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# Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients

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**Aims** Percutaneous coronary intervention (PCI) in diabetic patients is associated with an increased risk of restenosis and major adverse cardiac events (MACE). We assessed the impact of diabetes on long-term outcome after PCI with sirolimus-eluting (SES) and paclitaxel-eluting (PES) stents.

**Methods and results** In the SIRTAX trial, 1012 patients were randomized to treatment with SES ($n = 503$) or PES ($n = 509$). A stratified analysis of outcomes was performed according to the presence or absence of diabetes. Baseline characteristics were well balanced between SES and PES in patients with ($N = 201$) and without diabetes ($N = 811$). Clinical outcome was worse in diabetic compared with non-diabetic patients regarding death (9.0% vs. 4.1%, $P = 0.004$) and MACE (defined as cardiac death, myocardial infarction, or TLR; 19.9% vs. 12.7%, $P = 0.007$) at 2 years. Among diabetic patients, SES reduced MACE by 47% (14.8% vs. 25.8%, HR = 0.52, $P = 0.05$) and TLR by 61% (7.4% vs. 17.2%, HR = 0.39, $P = 0.03$) compared with PES at 2 years.

**Conclusion** Diabetic patients have worse prognosis than non-diabetic patients undergoing PCI with DES. Among the diabetic patient population of this trial, SES reduce repeat revascularization procedures and MACE more effectively than PES and to a similar degree as in non-diabetic patients.

**Keywords** Coronary disease • Stents • Drugs • Restenosis • Diabetes

## Introduction

Percutaneous coronary intervention (PCI) in diabetic patients is associated with an increased risk of adverse clinical outcome compared with those without diabetes.[1–4] Recently, a meta-analysis of four trials comparing sirolimus-eluting stents (SES) with bare metal stents (BMS) suggested an increased risk of mortality with SES, although event rates were unusually low in the BMS group.[5] Diabetic patients are also at increased risk of restenosis. Angiographic and ultrasonic studies suggest a higher degree of late loss (LL)[1] and neointimal hyperplasia[6] in diabetic compared with non-diabetic patients as potential mechanism underlying this phenomenon. In addition, diabetic patients tend to have smaller vessels,[7,8] and vessel size remains an important predictor of restenosis even in the era of drug-eluting stents (DES).[9,10]

SES[5,11–13] and paclitaxel-eluting stents (PES)[14–19] markedly reduce angiographic and clinical measures of restenosis compared with BMS in patients with and without diabetes. However, the relative efficacy of SES and PES in diabetic patients remains unclear. Several registries comparing SES and PES in diabetic patients revealed no differences in outcome regarding restenosis and repeat revascularization procedures.[20–23] A recent systematic

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review of 10 randomized trials indirectly comparing SES with PES reported superior outcome regarding restenosis and major adverse cardiac events (MACE) with SES in non-diabetic patients, whereas there was no difference between both stent types in diabetic patients.[24] One dedicated randomized trial directly comparing SES and PES in 250 diabetic patients observed significantly lower LL and restenosis in favour of SES,[25] but the study was not powered to detect differences in clinical outcome.

The objective of the present study was to evaluate the long-term clinical outcome of patients stratified according to diabetic status, which was a pre-specified stratified analysis of the randomized SIRTAX trial.[26]

# Methods

## Patient population and intervention

The design of the SIRTAX trial has been previously reported.[26] It was an observer blind, randomized controlled trial comparing safety and efficacy of SES and PES in 1012 patients undergoing PCI. Eligible patients had a history of stable angina or acute coronary syndrome and presented with at least one lesion with a diameter stenosis $\geq$50% in a vessel with a reference vessel diameter (RVD) between 2.25 and 4.00 mm suitable for stent implantation. There were no limitations on the number of treated lesions and vessels, or lesion length. The study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the institutional ethics committees at the University Hospitals of Bern and Zurich, Switzerland. All patients provided written informed consent.

Patients were randomly assigned on a 1 : 1 basis to treatment with SES (Cypher®; Cordis) or PES (Taxus®, Boston Scientific). Before or at the time of the procedure, patients received at least 100 mg of aspirin, a 300 mg loading dose of clopidogrel, and unfractionated heparin (70–100 U/kg of body weight). After the procedure, all patients were advised to maintain aspirin lifelong, and clopidogrel therapy was prescribed for 12 months irrespective of stent type.

