

# Late lumen loss and intima hyperplasia after sirolimus-eluting and zotarolimus-eluting stent implantation in diabetic patients: the diabetes and drug-eluting stent (DiabeDES III) angiography and intravascular ultrasound trial

Lisette Okkels Jensen<sup>1</sup>, MD, DMSci, PhD; Michael Maeng<sup>2</sup>, MD, PhD; Per Thayssen<sup>1</sup>, MD, DMSci; Anton Villadsen<sup>3</sup>, MD; Lars Krusell<sup>2</sup>, MD; Hans Erik Botker<sup>2</sup>, MD DMSci; Knud Erik Pedersen<sup>1</sup>, MD, DMSci; Jens Aaroe<sup>3</sup>, MD; Evald Hoj Christiansen<sup>2</sup>, MD, PhD; Thomas Vesterlund<sup>3</sup>, MD; Knud Noerregaard Hansen<sup>1</sup>, MD; Jan Ravkilde<sup>3</sup>, MD, DMSci; Hans Henrik Tilsted<sup>3</sup>, MD; Jens Flensted Lassen<sup>2</sup>, MD, PhD; Leif Thuesen<sup>2</sup>, MD, DMSci

Department of Cardiology, Odense University Hospital, Odense, Denmark; 2. Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark; 3. Department of Cardiology, Aarhus University Hospital, Aalborg, Denmark

## KEYWORDS

- zotarolimus-eluting stent
- sirolimus-eluting stent
- diabetes

## Abstract

**Aims:** Patients with diabetes mellitus have increased risk of in-stent restenosis after coronary stent implantation due to neointimal hyperplasia (NIH). The aim of this study was to use quantitative coronary angiography (QCA) and volumetric intravascular ultrasound (IVUS) to evaluate the effects of the sirolimus-eluting Cypher<sup>®</sup> stent (SES) and the zotarolimus-eluting Endeavor<sup>®</sup> stent (ZES) on angiographic late lumen loss and intima hyperplasia in diabetic patients.

**Methods and results:** In the DiabeDES III trial, 127 patients were randomised to SES or ZES stent implantation. Angiographic 10-month follow-up data were available in 105 patients, including 48 SES and 57 ZES treated patients. Angiographic endpoints were in-stent late lumen loss and minimal lumen diameter. IVUS endpoints included NIH volume and in-stent percent volume obstruction. Baseline clinical characteristics and lesion parameters were similar in the two groups. At 10-month follow-up, angiographic in-stent late lumen loss ( $0.14 \pm 0.37$  mm vs.  $0.74 \pm 0.45$  mm,  $p < 0.001$ ) was reduced and minimum lumen diameter was higher ( $2.36 \pm 0.53$  mm vs.  $1.96 \pm 0.65$ ,  $p < 0.001$ ) in the SES group as compared to the ZES group. As compared to the ZES group, NIH volume was significantly reduced in the SES group (median [interquartile range]:  $0.0$  mm<sup>3</sup> [0.0 to 1.2] vs.  $16.5$  mm<sup>3</sup> [6.2 to 31.1],  $p < 0.001$ ). In-stent% volume obstruction was significantly reduced in SES as compared to ZES (median [interquartile range]:  $0.0\%$  [0.0-0.7] vs.  $13.0\%$  [6.7-20.8],  $p < 0.001$ ).

**Conclusions:** In diabetic patients, the SES reduced angiographic late lumen loss and inhibited NIH more effectively than ZES.

\*Corresponding author: Department of Cardiology, Catheterization Laboratory, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark. E-mail: okkels@dadlnet.dk

## Background

Diabetes mellitus is an important risk factor for poor outcome after percutaneous coronary interventions (PCI) using bare metal stents.<sup>1-3</sup> Drug-eluting stents (DES) have shown to reduce restenosis and the need for repeat revascularisation in diabetic patients.<sup>4-6</sup> Angiographic and intravascular ultrasound (IVUS) studies suggest increased late lumen loss<sup>7</sup> and intimal hyperplasia<sup>8</sup> as mechanisms underlying high restenosis risk. A more diffuse and accelerated form of atherosclerosis in diabetic patients, accompanied by small vessel size, long lesions and greater plaque burden, may contribute to the well-documented increased risk of restenosis after stent implantation in these patients. In terms of late luminal loss, randomised studies in diabetic patients with angiographic endpoints have shown a significant advantage after implantation of sirolimus-eluting stents (SES) compared to paclitaxel-eluting stents (PES).<sup>9-12</sup> Also, reduced intimal hyperplasia has been documented in SES-compared to PES-treated diabetic patients.<sup>13</sup> A subgroup analysis of the diabetic participants from the SIRTAX trial demonstrated lower rates of major adverse coronary events and target lesion revascularisation after two years in SES-treated patients<sup>14</sup> and a recent meta-analysis found that SES was superior to PES in reducing the incidences of restenosis and target lesion revascularisation in patients with diabetes, with non-significant differences in terms of cardiac death, myocardial infarction, and stent thrombosis.<sup>15</sup>

It not yet determined, if a cobalt-based alloy stent coated with the antiproliferative agent, zotarolimus, and a phosphorylcholine polymer (Endeavor stent) might provide similar angiographic and clinical benefits as the SES in diabetic patents. Therefore, the present trial examined angiographic and IVUS outcomes of a zotarolimus-eluting coronary stent (ZES) versus SES in diabetic patients.

