Risk Score for Peri-Interventional Complications of Carotid Artery Stenting

Robert Hofmann, MD; Alexander Niessner, MD; Alexander Kypta, MD; Clemens Steinwender, MD; Jürgen Kammler, MD; Klaus Kerschner, MD; Michael Grund, MD; Franz Leisch, MD; Kurt Huber, MD

Background and Purpose—Routinely available independent risk factors for the peri-interventional outcome of patients undergoing elective carotid artery stenting (CAS) are lacking. The rationale of the study was to create a risk score identifying high-risk patients.

Methods—We prospectively enrolled 606 consecutive patients assigned to CAS at a secondary care hospital. Various biochemical, clinical, and lesion-related risk factors were prospectively defined. The primary end point reflecting periprocedural complications encompassed minor and major stroke, nonfatal myocardial infarction and all-cause mortality within 30 days.

Results—Three percent of patients (n=18) experienced a nonfatal minor (n=13) or major (n=5) stroke. 1.3% of patients (n=8) died from fatal stroke (n=4) or other causes (n=4). No myocardial infarction was observed within 30 days after stenting. Multivariable analysis revealed diabetes mellitus with inadequate glycemic control (HbA1c >7%), age ≥80 years, ulceration of the carotid artery stenosis, and a contralateral stenosis ≥50% as independent risk factors. A risk score formed with these variables showed a superior predictive value (C-statistic=0.73) compared with single risk factors. The presence of 2 or more of these risk factors identified patients with a risk of 11% for a periprocedural complication compared with 2% in patients with a score of 0 or 1.

Conclusions—In patients undergoing elective CAS, a risk score based on routinely accessible variables was able to identify patients at high-risk for atherothrombotic events and all-cause death within 30 days after the intervention. (Stroke. 2006; 37:2557-2561.)

Key Words: carotid stenosis ■ complications ■ risk factors

Despite a substantial progress in safety, carotid artery stenting (CAS) still entails a substantial risk of serious peri-interventional complications.1–3 The aim of the study was to find routinely available variables independently predicting peri-interventional complications after elective stenting within 30 days. In a second step, we combined independent risk factors to form a risk score identifying high-risk patients.

Materials and Methods

Study Design

We enrolled 624 consecutive white patients assigned to CAS between December 1997 and June 2005 at a secondary care hospital in a prospective registry database. Every patient underwent an independent neurological examination before CAS as well as 24 hours thereafter. Our research protocol was based on the assumption that CAS could be performed with results and complications comparable to carotid endarterectomy (CEA). Thus, CAS was performed in accordance to accepted surgical indications in asymptomatic patients with ≥80% stenosis of the extracranial carotid artery and symptomatic individuals with ≥60% stenosis. Patients were considered symptomatic if they experienced transient cerebral or retinal symptoms (TIA) or a prior stroke. 1.3% of patients (n=8) died from fatal stroke (n=4) or other causes (n=4). No myocardial infarction was observed within 30 days after stenting. Multivariable analysis revealed diabetes mellitus with inadequate glycemic control (HbA1c >7%), age ≥80 years, ulceration of the carotid artery stenosis, and a contralateral stenosis ≥50% as independent risk factors. A risk score formed with these variables showed a superior predictive value (C-statistic=0.73) compared with single risk factors. The presence of 2 or more of these risk factors identified patients with a risk of 11% for a periprocedural complication compared with 2% in patients with a score of 0 or 1.

Baseline Characteristics

We defined the following cardiovascular risk factors: obesity (body mass index >30 kg/m²), hypercholesterolemia (total cholesterol ≥200 mg/dL or LDL cholesterol ≥130 mg/dL), current treatment with cholesterol-lowering medication), diabetes mellitus (DM; history or a fasting glucose >125 mg/dL) with inadequate glycemic control (HbA1c >7%), hypertension, and current smoking. Regarding cardiovascular history, a prior CEA, known peripheral arterial
disease, known coronary artery disease, and a prior myocardial infarction (development of Q-waves on the ECG or elevated creatine kinase myocardial isoenzyme levels to more than twice the normal value) were assessed.

