Ninety-Day Outcome Rates of a Prospective Cohort of Consecutive Patients With Mild Ischemic Stroke

Pooja Khatri, MD, MSc; Mark R. Conaway, PhD; Karen C. Johnston, MD, MSc; for the Acute Stroke Accurate Prediction Study (ASAP) Investigators

Background and Purpose—Prior studies have shown that patients with mild ischemic stroke have substantial disability rates at hospital discharge. We sought to determine disability rates at 90 days among patients not treated with thrombolytic therapy and explore the role of early neurological worsening.

Methods—We reviewed a prospective cohort of 136 consecutive patients with mild deficits (National Institutes of Health Stroke Scale score ≤5) presenting within 24 hours of onset and no baseline disability. Baseline MRIs were performed on all subjects. Five-day MRIs were performed on a prespecified subcohort.

Results—Among 136 patients, 40 (29%; 95% CI, 22%–38%) had poor outcomes (modified Rankin Scale score 2–6) at 90 days. Early worsening (4-point National Institutes of Health Stroke Scale increase; 25% versus 1%, P<0.001) and acute infarct growth (>10% on MRI–diffusion-weighted imaging; 79% versus 53%, P=0.02) from baseline to 5 days were more common among those with poor outcome.

Conclusions—Patients with mild ischemic stroke have substantial rates (29%) of disability at 90 days. (Stroke. 2012;43: 560-562.)

Key Words: cerebral infarct ■ prognosis ■ stroke care

Over half of all ischemic strokes in the United States present with mild deficits (National Institutes of Health Stroke Scale [NIHSS] score ≤5). Mild stroke severity is the most common reason for exclusion from intravenous recombinant tissue-type plasminogen activator treatment despite early emergency department arrival. Whether recombinant tissue-type plasminogen activator treatment is indicated for mild stroke is not known, because they were largely excluded from the pivotal National Institute of Neurological Disorders and Stroke trials.4

More recent studies (Table 1) suggest significant disability at hospital discharge after “mild” or “improving” stroke.5-7 Previous studies with 90-day outcomes have included subjects with substantial deficits on presentation (NIHSS score >5) in their mild stroke definitions.8

We sought to determine 90-day outcomes of mild strokes (NIHSS score ≤5). We also considered the role of early neurological worsening.

Methods

The Institutional Review Board-approved Acute Stroke Accurate Prediction Study (ASAP) was designed to provide a validation data set for a previously developed predictive stroke outcome model. Consecutive subjects were prospectively enrolled at the University of Virginia from May 2000 to August 2005.9 Eligible subjects were ≥18 years old, within 24 hours of symptom onset, and without an MRI contraindication. Baseline characteristics, MRI on enrollment, and blinded in-person 90-day clinical outcomes were collected. Five-day MRI and NIHSS assessments were performed in subjects who agreed to participate in a substudy of early outcomes; all ASAP subjects were invited to participate.

For this analysis, we defined mild stroke as an NIHSS score ≤5 on enrollment. We excluded patients with premorbid disability (Glasgow Outcome Scale ≥3), recombinant tissue-type plasminogen activator treatment, or missing 90-day outcome.

Baseline characteristics were compared between good (modified Rankin Scale [mRS] score 0–1) and poor outcome (mRS 2–6) groups. NIHSS improvements (4-point decline) and worsening (4-point increase) from baseline to 90 days, and to 5 days when available, were also compared between these 2 groups. Among those with 5-day MRI assessments, we also compared changes in infarct volumes using computer-assisted volumetric software (Analyze software 6.1; Biomedical Imaging Resource, Rochester, MN) and prespecified a 10% increase in volume as clinically significant. Chi-squared (categorical) and Kruskal-Wallis (continuous) statistical tests were performed.

A multivariable model of 90-day outcome was developed with inclusion of variables with a possible association (P<0.20) followed by backward elimination (P>0.05). NIHSS worsening was not considered in the model due to its known association with disability.

Results

Of 301 patients, 164 presented with mild strokes. The 90-day outcome analysis was limited to 136 patients after excluding those with missing diffusion-weighted imaging data (n=7), loss to follow-up (n=7), stroke mimics (n=5), and thrombolytic therapy and explore the role of early neurological worsening.

