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Neointimal hyperplasia after sirolimus-eluting and paclitaxel-eluting stent implantation in diabetic patients: The Randomized Diabetes and Drug-Eluting Stent (DiabeDES) Intravascular Ultrasound Trial

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Aims Patients with diabetes have increased risk of in-stent restenosis after coronary stent implantation owing to neointimal hyperplasia (NIH). The aim of the study was to evaluate the extent and distribution of NIH with intravascular ultrasound (IVUS) after coronary artery stenting with sirolimus-eluting (Cypher) or paclitaxel-eluting (Taxus) stents in diabetic patients.

Methods and results One hundred and thirty diabetic patients were randomized to Cypher or Taxus stent implantation. IVUS was performed at 8 month follow-up. NIH volume was significantly reduced in the Cypher group when compared with the Taxus group: median (inter-quartile range) 0.0 (0.0–0.0) vs. 8.0 mm^3 (0.1–33.0), $P < 0.001$. Per cent NIH volume was also significantly lower in Cypher stents compared with Taxus stents: median (inter-quartile range) 0.0 (0.0–0.0) vs. 7.5% (0.1–27.0), $P < 0.001$. NIH was covering 5.4% of the stent length in the Cypher stents compared with 46.1% in the Taxus stents ($P < 0.001$). The incidence of diffuse NIH was significantly higher for Taxus than for Cypher stents (42.9 vs. 3.5%, $P < 0.001$). Taxus stents had more often NIH at the proximal stent edge compared with Cypher stents (45.1 vs. 7%, $P < 0.001$) and no Cypher stents had NIH at the distal stent edge compared with 35.5% of the Taxus stents ($P < 0.001$).

Conclusion In diabetic patients, the Cypher stent, compared with the Taxus stent, inhibited NIH more effectively and had a more focal NIH pattern including less involvement of the stent edges.

Keywords Drug-eluting stent • Diabetes mellitus • Intravascular ultrasound • Neointimal hyperplasia

Introduction

Diabetes mellitus is an important risk factor for poor outcome after percutaneous coronary interventions (PCI) using bare metal stents.[1–3] A more diffuse and accelerated form of atherosclerosis accompanied by smaller vessel size, long lesions, and greater plaque burden in diabetic patients may contribute to the well-documented increased risk of neointimal hyperplasia (NIH) and restenosis after stent implantation in these patients.[4–7] Drug-eluting stents are highly effective in reducing in-stent restenosis compared with bare metal stents, both in patients with and without diabetes.[8–19] Intravascular ultrasound (IVUS) has

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documented reduced NIH,[14–18] and angiography has shown reduced late lumen loss[8,9] after coronary drug-eluting stent implantation compared with bare metal stents. Recently, a meta-analysis showed that sirolimus-eluting stents were more effective than paclitaxel-eluting stents with regard to restenosis in non-diabetic patients but appeared to be comparable in patients with diabetes.[20] Currently, only one randomized study has compared the first two commercially available drug-eluting stents, i.e. the sirolimus-eluting Cypher stent and the paclitaxel-eluting Taxus stent in diabetic patients.[21] The present study is the first randomized multicentre IVUS study comparing NIH formation and distribution within the stent in diabetic patients treated with the Cypher stent vs. the Taxus stent.

Methods

Study population

From February 2005 to March 2006, 130 patients with diabetes mellitus and angiographically significant coronary stenoses in native coronary arteries (vessel diameter 2.25–4.0 mm) were enrolled in a non-blinded, randomized multicentre IVUS study at four Danish interventional centres (the DiabeDES study). The study is a substudy of the SORT OUT II trial[22] (Clinicaltrials.gov Identifier: NCT00388934). A flow diagram of the study is shown in *Figure 1*. Exclusion criteria were lesions in vein grafts. All patients provided written informed consent, and the local institutional review board (The Scientific Ethics Committee for the County of Aarhus, Denmark) approved the protocol (case no. 20040170).

