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CVN Interview

Impact of Multiple and Long Sirolimus-Eluting Stent Implantation on 3-Year Clinical Outcomes in the j-Cypher Registry

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Objectives Our aim was to study the relationships between total stent length (TSL) and long-term clinical outcomes after sirolimus-eluting stent (SES) implantation.

Background SES compared with bare-metal stent use for long lesion treatment is associated with reduced restenosis rates.

Methods Three-year follow-up data were available for 10,773 patients (14,651 lesions) that had been treated with only SES (Cypher, Cordis Corp., Warren, New Jersey) in the j-Cypher registry. Patients and lesions were divided into quartile groups: TSL per patient (Q1: 8 to 23 mm, Q2: 24 to 36 mm, Q3: 37 to 54 mm, Q4: 55 to 293 mm), and TSL per lesion (QA: 8 to 18 mm, QB: 19 to 23 mm, QC: 24 to 33 mm, QD: 34 to 150 mm).

Results In per-lesion data, longer TSL increased target lesion revascularization (TLR) rates but did not increase stent thrombosis rates ($p = 0.2324$). In per-patient data, the incidences of TLR remarkably increased with increasing TSL. Incidence of composite of death and myocardial infarction also increased with increasing TSL; however, after adjustment for baseline differences, there was no statistical significance. Definite stent thrombosis rate in group Q4 was significantly higher than in other groups, both unadjusted (hazard ratio: 1.770, $p = 0.0081$) and adjusted (hazard ratio: 1.727, $p = 0.0122$) for baseline differences.

Conclusions TSL per lesion and patient had significantly impacts on TLR rates. Longer TSL per patient was associated with increased incidence of stent thrombosis through 3 years. (J Am Coll Cardiol Intv 2010;3:180–8) © 2010 by the American College of Cardiology Foundation

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Multiple and long bare-metal stent (BMS) implantation is associated with a greater incidence of restenosis (1–3), with diffuse in-stent restenosis (ISR) being the most common pattern. Diffuse ISR is, in turn, the major risk factor for malignant recurrent ISR, and, therefore, long-segment BMS implantation is associated with a poor clinical outcome (4,5). Randomized clinical trials and registries including complex coronary lesions have shown that sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Warren, New Jersey) reduce the need for revascularization therapy and provide clinical efficacy in routine practice, as compared with BMS (6–13). This remains true even in the context of the current trend to use a drug-eluting stent (DES) for full coverage of atherosclerotic lesions (i.e., stented segment length tends to be longer than the lesion length) (6). SES implantation for long lesions with multiple stents is efficacious for reduction of restenosis (14–17); however, long-term safety remains a concern, particularly with regard to late and very late thrombosis (18–21).

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The relationships between total stent length (TSL) for DES and rates of late adverse events, including target lesion revascularization (TLR) and stent thrombosis (ST), have not been examined. Therefore, the objective of this study was to determine the 3-year cumulative incidences of clinical events including death, myocardial infarction, stroke, TLR, and ST according to TSL per lesion and per patient using data derived from the j-Cypher registry.

Methods

Study population. The design and 2-year outcome of the j-Cypher registry has been published previously (22). In brief, the j-Cypher registry is a physician-directed multicenter registry of consecutive patients undergoing SES implantation at 37 centers in Japan. The study protocol was approved by the relevant review boards or ethics committees in the participating centers (22). Written informed consent for enrollment in the registry was obtained from all patients.

Consecutive patients undergoing percutaneous coronary intervention (PCI) were registered in the PCI log form by technical staff at each center, and more than 50% of the case report forms were audited by the clinical research coordinators (22) in the data management center. Entry of detailed baseline and follow-up data for patients undergoing at least 1 SES implantation was performed via the Internet. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians at 30 days, 6 months, and 1 year after the procedure, and yearly thereafter. Upon reports of important clinical events such as death, myocardial infarction, and ST, original source documents were requested to be sent to the data center, and the events were evaluated by the clinical events committee (22).

Between August 2004 and November 2006, a total of 15,155 patients were enrolled in the registry from 29,555 consecutive patients undergoing PCI. SES implantation rates varied markedly among centers, with a median rate of 53% and a range of 16% to 92%. After exclusion of 2,331 patients who were registered more than once due to PCI for restenosis or new lesions, 12,824 patients were newly enrolled in the registry. Among 19,675 target lesions, 17,050 were treated exclusively with SES. Treatment for the remaining 2,625 lesions included BMS (1,259 lesions), a combination of SES and other stent types (495 lesions), other DES (60 lesions), nonstent PCI (672 lesions), failed procedures (139 lesions), and data not available (10 lesions). Finally, 10,773 patients who were exclusively treated with SES were identified as the population for the current analysis.

In this subanalysis of the j-Cypher registry, the patients and lesions were each grouped based on quartiles. For per-patient data for TSL, the lower, median, and upper borders of quartiles of TSL were 23, 36, and 54 mm, respectively, and for per-lesion data these borders were 18, 23, and 33 mm, respectively. Based on these data, there were 4 total stent length groups each per patient (TSL-P) and per lesion (TSL-L), respectively (Fig. 1).

