Poor Long-Term Functional Outcome After Stroke Among Adults Aged 18 to 50 Years
Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) Study

Nathalie E. Synhaeve, MD; Renate M. Arntz, MD; Noortje A.M. Maaijwee, MD; Loes C.A. Rutten-Jacobs, MSc; Henny C. Schoonderwaldt, PhD; Lucille D.A. Dorresteijn, PhD; Paul L.M. de Kort, PhD; Ewoud J. van Dijk, PhD; Frank-Erik de Leeuw, PhD

Background and Purpose—Stroke in young adults has a dramatic effect on life; therefore, we investigated the long-term functional outcome after transient ischemic attack, ischemic stroke, or intracerebral hemorrhage in adults aged 18 to 50 years.

Methods—We studied 722 young patients with first-ever stroke admitted between January 1, 1980, and November 1, 2010. Functional outcome was assessed by stroke subtype with the modified Rankin Scale and Instrumental Activities of Daily Living scale.

Results—After a mean follow-up of 9.1 (SD, 8.2) years, 32.0% of all patients had a poor functional outcome (modified Rankin Scale, >2); for ischemic stroke, this was 36.5%, for intracerebral hemorrhage 49.3%, and for transient ischemic attack 16.8%. At follow-up, 10.8% of transient ischemic attack, 14.6% of ischemic stroke, and 18.2% of intracerebral hemorrhage patients had a poor outcome as assessed by Instrumental Activities of Daily Living (<8).

Conclusions—Ten years after ischemic stroke or intracerebral hemorrhage in young adults, 1 of 8 survivors is still dependent in daily life. (Stroke. 2014;45:1157-1160.)

Key Word: prognosis

A pproximately 10% of all strokes occur in patients between 18 and 50 years.1,2 Uncertainty about their long-term functional outcome may affect the choices and family and career planning of young patients with stroke.

However, only few studies addressed the long-term functional outcome in young patients with stroke.3–5 None of these included the whole stroke spectrum ranging from transient ischemic attack (TIA), ischemic stroke (IS) to intracerebral hemorrhage (ICH).

Therefore, the objective of the present study was to evaluate the long-term functional outcome in young patients with stroke considering both motor activities and more complex daily tasks, after a TIA, IS, and ICH.

Materials and Methods
This study is part of the Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study, as described elsewhere.3 The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. Written informed consent was obtained from all patients.

Patients
The FUTURE study comprised all consecutive patients aged between 18 and 50 years with a TIA, IS, or ICH, admitted to the Radboud University Medical Center Nijmegen, the Netherlands, from January 1, 1980, to November 1, 2010. Patients with first-ever TIA, IS, or ICH were included in the present study. Patients alive were invited for follow-up assessment between November 1, 2009, and January 1, 2012.

Functional Outcome
The primary outcome was functional outcome measured by the modified Rankin Scale (mRS). Participants also completed the Instrumental Activities of Daily Living (iADL) scale, which assesses the ability to execute complex tasks necessary for an independent life.

We considered a mRS >2 or an iADL <8 a poor functional outcome. Because there is no commonly used cut-off value for the iADL, we have chosen a cut-off value of <8 to indicate poor outcome because patients are dependent in daily life with a score <8.

Statistical Analysis
Chi-square test was used to analyze poor functional outcome (mRS) by the presence of incident stroke (IS or ICH) and by time of admission (before 1980, 1990–2000, and after 2000). Odds ratios (95% confidence interval) are calculated by means of logistic regression for the risk of poor outcome in patients with IS only (because of small numbers with poor outcome in the other groups). Sex, age at event, duration of follow-up, National Institutes of Health Stroke Scale (NIHSS) at admission, incident strokes, and cardiovascular disease were considered confounders. We repeated this analysis without
incident events in the model to identify baseline variables predicting poor functional outcome.