Randomization, study lesion, and intervention

Patients were randomly assigned to receive a sirolimus-eluting (Cypher Select; Cordis, Johnson & Johnson) or a paclitaxel-eluting stent (Taxus Express-2, Boston Scientific) by telephone contact to a computer-generated randomization sequence. The randomly assigned stent was implanted in all lesions treated. In multivessel intervention, lesion location in the left anterior descending coronary artery was selected as study lesion. In combined circumflex and right coronary artery intervention, the right coronary lesion was used as study lesion. If more than one lesion was treated in the same vessel, the proximal lesion was chosen as a study lesion. Only one lesion (study lesion) for each patient was analysed according to this lesion selection. During the randomization procedure, the diabetic patients were stratified according to participation in the DiabeDES substudy. Prior to intervention, the patients were treated with a 300–600 mg clopidogrel loading dose and continued treatment with aspirin 75 mg daily. Unfractionated heparin was given intravenously at the beginning of the procedure. Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. After the intervention, clopidogrel 75 mg per day and aspirin 75 mg per day were continued for 12 months and lifelong, respectively. IVUS was performed at 8 month follow-up.

Intravascular ultrasound imaging protocol and analysis

IVUS was performed after the administration of 200 μg intracoronary nitroglycerin. The IVUS system (Galaxy or Clearview, Boston Scientific, Fremont, CA, USA) utilized a 40 MHz, 2.6 Fr IVUS catheter (Atlantis-Pro). Image acquisition using automated transducer pullback at 0.5 mm/s was performed from a point at least 10 mm distally to the stent to the aorto-ostial junction. Offline analysis was performed with a commercially available program for computerized planimetry (EchoPlaque, INDEC System, Mountain View, CA, USA) by an independent core laboratory (Odense University Hospital). Reproducibility for geometrical measurements in the Odense University Hospital has previously been published.[23,24] All IVUS core laboratory analyses were performed blinded to the treatment arm. Lumen, stent, and EEM cross-sectional areas (CSAs) were measured within the stent.[25] The proximal and distal stent edge was the most proximal and distal image CSA, respectively, within the stent. NIH was calculated as stent minus lumen measures at follow-up. Per cent NIH volume was defined as (NIH volume divided by the stent volume) multiplied by 100. The patterns of NIH were classified as focal (≤10 mm in length) or diffuse (>10 mm in length). Peri-stent plaque CSA was calculated as EEM CSA minus stent CSA in stented segments. Volumes were calculated using Simpson's rule.

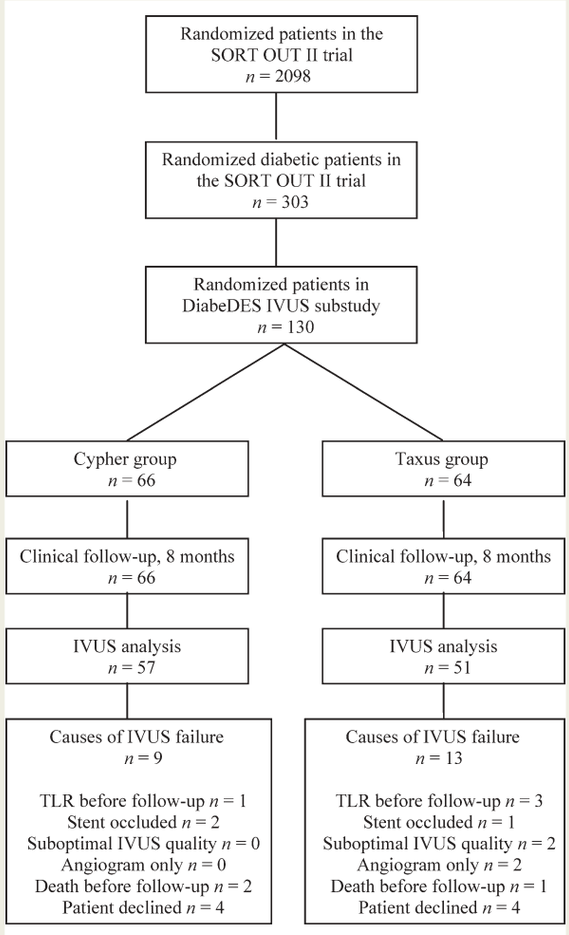

Figure 1 Flow diagram of the study.

Study endpoints

The primary endpoint of the study was in-stent NIH volume. Secondary endpoints were in-stent NIH percentage volume, patterns of NIH (focal or diffuse), and NIH at the stent edges. The clinical endpoints, namely total death, cardiac death, ST-segment elevation myocardial infarction (MI), non-ST-segment elevation MI, target lesion

revascularization by PCI or coronary artery bypass grafting (CABG), and ARC-defined stent thrombosis,[26] were assessed although the study was not powered to compare clinical events. All endpoints were evaluated blinded to treatment arm.

