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Heterogeneous Arterial Healing in Patients Following Paclitaxel-Eluting Stent Implantation

Comparison With Sirolimus-Eluting Stents

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Objectives We angioscopically compared paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) to explore differences in arterial healing.

Background Drug-eluting stents may demonstrate different arterial healing processes.

Methods Angioscopy was performed 9 ± 2 months after 30 PES and 36 SES were implanted initially in the native coronary artery. Heterogeneity of the neointimal coverage (NIC) as well as the dominant grade was examined. Neointimal coverage was defined as follows: grade 0 = fully visible struts; grade 1 = struts bulged into the lumen, but covered; grade 2 = embedded, but translucent struts; grade 3 = invisible struts. Heterogeneity was judged when the NIC grade variation ≥1. Thrombi and yellow plaques (YP) were also explored.

Results In-stent late loss (0.44 ± 0.44 mm vs. 0.13 ± 0.33 mm; $p < 0.0001$) and dominant NIC grade (1.8 ± 1.1 vs. 1.3 ± 0.7; $p = 0.02$) were greater in PES than in SES. Of PES, 48% showed the heterogeneity of 1 grade; 26% showed that of 2 grades. Of SES, 53% showed homogeneous coverage; the remaining SES showed the heterogeneity of 1 grade; and 72% showed dominant grade 1. Thrombi were more common in PES than in SES (43% vs. 19%; $p = 0.04$). Both stents commonly revealed YP (83% vs. 78%; $p = 0.76$).

Conclusions NIC was more heterogeneous in PES, associated with a higher incidence of thrombi. Homogeneous NIC may be an important factor for competent arterial healing. (J Am Coll Cardiol Intv 2009;2:453–8) © 2009 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have significantly reduced restenosis through an inhibitory effect on neointimal hyperplasia (1,2). Currently, concerns have been raised about late stent thrombosis (LST) and very LST after DES implantation as a negative aspect of the strong inhibition of neointimal proliferation (3–6). Pathological studies showed that incomplete neointimal coverage (NIC) following stenting contributes to LST (7,8). Using angioscopy, we have previously reported (9) that the NIC was not complete even 2 years after sirolimus-eluting stent (SES) implantation, associated with yellow plaques (YP) and subclinical thrombi, whereas bare-metal stents (BMS) showed complete NIC. The paclitaxel-eluting stent (PES) is also a first-generation DES that has been widely used in the real world. Although clarifying the differences in arterial healing between PES and SES is important to discuss clinical managements following DES, arterial healing following PES has not been angioscopically defined. Hence, using angioscopy, we sought to investigate the lumen/stent surfaces following PES and SES implantation for new lesions of the native coronary arteries.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
LL = late loss
LST = late stent thrombosis
NIC = neointimal coverage
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
YP = yellow plaques

Methods

Patients. This study was a nonrandomized, historical control study that included 40 patients with stable angina pectoris in whom 66 DES were implanted (35 men, age 35 to 85 years). The patients agreed to receive follow-up angioscopy as well as angiography 8 months after stenting. Among them, 19 patients were treated with SES alone (27 stents) (Cypher, Cordis, Miami Lakes, Florida); 14 patients were treated with PES alone (18 stents) (TAXUS Express 2, Boston Scientific, Natick, Massachusetts); 7 patients were treated with both SES (9 stents) and PES (12 stents). All patients received ticlopidine (200 mg/day) in addition to aspirin (100 to 200 mg/day) during the follow-up, except for 2 patients. Neither a glycoprotein IIb/IIIa inhibitor nor clopidogrel was used because they were not approved for stable angina pectoris in Japan.

Angiographic and angioscopic follow-up. Coronary angiography was performed after the administration of heparin (5,000 IU) into the femoral artery via the inserted sheath, and isosorbide dinitrate (2.5 mg) into the coronary artery. Subsequently, angioscopy was performed using Vecmova NEO (FiberTech, Tokyo, Japan). The detailed specifications and the procedures of the angioscope have been described elsewhere (10,11). Briefly, the optical fiber was placed at the distal segment of the coronary artery and was manually pulled back from the distal edge of the stent to the proximal edge under careful angioscopic and angiographic guidance. Angioscopic images consisted of 3,000 pixels with full color and were stored on digital videotapes for off-line analysis.

