A Validated Risk Score to Predict Outcomes after Carotid Stenting

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Background—Periprocedural outcome has been extensively investigated in patients undergoing carotid artery stenting. However, risk factors contributing to long-term mortality have not been comprehensively assessed. We aimed to establish a validated clinical risk score for long-term mortality in patients after carotid artery stenting.

Methods and Results—Two independent cohorts after successful carotid artery stenting (602 and 552 patients) were prospectively investigated. Multivariable Cox regression and bootstrap variable selection were used to select the best-fitting multivariable model. The mortality rate was 35% in the derivation and 39% in the validation cohort during a median follow-up of 6.5 and 7.4 years, respectively. The following variables were identified as most robust risk factors in the derivation cohort: age, heart failure, diabetes mellitus, relative lymphocyte count, prothrombin time, peripheral artery disease, and contralateral carotid occlusion. A weighted multimarker risk score yielded an area under the receiver operating characteristic curve of 0.79 in the derivation (P<0.001) and of 0.69 (P<0.001) in the validation cohort. In comparison, the best area under the receiver operating characteristic curves for single risk factors were 0.67 and 0.63, respectively. For optimal clinical use, a simplified risk score was also developed, which discriminated very well from very low to very high risk. The risk of all-cause mortality ranged from 8% for a score of 1 to 93% for a score of 7 (P<0.001) in the derivation and from 11% to 100% in the validation cohort (P<0.001).

Conclusions—A multimarker risk score outperformed the prognostic value of single risk factors for the prediction of long-term mortality. (Circ Cardiovasc Interv. 2012;5:00-00.)

Key Words: carotid artery stenting ■ outcome ■ risk stratification

Although there is sufficient evidence about the long-term outcome of patients after carotid artery stenting (CAS), potential risk factors affecting long-term course have not been sufficiently studied yet.1,2 In particular, coexisting diseases may dominate the long-term fate of patients with high-grade carotid stenosis irrespective of the treatment of carotid stenosis. So far, single risk factors such as medical high risk, diffuse proliferative hyperplasia after CAS, diabetes mellitus, low high-density lipoprotein cholesterol levels, low body mass index, and contralateral carotid occlusion have been described but no comprehensive risk assessment has been performed.3–7 The identification of a comprehensive risk profile determining mortality in this high-risk population with advanced age and high probability of generalized atherosclerotic disease is of particular clinical interest, specifically if reversible risk factors are included in the risk profile and late outcome may be improved by their treatment. A comprehensive risk management may be of particular relevance for patients with asymptomatic carotid stenosis in whom competing risks are more likely to impact late outcome.

We hypothesized that long-term mortality is determined by the presence of comorbidities in patients with CAS, and we studied what parameters are important predictors of survival. On the basis of a statistical selection, a clinically applicable risk score was designed. To validate our results, we confirmed our data in a second independent population of patients undergoing CAS. As a midterm survival analysis may help in the decision whether the patient may benefit from a reduced stroke rate attributed to CAS, we specifically analyzed mortality within 2 years after CAS.

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The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.112.972430/-/DC1.
WHAT IS KNOWN

• Periprocedural outcome has been extensively investigated in patients undergoing carotid artery stenting.
• However, information about the long-term outcome after carotid artery stenting is scarce.

WHAT THE STUDY ADDS

• Age, heart failure, diabetes, relative lymphocyte count, prothrombin time, peripheral artery disease, and contralateral carotid occlusion have been identified as strong and independent risk factors for long-term mortality after carotid artery stenting.
• A multimarker risk score outperformed the prognostic value of single risk factors.

Methods

Study Design

Derivation Cohort (Linz)

We prospectively enrolled 645 consecutive white patients assigned to CAS between December 1997 and June 2005 at a secondary care hospital in a prospective registry database as previously described in detail.1 CAS was performed in asymptomatic patients with >80% stenosis of an extracranial carotid artery and symptomatic patients with >60% stenosis. Being aware of the possibility to overestimate the degree of the lesion, it was decided to choose a more strict inclusion criteria for carotid stenosis of 80% for asymptomatic and of 60% for symptomatic patients at the time of inclusion than current guidelines would recommend.2 Symptoms were defined by a transient ischemic attack or a minor stroke within 120 days attributable to an ipsilateral carotid stenosis. The definition of a minor stroke was a new neurological deficit that was resolved fully within 30 days of increased the National Institutes of Health Stroke Scale score by ≤3. Patients were excluded if the intervention was not performed (n=8) or not successful (n=8), or data were not complete (n=27).

