Treatment of Left Anterior Descending Coronary Artery Disease With Sirolimus-Eluting Stents

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Background—Revascularization strategies often hinge on the presence and degree of left anterior descending coronary artery (LAD) stenosis. A decision for bypass surgery is often based on the durability of surgical LAD revascularization compared with percutaneous approaches. By decreasing restenosis, drug-eluting stents may have reduced the “reintervention gap” between surgery and percutaneous intervention, making the percutaneous route preferable.

Methods and Results—Of the 1101 patients in the SIRIUS trial, 459 with an LAD stenosis were randomized to percutaneous intervention with either sirolimus-eluting or bare-metal stents. Baseline demographic, clinical, and angiographic data were obtained. Patients had 1-year clinical and 8-month angiographic follow-up. Baseline characteristics were similar in both groups. The majority of lesions were tubular type B lesions (69.7%) with a mean diameter of 2.73 mm and a mean length of 14.0 mm. The binary in-stent restenosis rate was 2% for the sirolimus stent group and 41.6% for the bare-metal arm (relative risk, 0.05; 95% CI, 0.02 to 0.1; P<0.001). One-year major adverse events (defined as cardiac death, Q-wave and non-Q-wave myocardial infarction, or target vessel revascularization) was decreased 59% in the sirolimus-stent group (9.8% versus 24.9%; relative risk, 0.39; 95% CI, 0.26 to 0.61; P<0.001).

Subgroup analysis of 135 patients with proximal LAD lesions showed similar benefits. In-stent restenosis was 0 in the proximal LAD sirolimus-eluting group (n=67), compared with 38% in the bare-metal arm (n=68), and major adverse events demonstrated a similar trend, with a 50% decrease compared with control patients (10.4% versus 20.6%, P=NS).

Conclusions—Sirolimus-eluting stents significantly decrease revascularization rates in LAD lesions. At 1 year, sirolimus-eluting stent revascularization rates are comparable to historic single vessel bypass surgery revascularization rates.

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Key Words: angioplasty ■ stents ■ cardiovascular disease

Despite advances in technology and numerous clinical trials, the choice of which revascularization strategy is best for patients with left anterior descending coronary artery (LAD) disease remains controversial. Bypass surgery provides the most benefit in patients with proximal LAD stenoses who receive arterial revascularization with a mammary artery conduit.1–5 Percutaneous intervention has failed to match the outcomes obtained with bypass surgery, primarily because of significant requirements for repeat revascularization procedures because of restenosis.6–8 Recently, sirolimus-eluting stents have been shown to dramatically reduce restenosis.9,10 This reduction in restenosis may have narrowed the “reintervention gap” enough to eliminate the major advantage of bypass surgery for the treatment of LAD disease. The objective of this study was to determine the clinical outcome after percutaneous intervention of the LAD with sirolimus-eluting stents.

Methods

Study Design and Patient Eligibility

This analysis was composed of patients from a study of Sirolimus-Eluting Balloon-Expandable Stents in the Treatment of Patients with de novo Native Coronary Artery Lesions (the SIRIUS study).10 Briefly, SIRIUS was a randomized, double-blind trial performed at 53 investigational sites and complied with the Declaration of Helsinki regarding investigation in humans. It was approved by the US Food and Drug Administration and the Institutional Review Board at each participating center. All patients gave written informed consent.

Patients were eligible if they had a history of stable or unstable angina and signs of myocardial ischemia. In addition, patients were required to have a single de novo target lesion in a native coronary artery of 51% to 99% diameter stenosis and of 15 to 30 mm in length (visual angiographic estimates). Patients were excluded for recent myocardial infarction (within 48 hours), left ventricular ejection fraction <25%, or target lesions in a left main, ostial, or bifurcation location. Thrombotic and severely calcified lesions were also ex-
Coronary Stent Procedure

All patients received a loading dose of 300 to 375 mg of clopidogrel and then 75 mg/d for 3 months in addition to 325 mg/d aspirin. Lesions were treated by use of standard interventional techniques. Balloon predilation was mandated before stent placement. Stent assignment was blinded to both the physician and the patient. The sirolimus-eluting and standard stents were available in 8- and 18-mm lengths and in 2.5-, 3.0-, and 3.5-mm diameters. They were identical in appearance. The sirolimus-eluting stent contained 140 µg of sirolimus per square centimeter of stent surface area within a 5- to 10-µm-thick copolymer matrix designed to release ~80% of the total sirolimus dose in 30 days. Postdilation was allowed to optimize angiographic deployment. During the procedure, intravenous heparin boluses were administered. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the operator’s discretion.

