Delayed Arterial Healing and Increased Late Stent Thrombosis at Culprit Sites After Drug-Eluting Stent Placement for Acute Myocardial Infarction Patients

An Autopsy Study

Gaku Nakazawa, MD; Aloke V. Finn, MD; Michael Joner, MD; Elena Ladich, MD; Robert Kutys, MS; Erik K. Mont, MD; Herman K. Gold, MD†; Allen P. Burke, MD; Frank D. Kolodgie, PhD; Renu Virmani, MD

Background—The long-term safety of drug-eluting stents (DES) for acute myocardial infarction (AMI) remains uncertain. Using autopsy data, we evaluated the pathological responses of the stented segment in patients treated with DES for AMI and compared with patients with stable angina.

Methods and Results—From the CVPath Registry of 138 DES autopsies, we identified 25 patients who presented with AMI and had an underlying necrotic core with a ruptured fibrous cap. Twenty-six patients who had stable angina with thick-cap fibroatheroma treated by DES were selected as controls. Histomorphometric analysis was performed in patients with >30-day stent duration. We compared the response to stenting at the culprit site in these 2 groups and to nonculprit sites within each stent. Late stent thrombosis was significantly less frequent in stable (11%) than in AMI (41%; P=0.04) patients. Although neointimal thickness in the AMI culprit site was significantly less (median, 0.04 mm; interquartile range [IQR], 0.02 to 0.09 mm), the prevalence of uncovered struts (49%; IQR, 16% to 96%), fibrin deposition (63±28%), and inflammation (35%; IQR, 27% to 49%) were significantly greater compared with the culprit site in stable patients (neointimal thickness: 0.11 mm [IQR, 0.07 to 0.21 mm], P=0.008; uncovered struts: 9% [IQR, 0% to 39%], P=0.01; fibrin: 36±27%, P=0.008; inflammation, 17% [IQR, 7% to 25%], P=0.003) and the nonculprit site within each stent.

Conclusions—Vessel healing at the culprit site in AMI patients treated with DES is substantially delayed compared with the culprit site in patients receiving DES for stable angina, emphasizing the importance of underlying plaque morphology in the arterial response to DES. Our data suggest an increased risk of thrombotic complications in patients treated with DES for AMI. (Circulation. 2008;118:1138-1145.)

Key Words: myocardial infarction ■ stents ■ thrombosis

The approval of the current generation of polymeric Cypher and Taxus drug-eluting stents (DES) by the US Food and Drug Administration was based on randomized clinical trial data demonstrating impressive reductions in restenosis compared with standard bare metal stents in patients with stable or unstable angina without evidence of myocardial infarction.1,2 Although 2 randomized clinical trials of DES implantation for acute myocardial infarction (AMI) demonstrated no differences in rates of late stent thrombosis (LST) between bare metal stents (BMS) and DES, the long-term safety of this practice is still uncertain because of the short duration of follow-up (ie, 1 year).3,4 In fact, an increased risk of LST compared with BMS was more pronounced 6 months to 1 year after DES implantation.5–7 Recently, Sianos et al8 reported an extremely high incidence (ie, cumulative rate, 8.2%) of stent thrombosis in AMI patients with large thrombus burden at 2 years compared with those with small thrombus burden. Furthermore, Daemen et al9 found that acute coronary syndromes were an independent risk factor for LST in their large registry with 4 years of follow-up. These studies raise concerns about the long-term safety of using DES to treat AMI.

Editorial p 1117

Clinical Perspective p 1145

Using pathological data from patients who died after DES implantation, we have previously shown that both sirolimus- and paclitaxel-eluting stents (Cypher, Cordis, Johnson &
Johns Hopkins Company, Miami Lakes, Fla, and Taxus, Boston Scientific, Natick, Mass, respectively) cause substantial impairment in arterial healing characterized by incomplete endothelialization and persistence of fibrin compared with BMS at autopsy \(^{10,11}\) and that this delayed healing is the primary substrate underlying all cases of late thrombosis. Several additional risk factors for LST such as penetration of necrotic core, malapposition, excessive stent length, and bifurcation lesions were reported. Thrombus, along with an underlying necrotic core, is a frequent finding in culprit plaques in patients dying with AMI \(^{12}\). Because lipid-laden large necrotic cores and other factors such as thrombus affect drug distribution, \(^{13}\) the impact of these underlying lesion characteristics on arterial healing and perhaps long-term outcomes in patients receiving DES for this indication remains unknown. Using our autopsy database of patients dying after Cypher or Taxus DES implantation, we compared the vascular pathological responses to DES implantation in patients receiving DES for AMI with that of patients receiving them for stable angina.

