Restenosis following bare metal coronary stenting is common. The location and characteristics of restenotic lesions in patients who have undergone coronary stent implantation is not well described. The purpose of this study was to determine the location, type and temporal distribution of stent-related restenosis. We reviewed the clinical and angiographic characteristics of 203 consecutive patients with stent-related restenosis undergoing a repeat clinically-indicated coronary angiogram, 30 days to 1 year after the index procedure. All lesions within 10 mm of the proximal and distal margins of the stent were included in the analysis. An angiographic classification was developed based on lesion location. Class I lesions were those occurring within the stent, and Class II comprised those lesions occurring within 10 mm of the proximal and distal stent edge. We classified a total of 234 stent-related restenosis lesions. Class I lesions were found in 52% of patients, and Class II in 48%. Three-fifths of the patients who developed new lesions at a stent edge presented 1–3 months following the initial procedure, which was significantly earlier than other lesion types (p < 0.001). A substantial number of patients undergoing repeat angiography after stent placement have lesions proximate, but peripheral, to the stent. This may limit the effectiveness of stent-based efforts to reduce restenosis. The time interval between coronary stenting and symptom recurrence appears to vary according to lesion location.

Coronary stent implantation decreases restenosis rates when compared with percutaneous transluminal coronary angioplasty (PTCA), and the use of these endoluminal scaffolds has increased dramatically since their introduction. The most compelling reasons for stent placement are their favorable angiographic and clinical outcomes. Despite a reduction in restenosis associated with coronary stenting, clinical recurrence following bare metal stenting still occurs in approximately 15–20% of patients.

Treatment for in-stent restenosis is associated with a high rate of recurrence, particularly for nonfocal lesions. Diffuse in-stent restenosis can be treated with balloon PTCA and vascular brachytherapy. Intracoronary brachytherapy, including hospitalization costs, is expensive and subsequent restenosis risk persists. Thus, there has been excitement about the development of drug-eluting stents (DES) and the associated reduction in in-stent restenosis. RESTENOSIS rates, while reduced, persist following the placement of DES and appear to be particularly prevalent outside the stent.

The pattern of in-stent restenosis, following placement of bare metal stents, has been previously described as either diffuse (lesion > 10 mm in length) or focal (<10 mm in length). However, new lesions outside the stent have not been well characterized. Thus, we developed an angiographic classification to include lesions external, but proximal, to the stent. We then examined the relationship between lesion location and morphology to timing of symptomatic presentation leading to repeat angiography.

**Methods**

**Patient population.** We reviewed our interventional cardiology database for all percutaneous coronary interventions from January 1998 through December 2001.
There were 203 patients treated with a coronary stent who underwent a repeat coronary angiogram within 30 days to 1 year following stent implantation, who had either in-stent restenosis or a new lesion within 10 mm of the stented segment, and all were included in the study. For the purposes of our analysis, both in-stent restenosis and new lesions within 10 mm of the stented segment will be referred to as restenotic lesions. Repeat angiography was always symptom-driven. Of the 203 patients, 177 underwent repeat coronary intervention and 26 underwent coronary artery bypass surgery. Patients with stents in coronary bypass grafts were excluded. Demographic information was entered into the interventional database at the time of the procedure, and additional information was collected retrospectively from hospital charts by a data coordinator. The relationship between the type of restenosis and the timing of repeat procedures was analyzed for patients with a single restenotic lesion.

**Angiographic analysis.** All angiograms were analyzed by two independent observers using visual inspection. Restenosis was defined as ≥ 50% stenosis either within the stent or within 10 mm from the proximal or distal stent edge. Lesion length was measured as the distance in millimeters from the proximal shoulder to the distal shoulder of the lesion in the projection with the least amount of foreshortening, utilizing the diameter of the guiding catheter as a reference.

**Classification of restenosis.** Lesions were classified by two independent angiographers, with a third angiographer adjudicating any discrepancies in lesion classifications (Figure 1).

The following classification scheme was used:
- **Class I:** Patients with stenosis inside of the stent.
  - Ia. Focal (< 10 mm in length) lesion.
  - Ib. Intrastent (> 10 mm within the stent) lesion.
  - Ic. Total occlusion TIMI flow grade 0.
- **Class II:** Patients with stenosis outside of the stent.
  - IIa. Diffuse proliferative lesion (restenosis > 10 mm in length extending outside of the stent).
  - IIb. Edge restenosis: lesion at the proximal and/or distal margin of the stent.
  - Iic. New lesion within 10 mm of either the proximal or distal edge of the stent.
**Statistical analysis.** Data are presented as mean ± standard deviation (SD) or proportions where appropriate and compared by the t-test or Chi-squared test, respectively. Multivariable analysis was accomplished using logistic regression (STATA version 8.1; STATA Corporation College Station, Texas). A value of $p < 0.05$ was considered significant.