Validation Cohort (Vienna)

We prospectively enrolled 588 consecutive white patients assigned to CAS between January 1997 and December 2004 at a tertiary care hospital in a prospective registry database. CAS was performed based on clinical symptoms and an angiographically documented stenosis of >70%. Patients were excluded if no intervention was performed (n=1), or data were incomplete (n=35).

Both studies were performed according to the recommendations of the hospital’s ethics committee including informed written consent.

Baseline Characteristics

For both cohorts, laboratory parameters including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HbA1c, hemoglobin, creatinine, blood urea nitrogen, leucocyte count, differential blood cell count, quick activated partial thromboplastin time, aspartate-aminotransferase, alanin-aminotransferase, and de-ritis quotient were analyzed in venous blood samples taken the day before CAS. All measurements were performed in the central laboratory of both hospitals by staff unaware of the clinical data. Glomerular filtration rate was calculated by the Cockcroft-Gault formula. The following definitions of potential risk factors were applied to both cohorts: obesity (body mass index >30 kg/m²), hypercholesterolemia (total cholesterol >200 mg/dL or low-density lipoprotein cholesterol >130 mg/dL or current treatment with cholesterol-lowering medication), diabetes mellitus (history or a fasting glucose >125 mg/dL) with inadequate glycemic control (HbA1c >7%), hypertension (seated systolic blood pressure >140 mm Hg and diastolic pressure >90 mm Hg or a history of hypertension leading to antihypertensive treatment), and current smoking. Regarding the patient history of cardiovascular disease, we assessed a prior CEA, known significant coronary artery disease and 3 vessel disease (angiographically proven significant (>50%) or already treated stenosis of all 3 epicardial coronary arteries), angina pectoris 2 functional class 3 according to the Canadian Cardiovascular Society), prior myocardial infarction (development of Q-waves on the ECG or elevated creatine kinase-MB levels to more than twice the normal value), significant aortic stenosis or aortic valve surgery, aortocoronary bypass graft, and known peripheral arterial disease (PAD). Myocardial infarction and stroke were defined according to published guidelines.3,10,11 Heart failure was diagnosed based on clinical judgment confirmed by an objective diagnostic finding (elevated brain natriuretic peptides or decreased left ventricular function). In the validation cohort (Vienna), specifically a left ventricular function <40% was required for the diagnosis of heart failure. Missing continuous data were replaced by the mean value of the variable, and missing categorical variables were filled with 0 indicating the absence of the characteristic.

Carotid Artery Angiography and Stenting

The interventional procedures followed the guidelines of good clinical practice in both cohorts with routine use of protective devices (Filter Wire EZ; Boston Scientific, Natick, MA). After transfemoral access a 6F or 8F sheath were inserted. Bare carotid stents (Monorail Carotid Wallstent; Boston Scientific), or self-mounted slotted-tube stent (Palmaz-Schatz; Johnson & Johnson, Jo-Stent; Abbott) were used. The diameter of the stenosis was determined according to the NASCET criteria with the distal internal carotid artery serving as the reference segment. All lesions were calculated after the procedure with the use of a semiautomated device (Hicor, Siemens). Furthermore, we assessed the presence of a contralateral occlusion. All angiograms were reviewed and classified by at least 2 experienced physicians who were unaware of clinical, laboratory, and ultrasonic data. Discrepancies were resolved by consensus. In case of persistent disagreement, a third expert reader was consulted, and a final decision was reached by consensus. Premedication consisted of aspirin and thienopyridines starting 2 days before intervention. Patients were dismissed from hospital usually 2 days after successful intervention.

