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ステント留置後長期フォローアップにおけるステント間での OCT による血管治癒反応の比較検討

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Analysis of Long-term Arterial Healing Following Implantation of Different Types of Stents by Optical Coherence Tomography

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Brief Summary

This study was designed to compare long-term arterial healing in sirolimus- and paclitaxel-eluting stent (SES and PES) by using optical coherence tomography. At the follow-up, most SES showed a progressive increase in the average neointimal thickness, while PES showed variable changes. Long-term vessel healing were different for SES and PES. Progressive vessel healing was consistently observed in SES, whereas a heterogeneous process of delayed vessel healing was noted for PES.

Abstract

Background: Although drug-eluting stents have significantly reduced the mid-term incidence of target lesion revascularization, however, in vivo studies on long-term vessel healing of sirolimus-eluting and paclitaxel-eluting stents (SES and PES) are limited. So the aim of this study was to compare long-term arterial healing in SES and PES.

Methods: We evaluated 27 SES (23 patients) and 21 PES (20 patients) by serial optical coherence tomography (OCT) at 6 months (mid-phase) and ≥3 years (late-phase) after stenting and evaluated the change of neointimal thickness (NIT), the percentages of uncovered and malapposed struts, peri-strut low intensity area (region around stent struts homogenously lower-intensity appearance than surrounding tissue), thrombus, and atherogenic neointima.

Results: At the follow-up, most SES showed a progressive increase in the average NIT, while PES showed variable changes. Between mid-phase and late-phase, NIT increased significantly in SES (mid-phase: 94.1 ± 49.3, late-phase: 130.2 ± 78.7; P = 0.001), but decreased significantly in PES (mid-phase: 167.4 ± 122.9, late-phase: 136.0 ± 77.7; P = 0.04). The percentages of uncovered struts decreased significantly in SES, on the other hand, variable changes were observed in PES. Peri-strut low intensity area and thrombus formation decreased in SES, but largely remained unchanged in PES. The prevalence of atherogenic neointima was greater in the late-phase than the mid-phase in both groups, but similar for both the stents.

Conclusions: Long-term vessel healing were different for SES and PES. Progressive vessel healing was consistently observed in SES, whereas a heterogeneous process of delayed vessel healing was noted for PES.

Introduction

Drug-eluting stent (DES) have significantly reduced the mid-term incidence of in-stent restenosis and target lesion revascularization (TLR) by targeting acute-phase excessive proliferation of vascular smooth muscle cells occurring in response to mechanical injury.[1] However, late-phase clinical events, such as stent thrombosis and delayed restenosis, have been raised as possible concerns after first-generation DES implantation.[2] Multiple causes have been implicated in such events, including delayed arterial healing and atherogenic changes within neointimal tissue (neoatherosclerosis), which have been reported as morphological features of first-generation DES and important risk factors.[3] Further, a recent pathological study demonstrated significant differences in the vascular healing and differential mechanisms of late stent thrombosis between lesions treated with SES and PES.[4] However, in-vivo studies comparing sequential long-term vessel healing after SES versus PES treatment are limited.

Although first-generation DES are not among currently used standard options for the treatment of patients with coronary artery disease, they have been implanted in millions of patients worldwide. Hence, a detailed assessment of vessel healing may offer incremental information on patients at risk for future clinical events, potentially enabling more efficient patient follow-up. Therefore, the present optical coherence tomography (OCT) study focused on the process of long-term vessel healing after SES and PES implantation based on sequential OCT evaluation at mid-phase (6 months) and late-phase (≥3 years) follow-up among patients treated with first-generation DES.

Methods

We identified 225 consecutive patients treated with SES (Cypher; Cordis Corp., Miami Lakes, FL, USA) (SES-group) between October 2004 (when SES launched in Japan) and

May 2010, and 201 patients with PES (Taxus Express or Taxus Liberte; Boston Scientific Corp., Natick, MA, USA) (PES-group) between May 2007 (when PES launched in Japan) and May 2010.

Of these, 158 patients with SES and 90 patients with PES underwent routine 6-month follow-up coronary angiography with OCT examination (mid-phase). Among these, patients who met the inclusion and exclusion criteria were prospectively enrolled in this study for sequential angiographic and OCT examinations (mid-term: 6 months, late-phase: ≥3 years). The inclusion criteria for this study were as follows: (a) patients with a de novo coronary lesion (>50% diameter stenosis) treated with SES or PES, who underwent routine 6-month follow-up coronary angiography and OCT; (b) native vessel size of 2.5–3.5 mm in diameter, and (c) stable angina or acute coronary syndrome. The exclusion criteria were as follows: (1) patients with ST-elevated acute myocardial infarction, (2) TLR during follow-up, and (3) patients unsuitable for coronary angiography due to renal dysfunction or congestive heart failure. Further, in order to match the timing of late-phase follow-up in the SES and PES groups, we excluded SES patients whose late-phase follow-up would be >5 years after stenting. Eventually, 27 SES from 23 patients and 21 PES from 20 patients were enrolled in the study (Figure 1).

All patients were taking aspirin 100 mg/day. After stenting, patients were prescribed ticlopidine (200 mg/day) or clopidogrel (75 mg/day) for at least 1 year. This study was approved by the ethics committee of Kobe University and was carried out according to the guidelines of the Declaration of Helsinki. All enrolled study patients provided written informed consent to undergo follow-up OCT and for enrollment in this study.

In the present study, time-domain OCT (ImageWire; LightLab Imaging, Westford, MA, USA) with coronary artery occlusion (Helios^{TM}; LightLab Imaging) was used for imaging at the mid- and late-phase. The entire stented length was then imaged using an

automatic pullback system moving at 1 mm/s.

Offline OCT analysis was performed at 1-mm intervals using the dedicated software (LightLab Imaging Inc.). All images were analyzed by independent observers masked to the clinical presentation, lesion characteristics, and stent assignment. We used landmarks such as stent edge and side branches to match the location of the cross-sections between the mid-phase and late-phase examinations.

As a primary outcome of the quantitative OCT assessment, we measured neointimal thickness (NIT) of SES and PES at mid- and late-phase follow-up to compare differences of NIT changes between the two stents during the follow-up. Moreover, we analyzed other OCT findings such as the percentage of uncovered and malapposed struts to compare vessel healing between the stents. NIT was defined as the distance between the stent strut and lumen surface. An uncovered strut was defined as a strut with NIT = 0 μm. We assessed the ratio of uncovered struts to total struts per cross-section (RUST) and the frequency of cross-sections with RUST > 0.3, because a recent post-mortem study reported RUST to be the best morphometric predictor of late stent thrombosis.[5] Malapposition was defined as a maximum distance of more than 170 μm in SES and 130 μm in PES between the center reflection of the strut and the adjacent vessel surface.[6]

The frequencies of struts with a peri-strut low intensity area, a suggestive finding of fibrin deposition or impaired neointima maturation,[7] and those of stents with an extra-stent lumen (ESL) were also calculated. Peri-strut low intensity area was defined as the region around stent struts with a homogeneous lower-intensity appearance than the surrounding tissue on OCT images without significant signal attenuation behind the area.[8] ESL was defined as an external lumen of the stent struts.[9]

Qualitative analysis was performed for every frame, and the frequencies of intra-stent thrombi and atherogenic neointima being present were calculated. An intra-stent thrombus

was defined as a mass protruding beyond the stent strut into the lumen with significant attenuation behind the mass.[10] Atherogenic neointima was defined as neointima containing a diffuse border and signal-poor region with invisible struts underneath due to marked signal attenuation (Supplemental Figure S1).

Long-term (i.e., beyond 3 years) clinical follow-up data were obtained by either a review of the hospital records or telephone contact. The major clinical events studied were all causes of death, myocardial infarction, TLR, and stent thrombosis adjudicated according to the Academic Research Consortium classification.[11,12]

Statistical analysis was conducted with a commercially available Stat View 5.0 (SAS Institute, Cary, NC). Qualitative data are presented with frequencies, and quantitative data are shown as mean values ± SD. For continuous variables, comparisons between the 2 groups were performed using a 2-tailed, unpaired *t*-test or Wilcoxon's test. Discrete variables are presented as percentages and comparisons were performed by chi-square analysis or Fisher's exact test. A probability value *(P)* of less than 0.05 was considered statistically significant.

Results

The mean durations from stent implantation to the mid-phase and late-phase follow-up were 7.0 ± 2.3 months and 3.9 ± 0.4 years in the SES group, while those for PES were 7.3 ± 1.5 months and 3.6 ± 0.7 years, respectively. All patients had taken aspirin throughout the follow-up period in both the groups. No significant differences were noted in medication or laboratory data at late-phase follow-up between the 2 groups (Table 1).

