Pathological Correlates of Late Drug-Eluting Stent Thrombosis
Strut Coverage as a Marker of Endothelialization

Aloke V. Finn, MD*; Michael Joner, MD*; Gaku Nakazawa, MD; Frank Kolodgie, PhD; John Newell, AB; Mike C. John, MPH; Herman K. Gold, MD; Renu Virmani, MD

Background—Late stent thrombosis (LST) after Cypher and Taxus drug-eluting stent placement has emerged as a major concern. Although the clinical predictors of LST have been reported, specific morphological and histological correlates of LST remain unknown.

Methods and Results—From a registry totaling 81 human autopsies of drug-eluting stents, 46 (62 lesions) had a drug-eluting stent implanted >30 days. We identified 28 lesions with thrombus and compared those with 34 of similar duration without thrombosis using computer-guided morphometric and histological analyses. LST was defined as an acute thrombus within a coronary artery stent in place >30 days. Multiple logistic generalized estimating equations modeling demonstrated that endothelialization was the best predictor of thrombosis. The morphometric parameter that best correlated with endothelialization was the ratio of uncovered to total stent struts per section. A univariable logistic generalized estimating equations model of occurrence of thrombus in a stent section versus ratio of uncovered to total stent struts per section demonstrated a marked increase in risk for LST as the number of uncovered struts increased. The odds ratio for thrombus in a stent with a ratio of uncovered to total stent struts per section >30% is 9.0 (95% CI, 3.5 to 22).

Conclusions—The most powerful histological predictor of stent thrombosis was endothelial coverage. The best morphometric predictor of LST was the ratio of uncovered to total stent struts. Heterogeneity of healing is a common finding in drug-eluting stents with evidence of LST and demonstrates the importance of incomplete healing of the stented segment in the pathophysiology of LST. (Circulation. 2007;115:2435-2441.)

Key Words: complications • stents • thrombus • pathology • endothelium

Polymer-based sirolimus- (Cypher) and paclitaxel-eluting (Taxus) drug-eluting stents (DES) have become the treatment of choice for patients with symptomatic coronary artery disease undergoing percutaneous coronary revascularization. Although these stents have reduced rates of restenosis and late lumen loss compared with bare metal stents, late thrombosis, a life-threatening complication of this technology, has emerged as a major concern.1,2 Although its incidence remains low, the sheer number of DES implanted worldwide, combined with the often dire consequences of late thrombotic events, makes this a significant public health issue. We have previously demonstrated in pathological specimens from patients dying of late DES thrombosis that delayed arterial healing characterized by incomplete reendothelialization and persistence of fibrin is an important underlying substrate.3–6 Although clinical predictors such as withdrawal of antiplatelet therapy are known to play a role in determining the probability of late stent thrombosis (LST), the specific morphometric and histological parameters that significantly correlate with late thrombosis remain unknown.1,2,7

Using our database of all patients dying ≥30 days after Cypher or Taxus DES implantation, this study sought to determine the most powerful pathological risk factors for late thrombosis and to identify the high-risk features of DES that might be clinically evaluable.

Methods
From a registry totaling 81 human autopsies of Cypher and Taxus DES, all cases with evidence of ≥1 DES in place ≥30 days were examined (46 cases in total, 23 of which have been previously reported3–6). In cases of multiple stent deployment, overlapping and consecutively implanted DES were treated as 1 lesion, whereas DES

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including a gap of >5 mm were treated as separate lesions. The length of each stent was recorded and expressed as total treated length in case of overlapping stent deployment. Clinical histories and cardiac catheterization reports were reviewed when available. DES-related death was determined after a complete autopsy, including examination of the myocardium. The presence of an occlusive luminal thrombus or nonocclusive thrombus with distal embolization was considered stent-related cardiac death. None of the other major coronary arteries had evidence of severe stenosis or luminal thrombus.

Non–stent-related cardiac death was defined as a patent DES without evidence of thrombus or restenosis (luminal stenosis <75% cross sectional area) in association with ≥1 nonstented major coronary artery segments with evidence of severe narrowing (>75% cross-sectional area stenosis).

