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# Predictors of Death and Stroke After Carotid Angioplasty and Stenting

## A Subgroup Analysis of the Pro-CAS Data

Wolfram Theiss, MD; Peter Hermanek, MD; Klaus Mathias, MD; Hartmut Brückmann, MD; Jürgen Dembski, MD; Franz-Josef Hoffmann, MD; Rüdiger Kerner, MD; Franz Leisch, MD; Harald Mudra, MD; Karl-Ludwig Schulte, MD; Horst Sievert, MD; for the German Society of Angiology/Vascular Medicine and the German Society of Radiology

**Background and Purpose**—Little is known about the significance of patient characteristics, clinical indications, and technical details on the risk of carotid angioplasty and stenting (CAS). The purpose of this study was to test these parameters as to their predictive value for the peri-interventional risk of CAS.

**Methods**—Pro-CAS is a prospective, multicenter registry of CAS. Logistic regression analysis of possible predictive factors was performed on 5341 interventions that had been entered by 25 clinical centers between July 1999 and June 2005.

**Results**—The combined in-hospital mortality and stroke rate was 3.6%. The following were found to be significant predictors of peri-interventional stroke and death: center experience ( $\leq 50$  versus 51 to 150 versus  $\geq 151$  interventions), age, prior symptoms, primary intervention as compared with intervention for restenosis, angioplasty without stent, predilatation, and heparin dosage  $>5000$  IU. No statistically significant result was found for year of intervention, patient volume, gender, interval between symptoms and CAS, ocular versus neurological symptoms, side of CAS, degree of stenosis of the target lesion, presence of contralateral high-degree stenosis or occlusion, method of gaining access to the carotids, stent type, and use of a protection system.

**Conclusions**—Our findings underline the need for dedicated training and strict credentialing rules for CAS. In addition, they might help to identify subgroups of patients at differential risk for CAS and carotid endarterectomy and yield a basis for correcting risks due to differences in case mix in reports about CAS. (*Stroke*. 2008;39:000-000.)

**Key Words:** angioplasty and stenting ■ carotid stenosis ■ complications ■ outcome ■ registry

Despite the ongoing controversial debate about the precise value of carotid angioplasty and stenting (CAS) as compared with carotid endarterectomy, its use in everyday clinical practice has virtually exploded in many parts of the world. To control against the unrestricted use of the method and as a measure of quality assurance, the German Society of Angiology/Vascular Medicine and the German Society of Radiology installed a prospective registry of CAS (Pro-CAS) in 1999. Results of the first 3267 interventions that had been documented in this registry up to June 30, 2003, have been published in this journal in 2004.<sup>1</sup> Since then, the number of documented interventions has further increased steadily, thus providing an opportunity to analyze the data more in detail with the aim of defining patient characteristics and technical

modifications that might be predictive of the short-term outcome of CAS.

### Patients and Methods

Pro-CAS was installed and its protocol was approved by the review committees of the 2 supporting societies. Anonymous data were collected and evaluated by the Bavarian Permanent Working Party for Quality Assurance (Bayerische Arbeitsgemeinschaft für Qualitätssicherung, Munich, Germany), a nongovernmental, nonprofit agency set up for the sake of external quality assessment in medicine.

The registry is open to any investigator in Germany, Austria, and Switzerland who is active in CAS. To gain a comprehensive picture of CAS as it is practiced under routine conditions, no rules on indications, contraindications, or technical details of CAS are imposed on the participants, and they are asked to report all their patients in whom CAS is planned. Patients have to be registered

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prospectively at least 24 hours before the procedure is started, and they have to be followed and documented on standardized case report forms until discharge or death. The first interventions were entered in July 1999, and by June 2005, 6233 interventions had been enrolled by 55 institutions. Because the learning curve and the development of complications over the years were subjects of major interest for the present study, only centers that had started enrolling patients no later than June 2002 and that had been active at least up to June 2003 were taken into account for the present evaluation. This left us with 25 centers, which had performed 5341 interventions between July 1, 1999, and June 30, 2005.

