Application of a Continuous Regression Model of Restenosis to Saphenous Vein Grafts After Successful Percutaneous Transluminal Coronary Angioplasty or Directional Coronary Atherectomy

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OBJECTIVES
To evaluate a quantitative model of restenosis in patients with vein graft disease undergoing percutaneous transluminal coronary angioplasty (PTCA) or directional coronary atherectomy (DCA).

BACKGROUND
A quantitative relationship between acute gain and late loss has been developed to describe the late changes in lumen dimension after native vessel coronary intervention. This same relationship may also be seen after treatment of saphenous vein graft disease.

METHODS
Patients with native coronary artery stenoses (CAVEAT-I) or saphenous vein graft lesions (CAVEAT-II) were randomized to either DCA or PTCA, and data from these trials were analyzed retrospectively. Angiographic results of the target lesions were reviewed, and each lesion was assessed for vessel caliber and reference diameter, absolute minimal lumen diameter, percent diameter stenosis, percent stenosis of the cross-sectional area, acute gain and late loss. Linear regression models were used to determine late loss and to detect differences in angiographic outcomes.

RESULTS
Vein grafts had significantly larger reference vessel diameters than native coronary arteries; they also had significantly more acute gain and more late loss. Directional coronary atherectomy was associated with a larger acute gain in both studies. Patients undergoing DCA also experienced greater late loss although the effect was statistically significant only in the CAVEAT-I study. After adjusting for the acute gain, the treatment effect on late loss became nonsignificant in both studies.

CONCLUSIONS
In patients undergoing DCA or PTCA of saphenous vein graft narrowings, the relationship between late loss and acute gain is also demonstrated, similar to the device-independent relationships seen in native coronary lesions. In CAVEAT-II, larger degrees of acute gain were also associated with higher degrees of late lumen loss. (J Am Coll Cardiol 2000;35:619–23) © 2000 by the American College of Cardiology

Restenosis following percutaneous coronary revascularization has been studied extensively using quantitative angiographic methods, yielding insights into the dynamic changes occurring early and late after intervention. In addition, there is substantial interest in the relationship between initial gain and late loss.

Differences in restenosis rates among interventional devices have been related to the immediate angiographic outcome. Long-term angiographic outcomes were evaluated by Kuntz et al. (1). These investigators developed a quantitative model of procedural angiographic predictors of late loss (defined as postprocedural minimal lumen diameter [in mm]–minimal lumen diameter at six months [in mm]). Their modeling process also evaluated differences in late loss using different devices after adjusting for these procedural factors. However, their work was in native coronary artery lesions and not in saphenous vein graft disease.

This study first sought to validate the results found by Kuntz et al. (1) in patients undergoing native vessel coronary intervention in the Coronary Angioplasty Versus...
Abbreviations and Acronyms

CAVEAT-I = Coronary Angioplasty Versus Excisional Atherectomy Trial-I
CAVEAT-II = Coronary Angioplasty Versus Excisional Atherectomy Trial-II
DCA = directional coronary atherectomy
DS% = percent diameter stenosis
GLM = general linear models
MLD = absolute minimal lumen diameter
PTCA = percutaneous transluminal coronary angioplasty

**METHODS**

Study patients and angiographic analysis. CAVEAT-I and CAVEAT-II randomized patients with de novo native coronary artery stenosis (CAVEAT-I, 1,012 patients) or de novo saphenous vein graft lesions (CAVEAT-II, 305 patients) to either directional coronary atherectomy (DCA) or percutaneous transluminal coronary angioplasty (PTCA).

A validated edge-detection algorithm was used to analyze paired acute and six-month follow-up angiograms at the core angiographic laboratory at the Cleveland Clinic Foundation (4). The most severe hemiaxial end-diastolic frame selected from two orthogonal views without vessel shortening was used for analysis. Each lesion was assessed for reference diameter, absolute minimal lumen diameter (MLD), percent diameter stenosis (DS%), acute gain (MLD post–MLD pre), late loss (MLD immediately post–MLD at follow-up) and late loss index (late loss/initial gain).

**Statistical analysis.** Continuous variables are summarized as medians (25th, 75th percentiles). Frequencies are displayed as counts and percentages. We employed general linear models (GLM) using SAS statistical software to detect differences in angiographic factors for PTCA versus DCA and native arteries versus grafts.