**Methods**

**Patient Selection**

From the CVPath DES autopsy registry of 138 cases (collected from 2002 to September 2007), 25 patients presenting with AMI who were treated with DES and had an underlying necrotic core with a ruptured thin fibrous cap as the culprit lesion were included in the AMI patient group. Eight of these patients had a stent implanted for ≤30 days. The presence of a myocardial infarction in the distribution of the culprit lesion was confirmed in all AMI cases at autopsy. From the same registry, a total of 46 patients who presented with stable angina (defined according to the Canadian Cardiovascular Society Classification) had fibroatheroma (defined as necrotic core with a thick fibrous cap >100 μm) as an underlying plaque in the DES-treated segment. Of these, 20 were excluded from analysis for the following reasons: bifurcation treated with ≥2 stents (n=6), evidence of local hyperplasia (n=1), chronic total occlusion of the segment. Of these, 20 were excluded from analysis for the following reasons: bifurcation treated with ≥2 stents (n=6), evidence of local hyperplasia (n=1), chronic total occlusion of the segment.

**Histological Preparation**

All specimens were fixed in 10% buffered formalin. Epicardial coronary arteries were dissected off the heart and radiographed. Stented arteries were submitted for plastic embedding and serially cross sectioned at 2- to 3-mm intervals. In addition, proximal and distal nonstented coronary arteries were dehydrated and embedded in paraffin for further examination. All sections were stained with hematoxylin and eosin and Movat pentachrome as previously described.\(^{10,14}\)

**Pathological Assessment and Morphological Analysis**

The presence of acute thrombus was defined as a platelet-rich thrombus that occupied >30% of the cross-sectional area of the lumen; restenosis was defined as >75% cross-sectional area narrowing by neointimal formation.\(^{14}\) Cause of death was reported as stent related, non–stent-related cardiac, and noncardiac as previously defined.\(^{14}\) Briefly, stent-related death was determined after a complete autopsy, including examination of myocardium. The presence of a luminal thrombus with or without distal embolization was considered stent-related cardiac death. Non–stent-related cardiac death was defined as a patent DES without evidence of thrombus or restenosis in association with ≥1 nonstented major coronary arteries with severe cross-sectional area narrowing (>75%) or the presence of congestive heart failure and/or valvular heart disease.

Histological sections were evaluated for the identification of culprit sites (CSs) and non-CSs (NCSs). The CSs in patients with AMI were defined as the stented segments with presence of a necrotic core and a ruptured fibrous cap, whereas the CSs in patients with stable angina were selected as the sections with the longest underlying necrotic core and overlying thick fibrous cap (>100 μm). We compared CSs in AMI patients with CSs in patients with stable angina and NCSs within each stent (Figure 1).

Morphometric and histological analyses were performed with calibrated software (IPLab, Scanalytics, Inc, Rockville, Md) in patients who died >30 days after DES implantation. External elastic lamina, stent area, and necrotic core area were traced. Plaque area was calculated by the following formula: external elastic lamina area minus stent area. Fibrous cap thickness was measured at the thinnest portion of the fibroatheroma and at the remnant site of the ruptured plaque. The necrotic core arc also was recorded. Longitudinal necrotic core length and ruptured length were determined from the number of sections involved. Total stent length was determined from the radiographs. Neointimal thickness above the stent struts was defined as the mean thickness between the luminal surface of the strut and vessel lumen. The number of uncovered struts (defined as no coverage by any tissue except thrombus or fibrin/platelet complex) was recorded. The number of struts with fibrin deposition and the number of those surrounded by inflammation (defined as >10 inflammatory cells around a strut) were evaluated. The ratio of uncovered to total stent struts per section, percent struts with fibrin, and inflammation were calculated as previously described.\(^{14}\)