Results

Study Population

A total of 1005 patients fulfilled inclusion and exclusion criteria of the FUTURE study; of these patients, 46 were excluded because of a history of TIA or stroke, 82 were lost to follow-up, 153 refused to participate, and 2 did not provide any functional outcome measure resulting in 722 patients in the current analysis (Table 1). When compared among participants, patients lost to follow-up more often had an IS (76.8% versus 61.9%), less often a TIA (12.2% versus 28.8%; \( P=0.001 \)), and were younger at admission (38.0 versus 40.5 years; \( P=0.007 \)). When compared with patients, patients who refused to participate had a lower NIHSS at admission (median, 2 versus 3; \( P=0.016 \)).

Functional Outcome As Assessed by the mRS

At discharge, 5 patients (2.4%) with a TIA, 135 patients (30.2%) with an IS, and 46 patients (69.7%) with an ICH had a poor functional outcome. After a mean follow-up of 9.1 (SD, 8.2) years, a poor functional outcome was present in 35 patients (16.8%) with a TIA, 163 patients (36.5%) with an IS, and 33 patients (49.3%) with an ICH; of which 23 patients with TIA (11.1%), 122 patients with IS (27.3%), and 27 patients with ICH (40.3%) scored an mRS of 6 at follow-up (Figure).

Functional Outcome As Assessed by the iADL

At follow-up, 17 survivors (10.8%) with TIA, 41 (14.6%) with IS, and 6 (18.2%) with ICH had a poor outcome on the iADL.

Contributing Factors

A total of 22 patients with TIA (10.6%), 64 patients with IS (14.3%), and 5 patients with ICH (7.5%) had \( \geq 1 \) incident stroke during follow-up (\( P=0.167 \) for overall difference). Patients with an incident stroke (n=91) more often had a poor functional outcome than patients without a recurrent stroke (mRS \( >2 \): 54.9% versus 28.7%; \( P<0.001 \) and iADL \( <8 \): 33.3% versus 11.5%; \( P<0.001 \)).

In patients with the index event before 1990, between 1990 and 2000, and after 2000, the proportion with a poor functional outcome was 56.0%, 39.5%, and 18.3% (\( P<0.001 \) for overall difference). Between these groups there was no difference in outcome as assessed by the iADL. Stratification by stroke subtype showed a similar picture. There was no cohort effect with respect to age at index event or in the NIHSS at admission. Patients admitted before 1990 had more incident strokes than those admitted after 2000 (17.0% versus 10.1%; \( P=0.036 \)).

Risk Factors

Risk factors for poor functional outcome (mRS \( \geq 2 \)) included the NIHSS and age at admission, incident stroke, sex, incident cardiovascular disease, and follow-up duration. Significant risk factors for an iADL \( <8 \) were NIHSS at admission and incident stroke. This did not change after exclusion of incident events (Table 2).

Discussion

We showed that even after 10 years, \( \approx 1 \) of 8 patients (12.9%) with an IS or ICH at young age was not able to function independently. In patients with TIA, this was 1 of 15 (6.5%) survivors. The strongest predictor of long-term functional outcome was the severity of the initial stroke. Also, there was a clear relationship between the occurrence of \( \geq 1 \) incident strokes and poor long-term functional outcome, stressing the importance of optimal preventive strategies in this population.

Strengths of our study were the prospective and single-center design. Furthermore, our study has one of the longest follow-up durations and one of the largest cohorts.