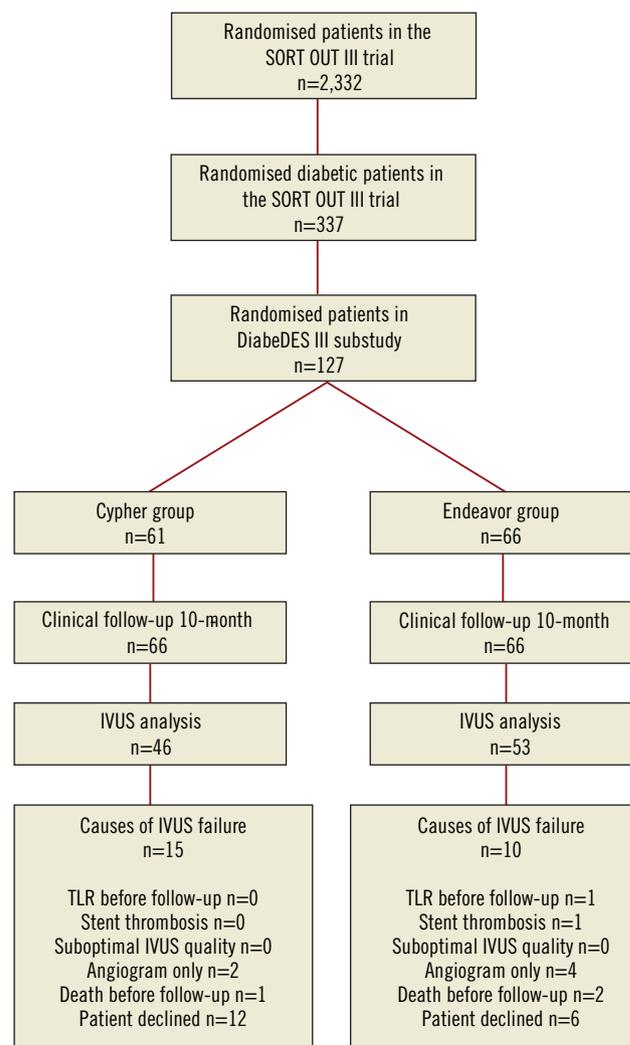
## Methods

### STUDY POPULATION

The SORT OUT III trial<sup>16</sup> was a single-blind, all-comer superiority trial in patients with coronary artery disease randomised to treatment with the ZES or SES. The primary endpoint was a composite of major adverse cardiac events within nine months: cardiac death, myocardial infarction, and target vessel revascularisation. From May 2006 to March 2007, 127 patients with diabetes mellitus and angiographically significant coronary stenoses in native coronary arteries (vessel diameter 2.25-4.0 mm) were enrolled in a pre-planned sub-study (the DiabeDES III study) of the Danish Organisation for Randomised Trials with Clinical Outcome (SORT OUT) III trial<sup>16</sup> (Clinicaltrials.gov Identifier: NCT00660478). A flow diagram of the study is shown in **Figure 1**. Exclusion criteria were lesions in vein grafts and expected survival <1 year. All patients provided written, informed consent, and the local institutional review board approved the protocol. Patients were considered to have diabetes if received dietary treatment, oral antidiabetic medication or insulin.

### RANDOMISATION, STUDY LESION AND INTERVENTION

Patients were randomly assigned to receive a SES (Cypher Select; Cordis, Johnson & Johnson, Warren, NJ, USA) or a ZES (Endeavor



**Figure 1.** Flow diagram of the study. Enrolment in the DiabeDES III substudy was stopped at 127 patients because the sample size calculation already allows an analysis with those patients.

Sprint, Medtronic, Santa Rosa, CA, USA) by telephone contact to a computer-generated randomisation sequence in the SORT OUT III trial. Patients were stratified by hospital and by presence/absence of diabetes. The randomly assigned stent was implanted in all lesions treated. In multivessel interventions, lesion location in the left anterior descending coronary artery was selected as the study lesion. In combined circumflex and right coronary artery interventions, the right coronary lesion was used as the study lesion. If more than one lesion was treated in the same vessel, the proximal lesion was chosen as the study lesion. Only one lesion (study lesion) for each patient was analysed. Prior to the intervention, 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.

## QUANTITATIVE CORONARY ANGIOGRAPHY (QCA)

Coronary angiograms obtained at baseline, at completion of the stenting procedure, and at 10-month follow-up were analysed by use of a computer-based off-line analysis system (Qangio® XA 7.0; Medis, Leiden, The Netherlands). The QCA analyses were performed at a core laboratory (Aarhus University Hospital, Skejby, Denmark). All measurements were performed on angiograms recorded after intracoronary administration of nitroglycerine. The same single, worst-view projection was used. The contrast-filled non-tapered catheter tip was used for calibration. We measured lesion length, lesion minimal luminal diameter (MLD) and reference vessel diameter. Using post intervention and follow-up angiograms, we measured MLD in the stent and in the reference segments (including 5 mm proximal and distal to the stent). In-stent late lumen loss was calculated as MLD in-stent post-intervention minus MLD in-stent at follow-up. Stent thrombosis was assessed by use of the Academic Research Consortium definitions.<sup>17</sup>

## IVUS IMAGING PROTOCOL AND ANALYSIS

IVUS was performed after administration of 200 µg intracoronary nitroglycerine. The IVUS system (Galaxy, Boston Scientific, Fremont, CA, USA) utilised 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. Off-line analysis was performed with a commercially available programme for computerised planimetry (EchoPlaque, INDEC System, MountainView, CA, USA) by a core laboratory (Odense University Hospital, Denmark). All IVUS core laboratory analyses were performed blinded. Lumen, stent and elastic external membrane (EEM) cross-sectional areas (CSA) were measured within the stent.<sup>18</sup> The proximal and distal stent edge was the most proximal and distal image CSA, respectively, within the stent. Neointimal hyperplasia (NIH) was calculated as stent minus lumen measures. Volume obstruction was defined as NIH volume divided by the stent volume multiplied by 100. Peri-stent plaque CSA was calculated as EEM CSA minus stent CSA in stented segments. Volumes were calculated using Simpson's rule.