**Statistical Analysis**

Continuous variables with normal distribution were expressed as mean±SD. Discrete variables and continuous variables with nonnormal distribution were expressed as median and interquartile range (IQR). Comparison between AMI and stable patients (>30 days) was tested by Student’s t test for normally distributed continuous variables and Fisher’s exact test for categorical values. A Wilcoxon rank-sum test was used to compare nonnormally distributed parameters or discrete variables. Comparisons between CS and NCS within each stent were performed with paired t tests for normally distributed parameters (eg, percent struts with fibrin deposition) and Wilcoxon signed-rank test for nonnormally distributed parameters (eg, neointimal thickness, percent uncovered struts, and percent struts with inflammation). Normality of distribution was tested with the Wilk-Shapiro test. Spearman’s correlation was used to demonstrate the relationship between cap thickness and uncovered struts. A value of P<0.05 was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

![Figure 1](http://circ.ahajournals.org/) Illustration of comparisons performed in the present study. A, CS vs NCS in AMI lesions (ruptured plaque). B, CS vs NCS in non-AMI lesion (fibroatheroma with thick fibrous cap).
Results

Patient and Lesion Data

Eight of 25 patients with AMI and 8 of 26 patients with stable angina died within 30 days after DES implantation; the remaining 17 AMI and 18 stable angina patients died >30 days after implant.

In patients who died within 30 days after DES implantation, patient characteristics, stent duration, and length, type, and number of stents were similar between patients with AMI and those with stable angina (Table 1). Stent thrombosis was observed in 4 patients with AMI (50%) and 4 patients with stable angina (50%). Likely causes of stent thrombosis in patients with AMI were plaque (necrotic core) prolapse (4 of 4, 100%), whereas those in patients with stable angina were long stents (>30 mm) (2 of 4, 50%) and malapposition (2 of 4, 50%).

Of 4 patients with AMI <30 days with stent thrombosis, 1 died suddenly at 6 days after percutaneous coronary intervention, 2 had significant distal embolization, and 1 died of cardiogenic shock. The remaining 4 of 8 patients with AMI <30 days died of non–stent-related cardiac causes despite rescue percutaneous coronary intervention having been performed. The causes of death were cardiac rupture (n=3) and cardiogenic shock (n=1). Of 4 stable angina patients with stent thrombosis, 3 died suddenly, and 1 was admitted to the hospital but died despite rescue percutaneous coronary intervention. Non–stent-related cardiac death was documented in 1 patient (diffuse coronary artery disease) who died suddenly 2 days after percutaneous coronary intervention. The remaining 3 patients died of noncardiac causes (1 sepsis, 1 pulmonary embolism, and 1 gastrointestinal bleeding).

In patients with >30-day stent duration, patient characteristics (ie, age and gender), stent duration, and type of stent were similar between the AMI and stable angina groups (Table 2). Multivessel disease was common in both groups. The incidence of LST was significantly higher in patients with AMI (7 of 14, 41%) compared with those with stable angina (2 of 18, 11%; P=0.04; Table 2). Very LST (>1 year) was observed in 2 patients with AMI (12%) and in no patients with stable angina.

In both groups, all patients with LST died of a stent-related cardiac cause (patients with AMI: n=7, 3 presented with AMI and 4 died suddenly; patients with stable angina: n=2, 1 presented with AMI and 1 died suddenly). Non-stent-related cardiac death was documented in 5 patients with AMI (2 had diffuse coronary artery disease and 3 had severe congestive heart failure) and 12 patients with stable angina (8 died with diffuse coronary artery disease, 2 had severe congestive heart failure, and 2 had severe valvular heart disease). Noncardiac death was documented in 5 patients with AMI (2 suicides, 1 brain trauma, 1 chronic obstructive pulmonary disease, and 1 pulmonary embolism) and 4 patients with stable angina (2 trauma related, 1 pneumonia, 1 accidental death; Table 2).

