A coronary aneurysm may occur after drug-eluting stent implantation and is known as one of the risk factors for stent thrombosis. Although the pathogenesis of coronary aneurysm remains unclear, several mechanisms including vessel wall injury, positive arterial remodeling, and hypersensitivity reaction of a coronary artery have been proposed. Coronary aneurysm is defined as a localized angiographic dilatation of the vessel lumen, 50% larger than the adjacent reference vessel, at late angiography. However, we have sometimes noted abnormal angiographic coronary dilatation at follow-up coronary angiography (CAG), <50% of the reference vessel, at the site of drug-eluting stent implantation, suggesting contrast staining outside the stent struts and named this finding peri-stent contrast staining (PSS). Little was known about optical coherence tomography findings of lesions with PSS.

**Background**—We have sometimes noted abnormal angiographic coronary dilatation, <50% of the reference vessel, at the site of sirolimus-eluting stent implantation, suggesting contrast staining outside the stent struts and named this finding peri-stent contrast staining (PSS). Little was known about optical coherence tomography findings of lesions with PSS.

**Methods and Results**—Between May 2008 and March 2010, we performed optical coherence tomography for 90 in-stent restenosis lesions after sirolimus-eluting stent implantation. We found PSS in 20 of the 90 lesions by coronary angiography. The differences in optical coherence tomography findings, including incomplete stent apposition, multiple interstrut hollows (MIH), strut coverage, and thrombus, were compared between lesions with PSS and those without PSS. PSS is defined as contrast staining outside the stent contour extending to >20% of the stent diameter measured by quantitative coronary angiography. MIH is defined as multiple hollows (the maximum depth >0.5 mm) existing between and outside well-apposed stent struts. Both incomplete stent apposition (60.0% versus 10%; P<0.001) and MIH (85.0% versus 25.7%; P<0.001) were frequently observed in lesions with PSS than in lesions without PSS. Among the 20 lesions with PSS, there was only 1 lesion in which we found neither MIH nor incomplete stent apposition, but only minor dissection. Uncovered struts (11.6% versus 3.9%; P=0.001), malapposed struts (2.0% versus 0.0%; P<0.001), and red thrombus (35% versus 10%; P=0.012) were frequently observed in lesions with PSS than in lesions without PSS.

**Conclusions**—PSS might be closely associated with 2 different optical coherence tomography findings, MIH and incomplete stent apposition, in lesions after sirolimus-eluting stent implantation. (Circ Cardiovasc Interv. 2012;5:649-656.)

**Key Words:** peri-stent contrast staining ■ optical coherence tomography ■ incomplete stent apposition ■ multiple interstrut hollows
relation to very late stent thrombosis (VLST) after drug-eluting stent implantation, and results of many studies in which ISA was assessed by optical coherence tomography (OCT) have been published in recent years. An ulcer-like appearance around the SES struts observed by OCT has been reported recently. We have also sometimes observed by OCT the existence of many cavities between and outside the strut struts at the site of stent implantation and named this finding multiple interstrut hollows (MIH). Little is known about the relationships between PSS and OCT findings including ISA and MIH. The aim of this study was therefore to determine the relationships between PSS and OCT findings including ISA and MIH at the site of SES implantation with PSS.

WHAT IS KNOWN

- Peri-stent contrast staining is found in ≥2% of lesions after sirolimus-eluting stent implantation.
- Peri-stent contrast staining appeared to be associated with subsequent target-lesion revascularization and very late stent thrombosis.
- Peri-stent contrast staining could be regarded as a relatively severe form of incomplete stent apposition.

WHAT THE STUDY ADDS

- Not only incomplete stent apposition but also multiple interstrut hollows were observed in the lesions with peri-stent contrast staining assessed with optical coherence tomography.
- Multiple interstrut hollows is a new optical coherence tomography finding suggesting abnormal vascular reaction after sirolimus-eluting stent implantation.

