ORIGINAL RESEARCH

Long-Term Clinical Outcomes of Late Stent Malapposition Detected by Optical Coherence Tomography After Drug-Eluting Stent Implantation

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Background—The relationship between late stent malapposition (LSM) and adverse cardiovascular events is controversial. Studies are needed to evaluate long-term (>5 years) clinical outcomes of LSM detected by optical coherence tomography (OCT) after drug-eluting stent implantation.

Methods and Results—We investigated long-term clinical outcomes of OCT-detected LSM in 351 patients who received drug-eluting stents and were examined by both poststent and follow-up OCT (175±60 days after drug-eluting stent implantation) from January 2009 to December 2011. LSM was observed in 99 patients (28%). We evaluated the cumulative rate of composite events (cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis). During 80.1±24.5 months of follow-up, very late stent thrombosis did not occur in any patients with LSM. The cumulative 8-year rate of composite events was 7.3% in patients with LSM and 10.5% in patients without LSM (P=0.822, log-rank test). We further divided patients into the following 4 groups: patients with both late-persistent and late-acquired stent malapposition (n=23), patients with late-persistent stent malapposition alone (n=45), patients with late-acquired stent malapposition alone (n=31), and patients without LSM (n=252). The cumulative 8-year rates of composite events were similar among these 4 groups (0%, 9.6%, 9.7%, and 10.5%, respectively; P=0.468 by log-rank test).

Conclusions—During long-term follow-up (>5 years), very late stent thrombosis did not occur in patients with OCT-detected LSM. The rates of adverse clinical events were similar between patients with LSM versus those without LSM. Presence of OCT-detected LSM was not associated with unfavorable clinical outcomes. **(*J Am Heart Assoc*.2019;8:e011817. DOI: 10.1161/JAHA.118.011817.)**

Key Words: coronary disease • drug-eluting stents • optical coherence tomography

Stent malapposition refers to the lack of contact between stent struts and the vessel wall.[1] This phenomenon can be detected by intracoronary imaging devices such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT); however, the clinical implications of IVUS- and OCT-detected late stent malapposition (LSM) are still under debate.[1] Compared with IVUS, OCT can detect stent malapposition with greater accuracy because of its higher resolution.[1,2] Theoretically, a coronary thrombus could form around the stent malapposition because of strut exposure and local flow disturbances,[3] potentially serving as a substrate for (very) late stent thrombosis. We previously reported that LSM was frequently detected by OCT, but the clinical outcomes of patients with LSM treated with drug-eluting stents (DESs) were favorable over >2 years of follow-up.[4] Studies are lacking regarding longer term (>5 years) clinical outcomes of OCT-detected LSM; therefore, in this study, we evaluated the longer term clinical outcomes of OCT-detected LSM in these patients.[4]

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Clinical Perspective

What Is New?

- The relationship between late stent malapposition noted on routine optical coherence tomography imaging after drug-eluting stent implantation and adverse cardiovascular events is still controversial.
- During long-term follow-up (>5 years), the rates of adverse clinical events were similar between patients with and without late stent malapposition.

What Are the Clinical Implications?

- The presence of late stent malapposition on follow-up optical coherence tomography was not associated with adverse cardiac events and does not need to be corrected.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

Using the OCT registry database of Severance Cardiovascular Hospital, we identified patients who underwent DES implantation for de novo coronary lesions from January 2009 to December 2011, as well as poststent and follow-up OCT.[4] OCT examination was performed at the discretion of operators. Exclusion criteria were as follows: (1) DES implanted to treat left main coronary disease, (2) overlapping DESs in the lesion, (3) clinical follow-up after DES implantation <1 year, (4) follow-up OCT performed >1 year after DES implantation, and (5) poor-quality OCT image.[4] Ultimately, 351 patients with 356 lesions were included in this study.[4] Figure 1 shows the flow diagram for patient selection. The DESs were chosen by operators at the time of implantation and included sirolimus-eluting stents (Cypher; Cordis), zotarolimus-eluting stents (Resolute or Integrity; Medtronic), everolimus-eluting stents (Xience V; Abbott Vascular), and biolimus A9–eluting stents (Nobori [Terumo Corp] or Biomatrix [Biosensors International]). The DESs were implanted using conventional techniques.[5] Unfractionated heparin was administered as an initial bolus of 100 IU/kg, with additional boluses administered during the procedure to achieve an activated clotting time of 250 to

