The Essen Stroke Risk Score Predicts Recurrent Cardiovascular Events
A Validation Within the REduction of Atherothrombosis for Continued Health (REACH) Registry

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Background and Purpose—Predictive scores are important tools for stratifying patients based on the risk of future (cerebro)vascular events and for selecting potential prevention therapy. Recently, the Essen Stroke Risk Score (ESRS) was derived from cerebrovascular patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. We aimed to validate the ESRS in a large cohort of outpatients with previous transient ischemic attack or stroke from the REduction of Atherothrombosis for Continued Health (REACH) Registry.

Methods—We included 15,605 outpatients with a qualifying stroke or transient ischemic attack and with clinical follow-up at 1 year. Patients with atrial fibrillation were excluded. We stratified 1-year cumulative rates for fatal and nonfatal stroke as well as combined major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) by the individually calculated stroke risk profile according to the ESRS and compared it with the 1-year event rates in the CAPRIE data subset of 6431 cerebrovascular patients.

Results—The 1-year rate for recurrent stroke (or combined cardiovascular events) in the stable outpatient population of REACH increased steadily and significantly from 1.82 (2.41) in patients with ESRS 0 to 6.84 (11.48) for ESRS ≥6. The overall as well as stratified risk of recurrent stroke and cardiovascular events was lower than for cerebrovascular patients in CAPRIE.

Conclusions—In outpatients with previous stroke or transient ischemic attack, the ESRS accurately stratifies the risk of recurrent stroke or major vascular events. Patients with a high ESRS should be candidates for intensified secondary prevention strategies. (Stroke. 2009;40:00-00.)

Key Words: ischemic stroke ■ risk prediction ■ secondary prevention ■ vascular events

The recurrence rate after ischemic stroke in community-based studies has been estimated at approximately 12% during the first year.1 Although this rate decreases to approximately 5% per annum during the next years, the rates of myocardial infarction and cardiovascular (CV) death become increasingly important in long-term follow-up studies.2 In patients with a previous stroke or transient ischemic attack (TIA), aspirin reduces the relative risk of recurrent CV events by approximately 13%, which corresponds to an absolute risk reduction of 1.5% per year.3 Although other preventive regimens have been shown to be more effective, the relatively low absolute risk reduction may not seem to justify the increased risk or additional expense. Therefore, identification of high-risk patients is an important aspect of in-hospital and outpatient treatment to ensure an optimal risk– and cost–benefit relation in view of ever tightening healthcare budgets. For this purpose, validated scores exist for prediction of first stroke4,5 as well as for prediction of recurrent stroke.6,7 Recently, the Essen Stroke Risk Score (ESRS; Table 1) was derived from the data subset of 6431 patients with ischemic stroke in the large-scale Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial8,9 and validated using the data set of the European Stroke Prevention Study II (ESPS-2).10,11 On a 10-point scale, the ESRS predicts 1-year risk of recurrent stroke and combined CV events (Table 1). To date, the ESRS has been validated only...
Table 1. Prevalence of Vascular Risk Factors Included in the ESRS in Cerebrovascular Patients From the REACH Registry With and Without Follow-Up

<table>
<thead>
<tr>
<th>Risk Factor (points allocated)</th>
<th>With Follow-Up (N=15 605)</th>
<th>Without Follow-Up (N=843)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65–75 years, % (1 point)</td>
<td>36.2</td>
<td>34.9</td>
<td>0.45</td>
</tr>
<tr>
<td>Age &gt;75 years, % (2 points)</td>
<td>29.7</td>
<td>29.9</td>
<td>0.91</td>
</tr>
<tr>
<td>Arterial hypertension, % (1 point)</td>
<td>82.9</td>
<td>84.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Diabetes mellitus, % (1 point)</td>
<td>36.9</td>
<td>40.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous myocardial infarction (MI), % (1 point)</td>
<td>16.9</td>
<td>19.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Other cardiovascular disease (except MI and atrial fibrillation), % (1 point)</td>
<td>23.5</td>
<td>24.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Peripheral arterial disease, % (1 point)</td>
<td>9.7</td>
<td>11.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Smoker, % (1 point)</td>
<td>51.6</td>
<td>49.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Previous TIA or ischemic stroke in addition to qualifying event, % (1 point)</td>
<td>17.7</td>
<td>24.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean ESRS sum score (maximum score = 9)</td>
<td>3.3</td>
<td>3.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Methods

