Restenosis occurs within the first 6 months after 30% to 50% of transcatheter procedures; it remains the major limitation to percutaneous coronary revascularization. In an attempt to reduce the rate of restenosis, previous studies have focused on understanding its mechanisms and predicting its occurrence. For example, animal models,6–11 human necropsy studies,12–22 and...
analyses of retrieved atherectomy specimens originally suggested that an exaggeration of the normal reparative processes following angioplasty-induced local vessel trauma leads to uncontrolled smooth muscle cell proliferation and restenosis. However, no one animal model completely simulates the vascular healing processes following catheter-induced trauma; most animal models of restenosis occur in the absence of underlying chronic atherosclerosis with its associated pathobiology and flow abnormalities; and pharmacologic and new angioplasty device strategies that prevent restenosis in animals have been strikingly ineffective in humans.

In addition retrospective clinical and angiographic analyses have identified several risk factors for restenosis after coronary angioplasty. These can be divided into (1) patient related factors such as gender, history of restenosis, diabetes, hyperlipidemia, hypertension, unstable angina, vasospastic angina, end stage renal disease, and continued smoking; (2) procedure-related factors such as balloon-to-artery ratio, presence of significant residual translesion gradient, small residual lumen, significant residual stenosis, and extent of dissection; and (3) lesion-related factors such as pretreatment vessel size, severity of pre-treatment stenosis, calcification, eccentricity, saphenous vein graft lesion location, ostial or proximal lesion location, left anterior descending lesion location, chronic total occlusions, and long lesion length.

One possible explanation for the failure of treatment strategies to reduce restenosis is an incomplete understanding of the process. Intravascular ultrasound (IVUS) allows transmural, tomographic imaging of coronary arteries in humans in vivo, providing unique insights into the pathology of coronary artery disease by defining vessel wall geometry and the major components of the atherosclerotic plaque. Sequential IVUS studies have been used to study mechanisms of angioplasty devices. These studies have indicated that intravascular ultrasound imaging of target lesions before and after catheter-based treatment consistently demonstrates more target lesion calcium, more extensive reference segment atherosclerosis, smaller final lumen dimensions, significant residual plaque burden, and greater degrees of tissue trauma than is evident by angiography.

We report the angiographic and intravascular ultrasound follow-up in patients studied who underwent IVUS imaging during coronary interventional procedures.

**METHODS**

IVUS studies were performed on 360 non-stented native coronary artery lesions in 351 patients in whom follow-up angiographic data was available in all and in who follow-up intravascular ultrasound data was available in 212. Devices included in this study were balloon angioplasty, directional coronary atherectomy (Devices for Vascular Intervention, Redwood City CA), high-speed rotational atherectomy (Heart Technology, Bellevue WA), and excimer laser angioplasty (Spectranetics/Advanced Interventional Systems, Colorado Springs, CO). Adjunct balloon angioplasty or directional atherectomy (after rotational atherectomy or excimer laser angioplasty) was common.

Clinical and Lesion Demographics. The hospital charts of all patients were reviewed independently by a Registered Nurse to obtain clinical demographics and laboratory results.

Angina was categorized as stable, accelerated, post-infarction, or at rest. A recent myocardial infarction occurred within 6 weeks prior to study; a remote myocardial infarction occurred more than 6 weeks prior to study. In addition, a history of coronary artery bypass surgery (including graft age) and the presence of multivessel coronary artery disease (> 50% diameter stenosis in two or more epicardial coronary arteries) were noted.

Risk factors for coronary artery disease that were tabulated included diabetes mellitus (medication dependent, including oral hypoglycemics and insulin), hypertension (medication dependent only), hypercholesterolemia (medication dependent or serum cholesterol ≥ 240 mg/dl), and smoking (still smoking or having stopped smoking less than 6 months prior to study). Laboratory data recorded included baseline admission hematocrit, platelet count, and serum creatinine.

Angiographic Analysis. Qualitative and quantitative coronary angiography was performed by an independent core angiographic laboratory blinded to the results of the ultrasound analysis. Standard qualitative angiographic variables were recorded. Quantitative coronary angiography (QCA) was performed using an automated edge detection algorithm (ARTREK, Quantitative Cardiac Systems, Ann Arbor, MI). Minimal
lumen diameter (MLD), reference diameter, and percent diameter stenosis before and after intervention and on follow-up were measured from multiple projections; and the results from the “worst” view were recorded. Angiographic restenosis was defined as a diameter stenosis 50%.

