Int J Cardiovasc Imaging (2013) 29:1693–1703
DOI 10.1007/s10554-013-0285-8

ORIGINAL PAPER

Neointimal coverage and vasodilator response to titanium-nitride-oxide-coated bioactive stents and everolimus-eluting stents in patients with acute coronary syndrome: insights from the BASE-ACS trial

Pasi Karjalainen

Received: 8 April 2013 / Accepted: 24 August 2013 / Published online: 31 August 2013

Abstract Incomplete stent endothelialization is associated with late and very late stent thrombosis. In a post hoc analysis of the BASE-ACS trial, we sought to assess neointimal coverage and coronary flow reserve (CFR) 9 months after implantation of titanium-nitride-oxide-coated bioactive stents (BAS) versus everolimus-eluting stents (EES) in patients with acute coronary syndrome (ACS). In the BASE-ACS trial, 827 patients with ACS were randomized to receive either BAS or EES. In the current study, we examined neointimal growth and strut coverage by optical coherence tomography and CFR by trans-thoracic echocardiography in 28 consecutive non-diabetic patients with the culprit lesion in the left anterior descending coronary artery. The primary endpoints were binary stent strut coverage and CFR at 9-month follow-up. A total of 13 patients were included in the BAS group (2,033 struts); 15 in the EES group (2,898 struts). Binary stent strut coverage was higher and malapposed struts lower with BAS versus EES (99.4 vs 89.2, and 0.2 vs 4.6 %, respectively, $p < 0.001$ for both). Neointimal hyperplasia thickness was greater with BAS versus EES (274.2 vs 100.1 μm, respectively, $p < 0.001$). CFR was lower with EES versus BAS (2.2 ± 0.8 vs 3.0 ± 0.5, respectively, $p = 0.001$). Abnormal CFR (<2.5) were detected in 10 patients in the EES group versus one in the BAS group ($p = 0.002$). The current study demonstrated that in patients with ACS, BAS resulted in improved neointimal stent strut coverage and better coronary vasodilator function as compared with EES at 9-month follow-up.

P. Karjalainen (✉)
Satakunta Central Hospital, Pori, Finland
e-mail: pasi.karjalainen@satshp.fi

Keywords Optical coherence tomography · Coronary flow reserve · Bioactive stents · Everolimus-eluting stents

Introduction

The introduction of drug-eluting stents (DES) has revolutionized the field of interventional cardiology, since it has reduced the incidence of in-stent restenosis by 50–70 % [1]. However, worrisome data from registries and meta-analyses emphasized higher rates of late and very stent thrombosis associated with DES [2]. Although the underlying mechanisms are poorly understood, incomplete neointimal coverage over stent struts is a recognized pathologic substrate for late and very late stent thrombosis [3, 4]. Angiography and intravascular ultrasound lack the needed resolution to assess thin layers of neointimal coverage of struts, whereas optical coherence tomography (OCT) has 10 times greater resolution than intravascular ultrasound [5]. Neointimal thickness can be accurately measured with OCT, which appears to be the imaging modality of choice for assessment of neointimal coverage over stent struts.

As a sign of endothelial dysfunction, abnormal response to intracoronary acetylcholine, i.e. coronary vasoconstriction, has also been reported after DES implantation in small non-randomized series [6–8]. However, no studies combined the anatomical OCT findings with coronary vasodilator function assessment following percutaneous coronary intervention in acute coronary syndrome (ACS). Coronary flow reserve (CFR) is the ratio of maximal coronary flow velocity during adenosine-induced hyperemia to coronary flow velocity at rest. It is influenced by both coronary flow through the epicardial coronary arteries and the microcirculation.

In the multi-center randomized controlled BASE-ACS trial, bioactive stents (BAS) proved non-inferior to everolimus-eluting stents (EES) regarding clinical outcome in patients presenting with ACS at 12-month follow-up [9]. The purpose of the current study is to compare OCT-derived neointimal strut coverage, strut malapposition, and trans-thoracic echocardiography-derived CFR between BAS and EES at 9-month follow-up.

Methods

Study population

The design of the original trial has been previously reported [9]. Briefly, the BASE-ACS (randomized comparison of titanium-nitride-oxide-coated BAS with EES in ACS) trial is a prospective multi-center single-blinded randomized controlled clinical trial, with the chief aim to evaluate non-inferiority in clinical outcome of Titan2® (Hexacath, Paris, France) BAS as compared with Xience V (Abbott Vascular, Santa Clara, CA, USA) EES in patients presenting with the whole spectrum of ACS. The study enrolled a total of 827 patients above 18 years, presenting with ACS, with at least 1 significant *de novo* lesion (defined as at least 50 % diameter stenosis by visual estimation) in a native coronary artery or coronary bypass graft. Main exclusion criteria were limited to unprotected left main disease or aorto-ostial lesions, intolerance to the study medications, planned surgery within 12 months of the index procedure, and life expectancy <12 months. Enrolled patients were randomly assigned in a 1:1 fashion to receive either BAS or EES.

The current substudy was conducted at 2 of the 14 BASE-ACS sites. All consecutive patients who had lesion treated in the left anterior descending coronary artery during the index procedure, and who agreed on undergoing follow-up angiography were eligible for the study (we enrolled 28 out of 36 eligible patients). Exclusion criteria included diabetes mellitus and a new *de novo* stenosis >50 % in the stented vessel. Quantitative coronary analysis was performed before and immediately after the index procedure, and at follow-up using the same angiographic projection.

The study was conducted according to the ethical guidelines of the American Physiological Society, and was approved by all participating hospitals' ethics committees, and all patients enrolled in the study provided written informed consent for participation. The BASE-ACS trial is registered with ClinicalTrials.gov, number NCT00819923; BASE-OCT substudy with number NCT01080859; and BASE-CFR substudy with number NCT01080872.

OCT examination and analysis

Optical coherence tomography images were obtained at 9 months after the index stenting procedure, immediately after follow-up angiography, with the C7Xr frequency-domain system (LightLab Imaging Inc., Westford, MA, USA) employing the non-occlusive technique via radial or femoral approach. A 0.014-inch guide-wire was introduced into the vessel using 6 F guiding catheter. An imaging catheter (Dragonfly, LightLab Imaging, Westford, MA, USA) was positioned distal to the stent and automated motorized pullback was performed at 20 mm/s during flush of 4–6 mL/s of iso-osmolar contrast to replace blood flow and permit visualization of the stented segment. During image acquisition, a segment length of 54 mm was visualized and continuous images were stored digitally for subsequent analysis.

