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Clinical impact of optical coherence tomography findings after drug-coated balloon treatment for patients with acute coronary syndromes

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The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Keywords: acute coronary syndrome, drug-coated balloon, optical coherence tomography, target lesion failure, plaque morphology, thrombus

[1]

[1] Abbreviations

ACS, acute coronary syndrome; CN, calcified nodule; DCB, drug-coated balloon; DES, drug-eluting stent; FA, flow area; LA, lumen area; LRT, large residual thrombus; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PE, plaque erosion; PR, plaque rupture; SRT, small residual thrombus; TA, thrombus area; TB, thrombus burden; TCFA, thin-cap fibroatheroma; TLF, target lesion failure; TV, thrombus volume

Highlights

- DCB is an option for specific lesion subsets in patients with ACS.
- Potential difficulties exist with angiography-based patient and lesion selection.
- Plaque morphology and residual TB may enable risk stratification.
- DCB could be considered an effective treatment for patients with PE.
- Stent implantation may be preferred if the residual TB is large in lesions with PR.

Abstract

Background: Drug-coated balloon (DCB) became a potential treatment option for patients with acute coronary syndrome (ACS); however, factors associated with target lesion failure (TLF) remain uncertain.

Methods: This retrospective, multicentre, observational study included consecutive ACS patients who underwent optical coherence tomography (OCT)-guided DCB treatment. Patients were divided into two groups according to the occurrence of TLF, a composite of cardiac death, target vessel-related myocardial infarction, and ischemia-driven target lesion revascularisation.

Results: We enrolled 127 patients in this study. During the median follow-up period of 562 (IQR: 342–1,164) days, 24 patients (18.9%) experienced TLF, and 103 patients (81.1%) did not. The cumulative 3-year incidence of TLF was 22.0%. The cumulative 3-year incidence of TLF was the lowest in patients with plaque erosion (PE) (7.5%), followed by those with rupture (PR) (26.1%) and calcified nodule (CN) (43.5%). Multivariable Cox regression analysis revealed that plaque morphology was independently associated with TLF on pre-PCI (percutaneous coronary intervention) OCT, and residual thrombus burden (TB) was positively associated with TLF on post-PCI OCT. Further stratification by post-PCI TB revealed a comparable incidence of TLF in patients with PR (4.2%) to that of PE if the culprit lesion had a smaller post-PCI TB than the cut-off value (8.4%). TLF incidence was high in patients with CN, regardless of TB size on post-PCI OCT.

Conclusions: Plaque morphology was strongly associated with TLF for ACS patients after DCB treatment. Residual TB post-PCI might be a key determinant for TLF, especially in patients with PR.

Introduction

New-generation drug-eluting stents (DES) have dramatically reduced the incidence of restenosis. However, coronary stent implantation is accompanied by various risks of intravascular complications, including stent thrombosis and in-stent restenosis [1, 2]. Recently, drug-coated balloons (DCB) have been reported to be non-inferior to stent implantation for small vessel coronary artery disease in chronic coronary syndrome (CCS) [3]. Several studies have shown the usefulness of the DCB strategy in the setting of acute coronary syndrome (ACS) [4, 5]. In addition, recent large-scale registry data has implied a lower risk of definite thrombosis than DES [6]. Considering these findings, DCB could be an alternative treatment option to stent implantation for specific lesion subsets not only in patients with CCS but in those with ACS. Conversely, the previous studies on the efficacy of DCB for patients with ACS showed the difficulty of lesion preparation and bail-out stenting rate were relatively high, even in carefully selected patients [4, 5].

The application of optical coherence tomography (OCT) imaging allows the accurate assessment of culprit lesion morphology and the optimisation of procedural results with its high image resolution [7]. Plaque composition, thrombogenicity, and inflammation may drive different outcomes following percutaneous coronary intervention (PCI) [8, 9]. However, no studies have systematically assessed the factors related to clinical outcomes after DCB treatment for patients with ACS. Therefore, this study aimed to investigate the prognostic risk

factors associated with target lesion failure (TLF) among ACS patients treated with DCB using OCT.

Methods

Study design

This retrospective, multicentre, observational study enrolled consecutive ACS patients who underwent DCB treatment. The inclusion criteria were: (1) patients with ACS who underwent OCT-guided PCI between Jan 2017 and Jan 2021; (2) patients whose culprit lesions were treated with DCB; and (3) patients ≥ 20 years old. Participating institutions, exclusion criteria, and detailed definitions of ACS are described in the Supplemental Material.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Kobe University Hospital. Informed consent was obtained as an opt-out on the Division of Cardiovascular Medicine, Kobe University Graduate School of Medicine website. This study was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000049605).

PCI procedure

In each institution, the DCB strategy was preferentially considered for lesions that achieved optimal lesion preparation after balloon angioplasty or for those deemed unsuitable for stent implantation (Supplemental Material). The information was ascertained from a review of medical records.

OCT image analysis and definitions

We retrospectively collected OCT images obtained before (pre-PCI) and immediately after the index PCI (post-PCI) with a frequency-domain OCT (ILUMIEN, Abbot Vascular, Santa Clara, CA, USA) or OFDI system (LUNAWAVE, Terumo, Tokyo, Japan). The use of thrombus aspiration or pre-dilatation by a less than 2 mm balloon was allowed before the OCT examination at pre-PCI.

Plaque morphology was classified into plaque rupture (PR), plaque erosion (PE), and calcified nodule (CN) according to the previously established criteria (Figure 1A-C) [10]. Intra- or interobserver agreements for PR, PE, and CN were within the acceptable range (intra-observer, kappa = 0.975; inter-observer, kappa = 0.959). Each plaque was classified into one of the following three categories: (1) fibrous plaque, (2) lipid plaque, or (3) calcified plaque [11]. Quantitative analysis was performed to evaluate flow area, lumen area, thrombus area (TA), thrombus volume, and thrombus burden (TB) according to a previously validated method [12]. Briefly, in each OCT frame, lumen area (LA) and flow area (FA) were

measured, and then the thrombus area (TA) was calculated as LA minus FA (Figure 1D). The LA was traced using the proprietary analysis software in the imaging frames where the luminal border was visible in at least three out of four image quadrants. In frames with difficulties in luminal border detection in more than one quadrant, the LA was extrapolated from the nearest proximal or distal frame with a visible lumen contour. Thrombus volume was calculated as the mean TA multiplied by the thrombus length, and TB (%) was calculated as mean TA (mm^2) divided by mean LA (mm^2) × 100%. Inter- and intra-observer agreements for measuring TB on calcified nodules were within the acceptable range (intra-observer, 0.933; inter-observer, 0.891 at pre-PCI; intra-observer, 0.928; inter-observer, 0.862 at post-PCI). A detailed methodology of OCT image analysis is described in the Supplemental Material.

Outcomes

The primary outcome of the study was TLF, which was a composite of cardiac death, target vessel-related myocardial infarction, and ischaemia-driven target lesion revascularisation (TLR). The detailed definitions of outcomes are described in the Supplemental Material. Cardiovascular events were ascertained from a review of medical records and confirmed by direct contact with the patients, their families, or physicians.

Statistical analysis

Categorical variables are presented as numbers (percentages) and were compared with a chi-square test or Fisher's exact test. Continuous variables are expressed as mean±standard deviation (SD) or median (interquartile range [IQR]) and were compared using the Student's t-test or the Mann–Whitney U test based on their distributions. Chi-square or Fisher exact tests for categorical outcomes with more than 2 degrees of freedom were applied for testing overall differences, and post-hoc tests for controlling type 1 error using Bonferroni correction were performed if the overall test was significant. Statistical significance was set at p value < 0.05. If the p value of the overall test was <0.05, then a two-group post-hoc comparison was performed using the Mann–Whitney U test or the independent samples Student's t-test for continuous outcomes, and chi-square or Fisher exact test for categorical outcomes; the test result was considered significant if the p value was <0.017 (i.e., 0.05 of 3). Receiver operating characteristic (ROC) analysis was used to determine the optimal cutoff value of TB at post-PCI associated with TLF. The cumulative incidence of clinical events was estimated by the Kaplan–Meier method, and the differences between groups were assessed with the log-rank test. Cox regression analysis was used to identify independent factors associated with TLF for all the variables evaluated in this study. Variables were adopted in the multivariable analysis if the p values in the univariable analysis were less than 0.15, and the stepwise algorithm was used for variable selection. Age and sex

were also included as variables in the multivariable analysis owing to their clinical relevance and potential confounding effects. Although they did not show a significant association with the dependent variable (p-value < 0.15), their inclusion was important for proper adjustment of important covariates and consideration of potential effect modifiers. We used multiple models if there were significant correlations among adjusted covariables. To assess intraobserver and interobserver variabilities, categorical data were compared using Cohen's kappa coefficient, and Lin's concordance correlation coefficient was used for continuous data. All statistical analyses were performed using the Microsoft R open software version 3.4.1 (R Development Core Team, Vienna, Austria).