Lesion and patient evaluation. Coronary angiographic parameters including reference vessel diameter, percentage stenosis diameter, and lesion length were assessed in each participating center by either visual assessment or quantitative angiography. A lesion was defined as the area covered by a single stent or multiple overlapping stents. When 2 stents were placed without overlap, the 2 treated areas were regarded as 2 separate lesions. When multiple overlapping stents were placed from the left main coronary artery to the left anterior descending coronary artery, these areas were also regarded as 2 separate lesions, despite placement of overlapping stents. Lesions located within 3 mm from the ostium were regarded as ostial lesions.

Death was regarded as cardiac in origin unless an obvious noncardiac cause could be identified. Myocardial infarction was adjudicated according to the definition in the ARTS (Arterial Revascularization Therapy Study) (23). TLR was defined as either PCI or coronary artery bypass graft

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
ISR = in-stent restenosis
PCI = percutaneous coronary intervention
RR = relative risk
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization
TSL = total stent length
TSL-L = total stent length group per lesion
TSL-P = total stent length group per patient

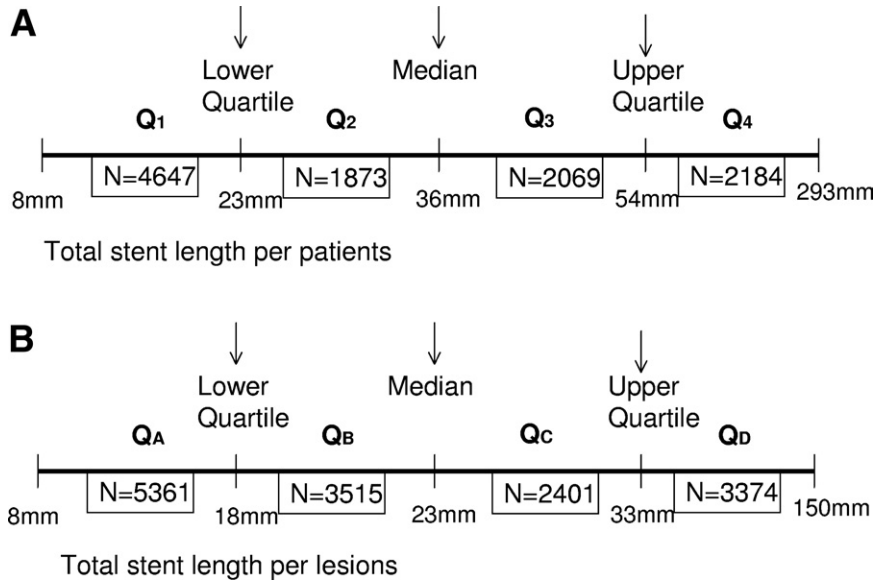


Figure 1. Classification of Patients and Lesions Into 4 Groups According to Quartile

Total stent length per patient **(A)** and per lesion **(B)** was divided into 4 groups according to quartile. Median of total stent length per patient was 36 mm. Lower quartile and upper borders of quartile were 23 and 54 mm (Q1: 8 to 23 mm [n = 4,647], Q2: 24 to 36 mm [n = 1,873], Q3: 37 to 54 mm [n = 2,069], Q4: 55 to 293 mm [n = 2,184]), respectively. Median of total stent length per lesion was 23 mm. Lower and upper borders of quartile were 18 and 33 mm (QA: 8 to 18 mm [n = 5,361], QB: 19 to 23 mm [n = 3,515], QC: 24 to 33 mm [n = 2,401], QD: 34 to 150 mm [n = 3,374]), respectively.

(CABG) surgery due to restenosis or thrombosis of the target lesion, including proximal and distal edge segments. ST was defined according to the Academic Research Consortium definition (24). Academic Research Consortium definite ST was used as the end point for ST in this study (22). The recommended antiplatelet regimen consisted of aspirin (≥81 mg daily) indefinitely and thienopyridine (200 mg ticlopidine or 75 mg clopidogrel daily) for at least 3 months. The duration of dual antiplatelet therapy was left to the discretion of each attending physician. In this study, cumulative 3-year rates of TLR were evaluated based on the TSL-P and TSL-L groupings; the cumulative 3-year incidence of definite ST was also evaluated in the same groups, while the cumulative 3-year incidence of death/myocardial infarction was evaluated in the TSL-P groups (i.e., at the patient level only because the definitions included events unrelated to the lesions per se).

Statistical analysis. Discrete variables are reported as numbers and percentages and continuous variables as means ± SD. Categorical variables were compared with the chi-square test, while continuous variables were compared using the Student *t* test. Clinical event rates at 1, 2, and 3 years were compared by chi-square test. Cumulative incidences were estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test.