Offline OCT analysis was performed independently by 2 investigators who were blinded to patient characteristics as well as the type of the stent used. Proprietary software (LightLab Imaging, Westford, MA, USA) was used to analyse continuous cross-sections at 1 mm longitudinal intervals (every 5 frames) within the stented segment. In each cross-section, the number of stent struts was counted. Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen, or covered if a layer of tissue was visible all over the reflecting surfaces (Fig. 1). Binary stent strut coverage was calculated as the number of covered struts as a percentage of all analyzed struts. In covered struts, the neointimal hyperplasia (NIH) thickness was measured from the strut marker to the endoluminal edge of the tissue coverage, following a straight line connecting the strut marker with the centre of gravity of the vessel. Stent cross-sectional area (CSA) and lumen CSA were traced semi-automatically. NIH area was calculated by subtracting lumen CSA from stent CSA. Percent NIH area was calculated by dividing the NIH area by the stent CSA multiplied by 100. A metallic strut typically appears as a bright signal-intense structure with dorsal shadowing. Apposition was assessed strut by strut, by measuring the distance between the strut marker and the lumen contour. The marker of each strut was placed at the endoluminal leading edge, at the mid-point of its long axis, and the distance was measured following a straight line connecting this marker with the center of gravity of the vessel (Fig. 1). Struts with distance to lumen contour greater than the sum of strut thickness + polymer thickness + 18 μm were considered as malapposed. A margin of 18 μm was added as a correction for half of the blooming. Given a coated strut thickness of 91 μm, we adopted a malapposition threshold of 110 μm for the Titan2® stent (91 + 0 + 18 = 109 μm). Similarly, given a strut thickness of 79 μm and a polymer thickness of 16 μm, we adopted the same malapposition

threshold (110 μm) for the Xience V stent (79 + 16 + 18 = 113 μm). Struts located at the ostium of side branches, with no vessel wall behind, were labelled as non-apposed side branch struts and excluded from the analysis. To evaluate the distribution of uncovered and malapposed struts as well as NIH thickness, all stents were divided in 3 sections with similar length; distal, middle and proximal part of stent. In-stent thrombus was defined as an irregular high- or low-backscattering (red or white thrombus) mass protruding into the vessel lumen discontinuous from the surface of the stent struts [10]. Inter-observer variability was assessed by evaluating 50 random cross-sectional images by 2 independent investigators.

Coronary flow reserve

Subjects were instructed to avoid large meals, caffeine, alcohol and tobacco for 12 h before the study. Transthoracic echocardiography including coronary flow velocity measurements was carried out with an Acuson Sequoia C 512 mainframe (Acuson Inc., Mountain View, CA, USA) using a 4.0 MHz transducer. Echocardiographic dimensions, wall motion abnormalities and valves were assessed using standard methods. All the coronary flow velocity measurements were carried out before coronary angiography and analyzed blinded to the clinical data. B-mode and color-Doppler mapping were used to