Methods

Study Design and Population

Between May 2008 and March 2010, we tried to observe the lesion using OCT at percutaneous coronary intervention in consecutive 122 in-stent restenosis (ISR) lesions after SES implantation. Thirty-two lesions were excluded because of poor image quality. Finally, 90 lesions in 83 patients in which we obtained the evaluable images of entire stented sites were included. All patients had angina or were proven to have myocardial ischemia by other modalities. We found PSS in 20 of the 90 lesions in 20 patients by CAG. We compared the differences between OCT findings including ISA, MIH, strut coverage, and existence of red or white thrombus in lesions with PSS and those without PSS. Furthermore, we examined the relationship between the morphology of PSS and OCT findings. Percutaneous coronary intervention was performed for all 90 lesions after assessment of the lesions using OCT.

Definition of OCT Findings of Multiple Interstrut Hollows, Incomplete Stent Apposition, Uncovered Stent Strut, and Red and White Thrombus

We defined MIH as (1) existence of hollows between and outside well-apposed stent struts and (2) the maximum depth of the hollows being ≥0.5 mm (Figure 1). The depth of the hollows was measured as follows: First, stent struts were traced manually in all cross-sections at 1-mm intervals through the stented site and stent area was decided. Second, the distance between the line marking stent area and the bottom of the hollows was measured. We set the threshold of MIH depth to 0.5 mm for the following reason. If there was no neointima or ISA at the stent lesion, the gap between the surface of the strut and endothelium between the struts was generally surmised about 0.12 mm of the thickness of the SES strut. If the gap reached 0.5 mm, a hollow could be clearly recognized. Furthermore, we defined PSS as contrast staining outside the stent contour extending to ≥20% of the stent diameter measured by quantitative CAG. PSS is classified into 4 morphological groups, monofocal, multifocal, segmental with irregular contour, and segmental with smooth contour, as was described previously.

Procedures for CAG and OCT

Cardiac catheterization was performed using a 6- or 7-F sheath and guiding catheter via the transradial or brachial approach. Intravenous heparin (about 100 U/kg adjusted depending on age) and intracoronary nitrates were administered at the beginning of the procedure. After initial angiography of the target vessel, OCT was performed to obtain whole information of the target vessel. A 0.016-inch OCT catheter (ImageWire, Light Lab Imaging) was advanced to the distal end of the stent through a 3-F occlusion balloon catheter. To remove the blood from the field of view, the occlusion balloon was inflated up to 0.6 atm at a proximal site of the lesion and warm lactated Ringer’s solution’s solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.7 mL/s. The entire lesion length was imaged with an auto-pullback at 1.5 mm/s and the OCT image visualized the target vessel. After all recordings, percutaneous coronary intervention was successfully performed for all lesions.

Image Analysis of CAG and OCT

Quantitative CAG analysis was performed with an automatic edge-detection system (MEDIS, QCA-CMS ver.6, the Netherlands). To assess the relationship between ISR pattern and the distance between PSS site and ISR site in 20 PSS cases, we measured the distance between PSS site with largest diameter and minimum lumen diameter site using QCA system. ISR pattern was classified as stent-edge ISR or non–stent-edge ISR. Stent-edge ISR was defined as restenosis occurring within 5 mm either side of and including the stent margin.

The OCT data were stored digitally and analyzed by an OCT imaging system (Light Lab Imaging). Cross-sectional OCT images were analyzed at every 1 mm of the stented site. Qualitative and Quantitative OCT assessment of MIH, ISA, maximal ISA area and distance, strut coverage, and existence of red or white thrombus were performed.

To assess interobserver variability in diagnosis of ISA and MIH, OCT images were analyzed independently by 2 experienced interventional cardiologists who were blinded to the clinical data. Furthermore, 1 of 2 observers evaluated all OCT images again at 4 months after initial evaluation to assess intraobserver variability in diagnosis ISA and MIH.

