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ORIGINAL ARTICLE
Lipid-Lowering Therapy

Enhanced Plaque Stabilization Effects of Alirocumab — Insights From Artificial Intelligence-Aided Optical Coherence Tomography Analysis of the Alirocumab for Thin-Cap Fibroatheroma in Patients With Coronary Artery Disease Estimated by Optical Coherence Tomography (ALTAIR) Study —

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Background: Proprotein convertase subtilisin/kexin type 9 inhibitors stabilize vulnerable plaque, reducing cardiovascular events. However, manual optical coherence tomography (OCT) analysis of drug efficacy is challenging because of signal attenuation within lipid plaques.

Methods and Results: Twenty-four patients with thin-cap fibroatheroma were prospectively enrolled and randomized to receive alirocumab (75 mg every 2 weeks) plus rosuvastatin (10 mg/day) or rosuvastatin (10 mg/day) alone. OCT images at baseline and 36 weeks were analyzed manually and with artificial intelligence (AI)-aided software. AI-aided OCT analysis showed significantly greater percentage changes in the alirocumab+rosuvastatin vs. rosuvastatin-alone group in fibrous cap thickness (FCT; median [interquartile range] 212.3% [140.5–253.5%] vs. 88.6% [63.0–119.6%]; P=0.006) and lipid volume (median [interquartile range] −30.8% [−51.8%, −16.6%] vs. −2.1% [−21.6%, 4.3%]; P=0.015). Interobserver reproducibility for changes in minimum FCT and lipid index was relatively low for manual analysis (interobserver intraclass correlation coefficient [ICC] 0.780 and 0.499, respectively), but high for AI-aided analysis (interobserver ICC 0.999 and 1.000, respectively). Agreements between manual and AI-aided OCT analyses of FCT and the lipid index were acceptable (concordance correlation coefficients 0.859 and 0.833, respectively).

Conclusions: AI-aided OCT analysis objectively showed greater plaque stabilization of adding alirocumab to rosuvastatin. Our results highlight the benefits of a fully automated AI-assisted approach for assessing drug efficacy, offering greater objectivity in evaluating serial changes in plaque stability vs. conventional OCT assessment.

Key Words: Artificial intelligence; Lipid-to-cap ratio; Low-density lipoprotein cholesterol; Optical coherence tomography; Proprotein convertase subtilisin/kexin type 9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors significantly lower low-density lipoprotein cholesterol (LDL-C) levels and decrease the risk of ischemic cardiovascular events.[1,2] In a previous prospective randomized study, namely the Alirocumab for Thin-Cap Fibroatheroma in Patients with Coronary Artery Disease Estimated by Optical Coherence Tomography (ALTAIR) study (UMIN000029533), we conducted detailed manual optical coherence tomography (OCT) analysis and demonstrated that the addition of the PCSK9 inhibitor alirocumab to statin therapy substantially increased fibrous cap thickness (FCT) and reduced the lipid plaque component.[3] However, precise quantification of FCT and lipid plaques via OCT is technically challeng-

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ing because of substantial OCT signal attenuation within lipid plaques and difficulties identifying the abluminal border during manual OCT analysis.[4] Indeed, a prior study demonstrated a relatively low interobserver agreement in FCT measurements, with an intraclass correlation coefficient (ICC) of 0.49.[5] Given that both FCT and the total amount of the lipid plaque component are powerful risk factors for future cardiovascular events, manual OCT analysis alone has its inherent limitations for practical use, including being a time-consuming procedure with limited reproducibility, particularly in quantifying the lipidic plaque component when evaluating the plaque stabilization effects of a PCSK9 inhibitor in vivo.

Recent advances in artificial intelligence (AI) have enabled the automated and quantitative evaluation of coronary plaque morphology by OCT, enhancing reproducibility and reducing subjectivity of OCT-based analysis.[6,7] Chu et al. demonstrated that the novel AI-aided OCT analysis can precisely predict FCT and quantify the lipid plaque burden by integrating information from adjacent proximal and distal image frames.[6] Based on these technological improvements, Hong et al. proposed a novel OCT index, namely the lipid to cap ratio (LCR; calculated by dividing the lipid plaque burden by FCT), and demonstrated that the LCR outperformed classic morphological parameters in predicting non-culprit vessel-related major adverse cardiovascular events (MACE).[8] Therefore, the aim of the present study was to evaluate the impact of adding the PCSK9 inhibitor alirocumab to rosuvastatin on plaque stabilization using AI-aided OCT software. In addition, we assessed the reproducibility of AI-aided OCT software compared with manual OCT analysis, aiming to determine whether AI-aided OCT software could overcome the limitations of manual OCT analysis.

Methods

Study Design and Population

In this study, we conducted a post hoc analysis of patients enrolled in the ALTAIR study, which is an open-label prospective randomized single-center trial.[3,9] Patients with LDL-C levels >70 mg/dL despite statin treatment were randomized in 1:1 to either the alirocumab group (alirocumab 75 mg every 2 weeks plus rosuvastatin 10 mg/day) or the rosuvastatin-alone group (rosuvastatin 10 mg/day). OCT imaging at baseline and 36 weeks was compared between the 2 groups. Blood samples for lipid levels were collected at baseline and at 36 weeks.

Patients who met the following criteria were eligible for inclusion in the ALTAIR study: (1) age >20 years; (2) having undergone percutaneous coronary intervention for acute coronary syndrome (ACS) or stable angina pectoris; (3) LDL-C levels >70 mg/dL despite statin treatment; and (4) having OCT-detected thin cap fibrous atheroma (TCFA) in non-culprit, angiographically intermediate lesions (diameter stenosis 30–70%). The exclusion criteria were as follows: (1) uncontrolled hypertension; (2) previous hemorrhagic stroke; or (3) previous PCSK9 inhibitor use. The design and detailed inclusion and exclusion criteria of the ALTAIR study have been published elsewhere[9] (**Supplementary Figure 1**).

