Can Early Neurosonology Predict Outcome in Acute Stroke?
A Metaanalysis of Prognostic Clinical Effect Sizes Related to the Vascular Status

Erwin Stolz, MD, PhD; Francesca Cioli, MD; Jens Allendoerfer, MD; Tibo Gerriets, MD; Massimo Del Sette, MD; Manfred Kaps, MD, PhD

**Background and Purpose**—Prediction of short- and long-term prognosis is an important issue in acute stroke care. This metaanalysis explores the prognostic value of initial bed-side transcranial ultrasound in acute stroke.

**Methods**—All studies prospectively applying TCCS or TCD within 24 hours of symptom onset in acute stroke, with a minimal cohort size of 20 patients, and reporting clinical outcome variables in relation to the vascular findings were included into this metaanalysis. Study quality was assessed by 2 independent reviewers.

**Results**—Twenty-five studies with 1813 included patients identified by electronic and manual search fulfilled the inclusion criteria. Middle cerebral artery (MCA) occlusion was associated with a significantly increased risk for a fatal course of stroke (OR 2.46, 95% CI 1.33 to 4.52). Patients with patent MCA were more likely to clinically improve within 4 days than patients with MCA occlusion (OR 11.11, 95% CI 5.44 to 22.69). Full recanalization within 6 hours after symptom onset was highly significantly associated with clinical improvement within 48 hours (OR 5.64, 95% CI 3.82 to 8.31) and functional independence after 3 months (OR 6.07, 95% CI 3.94 to 9.35).

**Conclusions**—Transcranial ultrasound provides important information on prognosis in patients with acute stroke. (Stroke. 2008;39:3255-3261.)

**Key Words:** transcranial Doppler sonography ■ transcranial color-coded duplex sonography ■ acute stroke ■ metaanalysis ■ outcome

For treatment of acute stroke patients, prediction of short- and long-term prognosis is an important issue. Easy to apply measures to identify patients at risk of secondary worsening are also needed. Several studies reported a prognostic value of the initial neurovascular status assessed by transcranial color-coded duplex (TCCS) or Doppler sonography (TCD), which are noninvasive and can be applied at the patients’ bed side. The aim of this metaanalysis was to determine the predictive value of early transcranial ultrasonography on outcome and the related effect sizes in acute stroke.

**Methods**

All studies prospectively applying TCCS or TCD within 24 hours of symptom onset in acute stroke, with a minimal cohort size of 20 patients, and reporting clinical outcome variables in relation to the vascular findings were included into this metaanalysis. Studies were identified by searching in electronic databases (Medline, ISI Web of Science, Current Contents, Google Scholar Edition) and hand searching in key journals as well as reference lists. The search spanned from 1982, the year in which TCD was introduced, to August 2006. No language restriction was applied. All manuscripts entered into the metaanalysis were scored by 2 independent reviewers who were blinded to each other’s initial judgment regarding the quality. An 8 points score (Table 1), which was based on the level of evidence criteria for prognostic studies (Center for Evidence-Based Medicine, Oxford, UK, http://www.cebm.net/levels_of_evidence.asp), was applied strictly, ie, for instance, when a manuscript did not explicitly state that the clinical observers were blinded to the ultrasound data, an unblinded study was assumed. Discrepancies were resolved by discussion; if this was not possible the lower quality score was applied. The agreement of the reviewers on the initial blinded evaluation of study quality was examined using an intraclass correlation coefficient. These analyses were carried out with SPSS 12.0 (SPSS, Inc.).

The metaanalysis was performed with Review Manager 4.2 (Cochrane Collaboration). Both a fixed (Mantel-Haenszel procedure) and a Bayesian random effects model (DerSimonian-Laird model) were used. Because most studies reported the vascular status of the middle cerebral artery (MCA), MCA occlusions were compared with primary patent intracranial vessels regarding the dichotomous outcome variables. During analysis it became clear, that some monocentric studies of the same groups reported overlapping recruitment periods, so that analysis was performed with and without studies with potentially overlapping patient cohorts. In this case, the study of the respective group with the largest patient cohort was chosen. The effect of intracranial vessel occlusions on outcome was expressed as

**Received** April 9, 2008; final revision received May 7, 2008; accepted May 12, 2008.

From the Department of Neurology (E.S., J.A., T.G., M.K.), Justus-Liebig-University, Germany; the Department of Neurology and Department of Neuroscience, Ophthalmology, and Genetics (F.C., M.D.S.), University of Genova, Italy; and the Ultrasound Subnet of the Competence Network Stroke (E.S., M.K.), Germany.