Study End Point

The primary end point was defined as an all-cause mortality. Data were acquired from the death registry of Statistics Austria. Furthermore, cardiovascular mortality was assessed as secondary end point. The cause of death was assessed with high reliability because a postmortem examination was performed in 33% (derivation cohort) and 36% (validation cohort). To avoid study participants being lost to follow-up because of emigration or other causes, telephone contact (to the subject or relatives) was additionally established to check on the patients’ vital status. This was done if a patient was not seen at the respective outpatient department within the preceding 12 months.

Statistical Analysis and Design of Risk Score

Continuous data are presented as median and 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. Cox proportional hazards models were applied to assess the association of baseline characteristics with mortality. Results of the Cox models are presented as hazard ratio (HR) and 95% CI. To assess the independent predictive value of baseline characteristics, we calculated the risk of death by multivariate Cox proportional hazards analysis. According to the tests, the proportional hazards assumption was not violated. Bootstrapping was used for internal validation in the derivation cohort. Samples with a size of 80% of
the original cohort were chosen. In each cohort, 100 repeats with forward selection ($P<0.1$) and 100 repeats with backward selection ($P<0.1$) were performed. Variables, which were selected in $>60\%$ of repeats, were selected for the final multivariable model. Risk scores were generated based on this variable selection. Estimates obtained from this multivariable model were corrected using parameter-wise shrinkage factors, which were estimated by leave-one-out resampling as proposed by Sauerbrei.13 Shrinkage factors are displayed in online-only Data Supplement 1 Generation of the Weighted Risk Score.

Nonlinear effects of predictors were evaluated considering model improvement by selected transformations of the continuous predictors.13 Pairwise interactions between predictors were checked 1-by-1 by adding corresponding product terms to the model. Receiver operating characteristic curves were used to evaluate the discriminative power of the generated risk scores. Kaplan–Meier curves were plotted to assess the survival of patients categorized by tertiles of the multimarker risk score. Log-rank tests were used to compare the predictive value averaged over time between patients in the first, second, and third tertile of the multimarker risk score.

A value of $P<0.05$ (2-tailed) was considered statistically significant. Statistical analyses were performed with the statistical software packages SPSS 18.0 (SPSS Inc, Chicago, IL) and STATA 11 (StataCorp LP).

Results

Follow-Up

In the derivation cohort (Linz), 602 successfully treated patients (93%) were included in the final analysis. The median follow-up time was 6.5 years, accumulating to 3969 years of follow-up. Two hundred and eleven patients (35%) died. One hundred and twenty-four patients (21%) died from cardiovascular causes. No patient was lost to follow-up. In the validation cohort (Vienna), 552 patients (94%) were treated with carotid stent implantation. In this cohort, the median follow-up time was 7.4 years accumulating to 3070 years of follow-up. Two hundred and seventeen patients (39%) died. One hundred and twelve patients (20%) died from cardiovascular causes. No patient was lost to follow-up in both cohorts.

Univariate Association

The following risk factors were significantly associated with outcome in both cohorts: age, serum hemoglobin levels, total leukocyte count, neutrophil count, lymphocyte count, serum creatinine, glomerular filtration rate, blood urea nitrogen, alanin-aminotransferase, prothrombin time (quick), diabetes mellitus, inadequate glycemic control, fasting glucose levels, hypercholesterolemia, PAD, previous TIA, and chronic heart failure (Table 1). High-density lipoprotein cholesterol was found to be a protective factor in the derivation cohort (Linz), whereas this effect was not recognized in the validation population (Vienna). Further, the presence of contralateral carotid artery occlusion was associated with mortality in the derivation but not in the validation cohort. In the validation cohort, aspartate-aminotransferase levels were higher in patients who died compared with controls. This association was not observed in the derivation cohort.

Selection of Multivariable Model

Complete data sets were available for 91% (n=550) in the derivation and 87% (n =485) in the validation cohort. Variables in Table 2 were selected using bootstrapping in the derivation cohort (Linz). Nonlinear transformations of predictors did not significantly improve the final model. No interaction between the selected variables was observed.

