




# One-year optical coherence tomography findings in patients with late and very-late stent thrombosis treated with intravascular imaging guided percutaneous coronary intervention

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## Abstract

Patients with late/very-late stent thrombosis (ST) are at high risk of recurrent-ST. The mechanisms of recurrent-ST are largely unknown. The objective is to describe the 1-year optical coherence tomography (OCT) findings of patients suffering from late/very-late ST treated with intravascular imaging guided percutaneous coronary intervention (PCI). All consecutive patients with late/very-late ST undergoing intravascular imaging guided PCI were screened to undergo coronary angiography and OCT examination at 1 year. Patients were classified according to the observation of stent malapposition as most contributing cause of the ST. Thirty-four patients were included. Stent malapposition was observed in 17 (50%) and the remaining 17 cases were classified as: neoatherosclerosis (n=9), underexpansion (n=3) and unknown mechanism (n=5). Patients with malapposition had a remarkable reduction of the malapposition volume (from 6.4 to 1.3 mm<sup>3</sup>; p=0.02) during the ST procedure, but this was not fully corrected in 13 (76.5%). At 12 months, two patients of the malapposition group presented with uneventful target vessel re-occlusion. Persistent malapposition was observed in nine patients (60.0%). Major coronary evaginations (46.7 vs. 0%; p=0.001) and uncovered struts (6.3 vs. 1.0%; p<0.001) were also more frequent in patients with malapposition than without malapposition. None of the patients had thin-cap fibroatheroma neoatherosclerosis. Contributing causes of late/very-late ST are diverse and have different healing patterns at 12 months. Patients with stent malapposition treated with intravascular imaging guided PCI showed poor re-healing; but patients with other causes of the ST showed optimal stent healing as assessed by OCT.

**Keywords** Intravascular ultrasound (IVUS) · Optical coherence tomography (OCT) · Percutaneous coronary intervention (PCI) · Stent thrombosis (ST)

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Marcos Ñato and Josep Gomez-Lara contributed equally to this work.

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## Introduction

Definite stent thrombosis (ST) is defined when signs of thrombus formation within the stent are proven by angiography or post-mortem pathology [1]. Definite ST is a rare but devastating complication after percutaneous coronary intervention (PCI) associated with high in-hospital mortality (6%) and with high risk of recurrent ST [2]. According to the time interval since the stent implantation, ST is classified into three groups: early ST ( $\leq 1$  month), late ST (1–12 months) and very-late ST ( $> 1$  year) [1]. Late and very-late ST are mainly attributed to stent-related causes such as stent malapposition, lack of stent healing, neoatherosclerosis and stent underexpansion [3–6].

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are recommended by current revascularization guidelines to explicate and correct underlying mechanical factors of the ST [7]. Intravascular imaging guidance has demonstrated its ability to reduce or correct stent malapposition and stent underexpansion avoiding the implantation of additional stents [5]. However, little is known regarding the best treatment for cases with in-stent neoatherosclerosis and for cases with other causes of ST. Moreover, the re-healing process of the stent after PCI has never been investigated.

The aim of the present study is to describe the 1-year OCT predictors of stent re-thrombosis (such as stent malapposition, lack of stent healing, in-stent thin-cap fibroatheroma neoatherosclerosis and stent underexpansion) of patients with late and very-late ST treated with intravascular imaging guided-PCI. Moreover, this study also aims to compare the 1-year OCT findings between patients with different stent-related causes of late/very-late ST observed at the ST procedure.

## Materials and methods

### Study design

This is a single-centre, observational, prospective study. All consecutive patients presenting with angiographic definite late and very-late ST (> 1 month after stent implantation) subsequently treated with PCI from June 2012 to June 2015 were screened to undergo coronary angiography and OCT imaging at 1 year [5]. The Supplementary Appendix summarizes the ST procedure, the inclusion and exclusion criteria and the intravascular imaging acquisitions. This study was approved by the local ethic committee of our institution and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

### Quantitative IVUS and OCT analyses

IVUS images were analyzed with the QIvus® dedicated software (Medis, Leiden, the Netherlands); OCT images were analyzed in the proprietary offline software (LightLab Imaging®, Westford, MA, Abbott) by a dedicated core-laboratory (BARCICORE-LAB, Barcelona, Spain). Two experienced analysts performed the adjudication of the main underlying cause of late/very-late ST by reviewing the angiographic and intravascular images. The following causes were investigated: stent malapposition, in-stent neoatherosclerosis, stent underexpansion and unknown causes.

Quantitative OCT analysis was performed at 1-mm intervals. The OCT software drew the lumen area automatically.

Stent area was drawn at the adluminal site of the metallic struts. The neointimal area was calculated as the difference between the stent and luminal areas. The neointimal thickness was automatically calculated from the center of the adluminal side of the strut to the lumen contour with the thickness ruler tool [8].

### Qualitative IVUS and OCT analyses

Malapposition was defined as a clear separation of the metallic struts from the vessel wall in the absence of a side branch in case of IVUS. In case of OCT, a distance from the endoluminal surface of the stent strut to the vessel wall larger than the strut thickness (+20 µm of the OCT resolution) was also defined as malapposition. In-stent neoatherosclerosis was defined as the observation of clear intra-stent plaque core with lipid or calcium echogenic characteristics as assessed by IVUS. In case of OCT, fibroatheroma neoatherosclerotic plaques were defined as signal-poor regions with high signal-attenuation and diffuse borders. Fibrocalcified neoatherosclerotic plaques were defined as signal-poor regions with low signal attenuation and clear plaque borders [9]. Stent underexpansion was defined when the minimal stent area was  $\leq 90\%$  of the distal reference lumen area [10]. Follow-up OCT recordings were also evaluated qualitatively in order to assess the following findings: the neointima pattern at the cross-section with largest neointima area, the presence of signal-rich bands and the observation of coronary evaginations [8].

