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Impact of late stent malapposition after drug-eluting stent implantation on long-term clinical outcomes

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HIGHLIGHTS

- Although OCT-detected LSM is not rare, the relationship between this phenomenon and adverse events is still controversial.
- In this study, cardiac death or (very) late stent thrombosis did not occur in patients with LSM during long-term follow-up.
- LSM detected in follow-up OCT examination does not have to be corrected by additional interventions.

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ABSTRACT

Background and aims: The impact of late drug-eluting stent (DES) malapposition detected by optical coherence tomography (OCT) on long-term clinical outcomes has not been clearly established. We evaluated long-term clinical outcomes of late stent malapposition (LSM) detected by OCT in a qualified study population.

Methods: A total of 428 patients were selected from previous randomized OCT studies that evaluated the degree of strut coverage of different DESs at a 3–12-month follow-up OCT examination. These patients were assigned to one of two groups based on the presence (n = 136) or absence (n = 292) of LSM on follow-up OCT images (performed at 7.0 ± 3.4 months after DES implantation). The cumulative rates of composite events (cardiac death, target-vessel-related myocardial infarction, target-vessel revascularization, and stent thrombosis) were compared between the two groups.

Results: During 73.7 ± 18.3 months of follow-up, cardiac death or (very) late stent thrombosis did not occur in either group. The cumulative rate of composite events was similar among the patients in each group (6.2% in patients with LSM *vs.* 11.7% in those without LSM) [hazard ratio (HR) = 0.569, 95% confidence interval (CI) = 0.257–1.257, $p = 0.163$]. Target vessel-related myocardial infarction occurred in 0.7% of patients with LSM *vs.* 1.5% of those without LSM (HR = 0.521, 95% CI = 0.058–4.670, $p = 0.560$). Target-vessel revascularization was performed in 5.4% of patients with LSM *vs.* 10.2% of those without LSM (HR = 0.574, 95% CI = 0.246–1.343, $p = 0.201$).

Conclusions: Cardiac death or (very) late stent thrombosis did not occur in patients with OCT-detected LSM during long-term follow-up. The presence of OCT-detected LSM was not associated with adverse clinical events.

1. Introduction

Stent malapposition refers to the lack of contact of stent struts with the vessel wall [1]. Due to its higher resolution, optical coherence tomography (OCT) can detect stent malapposition with greater accuracy than intravascular ultrasound (IVUS) [1,2]. Stent malapposition detected immediately after stent implantation is classified as acute stent malapposition, whereas malapposition detected during follow-up OCT examination is classified as late stent malapposition (LSM) [2]. Currently, the impact of OCT-detected LSM after drug-eluting stent (DES)

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implantation on long-term clinical outcomes has not been clearly established [1]. Few studies have evaluated clinical outcomes of OCT-detected LSM after DES implantation, and these had small study populations [3,4] and used a registry design [2]. There might be probably some biased conclusions derived from the previous studies [2–4], and they did not include long-term follow-up periods. Therefore, we investigated long-term clinical outcomes of OCT-detected LSM after DES implantation in a large population of qualified study patients whose follow-up OCT results were reported previously in six randomized OCT studies.

2. Patients and methods

2.1. Study population and procedures

Six randomized OCT studies were previously performed in our institute to compare the degree of strut coverage on follow-up OCT examination among various DESs, or to compare that between angiography-guided stenting *vs.* OCT-guided stenting [5–10]. The results of these studies were already published [5–10]. The experimental parameters of these studies are presented in Table 1. A total of 428 patients with follow-up OCT examination were included in these randomized studies, and all 428 patients were included in the present study. These patients were assigned to one of two groups according to the presence (n = 136) or absence (n = 292) of LSM on follow-up OCT images (performed at 7.0 ± 3.4 months after DES implantation). All coronary intervention procedures were performed according to current standard techniques [11]. All patients received at least 75 mg aspirin and a loading dose of 300 mg clopidogrel at least 12 h pre-intervention. Unfractionated heparin was administered in an initial bolus of 100 IU/kg, with additional boluses administered during the procedure to achieve an activated clotting time of 250–300 s. Post-procedural treatment included a 12-month prescription of dual antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel daily). The study protocol was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from each patient. Quantitative coronary angiographic analysis in each study was previously described [5–10].