A total of 830 matched cross-sections (mid-phase: 415, late-phase: 415) in SES and 628 matched cross-sections (mid-phase: 314, late-phase: 314) in PES were analyzed by OCT. Although the mean lumen area and mean minimal lumen area did not change significantly from the mid-phase to late-phase follow-up, the average NIT increased significantly in SES

but decreased significantly in PES over the follow-up period (Table 2). Most SES cases showed a progressive increase in the average NIT, while various types of NIT changes were observed in PES cases (Figure 2a and 2b). Significant differences were observed in the NIT changes between SES and PES (SES: +36.1 μm vs. PES: -31.4 μm, P = 0.0003). Based on the qualitative assessment of neointima, PES cases with decreased NIT were categorized into 3 types as follows: (1) NIT decrease with peri-strut low intensity area absorption, (2) regression of lower-intensity neointima as compared to standard neointimal tissue, and (3) regression of homogeneous neointima (Figure 4). Between the mid-phase and late-phase follow-up, SES showed a significant decrease in the percentage of uncovered struts, unlike PES, which showed no significant changes in both percentages (Table 2). Furthermore, most SES cases showed decrease in the percentage of uncovered struts during the follow-up period, while various types of changes such as NIT changes were observed in PES cases (Figure 2c and 2d). The percentage of malapposed struts showed no significant changes in both stents during the follow-up. The percentage of peri-strut low intensity area and the incidences of thrombi and ESL formation decreased from the mid-phase to late-phase follow-up in SES, while no significant changes were noted in PES (Table 2). The percentage of peri-strut low intensity area was lower in PES cases with increased NIT than those with no increase at mid-phase follow-up (0.4% vs. 13.7%, P = 0.04). Furthermore, percentage changes in peri-strut low intensity area during the follow-up period were numerically higher in PES cases with increased NIT than in those with no increase (+2.6% vs. -8.1%, P = 0.052). Late-acquired thrombus tended to be more frequent in PES than in SES (Figure 5) and was associated with a decrease or no change in NIT between the mid- and late-phase follow-up. Further, significant differences were noted in NIT changes between cases with completely resolved thrombus and those with late-acquired thrombus (Figure 6). The prevalence of atherogenic neointima at late-phase was not statistically different between both the groups (SES: 14.8%

vs. PES: 25.0%, P = 0.39). Representative OCT images of serial qualitative OCT findings are shown in Supplemental Figure S2.

Long-term clinical follow-up data after late-phase OCT examination (median: SES, 6.2 years; PES, 4.2 years) were obtained for all patients. One patient with SES and 2 patients with PES required TLR; no other clinical events were noted during the study period.

Discussion

To the best of our knowledge, this is a first report that compared serial changes in arterial healing following different types of first-generation DES by OCT.

Cases with delayed restenosis or late-phase TLR have been reported consistently.[13] Indeed, in this study, continued neointimal proliferation from the mid-phase to late-phase follow-up was observed in most of the SES-treated cases (74%) and in part of the PES-treated cases (38%); Interestingly, although the average NIT remained comparable between the SES- and PES-treated lesions at ≥3 years after stenting, as observed previously,[14] PES showed various patterns of delayed neointimal changes (decrease in 52.4% cases; increase, 28.6%; and no change, 19.0%); however, SES showed a progressive increase. This discrepancy may be explained by differences in the stent platform, polymer, duration of drug delivery, and the pharmacologic agents themselves. For example, SES elutes sirolimus for only a short duration (30–90 days), while PES produces consistent elution of paclitaxel, which may inhibit arterial healing.

Regression of intimal hyperplasia is frequent after bare-metal stent implantation; Nobuyoshi et al. reported a decrease in the extracellular matrix of the newly proliferating intima and subsequent fibrotic changes during the first 2–3 years after balloon angioplasty.[15] Peri-strut low intensity area around stent struts on OCT images has been suggested as indicative of the presence of fibrinogen surrounded by a proteoglycan extracellular matrix.[10]

We noted a lower prevalence and greater percentage of changes in peri-strut low intensity area with increased NIT than in those without. Therefore, we speculate that fibrotic maturation of the intimal hyperplasia (absorption of fluid elements such as extracellular matrix) and resolution of fibrin deposition may contribute to the observed regression of neointimal hyperplasia at the late-phase follow-up in PES. Alternatively, the neointimal tissue (areas hypointense to the surrounding normal tissue) detected in the mid-phase OCT images of several cases with decreased NIT may actually represent mural thrombi, which may have resolved during the follow-up period. (Figure 4b)

We noted that both SES and PES sometimes showed delayed arterial healing, with persistence of uncovered struts, malapposed struts, ESL, and/or in-stent thrombi even ≥3 years after stent deployment. However, overall, the percentage of uncovered struts and cross-sections with RUST > 0.3 in SES decreased significantly during follow-up, with an increase in the frequency of completely covered stents. These results were consistent with a previous OCT study[16] and may indicate that for SES, the healing process continued for up to 3 years. On the other hand, we noted various types changes in the percentage of uncovered struts were observed in PES cases. The percentage of uncovered struts decreased in most PES cases, while that increased or unchanged in some PES cases. Considering the changes of NIT and percentage of uncovered struts, most cases of both SES and PES have predictable healing patterns, however there may be some differences in vascular healing, with SES having a tendency to greater neointimal proliferation and struts coverage compared with PES.

The frequency of in-stent thrombi decreased in SES, but remained unchanged in PES; late-acquired thrombi were frequent in PES and were always associated with neointimal regression; more than half of the PES-treated lesions showed neointimal regression. A previous experimental study showed that relative to SES, PES showed a delay in the reestablishment of a functional endothelium[17]; further, a higher incidence of thrombus

attachment has been demonstrated in PES than in SES in human OCT[18] and angioscopic studies.[19] Further large-scale and longitudinal study is warranted to clarify the mechanism.

Evidence indicates that neoatherosclerosis is an important factor involved in late DES failure.[20] In this study, the prevalence of atherogenic neointima at the late-phase follow-up was similar for SES and PES (overall incidence up to 5 years: 18.8%) and was relatively lower than that noted in a previous pathological study (overall incidence up to 6 years: 31%).[20] This discrepancy might be attributed to the differences in patient and lesion characteristics between the 2 studies.

Study Limitations

First, this is a study evaluating the first-generation DES using the time-domain OCT which is different from the current standard OCT system. Frequency-domain OCT had not been approved for clinical use in Japan at the time of the mid-phase follow-up, so we considered that it would be better to use the same imaging system in order to accurately evaluate serial changes of vessel healing between the mid- and the late-phase follow-up. Secondly, this is a single-center study with a relatively small sample size owing to the invasive nature of the evaluation, raising a possibility of selection bias. Thirdly, we enrolled only event-free patients who were available for mid- and long-term follow-up OCT. Finally, considering multiple comparisons with the select nature of the patient population, the results of the study should be interpreted primarily for generating hypotheses; moreover, P values should be interpreted cautiously

Conclusion

Most cases of both SES and PES have predictable healing patterns, however there may be some differences in vascular healing, with SES having a tendency to greater neointimal

proliferation and struts coverage compared with PES. Considering the relatively high incidence of atherogenic changes within the neointima despite statin therapy, long-term follow-up OCT may prove beneficial for identifying patients at risk for future ischemic events.

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Disclosures

The authors have no potential conflicts of interest.

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Table 1. Baseline clinical characteristics at late-phase follow-up

Variable	SES (23 patients)	PES (20 patients)	p
Age (years)	67.9 ± 7.7	70.8 ± 6.1	0.21
Male (%)	78.9	73.7	0.70
BMI (kg/m^2)	23.7 ± 3.5	25.4 ± 3.4	0.14
Risk factors (%)			
Diabetes mellitus	61.0	60.0	0.95
Hypertension	61.0	80.0	0.17
Dyslipidemia	87.0	80.0	0.54
History of smoking	47.8	65.0	0.26
Hemodialysis	8.7	5.0	0.64
Ejection fraction (%)	58.4 ± 10.3	63.2 ± 8.1	0.14
Angina status (%)			
Stable/Unstable	91.3/8.7	85.0/15.0	0.52
Chronic total occlusion	18.2	10.0	0.45
Stent size			
Diameter (mm)	3.03 ± 0.39	2.93 ± 0.36	0.33
Length (mm)	22.3 ± 6.3	20.0 ± 6.5	0.22
Lesion characteristics (%)			
Vessel treated (LAD/LCX/RCA)	23/23/54	50/5/45	0.10
ACC-AHA class (A/B1/B2/C)	23/42/12/23	21/42/16/21	0.82
Duration of OCT follow-up			
Duration of mid-phase follow-up (m)	7.0 ± 2.3	7.3 ± 1.5	0.61

Duration of late-phase follow-up (y)	3.9 ± 0.4	3.6 ± 0.7	0.09
Medication at late-phase follow-up (%)			
Aspirin	100	100	1.0
Thienopyridine	47.4	68.4	0.19
Statin	89.5	89.5	1.0
ACE inhibitor or/and ARB	84.2	73.7	0.43
Beta-blocker	57.9	36.8	0.19
Mean duration of dual anti-platelet therapy (months)	26.4 ± 22.2	31.5 ± 15.4	0.43
Laboratory data at late-phase follow-up			
hs-CRP (mg/dL)	0.10 ± 0.22	0.10 ± 0.13	0.98
HDL-cholesterol (mg/dL)	46.6 ± 8.6	48.7 ± 14.0	0.58
LDL-cholesterol (mg/dL)	80.4 ± 18.7	84.2 ± 22.6	0.58
Triglyceride (mg/dL)	98.8 ± 32.5	119.6 ± 48.4	0.13
HbA_{1c} (%)	6.2 ± 0.7	5.9 ± 0.1	0.34

Values are presented as mean ± SD or percentages.