Target lesion location was designated as ostial, proximal, mid, and distal. Ostial lesions were those lesions that began within 3 mm of the major coronary artery ostium.

Lesion length was measured as the distance (in mms) from the proximal shoulder to the distal shoulder of the lesion in the projection that demonstrated the lesion with the least amount of foreshortening. Furthermore, lesions were characterized as discrete (< 10 mm in length), tubular (10–20 mm in length), or diffuse (> 20 mm in length).

An eccentric target lesion had one of its lumen edges in the outer one-quarter of the apparently normal lumen thereby indicating that there was three times as much plaque on one side of the lesion as on the other.

Angulation was present if the centerline through the lumen proximal to the lesion compared to the centerline through the lumen distal to the lesion was > 45°.

A tortuous artery had at least two bends of > 60° that had to be traversed to reach the target lesion.

An irregular lesion had abnormal vessel margins. Specifically, an ulcerated lesion had a small crater or luminal flap, potentially with discrete luminal widening beyond a narrow mouth in the area of stenosis. An aneurysm had widening of the lumen beyond the apparent normal contour of the artery.

Calcification was identified as readily apparent radiopacities within the vascular wall at the site of the stenosis and was classified as none/mild, moderate (radiopacities only noted during the cardiac cycle prior to contrast injection), and severe (radiopacities noted without cardiac motion prior to contrast injection).

Flow was graded according to the Thrombolysis in Myocardial Infarction (TIMI) study criteria.

Post-intervention dissections were identified as breaks in the apparent continuity of the arterial wall.

**IVUS Imaging Protocol.** Pre-angioplasty (as the first step in the procedure), post-angioplasty (as the last step in the procedure), and when follow-up IVUS was performed, 0.2 mg intracoronary nitroglycerin was administered. The ultrasound catheter was advanced approximately 10 mm beyond the target lesion and a slow imaging run was performed from beyond the target lesion to the aorto-ostial junction.

Studies were performed using one of three commercially available systems. The first (CVIS/InterTherapy Inc., Sunnyvale, CA) incorporated a single element 25 MHz transducer and an angled mirror mounted on the tip of a flexible shaft which was rotated at 1800 rpm within a 3.9 Fr short monorail polyethylene imaging sheath to form planar cross-sectional images in real time; with this system the transducer was withdrawn automatically at 0.5 mm/sec to perform the imaging sequence. The second (Hewlett Packard, Andover, MA and Boston Scientific Corporation, Watertown, MA) incorporated a single element 30 MHz beveled transducer rotated at 1800 rpm within a 3.5 Fr short monorail imaging catheter; with this system the catheter was advanced or withdrawn manually with fluoroscopic guidance to perform the imaging sequence. The third (Cardiovascular Imaging Systems, Inc, Sunnyvale CA) used a single element beveled transducer, mounted on the end of a flexible shaft, and rotated at 1800 rpm within either a 2.9 Fr long monorail/common distal lumen imaging sheath or within a 3.2 Fr short monorail imaging sheath. With this system the transducer was also withdrawn automatically at 0.5 mm/sec to perform the imaging sequence. Ultrasound studies were recorded on ½ inch high resolution s-VHS taped for off-line analysis.

**Quantitative IVUS Measurements.** Validation of normal coronary artery anatomy, plaque composition and morphology, and measurements of external elastic membrane cross-sectional area, residual lumen cross-sectional area, plaque + media cross-sectional area, and total wall thickness by intravascular ultrasound have been reported previously. The term external elastic membrane cross-sectional area is short-hand for area within the border between the hypoechoic media and the echoreflective adventitia, a reproducible measure of total arterial cross-sectional area. Because media thickness cannot be measured accurately, plaque + media cross-sectional area was used as a measurement of the amount of atherosclerotic plaque. Total wall (plaque + media) thickness was used to calculate the eccentricity index.