Full details of the rationale and design of the REACH Registry have been described elsewhere. In brief, the REACH Registry is an international, prospective, observational registry designed to provide up to 24 months of clinical follow-up of over 67,000 outpatients from 5473 sites in 44 countries. It has recently been extended to provide up to 48 months of clinical follow-up. Patients enrolled were aged ≥45 years and fulfilled at least one of the following 4 criteria: documented symptomatic (1) coronary artery disease (angina, myocardial infarction, or angioplasty/stent/bypass); (2) cerebrovascular disease (ischemic stroke or TIA); (3) peripheral arterial disease (historical or current intermittent claudication associated with ankle brachial index <0.9); or (4) at least 3 predefined atherothrombotic risk factors. Patients already in a clinical trial, hospitalized patients, or those who might have difficulty returning for a follow-up visit were excluded. Thus, stable outpatients were recruited consecutively between December 2003 and June 2004 mainly by general practitioners (42%) and internists (32%). They were evaluated at baseline for a range of demographic, medical, and laboratory characteristics before being re-evaluated annually for up to 48 months postbaseline to ascertain whether they experienced any clinical events or hospitalizations. One of 2 primary study outcomes is a combined end point of nonfatal stroke, nonfatal myocardial infarction, and CV death. The individual clinical events described constitute the predefined secondary end points of the study. End point events were not adjudicated. However, reports of ischemic stroke and TIA had to be sourced from a neurologist or hospital to ensure a reliable diagnosis.

The study design was approved by the Institutional Review Board in each participating country and all patients included in the analysis provided signed, informed consent. All data were collected centrally through use of a standardized international case report form completed at the study visit. To establish the presence of cerebrovascular disease at baseline, medical record documentation was required consisting of a hospital or neurologist report with the diagnosis of TIA or ischemic stroke (N=18,992). Like in large secondary prevention studies with antiplatelet agents, we excluded 2544 cerebrovascular patients with a history of atrial fibrillation. In the remaining 16,448 participants, REACH Registry physicians performed follow-up after 12±3 months in 94.9% for assessment of individual clinical events, yielding a population of 15,605 participants with complete follow-up. In comparison, participants without follow-up more often had diabetes, a previous history of stroke or TIA, and a higher ESRS sum score but were not significantly different with regard to age or other cardiovascular risk factors (Table 1).

Statistics

Categorical variables are presented as percentages and continuous variables as mean plus SD. χ² test and Fisher exact test, as appropriate, were used for comparison of categorical variables. Wilcoxon rank sum score was used for comparison of nonnormally distributed variables. To evaluate the performance of the ESRS, we calculated the area under the curve (AUC) by c-statistic and calibration χ² (survival modified Hosmer-Lemeshow). An AUC of 0.5 indicates no discrimination, and an AUC of 1.0 indicates perfect discrimination. All analyses were done with SAS software version 8.1 (SAS Institute Inc, Cary, NC).

Results

A history of TIA or ischemic stroke was diagnosed in 18,992 patients at baseline. After exclusions, a study population of 15,605 patients with complete follow-up information at 1 year was available for analysis. This included 9286 (59.6%) men with a mean age was 68.9±10.1 years. A qualifying stroke or TIA within 1 year preceding baseline was documented in 5594 (35.8%) patients or more than 1 year ago in 10,011 (64.2%). The prevalence of vascular risk factors at baseline is shown in Table 1. The event rate at 1 year for the entire cohort was 4.01% for fatal or nonfatal stroke and 6.05% for combined CV events. On stratification by individual ESRS, there was a steady increase in the rate of combined CV events with increasing ESRS (Table 2; Figure). For the combined CV end point, the AUC assessed by c-statistics was 0.60 (95% CI, 0.58 to 0.62). In the rate of fatal or nonfatal stroke, a steady increase was likewise observed with increasing ESRS (Table 3; Figure). The corresponding AUC assessed by c-statistics was 0.56 (95% CI, 0.53 to 0.58). In 5594 patients with a TIA or stroke within 1 year preceding baseline, 1-year rates of 5.8% for recurrent stroke (Table 3) and 7.9% for combined CV events (Table 2) could be found. In this subgroup with recent index events, AUC values were 0.59 (95% CI, 0.56 to 0.62) for recurrent stroke and 0.56 (95% CI, 0.53 to 0.59) for combined CV events. For comparison, Tables 2 and 3 also show data from 6431 cerebrovascular patients in the CAPRIE data set who had a 1-year rate of 6.3% for recurrent stroke and 8.0% for combined CV events.
Discussion

Although several previous scores have been suggested for risk stratification in secondary prevention, the ESRS is the first to provide reliable incidence rates for recurrent stroke and major CV events both in a controlled study (CAPRIE) and a less selected outpatient registry population (REACH). This study is an important validation of the ESRS that demonstrates its ability to generate prognostic risk information.

The REACH Registry is an international study in 44 countries. With the exception of African and Chinese populations, which were underrepresented in this study, our population can thus be regarded as representative for stable cerebrovascular patients worldwide. Nevertheless, several limitations need to be mentioned.

