Sirolimus-Eluting Stents for the Treatment of Obstructive Superficial Femoral Artery Disease
Six-Month Results

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Background—Stent implantation for obstructive femoropopliteal artery disease has been associated with poor long-term outcomes. This study evaluated the effectiveness of shape memory alloy recoverable technology (SMART) nitinol self-expanding stents coated with a polymer impregnated with sirolimus (rapamycin) versus uncoated SMART stents in superficial femoral artery obstructions.

Methods and Results—Thirty-six patients were recruited for this double-blind, randomized, prospective trial. All patients had chronic limb ischemia and femoral artery occlusions (57%) or stenoses (average lesion length, 85±57 mm). Patients were eligible for randomization after successful guidewire passage across the lesion. Eighteen patients received sirolimus-eluting SMART stents and 18 patients received uncoated SMART stents. The primary end point of the study was the in-stent mean percent diameter stenosis, as measured by quantitative angiography at 6 months. The in-stent mean percent diameter stenosis was 22.6% in the sirolimus-eluting stent group versus 30.9% in the uncoated stent group (P=0.294). The in-stent mean lumen diameter was significantly larger in the sirolimus-eluting stent group (4.95 mm versus 4.31 mm in the uncoated stent group; P=0.047). No serious adverse events (death or prolonged hospitalization) were reported.

Conclusions—The use of sirolimus-eluting SMART stents for superficial femoral artery occlusion is feasible, with a trend toward reducing late loss compared with uncoated stents. The coated stent also proved to be safe and was not associated with any serious adverse events. (Circulation. 2002;106:1505-1509.)

Key Words: claudication ■ peripheral vascular disease ■ stents ■ drugs ■ restenosis

Restenosis is more problematic with infragenual stent implantation than with stent implantation in the coronary arteries, with rates of 30% to 50%.1 Although preliminary results with coronary arterial brachytherapy are promising, there have also been problems stemming from late thrombosis and edge effects.2,3 Most systemic pharmacological approaches to suppressing neointimal proliferation have failed because of insufficient local drug concentrations.4 This has fostered attempts to deliver drugs locally using a stent-based platform. Here, local drug kinetics and release mechanisms are crucial.4,5

Until now, there have been no reports about the use of self-expanding, drug-eluting nitinol stents in humans. The stents used in this study were coated with a polymer impregnated with sirolimus (rapamycin, Wyeth Ayerst), a natural macrocyclic lactone with immunosuppressive activity. Sirolimus has a unique dual mechanism of action involving both antinflammatory and cytostatic antiproliferative effects resulting from inhibition of a signal transduction kinase, the mammalian target of rapamycin (mTOR).6 Sirolimus is capable of diminishing both rat and human smooth muscle cell proliferation and has shown impressive antirestenotic properties in coronary arteries.7–10 In human coronary arteries, sirolimus-eluting steel stents virtually abolished neointimal proliferation at 4 and 12 months of follow-up.7,8 This study is the first angiographically controlled, randomized, double-blind trial evaluating the 6-month outcomes of drug-eluting stents.
stent implantation in long-segment obstructions of the superficial femoral artery (SFA).

Methods

Patients
From February 2001 to July 2001, 36 patients with symptomatic peripheral artery disease classified as Rutherford stage 2 to 4 were treated in a multicenter, prospective, randomized, 2-arm study evaluating the efficacy and safety of sirolimus-eluting stents. The study was approved by the local Ethics Committee, and all procedures complied with good clinical practice guidelines. All patients gave written informed consent.

Patients were randomized to implantation of sirolimus-eluting nitinol self-expandable stents (SMART Nitinol Self-expanding Stent, Cordis; n = 18) or the same stent without the sirolimus/polymer coating (n = 18). Patients were recruited from 6 centers in Europe and Canada. All had obstructive, native, de novo, or restenotic lesions with a diameter stenosis >70% over a length that ranged from 7 to 20 cm or occlusions that ranged from 4 to 20 cm, in the SFA (corresponding to grade C lesions according to the Transatlantic Inter-Society Consensus Protocol). Complex, long lesions with a high incidence of total occlusion were chosen for stenting because this is the population in which the maximum difference can be shown, thereby reducing the sample size. Reference vessel diameter was 4 to 6 mm. Exclusion criteria included poor aortoiliac or common femoral inflow, thrombophlebitis, uremia, aneurysmal target vessels, previously stented lesions, tandem lesions, and ischemic tissue loss. Although patients are being followed noninvasively for 24 months, this report presents the 6-month findings.