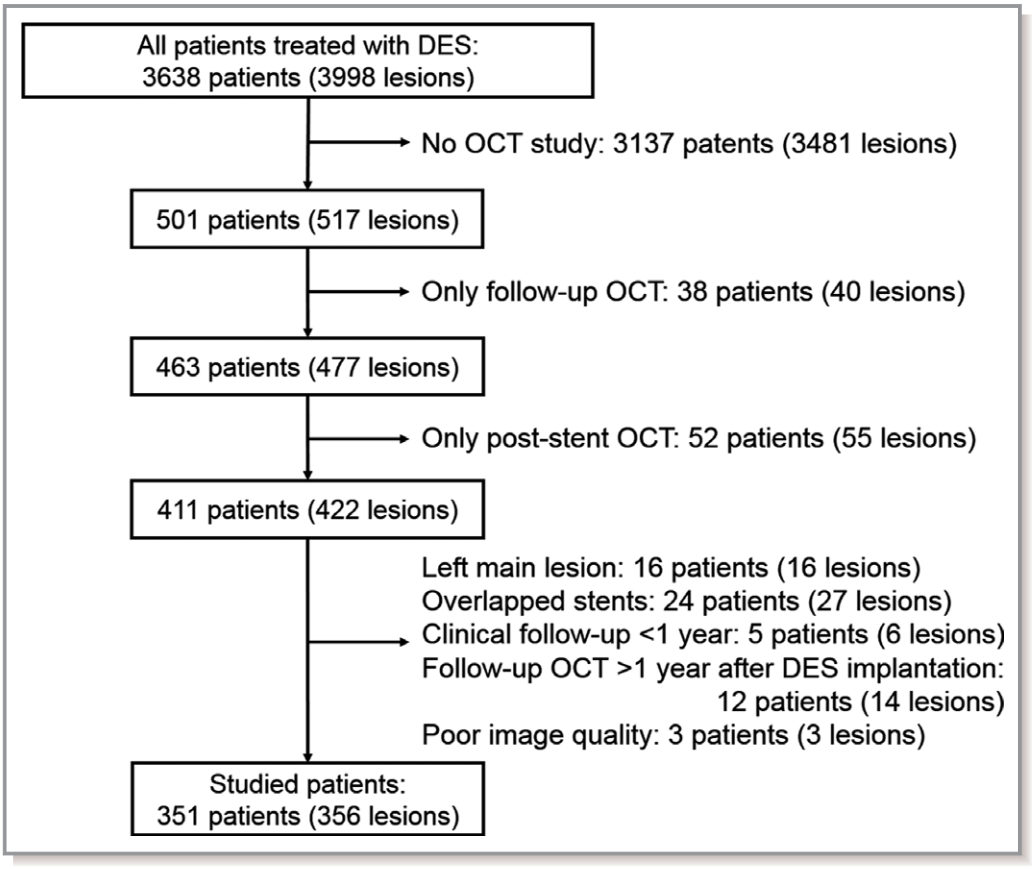

Figure 1. Flow diagram for patient selection. DES indicates drug-eluting stent; OCT, optical coherence tomography.

300 seconds. Dual antiplatelet therapy (aspirin and clopidogrel) was provided to each patient until the follow-up OCT was performed.[4] Maintenance or discontinuation of dual antiplatelet therapy after the follow-up OCT was at the discretion of treating physicians. The study protocol was approved by the institutional review board of our hospital, and written informed consent was obtained from each patient.

OCT Imaging and Analyses

We used 2 OCT systems in this study (M2 and C7-XR imaging systems; LightLab Imaging, St. Jude Medical).[6] All OCT images were analyzed at a core laboratory (Cardiovascular Research Center, Seoul, Korea) by analysts who were blinded to patient and procedural information.[4] Cross-sectional OCT images were analyzed at 1-mm intervals. A malapposed strut was defined as