ACC-AHA, American College of Cardiology-American Heart Association lesion classification; ACE, angiotensin conversion enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 2. Optical coherence tomography analysis

	SES			PES		
	Mid-phase	Late-phase	p	Mid-phase	Late-phase	p
Stent-based analysis						
Stent with 100% covered struts (n, %)	10 (37.0)	20 (74.1)	0.002	7 (35.0)	9 (45.0)	0.72
Stent with ESL (n, %)	17 (63.0)	11 (40.7)	0.03	5 (25.0)	5 (25.0)	1.00
Stent with in-stent thrombus (n, %)	8 (29.6)	3 (11.1)	0.06	7 (35.0)	6 (30.0)	0.72
Stent with atherogenic neointima (n, %)	1 (3.7)	4 (14.8)	0.18	0 (0)	5 (25.0)	0.02
Cross-section-based analysis						
Total number of cross-sections	415	415		314	314	
Mean lumen area (mm^2)	6.4 ± 2.5	6.1 ± 2.5	0.16	5.6 ± 2.1	5.7 ± 2.0	0.64
Mean minimal lumen area (mm^2)	5.0 ± 2.5	4.7 ± 2.4	0.18	4.3 ± 2.0	4.5 ± 1.8	0.43
Mean stent area (mm^2)	6.9 ± 2.4	7.0 ± 2.4	0.53	6.9 ± 2.0	6.8 ± 2.0	0.23
Mean neointimal area (mm^2)	0.6 ± 0.5	0.9 ± 0.7	0.002	1.3 ± 1.1	1.1 ± 0.7	0.17
Cross-section with RUST > 0.3 (n, %)	10 (2.2)	1 (0.4)	0.05	5 (2.9)	3 (0.8)	0.33

Strut-based analysis

Total number of struts	3550	3476	0.28	2551	2566	0.89
Mean neointimal thickness (μm)	94.1 ± 49.3	130.2 ± 78.7	0.0014	167.4 ± 122.9	136.0 ± 77.7	0.04
Uncovered struts (n, %)	129 (4.1)	27 (0.9)	0.002	62 (3.2)	32 (1.5)	0.28
Malapposed struts (n, %)	44 (1.4)	16 (0.4)	0.11	48 (2.3)	21 (0.8)	0.17
Struts with peri-strut low intensity area (n, %)	583 (15.4)	268 (8.4)	0.03	227 (10.4)	103 (5.1)	0.06

ESL, extra-stent lumen.

Figure legends

Figure 1. Study flows

AMI, acute myocardial infarction; CAG, coronary angiography; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; TLR, target lesion revascularization.

Figure 2. Different patterns of changes in average NIT and the percentage of uncovered struts of SES and PES

(a) Most SES cases showed a progressive increase in the average NIT, while various NIT changes are observed in PES cases. (b) The percentage of NIT change patterns in SES and PES. NIT not changed cases was defined as NIT changes within ± 0.5 μm during the follow-up period. (c) Most SES cases showed a decrease in the percentage of uncovered struts, while various changes were observed in PES cases. (d) The percentage of uncovered struts change patterns in SES and PES.

NIT, neointimal thickness; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent.

Figure 3. Representative cases of NIT increasing case in SES

NIT increased with SES during the follow-up period.

NIT, neointimal thickness; SES, sirolimus-eluting stent.

Figure 4. Representative cases of temporal NIT change in PES

(a) NIT decreased with PES during the follow-up period with peri-strut low intensity area absorption. (b) NIT decreased with PES showing a regression of neointima adjacent to

abnormal structures. (c) NIT decreased with PES showing a regression of homogeneous neointima. (d) NIT increased with PES.

NIT, neointimal thickness; PES, paclitaxel-eluting stent.

Figure 5. Incidence of intra-stent thrombi

Eight thrombi in SES (30%) and 7 thrombi in PES (33%) were observed in mid-phase; 6 of 8 thrombi in SES and 4 of 7 in PES resolved completely, while others persisted. At late-phase follow-up, 1 thrombus in SES and 3 in PES were newly observed.

PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

Figure 6. Relationship between NIT changes and time course of intra-stent thrombi

NIT changes differed significantly between cases with completely resolved thrombus and those with late-acquired thrombus.

NIT, neointimal thickness.