In the ALTAIR study, during a prerandomization runin phase, patients with prior statin therapy that did not involve rosuvastatin and with LDL-C levels >70 mg/dL at diagnosis were switched to rosuvastatin 10 mg/day. Statin-naïve patients with LDL-C levels >70 mg/dL at the time of diagnosis were started on rosuvastatin 10 mg/day immediately after percutaneous coronary intervention. In both cases, patients were eligible to participate in the ALTAIR study if their LDL-C levels remained >70 mg/dL at 2–4 weeks after rosuvastatin initiation. The target LDL-C level was 70 mg/dL.

The protocol of the present post hoc study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Kobe University Hospital. Informed consent was obtained in the form of an opt-out option on the website of the Division of Cardiovascular Medicine, Kobe University Graduate School of Medicine. The present study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000052130).

OCT Image Acquisition and Manual OCT Analysis

OCT images were acquired at baseline and at 36 weeks using a frequency-domain OCT system (ILUMIEN; Abbott Vascular, Santa Clara, CA, USA). A bolus intracoronary injection of nitroglycerin was administered before OCT imaging. Following calibration adjustment, a Dragonfly JP or Optis OCT imaging catheter (Abbott Vascular) was advanced distally to the target lesion over a 0.014-inch conventional angioplasty guidewire. After the catheter had been placed at the desired location, contrast medium was flushed through the guiding catheter at a rate of 2–4 mL/s for 3–6 s using an injector pump. When blood was completely displaced from the vessel segment by the contrast medium, the OCT scan was initiated and conducted throughout the entire target lesion at a rate of 20 mm/s using an automatic pullback device.

Offline OCT analysis was performed manually using dedicated software (Light Lab Imaging Inc., Westford, MA, USA) at a single core laboratory by 2 independent observers (T.Y. and Y. Sugizaki) blinded to the patients' clinical presentations and lesion characteristics. A region of interest was a non-culprit lesion with TCFA identified using either side of the stent and the first branch as reference on OCT films for each patient. Plaque tissue characterization was performed using previously validated criteria.[4] Specifically, the lipid core was identified and characterized as a region with poor signal intensity and diffuse borders. The fibrous cap was identified as a signal-rich band overlying the lipid core.[10] The minimum FCT, defined as the thickness of the signal-rich layer overlying the lipid-rich plaque, was measured at the thinnest part of the fibrous cap in 3 candidate frames selected upon visual screening of all contiguous frames; the smallest of the 3 values was retained. TCFA was defined as a plaque with a lipid arc ≥2 quadrants and the thinnest part of the fibrous cap <65 μm. To assess the lipid index, we measured the lipid core arc, defined as the largest arc in a signal-poor region, with diffuse borders on the cross-sectional OCT image at 0.2-mm intervals throughout the target lesion. Lipid core length was defined as the longitudinal length of the lipid-rich plaque (lipid core arc ≥90°). The mean lipid core arc was calculated for each lesion. Then, the lipid index was calculated by multiplying mean lipid core arc by lipid core length.[11] The time required for manual analysis of minimum FCT and the lipid index was recoded.

AI-Aided OCT Analysis

In addition to the manual analysis, OCT images were

analyzed using dedicated AI-aided OCT software (OctPlus, version 2.0; Shanghai Pulse Medical Technology, Inc., Shanghai, China) at a single core laboratory by 2 independent observers (T.Y. and Y.O.) blinded to the patient's clinical presentations and lesion characteristics. The methodology for automatic plaque characterization using AI-aided software has been described previously.[6,7] Briefly, lumen and internal elastic lamina contours were automatically delineated on all OCT cross-sections. Plaque composition, including lipidic, fibrous, and calcific tissues, was subsequently detected by the software and quantified. The 3 characteristics were further analyzed for various parameters, namely angle (°), thickness (mm), area (mm^2) and volume (mm^3). FCT was also analyzed at each frame and the minimum FCT was automatically determined in the target lesion. The lipid index was calculated by multiplying mean lipid core arc by lipid core length.[11] The LCR was automatically quantified using the lipid plaque burden divided by the FCT. The median value of the lipid plaque burden and the minimum value of FCT over 5 consecutive image frames were used to compute the LCR for each OCT image frame. The maximum LCR over the target lesion was used as lesion LCR for statistical analysis.[8] Other classic morphological parameters of the lesion with potential prognostic value, such as the presence of TCFA, defined as a maximum lipid angle >180° and FCT ≤65 μm, were also automatically determined by measuring the arc of the lipid core and FCT. The time required for AI-aided OCT analysis of minimum FCT and the lipid index was recorded.

Inter- and Intra-Observer Variability in Minimum FCT and Lipid Index for Manual and AI-Aided OCT Analysis, and Agreement Between Manual and AI-Aided OCT Analysis

This study evaluated inter- and intra-observer variability for minimum FCT and lipid index in both manual and AI-aided OCT analysis. Interobserver variability between 2 independent observers was evaluated, and 1 observer performed a repeat analysis to evaluate intra-observer variability for both manual and AI-aided OCT analysis. In addition, the agreements for minimum FCT and lipid index between manual and AI-aided OCT analysis were evaluated. These analyses were performed for each OCT dataset in the study, including baseline (n=24), follow-up (n=24), and the absolute change (n=24).

Endpoints

The primary endpoint in this study was the change in minimum FCT from baseline to the 36-week follow-up using AI-aided OCT software. Several OCT findings were considered secondary endpoints, including the changes in lipid volume, LCR, and minimum lumen area during the treatment period. We also compared the times for manual and AI-aided OCT analysis of minimum FCT and lipid index.

