Impact of Sirolimus-Eluting Stent Fracture on 4-Year Clinical Outcomes

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Background—Although stent fracture (SF) after sirolimus-eluting stent (SES) implantation has been recognized as one of the predisposing factors of in-stent restenosis, it remains uncertain whether SF can increase the risk of major adverse cardiac events (MACE), especially beyond 1 year after SES implantation. The aim of this study was to assess the impact of SF relative to non-SF on 4-year clinical outcomes after treatment with SES of comparable unselected lesions.

Methods and Results—A total of 874 lesions in 793 patients undergoing SES implantation and subsequent angiography 6 to 9 months after index procedure were analyzed. At 6- to 9-month angiographic follow-up, SF was identified in 70 of 874 lesions (8.0%). In-stent late loss was significantly higher in SF lesions versus non-SF lesions (0.42±0.59 mm versus 0.13±0.49 mm, P<0.001), resulting in a significantly higher in-stent restenosis rate (21.4% versus 4.1%, P<0.001). At 4 years, SF versus non-SF was associated with a significantly higher MACE rate (23.2% versus 12.6%, P=0.014), mainly driven by significantly higher target-lesion revascularization (18.8% versus 10.2%, P=0.029) rate. Adverse effects of SF on clinical outcomes occurred mostly within the first year (17.4% versus 6.6%, P=0.001), with similar MACE rate between 1 and 4 years (5.8% versus 5.9%, P=0.611). No significant differences between SF versus non-SF patients were observed in the cumulative frequency of very late stent thrombosis (2.9% versus 1.4%, P=0.281), death (0% versus 2.1%, P=0.252), or myocardial infarction (5.8% versus 2.9%, P=0.165).

Conclusions—SF of SES was associated with higher MACE rate up to 1 year, mainly driven by higher target-lesion revascularization, whereas no significant association was evident between years 1 and 4. (Circ Cardiovasc Interv. 2011;4:349-354.)

Key Words: angioplasty ■ coronary disease ■ follow-up studies ■ restenosis ■ stents

A number of trials documented that the use of sirolimus-eluting stents (SES) reduced restenosis and subsequent target-vessel revascularization rates, with similar safety compared with use of bare-metal stents,1-3 even in patients with off-label indications,4 resulting in widespread use of SES in clinical practice. On the other hand, the presence of stent fracture (SF) after SES implantation has been reported to be associated with an increased risk of in-stent restenosis, ranging from 15% to 60%,5-12 with higher cardiac event rates within a 1-year observation period.5-8,10,12 A recently published pathological study in 144 autopsy cases of patients who had received drug-eluting stents (DES) demonstrated that SF was detected in 29% of lesions, and the presence of SF with gap within the stent body was associated with a histological event, such as stent thrombosis or restenosis, in 67% of cases.13 Because the duration and severity of arterial responses at the site of SF, which may have an adverse effect on outcomes, as well as the time point at which the SF occurs after SES implantation remain uncertain, the clinical impact of SF on long-term outcomes should be evaluated. However, there are scant data on the clinical course of SF patients, particularly long-term follow-up data. Accordingly, the goal of the present study was to assess whether the presence of SF might influence long-term clinical outcomes, including rates of stent thrombosis, target-lesion revascularization (TLR), non-fatal myocardial infarction (MI), and death at 4 years, in routine clinical practice.

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Methods

Patient Population and Procedural Protocol

From June 2004 to June 2006, a total of 925 patients who underwent successful implantation with only SES (Cypher; Johnson & Johnson, Miami Lakes, FL) at our institutions were followed prospectively.

