# Risk Prediction for Adverse Events After Carotid Artery Stenting in Higher Surgical Risk Patients

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# Risk Prediction for Adverse Events After Carotid Artery Stenting in Higher Surgical Risk Patients

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***Background and Purpose***—The goal of carotid artery stenting is to decrease the risk of stroke or other adverse events from carotid artery disease. Choosing a treatment strategy requires patient-specific information regarding periprocedural risk of adverse neurologic events. The aim of this study was to predict individual patient risk after carotid artery stenting in patients at higher risk for carotid endarterectomy.

***Methods***—Subjects enrolled in the Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) worldwide study underwent carotid artery stenting with distal protection. Only patients with at least 1 anatomic or comorbid factor associated with elevated surgical risk were included. Preprocedural factors were used to develop a model and integer-based risk score predicting stroke or death within 30 days. The model was calibrated and internally validated using bootstrap resampling.

***Results***—Ten thousand one hundred eighty-six patients were included in the analysis. The overall rate of stroke or death was 3.6% at 30 days after carotid artery stenting. Independent predictors of adverse outcomes were increased age ($P$=0.006), history of stroke ($P$<0.001), history of transient ischemic attack presentation ($P$=0.001), recent (<4 weeks) myocardial infarction ($P$=0.006), dialysis treatment ($P$=0.007), need for cardiac surgery in addition to carotid revascularization ($P$=0.005), a right-sided carotid stenosis ($P$=0.006), a longer carotid plaque ($P$=0.012), the presence of a Type II or III aortic arch ($P$=0.035), and a tortuous carotid arterial system ($P$=0.004). The optimism-adjusted C-statistic was 0.691.

***Conclusions***—Commonly collected clinical and anatomic variables can identify patients at high and low risk for stroke or death after carotid artery stenting. **(*Stroke*. 2012;43:3218-3224.)**

**Key Words:** carotid arteries ■ risk factors ■ stenting ■ stents

Treatment options for patients with significant carotid atherosclerosis include surgical carotid endarterectomy (CEA), endovascular carotid artery stenting (CAS), and medical therapy. There has been significant effort to define the optimal treatment choices for specific patients, although this remains a controversial issue.[1] Current guidelines from independent international organizations advocate different approaches to this decision.[2] The 14 organization multisociety guidelines, which included the American Heart Association, American College of Cardiology, and Society for Vascular Surgery, advocate decision-making for CAS based on an individual's likelihood of complications and expected benefit. The guidelines also advocate a threshold of 6% as the upper limit of the acceptable rate of periprocedural stroke or death from CAS in symptomatic patients.[3] Previous guidelines have advocated a 6% threshold for carotid revascularization in symptomatic patients and a 3% threshold in asymptomatic patients based on complication rates from surgical studies.[4,5] These thresholds are based on anticipated complication rates of routine patients undergoing CEA rather than on expected risks or benefits of CAS compared with CEA or medical therapy. Recent reports from a large, randomized trial and meta-analysis question the role of CAS, compared with CEA, in asymptomatic patients.[6,7]

In clinical practice there is consensus that there are groups of patients at increased risk for complications with CEA due to unfavorable anatomical features, medical comorbidities, or both.[8–16] Separate international guidelines define "higher risk" patients slightly differently and use different approaches to discuss the appropriate mode or timing of carotid revascularization in these populations.[2]

Because understanding periprocedural risk is crucial in decision-making, previous groups have sought to generate risk models or scores to predict adverse events for individual patients undergoing CAS.[17–19] None of the previously published risk scores, however, are specifically applicable to higher surgical risk patients. Previous risk scores also were not developed in cohorts in which

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outcomes were evaluated using independent clinical end point committees.

The Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) randomized trial is the only randomized clinical trial to specifically enroll higher surgical risk patients for the comparison of CEA and CAS using modern techniques with embolic protection.[20] However, with only 334 patients, there was not sufficient data to determine what features were strongly associated with periprocedural risk.

The goal of this study is to develop and internally validate a model and bedside tool to predict death or stroke within 30 days of CAS in higher surgical risk patients using easily collected variables that can be assessed in routine clinical practice. The study population is drawn from the SAPPHIRE worldwide study, a single-arm prospective study of higher risk patients undergoing CAS with embolic protection. The prediction model generated here can be used to support decision-making.

