Plaque Echolucency Is Not Associated With the Risk of Stroke in Carotid Stenting

Markus Reiter, MD; Robert A. Bucek, MD; Isabella Effenberger, MD; Johanna Boltuch, MD; Wilfried Lang, MD; Ramazanali Ahmadi, MD; Erich Minar, MD; Martin Schillinger, MD

Background and Purpose—Plaque characteristics are suggested to play a potentially important role as risk factors for poor outcome after carotid artery stenting (CAS). We therefore correlated objectively and subjectively determined carotid plaque morphology with neurological complications after CAS.

Methods—We enrolled 698 consecutive patients undergoing elective CAS from a prospective single-center registry database and classified the preinterventional plaque status according to gray-scale median levels and the standardized Beletsky and Gray-Weale plaque scores. Patients were followed for 30-day neurological complications.

Results—Neurological complications including transient ischemic attack, minor and major stroke occurred in 5.9% (41/698) of the patients. Median gray-scale median, Beletsky and Gray-Weale scores were 45 (interquartile range [IQR] 25 to 70), 3.0 (IQR 2.0 to 3.0) and 2.0 (IQR 2.0 to 3.0), respectively. None of the scores was significantly associated with adverse outcome adjusting for traditional risk factors, medication, preinterventional symptoms, degree of stenosis, contralateral occlusion and use of cerebral protection, neither with respect to all neurological complications nor with respect to stroke and death (all \( P > 0.05 \)).

Conclusions—Plaque echolucency measured by objective and subjective grading did not identify patients with an increased risk of peri-interventional neurological events. Evaluation of plaque echolucency therefore cannot be recommended for risk stratification in CAS patients. (Stroke. 2006;37:2378-2380.)

Key Words: carotid artery plaque \( \square \) stents \( \square \) stroke

Identifying powerful determinants for adverse outcome after carotid artery stenting (CAS) is crucial to lower the risk of the procedure and to increase the benefit of the patient compared with medical treatment alone.\(^1\)\(^-\)\(^4\) Among the panel of potential risk factors, plaque characteristics are suggested to play a potentially important role. Biasi et al recently reported a significant association between neurological outcome after CAS and plaque morphology using a quantitative computer-assisted index of echogenicity called gray-scale median (GSM), suggesting that patients with echolucent plaques have an increased risk for complications.\(^5\) In addition to GSM analysis, several visual scores have been described for plaque characterization, but their value in the identification of high-risk plaques before carotid revascularization has not been determined yet.\(^6\)\(^-\)\(^7\) Therefore, we investigated the association between plaque morphology, measured by GSM and visual scores, and occurrence of neurological events and mortality after elective CAS.

Materials and Methods

We enrolled 698 consecutive patients from a prospective single-center registry database who underwent elective carotid stent placement between January 1997 and June 2005 by 3 operators. Candidates were initially identified on the basis of their clinical status and the presence of an angiographically documented stenosis of 70% or more (NASCET) and were included in the registry before treatment.\(^8\) Indications, premedication and technical details of the stent placement procedure are described in previous reports.\(^9\)\(^-\)\(^12\) Previously, we assessed the effect of patient age, individual learning curve of the physician performing the intervention, contralateral high-grade ICA stenosis or occlusion and the use of protection devices on the neurological outcome after CAS in partly overlapping patients.\(^9\)\(^-\)\(^12\)

Ultrasound Stenosis Grading and Plaque Evaluation

Ultrasound (US) was performed 1 day before treatment by using a XP10 scanner (Acuson) with a 5-MHz-linear probe or an Acuson Sequoia scanner (Siemens) with a 14-MHz-linear probe by 2 medical technical assistants and supervised by 1 of the authors (E.M.). B-mode settings were adjusted and standardized by using a maximum dynamic range (60 dB) and by setting the gain to ensure an almost noiseless vessel lumen (blood) and an echo-dense area of adventitia. Images were stored in tagged-imaged files format and then standardized as described previously on a personal computer by using Adobe Photoshop 7.0 (Adobe Systems) to calculate the GSM score.\(^5\)\(^-\)\(^13\) Additionally, the standardized images were classified in consensus by 2 observers (M.R., I.E.), not involved in the image analysis.

