

Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse clinical outcomes

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Aim Late-acquired incomplete stent apposition (ISA) has been documented after drug-eluting stent (DES) implantation; however, its clinical role remains controversial. We sought to investigate the incidence and long-term clinical consequences of late ISA after implantation of sirolimus- (SES) or paclitaxel-eluting stent (PES) in a non-selected population.

Methods and results From our database, we analysed 195 consecutive patients who underwent DES placement (175 with SES and 20 with PES) into native artery lesions and had serial intravascular ultrasound studies (IVUS) performed at index procedure and after 6–8 months. They were clinically followed for 29 ± 15 months (median of 24.3 months, interquartile range 18.1–31.6 months). Late ISA was defined as separation of at least one stent strut from the vessel wall in a segment without a side-branch and where the immediate post-implantation IVUS revealed complete apposition of stent struts. We identified 10 patients (5.1%) with late ISA, three patients after PES, and seven patients after SES implantation. ISA was localized almost exclusively at body of the stents (nine out of 10 cases). Mean ISA volume and length were $44.5 \pm 41.9 \text{ mm}^3$ and $7.4 \pm 11 \text{ mm}$, respectively. There was a marked increase in vessel volume from $416.0 \pm 163.9 \text{ mm}^3$ at baseline to $514.4 \pm 247.9 \text{ mm}^3$ at follow-up ($P = 0.001$) with no significant change in plaque volume (232.4 ± 52.7 at baseline and $226.4 \pm 22.3 \text{ mm}^3$ at follow-up, $P = 0.3$) in patients who presented with late-acquired ISA. During the follow-up period, one patient with SES and one patient with PES who presented late-acquired ISA had late stent thrombosis and acute myocardial infarction.

Conclusion Late-acquired ISA was observed in 5.1% of patients after DES implantation and is related to regional vessel positive remodelling. The relationship between late-acquired ISA and long-term adverse outcomes (e.g. stent thrombosis) requires further analysis.

Introduction

Lately, the introduction of drug-eluting stents (DESs) has been the major breakthrough in interventional cardiology.¹ Several clinical studies have shown that Sirolimus-eluting stents (SESs—Cypher; Cordis, Johnson & Johnson) and Paclitaxel-eluting stents (PES—Taxus; Boston Scientific Corp.) significantly reduce neointimal hyperplasia (NIH) and the need for repeat coronary revascularization when compared with bare-metal stents.^{2–5} However, concerns have been raised about the occurrence of late DES-thrombosis, particularly related to antiplatelet therapy discontinuation.⁶ Other potential contributory mechanism to the occurrence of late DES-thrombosis is the presence of

late incomplete stent apposition (ISA). Late ISA, previously described after application of intravascular brachytherapy and bare-metal stenting,^{7–9} has also been reported after DES implantation. Its occurrence ranged from 5 to 12% in the preliminary reports and did not seem to impact patient morbid-mortality at short- and medium-term clinical follow-up (up to 1 year).^{10–12} We sought to investigate the frequency of ISA (persistent and/or acquired) at follow-up and its relationship to adverse clinical events in a non-selected population treated with SES and PES.

Methods

Study population and protocol

In 2003, DESs were clinically and market approved for use in our country. As part of the initial experience of our institution with these new devices, all patients receiving DES in that year were

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asked to return for a pre-schedule angiographic and intravascular ultrasound studies (IVUS) follow-up after 6–8 months of the baseline procedure. Additionally, they should be clinically followed and non-invasively screened for ischaemia for a period of 2 years. According to the hospital policy at that time, in most cases, only one DES per patient was authorized to be deployed.

Between January and December 2003, we identified 195 consecutive patients with 200 lesions who underwent DES placement into *de novo* native coronary artery lesions with high-quality serial IVUS images acquired at index and follow-up (mean 6.1 ± 2.1 months). We did not enrol patients treated in the setting of acute myocardial infarction (MI), with lesions located in saphenous vein-grafts and with left main disease.

No patient refused to be submitted to a 6-month control angiography and IVUS study. Additionally, in this cohort, no patient was deemed clinically inappropriate (severe left ventricular dysfunction, renal failure, etc.) to be submitted to a 6-month control angiography and IVUS study. Nine patients initially enrolled were subsequently excluded from the final analysis due to poor-quality IVUS images.