Data Collection, Follow-Up, and Core Laboratory Analyses

Clinical follow-up was obtained in all patients at 30, 90, 180, 270, and 360 days. All data were submitted to a data coordinating center (CDAC/Harvard Clinical Research Institute, Harvard Medical School). All clinical end points were adjudicated by an independent and blinded Clinical Events Committee. A separate Data Safety Monitoring Board reviewed all data periodically to identify potential safety concerns.

Coronary angiograms were obtained at baseline and at the completion of the stent procedure. Of patients with LAD lesions, there were 178 patients in the bare-metal arm and 175 patients in the sirolimus stent arm who were assigned to mandated angiographic follow-up at 240 days. Angiograms were analyzed at the angiographic core laboratory (Brigham and Women’s Angiographic Core Laboratory) using a computer-based system (Medis). The proximal LAD was defined as the vessel between the circumflex takeoff and the first major septal or diagonal branch. Quantitative angiographic measurements of the target lesion were made at the “in-stent” zone (only the stented segment) and at the “in-segment” zone (the stented segment as well as the margins 5 mm proximal and distal to the stent). Binary restenosis was defined as a >50% diameter stenosis of the target lesion. Late lumen loss was defined as the difference between the minimum lumen diameter at the completion of the stent procedure and during follow-up.

Study End Points

The primary end point was target vessel failure, defined as cardiac death, Q-wave and non-Q-wave myocardial infarction, or target vessel revascularization (CABG or repeat PTCA) at 360 days. Secondary clinical end points included all-cause mortality, target lesion revascularization (TLR) (clinically driven CABG or repeat PTCA because of restenosis or closure of the target lesion), and stent thrombosis. All major adverse events (MACE) were determined for in-hospital, out-of-hospital, and cumulative for 360 days after stent placement. MACE was defined as all-cause death, myocardial infarction, and TLR.

Statistical Analysis

The treatment group differences were evaluated with Student’s t test for continuous variables, and χ² or Fisher’s exact test (where appropriate) for binary end points. Multiple linear and logistic regression analyses were also carried out.

The occurrence of event-free target vessel failure during the 360-day follow-up period was analyzed by use of Kaplan-Meier plots with the log-rank test. All statistical analyses were performed using the SAS system (version 8e), and reported probability values were 2-sided.

Results

Between February 2001 and August 2001, 459 patients with LAD lesions were randomly assigned to receive either the sirolimus-eluting stents (234 patients) or standard bare-metal stents (225 patients). Clinical and lesion characteristics are presented in Table 1. The groups were well matched, with no significant differences in cardiac risk factors, angina class, prior myocardial infarction, and TLR.

The primary end point was target vessel failure, defined as cardiac death, Q-wave and non-Q-wave myocardial infarction, or target vessel revascularization (CABG or repeat PTCA) at 360 days.
The lesions in both groups were treated similarly. Stenting was successful in all patients. The mean stent length was 20.7 mm, yielding a stent length-to-lesion length ratio of 1.6 for both groups. Glycoprotein IIb/IIIa inhibitors were given to 64% of patients at the discretion of the operator.

**Angiographic Outcomes**

Angiographic data at 8 months were available for 84.0% (147/178) of patients in the sirolimus stent arm and 83.7% (147/175) of patients in the bare-metal stent arm assigned to mandated angiographic follow-up. Baseline lesion dimensions were similar (Table 2). Postprocedure in-stent and in-segment minimal luminal diameter and percent diameter stenosis were similar (Table 2). Postprocedure in-stent and in-segment minimal luminal diameter and percent diameter stenosis were similar at baseline; however, at 8-month follow-up, results significantly favored the sirolimus stent arm. Baseline intravascular ultrasound indices were not different between sirolimus-eluting and control stents. At 8 months, vessel and stent volume were similar, but the sirolimus group demonstrated an increase in mean luminal area (6.8 versus 4.7 mm²; P<0.001) and a reduction in neointimal hyperplasia area (0.5 versus 2.6 mm²) and neointimal hyperplasia volume (2.8 versus 67 mm³) (P<0.001 for each comparison).

