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Running head: Statin failure evaluated by FDG PET/CT

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Abstract

Background: Asian patients with acute coronary syndrome (ACS) are frequently prescribed moderate-intensity statin in real practice, even during the early stage of ACS. Under assessment herein was the effect of moderate-intensity statin therapy on the resolution of plaque inflammation during the first month after ACS, a period with highest recurrent ischemic events, using dual time point ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT).

Methods: This prospective study included statin-naïve patients with ACS and non-calcified carotid plaques (≥ 3 mm on ultrasound images). Baseline FDG PET/CT images of the carotid arteries of the patients were obtained. Then, all patients received atorvastatin (20 mg/day); follow-up FDG PET/CT images of the carotid arteries were then obtained after 1 month of therapy. The primary endpoint measurement was the change in the target-to-background ratio (TBR) of the carotid artery between the initial and follow-up FDG PET/CT scans.

Results: Thirteen ACS patients completed the initial and follow-up FDG PET/CT scans. Moderate-intensity statin therapy failed to reduce plaque inflammation at 1 month after ACS (TBR 1.60 ± 0.20 at baseline vs. 1.50 ± 0.40 after therapy; $p = 0.422$) but significantly reduced serum low-density lipoprotein cholesterol (LDL-C) levels (mean LDL-C 101.2 ± 21.1 mg/dL at baseline vs. 70.7 ± 12.4 mg/dL after therapy; $p < 0.001$). Changes in the TBR and serum LDL-C levels were not correlated ($r = -0.27$, $p = 0.243$).

Conclusions: Dual time point FDG PET/CT imaging demonstrates that moderate-intensity statin therapy was insufficient in   suppressed plaque inflammation within the first month after ACS in Asian patients, even though achieving target LDL levels.

Key words: statin, ^{18}F-FDG PET/CT, low-density lipoprotein cholesterol, acute coronary syndromes

Introduction

High-intensity statin therapy has significantly improved the clinical outcomes of patients with acute coronary syndrome (ACS). Because the greatest risk for recurrent cardiovascular (CV) events occurs during the first month after ACS [1, 2], the early initiation of high-intensity statin therapy in ACS patients at the time of intense vascular inflammation improves their CV prognosis by systematically stabilizing highly inflamed plaques. Indeed, a previous study demonstrated the benefits of early statin therapy in reducing ischemic events within 30 days subsequent to ACS [3].

Statins are prescribed at lower starting doses to patients at risk of developing side effects: Asian, female, those with smaller body frame, age exceeding 65 years, kidney or liver disease, or excessive alcohol consumption. Asian patients especially, receive lower doses of statin in most clinical settings compared with their Western counterparts [4]. In clinical practice, only 14.2% of Korean ACS patients received high-intensity statin therapy even after percutaneous coronary intervention (PCI) [5]. Moreover, in the 2013 ACC/AHA guidelines, Asian ancestry is considered as a characteristic that might modify a decision to use high-intensity statin therapy [6]. However, no evidence exists that moderate-intensity statin therapy is sufficient to resolve plaque inflammation in earlier stages of ACS in Asians.

To address this issue, dual time point ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging of carotid arteries was used. FDG PET/CT provides a noninvasive measure of carotid plaque inflammation in patients [7] and successfully monitors alterations in plaque inflammation following therapy with simvastatin [8, 9] and antioxidant probucol

[10]. Under investigation in this study was the effect of moderate-intensity statin therapy on plaque inflammation in early-stage non-ST-segment elevation (NSTE)-ACS patients by performing a longitudinal spatial assessment of statin-modulated alterations of carotid FDG uptake. An assessment was also made as to whether changes in plasma low-density lipoprotein cholesterol (LDL-C) levels, a clinical marker of statin efficacy, correlated with changes in carotid FDG uptake.

