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Long-Term Luminal Change after Drug-Eluting Stent Implantation: Serial Angiographic Follow-Up Study of the ZEST Randomized Trial

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Objective: To evaluate long-term patterns of luminal changes after implantation of different types of drug-eluting stents (DES), we analyzed the serial angiographic outcomes of patients implanted with zotarolimus-eluting stents (ZES), sirolimus-eluting stents (SES), or paclitaxel-eluting stents (PES). Background: Little is known regarding long-term luminal changes after DES implantation. Methods: As a subgroup analysis of the ZEST trial, we performed complete angiographic evaluation immediately after the procedure and at 9 months and 2 years in 111 patients with 165 lesions (36 patients with ZES, 40 with SES, and 35 with PES). Results: Baseline clinical, angiographic, and procedural characteristics were similar among the three groups. Quantitative angiographic analysis revealed significant decreases in minimal luminal diameter 9 months after stent implantation in the ZES (from 2.71 ± 0.49 to 2.21 ± 0.42 mm, $P < 0.001$), SES (from 2.79 ± 0.49 to 2.58 ± 0.57 mm, $P < 0.001$), and PES (from 2.66 ± 0.45 to 2.19 ± 0.52 mm, $P < 0.001$) groups. However, significant late improvements with different degree in luminal diameter were observed between 9 months and 2 years in the ZES (from 2.21 ± 0.42 to 2.39 ± 0.58 mm, $P = 0.001$), SES (from 2.58 ± 0.57 to 2.66 ± 0.60 mm, $P = 0.039$), and PES (from 2.19 ± 0.52 to 2.43 ± 0.52 mm, $P < 0.001$) groups. Conclusion: Serial angiographic follow-up study revealed a biphasic luminal response after DES implantation, characterized by an early progression phase for the first 9 months and a late regression phase from 9 months to 2 years. © 2012 Wiley Periodicals, Inc.

Key words: quantitative coronary angiography; coronary artery disease; restenosis

INTRODUCTION

Drug-eluting stents (DES) have become the primary strategy for percutaneous coronary intervention, because they result in significantly reduced incidence of in-stent restenosis compared to bare metal stents (BMS) [1,2]. The early-generation DES, sirolimus- (SES), and paclitaxel-eluting stents (PES) showed long-term favorable clinical outcomes with sustained efficacy and acceptable safety [3–5]. However, very late stent thrombosis has been a critical limitation of first-generation DES, and recent study showed the potential relation between the luminal changes and the ongoing risk of very late stent thrombosis [6]. Similarly, other studies also have proposed luminal changes as surrogates of target-lesion revascularization after DES implantation [7,8].

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As such, although the relationship of luminal changes with ongoing propensity of late-stent thrombosis and late-catch-up phenomenon has been proposed, there are limited data regarding long-term serial angiographic luminal changes after DES implantation. To address this issue, and as a subgroup analysis of the ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PacliTaxel-Eluting Stent for Coronary Lesions) randomized clinical trial, we performed serial angiographic follow-up immediately after DES implantation, and 9 months and 2 years later, after implantation of three types of DES, zotarolimus-eluting stents (ZES), SES, and PES.

METHODS

Study Population

The study design of the ZEST trial has been described previously [9]. In brief, this prospective, randomized, single-blind, controlled trial was performed at 19 centers in Korea. A total of 2,645 patients was randomized 1:1:1 to undergo ZES (Endeavor; Medtronic Vascular), SES (Cypher select; Cordis, Johnson & Johnson, Miami Lakes, FL), or PES (Taxus Liberte, Boston Scientific Corp, Natick, MA) implantation between October 2006 and January 2008. Inclusion and exclusion criteria of the ZEST trial have been described [9].

The current angiographic follow-up analysis, which was a single-center substudy of the ZEST trial, included patients evaluated and treated at the Asan Medical Center, Seoul, Korea. Patients were eligible if they underwent complete long-term serial angiographic analyses (immediately after the procedure and at 9 months and 2 years). Additional eligibility criteria were symptom–free and negative results on serial stress tests (exercise treadmill tests or thallium scans) during the follow-up period. Exclusion criteria were significant (>70%) stenosis at any lesion during angiographic follow-up or patients who underwent repeat revascularization.

All patients provided written informed consent. This study was approved by the local Institutional Review Board at the Asan Medical Center, Seoul, Korea. The study and the statistical analysis were designed and interpreted by the authors, all of whom contributed to the final report and participated in the decision to submit the findings for publication. No stent manufacturer had any role in this study.

