Arterial Remodeling Influences the Development of Intimal Hyperplasia After Stent Implantation

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OBJECTIVES

We examined whether preinterventional arterial remodeling influenced the interventional results after stenting.

BACKGROUND

Arterial remodeling is seen in atherosclerotic lesions, and it may play an important role in the early stage of atherosclerosis.

METHODS

We examined 113 lesions that underwent elective stenting using tubular slotted stents under intravascular ultrasound guidance. The lesions were divided into three groups—adequate, intermediate, and inadequate remodeling group—according to preinterventional arterial remodeling. The patients were subjected to coronary angiography and intravascular ultrasound evaluation on average 6.4 months after stenting.

RESULTS

At baseline and immediately after stenting, there were no differences in quantitative angiographic analysis among remodeling groups. However, the plaque cross-sectional area (CSA) in the minimal lumen CSA at preintervention and intimal hyperplasia CSA at follow-up were significantly larger in the adequate remodeling group than in the inadequate remodeling group. The restenosis rate of stenting for the lesions with inadequate arterial remodeling was very low (9.4%). A significant positive correlation was found between preinterventional plaque CSA and intimal hyperplasia CSA at follow-up (r = 0.47, p < 0.0001). Moreover, remodeling index significantly correlated with relative intimal hyperplasia CSA (r = 0.28, p < 0.01).

CONCLUSIONS

Preinterventional arterial remodeling influenced the development of intimal hyperplasia after stenting. (J Am Coll Cardiol 2001;37:70–5) © 2001 by the American College of Cardiology

Recently, there has been an increase in the number of coronary angioplasties (1). Use of the Palmaz-Schatz stents has contributed to the reduction of in-hospital complications and the incidence of restenosis after catheter intervention, compared with conventional balloon angioplasty (2,3). The widespread use of these stents has not only improved the clinical outcomes of coronary angioplasty but has also reduced the costs associated with readmission for repeat revascularization (1). However, in-stent restenosis, which occurs in 20% to 30% of the lesions, still remains as the most important problem (4,5).

Recent studies have revealed that vascular remodeling may play an important role in the early stage of atherosclerosis. Compensatory enlargement of the coronary artery might delay the progression of lumen stenosis induced by the expanding atheromatous plaque (6–9). In contrast, inadequate compensatory enlargement results in relative vessel constriction at the lesion site, which might be an important contributing factor for the development of luminal narrowing along with plaque proliferation (10,11). Thus, we hypothesized that interventional procedures on the atherosclerotic lesions with different types of arterial remodeling might lead to different short- and long-term outcomes and that the suitable procedures for atherosclerotic lesions with adequate arterial remodeling might be different from those with inadequate arterial remodeling.

However, there is little information about the relation between arterial remodeling and interventional results. The purpose of this study was to examine whether the degree of preinterventional arterial remodeling influenced the development of neointimal hyperplasia after stenting.

METHODS

Patient population. From October 1996 through October 1998, we screened for inclusion in this study 210 consecutive patients with 231 lesions who underwent elective stenting using tubular slotted stents (either a Palmaz-Schatz stent or a Multi-Link stent) for native coronary artery stenosis at the Nagoya Daini Red Cross Hospital. The lesions were excluded when 1) intimal calcification at the target lesion was so severe that it precluded accurate quantification of intravascular ultrasound (IVUS) imaging (10 lesions), 2) IVUS study of the target lesion and reference segments could not be performed before the subsequent intervention (15 lesions), 3) pretreatment with an ablative device was performed before stenting (36 lesions), 4) there were major side branches between the proximal and distal reference segments (15 lesions), 5) distinct dissection was made at the stent edge after stenting (4 lesions), and 6) multiple stents were implanted (27 lesions). When multiple lesions existed, we included only the lesion that was treated first (11 lesions were excluded). Therefore, we selected 113 patients who had undergone stenting under IVUS guidance. There were 88 men and 25 women, and their mean age was 62.9 ± 8.3 years. These patients were subjected to follow-up...
Abnormales and Acronyms

CSA = cross-sectional area
EEM = external elastic membrane
IVUS = intravascular ultrasound
QCA = quantitative coronary angiography

Coronary angiography and IVUS study 4 to 10 months (mean of 6.4 ± 1.4 months) after stenting. Data on risk factors for coronary artery disease were obtained from clinical records at the time of stenting. Diabetess mellitus (medication-dependent only), hypertension (medication-dependent only) and hyperlipidemia (medication-dependent or serum total cholesterol ≥240 mg) were all examined. As for the location of the target lesion, the left anterior descending artery, the left circumflex artery and the right coronary artery were involved in 61, 10, and 42 instances, respectively. Seven stents were placed in restenotic lesions. The Palmaz-Schatz stent was used for 58 lesions, and the Multi-Link stent was used for 55 lesions. Study protocol was approved by the Ethics Committee of Nagoya Daini Red Cross Hospital, and written informed consent was obtained from all patients.

