Journal of the American College of Cardiology Vol. 47, No. 10, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.11.092

**EXPEDITED REVIEW**

# Incomplete Neointimal Coverage of Sirolimus-Eluting Stents

## Angioscopic Findings

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**OBJECTIVES** The goal of this study was to use angioscopy to investigate the amount of neointimal coverage after sirolimus-eluting stent (SES) implantation.

**BACKGROUND** Sirolimus-eluting stents reduce intimal hyperplasia.

**METHODS** We used angioscopy to evaluate 37 consecutive stented coronary artery lesions (15 SES and 22 bare-metal stents [BMS]) in 25 patients (18 men, 7 women) at 3 to 6 months after stent implantation. Angioscopic evaluation focused on: 1) neointimal coverage of stent struts, and 2) the existence of thrombi. The degree of neointimal coverage was classified as grade 0 when there was no neointimal coverage (similar to immediately after the implantation); grade 1 when stent struts bulged into the lumen, but were covered and still translucently visible; grade 2 when stent struts were visible but not clearly seen (not translucent); and grade 3 when stent struts were not visible because they were embedded in the neointima.

**RESULTS** Thrombi were identified in eight stented segments, tended to be more common with SES ($p = 0.14$), but were not seen on angiography. Three of the 15 SES (20%) had grade 0 neointimal coverage, and only 2 SES (13.3%) had complete coverage (grades 2/3). In contrast, all 22 BMS showed complete intimal coverage (grades 2/3). Thrombi were more common in stents with incomplete neointimal coverage ($p = 0.09$).

**CONCLUSIONS** The SES had incomplete neointimal coverage three to six months after implantation, and this was associated with subclinical thrombus formation. (J Am Coll Cardiol 2006;47:2108–11)


Sirolimus-eluting stents (SES) have remarkably reduced restenosis by inhibiting neointimal proliferation compared with bare-metal stents (BMS) (1,2). However, similar to vascular brachytherapy (VBT), SES may have an increased rate of late thrombosis (3–8). One pathologic study has related late thrombosis to incomplete neointimal coverage (7). Angioscopy is a robust tool capable of visualizing both stent strut neointimal coverage as well as intracoronary thrombus formation in vivo (9–11). We used angioscopy to investigate the amount of neointimal coverage and thrombus formation after SES implantation compared with BMS.

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## METHODS

**Patient population.** We evaluated 37 consecutive stented coronary artery lesions in 25 patients (18 men and 7 women, mean age 65 years, range 54 to 78 years) who agreed to follow-up angiography and angioscopy 3 to 6 months after stent implantation. Stents were implanted using standard techniques. We compared the angioscopic findings of 15 SES-treated lesions (Cypher, Cordis, Miami Lakes, Florida) with 22 BMS (Bx Velocity, Cordis, n = 5; Driver, Medtronic, Galway, Ireland, n = 4; Zeta, Guidant, Indianapolis, Indiana, n = 8; Express 2, Boston Scientific, Natick, Massachusetts, n = 4; and Duraflex, Goodman, Galway, Ireland, n = 1). Because SES did not become available until August 2004, all patients treated before this date received BMS, and all patients treated after this date received SES. The Medical Ethics Committee at Kansai Rosai Hospital approved this study, and patients gave written informed consent. All patients received dual-antiplatelet therapy (aspirin 100 mg and ticlopidine 200 mg) after the procedure; at the time of this study, clopidogrel was not approved in Japan.

**Angioscopic procedures and evaluation.** At follow-up, all stents were assessed with an 0.014-inch guidewire-compatible 4.5-F rapid-exchange coronary angioscope (Vecmova, Clinical Supply Corp., Gifu, Japan): BMS = 131 ± 48 days versus SES = 115 ± 48 days ($p$ = NS). The system and its use have been described elsewhere (9). Briefly, all patients were given a bolus of 5,000 IU heparin intravenously before angiography and angioscopy. The optical fiber was placed at the distal segment of the coronary

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Manuscript received July 31, 2005; revised manuscript received September 19, 2005, accepted November 1, 2005.