The following variables were identified as most robust risk factors (in descending order, Figure 1): age, heart failure, diabetes mellitus, relative lymphocyte count, prothrombin time (quick), PAD, and contralateral occlusion. In the derivation cohort, chronic heart failure was the strongest independent categorical risk factor with an adjusted HR of 2.74 ($P<0.001$), whereas age was the strongest independent continuous risk factor with an adjusted HR of 1.80 ($P<0.001$) for an increase of 1 SD (Table 2).

In the validation cohort, chronic heart failure was the strongest independent categorical (HR 4.09; $P<0.001$), and age was the strongest independent continuous risk factor for outcome (adjusted HR of 1.64 for an increase of 1 SD, $P<0.001$; Table 2).

Design of Risk Score

A weighted risk score was designed that included all 7 variables selected by bootstrapping. The impact of continuous variables was weighted by the increase in risk per SD with the mean equaling 0 (online-only Data Supplement 1). The weighted risk score yielded an area under the receiver operating characteristic curve (AUC) of 0.79 in the derivation cohort ($P<0.001$) and an AUC of 0.69 ($P<0.001$) in the validation cohort. In comparison, the best AUCs for single risk factors were 0.67 in the derivation cohort and 0.63 in the validation cohort (for age in both cohorts, $P<0.001$ for comparison with weighted risk score). For events within the first 2 years, the AUC was 0.73 in the derivation and 0.67 in the validation cohort (both $P<0.001$). Similarly, the AUC for cardiovascular mortality were 0.75 in the derivation cohort and 0.70 in the validation cohort. Identical AUCs were found when analyzing cardiovascular mortality within 2 years only (both cohorts $P<0.001$). When the weighted risk score was stratified into tertiles, we observed a 5-year survival of 91%, 73%, and 48% in the first, second, and third tertile, respectively ($P<0.001$ for all comparisons among tertiles, Figure 2A). Correspondingly, we found a 5-year survival of 86%, 74%, and 61% for the tertiles of the weighted risk score in the validation cohort ($P<0.001$ for all comparisons among tertiles, Figure 2B). With regard to midterm assessment of mortality, the third tertile of the risk score already showed a clear deviation from the other tertiles at 2 years in the derivation and validation cohort (both cohorts $P<0.001$ for events within 2 years compared with the other 2 tertiles, Figure 2). A similar spread of risk for tertiles of the weighted risk score were found for cardiovascular mortality ($P<0.001$ for all comparisons between tertiles, Figure 2C and 2D).

Furthermore, a risk score was developed for optimal use in clinical routine. Therefore, risk factors were categorized into 2 or 3 classes according to optimized cutoff values (Figure 3). The strongest risk factors, age, heart failure, and diabetes mellitus, contributed 2 points to the optimized risk score. The other risk factors added 1 point. As the relative lymphocytes count may not be available in all centers, we replaced it by the leukocytes count in the validation cohort. This optimized
<table>
<thead>
<tr>
<th>Table 1. Association of Clinical Baseline Characteristics with All-Cause Mortality</th>
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<td><strong>Derivation Cohort (Linz)</strong></td>
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<tr>
<td>Dead n=211</td>
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<tr>
<td><strong>General</strong></td>
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<td>Male/female, n</td>
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<td><strong>Baseline laboratory</strong></td>
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<td>Creatinine, mg/dL</td>
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<td>Glomerular filtration rate, mL/min per 1.73 m^2</td>
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<td>Blood urea nitrogen, mg/dL</td>
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<td>Leukocytes, G/L</td>
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<td>Monocytes, %</td>
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<td>Lymphocytes, %</td>
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<tr>
<td><strong>Cardiovascular risk factors</strong></td>
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<td>Diabetes mellitus, n</td>
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<tr>
<td>Inadequate glycemic control</td>
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<td>Fasting glucose, mg/dL</td>
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<td>Hyperlipidemia, n</td>
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<td>Hypertension, n</td>
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<td>Total cholesterol, mg/dL</td>
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<td>LDL, mg/dL</td>
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<td>Current smoking, n</td>
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<tr>
<td><strong>Cardiovascular history</strong></td>
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<td>Known PAD, n</td>
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<tr>
<td>Known CAD, n</td>
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<td>Prior stroke, n</td>
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<td>Prior TIA, n</td>
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<td><strong>Interventional data</strong></td>
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<tr>
<td>Contralateral occlusion, n(%)</td>
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<tr>
<td>Stent diameter, mm</td>
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<td>Stent length, mm</td>
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AST indicates aspartate-aminotransferase; ALT, alanin-aminotransferase; APTT, activated partial thromboplastin time; BMI, body mass index; DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CEA, carotid endarterectomy; PAD, peripheral artery disease; CAD, coronary artery disease; CCS classification of the Canadian Cardiovascular Society; PCI percutaneous coronary intervention; AGB, aortobronchial bypass graft; and TIA transitory ischemic attack.