## STUDY ENDPOINTS

The IVUS endpoints were in-stent NIH percentage volume and in-stent NIH volume. The angiographic endpoint was in-stent late lumen loss at 10-month follow-up. Secondary angiographic endpoints included the percentage stenosis at angiographic follow-up, the rate of restenosis (stenosis of more than 50 percent of the luminal diameter), and the in-stent minimal luminal diameter.

## STATISTICAL ANALYSIS

The statistical analysis was carried out using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as counts and percentages and compared by the Pearson Chi-Square test or the Fisher exact test. For continuous variables with a normal distribution, the mean ±1SD was reported. For variables not normally distributed, the median and interquartile 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) for the primary and secondary endpoints of interest are presented. The sample size calculation was based upon an estimated intima volume obstruction of 3% in the SES group and 8.5% in the ZES group with a SD of 10%, alpha error of 0.05, and a power of 80%. Thus, a minimum of 102 patients was pre-specified for enrolment. IVUS and angiographic data will only be available for patients returning for follow-up IVUS after 10 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. 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.

## Results

### CLINICAL CHARACTERISTICS

We randomised 127 patients to SES (n=61) or ZES implantation (n=66). Follow-up angiogram and IVUS were not performed for clinical or technical reasons in 22 patients (17.3%) (SES n=13; ZES n=9, p=NS): (i) one patient had a definite stent thrombosis after 135 days (ZES group) and target lesion revascularisation without IVUS, (ii) three patients died (ZES group; n=2 [one cardiac] and SES group; n=1) and (iii) six patients had only angiography performed at follow-up. Finally, eighteen patients declined to have the 10 month follow-up examination performed (SES group; n=12, ZES group; n=6) (**Figure 1**). Thus, follow-up angiograms were available in 105 (83%) patients (SES: n=48, ZES: n=57). The time interval between the index procedure and the follow-up did not differ significantly between the two groups SES 309.6±29.0 days vs. ZES 310.4±34.7 days, p=ns. The baseline characteristics of the completers were comparable to those not evaluated by IVUS and QCA at 10-month follow-up. Also, the baseline characteristics did not differ significantly between patients enrolled and not enrolled in the DiabeDES III sub study. Baseline clinical features 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. Number of treated vessels was also similar; rate of predilation did not differ significantly between the SES- and the ZES-treated patients. In both groups, one fourth of the patients were treated with glycoprotein IIb/IIIa inhibitor at the index procedure.

### ANGIOGRAPHIC OUTCOMES

Angiographic measures are shown in **Table 3**; angiographic follow-up was obtained for 105 patients (83%), at a mean of 313.1±41.6 days. The angiographic primary endpoint, late luminal loss was smaller in the SES group (0.14±0.37 mm vs. 0.74±0.45mm, p<0.001) than in the ZES group. Also, the percentage stenosis at

**Table 1. Clinical characteristics.**

	SES	ZES	p-value
Number	61	66	
Male gender, n (%)	46 (78.0)	46 (67.6)	0.194
Age, years	63.1±10.9	63.2±9.2	0.988
Indication			0.910
Stable angina pectoris, n (%)	36 (61.0)	42 (61.8)	
Non-ST-segment elevation MI / unstable angina pectoris, n (%)	19 (32.2)	23 (33.8)	
ST-segment elevation MI n (%)	2 (3.4)	2 (2.9)	
Other, n (%)	2 (3.4)	1 (1.8)	
Insulin treatment, n (%)	13 (21.3)	22 (33.3)	0.130
Oral treatment, n (%)	44 (72.1)	40 (60.6)	0.170
Previous PCI, n (%)	13 (23.6)	19 (29.2)	0.490
Haemoglobin A1c (%)	7.1±1.4	7.3±1.9	0.738
Previous CABG, n (%)	3 (5.7)	3 (4.7)	0.812
Previous MI, n (%)	13 (24.1)	20 (30.8)	0.417
Hypertension, n (%)	45 (78.9)	50 (76.9)	0.788
Lipid lowering treatment, n (%)	47 (82.5)	59 (90.8)	0.175
Body mass index (kg/m <sup>2</sup> )	30.6±5.6	29.0±5.5	0.122
Smoking, n (%)	16 (32.0)	23 (37.1)	0.574

