

# Five-Year Clinical Outcomes of a Polymer-Free Sirolimus-Eluting Stent Versus a Permanent Polymer Paclitaxel-Eluting Stent: Final Results of the Intracoronary Stenting and Angiographic Restenosis – Test Equivalence Between Two Drug-Eluting Stents (ISAR-TEST) Trial

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**Background:** Limited evidence exists regarding the long-term performance of polymer-free (PF) drug-eluting stents (DES) in comparison to permanent polymer DES. This study investigated the 5-year efficacy and safety of a PF sirolimus-eluting stent (PF-SES) versus a permanent polymer paclitaxel-eluting stent (PES) in the setting of the Intracoronary Stenting and Angiographic Restenosis-Test Equivalence Between Two Drug-Eluting Stents (ISAR-TEST) randomized trial. **Methods and Results:** A total of 450 patients undergoing percutaneous coronary intervention were randomized to receive either PF-SES (Yukon, Translumina;  $n = 225$ ) or PES (Taxus, Boston Scientific;  $n = 225$ ). Clinical follow-up was performed to 5 years after enrollment. The endpoints were major adverse cardiac events (MACE), target lesion revascularization (TLR), the composite of death or any myocardial infarction (MI) and stent thrombosis (ST). The incidence of MACE at 5 years was 27.3% (57 patients) in the PF-SES group and 31.7% (65 patients) in the PES group [hazard ratio (HR) = 0.87 [95% confidence interval (95% CI) = 0.61–1.24];  $P = 0.40$ ]. The combined incidence of death or MI was 16.6% (34 patients) in the PF-SES group and 20.0% (39 patients) in the PES group (HR = 0.86 [95% CI = 0.54–1.36];  $P = 0.52$ ). The incidence of TLR was 16.5% (34 patients) in the PF-SES group and 16.4% (33 patients) in the PES group (HR = 1.03 [95% CI = 0.64–1.66];  $P = 0.89$ ). ST occurred in 0.5% (one patient) in the PF-SES group and 1.6% (three patients) in the PES group (HR = 0.33 [95% CI = 0.03–3.14];  $P = 0.32$ ). **Conclusion:** Overall there was no significant difference in clinical outcomes between PF-SES and PES to 5 years. Extended follow-up supports the durability of efficacy and safety of PF-SES. © 2012 Wiley Periodicals, Inc.

**Key words:** drug-eluting stents; paclitaxel; polymer-free; restenosis; sirolimus

## INTRODUCTION

Drug-eluting stents (DES) demonstrate superior performance to bare metal stents in terms of antirestenotic efficacy and reduced need for revascularization [1]. However

concern exists relating to a higher risk of stent thrombosis (ST) very late after stent implantation (>12 months) as well as to a gradual delayed erosion of antirestenotic efficacy—both clinical conditions related to the pathophysiological spectrum of delayed arterial healing [2–6].

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**Conflict of interest:** A. Schömig and A. Kastrati hold a patent on microporous stent surface.

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The trial was registered at ClinicalTrials.gov (identifier: NCT00140530).

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Permanent polymer coating is used to bind antirestenotic drug to the stent platform and to facilitate controlled drug release in DES; however, these coatings remain in situ following drug elution. Human postmortem and animal studies have demonstrated an inflammatory response to polymer residue [7,8], and this may have a causal role in the etiology of delayed arterial healing, the substrate, which is thought to underlie both late ST (LST) and late restenosis [9–13].

The ISAR-TEST clinical trial compared a polymer-free sirolimus-eluting stent (PF-SES) with a permanent polymer paclitaxel-eluting stent (PES) in 450 randomized patients undergoing elective percutaneous coronary revascularization (PCI) in native vessels. The primary analyses have been previously reported and demonstrated that PF-SES and PES had equivalent efficacy and safety at 1 year [14]. However it is not known if the efficacy of PF-SES is maintained over the medium- and long-term or whether a clinical advantage over permanent polymer stents will emerge with extended clinical follow-up. The objective of this study was to directly compare the 5-year safety and efficacy outcomes in the patient groups treated with PF-SES and polymer-based PES in the ISAR-TEST clinical trial.

