flow ratio and 3D-quantitative coronary angiography analysis.**

Primary endpoint All patients	Alirocumab N=94	Placebo N=99	Difference % (95% CI)		OR (95% CI)	p-value			
Patients with QFR increase	50 (53% [43-63])	40 (40% [31-50])	13% (-2 to 28)		1.7 (0.9-3.0)	0.076			
Primary endpoint Patients with QFR ≤0.95	N=57	N=50							
Patients with QFR increase	37 (65% [52-76])	22 (44% [31-58])	20.9% (0.5-41.0)		2.4 (1.1 to 5.2)	0.031			
Secondary endpoints [all patients (vessels)]	Baseline			1-year follow-up		Change between baseline and 1-year follow-up			
	Alirocumab [N=94 (133)]	Placebo [N=99 (149)]	p-value	Alirocumab [N=94 (133)]	Placebo [N=99 (149)]	Alirocumab [N=94 (133)]	Placebo [N=99 (149)]	Difference in change	p-value
QFR	0.96 (0.91-0.98)	0.96 (0.91-0.99)	0.593	0.96 (0.92-0.98)	0.95 (0.89-0.98)	0.00 (-0.02 to 0.02)	-0.01 (-0.03 to -0.01)	-	-
Diameter stenosis, %	36.96±7.88	36.63±8.46	0.742	35.93±9.58	38.33±11.31	-1.03±7.28	1.70±8.27	-2.50 (-4.43 to -0.57)	0.011
Area stenosis, %	50.18±12.69	49.64±12.32	0.715	48.84±14.06	51.50±14.94	-1.35±11.68	1.86±11.74	-2.80 (-5.73 to 0.14)	0.062
Lesion length, mm	18.45±9.94	18.45±10.23	0.999	18.22±9.84	17.92±9.21	-0.23±8.29	-0.53±9.46	0.37 (-1.83 to 2.58)	0.739
Proximal diameter, mm	3.05±0.58	2.85±0.63	0.006	3.01±0.57	2.83±0.57	-0.05±0.31	-0.00±0.28	-0.02 (-0.10 to 0.05)	0.520
Minimum lumen diameter, mm	2.00±0.53	1.82±0.52	0.004	1.99±0.53	1.76±0.56	-0.01±0.26	-0.06±0.28	0.05 (-0.02 to 0.12)	0.130
Distal diameter, mm	2.88±0.68	2.57±0.63	<0.001	2.85±0.95	2.56±0.60	-0.03±0.68	-0.01±0.28	-0.02 (-0.10 to 0.05)	0.520

For the primary endpoint analyses, values are count (%). Patients with a QFR increase are those whose mean change in contrast vessel QFR across vessels is positive. The odds ratio (OR), associated 95% confidence interval (CI) and corresponding p-values were computed using a logistic model. For secondary endpoint analyses, p-values for continuous QFR at baseline are from Wilcoxon tests. For other variables, values are mean (SD) across vessels and differences in change are marginal differences with robustified 95% CIs and p-values computed using repeated mixed-effect models accounting for multiple vessels imaged per patient. Samples sizes correspond to number of patients (vessels). As per substudy design, vessels with diameter stenosis ≤25% were excluded. 3D: three-dimensional; QFR: quantitative flow ratio; SD: standard deviation



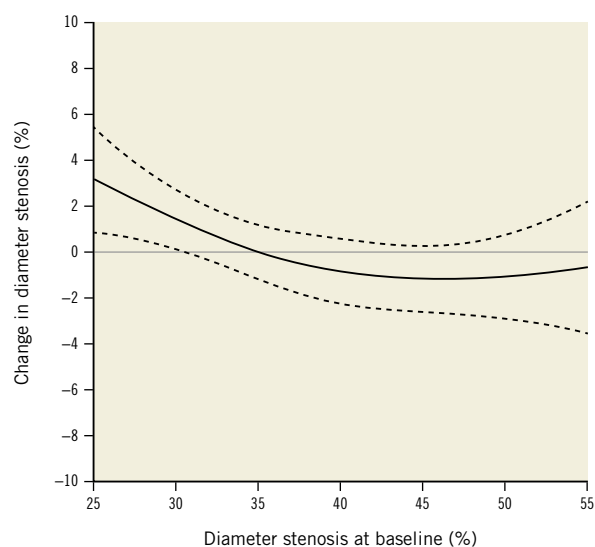
**Figure 2.** Waterfall plot illustrating quantitative flow ratio changes over time and boxplots with change in diameter stenosis (%). *A*) Each vertical line relates to 1 single patient and extends from the baseline quantitative flow ratio (QFR) value (averaged across non-infarct-related arteries [non-IRA] for each patient) to the QFR value at 1 year. Descending lines indicate a reduction in QFR over time, whereas ascending lines indicate an increase in QFR. Baseline values are placed in ascending order (red lines) for the alirocumab group and descending order for the placebo group (blue lines). *B*) Change in diameter stenosis (%) between baseline and follow-up. The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median, and the dashed 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 interquartile ranges from the first and third quartiles. Dots indicate more extreme values. Values are per vessel. The grey dashed line represents the mean for each group.



**Figure 3.** Relationship between change in diameter stenosis % and on-treatment low-density lipoprotein cholesterol. Relationship between change in diameter stenosis (DS%) and on-treatment low-density lipoprotein cholesterol (LDL-C) across 6 trials which investigated the effect of statins versus placebo: the Multicentre Anti Atheroma Study (MAAS)<sup>25</sup>, the Canadian Coronary Atherosclerosis Intervention Study (CCAIT)<sup>15</sup>, the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)<sup>24</sup>, the Lipoprotein and Coronary Atherosclerosis Study (LCAS)<sup>16</sup>, the Monitored Atherosclerosis Regression Study (MARS)<sup>18</sup>, and A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID)<sup>5</sup> and the PACMAN-AMI QFR substudy which investigated the effects of alirocumab and rosuvastatin versus rosuvastatin alone. The previous trials assessed DS% by 2D-quantitative coronary angiography (QCA), whereas the PACMAN-AMI QFR substudy assessed DS% by 3D-QCA. Solid squares represent active treatment groups and empty squares represent placebo groups. The regression analysis based on 7 publications was weighted by the number of patients in each trial. Regression analysis:  $\beta=0.013$ ;  $p<0.001$ . QFR: quantitative flow ratio; 2D: two-dimensional; 3D: three-dimensional

of stable patients receiving standard lipid-lowering therapy with statins (and ezetimibe if clinically indicated). In patients with increased QFR, they observed lower LDL-C levels than in those with decreased QFR. On-treatment LDL-C was identified as an independent predictor of QFR improvement.