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acquisition, according to the scores of Beletsky and Gray-Weale.\textsuperscript{6,7} The score of Beletsky has 3 stages: (1) soft plaque/organized thrombus, (2) intraplaque hemorrhage/fatty deposition, and (3) fibrosis/densely calcified plaques.\textsuperscript{6} Plaques classified in group 1 exhibited a lower density (\textless{}2 times of the blood density) than group 2, which in turn had a lower density than group 3 (as dense as the surrounding connective tissue with/without additional acoustic shadowing).\textsuperscript{6} The score of Gray-Weale uses the following stages: (1) dominantly echoluent, (2) substantially echoluent with small areas of echogenicity, (3) dominantly echogenic with small areas (<25\%) of echolucency, (4) uniformly echogenic, and (5) invisible because of heavy calcification.\textsuperscript{7}

### Neurological Evaluation

Neurological history and examination were routinely performed the day before, and the day after CAS by independent neurologists. Baseline cranial CT was mandatory in all patients. If neurological events were suspected, clinical evaluation with cranial CT was performed immediately. A transient ischemic attack (TIA) was defined as a focal ischemic neurological deficit with abrupt onset that resolved completely within 24 hours. A minor stroke was defined as a focal neurological deficit that lasted >24 hours and had a National Institutes of Health Stroke Scale (NIHSS) score \textlessthan{}4.\textsuperscript{14} A major stroke was defined as a focal neurological deficit that lasted >24 hours and had a NIHSS score >4.\textsuperscript{14}

### Statistical Methods

Data are given as counts (percentages) or medians (interquartile range [IQR]—range from the 25th to the 75th percentile). Univariate analyses were performed applying Yates corrected $\chi^2$ statistics, exact tests or Mann Whitney U tests, as appropriate. Multivariable logistic regression analysis was applied to assess the association between plaque morphology and neurological complications to adjust for potential confounding factors and to address potential interactions. A probability value <0.05 was considered statistically significant. Analyses were performed using SPSS (Version 12.0) or Stata (release 8.0).

### Results

#### Patients

Baseline patient characteristics and technical data of stent placement are presented in Table 1. Neurological complications occurred in 5.9\% (41/698). Rates of TIAs, minor and major strokes were 3\% (21/698), 1.3\% (9/698) and 1.6\% (11/698), respectively. Combined 30-day stroke-and-death rate was 2.9\% (20/698). Two fatal strokes occurred in 2 patients undergoing unprotected CAS, none in the group undergoing protected CAS. Segregating neurological complication rates for symptomatic and asymptomatic patients, we observed rates of TIAs, minor and major strokes of 3.8\% (8/208) versus 2.7\% (13/490), 1.4\% (3/208) versus 1.2\% (6/490) and 3.4\% (7/208) versus 0.8\% (4/490), respectively ($P=0.072$).

#### Plaque Characteristics and Complications

In 94 patients (13\%) GSM levels and Beletsky score could not be calculated because of poor imaging quality, and the Gray-Weale score could not be calculated in 4 patients (0.6\%). Median GSM, Beletsky and Gray-Weale scores were 45 (IQR 25 to 70), 3.0 (IQR 2.0 to 3.0) and 2.0 (IQR 2.0 to 3.0). By univariate analyses none of the indices was significantly different in patients with and without events with respect to all neurological complications or death ($P>0.05$).

GSM levels were then categorized as low (<25) and high (\textgeq{}25) as reported previously.\textsuperscript{3} The frequencies of neurological complications and strokes in patients with low versus high GSM levels were 2.7\% (4/146) versus 6.6\% (30/458; $P=0.13$) and 2.1\% (3/146) versus 3.1\% (14/458; $P=0.73$), respectively.

Being aware of several potential confounders we applied multivariable logistic regression analyses, which demonstrated no significant association of plaque morphology with neurological outcome (Table 2). Furthermore, we tested for interaction by log-likelihood-ratio tests and multiplicative interaction terms between use or nonuse of cerebral protection, neurological outcome and the GSM levels and the 2