Performance was assessed by 6-month in-stent percent diameter stenosis using the following hypothesis: H0: μb = μs H1: μb ≠ μs, where μb is the uncoated SMART stent 6-month in-stent percent diameter stenosis, μs is the sirolimus-coated SMART stent 6-month in-stent percent diameter stenosis, H0 is a null hypothesis, and H1 is an alternative hypothesis.

A sample size of 14 in each group would have 80% power to detect a difference in means of 20% diameter stenosis (the difference in-stent percent diameter stenosis, H0 is a null hypothesis, and H1 is an alternative hypothesis).

End Points
The primary end point of the study was the in-stent mean percent diameter stenosis by quantitative angiography at 6 months, as assessed by an independent core laboratory (Cardiovascular Research Foundation, New York, NY). The mean percent diameter stenosis was chosen as the primary end point instead of mean lumen diameter and late loss, which are quantitatively more sensitive, because percent diameter stenosis is independent of vessel diameter.

Secondary end points included duplex Doppler ultrasound, ankle-brachial index, hemodynamic failure, pharmakokinetic sampling, and incidence of serious adverse events. Serious adverse events, defined as death or prolonged hospitalization, were recorded, as were nonserious device-related adverse events according to standard classifications. The rate of minor complications, ie, those that did not meet the criteria for major complications, was also recorded.

Stents and Pharmacokinetic Analysis
The SMART stent is a self-expandable, crush-recoverable nitinol stent. Unconstrained stent diameters that were 1 to 2 mm larger than the reference vessel diameter were chosen. The translucent stent coating had a thickness of ~5 μm and was composed of an elastic copolymer combined with sirolimus in a 30:70 drug:copolymer weight ratio. The amount of drug per vessel area is equivalent to that used in the coronary application (90 μg/cm²). Depending on the randomization, these stents contained 1.2 mg of sirolimus or were uncoated. All stents were 80 mm in length.

Blood samples were drawn to measure the systemic-release kinetics of sirolimus before stent implantation and at 1, 2, 3, 6, and 24 hours after the procedure. The samples were analyzed by an independent pharmacokinetic laboratory (Analytical Unit, London, UK).

Stent Procedure
The day before the procedure, patients received 300 mg of aspirin (loading dose) if they were not already on aspirin. After an antegrade puncture and introduction of a sheath into the common femoral artery and after the lesion had been crossed with a guidewire, an intraarterial heparin bolus of 3000 to 5000 U (based on patient weight) was administered. A heparin infusion of 750 to 1000 U/h followed. Overnight (24-hour) treatment with heparin was permitted. It was recommended that patients receive 2 antplatelet drugs (aspirin plus either ticlopidine or clopidogrel) for 3 to 4 weeks after the procedure. All stents were implanted through a 7-French introduction sheath. A maximum of 3 stents per lesion could be implanted electively. Angiography was performed before and after stent placement.

Angiography and Secondary End Point Analysis
Thirty-three patients returned for repeat angiography at 6 months. Angiography was performed in at least 2 orthogonal projections with radiopaque rulers or calibration catheters (5-F, straight, Cordis) for reference. Binary restenosis was defined as ≥50% stenosis. In-stent restenosis and in-lesion restenosis (including a 5-mm segment on each end of the stent) were analyzed. Analyses of angiograms obtained at baseline and at the 6-month follow-up visit were performed by an independent core laboratory (Cardiovascular Research Foundation Angiographic Core Laboratory, New York, NY). The methodology used by the core laboratory was derived from the methods established for coronary angiographic analysis. Study films were accepted in cineangiogram, cut film, or digital formats. Cut films were converted into digital images using a digital scanner.

Quantitative measurements were made using the Cardiovascular Angiography Analysis System (CAAS II, Pie Medical, the Netherlands). Measurements were made by core laboratory technicians blinded to treatment allocation and were reviewed by the medical director. Lesion morphology, including lesion length and location and the presence of calcification or thrombus, and the occurrence of procedural complications were determined. Quantitative measurements at baseline and follow-up included lumen dimensions such as reference vessel diameter, minimal lumen diameter, percent diameter stenosis, and binary restenosis. The mean lumen diameter along the stented segment was also determined.

The clinical stage of the patients was classified according to the Rutherford criteria, the ankle-brachial index was measured, and adverse events were evaluated at baseline, discharge, 1 month (±7 days), and 6 months (±14 days). Duplex Doppler ultrasound was done at discharge, 1 month (±7 days), and 6 months (±14 days).