## Methods

### Study Population and Measurements

The SAPPHIRE worldwide study has been described.[21] Patients were enrolled from 364 centers across the United States and Canada. Patients were required to have either ≥50% carotid stenosis (determined by ultrasound or angiogram) if symptomatic (transient ischemic attack or stroke within 180 days) or ≥80% carotid stenosis if asymptomatic. Patients were required to have at least 1 factor that made them higher risk for CEA as determined by the enrolling physician. High-risk criteria include: age ≥75 years, Class III or IV New York Heart Association heart failure or left ventricular ejection fraction <30%, open heart surgery within 6 weeks, recent myocardial infarction within 4 weeks, unstable angina (Canadian Cardiovascular Society Class III/IV), coexistent cardiac and carotid disease requiring cardiac surgery and carotid revascularization, severe pulmonary disease, an abnormal cardiac stress test, contralateral carotid occlusion, postradiation therapy to the neck, recurrent stenosis at the site of prior CEA, high cervical internal carotid artery lesion or low common carotid artery lesion below the clavicle, and severe tandem lesions. Written informed consent was obtained using forms approved by Institutional Review Boards or Medical Ethics Committees at each center.

CAS procedures were performed using the ANGIOGUARD XP/RX Emboli Capture Guidewire distal protection device and the PRECISE OTW/RX Nitinol stent systems (Cordis, Warren, NJ). Patients were required to have arterial diameters consistent with safe device deployment. The target lesion and stent landing zone must be between 4 mm and 9 mm. The internal carotid artery at the ANGIOGUARD landing site must be between 3 mm and 7.5 mm. It was recommended that patients be treated with aspirin (81–325 mg daily) at least 72 hours before the procedure and thereafter. Either clopidogrel (300-mg load, 75 mg daily) or ticlopidine (250 mg twice daily) was recommended at least 24 to 48 hours before the procedure and continued at least 2 weeks after the procedure. Heparin was used during the procedure to attain activated clotting times >300 seconds before crossing the lesion.

All physicians performing procedures were stratified according to experience in carotid stenting generally and according to experience with the study device. Operators participated in a training program tailored to previous procedural volume and experience with study devices.[22]

Patients were evaluated at baseline, hospital discharge, and 30 days postprocedure. The baseline evaluation included a carotid ultrasound, angiogram, or both. The National Institutes of Health Stroke Scale and the modified Rankin Scale were performed by certified providers but not necessarily neurologists. Adverse events were assessed up to 30 days postprocedure. An independent Clinical Events Committee at the Harvard Clinical Research Institute, Boston, MA, adjudicated all major adverse events including stroke. Remote data monitoring of all end points was conducted in all patients, whereas onsite monitoring by review of medical records was conducted in approximately 15% of patients. The SAPPHIRE worldwide study is sponsored by Cordis. The authors, who had full access to the data, performed the analysis and did not receive funding from Cordis for the analysis.

### Candidate Predictors

Stroke was defined as a nonconvulsive, focal neurologic deficit of abrupt onset persisting for >24 hours with the deficit corresponding to a vascular territory.

We identified a list of variables to be considered in the multivariable model based on clinical relevance. These included sociodemographic information (age, sex, and race/ethnicity), medical history (hypertension, diabetes mellitus, dyslipidemia, hemodialysis, severe pulmonary disease), cardiovascular and neurovascular history (prior coronary artery disease, prior myocardial infarction, prior stroke, prior transient ischemic attack, prior coronary artery bypass grafting, prior carotid endarterectomy, prior peripheral angioplasty or stenting, prior heart failure, whether the carotid lesion was symptomatic), and factors associated with increased risk for CEA (low left ventricular ejection fraction or New York Heart Association Class III or IV heart failure, recent or planned heart surgery within 6 weeks, myocardial infarction within 4 weeks, recent unstable angina, severe pulmonary disease, a significantly abnormal cardiac stress test, age ≥75 years, contralateral carotid artery occlusion, contralateral laryngeal nerve palsy, history of neck radiation, tandem carotid lesions, previous CEA recurrent stenosis, or internal carotid artery lesion or a low common carotid artery lesion below the clavicle). We also considered anatomic and angiographic factors including the type of aortic arch (I, II, or III), the presence of significant aortic arch calcification, significant common carotid artery or internal carotid artery tortuosity, lesion calcification, lesion length, the presence of lesion ulceration, the presence of thrombus, and the presence of a significantly eccentric lesion.