Methods

Design and subjects

This study was a prospective observational study involving statin treatment and imaging assessment of atherosclerotic plaque inflammation using dual time point FDG PET/CT scans of carotid arteries. The study protocol was approved by the institutional review board of Seoul St. Mary's Hospital, Seoul, Korea (KC09MISV0195). All subjects provided written informed consent. Patients were eligible for this study if they presented with NSTE-ACS, underwent PCI and had non-calcified atherosclerotic plaques ≥ 3 mm in carotid arteries, as identified using cervical ultrasound (US) examination (Fig. 1). Patients with any of the following conditions were excluded: statin or thiazolinedione therapy within the prior 4 weeks; elevated liver enzyme levels (≥ 2.5 times the normal upper limit); congestive heart failure of New York Heart Association (NYHA) classification class 2 to 4; age < 18 years; and pregnancy. All patients first underwent initial FDG PET/CT scans of their carotid arteries within 7 days after index PCI, followed by statin treatment. One month later, follow-up FDG PET/CT scans of the carotid arteries were performed.

Statin therapy

All study subjects received 20 mg atorvastatin immediately after baseline

FDG PET/CT scanning. All medications, including antidiabetic medications, antiplatelet agents and antihypertensive medications, taken by patients prior to baseline FDG PET/CT scanning were continued.

^{18}F-FDG PET/CT imaging

After a minimum of 6 h of fasting, patients with blood sugar levels of less than 130 mg/dL were intravenously administered approximately 10 mCi of ^{18}F-FDG. Diabetic patients were instructed not to take oral anti-hyperglycemic agents or to inject insulins during fasting time. The patients were then encouraged to drink water and urinate often and had bed rest prior to image acquisition. 90 min after the FDG injection, PET/CT images of the neck region were obtained using a dedicated PET/CT scanner (High Definition Biograph Truepoint; Siemens, Germany). For carotid imaging, non-contrast-enhanced CT images were obtained from the skull base to the lower margin of the neck and were used for attenuation correction (40-section helical, 5 mm section slice). PET images were acquired at 10 min per bed position, from approximately 2 to 4 beds. Contrast enhancement was not performed throughout PET/CT imaging. One month after atorvastatin therapy, follow-up PET/CT images of carotid arteries of 13 of the 20 patients were obtained using the same imaging protocol.

^{18}F-FDG PET/CT analysis

The FDG-PET/CT images were visually evaluated for the presence of abnormal FDG uptake in the bilateral carotid arteries. FDG uptake in the arterial plaques was then quantified by measuring the standardized uptake value (SUV) corrected for body weight. The SUV was calculated usinga pixel activity value within the region of interest (ROI) placed on the entire vasculature obtained from consecutive, co-registered transaxial FDG-PET and non-contrast-enhanced CT

images. The SUV_{max} was recorded as the highest pixel activity value within the ROI for every slice of the vessel. The SUV_{max} was measured along carotid arteries at 5-mm intervals in an axial orientation. The mean SUV_{max} was calculated by averaging SUV_{max} values for all slices within arterial territories. The arterial target-to-background ratio (TBR) was calculated by dividing maximal arterial SUV by blood (jugular vein) FDG uptake to produce a blood-corrected arterial SUV ($SUV_{carotid/jugular}$). Additionally, metabolic lesion volumes (MLV) were computed for each patient's carotid artery lesions by adding all pixels with SUVs greater than the designated cut-off values (SUV cutoff was set at 1.0, or SUV_{max} of neck muscle was used) in manually defined ROIs. Two nuclear medicine physicians who were blinded to patient clinical information performed FDG uptake measurements, which were then averaged. When the difference in measurements between the two readers was greater than 20%, a third nuclear medicine physician helped to reach a consensus. The change in TBR (ΔTBR) was defined as the difference in TBR between baseline and follow-up PET/CT images of the neck.

The primary endpoint value was the absolute change in TBR within an index vessel after 1 month of atorvastatin therapy. The index vessel was defined as the carotid artery in which plaque buildup was detected using cervical ultrasound before treatment. In cases where both carotid arteries had detectable plaque buildup, the artery with the higher FDG uptake was chosen as the index vessel.

