Randomized Comparison of Sirolimus-Eluting Stent Versus Standard Stent for Percutaneous Coronary Revascularization in Diabetic Patients

The Diabetes and Sirolimus-Eluting Stent (DIABETES) Trial

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Background—Outcomes after percutaneous coronary interventions in diabetic patients are shadowed by the increased rate of recurrence compared with nondiabetic patients.

Methods and Results—We conducted a multicenter, randomized trial to demonstrate the efficacy of sirolimus-eluting stents compared with standard stents to prevent restenosis in diabetic patients with de novo lesions in native coronary arteries. The primary end point of the trial was in-segment late lumen loss as assessed by quantitative coronary angiography at 9-month follow-up. The trial was stratified by diabetes treatment status. One hundred sixty patients were randomized to sirolimus-eluting stents (80 patients; 111 lesions) or standard stent implantation (80 patients; 110 lesions). On average, reference diameter was 2.34±0.6 mm, lesion length was 15.0±8 mm, and 13.1% of lesions were chronic total occlusions. In-segment late lumen loss was reduced from 0.47±0.5 mm for standard stents to 0.06±0.4 mm for sirolimus stents (P<0.001). Target-lesion revascularization and major adverse cardiac event rates were significantly lower in the sirolimus group (31.3% versus 7.3% and 36.3% versus 11.3%, respectively; both P<0.001). Non–insulin-and insulin-requiring patients demonstrated similar reductions in angiographic and clinical parameters of restenosis after sirolimus-eluting stent implantation. During the 9-month follow-up, stent thrombosis occurred in 2 patients after standard stent implantation. Conversely, this phenomenon was not seen in the sirolimus stent group.

Conclusions—This randomized trial demonstrated that sirolimus stent implantation is safe and efficacious in reducing both angiographic and clinical parameters of restenosis compared with standard stents in diabetic patients with de novo coronary stenoses. (Circulation. 2005;112:2175-2183.)

Key Words: diabetes mellitus ■ restenosis ■ stents ■ trials

Diabetes mellitus is a pandemic that currently affects more than 150 million people worldwide.1 Atherosclerotic macrovascular disease accounts for the majority of morbidity and mortality associated with type 2 diabetes mellitus.2 Specifically, cardiovascular disease is responsible for 75% of all hospital admissions and 80% of deaths in diabetic patients.3–6 Furthermore, coronary artery disease in diabetics exhibits distinctive characteristics that infer an increased risk. Likewise, it is characterized by being diffuse, affecting more often the main stem and also the distal coronary tree,7 and it usually presents an accelerated progression.8,9 Revascularization procedures in this setting present worse long-term outcomes and increased restenosis rates than those in the nondiabetic population.10,11 Drug-eluting stents have been demonstrated to be efficacious in the treatment of lesions of low to moderate risk.12–17 The potential efficacy of such stents in the diabetic population derives from subgroup analyses from randomized trials in which only patients with single-vessel disease with relatively large vessels (>2.5 mm) were included.18–20 We conducted a trial specifically aimed to assess the efficacy of the sirolimus-eluting stent for the treatment of de novo coronary stenoses in diabetic patients.
Methods

Study Design and Eligibility

This multicenter, prospective, randomized study complied with the provisions of the Declaration of Helsinki with regard to investigation in humans and was approved by the institutional review boards at all 4 investigational sites. Written informed consent was obtained from all patients. Patients were eligible for the study if they were diabetic (either non-insulin-dependent or insulin-dependent), according to the World Health Organization Report. All patients included were undergoing pharmacological treatment (insulin or hypoglycemic agents) for at least 1 month and presented de novo coronary stenoses in 1, 2, or 3 native vessels with symptoms or objective evidence of ischemia. Stenoses had to be amenable for stent implantation, with vessel size smaller than 4.0 mm (as assessed visually on angiography). Major exclusion criteria included impaired glucose tolerance without pharmacological treatment, gestational diabetes, or transient hyperglycemia; stenoses located in saphenous bypass, arterial bypass grafting, unprotected left main, or that involved important side branches (>2 mm) that should be treated during the procedure; left ventricle ejection fraction <25%; prior treatment with intracoronary brachytherapy or other drug-eluting stent at target site; restenotic lesions; known allergies to aspirin, ticlopidine, and clopidogrel; acute coronary syndromes with persistent ST elevation <72 hours and/or creatine kinase (CK) twice the upper normal limit; non-ST-elevation acute coronary syndromes with CK twice the upper normal limit; severe hepatic or renal disease (creatinine clearance <30 mL/min or hepatic enzymes twice the upper normal limit); and life expectancy <1 year.

