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ORIGINAL ARTICLE

Effects of lowest-dose vs. highest-dose pitavastatin on coronary neointimal hyperplasia at 12-month follow-up in type 2 diabetic patients with non-ST elevation acute coronary syndrome: an optical coherence tomography analysis

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Abstract

Current ACC/AHA guidelines recommend high-dose statin therapy after coronary stenting, especially in diabetic patients; however, pitavastatin 4 mg or pitavastatin 1 mg are frequently used after coronary stenting in Asia, even in patients with acute coronary syndrome. We compared the effects of highest-dose and lowest-dose pitavastatin therapy on coronary neointimal hyperplasia at 12-month follow-up in diabetic patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) using optical coherence tomography. A total of 72 diabetic patients with NSTE-ACS were randomized to lowest-dose pitavastatin [1 mg ($n=36$)] or highest-dose pitavastatin [4 mg ($n=36$)] after everolimus-eluting stent implantation. The primary endpoint was to compare the normalized neointimal volume at 12-month follow-up. Normalized neointimal volume was significantly lower in the pitavastatin 4 mg group (4.00 ± 2.80 vs. 8.24 ± 2.83 mm^3/mm, $p<0.01$) at 12-month follow-up. There was also significant difference in neointimal area between the pitavastatin 4 mg group and pitavastatin 1 mg group (0.41 ± 0.28 vs. 0.74 ± 0.23 mm^2, $p<0.01$). Improvement of brachial artery flow-mediated dilation (baFMD) was significantly higher in the pitavastatin 4 mg group than in pitavastatin 1 mg group (0.15 ± 0.15 vs. -0.03 ± 0.19 mm, $p<0.001$). In addition, the improvement of adiponectin levels was significantly greater in the pitavastatin 4 mg group than in the pitavastatin 1 mg group (2.97 ± 3.98 vs. 0.59 ± 2.80 μg/mL, $p<0.05$). Pitavastatin 4 mg significantly improved inflammatory cytokines and lipid profiles compared to pitavastatin 1 mg during the 12-month follow-up, contributing to the reduction of neointimal hyperplasia and to the improvement of baFMD in diabetic patients with NSTE-ACS requiring coronary stenting. Thus, the administration of pitavastatin 4 mg can be safely and effectively used in high-risk patients requiring coronary stenting.

Trial registration NCT02545231 (Clinical Trial registration information: https://clinicaltrials.gov/ct2/show/NCT02545231)

Keywords Acute coronary syndrome · Diabetic patients · Pitavastatin · Optical coherence tomography

Introduction

In the era of second-generation drug eluting stents (DES), the acute and late complications of the stent implantation have been significantly reduced compared to those reported during bare metal stents or the first-generation DES use. The advances in stent polymers, stent struts, and eluted drugs reduced the rates of in-stent restenosis (ISR) from 35% to approximately 5% [1, 2]. Nevertheless, ISR is still a major worrisome complication, especially in type 2 diabetic patients. The incidence of ISR in patients with type 2 diabetes is significantly higher than in non-diabetic patients [3], because the former have a higher rate of endothelial

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dysfunction, which was found associated with the progression of atherosclerosis and neointimal proliferation after coronary stenting [4, 5]. However, in addition to the improvement in stent development, statin therapy can further reduce the ISR incidence. Previous researches showed that statins have positive effects on endothelial function, lowering the levels of low-density lipoprotein (LDL)-cholesterol and inflammatory cytokines, and inhibiting neointimal hyperplasia [6–8].

Current guidelines recommend high-intensity lipid-lowering therapy in patients with acute coronary syndrome (ACS) [9]. Nevertheless, Asian population can be considered for administration of lower statin doses [10]. In Asians, including Koreans, whose average body surface area and body weight are lower than those of Caucasian populations, statin administration decreases the level of LDL-cholesterol more powerfully, and sometimes lower statin doses are effective enough to achieve the same results as in Caucasians [11, 12]. A recent study in Korea revealed that moderate-dose statin therapy reduced more than 50% of a baseline LDL-cholesterol level > 190 mg/dL [13]. Accordingly, non-high intensity statins are not infrequently used in Korean patients requiring coronary stenting, even in patients with ACS [14]. However, data regarding the adequate dose of statin to effectively reduce the overgrowth of neointimal hyperplasia and improve the clinical outcomes in Koreans are lacking. Therefore, we prospectively compared the effects of pitavastatin 1 mg and 4 mg on neointimal hyperplasia after coronary stenting by using optical coherence tomography(OCT) and on the changes in vascular function and inflammatory markers in type 2 diabetic patients with ACS during a 12-month follow-up.

Materials and methods

Study patients

Patients aged 30–79 years were eligible for this study if they were: (1) newly diagnosed with type 2 diabetes or had type 2 diabetes and were receiving hypoglycemic agents, and (2) diagnosed with non-ST elevation ACS treated with successful coronary stent implantation (TIMI flow grade 3 after the procedure). A total of 163 consecutive patients were screened for inclusion at Korea University Anam Hospital Cardiovascular Center between March 2013 and April 2014 (Fig. 1). Exclusion criteria were: (1) hypersensitivity to pitavastatin; (2) unable to perform OCT; (3)serum creatinine > 2.0 mg/dL; (4) ST elevation acute myocardial infarction; (5) hemoglobin A_{1c} > 9%; (6) type 1 diabetes; (7) serum platelet level < 100,000/μL; (8) left main coronary artery lesion; (9) left ventricular ejection fraction < 40%; (10) hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase > twice the upper limit); (11) gastrointestinal disorder, such as Crohn's disease; (12) alcohol abuse; (13) steroid or hormone replacement therapy; (14) life expectancy less than 1 year; (15) known pregnancy, breast feeding, or intention to become pregnant during the study period; or (16) any condition that in the opinion of the investigator would make patient participation in this study unsafe or unsuitable.