Definition of OCT Findings of Multiple Interstrut Hollows, Incomplete Stent Apposition, Uncovered Stent Strut, and Red and White Thrombus

We defined MIH as (1) existence of hollows between and outside well-apposed stent struts and (2) the maximum depth of the hollows being ≥0.5 mm (Figure 1). The depth of the hollows was measured as follows: First, stent struts were traced manually in all cross-sections at 1-mm intervals through the stented site and stent area was decided. Second, the distance between the line marking stent area and the bottom of the hollows was measured. We set the threshold of MIH depth to 0.5 mm for the following reason. If there was no neointima or ISA at the stent lesion, the gap between the surface of the strut and endothelium between the struts was generally surmised about 0.12 mm of the thickness of the SES strut. If the gap reached 0.5 mm, a hollow could be clearly recognized. Furthermore, we defined PSS as contrast staining outside the stent contour extending to ≥20% of the stent diameter measured by quantitative CAG. The minimum dimension of PSS according to our definition was 0.5 mm (minimum stent size 2.5 mm multiplied by 0.2 equals 0.5 mm). Therefore, we set the threshold of MIH depth to 0.5 mm. ISA was defined as clear separation of ≥1 stent strut from the vessel wall on OCT, in a vessel segment not encompassing a side-branch exit. A stent strut was considered incompletely apposed if the distance between the center reflection of the strut and the vessel wall was greater than the width of the stent strut plus the polymer coating of SES (>160 μm). Uncovered stent strut was defined as a strut without visible tissue layer on the center reflection of the strut. Thrombus was defined as masses (dimension ≥250 μm) protruding into vessel lumen. Red thrombus was characterized by high backscatter with high attenuation. White thrombus was characterized by less backscattering and homogeneous with low attenuation.
Statistical Analysis
Continuous data are expressed as mean±SD. Intergroup categorical comparison was done by Fisher exact test, and difference in mean values was tested by Student t test, at a critical level of ≤5%. If the nonnormal distribution of data was confirmed by Shapiro-Wilk test, continuous data are expressed as median±quartile deviation (this is one half the difference between the 25th and 75th percentiles) and intergroup difference was tested by Mann-Whitney U test. Multiple lesions within the same patient were assumed to be independent of each other. We evaluated inter- and intraobserver variability in diagnosis of ISA and MIH using Cohen’s coefficient κ. All data were analyzed using SPSS software (version 11.0.1).

Results
Baseline Patient and Lesion Characteristics
The study population is as shown in Figure 2. Patient characteristics and lesion characteristics with and without PSS are shown in Table 1. There was no significant difference between patient characteristics or lesion characteristics with PSS and those without PSS except for sex (35.0% versus 8.6%; P=0.007).

OCT Analysis
The differences between OCT findings including ISA and MIH in lesions with PSS and those without PSS are shown in Figure 3. Both ISA (60.0% versus 10%; P<0.001) and MIH (85.0% versus 25.7%; P<0.001) were frequently observed in lesions with PSS than in lesions without PSS. Representative OCT findings in lesions with PSS are shown in Figures 4–6.

In lesions with PSS, both MIH and ISA were found in 10 lesions (50%) (Figure 7). There was only 1 case in which we found neither MIH nor ISA but only minor dissection (Figure 8).

The differences between OCT findings including strut coverage, strut malapposition, the maximal ISA area and distance, and existence of red or white thrombus in lesions with PSS and those without PSS are shown in Table 2. Uncovered struts (11.6% versus 3.9%; P=0.001), malapposed struts (2.0% versus 0.0%; P<0.001), and red thrombus (35% versus 10%; P=0.012) were frequently observed in lesions with PSS than in lesions without PSS. In ISA cases, the maximal ISA area (1.35±0.80 mm² versus 0.48±0.25 mm²; P=0.014; mean±SD) and the maximal ISA distance (0.67±0.26 mm