Statistical Analysis
Comparisons between the 2 treatment groups were made with Mann-Whitney-Wilcoxon, Kruskal-Wallis, and χ² tests. Continuous variables were expressed as mean±SD and dichotomous variables were expressed as numerator/denominator or percentage. All statistical tests were 2-sided. A probability value of <0.05 was considered statistically significant.

Results

Patient Characteristics
Baseline demographics were similar in the 2 treatment groups (Table 1), except that the percentage of patients who smoked or had diabetes was somewhat higher in the sirolimus-eluting stent group than in the uncoated stent group (32.9% versus 16.7%, P = 0.305, and 50.0% versus 28.8%,
### Table 1. Baseline Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sirolimus-Eluting Stent Group (n=18)</th>
<th>Uncoated Stent Group (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>11/7</td>
<td>16/2</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>ASA, %</td>
<td>38.9</td>
<td>38.9</td>
</tr>
<tr>
<td>1</td>
<td>38.9</td>
<td>38.9</td>
</tr>
<tr>
<td>2</td>
<td>33.3</td>
<td>44.4</td>
</tr>
<tr>
<td>3</td>
<td>27.8</td>
<td>16.7</td>
</tr>
<tr>
<td>Cardiomyopathy, %</td>
<td>38.9</td>
<td>33.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>50.0</td>
<td>28.8</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>61.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>72.2</td>
<td>66.7</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>32.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Rutherford classification, %</td>
<td>1+2</td>
<td>66.7</td>
</tr>
<tr>
<td>3+4</td>
<td>61.1</td>
<td>33.3</td>
</tr>
<tr>
<td>Mean lesion length, mm</td>
<td>82.9</td>
<td>88.6</td>
</tr>
<tr>
<td>Calcified lesion, %</td>
<td>100</td>
<td>46.7</td>
</tr>
<tr>
<td>Total occlusion, %</td>
<td>56.3</td>
<td>58.8</td>
</tr>
<tr>
<td>Mean no. of stents</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*ASA is the abbreviation for Appraisal of Self-Care Agency.13 In the ASA scale from 1 to 5, ASA 1 denotes a healthy patient, ASA 2 denotes slight systemic disease, and ASA 3 denotes pronounced systemic disease with reduction in performance.

†includes remote myocardial infarction (MI), occult MI, MI within 6 months, stable and unstable angina, symptomatic or poorly controlled ectopy or symptomatic arrhythmia, and congestive heart failure poorly managed by drugs.

### Table 2. Angiographic Findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sirolimus-Eluting Stent Group (n=18)</th>
<th>Uncoated Stent Group (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter, mm</td>
<td>4.81 (0.51)</td>
<td>4.82 (0.45)</td>
<td>0.9347</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>0.52 (0.75)</td>
<td>0.62 (0.89)</td>
<td>0.7451</td>
</tr>
<tr>
<td>Before procedure</td>
<td>3.93 (0.51)</td>
<td>3.75 (0.52)</td>
<td>0.2991</td>
</tr>
<tr>
<td>Immediately after procedure</td>
<td>88.9 (14.8)</td>
<td>87.0 (18.6)</td>
<td>0.7548</td>
</tr>
<tr>
<td>Before procedure</td>
<td>21.2 (8.1)</td>
<td>23.3 (9.5)</td>
<td>0.5545</td>
</tr>
<tr>
<td>After procedure, in stent</td>
<td>3.47 (0.71)*</td>
<td>2.94 (1.17)†</td>
<td>0.1248</td>
</tr>
<tr>
<td>In lesion</td>
<td>3.73 (0.77)*</td>
<td>3.28 (1.36)†</td>
<td>0.2465</td>
</tr>
<tr>
<td>Percent diameter stenosis</td>
<td>28.4 (12.6)</td>
<td>37.7 (24.5)</td>
<td>0.1774</td>
</tr>
<tr>
<td>In stent</td>
<td>22.6 (16.5)</td>
<td>30.9 (27.2)</td>
<td>0.2942</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.46 (0.72)</td>
<td>0.80 (1.19)</td>
<td>0.3224</td>
</tr>
<tr>
<td>In lesion</td>
<td>0.62 (0.60)</td>
<td>1.03 (1.30)</td>
<td>0.2523</td>
</tr>
<tr>
<td>In stent</td>
<td>4.95 (0.59)</td>
<td>4.31 (1.39)</td>
<td>0.047</td>
</tr>
<tr>
<td>In-stent mean lumen diameter, mm</td>
<td>0</td>
<td>5.9 (n=1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Total occlusion rate, %</td>
<td>0</td>
<td>23.5 (n=4)</td>
<td>0.1026</td>
</tr>
<tr>
<td>Restenosis rate, %</td>
<td>0</td>
<td>17.6 (n=3)</td>
<td>0.2273</td>
</tr>
</tbody>
</table>

*Values are mean at 6 months (± SD) unless otherwise noted.

