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Optimal Stent-Sizing With Intravascular Ultrasound Contributes to Complete Neointimal Coverage After Sirolimus-Eluting Stent Implantation Assessed by Angioscopy

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Objectives The aim of this study was to explore the determinants of neointimal coverage after sirolimus-eluting stent (SES).

Background Although SES has significantly reduced in-stent restenosis by inhibiting neointimal hyperplasia, insufficient neointimal coverage after stenting might result in adverse outcomes.

Methods We evaluated 28 SES lesions with both angioscopy and intravascular ultrasound (IVUS). Quantitative assessments of the lesions and stent expansion were performed by IVUS at the time of stent implantation, and degree of neointimal coverage was judged by angioscopy at follow-up (11 ± 6 months) whether the stent struts were embedded by the neointima ("complete/incomplete" neointimal coverage).

Results "Complete" coverage was identified in 10 (36%), and "incomplete" coverage was identified in 18 (64%). Time from the stenting to angioscopy as well as the lesion and procedural characteristics were similar between the complete and incomplete coverage groups. The IVUS parameters were also similar, except for the final minimum stent cross-sectional area (CSA) (7.0 ± 1.8 mm^2 in complete vs. 5.3 ± 1.9 mm^2 in incomplete, $p = 0.02$) and lumen CSA at the distal reference site (6.1 ± 1.4 mm^2 in complete vs. 4.9 ± 1.2 mm^2 in incomplete, $p = 0.02$). The ratio of the stent area to the vessel area was significantly larger in the complete coverage than in the incomplete coverage group (0.52 ± 0.11 vs. 0.39 ± 0.09, $p = 0.002$).

Conclusions Adequate stent sizing relative to the vessel size might contribute to the angioscopically complete neointimal coverage after SES implantation. (J Am Coll Cardiol Intv 2009;2:989–94)

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Drug-eluting stents (DES) have significantly reduced in-stent restenosis by inhibiting neointimal hyperplasia compared with bare-metal stents (BMS) (1,2). Conversely, concerns have been raised regarding possible increase in late stent thrombosis and death compared with BMS (3–7). Mechanisms of stent thrombosis remain unclear, although several pathological and clinical investigations have disclosed the potential mechanisms of stent thrombosis (8–17). Stent thrombosis might occur through the mechanisms of procedural-related factors, inadequate healing processes,

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and lack of neointima and/or re-endothelialization, similar to those after vascular brachytherapy (18–20). Although intravascular ultrasound (IVUS) is a useful device, by quantitatively measuring the degree of stent expansion as well as vessel diameters and areas, IVUS resolution is insufficient to detect thin neointimal coverage after DES. Angioscopy is a robust tool for the qualitative assessment of neointimal coverage after percutaneous coronary intervention in patients (21–25). Accordingly, we used angioscopy for the assessment of thin neointimal coverage after sirolimus-eluting stent (SES) implantation and IVUS for the quantitative assessment of the vessel characteristics in this study to explore the determinants of neointimal coverage after SES implantation.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CSA = cross-sectional area
DES = drug-eluting stent(s)
EEM = external elastic membrane
IVUS = intravascular ultrasound
MSA = minimum stent area
SES = sirolimus-eluting stent(s)

Methods

Patients. We evaluated 54 consecutive stented coronary artery lesions in 29 patients who had undergone SES implantation for de novo lesions and agreed to receive angioscopy at follow-up catheterization between January 2005 and December 2006. All patients received IVUS evaluation immediately after SES implantation. We excluded 26 of the 54 SES lesions from analysis, because SES had been implanted at ostial location and/or overlapped on other stents. Consequently, the analysis included 28 SES lesions from 15 patients (14 men, mean age 60 ± 11 years, age range 35 to 75 years). Hypertension included 1 or more of the following: antihypertensive medication, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg. Hyperlipidemia included 1 or more of the following: lipid-lowering medication, total cholesterol ≥220 mg/dl, low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, or triglycerides ≥150 mg/dl. Diabetes mellitus included 1 or more of the following: antihyperglycemic medication or insulin treated, HbA_{1C} >6.5%. The Ethics Committee at Kansai Rosai Hospital approved the study, and all patients gave written informed consent.

IVUS imaging. Post-procedural IVUS examination was performed after intracoronary administration of 1 to 2 mg isosorbide dinitrate with a commercially available IVUS system, which incorporated a 40-MHz transducer with a short monorail imaging sheath (Boston Scientific Corporation, Natick, Massachusetts). The IVUS catheter was advanced distal to the stented lesion, and imaging was performed retrograde until the aorto-ostial junction at the automatic pullback speed of 0.5 mm/s.

