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FULL RESEARCH PAPER
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Intake of high-intensity statin after acute myocardial infarction assessed by direct drug concentration measurement: association with LDL-C response and coronary plaque modifications in the PACMAN-AMI trial

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Background In real-world settings, adherence to preventive cardiovascular medications is often suboptimal. However, in clinical trials, adherence is crucial for ensuring the validity and generalizability of study results, and their clinical implications.

Methods and Aims This pre-specified sub-study of the PACMAN-AMI randomized controlled trial investigated the intake of protocol-mandated high-intensity statin background therapy in patients with acute myocardial infarction (AMI), as assessed by direct measurement of rosuvastatin or atorvastatin blood concentrations at 4 and 52 weeks using liquid chromatography tandem mass spectrometry analysis. We evaluated the correlation between statin intake and changes in low-density lipoprotein cholesterol (LDL-C) levels, as well as multi-modality intracoronary imaging endpoints.

Results Among 300 enrolled patients, four (1.3%) reported statin intolerance within 52 weeks. Of 255 patients with completed imaging follow-up and available blood samples, 3 (1.2%) and 5 (2.0%) had no detectable statin concentrations at 4 and 52 weeks, respectively, and were classified as non-adherent. At 52 weeks, adherent patients demonstrated numerically greater

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reductions in LDL-C (−2.73 vs. +0.07 mmol/L), intravascular ultrasound-assessed per cent atheroma volume (−1.54% vs. −0.15%), and near-infrared spectroscopy-assessed maximum lipid core burden index (−60.6 vs. 0.0), with a higher increase in optical coherence tomography-assessed fibrous cap thickness (+48.53 vs. +7.98 μm). Sensitivity analysis excluding non-adherent patients confirmed the robustness of the main study results.

Conclusion In the PACMAN-AMI trial, intake of high-intensity statin at 4 and 52 weeks post-AMI was excellent, with minimal statin intolerance. These findings, along with the consistent sensitivity analysis, affirm the validity and reliability of the primary study conclusions.

Trial Registration ClinicalTrials.gov: NCT03067844

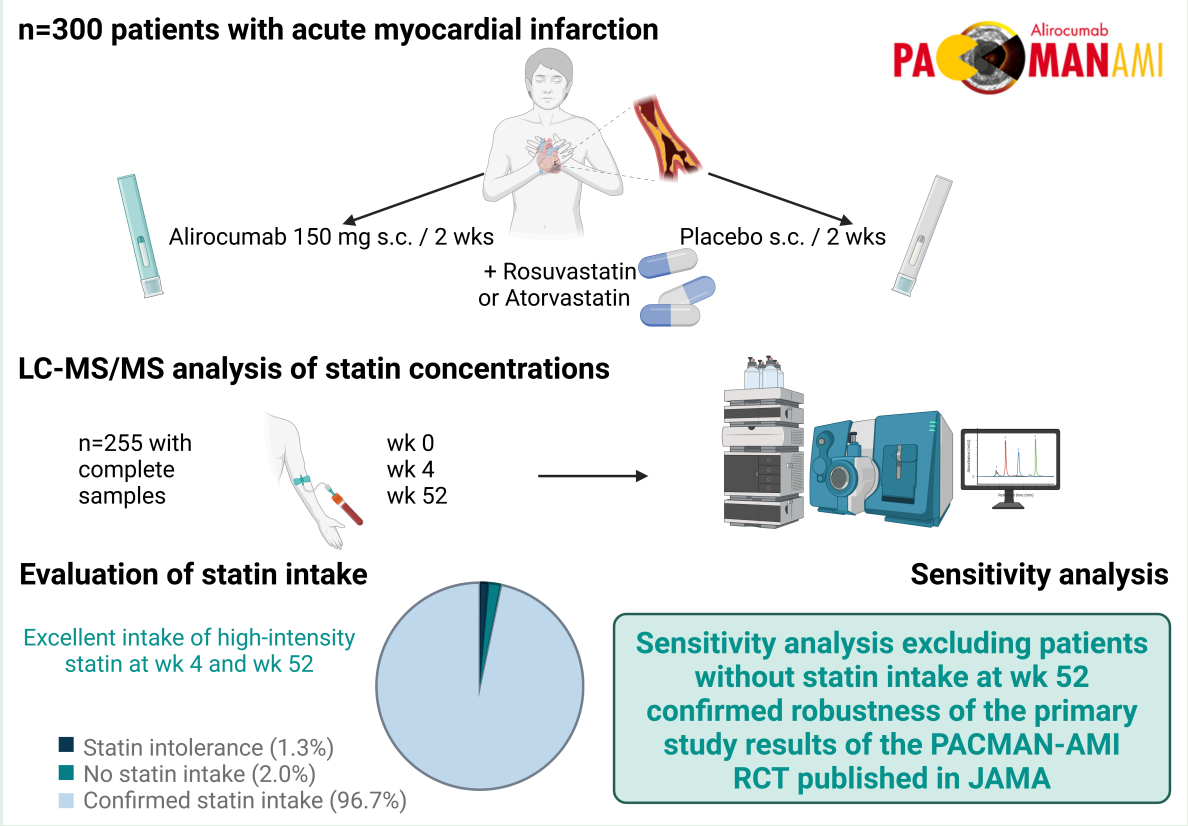
Lay Summary Statins are essential medications after a heart attack, helping to lower levels of harmful LDL cholesterol, slow the progression of atherosclerosis, and reduce the risk of future cardiovascular events. In clinical trials, it is crucial that participants take their prescribed therapies consistently to ensure the reliability and relevance of the study results.

This analysis from the PACMAN-AMI trial evaluated how well patients adhered to high-intensity statin therapy during the first year after a heart attack. Statin use was assessed by measuring drug levels in the blood. The findings were reassuring: almost all patients were taking their medication as prescribed, and side effects were very rare.

Patients who were adherent showed greater reductions in LDL cholesterol and more favourable changes in coronary artery structure, as assessed by advanced intracoronary imaging techniques. These findings strengthen the validity of the PACMAN-AMI trial's primary conclusions, published in *JAMA*.

Measuring statin levels in the blood may help identify patients who appear not to respond to treatment, even though they are supposedly taking intensive cholesterol-lowering therapy.

Graphical Abstract



Keywords Adherence • Intolerance • PCSK9 inhibition • Statin • Liquid chromatography tandem mass spectrometry

Introduction

Adherence to medications refers to the extent to which individuals consistently and accurately follow their prescribed drug regimen for a medical condition.[1] Adherence plays a significant role in achieving the intended health outcomes, reducing the risk of complications, and maintaining a good quality of life for individuals with chronic conditions, positively impacting health care costs.[2]

Despite the well-established benefits of multiple secondary prevention measures, including high-intensity lipid-lowering therapy,[3] adherence to preventive lifelong medications is generally suboptimal. Observational studies have commonly reported adherence rates of 50–70% across different chronic conditions and populations.[4,5] Furthermore, published real-world evidence suggests that adherence to secondary prevention medications, including statins, declines over time after acute myocardial infarction (AMI).[6] Factors, such as decreased perception of risk, patient or physician beliefs, complexity of the medication regimen, and drug side effects, may contribute to lower adherence in the years following AMI, as well as in chronic conditions such as arterial hypertension.[7]

Drug adherence in a randomized controlled trial (RCT) is an important factor that can affect the validity and generalizability of study findings.[8] High levels of drug adherence in the trial enhance both the internal and external validity and reliability of the study results, whereas poor drug adherence can lead to inaccurate results and may affect the ability to draw meaningful conclusions from the trial, including translation into future clinical decision making.[9] In clinical research, a commonly used benchmark for adherence is often set as intake of around 80% or higher of the doses as predefined in the protocol.[8] However, adherence levels can be affected by various factors, including the complexity of the medication regimen, duration of the trial, severity of the disease being treated, side effects of the medication, and support provided to participants to help them adhere to the treatment.

Methods to assess drug adherence can be classified as direct or indirect.[10] Indirect methods include physician's clinical judgement, self-report patient questionnaires, pill counts, pharmacy registry data, or electronic medication event monitoring systems. Although frequently used, indirect methods do not prove actual drug intake and tend to overestimate adherence rates.[11] Direct methods, in contrast, including directly observed therapy, measurement of drug/metabolite concentrations or other biologic markers in body fluids, or even ingestible electronic sensors,[12] prove actual intake of the medication, but they are time-consuming, costly, and rarely performed in routine practice.