In line with this previous non-randomised investigation, the QFR changes in our study were very small. We only observed a trend towards a significantly higher number of patients with a QFR increase when there was more intensive lipid-lowering over the entire spectrum of baseline QFR. This is likely related to the small degree of flow limitation at baseline, which was substantially higher (median QFR 0.83) in the study by Takenaka et al<sup>12</sup>. Accordingly, the results of our sensitivity analysis excluding vessels with the least flow limitation (i.e.,  $>0.95$ ) showed a significant difference in the primary endpoint favouring alirocumab. This may suggest that PCSK9 inhibition potentially induces a greater



**Figure 4.** Change in diameter stenosis according to baseline diameter stenosis. Absolute change in diameter stenosis (DS%) between baseline and follow-up according to DS% at baseline. The solid line is the fitted line from a spline mixed-effect model and the dashed lines show the 95% confidence intervals. The x-axis was cropped at 55% due to the small number of values.

improvement in coronary haemodynamics across the flow-limiting disease spectrum. This warrants further investigation in the future, i.e., in patients with flow-limiting stenoses. Alternatively, microvascular compensation may blunt the effect of PCSK9 inhibition in lower grade stenoses.

#### EFFECTS OF LIPID-LOWERING ON DS%

Although previous QCA trials with statins have consistently shown more patients with stenosis regression on statins than on placebo, on average, patients continued to have a progression of atherosclerosis<sup>15,16,18,24,25</sup>. ASTEROID was the first QCA study to show a reduction in DS% by 1.3% after 24 months of treatment with rosuvastatin 40 mg<sup>5</sup>. In general, comparisons of the PACMAN-AMI QFR substudy with previous QCA trials are limited by the inherent differences in 2D- versus 3D-QCA<sup>26</sup>. However, it is noteworthy, that alirocumab in combination with rosuvastatin reduced DS% after 1 year by almost the same amount as rosuvastatin 40 mg after 2 years in ASTEROID. We also observed an association between change in DS% and on-treatment LDL-C as shown in **Supplementary Figure 2**. These results are conceptually consistent with a previous summary of major QCA trials on statins, showing a positive linear relationship between change in DS% and on-treatment LDL-C<sup>5</sup>. The reproduced regression analysis updated by the current study findings is shown in **Figure 3**. Thus, in summary, the available evidence suggests, that the more intense the lipid-lowering, the higher the number of vessels with a decrease in DS% and the greater the magnitude of the effect.

Previous studies reported lesions with higher DS%<sup>18,19</sup> according to QCA, as well as plaque burden according to IVUS<sup>27</sup>, to be more responsive to lipid-lowering therapy. Our data support this



concept, as shown in **Figure 4**. Furthermore, we observed a trend towards more pronounced DS% reduction with alirocumab versus placebo with a higher degree of baseline stenosis, i.e., the raw difference in DS% between treatment groups incrementally increased in favour of alirocumab with higher baseline stenosis, reaching  $-3.98\%$  with DS%  $>45\%$  at baseline (**Supplementary Figure 3**). This suggests, that alirocumab might induce a more pronounced stenosis regression in more obstructive lesions.

### POTENTIAL CLINICAL IMPLICATIONS OF THE PACMAN-AMI QFR SUBSTUDY

PCSK9 inhibitors have been shown to reduce cardiovascular events<sup>28,29</sup>. Although we observed significant associations between QFR and DS% with the extent of atherosclerosis in intracoronary imaging (PAV and maxLCBI4 mm), our trial suggests that, in patients with non-obstructive lesions, there seems to be no meaningful improvement of coronary haemodynamics or reduction in angiographic DS%, and thus, PCSK9 inhibitors may rather act through plaque stabilisation than clinically relevant improvement in coronary physiology. Accordingly, these were the PACMAN-AMI main trial findings, showing plaque stabilisation with a 59% increase in minimum fibrous cap thickness (i.e., baseline: 107.0  $\mu\text{m}$ , follow-up: 169.6  $\mu\text{m}$ ), a decrease of lipid pool by 30% (i.e., baseline: 260.6 units, follow-up: 181.2 units) and a 5% relative reduction in plaque burden (i.e., baseline: 40.9%, follow-up 38.8%)<sup>7</sup>.

### Limitations

The results of this study must be discussed in the light of several limitations. 1) The study population consisted of 64% of the enrolled patients. For the majority of patients (i.e., 44 of 70 [63%]), this was related to the absence of any non-IRA with 3D-QCA DS%  $>25\%$ . Furthermore, to be able to follow small QFR changes over time, only the angiographic projections that met the highest quality standards at baseline and follow-up (e.g., 2 projections with optimal contrast and angulation, no overlap, no foreshortening) could be considered, and these quality criteria may have been applied more strictly in our analysis than in clinical settings or one-timepoint QFR studies for decision-making on ischaemia according to QFR (i.e.,  $\leq 0.80$  vs  $>0.80$ ). Furthermore, QFR only became available at Bern University Hospital in April 2019, whereas trial recruitment started in May 2017. Some of the technical issues with QFR (e.g., missing isocentre calibration, appropriate follow-up projections) were only detected (and addressed immediately) during dedicated data analysis from April 2019 onwards. However, we have compared the baseline characteristics of patients included versus those excluded from the QFR substudy and have found no differences in meaningful variables to affect the investigated outcomes. Further, among the included patients, baseline characteristics of the placebo and alirocumab groups were well balanced, so that, besides a limited sample size, the substudy as such may be regarded as valid. 2) By study design, patients with obstructive lesions with DS%  $\geq 50\%$  by visual estimation were excluded

