Stent Coverage and Neointimal Proliferation in Bare Metal Stents Postdilated With a Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stents: Prospective Randomized Study Using Optical Coherence Tomography at 6-Month Follow-Up

Tudor C. Poerner, MD*; Sylvia Otto, MD*; Johannes Gassdorf; Kristina Nitsche; Florian Janiak; Bruno Scheller, MD; Björn Goebel, MD; Christian Jung, MD; Hans R. Figulla, MD

**Background**—In this randomized trial, strut coverage and neointimal proliferation of a therapy of bare metal stents (BMSs) postdilated with the paclitaxel drug-eluting balloon (DEB) was compared with everolimus drug-eluting stents (DESs) at 6-month follow-up using optical coherence tomography. We hypothesized sufficient stent coverage at follow-up.

**Methods and Results**—A total of 105 lesions in 90 patients were treated with either XIENCE V DES (n=51) or BMS postdilated with the SeQuent Please DEB (n=54). At follow-up, comparable results on the primary optical coherence tomography end point (percentage uncovered struts 5.64±9.65% in BMS+DEB versus 4.93±9.29% in DES; P=0.366) were found. Thus, BMS+DEB achieved the prespecified noninferiority margin of 5% uncovered struts versus DES (difference between treatment means, 0.71%; one-sided upper 95% confidence interval, 4.14%; noninferiority P=0.04). Optical coherence tomography analysis showed significantly more global neointimal proliferation in the BMS+DEB group (15.7±7.8 versus 11.0±5.2 mm³ proliferation volume/cm stent length; P=0.002). No significant focal in-stent stenosis analyzed with angiography (percentage diameter stenosis at follow-up, 22.8±11.9 versus 16.9±10.4; P=0.014) and optical coherence tomography (peak local area stenosis, 39.5±13.8% versus 36.8±15.6%; P=0.409) was found.

**Conclusions**—Good stent strut coverage of >94% was found in both therapy groups. Despite greater suppression of global neointimal growth in DES, both DES and BMS+DEB effectively prevented clinically relevant focal restenosis at 6-month follow-up.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01056744.

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**Keywords:** coronary stenosis ▪ drug-eluting stents ▪ percutaneous coronary intervention ▪ tomography, optical coherence ▪ transluminal coronary balloon dilation

Paclitaxel drug-eluting balloons (DEBs) are newer intravascular devices that have been designed to limit the exposure of arterial structures to the antiproliferative drug in the absence of a polymer. DEBs proved to be effective for treatment of in-stent restenosis, de novo stenosis in small vessels, as well as in peripheral artery disease and carotid in-stent restenosis.1–4 However, successful use of drug-eluting balloons without stents in common de novo stenoses is limited for lesions without local flow-limiting vessel dissections and high-grade elastic recoil after lesion preparation.5–9

To date, there is limited knowledge on the combination of bare metal stent (BMS) postdilated with a drug-eluting balloon.10–12 Optical coherence tomography (OCT) is a new gold standard in intravascular imaging allowing the assessment of detailed vessel and stent structures with an axial resolution of 10 to 20 μm. Evolved algorithms to evaluate 2- and 3-dimensional proliferation parameters with OCT are of crucial importance to gain additional benefit compared with standard quantitative coronary angiography but are often deficient in reported OCT studies. Thus, we aimed to investigate an experimental combination of a BMS postdilated with a DEB in comparison with a newer-generation DES, which currently is the standard of care in percutaneous coronary interventions, on stent coverage and neointimal proliferation 6 months after implantation using OCT.

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From the 1st Department of Medicine, Division of Cardiology, University Hospital of Jena, Jena, Germany (T.C.P., S.O., J.G., K.N., F.J., B.G., C.J., H.R.F.); and Clinical and Experimental Interventional Cardiology, Internal Medicine III, University of Saarland, Saarbrücken, Germany (B.S.).

*Drs Poerner and Otto contributed equally to this work.


