Grading Carotid Intrastent Restenosis
A 6-Year Follow-Up Study

Carlo Setacci, MD; Emiliano Chisci, MD; Francesco Setacci, MD; Francesca Iacoponi, PhD; Gianmarco de Donato, MD

Background and Purpose—The accuracy of carotid ultrasound has not been well established in predicting intrastent restenosis (ISR) after carotid artery stenting (CAS). The aim of this study is to determine different degrees of ISR using ultrasound velocity criteria compared to percentage of stenosis at angiography.

Methods—This is a 6-year prospective study. After CAS procedure, each patient underwent angiography for measuring ISR (NASCET method) which was compared to peak systolic velocity (PSV), end diastolic velocity (EDV), and the ratio between PSV of internal carotid artery and common carotid artery (ICA/CCA). This was done within 48 hours, thus creating a baseline value. Ultrasound (US) examination was performed at day 30, at 3, 6, 9, and 12 months, and then yearly. Patients with an increase in PSV greater than 3 times the baseline value or in presence of PSV ≥200 cm/s underwent angiography.

Results—814 CAS procedures, 6,427 US examinations, and 1,123 angiographies were performed. ISR ≥70% and ISR ≥50% was detected, respectively, in 22 patients and in 73 patients. We defined velocity criteria for grading carotid ISR: PSV ≤104 cm/s, if <30% stenosis; PSV:105 to 174 cm/s if 30% to 50% stenosis; PSV:175 to 299 cm/s if a 50% to 70% stenosis; PSV ≥300 cm/s, EDV ≥140 cm/s, and ICA/CCA ≥3.8 if a ≥70% stenosis. Receiver operator characteristic (ROC) curves for ISR ≥70% were, respectively, for PSV, EDV, and ICA/CCA: 0.99, 0.98, and 0.99.

Conclusions—US grading of carotid ISR can guarantee a correct follow-up after CAS if new customized velocity criteria are validated by skilled operators using a specific protocol of follow-up in a certified laboratory. (Stroke. 2008;39:1189-1196.)

Key Words: follow-up study ■ stents ■ carotid stenosis ■ ultrasounds ■ angiography

Stroke is the third most common cause of death and the leading cause of disability in Western countries. Carotid artery stenting (CAS) is a viable alternative to carotid endarterectomy (CEA) for the prevention of stroke for some patients. Nowadays the number of patients undergoing CAS is increasing rapidly, and these patients require intensive follow-up to monitor the patency of the device and the potential development of an intrastent restenosis (ISR). An ISR could reduce the benefit of the CAS in preventing stroke.

Duplex ultrasound (US) scanning is the standard technique to follow up patients who have undergone CEA or medical therapy alone. US velocity criteria such as peak systolic velocity (PSV), end diastolic velocity (EDV), and the ratio between PSV of internal carotid artery and common carotid artery (ICA/CCA) correlate with angiographic percent stenosis in nonstented carotid artery. Particularly, the appropriate threshold velocities signifying different degrees of stenosis have been intensively analyzed and identified. However, US velocity criteria and threshold for different degrees of restenosis have not been well-established in patients who have undergone CAS.

The aim of this study is to show whether US examination is accurate for the follow-up of patients with stented carotid arteries and to determine US velocity criteria and their thresholds, compared to percentage of stenosis at angiography, highlighting a different degree of ISR.

Materials and Methods

Study Population
This is a prospective study. Consecutive patients underwent CAS during a period of 6 years (December 2000 to February 2006). Our indications for treatment were the presence of a symptomatic carotid artery stenosis ≥70% or an asymptomatic stenosis of at least 80% according to the Doppler US criteria reported by Carpenter. Written informed consent for surgery was obtained from all patients.

The endovascular procedure was routinely performed using a guiding catheter technique via a femoral access. Demographic variables and clinical, intraoperative, and follow-up data were entered in a specific database by the operating team. Clinical data and characteristics of carotid lesions, types of stents, and cerebral protection devices used are shown in Table 1.