The longest TSL-P group was considered as a risk factor for clinical outcomes, and the other 3 groups were combined as 1 comparison group. We used the Cox proportional hazard model to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the longest TSL-P group compared with the comparison group. Because the length of the stent was significantly associated with conditions of patients, we developed a propensity score for the longest TSL-P using logistic regression model, with the longest TSL-P as a response variable and the 16 variables (age, sex, body mass index, ST-segment elevation myocardial infarction, acute coronary syndrome, heart failure, prior PCI, prior CABG, prior myocardial infarction, prior stroke, peripheral artery disease, hemodialysis, estimated glomerular filtration rate <30 ml/min without hemodialysis, hypertension, current smoking, diabetes mellitus with insulin therapy) as explanatory variables. We developed Cox proportional hazard models to estimate the adjusted HRs for clinical events with variables of the longest TSL-P, propensity score, and the 16 variables mentioned in the preceding text. We used SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). Values of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics. Patient characteristics are shown in Table 1, top. Age, sex, or proportions of individuals with acute coronary syndrome at presentation, ST-segment elevation myocardial infarction, prior myocardial infarction, and hemodialysis status did not differ significantly

Table 1. Baseline Characteristics

Patient Characteristics	Q1	Q2	Q3	Q4	p Value
Number of patients	4,647	1,873	2,069	2,184	
Age (yrs)	68.3 ± 10.2	68.8 ± 9.9	68.4 ± 10.0	68.1 ± 10.6	0.1676
Age ≥80 yrs	580 (12.5%)	228 (12.2%)	254 (12.3%)	299 (13.7%)	0.4062
Women	1,179 (25.3%)	452 (24.1%)	491 (23.7%)	530 (24.2%)	0.4436
Body mass index (kg/m^2)	23.9 ± 3.3	24.0 ± 3.5	24.0 ± 3.3	24.0 ± 3.5	0.2861
Hypertension	3,421 (73.6%)	1,401 (74.8%)	1,589 (76.8%)	1,653 (75.6%)	0.0328
Diabetes	1,739 (37.4%)	723 (38.6%)	922 (44.6%)	1,014 (46.4%)	<0.0001
On insulin	353 (7.6%)	158 (8.4%)	226 (10.9%)	259 (11.9%)	<0.0001
Current smoking	902 (19.4%)	344 (18.4%)	387 (18.7%)	485 (22.2%)	<0.0001
eGFR <30 ml/min/1.73 m^2					
Without hemodialysis	19 (4.3%)	92 (5.2%)	104 (5.3%)	136 (6.6%)	0.0016
With hemodialysis	250 (5.4%)	100 (5.3%)	116 (5.6%)	127 (5.8%)	0.8770
ACS	975 (21.0%)	404 (21.6%)	445 (21.5%)	484 (22.25%)	0.7343
STEMI	305 (6.6%)	145 (7.7%)	139 (6.7%)	136 (6.3%)	0.2468
Prior myocardial infarction	1,259 (27.1%)	545 (29.1%)	614 (29.7%)	606 (27.7%)	0.1149
Prior stroke	384 (8.3%)	173 (9.2%)	203 (9.8%)	247 (11.3%)	0.0007
Peripheral vascular disease	508 (11.0%)	228 (12.2%)	237 (11.5%)	303 (13.9%)	0.0051
Prior heart failure	541 (11.6%)	246 (13.1%)	295 (14.3%)	378 (17.3%)	<0.0001
Prior PCI	2,341 (50.4%)	914 (48.8%)	1,021 (49.3%)	899 (41.2%)	<0.0001
Prior CABG	337 (7.3%)	130 (6.9%)	150 (7.2%)	170 (7.8%)	0.7686
Multivessel disease	1,647 (35.4%)	847 (45.2%)	1,233 (59.8%)	1,663 (76.1)	<0.0001
Ejection fraction (%)	59.3 ± 12.8	58.3 ± 13.9	57.9 ± 13.3	55.5 ± 13.7	<0.0001
Ejection fraction <40% (%)	9.1	11.3	10.9	14.9	<0.0001
Total stent length (mm)	19.6 ± 3.0	31.8 ± 3.6	45.5 ± 4.3	80.0 ± 25.1	<0.0001
Thienopyridine use ≥1 yr (%)	62.7	60.1	65.4	72.1	<0.0001
Lesion Characteristics	**QA**	**QB**	**QC**	**QD**	**p Value**
Number of lesions	5,361	3,515	2,401	3,374	
Lesion location					
LAD	2,040 (38.15%)	1,498 (42.6%)	1,090 (45.4%)	1,466 (43.4%)	<0.0001
LCX	1,427 (26.6%)	743 (21.1%)	428 (17.8%)	490 (14.5%)	<0.0001
RCA	1,613 (30.0%)	1,140 (32.4%)	814 (33.9%)	1,274 (37.8%)	<0.0001
LMCA	208 (3.9%)	110 (3.1%)	50 (2.1%)	129 (3.8%)	0.0003
Saphenous vein graft	58 (1.08%)	22 (0.63%)	16 (0.67%)	13 (0.38%)	0.0018
In-stent restenosis	535 (10.0%)	461 (13.1%)	335 (14.0%)	554 (16.4%)	<0.0001
Chronic total occlusion	125 (2.3%)	200 (5.7%)	262 (10.9%)	672 (19.9%)	<0.0001
Severe calcification	344 (6.4%)	263 (7.5%)	208 (8.7%)	453 (13.4%)	<0.0001
Bifurcation	830 (15.5%)	667 (19.0%)	472 (19.7%)	883 (26.2%)	<0.0001
Reference diameter pre <2.5 mm	1,508 (28.1%)	982 (27.9%)	753 (31.4%)	901 (26.7%)	0.002
Post-dilation (%)	2,026 (37.8%)	1,430 (40.7%)	1,261 (52.5%)	1,767 (52.5%)	<0.0001
Total stent length (mm)	17.4 ± 1.6	23.0 ± 0.3	29.6 ± 2.3	51.7 ± 15.7	<0.0001
Minimal stent size (mm)	2.94 ± 0.39	3.00 ± 0.41	2.86 ± 0.24	2.76 ± 0.33	<0.0001