Figure 1. Study flows

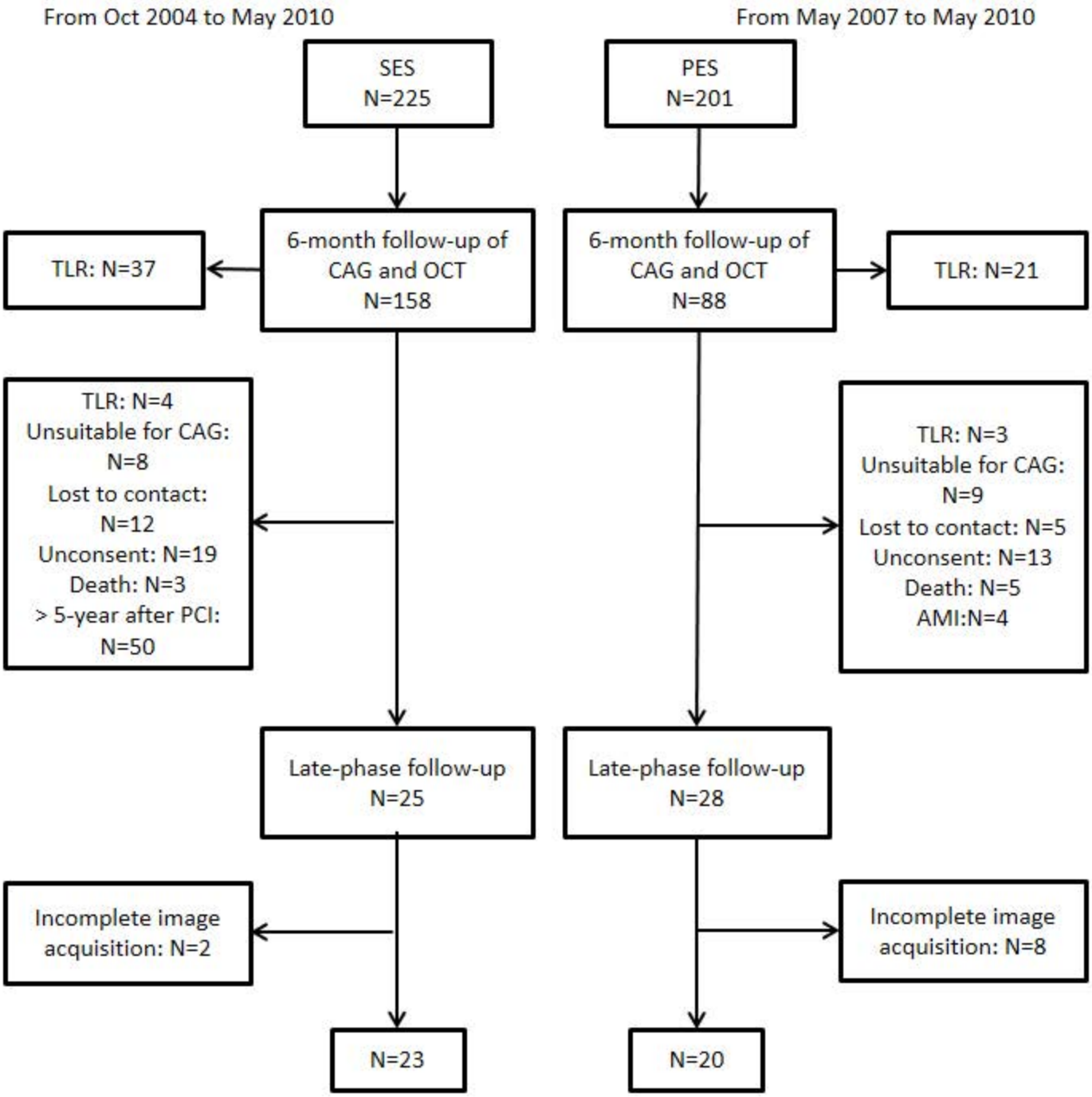


Figure 2. Different changes in OCT findings between SES and PES

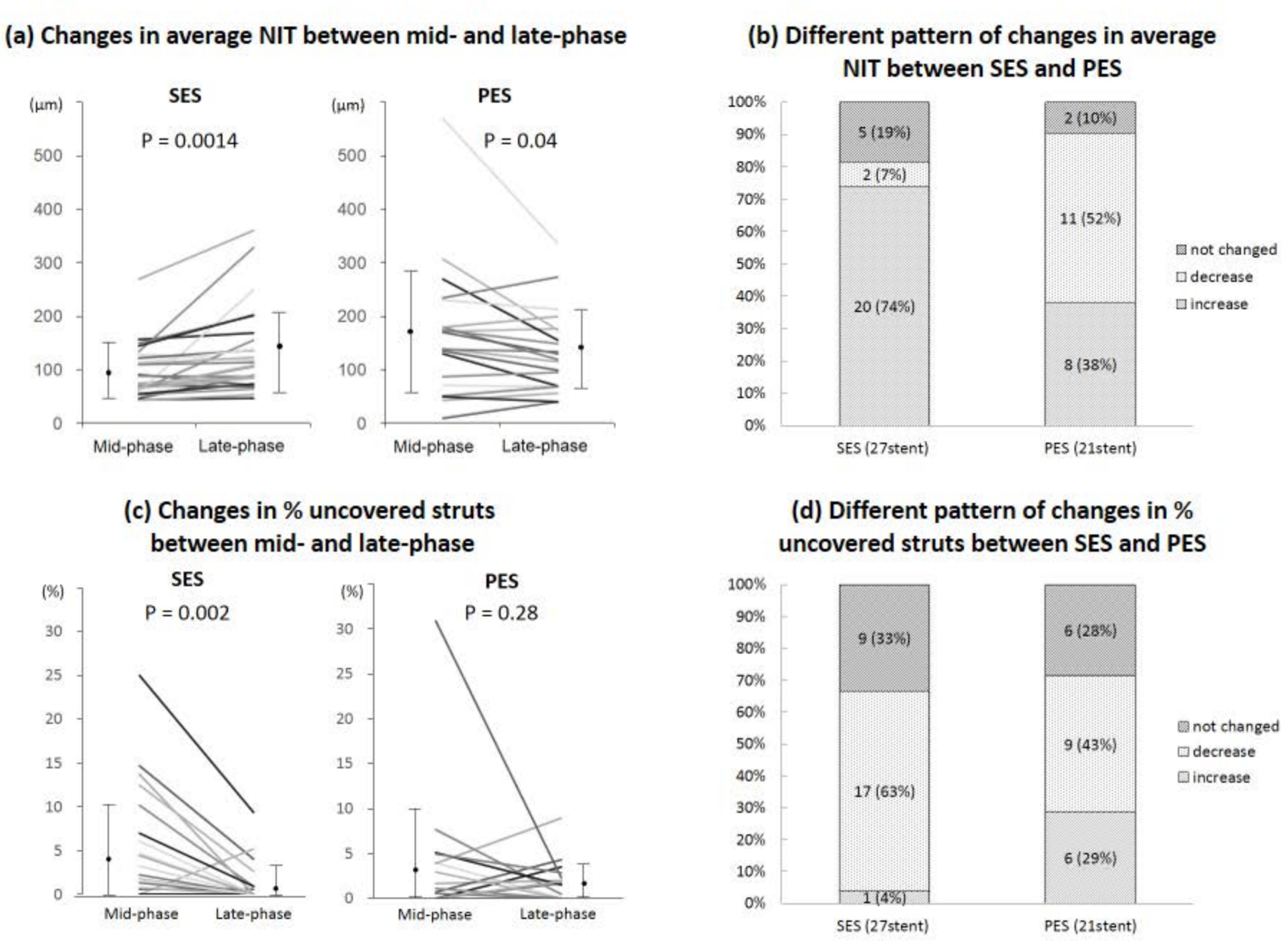
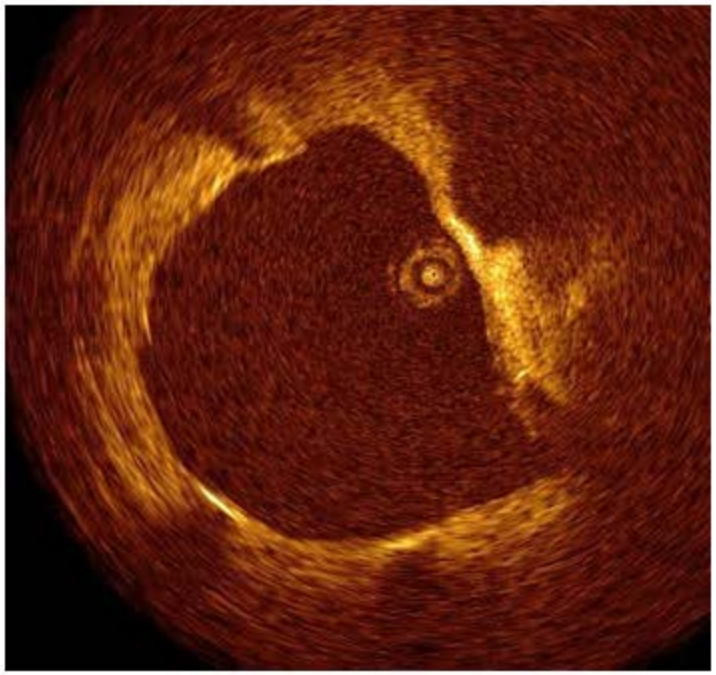


Figure 3. NIT increasing case in SES

7 months



63 months

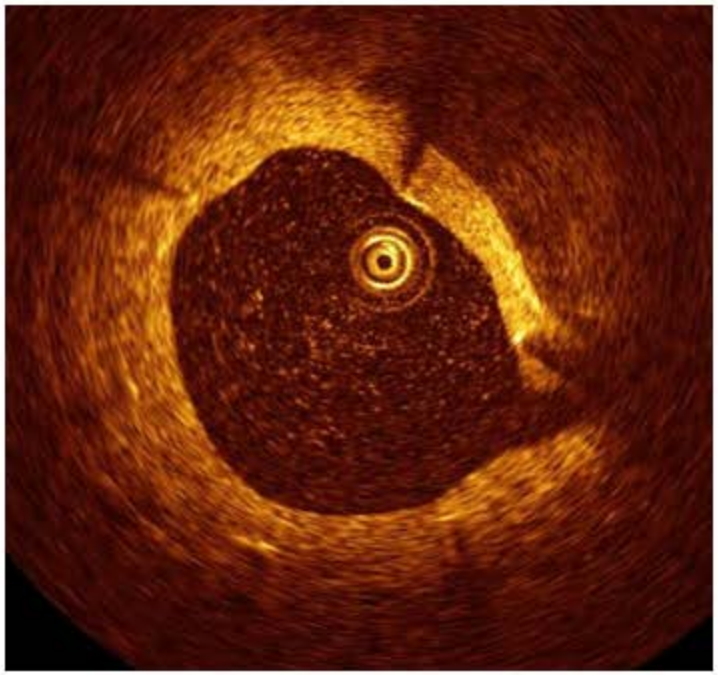
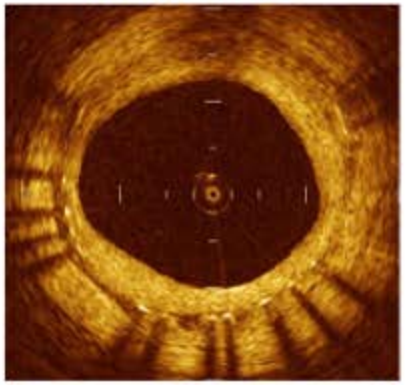


