Post–Sirolimus-Eluting Stent Restenosis Treated With Repeat Percutaneous Intervention
Late Angiographic and Clinical Outcomes

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Background—We evaluated the clinical and angiographic outcomes of patients presenting with restenosis after sirolimus-eluting stent (SES) implantation treated with repeated percutaneous intervention.

Methods and Results—A total of 24 consecutive patients have undergone repeated percutaneous intervention to treat post-SES restenosis (27 lesions). The restenosis was located within the stent in 93% of lesions. From the 27 lesions, 1 (4%) was re-treated with a bare stent, 3 (11%) were treated with balloon dilatation, and the remaining 23 lesions (85%) were treated with repeated drug-eluting stent implantation (SES in 12 lesions [44%], paclitaxel-eluting stents in 11 lesions [41%]). The event-free survival rate was 70.8% after a median follow-up of 279 days from the post-SES treatment. The overall recurrent restenosis rate was 42.9%. The risk of recurrent restenosis was increased for patients with hypercholesterolemia, previous angioplasty, failed brachytherapy, post-SES restenosis needing early (<6 months) treatment, and post-SES restenosis treated with balloon dilatation. The recurrent restenosis rate of originally de novo lesions re-treated with drug-eluting stents was 18.2%.

Conclusions—Even though de novo lesions treated with SES at baseline and re-treated with drug-eluting stents had reasonably better outcomes than other lesion types and strategies, our study shows that the treatment of post-SES restenosis is currently suboptimal and warrants further investigation. (Circulation. 2004;109:2500-2502.)

Key Words: atherosclerosis ■ coronary disease ■ restenosis ■ stents

Siroliimus-eluting stents (SESs) have recently proved effective in reducing restenosis and the need for repeated revascularization compared with conventional stenting.1-3 Nonetheless, repeated revascularization is still required in up to 5% of patients.1-4 However, the best treatment for patients with restenosis after SES implantation is currently unknown. Therefore, the goal of the present study was to evaluate the clinical and angiographic outcomes of patients undergoing repeated percutaneous intervention for post-SES restenosis.

Methods

Since April 2002, our institution has adopted a policy of using drug-eluting stents as the device of choice for all patients treated with percutaneous intervention, as described elsewhere.4 By October 2003, 631 consecutive patients had received at least 1 SES (79% of all patients treated in the period). From these, a total of 24 consecutive patients (3.8%) have undergone repeated percutaneous intervention for post-SES restenosis (27 lesions) and make up the present study population. Post-SES restenosis was defined as a significant luminal stenosis (>50% diameter stenosis by quantitative coronary angiography) located within the stent or in its 5-mm proximal or distal segments that was identified at an angiogram performed >3 months after the index procedure.

Patients were treated preferably with repeated implantation of drug-eluting stents according to our policy as explained above. SESs were available until March 2003; since then, paclitaxel-eluting stents have been used as the default drug-eluting stent at our hospital. Nevertheless, the final interventional strategy was left entirely to the discretion of the operator. All patients receiving repeated drug-eluting stent implantation were maintained on lifelong aspirin and on clopidogrel for at least 3 months.

Patients were followed up to assess the incidence of major cardiac adverse events, defined as all-cause death, nonfatal myocardial infarction (>2× creatine kinase increase with increased creatine kinase-MB), or repeated target lesion revascularization (reintervention to treat a significant lesion within the stented segment or within its 5-mm borders). Angiographic follow-up was obtained between 7 and 10 months after treatment of post-SES restenosis to evaluate the incidence of recurrent restenosis (>50% diameter stenosis).

Continuous variables were presented as median (interquartile range). Paired measurements were compared by use of the Wilcoxon signed-ranks test. Categorical variables were presented as counts and percentages and compared by use of Fisher’s exact test. All statistical tests were 2 tailed.

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Results

SESs were implanted at the index procedure to treat a de novo lesion in 70%, in-stent restenosis or failed brachytherapy in 26% (of these, 86% were Mehran class III or IV), and balloon restenosis in 4% (Table 1). The median length of SES implanted at the index procedure was 33 mm (interquartile range, 18 to 64 mm).

In most cases, post-SES restenosis was located within the stented portion (93%) (Table 1) and occurred without an apparent mechanical contributor (56%), as evaluated by angiography and intravascular ultrasound (the latter available for 67%). The median length of post-SES restenotic lesions was 11.2 mm (interquartile range, 6.6 to 17.1 mm); 14 lesions (52%) were short (<10 mm long), 5 lesions (19%) were multifocal, 7 lesions (26%) were >10 mm long, and 1 lesion (4%) presented as total vessel occlusion.

