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Randomised comparison of vascular response to biodegradable polymer sirolimus eluting and permanent polymer everolimus eluting stents: An optical coherence tomography study

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ABSTRACT

Background: Drug-eluting stents with biodegradable polymer coatings have shown promising outcomes in randomised studies.
Methods: We compared neointimal healing patterns including strut coverage and assessed neointimal maturity using a novel algorithm in coronary lesions treated with sirolimus-eluting stents with biodegradable polymer coating (BP-SES) or everolimus eluting stents with permanent polymer coating (PP-EES) using optical coherence tomography after 6 months.
Results: A total of 39 patients were randomised to BP-SES ($n = 19$) or PP-EES ($n = 20$) for the treatment of coronary lesions. Of those, 29 patients (14 BP-SES and 15 PP-EES) underwent optical coherence tomography (OCT) and angiography at 6-month follow-up. Tissue coverage and apposition were assessed in a total of 6162 struts (BP-SES, $n = 2889$; PP-EES, $n = 3273$). Neointimal maturity was assessed in 3672 neointimal regions above struts using grey scale intensity analysis. OCT analysis showed neointimal coverage of 2433 (BP-SES) vs. 2702 (PP-EES) struts (84.2% vs. 82.6%, $p = 0.70$), whereas the remainder was uncovered after 6 months. Mean neointimal thickness did not differ significantly between groups (54.3 ± 7.8 μm vs. 80 ± 14.6 μm, $p = 0.12$). The rate of malapposed struts was comparable between groups (1.3% vs. 2.2%, $p = 0.27$). Grey scale signal intensity analysis showed mature tissue coverage of struts in 46.2% in BP-SES vs. 31.8% in PP-EES ($p = 0.31$) of neointimal regions.
Conclusion: The present study showed comparable early vascular healing response characterised by neointimal coverage with mainly immature neointima in both BP-SES and PP-EES.

1. Introduction

Drug-eluting stents (DES) have dramatically reduced the frequency of in-stent restenosis and target lesion revascularisation by effectively inhibiting neointimal hyperplasia [1]. However, findings of delayed neointimal healing and incomplete endothelialisation gave rise to concerns about late stent thrombosis (LST) with first-generation DES [2,3]. LST and delayed vascular healing were less frequently observed in second generation everolimus eluting stents (EES) with permanent fluoropolymers when compared to first generation DES with permanent polymers in human autopsy studies [4]. However, the permanent presence of methacrylate based fluoropolymers in contact with the vessel wall still bears the potential of impaired vascular healing, a major risk factor for late stent thrombosis [5,6]. Novel biodegradable polymer DES were developed to overcome those late adverse outcomes providing technical improvements such as thinner stent struts, lower drug dosages and improved biocompatibility of polymers [7–9]. A novel sirolimus eluting stent with biodegradable polymer coating (BP-SES) showed promising results of target lesion failure after 12 months when compared to an EES with permanent polymer coating in a randomised trial [10]. However, little is known about vascular healing in the early phase of polymer degradation in BP-SES. Optical coherence

Abbreviations: BES, Biolimus eluting stent; BP-BES, Biolimus eluting stent with biodegradable polymer coating; BP-SES, Sirolimus eluting stent with biodegradable polymer coating; DES, Drug-eluting stent; EES, Everolimus eluting stent; GSI, Grey scale intensity; ISAR, Intracoronary Stenting and Antithrombosis Research Centre; IVUS, Intravascular ultrasound; LST, Late stent thrombosis; mTOR, Mammalian target of rapamycin; NIT, Neointimal thickness; OCT, Optical coherence tomography; PBMA, Polybutyl methacrylate; PLLA, Poly-L-lactic acid; PP-EES, Everolimus eluting stent with permanent polymer coating; PP-SES, Sirolimus eluting stent with permanent polymer; QCA, Quantitative coronary angiography; ROI, Region of interest; SES, Sirolimus eluting stent; VLST, Very late stent thrombosis; ZES, Zotarolimus eluting stent.

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tomography (OCT) is a light-based intracoronary imaging technique visualising strut coverage and apposition at a high-resolution of approximately 20 μm. Several validation studies have shown that OCT is more accurate in evaluating neointimal tissue after coronary stent implantation than intravascular ultrasound (IVUS) [11]. Novel findings on OCT evaluation include neointimal characterisation and have shown to differentiate between mature and immature neointimal tissue, which might offer important implications for the characterisation of vascular healing in contemporary DES [12].

