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ORIGINAL PAPER

Stent strut coverage of titanium-nitride-oxide coated stent compared to paclitaxel-eluting stent in acute myocardial infarction: TITAX-OCT study

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Abstract Drug-eluting stents (DES) have reduced the rate of restenosis but recent studies have raised concern over the risk of late stent thrombosis (LST). Incomplete stent endothelialization and delayed vascular healing have been associated with LST. The titanium-nitride-oxide coated bio-active stent (BAS) has shown promising results in patients with acute coronary syndromes, but there is little long-term optical coherence tomography (OCT) data comparing BAS with DES. The TITAX-AMI trial is a prospective, randomized, multicenter trial comparing BAS to paclitaxel-eluting stent (PES) in 425 patients with acute myocardial infarction. A total of 18 patients (9 per group) with no major cardiac events during follow-up, were enrolled in this substudy >36 months (mean 47 months) after stent implantation. Quantitative coronary angiography was performed and stent strut endothelialization and vascular healing were assessed with OCT. The binary stent strut coverage was significantly higher in the BAS group compared with the PES group (99.6 vs. 89.2%, $p < 0.001$) and there were less malapposed struts in the BAS group (0.2 vs. 13.8%, respectively, $p < 0.001$). The neointimal hyperplasia (NIH) thickness (266 ± 166 vs. 126 μm ± 126 μm, $p < 0.001$) and percentage of NIH area (26.2 vs. 7.6%, $p < 0.001$) were greater in the BAS group than in the PES group. Late incomplete endothelialization was not uncommon after PES implantation. Stents in the BAS group were completely endothelialized. This difference may contribute to the more common LST after PES implantation in the TITAX-AMI trial.

Keywords OCT · Titanium-nitride-oxide · BAS · Paclitaxel · Myocardial infarction · Endothelialization

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Introduction

The problem of in-stent restenosis (ISR) with bare metal stents (BMS) in percutaneous coronary intervention (PCI) led to the development of drug-eluting stents (DES). Utilization of DES has lowered the rate of restenosis but recent data have raised concern over the increased rate of late stent thrombosis (LST), a potentially fatal complication, associated with DES [1–5]. Coating stents with bio-active materials is another approach to solve the issue of ISR and LST. Titan2 (Hexacath, Paris, France) bio-active stent (BAS) is a stainless steel stent coated with plasma enhanced vapour deposition of titanium in a gas mixture of nitrogen and oxygen. It has proven to be safe and effective in reducing ISR in recent clinical studies [6–12].

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Optical coherence tomography (OCT) is a new imaging modality which provides high resolution intracoronary images allowing the assessment of stent strut tissue coverage and vascular healing after stent implantation [13]. OCT studies have shown remarkable heterogeneity in vascular healing process between different DES [14–20]. Incomplete DES endothelialization has been associated with LST in a histological study [5].

The TITAX-AMI trial is a prospective, randomized, multicenter trial comparing the effectiveness and long-term effects of BAS and paclitaxel-eluting stent (PES, Taxus Liberte, Boston Scientific, Calway, Ireland) in patients presenting with acute myocardial infarction. A total of 425 patients were enrolled and randomly assigned in a 1:1 fashion. Exclusion criteria included unprotected left main disease, ostial or restenotic lesions, contraindication to aspirin, clopidogrel or heparins, life expectancy of less than a year and need for a stent longer than 28 mm. The primary endpoint was a composite of myocardial infarction, target lesion revascularisation and cardiac death [11]. The 1-year follow-up data showed no significant difference in the primary endpoint between the two groups but a trend towards a higher rate of stent thrombosis in PES treated patients [11]. At 2 years follow-up, there was a significant difference in the occurrence of stent thrombosis in favour of BAS [12].

No long-term OCT data comparing the endothelialization and vascular healing of BAS and PES are currently available. The present study aims to evaluate the vascular healing and stent endothelialization in patients treated with BAS and PES in the setting of acute myocardial infarction.

Methods

Study population and design

For the purpose of the present study, the 180 patients participating in the TITAX-AMI trial at one of the centers, the Satakunta Central Hospital, were screened from the patient records and those who were free of major adverse cardiac events (primary end point of the TITAX-AMI trial) and ISR and the follow-up time was at least 36 months were identified. These patients were contacted by telephone and a total of 20 eligible patients were willing to participate in the study after giving their written informed consent. Two patients had to be later excluded form the analyses because of inadequate OCT image quality leaving 18 patients, 9 in both groups. A quantitative coronary angiogram (QCA) and an OCT image acquisition of the primary culprit lesion were performed at the follow-up. The study was approved by the ethics committee of the Satakunta Central Hospital and complies with the declaration of Helsinki. The primary end point of the study was the difference of binary stent strut coverage (%) between BAS and PES. Co-primary end points were mean NIH thickness (μm) and stent strut malapposition.

