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

Fabrizio Tomai, md[1]
Bernhard Reimers, md[2]
Leonardo De Luca, md[1]
Alfredo R. Galassi, md[3]
Achille Gaspardone, md[4]
Anna S. Ghini, md[1]
Valeria Ferrero, md[5]
Luca Favero, md[2]
Gaetano Gioffrè, md[4]
Francesco Prati, md[6]
Corrado Tamburino, md[3]
Flavio Ribichini, md[5]

OBJECTIVE — It is still controversial whether sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) are equally effective in patients with diabetes. In these patients, multiple individual variables may be responsible for neointimal hyperplasia, thus making difficult the comparison of the two drug-eluting stents (DES).

RESEARCH DESIGN AND METHODS — We designed a prospective, randomized study to compare the efficacy in prevention of restenosis of SES and PES, both implanted in the same diabetic patient with multiple de novo coronary artery lesions undergoing elective percutaneous coronary intervention. We enrolled 60 patients with diabetes with at least two significant de novo angiographic stenoses in different coronary segments. The primary end point was in-stent late luminal loss (LLL) at 8-month angiographic follow-up.

RESULTS — A total of 120 lesions were successfully treated with the randomly assigned DES (SES, $n = 60$; PES, $n = 60$). In-stent LLL was lower in the SES than in the PES group (0.26 ± 0.4 vs. 0.50 ± 0.6 mm; $P = 0.01$). Coronary lesions treated with SES presented a reduced in-stent LLL in 40 (68%) patients, while PES resulted in a lower in-stent LLL in 19 (32%) patients ($P = 0.0002$). At multivariable analysis, the type of DES implanted was the only independent predictor of in-stent LLL (odds ratio 2.3 [95% CI 1.1–5.0]; $P = 0.03$).

CONCLUSIONS — SES directly compared with PES in the same diabetic patient is associated with a decrease in the extent of in-stent LLL at 8 months, suggesting a reduced risk of restenosis.

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From the [1]Division of Cardiology, Department of Cardiovascular Sciences, European Hospital, Rome, Italy; the [2]Cardiology Department, Mirano Hospital, Mirano, Italy; the [3]Division of Cardiology, Department of Internal Medicine and Systemic Disease, Ferrarotto Hospital, University of Catania, Catania, Italy; the [4]Division of Cardiology, S. Eugenio Hospital, Rome, Italy; the [5]Institute of Cardiology, University of Verona, Verona, Italy; and the [6]Catheterization Laboratory, S. Giovanni Hospital, Rome, Italy.

Address correspondence and reprint requests to Fabrizio Tomai, MD, Division of Cardiology, Department of Cardiovascular Sciences, European Hospital, Via Portuense 700, 00149 Rome, Italy. E-mail: f.tomai@tiscali.it.

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Abbreviations: DES, drug-eluting stents; LLL, late luminal loss; MLD, minimal luminal diameter; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolumus-eluting stent.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetes is an important risk factor for poor outcomes after elective percutaneous coronary intervention (PCI) (1). In particular, diabetic patients are prone to a diffuse and rapidly progressive form of atherosclerosis, which increases their likelihood of requiring revascularization (1).

Several randomized trials and meta-analyses have shown that both sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) markedly reduce restenosis rates and the need for repeated revascularization procedures compared with bare metal stents in patients with diabetes (2–7). However, it is still controversial whether SES and PES are equally effective in prevention of restenosis in these patients. A recent prospective randomized trial demonstrated that use of SES is associated with a reduced risk of restenosis compared with use of PES in diabetic patients (8). On the other hand, recent meta-analyses (9,10), retrospective studies (11,12), and a large registry (13) revealed no difference between these two drug-eluting stents (DES) in terms of restenosis and target lesion revascularization.

Notably, in diabetic patients, multiple individual variables, including systemic inflammatory status, glycemic control over the time, insulin plasma levels, prothrombotic state, and type of and response to medical treatment, may be responsible for neointimal hyperplasia after coronary stenting (14), thus making difficult the comparison of the two DESs in different patient groups. We therefore designed a prospective, randomized, multicenter, nonsponsored study to directly compare the efficacy in prevention of restenosis of SES and PES, both implanted in the same diabetic patient to obviate for the multiple and unpredictable characteristics of this high-risk population.

