Restenosis and Stent Fracture Following Sirolimus-Eluting Stent (SES) Implantation

A Serial Quantitative Coronary Angiography (QCA) and Intravascular Ultrasound (IVUS) Study

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Background

Restenosis still occurs, even with the sirolimus-eluting stent (SES), and the precise mechanisms and the impact of stent fracture on restenosis have not yet been elucidated.

Methods and Results

Intravascular ultrasound (IVUS)-guided SES implantation was performed in 184 lesions in 151 patients with stable and unstable angina. Serial (pre-, post- and follow-up) quantitative coronary angiography analysis was obtained in 169 lesions in 138 patients (angiographic follow-up rate: 91%) and 12-month clinical follow-up was done in all patients. Restenosis occurred in 13 (7.7%) of 169 lesions. Stent fracture occurred in 4 (2.4%) of 169 lesions at follow-up. Of the 13 restenotic lesions, 8 had intimal hyperplasia, 4 had stent fracture, and 1 had late stent thrombosis at 7 months. Although multivariate logistic regression analysis revealed that minimal lumen area (min-LA) post (p=0.027), total stent length (p=0.003) and diabetes (p=0.052) were significant independent predictors of restenosis, univariate analysis showed that stent fracture was more common in the restenosis than in the non-restenosis groups (p=0.001).

Conclusions

Although min-LA post by IVUS, total stent length by QCA and diabetes are independent predictors for angiographic restenosis, stent fracture occurred in 4 lesions (2.4%) and all of them resulted in restenosis (31% of the restenosis). The impact of stent fracture and its potential role in the development of restenosis deserves further study. (Circ J 2007; 71: 1669–1677)

Key Words: Drug-eluting stent (DES); Intravascular ultrasound (IVUS); Quantitative coronary angiography (QCA); Restenosis; Sirolimus-eluting stent (SES); Stent fracture

Following the development of drug-eluting stents (DES) the interventional cardiologist seems to have overcome the nemesis of restenosis. The First-In-Man study and a randomized comparison of a sirolimus-eluting stent (SES) with a standard stent for coronary revascularization reported complete inhibition of restenosis in simple discrete lesions at 6 months.[1,2] However, recent randomized clinical trials using DES for lesions with low- or intermediate restenosis risk reported restenosis rates ranging from 2.3% to 16.7%.[3-12] Furthermore, the number of LES used and the stent length required for each lesion are both substantially increasing based on the recent recommended policy of full lesion coverage to avoid any potential injury at the stent edges.[3] Despite the increasing popularity of DES technologies worldwide, the precise mechanisms responsible for DES restenosis remain unclear. Several case reports have highlighted the occurrence of stent fracture (absence or deformity of a stent strut inside the stent) at follow-up, especially in patients experiencing restenosis with SES, however, the incidence of fracture and its impact on restenosis are poorly understood.[12-18]

The purpose of this study was to investigate the predictors of restenosis following SES implantation and to determine the incidence and impact of stent fracture. We prospectively performed the SES implantation under intravascular ultrasound (IVUS) Guidance in Native coronary Artery Lesions (SIGNAL) study at the Fujita Health University hospital.

Methods

Study Design and Endpoints

The SIGNAL study was designed as a prospective, single-center, angiographic and IVUS follow-up study to evaluate the acute and late efficacy, as well as safety of deployment, of SES. The primary endpoint was angiographic restenosis. The principal clinical endpoint was a composite
of major adverse cardiac events, including subacute stent thrombosis (≤30 days after the procedure), late stent thrombosis (>30 days after the procedure), death, Q-wave and non-Q-wave myocardial infarction, and need for target lesion revascularization.

Patient Selection

Patients with unstable and stable angina, a target lesion in a native coronary artery, elective stent implantation, and agreement to follow-up coronary angiography were included in the study. Patients were excluded from the study if they had a contraindication to anticoagulation and antithrombotic therapy or graft disease. The study was approved by local ethics committees and was carried out according to the guidelines of the Declaration of Helsinki. Written informed consent was given by all patients.