Optical coherence tomography

OCT images were obtained after coronary angiography using the LightLab C7-XR frequency domain optical coherence tomography system (LightLab Imaging, Inc., Westford, MA, USA) with the non-occlusive technique. A motorized pullback system was used at 20 mm/s and OCT images were acquired at 100 frames per second. OCT images were analyzed off-line by two independent investigators. Stent strut coverage, stent malapposition, neointimal hyperplasia (NIH) and possible thrombosis were evaluated at 1 mm intervals (every fifth frame) in cross-sectional images.

Visible stent struts were classified into five groups: (a) Apposed to the vessel wall and covered with neointima, (b) Apposed to the vessel wall and uncovered, (c) Malapposed and covered, (d) Malapposed and uncovered and (e) Stent struts over a side branch. Binary stent strut coverage was reported as percentage of covered struts [(a) and (c)] of all analyzed struts in categories (a)–(d) Struts overlaying a side branch (e) were not classified in terms of apposition and coverage and were excluded from these calculations. The distribution of struts in categories (b)–(e) were calculated as percentages of all analyzed struts.

A stent strut was defined as covered, if there was a visible layer of tissue covering it. The thickness of the neointimal layer over each covered strut was measured. The perpendicular distance from the endoluminal surface of the strut reflection to the border of the vessel lumen was measured for struts that seemed to be protruding to the lumen. A stent strut was classified as apposed, if the distance of the endoluminal surface of the strut reflection to the border of the vessel lumen

exceeded 110 μm for BAS and 130 μm for PES. Strut malapposition was defined as previously described, and 18 μm was used as a correction for half of the blooming effect [13]. As the strut thickness of the Titan 2 stent is 91 μm, this equals 109 μm, which was rounded up to full ten microns taking into account the axial resolution (10–20 μm) of frequency-domain OCT. For Taxus Liberte stent, we added the strut thickness of 97 μm and thickness of the polymer (16 μm) and 18 μm for blooming effect to get malapposition distance of 131 μm, again rounded down to 130 μm. The existence of a side branch in a cross section was recognized by evaluating previous and subsequent cross sections as needed. If the image quality of a cross section was inadequate to allow reliable measurements, subsequent cross section with adequate quality was used for measurements. Stent area (SA) and lumen area (LA) were traced manually. NIH area was calculated by subtracting LA from SA and per cent NIH area by dividing NIH area by SA multiplied by 100. If the lumen or stent area were not measurable, they were omitted.

Quantitative coronary angiography

QCA was performed off-line using appropriate software (Philips Medical Systems, Eindhoven, The Netherlands). Measurements were made in the same two orthogonal image projections before and after the procedure and at the follow-up visit. Reference vessel diameter, minimum luminal diameter and lesion length were obtained.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation and categorical variables as the absolute frequencies and percentage. The independent samples *t* test was used to compare continuous variables when appropriate. Chi-square test was used to compare categorical variables. Percentages of malapposed and uncovered stent struts and binary stent strut coverage were also analyzed at patient level and comparison between BAS and PES was performed with Mann–Whitney *U* test, as the variables were not normally distributed. Results of patient level analyses are presented as median and interquartile range. All statistical tests were 2-sided and a p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the patients are presented in Table 1. All patients were male and there were no significant differences between the groups in the baseline characteristics or coronary risk factors. Stents in the PES group were slightly longer than in the BAS group, but the difference was of borderline significance (18.7 ± 5.7 vs. 13.7 ± 4.4, $p = 0.054$). The mean follow-up was approximately 4 years in both groups. Data on QCA are presented in Table 2 and the results of the OCT analyses in Table 3. A total of 305 cross-sections and 3141 stent struts were analyzed. More cross sections and struts were analyzed in the PES group which was mainly due to differences in stent length (Tables 1, 3).