Statistical Analysis

All statistical analyses were performed using R open software version 3.4.1 (R Development Core Team, Vienna, Austria). Continuous variables are presented as the mean±SD or median with interquartile range (IQR), and were compared using Student's t-test for normally distributed data or the Mann-Whitney U test for data that were not normally distributed. Data at different time points were analyzed using Paired student's t-test or the Wilcoxon test, as appropriate. Categorical variables are presented as frequencies with percentages and were compared using the Chi-squared or Fisher's exact tests, as appropriate. The reproducibility of minimum FCT and the lipid index was assessed by means of ICC, and agreements between manual and AI-aided OCT analyses were assessed by means of Lin's concordance correlation coefficient (CCC) and Bland-Altman testing. Pearson correlation coefficients were used for correlation analysis. Statistical significance was set at 2-sided P<0.05.

Results

Study Population

Of the 228 patients screened, 24 were enrolled in the ALTAIR study, randomized in a 1:1 ratio, and treated with rosuvastatin 10 mg/day plus alirocumab (alirocumab group; n=12) or rosuvastatin 10 mg/day and no alirocumab (rosuvastatin-alone group; n=12; **Supplementary Figure 2**). All 24 patients underwent OCT at baseline and upon study completion, without significant difference in follow-up duration between the alirocumab and rosuvastatin-alone groups (median 38.2 [IQR 37.1–39.5] vs. 38.3 [IQR 37.0–39.7] weeks, respectively; P=0.977). Baseline characteristics did not differ between the 2 groups, including the concomitant use of ezetimibe or polyunsaturated fatty acids, which was not started or altered during the study period (**Table 1**).

Laboratory Results

There were no significant differences between the 2 groups regarding baseline laboratory parameters (**Table 2**). At 36 weeks, serum LDL-C levels were significantly lower in the alirocumab than rosuvastatin-alone group (median 27 [IQR 23–55] vs. 71 [IQR 64–77] mg/dL, respectively; P<0.0001), with a significantly greater percentage reduction in the alirocumab group (median −64.6% [IQR −71.2%, −60.2%] vs. −17.4% [IQR −28.7%, 1.6%], respectively; P<0.0001; **Table 2**).

AI-Aided OCT Findings

Table 3 summarizes AI-aided OCT findings. Baseline OCT findings did not differ between the 2 groups. Although minimum FCT increased significantly in both groups, at the 36-week follow-up it was significantly higher in the alirocumab than rosuvastatin-alone group (median 193.5 [IQR 171.3–226.0] vs. 123 [102.0–149.5] μm, respectively; P=0.002). The alirocumab group had a significantly greater absolute increase (median 135.5 [IQR 98.3–160.5] vs. 61.0 [IQR 44.5–74.8] μm; P=0.001) and percentage increase (median 212.3% [IQR 140.5–253.5%] vs. 88.6% [IQR 63.0–119.6%]; P=0.006; **Figure 1**) in minimum FCT than the rosuvastatin-alone group. Minimum lumen area did not increase in either group.

From baseline to the 36-week follow-up, lipid volume decreased significantly in the alirocumab group (median 21.1 [IQR 13.7–24.5] vs. 12.7 [IQR 8.6–18.0] mm^3; P<0.001), but not in the rosuvastatin-alone group (median 17.2 [IQR 8.9–25.4] vs. 14.7 [IQR 6.6–24.3] mm^3; P=0.622). Both the absolute decrease and the percentage decrease in lipid volume from baseline to the 36-week follow-up were significantly greater in the alirocumab group (median absolute change −4.9 [IQR −9.4 to −3.0] vs. −0.2 [IQR −1.6 to 0.6] mm^3, P=0.001; median percentage change −30.8% [IQR −51.8%, −16.6%] vs. −2.1% [IQR −21.6%, 4.3%], P=0.015;

Table 1. Clinical Characteristics of Patients at Baseline

	Alirocumab+rosuvastatin (n=12)	Rosuvastatin alone (n=12)	P value
Age (years)	69 [61~78]	72 [68~77]	0.590
Male sex	9 (75.0)	10 (83.3)	1.000
BMI (kg/m^2)	24.3 [22.5~25.8]	23.6 [23.4~24.2]	0.630
Medical history			
Hypertension	10 (83.3)	11 (91.7)	1.000
Diabetes	7 (58.3)	6 (50.0)	1.000
CKD	5 (41.7)	4 (33.3)	1.000
Family history of CAD	1 (8.3)	1 (8.3)	1.000
Smoking	7 (58.3)	8 (66.7)	1.000
Previous PCI	9 (75.0)	7 (58.3)	0.667
History of MI	7 (58.3)	4 (33.3)	0.414
History of CAD	9 (75.0)	7 (58.3)	0.667
ACS at baseline OCT	3 (25.0)	3 (25.0)	1.000
Medications at baseline			
Ezetimibe	0 (0.0)	1 (8.3)	1.000
PUFA	1 (8.3)	2 (16.7)	1.000
Anti-platelet therapy	12 (100)	12 (100)	1.000
β-blocker	7 (58.3)	10 (83.3)	0.371
ACEi or ARB	11 (91.7)	10 (83.3)	1.000
Antidiabetic medication	7 (58.3)	5 (41.7)	0.684

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fatty acid.

Table 2. Laboratory Results

Cholesterol	Change between baseline and follow-up			
	Alirocumab+rosuvastatin (n=12)			Rosuvastatin alone (n=12)
	Baseline	Follow-up	P value	Baseline
TC (mg/dL)	168 (150~183)	103* (97~110)	0.002	160 (139~175)
LDL-C (mg/dL)	90 (81~97)	27* (23~35)	0.002	84 (77~98)
HDL-C (mg/dL)	44 (35~58)	48 (40~53)	0.146	50 (39~58)
Non-HDL-C (mg/dL)	118 (109~126)	55* (51~64)	0.002	105 (100~125)
Triglyceride (mg/dL)	127 (117~156)	124 (80~159)	0.289	115 (97~120)