Results

Study population

Of 496 ACS patients who underwent OCT-guided PCI from Jan 2017 to Jan 2021, 312 patients were treated with stents, 21 patients with in-stent restenosis or stent thrombosis, 6 patients with shock status, 2 patients with target lesion in a left main coronary artery, 10 patients with missing data, 5 patients with insufficient OCT data quality, and 13 patients with undetermined culprit plaque morphology were excluded. Finally, a total of 127 ACS patients who underwent PCI with DCB were enrolled (Figure 2). The reasons for choosing treatment using a DCB were as follows: 25 lesions (19.7%) with very small vessel coronary disease; 1

patient (0.8%) scheduled for non-cardiac surgery; 59 patients (46.5%) with a high risk of bleeding complications; 23 lesions (16.4%) considered to develop stent fracture easily; and 65 lesions (51.2%) with bifurcation. The remaining 27 lesions (21.3%) were treated with DCB because the operator considered optimal lesion preparation was successfully achieved with balloon dilatation. During the median follow-up period of 562 (IQR: 342–1,164) days, 24 patients (18.9%) experienced TLF, and 103 patients (81.1%) did not. The overall cumulative 3-year incidence of TLF was 22.0%.

Comparison of baseline patient, lesion, and procedural characteristics between TLF and non-TLF groups

The baseline patient, lesion, and procedural characteristics are shown in Table 1. Patients with TLF had a significantly higher prevalence of chronic kidney disease and haemodialysis and had lower estimated Glomerular Filtration Rate (eGFR) levels than those in the non-TLF group. The peak value of CK was significantly higher, and the left ventricular ejection fraction was significantly lower in patients with TLF than those with non-TLF. The two groups had similar rates of patients with high bleeding risk and duration of dual antiplatelet therapy after PCI. Additionally, the location of the culprit lesion was identical between the two groups. The lesions in the TLF group had a numerically higher prevalence of

severe calcification than those in the non-TLF group. All procedural characteristics were comparable between the two groups.

Comparison of pre-PCI OCT findings between TLF and non-TLF groups

Table 2 summarises pre- and post-PCI OCT findings. The plaque morphology of the culprit lesions significantly differed between the two groups (p=0.002). The lesions in the TLF group had a significantly lower prevalence of PE compared with those in the non-TLF group (12.5% vs 47.6%, p=0.002). The prevalence of CN in the TLF group was higher than that in the non-TLF group (33.3% vs 14.6%, p=0.04), but it was not statistically significant. Regarding the qualitative analysis of pre-PCI OCT findings, there were significant differences in the prevalence of lipid, fibrous, and calcified plaques. The lesions with TLF had a significantly higher prevalence of TCFA, macrophage, and cholesterol crystal (TCFA, 54.2% vs 26.2%, p=0.008; macrophage, 75.0% vs 50.5%, p=0.03; cholesterol crystal, 62.5% vs 31.1%, p=0.004). As for the pre-PCI OCT measurements, reference area, minimum FA, and % area stenosis were not different between the two groups. Regarding thrombus analysis at pre-PCI, mean TA, TB and TV tended to be higher in the TLF group; however, there was no statistically significant difference between the two groups (mean TA, 0.40 [0.10–1.42] vs 0.21 [0–0.58], p=0.06; TB, 15.53 [3.01–30.39] vs 8.03 [0–17.18], p=0.07; TV, 2.45 [0.27–65.16] vs 0.98 [0–3.68], p=0.08) (Table 2).

Comparison of post-PCI OCT findings between TLF and non-TLF groups

Table 2 also shows post-PCI OCT findings. Minimum FA and acute FA gain were not significantly different, whereas % area stenosis was significantly higher in the TLF group. Mean TA, TB, and TV were significantly higher in the TLF group than in the non-TLF group (mean TA, 0.43 [0.28–0.92] vs 0.15 [0–0.40], p<0.001; TB, 9.23 [4.85–18.89] vs 3.6 [0–9.14], p<0.001; TV, 2.3 [0.38–9.87] vs 0.67 [0–1.90], p=0.0014, p<0.001). Additionally, in the TLR group compared with the non-TLR group, there was a smaller reduction of TB during the PCI procedure (23.9 [0–44.6] vs 57.8 [25.9–78.8], p=0.02). The prevalence and severity of dissections after PCI were comparable between the two groups.

The post-PCI OCT findings according to plaque morphology are shown in Supplemental Table 1. The residual TB at post-PCI was highest in patients with PR among the three groups.

Factors associated with TLF

Clinical outcomes during a median follow-up period of 562 (IQR: 342-1164) days are summarised in Table 3. The results of the univariable and multivariable Cox regression analysis for patient and lesion characteristics, pre-PCI OCT findings, and post-PCI OCT findings associated with TLF are summarised in Table 4. The multivariable patient and lesion characteristics model showed that there were no variables significantly associated with TLF.

At Cox regression analysis of pre-PCI OCT findings, the univariate analysis showed that plaque morphology (p=0.020), TCFA (HR: 2.86, 95%CI: 1.28–6.39, p=0.01), macrophage (HR: 2.77, 95%CI: 1.10–6.99, p=0.03), cholesterol crystal (HR: 3.43, 95%CI: 1.50–7.85, p=0.04), lipid index (HR: 1.02, 95%CI: 0.99–1.05, p=0.10), and TB (HR: 1.02, 95%CI: 1.02–1.04, p=0.048) were positively associated with TLF. Additionally, the multivariable pre-PCI OCT findings model showed that plaque morphology was an independent predictor of TLF (p<0.001). Specifically, compared to PR, PE was associated with a lower risk of TLF (HR: 0.46, 95%CI: 0.11-0.87, p=0.025), and CN was associated with a higher risk of TLF (HR: 4.27, 95%CI: 1.02-17.8, p=0.038). At pre-PCI OCT findings, minimum FA, calcification measurements, and thrombus measurements were not independently associated with TLF. The Kaplan–Meier curve demonstrated that the cumulative 3-year incidence of TLF in patients with PE was significantly lower than those with PR (7.5% vs 26.1%, HR: 4.85, 95%CI: 1.38–17.04, p=0.01) or CN (7.5% vs 43.5%, HR: 6.40, 95%CI: 1.70–24.1, p=0.006) (Figure 3A).

