Predictors for Neoatherosclerosis
A Retrospective Observational Study From the Optical Coherence Tomography Registry

Taishi Yonetsu, MD; Koji Kato, MD, PhD; Soo-Joong Kim, MD, PhD; Lei Xing, MD; Haibo Jia, MD, PhD; Iris McNulty, RN; Hang Lee, PhD; Shaosong Zhang, MD, PhD; Shiro Uemura, MD, PhD; Yangsoo Jang, MD, PhD; Soo-Jin Kang, MD, PhD; Seung-Jung Park, MD, PhD; Stephen Lee, MD; Bo Yu, MD, PhD; Tsunekazu Kakuta, MD, PhD; Ik-Kyung Jang, MD, PhD

Background—Recent studies have reported development of neoatherosclerosis (NA) inside the stents several years after stent implantation. The aim of this study was to determine the predictors for NA using optical coherence tomography.

Methods and Results—From a total of 1080 patients who underwent optical coherence tomography, we identified 179 stents in 151 patients in which the mean neointimal thickness was >100 µm. The presence of lipid-laden neointima or calcification inside the stents was defined as NA in the present study. Patient characteristics, stent type, and time since stent implantation (stent age) were compared between stents with or without NA. Univariable and multivariable logistic regression analyses were used to assess the independent predictors. In univariate analysis, stent age ≥48 months (Odds ratio [OR], 4.48; [95% CI, 2.68–9.65]; P<0.001), drug-eluting stents (OR, 2.66; [95% CI, 1.38–5.16]; P=0.004), age ≥65 years (OR, 1.91; [95% CI, 1.05–3.44]; P=0.032), current smoking (OR, 2.30; [95% CI, 1.10–4.82]; P=0.024), chronic kidney disease (OR, 4.17; [95% CI, 1.42–12.23]; P=0.009), and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockade use (OR, 0.42; [95% CI, 0.22–0.80]; P=0.008) were significant predictors. In multivariate analysis, stent age ≥48 months, all subtypes of drug-eluting stent, current smoking, chronic kidney disease, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade use remained independent predictors for NA.

Conclusions—In addition to the stent type and the stent age, patient characteristics, including current smoking, chronic kidney disease, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade, were associated with the presence of NA. This result may support the importance of secondary prevention after stent implantation.


Key Words: stents • atherosclerosis • neointima • restenosis • optical coherence tomography

Since bare-metal stents (BMS) were introduced in the early 1990s, coronary stenting has become the primary mode of revascularization for patients with coronary artery disease.1,2 Drug-eluting stents (DES) have dramatically reduced the restenosis and repeat revascularization rate, which has been the major limitation of BMS.3,4 Although DES has provided a great advance in percutaneous coronary intervention, some concerns remain in delayed complications such as (very) late stent thrombosis and late catchup.5,6 Recently, a growing number of reports have demonstrated the development of neoatherosclerosis (NA) inside both BMS and DES.7–10 These studies have suggested the potential impact of NA on late complications after stent implantations.

Nevertheless, the nature of NA has not been fully understood, and the predictors for these late changes have not been studied.

Clinical Perspective on p 666

Optical coherence tomography (OCT) is an emerging intracoronary diagnostic modality that provides high-resolution images of coronary artery in vivo.11 In addition to tissue characterization in native coronary plaques, OCT has been applied to characterize neointima after stent implantation.12 Indeed, several OCT studies revealed the development of lipid-laden neointima inside the stents, and OCT has become the modality of choice to study atherosclerotic change of neointima.7,8,10