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; MI: myocardial infarction

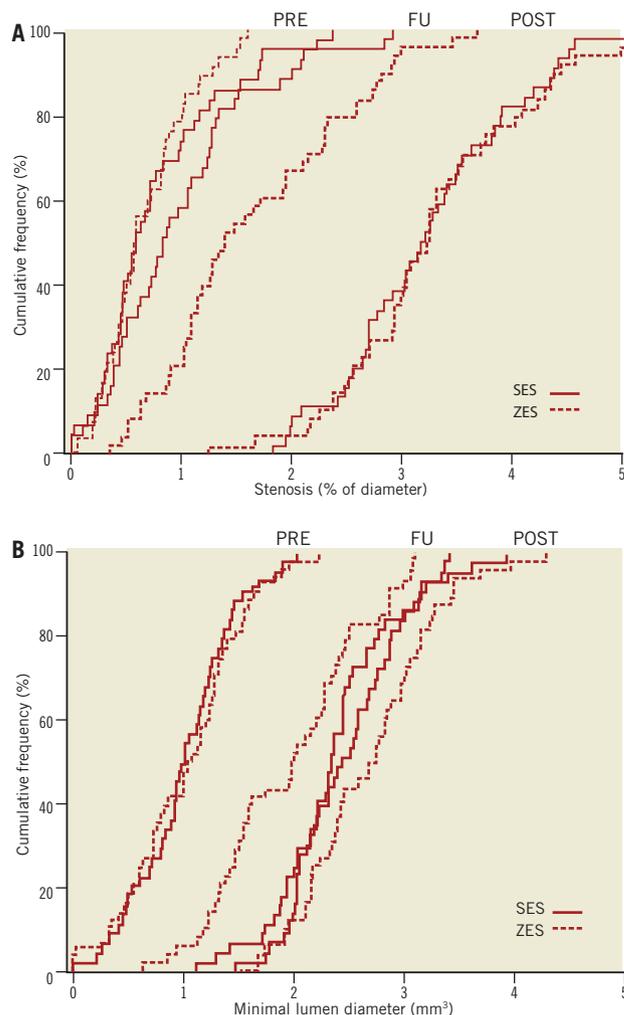
**Table 2. Lesion and procedural characteristics.**

	SES (n=61)	ZES (n=66)	p-value
Number of treated lesions per patient			0.193
1	40 (67.8)	49 (72.1)	
2	10 (16.9)	14 (20.6)	
≥3	7 (15.3)	5 (7.4)	
Predilatation – no (%)	41 (67.2)	45 (68.2)	0.907
Lesion type B2/C (%)	30 (50.8)	35 (51.5)	0.994
GP IIb/IIIa inhibitors – no (%)	14 (23.7)	16 (23.5)	0.979
Number of stents per patient (n)	2.1±1.2	1.8±1.4	0.663
No. of stents per study lesion	1.3±0.7	1.3±0.5	0.902
Lesion length – mm	17.5±11.4	17.0±10.7	0.795
Stent length – mm	21.8±12.7	21.0±11.0	0.712
Study vessel (%)			0.293
LAD	22 (44.0)	23 (39.0)	
LCX	11 (22.0)	8 (13.6)	
RCA	17 (34.0)	28 (47.5)	

follow-up was reduced (18.9±13.9% in the SES group vs. 32.9±17.0% in the ZES group; p<0.001). The rate of restenosis, defined as luminal diameter stenosis of more than 50 percent, was 4.1% (n=2) in the SES group vs. 17.9% (n=10) in the ZES group (p=0.027). Cumulative distribution curves demonstrated a reduction in the degree of minimal lumen diameter (Figure 2) and stenosis (Figure 2) in the SES group as compared to the ZES group. Distributions were similar at baseline and immediately after stent

**Table 3. Quantitative coronary angiography results: baseline and 10-month follow-up.**

	SES (n=48)	ZES (n=57)	p-value
Before intervention			
Reference vessel diameter (mm)	2.82±0.52	2.90±0.53	0.483
Minimal lumen diameter (mm)	1.00±0.46	1.01±0.52	0.924
Diameter stenosis (%)	64.2±15.6	65.1±16.8	0.796
Post-procedure			
Reference vessel diameter (mm)	2.94±0.51	3.08±0.57	0.204
Minimal lumen diameter (mm)	2.50±0.52	2.70±0.59	0.084
Diameter stenosis (%)	14.8±11.4	12.6±8.4	0.297
Follow-up, 10-month			
Reference vessel diameter (mm)	2.92±0.48	2.91±0.55	0.915
Minimal lumen diameter (mm)	2.36±0.53	1.96±0.65	0.002
Diameter stenosis (%)	18.9±13.9	32.9±17.0	<0.001
Late lumen loss (mm)	0.14±0.37	0.74±0.45	<0.001



**Figure 2. Cumulative distribution curve of (A) diameter stenosis before procedure, post-procedure and at follow-up, (B) minimal lumen diameter before procedure, post-procedure and at 10-month follow-up.**

placement. At follow-up, the distribution in the SES group was similar to the distribution immediately after stenting.

### IVUS MEASUREMENTS

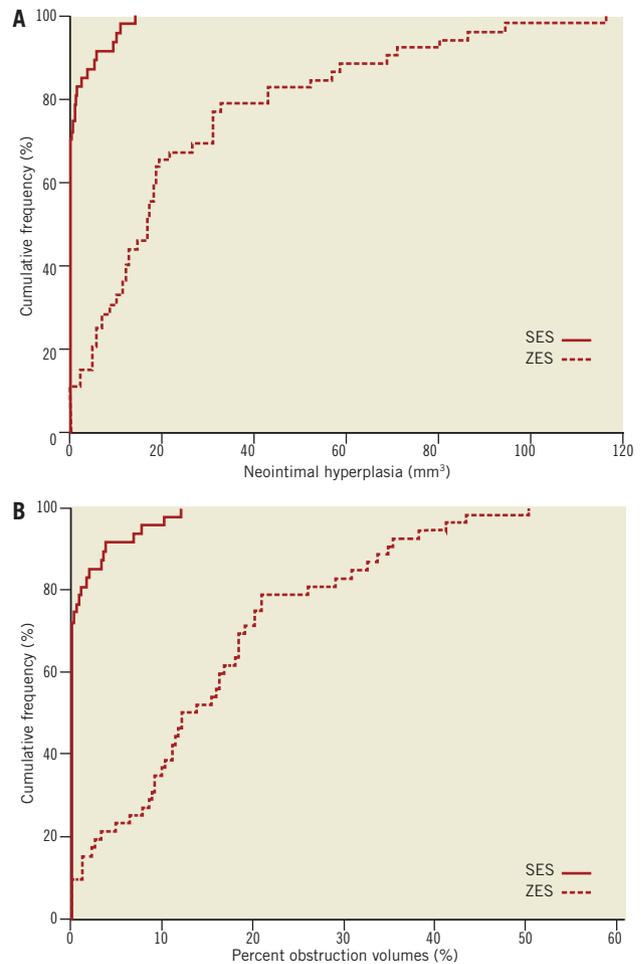
Intravascular ultrasound volumetric measures for patients with 10-month follow-up IVUS are shown in **Table 4**. Ten-month EEM, stent and lumen volumes were similar in the two groups.