IVUS analysis. Qualitative and quantitative analyses were performed, conforming to the criteria of the American College of Cardiology clinical expert consensus document on IVUS (26). With planimetry software (TapeMeasure, INDEC Systems, Inc., Capitola, California), stented segments and proximal and distal references were analyzed to obtain external elastic membrane cross-sectional area (EEM CSA) (mm^2), lumen CSA (mm^2), and minimum stent CSA (MSA) (mm^2). Plaque burden (%) was defined as (EEM CSA minus lumen CSA) divided by EEM CSA. The proximal and distal reference segments were the least-diseased image slices (largest lumen with least plaque) within 5 mm proximal and distal to the lesion but within the same segment and before any major side branch. Degree of the stent expansion was evaluated by 2 parameters: the ratio of the MSA to the average reference lumen CSA (stent-expansion index); and the ratio of the MSA to the average reference EEM CSA (stent-size index). Incomplete apposition was defined as 1 or more stent struts clearly separated from the vessel wall with the evidence of blood speckles behind the strut, excluding overlapped side branches (27).

Angioscopic procedures. At follow-up, all stented segments were assessed with a 4.5-F rapid-exchange coronary angioscope (Vecmova, Clinical Supply Corp., Gifu, Japan), which was compatible with a conventional 0.014-inch angioplasty guidewire and an 8-F guiding catheter. The system and procedure have been described elsewhere (22). In brief, the optical fiber was advanced at the distal segment of the coronary artery and was slowly pulled back from the distal edge of the stent to the proximal edge under angioscopic and angiographic guidance. The images were recorded onto a digital video disc for offline analysis. Voice announcements regarding the angiographic guidance were also recorded.

Angioscopic analysis. Angioscopic evaluation focused on the neointimal coverage over the stent struts. Neointimal coverage was classified into 4 grades as previously described (23). In brief: grade 0 = stent struts were fully visible, similar to immediately after implantation; grade 1 = stent struts bulged into the lumen and, although covered, were still transparently visible; grade 2 = stent struts were

embedded by the neointima but were translucently seen; and grade 3 = stent struts were fully embedded and were invisible by angioscopy. Neointimal coverage was evaluated in the entire stented segments, and if neointimal coverage was heterogeneous, the dominant pattern was adopted. We classified 28 stented segments into 2 groups on the basis of whether the stent struts were embedded by the neointima or not. Grade 0/1 was grouped as "incomplete" neointimal coverage, and grade 2/3 was grouped as "complete" coverage.

Quantitative coronary angiography. Coronary angiography was performed at least in 10 projections and was analyzed by quantitative coronary angiography with the Cardiovascular Angiography Analysis System (Pie Medical BV, Maastricht, the Netherlands). Minimal lumen diameter, reference diameter, and percent diameter stenosis before and after intervention were measured on the "worst view" (28).

Statistical analysis. Statistical analysis was performed with StatView 5.0 (SAS Institute, Cary, North Carolina). Continuous variables were expressed as mean ± SD. Unpaired Student *t* test was used to compare 2 groups. Categorical variables were expressed as frequency and analyzed by chi square or Fisher exact test. A probability value of <0.05 was considered statistically significant.

Results

Patients. Of the 15 patients analyzed, 14 (93%) presented multivessel diseases (53% had triple vessel disease), and 2 (13%) had previous myocardial infarction. Ten patients had hypertension (67%), 11 had hyperlipidemia (73%), 5 had diabetes mellitus (33%), and 4 were current smokers (27%) at the time of stent implantation.

Angioscopic findings. Angioscopic follow-up was performed 11 ± 6 months after SES implantation. Among the 28 SES-implanted lesions, angioscopic grades were distributed as: grade 0 = 0 (0%); grade 1 = 18 (64%); grade 2 = 8 (29%); and grade 3 = 2 (7%). Hence, 10 lesions showed complete coverage (36%), and 18 showed incomplete coverage.

Table 1. Clinical Characteristics

	Complete Coverage	Incomplete Coverage	p Value
Segments	10	18	
Age, yrs	63 ± 7	60 ± 14	0.5
Male	10 (100)	17 (94)	1.0
Prior MI	5 (50)	7 (39)	0.7
Risk factors			
Hypertension*	8 (80)	12 (67)	0.7
Hyperlipidemia†	7 (70)	12 (67)	1.0
Diabetes mellitus‡	4 (40)	3 (17)	0.2
Current smoker	3 (30)	5 (28)	1.0

Values are presented as n, mean ± SD, or n (%). *Receiving antihypertensive medication or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; †total cholesterol ≥220 mg/dl or low-density lipoprotein cholesterol ≥180 mg/dl or high-density lipoprotein cholesterol <40 mg/dl or triglyceride ≥150 mg/dl or receiving lipid-lowering treatment; ‡oral-agent or insulin treated or HbA_{1C} >6.5%.
MI = myocardial infarction.