Binary stent strut coverage was 99.6% for BAS and 89.2% for PES in the strut level analysis. When analyzed on patient level, median strut coverage was 100% (interquartile range 98.9–100%) for BAS and 94.0% for PES (83.5–96.8%) with a statistically significant difference ($p = 0.001$). There were uncovered struts in nearly half of the analyzed cross sections in the PES group (3.3% for BAS and 46.7% for PES). The distribution of stent strut apposition status and endothelial coverage in the study groups is presented in Fig. 1. The percentages of uncovered and malapposed struts and mean NIH thickness in individual patients are presented in Figs. 2 and 3. Stent strut malapposition was more common in the PES group (0.2% for BAS vs. 13.8% for PES, $p < 0.001$) and this difference remained significant in patient level analysis [0 (interquartile range 0–0%) vs. 4.41% (1.05–20.95%) respectively, $p = 0.001$). There was marked heterogeneity in the PES group and two patients had over 30% of analyzed stent struts classified as malapposed accounting for 217 of the total 271 malapposed struts in the whole PES group. If we exclude these two patients (one with overlapping stents) from the analysis, the proportions of uncovered and malapposed struts in the PES group are 7.2 and 4.1% respectively ($p = 0.001$ for both comparisons). A visible thrombus was seen in two patients (22.2%) in the PES group but not in the BAS group. There was a significant ($p < 0.001$) difference in the NIH thickness in favour of the PES group (Table 3).

Table 1 Patient and procedural characteristics

	BAS (n = 9)	PES (n = 9)	*p*
Age (years)	62 ± 6	58 ± 10	0.35
Male sex, n (%)	9 (100)	9 (100)	1.0
Diabetes, n (%)	2 (22)	2 (22)	1.0
Family history of CAD, n (%)	1 (11)	2 (22)	0.54
Hypertension, n (%)	5 (56)	5 (56)	1.0
Hypercholesterolemia, n (%)	5 (56)	3 (33)	0.36
Current smoking, n (%)	4 (44)	3 (33)	0.32
History of myocardial infarction, n (%)	1 (11)	0 (0)	0.32
Previous PCI, n (%)	2 (22)	0 (0)	0.15
NSTEMI, n (%)	5 (56)	4 (44)	0.65
STEMI, n (%)	4 (44)	5 (56)	0.65
Duration of clopidogrel treatment (months)	6.3 ± 2.4	11.3 ± 2.0	< 0.001
Stent diameter (mm)	3.14 ± 0.45	3.08 ± 0.40	0.30
Stent length (mm)	13.7 ± 4.4	18.7 ± 5.7	0.054
Predilatation, n (%)	5 (56)	7 (78)	0.33
Postdilatation, n (%)	3 (33)	4 (44)	0.64
Thrombus aspiration, n (%)	1 (11)	1 (11)	1.00
Lesion location, n (%)			0.82
LAD	7 (78)	6 (67)	
LCX	1 (11)	1 (11)	
RCA	1 (11)	2 (22)	

Values are mean ± SD unless otherwise indicated

BAS bioactive Titan-2 stent, *PES* paclitaxel-eluting Taxus stent, *CAD*, coronary artery disease, *PCI* percutaneous coronary intervention, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction

Table 2 Quantitative coronary angiography

	BAS (n = 9)	PES (n = 9)	*p*
Pre-intervention			
Reference vessel diameter (mm)	3.06 ± 0.38	3.05 ± 0.36	0.78
Lesion length (mm)	12.1 ± 4.1	12.4 ± 5.0	0.64
Minimal lumen diameter (mm)	0.18 ± 0.11	0.22 ± 0.13	0.34
Diameter stenosis (%)	94.2 ± 4.6	93.9 ± 8.5	0.26
Post-intervention			
Minimal lumen diameter (mm)	2.94 ± 0.31	2.94 ± 0.32	0.88
Diameter stenosis (%)	3.8 ± 5.6	3.6 ± 6.2	0.48
Acute gain (mm)	2.76 ± 0.42	2.72 ± 0.54	0.52
Follow-Up (months)	49 ± 5	44 ± 5	0.03
Minimal lumen diameter (mm)	2.48 ± 0.34	2.66 ± 0.40	0.21
Diameter stenosis (%)	15.6 ± 7.6	9.5 ± 9.5	0.06
Late loss (mm)	0.46 ± 0.36	0.28 ± 0.18	0.04

Values are mean ± SD unless otherwise indicated

BAS bioactive Titan-2 stent, *PES* paclitaxel-eluting Taxus stent

Discussion

To the best of our knowledge, this is the first study to evaluate the long-term vascular healing of BAS and PES by OCT. Our main finding was that the stents in the BAS group were nearly completely healed with good apposition and endothelial coverage while 10% of struts in the PES group had remained uncovered 4 years after implantation. Surprisingly, the proportion of malapposed struts in the PES group was as high