Study Procedures and Adjunct Drug Therapy

Lesions were treated using standard interventional techniques. Patients requiring interventions for ≥2 lesions received the same randomly assigned stent for all lesions, except when the assigned stent could not be inserted, in which case crossover to another device was allowed. There was no limit on the number of stents used to achieve complete lesion coverage. Predilation or direct stenting was at the discretion of the individual operator.

Before or during the procedure, all patients received at least 100 mg of aspirin and a 300–600 mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of 250 sec or longer. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, all patients received 100 mg/day of aspirin indefinitely as well as 75 mg/day clopidogrel for at least 12 months.

Quantitative Coronary Angiography

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up, and were assessed in the angiographic core laboratory (Asan Medical Center, Seoul, Korea) using an automated edge-detection system (CAAS V, Pie Medical Imaging) by two independent angiographers unaware of the allocated stent. Standard qualitative and quantitative analyses and definitions were used for angiographic analysis. Quantitative angiographic measurements were obtained within the stented segment (in-stent) and over the entire segment including the stent and its 5-mm proximal and distal margins (in-segment). Measured variables included the diameter of the reference vessel, the minimal luminal diameter, the degree of stenosis (%), and late luminal loss (the difference between the minimal luminal diameter after the procedure and at follow-up). Binary restenosis was defined as ≥50% diameter stenosis on follow-up angiography, and restenosis patterns were qualitatively assessed using the Mehran classification [10].

Statistical Analysis

All statistical analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago, IL). Categorical data are presented as frequencies and compared to chi-square statistics or Fisher's exact test. Continuous variables are presented as mean ± 1 SD. Paired numerical data were compared by the paired *t* test or Wilcoxon's signed rank test. Other continuous variables were compared using one-way or repeated measures analysis of variance with the Bonferroni correction for post hoc comparisons or the nonparametric Kruskal–Wallis test with Mann–Whitney test for post hoc corrections. Linear regression analysis was used to assess the predictors of long-term increase in luminal diameter. A P value <0.05 was considered statistically significant.

TABLE I. Baseline Characteristics of the Patients[a]

Characteristics	Zotarolimus-eluting stent (36 patients)	Sirolimus-eluting stent (40 patients)	Paclitaxel-eluting stent (35 patients)	*P* value
Clinical characteristics				
Age (years)	57.9 ± 9.4	57.4 ± 10.1	61.4 ± 8.2	0.145
Male sex (%)	28 (77.8)	31 (77.5)	23 (65.7)	0.414
Diabetes mellitus (%)	8 (22.2)	11 (27.5)	4 (11.4)	0.222
Hypertension (%)	17 (47.2)	23 (57.5)	11 (31.4)	0.076
Hyperlipidemia (%)	21 (58.3)	23 (57.5)	19 (54.3)	0.936
Current smoker (%)	8 (22.2)	11 (27.5)	7 (20.0)	0.730
Previous myocardial infarction (%)	1 (2.8)	2 (5.0)	2 (5.7)	0.822
Multivessel disease (%)	17 (47.2)	21 (52.5)	16 (45.7)	0.824
Left ventricular ejection fraction (%)	60.3 ± 4.8	58.9 ± 6.5	60.1 ± 5.3	0.506
Clinical indication (%)				0.689
Stable angina	17 (47.2)	20 (50.0)	20 (57.1)	
ACS	19 (52.8)	20 (50.0)	15 (42.9)	
Lesion characteristics				
Location (%)				0.548
Left anterior descending	30 (60.0)	30 (46.2)	23 (46.0)	
Left circumflex	8 (16.0)	17 (26.2)	12 (24.0)	
Right coronary	12 (24.0)	18 (27.7)	15 (30.0)	
Total occlusion (%)	5 (10.0)	4 (6.2)	5 (10.0)	0.687
Bifurcation lesions (%)	7 (14.0)	6 (9.2)	6 (12.0)	0.723
Procedural characteristics				
No. of stents per lesion	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	0.553
Length of stents per lesion (mm)	30.0 ± 15.0	32.3 ± 17.2	30.3 ± 14.8	0.689
Maximal stent diameter (mm)	3.5 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	0.905
Direct stenting (%)	6 (12.0)	13 (20.0)	4 (8.0)	0.164
Intravascular ultrasound guidance (%)	33 (66.0)	43 (66.2)	34 (68.0)	0.972

[a]Plus-minus values are mean ± SD. ACS denotes acute coronary syndrome.