2.2. OCT imaging and image analysis

We used two OCT systems in this study (M2 and C7-XR imaging systems, LightLab Imaging, Inc., St. Jude Medical, St. Paul, MN) [12]. The OCT procedures and image acquisition protocols were described previously [5–10]. All OCT images were analyzed using certified offline software (QIvus, Medis Medical Imaging Systems, Netherlands) at a core laboratory (Cardiovascular Research Center, Seoul, Korea). Images were analyzed by analysts who were blinded to patient and procedural information [12]. OCT was performed at post-intervention and at approximately 3–12 months after DES implantation, according to the specific protocol for each study. All cross-sectional images were analyzed at 1-mm intervals. The OCT images from three studies were measured at 0.2-mm intervals; these data were re-analyzed at 1-mm intervals [6,9,10]. The lumen border was traced at the boundary between the lumen and the leading edge of the neointima using semi-automatic algorithms. The cross-sectional area (CSA) of the lumen was defined as the area bounded by the lumen border. The stent CSA was delineated by tracing the stent contour. The neointimal hyperplasia CSA was calculated as the stent CSA minus the intra-stent lumen CSA. The neointimal hyperplasia thickness was measured as the distance between the neointimal endoluminal surface and the strut luminal surface; an uncovered strut was defined as having a neointimal hyperplasia thickness of 0 μm [13]. A malapposed strut was defined as a strut that was detached from the vessel wall as follows: sirolimus-eluting stent (≥160 μm, Cypher, Cordis, Warren, NJ, USA); zotarolimus-eluting stent (≥110 μm, Endeavor Resolute, Medtronic CardioVascular, Santa Rosa, CA, USA); everolimus-eluting stent (≥100 μm,

Table 1
Experimental parameters of six randomized studies.

OCT study	OCT time	No. of enrolled patients	No. of patients with follow-up OCT	Total no. of patients with follow-up OCT
Promus Element *vs.* Xience	Post-stent, 3 months	51 (51 lesions) *vs.*49 (49 lesions)	48 (48 lesions) *vs.*46 (46 lesions)	94 (94 lesions)
Nobori *vs.* Cypher	Post-stent, 6 months	60 (60 lesions) *vs.*60 (60 lesions)	51 (51 lesions) *vs.*52 (52 lesions)	103 (103 lesions)
OCT-guided *vs.* angiography-guided stenting	Post-stent, 6 months	58 (61 lesions) *vs.*59 (63 lesions)	50 (51 lesions) *vs.*51 (54 lesions)	101 (105 lesions)
Xience *vs.* Endeavor Resolute	Post-stent, 3 months	20 (20 lesions) *vs.*20 (21 lesions)	17 (17 lesions) *vs.*17 (18 lesions)	34 (35 lesions)
Xience *vs.* Cypher	Post-stent, 3 months, 12 months[a]	30 (33 lesions) *vs.*30 (31 lesions)	25 (28 lesions) *vs.*25 (26 lesions)	50 (54 lesions)
Biomatrix *vs.* Cypher	Post-stent, 3 months, 12 months[a]	30 (30 lesions) *vs.*30 (30 lesions)	22 (22 lesions) *vs.*24 (24 lesions)	46 (46 lesions)

OCT = optical coherence tomography.
[a] Follow-up OCT results at 12 months were used to determine late stent malapposition.

Table 2
Baseline clinical and lesional characteristics in patients with and without LSM.

	Patients with LSM (n = 136)	Patients without LSM (n = 292)	p value
Clinical characteristics			
Age (years)	62.6 ± 8.6	60.7 ± 9.3	0.048
Men	98 (72%)	218 (75%)	0.569
Hypertension	90 (66%)	168 (58%)	0.089
Diabetes mellitus	48 (35%)	91 (31%)	0.396
Dyslipidemia	93 (68%)	187 (64%)	0.379
Current smoking	41 (30%)	74 (25%)	0.296
Clinical presentation of acute myocardial infarction	7 (5%)	22 (8%)	0.360
Lesional characteristics	n = 139 lesions	n = 298 lesions	
Lesion in left anterior descending artery	74 (53%)	168 (56%)	0.539
Lesion length (mm)	16.4 ± 5.2	16.2 ± 5.1	0.750
Reference vessel diameter (mm)	3.1 ± 0.5	3.1 ± 0.5	0.121
Minimum luminal diameter (mm)			
Before procedure	0.9 ± 0.5	1.0 ± 0.4	0.216
After procedure	2.9 ± 0.4	2.9 ± 0.5	0.468
Follow-up	2.8 ± 0.4	2.7 ± 0.5	0.132
Acute gain (mm)	2.0 ± 0.6	1.9 ± 0.6	0.113
Late loss (mm)	0.1 ± 0.3	0.2 ± 0.4	0.294
Types of drug-eluting stents			
Cypher	42 (30%)	59 (20%)	0.016
Endeavor Resolute	32 (23%)	91 (31%)	0.104
Xience	26 (19%)	64 (22%)	0.505
Promus Element	15 (11%)	35 (12%)	0.771
Nobori or Biomatrix	24 (17%)	49 (16%)	0.830
Stent diameter (mm)	3.2 ± 0.4	3.2 ± 0.4	0.651
Stent length (mm)	18.8 ± 5.1	18.8 ± 4.8	0.889
Adjuvant post dilation	78 (56%)	166 (56%)	0.936
Maximum inflation pressure (atm)	16.2 ± 3.7	16.8 ± 4.0	0.330

LSM = late stent malapposition.
Values are presented as n (%) and mean ± standard deviation.