Table 1. Baseline Characteristics Stratified by Stroke Subtype

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>TIA</th>
<th>IS</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% of total)</td>
<td>722 (100)</td>
<td>208 (28.8)</td>
<td>447 (61.9)</td>
<td>67 (9.3)</td>
</tr>
<tr>
<td>Mean age at event, y (SD)</td>
<td>40.5 (7.8)</td>
<td>40.6 (8.0)</td>
<td>40.8 (7.6)</td>
<td>38.2 (8.5)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>344 (47.6)</td>
<td>94 (45.2)</td>
<td>215 (48.1)</td>
<td>35 (52.2)</td>
</tr>
<tr>
<td>Median NIHSS at admission (IQR)*</td>
<td>3 (1–9)</td>
<td>0 (0–1)</td>
<td>5 (2–10)</td>
<td>14 (5–18)</td>
</tr>
<tr>
<td>Mean follow-up, y (SD)</td>
<td>9.1 (8.2)</td>
<td>8.5 (8.0)</td>
<td>9.7 (8.2)</td>
<td>6.6 (8.2)</td>
</tr>
<tr>
<td>TOAST classification, n (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Large artery</td>
<td>165 (25.2)</td>
<td>46 (21.1)</td>
<td>119 (26.6)</td>
<td>...</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>86 (13.1)</td>
<td>27 (13.0)</td>
<td>59 (13.2)</td>
<td>...</td>
</tr>
<tr>
<td>Lacunar</td>
<td>65 (9.9)</td>
<td>11 (5.3)</td>
<td>54 (12.1)</td>
<td>...</td>
</tr>
<tr>
<td>Other determined</td>
<td>96 (14.7)</td>
<td>23 (11.1)</td>
<td>73 (16.3)</td>
<td>...</td>
</tr>
<tr>
<td>Multiple</td>
<td>17 (2.6)</td>
<td>2 (1.0)</td>
<td>15 (3.4)</td>
<td>...</td>
</tr>
<tr>
<td>Undetermined</td>
<td>226 (34.5)</td>
<td>99 (47.6)</td>
<td>127 (28.4)</td>
<td>...</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; IQR, interquartile range; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and TOAST, modified Trial of ORG 10172 in Acute Stroke Treatment.

*0.6% missing.
A limitation is the small number of patients with ICH, albeit the largest young ICH sample with long-term follow-up to date. Furthermore, length of stay affects mRS at discharge and as a consequence a single group of patients with one and the same mRS at discharge might actually be composed out of several groups (with longer and shorter lengths of stay), each with their potential of recovery and thereby functional status at follow-up.

**Table 2. Predictors of a Poor Functional Outcome in Ischemic Patients With Stroke**

<table>
<thead>
<tr>
<th></th>
<th>mRS &gt;2</th>
<th>IADL &lt;8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.88 (0.56–1.38)</td>
<td>0.578</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>1.05 (1.02–1.09)</td>
<td>0.002</td>
</tr>
<tr>
<td>NIHSS at admission (per point increase)</td>
<td>1.18 (1.13–1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>4.24 (2.31–7.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident cardiovascular disease*</td>
<td>3.74 (1.84–7.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>0.96 (0.93–0.99)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; IADL, Instrumental Activities of Daily Living; mRS, modified Rankin Scale; and OR, odds ratio.

*Incident cardiovascular disease: incident cardiac disease and/or peripheral artery disease.
Recruitment of this cohort included 30 years during which major improvements in stroke care and secondary prevention took place. This was reflected by the on average better outcome in patients who had been admitted more recently and the higher proportion of incident stroke in the before 1990 cohort when compared with the cohorts thereafter although obviously those with a long follow-up have been exposed much longer, have become older, and are likely to have experienced more comorbidity that all may have accounted for a poorer functional outcome.

In previous studies, poor functional outcome in patients with IS ranged from 3% to 7% after mean follow-up durations between 4 and 12 years. These studies showed a slightly better outcome than ours, possibly explained by our inclusion of older patients (≤50 instead of 45 years) or a longer follow-up in our study. Furthermore, in these previous studies, functional outcome was measured only by either the mRS or the Glasgow Outcome Scale, which are rather global scales for outcome. We intentionally used 2 different methods to determine functional outcome.

To conclude, prognosis after young ischemic and hemorrhagic stroke is rather poor; 1 of 8 young survivors with stroke is not able to live an independent life, even after ≅10 years after stroke.

Sources of Funding
This study was funded by the Dutch Epilepsy Fund (grant number 10–18).

Disclosures
None.

References
Poor Long-Term Functional Outcome After Stroke Among Adults Aged 18 to 50 Years: Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) Study

Stroke. 2014;45:1157-1160; originally published online February 27, 2014;
doi: 10.1161/STROKEAHA.113.004411
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/4/1157

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/