**Results**
A total of 130 men and 73 women were included. The average age was 63 ± 12 years. Diabetes mellitus was present in 36% of patients, medically-treated hypertension in 69%, and hyperlipidemia in 73% of patients (Table 1). There were no differences in the baseline characteristics of patients by group classification. There was a trend toward more Class II patients being male (67% Class II vs. 57% Class I), and for Class I patients to have more likely presented with unstable angina (57%) than the Class II patients (44%).

<table>
<thead>
<tr>
<th>Table 2. Angiographic findings ($n = 234$).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Restenosis Type</strong></td>
</tr>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>a. Focal ($&lt; 10$ mm in length)</td>
</tr>
<tr>
<td>b. Intrastent $&gt;10$ mm within the stent</td>
</tr>
<tr>
<td>c. Total occlusion TIMI flow 0</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>a. Diffuse proliferative lesion</td>
</tr>
<tr>
<td>b. Edge restenosis</td>
</tr>
<tr>
<td>c. Lesion $&lt;10$ mm from the stent margin</td>
</tr>
</tbody>
</table>

The mean time interval between procedures was 130 days (median = 116). Thirty percent of patients with restenotic lesions underwent their repeat procedure within 1 to 3 months, 49% within 3 to 6 months and 21% within 6 to 12 months. Patients who developed restenosis within 1 to 3 months were more likely to have an edge restenosis as compared to other lesion types ($p < 0.01$) (Table 3).

**Discussion**
Our results demonstrate the frequent occurrence (48%) of significant stenosis outside of bare metal stents in patients presenting with symptoms following coronary stent deployment. The majority of these stenoses also involve stenosis inside of the stent (diffuse proliferative and edge). Drug-eluting stents markedly reduce the incidence of in-stent restenosis,$^{7-9}$ but are unlikely to affect stenosis outside of the stent.$^{8,10}$ Therefore, these data suggest that stenosis outside the stent will continue to be a concern even with the widespread use of DES.

Restenosis has been the Achilles heel of percutaneous coronary intervention. Several pharmaceutical trials have shown no benefit in reducing restenosis$^{12,13}$ following coronary angioplasty. The development of coronary stents has been
associated with a 30% decrease in restenosis, but clinical trials have shown that restenosis still occurred frequently, particularly in patients with longer lesions, small diameter vessels and diabetes mellitus. Focal in-stent restenosis can generally be treated with balloon angioplasty with acceptably low recurrent restenosis rates. More extensive in-stent restenosis has unacceptably high recurrent restenosis rates following balloon angioplasty and debulking techniques. Coronary brachytherapy has been shown to decrease recurrent restenosis in high-risk patients, but is capital-intensive and not always successful.

Thus, the cardiology community embraced the excellent results to date with DES. In the SIRIUS trial, in-stent restenosis was reduced by 90% and target lesion revascularization by 75% with the use of the Cypher™ DES (Cordis Corp., Miami, Florida). The difference in recurrent restenosis at the proximal margin was not significantly different between DES and bare metal stents, and the majority of revascularizations were for lesions outside of the stent. In the TAXUS IV trial, there were significant reductions in clinical, angiographic and intravascular ultrasound measures of restenosis with the Taxus® DES (Boston Scientific Corp., Natick, Massachusetts). Target lesion revascularization at 9 months was reduced by 73% with the use of the Taxus DES, while target vessel revascularization was reduced by 61%. Of the patients receiving a Taxus stent who had undergone repeat revascularization at 9 months, 56% had lesions outside the stented segment.

Mehran et al. previously proposed an angiographic criteria for in-stent restenosis which was confirmed by intravascular ultrasound. In this analysis, 34% of patients had diffuse proliferative restenosis. Among the 37% of patients with focal restenotic lesions, the proportion occurring outside the stent was not specified. We expanded the Mehran classification to include restenosis at the edges of the stent and within 10 mm of the stent edge. In a consecutive series of patients undergoing repeat coronary intervention, over a 3-year period incorporating advanced stent technology, we found that 48% of restenotic lesions occur outside of the stent.