In the present sub-study of the PACMAN-AMI randomized controlled trial, we aimed to evaluate the intake of protocol-defined high-intensity statin background therapy in patients with AMI by direct measurement of rosuvastatin or atorvastatin blood concentrations at 4 and 52 weeks using liquid chromatography tandem mass spectrometry (LC-MS/MS), and to explore the correlation of statin intake at 52 weeks with the extent of LDL-C lowering and intracoronary imaging endpoints.

Methods

PACMAN-AMI trial design

The PACMAN-AMI trial, of which the design details and primary findings have been previously published,[13,14] was a European multi-centre randomized, double-blind, placebo-controlled study that aimed to assess the impact of intensive lipid-lowering therapy using alirocumab, in addition to high-intensity statin therapy with rosuvastatin or atorvastatin, on coronary atherosclerosis in patients who initially presented with AMI and underwent percutaneous coronary intervention (PCI) of the culprit lesion only. The evaluation of coronary atherosclerosis was conducted at baseline and 52-week follow-up through multi-modality intracoronary imaging, which included intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT).

Patients were deemed eligible for the trial according to the following criteria: (i) having two non-infarct-related arteries (non-IRA) with non-obstructive atherosclerotic disease, with visual estimates of angiographic diameter stenosis ranging from >20% to <50% and suitable for intracoronary imaging; (ii) LDL-C levels ≥3.23 mmol/L if patients were not on statin treatment or had not been on a stable statin regimen (≥4 weeks) at the time of screening; or LDL-C levels ≥1.81 mmol/L if patients were on an unchanged statin treatment for ≥4 weeks before enrolling in the study.

A total of 300 patients were enrolled in the trial, and they were randomly assigned in a 1:1 ratio to receive either subcutaneous alirocumab 150 mg every 2 weeks or a matching placebo. At both baseline and the 1-year follow-up, all patients underwent coronary angiography and intravascular imaging as a part of the assessment process.

PACMAN-AMI sub-study monitoring intake of background statin treatment

In the present pre-specified sub-study, we assessed background statin treatment by LC-MS/MS analysis of rosuvastatin and atorvastatin blood concentrations at the 4- and 52-week follow-up visits.[14] For this analysis, all 300 patients enrolled across the nine PACMAN-AMI study sites were considered eligible. We excluded patients who did not complete 52-week follow-up or serial imaging, those with documented total statin intolerance within 52 weeks or treatment with another statin than rosuvastatin or atorvastatin, and those with missing samples for statin concentration measurements at 52 weeks. The remaining patients were eligible for analysis and classified as adherent or non-adherent to their background statin therapy at 4 and 52 weeks according to the following criteria: patients with quantifiable or detectable concentrations of rosuvastatin or atorvastatin were classified as adherent, those with neither quantifiable nor detectable statin concentrations as non-adherent. Quantifiable statin concentrations were those higher than the lower limit of quantification (LLOQ) of the analytical method; detectable statin concentrations were those with a peak above the limit of detection (LOD) in the chromatogram but below the LLOQ of the analytical method. The laboratory team assessing statin blood concentrations was blinded to treatment assignment and LDL-C values during the study course and data analysis.

Beyond the patients classified as non-adherent, we also identified a subgroup exhibiting an unexpectedly low LDL-C response. This was defined as a decrease in LDL-C of less than 30% at week 52 from baseline if patients were statin-naïve at baseline, in accordance with recommendations for high-intensity statin therapy outlined in the contemporary guidelines on the management of dyslipidaemia,[15] or any increase in LDL-C if patients were on statin therapy at baseline, potentially reflecting intermittent adherence, pharmacodynamic resistance, or both.

LC-MS/MS analysis

Rosuvastatin and atorvastatin standards (i.e. rosuvastatin calcium salt and atorvastatin calcium salt) and deuterated internal standards (i.e. atorvastatin-d5 calcium salt and rosuvastatin-d6 sodium salt) were obtained from Toronto Research Chemicals (Toronto, Canada). LC-MS grade methanol was purchased from Huberlab (Aesch, Switzerland), formic acid (FA) was purchased from Merck/Sigma-Aldrich (Darmstadt, Germany), and ultrapure water was obtained by filtering double-distilled tap water using MilliQ instrumentation (Merck Millipore, Darmstadt, Germany).

The LC-MS/MS hardware consisted of a PAL-system autosampler (CTC Analytics, Zwingen, Switzerland), a Shimadzu Prominence series LC with a controller (CBM-20A), two pumps (LC-20AD), a degasser (DGU-20A5R)

and a column oven (CTO-20A, Shimadzu, Reinach, Switzerland), coupled to a 4000 QTrap triple quadruple mass spectrometer (AB Sciex, Darmstadt, Germany). An XBridge BEH C18 columns (3.5 µm, 4.6 × 100 mm, 130Å, Waters, Dättwil, Switzerland) with an XBridge BEH C18 3.5 µm guard column were used for chromatographic separation. Mobile phase A consisted of 0.1% FA in H_2O (pH ~ 2.5) and mobile phase B of 100% methanol. The initial gradient consisted of 5% mobile phase B for 0.25 min, linearly increasing to 95% B at 2.5 min, and remained at 95% until 3.5 min. Subsequently, the gradient was reduced to 5% B to re-equilibrate to starting conditions until 4.5 min. The flow rate was constant over the run at 1 mL/min, and the oven temperature was set to 50°C. The 4000 QTrap mass spectrometer was operated in positive electrospray ionization mode. Multiple reaction monitoring (MRM) was used with two transitions for each standard and internal standard (for details, see supplementary methods).

Serum samples at 4 and 52 weeks were obtained as previously described.[13,14] After defrosting and vortexing the serum samples, 100 µL of serum was mixed with 300 µL internal standard (IS) mix in 0.05% FA in methanol. The IS mix contained 6.67 ng/mL of atorvastatin-d5 and rosuvastatin-d6, equivalent to 5 ng/mL when mixed with the serum in the final sample. The sample preparation was done directly in the autosampler plate (0.7 mL blank MatrixTM tubes, Thermo Fisher Scientific), and after vortexing and centrifugation for 15 min at 3500 g (4500 rpm) and 4°C, 10 µL of the supernatant was directly injected into the LC-MS/MS system.

Calibration curves and QCs were prepared in blank serum purchased from the local blood bank, which was pretested for the absence of rosuvastatin and atorvastatin. Ten µL of each stock calibrator or QC solution was mixed with 90 µL of blank serum, after which the sample was processed with the IS mix as described above. Details on the preparation and storage of the stock solutions can be found in the supplementary methods. The standard curves for both statins ranged from 0.48 to 96.2 ng/mL, and the concentrations of the four QCs were 1.44, 14.4, and 28.9 ng/mL. Between-run accuracy and precision for the three QC levels were between 90.6% and 93.1%, and between 4.0% and 9.0%, respectively. The study was run using the 'In-Study Analysis Recommendations' of the FDA Center for Drug Evaluation and Research guidelines for bioanalytical method validation.[16] For sample quantitation, linear calibration curves were constructed from all eight calibrators using 1/x weighting with $R > 0.99$ (for $n = 4$ subjects with concentration above the upper limit of quantification, linear extrapolation was used). Accuracy parameters were used to assess calibration curves and QCs for each plate, i.e. ± 20% for the lowest point of the standard curve and the lowest QC, and between ±15% for all other calibrator points and QC levels. The LLOQ was defined separately for each 96-well sample plate and was either set at 0.5 ng/mL if two out of three within-run LOW QCs were within 80–120% accuracy or set at 1 ng/mL if this was not the case. The LOD was defined as a signal-to-noise ratio of 3:1.

Statistical analysis

Continuous variables are summarized as mean ± standard deviation (SD) and categorical variables as counts with percentages. Due to the small sample size in the non-adherent group, baseline characteristics, lipid parameters, imaging endpoints, and clinical outcomes are presented as raw numbers and percentages, without statistical comparisons. We conducted a between-arm comparison of the imaging endpoints after excluding statin non-adherent patients at 52 weeks, hence representing a sensitivity analysis considering only patients receiving the per-protocol study medication at the end of the study based on the measurements of statin blood concentrations. We used repeated mixed-effect models to compare the change in imaging variables between arms. These models account for repeated measures per patient (baseline and follow-up visits) and for the multiple vessels imaged per patient. Significance tests were two-tailed with a significance level set to 0.05. Statistical analyses were conducted in R version 4.2.0 [R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/].