### Statistical analysis

All patients included in the present study were divided into two categories according to the observation of stent malapposition as the main contributing cause of the ST: malapposition group versus other findings group. Categorical variables were presented as counts and percentages, and continuous variables as median [inter-quartile range (IQR)]. Comparisons of categorical variables were estimated with the Chi square test and comparisons of continuous variables were estimated using the Kruskal–Wallis non-parametric test. A two-sided  $p$  value  $\leq 0.05$  was considered statistically significant. Statistical analysis was performed with the SPSS software, version 20.0 (SPSS Inc., IL, USA).

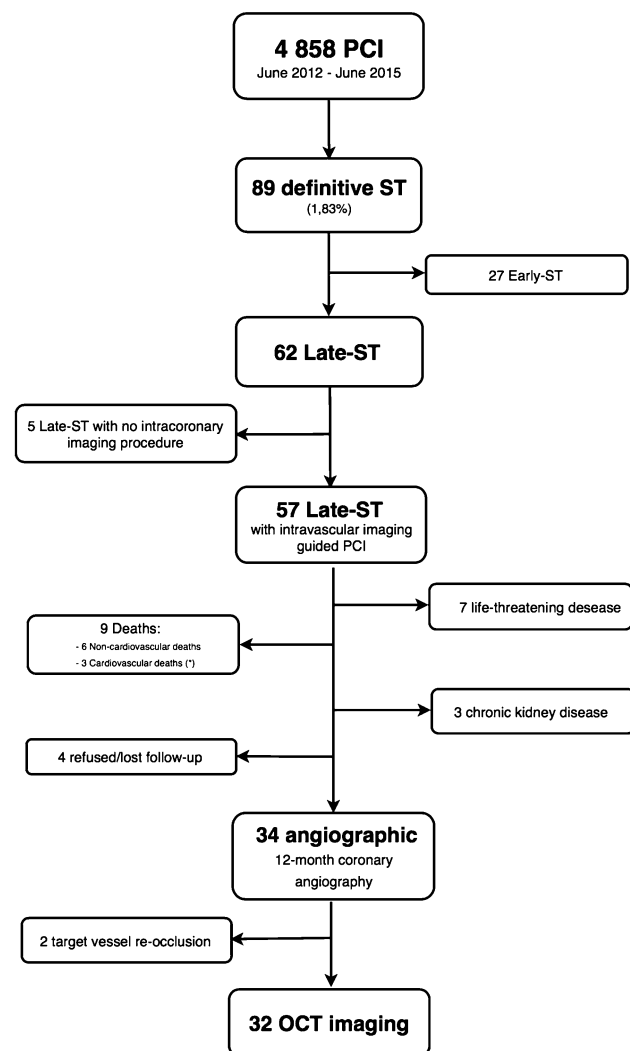
## Results

### Study population and classification

During the study period, a total of 89 patients with late and very-late ST undergoing PCI were registered out of 4.858 PCI procedures (1.8%). There were 27 early-ST (30%) and

62 late/very-late ST (70%). A total of 57 patients with late/very-late ST underwent intravascular-imaging-guided PCI and 34 of these patients underwent invasive angiographic follow-up at 12 months. At 1-year, two patients presented with complete target vessel occlusion and did not undergo OCT imaging. Figure 1 shows the flow chart of the study.

The 34 cases included were classified according to the main contributing cause of the ST as assessed by intravascular imaging prior PCI: malapposition group ( $n=17$ ) and other findings group ( $n=17$ ). The intravascular imaging causes of ST in the other findings group were: neoatherosclerosis ( $n=9$ ), stent underexpansion ( $n=3$ ) and unknown causes ( $n=5$ ).



**Fig. 1** Flow-chart of the study. \*All three patients died from cardiovascular causes were attributed to heart failure. *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention, *ST* stent thrombosis

## Clinical and procedural characteristics at the stent implantation procedure

Table 1 summarizes the clinical and procedural characteristics at the stent implantation procedure. Patients with stent malapposition as main contributing cause of late/very-late ST were treated with larger percentage of DES (52.9 vs. 35.3%;  $p=0.380$ ) and with smaller stents (IQR of 2.5–3.0 mm vs. 3.0–3.5 mm, respectively;  $p=0.033$ ) than patients without malapposition. Patients with malapposition had larger number of patients with hypertension (88.2 vs. 52.9%;  $p=0.024$ ).

## Clinical and procedural characteristics at the ST procedure

Table 2 summarizes the clinical and procedural characteristics at the ST procedure. The median stent age was 5.8 years without differences among the study groups. Most of the patients presented with STEMI (82.4%) at the time of the ST. Additional stent implantation was used in 32.4% of patients without differences among the study groups. There were no differences regarding the largest nominal balloon/stent used to treat the late-ST (IQR of 3.00–3.75 mm) and the predicted balloon/stent diameter to the previous stent diameter ratio (IQR of 1.10–1.35). However, all patients (100%) of the malapposition group were at least with 1 antiplatelet therapy versus 76.5% of patients of the other findings group ( $p=0.074$ ).