## Study endpoints and definitions

Adverse events were assessed in hospital, at 1, 6, and 9 months, 1 and 2 years. An independent clinical events committee unaware of the patients' treatment assignments adjudicated all endpoints.

The pre-specified primary endpoint was a composite of MACE, defined as cardiac death, myocardial infarction (MI), or ischaemia-driven revascularization of the target lesion at 9 months. Secondary endpoints included ischaemia-driven TLR, TVR, or target-vessel failure (TVF). TLR and TVR were considered to be driven by ischaemia if the stenosis of the target lesion or vessel was $\geq$50% on the basis of quantitative coronary angiography in the presence of ischaemic signs or symptoms, or if there was a stenosis of $\geq$70% in the absence of ischaemic signs or symptoms. TLR was defined as a repeated revascularization based on a stenosis within the stent or within the 5 mm borders proximal or distal to the stent. The diagnosis of periprocedural MI was established whenever new Q-waves of at least 0.4 s duration in at least two contiguous leads appeared on the electrocardiogram with an elevated creatine kinase MB fraction level, or in the absence of pathological Q waves, an elevation in creatine kinase levels to more than twice the upper limit of normal with an elevated creatine kinase MB or troponin I level. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either target vessel occlusion or thrombus within or adjacent to the previously successfully stented segment.

Angiographic core laboratory analysis was performed as previously described by angiogram readers unaware of the type of stent implanted.[26] Quantitative measurements included RVD, minimal luminal diameter (MLD), and % diameter stenosis.

## Statistical analysis

We pre-specified stratified analysis of the primary outcome according to the presence or absence of diabetes. All randomized patients were included in the analysis of primary and secondary clinical outcomes in the groups to which they were originally allocated to (intention-to-treat principle). Baseline characteristics were compared between diabetic and non-diabetic patients using $\chi^2$ test without taking into account the random allocation to SES or PES. We used a Cox proportional-hazards model to compare clinical outcomes between the groups. *P*-values for differences in clinical outcomes between diabetic and non-diabetic patients were derived from Cox proportional hazard models adjusted for treatment allocation. To determine whether there was an interaction between treatment effect and diabetic status, we used likelihood ratio tests. Analyses were performed in Stata 9.2 (Stata, Inc., College Station, TX, USA). No adjustments were made for multiple comparisons in secondary analyses; *P*-values are two-sided with a significance level of 0.05.

# Results

## Baseline clinical, angiographic, and procedural data

A total of 1012 patients were randomized to treatment with SES (503 patients with 694 lesions) and PES (509 patients with 715 lesions). Two hundred and one patients (20%) with 292 lesions were diabetic, of whom 43 patients (21.4%) required insulin. Among diabetic patients, 108 patients with 158 lesions received SES, whereas 93 patients with 134 lesions received PES.

Baseline clinical variables were well balanced between SES and PES in both, diabetic and non-diabetic patients (*Table 1*). Patients with diabetes compared with those without diabetes were older ($P < 0.001$), more commonly hypertensive ($P < 0.001$), more often female ($P = 0.01$), and had a higher rate of multivessel disease ($P = 0.05$). Previous MI ($P = 0.06$) tended to be more prevalent, whereas smoking ($P < 0.001$) was less frequent in diabetic than in non-diabetic patients. Target lesion location and angiographic lesion characteristics at baseline revealed no significant differences between SES and PES in diabetic and non-diabetic patients (*Table 2*). Procedural and angiographic results are summarized in Table *3*, showing similar outcome in SES- and PES-treated diabetic and non-diabetic patients. Clinical outcomes were obtained for 1007 (99.5%) of the 1012 randomized patients during 2 years of follow-up. Five patients lost to follow-up all belonged to the PES group, three patients were lost during the first and two patients during the second year.