Statistical analysis

The statistical analysis was carried out using SPSS 15.0. Categorical data were presented as counts and percentages and compared by the Pearson χ^2 test or the Fisher exact test. For continuous variables with a normal distribution, the mean $\pm$ 1 SD was reported. For variables not normally distributed, the median and inter-quartile ranges were reported. Continuous variables were compared using a Mann–Whitney test or a Student's *t*-test. Estimates of the differences between the groups [and associated 95% confidence interval (CI)] for the primary and secondary endpoints of interest are presented. The sample size calculation was based upon an estimated NIH of 5% in the Cypher stent group and 10% in the Taxus stent group with an SD of 10%, alpha error of 0.05, and a power of 80%. Thus, a minimum of 126 patients was pre-specified for enrolment. For the primary endpoint, IVUS data will be available only for patients returning for a follow-up IVUS after 8 months. Patients without IVUS data were excluded from the intention-to-treat analysis. The reasons for dropouts and proportions for each group have been reported. A sensitivity analysis has been carried out, including patients with occluded stent (estimating per cent NIH to be 100%). Estimating the remaining non-available cases would, from a clinical point of view, be incorrect. For the clinical endpoints, the data set will be 100% completed. Thus, according to ICH E9, the full analysis set have been used.

Results

Clinical characteristics

We randomized 130 patients to Cypher stent ($n = 68$) or Taxus stent implantation ($n = 62$). Follow-up IVUS was not performed for clinical or technical reasons in 14 patients: (i) four patients had TLR without IVUS before the scheduled 8 month follow-up, (ii) three patients had an occluded study lesion at 8 month follow-up, (iii) two patients had suboptimal follow-up IVUS quality, (iv) two patients had only angiography performed at follow-up, and (v) three patients died before the 8 month follow-up. Finally, eight patients declined to have the 8 month follow-up examination performed (Cypher $n = 4$, Taxus $n = 4$). Thus, follow-up IVUS was available in 108 (83%) patients (Cypher stent $n = 57$, Taxus stent $n = 51$). The Clearview IVUS console was used in 10 patients, and the Galaxy IVUS console was used in the other 98 patients. The baseline characteristics of the completers were comparable with those not evaluated by IVUS at 8 month follow-up. The clinical features at baseline are shown in *Table 1*.

Lesion and stent characteristics

The lesion and stent characteristics are shown in *Table 2*. Baseline angiographic reference vessel size, minimal lumen diameter, diameter stenosis, stent size, and stent length did not differ significantly between the two groups. The number of treated vessels was also similar in the two groups. Also, the rate of pre-dilation and post-dilation did not differ significantly between the Cypher- and the Taxus-treated patients. In both groups, half of the patients were treated with glycoprotein IIb/IIIa inhibitor at the index procedure.

Intravascular ultrasound measurements

IVUS volumetric measures for patients with 8 month follow-up IVUS are shown in *Table 3*. At 8 month follow-up, EEM, stent, and lumen volumes were similar in the Cypher and Taxus groups (*Figure 2*).

Neointimal hyperplasia

At the 8 month follow-up, no NIH could be detected in 46 (81%) of the Cypher stents compared with 11 (22%) of the Taxus stents ($P < 0.001$). NIH volume [median (inter-quartile range) 0.0 (0.0–0.0) vs. 8.0 mm^3 (0.1–33.0), $P < 0.001$; mean difference -16.4 mm^3 (95% CI) -21.9 to -11.0, $P < 0.001$)] and per cent NIH volume [median (inter-quartile range) 0.0 (0.0–0.0) vs. 7.5% (0.1–27.0), $P < 0.001$; mean difference -11.4% (95% CI -15.1 to -7.8), $P < 0.001$] were significantly lower in Cypher stents compared with Taxus stents (*Figure 3*). Including the three patients with occluded stent (estimating per cent NIH volume to be 100%), the per cent NIH volume was [median (inter-quartile range) 0.0%

