EXPEDITED PUBLICATIONS

The Pathology of Neoatherosclerosis in Human Coronary Implants
Bare-Metal and Drug-Eluting Stents

Gaku Nakazawa, MD,* Fumiyuki Otsuka, MD,* Masataka Nakano, MD,* Marc Vorpahl, MD,* Saami K. Yazdani, P H D,* Elena Ladich, MD,* Frank D. Kolodgie, P H D,* Aloke V. Finn, MD,† Renu Virmani, MD*

Gaithersburg, Maryland; and Atlanta, Georgia

Objectives
Human coronary bare-metal stents (BMS) and drug-eluting stents (DES) from autopsy cases with implant duration >30 days were examined for the presence of neointimal atherosclerotic disease.

Background
Neointimal atherosclerotic change (neoatherosclerosis) after BMS implantation is rarely reported and usually occurs beyond 5 years. The incidence of neoatherosclerosis after DES implantation has not been reported.

Methods
All available cases from the CVPath stent registry (n = 299 autopsies), which includes a total of 406 lesions—197 BMS, 209 DES (103 sirolimus-eluting stents [SES] and 106 paclitaxel-eluting stents [PES])—with implant duration >30 days were examined. Neoatherosclerosis was recognized as clusters of lipid-laden foamy macrophages within the neointima with or without necrotic core formation.

Results
The incidence of neoatherosclerosis was significantly greater in DES lesions (31%) than BMS lesions (16%; p < 0.001). The median stent duration with neoatherosclerosis was shorter in DES than BMS (DES, 420 days [interquartile range [IQR]: 361 to 683 days]; BMS, 2,160 days [IQR: 1,800 to 2,880 days], p < 0.001). Unstable lesions characterized as thin-cap fibroatheromas or plaque rupture were more frequent in BMS (n = 7, 4%) than in DES (n = 3, 1%; p = 0.17), with relatively shorter implant durations for DES (1.5 ± 0.4 years) compared to BMS (6.1 ± 1.5 years). Independent determinants of neoatherosclerosis identified by multiple logistic regression included younger age (p < 0.001), longer implant durations (p < 0.001), SES usage (p < 0.001), PES usage (p = 0.001), and underlying unstable plaques (p = 0.004).

Conclusions
Neoatherosclerosis is a frequent finding in DES and occurs earlier than in BMS. Unstable features of neoatherosclerosis are identified for both BMS and DES with shorter implant durations for the latter. The development of neoatherosclerosis may be yet another rare contributing factor to late thrombotic events.

From the *CVPath Institute, Inc., Gaithersburg, Maryland; and the †Emory University School of Medicine, Atlanta, Georgia. CVPath Institute provided full support for this work. Dr. Finn is supported by National Institutes of Health grant HL096970-01A1, the Carlyle Fraser Heart Center at Emory University, and a sponsored research agreement with Medtronic and St. Jude Medical; and is a consultant for Abbott Vascular and Cordis. Dr. Virmani receives research support from Medtronic AVE, Abbott Vascular, Atrium Medical, OrbusNeich Medical, Terumo Corporation, Cordis Corporation, BioSensors International, Biotronik, and Alchimedics; and is a consultant for Medtronic AVE, Abbott Vascular, W.L. Gore, Atrium Medical, and Lutonix. All other authors have reported that they have no relationships to disclose. Drs. Nakazawa and Otsuka contributed equally to this work.

Manuscript received July 26, 2010; revised manuscript received December 6, 2010, accepted January 5, 2011.

See page 1323

Percutaneous coronary interventions (PCI) involving stenting are the most widely performed procedures for the treatment of symptomatic coronary disease (1). Although first-generation drug-eluting stents (DES), including sirolimus-eluting stents (SES [Cypher, Cordis Corp., Miami Lakes, Florida]) and paclitaxel-eluting stents (PES [Taxus, Boston Scientific, Natick, Massachusetts]), have radically reduced restenosis (2,3), complications of late stent thrombosis (LST) and very late stent thrombosis (VLST) have emerged as an important but small limitation to this technology.