Percutaneous Coronary Intervention (PCI) Procedures

Stent implantation was performed according to standard clinical practice with radial or femoral approaches using guide catheters 6F or greater in size to facilitate subsequent quantitative coronary angiographic (QCA) analysis. A bolus of 8,000–10,000 IU of heparin (repeated if necessary) was administered during the procedure, followed by a combination of antithrombotic therapy. To ensure full expansion of the stent, high-pressure intra-stent balloon inflation was performed.

Antiplatelet Therapy

According to standard patient care, treatment with aspirin at a dose of 100–200 mg daily was started before the procedure and continued indefinitely. Treatment with ticlopidine at 200 mg daily was begun before the procedure and continued for at least 8 months to avoid subacute and late stent thrombosis. Regular blood counts were performed to screen for drug-induced agranulocytosis.

IVUS-Guided PCI Procedure

Stent and balloon sizes were determined using measurements of vessel dimension and plaque distribution made with IVUS. The IVUS criteria for optimal stent placement were originally derived from the MUSIC study: (1) good stent apposition with symmetric stent expansion; (2) full stent expansion with sufficient lumen area (ie, lumen area 80% or greater of the average reference lumen area pre-intervention); and (3) the absence of major dissection. To fulfill these criteria, repeated high-pressure intra-stent balloon inflation or additional stenting was performed if necessary.

Image Acquisition for IVUS

Following selective coronary angiography after intracoronary injection of nitrates, a mechanical intracoronary US-imaging catheter (40-MHz, 2.5Fr, Boston Scientific Co, Fremont, CA, USA) was introduced over a 0.014-inch guidewire before stenting, after stenting, and at follow-up. After the imaging catheter was passed into and beyond the lesion, motorized pullback was started to obtain an assessment of the target lesion. IVUS images were stored on super VHS videotape for off-line analysis.

Quantitative IVUS Assessment

Serial IVUS analysis pre-procedure, post-stenting and at 8-months follow-up was performed at the core laboratory of the Fujita Health University and the Aichi Medical University. Cross-sectional luminal area (LA) was defined as the integrated area central to the intimal leading edge echo. The total vessel cross-sectional area (VA) was defined as the area inside the interface between the plaque/media complex and adventitia (area inside the external elastic membrane). The lesion segment was defined from pre-intervention images, including the frame with the smallest LA, while the proximal and distal reference segments were defined as the location of the least amount of disease before the emergence of any major side branches. The corresponding frames at post-intervention and follow-up were determined by using peri- and intra-coronary landmarks such as calcium deposits, side branches, the distance from the stent extremity and venous structures.

QCA Analysis

QCA analyses were performed using the computer-based edge-detection Coronary Angiography Analysis System (CAAS II, Pie Medical, Maastrict, the Netherlands). Coronary angiograms were obtained in multiple views matched after intracoronary injection of nitrates. Interpolated reference vessel diameter (RD), minimal lumen diameter (MLD) and percentage diameter stenosis were obtained at baseline (pre-stenting), post-stenting and at follow-up using the guiding catheter from the QCA system as a scaling device. QCA analyses were performed at the independent core laboratory of the Fujita Health University and the Aichi Medical University. QCA measurements of the target lesion were obtained in the “in-stent” (including only the stented segment) and in the 5-mm adjacent segments (the stent margins 5 mm proximal and distal to the stent). Late loss represents the changes in MLD at follow-up (MLD-post stenting minus MLD at follow-up). Restenosis was defined as ≥50% diameter stenosis at follow-up.

Stent Fracture Definition

Stent fracture was defined as the significant disappearance of stent struts in the stent at follow-up in comparison with the presence of stent struts immediately after stent implantation by IVUS and newly developed fluoroscopic discontinuity of stent struts at follow-up.