Correspondence to Sylvia Otto, MD, Klinik für Innere Medizin I, Universitätshäklinikum Jena, Erlanger Allee 101, 07747 Jena, Germany. E-mail sylvia.otto@med.uni-jena.de

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WHAT IS KNOWN

- Everolimus drug-eluting stents reduce in-stent restenosis and late lumen loss compared with bare metal stents.
- Paclitaxel drug-eluting balloons are effective in the treatment of in-stent restenosis and de novo stenosis in small coronary arteries.
- The safety and efficacy of paclitaxel drug-eluting balloons with bare metal stents as compared with everolimus drug-eluting stents have not been thoroughly investigated.

WHAT THE STUDY ADDS

- At 6-month follow-up, everolimus drug-eluting stents were superior over the combination bare metal stents+paclitaxel drug-eluting balloon in terms of neointimal proliferation, whereas the strut coverage by optical coherence tomography and the clinical outcomes did not differ between treatment arms.

Methods

Trial Design

This study was designed as a prospective, randomized, investigator-initiated, single-center trial in a single-blind fashion, conducted at the University Hospital of Jena, Germany during June 2009 and February 2011. The study was approved by the local ethical committee. A schematic presentation of the study design is shown in Figure 1. The detailed design of the Optical Coherence Tomography to Evaluate Paclitaxel-Eluting Balloons and Everolimus-Eluting Coronary Stents (OCTOPUS) trial has already been published.13 Patients with indication for elective percutaneous coronary intervention according to current guidelines with a native coronary lesion suitable for stent placement and OCT imaging were eligible for study inclusion.14 After coronary angiography suitable lesions were 1:1 randomized in an alternating fashion to either the cobalt–chromium everolimus drug-eluting stent (DES) Xience V (DES; Abbott Vascular, IL) or the cobalt–chromium Coroflex Blue BMS postdilated with the DEB SeQuent Please (DEB, both BBraun Melsungen, Germany).15,16

Angiographic Analysis and Invasive 6-Month Follow-up

Quantitative coronary angiography was assessed offline by 2 independent observers (K.N. and S.O.), who were blinded to the implanted study device according to the 15-coronary tree segment system (CAAS version 5.9.2, 2012, Pie Medical Imaging, Maastricht, The Netherlands). Late lumen loss was defined as final minimal lumen diameter (MLD) at the end of the index procedure, MLD at follow-up, and net luminal gain was defined as MLD at follow-up, baseline MLD. Angiographic restenosis at 6-month follow-up was defined as >50% diameter stenosis of the stented lesion. Invasive follow-up including OCT imaging (M2 CV system, LightLab Imaging Inc, Westford, MA) was attempted after 6 months in all study patients. Extended OCT image analysis was performed in 1-mm intervals of the study stent and the 2 to 5 mm of the proximal and distal native vessel (OCT parameters in the Data Supplement).

Figure 1. Flow diagram of the patient progress through the phases of this randomized trial, indicating screening, enrollment, intervention allocation, and follow-up in both device groups. BMS indicates bare metal stent; DEB, paclitaxel drug-eluting balloon; DES, everolimus drug-eluting stent; f/u, follow-up; ISR, in-stent restenoses; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; and TLR, target lesion revascularization.

* 9 patients with > 1 suitable lesion were sequentially included in both device groups.
Aims of the Study
The investigated efficacy and safety parameters were as follows:

- Primary end point (safety OCT parameter): endothelial stent coverage at 6 months, defined as percentage of struts without coverage. Sample size was estimated aiming noninferiority of BMS+DEB treatment against DES as described below.
- Secondary end points (efficacy OCT parameters): neointimal proliferation of the study stent at 6 months, defined as peak relative neointimal area proliferation and relative neointimal volumetric proliferation within the study stent.

The pattern of neointimal in-stent proliferation with respect to focal and diffuse distribution was evaluated.

