Brief Rapid Communications

Preliminary Observations Regarding Angiographic Pattern of Restenosis After Rapamycin-Eluting Stent Implantation

Antonio Colombo, MD; Dejan Orlic, MD; Goran Stankovic, MD; Nicola Corvaja, MD; Vassilis Spanos, MD; Matteo Montorfano, MD; Francesco Liistro, MD; Mauro Carlino, MD; Flavio Airoldi, MD; Alaide Chieffo, MD; Carlo Di Mario, MD, PhD

Conclusions—The pattern of restenotic lesions after rapamycin-eluting stent implantation was focal and mostly inside the rapamycin-eluting stents. 1,2 Although in the first published report (RAVEL [Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions]), including only lesions covered by an 18-mm-long stent (mean lesion length, 9.56±3.33 mm), no patient had restenosis, in a recent trial (SIRIUS [US Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions]) dealing with longer lesions (mean lesion length, 14.4±5.7 mm), restenosis was observed in 9.2% of patients treated with rapamycin-eluting stents. The restenosis segment occurred at the stent margins or at the site of a gap in 64.5% of the cases, and 87% of the restenosis was focal. However, these studies enrolled only patients fulfilling strict inclusion criteria. The present report describes all of the cases of symptomatic restenosis so far detected after implantation of the rapamycin-eluting stent in unselected lesions.

Methods

For this analysis, all consecutive patients referred to Columbus Hospital and to San Raffaele Hospital from April 16 to December 6, 2002 who underwent percutaneous coronary intervention using rapamycin-eluting stent (Cypher, Cordis, a Johnson & Johnson Company) implantation were selected. Stenting procedures were performed in the usual fashion. 3 All stents were implanted with high-pressure (>12 atm) final stent dilatation with an attempt to fully cover the angiographic lesion with the stent. For lesions located at the bifurcation site, the T stenting technique was used to treat the main branch and the side branch. Intravascular ultrasound (IVUS) was rarely used, only when necessary according to the operator decision. At the time of drug-eluting stent implantation, an angiogram was performed with the stent at the desired location and before deployment to assess the exact location of the stent in reference to side branches. This information was used at the time of follow-up angiography to establish the correct location of the restenotic lesion. Patients receiving 2 or more stents or 1 long stent (33 mm) were treated with elective glycoprotein IIb/IIIa antagonists. Patients were pretreated with Ticlopidine or Clopidogrel. A loading dose of 300 mg Clopidogrel was given to patients who were not pretreated. Aspirin and Clopidogrel were continued for at least 3 months or up to 6 months to 1 year when 2 or more stents were implanted. Angiographic follow-up was suggested between 8 and 12 months after stenting, unless clinically indicated to be performed at an earlier time. Previously proposed classification of angiographic pattern of in-stent restenosis was used. 4 Focal restenosis was defined as a restenotic lesion ≤10 mm in length. Multifocal restenosis was defined as the presence in the same stented segment of >1 focal restenosis with a normal segment in between. Quantitative coronary...

Background—Restenosis after implantation of drug-eluting stents (DES) is a rare phenomenon, occurring more frequently than ever. 1,2 Although in the first published report (RAVEL [Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions]), including only lesions covered by an 18-mm-long stent (mean lesion length, 9.56±3.33 mm), no patient had restenosis, in a recent trial (SIRIUS [US Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions]) dealing with longer lesions (mean lesion length, 14.4±5.7 mm), restenosis was observed in 9.2% of patients treated with rapamycin-eluting stents. The restenosis segment occurred at the stent margins or at the site of a gap in 64.5% of the cases, and 87% of the restenosis was focal. However, these studies enrolled only patients fulfilling strict inclusion criteria. The present report describes all of the cases of symptomatic restenosis so far detected after implantation of the rapamycin-eluting stent in unselected lesions.

Methods and Results—We evaluated the pattern of restenosis occurring after implantation of DES in unselected lesions. From April 15 to December 6, 2002, we treated 368 patients with 735 lesions by using 841 rapamycin-eluting stents (Cypher, Cordis, a Johnson & Johnson Company). Mean baseline lesion length was 17.48±12.19 mm, and mean stent length was 27.59±14.02 mm. Follow-up ischemia-driven angiography was performed in 24 patients. Eleven patients had angiographic restenosis (≧50% diameter stenosis) in 14 stented segments (stent and 5 mm proximal and distal to the stent). The pattern of restenosis in all 14 stented segments was focal, and in 6 of them it was multifocal, occurring inside the stents. Mean length of restenotic lesions was 5.62±1.90 mm, with a range from 2.54 to 8.44 mm. One multifocal restenosis involved also the distal stent margin. Intravascular ultrasound evaluation at follow-up, performed in 2 patients, showed significant lumen obstruction attributable to in-stent hyperplasia in both cases. Individual cases can be viewed in the Data Supplement.

Conclusions—The pattern of restenotic lesions after rapamycin-eluting stent implantation was focal and mostly inside the stent. (Circulation. 2003;107:2178-2180.)