2. Methods

2.1. Study population and protocol

A total of 39 patients were randomly assigned to BP-SES ($n = 19$) and PP-EES ($n = 20$) in a single centre, randomised (1:1), open-label, two-arm clinical trial comparing BP-SES with PP-EES. Written informed consent to participation was obtained from all patients in accordance with the Declaration of Helsinki. This study was approved by the local ethics committee and registered at clinicaltrials.gov (study identifier: NCT01594736). Patients with stable and unstable angina pectoris were eligible for inclusion in this trial. Patients with acute myocardial infarction, left main disease, in-stent restenosis, bifurcation lesions, comorbid conditions associated with life expectancy <12 months or inability to adhere to dual antiplatelet therapy were excluded. For the p4urpose of the present study, clinical, angiographic, and OCT examination at 6 months of follow-up were prospectively scheduled in all patients enrolled between January 2012 and June 2013. Allocation to treatment was done by means of sealed, opaque envelopes containing a computer-generated sequence prior to stent implantation. All index interventions were performed using standard techniques. Pre- and post-dilatation were left to the operator's discretion. Prior to the index procedure, all patients received aspirin at a dose of 100 mg and a 600 mg loading dose of clopidogrel. After the procedure, all patients were advised to continue on aspirin (100 mg daily) and statins unless there were contraindications. Clopidogrel (75 mg daily) was prescribed for at least 1 year after stent implantation. Data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Centre (ISAR Centre, Munich, Germany). All events were adjudicated and classified by an experienced event adjudication committee blinded to the treatment groups.

2.2. Test devices

We compared a sirolimus-eluting stent with biodegradable polymer coating (BP-SES) (Orsiro, Biotronik AG, Buelach, Switzerland) that consists of a thin-strut 60–80 μm cobalt chromium stent (60 μm for diameters from 2.25 to 3.0 mm and 80 μm for diameters from 3.5 to 4.0 mm) with a biodegradable poly-L-lactic acid (PLLA) coating eluting sirolimus at a drug dose of 140 μg/mm^2 within 12–14 weeks to a thin-strut 81 μm cobalt–chromium stent with a permanent polymer coating (poly-*n*-butyl-methacrylate and co-polymer of vinylidine fluoride and hexafluoropropylene) containing everolimus at a dose density of 100 μg/mm^2 (PP-EES) (Xience PRIME, Abbott Vascular, Santa Clara, CA, USA) designed to release 80% of everolimus within the first 30 days after stent deployment [13].

2.3. Study endpoints

Our hypothesis was that BP-SES is non-inferior to PP-EES with regards to coverage of stent struts at 6 months after implantation assessed by OCT. The primary endpoint was neointimal tissue coverage at 6-month follow-up, which was assessed as mean neointimal thickness (NIT) and percentage of uncovered struts. Secondary endpoints included apposition of stent struts and tissue characterisation of the nascent neointimal tissue above stent struts.

2.4. Quantitative coronary angiography

Quantitative coronary angiographic analysis was performed before and after stenting and 6 months after index procedure, using a guiding catheter to calibrate the magnification and a validated automated edge detection algorithm (CMS version 7.1, Medis Medical Imaging Systems) as previously described [14]. The analyses were performed independently by two experienced independent observers in an independent core laboratory (ISAR centre, Munich, Germany) blinded to the clinical information. In-stent restenosis was defined as per cent diameter stenosis of >50% within the stent segment at the time of follow-up angiography.

2.5. OCT image acquisition

The methods of OCT image acquisition were described in a previous report [15]. Following administration of intravenous heparin and intracoronary nitrates OCT was performed using frequency domain OCT (C7XR system, LightLab Imaging, Westford, MA, USA) allowing acquisition at 100 frames per second with non-occlusive imaging technique. A standard guide wire was advanced distally in the target vessel and the OCT companion C7 Dragonfly catheter was advanced over the wire using rapid exchange technology. OCT imaging was performed at a pullback of 20 mm/s, during flush of 2–4 mL/s of isoosmolar contrast through the guiding catheter to replace blood flow and permit visualization of the stented segment and intima/lumen interface. If the stented segment was too long to be safely imaged in a single pullback, image acquisition was stopped and an additional pullback performed during a second contrast injection using anatomic landmarks such as side branches, calcifications for longitudinal view orientation.