Follow-Up Protocol for CAS
On completion of the CAS procedure, all patients underwent ipsilateral cervical carotid angiography to exclude significant resid-
Table 1. Patients and Lesion Characteristics

<table>
<thead>
<tr>
<th>Patients Characteristics</th>
<th>Type</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total procedures</td>
<td>814</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD*</td>
<td>73±8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>522</td>
<td></td>
<td>64.13</td>
</tr>
<tr>
<td>Symptomatic patients</td>
<td>385</td>
<td></td>
<td>47.3</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>316</td>
<td></td>
<td>38.82</td>
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<tr>
<td>Hypertension</td>
<td>561</td>
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<td>68.92</td>
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<tr>
<td>Diabetes</td>
<td>260</td>
<td></td>
<td>31.94</td>
</tr>
<tr>
<td>Polyvascular disease</td>
<td>323</td>
<td></td>
<td>39.68</td>
</tr>
<tr>
<td>Embolic protection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>device</td>
<td>Accunet filter</td>
<td>44</td>
<td>5.41</td>
</tr>
<tr>
<td></td>
<td>Filter wire</td>
<td>628</td>
<td>77.25</td>
</tr>
<tr>
<td></td>
<td>AngioGuard</td>
<td>127</td>
<td>15.62</td>
</tr>
<tr>
<td></td>
<td>Spider</td>
<td>8</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>MO.MA.</td>
<td>6</td>
<td>0.74</td>
</tr>
<tr>
<td>Need of predilation</td>
<td>60</td>
<td></td>
<td>7.37</td>
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<tr>
<td>Stent</td>
<td>Carotid wallstent</td>
<td>604</td>
<td>74.2</td>
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<tr>
<td></td>
<td>Nexstent</td>
<td>10</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>Precise</td>
<td>144</td>
<td>17.69</td>
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<tr>
<td></td>
<td>Acculink</td>
<td>49</td>
<td>6.02</td>
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<tr>
<td></td>
<td>Protégé</td>
<td>7</td>
<td>0.86</td>
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<tr>
<td>Ulceration†</td>
<td>225</td>
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<td>27.64</td>
</tr>
<tr>
<td>Calcification‡</td>
<td>316</td>
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<td>38.82</td>
</tr>
<tr>
<td>Restenosis post-CEA</td>
<td>116</td>
<td></td>
<td>14.25</td>
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<tr>
<td>Plaque component‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gray-Weale classification‡)</td>
<td>1</td>
<td>23</td>
<td>2.83</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>190</td>
<td>23.64</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>333</td>
<td>40.71</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>268</td>
<td>32.92</td>
</tr>
</tbody>
</table>

*Standard Deviation; †at angiography; ‡at ultrasound.

In-stent stenosis. Angiograms were obtained in interoposterior, oblique, and lateral views. The view demonstrating the highest degree of stenosis was used for the study. The degree of stenosis was determined with North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. The in-stent minimal luminal diameter was compared with the distal non-tapering portion of the ICA serving as the reference segment. Diameters were measured by an independent blinded observer using a software program for quantitative digital angiographic analysis available at the imaging station (MDQM; MEDCON Telemedicine Technology). Any residual stenosis 30% or greater was defined as a technical failure of CAS.

A US examination was performed within 48 hours of CAS and repeated at day 30, at 3, 6, 9, and 12 months, and then yearly. The US examination measured the patency of the stented artery, the values of PSV, EDV, and ICA/CCA, and evidence of an internal thrombus or neointimal flap. All examinations were performed in the same vascular laboratory, with the same US machines (Ultramark IU-22 and HDI 5000 ATL-Philips). The B-mode imaging frequency was 7 MHz, and the pulsed-wave Doppler frequency was 4 MHz.

Velocity in the ICA was determined at distal, middle, and proximal portions of the stent. In addition, velocity was measured at any area of in-stent narrowing identified on B-mode images. An angle of insonation of 60 degrees was used, with angle correction where necessary (40 to 60°). We attempted to maintain the insonation of 60° all the time if possible, to standardize the study methodology. The highest values for PSV, EDV, ICA/CCA was considered in our study in all US examinations.

The angiography performed in all patients at the end of CAS was compared to the US examination within 48 hours. Velocity data (PSV, EDV, ICA/CCA) were compared to the in-stent residual stenosis; this was the baseline value for each patient.

During the period of this study, patients with an increase in the value of PSV greater than 3 times the baseline value or in presence of a PSV ≥200 cm/s underwent a diagnostic angiography. Moreover, on 89 patients who underwent contralateral CAS, an angiography of the first stented carotid artery was performed during the second procedure.

