

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

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Objectives The aim of this study was to compare the frequency of incomplete stent apposition (ISA) and struts not covered by tissue at long-term follow-up (as assessed by optical coherence tomography [OCT]) in drug-eluting stents (DES) implanted during primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) versus DES implanted for unstable and stable angina.

Background Incomplete stent apposition and the absence of strut endothelialization might be linked to stent thrombosis. DES implanted for STEMI might have a higher risk of thrombosis.

Methods Consecutive patients in whom OCT was performed at least 6 months after DES implantation were included in the study. Stent struts were classified on the basis of the presence or absence of ISA and tissue coverage.

Results Forty-seven lesions in 43 patients (1,356 frames, 10,140 struts) were analyzed (49% stable angina, 17% unstable angina, 34% STEMI). Median follow-up time was 9 (range 7 to 72) months. Drug-eluting stents implanted during primary PCI presented ISA more often than DES implanted in stable/unstable angina patients (75% vs. 25.8%, $p = 0.001$). The frequency of uncovered struts was also higher in the STEMI group (93.8% vs. 67.7%, $p = 0.048$). On multivariate analysis, DES implantation in STEMI was the only independent predictor of ISA (odds ratio: 9.8, 95% confidence interval: 2.4 to 40.4, $p = 0.002$) and the presence of uncovered struts at follow-up (odds ratio: 9.5, 95% confidence interval: 1.0 to 90.3, $p = 0.049$).

Conclusions DES implanted for STEMI had a higher frequency of incompletely apposed struts and uncovered struts as assessed by OCT at follow-up. DES implantation during primary PCI in STEMI was an independent predictor of ISA and the presence of uncovered struts at follow-up. (J Am Coll Cardiol Intv 2009;2:445–52) © 2009 by the American College of Cardiology Foundation

Primary percutaneous coronary intervention (PCI) is the recommended treatment for ST-segment elevation myocardial infarction (STEMI) (1). Stent implantation during primary PCI presents some challenges, namely the presence of abundant thrombotic material that can potentially contribute to suboptimal stent deployment. The use of drug-eluting stents (DES) in this setting is under debate due to the concerns about a potentially higher risk of stent thrombosis in this population (2). Recent intravascular ultrasound (IVUS) studies suggest that the presence of incomplete stent apposition (ISA) is potentially linked to late stent thrombosis (3). Gradual absorption of the thrombus that was present during primary PCI has been postulated to contribute to late acquired stent malapposition (4). Endothelial strut coverage has been identified in pathological series as the most powerful histological predictor of stent thrombosis (5). DES inhibit neointimal proliferation to such an extent that it might not be visualized with conventional intracoronary imaging techniques such as IVUS. Optical coherence tomography (OCT) is a high-resolution light-based imaging modality that can provide a very detailed assessment of stent apposition and tissue strut coverage.

Abbreviations and Acronyms

BMS = bare metal stent(s)

DES = drug-eluting stent(s)

ISA = incomplete stent apposition

IVUS = intravascular ultrasound

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

The objective of the present study was to compare the frequency of ISA and uncovered struts (as assessed by OCT) at long-term follow-up in DES implanted during primary PCI for STEMI versus DES implanted for stable or unstable (IB/IIB/IIIB Braunwald classification) angina.

Methods

Patient sample. All consecutive patients between January 2007 and May 2008 in whom OCT was performed for follow-up of a DES implanted at least 6 months prior were included in the study. Exclusion criteria were repeated revascularization in the target vessel, depressed left ventricular function, coronary chronic total occlusions, and impaired renal function. All patients gave written informed consent.

OCT acquisition. The OCT acquisition was performed with a commercially available system for intracoronary imaging (LightLab Imaging, Westford, Massachusetts). The ImageWire (LightLab Imaging) was positioned distal to the region of interest with a double lumen catheter (Twin Pass catheter, Vascular Solutions Inc., Minneapolis, Minnesota) that had been placed in the artery over a conventional guidewire. The automated pullback was performed at 3 mm/s while the blood was removed by the continuous injection of iso-osmolar contrast (Iodixanol 320, Visipaque; GE Health Care, Carrigtobhill, County Cork, Ireland) at 37°C through

the guiding catheter. The data were digitally stored for offline analysis.