2.6. OCT analysis

Offline data analysis was performed using LightLab offline work stations equipped with proprietary Illumien software (Light Lab offline work station, St. Jude Medical, St. Paul, MN, USA) in a core laboratory (ISAR centre, Munich, Germany) by independent personnel blinded to stent-type allocation and clinical and procedural characteristics as previously described [16]. Cross-sectional OCT images were analysed at 1-mm intervals within the stented segment and 5-mm proximal and distal to the stent edges. A strut was considered suitable for analysis if it had a well-defined bright 'blooming' appearance and a characteristic shadow perpendicular to the light source. The number of stent struts was determined in each cross-section. Thickness of the tissue coverage on the luminal side of each strut was measured at the centre of the long axis of the strut. The inner contours of each strut reflection were delineated for each strut and its distance to the lumen contour was measured to determine intimal thickness.

Struts were adjudicated as covered by tissue if they had a positive intimal thickness greater than the axial resolution of OCT (20 μm) since the significance of stent coverage thickness that is measured to be lower than the axial resolution of OCT remains questionable [17]. Struts were classified as malapposed if they were protruding into the lumen at a distance greater than the sum of the strut and polymer thickness (71 μm for BP-SES ≤3.0 mm diameter, 91 μm for BP-SES with larger sizes, and 89 μm for PP-EES). Malapposed struts were classified as uncovered, since tissue surrounding malapposed struts is not well understood, and might represent thrombus formation. Lumen area and stent area were drawn in each cross-section. Neointimal area and percent area stenosis were calculated as previously described [18]. If any cavity beyond the visualized stent strut contour was observed, the area of extra stent cavity was calculated as: lumen area − stent area [16,19].

Cross-sections with side branches or poor quality of OCT images were excluded from this analysis. Neointimal tissue characterisation was performed as previously described [12]. In brief, exclusion criteria for grey scale intensity (GSI) analysis were: presence of stent struts penetrating into a necrotic core, stent struts overlying areas of severe calcification, bifurcation stenting and malapposition as all these variables may influence signal intensity of grey scales. OCT frames were further analysed for differences in optical luminescence after conversion into 8-bit grey-scale format to acquire data for tissue characterisation. Mean GSI was measured within neointimal tissue above stent struts using an Image J software algorithm (National Institutes of Health, Bethesda, MD, USA). A cut-off of 109.7 after normalization to the guide wire level was used to adjudicate mature neointimal tissue as preciously described [12].

2.7. Statistical analysis

The following assumptions were used to calculate the sample size: the percentage of evaluable strut segments not covered by neointima is 15% for both BP-SES and PP-EES, a 1-sided a-level of 0.05 and a power of 90%. Accordingly, a minimal number of 1713 evaluable strut segments will be needed for each randomization arm. A total number of 12 patients were calculated to provide the necessary number of struts for the analysis. To account for possible losses to follow-up, 19 patients in the BP-SES group and 20 patients in the PP-EES group were enrolled.

Data are presented as mean value ± standard deviation or median with interquartile range depending on the distribution. The distribution was tested using the Kolmogorov–Smirnov test. Categorical variables were compared using Pearson's chi-squared test with Yates' continuity correction and Fisher's exact test. Continuous variables were compared using the Welch's *t*-test if normally distributed or the Kruskal–Wallis rank sum test if not normally distributed. The analysis of primary and secondary endpoints was planned on an intention-to-treat basis. To account for the clustered nature of the data, generalised estimated equations were conducted for strut-level and frame-level OCT analysis to compare BP-SES and PP-EES. All statistical analyses were two-tailed and *p*-values ≤0.05 were considered statistically significant. Analyses were performed with R 2.15.1 (The R foundation for Statistical Computing, Vienna, Austria) and JMP 9.0.2 (SAS Institute Inc., Cary, NC, USA) statistical software.

3. Results

3.1. Study population

A total of 39 patients (39 lesions) were enrolled in this study. Ten patients (five BP-SES and five PP-EES) were excluded from the current analysis because of refusal to participate in angiographic and OCT follow-up. Only clinical information was available in those patients.

A total of 29 patients were available for angiographic and OCT follow-up. Finally, 14 patients with BP-SES (14 lesions) and 15 patients with PP-EES (15 lesions) patients were eligible for the present analysis. This yielded a total of 6162 struts for coverage analysis (2889 in BP-SES and 3273 in PP-EES). For characterisation of neointimal maturity, a total