Continuous variables were expressed as mean value ± SD.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LAD = left descending coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

among the 4 groups. However, patients in group Q4 had significantly higher incidences of diabetes (with or without insulin therapy), smoking habit, prior stroke, peripheral vascular disease, prior heart failure, poor left ventricular function (ejection fraction <40%), and multivessel disease compared with those in the other 3 groups. The number of treated lesions increased according to TSL per patient. The proportion of patients with thienopyridine use ≥1 year increased with increasing TSL per patient.

Lesion characteristics. Lesion characteristics are listed in Table 1, bottom. Proportions of adverse lesion morphologies, such as total occlusion and ostial or severely calcified lesions, increased according to TSL per lesion. Minimal stent size was smallest in group QD. In group

QA, the left circumflex coronary artery was a more frequent site of stent implantation while the left descending coronary artery and right coronary artery were less frequent sites compared with the other groups.

Cumulative 3-year clinical outcomes. Cumulative incidences of death, cardiac death, myocardial infarction, stroke, TLR, and definite ST are listed in Table 2.

Cumulative 3-year rates of TLR. The incidences of TLR rates in lesion and patient level were remarkably increased according to the TSL. The cumulative total 3-year TLR rate for all lesions was 8.1% (1,189 lesions). The 3-year TLR rates for the TSL-P groups were 7.47% in Q1; 10.99% in Q2 (hazard ratio [HR]: 1.53, 95% CI: 1.25 to 1.85, $p < 0.0001$ vs. Q1); 14.40% in Q3 (HR: 2.05, 95% CI: 1.73 to 2.43, $p < 0.0001$ vs. Q1); and 21.18% in Q4 (HR: 3.19, 95% CI: 2.74 to 3.71, $p < 0.0001$ vs. Q1) (Fig. 2A). The 3-year TLR rates for the TSL-L groups were 6.78% in QA; 8.08% in QB (HR: 1.24, 95% CI: 1.05 to 1.48, $p = 0.0135$ vs. QA); 10.96% in QC (HR: 1.71, 95% CI: 1.43 to 2.05, $p < 0.0001$ vs. QA); and 15.57% in QD (HR: 2.65, 95% CI: 2.28 to 3.07, $p < 0.0001$ vs. QA) (Fig. 2B).

Cumulative 3-year rates of definite ST, and composite of death and myocardial infarction. The 3-year definite ST rates in the TSL-L groups were 0.60% in QA; 0.54% in QB; 0.79% in QC; and 0.89% in QD (Fig. 3A). There were no significant differences in definite ST rates among the quartiles of TSL-L. In contrast to the per-lesion data, the cumulative 3-year definite ST rates in the TSL-P groups were 0.69% in Q1; 0.96% in Q2 (HR: 1.43, 95% CI: 0.81 to 2.55, $p = 0.2245$ vs. Q1); 0.97% in Q3 (HR: 1.41, 95% CI: 0.80 to 2.46,