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Among 925 patients, 793 patients (85.7%) with 874 lesions who underwent follow-up angiography 6 to 9 months after initial procedure, irrespective of clinical symptoms, were enrolled in the study. In these patients, percutaneous coronary intervention was performed according to standard techniques. Before the procedure, 81 to 162 mg of aspirin was prescribed and 10,000 IU of heparin was given if not contraindicated. The decision to perform predilation and postdilation balloon inflations, as well as the use of intravascular ultrasound (IVUS), was left to the discretion of the operator. No platelet glycoprotein IIb/IIIa receptor inhibitors were used in the present study because they were not available in Japan. After the procedure, all patients were advised to continue on aspirin (81 to 162 mg daily) for life unless there were contraindications. Ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was also prescribed for at least 3 months after stent implantation. Follow-up coronary angiography was performed at 6 to 9 months or earlier if they had recurrent symptoms. Written informed consent was obtained from patients in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committees. All adverse events at 4 years were confirmed by reviewing the medical records of the patients followed at our institutions, by telephone contact with the patients or a next of kin, or from information from referring physicians when patients were followed up elsewhere. Complete follow-up data on clinical events at 4 years were available in 91% of SF and 93% of non-SF cases. All patients reported in this study had clinical follow-up. In patients in whom complete 4-year follow-up was not available, outcomes were included in all Kaplan-Meier analyses until the point they were lost to follow-up. No extramural funding was used to support this work.

Quantitative Angiographic Analysis and Definitions

The angiograms were reviewed as a single group by 2 experienced observers blinded to the clinical information. Quantitative coronary analysis was performed, using the Cardiovascular Measurement System (CMS-MEDIS Medical Imaging Systems, Nuenen, The Netherlands). Contrast-filled guiding catheters were used for magnification calibration. Each angiographic sequence was preceded by intracoronary injection of nitroglycerin. SF was defined as a complete separation of stent struts, whereas SF occurred in 2 or more points per lesion in 19 of the 93 patients in whom complete 4-year follow-up was not available. Of the 93 points in which stent fracture occurred, 69 (72.4%) were located within 5 mm proximal or distal to the stent segment measured with quantitative coronary analysis on the follow-up angiography. Renal insufficiency was defined as serum creatinine level >1.5 mg/dL before percutaneous coronary intervention. Nonfatal MI was defined by a new Q-wave. MI was defined as death (all causes) and 2. Compared with non-SF patients, SF patients were significantly different from those of the 132 patients without angiofracture (data not shown). At follow-up, SF was present in 70 of 874 lesions (8.0%) and in 69 of 793 patients (8.7%). In 51 of 70 lesions (72.9%), SF was found at a single point, whereas SF occurred in 2 or more points per lesion in 19 lesions (27.1%). As a result, a total of 93 fractures in 70 lesions, for an average of 0.11 fractures per lesion, were observed. Of the 93 points in which stent fracture occurred, 63 fracture points (67.7%) were located within 5 mm proximal or distal to the margins of stent overlap.

Table 1. Baseline Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>No. of lesions</th>
<th>Fracture (n=69)</th>
<th>Nonfracture (n=724)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.8±10.6</td>
<td>65.8±9.7</td>
<td>0.331</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>79.7</td>
<td>80</td>
<td>0.959</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±3.6</td>
<td>24.2±2.9</td>
<td>0.572</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>40.6</td>
<td>42.3</td>
<td>0.786</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>71</td>
<td>66.7</td>
<td>0.467</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>63.8</td>
<td>62.3</td>
<td>0.809</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>8.7</td>
<td>14.6</td>
<td>0.175</td>
</tr>
<tr>
<td>Hemodialysis, %</td>
<td>0</td>
<td>4.1</td>
<td>0.062</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>47.8</td>
<td>36.9</td>
<td>0.073</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>82.6</td>
<td>64.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior infarction, %</td>
<td>40.6</td>
<td>38.1</td>
<td>0.688</td>
</tr>
<tr>
<td>Previous angioplasty, %</td>
<td>47.8</td>
<td>49.2</td>
<td>0.831</td>
</tr>
<tr>
<td>Previous bypass surgery, %</td>
<td>8.7</td>
<td>9.9</td>
<td>0.739</td>
</tr>
<tr>
<td>Clinical status, %</td>
<td>66.7</td>
<td>70</td>
<td>0.408</td>
</tr>
<tr>
<td>Stable angina</td>
<td>10.1</td>
<td>13.7</td>
<td>0.137</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>15.9</td>
<td>12.3</td>
<td>0.085</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57.5±11.3</td>
<td>56.4±11.4</td>
<td>0.408</td>
</tr>
<tr>
<td>Medical treatment, %</td>
<td>97.1</td>
<td>99.0</td>
<td>0.181</td>
</tr>
<tr>
<td>Aspirin</td>
<td>98.4</td>
<td>97.4</td>
<td>0.519</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>39.1</td>
<td>39.1</td>
<td>0.995</td>
</tr>
<tr>
<td>Statins</td>
<td>20.3</td>
<td>30.2</td>
<td>0.085</td>
</tr>
<tr>
<td>Values are expressed as mean±SD or percentages.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