## Clinical outcomes

Clinical events at 2-year follow-up stratified for diabetic status are summarized in Table *4*. Rates of death (9.0% vs. 4.1%, $P = 0.004$), cardiac death (7.0% vs. 2.1%, $P < 0.001$), target lesion

**Table 1 Baseline clinical characteristics**

| | Diabetic patients | | Non-diabetic patients | | *P*-value |
|---|---|---|---|---|---|
| | SES | PES | SES | PES | |
| Total (*n*) | 108 | 93 | 395 | 416 | |
| Age≥65 years [*n* (%)] | 62 (57.4) | 59 (63.4) | 155 (39.2) | 166 (39.9) | <0.001 |
| Males [*n* (%)] | 75 (69.4) | 67 (72.0) | 307(77.7) | 332 (79.8) | 0.01 |
| Hypertension [*n* (%)] | 86 (79.6) | 76 (81.7) | 216 (54.7) | 244 (58.7) | <0.001 |
| Hyperlipidaemia [*n* (%)] | 71 (65.7) | 52 (55.9) | 234 (59.2) | 240 (57.7) | 0.48 |
| Current smoking [*n* (%)] | 25 (23.2) | 16 (17.2) | 159 (40.3) | 165 (39.7) | <0.001 |
| Previous myocardial infarction [*n* (%)] | 38 (35.2) | 32 (34.4) | 107 (27.1) | 120 (28.9) | 0.06 |
| Stable angina pectoris [*n* (%)] | 60 (55.6) | 48 (51.6) | 186 (47.1) | 198 (47.6) | 0.11 |
| Acute coronary syndromes [*n* (%)] | 48 (44.4) | 45 (48.4) | 209 (52.9) | 218 (52.4) | 0.21 |
| Unstable angina [*n* (%)] | 6 (5.6) | 7 (7.5) | 22 (5.6) | 23 (5.5) | |
| Non-ST-elevation MI [*n* (%)] | 22 (20.4) | 23 (24.7) | 90 (22.8) | 100 (24.0) | |
| ST-elevation MI [*n* (%)] | 20 (18.5) | 15 (16.1) | 97 (24.6) | 95 (22.8) | |
| Multivessel disease [*n* (%)] | 75 (69.4) | 57 (61.3) | 225 (57.0) | 245 (58.9) | 0.05 |
| Left anterior descending coronary artery as target vessel [*n* (%)] | 57 (52.8) | 52 (55.9) | 211 (53.4) | 223 (53.6) | 0.86 |
| Small vessel disease [*n* (%)] | 57 (52.8) | 50 (53.8) | 186 (47.1) | 215 (51.7) | 0.34 |
| Long target lesion | 23 (21.3) | 19 (20.4) | 78 (19.8) | 98 (23.6) | 0.77 |

**Table 2 Baseline lesion characteristics**

| | Diabetic patients | | Non-diabetic patients | | *P*-value |
|---|---|---|---|---|---|
| | SES | PES | SES | PES | |
| Total number of lesions | 158 | 134 | 536 | 581 | |
| Target lesion coronary artery [*n* (%)] | | | | | |
| Left main | 3 (1.9) | 2 (1.5) | 8 (1.5) | 9 (1.6) | 0.82 |
| Left anterior descending | 74 (46.8) | 62 (46.3) | 250 (46.6) | 261 (44.9) | 0.82 |
| Left circumflex | 27 (17.1) | 29 (21.6) | 112 (20.9) | 110 (18.9) | 0.80 |
| Right | 52 (32.9) | 38 (28.4) | 157 (29.3) | 191 (32.9) | 0.93 |
| Bypass graft | 2 (1.3) | 3 (2.2) | 9 (1.7) | 10 (1.7) | 0.99 |
| ACC-AHA lesion class [*n* (%)] | | | | | |
| A | 29 (18.4) | 24 (17.9) | 102 (19.0) | 130 (22.4) | 0.37 |
| B1 | 70 (44.3) | 62 (46.3) | 230 (42.9) | 245 (42.2) | 0.46 |
| B2 | 37 (23.4) | 26 (19.4) | 137 (25.6) | 132 (22.7) | 0.43 |
| C | 22 (13.9) | 22 (16.4) | 67 (12.5) | 74 (12.7) | 0.35 |
| Angiographic measures | | | | | |
| Lesion length (mm ± SD) | 11.1 ± 5.4 | 11.8 ± 7.9 | 12.1 ± 7.4 | 12.5 ± 7.0 | 0.10 |
| Reference vessel diameter (mm ± SD) | 2.86 ± 0.41 | 2.74 ± 0.40 | 2.81 ± 0.40 | 2.84 ± 0.44 | 0.51 |
| Minimal lumen diameter (mm ± SD) | 0.55 ± 0.49 | 0.53 ± 0.46 | 0.52 ± 0.44 | 0.53 ± 0.42 | 0.59 |
| Stenosis (% lumen diameter ± SD) | 81.4 ± 15.0 | 80.8 ± 15.6 | 81.6 ± 15.1 | 81.3 ± 14.1 | 0.73 |