Major adverse cardiac events were monitored during clinical follow-up at 6 months and in cases of no-show by telephone. However, this study was not powered for clinical end points.

Sample Size Estimation
At the time of study planning OCT data about endothelial coverage of newer generation DES were not available. Taking reported data for stent strut coverage of sirolimus-eluting stents from Matsumoto et al.17 with the assumption of DES showing similar or less noncoverage and the noninferiority limit δ was set to 5% and the SD of outcome α was set to 10%. With 80% power (1−β) and a 1-sided significance level of 5% (α), we calculated a total sample size of 100 lesions with 50 lesions per group for this trial using 1:1 randomization.

Data Management and Statistical Analysis
Data were archived into a custom-made Microsoft Access (Microsoft Inc, Redmond) database, whose forms served as electronic case reports. All calculations were done using SPSS for Windows (version 19.0, SPSS, Chicago, IL). Continuous and normally distributed variables were analyzed with the Student t test. Categorical variables were analyzed with the Pearson χ2 test. Two-sided P values <0.05 were accepted as statistically significant. Baseline characteristics, procedural and lesion parameters, as well as major adverse cardiovascular events at 6-month follow-up were analyzed as intention to treat. All other variables were analyzed per protocol. Corresponding to previous pivotal clinical trials and observational studies in interventional cardiology and the current consensus, we analyzed our data assuming all lesions as independent observations because it has been shown that the effect of clustering (patients with >1 study lesion) is minimal and without practical relevance.18,19 Noninferiority hypothesis for the primary end point was tested using the confidence interval approach. A secondary sensitivity analysis on the intention-to-treat sample for the primary end point was conducted using multiple imputation for missing data (fully conditional specification model, 20 imputations, covariates for clinical, procedural, proliferation, and stent strut parameters).

Results
Study Population
A detailed participant flow chart of this trial is shown in Figure 1. A total of 105 lesions in 90 patients were 1:1 randomized and 9 patients received both BMS+DEB and DES. There

Table 1. Baseline Clinical Characteristics of the Study Population (n=105 Lesions, n=90 Patients), Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th></th>
<th>DES (n=48 Patients)</th>
<th>BMS+DEB (n=51 Patients)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and Clinical Characteristics</td>
<td>Mean±SD or n (%)</td>
<td>Mean±SD or n (%)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>68.2±8.5</td>
<td>68.9±9.5</td>
<td>0.702</td>
</tr>
<tr>
<td>Male sex</td>
<td>36 (75.0%)</td>
<td>36 (70.6%)</td>
<td>0.622</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (100%)</td>
<td>51 (100%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>25 (52.1%)</td>
<td>22 (43.1%)</td>
<td>0.373</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>34 (70.8%)</td>
<td>39 (76.5%)</td>
<td>0.379</td>
</tr>
<tr>
<td>Smoker/ex-smoker</td>
<td>18 (37.5%)</td>
<td>14 (27.5%)</td>
<td>0.761</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min</td>
<td>80.4±25.0</td>
<td>66.3±23.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>2.4±0.9</td>
<td>2.8±1.4</td>
<td>0.071</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>25 (52.1%)</td>
<td>21 (41.2%)</td>
<td>0.277</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3 (6.3%)</td>
<td>2 (3.9%)</td>
<td>0.719</td>
</tr>
<tr>
<td>Previous coronary artery bypass grafting</td>
<td>1 (2.1%)</td>
<td>2 (3.9%)</td>
<td>0.507</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>10 (20.8%)</td>
<td>12 (23.5%)</td>
<td>0.747</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>2 (4.2%)</td>
<td>3 (5.9%)</td>
<td>0.575</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; DEB, paclitaxel drug-eluting balloon; and DES, everolimus drug-eluting stent.