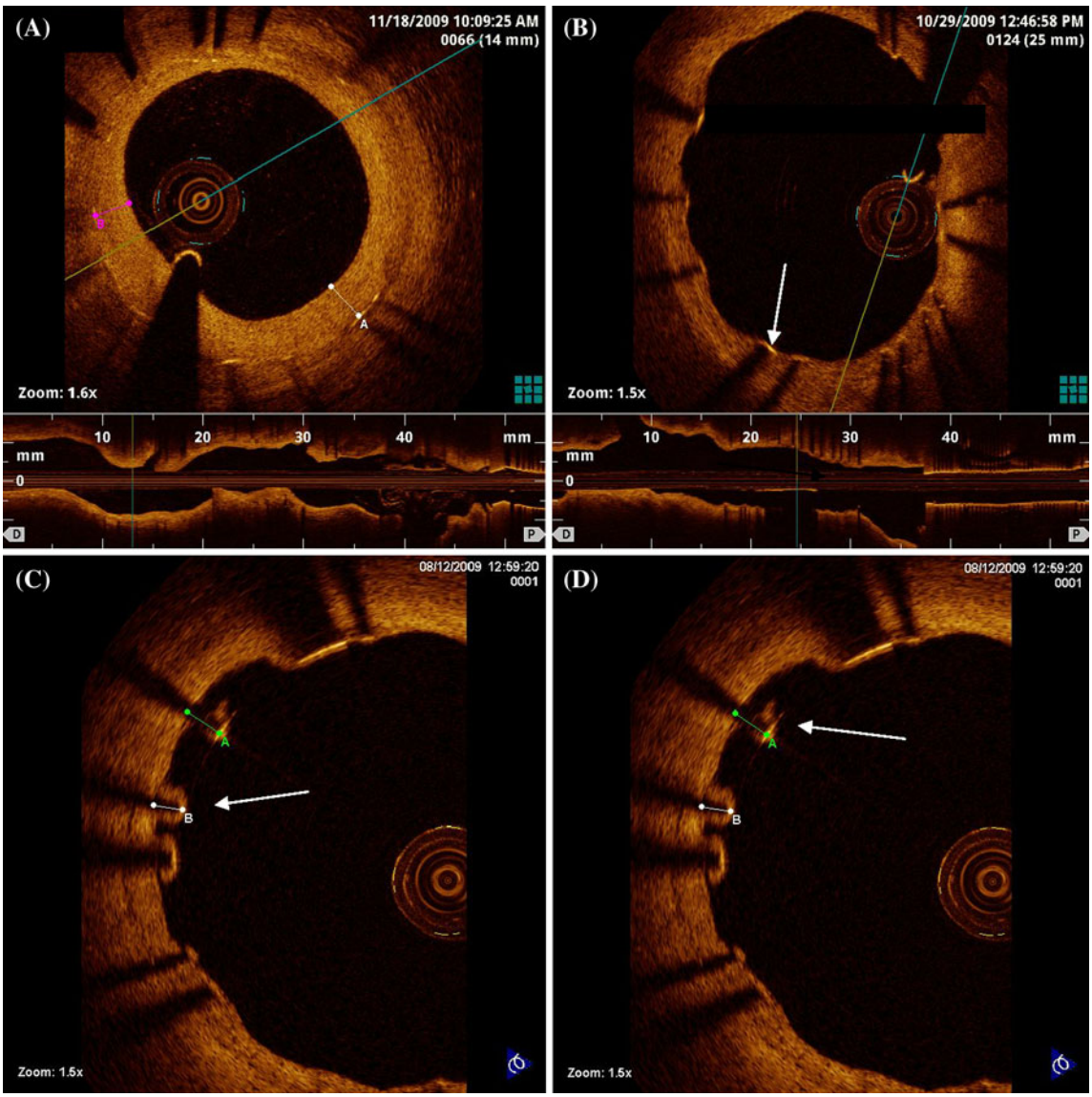

Fig. 1 Apposition and coverage of stent struts—apposition and coverage of struts: **A** apposed and covered, **B** apposed and uncovered, **C** malapposed and covered, **D** malapposed and uncovered

identify the distal left anterior descending coronary artery as previously described [11, 12]. Baseline flow velocity was measured with pulsed-wave Doppler as an average of at least 3 cardiac cycles. Hyperemia was induced by infusion of adenosine (Adenosin Item, Item Development AB, Sweden) at a rate of 0.14 mg/kg/min. Flow velocity profiles were recorded using pulsed-wave Doppler at rest and monitored throughout the adenosine infusion to confirm that highest flow velocity response during infusion was recorded. In offline analysis, the mean diastolic velocity was measured at baseline and during adenosine infusion. CFR was calculated as the hyperemia-to-baseline mean diastolic velocity ratio. Intra- and inter-observer variability of CFR measurements (coefficient of variation) in our laboratory were 2.6 ± 4.0 and 8.6 ± 9.8 %, respectively [11, 12].

Statistical analysis

The primary endpoints of the study were binary stent strut coverage and CFR. For OCT data, it was assumed that an average number of 150 struts per patient will be analyzed, and therefore we estimated that inclusion of 12 patients in each study group will show 5 % difference in binary stent strut coverage between BAS and EES (power 80 %, 2-sided type I error of 0.5). For CFR data, a sample size of 17 subjects was calculated for each group with a known SD of 0.7 for CFR and an assumed difference of 0.7 between the interventions ($\alpha = 0.05$, $\beta = 0.80$). Co-primary endpoints were the mean NIH thickness and stent strut malapposition. Continuous variables were reported as the mean $\pm$ standard deviation, as well as median and range. Fisher exact test, Mann–Whitney test and Spearman's test were used for univariate analyses. Continuous variables such as stent CSA, lumen CSA, NIH area, and NIH thickness were estimated as medians and the latter used for analysis. This was done because the number of measurements of stent area and lumen area for each stent was rather small (mean 17 ± 6, median 17, range 4–29). Percentages of malapposed stent struts and binary stent strut coverage were also analyzed at stent-level and comparison between BAS and EES was performed with Mann–Whitney U test, since the variables were not normally distributed. Results of stent-level analyses were presented as median and interquartile range. Pooled analysis of NIH thickness measurements was performed using Meta-analyst Beta 3.13 software (http://tuftscaes.org/meta_analyst/) in order to get a better estimation of NIH thickness as derived by a large number of measurements obtained by OCT. The results of pooled analysis were expressed as pooled proportions (%) with 95 % confidence interval (95 % CI). Because heterogeneity was anticipated among the observational studies, it was assessed a priori by a random effects model (DerSimonian–Laird). Meta-regression analysis was used to estimate the difference between the study groups. Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, Ill., USA).

Results

Baseline clinical and angiographic characteristics

In the BASE-ACS study, the rate of major adverse cardiac events were comparable between BAS and EES (9.6 vs 9.0 %, $p = 0.81$) at 12-month follow-up [9]. Baseline clinical characteristics of the 28 patients included in the OCT substudy (13 with BAS and 15 with EES) are presented in Table 1. Characteristics were similar in both study groups, except that patients in the EES group were older. Similarly, lesion and procedural characteristics were comparable between the 2 study groups (Table 2). Control angiography was performed at 10.1 ± 2.2 months in the

Table 1 Baseline clinical characteristics in the two individual study groups

	BAS (N = 13)	EES (N = 15)	*p value*
Age (years)	61 ± 9	69 ± 6	0.01
Male gender	10 (76.9)	13 (86.7)	0.51
Risk Factors			
Hypertension	4 (30.1)	6 (40.0)	0.62
Hypercholesterolemia	7 (53.8)	6 (40.0)	0.47
Current smoking	3 (23.1)	2 (13.3)	0.51
Medical history			
Myocardial infarction	0	0	
PCI/CABG	0	0	
Medications at discharge			
Aspirin	13 (100)	15 (100)	1.0
Clopidogrel	13 (100)	15 (100)	1.0
ACE-inhibitors/AT-antagonists	7 (53.8)	4 (26.7)	0.15
Beta-blockers	13 (100)	15 (100)	1.0
Nitrates	1 (7.7)	1 (6.7)	0.92
Statins	12 (92.3)	15 (100)	0.28
Indication for PCI			
Unstable angina	0	2 (13.3)	0.18
NSTEMI	8 (61.5)	9 (60.0)	0.94
STEMI	5 (38.5)	4 (26.7)	0.51

Continuous variables are presented as mean $\pm$ SD, while categorical variables are presented as frequency (percentage)

BAS bioactive stent, *EES* everolimus-eluting stent, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *ACE* angiotensin converting enzyme, *AT* angiotensin II receptor, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction

BAS group and 9.8 ± 2.0 months in the EES group ($p = 0.69$). Duration of clopidogrel treatment was similar in the 2 study groups (6.9 ± 2.3 vs 7.6 ± 2.8 months, $p = 0.49$, respectively). At follow-up angiography, more late loss was observed in the BAS group with a subsequent mean diameter stenosis (%) of 17.4 ± 14.2 for BAS and 6.6 ± 8.5 for EES (Table 2). On the other hand, no *de novo* lesions were observed in the stented vessels in either study group.

