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Two-Year Follow-Up of the Quantitative Angiographic and Volumetric Intravascular Ultrasound Analysis After Nonpolymeric Paclitaxel-Eluting Stent Implantation

Late "Catch-Up" Phenomenon From ASPECT Study

Duk-Woo Park, MD,* Myeong-Ki Hong, MD,* Gary S. Mintz, MD, FACC,‡ Cheol Whan Lee, MD,* Jong-Min Song, MD,* Ki-Hoon Han, MD,* Duk-Hyun Kang, MD,* Sang-Sig Cheong, MD,† Jae-Kwan Song, MD, FACC,* Jae-Joong Kim, MD,* Neil J. Weissman, MD, FACC,§ Seong-Wook Park, MD, FACC,* Seung-Jung Park, MD, FACC*

Seoul and GangNeung, Korea; New York, New York; and Washington, DC

OBJECTIVES This study used serial angiographic and intravascular ultrasound (IVUS) analysis to evaluate the long-term efficacy of a nonpolymeric, paclitaxel-eluting stent coating on intimal hyperplasia (IH) 2 years after implantation.

BACKGROUND Long-term efficacy of patients treated with nonpolymeric paclitaxel-eluting stents beyond 1 year has not been well determined.

METHODS Patients were randomized to placebo or 1 of 2 doses of paclitaxel (low dose, 1.28 $\mu g/mm^2$; high dose, 3.10 $\mu g/mm^2$). Complete after-procedure, 6-month, and 2-year angiographic and IVUS data were available in 53 patients (17, 17, and 19 patients, respectively).

RESULTS Baseline characteristics were similar among the 3 groups. Although 6-month minimal luminal diameter (MLD) was significantly smaller in placebo compared with paclitaxel-eluting stent patients (1.9 ± 0.6 mm in placebo, 2.5 ± 0.6 mm in low-dose, and 2.6 ± 0.5 mm in high-dose patients, $p = 0.004$), the MLDs at 2 years were similar (2.3 ± 0.6 mm, 2.3 ± 0.7 mm, and 2.0 ± 0.8 mm, respectively, $p = 0.4$). Despite a stepwise reduction in IH accumulation at 6 months (23 ± 18 mm^3 in placebo, 14 ± 11 mm^3 in low-dose, and 10 ± 12 mm^3 in high-dose, $p = 0.017$), the increase of IH volume from 6 months to 2 years was significantly greater in the high-dose patients (13 ± 14 mm^3 in high-dose vs. 4 ± 7 mm^3 in low-dose patients, $p = 0.074$; and vs. 1 ± 13 mm^3 in placebo, $p = 0.019$). Late target lesion revascularization (beyond 1 year) was performed in 2 high-dose patients.

CONCLUSIONS Despite the suppression of IH after non-polymeric paclitaxel-eluting stents compared with bare-metal stents at 6 months, a "late catch-up" IH growth was found in the high-dose patients at 2-year follow-up. (J Am Coll Cardiol 2006;48:2432–9) © 2006 by the American College of Cardiology Foundation

In-stent restenosis secondary to intimal hyperplasia (IH) has been the major limitation of coronary stenting (1,2). Medium-term results from several randomized clinical trials have shown that drug-eluting stents (DES) substantially reduce rates of angiographic restenosis and the need for repeat revascularization compared to bare-metal stents (BMS) (3–5). However, there are concerns about the long-term efficacy (late restenosis) and safety (late thrombosis) of DES (6,7) similar to intracoronary brachytherapy (8).

The ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial) was a 3-center, triple-blind, randomized, placebo-controlled trial of nonpolymer-encapsulated paclitaxel-coated stents to reduce in-stent restenosis (9). The intravascular ultrasound (IVUS) substudy was performed at a single center (Asan Medical Center); 81 patients had complete after-stent implantation and 6-month follow-up IVUS showing a stepwise reduction in IH accumulation within the stented segment (31 ± 22 mm^3 in the control group, 18 ± 15 mm^3 in the low-dose group, and 13 ± 14 mm^3 in the high-dose group, $p < 0.001$) (10). Given the concerns about the long-term results of DES, we report the 2-year angiographic and volumetric IVUS analysis from the ASPECT study.

METHODS

Study population. The current 2-year follow-up angiographic and IVUS analysis was a single-center (Asan Medical Center) substudy of the ASPECT study. Single de novo lesions in 177 patients were randomized to placebo or 1 of 2 doses of paclitaxel (low dose: 1.28 $\mu g/mm^2$ stent surface area; high dose: 3.10 $\mu g/mm^2$ for overall doses of 54 to 60 μg and 130 to 146 μg, respectively, depending on stent diameter). SupraG stents (Cook Cardiology)—a 316L

From the Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, *Seoul and †GangNeung, Korea; ‡Cardiovascular Research Foundation, New York, New York; and the §Washington Hospital Center, Washington, DC. This study was partly supported by Cardiovascular Research Foundation, Seoul, Korea, and Cook Cardiology; and by grants from the Korean Society of Circulation and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (0412-CR02-0704-0001).

