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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

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Objectives Using optical coherence tomography, we assessed the proportion of uncovered struts at 6-month follow-up in zotarolimus-eluting stents (ZES), specifically Endeavor (Medtronic CardioVascular, Santa Rosa, California) stents, and identical bare-metal stents (BMS) implanted in patients with ST-segment elevation myocardial infarction (STEMI).

Background Sirolimus- and paclitaxel-eluting stents implanted in STEMI have been associated with delayed healing and incomplete strut coverage. ZES are associated with a more complete and uniform strut coverage in stable patients, but whether this holds true also after STEMI is unknown.

Methods Forty-four patients with STEMI who underwent primary PCI were randomized to ZES or BMS (3:1 randomization). Angiographic, intravascular ultrasound, and optical coherence tomography follow-up was conducted at 6 months and clinical follow-up at 1 year. All images were analyzed by an independent core laboratory that was blind to stent assignments.

Results There were no differences between ZES and BMS in percentage of uncovered struts (median: 0.00% [interquartile range (IQR): 0.00% to 1.78%] vs. 1.98% [IQR: 0.21% to 7.33%], $p = 0.13$), maximum length of uncovered segments (0.00 [IQR: 0.00 to 1.19] mm vs. 1.38 [IQR: 0.65 to 3.30] mm, $p = 0.10$), percentage of malapposed struts (0.00% [IQR: 0.00% to 0.23%] vs. 0.15% [IQR: 0.00% to 5.81%], $p = 0.16$), and maximum length of malapposed segments (0.00 [IQR: 0.00 to 0.67] mm vs. 0.33 [IQR: 0.00 to 2.55] mm, $p = 0.20$). Neointimal response was similar between ZES and BMS (332 [IQR: 240 to 429] μm vs. 186 [IQR: 136 to 348] μm, $p = 0.99$) and evenly distributed. No late acquired malapposition was observed in both groups. There were no deaths, myocardial infarction, or stent thromboses at 1 year.

Conclusions This optical coherence tomography study found no difference in strut coverage and similar vessel response to ZES, when compared with identical BMS, implanted during primary percutaneous coronary intervention in STEMI patients. (Six-Month Coverage and Vessel Wall Response of the Zotarolimus Drug-Eluting Stent Implanted in AMI Assessed by Optical Coherence Tomography [OCTAMI]; NCT00704561) (J Am Coll Cardiol Intv 2010;3:680–7) © 2010 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) reduce neointimal hyperplasia (1,2) in comparison to bare-metal stents (BMS), but delayed healing in DES has been reported in autopsy registries, mainly in patients treated during acute ST-segment elevation myocardial infarction (STEMI) (3). The underlying necrotic core and intracoronary thrombus may increase the number of uncovered stent struts and possibly increase the incidence of DES late stent thrombosis (3,4). Optical coherence tomography (OCT) provides unique in vivo insights into stent strut coverage (5–7), and local relationship with thrombus formation (8). Nonrandomized OCT studies have found fewer uncovered struts in zotarolimus-eluting stents (ZES) compared with first-generation DES in stable angina and acute coronary syndrome (9), but it is still unknown if ZES implanted during primary percutaneous coronary intervention (PCI) would result in similar stent strut coverage as that of BMS. Therefore, we designed a prospective, randomized, controlled study to assess the 6-month stent coverage in consecutive STEMI patients randomly treated with the Endeavor ZES (Medtronic CardioVascular, Santa Rosa, California) or identical BMS (Driver, Medtronic CardioVascular) by using OCT.

Methods

Study design, patients, and procedures. The OCTAMI (Optical Coherence Tomography in Acute Myocardial Infarction) trial was designed as a single-center, prospective, randomized, controlled study with imaging analyses performed by an independent core laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center, Cleveland, Ohio). Core laboratory personnel were blinded to the treatment assignment.

Consecutive eligible patients were randomized to stent implantation with ZES or otherwise equivalent BMS in a 3:1 ratio. Only a single type of stent was allowed in each patient. The study protocol was approved by the local ethical committee with all patients providing written informed consent. Eligible patients presented with STEMI <12 h after symptom onset (prolonged chest pain for more than 20 min, unresponsive to nitroglycerin, and ST-segment elevation of at least 1 mm in 2 or more contiguous leads, or true posterior myocardial infarction), an infarct artery in a native coronary vessel with >70% diameter stenosis, a reference vessel diameter of 2.5 to 3.75 mm, and underwent primary PCI with stent implantation. Patients with left main disease, infarct lesions in bypass grafts, cardiogenic shock, renal failure, recent major bleeding, allergy to aspirin or clopidogrel, on anticoagulant therapy, or with no suitable anatomy for OCT (ostial lesions, extreme tortuosity, and large vessels >3.75 mm in diameter) were excluded.

