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Comparison of two different sampling intervals for optical coherence tomography evaluation of neointimal healing response after coronary stent implantation

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ABSTRACT

Background/objectives: Optical coherence tomography (OCT) is widely used for evaluation of healing response to stent implantation. We sought to test the agreement between the 1-mm and 0.6-mm sampling intervals for assessment of the percentage of uncovered and malapposed struts by OCT.
Methods: Thirty-eight patients presenting with acute coronary syndrome were randomized to receive either a titanium-nitride-oxide-coated stent (n = 19) or an everolimus-eluting stent (n = 19). Neointimal strut coverage and strut apposition were evaluated by OCT at 2-month follow-up. Two independent investigators performed offline OCT image analysis at 1-mm intervals. One investigator repeated the measurements at 0.6-mm intervals and measurements were compared between the two sampling intervals.
Results: At a median follow-up of 60 [8] days, 694 cross-sections (7603 struts) and 1138 cross-sections (12,331 struts) were analysed at 1-mm and at 0.6-mm intervals, respectively. The median [IQR] percentage of uncovered struts was 3.27% [11.1] versus 3.38% [9.76] (p = 0.001), and the mean (±SD) percentage was 7.69 ± 9.99% versus 6.27 ± 8.14% (p = 0.004), for the 1-mm sampling interval versus the 0.6-mm sampling interval analysis, respectively; the median percentage of malapposed struts was 0.42% [2.04] versus 0.12% [1.63], respectively, (p = 0.003). The intraclass correlation coefficient between the two observers for the percentage of uncovered struts was 0.95.
Conclusions: The OCT-evaluated strut-level measurements of neointimal healing after stent implantation differ significantly between the 1-mm and the 0.6-mm sampling intervals.

1. Introduction

Intracoronary optical coherence tomography (OCT) is a well-established method for evaluation of neointimal healing response to stent implantation immediately after the procedure, and at mid-term follow-up. In this context, the most widely acknowledged use of OCT is assessment of neointimal coverage of stent struts [1]. Modern frequency-domain OCT systems usually record 10 cross-sections per 1 mm [1]. Despite the large number of cross-sections recorded in an OCT pullback, only a limited number of these are eventually analysed, with the analysis commonly performed at 1-mm intervals. Previously, low variability of cross-sectional area measurements has been reported when images were analysed at sampling intervals ranging from 0.5 to 1 mm; in contrast, the variability of neointimal strut coverage may become high when images are analysed at 1-mm intervals [2]. Whether the indices of strut coverage and malapposition differ with different sampling intervals remains unclear. Therefore, we set out to test the agreement between the 1-mm and 0.6-mm sampling intervals for assessment of the percentage of uncovered and malapposed struts by coronary OCT.

2. Methods

2.1. Patient selection and study design

The study included 38 patients enrolled in the TIDES-OCT trial, a prospective multicentre single-blinded randomized controlled trial, designed to compare the early neointimal coverage and vasodilator response 2 months following percutaneous coronary intervention (PCI) with a titanium-nitride-oxide-coated bioactive stent (BAS) based on

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cobalt-chromium platform versus an everolimus-eluting stent (EES) based on platinum-chromium platform, in patients presenting with acute coronary syndrome (ACS) [3]. From January to August 2013, the trial enrolled 40 patients with ACS, and significant stenosis (≥50% by visual estimation) of a de novo culprit lesion. ACS included ST-elevation, non-ST-elevation myocardial infarction (MI), and unstable angina, as defined by the current European Society of Cardiology guidelines [4–6]. The main exclusion criteria were bleeding disorders or contraindication to dual antiplatelet therapy (DAPT), unprotected left main disease, ostial or bifurcation (side branch > 02 mm) lesions, multi-vessel disease, another de novo stenosis (≥30%) in the stented vessel. Enrolled patients were randomly assigned (1:1) to receive either BAS (OPTIMAX™, Hexacath, Paris, France) or EES (PROMUS Element™ Plus, Boston Scientific, Marlborough, MA, US) using computer-generated randomisation and sealed envelopes stratified by centre. The study investigators responsible for OCT data analysis were blinded to the study stent allocation.

2.2. Ethical issues

The study was initiated by the investigators, and conducted according to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2013. Informed written consent was obtained from every patient after full explanation of the study protocol. The ethics committees of the participating centers approved the study protocol. No industry representatives were involved in the data acquisition, analysis, interpretation, or drafting of the manuscript. The TIDES-OCT trial is registered under ClinicalTrials.gov, with number NCT02280720.

2.3. Optical coherence tomography image acquisition

OCT imaging was performed immediately after follow-up angiography (2 months following the index procedure) using 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 a 6F guiding catheter. An imaging catheter (Dragonfly, LightLab Imaging Inc., 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 iso-osmolar contrast. A segment length of 54 mm was visualized (100 cross-sections/s), and images were stored digitally for subsequent offline analysis.

2.4. Optical coherence tomography image analysis

Offline OCT analysis was performed using proprietary software (LightLab Imaging Inc., Westford, MA, USA). The first distal cross-section to show struts encompassing the lumen was assigned as the 'starting cross-section', and cross-sections were analysed thereafter at 1-mm sampling intervals (every fifth frame) within the stented segment. We excluded cross-sections with poor quality: >45° of the lumen border not visible for analysis, or those with severe blood or rotational artefact. If a cross-section was not suitable for analysis due to poor image quality, an adjacent cross-section was used instead. Analysis was repeated from the same 'starting cross-section' by 2 independent investigators blinded to patient characteristics and stent group allocation (observer 1 and 2). Finally, analysis was repeated by observer 1 at 0.6-mm sampling intervals (every third frame), and measurements were recorded; the main outcome variable for the repeat analysis was the median percentage of uncovered struts.