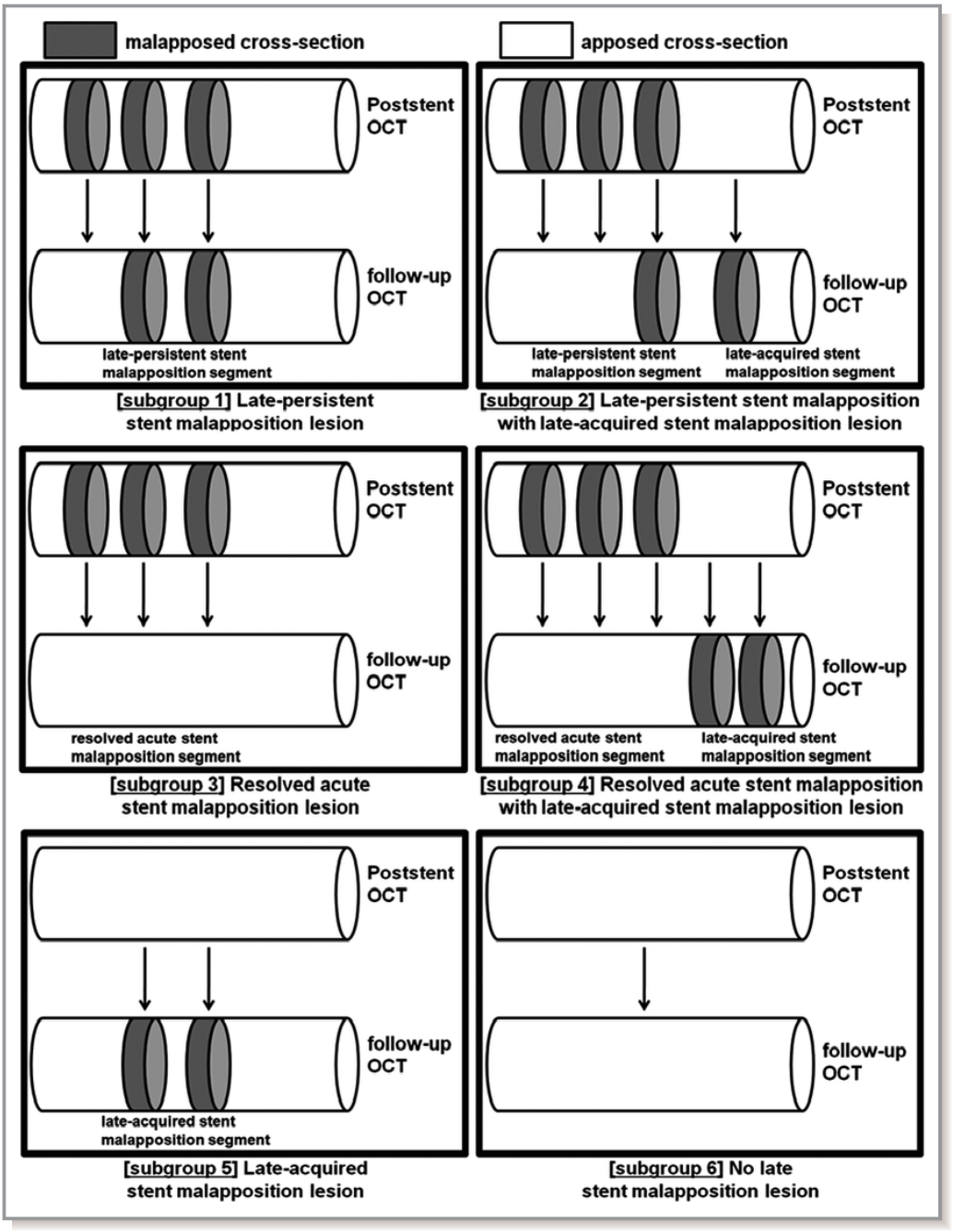

Figure 2. Classification of acute and late stent malapposition lesions based on poststent and follow-up optical coherence tomography (OCT) findings. Modified from Im et al[4] with permission from Wolters Kluwer Health, Inc.

a strut that was detached from the vessel wall as follows: Cypher, ≥160 μm; Resolute or Integrity, ≥110 μm; Xience V, ≥100 μm; Nobori or Biomatrix, ≥130 μm.[7] A coronary stent malapposition detected immediately after DES implantation is classified as *acute* stent malapposition, whereas one that is detected later (during follow-up OCT) is classified as *LSM*.[4] LSM can be further classified as *late-persistent* or *late-acquired* stent malapposition. A late-persistent stent malapposition is an acute stent malapposition that remains present at the follow-up OCT. A late-acquired stent malapposition is a newly developed stent malapposition that is identified on follow-up OCT despite complete stent apposition on immediate post-stent OCT.[4] If malapposed struts were detected by poststent OCT (ie, acute stent malapposition), each cross-section of the poststent OCT image was matched with cross-sections of the follow-up OCT image as accurately as possible based on the distance from fiduciary landmarks (eg, stent edges, side branches, or calcification).[4,8] The lesions were then classified as resolved acute stent malapposition lesions with or without late-acquired stent malapposition or as late-persistent stent malapposition lesions with or without late-acquired stent malapposition[4] (Figure 2). We then divided the patients into the following 2 groups: patients with LSM (subgroups 1, 2, 4, and 5 in Figure 2) and patients without LSM (subgroups 3 and 6 in Figure 2).

