Incidence and Clinical Impact of Stent Fracture After Everolimus-Eluting Stent Implantation

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Background—Stent fracture (SF) after drug-eluting stent implantation has recently become an important concern because of its potential association with in-stent restenosis and stent thrombosis. However, the incidence and clinical impact of SF after everolimus-eluting stent implantation remain unclear.

Methods and Results—A total of 1035 patients with 1339 lesions undergoing everolimus-eluting stent implantation and follow-up angiography 6 to 9 months after index procedure were analyzed. SF was defined as complete or partial separation of the stent, as assessed by plain fluoroscopy or intravascular ultrasound during follow-up. We assessed the rates of SF and major adverse cardiac events, defined as cardiac death, myocardial infarction, stent thrombosis, and clinically driven target lesion revascularization within 9 months. SF was observed in 39 of 1339 lesions (2.9%) and in 39 of 1035 patients (3.8%). Ostial stent location and lesions with hinge motion, tortuosity, or calcification were independent predictors of SF. The rate of myocardial infarction and target lesion revascularization were significantly higher in the SF group than in the non-SF group (5.1% versus 0.4%; P=0.018 and 25.6% versus 2.0%; P<0.001, respectively). Stent thrombosis was more frequently observed in the SF group than in the non-SF group (5.1% versus 0.4%; P=0.018). Major adverse cardiac events within 9 months were significantly higher in the SF group than in the non-SF group (25.6% versus 2.3%; P<0.001).

Conclusions—SF after everolimus-eluting stent implantation occurs in 2.9% of lesions and is associated with higher rate of major adverse cardiac events, driven by higher target lesion revascularization and stent thrombosis. (Circ Cardiovasc Interv. 2012;5:663-671.)

Key Words: stent fracture ■ everolimus-eluting stent ■ stent thrombosis

Drug-eluting stents (DES) have dramatically reduced the rates of in-stent restenosis (ISR) and subsequent target lesion revascularization (TLR) compared with bare-metal stents.1,2 However, widespread use of first-generation DES has drawn attention to several unresolved, clinically relevant issues. Particular concerns have been raised about the risks of DES, especially stent thrombosis (ST).3,4 Stent fracture (SF) after DES implantation has recently become an important concern because of its potential association with ISR, TLR, and ST.5 SF after sirolimus-eluting stent (SES) implantation has been reported to be associated with an increased risk of ISR, ranging from 15% to 60%, and with higher cardiac event rates within a 1-year observation period.6–11 A recently published pathological study of 144 autopsy cases with DES implantation detected SF in 29% of lesions, and SFs with gaps within the stent body were associated with histological events, such as ST or restenosis, in 67% of cases.12

The everolimus-eluting stent (EES) is a new-generation DES, based on a thin-strut, cobalt-chromium alloy platform and releases everolimus, a semisynthetic sirolimus analog, from an acrylic and fluoropolymer mixture.13 Newer-generation DESs have been designed for further enhanced safety and efficacy in patients undergoing percutaneous coronary intervention. Recent pivotal clinical trials have demonstrated the improved safety and efficacy of EES compared with paclitaxel-eluting stent.14,15 However, the incidence and clinical impact of SF after EES implantation remain unclear. The aim of the present study was to assess the incidence and clinical impact of SF after EES implantation.

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WHAT IS KNOWN

- Stent fracture after drug-eluting stent implantation has recently become an important concern because of its potential association with in-stent restenosis, target lesion revascularization, and stent thrombosis.
- The incidence and clinical impact of stent fracture after everolimus-eluting stent remain unclear.

WHAT THE STUDY ADDS

- Stent fracture after everolimus-eluting stent implantation occurs in 2.9% of lesions.
- Stent fracture is associated with higher rate of major adverse cardiac events, driven by higher target lesion revascularization and stent thrombosis.