Angiography and analysis. Initial and follow-up angiograms were performed in the same angiographic projections using either a 6F diagnostic or 8F guiding catheter. Isosorbide dinitrate (5 mg) was administered by intracoronary injection before each study. An independent investigator blinded to the results of IVUS analysis performed quantitative coronary angiography (QCA) analysis using the Coronary Measurement System (MEDIS, Leiden, The Netherlands). Reference diameter, minimal luminal diameter and diameter stenosis at end-diastole before and immediately after stenting (after the last adjunctive balloon inflation) and at follow-up were calculated on the computer screen with the use of the view that showed the most severe luminal narrowing, using the guiding catheter for magnification calibration reference. Angiographic restenosis was defined as ≥50% diameter stenosis at follow-up.

IVUS imaging. The IVUS studies were performed before and just after stenting, and at follow-up, using a 30-MHz 2.9F or 3.2F monorail intracoronary ultrasound catheter (Cardiovascular Imaging Systems, Sunnyvale, California). After diagnostic coronary angiography and before any intervention, a 0.014-in. (0.0356-cm) coronary guide wire was introduced into the target coronary artery that would undergo subsequent stenting. To avoid spasm and to obtain optimal vasodilatation, 5 mg of isosorbide dinitrate was administered before insertion of the IVUS catheter through a coronary guiding catheter over the guide wire. After the IVUS catheter was advanced more than 10 mm beyond the target lesion, a motorized auto pullback was performed at 0.5 mm/s to the aorto-ostial junction under fluoroscopic guidance. Immediately after stenting, and at follow-up, IVUS studies were performed using the same methods before any subsequent intervention for restenosis. All ultrasound images were recorded continuously on S-VHS videotape for off-line analysis.

IVUS analysis. Measurements of IVUS images were performed using a commercially available software program (TapeMeasure, Indec Systems, Capitola, California). In the end-diastolic frames, we measured cross-sectional area (CSA) within the external elastic membrane (EEM) and lumen CSA at the lesion site and at the proximal and distal reference sites. Plaque CSA was calculated as the EEM CSA minus the lumen CSA. Plaque index was defined as (the plaque CSA/the EEM CSA) × 100. When the IVUS catheter filled up the lumen owing to severe atherosclerosis, the lumen CSA was assumed to be equal to the size of the catheter. From the distal edge of stent to the proximal edge, image slices of 3 mm each were taken into the analysis system at follow-up, and the stent CSA and the lumen CSA were measured. The intimal hyperplasia CSA presented within the stent was calculated as the stent CSA minus the lumen CSA. Relative intimal hyperplasia CSA was calculated as (the intimal hyperplasia CSA/the stent CSA) × 100.

The lesion site was defined as the segment having the smallest lumen CSA according to IVUS study, and ≥50% diameter stenosis as assessed by QCA. All lesions underwent subsequent coronary stenting. The proximal and distal reference sites were defined according to previous reports (11,12).

Adequate compensatory arterial remodeling was defined as an EEM CSA at the lesion site that was larger than that at the proximal reference site, and inadequate compensatory arterial remodeling was defined as an EEM CSA at the lesion site that was smaller than that at the distal reference site. Intermediate arterial remodeling was defined as an EEM CSA at the lesion site that was intermediate between the proximal and distal reference sites. Remodeling index was also defined as follows: the target lesion EEM CSA divided by the average of the proximal and distal reference EEM CSA.

Statistical analysis. Data were expressed as mean values ± SD or percent. Differences among the examined groups were tested for significance by analysis of variance. When an overall difference was noted, the Fisher’s multiple range test was applied for the pairwise comparisons. The chi-square test was used across three groups for comparing categorical variables. All analyses were performed with a StatView statistical program (Version 5.0, SAS Institute, Cary, North Carolina). The differences were considered significant when p values were <0.05.

