A Volumetric Intravascular Ultrasound Comparison of Early Drug-Eluting Stent Thrombosis Versus Restenosis

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Objectives We compared intravascular ultrasound findings of drug-eluting stent (DES)-treated lesions that developed thrombosis versus in-stent restenosis (ISR).

Background Stent underexpansion is a predictor of both DES thrombosis and ISR. However, all underexpanded DES may not be equal.

Methods Intravascular ultrasound findings from 20 definite DES thrombosis patients (representing all definite thromboses from 1,407 consecutive DES patients undergoing intravascular ultrasound imaging) were compared with 50 risk-factor-balanced ISR patients with no evidence of stent thrombosis and 50 risk-factor-balanced "no-event" patients with neither thrombosis nor ISR.

Results Minimum stent area (3.9 ± 1.0 mm² vs. 5.0 ± 1.7 mm², p = 0.008), mean stent area (5.3 ± 1.0 mm² vs. 7.2 ± 2.0 mm², p = 0.001), and both focal (55.4 ± 13.2% vs. 74.9 ± 19.9%, p < 0.001) and diffuse stent expansion (77.4 ± 19.3% vs. 109.5 ± 23.1%, p < 0.001) were significantly smaller in the stent thrombosis group versus ISR and in both groups versus the "no-event" group. Minimum stent area <4.0 mm² (65% vs. 32%, p = 0.01) or <5.0 mm² (85% vs. 52%, p = 0.01) was more common in the stent thrombosis versus the ISR group and in both groups vs. "no-event" patients; and the relative length of the stent area <5 mm² was greatest in the stent thrombosis group (36.6 ± 37.7%), intermediate in the ISR group (22.8 ± 35.6%), and least in the "no-event" group (10.9 ± 26.4%), p = 0.04. In the stent thrombosis group, the minimum stent area site occurred in the proximal stent segment in 50% versus 24% in the ISR group (p = 0.03). There were no differences in edge dissection, stent fracture, or stent-vessel-wall malapposition among the groups.

Conclusions The DES-treated lesions that develop thrombosis or restenosis are often underexpanded, but underexpansion associated with thrombosis is more severe, diffuse, and proximal in location. (J Am Coll Cardiol Intv 2009;2:428–34) © 2009 by the American College of Cardiology Foundation
Drug-eluting stents (DES) reduce in-stent restenosis (ISR) and target lesion revascularization (1–5). With the use of dual antiplatelet therapy, the frequency of stent thrombosis is also relatively low (0.4% to 0.6%) (3,4). However, both DES restenosis and thrombus occur with greater frequency during routine, clinical, “real-world” procedures than in randomized trials (6,7). Although intravascular ultrasound (IVUS) studies have identified DES underexpansion as a predictor of both restenosis and thrombosis (7–9), no study has compared IVUS findings in DES thrombosis versus DES restenosis to understand whether patterns of stent underexpansion are similar or different in these 2 groups. The aim of the current study was to compare IVUS findings of patients with DES-treated lesions who developed stent thrombosis versus a matched group of DES-treated lesions that subsequently developed ISR and both groups with matched control patients in an attempt to discover why some underexpanded stents thrombose and others restenose. Are all underexpanded DES the same? Or is there an IVUS explanation why some thrombose and others restenose?

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Methods

Patient population. During the 39-month study period (October 2004 through December 2007), we identified 1,407 consecutive patients who underwent sirolimus-eluting stent (Cypher, Cordis, Miami Lakes, Florida) (74%) or paclitaxel-eluting stent (Taxus, Boston Scientific, Maple Grove, Minnesota) (26%) implantation at Columbia University Medical Center in whom IVUS was performed at the time of the original interventional procedure and/or at the time of stent thrombosis or ISR or scheduled event-free follow-up. The IVUS findings in this group of patients have not been reported although our group has previously performed and reported similar analyses in other groups of patients treated at other institutions.

Baseline demographic and procedural variables of all 1,407 patients were recorded and entered prospectively into a pre-specified database by a dedicated data-coordinating center. This study was approved by the institutional review board; written informed consent was obtained from all patients.