Using computer planimetry, the target lesion
was assessed by measuring:

1) lesion site external elastic membrane (EEM) cross-sectional area (CSA, mm²)
2) lesion site lumen CSA (mm²)
3) minimum lumen diameter (mm)
4) plaque+media (P + M) CSA area (mm²) = EEM CSA - lumen CSA
5) cross-sectional narrowing (%) =
   \[
   \frac{(P + M \text{ CSA}) - \text{ lumen CSA}}{\text{EEM CSA}} \times 100
   \]
6) eccentricity index =
   \[
   \frac{\text{maximum total wall thickness}}{\text{minimum total wall thickness}}
   \]

Although acoustic shadowing caused by lesion calcification made identification of the external elastic membrane in some lesions difficult, two types of extrapolation were useful. Briefly, because the cross-sectional geometry of the coronary artery was more or less circular, extrapolation of the circumference of the external elastic membrane was possible provided that each calcific deposit did not shadow more than 60° of the adventitial circumference. Also, real-time axial movement of the transducer just distal and proximal to a calcific deposit (or to find the smallest circumferential arc of calcium within a large calcific deposit) helped unmask and fill in contiguous parts of the adventitia that were otherwise shadowed by that deposit.60,75

When the atherosclerotic plaque abutted against the catheter, the lumen was assumed to be the size of the imaging catheter; therefore, 0.8 mm² was the smallest lumen that could be recorded. An eccentricity index of 1.0 indicated purely concentric target lesion plaque distribution.

The same anatomic image slice was analyzed pre-intervention, post-intervention, and on follow-up; and the differences were compared. Pre-intervention and post-intervention IVUS studies were compared to calculate acute arterial expansion (increase in EEM CSA) and acute atheroablation (decrease in P + M CSA) during the procedure.

Only lesions studied using motorized transducer pullback were included in the comparison of the acute and follow-up IVUS results. By using one or more reproducible axial landmarks (for example, the aorto-ostial junction, large proximal and/or distal side branches, or unusually shaped calcium deposits) and a known pullback speed, identical cross-sectional slices on serial studies could be identified for comparison. The anatomic slice selected for serial analysis had an axial location within the target lesion at the smallest follow-up lumen CSA (rather than at the smallest pre-intervention or post-intervention lumen CSA). In practice, the follow-up study was analyzed first to identify the anatomic slice with the smallest lumen; then, the distance from this anatomic slice to the closest identifiable axial landmark was measured (using seconds or frames of videotape); finally, this distance was used to identify the corresponding anatomic slice on the pre-intervention and post-intervention studies.

The target lesion lumen was normalized for a proximal reference segment.66 The reference segment was selected as the most normal-looking cross-section within 10 mm proximal to the target lesion, but distal to a major side branch. In circumstances when a proximal reference segment could not be identified (e.g., ostial lesion location or diffuse proximal disease extending back to a major side branch), then a distal reference (also within 10 mm of the target lesion, but proximal to a major side branch) was analyzed. Cross-sectional reference site measurements were similar to those made for the target lesion and included the EEM, lumen, and P + M CSA, cross-sectional narrowing, minimum lumen diameters, eccentricity index, and arc of calcium.

**Qualitative IVUS Image Analysis.** Target lesion plaque composition was assessed visually.76 The presence of significant amounts of calcium, hyper-echoic (but noncalcified plaque), or hypo-echoic plaque were tabulated independently for each lesion; for example, a mixed lesion containing both soft and fibrotic plaque elements was tabulated as containing both soft plaque and fibrotic plaque. Calcium produced bright echoes (brighter than the reference adventitia) with acoustic shadowing of deeper arterial structures; its location distribution, and extent were analyzed in detail.62 The location (superficial or deep) of target lesion calcium was defined as superficial (calcium at the intima-lumen interface), deep (more than half the distance from the intima-lumen interface to the external elastic membrane), or both (superficial and deep). Calcium was quantified using a protractor centered on the lumen by measuring the (1) total circumferential arc or calcium (in degrees) (2) superficial arc of calcium (in degrees) Dense fibrous tissue produced echoes that were as bright or brighter than the reference adventitia, but without acoustic shadowing. The absence of acoustic shadowing differentiated dense fibrous tissue from calcium.

Soft plaque was less dense than the reference adventitia. Soft plaque is heterogeneous containing various amounts of loose connective tissue,
lipid, intimal hyperplasia, or thrombus.