Both clinical imaging and autopsy studies suggest that the primary etiology of LST is the lack of complete endothelialization over stent struts. Interrogation of stented coronary arteries by angioscopy confirms that the incidence of uncovered struts in patients receiving DES is high, 20% at 2 years (4). However, the cause of LST is considered to be multifactorial, and other mechanisms in addition to delayed healing may be important in the pathophysiology of LST.
Although a thrombotic event related to atherosclerosis of native coronary vessels is a widely accepted cause of acute coronary syndromes and sudden death (5), there is little information in reference to lesion morphologies that may contribute to thrombosis associated with stents. Chen et al. (6) have reported that a significant number of patients with bare-metal stents (BMS) and restenosis present with acute myocardial infarction or unstable angina, raising the question whether these events might be attributable to plaque rupture within the neointima. Although we have also reported a case of sudden coronary death caused by plaque rupture secondary to atherosclerotic change developing within the neointima of a BMS (7), this phenomenon is believed to be rare and is thought to occur with extended implant durations beyond 5 years (8). The incidence of atherosclerosis occurring within DES and BMS implants at autopsy has not been examined systematically. The present investigation represents a histopathological study of atherosclerosis occurring within BMS and DES implants focused on the incidence, character, and temporal development, in particular as an underlying cause for acute coronary thrombosis.

**Methods**

**Patients and lesions.** All available material from the CVPath stent registry, which includes 299 consecutive autopsy cases (142 BMS, 157 DES [81 SES and 76 PES] patients) with 406 lesions of >30 days’ implant duration (197 BMS, 209 DES [103 SES and 106 PES] lesions) was reviewed. Hearts with multiple stents, overlapping, and consecutively implanted stents were treated as 1 lesion, whereas stents including a gap of >5 mm were treated as separate lesions, as previously described (9). The cause of death was reported as stent-related death (thrombosis and restenosis with or without diffuse coronary artery disease [CAD]), nonstent-related cardiac death, and noncardiac death as previously defined (9). All available clinical records were reviewed for the duration of implant, risk factors, and mechanism of death.

**Histologic preparation.** Hearts with stented arteries were fixed in 10% neutral buffered formalin, dissected off the heart, radiographed, and submitted for plastic embedding in methylmethacrylate. Coronary arteries were segmented at 2- to 3-mm intervals, and histologic sections were cut at 6 μm and stained with hematoxylin-eosin and Movat pentachrome, as previously described (9).

**Pathologic assessment.** Acute thrombosis was defined as a platelet-rich thrombus occupying >30% of the cross-sectional area of the lumen, and stent restenosis was defined as >75% cross-sectional area narrowing by neointimal formation. The native plaques (outside stent struts) were assessed and classified using our modified American Heart Association classification, to include traditional definitions of pathological intimal thickening, fibroatheroma, thin-cap fibroatheroma, and plaque rupture. Fibrotic lesions with or without calcification that did not show macrophage infiltration were noted separately (5). Atherosclerosis of the neointima within the stent was defined as peristrut foamy macrophage clusters with or without calcification, fibroatheromas, thin-cap fibroatheromas, and ruptures with thrombosis. In all cases, there was no communication of the lesion within the stent with the underlying native atherosclerotic plaque.

Immunohistochemistry for the identification of macrophages was carried out in selected cases using a CD68 antibody (dilution 1:800, Dako, Carpinteria, California), as previously described (10). The primary antibody was labeled using an LSAB kit (Dako) and positive staining visualized by a 3-amino-9-ethyl carbazole (AEC) substrate-chromogen system with Gill’s hematoxylin as a counterstain.

The data were analyzed on the basis of lesions and not by patients, as often the duration of multiple stents varies as patients undergo repeat PCI dictated by the onset of symptoms. The development of atherosclerotic change by duration of stent implantation was also assessed in addition to the regional placement of the stent.