Results—Among 136 patients, 40 (29%; 95% CI, 22%–38%) had poor outcomes (modified Rankin Scale score 2–6) at 90 days. Early worsening (4-point National Institutes of Health Stroke Scale increase; 25% versus 1%, P<0.001) and acute infarct growth (>10% on MRI–diffusion-weighted imaging; 79% versus 53%, P=0.02) from baseline to 5 days were more common among those with poor outcome.

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Over half of all ischemic strokes in the United States present with mild deficits (National Institutes of Health Stroke Scale [NIHSS] score ≤5).1 Mild stroke severity is the most common reason for exclusion from intravenous recombinant tissue-type plasminogen activator treatment despite early emergency department arrival.2,3 Whether recombinant tissue-type plasminogen activator treatment is indicated for mild stroke is not known, because they were largely excluded from the pivotal National Institute of Neurological Disorders and Stroke trials.4

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560-562.
premorbid disability (n=3), and recombinant tissue-type plasminogen activator treatment (n=6). The 90-day NIHSS analysis consisted of 131 patients due to 5 missing NIHSS values. The 5-day NIHSS and MRI analyses consisted of 96 patients.

Demographic characteristics, comorbidities, and outcomes for the mild stroke subcohort (n=136) are provided in Table 2. Poor 90-day outcome (mRS 2–6) was seen in 40 of 136 (29%; 95% CI, 22%–38%) cases. The mRS distribution consisted of 44 (32%) mRS 0, 52 (38%) mRS 1, 16 (12%) mRS 2, 10 (7%) mRS 3, 8 (6%) mRS 4, 1 (1%) mRS 5, and 5 (4%) mRS 6. Subjects with poor outcome had larger diffusion-weighted imaging infarcts at baseline and more frequent infarct growth (79% versus 53%) and NIHSS worsening (25% versus 1%) from baseline to 5 days.

Univariate association (P<0.20) was noted among age, gender, and 10% increase in diffusion-weighted imaging infarct volume (Table 1). Multivariable analysis showed age (OR, 1.05; 95% CI, 1.01–1.10; P=0.01) and increase in diffusion-weighted imaging infarct volume (OR, 3.57; 95% CI, 1.17–10.9; P=0.03) as independent predictors of poor 90-day outcome.

Discussion

Our finding of significant disability after “mild” stroke is consistent with prior studies but is more compelling, because it represents prospectively collected data of consecutive subjects that were assessed beyond hospital discharge at 90 days.

Patients with low NIHSS scores at presentation who do not appear to have deficits of a disabling nature may develop poor outcomes for the following reasons: (1) unmeasured neurological deficits (such as cognitive effects) or underappreciated deficits (such as isolated expressive aphasia) from

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### Table 1. Mild/Improving Ischemic Stroke Not Treated With Intravenous Recombinant Tissue-Type Plasminogen Activator

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Definition of Mild/Improving</th>
<th>No.</th>
<th>Outcome Measure</th>
<th>Rate (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-center* (Charleston, VA)</td>
<td>NIHSS ≤ 5</td>
<td>136</td>
<td>mRS 2–6 at 90 d</td>
<td>29% (22%–28%)</td>
</tr>
<tr>
<td>Single-center† (Calgary, Canada)</td>
<td>Judgment</td>
<td>98</td>
<td>mRS 3–6 at discharge</td>
<td>33% (24%–42%)</td>
</tr>
<tr>
<td>Single-center‡ (Boston, MA)</td>
<td>Judgment</td>
<td>41</td>
<td>Not discharged home</td>
<td>27% (16%–42%)</td>
</tr>
<tr>
<td>Multicenter state§ (California)</td>
<td>Judgment</td>
<td>32</td>
<td>Not discharged home/unable to walk at discharge</td>
<td>34% (20%–52%)</td>
</tr>
<tr>
<td>Single-center∥ (Zwolle, The Netherlands)</td>
<td>Judgment</td>
<td>27</td>
<td>mRS 2–6 at discharge</td>
<td>11% (4%–28%)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; CI, confidence interval.

*Current study.

†Ninety-five percent exact CIs calculated based on published data.