E.S. and F.C. contributed equally to this study.

Correspondence to Erwin Stolz, MD, PhD, Department of Neurology, Justus-Liebig-University, Am Steg 14, D-35385 Giessen, Germany. E-mail erwin.stolz@neuro.med.uni-giessen.de

© 2008 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.522714 3255
odds ratio. The Cochrane Q statistic was calculated to assess heterogeneity among the trials. Heterogeneity was assumed when the probability value was ≤ 0.1. Sensitivity analysis consisted of the comparison of fixed and random effects models, subgroup analyses regarding publication date and study quality, and funnel plots (odds ratio [OR] plotted against the standard error of log[OR]), if the number of studies was sufficiently high enough. Sensitivity and specificity for a specified clinical outcome and the presence of any type of MCA occlusion was calculated with Meta-DiSc 1.3, a free software package for meta-analysis of diagnostic and screening tests. Clinical improvement was defined as either improvement in the National Institute of Health Stroke Scale (NIHSS) of ≥ 4 or the Canadian Stroke Scale (CSS) of ≥ 1 points. Independence or dependence in the activities of daily living after 3 months were defined as a modified Rankin Scale (mRS) score of ≤ 2 or 3 to 6, respectively.

Results
Search initially identified 494 studies. Four hundred twenty-five publications were excluded because of the following reasons: not focused on topic (398), nonsystematic reviews (24), meeting reports, consensus statements, recommendations (9), studies on topic, but no use of ultrasound or only in follow-up (8), studies without reported clinical outcome variables (7), TCD or TCCS > 24 hour after symptom onset or no time reported when ultrasound was performed (7), cohort size < 20 patients (8). In 8 studies it was not possible to extract dichotomized outcome data related to the vascular status. Finally, 25 studies with a total cohort of 1813 patients were included in the analysis. Twelve studies examined the prognostic value of early ultrasound on clinical outcome in cohorts not treated with thrombolysis, 13 the effect of systemic or local thrombolysis (Table 2). Only 3 of 25 studies used a multicenter design, 22 studies were single center investigations. Only 6 studies had blinding of the clinical observers to the ultrasound data, or explicitly stated this fact. In only 8 investigations it was shown by multivariate analysis, that the ultrasound findings were independent variables.

Blinded agreement of 2 raters on the quality score for metaanalysis was excellent with an intraclass correlation coefficient of 0.85 (95% confidence interval 0.72 to 0.92, \( P < 0.001 \)).

Mortality
Without intervention by thrombolysis, presence of MCA branch or mainstem occlusion compared to patients presenting with acute stroke without intracranial occlusion diagnosed by ultrasound at hospital entry carried a significant risk of mortality within 3 months after symptom onset (n = 535 patients), both when random or fixed effects models were used and studies with potentially overlapping cohorts were excluded (n = 524 patients; Figure 1). In only one of these studies the clinical observers were blinded to the ultrasound data, in the remaining studies blinding was not performed or not specified. The consequences of a MCA mainstem occlusion were graver (OR 6.15, 95% CI 3.32 to 11.64, \( P < 0.0001 \), heterogeneity \( P = 0.02 \), n = 137 patients) than of a branch occlusion (OR 2.13, 95% CI 1.08 to 4.18, \( P = 0.03 \), heterogeneity \( P = 0.10 \), n = 267 patients) compared to primary patent intracranial vessels. However, this comparison was affected by a significant heterogeneity. For predicting a fatal course MCA mainstem or branch occlusion had a sensitivity of 0.79 (95% CI 0.68 to 0.88) and a specificity of 0.39 (95% CI 0.34 to 0.43).