RESULTS

Baseline Characteristics

Complete serial angiographic analyses immediately after the procedure and at 9 months and 2 years were available in 111 event–free patients (165 lesions): 36 (50 lesions) ZES, 40 (65 lesions) SES, and 35 (50 lesions) PES. The mean age of the overall population was 58.8 years, 82 (73.9%) were men and 23 (20.7%) had diabetes mellitus. Of the 111 patients, 57 (51.4%) presented with stable angina and 54 (48.6%) with acute coronary syndrome. The three DES groups had similar baseline clinical, angiographic, and procedural characteristics (Table I).

Quantitative Angiographic Analysis

Angiographic measurements at each time-point (baseline, postprocedure, 9 month, and 2 years) are shown in Table II. Over time, serial quantitative angiographic analysis showed biphasic luminal responses in all 3 DES groups, characterized by an early progression phase until 9 months after DES implantation and a late-regression phase from 9 months to 2 years (Table II, Fig. 1). We observed significant decreases in minimal luminal diameter from stent implantation to 9 months in all groups, from 2.71 ± 0.49 to 2.21 ± 0.42 mm in the ZES group ($P < 0.001$), from 2.79 ± 0.49 to 2.58 ± 0.57 mm in the SES group ($P < 0.001$), and from 2.66 ± 0.45 to 2.19 ± 0.52 mm in the PES group ($P < 0.001$). Although significant late improvements in luminal diameter were observed between 9 months and 2 years in all three groups, the degree of luminal change differed, from 2.21 ± 0.42 to 2.39 ± 0.58 mm in the ZES group ($P = 0.001$), from 2.58 ± 0.57 to 2.66 ± 0.60 mm in the SES group ($P = 0.039$), and from 2.19 ± 0.52 to 2.43 ± 0.52 mm in the PES group ($P < 0.001$).

Analyses of Δ minimal luminal diameter and Δ percent diameter stenosis in all three groups provided further evidence of a biphasic response (Table III). When we compared the three groups, we found that the serial increase of in-stent late luminal loss from immediately after the procedure to 9 months was significantly smaller in the SES than in the ZES and PES groups ($P < 0.001$), but that long-term in-stent luminal gain was more pronounced in the ZES and PES than in the SES group.

At 9 months, angiographic binary restenosis was identified in five focal lesions and three diffuse lesions, all of which had 50–70% diameter stenosis by quantitative analysis, with these patients being negative on stress tests and with no symptoms. Of these eight

TABLE II. Quantitative Angiographic Analysis at Each Time Point[a]

Characteristics	Zotarolimus-eluting stent (50 lesions)	Sirolimus-eluting stent (65 lesions)	Paclitaxel-eluting stent (50 lesions)	*P* value
Before procedure				
Lesion length (mm)	25.0 ± 14.3	26.3 ± 14.9	27.0 ± 14.4	0.797
Reference vessel diameter (mm)	3.09 ± 0.52	3.10 ± 0.44	3.03 ± 0.51	0.764
Minimal luminal diameter (mm)	1.03 ± 0.55	1.01 ± 0.56	0.86 ± 0.56	0.233
Diameter stenosis (%)	66.8 ± 17.6	68.9 ± 16.4	72.3 ± 17.0	0.202
Minimal luminal diameter (mm)				
In-stent minimal luminal diameter				
After procedure	2.71 ± 0.49	2.79 ± 0.49	2.66 ± 0.45	0.369
9-month[b]	2.21 ± 0.42	2.58 ± 0.57	2.19 ± 0.52	<0.001
2-year[b]	2.39 ± 0.58	2.66 ± 0.60	2.43 ± 0.52	0.025
In-segment minimal luminal diameter				
After procedure	2.39 ± 0.50	2.50 ± 0.54	2.38 ± 0.49	0.340
9-month[b]	2.12 ± 0.40	2.32 ± 0.57	2.03 ± 0.46	0.005
2-year[b]	2.21 ± 0.57	2.45 ± 0.59	2.20 ± 0.45	0.024
Diameter stenosis (%)				
In-stent diameter stenosis				
After procedure	8.6 ± 10.3	9.2 ± 7.8	11.1 ± 9.0	0.338
9-month[b]	25.2 ± 10.5	17.1 ± 12.6	27.2 ± 15.2	<0.001
2-year	19.5 ± 12.4	15.5 ± 13.0	18.9 ± 14.4	0.220
In-segment diameter stenosis				
After procedure	14.6 ± 8.2	14.7 ± 8.8	16.4 ± 9.1	0.508
9-month[b]	26.9 ± 8.8	22.9 ± 11.8	29.3 ± 15.5	0.017
2-year	23.3 ± 14.5	20.0 ± 13.1	23.7 ± 15.0	0.289
Binary restenosis (%)				
In-stent binary stenosis				
9-month	1 (2.0)	2 (3.1)	5 (10.0)	0.123
2-year	2 (4.0)	2 (3.1)	4 (8.0)	0.450
In-segment binary stenosis				
9-month	1 (2.0)	2 (3.1)	5 (10.0)	0.123
2-year	4 (8.0)	3 (4.6)	6 (12.0)	0.346
9-month restenosis pattern (%)				
Focal	0 (0)	2 (3.1)	3 (6.0)	0.216
Diffuse	1 (2.0)	0 (0)	2 (4.0)	0.280
Proliferative	0 (0)	0 (0)	0 (0)	1.000
Total occlusion	0 (0)	0 (0)	0 (0)	1.000
2-year restenosis pattern (%)				
Focal	2 (4.0)	3 (4.6)	3 (6.0)	0.892
Diffuse	2 (4.0)	0 (0)	2 (4.0)	0.264
Proliferative	0 (0)	0 (0)	1 (2.0)	0.314
Total occlusion	0 (0)	0 (0)	0 (0)	1.000