Antiplatelet therapy status was known for 12 of 17 patients (71%) with AMI and for 9 of 18 patients (50%) with stable angina with >30-day stent implant duration (P=0.21). There was no significant difference in antiplatelet therapy between patients with AMI and those with stable angina (P=0.16). Dual antiplatelet therapy (aspirin and clopidogrel) was confirmed in 3 of 12 patients (25%) in the AMI >30-day group and 5 of 9 patients (56%) with stable angina. Six of 12 patients (50%) in the AMI >30-day group and 1 of 9 patients

| Table 1. Patient and Lesion Characteristics in Cases of AMI Versus Stable Angina (≤30 Days) |
|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|
| AMI Patients ≤30-Day Implant Duration (n=8)   | Stable Angina Patients ≤30-Day Implant Duration (n=8) | P    |
| Age, y                                         | 70±11                                          | 60±14           | 0.15            |
| Male gender, n (%)                             | 7 (88)                                         | 7 (88)          | >0.99           |
| Stent duration, d*                             | 6 (1–7)                                        | 6 (2–14)        | 0.40            |
| Diseased vessels, n*                           | 2 (2–3)                                        | 2.5 (1.75–3)    | 0.87            |
| Cypher/Taxus, n                                 | 2/6                                            | 3/5             | 0.59            |
| Stents, n*                                      | 1.5 (1–2)                                      | 1 (1–1.75)      | 0.32            |
| Stent length, mm*                              | 26.5 (20.0–33.8)                               | 22.0 (17.8–40.5) | 0.63           |
| Stent length >30 mm, n (%)                     | 2 (25)                                         | 2 (25)          | >0.99           |
| Thrombosis total, n (%)                        | 4 (50)                                         | 4 (50)          | >0.99           |
| Cause of death, n (%)                          | Stent related                                  | 4 (50)          | 4 (50)          | 0.09            |
|                                          | Not stent related cardiac                      | 4 (50)          | 1 (10)          |
|                                          | Noncardiac                                    | 0 (0)           | 3 (30)          |
| Antiplatelet therapy, n                        | Dual (aspirin and clopidogrel)                 | 4/5             | 2/5             | 0.20            |
|                                          | Single (aspirin or clopidogrel)                | 1/5             | 3/5             |
|                                          | None                                          | 0/5             | 0/5             |
|                                          | Unknown                                       | 3/8             | 3/8             | >0.99           |

*Expressed as median (IQR).
In the stable group were on either aspirin or clopidogrel monotherapy at the time of death. Three of 12 patients (25%) in the AMI/AMI/H11022 30-day group and 3 of 9 patients (33%) in the stable group were receiving no antiplatelet therapy at the time of death (Table 2).

**Underlying Plaque Morphological Characteristics in AMI Versus Stable Patients (CS >30 Days)**

External elastic lamina and plaque areas were significantly larger in underlying culprit lesions from patients with AMI compared with those with stable angina. Necrotic core area (mm²), necrotic core arc (degrees), longitudinal length (mm), and cross-sectional necrotic core area (%) were significantly greater in the CSs of patients with AMI compared with those with stable angina. The fibrous cap was significantly thinner at the CSs of patients with AMI compared with the CSs of patients with stable angina. Penetration of necrotic core was observed only at AMI CSs (Table 3). Histological examination of AMI CSs showed a larger necrotic core, consistent with previous reports in terms of percent necrotic core area.12 However, the average fibrous cap thickness was greater than previously reported (23±19 μm),16 likely related to the measurements being performed in the adjoining visible remnants of the fibrous cap. (At the site of rupture, the partially healed fibrous cap is often curled and therefore impossible to measure accurately.) The proximal and distal nonstented coronary artery sections in all cases failed to show any other plaque rupture within the same vessel in patients with AMI and those with stable angina.

**Pathological Assessment and Morphometric Analysis**

**CS in Patients With AMI Versus CS in Patients With Stable Angina**

Stents with >30-day implant duration were assessed by morphometric analysis. We compared the vascular response to stenting as measured by histological end points at the CSs in patients with AMI versus those with stable angina to evaluate the effect of plaque morphology on measures of inflammation and healing (Figure 1A and 1B). AMI CSs had significantly less neointimal thickness (median, 0.04 mm; IQR, 0.02 to 0.09 mm, P=0.008; uncovered struts: 9% [IQR, 0% to 39%], P=0.01; fibrin: 36±27%, P=0.008; inflammation: 17% [IQR, 7% to 25%], P=0.003; Table 4 and Figure 2).

