Randomized Comparison of a Polymer-Free Sirolimus-Eluting Stent Versus a Polymer-Based Paclitaxel-Eluting Stent in Patients With Diabetes Mellitus

The LIPSIA Yukon Trial

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Objectives The objective of the study was to assess noninferiority of the polymer-free sirolimus-eluting Yukon Choice stent (Translumina GmbH, Hechingen, Germany) compared with the polymer-based Taxus Liberté stent (Boston Scientific, Natick, Massachusetts) with regard to the primary endpoint, in-stent late lumen loss, at 9 months in patients with diabetes mellitus.

Background The Yukon Choice stent has been evaluated in several randomized controlled trials before, albeit to date, there has been no trial that exclusively enrolled patients with diabetes mellitus.

Methods Patients with diabetes mellitus undergoing percutaneous coronary intervention for clinically significant de novo coronary artery stenosis were randomized 1:1 to receive either the polymer-free sirolimus-eluting Yukon Choice stent or the polymer-based paclitaxel-eluting Taxus Liberté stent.

Results A total of 240 patients were randomized. Quantitative coronary angiography was available for 79% of patients. Mean in-stent late lumen loss was 0.63 ± 0.62 mm for the Yukon Choice stent and 0.45 ± 0.60 mm for the Taxus Liberté stent. Based on the pre-specified margin, the Yukon Choice stent failed to show noninferiority for the primary endpoint. During follow-up, there were no significant differences between groups regarding death, myocardial infarction, stent thrombosis, target lesion revascularization, target vessel revascularization, or nontarget vessel revascularization.

Conclusions Compared with the Taxus Liberté stent, the polymer-free sirolimus-eluting Yukon Choice stent failed to show noninferiority with regard to the primary endpoint, in-stent late lumen loss, in patients with diabetes mellitus after 9-month follow-up. Both stents showed comparable clinical efficacy and safety. (Yukon Choice Versus Taxus Liberté in Diabetes Mellitus; NCT00368953) (J Am Coll Cardiol Intv 2011;4:452–9) © 2011 by the American College of Cardiology Foundation
Compared with bare-metal stents (BMS), commercially available drug-eluting stents (DES) effectively reduce rates of angiographic and clinical restenosis (1). Most DES currently used in clinical practice gradually release the active antiproliferative substance from durable polymers over the course of several weeks to months. However, permanent polymer coatings have been linked to delayed or incomplete re-endothelialization, possibly caused in part by a prolonged local inflammatory reaction (2). This might, in turn, favor stent thrombosis, a rare but clinically often fatal complication that is more likely to occur with DES than with BMS (3). Therefore, polymer-free DES might represent an attractive alternative.

The Yukon Choice stent system (Translumina GmbH, Hechingen, Germany) comprises a thin-strut stainless steel stent with a polymer-free microporous surface. Sirolimus is used as an antiproliferative agent and is deposited in the micropores using a dedicated coating machine without the use of a polymer.

The Yukon Choice stent has been studied in several randomized controlled trials before (4–6). However, there has been no trial exclusively enrolling patients with diabetes mellitus, a subgroup of patients at an increased risk for restenosis and stent thrombosis (2).

The LIPSIA Yukon trial is a prospective, multicenter trial comparing the polymer-free Yukon Choice stent with an established and widely used polymer-based stent (Taxus Liberté, Boston Scientific, Natick, Massachusetts) in patients with diabetes mellitus undergoing percutaneous coronary intervention for clinically significant de novo coronary artery stenosis.

**Methods**

**Patients.** Three cardiac centers in Germany participated in this prospective, randomized controlled trial (University of Leipzig Heart Center, Zentralklinik Bad Berka, and Chemnitz Heart Center). Patients 18 years of age or older of either sex were considered eligible if they had diabetes mellitus, presented with angina pectoris or a positive stress test, and displayed a de novo stenosis in a native coronary artery between 50% and 99% as visually estimated on invasive angiography amenable to percutaneous intervention with a single stent. Patients were randomized in a 1:1 ratio to either the polymer-free sirolimus-eluting Yukon Choice stent or the polymer-based paclitaxel-eluting Taxus Liberté stent. Diabetes was considered present if patients were undergoing treatment with oral antidiabetic drugs or insulin or had an established diagnosis of diabetes mellitus as evidenced from medical records.