[a]Plus-minus values are mean ± SD.

[b]*P* values of post hoc multiple comparisons for secondary angiographic outcomes. Bonferroni and Mann–Whitney corrections were made for multiple comparisons of continuous variables in secondary angiographic analyses; for 9-month in-stent minimal luminal diameter (zotarolimus- vs. sirolimus-stent; $P = 0.001$, zotarolimus- vs. paclitaxel-stent; $P = 1.000$, and sirolimus- vs. paclitaxel-stent; $P < 0.001$), for 2-year in-stent minimal luminal diameter (zotarolimus- vs. sirolimus-stent; $P = 0.041$, zotarolimus- vs. paclitaxel-stent; $P = 1.000$, and sirolimus- vs. paclitaxel-stent; $P = 0.103$), for 9-month in-segment minimal luminal diameter (zotarolimus- vs. sirolimus-stent; $P = 0.093$, zotarolimus- vs. paclitaxel-stent; $P = 1.000$, and sirolimus- vs. paclitaxel-stent; $P = 0.005$), for 2-year in-segment minimal luminal diameter (zotarolimus- vs. sirolimus-stent; $P = 0.070$, zotarolimus- vs. paclitaxel-stent; $P = 1.000$, and sirolimus- vs. paclitaxel-stent; $P = 0.054$), for 9-month in-stent diameter stenosis (zotarolimus- vs. sirolimus-stent; $P < 0.001$, zotarolimus- vs. paclitaxel-stent; $P = 0.978$, and sirolimus- vs. paclitaxel-stent; $P < 0.001$), and for 9-month in-segment diameter stenosis (zotarolimus- vs. sirolimus-stent; $P = 0.018$, zotarolimus- vs. paclitaxel-stent; $P = 0.506$, and sirolimus- vs. paclitaxel-stent; $P = 0.016$).

lesions, three returned to normal and four regressed at 2 years, while the remaining lesion showed an increased diameter stenosis at 2 years. At 2 years, angiographic restenosis was identified in 13 lesions, including 8 focal, 4 diffuse, and 1 proliferative lesions. Of these, eight lesions were newly developed and five were pre-existing lesions, suggesting that luminal changes after DES implantation were dynamic, not static.

Regression Group Analysis

A change in minimal luminal diameter >0.5 mm has been defined as significant [11]. Using this definition, 55 lesions (33.3%) showed significant progression from