At 10-month follow-up no NIH could be detected in 33 (70%) of the SES compared with four (7.5%) of the ZES ( $p<0.001$ ) patients. NIH volume (median interquartile range [IQR]: 0.0 mm<sup>3</sup> [0.0-1.2] vs. 16.5 mm<sup>3</sup> [6.2-31.1],  $p<0.001$ ), mean difference  $-23.6$  mm<sup>3</sup> (95% confidence interval [CI]:  $-31.5$  to  $-15.8$ ),  $p<0.001$  and intimal volume obstruction (median [IQR]: 0.0% [0.0-0.7] vs. 13.0% [6.7-20.8],  $p<0.001$ ) mean difference  $-14.7\%$  (95% CI:  $-18.4$  to  $-10.9$ ),  $p<0.001$  were significantly lower in SES compared with ZES (**Figure 3**). For insulin treated diabetic patient NIH volume (median IQR: 0.0% [0.0-1.9] vs. 16.4% [2.6-32.0],  $p<0.01$ ) and volume obstruction (0.0% [0.0-1.0] vs. 13.8% [1.8-24.7],  $p<0.01$ ) were significantly lower in SES treated patients. The same was seen in non-insulin treated diabetic patients where NIH volume (median IQR: 0.0% [0.0-0.4] vs. 16.5% [7.8-31.0],  $p<0.01$ ) and volume obstruction (0.0% [0.0-0.3] vs. 12.1% [8.6-20.6],  $p<0.01$ ) were significantly lower in SES compared to ZES treated patients.

At 10-month follow up incomplete stent apposition was observed in eight lesions (7.6%) (SES:  $n=5$  [10.4%], ZES:  $n=3$  [5.3%];  $p=0.68$ ). Incomplete stent apposition was seen in two patients presenting with STEMI (SES  $n=1$  and ZES  $n=1$ ) and two patients presenting with acute coronary syndrome (SES  $n=1$  and ZES  $n=1$ ) and the rest of the patients were treated for stable angina pectoris. Incomplete appositioned stent struts were not covered with neointimal hyperplasia.

### PATTERNS OF NIH DISTRIBUTION

NIH was covering  $7.6\pm 15.5\%$  of the stent length in the SES group compared to  $62.3\pm 31.9\%$  in the ZES stents ( $p<0.001$ ) (median interquartile range: 0.0% [0.0-12.5] vs. 69.5% [35.7-92.3],  $p<0.001$ ) mean difference  $-54.6\%$  (95% CI:  $-64.9$  to  $-44.4$ ),  $p<0.001$ . Evaluating only stents with NIH,  $27.1\pm 18.3\%$  of the stent length in the SES treated patients compared to  $67.5\pm 27.3\%$  in the ZES treated patients ( $p<0.001$ ) were covered. 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 Endeavor stents compared with Cypher stents (44.4% vs. 7.1%,  $p<0.001$ ). The mean per cent NIH volume at the most proximal stent CSA was 16.7% in the Endeavor stent group compared with 0.8% in the Cypher stent group mean difference  $-15.4\%$  (95% CI  $-31.9$  to 0.16),  $p=0.052$ . At the distal stent edge NIH was more often seen in Endeavor stents compared with Cypher stents (33.3% vs. 4.8%,  $p<0.001$ ). The mean percent NIH volume at the most distal stent CSA was 16.7% in the Endeavor stent group compared with 0.8% in the Cypher stent group (mean difference  $-9.5\%$  [95% CI  $-14.6$  to  $-4.3$ ],  $p<0.001$ ). **Figure 4** demonstrates an example with diffuse intima hyperplasia involving the proximal stent edge.



**Figure 3.** Cumulative distribution curve of (A) in-stent intimal hyperplasia volume at 10-month follow up, (B) percentage neointimal hyperplasia volume obstruction at 10-month follow-up.