OCT analysis. Offline analysis was performed with the proprietary LightLab software (LightLab Imaging). The analysts (Cardialysis BV, Rotterdam, the Netherlands) were blinded to clinical and procedural characteristics. The stented region was defined as the region between the first and the last frame with circumferentially visible struts. For this region 1 frame was selected every millimeter, and the lumen and stent area contours were drawn. Stent longitudinal symmetry ratio was defined as minimum stent area/maximum stent area.

INCOMPLETE STENT APPPOSITION DEFINITIONS AND MEASUREMENTS. Incomplete stent apposition was defined as separation of at least 1 stent strut from the vessel wall not related to a side branch (Fig. 1). A strut was considered incompletely apposed if the distance from the endoluminal surface of the strut to the vessel wall was higher than the sum of the metal and polymer thickness. The cutoff points used for each stent type were: paclitaxel-eluting stent (Taxus, Boston Scientific Corp., Natick, Massachusetts) 130 μm , sirolimus-eluting stent (Cypher Select, Cordis, Johnson & Johnson, Miami, Florida) 160 μm , everolimus-eluting stent (Xience V, Abbot Vascular, Santa Clara, California) 90 μm , and biolimus-eluting stent (Biomatrix

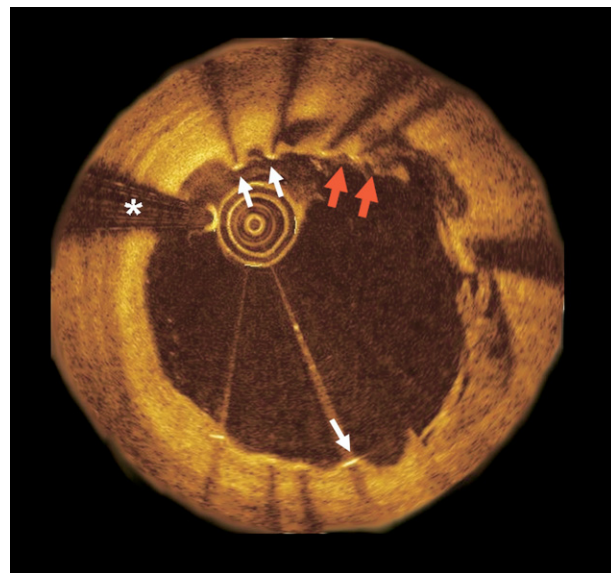


Figure 1. Incomplete Stent Apposition and Uncovered Struts

Optical coherence tomography cross section corresponding to a patient treated with drug-eluting stent implantation during primary percutaneous coronary intervention in the right coronary artery for an inferior ST-segment elevation myocardial infarction 9 months before. The **red arrows** indicate incomplete stent apposition, whereas the **white arrows** show some struts not covered by tissue. From 12 to 5 an irregular material suggestive of organized thrombus can be observed behind the struts. *Guidewire artefact.

III, Biosensors, Morges, Switzerland) 120 μm . The number of malapposed struts, the maximal incomplete stent apposition length (maximum distance from the endoluminal surface of the strut to the vessel wall), and the incomplete stent apposition area were measured. Calcification could not be accurately evaluated due to the shadow caused by stent struts in OCT.

STRUT COVERAGE DEFINITIONS AND MEASUREMENTS. The struts were classified as uncovered when a tissue layer on the endoluminal surface was not visible. In the covered struts, the tissue coverage thickness was measured per strut as the distance from the central aspect of the endoluminal surface of the strut to the lumen. The total tissue coverage area was calculated as: stent area – lumen area. The percentage of tissue coverage area was calculated as: tissue coverage area/stent area \times 100. The tissue coverage volume was calculated as: tissue coverage area \times stent length. The percentage of tissue coverage volume area was calculated as: tissue coverage volume/stent volume \times 100. The tissue coverage symmetry per frame was analyzed with the following ratio: (maximum tissue coverage thickness per frame – minimum tissue coverage thickness per frame)/maximum tissue coverage thickness per frame. This ratio can have values between 0 and 1. The closer the ratio is to 1 the higher is the asymmetry of the tissue coverage (Fig. 2). To evaluate the distribution of the uncovered struts along the