## METHODS

### Study Population and Device Description

Details of the ISAR-TEST study design, methods and patient population have been reported previously [14]. Briefly, the ISAR-TEST trial was a prospective, randomized, investigator-initiated trial conducted at two centers in Munich, Germany. Patients were eligible for inclusion if greater than 18 years old with symptoms of angina or objective evidence of coronary ischemia and with de-novo stenosis of a native coronary artery  $\geq 50\%$ . Patients were considered ineligible for the study if the target lesion was in the left main stem, cardiogenic shock was present, a myocardial infarction (MI) occurred within the 48 hr prior to enrollment, any malignancy or any comorbidity limiting life expectancy to less than 12 months was evident, contraindications existed to the main study medications (including sirolimus, paclitaxel, aspirin, heparin, stainless steel and clopidogrel), or if pregnancy was confirmed, suspected or planned. The study protocol was approved by the institutional Ethics Committee responsible for both participating centers. All patients gave their written informed consent for participation in this trial.

Randomization was performed after successful wiring of the target vessel and this was considered time zero in the study. Treatment allocation was made using sealed opaque envelopes containing a computer-generated sequence. Randomization was not stratified. Patients

were allocated to both groups concurrently and in equal numbers. The same assigned stent was implanted in all lesions in those patients with multiple lesions or with lesions requiring multiple stents. Patients were assigned to receive either a PF-SES (Yukon stent [Translumina, Hechingen, Germany]) or PES (Taxus stent, Boston Scientific, Natick, MA).

The PF stent platform consisted of a premounted, sand blasted, 316-L stainless steel microporous stent, which is coated on-site with sirolimus. A detailed description of the coating process, the sirolimus elution characteristics and the drug release profile of the permanent polymer stent are reported elsewhere [15,16].

### Study Protocol

A 600-mg loading dose of clopidogrel was given at least 2 hours prior to undergoing cardiac catheterization. Following the procedure, aspirin 200 mg per day was prescribed indefinitely and clopidogrel 150 mg per day until hospital discharge and then 75 mg daily for at least 6 months. Other medications ( $\beta$ -blockers, statins and ACE inhibitors) were prescribed as appropriate. Repeat coronary angiography was performed at 6–8 months or earlier if symptoms indicated.

Patients received follow-up telephone interviews at one and 9 months and then annually from year 1 to year 5. If chest pain or cardiac symptoms were reported during follow-up then patients were advised to consult their referring physician.

### Data Management, Endpoints, and Definitions

Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Center. All data were verified against source documentation, and all adverse events were adjudicated by an event verification committee blinded to treatment allocation. The primary endpoint for the present analysis was a composite endpoint of major adverse cardiac events (MACEs) consisting of all-cause death, any MI or target lesion revascularization (TLR) at 5 years post-enrollment. Secondary endpoints were the composite of death or any MI, definite or probable ST and TLR.

TLR was defined as any ischemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. Deaths were classified as cardiac or noncardiac according to hospital records, death certificates and telephone calls with the attending physician or the relatives. Cardiac death was defined as death due to any of the following: acute MI; cardiac perforation/pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or stroke suspected of being related to the procedure; death due to complication

of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery; or any death in which a cardiac cause could not be excluded.

MI related to procedure was defined as either an increase in CK-MB (or CK)  $\geq 3$  upper limit of normal (ULN) and at least 50% over the most recent pre-PCI levels, or the development of new ECG changes consistent with MI and CK-MB (CK) elevation higher than the ULN at two measurements for patients undergoing DES implantation in setting of stable angina pectoris or non-ST-segment elevation acute coronary syndrome and falling or normal CK-MB (CK) levels. Bypass surgery related MI was considered either CK-MB elevation  $\geq 10$  ULN and at least 50% over the most recent presurgery levels or CK-MB elevation  $\geq 5$  ULN and at least 50% over the most recent presurgery levels in addition to new abnormal Q-waves on the ECG. ST was classified according to Academic Research Consortium (ARC) criteria [17].

### Statistical Methods

The objective of this study was to assess the safety and efficacy of the PF-SES stent when compared with the PES at 5 years. Sample size calculation was based on the assessment of late lumen loss at follow-up angiography and has been described previously [14]. The analysis was performed on an intention-to-treat basis. In patients with multilesion interventions, only the first treated lesion was included in the analysis. Continuous data are presented as mean (SD) or median (25th to 75th percentiles), and compared using Student's *t*-test or Wilcoxon rank-sum test. Categorical data are presented as counts or proportions (%) and compared using chi square or Fisher's exact test. Survival was assessed using the methods of Kaplan-Meier and survival parameters were compared using Cox's proportional hazards model to calculate hazard ratios (HR) with 95% confidence intervals (CI) for PF-SES compared with PES. A two-sided *P*-value  $< 0.05$  was considered statistically significant.

Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, WA) was used for analysis.

### RESULTS

A total of 450 patients were enrolled in the study, 225 received the PF-SES and 225 were treated with the PES. The baseline clinical, angiographic and procedural characteristics were well matched in both groups (Table I). No patients were lost to follow-up during the study.

Clinical outcomes at 5 years are shown in Table II. There were no significant differences in MACEs, the primary composite endpoint (Fig. 1). The rate of TLR at 5 years did not differ significantly between groups

(Fig. 2). Outcomes for the composite endpoint of death or MI were also similar and are shown in Fig. 3. One patient in the PF-SES group developed acute ST within the first 30 days (0.5%), however there were no further episodes of definite ST associated with the PF stent at 5 years. Three patients in the PES group developed ST (1.6%), comprising of one episode within the first 30 days, one episode within the first year and one episode within the fourth year (HR = 0.33 [95% CI = 0.03–3.14], *P* = 0.32).

### DISCUSSION

The ISAR-TEST trial was a two-center randomized trial comparing the safety and efficacy of a novel PF-SES with a first-generation polymer-based PES. The present analysis represents the first report of extended follow-up with PF versus permanent polymer stents. The 5-year follow-up results provide several points of interest regarding both safety and efficacy: (i) overall clinical outcomes were similar with both stents; (ii) the equivalence in safety previously reported at 1 year was maintained to 5 years. Adverse events rarely occurred beyond 1 year for both PF-SES and PES. Of note, there were no ST beyond 30 days in the group treated with PF-SES; and (iii) regarding efficacy the equivalence in rates of TLR observed at 1 year was maintained to 5 years.

The safety outcomes for the PES are in keeping with long term findings previous PES trials [18,19]. The best evidence currently available concerning PF stents largely consists of data up to 2 years in clinical trials designed primarily to assess noninferiority of angiographic outcomes in comparison to both permanent-polymer DES and biodegradable-polymer DES [20–25]. This group has previously demonstrated that a PF-SES stent had equivalent antirestenotic efficacy and safety to both a biodegradable-polymer SES and a permanent-polymer SES at 2 years both in a randomized controlled trial of 605 patients [21], and in a larger real world, nonrandomized, prospective trial of 2588 patients [2].

However there is no reported data on the long-term safety and efficacy of DES with polymer-free technology. Such late comparative performance is important. Given the differences in design between the stent platforms it is reasonable to question whether late performance may differ. The equivalent safety profile and equivalent efficacy at 5 years between the PF-SES and the PES demonstrated in this study are, therefore, important findings.

There is significant evidence that an inflammatory response to the residue from permanent polymers contributes toward delayed arterial healing following DES implantation [7,8], and that this may be a significant factor in the incidence of LST seen with DES [9–13].