Statistical Analysis

Data were analyzed using the SAS statistical software (SAS Institute, Cary, NC, USA). All continuous variables are expressed as mean±SD. Differences in categorical variables were assessed using the chi-square test. The unpaired t-test was used to assess differences in continuous variables between 2 groups. To study the relationship between the binary outcome parameter (restenosis) and multiple categorical and continuous determinants, multiple logistic regression analysis was used. Univariate variables with a p-value <0.2 were entered into the multivariate models. Forward stepping was used to determine the independent predictors of restenosis. Following multiple logistic regression analysis, a receiver-operator characteristic (ROC) curve was constructed to determine the model discrimination and cutoff points for predicting restenosis. We analyzed the points of intersection of both sensitivity and specificity curves to assess the best cutoff values for predicting angiographic restenosis. A 2-tailed value of p<0.05 was considered significant.
Table 1 Comparison of Baseline Clinical and Angiographic Characteristics Between Non-Restenosis and Restenosis Patients

<table>
<thead>
<tr>
<th></th>
<th>Non-restenosis</th>
<th>Restenosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>125</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6±10.6</td>
<td>63.9±12.4</td>
<td>0.664</td>
</tr>
<tr>
<td>Male (%)</td>
<td>82.4</td>
<td>69.2</td>
<td>0.248</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>27.2</td>
<td>61.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>79.2</td>
<td>69.2</td>
<td>0.407</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>59.2</td>
<td>53.9</td>
<td>0.709</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>33.6</td>
<td>46.2</td>
<td>0.306</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>44.8</td>
<td>46.2</td>
<td>0.926</td>
</tr>
<tr>
<td>Ischemic symptoms (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>64.8</td>
<td>53.9</td>
<td>0.694</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>25.6</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>Subacute MI</td>
<td>9.6</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>No. of diseased vessels (%)</td>
<td>60.0</td>
<td>53.9</td>
<td>0.908</td>
</tr>
<tr>
<td>Single</td>
<td>32.8</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>7.2</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Duration between 1st &amp; 2nd angiography (months)</td>
<td>7.83±1.73</td>
<td>8.08±1.26</td>
<td>0.620</td>
</tr>
</tbody>
</table>

Lesions (n) 156 13

Target coronary artery (%) 125 13

RCA 25.0 30.8 0.863
LAD 39.1 38.4 –
LCX 31.4 30.8 –
LM 4.5 0 –

ACC/AHA lesion type (%) 125 13

A or B1 52.6 23.1 0.041
B2 or C 47.4 76.9 –

Stent size and length 125 13

Stent diameter (mm) 2.92±0.31 2.83±0.26 0.296
Stent length (mm) 23.3±8.6 34.5±9.9 0.001
Stent ratio 1.25±0.25 1.29±0.24 0.588

MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; ACC/AHA, American College of Cardiology/American Heart Association.

Results

Clinical Characteristics

To determine the safety and efficacy of deployment of SES, we electively deployed them with IVUS guidance in 184 lesions in 151 patients at the Fujita Health University Hospital between September 1, 2004 and July 15, 2005 following the official approval of SES use by the Japanese Ministry of Health, Labor and Welfare. All 151 patients had clinical follow-up at 12 months. Of the 151 patients, 138 had angiographic follow-up (patient angiographic follow-up rate: 91.3%) and the remaining 13 had clinical follow-up. Of the 138 patients, 125 did not have angiographic restenosis (non-restenosis group) and the remaining 13 had restenosis (restenosis group). The baseline clinical and angiographic characteristics comparison between the restenosis and non-restenosis groups is provided in Table 1. No significant difference was found between the 2 groups for clinical characteristics or follow-up duration, except with respect to the greater preponderance of diabetes mellitus (DM) in the restenosis group.

Angiographic Lesion Characteristics

Of the 184 lesions in 151 patients, 169 lesions in 138 patients had angiographic follow-up (lesion angiographic follow-up rate: 91.8%) and the remaining 15 lesions in 13 patients did not. Of the 169 lesions, 156 did not have restenosis and 13 lesions in 13 patients had restenosis (restenson-

Table 2 Comparison of Serial (Pre-, Post- and Follow-up) QCA and IVUS Between Non-Restenosis and Restenosis Patients