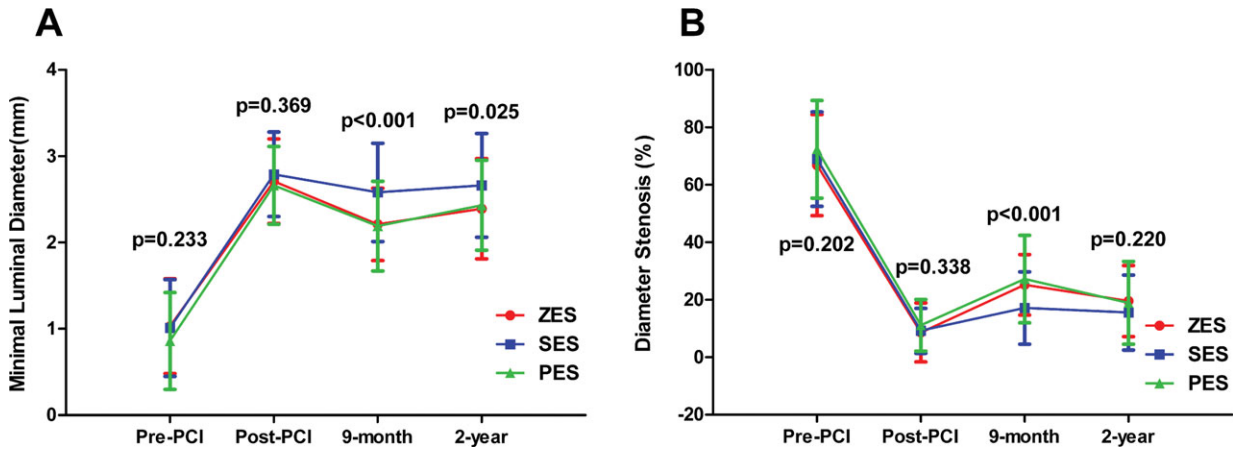

Fig. 1. In-stent minimal luminal diameter (A) and percent in-stent diameter stenosis (B) in the zotarolimus-eluting stents (ZES), sirolimus-eluting stents (SES), and paclitaxel-eluting stents (PES) groups.

TABLE III. Serial Changes in Angiographic Measurements[a]

Characteristics	Zotarolimus-eluting stent (50 lesions)	Sirolimus-eluting stent (65 lesions)	Paclitaxel-eluting stent (50 lesions)	*P* value
Postintervention to 9-month follow-up				
Δ Minimal luminal diameter (mm)				
In-stent[b]	0.50 ± 0.36	0.21 ± 0.40	0.48 ± 0.50	<0.001
In–segment	0.27 ± 0.35	0.18 ± 0.29	0.35 ± 0.48	0.203
Δ Diameter stenosis (%)				
In-stent[b]	−16.6 ± 12.4	−7.9 ± 14.5	−16.0 ± 15.9	0.001
In-segment	−12.2 ± 10.7	−8.3 ± 11.2	−12.9 ± 16.3	0.115
9-month to 2-year follow-up				
Δ Minimal luminal diameter (mm)				
In-stent	−0.18 ± 0.38	−0.07 ± 0.30	−0.24 ± 0.45	0.058
In-segment	−0.09 ± 0.41	−0.12 ± 0.28	−0.18 ± 0.47	0.713
Δ Diameter stenosis (%)				
In-stent[b]	5.7 ± 12.6	1.6 ± 11.0	8.3 ± 14.5	0.017
In-segment	3.6 ± 12.6	3.0 ± 11.1	5.5 ± 17.3	0.718
Postintervention to 2-year follow-up				
Δ Minimal luminal diameter (mm)				
In-stent	0.32 ± 0.39	0.13 ± 0.45	0.23 ± 0.42	0.058
In-segment	0.18 ± 0.44	0.06 ± 0.36	0.18 ± 0.47	0.202
Δ Diameter stenosis (%)				
In-stent	−10.9 ± 14.0	−6.3 ± 14.3	−7.8 ± 14.3	0.234
In-segment	−8.7 ± 15.3	−5.3 ± 13.5	−7.4 ± 15.6	0.464

[a]Plus-minus values are mean ± SD.

[b]*P* values of post hoc multiple comparisons for secondary angiographic outcomes. Bonferroni and Mann–Whitney corrections were made for multiple comparisons of continuous variables in secondary angiographic analyses; for postintervention to 9-month Δ in-stent minimal luminal diameter (zotarolimus- vs. sirolimus-stent; $P < 0.001$, zotarolimus- vs. paclitaxel-stent; $P = 0.448$, and sirolimus- vs. paclitaxel-stent; $P = 0.001$), for postintervention to 9-month Δ in-stent diameter stenosis (zotarolimus- vs. sirolimus-stent; $P = 0.005$, zotarolimus- vs. paclitaxel-stent; $P = 1.000$, and sirolimus- vs. paclitaxel-stent; $P = 0.009$), and for 9-month to 2-year Δ in-stent diameter stenosis (zotarolimus- vs. sirolimus-stent; $P = 0.249$, zotarolimus- vs. paclitaxel-stent; $P = 0.922$, and sirolimus- vs. paclitaxel-stent; $P = 0.016$).