Results

Patient population

Overall, 300 patients were enrolled, and 265 completed serial imaging follow-up. Among those, 256 (96.6%) patients received rosuvastatin, three (1.1%) atorvastatin, three (1.1%) received another statin than rosuvastatin or atorvastatin as defined per protocol, and another three (1.1%) had missing blood samples after 52 weeks (*Figure 1*). Within 52 weeks, four (1.5%) subjects did not tolerate any background statin therapy based on the patient's reporting. At week 4, rosuvastatin concentrations ranged from <0.5 to 116.7 ng/mL, and at week 52, they ranged from <0.5 to 105.9 ng/mL. One patient had an implausibly high concentration at week 52, likely due to a technical problem. Two patients (0.8%) had detectable but not quantifiable concentrations (i.e. peaks in the chromatogram above the LOD but below the LLOQ). The distribution of quantifiable rosuvastatin concentrations at the two time points is shown in *Figure 2*.

Of the 255 patients with completed serial follow-up and samples available for measurement of rosuvastatin or atorvastatin concentrations, five (2.0%) were classified as non-adherent to statin treatment at week 52. These patients tended to have arterial hypertension (60.0% vs. 42.0%), diabetes mellitus (40.0% vs. 9.2%), and peripheral artery disease (20.0% vs. 1.6%) as compared to those classified as adherent to statin treatment. Baseline characteristics and baseline medications in statin adherent vs. non-adherent patients at week 52 are summarized in *Table 1*.

All five patients classified as non-adherent at week 52 were classified as adherent at week 4. Among the five non-adherent patients at week 52, four were randomized to placebo and one to alirocumab. In contrast, there were three (1.2%) patients classified as non-adherent at week 4, of whom all were adherent at week 52. Among the three non-adherent patients at week 4, two were randomized to placebo and one to alirocumab. Among patients who died or withdrew consent between weeks 4 and 52, only one was classified as non-adherent to statin at week 4.

In total, 14 patients were classified as being non-adherent (5 subjects) or exhibiting a low LDL-C response (an additional 9 individuals) at week 52. Along with the higher prevalence of arterial hypertension, diabetes mellitus, and peripheral artery disease, these patients also had a higher mean body mass index (31.1 vs. 28.0 kg/m^2) than those who were adherent and had an expected LDL-C response at week 52.

All four patients with documented statin intolerance at week 52 had non-detectable concentrations of both rosuvastatin and atorvastatin, confirming the absence of pharmacologically relevant concentrations of the two statins, and supporting the validity of the applied bioanalytical assay.

Lipid parameters

The absolute reduction in the mean LDL-C at week 52 vs. baseline was numerically greater in adherent vs. non-adherent patients (−2.73 vs. +0.07 mmol/L), both among those who were randomized to placebo (i.e. statin only group) during the trial course (−2.06 vs. +0.12 mmol/L) and those randomized to alirocumab (−3.44 vs. −0.13 mmol/L), respectively. The changes of LDL-C in the five patients with statin non-adherence at 52 weeks are listed in *Table 2A*, and in the three patients with statin non-adherence at 4 weeks in *Table 2B*. The changes in total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, lipoprotein(a), apolipoprotein (Apo) A1, and Apo B in statin adherent (per randomization arm) vs. non-adherent patients are shown in *Table 3*. The correlations between change in LDL-C and statin concentrations at week 52 for all included patients (with a marginal difference between slopes for the two treatment groups of −0.01 [95%CI, −0.02 to −0.00]; *P*

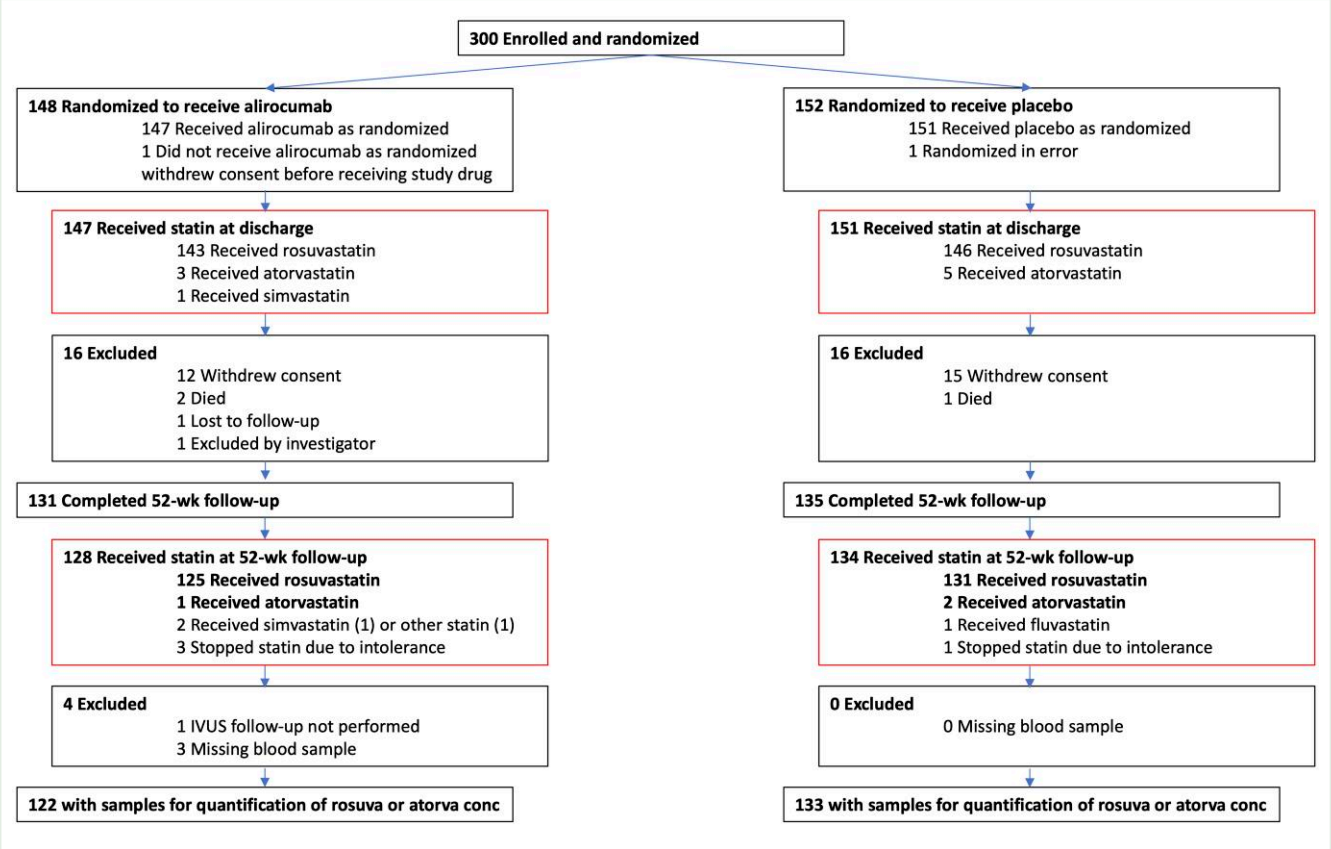


Figure 1 Patient flowchart. Among the three missing blood samples at week 52, two were lost during the cross-border transportation, and one was not collected.