Table 1 Clinical characteristics

	Cypher ($n = 68$)	Taxus ($n = 62$)	*P*-value
Male gender, *n* (%)	57 (83.8)	49 (79.0)	0.506
Age, years	62.6 $\pm$ 9.1	64.4 $\pm$ 8.4	0.248
Stable angina pectoris, *n* (%)	45 (66.2)	46 (74.2)	0.319
Diabetes type 2, *n* (%)	56 (82.4)	53 (85.5)	0.628
Insulin treatment, *n* (%)	29 (42.6)	24 (38.7)	0.722
Prior PCI, *n* (%)	10 (14.7)	14 (22.6)	0.248
Prior CABG, *n* (%)	4 (5.9)	1 (1.6)	0.206
Hypertension, *n* (%)	43 (63.2)	44 (71.0)	0.421
Hypercholesterolaemia, *n* (%)	59 (86.8)	58 (93.5)	0.355
HgbA1c, mmol/L	0.078 $\pm$ 0.013	0.074 $\pm$ 0.012	0.129
Body mass index, kg/m^2	30.2 $\pm$ 5.5	28.4 $\pm$ 5.2	0.060
Smoking, *n* (%)	26 (38.2)	16 (25.8)	0.139

Table 2 Lesion and procedural characteristics

	Cypher ($n = 68$)	Taxus ($n = 62$)	*P*-value
Number of treated lesions per patient			0.884
1	39 (57.4)	38 (61.3)	
2	21 (30.9)	19 (30.6)	
≥3	8 (11.8)	5 (8.1)	
Bifurcation lesions, *n* (%)	9 (13.2)	8 (12.9)	0.955
Pre-dilatation, *n* (%)	51 (75.0)	46 (74.2)	0.916
Post-dilatation, *n* (%)	23 (33.8)	18 (29.0)	0.557
GP IIb/IIIa inhibitors, *n* (%)	35 (51.5)	30 (48.4)	0.725
Number of stents per lesion	1.4 ± 0.8	1.3 ± 0.8	0.482
Lesion length, mm	20.3 ± 14.6	17.7 ± 10.5	0.264
Stent length, mm	24.5 ± 15.0	22.5 ± 13.1	0.408
Stent size, mm	3.1 ± 0.4	3.1 ± 0.4	0.381
Pre-intervention			
Minimal lumen diameter, mm	0.82 ± 0.48	0.80 ± 0.60	0.845
Reference diameter, mm	2.81 ± 0.66	2.79 ± 0.57	0.852
Diameter stenosis, %	70.1 ± 16.3	71.1 ± 20.1	0.767

Table 3 Volumetric intravascular ultrasound measurements at 8 month follow-up

	Cypher ($n = 57$)	Taxus ($n = 51$)	*P*-value
EEM, mm^3	307.1 ± 149.2	300.4 ± 139.0	0.810
Stent, mm^3	141.1 ± 79.5	138.9 ± 62.7	0.872
Lumen, mm^3	138.8 ± 76.7	121.7 ± 59.8	0.203
Peri-stent plaque, mm^3	169.1 ± 78.8	161.1 ± 80.0	0.604
Neointima, mm^3			
Mean (SD)	1.3 ± 3.6	17.7 ± 20.5	<0.001
Median (inter-quartile range)	0.0 (0.0–0.0)	8.0 (0.1–33.0)	<0.001
Percentage NIH volume			
Mean (SD)	1.0 ± 3.0	12.5 ± 13.4	<0.001
Median (inter-quartile range)	0.0 (0.0–0.0)	7.5 (0.1–27.0)	<0.001

(0.0–0.0)] in the Cypher stent group compared with 7.7% (0.7–26.4), $P < 0.001$, in the Taxus stent group, mean difference −9.8% (95% CI −16.6 to −2.9), $P = 0.006$.

Patterns of neointimal hyperplasia distribution

NIH was covering 5.4 ± 13.7% of the stent length in the Cypher stents compared with 46.1 ± 38.0% in the Taxus stents ($P < 0.001$) [median (inter-quartile range) 0.0 (0.0–0.0) vs. 41.7% (8.8–87.0), $P < 0.001$; mean difference −40.6% (95% CI −51.2 to −30.0), $P < 0.001$] (*Figure 4*). Evaluating only stents with NIH, 28.0 ± 18.7% of the stent length in the Cypher stents compared with 59.1 ± 32.9% in the Taxus stents ($P = 0.004$) was covered. The incidence of diffuse NIH was significantly higher for Taxus than for Cypher stents (42.9 vs. 3.5%, $P < 0.001$) (*Figure 5*). Also, the incidence of focal NIH was significantly higher for Taxus than for Cypher stents (34.7 vs. 18.8%, $P < 0.001$). The Taxus stents did still have more diffuse NIH than the Cypher stents when only stents with NIH were evaluated (55.3 vs. 18.2%, $P = 0.042$).