<table>
<thead>
<tr>
<th></th>
<th>Non-restenosis</th>
<th>Restenosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial QCA (n)</td>
<td>156</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>In-stent segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD-pre (mm)</td>
<td>2.45±0.52</td>
<td>2.29±0.47</td>
<td>0.265</td>
</tr>
<tr>
<td>MLD-pre (mm)</td>
<td>0.93±0.29</td>
<td>0.87±0.24</td>
<td>0.516</td>
</tr>
<tr>
<td>MLD-post (mm)</td>
<td>2.30±0.43</td>
<td>1.98±0.35</td>
<td>0.009</td>
</tr>
<tr>
<td>MLD-follow-up (mm)</td>
<td>2.19±0.39</td>
<td>0.82±0.45</td>
<td>0.001</td>
</tr>
<tr>
<td>Lesion length</td>
<td>21.9±8.5</td>
<td>25.5±8.8</td>
<td>0.149</td>
</tr>
<tr>
<td>Acute gain</td>
<td>1.37±0.44</td>
<td>1.17±0.36</td>
<td>0.110</td>
</tr>
<tr>
<td>Late loss</td>
<td>0.11±0.39</td>
<td>1.16±0.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Proximal segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD-pre (mm)</td>
<td>2.64±0.61</td>
<td>2.39±0.41</td>
<td>0.247</td>
</tr>
<tr>
<td>MLD-pre (mm)</td>
<td>2.18±0.61</td>
<td>1.95±0.50</td>
<td>0.328</td>
</tr>
<tr>
<td>MLD-post (mm)</td>
<td>2.47±0.55</td>
<td>2.26±0.55</td>
<td>0.241</td>
</tr>
<tr>
<td>MLD-follow-up (mm)</td>
<td>2.45±0.53</td>
<td>1.69±0.64</td>
<td>0.004</td>
</tr>
<tr>
<td>Distal segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD-pre (mm)</td>
<td>2.34±0.53</td>
<td>2.27±0.59</td>
<td>0.672</td>
</tr>
<tr>
<td>MLD-pre (mm)</td>
<td>1.94±0.61</td>
<td>1.87±0.64</td>
<td>0.666</td>
</tr>
<tr>
<td>MLD-post (mm)</td>
<td>2.16±0.60</td>
<td>2.03±0.55</td>
<td>0.450</td>
</tr>
<tr>
<td>MLD-follow-up (mm)</td>
<td>2.14±0.50</td>
<td>2.05±0.56</td>
<td>0.585</td>
</tr>
<tr>
<td>Serial IVUS (n)</td>
<td>92</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>VA pre (mm²)</td>
<td>12.9±4.23</td>
<td>11.7±2.23</td>
<td>0.342</td>
</tr>
<tr>
<td>LA pre (mm²)</td>
<td>2.49±1.21</td>
<td>2.10±0.44</td>
<td>0.290</td>
</tr>
<tr>
<td>LA post (mm²)</td>
<td>6.45±2.07</td>
<td>4.43±1.40</td>
<td>0.001</td>
</tr>
<tr>
<td>LA follow-up (mm²)</td>
<td>6.69±2.17</td>
<td>2.59±1.14</td>
<td>0.001</td>
</tr>
<tr>
<td>% stent area change</td>
<td>99±13%</td>
<td>88±21%</td>
<td>0.034</td>
</tr>
<tr>
<td>Stent fracture (n, %)</td>
<td>0 (0%)</td>
<td>4 (31%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*% stent area change = stent area at follow-up divided by stent area post. QCA, quantitative coronary angiography; IVUS, intravascular ultrasound; RD, reference vessel diameter; MLD, minimal lumen diameter; VA, vessel cross-sectional area; LA, luminal area.

Table 3 MACE in All 151 Patients

<table>
<thead>
<tr>
<th></th>
<th>Non-restenosis</th>
<th>Restenosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (n, %)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>SAT (n, %)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>LST (n, %)</td>
<td>1* (0.6%)</td>
<td>1* (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Death (n, %)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>MI (n, %)</td>
<td>1* (0.6%)</td>
<td>1* (0.6%)</td>
<td></td>
</tr>
<tr>
<td>TLR (n, %)</td>
<td>13* (8.6%)</td>
<td>13* (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Overall MACE (n, %)</td>
<td>15** (9.9%)</td>
<td>15** (9.9%)</td>
<td></td>
</tr>
</tbody>
</table>

*Same patient; **all MACE recorded even if one event led to another. MACE, major adverse cardiac events; AST, acute stent thrombosis; SAT, subacute stent thrombosis; LST, late stent thrombosis; TLR, target lesion revascularization. Other abbreviation see in Table 1.

sis rate; 7.7% [13 of 169 lesions]) (Table 1). No significant difference was found in lesion location in the coronary arteries. Although the nominal stent diameter used was similar between the 2 groups, the total stent length measured by QCA was significantly longer in the restenosis than in the non-restenosis group. The stent-to-artery ratio was not significantly different between the 2 groups.