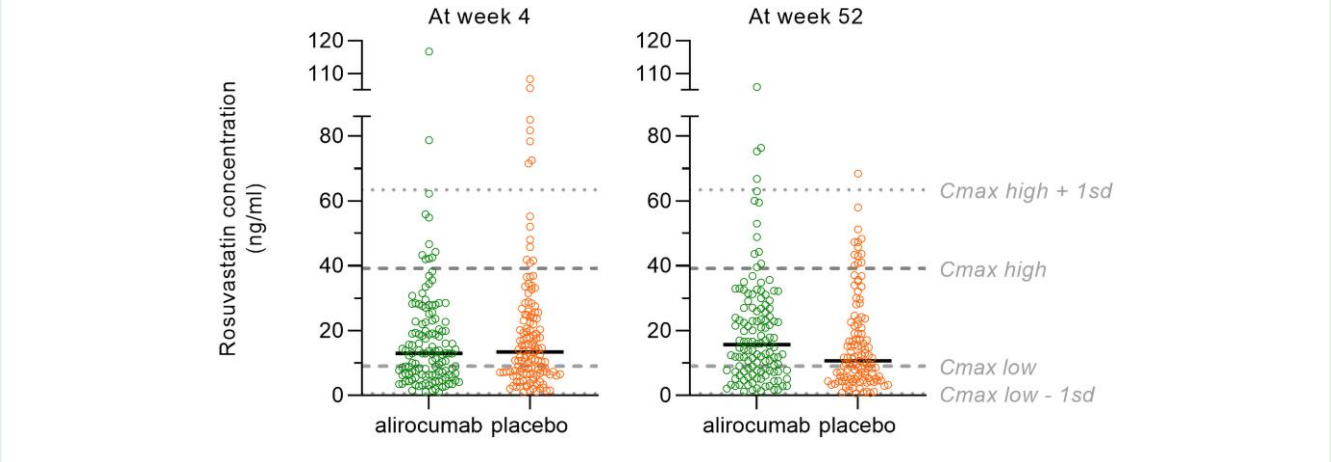


Figure 2 Rosuvastatin concentrations at week 4 and week 52. Distribution of quantifiable rosuvastatin concentrations in the alirocumab and placebo groups measured at weeks 4 and 52, respectively. Mean high and low C_{max} values with corresponding upper and lower standard deviations reported in the literature from different studies with adult subjects after intake of 20 mg rosuvastatin are shown as reference ($C_{max\ high}$ 39.2 ± 24.3 ng/mL, $C_{max\ low}$ 9.1 ± 8.5 ng/mL).[17] Medians are shown by thick horizontal lines. Blood samples were collected during follow-up visits, a few hours after statin intake, hence measured concentrations are approximately comparable to maximal blood concentrations (T_{max} 4 h) in most patients. *P*-values for between-arm comparisons derived from a linear model: at week 4, $P = 0.709$; at week 52, $P = 0.443$.

Table 1 Baseline characteristics in patients adherent and non-adherent to background statin therapy at week 52

	Total ($n = 255$)	Non-adherent ($n = 5$)	Adherent ($n = 250$)
Age (years)	57.8 (9.3)	59.0 (12.7)	57.8 (9.3)
Gender			
Male	216 (84.7%)	4 (80.0%)	212 (84.8%)
Female	39 (15.3%)	1 (20.0%)	38 (15.2%)
Body mass index	28.0 (4.3)	28.9 (5.2)	28.0 (4.3)
Active smoker	122 (47.8%)	2 (40.0%)	120 (48.0%)
Arterial hypertension	108 (42.4%)	3 (60.0%)	105 (42.0%)
Diabetes mellitus	25 (9.8%)	2 (40.0%)	23 (9.2%)
Diabetes type			
Type 1	2 (0.8%)	0 (0.0%)	2 (0.8%)
Type 2	23 (9.0%)	2 (40.0%)	21 (8.4%)
Insulin dependent	7 (2.7%)	1 (20.0%)	6 (2.4%)
Previous myocardial infarction	6 (2.4%)	1 (20.0%)	5 (2.0%)
Previous PCI	7 (2.7%)	1 (20.0%)	6 (2.4%)
Peripheral arterial disease	5 (2.0%)	1 (20.0%)	4 (1.6%)
Family history of CAD or CVD	82 (32.2%)	0 (0.0%)	82 (32.8%)
ATII antagonist	31 (12.2%)	1 (20.0%)	30 (12.0%)
Statin	33 (12.9%)	2 (40.0%)	31 (12.4%)
ACE inhibitor	17 (6.7%)	0 (0.0%)	17 (6.8%)
Beta blocker	22 (8.6%)	1 (20.0%)	21 (8.4%)
Ezetimibe	1 (0.4%)	0 (0.0%)	1 (0.4%)
Stratum of acute coronary syndrome			
NSTEMI	116 (45.5%)	2 (40.0%)	114 (45.6%)
STEMI	139 (54.5%)	3 (60.0%)	136 (54.4%)
Left ventricular ejection fraction	53.1 (10.4)	50.3 (9.0)	53.1 (10.5)

Values are count (percentage) or mean (SD).
ATII, angiotensin II; CAD, coronary artery disease; CVD, cardiovascular disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation acute myocardial infarction.

Table 2A Listing of the five patients classified as non-adherent to background statin therapy at week 52

Subject no.	POC LDL-C BS	LDL-C BS	LDL-C 4W	LDL-C 52W	Study arm
1	3.19	4.09	0.77[a]	3.96[b,c]	Alirocumab
2	3.30	3.85	2.15[a]	3.42[c]	Placebo
3	1.89	2.24	1.02[a]	2.72[c]	Placebo
4	4.50	4.59	1.68[a]	5.30[c]	Placebo
5	4.47	4.84	2.72[a]	4.57[c]	Placebo

[a]Adherent to statin treatment at 4 weeks.
[b]Evidence for non-adherence to alirocumab.
[c]No lipid-lowering treatment at 52 weeks. POC point-of-care LDL-C at baseline (BS); central laboratory LDL-C at baseline (BS), and 4- (4W) and 52-week (52W) follow-up (all in mmol/L).

= 0.018) and for those with no statin at baseline (−0.01 [95%CI, −0.02 to −0.00]; $P = 0.005$) are displayed in *Figure 3*.

Intracoronary imaging endpoints

Both, the reduction in IVUS-assessed per cent atheroma volume (PAV, −1.54 vs. −0.15%) and the reduction in NIRS-assessed maximum lipid core burden index within 4 mm (max. $LCBI_{4mm}$, −60.6 vs. 0.0) were numerically greater, whereas the increase of OCT-assessed minimum fibrous cap thickness (min. FCT, +48.53 vs. +7.98 μm) was numerically higher in adherent vs. non-adherent patients, respectively. An example of atherosclerotic plaque progression in the right coronary artery of a statin non-adherent patient is shown in *Figure 4*. The changes in other intracoronary imaging parameters are shown in *Table 4A*. There were no significant associations between the three main imaging endpoints and statin concentrations at week 52 (*Figure 5*).

Table 2B Listing of the three patients classified as non-adherent to background statin therapy at week 4

Subject no.	POC LDL-C BS	LDL-C BS	LDL-C 4W	LDL-C 52W	Study arm
1	3.15	3.30	0.57	0.81	Alirocumab
2	3.49	3.34	3.37	1.32	Placebo
3	3.79	4.33	3.89	2.18	Placebo

POC point-of-care LDL-C at baseline (BS); central laboratory LDL-C at baseline (BS), 4- (4W), and 52-week (52W) follow-up (all in mmol/L).

Table 3 Lipid parameters in patients adherent and non-adherent to background statin therapy at week 52

	Time Point	Non-adherent $n = 5$	Adherent Placebo $n = 129$	Adherent Alirocumab $n = 121$	Non-adherent vs. Placebo	Non-adherent vs. Alirocumab
Total cholesterol (mmol/L)	Baseline	5.2 (1.2)	5.3 (0.9)	5.3 (0.9)	−0.07	−0.11
	Follow-up	5.5 (1.2)	3.5 (0.7)	2.1 (0.6)	1.97	3.40
	Change	0.3 (−0.7 to 1.3)	−1.8 (−1.9 to −1.6)	−3.2 (−3.4 to −3.1)	2.04	3.51
LDL-C (mmol/L)	Baseline	3.9 (1.0)	3.9 (0.9)	4.0 (0.8)	0.01	−0.05
	Follow-up	4.0 (1.0)	1.9 (0.6)	0.5 (0.5)	2.15	3.46
	Change	0.1 (−0.5 to 0.7)	−2.1 (−2.2 to −1.9)	−3.4 (−3.6 to −3.3)	2.14	3.52
HDL-C (mmol/L)	Baseline	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	−0.06	−0.07
	Follow-up	1.0 (0.3)	1.2 (0.3)	1.3 (0.3)	−0.15	−0.23
	Change	0.0 (−0.2 to 0.2)	0.1 (0.1 to 0.1)	0.2 (0.1 to 0.2)	−0.09	−0.17
non-HDL-C (mmol/L)	Baseline	4.2 (1.1)	4.2 (0.9)	4.3 (0.9)	0.01	−0.02
	Follow-up	4.5 (1.0)	2.4 (0.7)	0.9 (0.6)	2.09	3.61
	Change	0.2 (−0.6 to 1.1)	−1.9 (−2.0 to −1.7)	−3.4 (−3.6 to −3.2)	2.08	3.63
Triglycerides (mmol/L)	Baseline	1.3 (0.9)	1.3 (1.0)	1.2 (0.7)	0.07	0.13
	Follow-up	1.5 (0.4)	1.4 (0.9)	1.0 (0.5)	0.11	0.48
	Change	0.2 (−0.7 to 1.1)	0.2 (0.0 to 0.3)	−0.2 (−0.3 to −0.0)	0.04	0.36
Lipoprotein(a) (nmol/L)	Baseline	107.8 (118.2)	68.6 (84.1)	62.1 (93.0)	39.23	45.68
	Follow-up	117.6 (146.1)	87.2 (105.9)	57.1 (90.8)	30.41	60.53
	Change	9.8 (−43.9 to 63.5)	18.6 (13.1 to 24.1)	−5.0 (−9.4 to −0.7)	−8.82	14.85
Apolipoprotein A1 (mmol/L)	Baseline	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	−0.03	−0.03
	Follow-up	1.2 (0.3)	1.3 (0.2)	1.3 (0.2)	−0.10	−0.16
	Change	0.0 (−0.2 to 0.3)	0.1 (0.1 to 0.1)	0.2 (0.2 to 0.2)	−0.07	−0.13
Apolipoprotein B (mmol/L)	Baseline	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	0.00	−0.01
	Follow-up	1.2 (0.3)	0.7 (0.2)	0.3 (0.2)	0.51	0.92
	Change	0.1 (−0.1 to 0.2)	−0.4 (−0.5 to −0.4)	−0.8 (−0.9 to −0.8)	0.51	0.92
High-sensitivity CRP (mg/L)	Baseline	4.6 (4.2)	5.7 (11.0)	6.3 (13.5)	−1.13	−1.75
	Follow-up	2.1 (1.1)	2.4 (5.0)	1.8 (2.7)	−0.27	0.29
	Change	−2.5 (−7.9 to 3.0)	−3.3 (−5.4 to −1.3)	−4.5 (−6.9 to −2.1)	0.86	2.05