Table 2. Procedural and Lesion Characteristics, Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th></th>
<th>DES (n=51 Lesions)</th>
<th>BMS+DEB (n=54 Lesions)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic and Procedural Characteristics</td>
<td>Mean±SD or n (%)</td>
<td>Mean±SD or n (%)</td>
<td></td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>16 (31.2%)</td>
<td>12 (22.2%)</td>
<td>0.558</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>15 (29.4%)</td>
<td>17 (31.5%)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>20 (39.2%)</td>
<td>25 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>Lesion type (ACC/AHA classification)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>0</td>
<td>0</td>
<td>0.476</td>
</tr>
<tr>
<td>Type B</td>
<td>40 (78.4%)</td>
<td>39 (72.2%)</td>
<td></td>
</tr>
<tr>
<td>Type C</td>
<td>11 (21.6%)</td>
<td>15 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Procedural parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 stent</td>
<td>46 (90.2%)</td>
<td>47 (87.0%)</td>
<td>0.601</td>
</tr>
<tr>
<td>≥2 stents</td>
<td>5 (9.8%)</td>
<td>7 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>Stent length</td>
<td>19.8±4.7</td>
<td>19.6±4.4</td>
<td>0.810</td>
</tr>
<tr>
<td>Direct stenting</td>
<td>12 (23.5%)</td>
<td>18 (33.3%)</td>
<td>0.256</td>
</tr>
<tr>
<td>Stent diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mm</td>
<td>20 (39.2%)</td>
<td>17 (31.5%)</td>
<td>0.407</td>
</tr>
<tr>
<td>3.0 mm</td>
<td>31 (60.8%)</td>
<td>37 (68.5%)</td>
<td></td>
</tr>
<tr>
<td>Ostial lesion</td>
<td>5 (9.8%)</td>
<td>4 (7.4%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Additional stenting</td>
<td>11 (21.6%)</td>
<td>13 (24.1%)</td>
<td>0.522</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>3 (5.9%)</td>
<td>6 (11.1%)</td>
<td>0.339</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>9 (17.6%)</td>
<td>12 (22.2%)</td>
<td>0.558</td>
</tr>
<tr>
<td>Side branch dilation</td>
<td>8 (15.7%)</td>
<td>3 (5.6%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Time of fluoroscopy, min</td>
<td>12.6±9.0</td>
<td>11.6±9.4</td>
<td></td>
</tr>
<tr>
<td>Postdilation</td>
<td>32 (62.7%)</td>
<td>54 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedural success</td>
<td>51 (100%)</td>
<td>54 (100%)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

ACC/AHA indicates American College of Cardiology/American Heart Association; BMS, bare metal stent; DEB, paclitaxel drug-eluting balloon; and DES, everolimus drug-eluting stent.
were 2 minor protocol deviations in each device group on the chosen stent length (DES, one 7-mm and one 12-mm long stent; BMS, one 18-mm and one 20-mm long stent). OCT imaging was unsuccessful in 4 patients (Figure 1). After randomization all baseline procedures including stent placement were successful (residual stenosis <20%; Thrombolysis in Myocardial Infarction (TIMI) III-flow, no flow-limiting dissections). There was no switching between the device groups after treatment assignment.

**Baseline Characteristics**

There were no significant differences between the 2 study groups on clinical characteristics except for a significant lower glomerular filtration rate and a trend toward a higher value of low-density lipoprotein cholesterol in the BMS+DEB group (Table 1). Table 2 reports procedural and lesion characteristics. Stent diameters between the 2 groups were well balanced. Most study lesions were rather complex (only type B/C according to the American College of Cardiology/American Heart Association classification). Postprocedural cardiac troponin I elevation ≥3× upper limit of normal) remained clinically silent in all 32 patients and did not lead to any medical measures (Table 3).

**Angiographic and OCT Outcomes at 6-Month Follow-Up**

Results of quantitative coronary angiography and OCT measurements are shown in Tables 3 and 4. Invasive follow-up analysis was obtained per protocol. From the 9 patients with multiple randomization 5 patients were lost for invasive follow-up (Figure 1).