Received May 01, 2012; accepted July 10, 2012.
From the Cardiology Division (T.Y., K.K., S-J.K., H.J., I.M., I-K.J.) and Biostatistics Center (H.L.), Massachusetts General Hospital and Harvard Medical School, Boston, MA (T.Y., K.K., S-J.K., H.J., I.M., I-K.J.); Division of Cardiology, College of Medicine, Kyung Hee University, Seoul, Korea (S-J.K.); Department of Cardiology, Second Affiliated Hospital of Harbin Medical University, Key Laboratories of Education Ministry for Myocardial Ischemia Mechanism and Treatment, Harbin, China (L.X., H.J., B.Y.); LightLab Imaging Inc, Westford, MA (S.Z.); First Department of Medicine, Nara Medical University, Nara, Japan (S.U.); Severance Cardiovascular Hospital, Yonsei University, Seoul, Korea (Y.J.); Asan Medical Center, Seoul, Korea (S-J.K., S-J.P); Queen Mary Hospital, Hong Kong University, Hong Kong (S.L.); and Division of Cardiology, Tsuchiura Kyodo Hospital, Ibaraki, Japan (T.K.).
The online-only Data Supplement is available at http://circimaging.ahajournals.orglookup/suppl/doi:10.1161/CIRCIMAGING.112.976167/-/DC1. Correspondence to Ik-Kyung Jang, MD, PhD, Cardiology Division, Massachusetts General Hospital, GRB 800, 55 Fruit Street, Boston, MA. E-mail ijang@partners.org and Bo Yu, MD, PhD, Second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, Nangang District, Harbin 150086, China. E-mail yubodr@163.com.
© 2012 American Heart Association, Inc.
Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.112.976167

660
Therefore, we sought to investigate the predictors for the development of NA using OCT.

**Methods**

**Study Population**

The Massachusetts General Hospital OCT Registry is a multicenter registry of patients undergoing OCT of the coronary arteries and includes 20 sites across 6 countries. Any patient who underwent OCT procedure was eligible for the registry. From a total of 1080 consecutive patients who were enrolled in the registry between August 2010 and October 2011, 448 patients with previously implanted stents were identified. From these patients, we excluded patients with unknown types of stents (n=82), endothelial progenitor cell capture stents (n=73), polytetrafluoroethylene-covered stents (n=1), and patients without sufficient demographic data (n=13). Stents with poor OCT image quality (n=12) and those treated by any interventional procedure before OCT imaging were also excluded (n=42). The remaining 297 stents from 225 patients were screened with OCT, and we selected stents with a mean neointimal thickness >100 µm on ≥3 consecutive cross-sectional frames at a 1 mm interval so that we could obtain a substantial amount of neointima to assess the tissue characteristics as previously reported. Therefore, 179 stents in 151 patients were included in the final analysis.

**Definitions**

Estimated glomerular filtration rate was calculated with the Modification of Diet in Renal Disease Study Group equation. In the present study, chronic kidney disease (CKD) was defined as having estimated glomerular filtration rate <60 mL/min per 1.73 m², consistent with the National Kidney Foundation classification stages 3 to 5. The use of statin, angiotensin-converting enzyme inhibitor (ACE-I), and angiotensin II receptor blocker (ARB) were recorded at the time of OCT procedure.

**OCT Image Acquisition**

The time-domain OCT system (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc, Westford, MA) or the frequency-domain OCT system (C7-XR OCT Intravascular Imaging System, St Jude Medical, St. Paul, MN) was used in this study. The technique of intracoronary OCT imaging has been previously described. All images were digitally stored, deidentified, and submitted to the Massachusetts General Hospital (Boston, MA) for analysis.

**OCT Analysis**

Cross-sectional OCT images were analyzed with an interval of 1.0 mm for quantitative and qualitative evaluation. Quantitative assessment was performed with the OCT off-line analysis software (LightLab Imaging Inc, Westford, MA). The stent and lumen areas were traced, and minimum, maximum, and mean neointimal thickness were semiautomatically determined. When the mean neointimal thickness was >100 µm, we proceeded to qualitative analysis.

Qualitative OCT assessment included the presence of lipid and calcification inside the stent as previously reported. Lipid was defined as a diffusely bordered signal-poor region with rapid signal attenuation (Figure [A]) that is differentiated from heterogenic (Figure [B]) and layered tissue (Figure [C]). Endoluminal and abluminal layers in heterogenic and layered tissue are more clearly delineated as compared with lipid tissue. Lipid-laden neointima was defined as a neointima with lipid. Calcification was defined as a clearly delineated signal-poor region with low backscatter (Figure [D]). The stent was considered to have NA when lipid-laden neointima or calcification was present.