immediately after the procedure to 9 months, whereas 108 (65.5%) lesions showed no interval change. Between 9 months and 2 years, however, 134 lesions (81.2%) showed no interval change and 27 (16.4%) showed regression (Fig. 2). When we compared patients with and without regression between 9 months and 2 years, both groups had similar baseline clinical, angiographic, and procedural characteristics except maximal stent diameter. Patients with regression had a larger maximal stent diameter at baseline (3.64 ± 0.40 mm vs. 3.46 ± 0.39 mm, $P = 0.034$). Luminal loss from immediately after the procedure to 9 months was more prominent in the late regression than in the non-regression group (Table IV). The increase in luminal diameter between 9 months and 2 years was significantly correlated with a larger decrease in luminal

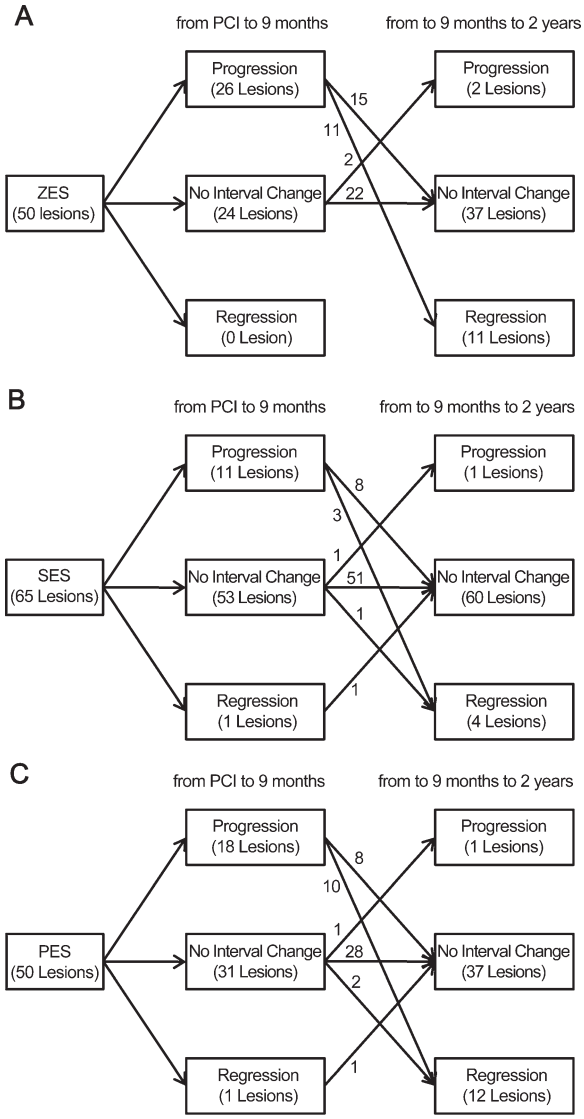

Fig. 2. Lesion changes in the (A) zotarolimus-eluting stents (ZES), (B) sirolimus-eluting stents (SES), and (C) paclitaxel-eluting stents (PES) groups.

diameter from immediately after the procedure to 9 months later ($r = 0.467$, $P < 0.001$), was significantly negatively correlated with minimal luminal diameter at 9 months ($r = 0.248$, $P = 0.001$), and was marginally associated with minimal luminal diameter immediately after DES implantation ($r = 0.152$, $P = 0.051$). A representative patient showing luminal improvement from 9 months to 2 years after DES implantation is shown (Fig. 3).

DISCUSSION

The main findings of this serial angiographic analysis were (1) the observation of a biphasic luminal response, characterized by early progression and later regression, after DES implantation and (2) because the luminal change was a dynamic rather than a static process, urgent intervention for patients with asymptomatic in-stent stenosis at 9 months may not be necessary.