**Statistical analysis.** Continuous variables with normal distribution were expressed as mean ± SD. Variables with non-normal distribution were expressed as median (interquartile range [IQR]). Comparisons of continuous variables with normal distribution were tested by Student t test. A Wilcoxon rank-sum test was used for comparisons of non-normally distributed continuous variables. Categorical variables were compared using the chi-square test. Normality of distribution was tested with the Wilk-Shapiro test. Multiple logistic generalized estimating equations (GEE) modeling (9) was performed to identify the determinants of stent neoatherosclerosis, in which age, sex, and significant variables (p < 0.05) among lesion characteristics (the number of stents, stent duration, indication of stent implantation, lesion location, stent length, overlapping stents, underlying plaque morphology, and stent type) in univariate analysis were entered as independent variables. The GEE modeling was necessary because of the clustered nature of >1 stented lesions in some cases, resulting in unknown correlations among measurements within lesion clusters. A value of p < 0.05 was considered statistically significant.

**Results**

**Patient characteristics.** Age, sex, and coronary risk factors were similar for patients receiving BMS or DES (Table 1). Patients receiving BMS had a higher prevalence of prior
history of myocardial infarction (p = 0.009) and coronary artery bypass grafts (p = 0.008) than patients receiving DES. Conversely, stent-related deaths from thrombosis were significantly more frequent for DES than BMS (20% vs. 4%, p < 0.001). Whereas in-stent restenosis as a cause of death was more frequent among BMS patients than DES patients (BMS, n = 40 [28%]; and DES, n = 11 [7%], p < 0.001), the incidences of nonstent-related death and non-cardiac death were similar between groups.

### Lesion characteristics.

The median stent implant duration was shorter in lesions treated with DES versus BMS (DES, median 361 days [IQR: 172 to 540 days], BMS, 721 days [IQR: 271 to 1,801 days]; p < 0.001) (Table 2). The shortest stent duration was 35 days for both SES and PES.

### Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>BMS (n = 142)</th>
<th>All (SES + PES) (n = 157)</th>
<th>SES (n = 81)</th>
<th>PES (n = 76)</th>
<th>p Value BMS vs. DES (SES + PES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62 ± 14</td>
<td>60 ± 12</td>
<td>60 ± 12</td>
<td>59 ± 12</td>
<td>0.143</td>
</tr>
<tr>
<td>Male</td>
<td>105 (74)</td>
<td>117 (75)</td>
<td>59 (73)</td>
<td>58 (76)</td>
<td>0.909</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67/94 (71)</td>
<td>90/114 (79)</td>
<td>41/56 (73)</td>
<td>49/58 (84)</td>
<td>0.215</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41/94 (44)</td>
<td>35/115 (30)</td>
<td>14/57 (25)</td>
<td>21/58 (36)</td>
<td>0.060</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>50/94 (53)</td>
<td>73/114 (64)</td>
<td>34/56 (61)</td>
<td>39/58 (67)</td>
<td>0.140</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>85/128 (66)</td>
<td>66/133 (50)</td>
<td>31/67 (46)</td>
<td>35/66 (53)</td>
<td>0.009</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>32/139 (23)</td>
<td>18/146 (12)</td>
<td>10/76 (13)</td>
<td>8/70 (11)</td>
<td>0.008</td>
</tr>
<tr>
<td>Number of stents per patient</td>
<td>1.4 ± 1.0</td>
<td>1.6 ± 1.1</td>
<td>1.6 ± 1.1</td>
<td>1.7 ± 1.1</td>
<td>0.062</td>
</tr>
</tbody>
</table>

### Cause of death

**Stent related**

- Thrombosis: 5* (4) vs. 32† (20) vs. 14 (17) vs. 18 (24) (p < 0.001)
- Restenosis without diffuse CAD: 19 (13) vs. 5 (3) vs. 2 (2) vs. 3 (4) (p = 0.001)
- Diffuse CAD with restenosis: 20 (14) vs. 4 (3) vs. 3 (4) vs. 1 (1) (p < 0.001)
- Nonstent-related cardiac
- Noncardiac
- Unknown

**Values are expressed as means ± SD or n (%).** *Among 5 patients with thrombosis in the BMS group, 4 patients had neointimal plaque rupture and 1 patient had restenosis only. †Among 32 patients with thrombosis in the DES group, 1 patient had neointimal plaque rupture, 2 patients had restenosis, and the rest had uncovered struts from varying etiologies.