Post-intervention dissections were defined as abrupt, focal interruptions in the continuity of the plaque or intima that extends axially, radially, or circumferentially spanning normal tissue planes particularly if not present on pre-intervention imaging.\textsuperscript{57,71,77} Echo-lucent zones without abrupt breaks in the continuity of the plaque or intima (potentially representing soft plaque elements) will not be counted as dissections. Also, echo-lucent zones at the junction of calcified and non-calcified elements that extended only radially (possibly representing echo drop-out) will not be counted. The number of distinct dissection planes in each target lesion were counted.

**Statistics.** Statistical analysis was performed using StatView 4.02 or BMDP.\textsuperscript{78} Quantitative data are presented as mean ± one standard deviation. Qualitative data are presented as frequencies. Comparisons between groups were performed using Mann-Whitney U-test or Wilcoxon test for continuous variables or Chi-square statistics and Fisher’s exact test for categorical variables.

**Dependent Angiographic Variables.** Univariate and multivariate logistic regression analysis were used to select the best clinical, angiographic, or intravascular ultrasound predictors of angiographic restenosis. Four dependent angiographic variables indicative of restenosis that were tested.

The primary endpoint was the binary angiographic definition of restenosis (defined as a follow-up diameter stenosis \( \geq 50\% \)).\textsuperscript{49} Univariate predictors of angiographic restenosis with a \( p \) value \(< 0.2\) were entered into the multivariate model. A forward elimination and maximum likelihood estimation were used to select the independent predictors of angiographic restenosis. The odds ratio (OR) and 95% confidence intervals are presented in the tables for both the univariate predictors and the final multivariate model. An odds ratio > 1 means an increased predicted risk for the variable listed; an odds ratio < 1 means a decreased risk.

**RESULTS**

**Clinical Demographics.** Clinical demographics in the overall patient cohort were as follows: 30\% had diabetes, 47\% had hypertension, 65\% had hypercholesterolemia, 11\% had a history of a recent myocardial infarction and 30\% had a history of a remote myocardial infarction, 28\% had unstable angina, and 26\% were smokers.

**Serial Angiographic Results (Table 1).** Lesion demographics in the overall cohort were as follows: 33\% were restenotic, 17\% were ostial in location, 47\% were anterior descending in location, 27\% were 10 mm in length, 61\% were eccentric, 34\% were calcified, 19\% were irregular, 19\% involved branch vessels (were at bifurcation sites), 6\% were total occlusions, and 11\% had TIMI flow less than grade 3.

Reference vessel size measured 3.10 ± 0.59 mm. Overall, the pre-intervention MLD measured 0.98 ± 0.52 mm and the diameter stenosis measured 69 ± 15\%. The post intervention MLD increased to 2.62 ± 0.68 mm, and the diameter stenosis decreased to 18 ± 13\%. At follow-up, there was attrition in MLD to 1.52 ± 0.92 mm with an associated increase in diameter stenosis to 51 ± 26\%; 203 target lesions were classified as restenotic lesions.

**Serial IVUS Results (Table 1).** Post-intervention, the improvement in lesion site lumen CSA (1.7 ± 0.9 mm\(^2\) to 6.3 ± 2.5 mm\(^2\), \( p < 0.0001\)) was due to a combination of vessel expansion (increase in EEM CSA from 19.1 ± 6.5 mm\(^2\) to 20.3 ± 6.6 mm\(^2\), \( p < 0.0001\)) and tissue ablation (decrease in P + M CSA from 17.4 ± 6.3 mm\(^2\) to 13.9 ± 5.6 mm\(^2\), \( p < 0.0001\)). The cross-sectional narrowing decreased from 90 ± 5\% to 68 ± 11\% (\( p < 0.0001\)).

At follow-up, the decrease in lumen CSA (to 4.0 ± 3.7 mm\(^2\), \( p < 0.0001\)) was due more to a decrease in EEM CSA (to 18.2 ± 6.4 mm\(^2\), \( p < 0.0001\)) than to an increase in P + M CSA (to 14.2 ± 5.4 mm\(^2\), \( p < 0.0001\)). Thus, 73\% of late lumen loss was explained by the decrease in EEM CSA. The change in lumen CSA correlated more strongly with the change in EEM CSA (\( r = 0.751, p < 0.0001\)) than with the change in P + M CSA (\( r = 0.284, p < 0.0001\)).