^{18}F-FDG PET/CT reproducibility test

FDG PET/CT reproducibility tests were performed at the participating institution using phantoms asa requisite condition for enrollment in unrelated international drug trials. The various PET/CT system parameters were also assessed for quality control on a daily and bimonthly basis as part of a routine

clinical practice.

Measurement of blood metabolic, lipid, and inflammatory parameters

Blood was collected before and 1 month after atorvastatin therapy for the measurement of serum metabolic, lipid, and inflammatory parameters. Fasting serum glucose, total cholesterol, triglyceride, direct LDL-C and direct high-density lipoprotein cholesterol (HDL-C) levels were measured using a Hitachi 7600 automatic chemistry analyzer (Hitachi Co., Tokyo, Japan) with reagents obtained from Sekisui Medical (Tokyo, Japan). High-sensitivity C-reactive protein (hsCRP) levels were measured using an immunoturbidimetric assay with reagents obtained from Wako Pure Chemical Industries (Osaka, Japan) and a Hitachi 7600 automatic chemistry analyzer. Serum insulin levels were measured according to the radioimmunoassay method using an immunoradiometric assay kit obtained from Dinabot Co. (Tokyo, Japan). Plasma matrix metalloproteinase-9 (MMP-9), monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, MN, USA). The homeostatic model assessment (HOMA) index was calculated based on serum glucose and insulin levels.

Statistical analysis

Assuming that 20% of patients would not be available for dual time point PET/CT, it was estimated that 18 patients would provide 80% power to detect an absolute decrease of 0.15 or greater in TBR, with a standard deviation of 0.2 and $\alpha = 0.05$ using 20 mg atorvastatin, based on the findings of a previous study [8].

Statistical analyses were performed using SPSS (v18.0; San Diego, CA). Data are expressed as the mean ± standard error of the mean (SEM). Paired Student t-

test was used to assess differences in FDG uptake and blood parameters before and after therapy. Unpaired Student t-tests were used to test differences in the FDG uptake and blood parameters according to statin response. Spearman's correlation coefficients (r-values) were calculated for correlations. A p-value of less than 0.05 was considered statistically significant.

Results

Characteristics of the study population

Twenty statin-naïve patients who underwent PCI and were found to have non-calcified plaques in their carotid arteries consented to undergo dual time point FDG PET/CT studies of their carotid arteries, and 13 patients completed both pre- and post-statin FDG PET/CT scans and laboratory exams (Fig. 1). 11 male and 2 female patients were included, with a mean age of 67.3 years (52–78 years). 9 patients presented with unstable angina, and 4 patients presented with NSTE myocardial infarction (NSTEMI). All patients received aspirin and clopidogrel. 7 patients had diabetes mellitus and all of them were using oral hypoglycemic agents. The clinical profile and PCI data are summarized in Table1.

Treatment effects of moderate-intensity atorvastatin on plasma lipid, metabolic and inflammatory parameters

Statin therapy significantly reduced serum total cholesterol ($p < 0.001$) and triglyceride ($p = 0.033$) levels. Serum LDL-C levels markedly decreased from 101.2 ± 21.1 mg/dL to 70.7 ± 12.4 mg/dL ($p < 0.001$) following 1 month of statin therapy (Table 2). However, no change in serum HDL-C levels was observed. After statin therapy, 5 patients had follow-up serum LDL-C levels greater than 70 mg/dL but less than 90 mg/dL. In contrast to these improved lipid profiles, plasma inflammatory markers such as hsCRP, MMP-9 and MCP-1 were not significantly

reduced despite statin therapy. Only PAI-1 responded to one-month statin therapy (p = 0.003).