**CS Versus NCS in Patients With AMI and Stable Angina**

In patients with AMI, neointimal thickness was significantly less at CSs compared with NCSs (CS: median, 0.04 mm; IQR, 0.07 to 0.21 mm, P=0.008; uncovered struts: 9% [IQR, 0% to 39%], P=0.01; fibrin: 36±27%, P=0.008; inflammation: 17% [IQR, 7% to 25%], P=0.003; Table 4 and Figure 1). Similarly, the percentage of uncovered struts, struts with inflammation, and struts with fibrin was signifi-

---

<table>
<thead>
<tr>
<th></th>
<th>AMI Patients &gt;30-Day Implant Duration (n=17)</th>
<th>Stable Angina Patients &gt;30-Day Implant Duration (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±15</td>
<td>57±11</td>
<td>0.80</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>14 (82)</td>
<td>16 (89)</td>
<td>0.33</td>
</tr>
<tr>
<td>Stent duration, d*</td>
<td>270 (65–465)</td>
<td>315 (113–570)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diseased vessels, n*</td>
<td>2 (2–3)</td>
<td>3 (1–3)</td>
<td>0.91</td>
</tr>
<tr>
<td>Cypher/Taxus, n</td>
<td>7/10</td>
<td>9/9</td>
<td>0.60</td>
</tr>
<tr>
<td>No. of stents*</td>
<td>1 (1–2)</td>
<td>1 (1–1.25)</td>
<td>0.46</td>
</tr>
<tr>
<td>Stent length, mm*</td>
<td>22.0 (20.0–44.0)</td>
<td>22.0 (15.3–32.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Stent length &gt;30 mm, n (%)</td>
<td>6 (35)</td>
<td>4 (22)</td>
<td>0.39</td>
</tr>
<tr>
<td>Thrombosis total, n (%)</td>
<td>7 (41)</td>
<td>2 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Very late thrombosis (&gt;1 y), n (%)</td>
<td>2 (12)</td>
<td>0 (0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Restenosis, n (%)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cause of death, n (%)</td>
<td>Stent-related</td>
<td>2 (11)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Not stent-related cardiac</td>
<td>5 (29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noncardiac</td>
<td>5 (29)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy, n</td>
<td>Dual (aspirin and clopidogrel)</td>
<td>5/9</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Single (aspirin or clopidogrel)</td>
<td>1/9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>3/12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>5/17</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Expressed as median (IQR).
Pathological Correlation of Uncovered Struts to the Thickness of Fibrous Cap

We explored whether there was a significant correlation between fibrous cap thickness and the presence of uncovered struts and found a significant negative correlation (i.e., the thinner the fibrous cap the more the presence of uncovered struts) \( r = -0.66, P = 0.0006 \); Figure 4). In addition, there was also a significant but weaker negative correlation between the duration of stent implantation and the presence of uncovered struts \( r = -0.39, P = 0.01 \). Similarly, fibrous cap thickness and neointimal thickness had a significant positive correlation \( r = 0.68, P = 0.0001 \), whereas a weaker correlation was observed between neointimal thickness and duration of implant \( r = 0.38, P = 0.03 \).

Discussion

Because the pivotal clinical trials that led to approval of Cypher and Taxus DES by the Food and Drug Administration excluded patients with AMI, the safety of DES for this indication remains uncertain.\(^1\)\(^,\)\(^2\) We initially reported that both sirolimus- and paclitaxel-eluting stents result in delayed arterial healing characterized by incomplete endothelialization and persistent fibrin deposition compared with BMS of similar implant duration and that this was the major pathological substrate underlying all cases of LST.\(^10\) In these cases, delayed arterial healing was consistently accompanied by additional pathological risk factors such as penetration of necrotic core, bifurcation/ostial lesion, or malposition. We hypothesized that each of these pathological or anatomic conditions might constitute additional barriers to healing. Our findings supported clinical studies demonstrating a higher incidence of LST\(^17\)\(^,\)\(^18\) for these so-called off-label uses.\(^19\)

Here, we extend our investigation to explore the effects of plaque characteristics on healing after DES implantation. Our comparative analysis suggests that culprit lesions from patients presenting with AMI respond differently to DES implantation than CSs from patients with stable angina and result in significantly delayed healing (compared with stable lesions or even NCSs within the same lesion). Our data support the contention that patients receiving DES for this indication may be at increased risk for LST as a result of excessively delayed healing at the CSs.