**Figure.** Representative Images of Neoatherosclerosis. **A**, Lipid-laden neointima is identified as a diffusely bordered signal-poor region with overlying signal-rich homogenous band (red arrows). **B**, Heterogeneous neointima is identified as a tissue showing a focally changing optical property and various backscattering patterns. **C**, Layered neointima is defined as a tissue composed of concentric layers of a high-scattering endoluminal layer and a low-scattering abluminal layer delineated by a clear border. **D**, Calcified neointima is defined as a signal-poor or heterogeneous region with a sharply delineated border (yellow arrowheads).
All OCT images were analyzed by 2 independent investigators (T.Y. and K.K.) who were blinded to the patients’ information. When there was discordance between the readers, consensus reading was obtained from a third independent investigator (S.K.).

Angiographic Analysis
Coronary angiograms at the time of OCT imaging were analyzed by off-line quantitative coronary angiography (Quanctor QCA 5.0, Pie Medical Imaging BV, Maastricht, the Netherlands). Reference diameter, minimum lumen diameter, diameter stenosis, and lesion length were measured.

Statistical Analysis
Categoric data were expressed as counts and proportions, and compared with a χ² test or Fisher exact test, depending on the data. Continuous measurements were expressed as mean±SD, and analyzed with the Student t test. Intra- and interobserver variability for the presence of NA, lipid-laden neointima, and calcification were estimated by means of kappa coefficient (k). Multiple logistic regression analyses were performed to determine the independent predictors for NA. We included the traditional cardiac risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and current smoking and the factors with P<0.100 in patient characteristics and stent demographics into the model. Subtypes of DES such as sirolimus-eluting stents (SES), paclitaxel-eluting stents (PES), zotarolimus-eluting stents (ZES), or everolimus-eluting stents (EES) were included in the model with BMS as the reference category. Receiver operating curve (ROC) analysis was performed to determine the predictability (sensitivity and specificity) of time duration from the stent implantation for the presence of lipid and calcification inside the stents. The Generalized Estimating Equations approach was used to take into account the within-subject correlation due to multiple stents analyzed within a single patient. All statistical analyses were performed with SPSS 17.0 (SPSS Inc, Chicago, IL). P<0.05 was considered statistically significant.

Results
Patient Characteristics
Patient characteristics are summarized in Table 1. Each value was compared between the patients with any stent that showed lipid-laden or calcified neointima on OCT (NA patients) and those without these changes (non-NA patients). There was no significant difference in age, sex, prevalence of hypertension, hyperlipidemia, and diabetes mellitus between the 2 groups. There was no significant difference in age, sex, prevalence of hypertension, hyperlipidemia, and diabetes mellitus between the 2 groups. ACE-I or ARB use was significantly more frequent in non-NA patients as compared with NA patients. There was a weak trend toward more frequent use of statins in non-NA patients, as compared with NA patients. CKD (stages 3–5) was significantly more frequent in NA patients as compared with non-NA patients. Creatinine level was significantly higher and estimated glomerular filtration rate was lower in NA patients as compared with non-NA patients. The frequency of lipid-laden or calcified neointima on OCT (NA patients) and those without these changes (non-NA patients) was compared with a χ² test. Intra- and interobserver variability were k=0.91 and k=0.95 for NA, k=0.91 and k=0.95 for lipid-laden plaque, and k=0.93 and k=0.94 for calcification.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Overall</th>
<th>NA</th>
<th>non-NA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>151</td>
<td>77</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62.6±10.7</td>
<td>63.9±11.0</td>
<td>61.3±11.4</td>
<td>0.139</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>121 (80.1)</td>
<td>62 (80.5)</td>
<td>59 (79.7)</td>
<td>0.903</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1.20±0.53</td>
<td>1.23±0.60</td>
<td>1.16±0.44</td>
<td>0.408</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>108 (71.5)</td>
<td>56 (72.7)</td>
<td>52 (70.3)</td>
<td>0.738</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>104 (68.8)</td>
<td>53 (68.8)</td>
<td>51 (68.9)</td>
<td>0.991</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>61 (40.4)</td>
<td>34 (44.2)</td>
<td>27 (36.5)</td>
<td>0.337</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>34 (22.5)</td>
<td>22 (28.6)</td>
<td>12 (16.2)</td>
<td>0.069</td>
</tr>
<tr>
<td>Total-chol, mg/dL</td>
<td>154.8±37.3</td>
<td>162.1±38.7</td>
<td>148.1±34.8</td>
<td>0.027</td>
</tr>
<tr>
<td>LDL-chol, mg/dL</td>
<td>86.0±28.4</td>
<td>91.3±30.7</td>
<td>80.9±25.3</td>
<td>0.032</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>159.0±188.0</td>
<td>193.2±243.1</td>
<td>132.5±116.9</td>
<td>0.083</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.13±1.37</td>
<td>1.38±1.89</td>
<td>0.88±0.30</td>
<td>0.030</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>90.9±30.7</td>
<td>85.4±33.4</td>
<td>96.3±27.0</td>
<td>0.032</td>
</tr>
<tr>
<td>CKD</td>
<td>14 (9.3)</td>
<td>11 (14.3)</td>
<td>3 (4.1)</td>
<td>0.030</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>127 (84.1)</td>
<td>61 (79.2)</td>
<td>66 (89.2)</td>
<td>0.094</td>
</tr>
<tr>
<td>ACE-VARB use, n (%)</td>
<td>102 (67.5)</td>
<td>46 (59.7)</td>
<td>56 (75.7)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