Clinical Follow-up

All patients were advised to maintain dual antiplatelet therapy (aspirin and clopidogrel) for ≥6 months after DES implantation.[4] During the follow-up period, most patients had a regular follow-up visit at an outpatient clinic. We investigated clinical events that were possibly related to LSM by reviewing medical records at our institute until the date of the last office visit. These events included cardiovascular death, target-lesion– and target vessel–related nonfatal myocardial infarction, target-lesion and target-vessel revascularization, and stent thrombosis. These clinical events were defined according to the recommendations of the Academic Research Consortium.[9] The event rates of each group were compared.

Statistical Analyses

Categorical variables are presented as number (percentage) and were compared using χ^2 or Fisher exact tests. Continuous variables are presented as mean±SD and were compared using Student *t* tests. Cumulative rates of composite clinical events (cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis) were estimated with the Kaplan–Meier method and compared among the groups with the log-rank test. We estimated hazard ratios with 95% CIs for the

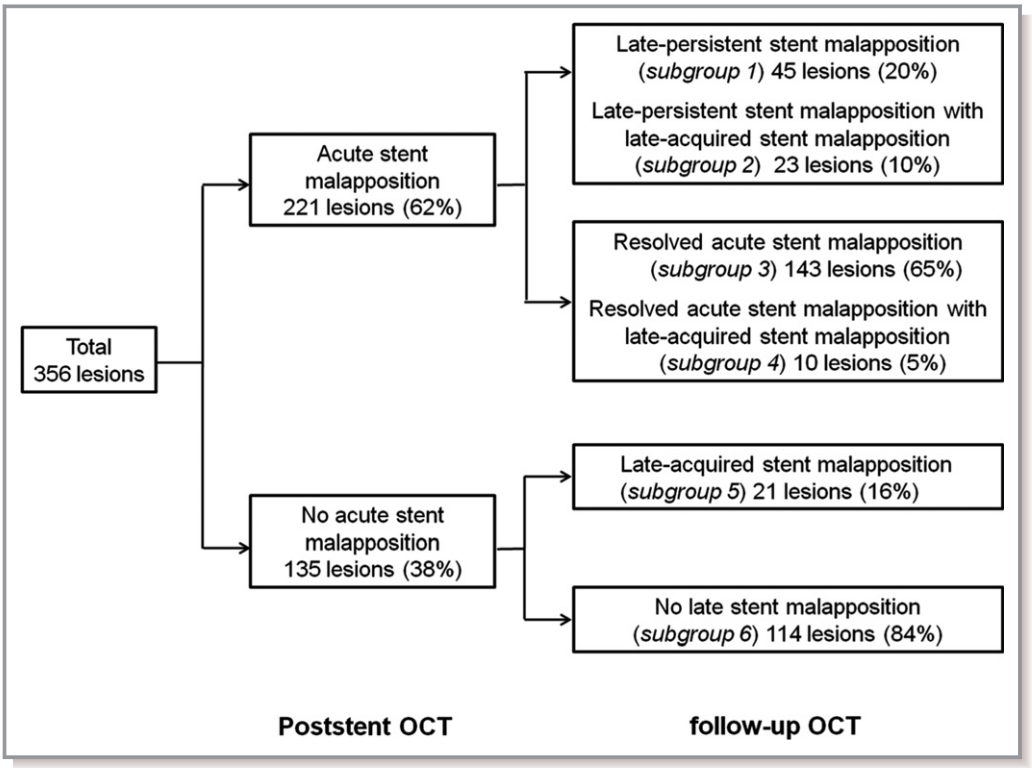

Figure 3. Incidences of acute and late stent malapposition detected on poststent and follow-up optical coherence tomography (OCT). Three subgroups represent late-acquired stent malapposition lesions (subgroups 2, 4, and 5). Modified from Im et al[4] with permission from Wolters Kluwer Health, Inc.

association of LSM with the composite events (cardiovascular death, target-vessel–related myocardial infarction, target vessel revascularization, and stent thrombosis) by Cox regression analysis, adjusted for baseline clinical and procedural variables. Variables with $P<0.05$ from univariate analyses were included in the analysis. Statistical analyses were performed using SPSS (v25.0; IBM Corp). $P<0.05$ was considered significant.

