JACC: CARDIOVASCULAR INTERVENTIONS VOL. 4, NO. 4, 2011

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

DOI: 10.1016/j.jcin.2010.11.016

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

Steffen Desch, MD,* Denis Schloma, MD,* Sven Möbius-Winkler, MD,* Sandra Erbs, MD,* Stephan Gielen, MD,* Axel Linke, MD,* Jiangtao Yu, MD,† Bernward Lauer, MD,† Klaus Kleinertz, MD,‡ Wilfried Dänschel, MD,‡ Gerhard Schuler, MD,* Holger Thiele, MD*

Leipzig, Bad Berka, and Chemnitz, Germany

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

From the *Department of Internal Medicine/Cardiology, University of Leipzig, Heart Center, Leipzig, Germany; †Department of Cardiology, Zentralklinik Bad Berka, Bad Berka, Germany; and the ‡Chemnitz Heart Center, Chemnitz, Germany. The study was supported by an unrestricted grant from Translumina GmbH (Hechingen, Germany), manufacturer of the Yukon Choice stent. Drs. Desch and Thiele received an unrestricted grant from Translumina GmbH (Hechingen), manufacturer of the Yukon Choice stent, for general support of the study. All other authors have reported that they have no relationships to disclose.

Manuscript received September 16, 2010; revised manuscript received October 16, 2010, accepted November 16, 2010.

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 system 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 sterile 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.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
MLD = minimal luminal diameter
QCA = quantitative coronary angiography

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

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 4, 2011
APRIL 2011:452–9

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 after 8 and 24 h.

The protocol was approved by the local Institutional Review Board and conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Follow-up. In-hospital follow-up was scheduled 9 months after the index procedure. Patients underwent a structured interview, were examined clinically, and were asked to undergo invasive angiography. Clinical events were verified by hospital charts and direct contact with the treating physician and adjudicated by a committee unaware of treatment assignment.

Quantitative coronary angiography. Baseline, post-procedural, and follow-up QCA analyses were performed in the core laboratory at the University of Leipzig Heart Center by an experienced single observer blinded to treatment assignment. Angiograms were analyzed with a semiautomated edge-detection software (QAngio XA Clinical Edition 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands). Catheter tip calibration was used in all patients.

Parameters assessed were reference vessel diameter, lesion length, minimal luminal diameter (MLD), percent diameter stenosis, late lumen loss (the difference between MLD immediately after the procedure and the MLD at follow-up), in-segment binary restenosis rate (restenosis defined as ≥50% diameter stenosis), and pattern of restenosis. Baseline grading of lesion complexity was performed according to a system proposed by the American Heart Association/American College of Cardiology (10) and patterns of restenosis were classified according to Mehran et al. (11). The QCA measurements were obtained for both the stented segment ("in-stent") and a segment covering the stented length as well as 5-mm distal and proximal margins ("in-segment").

Endpoints and definitions. The primary study endpoint was in-stent late lumen loss between groups at 9-month 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 pattern 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

(equaling 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 prespecified margin of 0.16 mm, the Yukon Choice stent, therefore, failed to show noninferiority for the primary