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Abbreviations and Acronyms

BMS	= bare-metal stents
DES	= drug-eluting stents
IH	= intimal hyperplasia
IVUS	= intravascular ultrasound
MLA	= minimum lumen area
MLD	= minimal luminal diameter
QCA	= quantitative coronary angiography

stainless-steel slotted-tube design 15 mm in length with diameters from 2.5 to 3.5 mm—were used in this study. The Cook's proprietary paclitaxel coating process was used to bond paclitaxel to the abluminal surface of the stents without the use of a polymer. After release of paclitaxel, only a BMS remains (9). The details regarding drug-release kinetics have previously been described (9,11).

Patients were pretreated with aspirin plus either ticlopidine or clopidogrel. Heparin was administered during the procedure according to standard practice. Glycoprotein IIb/IIIa inhibitors were not used. After the procedure, in addition to aspirin indefinitely, ticlopidine or clopidogrel was prescribed for 6 months. There was a single-center, 98-patient IVUS substudy of the ASPECT study in which 81 patients (25 placebo, 28 low-dose, and 28 high-dose patients) had baseline and 6-month follow-up IVUS data (10). Excluding 5 patients (2 placebo, 2 low-dose, and 1 high-dose patient) requiring target lesion revascularization for restenosis at 6 months, 76 patients were enrolled in this prospective 2-year follow-up study. All patients gave their written informed consent. This study was approved by the Asan Medical Center Institutional Review Board.

Quantitative coronary angiographic (QCA) analysis. Using the guiding catheter for magnification-calibration and an online system (ANCOR V2.0, Siemens, Erlangen, Germany), minimal luminal diameter (MLD) of the lesion and diameters of the reference segments were measured before and after stenting and at 6-month and 2-year follow-up. Angiographic restenosis was defined as stenosis of more than 50% of the luminal diameter. The late loss was defined as the difference between in MLD after procedure and at follow-up.

IVUS imaging and analysis. Intravascular ultrasound imaging was performed after intracoronary administration of 0.2 mg nitroglycerin using motorized transducer pullback (0.5 mm/s) and a commercial scanner (SCIMED, Freemont, California) consisting of a 30 MHz transducer within a 3.2-F imaging sheath.

Quantitative volumetric IVUS analysis was performed as previously described (10,12). Using computerized planimetry, stent and reference segments were measured every 1 mm. Reference segment external elastic membrane, lumen, and plaque and media (P&M = external elastic membrane minus lumen) areas were measured over a 5-mm length adjacent to each stent edge and also averaged. Stent, lumen, and IH (stent minus lumen) areas were measured every 1 mm within the stented segment; volumes were calculated using Simpson's rule. The minimum lumen area (MLA) was also measured. The primary end point of this analysis was the change in IH volume between 6-month versus 2-year follow-up.

Statistical analysis. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, Illinois). Categorical data are presented as frequencies and compared with chi-square statistics or Fisher exact test. Continuous variables are presented as mean ± 1 SD and compared using unpaired or paired *t* test and one-way or repeated measures analysis of variance with the Bonferroni correction for post hoc comparisons as appropriate. A p value <0.05 was considered statistically significant.

RESULTS

Clinical and angiographic data. Long-term clinical follow-up data were available in all patients enrolled in the IVUS substudy of the ASPECT study. There were no cardiac deaths, myocardial infarctions, or stent thromboses between 6-month and 2-year follow-up. Of 76 patients enrolled in the current 2-year follow-up study, 2-year angiography and IVUS were not available in 20 patients because of patient refusal (n = 15) or comorbid conditions (n = 5: old age 1, systemic vasculitis 1, contrast dye anaphylaxis 1, and malignancy 2). These 20 patients without 2-year follow-up angiography were clinically stable up to 2 years. Of the 56 remaining patients, 1 high-dose patient underwent revascularization at 12-month follow-up and 2 patients (1 low-dose and 1 high-dose) had a total occlusion pattern of in-stent restenosis at 2 years follow-up precluding follow-up IVUS examination. Therefore, complete serial (after-stent implantation, 6-month follow-up, and 2-year follow-up) QCA data were available in 55 patients (72%): 17 of 23 placebo patients (74%), 18 of 26 low-dose patients (69%), and 20 of 27 high-dose patients (74%) (p = 0.9). Complete serial (after-stent implantation, 6-month follow-up, and 2-year follow-up) IVUS data were available in 53 patients (70%): 17 of 23 placebo patients (74%), 17 of 26 low-dose patients (65%), and 19 (70%) of 27 high-dose patients (65%) (p = 0.8).