from the PACMAN-AMI trial. Since lesions with higher DS% seem to regress more with lipid-lowering therapy<sup>18,19</sup>, it is possible that PCSK9 inhibitors would induce greater DS% regression in more stenotic lesions and consequently larger changes in coronary haemodynamics. Also, from a clinical perspective, the primary interest would have been to examine the effects of PCSK9 inhibitors on obstructive/flow-limiting stenoses; however, the feasibility of such a study would be limited in the presence of current guidelines mandating interventional treatment of these stenoses. For feasibility reasons, we therefore investigated non-obstructive lesions. Further, whereas interventional treatment of obstructive/flow-limiting stenoses is mandated by current guidelines, less is known about the detailed effects of medical therapy on non-obstructive non-culprit lesions of AMI patients. Therefore, aiming at mechanistic insights of PCSK9 inhibitors, an important class of lesions was the target of the current investigation. 3) The study was limited to 1 year. 4) Vessels in the alirocumab arm were larger than in the placebo arm, which must be interpreted as a chance finding, since QFR/3D-QCA analysts were blinded to treatment allocation and intracoronary imaging findings. Although our main endpoints were QFR/3D-QCA changes over time, the effect of vessel size at baseline on the overall study findings might therefore be minimal but cannot be excluded as confounding. 5) Since QFR is based on the angiographic lumenogram, we could not assess the impact of positive remodelling. 6) We did not investigate the direct metabolic effects of PCSK9 inhibition on the coronary endothelium, which warrants investigation in future studies.

### Conclusions

In this prespecified randomised controlled trial substudy, treatment of AMI patients with the PCSK9 inhibitor alirocumab added to rosuvastatin for 1 year resulted in a significant 1.0% regression of 3D-QCA DS% compared to an increase of 1.7% with placebo. No difference in the change in coronary physiology was observed between treatment groups. However, alirocumab- as compared to placebo-treated patients with a baseline QFR  $\leq 0.95$  more frequently showed improvement in coronary haemodynamics.

### Impact on daily practice

Treatment of non-obstructive lesions from acute myocardial infarction (AMI) patients with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, alirocumab, as compared to placebo on top of rosuvastatin for 1 year leads to significant 1.0% angiographic stenosis regression. This does not translate into significant improvement in coronary physiology as assessed by quantitative flow ratio. Thus, PCSK9 inhibitors may rather act through plaque stabilisation than through improvement of coronary haemodynamics.

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## Conflict of interest statement

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## Supplementary data

**Supplementary Table 1.** Baseline characteristics and laboratory values of included vs excluded patients.

**Supplementary Table 2.** Medication at 1 year.

**Supplementary Table 3.** Quantitative flow ratio and 3D-quantitative coronary angiography analysis in patients with QFR  $\leq 0.95$ .

**Supplementary Figure 1.** Quantitative flow ratio and diameter stenosis at baseline and 1 year.

**Supplementary Figure 2.** Change in diameter stenosis according to on-treatment low-density lipoprotein cholesterol.

**Supplementary Figure 3.** Between-group differences in changes in diameter stenosis according to baseline diameter stenosis.

**Supplementary Figure 4.** Association between QFR and DS% with PAV (IVUS).

**Supplementary Figure 5.** Association between QFR and DS% with maxLCBI4 mm (NIRS).

**Supplementary Figure 6.** Association between QFR and DS% with minFCT (OCT).

**Supplementary Figure 7.** Association between change in DS% and change in intracoronary imaging endpoints.

The supplementary data are published online at:

<https://eurointervention.pcronline.com/>

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## Supplementary data

**Supplementary Table 1. Baseline characteristics and laboratory values of included vs excluded patients.**

Baseline Characteristics	N	Excluded (N=107)	N	Included (N=193)	p-value
Age (years)	107	58.8 ±10.8	193	58.4 ±9.0	0.73
Sex (female)	106	20 (19%)	193	36 (19%)	>0.99
Type of AMI, n (%)					
NSTEMI	107	53 (50%)	193	89 (46%)	0.63
STEMI		54 (50%)		104 (54%)	
Statin/LDL-C status at baseline, n (%)					
- On statin for at least 4 weeks prior to PCI and LDL-C ≥70 mg/dl	107	12 (11%)	193	24 (12%)	0.85
- No statin and LDL-C ≥125 mg/dl		95 (89%)		69 (88%)	
BMI (kg/m <sup>2</sup> )	105	27.5 ±4.4	193	27.9 ±4.3	0.41
Systolic blood pressure (mmHg)	105	129.2 ±22.9	193	126.1 ±20.7	0.23
Diastolic blood pressure (mmHg)	105	78.1 ±15.6	193	74.6 ±13.6	0.046
Heart rate (/min)	105	78.8 ±13.9	193	78.1 ±14.2	0.72
Family history of CAD or CVD, n (%)	106	35 (33%)	193	63 (33%)	>0.99
Peripheral arterial disease, n (%)	106	1 (0.9%)	193	5 (3%)	0.43
Diabetes mellitus, n (%)	106	13 (12%)	193	18 (9%)	0.44
Diabetes type, n (%)					
Type 1	13	0 (0%)	18	2 (1%)	0.50
Type 2		13 (12%)		8 (8%)	
Arterial hypertension, n (%)	106	47 (44%)	193	83 (43%)	0.90
Hypercholesterolemia, n (%)	106	81 (76%)	193	157 (81%)	0.30
Active smoker, n (%)	106	46 (43%)	193	96 (50%)	0.28
Previous myocardial infarction, n (%)	106	4 (4%)	193	3 (2%)	0.25
Previous PCI, n (%)	106	4 (4%)	193	3 (2%)	0.25
Previous CABG, n (%)	106	0 (0%)	193	0 (0%)	-
Premature CAD <sup>a</sup> , cerebral or peripheral vascular disease, n (%)	106	16 (15%)	193	33 (17%)	0.74
History of congestive heart failure, n (%)	106	0 (0%)	193	0 (0%)	-
History of stroke, n (%)	106	2 (2%)	193	1 (0.5%)	0.29
History of TIA, n (%)	106	0 (0%)	193	4 (2%)	0.30
<b>Laboratory Values</b>					
Baseline LDL-C (mg/dL)	105	152.4 ±34.1	193	152.4 ±33.7	0.99
HbA1c (%)	90	5.8 ±1.1	178	5.8 ±0.9	0.84
Creatinine (μmol/l)	105	75.2 ±13.8	192	76.0 ±14.5	0.64
CK (U/L)	102	621 ±988	185	623 ±958	0.99
hs-Troponine (ng/l)	104	1302 ±3222	186	1037 ±2545	0.44

Values are mean±standard deviation (SD) or number (%). P-values are from Student t-tests or Fisher's exact tests. a) <55 years in males and <60 years in females (first degree relatives). AMI = acute myocardial infarction, BMI = body mass index, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CK = creatine kinase, CVD = cardiovascular disease, hs= high sensitivity, LDL-C = low-density lipoprotein cholesterol, NSTEMI = non-ST-elevation myocardial infarction, ULN = upper limit of norm. PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction, TIA = transitory ischemic attack.