NA indicates neoatherosclerosis; Total-chol, total cholesterol; LDL-chol, low-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACE-I, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

Significant difference was observed among the 4 subtypes of DES (P=0.086). Time since stent implantation was significantly longer in NA stents. In the NA stent group, time since stent implantation was significantly longer in BMS as compared with DES (68.9±46.3 versus 25.8±22.1 months, P<0.001), whereas no significant difference was observed in non-NA stents (21.3±33.0 versus 13.1±13.6 months, P=0.123). There was no significant difference in stent location between the 2 groups.

Quantitative Coronary Angiography and OCT Measurements
Quantitative analysis of angiograms and OCT are summarized in Table 2. Minimum lumen diameter was smaller and diameter stenosis was significantly greater in NA stents than in non-NA stents on angiograms. OCT measurements showed significantly greater mean and maximum neointimal hyperplasia thickness in NA stents as compared with those in non-NA stents.

Qualitative OCT Analysis
Of all 3633 OCT cross-sections in 179 stents, 139 (3.8%) cross-sections were excluded from the analysis due to suboptimal image quality. Therefore, a total of 3494 cross-sections were analyzed in the present study. Lipid-laden neointima was observed in 84 stents (46.9%), and calcification was observed in 8 stents (4.5%). Inter- and intraobserver variabilities were k=0.91 and k=0.95 for NA, k=0.91 and k=0.95 for lipid-laden plaque, and k=0.93 and k=0.94 for calcification.