We analyzed CAVEAT-I and CAVEAT-II patients separately. For each study, univariable regression models tested the differences in the distributions of angiographic factors for the two devices. All of the angiographic factors were first evaluated for normality and were determined to have met this assumption.

Late loss was evaluated further within each of the two CAVEAT studies. First, models with all two-way combinations of acute gain, pre-MLD and post-MLD determined which combination of two of these three factors best predicted late loss. Next, stepwise variable selection, using as potential covariates the primary two MLD measures—pre- and post-percent stenosis and pre- and post-diameter stenosis—gave a set of angiographic factors that were jointly related to the six-month outcome of interest. Variables were retained if they were significant multivariable predictors at alpha = 0.05.

The key angiographic factor(s) found in the stepwise process as well as the randomized treatment were included into a regression model of late loss. This tested the treatment effect after adjusting for the pre- and post-procedural results. Then the interaction of treatment with the angiographic factor(s) was tested. These two sets of analyses allowed us to see if the treatment effect remained after taking angiographic results into account and whether the effect of pre- or post-procedural results on six-month outcome was similar for the two procedures.

Of special interest was the relationship between early gain and late loss. Therefore, the effect of early gain on late loss was also tested in a similar fashion, regardless of the stepwise results. Three sets of predictors were modeled: early gain, early gain plus treatment and early gain, treatment and the interaction of the two.

**RESULTS**

The baseline characteristics of the patients in the two trials have been previously described. Within each trial, patients randomized to either PTCA or DCA had similar baseline clinical characteristics (Table 1). Patients in CAVEAT-II, however, were older, more often male, had more comorbidities and had evidence of more serious coronary disease than patients in CAVEAT-I. Angiographic follow-up was available in 700 patients (87% of successful procedures) in CAVEAT-I and in 197 patients (82% of successful procedures) in CAVEAT-II.

**Early gain.** The baseline quantitative coronary angiographic findings can be seen in Table 2. Vein grafts had significantly larger reference vessel diameters (p < 0.001) and significantly more early gain than native coronary arteries (p < 0.001). There was little difference in baseline diameter stenosis between the two lesion types: 72.1% versus 72.6%. Within each study, DCA was associated with a significantly larger early gain than PTCA (p < 0.001 for each).

**Late loss.** Patients with disease in their native coronary arteries who were randomized to DCA had significantly greater late loss than those randomized to PTCA (p < 0.001). The two groups were not statistically different in both follow-up minimal lumen diameter (p = 0.205) and diameter stenosis (p = 0.074). Thus, the increased late loss in the DCA group appeared to be due to increased initial early gain. Effect of treatment type on late loss became nonsignificant (p = 0.108) when adjusted for early gain. It appears that the trend is for most of the treatment difference...
in late loss to be in patients with small early gains (Fig. 1). However, the test for an interaction of early gain and treatment was not significant (p = 0.403).

In patients with vein grafts, the effect of treatment on late loss was not significantly different (p = 0.556), and the absolute difference in late loss for the two treatment arms did not differ significantly from the absolute difference seen in CAVEAT-I. As with CAVEAT-I, the two treatment arms in CAVEAT-II had similar minimal lumen diameter (p = 0.282) and percent stenosis at follow-up (p = 0.168). After adjusting for acute gain, the treatment type remained nonsignificant (p = 0.487). Figure 2 shows the relationship

Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAVEAT-I</th>
<th>CAVEAT-II</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCA</td>
<td>PTCA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N = 512)</td>
<td>(N = 500)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)*†</td>
<td>59 (51, 67)</td>
<td>59 (52, 67)</td>
<td>0.822</td>
</tr>
<tr>
<td>Male gender (%)†</td>
<td>75</td>
<td>70</td>
<td>0.087</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>82 (73, 92)</td>
<td>82 (72, 93)</td>
<td>0.532</td>
</tr>
<tr>
<td>Height (cm)*</td>
<td>173 (165, 178)</td>
<td>173 (165, 178)</td>
<td>0.947</td>
</tr>
<tr>
<td>Diabetes (%)†</td>
<td>19</td>
<td>19</td>
<td>0.793</td>
</tr>
<tr>
<td>Current smoker (%)†</td>
<td>29</td>
<td>28</td>
<td>0.748</td>
</tr>
<tr>
<td>Hypertension (%)†</td>
<td>52</td>
<td>54</td>
<td>0.557</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)†</td>
<td>46</td>
<td>44</td>
<td>0.560</td>
</tr>
<tr>
<td>History of MI (%)†</td>
<td>44</td>
<td>41</td>
<td>0.345</td>
</tr>
<tr>
<td>Unstable angina (%)†</td>
<td>66</td>
<td>71</td>
<td>0.133</td>
</tr>
<tr>
<td>Ejection fraction*†</td>
<td>59 (50, 65)</td>
<td>60 (50, 65)</td>
<td>0.280</td>
</tr>
</tbody>
</table>