Table 2. Cumulative Clinical Event Rates Through 3 Years

	Q1	Q2	Q3	Q4	p Value
Death					
At 1 yr	3.21%	4.27%	4.20%	3.94%	0.0845
At 2 yrs	5.23%	6.14%	6.72%	7.10%	0.0099
At 3 yrs	6.67%	7.42%	8.46%	8.56%	0.0125
Cardiac death					
At 1 yr	1.72%	2.62%	2.32%	2.84%	0.0139
At 2 yrs	2.50%	3.42%	3.43%	3.98%	0.0058
At 3 yrs	2.97%	4.06%	3.96%	4.76%	0.0019
Myocardial infarction					
At 1 yr	1.31%	1.28%	1.74%	2.43%	0.0041
At 2 yrs	1.61%	1.92%	2.37%	3.00%	0.0022
At 3 yrs	1.92%	2.72%	3.04%	3.71%	0.0001
Stroke					
At 1 yr	1.46%	1.76%	1.69%	2.47%	0.0318
At 2 yrs	2.35%	2.67%	2.71%	3.62%	0.0281
At 3 yrs	3.03%	3.26%	3.00%	4.12%	0.0993
Target lesion revascularization					
At 1 yr	3.83%	5.93%	7.78%	12.23%	<0.0001
At 2 yrs	5.25%	8.01%	10.92%	16.44%	<0.0001
At 3 yrs	7.47%	10.99%	14.40%	21.18%	<0.0001
Definite stent thrombosis					
At 1 yr	0.45%	0.48%	0.63%	0.73%	0.3057
At 2 yrs	0.58%	0.75%	0.87%	1.05%	0.1878
At 3 yrs	0.69%	0.96%	0.97%	1.42%	0.0353

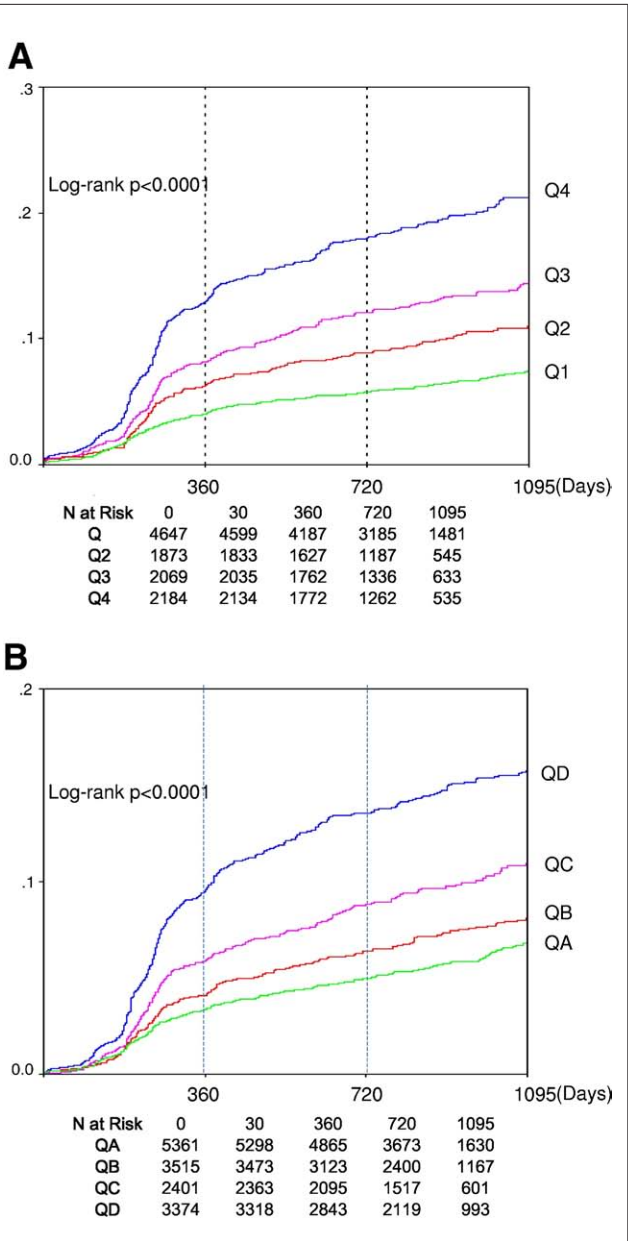
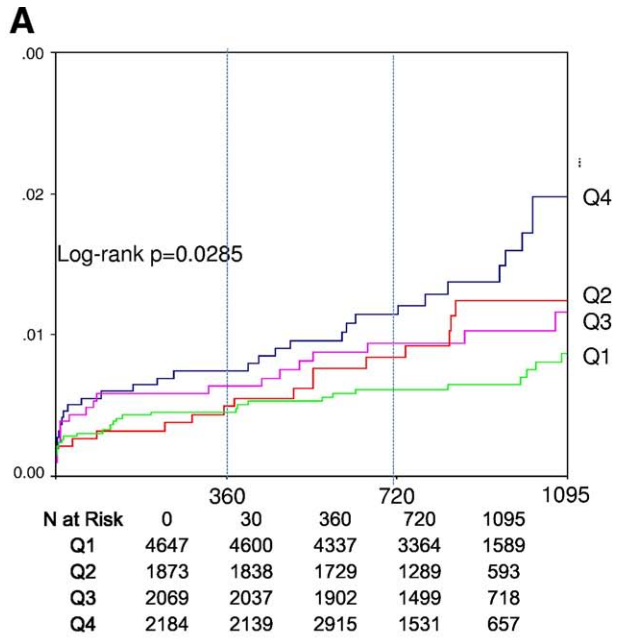


Figure 2. Cumulative TLR Rates Based on TSL-P and TSL-L

Estimated target lesion revascularization (TLR) rates based on **(A)** total stent length per patient (TSL-P) and **(B)** total stent length per lesion (TSL-L) up to 3 years before adjustment for baseline characteristics. The incidences of TLR rates in both patient and lesion level were increasing remarkably (log-rank $p < 0.0001$ in TSL-P and TSL-L) according to total stent length before adjustment for baseline characteristics.