Stented arteries were fixed in 10% buffered formalin, dissected off the heart, radiographed, and submitted for plastic embedding. Arteries were serially sectioned 2 to 3 mm apart and stained with hematoxylin and eosin and Movat pentachrome as previously described.8 Movat pentachrome stains nuclei black, elastic fascicles dark purple to black, collagen and reticulum fibers yellow, proteoglycans blue to bluish green, fibrin red, and smooth muscle cells red. Immunohistochemistry for identification of endothelial cells was performed in randomly selected cases using a CD31/CD34 antibody cocktail. (This approach has recently been shown to be superior in labeling endothelial cells compared with the conventional method of using a single monoclonal antibody to CD31.)9 Resin sections (8 μm) were deplastized in warm xylenes, 2-methoxyethyl acetate, and acetone, followed by incubation in a graded series of alcohols to deionized water. Antigen retrieval was performed using steam heat with the sections in EDTA buffer (pH 8.0). The slides were then placed in 3.0% H2O2 for 20 minutes, followed by immunostaining using a cocktail of endothelial markers CD31 (dilution, 1:100; Dako, Carpinteria, Calif) and CD34 (dilution, 1:4000; MONOSAN, Uden, the Netherlands) diluted in PBS (pH 7.5) at 4°C overnight. The primary antibodies were labeled with an LSAB kit (Dako); positive staining was visualized by a 3-amino-9-ethylcarbazole substrate-chromogen system, and the sections were counterstained with Gill’s hematoxylin.

Stent thrombosis was defined as occlusive or nonocclusive thrombus, with the thrombus being composed predominantly of platelets. A nonocclusive thrombus was defined as a platelet-rich thrombus that occupied >30% of the cross-sectional area of the lumen. The requirement for a platelet component to the thrombus differentiates stent thrombosis from fibrin deposition, which is uniformly observed that occupied a nonocclusive thrombus was defined as a platelet-rich thrombus, with the thrombus being composed predominantly of platelets. Hematoxylin.

IPLab software (IPLab Spectrum software, Scanalytics Inc, Vienna, VA) on sections from stents implanted >30 days. Digital images were captured (×20 magnification), and area and thickness measurements, including the external elastic lamina area, plaque burden area, stent area, lumen area, and neointimal thickness above each strut, were determined. For comparison of DES with and without mural thrombi, the percentage of fibrin surrounding strut struts and surface endothelialization was assessed on hematoxylin and eosin– and Movat pentachrome–stained sections at a magnification of ×200 to overcome bias in measurements. This was further confirmed in selected cases to be endothelial by immunohistochemical staining. The number of stent struts without neointimal coverage and/or surface endothelium was counted for each consecutive section, and the total number of sections, including uncovered stent struts, was recorded. The cumulative stent length lacking neointimal coverage was calculated with the following formula: stent length divided by the number of sections times the sum of uncovered sections per stent. Neointimal thickness distribution in cases with and without LST was plotted as histograms and analyzed for heterogeneity of variance.

To further examine the relationship between uncovered stent struts and/or luminal fibrin thrombosis (over a strut lacking neointima) to luminal platelet-rich thrombus, the number of such struts with luminal thrombus was plotted against total number of uncovered and/or struts with mural fibrin.

To evaluate the relationship between cross-sectional strut distribution and the risk for LST, the number of stent struts per section was counted, and the distances between individual stent struts were digitally measured.

To identify the exact location of sites at risk for stent thrombosis, consecutively cut sections were separated into proximal, middle, and distal segments of the stented arteries and analyzed for the presence of uncovered stent struts and platelet-rich thrombi.

**Statistical Analysis**

Continuous variables are expressed as mean ± SD. Nonnormally distributed variables were either log transformed to normal or compared between groups with the Wilcoxon rank-sum test. Normality of distribution was tested with the Wilk-Shapiro test. A value of P < 0.05 was considered statistically significant. Differences between patients with and without thrombosed lesions were tested by Fisher’s exact test.