Percutaneous coronary intervention was performed according to standard techniques. Direct stenting, thrombus aspiration, and use of glycoprotein IIb/IIIa inhibitors were allowed and left to the operator's discretion. All patients were pre-treated with aspirin 250 mg intravenously and clopidogrel 300 mg orally before PCI, followed by daily administration of clopidogrel 75 mg for at least 6 months after discharge and aspirin indefinitely. During PCI, patients received unfractionated heparin to maintain an activated clotting time of 300 s or more. Patients were readmitted for planned imaging follow-up at 6 months.

Quantitative coronary angiography. Quantitative coronary angiograms at baseline, immediately after PCI, and at follow-up were performed in at least 2 orthogonal views after 200 μg of intracoronary nitroglycerin. Digital coronary angiograms were analyzed off-line at the core laboratory with a validated automated edge detection system (CAAS II, PIE Medical, Maastricht, the Netherlands). Angiographic measurements were made in the same 2 projections at pre-PCI, post-PCI, and follow-up. The stented segment plus 5-mm distal and proximal edges were selected for analysis. Reference vessel diameter, minimum luminal diameter, percent diameter stenosis, and lesion length were obtained. Late lumen loss was calculated as the change in MLD from post-procedure to follow-up. Binary angiographic restenosis was defined as diameter stenosis ≥50% at 6-month follow-up.

Intravascular ultrasound (IVUS). IVUS was performed post-PCI and at 6-month follow-up using a 40-MHz Atlantis SR Pro catheter (Boston Scientific, Fremont, California). The IVUS imaging was carried out with motorized pullback at 1 mm/s to include the stent and at least 5 mm proximal and distal to the stent. All IVUS data were digitally stored for independent quantitative and qualitative analyses at the Core Laboratory with validated detection software (Curad, version 4.32, Wijk bij Duurstede, the Netherlands). Quantitative analysis included measurements every 0.5 mm of the external elastic membrane (EEM), stent, and lumen cross-sectional area (CSA). Plaque plus media CSA was counted as EEM minus lumen. Neointimal hyperplasia (NIH) was calculated as the difference between stent and lumen. Percent NIH volume obstruction was computed as NIH divided by stent volume. Qualitative analysis included stent malapposition, defined as blood speckle behind stent struts categorized as

Abbreviations and Acronyms

AIT = abnormal intraluminal tissue
BMS = bare-metal stent(s)
CSA = cross-sectional area
DES = drug-eluting stent(s)
EEM = external elastic membrane
IVUS = intravascular ultrasound
NIH = neointimal hyperplasia
OCT = optical coherence tomography
PCI = percutaneous coronary interventions
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
SIT = strut-level intimal thickness
STEMI = ST-segment elevation myocardial infarction
ZES = zotarolimus-eluting stent(s)

Table 1. Baseline Clinical and Procedural Characteristics

	ZES (n = 33)	BMS (n = 11)	p Value
Age, yrs	61.1 ± 11.4	61.1 ± 12.4	0.99
Male sex	25 (75.8)	9 (81.8)	1.00
Diabetes mellitus	4 (12.1)	2 (18.2)	0.63
Hypertension	16 (48.4)	6 (54.6)	1.00
Hyperlipidemia	10 (30.3)	7 (63.6)	0.08
Current smoker	23 (69.7)	6 (54.5)	0.47
Prior myocardial infarction	3 (9.1)	1 (9.1)	1.00
Prior PCI	3 (9.1)	1 (9.1)	1.00
Symptoms onset to PCI, h	3.6 ± 2.5	3.2 ± 1.5	0.62
Infarct-related artery			
Left anterior descending	12 (36.4)	2 (18.2)	0.46
Left circumflex	5 (15.1)	2 (18.2)	1.00
Right coronary artery	16 (48.5)	7 (63.6)	0.49
Initial TIMI flow grade 0/1, 2, 3, %	53, 25, 22	50, 30, 20	1.00
Post-PCI TIMI flow grade 0/1, 2, 3, %	0, 6, 94	0, 10, 90	1.00
Thrombus aspiration	7 (21)	4 (36)	0.31
Direct stenting	15 (45.4)	4 (36.4)	0.73
Maximum balloon pressure at implant, atm	17.5 ± 2.4	18.3 ± 2.3	0.34
Post-dilation	15 (45.5)	7 (63.6)	0.49

Data presented as n (%) or mean ± SD unless otherwise noted. The following tests were used: for categorical variables, Fisher exact; for ordinal variables, Mann-Whitney *U*; and for continuous variables, analysis of variance or Wilcoxon rank sum.