Quantitative coronary angiography. Coronary angiography was performed in at least 10 projections, and the view showing the most severe stenosis was selected for quantitative coronary angiography (12). Quantitative coronary angiography was performed using the CASS system (Pie Medical BV, Maastricht, the Netherlands) before stenting, immediately after stenting, and also at follow-up with the same angle of projection.

Angioscopic analysis. Angioscopic images were analyzed as follows: 1) the dominant degree of NIC over the stent; 2) heterogeneity of NIC; 3) existence of thrombus; and 4) existence of YP underneath the stent. Neointimal coverage over the stent was classified into 4 grades as previously described (9,13,14). In brief, grade 0 = stent struts were fully visible, similar to immediately after implantation; grade 1 = stent struts bulged into the lumen and, although covered, were still transparently visible; grade 2 = stent struts were embedded by the neointima, but were translucently seen; grade 3 = stent struts were fully embedded and were invisible by angioscopy. Neointimal coverage was evaluated in the entire stented segments, and if different NIC grades of more than or equal to 1 grade were present, the NIC was judged as heterogeneous. Struts that crossed the side branch were excluded from grading because they all showed grade 0 regardless of the stent types. The stent edges were also excluded from the heterogeneity analysis. Stent overlapped segments were also evaluated separately. Thrombus was defined based on the criteria adopted by the European Working Group on Coronary Angioscopy (15). The angioscopic definition of YP was adopted from the earlier reports (10,11,16), and the existence of YP underneath the stent was evaluated.

Statistical analysis. All results are expressed as mean ± SD [median] unless otherwise stated. Comparisons between the 2 groups were done with the Wilcoxon rank sum test. Categorical variables were analyzed with Fisher exact test for 2×2 comparisons; for more than 2×2 comparisons, the chi-square test was used. Analyses for quantitative coronary angiography and angioscopic findings were performed per stent, but not per patient. Statistical significance was defined as $p < 0.05$. All calculations were performed using JMP 7.0.1 (SAS Institute, Cary, North Carolina).

Results

Patients. Patient, lesion, and procedure characteristics were equally distributed between the PES and the SES groups (Tables 1 and 2), except that the duration from the stent implantation to the follow-up angiography and angioscopy

Table 1. Patient and Lesion Characteristics

	PES	SES	p Value
No. of patients	21	26	
Age, yrs	67 ± 9.7 [66]	67 ± 9.6 [68]	0.73
Male	18 (86)	21 (81)	0.72
Coronary risk factors			
Hypertension	14 (67)	20 (77)	0.52
Dyslipidemia	14 (67)	21 (81)	0.33
Diabetes mellitus	9 (43)	10 (38)	0.77
Smoking	13 (62)	13 (50)	0.56
Multivessel disease	18 (86)	25 (96)	0.31
History of previous MI	6 (29)	8 (31)	1.00
No. of stents	30	36	
LAD/LCX/RCA	11 (37)/4 (13)/15 (50)	18 (50)/4 (11)/14 (39)	0.55
Type B2/C lesions*	23 (77)	31 (86)	0.36

Data are presented as mean ± SD [median] or n (%). *Based on American College of Cardiology/American Heart Association classification.
LAD = left anterior descending artery; LCX = left circumflex artery; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); RCA = right coronary artery; SES = sirolimus-eluting stent(s).

were slightly longer in SES (9.2 ± 1.5 [9.2] months) than in PES (8.4 ± 1.7 [8.0] months; p = 0.01).

Quantitative coronary angiography. Quantitative coronary angiographic findings in the PES and the SES groups are shown in Table 2. Although there were no statistical differences between them, baseline lesion length tended to be longer in SES than in PES; reference diameter tended to be larger in SES than in PES. Although a post-interventional angiogram as well as procedural characteristics were similar between PES and SES, in-stent late loss (LL) from the post-intervention to follow-up was smaller in SES (0.13 ± 0.33 [0.08] mm) than in PES (0.44 ± 0.44 [0.32] mm; p < 0.0001), and resulted in the smaller minimal lumen diameter and a larger percent diameter stenosis at follow-up in PES than in SES. Three PES and a SES showed in-stent restenosis (>50% of diameter stenosis) at follow-up angiography. Among them, all the PES received target lesion revascularization, but the SES did not.