In all angiography procedures, patency and fracture of the device implanted and the in-stent value of restenosis as described above (NASCET method) was evaluated. Patients with an ISR ≥70% (documented at angiography) underwent additional endovascular surgery.

The results of all angiography were always compared to the US velocity data by blinded operators.

Statistical Analysis

All the parameters of this study are expressed as mean±SD. In all tests, probability value <0.05 is considered to indicate statistical significance. The variables analyzed are PSV, EDV, and ICA/CCA versus the carotid in-stent percentage of stenosis at angiography (% of stenosis). These variables are compared with the Pearson coefficient of correlation (R) and the relative probability value. Box plots and scatter plots were constructed to visualize the correlations and the distributions of percentage of stenosis classes. Thresholds for different classes of percentage of stenosis were created (1=<30%, 2=30% to 50%, 3=50% to 70%; 4=≥70%), and receiver operator characteristic (ROC) curves were generated for sensitivity and specificity of various velocity criteria for the above-mentioned classes. A function intended to determine the PSV trend in relation to the percentage of stenosis was created and is represented graphically (SAS System v.9.0, Inc).

Results

814 CAS procedures were performed during the study period. Technical failure of CAS was 2.2% (18/814). The mean follow-up period was 1364 days (4 to 2190 days). 21 patients died during the 6-year follow-up (4 to 1051 day postop). The entire protocol of follow-up was completed by 29 patients at 6 years, 103 patients at 5 years, 198 patients at 4 years, 374 patients at 3 years, 552 patients at 2 years, and 783 patients at 1 year. 6427 US examinations and 1123 angiographies were performed with a ratio of about 6:1 between US scans and angiographies. ISR ≥70% was detected in 22 patients, whereas ISR ≥50% was detected in 73 patients (all cases confirmed by angiography). 3 intrastent thromboses, no intimal flap, dissections and asymptomatic intrastent occlusions were detected at US examinations and angiography. No stent fracture was identified at angiography. Two of the ISR ≥70% patients were symptomatic (9%). Patients with ISR ≥70% underwent a new endovascular procedure and exited from the study population.

Scatter plots of PSV, EDV, ICA/CCA are designed as a function of percentage of stenosis at angiography. The R coefficient for any velocity criteria was always significant in cases of percentage of stenosis with a probability value equal to 0.0001, as shown in Figure 1 (PSV versus % stenosis: R=0.55; EDV versus % stenosis: R=0.49; ICA/CCA versus % stenosis: R=0.71).

The percentage values of stenosis at angiography and the corresponding values of PSV, EDV, and ICA/CCA observed...
Figure 1. Scatter plots of PSV (A), EDV (B), ICA/CCA (C) are plotted as a function of percentage of stenosis at angiography. PSV indicates peak systolic velocity; EDV, end diastolic velocity; ICA/CCA, ratio between PSV of internal carotid artery and common carotid artery. The R coefficient is always significant with a probability value equal to 0.0001 (PSV-stenosis: $R=0.55$; EDV-stenosis: $R=0.49$; ICA/CCA-stenosis: $R=0.71$).
Figure 2. The distributions of classes of stenosis (1=\(<30\%\), 2=30\% to 50\%, 3=50\% to 70\%; 4=\(\geq70\%\)) at angiography versus PSV (A), EDV (B), ICA/CCA (C) using box plots. PSV indicates peak systolic velocity; EDV, end diastolic velocity; ICA/CCA, ratio between PSV of internal carotid artery and common carotid artery.
Table 2. Potential Thresholds in Predicting Different Degree of Percentage Stenosis at Angiography for Diverse Velocity Criteria

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>PSV(cm/s)</th>
<th>EDV(cm/s)</th>
<th>ICA/CCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>≤104</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>30 to 50</td>
<td>105–174</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>50 to 70</td>
<td>175–299</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>≥70</td>
<td>≥300</td>
<td>≥140</td>
<td>≥3.8</td>
</tr>
</tbody>
</table>

PSV indicates peak systolic velocity; EDV, end diastolic velocity; ICA/CCA, ratio between PSV of internal carotid artery and common carotid artery.

at US scans have been ordered into 4 classes: (1) % stenosis <30, (2) % stenosis 30 to 50, (3) % stenosis 50 to 70 and (4) % stenosis ≥70. The distributions of each class of stenosis are represented using box plots, as shown in Figure 2.