Results

The mean follow-up duration after DES implantation was 80.1±24.5 months, and follow-up OCT was performed on average 175±60 days after DES implantation.[4] Even though LSM was identified at follow-up OCT, no interventional procedure was performed for the lesions with LSM. Patients were divided into the following groups based on acute, late-persistent, or late-acquired stent malapposition detected by poststent and follow-up OCT: patients with LSM (subgroups 1, 2, 4, and 5 in Figure 3; 99 patients with 99 lesions) versus patients without LSM (subgroups 3 and 6 in Figure 3; 252 patients with 257 lesions). Baseline characteristics of the 2 groups are summarized in Table 1. Compared with patients without LSM, those with LSM showed a higher rate of calcified lesions, larger reference vessel diameter, higher preintervention percentage diameter stenosis, and larger stent diameter.

We compared clinical events for these 2 groups and found that the rates of individual and composite events were similar (Table 2). No very late stent thrombosis occurred in either group. Figure 4 shows the Kaplan–Meier curves for the composite events of cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis. The cumulative 8-year rate of composite events was 7.3% in patients with LSM and 10.5% in patients without LSM ($P=0.822$ by log-rank test). We further divided patients into the following 4 groups: late-persistent stent malapposition alone (subgroup 1; 45 patients with 45 lesions), both late-persistent and late-acquired stent malapposition (subgroup 2; 23 patients with 23 lesions), late-acquired stent malapposition alone (subgroups 4 and 5; 31 patients with 31 lesions), and no LSM (subgroups 3 and 6; 252 patients with 257 lesions). The cumulative 8-year rates of composite events were also similar among these 4 groups (9.6%, 0%, 9.7%, and 10.5%, respectively; $P=0.468$ by log-rank test; Figure 5).

Of all 351 enrolled patients, 269 patients (77%) were treated with new-generation DESs and the other 82 patients (23%) were treated with a first-generation DES. The number of patients with late-persistent stent malapposition was 31 (12%) with new-generation DESs and 14 (17%) with first-generation DES ($P=0.188$). The number of patients with late-acquired stent malapposition was 41 (15%) with new-generation DESs and 13 (16%) with a first-generation DES ($P=0.893$).

Table 1. Baseline Patient Characteristics

	Patients With Late Stent Malapposition (n=99)	Patients Without Late Stent Malapposition (n=252)	*P* Value
Clinical characteristics			
Age, y	67.5±16.4	69.4±19.2	0.382
Male sex	66 (67)	174 (69)	0.720
Hypertension	59 (60)	152 (61)	0.997
Diabetes mellitus	29 (30)	75 (30)	0.985
Dyslipidemia	59 (60)	130 (52)	0.176
Current smoking	23 (24)	48 (19)	0.350
Clinical presentation of acute coronary syndrome	35 (35)	71 (28)	0.187
Procedural characteristics			
Lesions, n	99	257	
Lesion in left anterior descending artery	61 (62)	139 (54)	0.199
Type B2 or C lesion	43 (45)	113 (46)	0.887
Calcified lesion	27 (27)	32 (13)	0.001
Reference vessel diameter, mm	3.09±0.47	2.93±0.40	0.020
Preintervention minimal lumen diameter, mm	0.96±0.57	1.06±0.44	0.263
Postintervention minimal lumen diameter, mm	2.77±0.37	2.70±0.40	0.301
Preintervention diameter stenosis, %	69±18	64±14	0.046
Postintervention diameter stenosis, %	13±9	11±8	0.125
Lesion length, mm	17.7±6.8	17.7±6.3	0.976
Stent diameter, mm	3.22±0.35	3.13±0.36	0.035
Stent length, mm	19.3±5.4	18.7±5.2	0.397
Types of DES			
First-generation DES			
Sirolimus-eluting stent	27 (27)	56 (22)	0.273
New-generation DES			
Zotarolimus-eluting stent	29 (29)	91 (35)	0.274
Everolimus-eluting stent	4 (4)	26 (10)	0.064
Biolimus-eluting stent	39 (40)	84 (33)	0.233
Predilation	99 (100)	253 (98)	0.579
Postdilation	55 (56)	143 (56)	0.988
Maximum pressure in the dilated vessel, atm	13±3	14±3	0.113

Data are shown as mean±SD or n (%) except as noted. DES indicates drug-eluting stent.