The change in EEM CSA was bidirectional. Forty-seven lesions (22\%) showed an increase in EEM CSA. Despite a greater increase in P + M CSA (1.5 ± 2.5 mm\(^2\) vs. 0.5 ± 2.0 mm\(^2\), \( p = 0.0009\)), lesions exhibiting an increase in EEM CSA had (1) no change in lumen CSA (0.1 ± 3.3 mm\(^2\) vs. a decrease in lumen CSA of 3.6 ± 2.3 mm\(^2\) for lesions with a decrease in EEM CSA, \( p < 0.0001\)), (2) a reduced restenosis rate (26\% vs. 62\% for lesions with a decrease in EEM CSA, \( p < 0.0001\)), and (3) a 49\% incidence of late lumen gain (vs. 1\% for lesions with no increase in EEM CSA, \( p < 0.0001\)).

**Univariate Predictors of Restenosis.** In this patient cohort, patient age, male gender, patient race, hypertension, smoking, diabetes mellitus,
unstable angina, multivessel disease, and recent or remote myocardial infarction were not significant univariate predictors of restenosis.

Table 2 lists the univariate angiographic predictors of restenosis at the $p < 0.05$ level. Other predictors at the $p < 0.2$ level (and therefore tested in the multivariate model) included (1) the use of rotational atherectomy, (2) lesions greater than 10 mm in length, (3) vessel tortuosity, (4) total occlusion lesions, and (5) pre-intervention TIMI (Thrombolysis In Myocardial Infarction) flow less than Grade 3. Left anterior descending or ostial lesion location, target lesion calcification, and prior catheter-based intervention were not univariate predictors of restenosis.

Table 3 lists the univariate IVUS predictors of restenosis at the $p < 0.05$ level. Other predictors at the $p < 0.2$ level (and therefore tested in the multivariate model) included (1) lesion maximum wall thickness $(P + M)$ (2.3 ± 0.6 mm), (2) target lesion calcium $(110 ± 107\degree)$, and (3) the post-intervention $P + M$. Ultrasound variables that were not predictive at the $p < 0.2$ level included plaque composition (ie., hypoechoic vs. hyperechoic vs. calcific plaque composition), calcium location and arc of superficial calcium, minimum wall thickness, plaque alation, and dissections post-intervention.

**Multivariate Predictors of Restenosis.** Using multivariate logistic regression analysis, the only independent predictors of restenosis were the IVUS reference lumen CSA (Odds ratio = 0.89, 95% confidence interval = 0.83–0.96, $p < 0.001$), the pre-intervention angiographic diameter stenosis (Odds ratio = 1.28, 95% confidence interval = 1.07–1.53, $p < 0.01$), and the post-intervention IVUS cross-sectional narrowing (Odds ratio = 1.67, 95% confidence interval = 1.29–2.16, $p < 0.001$). A predictive model relating angiographic restenosis to the cross-sectional narrowing was then constructed.

**DISCUSSION**

The pathophysiology of restenosis is complex and incompletely understood. Catheter-induced vascular injury causes immediate and progressive release of thrombogenic, vasoactive, and mitogenic factors leading to platelet aggregation, thrombus formation, inflammatory changes, with activation of macrophages and smooth muscle cells. These events induce the production and release of growth factors and cytokines which in turn may promote their own synthesis and release from target cells. Thus, a self perpetuating cascade is initiated which results in the migration of smooth muscles cells from their usual location in the media to the intima where they undergo a phenotype change, produce extracellular matrix, and proliferate.

The restenotic lesion is, therefore, thought to be a proliferative lesion with both cellular and matrix components causing an increased tissue mass. As the understanding of this process has advanced, attempts have been made to attack restenosis by interfering with this cascade. Although the results in animal models have been impressive, pharmacologic trials using anti-proliferative agents in humans have been disappointing.

Recently, data from various sources have begun to challenge the traditional injury-proliferation restenosis hypothesis. New studies of retrieved atherectomy specimens have shown only a low level of active cellular proliferation in restenotic coronary lesions. In addition, animal studies have suggested that cellular proliferation may be a universal response to the trauma of transcatheter therapy regardless of the development of restenosis; the presence or absence of compensatory arterial dilatation (accommodating the increase in tissue mass) was the greater determinant of restenosis. Furthermore, late arterial contraction has now been shown to cause restenosis in the absence of extensive cellular proliferation. Finally, recent re-examination of original animal experiments (using different quantitative analyses) now indicate that arterial remodeling (which was once ignored) is, in fact, an important part of the restenosis process.