SES and PES were used in 175 patients (177 lesions) and 20 patients (23 lesions), respectively. All interventions were performed according to current standard guidelines. Patients were pre-medicated with aspirin (200 mg), which was continued indefinitely. Additionally, they received clopidogrel (loading dose of 300 mg) initiated 24 h before intervention or ticlopidine (250 mg bid) administered 72 h before the procedure. Patients were recommended to stay on thienopyridines for a minimum of 3 and 6 months after SES and PES deployment, respectively. SES was the predominant DES included in this sample because they were first approved for clinical use in our country.

Baseline and follow-up demographic and clinical data were obtained from personal interview and hospital record chart review.

Local ethics committee approved this study and all patients signed a written informed consent at the beginning of the study.

Definition of major cardiac events and clinical follow-up

Death was classified as cardiac vs. non-cardiac. MI was defined as an elevation of CK-MB fraction to a value three times above the upper limit of the normal range. Target-lesion revascularization was defined as a repeat percutaneous or surgical intervention of the stented lesion.

Stent thrombosis was classified in accordance to the definition previously published by Jeremias *et al.*¹³ and included any of the following: angiographic documentation of partial or total stent occlusion with or without the presence of thrombus, sudden cardiac death, and MI not clearly attributable to another coronary lesion. Coronary aneurysm was defined as an increase in external elastic membrane and lumen cross-sectional area (CSA) greater than 150% of the proximal reference.¹⁴

Intravascular ultrasound studies imaging and analysis

Serial intravascular ultrasound procedures were performed after intracoronary administration of 0.1–0.2 mg of nitroglycerin, with a motorized transducer pullback system (0.5 mm/s) and commercial scanners (CVIS and Galaxy 2, Boston Scientific Corporation) consisting of a rotating 40 MHz transducer with a 2.6 Fr imaging sheath. The imaging catheter was advanced approximately 10 mm beyond the stent into the distal vessel. All IVUS images were recorded on 0.5-in. high-quality VHS videotapes or CD/DVD for off-line analysis. Qualitative analysis for the presence of ISA was performed by reviewing all follow-up IVUS images from the 195 patients. Next, index (immediately after stent deployment) images were reviewed side-by-side to exclude cases where incomplete apposition was present at the time of stent implantation. Late ISA was defined as

a clear separation of at least one stent strut from the vessel wall with evidence of blood speckle behind the stent, in a segment without a side-branch and where the immediate post-implantation IVUS revealed complete apposition of stent struts. Persistent ISA was defined as ISA observed at baseline and follow-up. The determination of ISA was based on a consensus of two experienced IVUS analysts (D.A.S. and A.A.A.).

Quantitative intravascular ultrasound studies analysis

The IVUS images obtained were digitized to perform quantitative and qualitative analysis according to the criteria of the American College of Cardiology's Clinical Expert Consensus Document on IVUS.¹⁴ A coronary segment beginning at the distal stent edge and extending to its proximal edge was analysed. A computer-based contour detection program was used for automated 3D-reconstruction of the stented segment (Echoplague, Indec Systems, Inc., Mountain View, CA, USA). CSA measurements every 0.5 mm included lumen, stent, and external elastic membrane CSA. Calculations included total vessel volume, stent volume, lumen volume, NIH volume, and ISA volume. Moreover, ISA depth (mm) and number of malapposed stent struts were measured at the segment of greatest strut-vessel wall separation at follow-up IVUS imaging. ISA length and maximal ISA area were measured as well. Percentage of ISA (% ISA) was calculated dividing ISA volume by vessel volume at the follow-up IVUS and refers to the magnitude of stent malapposition.

Statistical analysis

All statistical analyses were performed with commercially available software (SPSS9.0, SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean \pm standard deviation or as median (interquartile range) as appropriate. Delta (Δ) values for each measurement were calculated as follow-up minus post procedure. Comparisons between post-intervention and follow-up measurements were performed with a paired two-tailed Student's *t*-test. When three groups were compared, overall probability values were derived from one-way ANOVA. Categorical data are presented as counts and percentages and compared using Fisher's exact test. The composite of major adverse events during follow-up were analysed by the Kaplan–Meier method. All statistical tests were performed at a 0.05 level of significance.

