Predicting Functional Outcome After Intra-Arterial Thrombolysis: Aspects of ASPECTS

To the Editor:

I read with great interest the article by Dr Hill and colleagues about using the ASPECTS score in patients who received intra-arterial thrombolysis.1,2 ASPECTS is a validated score that identifies those patients with acute stroke who can benefit from intravenous thrombolysis. It assesses 10 regions of the brain on the CT scans and assigns a score of 1 for a normal region and 0 for an area showing signs of ischemia.2,3 In addition, ASPECTS also helps predict the risk of intracerebral hemorrhage (OR = 14; CI 1.8 to 117).2

This time, the authors assessed the baseline and 24-hour CT scans of patients enrolled in the PROACT II study using the ASPECTS score.1 PROACT II was a clinical trial that randomized acute stroke patients with documented middle cerebral artery (MCA) occlusion, <6 hours of symptoms onset, to receive 9 mg intra-arterial recombinant pro-urokinase (r-proUK) plus heparin or heparin alone.

In summary, Dr Hill and his colleagues evaluated if ASPECTS could predict the benefit from the treatment with intra-arterial thrombolysis. The authors compared the risk ratios for outcomes between proUK versus control groups stratified by a baseline ASPECTS score (>7 and <7). They defined primary (modified Rankin Scale [mRS] score=0 to 2) and secondary outcomes (mRS=0 to 1, NIHSS score=0 to 1, Barthel Index=0 to 1, mortality rate), as in their former article.3 They found a statistically significant difference exclusively in the primary outcome between the treatment and control groups, only in those patients with ASPECTS >7. They stated that “the results from the present study support the concept that the use of ASPECTS can identify stroke patients with MCA occlusion who will receive particular benefit from intra-arterial thrombolysis.”

ASPECTS is a useful tool with practical implications in the decision whether to give intravenous tissue plasminogen activator. However, it has limitations.

First, (1) it applies only to specific areas of the brain. As the authors stated, this score is not applicable to lacunar strokes, ischemic changes in the anterior and posterior cerebral arteries, or brain stem infarctions. (2) The thrombolytic drug used in PROACT II was r-proUK. This drug has not been approved by or brain stem infarctions. (2) The thrombolytic drug used in PROACT II was r-proUK. This drug has not been approved by

Second, subgroup analyses are prone to bias.5

Third, in the first article the authors showed that ASPECTS predicts functional independence at 90 days in patients receiving intravenous thrombolytic therapy.2 Interestingly, if we apply the same methodology, the present study would be negative (no statistical significant difference between ASPECTS >7 and <7 in the treatment arm for all primary and secondary outcomes) (Table). In other words, contrary to authors conclusion, ASPECTS is not useful in predicting functional independence in patients receiving intra-arterial thrombolysis.

How can the authors be sure that the published data are not the result of chance from multiple subgroups analyses?. Although this tool could be useful in intravenous tissue plasminogen activator studies, some aspects of the ASPECTS score in intra-arterial thrombolysis remain to be elucidated.

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Response

We thank Dr Saposnik for his interest in ASPECTS for the assessment of baseline CT scans in patients with acute stroke. He raises a number of points to which we have the following responses.

ASPECTS was designed for the assessment of middle cerebral artery territory ischemia. This is not a limitation of the present study because the PROACT-II trial randomized only patients with proven occlusion in the middle cerebral artery. The fact that