In the Cox regression analysis of post-PCI OCT findings, the multivariable analysis (post-PCI OCT findings model) showed that TB (HR: 1.08, 95%CI: 1.04–1.12, p<0.001) was independently associated with TLF, and % area stenosis (HR: 1.17, 95%CI: 0.998–1.37, p=0.053) tended to be related to TLF, but was not statistically significant. ROC analysis of TB at post-PCI showed that the cutoff value of this parameter for identifying patients with

189 subsequent TLF was 8.4% (sensitivity, 70.8%, specificity, 68%; area under the curve, 0.72,
190 95% CI: 0.60–0.84).
191 According to this cutoff value, each patient group based on the plaque morphology
192 of culprit lesions was further divided into large (LRT: TB at post-PCI > 8.4%) or small (SRT:
193 TB at post-PCI ≤ 8.4%) residual thrombus groups. The incidence of TLF in patients with PR
194 with LRT, PR with SRT, PE with LRT, PE with SRT, CN with LRT, and CN with SRT was
195 46.2%, 3.9%, 5.9%, 5.7%, 50%, and 29.4%, respectively. In-hospital TLR was required in
196 three out of 26 (11.5%) PR patients with LRT, whereas in one out of 101 (1.0%) remaining
197 patients (Supplemental Table 2). In the analysis for Supplemental Table 3, each comparison
198 was performed for each category of the variable, using PE with SRT, PR with SRT, or CN
199 with SRT as the reference category. The Kaplan–Meier curve with log-rank analysis
200 demonstrated that the cumulative 3-year incidence of TLF in patients with PR with LRT, CN
201 with LRT, and CN with SRT was significantly higher than that in those with PE with SRT
202 (47.9% vs 9.0%, HR: 10.52, 95%CI: 2.35–47.08, p=0.0021, 58.3% vs 9.0%, HR: 8.42,
203 95%CI: 1.40–50.43, p=0.020, 33.9% vs 9.0%, HR: 5.44, 95%CI: 1.06–28.04, p=0.043,
204 respectively). In contrast, the cumulative 3-year incidence of TLF in patients with PR with
205 SRT and PE with LRT was comparable with that in those with PE with SRT (4.2% vs 9.0%,
206 HR: 0.63, 95%CI: 0.057-6.94, p=0.71; 5.9% vs 9.0%, HR: 0.94, 95%CI: 0.085-10.37,
207 p=0.96, respectively). The cumulative 3-year incidence of TLF in patients with CN with LRT,

CN with SRT, and PR with LRT was significantly higher than that in those with PR with SRT (58.3% vs 4.2%, HR: 13.39, 95%CI: 1.39-128.8, p=0.03; 33.9% vs 4.2%, HR: 8.66, 95%CI: 1.01-74.1, p=0.04; 47.9% vs 4.2%, HR: 16.74, 95%CI: 2.17-129.0, p=0.007, respectively). Conversely, those with PE with LRT and PE with SRT were comparable with those with PR with SRT (5.9% vs 4.2%, HR: 1.49, 95%CI: 0.09-23.9, p=0.78; 9.0% vs 4.2%, HR: 1.59, 95%CI: 0.14-17.6, p=0.71, respectively). The cumulative 3-year incidence of TLF in patients with CN and LRT was comparable to that in patients with CN and SRT (58.3% vs 33.9%, HR: 1.55, 95%CI: 0.37–6.48, p=0.55) (Figure 3B, Supplemental Table 3). Representative cases are described in Figure 4.

Discussion

To the best of our knowledge, this is the first study evaluating factors associated with TLF after DCB treatment for patients with ACS using OCT. The main findings of the current study can be summarised as follows: (1) overall, 3-year cumulative incidence of TLF in patients with ACS after DCB treatment was 22.0%; (2) regarding pre-PCI OCT findings, plaque morphology was an independent predictor of TLF. Specifically, compared to PR, PE was associated with a lower risk of TLF, and CN was associated with a higher risk of TLF; (3) regarding post-PCI OCT findings, residual TB after DCB treatment was independently associated with TLF; (4) the overall incidence of TLF was significantly lower in patients with

PE than in those with PR and CN. However, when further stratified by post-PCI TB, the incidence of TLF in patients with PR was comparable to that of PE if the culprit lesion had a smaller TB than the cutoff value (8.4%). Conversely, the incidence of TLF was high in patients with CN regardless of the size of the TB. These findings indicate the potential implication of detailed OCT assessment at pre- and post-PCI for the risk stratification of ACS patients undergoing DCB treatment.

Mangner et al. reported the clinical outcome of ACS patients with small vessel coronary artery disease treated with DCB versus DES [13]. They reported that, at 3 years, there was no difference in the incidence of TVR between ACS patients treated with DCB and those with DES (10.1% and 8.4%, respectively). The REVELATION trial was a prospective randomised trial comparing DCB with DES for STEMI patients with large coronary artery disease [4]. They reported that DCB showed no significant difference in late lumen loss, and TLR rate at 9 month was as low as 3% (2 out of 58 patients). Considering these data, DCB could be an alternative treatment option to stent implantation for specific lesion subsets in patients with ACS. However, the REVELATION trial applied strict inclusion criteria that the subjects were registered only if the residual stenosis was <50% after thrombus aspiration or balloon pre-dilatation. Another study (PEPCAD NSTEMI trial) investigating the efficacy of DCB compared with coronary stents in the setting of NSTEMI included only patients who had small thrombus on angiography and excluded patients with large angiographical

246 thrombus [5]. However, despite such strict inclusion criteria, the bail-out stenting rate of
247 these trials was relatively high; 18.3% (11 out of 60 patients) and 15.4% (19 out of 123
248 patients) for the REVELATION and PEPCAD NSTEMI trials, respectively. Considering the
249 bail-out stenting rate of around 5% in previous studies that mainly enrolled patients with CCS
250 [3], these data indicate potential difficulties of the angiography-based patient and lesion
251 selection for the effective treatment with DCB-only strategy in ACS patients. However, no
252 study has directly assessed the risk factors associated with a worse prognosis among ACS
253 patients after DCB treatment. Thus, we investigated prognostic factors independently
254 associated with subsequent TLF among ACS patients after DCB treatment.
255 In the present study, we tried to evaluate the qualitative and quantitative
256 characteristics of ACS culprit lesions for a more accurate risk stratification. For this purpose,
257 we applied OCT evaluation for culprit plaque morphology and residual TB. Patient and lesion
258 characteristics were not associated with TLF; however, plaque morphology at pre-OCT was
259 independently associated with TLF. Recently, several studies have indicated the potential
260 utility of intravascular imaging to determine potential lesion subsets that could be effectively
261 treated with anti-thrombotic therapy without stenting. Jia et al. demonstrated the feasibility of
262 adopting anti-thrombotic therapy without stenting for STEMI patients caused by PE [14].
263 However, the EROSION study included only patients who had ACS culprit lesions with mild
264 to moderate stenosis (%DS<70%) after thrombus aspiration. Among 103 patients diagnosed

265 as PE, 32 patients (31% of patients with PE) were excluded because of the presence of >70%
266 of stenosis. Additionally, balloon angioplasty was not permitted before and after the
267 enrollment; instead, aggressive anti-thrombotic therapy was required with over 60% of use of
268 glycoprotein IIb/IIIa inhibitor and 100% of dual antiplatelet therapy with aspirin and
269 Ticagrelor. On the other hand, a higher degree of percentage of area stenosis was associated
270 with worse clinical outcome [15]. Since many of ACS culprit lesions have >70% of stenosis
271 after thrombus aspiration and increased risk of bleeding in the real-world ACS population, we
272 considered the need for data on the safety and the efficacy of DCB treatment followed by
273 standard dual antiplatelet therapy (aspirin plus clopidogrel or prasugrel) in a real-world
274 patient database. In the current study, 15.7% of patients who underwent DCB treatment for
275 ACS required TVR. This finding aligns with a previous study where 10.1% of ACS patients
276 underwent TVR following DCB treatment. However, it is worth noting that the prevalence of
277 ST-elevated myocardial infarction was 44.1% in the present study compared to 7% in the
278 previous study [13]. Additionally, we found that patients with PE had a feasible clinical
279 outcome after DCB treatment in the real-world ACS population, while those with CN had a
280 worse clinical outcome. The previous studies investigating clinical outcomes of DES strategy
281 for PR, PE, and CN patients showed the incidence of TLF was 7%, 12%, and 38% at 3 years,
282 respectively [8, 16]. While direct comparisons between the clinical outcomes of the DCB
283 strategy in the present study and those of DES in the previous study should not be made, it is

worth noting that the clinical outcomes of DCB treatment for patients with PE and CN (with incidences of TLF at 5.8% and 34.8%, respectively) appeared to be similar to those of DES. However, the clinical outcome of DCB treatment for patients with PR (with an incidence of TLF at 25%) appeared to be worse than that of DES in the previous study.

To benefit the most from DCB, the infiltration of paclitaxel released from the DCB is essential. Although multiple factors have been reported to affect its infiltration, plaque component and physical barrier are currently considered two major components. Previous studies demonstrated that the deposition of paclitaxel in the human aorta is inversely proportional to the lipid content. The lipid content in atherosclerotic plaques weakens the effectiveness of lipophilic drugs. In the present study, TCFA was more frequent and lipid index tended to be larger in lesions with TLF. Conversely, the extracellular matrix, which is abundant in PE plays a crucial role in the distribution and retention of lipophilic drugs. Because drugs bind to histone proteins for transmembrane transportation, these proteins can promote drug delivery and retention [17]. Regarding calcified plaque, Fanelli et al. found that DCBs were ineffective in lesions with severe calcification, and corresponding tests proposed that calcium inhibited drug absorption [18]. Considering different characteristics of plaque components among plaque morphology, lesions with PE might respond better to DCB than those with PR and CN.