revascularization (11.9% vs. 10.0%, $P = 0.33$), and MACE (19.9% vs. 12.7%, $P = 0.007$) were higher in diabetic than in non-diabetic patients at 2 years.

Among diabetic patients, SES more effectively reduced MACE than PES (14.8% vs. 25.8%, HR = 0.52; 95% CI 0.28–0.99; $P = 0.05$) (*Figure 1A*). This difference was largely driven by a reduction in the risk of TLR in favour of SES (7.4% vs. 17.2%, HR = 0.39; 95% CI 0.17–0.90; $P = 0.03$) (*Figure 1B*). The therapeutic benefit of SES over PES in diabetic patients was maintained at 2 years of follow-up. SES compared with PES reduced rates of MACE (HR = 0.42, 95% CI 0.19–0.93, $P = 0.03$) and TLR (HR = 0.36, 95% CI 0.13–0.98, $P = 0.05$) to a similar degree in non-insulin-dependent diabetics as in non-diabetic patients. In contrast, rates of MACE were similar for SES (20.0%) and PES (23.5%) in

**Table 3** Procedural results

| | Diabetic patients | | Non-diabetic patients | | *P*-value |
|---|---|---|---|---|---|
| | SES | PES | SES | PES | |
| Total number of lesions | 158 | 134 | 536 | 581 | |
| Procedures | | | | | |
| Lesions treated per patient ($n \pm$ SD) | 1.46 ± 0.65 | 1.44 ± 0.63 | 1.36 ± 0.57 | 1.40 ± 0.59 | 0.13 |
| Stents per lesion ($n \pm$ SD) | 1.14 ± 0.45 | 1.13 ± 0.40 | 1.11 ± 0.36 | 1.16 ± 0.46 | 0.90 |
| Minimal stent diameter (mm ± SD) | 2.89 ± 0.40 | 2.80 ± 0.36 | 2.88 ± 0.37 | 2.91 ± 0.37 | 0.10 |
| Stent length per lesion (mm ± SD) | 18.5 ± 10.7 | 18.7 ± 12.1 | 18.7 ± 10.2 | 19.0 ± 10.3 | 0.71 |
| Maximal pressure (atm ± SD) | 14.4 ± 3.2 | 13.9 ± 2.7 | 14.4 ± 3.2 | 14.1 ± 2.9 | 0.65 |
| Angiographic results | | | | | |
| Final minimal lumen diameter (mm ± SD) | | | | | |
| In-stent | 2.66 ± 0.36 | 2.62 ± 0.41 | 2.65 ± 0.37 | 2.69 ± 0.38 | 0.34 |
| In-segment | 2.57 ± 0.40 | 2.55 ± 0.40 | 2.55 ± 0.41 | 2.61 ± 0.44 | 0.66 |
| Final stenosis (% of lumen diameter ± SD) | | | | | |
| In-stent | 7.57 ± 4.75 | 6.82 ± 8.24 | 7.20 ± 4.75 | 6.78 ± 4.67 | 0.58 |
| In-segment | 8.92 ± 7.47 | 8.92 ± 6.61 | 8.87 ± 7.32 | 8.26 ± 6.56 | 0.62 |
| Acute gain (mm ± SD) | | | | | |
| In-stent | 2.11 ± 0.51 | 2.09 ± 0.51 | 2.13 ± 0.52 | 2.16 ± 0.51 | 0.23 |
| In-segment | 2.10 ± 0.53 | 1.94 ± 0.57 | 2.06 ± 0.53 | 2.10 ± 0.55 | 0.33 |

