Effectiveness and Safety of Sirolimus-Eluting Stents in the Treatment of Restenosis After Coronary Stent Placement

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Background—In-stent restenosis is notoriously difficult to treat by repeat catheter intervention because of its propensity for aggressive recurrent neointimal formation. This study sought to assess the effectiveness and safety of the sirolimus-eluting stent in the treatment of in-stent restenosis.

Methods and Results—The study was designed as a prospective multicenter registry. We included 162 patients with in-stent restenosis of a native coronary artery who had a clinical indication for repeat intervention. Patients were scheduled for follow-up angiography at 6 months. The primary end point was in-lesion late loss. Follow-up angiography was performed in 155 patients. We obtained an in-lesion late loss of 0.08±0.49 mm and a binary restenosis rate of 9.7% (15/155), which prompted reintervention in 7.4% (12/162) at 9 months. The 9-month rate of death was 1.2% (2/162) and that of nonfatal myocardial infarction was 1.2% (2/162).

Conclusions—Sirolimus-eluting stents were highly efficacious and safe in the treatment of in-stent restenosis. Our study provides rationale for the use of sirolimus-eluting stents in the treatment of in-stent restenosis. (Circulation. 2005;111:2107-2111.)

Key Words: restenosis • sirolimus • stents

Compared with balloon angioplasty, stents reduce the risk of restenosis after percutaneous treatment of de novo native vessel coronary artery stenoses.1–4 Nevertheless, restenosis continues to present a major problem after coronary placement of bare stents, occurring at a rate of 15% to 50%, depending on stent type, lesion characteristics, and patient subset.5,6 Recurrence after catheter-based treatment of in-stent restenosis is frequent; in unselected cohorts, it affects ≥40% of treated restenoses, about two thirds of which require repeat intervention.7,8 The clinical course may be more benign if in-stent restenosis is focal, but in more than one half of the patients presenting with diffuse in-stent restenosis, the chance of definite treatment by repeat catheter-based therapy is <50%.7

Various catheter-based treatment modalities for in-stent restenosis have been tested, but only brachytherapy has proved effective in the inhibition of recurrence.9–16 Nevertheless, coronary brachytherapy is logistically more demanding than other catheter-based treatment modalities, and there is continued concern about the risk of edge restenosis and late stent thrombosis.10 In the search for alternative treatment options for in-stent restenosis, drug-eluting stents hold promise. Specifically, for the sirolimus-eluting stent, an increasing experience with the sirolimus-eluting stent in the treatment of in-stent restenosis not only after primary stent placement but also after treatment for recurrence.17–19 Apart from preliminary encouraging reports,20,21 there was, however, no large experience with the sirolimus-eluting stent in the treatment of in-stent restenosis. Therefore, we conducted the Multicenter, Nonrandomized Sirolimus-Eluting Stent in the Treatment of Patients With an In-Stent Restenotic Native Coronary Artery Lesion (TROPICAL) study to assess the effectiveness and safety of the sirolimus-eluting stent in patients with in-stent restenosis in a native coronary artery lesion.

Methods

Study Design and Patient Selection

The study was designed as a prospective multicenter registry to assess the extent of recurrent neointimal formation after the placement of a sirolimus-eluting stent for treatment of in-stent restenosis.

The online-only Data Supplement, which lists the sites and investigators that participated in the TROPICAL study, can be found with this article at http://www.circulationaha.org

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Patients were eligible for the study if they had a clinical indication for repeat percutaneous catheter intervention for an in-stent restenosis in a native coronary artery ≥4 weeks after the initial percutaneous catheter intervention. On visual estimation, percent diameter stenosis had to be ≥60%; vessel size, between 2.5 and 3.0 mm; and lesion length, ≥45 mm. Principal exclusion criteria were total occlusion at the site of in-stent restenosis; previous brachytherapy; lesion in the unprotected left main; myocardial infarction within the preceding 14 days; contraindication to aspirin, clopidogrel, or heparin; and severe concomitant disease interfering with follow-up.

All patients gave written informed consent. The trial complied with the provisions of the Declaration of Helsinki with regard to investigations involving human subjects and was approved by the institutional ethics committee of each participating center.