Continuous data are 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.
risk score discriminated very well from very low to very high risk. The risk of all-cause mortality during the entire follow-up ranged from 8% for a score of 1 to 93% for a score of 7 (for trend, \( P < 0.001 \), Figure 3A) in the derivation cohort and from 11% to 100% in the validation cohort (for trend, \( P < 0.001 \), Figure 3B). A similar spread of risk was found for cardiovascular mortality ranging from 5% to 57% in the derivation cohort and from 2% to 100% in the validation cohort (for trend, both \( P < 0.001 \), Figure 3C and 3D). The predictive value of the score was not affected by the symptomatic status of the patient (for interaction \( P = 0.62 \)).

**Discussion**

This study aimed to identify prognosticators of long-term mortality in patients after CAS. On the basis of a stringent statistical selection, age, heart failure, and diabetes mellitus were found to be the most important risk factors. The relative lymphocyte count, quick (prothrombin time), PAD, and contralateral occlusion were selected as further robust risk factors. A risk score that encompasses these selected variables yielded an excellent predictive in the original derivation cohort and was validated in an independent external cohort. This risk score predicted cardiovascular mortality to a similar extent. Finally, a simplified risk score optimized for clinical use was developed. This optimized risk score was based on categories of the selected variables and discriminated very well with a mortality of about 10% for 1 point and a mortality of >90% for \( \geq 7 \) points.

So far, risk assessment in patients with CAS has focused on the periprocedural outcome.\(^{14-16}\) However, data on long-term outcome after CAS are rather rare.\(^{2} \) Available data about risk assessment of long-term outcome mainly focused on isolated variables.\(^{3} \) However, as shown by the AUC for isolated variables in our cohort, their predictive value is inferior to that of a comprehensive risk score. With regard to long-term mortality after CAS, no data have been published on age or heart failure, the 2 strongest independent isolated predictors of mortality in our cohort. Although senescence cannot be influenced by any kind of intervention, adequate treatment of chronic heart failure clearly improves survival.\(^ {17} \) In this context, patients with CAS may benefit from routine screening for heart failure, which has been found in up to 10% of patients and subsequent treatment.\(^ {4} \) In our cohort, particularly patients with inadequate glycemic control had a poor survival after CAS. Thus screening for inadequate glycemic control by HbA\(_1c\) and a more stringent glycemic control may be another very effective measure in CAS patients to improve long-term mortality. The relative lymphocyte count may be another specific predictor of long-term mortality in CAS patients. In both cohorts, a reduced relative lymphocyte count, typically reflecting acute activation of the cellular immune system, was associated with an increased risk in this cohort of patients after CAS. Moreover, prothrombin time, which may reflect liver function, was another robust risk factor. Prothrombin time may have also been affected by oral anticoagulation. However, as patients are required to stop oral anticoagulation for at least 3 days before intervention, it is unlikely that treatment may have affected the predictive value of prothrombin time. Indeed, prothrombin time remained a
significant risk predictor when patients with (stopped) oral anticoagulation were excluded from the analysis (data not shown). Our finding about prothrombin time corresponds to a previous publication by Ketch et al., which shows that a prothrombin time-derived fibrinogen assay predicts major adverse cardiovascular events after myocardial infarction. Although increased prothrombin time is subject to treatment by vitamin K or fresh frozen plasma, it is questionable whether the long-term risk associated with decreased liver function may be modified by treatment. Screening for concomitant PAD may be another important tool to improve risk prediction in addition to its importance for the vascular access. PAD was associated with a 1.6- to 2-fold increased risk of mortality and was found in up to 44% of patients. Finally, with regard to contralateral carotid occlusion, we extended data from Keldahl et al. who found a slight but not significant increase of mortality during a mean follow-up of 4 years in patients undergoing CAS with contralateral carotid occlusion. In our derivation but not in our validation cohort, contralateral occlusion was associated with a 1.7-fold increased risk of mortality. Contralateral occlusion may affect the hemodynamic situation and may furthermore be a measure of the extent of carotid artery disease.