Dual time point FDG PET/CT of carotid arteries

As assessed by 90-min post-FDG PET/CT images, no significant difference was noted in FDG uptake parameters before and after statin therapy (Table 2). Baseline and follow-up TBR values (1.60 ± 0.2 vs. 1.50 ± 0.40, respectively) were not significantly different (p = 0.422). Additionally, statin therapy did not alter any other FDG uptake parameter: (1) SUV_{max} (baseline 2.2 ± 0.5 vs. post-statin 2.0 ± 0.3, p = 0.174); (2) the MLV of carotid lesions with a fixed SUV cutoff of 1.0 ($MLV_{1.0}$; baseline 705.4 ± 724.2 mm^3 vs. post-statin $733.1 \pm 1,213.1$ mm^3, p = 0.926); (3) MLV with each patient's sternocleidomastoid (SCM) muscle SUV_{max} as the cutoff (MLV_{SCM}; baseline $1,683.8 \pm 1,612.5$ mm^3 vs. $1,149.2 \pm 872.6$ mm^3, p = 0.349). When individually analyzed, nine patients had decreased TBR values at follow-up ("statin-responder by PET" group; Fig. 2A), and 4 patients showed similar or paradoxically increased TBR despite adequate statin therapy ("statin-non-responder by PET" group; Fig. 2B, C). The mean follow-up plasma LDL-C levels were 69.8 ± 13.7 mg/dL in the "statin-responder by PET" group and 72.9 ± 9.9 mg/dL in the "statin-nonresponder by PET" group, and no significant difference was found between the two groups (p = 0.691).

Comparison of changes in the blood inflammatory markers and FDG uptake parameters between patients with post-statin LDL levels of less than and greater

than 70 mg/dL

No differences in blood inflammatory parameters, including hsCRP, MMP-9, MCP-1 and PAI-1, or in FDG PET/CT parameters, including the mean SUV_{max}, TBR, $MLV_{1.0}$ and MLV_{SCM} were observed between the two groups (Table 3).

Comparison of changes in the blood inflammatory marker between statin responder by PET and non-responder

The inflammatory markers and FDG uptake markers were compared between PET-CT responder and non-responder. There were significant differences in MMP-9 change (ΔMMP-9) (baseline-follow-up) (responder -1.99 ± 3.02 vs. 3.04 ± 2.31, p = 0.042), however no significant differences were noted in other inflammatory markers (Table 4).

Correlation between plasma LDL-C levels and carotid FDG uptake

No correlation was observed between baseline serum LDL-C levels and the TBR (r = –0.57, p = 0.54) and between ΔLDL-C and ΔTBR (r = –0.35, p = 0.264). Additionally, no significant correlations were found between ΔLDL-C and changes in three other FDG uptake parameters were ΔSUV_{max}, $\Delta MLV_{1.0}$ and ΔMLV_{SCM} (r = –0.15, p = 0.623; r = 0.268, p = 0.377; and r = 0.600, p = 0.067, respectively). In the analysis between FDG uptake parameters and inflammatory markers, no correlation was observed between ΔTBR and changes in inflammatory markers ΔCRP, ΔMMP-9, ΔPAI-1 and ΔMCP-1 (r = –0.086, p= 0.872; r = –0.667, p = 0.071; r = –0.591, p = 0.056; r = –0.471, p = 0.265)

Discussion

In this prospective dual time point study of carotid FDG uptake, moderate-intensity statin therapy occasionally failed to suppress plaque inflammation in

ACS patients. Although moderate-intensity statin therapy successfully achieved target plasma LDL-C levels of approximately 70 mg/dL in all patients with ACS, about 31% (4 out of 13) patients failed to lower the levels of plasma and imaging biomarkers of plaque inflammation during the early stage following ACS, whereas 69% (9 out of 13) succeeded.

The early initiation of high-intensity statin therapy significantly improved early and late clinical outcomes in ACS patients compared with standard-dose statin therapy [11, 12]. Observational studies have also supported the early use of high-intensity statin therapy in ACS patients [13]. However, many practitioners believe that Asians require lower statin doses [4], and the recommended doses of most statins approved in Japan are indeed much lower than those in the US [14]. A JAPAN-ACS study further demonstrated that 20 mg/day of atorvastatin led to the significant regression of coronary atherosclerosis after 8–12 months of therapy [15]. However, no studies have validated the hypothesis that moderate-intensity statin therapy is sufficient to reduce plaque inflammation within 30 days after ACS in Asian patients.