BMS = bare-metal stent(s); PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; ZES = zotarolimus-eluting stent(s).

persistent (visible at post-procedure and follow-up), resolved (visible only at post-procedure), and late acquired (visible only at follow-up).

Optical coherence tomography. The OCT imaging was obtained at 6-month follow-up and performed after intracoronary nitroglycerin injection. A time domain OCT system (M2CV OCT Imaging System, LightLab Imaging, Westford, Massachusetts) was used. The occlusive technique was adopted to completely remove blood from the artery (6). Images were acquired with an automated pullback at a rate of 1.0 mm/s, then digitally stored and submitted to the core laboratory for offline evaluation and subsequent analyses. All cross-sectional images (frames) were initially screened for quality assessment and excluded from analysis if any portion of the image was out of the screen, a side branch occupied >45° of the cross-section, or the image had poor quality caused by residual blood, sew-up artifact, or reverberation (10). Strut-level analysis was performed considering all analyzable frames (0.06-mm intervals) along the entire target segment. A dedicated automated contour-detection system (OCT system software version B.0.1, LightLab Imaging) developed in collaboration with the Imaging Core Laboratory was used for measurements. Lumen, stent, and NIH areas and volumes were calculated in a similar fashion of IVUS methodology at 0.5-mm intervals. A strut was considered suitable for analysis only if it had: 1) well-defined bright "blooming" appearance; and 2) characteristic shadow perpendicular to the light source. The inner and outer contours of each strut reflection (blooming) were delineated semiautomatically. The center of the luminal surface of the strut blooming was determined for each strut and its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness (SIT). Struts covered by tissue had positive SIT values, whereas protruding uncovered struts or malapposed struts had negative SIT values. Data were stored in an integrated database system, which corrects for strut thickness of different stent types once the study is completed and data are locked, thus allowing for blinding of the readers. Strut malapposition was determined when the negative value of SIT was higher than the strut thickness, according to each stent manufacturer's specifications, with addition of a compensation factor of 20 μm to correct for strut blooming. The blooming compensation factor was determined based on analysis of 2,250 struts. To determine reproducibility of OCT measurements, quantitative analyses in 333 struts were performed by 2 independent analysts and were repeated 3 months after the initial analysis. The difference in SIT measurements between 2 analysts was 0.01 ± 0.02 μm (r = 0.997). Highly reproducible measurements for strut apposition and coverage using the described methodology have been reported (11). Qualitative imaging assessment was performed in every frame for presence of

Table 2. Baseline and Follow-Up Quantitative Coronary Angiographic Analysis

	ZES (n = 32)	BMS (n = 10)	p Value
Pre-procedure			
RVD, mm	2.81 (2.42 to 3.32)	3.10 (2.82 to 3.68)	0.31
MLD, mm	0.26 (0.00 to 0.89)	0.04 (0.00 to 0.70)	0.53
DS, %	92.0 (68.5 to 100.0)	98.5 (81.0 to 100.0)	0.36
Lesion length, mm	19.5 (10.4 to 25.5)	15.8 (10.3 to 22.9)	0.29
Post-PCI			
In-stent MLD, mm	2.80 (2.57 to 3.08)	2.70 (2.49 to 2.86)	0.80
In-lesion MLD, mm	2.42 (1.88 to 2.72)	2.39 (2.04 to 2.65)	0.92
In-lesion acute gain, mm	1.86 (1.52 to 2.33)	2.03 (1.82 to 2.40)	0.52
In-stent DS, %	10.00 (7.0 to 16.5)	12.0 (9.0 to 17.0)	0.64
Stent length, mm	26.3 (17.2 to 36.3)	21.1 (15.8 to 23.7)	0.01
Follow-up			
In-stent MLD, mm	2.18 (1.76 to 2.33)	2.24 (1.55 to 2.60)	0.84
In-lesion MLD, mm	2.05 (1.72 to 2.27)	2.21 (1.82 to 2.41)	0.36
In-stent DS, %	27.5 (20.5 to 39.5)	37.0 (21.0 to 51.0)	0.32
In-stent late loss, mm	0.59 (0.33 to 0.97)	0.70 (0.06 to 1.13)	0.78
In-lesion late loss, mm	0.26 (–0.06 to 0.71)	0.34 (–0.01 to 0.48)	0.83
In-stent binary restenosis	4 (12.5)	3 (30.0)	0.33

Categorical variables are presented as n (%), and ordinal and continuous variables are presented as median (interquartile range). Test for comparison between 2 stent types: nonparametric Mann-Whitney *U* for continuous or ordinal variables, and Fisher exact for categorical variables.