**Table 4** Clinical events through 2 years stratified by diabetes

| | Diabetic patients | | | | Non-diabetic patients | | | | *P*-value for interaction* |
|---|---|---|---|---|---|---|---|---|---|
| | SES | PES | Hazard ratio (95% CI) | *P*-value | SES | PES | Hazard ratio (95% CI) | *P*-value | |
| Total number of patients (*n*) | 108 | 93 | | | 395 | 416 | | | |
| Events at 24 months [*n* (%)] | | | | | | | | | |
| Death | 9 (8.3) | 10 (10.8) | 0.75 (0.30–1.83) | 0.52 | 16 (4.1) | 17 (4.1) | 0.98 (0.50–1.95) | 0.99 | 0.62 |
| Cardiac death | 7 (6.5) | 7 (7.5) | 0.83 (0.29–2.37) | 0.73 | 6 (1.5) | 11 (2.6) | 0.57 (0.21–1.54) | 0.27 | 0.61 |
| Myocardial infarction | 2 (1.9) | 6 (6.5) | 0.28 (0.06–1.38) | 0.12 | 16 (4.1) | 18 (4.3) | 0.93 (0.48–1.83) | 0.84 | 0.15 |
| Q-wave | 0 (0.0) | 2 (2.2) | 0.17 (0.01–3.56) | 0.13 | 8 (2.0) | 5 (1.2) | 1.69 (0.55–5.16) | 0.36 | 0.14 |
| Non-Q-wave | 2 (1.9) | 4 (4.3) | 0.43 (0.08–2.33) | 0.32 | 8 (2.0) | 13 (3.1) | 0.64 (0.27–1.55) | 0.33 | 0.65 |
| Target lesion revascularization | 8 (7.4) | 16 (17.2) | 0.39 (0.17–0.90) | 0.03 | 31 (7.9) | 50 (12.0) | 0.64 (0.41–1.00) | 0.05 | 0.32 |
| Percutaneous | 6 (5.6) | 14 (15.1) | 0.33 (0.13–0.86) | 0.02 | 29 (7.3) | 44 (10.6) | 0.68 (0.42–1.08) | 0.10 | 0.19 |
| Surgical | 2 (1.9) | 4 (4.3) | 0.41 (0.08–2.25) | 0.31 | 3 (0.8) | 10 (2.4) | 0.31 (0.09–1.13) | 0.08 | 0.80 |
| Target vessel revascularization | 10 (9.3) | 17 (18.3) | 0.48 (0.22–1.05) | 0.07 | 37 (9.4) | 57 (13.7) | 0.67 (0.44–1.02) | 0.06 | 0.47 |
| Percutaneous | 8 (7.4) | 15 (16.1) | 0.41 (0.17–0.97) | 0.04 | 35 (8.9) | 51 (12.3) | 0.70 (0.46–1.08) | 0.11 | 0.28 |
| Surgical | 2 (1.9) | 4 (4.3) | 0.41 (0.08–2.25) | 0.31 | 3 (0.8) | 10 (2.4) | 0.31 (0.09–1.13) | 0.08 | 0.80 |
| Stent thrombosis | 1 (0.9) | 3 (3.2) | 0.27 (0.03–2.60) | 0.26 | 11 (2.8) | 11 (2.6) | 1.06 (0.46–2.43) | 0.94 | 0.25 |
| Major adverse cardiac events | 16 (14.8) | 24 (25.8) | 0.52 (0.28–0.99) | 0.05 | 40 (10.1) | 63 (15.1) | 0.65 (0.44–0.96) | 0.03 | 0.58 |
| Target vessel failure | 18 (16.7) | 25 (26.9) | 0.57 (0.31–1.04) | 0.07 | 44 (11.1) | 70 (16.8) | 0.64 (0.44–0.93) | 0.03 | 0.73 |
| Death, myocardial infarction, or stent thrombosis | 11 (10.2) | 16 (17.2) | 0.52 (0.22–1.19) | 0.12 | 31 (7.9) | 33 (7.9) | 1.06 (0.63–1.76) | 0.85 | 0.15 |

**P*-values for interaction relate to differences in hazard ratios between diabetic and non-diabetic patients.
Hazard ratios and *P*-values are from Cox Proportional Hazards Models.