FDG PET/CT was employed in this study, which can precisely map, quantify, and track alterations in statin-induced plaque inflammation, to image carotid arteries [8]. Additionally, all patients selected who presented with NSTE-ACS and were treated with drug-eluting stent (DES) implantation and dual antiplatelet therapy; thus, the anti-inflammatory effect of statins on atherosclerotic plaques could be observed exclusively. Although the systemic inflammatory state in ACS can affect carotid plaque inflammation, the choice to include ACS patients in this study was made. Although statins exert both systemic and local effects during this critical period after ACS, and the degree of statin efficacy differs when acting systemically versus locally, statin therapy should nevertheless suppress the inflammatory burden in carotid plaques. With this unique study design, it was

observed that moderate-intensity statin therapy during the first month after ACS often succeeds but sometimes fails to resolve plaque inflammation in Asian patients.

Notably, poor correlations were observed both between changes in carotid FDG uptake parameters and those in LDL-C levels and between changes in carotid FDG uptake parameters and other plasma inflammatory markers following statin therapy during the acute period of ACS. In contrast, previous studies have shown associations between reduced carotid FDG uptake and decreased LDL-C levels [9] and between decreased MMP-1 and hsCRP levels [16, 17]. The following factors might have contributed to this discrepancy between FDG uptake and blood metabolic and inflammatory markers: (1) Inadequacy of serum LDL-C levels as a barometer of plaque inflammation, especially in the highly vulnerable period followed by plaque rupture; (2) Shortcomings of the clinical FDG PET/CT system currently used to quantify the inflammatory state in atherosclerotic lesions; and/or (3) Insufficiency of the duration of medication to clarify a mutual correlation; (4) Change in FDG uptake contributable to factors other than that of statin [18]. Atherosclerotic plaques are often dynamic in vivo and the FDG uptake is often transient throughout longitudinal clinical course with or without specific treatments [19, 20].

Using FDG uptake to measure the number and metabolic activity of macrophages in a given plaque and measuring serum LDL concentrations may be incongruent because these measures represent two closely related but distinct aspects of complex activities in a vulnerable plaque. Indeed, LDL-C might not mark all of the benefits of statin therapy, and there is insufficient evidence to state that achieving target LDL-C levels (< 70 mg/dL) will decrease CV events in the critical period after ACS [21]. In terms of FDG uptake, although the change in vascular inflammation independent of stain was not excluded (i.e. changes in the

course of ACS), it is reasonable to expect statin does contribute to vascular inflammatory status, but may depend on the dosage.

Limitations of the study

This study has several limitations. First, the duration of moderate-intensity statin therapy only lasted for one month; this period may be insufficient to draw a firm conclusion regarding whether moderate-intensity statin therapy can reduce plaque inflammation in Asian ACS patients. Most similar studies demonstrating the anti-inflammatory action of statins on plaques used treatments lasting 3 months [8, 22]. However, the objective of this study was to investigate whether moderate-intensity statin therapy was sufficient to resolve plaque inflammation within the first month after ACS, which represents the period of highest risk for recurrent CV events. A previous study showed that the effect of statins on reducing FDG uptake can be observed within as early as 4 weeks and that this reduction was in turn correlated with a further reduction after 12 weeks [22]. Additionally, a small, randomized study in Asian ACS patients showed that fluvastatin exerted a significant dose-dependent anti-inflammatory effect in as early as 1 week [23]. Consequently, the authors hypothesized that the anti-inflammatory effect of moderate-intensity statin therapy might be observed and measured using PET/CT within as early as 4 weeks after therapy if the statin is to be effective. If statin therapy is as effective as currently believed, the intensity of statin therapy rather than the 4-week time frame likely dictates the outcome. This needs to be studied separately in a similar patient population.