stent we calculated the percentage of frames with at least 1 uncovered strut in the lesions that showed uncovered struts. **Statistical analysis.** Statistical analysis was performed with SPSS 12.0.1 for Windows (SPSS Inc., Chicago, Illinois). Categorical variables are expressed as percentages and continuous variables are expressed as mean \pm SD, median and (range), or median and (interquartile range). The ISA and strut coverage comparisons were performed per lesion. Chi-square was used for the comparisons of categorical variables between groups. For the comparisons of continuous variables, the Student *t* test or nonparametric (Mann-Whitney) test was used according to their distribution. Multiple logistic regression analysis was performed to assess independent predictors of ISA and uncovered struts. Variables considered clinically relevant and with $p < 0.15$ in the univariate analysis were included in the models.

Results

Clinical and procedural characteristics. Fifty patients followed up with OCT after DES implantation were initially enrolled in the study. Seven patients were excluded for image quality not appropriate for analysis. Finally, 43 patients (47 vessels, 47 lesions) were included (16 STEMI, 27 stable/unstable angina).

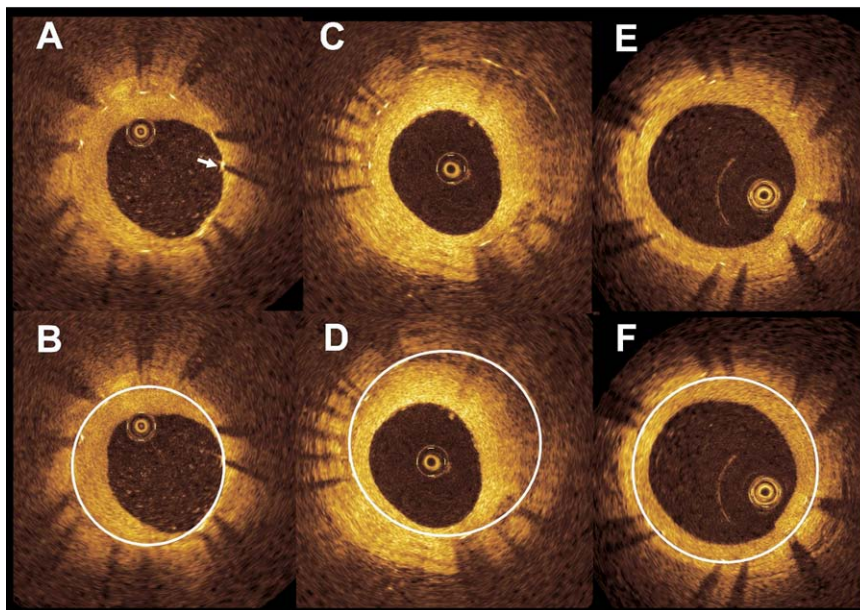


Figure 2. Tissue Coverage Symmetry Patterns

(A and B) Asymmetric tissue coverage with uncovered struts: whereas some struts are covered by a thick layer of tissue, other struts (from 2 to 5) are covered by a very thin layer, and there is even 1 uncovered strut (indicated by the white arrow). (C and D) Asymmetric tissue coverage without uncovered struts: all the struts are covered by tissue that shows very different thickness along the vessel circumference. (E and F) Symmetric tissue coverage: all the struts are covered by tissue that shows similar thickness along the vessel circumference.