Exclusion criteria were significant unprotected left main disease (≥50% stenosis by visual estimate), total occlusion of the target vessel, in-stent restenosis, stenoses of bypass grafts, bifurcation lesions (side branch diameter >2 mm), thrombus in target lesion, indication for coronary bypass surgery, contraindications to contrast medium or any of the medications used during the intervention and thereafter, acute myocardial infarction (within 48 h after symptom onset), severe disorders of hemostasis or platelet aggregation, pregnancy, participation in another trial, and severe comorbidities such as malignancy.

**Stent systems.** The commercially available Yukon Choice stent comprises of a thin-strut (87-μm) stainless steel stent with a microporous surface. Sirolimus is used as an antiproliferative agent and is sprayed on the stent surface using an ethanolic 2% sirolimus coating solution and a dedicated stent coating machine without the use of a polymer or any other additional substances. The sterility coating process has to be performed directly in the catheterization laboratory. The concept has been applied in several randomized controlled clinical trials before (4–6). The stent system has received CE mark approval in the European Union and is available in different markets in Europe and Asia. Efficacy and safety of the Taxus Liberté stent and its predecessor (the Taxus Express 2 stent using a slightly different platform) have been validated extensively (7,8).

**Randomization and interventions.** After guidewire crossing of the lesion, eligible patients willing to take part in the study were randomly assigned to the treatment groups via an Internet-based system (9) using a computer-generated list of random numbers. The randomization list was generated and maintained by a physician not involved in the clinical conduct of the study. Interventionalists performing the stent implantation procedure were aware of treatment assignment. However, quantitative coronary angiography (QCA) analysis or collection of clinical patient data were performed by blinded personnel. Patients were not informed of treatment assignment until completion of the study.

Lesions were required to be amenable to percutaneous intervention with a single stent no longer than 24 mm and a maximum diameter of 3.5 mm (the rationale being that the Yukon Choice stent was only available at a maximum length of 24 mm and the Taxus Liberté stent only at a maximum diameter of 3.5 mm at the time of enrollment). Additional stents were allowed only in cases of incomplete lesion coverage, complications such as dissection, or otherwise suboptimal results. In these cases, it was mandated to use the same stent type as randomized and to change to other stent systems only for technical failure of the randomly assigned stent type or inability to cross the lesion. In patients with 2 or more stenoses suitable for inclusion, only 1 lesion was allowed to enter the study (n = 3). Before
randomization, the interventionalist decided which lesion to include. The choice between lesion pre-dilation or direct stenting as well as requirement of post-dilation was left to the discretion of the interventionalist.

All patients received intravenous unfractionated heparin at a dose of 100 international units (IU) per kilogram body weight or guided by activated clotting time if glycoprotein IIb/IIIa inhibitors were given. If not pre-loaded, patients received a loading dose of 600-mg clopidogrel immediately before the intervention followed by 75 mg per day for 12 months. Aspirin at a dose of 100 mg per day was recommended indefinitely. The choice whether to administer glycoprotein IIb/IIIa inhibitors was left to the discretion of the interventionalist. After percutaneous coronary intervention, patients stayed in the hospital for a minimum of 24 h before discharge. A 12-lead electrocardiogram was recorded immediately after the procedure and creatine kinase and creatine kinase-myocardial band subfraction were collected before discharge. A 12-lead electrocardiogram was recorded immediately after the procedure and the MLD at follow-up angiography. Secondary angiographic endpoints included in-segment late lumen loss at 9 months, MLD and percent diameter stenosis after the procedure and at 9 months, in-segment binary restenosis rate, and patterns of restenosis.