RESULTS

Among all coronary arteries in which stent implantation had been performed, 52 (46%) coronary arteries showed adequate compensatory arterial remodeling, 32 (28%) coronary
arteries showed inadequate arterial remodeling, and 29 (26%) showed intermediate arterial remodeling.

**Clinical characteristics and angiographic results.** Clinical lesions, and implanted stent characteristics are shown in Table 1. The lesions treated by stent were distributed into three groups according to the coronary artery remodeling attained; there were no significant differences in baseline clinical characteristics among the three remodeling groups. Similarly, the lesion morphology and diameters, lengths and types of implanted stents were comparable among the three groups.

The QCA results are summarized in Table 2. At baseline and immediately after stenting, there were no differences in the reference diameter, minimal luminal diameter or diameter stenosis among the three remodeling groups. At follow-up, the inadequate remodeling group had significantly larger minimal luminal diameter than the adequate remodeling group (p < 0.05). Angiographic restenosis was more frequently observed in the adequate remodeling group than in the inadequate remodeling group (28.8% and 9.4%, respectively).

**IVUS results.** Table 3 shows the overall quantitative IVUS results in each arterial remodeling group. Among the three remodeling groups, no significant differences were seen in the minimal lumen CSA, the proximal and distal reference EEM CSA at preintervention, or in the minimal stent CSA immediately after the intervention. The adequate remodeling group had significantly larger EEM CSA and plaque CSA at the site of the minimal lumen CSA before the intervention than the intermediate and inadequate remodeling groups. At follow-up, the minimal lumen CSA was smaller, and the intimal hyperplasia CSA was larger in the adequate remodeling group than in the inadequate remodeling group (p < 0.01 and p < 0.01, respectively), though no significant difference was found in the stent CSA.

**Correlation among plaque burden, remodeling and intimal hyperplasia.** Correlation between preinterventional plaque CSA and in-stent intimal hyperplasia CSA is shown in Figure 1. A significant positive correlation was found between preinterventional plaque CSA and intimal hyperplasia CSA at follow-up (r = 0.47, p < 0.0001). Moreover, the remodeling index significantly correlated with the relative intimal hyperplasia CSA (r = 0.28, p < 0.01). Multiple regression analysis revealed that both plaque burden and types of arterial remodeling were significant independent variables for predicting intimal hyperplasia CSA (p < 0.001 and p < 0.05, respectively).

**DISCUSSION**

The main findings in this study were that preinterventional plaque CSA and the degree of intimal hyperplasia after stenting were significantly larger in the adequate remodeling group than in the inadequate remodeling group. Moreover, both preinterventional plaque burden and remodeling index correlated with the extent of in-stent neointimal hyperplasia.

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**Table 1. Clinical Characteristics, Lesion Morphology and Stent Form**

<table>
<thead>
<tr>
<th></th>
<th>Adequate (n = 52)</th>
<th>Intermediate (n = 29)</th>
<th>Inadequate (n = 32)</th>
<th>p Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women</td>
<td>42/10</td>
<td>23/6</td>
<td>23/9</td>
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<tr>
<td>Age (yrs)</td>
<td>63.3 ± 9.5</td>
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<tr>
<td>DM (%)</td>
<td>13 (25%)</td>
<td>8 (28%)</td>
<td>9 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>HT (%)</td>
<td>29 (56%)</td>
<td>11 (38%)</td>
<td>16 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>HL (%)</td>
<td>34 (65%)</td>
<td>17 (59%)</td>
<td>24 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Type B2/C (%)</td>
<td>24 (46%)</td>
<td>11 (38%)</td>
<td>15 (47%)</td>
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<td>Stent diameter (mm)</td>
<td>3.3 ± 0.3</td>
<td>3.3 ± 0.3</td>
<td>3.4 ± 0.3</td>
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</tr>
<tr>
<td>Stent length (mm)</td>
<td>14.0 ± 1.7</td>
<td>14.2 ± 1.5</td>
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</tr>
<tr>
<td>PS/ML</td>
<td>26/26</td>
<td>14/15</td>
<td>18/14</td>
<td>NS</td>
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**Table 2. Quantitative Coronary Angiographic Results**