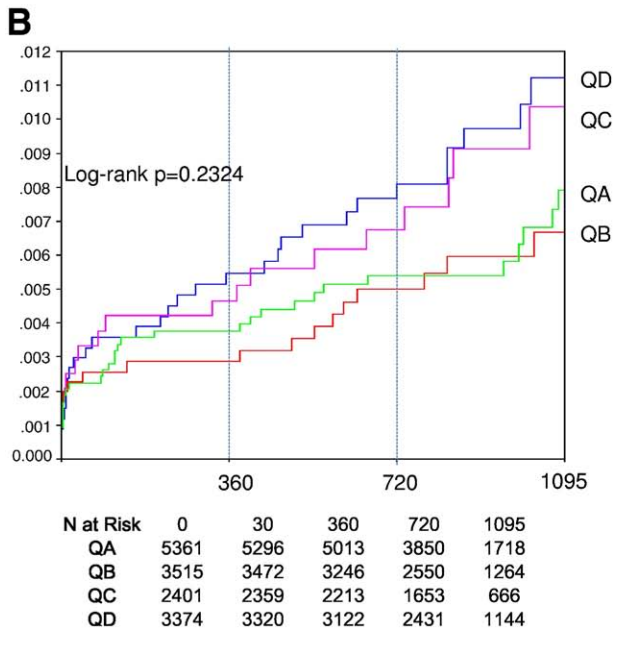


Figure 3. Three-Year Cumulative Incidences of Definite ST Based on TSL-P and TSL-L

Estimated definite stent thrombosis (ST) rates based on **(A)** TSL-P and **(B)** TSL-L up to 3 years before adjustment for baseline characteristics. There were no significant differences in definite ST rates in lesion level data according to total stent length **(B)**. However, the incidences of definite ST in the longest total stent length group per patient, group Q4, was significantly higher than that in the shorter stent length group **(A)**. Abbreviations as in Figure 2.

p = 0.2307 vs. Q1); and 1.42% in Q4 (HR: 2.11, 95% CI: 1.29 to 3.47, p = 0.0031 vs. Q1) (Fig. 3B). The ST rate in group Q4 was significantly higher than that in group Q1.

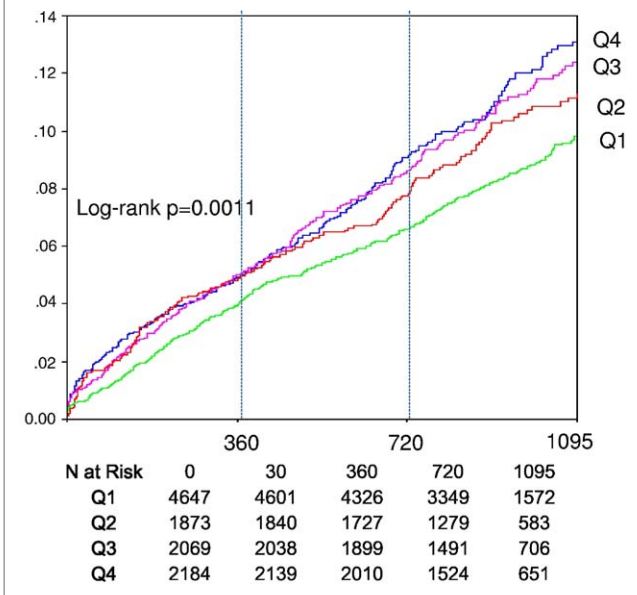


Figure 4. Three-Year Cumulative Incidence of Death and MI in the TSL-P Groups

Estimated composite of death and myocardial infarction (MI) rates in total stent length per patient (TSL-P). Cumulative 3-year incidences of composite of death and MI increased significantly according to the increase in TSL-P before adjustment for baseline characteristics.

The incidence of composite of death and myocardial infarction also increased according to increases in TSL per patient (Fig. 4). HRs of clinical events before and after adjustment are shown in Table 3. TLR and definite ST rate in Q4 remained significantly higher than in other stent length groups; however, death and myocardial infarction rate in Q4 was not statistically significant after adjustment for baseline characteristics.

Discussion

Although the efficacy and safety of multiple DES implantation for long coronary lesion treatment has been the subject of previous reports (15–17), the follow-up periods

Table 3. Unadjusted and Adjusted HRs for Clinical Events in Group Q4 as Compared With Group Q1, Q2, and Q3

	HR	95% CI	p Value
Unadjusted HRs of clinical event rates			
Target lesion revascularization	2.343	2.070–2.651	<0.0001
Definite stent thrombosis	1.770	1.160–2.702	0.0081
Death/myocardial infarction	1.217	1.049–1.413	0.0096
Adjusted HRs of clinical event rates			
Target lesion revascularization	2.355	2.079–2.668	<0.0001
Definite stent thrombosis	1.727	1.126–2.646	0.0122
Death/myocardial infarction	1.057	0.909–1.230	0.4684

CI = confidence interval; HR = hazard ratio.

were usually limited to 6 to 12 months, and the sample sizes were generally small.