Values are mean (SD) or mean change (95% CI). Differences shown are (i) between non-adherent and adherent patients (to background statin therapy) from the placebo group, (ii) between non-adherent and adherent patients from the alirocumab group.

Along the same lines, patients who were adherent and exhibited an expected LDL-C response showed numerically greater reductions in PAV (−1.59 vs. −0.22%) and max. $LCBI_{4mm}$ (−60.3 vs. −47.9), along with a more pronounced increase in min. FCT (+49.4 vs. +19.1 μm), compared with those classified as non-adherent or having a low LDL-C response (*Table 4B*).

Clinical and safety outcomes

Adverse events occurred in 182 of 250 adherent and all 5 non-adherent patients. Major adverse cardiovascular events (MACE), defined as a composite of death, myocardial infarction, stroke, transient ischaemic attack, or ischemia-driven coronary revascularization, were reported in 38 adherent and 2 non-adherent patients, with most events attributed to ischemia-driven revascularization (36 and 2, respectively). Local injection site reactions occurred in 11 adherent and 1 non-adherent patient, whereas general allergic reactions ($n = 3$), neurocognitive events ($n = 3$), and alanine aminotransferase (ALT) elevation ($n = 1$) were observed only among adherent patients.

The same trend, characterized by higher rates of MACE and adverse events in non-adherent patients, was also observed when comparing

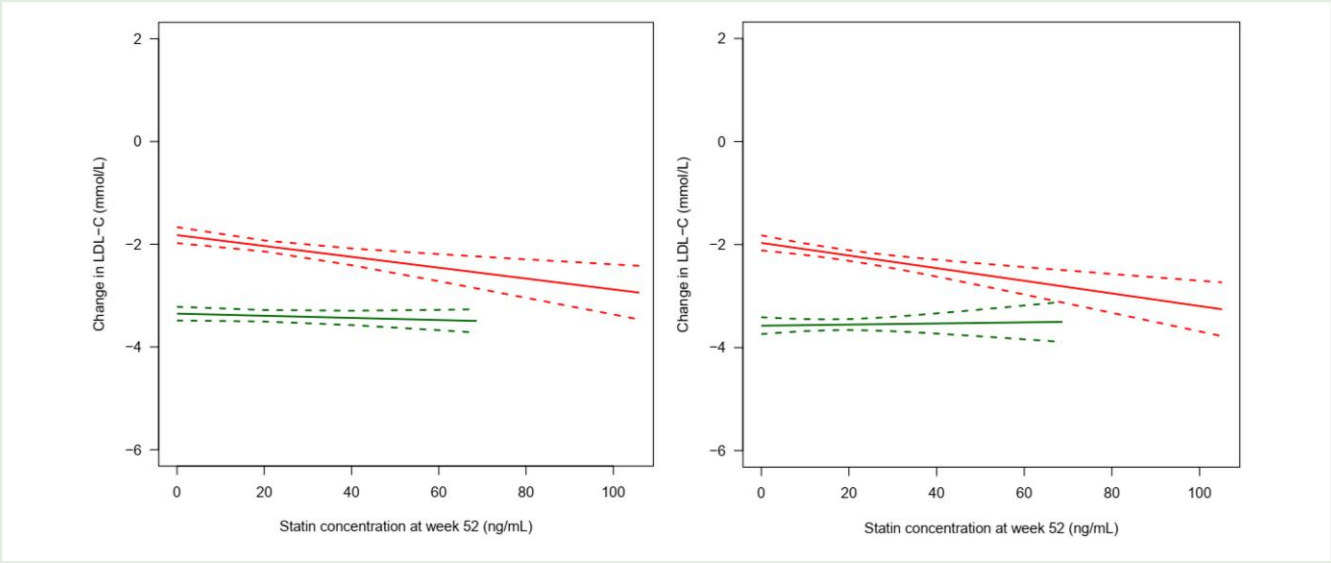


Figure 3 Association between change in LDL-C from baseline and statin concentration at week 52. The alirocumab group is displayed in green and the placebo group in red. Solid and dashed lines are fitted lines and 95% CIs extracted from a linear model with statin concentration at week 52 fitted as a fixed effect for (*A*). all included patients (left): marginal difference between slopes: −0.01 (−0.02 to −0.00); $P = 0.018$. All 255 patients with completed serial follow-up and samples available for quantification of rosuvastatin or atorvastatin concentrations were included in this analysis. (*B*) patients with no statin at baseline (right): marginal difference between slopes: −0.01 (−0.02 to −0.00); $P = 0.005$. A total of 222 patients with no statin at baseline, who completed serial follow-up and had samples available for quantification of rosuvastatin or atorvastatin concentrations, were included in this analysis.

patients who were adherent and demonstrated an expected LDL-C response with those who were non-adherent or had a low LDL-C response.

Sensitivity analysis of the primary results of PACMAN-AMI study

After exclusion of the statin non-adherent patients, the analysis of patient population receiving per-protocol rosuvastatin or atorvastatin rendered the following results for the primary and the two powered secondary endpoints. At 52 weeks, the mean change in PAV was −2.16% with alirocumab vs. −0.97% with placebo [difference, −1.19% (95%CI, −1.77% to −0.60%); $P < 0.001$]. The mean change in maximum $LCBI_{4mm}$ was −82.86 with alirocumab vs. −39.78 with placebo [difference, −42.73 (95%CI, −72.77 to −12.70); $P = 0.005$], whereas the mean change in minimum FCT was +64.83 μm with alirocumab vs. +33.96 μm with placebo [difference, +30.33 μm (95%CI, +11.76 to +48.90); $P = 0.001$]. All these outcomes were close to identical as compared to the results of the primary analysis, including the full intention-to-treat patient population.[12] In addition, mean change in mean macrophage angle was −26.13° with alirocumab vs. −16.04° with placebo [difference, −10.42° (95%CI, −15.20 to −5.65); $P < 0.001$]. The changes in other intracoronary imaging parameters in patients with alirocumab vs. placebo are summarized in *Table 5*.

Discussion

In the PACMAN-AMI trial, the intake of high-intensity statin background therapy assessed by direct measurement of drug concentrations in blood at 4 and 52 weeks after AMI was very high, while the rate of statin intolerance was low. After exclusion of statin non-adherent patients, the sensitivity analysis with the patient population receiving per-protocol background therapy with rosuvastatin or atorvastatin at week 52 confirmed the results of the primary analysis, including the full intention-to-treat population of the PACMAN-AMI trial, supporting the validity of study findings.