Plaque Morphology Influences Local Healing Characteristics After DES Placement

Because plaque rupture is the most frequent cause of AMI (accounting for >75% of acute coronary thrombi),\(^1\)\(^2\) strut...
penetration of necrotic core is frequently found at these sites. In patients who died ≤30 days after DES implantation, the incidence of stent thrombosis was similar between patients with AMI and those with stable angina. All early stent thromboses in patients with AMI were associated with plaque prolapse. However, in patients with stents implanted >30 days, the CSs of patients presenting with AMI had less neointimal growth and greater inflammation, fibrin deposition, and uncovered struts compared with NCSs within the same stent. Moreover, the CSs in these patients showed greater delayed arterial healing with evidence of persistent fibrin deposition and incomplete stent strut coverage compared with patients presenting with stable angina and having underlying fibroatheromatous plaques. Given these results, our data demonstrating the higher prevalence of LST in patients with AMI versus those with stable angina are not surprising.

These findings reinforce our previous report demonstrating heterogeneity of healing within the same stent. Although other factors may affect the rate of healing after DES implantation, the underlying plaque morphology is the most reasonable explanation for our findings of delayed healing at the CS of ruptured plaque as opposed to NCSs and CSs from stable patients. Although it is not known how plaque morphology affects healing, there are several likely possibilities. Because sirolimus and paclitaxel are highly lipophilic, it is likely that these agents have high affinity for lipid-rich plaques (ie, necrotic core) and dwell there for longer periods of time because of greater strut penetration compared with when struts are exposed to more fibrotic types of plaque. In addition, the lipid-rich necrotic cores are more avascular compared with the more fibrous dominant regions of plaques and have fewer cells. Therefore, these areas are less likely to be covered by migrating and proliferating cells from adjacent areas. Ruptured fibrous caps are either devoid of smooth muscle cells or thinly populated with smooth muscle cells.

penetration of necrotic core is frequently found at these sites. In patients who died ≤30 days after DES implantation, the incidence of stent thrombosis was similar between patients with AMI and those with stable angina. All early stent thromboses in patients with AMI were associated with plaque prolapse. However, in patients with stents implanted >30 days, the CSs of patients presenting with AMI had less neointimal growth and greater inflammation, fibrin deposition, and uncovered struts compared with NCSs within the same stent. Moreover, the CSs in these patients showed greater delayed arterial healing with evidence of persistent fibrin deposition and incomplete stent strut coverage compared with patients presenting with stable angina and having underlying fibroatheromatous plaques. Given these results, our data demonstrating the higher prevalence of LST in patients with AMI versus those with stable angina are not surprising.

These findings reinforce our previous report demonstrating heterogeneity of healing within the same stent. Although other factors may affect the rate of healing after DES implantation, the underlying plaque morphology is the most reasonable explanation for our findings of delayed healing at the CS of ruptured plaque as opposed to NCSs and CSs from stable patients. Although it is not known how plaque morphology affects healing, there are several likely possibilities. Because sirolimus and paclitaxel are highly lipophilic, it is likely that these agents have high affinity for lipid-rich plaques (ie, necrotic core) and dwell there for longer periods of time because of greater strut penetration compared with when struts are exposed to more fibrotic types of plaque. In addition, the lipid-rich necrotic cores are more avascular compared with the more fibrous dominant regions of plaques and have fewer cells. Therefore, these areas are less likely to be covered by migrating and proliferating cells from adjacent areas. Ruptured fibrous caps are either devoid of smooth muscle cells or thinly populated with smooth muscle cells.

penetration of necrotic core is frequently found at these sites. In patients who died ≤30 days after DES implantation, the incidence of stent thrombosis was similar between patients with AMI and those with stable angina. All early stent thromboses in patients with AMI were associated with plaque prolapse. However, in patients with stents implanted >30 days, the CSs of patients presenting with AMI had less neointimal growth and greater inflammation, fibrin deposition, and uncovered struts compared with NCSs within the same stent. Moreover, the CSs in these patients showed greater delayed arterial healing with evidence of persistent fibrin deposition and incomplete stent strut coverage compared with patients presenting with stable angina and having underlying fibroatheromatous plaques. Given these results, our data demonstrating the higher prevalence of LST in patients with AMI versus those with stable angina are not surprising.