Both neointimal thickness and duration of stent implantation were log transformed to normalize the distributions of these variables and to stabilize their variances, as confirmed by the Wilk-Shapiro test and the Levene robust test for variances, respectively. Subsequently, the logarithmic form of these variables was entered into parametric tests.

Multiple logistic generalized estimating equations (GEE) modeling was performed on all morphometric and histological parameters as independent variables versus presence of thrombus as the binary dependent variable using the STATA xtgee program (STATA Corp, College Station, Tex) with an assumed binomial family distribution, a logistic link function, and an exchangeable structure in the correlation matrix. GEE was necessary because of the clustered nature of >1 individual lesion measured from some patients—resulting in unknown correlations among measurements within these lesion clusters. An optimum cut point in the variable ratio of uncovered to total struts per section (RUTSS) was derived by receiver-operating characteristic curve analysis, selecting a cut point that produced approximately equal sensitivity and specificity of the observed resulting classifications with respect to thrombus.

Multiple linear GEE estimation was used to find the best morphometric correlates of stent endothelialization as the dependent variable using xtgee with an assumed gaussian family distribution, an identity link function, and an assumed exchangeable structure for the within cluster correlation matrix. This linear model of endothelialization was important because endothelialization generally is not directly accessible to in vivo measurement, whereas other morphometric variables potentially are accessible in vivo. The result of this linear model was used to select the best morphometric explanatory variable for use in the logistic model of stent thrombus formation. The GEE approach to linear regression was required for the same reason as the logistic model of lesion thrombus. All analyses were performed with STATA statistics software (release 9).

All 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.

**Results**

**Lesion Characteristics**

Within these 81 cases (109 lesions), 62 lesions (46 patients) had DES implanted >30 days and were included in the DES study group. We identified 28 lesions (23 patients) with thrombus formation and compared those with 34 lesions (23 patients) of similar duration without evidence of in-stent thrombosis (254 ± 235 days for lesions with LST versus 244 ± 289 days for those without; P = NS). In cases with mural thrombus formation, 13 occlusive and 15 nonocclusive thrombi were detected. In these lesions with thrombus for-
patients (6%) with LST and 1 of 14 patients (7%) with patent DES were on clopidogrel monotherapy; and 2 of 18 patients (11%) in the LST group and 6 of 14 patients (43%) in the patent DES group were not on antiplatelet therapy at the time of death. None of the differences shown in Table 1 were statistically significant by Fisher exact test.

Indications for stent implantation were stable angina in 13 patients with LST and in 19 patients with patent DES. Acute coronary syndromes were the indication in 10 patients with LST and in 4 patients with patent DES.

A cardiac cause of death was documented in 20 patients with LST (10 sudden cardiac deaths, 10 acute myocardial infarctions), and all cardiac deaths were considered stent related. In the LST group, 3 patients died of noncardiac causes. Two suffered cerebrovascular accidents, which were the cause of death, and 1 received a heart transplant for end-stage ischemic heart disease. In 15 patients with patent DES, 2 patients died suddenly and were found to have severe in-stent restenosis. The other 13 died of sudden cardiac death with evidence of severe narrowing (ie, >75% cross-sectional area stenosis) of at least 1 major nonstented coronary artery segment. Eight patients with patent DES were diagnosed as having noncardiac deaths (pneumonia, 1; stroke, 2; trauma, 1; pulmonary embolism, 2; gastrointestinal bleeding, 2).

Morphometric and Histological Comparisons of Thrombosed and Patent DES Lesions

The external elastic lamina, plaque area, and stent area were significantly greater in lesions with mural thrombus compared with patent DES lesions (Table 2). Neointimal thickness was greater in patent DES lesions, whereas the percentage of endothelialization was significantly greater in patent DES lesions. Fibrin score was significantly greater in DES lesions with thrombus. We compared the neointimal thickness in thrombosed and patent DES lesions and found a marked shift toward less neointimal growth in DES with mural thrombus formation.