Proximal and distal stent edges

The analysis of the proximal and distal stent edges showed a significant difference between the two stent groups. NIH at the proximal stent edge was more often seen in Taxus stents compared with Cypher stents (45.1 vs. 7%, $P < 0.001$). The mean per cent NIH volume at the most proximal stent CSA was 13.9% in the Taxus stent group compared with 1.5% in the Cypher stent group ($P < 0.001$) [mean difference −12.4% (95% CI −17.8 to −7.0), $P < 0.001$]. None of the Cypher stents had NIH at the distal stent edge compared with 35.5% of the Taxus stents ($P < 0.001$). The number of lesions with NIH at the proximal stent edge was not significantly higher for post-dilated lesions compared with lesions without post-dilatation (31.4 vs. 21.9%, $P = 0.344$).

Clinical events

Eight month clinical outcome was available in all patients ($n = 130$, 100%). The incidence of major adverse cardiac events did not differ in the two groups (*Table 4*). There were no definite stent thromboses. Three patients died during the follow-up period. One patient died of a verified pancreas cancer. The two other patients, one in each group, died suddenly (86 days and 285 days after index PCI). Both cases were classified as cardiac death and thus as possible stent thrombosis. Autopsy was not performed in any of the patients.

Discussion

This is the first randomized multicentre IVUS comparison of the Cypher vs. the Taxus stent in diabetic patients. We found that the NIH response differed between patients treated with Cypher or Taxus stents. Thus, the Taxus stent generated more NIH and had more diffuse NIH when compared with the Cypher stent. Also, the NIH at the proximal stent edge was more often seen in Taxus stents compared with Cypher stents, and at the distal edge, NIH was seen only in the Taxus stents.

Inhibitory effect on neointimal hyperplasia

The Cypher stent showed a significant inhibition of NIH compared with the Taxus stent. No NIH could be detected by IVUS in 85% of the Cypher stents compared with 24% of the Taxus stents. NIH is the main component of in-stent restenosis after stent implantation and reflects the degree of neointimal proliferation.[27] The per cent