Study design

This study was a prospective, open-label, single-blinded, randomized trial. A total of 72 patients underwent the randomization in a 1:1 ratio to receive a lowest-dose pitavastatin (1 mg) or highest-dose pitavastatin (4 mg) for 12 months. The investigators who performed OCT analysis and brachial artery flow-mediated dilation (baFMD) were unaware of the randomization assignments until the final data were obtained. The study was approved by the Korea University Hospital Institute Review Board, and written informed consent was obtained from all participants or their legal guardians before their inclusion in the study. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

Endpoints

The primary endpoint was a comparison of differences in normalized neointimal volume using OCT in the pitavastatin 1 mg and pitavastatin 4 mg groups during a 12-month follow-up. The secondary endpoints compared the changes in vascular function and inflammatory cytokines. Vascular function was evaluated by baFMD, brachial-ankle pulse wave velocity (PWV), and augmentation index. The levels of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, high-sensitive C-reactive protein (hsCRP), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and adiponectin were compared.

Coronary angiography and OCT image analysis

All patients were asked to return after 12 months for angiographic follow-up. If clinically indicated, the follow-up angiography was performed earlier. All participating patients received everolimus-eluting stents (EES) (Xience Prime®, Abbott Lab., IL, USA) according to the study protocol. Coronary angiograms were obtained at baseline, immediately after stenting, and at the 12-month follow-up. All angiographic and clinical data were analyzed by individuals who were unaware of the patients' treatment assignments. End-diastolic frames were chosen for quantitative analysis, which was performed using a computer-based TCS system,

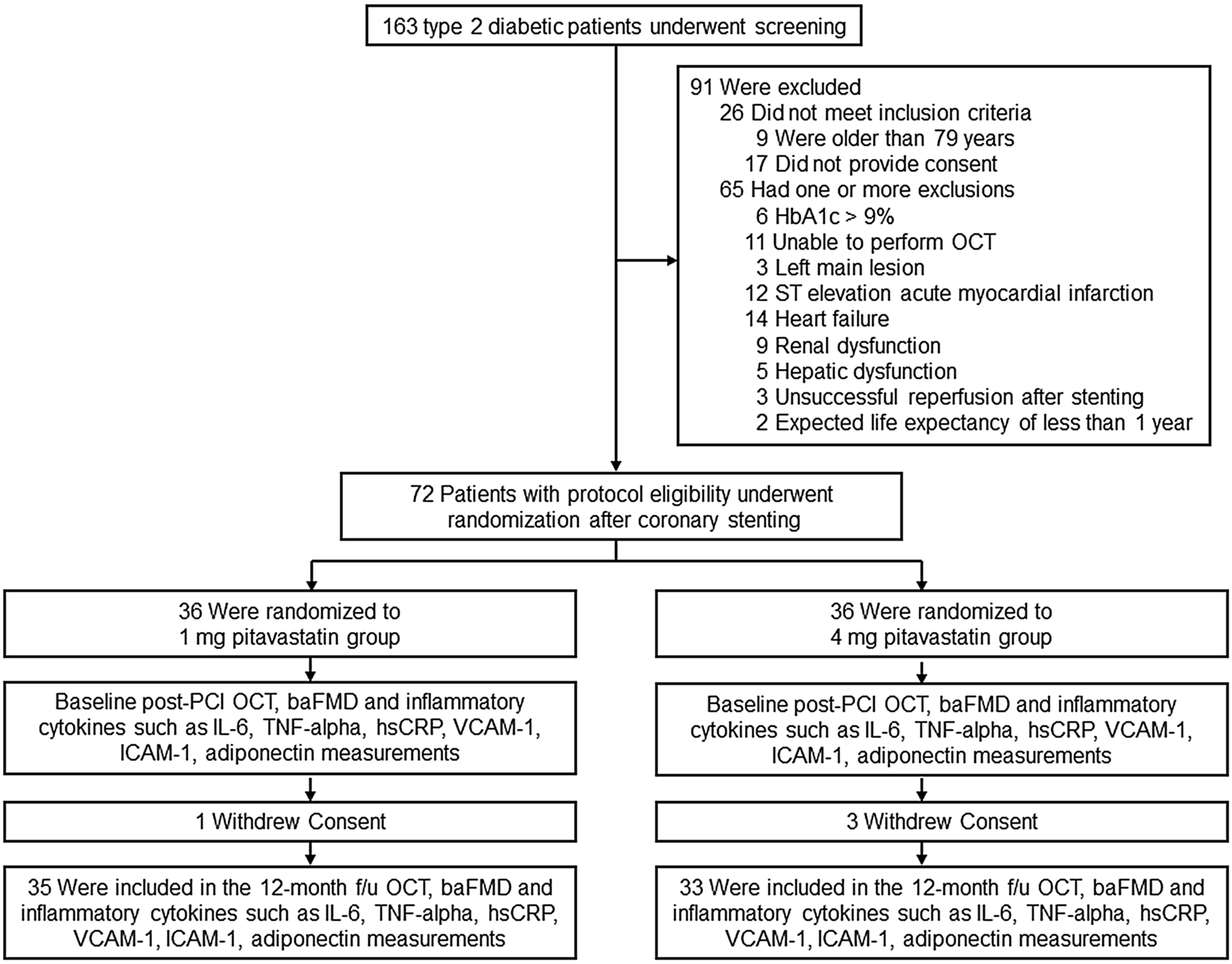

Fig. 1 Study protocol. A total of 72 patients underwent randomization in a 1:1 ratio to receive a low-dose(1 mg) or moderate-dose pitavastatin (4 mg) therapy for 12 months. *baFMD* brachial artery flow-mediated dilation, *hsCRP* high sensitivity C-reactive protein, *sICAM-1* soluble intercellular adhesion molecule-1, *IL* interleukin, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention, *TNF* tumor necrosis factor, *sVCAM-1* soluble vascular cell adhesion molecule-1

Version 2.02 (Medcon Ltd., Tel-Aviv, Israel). Balloon angioplasty and stent implantation were performed according to the standard clinical practice.

