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
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 multivariable proportional hazard model (Cox Regression), including cardiovascular risk factors (Table 1), which were used for computation of prognostic indices (PI)\textsuperscript{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.\textsuperscript{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.

Table 1. Baseline Characteristics of 214 Patients Undergoing CEA for ACAS and Adverse Events (Within 8.5 Years Post-CEA)

<table>
<thead>
<tr>
<th>Scale variables, mean±SD</th>
<th>All Patients</th>
<th>&lt;75 y (n=130)</th>
<th>≥75 y (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age sample/surgery, y</td>
<td>70.5±10.3</td>
<td>64.1±7.4</td>
<td>80.5±4.3</td>
</tr>
<tr>
<td>Patient age, y</td>
<td>77.1±9.7</td>
<td>71.4±7.6</td>
<td>85.9±4.6</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>14.9±8.7</td>
<td>13.4±6.8</td>
<td>17.2±10.6</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.1±0.8</td>
<td>1.1±0.8</td>
<td>1.2±0.6</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>205.6±40.2</td>
<td>207.5±42.3</td>
<td>202.6±36.4</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>53.1±14.0</td>
<td>52.6±13.7</td>
<td>53.7±14.7</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>120.2±34.4</td>
<td>120.0±35.6</td>
<td>120.5±32.6</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>159.3±88.5</td>
<td>168.1±96.7</td>
<td>144.9±71.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dichotomous variables, n (%)</th>
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<tbody>
<tr>
<td>Sex, male</td>
<td>126 (59)</td>
<td>76 (59)</td>
<td>50 (60)</td>
</tr>
<tr>
<td>History of MCI</td>
<td>53 (25)</td>
<td>32 (25)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>76 (36)</td>
<td>45 (35)</td>
<td>31 (37)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>174 (81)</td>
<td>106 (82)</td>
<td>68 (81)</td>
</tr>
<tr>
<td>Smoking</td>
<td>65 (30)</td>
<td>49 (38)</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (21)</td>
<td>25 (19)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Acetlyc acid</td>
<td>171 (80)</td>
<td>101 (78)</td>
<td>70 (83)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>105 (49)</td>
<td>72 (55)</td>
<td>33 (39)</td>
</tr>
<tr>
<td>Statins</td>
<td>114 (53)</td>
<td>81 (62)</td>
<td>33 (39)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events (AE)</th>
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</thead>
<tbody>
<tr>
<td>TIA</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Stroke, all</td>
<td>22 (10)</td>
<td>8 (6)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Stroke, nonfatal</td>
<td>11 (5)</td>
<td>4 (3)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Stroke, fatal</td>
<td>11 (5)</td>
<td>4 (3)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Cardiac events, all</td>
<td>57 (27)</td>
<td>28 (22)</td>
<td>29 (35)</td>
</tr>
<tr>
<td>Cardiac events, nonfatal</td>
<td>25 (12)</td>
<td>16 (12)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Cardiac events, fatal</td>
<td>32 (15)</td>
<td>12 (9)</td>
<td>20 (24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perioperative AE (30 d)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Stroke, nonfatal</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stroke, fatal</td>
<td>2 (0.9)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction, fatal</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Deaths</td>
<td>114 (53)</td>
<td>38 (29)</td>
<td>56 (67)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>32 (15)</td>
<td>12 (9)</td>
<td>20 (24)</td>
</tr>
<tr>
<td>Vascular</td>
<td>15 (7)</td>
<td>6 (5)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>47 (22)</td>
<td>20 (15)</td>
<td>27 (32)</td>
</tr>
</tbody>
</table>

\textsuperscript{ACAS indicates asymptomatic internal carotid artery stenosis; CEA, carotid endarterectomy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCI, myocardial infarction; and TIA, transient ischemic attack.}

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 multivariable 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.\textsuperscript{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 (\( y^2=4.47; P=0.813 \)). 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; \( P=0.002 \)) 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)\textsuperscript{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 PIs 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>PI-Based Quintiles Survival Rate (%)</th>
<th>&lt;75 y</th>
<th>≥75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>Events</td>
<td>Censored</td>
<td>Survival</td>
</tr>
<tr>
<td>1 97.6 42 32.3 0 0.0</td>
<td>2 83.7 37 28.5 6 7.1</td>
<td>3 86.0 32 24.6 11 13.1</td>
<td>4 65.1 15 11.5 28 33.3</td>
</tr>
</tbody>
</table>

n=absolute number of patients, % of patients per age group. PI indicates prognostic index.
Disclosures
None.

References
Homocysteine Improves Risk Stratification in Patients Undergoing Endarterectomy for Asymptomatic Internal Carotid Artery Stenosis
Nikolaus Duschek, Samarth Ghai, Fahrudin Sejkic, Jürgen Falkensammer, Edda Skrinjar, Kurt Huber, Johann Wojta, Thomas Waldhör, Wolfgang Hübl and Afshin Assadian

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/content/46/2/e55.full.pdf

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The version of the article, “Homocysteine Improves Risk Stratification in Patients Undergoing Endarterectomy for Asymptomatic Internal Carotid Artery Stenosis” by Duschek et al that published online ahead-of-print on June 11, 2013, and appears in the August issue (Stroke. 2013;44:2311–2314) contained an error in the text.

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.


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.