Our classification system was aimed at understanding the mechanism for the location of the restenotic lesion and it overlaps with the concept of in-stent (including the stented segment) and in-segment (including the stented segment and 5 mm margins on either side). Class I lesions would all be in-stent. Among Class II lesions, IIa would be in-segment, IIb would be in-segment and the majority of IIc lesions would be out of segment.

The etiology of restenosis occurring external to the stent is likely multifactorial. Diffuse proliferative restenosis, which occurred in 34% of lesions outside of the stent (Class II), is an aggressive restenotic response primarily within the stent, with extension to the stent edge and beyond. Patients receiving DES, who otherwise would have diffuse proliferative restenosis, would be expected to continue to have restenosis occur outside of the stent where the effects of the drug would be least active. Edge restenosis, which had previously been described following coronary brachytherapy and implantation of DES, occurred in 32% of Class II lesions. Balloon injury, caused by pre- and postdilatation balloon inflation and balloon overhang of the stent during implantation, can cause a concomitant injury-restenotic response. Patients with edge restenosis presented earlier than patients with other patterns of restenosis. This is consistent with a typical plain-old balloon angioplasty response to restenosis in which clinical recurrence within 6 to 12 weeks is most common. Additionally, Attila et al. hypothesized that edge restenosis may be related to low-oscillating shear stress causing expression of several growth factors, which leads to intimal proliferation and restenosis. These changes are probably more prominent within the first few months after stent implantation, which in turn may explain the earlier occurrence of edge restenosis. Edge restenosis, seen in the SIRIUS trial, occurred more commonly at the proximal
edge. This may reflect preferential diffusion of sirolimus downstream and/or a manifestation of postdilatation strategies, including pullback of the stent balloon, which would cause more tissue injury proximally.

Following the release of the SIRIUS trial results, recommendations aimed at reducing restenosis outside the stent emphasized employing diligence during implantation to minimize balloon injury outside the stented segment, and the use of longer DES has been advocated to cover the entire diseased segment. It has recently been shown that longer DES lengths do increase the risk of restenosis, though not as much as longer bare metal stents. The E-SIRUIS trial, utilizing these techniques, showed a decreased incidence of in-segment, out-of-stent restenosis. In SIRIUS, the incidence of out-of-segment restenosis was highest in those patients likely to have diffuse disease, e.g., diabetes and long lesions. In “real world” DES implantation, it is likely that many patients with more diffuse disease will be treated. Intravascular ultrasound studies have shown that coronary artery disease is a diffuse disease and angiography will often underestimate or not detect significant atherosclerotic plaque. It is plausible, though unproven, that the utilization of intravascular ultrasound to identify appropriate areas of the artery to implant the stent would minimize stent edge injury.

Our study demonstrated the frequent occurrence of restenosis outside bare metal coronary stents. In the era of DES, treatment to minimize restenosis needs to incorporate strategies to decrease balloon injury in the non-stented segment. Using longer DES should help reduce, but will not eliminate, this problem.

Study limitations. This is a retrospective analysis and is, therefore, subject to the limitations pertinent to this type of clinical investigation. The study was performed in a single institution and has the limitations inherent in any single-center analysis. Differences in patient population and operator technique may not allow generalization of our results to all institutions. As a regional center, the majority of our patients required urgent percutaneous coronary intervention, and thus our patient population may differ from those treated at other institutions. There were 7 interventionalists who worked during the time frame of this study and it is possible that difference in technique could have contributed to the outcome. However, all operators worked with the same interventional fellows and all adhered to the premise to cover the full extent of the lesion with the stent. Edge dissections were always stented. A minority of our patients had direct stenting performed and debulking techniques were not utilized in these patients. After the index percutaneous coronary intervention, patients may have presented with clinical symptoms to other facilities and thus would be excluded from this analysis. However, as we are the only interventional center in a large geographic area, most interventional patients return to our center for subsequent care. Quantitative coronary analysis was not utilized in our study, but all angiograms were reviewed by two observers, and a third observer was utilized if there were differences of opinion.

Conclusions
In-stent restenosis presents with various angiographic patterns. A substantial number of patients undergoing repeat angiography for recurrent symptoms following initial bare metal stent placement have lesions outside the stent. Patients who present early are more likely to have a stenosis at the stent edge. The occurrence of new lesions outside the stent may limit the effectiveness of stent-based effort to reduce restenosis. New strategies to limit restenosis outside the stent need to be explored.

Acknowledgements. We wish to thank Walter J. Kroll for his excellent technical support, and acknowledge Scott A. Mulvey for his assistance in data collection.