Before the index procedure, a telephonic randomization was performed with a computer-generated code to randomly assign eligible patients to treatment with sirolimus-eluting stent (Cypher, Cordis) or standard stent (Bx Velocity/Sonic, Cordis) in a 1:1 ratio. Randomization was performed after written informed consent was signed. For patients with a single chronic total occluded vessel, randomization was performed after the occlusion was crossed with a wire. The randomization was centralized and stratified by diabetes treatment status: insulin-dependent or non-insulin-dependent.

Coronary Stent Procedure

Coronary angioplasty was performed according to standard rules and the experience of the operator. Neither ablative techniques (rotablator, directional atherectomy) nor cutting balloons were allowed. However, predilation with the use of a conventional balloon before stent implantation was optional. In case of predilation, the use of a balloon shorter than the stent was required in accordance with previously reported recommendations in the attempt to avoid geographic miss. Both stent types were available in lengths of 8, 13, 18, 23, 28, and 33 mm and in sizes of 2.25, 2.5, 2.75, 3.0, and 3.5 mm. Multiple stent implantations were allowed to cover the entire diseased segment. In this event, a minimal overlapping (~1 mm) between stents was recommended. When multisegment or multivessel stent deployment was performed, all implanted stents had to be of the same randomly assigned type. All patients were treated with oral aspirin (100 to 300 mg/d) and clopidogrel (loading dose 300 mg, then 75 mg/d for 1 year). During the procedure, an intravenous heparin bolus (100 IU/kg, or 70 IU/kg in case of administration of glycoprotein IIb/IIIa inhibitors) was administered. The use of glycoprotein IIb/IIIa inhibitors was recommended per protocol.

Data Collection, Follow-Up, and Core Laboratory Analyses

The study was designed by the authors, who had full access to the data, analyzed the data, and controlled all decisions with regard to publication. This trial was not sponsored by industry. Clinical follow-up information was obtained for all patients by the research coordinators at each site during hospitalization, at 30 days, and at 270 days and sent to a centralized coordinating center (San Carlos University Hospital, Madrid, Spain). Additional clinical follow-up is scheduled at 12 months, 13 months (1 month after clopidogrel withdrawal), and 2 years. All clinical end points were adjudicated by an independent clinical events committee that was unaware of the treatment group assignments.

Coronary angiograms, obtained at baseline, at completion of the stenting procedure, and at 270 days of follow-up, were submitted to the independent angiographic core laboratory (Health Science Center Jacksonville, University of Florida, Jacksonville, Fl) and were analyzed with the use of a computer-based system (CASS). The angiographic analysis was blinded to treatment assignment. Late luminal loss was defined as the difference between the minimal luminal diameter at the completion of the stenting procedure and that measured during follow-up. “Binary” restenosis was defined as stenosis of more than 50% of the luminal diameter in the target lesion at follow-up. Quantitative angiographic measurements of the target lesion were obtained in the “in-stent” zone (which included only the stented segment) and in the “in-segment” zone (which included the stented segment and the margins 5 mm proximal and distal to the stent).