DS = diameter stenosis; MLD = minimum lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

abnormal intraluminal tissue (AIT). We defined AIT as any mass protruding beyond the stent struts into the lumen, with irregular surface and a sharp intensity gap between mass and neointimal (12,13). Interobserver and intraobserver variability showed substantial agreement for AIT qualitative assessment (kappa = 0.755 and 0.885, respectively).

Clinical follow-up and end points. Clinical follow-up was performed at 1, 6, and 12 months in all patients to assess the occurrence of major adverse cardiac events (defined in Online Appendix), including cardiac death, reinfarction, stroke, and target lesion and target vessel revascularization. The incidence of stent thrombosis was also evaluated per the Academic Research Consortium's definitions of definite/probable (14).

The primary end point was the percentage of uncovered stent struts at 6 months. Secondary imaging end points included the rate of apposed strut without neointima, percentage malapposed struts without neointima, percentage net volume obstruction by OCT, and rate of late acquired malapposed struts as determined by IVUS.

Statistical methods. Data are expressed as median (interquartile) for continuous variables, and ordinal variables and percentages for categorical variables. The differences between treatment groups were evaluated by analysis of variance or Wilcoxon rank sum scores for continuous variables, if appropriate. Fisher exact test was utilized for the analysis of categorical variables and Mann-Whitney *U* test was used for ordinal variables. All statistical analyses were performed with the use of SAS software (version 9.1, SAS Institute, Cary, North Carolina), and all reported p values are 2-sided. The null hypothesis was of no difference in 6-month percentage of uncovered stent struts, with an alternative hypothesis of lower rate of uncovered struts in the ZES group. Due to unavailability of OCT data on ZES coverage in STEMI, no evidence-based power calculation was possible at the time of the study design. Nonetheless, we envisioned that, expecting a 2.0 ± 5.0% versus 6.0 ± 5.0% rate of uncovered stent struts at 6 months, and aiming for a 5% 2-tailed alpha and 90% power, at least 44 patients were needed with an allocation ratio of 3:1.

Results

Between April and October 2008, 44 consecutive eligible patients were randomly assigned to the 2 treatment groups (33 to ZES and 11 to BMS), with all patients receiving the allocated stent and none crossing over to the other stent group. All 44 patients had a primary PCI procedure with successful stent implantation (47 ZES and 12 BMS); 42 of 44 enrolled patients had follow-up imaging at 6 months (96%) as required by protocol, with 2 asymptomatic patients refusing to return for elective control. There were no significant differences between groups on baseline clinical and procedural characteristics (Table 1).

Table 3. OCT Quantitative and Qualitative Analysis at 6-Month Follow-Up

	ZES (n = 32)	BMS (n = 10)	p Value
Strut-level analysis			
Struts/patient, n	3,469 (2,743 to 4,742)	2,518 (1,935 to 3,386)	0.003
Analyzed struts/cross-section, n	8.61 (8.06 to 10.06)	8.79 (8.52 to 9.32)	0.79
Uncovered struts, %	0 (0 to 1.78)	1.98 (0.21 to 7.33)	0.14
Uncovered, nonmalapposed struts, %	0 (0 to 0.85)	0.31 (0.21 to 6.05)	0.16
Uncovered, malapposed struts, %	0 (0 to 0.23)	0.15 (0 to 5.81)	0.16
Stent with >10% uncovered struts	1 (3.1)	2 (20.0)	0.14
Maximum length of uncovered segment, mm	0 (0 to 1.19)	1.38 (0.65 to 3.30)	0.10
Maximum length of malapposed segment, mm	0 (0 to 0.67)	0.33 (0 to 2.55)	0.20
Neointimal hyperplasia, μm	332 (240 to 429)	186 (136 to 348)	0.99
AIT related with uncovered strut	1 (3.1)	1 (10.0)	0.42
AIT related with malapposed strut	3 (9.4)	2 (20.2)	0.58
Planar and volumetric analysis			
Stent area, mm^2	8.18 (7.11 to 10.29)	7.56 (7.18 to 9.05)	0.93
Lumen area, mm^2	5.73 (4.23 to 6.63)	5.91 (4.58 to 7.52)	0.57
Neointimal area, mm^2	2.78 (2.28 to 3.83)	1.79 (0.61 to 2.82)	0.33
Stent volume, mm^3	213.5 (160.8 to 319.5)	171.4 (121.4 to 234.0)	0.13
Lumen volume, mm^3	150.9 (103.6 to 212.7)	115.8 (76.4 to 183.3)	0.38
Neointimal volume, mm^3	85.2 (47.3 to 114.3)	38.3 (14.0 to 51.4)	0.09
Net volume obstruction, %	36.28 (24.19 to 45.77)	22.26 (8.26 to 38.06)	0.53

Categorical variables are presented as n (%), and ordinal and continuous variables are presented as median (interquartile range). Test for comparison between 2 stent types: nonparametric Mann-Whitney *U* for continuous or ordinal variables, and Fisher exact for categorical variables.