Clinical Improvement
Patient MCA versus MCA branch or mainstem occlusion diagnosed on hospital admission was associated with a significantly higher chance for clinical improvement within 4 days after symptom onset in cohorts not treated with thrombolysis (Figure 2; n = 329 patients). MCA branch occlusions carried a lower risk for lack of clinical improvement than MCA mainstem occlusions (OR 8.64, 95% CI 3.81–19.59, \( P < 0.001 \), heterogeneity \( P = 0.01 \), n = 98 patients versus OR 67.20, 95% CI 19.63 to 229.98, \( P < 0.001 \), heterogeneity \( P = 0.24 \), n = 83 patients) compared with a patent MCA on admission. Heterogeneity for this comparison resulted from the differences in study quality, with a markedly higher OR for a study quality > 5. For lack of clinical improvement initial diagnosis of MCA occlusion had a sensitivity of 0.87 (95% CI 0.80 to 0.93), and a specificity of 0.59 (95% CI 0.52 to 0.65).

Functional Outcome
In only 3 studies it was possible to extract data on functional outcome after 3 months related to the initial vascular status without intervention by thrombolysis. Patients with any type of MCA occlusion compared with initially patent MCA had a significantly higher chance to be functionally dependent after 3 months (OR 1.94, 95% CI 1.26 to 3.00, \( P < 0.003 \), n = 399 patients; sensitivity 0.96 [95% CI 0.92 to 0.98], specificity 0.39 [95% CI 0.33 to 0.47]). This risk was lower for MCA branch occlusions (OR 1.93, 95% CI 1.19 to 3.12, \( P < 0.01 \), heterogeneity \( P < 0.02 \), n = 193 patients) than for MCA mainstem occlusions (OR 16.43, 95% CI 6.62 to 40.75, \( P < 0.0001 \), heterogeneity \( P < 0.03 \), n = 61 patients). However, we found an overall significant heterogeneity (\( P < 0.0004 \)) between the studies. Only one study stated blinding of the clinical observers. All studies ascertained independence of the ultrasound data from other variables including initial stroke severity by multivariate analysis.

