Drug-Eluting Stent Restenosis
The Pattern Predicts the Outcome

John Cosgrave, MRCP,* Gloria Melzi, MD,* Giuseppe G. L. Biondizi-Zoccai, MD,† Flavio Airoldi, MD,‡ Alaide Chieffo, MD,‡ Giuseppe M. Sangiorgi, MD,* Matteo Montorfano, MD,‡ Iassen Michev, MD,‡ Mauro Carlino, MD,‡ Erminio Bonizzoni, PhID,§ Antonio Colombo, MD, FACC*‡
Milan, Italy

OBJECTIVES

We sought to determine if the angiographic pattern of in-stent restenosis in drug-eluting stents (DES) maintains its prognostic importance.

BACKGROUND

The pattern of restenosis in the bare-metal stent era had a significant impact on therapeutic outcomes.

METHODS

We identified a total of 250 consecutive restenotic lesions in 203 patients (66.4% sirolimus-eluting stents and 33.6% paclitaxel-eluting stents). We divided these lesions into two groups: focal, defined as ≤10 mm, 163 lesions (65.2%); and nonfocal, which were diffuse, proliferative, or obstructive, 87 lesions (34.8%). The end points analyzed were angiographic restenosis and target lesion revascularization (TLR).

RESULTS

Diabetes was the only clinical variable associated with the pattern of restenosis (28.8% focal compared with 52.9% diffuse; p = 0.0001). Angiographic follow-up of the treatment of restenosis was available in 61.2% of the lesions and was similar between the two groups. The rate of angiographic restenosis was 17.8% in the focal group and 51.1% in the nonfocal group (p = 0.0001). The incidence of TLR also increased with the type of restenosis treated (9.8% and 23%, respectively; p = 0.007). An adjusted multivariate analysis revealed that the pattern of restenosis remained associated with both the occurrence of restenosis and TLR (odds ratio [OR] 5.1 [95% confidence interval (CI) 1.1 to 23], p = 0.03; and OR 3.61 [95% CI 1.2 to 10.9], p = 0.02; respectively).

CONCLUSIONS

Similar to bare-metal stent data, the angiographic pattern of restenosis following DES implantation is prognostically important. Diabetes is a significant predictor of the pattern of restenosis in the DES era. (J Am Coll Cardiol 2006;47:2399–404) © 2006 by the American College of Cardiology Foundation

The two commercially available drug-eluting stents (DES)—sirolimus-eluting (SES) (Cypher, Cordis/Johnson & Johnson, Warren, New Jersey) and paclitaxel-eluting (PES) (Taxus, Boston Scientific, Natick, Massachusetts)—have dramatically reduced the rate of restenosis (1–8). Not only is restenosis less common, but it is also more likely to be focal than nonfocal (2,7,9,10).

Traditionally focal restenosis has a more benign prognosis (11). Whether this hypothesis remains true in the drug-eluting stent (DES) era is currently unknown.

METHODS

Between October 2002 and October 2004 all patients treated for DES restenosis were prospectively entered into a dedicated database. In-stent restenosis (ISR) was defined as a luminal stenosis of >50% by quantitative coronary angiography located within the stent or within 5 mm of the stent edges. We divided the lesions into two groups: focal and nonfocal. Focal ISR lesions were defined as ≤10 mm in length and positioned at the body of the stent, the proximal or distal margin, or a combination of these sites (multifocal ISR). Nonfocal ISR comprised diffuse intrastent (lesions >10 mm in length and confined to the stent), diffuse proliferative (lesions >10 mm in length and extending beyond the margins of the stent), and occlusive lesions.

There were no exclusion criteria. Patients provided signed informed consent for the procedure and to allow the data to be utilized for research purposes. Procedural anticoagulation and antiplatelet therapy followed standard protocols (12). Interventional approach and the choice of therapy for the restenotic lesion were at the operator’s discretion.

Clinical follow-up was performed by telephone contact or office visit at 1, 6, 9, and 12 months after the index procedure. Angiographic follow-up was suggested for all patients at nine months after procedure. We analyzed target lesion revascularization (TLR) and angiographic restenosis calculated on a per-lesion basis. Cardiac death, myocardial infarction, target vessel revascularization (TVR), and major adverse cardiac events (MACE) were considered secondary end points. The MACE was defined as a composite of death, myocardial infarction, and TVR, which was evaluated on a per-patient basis.

All deaths were considered cardiac unless otherwise documented. A non–Q-wave myocardial infarction was defined as a total creatine kinase elevation of greater than two times the upper limit of normal in combination with an elevation in the creatine kinase-MB fraction. If this enzyme
continuous variables were compared using Student's t-test, whereas differences in location parameters of continuous variables were tested with Student t test or Wilcoxon rank sum test. Fisher exact test was used when the parametric assumptions underlying chi-square did not hold (conventionally when the number of events in one or more classes is <5). Wilcoxon rank sum test was used when the parametric assumptions underlying Student t test did not hold (in general when data are expressed as scores or when it is universally accepted that they are not normal distributed). All the categoric variables were compared with chi-square test, apart from prior brachytherapy, previous multiple restenosis, periprocedural myocardial infarction, cardiac death, and follow-up myocardial infarction. All continuous variables were compared using Student t test, apart from late loss.