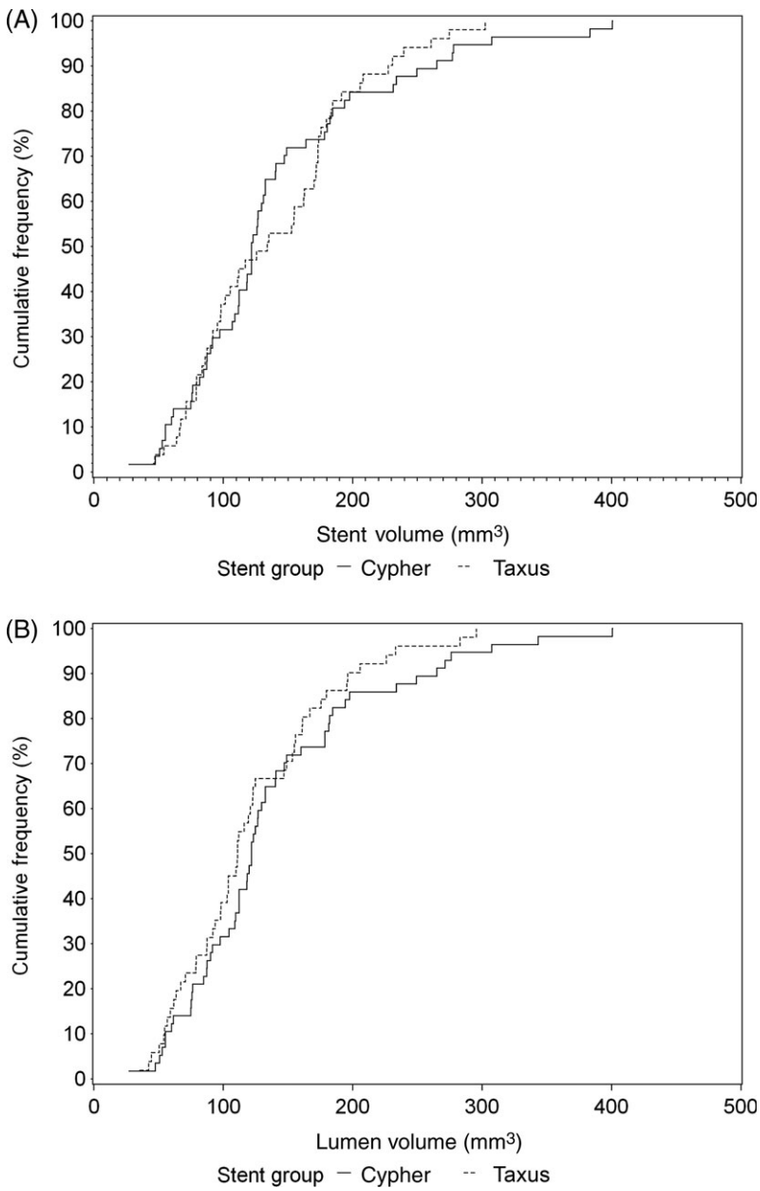

Figure 2 Cumulative distribution curve of (*A*) stent volume and (*B*) in-stent lumen volume at follow-up.

neointimal free length of the stents, a measure of NIH homogeneity, measured 95% in the Cypher stents group compared with 54% in the Taxus stent group. Quantification of focal and diffuse NIH distribution did also demonstrate significantly more diffuse NIH in the Taxus stent group. For the Taxus stent, the per cent neointimal free length of the stents is comparable with studies in non-diabetics or studies containing a limited number of diabetic patients.[28,29] This study is in accordance with a previous randomized angiographic study comparing the effect of Cypher and Taxus stent treatment in diabetic patients.[21] Here, the paclitaxel stent was associated with a higher rate of in-segment late luminal loss compared with the sirolimus stent. An IVUS study diabetic patients[15] treated with sirolimus-eluting stents showed similar NIH volume and per cent NIH volume as the Cypher stent group in this study. Also, the NIH in this study is concordant with the TAXUS-I,[30] TAXUS-II,[16,31] and TAXUS-IV[16] studies in non-diabetics or a limited number of diabetic patients where per cent NIH volume was 14.8, 7.8, and 12.2%, respectively. In contrast, in earlier IVUS substudies, sirolimus-eluting stents have been characterized by the near absence of measurable in-stent tissue[17,27] remaining minimal with long-term follow-up.[32] The diabetic subpopulation in the RAVEL study showed a similar low per cent NIH volume as the patients treated with Cypher stents in this study.[14]