Methods

Patient Population and Procedural Protocol

From February 2010 to February 2011, a total of 1208 patients with 1562 lesions who underwent successful implantation with only EES (Xience V, Abbott Vascular, Santa Clara, CA; Promus, Boston Scientific, Natick, MA) at Kokura Memorial Hospital and Chidoribashi Hospital were followed prospectively. Of these, 1035 patients (85.7%) with 1339 lesions who underwent follow-up angiography 6 to 9 months after the initial procedure, irrespective of clinical symptoms, or before 6 months for recurrent symptoms were enrolled in this study. All interventions were performed using standard techniques. Predilation, postdilation, and use of intravascular ultrasound (IVUS) were left to the operator's discretion. After the procedure, all patients were advised to continue on aspirin (81–162 mg daily) for life unless there were contraindications. Either ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was also prescribed for at least 1 year after stent implantation. Written informed consent to participation was obtained from all patients in accordance with the Declaration of Helsinki, and this study was approved by the ethics committee of Kokura Memorial Hospital and Chidoribashi Hospital.

Quantitative Angiographic Analysis

Coronary angiography was performed after intracoronary administration of 0.2 mg nitroglycerin. Quantitative coronary angiographic analysis was performed before and after stenting and during follow-up angiography, using a guiding catheter to calibrate the magnification and a validated automated edge detection algorithm (CASS 5.7, Pie Medical Imaging, Eindhoven, The Netherlands). The analyses were performed independently by 2 experienced observers (M.H. and S.M.) blinded to the clinical information. The target lesion for measurement of minimal lumen diameter included 5-mm margins proximal and distal to the stent, as well as the stent itself. ISR was defined as a percent diameter stenosis of ≥50% within the stent at the time of follow-up. In-segment restenosis was defined as a percent diameter stenosis of ≥50% either within the stented segment or within the 5 mm proximal or distal to the stent segment. The angiographic ISR patterns were classified as focal or diffuse according to the Mehran classification. A hinge motion lesion was defined as having ≥16° difference in angle between diastole and systole before the procedure.

Definitions of Stent Fracture, Major Adverse Cardiac Events, and ST

SF was defined as complete or partial separation of stent segments observed by plain fluoroscopy without contrast injection or IVUS at follow-up angiography. The angiographic diagnosis of SF required an independent view and the agreement of 2 independent cardiologists (T.H. and S.S.). Angiographic SF was classified according to the Popma classification as type 1 (minor), type 2 (V-form), type 3 (complete separation without displacement), or type 4 (complete separation with displacement). Diagnosis of SF by IVUS required careful review of the IVUS images and the agreement of 2 independent cardiologists (T.D. and M.H.). SF observed by IVUS was classified according to the Doi classification as complete (complete separation of the stent into ≥2 pieces separated by image slices with no visible struts) or partial (the absence of struts over ≥1/3 of the stent circumference). Major adverse cardiac events (MACE) were defined as cardiac death, myocardial infarction, clinically driven TLR, and ST during the follow-up period. Myocardial infarction was defined as a new Q wave >0.04 seconds or elevation of serum creatine kinase levels to greater than twice the upper limit of normal values, with an elevated myocardial band fraction and troponin I level and associated with chest pain. A clinically driven TLR was defined as treatment for recurrent angina pectoris before follow-up angiography or a ≥70% diameter stenosis on follow-up angiography in the presence of signs or symptoms of myocardial ischemia. The timing and diagnostic certainty of SF were assessed according to the Academic Research Consortium definition.

Statistical Analysis

Statistical analysis was performed using JMP, version 8.0.2 (SAS Institute Inc, Cary, NC). Data are presented as values and percentages, mean±SD, or median (interquartile range). Categorical variable were compared between groups with the χ² test or Fisher exact test, as appropriate. Continuous variables were compared between groups using the Student unpaired t test or the Mann-Whitney U test, based on the distribution. Multivariable logistic regression analysis was used for the lesion-based analysis of the risk factors for SF. The following 8 variables with P<0.05 in the univariate analysis were tested for their multivariate predictive value: ostial stent location, calcification, tortuosity, hinge motion, chronic total occlusion, stent overlap, right coronary artery, and total stent length. The final model was constructed using the 4 variables: hinge motion, ostial stent location, tortuosity, and calcification selected by forward stepwise method, with entry and exit criteria set at the P=0.05 and P=0.10 levels, respectively. As the complete follow-up information was obtained, the χ² test was used to compare the rate of MACE at 9 months between patients with SF and those without SF. A 2-sided P<0.05 was considered statistically significant.

Results

Coronary angiography was performed 233 (interquartile range, 185–246) days after the index procedure. Baseline characteristics of the 1035 patients with follow-up angiography included in this study were not significantly different from those of the 173 patients without angiography (data not shown). At follow-up, SF was recognized in 39 of 1339 lesions (2.9%) and in 39 of 1035 patients (3.8%).