The main purpose of our statistical analysis was to test the association between the pattern of restenosis (focal or nonfocal) and events (restenosis rate and TLR). To avoid bias due to causal confounding effects of extraneous variables, a stratified logistic regression analysis was carried out using selected potential confounding factors as stratification variables (diabetes mellitus, stent diameter at index, stent length at index, lesion length, and type of stent that restenosed). Confounding factors were detected both on an epidemiologic basis, by selecting variables based on prior judgments of their clinical relevance, and on a statistical basis, by testing for the relation to both the exposure (pattern of restenosis) and the outcome (restenosis or TLR) (14). The p value used as a cut-off to define potential confounder on statistical basis was ≥0.10. Stent diameter at index, stent length at index, and lesion length were found statistically associated to the independent variable (pattern of restenosis) and to both outcomes (restenosis and TLR), whereas diabetes and type of stent that restenosed were found statistically associated to the independent variable and to restenosis only.

Because observations recorded in the same patient cannot be considered independent, the sandwich estimator of variance-covariance matrix was used to take into account clustered data (more lesions within the same subject). The variance-covariance matrix of odds ratio (OR) estimates is obtained by default with every statistical software package. The sandwich version of the variance-covariance matrix, also called “robust covariance-matrix” is provided as an option only by specialized software (SAS Institute, Cary, North Carolina) (15).

The results were reported as adjusted OR with associated 95% confidence interval (CI) and p value. The Statistical Analysis System program version 9.1 (SAS Institute) was used for data analysis.

**RESULTS**

During the study period a total of 250 lesions in 203 patients were treated; 65.2% (163) were focal and 34.8% (87) were nonfocal. Of the nonfocal lesions, 24.3% were diffuse, 2.4% proliferative, and 8% obstructive. Baseline demographic and procedural data are presented in Table 1. The only differences between the two groups were a higher incidence of diabetes mellitus, a longer stent length, and an increased likelihood of the index lesion being an occlusion in the group treated for nonfocal restenosis. During the procedure, operators implanted another DES in 69% of nonfocal lesions versus 57.1% of focal lesions (p = 0.043). Intravascular ultrasound use and balloon inflation pressures were similar, although the maximum balloon diameter was larger in the focal group.

**Quantitative angiographic analysis.** Serial quantitative coronary angiography data are shown in Table 2. Angiographic follow-up was available in 101 lesions in the focal group (64.3%) and 47 lesions (55.3%) in the nonfocal group (p = 0.57) (Fig. 1). There was a highly significant difference in restenosis rates following retreatment between the groups (17.8% compared with 51.1%; p = 0.0001). This difference
was confirmed following adjustment for potential confounding variables (OR 5.0 [95% CI 1.1 to 23.0]; p = 0.03). The late lumen loss was lower in the focal group (0.46 [IQR 0.11 to 0.83] compared with 1.08 [IQR 0.14 to 1.8]; p = 0.007). The pattern of subsequent restenosis at follow-up remained the same in 50%, became worse in 26.2%, and improved in 23.8% (Fig. 2). Because the restenosis rate was so high in the nonfocal group, we carried out a subgroup analysis to determine if there were any features associated with the risk to develop a second restenosis in this group. The only difference was a numerically higher use of balloon angioplasty for the treatment of the nonfocal lesions that developed a second restenosis. Of the 24 lesions with nonfocal pattern that developed a second restenosis, 9 of them were treated with conventional (“plain old”) balloon angioplasty (POBA) while only 4 of 23 lesions which did not develop a second restenosis were treated with POBA at the time of the initial restenosis (37.5% vs. 17.4%; p = 0.19).

Clinical outcomes. There were no in-hospital deaths or periprocedural revascularizations (Table 3). Two patients, both in the focal group, developed a periprocedural non–Q-wave myocardial infarction. Median clinical follow-up was 13.7 months (IQR 10.7 to 19), and only one patient (in the focal group) was lost to follow-up. The TLR rate was 9.8% in the focal group compared with 23% in the nonfocal group (p = 0.007), and no patients required surgical revascularization (Fig. 3). Again, adjustment for potential confounding variables confirmed our results (OR 3.6 [95% CI 1.1 to 10.9]; p = 0.02).

For focal restenotic lesions, the TLR rate following repeated DES implantation was 8.6% compared with 11.4% following POBA (p = 0.6). For nonfocal restenotic lesions, the TLR rate following DES implantation was 22.6% and following POBA 24% (p = 1.0).

DISCUSSION

The main findings of this report are: 1) the pattern of DES restenosis is a predictor of the need for subsequent reintervention; and 2) diabetes mellitus remains a significant predictor of the pattern of restenosis.