QCA Analysis

No significant difference was found between the non-restenosis and restenosis groups in the baseline reference vessel size (RD-pre), MLD pre-procedure (MLD-pre) and lesion length (Table 2). MLD-post procedure was significantly greater in the non-restenosis group than in the restenosis group (p=0.009) and this greater lumen immediately after the procedure in the non-restenosis group carried over to follow-up (Table 2). MLD follow-up was significantly greater in the non-restenosis than in the restenosis groups (p=0.001). Although lesion length was similar

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between the 2 groups, late loss was significantly larger in the restenosis group than in non-restenosis group (p=0.001) (Table 2).

In the 5-mm segment proximal to the stent edge, RD-pre, MLD-pre and MLD-post were similar between the non-restenosis and restenosis groups (Table 2). At follow-up, MLD was significantly greater in the non-restenosis than in the restenosis patients, because 3 lesions had restenosis in both the proximal 5-mm segment and the within in-stent segment (Table 2). However, such a tendency was not seen in the 5-mm segment distal to the stent edge.

**IVUS Findings**

Although IVUS guidance was used in all procedures, pre-procedure images were not obtainable in 10 lesions (5.4%) because they could not be crossed before PCI. However, IVUS images were obtained in these 10 lesions following SES implantation. To achieve optimal stent implantation, stent deployment with high-pressure stent balloon inflations (≥16 atm), high-pressure intra-stent balloon inflations post-stenting (≥14 atm) and/or additional stent implantations were performed in all lesions. Serial (pre-, post- and follow-up) IVUS was obtained in 105 lesions (62.1% of the 169 lesions) (Table 2).

Although baseline VA-pre and minimal LA-pre were similar between the 2 groups, minimal LA after stenting was significantly greater in the non-restenosis group than that in the restenosis group (6.45±2.07 mm² vs 4.43±1.40 mm², p=0.001). This favorable larger LA-post subsequently became a greater LA at follow-up (6.69±2.17 mm² vs 2.59±1.14 mm², p=0.001) (Table 2).

**Stent Fracture Detected by IVUS and Angiography**

Although stent fracture was observed in 4 lesions in the restenosis group, none was seen in the non-restenosis group at follow-up (p=0.001). Of the 4 lesions, 1 was located in the right coronary artery, 2 were in the left circumflex coronary artery and 1 was in the left anterior descending coronary artery (Figs 3–7). The incidence of stent fracture was 2.4% (4/169 lesions) in our high angiographic follow-up rate series (91.8%). Although stent area at follow-up decreased to 88±21% of the area immediately after stenting in the restenosis group, stent area at follow-up was similar (99±13%) to that immediately after stenting in the non-restenosis group (Table 2).

**Clinical Outcomes**

Clinical follow-up was obtained in all 151 patients (100%). Acute and subacute stent thrombosis did not occur in any patient. Late angiographic stent thrombosis with acute myocardial infarction occurred in 1 patient (0.7%) at 7 months after stent implantation in the proximal left anterior descending artery, despite continuous administration of aspirin and ticlopidine. This patient was treated immediately by PCI and TIMI Grade III flow was quickly restored. IVUS examination was done following the successful initial balloon inflation.

**Multivariate Analysis Results**

Multivariate logistic regression analyses to evaluate the respective contribution of the clinical, angiographic and IVUS variables to restenosis indicated that smaller LA-post by IVUS (p=0.027), longer total stent length by QCA (p=0.003) and DM (p=0.032) were significant independent predictors for stent restenosis at follow-up (Fig 1). Univariate analysis indicated that the incidence of stent fracture was significantly different between the restenosis and non-restenosis groups (Table 2). However, stent fracture could not be regarded as a predictor of restenosis, because stent deployment with high-pressure stent balloon inflations (≥16 atm), high-pressure intra-stent balloon inflations post-stenting (≥14 atm) and/or additional stent implantations were performed in all lesions. Serial (pre-, post- and follow-up) IVUS was obtained in 105 lesions (62.1% of the 169 lesions) (Table 2).