This is the first publication based on a large population registry (number of patients >10,000) with long-term (up to 3 years) follow-up and outcome data analyzed across different stent lengths.

At 3-year follow up, increases in TSLs both per lesion and per patient were associated with incremental increase in TLR rates, while only TSL per patient was significantly associated with ST in unadjusted and adjusted data analyses. The incidences of composite of death and myocardial infarction also increased according to increased TSL per patient, however, there were no significant differences in the adjusted risk of composite of death and myocardial infarction according to the TSL-P.

Long and multiple BMS stent implantation is associated with increased restenosis and ST rates (1–4), whereas SES implantation has been shown to reduce restenosis and the need for revascularization in several randomized clinical trials and large registries (6–17). Consistent with previous reports (25,26), long and multiple SES implantation is associated with increased risks of restenosis and need for revascularization in this study, regardless of evaluation based on TSL per lesion or per patient. However, the frequency of repeat revascularization was lower compared with BMS implantation (6–9), despite the potential damage to the vessel wall and the high metal density.

However, the 3-year TLR rates were as high as 21.2% in group Q4 (TSL per patient 56 to 293 mm) and 15.6% in group QD (TSL per lesion 34 to 150 mm). This result is consistent with the finding in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial (27) that the rate of the major adverse cardiac events increased as the SYNTAX score increased. Therefore, we should admit that the complex procedures with extensive coverage of the coronary artery with SES are associated with substantial risk of repeated procedures. When these types of complex procedures are planned, the risk and the benefit against CABG surgery should be seriously assessed. Also, the recently reported FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial result suggested that PCI guided by physiologic lesion assessment in patients with multivessel disease resulted in less lesions treated and improved clinical outcome (28). Our observation is in line with this FAME trial result.

While inhibition of cellular proliferation results in reduced neointimal hyperplasia and lower restenosis rates with SES, it may also delay endothelialization of the stent surface and increase the risk of ST. For instance, in the Bern and Rotterdam study, ST was reported to occur at a continuous rate of 0.4% to 0.6% per year for up to 4 years without diminution (29). The mechanism underlying late thrombotic events has not been fully elucidated, but several hypotheses have been proposed, including impaired re-endothelialization from angioscopic (30) or autopsy findings (31), hypersensitivity to polymers (32), and nonresponsiveness to thienopyridine and aspirin (33). Premature discontinuation of dual antiplatelet therapy has been associated with a higher incidence of ST, and this has led to the recommendation of therapy with aspirin and thienopyridine for at least 12 months (34). However, in a recent observational study based on the j-Cypher registry, Kimura et al. (22) reported an annual incidence of definite ST of 0.2% in Japan, with no apparent clinical benefit of thienopyridine beyond 6 months after SES implantation. In our analysis, the incidence of definite ST was higher in the long stent group despite higher rates of thienopyridine use for more than 1 year. Optimal duration of dual antiplatelet therapy in patients undergoing PCI with extensive metal coverage is yet to be defined.

Previous data have demonstrated that stent length is a risk factor for acute and late ST (35,36) and major adverse cardiac events, including a meta-analysis of 10 randomized studies that met the criteria of 9 to 12 months follow-up and antiplatelet therapy of only 2 to 3 months. Orlic et al. (37) reported that stent length per lesion and per patient are powerful indicators for major adverse cardiac events in treatment of multivessel disease with SES implantation; however, this report also had a short follow-up period of 6 months. Data from the Spanish registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivo) (38) and the Israeli arm of the e-Cypher registry (39) also show that stent length is an independent predictor of subacute and late ST for up to 3 years. In the second of these 2 analyses, stent length was used to denote the stent length per lesion, but the results differ from ours since stent length per lesion was not associated with a risk for ST. The long stent implanted group had several adverse risks affecting long-term clinical events; therefore, the incidences of death and myocardial infarction through 3 years were significantly increased according to increase TSL-P.

The SYNTAX trial showed an ST rate of 3.3% after 1 year (35). In this trial, the mean TSL was 86.1 mm with 4.6 stents used to cover 3.6 lesions/patient. The 3.3% ST rate at 1 year suggests that complex procedures with implantation of longer and multiple stents to treat multivessel disease may be associated with an increased risk for ST. Our data also documented higher ST rates in patients (group Q4) with the longest TSL, and ST rates increased with number of stents. However, the definite ST rate of 1.42% at 3 years in group Q4 in our patients with mean stent length of 80.0 mm is markedly lower than 3.3% rate at 1 year reported in the SYNTAX trial. The different ST rates in these studies could be due to ethnic differences, but the details remain to be determined.