**Carotid Artery Angiography and Stenting**

Our interventional procedures followed the guidelines of good clinical practice. Premedication consisted of aspirin (100 mg/d) and clopidogrel (75 mg) or ticlopidine (500 mg/d) starting 2 days before the intervention. After obtaining vascular access, a bolus of 5000 U IV heparin-sodium was given. No further heparin was added during or after the procedure. The diameter of the stenosis was determined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. All lesions were calculated after the procedure with the use of a semiautomatic device (Hicor, Siemens). The following morphological criteria were defined in accordance to definitions in coronary arteries by Goldstein et al: irregular surface (irregular margins or overhanging edges), ulceration (presence of contrast and hazy contour beyond the vessel lumen), and thrombus (intraluminal filling defect consistent with thrombus) as well as calcification. Furthermore, we assessed the presence of a contralateral stenosis (intraluminal filling defect consistent with thrombus) as well as contrast and hazy contour beyond the vessel lumen), and thrombus (intraluminal filling defect consistent with thrombus) as well as calcification. For CAS, we initially used stents developed for use in coronary arteries. In parallel to the introduction of stenting without predilatation in coronary arteries, we also applied this technique to carotid stenoses. Finally, in July 2002 we started to use self-expanding stents and distal emboli protective devices routinely. Combined antiplatelet therapy with aspirin and clopidogrel or ticlopidine was prescribed for 30 days after CAS.

**Follow-Up and Study End Point**

The follow-up visit at the hospital 30 days after the procedure included a clinical history with respect to cardiovascular adverse events, a neurological examination performed by an independent neurologist, ECG, and Doppler flow velocity measurement of the carotid arteries. In patients who were not able to come to the hospital (n=17, 2.8%), an interrogation by telephone was used for obtaining clinical data.

The primary end point reflecting periprocedural complications encompassed minor and major stroke, nonfatal myocardial infarction and all-cause mortality within 30 days. Neurological events were classified according to Brott et al.7

**Statistical Analysis and Design of Risk Score**

According to the Kolmogorov-Smirnov test, continuous data were not normally distributed and thus are presented as median (interquartile range) and were analyzed using the Mann Whitney U test. Dichotomous data are shown as n (%) and analyzed using the χ² test or the Fisher exact test where appropriate.

For the formation of a risk score, we chose variables which are easily accessible during routine patient care. Candidate variables were arranged in a dichotomous way and selected by forward and backward logistic regression (P<0.2 for selection) for the final model from (1) baseline laboratory, (2) cardiovascular risk factors, (3) cardiovascular history and (4) lesion-related variables in addition to demographic data. The performance of the risk score was evaluated using the area under the receiver operating characteristic (ROC) curve (C-statistic). A value of P=0.05 (2-tailed) was considered statistically significant. All statistical analyses were performed with the statistical software package SPSS 12.0 (SPSS, Inc).

**Results**

**Follow-Up**

Eight of 624 consecutive patients were referred to CEA because of severe circumferential calcifications or variations of the aortic arch. Baseline characteristics (n=6) or follow-up data (n=4) were missing for 10 patients. None of these patients experienced an in-hospital stroke or death. The final analysis included 606 patients with 628 CAS procedures attributable to bilateral interventions in 22 patients. 1.3% of patients (n=8) died from fatal stroke (n=4) or nonstroke related death (n=4). Three percent of patients (n=18) experienced a nonfatal major (n=5) or minor (n=13) stroke within 30 days. No myocardial infarction was observed within 30 days after stenting. In total, 4.3% of patients (n=26) experienced a peri-interventional complication as defined by the primary end point. The frequency of peri-interventional complications was 6.4% in symptomatic patients compared with 3.1% in asymptomatic patients (P=0.055).

Twenty-two events (85%) occurred within 48 hours.

**Univariate Influence of Baseline Characteristics**

Patients with a periprocedural complication were significantly older. They had more often DM with inadequate glycemic control whereas DM irrespective of glycemic control showed only a borderline risk for peri-interventional complications. Furthermore, higher LDL and lower hemoglobin levels before CAS were found in patients with peri-interventional complications (Table 1). Assessment of the treated carotid stenosis showed that patients with an end point had more often a stenosis with irregular surface and ulceration (Table 2).

Furthermore, individuals with a contralateral stenosis ≥50% were at increased risk for periprocedural complications.

**Multivariable Analysis and Risk Score**

Age ≥80 years, DM with an inadequate glycemic control, ulceration of the lesion and a contralateral stenosis ≥50% were selected by forward and backward selection. All 4 variables were significant univariate as well as multivariable predictive risk factors for a periprocedural complication (Table 3). Additional adjustment for the presence of clinical symptoms did not change their independent predictive value (Table 3). The areas under the ROC curve were between 0.58 to 0.61 for single risk factors (Table 3). The risk score formed with these variables showed a highly significant increase of risk with the number of risk factors (Figure). This resulted in an odds ratio of 4.9 (95% CI, 2.2 to 11) for an adverse event in patients with a score of 2 or more. When evaluating the influence of procedural changes over time on the predictive value of the risk score, we neither found a significant interaction between the risk score and the year of enrollment in the prediction of adverse events (P=0.14) nor did the predictive value of the risk score change after adjustment for the year of enrollment (adjusted odds ratio: 4.9 for an adverse event in patients with a score ≥2; 95% CI, 2.2 to 11).