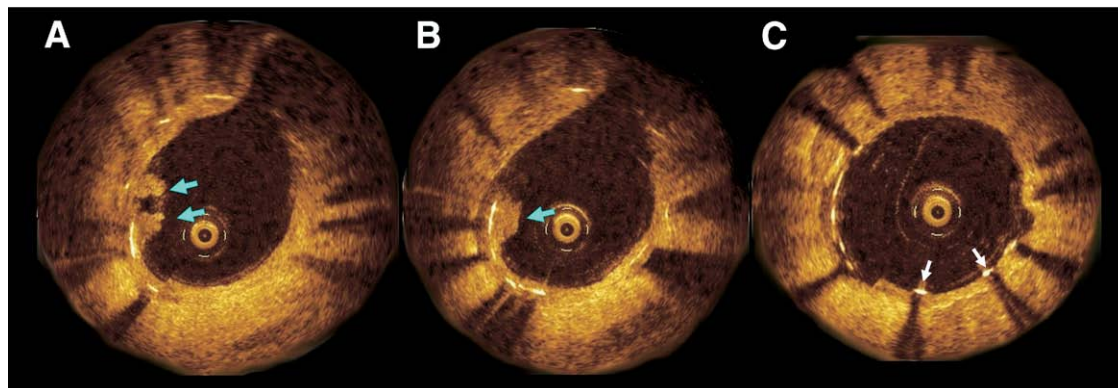


Figure 3. Struts Covered by Organized Thrombus

Optical coherence tomography cross-sections corresponding to a drug-eluting stent implanted in the left anterior descending coronary artery more than 4 years ago due to an anterior ST-segment elevation myocardial infarction. (A and B) The blue arrows indicate the presence of an irregular, highly reflective material (suggestive of organized thrombus) covering some struts. (C) Represents a cross section more proximal where some uncovered struts can be observed (white arrows).

The mean age was 64.5 ± 11.7 years, and 63.8% were men. Regarding cardiac risk factors, 47.8%, 21.3%, and 70.2% had hypertension, diabetes mellitus, and hyperlipidemia, respectively, and 19.1% were smokers. The studied vessel was the left anterior descending in 57%, the circumflex in 19%, and the right coronary artery in 24% of the lesions. The indication for stent implantation was stable angina in 47% (20 of 43), unstable angina in 16% (7 of 43) and STEMI in 37% (16 of 43). The stent implanted was Taxus in 10.6%, Cypher Select in 55.3%, Xience V in 2.1%, and Biomatrix III in 32%. The median time to follow-up angiography and OCT examination was 9 (7 to 72) months. The mean stent diameter, stent number, and stent imaged length were 2.9 ± 0.3 mm, 1.8 ± 0.8 , and 28 ± 15 mm, respectively.

OCT quantitative analysis. A total of 10,140 struts from 1,356 frames were analyzed. The mean lumen area, mean stent area, and mean neointimal area were 6.42 ± 2.11 mm², 7.11 ± 2.06 mm², and 0.67 ± 0.47 mm², respectively. The stent symmetry ratio was 0.63 ± 0.16 .

ISA frequency by OCT. The frequency of incompletely apposed struts was 68 of 10,140 (0.6%). Forty-five of the 68 incompletely apposed struts (66.1%) were not covered by tissue. Forty of 1,356 frames (2.9%) had at least 1 incompletely apposed strut. In 20 of 47 lesions (42.6%), incomplete stent apposition of at least 1 strut was found. In the lesions with ISA, the mean percentage of frames with ISA was $9.3 \pm 7.1\%$.

Strut coverage by OCT. The frequency of uncovered struts in the total sample was 6.1% (624 of 10,140). Twenty-one percent (285 of 1,356) of all the frames analyzed presented at least 1 uncovered strut. In 36 of 47 lesions (76.6%), at least 1 uncovered strut was visualized. The mean neointima symmetry ratio was 0.73 ± 0.13 . Twenty-six struts of the

10,140 (0.2%) were covered by an irregular material suggestive of organized thrombus (Fig. 3).

STEMI patients. Sixteen of the 47 lesions studied were treated with DES implantation during primary PCI for STEMI. Table 1 shows the baseline characteristics of the STEMI patients in comparison with the rest of the sample. The time to follow-up was 11.5 months (range 7 to 59

Table 1. Baseline Characteristics in STEMI and Stable/Unstable Angina Patients

	STEMI	Stable/Unstable Angina	p Value
Age (yrs)	64 ± 12	64 ± 11	0.85
Male (%)	50.0	71.0	0.13
Hypertension (%)	50.0	46.7	0.53
DM (%)	31.3	16.1	0.2
Dyslipidemia (%)	75.0	67.7	0.43
Smoker (%)	31.3	12.9	0.13
Family history (%)	62.5	67.7	0.48
Vessel (%)			0.46
LAD	68.8	51.6	
LCX	18.7	19.4	
RCA	12.5	29.0	
Stent type (%)			0.48
Taxus	13.3	9.7	
Cypher	53.3	54.8	
Xience	6.7	0.0	
Biomatrix	26.7	35.5	
Number of stents	1.53 ± 0.52	2.03 ± 0.94	0.08
Stent-imaged length (mm)	24.9 ± 10.5	29.9 ± 17.6	0.3