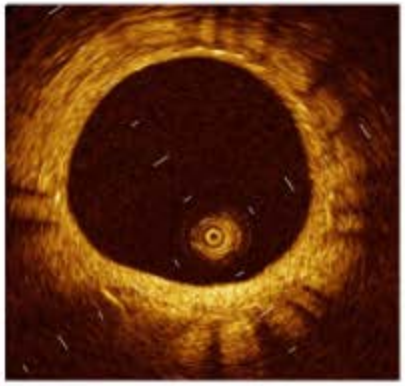
Figure 4. Temporal NIT changes in PES

(a) NIT decreasing case in PES: peri-strut low intensity area absorbed pattern

8 months

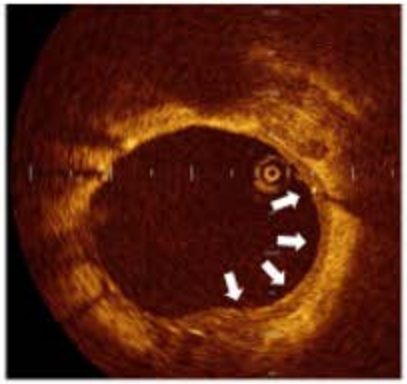


41 months

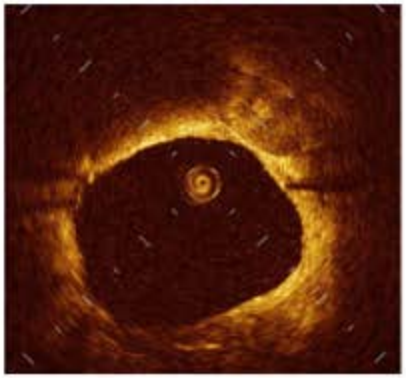


(b) NIT decreasing case in PES: regression of abnormal structure pattern

6 months

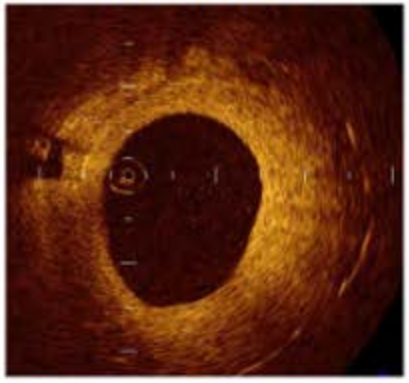


42 months

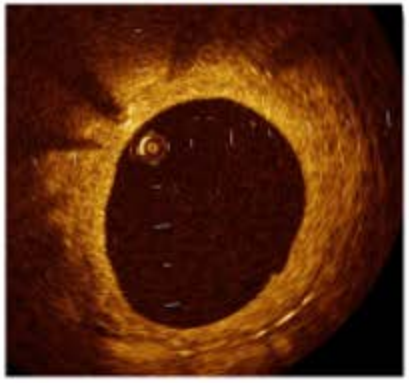


(c) NIT decreasing case in PES: regression of homogeneous neointima pattern

6 months

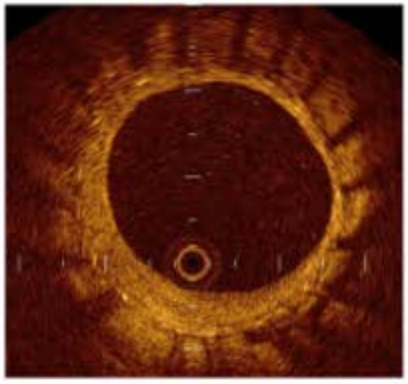


34 months



(d) NIT increasing case in PES:

9 months



29 months

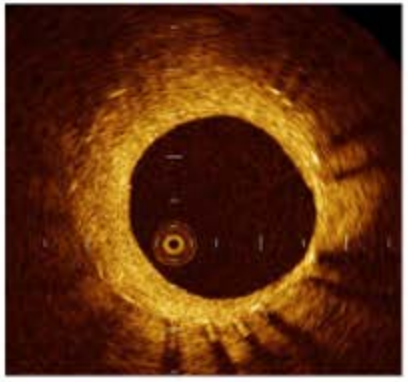


Figure 5. Incidence of intra-stent thrombi during the follow-up period

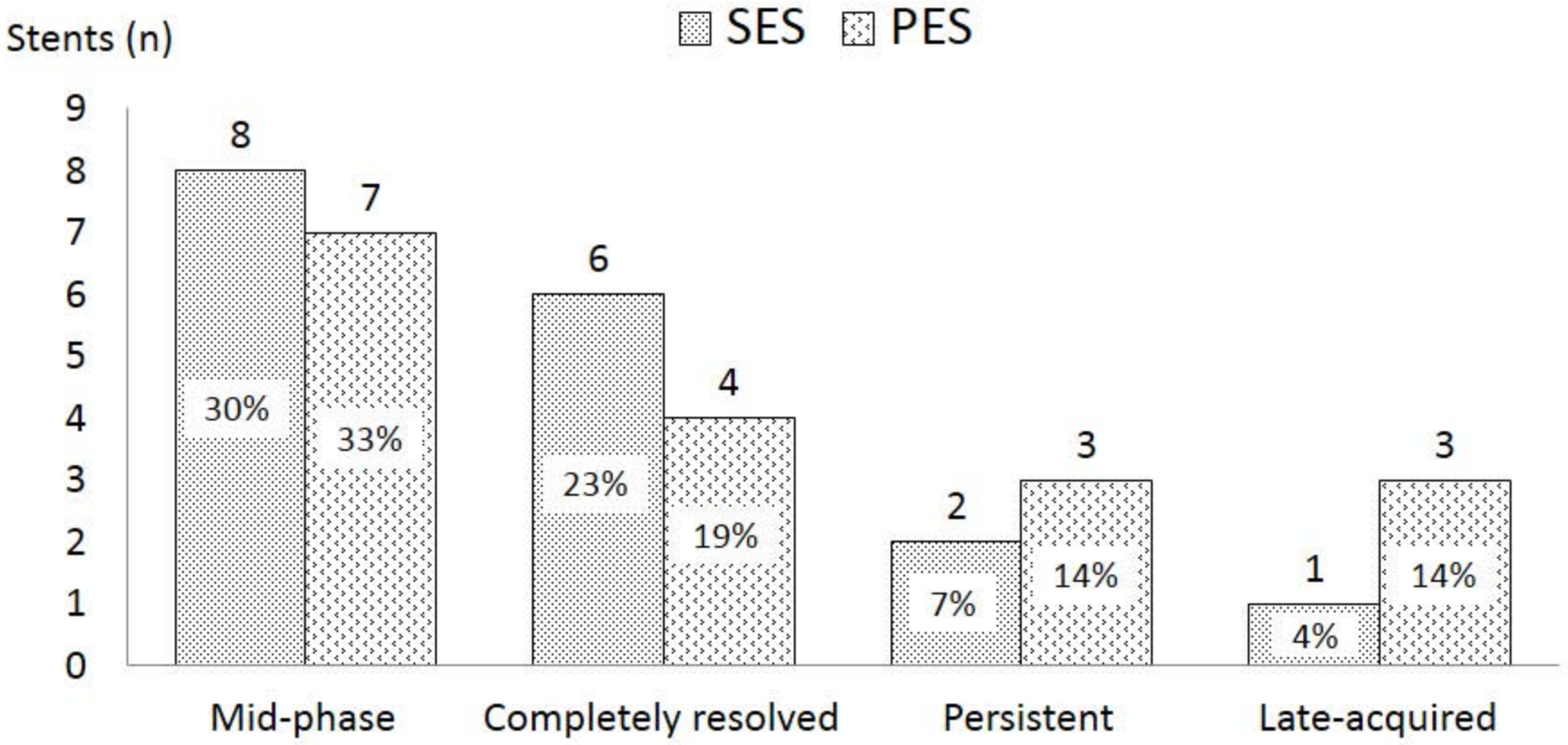
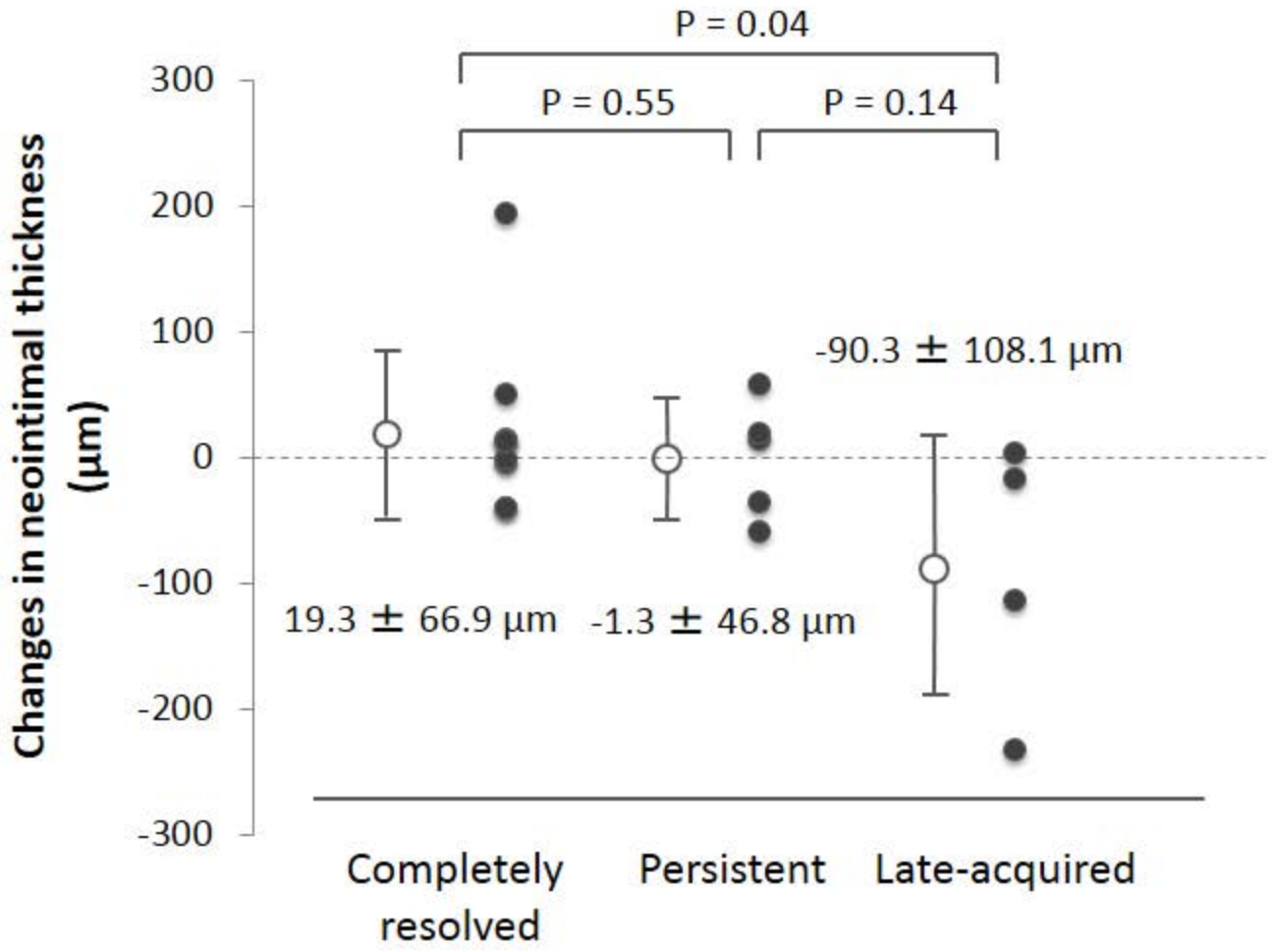
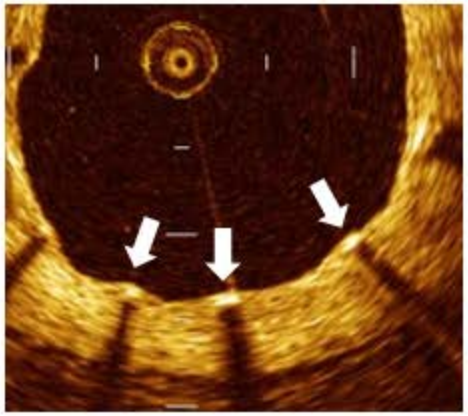
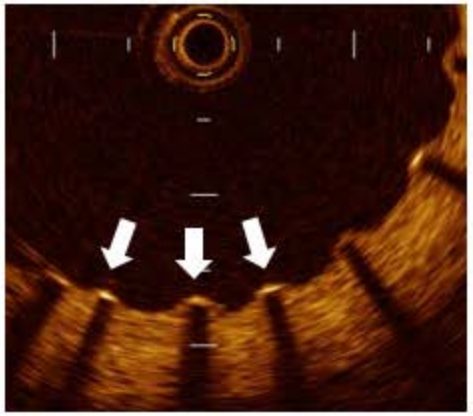