RESEARCH DESIGN AND METHODS

— Patients were enrolled from 20 October 2005 through 6 March

2006 in five Italian high-volume interventional cardiology centers. Patients were considered eligible if they presented diabetes, angina pectoris and/or a positive stress test, and the presence of at least two significant angiographic stenoses in different native coronary vessels or in the same vessel but two different coronary segments.

Patients were jointly evaluated in each institution by a cardiovascular team composed of a cardiac surgeon, an interventional cardiologist, and a clinician. The final decision of patient enrollment was made after comprehensive review of all relevant factors. To be enrolled in the study, patients had to be considered suitable for PCI by the cardiovascular team.

Diagnosis of diabetes was confirmed in all patients receiving active treatment with an oral hypoglycemia agent or insulin; for patients with a diagnosis of diabetes receiving dietary therapy alone, enrollment in the trial required documentation of an abnormal blood glucose level after an overnight fast or an abnormal glucose tolerance test.

Exclusion criteria included ST-segment elevation myocardial infarction; a target lesion in the left main trunk; coronary artery bypass graft; in-stent restenosis; two or more lesions in the same coronary segment unsuitable to be treated with one DES; any contraindication to the use of aspirin, heparin, and/or clopidogrel; and lack of consent to participate in the study.

The study protocol was approved by the institutional ethics committees at all participating centers. All patients provided written informed consent before catheterization for participation in the study.

PCI was performed via a 6F or 7F sheath in the femoral or radial artery according to standard clinical practice. After the guide wire had crossed the lesion, patients were randomly assigned to receive an SES (Cypher; Johnson & Johnson, New Brunswick, NJ) or a PES (Taxus; Boston Scientific, Marlborough, MA) with the use of sealed envelopes containing a computer-generated randomization sequence for coronary vessel (left anterior descending, left circumflex, or right coronary artery). In patients with multivessel disease and more than one lesion in the same vessel but different coronary segments, the assigned DES was implanted in the more proximal lesion. For enrolled patients with single-vessel disease and two or more significant stenoses in different coronary segments, a second envelope containing a computer-generated randomization sequence for coronary segment (proximal or mid-distal portion of the vessel) was used. For patients with multivessel disease requiring implantation of more than two stents, the type of stent implanted in the remaining lesions (or vessels) was left to the operator's discretion and was excluded from the angiographic analysis. The implantation of multiple overlapping coronary DESs was allowed in case of incomplete lesion coverage and/or endoluminal injury requiring additional stent coverage beyond the margins of the initial stent deployed.

Periprocedural antithrombotic therapy consisted of aspirin and heparin at standard dosages and clopidogrel at a loading dose of 300 mg. Platelet glycoprotein IIb/IIIa inhibitors were given only to patients with acute coronary syndromes. After the intervention, the protocol mandated use of antiplatelet therapy consisting of 100 mg/day aspirin indefinitely and 75 mg/day clopidogrel for at least 6 months.

All patients were asked to return for coronary angiography at 8 months after the procedure (or earlier if symptoms occurred). Relevant data were collected and entered into a computerized database by specialized personnel at the clinical data management center (European Hospital, Rome, Italy). All data were verified with the use of hospital records or records of family physicians.

Quantitative coronary angiography

Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed offline in a quantitative angiographic core laboratory (Rome Heart Research, Rome, Italy) with an automated edge-detection system (CMS; Medis Medical Imaging Systems) (15) by experienced personnel unaware of the study protocol.

All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin. The contrast-filled nontapered catheter tip was used for calibration. The reference diameter was determined by interpolation. Variables measured included the reference diameter of the vessel, the minimal luminal diameter (MLD), extent of stenosis (the difference between the reference diameter and the MLD, divided by the reference diameter and multiplied by 100), late luminal loss (LLL) (the difference between the MLD at the end of the procedure and the MLD at follow-up), and net luminal gain (the difference between the MLD at follow-up and the MLD before the procedure).