Results

Among the 195 patients included in this analysis, late ISA was documented in 10 patients (5.1%): seven patients treated with SES and three patients treated with PES. Another 13 (6.6%) patients had persistent ISA (12 treated with SES and one with PES). Comparison of baseline clinical and procedural characteristics of these patients is shown in *Table 1*. Patients with ISA (persistent and late acquired) were treated with longer stents than patients without ISA (25.8 ± 10.9 and 24.3 ± 10.7 vs. 21.5 ± 6.5 , $P = 0.047$). Also, in the ISA population, final dilatation was performed with bigger balloon (3.5 ± 0.5 and 3.4 ± 0.2 vs. 3.2 ± 0.4 , $P = 0.005$) despite the comparable reference vessel size for all three groups (*Table 1*). Patients with late ISA had it mainly at the body of the stent (nine out of 10 patients) while all persistent ISA cases happened at the proximal edge of the stents. Multiple stents (>2) were deployed in only five patients and no ISA was noticed at the overlapping segment. At the follow-up, one case of late ISA appeared as a coronary aneurysm. Two patients (three vessels) had multiple sites of ISA within the stent.

Table 1 Baseline and procedural characteristics

	Without ISA	Persistent ISA	Late ISA	P-Value
No. of patients	172	13	10	
Age (year)	59.1 ± 9.3	61.7 ± 9.9	56.8 ± 13.0	0.5
Gender, male <i>n</i> (%)	117 (68)	9 (69)	8 (80)	0.5
Cigarette smoking, <i>n</i> (%)	102 (59)	7 (56)	5 (50)	0.5
Diabetes mellitus, <i>n</i> (%)	93 (54)	5 (38)	5 (50)	0.5
Hypertension, <i>n</i> (%)	122 (71)	7 (69)	7 (70)	0.9
ACS, <i>n</i> (%)	40 (23)	1 (8.3)	1 (10)	0.1
Location, <i>n</i> (%)				
LAD	90 (52)	7 (46)	6 (55)	1.0
LCX	21 (12)	2 (13)	1 (9)	0.8
RCA	63 (36)	6 (40)	4 (36)	0.9
Stent artery ratio	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	0.3
Total stent length	21.5 ± 6.5	25.8 ± 10.9	24.4 ± 10.7	0.047*
Post inflation, <i>n</i> (%)	78 (45)	8 (54)	5 (45)	0.7
Final balloon size (mm)	3.2 ± 0.4	3.5 ± 0.5	3.4 ± 0.2	0.005*
Maximal inflation pressure (atm)	14.4 ± 2.7	14.5 ± 1.6	14.2 ± 3.9	0.9

ACS, acute coronary syndromes; QCA, quantitative coronary angiography; N/A, not applicable. Values are expressed as relative percentages or mean ± SD. *P-value denotes statistically significant difference between patients with ISA (persistent and late acquired) vs. patients without ISA. The comparison between patients with persistent and late-acquired ISA did not show significant difference.

Table 2 Quantitative intravascular ultrasound studies analysis

	Without ISA	Persistent ISA	Late ISA	P-value
Vessel volume (mm ³)				
Post-stent	430.1 ± 89.4	424.5 ± 187.6	416.0 ± 163.9	0.9
Follow-up	426.6 ± 15.2	435.0 ± 177.4	514.4 ± 247.9	0.0009*
Δ	-3.6 ± 74.1	12.6 ± 33.9	98.4 ± 110.0	0.0009*
Stent volume (mm ³)				
Post-stent	187.9 ± 51.8	180.1 ± 89.9	203.1 ± 108.2	0.6
Follow-up	200.9 ± 12.4	199.3 ± 109.2	212.6 ± 107.6	0.6
Δ	12.9 ± 39.2	6.4 ± 27.7	9.4 ± 26.4	0.8
Lumen volume (mm ³)				
Post-stent	189.4 ± 48.5	177.1 ± 85.4	202.9 ± 19.2	0.5
Follow-up	185.6 ± 15.3	173.4 ± 65.2	194.3 ± 10.8	0.06
Δ	-6.7 ± 3.2	-5.7 ± 2.7	-8.3 ± 2.4	0.03*
Plaque volume (mm ³)				
Post-stent	240.3 ± 37.6	244.4 ± 98.5	232.4 ± 52.7	0.8
Follow-up	235.7 ± 28.1	238.6 ± 80.4	226.4 ± 22.3	0.5
Δ	-4.5 ± 9.6	-6.4 ± 5.9	-5.9 ± 4.2	0.6
NIH volume (mm ³)	4.5 ± 0.4	3.7 ± 5.2	8.5 ± 6.2	<0.0001*
ISA volume (mm ³)	N/A	19.9 ± 31.2	44.5 ± 41.9	0.1
ISA depth (mm)	N/A	0.7 ± 0.3	0.9 ± 0.6	0.3
ISA length (mm)	N/A	2.2 ± 0.7	7.4 ± 11	0.1
Malapposed struts, <i>n</i>	N/A	3.3 ± 1.3	3.0 ± 1.8	0.6
% ISA	N/A	1.0 ± 0.2	5.2 ± 8.7	0.09