### Table 2 Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>BMS (197 Lesions)</th>
<th>All (SES + PES) (209 Lesions)</th>
<th>SES (103 Lesions)</th>
<th>PES (106 Lesions)</th>
<th>p Value BMS vs. DES (SES + PES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent duration, days</td>
<td>721 (271–1,801)</td>
<td>361 (172–540)</td>
<td>361 (180–541)</td>
<td>270 (149–473)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
| Indication for stent implantation
- Stable angina pectoris | 150 (76)         | 150 (72)                      | 72 (70)           | 78 (74)           | 0.316                           |
- Unstable angina pectoris/AMI | 47 (24)        | 59 (28)                       | 31 (30)           | 28 (26)           |                                |
| Lesion location
- Left main coronary artery | 4 (2)           | 6 (3)                         | 2 (2)             | 4 (4)             | 0.501                           |
- Left anterior descending artery | 73 (37)        | 87 (42)                       | 41 (40)           | 46 (43)           |                                |
- Left circumflex artery | 45 (23)         | 51 (24)                       | 24 (23)           | 27 (26)           |                                |
- Right coronary artery | 75 (38)         | 65 (31)                       | 36 (35)           | 29 (27)           |                                |
| Proximal lesion      | 77/161 (48)     | 102/202 (51)                  | 45/98 (46)        | 57/104 (55)       | 0.613                           |
| Mid/distal lesion    | 84/161 (52)     | 100/202 (49)                  | 53/98 (54)        | 47/104 (45)       |                                |
| Stent length, mm     | 16.0 (12.0–24.0) | 22.0 (15.5–30.0)              | 21.0 (15.0–30.0)  | 22.0 (15.8–30.3)  | < 0.001                         |
| Overlapping stents   | 36 (18)         | 63 (30)                       | 30 (29)           | 33 (31)           | 0.005                           |
| Underlying plaque morphology
- Ruptured plaque/TCFA | 26 (13)         | 49 (23)                       | 28 (27)           | 21 (20)           | 0.008                           |
- Fibroatheroma        | 86 (44)         | 104 (50)                      | 44 (43)           | 60 (57)           | 0.261                           |
- Fibrocalcific        | 29 (15)         | 16 (7)                        | 8 (8)             | 8 (7)             | 0.023                           |
- Pathologic intimal thickening | 47 (24)     | 20 (10)                       | 13 (12)           | 7 (7)             | < 0.001                         |
- Others               | 9 (4)           | 20 (10)                       | 10 (10)           | 10 (9)            | 0.051                           |

**Values are expressed as median (interquartile range) or n (%).** *Includes underlying restenotic lesion, calcified nodule, and dissection.

AMI = acute myocardial infarction; TCFA = thin-cap fibroatheroma; other abbreviations as in Table 1.
and 31 days for BMS, whereas the longest stent duration was 1,800 days for SES, 1,814 days for PES, and 7,201 days for BMS. Indications for stent implantation and lesion location were comparable between groups. Stent lengths were significantly longer in DES (22.0 mm [IQR: 15.5 to 30.0 mm]) than in BMS (16.0 mm [IQR: 12.0 to 24.0 mm]; \( p < 0.001 \)). The prevalence of overlapping stents was also significantly higher in DES (30%, vs. BMS 18%; \( p = 0.005 \)). Notably, the underlying plaque morphology was different, with unstable lesions (i.e., ruptured plaques and thin-cap fibroatheroma) more commonly found in DES as compared with BMS (\( p = 0.008 \)). However, fibrocalcific and pathologic intimal thickening were significantly more frequent in BMS than DES (\( p = 0.023 \) and \( p < 0.001 \), respectively).