Figure 6. Relationship between changes in NIT and time course of intra-stent thrombi

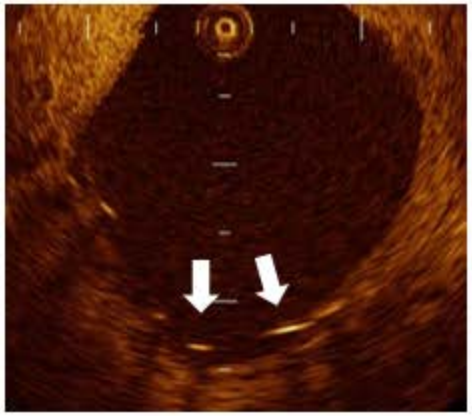




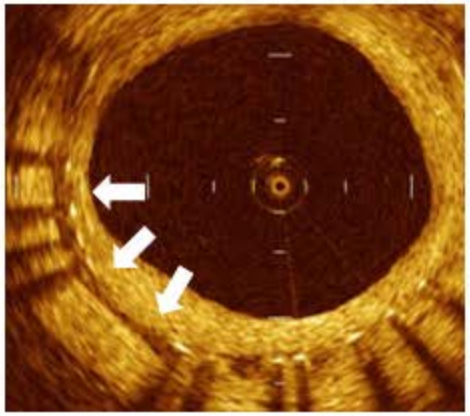
(a) covered strut



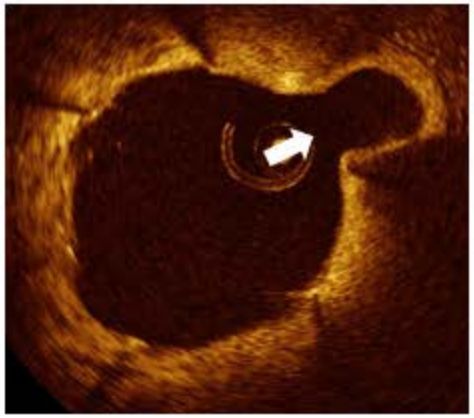
(b) uncovered strut



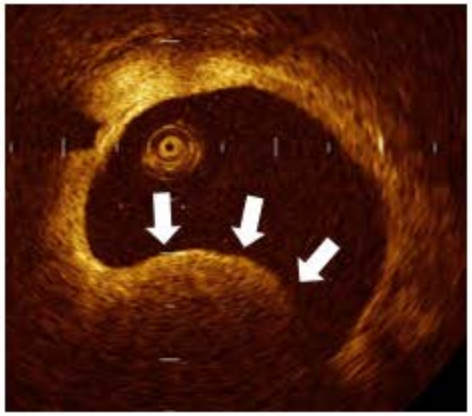
(c) malapposed strut



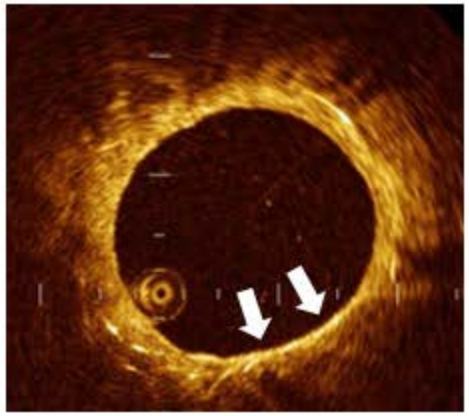
(d) peri-strut low intensity area



(e) extra stent lumen



(f) intra-stent thrombus



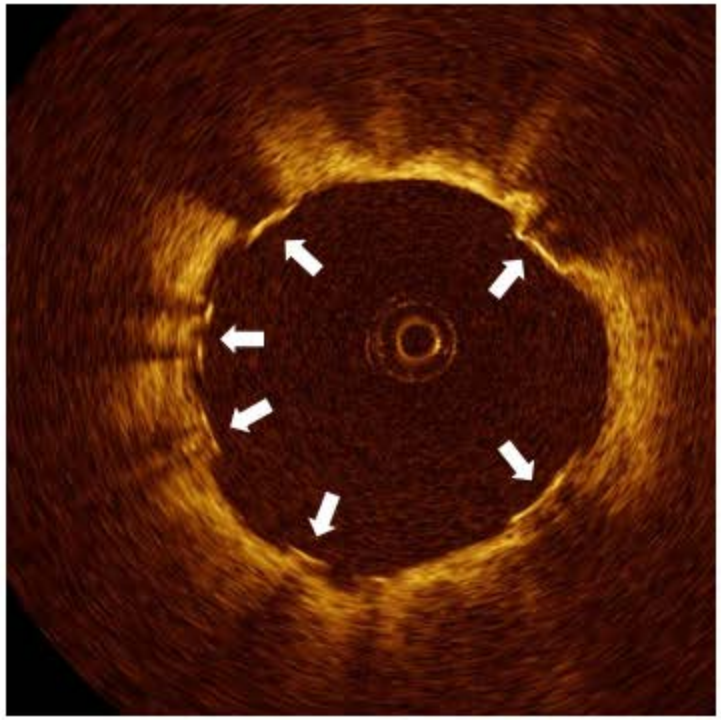