Coronary Intervention, Study Protocol, and Data Management

All lesions had to be predilated with standard balloon angioplasty techniques. Thereafter, the lesion was covered with 1 or 2 sirolimus-eluting stents (CYPHER, Cordis). For the study, sirolimus-eluting stents 8, 18, or 33 mm in length and 2.5 or 3.0 mm in diameter were available. No more than 2 stents were allowed. Focal restenoses were treated by circumscribed stent placement, unless they occurred early within the first 4 months. In this event, the entire stented segment was covered with a sirolimus-eluting stent. The study protocol mandated (1) restricting predilation to the restenosis and to the minimum needed to ensure safe placement of the sirolimus-eluting stent, (2) covering the predilated segment plus a safety margin of 5 mm at both ends with the sirolimus-eluting stent; (3) using adequate inflation pressures (≥12 atm) to ensure full expansion of the sirolimus-eluting stent, and (4) overlapping the stents by ≥3 mm if 2 stents were needed. Peri-interventional antithrombotic regimen was left to the operator’s discretion; however, preloading with clopidogrel and administering heparin to achieve and maintain an activated clotting time of >250 seconds during percutaneous catheter intervention were recommended. After the intervention, all patients received aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for ≥3 months.

Plasma concentrations of creatine kinase and its MB isoenzyme were systematically determined for 48 hours after the intervention. For angiographic restudy and clinical evaluation, patients returned to the hospital at 6 months. We also performed a phone interview at 30 and 270 days. Case-report forms were completed at each site, monitored by independent study monitors, and submitted to the data-coordinating center (see below). An independent clinical events committee adjudicated all events.

Quantitative Angiography

Standard image acquisition was performed with ≥2 angiographic projections of the stenosis. Images were forwarded to the Brigham and Women’s Hospital Angiographic Core Laboratory for review. All procedural and follow-up angiograms were reviewed using standard morphological criteria.22,23 Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by ≥20%. Quantitative angiographic analysis was performed with a validated automated edge-detection algorithm (Medis CMS).24 Images selected for analysis were identified from angiographic projections that demonstrated the stenosis in an unforeshortened view that minimized the degree of vessel overlap. The contrast-filled injection catheter was used as the calibration source. A 5- to 10-mm segment of reference diameter proximal and distal to the stenosis was used to calculate the average reference vessel diameter at baseline, after stent implantation, and at follow-up. Side branches and other anatomic landmarks were used to identify and maintain the consistency of the measurement length during the follow-up period. Minimal lumen diameters (MLDs) were measured at these same time points within the stent plus an adjacent 5 mm of the region on each side of the sirolimus-eluting stent (in-lesion analysis).

Percent diameter stenosis was defined as follows: [1−(MLD/reference vessel diameter)]×100. Binary angiographic restenosis was defined as >50% diameter stenosis at follow-up. Acute gain was defined as the MLD immediately after the procedure minus the MLD before the procedure; late loss was defined as the MLD immediately after the procedure minus the MLD at the 6-month follow-up. Net gain was the difference between minimal luminal diameter at follow-up and predilatation MLD.

Study End Points

The primary end point was the in-lesion late loss at follow-up. The prespecified secondary angiographic end point was the proportion of patients with an in-lesion percent diameter stenosis of ≥50% at follow-up. As a secondary clinical end point, we assessed the rate of target vessel revascularization. We also analyzed other angiographic indexes of restenosis, including late loss, loss index, and percent diameter stenosis, as well as the incidence of total occlusions.

As a safety end point, we monitored the rates of death resulting from any cause and of nonfatal myocardial infarction. Myocardial infarction was defined as the presence of new Q waves in ≥2 contiguous ECG leads or an elevation of creatine kinase or its MB isoenzyme to ≥3 times the upper limit of normal in 2 samples during hospitalization or to ≥2 times the upper limit of normal after discharge.

Statistical Analysis

The prespecified sample size was 160 patients. Discrete variables are reported as counts (percentages); continuous variables, as mean±SD. We assessed the influence of covariates on late loss by the general linear model. Logistic regression analysis was used to identify predictors of restenosis. All baseline variables shown in Tables 1 and 2 were entered into the multivariate models. A value of P<0.05 in the 2-tailed test was regarded as significant.

Results

Baseline Characteristics and Follow-Up

From December 27, 2002, to July 14, 2003, we enrolled 162 patients at 11 European centers. The sirolimus-eluting stent was successfully placed in all patients. Follow-up angiography was performed in 155 patients (95.7%) after a median of 187 days (interquartile range, 181 to 195 days). Reasons for missing angiography were death in 1 patient, patient refusal in 2 patients, and loss to clinical follow-up in 4 patients. Baseline demographic, clinical, and angiographic characteristics and procedural variables are shown in Tables 1 and 2; the Figure depicts the cumulative distribution function of the preprocedural and postprocedural MLDs and the MLD at the 6-month follow-up.
TABLE 2. Baseline Angiographic and Procedural Characteristics