Effect of Vessel Recanalization
Full recanalization within 6 hours after symptom onset after initial diagnosis of MCA branch or mainstem occlusion in a 3-hour time window was highly significantly associated with...
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>No.</th>
<th>Stroke Severity</th>
<th>Recruitment Period</th>
<th>Time Window (min)</th>
<th>Modality</th>
<th>Blinding of Clinical Observers</th>
<th>No. of Centers</th>
<th>Multivariate Analysis</th>
<th>OS</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexandrov et al, 1994</td>
<td>Cohort</td>
<td>75</td>
<td>CSS n.s.</td>
<td>n.s</td>
<td>480±240</td>
<td>TCD</td>
<td>Yes.</td>
<td>1</td>
<td>No.</td>
<td>6</td>
<td>SP</td>
</tr>
<tr>
<td>Alexandrov et al, 2000a</td>
<td>Cohort</td>
<td>36</td>
<td>NIHSS 19</td>
<td>1998–1999</td>
<td>&lt;132±54</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Alexandrov et al, 2000b</td>
<td>Cohort</td>
<td>44</td>
<td>NIHSS 6</td>
<td>n.s</td>
<td>165±96</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>3</td>
<td>SP</td>
</tr>
<tr>
<td>Alexandrov et al, 2001</td>
<td>Cohort</td>
<td>65</td>
<td>NIHSS 17</td>
<td>1999–2000</td>
<td>&lt;135±61</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Alexandrov and Grotta 2002</td>
<td>Cohort</td>
<td>60</td>
<td>NIHSS 16</td>
<td>n.s</td>
<td>&lt;130±32</td>
<td>TCD</td>
<td>No.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Alexandrov et al, 2004</td>
<td>Cohort</td>
<td>126</td>
<td>NIHSS 16</td>
<td>n.s</td>
<td>&lt;150 median</td>
<td>TCD</td>
<td>Yes.</td>
<td>5</td>
<td>Yes.</td>
<td>7</td>
<td>i.v. rt-PA + cTCD, i.v. rt-PA + iTCD</td>
</tr>
<tr>
<td>Allendoerfer et al, 2006</td>
<td>Cohort</td>
<td>361</td>
<td>NIHSS 11</td>
<td>2000–2002</td>
<td>&lt;186 (median)</td>
<td>TCD+TCCS</td>
<td>Yes.</td>
<td>18</td>
<td>Yes.</td>
<td>8</td>
<td>SP</td>
</tr>
<tr>
<td>Arauz-Gongora et al, 1998</td>
<td>Cohort</td>
<td>37</td>
<td>NIHSS n.s.</td>
<td>n.s</td>
<td>≤1440</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>SP</td>
</tr>
<tr>
<td>Baracchini et al, 2000</td>
<td>Cohort</td>
<td>62</td>
<td>UNSS 13</td>
<td>n.s</td>
<td>348±210</td>
<td>TCD</td>
<td>n.s.</td>
<td>7</td>
<td>Yes.</td>
<td>7</td>
<td>SP</td>
</tr>
<tr>
<td>Christou et al, 2000</td>
<td>Cohort</td>
<td>36</td>
<td>NIHSS 19</td>
<td>1998–1999</td>
<td>&lt;132±54</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Felberg et al, 2002</td>
<td>Cohort</td>
<td>53</td>
<td>NIHSS 18</td>
<td>n.s</td>
<td>&lt;127±30</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Fieschi et al, 1989</td>
<td>Cohort</td>
<td>80</td>
<td>CSS 5</td>
<td>n.s</td>
<td>&lt;240</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>5</td>
<td>SP</td>
</tr>
<tr>
<td>Goertler et al, 1998</td>
<td>Cohort</td>
<td>20</td>
<td>NIHSS 17</td>
<td>n.s</td>
<td>≤300</td>
<td>TCCS</td>
<td>Yes.</td>
<td>1</td>
<td>Yes.</td>
<td>7</td>
<td>SP</td>
</tr>
<tr>
<td>Labiche et al, 2003a</td>
<td>Cohort</td>
<td>54</td>
<td>NIHSS 16</td>
<td>n.s</td>
<td>&lt;130±32</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Marinoni et al, 1991</td>
<td>Cohort</td>
<td>22</td>
<td>CSS 5</td>
<td>1987–1989</td>
<td>≤300</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>SP</td>
</tr>
<tr>
<td>Molina et al, 2001a</td>
<td>Cohort</td>
<td>24</td>
<td>NIHSS 17</td>
<td>2000–2001</td>
<td>&lt;180</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>Yes.</td>
<td>5</td>
<td>i.v. rt-PA + cTCD, SP + cTCD</td>
</tr>
<tr>
<td>Molina et al, 2001b</td>
<td>Cohort</td>
<td>53</td>
<td>NIHSS 17</td>
<td>1999–2000</td>
<td>&lt;360</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>Yes.</td>
<td>5</td>
<td>SP</td>
</tr>
<tr>
<td>Molina et al, 2002</td>
<td>Cohort</td>
<td>32</td>
<td>NIHSS 18</td>
<td>2000–2001</td>
<td>&lt;157±37</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>Yes.</td>
<td>5</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Postert et al, 1999</td>
<td>Cohort</td>
<td>90</td>
<td>ESS 50</td>
<td>1997–1999</td>
<td>≤720</td>
<td>TCCS</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>SP</td>
</tr>
<tr>
<td>Postert et al, 1998</td>
<td>Cohort</td>
<td>20</td>
<td>ESS 24</td>
<td>n.s</td>
<td>≤720</td>
<td>TCCS</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>SP</td>
</tr>
<tr>
<td>Ribo et al, 2005</td>
<td>Cohort</td>
<td>122</td>
<td>NIHSS 17</td>
<td>2002–2004</td>
<td>&lt;223 (median)</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Ribo et al, 2006</td>
<td>Cohort</td>
<td>179</td>
<td>NIHSS 17</td>
<td>2002–2005</td>
<td>&lt;171 (median)</td>
<td>TCD</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Sekuranja et al, 2006</td>
<td>Cohort</td>
<td>33</td>
<td>NIHSS 14</td>
<td>2003–2005</td>
<td>&lt;149 (mean)</td>
<td>TCCS</td>
<td>n.s.</td>
<td>1</td>
<td>No.</td>
<td>3</td>
<td>i.v. + i.a. rt-PA</td>
</tr>
<tr>
<td>Thomassen et al, 2005</td>
<td>Cohort</td>
<td>36</td>
<td>NIHSS 13</td>
<td>1998–2002</td>
<td>&lt;160 (mean)</td>
<td>TCD</td>
<td>Yes.</td>
<td>1</td>
<td>No.</td>
<td>4</td>
<td>i.v. rt-PA + cTCD</td>
</tr>
<tr>
<td>Toni et al, 1998</td>
<td>Cohort</td>
<td>93</td>
<td>CSS 5</td>
<td>n.s</td>
<td>&lt;300</td>
<td>TCD</td>
<td>Yes.</td>
<td>1</td>
<td>Yes.</td>
<td>7</td>
<td>SP</td>
</tr>
</tbody>
</table>