Xience, Abbott Vascular, Santa Clara, CA, USA, and Promus Element, Boston Scientific, Natrick, MA, USA); and biolimus-eluting stent (≥130 μm, Nobori, Terumo Corp., Tokyo, Japan, and Biomatrix, Biosensors International, Singapore) [5–10]. Stent malapposition was defined as the presence of any malapposed struts, and LSM was defined as stent malapposition detected on follow-up OCT examination. To evaluate the magnitude of malapposition, we measured the maximum distances between the malapposed strut and vessel wall, maximum lengths of segments with malapposed struts, and maximum extra-stent luminal CSA. The percentage of uncovered or malapposed struts was calculated as the ratio of the number of uncovered or malapposed struts to the total number of struts in all cross-sectional OCT images. Interobserver and intraobserver variability in OCT-measured distances and areas were calculated and reported in the previous studies [14,15].

2.3. Clinical follow-up

The patients who underwent DES implantation in our institute strongly wanted to have a regular follow-up at out-patient clinic in our institute because of highest quality of patients' care. Therefore, these patients almost had a regular visit at out-patient clinics in our institute with higher follow-up rate during long-term follow-up. It was available to make an accurate determination of clinical events. The clinical data were obtained from medical record reviews in our institute. During the follow-up period, we investigated clinical events that were possibly related to LSM. These events included cardiac death, target lesion/vessel-related nonfatal myocardial infarction, target lesion/vessel revascularization, and stent thrombosis. All clinical events were defined according to the Academic Research Consortium [16]. The cumulative rates of composite events (cardiac death, target vessel-related myocardial infarction, target vessel revascularization, and stent thrombosis) were compared between the two groups.

2.4. Statistical analyses

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) or SPSS version 25.0 (SPSS, Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation (SD) and compared using Student's t-test. Categorical variables were reported as a number (percentage) and compared using the Chi-square test or Fisher's exact test. The OCT results for each lesion were reported as median values (interquartile ranges) and compared using mixed models (including individual studies and patients as random effects) due to the clustered data in the present study. The cumulative incidences of clinical events were calculated using Kaplan-Meier estimates and compared using the Cox regression model (including each study as a random effect). In addition, propensity score matching were performed to adjust clinical variables which can influence patients' clinical outcomes (age, sex, clinical presentation of acute myocardial infarction, and cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and current smoking). When matching the two groups, the match ratio was 1:1 by propensity scores with available pair matching method. A p-value < 0.05 was considered as statistically significant for all analyses.

3. Results

This study analyzed 428 patients from six randomized OCT studies. LSM was observed in 136 patients (32%). Baseline clinical and lesional characteristics in patients with and without LSM are presented in Table 2. Patients with LSM were older than those without LSM (62.6 ± 8.6 *vs.* 60.7 ± 9.3 years, respectively, $p = 0.048$). Cypher stent was used more frequently in patients with LSM than in those without LSM (30% *vs.* 20%, respectively, $p = 0.016$). Follow-up OCT examination was performed at a mean 7.0 ± 3.4 months after DES implantation. Additional interventional procedures were not performed

Table 3
Optical coherence tomography results at follow-up.