Age, gender, and cardiovascular risk factors are compared per patient (ST-segment elevation myocardial infarction [STEMI] = 16 stable/unstable angina = 27). The rest of the variables are compared per lesion (STEMI = 16 stable/unstable angina = 31).

DM = diabetes mellitus; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery.

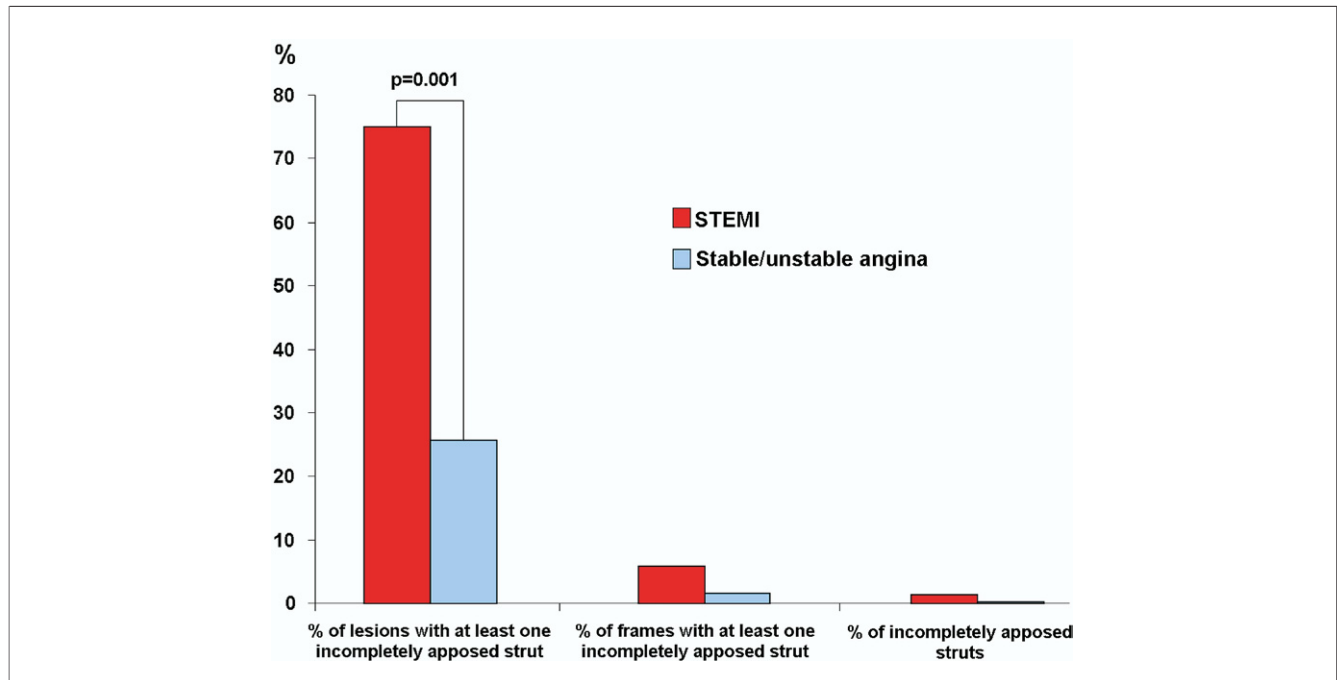


Figure 4. Difference in ISA Frequency Between STEMI and Stable/Unstable Angina Patients

Incomplete stent apposition (ISA) frequency is shown per lesion (number of lesions with at least 1 incompletely apposed strut/total number of lesions), per frame (number of frames with at least 1 incompletely apposed strut/total number of frames), and per strut (number of incompletely apposed struts/total number of struts). STEMI = ST-segment elevation myocardial infarction.

months) for the STEMI group and 9 months (range 9 to 72 months) for the rest of the patients. There were no significant differences in lumen area (6.5 ± 2.0 vs. 6.4 ± 2 for STEMI and stable/unstable angina, respectively, $p = 0.86$), stent area (7.2 ± 2.0 vs. 7.0 ± 2.0 for STEMI and stable/unstable angina, respectively, $p = 0.78$), or stent symmetry ratio (0.58 ± 0.17 vs. 0.65 ± 0.15 for STEMI and stable/unstable angina, respectively, $p = 0.13$).