NIH, neointimal hyperplasia; N/A, non-applicable.

*P-value denotes statistically significant difference between patients with late-acquired ISA vs. patients with persistent ISA and patients without ISA. The comparison between patients with persistent ISA and patients without ISA did not show significant difference.

Post-stenting and follow-up IVUS measurements are shown in *Table 2*. While patients without ISA presented a slight reduction in the vessel volume (EEM volume) between baseline and follow-up ($\Delta = -3.6 \pm 74.1$) and patients with persistent ISA exhibited just a modest non-significant increase in the EEM volume ($\Delta = +12.6 \pm 33.9$), patients with late-acquired ISA evolved with significant increase in vessel volume in the same period ($\Delta = +98.42 \pm 110.0$, $P < 0.0009$). Moreover, when compared to the patients

without ISA and with persistent ISA, patients with late-acquired ISA presented a significant decrease in lumen volume ($\Delta = -8.3 \pm 2.4$ vs. -6.7 ± 3.2 vs. -5.7 ± 2.7 , $P = 0.03$) at the expenses of a marked increase in the volume of in-stent NIH (8.5 ± 6.2 for patients with late ISA vs. 4.5 ± 0.4 for patients without ISA and 3.7 ± 5.2 for patients with persistent ISA, $P < 0.001$).

Table 3 shows the comparison of clinical outcomes among the three groups (non-ISA, persistent ISA, and late-acquired

Table 3 Adverse clinical events and presence of incomplete stent apposition

	Without ISA	Persistent ISA	Late ISA	P-value
Patients, n	172	13	10	N/A
Up to 12 months				
Cardiac death	1 (0.6%)	0	0	0.9
MI	0	0	0	1.0
TLR	7 (4%) ^a	0	0	1.0
Stent thrombosis	0	0	0	1.0
After 12 months				
Cardiac death	1 (0.6%)	1 (7.7%)	0	0.2
MI	0	0	2 (20%) ^b	0.002*
TLR	1 (0.6%) ^a	0	2 (20%) ^b	0.007*
Stent thrombosis	0	0	2 (20%)	0.002*

MI, myocardial infarction; TLR, target lesion revascularization. Values are presented as absolute numbers.

^aDue to restenosis.

^bDue to stent thrombosis.

*P-value denotes statistically significant difference between patients with late acquired.

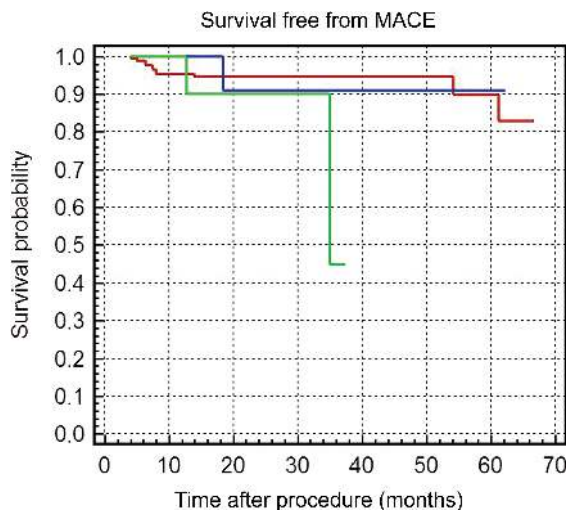


Figure 1 Kaplan-Meier event-free survival (%) for patients without incomplete stent apposition (red), with persistent incomplete stent apposition (blue), and late incomplete stent apposition (green). Major adverse clinical events (MACE): cardiac death, myocardial infarction (MI), and target-lesion revascularization (TLR).