Quantitative coronary analysis was used to evaluate the stented area ("in stent") and the area that included the stented segment as well as the 5-mm margins proximal and distal to the stent ("in segment"). We also evaluated the stent volume (postprocedural mean stent area of the stented segment × stent length), lumen volume (mean luminal area of the stented segment at follow-up × stent length), neointimal volume (stent volume − lumen volume), and percentage of neointimal obstruction (neointimal volume/stent volume × 100), as recently proposed by Tsuchida et al. (16). The complexity of the lesions was defined according to the modified grading system of the American College of Cardiology–American Heart Association (17).

Study end points

The primary end point of the study was in-stent LLL by quantitative coronary angiography at 8-month follow-up angiography. We chose in-stent LLL as the primary end point because it has been demonstrated to be a more reliable predictor of restenosis than in-segment LLL (18). We also evaluated in-segment LLL, angiographic restenosis (defined as in-segment stenosis of at least 50% on follow-up angiography), and volumetric measurements at the time of angiographic follow-up.

Statistical analysis

We calculated that a sample size of 55 patients, i.e., 110 lesions (55 per stent group), was needed for detection of a difference between the two DESs for in-stent LLL of 0.27 ± 0.5 mm, with an 80% power and a two-sided α error of 5%. This assumption was based on the results of the only available randomized head-to-head comparison trial with SES and PES in diabetic patients, which showed an in-stent LLL of 0.19 ± 0.44 and 0.46 ± 0.64 mm, respectively (8). Assuming a 10% dropout rate, we set a goal of 60 patients (120 lesions) for the study.

Sample size was calculated with the use of Query Advisor (version 4.0; Statistical Solutions) according to the method of O'Brien and Muller. Comparisons of the continuous or discrete variables between stent groups were performed using a two-tailed, unpaired *t* test or a χ^2 test, respectively. To investigate the independent

Table 1—*Baseline characteristics of the total study population*

Characteristics	Total population
n	60
Age (years)	65.2 ± 10
Sex (male)	44 (73.3)
Type 1 diabetes	7 (11.6)
Type 2 diabetes	53 (88.4)
Diagnosis of diabetes (months)	79.5 ± 64.1
Fasting insulin (pmol/l)	36.3 ± 12.3
Preprocedural A1C (%)	7.6 ± 1.8
Preprocedural glycemia (mg/dl)	164 ± 74.5
Hypertension	49 (81.6)
Current smoker	12 (20)
Family history of CAD	22 (36.6)
Total cholesterol (mg/ml)	179.5 ± 45.7
Triglycerides (mg/dl)	155 ± 103.2
Chronic renal insufficiency*	13 (21.6)
Previous MI	26 (43.3)
Previous CABG	2 (0.3)
Previous PCI	3 (0.5)
ACS	32 (53.3)
Troponin I (ng/ml)	0.4 ± 1.8
Creatine kinase–MB isoenzyme (ng/ml)	155 ± 5.4
CRP (mg/dl)	0.9 ± 1.2
Multivessel disease	55 (91.6)
Ejection fraction (%)	54.5 ± 8.6
Sulphonil ureas	21 (35)
Biguanide	25 (41.6)
Other antidiabetes drugs	8 (13.3)
Statins	48 (80)
ACE inhibitors or ARBs	50 (83.3)
Aspirin	53 (88.3)
Thienopyridine-derived agents	48 (80)
Glycoprotein IIb/IIIa	8 (13.3)
Calcium channel blockers	21 (35)
β-blockers	36 (60)

Data are means ± SD or *n* (%). ARB, angiotensin receptor blocker; ACS, acute coronary syndrome; CAD, coronary artery disease; CABG, coronary artery bypass grafing; CRP, C-reactive protein; MI, myocardial infarction. *Defined as a serum creatinine level ≥1.5 mg/dl (≥132 μmol/l).

predictors of in-stent LLL, a multivariable regression analysis was performed in which all variables known to be relevant for the study end point (type of DES, target vessel, lesion location, lesion type, vessel size, stent length, MLD before procedure, and stenosis before procedure) were entered as independent variables. Data are expressed as mean ± SD unless otherwise indicated. Values of $P < 0.05$ were considered significant.