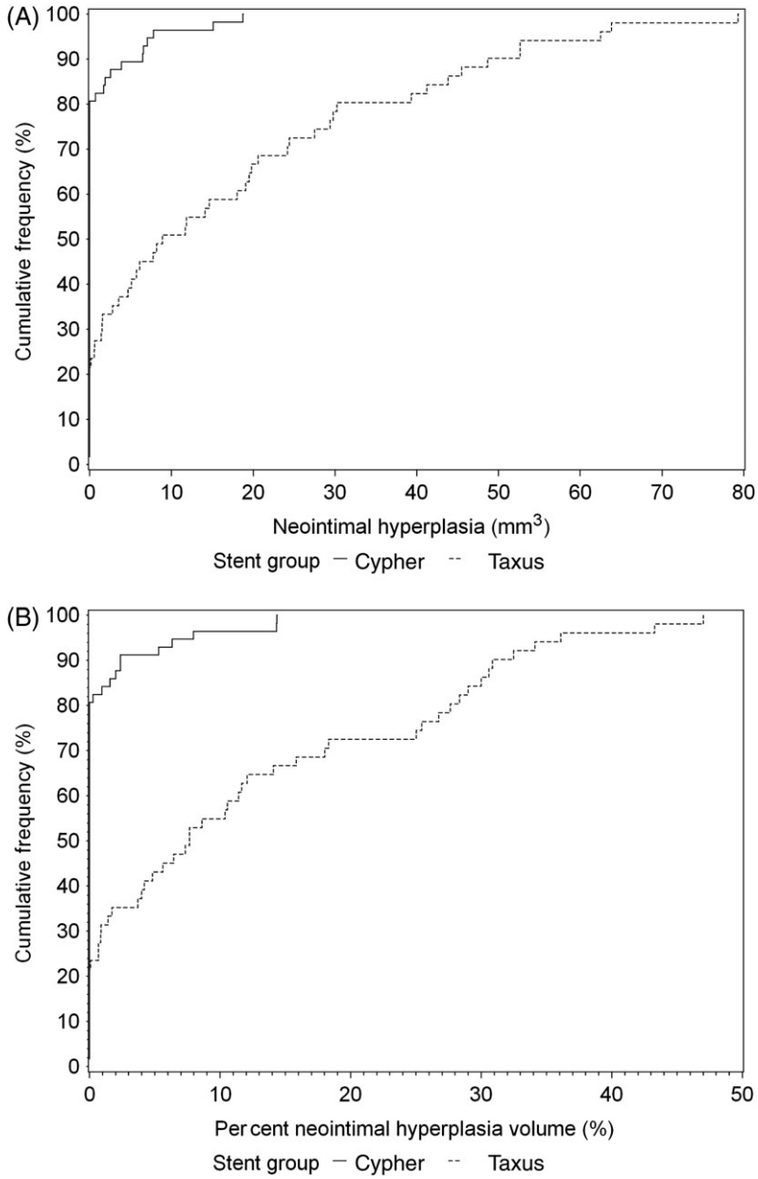

Figure 3 Cumulative distribution curve of (*A*) in-stent neointimal hyperplasia volume at 8 month follow-up, (*B*) percentage neointimal hyperplasia volume at follow-up. Although stent volume is similar, the neointimal hyperplasia and per cent of obstruction volume curves are significantly shifted to the left for the Cypher stent group.

Proximal-edge neointimal hyperplasia is more common than distal-edge neointimal hyperplasia

Restenosis after treatment with sirolimus- and paclitaxel-eluting stents appears to occur more frequently at the margins of the DES.[27,33,34] Especially, the proximal stent-edge seems to have a higher incidence of restenosis,[33,34] which may be more pronounced in paclitaxel stents.[33,35] This is concordant with the results of this study, where the proximal stent edge more often was covered by NIH than the distal stent edge. Also, NIH at the proximal stent edge was more frequent in Taxus than in Cypher stents and resulted in a smaller CSA of the proximal stent. At the distal stent edge, only Cypher stents were free from NIH. In the TAXUS II study,[18] it was demonstrated that longitudinal distribution of NIH throughout the stent was uniform with an increased amount of NIH from distal to proximal in the stent. The reason for this observation is not clear. The number of post-dilations did not differ between the two groups. A uniformly distributed neointima along the stent would indicate a homogeneous longitudinal drug diffusion pattern from the stent. The vessel diameter is

