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CLINICAL RESEARCH **Interventional Cardiology**

Late Incomplete Stent Apposition After Sirolimus-Eluting Stent Implantation

A Serial Intravascular Ultrasound Analysis

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OBJECTIVES We sought to identify the frequency of incomplete stent apposition (ISA) in sirolimus-eluting stents (SES) and clarify its findings and clinical sequelae.

BACKGROUND Late-acquired ISA has been reported in bare-metal stents (BMS) and brachytherapy and recently in drug-eluting stents. However, the characteristics of late ISA in SES have not been clarified.

METHODS From the SIRIUS trial, a randomized, multicenter study comparing SES and BMS, serial qualitative intravascular ultrasound (IVUS; at stent implantation and eight-month follow-up) was available in 141 patients (BMS: n = 61; SES: n = 80). The IVUS images were reviewed for the presence of ISA.

RESULTS Incomplete stent apposition at follow-up was observed in 19 patients (BMS: n = 6 [9.8%]; SES: n = 13 [16.3%]; p = NS). Among these, 12 had ISA after intervention and at follow-up (persistent ISA). Late-acquired ISA was seen in the remaining seven cases, all from the SES group (BMS: n = 0; SES: n = 7 [8.7%]; $p < 0.05$). In late-acquired ISA, there was an increase in external elastic membrane area (after intervention: 16.2 ± 2.7 mm^2; follow-up: 18.9 ± 3.6 mm^2; $p < 0.05$). The location of stent-vessel wall separation was primarily at the stent edges in persistent ISA cases, whereas late-acquired ISA in SES occurred mostly in the mid portion of the stent. There were no negative clinical events reported for any ISA cases at 12-month clinical follow-up.

CONCLUSIONS Late ISA was observed in 8.7% of patients after SES implantation. There were no negative clinical events associated with this IVUS finding at 12-month clinical follow-up; however, careful long-term follow-up will be necessary. (J Am Coll Cardiol 2005;46:1002–5) © 2005 by the American College of Cardiology Foundation

In recent years, stent-based local drug delivery has emerged as a promising technology to reduce restenosis. Several clinical studies have shown that drug-eluting stents (DES) achieve a striking inhibition of neointimal hyperplasia (1–6).

Drug-eluting stents, as well as intravascular brachytherapy, target several mechanisms to decrease proliferation of vascular smooth muscle cells, which contribute to the restenotic process. However, intravascular brachytherapy was later associated with a considerably high incidence of late thrombosis, complicating the clinical outcomes (7,8). Through the use of intravascular ultrasound (IVUS), several unusual observations, including unhealed stent edge dissections and incomplete stent apposition (ISA), were made after brachytherapy (9,10). This unusual IVUS finding has received much attention, given the concern that ISA could possibly contribute to one of the factors related to thrombosis (8,11). To date, the incidence of incomplete apposition in DES, however, has not been well investigated. Thus, the aim of our study was to identify the frequency of ISA in sirolimus-eluting stents (SES) and clarify its findings and clinical sequelae.

METHODS

Study population and protocol. The study population consisted of patients with completed serial IVUS analysis from the Sirolimus-Eluting Stent in De Novo Coronary Lesions (SIRIUS) trial (12), a multicenter, randomized, double-blind study that evaluated the safety and effectiveness of the sirolimus-coated Bx Velocity stent compared with the uncoated Bx Velocity balloon-expandable stent (Cordis Corp., Warren, New Jersey) in de novo native coronary artery lesions. At 16 sites, IVUS was performed after the procedure and at eight-month follow-up. Lesions ≥15 mm and ≤30 mm in length and vessels ≥2.5 mm and ≤3.5 mm in diameter were included. Multiple stent use was allowed as needed at the operator's discretion. Two types of stent length (8 and 18 mm) were available for both groups,

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Abbreviations and Acronyms

BMS = bare-metal stent
DES = drug-eluting stent
EEM = external elastic membrane
ISA = incomplete stent apposition
IVUS = intravascular ultrasound
SES = sirolimus-eluting stent
SIRIUS = Sirolimus-Eluting Stent in De Novo Coronary Lesions study

with diameter line-ups of 2.5, 3.0, and 3.5 mm. Protocols were approved by the local human subjects committee in all participating institutions, and all patients gave written, informed consent.