In the current study, IVUS data from human coronary arteries supports the emerging new animal model data. The impact of a change in EEM CSA on lumen dimensions could be differentiated from the change in $P + M$ CSA. Serial ultrasound imaging indicated that (1) a decrease in total arterial (EEM) CSA accounted for 70–75% of late lumen loss and (2) late lumen loss correlated better with a decrease in EEM CSA than with an increase in $P + M$ CSA.

This study does not seek to address the reasons for a decrease in EEM CSA. However, several mechanisms can be postulated including (1) fibrosis of the vessel wall, especially of the adventitia in response to deep wall injury; (2) programmed cell death (apoptosis); (3) changes in the extracellular matrix composition and structure; and (4) responses to shear stress-induced changes in vasomotor tone. Importantly, these findings cannot exclude a possible relationship...
between early cellular proliferation and a disproportional late decrease in EEM CSA resulting in exaggerated late lumen loss and restenosis in some patients.

In this study the change in EEM CSA was, in fact, bidirectional. Approximately 20% of lesions showed a compensatory increase in EEM CSA. This resulted in a decreased incidence of restenosis and an increased incidence of late lumen gain despite an increase in plaque mass, analogous to adaptive (compensatory) arterial remodeling early in the atherosclerotic disease process. As originally described by Glagov, adaptive remodeling in noninstrumented arteries delays the development of focal stenoses despite significant plaque accumulation. Lumen dimensions are preserved until plaque occupies 40–50% of the CSA within the internal elastic membrane (40–50% cross-sectional narrowing or plaque burden). Although the process post-intervention may be different, adaptive arterial remodeling (an increase in EEM CSA) is the probable explanation for the occasional improvement in lumen dimensions seen during the follow-up period after catheter-based interventions.

Thus, restenosis appears to be determined primarily by the direction and magnitude of the change in EEM CSA, in other words, by arterial remodeling. An increase in EEM CSA (compensatory arterial dilatation) is adaptive while a decrease in EEM CSA leads to lumen compromise and restenosis.

Supportive Evidence and the Impact of Endovascular Stents. Several studies support these findings. Data from the Serial intravascular Ultrasound analysis of Restenosis (SURE) trial (IVUS pre-intervention and immediately, 24 hours, 1 month, and 6 months post-intervention) indicate (1) the serial changes in lumen CSA parallel the serial changes in EEM CSA and (2) that remodeling is a late even and, therefore, is distinct from passive elastic recoil. Data from the Optimal Atherectomy Restenosis Study (OARS) indicates that nearly all of the late lumen loss post directional coronary atherectomy is the result of arterial remodeling and that the remodeling process extends to the contiguous proximal reference segments. Endovascular stents, that merely scaffold the inner vascular lumen preventing recoil and remodeling without diminishing proliferative potential, could blunt this adaptive response.
responses, have been shown to reduce restenosis in two randomized clinical trials, the STent REStenosis Study (STRESS) and Benestent.137,138 Serial intravascular ultrasound results have indicated that stents do not recoil chronically and that all of instent restenosis is the result of neointimal hyperplasia.139 Thus, even though there may be a stent-related increase in neointimal tissue proliferation, stents appear to reduce restenosis by withstanding the remodeling forces that lead to restenosis after other types of interventions.137–139

Importance of the IVUS Cross-sectional Narrowing. Indirect evidence in support of arterial remodeling as a major determinant of restenosis comes from the current analysis of the predictors of restenosis. The residual cross-sectional narrowing (the % of total arterial CSA occupied by atherosclerotic plaque at the conclusion of the procedure) may be the most powerful post-intervention predictor of restenosis. Mathematically, it can be shown that the impact of a change in EEM CSA is directly related to the residual cross-sectional narrowing (Figure 6). For example, in normal arteries, a 50% decrease in arterial (EEM) CSA would be necessary to produce a 50% decrease in lumen CSA. Conversely, in arteries with a significant residual cross-sectional narrowing, even a small decrease in arterial (EEM) CSA would have a profound impact on lumen CSA. If, as in the current study, the post-intervention cross-sectional narrowing averaged 68%, a 45%–60% late lumen loss would require only a 15–20% decrease in arterial (EEM) CSA.56 Thus, these findings also support the importance of arterial remodeling as a mechanism of restenosis. The preliminary results of Phase II of the GUIDE Study (a multicenter study, with blinded post-intervention imaging) has come to virtually the same conclusion that the ultrasound findings, particularly the residual cross-sectional narrowing, is the most powerful predictors of restenosis.140