**Stent Strut Analysis**

Altogether, 193.9±71.2 struts were analyzed in the DES group, and 219.1±78.8 struts were analyzed in the BMS+DEB group (P=0.123; Table 5). Overall sufficient strut coverage was found without a significant difference in both groups at 6 months. The difference in percentage uncovered struts between treatment means given as BMS+DEB minus DES was 0.71% with a SE of 2.61% and its upper 1-sided 95% confidence interval was 4.14% (Table 5; Figure 2). Consequently, the noninferiority P value with respect to the prespecified 5% margin was 0.040, allowing to claim noninferiority of BMS+DEB treatment with respect to the primary end point in per protocol analysis. Furthermore, intention-to-treat analysis after imputation of missing values yielded a mean difference between treatment arms of 1.16% and an upper 1-sided 95% confidence interval of 4.53%, which is still below the hypothesized 5% margin. Considering the low numbers of malapposed struts, 1.3±2.3% (DES) versus 2.2±4.9% (BMS+DEB; P=0.256) an overall sufficient stent expansion can be anticipated.

No clusters of incomplete strut apposition have been found in either device group. Single uncovered struts were scatterly distributed along the stent without any recognizable spatial pattern.

### Table 3. Adverse Events at Baseline and Within 6 Months After Index Procedure, per Patient-Level Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DES No Device Overlap (n=39 Patients)</th>
<th>All DES (n=48 Patients*)</th>
<th>BMS+DEB No Device Overlap (n=42 Patients)</th>
<th>All BMS+DEB (n=51 Patients*)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural microinfarction</td>
<td>8 (20.5%)</td>
<td>10 (20.8%)</td>
<td>15 (35.7%)</td>
<td>19 (37.3%)</td>
<td>0.130/0.073</td>
</tr>
<tr>
<td>MACE within 6 mo</td>
<td>4 (10.3%)</td>
<td>5 (10.4%)</td>
<td>5 (11.9%)</td>
<td>5 (9.8%)</td>
<td>0.182/0.919</td>
</tr>
<tr>
<td>Follow-up interval, d</td>
<td>190±17</td>
<td>188±19</td>
<td>183±34</td>
<td>186±32</td>
<td>0.274/0.715</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.999/0.999</td>
</tr>
<tr>
<td>Revascularization</td>
<td>4 (10.3%)</td>
<td>5 (10.4%)</td>
<td>3 (7.1%)</td>
<td>3 (5.9%)</td>
<td>0.620/0.408</td>
</tr>
<tr>
<td>TVR</td>
<td>1 (2.6%)</td>
<td>2 (4.2%)</td>
<td>1 (2.4%)</td>
<td>1 (2.0%)</td>
<td>0.959/0.522</td>
</tr>
<tr>
<td>TLR</td>
<td>1 (2.6%)</td>
<td>2 (4.2%)</td>
<td>1 (2.4%)</td>
<td>1 (2.0%)</td>
<td>0.959/0.522</td>
</tr>
<tr>
<td>Non-TVR</td>
<td>3 (7.7%)</td>
<td>3 (6.3%)</td>
<td>1 (2.4%)</td>
<td>1 (2.0%)</td>
<td>0.271/0.279</td>
</tr>
<tr>
<td>Death</td>
<td>0 (%)</td>
<td>0</td>
<td>2 (4.8%), noncardiovascular</td>
<td>2 (3.9%)</td>
<td>0.167/0.166</td>
</tr>
</tbody>
</table>

Values represent mean±SD or n (%). BMS indicates bare metal stent; DEB, paclitaxel drug-eluting balloon; DES, everolimus drug-eluting stent; MACE, major adverse cardiovascular events; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*Including the 9 patients who have been sequentially randomized in both groups.