Patients who were non-adherent to statin treatment had numerically more often co-morbidities, a lower reduction in LDL-C, less decrease in atheroma volume and lipid content, less plaque stabilization, and more frequently adverse events. Moreover, the proportion of patients with complete statin intolerance in our study was low, in line with the rates reported from several other RCTs.[18] A large discrepancy in adherence rates between randomized controlled trials and real-world evidence exists.[1,19] In the setting of observational research, a meta-analysis by Chowdhury et al., including data from 44 real-world studies with almost two million participants, reported that adherence rates to statin therapy varied widely, with a point estimate of 54%.[20] Good adherence to statin therapy was associated with a 15% relative risk reduction in any cardiovascular disease and a 45% relative risk reduction in all-cause mortality. In a systematic review and meta-analysis by Naderi et al., analysing real-world data from 20 studies involving over 375 000 patients, adherence rates to statin treatment ranged from 57% in the primary to 76% in the secondary prevention.[21] Another systematic review and meta-analysis by Ofori-Asenso et al. analysed data from more than three million older statin users in 82 studies conducted in over 40 countries.[22] At 1-year follow-up, 60% (primary prevention 48% and secondary prevention 62%) of the users were adherent. Among new statin users, 48% were non-adherent and 24% discontinued treatment within the first year. All these studies highlight the great variability in adherence rates to statin therapy and the need for individualized stratification and comprehensive interventions to improve adherence and optimize cardiovascular risk reduction.[23]

In contrast, the adherence rate to statin treatment in the PACMAN-AMI trial was very high (98%). This is in line with the evidence from other RCTs, with reported adherence rates ranging from 65% to

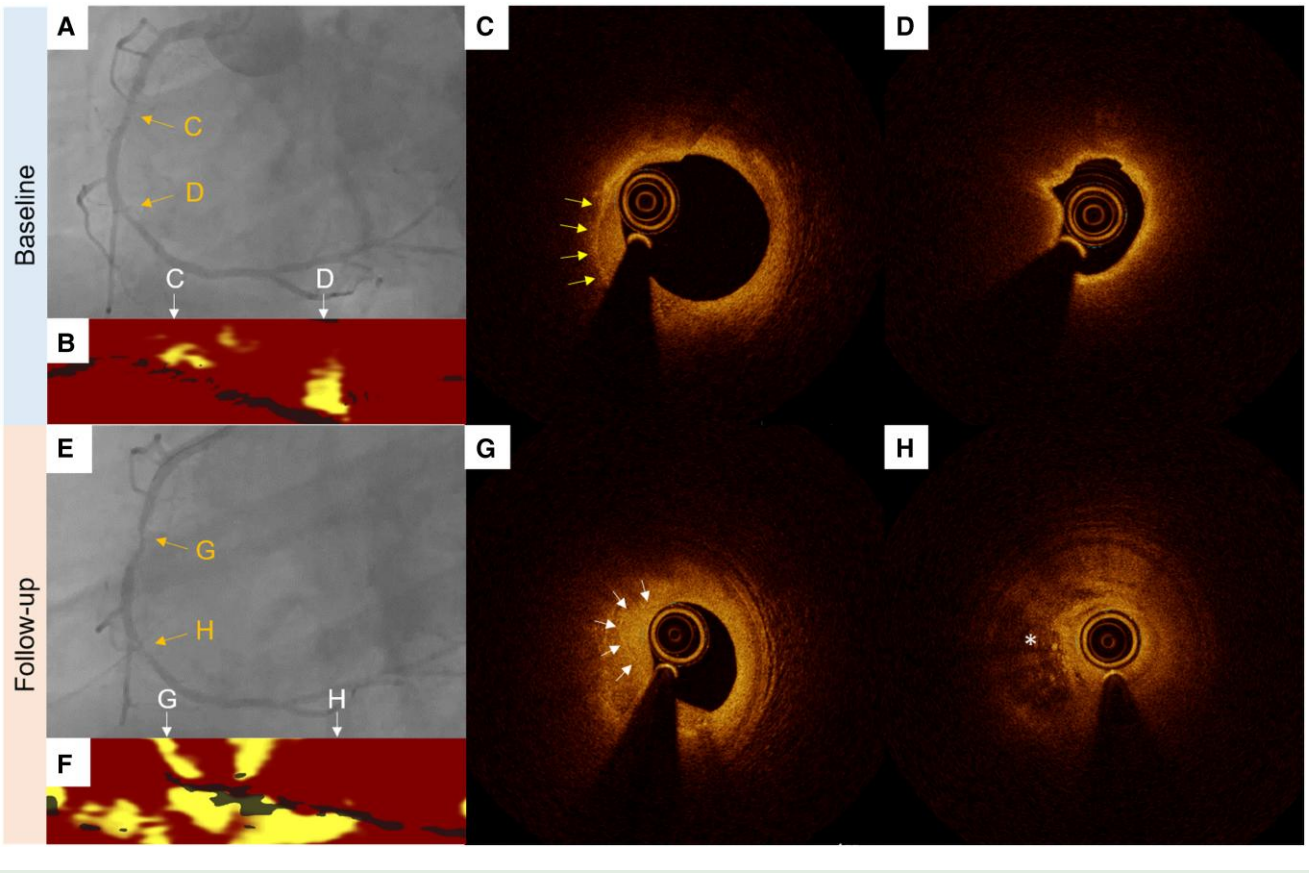


Figure 4 Example of atherosclerotic plaque progression in the right coronary artery of a statin non-adherent patient. Coronary angiography (CAG) and intracoronary imaging of the right coronary artery (RCA) at baseline (*A–D*) and 52 weeks (*E–H*) are presented. At baseline, CAG revealed moderate stenoses in proximal and mid-RCA (*A*). Near-infrared spectroscopy (NIRS) demonstrated a high maximum lipid core burden index 4 mm (max. $LCBI_{4mm}$) value of 519 (*B*). Optical coherence tomography (OCT) revealed a thick cap fibroatheroma with layered plaque (yellow arrow) in the proximal RCA (*C*) and a thin cap fibroatheroma in mid-RCA (*D*). After 52 weeks, CAG showed lesion progression in RCA (*E*). NIRS demonstrated an increased max. $LCBI_{4mm}$ value of 852 (*F*), and OCT revealed lumen narrowing with new layered plaque (white arrow) in proximal RCA (*G*) and intraplaque haemorrhage (asterisk) in mid-RCA (*H*).

more than 99%.[19] However, adherence, especially in the trials reporting high rates, was only indirectly assessed and not confirmed by drug concentration measurements. In addition, reported adherence rates are higher in the first year after study inclusion and typically decline with increasing treatment duration and number of prescribed medication.[24–26] The high adherence rate observed in the PACMAN trial should be interpreted within the context of a well-executed randomized study. This study benefited from strong participant's motivation and interest, largely attributable to their enrolment in the acute phase of myocardial infarction, a period when patients are particularly motivated to follow recommendations for secondary prevention strategies.

Our findings further indicate a very low prevalence of true (i.e. with a direct causal link between statin use and adverse effects) statin intolerance (1–2%) and align well with results of previous RCTs.[27,28] This underscores the notion that statin intolerance is often a subjective phenomenon and supports available evidence that side effects are often over-attributed to statins. Indeed, the nocebo effect in statin therapy has been elegantly demonstrated in prior N-of-1 trials.[29] However, true statin intolerance was shown to be associated with an increased risk for recurrent myocardial infarction and coronary events,[30] and may be best addressed in a specialized lipid clinic certified to prescribe contemporary non-statin lipid-lowering therapies. A key strength of our study is the use of direct measurement to confirm excellent statin adherence in this highly motivated patient population, within which true statin intolerance was markedly lower than previously reported in real-world settings. This highlights patient education and guidance as critical and modifiable factors for optimizing long-term medication adherence, as demonstrated by a multifaceted, physician-led intervention in a pragmatic RCT.[31]

To the best of our knowledge, the present study is the first one reporting on the intake of high-intensity statin therapy assessed by a direct measurement of drug concentrations in blood. The high rate of statin intake and its correlation with the extent of LDL-C lowering, regression of atherosclerosis, and stabilization of coronary plaques is reassuring. It emphasizes the fact that the observed additional effects of the study medication compared to placebo can specifically be attributed to the benefits of the PCSK9 inhibitor as outlined in the study protocol, without being biased by a potential difference in the use of background statin therapy between the study groups. In patients with extensive LDL-C lowering delivered by a combination of intensive lipid-lowering therapy, particularly high-intensity statins and PCSK9 inhibitors, eventually physicians and/or patients themselves tend to discontinue statin treatment due to the fear of potential consequences

Table 4A Imaging endpoints in patients adherent and non-adherent to background statin therapy at week 52