ISA in STEMI patients. Figure 4 represents the frequency of ISA in lesions treated with DES implantation for STEMI and the rest of the lesions. Table 2 shows the differences in the number of incompletely apposed struts (covered and not covered), maximum ISA length, and ISA area in lesions treated for STEMI and lesions treated for stable/unstable angina.

Uncovered struts in STEMI patients. Figure 5 shows the difference in frequency of uncovered struts between lesions treated for STEMI and lesions treated for stable/unstable angina. The number of uncovered struts; the mean tissue coverage thickness, area, and volume; and the tissue coverage symmetry ratio in both groups are indicated in Table 3. **Predictors of ISA.** Multiple logistic regression analysis was performed to determine the independent predictors of ISA. The following variables were included in the model: age, follow-up time, stent length, stent symmetry ratio, and stent implantation during primary PCI. The only independent predictor of ISA was DES implantation during primary PCI for STEMI (odds ratio: 9.8, 95% confidence interval: 2.4 to 40.4, $p = 0.002$).

Table 2. Differences in ISA Between Lesions Treated With Drug-Eluting Stent Implantation for STEMI and for Stable/Unstable Angina

	STEMI (n = 16)	Stable/Unstable Angina (n = 31)	p Value
Number of incompletely apposed struts	2 (0-13)	0 (0-5)	0.001
Number of incompletely apposed uncovered struts	1 (0-13)	0 (0-4)	<0.001
Number of incompletely apposed covered struts	0.5 (0-3)	0 (0-5)	0.02
ISA area (mm ²)	0.28 (0.17-0.67)	0.35 (0.23-0.44)	0.5
Maximum ISA length (μm)	235 (162-297)	250 (230-600)	0.4

Number of struts is expressed as median and range. Incomplete stent apposition (ISA) area and maximum ISA length are expressed as median (interquartile range).
STEMI = ST-segment elevation myocardial infarction.

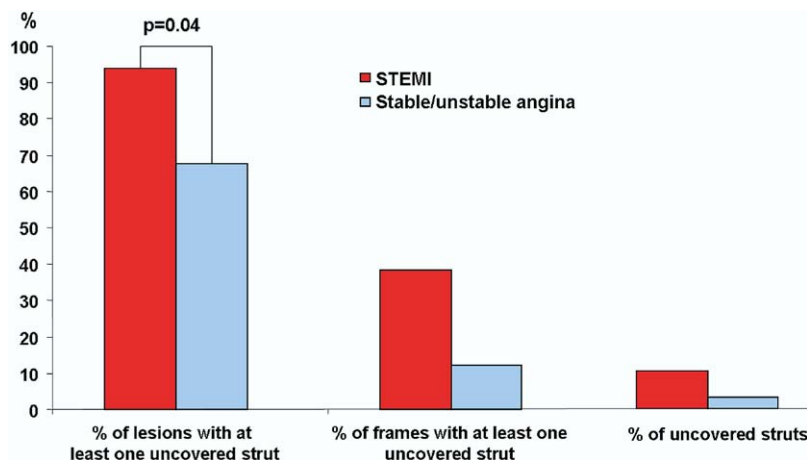


Figure 5. Difference in Uncovered Strut Frequency Between STEMI and Stable/Unstable Angina Patients

Data are shown per lesion (lesions with at least 1 uncovered strut/total number of lesions), per frame (frames with at least 1 uncovered strut/total number of frames), and per strut (number of uncovered struts/total number of struts). STEMI = ST-segment elevation myocardial infarction.