Optical coherence tomography data were analyzed at the Korea University OCT Core Laboratory, and all OCT data were analyzed by individuals who were unaware of the patients' treatment assignments. OCT was performed after intracoronary administration of 200 µg of nitroglycerin injection. OCT images have been acquired using a nonocclusive technique using the C7XR system (LightLab Imaging Inc., Westford, MA, USA), and images were digitally stored for the subsequent analysis. Quantitative strut-level OCT analysis was performed at 0.5 mm intervals and OCT lesions were defined according to International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT) consensus standard [15]. Mean area and volumes of the lumen, stent, and neointimal hyperplasia were calculated along the entire stented segment. The normalized neointimal volume (mm^3/mm) was calculated as the volume divided by the measured length . Neointima was the tissue between the luminal border and the inner border of the struts [16]. To characterize the neointimal tissue, homogeneous neointima was defined as a uniform signal-rich band without focal variation or attenuation and heterogeneous neointima as focally changing optical properties and various backscattering patterns [17]. For the measurements of a neointimal unevenness score in each cross section, the maximal neointimal thickness in one cross section was divided by the average neointimal thickness of the cross section [18].

Measurement of secondary endpoints

Measurement of baFMD, PWV, central BP, augmentation index, and laboratory analysis were performed according to our previous trial [19].

Statistical analysis

Data were expressed as mean ± standard deviation for the continuous variables, and as number and percentage of patients for the categorical variables. Fisher's exact test or chi-square test was used for categorical variables. The results of the two groups were compared using the unpaired Student's *t* test, and the comparisons of the results obtained before and after the treatment were analyzed using the paired *t* test when normally distributed or Wilcoxon signed-rank test when not normally distributed. The sample size of the study was determined based on the estimation of the primary end point of normalized neointimal volume obtained in our previous trial [20]. We assumed a normalized neointimal volume of 1.88 ± 1.0 mm^3/1 mm in pitavastatin 4 mg group and 2.64 ± 1.4 mm^3/1 mm in pitavastatin 1 mg group. Using a two-sided test for differences in independent binomial proportions with an α level of 0.05, we calculated that 58 patients (29 patients for each group) would have to undergo randomization for the study to have an 80% power to detect a difference in normalized neointimal volume between the 2 groups; therefore, we enrolled 36 patients in each group to account for 20% loss in the OCT follow-up. This study used a per-protocol analysis. p value < 0.05 was considered statistically significant. SAS software (version 9.3; SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Patient characteristics

Baseline patient characteristics of mean age, body mass index, risk factors, and medications on admission were similar between the pitavastatin 1 mg ($n = 35$) and pitavastatin 4 mg ($n = 33$) groups (Table 1).

OCT parameters and clinical outcomes at 12-month follow-up

Quantitative OCT analyses are shown in Table 2. Normalized neointimal volume was significantly lower in the pitavastatin 4 mg group (4.00 ± 2.80 vs. 8.24 ± 2.83 mm^3/mm, $p < 0.01$) at 12-month follow-up (Table 2, Fig. 2a). There was also significant difference in neointimal area between the pitavastatin 4 mg group and pitavastatin 1 mg group (0.41 ± 0.28 vs. 0.74 ± 0.23 mm^2, $p < 0.01$) (Fig. 2b). However, neointimal hyperplasia thickness did not reach the statistical significance ($p = 0.35$). Neointimal thickness was significantly correlated with baseline glucose level and HbA1c level ($r = 0.61$, $p = 0.002$ and $r = 0.56$, $p = 0.01$, respectively). Other factors including demographic, laboratory, angiographic, or OCT findings did not significantly affect the neointimal thickness. LDL-cholesterol changes of − 30 or − 50% from baseline did not affect mean neointimal hyperplasia area ($p = 0.63$ and $p = 0.97$, respectively). At 12-month follow-up, there were no significant clinical events between pitavastatin 1 and 4 mg.

Changes in brachial artery flow-mediated dilation and aortic stiffness

Improvement in baFMD was significantly greater in the pitavastatin 4 mg group (0.15 ± 0.15 vs. − 0.03 ± 0.19 mm, $p < 0.001$) (Table 3, Fig. 3). Measurement of brachial artery dilation after nitroglycerine did not show significant differences between the groups. Administration of pitavastatin 4 mg significantly increased the FMD compared to pitavastatin 1 mg (OR 114.6, 95% CI 3.87–3397.2, $p = 0.006$) after adjusting age, sex, body mass index, smoking, hypertension, and diabetes during the follow-up. However, LDL lowering effects did not significantly affect the improvement of FMD. There was no significant correlations between improvement of FMD and the normalized neointimal hyperplasia volume or mean neointimal hyperplasia area ($p = 0.14$ and $p = 0.11$, respectively). No significant differences in PWV, ankle-brachial index, central BP, or augmentation index were detected between the groups (Table 4).