### CLINICAL EVENTS

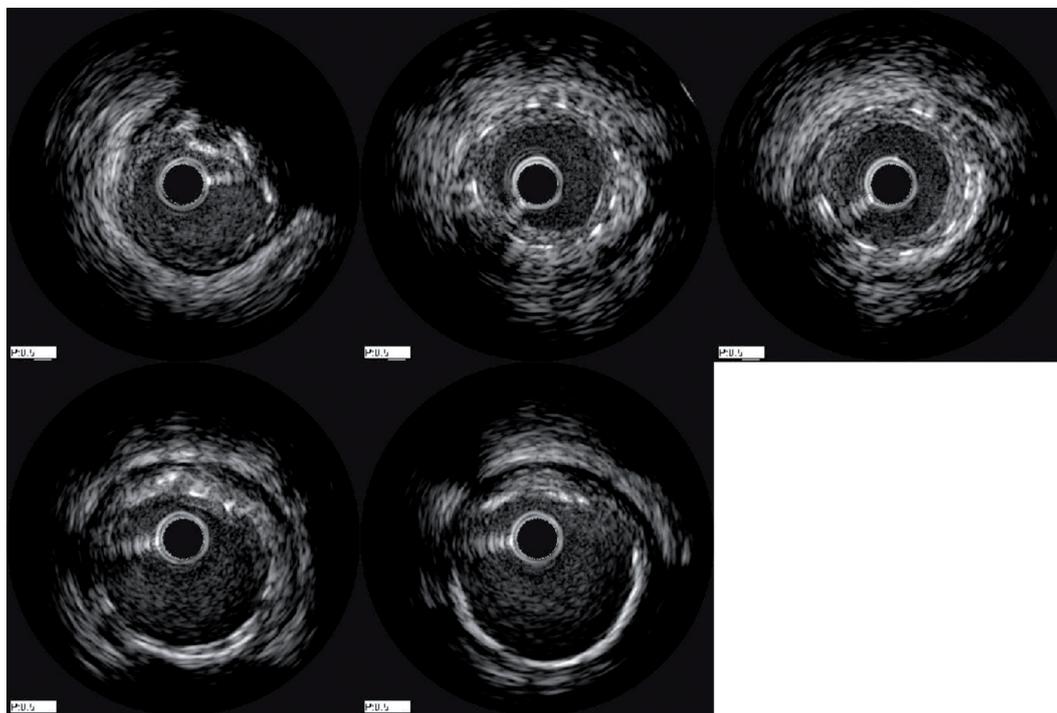
Ten-month clinical outcome were available in all patients ( $n=127$ , 100%). The incidence of major adverse cardiac events was low and did not differ in the two groups (**Table 5**). There was one definite stent thrombosis in the ZES group after 135 days. Three patients died during the follow-up period. One death was cardiac after 245 days, and thus a possible stent thrombosis.

### Discussion

This is the first randomised multicentre angiographic and IVUS comparison of the SES versus the ZES in diabetic patients. We found that the NIH response differed between SES-treated and ZES-treated patients. Thus, the ZES generated more NIH, had more angiographic late lumen loss, and higher diameter stenosis at follow up compared to the SES.

### ANGIOGRAPHIC LATE LUMEN LOSS

In-stent late lumen loss reflects the degree of neointima formation and has been shown to correlate with development of restenosis



**Figure 4.** Example of in-stent intimal hyperplasia in an Endeavor stent: (1) proximal reference segment; (2) proximal stent edge with intimal hyperplasia; (3) mid stent with intimal hyperplasia; (4) distal stent edge; (5) distal reference segment.

**Table 4. Volumetric intravascular ultrasound measurements at 10-month follow-up.**

	SES (n=46)	ZES (n=53)	p-value
Follow up, 10-month			
EEM (mm <sup>3</sup> )	365 ±251	350±179	0.724
Stent (mm <sup>3</sup> )	151±96	153±81	0.905
Lumen (mm <sup>3</sup> )	146±94	124±66	0.167
Peri-stent plaque (mm <sup>3</sup> )	214±163	196±116	0.536
NIH (mm <sup>3</sup> )			
Mean (SD)	1.5±3.3	25.1±27.0	<0.001
Median (inter-quartile range)	0.0 (0.0 – 1.2)	16.5 (6.2-31.1)	<0.001
Volume obstruction (%)			
Mean (SD)	1.2±2.7	15.8±12.6	<0.001
Median (inter-quartile range)	0.0 (0.0-0.7)	13.0 (6.7-20.8)	<0.001
Incomplete stent apposition n,(%)	5 (10.4)	3 (5.3)	0.321
EEM: external elastic membrane; NIH: neointimal hyperplasia			

after DES implantation<sup>19,20</sup>. In terms of late lumen loss, previous randomised angiographic studies in diabetic patients have shown a significant advantage in SES-treated patients compared to PES-treated patients.<sup>9-12</sup> Similarly, the present study documented superiority of SES to ZES. In the ENDEAVOR II trial,<sup>21</sup> the in-stent late lumen loss was 0.61±0.46 mm in the ZES-treated diabetic and non-diabetic patients, which is less than the 0.74±0.45 mm we found in

**Table 5. Clinical events at 10-month follow-up.**

	SES (n=61)	ZES (n=66)	p-value
Death (all cause)	1	2	
Cardiac death	0	1	
Definite stent thrombosis	0	1	
Probable stent thrombosis	0	0	
Possible stent thrombosis	0	1	
Myocardial infarction	0	1	
ST-segment elevation MI	0	1	
Non-ST-segment elevation MI	0	0	
Target lesion revascularisation	0	1	
PCI	0	1	
CABG	0	0	
Number of patients with MACE	1	3	0.382
MACE denotes major adverse cardiac events and includes cardiac death, myocardial infarction, stent thrombosis, and target lesion revascularisation before the 10 months scheduled angiographic and IVUS follow up. Eight patients had PCI TLR at the follow-up day after the IVUS acquisition (SES n=2 [4.4%] vs. ZES n=6 [11.3%], p=0.215).MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting			

our ZES-treated diabetic population. In the ENDEAVOR III trial,<sup>22</sup> where only 30% of the patients had diabetes mellitus, the in-stent late lumen loss was 0.34±0.44 showing that diabetic patients have more late lumen loss than non-diabetic Endeavor stent treated patients.