RESULTS — Of 167 consecutive diabetic patients who met inclusion/exclusion criteria, 94 (56.3%) underwent surgical revascularization and 13 (7.8%) were treated with pharmacologic therapy after joint evaluation of the cardiovascular team. The remaining 60 (35.9%) patients were enrolled in the study and randomly assigned to receive both an SES and a PES in different coronary lesions. Among a total of 146 coronary lesions in different coronary segments successfully treated with stent implantation, 120 received a randomly assigned DES (SES, $n = 60$; PES, $n = 60$); the remaining 26 coronary lesions were treated with bare metal stents and not considered for angiographic analysis.

Clinical characteristics, biochemical markers, and pharmacological therapy at the time of enrollment of total population are summarized in Table 1. Baseline angiographic characteristics of the lesions and procedural variables of patients treated with SES or PES are displayed in Table 2.

Angiographic results

Follow-up angiography at 8 months was performed in all 59 patients alive (one patient died from SES thrombosis 18 days after the index intervention, as demonstrated at autopsy). The median duration of angiographic follow-up was 246 days (10th–90th percentiles 113–267).

Table 2—*Angiographic and procedural characteristics*

Characteristics	SES	PES	*P*
n	60	60	
DES implanted	69	67	0.8
Location of treated lesion			0.45
Left anterior descending coronary artery	21 (35)	27 (45)	
Left circumflex coronary artery	21 (35)	20 (33)	
Right coronary artery	18 (30)	13 (22)	
Vessel site			0.58
Proximal	29 (48)	26 (43)	
Middle distal	31 (52)	34 (57)	
Lesion type			0.2
A-B1	30 (50)	23 (38)	
B2-C	30 (50)	37 (62)	
CTO	1 (1.7)	2 (3.3)	0.9
Bifurcation lesions			0.8
1 DES	9 (15)	11 (18.3)	
2 DES	2 (3.3)	1 (1.6)	
Baseline TIMI flow			0.9
0	3 (5)	4 (6.7)	
1	13 (21.7)	12 (20)	
2	11 (18.3)	11 (18.3)	
3	33 (55)	33 (55)	
Post-procedural TIMI flow			0.2
1	1 (1.7)	1 (1.7)	
2	0	3 (5)	
3	59 (98.3)	56 (93.3)	
Direct stenting	23 (38.3)	15 (25)	0.1
Postdilation	10 (16.7)	16 (26.7)	0.2
Stent length (mm)	25.7 ± 14.2	26.1 ± 11.8	0.9
Stent diameter (mm)	2.96 ± 0.3	2.97 ± 0.3	0.9
Lesion length (mm)	21.8 ± 15.7	19.7 ± 8.1	0.3
Reference vessel diameter (mm)	2.9 ± 0.4	2.9 ± 0.3	0.7
Preprocedural MLD (mm)	0.9 ± 0.3	0.87 ± 0.3	0.5
Postprocedural MLD (mm)	2.9 ± 0.3	2.9 ± 0.3	0.7
In-lesion acute gain (mm)	1.9 ± 0.3	2.0 ± 0.4	0.1
Preprocedural diameter stenosis (%)	66.9 ± 10.5	67.7 ± 10.6	0.7
Postprocedural diameter stenosis (%)	4.3 ± 3.2	4.4 ± 3.6	0.8
Stent volume (mm^3)	177 ± 104	184 ± 84	0.7

Data are means ± SD, *n*, or *n* (%). CTO, chronic total occlusion; TIMI, thrombolysis in myocardial infarction.