Cholesterol	Change between baseline and follow-up		Absolute change		
	Rosuvastatin alone (n=12)		Alirocumab+ rosuvastatin (n=12)	Rosuvastatin alone (n=12)	P value (between groups)
	Follow-up	P value			
TC (mg/dL)	145 (131~156)	0.012	−65 (−71~−49)	−13 (−30~−9)	<0.0001
LDL-C (mg/dL)	71 (64~77)	0.015	−59 (−64~−44)	−12 (−28~−1)	<0.0001
HDL-C (mg/dL)	44 (41~47)	0.247	4 (1~6)	−1 (−12~2)	0.068
Non-HDL-C (mg/dL)	102 (83~109)	0.031	−67 (−71~−37)	−12 (−22~−6)	<0.0001
Triglyceride (mg/dL)	134 (108~156)	0.084	−32 (−69~39)	15 (−1~42)	0.128

Unless indicated otherwise, data are given as the median (interquartile range). *P<0.05 compared with rosuvastatin alone at the same time point. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Figure 1). Although LCR decreased significantly in both groups, at the 36-week follow-up it was significantly lower in the alirocumab than rosuvastatin-alone group (median 0.04 [IQR 0.02 to 0.05] vs. 0.12 [IQR 0.08 to 0.20], respectively; P=0.008). The alirocumab group had a significantly greater absolute decrease (−0.19 [−0.25, −0.13] vs. −0.11 [−0.14, −0.07]; P=0.045) and percentage decrease (−84.7% [−92.9%, −72.4%] vs. −38.2% [−66.5%, −28.1%]; P=0.004) in LCR than the rosuvastatin-alone group (**Figure 1**).

Overall, there was a significant negative correlation

Table 3. AI-Aided OCT Measurements

	Change between baseline and follow-up			
	Alirocumab+rosuvastatin (n=12)			Rosuvastatin alone (n=12)
	Baseline	Follow-up	P value	Baseline
Lesion length (mm)	13.8 (12.3~15.8)	13.8 (12.2~15.7)	0.205	12.9 (11.8~14.2)
Minimum lumen area (mm^2)	3.81 (2.20~4.69)	3.78 (2.27~4.86)	0.754	3.48 (3.15~4.94)
Minimum % plaque area	65.1 (56.8~69.8)	65.1 (59.5~71.4)	0.209	57.9 (51.1~61.6)
Plaque volume (mm^3)	80.0 (63.2~102.9)	76.7 (53.9~87.5)	0.151	69.1 (44.9~92.8)
% Lipid volume	24.7 (21.8~28.2)	15.3 (13.5~19.6)	0.021	24.9 (18.1~30.9)
% Fibrous volume	58.7 (53.2~61.1)	63.5 (57.2~67.0)	0.168	59.8 (55.4~62.3)
% Calcification volume	2.3 (0.9~5.3)	7.5 (0.5~10.5)	0.058	1.3 (0.5~2.9)
% Guidewire artifact volume	12.1 (9.6~12.9)	12.7 (10.6~14.2)	0.470	13.7 (10.8~16.1)
Lipid plaque analysis				
Minimum FCT (μm)	66.0 (57.8~68.5)	193.5* (171.3~226.0)	<0.001	59.0 (52.8~83.0)
Max lipid arc (o)	256.4 (194.1~294.1)	206.2 (174.0~263.5)	0.147	218.2 (146.3~264.5)
Lipid index	1,871 (1,035~2,235)	1,249 (593~1,483)	<0.001	1,313 (559~2,015)
Lipid volume (m^3)	21.1 (13.7~24.5)	12.7 (8.6~18.0)	<0.001	17.2 (8.9~25.4)
Lipid-to-cap ratio	0.22 (0.18~0.35)	0.04* (0.02~0.05)	<0.001	0.23 (0.18~0.28)

	Change between baseline and follow-up		Absolute change		
	Rosuvastatin alone (n=12)		Alirocumab+ rosuvastatin (n=12)	Rosuvastatin alone (n=12)	P value (between groups)
	Follow-up	P value			
Lesion length (mm)	12.7 (11.6~14.8)	0.261	–0.1 (–0.3~0.0)	–0.1 (–0.4~0.0)	0.906
Minimum lumen area (mm^2)	3.63 (2.85~4.58)	0.906	0.09 (–0.39~0.37)	0.05 (–0.38~0.23)	0.686
Minimum % plaque area	60.7 (48.1~70.4)	0.110	3.6 (–1.4~5.6)	2.5 (–0.75~5.73)	0.843
Plaque volume (mm^3)	58.6 (42.6~81.8)	0.970	–7.4 (–9.3~–3.5)	2.3 (–5.9~5.9)	0.266
% Lipid volume	19.6 (17.9~30.7)	0.910	–7.7 (–10.4~–2.0)	0.1 (–3.7~2.83)	0.033
% Fibrous volume	59.5 (53.1~69.3)	0.970	3.7 (–1.1~8.3)	0.1 (–2.8~3.0)	0.341
% Calcification volume	2.3 (0.2~4.5)	0.168	0.6 (–0.1~3.0)	0.2 (–0.1~1.2)	0.643
% Guidewire artifact volume	11.3 (9.8~14.8)	0.443	1.6 (–0.6~2.5)	–1.3 (–2.4~0.5)	0.328
Lipid plaque analysis					
Minimum FCT (μm)	123.0 (102.0~149.5)	<0.001	135.5 (98.3~160.5)	61.0 (44.5~74.8)	0.0011
Max lipid arc (o)	241.3 (153.4~255.9)	0.970	–20.1 (–46.3~–1.6)	2.2 (–13.0~8.1)	0.112
Lipid index	719 (550~1,721)	0.791	–423 (–842~–336)	–5 (–133~102)	0.0011
Lipid volume (m^3)	14.7 (6.6~24.3)	0.622	–4.9 (–9.4~–3.0)	–0.2 (–1.6~0.6)	0.0014
Lipid-to-cap ratio	0.12 (0.08~0.20)	0.021	–0.19 (–0.25~–0.13)	–0.11 (–0.14~–0.07)	0.045

Unless indicated otherwise, data are given as the median (interquartile range). *P<0.05 compared with rosuvastatin alone. AI, artificial intelligence; FCT, fibrous cap thickness; OCT, optical coherence tomography.

between the percentage change in minimum FCT and LDL-C (R=−0.507, P=0.012), and a significant positive correlation between LCR and LDL-C (R=0.486, P=0.016; **Supplementary Figure 3**). Images from representative cases are shown in **Figure 2**.

