Homocysteine Improves Risk Stratification in Patients Undergoing Endarterectomy for Asymptomatic Internal Carotid Artery Stenosis

Nikolaus Duschek, MD; Samarth Ghai, MD; Fahrudin Sejkic, MD; Jürgen Falkensammer, MD; Edda Skrinjar, MD; Kurt Huber, MD; Johann Wojta, MD; Thomas Waldhör, MD; Wolfgang Hübl, MD; Afshin Assadian, MD

Background and Purpose—A limited life expectancy reduces the benefit from carotid endarterectomy (CEA) for treatment of asymptomatic internal carotid artery stenosis. The aim of this study was to assess homocysteine as stratifying biomarker to improve prediction of postoperative survival.

Methods—This was a single-center cohort study 2003 to 2012. Two hundred and fourteen consecutive patients (<75 years, n=130; ≥75 years, n=84) undergoing CEA for their asymptomatic internal carotid artery stenosis were observed for 8.5 years for the occurrence of death after CEA as primary end point (EC-nr: 04-067-0604). Homocysteine and major cardiovascular risk factors were used for computation of prognostic indices. Cumulative survival of prognostic indices–based quintiles was estimated by Kaplan–Meier curves.

Results—Total homocysteine had a significant effect on postoperative survival (P<0.0001). Total homocysteine–based quintiles of prognostic indices showed a better prediction of the survival of the patients than age alone. This caused reclassification of 17 patients (20.2%) >75 years as fit for surgery, but also indicated a high risk for 19 patients (14.6%) <75 years. In the majority (79.8%) of patients aged >75 years, statistically, CEA could not be advised because of a significantly reduced 5-year survival rate.

Conclusions—High plasma homocysteine levels suggest that older patients with asymptomatic carotid stenosis might rather benefit from intensive medical therapy than from CEA. (Stroke. 2013;44:2311-2314.)

Key Words: carotid stenosis ▪ endarterectomy, carotid ▪ homocysteine ▪ risk stratification

The aim of carotid endarterectomy (CEA) is to prevent stroke by removal of the internal carotid artery stenosis and, thus, embolicigenic material. In accordance with the STROBE criteria,1,2 the study has been reclassified as a single-center cohort study, as its participants were sampled on the basis of exposure and the outcome was assessed during follow-up. Moreover, medical therapy has advanced and the benefit from CEA for asymptomatic internal carotid artery stenosis (ACAS) is further reduced, if not eliminated.3,4 Because myocardial infarction is responsible for up to 50% of perioperative deaths and causes more postoperative deaths than strokes,3 a prediction of cardiovascular and, thus, overall mortality would help to improve prediction of postoperative survival. A potential candidate for risk stratification in carotid surgery is the amino acid homocysteine, which is a widely acknowledged risk factor for cardiovascular adverse events.

The aim of this study was to assess plasma levels of total homocysteine (tHcy) as biomarker to predict postoperative survival in patients with high-grade ACAS.

Methods

Patients This was a single-centered, nonrandomized, open-labeled cohort study from 2003 to 2012 (mean observation, 102±4 months). From January 2003 to April 2004, 214 consecutive patients (88 women, 126 men) undergoing carotid surgery for their high-grade ACAS were included after giving their written informed consent. Patients were monitored annually for the occurrence of death as primary outcome. Data were crosschecked with the Austrian public death registry with January 1, 2012, as the census date. The Local Ethics Committee approved the study (EC-nr: 04-067-0604). All patients included were diagnosed with high-grade ACAS, that is, unilateral or bilateral stenosis of 70% to 99%. Exclusion criteria comprised any previous symptomatic internal carotid artery stenosis, a previous ipsilateral CEA, high surgical risk, or any life-threatening condition other than carotid stenosis. Before discharge from the hospital, it was ensured that each patient received best medical treatment.

Surgery and Samples Surgery was standardized by performing only eversion endarterectomy under local anesthesia with the systemic administration of...
5000 IU of Heparin before clamping of the carotid arteries. Blood was drawn from fasting individuals within 14 days before CEA. Homocysteine was measured with an AxSYMPlusImmunology-analyzer (Abbott Diagnostics, IL).

### Statistical Analysis

The effect of tHcy on survival was estimated in a multivariate proportional hazard model (Cox Regression), including cardiovascular risk factors (Table 1), which were used for computation of prognostic indices (PI)\(^6\) for the primary end point. PIs equal the sum of the product of mean-centered covariate values and their corresponding parameter estimates for each case.\(^6\) The discriminative ability of the PI was determined by the ROC-Curves (area under the curve [AUC]), calibration by Hosmer–Lemeshow test (goodness-of-fit). The stratification power of PI-quintiles over time was estimated by Kaplan–Meier curves. A 2-sided \(P\) value of <0.05 was considered to indicate statistical significance.

### Outcomes

The primary outcome of this study was defined as death of any cause within 5 years after CEA.