Table 2. Lesion and Procedural Characteristics

	Complete Coverage	Incomplete Coverage	p Value
Vessels (LAD/LCX/RCA)	3/5/2	10/4/4	0.3
Location (proximal/middle/d)	8/2/0	1/9/8	0.2
Direct stenting	6 (60)	5 (28)	0.1
After dilation	2 (20)	8 (44)	0.2
Maximum balloon inflation, atm	15 ± 4	16 ± 3	0.9
Maximum balloon diameter, mm	3.3 ± 0.4	3.3 ± 0.3	0.8

Values are presented as n, n (%), or mean ± SD.
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; Prox. = proximal; Mid. = middle.

Clinical and procedural characteristics. Clinical and procedural characteristics are listed in Tables 1 and 2. There were no differences in follow-up duration (10 ± 5 months vs. 11 ± 7 months, p = 0.8), stent diameter (3.2 ± 0.4 mm vs. 3.0 ± 0.4 mm, p = 0.2), stent length (23 ± 4 mm vs. 24 ± 5 mm, p = 0.6) between the complete and the incomplete coverage groups.

Angiographic measurements. There were no significant differences in pre-procedural angiographic findings between the complete coverage and the incomplete coverage groups: reference diameter (2.9 ± 0.5 mm vs. 2.7 ± 0.4 mm, p = 0.2), minimal lumen diameter (0.6 ± 0.3 mm vs. 0.6 ± 0.3 mm, p = 0.4), lesion length (14 ± 10 mm vs. 16 ± 6 mm, p = 0.7), and percent diameter stenosis (79 ± 9% vs. 79 ± 10%, p = 1.0). Post-procedural minimal lumen diameter (2.6 ± 0.9 mm vs. 2.4 ± 0.2 mm, p = 0.4), and percent diameter stenosis (16 ± 13% vs. 15 ± 6%, p = 0.7) were also similar between the groups.

IVUS findings. The post-procedural IVUS findings are shown in Table 3. Incomplete stent apposition was revealed in 3 segments (30%) in complete coverage and in 4 (22%) segments in incomplete coverage (p = 0.7).

Discussion

The present study demonstrated that a higher ratio of the stent area to the vessel area (i.e., "optimal stent sizing") might contribute to the angioscopically complete neointimal coverage after SES implantation. This was in accordance with the earlier angioscopic (22,29) and IVUS observations in BMS (30). Histopathological studies also demonstrated the effect of overexpansion on the neointimal proliferation in animal models (31,32). Farb et al. investigated the histology of 55 stents in human coronary vessels and found that neointimal thickness was significantly greater when medial damage was present at the strut site than when the

Table 3. IVUS Parameters

	Complete Coverage	Incomplete Coverage	p Value
Proximal reference EEM CSA, mm^2	16.3 ± 2.6	17.4 ± 4.4	0.5
Proximal reference lumen CSA, mm^2	8.6 ± 2.0	8.8 ± 3.9	0.8
Proximal reference plaque burden, %	47 ± 14	51 ± 12	0.4
Distal reference EEM CSA, mm^2	10.7 ± 3.4	9.4 ± 2.4	0.3
Distal reference lumen CSA, mm^2	6.1 ± 1.4	4.9 ± 1.2	0.02
Distal reference plaque burden, %	40 ± 13	47 ± 8	0.06
Minimum stent CSA, mm^2	7.0 ± 1.8	5.3 ± 1.9	0.02
Stent-size index*	0.52 ± 0.11	0.39 ± 0.09	0.002
Stent-expansion index†	0.95 ± 0.18	0.80 ± 0.22	0.08

Values are presented as mean ± SD. *Stent-size index was defined as the ratio of the minimum stent area to the average reference external elastic membrane (EEM) cross-sectional area (CSA); †stent-expansion index was defined as the ratio of the minimum stent area to the average reference lumen CSA.
IVUS = intravascular ultrasound.

