Coronary Restenosis After Sirolimus-Eluting Stent Implantation
Morphological Description and Mechanistic Analysis From a Consecutive Series of Cases

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Background—We describe the clinical and morphological patterns of restenosis after sirolimus-eluting stent (SES) implantation.

Methods and Results—From 121 patients with coronary angiography obtained 30 days after SES implantation, restenosis (diameter stenosis >50%) was identified in 19 patients and 20 lesions (located at the proximal 5-mm segment in 30% or within the stent in 70%). Residual dissection after the procedure or balloon trauma outside the stent was identified in 83% of the proximal edge lesions. Lesions within the stent were focal, and stent discontinuity was identified in some lesions evaluated by intravascular ultrasound.

Conclusions—Sirolimus-eluting stent edge restenosis is frequently associated with local trauma outside the stent. In-stent restenosis occurs as a localized lesion, commonly associated with a discontinuity in stent coverage. Local conditions instead of intrinsic drug-resistance to sirolimus are likely to play a major role in post-SES restenosis. (Circulation. 2003; 108:257-260.)

Key Words: restenosis ■ stents ■ angioplasty

Sirolimus-eluting stents (SES) have been reported to reduce restenosis by inhibiting neointimal growth, though post-SES restenosis may still occur in some cases. Currently, the clinical and morphological features of restenosis after SES implantation are unknown. In this study, we describe a consecutive series of patients with angiographic restenosis after SES implantation.

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Methods
Since April 2002, SES (Cypher; Cordis Europa NV) have been used as the device of choice for percutaneous coronary intervention in our institution, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, a single-center registry designed to evaluate the impact of SES implantation in the “real world.” During follow-up, coronary angiograms were obtained as clinically indicated by symptoms or positive ischemic tests. In addition, follow-up angiograms were obtained at 6±1 month for “complex” patients, typically with SES implantation to treat in-stent restenosis, bifurcations, left main, chronic total occlusions, very small vessels (SES diameter 2.25 mm), long stented length (>36 mm), and acute myocardial infarction. Intravascular ultrasound (IVUS) was performed at the discretion of the operator. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all patients.

Binary restenosis was defined by diameter stenosis >50% and classified as (1) in-stent, if inside the stent, or (2) edge restenosis, if located within the 5-mm segments distal or proximal to the stent margins. Restenosis at an ostial location was classified as in-stent, unless clearly located outside the limits of the SES, in which case it was classified as edge restenosis. Discrete variables were presented as counts and percentages. Continuous variables were presented as mean±SD and compared by Student’s t test.

Results
To date, 192 patients with at least one of the aforementioned “complex” characteristics have completed ≥7 months from the index procedure. A coronary angiogram performed >30 days after the angioplasty was obtained in 121 patients (221 lesions). Among these, post-SES restenosis was identified in 19 patients and 20 lesions (Table). IVUS was available at follow-up for 11 patients with restenosis (58%). In total, 6 lesions (30%) were located at the proximal edge and 14 were
Patients With Restenosis After Sirolimus-Eluting Stent Implantation: Clinical, Procedural, and Morphological Characteristics

| Patient No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | Total |
|-------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|     |
| Age, y      | 63| 77| 52| 66| 70| 78| 77| 58| 69| 43 | 58 | 50 | 52 | 50 | 46 | 72 | 45 | 48 | 61 | 56 ± 11 |
| Gender      | M | M | M | M | M | F | M | M | M | M | M | M | M | M | M | M | M | M | 89% (men) |
| Diabetes    | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 37% |
| Symptoms/ischemia at follow-up | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 58% |
| Lesions treated | 1 | 1 | 1 | 3 | 1 | 3 | 2 | 3 | 2 | 3  | 2  | 3  | 2  | 1  | 2  | 2  | 1  | 1  | 2  | 42 |
| Lesions with restenosis | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 20 (48%) |
| Vessel      | LAD| LAD| LAD| DG| SVG| LAD| LCx| RCA| RPL| LCx| DG| DG| LAD| RCA| SVG| LCx| RCA| DG| ... |
| Procedural, angiographic, and IVUS findings | | | | | | | | | | | | | | | | | | | |
| Treatment of previous in-stent restenosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 25% |
| Moderate/severe calcification | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 25% |
| CT0         | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 35% |
| Trauma outside the stent/residual dissection | + | + | + | + | 0 | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 83%† |
| Residual edge lesion‡ | 0 | 0 | + | + | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 33%† |
| After dilation with balloon ≥0.5 mm larger | + | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 45% |
| Bifurcation stenting | 0 | 0 | +§ | 0 | 0 | +§ | 0 | 0 | +|| | 0  | +|| | +|| | 0  | +§ | 0  | 0  | 0  | 0  | +| 35% |
| Ostial       | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 30% |
| Stented length >33 mm | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 40% |
| 2.25-mm diameter SES | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 15% |
| Stent fracture or gap between stents¶ | 0 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0 | + | 0 | 0 | + | 50%# |
| Stent underexpansion at restenosis site¶ | 0 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | + | 0 | 0 | 0 | 0 | 25%# |
| No. of any above (‡+diabetes) | 2 | 3 | 5 | 5 | 4 | 3 | 2 | 1 | 3 | 3 | 4 | 3 | 2 | 3 | 5 | 4 | 3 | 5 | 5 | 4 | Range 1–5 |
| Post-SES restenosis characteristics | | | | | | | | | | | | | | | | | | | |
| Location | prox | prox | prox | prox | prox | prox | in-st | in-st | in-st | in-st | in-st | in-st | in-st | in-st | in-st | in-st | in-st | in-st | in-st |
| Total occlusion | 0 | 0 | 0 | 0 | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10% |
| Focal lesion (length <10 mm) | + | + | + | 0 | 0 | + | + | + | 0 | 0 | 0 | 0 | + | + | + | + | + | + | + | + | + | +** + | +** + | +** + | 86%†† |