Study End Points

The primary end point of this study was in-segment late lumen loss as assessed by quantitative coronary angiography at 270-day follow-up. The secondary end points included other angiographic parameters of restenosis, such as binary restenosis and minimal luminal diameter at 270-day follow-up; major adverse cardiac events, including cardiac death, myocardial infarction, target lesion (in-segment zone) revascularization at 1, 9, 12, and 24-month follow-up; and stent thrombosis. Myocardial infarction after the procedure was defined as the occurrence of prolonged typical chest pain and/or either the development of pathological Q waves that lasted at least 0.04 second in at least 2 contiguous leads with an elevated CK-MB fraction level or, in the absence of pathological Q waves, an elevation in CK levels to more than twice the upper limit of normal with an elevated CK-MB level. For this purpose, CK, CK-MB, and troponin levels were obtained before the index procedure and at 6 hours and 24 hours after the procedure. Additional blood samples were obtained in the event of chest pain, abnormal ECG, or elevated enzymes. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel. In the absence of angiographic confirmation, either acute myocardial infarction in the distribution of the treated vessel or sudden death was considered as stent thrombosis.

Statistical Analysis

The planned sample size of 160 patients provided 90% statistical power to detect a 56% difference in the primary end point at 270-day follow-up (from in-segment late loss of 0.73 mm in the standard stent group to 0.32 mm in the sirolimus stent group) with an SD of 0.79 and α-error of 0.05. We prespecified that the efficacy analysis and the safety evaluation were to be based on data from all patients who underwent randomization (intention-to-treat analysis). Quantitative variables are presented as mean±SD and categorical variables as percentages. Quantitative variables were compared by means of the Student t test after evaluation of normal distribution (Kolmogorov-Smirnov test). Categorical variables were compared by means of the χ2 test or Fisher exact test when at least 25% of values showed an expected cell frequency below 5. The analyses of the primary end point and quantitative secondary end points were based on a test of differences in means. Clinical secondary end points were compared on a per patient basis. Stratified analyses were performed to assess efficacy in the following prespecified variables: diabetes status, gender, left anterior descending artery, use of glycoprotein IIb/IIIa inhibitors, chronic total occlusion, lesion length, and stent size. Risk ratio and 95% CIs for in-segment restenosis were assessed between stent types. To identify clinical and angiographic factors that might be related to restenosis, backward logistic-regression models were used that included those variables with a probability value <0.1 on univariate analysis. In addition, to take into account the intrasubject variability, the analysis of lesions (repeated assessments) was adjusted by means of a general-
ized estimating equations model. Risk ratio was evaluated from a logistic regression model by having the final expression for the OR as $e$ to the $/H9252$-coefficient. The number needed to treat was calculated as the inverse of the absolute risk reduction. All statistical analyses were performed with the use of SPSS software (version 12.0) or STATA (version 9.0), and all reported probability values were 2-sided. We assumed significance at the 5% level ($/H11021 \leq 0.05$).

Results

Baseline Characteristics

The flow diagram of patients included in the present trial is depicted in Figure 1. Between February 2003 and November 2003, 170 patients were eligible for the study. Seven of them refused to be included in the trial, and 3 additional patients were not finally randomized because of the impossibility of crossing a total chronic occlusion when this was the only stenosis to be treated. In the end, 160 patients were randomly allocated to one of the treatment groups. One hundred eleven lesions were treated with stents in the 80 patients allocated to sirolimus stents, whereas 110 lesions were stented in the 80 patients allocated to standard stents. No crossover of stent type was reported by the investigators.

Baseline characteristics are presented in Table 1. The groups were well matched, with no differences in cardiac coronary risk factors or prior cardiac history. Mean age was $66.5 \pm 9$ years, and 62.5% of the patients were male. After subrandomization, one third of the patients were undergoing treatment with insulin, whereas two thirds were non-insulin-dependent diabetics. No differences were observed with the type of oral agents used between groups; glitazones were used in only 1.9% of patients. Multivessel disease was identified in 65% of the patients.