When analyzing our data, we chose to divide the lesions into two groups: focal and nonfocal. We took this approach because of the relatively low incidence of proliferative and occlusive restenosis which could have limited the accuracy of our analysis. This higher prevalence of focal restenosis concurs with previous studies (2,7,9,10).

Our data show for the first time that the pattern of restenosis retains its prognostic importance in the era of DES implantation. Similarly to the Mehran et al. (11) data, ours have shown that the incidence of TLR increases with the severity of the pattern of restenosis treated. In the present study, there is a corresponding increase in angiographic restenosis. This should be interpreted cautiously.
owing to the low rate of angiographic follow-up, which can artificially elevate the incidence of angiographic restenosis. Despite this caveat it is important to point out that the two groups had similar follow-up rates. It is interesting to note that in the Mehran et al. (11) work diabetes mellitus and the occurrence of previous restenosis were important predictors of TLR. In fact, both were more significant predictors than the pattern of restenosis, with odds ratios of 2.8 and 2.7, respectively, whereas the odds ratio for the pattern of restenosis was 1.7. In contrast, in our data the pattern of restenosis was the only significant predictive factor of TLR on multivariate analysis (p = 0.02).

This data has important implications in the management of these patients who by definition have already failed our current best therapy. Currently little data are available on the optimal management of DES restenosis (16). It is

Figure 1. Clinical status and results of noninvasive functional tests in patients with and without angiographic follow-up. EST = stress EKG or myocardial scintigraphy or stress echocardiogram.

![Diagram](image)

**Pattern at index**  
Focal 18  
Diffuse 14  
Proliferative 2  
Oclusive 8

**Pattern at follow-up**  
Focal 22  
Diffuse 5  
Proliferative 0  
Oclusive 15

Figure 2. Pattern of restenosis at baseline and follow-up of the lesions treated which restenosed for the second time.
particularly relevant to any discussion of the management of DES restenosis that we consider that in the bare-metal stent era the TLR rate of focal restenosis was between 19% and 35% (11,17). The corresponding TLR rate in our experience is 9.8%, and even when the pattern is nonfocal the 23% TLR rate represents a significant improvement.

The different strategies used by the operators in this study including repeat DES implantation were all safe with a very low rate of periprocedural MACE and no episodes of subacute or late thrombosis. The optimal percutaneous treatment of DES restenosis remains unclear, and our data do not demonstrate any clear advantage for either modality.

**Study limitations.** This study has the limitations inherent to the analysis of retrospective data; however, it is difficult to see how these data could be obtained in a randomized fashion. Another limitation is the low rate of angiographic follow-up, albeit similar in the two groups. The majority of patients who refused angiography were clinically stable (91% asymptomatic) and had negative noninvasive tests for ischemia. This cohort of patients has undergone many procedures and are understandably reluctant to return for angiography in the absence of symptoms or noninvasive evidence of ischemia.

**Conclusions.** From this analysis of restenotic DES lesions we can conclude that the pattern of restenosis retains its importance in the DES era and that diabetes mellitus remains predictive of the pattern of restenosis.

---

**Table 3. In-Hospital and Follow-Up Clinical Events in the Total Cohort, According to the Pattern of Restenosis**

<table>
<thead>
<tr>
<th></th>
<th>Focal</th>
<th>Nonfocal</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural/in-hospital death</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Procedural/in-hospital CABG</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Periprocedural MI</td>
<td>1.5% (2)</td>
<td>0</td>
<td>0.54</td>
</tr>
<tr>
<td>Acute thrombosis</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Clinical follow-up (days)</td>
<td>447 ± 218</td>
<td>447 ± 214</td>
<td>0.99</td>
</tr>
<tr>
<td>Subacute thrombosis</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Late thrombosis</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>MACE</td>
<td>18.9% (25)</td>
<td>29.6% (21)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>3% (4)</td>
<td>4.2% (3)</td>
<td>0.69</td>
</tr>
<tr>
<td>MI at follow-up</td>
<td>0</td>
<td>2.8% (2)</td>
<td>0.12</td>
</tr>
<tr>
<td>TVR (per patient)</td>
<td>15.9% (21)</td>
<td>22.5% (16)</td>
<td>0.25</td>
</tr>
<tr>
<td>TLR (per pattern)</td>
<td>11.4% (15)</td>
<td>22.5% (16)</td>
<td>0.04</td>
</tr>
<tr>
<td>TVR (per lesion)</td>
<td>14.7% (24)</td>
<td>23% (20)</td>
<td>0.12</td>
</tr>
<tr>
<td>TLR (per lesion)</td>
<td>9.8% (16)</td>
<td>23% (20)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data are presented as percentage and absolute numbers.

CABG = coronary artery bypass graft; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

---

**Figure 3.** Clinical status and results of noninvasive functional tests in patients with and without target lesion revascularization (TLR). CX = circumflex; EST = stress EKG or myocardial scintigraphy or stress echocardiogram; ISR = in-stent restenosis; IVUS = intravascular ultrasound; LAD = left anterior descending; QCA = quantitative coronary angiography; RCA = right coronary artery.
REFERENCES