### TABLE 2. Comparison of Morphometric and Characteristics Between Lesions With and Without DES LST

<table>
<thead>
<tr>
<th></th>
<th>DES Lesions With Thrombus (n=28)</th>
<th>DES Lesions Without Thrombus (n=34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, d</td>
<td>173 (66, 433)</td>
<td>127 (31, 400)</td>
<td>NS</td>
</tr>
<tr>
<td>External elastic lamina area, mm²</td>
<td>17.2±4.6</td>
<td>13.2±5.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Stent area, mm²</td>
<td>7.5±2.0</td>
<td>6.7±3.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Plaque area, mm²</td>
<td>9.7±3.9</td>
<td>6.5±3.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Neointimal thickness, mm</td>
<td>0.074 (0.033, 0.129)</td>
<td>0.11 (0.071, 0.19)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Fibrin score</td>
<td>2.4±1.3</td>
<td>1.2±1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Endothelialization, %</td>
<td>40.5±29.8</td>
<td>80.0±25.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uncovered struts/section, n</td>
<td>5.0±2.7</td>
<td>2.0±2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stent length without neointima, mm</td>
<td>20.1±11.5</td>
<td>9.9±10.1</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mean inter strut distance, mm</td>
<td>0.52±0.24</td>
<td>0.70±0.25</td>
<td>0.004</td>
</tr>
<tr>
<td>Uncovered struts/total struts per section</td>
<td>0.50±0.23</td>
<td>0.19±0.25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD or median (IQR), as appropriate. IQR indicates interquartile range for nonnormal variables.

*By t test on normal logarithm of values.
Average total stent length was 25.9±11.5 in thrombosed stents versus 20.3±9.6 mm in nonthrombosed stents (P=0.04). We examined whether the cumulative stent length without neointimal coverage also was different in lesions with DES thrombosis versus those without thrombus. Patent DES had an average stent length without neointimal coverage of 9.9±10.1 versus 20.1±11.5 mm for lesions with thrombus (P<0.0004). The mean number of stent struts per section without neointimal coverage (ie, number of uncovered struts per section) also was significantly greater in DES lesions with thrombosis compared with those without thrombosis (Table 2).

Moreover, the average distance between individual stent struts was significantly shorter in DES lesions with mural thrombus formation compared with patent DES lesions (Table 2). There also was a good correlation between the mean number of uncovered struts per section and the average distance between stent struts (r=−0.41, P=0.001), with most uncovered stent struts showing less internistrut distance than covered stent struts.

Next, we explored the interrelationship of stent struts lacking neointimal coverage and the number of struts surrounded by platelet-rich thrombi and found a significant correlation between these parameters (r=0.43, P<0.001). On further examination, we found heterogeneity of coverage of stent struts, both within individual cross sections and between sections from the same stent. Within the same DES, although some struts show healing as demonstrated by neointimal growth, others remain bare and serve as a nidus for mural thrombus formation (Figure 1). Within a DES, the middle section of the stent (versus the proximal and distal ends) was the most common location of stent struts lacking neointimal coverage and was the most common site of thrombus formation (Figure 2).

Pathological Correlates of LST in Lesions
Among the morphological and histological parameters listed in Table 2, multivariable GEE logistic modeling demonstrated that endothelialization was the best classifier of thrombosis. The 2 complete patient variables included as candidate predictors of thrombus in this model of lesions were age and gender. In addition, the use of bifurcation stenting per lesion was included as a candidate predictor, along with all the morphometric measurements.

Multiple linear GEE analysis was performed to find significant correlations between endothelialization and various morphometric parameters. Significant joint explanatory variables detected by the multiple linear analysis were the following: RUTSS, uncovered struts per section, stent length, total length without neointima, and log (neointimal thickness). Of these, the RUTSS was the single most significant correlate of endothelialization (Z=−13; P<0.00005).