for confounders. A 2-sided probability value of <0.05 was considered statistically significant.

Results

Coronary angiography was repeated 7.6±4.0 months after the index procedure. Baseline characteristics of the 793 patients with follow-up angiography included in this report were not significantly different from those of the 132 patients without angiography (data not shown). At follow-up, SF was present in 70 of 874 lesions (8.0%) and in 69 of 793 patients (8.7%). In 51 of 70 lesions (72.9%), SF was found at a single point, whereas SF occurred in 2 or more points per lesion in 19 lesions (27.1%). As a result, a total of 93 fractures in 70 lesions, for an average of 0.11 fractures per lesion, were observed. Of the 93 points in which stent fracture occurred, 63 fracture points (67.7%) were located within 5 mm proximal or distal to the margins of stent overlap.

Clinical and Lesion Characteristics

Baseline clinical and anatomic features are shown in Tables 1 and 2. Compared with non-SF patients, SF patients were...
more likely to have multivessel disease, right coronary artery lesions, and lesions with tortuosity and chronic total occlusion. There was a lower incidence of left anterior descending artery lesions and lesions produced by in-stent restenosis in SF patients than in non-SF patients.

**Procedural and Angiographic Results**

Table 3 compares the procedural characteristics and quantitative coronary analysis results of the 2 study groups. In SF patients, the number of stents per lesion was significantly larger (P<0.001) and total stent length was significantly longer (P<0.001) than that of non-SF patients. No significant differences were observed between the 2 groups in terms of stent size, maximum inflation pressure or frequency of IVUS use, or direct stenting. At baseline, SF patients had longer lesion (P<0.001) and higher diameter stenosis (P=0.004), whereas mean vessel size and minimal lumen diameter were similar in the 2 groups. At follow-up, SF patients showed significantly lower in-stent minimal lumen diameter (P=0.001) and higher late lumen loss in the stented segment (P<0.001) compared with those of non-SF patients. As a result, in-stent restenosis occurred more frequently in SF patients (21.4%) as compared with non-SF patients (4.1%, P<0.001). In SF, restenosis was observed at SF sites in 13 of 15 restenotic lesions (86.7%). Additionally, the differences in restenosis rates remained significant when outcomes were compared in the in-segment zone (22.9% versus 7.6%, P<0.001).

**Clinical Outcomes**

The cumulative cardiac event rates at 1 and 4 years after the procedure are presented in Table 4 and Figures 1, 2, and 3. At 1 year, the cumulative incidence of TLR was significaantly higher in SF patients than in non-SF patients (P=0.005), whereas there were no statistically differences in rates of death and nonfatal MI between the 2 groups. As a result, SF versus non-SF was associated with a significantly higher 1-year MACE rate (P=0.001). Similarly, the 4-year cumulative risk rates of TLR and MACE were significantly increased in SF patients (P=0.029 and 0.014, respectively). There were no significant differences in the 4-year cumulative rates of death and nonfatal MI between the 2 groups. During the clinical follow-up from 1 to 4 years, increases in the rates of death, nonfatal MI, TLR, and MACE were similar between SF and non-SF patients. The difference in the rates of TLR and MACE peaked at approximately 1 year and remained constant through 4 years of follow-up (Figure 1).