Table 2. Clinical Events During Follow-up*

	Patients With Late Stent Malapposition (n=99)	Patients Without Late Stent Malapposition (n=252)	*P* Value†
Follow-up duration, mo	80.5±19.8	79.9±26.1	0.825
Duration of DAPT, mo	13.9±6.6	14.3±8.7	0.651
At least 12 mo of DAPT	78 (79)	184 (73)	0.263
Cardiovascular death	0 (0)	1 (0.4, −0.4 to 1.2)	0.522
Target-lesion–related MI	0 (0)	2 (0.9, −0.3 to 2.1)	0.676
Target-vessel–related MI	0 (0)	2 (0.9, −0.3 to 2.1)	0.676
Target-lesion revascularization	2 (2.1, −0.6 to 4.8)	13 (5.8, 2.7–8.9)	0.151
Target-vessel revascularization	7 (7.3, 2.0–12.6)	20 (10.1, 5.4–14.8)	0.615
Stent thrombosis (definite or probable)	0 (0)	0 (0)	…
Composite of cardiovascular death, target-lesion–related MI, target-lesion revascularization, and stent thrombosis	2 (2.1, −0.6 to 4.8)	14 (6.3, 3.0–9.6)	0.293
Composite of cardiovascular death, target-vessel–related MI, target-vessel revascularization, and stent thrombosis	7 (7.3, 2.0–12.6)	21 (10.5, 5.8–15.2)	0.822

*Data are expressed as mean±SD, n (%), or number of patients (cumulative 8-year rate of event [%], 95% CI). DAPT indicates dual antiplatelet therapy; MI, myocardial infarction.
†By the log-rank test.

In all 99 patients with LSM, the cumulative 8-year rates of composite events were compared for patients with late-acquired stent malapposition (subgroups 2, 4, and 5) versus those with late-persistent stent malapposition (subgroup 1; Figure 6A), with malapposition distance ≥400 versus <400 μm (Figure 6B), and with malapposition length ≥1 versus <1 mm (Figure 6C). None of these comparisons achieved statistically significant differences.

LSM on follow-up OCT and variables with $P<0.05$ from univariate analyses were entered into the Cox regression model to identify independent predictors of the composite events and to calculate their adjusted hazard ratio (Table 3). LSM on follow-up OCT was not the independent predictor of the composite events (hazard ratio: 0.48; 95% CI, 0.13–1.79; $P=0.273$).

Discussion

During long-term follow-up after DES implantation (80.1±24.5 months), the cumulative rates of composite events did not differ significantly for patients with versus without OCT-detected LSM. To the best of our knowledge, this study is unique in its long-term follow-up (>5 years) for evaluation of clinical outcomes of OCT-detected LSM and its larger number of patients.

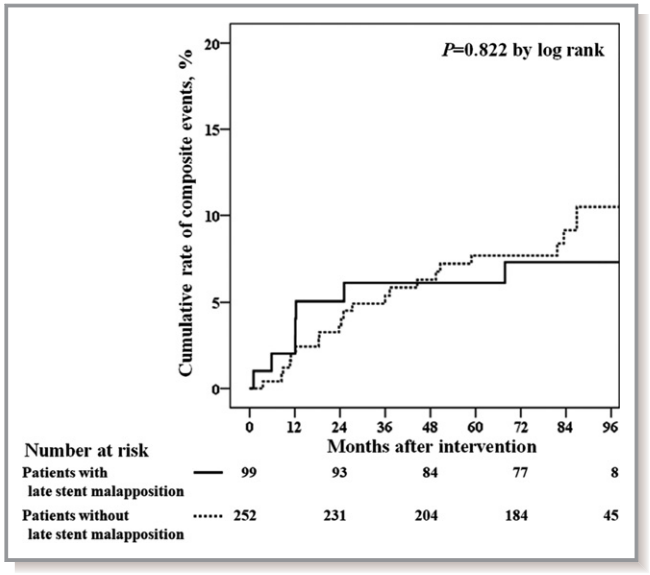

Figure 4. Cumulative 8-year rate of composite events (cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis), as estimated by Kaplan–Meier curves (late stent malapposition vs no late stent malapposition).