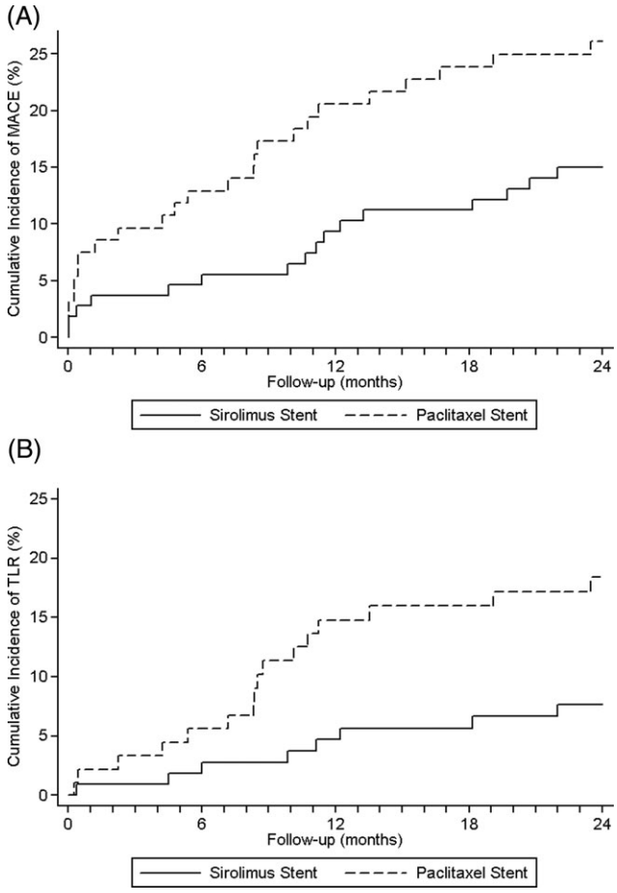


**Figure 1** Kaplan–Meier cumulative event curves of (*A*) major adverse cardiac events in patients with diabetes stratified for stent type and (*B*) target lesion revascularization in patients with diabetes stratified for stent type.

insulin-dependent diabetic patients (HR = 0.80, 95% CI 0.28–2.31, $P = 0.68$).

There were no significant differences between SES and PES in diabetics with respect to death ($P = 0.52$), cardiac death ($P = 0.73$), or MI ($P = 0.12$) at 2 years. Stent thrombosis amounted to 0.9% for SES and 3.2% for PES (HR = 0.27; 95% CI 0.03–2.60, $P = 0.25$), and the composite of death, MI, or stent thrombosis was 10.2% for SES and 17.2% for PES (HR = 0.52, 95% CI 0.22–1.19, $P = 0.12$) in diabetic patients.

Among patients without diabetes, the rates of MACE (10.4% vs. 15.1%, HR = 0.65, 95% CI 0.44–0.96; $P = 0.04$) and TLR (7.9% vs. 12.0%, HR = 0.64, 95% CI 0.41–1.00, $P = 0.05$) were lower for SES than for PES at 2 years. There were no significant differences regarding death ($P = 0.99$), cardiac death ($P = 0.27$), or MI ($P = 0.84$) during long-term follow-up. Similarly, there were no differences regarding stent thrombosis (SES: 2.8% vs. PES: 2.6%, HR = 1.06; 95% CI 0.46–2.43, $P = 0.94$) and the composite of death, MI, or stent thrombosis (SES: 7.9% vs. PES: 7.9%, HR = 1.06, 95% CI 0.63–1.76, $P = 0.85$) in non-diabetic patients. None of the tests for interaction between diabetes status and treatment effect of SES compared with PES reached conventional levels of statistical significance.

## Discussion

The principal findings of the present study can be summarized as follows.

(i) Diabetic patients have worse prognosis than non-diabetic patients undergoing PCI with DES.
(ii) SES more effectively reduce the rates of MACE and TLR than PES in diabetic patients.
(iii) The therapeutic benefit of SES over PES in diabetic patients was maintained over 2 years of follow-up.
(iv) There were no significant differences between SES and PES in diabetic patients with respect to death, cardiac death, or MI over 2 years of follow-up.