Cox proportional hazards regression analysis was performed to adjust for confounders. After adjusting for the factors that are seen as clinically important for MACE, namely, age, diabetes, renal insufficiency, multivessel disease, prior infarction, acute MI, and left ventricular ejection fraction, the association of SF and MACE at 4 years remained significant (hazard ratio, 1.91; 95% confidence interval, 1.10 to 3.33; P=0.023). Similarly, when all group differences with P=0.10 (hemodialysis, current smoking, multivessel disease, the use of β-blockers, right coro-
nary artery, in-stent restenosis, tortuosity, chronic total occlusion, and total stent length) were forced in the model, the association of SF and MACE at 4 years remained significant (hazard ratio, 1.96; 95% confidence interval, 1.02 to 3.76; P = 0.043).

Table 5 summarizes the frequency of very late stent thrombosis up to 4 years. According to the Academic Research Consortium definitions, the cumulative incidence of any very late stent thrombosis during 4 years was not different between the 2 groups. No significant differences were observed in rates of very late stent thrombosis when the events were assessed as “definite” or “probable” in the 2 groups. Very late stent thrombosis (1 to 4 years) occurred in 2 patients (2.9%) in the SF group at 999 and 1218 days after the index procedure and in 10 patients (1.4%) in the non-SF group at 441, 484, 570, 627, 895, 990, 1157, 1318, 1404, and 1457 days (P = 0.281). In addition, frequencies of early cessation of thienopyridine therapy within 6 months after the index procedure were similar in the 2 groups, at 19.4% in the SF group and 13.6% in the non-SF group (P = 0.567).

Figure 1. Kaplan-Meier plot of cumulative incidence of major adverse cardiac events (MACE) through 4 years after index intervention. Solid line indicates fracture patients; dashed line, nonfracture patients. CI indicates confidence interval.

Figure 2. Kaplan-Meier plot of cumulative incidence of target-lesion revascularization (TLR) through 4 years after index intervention. Solid line indicates fracture patients; dashed line, nonfracture patients. CI indicates confidence interval.

Table 5. Cumulative Major Cardiac Events at 1 and 4 Years After Procedure

<table>
<thead>
<tr>
<th>Event</th>
<th>Fracture (n%)</th>
<th>Nonfracture (n%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>0 (0.0)</td>
<td>15 (2.1)</td>
<td>0.252</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>4 (5.8)</td>
<td>21 (2.9)</td>
<td>0.165</td>
</tr>
<tr>
<td><strong>Target lesion revascularization</strong></td>
<td>13 (18.8)</td>
<td>74 (10.2)</td>
<td>0.029</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>11 (15.9)</td>
<td>63 (8.7)</td>
<td>0.048</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>2 (2.9)</td>
<td>11 (1.5)</td>
<td>0.314</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>16 (23.2)</td>
<td>91 (12.6)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).

Figure 3. Kaplan-Meier plot of cumulative incidence of nonfatal myocardial infarction (MI) or death through 4 years after index intervention. Solid line indicates fracture patients; dashed line, nonfracture patients. CI indicates confidence interval.

### Discussion

The major findings of the present study are as follows: (1) patients with SF after SES implantation had significantly higher...
late loss and significantly higher rates of restenosis at 6- to 9-month angiographic follow-up and TLR and MACE at 1 year compared with non-SF patients; (2) at 4 years, moreover, SF versus non-SF patients had significantly higher rates of TLR and composite MACE, without an increased risk of very late stent thrombosis; (3) between 1 and 4 years, however, stent thrombosis, MI, death, and TLR were uncommon and occurred with similar frequency in SF and non-SF patients.