(g) atherogenic neointima

Supplemental Figure S1

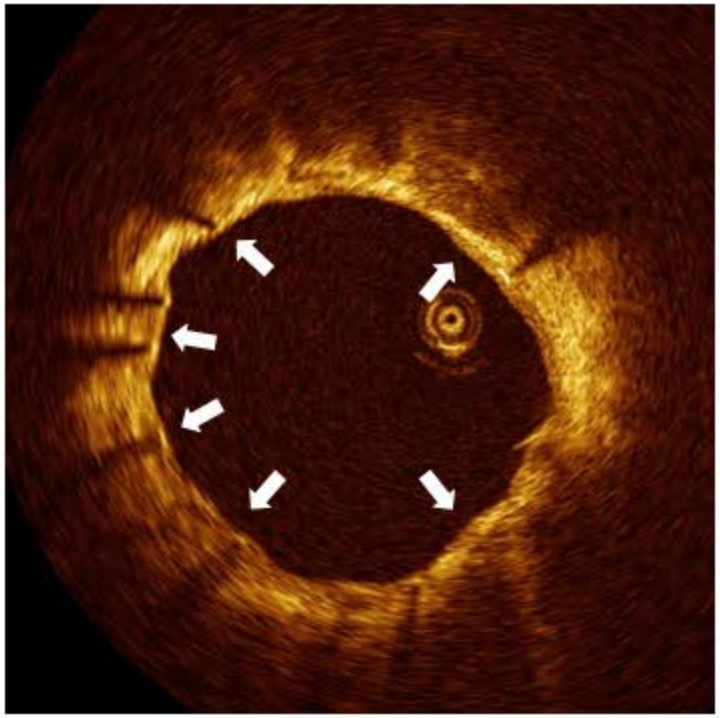
Supplemental Figure S2 (a):

Uncovered to covered strut in SES

7 months



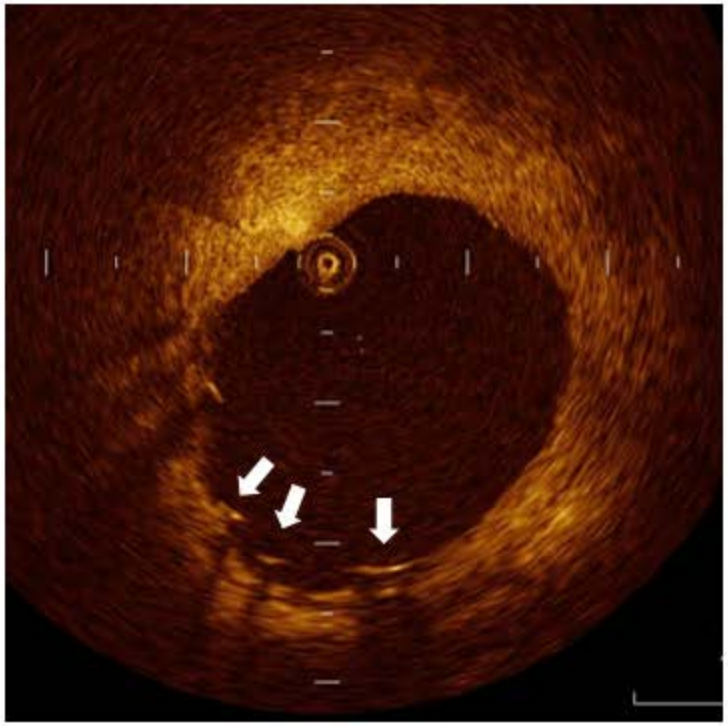
60 months



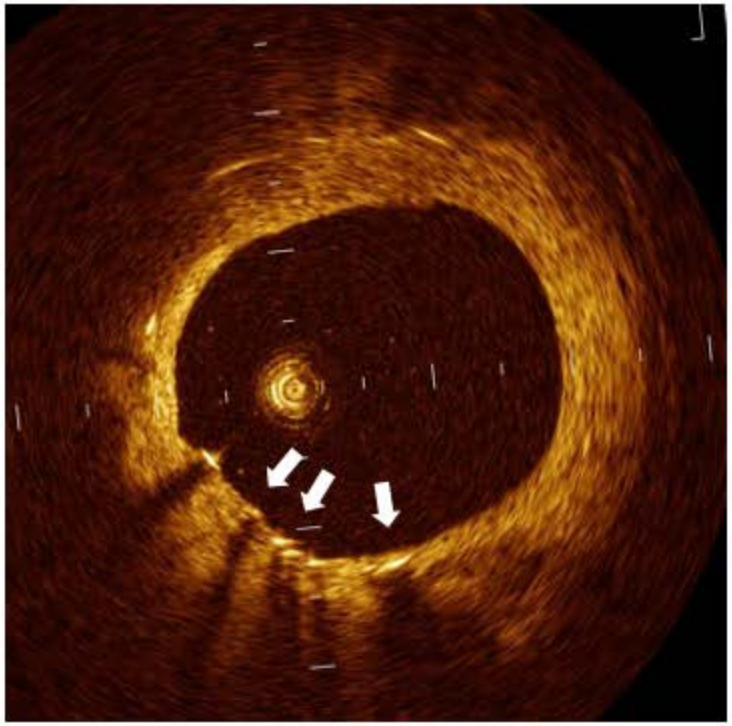
Supplemental Figure S2 (b):

Malapposed to apposed strut in PES

11 months



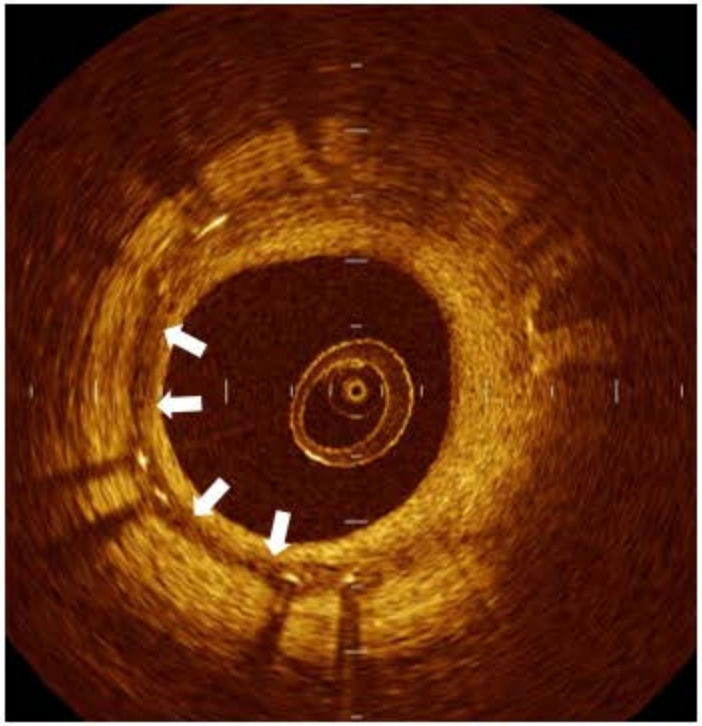
57 months



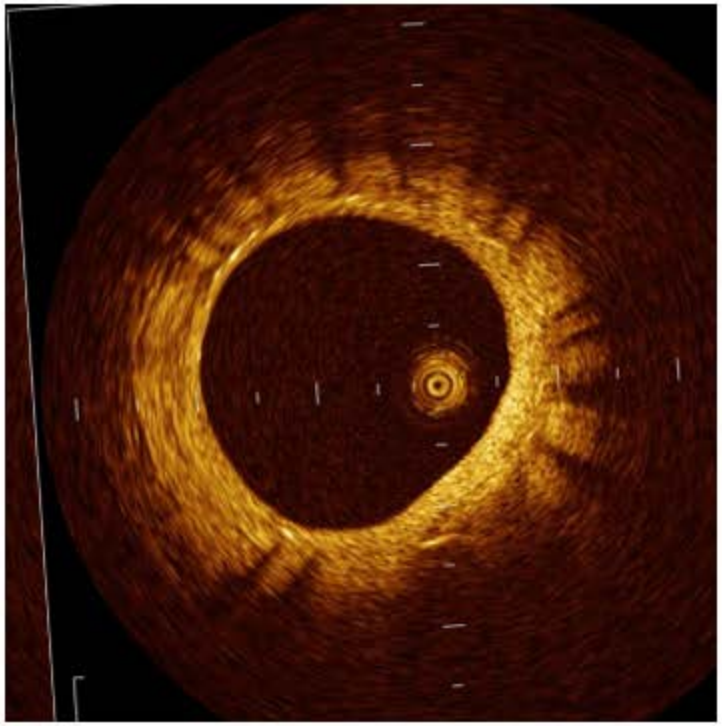
Supplemental Figure S2 (c):