<table>
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<th>Adequate (n = 52)</th>
<th>Intermediate (n = 29)</th>
<th>Inadequate (n = 32)</th>
<th>p Value (ANOVA)</th>
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<tr>
<td>Preintervention</td>
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<td>Reference diameter (mm)</td>
<td>3.1 ± 0.9</td>
<td>3.0 ± 0.6</td>
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<td>Minimal luminal diameter (mm)</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.6</td>
<td>1.1 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>67.3 ± 11.9</td>
<td>63.3 ± 15.9</td>
<td>63.9 ± 14.3</td>
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</tr>
<tr>
<td>Immediately after intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter (mm)</td>
<td>3.1 ± 0.6</td>
<td>3.2 ± 0.5</td>
<td>3.1 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>10.5 ± 7.8</td>
<td>8.4 ± 7.0</td>
<td>10.4 ± 8.0</td>
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<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter (mm)</td>
<td>2.0 ± 0.8*</td>
<td>1.9 ± 0.6†</td>
<td>2.4 ± 0.7</td>
<td>&lt; 0.01</td>
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<td>Diameter stenosis (%)</td>
<td>35.6 ± 22.1*</td>
<td>33.4 ± 22.1</td>
<td>24.2 ± 14.8</td>
<td>&lt; 0.05</td>
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*p < 0.05 vs. inadequate remodeling group; †p < 0.01 vs. inadequate remodeling group; NS = not significant.
Remodeling and coronary stenosis. It had been believed
that the luminal narrowing of arteries in patients with
coronary artery disease depended mainly on the accumula-
tion of atherosclerotic plaques along the arterial wall.
However, based on the results of histopathological (6)
and IVUS studies (7–9), the degree of arterial remodel-
ing, which occurs to compensate for the accumulation of plaque,
contributed to the narrowing of the lumen at the athero-
sclerotic lesion. Glagov et al. (6) revealed that compensatory
arterial enlargement prevented the luminal area from en-
croachment by the expanding plaque in the early stages of
atherosclerosis; but when plaque expansion progressed,
occupying ≥40% of the EEM CSA, this protective mech-
anism failed to compensate for further increases of plaque
mass, and the luminal area decreased. Inadequate arterial
enlargement was observed in some of the atherosclerotic

### Table 3. Quantitative Intravascular Ultrasound Results

<table>
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<th>Inadequate (n = 32)</th>
<th>p Value (ANOVA)</th>
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<td><strong>Preintervention</strong></td>
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<td></td>
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<tr>
<td>Lesion site</td>
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<tr>
<td>EEM CSA (mm²)</td>
<td>18.0 ± 5.0</td>
<td>13.7 ± 3.4†</td>
<td>12.7 ± 4.1†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Lumen CSA (mm²)</td>
<td>2.4 ± 0.8</td>
<td>2.3 ± 1.0</td>
<td>2.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque CSA (mm²)</td>
<td>15.7 ± 4.8</td>
<td>11.3 ± 3.3†</td>
<td>10.3 ± 3.8†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Plaque index (%)</td>
<td>86.0 ± 5.3</td>
<td>82.5 ± 6.6*</td>
<td>79.8 ± 8.8†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Reference site</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Proximal EEM CSA (mm²)</td>
<td>17.3 ± 5.1</td>
<td>16.5 ± 4.1</td>
<td>18.4 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Distal EEM CSA (mm²)</td>
<td>13.5 ± 4.8</td>
<td>12.3 ± 3.4</td>
<td>14.8 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Immediately after intervention</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Minimal stent CSA (mm)</td>
<td>10.1 ± 3.3</td>
<td>9.7 ± 2.7</td>
<td>10.4 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen CSA (mm²)</td>
<td>4.9 ± 2.3</td>
<td>5.3 ± 2.2</td>
<td>6.6 ± 3.2†</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Stent CSA (mm²)</td>
<td>9.8 ± 2.9</td>
<td>9.2 ± 2.5</td>
<td>10.2 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>IH CSA (mm²)</td>
<td>5.0 ± 2.5</td>
<td>3.8 ± 2.0*</td>
<td>3.6 ± 2.7†</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Relative IH CSA (%)</td>
<td>50.7 ± 19.3</td>
<td>41.5 ± 18.3</td>
<td>35.2 ± 20.1†</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. adequate remodeling group; †p < 0.01 vs. adequate remodeling group; NS = not significant

EEM = external elastic membrane; CSA = cross-sectional area; plaque index = (plaque CSA/EEM CSA) × 100; IH = intimal hyperplasia; relative IH CSA = (IH CSA/Stent CSA) × 100.