**Incidence of neoatherosclerosis.** Representative images of newly formed atherosclerotic changes within the neointima in various stents are shown in Figure 1. Notably, 85% (177 lesions) DES were implanted for 2 years or less with no lesions extending beyond 6 years, while 45% (88 lesions) BMS were implanted for 2 years or less and 17% (33 lesions) had durations of >6 years (Table 3). The incidence of any neoatherosclerosis was greater in DES (n = 64, 31%) than BMS (n = 31, 16%) lesions (\( p < 0.001 \)). Nearly one-half the DES lesions with neoatherosclerosis (31 of 64 lesions, 48%) contained peristrut foamy macrophage clusters, and the other half showed fibroatheromas. A significant temporal relationship was found among BMS and DES; atherosclerotic change occurred in significantly shorter implant durations for DES than for BMS (DES, 420 days [IQR:
The incidence of neoatherosclerosis was also evaluated based on the implant duration (Table 3). For those implants of ≤2 years, the DES group had a greater incidence of any neoatherosclerosis (DES 29% vs. BMS 0%, p < 0.001), which was represented by a greater incidence of foamy macrophage clusters (DES 14% vs. BMS 0%, p < 0.001) as well as fibroatheromas (DES 13% vs. BMS 0%, p < 0.001). For durations between 2 years and 6 years, the DES group still expressed a higher incidence of neoatherosclerosis (DES 41% vs. BMS 22%, p = 0.053) (Table 3). The incidence of any neoatherosclerotic change was greater in SES than in PES for implant durations of 2 years or less (SES 37% vs. PES 21%, p = 0.021), although differences did not remain with stents implanted for 2 to 6 years (SES 44% vs. PES 38%, p = 0.719).

In regard to the location of the stent and the development of atherosclerosis, the incidence of atherosclerotic change in proximal lesions was significantly higher than those in mid/distal lesions in BMS (27% vs. 12%, respectively; p = 0.014); however, this difference was not seen in DES (33% vs. 30%, p = 0.611) (Table 3).

More advanced lesions—unstable plaque, namely, thin-cap fibroatheroma and ruptured plaques with thrombosis (Figs. 2D to 2I)—were seen for both BMS (n = 7, 4%) and DES (n = 3, 1%), where the majority of BMS were >5 years (average implant duration 6.1 ± 1.5 years) whereas for DES, unstable neoatherosclerotic lesions were identified with devices implanted ≤2 years (1.1, 1.4, and 1.9 years).
Details of the 10 patients (7 BMS and 3 DES) with thin-cap fibroatheroma or plaque rupture within the in-stent neointima are provided in the visual Table 4.

The incidence of neoatherosclerosis did not differ between patients with stent-related death and patients with nonstent-related death, both in BMS (18% vs. 20%, p = 0.848) and in DES (27% vs. 42%, p = 0.099). In patients with stent-related death, the incidence of neoatherosclerosis was comparable between BMS and DES (18% vs. 27%, p = 0.339), whereas in patients with nonstent-related death, DES had a higher incidence of neoatherosclerosis than BMS (42% vs. 20%, p < 0.001).

A multiple logistic GEE modeling identified younger age (odds ratio [OR]: 0.963, 95% confidence interval [CI]: 0.942 to 0.983; p < 0.001), longer implant duration (OR: 1.028, 95% CI: 1.017 to 1.041; p < 0.001), SES usage (OR: 6.534, 95% CI: 3.387 to 12.591; p < 0.001), PES usage (OR: 3.200, 95% CI: 1.584 to 6.469; p = 0.001), and underlying unstable plaque (OR: 2.387, 95% CI: 1.326 to 4.302; p = 0.004) as independent risk factors for neoatherosclerosis (Table 5).