Table 3—*Angiographic findings at follow-up among the 59 patients alive at 8 months*

Quantitative coronary angiography data	SES	PES	*P*
n	59	59	
In-stent restenosis	3 (5.1)	5 (8.5)	0.5
In-lesion restenosis	5 (8.5)	8 (13.5)	0.4
In-stent diameter stenosis (%)	11.2 ± 14.6	17.2 ± 18.8	0.05
In-lesion diameter stenosis (%)	15.2 ± 19.9	20.5 ± 21.4	0.2
In-stent MLD (mm)	2.6 ± 0.5	2.4 ± 0.6	0.05
In-lesion MLD (mm)	2.5 ± 0.7	2.3 ± 0.7	0.1
In-stent LLL (mm)	0.26 ± 0.4	0.50 ± 0.6	0.01
In-lesion LLL (mm)	0.41 ± 0.6	0.68 ± 0.6	0.04
Lumen volume (mm^3)	159 ± 105	142 ± 61	0.3
Neointimal volume (mm^3)	17.6 ± 28.6	41.9 ± 51.3	0.002
Neointimal obstruction (%)	10.2 ± 15.5	19.5 ± 19.3	0.005

Data are means ± SD, percentages, or *n* (%).

Table 3 shows the results of the quantitative analysis of follow-up angiograms. Both in-segment and in-stent LLLs were significantly lower in the SES group (0.41 ± 0.6 vs. 0.68 ± 0.6 mm, $P = 0.04$, and 0.26 ± 0.4 vs. 0.50 ± 0.6 mm, $P = 0.01$, respectively). Accordingly, the percentage of neointimal obstruction was significantly reduced in SES-treated lesions (10.2 ± 15.5 vs. 19.5 ± 19.3%, $P = 0.005$). Coronary lesions treated with SES presented a reduced in-stent LLL in 40 (68%) patients, while PES resulted in a lower in-stent LLL in 19 (32%) patients ($P = 0.0002$). Figure 1 shows the cumulative rate of in-stent LLL at follow-up angiography.

The rates of in-segment and in-stent restenosis and angiographic diameter stenosis were lower in the SES group even if not statistically different. Target-lesion revascularization was performed by PCI on five (8.6%) coronary lesions treated with SES and eight (13.8%) with PES ($P = 0.5$). At multivariable analysis, type of DES implanted was the only independent predictor of in-stent LLL (odds ratio 2.3 [95% CI 1.1–5.0]; $P = 0.03$).

CONCLUSIONS — This prospective, randomized, multicenter study demonstrates that in the same diabetic patient with multiple de novo coronary artery lesions, use of SES is associated with a lower rate of LLL at 8 months compared with that associated with PES use. Indeed, coronary lesions treated with SES presented a reduced in-stent LLL in the majority of patients.

In-stent LLL reflects the degree of neointimal growth, which is the main cause of coronary restenosis. Indeed, there is a close relationship between in-stent LLL and incidence of binary restenosis (18), as well as target vessel revascularization (19), thus implying that the assessment of in-stent LLL can be regarded as an appropriate marker for assessing the efficacy of a DES (18,19). A well-known limitation of LLL is that it represents only a surrogate for clinical end points (18,19), which, however, could not be taken into account in this study because both SES and PES were implanted in the same patient.

Our data are in accordance with those of the recently published ISAR (In-Stent Angiographic Restenosis)-DIABETES trial (8), which randomized 250 patients with diabetes to receive SES or PES. PES was associated with a higher rate of in-segment LLL and an increased risk of angiographic restenosis compared with that for SES. Our study was not sufficiently powered to assess incidence of angiographic restenosis even if there was a trend toward lower incidence of restenosis in the SES group.

Notably, the present study strengthens the main finding of the ISAR-DIABETES trial, since it demonstrates for the first time that the superiority of SES to PES is independent of all specific pathophysiological and clinical features of the diabetic population. Indeed, in these patients, coronary restenosis resulting from neointimal hyperplasia (which causes LLL) is a very complex process, influenced by several pathophysiological mechanisms, including vascular inflammation, endothelial dysfunction, enhanced prothrombotic status, and insulin resistance (1). The role played by these mechanisms may also vary among different diabetic patients, but it is equalized in our clinical research model. Furthermore, a variety of individual features of the diabetic patient may influence the restenotic process, such as glycemic control over time, associated medical treatments and comorbidities, response to treatment, and associated risk factors (1). Thus, all these variables, which may influence the restenotic process differently in each individual patient, may adversely affect any comparison between patient groups treated with different DESs. However, the majority of these variables were not specifically taken into account in previous studies. The particular design of our study, in which both SES and PES were implanted in the same diabetic patient after randomization for coronary vessel and segment, permitted adjustment of the results for all these variables. Moreover, we