ISA). After 29 ± 15 months of follow-up (median of 24.3 months, interquartile range 18.1–31.6 months), two patients with late ISA had angiographically documented stent thrombosis manifested as acute ST-elevation MI. These patients had multiple segments of IVUS-detected malapposition and an ISA/vessel volume ratio (% ISA) > 10% at follow-up. Analysis of the outcome data for the differing follow-up times is shown in *Figure 1* and did not significantly differ among patients without ISA and patients with persistent ISA or late ISA.

Discussion

The major findings of this serial IVUS comparative study are the following: (i) the rates of persistent and late-acquired

ISA after DES are similar to those previously reported after bare-metal stent implantation and vascular brachytherapy; (ii) an increase in the vessel volume (positive remodelling) is the IVUS-detected mechanism to explain late ISA occurrence; (iii) although persistent ISA could not be correlated to any adverse clinical event, the occurrence of late-acquired ISA, in this series of patients, was associated with two cases of very late stent thrombosis.

Late-acquired ISA is not a recently described phenomenon. Its occurrence has been reported following percutaneous treatment of coronary artery disease with bare metal stent implantation and also after the intravascular brachytherapy for the treatment of stent restenosis. Hong *et al.*¹⁵ analysing 881 patients (992 native lesions) treated with a bare-metal stent implantation identified late ISA in 5.4% of the cases, especially following directional coronary atherectomy and after primary stenting in acute MI. After intravascular brachytherapy, the reported incidence of late ISA varies considerably in the literature. Okura *et al.*¹⁶ analysing 44 patients from the PREVENT trial who were treated with stent and radiation with phosphorus-23, noticed an incidence of late ISA of 22%. Kalinczuk *et al.*¹⁷ analysing a consecutive series of 159 patients treated with phosphorus-32 radioactive stent implantation identified 15 cases of late-acquired ISA (9.4%).

Preliminary reports from multicentric randomized studies and single centre registries have shown different incidences of late ISA following DES deployment. Ako *et al.*¹⁰ analysing 80 patients treated with SES in the SIRIUS trial identified an incidence of late ISA of 8.7%. Tanabe *et al.*¹¹ analysing 219 patients enrolled in the TAXUS 2 trial, 113 treated with the slow-release and 116 with moderate-release paclitaxel stents, noticed the presence of late ISA in 8.0 and 9.5%, respectively. Hong *et al.*¹⁸ analysing 557 'real world' patients (705 native lesions) treated with either SES or PES identified an overall incidence of late ISA of 12.1%.

In the previously mentioned study conducted by Ako *et al.*,¹⁰ the authors identified a predominant location of late ISA in the body of the SES (78%), whereas persistent ISA, most of the time, was noticed at the edges of the stent (83%, $P < 0.01$). This same pattern was identified in our analysis. The explanation for these findings might be related to the mechanism behind ISA. While persistent ISA is most of the time related to technical aspects and plaque composition (more frequently noticed after the treatment of calcified lesions) at the baseline procedure, late-acquired ISA is more commonly related to regional remodelling, as previously demonstrated after bare metal stent implantation and vascular brachytherapy.^{19,20}

Previous studies, with short-to-middle term follow-up, have suggested that late-acquired ISA was not associated with adverse clinical events following BMS, PES, and SES implantation. The current study is the first to report long-term follow-up (> 1 year) of patients with late ISA and reports two cases of late stent thrombosis leading to acute MI and target-vessel revascularization during long-term follow-up. One patient developed stent thrombosis 40 months after the implantation of a SES in the right coronary artery (RCA) while on aspirin therapy, and was successfully treated with balloon angioplasty (*Figure 2*). The other patient suffered an anterior MI 381 days after implantation of a PES in the left anterior descending artery.