**Clinical Outcomes**

Although in-hospital events were similar in both groups, there was a significant, 59% decrease in the combined end point of all-cause death, myocardial infarction, and TLR (MACE) at 1 year in the sirolimus stent patients (9.8% versus 24.9%; relative risk, 0.39; 95% CI, 0.26 to 0.61; P<0.001; Table 3). The decrease in MACE was driven primarily by a significant, 74% decrease in TLR and a 55% decrease in target vessel failure for sirolimus stent patients. Proximal LAD sirolimus-stented patients demonstrated a similar trend, with a 50% reduction in this combined end point of all-cause death, myocardial infarction, and TLR (MACE) compared with control patients (10.4% versus 20.6%, P=NS). Kaplan-Meier event-free survival is shown in Figure 2.

**Discussion**

We found that in patients with a single LAD stenosis, implantation of sirolimus-eluting stents, compared with bare-
metal stents, decreases neointimal hyperplasia, angiographic restenosis, and clinical events at 12 months with no additional adverse events. The lesion types and lengths present in this trial are representative of lesions found in everyday practice. This is supported by the control bare-metal restenosis rate of 41%, which is consistent with angiographic restenosis rates of 19% to 44% found in the literature of LAD intervention.\textsuperscript{11–16} Although ostial, multiple, and bifurcation lesions were excluded, the 2% binary in-stent restenosis rate seen in our study remains impressive and clinically relevant.

Our study also found significant benefit in proximal LAD lesions, which are known to be at increased risk for resteno-

**Figure 1.** A, Cumulative frequency of minimal luminal diameter preprocedure, postprocedure, and at 8-month follow-up for sirolimus-eluting stents. B, Cumulative frequency of minimal luminal diameter preprocedure, postprocedure, and at 8-month follow-up for bare-metal stents.

**TABLE 3. Major Adverse Cardiac Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Sirolimus, % (n)</th>
<th>Bare Metal, % (n)</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital MACE</td>
<td>3.4% (8/234)</td>
<td>1.3% (3/225)</td>
<td>2.56 (0.72, 9.09)</td>
<td>0.222</td>
</tr>
<tr>
<td>Total MACE to 360 days</td>
<td>9.8% (23/234)</td>
<td>24.9% (58/225)</td>
<td>0.39 (0.26, 0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All death</td>
<td>0.9% (2/234)</td>
<td>1.3% (3/225)</td>
<td>0.64 (0.11, 3.75)</td>
<td>0.680</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.4% (1/234)</td>
<td>0.9% (2/225)</td>
<td>0.48 (0.05, 5.00)</td>
<td>0.617</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.8% (9/234)</td>
<td>2.7% (6/225)</td>
<td>1.44 (0.52, 3.97)</td>
<td>0.602</td>
</tr>
<tr>
<td>TLR*</td>
<td>6.0% (14/234)</td>
<td>23.1% (52/225)</td>
<td>0.26 (0.16, 0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TVF†</td>
<td>12.0% (28/234)</td>
<td>27.5% (62/225)</td>
<td>0.43 (0.29, 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent thrombosis to 30 days</td>
<td>0.0% (0/234)</td>
<td>0.4% (1/225)</td>
<td>0.00</td>
<td>0.490</td>
</tr>
<tr>
<td>Late thrombosis to 360 days</td>
<td>0.4% (1/234)</td>
<td>0.0% (0/225)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Subacute closure</td>
<td>0% (0/234)</td>
<td>0.0% (0/225)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

*TLR at 360 days.
†Target vessel failure at 360-day follow-up is the primary end point (defined as cardiac death, Q-wave and non-Q-wave myocardial infarction, or target vessel revascularization).
This trial showed MACE rates of 9.8% for all LAD lesions and 10.4% for proximal LAD lesions despite binary restenosis rates of 2% and 0%, respectively. This discrepancy has been shown in other drug-eluting stent trials as well. Although some of these events may be because of de novo lesions or progressive disease, the vast majority in our trial were a result of proximal in-segment restenosis, which most likely represents a “geographic miss” between the predilation balloon and the stented segment. As such, it is possible that with more precise stenting, the use of longer stents, the use of shorter balloons, and perhaps use of less predilation, better results will be attainable in the future.