TABLE IV. Serial Changes in Angiographic Measurements in Patients with and without Regression[a]

Characteristics	Regression (27 lesions)	No regression (138 lesions)	*P* value
Postintervention to 9-month follow-up			
Δ Minimal luminal diameter (mm)			
In-stent	0.84 ± 0.45	0.29 ± 0.38	<0.001
In-segment	0.61 ± 0.53	0.19 ± 0.30	0.001
Δ Diameter stenosis (%)			
In-stent	−26.3 ± 13.1	−10.4 ± 13.7	<0.001
In-segment	−22.8 ± 13.5	−8.5 ± 11.5	<0.001
9-month to 2-year follow-up			
Δ Minimal luminal diameter (mm)			
In-stent	−0.74 ± 0.27	−0.05 ± 0.28	<0.001
In-segment	−0.53 ± 0.45	−0.05 ± 0.32	<0.001
Δ Diameter stenosis (%)			
In-stent	22.8 ± 8.9	1.3 ± 10.3	<0.001
In–segment	18.7 ± 12.8	1.04 ± 11.9	<0.001
Postintervention to 2-year follow-up			
Δ Minimal luminal diameter (mm)			
In-stent	0.10 ± 0.41	0.24 ± 0.43	0.135
In-segment	0.08 ± 0.50	0.14 ± 0.41	0.458
Δ Diameter stenosis (%)			
In-stent	−3.6 ± 10.7	−9.0 ± 14.7	0.027
In-segment	−4.2 ± 14.2	−7.5 ± 14.8	0.281

[a]Plus-minus values are mean ± SD.

Serial luminal changes after balloon angioplasty and BMS implantation have been documented to be dynamic over time. Three phases of lumen changes have been observed after balloon angioplasty: an early restenosis phase, an intermediate regression phase, and a late plateau phase [11–13]. Similarly, long-term luminal responses after BMS implantation were also found to be triphasic, consisting of an early restenosis phase (until 6 months), an intermediate-term regression phase (from 6 months to 3 years), and a late renarrowing phase beyond 4 years [14].

Less is known, however, about long-term angiographic outcomes of DES, with serial luminal changes over time after DES implantation being poorly described. The first-in-man study of SES showed a triphasic pattern of luminal change following SR (slow release) SES implantation, similar to BMS. Luminal changes over 4 years in 13 patients were characterized by an early restenosis phase until 1 year, an intermediate-term regression phase between 1 and 2 years, and a late renarrowing phase between 2 and 4 years [15]. The 2-year angiographic evaluation of the SPIRIT II and Taxus II trials showed that late lumen loss from the first to second angiographic follow-up after PES implantation was not additive [16,17]. Recently, two