The results of manual OCT measurements were similar to those obtained with AI-aided OCT analysis (**Supplementary Table**).

Comparison of Manual and AI-Aided OCT Analysis

Table 4 presents inter- and intra-observer variability for both manual and AI-aided OCT analysis, as well as the agreement between manual and AI-aided OCT analysis for minimum FCT and lipid index. In the case of manual OCT analysis for minimum FCT and lipid index, interobserver reproducibility was relatively low (ICC 0.438–0.780 and 0.499–0.733, respectively), whereas intra-observer was high (all ICC >0.90). By evaluating inter- and intra-observer variability in AI-aided OCT analysis, there was an excellent correlation seen, with ICC >0.999 for minimum FCT and lipid index. The agreements between manual and AI-aided OCT analyses were within the acceptable range for minimum FCT and lipid index (CCC 0.629–0.890 and 0.833–0.945, respectively). Moreover, there were significant positive correlations for both minimum FCT and lipid index between AI-aided and manual OCT analysis (**Figure 3**). The limits of agreement for minimum FCT at baseline and at follow-up and the absolute change in minimum FCT were −24.7 to 9.2 μm; −59.1 to 52.8 μm; and −56.7 to 65.9 μm, respectively. The limits of agreement for the lipid index at baseline and at follow-up and the absolute change in the lipid index were −477.8 to 572.4; −397.5 to 545.9; and −460.4 to 514.3, respectively (**Figure 4**).

Mean times for AI-aided analysis were significantly shorter than for manual OCT analysis for minimum FCT (103.5±13.4 vs. 183.0±22.6 s; P<0.001) and lipid index

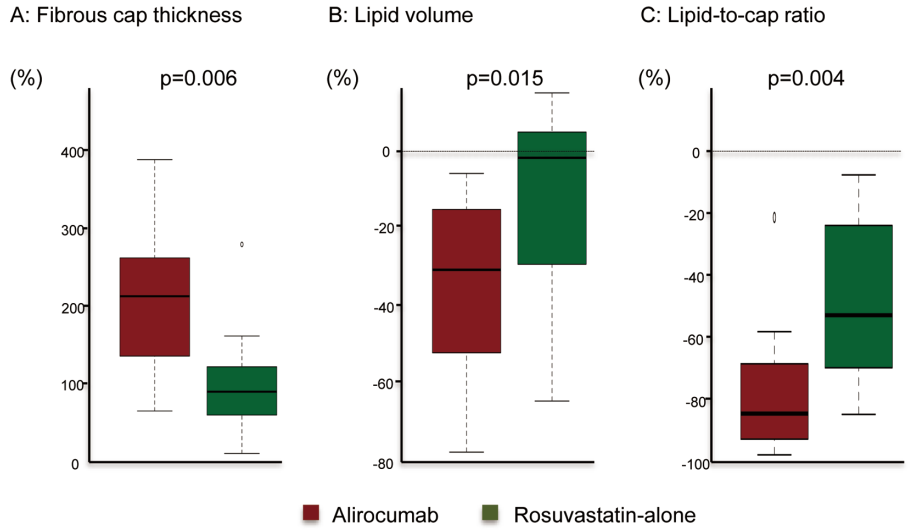

Figure 1. Percentage changes in plaque characteristics identified by artificial intelligence-aided optical coherence tomography analysis: (**A**) fibrous cap thickness (FCT); (**B**) lipid volume; and (**C**) the lipid to cap ratio (LCR). The percentage increase in FCT and the percentage decreases in lipid volume and LCR were significantly greater in the group treated with alirocumab plus rosuvastatin (alirocumab group) than in the group treated with rosuvastatin alone. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

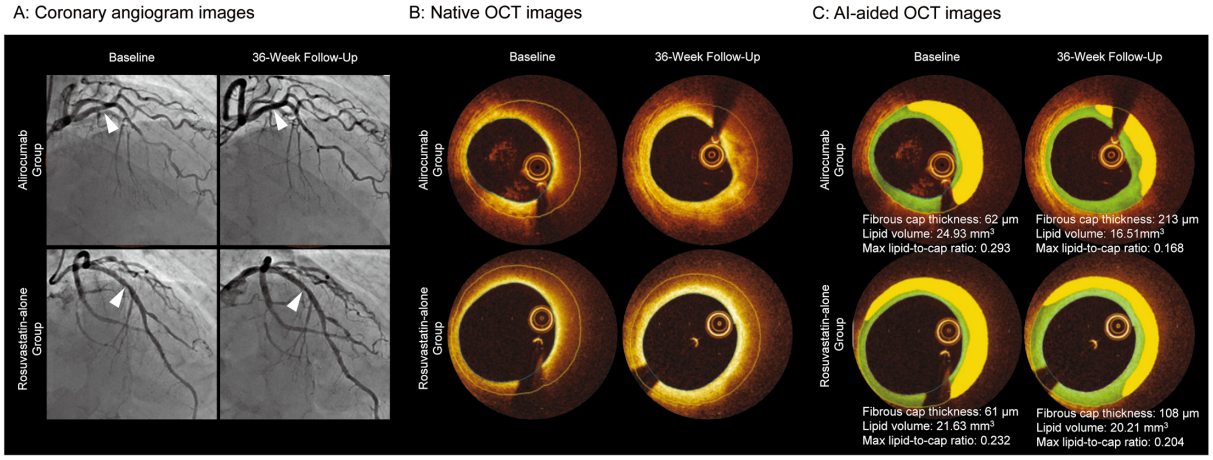

Figure 2. Representative image of serial angiograms and optical coherence tomography (OCT) from the alirocumab plus rosuvastatin (alirocumab) and rosuvastatin-alone groups at baseline and the 36-week follow-up. (**A**) Angiogram images. Arrowheads indicate target lesion. (**B**) Native OCT images. (**C**) Artificial intelligence (AI)-aided OCT images. Yellow indicates lipid plaque; green indicates fibrous plaque.