Table 1. Clinical and Angiographic Characteristics at Baseline

Variable	Yukon Choice (n = 120)	Taxus Liberté (n = 116)	p Value
Age, yrs	67.0 ± 9.5	67.3 ± 9.1	0.81
Male	83 (69)	79 (68)	0.97
Cardiovascular risk factors			
Current smoking	28 (23)	31 (27)	0.65
Hypertension	118 (98)	112 (97)	0.65
Peripheral artery disease	17 (14)	11 (10)	0.36
Family history of coronary artery disease	46 (38)	50 (43)	0.54
Body mass index, kg/m^2	31.0 ± 4.8	30.5 ± 4.7	0.39
Left ventricular ejection fraction, %	57.6 ± 12.6	57.3 ± 11.0	0.87
HDL cholesterol, mmol/l	1.24 ± 0.36	1.25 ± 0.33	0.80
LDL cholesterol, mmol/l	2.89 ± 0.99	3.09 ± 1.06	0.16
Glycosylated hemoglobin, %	7.2 ± 1.5	7.1 ± 1.2	0.75
Glomerular filtration rate, ml/min/1.73 m^{2*}	73.8 ± 23.4	74.7 ± 22.2	0.79
Prior myocardial infarction	26 (22)	26 (22)	1.0
Prior percutaneous coronary intervention	38 (32)	33 (28)	0.69
Prior coronary artery bypass grafting	6 (5)	12 (10)	0.19
Medication			
Aspirin	86 (72)	85 (73)	0.90
Statin	85 (71)	79 (68)	0.75
ACE inhibitor or ARB	105 (88)	102 (88)	1.0
Beta blocker	96 (80)	87 (75)	0.45
Diabetes mellitus			
Diet only	24 (20)	17 (15)	0.36
Diet + oral antidiabetics	42 (35)	50 (43)	0.25
Insulin	54 (45)	49 (42)	0.77
Glycoprotein IIb/IIIa-inhibitor use	8 (7)	8 (7)	1.0
Lesion length, mm	13.7 ± 4.5	13.6 ± 6.4	0.87
Minimal luminal diameter, mm	0.6 ± 0.3	0.6 ± 0.3	0.73
Reference diameter, mm	2.90 ± 0.58	2.98 ± 0.58	0.34
Stenosis, % luminal diameter	79 ± 9	80 ± 9	0.45
Lesion complexity according to AHA and ACC (10)			0.20
A	23 (19)	28 (24)	
B1	58 (48)	41 (35)	
B2	21 (18)	29 (25)	
C	18 (15)	18 (16)	
Calcification	18 (15)	27 (23)	0.16

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.