### Table 1. Demographic Data and Clinical Characteristics of 698 Patients Undergoing Carotid Artery Stenting

| Age (years) | 73 (64 to 77) |
| Male sex (%) | 482 (69\%) |
| Diabetes mellitus (%) | 253 (36\%) |
| Hypertension (%) | 541 (78\%) |
| Smoking (%) | 137 (20\%) |
| Hyperlipidemia (%) | 565 (81\%) |
| Statin treatment (%) | 528 (76\%) |
| History of myocardial infarction (%) | 126 (18\%) |
| History of TIA* (%) | 144 (21\%) |
| History of minor stroke* (%) | 13 (2\%) |
| History of major stroke* (%) | 50 (7\%) |
| Degree of carotid stenosis ipsilateral (%) | 85 (80\% to 90\%) |
| Degree of carotid stenosis contralateral (%) | 25 (20\% to 55\%) |
| Contra lateral occlusion | 68 (10\%) |
| Technical success of CAS (%) | 671 (96.1\%) |
| Use of protection device (%) | 227 (33\%) |
| Predilatation (%: otherwise direct stenting) | 586 (84\%) |
| Amount of contrast agent (ml) | 180 (160 to 220) |
| Duration of fluoroscopy (min) | 16.8 (13.5 to 22.0) |

Data are given as counts (%) or median (IQR).

*Ipsilateral within 6 months.

#### Table 2. Risk for Neurological Complications (TIAs, Minor and Major Strokes, Death) and Stroke/Death After Carotid Artery Stenting According to Predefined Indices of Plaque Characteristics*

<table>
<thead>
<tr>
<th>Risk for neurological complications</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSM \textlessthan{}25</td>
<td>0.39</td>
<td>0.12 to 1.12</td>
<td>0.079</td>
</tr>
<tr>
<td>Beletsky</td>
<td>1.01</td>
<td>1.0 to 1.02</td>
<td>0.059</td>
</tr>
<tr>
<td>Gray-Weale</td>
<td>1.17</td>
<td>0.87 to 1.57</td>
<td>0.31</td>
</tr>
<tr>
<td>Risk for stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSM \textlessthan{}25</td>
<td>0.59</td>
<td>0.14 to 2.41</td>
<td>0.46</td>
</tr>
<tr>
<td>Beletsky</td>
<td>1.42</td>
<td>1.00 to 3.03</td>
<td>0.054</td>
</tr>
<tr>
<td>Gray-Weale</td>
<td>1.17</td>
<td>0.76 to 1.47</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Results obtained by multivariable logistic regression analysis adjusting for traditional risk factors (age, sex, diabetes, hypertension, hyperlipidemia, smoking), medication (statins), symptoms (symptomatic vs asymptomatic stenosis), degree of stenosis (in 5\% increments), contralateral occlusion and use of cerebral protection.
predefined scores, without detecting a significant effect modification or change of the model fit. Similarly, no interaction for symptomatic versus asymptomatic patients was observed. Including the 94 patients with inconclusive GSM scores attributable to heavy calcification as a separate category, we observed no significantly increased risk for neurological complications or stroke in the multivariable model (all \( P > 0.05 \)).

**Discussion**

We investigated a potential influence of carotid plaque morphology on the neurological outcome after CAS. Neither objective GSM measurement nor subjective grading according to standardized scores was significantly correlated to adverse neurological outcome. These findings are in contrast to the only previously published study by Biasi et al, who reported a significantly higher risk for neurological complications of plaques with a GSM below 25.\(^5\)

Several issues may account for this discrepancy: Biasi et al performed a multicenter trial and included the images of 11 participating centers, which were recorded on video tape (analog) and then transferred onto a personal computer (digital) for further standardization, thus potentially resulting in a loss of image information.\(^9\) The images used in our study were stored immediately as digital images interfaced with the ultrasound machine and therefore could be directly analyzed without further transfer procedures. Besides these potential differences in image quality, a significant influence of investigator and laboratory on the evaluation of carotid stenosis is well known, suggesting a more homogenous dataset obtained by our single-center trial compared with the multicenter (11 different laboratories and US machines) study by Biasi.\(^5,15\) Furthermore, a mathematical limitation of the study by Biasi et al is the relatively low number of events (23/418 patients), resulting in high standard deviations of GSM values, which might have caused false-positive results—in the present study the sample size and number of events was quite large, false-negative results still cannot be completely ruled out. Furthermore, the time interval for data acquisition was long, and considerable technical developments may have influenced our findings. Nevertheless, we tried to statistically account for presumably important changes, like the introduction of cerebral protection devices, and found a consistent lack of association between GSM levels and the Beletsky and Gray-Weale scores, respectively, and neurological outcome.

**Conclusions**

Plaque echolucency measured by objective and subjective grading did not identify patients with an increased risk of peri-interventional neurological events. Evaluation of plaque echolucency therefore cannot be recommended for risk stratification in CAS patients.

**Disclosures**

None.

**References**

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