N indicates cohort size; OS, quality score; RCT, randomized controlled trial; CCS, case-control study; CSS, Canadian stroke scale; NIHSS, National Institute of Health stroke scale; UNSS, unified neurologic stroke scale; ESS, European stroke scale; n.s., not specified; TCD, transcranial Doppler sonography; TCCS, transcranial color-coded duplex sonography; mRS, modified Rankin scale; SP, secondary prophylaxis; no thrombolysis; i.v.-rt-PA, systemic thrombolysis with rt-PA; i.a.-rt-PA, intraarterial thrombolysis with rt-PA; cTCD, continuous TCD; iTCD, intermittent TCD.
clinical improvement within 48 hours after acute stroke in a total sample of 620 patients (Figure 3; sensitivity 0.63 [95% CI 0.56 to 0.70], specificity 0.75 [95% CI 0.70 to 0.80]). However, this result was affected by a significant heterogeneity within the studies which partly was related to the study quality, but also a publication bias needs to be assumed based on the funnel plot (Figure 4). In only two of the studies reporting ultrasound data related to clinical improvement clinical observers were blinded,\textsuperscript{9,27} in all other studies this was either not reported or not done. Consistently, without significant heterogeneity, full recanalization within 6 hours carried a significantly higher chance to be functionally independent after 3 months (OR 6.07, 95% CI 3.94–9.35, \(P < 0.00001\), \(n = 972\) patients).\textsuperscript{8,10,13,17,21,25–27}