(103.5±13.4 vs. 494.6±183.5 s; P<0.001; **Supplementary Figure 4**).

Discussion

In the present study, we investigated the effect of adding alirocumab to rosuvastatin on plaque stabilization using an objective approach with AI-aided OCT software. The main findings of this study can be summarized as follows. First, AI-aided OCT analysis objectively showed that combining alirocumab with rosuvastatin led to greater plaque stabilization than rosuvastatin alone, significantly improving lipid volume, minimum FCT, and LCR. Second, the percentage changes in minimum FCT and LCR were significantly correlated with LDL-C levels. Third, interobserver reproducibility in manual OCT analysis for minimum FCT and lipid index was relatively low, but interobserver reproducibility in AI-aided OCT analysis was high. Intra-observer reproducibility in manual and AI-aided analysis, and the agreements between manual

Table 4. Inter- and Intra-Observer Variability in Manual and AI-Aided OCT Analysis, and Agreement Between Methods for Minimum FCT and Lipid Index

	Manual analysis		AI-aided analysis	
	Observer 1	Observer 2	Observer 1	Observer 2
Minimum FCT (μm)				
At baseline	50 (50~60)	60 (50~60)	62.5 (55.0~80.3)	62.5 (55.0~79.3)
At follow-up	125 (77.5~190)	150 (120~200)	157 (122.3~190.3)	157 (122.3~191.5)
Absolute change	75 (35~140)	85 (67.5~132.5)	86.5 (55.8~137.5)	86.5 (54.8~140)
Lipid index				
At baseline	1,886.3±1,070.5	1,559.8±850.9	1,512.5±764.4	1,513.5±764.6
At follow-up	1,628.6±932.5	1,241.3±728.2	1,167.1±729.8	1,166.6±744.6
Absolute change	−257.7±327.6	−318.5±392.0	−345.5±452.2	−346.9±462.7

	Manual analysis		AI-aided analysis		CCC between manual and AI-aided analysis
	Interobserver ICC	Intra-observer ICC	Interobserver ICC	Intra-observer ICC	
Minimum FCT (μm)					
At baseline	0.438	0.909	0.999	1.000	0.629
At follow-up	0.785	0.989	0.999	1.000	0.890
Absolute change	0.780	0.988	0.999	1.000	0.859
Lipid index					
At baseline	0.733	0.980	1.000	1.000	0.945
At follow-up	0.625	0.983	1.000	1.000	0.943
Absolute change	0.499	0.902	1.000	1.000	0.833

Unless indicated otherwise, data are given as the mean ± SD or median (interquartile range). CCC, concordance correlation coefficient; ICC, intraclass correlation coefficient. Other abbreviations as in Table 3.

and AI-aided OCT analyses, were within the acceptable range. Fourth, the mean times for AI-aided analysis of FCT and lipid index were significantly shorter than those for manual OCT analysis. To the best of our knowledge, this is the first study investigating the effect of adding alirocumab to rosuvastatin on plaque stabilization using an objective approach with AI-aided OCT software.

Previous large-scale randomized trials demonstrated that, compared with statin monotherapy, the use of a PCSK9 inhibitor in combination with a statin significantly reduced the incidence of ACS.[1,2] Several investigators have studied the effects of PCSK9 inhibitors on plaque stabilization using various imaging modalities, identifying plaque stabilization as the primary mechanism underlying the preventive effects on of PCSK9 inhibitors against ACS occurrence. Of the various imaging-based findings, the presence of TCFA is regarded as one of the major morphological indicators for predicting future ACS events. However, TCFA detected by OCT exhibits relatively low positive predictive value (10.4%) and high negative predictive value (97.6%) for predicting future cardiac death or myocardial infarction,[12] suggesting the presence of TCFA alone may not be sufficient for the accurate risk stratification of patients with coronary artery disease.

In addition to the presence of TCFA, several studies have consistently reported the importance of the total amount of lipid plaque component within the plaque. Kubo et al. reported that the combined feature of lipid-rich plaque and TCFA was highly specific for predicting future ACS, rather than using TCFA alone.[13] In addition, Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II), which identifies vulnerable plaques and patients using intracoronary near-infrared spectroscopy and intravascular ultrasound, showed that a high lipid content and large plaque burden in non-culprit lesions, as assessed by near-infrared spectroscopy and intravascular ultrasound, increased the risk of future adverse cardiac events in patients with recent myocardial infarction.[14] These studies indicate that for more accurate risk stratification for future cardiovascular events, approaches should consider not only FCT but also the total amount of lipid plaque component. However, because OCT alone cannot directly assess lipid volume due to signal attenuation, previous OCT studies, including the ALTAIR study, used the lipid index, which combines lipid angle and length as surrogate markers of lipid plaque burden. In contrast, the present AI-aided software goes beyond these limitations by enabling direct evaluation of the lipid plaque volume in vivo.[6,7] Previous studies have validated the accuracy of this AI-aided software in evaluating lipid plaque volume by showing a significant correlation between AI-aided evaluation results with core laboratory OCT analysis (R^2=0.98, P<0.001) and intravascular ultrasound analysis (ICC=0.81, P<0.001), regardless of whether the media could be visualized or not.[6,15] Furthermore, the ability of the AI-aided software to directly assess the lipid plaque burden allows fully automated calculation of the LCR, which integrates FCT and the amount of lipid content inside the plaque. In a recent study involving 604 patients with ACS, Hong et al. demonstrated