	Patients with LSM (n = 139 lesions)	Patients without LSM (n = 298 lesions)	p value
Time to follow-up OCT (months)	7.1 ± 3.5	7.0 ± 3.4	0.683
Total no. of analyzed struts	70,290	134,665	
Percentage of malapposed struts (%)	1.2 (0.6–3.1)	–	–
Percentage of uncovered struts (%)	8.7 (4.2–17.6)	2.9 (0.6–7.1)	0.003
Percentage of both of malapposed and uncovered struts (%)	0.6 (0.2–1.7)	–	–
Neointimal hyperplasia thickness (μm)	44.6 (34.4–66.3)	68.8 (49.0–101.4)	0.019
Total no. of analyzed cross-section	6,955	13,235	
Stent CSA (mm^2)	7.5 (6.1–9.1)	7.6 (6.1–8.8)	0.604
Lumen CSA (mm^2)	7.1 (5.6–8.6)	6.9 (5.6–8.1)	0.131
Minimal stent CSA (mm^2)	6.2 (5.2–7.9)	6.6 (4.9–7.9)	0.955
Neointimal hyperplasia CSA (mm^2)	0.3 (0.2–0.5)	0.5 (0.3–0.9)	0.003
Percentage of neointimal hyperplasia CSA (%)	4.4 (3.2–6.2)	7.3 (4.7–11.9)	0.003
Cross-sections with any malapposed strut (%)	9.7 (5.0–19.0)	–	–
Cross-sections with any uncovered strut (%)	45.5 (29.4–71.2)	19.2 (5.6–41.7)	0.001
Cross-sections with uncovered strut > 0.3	5.3 (0.0–25.0)	0.0 (0.0–6.3)	0.005
Maximal malapposed distance (μm)	267.0 (190.0–390.0)	–	–
Maximal length of segments with malapposed struts (mm)	0.6 (0.2–1.0)	–	–
Maximal extra-stent luminal CSA (mm^2)	0.8 (0.5–1.3)	–	–
Maximal length of segments with uncovered struts (mm)	2.2 (1.0–5.0)	1.0 (0.2–2.8)	0.004

LSM = late stent malapposition, OCT = optical coherence tomography, CSA = cross-sectional area.
Values are presented as n (%), mean ± standard deviation, and median (interquartile ranges).

due to the presence of LSM at follow-up OCT examination. Table 3 presents follow-up OCT results for the two groups. At strut-level analysis, the percentage of malapposed struts was 1.2% (0.6–3.1%) in patients with LSM. Patients with LSM had a greater percentage of uncovered struts [8.7% (4.2–17.6%)] than those without LSM [2.9% (0.6–7.1%)] (p = 0.003). Patients with LSM had smaller neointimal hyperplasia thickness [44.6 μm (34.4–66.3 μm)] than those without LSM [68.8 μm (49.0–101.4 μm)] (p = 0.019). At cross-section-level analysis, patients with LSM had smaller neointimal hyperplasia CSA [0.3 mm^2 (0.2–0.5 mm^2)] than those without LSM [0.5 mm^2 (0.3–0.9 mm^2)] (p = 0.003). In patients with LSM, the maximum malapposed distance was 267 μm (190–390 μm) and the maximum length of segments with malapposed struts was 0.6 mm (0.2–1.0 mm).

Clinical events are presented in Table 4. During 73.7 ± 18.3 months of follow-up, cardiac death or (very) late stent thrombosis did not occur in either group. The cumulative rates of composite events were similar among the patients in each group, 6.2% in patients with LSM *vs.* 11.7% in those without LSM [hazard ratio (HR) = 0.569, 95% confidence interval (CI) = 0.257–1.257, p = 0.163]. Target vessel-related myocardial infarction occurred in 0.7% of patients with LSM *vs.* 1.5% of those without LSM (HR = 0.521, 95% CI = 0.058–4.670, p = 0.560). Target vessel revascularization was performed in 5.4% in patients with LSM *vs.* 10.2% of those without LSM (HR = 0.574, 95% CI = 0.246–1.343, p = 0.201). Fig. 1 presents the Kaplan-Meier curves of the composite event rates in both groups. After propensity score matching, Supplementary Table 1 shows baseline clinical and lesional characteristics between the two groups. Supplementary Table 2 also shows similar rates of clinical events during long-term follow-up between the two groups. Supplementary Fig. 1 shows the Kaplan-Meier curves of the composite event rates in both groups after propensity score matching.

4. Discussion

This study analyzed qualified patients from six randomized OCT studies. Cardiac death or (very) late stent thrombosis did not occur in patients with OCT-detected LSM during 73.7 ± 18.3 months of follow-up. There was no significant difference of rates of adverse clinical events between patients with LSM and those without LSM.

OCT can detect minimal stent malapposition with greater accuracy than IVUS. Thus, we can reliably use OCT to identify stent malapposition that would not have been detected by IVUS [17]. This superior resolution of OCT enabled us to detect a higher proportion of malapposed struts in OCT images (up to 50% of stents implanted under OCT evaluation) than in IVUS images (approximately 15% of stents implanted under IVUS evaluation) [1,18]. Although OCT-detected LSM is not a rare phenomenon in DES-treated patients (32% incidence rate in the present study), the relationship between this phenomenon and adverse cardiac events is still controversial [1]. Currently, no study has prospectively demonstrated that LSM detected in routine OCT imaging was associated with a higher rate of future adverse events. In the present study, OCT-detected LSM was not associated with a higher rate of adverse cardiac events.