The frequency of lipid-laden neointima was significantly higher in DES than in BMS (56.6% versus 32.9%, P=0.002). In DES, ROC analysis showed a cutoff value of 14 months
Table 2. Stent Characteristics and Angiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>NA</th>
<th>non-NA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, %</td>
<td>179</td>
<td>84</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>DES, n (%)</td>
<td>106 (59.2)</td>
<td>60 (71.4)</td>
<td>46 (48.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>SES, n (%)</td>
<td>58 (32.4)</td>
<td>31 (36.9)</td>
<td>27 (28.4)</td>
<td>0.086</td>
</tr>
<tr>
<td>PES, n (%)</td>
<td>19 (10.6)</td>
<td>15 (17.9)</td>
<td>4 (4.2)</td>
<td></td>
</tr>
<tr>
<td>ZES, n (%)</td>
<td>13 (7.3)</td>
<td>8 (9.5)</td>
<td>5 (5.3)</td>
<td></td>
</tr>
<tr>
<td>EES, n (%)</td>
<td>16 (8.9)</td>
<td>6 (7.1)</td>
<td>10 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Stent age, mo</td>
<td>26.9±32.7</td>
<td>38.1±36.3</td>
<td>17.3±25.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMS</td>
<td>36.9±43.8</td>
<td>68.9±46.3</td>
<td>21.3±33.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DES</td>
<td>20.3±19.8</td>
<td>25.8±22.1</td>
<td>13.1±13.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Stent location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA, n (%)</td>
<td>65 (36.3)</td>
<td>34 (40.5)</td>
<td>31 (32.6)</td>
<td></td>
</tr>
<tr>
<td>LAD, n (%)</td>
<td>85 (47.5)</td>
<td>36 (42.9)</td>
<td>49 (51.6)</td>
<td>0.475</td>
</tr>
<tr>
<td>CX, n (%)</td>
<td>29 (16.2)</td>
<td>14 (16.7)</td>
<td>15 (15.8)</td>
<td></td>
</tr>
<tr>
<td>QCA analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.46±0.65</td>
<td>1.36±0.65</td>
<td>1.56±0.64</td>
<td>0.049</td>
</tr>
<tr>
<td>DS, %</td>
<td>50.6±17.7</td>
<td>54.3±17.1</td>
<td>47.2±17.6</td>
<td>0.009</td>
</tr>
<tr>
<td>RD, mm</td>
<td>2.94±0.64</td>
<td>2.94±0.57</td>
<td>2.95±0.69</td>
<td>0.898</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>10.6±4.7</td>
<td>10.9±4.1</td>
<td>10.3±5.2</td>
<td>0.427</td>
</tr>
<tr>
<td>OCT measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum NIH thickness, mm</td>
<td>0.19±0.16</td>
<td>0.20±0.15</td>
<td>0.17±0.16</td>
<td>0.166</td>
</tr>
<tr>
<td>Mean NIH thickness, mm</td>
<td>0.40±0.21</td>
<td>0.46±0.20</td>
<td>0.34±0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum NIH thickness, mm</td>
<td>0.68±0.34</td>
<td>0.81±0.36</td>
<td>0.56±0.28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NA indicates neatherosclerosis; DES, drug-eluting stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent; EES, everolimus-eluting stent; BMS, bare-metal stent; RCA, right coronary artery; LAD, left anterodescending artery; CX, left circumflex; QCA, quantitative coronary angiography; MLD, minimum lumen diameter; DS, diameter stenosis; RD, reference diameter; and OCT, optical coherence tomography; and NIH, neointimal hyperplasia.

(1.2 years) for differentiating the stents with lipid-laden neointima (sensitivity 51.7%, specificity 87.0%, area under the curve 0.692). Among BMS, ROC analysis showed a cutoff value of 55 months (4.6 years) with 66.7% sensitivity and 89.8% specificity (area under the curve 0.827).

Calcification was observed in both BMS and DES (7 BMS and 1 DES). Median duration from the stent implantation was 110 months (9.2 years) among the stents with calcification, and the earliest calcification was observed at 72 months (6.0 years) after BMS implantation. All of the calcifications were accompanied by lipid-laden neointima in the same stents. ROC analysis demonstrated a cutoff value of 71 months (5.9 years) with sensitivity 100.0%, specificity 92.4%, and area under the curve 0.97.

Predictors for NA

Univariate and multivariate logistic regression analyses were performed to determine the predictors for NA OCT (Table 3). In univariate analysis, stent age ≥48 months, DES, age ≥65 years, current smoking, CKD, and the use of ACE-I or ARB were significant predictors for NA. In subtypes of DES, SES and PES were significantly associated with NA whereas no significant association was observed in ZES and EES. Traditional cardiac risk factors, including hypertension, hyperlipidemia, and diabetes mellitus, showed no significant association with the development of NA.

Twenty-one patients were excluded from the first multiple logistic regression model due to lack of low-density lipoprotein cholesterol or triglyceride level, and 155 stents from 130 patients were included in the first model. For the final model, high low-density lipoprotein cholesterol or triglyceride level was excluded from the analysis because of low levels of significance in the model. Therefore, we analyzed 179 stents from 151 patients in the final model.