**Supplementary Table 2. Medication at 1 year.**

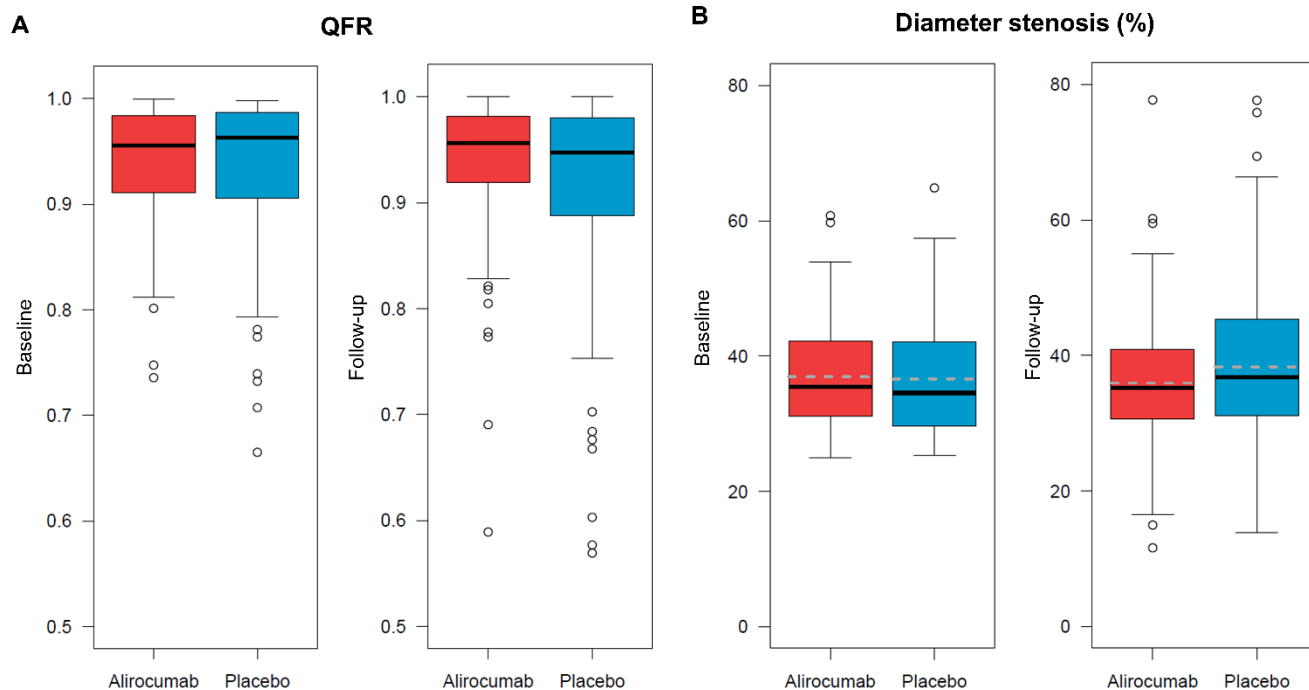
	N	Alirocumab (N=94)	N	Placebo (N=99)	p-value
Statin, n (%)	94	92 (98%)	99	98 (99%)	0.61
Statin type, n (%)					
Atorvastatin	92	1 (1%)	98	1 (1%)	0.87
Rosuvastatin		90 (96%)		96 (97%)	
Ezetimibe, n (%)	94	1 (1%)	99	3 (3%)	0.62
Aspirin, n (%)	94	90 (96%)	99	98 (99%)	0.20
Clopidogrel, n (%)	94	7 (7%)	99	6 (6%)	0.78
Ticagrelor, n (%)	94	60 (64%)	99	70 (71%)	0.36
Prasugrel, n (%)	94	14 (15%)	99	15 (15%)	1.00
Novel oral anticoagulant, n (%)	94	5 (5%)	99	3 (3%)	0.49
ACE inhibitor, n (%)	94	52 (55%)	99	56 (57%)	0.89
ATII antagonist, n (%)	94	25 (27%)	99	24 (24%)	0.74
Betablocker, n (%)	94	77 (82%)	99	76 (77%)	0.48
Calcium antagonist, n (%)	94	10 (11%)	99	13 (13%)	0.66
Oral antidiabetics, n (%)	94	8 (8.5%)	99	9 (9.1%)	>0.99
Insulin, n (%)	94	4 (4%)	99	2 (2%)	0.44

Values are mean±standard deviation (SD) or number (%). P-values are from Fisher's exact tests. ACE = angiotensin converting enzyme, ATII = angiotensin II receptor antagonist.