Lesion characteristics were also well matched between groups (Table 2). The majority of treated lesions (80.1%) were class B2 or C according to the American College of Cardiology/American Heart Association classification, the average reference diameter was $2.34 \pm 0.6$ mm, and mean lesion length was $15.0 \pm 8$ mm after chronic total occlusions (13.1% of lesions) were excluded from the analysis. Insulin-dependent diabetics presented a trend toward a smaller reference diameter and more severe stenoses than non-insulin-dependent diabetics (reference diameter $2.24 \pm 0.5$ versus $2.39 \pm 0.6$ mm, $P=0.08$ and percentage diameter stenosis $65 \pm 17\%$ versus $60 \pm 13\%$, $P=0.07$).

The clinical and angiographic characteristics of the present cohort of patients conferred upon them a much higher risk profile than for diabetics in previously reported substudies $^{18-20}$ (Tables 1 and 2). Indeed, in the present study population, 66% of lesions presented a reference diameter
smaller than 2.5 mm, 13% were chronic total occlusions, and 43% were longer than 20 mm by quantitative coronary angiography. In addition, 65% of patients had multivessel disease, 32% had a creatinine clearance \( < 60 \) mL/min, and 51% evidenced poor metabolic glycemic control at the index procedure, defined as glycohemoglobin A\(_1c\) \( > 7\%\).

**Procedural Data and In-Hospital Outcomes**

There were no differences between groups in terms of procedural data. Glycoprotein IIb/IIIa inhibitors were administered in 59% of the patients. Multivessel stenting was performed in 23.1% of patients and multisegment stenting in 13.8%. Mean \( \pm \) SD stent length was \( 23 \pm 12 \) mm (range 8 to 87 mm); \( 1.4 \pm 0.6 \) lesions were treated per patient, and \( 1.6 \pm 0.9 \) stents were implanted per patient. Forty-six percent of the implanted stents were \( 3.0 \) mm. Overlapping stenting was needed in 17.2% of lesions, whereas direct stenting was performed in 34.4% of lesions.

During hospitalization, no major adverse cardiac events occurred in the sirolimus stent group. Conversely, 1 cardiac death secondary to cardiac rupture (confirmed at necropsy) and 3 periprocedural non–Q-wave myocardial infarctions were observed in the standard stent group, with an increase in CK levels of \( < 3 \) times the upper normal limit.

### TABLE 1. Baseline Clinical and Lesion Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>All Patients (n=160)</th>
<th>Sirolimus Stent Group (n=80)</th>
<th>Standard Stent Group (n=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.5±9</td>
<td>65.9±9</td>
<td>67.2±10</td>
<td>0.38</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>62.5</td>
<td>62.5</td>
<td>62.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Insulin-dependent, %</td>
<td>33.1</td>
<td>32.5</td>
<td>33.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Non–insulin-dependent, %</td>
<td>66.9</td>
<td>67.5</td>
<td>66.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>61.3</td>
<td>61.3</td>
<td>61.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66.3</td>
<td>66.3</td>
<td>66.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>47.5</td>
<td>45.0</td>
<td>50.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Body mass index, %</td>
<td>29.1±4</td>
<td>29.3±4</td>
<td>28.8±3</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>36.9</td>
<td>31.3</td>
<td>42.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Previous angioplasty or cardiac surgery, %</td>
<td>18.7</td>
<td>20.0</td>
<td>17.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Clinical status, %</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>6.9</td>
<td>5.0</td>
<td>8.8</td>
<td></td>
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<tr>
<td>Exertional angina</td>
<td>30.0</td>
<td>30.0</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Unstable angina troponin (−)</td>
<td>40.0</td>
<td>45.0</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Unstable angina troponin (+)</td>
<td>17.5</td>
<td>15.0</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Elective post–myocardial infarction</td>
<td>5.6</td>
<td>5.0</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>65.0</td>
<td>61.3</td>
<td>68.8</td>
<td>0.32</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>65.4±13</td>
<td>66.9±13</td>
<td>63.8±13</td>
<td>0.13</td>
</tr>
<tr>
<td>Glycated hemoglobin A(_1c), %</td>
<td>7.3±1.4</td>
<td>7.4±1.5</td>
<td>7.3±1.4</td>
<td>0.65</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>72.9±26</td>
<td>70.7±23</td>
<td>75.3±30</td>
<td>0.70</td>
</tr>
<tr>
<td>Peripheral vasculopathy, %</td>
<td>10.6</td>
<td>11.3</td>
<td>10.0</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean \( \pm \) SD.