### Table 4. Quantitative Coronary Angiography at Baseline and Follow-Up, per Protocol Analysis

<table>
<thead>
<tr>
<th>QCA Parameters (Baseline and 6-Mo f/u)</th>
<th>DES (n=48 Lesions)</th>
<th>BMS+DEB (n=42 Lesions)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLD, mm</td>
<td>2.61±0.31</td>
<td>2.59±0.36</td>
<td>0.846</td>
</tr>
<tr>
<td>Baseline MLD, mm</td>
<td>0.64±0.33</td>
<td>0.69±0.37</td>
<td>0.505</td>
</tr>
<tr>
<td>Postprocedure MLD, mm</td>
<td>2.31±0.33</td>
<td>2.24±0.38</td>
<td>0.306</td>
</tr>
<tr>
<td>MLD at 6 mo f/u, mm</td>
<td>2.16±0.39</td>
<td>2.0±0.44</td>
<td>0.065</td>
</tr>
<tr>
<td>Baseline stenosis, %</td>
<td>75.3±11.6</td>
<td>72.5±14.4</td>
<td>0.323</td>
</tr>
<tr>
<td>Postprocedure stenosis, %</td>
<td>10.7±7.9</td>
<td>13.1±9.8</td>
<td>0.204</td>
</tr>
<tr>
<td>Stenosis at 6 mo f/u</td>
<td>16.9±10.4</td>
<td>22.8±11.9</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Values represent mean±SD. BMS indicates bare metal stent; DEB, paclitaxel drug-eluting balloon; DES, everolimus drug-eluting stent; f/u, follow-up; LA, lumen area; LD, lumen diameter; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; and RLD, reference lumen diameter.
Proliferation Analysis

MLD was smaller in the BMS+DEB Ø 3.0 mm subgroup after 6 months (2.15±0.37 versus 2.37±0.27 mm; \(P=0.52\)). Late lumen loss was greater in the BMS+DEB group (0.16±0.15 versus 0.24±0.21 mm; \(P=0.034\)). Although angiographic percentage diameter stenosis was greater in the DEB stent group (22.8±11.9 in BMS+DEB versus 16.2±10.4 in DES; \(P=0.014\)), no significant differences in terms of clinically driven revascularization for in-stent restenosis (2: DES, 1: BMS+DEB; \(P=0.613\); Table 3) were found at 6 months. Moreover, no significant in-stent restenosis of >50% was found in either treatment group. Corresponding to these results, the net luminal gain was higher in the DES group (1.5±0.4 versus 1.3±0.6 mm; \(P=0.064\); Table 4), but failed to reach significance level in this sample size. The cumulative MLD percentage, as well as late lumen loss and net luminal gain at different phases, is shown in Figure 3.

OCT analysis on focal in-stent stenosis (percentage peak focal area stenosis, percentage peak diameter stenosis) did not show any significant differences between the study groups (Table 5). However, the efficacy OCT parameters, relative and absolute proliferation areas, were significantly greater in BMS+DEB compared with DES (Table 5). Volumetric OCT assessment confirmed these results (Table 5). Absolute proliferation volumes and the efficacy OCT parameters (relative proliferation volumes and proliferation volumes standardized per centimeter stent length) were significantly higher in BMS+DEB-treated lesions (Table 5; Figure 4).

Clinical Outcomes and Adverse Events

There were 2 adverse events in the BMS+DEB group in terms of vascular access site complications with 1 requiring surgical hematoma revision. Within 3 months after study inclusion, 2 non–cardiovascular-related deaths were observed in the BMS+DEB group. At 6 months there were 2 in-stent restenoses with the need for target lesion revascularization in the DES group and 1 in-stent restenoses with target lesion revascularization in the BMS+DEB group (\(P=0.522\) 1-sided; Table 3).