**Supplementary Table 3. Quantitative flow ratio and 3D-quantitative coronary angiography analysis in patients with QFR ≤0.95.**

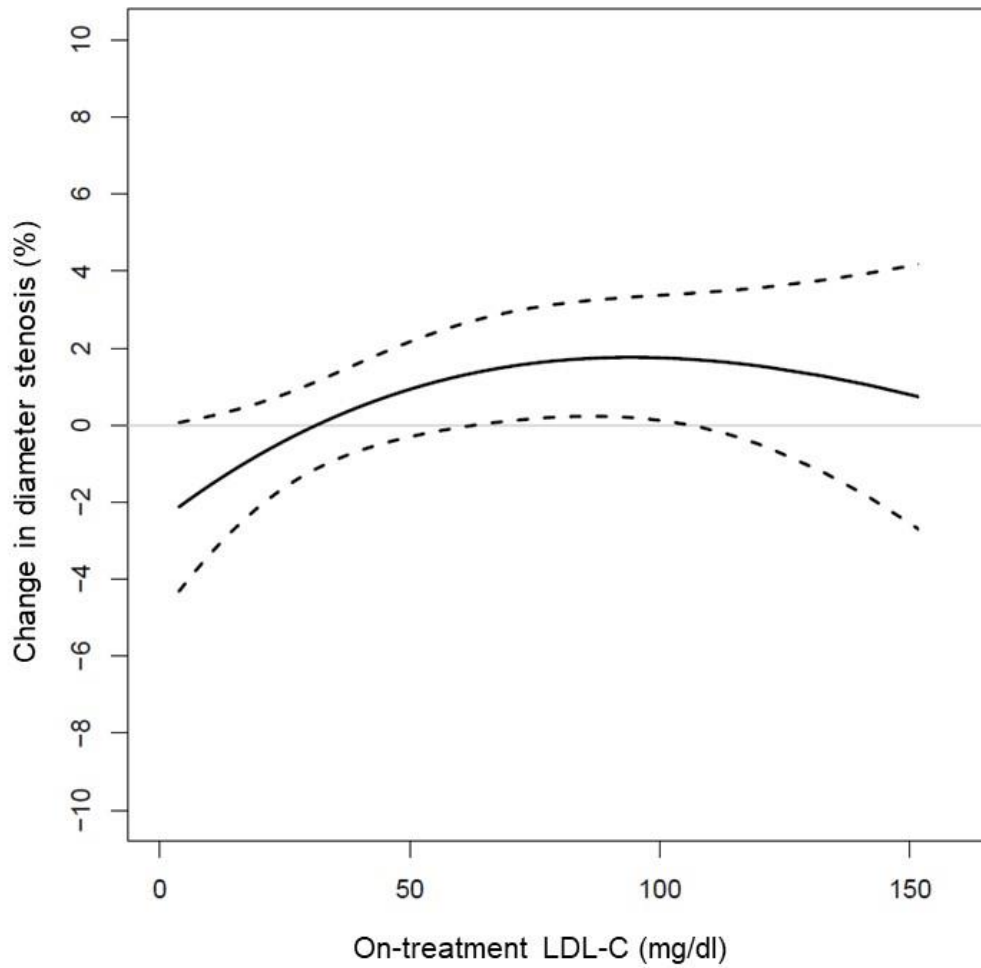
[Number of patients (vessels)]	Baseline			1-Year Follow-up		Change between baseline and 1-Year Follow-up			
	Alirocumab [N=57 (64)]	Placebo [N=50 (60)]	p-value	Alirocumab [N=57 (64)]	Placebo [N=50 (60)]	Alirocumab [N=57 (64)]	Placebo [N=50 (60)]	Difference in change	p-value
QFR	0.91 [0.88-0.93]	0.89 [0.83-0.92]	0.062	0.92 [0.87-0.95]	0.87 [0.82-0.92]	0.01 [-0.02-0.05]	-0.01 [-0.06-0.03]	-	-
Diameter stenosis, %	41.18±7.57	43.60±7.82	0.082	39.65±9.96	46.34±10.77	-1.53±7.63	2.74±9.67	-4.11 (-7.41 to -0.80)	0.015
Area stenosis, %	57.30±10.33	58.97±10.30	0.369	54.17±13.34	61.21±13.20	-3.13±10.62	2.24±12.47	-5.10 (-9.44 to -0.75)	0.022
Lesion length, mm	21.10±10.45	21.49±11.97	0.834	20.29±9.52	20.19±9.74	-0.77±9.05	-1.30±11.41	0.89 (-2.87 to 4.65)	0.640
Proximal diameter, mm	3.07±0.56	2.73±0.53	0.001	3.04±0.60	2.70±0.47	-0.03±0.31	-0.03±0.28	0.07 (-0.19 to 0.32)	0.611
Minimal lumen diameter, mm	1.82±0.46	1.53±0.35	<0.001	1.84±0.50	1.45±0.42	0.02±0.24	-0.08±0.30	0.10 (0.00 to 0.20)	0.050
Distal diameter, mm	2.77±0.61	2.40±0.54	0.001	2.82±1.16	2.39±0.50	0.06±0.91	-0.01±0.24	-0.00 (-0.10 to 0.10)	0.969

For QFR, values are median [interquartile range (IQR)] and p-values at baseline are from Wilcoxon tests. For other variables, values are mean (SD) across vessels and differences in change are marginal differences with robustified 95% confidence intervals and p-values computed using repeated mixed-effect models accounting for multiple vessels imaged per patient. Samples sizes correspond to number of patients (vessels). As per substudy design, vessels with diameter stenosis ≤25% were excluded. QFR = Quantitative Flow Ratio.