**Abbreviations and Acronyms**

BMS = bare-metal stent
IVUS = intravascular ultrasound
SES = sirolimus-eluting stent
VBT = vascular brachytherapy

artery and slowly pulled back from the distal edge of the stent to the proximal edge under angioscopic and angiographic guidance.

Angioscopic evaluation focused on: 1) the degree of stent strut neointimal coverage, and 2) the existence of red or white thrombi. Neointimal coverage was classified into four grades (Fig. 1). Grade 0 was defined as stent struts that were fully visible, similar to immediately after implantation. Grade 1 was defined as stent struts that bulged into the lumen and, although covered, were still transparently visible. Grade 2 was defined as stent struts that were visible, but not clearly seen (i.e., they were translucent). Grade 3 was defined as stent struts that were not visible by angioscopy (i.e., they were embedded in the neointima). Struts that crossed side branches were excluded from grading because they all showed grade 0 coverage. (This grading system evolved from one previously reported [11].) Taken together, grade 0/1 indicated incomplete neointimal coverage, whereas grade 2/3 indicated complete coverage. In three SES and three BMS, neointimal coverage was heterogeneous; in these six cases the dominant pattern was tabulated.

**Angiographic assessment.** Coronary angiography was performed in 10 regular projections, and quantitative coronary angiography performed using the CASS system (Pie Medical Imaging B.V., Maastricht, the Netherlands) with the "worst view" used to assess the severity of the stenosis (12).

**Statistical analysis.** Statistical analysis was performed using StatView 5.0 (SAS Institute, Cary, North Carolina). Continuous variables were expressed as mean ± 1 SD and analyzed by unpaired Student *t* test or analysis of variance. Categorical variables were expressed as frequencies and analyzed by chi-square statistics or Fisher exact test (for 2 × 2 comparisons); $p < 0.05$ was considered significant.

## RESULTS

**Patient and lesion characteristics.** There were no significant differences in demographics (age, gender, past history, and coronary risk factors) between patients receiving BMS versus SES (data not shown). Lesion characteristics were also similar between the two groups (Table 1). There was no difference in diabetes frequency between BMS (n = 15; 68.2%) and SES (n = 11; 73.3%) (p = 1.0). There was no