Despite the lack of evidence from prospective studies using routine OCT imaging, the European expert consensus recently recommended that extensively malapposed struts should be avoided following stent implantation and should be corrected when anatomically feasible [1]. This recommendation was based on three registry OCT studies, in which stent malapposition was frequently detected in patients with stent thrombosis [19–21]. However, the patients in those studies were highly selected and had stent thrombosis; they were not the general DES-treated patients [19–21]. Furthermore, stent malapposition was not the only abnormality responsible for stent thrombosis. Other stent abnormalities such as under-expansion or uncovered struts were simultaneously identified in some patients with stent thrombosis and stent malapposition [21]. Therefore, the presence of stent malapposition might not be a binary variable, but rather the extent of stent malapposition might be important in determining the risk for thrombosis [22].

One recent OCT registry study of 64 patients with very late DES thrombosis reported that maximum distance and length of LSM were 440 μm (300–580 μm) and 1.56 mm (0.99–2.13 mm), respectively [21]. Another OCT study of 98 patients with very late DES thrombosis reported that the maximum distance of LSM were 710 μm (465–1175 μm) [23]. The maximum distance and length of LSM in the present study were 267 μm (190–390 μm) and 0.6 mm (0.2–1.0 mm), respectively. These results suggest that the occurrence of LSM without extensive severity on routine follow-up OCT imaging might not be associated with adverse cardiac events.

Several studies reported high frequencies of OCT-detected stent malapposition [1,2,18], although the occurrence of stent thrombosis was actually quite limited in our real-world practice. One randomized OCT study in non-complex lesions reported that LSM was observed in 17.6% of patients with OCT-guided DES implantation and in 33.3% of

Table 4
Clinical events during follow-up*.

	Patients with LSM (n = 136)	Patients without LSM (n = 292)	p value
Follow-up duration (months)	75.0 ± 16.1	73.0 ± 19.2	0.304
Cardiovascular death	0 (0%)	0 (0%)	–
Target lesion-related myocardial infarction	1 (0.7%)	4 (1.5%)	0.560
Target vessel-related myocardial infarction	1 (0.7%)	4 (1.5%)	0.560
Target lesion revascularization	3 (2.2%)	12 (6.2%)	0.266
Target vessel revascularization	7 (5.4%)	23 (10.2%)	0.201
Stent thrombosis (definite or probable)	0 (0%)	0 (0%)	–
Composite of cardiovascular death, target lesion-related myocardial infarction, target lesion revascularization, and stent thrombosis	4 (3.0%)	16 (7.7%)	0.209
Composite of cardiovascular death, target vessel-related myocardial infarction, target vessel revascularization, and stent thrombosis	8 (6.2%)	27 (11.7%)	0.163

LSM = late stent malapposition.
*Data are expressed as no. of events (cumulative 8-year rate of event).

Fig. 1. Cumulative rate of composite events (cardiovascular death, target vessel-related myocardial infarction, target vessel revascularization, and stent thrombosis) calculated with Kaplan-Meier curves (patients with LSM *vs*. those without LSM).
LSM = late stent malapposition.

patients with angiography-guided DES implantation [7]. Considering the number of coronary interventions without imaging guidance, and daily catheterization activity in general DES-treated patients with complex lesions (i.e., calcified lesions, bifurcation lesions, and diffuse long lesions), the actual frequency of LSM may be higher than expected. However, few studies have included long-term follow-up examination to evaluate the relationship between LSM and adverse clinical events in OCT-detected LSM and in general patients treated with DES implantation. In the present study, cardiac death or (very) late stent thrombosis did not occur in patients with OCT-detected LSM during long-term follow-up. LSM detected in routine follow-up OCT examination does not have to be corrected by additional intervention.

The present study has several limitations. First, there might be a selection bias because we only included patients who underwent follow-up OCT examination in six randomized studies. Second, the study protocols of the six randomized studies differed (e.g., inclusion/exclusion criteria or timing of follow-up OCT examination). Third, patients with complex coronary lesions were not enrolled in the study, and this might be associated with the low incidence of adverse cardiac events observed during the follow-up period. Finally, there were no long-term clinical follow-up schedules for the patients within the original protocol of previous randomized studies.

In conclusion, the rates of adverse clinical events were similar in patients with LSM and those without LSM during long-term follow-up. The occurrence of LSM without extensive severity might not be associated with adverse cardiac events.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Conception and design or analysis and interpretation of data, or both: all authors.

Drafting of the manuscript or revising it critically for important intellectual content; all authors.

Final approval of the manuscript submitted: Myeong-Ki Hong.

Appendix A. Supplementary data

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