All patients were pre-medicated with 325 mg of aspirin that was continued indefinitely. A loading dose of 600 mg of clopidogrel was administered in the catheterization laboratory, and clopidogrel 75 mg/day was recommended for 12 months after the procedure. At the beginning of the procedure, a bolus of bivalirudin was administered at a dose of 0.75 mg/kg to achieve an activated clotting time ≥250 s followed by intravenous bivalirudin at 1.75 mg/kg/h. Glycoprotein IIb/IIIa inhibitors were used electively (and infrequently) at the discretion of the operator.

All “definite” stent thrombosis patients were included in the current analysis. According to the Academic Research Consortium, “definite” stent thrombosis was an acute coronary syndrome with angiographic evidence of thrombus or occlusion. Stent thrombosis was categorized as early (0 to 30 days), late (31 to 360 days), or very late (>360 days) (10).

Fifty ISR patients without stent thrombosis were then identified. These ISR patients were risk-factor-balanced versus stent thrombosis patients by: 1) DES type; 2) diabetes; 3) coronary artery; 4) bifurcation lesion location; and 5) reference external elastic membrane (EEM) cross-sectional area (CSA). In-stent restenosis was defined as an angiographic diameter stenosis of >50%.

Finally, using the same criteria, we identified a consecutive series of 50 patients without any evidence of DES thrombosis or restenosis who underwent routine angiographic and IVUS follow-up.

IVUS imaging and analysis. All IVUS studies were performed after the intracoronary administration of 0.1 to 0.2 mg nitroglycerin using only 1 type of commercially available IVUS system (Boston Scientific, Fremont, California). The IVUS catheter was advanced >10 mm distal to the lesion, and imaging was performed within the stent to the proximal reference at an automatic pullback speed of 0.5 mm/s. The IVUS data were recorded onto a high-resolution, half-inch, s-VHS tape or digital media for later offline analysis.

Stent malapposition was the lack of contact between any strut and the underlying vessel wall. Dissection was a tear in the plaque parallel to the vessel wall with visualization of blood flow in the false lumen (confirmed, if necessary, with saline or contrast injection). Stent fracture was the absence of stent struts for at least one-third of the stent circumference in ≥1 frame.

Using planimetry software (EchoPlaque, INDEC Systems, Mountain View, California), measurements of EEM, lumen, plaque and media (= EEM – lumen), and stent CSA were performed every 1 mm within the stent and proximal and distal reference segments. Plaque burden was plaque and media CSA divided by EEM CSA. Volumes were calculated using Simpson’s rule and normalized for stent length. Proximal and distal reference segment measurements included: 1) least-diseased image slices (maximum lumen with least plaque); and 2) most-diseased image slices (smallest lumen and greatest plaque) proximal and distal to the stent edge, but before any major side branch. Mean reference lumen CSA was the average of proximal
and distal “least-diseased” reference lumen CSAs. Focal stent expansion was minimum stent area (MSA) divided by mean reference lumen CSA. Diffuse stent expansion was mean stent CSA divided by mean reference lumen CSA. Stent symmetry was maximum stent diameter divided by minimum stent diameter at MSA site. Axial stent symmetry was maximum stent CSA divided by minimum stent CSA.

**Statistics.** Statistical analysis was performed using SPSS 11.5 (SPSS Inc., Chicago, Illinois). Continuous variables were presented as mean ± SD and compared using analysis of variance with post-hoc analysis using the Bonferroni correction. Categorical data were compared using chi-square statistics or Fisher exact test. P values <0.05 were considered statistically significant except for post-hoc analysis when <0.017 (0.05 divided by 3) was required for significance.

**Results**

**Patients and procedures.** Twenty patients with angiography-confirmed stent thrombosis (17 Cypher stents and 3 Taxus stents) had IVUS imaging at the time of stent thrombosis (n = 14), at the time of stent implantation (n = 2), or both (n = 4). Seventeen (85%) had early stent thrombosis, and 3 (15%) had late stent thrombosis; none had very late stent thrombosis. The median time between the index procedure and the thrombotic event was 9.0 days. Fifty-three percent (9 of 17) of the early cases occurred <1 week from the index procedure; and 67% (2 of 3) of the late thrombosis cases occurred <6 months from the index procedure.

Of the 50 ISR patients, 35 had IVUS imaging only at the time of ISR, whereas 15 patients had IVUS imaging both at the time of stent implantation and ISR. The median time between index and ISR was 8.3 months.