SES have been invariably shown to afford lower LL in all trials with angiographic follow-up directly comparing SES and PES.[25–31] Although the impact of small differences of LL on clinical

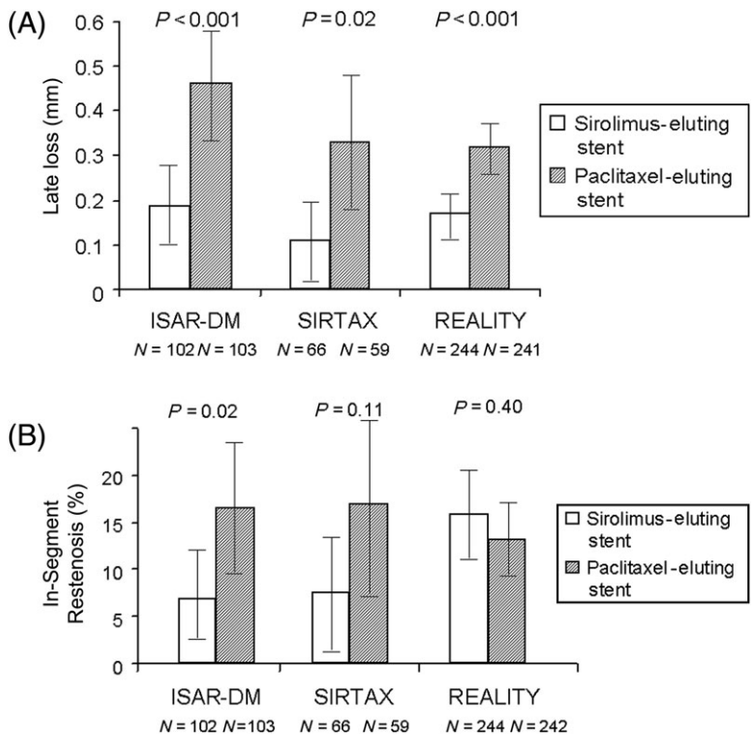


**Figure 2** Bar graph (with 95% confidence intervals) showing (*A*) late luminal loss for three trial directly comparing sirolimus-eluting (SES) and paclitaxel-eluting (PES) stents: ISAR-DIABETES, REALITY, SIRTAX and (*B*) in-segment binary restenosis for three trial directly comparing SES and PES: ISAR-DIABETES, REALITY, SIRTAX.

outcome at the low end of the scale remains a source of debate, it may be of particular importance in diabetic patients with smaller vessels.[1,6] Since a constant amount of neointimal hyperplasia results in a proportionally higher grade diameter stenosis in small as opposed to large vessels, the more potent suppression of neointimal hyperplasia associated with SES compared with PES results in lower rates of restenosis and TLR in small vessel studies.[9,10,30,32] Along this line, three trials with a sizeable diabetic patient population (ISAR-DIABETES:[25] $N = 250$; REALITY:[29] $N = 486$; SIRTAX: $N = 201$) consistently showed significantly lower LL in favour of SES (*Figure 2A*). Binary restenosis was remarkably similar among diabetic patients in ISAR-DIABETES (SES: 6.9%; PES 16.5%) and the present study (SES: 7.6%; PES: 17.0%) as was TLR. Surprisingly and for reasons which are not clear, binary restenosis (SES: 15.9%; PES: 13.2%, $P = 0.20$; *Figure 2B*) tended to be higher in SES- than in PES-treated diabetic patients in REALITY despite overall lower LL, whereas the relative risk (RR) reduction of restenosis afforded by SES among non-diabetic patients was similar in the present study (SES: 6.4% vs. 10.8%, $P = 0.07$) and REALITY (7.2% vs. 10.3%, $P = 0.06$).