*Medians 25th, 75th percentiles; †For comparison of CAVEAT-I vs. CAVEAT-II, p value < 0.05.

p values for categorical values are calculated using a Log-likelihood chi-square. p values for continuous variables are calculated using a Wilcoxon signed-rank test.

CAVEAT-I, II = Coronary Angioplasty Versus Excisional Atherectomy Trial-I, -II; DCA = directional coronary atherectomy; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Table 2. Angiographic Indexes at Baseline and Late (6 Months) After Intervention

<table>
<thead>
<tr>
<th>Procedure results</th>
<th>CAVEAT-I</th>
<th>CAVEAT-II</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successes</td>
<td>425 (88.9%)</td>
<td>376 (79.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Failures</td>
<td>53 (11.1%)</td>
<td>96 (20.3%)</td>
<td></td>
</tr>
<tr>
<td>Successful procedures</td>
<td>372 (87.5%)</td>
<td>328 (87.2%)</td>
<td>0.900</td>
</tr>
<tr>
<td>With angio F/U</td>
<td>103 (83.1%)</td>
<td>94 (80.3%)</td>
<td>0.585</td>
</tr>
<tr>
<td>Patients missing</td>
<td>34 (6.6%)</td>
<td>28 (5.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Angio F/U = angiography follow-up; CAVEAT-I, II = Coronary Angioplasty Versus Excisional Atherectomy Trial-I, -II; DCA = directional coronary atherectomy; DS = percent diameter stenosis; MLD = minimal lumen diameter; PTCA = percutaneous transluminal coronary angioplasty.

*For comparison of CAVEAT-I vs. CAVEAT-II, p value < 0.05.

p values for categorical values are calculated using a Log-likelihood chi-square. p values for continuous variables are calculated using a Wilcoxon signed-rank test.
between early gain and late loss for the two treatment arms. The test for an interaction between these two factors was not significant \( p = 0.312 \).

**Multivariable analysis of late loss.** Multivariable analysis was performed to assess relationships between geometric determinants and late loss in vein grafts compared with native coronary lesions. In CAVEAT-I, when late loss was modeled with pre- and post-angiographic variables, preminimal luminal diameter, postminimal luminal diameter and postpercent stenosis were all found to be significant independent predictors of late loss \( p = 0.001 \) for each after adjusting for the other two factors). After adjusting for these three angiographic variables, the effect of treatment type (i.e., PTCA vs. DCA) on late loss was no longer significant \( p = 0.802 \). There was also no significant interaction of device type with these three procedural factors. In contrast, in CAVEAT-II only pre- and post-minimal luminal diameters were significant independent predictors of late loss \( p = 0.003 \) and \( <0.001 \), respectively); postprocedural stenosis did not remain significant after adjusting for pre- and post-minimal luminal diameters. In addition, the treatment type in CAVEAT-II was nonsignificant both unadjusted in the univariable model \( p = 0.556 \) (unlike CAVEAT-I) and after adjusting for the pre- and post-minimal luminal diameter in the multivariable model \( p = 0.494 \).

**DISCUSSION**

Restenosis after percutaneous revascularization in saphenous vein grafts has been less well studied than restenosis in native coronary arteries, due, in part, to fewer well-controlled trials of vein graft revascularization procedures and, in part, to the lack of a laboratory model of vein graft restenosis. Until now, it has been unknown whether similar principles of restenosis in native coronary arteries apply to vein grafts.