### Pharmacokinetic Analysis

Blood samples were drawn from 13 patients receiving the sirolimus-eluting stent. The mean systemic concentration of sirolimus was 31.1±14.5 ng/mL after 1 hour, 26.3±12.5 ng/mL at 2 hours, 22.3±9.8 ng/mL at 3 hours, 17.5±6.2 ng/mL at 6 hours, and 10.1±4.4 ng/mL at 24 hours after the procedure. The highest sirolimus peak measured was 59.0 ng/mL in a patient who received 3 stents. No sirolimus was detected in the blood samples drawn from 13 patients who received the uncoated stents.

### Adverse Events

One patient was diagnosed with inflammation in the treated leg 2 days after stent implantation. This patient was treated with antibiotics and discharged in the usual time frame with no additional untoward events. However, 2 months later and 4 months after that, the patient reported knee pain in the treated leg and was diagnosed with gout. Another patient reported redness and swelling of the foot 5 days after treatment. This patient was treated for suspected cellulitis, and the symptoms resolved without further specific therapy.

Both patients had received the sirolimus-eluting stents. Stent fractures (defined as ≥1 broken strut) were detected in 6 of 33 patients, 3 in each treatment group, who had follow-up angiograms. In all 6 patients, multiple stents (n=3) had been implanted, but none of the patients had any clinical symptoms.

### Quantitative Angiography

Technical success was achieved in all procedures. At 6 months, 3 patients refused angiography. The in-stent mean percent diameter stenosis by quantitative angiography immediately after the procedure was 21.2±18% in the sirolimus-eluting stent group and 23.3%±9.5% in the uncoated stent group (P=0.554; Table 2). At the 6-month follow-up, the...
SFA obstructions. This is the first study to demonstrate that self-expanding stents with uncoated nitinol stents in long lesions can achieve low in-stent restenosis rates. After 6 months, no intimal hyperplasia is evident inside the stent or at the stent edges (arrows denote beginning and end of stent). There is mild restenosis proximal to the treated segment.

Data for a 77-year-old patient with intermittent claudication. A, Intraarterial digital subtraction angiography before treatment shows high-grade stenosis of the distal superficial femoral artery (length, 7 cm). B, After implantation of the sirolimus-eluting SMART nitinol stent, restoration of patency can be seen. C, After 6 months, no intimal hyperplasia is evident inside the stent or at the stent edges (arrows denote beginning and end of stent). There is mild restenosis proximal to the treated segment.

mean percent diameter stenosis was 22.6±16.5% in the sirolimus-eluting stent group and 30.9±27.2% in the uncoated stent group (P=0.294; Table 2). Also at 6 months, the in-stent mean lumen diameter was 4.95±0.59 mm in the sirolimus-eluting stent group and 4.31±1.39 mm in the uncoated stent group (P=0.047). The in-stent mean lumen diameter of 4.95 mm in the sirolimus-coated stent group was larger than the reference diameter (4.81 mm). With self-expanding stents that are 1 to 2 mm larger than the vessel diameter, a “step-up/step-down” effect between the reference vessel and the stented area is often seen. In other words, the vessel diameter within the stented area is noticeably larger than the vessel diameter proximal to the stent. As a result, with suppression of intimal hyperplasia, it would be possible for the in-stent mean diameter to be larger than the reference diameter.

The occlusion rate was 0% in the sirolimus-coated stent group and 5.9% (n=1) in the uncoated stent group. The binary in-lesion restenosis rate was 0% in the sirolimus-coated stent group and 23.5% (P=0.10) in the uncoated stent group. No secondary revascularization procedures were required in either treatment group.

Restoration of patency in the SFA after implantation of sirolimus-eluting stents is shown in the Figure. The ankle-brachial index was higher at discharge and at 1-month and 6-month follow-up compared with the index at screening in both treatment groups. Similarly, more patients in both groups were classified as Rutherford stages 1 and 2, and fewer as stages 3 and 4, at discharge and follow-up than at screening.