### TABLE 2. Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th>Lesion Characteristics</th>
<th>All Lesions (n=221)</th>
<th>Sirolimus Stent Lesions (n=111)</th>
<th>Standard Stent Lesions (n=110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length,* mm</td>
<td>15.0±8</td>
<td>14.6±8</td>
<td>15.3±8</td>
<td>0.50</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.34±0.6</td>
<td>2.33±0.6</td>
<td>2.35±0.6</td>
<td>0.80</td>
</tr>
<tr>
<td>Minimal luminal diameter, mm</td>
<td>0.9±0.4</td>
<td>0.9±0.4</td>
<td>0.9±0.4</td>
<td>0.57</td>
</tr>
<tr>
<td>Percentage diameter stenosis, %</td>
<td>62±17</td>
<td>61±17</td>
<td>63±16</td>
<td>0.40</td>
</tr>
<tr>
<td>Chronic total occlusion, %</td>
<td>13.1</td>
<td>12.6</td>
<td>13.6</td>
<td>0.82</td>
</tr>
<tr>
<td>B2/C class lesion, %</td>
<td>80.1</td>
<td>79.3</td>
<td>80.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Treated artery, %</td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>41.2</td>
<td>38.7</td>
<td>43.6</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>22.6</td>
<td>21.6</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>36.2</td>
<td>39.6</td>
<td>32.7</td>
<td></td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean \( \pm \) SD.

*Chronic total occlusions were excluded from the analysis of lesion length.
Quantitative Coronary Angiography

Quantitative coronary angiography was available in 92.7% of the lesions allocated to the sirolimus stent group and 91.8% of the lesions allocated to the standard stent group. Mean in-segment late lumen loss (the primary end point of the study) was reduced significantly in the sirolimus stent group, with an 87% in-segment relative reduction (0.47±0.5 mm for standard stent versus 0.06±0.4 mm for sirolimus stent; *P<0.001*). This was mainly due to a marked reduction in in-stent late lumen loss (87% relative reduction: 0.67±0.5 mm for standard stent versus 0.09±0.4 mm for sirolimus stent; *P<0.001*; Table 3). Frequency distribution curves of late loss in both groups are depicted in Figure 2. Similarly, binary restenosis was significantly reduced in both in-segment and in-stent zones (33.7% for standard stenting versus 7.8% for sirolimus stenting and 31.7% for standard stent versus 3.9% for sirolimus stent, respectively; *P<0.0001* for both comparisons). The length of the restenotic segment (defined as the length of the coronary segment presenting >50% diameter stenosis at follow-up angiography) showed a trend to be shorter in the sirolimus stent group (18.4±11 mm for standard stent versus 11.9±7 mm for sirolimus stent; *P=0.07*). In addition, lesions treated with standard stents showed a trend toward presenting occlusive restenosis more often than those treated with sirolimus stents (5.5% versus 0.9%, respectively; *P=0.07*). The incidence of significant edge effect was low and comparable between groups (2% for standard stenting versus 3.9% for sirolimus stenting, respectively; *P=0.68*). Cumulative frequency distribution curves of minimal luminal diameter are depicted in Figure 3. A shift to the left was observed in the standard stent curve compared with the sirolimus stent curve, which demonstrates the more favorable late angiographic findings in that group.

Clinical Outcomes at 30 and 270 Days

At 30-day follow-up, 1 additional cardiac death due to sudden death occurred in the standard stent group that was adjudicated as stent thrombosis by the clinical events committee (6.3% cumulative major adverse event rate at 30 days), whereas no events were observed in the sirolimus stent group (0% cumulative major adverse event rate; *P=0.10*).