## Intravascular imaging findings at the ST procedure

A total of 34 patients with late/very-late ST were imaged with intravascular imaging techniques during the ST procedure (28 with IVUS and 6 with OCT). In total 89 pull-back acquisitions were obtained (2.6 per patient). Table 1 of the Supplementary Appendix shows the quantitative findings. The reference lumen area was numerically smaller in patients with malapposition as main contributing cause of the thrombosis (IQR of 4.7–8.8 mm<sup>2</sup>) than in patients without malapposition (IQR of 6.3–10.3 mm<sup>2</sup>);  $p=0.494$ . Mean stent area was smaller in the malapposition group (IQR of 5.1–8.1 mm<sup>2</sup>) than in the other findings group (IQR of 7.5–9.6 mm<sup>2</sup>);  $p=0.033$ . All lumen and stent size measurements increased after balloon dilatation or additional stent implantation. Although malapposition was remarkably reduced in the malapposition group (from 6.4 to 1.3 mm<sup>3</sup> of malapposition volume;  $p=0.02$ ), it persisted in the majority of cases (76.5%) at the end of the PCI.

**Table 1** Clinical and procedural characteristics at stent implantation procedure

	All patients (n = 34)	Malapposition (n = 17)	Other findings (n = 17)	p
Patient age (years) (IQR)	51.7 (45.0–59.1)	51.5 (47.3–66.4)	47.7 (41.1–52.9)	0.474
Males, n (%)	32 (94.1)	15 (88.2)	17 (100.0)	0.145
Smoking status, n (%)				0.443
No smoking	7 (20.6)	5 (29.4)	2 (11.8)	
Current smoker	16 (47.1)	7 (41.2)	9 (52.9)	
Previous smoker	11 (32.4)	5 (29.4)	6 (35.3)	
Hypertension, n (%)	24 (70.6)	15 (88.2)	9 (52.9)	0.024
Hypercholesterolemia, n (%)	31 (91.2)	17 (100)	14 (82.4)	0.070
Diabetes mellitus, n (%)	8 (23.5)	5 (29.4)	3 (17.6)	0.419
Previous CABG, n (%)	2 (6.1)	2 (11.8)	0 (0)	0.157
Ejection fraction (%), median (IQR)	55.0 (50.0–60.0)	55.0 (50.0–60.0)	55.5 (50.0–62.0)	0.780
Clinical indication, n (%)				0.108
Stable or silent ischemia	4 (11.8)	2 (11.8)	2 (11.8)	
Non-STEMI	13 (38.2)	9 (52.9)	4 (23.5)	
STEMI	17 (50.0)	6 (35.3)	11 (64.7)	
Culprit vessel, n (%)				0.749
LAD	18 (52.9)	8 (47.1)	10 (58.8)	
LCF	5 (14.7)	3 (17.6)	2 (11.8)	
RCA	11 (32.4)	6 (35.3)	5 (29.4)	
Stent type, n (%)				0.380
BMS	16 (47.1)	6 (35.3)	10 (58.8)	
DES	15 (44.1)	9 (52.9)	6 (35.3)	
Unknown	3 (8.8)	2 (11.8)	1 (5.9)	
Number of stents (n), median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.709
Stent length (mm), median (IQR)	23.0 (18.0–24.0)	23.0 (18.0–24.0)	23.0 (18.0–28.0)	0.475
Minimal stent diameter (mm), median (IQR)	3.0 (2.5–3.5)	3.0 (2.5–3.0)	3.0 (3.0–3.5)	0.033

All quantitative values are presented as median (inter-quartile range); p value indicates the non-parametric differences between the study groups  
*BMS* bare-metal stent, *CABG* coronary artery by-pass graft, *DES* drug-eluting stent, *LAD* left anterior artery, *LCF* left circumflex, *RCA* right coronary artery, *STEMI* ST-elevation myocardial infarction

### Quantitative coronary angiography analysis and OCT findings at 12 months

A total of 34 patients underwent coronary angiography at 12 months. Two patients of the malapposition group presented with target vessel re-occlusion due to probable uneventful recurrent ST; and did not undergo OCT imaging. Figure 1 of the Supplementary Appendix shows the angiographic and intravascular images of those patients. Figure 2 shows the evolution of the patients according to the cause of late/very-late ST. Table 2 of the Supplementary Appendix shows the quantitative coronary angiography analysis results.

Table 3 shows the OCT findings of the 32 patients imaged with OCT at 12 months. A total of 1149 cross-sections were analyzed: 155 reference distal cross-sections (13.5%), 859 in-stent cross-sections (74.8%) and 135 reference proximal cross-sections (11.7%). There were 15 in-stent cross-sections

not analyzed due to blood artifacts. A total of 7790 struts were analyzed. Patients with malapposition presented with larger percentage of uncovered struts (IQR of 3.0–10.7%) than patients without malapposition (IQR of 0.5–2.3%);  $p < 0.001$ . Percentage of malapposed struts was also larger in the malapposition group (IQR of 0–4.3%) than in the other findings group (IQR of 0–0%). Patients with malapposition presented with larger number of major coronary evaginations (46.7%) than patients without malapposition (0%);  $p = 0.001$ . Intraluminal thrombus was observed in two patients of the malapposition group at 12 months (2 vs. 0;  $p = 0.145$ ). Intraluminal thrombus occupied  $< 10\%$  of the lumen area, had a maximal extension of 1.5–2 mm and was attached to persistent malapposed struts in both patients. Figure 2 of the Supplementary Appendix shows both cases with intraluminal thrombus. There were 16 patients with in-stent neoatherosclerosis (50.0%) without differences between the study groups. None of the neoatherosclerotic