Stent area (SA) and lumen area (LA) were measured semi-automatically in each cross-section. Neointimal hyperplasia (NIH) area was defined as SA-LA, and the percent NIH area was calculated as the ratio of NIH area to the SA, multiplied by 100. In each cross-section, the total number of struts was counted. In per-strut analysis, each strut was 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. The percentage of uncovered struts was calculated as the ratio of uncovered struts to total struts multiplied by 100. In covered struts, NIH thickness was measured from the strut marker to the endoluminal edge of the tissue coverage, following a straight line connecting the marker with the center of gravity of the vessel. Apposition was assessed by measuring the distance between the strut marker and the lumen contour following a straight line connecting the marker with the center of gravity of the vessel. A margin of 18 μm was added as a correction for half the blooming. Given a coated strut thickness of 75 μm, we adopted a malapposition threshold of 100 μm for the BAS (75 μm + 18 = 93 μm). Similarly, given a strut thickness of 81 μm and a polymer thickness of 7 μm, we adopted a malapposition threshold of 110 μm for the EES (81 μm + 7 μm + 18 = 106 μm). Struts covering a side branch were labelled as non-apposed side branch (NASB) struts, and were excluded from analysis.

Table 1
Baseline clinical characteristics of the two individual study groups.

Variable	BAS (n = 19)	EES (n = 19)	p value
Age (years)	59.5 ± 9.47	68.2 ± 7.24	0.003
Male sex	14 (73.7%)	11 (57.9%)	0.495
Risk factors			
Diabetes	1 (5.3%)	3 (15.8%)	0.604
Hypertension	12 (63.2%)	16 (84.2%)	0.269
Hypercholesterolemia	11 (57.9%)	16 (84.2%)	0.151
Current smoking	7 (36.8%)	4 (21.1%)	0.476
Medical history			
Prior myocardial infarction	2 (10.5%)	4 (21.1%)	0.660
Prior PCI	3 (15.8%)	4 (21.1%)	1.0
Prior CABG	0	1 (5.3%)	1.000
Indication for PCI			
Unstable angina	2 (10.5)	5 (26.3)	0.127
NSTEMI	8 (42.1)	11 (57.9)	
STEMI	9 (47.4)	3 (15.8)	

Continuous variables are presented as mean ± SD, whereas categorical variables are presented as frequency (percentage). BAS, bioactive stent; CABG, coronary artery bypass grafting; EES, everolimus-eluting stent; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2
Median [IQR] percentage of uncovered and malapposed struts in the two sampling intervals stratified by stent group.

Stent group	1-mm interval	0.6-mm interval	p value
Percent uncovered struts			
BAS	0.77 [2.0] %	0.45 [1.6] %	0.273
EES	10.6 [9.1] %	9.8 [6.7] %	0.002
Overall	3.27 [11.1] %	3.38 [9.76] %	0.001
Percent malapposed struts			
BAS	0 [1.45] %	0 [1.09] %	0.031
EES	0.59 [3.85] %	0.55 [2.77] %	0.151
Overall	0.42 [2.04] %	0.12 [1.63] %	0.003

Pairwise Wilcoxon signed-rank sum was used to calculate the p-values. BAS indicates bioactive stent; EES, everolimus-eluting stent.

2.5. Statistical analysis

The primary endpoint of the study was the median percentage of uncovered struts in the 1-mm compared with the 0.6-mm sampling interval analysis, at 2-month follow-up. For the analysis of interval difference, we assumed that a sample size of 22 patients per group is adequate. The study was explorative in nature and the sample size was calculated for the difference in the stent healing effect between the two intervals (effect size of 5% and expected standard deviation (SD) of 5% in stent-level analysis (power of 80%, 2-sided type I error of 0.05). Continuous variables were tested for normality with Kolmogorov-Smirnov test, and were reported as mean ± SD or as median and interquartile range [IQR], where appropriate. Fisher exact test, independent samples t-test, Mann-Whitney *U* test, and Spearman's test were used for univariate analyses. In order to account for the different percentage of uncovered and malapposed struts in the 2 stent groups, comparisons of strut coverage and malapposition between the 2 alternative sampling intervals (0.6-mm and 1-mm intervals) was stratified based on the stent group, and Pairwise Wilcoxon signed-rank sum was used due to the skewed distribution of these variables. Pooled regression analysis of the percentage of uncovered struts was performed using random effects model (DerSimonian–Laird). Inter-observer variability was estimated in Bland-Altman analysis for the following indices: the percentage of uncovered struts, the mean NIH thickness, the percentage of malapposed struts and the mean malapposition distance. To assess inter-observer agreement, Bland-Altman plots were produced and mean difference and 95% limits of agreement were calculated. The coefficient of variation (within which 95% of all differences are included) was calculated as twice the standard

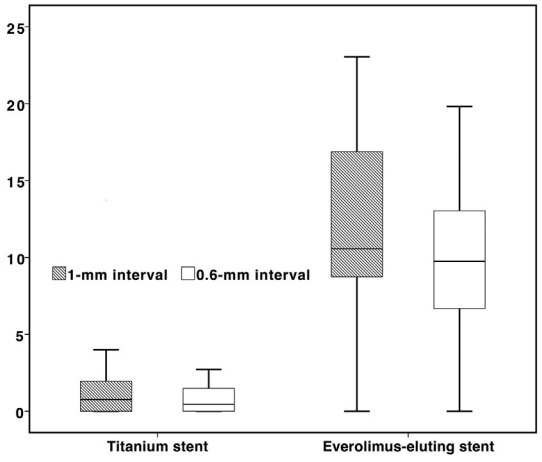

Fig. 1. The median percentage of uncovered struts assessed in the 2 sampling intervals stratified by stent group.

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