IVUS imaging and analysis. After administration of intracoronary nitroglycerin, IVUS images were acquired using commercially available imaging systems with automated transducer pullback (0.5 mm/s). The IVUS images were interpreted at an independent core laboratory (Stanford Cardiovascular Core Analysis Laboratory) blinded to the treatment protocols.

Qualitative analysis involved review of all IVUS tapes for the presence of ISA. Incomplete stent apposition was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches. Resolved ISA was defined as ISA observed at baseline but not at follow-up. Persistent ISA was defined as ISA observed both at baseline and follow-up. Late-acquired ISA was defined as ISA observed at follow-up but not at baseline. Typical IVUS images of late-acquired ISA are shown in Figures 1 and 2. The adjudication of the opinions was based on the consensus of three independent analysts (J. A., Y. H., and S. S.).

Quantitative analysis was performed using computerized planimetry (TapeMeasure, Indec Systems Inc., Mountain View, California). Quantitative measurements of incompletely apposed sections included the external elastic membrane (EEM), stent, and lumen area. The angle of ISA was measured using an electronic protractor centered on the lumen. We also measured the baseline plaque thickness corresponding to the apposed and non-apposed wall segments. Quantitative measurements were performed at the area of greatest stent-lumen separation at follow-up IVUS imaging and matched with the corresponding image from after the intervention.

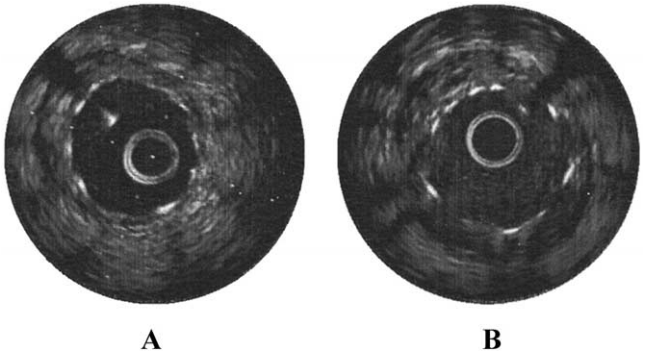

Figure 1. Intravascular ultrasound images of sirolimus-eluting stents with late incomplete stent apposition **(A)** after stent implantation and **(B)** at eight-month follow-up. The stent was well apposed to the vessel wall at the time of implantation.

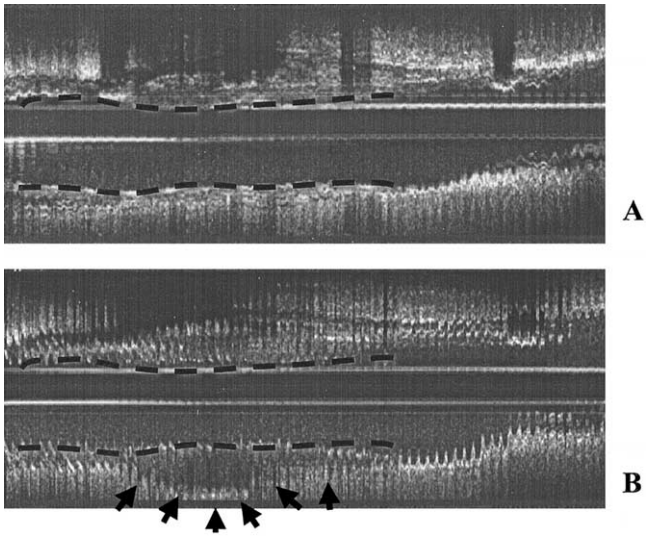

Figure 2. Longitudinal images showing late incomplete stent apposition after sirolimus-eluting stent implantation: **(A)** after stent implantation; **(B)** at eight-month follow-up. Detachment of the vessel wall **(arrows)** from stent strut **(dotted lines)** was observed in the mid portion of the stent and in the relatively normal side of the vessel wall.