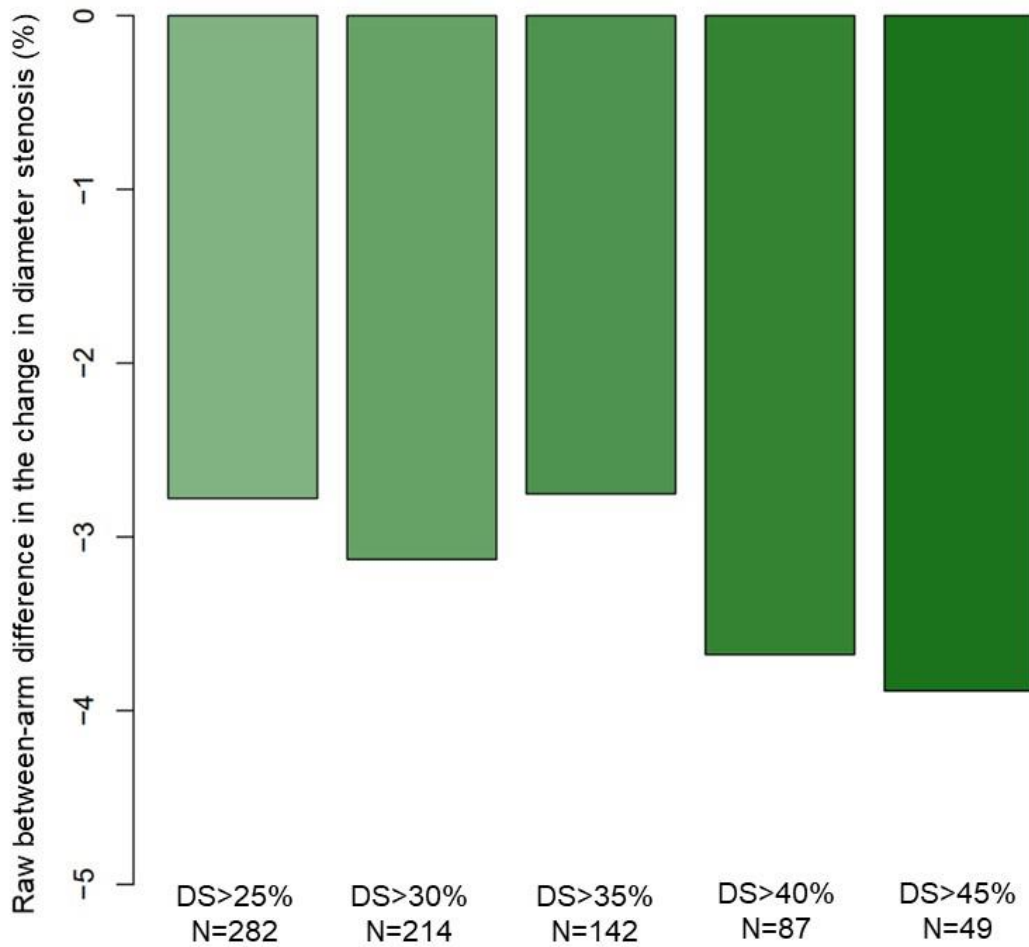
**Supplementary Figure 1.** Quantitative flow ratio and diameter stenosis at baseline and 1 year. The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median and the dashed line indicating the mean. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. Dots indicate more extreme values. Values are per vessel. The grey dashed line represents the mean for each group. QFR = Quantitative Flow Ratio.





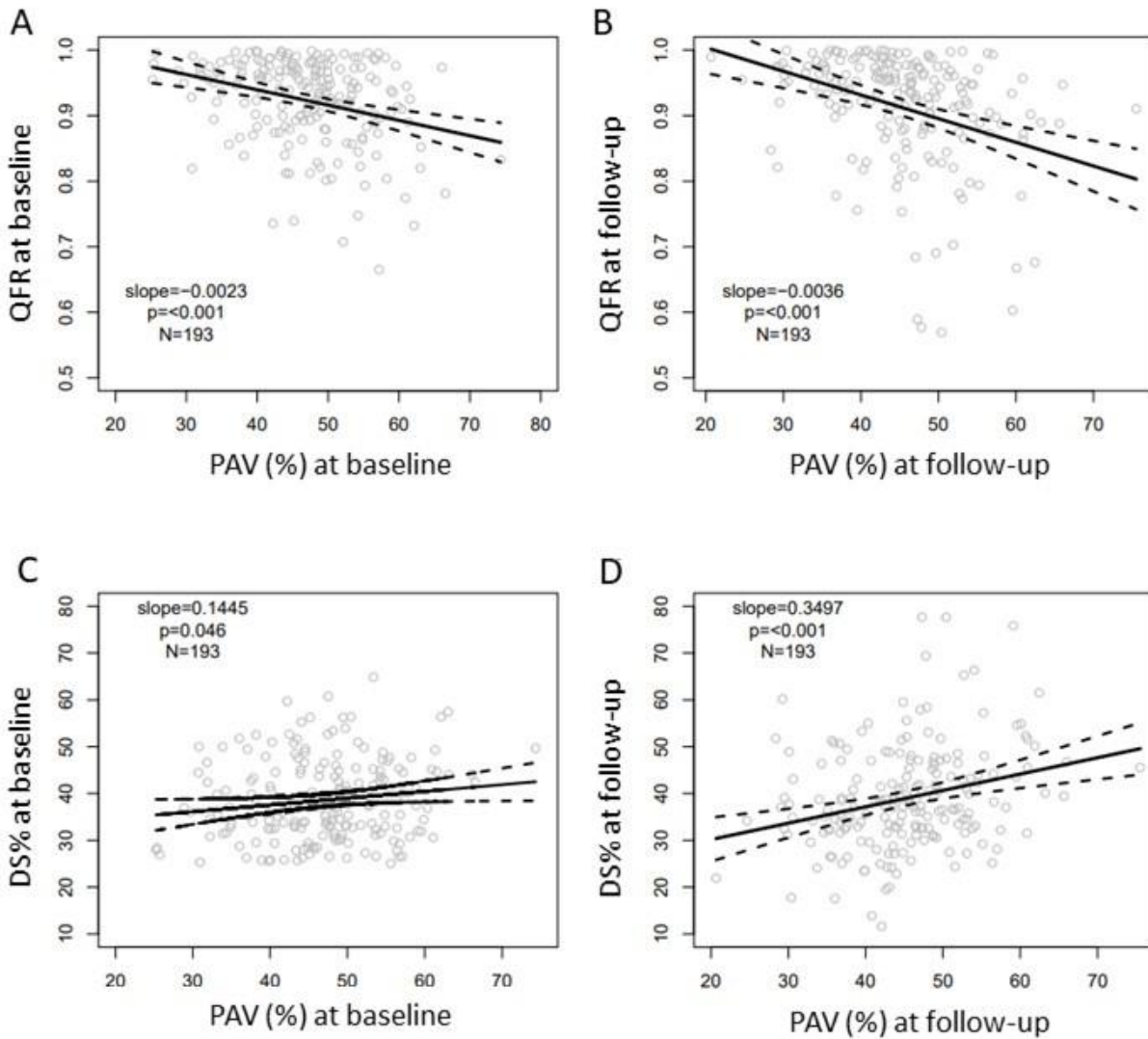
**Supplementary Figure 2.** Change in diameter stenosis according to on-treatment low-density lipoprotein cholesterol.