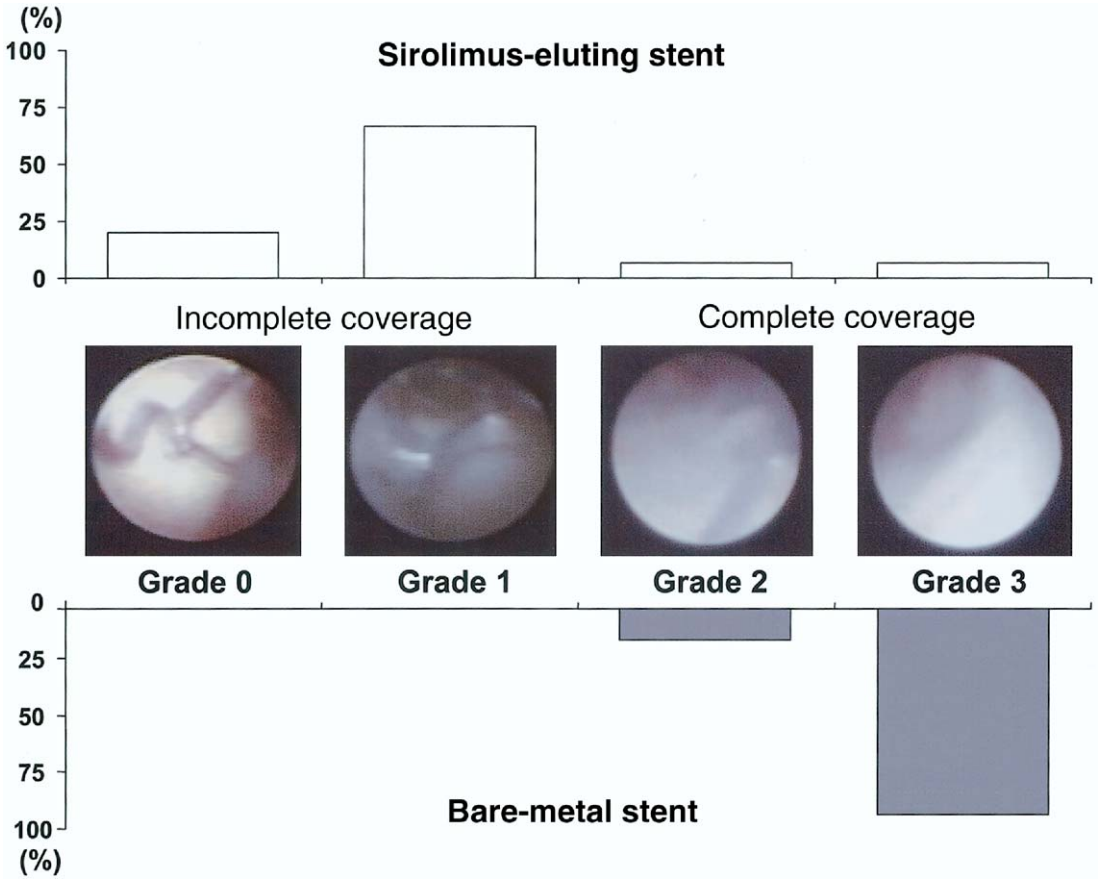


**Figure 1.** Angioscopic images show the grading for neointimal stent strut coverage. Neointimal coverage was more complete with bare-metal stents compared with sirolimus-eluting stents ($p < 0.0001$).

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**Table 1.** Lesion Characteristics

| | BMS | SES | p Value |
|---|---|---|---|
| n | 22 | 15 | |
| Vessels (LAD/LCX/RCA) | 7/4/11 | 6/2/7 | 0.9 |
| Location (proximal/middle/distal) | 7/15/0 | 5/8/2 | 0.2 |
| Infarct related artery (n) | 11 | 4 | 1.0 |
| Stent diameter (mm) | 3.2 ± 0.3 | 3.0 ± 0.4 | 0.2 |
| Stent length (mm) | 22.1 ± 4.8 | 22.7 ± 8.8 | 0.7 |

BMS = bare-metal stent; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; SES = sirolimus-eluting stent.

significant difference in duration of dual-antiplatelet therapy between BMS (85 ± 58 days) versus SES (115 ± 47 days, p = 0.1).

**Angiographic assessment.** There were no differences in quantitative coronary angiography findings between BMS and SES groups before and immediately after stent implantation (Table 2). At follow-up, the SES group had a larger minimal lumen diameter than the BMS group (Table 2). Therefore, late loss was significantly higher in BMS than in SES group (0.8 ± 0.6 mm in BMS vs. 0.2 ± 0.4 mm in SES, p = 0.0013).

**Angioscopic findings.** Thrombi were identified in eight stented segments. All were mural thrombi, none were occlusive, and none were detectable by angiography. Five red thrombi were detected in 15 SES (33%), whereas 2 red thrombi and 1 white thrombus were detected in 22 BMS (14%), p = 0.14.

Angioscopic grades of neointimal coverage were markedly different between BMS and SES (p < 0.0001) (Fig. 1). Three of 15 SES (20%) had grade 0 coverage, and only 2 (13.3%) had complete coverage (grades 2/3). In contrast, all 22 BMS had complete intimal coverage (grades 2/3). The grade of neointimal coverage was related to the duration of follow-up in BMS (p = 0.058), but not in SES (p = 1.0).