Unadjusted and Adjusted OR for Outcome Stratified by ASPECTS in the r-ProUK Treatment Arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASPECTS&gt;7 ProUK</th>
<th>ASPECTS&lt;7 ProUK</th>
<th>Unadjusted Values</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0−2</td>
<td>n=46</td>
<td>n=59</td>
<td>ARR</td>
<td>RRR %</td>
</tr>
<tr>
<td></td>
<td>23 (50)</td>
<td>21 (35.6)</td>
<td>14.4</td>
<td>40</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS 0−1</td>
<td>12 (26.1)</td>
<td>8 (13.6)</td>
<td>12.5</td>
<td>92</td>
</tr>
<tr>
<td>BI 90</td>
<td>24 (62.2)</td>
<td>21 (35.6)</td>
<td>16.6</td>
<td>47</td>
</tr>
<tr>
<td>Mortality</td>
<td>11 (23.9)</td>
<td>16 (27.1)</td>
<td>−3.2</td>
<td>12</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>4 (8.7)</td>
<td>9 (15.3)</td>
<td>−6.6</td>
<td>43</td>
</tr>
<tr>
<td>Recanalization at 120 min</td>
<td>27 (58.7)</td>
<td>41 (69.5)</td>
<td>−10.8</td>
<td>16</td>
</tr>
</tbody>
</table>

Note that all 95% CIs include 1.0, the difference is not statistically significant by usual standards.

ProUK indicates pro-Urokinase treatment arm; NA, not available; ASPECTS, Alberta Stroke Program Early CT Score; ARR, absolute risk reduction; RRR, relative risk reduction; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale score; mRS, modified Rankin Scale score; BI, modified Barthel Index score; ICH, intracerebral hemorrhage.
pro-urokinase is not licensed is not a limitation of the present study.

Because additional analyses from clinical trials do not usually assess randomized comparisons, these analyses are generally prone to confounding, not bias. Whereas confounding can be corrected by multivariable analyses, bias cannot. In our study, we adjusted the results for possible confounders using multivariable analysis. We acknowledge the concern about multiple testing. These analyses were post-hoc and were meant to be hypotheses generating, not confirmatory.

The original ASPECTS study did not have a control group, but was a case series of stroke patients receiving intravenous tissue plasminogen activator. PROACT II, however, was a prospective, randomized, controlled study, and thus comparisons between r-proUK and control are the most appropriate. Nevertheless, Dr Saposnik has performed a subgroup analysis of his own and inadvertently has used odds ratios in reporting his findings. Odds ratios overestimate the true effect size when the outcome of interest is common, as in this case. The risk ratios for the proposed comparisons are shown in the Table. All of the comparisons involve a cohort of only 105 patients and hence the risk ratios have wide confidence intervals. Contrary to Dr Saposnik’s assertion, ASPECTS is likely predictive of outcome and hemorrhage within this cohort of patients. The direction and effect size of the risk ratios are similar to what has been previously reported. The fact that the risk ratios do not reach the conventional level of statistical significance, because of the small sample size, does not negate a plausible biological effect. In fact, these results support the notion that the ASPECTS is a robust scoring system for the assessment of baseline CT scans in patients with acute stroke that may be used to select the best candidates for intra-arterial thrombolysis.

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Outcome in the ProUK Cohort by ASPECTS Score

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ProUK Cohort</th>
<th>ASPECTS &gt;7 (n=46), %</th>
<th>ASPECTS &lt;7 (n=59), %</th>
<th>Risk Difference</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>mRS 0–2</td>
<td>50.0</td>
<td>35.6</td>
<td>14.4</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td></td>
<td>mRS 0–1</td>
<td>37.0</td>
<td>20.3</td>
<td>16.7</td>
<td>1.8 (0.97-3.4)</td>
</tr>
<tr>
<td></td>
<td>NIHSS 0–1</td>
<td>26.1</td>
<td>13.6</td>
<td>12.5</td>
<td>1.9 (0.9-4.3)</td>
</tr>
<tr>
<td></td>
<td>BI ≥90</td>
<td>52.2</td>
<td>35.6</td>
<td>16.6</td>
<td>1.5 (0.9-2.3)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>23.9</td>
<td>27.1</td>
<td>-3.2</td>
<td>0.9 (0.5-1.7)</td>
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<td></td>
<td>Symptomatic ICH</td>
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<td>0.6 (0.2-1.7)</td>
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