Changes in inflammatory markers and lipid profiles during the 12-month follow-up

Pitavastatin 4 mg, but not pitavastatin 1 mg, showed significant decreases in hsCRP levels (Table 5). Improvement of adiponectin was significantly higher in the pitavastatin 4 mg group than in pitavastatin 1 mg group (2.97 ± 3.98 vs. 0.59 ± 2.80 μg/mL, $p < 0.05$). The HOMA index improved in both groups(Table 5). Changes from baseline in LDL-cholesterol levels decreased significantly in pitavastatin 4 mg group compared to pitavastatin 1 mg group at the 12-month follow-up (− 41.0 ± 38.5 vs. − 18.9 ± 29.1 mg/dL, $p < 0.05$). The percent reduction of LDL-cholesterol from baseline was 17% in pitavastatin 1 mg group and 36% in pitavastatin 4 mg group. The percentage of patients who reached the LDL-cholesterol goal (< 100 mg/dL) was significantly higher in pitavastatin 4 mg group than in pitavastatin 1 mg group (85.3 vs. 61.5%, $p = 0.04$). In addition, the percentage of patients who reached the LDL-cholesterol goal (< 70 mg/dL) was higher, although statistically not significant, in the

Table 1 Baseline demographic and angiographic characteristics

Variable	Pitavastatin 1 mg (*n* = 35)	Pitavastatin 4 mg (*n* = 33)	*p* value
Age (years)	65.7 ± 8.97	62.4 ± 9.00	0.14
Male sex	22 (62.9%)	25 (75.8%)	0.25
Body mass index (kg/m^2)	25.0 ± 3.0	24.9 ± 2.3	0.90
Diagnosis			0.31
Unstable angina	28 (80.0%)	29 (87.9%)	
Non-ST elevation MI	7 (20.0%)	4 (12.1%)	
Risk factors			
Hypertension	23 (65.7%)	21 (63.6%)	0.86
Current smoking	11 (31.4%)	8 (24.2%)	0.72
Past history of stroke	0 (0%)	1 (3.0%)	0.30
Medication on admission			
Aspirin	35 (100%)	33 (100%)	0.99
Clopidogrel	33 (94.3%)	29 (87.9%)	0.36
Ticagrelor	2 (5.7%)	2 (6.1%)	0.95
Prasugrel	0 (0%)	2 (6.1%)	0.14
ACE inhibitor	11 (31.4%)	11 (33.3%)	0.87
ARB	11 (31.4%)	8 (24.2%)	0.51
β-blocker	19 (54.3%)	16 (48.5%)	0.63
CCB	15 (42.9%)	9 (27.3%)	0.18
Diuretics	7 (20.0%)	3 (9.1%)	0.20
Metformin	15 (42.9%)	18 (54.5%)	0.34
Glimepiride	18 (51.4%)	11 (33.3%)	0.14
Pioglitazone	12 (34.3%)	11 (33.3%)	0.94
DPP-4 inhibitor	7 (20.0%)	4 (12.1%)	0.39
Insulin	1 (2.9%)	1 (3.0%)	0.97
Diuretics	7 (20.0%)	3 (9.1%)	0.20
Angiographic features	56 lesions	42 lesions	
Diseased vessel			0.19
1-vessel disease	10 (28.6%)	14 (42.4%)	
2-vessel disease	14 (40.0%)	14 (42.4%)	
3-vessel disease	11 (31.4%)	5 (15.2%)	
Target coronary artery			0.58
Left main	2 (3.6%)	4 (9.5%)	
Left anterior descending	27 (48.2%)	18 (42.9%)	
Left circumflex	12 (21.4%)	7 (16.7%)	
Right	15 (26.8%)	13 (31.0%)	
Pre-procedural angiography			
Lesion length (mm)	21.60 ± 12.07	25.42 ± 15.27	0.36
Proximal reference vessel diameter (mm)	3.22 ± 0.65	2.97 ± 0.75	0.23
Distal reference vessel diameter (mm)	2.92 ± 0.95	2.73 ± 1.01	0.52
Minimal lumen diameter (mm)	0.68 ± 0.52	0.58 ± 0.47	0.51
Immediately after index procedure			
Stent diameter (mm)	2.92 ± 0.41	2.98 ± 0.44	0.48
Stent length (mm)	23.23 ± 9.66	27.31 ± 14.97	0.11
Stent number (/patient)	1.68 ± 0.77	1.55 ± 0.67	0.46
Proximal reference vessel diameter (mm)	3.30 ± 0.52	3.14 ± 0.55	0.33
Distal reference vessel diameter (mm)	3.16 ± 0.50	3.00 ± 0.54	0.31
Minimal lumen diameter (mm)	2.96 ± 0.45	2.98 ± 0.48	0.20
12-month follow-up angiography			
Proximal reference vessel diameter (mm)	3.27 ± 0.55	3.16 ± 0.61	0.55
Distal reference vessel diameter (mm)	3.11 ± 0.52	3.03 ± 0.60	0.66
Minimal lumen diameter (mm)	3.07 ± 0.59	2.83 ± 0.83	0.33

Table 1 (continued)

Values are presented as mean ± standard deviation or n (%)

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *DPP-4* dipeptidyl peptidase-4

Table 2 Comparison of optical coherence tomographic parameters at 12-month follow-up