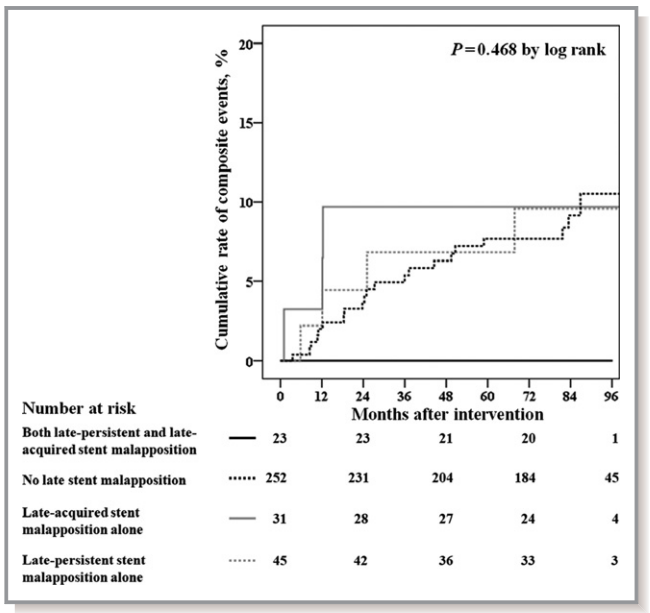

Figure 5. Cumulative 8-year rate of composite events (cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis), as estimated by Kaplan–Meier curves (both late-persistent and late-acquired stent malapposition vs late-persistent stent malapposition alone vs late-acquired stent malapposition alone vs no late stent malapposition).

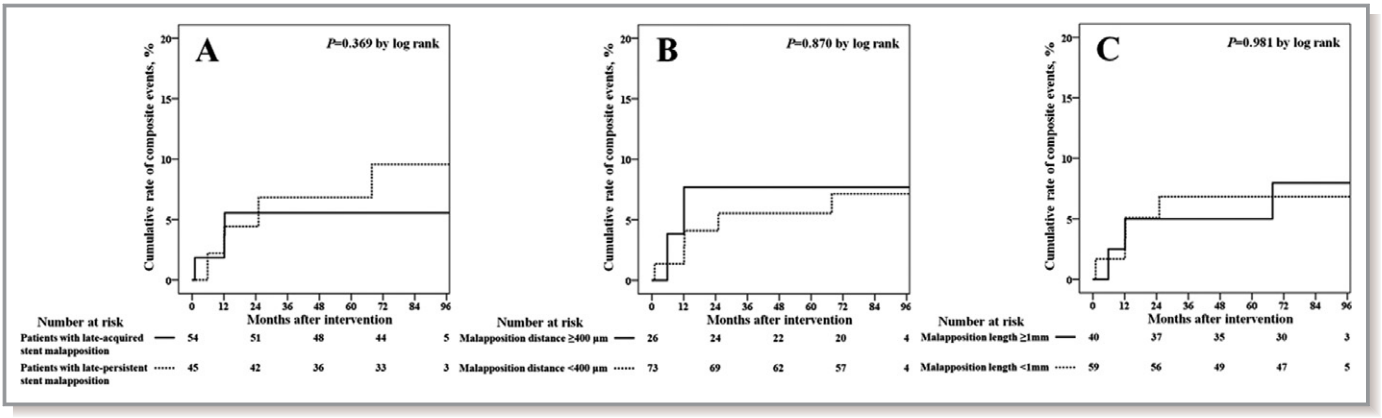

Figure 6. Cumulative 8-year rate of composite events (cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis), as estimated by Kaplan–Meier curves for patients with late-acquired vs late-persistent stent malapposition (A), malapposition distance ≥400 vs <400 μm (B), and malapposition length ≥1 vs <1 mm (C).

Most studies evaluating long-term clinical outcomes in patients with LSM after DES were performed with IVUS. The use of both poststent and follow-up IVUS evaluations can discriminate late-acquired stent malapposition from late-persistent stent malapposition. Hong et al reported favorable long-term (3 years) clinical outcomes in 80 patients with late-acquired stent malapposition among 532 DES-treated patients who underwent both poststent and follow-up IVUS examinations.[10,11] Other studies have also reported favorable long-term clinical outcomes in patients treated with a bare-metal stent or DES who had late-acquired stent malapposition.[12–14] However, a study of 195 DES-treated patients suggested that late-acquired stent malapposition may have been a risk factor for late DES thrombosis in 23 patients with late-acquired stent malapposition.[15] Furthermore, 5-year follow-up of 194 DES-treated patients reported that LSM (late-acquired or late-persistent) was associated with a higher rate of very late DES thrombosis in 37 patients with LSM.[16] Unfortunately, discrimination between late-acquired and late-persistent stent malapposition was not possible in that study because poststent IVUS data were not available.[16] Of note, patients in those previous studies were treated with first-generation DESs.[10–16] Because of these conflicting results, the relationship between IVUS-detected LSM and adverse cardiovascular events remains unclear.[1,17]