**Discussion**

The present study suggests that in-stent neoatherosclerosis occurs in both BMS and DES; however, for DES implants, it is observed more frequently and at an earlier time point (median 420 days) as compared with BMS (median 2,160 days). For stent-related deaths, in-stent neoatherosclerosis incidence was similar for BMS and DES (18% vs. 20%). However, for nonstent-related death, the incidence of neoatherosclerosis was more frequent for DES than BMS (42% vs. 20%, p < 0.001). Moreover, neoatherosclerosis in DES shows unstable characteristics by 2 years after implant, whereas similar features in BMS occur at relatively later times (average implant duration 6 years). These observa-

**Figure 2** Representative Cases Showing Atherosclerotic Change After PES, SES, and BMS Implantation

(A to C) Histologic sections from a 65-year-old woman with a PES implanted in the left circumflex artery 14 months antemortem, who died of traumatic brain injury. (A) A low-power image shows a patent lumen with moderate neointimal growth; (B) foamy macrophage infiltration and necrotic core formation with cholesterol clefts is seen at high magnification. (C) Same section as (B) showing CD68-positive macrophages in the neointima (* indicates stent strut). (D) Histological sections from a 59-year-old man (Patient #10 in Table 4) with SES implanted for 23 months, who died of stent thrombosis. The thrombus (Th) was more apparent in the distal section taken 3 mm apart. (E) Note thin-cap fibroatheroma with fibrous cap disruption (arrows), from boxed area in D. (F) The CD68-positive macrophages are seen in the fibrous cap and in the underlying necrotic core (arrows). (G) Histologic section from a 47-year-old man (Patient #8 in Table 4) who had a BMS implanted 8 years before death. Note occlusive thrombus (Th) in the lumen and ruptured plaque (boxed area), which is shown at higher magnification in H with large number of macrophages within the lumen as well as at the ruptured cap. (I) Note large number of CD68-positive macrophages at the site of rupture. Abbreviations as in Figure 1.
tions raise the question whether neoatherosclerosis seen within DES as well as BMS at follow-up may in part be responsible for some late thrombotic events. The implications of current findings may be of practical importance as the usage of DES implants continues to increase worldwide. The occurrence of uncovered struts complicated by a dysfunctional endothelium remains the primary cause of LST in DES; nevertheless, the present study adds another risk factor, namely, in-stent plaque rupture, although a rare event.

Although the underlying processes responsible for the development of neoatherosclerosis after stent implantation are likely multifactorial, we hypothesize that it may involve the inability to maintain a fully functional endothelialized luminal surface within the stented segment (11). The endothelium normally provides an efficient barrier against the excessive uptake of circulating lipid, and that may no longer be true in the in-stent regions of DES and BMS (12). In the present study, BMS exhibited greater trends for neoatherosclerotic changes occurring in the more proximal than distal lesions relative to DES, thus indicating divergent mechanisms by which neoatherosclerosis attributed to DES may be more related to incomplete endothelialization as opposed to shear stress for BMS. These findings in the BMS may be more akin to the development of atherosclerosis in native coronary arteries, and is most prominent in the proximal regions of the coronary arteries (13).

Recently, chronic endoplasmic reticular stress in endothelial cells at athero-susceptible sites with arterial flow disturbances has been linked to inflammation (14). Shear-induced changes in endothelial phenotype (collectively known as mechanotransduction) may promote the expression of transmembrane proteins, like integrins and platelet endothelial cell adhesion molecule-1, which further allow inflammatory cell attachment and migration to subendothelial spaces (13). Changes in endothelial cell permeability could presumably allow greater amounts of lipoproteins to enter the subendothelial space, with an affinity for matrix proteins, in particular proteoglycans that promote their retention (15).