Discussion
This trial was conducted to compare sirolimus-eluting nitinol self-expanding stents with uncoated nitinol stents in long SFA obstructions. This is the first study to demonstrate that controlled drug release is also feasible using a self-expandable nitinol stent platform. The results in this trial can be explained by the scaffolding characteristics of the stent and the potent cytostatic effects of sirolimus, which binds to a specific cytosolic receptor protein (FK-binding protein [FKBP]-12). The sirolimus/FKBP complex then binds to the mammalian target of rapamycin (mTOR), an important growth factor and signal transduction kinase, and inhibits its activation.14 This leads to cell-cycle arrest in the late G1 phase.9,15,16 In addition to this mechanism, the upregulation of FKBP-12 observed in human neointimal smooth muscle cells supports the antirestenotic effects of sirolimus.17 Sirolimus also exerts antiinflammatory effects in the vessel wall.18

The results at 6 months demonstrate inhibition of in-stent neointimal proliferation, reflecting a trend toward a reduction in late loss. The rate of binary in-stent restenosis was 0% in the sirolimus-eluting stent group and 23.5% in the uncoated stent group, even though this was a patient population with long lesions (mean length, 85 mm), 57% of which were totally occluded before stenting. The fact that the late loss is greater in-stent than in-lesion does not imply that there is more hyperplasia in the stent. Rather, this is a reflection of the fact that there is more early gain and subsequently more late loss within the stent than in-lesion. The net gain (the difference between early gain and late loss) in the sirolimus arm was 3.21±0.95 mm in-stent versus 2.95±0.79 mm in-lesion and, in the control arm, 2.66±1.95 mm in-stent versus 2.32±1.14 mm in-lesion. Therefore, the net gain values demonstrate the true reduction of intimal hyperplasia seen with the sirolimus stent.

Interestingly, the restenosis rates for the uncoated stent were much lower than what had been expected from results reported in the published literature. Precise restenosis rates are lacking for the femoropopliteal region because of incomplete or absent angiographic follow-up in most studies.19,20 Patency rates 12 months after the placement of Wallstents and Palmaz stents in mostly short SFA lesions have been reported to range from 22% to 61%.1,14,15 Duplex ultrasound follow-up in a group of 55 patients, most of whom were treated with femoral Wallstents, showed a primary 6-month patency rate of only 47%.1 The Transatlantic Inter-Society Consensus Group summarized the results of femoropopliteal stenting as follows: in a comparison of 11 trials involving femoropopliteal artery stenting in 585 patients, the primary patency rate was 67% (range, 22% to 81%) at 23 months and 58% at 36 months. For percutaneous transluminal angioplasty (8 trials comprising 1241 patients), the patency rates were 61% at 12 months and 51% at 36 months.12

Stent fractures occurred in both the drug-eluting and control stents. All fractures occurred in lesions with 3 overlapping stents, but all of the patients were clinically asymptomatic. These fractures may be due to both the long length of the stented vessel and the overlapping of stents, leading to “splinting” of the vessel in certain places, with resultant hinge points. Vessel compression and movement may have played a role in the development of hinge points.

Although only some of the variables measured in this small group of patients showed a significant difference between the 2 groups in favor of the sirolimus-eluting stent, all variables...
showed a positive trend in that direction. The baseline characteristics of the 2 groups were also not randomly distributed and may have been skewed against the sirolimus-eluting stent group, thus making it more difficult to achieve a statistically significant difference.

The peak early systemic sirolimus blood concentration of 59 ng/mL is below the peak blood level of 211 ng/mL found to be safe in human studies. Furthermore, the mean concentration beyond 24 hours is below the therapeutic range of sirolimus (9 to 17 ng/mL) recommended for the prevention of renal transplant rejection. Therefore, the occurrence of systemic adverse events is unlikely. Two patients in this trial developed localized erythema a few days after the intervention. Both were treated with antibiotics for suspected cellulitis, and the erythema resolved without further therapy. In one patient, gout was considered the most likely diagnosis on the basis of the clinical information available. However, we cannot rule out the possibility that these events may have been related to drug elution. These patients will be reevaluated at 24 months.

In the meantime, these encouraging data should lead to larger randomized, controlled trials of this form of treatment for patients with SFA disease. The goals are to improve vascular patency and limb perfusion, as well as to maximize quality of life while minimizing the costs of care by making minimally invasive therapies a competitive and valid alternative to open surgical procedures in a broader range of patients.

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References
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