## INHIBITORY EFFECT ON NEOINTIMAL HYPERPLASIA

The SES showed a significant inhibition of NIH compared with the ZES. No NIH could be detected by IVUS in 70% of the SES compared with 7.5% of the ZES. NIH is the main component of in-stent restenosis after stent implantation and reflects the degree of neointimal proliferation.<sup>23</sup> In the first DiabeDES trial<sup>13</sup>, where we compared the vascular response after SES or PES implantation; 24% of the Taxus stents were free from NIH and the median volume obstruction in PES was 7.5% compared to 13.0% in the ZES group in the present study. In SES treated patients the median volume obstruction was zero in both trials.<sup>13</sup>

The percent intimal free length of the stents, a measure of NIH homogeneity, measured 92.4% in the SES group compared to 37.7% in the ZES group. The NIH findings in the present study is concordant with the ENDEAVOR II<sup>24</sup>, III<sup>25,26</sup> and IV<sup>27</sup> studies where percent NIH volume obstruction was 17.6%, 16.1% and 16.6%, respectively. In the TAXUS-I<sup>28</sup>, TAXUS-II<sup>29,30</sup> and TAXUS-IV<sup>30</sup> studies including diabetic and non-diabetic patients the NIH volume obstruction was 14.8%, 7.8% and 12.2%, respectively. In earlier IVUS studies the SES has been characterised by a near absence of measurable in-stent tissue<sup>23,31</sup> after long term follow-up.<sup>32</sup> The diabetic subpopulation in the RAVEL study<sup>33</sup>, the SES treated patients in the DIABETES Trial<sup>34</sup>, and the first DiabeDES trial showed a low percent IH volume obstruction, similar to the SES patients of the present study.<sup>13</sup>

The rate of clinical endpoints was low in both groups. A recent report from the Swedish Angiography and Angioplasty Registry<sup>35</sup> showed that clinical restenosis in diabetic patients were twice as frequent in ZES than in the other DES types, in line with our finding of increased late lumen loss in after ZES implantation.

## Limitations

Our randomised study requires scrutiny for using a surrogate endpoint for testing the efficacy of two different DES without being powered for clinical endpoints. Only percent NIH volume can be determined by follow-up IVUS. Percent NIH volume is a measure of efficacy, as detection of incomplete stent apposition; peri-stent remodelling and edge effects would require both post-implantation and follow-up IVUS. Angiographic in-stent late lumen loss, which was used, also only covers the stented segment and not the stent edges. A long term study with clinical follow up is needed in diabetic patients to confirm whether the differences in NIH translate into clinical outcome.

## Conclusions

In diabetic patients, SES inhibited intima hyperplasia and reduced angiographic late lumen loss more effectively than the ZES.

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data collection, analysis, or interpretation. Neither had access to the clinical trial database or the opportunity to review the manuscript.

## Conflict of interest statement

The authors have no conflict of interest to declare.

## References

1. Abizaid A, Kornowski R, Mintz GS, Hong MK, Abizaid AS, Mehran R, Pichard AD, Kent KM, Satler LF, Wu H, Popma JJ, Leon MB. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol* 1998;32:584-589.
2. Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. *JAMA* 2005;293:1501-1508.
3. Kornowski R, Mintz GS, Kent KM, Pichard AD, Satler LF, Bucher TA, Hong MK, Popma JJ, Leon MB. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. *Circulation* 1997;95:1366-1369.
4. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, Midwall J, Simonton CA, Keim E, Wang P, Kuntz RE, Moses JW. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolimus-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 2004;109:2273-2278.
5. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, Gomez-Hospital JA, Alfonso F, Hernandez-Antolin R, Goicolea J, Banuelos C, Escaned J, Moreno R, Fernandez C, Fernandez-Aviles F, Macaya C. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation* 2005;112:2175-2183.
6. Hermiller JB, Raizner A, Cannon L, Gurbel PA, Kutcher MA, Wong SC, Russell ME, Ellis SG, Mehran R, Stone GW. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45:1172-1179.
7. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 1998;32:1866-1873.
8. Kornowski R, Mintz GS, Kent KM, Pichard AD, Satler LF, Bucher TA, Hong MK, Popma JJ, Leon MB. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. *Circulation* 1997;95:1366-1369.
9. Dibra A, Kastrati A, Mehilli J, Pache J, Schühlen H, von BN, Ulm K, Wessely R, Dirschinger J, Schomig A. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005;353:663-670.
10. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, Hong MK, Rhee KS, Chae JK, Ko JK, Park JH, Lee JH, Choi SW, Jeong JO,