These findings reinforce our previous report demonstrating heterogeneity of healing within the same stent. Although other factors may affect the rate of healing after DES implantation, the underlying plaque morphology is the most reasonable explanation for our findings of delayed healing at the CS of ruptured plaque as opposed to NCSs and CSs from stable patients. Although it is not known how plaque morphology affects healing, there are several likely possibilities. Because sirolimus and paclitaxel are highly lipophilic, it is likely that these agents have high affinity for lipid-rich plaques (ie, necrotic core) and dwell there for longer periods of time because of greater strut penetration compared with when struts are exposed to more fibrotic types of plaque. In addition, the lipid-rich necrotic cores are more avascular compared with the more fibrous dominant regions of plaques and have fewer cells. Therefore, these areas are less likely to be covered by migrating and proliferating cells from adjacent areas. Ruptured fibrous caps are either devoid of smooth muscle cells or thinly populated with smooth muscle cells.

penetration of necrotic core is frequently found at these sites. In patients who died ≤30 days after DES implantation, the incidence of stent thrombosis was similar between patients with AMI and those with stable angina. All early stent thromboses in patients with AMI were associated with plaque prolapse. However, in patients with stents implanted >30 days, the CSs of patients presenting with AMI had less neointimal growth and greater inflammation, fibrin deposition, and uncovered struts compared with NCSs within the same stent. Moreover, the CSs in these patients showed greater delayed arterial healing with evidence of persistent fibrin deposition and incomplete stent strut coverage compared with patients presenting with stable angina and having underlying fibroatheromatous plaques. Given these results, our data demonstrating the higher prevalence of LST in patients with AMI versus those with stable angina are not surprising.

These findings reinforce our previous report demonstrating heterogeneity of healing within the same stent. Although other factors may affect the rate of healing after DES implantation, the underlying plaque morphology is the most reasonable explanation for our findings of delayed healing at the CS of ruptured plaque as opposed to NCSs and CSs from stable patients. Although it is not known how plaque morphology affects healing, there are several likely possibilities. Because sirolimus and paclitaxel are highly lipophilic, it is likely that these agents have high affinity for lipid-rich plaques (ie, necrotic core) and dwell there for longer periods of time because of greater strut penetration compared with when struts are exposed to more fibrotic types of plaque. In addition, the lipid-rich necrotic cores are more avascular compared with the more fibrous dominant regions of plaques and have fewer cells. Therefore, these areas are less likely to be covered by migrating and proliferating cells from adjacent areas. Ruptured fibrous caps are either devoid of smooth muscle cells or thinly populated with smooth muscle cells.

penetration of necrotic core is frequently found at these sites. In patients who died ≤30 days after DES implantation, the incidence of stent thrombosis was similar between patients with AMI and those with stable angina. All early stent thromboses in patients with AMI were associated with plaque prolapse. However, in patients with stents implanted >30 days, the CSs of patients presenting with AMI had less neointimal growth and greater inflammation, fibrin deposition, and uncovered struts compared with NCSs within the same stent. Moreover, the CSs in these patients showed greater delayed arterial healing with evidence of persistent fibrin deposition and incomplete stent strut coverage compared with patients presenting with stable angina and having underlying fibroatheromatous plaques. Given these results, our data demonstrating the higher prevalence of LST in patients with AMI versus those with stable angina are not surprising.

These findings reinforce our previous report demonstrating heterogeneity of healing within the same stent. Although other factors may affect the rate of healing after DES implantation, the underlying plaque morphology is the most reasonable explanation for our findings of delayed healing at the CS of ruptured plaque as opposed to NCSs and CSs from stable patients. Although it is not known how plaque morphology affects healing, there are several likely possibilities. Because sirolimus and paclitaxel are highly lipophilic, it is likely that these agents have high affinity for lipid-rich plaques (ie, necrotic core) and dwell there for longer periods of time because of greater strut penetration compared with when struts are exposed to more fibrotic types of plaque. In addition, the lipid-rich necrotic cores are more avascular compared with the more fibrous dominant regions of plaques and have fewer cells. Therefore, these areas are less likely to be covered by migrating and proliferating cells from adjacent areas. Ruptured fibrous caps are either devoid of smooth muscle cells or thinly populated with smooth muscle cells.
Higher drug concentrations in these areas may also heavily influence healing by retarding smooth muscle cell proliferation and endothelial regrowth. Thrombus burden also may play a role by increasing drug uptake by the thrombus as shown by Hwang et al.13 with paclitaxel-eluting stents.