**TABLE 1. Demographic, Clinical, Angiographic, and Procedural Patient Characteristics**

	PF-SES	PES	<i>P</i>
Patients	225	225	
Age (yr)	66.8 ± 10.5	66.6 ± 10.2	0.88
Women ( <i>n</i> ; %)	56 (25)	48 (21)	0.37
Diabetes mellitus ( <i>n</i> ; %)	73 (32)	58 (26)	0.12
Current smoker ( <i>n</i> ; %)	43 (19)	39 (17)	0.63
Arterial hypertension ( <i>n</i> ; %)	142 (63)	155 (69)	0.20
Hypercholesterolemia ( <i>n</i> ; %)	165 (73)	170 (76)	0.59
Unstable angina ( <i>n</i> ; %)	94 (42)	99 (44)	0.63
Prior MI ( <i>n</i> ; %)	72 (32)	71 (32)	0.92
Prior aortocoronary bypass surgery ( <i>n</i> ; %)	25 (11)	25 (11)	1.0
Left ventricular ejection fraction (%)	54.0 ± 14.1	55.3 ± 13.5	0.33
Number of lesions treated	1.2 ± 0.44	1.1 ± 0.36	0.13
Target vessel			0.48
Left anterior descending coronary artery ( <i>n</i> ; %)	88 (39)	96 (43)	
Left circumflex coronary artery ( <i>n</i> ; %)	78 (35)	66 (29)	
Right coronary artery ( <i>n</i> ; %)	59 (26)	63 (28)	
Complex (type B2/C) lesions ( <i>n</i> ; %)	168 (75)	176 (78)	0.37
Vessel size (mm)	2.72 ± 0.46	2.73 ± 0.49	0.94
Lesion length (mm)	12.6 ± 5.9	12.9 ± 7.0	0.59
Minimal lumen diameter procedure (mm)	1.14 ± 0.40	1.14 ± 0.42	>0.99
Diameter stenosis prior to procedure (%)	58.3 ± 12.4	58.1 ± 12.7	0.87
Number of stents per lesion	1.16 ± 0.38	1.08 ± 0.26	0.006
Minimal lumen diameter after procedure	2.57 ± 0.43	2.59 ± 0.42	0.61
Diameter stenosis after procedure	9.0 ± 5.9	8.7 ± 7.0	0.63
Late lumen loss			
In-stent (mm)	0.48 ± 0.61	0.48 ± 0.58	0.98
In-segment (mm)	0.34 ± 0.59	0.24 ± 0.57	0.09
Minimal lumen diameter			
In-stent (mm)	2.10 ± 0.68	2.11 ± 0.70	0.96
In-segment (mm)	1.93 ± 0.65	1.93 ± 0.68	0.98
Diameter stenosis			
In-stent (%)	25.04 ± 20.79	25.66 ± 19.28	0.77
In-segment (%)	31.64 ± 18.84	31.97 ± 18.72	0.87
Angiographic restenosis			
In-stent ( <i>n</i> ; %)	23 (12.6)	21 (11.6)	0.78
In-segment ( <i>n</i> ; %)	26 (14.2)	28 (15.5)	0.73

Values are mean ± SD or *n* (%). PF-SES, polymer-free sirolimus-eluting stent; PES, paclitaxel-eluting stent.

**TABLE 2. Clinical Outcomes at 5 Years**

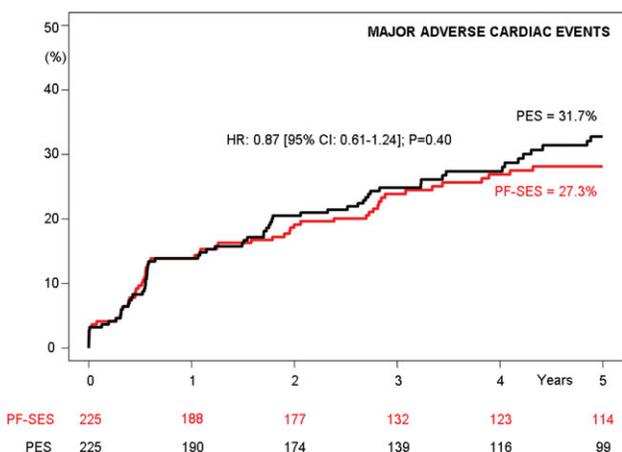
	PF-SES	PES	Hazard ratio	<i>P</i> -value
Patients	225	225		
Death, MI, or TLR (MACEs)	57 (27.3)	65 (31.7)	0.87 [0.61–1.24]	0.40
Death or MI	34 (16.6)	39 (20.0)	0.86 [0.54–1.36]	0.52
TLR	34 (16.5)	33 (16.4)	1.03 [0.64–1.66]	0.89
Stent thrombosis	1 (0.5)	3 (1.6)	0.33 [0.03–3.14]	0.32
Cardiac death or MI	30 (14.9)	27 (13.9)	1.10 [0.65–1.85]	0.67
MI	17 (8.1)	10 (5.0)	1.70 [0.78–3.71]	0.16
All-cause death	20 (10.2)	31 (16.2)	0.63 [0.36–1.10]	0.10
Cardiac death	16 (8.4)	19 (10.1)	0.82[0.42–1.59]	0.60

Data are shown as number (percentage) by Kaplan–Meier analysis; hazard ratios [95% confidence interval] were calculated using Cox's proportional Hazards model. DES, drug-eluting stent; MACEs, major adverse cardiac events; MI, myocardial infarction; PES, paclitaxel-eluting stent; PF-SES, polymer-free sirolimus-eluting stent; TLR, target lesion revascularization.