Clinical events recorded were all-cause death, definite or presumed cardiac death, myocardial infarction, requirement of emergency bypass surgery at the baseline intervention, stent thrombosis, target lesion revascularization, target vessel revascularization, and nontarget vessel revascularization. Furthermore, we performed a pre-specified analysis of a combined major cardiovascular events endpoint consisting of definite or presumed cardiac death, myocardial infarction, requirement of emergency bypass surgery at the baseline intervention, definite stent thrombosis, and target lesion revascularization. To avoid double counting of patients with more than 1 event, each patient contributed only once to the composite major cardiovascular events endpoint.

Any death was defined as cardiac unless an unequivocal noncardiac cause could be established (12). This included any death of unknown cause. Periprocedural myocardial infarction was defined as an elevation of creatine kinase-myocardial band >3× the upper reference limit within the first 48 h after the index intervention. Thereafter, myocardial infarction was defined as an increase in the creatine kinase-myocardial band levels above the reference limit. The diagnosis of definite, probable, or possible stent thrombosis was made according to consensus criteria published by the Academic Research Consortium (12). Target lesion revascularization was defined as any clinically indicated repeat percutaneous intervention of the target lesion (= treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent) or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion (12). Revascularization was considered clinically indicated if follow-up angiography showed a percent diameter stenosis ≥50%, and 1 or more of the following: 1) positive history of angina pectoris; 2) objective signs of ischemia on noninvasive testing; or 3) abnormal invasive fractional flow reserve results. Target vessel revascularization was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel (including the target lesion) (12).

**Statistical analysis.** The objective of the study was to assess noninferiority of the Yukon Choice stent system compared with the Taxus Liberté stent with regard to the primary endpoint, in-stent late lumen loss. The sample size was thus calculated using a 1-tailed t test to show noninferiority of the Yukon Choice stent. Based on previous studies in diabetic patients, we expected a mean late lumen loss of 0.46 mm for the Taxus Liberté stent system and no significant differences in mean late lumen loss between groups (13,14). The standard deviation for late lumen loss was presumed to be 0.40 mm. The noninferiority margin was set at 0.16 mm
(equalling 35% of 0.46 mm). Based on these assumptions, 100 patients per treatment group needed to be analyzed to provide a statistical power of 0.80 at a 1-sided alpha of 0.025. Adjusting for a rate of 20% of patients not returning for invasive angiography, 120 patients were scheduled for randomization in each group totaling 240 patients. Sample size was calculated using ADDPLAN (ADDPLAN GmbH, Cologne, Germany).

For categorical variables, baseline characteristics were compared using chi-square testing (or Fisher exact test in cases of small cell counts). For continuous data with normal distribution, an independent samples t test was used. Otherwise, the nonparametric Wilcoxon rank-sum test was used. Categorical variables are expressed as number and percentage of patients. Continuous data are reported as mean ± SD. The hypothesis testing for the primary endpoint was performed using a 1-sided noninferiority test for which a p value < 0.025 was considered statistically significant. For all other analyses, the significance level was set at 0.05. Statistical analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, Illinois) and SiZ (Cytel Inc., Cambridge, Massachusetts). Analysis of clinical data were performed according to the intention-to-treat principle using all randomized patients regardless of the treatment actually received. For QCA data, a slightly different approach was used: Only patients who had received at least 1 study stent in the target lesion were included in the analysis.

**Results**

**Patient characteristics.** Between September 2006 and December 2008, 240 patients were randomized and allocated to either the polymer-free sirolimus-eluting Yukon Choice stent or the polymer-based paclitaxel-eluting Taxus Liberté stent. Two patients withdrew consent to use data in any form and another 2 patients were inadvertently randomized twice concerning the same lesion, which was recognized only after completion of the study upon data analysis. Therefore, 236 patients remained for further analysis. Overall, both groups had similar baseline risk profiles and comparable lesion characteristics (Table 1).