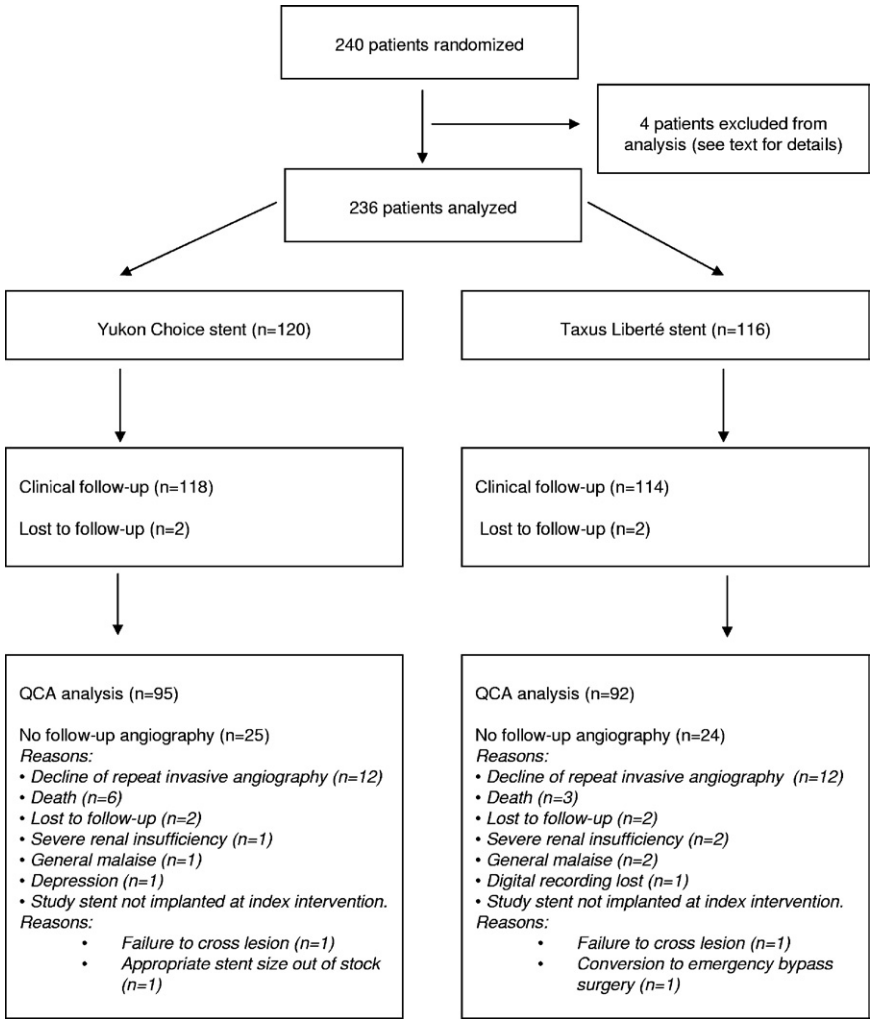

Figure 1. Study Flow Chart

Flow chart showing number of patients enrolled and patients receiving clinical and angiographic follow-up. QCA = quantitative coronary angiography.

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

Table 2. Results of Quantitative Coronary Angiography

Variable	Yukon Choice (n = 95)	Taxus Liberté (n = 92)	p Value
Stent length, mm	16.2 ± 4.3	17.3 ± 4.9	0.13
Stent diameter, mm	3.0 ± 0.3	2.9 ± 0.3	0.52
Pre-dilation	33 (35)	25 (27)	0.34
Post-dilation	6 (5)	6 (5)	1.0
>1 stent implanted	18 (19)	14 (15)	0.63
Minimal luminal diameter, in-stent, mm			
After PCI	2.4 ± 0.5	2.5 ± 0.5	0.17
At follow-up	1.8 ± 0.8	2.1 ± 0.7	0.01
Minimal luminal diameter, in-segment, mm			
After PCI	2.2 ± 0.6	2.2 ± 0.5	0.27
At follow-up	1.7 ± 0.7	1.9 ± 0.7	0.02
Stenosis, in-stent, % luminal diameter			
After PCI	20 ± 9	19 ± 8	0.19
At follow-up	39 ± 22	33 ± 20	0.06
Stenosis, in-segment, % luminal diameter			
After PCI	29 ± 11	28 ± 11	0.62
At follow-up	42 ± 21	37 ± 19	0.08
Late lumen loss, in-stent, mm	0.63 ± 0.62	0.45 ± 0.60	0.04
Late lumen loss, in-segment, mm	0.44 ± 0.65	0.29 ± 0.59	0.11
In-segment binary angiographic restenosis	17 (18)	14 (15)	0.77
Pattern of restenosis			0.66
IA	—	—	
IB	4 (23)	7 (50)	
IC	6 (35)	4 (29)	
ID	1 (6)	—	
II	2 (12)	1 (7)	
III	3 (18)	1 (7)	
IV	1 (6)	1 (7)	

Data are mean ± SD or n (%).
PCI = percutaneous coronary intervention.

stent system failed to show noninferiority for the primary endpoint, in-stent late lumen loss. There were no significant differences in clinical outcome.

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 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 3. Clinical Outcome

Variable	Yukon Choice (n = 118)	Taxus Liberté (n = 114)	p Value
All-cause death	6 (5)	3 (3)	0.5
Definite or presumed cardiac death	4 (3)	3 (3)	1.0
Myocardial infarction	4 (3)	1 (1)	0.37
Procedure-related	—	1 (1)	
Nonprocedure-related	4 (3)	—	
Conversion to emergency bypass surgery at index intervention	—	1 (1)	0.49
Stent thrombosis			
Definite	—	—	
Probable	—	—	
Possible	4 (3)	3 (3)	1.0
Target lesion revascularization	12 (11)	14 (13)	0.66
Target vessel revascularization	25 (22)	29 (26)	0.51
Nontarget vessel revascularization	13 (12)	17 (15)	0.42

Data are n (%).