As reported previously, baseline clinical characteristics were similar among the 3 groups (Table 1). No differences existed in baseline characteristics when comparing patients with and without 2-year angiographic follow-up in the overall IVUS cohort, with the exception of smoking (p = 0.021). Angiographic measures are shown in Table 1. Angiographic data were also similar between patients with and without 2-year follow-up in the overall IVUS cohort, except that 6-month MLD was larger in patients with 2-year follow-up (2.3 ± 0.7 mm vs. 1.6 ± 0.9 mm, p = 0.001). Reference vessel diameter and before- and after-procedure MLD were similar among the 3 groups. Six-month QCA MLD was significantly smaller in placebo patients compared with paclitaxel-eluting stent patients

Table 1. Baseline Characteristics

	2-Year Follow-Up Population				
	Total	**Placebo**	**Low Dose**	**High Dose**	**p Value**
Number of patients	55	17	18	20	
Age (yrs)	57 ± 9	56 ± 8	58 ± 11	56 ± 8	0.6
Male gender, n (%)	42 (76)	13 (77)	13 (72)	16 (80)	0.8
Diabetes mellitus, n (%)	6 (11)	2 (12)	3 (17)	1 (5)	0.5
Hypercholesterolemia, n (%)	4 (7)	1 (6)	2 (11)	1 (5)	0.8
Hypertension, n (%)	21 (38)	4 (24)	8 (44)	9 (45)	0.4
Current smoking, n (%)	23 (42)	6 (35)	8 (44)	9 (45)	0.8
Clinical presentation, n (%)					0.6
Stable angina	24 (44)	7 (41)	7 (39)	10 (50)	
Unstable angina	17 (31)	7 (41)	4 (22)	6 (30)	
MI >72 h	14 (26)	3 (18)	7 (39)	4 (20)	
Diseased vessels, n (%)					0.9
1	39 (71)	11 (65)	13 (72)	15 (75)	
2	12 (22)	5 (29)	4 (22)	3 (15)	
3	4 (7)	1 (6)	1 (6)	2 (10)	
Vessel stented					0.8
LAD	27 (49)	7 (41)	8 (44)	12 (60)	
RCA	15 (27)	6 (35)	6 (33)	3 (15)	
LCX	11 (20)	4 (24)	3 (17)	4 (20)	
Ramus	2 (4)	0 (0)	1 (6)	1 (5)	
Reference diameter, mm	2.9 ± 0.4	2.9 ± 0.3	3.0 ± 0.4	2.9 ± 0.4	0.3
Minimum lumen diameter, mm					
Before-intervention	0.6 ± 0.3	0.6 ± 0.4	0.6 ± 0.3	0.5 ± 0.3	0.4
After-intervention	2.8 ± 0.4	2.7 ± 0.4	3.0 ± 0.4	2.9 ± 0.3	0.2
6 months	2.3 ± 0.7	1.9 ± 0.6	2.5 ± 0.6	2.6 ± 0.5	0.004
2 years	2.2 ± 0.7	2.3 ± 0.6	2.3 ± 0.7	2.0 ± 0.8	0.4
Binary restenosis at 2 yrs, n (%)	8 (15)	1 (6)	2 (11)	5 (25)	0.3

The p values indicate comparisons among the 3 groups in 2-year follow-up population.
LAD = left anterior descending, LCX = left circumflex, MI = myocardial infarction, RCA = right coronary artery.

(1.9 ± 0.6 mm in placebo patients vs. 2.5 ± 0.6 mm in low-dose patients, p = 0.023; vs. 2.6 ± 0.5 mm in high-dose patients, p = 0.006). However, these differences were not maintained at 2-year angiographic follow-up, at which time the angiographic MLD measured 2.3 ± 0.6 mm, 2.3 ± 0.7 mm, and 2.0 ± 0.8 mm in placebo, low-dose, and high-dose patients, respectively (p = 0.4). Late lumen loss during the first 6 months was significantly larger in placebo patients (0.8 ± 0.7 mm in placebo patients vs. 0.5 ± 0.6 mm in low-dose patients, p = 0.3; vs. 0.3 ± 0.5 mm in high-dose patients, p = 0.041). Conversely, late lumen loss between 6 months and 2 years follow-up was −0.4 ± 0.5 mm in placebo, 0.2 ± 0.6 mm in low-dose, and 0.6 ± 0.8 mm in high-dose patients (p = 0.001). In post-hoc analysis, there was more late lumen loss in low- and high-dose patients compared with placebo patients (p = 0.038 and p < 0.001, respectively). Cumulative frequency distribution curves of the MLD before intervention, after procedure, and at follow-up are shown in Figure 1.