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fracture was also found at follow-up, as well as restenosis. We therefore excluded stent fracture as a variable factor from the multivariate analysis model.

ROC curves were constructed to determine the model discrimination and cutoff points of LA-post by IVUS and total stent length by QCA for predicting restenosis. To obtain the best cutoff values for predicting angiographic restenosis following SES, the points of intersection of both sensitivity and specificity curves were analyzed (Fig 2). The best cutoff values were 5.0 mm² for LA-post and 30 mm for...
total stent length (Fig 2). Although the sensitivity and specificity for min-LA post of 5.0 mm² to predict angiographic restenosis was 77% (10/13) and 72% (107/149), respectively, the sensitivity and specificity for total stent length of 30 mm to predict restenosis was 69% (9/13) and 77% (120/156), respectively (Fig 2).

Discussion
This prospective single center study (SIGNAL) has demonstrated a procedural success rate for SES implantation with IVUS guidance and an acceptably low restenosis rate (7.7%), despite complex lesion morphology (majority of the lesions having been type B2/C). Univariate analysis revealed that DM, longer total stent length by QCA, smaller MLD-post by QCA, smaller min-LA post by IVUS and the occurrence of stent fracture were significantly related to stent restenosis. Multivariate analysis also indicated that the presence of DM, smaller min-LA post by IVUS, and longer total stent length by QCA were independent predictors for angiographic restenosis at follow-up. Although stent fracture occurred in only 4 of 169 lesions (2.4%), all 4 affected patients experienced restenosis at follow-up in this series.
Incidence and Possible Mechanism of Stent Fracture

Although hitherto 7 cases of coronary DES fracture have been reported in the literature, the precise incidence of stent fracture has not yet been fully examined, mainly because of the lack of serial IVUS and QCA examinations. A study by Lemos et al reported 2 cases of stent fracture out of 20 restenotic lesions in a case series of 121 patients. Our angiographic follow-up rate was 91.6% and the majority of the lesions had IVUS follow-up (61.5% of the angiographic follow-up lesions). Our study results clearly indicated that the incidence of stent fracture was 2.4% (4 of 164 lesions) and all affected patients experienced restenosis. It has been speculated that stent strut overstretching and mechanical stress, such as repetitive kinking of the stent body, during the cardiac cycle may play a role in the occurrence of stent fracture, because stent fracture in the right coronary artery or saphenous vein grafts has been frequently reported. In our study, 1 lesion was located in the right coronary artery, 2 in the circumflex coronary artery and 1 in the left anterior descending coronary artery.

To examine the possible mechanism of SES fracture, we combined our 4 cases with the 7 reported in the literature. Of the 11 cases 6 (54%) DES fractures occurred in the proximal segments of the right coronary artery (American Heart Association segments 1–2). Because the right coronary artery moves more dynamically than the left coronary artery during the cardiac cycle, such aggressive coronary movement might induce stent fracture. Although we also measured the angulations at the hinge point during the cardiac cycle, the angulations were less than 45 degrees (ranging from 10 to 32 degrees). Other mechanisms, such as overstretching of the stent diameter, might play a role in the occurrence of stent fracture, although stent-to-artery ratios ranged from 1.14 to 1.28 in our fracture cases and there was no difference in the stent-to-artery ratio between restenotic and non-restenotic groups (Table 1). Halkin et al speculated that aggressive overstretching of the stent might be main mechanism of this phenomenon. Because 3 of our 4 cases with fracture had multiple overlapping SES, overlapped stents might relate to this phenomenon. We speculate that a combination of aggressive movement during the cardiac cycle, the angulations at the hinge points, overstretching and overlapping of stents may play a role in stent fracture.