AIT = abnormal intraluminal tissue; OCT = optical coherence tomography; other abbreviations as in Table 1.

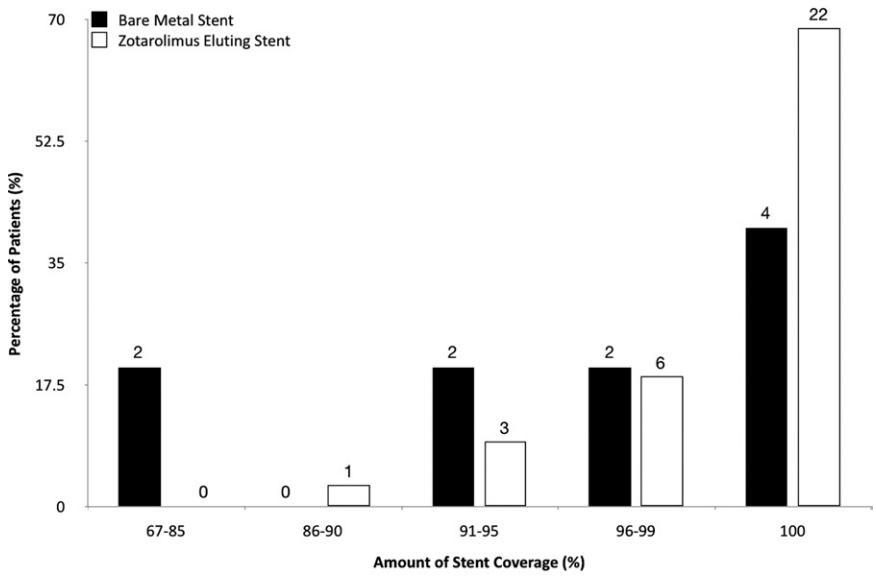

Figure 1. Distribution of Stent Strut Coverage in STEMI Patients

Distribution of percentage strut coverage measured by optical coherence tomography at 6 months, in ST-segment elevation myocardial infarction (STEMI) patients treated with bare-metal stents (n = 10) **(solid bars)** and zotarolimus-eluting stents (n = 32) **(open bars)**. Similar distribution was observed for zotarolimus-eluting stents and bare-metal stents (p = 0.14). No specific cutoff for "optimal" stent strut coverage was chosen given the lack of reliable data in support from previous validation studies of any specific threshold.

Quantitative coronary angiography. Pre- and post-intervention angiographic measurements were similar for ZES and BMS (Table 2). However, stent length was higher in ZES compared with BMS (28.3 ± 12.9 vs. 20.3 ± 5.9, p = 0.01). In-stent late lumen loss did not differ between groups.

OCT analysis. Of 20,337 total frames collected by OCT, 17,088 (84%) were analyzed. Frames were excluded from analysis because of either bifurcation location (2,049; 10.1%) or any image artifact (1,200; 5.9%). At 6 months, on a per-patient basis, no significant difference was observed between ZES and BMS in percentage of uncovered struts (median: 0.00% [0.00% to 1.78%] vs. 1.98% [0.21% to 7.33%], p = 0.13) (Table 3) (Fig. 1). In addition, no differences were observed for both uncovered apposed and malapposed struts (0.0% vs. 0.3%, p = 0.16; 0.0% vs. 0.2%, p = 0.16, respectively), as well as for maximum lengths of uncovered (0.00 mm vs. 1.38 mm, p = 0.10) and malapposed segments (0.00 mm vs. 0.33 mm, p = 0.20). Similarly, homogeneous coverage was observed along the entire length of the stent for ZES and BMS (p = 0.16) (Fig. 2). Strut-level neointimal thickness and percent volume obstruction also did not differ between groups. Frequency of AIT related with uncovered and malapposed struts were similar between ZES and BMS (3.1% vs. 10%, p = 0.42; 9.4% vs. 20.2%, p = 0.58, respectively).

IVUS analysis. Table 4 shows that IVUS data were similar between the groups at post-procedure and 6-month follow-up. The median net volume obstruction was 24.4% for ZES and 15.1% for BMS (p = 0.21). The increase in mean EEM CSA observed after ZES implantation (but not after BMS) did not result in any late acquired stent malapposition.