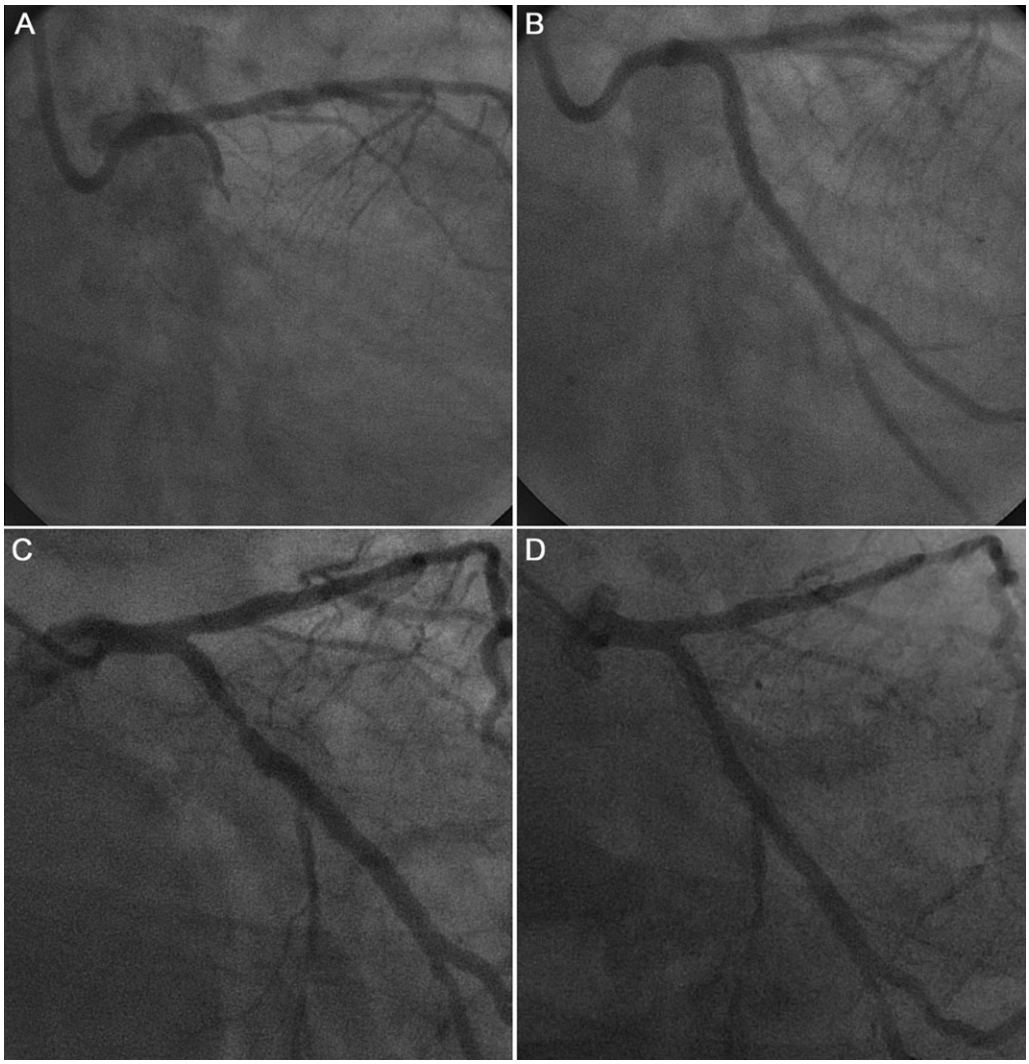

Fig. 3. Representative images showing marked luminal improvement. Paclitaxel-eluting stent implantation was performed in this patient for the left circumflex coronary artery. The in-stent minimal luminal diameter improved from 0 mm before the intervention (A) to 3.00 mm immediately after the implantation of the stent (B). At 9 months (C), the diameter had decreased to 1.55 mm, but at 2 years (D), it had increased to 2.99 mm.

large registry studies revealed that lumen diameter following SES and PES implantation progressively narrowed over 2 years [18,19]. These cumulative findings indicate that long-term luminal changes after DES implantation are not uniform, but diverse. Consistent with the pattern observed after BMS implantation, we found that luminal changes after DES implantation are biphasic, suggesting that this may be a best-case scenario after DES.

We also found that later increases in luminal diameter, between 9 months and 2 years after DES implantation, were significantly correlated with larger decreases in luminal diameter between postintervention and 9 month follow-up angiography, suggesting that larger intimal hyperplasia is associated with a greater potential for late regression. Fibrotic maturation of the intimal hyperplasia after DES implantation may be one of the mechanisms of the observed regression in the lumen [11]. However, the precise mechanism of this regression remains elusive and cannot be clearly explained by our data.

Regarding the clinical impact of our findings, we found that some revascularization events were driven by angiographic follow-up alone in asymptomatic patients with severe percent diameter stenosis, because we assumed that these patients would soon likely become symptomatic and require revascularization, with 10% of these revascularizations due to an "oculostenotic reflex" [7]. Although we identified eight lesions with angiographic binary restenosis at 9 months, seven regressed

spontaneously, with only one progressing between 9 months and 2 years. These findings indicate that patients with in-stent restenosis at 9 months may be safely observed without repeated intervention, if these patients are asymptomatic or do not have evidence of ischemia.

Our study had several limitations. First, we assessed only event–free patients in single center of the ZEST trial. Because this cohort did not completely reflect the characteristics of the overall study population, there was a potential for selection bias. Because our study is a 2-year angiographic follow-up study, it cannot rule out a third phase of renarrowing like what is observed in other studies [15]. Therefore, our findings should be confirmed through larger and longer-term follow-up studies. Second, our study checked at only two each time point (9 months and 2 years) after DES implantation. Therefore, we could not exactly assess the maximum restenosis time. Further investigations by other groups are necessary to resolve these issues. Third, our study included patients without significant stenosis causing ischemia over time and with mean reference diameters larger than those of patients in previous studies [7,8,20], suggesting that our patients may be highly selected and represent a "best-case scenario." Fourth, previous studies have suggested a potential error to detect precise lumen and stent boundaries by quantitative coronary angiography [17]. Therefore, for studies like current work in which the luminal diameter needs to be estimated with maximum precision, novel modalities like intravascular ultrasound may be better trusted or at least can be used as a complementary method. Unfortunately, systemic follow-up of intravascular ultrasound was not performed in this study. Finally, because we evaluated the two first-generation and the earliest second-generation DESs, the applicability of our findings to the next generation of DES may be limited.

CONCLUSIONS

This serial angiographic follow-up study of patients in the ZEST randomized trial showed a biphasic luminal response after DES implantation characterized by an early progression phase until 9 months and a late regression phase from 9 months to 2 years, suggesting the possibility of heterogenous luminal responses after DES implantation. These findings should be confirmed in large, prospective clinical trials.

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