Being aware that risk scores with a superior predictive value should also be applicable in a real-world setting and are underused because of their complex application, we aimed to calculate an easily applicable score optimized for clinical routine. Therefore variables were categorized to 2 to 3 categories as previously recommended. The strongest risk factors age, heart failure, and diabetes mellitus more strongly influenced the risk score by contributing 2 points to the optimized risk score. The final optimized risk score can be easily computed by hand and is cost-effective because no measurements in addition to routine-measurements are required.
Despite its simplified use, this optimized score discriminated very well between low- and high-risk patients. For example, a 74-year-old man with a well-controlled diabetes mellitus and PAD would reach 2 points corresponding to a long-term mortality risk of 23% (Figure 3A). In contrast, a patient with the same medical conditions who also has a contralateral carotid occlusion and has a quick value of 80% and a relative lymphocyte count of 20% would gain 5 points corresponding to a dramatically higher long-term mortality risk of 69% (Figure 3A). Awareness of the mortality risk of a patient may have an important impact on the management of the patient including closer clinical visits and a more aggressive modification of modifiable risk factors such as diabetes mellitus.

Limitations
We are aware of several limitations of our study. Because patients undergoing CAS were exclusively evaluated, we cannot comment on outcome of patients with CEA or receiving conservative treatment only. However, as patients with a simplified score of ≥7 have a 2-year mortality >50% (data not shown), one may speculate that this minority of patients (<3% of both populations) may not benefit from a reduced stroke rate because of CAS. It also needs to be mentioned that the score may not help with the decision whether to perform carotid stenting. Although ascertainment of data has been >90% filling of missing data, variables used in the score may have weakened the predictive power of the score. Furthermore, different health care systems may provide different laboratory measures, and included laboratory values may be widely used but not available at every medical center treating patients after CAS.

Conclusion
Although lesion-related factors dominate the short-term risk of patients undergoing CAS, pre-existing comorbidities may be even more important for the long-term fate. This study approached for the first time long-term risk prediction of mortality after CAS in a comprehensive way. Thereby the importance of the comorbidities, diabetes mellitus, heart failure, and PAD was identified by stringent statistical methods, which merits screening of these diseases in patients undergoing CAS. A comprehensive risk score furthermore included age, leukocytes, prothrombin time, and contralateral occlusion as important risk factors. Thereby long-term prediction of mortality was achieved, which outperformed the prognostic value of single risk factors.
Disclosures

None.

 References


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Supplemental Material

Supplemental Data 1 Generation of the Weighted Risk Score

General:
Weighted risk score = (V1 – mean of V1)* beta coefficient of V1 * shrinkage factor of V1 +
(V2 – mean of V2) * beta coefficient of V2 * shrinkage factor of V2 + (V3 – mean of V3) *
beta coefficient of V3 * shrinkage factor of V3 + …+ (Vn – mean of Vn) * beta coefficient of
Vn * shrinkage factor of Vn.

Weighted Risk Score:
Weighted Risk Score = (age – 4.243) * 4.419 * 0.87 + heart failure * 1.006 * 0.91 + diabetes
* 0.522 * 0.91 + (relative lymphocyte count – 3.123) * -0.582 * 1.03 + (quick – 4.51) * -0.79
* 1.16 + PAD * 0.369 * 0.66 + contralateral occlusion * 0.379 * 0.67

Beta coefficients derived from a multivariable Cox regression model including all (log-
transformed) variables of the model. Parameterwise shrinkage factors were estimated by
leave-one-out resampling.

n = number of variables of the risk score; diabetes = 1 if yes, diabetes = 2 if diabetes yes and
HbA1c > 7%; PAD = peripheral artery disease; quick = prothrombin time; V = variable