Another important factor of prognosis after DCB treatment for ACS patients was different physical barrier by thrombus and different thrombogenicity according to lesion morphology. In a previous experimental study, thrombus positioned between stent and vessel wall could decrease diffusion, retention, and uptake of drug, inhibiting effective drug delivery to the vessel wall [19]. Therefore, a reduced or inhomogeneous drug distribution could occur after DCB treatment for thrombus-rich lesions. Indeed, in the current study, residual TB at post-OCT and not at pre-OCT was strongly related with TLF. Interestingly, in patients with PR, residual TB after PCI stratified the future risk of TLF, while PE had a low incidence and CN had a high incidence of TLF regardless of residual TB. In general, a ruptured site releases highly thrombogenic substrates such as lipid and tissue factors [20]. Conversely, eroded plaques do not contain a large necrotic core but exhibit a proteoglycan-rich matrix and smooth muscle cells, which have less tissue factor and inflammation, resulting in lower local thrombogenicity [20]. We currently speculate that such a difference in local thrombogenicity between lesions with PR and those with PE might affect the extent of residual thrombus, its time course afterwards, and different outcomes after DCB treatment. In the EROSION study, anti-thrombotic therapy decreased most of the residual thrombus in PE during the initial 1 month [14]. We found that lesions with PE had a favourable prognosis regardless of the extent of the residual thrombus. These data may indicate that the residual thrombus in lesions with PE might follow a relatively favourable time course regardless of its volume in patients

with ACS. On the other hand, PR had high thrombogenicity, which may induce progressive thrombus development after the DCB treatment [20]. Large residual thrombus could decrease FA, and disturbance of blood flow caused by luminal narrowing might induce further thrombus development, especially in lesions with PR [21]. Considering that in-hospital TLR was required in 3 out of 26 (11.5%) PR patients with LRT, whereas 1 out of 101 (1.0%) in the remaining patients, stent implantation might be preferred if residual thrombus volume after PCI is large, especially in lesions with PR.

Limitations

First, as a retrospective study, our results are subject to selection bias. More specifically, the registry included only those patients who could complete their treatment only with DCB according to the operator's discretion. Therefore, the issue of selection bias cannot be avoided. Second, there was a lack of pathological assessment; we identified some OCT features associated with TLF; however, we could not reveal what the OCT features indicated pathologically. Especially the signal attenuation caused by a large red thrombus can potentially mask the vessel wall, obstructing thrombus measurements. However, OCT is the ideal modality to evaluate intracoronary thrombus *in vivo*. We used a previously published method for these cases, which showed adequate feasibility and reproducibility [12].

Conclusion

Plaque morphology at pre-PCI OCT was strongly associated with TLF for ACS patients after DCB treatment. Additionally, post-PCI residual TB might be an important factor, especially in patients with PR. Detailed OCT assessment at pre- and post-PCI may have implications for the risk stratification of ACS patients undergoing DCB treatment.

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Ethics approval and informed consent: The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Kobe University Hospital. Informed consent was obtained as an opt-out on the Division of Cardiovascular Medicine, Kobe University Graduate School of Medicine website. This study was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000049605).

Data statement:

The data that support the findings of this study are available from the corresponding author, HO, upon reasonable request.

359

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Figure legends

Figure 1: Representative OCT images of plaque morphology and assessment method of LA, FA, and TA

A) Plaque rupture, B) Plaque erosion, C) Calcified nodule, D) Assessment method of LA, FA, and TA: TB=8.4 (%). FA, flow area; LA, lumen area; OCT, optical coherence tomography; TA, thrombus area; TB, thrombus burden

Figure 2: Study flowchart

ACS, acute coronary syndrome; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; DCB, drug-coated balloon, TLF: target lesion failure

Figure 3: Kaplan–Meier curves for the cumulative incidence of TLF

A) Kaplan–Meier curves stratified by culprit plaque morphology; B) Kaplan–Meier curves stratified by culprit plaque morphology and residual TB after PCI.

CI, confidence interval; CN, calcified nodule**;** HR, hazard ratio; LRT, large residual thrombus; PE, plaque erosion; PCI, percutaneous coronary intervention; PR, plaque rupture; SRT, small residual thrombus; TLF, target lesion failure; TB, thrombus burden

Figure 4: Representative cases

A) A representative case of PE

A 49-year-old woman presented with STEMI.

1) Baseline CAG showed a total occlusion in the proximal LAD. OCT images (a-c) indicated PE with thrombus. 2) CAG showed a 30% stenosis after PCI, and OCT images (a–c) showed a large residual thrombus after DCB (white arrowhead). The residual TB was 10.1%. 3) Twelve months later, CAG and OCT images (a–c) showed no significant stenosis without thrombus. The minimal FA increased from 4.6 to 5.1 mm^2.

B) A representative case of PR with SRT

An 89-year-old man presented with STEMI.

1) Baseline CAG showed severe stenosis in the middle LAD. OCT images (a-c) indicated PR with thrombus. *Indicates PR. 2) After PCI with DCB, CAG showed no significant stenosis, and OCT images (a–c) showed a small residual thrombus (white arrowhead). The residual TB was 1.3%. 3) Twelve months later, CAG and OCT images (a–c) showed no significant stenosis without thrombus. The minimal FA increased from 3.6 to 5.3 mm^2.

C) A representative case of PR with LRT

A 59-year-old man presented with STEMI.

1) Baseline CAG showed a total occlusion in the middle RCA. OCT images (a-c) indicated PR with thrombus. *Indicates PR. 2) After PCI with DCB, CAG showed a 30% stenosis, and

OCT images (a–c) showed a large residual thrombus (white arrowhead). The residual TB is 15.4%. 3) Six months later, the patient had effort-related chest pain. CAG and OCT showed severe stenosis at the lesion previously treated with DCB. The minimal FA decreased from 3.1 to 0.7 mm^2.

CAG, coronary angiography; DCB, drug-coated balloon; LAD, left anterior descending artery; LRT, large residual thrombus; OCT, optical coherence tomography; PE, plaque erosion; PR, plaque rupture; RCA, right coronary artery; SRT, small residual thrombus; STEMI, ST-segment elevation myocardial infarction

515 **Table 1. Baseline patient, lesion and procedural characteristics**

Variable	All lesions (n=127)	TLF (n=24)	non-TLF (n=103)	P value
Median follow-up period	562 (342–1,164)	101 (229–340.75)	727 (456–1,206)	<0.001
Baseline patient characteristics				
Age (yr.)	69.0±12.4	69.0±9.2	69.0±13.0	0.99
Sex male, n (%)	92 (72.4%)	19 (79.2%)	73 (70.9%)	0.42
Hypertension, n (%)	90 (70.9%)	19 (79.2%)	71 (68.9%)	0.32
Dyslipidemia, n (%)	81 (63.8%)	15 (62.5%)	66 (64.1%)	0.89
Diabetes Mellitus, n (%)	61 (48.0%)	15 (62.5%)	46 (44.7%)	0.12
Current smoker, n (%)	39 (31.5%)	6 (25.0%)	33 (33%)	0.45
Prior PCI, n (%)	17 (13.4%)	4 (16.7%)	13 (12.6%)	0.60
Chronic Kidney Disease, n (%)	58 (45.7%)	16 (66.7%)	42 (40.8%)	0.02
Haemodialysis, n (%)	11 (8.7%)	5 (20.8%)	6 (5.8%)	0.02
LVEF (%)	55.0±7.4	49.3±14.4	56.9±10.3	0.004
High bleeding risk, n (%)	59 (46.5%)	10 (41.7%)	49 (47.6%)	0.66
Clinical presentation				0.67
uAP, n (%)	25 (19.7%)	3 (12.5%)	22 (21.4%)	
NSEMI, n (%)	46 (36.2%)	9 (37.5%)	37 (35.9%)	
STEMI, n (%)	56 (44.1%)	12 (50.0%)	44 (42.7%)	
Laboratory data				
estimated GFR, ml/min/1.73 m^2	59.1±23.6	51.3±28.2	60.9±22.0	0.07
LDL level, mg/dl	112.1±36.1	96.1±34.3	116.1±35.4	0.13
HbA1c, %	6.7±3.8	6.5±1.2	6.7±4.1	0.74
Peak CK, IU/L	372 (153.5–1,207.3)	1092 (200.3–1,997.5)	324 (142–935.3)	0.03