Clinical Characteristics

The baseline clinical characteristics of the SF and non-SF groups are shown in Table 1. The 2 groups differed significantly only in left ventricular ejection fraction, hemodialysis, previous coronary artery graft bypass, and insulin use rates.

Angiographic and Procedural Characteristics and Results

The angiographic and procedural characteristics and results of both groups are shown in Table 2. Compared with non-SF group, SF group had considerably greater lesion complexity. Although the stent size was similar between the 2 groups, significant differences in total stent length, number of stents...
per lesion, and the rate of stent overlap lesion (all $P<0.001$) were observed. Of the 1339 lesions, 973 and 366 lesions were treated with 1 stent and $\geq 2$ stents, respectively. The SF rates of 1 stent and $\geq 2$ stents were 1.27% (17 lesions) and 1.64% (22 lesions), respectively. Preprocedure percent diameter stenosis and lesion length were significantly smaller and longer in the SF group than in the non-SF group ($P=0.035$ and 0.005, respectively). In SF lesions with hinge motion, the point of fracture was well accorded with the point of hinge motion. At follow-up, ISR and in-segment restenosis occurred more frequently in the SF group than in the non-SF group ($P<0.001$, respectively). In the SF group, ISR was observed at all SF sites of all affected lesions. The angiographic patterns of ISR were mostly focal (79.3%) in both groups.

### Classification and Independent Predictors of Stent Fracture

Among 39 SFs, there were 32 angiographically visible SFs, in which 21 (53.8%) were type 2, 10 (25.6%) were type 3, and 1 (2.6%) was type 4. Seven SFs (17.9%) were not angiographically visible and were detected only by IVUS. We defined them as angiographically unclassified. In this study, IVUS was performed only in patients undergoing TLR, and there were 21 SFs (53.8%) detected by IVUS and careful review of angiogram. Of 21 SFs detected by IVUS, 12 (57.1%) were complete, and 9 (42.9%) were partial. Figure 1 shows a representative case of SF. The SFs were located in the midportion (66.7%), proximal portion (15.4%), distal portion (2.6%), and overlap portion (15.4%). Figure 2A and 2B shows the

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=1035)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=996)</th>
<th>$\rho$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions</td>
<td>1339</td>
<td>39</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69.7±9.6</td>
<td>69.3±9.9</td>
<td>69.7±9.6</td>
<td>0.79</td>
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<tr>
<td>Male, %</td>
<td>782 (75.6)</td>
<td>26 (66.6)</td>
<td>756 (75.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>852 (82.3)</td>
<td>34 (87.1)</td>
<td>818 (82.1)</td>
<td>0.39</td>
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<tr>
<td>Diabetes, %</td>
<td>476 (44.2)</td>
<td>19 (48.7)</td>
<td>457 (45.8)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>786 (75.9)</td>
<td>29 (74.3)</td>
<td>757 (76.0)</td>
<td>0.81</td>
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<tr>
<td>Hemodialysis, %</td>
<td>60 (5.8)</td>
<td>8 (20.5)</td>
<td>52 (5.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>203 (19.6)</td>
<td>7 (17.9)</td>
<td>196 (19.6)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>285 (27.5)</td>
<td>9 (23.0)</td>
<td>276 (27.7)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

SF indicates stent fracture; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CI, cerebral infarction; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and OHA, oral hypoglycemia agent.

Categorical variables are expressed as n (%) and continuous variable as mean±SD.

*SF risk versus non-SF risk.
Table 2. Angiographic and Procedural Characteristics