The relatively faster development of neoatherosclerosis in DES than in BMS is probably related to drug effects, which are also responsible for incomplete endothelialization. Previous animal studies of DES (11) suggest that the regenerating endothelial lining could be incompetent, and therefore may result in endothelial cells activation, which leads to monocyte adherence with subsequent subendothelial migration. Incomplete (delayed) endothelial regrowth and recovery observed with SES or PES that may contribute to atherogenesis is characterized by poor cell-to-cell contacts identified by decreased expression of platelet endothelial cell adhesion molecule-1 and antithrombotic mediators such as thrombomodulin (11).

Experimental evidence suggests that neoatherosclerosis within stents can be associated with delayed arterial healing compounded by lethal injury to smooth muscle cells and endothelial cells. We have reported that a $^{32}$P β-emitting stent implanted, with activities ranging from 6 μCi to 48 μCi, showed focal evidence of atherosclerotic change in normal arteries of New Zealand White rabbits examined at 6 and 12 months (16). Considering it is well known that atherosclerosis does not develop in normal arteries of the rabbit in the absence of hypercholesterolemia, these results suggest that the atherogenic process is inherent to process occurring within the stent itself.

In humans, 2 pathology studies have reported neoatherosclerotic change occurring in vein graft and in native coronary arteries with foam cell infiltration after BMS implants (17,18). Previous clinical studies have also suggested endothelial dysfunction after SES implantation by showing impaired vasomotor function in the adjacent segment of stents (19), although the precise mechanism for the endothelial dysfunction in the stented segment in humans remains unknown.

**Clinical relevance.** Coronary SES implants in 57 patients recently interrogated by angiography showed a 35% increase in the maximum yellow color of the neointima within 10 months of follow-up (20). Even among lesions that did not express yellow plaque at baseline, yellow color was detected in 95% of SES implants, suggesting a neoatherosclerotic change in response to the stent.

A retrospective analysis of 4,503 patients with at least 1 BMS implant, reported by Doyle et al. (21), showed that the incidence of stent thrombosis was 0.8% at 1 year and 2% at 10 years, which is lower than reported for DES (SES and PES), 2.9% at 3 years, involving an all-comer registry of 8,146 patients (22). In contrast, a meta-analysis of 18,023 patients reported by Stettler et al. (23) revealed that mortality risks were similar between BMS and DES (SES and PES), although several trials included in the meta-analysis evaluated only cardiac and not all-cause mortality. The
### Table 4 Patients With TCFA or Plaque Rupture Within Neointima After Stent Implantation