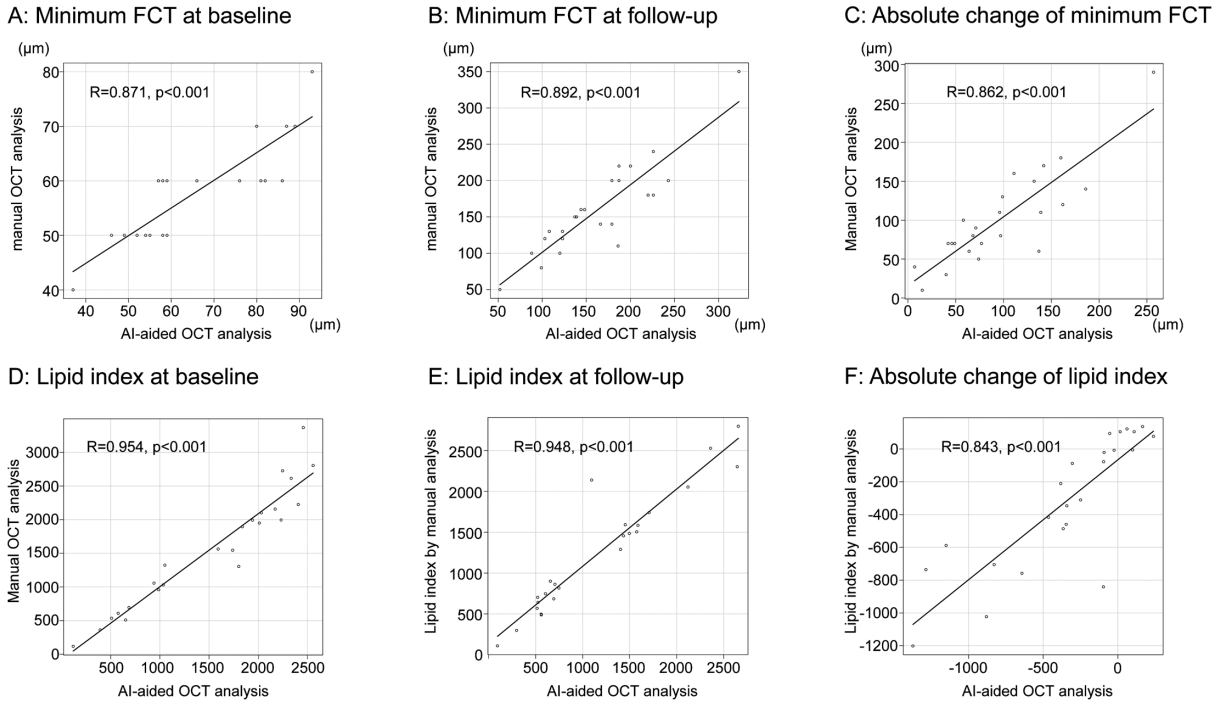

Figure 3. Correlations between manual and artificial intelligence (AI)-aided optical coherence tomography (OCT) analysis. There were significant correlations between manual and AI-aided OCT analysis for (**A**) minimum fibrous cap thickness (FCT) at baseline, (**B**) minimum FCT at follow-up, (**C**) absolute change in minimum FCT, (**D**) lipid index at baseline, (**E**) lipid index at follow-up, and (**F**) absolute change in lipid index.

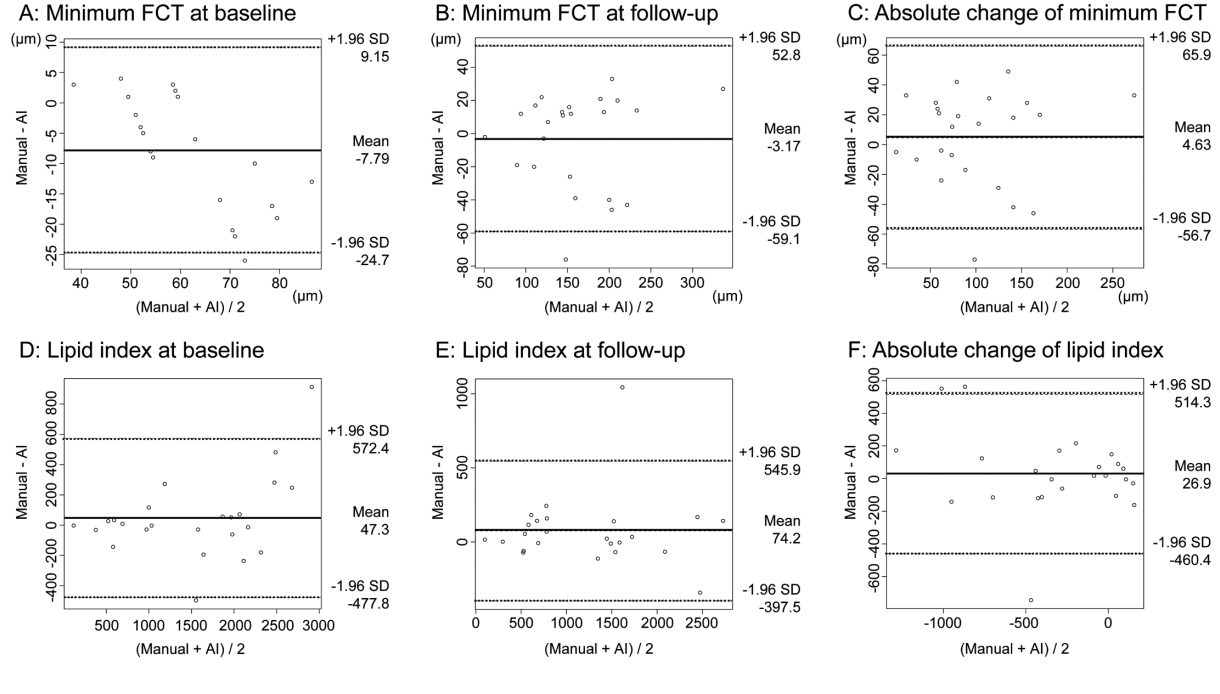

Figure 4. Bland-Altman plots showing good agreements manual and artificial intelligence (AI)-aided optical coherence tomography (OCT) analysis for (**A**) minimum fibrous cap thickness (FCT) at baseline, (**B**) minimum FCT at follow-up, (**C**) absolute change in minimum FCT, (**D**) lipid index at baseline, (**E**) lipid index at follow-up, and (**F**) absolute change in lipid index.