Predictors of uncovered struts. In the multivariate model for uncovered struts predictors, the following variables were included: age, follow-up time, stent length, stent area, and stent implantation during primary PCI. Drug-eluting stent implantation during primary PCI for STEMI was the only independent predictor of uncovered struts at follow-up (odds ratio: 9.5, 95% confidence interval: 1.0 to 90.3, $p = 0.049$).

Discussion

To our knowledge this is the first such study to use the high-resolution capabilities of intracoronary OCT to examine stent strut apposition and tissue coverage at follow-up in patients with STEMI treated with primary PCI. The main findings are: 1) DES implanted for STEMI had a higher frequency of incompletely apposed

and uncovered struts as assessed by OCT at follow-up, and 2) DES implantation during primary PCI in STEMI is an independent predictor of both ISA and the presence of uncovered struts at follow-up.

Drug-eluting stents have consistently demonstrated a reduction in restenosis rates when compared with bare-metal stents (BMS) in different clinical settings, including primary PCI for the treatment of STEMI (6). However, concerns have been raised about a potentially higher risk of stent thrombosis after DES implantation during primary PCI (7). Furthermore, ISA and lack of complete stent endothelialization have been identified as factors related to stent thrombosis (4,5).

ISA. Overall the frequency of incompletely apposed struts was very low (0.6%). In our study patients with STEMI treated with DES implantation during primary PCI had a higher frequency of ISA. Our results are in concordance with IVUS studies that have identified a higher incidence of late ISA in STEMI patients, especially when treated with DES. Hong et al. (8) reported an incidence of late ISA after primary PCI in STEMI of 11.5% after BMS implantation and 31.8% after DES implantation. In our sample, 75% of the lesions treated with DES during primary PCI showed evidence of ISA. The higher frequency of ISA observed in the present study can be explained by the higher resolution of OCT in comparison with IVUS (9). The results of the present study are also in line with a recent OCT study that identified a higher incidence of ISA in sirolimus-eluting stents implanted in unstable versus stable angina patients (33% vs. 4%) (10).

The dissolution of thrombus jailed after stent implantation during primary PCI has been postulated as 1 of the possible causes of the higher incidence of late ISA in

Table 3. Differences in Strut Coverage Between Lesions Treated With Drug-Eluting Stent Implantation for STEMI and for Stable/Unstable Angina

	STEMI (n = 16)	Stable/Unstable Angina (n = 31)	p Value
Number of uncovered struts	26.8 ± 20.8	6.2 ± 7.5	0.001
Uncovered strut distribution (%)	40.7 ± 25.2	16.4 ± 19.8	0.001
Mean tissue coverage area (mm ²)	0.72 ± 0.63	0.65 ± 0.37	0.68
% tissue coverage area	12.4 ± 9.9	11.0 ± 6.9	0.58
Tissue coverage volume (mm ³)	17.7 ± 21.6	21.9 ± 22.04	0.54
% tissue coverage volume	10.0 ± 9.4	10.3 ± 6.7	0.91
Tissue coverage thickness (μm)	110 ± 48	90 ± 53	0.22
Tissue coverage symmetry ratio	0.79 ± 0.23	0.70 ± 0.13	0.02

STEMI = ST-segment elevation myocardial infarction.

STEMI patients (4). Plaque rupture (characterized by a necrotic core with an overlying thin-ruptured cap infiltrated by macrophages and with paucity of smooth muscle cells) is the most frequent underlying substrate in STEMI. Stent implantation over a ruptured plaque with strut penetration into necrotic core has also been related to ISA in acute coronary syndromes (11). The clinical implications of ISA are controversial. Several studies have reported that the presence of ISA after DES implantation is not associated with adverse events at long-term follow-up (8,12,13). However, recently published IVUS observations suggest a possible relation between incomplete DES apposition and subsequent stent thrombosis (3,4). The clinical significance of ISA as detected by OCT is poorly understood. In fact, incomplete apposition of stent struts is a relatively common finding by OCT, although the vast majority of the patients do not experience clinical events in the long term (14). In addition, not all patients that experience DES thrombosis show strut malapposition (15,16). In the present study none of the patients with ISA as assessed by OCT presented with adverse clinical events.