Impact of Stent Fracture on Restenosis

It has been assumed that stent fracture would constitute a new potential mechanism of restenosis after SES because the close attachment of the DES strut to the vessel wall is theoretically necessary for the drug to prevent neointimal hyperplasia. Encompassing the combination of the 7 literature cases and our own 4 cases, 10 cases showed restenosis at follow-up and the remaining case had 30% luminal narrowing despite complete inhibition of neointimal hyperplasia in the rest of the stent segment.

Takebayashi et al reported that in 49 lesions with IVUS follow-up, restenotic lesions had a smaller LA, thicker neointimal hyperplasia and fewer stent struts in comparison with non-restenotic lesions. Fewer numbers of stent struts or late incomplete stent strut coverage because of stent fracture could result in incomplete inhibition of intimal hyperplasia and subsequently in restenosis at follow-up.

To our knowledge this is the first study to perform a high percentage of IVUS examinations prior to stenting (95%), have a high rate of follow-up QCA (91%), with the majority of patients having follow-up IVUS examination (62%), and all restenosis cases being studied by IVUS at follow-up. Other studies may have underestimated the occurrence of stent fracture, because IVUS follow-up was not performed prospectively and systematically as it was in this study. Without careful IVUS follow-up, some stent fractures may not be easy to detect by angiography alone and the restenosis simply treated by additional SES without precise IVUS quantification.

Restenosis Predictors for SES

Several studies examined the restenosis predictors following SES. Kastrari et al found that vessel size, MLD-post and stent type were important predictors of angiographic restenosis. Hong et al showed that the independent predictors of angiographic restenosis after SES implantation were stent length and minimal LA-post by IVUS. Lemos et al found that reference vessel size, total stent length, DM, instantaneous restenosis, ostial location and the left anterior descending artery lesion location were significant predictors of restenosis.
Our multivariate analysis revealed that min-LA post by IVUS (the best cutoff value of 5.0 mm²), total stent length by QCA (the best cutoff value of 30 mm) and DM were independent predictors for angiographic restenosis. Although Sonoda et al indicated that min-LA post-SES greater than 5.0 mm² was the threshold for predicting adequate follow-up LA, Hong et al recently reported that the min-LA post and stent length that best separated restenosis from non-restenosis were 5.5 mm² and 40 mm, respectively.²⁹,³⁰ Although baseline reference vessel size, lesion length and the prevalence of DM were different among the 3 studies, these different clinical and lesion characteristics would produce similar but not identical cutoff values of min-LA post and stent length.

The previous studies and our current study still emphasize the importance of greater lumen dimension post-stenting, stent length and DM, similar to predictors of restenosis identified in the bare metal stent era.²⁹–³³ Although in a more detailed comparison of post-stenting IVUS and QCA measurements, Hoffman et al reported that post intervention luminal dimension by IVUS was a stronger predictor than that by QCA for bare metal stents, our current results, as well as those by Hong et al, also indicate similar findings were obtained, even for DES.³²,³³ Furthermore, our serial QCA and IVUS study highlights the importance of the occurrence of stent fracture in addition to lumen dimension-post, total stent length and DM. Although the overall restenosis rate was low (7.7% in our study), the incidence of stent fracture was also low (2.4% in our study), but all affected patients experienced restenosis. Given that the incidence of stent fracture is of a similar order of magnitude to the incidence of restenosis following SES implantation, the impact of stent fracture on long-term procedural outcomes cannot be ignored.

Study Limitations

Our study is limited by small numbers and the fact that the SIGNAL study was only a single-center study. A larger study population and the use of multiple centers are necessary to further validate the current findings. Second, a prospective randomized controlled study comparing the current strategy of full lesion coverage against the so-called “spotty stent” approach would be necessary to determine the real impact of DES length on restenosis. However, either long or spotty stenting would be difficult to determine in the protocol because such choices are involved in a large part in the so-called “individual component” of surgeon preference.

Conclusions

This prospective single center study (SIGNAL) has demonstrated that min-LA post by IVUS, total stent length and DM are independent predictors of categorical restenosis. Stent fracture occurred in 4 lesions (2.4%) and all of them resulted in restenosis (31% of the restenosis cases). The role of stent fracture in the development of restenosis warrants further study.

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