Angioscopic findings. Dominant NIC grade was significantly different between PES and SES (Fig. 1). The average grade was greater in PES (1.8 ± 1.1 [2] grades) than in SES (1.3 ± 0.7 [1] grades; p = 0.02). Although the majority of

Table 2. Procedural Characteristics and Serial Changes in Quantitative Coronary Angiography Data

	PES	SES	p Value
No. of stents	30	36	
Stent diameter, mm	3.00 ± 0.37 [3.00]	3.10 ± 0.35 [3.00]	0.25
Stent length, mm	21.8 ± 7.80 [24.0]	24.7 ± 4.63 [23.0]	0.22
Stent-to-artery ratio	1.11 ± 0.14 [1.09]	1.08 ± 0.14 [1.04]	0.15
Quantitative coronary angiography			
Pre-intervention			
Lesion length, mm	15.5 ± 6.09 [15.3]	18.8 ± 6.54 [20]	0.053
Reference diameter, mm	2.73 ± 0.52 [2.67]	2.91 ± 0.41 [3.00]	0.07
Minimal lumen diameter, mm	0.69 ± 0.35 [0.74]	0.61 ± 0.34 [0.68]	0.31
Diameter stenosis, %	75.5 ± 10.2 [72.5]	78.5 ± 11.8 [76.5]	0.22
Post-intervention			
Minimal lumen diameter, mm	2.67 ± 0.40 [2.68]	2.76 ± 0.38 [2.82]	0.23
Diameter stenosis, %	13.6 ± 6.92 [15.0]	11.8 ± 5.78 [12.0]	0.25
Follow-up			
Minimal lumen diameter, mm	2.23 ± 0.53 [2.26]	2.63 ± 0.43 [2.72]	0.0009
Diameter stenosis, %	22.5 ± 15.7 [20.5]	16.0 ± 10.7 [15.0]	0.046
In-stent late loss, mm	0.44 ± 0.44 [0.32]	0.13 ± 0.33 [0.08]	<0.0001
Follow-up duration, months	8.4 ± 1.7 [8.0]	9.2 ± 1.5 [9.2]	0.01

Data are presented as mean ± SD [median] or n (%).
Abbreviations as in Table 1.

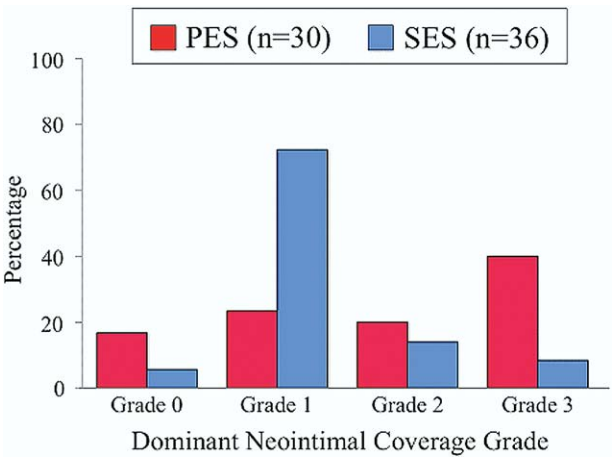

Figure 1. Distribution of Dominant Neointimal Coverage Grades at Follow-Up in PES and in SES

Although 72% of sirolimus-eluting stents (SES) showed the dominant neointimal coverage of grade 1, paclitaxel-eluting stents (PES) showed widely dispersed neointimal coverage. PES versus SES, p = 0.0006 by chi-square test.

SES showed grade 1 (n = 26, 72%), PES showed dispersed NIC grades. Within the stents, NIC was more heterogeneous in PES than in SES (Fig. 2). Of SES, 47% had heterogeneous NIC, but all of them showed heterogeneity of 1 grade. In contrast, PES showed a higher incidence of heterogeneity (74%); the heterogeneity of 1 grade was detected in 48%; the heterogeneity of 2 grades was detected in 26%, which was not observed in SES. A representative case is shown in Figure 3.

All the thrombi detected were mural and subclinical and were more frequently observed in PES (43%) than in SES (19%; p = 0.04). One of these thrombi was white, which

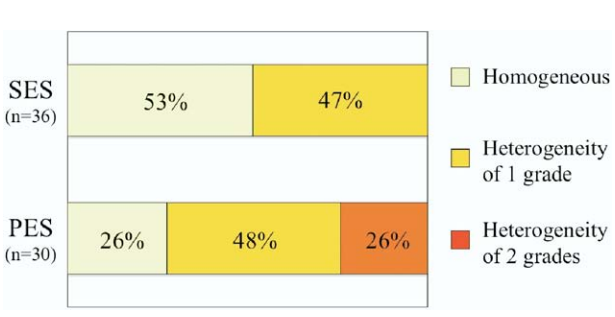

Figure 2. Heterogeneity of NIC Grades in PES and in SES

Forty-seven percent of SES showed the heterogeneity of 1 grade. Fifty-three percent demonstrated homogenous neointimal coverage (NIC). In contrast, 74% of PES showed heterogeneous NIC: 48% showed the heterogeneity of 1 grade; 26% showed the heterogeneity of 2 grades, which was not observed in SES. PES versus SES, p = 0.002 by chi-square test. Abbreviations as in Figure 1.