Alterations in peri-strut low intensity area in PES

8 months



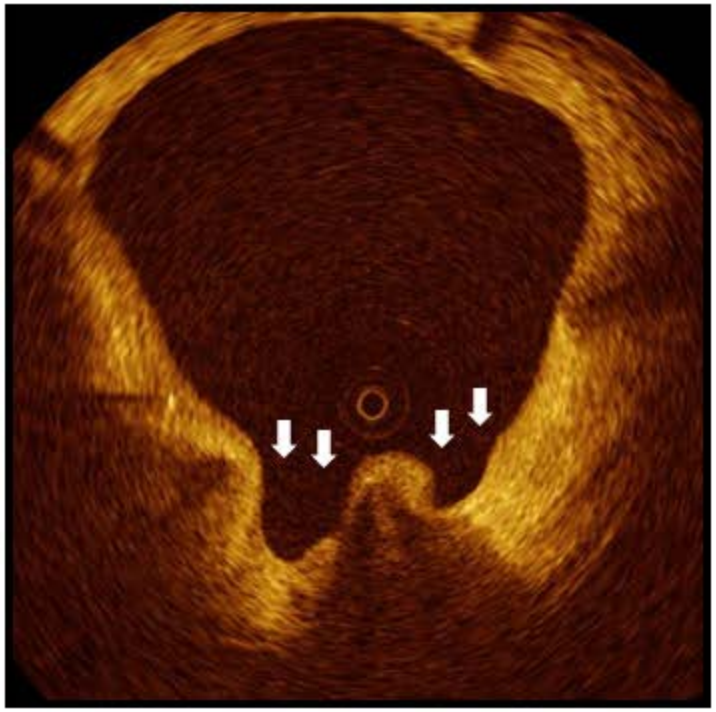
41 months



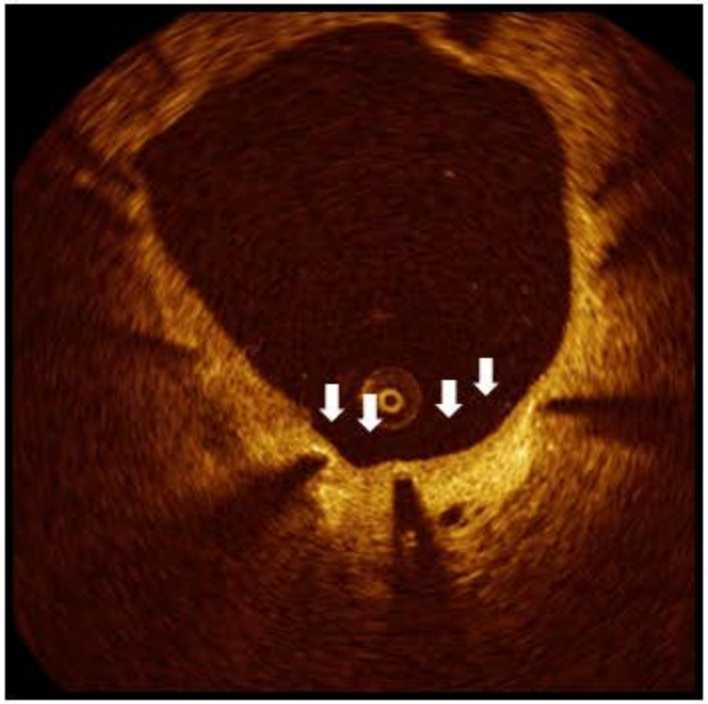
Supplemental Figure S2 (d):

Disappearance of extra-stent lumen in SES

6 months



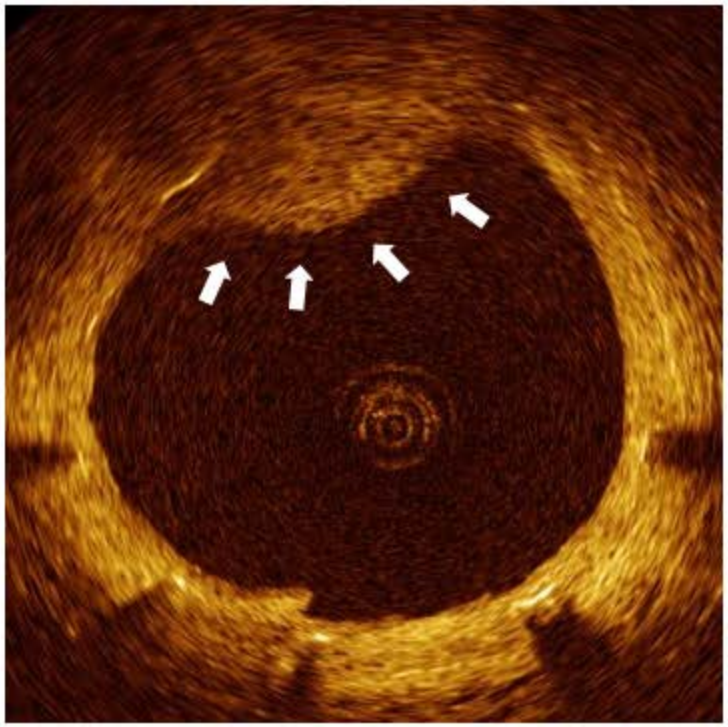
64 months



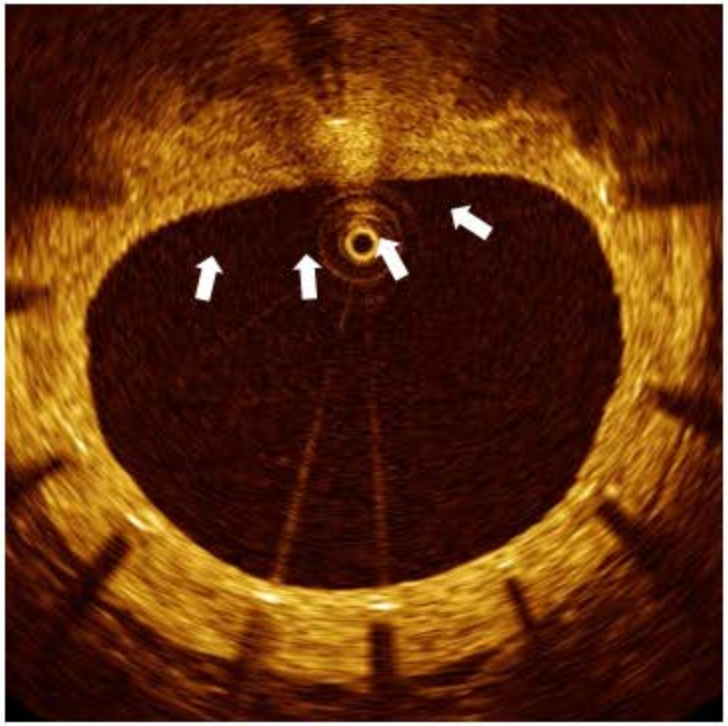
Supplemental Figure S2 (e):

Resolution of intra-stent thrombus in SES

6 months



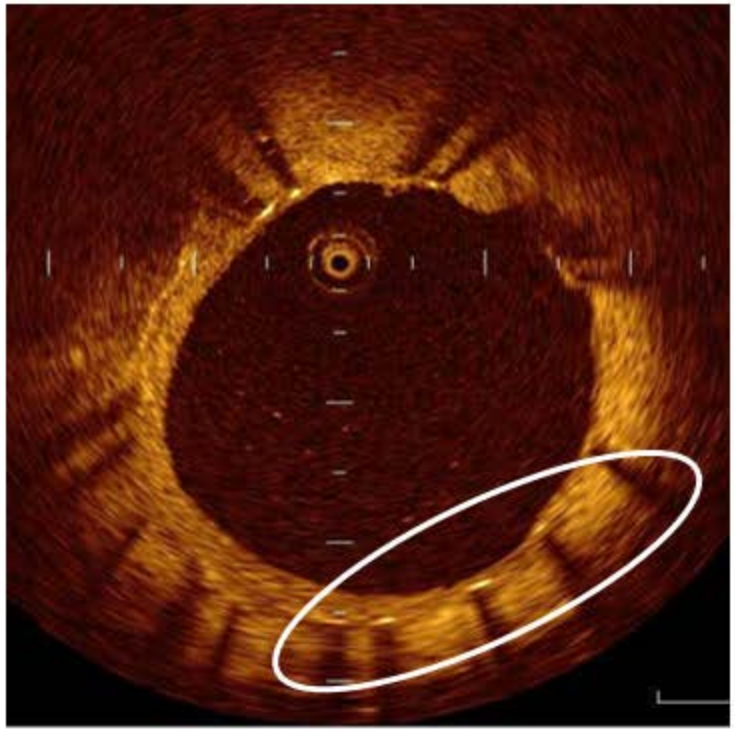
58 months



Supplemental Figure S2 (f):

Formation of atherogenic neointima in PES

7 months



36 months