<table>
<thead>
<tr>
<th>Lesion location, n (%)</th>
<th>Stents placed, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>92 (56.8)</td>
</tr>
<tr>
<td>LCx</td>
<td>33 (20.4)</td>
</tr>
<tr>
<td>RCA</td>
<td>34 (21.0)</td>
</tr>
<tr>
<td>LM</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Diffuse in-stent restenosis pattern, n (%)</td>
<td>118 (72.8)</td>
</tr>
<tr>
<td>Eccentric lesion, n (%)</td>
<td>77 (47.5)</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>2.56±0.39</td>
</tr>
</tbody>
</table>

Before procedure

<table>
<thead>
<tr>
<th>MLD, mm</th>
<th>Diameter stenosis, %</th>
<th>Lesion length, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.76±0.29</td>
<td>70.3±10.2</td>
<td>15.8±7.7</td>
</tr>
</tbody>
</table>

Procedural variables

<table>
<thead>
<tr>
<th>Patients treated with stent, n (%)</th>
<th>Stents placed, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>162 (100)</td>
<td>103 (63.6)</td>
</tr>
<tr>
<td>1</td>
<td>48 (29.6)</td>
</tr>
<tr>
<td>2</td>
<td>11 (6.8)</td>
</tr>
</tbody>
</table>

| Stent length, mm | 18.9±4.9 | Peri-interventional anti-GP IIb/IIIa, n (%) | 7 (4.3) |

After procedure

<table>
<thead>
<tr>
<th>MLD, mm</th>
<th>Diameter stenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.96±0.40</td>
<td>27.5±10.2</td>
</tr>
</tbody>
</table>

Efficacy of Sirolimus-Eluting Stents

As illustrated by the cumulative distribution of MLDs (see the Figure), there was minimal late loss during follow-up, amounting to 0.08±0.49 mm (95% CI, 0.003 to 0.16 mm). This resulted in a binary in-lesion restenosis rate of 9.7% (15/155), which prompted target lesion revascularization in 7.4% (12/162) at 9 months. Consistent with the observations on late loss, all other angiographic indexes showed a low tendency to recurrence after implantation of a sirolimus-eluting stent for treatment of in-stent restenosis (Table 3).

In-lesion late loss in patients with diabetes was not higher than that in patients without diabetes (−0.01±0.39 mm in diabetics versus 0.12±0.53 mm in nondiabetics; P=0.17); however, there was trend toward higher in-lesion late losses with tertiles of lesion length (P=0.09). In-lesion late loss was −0.04±0.25 mm for lesions <10.8 mm in length, 0.08±0.58 mm for lesions between 10.8 and 18.0 mm in length, and 0.17±0.55 mm for longer lesions. In our multivariate analysis, however, lesion length, like diabetes, was not significantly associated with late loss after placement of a sirolimus-eluting stent for treatment of in-stent restenosis. We also did not identify any significant predictor of restenosis within TROPICAL by either univariate or multivariate analysis.

Safety of Sirolimus-Eluting Stents

During the 9-month follow-up, 2 patients (1.2%) died. One patient died as a result of pump failure at day 127 after non–Q-wave infarction resulting from possible stent thrombosis; the other patient died at day 197 after coronary artery bypass surgery for proliferative restenosis in severe multivessel disease. In addition, there were 2 (1.2%) nonfatal infarctions, both non–Q-wave: 1 at day 109 caused by stent thrombosis after discontinuation of aspirin and clopidogrel and 1 at day 0 resulting from peri-interventional side-branch occlusion.

Discussion

In-stent restenosis is notoriously difficult to treat by repeat catheter intervention because of its propensity for aggressive recurrent neointimal formation. An average late loss >1 mm is to be expected after conventional treatment of in-stent restenosis, whereas recent studies report a late loss of ≈0.8 mm after stent placement for de novo native coronary stenosis. Although brachytherapy for in-stent restenosis was superior to conventional treatment in various studies, in-lesion late losses still ranged from 0.22±0.84 to 0.64±0.69 mm, depending on clinical setting, radiation source, and angiographic core laboratory (Table 4). In this context, the late loss of 0.08±0.49 mm that we found in TROPICAL is remarkable. It underscores the unique antiproliferative efficacy of sirolimus that has previously been documented in de novo native coronary artery stenoses. The late loss in TROPICAL was on the same order of magnitude or even lower than that reported after placement of a sirolimus-eluting stent for de novo native coronary coronary stenosis.