At 270-day follow-up, the rate of major cardiac adverse events was significantly lower in the sirolimus stent group (36.3% versus 10.0%, *P<0.001*) at the expense of a significant reduction in the need for subsequent revascularization (31.3% versus 6.3%, *P<0.001*). One patient in the sirolimus stent group died of refractory heart failure. The late (between 30 and 270 days) stent thrombosis rate was 0% in the sirolimus stent group. Conversely, 1 patient from the standard stent group presented with stent thrombosis that led to a non-Q-wave myocardial infarction 2 months after the index procedure. In this patient, clopidogrel treatment was withdrawn 1 week before the event owing to gastrointestinal surgery.

Insulin-Dependent Versus Non–Insulin-Dependent Diabetics

In-segment and in-stent late loss and restenosis rates were significantly reduced in both insulin-dependent and non–insulin-dependent diabetic patients treated with sirolimus
stent implantation (Table 3), as were target-lesion revascularization rates (from 33.3% to 5.9% for insulin-dependent diabetics, \(P < 0.001\), and from 23% to 5.2% for non-insulin-dependent diabetics, \(P = 0.002\)).

Subgroup Analyses

The relative reduction in the risk of restenosis with the use of the sirolimus stent was concordant in all the prespecified variables for subgroup analyses (Figure 4). The association of known clinical angiographic risk factors for restenosis with the treatment effect of the sirolimus stent was evaluated with multivariable logistic regression modeling of the rate of in-segment restenosis within 270 days adjusted by means of the generalized estimating equation method to account for repeated assessments. In this model, the sirolimus stent was significantly associated with a reduced risk of restenosis (OR 0.28, 95% CI 0.10 to 0.76; \(P = 0.01\)), as were age (OR 0.97, 95% CI 0.94 to 0.99, \(P = 0.03\)) and minimal luminal diameter after stent implantation (OR per 1-mm increment 0.42, 95% CI 0.16 to 1.14, \(P = 0.09\)). In addition, stent length was associated with an increased risk of restenosis (OR per 1-mm increment 1.03, 95% CI 1.00 to 1.07, \(P = 0.03\)). The number of lesions that needed to be treated with a sirolimus stent to avoid an episode of in-segment restenosis was 4 (95% CI 3 to 6).

Figure 2. Frequency distribution of in-segment late lumen loss values at 270-day follow-up for all lesions treated with sirolimus-eluting stent (left) and standard stent (right). \(P = 0.02\) for sirolimus stents and \(P = 0.43\) for standard stent by Kolmogorov-Smirnov test.

Figure 3. Cumulative frequency distribution curves for minimal luminal diameter in the group that received sirolimus-eluting stent and in the group that received standard stent before and immediately after the intervention and at 270 days.
Discussion

This is the first trial specifically designed to evaluate the efficacy of sirolimus-eluting stent implantation in patients with diabetes mellitus. A marked reduction in late lumen loss was demonstrated in patients treated with sirolimus stents at 9-month follow-up (primary end point of the study). This was accompanied by an important reduction in angiographic restenosis (in-stent and in-segment zones) and clinical restenosis rates (ie, target-lesion revascularization). In addition, this benefit in clinical events occurred in the absence of thrombotic complications related to use of the sirolimus stent. Finally, these favorable angiographic and clinical effects were demonstrated both in insulin-requiring and non–insulin-requiring diabetic patients.

On average, late lumen loss was close to 0 in the sirolimus stent group. The frequency distribution curve of late loss values of sirolimus stents was markedly skewed to the left and missed the normal distribution (Kolmogorov-Smirnov test P = 0.43; Figure 2). This distinctive behavior mimics that of a recently published series of patients treated with sirolimus stents. Although in the sirolimus group, this pattern may reflect the all-or-none response of restenosis phenomenon, the pattern observed in the standard stent group presents the classic normal distribution representative of a continuous phenomenon. Of interest is the lower-than-expected late loss observed in the standard stent group. However, despite this fact, sirolimus-eluting stent implantation presented both angiographic and clinical benefit compared with standard stent implantation. Furthermore, in-stent late loss in the standard group observed in the present study compared well with the late loss described in other small-vessel trials published previously. This fact highlights the importance of vessel size in determination of sample size based on late loss.