Variable	Pitavastatin 1 mg (n = 35)	Pitavastatin 4 mg (n = 33)	p value
Post PCI			
Minimal lumen area (mm^2)	6.47 ± 1.66	7.91 ± 4.03	0.31
Minimal stent area (mm^2)	5.07 ± 1.39	5.72 ± 3.68	0.61
Stent malapposition (%)	2 (5.7%)	0 (0.0%)	0.49
Stent edge dissection (%)	0 (0.0%)	2 (6.1%)	0.23
Presence of thrombi (%)	6 (17.1%)	5 (15.2%)	0.99
Presence of tissue protrusion (%)	7 (20.0%)	8 (24.2%)	0.77
Quantitative measurements			
Cross-sectional level analysis			
Mean lumen area (mm^2)	5.70 ± 1.52	5.97 ± 2.60	0.77
Mean NIH area (mm^2)	0.74 ± 0.23	0.41 ± 0.28	<0.01
Lumen volume (mm^3)	115.87 ± 44.88	151.16 ± 66.63	0.15
Stent volume (mm^3)	127.21 ± 50.95	165.39 ± 71.57	0.15
Normalized NIH volume (mm$^{3/}$mm)	8.24 ± 2.83	4.00 ± 2.80	<0.01
NIH thickness (μm)	140.40 ± 288.40	63.45 ± 44.83	0.35
Strut-level analysis			
Struts (n)	188.73 ± 76.6	221.31 ± 74.88	0.31
Covered struts (%)	97.04 ± 2.44	97.16 ± 6.30	0.96
Covered protruding struts (%)	17.53 ± 16.01	21.05 ± 16.51	0.58
Uncovered struts (%)	2.96 ± 2.44	2.89 ± 6.27	0.97
Malapposed struts (%)	0.04 ± 0.13	0.06 ± 0.18	0.71
Exposed struts (%)	0.31 ± 0.34	0.07 ± 0.29	0.06
Qualitative measurements			
Persistent malapposition (%)	1 (2.9%)	0 (0.0%)	0.99
Stent edge dissection (%)	0 (0.0%)	0 (0.0%)	NA
Presence of thrombi (%)	1 (2.9%)	0 (0.0%)	0.99
Plaque prolapse (%)	0 (0.0%)	0 (0.0%)	NA
Heterogenous pattern (%)	1 (2.9%)	2 (6.1%)	0.61
Homogenous pattern (%)	34 (97.1%)	31 (93.9%)	
Layered pattern (%)	0 (0.0%)	0 (0.0%)	
Neovascularization (%)	0 (0.0%)	0 (0.0%)	NA
Lipid-laden neointima (%)	0 (0.0%)	0 (0.0%)	NA
Thin-cap neoatheroma (%)	0 (0.0%)	0 (0.0%)	NA

Values are presented as mean ± standard deviation or n (%)

NIH neointimal hyperplasia

pitavastatin 4 mg group than in the pitavastatin 1 mg group (44.1 vs. 26.9%, $p = 0.18$).

Discussion

This prospective, single-blinded, randomized study compared the effects of highest-dose pitavastatin (4 mg) with lowest-dose pitavastatin (1 mg) on neointimal hyperplasia, vascular function, and inflammatory cytokines over a 12-month follow-up in diabetic patients with non-ST elevation ACS. Administration of pitavastatin 4 mg when compared to pitavastatin 1 mg significantly decreased neointimal hyperplasia during the 12-month follow-up; moreover, this study demonstrated that pitavastatin 4 mg significantly improved the brachial artery endothelial dysfunction in type 2 diabetic patients requiring coronary stenting. In addition, pitavastatin 4 mg significantly increased the circulating

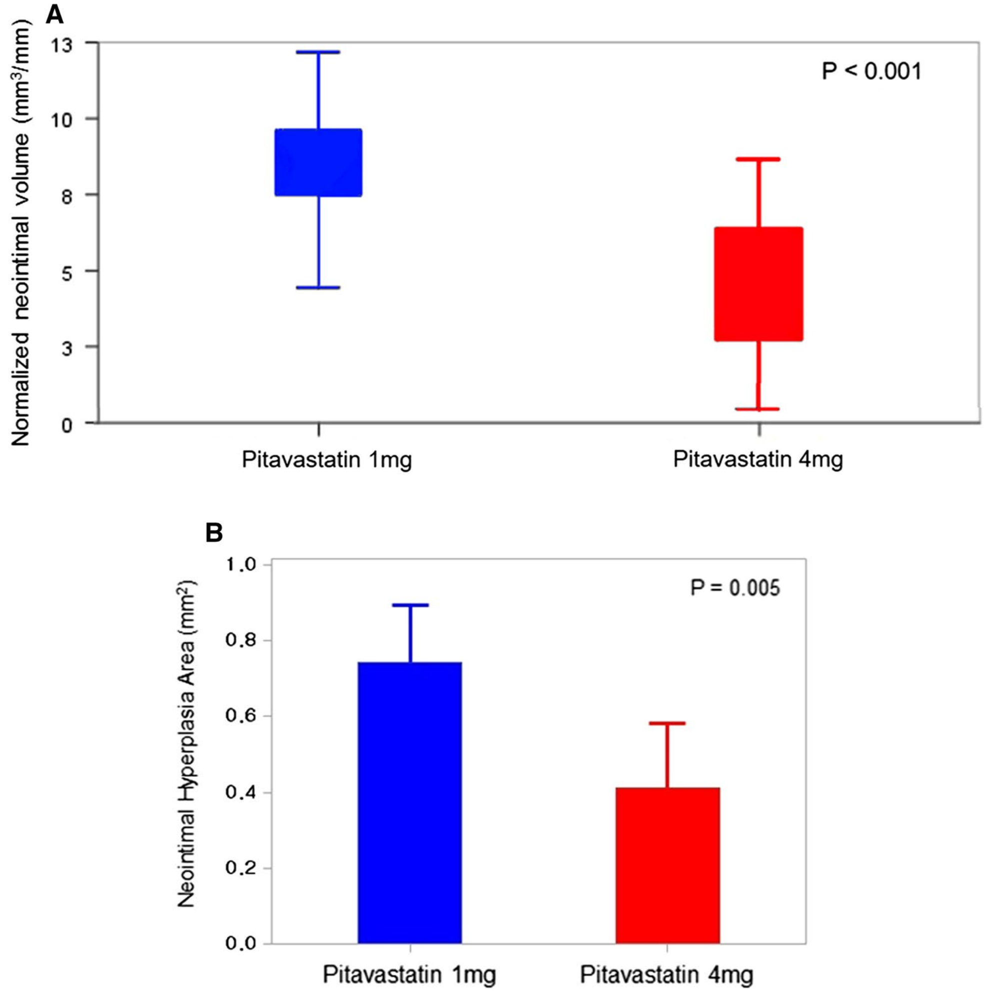

Fig. 2 **a** Comparison of normalized neointimal hyperplasia volume at 12-month follow-up. **b** Comparison of neointimal hyperplasia area at 12-month follow-up