Because the most powerful morphometric predictor of endothelialization was the RUTSS, we used univariable GEE logistic regression to analyze the probability of thrombus as classified by this ratio. The odds ratio estimated for LST in lesions having an RUTSS >30% is 9.0 (95% CI, 3.5 to 22.0). This cut point was determined by estimating classifications of thrombus versus patent DES via use of the RUTSS variable in a receiver-operating characteristic curve analysis and balancing sensitivity and specificity at 75% and 76%, respectively. To generate the RUTSS, we examined an average of 5.3±2.7 sections per stent.

Discussion
Although clinical predictors of late DES thrombosis have been identified, the specific morphometric and histological parameters that best correlate with risk for this event remain unknown. Using human pathological data, we have shown for the current generation of polymeric DES that endothelialization is the best classifier of LST. Of the various morphometric parameters we examined, multiple linear GEE analysis demonstrated that the RUTSS best correlated with endothelialization. Within the same DES, although some struts show healing as demonstrated by neointimal growth, others remain bare and serve as a nidus for mural thrombus formation. A univariable logistic GEE model of occurrence of thrombus in a stent section versus RUTSS shows that there is a considerable elevation of risk of thrombus as the RUTSS increases.

Mechanisms of Heterogeneity of Stent Strut Coverage
Our data demonstrate that nonuniform healing with DES (as indicated by the number of uncovered struts per cross section) greatly increased thrombotic risk. Previous pathological studies have shown an association between lack of neointimal stent coverage and thrombus formation. Although the mechanisms by which the current-generation DES induce nonuniform incomplete healing are not fully understood, lesion characteristics; drug properties, dose, and distribution; and polymer biocompatibility together play important roles. Underlying plaque morphology may affect the rate of healing when stent struts penetrate deeply into a necrotic core and are not in contact with cellular areas. Eccentric plaques may prevent uniform strut deployment, thereby increasing local toxicity resulting from higher concentrations of drug and polymer. Indeed, sections with evidence of thrombosis showed significantly lower internustrut distances, which correlated with less neointimal growth. Local concentrations of drug are ultimately highly spacing dependent, and the variance in distance between struts will amplify differences in concentrations, leading to biological effects. Heterogeneity in loaded dose of drug varies from strut to strut, and greater retention of lipophilic drugs in different regions of plaque affects arterial drug concentration and results in nonuniform healing. The relationship between local drug concentration and cellular repair is underscored by data from overlapping versus nonoverlapping Cypher and Taxus stents in the rabbit iliac model.

It also has been reported in a small number of patients that the nonabsorbable polymers in Cypher and Taxus provoke chronic eosinophilic infiltration of the arterial wall, suggesting hypersensitivity reactions in a small number of cases. To what extent polymer-induced inflammation also plays a role in retarding healing is unknown, but in some cases, it clearly is causal in inducing thrombosis.

Restenosis Versus Thrombosis
The severe decrease in late loss and neointimal formation generated by the current-generation Food and Drug Admin-
Figure 1. A and B, Heterogeneity of neointimal healing after DES placement. A 34-year-old woman underwent placement of 1 Cypher (22 × 3 mm) stent in the proximal left circumflex artery for acute myocardial infarction 2 years antemortem. The patient was admitted to the emergency room with ST-elevation myocardial infarction and subsequently died. Consecutive sections of Cypher DES were cut 3 mm apart and stained with Movat pentachrome (A), and neointimal thickness (above each strut) and number of uncovered stent struts were measured (B). There is greater neointimal growth above each strut (x) and fewer uncovered stent struts (red circle) within the proximal and distal stented portions, with an absence of luminal thrombus formation. At the site of thrombus formation (sections 5 and 6), neointimal thickness is minimal, and the number of uncovered stent struts is maximal. C, Movat pentachrome–stained sections 5 and 7 show detailed histology. There is a platelet-rich thrombus surrounding stent struts lacking neointima in section 5. High-power images (I, II) show uncovered stent struts with extensive underlying fibrin deposition (gray arrowhead), luminal platelet-rich thrombus (Thr), and lack of endothelialization (II; black arrowhead) after immunostaining for CD31/CD34. However, positive staining (brown) is observed within medial microvessels containing CD31/CD34-positive endothelial cells (white arrowhead). In contrast, there is a well-healed neointima with complete strut coverage in section 7. High-power images (III, IV) show stent struts embedded into neointima composed of smooth muscle cells and proteoglycans; there is an absence of luminal thrombus, and endothelial cells are abundant above stent struts (IV, white arrowhead) with positive staining (brown).
istration–approved DES may not be required to produce major reductions in restenosis and the need for target lesion revascularization. Ellis et al\textsuperscript{16} demonstrated that the relationship between late loss and target lesion revascularization is curvilinear, with a late loss of 0 to 0.75 mm residing on a relatively flat portion of the curve for revascularization and larger degrees of late loss on a much steeper part of the curve. Reductions in in-stent late loss $<$0.75 mm only incrementally lower the risk of target lesion revascularization. The Taxus stent had a reported late loss of more than double that of the Cypher stent (0.39 versus 0.17 mm), but rates of revascularization do not differ significantly in their respective pivotal trials.\textsuperscript{17,18}