**Table 1. Demographics/Baseline Characteristics**

| Characteristic | Mean (±SD) or Percentage |
|---|---|
| Age, y | 72.3±9.7 |
| Male | 61.1% |
| Symptomatic | 29.8% |
| White | 91.6% |
| Hypertension | 82.3% |
| Diabetes | 32.7% |
| Prior myocardial infarction | 19.3% |
| Prior carotid endarterectomy | 27.8% |
| History of stroke | 22.5% |
| History of TIA | 22.7% |
| History chronic kidney disease (creatinine >2.5 mg/dL) | 5.1% |
| Dialysis | 1.4% |

Total number of patients=10186.
TIA indicates transient ischemic attack.

**Table 2. High-Risk Characteristics for Carotid Endarterectomy**

| Characteristic | Percentage of Total Subjects (n=10 186) |
|---|---|
| Physiologic high-risk characteristic | |
| CHF (Class III or IV) or LVEF ≤30% | 11.0% |
| Heart surgery in 6 weeks | 0.9% |
| MI within 4 weeks | 1.7% |
| Unstable angina | 4.2% |
| Severe pulmonary disease | 12.2% |
| Abnormal stress test | 10.6% |
| Age >75 y | 39.8% |
| Severe simultaneous cardiac disease requiring surgery and carotid disease | 3.8% |
| Anatomic high-risk characteristic | |
| Contralateral occlusion | 13.0% |
| Contralateral laryngeal palsy | 0.5% |
| Postneck radiation | 7.1% |
| Tandem lesions | 2.5% |
| High ICA or CCA lesions below clavicle | 10.4% |
| Previous CEA recurrent stenosis | 23.1% |

CHF indicates congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ICA, internal carotid artery; CCA, common carotid artery; CEA, carotid endarterectomy.

## Statistical Analysis

We first examined the univariate associations of a composite end point of stroke or death at 30 days with all candidate variables. Next, multivariable logistic regression was performed using candidates with univariate $P<0.2$. We performed backward elimination of candidates until only variables with $P<0.05$ remained. Age and lesion length were entered as linear functions based on their monotonic relationships with the end point.

Internal validation and calibration were performed using bootstrapping (resampling with replacement) techniques.[23] We generated 1000 bootstrap samples with repetition of the variable selection procedure and the final model coefficients were adjusted based on a linear calibration slope.[24] We assessed discrimination as measured by the C-statistic and calibration based on comparing observed and predicted event rates across deciles of predicted risk over bootstrapped samples. We also adjusted the reported model discrimination based on bootstrap methods to adjust for model optimism and overfitting. The adjusted C-statistic was calculated: adjusted performance=apparent performance in the original sample–average(bootstrap model performance in bootstrap sample–bootstrapped model performance in original sample).[25]

The β coefficients from the model were used to generate point scores for an integer-based tool.[26]

Given previous literature relating operator experience to outcomes with CAS,[27,28] we evaluated whether the addition of operator experience (coded as a binary variable of >25 procedures as the primary operator and >10 using the study devices or >25 procedures as the primary or secondary operator and >13 as the primary operator) improved the final model based on likelihood ratio testing and based on the calculation of the integrated discrimination improvement index.[29]

Analyses were performed using STATA 11.2 (Statacorp, College Station, TX).

## Results

The study population included 10 186 patients who underwent CAS with distal protection between October 30, 2006, and September 30, 2010. Mean age was 72.3±9.7 years, and 38.9% of patients were women. History of stroke was present in 22.5% of patients and history of transient ischemic attack in 22.7%. Symptomatic carotid lesions were present in of 29.8% of patients (Table 1). The most common high surgical risk feature for CEA was age ≥75 years. The frequency of other high surgical risk features is in Table 2. Successful use of the study embolic protection device occurred in 96.4% of patients.