At 2-year follow-up, the rate of restenosis was 6% in the placebo group, 11% in the low-dose group, and 25% in the high-dose group (p = 0.3). One high-dose patient underwent revascularization after the 2-year follow-up. The other patients were treated with medication because of the lack of

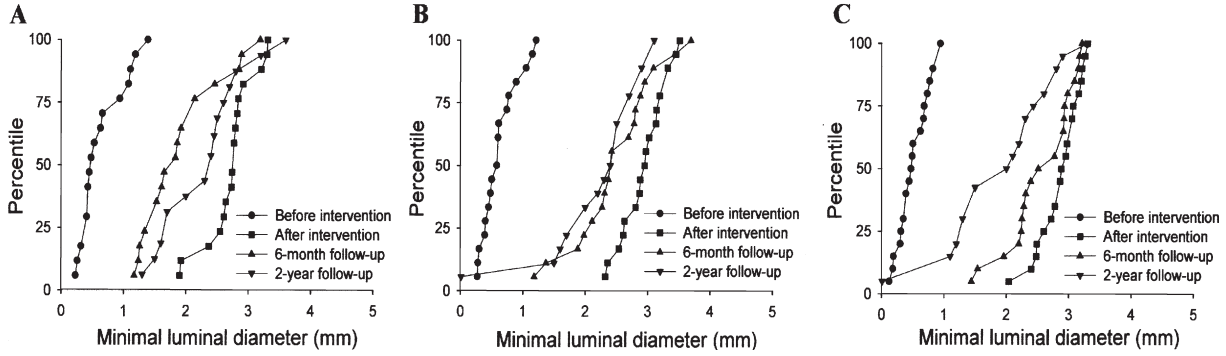

Figure 1. Comparison of the cumulative distribution of the minimal luminal diameter (MLD) between all 3 groups (**A** = placebo; **B** = low dose; **C** = high dose) before and after stenting and at 6-month and 2-year follow-up. Minimal luminal diameter by quantitative coronary angiographic analysis in each group showed significant changes over time (p < 0.001), and these serial changes of MLD were significantly different among the 3 groups (p = 0.002).

Table 2. Intravascular Ultrasound Measurements

	2-Year Follow-Up Population				
	Total	**Placebo**	**Low Dose**	**High Dose**	**p Value**
Number of patients	53	17	17	19	
After intervention					
Proximal reference segment					
Mean EEM area, mm^2	15.2 ± 4.2	15.4 ± 4.5	17.4 ± 4.6	13.5 ± 3.0	0.1
Mean lumen area, mm^2	8.0 ± 2.8	7.7 ± 2.3	9.9 ± 3.7	6.9 ± 1.8	0.031
Mean P&M area, mm^2	7.2 ± 2.8	7.6 ± 3.4	7.4 ± 2.8	6.6 ± 2.1	0.6
Stented segment					
Stent volume, mm^3	109 ± 27	105 ± 28	117 ± 29	105 ± 25	0.4
Lumen volume, mm^3	109 ± 27	104 ± 27	117 ± 29	105 ± 25	0.3
IH volume, mm^3	0.4 ± 2.8	1 ± 5	0	0	0.4
Minimum lumen area, mm^2	6.0 ± 1.7	5.8 ± 1.8	6.5 ± 1.8	5.8 ± 1.5	0.4
Distal reference segment					
Mean EEM area, mm^2	12.3 ± 4.3	12.1 ± 4.2	12.3 ± 4.9	12.5 ± 4.2	1.0
Mean lumen area, mm^2	6.9 ± 2.5	7.1 ± 2.3	7.0 ± 2.7	6.8 ± 2.6	0.9
Mean P&M area, mm^2	5.3 ± 2.7	4.9 ± 3.1	5.3 ± 3.0	5.7 ± 2.3	0.8
Six-month follow-up					
Proximal reference segment					
Mean EEM area, mm^2	14.8 ± 4.0	14.7 ± 3.6	16.2 ± 5.8	14.0 ± 3.0	0.4
Mean lumen area, mm^2	7.7 ± 3.0	7.1 ± 2.1	8.9 ± 4.4	7.3 ± 2.2	0.3
Mean P&M area, mm^2	7.2 ± 2.3	7.6 ± 2.9	7.3 ± 2.5	6.6 ± 1.6	0.6
Stented segment					
Stent volume, mm^3	108 ± 27	104 ± 27	115 ± 30	105 ± 24	0.4
Lumen volume, mm^3	92 ± 26	81 ± 23	100 ± 31	95 ± 22	0.093
IH volume, mm^3	16 ± 15	23 ± 18	14 ± 11	10 ± 12	0.017*
Minimum lumen area, mm^2	4.5 ± 1.7	3.5 ± 1.4	5.1 ± 2.0	4.9 ± 1.3	0.010†
Distal reference segment					
Mean EEM area, mm^2	12.1 ± 3.9	11.9 ± 3.9	12.2 ± 4.4	12.2 ± 3.9	1.0
Mean lumen area, mm^2	6.6 ± 2.2	6.8 ± 1.6	6.8 ± 2.4	6.5 ± 2.7	1.0
Mean P&M area, mm^2	5.4 ± 2.4	5.1 ± 3.0	5.4 ± 2.4	5.7 ± 2.0	0.6
Two-year follow-up					
Proximal reference segment					
Mean EEM area, mm^2	14.5 ± 3.5	14.5 ± 3.4	15.7 ± 4.8	13.7 ± 2.2	0.4
Mean lumen area, mm^2	8.2 ± 2.8	7.8 ± 2.5	9.2 ± 4.0	7.7 ± 2.0	0.4
Mean P&M area, mm^2	6.4 ± 2.1	6.6 ± 2.6	6.5 ± 2.3	5.9 ± 1.3	0.7
Stented segment					
Stent volume, mm^3	107 ± 26	103 ± 26	113 ± 29	105 ± 24	0.5
Lumen volume, mm^3	85 ± 26	78 ± 25	95 ± 28	82 ± 25	0.142
IH volume, mm^3	22 ± 15	25 ± 19	18 ± 10	23 ± 14	0.4
Minimum lumen area, mm^2	4.1 ± 1.7	3.7 ± 1.6	4.7 ± 1.8	3.8 ± 1.7	0.2
Distal reference segment					
Mean EEM area, mm^2	11.9 ± 3.6	11.7 ± 3.6	12.0 ± 4.1	11.9 ± 3.6	0.9
Mean lumen area, mm^2	6.4 ± 2.2	6.5 ± 1.9	6.5 ± 2.1	6.2 ± 2.6	0.9
Mean P&M area, mm^2	5.5 ± 2.3	5.2 ± 2.7	5.5 ± 2.6	5.7 ± 1.8	0.6