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age, yrs</th>
<th>Sex</th>
<th>Stent Type</th>
<th>Location</th>
<th>No. of Stents</th>
<th>Stent Length, mm</th>
<th>Implant Indication</th>
<th>Implant Duration, Months</th>
<th>Cause of Death</th>
<th>Representative Images</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thin-cap fibroatheroma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58 M</td>
<td>M</td>
<td>BMS (NIR)</td>
<td>LAD Proximal</td>
<td>1</td>
<td>18</td>
<td>SAP</td>
<td>61</td>
<td>Noncardiac</td>
<td><img src="image1.jpg" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td>63 M</td>
<td>M</td>
<td>BMS (Multi-Link)</td>
<td>RCA mid</td>
<td>1</td>
<td>18</td>
<td>SAP</td>
<td>98</td>
<td>Nonstent-related cardiac</td>
<td><img src="image2.jpg" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td>73 M</td>
<td>M</td>
<td>BMS (Bx Velocity)</td>
<td>RI Proximal</td>
<td>1</td>
<td>16</td>
<td>SAP</td>
<td>50</td>
<td>Noncardiac</td>
<td><img src="image3.jpg" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td>40 F</td>
<td>F</td>
<td>DES (SES)</td>
<td>RCA proximal</td>
<td>1</td>
<td>23</td>
<td>AMI</td>
<td>17</td>
<td>Stent-related (thrombosis)</td>
<td><img src="image4.jpg" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td>67 M</td>
<td>M</td>
<td>DES (SES)</td>
<td>RCA proximal</td>
<td>1</td>
<td>13</td>
<td>SAP</td>
<td>13</td>
<td>Nonstent-related cardiac</td>
<td><img src="image5.jpg" alt="Image" /></td>
</tr>
<tr>
<td><strong>Plaque rupture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>43 M</td>
<td>M</td>
<td>BMS (Mini-Crown)</td>
<td>LAD proximal</td>
<td>1</td>
<td>14</td>
<td>SAP</td>
<td>84</td>
<td>Stent-related (thrombosis)</td>
<td><img src="image6.jpg" alt="Image" /></td>
</tr>
<tr>
<td>7</td>
<td>87 F</td>
<td>F</td>
<td>BMS (2 AVE)</td>
<td>RCA proximal</td>
<td>2</td>
<td>60</td>
<td>SAP</td>
<td>61</td>
<td>Stent-related (thrombosis)</td>
<td><img src="image7.jpg" alt="Image" /></td>
</tr>
<tr>
<td>8</td>
<td>47 M</td>
<td>M</td>
<td>BMS (3 Gianturco-Roubin II)</td>
<td>RCA proximal</td>
<td>3</td>
<td>90</td>
<td>SAP</td>
<td>96</td>
<td>Stent-related (thrombosis)</td>
<td><img src="image8.jpg" alt="Image" /></td>
</tr>
<tr>
<td>9</td>
<td>43 M</td>
<td>M</td>
<td>BMS (5 Multi-Link Zeta)</td>
<td>RCA proximal/distal</td>
<td>5</td>
<td>70</td>
<td>SAP</td>
<td>61</td>
<td>Stent-related (thrombosis)</td>
<td><img src="image9.jpg" alt="Image" /></td>
</tr>
<tr>
<td>10</td>
<td>59 M</td>
<td>M</td>
<td>DES (SES)</td>
<td>RCA distal</td>
<td>1</td>
<td>23</td>
<td>AMI</td>
<td>23</td>
<td>Stent-related (thrombosis)</td>
<td><img src="image10.jpg" alt="Image" /></td>
</tr>
</tbody>
</table>

LAD = left anterior descending artery; RCA = right coronary artery; RI = ramus intermedius; SAP = stable angina pectoris; other abbreviations as in Tables 1 and 2.
largest registry (Swedish Coronary Angiography and Angioplasty Registry), reported by Lagerqvist et al. (24), involved 73,798 stents from 42,150 patients with DES and BMS and showed a biphasic incidence of LST, with higher rates in the first year in BMS followed by a higher rate in DES from 1 to 3 years, for unadjusted cumulative probability of acute occlusion. However, after adjustment for background and procedure characteristics, no differences were observed at 3 years. As compared with large clinical trials, our study shows apparently higher rates of stent thrombosis, probably because the population may be biased toward patients dying of DES complications (all comers without adjustment). In addition, our population is nonrandomized, and unknown confounders could exist even after adjustment by multivariate GEE modeling. Despite these shortcomings, to our knowledge, the present study represents the first report demonstrating the incidence and type of neoatherosclerosis within DES and BMS from a large series of stents implanted in native human coronary arteries. Because only histologic studies can provide sufficient detail to accurately characterize neoatherosclerosis within stents, our results offer important insights into late cardiac events attributed to stents.

Conclusions

The current pathology study suggests that neoatherosclerosis is a frequent finding in DES, and occurs significantly earlier in DES as compared with BMS; however, complications are more frequent for BMS than for DES and are likely due to longer implant duration. These observations suggest that neoatherosclerosis could be accelerated in DES, and in rare cases, contribute to very late thrombotic events in both BMS and DES.

Reprint requests and correspondence: Dr. Renu Virmani, CV-Path Institute, Inc., 19 Firstfield Road, Gaithersburg, Maryland 20878. E-mail: rvirmani@cvpath.org.

REFERENCES


Key Words: bare-metal stent • drug-eluting stent • neoatherosclerosis • pathology.