In the first multivariate logistic model, stent age ≥48 months, all subtypes of DES (SES, PES, ZES, and EES), age ≥65 years, and current smoking were independent predictors for NA. In the final model, stent age ≥48 months, all subtypes of DES, current smoking, CKD, and ACE-I or ARB use were independent predictors for NA.

Discussion

To the best of our knowledge, this is the first OCT study demonstrating predictors for the development of NA after stent implantation. The present study demonstrated that: (1) stent age, first generation DES (SES and PES), age of the patient, current smoking, CKD, and ACE-I or ARB use were significantly associated with the development of NA in the univariate analyses; (2) multivariate analysis showed that stent age, all subtypes of DES, current smoking, CKD, and ACE-I/ARB use were independent predictors for NA; (3) cutoff durations to develop NA in DES and BMS were 14 months and 55 months, respectively; (4) calcification was observed only in old stents implanted >72 months before imaging.

Since the first OCT article demonstrating the presence of NA, including lipid-laden neointima and calcification, this phenomenon has been thrust to the center of topics regarding late stent complication in DES and BMS as a possible underlying mechanism of stent thrombosis or acute coronary syndrome.7–10

Our data delineated the risk factors for NA from a retrospective analysis. It is interesting to note that traditional clinical risk factors for atherosclerosis in native coronary arteries, such as hypertension, hyperlipidemia, or diabetes mellitus, were not associated with NA in the present study. This may suggest different mechanisms or processes in the development of atherosclerosis inside the stents from those in the native coronary arteries. In our study, smoking and ACE-I/ARB were associated with NA, which suggests that development of NA may at least be partly prevented and emphasizes the importance of secondary prevention.

Stent Age and NA

Previous OCT studies demonstrated more frequent lipid-laden neointima in late restenosis of BMS, as compared with early restenosis.7,9 Also in DES, Kang et al10 demonstrated that the incidence of thin-cap fibroatheroma increases over time and that the best cutoff to predict thin-cap fibroatheroma was 20 months. Irrespective of stent type, stent age is obviously one of the strongest promoting factors for NA. In the present study,
we assessed the cutoff values to differentiate the stents with NA in both BMS and DES. ROC analysis revealed that the best cutoff to detect lipid-laden neointima was 55 months for BMS and 14 months for DES. The mean time since stent implantation was significantly longer in BMS with NA as compared with DES with NA (68.9±46.3 versus 25.8±22.1 months, P<0.001). Our data supports the earlier development of NA in DES in comparison with BMS as previously reported in pathological studies.17,21 Beyond a class effect of DES, different kinds of DES may lead to the early development of NA after DES implantation.17,21 Among them, EES and SES showed different vascular responses.22 In the univariate analysis, smoking and NA were consistent with our data. In the native coronary artery, intimal calcification develops in the second decade of life, and the prevalence increases over time.20 Similar to native arteries, the development of NA among subtypes of DES is independent of the time from the implantation, suggesting that it takes ≈6 years to develop a calcified neointima. Stent ages in the previous case reports were 8 and 10 years,18,19 which were consistent with our data. In the native coronary artery, intimal calcification develops in the second decade of life, and the prevalence increases over time.20 Similar to native arteries, we found a close relationship between calcified neointima and stent age; however, further investigation is required to clarify the nature of calcified neointima.

DESA and NA

Nakazawa et al17,21 suggested the different time course of vascular healing and NA between DES and BMS in their histopathological studies. They demonstrated that atherosclerotic change was observed in >40% of DES by 9 months, whereas BMS did not develop any NA until 2 years and rarely up to 4 years. This may indicate the early onset of NA in DES. In the present study, we revealed that DES was an independent predictor for NA, which is consistent with the previous pathological study. DES inhibits endothelialization and delays vascular healing to the endothelial damage. Impaired endothelium would allow lipid transport across the wall, which may lead to the early development of NA after DES implantation.17,21 Beyond a class effect of DES, different kinds of DES show different vascular responses.22 In the univariate analysis, NA was significantly associated with first generation DES (SES/PES) whereas second generation DES (ZES/EES) did not show a significant association. Although all the subtypes of DES were independent predictors for NA in multivariate models, the underlying vascular response might be different among them. In the present study, the number of each DES subtype was limited, and long-term data of ZES and EES were lacking because of the short duration since implantation. Further studies are warranted to delineate differences in the development of NA among subtypes of DES.