Clinical outcomes. Clinical follow-up was complete in all patients at 1 year. There were no episodes of death, myocardial infarction, or stent thrombosis. The total major adverse cardiac events rate was 11.4% (5 of 44) and included 3 target lesion revascularizations (2 in ZES, 1 in BMS) and 2 target vessel revascularizations (ZES), with no statistically significant differences between the groups.

Discussion

This OCT study found similar strut coverage and vessel response in ZES compared with an identical BMS implanted during primary PCI. The main findings were the following: 1) ZES, compared with BMS, had a similar incidence of uncovered struts, with stent strut coverage evenly distributed and greater than 98% at 6-month follow-up; 2) the rate of strut malapposition with ZES was <1% with no late acquired malapposition; 3) no difference in NIH area and percentage area obstruction were measured by OCT strut-level analysis; and 4) similarly low rates of AIT associated with uncovered and malapposed struts were observed in ZES and BMS.

Several studies support the mid-term safety of first-generation DES use in acute myocardial infarction (1,2,15,16). However, their long-term safety has been ques-

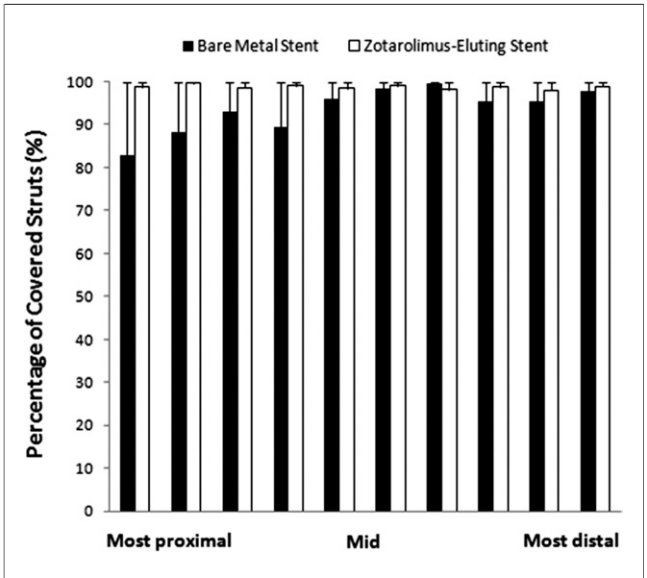

Figure 2. Longitudinal Pattern of Percentage Strut Coverage Between 2 Stent Types

Longitudinal pattern of percentage strut coverage, measured by optical coherence tomography within bare-metal stents (n = 10) **(solid bars)** and zotarolimus-eluting stents (n = 32) **(open bars)** at 6-month follow-up. The evaluation compared data for 10 subsegments covering the length of stents. The rate of coverage in different subsegments along the stent does not change significantly in zotarolimus-eluting stents (p = 0.98) and bare-metal stents (p = 0.41). No difference was detected in percentage of coverage between 2 stent types with linear mixed model (p = 0.16), after adjusting for the subsegments effect.

tioned (3,17). In animal models, endothelialization has been shown to occur earlier and more homogeneously in ZES than in sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) with less inflammatory response and fibrin adhesion on strut surface (18,19). Further, tests of endothelial function suggested normal vasodilatory response by 28 days with ZES and BMS, whereas endothelial dysfunction up to 6 months after implantation has been observed with SES and PES (20,21).

Optical coherence tomography allows accurate in vivo strut-level analysis to measure completeness of stent coverage and amount of neointima in DES (5,11,22,23). Unlike pathology that selectively analyzes cross-sections every 2 to 3 mm, OCT can collect data every 0.06 mm, making possible a more meticulous assessment of the heterogeneity in strut coverage (10). Few OCT data regarding DES implanted during primary PCI are available. Sirolimus-eluting stent implanted in STEMI was identified as an independent predictor of uncovered/malapposed struts at 9-month OCT (24). The 13-month coverage of PES implanted in STEMI was assessed in 118 consecutive patients from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial (25). Guagliumi et al. (25) found that PES resulted in a significantly higher rate of uncovered and malapposed stent struts than BMS.

In the present study, ZES resulted in a very low rate of uncovered struts and length of uncovered segment, which is similar to BMS results. Of note, these high rates of strut coverage were observed at 6-month follow-up. A recent OCT study in non-STEMI patients (9) showed almost complete neointimal coverage at 9 months in ZES, with a very low rate (0.3%) of uncovered struts and absence of thrombus. As opposed to SES, ZES showed similar coverage independent of clinical presentation (26). Our results confirm that coverage of ZES is similar in STEMI to that observed in non-STEMI patients.