### Table 2. Characteristics and Outcomes of the Mild Stroke ASAP Subcohort

<table>
<thead>
<tr>
<th></th>
<th>All Mild Strokes</th>
<th>Good Outcome at 90 D</th>
<th>Poor Outcome at 90 D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full mild stroke cohort with 90-day mRS outcome data (n=136)</td>
<td>(n=136)</td>
<td>(n=96)</td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>68 (57–78)</td>
<td>65 (56–74)</td>
<td>75 (64–81)</td>
<td>0.003</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>71 (52%)</td>
<td>56 (58%)</td>
<td>15 (38%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>45 (33%)</td>
<td>30 (31%)</td>
<td>15 (38%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Prior stroke, no. (%)</td>
<td>35 (26%)</td>
<td>23 (24%)</td>
<td>12 (30%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Lacunar infarct based on TOAST criteria, no. (%)</td>
<td>66 (49%)</td>
<td>48 (50%)</td>
<td>18 (45%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Subset with 90-d NIHSS outcome data (n=131)</td>
<td>(n=131)</td>
<td>(n=93)</td>
<td>(n=38)</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>0.32</td>
</tr>
<tr>
<td>90-d NIHSS, median (IQR)</td>
<td>1 (0–3)</td>
<td>0 (0–2)</td>
<td>3 (1–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4-point NIHSS improvement from baseline to 90 d, no. (%)</td>
<td>15 (11%)</td>
<td>15 (16%)</td>
<td>0 (0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>4-point NIHSS worsening from baseline to 90 d, no. (%)</td>
<td>9 (7%)</td>
<td>0</td>
<td>9 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subset with 5-day MRI and NIHSS scores (n=96)</td>
<td>(n=96)</td>
<td>(n=72)</td>
<td>(n=24)</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>3 (2–4)</td>
<td>2 (1–4)</td>
<td>3 (2–4)</td>
<td>0.18</td>
</tr>
<tr>
<td>5-d NIHSS, median (IQR)</td>
<td>2 (0–4)</td>
<td>1 (0–3)</td>
<td>3 (2–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90-d NIHSS, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>3 (1–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4-point NIHSS improvement from baseline to 5 d, no. (%)</td>
<td>3 (3%)</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>4-point NIHSS worsening from baseline to 5 d, no. (%)</td>
<td>7 (7%)</td>
<td>1 (1%)</td>
<td>6 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline DWI infarct volume, mL, median (IQR)</td>
<td>5 (0–26)</td>
<td>4 (0–17)</td>
<td>14 (1–63)</td>
<td>0.04</td>
</tr>
<tr>
<td>5-d DWI infarct volume, mL, median (IQR)</td>
<td>11 (0–50)</td>
<td>9 (0–31)</td>
<td>31 (3–140)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;10% DWI infarct growth, no. (%)</td>
<td>57 (59%)</td>
<td>38 (53%)</td>
<td>19 (79%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ASAP indicates Acute Stroke Accurate Prediction Study; mRS, modified Rankin Scale; IQR, interquartile range; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging.
the incident stroke event; (2) early neurological worsening of the incident stroke; or (3) additional medical events such as a distinct stroke recurrences or other vascular events related to the same comorbidities that caused their stroke. We found that early worsening was associated with poor outcome based on a higher proportion of diffusion-weighted imaging infarct growth and an increased frequency of NIHSS worsening. This is consistent with analyses of the overall ASAP cohort.9

We lack details regarding the potentially disabling nature of the incident stroke event and medical complications after the incident stroke. An additional limitation of our analysis is the absence of data regarding large-vessel occlusion, a known predictor of poor outcome after mild stroke. Additionally, it should be noted that baseline NIHSS scores were acquired within 24 hours, not necessarily at presentation in the emergency department, like in prior cohorts; our cohort could represent a more stably mild stroke group. Furthermore, this is a single-center, referral-based cohort collected from 2000 to 2005, and clinical outcomes may reflect these limitations. Nevertheless, our analysis suggests that approximately one third of so-called mild strokes have significant disability that persists at 3 months. We also show that early neurological worsening and infarct expansion are associated with this poor outcome. Future studies of this large subgroup of ischemic strokes are warranted.

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References
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