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 4, 2011
APRIL 2011:452–9

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.

Reprint requests and correspondence: Dr. Steffen Desch, Department of Internal Medicine/Cardiology, University of Leipzig, Heart Center, Strümpellstrasse 39, 04289 Leipzig, Germany. E-mail: stdesch@web.de.

REFERENCES

1. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009;119:3198–206.
2. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;56:S1–42.
3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.
4. Hausleiter J, Kastrati A, Wessely R. Prevention of restenosis by a novel drug-eluting stent system with a dose-adjustable, polymer-free, on-site stent coating. Eur Heart J 2005;26:1475–81.
5. Mehilli J, Byrne RA, Wieczorek A, et al., for the ISAR-TEST-3 Investigators. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. Eur Heart J 2008;29:1975–82.
6. Mehilli J, Kastrati A, Wessely R, et al., for the ISAR-TEST Investigators. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. Circulation 2006;113:273–9.
7. Stone GW, Ellis SG, Cox DA, et al., for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
8. Turco MA, Ormiston JA, Popma JJ, et al. Polymer-based, paclitaxel-eluting Taxus Liberte stent in de novo lesions: the pivotal Taxus ATLAS trial. J Am Coll Cardiol 2007;49:1676–83.
9. University of Leipzig. LIPSIA - TRIALS Randomisations und Erfassungs System. Available at: http://www.uni-leipzig.de/~kard/LIPSIA. Accessed March 14, 2011.
10. Ellis SG, Vandormael MG, Cowley MJ, et al., for the Multivessel Angioplasty Prognosis Study Group. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Circulation 1990;82:1193–202.
11. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8.
12. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344C51.
13. Dibra A, Kastrati A, Mehilli J, et al., for the ISAR-DIABETES Study Investigators. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663–70.
14. Hermiller JB, Raizner A, Cannon L, et al., for the TAXUS-IV Investigators. Outcomes with the polymer-based paclitaxel-eluting Taxus stent in patients with diabetes mellitus: the Taxus-IV trial. J Am Coll Cardiol 2005;45:1172–9.
15. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.
16. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus. J Am Coll Cardiol 2008;52:727–33.
17. Maeng M, Jensen LO, Galloe AM, et al. Comparison of the sirolimus-eluting versus paclitaxel-eluting coronary stent in patients with diabetes mellitus: the diabetes and drug-eluting stent (DiabeDES) randomized angiography trial. Am J Cardiol 2009;103:345–9.
18. Ruef J, Storger H, Schwarz F, Haase J. Increased restenosis rates 12 months after coronary implantation of the sirolimus-eluting Yukon-choice stent compared to the paclitaxel-eluting Taxus stent. Clin Cardiol 2010;33:E33–8.
19. Byrne RA, Iijima R, Mehilli J, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. J Am Coll Cardiol Intv 2009;2:291–9.
20. Byrne RA, Kufner S, Tiroch K, et al., for the ISAR-TEST-3 Investigators. Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results. Heart 2009;95:1489–94.
21. Moore P, Barlis P, Spiro J, et al. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. J Am Coll Cardiol Intv 2009;2:437–44.
22. Kaul S, Diamond GA. Making sense of noninferiority: a clinical and statistical perspective on its application to cardiovascular clinical trials. Prog Cardiovasc Dis 2007;49:284–99.
23. Mauri L, Orav EJ, Candia SC, Cutlip DE, Kuntz RE. Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. Circulation 2005;112:2833–9.
24. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605–13.
25. Zhang F, Dong L, Ge J. Meta-analysis of five randomized clinical trials comparing sirolimus- versus paclitaxel-eluting stents in patients with diabetes mellitus. Am J Cardiol 2010;105:64–8.

Key Words: diabetes mellitus ■ late lumen loss ■ paclitaxel ■ sirolimus ■ stents.