CTO indicates chronic total occlusion; DG, diagonal; IVUS, intravascular ultrasound; in-st, in-stent restenosis; LAD, left anterior descending; LCx, left circumflex artery; NA, IVUS not available; prox, proximal edge restenosis; RCA, right coronary artery; RPL, right posterolateral branch; SES, sirolimus-eluting stent; SVG, saphenous vein graft; +, present; and 0, absent.

*After brachytherapy.
†Relative to proximal edge restenosis.
‡Angiographic diameter stenosis >30% or IVUS plaque burden >50%.
§Main vessel restenosis.
∥Side branch restenosis.
¶Diagnosed by IVUS.
#Relative to the No. of in-stent restenoses with available IVUS.
**More than 1 "focal" site.
††Relative to the No. of in-stent restenoses.

In-stent (70%). Local injury outside the stent was observed in 5 cases of edge restenosis (83%), as evidenced by the presence of angiographic or IVUS residual dissection after the procedure (patients 1, 3, and 4), by balloon dilation at a nonstented area in a patient with extensive manipulation before and after implantation of 4 stents for acute occlusion (patient 2), or by balloon postdilation outside the stent (patient 5).
Among the 14 in-stent lesions, 12 (86%) were focal (restenosis length <10 mm) and presented a peculiar angiographic pattern manifested by a very localized stenotic site bordered by segments without evidence of lumen compromise (Figure, A). Stenosis length decreased from $19.1 \pm 19.1$ mm at baseline to $7.6 \pm 5.6$ mm at follow-up ($P=0.046$). The ratio of restenosis length/stent length was $0.3 \pm 0.2$. A gap between stents or stent fracture at the site of the restenosis was detected by IVUS in 4 patients at follow-up. A gap was diagnosed by the absence of stent struts in at least one IVUS cross section in the examination of the region between two stents (patients 13, 18, and 19); a stent fracture was diagnosed by the nonvisualization of struts within the stent (patients 15 and 18). One patient presented both stent gap and fracture in separate sites (patient 18). In this patient, no IVUS was performed at the index procedure (IVUS was done only at follow-up). In the other patient with stent fracture (patient 15), the stent discontinuity was not evident after the procedure, being only detected at the follow-up. In all cases, the stent gap or fracture could not be noticed angiographically and measured <1 mm in length by IVUS (Figure, A).

Among the 6 ostial lesions (30%), the ostium was not covered by the stent at angiographic inspection in 1 case (classified as proximal edge restenosis). The remaining 5 lesions appeared to be fully covered by the stent on angiography. IVUS was available for only one of these cases. In this patient, although angiographically unnoticed, a short area at the ostium was observed to be uncovered by SES (Figure, B). Among the 6 ostial lesions, 4 were located in the side branch of bifurcation stenting treatment, all treated with “T” stent technique (stent in the side branch implanted with its proximal border located at the ostium of the branch; stent in the main vessel implanted encompassing the side branch ostium, thereby creating a “T” configuration).

**Discussion**

In $\approx 90\%$ of patients with in-stent restenosis after SES implantation, the lesion was very localized and bordered by segments with no evidence of neointima. The effect of the drug in the nonrestenotic portions indicates that an intrinsic resistance to sirolimus was unlikely in most of our patients. Among lesions evaluated by IVUS, stent discontinuity was identified in 36% of cases (and in 50% of restenosis located inside the stent), suggesting that a decrease in local drug availability may have contributed to the development of restenosis in these cases. Accordingly,
our findings suggest that incomplete lesion coverage by
the SES also may influence the occurrence of restenosis at
the stent borders and at ostial sites. We may speculate that
although no clinical data are currently available, tech-
niques that ensure complete vessel scaffolding could
constitute an alternative for SES implantation at bifurca-
tions. Edge restenosis occurred more frequently in the
proximal than in the distal stent border. Whether this
finding is associated with a more effective drug effect in
the outflow stent border remains to be clarified. In addi-
tion, 37% of our cases were diabetics. It may be hypoth-
esized that the presence of diabetes mellitus may lead to a
higher predisposition to post-SES restenosis.

The current study presents several limitations. Angio-
graphic follow-up was available for complex patients or for
those with recurrent symptoms, therefore precluding an
evaluation of the total restenosis rate for the global treated
population. Moreover, the lack of IVUS limits a more
detailed description of the mechanisms involved in the
occurrence of post-SES restenosis in some patients.

Conclusions
Restenosis after sirolimus-eluting stent placement occurs
within or adjacent to the stent. Edge restenosis is fre-
quently associated with local trauma outside the stented
segment. In-stent restenosis occurs as a very localized
lesion, associated with complex anatomy (especially ostial
lesions), stent discontinuity, or diabetes. A systemic drug
resistance to sirolimus seemed to be unlikely in most
patients.

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