Of the 50 control patients, 34 had IVUS imaging only at the time of scheduled follow-up, and 16 patients had IVUS imaging both at the time of stent implantation and follow-up. The median time between index and event-free follow-up was 8.1 months.

There were no significant differences among stent thrombosis, ISR, and no-event groups regarding baseline clinical and angiographic characteristics (Table 1). In the stent thrombosis group, 11 lesions (55%) were treated with 1 stent; 6 lesions (30%) with 2 stents; and 3 lesions (15%) with 3 stents. In the ISR group, 27 lesions (54%) were treated with 1 stent; 19 lesions (38%) with 2 stents; and 4 lesions (8%) with 3 stents. In the no-event group, 34 lesions (68%) were treated with 1 stent; 12 lesions (24%) with 2 stents; and 4 lesions (8%) with 3 stents. None of the stent thrombosis patients stopped dual antiplatelet therapy prematurely.

**IVUS findings.** The IVUS findings are presented in Table 2. Although reference EEM and proximal or distal reference lumen CSAs tended to be larger, MSA (3.9 ± 1.0 mm² vs. 5.0 ± 1.7 mm², p = 0.008), minimum stent diameter (1.9 ± 0.3 mm vs. 2.3 ± 0.4 mm, p = 0.001), and mean stent CSA (5.3 ± 1.0 mm² vs. 7.2 ± 2.0 mm², p = 0.001) were significantly smaller in stent thrombosis patients than in ISR patients (see Fig. 1 for individual patient data).

**Table 1. Baseline Clinical and Angiographic Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Stent Thrombosis (n = 20)</th>
<th>ISR (n = 50)</th>
<th>No Events (n = 50)</th>
<th>p Value</th>
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<tr>
<td>Age, yrs</td>
<td>62.4 ± 11.2</td>
<td>59.9 ± 11.8</td>
<td>62.9 ± 9.3</td>
<td>0.46</td>
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<tr>
<td>Male</td>
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<td>36 (72)</td>
<td>36 (72)</td>
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<tr>
<td>Diabetes</td>
<td>9 (45)</td>
<td>22 (44)</td>
<td>26 (52)</td>
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<td>Hypertension</td>
<td>16 (80)</td>
<td>43 (86)</td>
<td>40 (80)</td>
<td>0.70</td>
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<tr>
<td>Hyperlipidemia</td>
<td>17 (85)</td>
<td>45 (90)</td>
<td>42 (84)</td>
<td>0.66</td>
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<tr>
<td>Smoking</td>
<td>5 (25)</td>
<td>22 (44)</td>
<td>22 (44)</td>
<td>0.25</td>
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<tr>
<td>Previous myocardic infarction</td>
<td>6 (30)</td>
<td>19 (38)</td>
<td>10 (20)</td>
<td>0.14</td>
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<tr>
<td>Unstable angina</td>
<td>8 (40)</td>
<td>20 (40)</td>
<td>11 (22)</td>
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<td>Stent implanted</td>
<td></td>
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<td></td>
<td>0.83</td>
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<tr>
<td>Sirolimus-eluting stent</td>
<td>17 (85)</td>
<td>40 (80)</td>
<td>42 (84)</td>
<td></td>
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<tr>
<td>Paclitaxel-eluting stent</td>
<td>3 (15)</td>
<td>10 (20)</td>
<td>8 (16)</td>
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<td>Target coronary artery</td>
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<td>Left anterior descending artery</td>
<td>12 (60)</td>
<td>33 (66)</td>
<td>32 (64)</td>
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<td>Left circumflex artery</td>
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<td>5 (10)</td>
<td>7 (14)</td>
<td></td>
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<tr>
<td>Right coronary artery</td>
<td>5 (25)</td>
<td>12 (24)</td>
<td>11 (22)</td>
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<tr>
<td>Bifurcation lesion</td>
<td>5 (25)</td>
<td>10 (20)</td>
<td>7 (14)</td>
<td>0.52</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.2 ± 0.7</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± 1 SD or n (%).

ISR = in-stent restenosis.
The MSA was located in the proximal half of the stent in 10 of 20 stent thrombosis lesions versus 12 of 50 ISR lesions (p = 0.03).