Medications at discharge				
Statin, n (%)	117 (92.1%)	21 (87.5%)	96 (93.2%)	0.40
Type of antiplatelet				0.68
Clopidogrel, n (%)	9 (7.1%)	2 (8.3%)	7 (6.8%)	
Prasugrel, n (%)	118 (92.9%)	22 (91.7%)	96 (93.2%)	
Duration of DAPT, months	5.24±2.79	5.75±3.75	5.13±2.53	0.33
Baseline lesion characteristics				
Target vessel: LAD/ LCX/ RCA, %	41.7/ 28.3/ 29.9	37.5/ 20.8/ 41.7	42.7/ 30.1/ 27.2	0.39
Lesion location: Proximal/ mid/ distal, %	37.0/ 35.4/ 27.6	45.8/ 25.0/29.2	35.0/ 37.9/ 27.2	0.45
Calcification, n (%)	42 (33.1%)	12 (50.0%)	30 (29.1%)	0.051
Bifurcation, n (%)	65 (51.2%)	12 (50.0%)	53 (51.5%)	0.90
Multivessel disease, n (%)	55 (43.3%)	12 (50.0%)	43 (41.7%)	0.47
Pre-TIMI flow grade 0/1, n (%)	46 (36.2%)	10 (41.7%)	36 (35.0%)	0.54
Post-TIMI flow grade 3, n (%)	127 (100%)	24 (100%)	103 (100%)	1.0
Procedural characteristics				
Thrombectomy, n (%)	40 (31.5%)	10 (41.7%)	30 (29.1%)	0.24
Rotational atherectomy, n (%)	15 (11.8%)	5 (20.8%)	10 (9.7%)	0.13
Orbital atherectomy, n (%)	6 (4.8%)	1 (4.2%)	5 (4.9%)	0.88
Pre-dilatation balloon diameter, mm	2.62±0.60	2.57±0.74	2.63±0.56	0.64
Pre-dilation balloon maximum pressure, atm	11.6±5.90	10.4±5.76	11.8±5.85	0.41
DCB diameter, mm	2.76±0.45	2.80±0.52	2.76±0.44	0.69
DCB length, mm	25.2±11.7	22.3±6.31	25.9±12.5	0.18
DCB inflation pressure, atm	7.7±2.8	8.07±2.26	7.65±2.90	0.61

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Values are expressed as average±standard deviation, median (25th, 75th percentiles) or n (%)

PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; uAP, unstable angina pectoris; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; GFR, Glomerular Filtration Rate; LDL, low-density lipoprotein; CK, creatinine kinase; DAPT, dual antiplatelet therapy; TIMI, Thrombolysis in Myocardial Infarction; DCB, drug-coated balloon

525 **Table 2. OCT findings**

Variables	All lesions (n=127)	TLF (n=24)	non-TLF (n=103)	P value
Pre-PCI OCT findings				
Plaque morphology				0.002
Plaque rupture, n (%)	52 (40.9%)	13 (54.2%)	39 (37.9%)	
Plaque erosion, n (%)	52 (40.9%)	3 (12.5%)	49 (47.6%)	
Calcified nodule, n (%)	23 (18.1%)	8 (33.3%)	15 (14.6%)	
Qualitative analysis				
Plaque characteristics				0.003
Fibrous plaque, n (%)	32 (25.2%)	1 (4.2%)	31 (30.1%)	
Lipid plaque, n (%)	75 (59.1%)	15 (62.5%)	60 (58.3%)	
Calcified plaque, n (%)	20 (15.7%)	8 (33.3%)	12 (11.7%)	
TCFA, n (%)	40 (31.5%)	13 (54.2%)	27 (26.2%)	0.008
Macrophage, n (%)	70 (55.1%)	18 (75.0%)	52 (50.5%)	0.03
Cholesterol crystal, n (%)	47 (37.0%)	15 (62.5%)	32 (31.1%)	0.004
Microchannels, n (%)	24 (19.0%)	5 (20.8%)	19 (18.5%)	0.79
Thrombus, n (%)	98 (77.2%)	21 (87.5%)	77 (74.8%)	0.18
Quantitative analysis				
Reference area, mm^2	4.99 ± 2.18	5.55 ± 2.22	4.89 ± 2.14	0.17
Minimal flow area, mm^2	1.16 ± 0.66	1.21 ± 0.57	1.15 ± 0.68	0.73
% area stenosis, %	73.6 ± 15.2	75.6 ± 11.9	73.2 ± 15.9	0.48
Lipid index	1228.6 ± 1410.4	1679.1 ± 1532.2	1126.1 ± 1360.5	0.09
Maximum calcium thickness, μm	448.7 ± 650.0	656.8 ± 753.7	403.4 ± 616.3	0.10
Maximum calcium arc, degree, °	71.9 ± 109.3	102.3 ± 124.4	65.2 ± 104.4	0.15
Calcium length, mm	2.73 ± 5.09	4.45 ± 5.40	2.35 ± 4.94	0.12
Mean thrombus area, mm^2	0.23 (0–0.63)	0.40 (0.10–1.42)	0.21 (0–0.58)	0.06
Thrombus burden, %	8.5 (0–22.2)	15.53 (3.01–30.39)	8.03 (0–17.18)	0.07
Thrombus volume, mm^3	1.04 (0–4.34)	2.45 (0.27–65.16)	0.98 (0–3.68)	0.08

Post-PCI OCT findings				
Minimal flow area, mm^2	3.56 ± 1.20	3.34 ± 0.96	3.61 ± 1.24	0.35
% area stenosis, %	33.3 ± 17.3	43.1 ± 18.5	31.1 ± 16.2	0.003
Acute flow area gain, mm^2	2.40 ± 1.26	2.47 ± 1.32	2.11 ± 0.91	0.23
Mean thrombus area, mm^2	0.22 (0–0.47)	0.43 (0.28–0.92)	0.15 (0–0.40)	<0.001
Thrombus burden, %	4.5 (0–22.2)	9.23 (4.85–18.89)	3.60 (0–9.14)	<0.001
Thrombus volume, mm^3	0.88 (0–2.74)	2.30 (0.38–9.87)	0.67 (0–1.90)	0.001
Reduction of thrombus burden*, %	52.1 (3.8–75.3)	33.8 (0–44.6)	57.8 (25.9–78.8)	0.02
Dissection (intimal, medial), n (%)	48 (10, 38) (37.8%)	9 (2, 7) (37.5%)	39 (8, 31) (37.9%)	1.0
Length of the dissection, mm	2.14 ± 3.37	2.25 ± 4.59	1.92 ± 2.92	0.67
Maximal arc of the dissection, °	39.6 ± 61.4	33.8 ± 62.2	37.2 ± 59.4	0.81
Linear rim of tissue with a width >200 μm, n (%)	28 (58.3%)	4 (44.4%)	24 (61.5%)	0.46
Hematoma, n (%)	6 (4.7%)	1 (4.2%)	5 (4.9%)	0.92

Values are expressed as average±standard deviation, median (25th, 75th percentiles) or n (%)

* Reduction of thrombus burden was calculated for 98 lesions (21 lesions in the TLF group and 77 lesions in the non-TLF group).