The number of interventions that had been performed at a given center, before they started enrolling patients in the registry, covered a range from 0 to 1200 (median, 38). The total number of interventions recorded in the registry by the different institutions (median, 140; range, 10 to 806) and the number of interventions performed per year at a given institution (median, 23; range, 1 to 216; quartiles 11 to 50) varied considerably. Consequently, the experience that a center had gained with CAS at any given new intervention varied from 0 (very first patient) to 2005, because it represents the sum of interventions before joining the registry and the number of interventions recorded in the registry up to this point. These values form the basis for the analysis of the learning curve of the centers. No attempt was made to analyze the learning curve of individual operators.

Diameter stenosis is determined locally according to NASCET criteria.<sup>2</sup> Stroke is defined as a neurological deficit persisting longer than 24 hours, minor stroke resulting in Grades 1 or 2, and major stroke in Grades 3 to 5 on a modified Rankin scale.<sup>3</sup> The combined end point of any in-hospital death or stroke or visual defect persisting >24 hours was prospectively defined as the primary end point.

Absolute numbers and percentages were computed to describe the patient population, technical details, and clinical outcome. The associations between potential predictors of interventional risk and the combined end point of any in-hospital death or stroke or visual defect persisting >24 hours were assessed first by univariate methods and then by multivariate logistic regression methods. Univariate comparisons were performed with single ORs in the case of dichotomous predictors and  $k-1$  ORs for  $k$ -level predictors. Continuous predictors were suitably categorized to maximize heterogeneity of the response across respective categories. Ninety-five percent CIs as well as 2-tailed probability values for  $z$ -tests of equality of proportions were computed.

Variables were initially considered for inclusion in the multivariate model if they were significant at the 0.05 level in the univariate analysis; variables structurally relevant only to subsets of the patient population or variables with substantial proportions of missing values (>10%) were excluded in this analysis. Stepwise logistic regression was used for model selection with significance levels for inclusion or removal of predictors set at 0.05. For all logistic regression models values, the Hosmer-Lemeshow goodness of fit test, Nagelkerke's maximum rescaled pseudo  $R^2$  as well as the area under the curve for the initial quarter of the receiver operating characteristic (false-positive rate <0.25) were computed. Angioplasty with or without stent was forced into the model at a later stage on clinical grounds, although it failed to meet significance in the univariate analysis.

In an additional step, explorative multivariate analyses of variables that were applicable only to parts of the patient population or that were missing in more than 10% of records were carried out by including them singly or in pairs together with the factors found to be significant in the initial logistic regression analysis. ORs and 95% CIs were calculated for each risk factor. SAS statistical software version 9.1 was used for data analysis.

## Results

The median age of the patients was 70 years (range, 32 to 96 years). The internal carotid artery was the target lesion in 98.0% of the interventions, the common carotid artery in 1.9%, and the external carotid artery in 8 cases. In 7 of the latter, the external carotid artery served as the essential

collateral vessel for an occluded internal carotid artery; one patient had an ipsilateral minor stroke with the common and internal carotid artery patent.

Platelet inhibitors were given in preparation for the intervention in 98.9%. During the procedure, heparin (median, 5000 IU; range, 1000 to 22 000 IU) was given to all but 5 patients who were given lepirudin ( $n=2$ ) or danaparoid ( $n=3$ ). The median postinterventional hospital stay was 2 days (quartiles 1 to 4). CAS was successful in 98.3%. Twenty-three patients died 1 to 69 days (median, 7 days) after the intervention resulting in a mortality rate of 0.4%. A stroke or visual deficit persisting >24 hours occurred in 3.5% (major stroke 0.9%; minor stroke 2.4%; retinal ischemia 0.1%). The combined mortality and stroke rate was 3.6%.

Major characteristics of the patient population and technical details and their association with the combined end point of any in-hospital death or stroke or visual defect persisting >24 hours as calculated by univariate analysis are listed in Table 1. In addition, the following were tested and found to have no predictive value on univariate analysis: degree of stenosis ( $P=0.4041$ ), catheterization technique ( $P=0.3717$ ), final balloon diameter ( $P=0.6893$ ), stent type ( $P=0.7026$ ), stent positioned exclusively in the internal carotid artery versus overlapping from the common to internal carotid artery ( $P=0.8624$ ), and type of protection device ( $P=0.6042$ ).