Key Words: restenosis ■ stents ■ angiography

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From Columbus Hospital (A.C., D.O., G.S., N.C., V.S., C.D.M.) and San Raffaele Hospital (A.C., M.M., F.L., M.C., F.A., C.D.M.), Milan, Italy. Supplemental case information is available in the online-only Data Supplement at http://www.circulationaha.org. Correspondence to Antonio Colombo, MD, EMO Centro Cuore Columbus, Via M. Buonarroti 48, 20145, Milan, Italy. E-mail info@emocolumbus.it © 2003 American Heart Association, Inc.
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angiography analysis was performed using a validated edge-detection program (CMS version 5.2, MEDIS, Leiden, Netherlands). When the pattern of restenosis was multifocal, we performed quantitative coronary angiography analysis for each focal lesion separately.

**Results**

A total of 368 patients with 735 lesions were treated with 841 rapamycin-eluting stents. Mean baseline lesion length was $17.48 \pm 12.19$ mm, and mean stent length was $27.59 \pm 14.02$ mm. Mean baseline reference vessel diameter was $2.69 \pm 0.53$ mm.

Follow-up angiography was performed in 24 patients returning at a mean of $4.1 \pm 2.0$ months from the time of stenting for symptoms or signs suggestive of ischemia. Follow-up angiography was motivated by angina or positive stress test in 21 patients, scheduled follow-up in 2 asymptomatic patients, and planned procedure on another vessel in 1 patient. Eleven patients had angiographic restenosis ($\geq 50\%$ diameter stenosis) in 14 stented segments (stent and 5 mm proximal and distal to the stent). Mean time of follow-up angiography for these 11 patients was $5.09 \pm 1.37$ (from 2.7 to 7.2) months. Major clinical and procedural characteristics are presented in the Table. All of the individual lesions with the still frames at baseline after stenting and at the time of detection of restenosis are accessible in the online-only Data Supplement. The Figure shows the localization and length of each restenotic segment in relation to the im-

### Baseline Clinical and Angiographic Characteristics

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<th>Patient</th>
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<th>Sex</th>
<th>DM</th>
<th>Angina Type</th>
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<th>Vessel Segment</th>
<th>Lesion Type</th>
<th>No. Stents/ Lesion</th>
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<th>Max BD, mm</th>
<th>Max BP, mm Hg</th>
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BD indicates balloon diameter; BP, balloon pressure; D, diagonal branch; DM, diabetes mellitus; IM, intermediate branch; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; NID, non-insulin–dependent diabetes mellitus; OM, obtuse marginal branch; RCA, right coronary artery; and RVD, reference vessel diameter.

*Modified ACC/AHA lesion classification.
†Repeated numbers denote the presence of multiple lesions in the same patient.

Angiography analysis was performed using a validated edge-detection program (CMS version 5.2, MEDIS, Leiden, Netherlands). When the pattern of restenosis was multifocal, we performed quantitative coronary angiography analysis for each focal lesion separately.
planted stents and to their margins in patients with and without overlapping stents. One patient who developed subacute stent thrombosis 3 days after stenting was not included in this report.

The pattern of restenosis in all 14 stented segments was focal, and in 6 of them it was multifocal. Mean length of restenotic lesions was $5.62 \pm 1.90$ mm, with a range from 2.54 to 8.44 mm. One multifocal restenosis involved also the distal stent margin. IVUS evaluation at follow-up, performed in 2 patients, showed significant lumen obstruction attributable to in-stent hyperplasia in both cases.

**Discussion**

The most important and interesting finding of this report is that all the restenotic lesions were focal. Six were multifocal. This observation is concordant with findings in the Sirius trial, where 87% of restenotic lesions were focal. Another interesting finding of this report is that all restenotic lesions were located in the body of the stent, except 1 multifocal restenosis involving also the distal margin of the stent. This observation is different from findings in the Sirius trial and in the Taxus II trial (presented at Transcatheter Cardiovascular Therapeutics 2002). In both studies dealing with 2 different types of drug-eluting stents, most of the restenotic lesions were located near the stents margins or at the site of a gap between 2 stents (64.5% in the Sirius trial and 83.3% in Taxus II trial). Another observation is that 4 of 6 multifocal restenoses occurred in diabetic patients.

We can assume that in this study, the operator took a lesson from the initial report of the Sirius trial (J. Moses, M. Leon, personal communications, May, 2002) and used the Cypher stent with the objective to fully cover the baseline lesions. This approach contributed to lower any persistent restenosis with the occurrence of only 1 pattern of restenosis that is in-stent. Possible explanations are stent under expansion, uneven distribution of drug release, or nonuniform coating. In some complex lesions, asymmetrical stent expansion or suboptimal stent geometry can influence drug delivering. Unfortunately, the lack of baseline IVUS evaluation and, more importantly, of IVUS evaluation in all restenotic lesions do not permit us to draw any conclusion in this regard. Whether the present approach to fully cover the lesion with wide stent margins is the cause of lowering the incidence of peri-stent restenosis is unclear but certainly possible. Subsequent studies will be required to confirm the validity of this technique.

**What Are the Possible Practical Implications From These Findings?**

We can state that the approach to fully cover the lesion seems to contribute to lower the incidence of peri-stent restenosis. When dealing with complex lesions, the problem of in-stent restenosis may not be completely eliminated with present devices and approaches. Additional information is necessary to better elucidate these phenomena and to find appropriate solutions.

**References**

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