The C-statistic for the risk score yielded a value of 0.73. Adding the presence of clinical symptoms to the risk score did not further improve its predictive value (C-statistic 0.72). Because the assessment of the lesion morphology may not be routinely available in all interventional centers, we designed an alternative score by replacing ulceration with the presence of clinical symptoms. The resulting score showed a slightly lower predictive value (C-statistic 0.69).

**Discussion**

This is the first study systematically investigating risk factors associated with periprocedural adverse events after CAS in a large patient cohort.
TABLE 1. Association of Clinical Baseline Characteristics With Adverse Events Within 30 Days After CAS

<table>
<thead>
<tr>
<th></th>
<th>Adverse Event, n=26</th>
<th>Event-Free, n=580</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (62%)</td>
<td>392 (68%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Age, y</td>
<td>77 (67.2–80.2)</td>
<td>71.3 (63.5–76.6)</td>
<td>0.038</td>
</tr>
<tr>
<td>Age ≥80 y</td>
<td>8 (31%)</td>
<td>86 (15%)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Baseline Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.8 (12–14.5)</td>
<td>13.9 (12.7–14.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1 (1–1.4)</td>
<td>1.1 (0.9–1.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Leukocytes, 1000/ml</td>
<td>7.7 (6.3–9.4)</td>
<td>7.2 (6.1–8.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Fibrinogen, mg/dl</td>
<td>394 (336–497)</td>
<td>366 (316–426)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Cardiovascular Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>5 (19%)</td>
<td>147 (26%)</td>
<td>0.31</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5 (25–29.2)</td>
<td>27 (24.7–30)</td>
<td>0.7</td>
</tr>
<tr>
<td>DM</td>
<td>12 (46%)</td>
<td>167 (29%)</td>
<td>0.058</td>
</tr>
<tr>
<td>With HbA1c &gt;7%</td>
<td>8 (31%)</td>
<td>72 (12%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (73%)</td>
<td>451 (78%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>19 (79%)</td>
<td>484 (84%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>214 (196–265)</td>
<td>204 (169–240)</td>
<td>0.19</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>137 (121–178)</td>
<td>122 (92–153)</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>46 (38–55)</td>
<td>48 (40–57)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3 (12%)</td>
<td>46 (8%)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Cardiovascular History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CEA</td>
<td>1 (3.8%)</td>
<td>50 (8.6%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Known PAD</td>
<td>6 (23%)</td>
<td>98 (17%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Known CAD</td>
<td>13 (50%)</td>
<td>266 (46%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0 (0%)</td>
<td>42 (8%)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; PAD, peripheral artery disease; CAD, coronary artery disease; MI, myocardial infarction.

Continuous data were shown as median (interquartile range) and analyzed using Mann Whitney U test. Dichotomous data are shown as n (%) and analyzed using χ² test or Fisher exact test when appropriate.

Consistent with our results the lead-in phase of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) study comparing the efficacy of CEA and CAS including 749 patients showed that death and stroke were more common in patients ≥80 years compared with patients between 70 and 80 years and patients below 70 years (12.1% versus 5.3% versus 1.3% to 1.7%).

Lesion-related factors appear to have a significant impact on the outcome of CAS as shown in several observational studies. The presence of a contralateral stenosis or occlusion has been shown to increase the risk of CAS. Analyzing contralateral stenosis and occlusion separately, we found a significant and independent association of contralateral stenosis but surprisingly not of complete occlusion with an adverse outcome. The distribution of the variable contralateral occlusion may be influenced by its infrequent occurrence. The meaning of this observation remains to be elucidated. Also in our present study, a location of the lesion at the ostium of the internal carotid artery did not reach statistical significance although a trend in favor of more adverse events could be demonstrated.

There is an increasing interest concerning plaque composition and plaque morphology. Spagnoli et al studied histologically 269 carotid plaques after CEA and found thrombus formation or an inflammatory infiltrate in 74% of plaques from patients with ipsilateral stroke, compared with 14% of plaques from asymptomatic patients. A general accepted definition of a vulnerable plaque has not yet been found leaving the ideal method of visual plaque characterization an open question. Most authors found the presence of thrombus to be associated with ischemic events. However, in all of these studies the spontaneous clinical course of the patients was investigated rather than the complication rate of a stenting procedure. Therefore, these studies are not comparable to our results. In the current era of emboli-protection devices the presence of a thrombus does not seem to play such an important role anymore than it does in the occurrence of spontaneous, nonintervention-related ischemic events. On the other hand, the detection of ulceration might reflect a more extensive pathology of the atherosclerotic plaque prone to thromboembolic events when touched with an interventional device thus revealing an independent risk factor for CAS.