<table>
<thead>
<tr>
<th>Location of target lesion, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>RCA</td>
<td>421 (31.4)</td>
<td>26 (66.6)</td>
<td>395 (30.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>LAD</td>
<td>535 (40.0)</td>
<td>6 (15.4)</td>
<td>529 (40.7)</td>
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<tr>
<td>LCX</td>
<td>295 (22.0)</td>
<td>6 (15.4)</td>
<td>289 (22.2)</td>
<td></td>
</tr>
<tr>
<td>LMT</td>
<td>81 (6.0)</td>
<td>0 (0.0)</td>
<td>81 (6.2)</td>
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<tr>
<td>SVG</td>
<td>5 (0.4)</td>
<td>1 (2.6)</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>LITA</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
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<table>
<thead>
<tr>
<th>Lesion type, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>111 (8.3)</td>
<td>0 (0.0)</td>
<td>111 (8.5)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>314 (23.4)</td>
<td>2 (5.1)</td>
<td>312 (24.0)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>282 (21.1)</td>
<td>5 (12.8)</td>
<td>277 (21.3)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>632 (47.2)</td>
<td>32 (82.0)</td>
<td>600 (46.1)</td>
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<table>
<thead>
<tr>
<th>In-stent restenosis, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>199 (14.9)</td>
<td>9 (23.0)</td>
<td>190 (14.6)</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcification, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>107 (8.0)</td>
<td>11 (28.2)</td>
<td>96 (7.3)</td>
<td>0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Tortuosity, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>280 (20.9)</td>
<td>33 (84.6)</td>
<td>247 (19.0)</td>
<td>&lt;0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Hinge motion, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>112 (8.4)</td>
<td>28 (71.7)</td>
<td>84 (6.4)</td>
<td>&lt;0.001</td>
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<table>
<thead>
<tr>
<th>Bifurcation, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>409 (30.5)</td>
<td>7 (17.9)</td>
<td>402 (30.9)</td>
<td>0.11</td>
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<table>
<thead>
<tr>
<th>1 stent use, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>199 (14.9)</td>
<td>9 (23.0)</td>
<td>190 (14.6)</td>
<td>0.16</td>
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</table>

<table>
<thead>
<tr>
<th>Ostial location, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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<tbody>
<tr>
<td>138 (10.3)</td>
<td>9 (23.0)</td>
<td>129 (9.9)</td>
<td>0.01</td>
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<table>
<thead>
<tr>
<th>Chronic total occlusion, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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<tbody>
<tr>
<td>2.8±0.4</td>
<td>2.8±0.3</td>
<td>2.8±0.4</td>
<td>0.42</td>
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<table>
<thead>
<tr>
<th>Total stent length, mm</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>29.9±18.5</td>
<td>44.2±26.2</td>
<td>29.4±18.0</td>
<td>&lt;0.001</td>
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<table>
<thead>
<tr>
<th>No. of stents per lesion, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>199 (14.9)</td>
<td>9 (23.0)</td>
<td>190 (14.6)</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximal pressure, atm</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>13.2±4.0</td>
<td>14.3±5.2</td>
<td>13.1±4.0</td>
<td>0.15</td>
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<table>
<thead>
<tr>
<th>Post dilation, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>424 (31.7)</td>
<td>19 (48.7)</td>
<td>405 (31.1)</td>
<td>0.02</td>
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<table>
<thead>
<tr>
<th>Stent overlap, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>352 (26.3)</td>
<td>22 (56.4)</td>
<td>330 (25.3)</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>IVUS use, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>660 (49.3)</td>
<td>25 (64.1)</td>
<td>635 (48.8)</td>
<td>0.06</td>
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<table>
<thead>
<tr>
<th>QCA results</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length, mm</td>
<td>23.0±11.8</td>
<td>28.8±12.9</td>
<td>22.7±11.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>

| RVD at baseline, mm         | 2.59±0.93       | 2.68±0.46| 2.59±0.94       | 0.53     |

| MLD, pre, mm                | 0.52±0.33       | 0.46±0.33| 0.52±0.33       | 0.27     |

| % DS, pre, %                | 77.1±13.1       | 83.4±13.2| 76.9±13.1       | 0.035    |

| MLD, post, mm               | 2.16±0.99       | 2.30±0.44| 2.15±1.01       | 0.38     |

| % DS, post, %               | 16.4±7.2        | 14.9±5.9 | 16.5±7.2        | 0.17     |

<table>
<thead>
<tr>
<th>In-stent restenosis, %</th>
<th>Overall (n=1339)</th>
<th>SF (n=39)</th>
<th>Non-SF (n=1300)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>73 (5.5)</td>
<td>22 (56.4)</td>
<td>51 (3.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Diffuse                     | 19 (1.4)        | 6 (15.4)| 13 (1.0)        | <0.001   |

| Overall                     | 92 (6.9)        | 28 (71.8)| 64 (4.9)        | <0.001   |

SF indicates stent fracture; RCA, right coronary artery; LAD, left coronary artery; LCX, left circumflex artery; LMT, left main trunk; SVG, saphenous vein graft; LITA, left internal thoracic artery; IVUS, intravascular ultrasound; QCA, quantitative coronary angiography; RVD, reference vessel diameter; DS, diameter stenosis; and MLD, minimal lumen diameter.