- Seong IW, Cho YH, Lee NH, Kim JH, Chun KJ, Kim HS, Park SJ. A randomized comparison of sirolimus- versus Paclitaxel-eluting stent implantation in patients with diabetes mellitus. *J Am Coll Cardiol* 2008;52:727-733.
11. Maeng M, Jensen LO, Galloe AM, Thayssen P, Christiansen EH, Hansen KN, Helqvist S, Botker HE, Lassen JF, Thuesen L. 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;103:345-349.
  12. Tomai F, Reimers B, De LL, Galassi AR, Gaspardone A, Ghini AS, Ferrero V, Favero L, Gioffre G, Prati F, Tamburino C, Ribichini F. Head-to-head comparison of sirolimus- and paclitaxel-eluting stent in the same diabetic patient with multiple coronary artery lesions: a prospective, randomized, multicenter study. *Diabetes Care* 2008;31:15-19.
  13. Jensen LO, Maeng M, Thayssen P, Christiansen EH, Hansen KN, Galloe A, Kelbaek H, Lassen JF, Thuesen L. Neointimal hyperplasia after sirolimus-eluting and paclitaxel-eluting stent implantation in diabetic patients: the Randomized Diabetes and Drug-Eluting Stent (DiabeDES) Intravascular Ultrasound Trial. *Eur Heart J* 2008;29:2733-2741.
  14. Billinger M, Beutler J, Taghetchian KR, Remondino A, Wenaweser P, Cook S, Togni M, Seiler C, Stettler C, Eberli FR, Luscher TF, Wandel S, Juni P, Meier B, Windecker S. Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients. *Eur Heart J* 2008;29:718-725.
  15. 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;105:64-68.
  16. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, Abildgaard U, Christiansen EH, Engstrom T, Krusell LR, Ravkilde J, Hansen PR, Hansen KN, Abildstrom SZ, Aaroe J, Jensen JS, Kristensen SD, Botker HE, Madsen M, Johnsen SP, Jensen LO, Sorensen HT, Thuesen L, Lassen JF. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet* 2010;375:1090-1099.
  17. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-2351.
  18. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:1478-1492.
  19. 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;112:2833-2839.
  20. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. *Circulation* 2005;111:3435-3442.
  21. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006;114:798-806.
  22. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG, Badre SS, Mauri L, Thompson KP, LeNarz LA, Kuntz RE. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2006;48:2440-2447.
  23. Popma JJ, Leon MB, Moses JW, Holmes DR, Jr., Cox N, Fitzpatrick M, Douglas J, Lambert C, Mooney M, Yakubov S, Kuntz RE. Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. *Circulation* 2004;110:3773-3780.
  24. Sakurai R, Hongo Y, Yamasaki M, Honda Y, Bonneau HN, Yock PG, Cutlip D, Popma JJ, Zimetbaum P, Fajadet J, Kuntz RE, Wijns W, Fitzgerald PJ. Detailed intravascular ultrasound analysis of Zotarolimus-eluting phosphorylcholine-coated cobalt-chromium alloy stent in de novo coronary lesions (results from the ENDEAVOR II trial). *Am J Cardiol* 2007;100:818-823.
  25. Miyazawa A, Ako J, Hongo Y, Hur SH, Tsujino I, Courtney BK, Hassan AH, Kandzari DE, Honda Y, Fitzgerald PJ. Comparison of vascular response to zotarolimus-eluting stent versus sirolimus-eluting stent: intravascular ultrasound results from ENDEAVOR III. *Am Heart J* 2008;155:108-113.
  26. Sakurai R, Bonneau HN, Honda Y, Fitzgerald PJ. Intravascular ultrasound findings in ENDEAVOR II and ENDEAVOR III. *Am J Cardiol* 2007;100:71M-76M.
  27. Waseda K, Miyazawa A, Ako J, Hasegawa T, Tsujino I, Sakurai R, Yock PG, Honda Y, Kandzari DE, Leon MB, Fitzgerald PJ. Intravascular ultrasound results from the ENDEAVOR IV trial: randomized comparison between zotarolimus- and paclitaxel-eluting stents in patients with coronary artery disease. *JACC Cardiovasc Interv* 2009;2:779-784.
  28. Grube E, Silber S, Hauptmann KE, Buellesfeld L, Mueller R, Lim V, Gerckens U, Russell ME. Two-year-plus follow-up of a paclitaxel-eluting stent in de novo coronary narrowings (TAXUS I). *Am J Cardiol* 2005;96:79-82.
  29. Serruys PW, Degertekin M, Tanabe K, Russell ME, Guagliumi G, Webb J, Hamburger J, Rutsch W, Kaiser C, Whitbourn R, Camenzind E, Meredith I, Reeves F, Nienaber C, Benit E, Disco C, Koglin J, Colombo A. Vascular responses at proximal and distal edges of paclitaxel-eluting stents: serial intravascular ultrasound analysis from the TAXUS II trial. *Circulation* 2004;109:627-633.
  30. Weissman NJ, Koglin J, Cox DA, Hermiller J, O'Shaughnessy C,

- Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Kutcher M, Wong SC, Strickland W, Mooney M, Russell ME, Ellis SG, Stone GW. Polymer-based paclitaxel-eluting stents reduce in-stent neointimal tissue proliferation: a serial volumetric intravascular ultrasound analysis from the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45:1201-1205.
31. Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, Guagliumi G, Wijns W, Lindeboom WK, Ligthart J, de Feyter PJ, Morice MC. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RANDOMIZED study with the sirolimus-eluting VELOCITY balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. *Circulation* 2002;106:798-803.
32. Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW, Sousa AG. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation* 2005;111:2326-2329.
33. Abizaid A, Costa MA, Blanchard D, Albertal M, Eltchaninoff H, Guagliumi G, Geert-Jan L, Abizaid AS, Sousa AG, Wuelfert E, Wietze L, Sousa JE, Serruys PW, Morice MC. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Insights from the RAVEL Trial. *Eur Heart J* 2004;25:107-112.
34. Jimenez-Quevedo P, Sabate M, Angiolillo DJ, Costa MA, Alfonso F, Gomez-Hospital JA, Hernandez-Antolin R, Banuelos C, Goicolea J, Fernandez-Aviles F, Bass T, Escaned J, Moreno R, Fernandez C, Macaya C. Vascular effects of sirolimus-eluting versus bare-metal stents in diabetic patients: three-dimensional ultrasound results of the Diabetes and Sirolimus-Eluting Stent (DIABETES) Trial. *J Am Coll Cardiol* 2006;47:2172-2179.
35. Frobert O, Lagerqvist B, Carlsson J, Lindback J, Stenstrand U, James SK. Differences in restenosis rate with different drug-eluting stents in patients with and without diabetes mellitus: a report from the SCAAR (Swedish Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2009;53:1660-1667.