In the pre-DES era, SF was considered a rare event typically observed with the use of stents in anatomic locations associated with unique implant technique or when exposed to traumatic extravascular forces.15 In the current era, however, a 1.9% to 16.0% incidence of SF after SES implantation has been recognized as one of the clinically relevant contributors to focal in-stent restenosis.5–12 In the current study, SF patients had a significantly higher rate of in-stent restenosis at 6 to 9 months, as compared with non-SF patients. An increase in mechanical stimulation of the vessel wall, the loss of mechanical scaffolding of the stent, and a decrease in local drug delivery may have predominantly contributed to the higher rates of in-stent restenosis.12,16,17 Moreover, the analyses of several single-center studies showed that SF resulted in higher frequencies of TLR and/or MACE, without an increased risk of very late stent thrombosis. These observations therefore suggest that even if SF is identified, repeat revascularization should be considered carefully, dependent on clinical symptom, extent, and/or severity of myocardial ischemia on functional testing and associated anatomic severity of coronary lesions. Finally, no optimal intervention strategy (balloon angioplasty, bare-metal stents, homogenous DES, or heterogeneous DES) of in-stent restenosis at fracture sites to date has been well established because there have been few studies on the topic of this issue. Avoidance of unnecessary long- and/or overlapping SES implantation for lesions at high-risk for SF might help prevent restenosis.

### Study Limitations

Several potential limitations must be mentioned. First, it is a retrospective study on a limited number of patients, especially those with SF. Therefore, the selection bias may exist in these 2 groups, and it may lead to a biased conclusion. Nevertheless, to the best of our knowledge, this study has the largest sample size of SES fracture and the longest follow-up periods. Confirmatory studies with a larger number of patients for longer concomitant study periods are required to clarify this issue. Second, IVUS at follow-up was not performed in all patients. In our study, 61% of SF was confirmed by using IVUS as well as careful plain fluoroscopic examination, which was reported to be useful for detecting SF of SES because of its radiopacity and better fluoroscopic visualization.20 On the other hand, sensitivity of plain fluoroscopic examination and IVUS to identify SF is limited,13 and it is possible that fracture or separation of a single-strut filament has not been identified, dependent on conditions of the examination. Third, the time point at which SF occurs after SES implantation was not assessed in the current study. It may play a crucial role in the occurrence of restenosis in patients with SF because the efficacy of SES on restenosis is closely related to the release of an active therapeutic compound.

It is possible that SF can occur after the onset of early events as well as after 6- to 9-month angiographic evaluation of SF.
Fourth, this study does not elucidate whether extended dual antiplatelet therapy should be considered in SF patients because of lack of available data for long-term antiplatelet therapy. Finally, SF can occur in other type of DES and bare-metal stents as well as SES. Our results apply only to SES and may not be generalized to all DES types.

Conclusions
The present study suggests that although SF patients have a higher MACE rate at 4 years compared with non-SF patients, the increases in the rates of the events (very late stent thrombosis, MI, death, and TLR) between years 1 and 4 are low and not significantly different between the 2 groups.

Acknowledgments
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Disclosures
None.

References

CLINICAL PERSPECTIVE
The presence of stent fracture (SF) after sirolimus-eluting stent implantation has been reported to be associated with an increased risk of in-stent restenosis and major adverse cardiac events rates within a 1-year observation period. However, it remains uncertain whether SF can increase the risk of major adverse cardiac events beyond 1 year after sirolimus-eluting stent implantation. Accordingly, we sought to evaluate whether SF might influence long-term clinical outcomes, including rates of stent thrombosis, target-lesion revascularization, nonfatal myocardial infarction, and death at 4 years. We found that patients with SF had higher rates of restenosis at 6- to 9-month angiographic follow-up and subsequent target-lesion revascularization and major adverse cardiac events at 1 year than those without SF. Between 1 and 4 years, however, stent thrombosis, myocardial infarction, death, and target-lesion revascularization were uncommon and occurred with similar frequency in SF and non-SF patients.
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