Categorical variables are expressed as n (%) and continuous variable as mean±SD.

*SF risk versus non-SF risk.
classification of angiographic SF and the relationship between angiographic SF classification and TLR, ST, and MACE.

The independent predictors of SF after EES implantation by multivariate logistic regression analysis are shown in Table 3. Hinge motion (odds ratio, 14.57; 95% CI, 5.94–39.78; P<0.001), ostial stent location (odds ratio, 12.38; 95% CI, 4.03–37.46; P<0.001), tortuosity (odds ratio, 5.45; 95% CI, 1.81–17.58; P=0.002), and calcification (odds ratio, 4.27; 95% CI, 1.75–10.17; P=0.001) were identified as predictors of SF after EES implantation.

**Clinical Outcomes**

Clinical follow-up information in the SF and the non-SF group at 9 months was completely obtained. The MACE rates 9 months after EES implantation are shown in Table 4 and Figure 3. The MACE rate at 9 months was significantly higher in the SF group than in the non-SF group (25.6% versus 0.4%; P<0.001), whereas the rate of cardiac death did not differ significantly between the 2 groups. The cumulative incidence of ST within 9 months after implantation was significantly higher in the SF group (25.6% versus 2.0%; P<0.001, respectively), whereas the rate of cardiac death did not differ significantly between the 2 groups. The cumulative incidence of ST within 9 months after implantation was significantly higher in the SF group (25.6% versus 0.4%; P<0.001). All ST were definite ST. No significant difference in the rate of early ST was observed between the 2 groups, and no early ST occurred in the SF group. In contrast, late ST was more frequently observed in the SF group than in the non-SF group (5.1% versus 0.1%; P=0.004).

**Discussion**

The main findings of the present study are as follows: (1) the incidence of SF after EES implantation was 2.9% of lesions, (2) SF was associated with higher rates of TLR and MACE, (3) ostial stent location and lesions with hinge motion, calcification, or tortuosity were identified as independent predictors of SF, and (4) the incidence of ST was significantly higher in the SF group than in the non-SF group.

The incidence of SF in clinical setting has been reported to be 0.84% to 8.4%. Several studies have demonstrated that SES is more likely to cause SF because of its closed-cell design and because of being made of stainless steel with low flexibility and conformability. The EES is a new-generation DES and features a thin-strut, flexible, cobalt-chromium platform, which is expected to prevent SF. Although several clinical studies have shown the efficacy and safety of EES compared with those of early paclitaxel-eluting stent, the incidence and clinical impact of SF remain unclear. In the present study, SF after EES implantation was observed in 2.9% of lesions. Although the incidence of SF after EES implantation was lower and higher than that previously reported for SES (3.2%–8.4%) and paclitaxel-eluting stent (2.4%), SF did occur even in EES in real-world practice. To place these results in perspective, we analyzed the incidence of SF in patients treated with SES and paclitaxel-eluting stent during the present study period. A total of 79 patients were treated with SES, of which 66 patients (83.5%) underwent follow-up coronary angiography, with SF observed in 3 of 73 lesions (4.1%) by angiography or IVUS. Of 74 patients treated with paclitaxel-eluting stent, 68 patients (91.8%) underwent coronary angiography after the index procedure, with SF observed in 1 of 75 lesions (1.3%) by angiography. Although it was statistically difficult to compare them with EES, these results were consistent with previous studies.

SF has been associated with higher potential risks of ISR, TLR, and ST. The mechanisms of ISR in SF are probably related to the lower drug delivery at the fracture site and higher mechanical irritation by the fractured struts, causing smooth
muscle cell proliferation and impaired re-endothelialization.