Smoking and NA

Smoking is a well-known risk factor for coronary artery disease.23 In addition, smoking cessation dramatically reduces the risk for recurrent events in patients with coronary artery disease to the level of nonsmokers within 3 years.24 Nicotine enhances angiogenesis and arteriogenesis via nicotinic acetylcholine receptors in endothelial cells,25,26 Cigarette smoke contains a...
large number of oxidants and carbon monoxide as well, which induce endothelial injury and lead to atherosclerosis. Hypoxia also plays a role in atherosclerosis. It can either reduce endothelial thrombomodulin expression or activate factor X. Moreover, hypoxic cells activate a number of pathways that affect cell signaling and gene regulation, including hypoxia-inducible factor (HIF) 1 and HIF-2. 21 Direct chemical damage from those toxic components and angiogenesis following exposure to nicotine are the key effects of cigarette smoking.

In the present study, current smoking showed a significant effect on the development of NA, whereas no significant association was observed in the other coronary risk factors including hypertension, hyperlipidemia, and even in diabetes mellitus. Given the metallic materials beneath the intimal tissue, endothelial function in neointima can be inhibited especially in DES, which may affect the impaired recovery from endothelial injury in patients with smoking. Moreover, angiogenesis also may have exaggerated the development of lipid within a neointima.

CKD and NA

Previous studies have reported that patients with CKD are at increased risk of adverse cardiac events after stent implantation, 28,29 and the incidence of stent thrombosis was also reported to be associated with CKD after DES implantation. 30 However, there has been no study showing the association between NA and CKD. The present study revealed a significant impact of CKD (estimated glomerular filtration rate ≤60 mL/min per 1.73 m²) on NA in univariate and multivariate analysis. Generally, patients with CKD are accompanied by systemic abnormalities including high oxidative stress, endothelial dysfunction, and inflammatory status. 31 Those factors can induce endothelial damage, promote lipid proliferation, and lead to plaque vulnerability.

The Use of ACE-I/ARB and NA

Given sufficient evidence from large clinical trials, ACE-I and ARB are widely used to reduce the cardiovascular events in secondary prevention of coronary heart disease. 32–34 Moreover, it has been reported that pharmacologic therapy with ACE-I or ARB reduced neointima proliferation and restenosis after stent implantation. 35-37 It was speculated that the tissue renin-angiotensin system inside the stent may play a role in neointima formation. However, the impact on late stent complication, such as stent thrombosis and late restenosis, has not been investigated. In the present study, the use of ACE-I or ARB was significantly, inversely associated with the presence of NA inside the stent in both the univariate and multivariate analyses. Our results are consistent with previous studies. Prospective studies to evaluate the effect of ACE-I/ARB on the prevention of NA are warranted.

Limitations
First, it was a retrospective observational study; therefore, selection bias may have influenced the results. Second, we excluded the stents with neointimal thickness ≤100 µm to assess the characteristic of neointimal tissue, which may have led to a selection bias. We excluded these stents because it is impossible to analyze the nature of the tissue when the amount of neointimal tissue is too small. In a previous study in which tissue property analysis was performed, the stents with neointimal hyperplasia ≤100 µ were excluded because even the analysis software could not accurately analyze the tissue property signals. 39 Third, 4 types of DESs, including SES, PES, ZES, and EES, were included in the present study. Because of the relatively small number of each DES subtype and lack of long-term follow-up data of second generation DES, we could not precisely evaluate the difference in the nature of NA among the subtypes of DES. Fourth, our registry database did not have information on the subclass and dosage of statin or ACE-I/ARB that may have affected the development of NA. Fifth, although the identification of lipid-rich plaque by OCT was validated with a histopathological study, 11 the pathological data regarding neointimal patterns in OCT is limited. OCT may have over- or underestimated the presence of lipids.