	Time Point	Non-adherent	Adherent
IVUS		*n* = 9 (5)	*n* = 508 (250)
Per cent atheroma volume (%)	Baseline	41.63 (10.16)	42.08 (9.38)
	Week 52	41.48 (10.30)	40.54 (9.35)
	Change	−0.15 (−3.29 to 2.99)	−1.54 (−1.82 to −1.26)
Normalized total atheroma volume (mm^3)	Baseline	248.10 (136.57)	253.20 (116.05)
	Week 52	240.90 (127.01)	232.67 (106.87)
	Change	−7.20 (−23.94 to 9.54)	−20.53 (−23.15 to −17.90)
NIRS		*n* = 8 (5)	*n* = 487 (248)
Maximum $LCBI_{4mm}$	Baseline	206.88 (201.32)	269.78 (191.26)
	Week 52	206.88 (280.12)	209.21 (184.71)
	Change	0.00 (−179.76 to 179.76)	−60.57 (−75.38 to −45.77)
LCBI (ROI)	Baseline	60.88 (65.18)	78.78 (81.45)
	Week 52	75.00 (114.41)	57.22 (72.33)
	Change	14.12 (−89.40 to 117.65)	−21.56 (−27.53 to −15.59)
OCT		*n* = 5 (3)	*n* = 350 (209)
Minimum FCT (μm)	Baseline	152.91 (108.94)	107.85 (77.56)
	Week 52	160.90 (65.69)	156.38 (92.10)
	Change	7.98 (−112.56 to 128.53)	48.53 (39.42 to 57.63)
Mean FCT (μm)	Baseline	367.52 (144.74)	328.90 (105.11)
	Week 52	441.78 (102.79)	404.22 (105.57)
	Change	74.26 (−61.67 to 210.20)	75.32 (62.86 to 87.79)
Mean macrophage angle (°)	Baseline	64.70 (36.04)	57.83 (20.88)
	Week 52	49.06 (39.42)	37.00 (21.88)
	Change	−15.64 (−32.38 to 1.11)	−20.83 (−23.21 to −18.45)

Numbers refer to imaged vessels (patients) for each imaging modality. Values are mean (SD) or mean change (95% CI) across vessels.
IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy; $LCBI_{4mm}$, lipid core burden index within 4 mm; ROI, region of interest; OCT, optical coherence tomography; FCT, fibrous cap thickness.

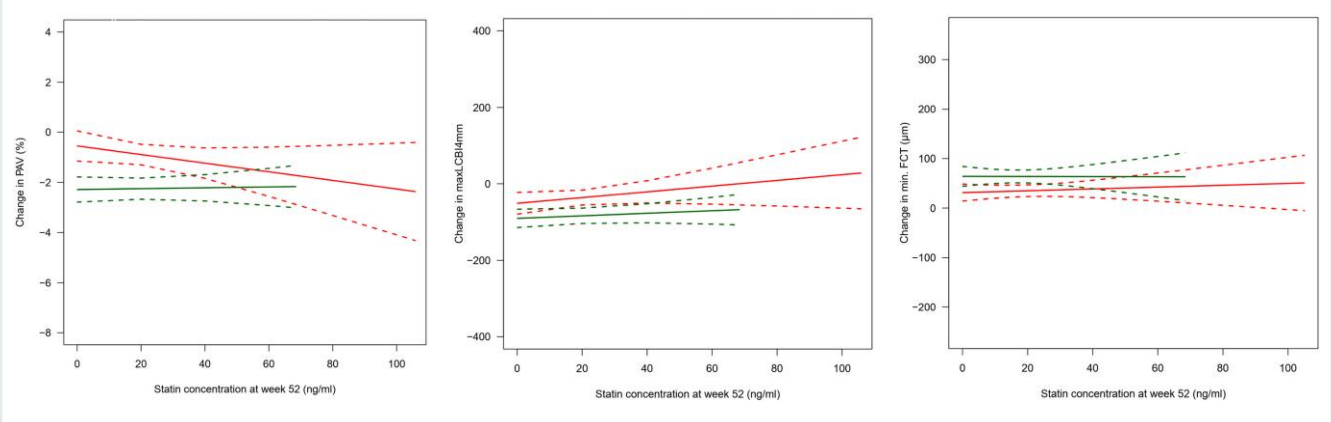


Figure 5 Associations between changes in imaging endpoints and statin concentration at week 52. The alirocumab group is displayed in green and the placebo group in red. Solid and dashed lines are fitted lines and 95% CIs extracted from mixed-effect models with statin concentration at week 52 fitted as a fixed effect. Marginal difference between slopes: (*A*) +0.02 (−0.01 to +0.05); $P = 0.17$ for change in PAV (left), (*B*) −0.42 (−1.69 to +0.85); $P = 0.52$ for change in max. $LCBI_{4mm}$ (middle), and (*C*) −0.20 (−1.31 to +0.91); $P = 0.73$ for change in min. FCT (right). PAV, per cent atheroma volume; max. $LCBI_{4mm}$, maximum lipid core burden index within 4 mm; min. FCT, minimum fibrous cap thickness.

of extremely low LDL-C concentrations, such as neurocognitive disorders, diabetes mellitus, cataract, or lack of cholesterol-derived hormones. However, the occurrence of these side effects was closely monitored throughout the extensive drug development programmes of PCSK9 inhibitors and, more general, in studies with intensive lipid lowering leading to very low LDL-C levels, and did not prove to be

Table 4B Imaging endpoints in patients who were adherent and exhibited an expected LDL-C response versus those who were non-adherent or had a low LDL-C response at week 52

	Time Point	Non-responder	Responder
IVUS		*n* = 28 (14)	*n* = 489 (241)
Percent atheroma volume (%)	Baseline	42.26 (10.09)	42.06 (9.36)
	Week 52	42.03 (10.60)	40.47 (9.29)
	Change	−0.22 (−1.30 to 0.86)	−1.59 (−1.88 to −1.31)
Normalized Total Atheroma Volume (mm^3)	Baseline	263.24 (115.92)	252.53 (116.40)
	Week 52	255.98 (110.09)	231.49 (106.91)
	Change	−7.26 (−14.94 to 0.42)	−21.04 (−23.74 to −18.34)
NIRS		*n* = 27 (14)	*n* = 468 (239)
Maximum $LCBI_{4mm}$	Baseline	220.33 (190.92)	271.55 (191.23)
	Week 52	172.41 (199.85)	211.29 (185.41)
	Change	−47.93 (−126.78 to 30.93)	−60.26 (−75.28 to −45.25)
LCBI (ROI)	Baseline	52.11 (61.97)	80.01 (81.96)
	Week 52	42.48 (67.41)	58.37 (73.34)
	Change	−9.63 (−43.11 to 23.85)	−21.64 (−27.74 to −15.53)
OCT		*n* = 17 (9)	*n* = 338 (203)
Minimum FCT (μm)	Baseline	106.09 (69.88)	108.60 (78.54)
	Week 52	125.23 (66.94)	158.01 (92.58)
	Change	19.14 (−17.71 to 55.98)	49.41 (40.07 to 58.75)
Mean FCT (μm)	Baseline	336.92 (97.20)	329.07 (106.12)
	Week 52	392.94 (99.97)	405.35 (105.86)
	Change	56.02 (16.73 to 95.31)	76.28 (63.44 to 89.12)
Mean macrophage angle (°)	Baseline	56.02 (27.52)	58.05 (20.81)
	Week 52	49.11 (31.51)	36.53 (21.49)
	Change	−6.91 (−16.97 to 3.15)	−21.53 (−23.93 to −19.12)

Numbers refer to imaged vessels (patients) for each imaging modality. Values are mean (SD) or mean change (95% CI) across vessels.
IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy; $LCBI_{4mm}$, lipid core burden index within 4 mm; ROI, region of interest; OCT, optical coherence tomography; FCT, fibrous cap thickness.

of concern.[32] Potentially, discontinuation of high-intensity statin background treatment in the PCSK9 inhibitor group could have skewed the true effect of PCSK9 inhibition on the extent of LDL-C lowering and would likely have impacted negatively on the beneficial changes in atherosclerosis as evaluated by intracoronary imaging techniques.