Statistical analysis. Statistical analysis was performed using StatView 5.0 (SAS Institute Inc., Cary, North Carolina). Continuous data are presented as the mean value ± SD, and categorical data are presented as frequencies. Continuous variables between persistent ISA and late-acquired ISA were compared by use of the unpaired Student *t* test; otherwise, the paired Student *t* test was used for comparing continuous variables. Categorical variables were compared using chi-square statistics or the Fisher exact test. The Fisher exact test was used if there was an expected cell value <5. Significance was assumed at a value of $p < 0.05$.

RESULTS

A total of 1,101 patients were enrolled in the SIRIUS trial, with serial qualitative IVUS analyses available in 141 patients (bare-metal stents [BMS]: n = 61; SES: n = 80). Table 1 summarizes the frequency of ISA in the SIRIUS trial. At follow-up, ISA was observed in 19 patients (BMS: n = 6

Table 1. Frequency of ISA in BMS and SES

	BMS (n = 61)	SES (n = 80)
Resolved ISA	3 (4.9%)	7 (8.7%)
Persistent ISA	6 (9.8%)	6 (7.5%)
Late-acquired ISA	0	7 (8.7%)*

*$p < 0.05$. Data are presented as the number (%) of subjects.
BMS = bare-metal stents; ISA = incomplete stent apposition; SES = sirolimus-eluting stents.

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[9.8%]; SES: n = 13 [16.3%]; p = NS). A synchronous comparison between the post-interventional IVUS image and the follow-up IVUS image showed 12 cases of ISA within both vessel segments (persistent ISA) (BMS: n = 6 [9.8%]; SES: n = 6 [7.5%]; p = NS). The other seven cases, all of which were randomized to the SES group, demonstrated ISA only at follow-up (late-acquired ISA). In 10 cases, ISA observed at baseline was resolved and was not present at follow-up (resolved ISA). In patients with late-acquired ISA, there were six males and one female (ages 56 ± 11 years), with cardiac risk factors of hypercholesterolemia in one (14%), diabetes mellitus in one (14%), and hypertension in five (71%). In two late-acquired ISA cases, there were two loci of stent-vessel separation within one stented segment.

Among SES, the frequency of late-acquired ISA was 8.7% (5 of 57) with single stent implantation and 8.7% (2 of 23) with multiple stent implantations. There was no late-acquired ISA originating from stent overlap. Three late-acquired ISA segments showed an increase >20% in EEM, including one angiographically apparent aneurysm. The increased area for both the EEM and lumen was seen without change in plaque area (Table 2). Seven of nine late-acquired ISA segments were directly associated with the nearly normal vessel walls with thinner baseline plaque than the opposite arc. The average baseline plaque was thinner on the non-apposed side than on the opposite side (0.47 ± 0.28 mm vs. 1.1 ± 0.58 mm, respectively; $p < 0.05$).

Table 3 shows comparative data between cases of persistent ISA versus late-acquired ISA. Late-acquired ISA had greater lumen separation from stent struts, with positive vessel remodeling. The location of stent-vessel wall separation was primarily at the edges in persistent ISA, whereas late-acquired ISA of SES occurred mostly in the mid portion of the stent.

DISCUSSION

This serial IVUS comparative study from the SIRIUS trial identified an 8.7% incidence of late-acquired ISA seen only in the SES group. Similarly, the RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial reported a 20% incidence of ISA in SES at follow-up (6). However, the RAVEL trial lacked post-stent IVUS analysis; therefore, both late-acquired ISA and persistent ISA were considered to be included, contributing to the high incidence reported. In our present study, late-acquired ISA did not occur in the BMS group. Late-acquired ISA is reported to occur at a frequency of 1% to 5% with BMS implantation (13,14). Although direct comparisons between these studies cannot be made because of patient differences and multi-device approaches (13), our results suggest that ISA occurred with a greater incidence in SES compared with BMS.

Table 2. Baseline and Follow-Up Intravascular Ultrasound Cross-Sectional Measurements of Late-Acquired Incomplete Stent Apposition

	After Intervention	Follow-Up
EEM (mm^2)	16.2 ± 2.7	18.9 ± 3.6*
PA (mm^2)	8.0 ± 2.0	8.0 ± 2.1
LA (mm^2)	8.2 ± 1.9	11.0 ± 2.8*

*$p < 0.05$. Values are presented as mean ± SD.
EEM = external elastic membrane area; LA = lumen area; PA = plaque area.