Stepwise logistic regression analysis revealed statistically significant adjusted ORs for the predictors experience of the institution, patients age, prior symptoms, prior carotid intervention or surgery, use of a stent, predilatation, and the dosage of heparin with respect to the combined outcome of in-hospital death or stroke (Figure). Although the goodness of fit test revealed no departures from the logistic model assumption ( $\chi^2=4.8132$ ,  $P=0.7773$ ), the pseudo  $R^2=0.0517$  as well as the partial area under the curve=0.2584 indicate major deficiencies in the explanatory power of the multivariate analysis. Similar performance characteristics were found for the additional regression analyses on subsets of the data (average  $R^2=5\%$ ; average area under the curve=26%).

Subsequently, analysis of variables that were met only by part of the patient population or that were only available for a portion of the total patient cohort was carried out with adjustment for the factors found to be significant in the logistic regression analysis. None of these variables proved to be of predictive value for outcome (Table 2).

## Discussion

We deliberately dispensed with any rules or restrictions concerning clinical routines and the performance of CAS, because we wanted to document and analyze the results of CAS in a real-world setting. This results in several differences in comparison to randomized studies or postmarketing studies with strict protocols, the most important ones being the lack of 100% neurological control and the absence of 30-day outcomes.

In fact, only 89.4% of the patients were seen by a board-certified neurologist before the intervention, and only 70.1% were seen by a neurologist both before and after the

**Table 1. Patient Characteristics and Technical Details\***

Variable	No. Variables/Total	Periprocedural Stroke or Death	P
Year			0.0294
July 1, 1999, to June 30, 2000	461/5341	6.1%	
July 1, 2000, to June 30, 2001	705/5341	3.8%	
July 1, 2001, to June 30, 2002	793/5341	3.8%	
July 1, 2002, to June 30, 2003	995/5341	2.6%	
July 1, 2003, to June 30, 2004	1130/5341	3.7%	
July 1, 2004, to June 30, 2005	1257/5341	3.0%	
Center experience			0.0010
Interventions 1 to 50	471/5341	5.9%	
Interventions 51 to 150	1089/5341	4.5%	
Interventions 151 and higher	3781/5341	3.0%	
Patient volume			0.0014
≤50 interventions/year	2067/5341	4.6%	
>50 interventions/year	3274/5341	2.9%	
Age			<0.0001
<60 years	679/5341	1.3%	
60–69 years	1811/5341	3.0%	
70–79 years	2133/5341	3.8%	
≥80 years	718/5341	6.3%	
Gender†			0.4158
Male	3421/4834	3.5%	
Female	1413/4834	3.0%	
Symptomatic status			0.0019
Symptomatic	2921/5333	4.3%	
Asymptomatic	2412/5333	2.7%	
Type of symptoms leading to CAS‡			0.1007
Transient monocular blindness	381/2884	2.6%	
Transient ischemic stroke	1359/2884	4.4%	
Stroke	1144/2884	4.5%	
Interval between symptoms and CAS‡			0.7821
≤2 weeks	609/2344	3.6%	
2–4 weeks	326/2344	4.3%	
2–12 weeks	763/2344	4.6%	
>12 weeks	646/2344	3.9%	
Target lesion native versus recurrent			0.0019
Native stenosis	4905/5338	3.8%	
Prior carotid artery surgery	310/5338	1.3%	
Prior carotid percutaneous angioplasty/CAS	123/5338	0	

(Continued)

**Table 1. Continued**

Variable	No. Variables/Total	Periprocedural Stroke or Death	P
Contralateral carotid stenosis ≥90% or occlusion			0.1090
Yes	717/3025	2.4%	
No	2308/3025	3.6%	
Side of target lesion	0.1632		
Right	2611/5336	3.2%	
Left	2725/5336	3.9%	
Stenting			0.3989
By routine	5099/5270	3.5%	
No stent or elective stenting	171/5270	4.7%	
Predilatation‡			0.0356
Yes	2645/5147	4.1%	
No (=primary stenting)	2502/5147	3.0%	
Protection device†			0.6517
No	1166/4709	3.4%	
Yes	3543/4709	3.2%	
Heparin			0.0019
≤5000 IU	3153/5341	2.9%	
>5000 IU	2188/5341	4.5%	