Table 1. Patients and Lesion Characteristics of 90 Lesions With and Without PSS

<table>
<thead>
<tr>
<th></th>
<th>Total (n=90)</th>
<th>PSS (+) (n=20)</th>
<th>PSS (−) (n=70)</th>
<th>Univariate P Value</th>
</tr>
</thead>
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<tr>
<td>Sex, F (%)</td>
<td>13 (14.4%)</td>
<td>7 (35.0%)</td>
<td>6 (8.6%)</td>
<td>0.007</td>
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<td>Age, y</td>
<td>69.6±9.0</td>
<td>70.6±10.6</td>
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<td>HT, n (%)</td>
<td>65 (72.2%)</td>
<td>15 (75.0%)</td>
<td>50 (71.4%)</td>
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<tr>
<td>DM, n (%)</td>
<td>45 (50.0%)</td>
<td>10 (50.0%)</td>
<td>35 (50.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>HL, n (%)</td>
<td>44 (48.9%)</td>
<td>10 (50.0%)</td>
<td>34 (48.6%)</td>
<td>1.000</td>
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<tr>
<td>ACS, n (%)</td>
<td>17 (18.9%)</td>
<td>6 (30.0%)</td>
<td>11 (15.7%)</td>
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</tr>
<tr>
<td>Lesion, n (%)</td>
<td>34 (37.8%)</td>
<td>7 (35%)</td>
<td>27 (38.6%)</td>
<td>1.000</td>
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<tr>
<td>RCA</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>LAD</td>
<td>44 (48.9%)</td>
<td>10 (50.0%)</td>
<td>34 (48.6%)</td>
<td>1.000</td>
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<tr>
<td>LCX</td>
<td>10 (11.1%)</td>
<td>3 (15.0%)</td>
<td>7 (10.0%)</td>
<td>0.686</td>
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<tr>
<td>Graft</td>
<td>2 (2.2%)</td>
<td>0 (0.0%)</td>
<td>2 (2.9%)</td>
<td>1.000</td>
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<tr>
<td>RD, mm</td>
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<td>2.84±0.40</td>
<td>2.82±0.39</td>
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<tr>
<td>Duration, mo</td>
<td>24.7±15.3</td>
<td>26.2±12.4</td>
<td>24.3±16.1</td>
<td>0.619</td>
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</table>

PSS, peri-stent contrast staining; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; ACS, acute coronary syndrome at sirolimus-eluting stent implantation; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RD, referential diameter; Duration, mean period between sirolimus-eluting stent implantation and the examination using optical coherence tomography.

All continuous data are expressed as mean±SD.
versus 0.42±0.09 mm²; P=0.032; mean±SD) were greater in lesions with PSS than in lesions without PSS.

The relationship between the morphology of PSS and OCT findings is shown in Table 3. There was no difference between the prevalences of MIH and ISA in focal type of PSS and those in segmental type of PSS (77.8% versus 90.9%; P=0.566; 66.7% versus 54.5%; P=0.670, respectively).

In PSS cases, the distance between PSS site and minimum lumen diameter site are as shown in Table 4. In 20 PSS cases, stent-edge ISR was found in 8 cases. In these 8 stent-edge ISR cases, PSS was frequently observed within 5 mm of ISR site, in comparison with non–stent-edge ISR cases (62.5% versus 8.3%; P=0.0181).

The changes of angiographic and OCT findings at the PSS site before and after percutaneous coronary intervention are also shown in Table 4. PSS disappeared angiographically in 5 of 20 cases. In these 5 cases, no ISA was observed and MIH was observed in only 2 cases.

Reproducibility of OCT Analysis

Inter- and intraobserver variability (κ values) in the qualitative OCT assessment was as follows: 0.90/0.93 for ISA, 0.91/0.93 for MIH.

Figure 3. The prevalence of optical coherence tomography findings of incomplete stent apposition (ISA) and multiple interstruts hollows (MIH) in patients with peri-stent contrast staining (PSS) and without PSS. Both ISA and MIH were more frequently observed in lesions with PSS than in lesions without PSS.

Figure 4. Optical coherence tomography (OCT) findings in representative cases of peri-stent contrast staining (PSS), after sirolimus-eluting stent implantation. A and B, coronary angiography (CAG) showed PSS at left circumflex artery lesion (LCX). C, Magnified view of PSS. D to F, OCT showed multiple interstruts hollows (MIH). Hollows existed between and outside well-apposed stent struts.