Study limitations. This study has several limitations. First, it was performed as a nonrandomized, observational, and single-arm study. The absence of the control group under-

going CABG makes it difficult to make any recommendation on the selection of coronary revascularization strategy. Second, in our current analysis, stent fracture, which is observed as an extension of stent length and causes refractory restenosis, was not analyzed. Third, clinically driven and angiographically driven TLR were not differentiated. Relatively high rates of follow-up angiography might exaggerate the differences in TLR rate across the quartiles of TSL.

Conclusions

Overall, our results suggest that the use of long and multiple SES to fully cover a lesion was associated with a high incidence of TLR, but not associated with increased ST for up to 3 years. However, treatment of multiple lesions with extensive metal coverage of the coronary artery increased the risk of TLR and ST. Total stent length was not associated with an increasing risk of death and myocardial infarction after adjustment of baseline characteristics.

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REFERENCES

1. Kobayashi Y, De Gregorio J, Kobayashi, N, et al. Stented segment length as an independent predictor of restenosis. J Am Coll Cardiol 1999;34:651–9.
2. Kastrati A, Elezi S, Dirschinger J, et al. Influence of lesion length on restenosis after coronary stent placement. Am J Cardiol 1999; 83:1617–22.
3. Colombo A, Goldberg SL, Almagor Y, et al. A novel strategy for stent deployment in the treatment of acute or threatened closure complicating balloon coronary angioplasty: use of short or standard (or both) single or multiple Palmaz-Schatz stents. J Am Coll Cardiol 1993;22:1887–91.
4. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;10:1872–8.
5. Shiran A, Mintz GS, Waksman R, et al. Early lumen loss after treatment of in-stent restenosis: an intravascular ultrasound study. Circulation 1998;98:200–3.
6. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
7. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
8. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004;43:1110–5.
9. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093–9.
10. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190–5.
11. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. Circulation 2006;113:1434–41.
12. Abbott JD, Voss MR, Nakamura M, et al. Unrestricted use of drug-eluting stents compared with bare-metal stents in routine clinical practice. J Am Coll Cardiol 2007;50:2029–36.
13. Williams DO, Abbott JD, Kip KE; DEScover Investigators. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents: report of the DEScover registry circulation. Circulation 2006;114:2154–62.
14. Degertekin M, Arampatzis CA, Lemos PA, et al. Very long sirolimus-eluting stent implantation for de novo coronary lesions. Am J Cardiol 2004;93:826–9.
15. Tsagalou E, Chieffo A, Iakovou I, et al. Multiple overlapping drug-eluting stents to treat diffuse disease of the left anterior descending coronary artery. J Am Coll Cardiol 2005;45:1570–3.
16. Kim YH, Park SW, Lee SW, et al. Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease. Circulation 2006;114:2148–53.
17. Kim YH, Park SW, Lee CW, et al. Comparison of sirolimus-eluting stent, paclitaxel-eluting stent and bare metal stent in the treatment of long coronary lesions. Catheter Cardiovasc Interv 2006;67:181–7.
18. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
19. Lagerqvist B, James SK, Stenestrand U, et al. Longterm outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
20. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
21. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
22. Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987–95.
23. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials. A case for standardized definitions. Circulation 2007;115:2344–51.
25. Lee CW, Park DW, Lee BK, et al. Predictors of restenosis after placement of drug-eluting stents in one or more coronary arteries. Am J Cardiol 2006;97:506–11.
26. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.
27. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
28. Tonino PA, De Bruyne B, Pijls NH, et al., FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
29. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice: 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
30. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108–11.

31. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.
32. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.
33. Gori AM, Marcucci R, Migliorini A, et al. Incidence and clinical impact of dual nonresponsiveness to aspirin and clopidogrel in patients with drug-eluting stents. J Am Coll Cardiol 2008;52:734–9.
34. Grines CL, Bonow RO, Casey DE Jr., et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. J Am Coll Cardiol 2007;49:734–9.
35. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45:954–9.
36. Cutlip DE, Baim DS, Ho KKL, et al. Stent thrombosis in the modern era. A pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.
37. Orlic D, Bonizzoni E, Stankovic G, et al. Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: immediate and mid-term results. J Am Coll Cardiol 2004;43:1154–60.
38. de la Torre-Hernandez JM, Alfonso F, Hernandez F, et al. Drug-eluting stent thrombosis: results from the multicenter Spanish Registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivo). J Am Coll Cardiol 2008;51:986–90.
39. Planer D, Beyar R, Almagor Y, et al. Long-term (>3 years) outcome and predictors of clinical events after insertion of sirolimus-eluting stent in one or more native coronary arteries (from the Israeli arm of the e-Cypher registry). Am J Cardiol 2008;101:953–9.

Key Words: stent ■ follow-up studies ■ coronary artery disease ■ long stent ■ clinical outcomes.