Strut coverage. DES inhibits neointimal proliferation to such an extent that it might not be detectable by IVUS (17). The high resolution of OCT allows the visualization and measurement of tiny layers of tissue covering the stent struts (18). In the present study, the global frequency of uncovered individual struts was 6.1%, and a high proportion of lesions (36 of 47) presented uncovered struts. This is in agreement with different OCT studies recently published reporting strut coverage in DES at follow-up (14,19). A long-term follow-up with OCT in a group of patients treated with sirolimus-eluting stents revealed that 81% of the patients presented uncovered struts at 2 years' follow-up (20). In the present study 8 of the 9 lesions with more than 2 years' follow-up demonstrated uncovered struts by OCT, and interestingly, in 6 of those 8 lesions the DES were implanted during primary PCI. The frequency of struts with no visible coverage was significantly higher in STEMI patients treated during primary PCI (15 of 16 lesions). Likewise, the distribution of uncovered struts within the stent was more spread in STEMI patients (reflected in a higher proportion of frames with uncovered struts). The mean neointimal thickness did not differ between STEMI and stable/unstable angina patients, but the neointima showed a more asymmetric distribution in STEMI patients. Our findings are in agreement with pathological studies showing delayed endothelialization at the culprit site in acute myocardial infarction patients treated with DES compared with the culprit site in patients receiving DES for stable angina (21). A recent study, reporting a lower incidence of full tissue coverage in unstable angina than in stable angina, is also in line with our observations (10). Pathological data suggest a relation between arterial healing and underlying plaque morphology. In an autopsy study, Nakazawa et al.

(21) found a higher percentage of uncovered struts in patients with stents implanted in plaques with high-risk features (such as plaque rupture and thin cap fibroatheroma) as compared with those with stable plaque morphology. Despite a lack of OCT assessment during the primary PCI procedure in our study, it is accepted that plaque rupture is the most frequent underlying event leading to STEMI (22). The stent contact with an avascular tissue such as necrotic core and the different drug distribution due to the presence of thrombus are some of the factors that could explain the delayed coverage of struts in unstable patients (21,23). The more asymmetric distribution in the cross section of the tissue covering the struts found in STEMI patients might also be related with the eccentricity and composition of the plaque underlying the stent implantation (24). Endothelial struts coverage has been identified in pathological series as the most powerful histological predictor of stent thrombosis (5). Pathological data in humans suggest that neointimal coverage of stent struts might be a surrogate marker of endothelialization (25). However, Kubo et al. (10) reported that the presence of a higher incidence of uncovered struts by OCT in unstable patients was not associated with adverse outcomes at 9 months. In the present study no adverse events occurred at follow-up even when the frequency of uncovered struts was high. The clinical significance of the presence of uncovered struts as assessed by OCT remains unknown and would require specific long-term follow-up studies. Despite the high resolution of the technique, coverage of the strut with an individual cell layer cannot be excluded. Currently, OCT cannot adequately distinguish the tissue type covering the struts (e.g., a neointimal layer from fibrin). Furthermore, different types of neointimal tissue with different optical properties can be observed and might have different functionality (26). The development of quantitative tissue characterization by OCT might be helpful to better understand the clinical implications of strut tissue coverage.

Study limitations. The present study is observational and nonrandomized. No formal sample size calculation was performed. Another limitation is the lack of serial OCT assessments with OCT only performed at long-term follow-up. Therefore, it was not possible to distinguish between persistent and late-acquired ISA. The presence of positive remodeling as a cause of late ISA (as demonstrated previously in IVUS) cannot be excluded. Likewise, no information was available about the underlying plaque in which the stent was implanted. Only DES were included in the study. Therefore we cannot exclude that BMS would not have behaved similarly when implanted in the setting of STEMI.

Conclusions

DES implanted for STEMI had a higher frequency of incompletely apposed struts and uncovered struts as assessed

by OCT at follow-up. Drug-eluting stent implantation during primary PCI in STEMI was an independent predictor of ISA and the presence of uncovered struts at follow-up. Whether these findings have a causal link to the heightened rate of stent thrombosis in STEMI patients remains to be confirmed by larger studies.

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