Figure 5. Optical coherence tomography (OCT) findings in representative cases of peri-stent contrast staining (PSS), after sirolimus-eluting stent implantation. A and B, CAG showed PSS at left anterior descending artery lesion. C, Magnified view of PSS. D to F, OCT showed incomplete stent apposition (ISA), at proximal site and MIH at distal site.
We recently defined PSS as an angiographical finding of contrast medium stain outside the stent and reported that PSS is associated with stent thrombosis in lesions after SES implantation. In this study, we systematically assessed OCT findings in the lesions with PSS to clarify the pathophysiology of stent thrombosis in lesions with PSS. The most important finding of this study is that ISA and MIH were frequently observed in lesions with PSS after SES implantation. Although we previously reported that PSS could be regarded as a relatively severe form of ISA, not only ISA but also MIH was frequently observed in lesions with PSS in this study. Furthermore, uncovered struts, malapposed struts, and red thrombus were frequently observed in the lesions with PSS compared with the lesions without PSS. These results suggested that PSS was associated with endothelial delayed healing and could be a risk factor for stent thrombosis. These results were consistent with our previous report.

Although intravascular ultrasound finding of ISA is known as one of the risk factors for stent thrombosis, OCT finding of ISA remains unclear whether it can be a risk factor for stent thrombosis or not. In this study, the maximal ISA area and distance were greater in lesions with PSS than in lesions without PSS. This result might suggest that greater area and distance of ISA could be associated with stent thrombosis. However, it is still not known whether MIH can be related to stent thrombosis.

Several mechanisms of ISA including positive arterial remodeling, vessel wall injury at stent implantation, dissolution of jailed thrombus or plaque debris, and hypersensitivity...
reaction of coronary artery have been proposed, but the mechanism of PSS is still unclear. Kon et al reported a case with PSS in a lesion after SES implantation. In that case, serial changes in PSS leading to a coronary aneurysm as well as histopathological evidence of hypersensitivity reaction were found. Inflammatory cells had also infiltrated the media, causing medial destruction, which might result in loss of elastic integrity of the vessel wall leading to ISA. Little is known about the pathophysiology of MIH. Moreover, it is not known whether MIH is a precondition of ISA or not. In our study, MIH and ISA coexisted in half of the PSS cases, and they coexisted at the same site in some cases. Although the pathogenesis of MIH remains unclear, these results suggest that the pathophysiology of MIH might be the same as that of ISA. We speculated that only the intima, and not the media, of the vessel wall is infiltrated and destroyed by inflammatory cells in the lesion with MIH.

Peri-stent ulcer-like formation after drug-eluting stent implantation has recently been reported. Sawada et al reported a case with VLST after SES implantation in which they observed partial stent malapposition and ulcer-like appearance around the SES struts by OCT. Morino et al also reported a case with PSS after SES implantation. They found an unusual bell-shaped appearance by OCT in the lesion. The OCT findings of their cases were similar to those of MIH. Though the above reports were for only 1 case, we collected data for cases of the same condition and made a systematic evaluation of the findings using OCT in our study. Goto et al reported that peri-stent ulcer-like appearance by OCT was observed in 50% of the lesions after SES implantation. The definition of peri-stent ulcer-like appearance was unclear, and the incidence of peri-stent ulcer-like appearance was high compared with the incidence of MIH in our study. Peri-stent ulcer-like appearance in their study might be different from MIH in our study. In these past reports, the definition of MIH is not clear. In our study, we defined MIH quantitatively and showed close associations among ISA, MIH, and PSS, which has been proven to have a relationship with stent thrombosis. In this regard, our OCT finding of MIH might have a close association with stent thrombosis and have clinical significance.

Intravascular ultrasound finding of ISA is known as one of the risk factors for stent thrombosis, and Lee et al reported the significance of serial change in stent malapposition in patients with VLST. We also reported that the progression of PSS is associated with VLST in patients after SES implantation. Moreover, Kon et al reported that the progression of PSS was associated with VLST in a case report. In this regard, serial assessment of PSS including ISA and MIH might be important and might clarify the pathophysiology of stent thrombosis.