Table 3 Optical coherence tomographic measurements

	BAS (n = 9)	PES (n = 9)	*p*
Cross sections analysed (n)	123	182	
Total number of struts analysed (n)[a]	1,171	1,970	
Struts per cross section (n)	9.5 ± 2.9	10.8 ± 3.1	0.42
NIH thickness (μm)	265.8 ± 165.5	126.3 ± 126.4	<0.001
Stent area (mm)[b]	9.06 ± 2.37	8.83 ± 1.79	0.41
Lumen area (mm)[b]	6.54 ± 1.73	8.56 ± 2.41	<0.001
NIH area (mm)[b]	2.45 ± 1.50	0.59 ± 1.14	<0.001
% NIH area	26.2 ± 12.7	7.6 ± 13.5	<0.001
Binary stent strut coverage (%)[b]	99.6	89.2	<0.001
Uncovered stent struts, n (%)	5 (0.4)	212 (10.8)	<0.001
Cross sections with uncovered struts, n (%)	4 (3.3)	85 (46.7)	<0.001
Malapposed stent struts, n (%)	2 (0.2)	271 (13.8)	<0.001
Cross sections with malapposed struts, n (%)	1 (0.8)	73 (40.1)	<0.001
Presence of thrombi, n (%)	0 (0.0)	2 (22.2)	0.15

Values are mean ± SD unless otherwise indicated

BAS bioactive Titan-2 stent, *PES* paclitaxel-eluting Taxus stent

[a] Including struts over a side branch

[b] Struts over a side branch excluded

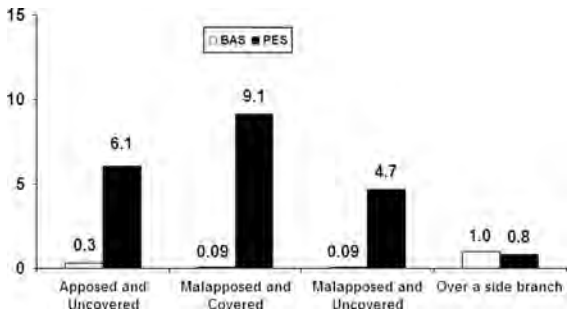

Fig. 1 Classification of stent struts. *BAS* bioactive Titan-2 stent, *PES* paclitaxel-eluting stent

as 13.8%. On the other hand, the mean neointimal thickness was significantly less in the PES group and similar difference in late loss was also seen on QCA.

Titanium is widely used in surgical implants and prostheses due to its biocompatible properties and titanium-nitride-oxide coating of the BAS is considered to have bioactive pro-healing properties. The superior endothelialization of BAS shown in the present study may also be due to the absence of polymer and drug, both of which are known to be associated with delayed vessel healing. The price of good vascular healing is thicker NIH and larger late lumen loss. However, as was shown in the main trial, this was rarely associated with clinical symptoms [11, 12].

In previous OCT studies performed 6–13 months after implantation, the prevalence of uncovered struts for PES has varied between 4–11.9 and 0.5–2.3% of struts have been malapposed [14–20]. Our findings are in agreement with the recently published OCT substudy of the HORIZONS-AMI trial where the percentage of covered struts for PES was 94.3% 13 months after acute myocardial infarction [20].

On the other hand, our findings on PES clearly differ from the OCT substudy of the SIRTAX late trial, where only 1.5% of PES struts were uncovered 5 years after implantation and and 0.7% were malapposed [21]. However, the definition of strut malapposition (>160 μm) in SIRTAX late differed from present study (130 μm).

Secondly, the present study population consisted of patients with myocardial infarction which seems to have a negative effect on strut coverage and malapposition [15]. In an OCT study comparing stent strut coverage between patients treated with DES for ACS or stable coronary artery disease, the incidence of uncovered and malapposed struts was significantly higher in ACS patients after 9 months follow-up [15]. Different mechanisms for this have been postulated including high lipid-affinity of the drugs used in DES or large thrombus burden and drug uptake of the thrombus leading to increased drug concentrations. The different patophysiology of the plaques in ACS than in stable coronary artery disease has also been proposed to cause delayed endothelialization. Also, the later lysis of jailed thrombus between the vessel wall and the stent may play a role. In previous OCT studies, the varying proportion of ACS patients may have had an effect on the lower rates of malapposed