Table 3 Comparison of changes in brachial artery flow-mediated dilation during the 12-month follow-up between pitavastatin 1 and 4 mg groups

Variables	Pitavastatin 1 mg (*n* = 35)		Pitavastatin 4 mg (*n* = 33)	
	Baseline	After 12 months	Baseline	After 12 months
Pre-FMD (mm)	3.72 ± 0.57	3.66 ± 0.54	3.83 ± 0.62	3.83 ± 0.59
Changes from baseline	− 0.05 ± 0.15		− 0.00 ± 0.01	
Post-FMD (mm)	4.01 ± 0.59	3.96 ± 0.53*	4.09 ± 0.61	4.26 ± 0.61*
Changes from baseline	− 0.03 ± 0.19†		0.15 ± 0.15†	
Pre-NTG (mm)	3.72 ± 0.57	3.66 ± 0.54	3.83 ± 0.62	3.83 ± 0.59
Changes from baseline	− 0.04 ± 0.15		− 0.03 ± 0.13	
Post-NTG (mm)	4.36 ± 0.61	4.23 ± 0.56	4.42 ± 0.65	4.40 ± 0.61
Changes from baseline	− 0.08 ± 0.20		− 0.04 ± 0.16	

Values are presented as mean ± standard deviation

FMD flow-mediated dilation, *NTG* nitroglycerine, *Post-FMD* post-hyperemia flow-mediated dilation

**p* < 0.05 compared between pitavastatin 1 and 4 mg

†*p* < 0.01 compared between pitavastatin 1 and 4 mg

adiponectin levels and decreased the LDL-cholesterol levels during the 12-month follow-up. The anti-inflammatory and anti-atherogenic effects of pitavastatin 4 mg might contribute to the observed decreases in neointimal hyperplasia and improvement in the brachial artery endothelial function.

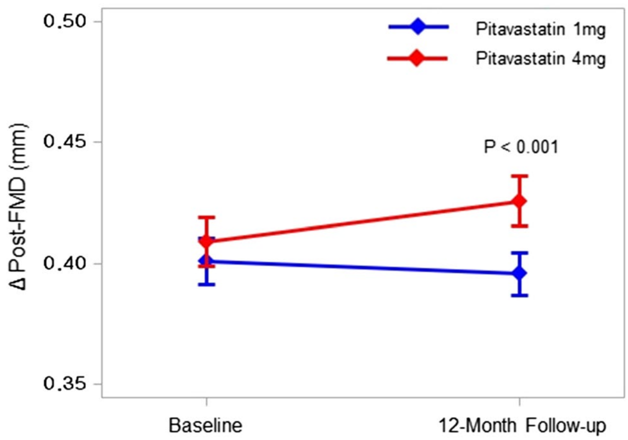

Fig. 3 Changes of brachial artery flow-mediated dilation at 12-month follow-up. *Δ Post-FMD* changes of post-hyperemia flow-mediated dilation, *baFMD* brachial artery flow-mediated dilation

Among DESs, EES which was used in our study demonstrated low rates of strut malapposition and uncovered struts [21]. In our study, the rates of strut malapposition and uncovered struts were 0.05 and 2.9%, respectively, similar to the previous Korean data [22]. During follow-up periods, previous studies reported the lowest rate of subclinical thrombi in EES. In our study, the rate of thrombi was only 1.5% (1/68) which was even lower than that of previous data. Considering the mid-term mean neointimal thickness of EES was as low as 100 µm, the present study showed almost the same results with mean neointimal thickness of 98.7 ± 196.8 µm. In comparison to Korean data of 164 ± 95 µm, mean neointimal thickness of our study was even lower [23]. These improved biocompatibilities of EES were reiterated in our study. We enrolled the 11 (16.2%) patients with non-ST elevation MI in our study. In a meta-analysis, prevalence of culprit plaque rupture and thin-cap fibro-atheroma (TCFA) were 55.6 and 56.3%, respectively [24]. However, the plaque rupture was identified in only 18.2% of patients in our study. TCFA were also shown in only 18.2% of patients in this study. Because the number of enrolled patients was relatively small, the incidence of plaque rupture and TCFA were low.

Neointimal hyperplasia starts within weeks after the stent implantation. Smooth muscle cells proliferate inwards, triggered by endothelial damage, endothelial dysfunction, and white blood cell adhesions [25]. Diabetes mellitus exaggerates these processes after coronary stenting [26]. Neointimal proliferation showed strong correlations with the degree of inflammation and LDL-cholesterol levels [27]. Accordingly, the modulation of the inflammatory response and LDL-cholesterol lowering are crucial in decreasing the neointimal hyperplasia. Statins are known for their anti-inflammatory and anti-proliferative effects on the smooth muscle cells [28]. Pleiotropic effects of statins, including the inhibition of monocytes, cell adhesion molecules, and nuclear transcription factors, have additional effects on attenuation of neointimal hyperplasia [29, 30]. In previous studies, pitavastatin significantly reduced the plasminogen activator inhibitor-1