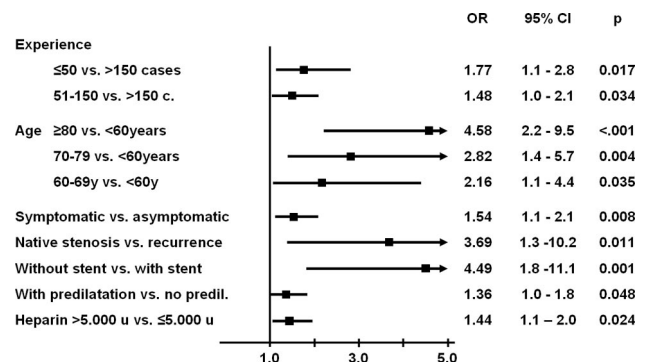
\*Univariate analysis of periprocedural stroke and/or death for these variables.

†Variables documented only beginning in October 2000.

‡Variables applying only to part of the patients. All other deviations from the total number of 5341 interventions are due to missing values.

intervention. Depending on structural particularities, individual institutions presented their patients routinely to a neurologist both before and after the intervention, whereas others did so only occasionally (“on demand”). Analysis of the stroke and death rate revealed no statistically significant difference between these 2 types of centers (Table 3;  $P=0.4475$  on univariate analysis and  $P=0.1818$  after correction for the parameters listed in the Figure) suggesting that there was little or no underreporting of adverse events due to lack of 100% board-certified neurological control.

At present, the German health system does not require registry data to extend beyond discharge. Therefore, reporting events in our registry is restricted to the duration of the



**Figure.** Multivariate predictors of periprocedural stroke and/or death. 95% CI indicates 95% Wald confidence limits.

**Table 2. Predictive Value of Variables With >10% Missing Values or Applying Only to Part of the Patient Population\***

Effect	P
Male versus female	0.3056
Symptoms leading to CAS	
Transient monocular blindness versus transient ischemic attack versus stroke	0.2964
Time from symptoms until CAS	
≤7 days versus >7 days	0.6194
Presence versus absence of contralateral high-grade stenosis or occlusion	0.1208
No protection device versus with protection device	0.3853

\*Data corrected for center experience, age, presence of symptoms, use of stents, predilatation, and heparin dosage.

hospital stay, ie, a median of 2 days. Because 15% to 25% of periprocedural strokes occur later during the subsequent days of the customary 30-day observation period,<sup>4-6</sup> the number of periprocedural strokes documented in our registry is lower than those reported by such studies.

Mandatory board-certified neurological control before and after the intervention and compulsory 30-day examinations would have kept a number of investigators from participating in the registry and would thus have run contrary to our intention of a truly representative picture of clinical routine as practiced in the medical community. Restricting our analysis to interventions with complete neurological assessment would have led to a similar distortion. We therefore rather accepted some uncertainty as to the exact number of peri-interventional complications than giving up the “real-world” character of our data. In addition, this imprecision is of little importance for the present analysis, because its major subject is not the absolute number of peri-interventional complications, but rather the relative importance of epidemiological, technological, and institutional characteristics in a real-world setting, in which results can be correlated to a wide spectrum of patient characteristics and methods and devices that may be used in clinical everyday routine.

### Learning Curve, Patient Volume, and Temporal Trends

Probably the most important finding in our analysis is the documentation of a significant learning curve. In evaluating the applications of stent operators who wanted to participate in the CREST trial, it was found that 94 operators who had performed fewer than 15 CAS procedures in NASCET-equivalent cases had a stroke/death rate of 7.1% as compared with 3.7% of the 9 operators who had performed 15 or more CAS procedures.<sup>7</sup> Although we analyzed institutional experience rather than individual operator experience, our data suggest that the individual learning curve must extend well beyond the first 15 cases when we take into consideration that the median number of operators per center was 2 (range, 1 to 4) and that neurological complications and/or death occurred 1.76 times more often in the first 50 interventions of an institution and 1.48 times more often for interventions 51 to 150 as compared with later on, when experience with more than 150 interventions had been accumulated.