Table 2 Lesion and procedural characteristics in the two individual study groups

	BAS (N = 13)	EES (N = 15)	*p value*
AHA/ACC lesion type			
A	1 (7.7)	2 (13.3)	
B1/B2	9 (69.2)	11 (73.3)	
C	3 (23.1)	2 (13.3)	
Bifurcation lesion	7 (53.8)	6 (40.0)	0.47
Calcified lesion	8 (61.5)	6 (40.0)	0.26
Thrombus	8 (61.5)	6 (40.0)	0.26
Stent diameter (mm)	3.10 ± 0.38	3.12 ± 0.35	0.88
Stent length (mm)	15.8 ± 5.1	18.7 ± 5.9	0.18
Post-TIMI flow grade 3	13 (100)	15 (100)	1.0
Radial access	10 (76.9)	9 (60.0)	0.35
Thrombus aspiration	4 (30.8)	4 (26.7)	0.81
Pre-dilatation	7 (63.6)	11 (73.3)	0.29
Post-dilatation	4 (30.8)	7 (46.7)	0.40
Pre-Intervention			
Reference vessel diameter (mm)	3.00 ± 0.37	3.04 ± 0.35	0.79
Lesion length (mm)	12.4 ± 5.2	13.9 ± 4.6	0.41
Minimal lumen diameter (mm)	0.11 ± 0.07	0.21 ± 0.16	0.08
Diameter stenosis (%)	96.2 ± 4.5	92.9 ± 8.3	0.22
Post-Intervention			
Minimal lumen diameter (mm)	2.90 ± 0.31	2.93 ± 0.32	0.81
Diameter stenosis (%)	3.4 ± 5.3	3.6 ± 5.6	0.76
Acute gain (mm)	2.79 ± 0.39	2.73 ± 0.42	0.42
Follow-up, months	10.1 ± 2.2	9.8 ± 2.0	0.69
Duration of clopidogrel treatment (months)	6.9 ± 2.3	7.6 ± 2.8	0.49
Minimal lumen diameter (mm)	2.41 ± 0.38	2.74 ± 0.44	0.06
Diameter stenosis (%)	17.4 ± 14.2	6.6 ± 8.5	0.003
Late loss (mm)	0.49 ± 0.34	0.19 ± 0.24	0.001

Continuous variables are presented as mean ± SD, while categorical variables are presented as frequency (percentage)

BAS bioactive stent, *EES* everolimus-eluting stent, *TIMI* thrombolysis in myocardial infarction

Optical coherence tomography data

Optical coherence tomography image acquisition was successful in all patients and no OCT procedure-related complications. The primary endpoint of binary stent strut coverage was significantly higher in the BAS as compared with the EES group (99.4 vs 89.2 %, $p < 0.001$, respectively) (Table 3). In stent-level analysis, the median (interquartile range) strut coverage was 99.4 % (98.6–100 %) for BAS and 94.1 % (83.8–97.3 %) for EES ($p < 0.001$). Stent strut malapposition was less common in the BAS group (0.2 % for BAS vs 4.6 % for EES, $p < 0.001$) and this difference remained significant in stent-level analysis [0.0 % (0.0–0.2 %) vs 1.5 % (0.0–6.4 %) respectively, $p = 0.003$]. The mean NIH thickness was 274.2 μm (median 250, range 10–950 μm) in the BAS group and 100.1 μm (median 70, range 10–110) in the EES group ($p < 0.001$). Pooled analyses showed that the mean NIH thickness was 277 μm (95 % CI 228–326) in the BAS group and 94 μm (95 % CI 78–111) in the EES group (mean difference at meta-regression: 161 μm) (Fig. 2). None of the clinical and procedural variables were associated with strut coverage or NIH thickness. Small intra-stent thrombus was seen in 1 patient in EES group during the OCT. Figure 3 presents the distribution of strut-lumen distance in the study groups across all visible struts. A higher rate of negative measurements was observed with EES as a sign of stent strut malapposition. When the stent was divided into distal, middle and proximal parts, the mean NIH thickness was 261, 302, and 271 μm in the BAS group; and 109, 103, and 82 μm in the EES group, respectively. In the EES group, 13.9 % of struts were uncovered in the proximal end of the stent (distal end 9.1 %, $p < 0.001$), whereas a similar proportion of malapposed struts were observed in the middle and proximal part of EES (Fig. 4). Inter-observer variability for the same cross-sectional measurements of NIH thickness was 6 ± 9 μm (r = 0.954). In addition, inter- and intra-observer analysis of stent strut apposition and coverage were highly reproducible with virtually perfect agreement (κ = 0.867 and 0.894, respectively).

Coronary flow reserve data

Average CFR was significantly lower in the EES group as compared with the BAS group (2.2 ± 0.8 vs 3.0 ± 0.5, $p = 0.001$). CFR values below 2.5 were detected in 10 (66.7 %) patients with EES, but only in 1 (7.7 %) patient with BAS ($p = 0.002$, Fig. 5). The ejection fraction was comparable in patients with low CFR (<2.5) and those with normal CFR (69 ± 10 vs 66 ± 11, $p = 0.38$). None of the patients had anterior wall akinesia (as a sign of transmural scar) in either group, and even local hypokinesia was rare (EES n = 1, BAS n = 2).

Table 3 Optical coherence tomography measurements in the two individual study groups

	BAS (N = 13)	EES (N = 15)	*p value*
Cross sections analysed	214	284	
Total number of struts analysed	2,033	2,898	
Struts per cross-section	9.5 ± 2.8	10.2 ± 3.1	0.83
NIH thickness (μm)	274.2 ± 168.3	100.1 ± 101.0	<0.001
Stent CSA (mm^2)	6.7 ± 2.0	6.8 ± 2.3	0.92
Lumen CSA (mm^2)	4.7 ± 1.6	6.2 ± 2.5	<0.001
NIH area (mm^2)	2.0 ± 1.1	0.6 ± 0.8	<0.001
% NIH area	29.7 ± 12.3	10.8 ± 16.2	<0.001
Strut analysis			
Binary stent strut coverage (%)	99.4	89.2	<0.001
Apposed and uncovered	10 (0.5)	213 (7.3)	<0.001
Malapposed and covered	1 (0.05)	31 (1.1)	<0.001
Malapposed and uncovered	3 (0.1)	101 (3.5)	<0.001
Strut over a side branch	56 (2.8)	76 (2.6)	0.66
Uncovered stent struts	13 (0.6)	314 (10.8)	<0.001
Cross-sections with uncovered struts	10 (4.7)	105 (37.0)	<0.001
Malapposed stent struts	4 (0.2)	132 (4.6)	<0.001
Cross-sections with malapposed struts	3 (1.4)	37 (13.0)	<0.001
Presence of thrombus	0 (0)	1 (6.7)	0.67