Vessel size in the present trial was rather small, with data from the core laboratory documenting an average reference diameter of 2.34 mm. More than 50% of the stents finally implanted were ≥3.0 mm, and overall balloon-to-artery ratio was rather high (1.3 ± 0.3 mm). Diabetic patients usually present with long lesions and diffuse disease (43% of lesions were longer than 20 mm, and 17% of patients received overlapping stents). In such a scenario, the use of the interpolated method to calculate the vessel reference diameter may underestimate the vessel size compared with the visual assessment that is used to select the stent size. This phenomenon was also observed in the cohort of patients with...
very small vessels included in the Ravel trial. In that study, those vessels with reference diameter smaller than 2.36 mm (stratum I) presented a balloon-to-artery ratio of 1.3 ± 0.1. Interestingly, 60.4% of the stents implanted in those vessels were sized ≥3.0 mm. Conversely, in large vessels (stratum III; >2.84 mm in reference vessel diameter), the balloon-to-artery ratio was 1.0 ± 0.1.

As observed in previous trials, the beneficial effect of drug-eluting stent implantation was tarnished by the occurrence of edge effect. Overall, the degree of late loss at stent edges was comparable between the 2 groups (Table 3). However, in the sirolimus stent group, 50% of the restenoses were located at the stent edges (3.9%). Conversely, in the standard stent group, 94% of the restenoses were located within the stent. One of the plausible explanations for this phenomenon includes the profound inhibitory effect of sirolimus, as demonstrated by the virtual abolishment of late loss, which may magnify the small degree of lumen loss at the edges, resulting in significant restenosis by quantitative coronary angiography analysis. Geographical miss may also explain some of the failures at stent edges. Both injury at the peri-stent zone and incomplete coverage of the preexisting lesion may stimulate plaque proliferation, because it occurred with the use of intracoronary brachytherapy.

Insulin-dependent diabetics treated with a sirolimus stent evidenced the same degree of angiographic and clinical benefit as diabetics treated with oral agents. This finding expands the benefit of rapamycin stents into a higher-risk population with smaller vessels and more severe stenoses. In contrast, the SIRIUS trial failed to demonstrate benefit from sirolimus-eluting stent use in the subgroup of insulin-requiring diabetic patients owing to the high incidence of edge effect.

Dual antiplatelet treatment (aspirin and clopidogrel) was prescribed for 1 year in both groups. In addition, the use of glycoprotein IIb/IIIa inhibitors during the procedure was ultimately accomplished in >59% of patients. Under this antiplatelet regimen, not a single stent thrombosis in the sirolimus-eluting stent group has been reported at 270-day follow-up, which suggests that the use of this stent in patients with diabetes mellitus is safe.

Study Limitations

This trial was not blinded; however, primary and secondary angiographic end points were analyzed by an independent core laboratory that had no access to randomization code. In addition, clinical events were adjudicated by the independent events committee in a blinded manner.

Restenotic lesions were excluded from the trial. Thus, the efficacy of sirolimus-eluting stents in diabetic patients with restenosis cannot be extrapolated from our results. Eight percent of the patients did not return for angiographic follow-up; however, baseline clinical and angiographic characteristics of this subgroup of patients did not differ from those who underwent the 9-month angiographic follow-up.

The use of stainless steel stents for the control group may magnify the efficacy of sirolimus-eluting stents. The potential of cobalt-chromium stents compared with drug-eluting stent requires further assessment in randomized clinical trials.

The present trial was not designed to demonstrate whether diabetic patients had to be treated with percutaneous coronary intervention or coronary bypass grafting. This will be addressed in upcoming randomized trials comparing surgery versus drug-eluting stent implantation.

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References