**Table 3. Periprocedural Stroke or Death Rate in Relation to Examination by a Board-Certified Neurologist\***

Centers With Neurological Examination	
By Routine	On Demand
148/4014 (3.7%)	43/1327 (3.2%)

\*For explanation, see text (“Discussion”).

Although a decreasing rate of neurological complications over the years has been reported repeatedly in single-center studies<sup>8,9</sup> and in multicenter registries,<sup>10,11</sup> this usually has been attributed to the refinement of technical details and the improvement of devices rather than to experience. In our multivariate analysis, the positive temporal trend over the years and the positive correlation with patient volume that are also apparent in our data on univariate analysis disappear in the multivariate analysis, when institutional experience is included, thus stressing the overwhelming importance of experience.

This long learning phase may explain the disappointing results of CAS in the recently published EVA-3S study,<sup>5</sup> in which trial investigators could participate with as little experience as 5 CAS procedures or even without any prior CAS experience at all when supervision by an experienced tutor was guaranteed, and the 30-day incidence of any stroke or death was a surprisingly high 9.6%. This contrasts with the 5.6% that have been reported recently for symptomatic lead-in patients of CREST,<sup>12</sup> a trial with particularly strict credentialing rules for participants, and highlights the importance of establishing criteria for credentialing operators for CAS as has recently been suggested by several professional organizations.<sup>13</sup>

### Patient Characteristics

The highly significant correlation between outcome and age with a particularly high complication rate in patients aged 80 years or older is in good accordance with other data in the literature.<sup>4,6,9,14,15</sup> This contrasts with carotid endarterectomy, in which no correlation between acute complications and age was found in a meta-analysis of randomized trials comparing medical treatment and carotid endarterectomy.<sup>16</sup> Although it cannot be ruled out that the lack of an age effect in this meta-analysis was due at least in part to a selection bias caused by a study protocol that preferentially excluded surgical high-risk patients, it appears plausible that progressive development of atherosclerotic plaque in the aorta and the cerebrovascular territory might increase the risk of cerebral emboli in older patients in a CAS-specific way and that carotid endarterectomy may be the preferred procedure in older patients who have no general contraindications to surgery.

In contrast, a preference for CAS can be seen in cases of recurrent stenosis after carotid endarterectomy and in patients with high-degree contralateral carotid involvement. Our data confirm the assumption that CAS is particularly safe in recurrent stenosis.<sup>17</sup> This is in contrast to carotid endarterectomy, in which surgery for restenosis is associated with a

significantly higher risk than primary surgery.<sup>18</sup> Accordingly, consensus conferences have agreed that carotid restenosis constitutes one of the established indications for CAS.<sup>13,19</sup> Contralateral carotid occlusion has been found to be a significant independent predictor for 30-day death or stroke in patients undergoing endarterectomy.<sup>16,20</sup> Our data show that contralateral high-degree stenosis or occlusion do not increase the rate of peri-interventional complications in CAS and thus confirm the recommendation of a recent consensus document<sup>13</sup> that CAS should be preferred over surgery in cases with contralateral high-degree stenosis or occlusion.

Because the risk of stroke is largest in the very first weeks after preliminary symptoms, early carotid repair is of particular benefit. As for surgery, early operation is now preferred, because the perioperative risk was not increased in early carotid endarterectomy during the first weeks after the last symptomatic event as compared with late carotid endarterectomy during the following months in patients with stable symptoms,<sup>16,18</sup> and our data show that the same is true for CAS.

### Technical Details and Periprocedural Medication

In contrast to the great importance of center experience, modifications of technical details of CAS seem to be of minor importance. The only variables that showed some influence on outcome were predilatation and routine use of stents. Predilatation proved to be marginally disadvantageous with an OR of 1.36. The rate of interventions performed without a stent or with elective implantation of a stent has remained almost constant with 1.5% for July 1999 to June 2002 and 1.7% for July 2002 to June 2005. Our data now show a significantly lower rate of complications with routine implantation of a stent.