### Figure 1.
Odds ratio (OR) for survival or death after acute stroke related to patency or occlusion of the middle cerebral artery in patient cohorts not treated with thrombolysis.

```plaintext
<table>
<thead>
<tr>
<th>Study</th>
<th>MCA patent n/N</th>
<th>MCA occlusion n/N</th>
<th>OR (fixed)</th>
<th>Weight (%)</th>
<th>OR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fieschi 1989</td>
<td>23/31</td>
<td>35/47</td>
<td>48.16</td>
<td>0.99 (0.35, 2.78)</td>
<td></td>
</tr>
<tr>
<td>Marioni 1991</td>
<td>8/10</td>
<td>7/12</td>
<td>8.54</td>
<td>2.06 (0.42, 18.69)</td>
<td></td>
</tr>
<tr>
<td>Postert 1999</td>
<td>0/9</td>
<td>0/9</td>
<td>1.98</td>
<td>16.08 (0.75, 343.62)</td>
<td></td>
</tr>
<tr>
<td>Baracchini 2000</td>
<td>19/19</td>
<td>39/54</td>
<td>22.16</td>
<td>1.50 (0.36, 6.19)</td>
<td></td>
</tr>
<tr>
<td>Allendörffer 2006</td>
<td>101/103</td>
<td>159/170</td>
<td>3.53</td>
<td>15.30 (0.87, 269.35)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>194</td>
<td>341</td>
<td>100.00</td>
<td>2.46 (1.33, 4.52)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 178 (MCA patent), 284 (MCA occl.)
Heterogeneity: \( Chi^2 = 6.65, df = 5 (p = 0.25), I^2 = 25.1 \%
Overall effect: Z = 2.88 (p = 0.004)

Fixed effects model (n=6)
Random effects model (n=6)

### Figure 2.
Odds ratio (OR) for clinical improvement within the first 4 days after acute stroke related to patency or occlusion of the middle cerebral artery in patient cohorts not treated with thrombolysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>MCA patent n/N</th>
<th>MCA occlusion n/N</th>
<th>OR (fixed)</th>
<th>Weight (%)</th>
<th>OR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marioni 1991</td>
<td>2/10</td>
<td>1/22</td>
<td>0.25</td>
<td>948.00 (17.32, 50968.79)</td>
<td></td>
</tr>
<tr>
<td>Alexandre 1994</td>
<td>10/10</td>
<td>0/22</td>
<td>5.96</td>
<td>18.89 (0.81, 311.99)</td>
<td></td>
</tr>
<tr>
<td>Aras-Gongora 1998</td>
<td>5/5</td>
<td>13/32</td>
<td>17.54</td>
<td>17.31 (0.82, 353.21)</td>
<td></td>
</tr>
<tr>
<td>Gouter 1998</td>
<td>7/7</td>
<td>6/13</td>
<td>3.22</td>
<td>6.56 (1.41, 28.85)</td>
<td></td>
</tr>
<tr>
<td>Postert 1999</td>
<td>40/43</td>
<td>27/47</td>
<td>31.00</td>
<td>9.88 (2.87, 36.53)</td>
<td></td>
</tr>
<tr>
<td>Alexandrov 2000</td>
<td>20/27</td>
<td>3/8</td>
<td>2.96</td>
<td>43.33 (3.71, 50.08)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>140</td>
<td>189</td>
<td>100.00</td>
<td>11.11 (5.44, 22.69)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 125 (MCA patent), 88 (MCA occl.)
Heterogeneity: \( Chi^2 = 5.53, df = 6 (p = 0.23), I^2 = 28.6 \%
Overall effect: Z = 4.61 (p = 0.00001)

Fixed effects model (n = 7)
Random effects model (n = 7)

Study quality
- Quality \(6 + 7\) (n = 2)
- Quality \(3 + 5\) (n = 5)
- Blinded studies (n = 3)
- Unblinded studies or not specified (n = 4)
Discussion

The main results of this metaanalysis are fairly clear and straightforward: Diagnosis of MCA mainstem or branch occlusion by TCD or TCCS on admission without thrombolytic treatment is affected with a significantly increased chance to take a fatal course (Figure 1). These patients also have a more than 10-times higher chance not to clinically improve within the first days after stroke compared to patients with primary patent intracranial vessels (Figure 2).

Only 3 ultrasound studies examined the functional outcome of patients not treated with thrombolysis. Patients with MCA occlusion have a nearly 2-fold higher chance to be left functionally dependent 3 months after stroke. However, this result was suffered of significant heterogeneity between the studies. Obviously, the vascular status on admission carries important information on the clinical prognosis of acute stroke patients. It may also be possible to identify a subgroup of patients at particular risk of secondary deterioration.

However, these data have further implications: When planning studies on acute stroke treatments the initial vascular status is an important confounding variable and stratification is necessary, considering the fact that patients with primary patent intracranial vessels have a more than 10-fold higher chance to clinically improve within the first 4 days.

In patients with initially occluded MCA, recanalization within 6 hours after symptom onset is associated with a more than 5-fold chance for clinical improvement and functional independence 3 months after stroke. This is the rational for any recanalizing therapy.

Eight of the 25 studies included in this metaanalysis were able to show that the ultrasound findings are independent from other variables especially the clinical impression and initial stroke severity. This is of relevance, because transcranial ultrasound is able to provide additional prognostic information as a bed-side method. For most tests for outcome sensitivity was better than the specificity, ie, false-negatives are less common than false-positives. This makes ultrasound a good screening test in these clinical situations. Although approximately 20% of transcranial ultrasound examinations