Change in diameter stenosis according to on-treatment low-density lipoprotein cholesterol (LDL-C). The solid line is the fitted line from a spline mixed-effect model and the dashed lines show the 95% confidence intervals. The x-axis was cropped at LDL-C = 150mg/dL due to the small number of values.



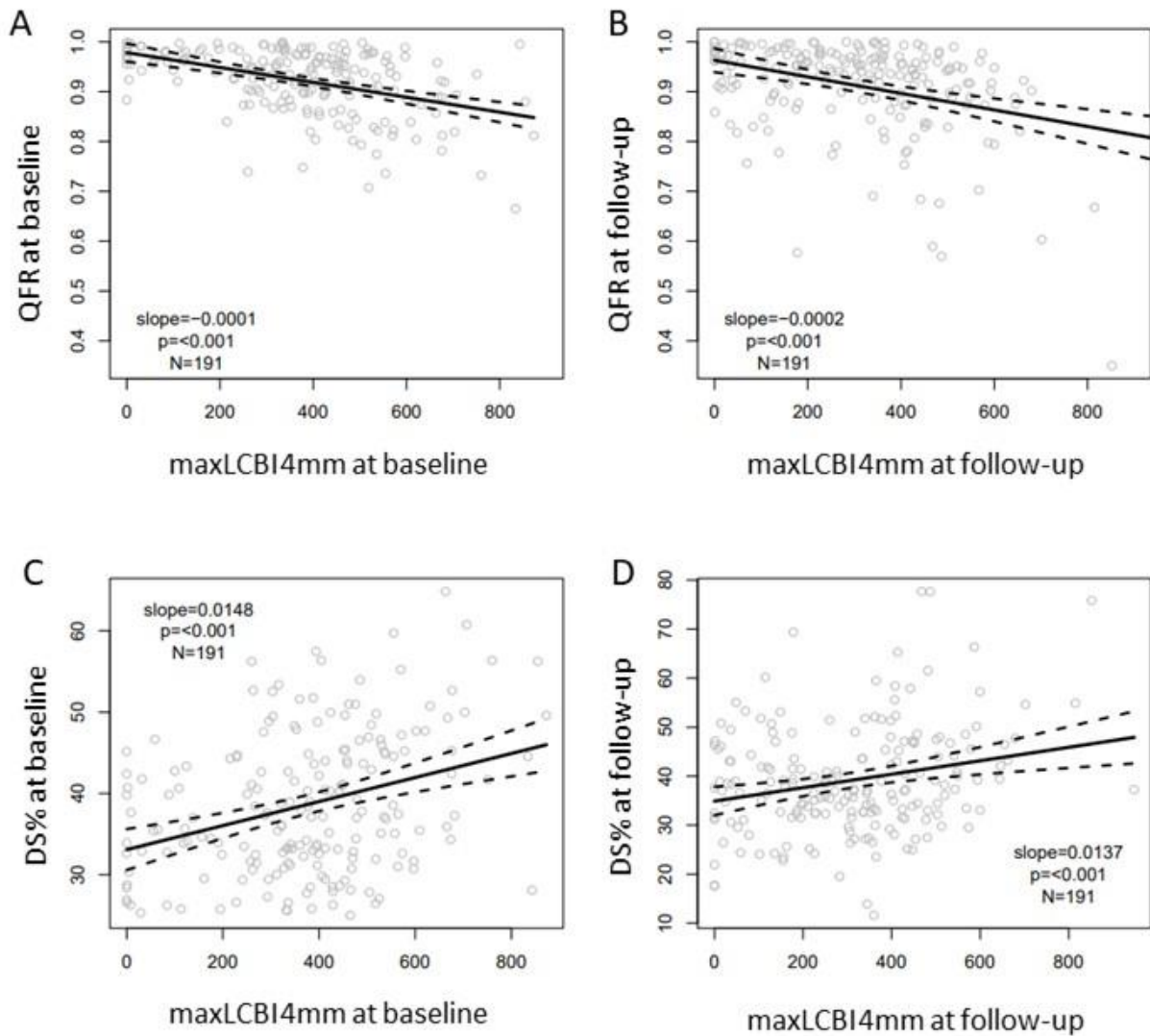
**Supplementary Figure 3.** Between-group differences in changes in diameter stenosis according to baseline diameter stenosis.

Raw between-arm difference (alirocumab vs. placebo) in the change in diameter stenosis (DS%) between baseline and follow-up according to DS% >25% (=all vessels), >30%, >40%, and >45% at baseline (mean across both arms).