Continuous variables are presented as mean ± SD, while categorical variables are presented as frequency (percentage)

BAS indicates bioactive stent, *EES* everolimus-eluting stent, *NIH* neointimal hyperplasia; *CSA* cross-sectional area

Discussion

Major findings

The BASE-ACS study was the first prospective randomized trial to compare BAS with EES in patients with ACS and it demonstrated a similar clinical outcome with BAS and EES at 12-month follow-up [9]. In the current substudy, the frequency of uncovered stent struts was significantly higher with EES than BAS at 9-month follow-up, and coronary vasodilator capacity was often blunted with EES at 9-month follow-up, whereas it was within normal range in most patients with BAS. These findings suggest better vascular functional healing with BAS as compared with EES at 9-month follow-up. The more pronounced NIH over BAS was a logical price to pay for the better tissue coverage.

Neointimal stent strut coverage

DES effectively prevent in-stent restenosis but have been associated with increased risk of late stent thrombosis. Potential substrates of late stent thrombosis include poor endothelialisation and delayed vascular healing, which contrasts with nearly complete stent endothelialisation associated with bare-metal stents [3, 4]. In addition, toxicity of the drug and polymer along with subsequent incomplete strut neointimal coverage have been associated with pathological vascular response with DES [3, 4]. Previous OCT studies demonstrated considerable rates of uncovered struts with sirolimus-eluting stents (2.1–14.2 %) as well as with paclitaxel-eluting stents (4.9–12.9 %) at 6–9-months follow-up [13–22]. In the current study, the percentage of uncovered struts associated with EES (10.8 %) was in line with earlier studies of first-generation DES. An OCT substudy of the RESOLUTE All-Comers trial demonstrated that the rate of uncovered struts associated with EES at 13-month follow-up was 5.8 % [23]. Recently, a rate of 0.3–0.9 % of uncovered struts was observed with OCT in patients who received zotarolimus-eluting stents [14, 16, 20, 21, 24]. These numbers are comparable with that observed in the current study with BAS (0.6 %).

Neointimal hyperplasia thickness

As expected, the mean NIH thickness was significantly lower in the EES group, since EES is essentially designed to reduce in-stent restenosis. Previous studies have shown a mean NIH thickness of 31–88 μm with sirolimus-eluting stents which is comparable to the measures we observed with EES [13–20]. On the other hand, NIH thickness tended to be greater with paclitaxel-eluting stents (90–200 μm) and zotarolimus-eluting stents (210–333 μm) in previous observational studies when compared to present findings with EES [13, 14, 16, 17, 20–24]. Furthermore, late loss measured by angiography correlated with OCT measurements, and therefore patients with larger late loss potentially had thicker NIH compared with those with smaller late loss. In the current study, NIH thickness in BAS group was comparable to zotarolimus-eluting stents in previous studies. Of note, angiographic late loss is estimated to be 0.5–0.6 with BAS and zotarolimus-eluting stents, alike, according to previous studies [25–27].

Stent strut malapposition

The percentage of malapposed struts was considerable in the EES group at 9-month follow-up. According to previous data, the rate of malapposed struts was 0.4–2.6 % with sirolimus-eluting stents, ~1.5 % with paclitaxel-eluting stents and 0.2–0.8 % with zotarolimus-eluting stents at 6–9-