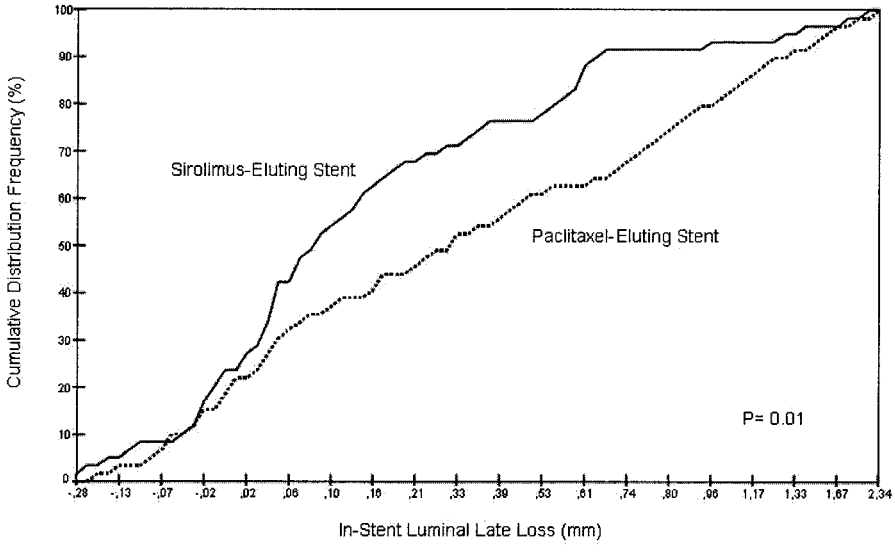

Figure 1—*Cumulative rates of in-stent LLL at follow-up angiography.*

found that the type of DES was the only independent predictor of in-stent LLL.

Several factors may be responsible for the observed better angiographic performance of SES: *1*) a more profound inhibition of neointimal hyperplasia due to sirolimus, an immunosuppressive drug with anti-inflammatory properties; *2*) a greater elution of the drug in a shorter time as a result of polymer coating of SES; and *3*) a more uniform distribution of the drug as a result of closed-cell design of the BxVelocity stent.

The present study group represents one-third of the total diabetic population with multivessel disease who underwent coronary angiography during the study period. In fact, we preferred to enroll only patients deemed suitable for PCI by a joint evaluation of a cardiac surgeon and an interventional cardiologist. Nevertheless, surgical revascularization remains the recommended strategy for diabetic multivessel coronary artery disease (1). Ongoing trials of PCI with DES versus coronary artery bypass graft will provide more data on the best revascularization treatment in diabetic patients.

In summary, this multicenter, randomized study demonstrates that SES, directly compared with PES in the same diabetic patient with multiple de novo coronary artery lesions, is associated with a decrease in the extent of in-stent LLL at 8 months, suggesting a reduced risk of restenosis. The better angiographic performance of SES does not necessarily translate into long-term clinical benefits.

APPENDIX

Participants

F. Tomai, L. De Luca, A.S. Ghini, P. Corvo, and G. De Persio (Division of Cardiology, Department of Cardiovascular Sciences, European Hospital, Rome, Italy); B. Reimers and L. Favero (Cardiology Department, Mirano Hospital, Mirano, Italy); A.R. Galassi and C. Tamburino (Division of Cardiology, Department of Internal Medicine and Systemic Disease, Ferrarotto Hospital, University of Catania, Catania, Italy); A. Gaspardone, G. Gioffrè, and C. Citone (Division of Cardiology, S. Eugenio Hospital, Rome, Italy); F. Ribichini and V. Ferrero (Institute of Cardiology, University of Verona, Verona, Italy); and F. Prati, Catheterization Laboratory, S. Giovanni Hospital, Rome, Italy.

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