Second, the present study lacks a control group. The results of a single group "before-after" study such as the present one should be interpreted with caution. The result of the present study should not be considered conclusive on thequestion as to whether moderate-intensity statin is justified in treating Asian NSTE-ACS

patients. Although not conclusive, the results presented suggest that because moderate-intensity statin therapy inconsistently "cool down" inflammatory status in atherosclerotic plaques in this study population, high-dose statin therapy might be more beneficial for patients with certain ACSs, even in patients at risk of developing statin side effects.

Third, the conclusion of this study is based on a small number of patients who underwent initial and follow-up FDG PET/CT scans. Regrettably, there were difficulties in recruiting patients who met our strict inclusion criteria consenting to undergo two FDG PET/CT exams. Thus, there was an inability to draw definitive conclusions. Although the sample was small, it showed that 30% of ACS patients exhibited significant carotid plaque inflammation despite good statin compliance and the achievement of target LDL goals and that moderate-intensity statin therapy is insufficient during an early stage after ACS.

Fourth, in the analysis of FDG PET/CT imaging, plaques 3 mm or greater on carotid artery US were selected and this criterion may have been an insufficient predictor of true plaque inflammation. The measured TBR as well as LDL levels were relatively low and the present patient group may not represent patients with a heavy inflammatory burden of plaques.

Additionally, the non-enhance CT used in the present FDG PET/CT imaging may have limited the resolution of atherosclerotic plaques.

Conclusion

In summary, by using *dual time point* FDG PET/CT images of carotid arteries in ACS patients, this study demonstrates that early moderate-intensity statin therapy does not guarantee resolution of atherosclerotic plaque inflammation after 1 month of statin therapy and the present data indicate it may fail in 30% of patients. Furthermore, plasma LDL-C levels do not reflect the status of local

plaque inflammation.

Conflicts of interest: None declared

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Table 1 Baseline characteristics of patients in the study (n = 13).

Age [years] (range)	67.3 (52–78)
Male	11 (84.6%)
Diagnosis at presentation:	
Unstable angina	9 (69.2%)
NSTEMI	4 (30.8%)
Hypertension	9 (69.2%)
Diabetes mellitus	7 (53.8%)
Current smoker	3 (23.1%)
BMI [kg/m^2]	24.7 ± 2.5
Atorvastatin dose: 20 mg	13 (100%)
Other medications:	
Aspirin	13 (100%)
Clopidogrel	13 (100%)
ARB/ACEI	12 (92.3%)
β-blocker	10 (76.9%)
PCI data:	
Three vessel disease	3 (23.0%)

Two vessel disease	3 (23.0%)
One vessel disease	7 (53.8%)
Mean stent diameter [mm]	3.08 ± 0.29
Total stent length [mm]	39.4 ± 20.4
Total number of stent	1.69 ± 0.85
Number of B2 or C	0.77 ± 0.83
Peak creatinine kinase-MB [ng/mL]	159.2 ± 165.3
Peak troponin I [ng/mL]	132.2 ± 143.9

ARB/ACEI — angiotensin receptor blocker/angiotensin-converting enzyme inhibitor;
BMI — body mass index; NSTEMI — non-ST-segment elevation myocardial infarction;
PCI — percutaneous coronary intervention

Table 2 Baseline and post-statin therapy values of serum lipid, metabolic and
inflammatory markers as well as fluorodeoxyglucose (FDG) uptake parameters.