Table 4 Comparison of changes in pulse wave velocity and blood pressure values during the 12-month follow-up between Pitavastatin 1 mg and 4 mg groups

Variables	Pitavastatin 1 mg (n = 35)		Pitavastatin 4 mg (n = 33)	
	Baseline	After 12 months	Baseline	After 12 months
Right PWV (cm/s)	1748 ± 260	1866 ± 624	1697 ± 257	1655 ± 308
Changes from baseline	118 ± 467		19 ± 307	
Left PWV (cm/s)	1735 ± 249	1840 ± 520	1697 ± 257	1665 ± 308
Changes from baseline	91 ± 338		− 5 ± 302	
Right ABI (%)	1.10 ± 0.14	1.09 ± 0.09	1.12 ± 0.08	1.11 ± 0.12
Changes from baseline	− 0.06 ± 0.09		0.01 ± 0.10	
Left ABI (%)	1.10 ± 0.11	1.11 ± 0.11	1.13 ± 0.10	1.09 ± 0.10
Changes from baseline	− 0.01 ± 0.12		− 0.02 ± 0.07	
SBP (mmHg)	133 ± 16	136 ± 19	134 ± 14	132 ± 13
Changes from baseline	2 ± 21		2 ± 17	
DBP (mmHg)	71 ± 11	85 ± 20	73 ± 15	77 ± 14
Changes from baseline	13 ± 21		6 ± 14	
cSBP (mmHg)	133 ± 19	129 ± 35	133 ± 21	131 ± 21
Changes from baseline	− 6 ± 37		− 1 ± 24	
AI (%)	75.9 ± 15.3	81.1 ± 11.8	77.8 ± 9.7	77.5 ± 10.0
Changes from baseline	2.1 ± 9.9		− 0.7 ± 8.2	

Values are presented as mean ± standard deviation

ABI ankle-brachial index, *AI* augmentation index, *cSBP* estimated central systolic blood pressure, *DBP* diastolic blood pressure, *PWV* pulse wave velocity, *SBP* systolic blood pressure

Table 5 Comparison of inflammatory markers levels, insulin resistance, and lipid profiles during the 12-month follow-up

Variables	Pitavastatin 1 mg (*n* = 35)		Pitavastatin 4 mg (*n* = 33)	
	Baseline	After 12 months	Baseline	After 12 months
IL-6 (pg/mL)	6.05 ± 2.60	5.16 ± 1.72	5.51 ± 2.27	4.79 ± 1.77
Changes from baseline	− 0.89 ± 2.89		− 0.72 ± 2.72	
TNF-α (pg/mL)	7.50 ± 2.40	6.95 ± 1.62	6.86 ± 2.58	6.55 ± 1.32
Changes from baseline	− 0.55 ± 3.04		− 0.31 ± 3.05	
hsCRP (mg/L)	2.89 ± 2.56	2.46 ± 1.36	2.73 ± 2.34	1.92 ± 0.86*†
Changes from baseline	− 0.43 ± 1.90		− 0.81 ± 2.43	
Adiponectin (μg/mL)	4.21 ± 2.65	4.80 ± 1.88	4.48 ± 3.19	7.44 ± 2.88*†
Changes from baseline	0.59 ± 2.80		2.97 ± 3.98†	
sICAM-1 (ng/mL)	772 ± 293	898 ± 214	838 ± 233	976 ± 193*
Changes from baseline	126 ± 388		137 ± 328	
sVCAM-1 (ng/mL)	899 ± 240	934 ± 227	938 ± 212	990 ± 188
Changes from baseline	35 ± 274		52 ± 263	
Fasting insulin (μU/mL)	11.6 ± 3.0	8.7 ± 1.4*	12.2 ± 2.8	8.1 ± 1.8*
Changes from baseline	− 2.9 ± 2.3		− 4.1 ± 2.2†	
Fasting glucose (mmol/L)	8.1 ± 1.8	7.4 ± 1.3	7.7 ± 1.5	7.2 ± 1.2
Changes from baseline	− 0.7 ± 2.0		− 0.6 ± 1.9	
HOMA index	4.2 ± 1.4	2.9 ± 0.8*	4.3 ± 1.6	2.6 ± 0.8*
Changes from baseline	− 1.3 ± 1.3		− 1.7 ± 1.4	
HbA_{1c} (%)	7.5 ± 0.9	7.3 ± 0.6	7.5 ± 0.9	7.1 ± 0.5*
Changes from baseline	− 0.2 ± 1.0		− 0.4 ± 1.0	
Total cholesterol (mg/dL)	168.9 ± 35.0	147.1 ± 35.0*	172.0 ± 41.6	135.6 ± 23.2*
Changes from baseline	− 17.2 ± 33.6		− 34.3 ± 44.3	
LDL-cholesterol (mg/dL)	113.5 ± 29.4	91.5 ± 29.2*	112.9 ± 36.3	73.3 ± 21.0*†
Changes from baseline	− 18.9 ± 29.1		− 41.0 ± 38.5†	
HDL-cholesterol (mg/dL)	41.2 ± 11.0	43.8 ± 12.0	41.5 ± 9.7	41.0 ± 8.7
Changes from baseline	3.3 ± 9.8		− 0.2 ± 8.2	
Triglycerides (mg/dL)	145.6 ± 77.3	138.3 ± 67.2	175.3 ± 118.6	151.6 ± 98.2
Changes from baseline	− 14.2 ± 106.8		− 25.6 ± 76.4	

Values are presented as mean ± standard deviation

CRP C-reactive protein, *HDL* high-density lipoprotein, *HOMA* homeostatic model assessment, *sICAM-1* soluble intercellular adhesion molecule-1, *IL* interleukin, *LDL* low-density lipoprotein, *TNF* tumor necrosis factor, *sVCAM-1* soluble vascular cell adhesion molecule-1

*$p < 0.05$ compared to baseline values of each group

†$p < 0.05$ compared to values of the low-dose pitavastatin

and endothelin-1 levels [31], and significantly inhibited the neointimal hyperplasia after stenting [32]. In this study, pitavastatin 4 mg, which is categorized as a moderate statin dose, but is actually the highest pitavastatin dose available on the market, reduced the neointimal hyperplasia after coronary stenting due to its beneficial pleiotropic effects in addition to the effective LDL-cholesterol lowering.