The values of percentage of stenosis and the corresponding values of PSV, EDV, and ICA/CCA grouped together in classes are (mean value±SD): stenosis <30%: PSV:68.46±21.21 cm/s, EDV:27.20±10.46 cm/s, ICA/CCA:1.35±0.13; 30% to 50% stenosis: PSV:142.32±35.51 cm/s, EDV:58.84±23.53 cm/s, ICA/CCA:1.97±0.39; 50% to 70% stenosis: PSV:266.36±34.68 cm/s, EDV:123.5±18.42 cm/s, ICA/CCA:3.38±0.44; ≥70% stenosis: PSV:377.56±58.33 cm/s, EDV:148.44±19 cm/s, ICA/CCA:4.08±0.71. A few intervals for several velocity criteria (EDV, ICA/CCA) intersect each other and subsequently some observations could point toward multiple classes, leading to a mistaken classification for threshold velocity criteria. However, the PSV values can be used to obtain potential thresholds in predicting different degrees of percentage of stenosis: a <30% stenosis: PSV ≤104 cm/s; a 30% to 50% stenosis: PSV 105 to 174 cm/s; a 50% to 70% stenosis: PSV 175 to 299 cm/s; whereas a ≥70% stenosis: PSV ≥300 cm/s. The EDV, ICA/CCA values failed to yield satisfactory thresholds for different degrees of stenosis, but 2 reference values for an ISR (≥70% of stenosis) were identified: EDV ≥140 cm/s, ICA/CCA ≥3.8. See Table 2.

ROC curves were generated to evaluate the sensitivity and specificity for identified threshold values of PSV for the 4 different classes of percentage of stenosis and for EDV and ICA/CCA in case of percentage of stenosis ≥70. All variables demonstrated significant discriminating capacity. The assumed PSV, EDV, and ICA/CCA values from the areas under the ROC curve are respectively: for PSV and stenosis <30%: =0.94; 30% to 50% stenosis =0.96; 50% to 70% stenosis =0.98; ≥70% stenosis =0.99 and for EDV and ICA/CCA ≥70% stenosis the values are respectively 0.98 and 0.99.

We therefore created a function intended to determine the PSV trend in relation to the percentage of stenosis at angiography. Because the population study is unbalanced, with 88.3% of the observations for patients with intrastent stenosis <50%, we separated the observations into 2 groups. The first group contains the observations with a percentage of stenosis less than 50%. The second group contains the observations with a percentage of stenosis greater than or equal to 50%. The correlation between percentage of stenosis and PSV in the first group corresponds to a value of R of 0.37 (P<0.0001) and in the second group to a value of R of 0.87 (P<0.0001).

The sample statistics for the first and the second group have, respectively, a mean percentage of stenosis of 7.29±7.7 with a mean PSV of 69.41±22.9 and 67.76±9.96 with a mean PSV of 286.90±78.71. There are 2 equations, one for each group, representing the model that compares PSV to the percentage of stenosis at angiography. The R values for the models are 0.37 and 0.91, respectively. Both models display the quadratic form of the percentage of stenosis (S): log (PSV)=αS+βS², and the regression is represented in Figure 3. In the first model both α and β have the same probability value (<0.0001), whereas in the second model α has a probability value <0.0001 and β has a probability value =0.02.

Discussion

CAS induces permanent alterations of the physiological flow behavior. In particular, the compliance mismatch between the native carotid artery and the stented segment,23 the positive arterial remodelling (stent expansion),24,25 and the enhanced stiffness of the stent-arterial wall complex16 can induce alterations in compliance and in carotid hemodynamics and modifications of Peterson’s elastic modulus of the stented vessel.16 Moreover, changes in wall shear stress can bring endothelial dysfunction ultimately leading to intimal hyperplasia and restenosis26–28 (negative arterial remodelling).25 These alterations lead to an increase in velocity and emphasize the need to develop customized velocity criteria for use in the follow-up of patients who have undergone CAS.16–21 Many authors reported Doppler-US criteria developed for nonstented arteries could not be utilized for stented arteries.14,15 many studies have reported altered blood flow velocity after CAS, and some investigators disagree about the reliability of US examination after CAS.14,15

The literature is not conclusive about CAS follow-up.13,16–21 Different velocity thresholds for a particular degree of ISR can be found, as shown in Table 3.