Death occurred in 123 patients (1.2%) and stroke in 301 (3.0%) within 30 days of CAS. A total of 366 patients had either stroke or death within 30 days. Two hundred forty-five strokes were ipsilateral (79.5% of strokes) and 276 were ischemic (91.7%). Lacunar strokes occurred in 33 subjects (11.9% of ischemic strokes). There were 25 hemorrhagic strokes.

The final multivariable model with calibration slope-adjusted coefficients is presented in Table 3. There are 10 significant predictors in the final model. The raw C-statistic was 0.709 and the optimism-adjusted C-statistic is 0.691. Over 100 bootstrapped samples, the predicted probability of death or stroke within 30 days was well calibrated with

**Table 3. Final Logistic Regression Model for Death or Stroke at 30 D After Carotid Artery Stenting**

| Variable | Adjusted Beta | Adjusted OR | 95% CI for Adjusted OR | *P* Value |
|---|---|---|---|---|
| Age per 10 y | 0.417 | 1.520 | 1.32–1.81 | <0.001 |
| Stroke | 0.731 | 2.080 | 1.55–2.75 | <0.001 |
| Transient ischemic attack | 0.534 | 1.710 | 1.24–2.22 | 0.001 |
| Myocardial infarction within 4 wk | 1.025 | 2.790 | 1.34–5.82 | 0.006 |
| Dialysis | 0.986 | 2.680 | 1.34–6.01 | 0.007 |
| Need for concomitant cardiac surgery plus carotid revascularization | 0.772 | 2.160 | 1.27–3.77 | 0.005 |
| Left-sided lesion | –0.385 | 0.680 | 0.51–0.89 | 0.006 |
| Lesion length per 10 mm | 0.183 | 1.200 | 1.03–1.33 | 0.012 |
| Type II or Type III aortic arch | 0.291 | 1.240 | 1.02–1.49 | 0.035 |
| Two 90° bends | 0.463 | 1.590 | 1.17–2.21 | 0.004 |
| Constant | –7.350 | | | |

The optimism-adjusted C-statistic=0.691. The associated Hosmer-Lemeshow *P=0.62*.

the observed rates of death or stroke (Figure 1; Hosmer-Lemeshow $P$=0.62).

An integer-based tool intended for bedside use is shown in Figure 2. Individuals with ≤8 points have a predicted risk of death or stroke of <3% at 30 days. The C-statistic of the integer-based score is 0.683. Individuals with >12 points have a predicted rate of death or stroke >6%. We also demonstrate that the rate of observed events was similar to the rate of events predicted based on the bedside tool (Figure 3).

The addition of 2 different binary variables for operator experience did not significantly improve the final model based on likelihood ratio testing or based on calculation of the integrated discrimination improvement (0.00027, $P$=0.45 or 0.00030, $P$=0.49).

## Discussion

In a large study of patients at higher risk for CEA, commonly collected variables were able to identify patients at high and low risk for stroke or death after CAS. We generated a risk model and simple risk score to predict stoke or death within 30 days using these variables. We found that elevated age, history of stroke, history of transient ischemic attack, recent myocardial infarction, the need for both cardiac surgery and carotid revascularization, dialysis treatment, the presence of a Type II or III aortic arch, a right-sided carotid stenosis, a longer carotid plaque, and a severely tortuous carotid arterial system were all important risk factors for the development of stroke or death within 30 days of CAS. These findings are consistent with previous observations regarding the risk factors for adverse events associated with CAS.[30–34] Our findings also reinforce that in addition to comorbid conditions, anatomic and lesion-specific considerations simultaneously confer risk and should be factored into the decision about carotid revascularization with CAS.