Treatment of proximal LAD stenoses remains controversial. Previous trials comparing isolated mammary bypass surgery with balloon angioplasty have documented similar survival rates but lower reintervention rates favoring surgery.20,21 Although stenting has reduced the need for repeat procedures, thereby reducing the “reintervention gap” between percutaneous and surgical revascularization, surgery has continued to demonstrate a reduced need for repeat procedures.7,8

A recent trial randomized patients with isolated proximal LAD stenosis to bare-metal stenting versus minimally invasive internal mammary artery implantation.12 Reported baseline characteristics were similar to those of our patients (mean age, 62 years; 29% diabetics; mean ejection fraction, 63%; and 60% type B lesions). Stent patients received an average of 15 mm of stent and had a reference diameter of 3.03 mm. At 6-month follow-up, patients randomized to surgery had less need for reintervention (8% versus 29%, P<0.003) but no differences in death or myocardial infarction. Their combined end point rate of death, myocardial infarction, and TLR of 15% for surgical patients compares favorably with our sirolimus-treated proximal LAD rate of 10.4%. Their surgically treated TLR rate of 8% is also similar to our TLR rate of 9% (Table 4). Thus, the sirolimus-eluting stents may have eliminated the “reintervention gap” between the surgical and catheter-based intervention for isolated proximal LAD stenosis. Whether these results will be duplicated in randomized clinical trials, in patients with multivessel disease, and over periods longer than 1 year is unknown.

**Limitations**

Although the results of this subgroup analysis are consistent with the overall findings of the SIRIUS trial and are supported by a high degree of statistical significance, this was a retrospective study. Also, the use of mandated angiographic follow-up in the majority of patients most likely elevated the...

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**TABLE 4. Trials of Stent Implantation for Isolated Proximal LAD Stenosis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N</th>
<th>Primary End Point</th>
<th>Follow-Up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diegeler et al12</td>
<td>Bare metal stent vs LIMA</td>
<td>220</td>
<td>Cardiac death, MI, TLR</td>
<td>6-month angiographic</td>
<td>Primary combined end point 31% vs 15% for surgery (P=0.02). TLR 29% vs 8%.</td>
</tr>
<tr>
<td>Drenth et al12</td>
<td>Bare metal stent vs LIMA</td>
<td>102</td>
<td>Death (any), MI, stroke, TVR</td>
<td>Mean F/U 2.9 y. Clinical F/U.</td>
<td>Primary combined end point 23.5% vs 9.8% for surgery (P=0.07). TLR 15.7% vs 4.1%</td>
</tr>
<tr>
<td>Goy et al14</td>
<td>Bare metal stent vs LIMA</td>
<td>123</td>
<td>Cardiac death, MI, “repeat revascularization”</td>
<td>Mean F/U 2.4 y. 6-month ETT and clinical F/U</td>
<td>Primary combined end point 31% vs 7% for surgery (P&lt;0.001). Repeat revascularization 24% vs 0%</td>
</tr>
<tr>
<td>Current trial</td>
<td>Bare metal stent vs Sirolimus-eluting stent</td>
<td>459</td>
<td>TVF (cardiac death, MI, TVR)</td>
<td>8-month angiographic. 1 year clinical</td>
<td>Primary combined end point 27.6% vs 12% (bare metal vs sirolimus, P&lt;0.001). For prox-LAD subgroup: cardiac death, MI, TLR 20.6% vs 10.4%. TLR 19.3% vs 9%.</td>
</tr>
</tbody>
</table>

LIMA indicates left internal mammary bypass; MI, myocardial infarction; TVR, target vessel revascularization; TVF, target vessel failure; F/U, follow-up; and ETT, exercise tolerance test.
clinical end points of TLR, target vessel revascularization, and target vessel failure by increasing the odds of revascularization for patients with borderline symptoms and moderate angiographic restenosis. Generally, this bias would affect both arms of a trial equally. However, given that the bare-metal stent arm had much more neointimal hyperplasia and thus many more borderline restenotic lesions, it is possible there was more angiographically driven revascularization in this group than in the sirolimus stent group.

Conclusions
We have shown that LAD intervention with sirolimus-eluting stents significantly reduces angiographic restenosis and clinical events compared with bare-metal stents. The low rate of repeat revascularization compares favorably to previous reports of patients undergoing bypass surgery for LAD disease. Sirolimus stent implantation into patients with LAD stenoses may provide long-term results similar to those of bypass surgery.

Acknowledgment
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References
17. O’Keefe JH, Kreamer TR, Jones PG. Isolated left anterior descending coronary artery disease: percutaneous transluminal coronary angioplasty versus stenting versus left internal mammary artery bypass grafting. Circulation. 1999;100(suppl II);II-114–II-118.
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