Several reports from registries and meta-analyses challenge the notion that SES are more effective than PES in diabetic patients. Thus, Ong *et al.*[20] reported no significant difference between SES (145 patients) and PES (148 patients) in diabetic patients regarding death (7.7% vs. 7.2%, $P = 0.90$), and the composite of death and MI (14.1% vs. 10.0%, $P = 0.30$) at 1 year. A non-significant trend in favour of PES was noted with respect to TLR (8.8% vs. 5.7%, $P = 0.08$) and MACE (20.4% vs. 15.6%, $P = 0.12$), which was maintained at 2-year follow-up.[23] Stankovic *et al.*[21] also observed no difference between SES and PES regarding TLR (18.4% vs. 15.9%, $P = 0.61$) and MACE (27.2% vs. 22.1%, $P = 0.35$) in 260 consecutive diabetic patients at 9 months. Similarly, Kuchulakanti *et al.*[33] reported comparable outcomes of SES and PES with respect to death (7% vs. 7%, $P = 1.0$), MI (17% vs. 20%, $P = 0.32$), revascularization, and MACE (11% vs. 12%, $P = 0.52$) at 6 months follow-up. When comparing the results of these registries with the present study, the non-randomized nature and the absence of prospectively defined outcome parameters of the former need to be considered, potentially leading to confounding by indication and performance bias, and spurious findings related to multiple testing.

A systematic review analysed 10 randomized trials with 4513 patients comparing SES (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, SES-SMART, DIABETES) or PES (TAXUS I, II, IV, VI) with BMS.[24] Using indirect comparisons in which two interventions were compared through their estimated RR vs. BMS, separate analyses were performed for the overall population and for patients with and without diabetes. In patients without diabetes, SES were superior to PES with respect to in-stent (RR = 0.21, 95% CI 0.10–0.48, $P < 0.001$), and in-segment restenosis (0.47, 0.24–0.92, $P = 0.027$), TLR (0.54, 0.30–0.99, $P = 0.045$), and MACE (0.46, 0.26–0.83, $P = 0.010$). In contrast, there were no significant differences

between the two DES in patients with diabetes for all of the above endpoints. The mean RVD was smaller for SES (RVD = 2.52 mm) than for PES (RVD = 2.81 mm) treated vessels, and confounding by vessel diameter may have diminished the true difference between the devices in terms of restenosis and repeat revascularization. For MACE, there was overlap of confidence intervals of the treatment effects observed in the systematic review using indirect comparisons and those of the current study for both, diabetic and non-diabetic individuals. Regarding TLR, the present study showed a more pronounced effect of SES compared with PES in diabetic patients, whereas estimates were again comparable in both studies for non-diabetic individuals. In view of the fact that the present study included a considerably smaller number of diabetic patients than the previous indirect analysis, the lower estimates could be influenced by chance. On the other hand, it has been shown previously that adjusted indirect comparisons not always agree with the results of head to head randomized trials.[34]

A meta-analysis of four trials suggested an increased risk of mortality with SES compared with BMS in diabetic, but not in non-diabetic patients.[5] Event rates were unusually low in the BMS group with no difference in mortality between diabetic and non-diabetic patients. Chance could therefore have contributed to these results, despite their statistical significance. More recently, a network meta-analysis of 38 trials in 18 023 patients observed no difference regarding the risk of death or MI between SES, PES, and BMS at any time point during long-term follow-up to 4 years.[35] A stratified analysis in 3762 diabetic and 10 355 non-diabetic patients confirmed that the presence or absence of diabetes did not alter the comparative safety of these stent types in terms of death or the combined endpoint of death or MI. Among diabetic patients, the risks of death or the composite of death or MI were similar in SES, PES, and BMS.

## Study limitations

This study is a subgroup analysis of a randomized trial not primarily dedicated to diabetic patients and was not adequately powered to detect treatment-subgroup interactions. However, patient and lesion characteristics were similar between SES- and PES-treated patients, minimizing the risk of selection bias. Moreover, prospective follow-up at predefined intervals allowed to extend the observation period to 2 years of follow-up. Differences regarding medical treatment with evidence-based medications including beta-blockers, angiotensin-converting enzyme inhibitors, and statins may have important effects on long-term clinical outcome, particularly in high-risk individuals such as diabetic patients. Owing to incomplete data collection and validation, the present manuscript does not address potential differences between the treatment groups regarding medical treatment.

# Conclusions

Diabetic patients continue to have worse prognosis than non-diabetic patients when undergoing PCI with DES. Compared with PES, SES more effectively reduce repeat revascularization procedures and MACE in the diabetic patient population of this trial. In light of the heterogeneous outcome with SES and PES in diabetic patients emerging from registries, indirect and direct comparisons, and meta-analyses, a large scale, multi-centre trial comparing the efficacy of the two DES in diabetic patients is desirable.

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