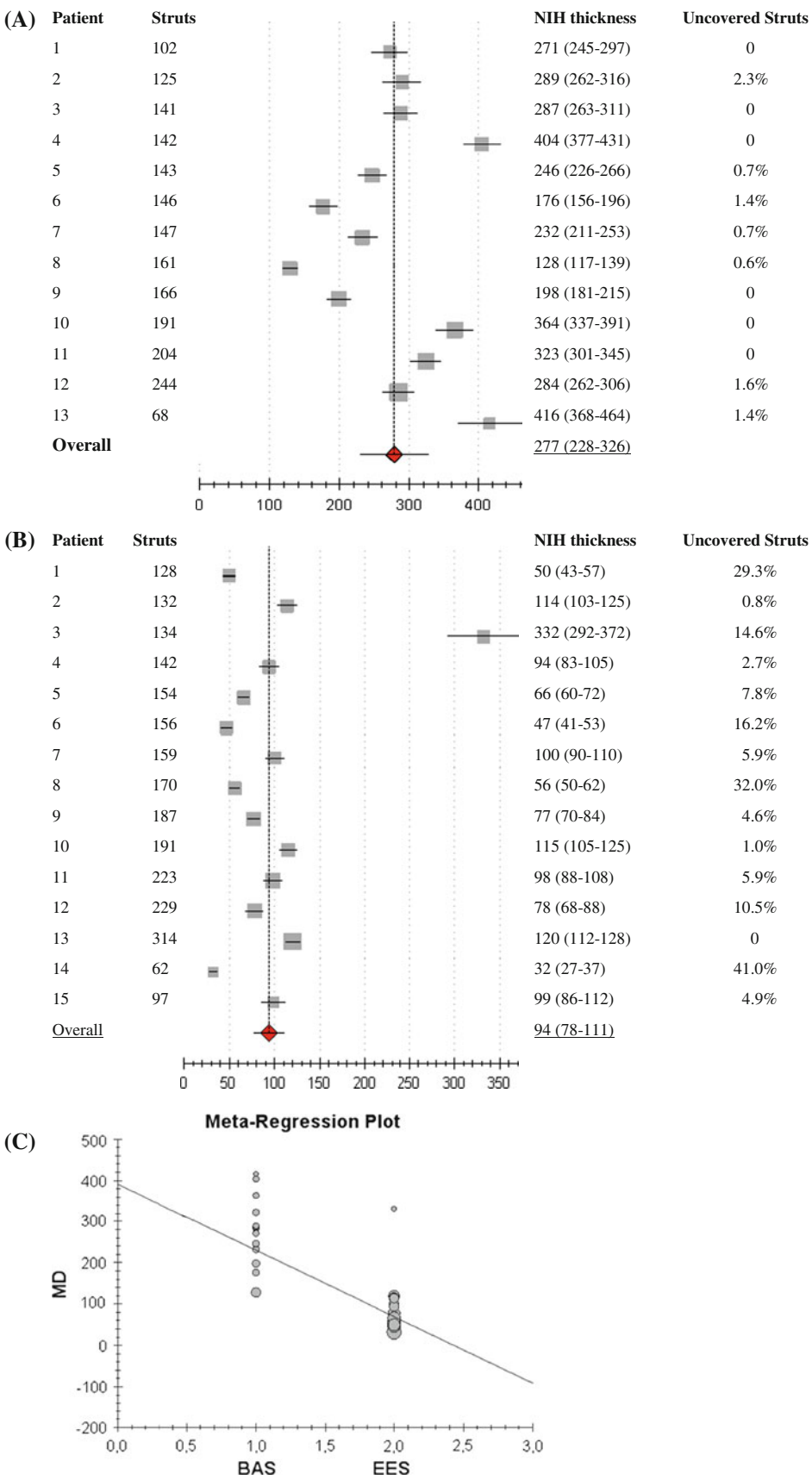

Fig. 2 Neointimal hyperplasia thickness and percentage of uncovered struts—distribution of neointimal hyperplasia thickness and percentage of uncovered struts 9 months after stent implantation in the BAS (**A**) and EES (**B**) groups, mean difference at meta-regression (**C**). *BAS* indicates bioactive stents, *EES* everolimus-eluting stents, *MD* mean difference, *NIH* neointimal hyperplasia

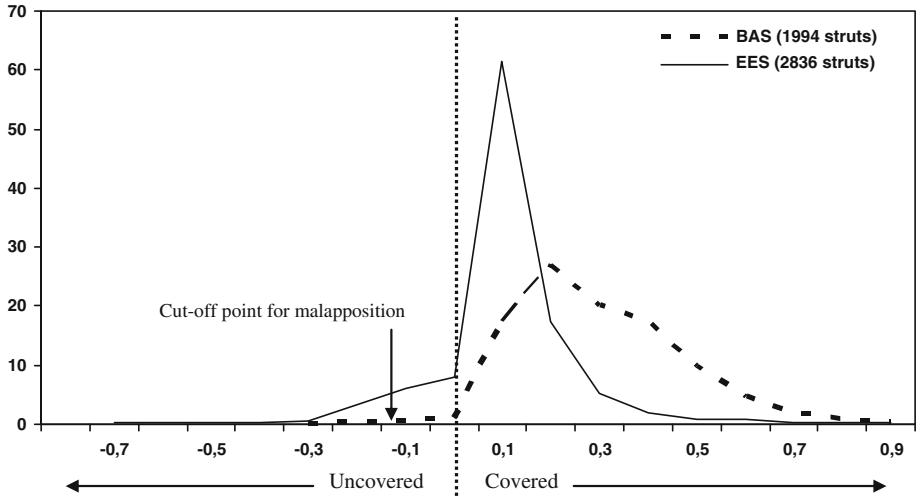

Fig. 3 Strut-lumen distance—frequency distribution of strut-lumen distance in the bioactive and everolimus-eluting stent groups

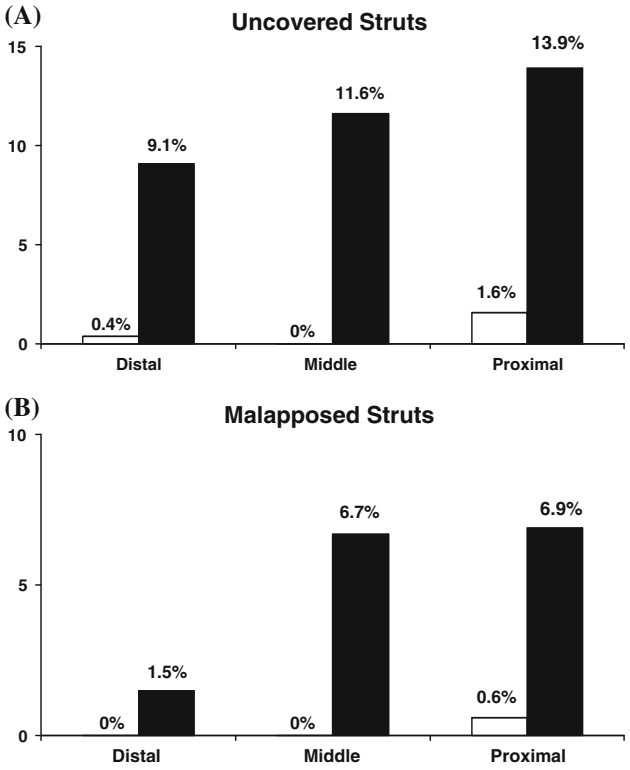

Fig. 4 Distribution of uncovered and malapposed struts—distribution of uncovered (**A**) and malapposed (**B**) struts in the distal, middle, and proximal parts of the stent in the bioactive and everolimus-eluting stent groups. *White bars* indicate bioactive stents, *black bars* everolimus-eluting stents

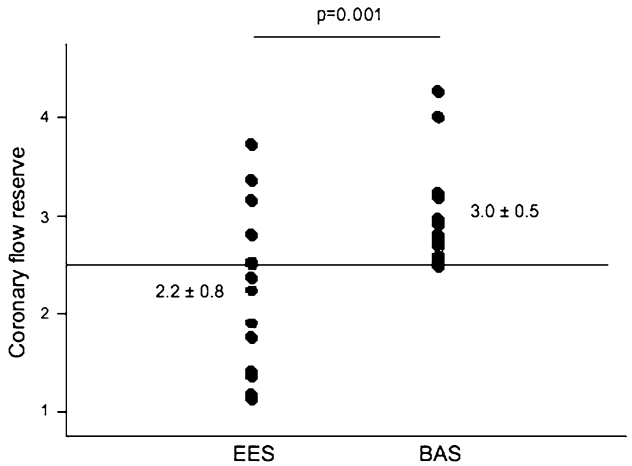

Fig. 5 Coronary flow reserve values—individual coronary flow reserve values in the bioactive and everolimus-eluting stent groups. *BAS* indicate bioactive stents, *EES* everolimus-eluting stents