**Table 2** Clinical and procedural characteristics at ST procedure

	All patients (n = 34)	Malapposition (n = 17)	Other findings (n = 17)	p
Stent age, year (IQR)	5.8 (2.2–8.6)	5.6 (3.5–8.0)	7.7 (1.6–8.9)	0.474
Clinical presentation, n (%)				0.511
Non-STEMI	6 (17.6)	4 (23.5)	2 (11.8)	
STEMI	28 (82.4)	13 (76.5)	15 (88.2)	
Killip class, n (%)				1.000
I	28 (82.4)	14 (82.4)	14 (82.4)	
>I	6 (17.6)	3 (17.6)	3 (17.6)	
Antiplatelet treatment, n (%)				0.074
None	4 (11.8)	0	4 (23.5)	
Single	25 (73.5)	15 (88.2)	10 (58.8)	
Dual	5 (14.7)	2 (11.8)	3 (17.7)	
Initial TIMI-flow (%)				0.534
0	21 (61.8)	11 (64.7)	10 (58.8)	
1	4 (11.8)	2 (11.8)	2 (11.8)	
2	2 (5.9)	0 (0)	2 (11.8)	
3	7 (20.6)	4 (23.5)	3 (17.6)	
Thrombus aspiration, n (%)	27 (79.4)	13 (76.5)	14 (82.4)	0.671
Iib/IIIa inhibitors, n (%)	20 (60.6)	7 (43.8)	13 (76.5)	0.055
Intravascular imaging, n (%)				1.000
IVUS	28 (82.4)	14 (82.4)	14 (82.4)	
OCT	6 (17.65)	3 (17.6)	3 (17.6)	
Intravascular imaging pullbacks, median (IQR)	2 (2–3)	2 (2–3)	2 (2–2)	0.112
Number of balloons, median (IQR)	1 (1–2)	2 (1–3)	1 (1–2)	0.132
Drug eluting balloons, n (%)	2 (5.9)	0	2 (11.8)	0.169
Additional stent implantation, n (%)	11 (32.4)	5 (29.4)	6 (35.3)	0.714
Largest balloon/stent size used to treat ST (mm)	3.50 (3.00–3.75)	3.25 (3.00–3.50)	3.50 (3.25–3.75)	0.655
Predicted balloon/stent diameter to previous stent diameter ratio, median (IQR)	1.22 (1.10–1.35)	1.24 (1.13–1.35)	1.20 (1.09–1.31)	0.430
Final TIMI-flow, n (%)				0.310
2	1 (2.9)	1 (5.9)	0	
3	33 (97.1)	16 (94.1)	17 (100)	

All quantitative values are presented as median (inter-quartile range); p value indicates the non-parametric differences between the study groups *IVUS* intravascular ultrasound, *OCT* optical coherence tomography, *STEMI* ST-elevation myocardial infarction

plaques were thin-cap fibroatheromas. Figures 3 and 4 shows 2 cases with malapposition and neoatherosclerosis.