	Baseline	Post-statin	P
Total cholesterol [mg/dL]	163.9 ± 18.5	129.0 ± 18.6	< 0.001
Triglycerides [mg/dL]	131 ± 81.9	99.5 ± 51.8	0.033
LDL cholesterol [mg/dL]	101.2 ± 21.1	70.7 ± 12.4	< 0.001
HDL cholesterol [mg/dL]	36.5 ± 8.1	38.4 ± 9.3	0.373
Glucose [mg/dL]	126.5 ± 32.9	107.0 ± 14.2	0.029
hsCRP [mg/dL]	0.60 ± 0.82	0.21 ± 0.24	0.073
MMP-9 [ng/mL]	3.6 ± 2.8	3.7 ± 3.0	0.935
PAI-1 [ng/mL]	40.4 ± 23.6	21.6 ± 11.0	0.003
MCP-1 [pg/mL]	32.7 ± 21.1	33.0 ± 9.0	0.965
Mean SUV_{max}	2.2 ± 0.5	2.0 ± 0.3	0.174
TBR	1.6 ± 0.2	1.5 ± 0.4	0.422
$MLV_{1.0}$ [mm^3]	705.4 ± 724.2	733.1 ± 1213.1	0.926

MLV$_{SCM}$ [mm^3]	1683.8 ± 1612.5	1149.2 ± 872.6	0.349

HDL — high-density lipoprotein; hsCRP — high-sensitivity C-reactive protein; LDL — low-density lipoprotein; MCP-1 — monocyte chemoattractant protein-1; MLV$_{1.0}$ — metabolic lesion volume computed using an SUV cutoff of 1.0; MLV$_{SCM}$ — metabolic lesion volume computed using an SUV cutoff of sternocleidomastoid muscle; MMP-9 — matrix metalloproteinase-9; PAI-1 — plasminogen activator inhibitor-1; SUV$_{max}$ — maximum standardized uptake value; TBR — ratio of the maximum standardized uptake value of the carotid plaque over the maximum standardized uptake value of the jugular vein

Table 3 Comparison of the changes in plasma inflammatory markers and fluorodeoxyglucose (FDG) uptake parameters between statin responders and statin non-responders.

Δparameters (baseline-follow up)	Post-statin LDL-C ≤ 70 mg/dL (n = 8)	Post-statin LDL-C > 70 mg/dL (n = 5)	P
ΔhsCRP [mg/dL]	0.34 ± 0.74	0.44 ± 0.58	0.814
ΔMMP-9 [ng/mL]	0.18 ± 2.4	-0.40 ± 5.08	0.843
ΔPAI-1 [ng/mL]	16.8 ± 21.3	21.7 ± 10.6	0.349
ΔMCP-1 [pg/mL]	−10.7 ± 7.8	7.9 ± 28.1	0.246
Mean ΔSUV$_{max}$	0.1 ± 0.5	0.4 ± 0.5	0.356
ΔTBR	0.1 ± 0.5	0.1 ± 0.3	0.926
ΔMLV$_{1.0}$ [mm^3]	−283.8 ± 1206.0	382.0 ± 649.2	0.825
ΔMLV$_{SCM}$ [mm^3]	113.8 ± 991.9	1208.0 ± 3013.4	0.354

Δ — change; hsCRP — high-sensitivity C-reactive protein; MCP-1 — monocyte chemoattractant protein-1; MLV$_{1.0}$ — metabolic lesion volume computed using SUV cutoff of 1.0; MLV$_{SCM}$ — metabolic lesion volume computed using an SUV cutoff of sternocleidomastoid muscle; MMP-9 — matrix metalloproteinase-9; PAI-1 — plasminogen activator inhibitor-1; SUV$_{max}$ — maximum standardized uptake value; TBR — ratio of maximum standardized uptake value of carotid plaque over maximum standardized uptake value of the jugular vein

Table 4 Comparison of changes in plasma inflammatory markers and fluorodeoxyglucose (FDG) uptake parameters between positron emission tomography/computed tomography

(PET/CT) responders and non-responders.