suffer from insufficient acoustic penetration conditions, in
more than 90% of these patients diagnosis is possible by
application of ultrasound contrast agents. Reservations re-
garding the application of ultrasound in the setting of acute
stroke are frequently expressed. In a study comparing neuro-
sonology with a reference method in 58 acute stroke pa-
tients in 11 patients MRI was inconclusive or not possible
because of extensive movement artifacts (6 patients) or
contraindications (5 patients). In 8 further critically ill pa-
tients MRI was not performed because of insufficient ability
to monitor vital parameters in the scanner. However, in 54
patients (93%) ultrasound examination was possible and
conclusive. Transcranial ultrasound can serve as one of the
methods to evaluate vessel status in acute stroke and seems
especially useful for follow-up examinations.

During the first 3 hours after symptom onset nothing more
than clinical knowledge, a simple computed tomography
(CT) scan to exclude intracranial hemorrhage, and a watch
are necessary to initiate systemic thrombolysis based on the
current scientific studies. However, transcranial ultrasound
may be used in the 3- to 6-hour time window to identify
patients who might benefit from a bridging approach when
systemic thrombolysis did not lead to recanalization or
who may profit from a primary interventional approach.

Relevant (>20%) MRI perfusion/diffusion mismatch
seems to be able to select subgroups of patients even beyond
3 hours after symptom onset who profit from thrombolysis,
although randomized trials are lacking. Surprisingly, only
few studies have so far examined the relationship between the
presence of a mismatch and the vascular status: a relevant
mismatch ratio (>1.2) without vessel occlusion is rare (5%)
and the presence of occlusion mirrors the presence of a
mismatch with a sensitivity of 92% and a specificity of 95%.
This again highlights the importance of knowledge of the
vascular status of patients with acute stroke.

Several major shortcomings of the included studies have to
be mentioned. Only 6 of the 24 studies (25%) implemented
blinding of the clinical observers to the ultrasound data; in the
remaining 18 investigations blinding was not performed or
not explicitly mentioned. However, in the cases where a
direct comparison of the effects in blinded studies and studies
not mentioning blinding was possible in a sensitivity analysis,
no marked differences could be observed. Twenty-two inves-
tigations were single center studies by 9 research groups with
partly overlapping recruitment periods within the same group.
Consequently, only 5 studies reached a quality score of ≥7
(Tables 1 and 2). Therefore, there is still great opportunity for
improvement in the field of ultrasound research. These
sources of bias have been recognized as far as possible in the
sensitivity analysis.

Additional bias is introduced in this metaanalysis by
unequal access to stroke unit treatment and certain treatment
options such as decompressive craniotomy or thrombolysis in cohorts recruited in the 1990s. Another reason for heterogeneity also appears the variable ratios of MCA mainstem and branch occlusions as well as patent vessels (Figure 5), which also depends on the time interval between stroke onset and ultrasound examination. Additional reason for bias is the heterogeneous treatments used. These factors could not be controlled for in this metaanalysis. Heterogeneity also results from the fact that several studies were accomplished to analyze specific stroke treatments rather than prognosis. Then it needs to be mentioned that the 25 studies in this metaanalysis originate from only 12 different groups introducing further bias as illustrated in Figure 4. Stratification of our analyses by initial stroke severity would also be desirable, but could not be accomplished because the necessary data could not be extracted from the studies.

Considering these limitations of this metaanalysis the random effects model is probably more relevant than the fixed effects model. Both models have been included in the analysis.

In summary, this metaanalysis highlights the importance of the knowledge of the vascular status in acute stroke.

Disclosures

None.

References

Can Early Neurosonology Predict Outcome in Acute Stroke?: A Metaanalysis of Prognostic Clinical Effect Sizes Related to the Vascular Status
Erwin Stolz, Francesca Cioli, Jens Allendoerfer, Tibo Gerriets, Massimo Del Sette and Manfred Kaps

*Stroke*. 2008;39:3255-3261; originally published online October 9, 2008; doi: 10.1161/STROKEAHA.108.522714

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/39/12/3255

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/