Although no randomized studies have ever been performed to prove the value of protection devices, they are almost considered standard in many parts of the world,<sup>13</sup> and they have become mandatory in some large-scale trials such as CREST<sup>21</sup> and EVA-3S.<sup>5</sup> This is mainly based on theoretical considerations and on the comparison of complication rates in newer trials with historic controls. However, reports of deployment problems, device failure, and adverse neurological reactions in a number of cases<sup>22</sup> document that protection devices may cause complications of their own, and the decreased frequency of neurological complications in comparison to historical controls<sup>15,23</sup> may rather be due to increasing interventional skill and improved periprocedural antithrombotic regimens than to the use of protection devices.<sup>24</sup> Our own registry data involving patients who were treated during the same time period with and without protection devices revealed no difference in the combined stroke and death rate between patients treated with and without protection devices. This is in accordance with a subgroup analysis of SPACE, in which no difference was found whether protection devices were used.<sup>6</sup> On the other hand, the true value of protection devices might be underestimated in our registry and in SPACE, because their use is associated with a long learning curve.<sup>10</sup> According to the rules of evidence-based medicine, it thus appears warranted to test the clinical value of protection devices in randomized trials.

There is no generally accepted, evidence-based dosage scheme for anticoagulation during CAS, and the dosages used by the interventionalists of our registry varied widely. Although the higher complication rate of heparin dosages above 5000 IU that we found in our analysis might totally or in part be due to a negative selection bias favoring higher heparin dosages in more complex and longer interventions, our data suggest that dosages above 5000 IU in uncomplicated CAS bear no advantage over lower doses.

### Limitations and Summary

There are several limitations to our analysis. The most important ones are the absence of 100% neurological control, the lack of 30-day data, and the absence of on-site inspections and of central evaluation of the angiographies. Nevertheless, we believe that the setup of the registry, including prospective registration of patients before the intervention, central and independent data evaluation, and the large number of interventions, is a relatively solid basis for our analysis.

The major findings are the long learning phase required for achieving competence in performing CAS, the safety of early CAS in symptomatic patients, the apparent equivalence of CAS with and without protection devices, and the suggestion of some patient characteristics that might help to identify subgroups of patients at differential risk for CAS and carotid endarterectomy. However, the area under the curve and the adjusted pseudo  $R^2$  values are low and thus suggest that multiple other, hitherto unknown factors and chance are also of great importance for the risk of peri-interventional stroke and death.

### Participating Centers and Investigators

Austria: F. Leisch, Linz. Germany: J.C. Dembski, Koblenz; K. Haerten, Wesel; W.L. Heindel, Münster; F.-J. Hoffmann, Neunkirchen; I. Janicke, Duisburg; H. Kaiser, Kusel; R. Kerner, Kevelaer; K. Mathias, Dortmund; H. Mudra, München-Neuperlach; H. Mühling, München; N. Reifart, Bad Soden; C. Rock, Deggendorf; G. Rupp-Heim, Göppingen; K.-L. Schulte, Berlin; H. Sievert, Frankfurt; Ch. Stelzner, Dresden; M. Stengel, Bruchsal; K. Theisen, München; W. Theiss, München; J. Waigand, Berlin; E. Wedell, Bad Neustadt; M. Wilaschek, Berlin; T. Zeller, Bad Krozingen; and Ch. Zur, Bad Saarow.

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### Disclosures

K.M. is on the Speakers Bureau and has received honoraria from Abbott, Boston Scientific, and Cordis and is a consultant for Abbott. H.M. is on the Speakers Bureau and has received honoraria from Abbott, Angiomed, Boston Scientific, and Cordis and is a consultant for Boston Scientific. H.S. has received study honoraria from Abbott, Angiomed, Boston Scientific, Kensey Nash, and Lumen Biomedical and has received honoraria for training/proctoring from Abbott, Angiomed, Boston Scientific, Cordis, ev3, and Gore and is a consultant for Abbott, Angiomed, Boston Scientific, Cordis, ev3, Gore, and Lumen Biomedical.

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