The p values indicate analysis of variance among the 3 groups in 2-year follow-up population. Post hoc comparisons: *p = 0.148 placebo vs. low dose and p = 0.016 placebo vs. high dose. †p = 0.018 placebo vs. low dose and p = 0.030 placebo vs. high dose.

EEM = external elastic membrane; IH = intimal hyperplasia; P&M = plaque and media.

symptom or non-critical stenosis without the evidence of myocardial ischemia.

IVUS analysis. Intravascular ultrasound measurements are shown in Table 2. After-intervention IVUS measurements were comparable between patients with and without 2-year IVUS follow-up in the overall IVUS cohort, with the exception of larger MLA in patients with 2-year follow-up (6.0 ± 1.7 mm^2 vs. 5.1 ± 1.8 mm^2, p = 0.024). Six-month IVUS measurements showed more favorable MLA (in-stent: 4.5 ± 1.7 mm^2 vs. 2.9 ± 1.7 mm^2, p < 0.001; proximal reference: 7.7 ± 3.0 mm^2 vs. 5.5 ± 2.3 mm^2, p = 0.004; and distal reference: 6.6 ± 2.2 mm^2 vs. 5.4 ± 2.4 mm^2, p = 0.041) and volume (stent: 108 ± 27 mm^3 vs. 94 ± 29 mm^3, p = 0.032; lumen: 92 ± 26 mm^3 vs. 65 ± 30 mm^3, p < 0.001; IH: 16 ± 15 mm^3 vs. 29 ± 22 mm^3, p = 0.006) in patients with 2-year IVUS follow-up because patients with severe obstruction needing repeat intervention were excluded for long-term 2-year study.

After-intervention stent and reference measurements were similar among the 3 groups. There was a decrease in lumen volume and an increase in IH volume at 6 months follow-up in all 3 groups (p < 0.001 for all comparisons). However, with increasing doses of paclitaxel, there was less IH accumulation within the stented segment (23 ± 18 mm^3 in placebo vs. 14 ± 11 mm^3 in low-dose, p = 0.148; vs. 10 ± 12 mm^3 in high-dose stents, p = 0.016). Like the QCA MLD, the 6-month IVUS MLA was significantly