struts were in contact with the intact media (33). They also found that medial damage and stent over-sizing relative to the reference arterial lumen were associated with increased neointimal growth. Because vessel injury associated with overstretching might lead to surplus neointimal proliferation (34,35), it is not surprising to see less extent of neointimal hyperplasia in the lesions with stent undersizing. In this study, large MSA and large lumen CSA at distal reference site were also identified as univariate predictors for complete neointimal coverage. Although smaller final stent area has been reported as a predictor of in-stent restenosis after BMS implantation (36,37), it does not conflict with our results. Earlier IVUS studies reported a positive correlation between the stent area and the neointimal area (38,39). Hoffmann et al. (30) have reported contribution of aggressiveness of the stent implantation technique to tissue proliferation inside the stent. Large stent area abolished the impact of neointimal hyperplasia in terms of restenosis. Hence, "the bigger, the better" theory has been accepted to prevent clinical restenosis after BMS implantations. In the present study, large lumen CSA at the reference site was also associated with complete neointimal coverage, and IVUS showed no difference in EEM CSA between the groups. Thus, neointimal coverage was not necessarily attenuated in small vessels but was attenuated in the vessels that were diffusely diseased with large plaque burden. Surprisingly, these univariate predictors coincided with the recent IVUS study that demonstrated IVUS predictors for DES thrombosis included small minimum stent area and large residual disease at the stent edges (16).

Although an IVUS study revealed the high prevalence of incomplete stent apposition in patients with stent thrombosis (40), the impact of incomplete stent apposition on clinical events has still been controversial (41,42). In our study population, 22 of the 28 lesions underwent follow-up IVUS. Follow-up IVUS revealed incomplete stent apposition in 11 lesions (3 lesions, 50%, in complete coverage; 8 lesions, 50%, in incomplete coverage, p = 1.0). There were no significant differences with regard to the stent malapposition and neointimal coverage by follow-up IVUS in our study population.

Clinical implications. Earlier studies have shown that incomplete neointimal coverage within the stents has a trend toward thrombus formation with/without clinical presentation (15,17,23,24). In addition, several experimental models revealed incomplete re-endothelialization associated with thrombosis in irradiated vessels (18,20). Significant suppression of neointimal formation is considered as a cause of late thrombosis after vascular brachytherapy. In fact, re-stenting into irradiated segment increased the frequency of stent thrombosis (43,44). A pathological study revealed fatal late coronary stent thrombosis cases had incomplete neointimal healing over the stent (11). A recent pathological study of late DES thrombosis also demonstrated that incomplete neointimal coverage of stent struts was the most important morphometric predictor of late stent thrombosis (17). A previous IVUS study also disclosed that stent underexpansion was related to SES thrombosis (45). In the present study, the stented segments with smaller stent area relative to the vessel size were more prone to incomplete neointimal formation after stenting than those with larger stent area. Thus, it is reasonable to speculate that stent implantation with under-expansion that caused stent thrombosis has incomplete neointimal coverage.

An IVUS study showed that SES had a lower optimal MSA threshold (5.0 mm^2) compared with BMS (6.5 mm^2) to predict adequate follow-up patency (46). Although aggressive stent expansion might be unnecessary with SES for the prevention of restenosis, the present results indicate that adequate stent area relative to the vessel area might still be important to prevent thrombosis by adequate neointimal formation. Recently, IVUS guidance at the time of DES implantation has been reported to be an independent predictor of freedom from stent thrombosis (47). The vessel size (i.e., EEM CSA) as well as the plaque distribution cannot be estimated with angiography but needs IVUS guidance. Considering the advantage of IVUS guidance over angiographic guidance, we evaluated degree of stent expansion not only by using "stent-expansion index" (MSA/average reference lumen CSA) but by using "stent-size index" (MSA/average reference EEM CSA). Although both angiographic measurements and stent-expansion index were similar between the complete and the incomplete coverage groups in the present study, IVUS evaluation disclosed the significant difference in stent-size index between the groups. With IVUS guidance, the adequate stent diameter and length can be selected, and stent expansion can be controlled safely in accordance with the vessel size. Taken together, IVUS-guided adequate stent expansion relative to the vessel size might be important to avoid not

only stent restenosis but also stent thrombosis after SES implantation.

Study limitations. This study was a single-center, nonrandomized, retrospective study with a small sample size. Nonetheless, this study was the first to explore the contributors to neointimal coverage after SES implantation with both angioscopy and IVUS. Pre-procedural and follow-up IVUS were not consistently performed in this study. Variety of tissue characteristics at the target lesion, such as lipid pool and calcification, might have affected the stent expansion as well as the subsequent neointimal proliferation. However, an earlier IVUS study showed that pre-procedural IVUS findings were not related to stent expansion (48). Further systematic investigation should be required to clarify the relationships of the pre-procedural tissue characteristics, stent expansion, and neointimal proliferation. This study only investigated neointimal morphology; local endothelial functions remain unclear.

Conclusions

Adequate stent sizing with IVUS relative to the vessel size might contribute to the complete neointimal coverage after SES implantation.

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Key Words: angioscopy ■ intravascular ultrasound ■ neointima ■ sirolimus-eluting stent.