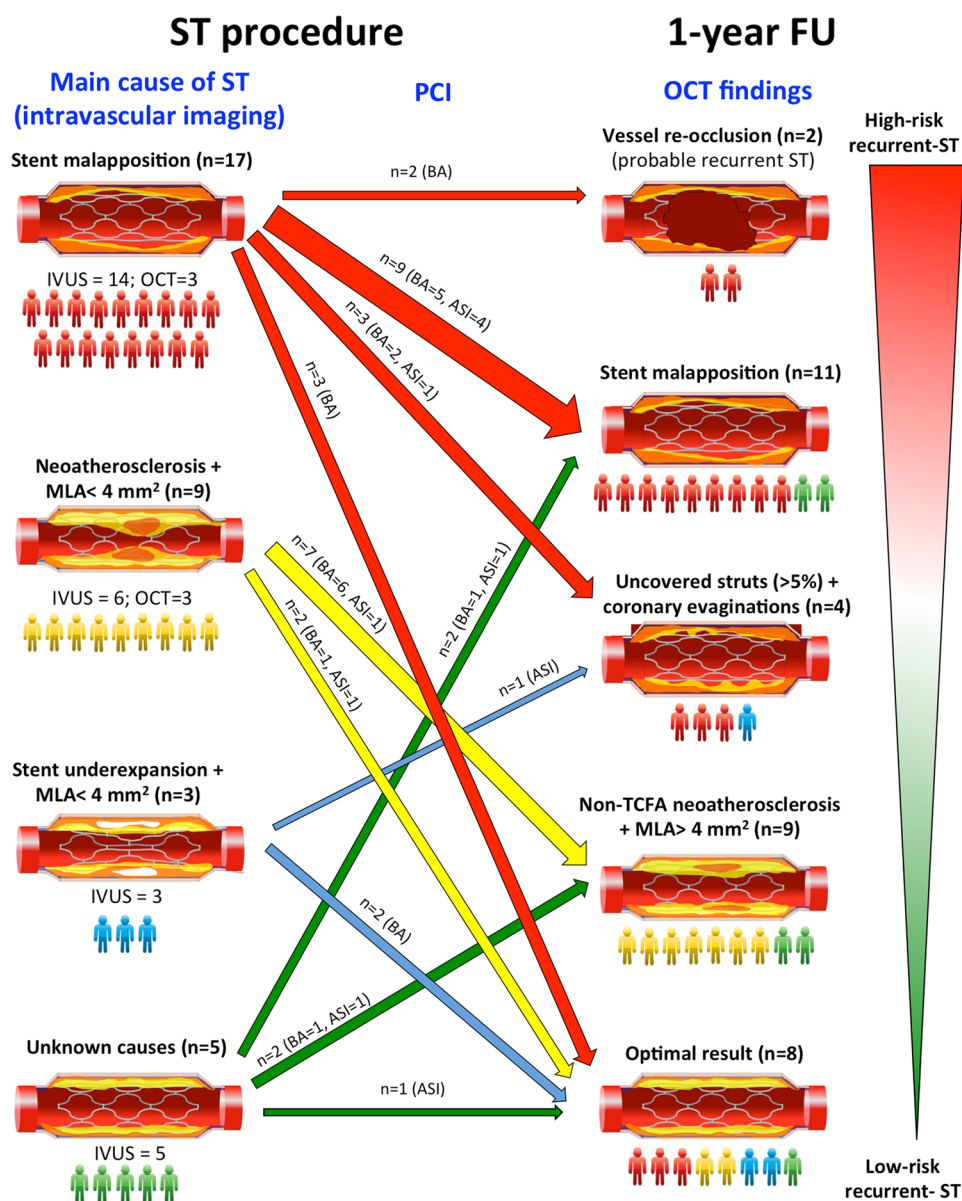
## Discussion

The main findings of the present study are: (1) Intravascular imaging techniques are able to discern most of the stent-related contributing causes of late/very-late ST; (2) Stent malapposition is the most common finding in patients with late/very-late ST, and is numerically more frequent with DES; (3) Neoatherosclerosis is the second cause of late-ST, and is numerically more frequent with bare-metal stents (BMS); (4) The stent healing pattern differs according to the

pre-existing main contributing cause of the ST, as assessed by OCT, at 1 year; (5) Patients with late/very-late ST attributed to stent malapposition present with high-risk features for recurrent ST, such as, large amount of uncovered struts, coronary evaginations and persistent malapposed struts at 1 year, despite the use of intravascular imaging guidance at the ST; (6) In contrast, patients with neoatherosclerosis, under-expansion or no evident cause of late/very-late ST present with low-risk healing pattern of recurrent ST as assessed by OCT at 12 months.

The cumulative incidence of late/very-late ST is around 0.8% with BMS, 0.7–1.5% with first-generation DES and 0.5–0.7% with second-generation DES at 2–3 years follow-up [11]. Although its incidence decreases 5 years after

**Fig. 2** Serial intravascular imaging findings according to the main contributing cause of the late/very-late ST. *ASI* additional stent implantation, *BA* balloon angioplasty, *IVUS* intravascular ultrasound, *MLA* minimal lumen area, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention, *ST* stent thrombosis



the stent implantation, there are documented cases up to 20 years after the stent implantation [12, 13]. Therefore, it is plausible that PCI for late-ST will be performed more frequently in the following years.

So far, there is no consensus of the recommended treatments in case of angiographic definite late/very-late ST. Current revascularization guidelines recommend the use of intravascular imaging techniques to assess the mechanisms of stent failure (recommendation class IIa; level C) [7]. Thrombus aspiration and use of glycoprotein IIb/IIIa inhibitors have been associated with better procedural outcomes and lower risk of recurrent thrombosis [14]. In contrast, additional stent implantation has been related with worse cardiac outcomes as compared to no additional stent implantation [2, 15, 16]. Most of the clinical outcomes observed in

patients treated with additional stent were related to cardiac death or recurrent ST at mid-term follow-up [2].

The present study is the first investigation of the healing process after intravascular imaging-guided PCI for late/very-late ST. According to the present study, malapposition is the most common contributing cause of late/very-late ST. By reviewing the intravascular images of the ST procedure, there were four cases (23.5%) with suspected positive vessel remodeling causing late-acquired stent malapposition. It is noteworthy that patients with malapposition had numerically smaller stent diameters than patients with other underlying substrates of late/very-late ST; despite all patients had similar reference lumen areas during the ST procedure and at 1-year follow-up. Therefore, it is plausible that the main contributing cause of the malapposition was