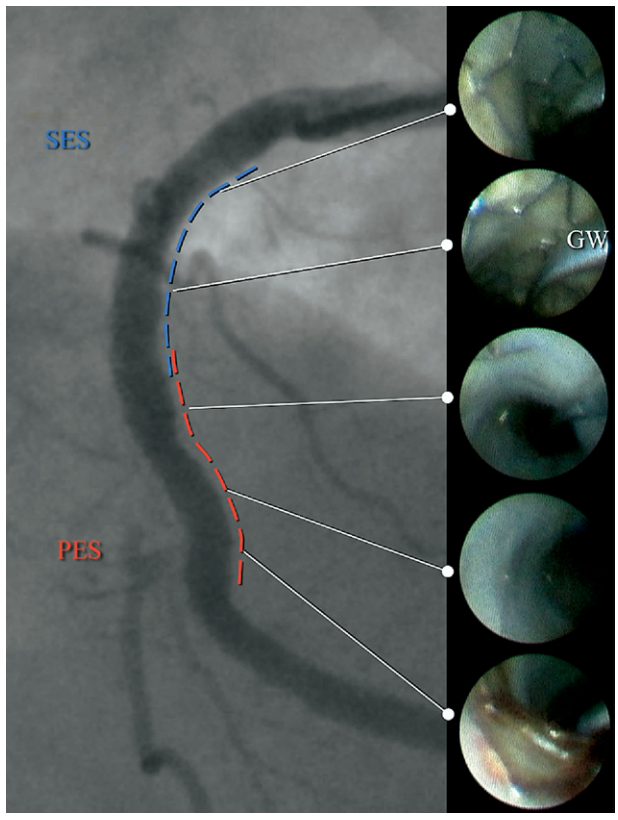

Figure 3. Coronary Angiograms and Angioscopic Images 8 Months After the Tandem Implantation of SES and PES

Angiograms at follow-up revealed no restenosis at the segment of SES (3.5 × 23 mm) and PES (3.5 × 24 mm) implanted in tandem. Angioscopic images of SES showed homogeneous NIC of grade 1. In contrast, PES showed the heterogeneity of 2 grades; the dominant degree of NIC was grade 2 in PES; the distal segment showed NIC of grade 0, with mural red thrombi adhered on the yellow plaques and the naked stent struts. **Dashed blue line** = SES-implanted site; **dashed red line** = PES-implanted site. GW = guide wire; other abbreviations as in Figures 1 and 2.

was detected in a SES that showed NIC of grade 1. The remaining 19 thrombi were red thrombi. All the thrombi were present at the site of grade 0/1. Yellow plaques were similarly common in PES (83%) and in SES (78%; p = 0.76). Most of them were detected underneath the neointima of grades 0 to 2 (88%).

A total of 12 segments were overlapped: PES covering PES (n = 1); SES covering SES (n = 4); PES covering SES (n = 3); SES covering PES (n = 4). Five segments were overlapped with the same DES. The PES covering PES showed grade 2, and the nonoverlapped segments revealed grade 3. Three of the SES covering SES showed grade 1 throughout the stent. The other SES covering SES revealed grade 3, which was associated with moderate stenosis (<50% of diameter stenosis). The other 7 segments were overlapped with SES and PES, which in general showed low-grade coverage that was similar to the nonover-

lapped segments, except for a SES covering PES, which showed grade 3 with moderate stenosis: SES covering PES showed grade 0 (n = 2) to grade 1 (n = 1); PES covering SES showed grade 1 (n = 2) to grade 2 (n = 1). Exposed struts were only seen in the segments of SES covering PES in this limited observation.