Overall, 13 of 20 (65%) stent thrombosis lesions had an MSA <4.0 mm² versus 16 of 50 (32%) ISR lesions versus 6 of 50 (12%) no-event lesions (p < 0.001). Overall, 17 of 20 (85%) stent thrombosis lesions had an MSA <5.0 mm² versus 26 of 50 (52%) ISR lesions versus 13 of 50 (26%) no-event lesions (p < 0.001). When stent CSA was compared with the reference lumen, focal stent expansion measured 55.4 ± 13.2% in stent thrombosis patients versus 74.9 ± 19.9% in ISR patients versus 79.0 ± 17.8% in no-event patients (p < 0.001); and diffuse stent expansion measured 77.4 ± 19.3% in stent thrombosis patients versus 109.5 ± 23.1% in ISR patients versus 100.0 ± 18.0% in no-event patients (p < 0.001). Focal stent expansion and diffuse stent expansion for DES thrombosis, restenosis, and no-event groups are shown in Figure 2.

The relative length of the stented segment with a stent area <4 mm² (14.3 ± 21.0% vs. 13.5 ± 27.7% vs. 3.2 ± 10.1%, analysis of variance of p = 0.06) were similar among the 3 groups: stent thrombosis versus ISR versus no-event.
However, the relative length of the stented segment with a stent area ≤5 mm² was greatest in stent thrombosis patients (36.6 ± 37.7%), intermediate in ISR patients (22.8 ± 35.6%), and least in no-event patients (10.9 ± 26.4%), analysis of variance of p = 0.03.

Stent asymmetry was greater in stent thrombosis patients than in ISR patients and no-event patients. However, there was no significant difference in edge dissection, stent fracture, or late stent-vessel wall malapposition among the 3 groups. There was 1 distal stent edge (type B angiographic) dissection in the stent thrombosis group; this patient developed stent thrombosis 2 days after stent implantation. Two stent fractures (both in the right coronary artery) were noted, 1 in the stent thrombosis group and another in the ISR group.

The IVUS findings were similar when only the Cypher stents were analyzed or compared with Taxus stents and when only early stent thrombosis cases were analyzed or compared with late stent thrombosis.

### Discussion

Previous studies—including reports from our group using totally different patient cohorts—have shown that stent underexpansion is a consistent finding with bare-metal stent and DES thrombosis and restenosis (8,9,11–17). The present study confirmed the importance of stent underexpansion and extended this observation to show that underexpansion may be more severe, more diffuse, and more often proximal in DES that thrombose versus those that restenose. Conversely, the present study did not show any other quantitative or qualitative grayscale IVUS features separating these 2 DES-related complications including strut fracture and stent-vessel wall malapposition.

Atherosclerosis, neointimal hyperplasia, and stent thrombosis predominantly develop at sites of low wall shear stress (18–20). Sukavaneshvar et al. (21) have demonstrated that increased radial transport of blood components and low wall shear stress promote platelet-dependent thrombosis. According to Hagen-Poiseuille law, wall shear stress is inversely proportional to the cube of the radius. However, especially when assessing thrombus formation, precise intrastent "local" wall shear stress is more complicated and dependent on 3-dimensional anatomical characteristic of the stent in relation to the intravascular blood flow velocity profile as well as the geometry of stent inflow. Most previous in vivo studies neglected 3-dimensional stent expansion characteristics such as underexpanded stent segment length, axial stent symmetry, site of maximum stent underexpansion, and overall stent volume; these may affect blood flow and lead to stent thrombosis or neointimal hyperplasia. In the present study, the 3-dimensional characteristics of the stent—mean stent area, diffuse stent underexpansion, and upstream location of the MSA site—best differentiated thrombosis patients from ISR patients. Previous studies showed that inflow/outflow disease was a risk factor for restenosis or thrombosis, and that residual reference segment stenosis was associated with stent thrombosis (8,21).

Stent underexpansion is common despite systematic use of high-pressure inflations and modern stent designs, but the incidence of stent thrombosis and ISR remain relatively

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**Figure 1. Distribution of Minimum and Mean Stent Areas**

Individual values comparing minimum and mean stent areas for drug-eluting stent (DES) thromboses, restenoses, and no-event groups are shown (open squares = DES thrombosis, solid squares = DES restenosis, and open triangles = no event). CSA = cross-sectional area; MSA = minimum stent area.