To our knowledge, this is the largest study—in terms of population study and time of follow-up—of the correlation of US velocity criteria to percentage of stenosis at angiography in patients who have undergone CAS.

Creating a baseline value is important to reduce the number of false restenoses, because the values of velocity tend to be much higher in stented artery than in native carotid. Immediate poststenting US examination provides a valuable baseline value for future follow-up comparisons.16 ISR continues to be the “Achilles heel” of catheter surgery, and the incidence of ISR of CAS is variable in different reports from 1% to 50%.17,29–33 In our study the incidence of ISR (>70%) was 2.7%. Recurrent stenosis in the course of artery healing after endovascular treatment is considered the biological over-response to vascular injury secondary to endovascular surgery.25

Our data indicate that PSV, EDV, and ICA/CCA increase with stenosis to a greater extent in stented carotid arteries than in native arteries and confirmed the strong correlations between angiographic measurement and PSV, EDV, and ICA/CCA. Measuring PSV is the most important component.
Figure 3. Correlation of PSV and NASCET angiographic measurements in stented carotid arteries. Percentage of stenosis at angiography: % of stenosis (S): log (PSV) = αS + βS². A, Observations with a percentage of stenosis less than 50%. R = 0.37 (P < 0.0001). B, Observations with a percentage of stenosis greater than or equal to 50%. R = 0.87 (P < 0.0001). PSV indicates peak systolic velocity; SD, standard deviation.
of the carotid Doppler examination. As a function of the area of the residual lumen, PSV increases with the narrowing of a stented artery, implying its usefulness for grading carotid intrastent stenosis, although factors such as ICA/CCA and EDV provide additional valuable information for quantifying the stenosis but with less accuracy of PSV. However, both ultrasound (screening test) and angiography (gold standard) are operator and machine dependent, with considerable variability in the equipment used and the criteria for interpretation. It is also erroneous to apply the same rigid velocity cut-off to different ultrasound machines, because the frequencies and geometry of the beams vary widely. As a result, velocity recorded in one laboratory may differ significantly from that recorded in another laboratory.

Therefore, it is now widely accepted that individual laboratories validate the customized velocity criteria instead of adopting reported criteria from other laboratories. Because grading carotid intrastent stenosis is an essential part of determining the risk of stroke, its accuracy should be assessed regularly with a prospective registry of ultrasound and other correlative methods, usually angiography. Rigorous training at an established laboratory followed by an on-site prospective comparison of ultrasound findings with angiography is always necessary.

In our laboratory we have found values of PSV $\geq$300 cm/s, EDV $\geq$140 cm/s, and ICA/CCA $\geq$3.8 as criteria for stenosis $\geq$70%. The specificity and sensitivity obtained by combining these parameters together are high (99% and 98%, respectively). When defining an ISR the velocity cut-off has to be set higher in the screening test; this increases specificity at the cost of sensitivity.

The mathematical function that we constructed (log (PSV)=$\alpha S + \beta S^2$, where (S) is the % of stenosis) is intended to highlight the upward tendency of the curve between the percentage of stenosis at angiography and log (PSV) values. For each increment in the percentage of stenosis there is a corresponding exponential increase in PSV, and this is described well by a curve with a quadratic function, where there are significant coefficients ($\alpha$ and $\beta$).

A weakness of our study is the small number of patients with ISR $\geq$50%; 95 (11.7%) patients out of the total number of 814 patients.

### Summary

The compliance and the flow characteristics of a stented carotid artery are extremely different when compared to a native artery. Ultrasound grading of carotid intrastent stenosis needs customized validated criteria because the standard velocity criteria used for nonstented carotid arteries are inappropriate. The new thresholds of velocity criteria for different degrees of ISR have to be increased. In our experience we found the discriminator value of PSV $\geq$300 cm/s, EDV $\geq$140 cm/s, and ICA/CCA $\geq$3.8 as able to individuate a ISR $\geq$70%. A greater sensitivity and specificity of ultrasound screening can be achieved by applying diagnostic criteria specific to each validated laboratory. Our study confirms the high accuracy of PSV as an index of ISR and emphasizes the need for regular US examinations and clinical follow-up of patients after CAS to monitor long-term complications.

### Disclosures

None.

### References

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