**Procedural outcome and QCA.** In 1 patient in each treatment arm, the study stent failed to cross the stenosis and BMS were used instead. In 4 patients in the Yukon arm and 2 patients in the Taxus arm, the study stent was unable to completely cover the lesion and subsequently additional BMS were successfully implanted. Angiographic follow-up was performed after a mean of 9.3 months with no significant differences between groups (p = 0.82). Quantitative coronary angiography was available for 95 patients (79%) in the Yukon Choice and 92 patients (79%) in the Taxus Liberté arms, respectively (p = 1.00). Reasons for missing QCA analyses are shown in Figure 1 and results are summarized in Table 2. Mean in-stent late lumen loss was significantly lower for the Taxus Liberté than for the Yukon Choice stent (point estimate 0.45 mm vs. 0.63 mm). Thus, the absolute difference in mean in-stent late lumen loss between the groups was 0.18 mm, with an upper limit of the 95% confidence interval of 0.33 mm. Based on the pre-specified margin of 0.16 mm, the Yukon Choice stent, therefore, failed to show noninferiority for the primary

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**Table 1. Clinical and Angiographic Characteristics at Baseline**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yukon Choice (n = 120)</th>
<th>Taxus Liberté (n = 116)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>67.0 ± 9.5</td>
<td>67.3 ± 9.1</td>
<td>0.81</td>
</tr>
<tr>
<td>Male</td>
<td>83 (69)</td>
<td>79 (68)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>28 (23)</td>
<td>31 (27)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>118 (98)</td>
<td>112 (97)</td>
<td>0.65</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>17 (14)</td>
<td>11 (10)</td>
<td>0.36</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>46 (38)</td>
<td>50 (43)</td>
<td>0.54</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.0 ± 4.8</td>
<td>30.5 ± 4.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57.6 ± 12.6</td>
<td>57.3 ± 11.0</td>
<td>0.87</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.24 ± 0.36</td>
<td>1.25 ± 0.33</td>
<td>0.80</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>2.89 ± 0.99</td>
<td>3.09 ± 1.06</td>
<td>0.16</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, %</td>
<td>7.2 ± 1.5</td>
<td>7.1 ± 1.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min/1.73 m²*</td>
<td>73.8 ± 23.4</td>
<td>74.7 ± 22.2</td>
<td>0.79</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>26 (22)</td>
<td>26 (22)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>38 (32)</td>
<td>33 (28)</td>
<td>0.69</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>6 (5)</td>
<td>12 (10)</td>
<td>0.19</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
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</tr>
<tr>
<td>Aspirin</td>
<td>86 (72)</td>
<td>85 (73)</td>
<td>0.90</td>
</tr>
<tr>
<td>Statin</td>
<td>85 (71)</td>
<td>79 (68)</td>
<td>0.75</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>105 (88)</td>
<td>102 (88)</td>
<td>1.0</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>96 (80)</td>
<td>87 (75)</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet only</td>
<td>24 (20)</td>
<td>17 (15)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diet + oral antidiabetics</td>
<td>42 (35)</td>
<td>50 (43)</td>
<td>0.25</td>
</tr>
<tr>
<td>Insulin</td>
<td>54 (45)</td>
<td>49 (42)</td>
<td>0.77</td>
</tr>
<tr>
<td>Glycoprotein Iib/Illa-inhibitor use</td>
<td>8 (7)</td>
<td>8 (7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.7 ± 4.5</td>
<td>13.6 ± 4.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Minimal luminal diameter, mm</td>
<td>0.6 ± 0.3</td>
<td>0.6 ± 0.3</td>
<td>0.73</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.90 ± 0.58</td>
<td>2.98 ± 0.58</td>
<td>0.34</td>
</tr>
<tr>
<td>Stenosis, % luminal diameter</td>
<td>79 ± 9</td>
<td>80 ± 9</td>
<td>0.45</td>
</tr>
<tr>
<td>Lesion complexity according to AHA and ACC (10)</td>
<td>0.20</td>
<td>0.20</td>
<td>0.00</td>
</tr>
<tr>
<td>A</td>
<td>23 (19)</td>
<td>28 (24)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>58 (48)</td>
<td>41 (35)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>21 (18)</td>
<td>29 (25)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>18 (15)</td>
<td>18 (16)</td>
<td></td>
</tr>
<tr>
<td>Calcification</td>
<td>18 (15)</td>
<td>27 (23)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Data are mean ± SD or n (%). *Estimated according to MDRD (Modification of Diet in Renal Disease) formula (15). ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
endpoint, in-stent late lumen loss. In the study protocol, we did not specifically pre-specify testing for superiority once noninferiority is rejected. However, had such an analysis been planned, 2-tailed results would show superiority for the Taxus Liberté stent over the polymer-free sirolimus-eluting Yukon Choice stent system with regard to the primary endpoint ($p = 0.04$). At follow-up, 17 (18%) angiographic target lesion restenoses were found in the Yukon Choice arm and 14 (15%) in the Taxus Liberté arm ($p = 0.77$). Of these, 12 (11%) and 14 (13%) required clinically indicated percutaneous reintervention or bypass surgery ($p = 0.66$). Morphological appearances of restenoses are presented in Table 2.