The amount and distribution of NIH observed with ZES in this study is consistent with the neointima response reported in previous IVUS studies in non-STEMI patients (27,28). Specifically, NIH was similar in ZES and BMS as determined by both IVUS and OCT, with concordant findings of similar rates of repeat revascularization in ZES and BMS. The relationship among neointimal thickness, uncovered struts, and local thrombus formation has also been recently addressed by OCT following SES implantation (8,29). Although the number of uncovered struts and the uneven NIH were determinant factors for local thrombus formation, the degree of neointimal growth, as measured by OCT, had no influence on subclinical thrombus. Our data suggested that neointimal coverage in ZES implanted in STEMI was evenly distributed within the stent, thus suggesting a contrast with the uneven neointimal formation observed with first-generation DES (17). Accordingly, the incidence of AIT related to uncovered struts in ZES was equally low.

The clinical association between late acquired malapposition in DES and subsequent stent thrombosis remains controversial. Nevertheless, malapposed struts associated with positive remodeling has been recently associated with late stent thrombosis (30). In the present study, the increase in mean EEM CSA observed after ZES implantation (but not after BMS) did not result in IVUS late acquired malapposition, and <1% of ZES struts were malapposed at 6-month by OCT.

Study limitations. Strut coverage assessed by intravascular OCT must be interpreted with caution as it does not have endothelial cell level resolution or provide functional tissue differentiation. Furthermore, current OCT systems cannot differentiate between very small amounts of thrombus or fibrin deposition, or even inflammatory cellular response from the underlying NIH. This study enrolled a very small group of patients, and it was not powered to investigate the relationship between OCT findings and clinical outcomes. To address the limitation due to the industry sponsorship of the study, the investigators had full control in data analysis and final decision in the manuscript text, including responses to reviewers. Finally, pre-PCI or post-PCI OCT

Table 4. IVUS Quantitative and Qualitative Analysis at the In-Stent Level

	ZES (n = 32)	BMS (n = 10)	p Value
Post-procedural stent segment			
Mean EEM CSA, mm^2	15.5 (14.6 to 18.6)	18.6 (14.8 to 21.7)	0.18
Mean lumen CSA, mm^2	8.0 (7.3 to 10.3)	7.9 (6.9 to 9.6)	0.92
Mean stent CSA, mm^2	7.9 (7.3 to 10.2)	7.9 (6.9 to 9.6)	0.91
Mean plaque + media CSA, mm^2	7.7 (6.9 to 9.1)	10.7 (6.6 to 14.4)	0.06
Stent length, mm	29.8 (22.7 to 40.6)	24.2 (17.7 to 26.9)	0.005
Follow-up stent segment			
Mean EEM, mm^2	16.5 (15.1 to 19.2)	18.2 (16.1 to 20.9)	0.22
Mean lumen CSA, mm^2	6.7 (5.4 to 7.9)	6.8 (5.6 to 8.1)	0.97
Mean stent CSA, mm^2	8.3 (7.7 to 10.2)	7.6 (7.0 to 9.4)	0.63
Mean plaque + media CSA, mm^2	8.0 (6.8 to 9.3)	10.6 (6.2 to 13.9)	0.13
Net volume obstruction, %	24.4 (16.4 to 33.2)	15.1 (4.7 to 26.4)	0.89
Change from index to follow-up			
Mean change in EEM CSA, mm^2	0.72 (–0.12 to 1.42)	–0.47 (–1.84 to 0.04)	0.01
Mean change in plaque + media CSA, mm^2	0.39 (–0.50 to 0.95)	–0.19 (–1.35 to 0.30)	0.04
Mean change % in EEM CSA, mm^2	4.68 (–0.67 to 9.07)	–2.67 (–6.24 to 0.18)	0.01
Stent malapposition, n (%)			
Post-procedure	7 (21.9)	2 (20.0)	1.00
Persistent at follow-up	5 (15.6)	1 (10.0)	1.00
Late acquired	0	0	—

Categorical variables are presented as n (%), and ordinal and continuous variables are presented as median (interquartile range). Test for comparison between 2 stent types: nonparametric Mann-Whitney *U* for continuous or ordinal variables, and Fisher exact for categorical variables.

CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; other abbreviations as in Table 1.

was not performed, mainly for concerns about patient safety, thus limiting our ability to appraise the impact of plaque type or early procedural results on 6-month vessel responses.

Conclusions

This OCT study found similar 6-month strut coverage and vessel response in ZES and BMS implanted during primary PCI. Long-term follow-up in more patients is required to establish the clinical significance of these imaging findings regarding stent thrombosis and restenosis.