month follow-up [14–24]. In the current study, the frequency of malapposed struts at 9-month follow-up was higher with EES compared with BAS. Intra-vascular ultrasound studies showed that late stent malapposition occurred in 12.1 % of first-generation DES at 6 months, mostly due to positive vessel remodelling [28]. A recent meta-analysis demonstrated that the rates of late stent malapposition were significantly higher with DES versus bare-metal stents [29]. Similarly, in patients with ST-elevation myocardial infarction who underwent primary angioplasty, the incidence of late stent malapposition was more common with paclitaxel-eluting stents versus bare-metal stents [30]. However, late stent malapposition in these reports was not associated with adverse clinical events. In the current study, the mean percentage of malapposed struts per patient was higher in the EES group (4.6 % for EES vs 0.2 % for BAS) indicating substantial strut malapposition with EES. Comparably, the rate of malapposed struts associated with EES in the OCT substudy of the RESOLUTE All-Comers trial was 1.4 % at 13-month follow-up [23].

Coronary flow reserve

The functional healing was assessed using CFR measurement, which was previously shown to predict adverse events and prognosis when added to standard evaluation in

large unselected patient populations, as well as in high risk patients with ACS [31–33]. In a mechanistic sense, CFR reflects global atherosclerotic burden, endothelial dysfunction, and microvascular damage, more than just mirroring focal coronary disease [33]. Our study protocol attempted to minimize the effects of the major confounding factors in CFR assessment. Hemodynamically significant epicardial stenosis, or in the absence of stenosis, coronary microvascular dysfunction can decrease CFR [11]. Restenosis and de novo stenosis were ruled out by angiography. Diabetics, who are prone to coronary microvascular dysfunction, were excluded from the study and none of the patients had transmural infarcts in either group. Older age is known to attenuate CFR response by increasing baseline flow. It is likely that the difference in age could explain, at least in part, the CFR difference between the 2 groups [34].

To the best of the authors' knowledge, the current study was the first to use trans-thoracic echocardiography-derived CFR in combination with OCT in the assessment of long-term vessel healing after coronary stenting. Previously, impaired vasomotor function was detected at long-term follow-up after sirolimus-eluting stent implantation using rapid atrial pacing, intracoronary acetylcholine infusion, or dynamic exercise to induce vasodilation [35–37]. These invasive procedures involve a potential, albeit little, risk for complications. The rationale for choosing trans-thoracic echocardiography-derived CFR measurement was the safety and repeatability of this non-invasive method.

Although we have no certain information regarding the mechanisms responsible for lower CFR in patients with EES, earlier research provides helpful clues. Functional endothelial re-growth is important because, besides providing essential antithrombotic factors, more intact endothelium may better preserve vasodilator function. Previously, paclitaxel and sirolimus have been shown to increase tissue factor mRNA and protein expression in endothelial cells in vitro [38, 39], and these agents are known to increase local production of plasminogen activator inhibitor PAI-1 in cultured endothelial cells [40], which in turn may promote prothrombotic activity. Another potential explanation is that atherosclerosis and other plaque-related factors such as thrombus may affect the arterial responses to DES [41]. All patients had ACS during the index procedure. Taken together, in the case of incomplete stent strut coverage, there may be lack of functional endothelium, which would provide essential antithrombotic and vasodilator substances such as nitric oxide, and thus maintain structural integrity of the vessel wall.

Limitations of the study

The current study included a relatively limited sample size and therefore the results should be interpreted cautiously. Second, the current OCT technology cannot detect tissue coverage <10 μm, and thus cannot differentiate ultra-thin layers of neointima. Moreover, OCT data before and immediately after the index procedure were not available. Additionally, our findings apply to a highly selected cohort of patients with ACS who are non-diabetic and had lesions treated in the left anterior descending coronary artery during the index procedure. And although the cohort included nearly 50 % bifurcation lesions, non-apposed side branch struts were excluded from analysis. This might introduce selection bias. Furthermore, it should be noted that some OCT studies performed OCT cross-sectional analysis at 0.6 mm intervals, in contrast to the analysis at 1 mm intervals adopted in our study [22, 24]. These non-direct comparisons should be interpreted with caution, as different methodologies of OCT analysis can lead to different results. Finally, this study is underpowered to correlate clinical endpoints with OCT findings. Therefore, larger studies are needed to address the clinical implications of these results.

Conclusion

The current substudy demonstrated that in patients presenting with ACS, BAS with a titanium-nitride-oxide coating results in improved strut neointimal coverage as compared with EES at 9-month follow-up. Additionally, EES was associated with reduced coronary vasodilator function.

Conflict of interest The authors have no conflict of interests to declare.

References

1. Stone GW, Ellis SG, Cox DA et al (2004) A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 350:221–231
2. Daemen J, Wenaweser P, Tsuchida K et al (2007) Early and late coronary stent thrombosis of sirolimus eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 369:667–678
3. Joner M, Finn AV, Farb A et al (2006) Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 48:193–202
4. Finn AV, Joner M, Nakazawa G et al (2007) Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 115:2435–2441
5. Prati F, Regar E, Mintz GS et al (2010) Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J 31:401–415
6. Fujii K, Kawasaki D, Oka K et al (2011) Endothelium-dependent coronary vasomotor response and neointimal coverage of