Of the 27 post-SES restenotic lesions, 3 (11%) were treated with balloon dilatation in small segments not considered suitable for repeat stenting, and 1 lesion (4%) in a large saphenous graft was treated with a polytetrafluoroethylene-covered stent. For the remaining 23 post-SES restenoses (85%), repeated drug-eluting stent implantation was chosen as the therapeutic strategy. SESs were implanted in 12 lesions (44%) (patients treated up to March 2003), and paclitaxel-eluting stents were used for 11 lesions (41%) (patients treated since March 2003). For lesions treated with repeated stent implantation, the stented length was significantly shorter in the repeated procedure than in the index procedure (median, 17 versus 33 mm; interquartile range, 8 to 30 mm versus 20 to 65 mm, respectively; \( P<0.01 \)).

Complete clinical follow-up was available for all patients at a median of 490 days (interquartile range, 467 to 517 days) from the index procedure (median, 279 days; range, 251 to 307 days from the post-SES treatment). A 78-year-old patient died 412 days after the index procedure (209 days after post-SES restenosis treatment) as a result of pneumonia and progressive heart failure. One patient (post-SES restenosis treated with directional atherectomy followed by implantation of 2 additional SESs) presented with acute myocardial infarction resulting from subacute stent thrombosis 3 days after treatment of the SES restenosis. He underwent successful urgent reintervention with implantation of another SES and was discharged with no complications thereafter. The treated segment was widely open at angiographic follow-up. There were no other myocardial infarctions during the follow-up period. Target lesion revascularization resulting from recurrent restenosis was required in 5 patients (20.8%). The event-free survival rate was 70.8%.

Angiographic follow-up was obtained for 18 patients with 21 lesions (75% of patients, 78% of lesions) at a median of 281 days (interquartile range, 254 to 305 days). Overall, there were 9 lesions (42.9%) with recurrent restenosis after percutaneous treatment of post-SES restenosis (Table 2). In 3 of these cases (14.3%), the target vessel was totally occluded at the original lesion site (1 lesion) or in its proximal portion (2 lesions). In the latter cases, direct assessment of the treated site (mid/distal vessel for both lesions) was not possible. No patient presenting with total occlusion at late angiogram had clinical evidence of recurrence.

### TABLE 1. Patient and Lesion Characteristics (n=24 patients, 27 lesions)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>60 (50–70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, %</td>
<td>71</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>46</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>67</td>
</tr>
<tr>
<td>Treated vessel, %</td>
<td>9</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>44</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>26</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>15</td>
</tr>
<tr>
<td>Left main coronary</td>
<td>4</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>11</td>
</tr>
<tr>
<td>Ostial location, %</td>
<td>30</td>
</tr>
</tbody>
</table>

**Lesion characteristics at index procedure, %**
- Chronic total occlusion (>1 mo) | 26 |
- Lesion type at index procedure, %
  - De novo lesion | 70 |
  - Balloon restenosis | 4 |
  - In-stent restenosis | 15 |
  - Postbrachytherapy restenosis | 11 |
- Mehran classification at index procedure,* %
  - Type I or II | 14 |
  - Type III | 43 |
  - Type IV | 43 |
- SESs implanted at index procedure, n | 1 (1–3) |
- Total length of SES implanted at index procedure, mm | 33 (18–64) |

**Lesion characteristics of post-SES restenosis, %**
- Restenosis location
  - In-stent | 93 |
  - Proximal edge | 4 |
  - Distal edge | 4 |
- Possible mechanical contributors for restenosis†
  - Ostial location | 30 |
  - Gap or fracture between SES | 11 |
  - Trauma outside the stent/residual dissection | 7 |
  - Stent underexpansion | 7 |
  - No apparent mechanical factor | 56 |
- Lesion length of post-SES restenosis, mm | 11.2 (6.6–17.1) |
- Treatment of the post-SES restenosis, %
  - Balloon dilatation | 11 |
  - Bare-stent implantation | 4 |
  - Repeated SES implantation | 44 |
  - Paclitaxel-eluting stent implantation | 41 |
- Total length of repeated stent implantation,‡ mm | 17 (8–30) |

Numbers in parentheses are interquartile range.
*Related to in-stent restenosis or postbrachytherapy restenosis at the index procedure (n=7).
†Categories not mutually exclusive (intravascular ultrasound examination available for 18 lesions [67%]).
‡Related only to lesions treated with repeated stent implantation (n=24 lesions).
sudden thrombotic occlusion during follow-up, and the lesions were classified as recurrent restenosis.