Our study differs from previous studies that have considered CAS risk prediction[17–19] and represents an improvement in a number of ways. First, we were able to use data from many centers across the spectrum of clinical practice. Our study used routine, impartial clinical end point adjudication and the administration of standard stroke assessment tools not available in previous studies that generated risk models. Most importantly, however, our study is restricted to higher surgical risk patients who were not well represented in the original surgical studies that led to the adverse event rate thresholds that are present in the multisociety guidelines.[35–38] Nonrandomized studies have demonstrated higher rates of adverse events with CEA in patients with multiple risk factors.[10,11,39] In routine clinical practice, clinicians are currently referring patients with more severe comorbid conditions to CAS and rather than to CEA more frequently.[40] Thus, even without adequate tools to precisely predict the risk of adverse events after CAS for high surgical risk patients, clinicians are more likely to refer the most severely ill patients to CAS rather than to CEA. The risk prediction model presented here will now allow clinicians to assess CAS risk in a more quantitative manner than previously possible.

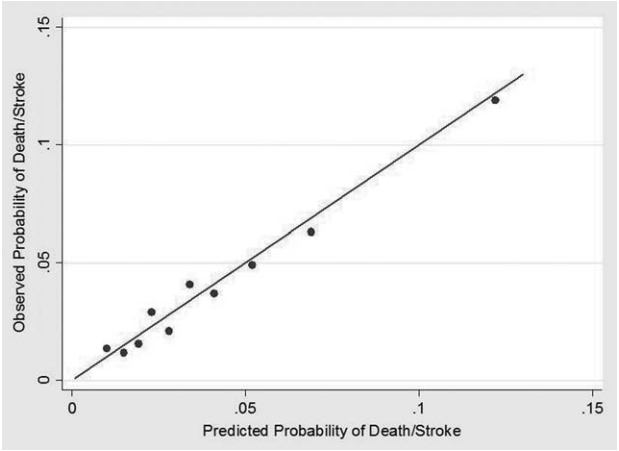



**Figure 1.** Observed versus predicted probability of death or stroke within 30 days with the full model over 100 bootstrapped samples. Individuals are grouped into 10 deciles based on their predicted probability of death or stroke in 30 days. Displayed line is y=x.

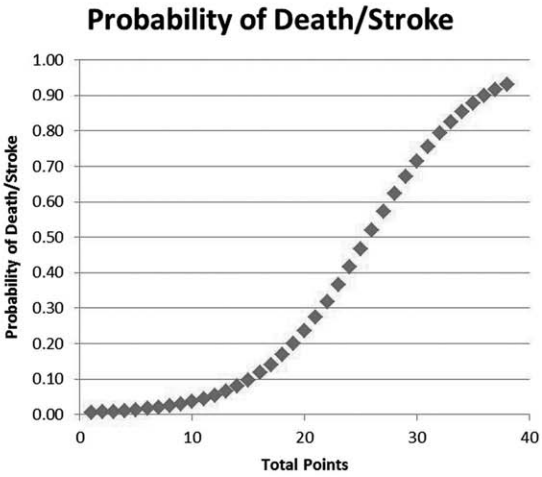
Our analyses should be interpreted in the context of important limitations. Although we retained a large number of clinically relevant variables in our model, the discriminative ability of the model was modest. Whereas our reported discrimination compares favorably with the discrimination of previously reported models, there may be unobserved social, biological, or procedural factors associated with stroke or death after CAS that are not accounted for in our models. We also are limited by the fact that not every patient was subject to evaluation by a neurologist to ascertain the end point of stroke. Although certified study coordinators administered standard assessment tools, ascertainment of postprocedure complications may be lower than if neurologists performed routine assessments. We are also limited by self-reporting of angiographic data elements without core laboratory data ascertainment. External validity of the model can also be questioned given that the model was developed in patients who underwent CAS using specific study devices. Finally, although the goal was to present a clinically useful prediction model, our analysis only reflects risk for CAS. We did not consider the relative treatment effect compared with other therapies, including CEA or medical therapy without revascularization.

Although our risk score quantifies the risk for individuals contemplating CAS, a particular score for a given individual does not imply that CAS is appropriate therapy. There remain major controversies, specifically with regard to the role of medical therapy alone, in this population. The role of medical therapy alone is particularly important to study in elderly patients, in those with significant comorbidities, and in asymptomatic patients.