PCI, percutaneous coronary intervention; OCT, optical coherence tomography; PR, plaque rupture; PE, plaque erosion; CN, calcified nodule; TCFA, thin cap fibroatheroma

Table 3. Clinical outcomes

Variable	No. of patients (%)
Cardiac death, n, (%)	4 (3.2%)
Target vessel MI, n, (%)	2 (1.6%)
Target lesion revascularisation, n, (%)	19 (15.0%)
Target lesion revascularisation in hospital, n, (%)	4 (3.1%)
Target lesion failure, n, (%)	24 (18.9%)

Values are expressed as n (%)

MI, myocardial infarction

Table 4. Uni- and Multivariable Cox regression analysis of patient and lesion characteristics, pre-PCI OCT findings and post-PCI OCT findings associated with TLF

variable	Univariate, HR (95%CI)	P value	Multivariable model 1		Multivariable model 2	
			HR (95%CI)	P value	HR (95%CI)	P value
Patient and lesion characteristics models						
Age	1.01 (0.97–1.03)	0.96	1.01 (0.97–1.05)	0.79	0.99 (0.96–1.04)	0.86
Sex male	1.60 (0.60–4.28)	0.35	1.76 (0.57–5.42)	0.32	1.75 (0.58–5.26)	0.32
Diabetes Mellitus	1.85 (0.81–4.22)	0.15	1.21 (0.49–2.99)	0.68	1.24 (0.50–3.08)	0.64
Chronic Kidney Dysfunction	2.67 (1.14–6.24)	0.02			1.85 (0.69–4.93)	0.22
Haemodialysis	3.02 (1.12–8.13)	0.03	1.96 (0.58–6.57)	0.28		
LVEF (per 5%)	0.78 (0.66–0.93)	0.0051	0.90 (0.72–1.12)	0.35	0.86 (0.71–1.05)	0.13
Calcification	2.03 (0.91–4.51)	0.08	1.50 (0.57–3.95)	0.42	1.79 (0.73–4.38)	0.20
Pre-PCI OCT findings models			**Multivariable model 3**			
Plaque morphology (reference: PR)	-	0.020	-	<0.001		
PE	(0.21 [0.06–0.72])	(0.014)	(0.46 [0.11–0.87])	(0.025)		
CN	(1.32 [0.55–3.18])	(0.54)	(4.27 [1.02–17.8])	(0.038)		
TCFA	2.86 (1.28–6.39)	0.010	2.21 (0.68–8.27)	0.17		
Macrophage	2.77 (1.10–6.99)	0.03	1.47 (0.42–3.87)	0.46		
Cholesterol crystal	3.43 (1.50–7.85)	0.004	2.51 (0.86–8.32)	0.14		
Lipid index (per 100)	1.02 (0.99–1.05)	0.10	1.03 (0.99–1.03)	0.18		
Minimum flow area	1.02 (0.58–1.80)	0.94				
% area stenosis (per 5 %)	1.012 (0.98–1.04)	0.41				
Reference vessel area	1.12 (0.95–1.33)	0.19				
Thrombus burden (per 1%)	1.02 (1.02–1.04)	0.048	1.02 (0.99–1.05)	0.15		
Post-PCI OCT findings models			**Multivariable model 4**			
Minimum flow area	0.84 (0.58–1.21)	0.35				
% area stenosis (per 5 %)	1.21 (1.07–1.37)	0.002	1.17 (0.998–1.37)	0.053		

Reference vessel area	1.16 (0.97–1.39)	0.11	1.10 (0.857–1.42)	0.45		
Thrombus burden (per 1%)	1.09 (1.053–1.13)	<0.001	1.08 (1.042–1.12)	<0.001		
Reduction of thrombus burden, % (per 10)	0.97 (0.938–1.00)	0.06	0.99 (0.96–1.03)	0.70		

Multivariable model 1 was adjusted for age, sex, diabetes mellitus, haemodialysis, LVEF, and calcification. Multivariate model 2 was adjusted for age, sex, diabetes mellitus, chronic kidney disease, LVEF and calcification. Multivariate model 3 was adjusted for plaque morphology, TCFA, macrophages, cholesterol crystals, lipid index, and thrombus burden at pre-PCI OCT. Multivariate model 4 was adjusted for % area stenosis, reference vessel area, thrombus burden, and reduction of thrombus burden on post-PCI OCT. PCI, percutaneous coronary intervention; OCT, optical coherence tomography; TLF, target lesion failure; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; CK, creatine kinase; PR, plaque rupture; CN, calcified nodule; PE, plaque erosion; TCFA, thin cap fibroatheroma

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Figure 1: Representative OCT images of plaque morphology and assessment method of LA, FA, and TA on OCT image.