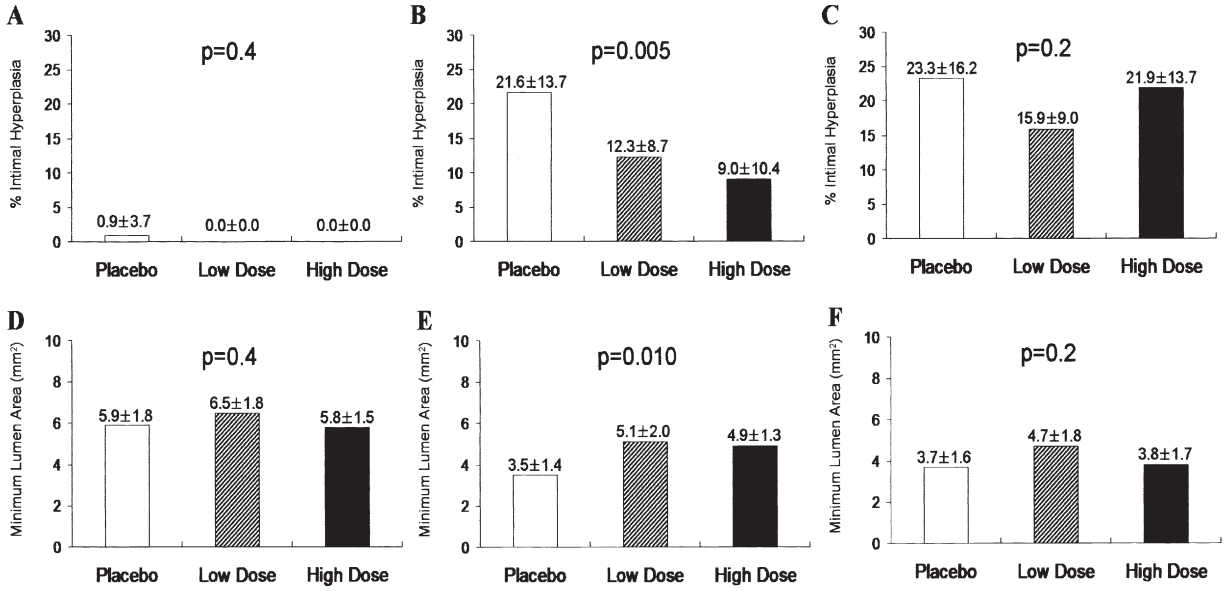

Figure 2. Comparison of the percent of intimal hyperplasia (IH) **(A,B,C)** and the minimal lumen area **(D,E,F)** among all 3 groups after stenting **(A and D)** and at 6-month **(B and E)** and 2-year **(C and F)** follow-up. The percent IH was significantly different (p = 0.005) at 6 months, but similar (p = 0.2) at 2-year follow-up among the 3 groups.

smaller in placebo patients compared with paclitaxel-eluting stent patients (3.5 ± 1.4 mm^2 in placebo vs. 5.1 ± 2.0 mm^2 in low-dose stents, p = 0.018, and vs. 4.9 ± 1.3 mm^2 in high-dose stents, p = 0.030). However, at 2-year follow-up, there was no difference in IH volume (p = 0.4) or MLA (p = 0.2) among the 3 groups. Figure 2 shows the comparison of the percent of IH (IH volume/stent volume) and the MLA at the 3 time points (after-intervention, 6 months, and 2 years). The percent of IH was significantly different (p = 0.005) at 6 months, but similar (p = 0.2) at 2-year follow-up among the 3 groups.

As shown in Table 3, there was a dose-dependent *decrease* in IH volume accumulation (p = 0.037) from after intervention to 6-month follow-up: p = 0.22 comparing placebo to low dose and p = 0.038 comparing placebo to high dose, but p = 1.0 comparing low dose to high dose. There were comparable results for measurements of MLA. However, between 6 months and 2 years, there was a dose-dependent *increase* in additional IH volume accumulation (p = 0.016), especially among high-dose patients: p = 1.0 comparing placebo to low dose, p = 0.019 comparing placebo to high dose, and p = 0.074 comparing low dose to high dose. There were similar results for measurements of MLA.

In these cohorts, there were no significant changes in reference segment measurements whether analyzed as a volume (Table 3) or millimeter by millimeter from the stent edge (Fig. 3). Comparing the change of IH area among the 3 groups, the placebo group showed that a decrease in IH area from 6 months to 2 years occurred mainly within the stented segment that had a lot of neointima at 6 months, suggesting compaction of the neointima. In contrast, the increase of neointima was uniform over the length of the stent in the paclitaxel-coated stents, with more significant growth in high-dose patients (Fig. 3).

DISCUSSION

The current study demonstrated that despite the 6-month suppression of IH after non-polymer-encapsulated paclitaxel-eluting stents compared with BMS, there was a "late catch-up" of IH growth during the subsequent 18 months. Although there was greater 6-month suppression of IH within high-dose stents, this was followed by a greater increase in IH at 2 years in the same high-dose stents. Delayed neointimal regrowth in the paclitaxel-eluting stent groups was diffuse over the entire length of the stent. Conversely, the placebo group showed a partial compaction of the neointima between 6 months and 2 years. These findings were in contrast with an early 6-month IH response shown in the previous study (13).

Drug-eluting stents significantly reduce restenosis rates to <10% (3–5). However, there are limited data on efficacy beyond 1 year follow-up. Recent angiographic and IVUS reports from the "first-in-humans" study of the sirolimus-eluting stent demonstrated sustained efficacy 2 and 4 years after implantation (14,15). Also, in the IVUS substudy of the TAXUS-II trial, polymer-based paclitaxel-eluting stents showed persistent neointimal suppression between 6 months and 2 years follow-up (16).

Conversely, previous animal studies have documented that late neointimal growth develops despite marked early suppression of neointimal formation within DES compared with BMS (17,18). Carter et al. (17) showed that long-term inhibition of neointimal hyperplasia after polymer-based sirolimus-eluting stents was not maintained, partly because of inflammation and delayed cellular proliferation in the porcine coronary model. Similar findings are observed in preclinical animal study using polymer-coated palictaxel-eluting stents, showing not only dose-dependent reduction

