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

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The aim of carotid endarterectomy (CEA) is to prevent stroke by removal of the internal carotid artery stenosis and, thus, embolic material. However, the efficacy of CEA in asymptomatic patients, requiring a minimum life expectancy of 5 years to compensate for perioperative adverse events, remains controversial. Moreover, medical therapy has advanced and the benefit from CEA for asymptomatic internal carotid artery stenosis (ACAS) is further reduced, if not eliminated. Because myocardial infarction is responsible for up to 50% of perioperative deaths and causes more postoperative deaths than strokes, 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.

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 prospective, nonrandomized case series from 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;44:00-00.)

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

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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 propor-
tional hazard model (Cox Regression), including cardiovascular risk
factors (Table 1), which were used for computation of prognostic indi-
ces (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 de-
termined by the ROC-Curves (area under the curve [AUC]), calibration by

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>161.8±96.7</td>
<td>144.9±71.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dichotomous variables, n (%)</th>
<th>All Patients</th>
<th>&lt;75 y (n=130)</th>
<th>≥75 y (n=84)</th>
</tr>
</thead>
<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>Acetylic 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>
<th>All Patients</th>
<th>&lt;75 y (n=130)</th>
<th>≥75 y (n=84)</th>
</tr>
</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>All Patients</th>
<th>&lt;75 y (n=130)</th>
<th>≥75 y (n=84)</th>
</tr>
</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>

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.

Hosmer–Lemeshow test (goodness-of-fit). The stratification power of
PI-quintiles over time was estimated by Kaplan–Meier curves. A 2-sid-
ed 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 sur-
vival 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 sur-
vival 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 (χ²=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 asso-
ciated with a higher cardiac risk (HR=3.25; 95% CI, 2.0–5.2;
P<0.0001) 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 stratifi-
cation in patients undergoing surgery for their ACAS than
age alone. Our prognostic model for 5 years postoperative sur-
vival 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)\(^7\) 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 car-
diac 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.

Conclusion
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.

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).

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>&lt;75 y</th>
<th>≥75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival Rate (%)</td>
<td>n</td>
<td>Age Group (%)</td>
</tr>
<tr>
<td>1</td>
<td>97.6</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>83.7</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>86.0</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>65.1</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>41.9</td>
<td>4</td>
</tr>
</tbody>
</table>

n=absolute number of patients, % of patients per age group. PI indicates prognostic index.
Disclosures

None.

References

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