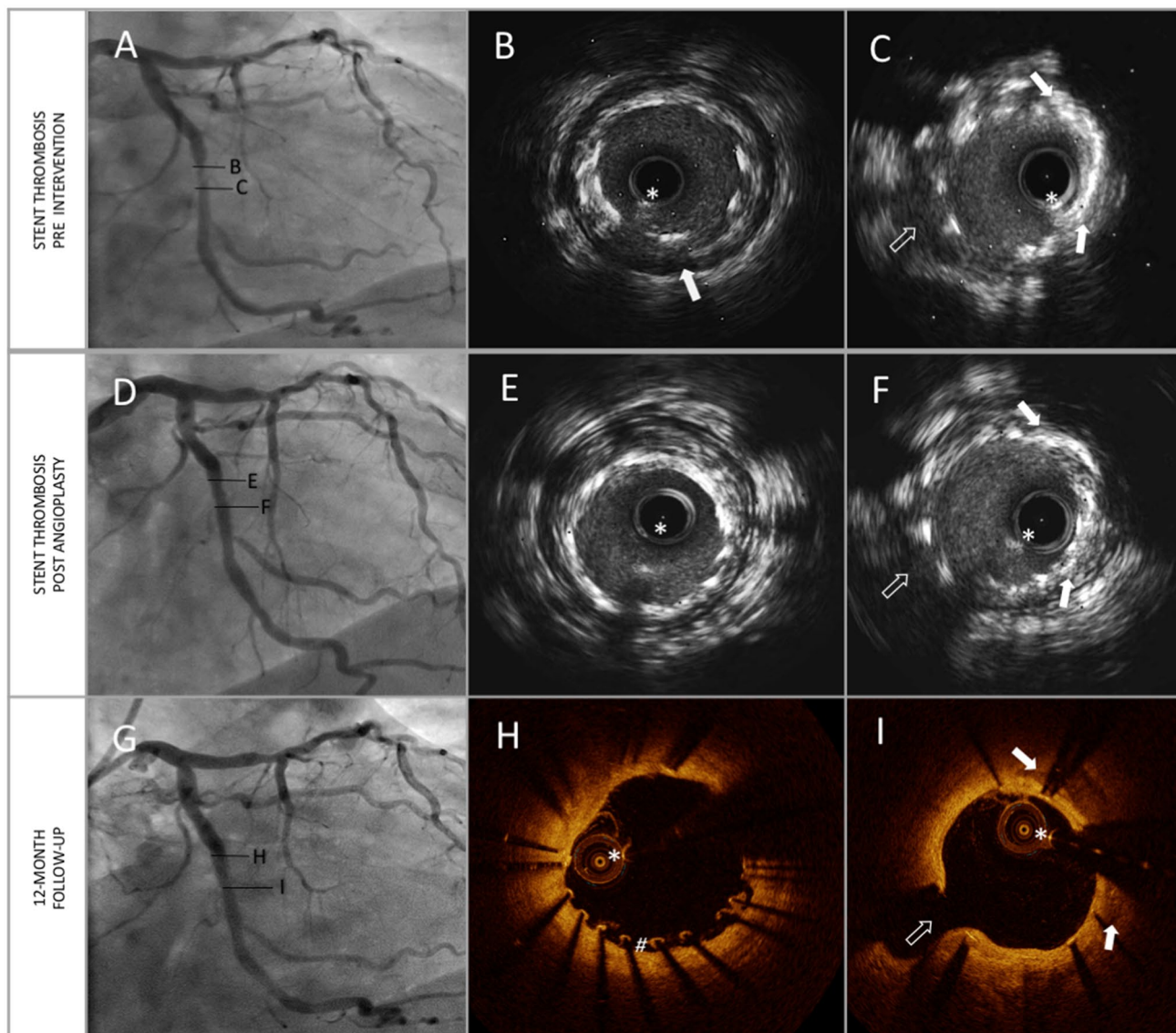
**Table 3** OCT findings at 12 months

n = 32	All (n = 32)	Malapposition (n = 15)	Other findings (n = 17)	p
<b>Qualitative OCT findings at 12 months</b>				
Neointima pattern, n (%)				0.599
Homogeneous	20 (62.5)	10 (66.7)	10 (58.8)	
Heterogeneous	11 (34.4)	4 (26.7)	7 (41.2)	
Layered	1 (3.1)	1 (6.6)	0	
Lesions with malapposition, n (%)	11 (34.4)	9 (60.0)	2 (11.8)	0.009
Lesions with RUTTS > 30%, n (%)	6 (18.8)	5 (33.3)	1 (5.9)	0.112
Coronary evaginations, n (%)	20 (62.5)	13 (86.7)	7 (41.2)	0.008
Major coronary evaginations, n (%)	7 (21.9)	7 (46.7)	0	0.001
In-stent neoatherosclerosis	16 (50.0)	7 (46.7)	9 (52.9)	0.723
Thin-cap fibroatheroma	0	0	0	NA
Signal-rich bands, n (%)	17 (53.1)	9 (60.0)	8 (25.0)	0.175
Intraluminal thrombus, n (%)	2 (6.3)	2 (13.3)	0	0.145
<b>Quantitative OCT findings at 12 months</b>				
Stent length (mm)	24.5 (19.0–30.0)	27.0 (22.0–31.0)	23.0 (19.0–30.0)	0.411
Reference lumen area (mm <sup>2</sup> )	7.6 (5.5–8.9)	6.4 (3.6–8.5)	8.1 (6.1–9.3)	0.123
Minimal lumen area (mm <sup>2</sup> )	4.0 (3.1–5.3)	3.7 (2.8–5.5)	4.2 (3.7–4.8)	0.313
Mean lumen area (mm <sup>2</sup> )	6.2 (5.2–8.5)	6.2 (4.3–7.8)	6.4 (5.9–9.4)	0.502
Maximal lumen area (mm <sup>2</sup> )	8.7 (7.2–10.8)	8.7 (6.9–10.9)	8.6 (7.9–10.7)	0.823
Minimal stent area (mm <sup>2</sup> )	6.0 (4.8–8.8)	4.9 (4.2–6.1)	6.4 (5.5–9.5)	0.009
Mean stent area (mm <sup>2</sup> )	8.1 (7.2–10.4)	7.6 (6.1–8.9)	9.1 (7.7–11.9)	0.069
Maximal stent area (mm <sup>2</sup> )	10.1 (9.1–11.8)	9.3 (7.3–10.5)	11.2 (9.9–13.5)	0.049
Minimal neointima area (mm <sup>2</sup> )	0.4 (0.2–0.8)	0.2 (0.1–0.4)	0.6 (0.3–0.8)	0.027
Mean neointima area (mm <sup>2</sup> )	1.6 (0.9–2.6)	1.2 (0.7–1.7)	2.1 (1.5–3.4)	0.005
Maximal neointima area (mm <sup>2</sup> )	3.9 (2.3–5.3)	2.9 (1.6–4.3)	4.5 (3.7–5.3)	0.040
Minimal malapposition area (mm <sup>2</sup> )	0 (0–0.4)	0.3 (0–0.7)	0 (0–0)	0.016
Mean malapposition area (mm <sup>2</sup> )	0 (0–0.7)	0.7 (0–1.4)	0 (0–0)	0.009
Maximal malapposition area (mm <sup>2</sup> )	0 (0–0.7)	0.7 (0–2.1)	0 (0–0)	0.009
Area stenosis (%)	54.3 (41.1–67.4)	56.8 (42.3–68.9)	51.2 (40.1–66.2)	0.602
Stent expansion index	0.97 (0.83–1.32)	0.91 (0.83–1.29)	1.00 (0.83–1.35)	0.655
Uncovered struts (%)	2.4 (0.7–6.0)	6.3 (3.0–10.7)	1.0 (0.5–2.3)	<0.001
Lesions > 5% uncovered struts, n (%)	10 (31.25)	8 (53.3)	2 (11.8)	0.011
Lesions > 10% uncovered struts, n (%)	5 (15.63)	5 (33.3)	0	0.010
Malapposed struts (%)	0 (0–1.2)	1.3 (0–4.3)	0 (0–0)	0.008
Lesions > 5% malapposed struts, n (%)	3 (9.38)	3 (20.0)	0	0.053
Neointima thickness (µm)	185.5 (101.0–299.1)	111.9 (81.7–253.6)	232.1 (166.4–445.8)	0.024