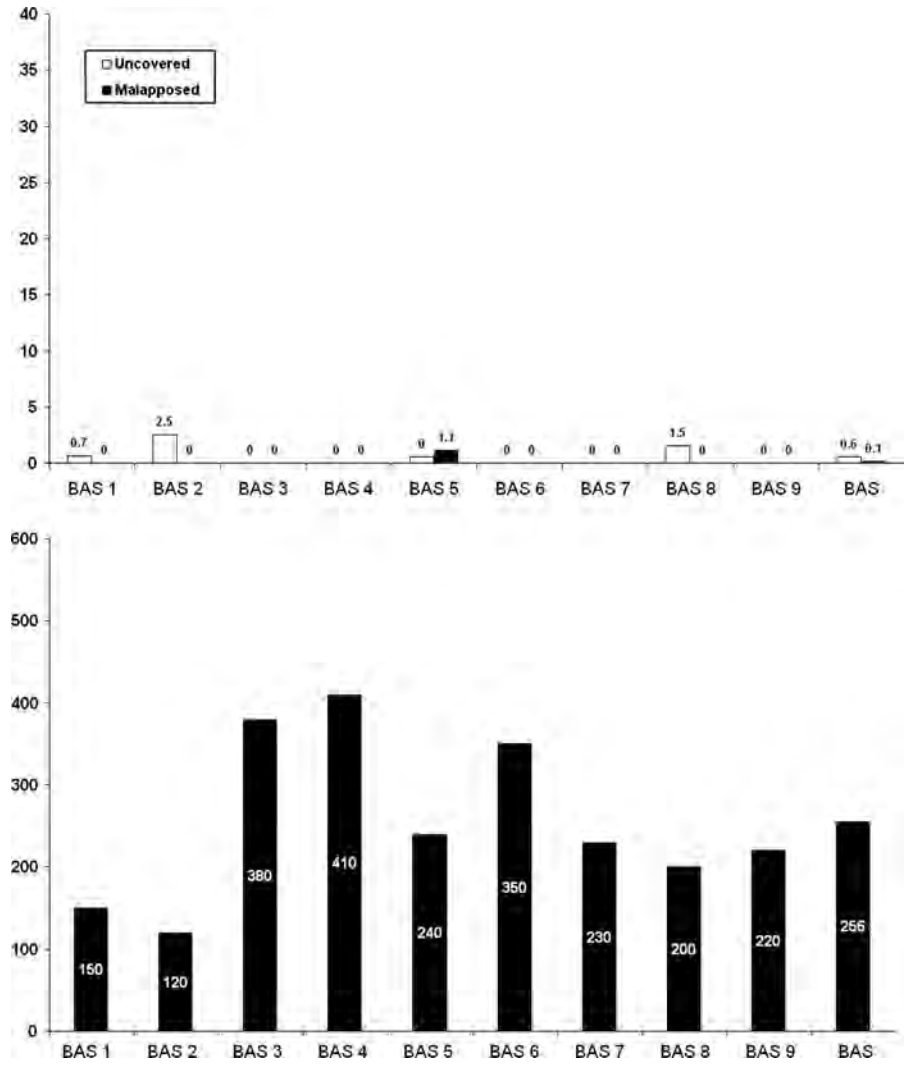

Fig. 2 Percentage (%) of uncovered and malapposed struts (*upper panel*) and the mean thickness (μm) of neointimal hyperplasia (NIH) (*lower panel*) in the 9 patients with bio-active stents (BAS)

and uncovered struts reported on PES treated patients [14–19].

Although the rate of uncovered struts in the PES group was comparable to previous studies, the percentage of struts classified as malapposed was remarkably higher. Patients in the PES group showed marked heterogeneity in vascular healing (Fig. 2). As previously noted, there were two patients in the PES group with exceptionally high amount of strut malapposition and the differences in malapposition clearly diminished on patient level analysis, but remained significant. Of note, one of the patients had overlapping stents which may increase the rate of malapposition [16]. BAS with its thicker NIH layer is more forgiving in case of initial suboptimal dilatation of the stent. However, there were no significant differences in procedural features between the two groups (Table 1).