## Conclusions

We developed and validated a predictive model and integer-based tool to predict the occurrence of death or stroke within

| | Category | Points |
|---|---|---|
| Age (years) | <50 | 0 |
| | 50-59 | 2 |
| | 60-69 | 4 |
| | 70-79 | 6 |
| | 80-89 | 8 |
| | >89 | 10 |
| History of stroke (y/n) | no | 0 |
| | yes | 3 |
| History of TIA (y/n) | no | 0 |
| | yes | 3 |
| MI within 4 weeks (y/n) | no | 0 |
| | yes | 5 |
| Synchronous need for cardiac surgery and carotid revascularization (y/n) | no | 0 |
| | yes | 4 |
| Dialysis (y/n) | no | 0 |
| | yes | 5 |
| Aortic arch type II or III (y/n) | no | 0 |
| | yes | 1 |
| Right-sided lesion (y/n) | no | 0 |
| | yes | 2 |
| Lesion length (mm) | <7 | 0 |
| | 7-21 | 1 |
| | 22-30 | 2 |
| | >30 | 3 |
| Two 90-degree bends (y/n) | no | 0 |
| | yes | 2 |




| Risk Groups |
|---|
| Less than 3% risk ➔ 8 points or less |
| 3%-6% risk➔ 9-12 points |
| 6%-10% risk➔ 13-15 points |
| More than 10% risk➔ 16 or more points |

**Figure 2.** Bedside prediction tool for death or stroke at 30 days after carotid artery stenting. The total point score gives the predicted probability for death or stroke at 30 days according to the following equation:

$$\text{Death or stroke at 30 days} = \frac{1}{1+\exp\left[-\left(-5.38+\left(0.21*\left(\text{total points}\right)\right)\right)\right]}.$$

TIA indicates transient ischemic attack; MI, myocardial infarction.

30 days of CAS. The prospective use of individualized assessments may support rational decision-making for the treatment of carotid atherosclerosis and may aid communication between clinicians and patients before CAS. In the future, prospective testing should be performed to ascertain whether this model improves patient outcomes and understanding.

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## Disclosures

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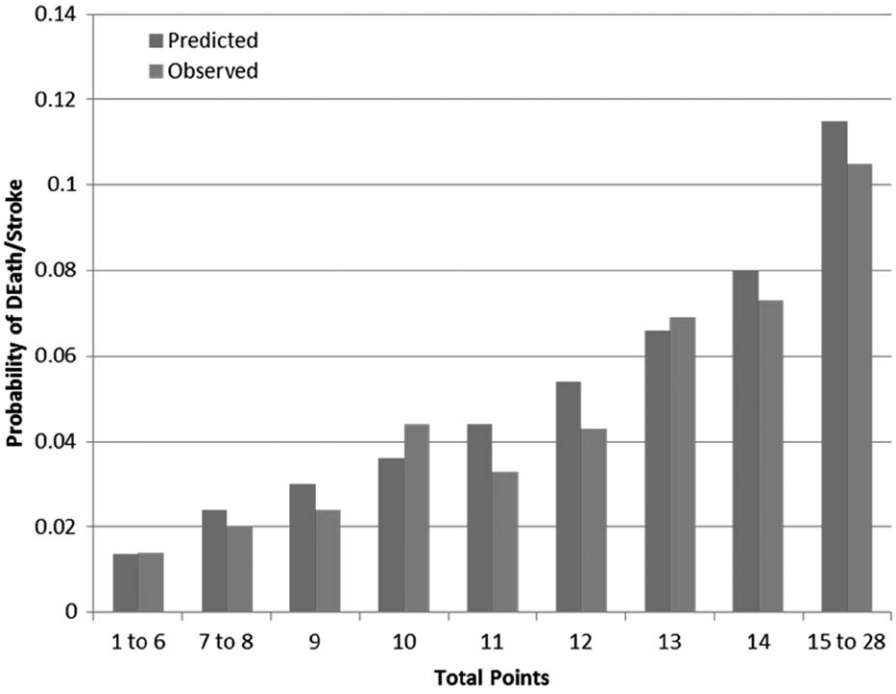


**Figure 3.** Observed versus predicted probability of death or stroke at 30 days using the bedside tool over 100 bootstrapped samples.


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