that LCR of the non-culprit lesion was the most sensitive marker to predict non-culprit vessel-related MACE (LCR >0.33, sensitivity 92.3%; TCFA, sensitivity 34.6%).[8] More specifically, patients with LCR >0.33 had 19-fold higher risk of non-culprit vessel-related MACE at 2 years, whereas patients with TCFA alone had only a 2.8-fold higher risk of events.[8]

Given these considerations, AI-aided OCT analysis has the potential to more directly and accurately assess the efficacy of drugs affecting plaque stability. Our study showed considerable fibrous cap thickening, a reduction in lipid plaque, and a substantial decrease in LCR attributed to alirocumab added to rosuvastatin compared with rosuvastatin alone, as assessed by AI-aided OCT analysis. These results underscore the greater contribution of alirocumab to plaque stabilization and potential future risk reduction, provided by more objective and accurate AI-based assessment compared with conventional manual OCT analysis.

Several studies have assessed the effects of PCSK9 inhibitors on plaque stabilization using manual OCT analysis. HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) was a randomized multicenter double-blind placebo-controlled clinical trial evaluating the effects of adding the PCSK9 inhibitor evolocumab to intensive statin on plaque stabilization using OCT in patients with non-ST-elevation myocardial infarction.[16] That study demonstrated a greater increase in minimum FCT and a decrease in lipid arc with evolocumab plus statins compared with statins alone.[16] The fact that HYUGENS was a rigorously designed clinical trial provides strong evidence for plaque stabilization by PCSK9 inhibitors. Consistent with HUYGENS, the ALTAIR study,[3] which used manual OCT analysis, also showed that, compared with rosuvastatin alone therapy, the addition of alirocumab to rosuvastatin resulted in a significantly greater increase in FCT and decrease in the lipid index. In the manual OCT analysis in the ALTAIR study, the minimum FCT was measured manually as the line extending from the vessel lumen to the inner border of the lipid pool in the cross-section where the fibrous cap appears to be thinnest on visual inspection. For the lipid index, analysts manually reviewed consecutive cross-sections to identify segments with lipid plaque and measured each lipid arc and total lipid length. Although these manual methods may seem effective, they are subjective and thus prone to interobserver variability. Indeed, Kim et al.[5] and Brown et al.[17] reported low interobserver ICCs of 0.49 and 0.52, respectively, for FCT. Furthermore, in the present study, using the ALTAIR study dataset, interobserver reproducibility for the FCT and lipid index was relatively low, ranging from 0.438 to 0.785 for FCT and from 0.499 to 0.733 for the lipid index. These findings indicate that approaches with more objective and higher reproducibility than manual OCT analysis are warranted to evaluate the plaque stabilization effects of PCSK9 inhibitors.

AI has facilitated automated and quantitative plaque evaluation using OCT, enhancing reproducibility and reducing subjectivity. Garg et al. demonstrated acceptable reproducibility for vulnerable plaque features, including minimum FCT and lipid area, when assessed using AI-aided OCT software (interobserver ICC for minimum FCT: 0.99; interobserver ICC for lipid area: 0.99).[7] In addition, our study found excellent correlations with ICC >0.999 for minimum FCT and lipid index by evaluating inter- and intra-observer variability in AI-aided OCT analysis. The reliability of AI-aided OCT analysis was further supported by agreements between manual and AI-aided OCT analyses for minimum FCT and lipid index falling within an acceptable range. Finally, consistent with HYUGENS, our study demonstrated a greater increase in minimum FCT and lipid index even with objective analysis using AI-aided OCT software. Fully automated AI-aided OCT analysis not only ensured reproducibility but also considerably reduced the time required for analysis. These results suggest that AI-assisted OCT analysis may be a preferable option for the more accurate risk stratification of patients with coronary artery disease and to assess the efficacy of drugs in stabilizing plaques. Further studies are warranted to validate our findings.

This study has several limitations. First, this was a single-center study with a relatively small number of patients and short follow-up. Thus, selection bias could not be excluded. However, we used the dataset from an open-label prospective randomized study. Further studies with larger sample sizes are required to validate our findings. Second, there have been no validation studies of AI-aided OCT software for patients with ACS. It is unclear whether we can apply the AI-aided OCT analysis for patients with ACS. However, in the present study we included only non-culprit lesions in patients with ACS, which may allow us to use AI-aided software for these lesions, as we have done for patients with chronic coronary syndrome. Third, the strong signal attenuation caused by lipid plaque precludes visibility of the external lamina layer, which is an inherent limitation of OCT images. No method can determine the deep boundaries of the lipid core and the external elastic lamina behind the lipid from OCT images. However, the AI model integrated information from adjacent proximal and distal image frames to make a plausible prediction and reliably extrapolate the invisible part of the external lamina.[6] Fourth, some cases in the present study may involve vessels with positive remodeling, making it challenging to accurately predict the vessel wall using only information from the proximal and distal image frames in close proximity.

Conclusions

AI-aided OCT analysis objectively showed a greater plaque stabilization effect of adding alirocumab to rosuvastatin compared with rosuvastatin alone. Our results highlight the potential benefits of a fully automated AI-assisted approach for assessing drug efficacy, offering greater objectivity and reliability in evaluating serial changes in plaque stability in a short time compared with conventional manual OCT assessment.

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IRB Information

This study was approved by the Ethics Committee of Kobe University Hospital (Reference no. B230141).

Data availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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