All quantitative values are presented as median (inter-quartile range); RUTTS ratio uncovered to total stent/struts

stent under-size during the stent implantation. Moreover, although larger number of intravascular imaging acquisitions, larger number of balloon dilatations and larger predicted balloon to stent diameter ratio were performed, it is noteworthy that malapposition was not fully corrected in 76.5% of cases (of the malapposition group) during the ST procedure. Nevertheless, the amount of malapposition volume was reduced > 75% from pre-intervention to post-intervention during the ST procedure in this group, as assessed by intravascular imaging. It is probable that caution to prevent coronary perforation and thrombus embolization

by aggressive balloon dilatation might have withheld the operators to fully correct the malapposition in the majority of cases. In addition, it was unknown whether leaving mild stent malapposition could be re-healed after PCI of the ST procedure. According to previous serial OCT studies including elective patients, the healing process after DES implantation is capable to integrate most of the “acute” malapposed struts into the vessel wall at 1-year follow-up [17, 18]. Maximal incomplete strut apposition distances < 270 µm after drug-eluting stent implantation were grossly covered and reaposed to the vessel wall at 6 months; only huge



**Fig. 3** Case with stent malapposition as main contributing cause of late-ST. **a** Very-late ST of a 2.5×32 mm paclitaxel-eluting stent implanted in mid-LCX 5 years ago; **b** IVUS image with malapposition as main cause of late ST (white arrow); **c** IVUS image with calcified plaque (white arrows) outside the stent and a side-branch

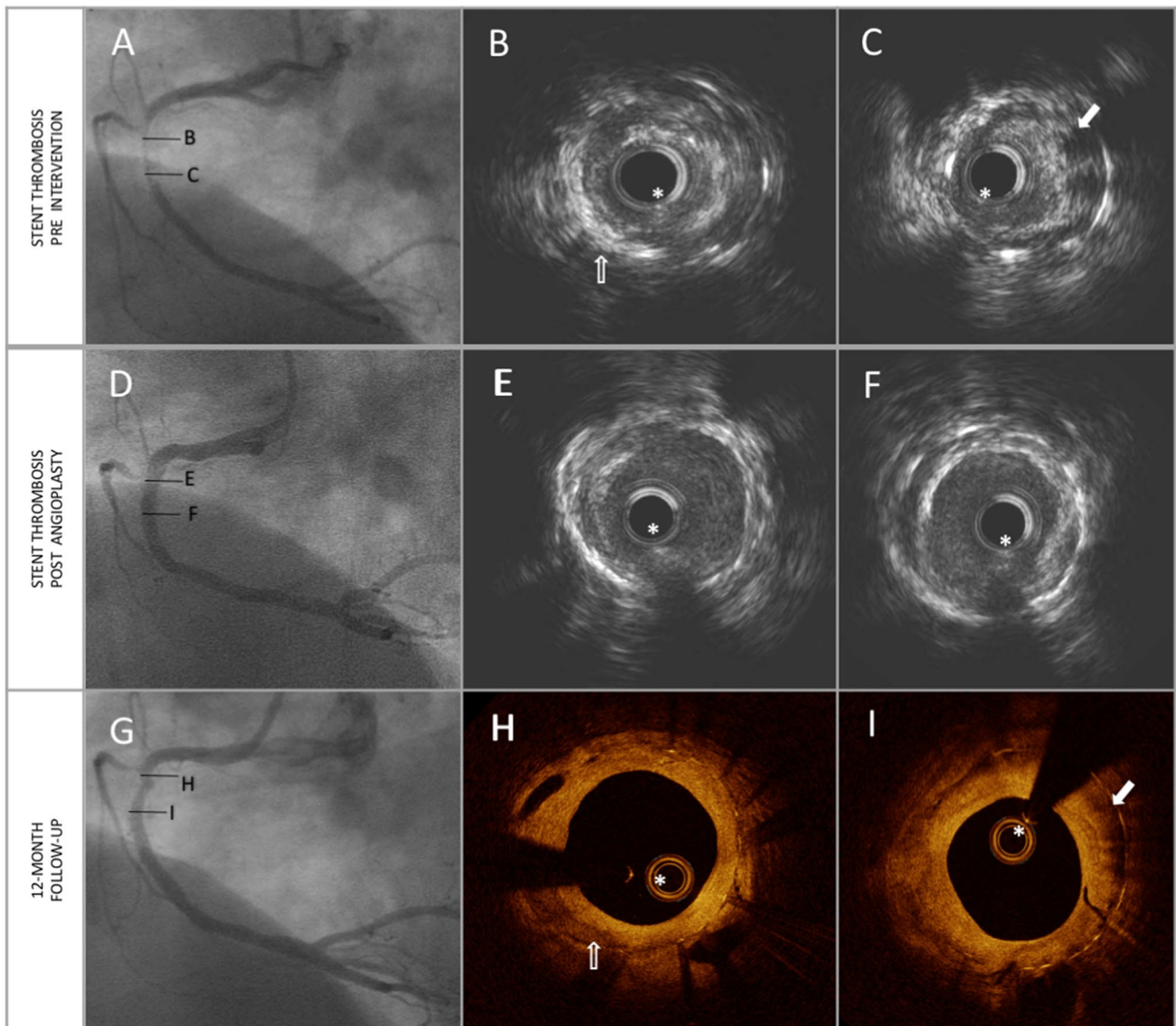
(transparent arrow). **d** Angiographic result after 3.0×15 mm non-compliant balloon angioplasty; **e**, **f** IVUS images after balloon angioplasty, without stent malapposition; **g** 12 month follow-up angiography; **h**, **i** uncovered struts (#) as assessed by OCT at 12 month follow-up. \*Intracoronary wire with acoustic and light shadow