Table 3. Serial Changes for Each Intravascular Ultrasound Measurement

	Placebo	Low Dose	High Dose	p (ANOVA)
Number of patients	17	17	19	
Post-intervention to 6-month follow-up				
Proximal reference segment				
ΔMean EEM area, mm^2	−0.7 ± 2.3	−1.1 ± 1.7	0.5 ± 1.3	0.1
ΔMean lumen area, mm^2	−0.6 ± 1.4	−1.0 ± 1.8	0.4 ± 1.1	0.056
ΔMean P&M area, mm^2	−0.1 ± 1.5	−0.1 ± 1.0	0.1 ± 1.2	0.9
Stented segment				
ΔStent volume, mm^3	−1 ± 6	−2 ± 11	0 ± 11	0.8
ΔLumen volume, mm^3	−23 ± 20	−17 ± 15	−10 ± 18	0.115
ΔIH volume, mm^3	22 ± 17	14 ± 11	11 ± 12	0.037*
ΔMinimum lumen area, mm^2	−2.3 ± 1.8	−1.4 ± 1.2	−0.9 ± 1.1	0.021†
Distal reference segment				
ΔMean EEM area, mm^2	−0.2 ± 1.4	−0.1 ± 1.0	−0.3 ± 1.8	0.9
ΔMean lumen area, mm^2	−0.4 ± 1.4	−0.2 ± 1.1	−0.3 ± 1.7	0.9
ΔMean P&M area, mm^2	0.2 ± 1.0	0.1 ± 0.9	0 ± 1.0	0.9
Six-month to 2-year follow-up				
Proximal reference segment				
ΔMean EEM area, mm^2	−0.2 ± 1.7	−0.5 ± 1.1	−0.3 ± 1.3	0.9
ΔMean lumen area, mm^2	0.7 ± 1.4	0.3 ± 1.1	0.4 ± 1.0	0.8
ΔMean P&M area, mm^2	−1.0 ± 1.3	−0.8 ± 0.9	−0.7 ± 0.8	0.9
Stented segment				
ΔStent volume, mm^3	−2 ± 5	−2 ± 6	0 ± 6	0.5
ΔLumen volume, mm^3	−3 ± 11	−5 ± 9	−13 ± 14	0.035‡
ΔIH volume, mm^3	1 ± 13	4 ± 7	13 ± 14	0.016§
ΔMinimum lumen area, mm^2	0.2 ± 0.8	−0.3 ± 1.2	−1.1 ± 1.3	0.003‖
Distal reference segment				
ΔMean EEM area, mm^2	−0.2 ± 1.2	−0.2 ± 1.5	−0.3 ± 1.1	1.0
ΔMean lumen area, mm^2	−0.3 ± 1.2	−0.2 ± 1.4	−0.4 ± 1.8	1.0
ΔMean P&M area, mm^2	0.1 ± 1.3	−0.1 ± 1.0	0 ± 1.1	0.9

Post hoc comparisons: *p = 0.220 placebo vs. low dose and p = 0.038 placebo vs. high dose; †p = 0.293 placebo vs. low dose and p = 0.018 placebo vs. high dose; ‡p = 1.000 placebo vs. low dose, p = 0.046 placebo vs. high dose, and p = 0.145 low dose vs. high dose; §p = 1.000 placebo vs. low dose, p = 0.019 placebo vs. high dose, and p = 0.074 low dose vs. high dose; ‖p = 0.411 placebo vs. low dose, p = 0.002 placebo vs. high dose, and p = 0.122 low dose vs. high dose.
Abbreviations as in Table 2.

in neointimal hyperplasia, but also histologic findings of delayed healing and local toxicity after high-dose paclitaxel associated with delayed neointimal growth (18).

One previous human trial with 7-hexanoyltaxol (QP2)-eluting polymer stents (QuaDDS, Quanam, Santa Clara, California) reported favorable angiographic results at 6 months but a significant number of late, accelerated in-stent restenoses after 12 months (19). It was suggested that delayed healing with persistent fibrin deposits and varying degrees of inflammation might have caused the delayed restenosis (20). The persistent inflammation and delayed healing process have been significantly associated with a later occurrence of restenosis ("late catch-up phenomenon"). A similar phenomenon has been also observed at long-term (3 to 5 years) follow-up in patients who were treated with intracoronary brachytherapy (21,22). These clinically relevant limitations of radiation have shortened the therapeutic applicability of intracoronary brachytherapy for treating atheromatous coronary artery disease. However, despite concerns about the possibility that delayed vascular healing after DES implantation is associated with delayed neointimal growth,