**Vein grafts as arterial conduits.** There are notable differences in the anatomical/histological properties of coronary arteries and saphenous veins (Table 3), particularly when the vein is used as an arterial conduit \( (5,6) \). This results from several factors: increased intraluminal pressure, graft wall ischemia, thrombosis or fibrin deposition from either ischemia or trauma or both, with secondary repair of the damaged endothelium and intima. As a consequence, histological examination of vein grafts in place from two to 72 months reveals a marked increase in fibrous tissue in all three layers \( (5) \). In older grafts, atherosclerosis becomes more of a problem.

Vein graft histology and response to angioplasty vary in relation to the age of the graft \( (7) \). Graft compromise within the first month of insertion is usually due to thrombosis secondary to technical operative factors. The histology of stenoses of vein grafts treated within 1 year of insertion is characterized by intimal thickening secondary to cellular or acellular fibrocollagenous tissue and thick fibrotic medial and adventitial layers. The dilating mechanism has, there-

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**Table 3. Differences Between Native Coronary Arteries and Saphenous Vein Grafts**

<table>
<thead>
<tr>
<th>Layers</th>
<th>Native Coronary Arteries</th>
<th>Saphenous Vein Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima</td>
<td>IEL present</td>
<td>No IEL present</td>
</tr>
<tr>
<td>Media</td>
<td>Thicker</td>
<td>Thin</td>
</tr>
<tr>
<td>Adventitia</td>
<td>EEL present</td>
<td>No EEL present</td>
</tr>
</tbody>
</table>

IEL = internal elastic lamina; EEL = external elastic lamina.
fore, been postulated to be graft stretching rather than intimal compression. Graft “restenosis” represents restitution of tone of the overstretched segment. For grafts older than one year, the stenoses are usually composed of atherosclerotic plaque associated with intimal fibrous thickening, which is morphologically similar to native coronary arteries. The mechanism of dilation in these older grafts is similar to coronary artery PTCA, i.e., plaque splitting, cracking or breaking with or without localized intimal/medial dissection. In this study, most of the grafts were considerably older than one year (median graft age over nine years).

**Theories of restenosis after percutaneous revascularization.** Theories of restenosis following percutaneous revascularization center on two major issues: neointimal proliferation and geometric remodeling (8). Several mechanisms have been postulated to explain remodeling after coronary angioplasty (9) including: 1) fibrosis of the vessel wall, especially of the adventitia in response to deep wall injury, 2) apoptosis, 3) changes in the extracellular matrix composition and structure, and 4) responses to shear stress-induced changes in vasomotor tone. The media is not likely to be responsible for remodeling. Analysis of severely narrowed coronary arteries has repeatedly shown depletion of medial components; therefore, meaningful reduction in medial thickness accounting for a decrease in the cross-sectional area would be unlikely (10). Interestingly, it is the thickness of the media that most distinguishes veins from arteries. Thus, if the media indeed plays a minor role in restenosis, arteries and veins would be expected to respond similarly to injury despite differences in medial thickness.

**A quantitative model of restenosis applied to vein grafts.** A quantitative model of restenosis (1) has been developed and applied to native coronary arteries. With this model, apparent differences in restenosis rates among different interventional devices are related to the immediate outcome achieved rather than the device used. Our study first sought to validate these results in native coronary arteries and then tested this model in patients undergoing saphenous vein graft intervention. The most notable finding is that, despite histological/anatomical differences and differences in vessel caliber between native coronary arteries and saphenous vein grafts, there were no differences in late loss using the two devices, similar to findings in the native coronary vessels. Because of a larger reference vessel size, both acute gain and late loss were greater in vein grafts compared with native vessels.

**Study limitations.** This is a retrospective study of a subgroup of patients of a larger study comparing DCA with PTCA. Only lesions amenable to both interventions were studied, which may have selected a group of patients with similar plaque/vessel characteristics. A histological comparison of the atherectomy samples may have provided additional insight into both differences between and similarities in vein grafts and native vessels.

**Conclusions.** Our results closely mirrored those reported in prior quantitative angiographic studies. In the largest of these studies, univariable analysis showed that device type influenced late angiographic outcome, although correction of the multivariable model by the postprocedure minimal luminal diameter negated this effect (1). Therefore the final multivariable linear and logistic models demonstrated that the outcomes were determined independently by the immediate results alone and not by the device used. These findings were observed in both the CAVEAT-I and CAVEAT-II studies, suggesting that restenosis is primarily determined by the immediate result alone. This finding should be restudied prospectively using an appropriately-sized patient population.

**REFERENCES**