Clinical events. Clinical follow-up was available for 232 (98%) of patients after a mean of 8.9 months with no significant differences between groups ($p = 0.34$) (Fig. 1).

During follow-up, there were no significant differences between stent groups regarding all-cause death, definite or presumed cardiac death, myocardial infarction, requirement of emergency bypass surgery at the baseline intervention, stent thrombosis, target lesion revascularization, target vessel revascularization, or nontarget vessel revascularization (Table 3). The pre-specified combined major cardiovascular events endpoint also showed no differences (Yukon Choice: 17 events; Taxus Liberté: 17 events; $p = 1.0$).

Discussion

The major results of this prospective, randomized controlled multicenter trial can be summarized as follows: compared with the paclitaxel-eluting polymer-based Taxus Liberté stent, the sirolimus-eluting polymer-free Yukon Choice
stent system might have resulted in altered drug release kinetics and uptake into the vessel wall. It has also been speculated that the total amount of drug coated onto the struts of the Yukon Choice stent might be too low resulting in suboptimal antiproliferative efficacy (18). However, a dose-finding study for the polymer-free Yukon stent found that a 2% sirolimus coating solution has a strong antirestenotic efficacy with a late loss of 0.46 mm after 9 months angiographic follow-up (4).

Another important aspect relates to a postulated late “catch-up” phenomenon of polymer-based DES. In a previous study comparing the Cypher, Taxus Express 2, and first-generation Yukon stent (predecessor of the Yukon Choice stent with a slightly different stent platform), angiographic follow-up was performed between 6 and 8 months and again 2 years after stent implantation (19). Whereas both the Cypher and Taxus Express 2 stent continued to show ongoing increases in late lumen loss between the 2 time points, this was not the case for the Yukon stent. It was hypothesized that the permanent polymer coating of the Cypher and Taxus Express 2 stents might lead to a persisting inflammatory response resulting in delayed healing and continued neointimal formation. In the present study, angiographic follow-up at 9 months might, therefore, have been suboptimal to detect the true final differences in late lumen loss between the 2 stents.

Previous trials of the Yukon/Yukon Choice stent system. The first-generation Yukon stent has been used in several randomized controlled trials before, albeit to date, there has been no trial exclusively enrolling patients with diabetes mellitus (4–6). A comparison between the Yukon stent and a paclitaxel-eluting stent (Taxus Express 2) in 450 patients with coronary heart disease reported a mean in-stent late lumen loss of 0.48 mm for both groups—a result demonstrating noninferiority of the Yukon stent (6). Only a subset