zotarolimus-eluting stents 3 months after implantation. Heart 97:977–982
7. Kim JW, Seo HS, Park JH et al (2009) A prospective, randomized, 6-month comparison of the coronary vasomotor response associated with a zotarolimus-versus a sirolimus-eluting stent: differential recovery of coronary endothelial dysfunction. J Am Coll Cardiol 53:1653–1659
8. Obata J, Nakamura T, Kitta Y et al (2009) Treatment of acute myocardial infarction with sirolimus-eluting stents results in chronic endothelial dysfunction in the infarct-related coronary artery. Circ Cardiovasc Interv 2:384–391
9. Karjalainen PP, Niemelä M, Airaksinen JK et al (2012) A prospective randomised comparison of titanium-nitride-oxide-coated bioactive stents with everolimus-eluting stents in acute coronary syndrome: the BASE-ACS trial. EuroIntervention 8:306–315
10. Kume T, Akasaka T, Kawamoto T et al (2006) Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol 97:1713–1717
11. Kiviniemi T (2008) Assessment of coronary blood flow and the reactivity of the microcirculation non-invasively with transthoracic echocardiography. Clin Physiol Funct Imaging 28:145–155
12. Kiviniemi TO, Toikka JO, Koskenvuo JW et al (2007) Vasodilation of epicardial coronary artery can be measured with transthoracic echocardiography. Ultrasound Med Biol 33:362–370
13. Murakami D, Takano M, Yamamoto M et al (2009) Advanced neointimal growth is not associated with a low risk of in-stent thrombus. Optical coherence tomographic findings after first-generation drug-eluting stent implantation. Circ J 73:1627–1634
14. Kim JS, Jang IK, Kim TH et al (2009) Optical coherence tomography evaluation of zotarolimus-eluting stents at 9-month follow-up: comparison with sirolimus-eluting stents. Heart 95:1907–1912
15. Katoh H, Shite J, Shinke T et al (2009) Delayed neointimalization on sirolimus-eluting stents: 6-month and 12-month follow up by optical coherence tomography. Circ J 73:1033–1037
16. Kim JS, Fan C, Choi D et al (2011) Different patterns of neointimal coverage between acute coronary syndrome and stable angina after various types of drug-eluting stents implantation; 9-month follow-up optical coherence tomography study. Int J Cardiol 146:341–346
17. Kim JS, Kim TH, Fan C et al (2010) Comparison of neointimal coverage of sirolimus-eluting stents and paclitaxel-eluting stents using optical coherence tomography at 9 months after implantation. Circ J 74:320–326
18. Moore P, Barlis P, Spiro J et al (2009) A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. JACC Cardiovasc Interv 2:437–444
19. Barlis P, Regar E, Serruys PW et al (2010) An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. Eur Heart J 31:165–176
20. Kim JS, Hong MK, Fan C et al (2010) Intracoronary thrombus formation after drug-eluting stents implantation: optical coherence tomographic study. Am Heart J 159:278–283
21. Motreff P, Souteyrand G, Levesque S et al (2009) Comparative analysis of neointimal coverage with paclitaxel and zotarolimus drug-eluting stents, using optical coherence tomography 6 months after implantation. Arch Cardiovasc Dis 102:617–624
22. Guagliumi G, Sirbu V, Musumeci G et al (2010) Strut coverage and vessel wall response to a new generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: optical coherence tomography drug-eluting stent investigation (OCTDESI). Circ Cardiovasc Interv 3:367–375
23. Gutiérrez-Chico JL, van Geuns RJ, Regar E et al (2011) Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. Eur Heart J 32:2454–2463
24. Guagliumi G, Sirbu V, Bezerra H et al (2010) Strut coverage and vessel wall response to zotarolimus eluting and bare-metal stents implanted in patients with st-segment elevation myocardial infarction: the OCTAMI (optical coherence tomography in acute myocardial infarction) study. JACC Cardiovasc Interv 3:680–687
25. Fajadet J, Wijns W, Laarman GJ et al (2010) Long-term follow-up of the randomised controlled trial to evaluate the safety and efficacy of the zotarolimus-eluting driver coronary stent in de novo native coronary artery lesions: five year outcomes in the ENDEAVOR II study. EuroIntervention 6:562–567
26. Windecker S, Simon R, Lins M et al (2005) Randomized comparison of a titanium-nitride-oxide-coated stent with a stainless steel stent for coronary revascularization: the TINOX trial. Circulation 111:2617–2622
27. Karjalainen P, Ylitalo A, Airaksinen J, Nammas W (2010) Titanium-nitride-oxide-coated titan-2 bioactive coronary stent: a new horizon for coronary intervention. Expert Rev Med Devices 7:599–604
28. Hong MK, Mintz GS, Lee CW et al (2006) Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. Circulation 113:414–419
29. Hassan AK, Bergheanu SC, Stijnen T et al (2010) Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. Eur Heart J 31:1172–1180
30. Guo N, Maehara A, Mintz GS et al (2010) Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) trial. Circulation 122:1077–1084
31. Cortigiani L, Rigo F, Gherardi S et al (2012) Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. JACC Cardiovasc Imaging 5:1079–1085
32. Cortigiani L, Rigo F, Gherardi S et al (2013) Prognostic implication of Doppler echocardiographic derived coronary flow reserve in patients with left bundle branch block. Eur Heart J 34:364–373
33. Ascione L, Carlomagno G, Sordelli C et al (2013) Dipyridamole coronary flow reserve stratifies prognosis in acute coronary syndrome patients without left anterior descending disease. Eur Heart J Cardiovasc Imaging 14:858–864
34. Beanlands RS, Muzik O, Melon P et al (1995) Noninvasive quantification of regional myocardial flow reserve in patients with coronary atherosclerosis using nitrogen-13 ammonia positron emission tomography. Determination of extent of altered vascular reactivity. J Am Coll Cardiol 26:1465–1475
35. Hofma SH, van der Giessen WJ, van Dalen BM et al (2006) Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. Eur Heart J 27:166–170
36. Togni M, Windecker S, Cocchia R et al (2005) Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol 46:231–236
37. Fuke S, Maekawa K, Kawamoto K et al (2007) Impaired endothelial vasomotor function after sirolimus-eluting stent implantation. Circ J 71:220–225
38. Stähli BE, Camici GG, Steffel J et al (2006) Paclitaxel enhances thrombin-induced endothelial tissue factor expression via c-Jun terminal NH2 kinase activation. Circ Res 99:149–155
39. Steffel J, Latini RA, Akhmedov A et al (2005) Rapamycin, but not FK-506, increases endothelial tissue factor expression:

implications for drug-eluting stent design. Circulation 112:2002–2011
40. Muldowney JA 3rd, Stringham JR, Levy SE et al (2007) Antiproliferative agents alter vascular plasminogen activator inhibitor-1 expression: a potential prothrombotic mechanism of drug-eluting stents. Arterioscler Thromb Vasc Biol 27:400–406
41. Finn AV, Nakazawa G, Joner M et al (2007) Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 27:1500–1510