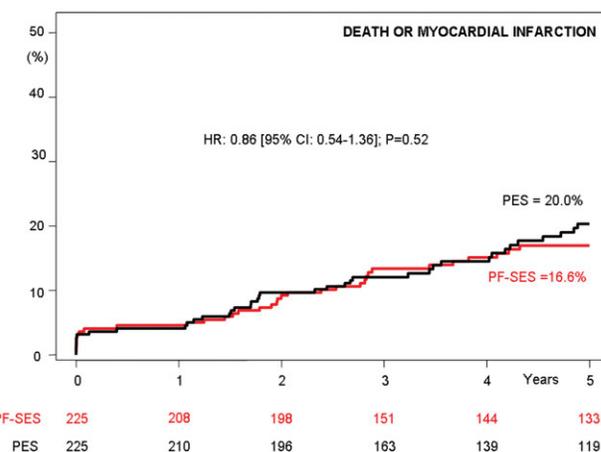
Although the rate of ST was lower in the PF-PES group, and there was no ST in the PF-SES group beyond 30 days, this study was not powered to detect differences in rare adverse events such as ST.

#### LIMITATIONS OF THE STUDY

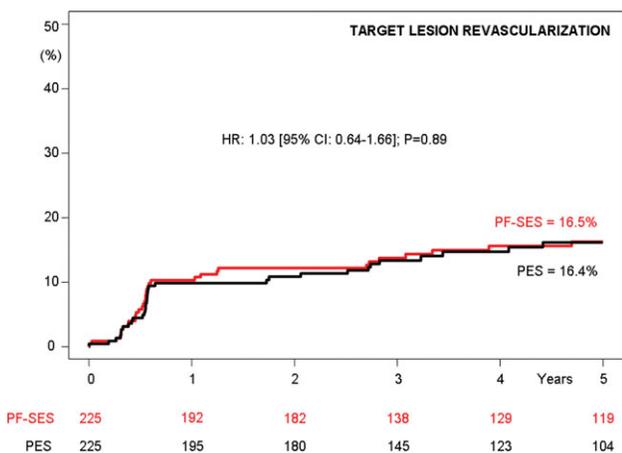
Although follow-up angiography during the first year provides useful information regarding lumen renarrowing, clinical follow-up is preferable for evaluating long-term



**Fig. 1.** Cumulative incidence of primary endpoint major adverse cardiac events. CI, confidence interval; HR, hazard ratio; PES, paclitaxel-eluting stent; PF-SES, polymer-free sirolimus-eluting stent; numbers shown represent patients at risk.



**Fig. 3.** Cumulative incidence of death or any myocardial infarction. CI, confidence interval; HR, hazard ratio; PES, paclitaxel-eluting stent; PF-SES, polymer-free sirolimus-eluting stent; numbers shown represent patients at risk.



**Fig. 2.** Cumulative incidence of target vessel revascularization. CI, confidence interval; HR, hazard ratio; PES, paclitaxel-eluting stent; PF-SES, polymer-free sirolimus-eluting stent; numbers shown represent patients at risk.

device performance. However, this trial was powered to detect primary angiographic outcomes at 6-8 months and comparisons beyond this time point, as well as relating to clinical outcomes, should be regarded as post hoc and hypothesis generating. Furthermore, it should be acknowledged that the current report is not powered to detect differences in rarely occurring clinical events such as MI and LST. As such, it is not able to assess noninferiority or superiority of long term safety or efficacy. Aggregate analysis of large scale long-term trials may provide the means to effectively address the issues of LST and long-term safety in general. In addition, although clinical follow-up was performed by specialized personnel of the Clinical Data Management Center, telephone follow-up might not be sensitive enough to capture oligo- or asymptomatic MI. The reported results relate to a general population undergoing elective PCI in the context of a clinical trial.

Larger scale prospective observational and registry data may also contribute to our understanding of the performance of PF stents outside of the clinical trial setting and may provide insight into outcomes of the use of PF stents in high-risk patients and in high-risk lesions. The comparator stent used in this study was a first-generation PES which although now used relatively infrequently in clinical practice, was in routine clinical use at the time the study was undertaken.

**CONCLUSION**

The 5-year follow-up of the ISAR-TEST study demonstrates equivalent long-term efficacy and safety between a PF-SES and a permanent-polymer PES. These findings provide a sound basis to test the hypothesized late performance advantage of this technology in large-scale studies powered for clinical endpoints.

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