In the present study, the rates of clinically driven TLR and MACE were significantly higher in lesions with SF than in those without SF. Although SF was associated with MACE, it remains unclear when SF occurred after stent implantation. In the present study, 17 patients underwent angiography before follow-up angiography because of clinical symptoms. Of these, SF was observed in 5 patients. In 5 SF patients, ST occurred in 2 patients at 52 and 61 days after EES implantation, and 3 patients underwent repeat revascularization at 65, 125, and 149 days. Furthermore, the rates of SF and MACE were higher in SF patients detected before follow-up angiography than in those at follow-up angiography (29.4% versus 3.4% and 100% versus 17.4%; P<0.001, respectively). Therefore, SF might be one of the causes of cardiac adverse events in the early phase after EES implantation.

Table 3. Multivariate Logistic Regression Analysis of Stent Fracture

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hinge motion</td>
<td>14.57</td>
<td>5.94–39.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ostial stent location</td>
<td>12.38</td>
<td>4.03–37.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tortuosity</td>
<td>5.45</td>
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<td>0.002</td>
</tr>
<tr>
<td>Calcification</td>
<td>4.27</td>
<td>1.75–10.17</td>
<td>0.001</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

Table 4. Cumulative Incidences of Major Cardiac Events Within 9 Months After EES Implantation

<table>
<thead>
<tr>
<th></th>
<th>SF (n=39)</th>
<th>Non-SF (n=996)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>10 (25.6)</td>
<td>23 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1 (2.6)</td>
<td>3 (0.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>MI</td>
<td>2 (5.1)</td>
<td>4 (0.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>TLR</td>
<td>10 (25.6)</td>
<td>20 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>10 (25.6)</td>
<td>13 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>0 (0.0)</td>
<td>7 (0.7)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Stent thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>2 (5.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Probable</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Overall</td>
<td>2 (5.1)</td>
<td>4 (0.4)</td>
</tr>
</tbody>
</table>

EES indicates everolimus-eluting stent; SF, stent fracture; MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization; PCI, percutaneous coronary intervention; and CABG, coronary artery graft bypass.

Categorical variables are expressed as n (%).
An IVUS study showed that some SFs after SES implantation were associated with coronary aneurysm formation and that complete SF was more frequent in lesions with aneurysm than those without aneurysm. A pathological study has demonstrated that the nonerodable polymer of SES induces inflammatory infiltrates characterized by eosinophils, lymphocytes, and giant cells (hypersensitivity reaction), resulting in positive remodeling and malapposition. These responses may be responsible for coronary aneurysm formation. Conversely, the fluorinated copolymer of EES is biocompatible and designed to elicit a less inflammatory reaction, and there has been to date only 1 case report of coronary aneurysm formation after EES implantation. No coronary aneurysm formation was observed in the present study. Therefore, coronary aneurysm formation after EES implantation is likely to be a very rare complication, and the mechanism of association of SF with aneurysm may be unlikely with EES.