Table 3. Persistent and Late-Acquired ISA

	Persistent ISA	Late-Acquired ISA	p Value
Gap, mm	0.4 ± 0.1	0.7 ± 0.3	<0.05
Arc (°)	103 ± 19	145 ± 53	<0.05
Follow-up LA, mm^2	9.0 ± 2.2	11.0 ± 2.9	NS
Follow-up EEM, mm^2	17.9 ± 5.7	18.9 ± 3.6	NS
ΔEEM, mm^2	0.0 ± 1.4	2.6 ± 3.2	<0.05
Location (%)			<0.01
Mid portion	17	78	
Stent edges	83	22	

Values are presented as mean value ± SD or frequencies.
ΔEEM = follow-up EEM − post-intervention EEM; other abbreviations as in Tables 1 and 2.

The mechanism of late-acquired ISA in SES was mainly focal positive vessel remodeling, as previously reported in BMS (14,15). In three ISA segments, there was an increase >20% in vessel area. The plaque area was not significantly different between post-intervention and follow-up, which suggests that plaque regression (9), as seen with intravascular brachytherapy, is not the primary reason for late-acquired ISA in SES. Incomplete stent apposition was mainly observed on the relatively disease-free side of the vessel wall (78%), which lends further support to this theory. More injury to the vasoelastic normal wall, coupled with a drug that may delay the healing process, could contribute to this phenomenon.

The frequency of ISA per patient was quite similar in both single and multiple stent cases. In addition, late-acquired ISA was not seen originating from stent overlap. Thus, late-acquired ISA may not be a dose-dependent event of sirolimus. From our patient subset, multiple stenting did not seem to predispose vessel wall separation from stent struts; however, studies involving a larger patient population may be necessary to confirm this observation.

Previous reports demonstrated ISA at the edges of the stent in intravascular brachytherapy (16), as well as ISA after BMS implantation (13). In the present study, late-acquired ISA in SES largely occurred in the mid portion of the stent. The location within the stent, distinct from previous reports, characterizes late-acquired ISA with SES, in agreement with the results of the RAVEL trial. The different locations of ISA indicate involvement of different biologic processes in the focal positive remodeling and subsequent development of ISA in SES. It is intriguing to note that there is relatively less efficacy of neointimal

suppression at the edges in SES (17). This asymmetric distribution of neointimal tissue within the stent may be associated with the location of late-acquired ISA with SES. Late-acquired ISA may occur due to profound localized inhibition of neointimal formation in disease-free segments of the vessel, delaying early reparative events that usually enable the vessel wall to incorporate a stent. Flow dynamics in these segments may also favor positive remodeling of the artery at sites of delayed neointimal formation, resulting in late-acquired ISA.

Incomplete stent apposition at the stent edges provides an exit for both inward and outward blood flow. On the other hand, there is a hypothetical concern that non-apposed segments in the middle of the stent may produce a different blood flow property with its cul-de-sac formation. Despite findings of either persistent or late-acquired ISA, no negative clinical events were associated with these cases at 12-month clinical follow-up. The three-year data from RAVEL trial also fail to show any increase in adverse cardiac events, despite the high incidence of incomplete apposition at follow-up (18). It is still unclear whether this particular IVUS finding may relate to future adverse events. We have yet to elucidate the natural history of this unusual IVUS finding. However, in view of the increased incidence of late-acquired ISA in SES, careful long-term follow-up is warranted.

Study limitations. First, this study is based on a relatively small number of late-acquired ISA cases, raising the possibility of selection bias. Second, IVUS is unable to identify neointima <100 μm in thickness and acellular proteinaceous material; thus, we are not able to evaluate re-endothelialization surrounding the stent struts. Third, there is a lack of evidence on clinical sequelae related to this particular morphologic IVUS finding.

Conclusions. Serial IVUS analysis from the SIRIUS trial found an 8.7% incidence of late ISA after SES implantation, with late ISA being observed primarily in the middle of the stent. Despite freedom from clinical events, careful long-term follow-up may be necessary, especially in a case environment that may have variable antiplatelet therapy.

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