**Figure 2. Comparison of Stent Expansion**

Focal stent expansion and diffuse stent expansion (both mean ± 1 SD) for drug-eluting stent thromboses, restenoses, and no-event groups are shown. ISR = in-stent restenosis.
low. Thus, mechanical problems resulting in a suboptimal stent deployment cannot explain all cases of stent thrombosis. In addition, predictors of stent thrombosis also include diabetes, low left ventricular ejection fraction, renal failure, bifurcation lesion locations, and premature discontinuation of antiplatelet therapy—clinical factors typically unrelated to stent underexpansion (6,10,22–26).

Delayed endothelialization associated with DES implantation may extend the risk of thrombosis beyond 30 days. Nevertheless, 17 of our 20 DES thrombosis patients had their events within 30 days.

Mechanical factors (such as underexpansion) are probably more important in early DES thrombosis, whereas biologic factors are more important in late DES thrombosis, especially very late DES thrombosis. Other nonmechanical causes of DES thrombosis may include inflammation, hypersensitivity, poor vessel wall healing, strut penetration into a necrotic core, and aneurysm formation (27). There has been a recent focus on very late post-DES thrombosis (28). In a study of 13 patients (8 Cypher and 5 Taxus) with very late (>12 months) stent thrombosis, the predominant IVUS finding was incomplete stent-vessel wall apposition averaging 8 mm² in CSA in 10 of 13 patients (29). Incomplete stent apposition occurs as a result of positive remodeling and has been associated with lack of stent re-endothelialization (30). In our study, stent malapposition did not differentiate DES thrombosis from restenosis from controls, but we had few cases of late DES thrombosis and no cases of very late DES thrombosis. Given that 85% of our DES thrombosis events occurred within 30 days and that the median time to thrombosis in these 17 patients was 9.0 days, it is unlikely that positive remodeling would have occurred in so short a time. Therefore, stent malapposition at the time of the event most likely persisted from implantation.

Minimum stent area is also a major predictor of clinical, angiographic, or IVUS DES restenosis. Once intimal hyperplasia is suppressed, the impact of MSA becomes magnified. In a substudy of the SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) trial, the post-intervention MSA that best separated “adequate” from “inadequate” patency was 5.0 mm² with a positive predictive value of 90% (15). The present study further confirmed the importance of MSA as a contribution to DES restenosis, but suggested that underexpansion in DES restenosis is more focal and more distal.

Unlike previous reports, a significant residual edge plaque burden or longitudinal geographical miss did not predict DES edge restenosis or thrombosis (8,17,31). The current analysis was performed on patients treated after the relationship between uncovered inflow/outflow disease and stent thrombosis and was identified leading to more complete lesion coverage.

Study limitations. This was a retrospective study. However, despite the recent focus on DES thrombosis, this complication is uncommon; most IVUS series contain few patients; and most cases of DES thrombosis do not have IVUS evaluation. Of the 20 stent thrombosis patients, 4 were imaged both at the time of stent implantation and stent thrombosis, 14 were imaged only at the time of stent thrombosis, and 2 were imaged only at implantation; because imaging was not done in a uniform fashion, this might have introduced some bias. However, 18 of 20 were imaged at the time of thrombosis, and stents do not recoil after implantation. We were not able to assess the reasons for stent underexpansion in these patients, and we do not know the overall denominator of patients with stent underexpansion. The current findings do not apply to patients with very late (>1 year) stent thrombosis; 85% had early stent thrombosis (<1 month), 15% had late stent thrombosis (1 month to 1 year), and none had very late stent thrombosis. Finally, it is likely that there are still many factors—including, for example, delayed endothelialization, vessel wall pathology, poor responsiveness to dual antiplatelet therapy—that cannot be assessed using IVUS, but that are important contributors to stent thrombosis.

Conclusions

Although stent underexpansion contributes to both DES thrombosis and restenosis, the current study suggests that not all underexpanded DES are equal and that there is a difference between underexpanded stents that thrombose versus underexpanded stents that restenose. Underexpansion in DES that thrombose is more severe, more diffuse, and more often proximal in location.

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REFERENCES


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