**BMS and LST**

LST is not just limited to DES but also has been reported after the use of BMS. We previously reported 13 cases of LST after BMS implantation.22 The underlying mechanisms of LST identified in that study were bifurcation stenting (n=5), radiation therapy (n=3), plaque disruption in an adjoining nonstented artery (n=2), restenosis (n=1), and lipid core prolapse after stenting (n=2). Among 132 patients with BMS, LST incidence at autopsy was 9.8%, a much lower rate of thrombosis compared with our DES cases (ie, 50%).14 Similarly, the median time to thrombosis in BMS was 70 days (IQR, 33 to 127 days), which was a much shorter period than that reported in the present and previously published studies of DES, consistent with the prolonged duration of healing with DES compared with BMS.10,14

In a recent clinical retrospective study of LST after BMS implantation in 4503 patients, the cumulative incidence of stent thrombosis was 0.5% at 30 days, 0.8% at 1 year, and 2.0% at 10 years.23 In addition, if saphenous vein graft interventions were excluded, the incidence of LST in off-label BMS use was no different, consistent with the protracted healing with DES compared with BMS.10,14

**Clinical Implication**

The present study demonstrates that DES use for patients presenting for coronary intervention with AMI is associated with delayed arterial healing specifically at the CS compared with patients with stable angina. Because healing is delayed for long periods of time (ie, >1 year), the safety of using DES for AMI cannot be determined by relatively short-term clinical studies when patients are on a prolonged antiplatelet regimen. Our data suggest that the use of DES for this indication may result in a higher frequency of stent thrombosis than when patients receive DES for “stable” indications, especially if the latter do not involve additional barriers to healing such as bifurcations or long stents.

Although randomized long-term data from patients receiving DES versus BMS for AMI are lacking,3,4 some data from retrospective studies and registries support this conclusion. Recently, Kastrati et al24 published a meta-analysis of 8 randomized trials comparing DES with BMS in 2786 ST-elevation myocardial infarction patients. During the limited follow-up of 1 to 2 years, no differences in stent thrombosis, myocardial infarction, or death occurred. However, it must also be noted that outcomes were generally good, with death occurring in just 4.6% of patients and reinfarction in 3.5%, raising the issue of how applicable these results are to a broad ST-elevation myocardial infarction population. Although several registries of DES for AMI have enrolled higher-risk patients, registry data are imperfect, are subject to selection bias, and demonstrated inconsistent outcomes regarding this subject. Recently, Mauri et al25 presented data from the Massachusetts Registry evaluating 8000 patients with AMI treated with DES or BMS. DES patients demonstrated a 2.7% reduction in risk-adjusted mortality compared with patients treated with BMS at the 2-year follow-up. However, Sianos et al26 published a retrospective study of the effectiveness of DES for ST-elevation myocardial infarction and demonstrated a 2-year angiographic rate of stent thrombosis of 3.2% that increased to 8.2% in those with large thrombus burden. More recently, Steg et al27 reported results from a registry of DES versus BMS for ST-elevation myocardial infarction showing a significantly higher rate of death between 180 and 730 days after stent placement for DES versus BMS (hazard ratio, 6.7; P=0.002), whereas there was no increased risk in patients treated for non-AMI. Undoubtedly, only prospective studies with much longer follow-up are necessary before we can say definitively whether DES are associated with improved long-term clinical outcome in patients with AMI. Until that time, routine DES implantation for AMI cannot be recommended.

**Conclusions**

In pathological series of patients who died after DES implantation, a higher prevalence of LST was observed in AMI than in stable patients. CSs in AMI are associated with substantial delay in healing compared with NCSs and CSs from stable patients, emphasizing the effects of the underlying plaque morphology as an important substrate for healing after DES placement. Although the safety of this practice is uncertain, our data suggest a significantly increased risk of late thrombotic complications that should be expected in patients treated with DES for AMI.

**References**


Delayed Arterial Healing and Increased Late Stent Thrombosis at Culprit Sites After Drug-Eluting Stent Placement for Acute Myocardial Infarction Patients: An Autopsy Study

Gaku Nakazawa, Aloeke V. Finn, Michael Joner, Elena Ladich, Robert Kutys, Erik K. Mont, Herman K. Gold, Allen P. Burke, Frank D. Kolodgie and Renu Virmani

_Circulation_. 2008;118:1138-1145; originally published online August 25, 2008; doi: 10.1161/CIRCULATIONAHA.107.762047

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/11/1138