malapposition distances ( $\geq 850 \mu\text{m}$ ) were associated with persisting malapposed and uncovered struts at 6 months [17]. According to the present study including patients with ST, residual malapposition persisted in 60% of patients and re-healing of persistent malapposition was not observed in most of the cases at 1-year follow-up. In fact, two patients of the malapposition group presented with asymptomatic target vessel re-occlusion at 12 months; two patients presented with intraluminal thrombus in OCT cross-sections with malapposed struts at 12 months; and three patients with persistent stent malapposition underwent new PCI with balloon angioplasty at 1-year. Therefore, more aggressive

dilatations and most extensive correction of the malapposition should have been advisable during the ST procedure.

It is well known that OCT is the best intravascular imaging technique to visualize the stent healing, apposition and neoatherosclerosis [5, 7]. However, the OCT signal is unable to visualize structures behind red thrombus and can ignore the main causes of the ST in cases with persistent thrombus after intensive thrombus aspiration or balloon dilatation [3]. IVUS has poorer resolution compared to OCT. However, its use in ST is not limited by thrombus. Moreover, IVUS enables visualization of the elastic external membrane (EEM) and therefore identification of positive vessel remodeling





**Fig. 4** Case with in-stent neoatherosclerosis as cause of late-ST. **a** Very-late 3.5×22 mm BMS thrombosis (8 years after implantation) in mid-RCA; **b** hyper-echogenic core (transparent arrow) with acoustic shadow hampering the visualization of the stent struts (probable neoatherosclerotic calcified plaque); **c** hypo-echogenic core (white arrow) corresponding to neoatherosclerotic lipid core plaque as main contributing cause of the very-late ST; **d** final result after PCI with

a 4.0 mm non-compliant balloon angioplasty of the ST; **e, f** IVUS images after balloon angioplasty showing large lumen area. **g** Elective 1 year angiography; **h, i** OCT images showing large lumen area with neoatherosclerotic calcified plaque (transparent arrow) and thick-cap fibroatheroma plaque at 1 year (white arrow). \*Intracoronary wire with acoustic and light shadow

after stent implantation by comparing the largest in-stent EEM with the EEM of the reference non-stent segments [19]. Therefore, IVUS and OCT imaging in patients with ST are useful and give complementary information. In the present study, it is possible that the five patients with no evident stent-related cause of late/very-late ST, imaged with IVUS, had underlying mild malapposition or unseen neoatherosclerosis since it was evident at follow-up OCT.

The present study has several limitations. First, this is an observational study and the number of patients included

is low. Therefore, all comparisons performed between the study groups must be interpreted with caution and are hypothesis generating. Second, there was no specific protocol for the treatment of ST and all decisions were left to the operator's discretion. Finally, the assessment of the main contributing causes of ST with two different intravascular imaging techniques may have important variability, specially in cases with in-stent neoatherosclerosis.

## Conclusions

Stent-related main contributing causes of late/very-late ST are diverse and have different healing patterns, as assessed by OCT, at 12 months. In cases with stent malapposition as main underlying substrate of ST, the observation of uncovered struts, major coronary evaginations and persistent malapposed struts is frequent at 12 months. In those cases, intravascular-imaging guided procedures reduced the amount of malapposition at the ST procedure, but the re-healing of the stent was not able to correct the remaining lack of strut coverage/malapposition. In contrast, cases with in-stent neoatherosclerosis, stent underexpansion or no evident main contributing cause of late/very-late ST, the 1-year OCT healing pattern indicates a low risk of recurrent ST. Although further investigations are required, patients with malapposition as main contributing cause of late/very-late ST warrants watchful follow-up of these cases.

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## Compliance with ethical standards

**Conflict of interest** None of the authors declare conflict of interest with the present study.

**Ethical approval** All procedures were in accordance with the ethical standards of the local ethic's committee and with the 1964 declaration of Helsinki and its later amendments.

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