The presence of clinical symptoms has been shown to be a potential risk factor for periprocedural complications after CAS in several studies. However, this association has not been consistently reported with other studies showing no significant difference. Thus, the observed borderline significance between presence of clinical symptoms and periprocedural complications after CAS is within the range of the published literature. A potential explanation for these conflicting results may be different inclusion criteria for symptomatic and asymptomatic patients. Based on our data we assume that ulceration reflecting lesion instability is more important for the prediction of future events because this variable includes also so far...
asymptomatic patients with a vulnerable lesion and refers directly to the target lesion.

DM with an inadequate glycemic control defined by an HbA1c of ≥7% was the strongest independent risk predictor for peri-interventional complications with an adjusted odds ratio of 3.8. These results for CAS are consistent with the outcome after coronary stenting. In a study of Corpus et al, an HbA1c of ≥7% at the time of coronary artery intervention has been demonstrated to increase the rate of ischemia-driven target lesion revascularization, hospitalization, and recurrent angina. The pathophysiological mechanisms have been attributed to hyperglycemia induced vascular endothelial cell damage with subsequent vasomotor dysfunction and increased extra- and intracellular proliferation. In addition, an augmentation of the inflammatory response after vascular damage from endovascular intervention has been found. LDL cholesterol did not reach significance in our multivariable analysis most likely attributable to the almost equally distributed statin therapy in patients with adverse events as well as event-free patients.

The use of protection devices did not have a significant influence on periprocedural complications in our study. However, the number of patients with protection devices was not powered to analyze its influence on peri-interventional complications in this cohort.

### TABLE 3. Independent Risk Predictors of Adverse Events Within 30 Days After CAS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
<th>ROC Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>DM with HbA1c &gt;7%</td>
<td>3.1 (1.3–7.5)</td>
<td>0.01</td>
<td>3.7 (1.5–9.1)</td>
</tr>
<tr>
<td>Age ≥80 y</td>
<td>2.6 (1.1–6.1)</td>
<td>0.033</td>
<td>2.7 (1.1–6.6)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>2.4 (1.0–5.5)</td>
<td>0.038</td>
<td>2.5 (1.1–5.8)</td>
</tr>
<tr>
<td>Contralateral stenosis ≥50%</td>
<td>2.5 (1.1–5.7)</td>
<td>0.026</td>
<td>2.3 (1.0–5.4)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>2.1 (1.0–4.7)</td>
<td>0.06</td>
<td>2.1 (0.9–4.7)</td>
</tr>
</tbody>
</table>

AUC indicates area under curve.

Variables with an independent influence on peri-procedural complications after carotid stenting were selected from Tables 1 and 2 using forward and backward logistic regression. In addition, the variable “symptomatic” was included because of its potential predictive value shown in previous studies. Continuous data were arranged in a dichotomous way with the cut-off shown in brackets: anemia (hemoglobin <12 g/dl), renal insufficiency (creatinine >1.3 mg/dl), inflammatory activation (leukocyte count >10^3/mL or fibrinogen >450 mg/dl), high-grade carotid stenosis (≥90%) and extended lesion length (≥15 mm).

Risk score for adverse events within 30 days after carotid artery stenting. The risk score was formed using the variables age ≥80 years, DM with inadequate glycemic control, the morphological feature ulceration and contralateral stenosis ≥50%. Bars show the frequency of adverse events after carotid stenting within 30 days with the number of present risk factors. The frequency of score “0” was 200, of “1” 265, of “2” 115, “3” 26 and “4” 0.
Identification of high-risk patients may influence the clinical management. This may affect the estimation of the balance between benefit and risk of the intervention. On the other hand, a risk of only 2% in patients with a risk score below 2 may affect the decision-making process in favor of an intervention. The new risk score presented in this study based on a rigid statistical evaluation exceeds the predictive value of reported single risk factors as shown by ROC curves and odds ratios. The alternative risk score which was formed by replacing ulceration with presence of clinical symptoms may be of particular interest in centers where clinical symptoms have been shown to be a strong predictor for periprocedural complications. This alternative approach likewise had a higher predictive value than single risk factors.

In summary, in patients undergoing elective stenting of a carotid artery stenosis, a risk score based on routinely accessible variables can identify patients at high risk for atherothrombotic events and all-cause death within 30 days after the intervention. This convenient risk score is likely to be useful in patient management after CAS. However, its predictive value has to be validated in independent cohorts. Moreover, our data strongly support the correction of an inadequate glycemic control in patients with DM before elective CAS.

Disclosures

None.

References

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