Discussion

The present study compared the vascular lumen/stent surfaces in patients following PES implantation with those following SES using angioscopy. Late loss was slightly, but statistically greater in PES than in SES. Although 72% of SES showed the dominant NIC of grade 1, PES showed widely dispersed NIC grades. Within the stents, NIC was more heterogeneous in PES than in SES. Thrombi were more frequently observed in PES (43%) than in SES (19%, p = 0.04). Yellow plaques were commonly detected both in PES (83%) and in SES (78%, p = 0.76).

Late losses in each group of this study were similar to those found in several other clinical studies for these stents (1,2,17). Similar to SES, PES is one of the first generation DES to reduce LL and target lesion revascularization by inhibiting neointimal hyperplasia. It has been pointed out, however, that incidence of LST may be higher following PES or SES placements than following BMS placements (3–6). Since the beginning of the BMS era, pathological studies have indicated that incomplete NIC causes LST (7). Another pathological study also suggested that incomplete NIC over SES and PES causes LST (8). In our previous study, a zotarolimus-eluting stent (Endeavor, Medtronic, Minneapolis, Minnesota), which demonstrated greater LL than SES, appeared to have angioscopically more competent NIC than SES (14). Although PES showed intermediate LL among these DES (17), PES revealed heterogeneous NIC, which did not cover the stent struts as well as the underlying YP completely. Both intra- and interstent heterogeneities of NIC grades were more significant in PES, while PES was associated with a higher frequency of thrombi than SES. Several meta-analyses revealed the higher incidence of LST in PES than in SES, whereas PES had higher LL than SES (18,19). The results of this study may explain the mechanism of the higher incidence of LST in PES in spite of the greater LL in PES than in SES. Angioscopically, thrombus adheres to the sites of incomplete NIC following DES placement (9,13).

In the present study, PES had a similar incidence of YP as did SES. Using angioscopy, Miyamoto et al. (20) demonstrated that intimal wall thickness and percent yellow saturation correlated inversely in vitro; that is, angioscopic color reflected the thickness of the fibrous cap. A clinical study using optical coherence tomography also demonstrated the relationship between the fibrous cap thickness and the yellow saturation of YP in angioscopy (21). Yellow plaque was reduced following BMS or zotarolimus-eluting stent placement, possibly by covering the YP with the neointimal development. Neointima covering the YP may have a "plaque-sealing effect" to stabilize plaques (9,11,14). In fact, although the event rate following BMS implantation was higher in target lesions than in nontarget lesions due to restenosis in year 1, the target lesions (i.e., stented segments) were clinically stable from year 2 through year 5 (target lesion = 1.7% vs. nontarget lesion = 6.3%) (22). This may be due to a lesion stabilization effect of the neointima. Our previous angioscopic studies (9,14) suggested that this plaque-sealing effect may not be expected in SES implantation due to the lack of neointimal development. Paclitaxel-eluting stents may also lack this protective sealing effect because both SES and PES showed a high incidence of YP. Although PES had a higher incidence of grade 3 than did SES, both without restenosis, the heterogeneity of NIC following PES hampered the YP sealing effect as observed in BMS or zotarolimus-eluting stents.

Clinical implications. The present study demonstrated heterogeneous NIC following PES, which resulted in the higher incidence of thrombus adhesion as well as partially incomplete NIC. These angioscopic results endorse the recommendation of dual antiplatelet therapy for at least 1 year for patients treated with DES including PES (23,24). It is important to recognize from this study the homogeneous NIC following stenting may also be an indispensable factor to developing next-generation stents.

Study limitations. This study was a single center, nonrandomized, historical control study with a small sample size. The follow-up term in this study was slightly longer in SES than in PES. However, NIC 3 months to 1 year after SES implantation was similar when serially compared using angioscopy (9). The follow-up term may be too short to understand the chronological changes in arterial healing following PES. Long-term, serial angioscopic follow-up study is necessary for this purpose. Although statistically insignificant, PES tended to have more restenosis (n = 3) than SES (n = 1; p = 0.3). This may bias the angioscopic observation. Nonetheless, this may also be clinically relevant because meta-analyses including a large number of patients have indicated higher rates of restenosis and target lesion revascularization rates in PES than in SES (18,19). Although 7 patients were treated with both PES and SES, analyses in the quantitative coronary angiography and angioscopy were performed per stent without correction for correlated observations in the same patients.

Conclusions

Neointimal coverage grades were more heterogeneous in PES than in SES and were associated with a higher incidence of thrombi in PES. Homogeneous NIC may be

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an important factor for competent arterial healing following DES.

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Key Words: angioscope ■ imaging ■ neointima ■ stent.