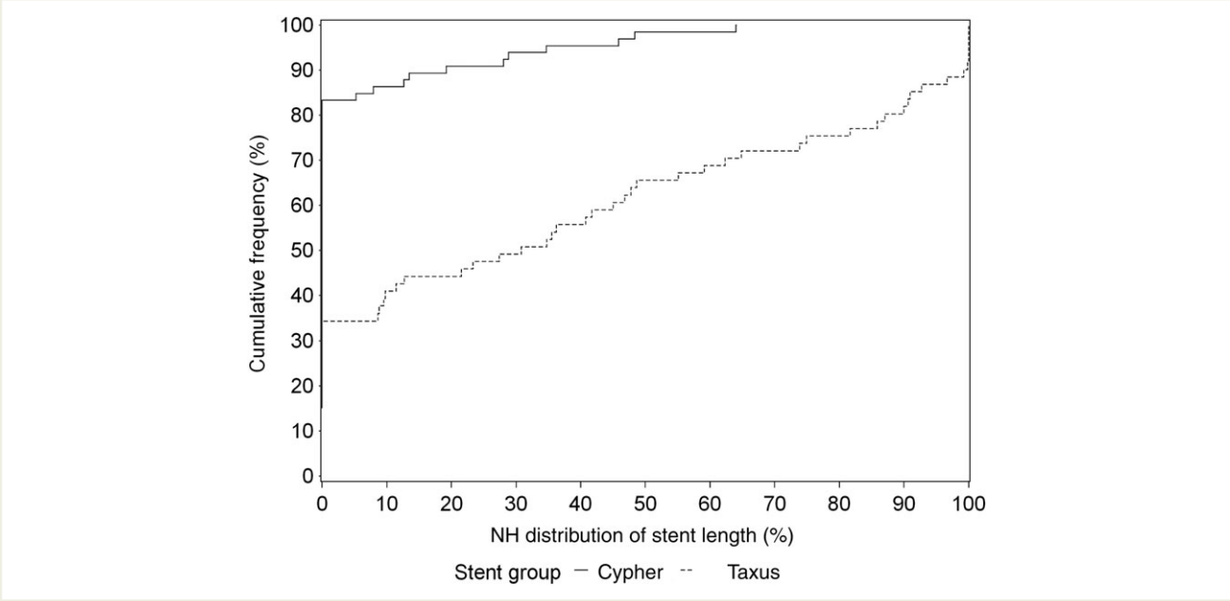

Figure 4 Cumulative distribution curve of the length of stent with neointimal hyperplasia.

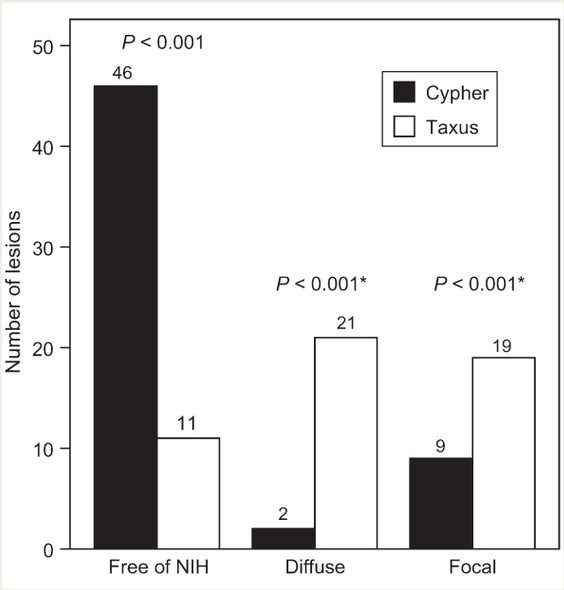

Figure 5 The distribution of focal and diffuse neointimal hyperplasia and of stents without neointimal hyperplasia.

Table 4 Clinical events at 8 month follow-up

	Cypher ($n = 68$)	Taxus ($n = 62$)	*P*-value
Death (all cause)	2	1	
Cardiac death	1	1	
Definite stent thrombosis	0	0	
Probable stent thrombosis	0	0	
Possible stent thrombosis	1	1	
MI	0	2	
ST-segment elevation MI	0	0	
Non-ST-segment elevation MI	0	2	
Target lesion revascularization	1	3	
PCI	0	2	
CABG	1	1	
MACE	3	6	0.309
PCI at follow-up procedure after IVUS acquisition	3	6	

MACE denotes major adverse cardiac events and includes cardiac death, MI, stent thrombosis, and target lesion revascularization.

likely to be smaller at the distal part of the stented segment and would theoretically receive a greater barotrauma and balloon injury. However, this does not seem to influence NIH in DES in general.

It should be emphasized that the axial resolution of IVUS is ~200 μm and does not permit any assessment of the endothelialization of the stent. A small amount of NIH may theoretically reduce the risk of stent thrombosis by covering the stent struts without leading to restenosis. Therefore, the observed differences between the Cypher and the Taxus stents should not be interpreted as evidence of differences with regard to clinical endpoints such as restenosis and TLR. However, since NIH results in a proportionally higher grade diameter stenoses in small as opposed to large vessels, and diabetic patients more often have smaller vessels, the more potent suppression of NIH associated with Cypher stents, compared with Taxus

stents, is in accordance with the clinical outcome in diabetic patients in the SIRTAX trial.[36]

Limitations

The interpretation of this study requires consideration of several limitations. First, only per cent NIH volume can be determined by follow-up IVUS. Per cent NIH volume is a measure of efficacy, as the detection of incomplete stent apposition and edge effects would require both post-implantation and follow-up IVUS. Second, lesions with total occlusion ($n = 3$) or patients having TLR before the scheduled 8 month follow-up were not assessed with IVUS follow-up.

Conclusions

In diabetic patients, direct comparison of Cypher and Taxus stents shows that the Cypher stent inhibits NIH more effectively than the Taxus stent. Further, the Taxus stent has more frequent diffuse NIH involvement of the stent edges.

Conflict of interest: none declared.

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