Clinical and Procedural Implications and Caveats. An aggressive interventional strategy designed to maximize the lumen area and minimize the residual cross-sectional narrowing to provide “room” for remodeling forces may be overly simplistic. The OARS study involves an ultrasound-guided directional coronary atherectomy strategy with encouraged post-atherectomy adjunct balloon dilatation to maximize lumen dimensions and minimize residual diameter stenosis and cross-sectional narrowing. The restenosis rate in the OARS study is less than reported in CAVEAT. However, an overly aggressive atherectomy strategy may cause undue vessel trauma to lead to an increase in short- and long-term procedural complications. For example, one single center experience has showed that an aggressive multi-device interventional approach designed to reduce the residual cross-sectional narrowing actually increased restenosis (Tobis, unpublished results, with permission). Our own experience with rotational atherectomy followed by adjunct directional coronary atherectomy has shown that the only predictor of late target lesion revascularization (a clinical surrogate for restenosis) was the overall atherectomy index (the overall contribu-

<table>
<thead>
<tr>
<th>N</th>
<th>Total</th>
<th>No Restenosis</th>
<th>Restenosis</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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<td></td>
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<tr>
<td>EEM CSA (mm²)</td>
<td>18.8 ± 7.2</td>
<td>20.1 ± 8.8</td>
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<td>Lumen CSA (mm²)</td>
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<td>10.5 ± 4.8</td>
<td>8.7 ± 3.3</td>
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<td>0.84–0.95</td>
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<td>CSN (%)</td>
<td>49 ± 13</td>
<td>47 ± 13</td>
<td>50 ± 12</td>
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<td>Eccentricity index</td>
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<td>Lumen CSA (mm²)</td>
<td>1.7 ± 0.9</td>
<td>1.9 ± 1.1</td>
<td>1.6 ± 0.7</td>
<td>0.70</td>
<td>0.53–0.92</td>
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<td>MLD (mm)</td>
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<td>1.4 ± 0.2</td>
<td>0.35</td>
<td>0.12–0.99</td>
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<td>CSN (%)</td>
<td>90 ± 5</td>
<td>89 ± 6</td>
<td>91 ± 5</td>
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<td>Lumen CSA (mm²)</td>
<td>6.3 ± 2.5</td>
<td>7.1 ± 2.7</td>
<td>5.8 ± 2.3</td>
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<td>0.73–0.89</td>
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<td>MLD (mm)</td>
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<td>0.39</td>
<td>0.25–0.62</td>
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<td>CSN (%)</td>
<td>68 ± 11</td>
<td>64 ± 11</td>
<td>71 ± 10</td>
<td>1.80</td>
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<td>Acute expansion (mm²)</td>
<td>1.9 ± 1.9</td>
<td>2.2 ± 2.2</td>
<td>1.6 ± 1.7</td>
<td>0.83</td>
<td>0.72–0.96</td>
<td>&lt; 0.05</td>
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</table>

Abbreviations: 95% CI = 95% confidence interval, CSA = cross-sectional area, CSN = cross-sectional narrowing, EEM = external elastic membrane, MLD = minimum lumen diameter, OR = odds ratio
tion of tissue removal to lumen enlargement). Thus, as a means of optimizing post-procedural lumen dimensions, aggressive multidevice atherectomy may be more deleterious than an approach of less aggressive multidevice atherectomy with facilitated vessel expansion.

**Conclusions.** Restenosis appears to be determined primarily by the direction and magnitude of arterial remodeling (EEM CSA). An increase in EEM CSA is adaptive while a decrease in EEM CSA contributes to restenosis. The most powerful predictor of restenosis was the IVUS post-procedural cross-sectional narrowing. Mathematically, cross-sectional narrowing may be its relationship to remodeling (change in EEM CSA). An increase of arterial remodeling (EEM CSA) is adaptive while a decrease in EEM CSA contributes to restenosis. The most powerful predictor of restenosis was the IVUS post-procedural cross-sectional narrowing.

**REFERENCES**


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