Other beneficial effect of pitavastatin 4 mg was the improvement of brachial artery endothelial function. Although endothelial dysfunction contributes to the progression of atherosclerosis, endothelial dysfunction could be improved by several methods, including statin therapy [33]. baFMD, a non-invasive technique to access the endothelial function, was significantly increased after 12-month of administering pitavastatin 4 mg in this study when compared to pitavastatin 1 mg (Table 3), and using the highest-dose pitavastatin could be a reliable option to improve the endothelial dysfunction in diabetic patients, subsequently leading to the decrease in neointimal hyperplasia. The increases of baFMD indicate enhanced nitric oxide dependent anti-inflammatory, anti-proliferative, and antithrombotic properties. Impaired baFMD is an independent predictor of ISR after stenting [34]. It can be anticipated that both increases in nitric oxide release and decreases in smooth muscle cell proliferation synergistically contributed to the decreased neointimal hyperplasia.

The significant increase of adiponectin concentration in this study expedited the improvement of neointimal hyperplasia and endothelial dysfunction after stenting in type 2 diabetes. Adiponectin has a direct effect on endothelial function, stimulates nitric oxide production in endothelial cells, and inhibits several essential steps of neointimal proliferation [35]. In this study, we could not find significant differences in other inflammatory cytokines between the two groups and from the each group baseline values, excluding hsCRP. In addition, 30 or 50% reduction of LDL-cholesterol from baseline was not correlated with the mean neointimal hyperplasia area. Although LDL-cholesterol lowering effect is a main factor for preventing neointimal hyperplasia, anti-inflammatory effects by statin also significantly contribute to the prevention of neointimal hyperplasia [32]. Previous studies showed that degree of inflammation was strongly related to neointimal formation and statin also had anti-proliferative effects on smooth muscle cells [27, 36]. Thus, we speculated that the pitavastatin 4 mg facilitates the delay of neointimal hyperplasia and the improvement of endothelial function by its pleiotropic effects in addition to its effective LDL-cholesterol lowering.

Not a few Korean patients with coronary artery disease have been administrated with either moderate or low-dose statins [37]. Although there are some controversies, the low- and moderate-dose statins have been frequently used to effectively lower the LDL-cholesterol level in Asia [38–41]. Although the 2013 ACC/AHA guideline recommend high-dose statin therapy in patients with coronary artery disease, the guideline mentioned that the Asian ancestry may influence the initial choice of statin dose [9]. In fact, the LDL-cholesterol lowering effects of moderate-dose statin regimens were higher in Asian patients than in Caucasians [39]. Other study in Korea showed that almost half of the patients with moderate-dose statin had a reduction in LDL-cholesterol levels greater than 50% [42]. The mechanisms of different response to statins in Asians are not totally understood, but both genetic and environmental factors are suggested. The genetic polymorphism could cause different responses according to their ethnic groups [43]. In addition, the smaller body size of Asians compared to Caucasians could be one of the causes for different response [39]. The guidelines provided by the ACC/AHA are mainly influenced by 5 studies: PROVE-IT, A to Z, TNT, DEAL, and SEARCH trials [44]. However, these trials included less than 10% of Asians, and the Korea lipid guideline mentioned the possible use of moderate-dose statins in patients with coronary artery disease, reflecting the different ethnic background [45]. More randomized, prospective, large-scale clinical trials are needed in Asian patients to confirm the effects of different ethnicity on the statin doses mentioned in the current ACC/AHA or ESC guidelines. In this study, although LDL-cholesterol reduction was 36% in the pitavastatin 4 mg group, the administration of the highest-dose pitavastatin showed significantly decreased neointimal hyperplasia and improvement of baFMD without any cardiovascular events during a 12-month follow-up. Baseline LDL-cholesterol level in this study was only 110 mg/dL, which can be considered relatively low in these high-risk patients and the additional 36% reduction from this relatively low baseline LDL-cholesterol level was noteworthy.

Limitations

Although this study was adequately powered to compare the normalized neointimal hyperplasia volume with OCT between the 2 groups, the size of the study population was not enough to draw any conclusions about cardiovascular events of pitavastatin during the follow-up. Because this study was confined to type 2 diabetic patients with non-ST elevation ACS, our findings should not be extrapolated to broad-spectrum of patients after coronary stent implantation. Although there were limited baseline OCT images before stent implantation, no significant differences in plaque vulnerability were found between the two groups in this study.

Conclusions

In conclusion, type 2 diabetic patients with coronary stenting treated with pitavastatin 4 mg may not only benefit from its LDL-cholesterol lowering effects, but also from its anti-inflammatory effects, thereby eventually showing decreased neointimal hyperplasia and improved endothelial dysfunction. LDL-cholesterol level was efficiently decreased, and neointimal hyperplasia was effectively reduced with highest-dose pitavastatin in this study. Thus, the administration of pitavastatin 4 mg could be more beneficial than pitavastatin 1 mg in diabetic patients with non-ST elevation ACS and could be safely and effectively used in high-risk patients requiring coronary stenting.

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Compliance with ethical standards

Conflict of interest None of the authors have conflict of interest to declare.

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