Like with all registries, the influence of recruitment bias (which may vary geographically) cannot be known. Physicians were instructed to recruit consecutive patients, but unlike in controlled trials, there were no log book audits to ensure compliance with such instructions. Also, by focusing on stable outpatients, the mean risk of enrolled patients is lower than if inpatients with acute cerebrovascular disease had also been included. As a consequence, the 1-year absolute risk for fatal and nonfatal stroke in the REACH Registry was lower by 1.95% and for combined CV events by 2.29% compared with CAPRIE, which was consistent over various risk strata. However, when including only participants with a qualifying event within 1 year before baseline assessment, event rates became very similar to CAPRIE and predictive accuracy for prediction of recurrent stroke was slightly increased. Second, the role of atrial fibrillation was not investigated nor included in development of the ESRS. However, atrial fibrillation has not been identified as an independent risk factor for recurrent stroke in patients treated with oral anticoagulation in other follow-up studies either. Finally, the relatively low predictive accuracies may not justify reliance on the given prediction for individual treatment decisions. In comparison, another clinical scoring system, developed by Hankey et al, predicting various vascular events (stroke, coronary events, vascular death) at 1 and 5 years of follow-up, showed higher predictive accuracies. Both systems, however, seem particularly useful when used in combination.

Table 2. One-Year Cumulative Rates for Combined Cardiovascular Events (nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) in REACH and CAPRIE Patients With Cerebrovascular Disease Stratified by the ESRS

<table>
<thead>
<tr>
<th>ESRS Point</th>
<th>REACH</th>
<th>REACH With Qualifying Event ≤1 Year</th>
<th>CAPRIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum</td>
<td>Event Rate, %</td>
<td>Event Rate, %</td>
<td>Event Rate, %</td>
</tr>
<tr>
<td>0</td>
<td>222</td>
<td>2.41</td>
<td>0.00–4.82</td>
</tr>
<tr>
<td>1</td>
<td>1317</td>
<td>3.50</td>
<td>2.34–4.66</td>
</tr>
<tr>
<td>2</td>
<td>3017</td>
<td>4.35</td>
<td>3.42–5.27</td>
</tr>
<tr>
<td>3</td>
<td>4208</td>
<td>5.30</td>
<td>4.40–6.18</td>
</tr>
<tr>
<td>4</td>
<td>3559</td>
<td>6.65</td>
<td>5.56–7.73</td>
</tr>
<tr>
<td>5</td>
<td>2054</td>
<td>8.45</td>
<td>6.90–9.98</td>
</tr>
<tr>
<td>6</td>
<td>893</td>
<td>9.24</td>
<td>6.98–11.45</td>
</tr>
<tr>
<td>&gt;6</td>
<td>335</td>
<td>11.48</td>
<td>7.57–15.23</td>
</tr>
<tr>
<td>Total</td>
<td>15605</td>
<td>6.05</td>
<td>5.39–6.71</td>
</tr>
</tbody>
</table>

Figure. One-year cumulative rates for fatal or nonfatal stroke (white bars) and combined major cardiovascular events (shaded bars) with 95% CIs (error bars) stratified by the Essen Stroke Risk Score in REACH patients with cerebrovascular disease.
years found an AUC value of 0.65 on external validation in the UK TIA cohort. Likewise, the SPI-II found an AUC of 0.63 for prediction of stroke or death within 2 years in independent research populations. Both scores therefore showed slightly superior predictive accuracy compared with the ESRS for the combined end point of recurrent stroke/cardiovascular death in patients with recent cerebrovascular events. Neither one of these instruments, however, has been validated for prediction of stroke or combined CV events in stable outpatients with cerebrovascular disease. We could not compare the predictive accuracy between these scales and the ESRS in our study population because not all variables from the other scales had been prospectively documented.

In contrast to other validated scales, the ESRS is easy to calculate and shows an almost linear risk increase. A high recurrent stroke risk in secondary prevention trials has been previously defined as >4%/year, which applies to approximately half of all patients included in CAPRIE or ESPS2 and corresponds to an ESRS >2 in these trials. Applied to a stable outpatient population, a recurrent stroke risk >4%/year corresponds to an ESRS >3, which represents 43.8% of the cerebrovascular patients in REACH.

Retrospective analyses have suggested that a combination therapy of dipyridamole/aspirin or clopidogrel monotherapy, compared with aspirin alone, may be particularly beneficial in patients at high risk as assessed by the ESRS. Thus, a stratification of patients according to risk of recurrent stroke may possibly lead to further optimized treatment regimens in addition to modification of stroke risk factors. Unfortunately, the efficacy of different medication regimens could not be tested in this observational study.

In conclusion, the ESRS was shown to predict stroke and combined CV events reasonably well in both stable outpatients with cerebrovascular disease and inpatients with stroke included in secondary prevention trials and therefore lends itself for risk stratification in research populations and individual patients.

Appendix


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