In this study, ISA or MIH was observed in lesions without PSS, though the prevalence of these findings was low. This was because OCT has higher spatial resolution than CAG. It is not clear whether these findings in lesions without PSS

| Table 2. The Differences Between OCT Findings in Lesions With PSS and Those Without PSS |
|---------------------------------------------|-----------------|-----------------|
| Number of analyzed cross-sections/patient,* n | 28±5.0          | 28±5.0          |
| Number of analyzed struts/patient, n        | 208±36          | 208±44          |
| Number of uncovered struts/patients,* n     | 23.0±27.8       | 7.0±14.0        |
| Frequency of uncovered struts/patients,* %  | 11.6±10.0       | 3.9±6.0         |
| Number of malapposed struts/patient,* n     | 4.5±16.8        | 0.0±0.0         |
| Frequency of malapposed struts/patients,* % | 2.0±7.0         | 0.0±0.0         |
| Red thrombus, n (%)                         | 7 (35)          | 7 (10)          |
| White thrombus, n (%)                       | 1 (5)           | 8 (11)          |
| ISA cases                                   | n=12            | n=7             |
| Maximal ISA area, mm²                       | 1.35±0.80       | 0.48±0.25       |
| Maximal ISA distance, mm                    | 0.67±0.26       | 0.42±0.09       |
| Number of malapposed struts/patient,* n     | 15.5±13.5       | 2.0±6.0         |
| Frequency of malapposed struts/patients,* % | 6.4±6.0         | 1.0±3.0         |

OCT indicates optical coherence tomography; PSS, peri-stent contrast staining; and ISA, incomplete stent apposition. Continuous data with an asterisk are expressed as median=quartile deviation. Other continuous data are expressed as mean±SD.

| Table 3. Relationship Between the Morphology of PSS and OCT Findings |
|-----------------------------|-----------------|-----------------|
| N (%)                        | MIH+  | MIH+  | MIH+  | MIH+  |
| Focal type                   |       |       |       |       |
| Monofocal                    | 9 (45) | 5     | 2     | 1     |
| Multifocal                   | 5 (25) | 3     | 0     | 1     |
| Segmental type               | 4 (20) | 2     | 2     | 0     |
| Irregular-contour           | 11 (55) | 5    | 5    | 1     |
| Smooth-contour              | 5 (25) | 3     | 1     | 1     |

PSS indicates peri-stent contrast staining; OCT, optical coherence tomography; MIH, multiple interstrut hollows; and ISA, incomplete stent apposition.

...
were associated with stent thrombosis. Further examination is needed.

In this study, there was a case in which we found neither MIH nor ISA but only minor dissection. In this case, minor dissection remained without restoration of the vessel injury just after SES implantation due to sirolimus-mediated delayed wound healing.

All of the lesions in this study were ISR lesions. We examined the distances between PSS site and ISR site in PSS cases and found that PSS was also located at stent-edge site in 5 of 8 stent-edge ISR cases. This result suggested that mechanical stress of stent-edge on the vessels might be related to not only ISR but also PSS.

There are several limitations in this study. First, all of the lesions in this study were ISR lesions and there might be selection bias. It might be better to perform OCT for nonrestenosis lesions with PSS after SES implantation. Second, we should assess PSS lesions after implantation of other DESs by OCT because we do not know whether MIH is a specific OCT finding in lesions after SES implantation or not. Third, we could not find a difference in OCT findings among the morphological types of PSS. A study with a larger number of subjects is needed to clarify the association between morphology of PSS and OCT findings. Finally, we could not perform serial follow-up OCT to assess PSS. Serial observation of PSS with OCT might provide more information about the cause and course of PSS.

Conclusions
PSS might be closely associated with 2 different OCT findings, MIH and ISA, in lesions after SES implantation.

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Disclosures
None.

References
Optical Coherence Tomography Findings in Lesions After Sirolimus-Eluting Stent Implantation With Peri-Stent Contrast Staining

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