Not surprisingly, all five patients classified as non-adherent to statin therapy at week 52 in our study had their on-treatment LDL-C at the highest decile, notwithstanding one patient allocated to the alirocumab group. Interestingly, LDL-C of this particular patient was only marginally lowered from 4.09 mmol/L at baseline to 3.96 mmol/L at week 52. This almost negligible effect on LDL-C is not compatible with installed PCSK9 inhibitor treatment, and in fact, post-hoc analysis revealed a massive decrease in serum PCSK9 concentration at week 52 vs. week 4 in this patient. This finding is compatible with a withdrawal of PCSK9 inhibition therapy and supports the likelihood of non-adherence not only to background statin but also to PCSK9 inhibitor treatment.[33] Indeed, patients who are non-adherent to a single drug are often more prone to non-adherence to multiple medications. This phenomenon, known as medication non-adherence clustering, has been described previously in studies with antihypertensive and lipid-lowering therapies.[34,35] Among statin non-adherent patients, we report a gapless correlation of neither quantifiable nor detectable statin blood concentrations with a negligible change in LDL-C. Thus, measurement of drug concentrations in patients with persistently high LDL-C despite high-intensity lipid-lowering therapy seems to be reasonable in such situations to confirm suspected non-adherence.

Our study has several limitations. First, per protocol, no blood sampling between week 4 and 52 was mandated, and we cannot exclude that more patients than detected were actually non-adherent during the study course and took their statin solely prior to the scheduled follow-up visits. Due to the relatively short half-lives of atorvastatin and rosuvastatin (approx. 20 h), detectable concentrations only confirm statin intake for approx. 3–4 days prior to sampling and do not allow to assess adherence for the time between the two follow-up visits. If the last statin intake had occurred more than 5 half-lives prior to sampling, it is likely that concentrations have declined to an undetectable level by the time of sampling and this intake could not be detected anymore. Although it cannot be excluded, it is unlikely that within the first 12 months after having experienced an AMI, a significant number of patients would deliberately have timed their statin intake just before the scheduled study visits. Second, due to the efficient uptake of modern statins into hepatocytes, bioavailability is low, and blood concentrations of statins are variable. Thus, even after regular statin intake, blood concentrations in patients with efficient hepatic uptake can be very low and do not necessarily indicate omitted statin intake in the preceding days. To account for this, patients who only had detectable concentrations that were too low for reliable quantification (i.e. concentrations below LLOQ) were also classified as adherent. Statin metabolites were not

Table 5 Imaging endpoints in patients receiving per-protocol rosuvastatin or atorvastatin at week 52 (sensitivity analysis of the primary results of PACMAN-AMI study)

Imaging variables	Time Point	Alirocumab	Placebo	Difference (95% CI)	*P*-Value
IVUS		*n* = 245 (121)	*n* = 263 (129)		
Per cent atheroma volume (%)	Baseline	40.89 (8.77)	43.18 (9.81)	2.18 (0.22 to 4.14)	0.029
	Week 52	38.73 (8.34)	42.21 (9.93)	3.37 (1.40 to 5.33)	<0.001
	Change	−2.16 (−2.57 to −1.74)	−0.97 (−1.33 to −0.60)	1.19 (0.60 to 1.77)	<0.001
Normalized total atheroma volume (mm^3)	Baseline	257.24 (120.31)	249.43 (112.03)	−9.59 (−33.35 to 14.18)	0.428
	Week 52	230.99 (106.48)	234.24 (107.42)	1.83 (−19.89 to 23.54)	0.868
	Change	−26.25 (−30.38 to −22.13)	−15.19 (−18.40 to −11.99)	11.42 (5.40 to 17.43)	<0.001
NIRS		*n* = 235 (120)	*n* = 252 (128)		
Maximum $LCBI_{4mm}$	Baseline	261.34 (185.87)	277.64 (196.19)	11.42 (−26.35 to 49.19)	0.552
	Week 52	178.48 (171.07)	237.86 (192.53)	54.16 (16.36 to 91.95)	0.005
	Change	−82.86 (−104.60 to −61.13)	−39.78 (−59.78 to −19.78)	42.73 (12.70 to 72.77)	0.005
LCBI (ROI)	Baseline	74.48 (77.59)	82.79 (84.85)	6.80 (−9.79 to 23.40)	0.420
	Week 52	44.36 (58.39)	69.21 (81.56)	23.65 (8.74 to 38.55)	0.002
	Change	−30.12 (−38.80 to −21.44)	−13.58 (−21.73 to −5.43)	16.84 (4.85 to 28.84)	0.006
OCT		*n* = 161 (98)	*n* = 189 (111)		
Minimum FCT (μm)	Baseline	105.83 (68.21)	109.56 (84.86)	3.57 (−13.94 to 21.08)	0.688
	Week 52	170.66 (98.27)	144.21 (84.87)	−26.76 (−47.82 to −5.70)	0.013
	Change	64.83 (50.30 to 79.36)	33.96 (22.86 to 45.06)	−30.33 (−48.90 to −11.76)	0.001
Mean FCT (μm)	Baseline	329.24 (96.09)	328.61 (112.49)	−1.07 (−24.61 to 22.46)	0.928
	Week 52	420.34 (109.06)	390.49 (100.77)	−29.78 (−53.33 to −6.23)	0.013
	Change	91.10 (72.44 to 109.76)	62.20 (45.82 to 78.58)	−28.71 (−54.65 to −2.76)	0.030
Mean macrophage angle (°)	Baseline	58.32 (19.62)	57.39 (21.97)	−0.86 (−5.05 to 3.33)	0.686
	Week 52	31.99 (21.16)	41.42 (21.59)	9.56 (5.49 to 13.64)	<0.001
	Change	−26.13 (−29.59 to −22.68)	−16.04 (−19.15 to −12.93)	10.42 (5.65 to 15.20)	<0.001

Numbers refer to imaged vessels (patients) for each imaging modality. Analyses were conducted on vessel-level values at two time points (baseline and week 52) using repeated-measures mixed-effect models accounting for the multiple vessels per patient. Values are vessel-level mean (SD), or vessel-level mean change (95% CI). Difference in change are marginal differences computed from mixed-effect models.
IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy; $LCBI_{4mm}$, lipid core burden index within 4 mm; ROI, region of interest; OCT, optical coherence tomography; FCT, fibrous cap thickness.

used for rosuvastatin adherence assessment, as no published reference data were available (in contrast to atorvastatin).[36] Third, the group of patients classified as non-adherent to statin treatment was very small, precluding any valid statistical comparisons. Thus, we mostly used descriptive methodology throughout our report. To address this limitation, which also reflects a key strength of this work, we identified an additional subgroup of patients with unexpectedly low LDL-C response. The number of patients across both subgroups (14 in total), together with the coherent effects observed in intracoronary imaging and clinical endpoints, underscores both the high adherence to and acceptance of statin therapy in our study, and reinforces the consistency of our findings. Fourth, 35 (11%) patients did not complete serial imaging follow-up, including three who died. It is conceivable that this subgroup included a higher proportion of non-adherent individuals. However, a sensitivity analysis applying multiple imputation to address missing data revealed no meaningful differences—including the rate of non-adherence and its association with imaging endpoints—between completers and those who dropped out. Lastly, we systematically measured concentrations of rosuvastatin and atorvastatin only, and we therefore were not able to either confirm or exclude the presence of other statins in the blood samples collected. This likely had a limited effect on our results, as in total only three patients were documented as having taken other statins than the two statins pre-specified in the protocol.

In conclusion, the intake of high-intensity statin background therapy at 4 weeks and 52 weeks after AMI was very high and the rate of statin intolerance was low, despite the fact that statins were initiated in the acute setting in largely (>85%) statin-naïve patients, and in combination with a newly-initiated PCSK9 inhibitor in half of patients, pointing to the feasibility and acceptance of early, intensive combination lipid-lowering therapy. This together with the congruent results of the sensitivity analysis, including all patients with confirmed detection of per-protocol background statin concentrations, reinforces the validity and reliability of the primary findings of the PACMAN-AMI trial, demonstrating beneficial effects of PCSK9 inhibitor alirocumab on coronary atherosclerosis in reducing both plaque burden and plaque vulnerability. The seamless correlation of neither quantifiable nor detectable statin blood concentrations with a negligible decrease in LDL-C among statin non-adherent patients warrants measurement of drug concentrations in patients with high LDL-C despite high-intensity lipid-lowering therapy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Authors' contributions

Vvd.V., L.R., M.H., and D.S. contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. Vvd.V., M.H., and D.S. drafted the manuscript. J.D.H., R.K., S.B., Y.U., G.C.M.S., S.S., F.G.B., M.A., C.K., J.F.I., F.M., R.Jv.G., J.D., T.E., A.S.O., I.L., C.V.B., C.M.M., S.W., K.C.K., M.M., S.L., and L.R. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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