The following characteristics were associated with increased incidence of recurrent restenosis after treatment of post-SES restenosis: (1) hypercholesterolemia (lipid-lowering therapy or total cholesterol >200 mg/dL; n = 13) versus no hypercholesterolemia (n = 8; recurrent restenosis, 69% versus 0% respectively; P < 0.01); (2) history of previous angioplasty at the index procedure (n = 12) versus no previous angioplasty (n = 9; 67% versus 11%; P = 0.02); (3) previous brachytherapy at the treated site (n = 3) versus no brachytherapy (n = 18; 100% versus 33%; P = 0.06); (4) post-SES restenosis treated with balloon dilatation (n = 3) versus other treatments (n = 18; 100% versus 33%; P = 0.06); and (5) post-SES restenosis needing treatment before 6 months from the index procedure (n = 5) versus late treatment (n = 16; 100% versus 25%; P < 0.01). Interestingly, there were no differences in the incidence of recurrent restenosis between short (<10 mm) post-SES restenosis (n = 11) and long (>10 mm), multifocal, or total occlusion post-SES restenosis (n = 10; 36.4% versus 50.0%; P = 0.7). In addition, no differences in rates of recurrent restenosis were seen between diabetics (n = 9) and nondiabetics (n = 12; 33.3% versus 50.0%; P = 0.7). The recurrent restenosis rate of 17 lesions re-treated with drug-eluting stents was 29.4%, with no major differences between SESs or paclitaxel-eluting stents (33.3% versus 25.0%, respectively; P = 1.0). For de novo lesions at the index procedure that were re-treated with drug-eluting stents (n = 11), the incidence of recurrent restenosis was 18.2% (recurrent restenosis for the remaining lesions, 70.0%; P = 0.03).

<table>
<thead>
<tr>
<th>Lesion Characteristic</th>
<th>Reference Diameter, mm</th>
<th>Minimal Luminal Diameter, mm</th>
<th>Diameter Stenosis, %</th>
<th>Lesion Length, mm</th>
<th>Late Loss, mm</th>
<th>Restenosis Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline index procedure</td>
<td>2.49 (2.21–2.88)</td>
<td>0.49 (0–0.81)</td>
<td>81.0 (63.5–100)</td>
<td>18.0 (9.39–37.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>After index SES implantation</td>
<td>...</td>
<td>2.08 (1.40–2.27)</td>
<td>18.0 (13.5–32.5)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Post-SES restenosis</td>
<td>...</td>
<td>0.89 (0.51–1.15)</td>
<td>69.0 (60.5–81.0)</td>
<td>10.2 (5.8–17.5)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>After treatment of post-SES restenosis</td>
<td>...</td>
<td>2.16 (1.65–2.70)</td>
<td>19.0 (4.0–31.5)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Late angiographic follow-up</td>
<td>...</td>
<td>1.24 (0.51–2.30)</td>
<td>48.0 (22.4–79.5)</td>
<td>5.4 (3.8–21.2)</td>
<td>0.74 (–0.08–1.38)</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Numbers in parentheses are interquartile range. *Related to 21 lesions with angiographic follow-up (78%).

Discussion

The main finding of the present study was that repeated percutaneous intervention for post-SES restenosis was associated with relatively high rates of recurrent restenosis (overall, 42.9%), especially for patients with hypercholesterolemia, previous angioplasty, failed brachytherapy, post-SES restenosis needing early (<6 months) treatment, and post-SES restenosis treated with balloon dilatation. Nonetheless, repeated drug (sirolimus or paclitaxel) -eluting stent implantation, the most frequently used treatment in our series, appeared to be safe, with no documented complications related to re-exposure to local antiproliferative agents. Of note, de novo lesions at baseline that were re-treated with drug-eluting stents had reasonably better outcomes (recurrent restenosis, 18.2%) compared with the remaining lesions.

Our results underscore the complex nature of lesions presenting with restenosis after initial SES implantation. Previous observations have shown that local features and diabetes may play an important role in post-SES restenosis. Interestingly, the identification of a presumed contributing mechanical factor, diabetes, and restenotic lesion length did not influence the outcomes after re-treatment in our series. One may speculate whether forms of constitutional or acquired cellular mechanisms leading to drug resistance may influence the recurrence of post-SES restenosis. It is worth noting that the recurrence rates were significantly increased for patients with failed brachytherapy and for those who needed early re-treatment (the latter may be related by a more aggressive restenotic process).

The present study has several limitations related to its small sample size; its nonrandomized, observational design; and the heterogeneity of the study population. Nevertheless, our study shows that the treatment of this new medical condition, namely post-SES restenosis, is currently suboptimal and warrants further investigation.

Acknowledgments

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References

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