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REFERENCES

1. Spaulding C, Henry P, Teiger E, et al. Sirolimus eluting stents compared with bare metal stents for acute myocardial infarction. N Engl J Med 2006;355:1093–104.
2. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946–59.
3. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138–45.
4. Hwang C-W, Levin AD, Jonas M, Li PH, Edelman ER. Thrombus modulates arterial drug distribution for drug-eluting stents. Circulation 2005;111:1619–26.
5. Matsumoto D, Shite J, Shinke T, et al. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluation by optical coherence tomography. Eur Heart J 2007;28:961–7.
6. Guagliumi G, Sirbu V. Optical coherence tomography: high resolution intravascular imaging to evaluate vascular healing after coronary stenting. Catheter Cardiovasc Interv 2008;72:237–47.
7. Xie Y, Takano M, Murakami D, et al. Comparison of neointimal coverage by optical coherence tomography of a sirolimus-eluting stent versus a bare-metal stent three months after implantation. Am J Cardiol 2008;102:27–31.
8. Otake H, Shite J, Ako J, et al. Local determinates of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography. J Am Coll Cardiol Intv 2009;2:459–66.
9. Kim J-S, Jang I-K, Kim J-S, et al. Optical coherence tomography evaluation of zotarolimus-eluting stents at 9-month follow up: comparison with sirolimus-eluting stents. Heart 2009;95:1907–12.
10. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review. J Am Coll Cardiol Intv 2009;2:1035–46.
11. Gonzalo N, Garcia-Garcia HM, Serruys PW, et al. Reproducibility of quantitative optical coherence tomography for stent analysis. EuroIntervention 2009;5:224–32.
12. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol 2006; 97:1713–7.

13. Kume T, Okura H, Kawamoto T, et al. Images in cardiovascular medicine. Fibrin clot visualized by optical coherence tomography. Circulation 2008;118:426–7.
14. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
15. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. Eur Heart J 2007;28:2706–13.
16. De Luca G, Valgimigli M, Spaulding C, et al. Short and long-term benefits of sirolimus-eluting stent in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. J Thromb Thrombolysis 2009;28:200–10.
17. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.
18. Nakazawa G, Finn AV, John MC, Kolodgie FD, Virmani R. The significance of preclinical evaluation of sirolimus-, paclitaxel-, and zotarolimus-eluting stents. Am J Cardiol 2007;100 Suppl 2:S36–44.
19. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.
20. Kim JW, Suh SY, Choi CU, et al. Six-month comparison of coronary endothelial dysfunction associated with sirolimus-eluting stent versus paclitaxel-eluting stent. J Am Coll Cardiol Intv 2008;1:65–71.
21. Kim JW, Seo HS, Park JH, et al. 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 2009;53:1653–9.
22. Suzuki Y, Ikeno F, Koizumi T, et al. In vivo comparison between optical coherence tomography and intravascular ultrasound for detecting small degrees of in-stent neointima after stent implantation. J Am Coll Cardiol Intv 2008;1:168–73.
23. Nakazawa G, Granada JF, Alviar CL, et al. Anti-CD34 antibodies immobilized on the surface of sirolimus-eluting stents enhance stent endothelialization. J Am Coll Cardiol Intv 2010;3:68–75.
24. Gonzalo N, Barlis P, Serruys PW, et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. J Am Coll Cardiol Intv 2009;2:445–52.
25. Guagliumi G, Sirbu V, Costa M, et al. Long-term strut coverage of paclitaxel-eluting stents compared with bare-metal stents implanted during primary PCI in acute myocardial infarction: a prospective, randomized, controlled study performed with optical coherence tomography. HORIZONS-OCT (abstr). Circulation 2008;118:2315.
26. Kim JS, Fan C, Choi D, et al. 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 2009 Aug 24 [E-pub ahead of print].
27. Miyazawa A, Ako J, Hongo Y, et al. Comparison of vascular response to zotarolimus-eluting stent versus sirolimus-eluting stent: intravascular ultrasound results from ENDEAVOR III. Am J Cardiol 2008;155:108–13.
28. Waseda K, Miyazawa A, Ako J, et al. Intravascular ultrasound results from the ENDEAVOR IV trial: randomized comparison between zotarolimus- and paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol Intv 2009;2:779–84.
29. Murakami D, Takano M, Yamamoto M, et al. 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 2009;73:1627–34.
30. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–9.

Key Words: acute myocardial infarction ■ coronary artery disease ■ optical coherence tomography ■ stent coverage ■ zotarolimus-eluting stent.

APPENDIX

For definitions of major adverse cardiac events, please see online version of this article.