### Results

Demographic data of 214 patients are described in Table 1. A perioperative stroke and death rate of 0.93% each was reported. After 8.5 years, survival amounted to 56.1%; the 75th percentile was reached after 58.0±5.6 months. Overall, vascular adverse events amounted to 22 strokes and 57 cardiac events, as shown in Table 1; causes of death comprised 15 vascular, 32 cardiac, and 47 nonvascular deaths. A highly significant effect on survival in the multivariate proportional hazard model (hazard ratio [HR]=1.048 per μmol/L; 95% confidence interval [CI], 1.03–1.07; \(P<0.0001\)) was shown by tHcy. As expected, patient age at sample retrieval/surgery also showed a highly significant effect (HR=1.091 per year; 95% CI, 1.06–1.13; \(P<0.0001\)). After removal of nonsignificant effects from the multivariate regression model, the variables homocysteine, age, smoking, and sex emerged as significant variables and were used for the computation of a prognostic model for 5-year postoperative survival yielding PIs.\(^6\) The discriminative ability of age rendered an AUC of 0.69±0.04. This was significantly increased, when the effect of tHcy was added to age (AUC of 0.74±0.04). The Hosmer–Lemeshow test indicated good calibration (\(χ^2=4.47\); \(P=0.813\)). PI-based quintiles showed a good stratification of the survival estimate of the patients (\(P<0.0001\)), as illustrated in the Figure. Within 5 years, each increment of PI was associated with a higher cardiac risk (HR=3.25; 95% CI, 2.0–5.2; \(P<0.001\)) than stroke (any) risk (HR=1.86; 95% CI, 1.1–3.2; \(P=0.023\)). After adjustment for risk factors, postoperative stroke risk remained significantly higher in patients with high tHcy levels (HR=2.75; 95% CI, 1.1–6.7; \(P=0.025\)) or PI despite performed CEA. Finally, to assess the effect (reclassification) of our prognostic model for 5 years, we estimated the percentage distribution of age groups over the quintiles of PIs, as shown in Table 2. In 14.6% of patients <75 years, the estimated survival rate was ≤65.1%. On the contrary, 20.2% of patients ≥75 years had a 5-year survival rate of ≥83.7%. In 79.8% of patients ≥75 years, survival rate was ≤65.1% in 5 years.

### Discussion

A PI including tHcy, as well as age, showed a better risk stratification in patients undergoing surgery for their ACAS than age alone. Our prognostic model for 5 years postoperative survival performs better than currently used clinical indices, like the CHADS2 (Congestive Heart failure, Hypertension, Age >75 years, Diabetes mellitus, prior Stroke, or transient ischemic attack) index (AUC, 0.68–0.72)\(^2\) and even improved for prediction of long-term survival (8.5 years; AUC, 0.8±0.03). Furthermore, with each increment of tHcy or PI, the risk of cardiac death, thereby limiting the benefit from CEA, increases even more than stroke risk. Additionally, the increased stroke risk predicted by high compared with low tHcy levels is likely to remain highly significant despite performed CEA, further...
questioning the benefit from surgery. This suggests best medical treatment eventually including B-vitamins, taking into account folate status, B12 status, and renal function, as treatment in older hyperhomocysteinemic patients with ACAS.4,8

Limitations
This study lacks a control group with high-grade ACAS not undergoing CEA, in which adverse events are correlated to homocysteine levels.

Conclusions
Inclusion of the cardiovascular biomarker homocysteine allows a better risk stratification of postoperative survival in elderly patients than by age alone. Given their increased risk of cardiac death, because tHcy-related and not ACAS-related cardiac risk increases more than stroke risk, the need for CEA in hyperhomocysteinemic patients with ACAS should be carefully considered, prompting intensive medical therapy rather than CEA as adequate treatment.

Table 2. Percentage Distribution of Age Groups (< and ≥75 Years) Over Survival-Quintiles of PI-Based on Homocysteine, Age, Sex, and Smoking for a Postoperative Survival of 5 Years

<table>
<thead>
<tr>
<th>PI-Based Quintiles (tHcy, Age, Sex, Smoking)</th>
<th>Survival Rate (%)</th>
<th>&lt;75 y</th>
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n=absolute number of patients, % of patients per age group. PI indicates prognostic index.

Figure. Survival estimates based on prognostic indices (PI)-based quintiles (Kaplan–Meier curves), illustrating a good discriminatory power of the prognostic model over a range of 50% mortality (dotted line set at 5 years).
Disclosures

None.

References


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An erratum has been published regarding this article. Please see the attached page for:
/content/46/2/e55.full.pdf
In accordance with the STROBE criteria, the study has been reclassified as a single-center cohort study, as its participants were sampled on the basis of exposure and the outcome was assessed during follow-up.


The authors regret the error.

This correction has been made to the online version of the article, which is available at http://stroke.ahajournals.org/content/44/8/2311.