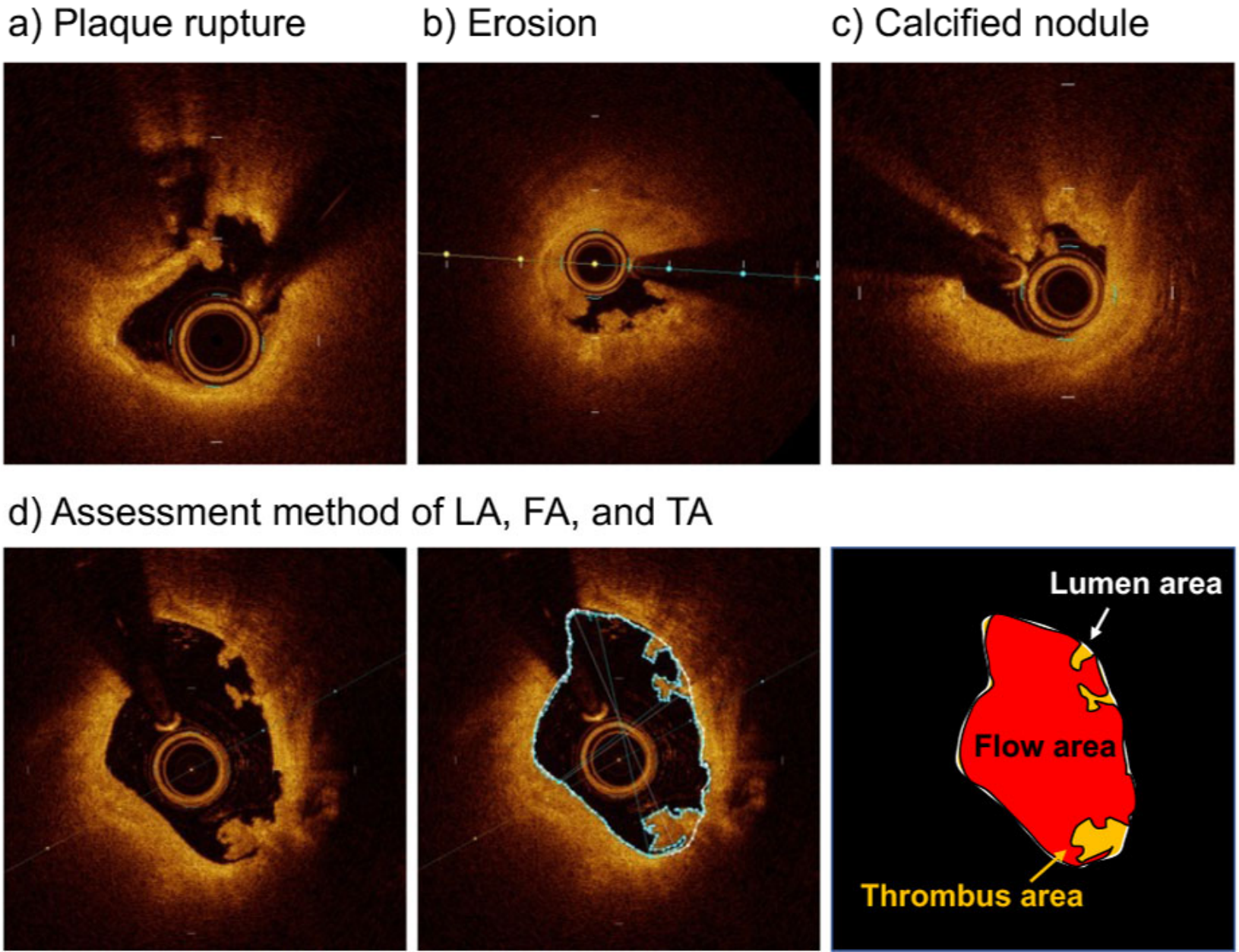


Figure 2: Study flowchart

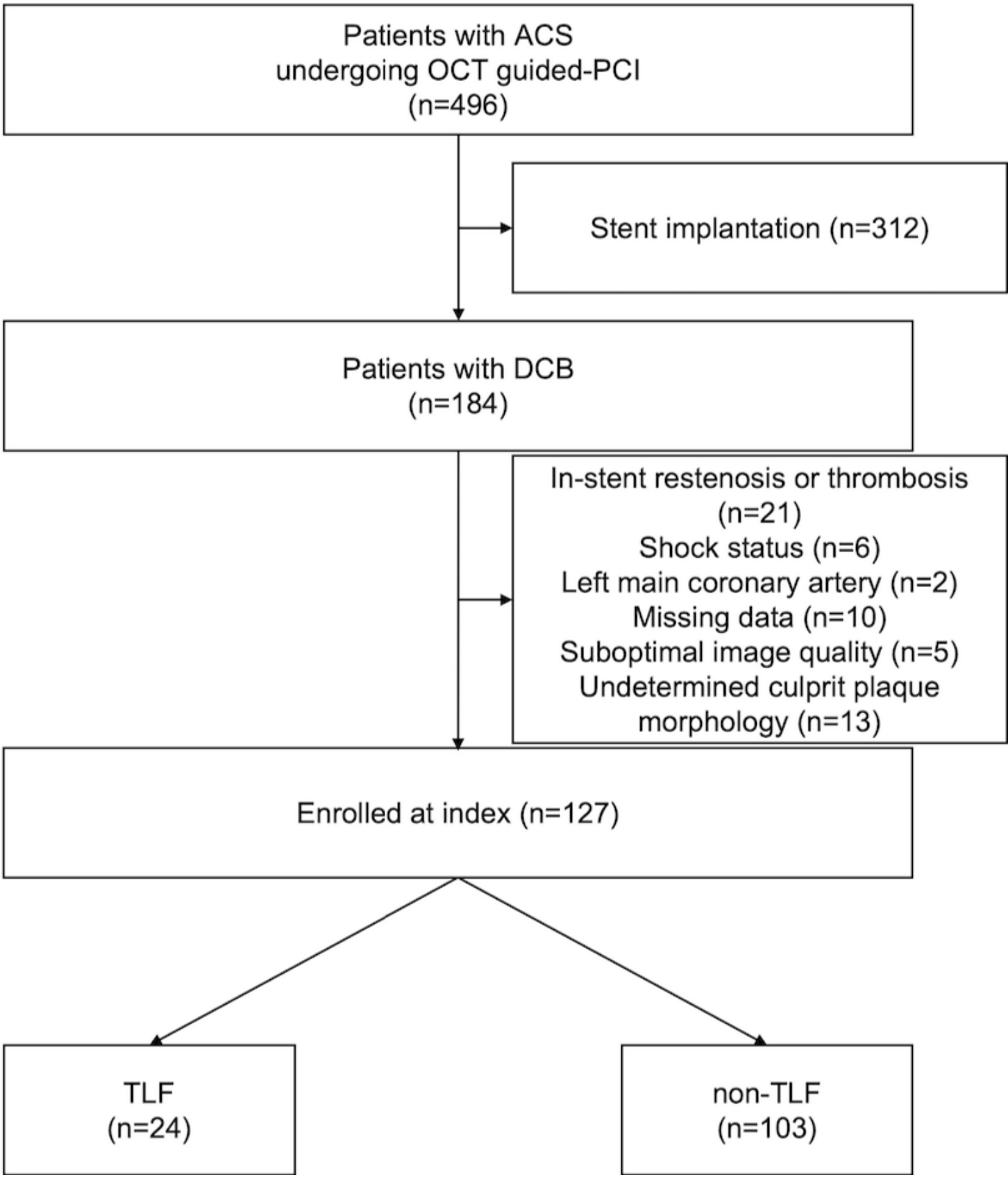
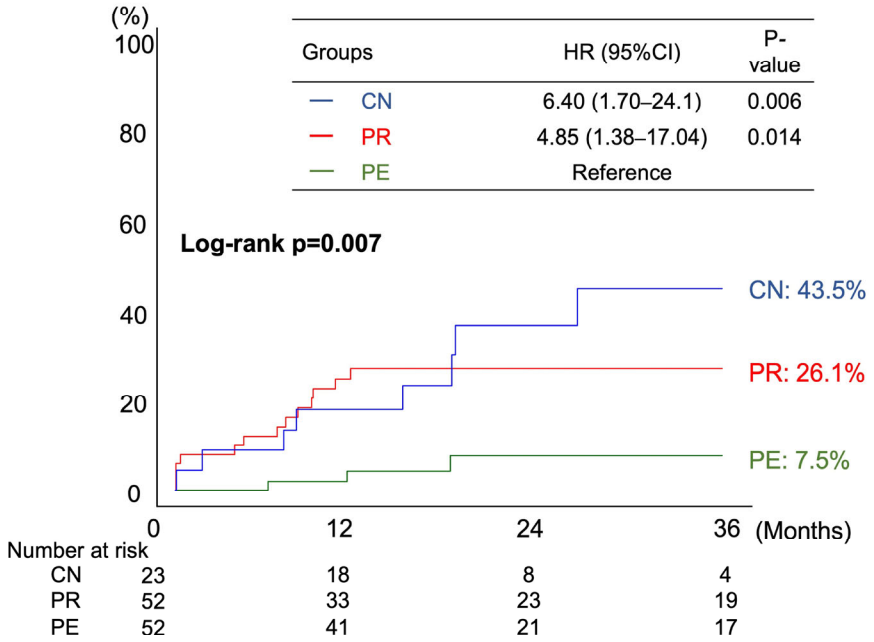


Figure 3 (A): Kaplan–Meier curves showing the cumulative incidence of TLF stratified by culprit plaque morphology



(B): Kaplan–Meier curves showing the cumulative incidence of TLF stratified by culprit plaque morphology and residual thrombus burden after PCI

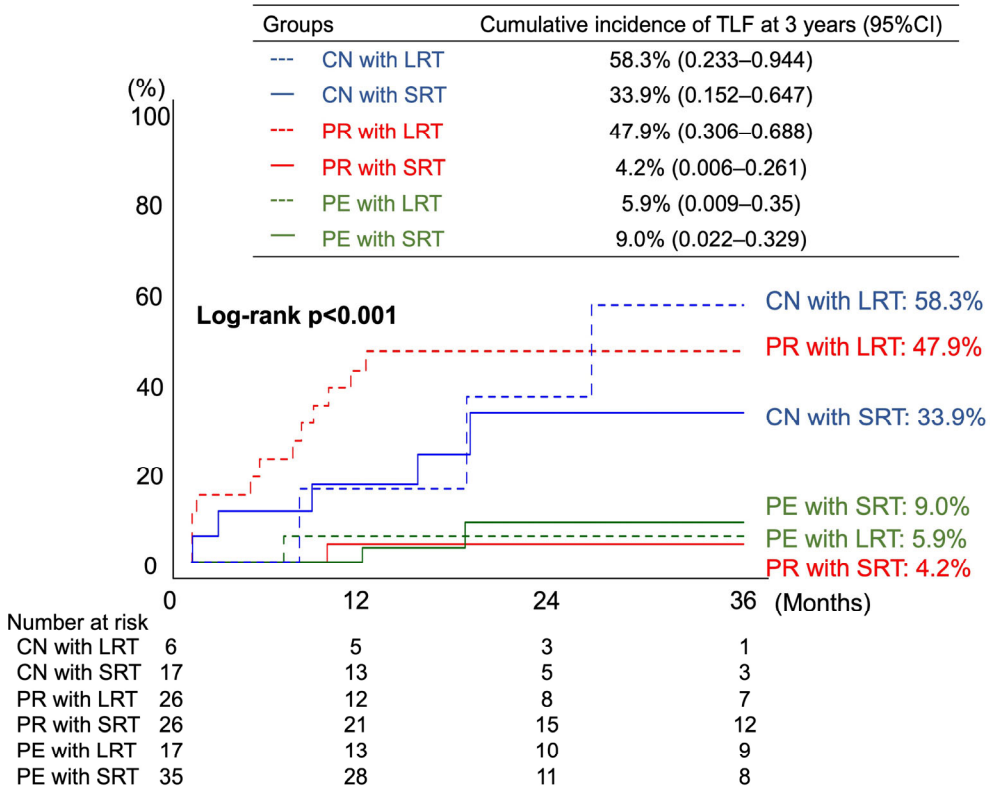
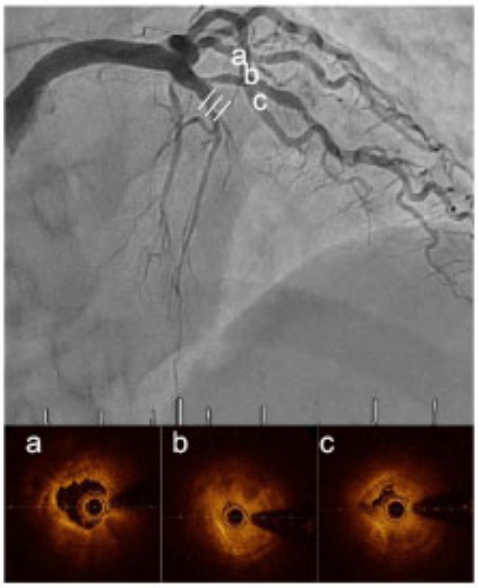