Our data raise the possibility that a more liberal approach to reductions in late loss and suppression of neointimal growth may be able to reduce the risk of thrombosis by encouraging a higher percentage of strut-related neointimal coverage without significantly increasing target lesion revascularization. However, this hypothesis requires validation in prospective randomized clinical trials.

### Evaluation of DES in Clinical Trials

Among the morphometric parameters examined, the RUTSS rather than the average volume of neointimal growth most powerfully estimates risk for LST because it is an excellent surrogate indicator of endothelialization and therefore a marker of delayed healing. This has important implications for predicting the thrombotic risk of DES in clinical trials. Uneven coverage of stent struts by neointima cannot be determined by calculating late loss from follow-up angiography. Other modalities are needed to determine strut distribution and the number of uncovered struts over the entire stent length at follow-up.

On the basis of our analysis, there is a continuum of risk for individuals that increases with the RUTSS per cross section. Our univariable logistic GEE model of occurrence of thrombus in a stent section versus RUTSS shows that in a stent with 30% uncovered struts, the odds ratio for thrombus is 9.0 (95% CI, 3.5 to 22.0) compared with a stent with complete coverage.

### Study Limitations

Because this is an autopsy study, the results may not be representative of all patients who receive Cypher and Taxus DES for approved indications and survive. Moreover, the small number of patients in this autopsy study and the fact that we could not obtain complete clinical data on all subjects did not allow us to explore the relative contribution of previously reported clinical risk factors for DES LST (such as clopidogrel withdrawal) to the pathological risk factors identified in our study. Moreover, although our data demonstrate a strong correlation between lack of coverage of stent struts and LST, validating the predictive value of this correlation requires testing in larger prospective clinical trials.

### Conclusion

The underlying pathology in cases of LST indicates incomplete neointimal coverage of stent struts as the most important morphometric predictor of LST because it is the most powerful surrogate indicator of endothelialization. Both plaque- and device-related issues likely play a role in promoting uneven healing.

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### Disclosures

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### References


CLINICAL PERSPECTIVE

Late stent thrombosis after Cypher and Taxus drug-eluting stent placement has emerged as a major concern. Although the clinical predictors of late stent thrombosis have been reported, its specific morphological and histological correlates remain unknown. Using human pathological data from autopsy patients in whom death occurred >30 days after drug-eluting stent placement, multiple logistic generalised estimating equations analysis demonstrated that endothelialization of the stent was the best predictor of thrombosis. The morphometric parameter that best correlated with endothelialization was the ratio of uncovered to total stent struts per section; the risk of thrombosis increases in parallel with the ratio of uncovered to total stent struts per section. Heterogeneity of healing is a common finding in cases of late drug-eluting stent thrombosis, and thrombus associated with uncovered struts seems to occur with greater frequency in the middle portion of the stent compared with the proximal and distal segments.
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