Discussion

To the best of our knowledge, the present study is currently the largest OCT trial with 105 included lesions, investigating a combination therapy of BMS postdilated with the SeQuent Please balloon in 51 patients versus the current standard-of-care Xience V DES in 48 patients in a randomized fashion with a 6-month invasive follow-up.
Coverage

According to former histological studies the risk for late stent thrombosis is significantly enhanced if ≥30% of stent struts are uncovered. In this study, we found good stent coverage and no significant differences between the 2 studied devices after 6 months. Our findings are in agreement with a previous study that investigated the sequential application of a cobalt–chromium BMS with the Moxy DEB (Lutonix, Maple Grove), revealing 5.3% uncovered struts after 6 months as well. Currently, published data suggest that stent coverage of newer-generation DES might be completed even much earlier. Kim et al found similar results for coverage of DES and zotarolimus-eluting stents (4.7±5.7% and 6.2±6.9% uncovered struts) already 3 months after implantation.

The amount of malapposed struts and the malapposition distance are associated with delayed endothelial coverage and long-term adverse events after stent implantation. However, the number of malapposed struts in this trial is negligible.

Proliferation

We evaluated the pattern of in-stent neointimal proliferation on focal versus diffuse proliferation. The results of the Paclitaxel Eluting PTCA Balloon Catheter in Coronary Artery Disease (PEPCAD) III trial comparing DEB+BMS versus the sirolimus-eluting-stent Cypher were discouraging because there were significantly more revascularization procedures because of in-stent and in-segment restenosis in the DEB+BMS group after 9 months. There are important issues of the PEPCAD III trial design that might be responsible for the negative outcome. Unfavorable geometric proportions between DEB and BMS and a not yet fully understood interaction between the crimped BMS and the underlying DEB on drug delivery and distribution may have played an important role. In our trial, all BMSs were systematically postdilated with a safety margin of 2.0 to 2.5 mm larger balloon to avoid geographic mismatch and to prevent edge stenosis. By applying the mentioned procedural facts edge stenoses (candy wrapper effect) were successfully prevented in the DEB stent group. The DEB stent procedure showed more late lumen loss (P=0.034) and less net luminal gain (P=0.064) after 6 months. Also, neointimal...
proliferation volumes (efficacy parameter) were significantly higher in the BMS+DEB group. However, neo-intima seemed diffusely proliferated throughout the entire stent and was not a focal problem because we did not find differences on percentage focal area stenosis in OCT (Figure 4). Thus, we cannot anticipate whether the greater, but diffuse proliferation in the DEB stent group possibly translate into a relevant in-stent restenoses at a later stage. In a study from Ali et al, comparing DEB+BMS versus DEB, significant differences for binary restenosis, major adverse cardiovascular events, or revascularization procedures after 9 months were also not observed. Previously reported data of neo-intimal proliferation after a DEB stent procedure is similar to ours (relative proliferation volume: 26.1% in this trial versus 25.1% in Gutiérrez-Chico et al). The DEB stent procedure of de novo coronary lesions suppresses neo-intimal hyperplasia effectively despite a complex patient cohort with 44.4% diabetic patients, 11.1% chronic total occlusions, 22% bifurcation lesions, and absent type A target lesions in this trial. Nevertheless, DESs inhibit neo-intimal growth stronger compared with first-generation DES and compared with a DEB stent procedure. However, a late clinical catch-up phenomenon for restenosis has been described in DES, which seems to stem from polymer-associated development of in-stent neointeratherosclerosis. Drug-eluting balloons are polymer-free coated with a hydrophilic carrier and drug release occurs as a single-shot. To date, no data on neointeratherosclerosis after a DEB stent procedure is available. Yet, no final conclusion can be drawn for the value and the long-term outcome of a BMS+DEB procedure, but as suggested by a recent meta-analysis this strategy is promising when only bare metal stenting is possible and the risk of restenosis is deemed high. Finally, patients who underwent the BMS+DEB procedure had higher low-density lipoprotein levels and a lower glomerular filtration rate compared with the DES group what might have contributed to more stent proliferation in this trial.

**Value of OCT In-Stent Trials**

OCT has the capability to carve out distinct differences. Angiography underestimated the percentage focal area stenosis after 6 months. With OCT assessment, we were able to detect the pattern of proliferation in both studied devices, which was mainly diffuse and not focal.