Table 3. Independent Predictor of the Composite Events*

	Hazard Ratio (95% CI)	*P* Value†
Late stent malapposition	0.48 (0.13–1.79)	0.273
Calcified lesion	0.96 (0.25–3.69)	0.953
Reference vessel diameter	0.46 (0.08–2.61)	0.377
Preintervention diameter stenosis	1.03 (1.00–1.06)	0.078
Stent diameter	1.01 (0.12–8.33)	0.995

*Composite events are cardiovascular death, target-vessel–related myocardial infarction, target-vessel revascularization, and stent thrombosis.
†By Cox regression analysis.

Stent malapposition can be more reliably detected by OCT than by IVUS[1]; however, few studies evaluating long-term clinical outcomes of patients with OCT-detected LSM have had adequate sample sizes. The proportion of malapposed stent struts detected by OCT (up to 50% of stents implanted) is higher than the proportion detected by IVUS (≈15% of stents implanted).[1,18] We previously reported that LSM was frequently detected in 351 DES-treated patients who underwent both poststent and follow-up OCT examination, but clinical outcomes of the patients with LSM (late-acquired or late-persistent) were favorable during the 2-year follow-up period.[4] The population of that study was the DES-treated patients who underwent routine OCT imaging and had a follow-up observation of subsequent adverse events in daily clinical practice. In the present study, we evaluated these patients over a longer follow-up period and found no significant difference in rates of adverse events of patients with versus without LSM. In contrast, 3 recent registry studies of patients presenting with stent thrombosis consistently identified stent malapposition as a frequent underlying abnormality.[1,19–21] Therefore, the European expert consensus recently recommended that extensively malapposed struts should be avoided following stent implantation and should be corrected when anatomically feasible.[1] However, the participants in those studies were highly selected patients who suffered from rare stent thrombosis, not the general DES-treated patients. In addition, stent malapposition was not the only finding responsible for stent thrombosis. Other stent abnormalities such as underexpansion or uncovered struts were also identified in some patients with stent thrombosis and stent malapposition.[19–21] Considering the high frequency of OCT-detected stent malapposition in daily clinical practice,[1,4,18] the number of patients with OCT-detected stent malapposition

who develop stent thrombosis may be very small.[19–21] Consequently, longer term (>5 years) follow-up studies are necessary to better understand the relationship between adverse clinical events and LSM detected by OCT in daily clinical practice, not in selected patients who presented with stent thrombosis. However, studies evaluating relationships between adverse clinical events and OCT-detected LSM during longer term (>5 years) follow-up were lacking. Some registry studies have already reported that acute stent malapposition on poststent OCT were not associated with worse outcomes.[22,23] In the present study, no very late stent thrombosis occurred in patients with OCT-detected LSM during 80.5±19.8 months of follow-up. According to our results, the simple presence of LSM on follow-up OCT was not associated with adverse cardiac events and did not need to be corrected. Even after the discontinuation of dual antiplatelet therapy, hard end points such as cardiovascular death, myocardial infarction, or stent thrombosis had not occurred in patients with LSM.

The favorable clinical outcomes observed in the present study may be explained as follows.[4] First, although large-sized stent malapposition has been associated with late stent thrombosis, small-sized stent malapposition that was detected by OCT may not have a clinically important effect.[4,24] Second, continuous neointimal healing during the follow-up period may decrease stent malapposition.[4,25,26] Third, most lesions (77%) were implanted with a new-generation DES in this study.[4]

The current study has several limitations. First, our study has potential selection bias because of its cross-sectional design and relatively small number of patients. Of all patients implanted with a DES, a small proportion were included and analyzed in this study. They were stable patients who underwent follow-up OCT without additional intervention. This might have caused sampling bias. Second, patients treated with first-generation DESs were also included in the study, and this limits the general application of our results to the current clinical field. Third, the rate of hard end points such as cardiovascular death, myocardial infarction, and stent thrombosis was low, suggesting the possibility of a low-risk population.

Conclusions

During 80.1±24.5 months of follow-up, very late stent thrombosis did not occur in 351 patients with OCT-detected LSM. The rates of adverse clinical events were similar for patients with and those without LSM.

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Disclosures

None.

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