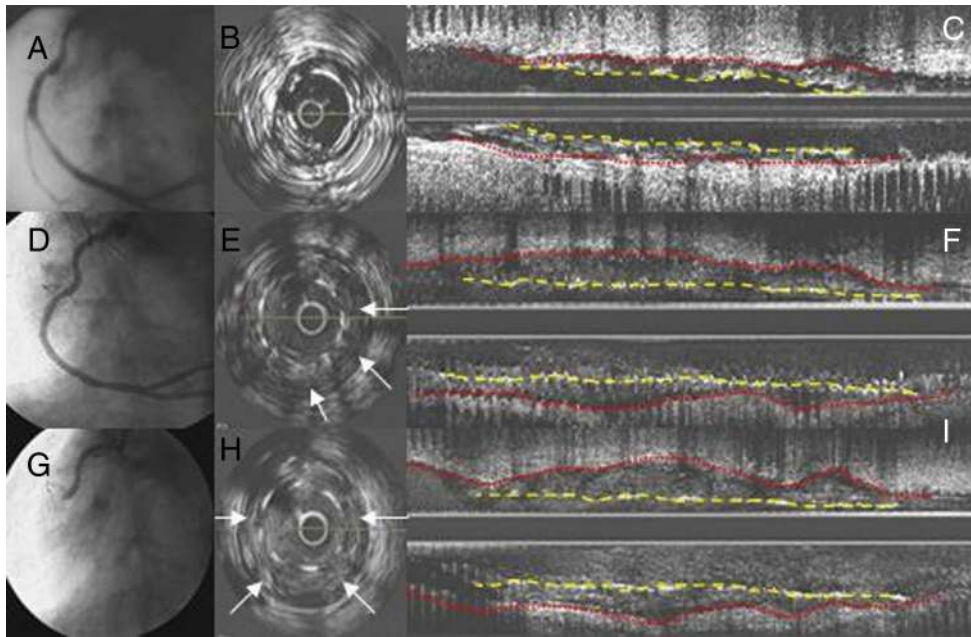


Figure 2 Top: baseline angiogram showing excellent post-procedure angiographic result of a mid-RCA lesion treated with a 3.5×18 mm Cypher stent (A). IVUS study performed right after stent implantation (B and C) confirmed the outstanding acute result. Middle: at 6 months, angiogram showed maintenance of the acute result (D); however, at the IVUS study done at that time, a clear evidence of strut separation from the vessel wall (white arrow, E) and increase in the vessel size (red dashed line, F) indicative of positive remodelling could already be noticed. Bottom: after 1152 days, the patient was admitted to the hospital with acute myocardial infarction due to stent thrombosis (G). The IVUS study done right after crossing the lesion with the wire showed an impressive progression of the diffuse positive remodelling response in the segment treated with the drug-eluting stent (H and I). The dashed line in yellow corresponds to the stent contour. The dashed line in red corresponds to external elastic membrane contour.

Primary balloon angioplasty was successfully performed. Interestingly, this patient also demonstrated late ISA in the RCA, suggesting a possible individual biological predisposition. Of note, while the mean vessel volume increase in the population with late ISA was $<25\%$ (in average 23%) and $\%$ ISA was 5.2 ± 8.7 , among the two patients who presented adverse clinical outcomes, IVUS showed a vessel volume growth $>35\%$ (around 38%) and a mean $\%$ ISA of 13.2 ± 8.7 . The magnitude of the malapposition (ISA/vessel volume index) might be related to the occurrence of these clinical adverse events.

Study limitations

Our study is a consecutive but retrospective observational analysis from a single centre experience. SESs were the predominant DES used in this series of patients preventing any comparison between these two DES. Due to the lack of pre-intervention IVUS data, the correlation between plaque characteristic and ISA could not be evaluated. Also, only a few number of lesions required more than one DES ($n = 5$), precluding any definite conclusion regarding the incidence and long-term clinical outcomes in the subset of patients with multiple and overlapping stents. Moreover, the time to follow-up IVUS (6–8 months in our study) could reflect in the incidence of ISA (e.g. the later the follow-up, the more chance of ISA having occurred).

Conclusions

In the current study, the overall incidence of IVUS-detected late incomplete DES apposition was 5.1% whereas persistent ISA was noticed in 6.6% of the cases. The mechanism to explain the late ISA formation is related to regional vessel positive remodelling. While persistent ISA does not seem

to impact clinical outcomes, the presence of late-acquired ISA was associated with two cases of serious life-threatening complications in this series of patients. The relationship between late-acquired stent malapposition and long-term stent thrombosis requires further analysis.

Conflict of interest: none declared.

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