The placement of sirolimus-eluting stents was efficacious, with an overall long-term angiographic success rate of >90%. Notably, in about one quarter of the patients with recurrence, the stenosis was not severe enough to be considered clinically relevant, and reintervention was not indicated. Thus, the low late loss after sirolimus-eluting stents for...
in-stent restenosis translated into a low rate of clinical and angiographic re-restenosis.

With the intention to assess the antiproliferative efficacy of sirolimus-eluting stents in the setting of in-stent restenosis, TROPICAL primarily addressed angiographic end points. As in most studies, angiographic follow-up was performed at 6 months. Serial angiographic and intravascular sonographic follow-up after sirolimus-eluting stent placement revealed no risk of late restenosis and confirmed that 6-month angiography adequately reflects the minimal neointimal formation within sirolimus-eluting stents.26 The beneficial clinical outcome of TROPICAL at 9 months with a reintervention rate of 7.4% is also consistent with a stable angiographic result. Nevertheless, longer follow-up periods and more patients are needed to delineate the full clinical benefit of sirolimus-eluting stents in the treatment of in-stent restenosis.

Although there was a trend toward larger late losses with increasing lesion length, we did not identify any clinical, angiographic, or procedural feature that was associated with a major loss of efficacy of sirolimus-eluting stents. On the other hand, the study was not powered to identify weak predictors of recurrence after treatment of in-stent restenosis with sirolimus-eluting stents.

Although TROPICAL reports, to the best of our knowledge, the first large multicenter experience with sirolimus-eluting stents in the treatment of the first in-stent restenosis, there have been previous publications on smaller studies in this field. In the first studies in humans, in-lesion late losses were 0.16±0.47 mm (n=25) in the Sao Paolo experience and 0.26±0.67 mm in the Rotterdam experience.20,21,27 Likewise, in the 44 patients with native in-stent restenosis of the rapamycin-eluting stent evaluated in the Rotterdam Cardiology Hospital (RESEARCH) registry, in-lesion late loss was 0.17±0.76 mm.24–30 On the other hand, an in-lesion late loss of 0.45±0.40 was found in 10 patients after extensive intravascular ultrasound–guided high-pressure balloon optimization of stent expansion31 and of 0.39±0.54 mm in 22 patients with very diffuse in-stent restenosis.32 This is similar to the results of ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-stent Restenosis),33 which reported an in-lesion late lumen loss of 0.45 mm in the 100 patients treated with sirolimus-eluting stents for in-stent restenosis. The in-lesion late loss that we found in TROPICAL is smaller than any other previously reported. One reason for this difference may be the exclusion of patients with total occlusion at the site of in-stent restenosis in TROPICAL. Patients with a totally occluded stent present with the most aggressive neointimal formation and have the highest risk of recurrence.7 Supporting this interpretation, analysis of the RESEARCH patients without total in-stent occlusion revealed an in-lesion late loss of 0.11±0.67 mm, which is similar to that in TROPICAL. Another reason for the low in-lesion late loss in TROPICAL may have been our efforts to limit balloon trauma during the procedure, particularly the meticulous minimization of the predilated lesion length. This can be expected to reduce edge problems, which in other studies such as ISAR-DESIRE may have contributed substantially to in-lesion late loss. In ISAR-DESIRE,33 in-lesion late loss was substantially higher than in-stent late loss, ie, 0.45 versus 0.21 mm.

### Study Limitations

According to governmental regulations, access to coronary brachytherapy is restricted in most European countries, and the scattered coronary brachytherapy facilities use diverse devices. Therefore, in TROPICAL, we did not perform a randomized comparison with brachytherapy, the current standard of care in the treatment of in-stent restenosis. Because of the nonrandomized design of TROPICAL, the question of whether brachytherapy or placement of a drug-eluting stent is the best treatment option for in-stent restenosis is still unanswered. By historical comparison, however, it is conspicuous that the point estimate of in-lesion late loss in TROPICAL is substantially lower than that in any previous major brachytherapy trial (Table 4). The potential benefit of sirolimus-eluting stents compared with brachytherapy remains to be delineated by the ongoing Sirolimus for In-Stent Restenosis (SIRS) trial.

### Implications

The results of TROPICAL demonstrate that, in the treatment of in-stent restenosis, sirolimus-eluting stents are highly efficacious and safe. No previous treatment modality for in-stent restenosis has ever achieved the low (<10%) rates of angiographic or clinical recurrence that we found in TROPICAL. Thus, the TROPICAL trial provides rationale for the use of sirolimus-eluting stents in the treatment of in-stent restenosis.

### Acknowledgment

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