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yukon Choice (n = 99)</th>
<th>Taxus Liberté (n = 92)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent length, mm</td>
<td>16.2 ± 4.3</td>
<td>17.3 ± 4.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.0 ± 0.3</td>
<td>2.9 ± 0.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Pre-dilation</td>
<td>33 (35)</td>
<td>25 (27)</td>
<td>0.34</td>
</tr>
<tr>
<td>Post-dilation</td>
<td>6 (5)</td>
<td>6 (5)</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;1 stent implanted</td>
<td>18 (19)</td>
<td>14 (15)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Minimal luminal diameter, in-stent, mm
- After PCI: 2.4 ± 0.5 vs. 2.5 ± 0.5 (p = 0.17)
- At follow-up: 1.8 ± 0.8 vs. 2.1 ± 0.7 (p = 0.01)

Minimal luminal diameter, in-segment, mm
- After PCI: 2.2 ± 0.6 vs. 2.2 ± 0.5 (p = 0.27)
- At follow-up: 1.7 ± 0.7 vs. 1.9 ± 0.7 (p = 0.02)

Stenosis, in-stent, % luminal diameter
- After PCI: 20 ± 9 vs. 19 ± 8 (p = 0.19)
- At follow-up: 39 ± 22 vs. 33 ± 20 (p = 0.06)

Stenosis, in-segment, % luminal diameter
- After PCI: 29 ± 11 vs. 28 ± 11 (p = 0.62)
- At follow-up: 42 ± 21 vs. 37 ± 19 (p = 0.08)

Late lumen loss, in-stent, mm
- 0.65 ± 0.29 vs. 0.5 ± 0.17 (p = 0.02)

Late lumen loss, in-segment, mm
- 0.64 ± 0.65 vs. 0.29 ± 0.59 (p = 0.11)

In-segment binary angiographic restenosis
- 17 (18) vs. 14 (15) (p = 0.77)

Pattern of restenosis
- IA: — vs. —
- IB: 4 (23) vs. 7 (50)
- IC: 6 (35) vs. 4 (29)
- ID: 1 (6) vs. —
- II: 2 (12) vs. 1 (7)
- III: 3 (18) vs. 1 (7)
- IV: 1 (6) vs. 1 (7)

Data are mean ± SD or n (%).

PCI = percutaneous coronary intervention.

The late lumen loss point estimate of 0.45 mm for the Taxus Liberté stent measured in the present study is well in line with previous trials examining paclitaxel-eluting stents in diabetic patients (13,14,16,17). Late lumen loss data for the Yukon Choice stent system in patients with diabetes mellitus have so far not been published. The exact reasons for the higher late lumen loss in the Yukon Choice arm remain unclear. In a previous trial of diabetic patients with angiographic follow-up after 6 months, a polymer-based sirolimus-eluting stent (Cypher, Cordis, Johnson & Johnson, Bridgewater, New Jersey) showed significantly lower in-stent late lumen loss than a paclitaxel-eluting stent (Taxus Express 2) did (0.19 ± 0.44 mm vs. 0.46 ± 0.64 mm, p < 0.001) (13). Therefore, it seems unlikely that sirolimus itself played a dominant role for the observed differences. The polymer-free coating strategy of the Yukon Choice stent system might have resulted in altered drug release
of patients (29%) had diabetes mellitus, which might, in part, explain the significantly lower late lumen loss value in the Yukon arm compared with the present trial.

In another trial, the first-generation Yukon stent failed to show noninferiority compared with the Cypher stent with regard to in-stent late lumen loss in a mixed population of patients with coronary heart disease at 9 months angiographic follow-up, enrolling approximately one-quarter of patients with diabetes mellitus (mean late lumen loss: 0.47 ± 0.56 mm vs. 0.23 ± 0.46 mm, p = 0.94 for noninferiority) (5). However, 2-year follow-up data of the same patient cohort have recently been published, again showing a late catch-up phenomenon for the Cypher stent, but no catch-up for the polymer-free Yukon stent (20).