Δparameters (baseline-follow up)	PET-CT responders (n = 9)	PET-CT non-responders (n = 4)	P
ΔTBR	0.59 ± 0.71	–0.64 ± 1.01	0.026
ΔhsCRP [mg/dL]	0.44 ± 0.78	1.39 ± 1.46	0.332
ΔMMP-9 [ng/mL]	–1.99 ± 3.02	3.04 ± 2.31	0.042
ΔPAI-1 [ng/mL]	18.5 ± 14.6	28.30 ± 20.15	0.501
ΔMCP-1 [pg/mL]	4.63 ± 27.0	–10.29 ± 2.13	0.246

Δ — change; hsCRP — high-sensitivity C-reactive protein; MCP-1 — monocyte chemoattractant protein-1; MMP-9 — matrix metalloproteinase-9; PAI-1 — plasminogen activator inhibitor-1; TBR — ratio of the maximum standardized uptake value of carotid plaque over the maximum standardized uptake value of the jugular vein

Figure 1. Study design — flow chart of the patient enrollment process and study schema.

Figure 2. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) images — representative dual time point FDG PET/CT images of carotid arteries according to the response to statin therapy. **A.** "Responder by FDG PET/CT". Ill-defined FDG activity is noted in the bilateral carotid arteries of a 64-year-old male. Coronal and axial images were obtained before (left column) and after (right column) statin therapy. The PET image acquisition time was set at 10 min per bed to improve sensitivity. The red arrows point to the right carotid artery, and white arrows point to the left carotid artery. Focal FDG uptake in the periphery of the carotid arteries reveals a decreased intensity and extent after statin therapy, despite a post-statin low density lipoprotein cholesterol (LDL-C) level of 86 mg/dL (above the target LDL-C level). The ratio of the maximum standardized uptake value of carotid plaque over the maximum standardized uptake value of the jugular vein (TBR) changed from 1.59 to 1.15, with baseline carotid maximum standardized uptake value (SUV_{max}) of 2.24 and jugular vein SUV_{max} of 1.41, and follow-up carotid 1.70 and jugular 1.48. Black arrowheads point to focal calcifications in the right carotid artery wall, which does not correspond to the highest FDG uptake focus as previously reported [18] but rather functions as a landmark for analyzing dual time point images in this study. **B.** "Nonresponder by FDG PET/CT." Multi-focal FDG

uptake areas are noted along the bilateral carotid arteries of a 56-year-old male. Coronal and axial images were obtained before (left column) and after (right column) statin therapy. The red arrows point to the right carotid artery, and the white arrows point to the left carotid artery. Post-statin images show a similar focal FDG uptake intensity and extent in the periphery of   carotid arteries compared with pre-statin images, despite a low post-therapy LDL-C level of 50.6 mg/dL. TBR was essentially unchanged from 1.48 to 1.47, with baseline carotid SUV_{max} of 1.85 and jugular vein SUV_{max} of 1.25, and follow-up carotid 2.01 and jugular 1.37. **C.** "Nonresponder by PET/CT." Ill-defined focal FDG uptake areas are present in the bilateral carotid arteries of a 78-year-old male. Coronal and axial images were obtained before (left column) and after (right column) statin therapy. Red arrows point to the right carotid artery, and white arrows to the left carotid artery. The FDG uptake in the periphery of carotid arteries shows a similar or increased intensity and extent after therapy, suggesting a lack of improvement in plaque inflammation despite a low post-therapy LDL-C level of 61 mg/dL. TBR was increased from 1.69 to 2.18, with baseline carotid SUV_{max} of 2.67 and jugular vein SUV_{max} of 1.58, and follow-up carotid 2.62 and jugular 1.20.

NSTE-ACS patients who underwent PCI

Exclusion :
Age < 18 years, pregnancy, elevated liver enzyme,
congestive heart failure (NYHA II-IV), prior statin
or thiazolinedione therapy

**Screen non-calcified plaque ≥ 3mm on
carotid ultrasound**

Completed baseline ^{18}F-FDG PET CT (n=20)

n=2 refused to take atorvastain

Atorvastatin 20 mg (n=18)

n=5 failed to completed f/u ^{18}**F-FDG PET/CT**

Completed 1 months f/u ^{18}F-FDG PET/CT (n=13)