The relationship between the degree of neointimal coverage and the presence of thrombi is shown in Table 3. In the entire cohort of 37 stented lesions, there was a tendency for thrombi to be correlated with incomplete neointimal coverage (p = 0.09 by Fisher exact test).

**Table 2.** Quantitative Coronary Angiography Findings

| | BMS | DES | p Value |
|---|---|---|---|
| Pre-procedure | | | |
| Reference vessel diameter (mm) | 2.8 ± 0.4 | 2.7 ± 0.5 | 0.7 |
| Lesion length (mm) | 16.7 ± 6.1 | 16.6 ± 8.1 | 1.0 |
| Minimal lumen diameter (mm) | 0.8 ± 0.6 | 0.6 ± 0.5 | 0.2 |
| Diameter stenosis (%) | 73.7 ± 12.0 | 77.5 ± 18.1 | 0.4 |
| Post-stent implantation | | | |
| Minimal lumen diameter (mm) | 2.6 ± 0.3 | 2.6 ± 0.5 | 1.0 |
| Diameter stenosis (%) | 15.2 ± 5.9 | 18.3 ± 5.4 | 0.1 |
| Follow-up | | | |
| Minimal lumen diameter (mm) | 1.8 ± 0.6 | 2.3 ± 0.7 | 0.0255 |
| Diameter stenosis (%) | 32.2 ± 20.4 | 22.5 ± 17.7 | 0.1 |

BMS = bare-metal stent; DES = drug-eluting stent.

**Table 3.** Relationship Between Intimal Coverage and Thrombus

| | Incomplete (Grade 0/1) | Complete (Grade 2/3) |
|---|---|---|
| Thrombus present | 5 | 3 |
| Thrombus absent | 8 | 21 |

## DISCUSSION

The present study showed significant differences between neointimal coverage of BMS versus SES three to six months after implantation. All BMS had complete neointimal coverage, whereas neointima covering of SES struts was more lucent and less complete. Furthermore, incomplete neointimal coverage was associated with thrombus formation that tended to be more common in SES than in BMS.

Intravascular ultrasound (IVUS) studies showed that in-stent restenosis was secondary to neointimal hyperplasia. Earlier angioscopic studies showed that complete neointimal coverage was the rule in BMS (9–11). The IVUS studies also showed that drug-eluting stents reduced in-stent restenosis by inhibiting neointimal hyperplasia. Furthermore, one previous IVUS study showed that nonpolymeric paclitaxel-eluting stents not only inhibited intimal hyperplasia, but also increased the neointimal-free length of the stents; the length of stent that was free of IVUS-detectable intimal hyperplasia measured 3.2 ± 4.8 mm in placebo stents, 6.1 ± 5.6 mm in low-dose stents, and 8.7 ± 6.1 mm in high-dose stents (p = 0.0029) (13). The current study extended these observations by showing that SES not only suppressed intimal hyperplasia, but also left a significant portion of the stent struts fully exposed and uncovered, similar to immediately after implantation.

In the current study, the lack of neointimal strut coverage was associated with thrombus formation. One previous pathological study reported that impaired healing (i.e., failure to form a complete neointimal layer over the stent struts) extended the window during which stents were prone to thrombosis (7), and VBT also inhibited neointimal growth. In patients treated with VBT, the lack of re-endothelialization and late thrombosis were related, especially in the setting of new stent implantation (7,14). On the other hand, prolonged intensive antiplatelet therapy or reduced restenting when treating in-stent restenosis with VBT decreased the late stent thrombosis rate (8).