Intracoronary thrombus formation has been reported after DES implantation in one OCT study [22]. Stent type, length and size and the amount of uncovered and malapposed struts were associated with thrombus formation [22]. Small thrombi attached to an uncovered strut were also seen on two patients in the PES group underscoring the association of delayed stent endothelialization and susceptibility to LST. These patients were naturally asymptomatic. Our findings may explain the previously reported higher incidence of LST in the PES group, although the

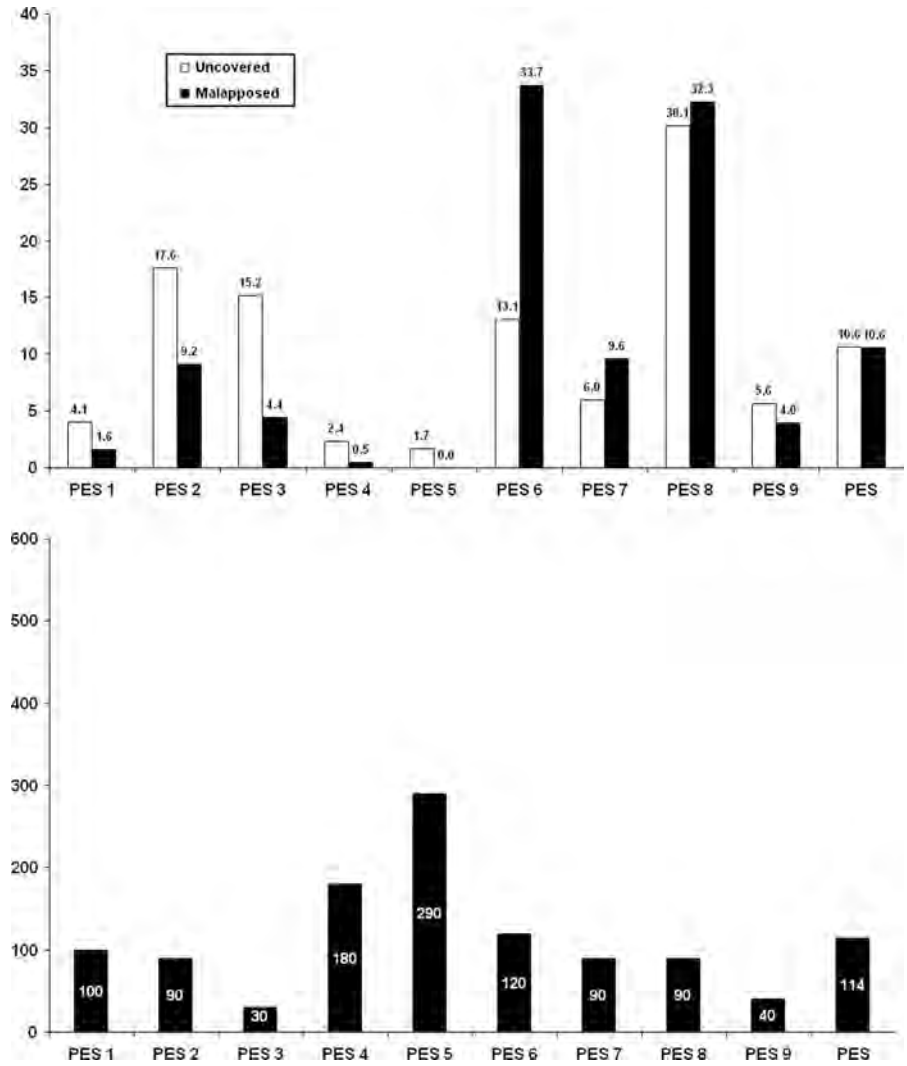

Fig. 3 Percentage (%) of uncovered and malapposed struts (*upper panel*) and the mean thickness (μm) of neointimal hyperplasia (NIH) (*lower panel*) in the 9 patients with paclitaxel-eluting stents (PES)

association of OCT findings and clinical end-points is debatable [12]. Further studies are needed to confirm these results.

Study limitations

The small size of the study groups is an obvious limitation. In the TITAX-AMI trial, the patients were randomly assigned to receive either BAS or PES, but the patients were not randomly selected for the present OCT analysis, and thus selection bias is possible. Only asymptomatic event-free patients were included and so it is possible that our results differ from patients who had suffered an adverse event during the 3–5 years of follow-up. Another limitation is the unblinded analysis of OCT studies. This was mainly due to the definition of stent strut malapposition, which depends on the different thickness of the stent strut for BAS and PES. In practice, the differences in the neointimal thickness and the visual appearance of the OCT images between the two stents are obvious to the investigator disabling the blinding procedures. If uniform cut-point for malapposition was used for both stents, this again would lead to underestimation of strut malapposition in the stent with thinner struts. The lack of baseline OCT data is another limitation. Thus it is not possible to tell whether the observed malapposition was due to incomplete stent expansion during the PCI or related to the delayed vascular healing process, or both.

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Conflict of interest None.

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