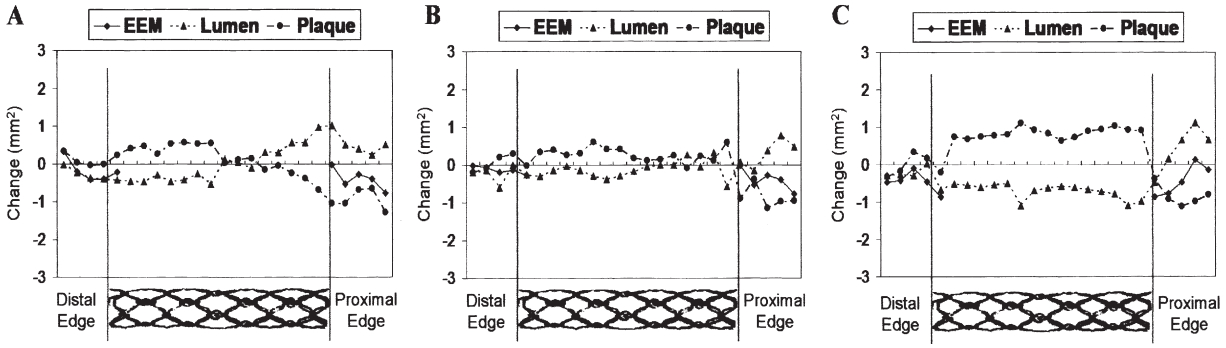

Figure 3. The serial changes in reference segment external elastic membrane (EEM), plaque, and lumen and in intra-stent lumen and intimal hyperplasia areas from 6-month to 2-year follow-up are shown (**A** = placebo; **B** = low dose; **C** = high dose). Measurements were made every 1 mm.

long-term durability has not been yet fully evaluated in the DES clinical studies.

The current IVUS substudy form th ASPECT study demonstrated encouraging dose-dependent reduction of IH at 6 months that was almost entirely eliminated at 2 years, especially in patients receiving high-dose paclitaxel-eluting stents. The precise mechanism for the development of late IH proliferation in paclitaxel-eluting stents remains elusive. However, dose-dependent late IH proliferation may be due to delayed healing and the local vascular toxic effect of high-dose paclitaxel, which was suggested in the preclinical study (18). Additionally, there is the possibility that uncontrolled and non-sustained drug delivery from a metal stent without a polymer coating might have an influence on the long-term inhibition of neointimal hyperplasia. Nonpolymeric paclitaxel delivery used in the current study might be the reason for the late progression of IH, especially at the higher dose of paclitaxel. Therefore, extension of these findings to clinically available polymer-based paclitaxel-eluting stents is, at best, speculative.

Other clinical trials (DELIVER and ELUTES [European evaluation of pacliTaxel-Eluting Stent]) using a similar high dose of paclitaxel (2.7 to 3.0 $\mu g/mm^2$) and a proprietary nonpolymeric coating process showed that paclitaxel-coated stents significantly decreased late loss and/or subsequent restenosis 6 to 8 months after the procedure (11,23). Because the long-term results from the DELIVER and ELUTES trials have not been reported, it cannot be predicted whether dose-dependent late IH regrowth after implantation of non-polymeric paclitaxel-eluting stents is unique to the ASPECT study.

The findings in the current study may not be directly applicable in other clinical trials of polymer- and nonpolymer-based paclitaxel- and sirolimus-eluting stents owing to considerable differences in stent platforms; polymers; and coated drugs, drug dose, and drug release kinetics. However, considering the fact that very modest but continued neointimal regrowth is found in the long-term follow-up of the "first-in-humans" study of the sirolimus-eluting stent and the TAXUS-II IVUS substudy (14–16), further investigations are needed to evaluate the clinical significance of this phenomenon and the appropriate length of follow-up in patients receiving DES.

Interestingly, patients in the current study showed a benign clinical course during long-term follow-up, despite the considerable number of angiographic restenoses. Our practice pattern is not to treat angiographic restenosis unless the patient is symptomatic or has objective evidence of myocardial ischemia.

Finally, the discrepancy between QCA MLD and IVUS neointimal hyperplasia volumes, especially in the placebo group, deserves some comment. Quantitative coronary angiography measures the MLD at the worst location regardless of its axial location. The worst location can, in fact, shift during short or long-term follow-up. Conversely, IVUS measures IH volume along the entire stent. Therefore, it is possible for QCA MLD to improve while IH volume progresses.

Study limitations. This was a prospective analysis from a single center. This study was a serial long-term follow-up study of patients enrolled in the 6-month IVUS substudy of the ASPECT study. Although clinical data were available in all patients, complete 6-month and 2-year serial angiographic and IVUS follow-up was limited. However, comparable baseline clinical demographics and angiographic and IVUS data before and after intervention and at 6 months indicate that the current cohort is representative of the overall IVUS substudy. The current observations are not necessarily applicable to the other DES systems owing to possible selection bias, small patient numbers in the current study, and the fact that this is a unique device. Also, the current patients may represents a "best-case scenario" in the ASPECT study because of exclusion of patients with major cardiac events or repeat intervention before 2-year follow-up.

Conclusions. Despite the marked 6-month suppression of IH after nonpolymer-encapsulated paclitaxel-eluting stents compared with BMS, the anti-proliferative effect was not maintained in patients receiving high-dose stents at 2-year follow-up, suggesting the possibility of incomplete healing and/or local toxicity of nonpolymeric high-dose paclitaxel delivery.

Reprint requests and correspondence: Dr. Seung-Jung Park, Departments of Medicine, University of Ulsan College of Medicine, Cardiac Center, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sjpark@amc.seoul.kr.

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