One earlier serial angioscopic study showed that intimal coverage of BMS proceeded gradually with subsequent neointimal remodeling (shrinkage) up to two years (11). Similarly, in the current analysis the grade of neointimal coverage in BMS was related to the time from implantation to angioscopic follow-up even though all angioscopic studies were performed within six months. A recent case report on the pathology of SES-treated lesions showed that endothelial coverage was >80% complete after 16 months (15). In the current study, neointimal coverage was unrelated to the time from DES implantation to angioscopic follow-up when all follow-up studies were performed within six

months; therefore, the time course for neointimal coverage is more prolonged than with BMS. On the other hand, late catch-up after VBT has been well shown, and SES may have a similar late catch-up potential (16,17). Longer-term serial angioscopic observations will be necessary to clarify the chronological findings; however, these data may be difficult to obtain.

**Study limitations.** The structural designs of the stents used in our study were not identical between the BMS and the SES groups. Therefore, we could not exclude effects of mechanical designs on the angioscopic findings. This was not a serial study; therefore, we could not compare the chronological course of neointimal coverage between BMS and SES. All angioscopic studies were performed within six months after implantation, and the interval from implantation to follow-up ranged from three to six months. Longer-term study (beyond 12 months) will be required to address the issue of late, late thrombosis. Finally, this study only investigated neointimal morphology; local endothelial function remained unclear; and grade 1 with a functional neointima might be as good as grade 2 or 3 coverage.

**Conclusions.** Angioscopic findings of neointimal coverage within six months after implantation were quite different between BMS and SES. The SES had incomplete neointimal coverage three to six months after implantation, and this was associated with subclinical thrombus formation. This supports prolonged dual-antiplatelet therapy for patients treated with SES.

### Acknowledgment

The authors gratefully acknowledge Mr. Kenji Yamamoto and Mr. Teruo Nakatsuka for recording angioscopic images.

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## REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stent versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
2. Morice MC, Serruys PW, Sousa JE, et al., RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent versus standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
3. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation 2004;109:1930–2.
4. McFadden EP, Stabile E, Roger E, et al. Late thrombosis in drug-eluting stents after discontinuation of anti-platelet therapy. Lancet 2004;364:1519–21.
5. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis events with drug-eluting stent. J Am Coll Cardiol 2005;45:2088–92.
6. Lakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
7. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003;108:1701–6.
8. Waksman R, Ajani AE, White LR, et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary γ-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). Circulation 2001;103:2332–5.
9. Sakai S, Mizuno K, Yokoyama S, et al. Morphologic changes in infarct-related plaque after coronary stent placement: a serial angioscopy study. J Am Coll Cardiol 2003;42:1558–65.
10. Ueda Y, Nanto S, Komamura K, Kodama K. Neointimal coverage of stents in human coronary arteries observed by angioscopy. J Am Coll Cardiol 1994;23:341–6.
11. Asakura, M, Ueda, Y, Nanto S, et al. Remodeling of in-stent neointima, which became thinner and transparent over 3 years' serial angiographic and angioscopic follow-up. Circulation 1998; 97:2003–6.
12. Haase J, Escaned J, van Swijndregt EM, et al. Experimental validation of geometric and densitometric coronary measurements on the new generation Cardiovascular Angiography Analysis System (CASS II). Cathet Cardiovasc Diagn 1993;30:104–14.
13. Mintz GS, Hong MK, Raizner AE, et al. Intravascular ultrasound assessment of neointima distribution and the length of stent that was free of intravascular ultrasound-detectable intimal hyperplasia in paclitaxel-eluting stents. Am J Cardiol 2005;95:107–9.
14. Cheneau E, John MC, Fournadjiev J, et al. Time course of stent endothelialization after intravascular radiation therapy in rabbit iliac arteries. Circulation 2003;107:2153–8.
15. Guagliumi G, Farb A, Musumeci G, et al. Sirolimus-eluting stent implanted in human coronary artery for 16 months: pathological findings. Circulation 2003;107:1340–1.
16. Teirstein PS, Massullo V, Jani S, et al. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2000;101:360–5.
17. Grise MA, Massullo V, Jani S, et al. Five-year clinical follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2002;105:2737–40.