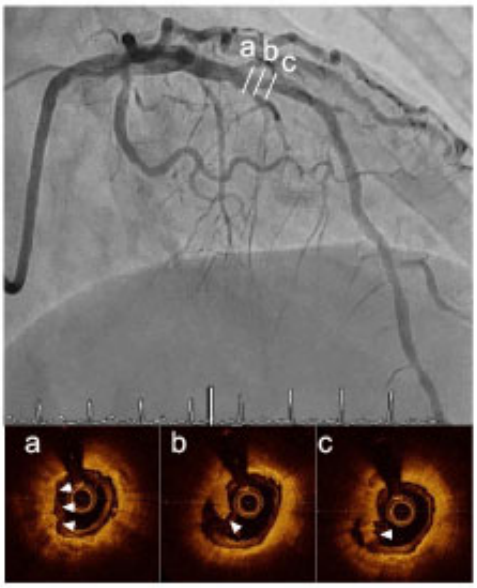
Figure 4. Representative cases

A) A representative case of PE with LRT

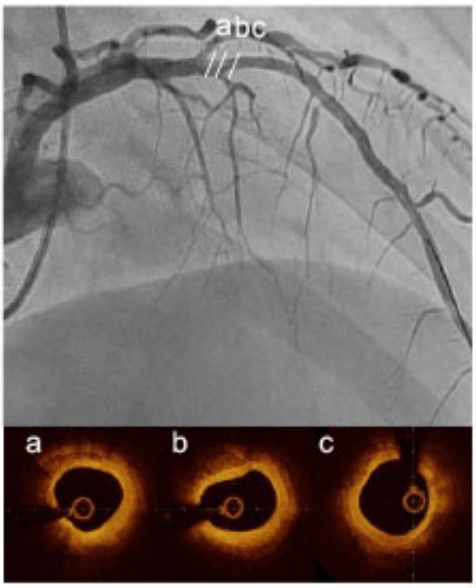
1) CAG and OCT images at pre PCI



2) CAG and OCT images at post PCI

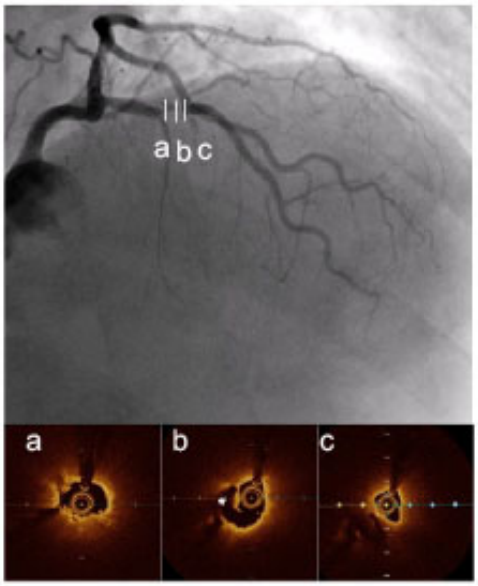


3) CAG and OCT images 12 months after PCI

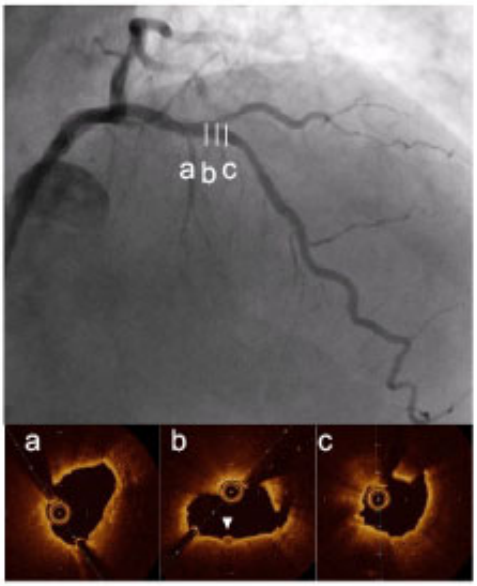


B): A representative case of PR with SRT

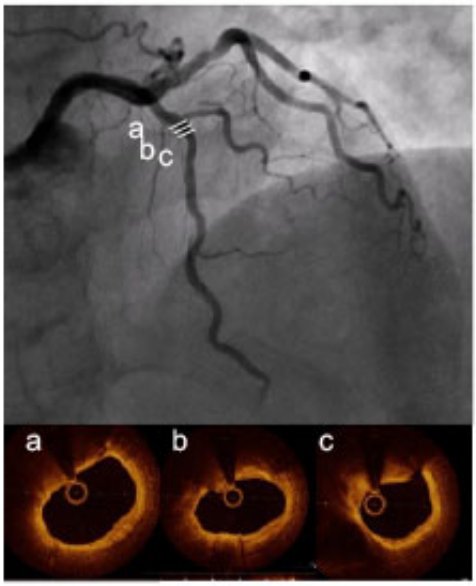
1) CAG and OCT images at pre PCI



2) CAG and OCT images at post PCI

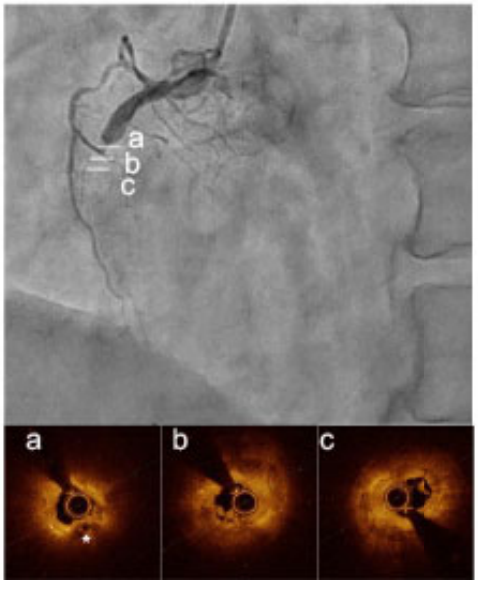


3) CAG and OCT images 12 months after PCI

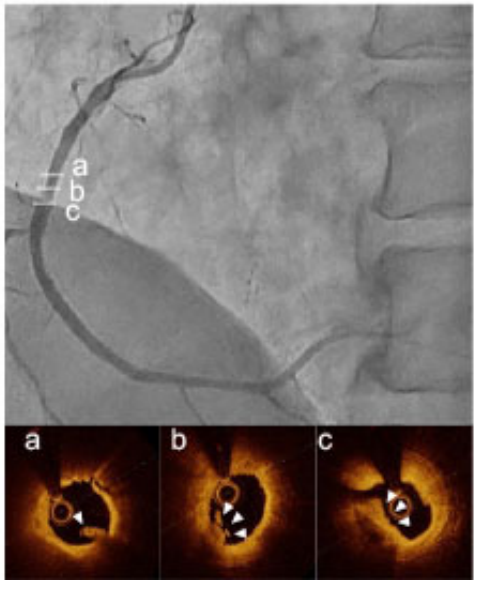


C) A representative case of PR with LRT

1) CAG and OCT images at pre PCI



2) CAG and OCT images at post PCI



3) CAG and OCT images 6 months after PCI