**Clinical Implications**

Data for the duration of dual antiplatelet therapy after drug-eluting stent implantation are discordant and current American and European guidelines recommend between 6, 12, and >12 months of dual antiplatelet therapy. We could demonstrate >94% stent coverage in both devices, which is sufficient according to the previous histological findings and adds value to the concept of shortening dual antiplatelet therapy.

**Limitations**

This study was not intended to show possible differences of clinical end points. Twelve patients (15 lesions) were lost to follow-up, of whom the majority belonged to the BMS+DEB group, which we interpret as nonrelated to device type and probably explained solely by hazard in the presence of a small sample size. Still, clinical information was available for all patients. Adverse events were adjudicated by the authors (T.P. and S.O.), but not by an independent clinical committee. Six patients developed ventricular arrhythmias with the need for defibrillation and 1 patient showed symptomatic ST-segment elevation because of the older occlusive OCT technique. All patients recovered quickly with no remaining medical conditions.

**Conclusions**

Overall, sufficient strut coverage in >94% of analyzed struts was found on both stent devices. Both the Xience V DES and the combination therapy of BMS postdilated with the SeQuent Please DEB effectively prevented clinically relevant focal restenosis at 6-month follow-up. Candy-edge stenoses were eliminated by avoiding geographical mismatch and using a safety margin for the DEB. Suppression of neo-intimal growth in the entire stent was significantly greater in DES in both quantitative coronary angiography and OCT analysis. Whether this translates in clinical events at the long-term course of a DEB stent procedure needs to be addressed by further investigations.

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**References**


Stent Coverage and Neointimal Proliferation in Bare Metal Stents Postdilated With a Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stents: Prospective Randomized Study Using Optical Coherence Tomography at 6-Month Follow-Up

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SUPPLEMENTAL MATERIAL

Methods

Measured and calculated OCT Parameters

Assessment of neointimal proliferation by cross-section analysis

The following parameters were obtained in each cross-section analysis:

- LA: lumen area
- LD: lumen diameter
- SA: stent area
- SD: stent diameter
- PD: proliferation thickness

Computational assessment of neointimal proliferation

The percentage of analyzed stent length in relation to the intended full stent length was computed. The aforementioned 2-dimensional (2D) OCT measurements were used to calculate parameters of focal in-stent proliferation:

- PA (mm²): neointimal proliferation area = SA – LA
- Peak local area stenosis (%) = (1- Minimal LA / Maximal LA within stent) * 100
- Peak diameter stenosis (%) = (SD – LD) * 100
- Peak relative proliferation area (%) = (1- Minimal LA / SA within the same frame) * 100

Volumetric parameters were computed through the integral of area measurements over the stent length:

- LVol (mm³): lumen volume
- SVol (mm³): stent volume
- PVol (mm³): proliferation volume

Relative proliferation parameters were calculated to ensure comparability and to exclude potential bias stemming from different stent lengths or incomplete OCT analysis:

- Relative PVol (%) = (PVol / analyzed stent length) * 100
- Standardized PVol (mm³/ cm stent length) = PVol / analyzed stent length
Assessment of stent struts by cross-section analysis

Struts were classified as:
- embedded (contained within the vessel wall)
- apposed and covered, if tissue was seen above the strut
- apposed and uncovered, if no tissue was detected
- malapposed
- laying over a side branch ostium.

Struts were defined as malapposed if the distance of the abluminal strut side to the luminal vessel wall was > 100 µm. Discordance between the two investigators was resolved by consensus reading (T.C.P., S.O.) Struts over side branch ostia were excluded from the final analysis.

Computational assessment of stent strut coverage

The percentage of uncovered stent struts was calculated in relation to all analyzed struts per stent:

- Uncovered struts (%) = uncovered struts / analyzed struts * 100

OCT runs were also analyzed for intracoronary thrombus formation.