A nonrandomized single center registry comparing the Yukon Choice and the Taxus Liberté stent in 410 patients with symptomatic coronary artery disease covering a wide clinical spectrum (including, e.g., acute coronary syndrome) reported a higher rate of target lesion revascularization at 9 and 12 months to the disadvantage of the Yukon Choice stent (18). However, the investigators also pointed to the fact that, because of superior flexibility and trackability, the Yukon Choice stent might have been used preferentially in more complex lesions than the Taxus Liberté stent was (18).

The differences in the late catch-up behavior of the polymer-free Yukon stent might be further explained by another randomized controlled clinical trial comparing the Cypher stent with the Yukon stent using optical coherence tomography. The study showed better stent strut coverage (97.2% vs. 88.3% after 3 months, p = 0.03) and a significantly lower number of protruding struts for the Yukon stent (4.8 vs. 26.5, p = 0.001), indicating a superior healing process (21).

**Margin of noninferiority.** The choice of the noninferiority margin is of great importance. Selecting an appropriate margin can be based on both statistical and clinical grounds (22). Statistical reasoning is based on obtaining an estimate of the therapeutic effect of the active control (paclitaxel-eluting stent) over “placebo” (BMS for the present situation) from historical data. The choice of margin is then set at a fraction of the active control effect to ensure with high probability that (as a minimal requirement) the new treatment (Yukon Choice stent) is at least more efficacious than bare-metal stenting. With the approach based on clinical judgment, the margin is set on the maximum clinically acceptable difference that one is willing to give up in return for the potential secondary benefits of the new therapy. For the present study, the decision to adopt a margin of noninferiority of 0.16 mm was based on a previous trial in diabetic patients that reported a mean in-stent late lumen loss of 0.46 mm for a paclitaxel-eluting stent (13). The margin corresponds to one-third of this observed late lumen loss.

**Study limitations.** The primary endpoint, in-stent late lumen loss, as a measure of neointimal hyperplasia is a surrogate endpoint and not a truly patient-relevant endpoint. Although its predictive strength for the clinical endpoint target lesion revascularization has been validated (23), the limitations of surrogate endpoint should be kept in mind (24).

The limited sample size might have prevented the detection of differences in clinical outcome reflecting the possibility of type II error (the error of failing to observe a difference when in truth there is one).

The selection of an appropriate control stent is of major importance in comparative studies of DES. We used the paclitaxel-eluting Taxus Liberté stent as a comparator. Recent meta-analytic data of randomized controlled trials in patients with diabetes mellitus indicate that the Cypher stent might be superior to polymer-based paclitaxel-eluting stents with regard to target lesion revascularization albeit without differences in death, stent thrombosis, and myocardial infarction (25). However, this was unclear at the time of planning the trial design.

Sample size calculation was based on 100 patients in each arm to provide a statistical power of 0.80. However, as explained earlier, QCA was available in only 95 patients (Yukon Choice) and 92 patients (Taxus Liberté), respectively. However, given the final results it is highly unlikely that QCA of 100 patients per arm would have resulted in demonstration of noninferiority for the Yukon Choice stent.

Finally, we enrolled only patients with diabetes mellitus and clinically stable coronary heart disease and used relatively stringent angiographic inclusion criteria excluding, for example, chronic total occlusions, bifurcation lesions, in-stent restenoses, or bypass graft stenoses. Therefore, the results obtained in the present study should not be uncritically extrapolated to different patients or lesion types.

**Conclusions**

In this randomized head-to-head comparison in patients with diabetes mellitus, the polymer-free sirolimus-eluting Yukon Choice stent system failed to demonstrate noninferiority compared with the Taxus Liberté stent with regard to the primary endpoint, in-stent late lumen loss, at 9-month angiographic follow-up. There were no significant differences in angiographic binary restenosis rate or clinical events such as target lesion revascularization. For a final conclusion regarding the clinical outcome of the 2 different stent coating concepts, it is essential to obtain long-term follow-up data to evaluate the influence of late catch-up and to further study rare safety endpoints such as very late stent thrombosis.

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