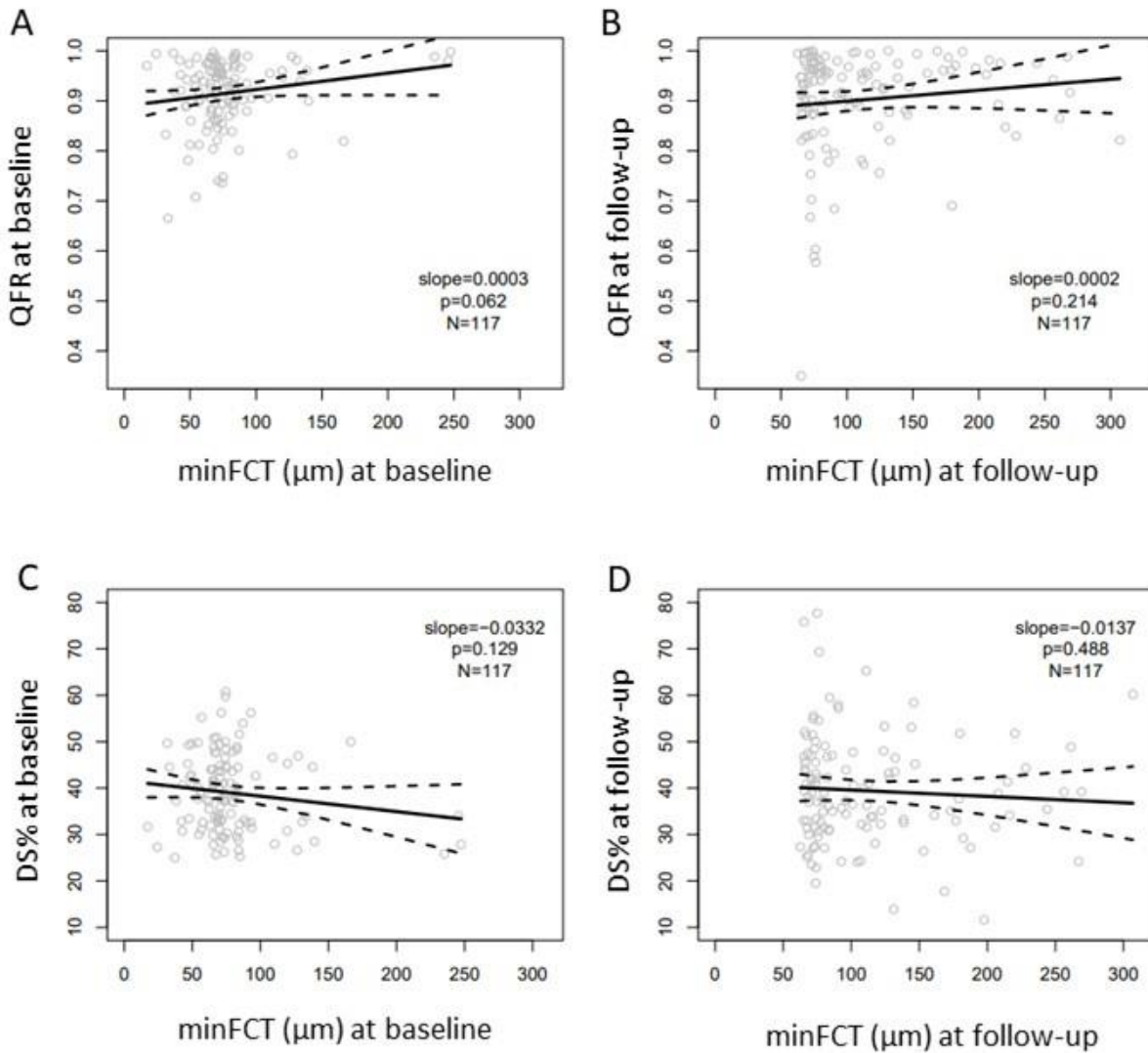


**Supplementary Figure 4.** Association between QFR and DS% with PAV (IVUS).

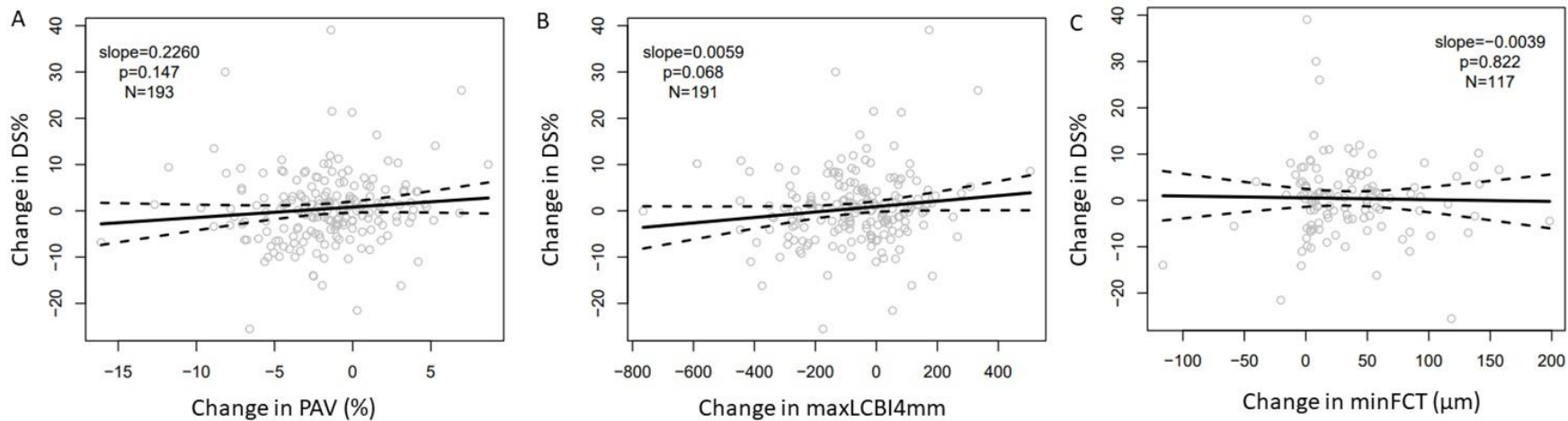
Association between Quantitative Flow Ratio (QFR) (A) and diameter stenosis (DS%) (C) with percent atheroma volume (PAV) according to intravascular ultrasound (IVUS) at baseline and follow-up (B, D). Lines are quantile regression lines (QFR) or linear regressions (DS%) and associated 95% confidence intervals.



**Supplementary Figure 5.** Association between QFR and DS% with maxLCBI4 mm (NIRS). Association between Quantitative Flow Ratio (QFR) (A) and diameter stenosis (DS%) (C) with maximum lipid core burden index (maxLCBI4mm) according to near infrared spectroscopy (NIRS) at baseline and follow-up (B, D). Lines are quantile regression lines (QFR) or linear regressions (DS%) and associated 95% confidence intervals.



**Supplementary Figure 6.** Association between QFR and DS% with minFCT (OCT). Association between Quantitative Flow Ratio (QFR) (A) and diameter stenosis (DS%) (C) with minimum fibrous cap thickness (minFCT) according to optical coherence tomography (OCT) at baseline and follow-up (B, D). Lines are quantile regression lines (QFR) or linear regressions (DS%) and associated 95% confidence intervals.



**Supplementary Figure 7.** Association between change in DS% and change in intracoronary imaging endpoints.

Association between change in diameter stenosis (DS%) and change in A) percent atheroma volume (PAV), B) change in maximum lipid core burden index 4mm (maxLCBI4mm), and C) change in minimum fibrous cap thickness (minFCT) from baseline to follow-up. Lines are linear regressions and associated 95% confidence intervals.