Figure 1. Correlation between preinterventional lesion site plaque cross-sectional area and in-stent intimal hyperplasia.
coronary arteries (10,11), and it might contribute to the progression of luminal narrowing by shrinking the EEM. Thus, the development of coronary stenosis would be closely related to the degree of arterial remodeling.

Remodeling and intimal hyperplasia. The mechanisms of restenosis in stented lesions differ from those in nonstented lesions (13–16). In nonstented lesions, late constriction of the EEM CSA after angioplasty appeared to play a more significant role in causing restenosis than did neointimal proliferation. On the other hand, in stented lesions, stents prevented the remodeling process of late vessel-constriction, and restenosis was the result of uniform neointimal tissue proliferation throughout the stent (17,18). Therefore, it is important to suppress in-stent neointimal hyperplasia.

Predictors for in-stent restenosis were reported, including 1) longer stented segment, 2) reference vessel diameter, 3) percent diameter stenosis after stenting, 4) preinterventional plaque burden at the lesion site, 5) final luminal area, and 6) residual plaque burden outside the stent (19–21). In our study, no differences were seen in reference diameter, reference EEM CSA, and minimal lumen CSA at preintervention, or in the QCA and IVUS results immediately after stenting among the groups. However, the adequate remodeling group had a significantly larger restenosis rate, neointimal hyperplasia CSA and preinterventional plaque CSA at the lesion site than did the inadequate remodeling group.

Furthermore, the preinterventional plaque CSA at the lesion site correlated with the amount of in-stent neointimal hyperplasia at follow-up. Thus, the larger the preinterventional plaque burden is, the severer the degree of neointimal hyperplasia is. The underlying mechanism by which plaque burden is related to neointimal hyperplasia remains to be elucidated, but deep vessel injury might be aggravated in proportion to the amount of plaque burden because the stretching force needed to expand the vessel is proportionate to the vessel wall resistance manifested by the amount of the plaque burden (22). Carter et al. (23) demonstrated the correlation between neointimal hyperplasia and the extent of plaque or medial compression by the stent. Their experimental study with rabbits might support the hypothesis.

Remodeling and atherectomy before stenting. Moussa et al. (22) evaluated 62 patients with 75 lesions who underwent directional coronary atherectomy before stenting and angiographic evaluation 5.7 months after stenting. They concluded that plaque removal by directional coronary atherectomy before stenting might reduce angiographic restenosis and the need for repeated coronary interventions. However, it remains unclear whether we should always remove plaque by atherectomy, because aggressive atherectomy could result in an increased incidence of complications. We clearly demonstrated that the restenosis rate of stenting for the lesions with inadequate arterial remodeling was very low (9.4%) by comparison with adequate remodeling (28.8%). This result is comparable to the previous report in which the restenosis rate of stenting after optimal lesion debulking was 11% (22). In addition, in the atherosclerotic lesions with inadequate arterial remodeling, plaque burden at the lesion site may be less than that at the reference site (11). When the target lesion shows adequate arterial remodeling and the plaque burden is large, atherectomy before stenting might be a useful procedure for suppressing the development of in-stent neointimal hyperplasia and restenosis. Conversely, when the target lesion shows inadequate arterial remodeling, plaque removal before stenting might be unnecessary. However, we have no data to support this hypothesis. It should be verified by a randomized study that compares lesions with adequate remodeling, subjected to plaque debulking before stenting, with their negative controls.

Study limitations. To evaluate the relation between the degree of preinterventional arterial remodeling and in-stent neointimal hyperplasia, we excluded the lesions where pretreatment with an atheroablative device was performed before stenting. Moreover, the small number of study patients did not allow comparison between the lesions subjected to plaque debulking before stenting and those subjected to stenting alone, within the group of lesions showing adequate arterial remodeling.

Conclusions. Our data revealed that preinterventional arterial remodeling influenced the development of intimal hyperplasia after stenting and that preinterventional plaque burden and remodeling index correlated with the extent of in-stent neointimal hyperplasia.

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We thank the cardiologists and the catheterization laboratory staff at Nagoya Daini Red Cross Hospital for their participation in this study. We also thank Dr. Ogino and Dr. Kinugawa, Tottori University, for their assistance in the preparation of this manuscript.

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