Several studies have shown that right coronary artery or saphenous vein graft, overlap stenting, longer stent length, lesions with hinge motion, and SES use are associated with SF. In the present study, ostial stent location and lesions with hinge motion, tortuosity, or calcification were independent predictors of SF after EES implantation. Among these, hinge motion and tortuosity contributed most greatly to the incidence of SF. Extreme repetitive contraction and flexion of the vessel produce excessive mechanical vessel wall stress. Closed-cell design stents, such as SES, induce greater vessel straightening than open-cell design stents do, creating hinge points during cardiac contraction that may become prone to fracture over time. Although EES has an open-cell design and cobalt-chromium platform with high flexibility and conformability, metal fatigue occurs at hinge point during the cardiac cycle. Furthermore, considerable attention has recently been focused on longitudinal stent deformation (LSD) in patients treated with new-generation thin-strut DES. Williams et al reported 9 cases of LSD during a 4-year period, presenting 0.2% of cases and affecting 0.097% of stents deployed. There were several mechanisms for this complication, including compression by postdilation balloons, guide catheter extensions, and proximal embolic protection devices. In the present study, there was no evidence of LSD at the index procedure. However, 3 cases with SF because of LSD were detected in 39 cases with SF. Figure 4 shows a representative case of SF because of LSD. All LSD cases were recognized in angiographic type 2 SF using IVUS. Therefore, LSD may be one of the mechanisms for SF in the thin-strut DES. In any case, some few SFs are unavoidable even in EES. Most important point, however, is not the incidence of SF itself but the impact of SF on clinical outcomes, such as TLR and ST. In the present study, SF was associated with higher MACE, driven by higher rate of TLR and ST. Therefore, further improvements in stent design and materials are needed to prevent the occurrence of SF. In particular, stent longitudinal integrity may be a key parameter in the development of newer-generation DES.
ST is a rare but potentially life-threatening complication that has raised intriguing issues in the DES era, and awareness of SF as a potential complication after DES implantation and a contributor to ST has been increasing. A recent meta-analysis has demonstrated that EES use greatly and significantly reduces ST compared with the use of other DESs. However, this meta-analysis contains no data on the relationship between ST and SF after EES implantation. A pathological analysis has shown that the incidence of SF at autopsy was 29% in lesions with DES, and adverse pathological findings, such as ST and restenosis, were observed at high rates in lesions with grade V SF. In the present study, ST occurred in 2 patients with SF. Of these, one was a complete SF by IVUS and angiographic type 3, whereas the other was complete SF by IVUS but was angiographically unclear because of severe calcification. As a result, ST was thought to be associated with lesions with high-grade SF. These findings were consistent with the pathological findings. The pathophysiology of ST is multifactorial and includes stent-, procedure-, and patient-related factors. An IVUS study has shown that early ST may be related to procedural factors, such as residual target lesion thrombus or dissection, stasis, stent underexpansion, or a combination of these. On the other hand, several studies have demonstrated that late ST may be more frequently related to incomplete healing and inadequate neointimal coverage. In the present study, only late ST was observed in lesions with SF. Although why SF leads to ST is not fully understood, the lack of stent integrity may delay healing and thus influence the incidence of ST. Furthermore, premature discontinuation of dual antiplatelet therapy is perhaps the strongest clinical predictor of ST after DES implantation. Among 6 patients with ST, only 1 without SF had interrupted dual antiplatelet therapy for 1 week before the occurrence of late ST. Therefore, SF may be an important contributor to ST, regardless of the discontinuation of dual antiplatelet therapy.

Study Limitations
There are several limitations in the present study. First, follow-up angiography was not performed in all patients. Therefore, selection bias may exist in the present study and may have biased the conclusion. Nevertheless, to the best of our knowledge, this is the first study to assess the incidence and clinical impact of SF after EES implantation. A larger study population is necessary to further validate the current findings. Second, IVUS was performed only in patients undergoing TLR. In the present study, 53.8% of SF was confirmed by IVUS, as plain fluoroscopy and IVUS was insufficient to detect minor SF. However, the resolution of plain fluoroscopy and IVUS was insufficient to detect minor SF, such as separation of a single-strut filament. Therefore, the present study may have underestimated the incidence of SF and showed high TLR in the SF group. A newer imaging method for detecting SF, optical coherence tomography may be useful for SF diagnosis. Third, we could not distinguish late ST from thrombosis because of ISR completely. We performed IVUS after thrombus aspiration and predilation using small balloon in all SF cases with ST. IVUS revealed that there were thrombi at the culprit site and less neointimal hyperplasia within the stent, except for the culprit site. Furthermore, the location of SF was well accorded with minimal lumen area. However, IVUS could not distinguish thrombus from neointimal hyperplasia completely. Therefore, neointimal hyperplasia may be associated with late ST in the present study. Finally, the impact of SF after EES implantation on long-term clinical outcomes is not assessed in this study. Umeda et al reported that SF after SES was not significantly associated with MACE between 1 and 4 years after the index procedure. Further study is needed to assess whether SF after EES might influence long-term clinical outcomes.

Conclusions
SF after EES implantation occurs in 2.9% of lesions and is associated with higher MACE, driven by higher rate of TLR and ST. Ostial stent location and lesions with hinge motion, tortuosity, or calcification are independent predictors of SF.

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Disclosures
None.

References
Fracture of Everolimus-Eluting Stents


Incidences and Clinical Impact of Stent Fracture After Everolimus-Eluting Stent Implantation
Shoichi Kuramitsu, Masashi Iwabuchi, Takuya Haraguchi, Takenori Domei, Ayumu Nagae, Makoto Hyodo, Kyohei Yamaji, Yoshimitsu Soga, Takeshi Arita, Shinichi Shirai, Katsuhiro Kondo, Kenji Ando, Koyu Sakai, Masahiko Goya, Yoshitaka Takabatake, Shinjo Sonoda, Hiroyoshi Yokoi, Fumitoshi Toyota, Hideyuki Nosaka and Masakiyo Nobuyoshi

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