Conclusions

In addition to the stent characteristics, such as stent type and time since stent implantation, patient characteristics, including current smoking status and the use of ACE-I or ARB, may have been related to the development of NA inside the stents. These results may highlight the importance of secondary prevention after stent implantation regardless of the stent type.

Disclosures

Dr. Jang received a research grant and consulting fee from LightLab Imaging/St Jude Medical, and Dr. Zhang is an employee of LightLab Imaging/St Jude Medical. This study was supported by research grants from St Jude Medical, the Cardiology Division of Massachusetts General Hospital, and Dr. John Nam.

References

Very late stent thrombosis was first reported a decade ago and remains a concern even with the introduction of drug-eluting stents. Neointima inside stents develops lipid-laden plaque, calcification, disruption, macrophage infiltration, and thrombosis, which is termed neatherosclerosis. The true incidence, exact mechanisms, predictors, and treatment of this pathology are incompletely understood. This study reports predictors for the development of neatherosclerosis. In addition to stent type (drug-eluting stent) and stent age (>48 months), other modifiable predictors such as current smoking, chronic kidney disease, and usage of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker were identified. These predictors may help to understand underlying mechanisms leading to late stent thrombosis and may help develop strategies to prevent the development of neatherosclerosis. If these findings are confirmed, subsequent studies can determine whether modifying these predictors can reduce the incidence of neatherosclerosis.
Predictors for Neoatherosclerosis: A Retrospective Observational Study From the Optical Coherence Tomography Registry


_Circ Cardiovasc Imaging_. 2012;5:660-666; originally published online July 13, 2012;
doi: 10.1161/CIRCIMAGING.112.976167

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/5/5/660

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2012/07/13/CIRCIMAGING.112.976167.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/
Acknowledgements

The MGH OCT Registry

Executive Board: William Dec (Massachusetts General Hospital and Harvard Medical School, Boston, MA); Ik-Kyung Jang (Massachusetts General Hospital and Harvard Medical School, Boston, MA); Kyoichi Mizuno (Nippon Medical School, Tokyo, Japan); Yang-Soo Jang (Severance Cardiovascular Hospital, Yonsei University, Seoul, Korea); and Abhiram Prasad (Mayo Clinic, Rochester, MN).

Advisors: Valentin Fuster (The Mt. Sinai Hospital, New York, NY) and James Fujimoto (Massachusetts Institute of Technology).

Publication Committee: Jagat Narula (The Mt. Sinai Hospital, New York, NY); Shiro Uemura (Nara Medical University, Nara, Japan); Jingbo Hou (The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China); and Owen C. Raffel (Prince Charles Hospital, Brisbane, Australia).

Statistician: Hang Lee (Biostatistics Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA)

Data Manager: Christina Kratlian (Massachusetts General Hospital, Boston, MA)

Investigators: Owen C. Raffel; Harry Lowe (Concord Repatriation General Hospital, Sydney, Australia); Peter Barlis (The Northern Hospital, Melbourne, Australia); Bo Yu (The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China); Stephen Lee (Queen Mary Hospital, Hong Kong University, Hong Kong); Tsunekazu Kakuta (Tsuchiura Kyodo General Hospital, Tsuchiura, Japan); Kyoichi Mizuno; Shiro Uemura; Tomonori Itoh (Iwate Medical School, Morioka, Japan); Soo-Joong Kim (Kyung Hee Medical Center, Seoul, Korea); Chang-Bum Park (Kyung Hee University, Seoul, Korea);
Yang-Soo Jang; So-Yeon Choi (Ajou University Hospital, Suwon, Korea); Seung-Jung Park (Asan Medical Center, Seoul, Korea); Stanley Chia (National Heart Centre Singapore, Singapore); Harold L. Dauerman (University of Vermont, Burlington, VT); Abhiram Prasad; Catalin Toma (University of Pittsburgh, Pittsburgh, PA); and Ik-Kyung Jang.